Dossier zur Nutzenbewertung gemäß § 35a SGB V

Osimertinib (TAGRISSO®)

AstraZeneca GmbH

Modul 4 A – Anhang 4-G

Osimertinib in Kombination mit Pemetrexed und platinhaltiger Chemotherapie zur Erstlinientherapie von erwachsenen Patienten mit fortgeschrittenem NSCLC, deren Tumoren EGFR-Mutationen als Deletion im Exon 19 oder Substitutionsmutation im Exon 21 (L858R) aufweisen

Weitere Analysen und Kaplan-Meier-Plots zu den in Abschnitt 4.3.1.3 gezeigten Ergebnissen

Stand: 23.07.2024

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Table 3.2.1 FLAURA-2: Summary of analysis of time to first adverse event
(total, and by SOC and PT occurring with frequency >=10 patients and at least 1% in either treatment arm)
Safety Analysis Set, DCO 03APR2023

	Osi + Chemo (N=276)			Osi (N=275)					
	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]	Hazard Ratio [b]	[95%-KI] [b]	2-seitiger p-Wert [b]
UE	276	276 (100)	0,1 [0,1; 0,2]	275	268 (97,5)	0,3 [0,3; 0,3]	2,04	[1,70; 2,45]	<0,0001*
SOC: Allgemeine Erkrankungen und Beschwerden am Verabreichungsort	276	167 (60,5)	4,3 [2,3;10,5]	275	89 (32,4)	NE [NE; NE]	2,46	[1,92; 3,15]	<0,0001*
PT: Asthenie	276	26 (9,4)	NE [NE; NE]	275	7 (2,5)	NE [NE; NE]	3,30	[1,67; 6,53]	0,0006*
PT: Ermuedung	276	76 (27,5)	NE [NE; NE]	275	26 (9,5)	NE [NE; NE]	2,97	[2,01; 4,38]	<0,0001*
PT: Fieber	276	31 (11,2)	NE [NE; NE]	275	15 (5,5)	NE [NE; NE]	2,01	[1,13; 3,59]	0,0178*
PT: Gesichtsoedem	276	10 (3,6)	NE [NE; NE]	275	2 (0,7)	NE [NE; NE]	3,72	[1,20; 11,53]	0,0230*
PT: Oedem peripher	276	42 (15,2)	NE [NE; NE]	275	12 (4,4)	NE [NE; NE]	3,08	[1,81; 5,26]	<0,0001*
PT: Schleimhautentzuendung	276	24 (8,7)	NE [NE; NE]	275	14 (5,1)	NE [NE; NE]	1,76	[0,93; 3,33]	0,0805
PT: Thoraxschmerz nicht kardialen Ursprungs	276	10 (3,6)	NE [NE; NE]	275	10 (3,6)	NE [NE; NE]	0,97	[0,40; 2,33]	0,9435
PT: Unwohlsein	276	19 (6,9)	NE [NE; NE]	275	3 (1,1)	NE [NE; NE]	4,34	[1,88; 10,02]	0,0006*
SOC: Augenerkrankungen	276	51 (18,5)	NE [NE; NE]	275	29 (10,5)	NE [NE; NE]	1,77	[1,14; 2,74]	0,0108*

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[a] Median time to event based on the Kaplan Meier estimate. NE = Not estimable as median (or 95% CLs) is not reached.
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	Osi + Chemo (N=276)			Osi (N=275)					
	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]	Hazard Ratio [b]	[95%-KI] [b]	2-seitiger p-Wert [b]
PT: Traenensekretion verstaerkt	276	16 (5,8)	NE [NE; NE]	275	1 (0,4)	NE [NE; NE]	5,92	[2,29; 15,32]	0,0002*
PT: Trockenes Auge	276	12 (4,3)	NE [NE; NE]	275	8 (2,9)	NE [NE; NE]	1,47	[0,61; 3,53]	0,3916
SOC: Erkrankungen der Atemwege, des Brustraums und Mediastinums	276	120 (43,5)	NE [NE; NE]	275	102 (37,1)	NE [NE; NE]	1,24	[0,95; 1,61]	0,1144
PT: Dyspnoe	276	16 (5,8)	NE [NE; NE]	275	17 (6,2)	NE [NE; NE]	0,92	[0,46; 1,82]	0,8117
PT: Epistaxis	276	20 (7,2)	NE [NE; NE]	275	18 (6,5)	NE [NE; NE]	1,12	[0,60; 2,13]	0,7167
PT: Husten	276	31 (11,2)	NE [NE; NE]	275	29 (10,5)	NE [NE; NE]	1,03	[0,62; 1,71]	0,9034
PT: Lungenembolie	276	13 (4,7)	NE [NE; NE]	275	5 (1,8)	NE [NE; NE]	2,34	[0,93; 5,90]	0,0719
PT: Schluckauf	276	11 (4,0)	NE [NE; NE]	275	1 (0,4)	NE [NE; NE]	5,37	[1,73; 16,67]	0,0036*
PT: Schmerzen im Oropharynx	276	18 (6,5)	NE [NE; NE]	275	7 (2,5)	NE [NE; NE]	2,39	[1,09; 5,23]	0,0296*
SOC: Erkrankungen der Geschlechtsorgane und der Brustdruese	276	13 (4,7)	NE [NE; NE]	275	15 (5,5)	NE [NE; NE]	0,85	[0,41; 1,79]	0,6768

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	Osi + Chemo (N=276)			Osi (N=275)					
	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]	Hazard Ratio [b]	[95%-KI] [b]	2-seitiger p-Wert [b]
SOC: Erkrankungen der Haut und des Unterhautgewebes	276	191 (69,2)	1,2 [0,7; 2,1]	275	184 (66,9)	1,4 [1,1; 2,1]	1,08	[0,88; 1,32]	0,4638
PT: Alopezie	276	24 (8,7)	NE [NE; NE]	275	15 (5,5)	NE [NE; NE]	1,62	[0,87; 3,04]	0,1311
PT: Ausschlag	276	77 (27,9)	NE [NE; NE]	275	57 (20,7)	NE [NE; NE]	1,45	[1,03; 2,03]	0,0330*
PT: Ausschlag makulo-papuloes	276	18 (6,5)	NE [NE; NE]	275	19 (6,9)	NE [NE; NE]	0,93	[0,49; 1,78]	0,8370
PT: Dermatitis akneiform	276	37 (13,4)	NE [NE; NE]	275	36 (13,1)	NE [NE; NE]	1,03	[0,65; 1,62]	0,9121
PT: Nagelerkrankung	276	3 (1,1)	NE [NE; NE]	275	10 (3,6)	NE [NE; NE]	0,34	[0,11; 0,997]	0,0493*
PT: Palmar-plantares Erythrodysaesthesiesyndrom	276	15 (5,4)	NE [NE; NE]	275	9 (3,3)	NE [NE; NE]	1,63	[0,73; 3,64]	0,2288
PT: Pruritus	276	22 (8,0)	NE [NE; NE]	275	31 (11,3)	NE [NE; NE]	0,67	[0,39; 1,14]	0,1413
PT: Trockene Haut	276	50 (18,1)	NE [NE; NE]	275	66 (24,0)	NE [NE; NE]	0,72	[0,50; 1,04]	0,0828
SOC: Erkrankungen der Nieren und Harnwege	276	52 (18,8)	NE [NE; NE]	275	26 (9,5)	NE [NE; NE]	1,97	[1,26; 3,06]	0,0029*
PT: Haematurie	276	12 (4,3)	NE [NE; NE]	275	7 (2,5)	NE [NE; NE]	1,67	[0,68; 4,10]	0,2663

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(total, and by SOC and PT occurring with frequency >=10 patients and at least 1% in either treatment arm)
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	Osi + Chemo (N=276)			Osi (N=275)					
	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]	Hazard Ratio [b]	[95%-KI] [b]	2-seitiger p-Wert [b]
SOC: Erkrankungen des Blutes und des Lymphsystems	276	174 (63,0)	2,8 [2,1; 3,5]	275	48 (17,5)	NE [NE; NE]	4,67	[3,57; 6,12]	<0,0001*
PT: Anaemie	276	128 (46,4)	NE [NE; NE]	275	22 (8,0)	NE [NE; NE]	5,61	[4,05; 7,75]	<0,0001*
PT: Febrile Neutropenie	276	11 (4,0)	NE [NE; NE]	275	0	NE [NE; NE]	NC	NC	0,0010*
PT: Leukopenie	276	35 (12,7)	NE [NE; NE]	275	11 (4,0)	NE [NE; NE]	3,02	[1,69; 5,38]	0,0002*
PT: Neutropenie	276	68 (24,6)	NE [NE; NE]	275	9 (3,3)	NE [NE; NE]	5,26	[3,36; 8,23]	<0,0001*
PT: Thrombozytopenie	276	51 (18,5)	NE [NE; NE]	275	12 (4,4)	NE [NE; NE]	3,70	[2,26; 6,06]	<0,0001*
SOC: Erkrankungen des Gastrointestinaltrakts	276	226 (81,9)	0,3 [0,2; 0,4]	275	171 (62,2)	2,6 [1,4; 5,3]	2,06	[1,68; 2,53]	<0,0001*
PT: Abdominalschmerz	276	12 (4,3)	NE [NE; NE]	275	7 (2,5)	NE [NE; NE]	1,66	[0,68; 4,08]	0,2688
PT: Diarrhoe	276	120 (43,5)	NE [NE; NE]	275	112 (40,7)	NE [NE; NE]	1,11	[0,85; 1,43]	0,4452
PT: Dyspepsie	276	12 (4,3)	NE [NE; NE]	275	6 (2,2)	NE [NE; NE]	1,92	[0,76; 4,84]	0,1664
PT: Erbrechen	276	73 (26,4)	NE [NE; NE]	275	17 (6,2)	NE [NE; NE]	3,90	[2,58; 5,90]	<0,0001*
PT: Gastrooesophageale Refluxerkrankung	276	22 (8,0)	NE [NE; NE]	275	7 (2,5)	NE [NE; NE]	2,90	[1,40; 6,02]	0,0041*

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PT: Haemorrhoiden	276	10 (3,6)	NE [NE; NE]	275	3 (1,1)	NE [NE; NE]	2,92	[0,98; 8,67]	0,0533
PT: Mundtrockenheit	276	15 (5,4)	NE [NE; NE]	275	4 (1,5)	NE [NE; NE]	3,24	[1,32; 7,97]	0,0104*
PT: Mundulzeration	276	18 (6,5)	NE [NE; NE]	275	10 (3,6)	NE [NE; NE]	1,78	[0,85; 3,74]	0,1256
PT: Obstipation	276	81 (29,3)	NE [NE; NE]	275	28 (10,2)	NE [NE; NE]	3,02	[2,07; 4,41]	<0,0001*
PT: Schmerzen Oberbauch	276	20 (7,2)	NE [NE; NE]	275	7 (2,5)	NE [NE; NE]	2,57	[1,21; 5,47]	0,0142*
PT: Stomatitis	276	68 (24,6)	NE [NE; NE]	275	50 (18,2)	NE [NE; NE]	1,42	[0,99; 2,04]	0,0576
PT: Uebelkeit	276	119 (43,1)	NE [NE; NE]	275	28 (10,2)	NE [NE; NE]	4,54	[3,28; 6,30]	<0,0001*
SOC: Erkrankungen des Nervensystems	276	103 (37,3)	NE [NE; NE]	275	75 (27,3)	NE [NE; NE]	1,49	[1,11; 2,00]	0,0082*
PT: Dysgeusie	276	17 (6,2)	NE [NE; NE]	275	11 (4,0)	NE [NE; NE]	1,55	[0,74; 3,25]	0,2458
PT: Kopfschmerzen	276	26 (9,4)	NE [NE; NE]	275	26 (9,5)	NE [NE; NE]	0,95	[0,55; 1,64]	0,8604
PT: Periphere Neuropathie	276	13 (4,7)	NE [NE; NE]	275	6 (2,2)	NE [NE; NE]	2,07	[0,84; 5,10]	0,1120
PT: Periphere sensorische Neuropathie	276	11 (4,0)	NE [NE; NE]	275	1 (0,4)	NE [NE; NE]	5,22	[1,68; 16,22]	0,0042*

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PT: Schwindelgefuehl	276	32 (11,6)	NE [NE; NE]	275	16 (5,8)	NE [NE; NE]	1,91	[1,09; 3,37]	0,0247*
SOC: Erkrankungen des Ohrs und des Labyrinths	276	23 (8,3)	NE [NE; NE]	275	12 (4,4)	NE [NE; NE]	1,77	[0,91; 3,43]	0,0928
SOC: Gefaesserkrankungen	276	46 (16,7)	NE [NE; NE]	275	37 (13,5)	NE [NE; NE]	1,23	[0,80; 1,90]	0,3375
PT: Hypertonie	276	18 (6,5)	NE [NE; NE]	275	15 (5,5)	NE [NE; NE]	1,18	[0,60; 2,34]	0,6327
SOC: Gutartige, boesartige und nicht spezifizierte Neubildungen (einschl. Zysten und Polypen)	276	11 (4,0)	NE [NE; NE]	275	8 (2,9)	NE [NE; NE]	1,32	[0,54; 3,26]	0,5408
SOC: Herzerkrankungen	276	58 (21,0)	NE [NE; NE]	275	41 (14,9)	NE [NE; NE]	1,43	[0,96; 2,11]	0,0780
SOC: Infektionen und parasitaere Erkrankungen	276	183 (66,3)	8,4 [5,1;12,8]	275	167 (60,7)	9,9 [7,2;13,5]	1,08	[0,88; 1,34]	0,4521
PT: COVID-19	276	57 (20,7)	NE [NE; NE]	275	39 (14,2)	NE [NE; NE]	1,28	[0,85; 1,91]	0,2329
PT: Harnwegsinfektion	276	36 (13,0)	NE [NE; NE]	275	28 (10,2)	NE [NE; NE]	1,28	[0,78; 2,08]	0,3302
PT: Infektion der oberen Atemwege	276	16 (5,8)	NE [NE; NE]	275	9 (3,3)	NE [NE; NE]	1,70	[0,78; 3,73]	0,1846
PT: Konjunktivitis	276	16 (5,8)	NE [NE; NE]	275	3 (1,1)	NE [NE; NE]	3,81	[1,55; 9,38]	0,0036*

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PT: Paronychie	276	65 (23,6)	NE [NE; NE]	275	73 (26,5)	NE [NE; NE]	0,84	[0,60; 1,17]	0,2954
PT: Pneumonie	276	15 (5,4)	NE [NE; NE]	275	16 (5,8)	NE [NE; NE]	0,90	[0,45; 1,83]	0,7792
SOC: Leber- und Gallenerkrankungen	276	25 (9,1)	NE [NE; NE]	275	7 (2,5)	NE [NE; NE]	3,16	[1,58; 6,32]	0,0011*
SOC: Psychiatrische Erkrankungen	276	50 (18,1)	NE [NE; NE]	275	28 (10,2)	NE [NE; NE]	1,79	[1,15; 2,80]	0,0099*
PT: Schlaflosigkeit	276	34 (12,3)	NE [NE; NE]	275	18 (6,5)	NE [NE; NE]	1,88	[1,09; 3,23]	0,0232*
SOC: Skelettmuskulatur-, Bindegewebs- und Knochenerkrankungen	276	85 (30,8)	NE [NE; NE]	275	91 (33,1)	NE [NE; NE]	0,86	[0,64; 1,15]	0,3090
PT: Arthralgie	276	28 (10,1)	NE [NE; NE]	275	32 (11,6)	NE [NE; NE]	0,81	[0,49; 1,35]	0,4192
PT: Brustschmerzen die Skelettmuskulatur betreffend	276	11 (4,0)	NE [NE; NE]	275	15 (5,5)	NE [NE; NE]	0,69	[0,32; 1,50]	0,3542
PT: Muskelspasmen	276	9 (3,3)	NE [NE; NE]	275	15 (5,5)	NE [NE; NE]	0,58	[0,26; 1,30]	0,1847
PT: Myalgie	276	8 (2,9)	NE [NE; NE]	275	14 (5,1)	NE [NE; NE]	0,56	[0,24; 1,29]	0,1725
PT: Rueckenschmerzen	276	23 (8,3)	NE [NE; NE]	275	26 (9,5)	NE [NE; NE]	0,84	[0,48; 1,46]	0,5287

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[b] p-value is estimated using unstratified log-rank test. Hazard ratio and 95% confidence interval derived from U and V statistics. Breslow method is used for handling ties. NC = not calculable. Hazard ratio <1 favours Osimertinib+Chemo. * p<0.05.
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Table 3.2.1 FLAURA-2: Summary of analysis of time to first adverse event
(total, and by SOC and PT occurring with frequency >=10 patients and at least 1% in either treatment arm)
Safety Analysis Set, DCO 03APR2023

	Osi + Chemo (N=276)			Osi (N=275)					
	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]	Hazard Ratio [b]	[95%-KI] [b]	2-seitiger p-Wert [b]
PT: Schmerz in einer Extremitaet	276	8 (2,9)	NE [NE; NE]	275	16 (5,8)	NE [NE; NE]	0,49	[0,22; 1,08]	0,0769
SOC: Stoffwechsel- und Ernaehrungsstoerungen	276	137 (49,6)	12,1 [6,7; NE]	275	81 (29,5)	NE [NE; NE]	2,01	[1,54; 2,62]	<0,0001*
PT: Appetit vermindert	276	85 (30,8)	NE [NE; NE]	275	26 (9,5)	NE [NE; NE]	3,35	[2,30; 4,86]	<0,0001*
PT: Hypalbuminaemie	276	17 (6,2)	NE [NE; NE]	275	13 (4,7)	NE [NE; NE]	1,28	[0,62; 2,62]	0,5009
PT: Hyperglykaemie	276	12 (4,3)	NE [NE; NE]	275	11 (4,0)	NE [NE; NE]	1,08	[0,48; 2,44]	0,8588
PT: Hyperurikaemie	276	12 (4,3)	NE [NE; NE]	275	6 (2,2)	NE [NE; NE]	1,90	[0,75; 4,79]	0,1736
PT: Hypokaliaemie	276	18 (6,5)	NE [NE; NE]	275	13 (4,7)	NE [NE; NE]	1,34	[0,66; 2,71]	0,4177
PT: Hypokalzaemie	276	9 (3,3)	NE [NE; NE]	275	10 (3,6)	NE [NE; NE]	0,90	[0,37; 2,21]	0,8191
PT: Hypomagnesiaemie	276	18 (6,5)	NE [NE; NE]	275	3 (1,1)	NE [NE; NE]	4,30	[1,83; 10,13]	0,0008*
PT: Hyponatriaemie	276	16 (5,8)	NE [NE; NE]	275	12 (4,4)	NE [NE; NE]	1,36	[0,65; 2,86]	0,4131
SOC: Untersuchungen	276	170 (61,6)	4,9 [3,0; 7,2]	275	98 (35,6)	NE [NE; NE]	2,20	[1,73; 2,80]	<0,0001*

The time to event endpoint is defined as the time from first dose of study treatment to first onset of the respective AE if the AE has occurred by 28 days following the date of last dose of study treatment.
Any patient that has not experienced the AE will be censored at the earliest of the date of Osimertinib/Osimertinib+Chemo discontinuation+28 days, administration of subsequent therapy or death.
All AEs are coded using MedDRA version 25.1.
[a] Median time to event based on the Kaplan Meier estimate. NE = Not estimable as median (or 95% CLs) is not reached.
[b] p-value is estimated using unstratified log-rank test. Hazard ratio and 95% confidence interval derived from U and V statistics. Breslow method is used for handling ties. NC = not calculable. Hazard ratio <1 favours Osimertinib+Chemo. * p<0.05.
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Table 3.2.1 FLAURA-2: Summary of analysis of time to first adverse event
(total, and by SOC and PT occurring with frequency >=10 patients and at least 1% in either treatment arm)
Safety Analysis Set, DCO 03APR2023

	Osi + Chemo (N=276)			Osi (N=275)					
	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]	Hazard Ratio [b]	[95%-KI] [b]	2-seitiger p-Wert [b]
PT: Alaninaminotransferase erhoeht	276	56 (20,3)	NE [NE; NE]	275	21 (7,6)	NE [NE; NE]	2,68	[1,71; 4,19]	<0,0001*
PT: Aspartataminotransferase erhoeht	276	48 (17,4)	NE [NE; NE]	275	13 (4,7)	NE [NE; NE]	3,37	[2,04; 5,56]	<0,0001*
PT: Auswurffraktion verkleinert	276	17 (6,2)	NE [NE; NE]	275	9 (3,3)	NE [NE; NE]	1,72	[0,79; 3,71]	0,1699
PT: Elektrokardiogramm QT verlaengert	276	24 (8,7)	NE [NE; NE]	275	23 (8,4)	NE [NE; NE]	1,02	[0,58; 1,81]	0,9434
PT: Gamma-Glutamyltransferase erhoeht	276	17 (6,2)	NE [NE; NE]	275	2 (0,7)	NE [NE; NE]	4,95	[2,01; 12,17]	0,0005*
PT: Gewicht erhoeht	276	13 (4,7)	NE [NE; NE]	275	3 (1,1)	NE [NE; NE]	3,52	[1,32; 9,37]	0,0119*
PT: Gewicht erniedrigt	276	32 (11,6)	NE [NE; NE]	275	22 (8,0)	NE [NE; NE]	1,46	[0,86; 2,49]	0,1625
PT: Kreatinin im Blut erhoeht	276	46 (16,7)	NE [NE; NE]	275	12 (4,4)	NE [NE; NE]	3,26	[1,95; 5,46]	<0,0001*
PT: Laktatdehydrogenase im Blut erhoeht	276	13 (4,7)	NE [NE; NE]	275	11 (4,0)	NE [NE; NE]	1,18	[0,53; 2,64]	0,6777

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Any patient that has not experienced the AE will be censored at the earliest of the date of Osimertinib/Osimertinib+Chemo discontinuation+28 days, administration of subsequent therapy or death.
All AEs are coded using MedDRA version 25.1.
[a] Median time to event based on the Kaplan Meier estimate. NE = Not estimable as median (or 95% CLs) is not reached.
[b] p-value is estimated using unstratified log-rank test. Hazard ratio and 95% confidence interval derived from U and V statistics. Breslow method is used for handling ties. NC = not calculable. Hazard ratio <1 favours Osimertinib+Chemo. * p<0.05.
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Table 3.2.1 FLAURA-2: Summary of analysis of time to first adverse event
(total, and by SOC and PT occurring with frequency >=10 patients and at least 1% in either treatment arm)
Safety Analysis Set, DCO 03APR2023

	Osi + Chemo (N=276)			Osi (N=275)					
	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]	Hazard Ratio [b]	[95%-KI] [b]	2-seitiger p-Wert [b]
PT: Leukozytenzahl erniedrigt	276	44 (15,9)	NE [NE; NE]	275	18 (6,5)	NE [NE; NE]	2,47	[1,50; 4,07]	0,0004*
PT: Lymphozytenzahl erniedrigt	276	13 (4,7)	NE [NE; NE]	275	13 (4,7)	NE [NE; NE]	0,99	[0,46; 2,14]	0,9872
PT: Neutrophilenzahl erniedrigt	276	62 (22,5)	NE [NE; NE]	275	16 (5,8)	NE [NE; NE]	3,58	[2,29; 5,58]	<0,0001*
PT: Renale Kreatininclearance vermindert	276	13 (4,7)	NE [NE; NE]	275	0	NE [NE; NE]	NC	NC	0,0004*
PT: Thrombozytenzahl vermindert	276	51 (18,5)	NE [NE; NE]	275	19 (6,9)	NE [NE; NE]	2,67	[1,67; 4,27]	<0,0001*
PT: Transaminasen erhoeht	276	10 (3,6)	NE [NE; NE]	275	2 (0,7)	NE [NE; NE]	3,80	[1,23; 11,80]	0,0206*
SOC: Verletzung, Vergiftung und durch Eingriffe bedingte Komplikationen	276	41 (14,9)	NE [NE; NE]	275	25 (9,1)	NE [NE; NE]	1,63	[1,004; 2,64]	0,0481*

The time to event endpoint is defined as the time from first dose of study treatment to first onset of the respective AE if the AE has occurred by 28 days following the date of last dose of study treatment.
Any patient that has not experienced the AE will be censored at the earliest of the date of Osimertinib/Osimertinib+Chemo discontinuation+28 days, administration of subsequent therapy or death.
All AEs are coded using MedDRA version 25.1.
[a] Median time to event based on the Kaplan Meier estimate. NE = Not estimable as median (or 95% CLs) is not reached.
[b] p-value is estimated using unstratified log-rank test. Hazard ratio and 95% confidence interval derived from U and V statistics. Breslow method is used for handling ties. NC = not calculable. Hazard ratio <1 favours Osimertinib+Chemo. * p<0.05.
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Table 3.2.2 FLAURA-2: Summary of analysis of time to first serious adverse event
(total, and by SOC and PT occurring with frequency >=10 patients and at least 1% in either treatment arm)
Safety Analysis Set, DCO 03APR2023

	Osi + Chemo (N=276)			Osi (N=275)					
	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]	Hazard Ratio [b]	[95%-KI] [b]	2-seitiger p-Wert [b]
SUE	276	104 (37,7)	NE [NE; NE]	275	53 (19,3)	NE [NE; NE]	2,10	[1,53; 2,87]	<0,0001*
SUE SOC: Erkrankungen der Atemwege, des Brustraums und Mediastinums	276	15 (5,4)	NE [NE; NE]	275	19 (6,9)	NE [NE; NE]	0,76	[0,39; 1,48]	0,4161
SUE SOC: Erkrankungen des Blutes und des Lymphsystems	276	18 (6,5)	NE [NE; NE]	275	0	NE [NE; NE]	NC	NC	<0,0001*
SUE SOC: Erkrankungen des Gastrointestinaltrakts	276	13 (4,7)	NE [NE; NE]	275	4 (1,5)	NE [NE; NE]	2,90	[1,12; 7,50]	0,0283*
SUE SOC: Herzerkrankungen	276	10 (3,6)	NE [NE; NE]	275	4 (1,5)	NE [NE; NE]	2,30	[0,80; 6,55]	0,1204
SUE SOC: Infektionen und parasitaere Erkrankungen	276	29 (10,5)	NE [NE; NE]	275	22 (8,0)	NE [NE; NE]	1,27	[0,73; 2,20]	0,3927
SUE SOC: Untersuchungen	276	10 (3,6)	NE [NE; NE]	275	1 (0,4)	NE [NE; NE]	5,16	[1,58; 16,83]	0,0066*

The time to event endpoint is defined as the time from first dose of study treatment to first onset of the respective AE if the AE has occurred by 28 days following the date of last dose of study treatment.
Any patient that has not experienced the AE will be censored at the earliest of the date of Osimertinib/Osimertinib+Chemo discontinuation+28 days, administration of subsequent therapy or death.
All AEs are coded using MedDRA version 25.1.
[a] Median time to event based on the Kaplan Meier estimate. NE = Not estimable as median (or 95% CLs) is not reached.
[b] p-value is estimated using unstratified log-rank test. Hazard ratio and 95% confidence interval derived from U and V statistics. Breslow method is used for handling ties. NC = not calculable. Hazard ratio <1 favours Osimertinib+Chemo. * p<0.05.
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Table 3.2.4 FLAURA-2: Summary of analysis of time to first adverse event with max. CTCAE grade 3 or higher (total, and by SOC and PT occurring with frequency >=10 patients and at least 1% in either treatment arm)
Safety Analysis Set, DCO 03APR2023

	Osi + Chemo (N=276)			Osi (N=275)					
	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]	Hazard Ratio [b]	[95%-KI] [b]	2-seitiger p-Wert [b]
UE mit CTCAE Grad >=3	276	176 (63,8)	3,1 [2,7; 6,9]	275	75 (27,3)	NE [NE; NE]	3,32	[2,58; 4,27]	<0,0001*
G>=3 SOC: Allgemeine Erkrankungen und Beschwerden am Verabreichungsort	276	10 (3,6)	NE [NE; NE]	275	2 (0,7)	NE [NE; NE]	3,80	[1,23; 11,79]	0,0207*
G>=3 SOC: Erkrankungen der Atemwege, des Brustraums und Mediastinums	276	15 (5,4)	NE [NE; NE]	275	19 (6,9)	NE [NE; NE]	0,76	[0,39; 1,49]	0,4198
G>=3 SOC: Erkrankungen des Blutes und des Lymphsystems	276	97 (35,1)	NE [NE; NE]	275	6 (2,2)	NE [NE; NE]	7,19	[4,88; 10,61]	<0,0001*
G>=3 PT: Anaemie	276	55 (19,9)	NE [NE; NE]	275	1 (0,4)	NE [NE; NE]	7,68	[4,55; 12,99]	<0,0001*
G>=3 PT: Febrile Neutropenie	276	11 (4,0)	NE [NE; NE]	275	0	NE [NE; NE]	NC	NC	0,0010*
G>=3 PT: Neutropenie	276	37 (13,4)	NE [NE; NE]	275	2 (0,7)	NE [NE; NE]	6,44	[3,43; 12,06]	<0,0001*
G>=3 PT: Thrombozytopenie	276	19 (6,9)	NE [NE; NE]	275	3 (1,1)	NE [NE; NE]	4,44	[1,92; 10,23]	0,0005*
G>=3 SOC: Erkrankungen des Gastrointestinaltrakts	276	20 (7,2)	NE [NE; NE]	275	4 (1,5)	NE [NE; NE]	3,83	[1,72; 8,53]	0,0010*

The time to event endpoint is defined as the time from first dose of study treatment to first onset of the respective AE if the AE has occurred by 28 days following the date of last dose of study treatment.
Any patient that has not experienced the AE will be censored at the earliest of the date of Osimertinib/Osimertinib+Chemo discontinuation+28 days, administration of subsequent therapy or death.
All AEs are coded using MedDRA version 25.1.
[a] Median time to event based on the Kaplan Meier estimate. NE = Not estimable as median (or 95% CLs) is not reached.
[b] p-value is estimated using unstratified log-rank test. Hazard ratio and 95% confidence interval derived from U and V statistics. Breslow method is used for handling ties. NC = not calculable. Hazard ratio <1 favours Osimertinib+Chemo. * p<0.05.
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Table 3.2.4 FLAURA-2: Summary of analysis of time to first adverse event with max. CTCAE grade 3 or higher (total, and by SOC and PT occurring with frequency >=10 patients and at least 1% in either treatment arm)
Safety Analysis Set, DCO 03APR2023

	Osi + Chemo (N=276)			Osi (N=275)					
	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]	Hazard Ratio [b]	[95%-KI] [b]	2-seitiger p-Wert [b]
G>=3 SOC: Herzerkrankungen	276	12 (4,3)	NE [NE; NE]	275	5 (1,8)	NE [NE; NE]	2,24	[0,86; 5,80]	0,0969
G>=3 SOC: Infektionen und parasitaere Erkrankungen	276	24 (8,7)	NE [NE; NE]	275	21 (7,6)	NE [NE; NE]	1,11	[0,62; 1,98]	0,7379
G>=3 SOC: Stoffwechsel- und Ernaehrungsstoerungen	276	14 (5,1)	NE [NE; NE]	275	8 (2,9)	NE [NE; NE]	1,75	[0,76; 4,04]	0,1892
G>=3 SOC: Untersuchungen	276	62 (22,5)	NE [NE; NE]	275	16 (5,8)	NE [NE; NE]	3,56	[2,28; 5,55]	<0,0001*
G>=3 PT: Neutrophilenzahl erniedrigt	276	31 (11,2)	NE [NE; NE]	275	2 (0,7)	NE [NE; NE]	6,00	[3,03; 11,87]	<0,0001*
G>=3 PT: Thrombozytenzahl vermindert	276	21 (7,6)	NE [NE; NE]	275	0	NE [NE; NE]	NC	NC	<0,0001*

The time to event endpoint is defined as the time from first dose of study treatment to first onset of the respective AE if the AE has occurred by 28 days following the date of last dose of study treatment.
Any patient that has not experienced the AE will be censored at the earliest of the date of Osimertinib/Osimertinib+Chemo discontinuation+28 days, administration of subsequent therapy or death.
All AEs are coded using MedDRA version 25.1.
[a] Median time to event based on the Kaplan Meier estimate. NE = Not estimable as median (or 95% CLs) is not reached.
[b] p-value is estimated using unstratified log-rank test. Hazard ratio and 95% confidence interval derived from U and V statistics. Breslow method is used for handling ties. NC = not calculable. Hazard ratio <1 favours Osimertinib+Chemo. * p<0.05.
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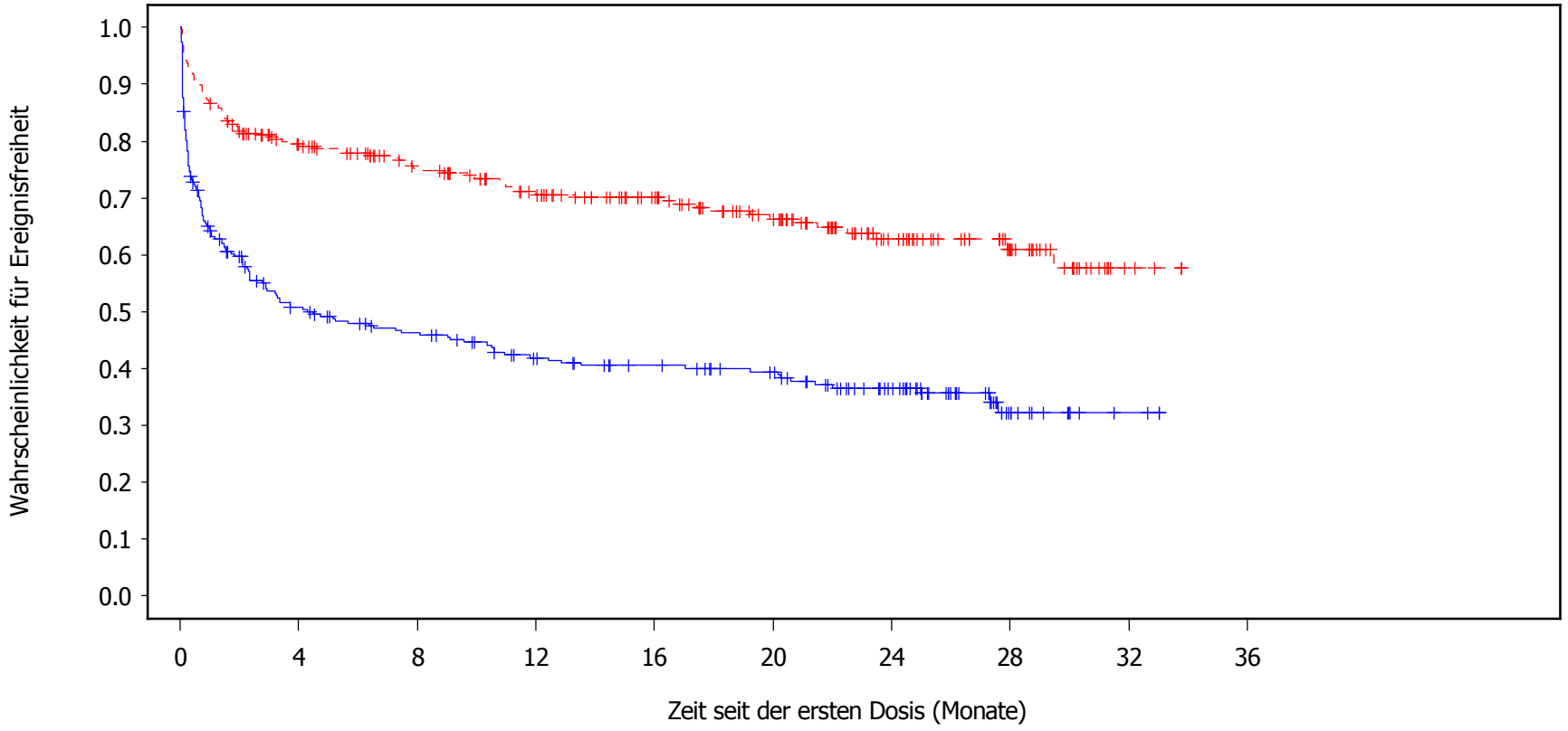
Figure 3.3.2 FLAURA-2: Kaplan-Meier plot of time to first occurrence of SOC: Allgemeine Erkrankungen und Beschwerden am Verabreichungsort
Safety Analysis Set, DCO 03APR2023



Anzahl an Patienten unter Risiko:

276	128	110	91	81	72	49	13	2	0	Osi + Chemo
275	200	172	147	124	96	57	30	3	0	Osi

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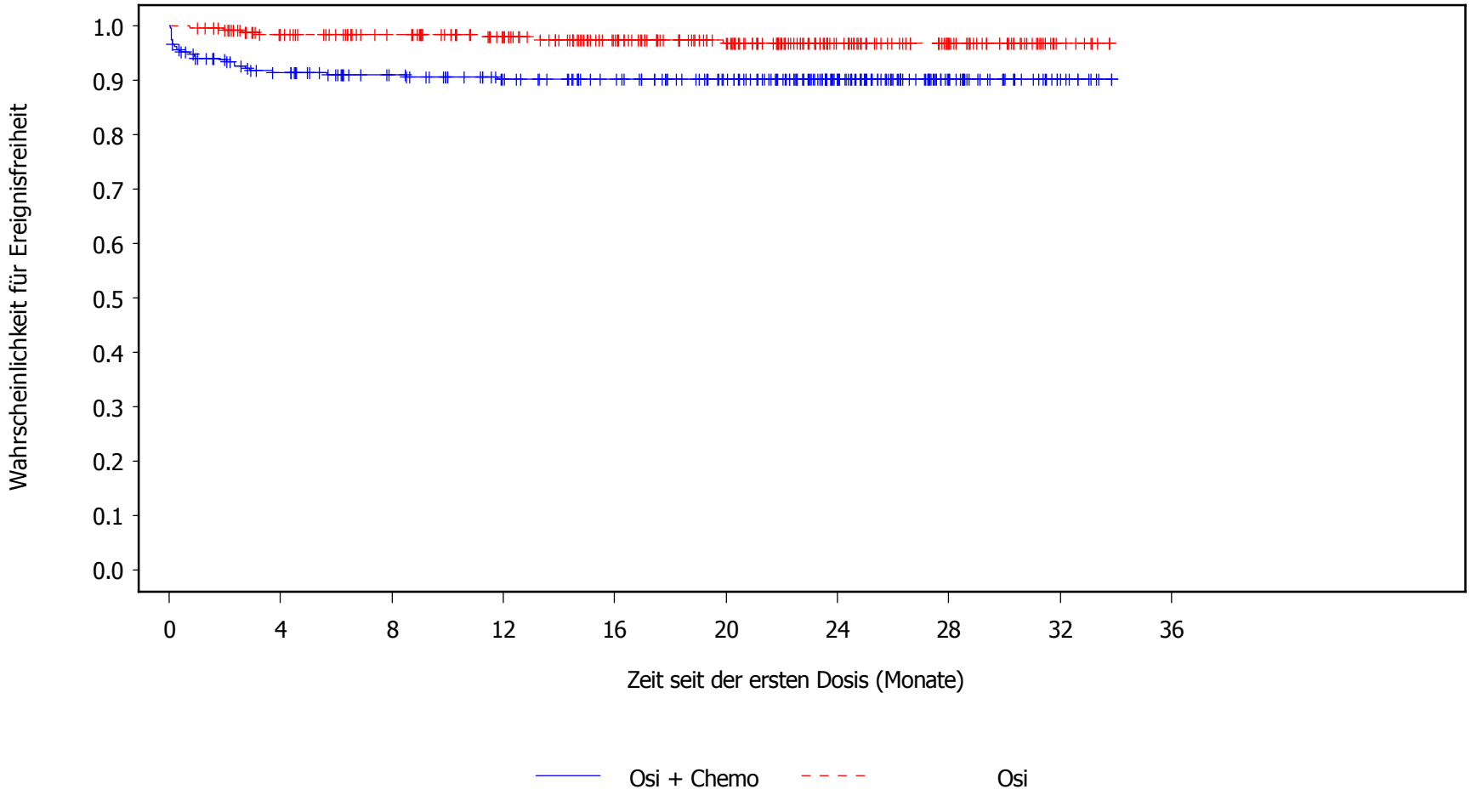
Figure 3.3.3 FLAURA-2: Kaplan-Meier plot of time to first occurrence of PT: Asthenie
Safety Analysis Set, DCO 03APR2023



Anzahl an Patienten unter Risiko:

276	234	213	194	177	154	101	41	10	0	Osi + Chemo
275	249	229	203	168	135	79	44	7	0	Osi

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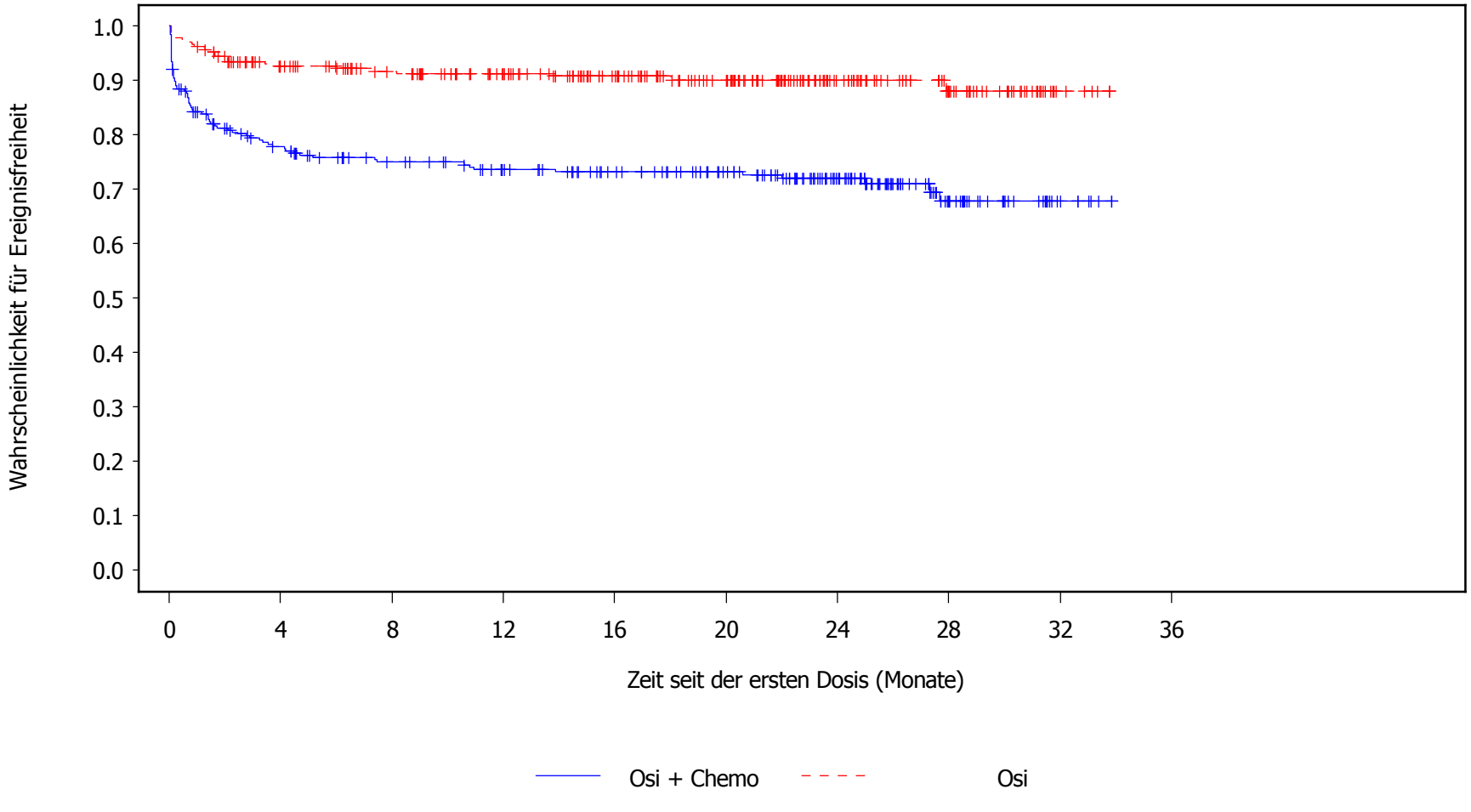
Figure 3.3.4 FLAURA-2: Kaplan-Meier plot of time to first occurrence of PT: Ermuedung
Safety Analysis Set, DCO 03APR2023



Anzahl an Patienten unter Risiko:

276	198	176	162	146	127	89	35	7	0	Osi + Chemo
275	233	211	187	157	127	73	39	5	0	Osi

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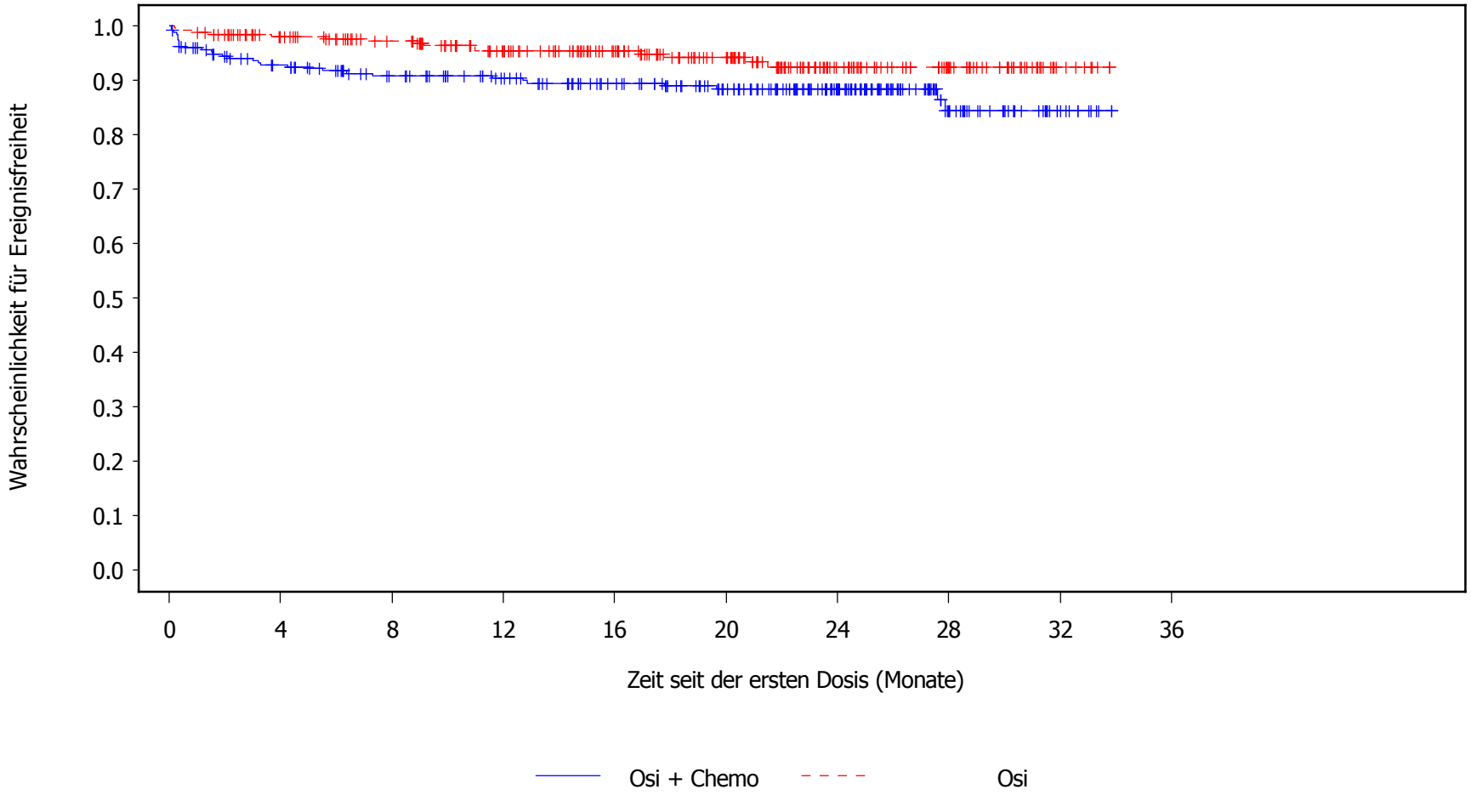
Figure 3.3.5 FLAURA-2: Kaplan-Meier plot of time to first occurrence of PT: Fieber
Safety Analysis Set, DCO 03APR2023



Anzahl an Patienten unter Risiko:

276	240	216	198	176	150	103	38	10	0	Osi + Chemo
275	248	226	196	163	129	74	41	7	0	Osi

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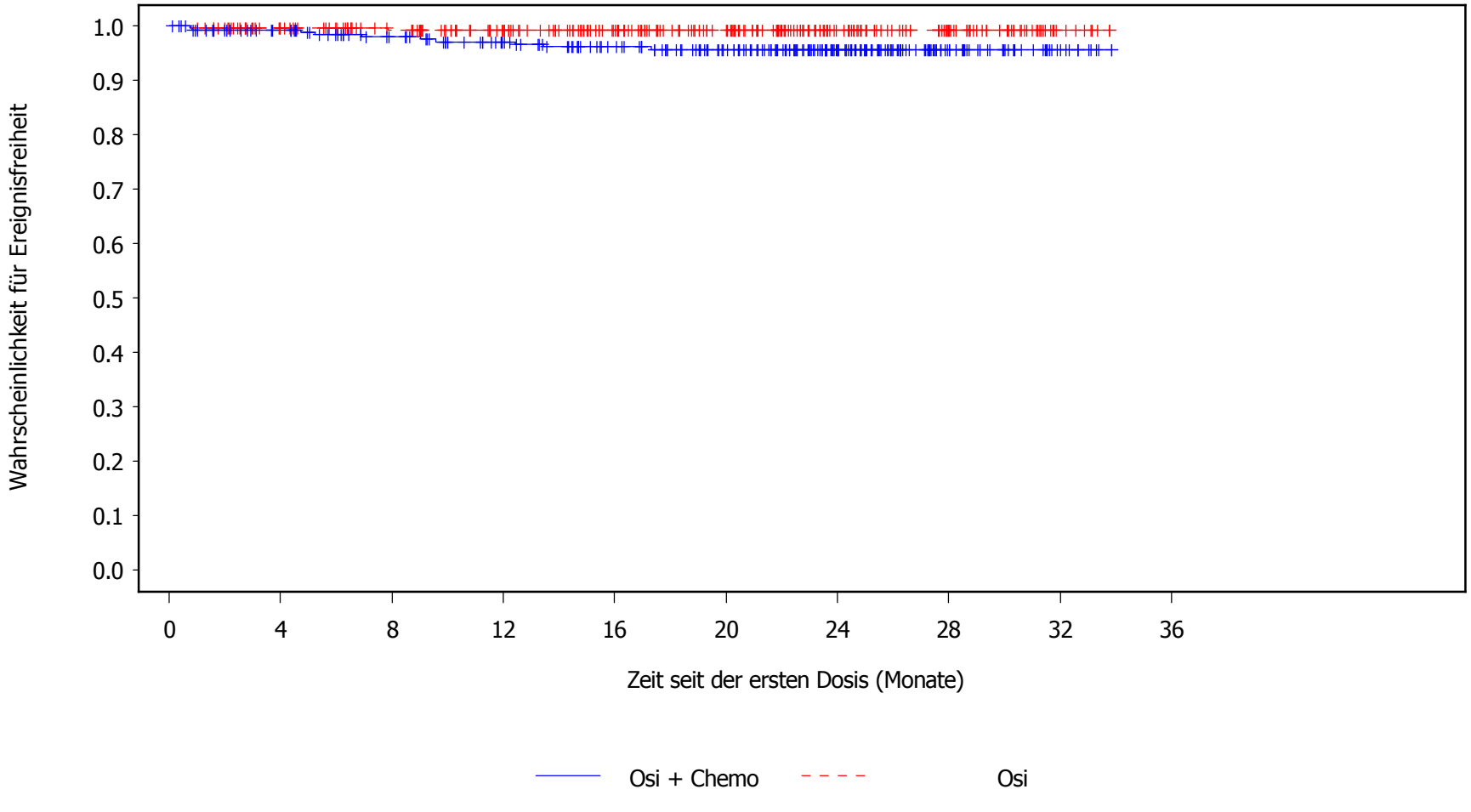
Figure 3.3.6 FLAURA-2: Kaplan-Meier plot of time to first occurrence of PT: Gesichtsoedem
Safety Analysis Set, DCO 03APR2023



Anzahl an Patienten unter Risiko:

276	254	231	211	187	158	103	42	11	0	Osi + Chemo
275	252	230	204	171	136	80	44	7	0	Osi

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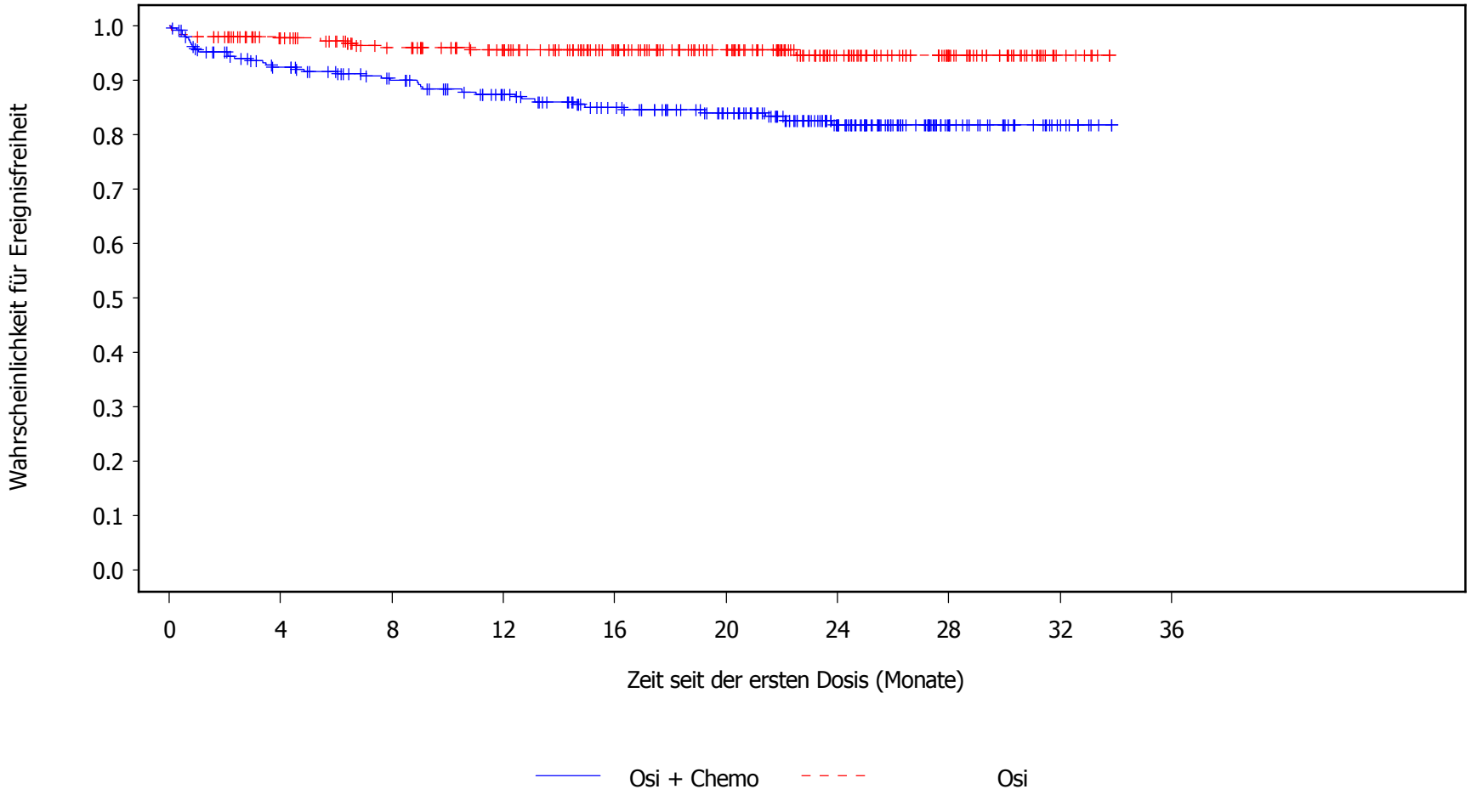
Figure 3.3.7 FLAURA-2: Kaplan-Meier plot of time to first occurrence of PT: Oedem peripher
Safety Analysis Set, DCO 03APR2023



Anzahl an Patienten unter Risiko:

276	237	215	192	167	143	91	34	10	0	Osi + Chemo
275	248	224	201	167	133	79	43	7	0	Osi

root/cdar/d516/payer_germany/ar/d5169c00001_payer_germany/tlf/prod/program/ttemainae.sas gttemainaebag 24OCT2023:11:33 kvbv306

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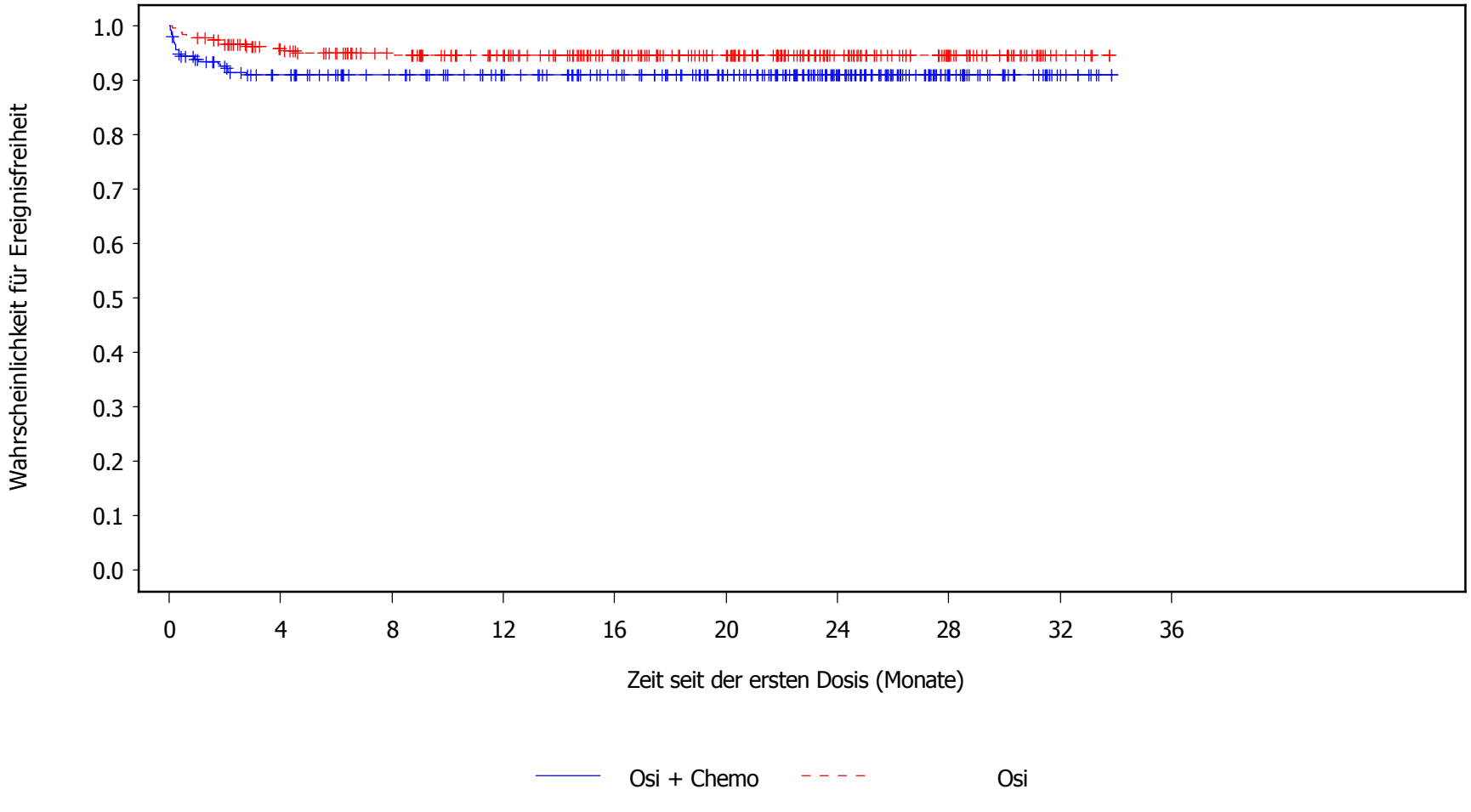
Figure 3.3.8 FLAURA-2: Kaplan-Meier plot of time to first occurrence of PT: Schleimhautentzuendung
Safety Analysis Set, DCO 03APR2023



Anzahl an Patienten unter Risiko:

276	232	214	197	179	152	101	41	9	0	Osi + Chemo
275	243	220	196	162	129	77	41	6	0	Osi

root/cdar/d516/payer_germany/ar/d5169c00001_payer_germany/tlf/prod/program/ttemainae.sas gttemainaebah 24OCT2023:11:33 kvbv306

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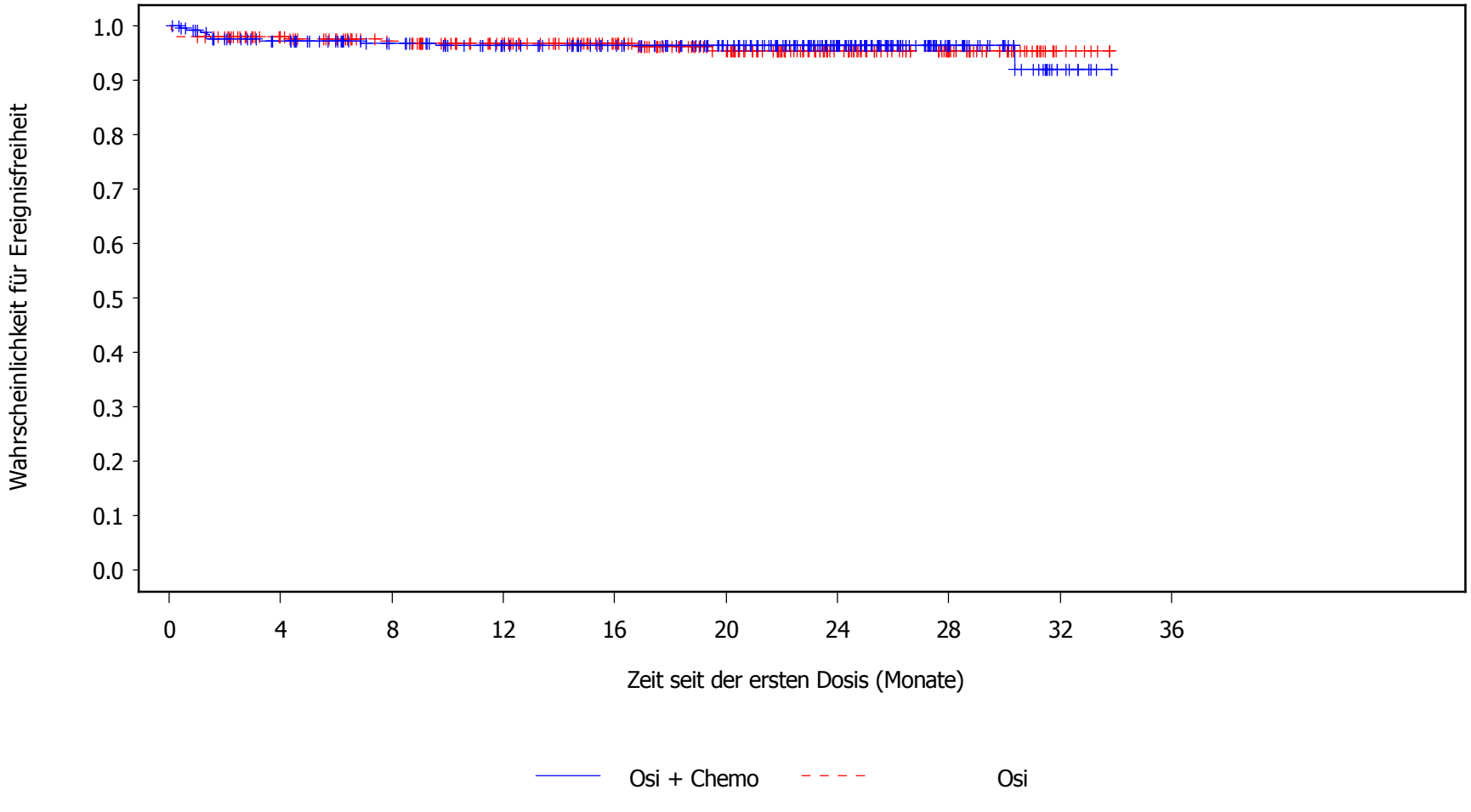
Figure 3.3.9 FLAURA-2: Kaplan-Meier plot of time to first occurrence of PT: Thoraxschmerz nicht kardialen Ursprungs
Safety Analysis Set, DCO 03APR2023



Anzahl an Patienten unter Risiko:

276	249	227	209	189	163	108	43	9	0	Osi + Chemo
275	248	225	200	166	129	77	41	6	0	Osi

root/cdar/d516/payer_germany/ar/d5169c00001_payer_germany/tlf/prod/program/ttemainae.sas gttemainaebai 24OCT2023:11:33 kvbv306

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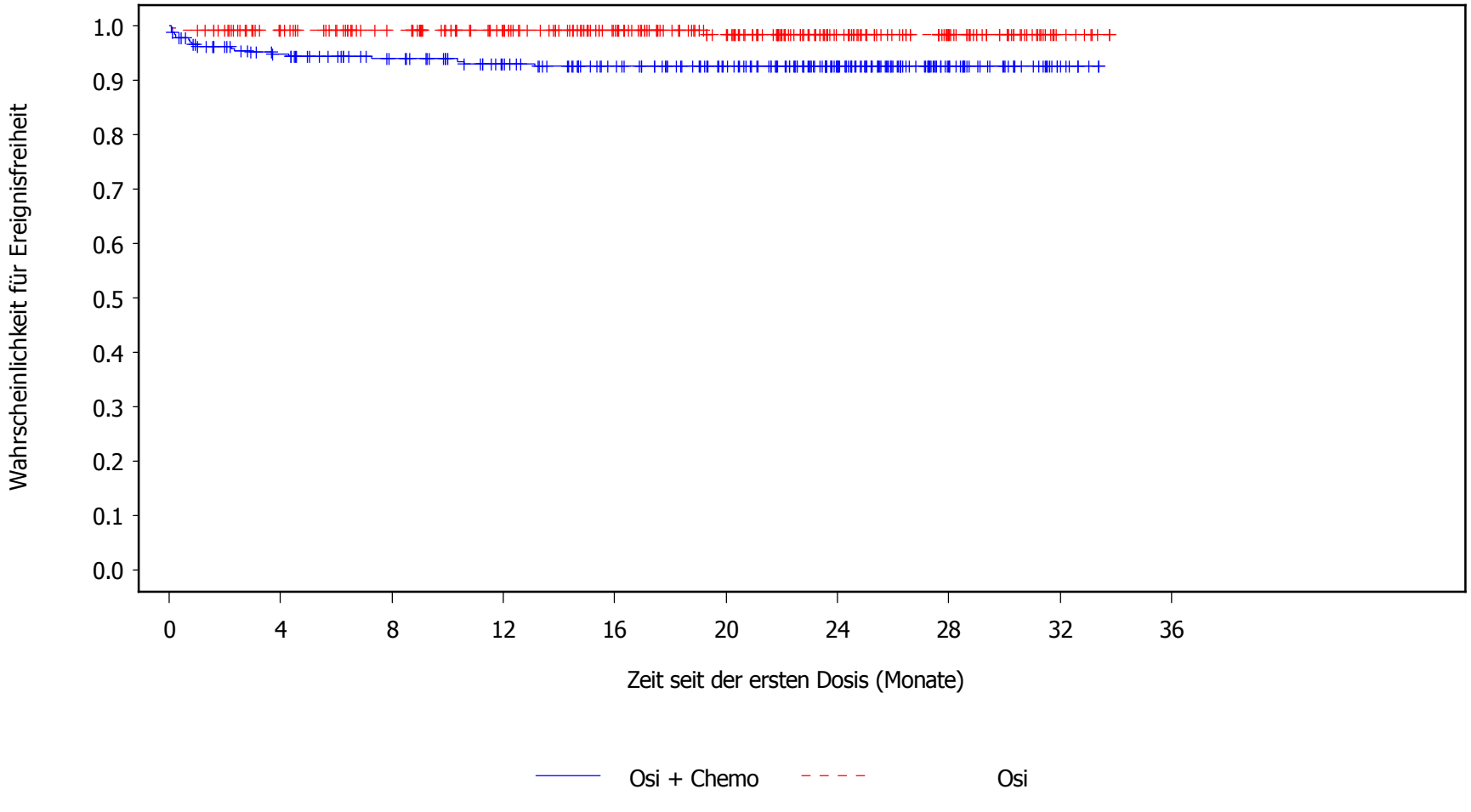
Figure 3.3.10 FLAURA-2: Kaplan-Meier plot of time to first occurrence of PT: Unwohlsein
Safety Analysis Set, DCO 03APR2023



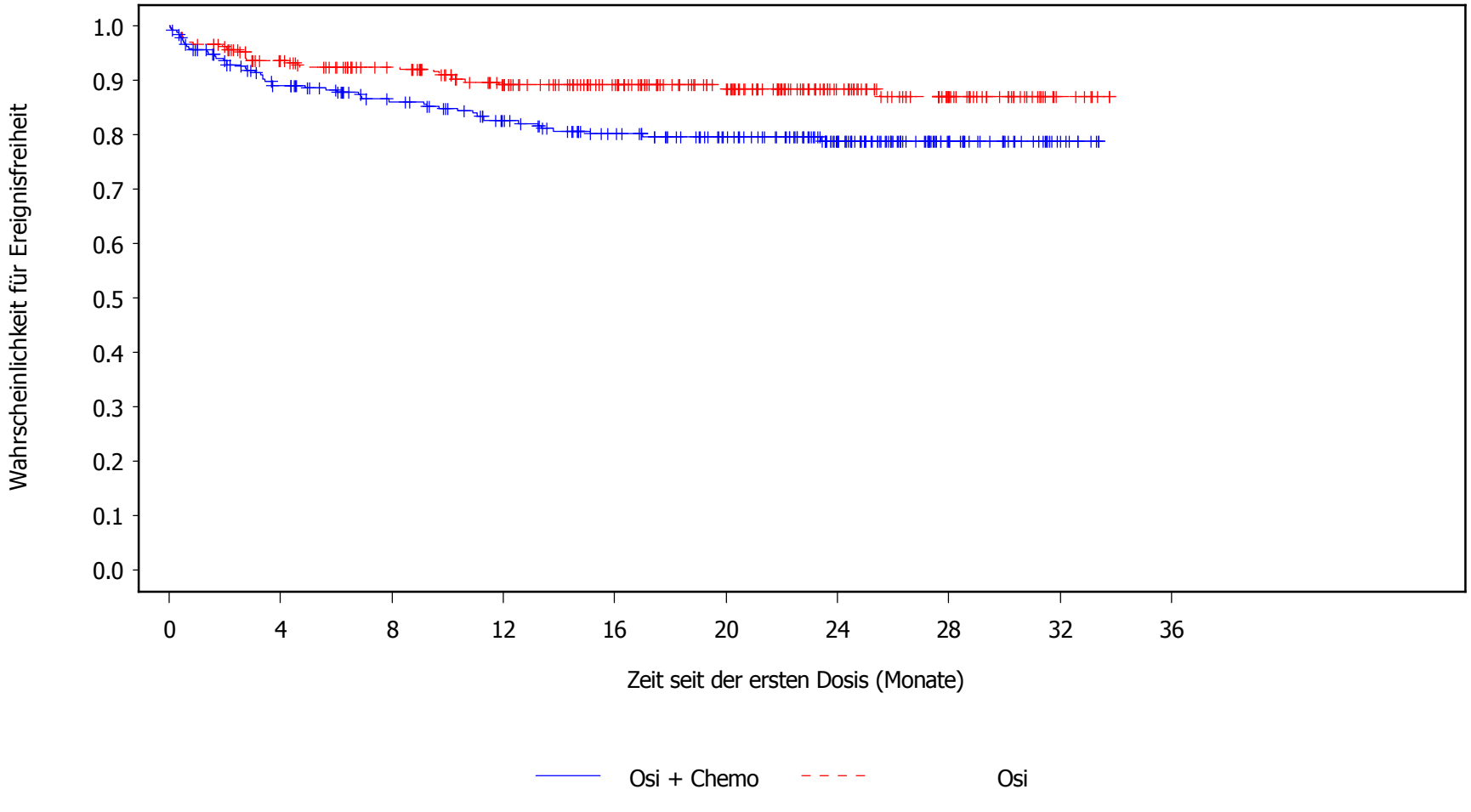
Anzahl an Patienten unter Risiko:

276	242	221	201	178	152	103	40	8	0	Osi + Chemo
275	251	230	204	170	134	80	44	7	0	Osi

root/cdar/d516/payer_germany/ar/d5169c00001_payer_germany/tlf/prod/program/ttemainae.sas gttemainaebaj 24OCT2023:11:33 kvbv306

Nutzenbewertung nach AMNOG Seite 1 von 1

Figure 3.3.11 FLAURA-2: Kaplan-Meier plot of time to first occurrence of SOC: Augenerkrankungen
Safety Analysis Set, DCO 03APR2023



Anzahl an Patienten unter Risiko:

276	227	201	179	156	133	91	36	8	0	Osi + Chemo
275	238	214	184	155	120	71	37	6	0	Osi

root/cdar/d516/payer_germany/ar/d5169c00001_payer_germany/tlf/prod/program/ttemainae.sas gttemainaebak 24OCT2023:11:33 kvbv306

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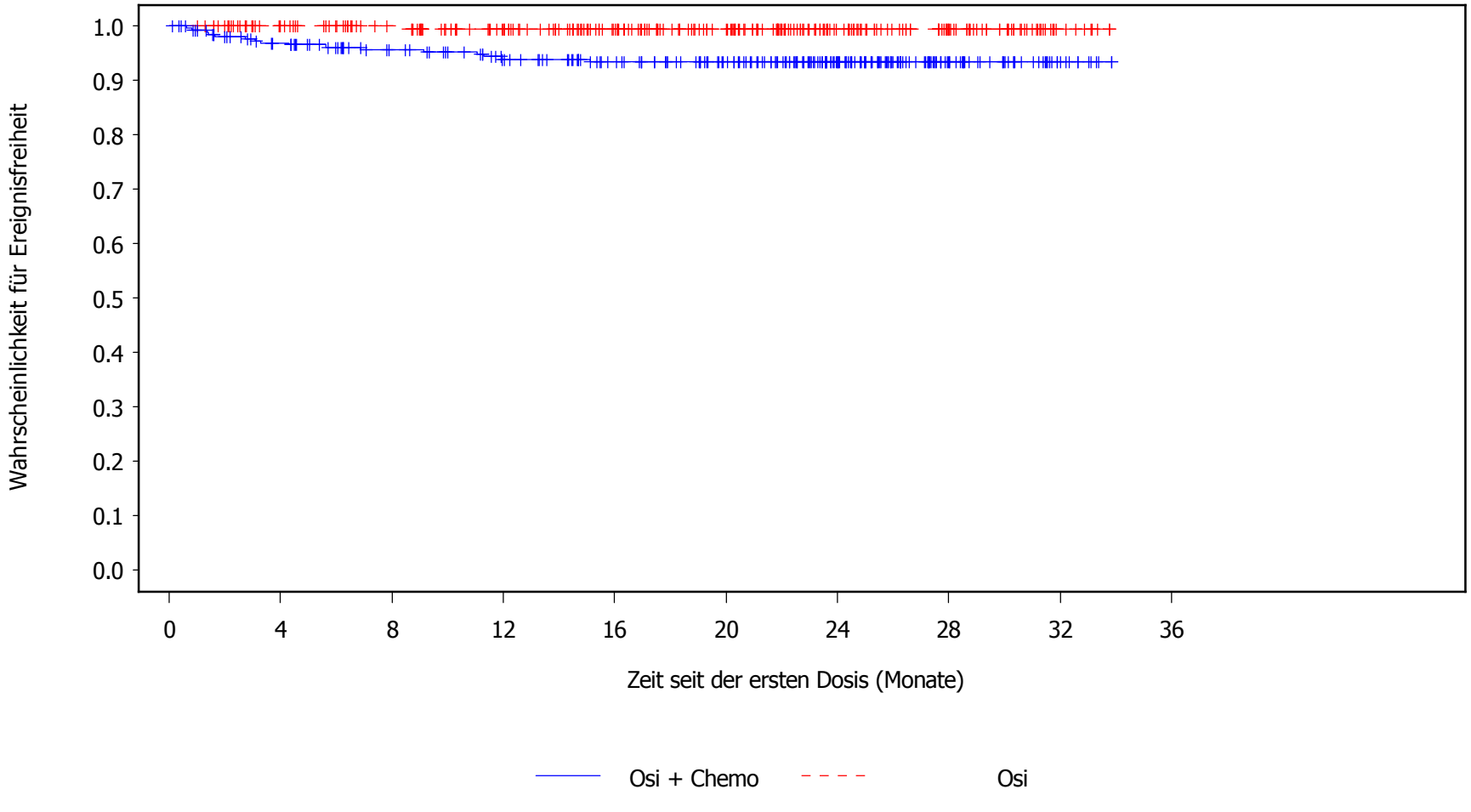
Figure 3.3.12 FLAURA-2: Kaplan-Meier plot of time to first occurrence of PT: Traenensekretion verstaerkt
Safety Analysis Set, DCO 03APR2023



Anzahl an Patienten unter Risiko:

276	248	224	205	183	158	105	42	10	0	Osi + Chemo
275	253	232	206	171	136	80	44	7	0	Osi

root/cdar/d516/payer_germany/ar/d5169c00001_payer_germany/tlf/prod/program/ttemainae.sas gttemainaebal 24OCT2023:11:33 kvbv306

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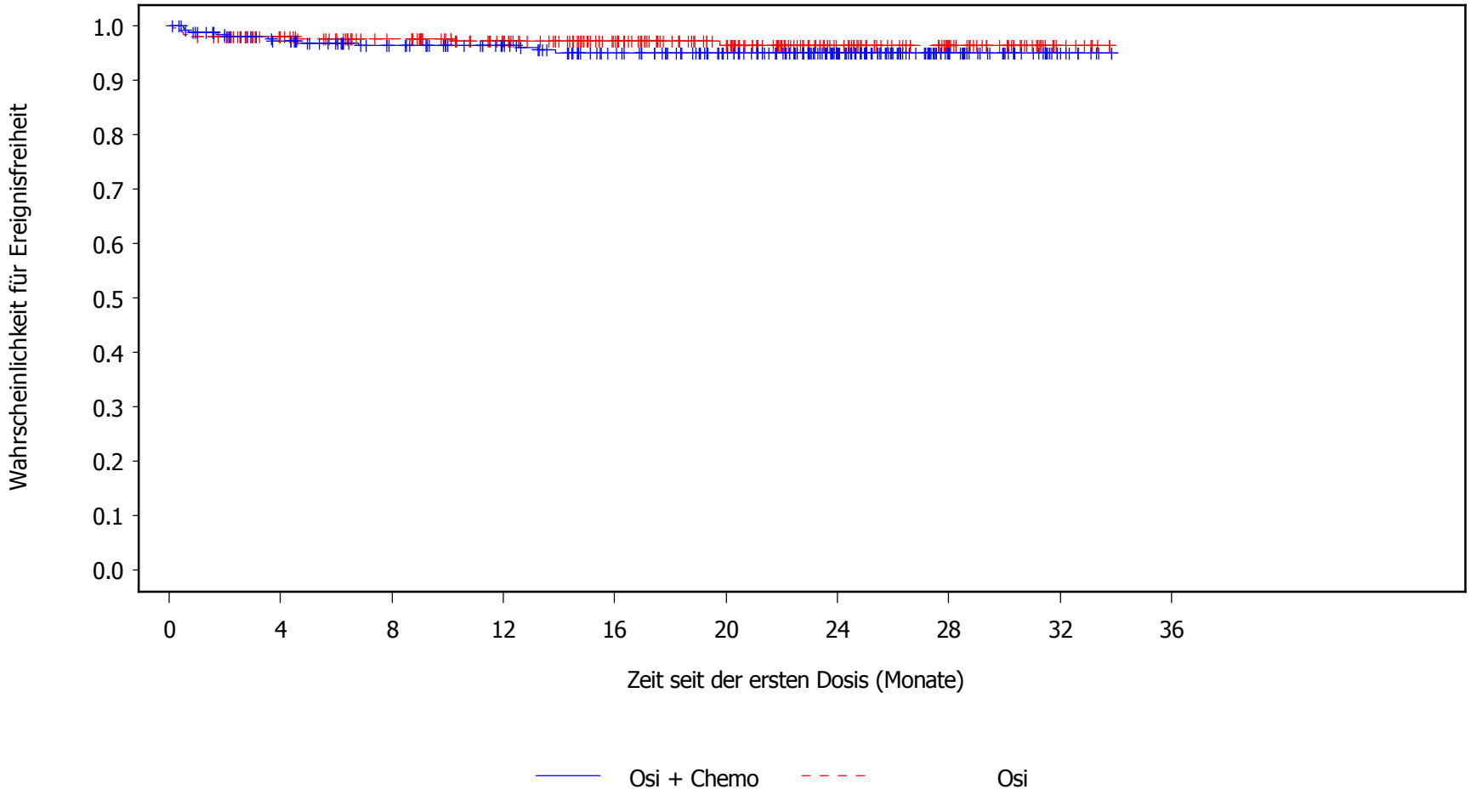
Figure 3.3.13 FLAURA-2: Kaplan-Meier plot of time to first occurrence of PT: Trockenes Auge
Safety Analysis Set, DCO 03APR2023



Anzahl an Patienten unter Risiko:

276	249	226	209	184	156	106	43	10	0	Osi + Chemo
275	249	227	200	166	131	77	41	7	0	Osi

root/cdar/d516/payer_germany/ar/d5169c00001_payer_germany/tlf/prod/program/ttemainae.sas gttemainaebam 24OCT2023:11:33 kvbv306

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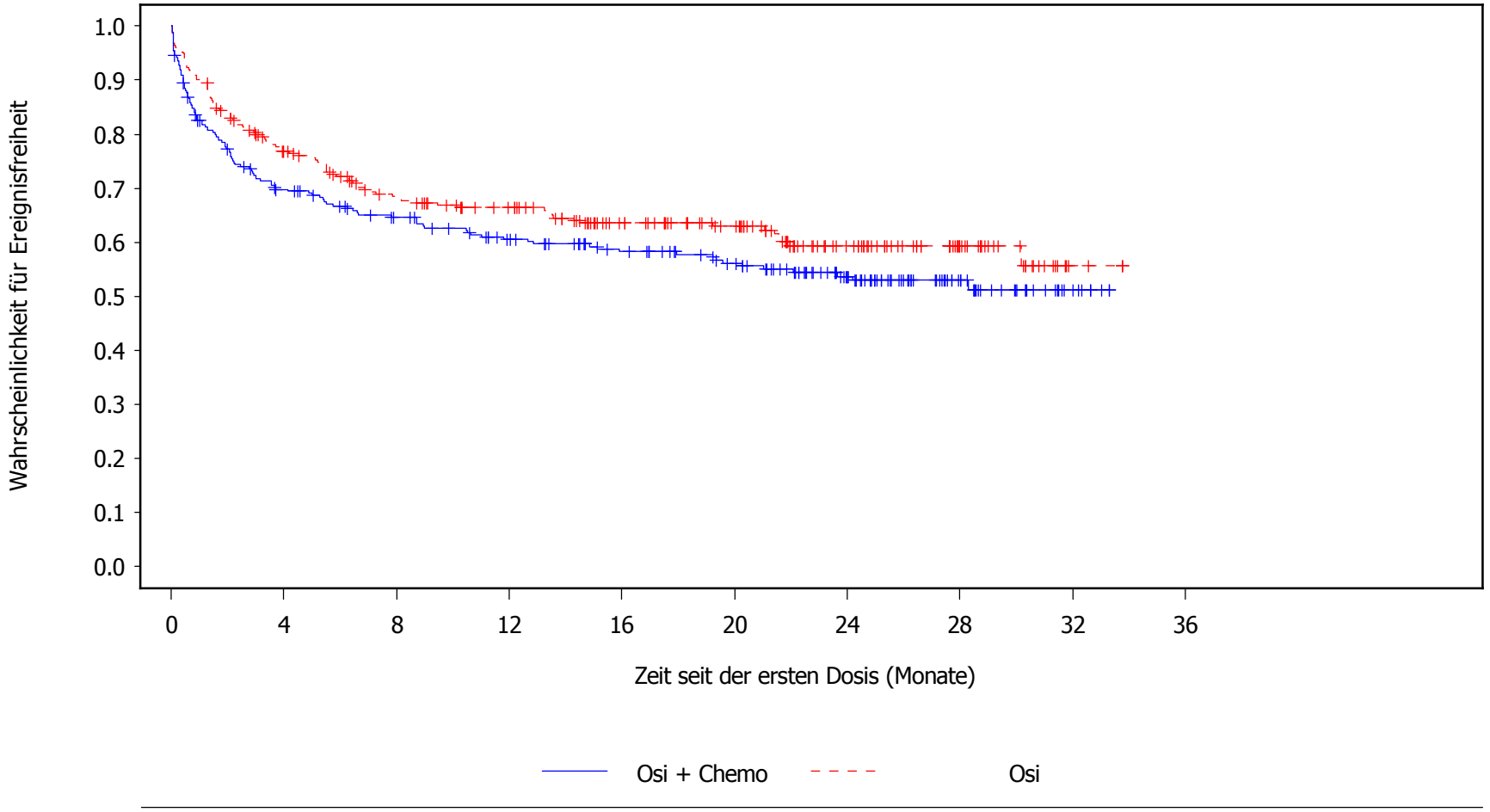
Figure 3.3.14 FLAURA-2: Kaplan-Meier plot of time to first occurrence of SOC: Erkrankungen der Atemwege, des Brustraums und Mediastinums
Safety Analysis Set, DCO 03APR2023



Anzahl an Patienten unter Risiko:

276	183	160	140	121	104	70	32	7	0	Osi + Chemo
275	199	166	148	118	99	60	28	2	0	Osi

root/cdar/d516/payer_germany/ar/d5169c00001_payer_germany/tlf/prod/program/ttemainae.sas gttemainaeban 24OCT2023:11:33 kvbv306

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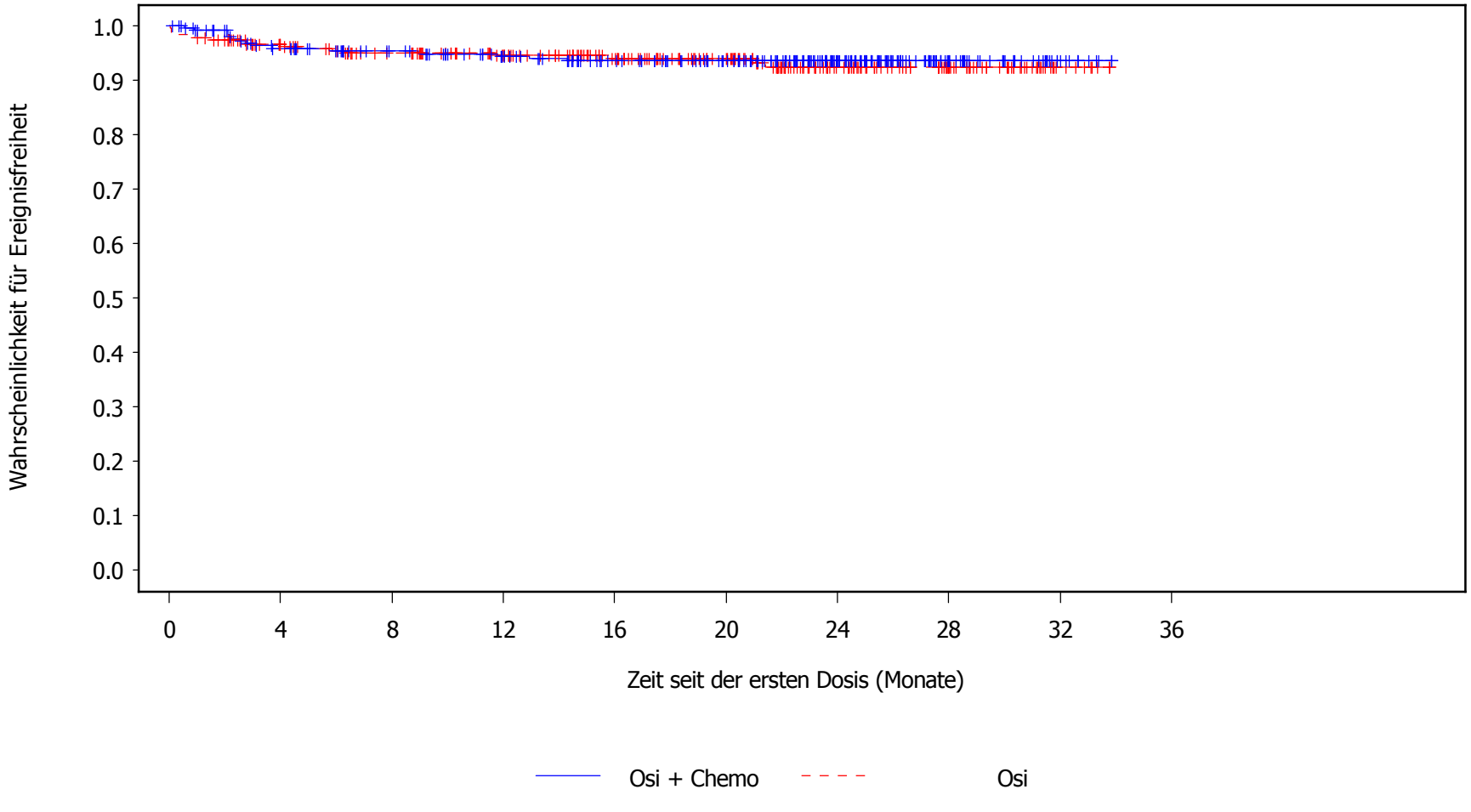
Figure 3.3.15 FLAURA-2: Kaplan-Meier plot of time to first occurrence of PT: Dyspnoe
Safety Analysis Set, DCO 03APR2023



Anzahl an Patienten unter Risiko:

276	245	225	207	184	160	105	42	10	0	Osi + Chemo
275	246	223	199	166	133	79	43	7	0	Osi

root/cdar/d516/payer_germany/ar/d5169c00001_payer_germany/tlf/prod/program/ttemainae.sas gttemainaebao 24OCT2023:11:33 kvbv306

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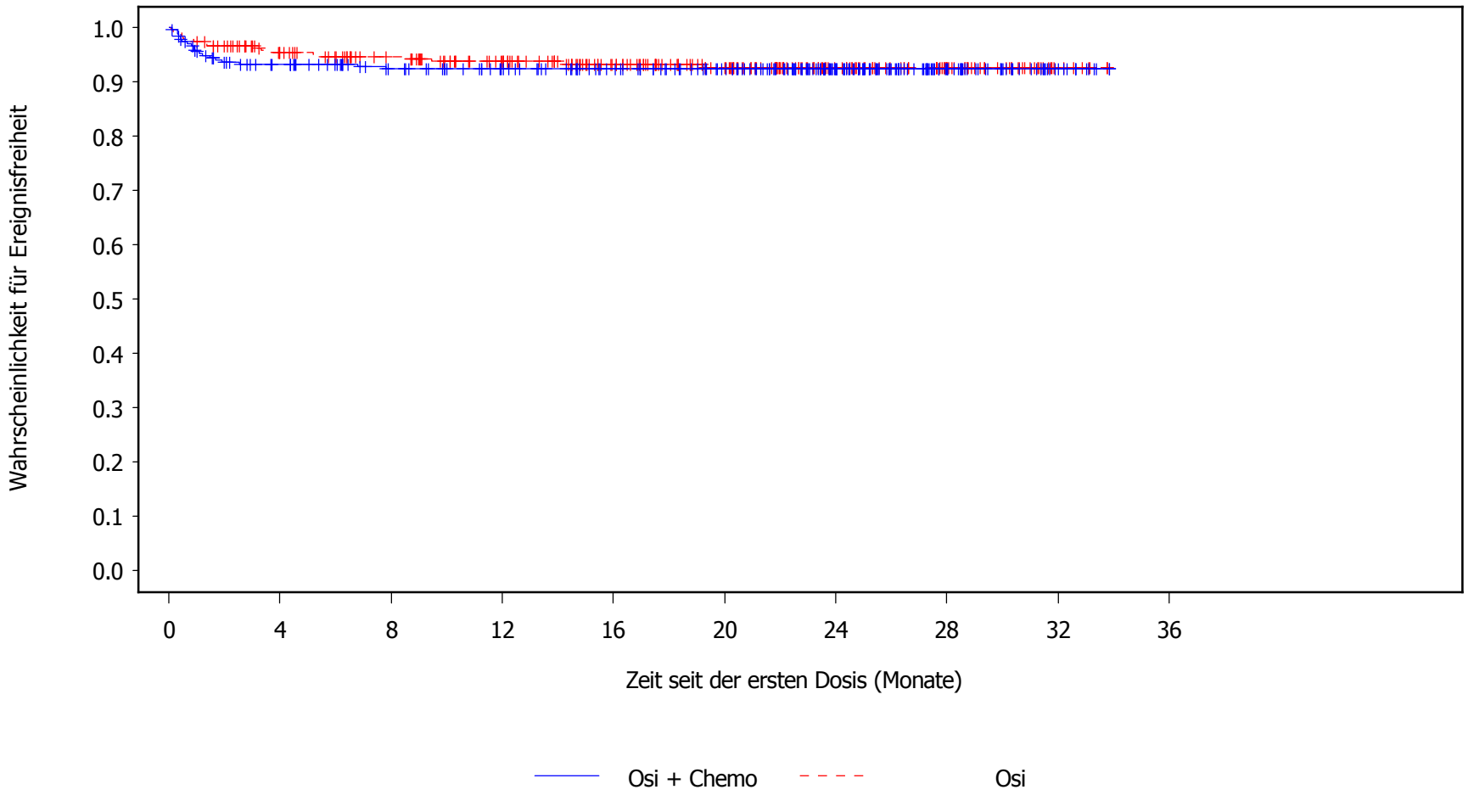
Figure 3.3.16 FLAURA-2: Kaplan-Meier plot of time to first occurrence of PT: Epistaxis
Safety Analysis Set, DCO 03APR2023



Anzahl an Patienten unter Risiko:

276	238	216	200	179	156	103	44	11	0	Osi + Chemo
275	242	220	194	158	126	73	39	6	0	Osi

root/cdar/d516/payer_germany/ar/d5169c00001_payer_germany/tlf/prod/program/ttemainae.sas gttemainaebap 24OCT2023:11:33 kvbv306

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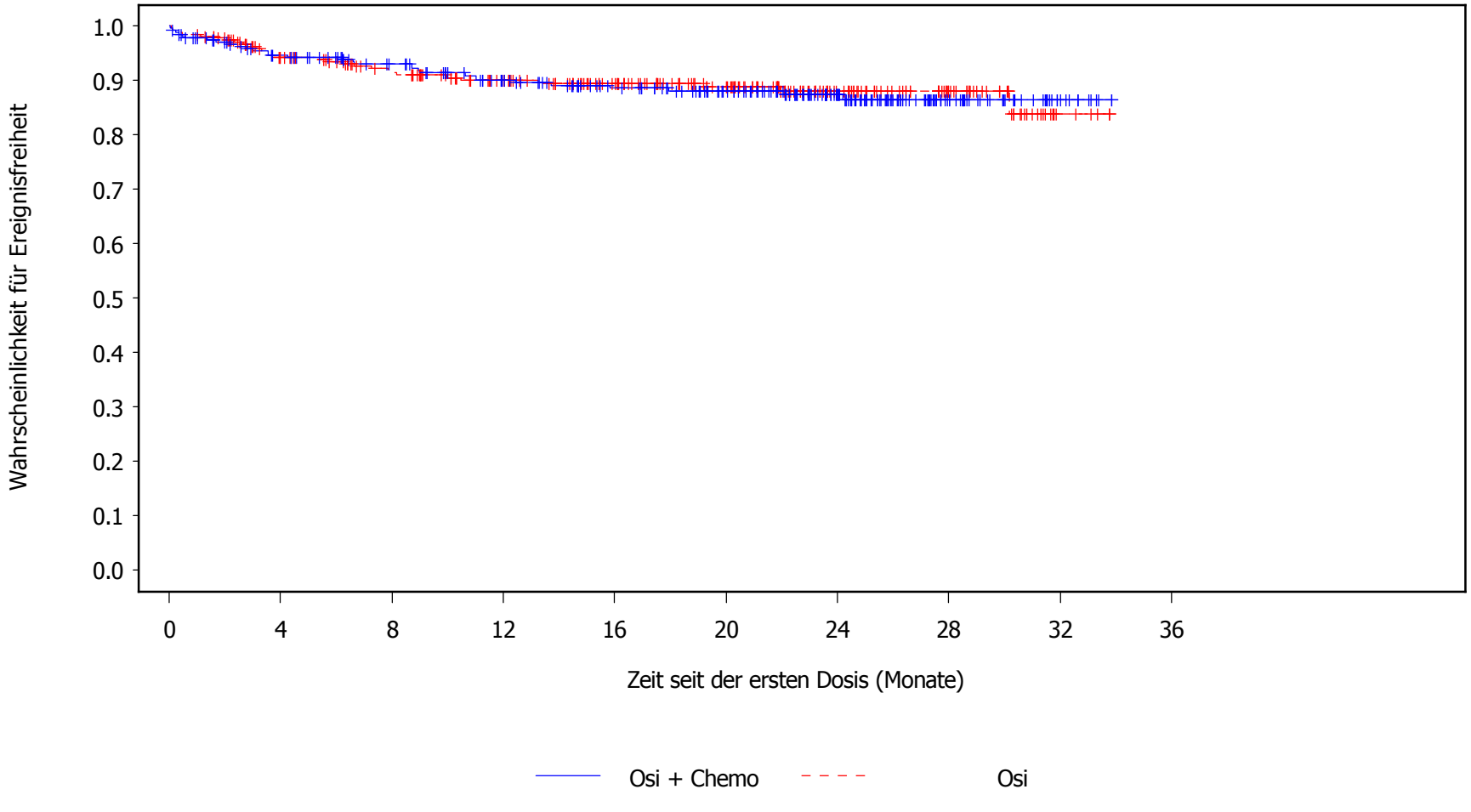
Figure 3.3.17 FLAURA-2: Kaplan-Meier plot of time to first occurrence of PT: Husten
Safety Analysis Set, DCO 03APR2023



Anzahl an Patienten unter Risiko:

276	243	221	198	175	151	102	43	11	0	Osi + Chemo
275	238	215	188	158	126	73	38	4	0	Osi

root/cdar/d516/payer_germany/ar/d5169c00001_payer_germany/tlf/prod/program/ttemainae.sas gttemainaebaq 24OCT2023:11:33 kvbv306

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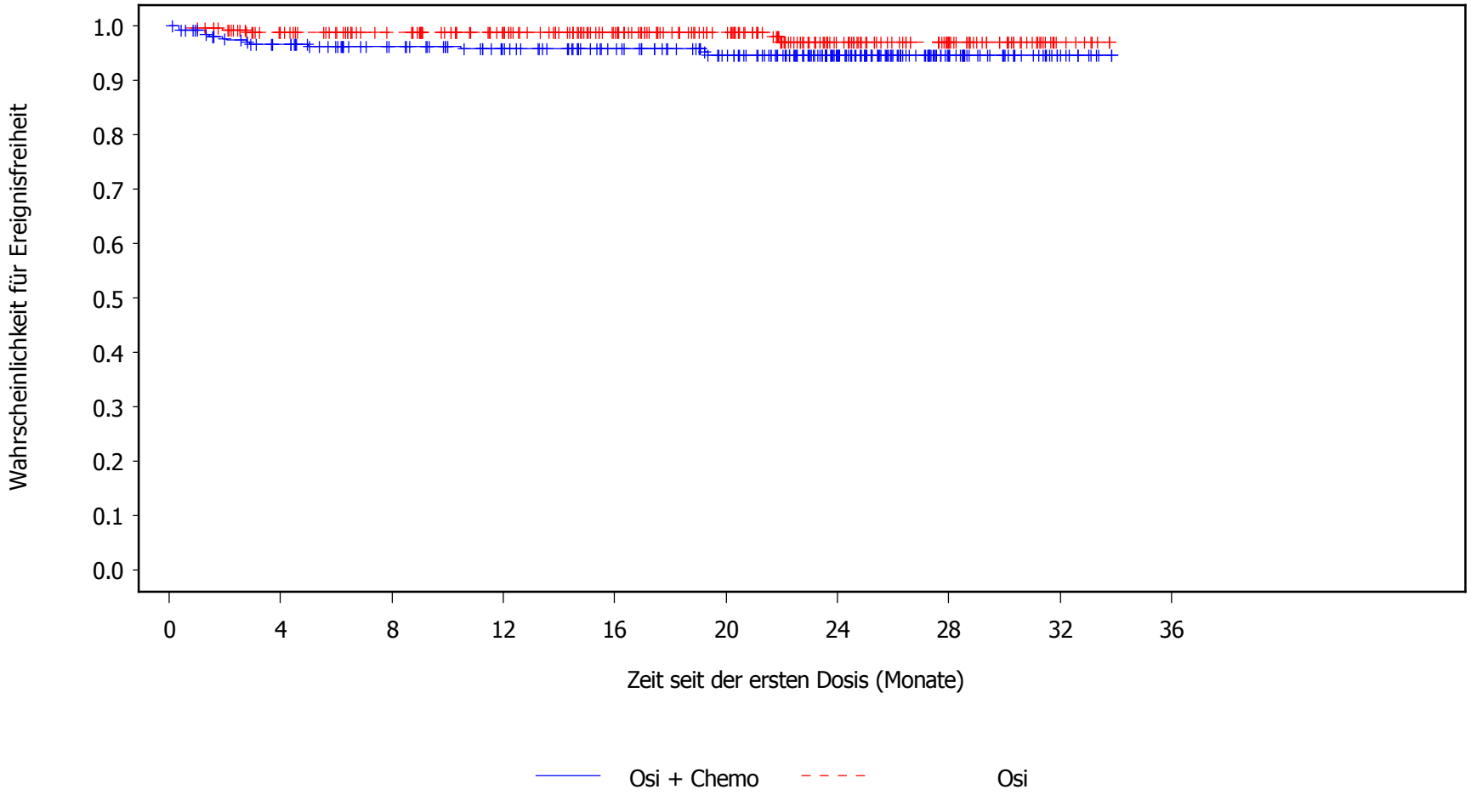
Figure 3.3.18 FLAURA-2: Kaplan-Meier plot of time to first occurrence of PT: Lungenembolie
Safety Analysis Set, DCO 03APR2023



Anzahl an Patienten unter Risiko:

276	250	228	210	188	163	109	44	11	0	Osi + Chemo
275	251	230	205	170	135	79	43	7	0	Osi

root/cdar/d516/payer_germany/ar/d5169c00001_payer_germany/tlf/prod/program/ttemainae.sas gttemainaebar 24OCT2023:11:33 kvbv306

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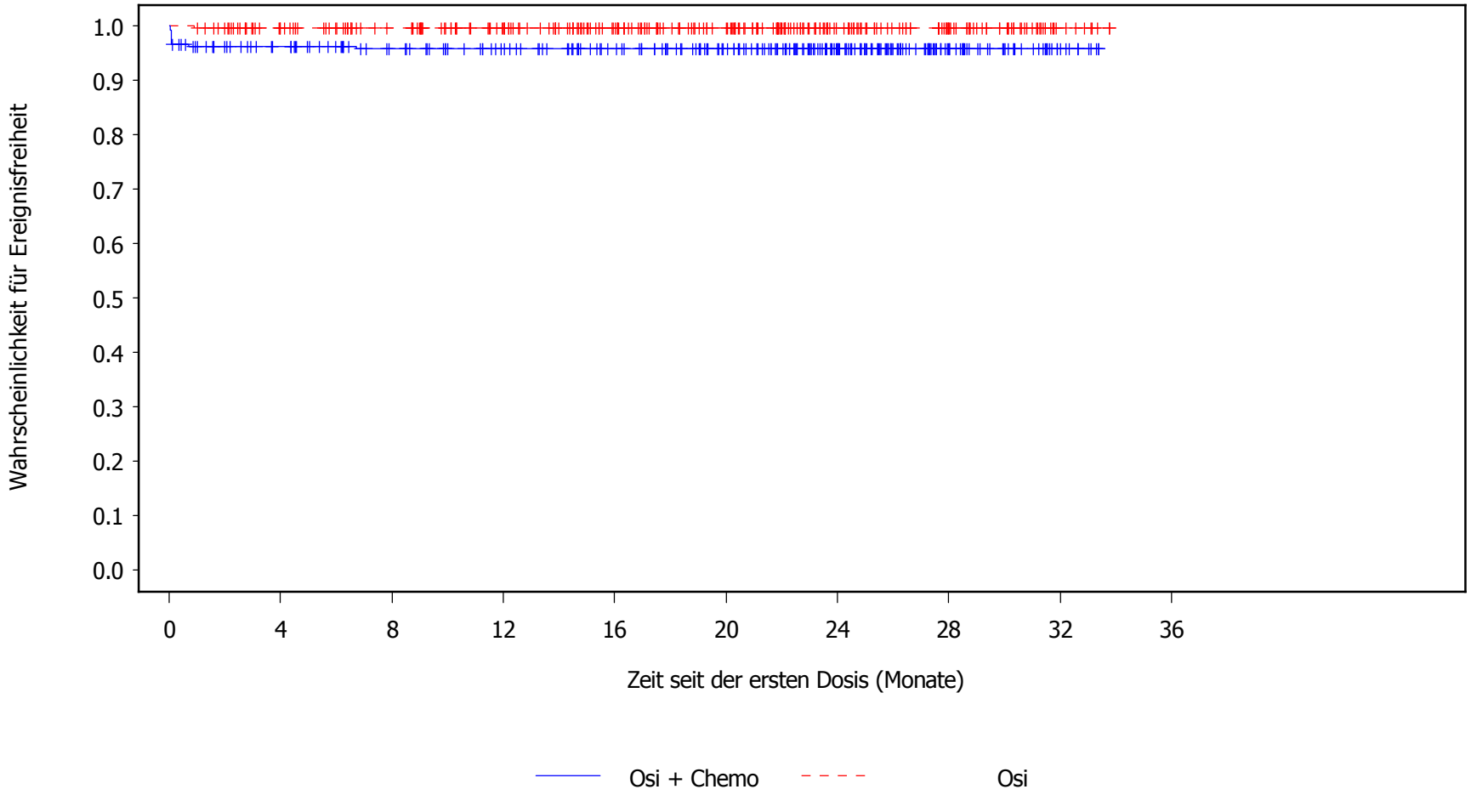
Figure 3.3.19 FLAURA-2: Kaplan-Meier plot of time to first occurrence of PT: Schluckauf
Safety Analysis Set, DCO 03APR2023



Anzahl an Patienten unter Risiko:

276	246	225	208	186	158	106	43	10	0	Osi + Chemo
275	253	232	206	171	136	80	44	7	0	Osi

root/cdar/d516/payer_germany/ar/d5169c00001_payer_germany/tlf/prod/program/ttemainae.sas gttemainaebas 24OCT2023:11:33 kvbv306

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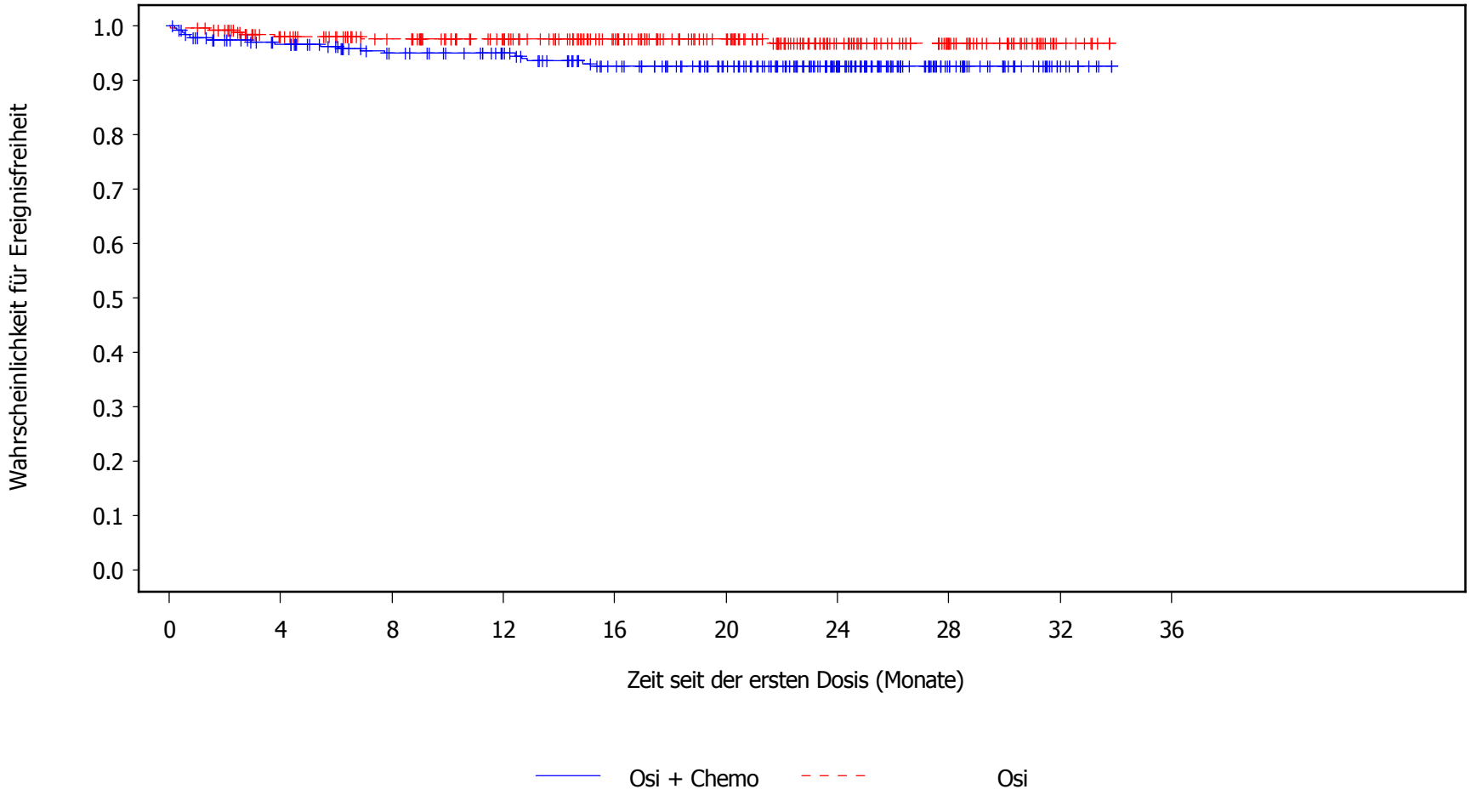
Figure 3.3.20 FLAURA-2: Kaplan-Meier plot of time to first occurrence of PT: Schmerzen im Oropharynx
Safety Analysis Set, DCO 03APR2023



Anzahl an Patienten unter Risiko:

276	247	223	209	183	156	103	43	10	0	Osi + Chemo
275	248	226	201	166	132	78	43	7	0	Osi

root/cdar/d516/payer_germany/ar/d5169c00001_payer_germany/tlf/prod/program/ttemainae.sas gttemainaebat 24OCT2023:11:33 kvbv306

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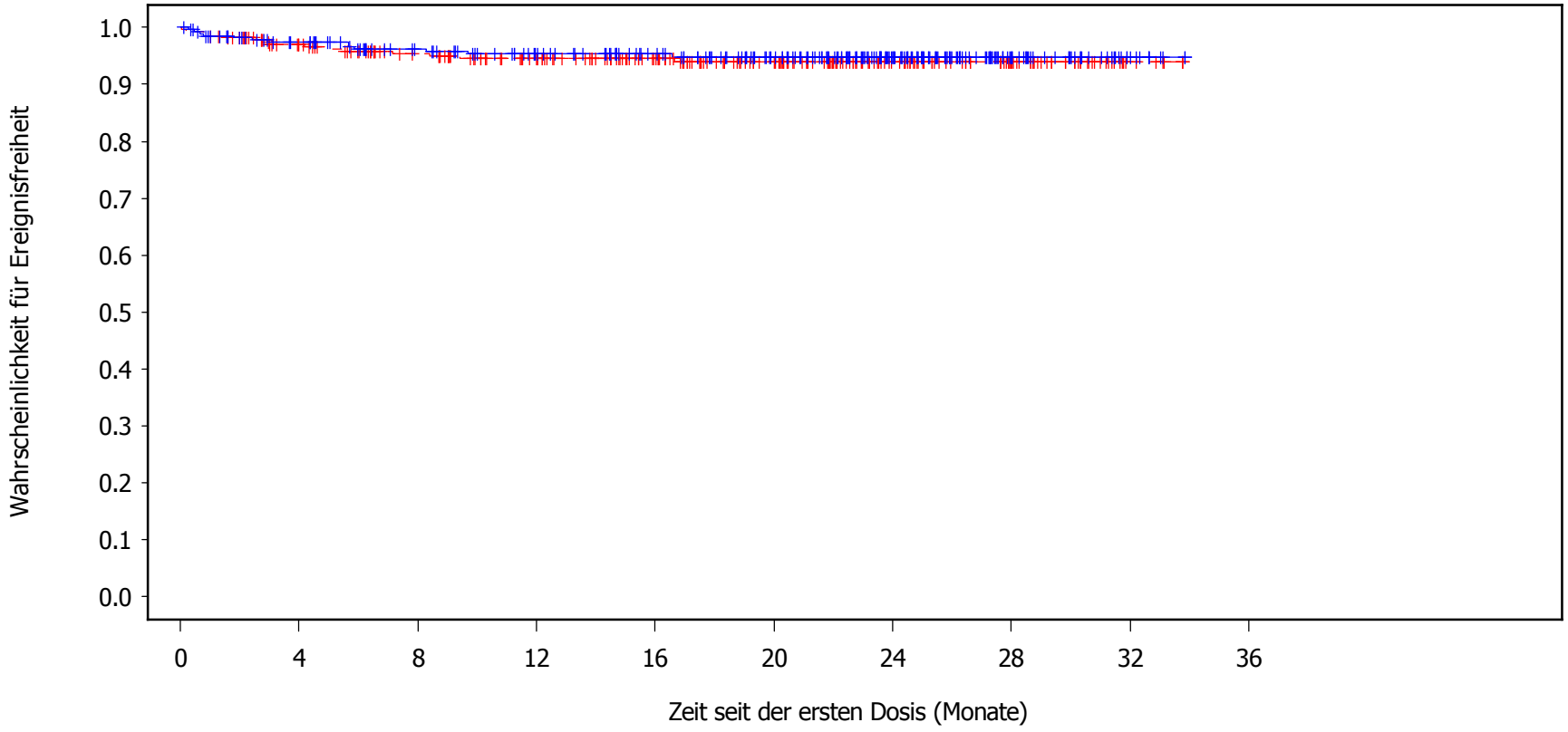
Figure 3.3.21 FLAURA-2: Kaplan-Meier plot of time to first occurrence of SOC: Erkrankungen der Geschlechtsorgane und der Brustdruese
Safety Analysis Set, DCO 03APR2023



Anzahl an Patienten unter Risiko:

276	249	225	206	185	157	101	39	9	0	Osi + Chemo
275	246	221	196	162	126	74	39	5	0	Osi

root/cdar/d516/payer_germany/ar/d5169c00001_payer_germany/tlf/prod/program/ttemainae.sas gttemainaebau 24OCT2023:11:33 kvbv306

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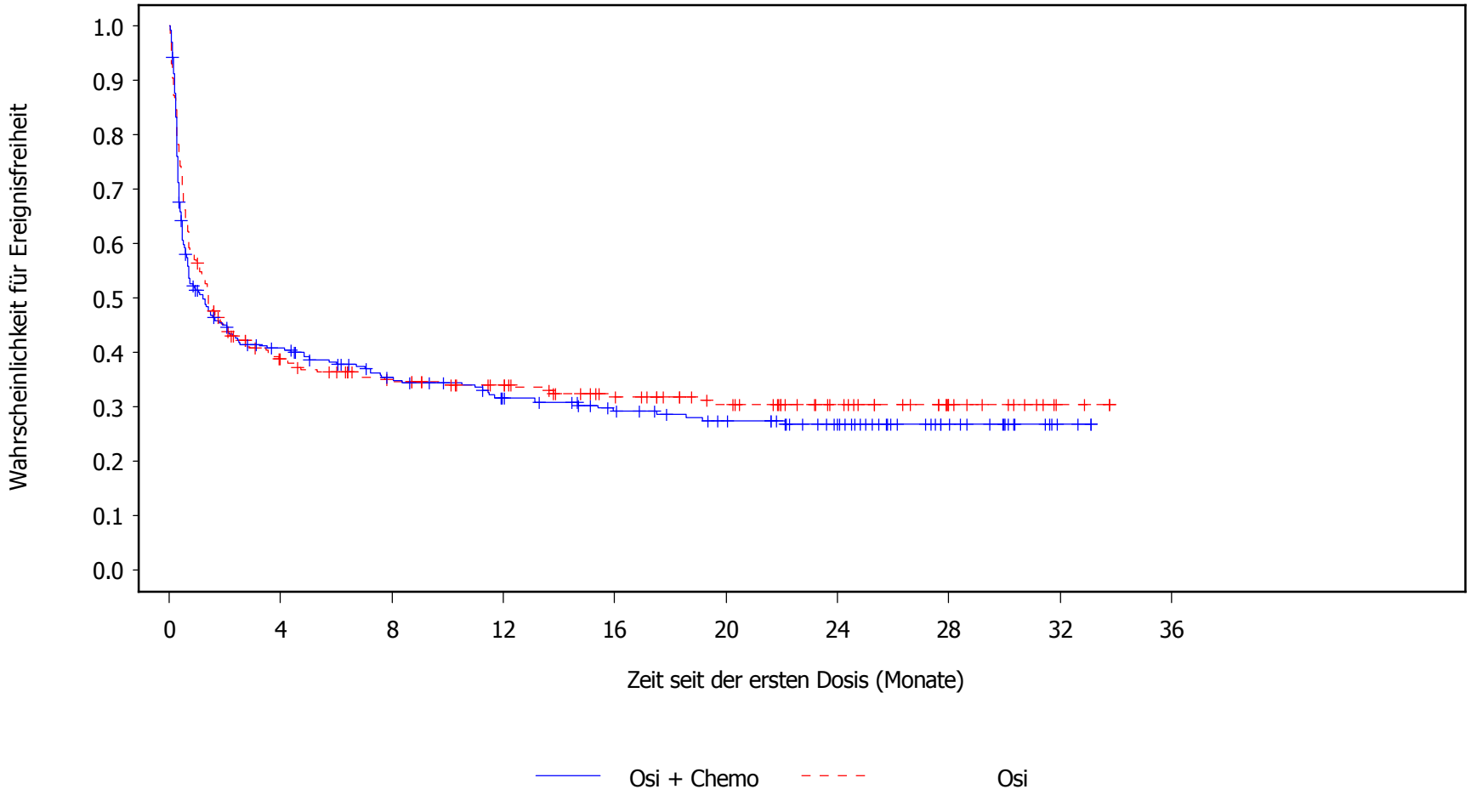
Figure 3.3.22 FLAURA-2: Kaplan-Meier plot of time to first occurrence of SOC: Erkrankungen der Haut und des Unterhautgewebes
Safety Analysis Set, DCO 03APR2023

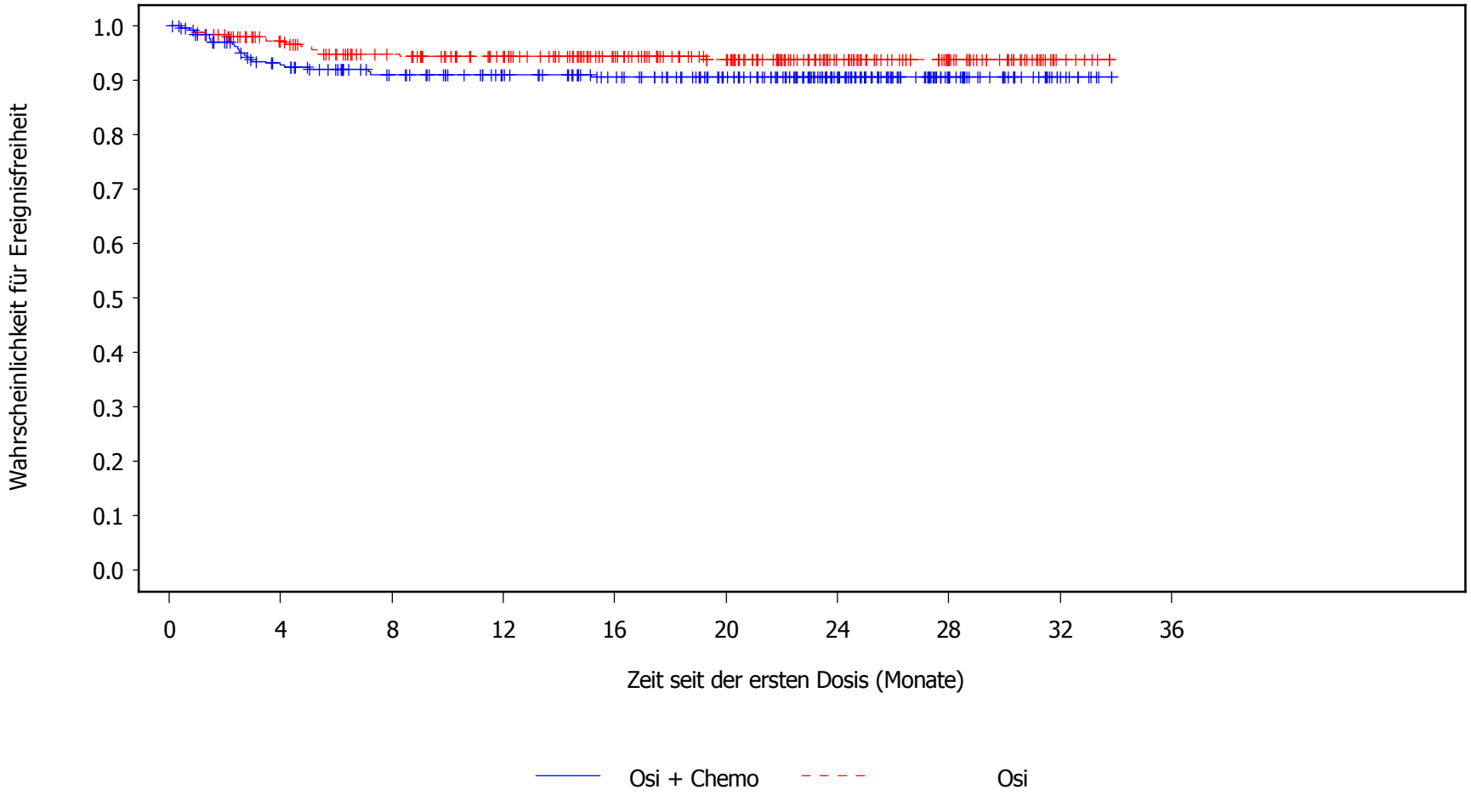


Anzahl an Patienten unter Risiko:

276	103	81	67	55	46	33	16	2	0	Osi + Chemo
275	96	78	68	53	41	27	12	2	0	Osi

root/cdar/d516/payer_germany/ar/d5169c00001_payer_germany/tlf/prod/program/ttemainae.sas gttemainaebav 24OCT2023:11:33 kvbv306

Figure 3.3.23 FLAURA-2: Kaplan-Meier plot of time to first occurrence of PT: Alopezie
Safety Analysis Set, DCO 03APR2023



Anzahl an Patienten unter Risiko:

276	237	213	195	176	150	100	43	11	0	Osi + Chemo
275	246	219	195	161	131	78	42	6	0	Osi

root/cdar/d516/payer_germany/ar/d5169c00001_payer_germany/tlf/prod/program/ttemainae.sas gttemainaebaw 24OCT2023:11:33 kvbv306

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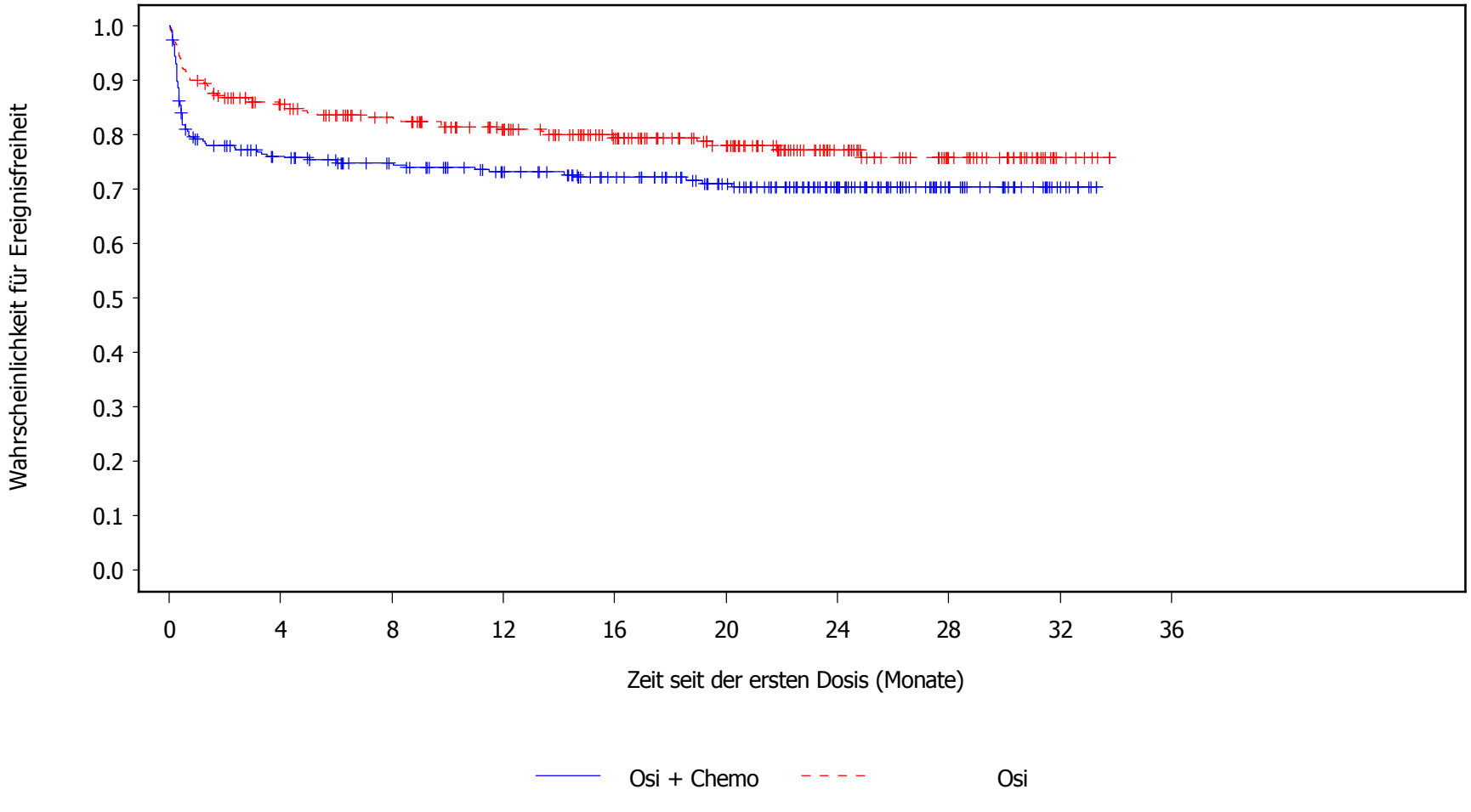
Figure 3.3.24 FLAURA-2: Kaplan-Meier plot of time to first occurrence of PT: Ausschlag
Safety Analysis Set, DCO 03APR2023



Anzahl an Patienten unter Risiko:

276	194	176	157	137	113	76	35	9	0	Osi + Chemo
275	219	195	168	137	107	63	34	6	0	Osi

root/cdar/d516/payer_germany/ar/d5169c00001_payer_germany/tlf/prod/program/ttemainae.sas gttemainaebax 24OCT2023:11:33 kvbv306

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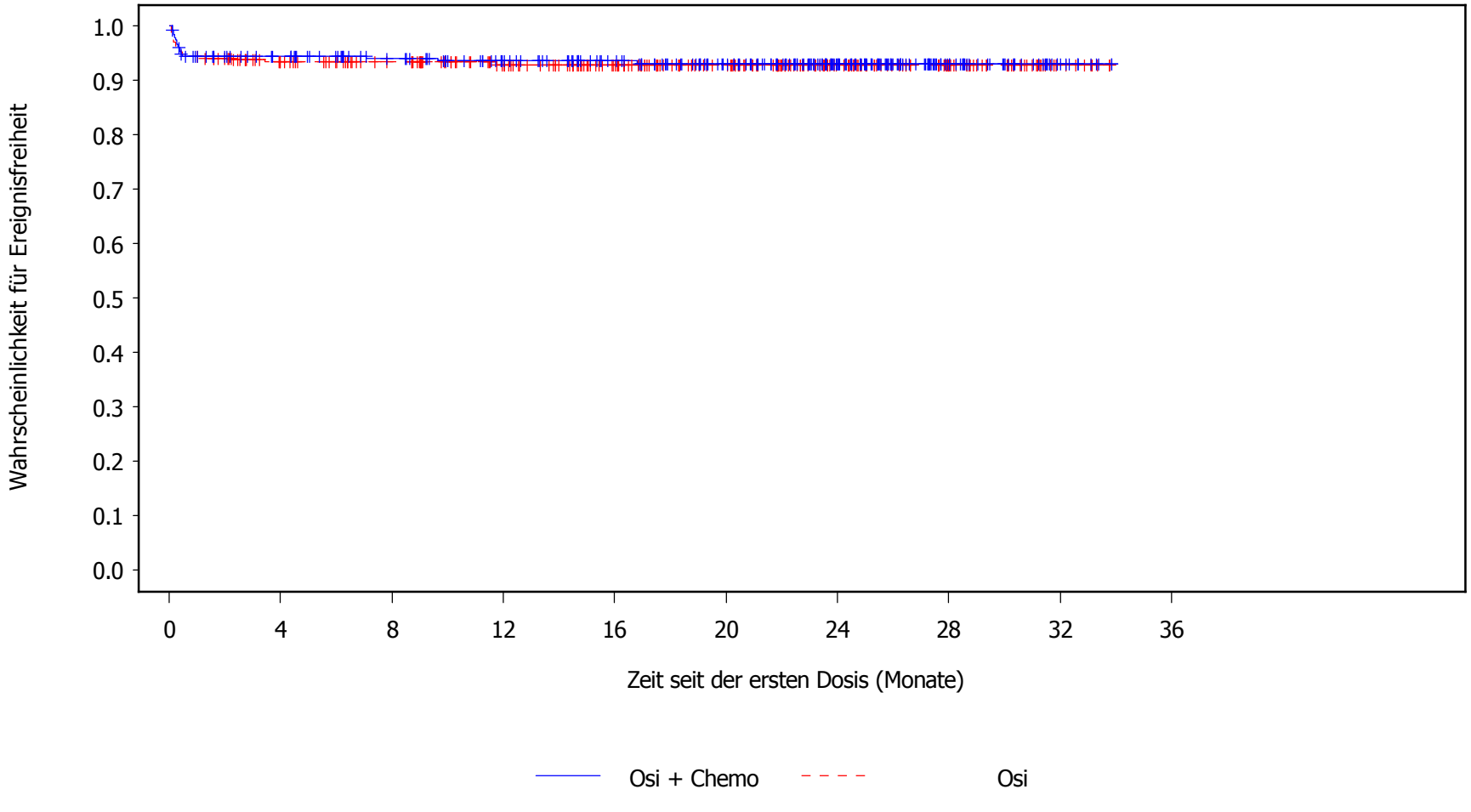
Figure 3.3.25 FLAURA-2: Kaplan-Meier plot of time to first occurrence of PT: Ausschlag makulo-papuloes
Safety Analysis Set, DCO 03APR2023

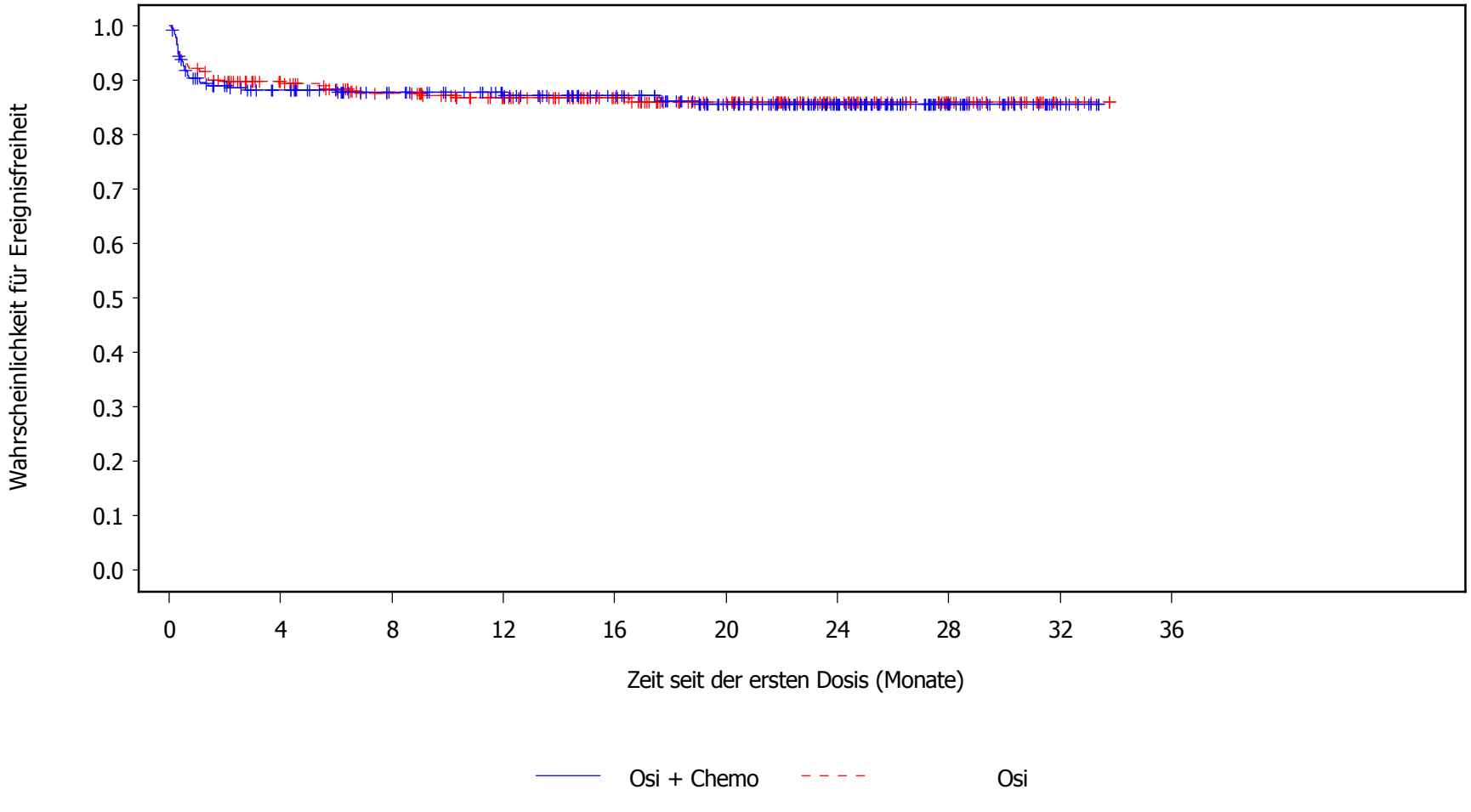


Anzahl an Patienten unter Risiko:

276	242	222	203	181	153	103	41	10	0	Osi + Chemo
275	236	216	191	159	126	76	41	7	0	Osi

root/cdar/d516/payer_germany/ar/d5169c00001_payer_germany/tlf/prod/program/ttemainae.sas gttemainaebay 24OCT2023:11:33 kvbv306

Figure 3.3.26 FLAURA-2: Kaplan-Meier plot of time to first occurrence of PT: Dermatitis akneiform
Safety Analysis Set, DCO 03APR2023



Anzahl an Patienten unter Risiko:

276	224	203	187	168	140	94	40	9	0	Osi + Chemo
275	225	200	177	145	115	68	34	5	0	Osi

root/cdar/d516/payer_germany/ar/d5169c00001_payer_germany/tlf/prod/program/ttemainae.sas gttemainaebaz 24OCT2023:11:33 kvbv306

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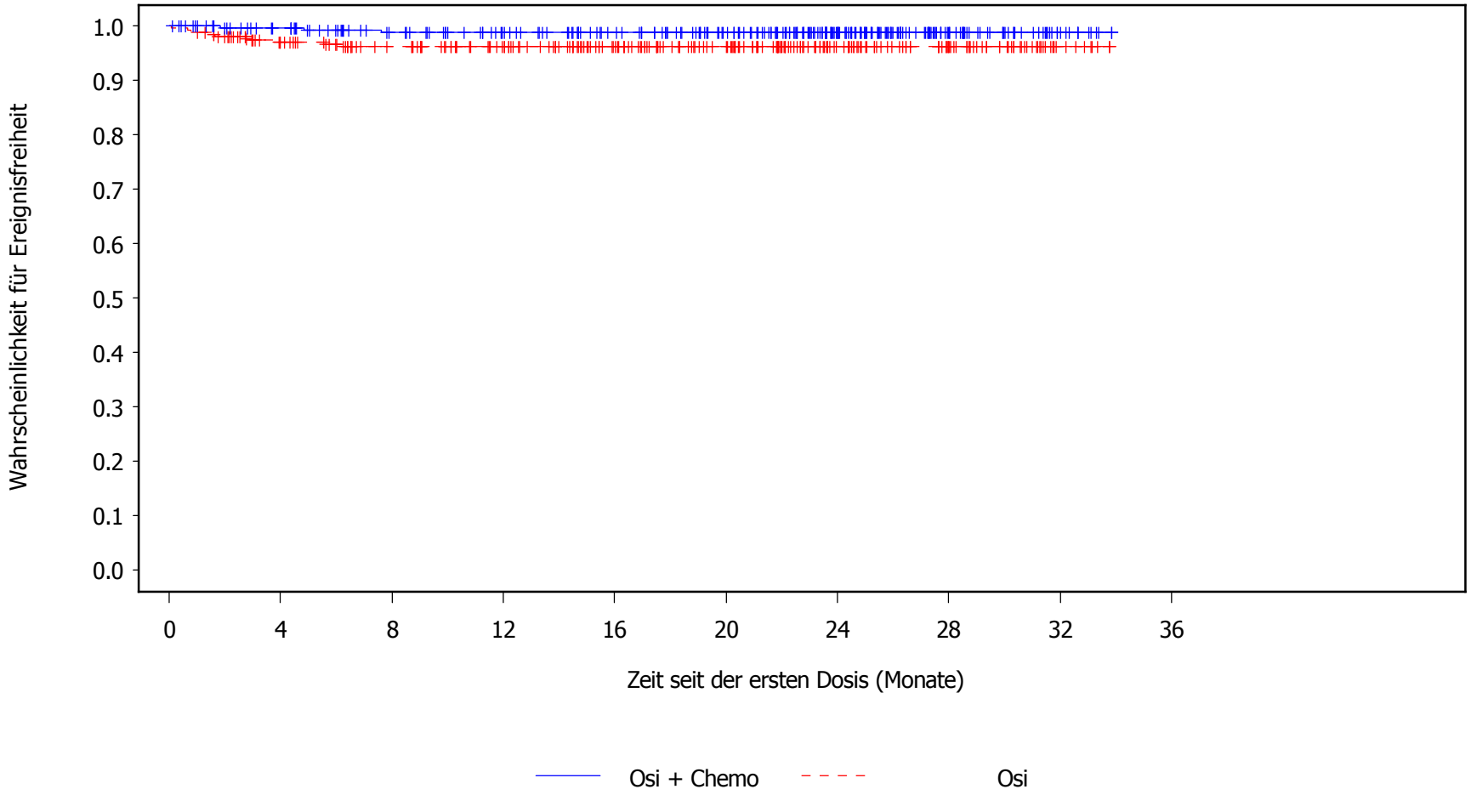
Figure 3.3.27 FLAURA-2: Kaplan-Meier plot of time to first occurrence of PT: Nagelerkrankung
Safety Analysis Set, DCO 03APR2023

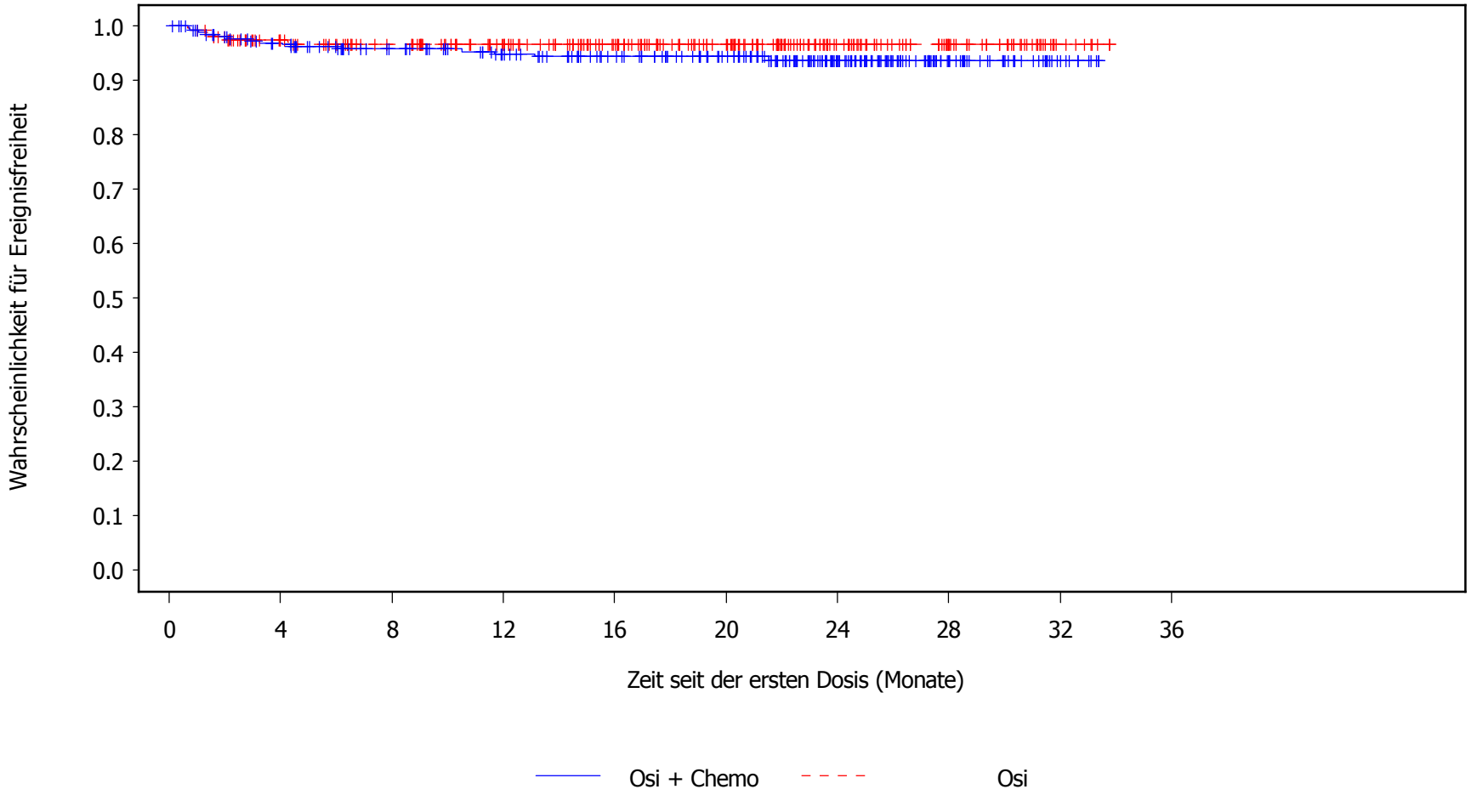


Anzahl an Patienten unter Risiko:

276	255	232	214	192	165	110	45	11	0	Osi + Chemo
275	245	222	199	164	131	77	43	7	0	Osi

root/cdar/d516/payer_germany/ar/d5169c00001_payer_germany/tlf/prod/program/ttemainae.sas gttemainaebba 24OCT2023:11:33 kvbv306

Figure 3.3.28 FLAURA-2: Kaplan-Meier plot of time to first occurrence of PT: Palmar-plantares Erythrodysaesthesiesyndrom
Safety Analysis Set, DCO 03APR2023



Anzahl an Patienten unter Risiko:

276	248	224	205	183	159	103	42	10	0	Osi + Chemo
275	246	224	198	165	130	75	39	7	0	Osi

root/cdar/d516/payer_germany/ar/d5169c00001_payer_germany/tlf/prod/program/ttemainae.sas gttemainaebbb 24OCT2023:11:33 kvbv306

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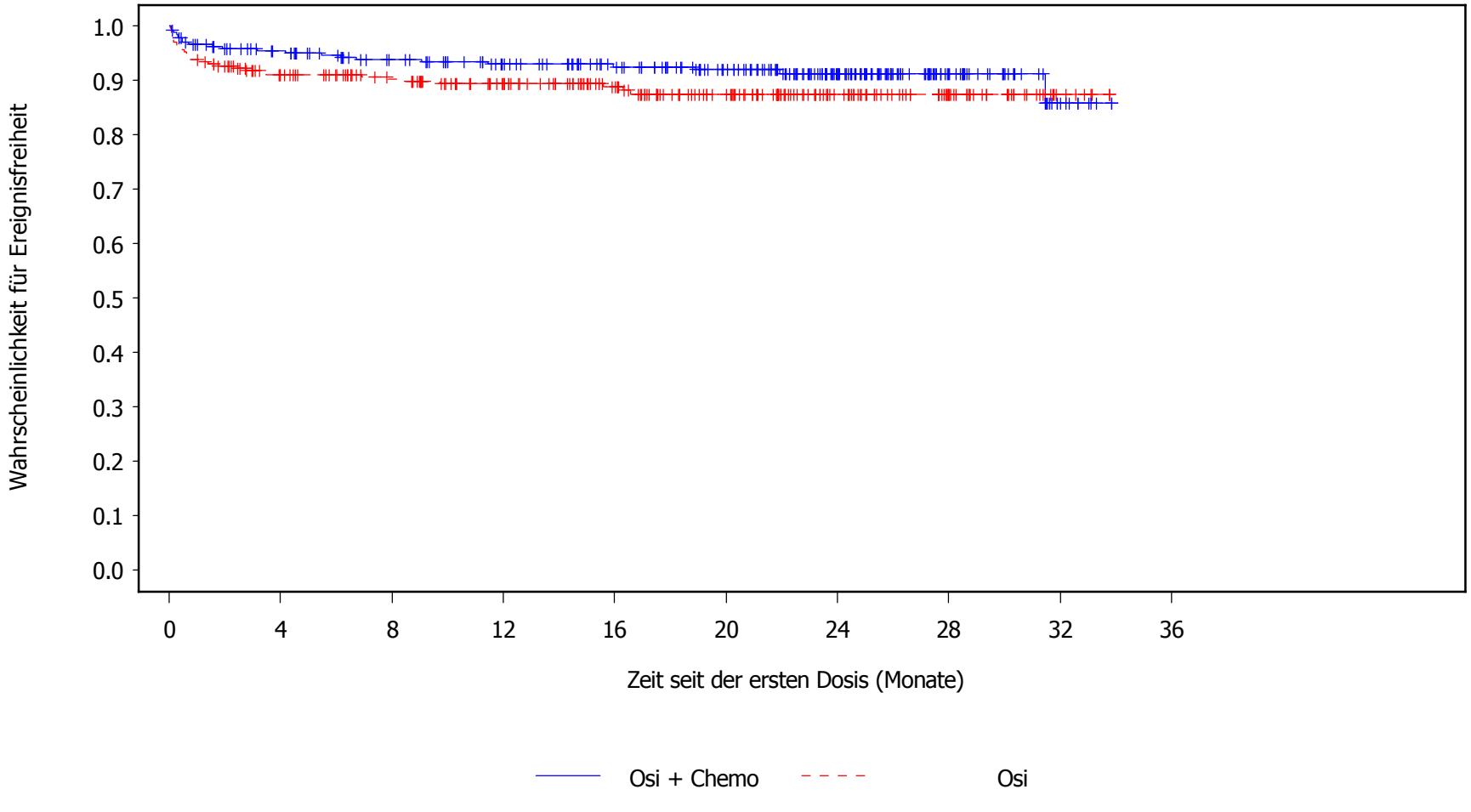
Figure 3.3.29 FLAURA-2: Kaplan-Meier plot of time to first occurrence of PT: Pruritus
Safety Analysis Set, DCO 03APR2023



Anzahl an Patienten unter Risiko:

276	244	222	203	181	155	102	41	9	0	Osi + Chemo
275	229	206	179	148	115	69	35	6	0	Osi

root/cdar/d516/payer_germany/ar/d5169c00001_payer_germany/tlf/prod/program/ttemainae.sas gttemainaebbc 24OCT2023:11:33 kvbv306

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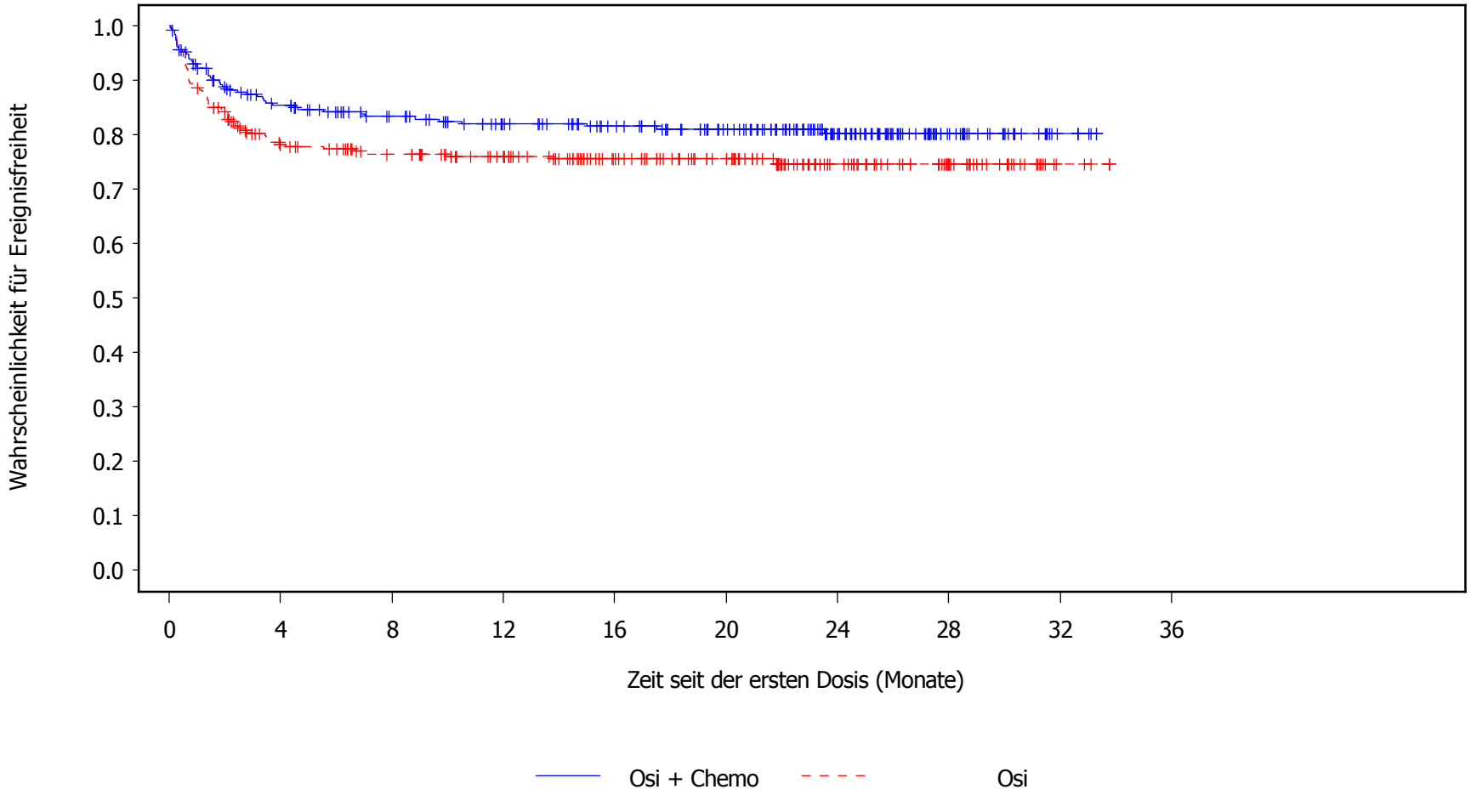
Figure 3.3.30 FLAURA-2: Kaplan-Meier plot of time to first occurrence of PT: Trockene Haut
Safety Analysis Set, DCO 03APR2023



Anzahl an Patienten unter Risiko:

276	218	194	175	157	134	86	34	6	0	Osi + Chemo
275	196	177	156	125	102	59	31	3	0	Osi

root/cdar/d516/payer_germany/ar/d5169c00001_payer_germany/tlf/prod/program/ttemainae.sas gttemainaebbd 24OCT2023:11:33 kvbv306

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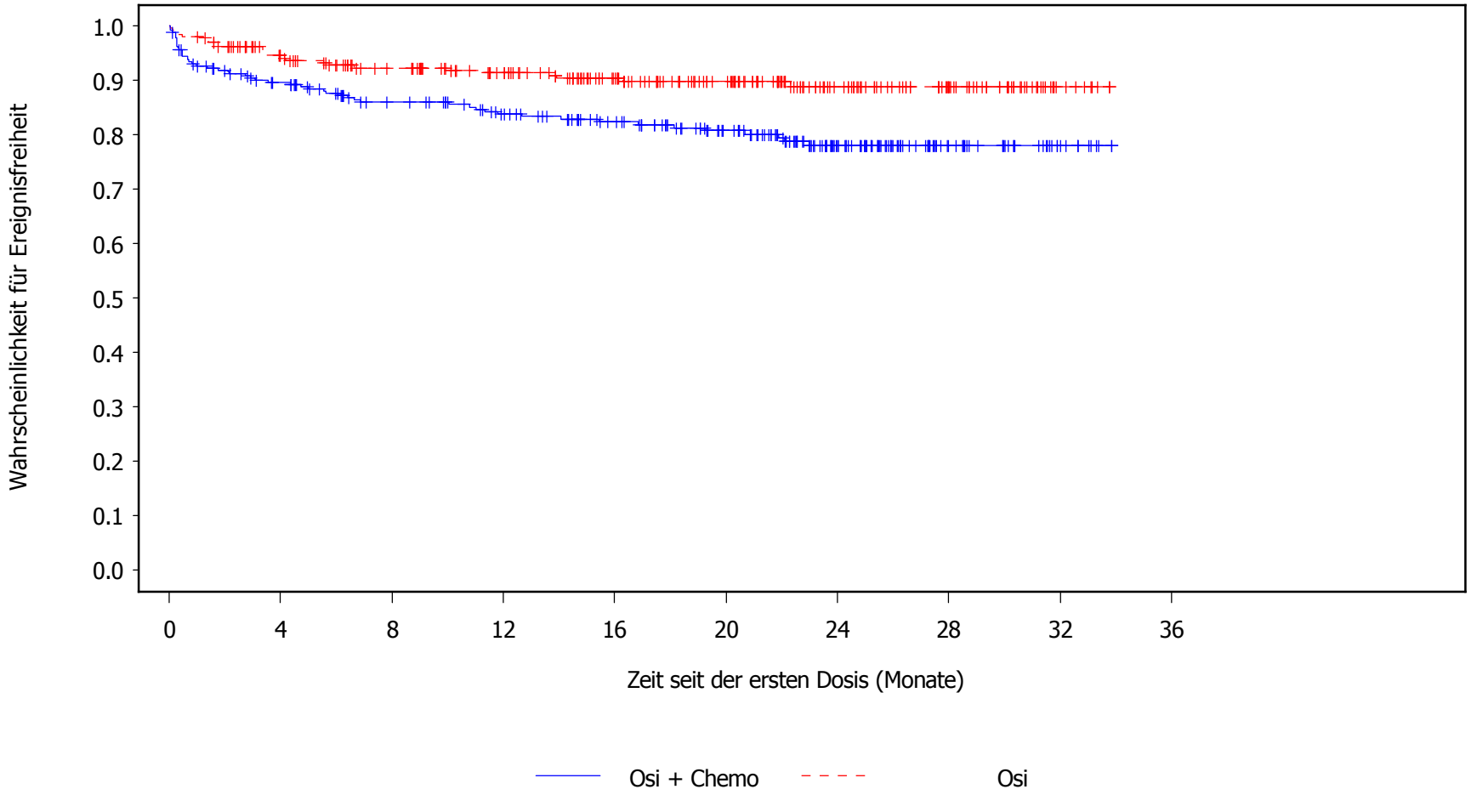
Figure 3.3.31 FLAURA-2: Kaplan-Meier plot of time to first occurrence of SOC: Erkrankungen der Nieren und Harnwege
Safety Analysis Set, DCO 03APR2023



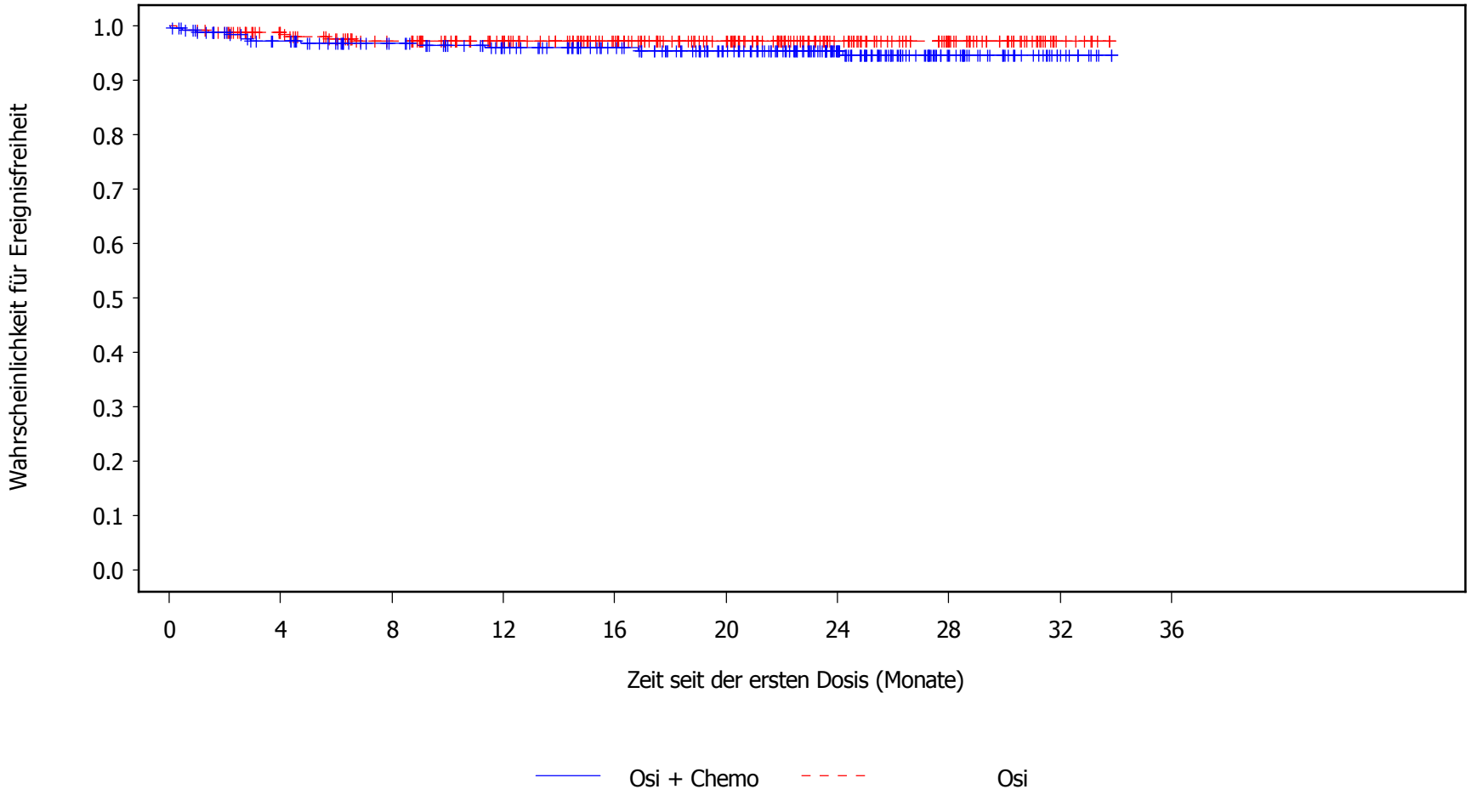
Anzahl an Patienten unter Risiko:

276	232	204	186	164	135	85	34	10	0	Osi + Chemo
275	240	213	189	154	122	74	41	7	0	Osi

root/cdar/d516/payer_germany/ar/d5169c00001_payer_germany/tlf/prod/program/ttemainae.sas gttemainaebbe 24OCT2023:11:33 kvbv306

Nutzenbewertung nach AMNOG Seite 1 von 1

Figure 3.3.32 FLAURA-2: Kaplan-Meier plot of time to first occurrence of PT: Haematurie
Safety Analysis Set, DCO 03APR2023



Anzahl an Patienten unter Risiko:

276	249	227	207	185	156	104	43	11	0	Osi + Chemo
275	250	225	199	166	132	80	44	7	0	Osi

root/cdar/d516/payer_germany/ar/d5169c00001_payer_germany/tlf/prod/program/ttemainae.sas gttemainaebbf 24OCT2023:11:33 kvbv306

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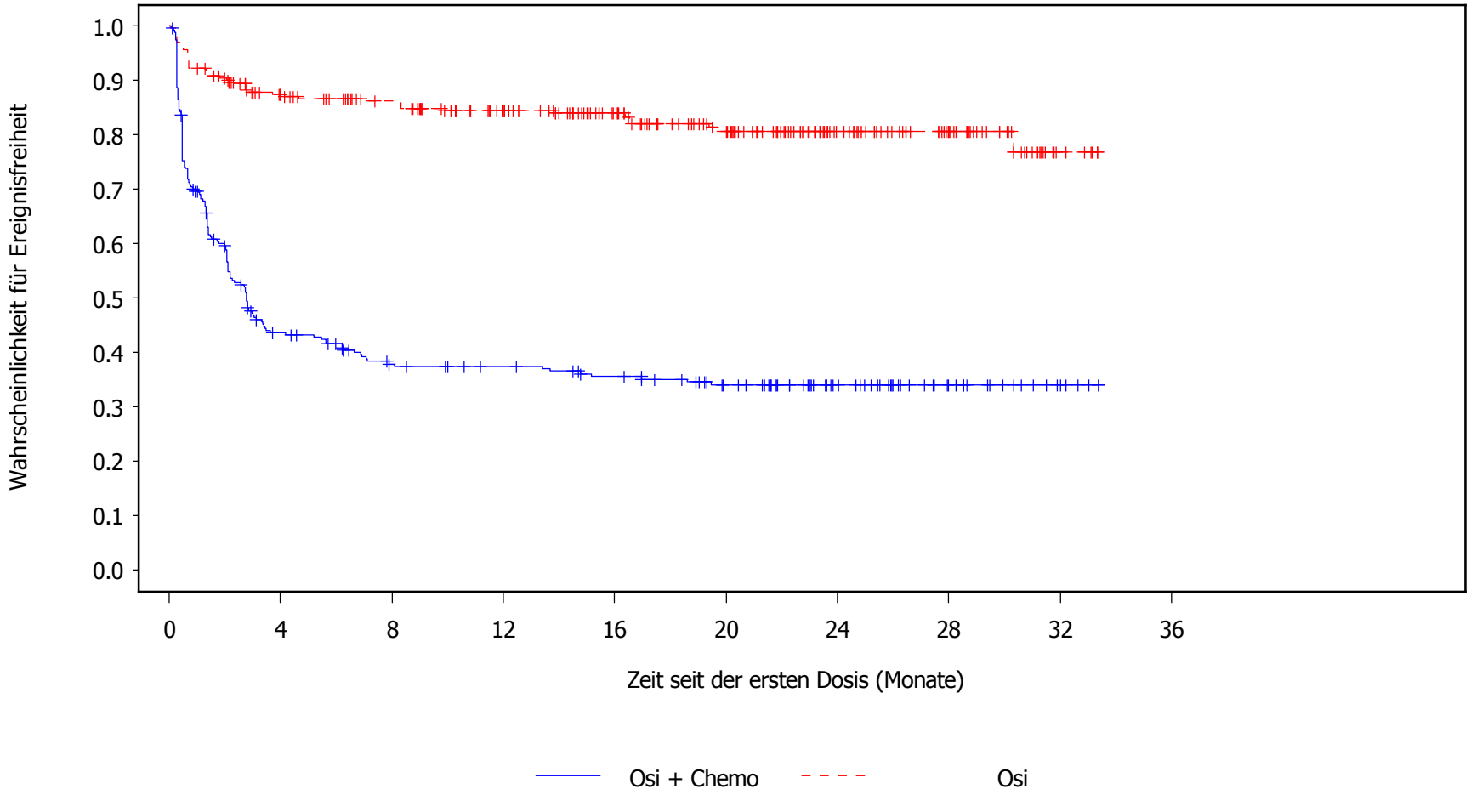
Figure 3.3.33 FLAURA-2: Kaplan-Meier plot of time to first occurrence of SOC: Erkrankungen des Blutes und des Lymphsystems
Safety Analysis Set, DCO 03APR2023



Anzahl an Patienten unter Risiko:

276	111	88	81	73	59	36	17	5	0	Osi + Chemo
275	220	201	172	141	111	66	39	5	0	Osi

root/cdar/d516/payer_germany/ar/d5169c00001_payer_germany/tlf/prod/program/ttemainae.sas gttemainaebbg 24OCT2023:11:33 kvbv306

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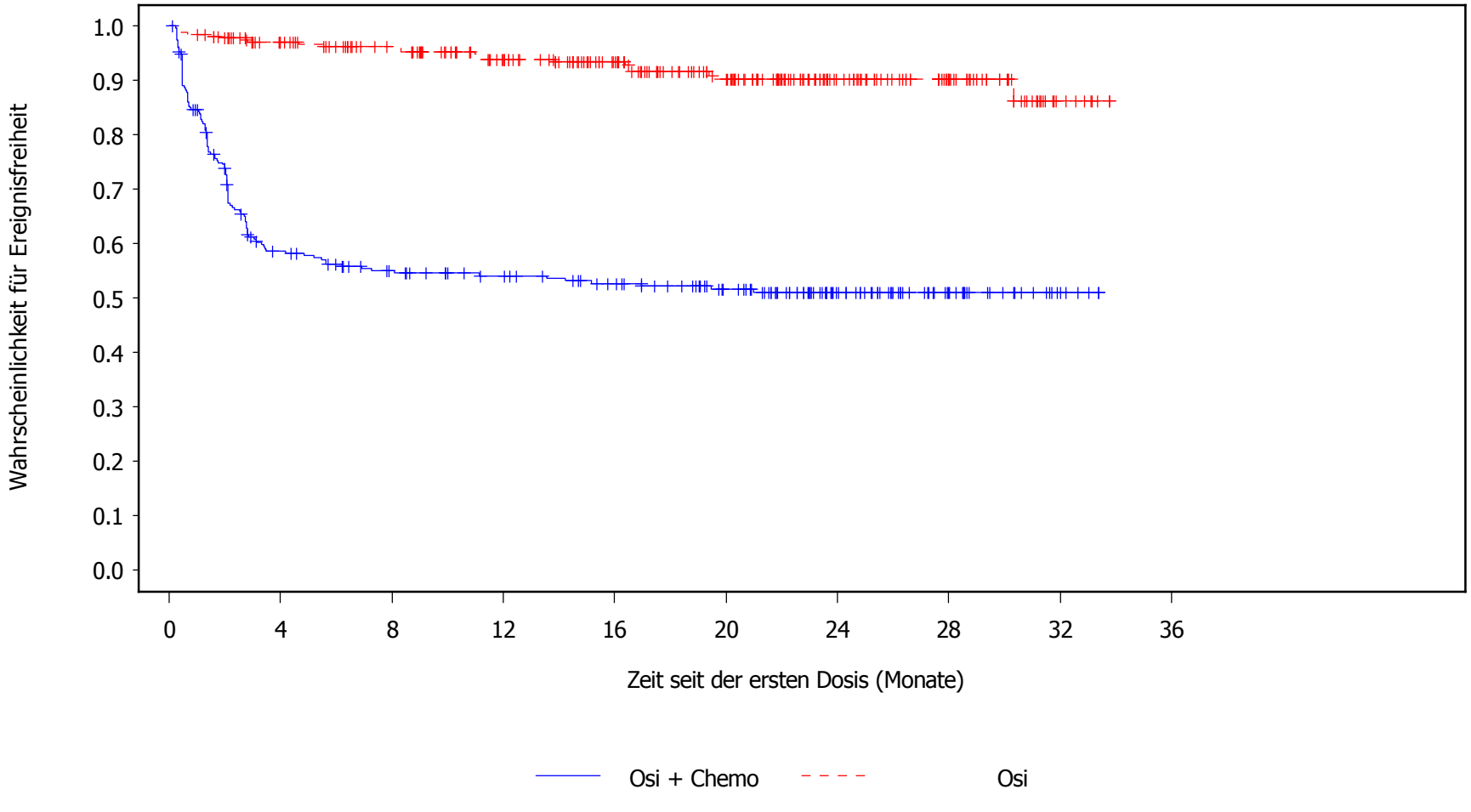
Figure 3.3.34 FLAURA-2: Kaplan-Meier plot of time to first occurrence of PT: Anaemie
Safety Analysis Set, DCO 03APR2023



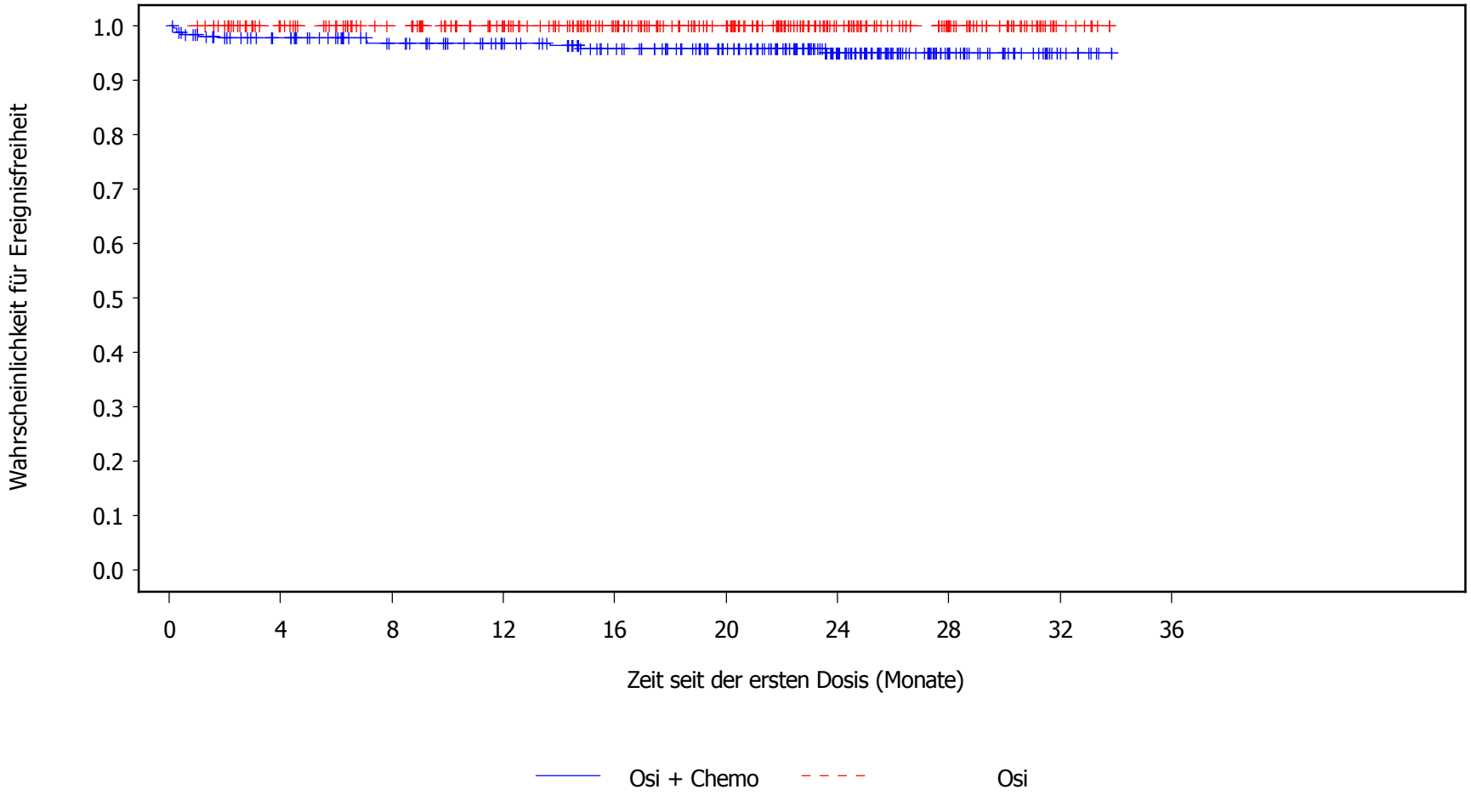
Anzahl an Patienten unter Risiko:

276	150	131	120	108	89	53	24	5	0	Osi + Chemo
275	246	225	194	161	125	73	42	7	0	Osi

root/cdar/d516/payer_germany/ar/d5169c00001_payer_germany/tlf/prod/program/ttemainae.sas gttemainaebbh 24OCT2023:11:33 kvbv306

Nutzenbewertung nach AMNOG Seite 1 von 1

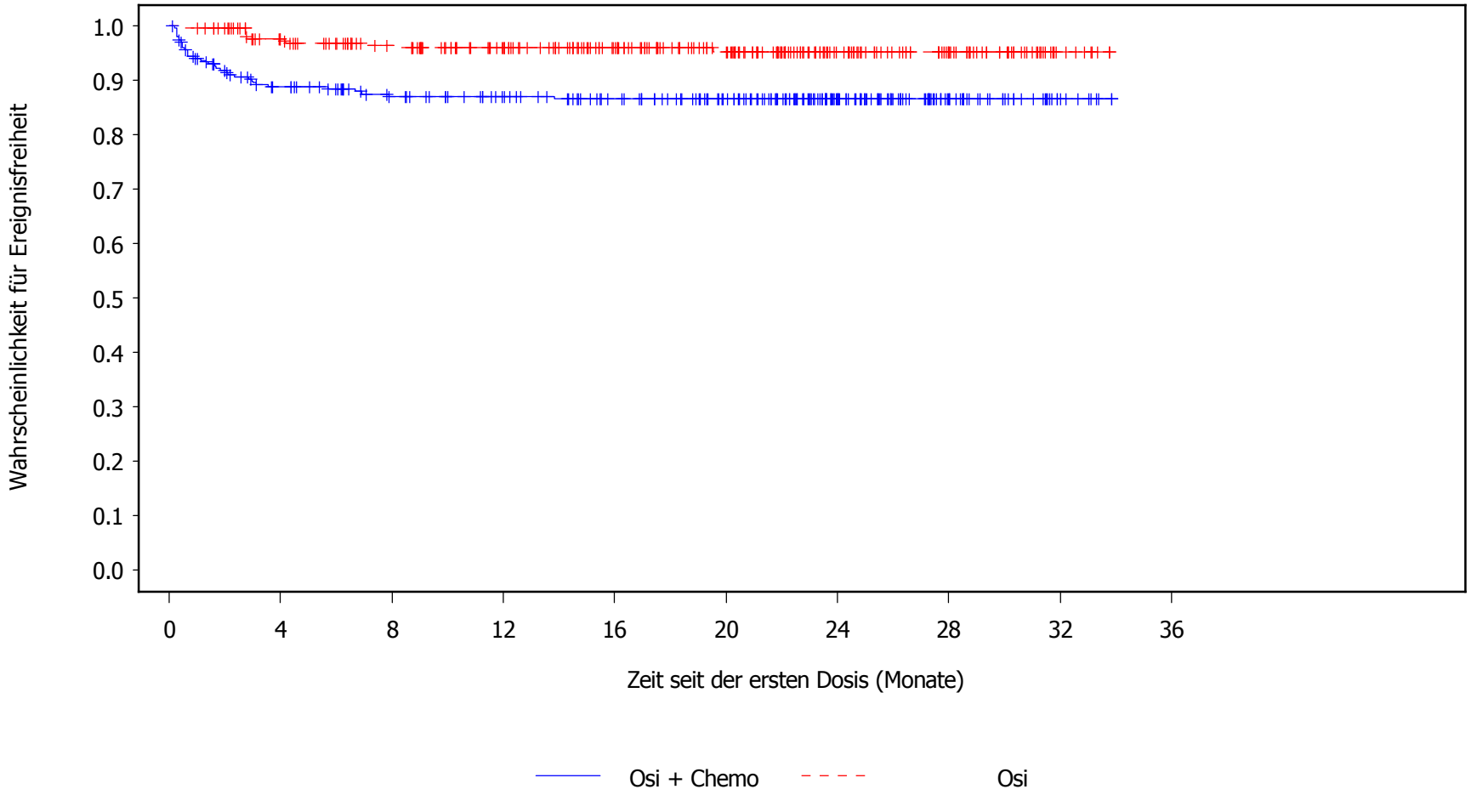
Figure 3.3.35 FLAURA-2: Kaplan-Meier plot of time to first occurrence of PT: Febrile Neutropenie
Safety Analysis Set, DCO 03APR2023



root/cdar/d516/payer_germany/ar/d5169c00001_payer_germany/tlf/prod/program/ttemainae.sas gttemainaebbi 24OCT2023:11:33 kvbv306

Nutzenbewertung nach AMNOG Seite 1 von 1

Figure 3.3.36 FLAURA-2: Kaplan-Meier plot of time to first occurrence of PT: Leukopenie
Safety Analysis Set, DCO 03APR2023



Anzahl an Patienten unter Risiko:

276	226	204	189	171	147	90	38	8	0	Osi + Chemo
275	247	223	196	162	129	76	43	7	0	Osi

root/cdar/d516/payer_germany/ar/d5169c00001_payer_germany/tlf/prod/program/ttemainae.sas gttemainaebbj 24OCT2023:11:33 kvbv306

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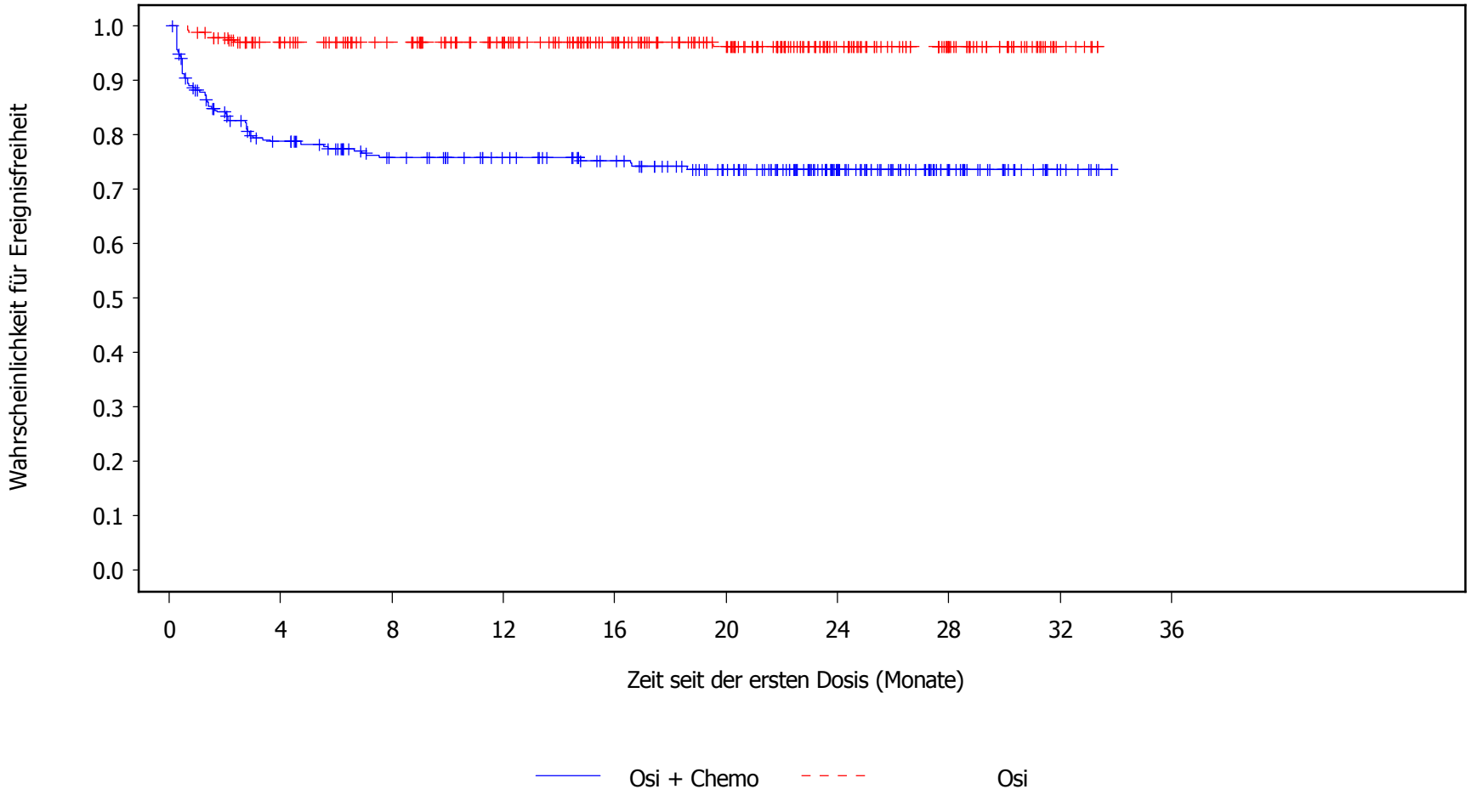
Figure 3.3.37 FLAURA-2: Kaplan-Meier plot of time to first occurrence of PT: Neutropenie
Safety Analysis Set, DCO 03APR2023



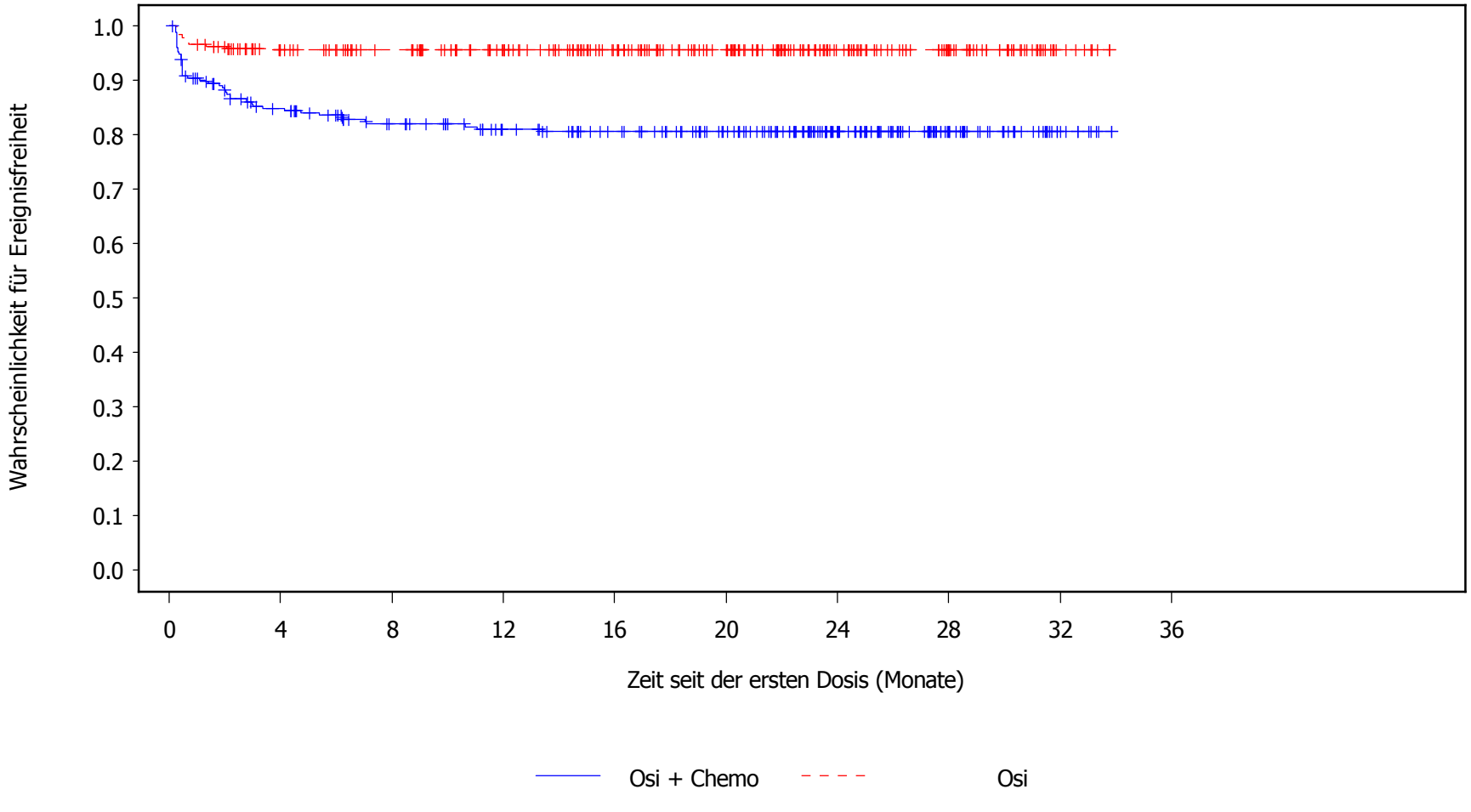
Anzahl an Patienten unter Risiko:

276	200	174	161	146	123	76	35	8	0	Osi + Chemo
275	245	224	198	164	131	78	42	6	0	Osi

root/cdar/d516/payer_germany/ar/d5169c00001_payer_germany/tlf/prod/program/ttemainae.sas gttemainaebbk 24OCT2023:11:33 kvbv306

Nutzenbewertung nach AMNOG Seite 1 von 1

Figure 3.3.38 FLAURA-2: Kaplan-Meier plot of time to first occurrence of PT: Thrombozytopenie
Safety Analysis Set, DCO 03APR2023



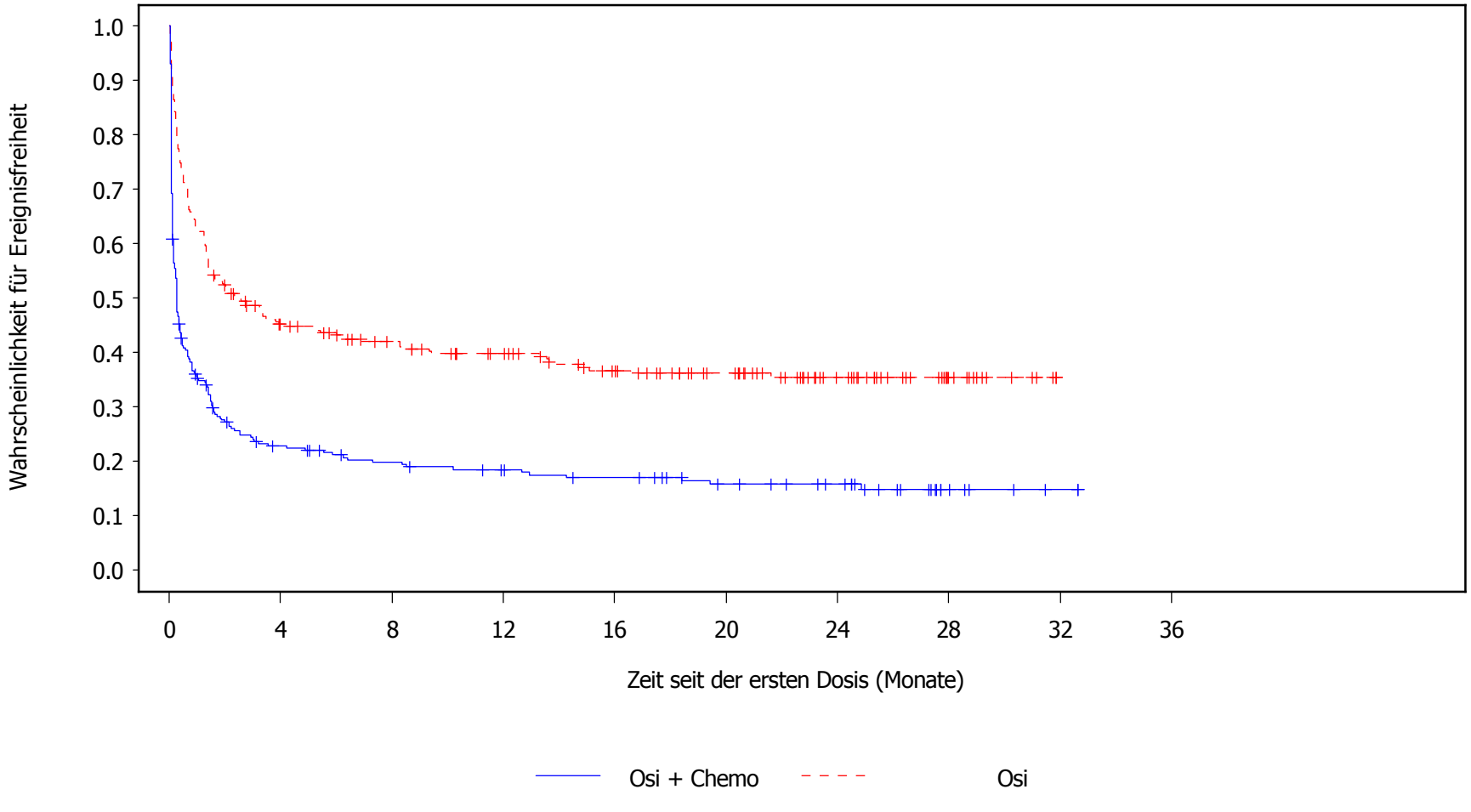
Anzahl an Patienten unter Risiko:

276	218	193	175	159	136	90	41	9	0	Osi + Chemo
275	241	222	197	163	130	77	44	7	0	Osi

root/cdar/d516/payer_germany/ar/d5169c00001_payer_germany/tlf/prod/program/ttemainae.sas gttemainaebbl 24OCT2023:11:33 kvbv306

Nutzenbewertung nach AMNOG Seite 1 von 1

Figure 3.3.39 FLAURA-2: Kaplan-Meier plot of time to first occurrence of SOC: Erkrankungen des Gastrointestinaltrakts
Safety Analysis Set, DCO 03APR2023



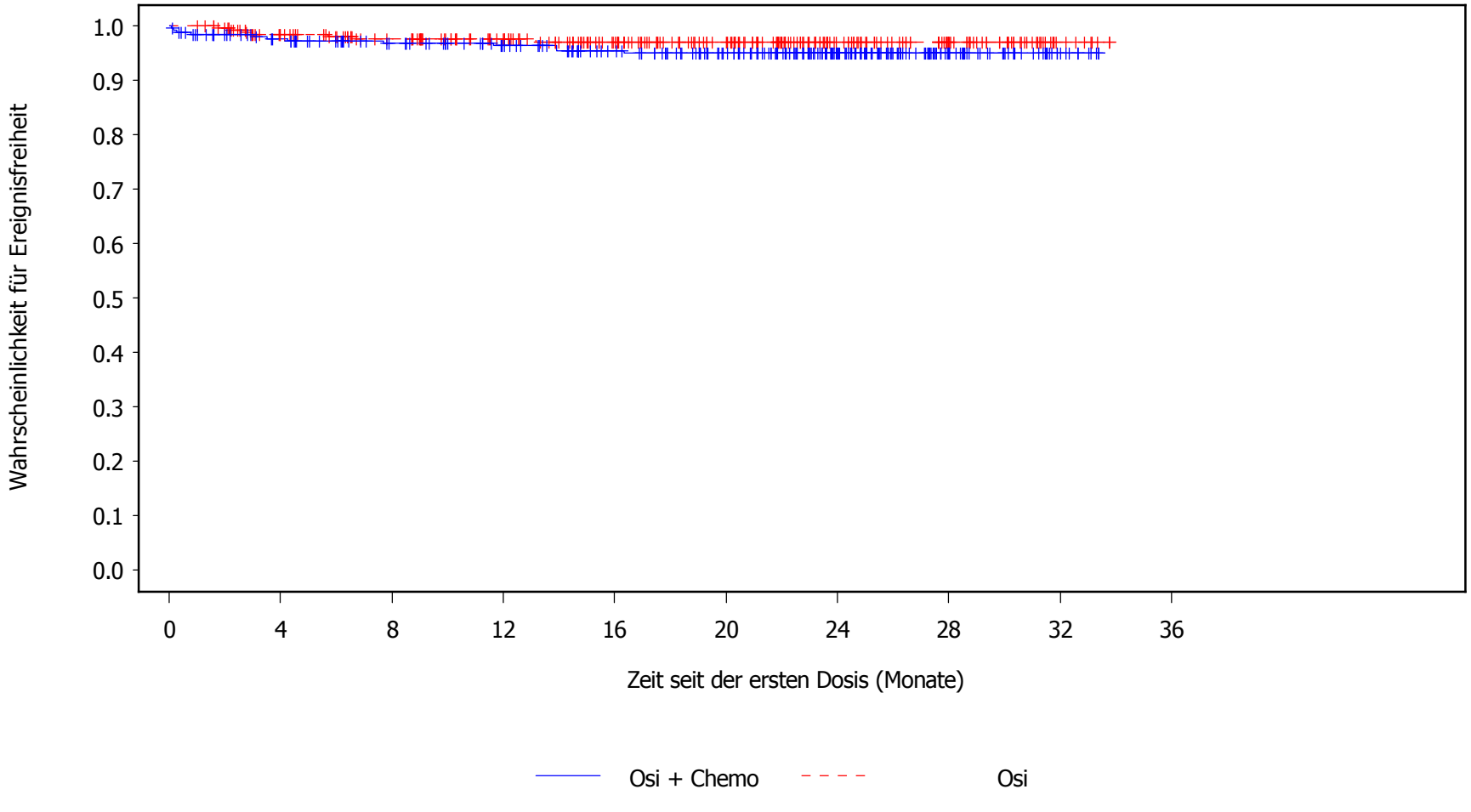
Anzahl an Patienten unter Risiko:

276	56	45	39	34	26	21	6	1	0	Osi + Chemo
275	116	98	84	68	54	33	12	0	0	Osi

root/cdar/d516/payer_germany/ar/d5169c00001_payer_germany/tlf/prod/program/ttemainae.sas gttemainaebbm 24OCT2023:11:33 kvbv306

Nutzenbewertung nach AMNOG Seite 1 von 1

Figure 3.3.40 FLAURA-2: Kaplan-Meier plot of time to first occurrence of PT: Abdominalschmerz
Safety Analysis Set, DCO 03APR2023



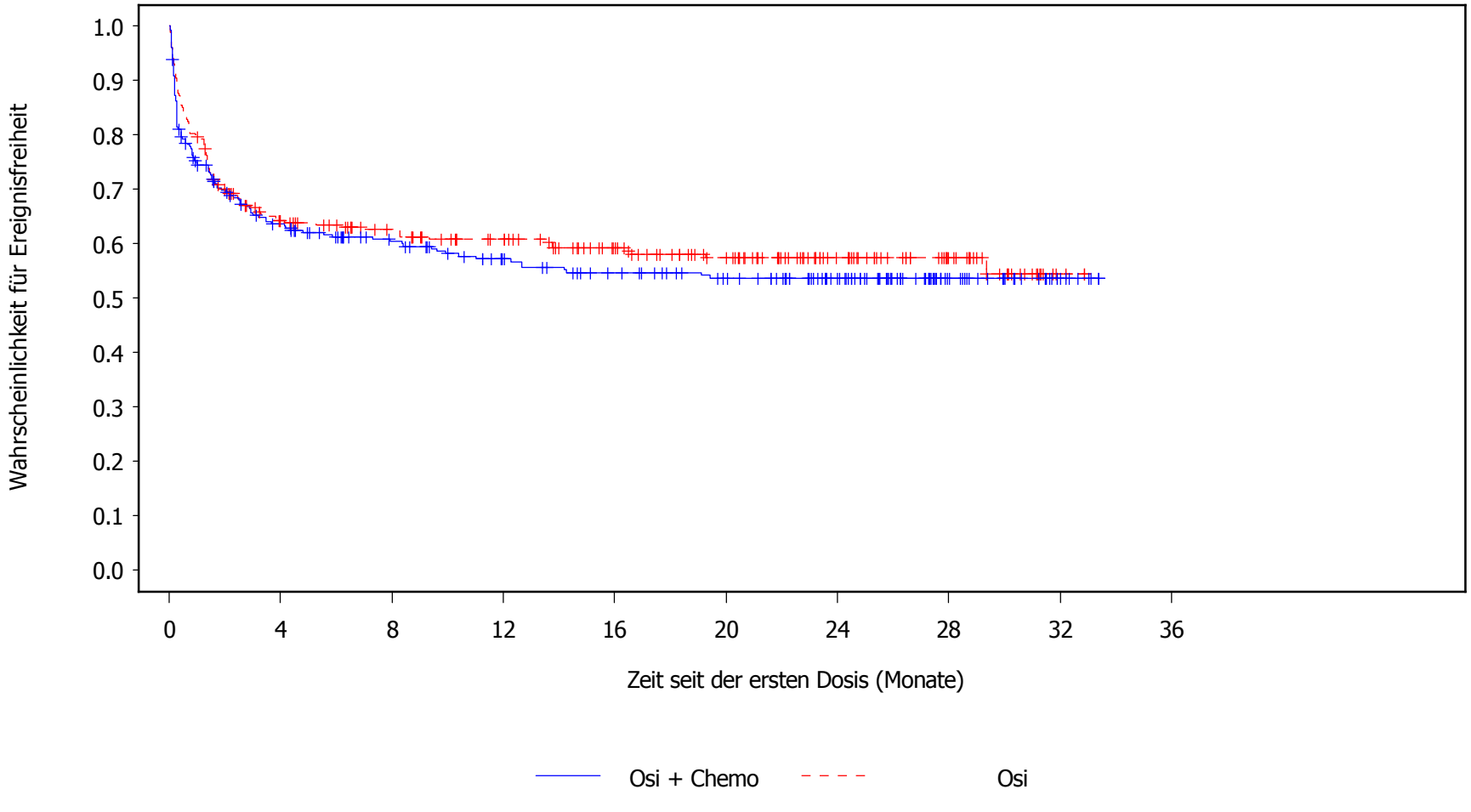
Anzahl an Patienten unter Risiko:

276	250	228	211	188	161	107	43	10	0	Osi + Chemo
275	249	226	201	167	133	78	43	7	0	Osi

root/cdar/d516/payer_germany/ar/d5169c00001_payer_germany/tlf/prod/program/ttemainae.sas gttemainaebbn 24OCT2023:11:33 kvbv306

Nutzenbewertung nach AMNOG Seite 1 von 1

Figure 3.3.41 FLAURA-2: Kaplan-Meier plot of time to first occurrence of PT: Diarrhoe
Safety Analysis Set, DCO 03APR2023



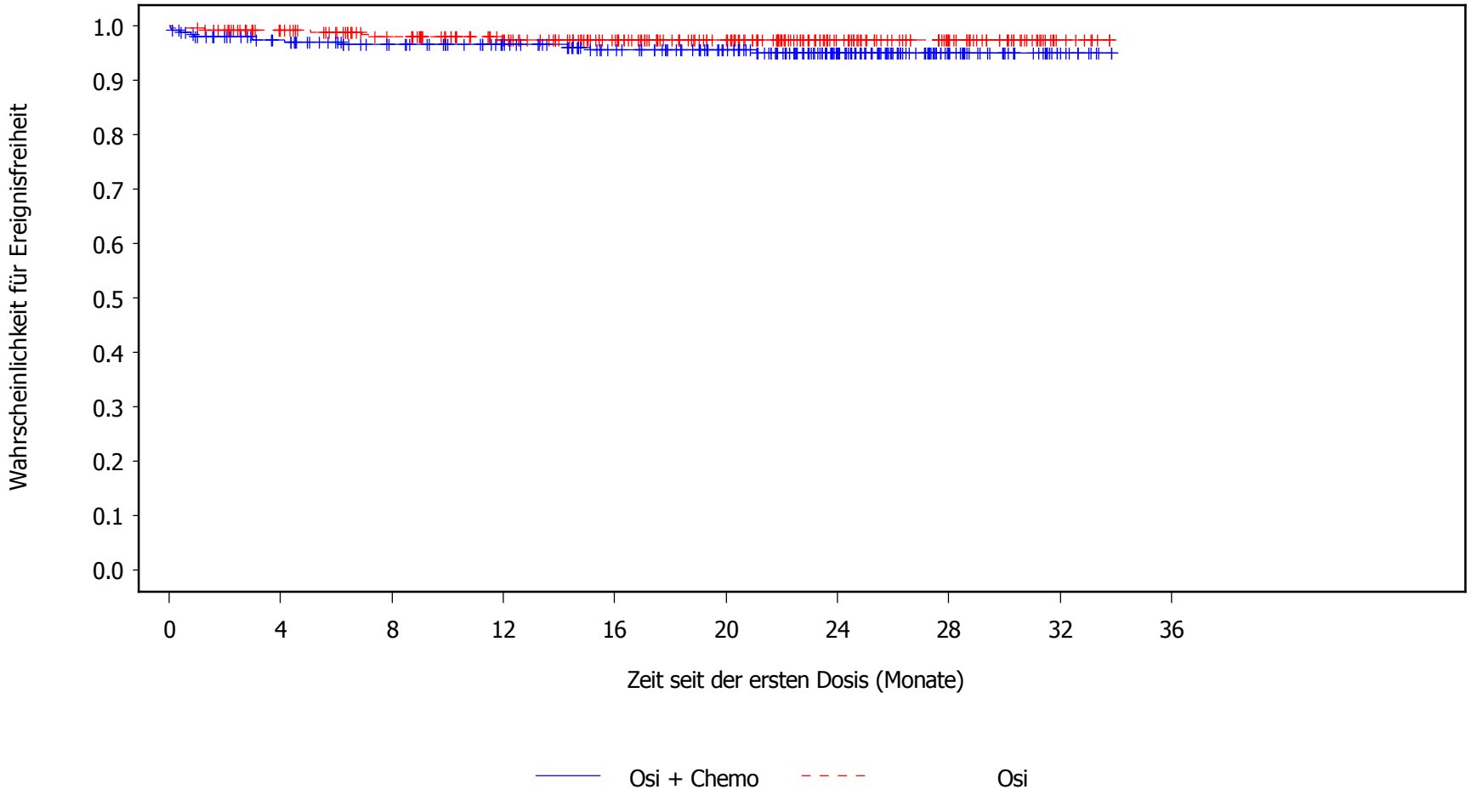
Anzahl an Patienten unter Risiko:

276	162	136	117	104	92	69	28	7	0	Osi + Chemo
275	161	142	125	103	83	53	28	2	0	Osi

root/cdar/d516/payer_germany/ar/d5169c00001_payer_germany/tlf/prod/program/ttemainae.sas gttemainaebbo 24OCT2023:11:33 kvbv306

Nutzenbewertung nach AMNOG Seite 1 von 1

Figure 3.3.42 FLAURA-2: Kaplan-Meier plot of time to first occurrence of PT: Dyspepsie
Safety Analysis Set, DCO 03APR2023



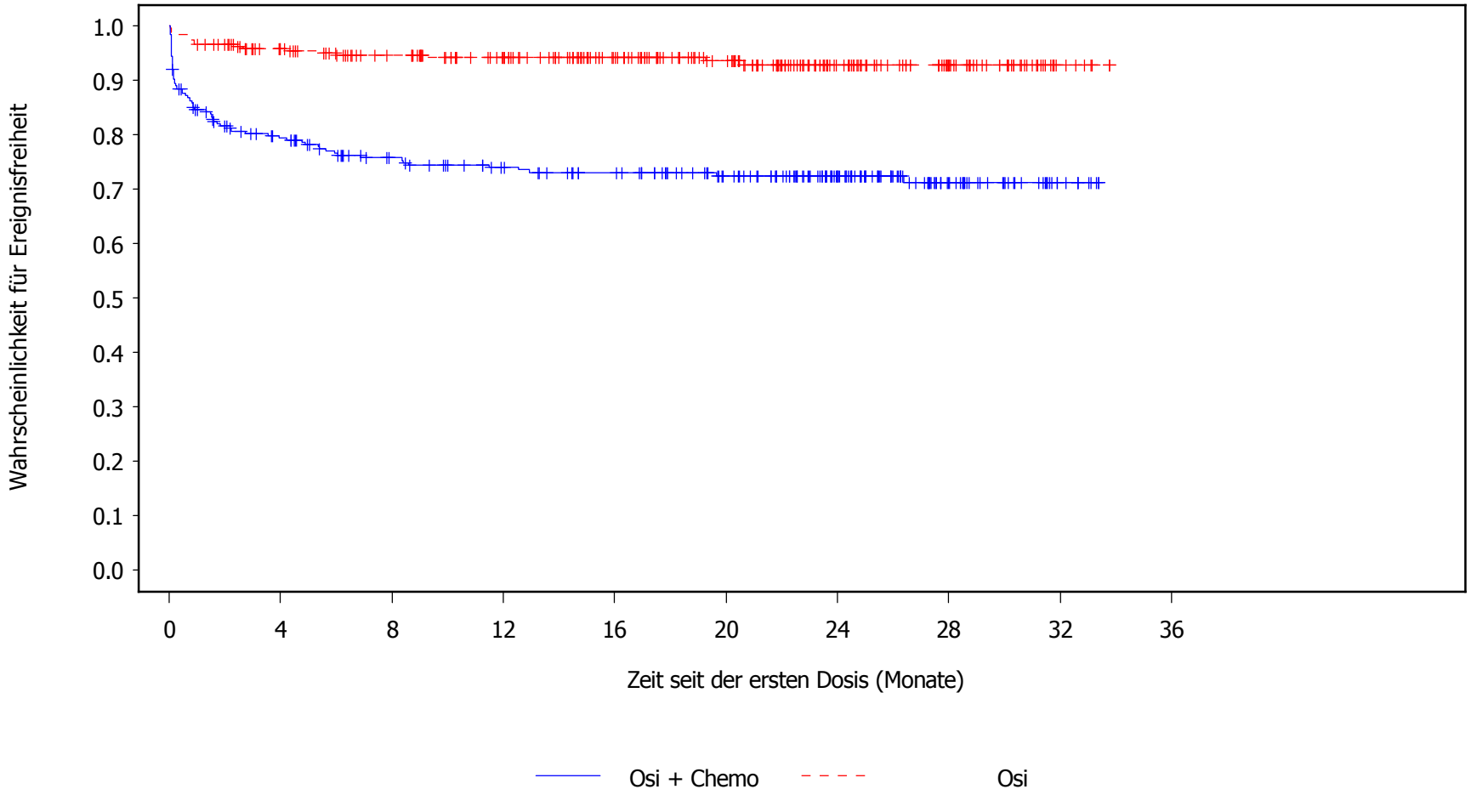
Anzahl an Patienten unter Risiko:

276	249	227	210	186	161	106	44	11	0	Osi + Chemo
275	252	228	201	168	134	79	43	7	0	Osi

root/cdar/d516/payer_germany/ar/d5169c00001_payer_germany/tlf/prod/program/ttemainae.sas gttemainaebbp 24OCT2023:11:33 kvbv306

Nutzenbewertung nach AMNOG Seite 1 von 1

Figure 3.3.43 FLAURA-2: Kaplan-Meier plot of time to first occurrence of PT: Erbrechen
Safety Analysis Set, DCO 03APR2023



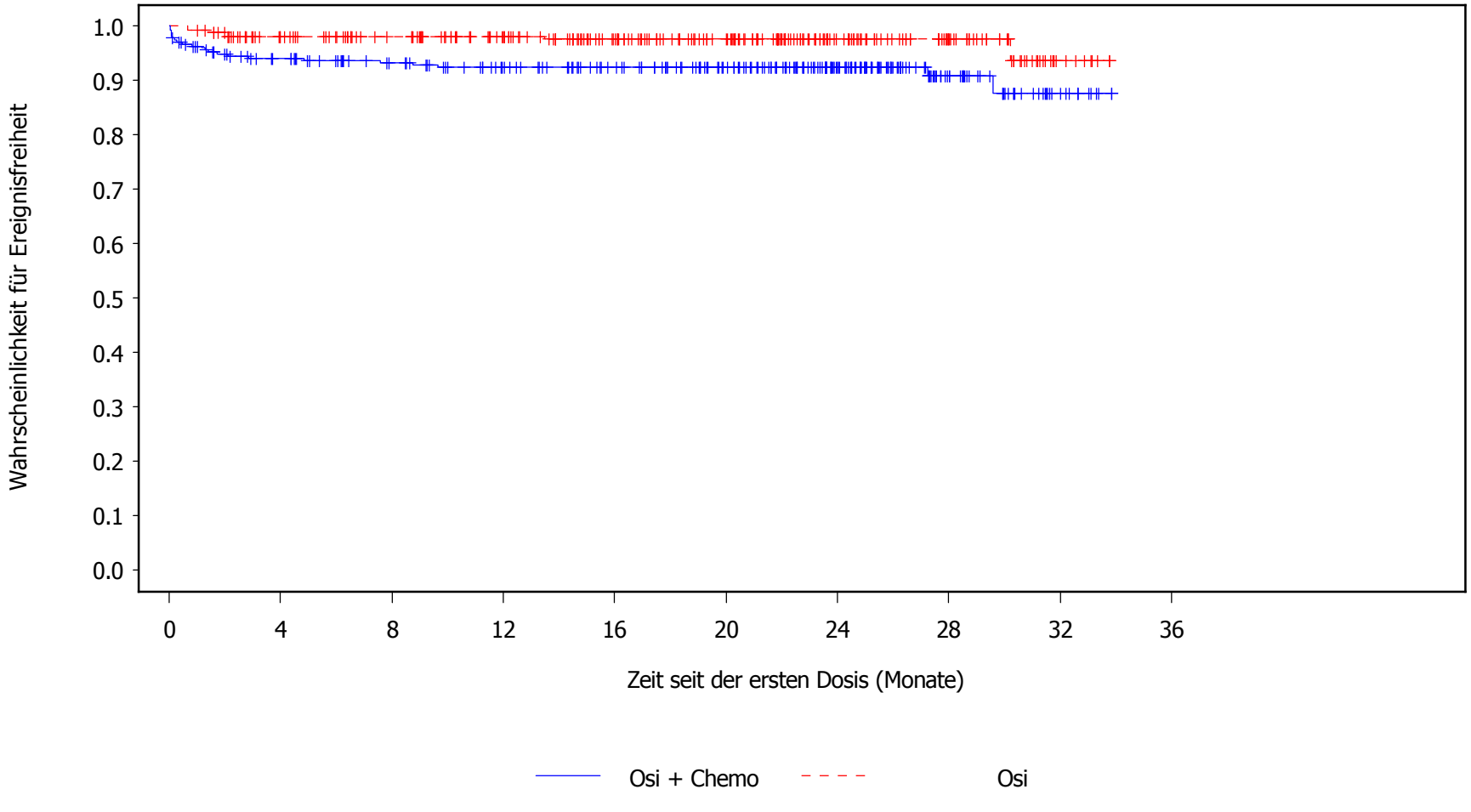
Anzahl an Patienten unter Risiko:

276	203	177	162	151	128	88	36	8	0	Osi + Chemo
275	243	221	197	162	129	76	41	6	0	Osi

root/cdar/d516/payer_germany/ar/d5169c00001_payer_germany/tlf/prod/program/ttemainae.sas gttemainaebbq 24OCT2023:11:33 kvbv306

Nutzenbewertung nach AMNOG Seite 1 von 1

Figure 3.3.44 FLAURA-2: Kaplan-Meier plot of time to first occurrence of PT: Gastrooesophageale Refluxerkrankung
Safety Analysis Set, DCO 03APR2023



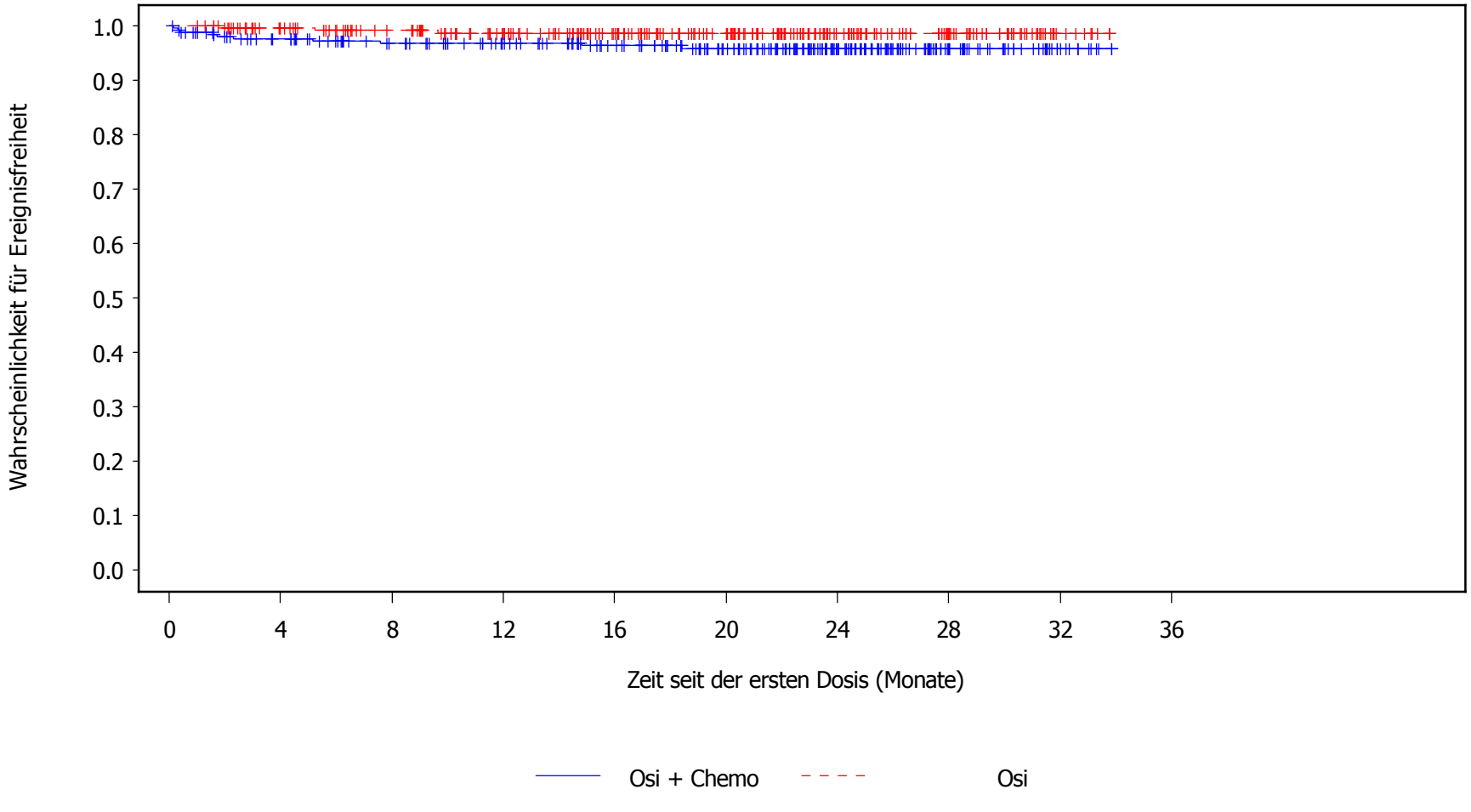
Anzahl an Patienten unter Risiko:

276	240	220	201	181	154	103	42	11	0	Osi + Chemo
275	248	227	202	167	135	79	43	7	0	Osi

root/cdar/d516/payer_germany/ar/d5169c00001_payer_germany/tlf/prod/program/ttemainae.sas gttemainaebbr 24OCT2023:11:33 kvbv306

Nutzenbewertung nach AMNOG Seite 1 von 1

Figure 3.3.45 FLAURA-2: Kaplan-Meier plot of time to first occurrence of PT: Haemorrhoiden
Safety Analysis Set, DCO 03APR2023



Anzahl an Patienten unter Risiko:

276	250	228	210	187	158	102	42	11	0	Osi + Chemo
275	252	230	203	168	133	80	44	7	0	Osi

root/cdar/d516/payer_germany/ar/d5169c00001_payer_germany/tlf/prod/program/ttemainae.sas gttemainaebbs 24OCT2023:11:33 kvbv306

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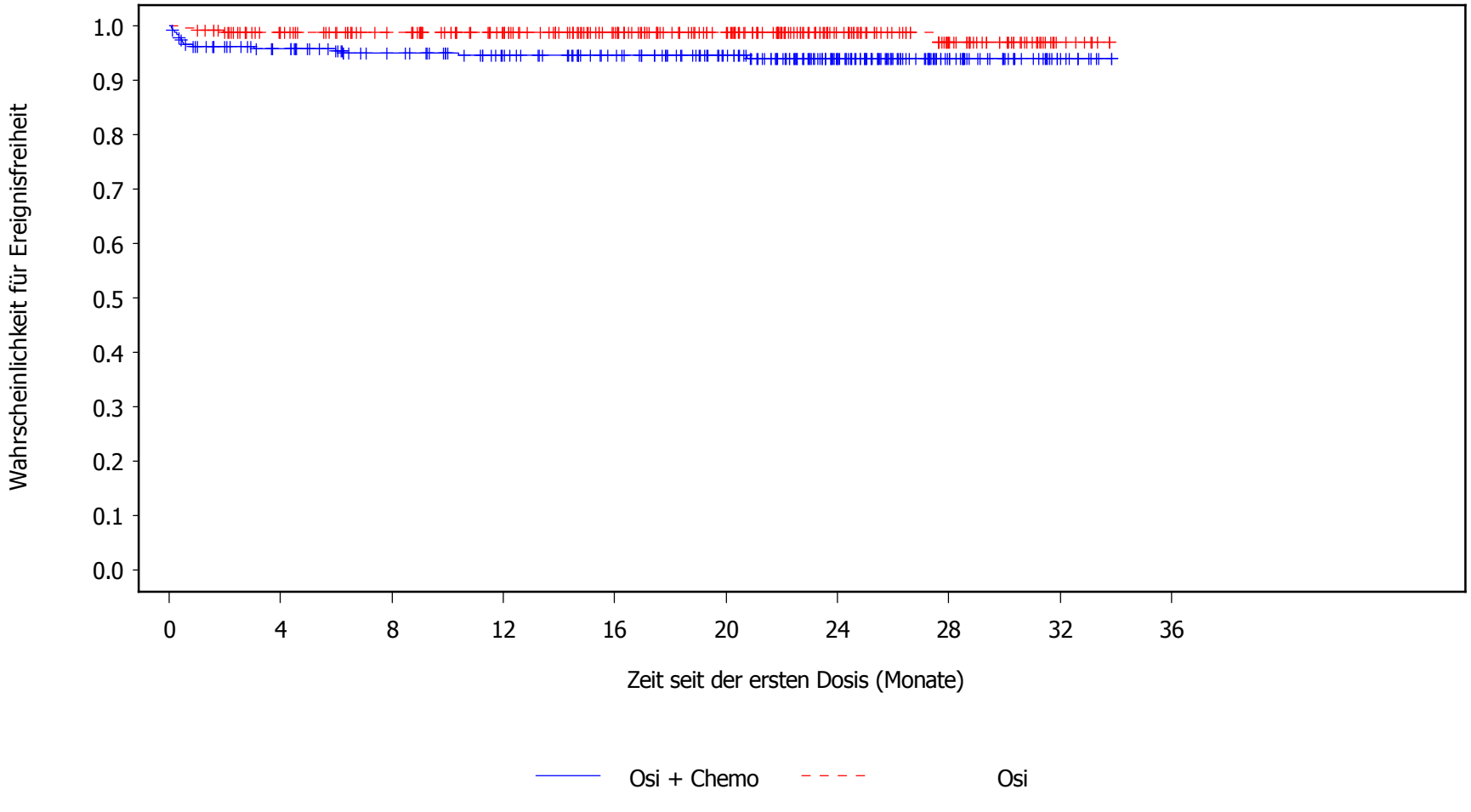
Figure 3.3.46 FLAURA-2: Kaplan-Meier plot of time to first occurrence of PT: Mundtrockenheit
Safety Analysis Set, DCO 03APR2023



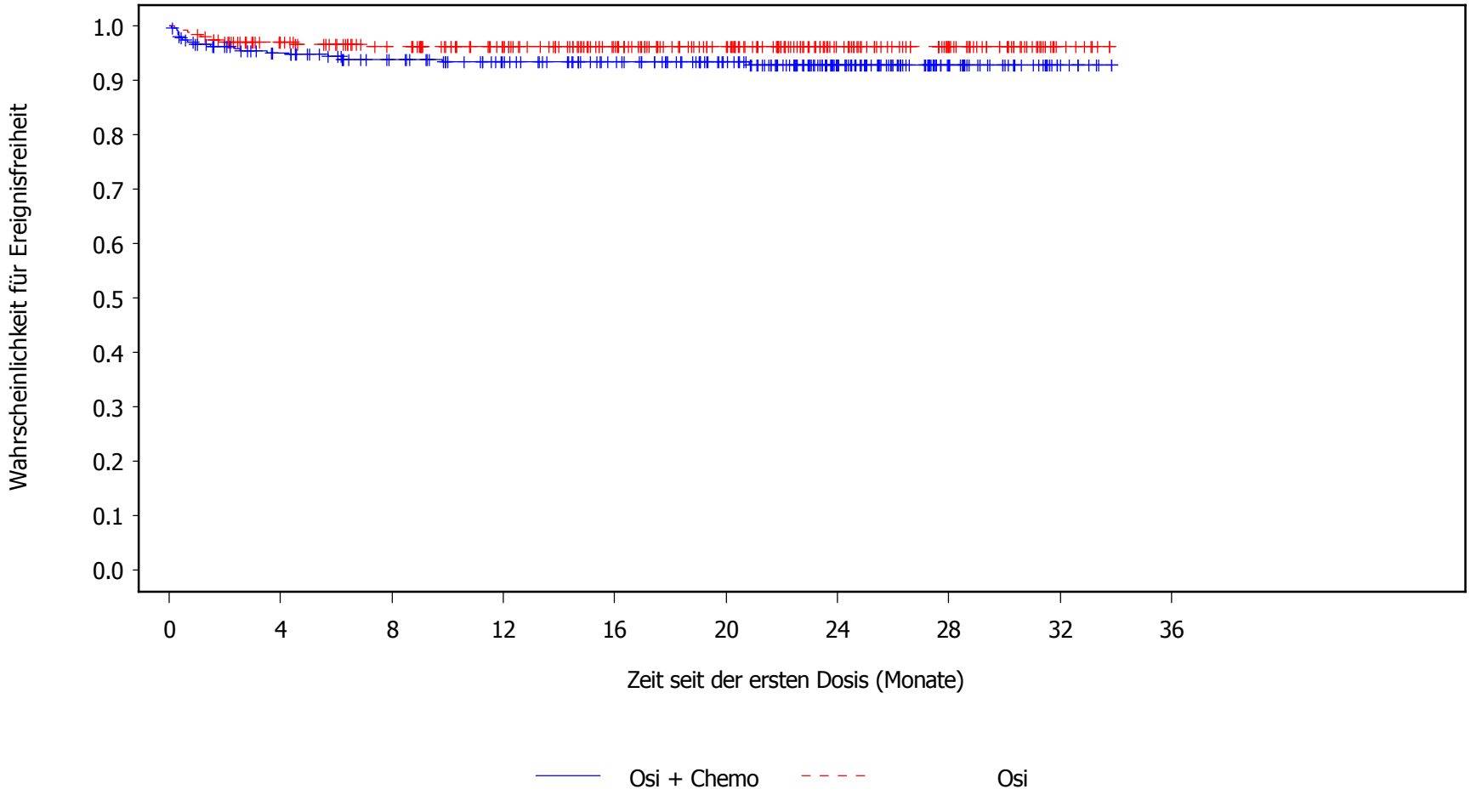
Anzahl an Patienten unter Risiko:

276	245	223	205	185	158	104	45	11	0	Osi + Chemo
275	251	231	206	171	136	80	43	7	0	Osi

root/cdar/d516/payer_germany/ar/d5169c00001_payer_germany/tlf/prod/program/ttemainae.sas gttemainaebbt 24OCT2023:11:33 kvbv306

Nutzenbewertung nach AMNOG Seite 1 von 1

Figure 3.3.47 FLAURA-2: Kaplan-Meier plot of time to first occurrence of PT: Mundulzeration
Safety Analysis Set, DCO 03APR2023



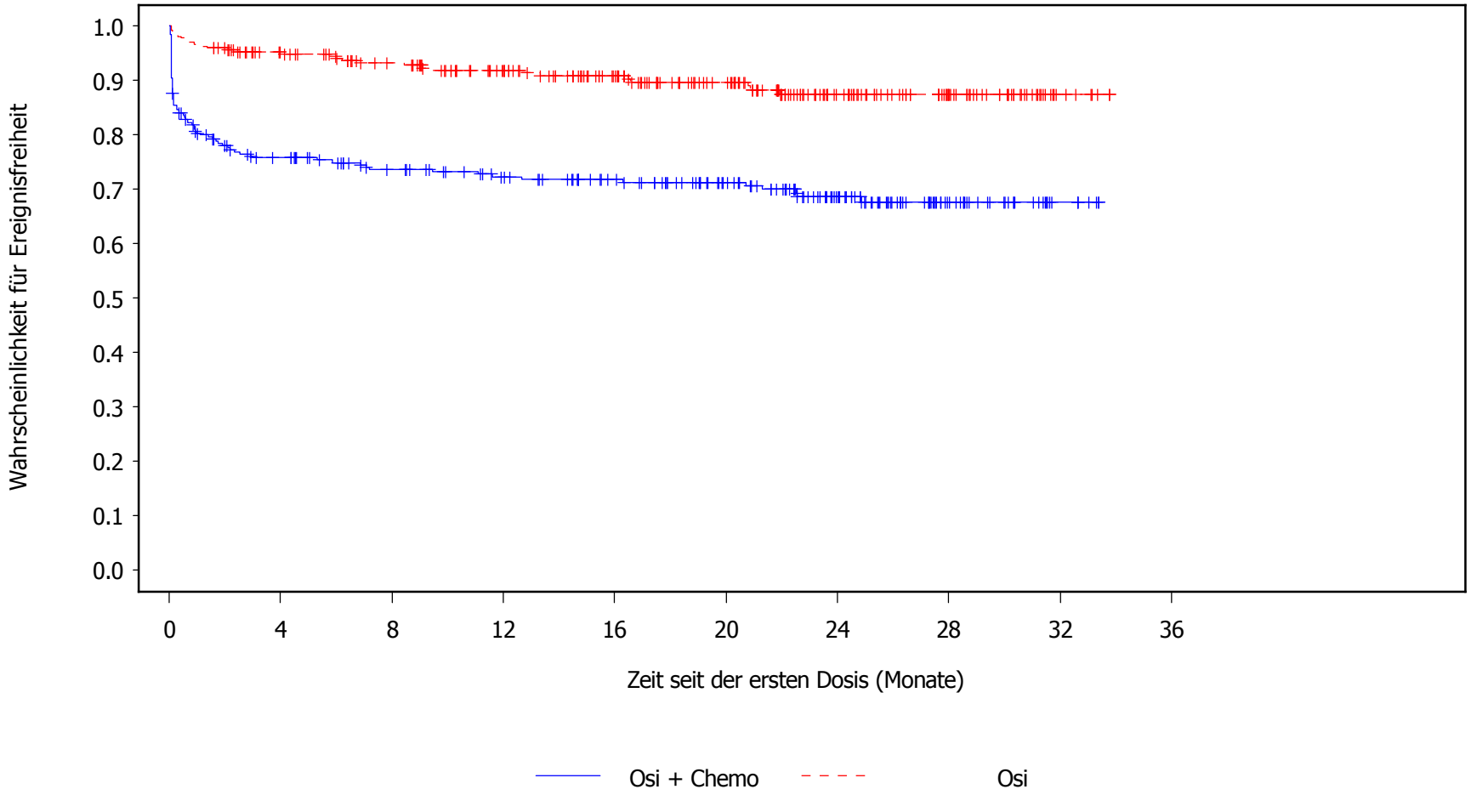
Anzahl an Patienten unter Risiko:

276	243	221	202	181	153	98	41	9	0	Osi + Chemo
275	245	223	197	164	130	78	44	7	0	Osi

root/cdar/d516/payer_germany/ar/d5169c00001_payer_germany/tlf/prod/program/ttemainae.sas gttemainaebbu 24OCT2023:11:33 kvbv306

Nutzenbewertung nach AMNOG Seite 1 von 1

Figure 3.3.48 FLAURA-2: Kaplan-Meier plot of time to first occurrence of PT: Obstipation
Safety Analysis Set, DCO 03APR2023



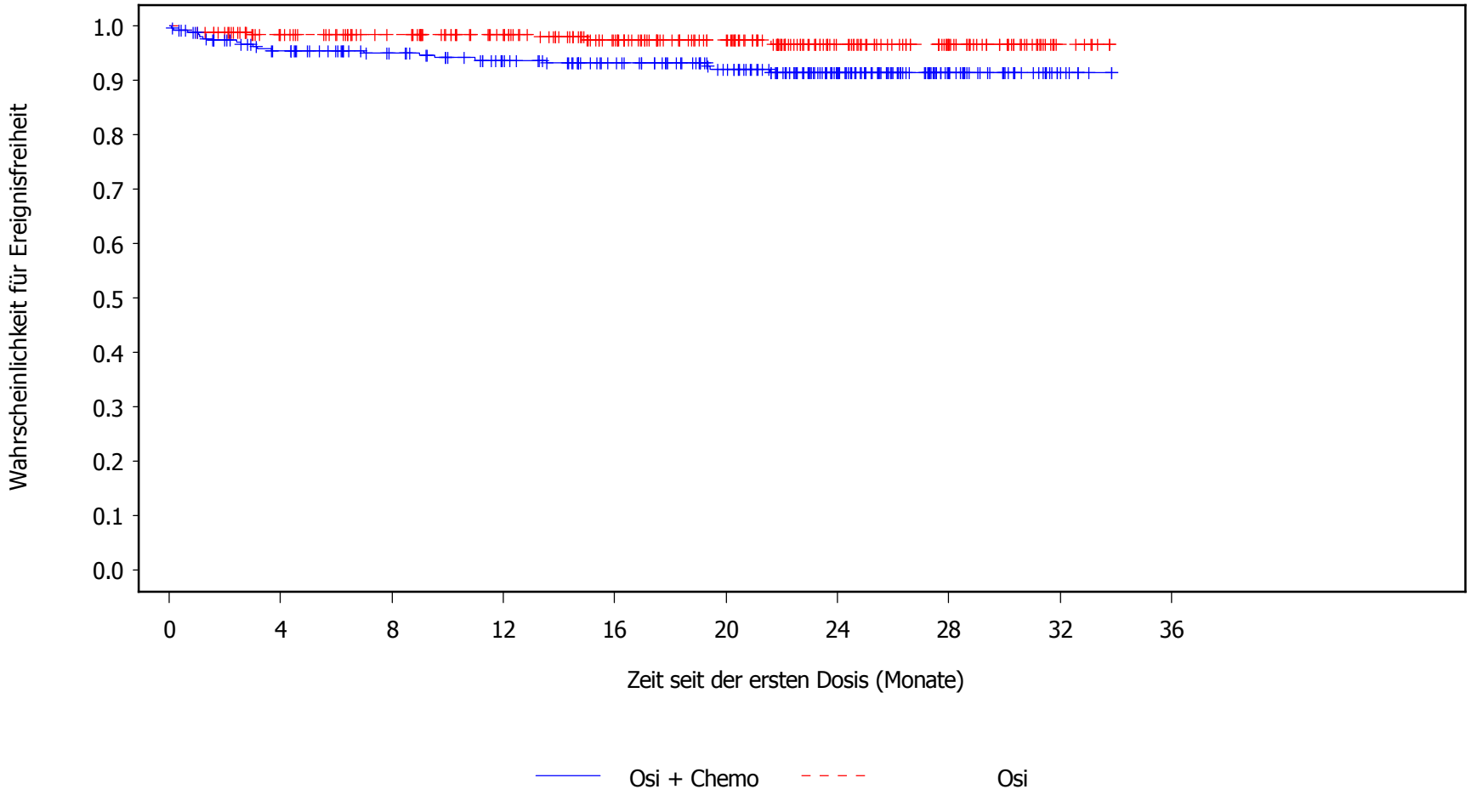
Anzahl an Patienten unter Risiko:

276	193	172	157	140	116	77	31	6	0	Osi + Chemo
275	244	221	193	162	128	76	41	6	0	Osi

root/cdar/d516/payer_germany/ar/d5169c00001_payer_germany/tlf/prod/program/ttemainae.sas gttemainaebbv 24OCT2023:11:33 kvbv306

Nutzenbewertung nach AMNOG Seite 1 von 1

Figure 3.3.49 FLAURA-2: Kaplan-Meier plot of time to first occurrence of PT: Schmerzen Oberbauch
Safety Analysis Set, DCO 03APR2023



Anzahl an Patienten unter Risiko:

276	244	222	203	181	154	101	40	8	0	Osi + Chemo
275	249	228	203	167	133	77	43	6	0	Osi

root/cdar/d516/payer_germany/ar/d5169c00001_payer_germany/tlf/prod/program/ttemainae.sas gttemainaebbw 24OCT2023:11:33 kvbv306

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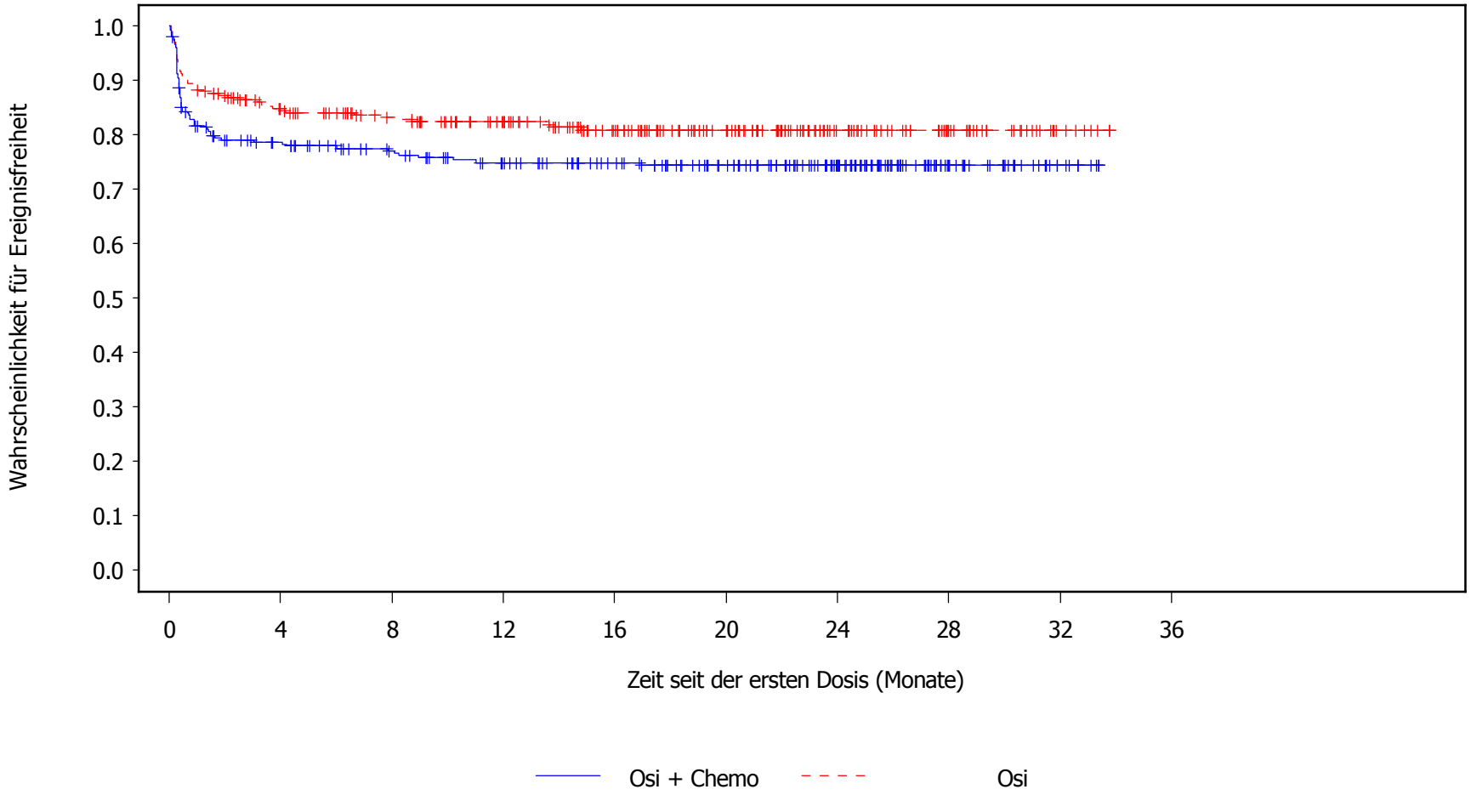
Figure 3.3.50 FLAURA-2: Kaplan-Meier plot of time to first occurrence of PT: Stomatitis
Safety Analysis Set, DCO 03APR2023



Anzahl an Patienten unter Risiko:

276	201	180	163	144	122	86	31	8	0	Osi + Chemo
275	215	192	168	137	105	60	30	6	0	Osi

root/cdar/d516/payer_germany/ar/d5169c00001_payer_germany/tlf/prod/program/ttemainae.sas gttemainaebbx 24OCT2023:11:33 kvbv306

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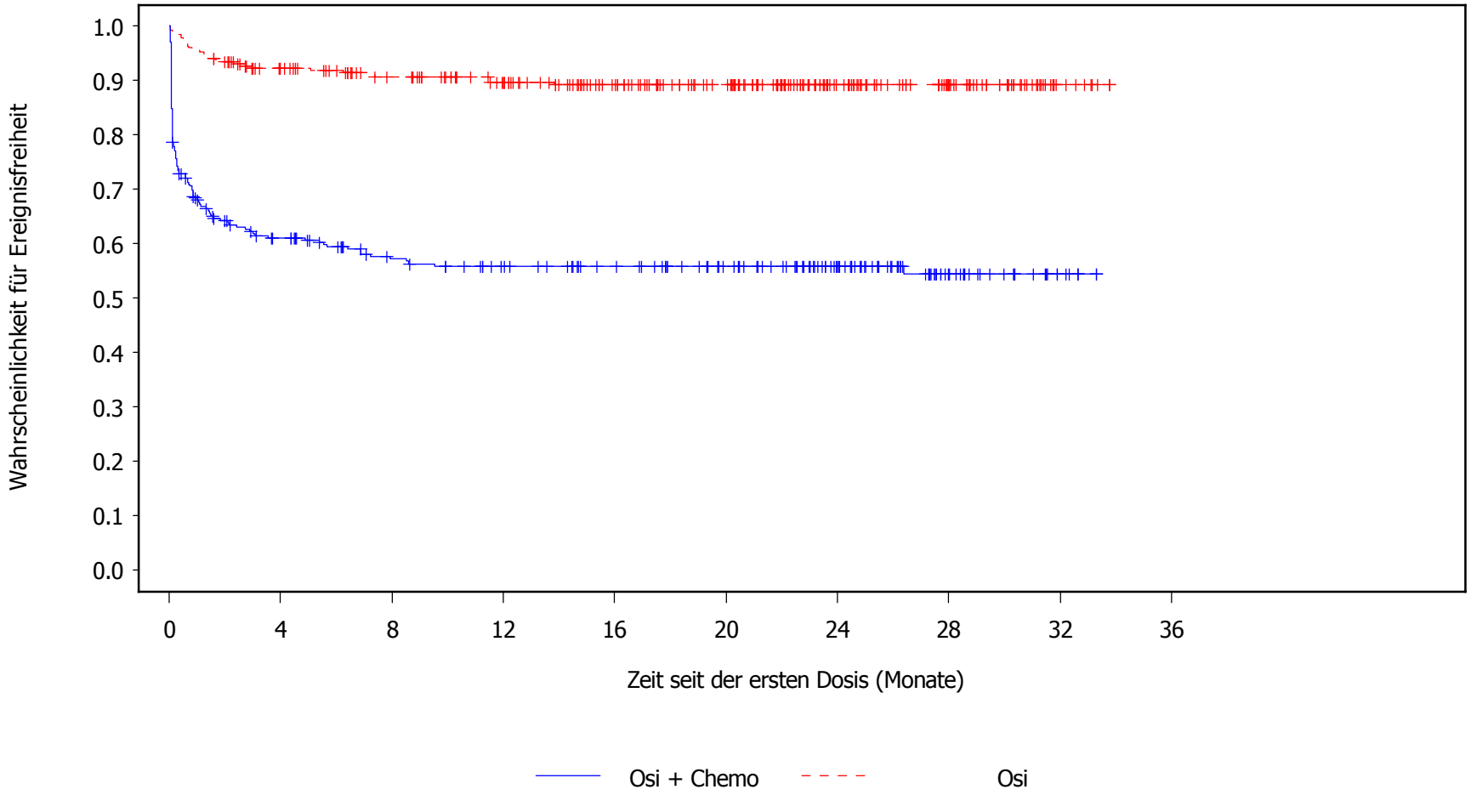
Figure 3.3.51 FLAURA-2: Kaplan-Meier plot of time to first occurrence of PT: Uebelkeit
Safety Analysis Set, DCO 03APR2023



Anzahl an Patienten unter Risiko:

276	153	129	117	106	91	63	26	6	0	Osi + Chemo
275	235	212	189	159	131	78	44	7	0	Osi

root/cdar/d516/payer_germany/ar/d5169c00001_payer_germany/tlf/prod/program/ttemainae.sas gttemainaebby 24OCT2023:11:33 kvbv306

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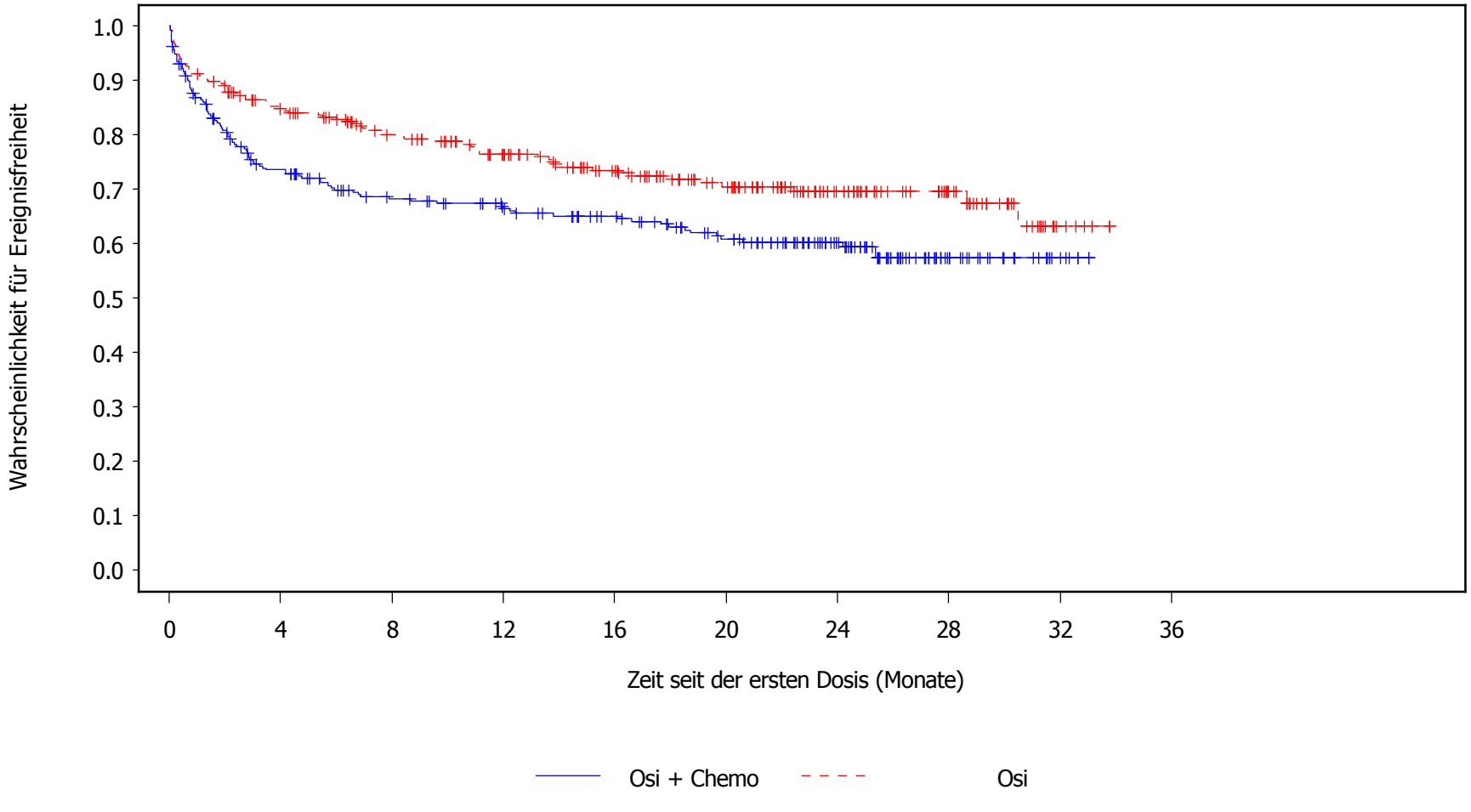
Figure 3.3.52 FLAURA-2: Kaplan-Meier plot of time to first occurrence of SOC: Erkrankungen des Nervensystems
Safety Analysis Set, DCO 03APR2023



Anzahl an Patienten unter Risiko:

276	189	161	146	130	109	75	26	6	0	Osi + Chemo
275	220	190	165	138	107	64	34	5	0	Osi

root/cdar/d516/payer_germany/ar/d5169c00001_payer_germany/tlf/prod/program/ttemainae.sas gttemainaebbz 24OCT2023:11:33 kvbv306

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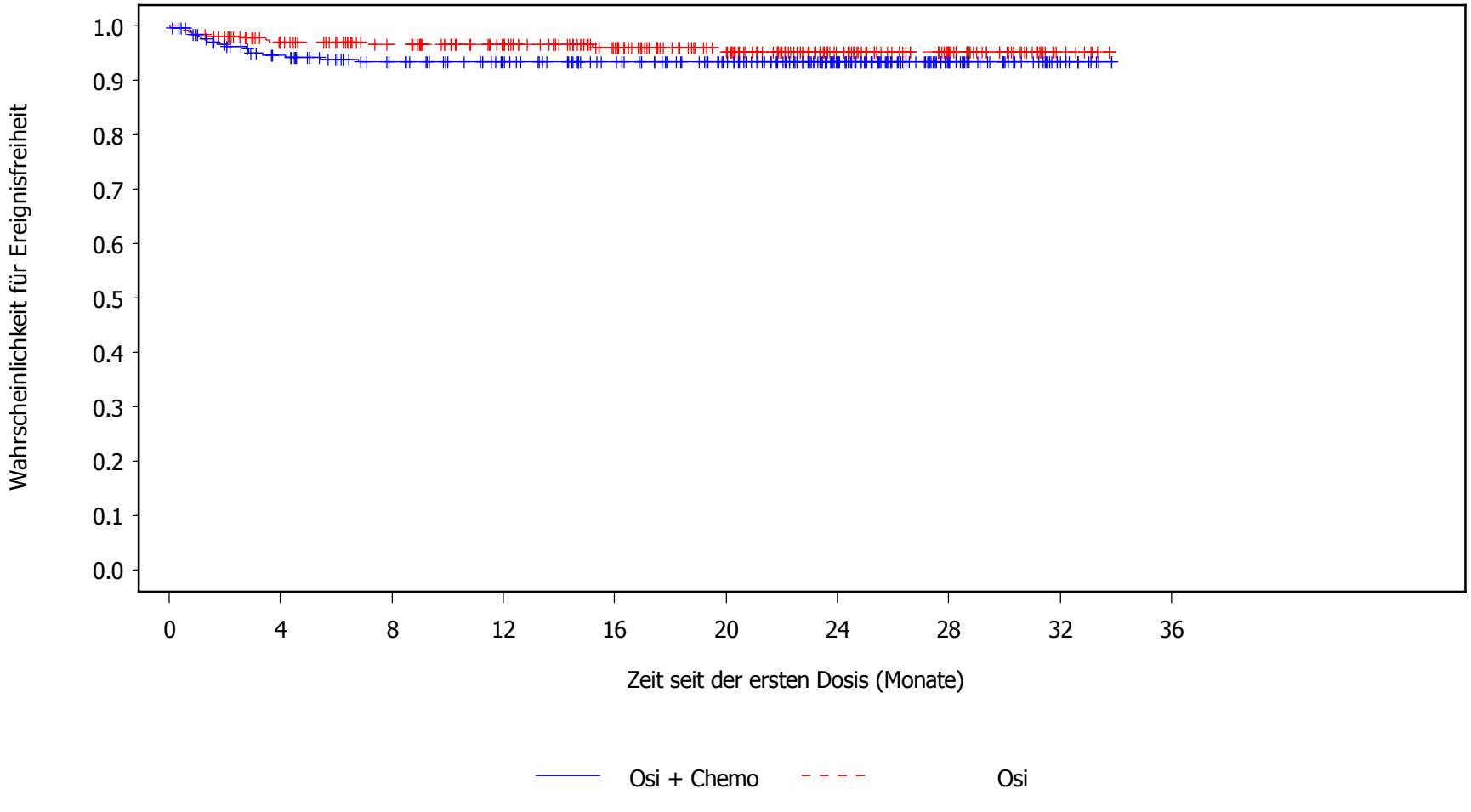
Figure 3.3.53 FLAURA-2: Kaplan-Meier plot of time to first occurrence of PT: Dysgeusie
Safety Analysis Set, DCO 03APR2023



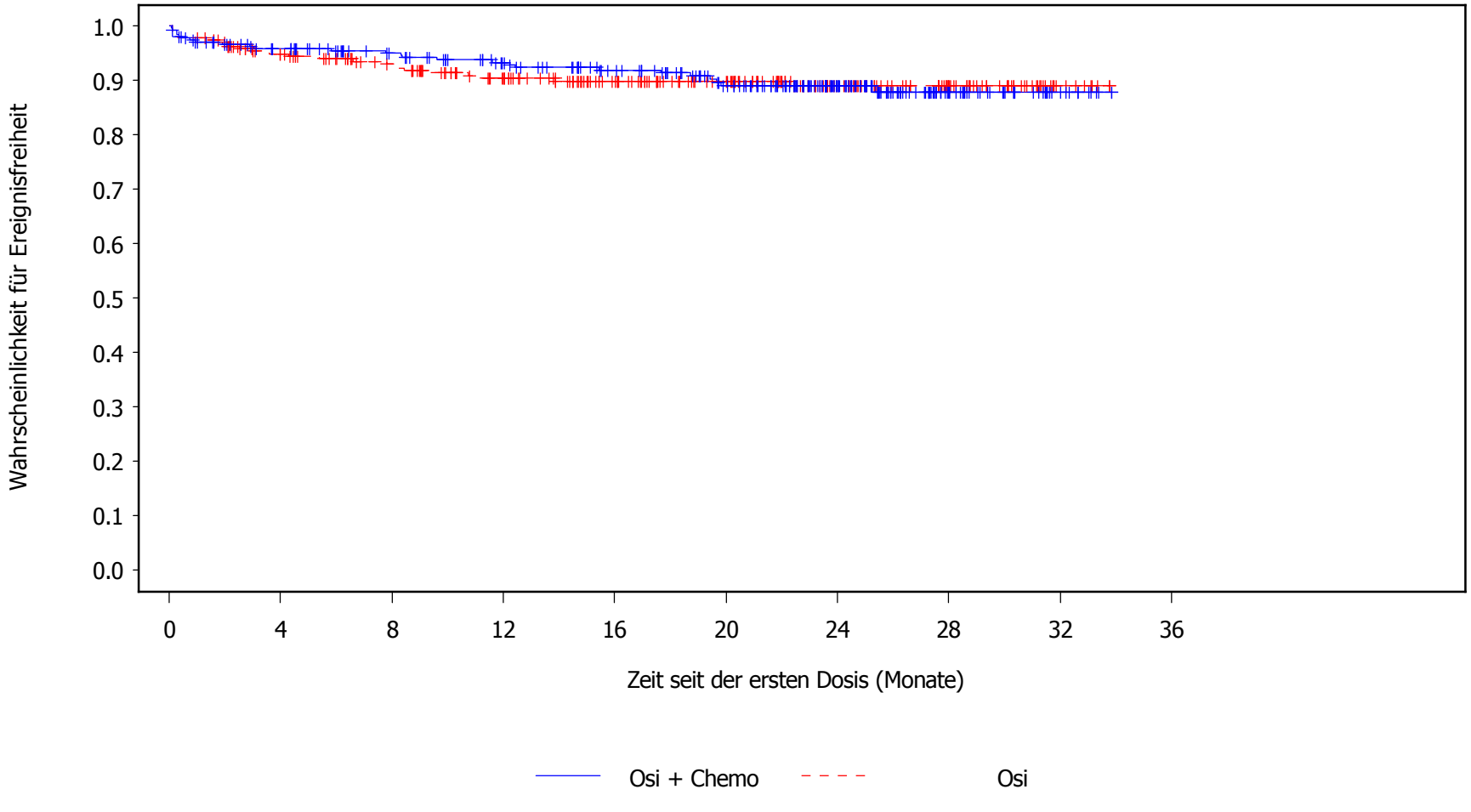
Anzahl an Patienten unter Risiko:

276	242	219	202	182	159	107	44	11	0	Osi + Chemo
275	247	225	199	166	131	78	43	7	0	Osi

root/cdar/d516/payer_germany/ar/d5169c00001_payer_germany/tlf/prod/program/ttemainae.sas gttemainaebca 24OCT2023:11:33 kvbv306

Nutzenbewertung nach AMNOG Seite 1 von 1

Figure 3.3.54 FLAURA-2: Kaplan-Meier plot of time to first occurrence of PT: Kopfschmerzen
Safety Analysis Set, DCO 03APR2023



Anzahl an Patienten unter Risiko:

276	245	223	203	181	152	99	38	11	0	Osi + Chemo
275	242	218	189	155	126	76	42	7	0	Osi

root/cdar/d516/payer_germany/ar/d5169c00001_payer_germany/tlf/prod/program/ttemainae.sas gttemainaebcb 24OCT2023:11:33 kvbv306

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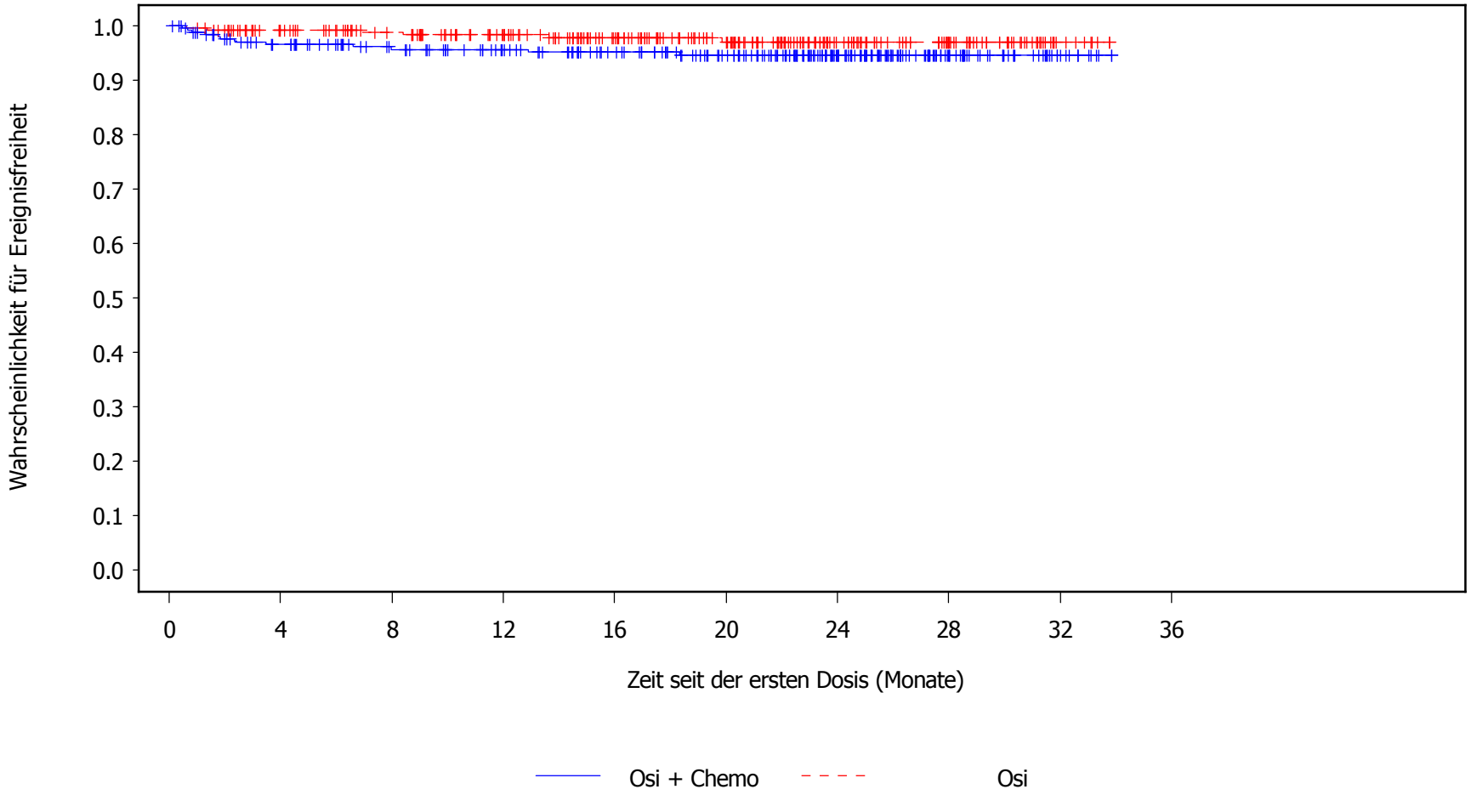
Figure 3.3.55 FLAURA-2: Kaplan-Meier plot of time to first occurrence of PT: Periphere Neuropathie
Safety Analysis Set, DCO 03APR2023



Anzahl an Patienten unter Risiko:

276	247	225	207	185	158	105	43	11	0	Osi + Chemo
275	251	229	202	166	131	77	43	7	0	Osi

root/cdar/d516/payer_germany/ar/d5169c00001_payer_germany/tlf/prod/program/ttemainae.sas gttemainaebcc 24OCT2023:11:33 kvbv306

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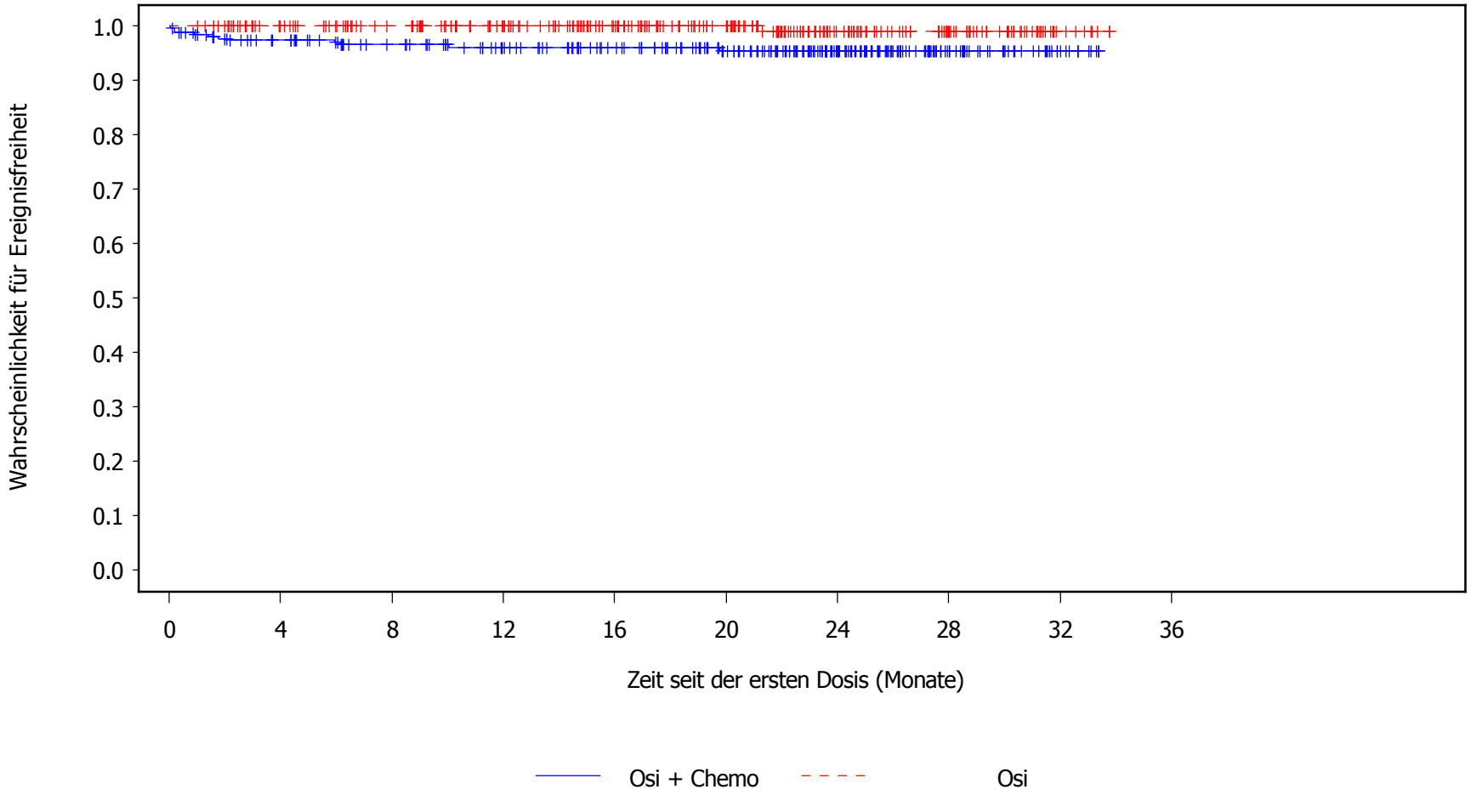
Figure 3.3.56 FLAURA-2: Kaplan-Meier plot of time to first occurrence of PT: Periphere sensorische Neuropathie
Safety Analysis Set, DCO 03APR2023



Anzahl an Patienten unter Risiko:

276	249	228	209	187	158	104	41	10	0	Osi + Chemo
275	253	232	206	171	136	79	43	7	0	Osi

root/cdar/d516/payer_germany/ar/d5169c00001_payer_germany/tlf/prod/program/ttemainae.sas gttemainaebcd 24OCT2023:11:33 kvbv306

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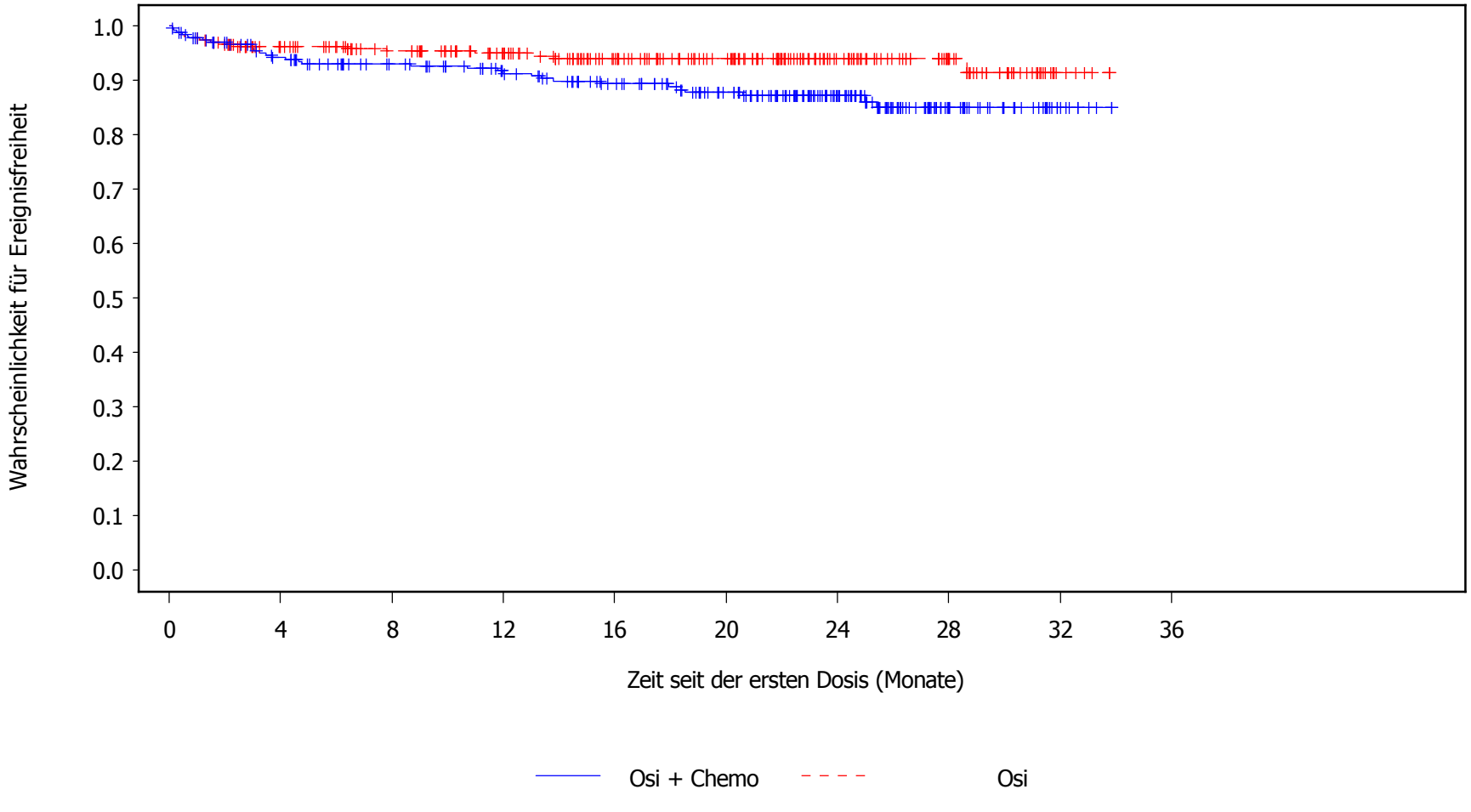
Figure 3.3.57 FLAURA-2: Kaplan-Meier plot of time to first occurrence of PT: Schwindelgefuehl
Safety Analysis Set, DCO 03APR2023

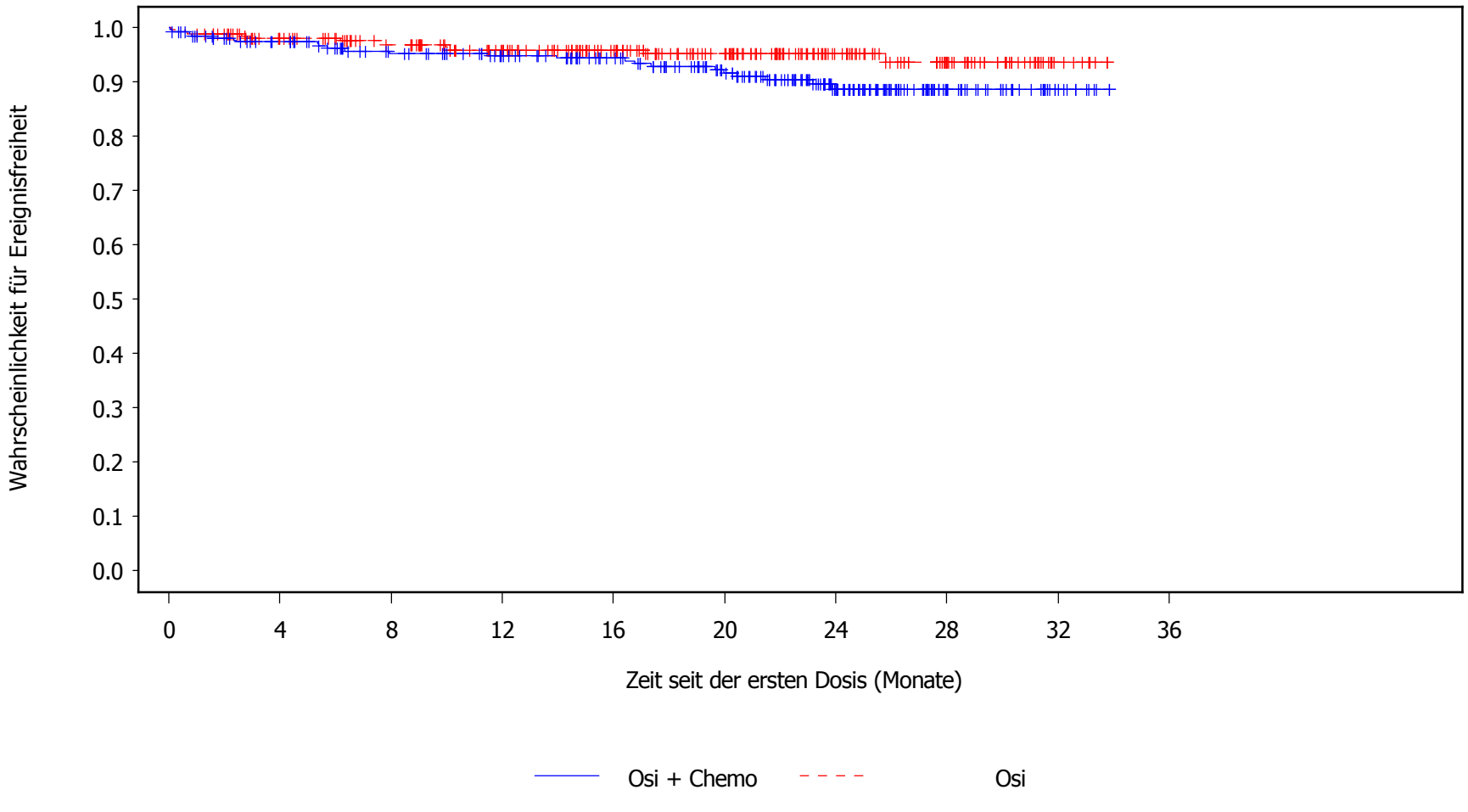


Anzahl an Patienten unter Risiko:

276	241	218	198	176	148	97	37	8	0	Osi + Chemo
275	243	220	196	160	130	76	40	5	0	Osi

root/cdar/d516/payer_germany/ar/d5169c00001_payer_germany/tlf/prod/program/ttemainae.sas gttemainaebce 24OCT2023:11:33 kvbv306

Figure 3.3.58 FLAURA-2: Kaplan-Meier plot of time to first occurrence of SOC: Erkrankungen des Ohrs und des Labyrinths
Safety Analysis Set, DCO 03APR2023



Anzahl an Patienten unter Risiko:

276	249	224	207	185	154	98	38	10	0	Osi + Chemo
275	248	224	197	163	130	78	42	7	0	Osi

root/cdar/d516/payer_germany/ar/d5169c00001_payer_germany/tlf/prod/program/ttemainae.sas gttemainaebcf 24OCT2023:11:33 kvbv306

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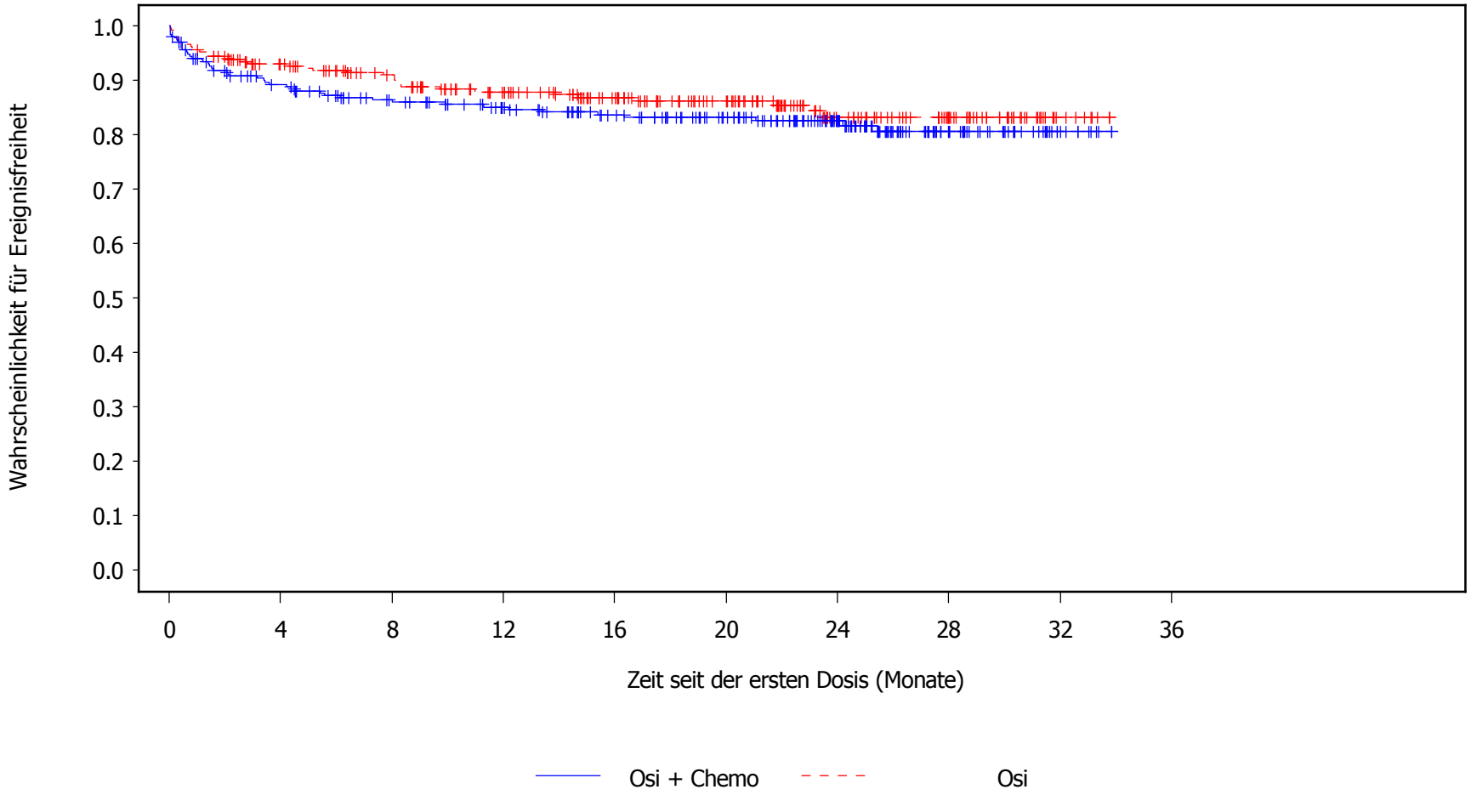
Figure 3.3.59 FLAURA-2: Kaplan-Meier plot of time to first occurrence of SOC: Gefaesserkrankungen
Safety Analysis Set, DCO 03APR2023

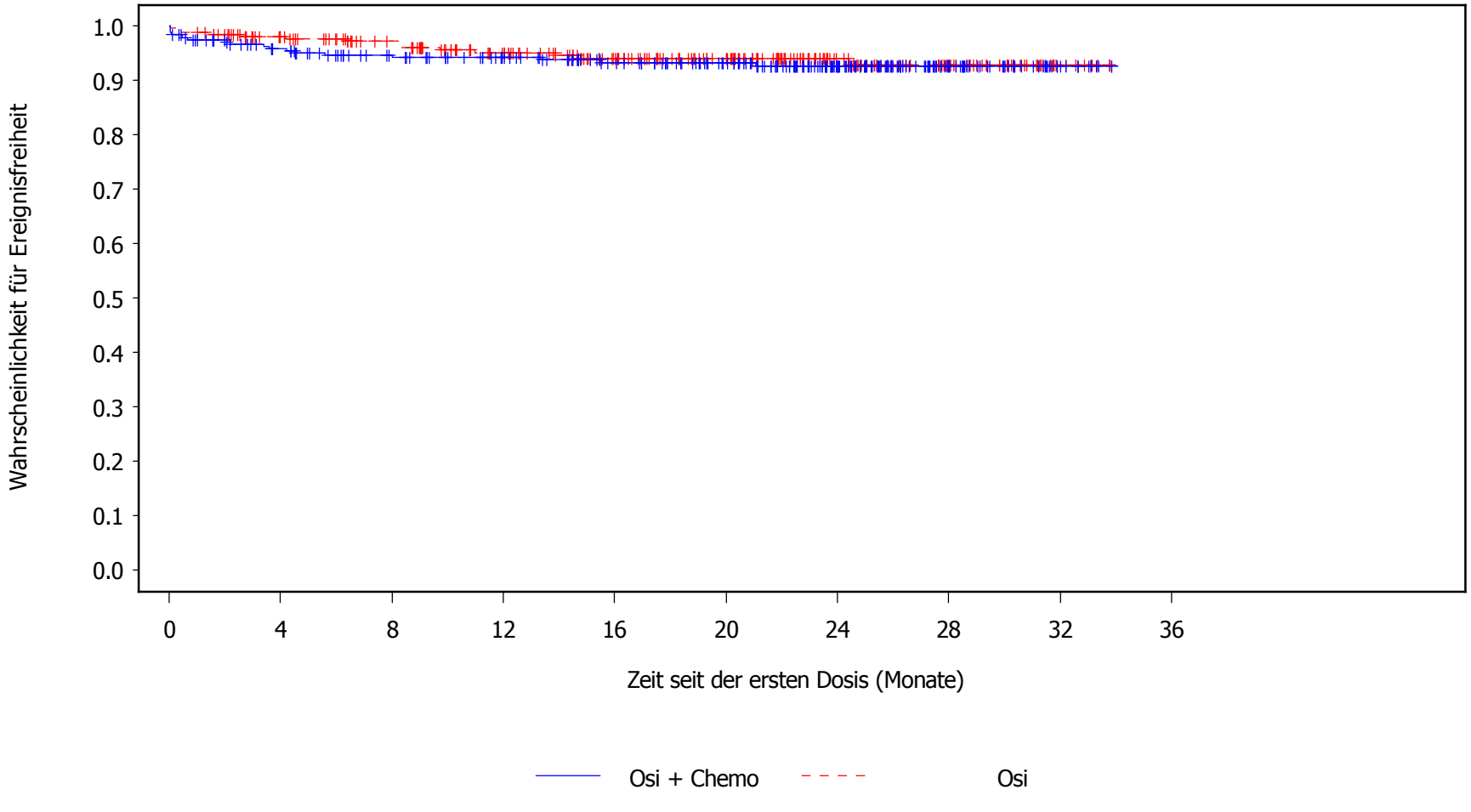


Anzahl an Patienten unter Risiko:

276	230	206	188	165	141	98	40	9	0	Osi + Chemo
275	236	212	183	153	121	70	42	7	0	Osi

root/cdar/d516/payer_germany/ar/d5169c00001_payer_germany/tlf/prod/program/ttemainae.sas gttemainaebcg 24OCT2023:11:33 kvbv306

Figure 3.3.60 FLAURA-2: Kaplan-Meier plot of time to first occurrence of PT: Hypertonie
Safety Analysis Set, DCO 03APR2023



Anzahl an Patienten unter Risiko:

276	245	222	204	180	156	104	43	10	0	Osi + Chemo
275	248	225	196	163	129	76	43	7	0	Osi

root/cdar/d516/payer_germany/ar/d5169c00001_payer_germany/tlf/prod/program/ttemainae.sas gttemainaebch 24OCT2023:11:33 kvbv306

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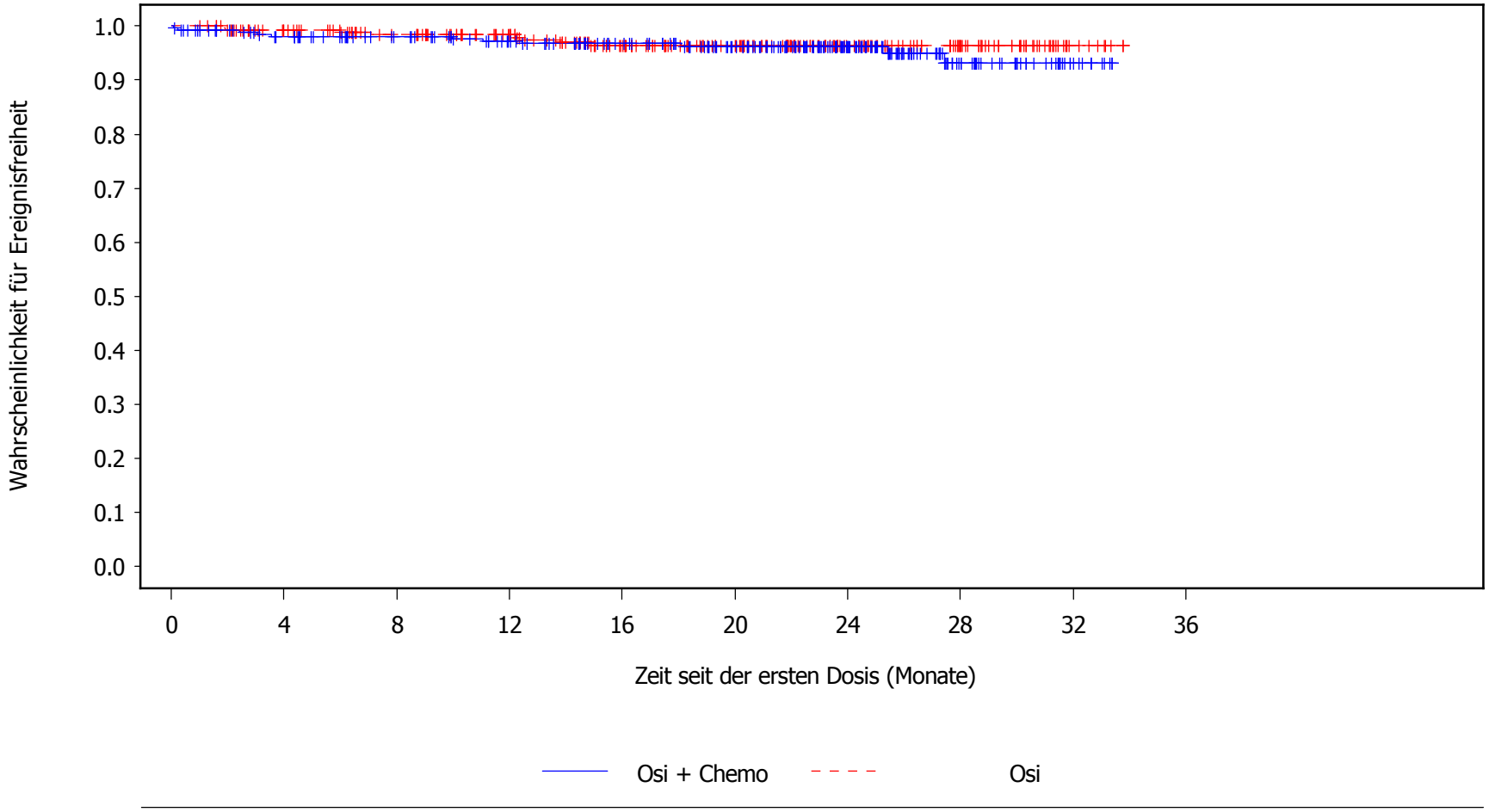
Figure 3.3.61 FLAURA-2: Kaplan-Meier plot of time to first occurrence of SOC: Gutartige, boesartige und nicht spezifizierte Neubildungen (einschl. Zysten und Polypen)
Safety Analysis Set, DCO 03APR2023

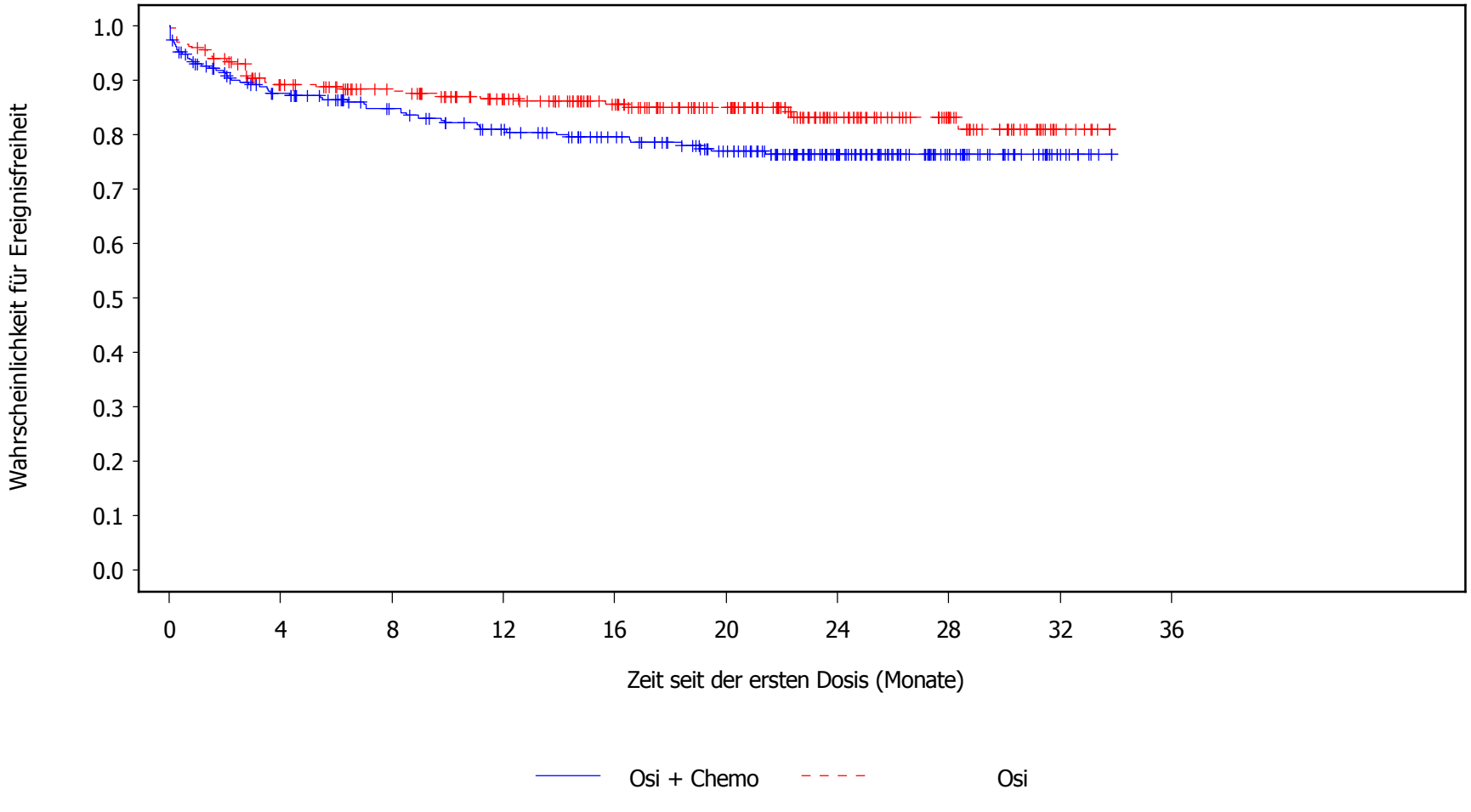


Anzahl an Patienten unter Risiko:

276	252	232	212	189	161	105	41	10	0	Osi + Chemo
275	252	229	204	168	136	80	44	7	0	Osi

root/cdar/d516/payer_germany/ar/d5169c00001_payer_germany/tlf/prod/program/ttemainae.sas gttemainaebci 24OCT2023:11:33 kvbv306

Figure 3.3.62 FLAURA-2: Kaplan-Meier plot of time to first occurrence of SOC: Herzerkrankungen
Safety Analysis Set, DCO 03APR2023



Anzahl an Patienten unter Risiko:

276	225	200	181	162	137	88	43	10	0	Osi + Chemo
275	229	208	182	153	120	72	41	7	0	Osi

root/cdar/d516/payer_germany/ar/d5169c00001_payer_germany/tlf/prod/program/ttemainae.sas gttemainaebcj 24OCT2023:11:33 kvbv306

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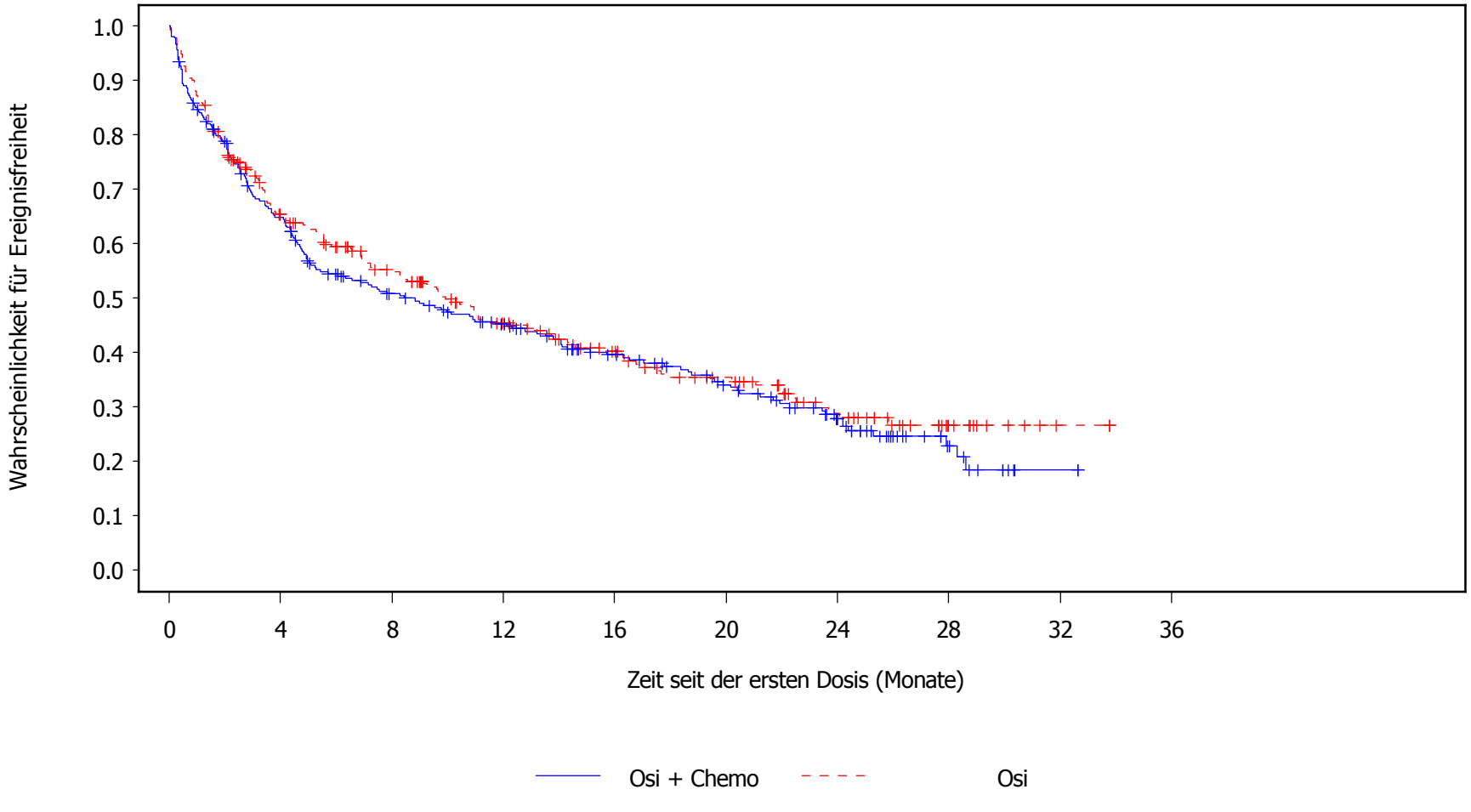
Figure 3.3.63 FLAURA-2: Kaplan-Meier plot of time to first occurrence of SOC: Infektionen und parasitaere Erkrankungen
Safety Analysis Set, DCO 03APR2023



Anzahl an Patienten unter Risiko:

276	171	122	101	77	59	37	12	1	0	Osi + Chemo
275	166	126	93	70	53	31	11	1	0	Osi

root/cdar/d516/payer_germany/ar/d5169c00001_payer_germany/tlf/prod/program/ttemainae.sas gttemainaebck 24OCT2023:11:33 kvbv306

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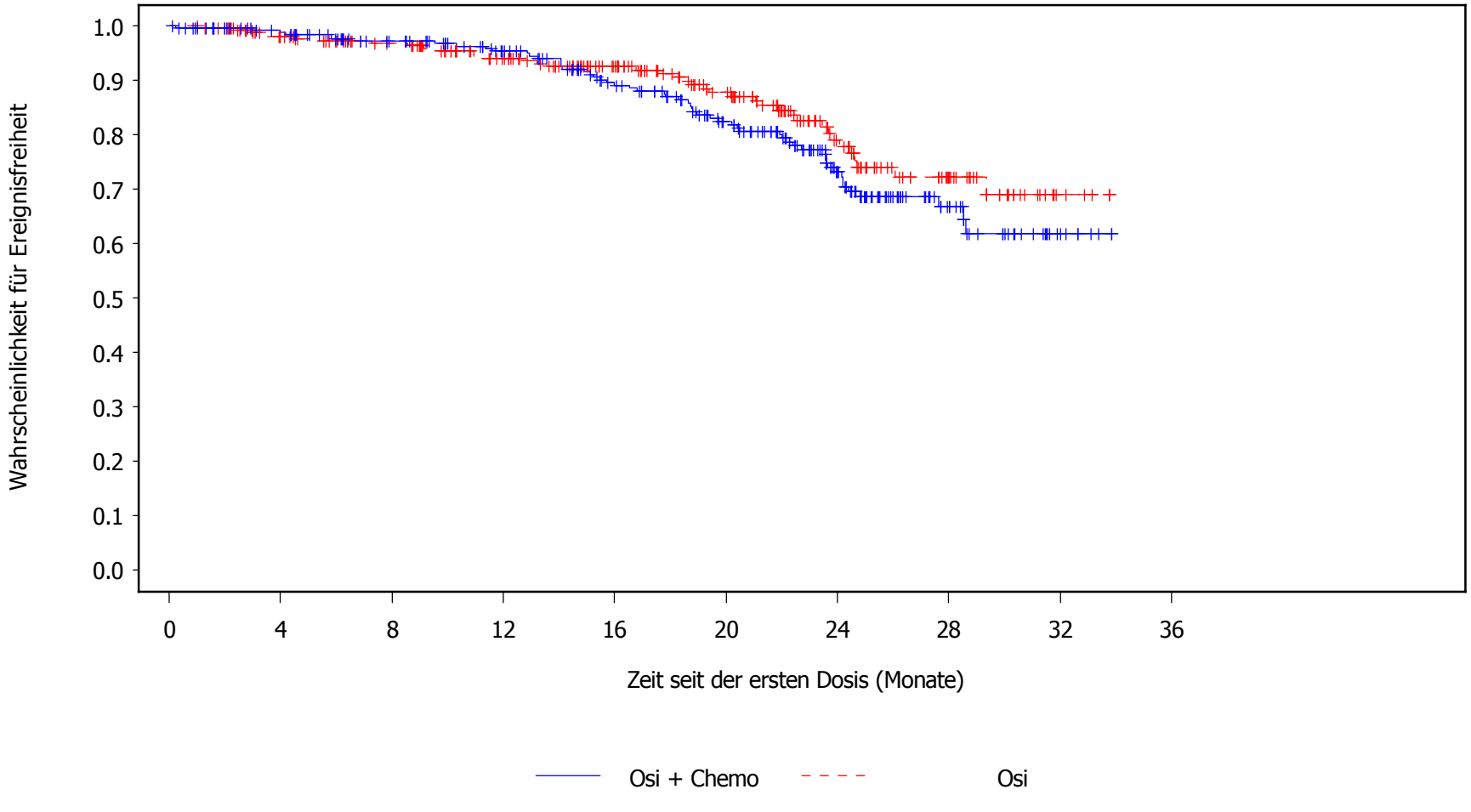
Figure 3.3.64 FLAURA-2: Kaplan-Meier plot of time to first occurrence of PT: COVID-19
Safety Analysis Set, DCO 03APR2023



Anzahl an Patienten unter Risiko:

276	256	230	208	175	139	83	33	7	0	Osi + Chemo
275	248	225	195	158	119	66	31	4	0	Osi

root/cdar/d516/payer_germany/ar/d5169c00001_payer_germany/tlf/prod/program/ttemainae.sas gttemainaebcl 24OCT2023:11:33 kvbv306

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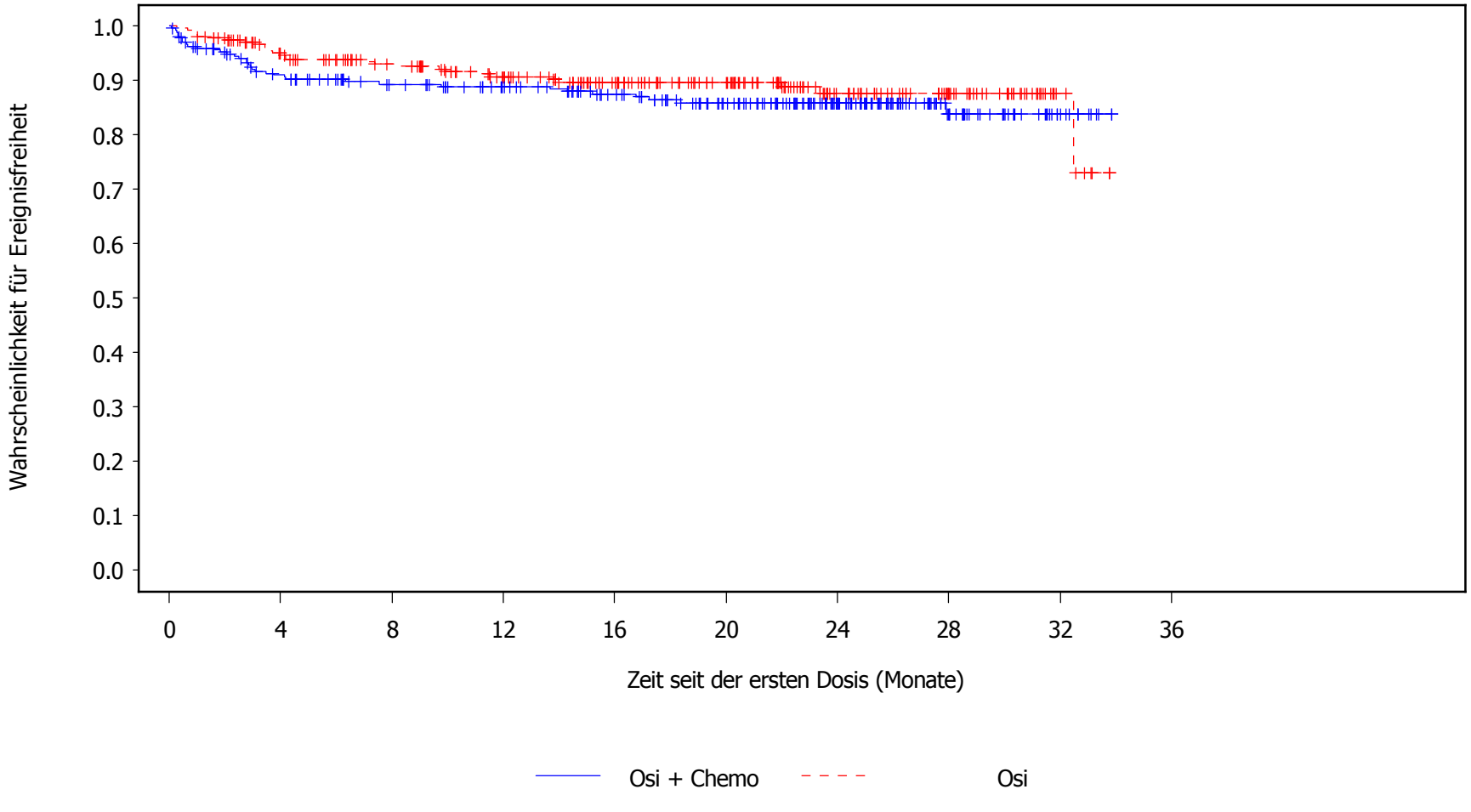
Figure 3.3.65 FLAURA-2: Kaplan-Meier plot of time to first occurrence of PT: Harnwegsinfektion
Safety Analysis Set, DCO 03APR2023

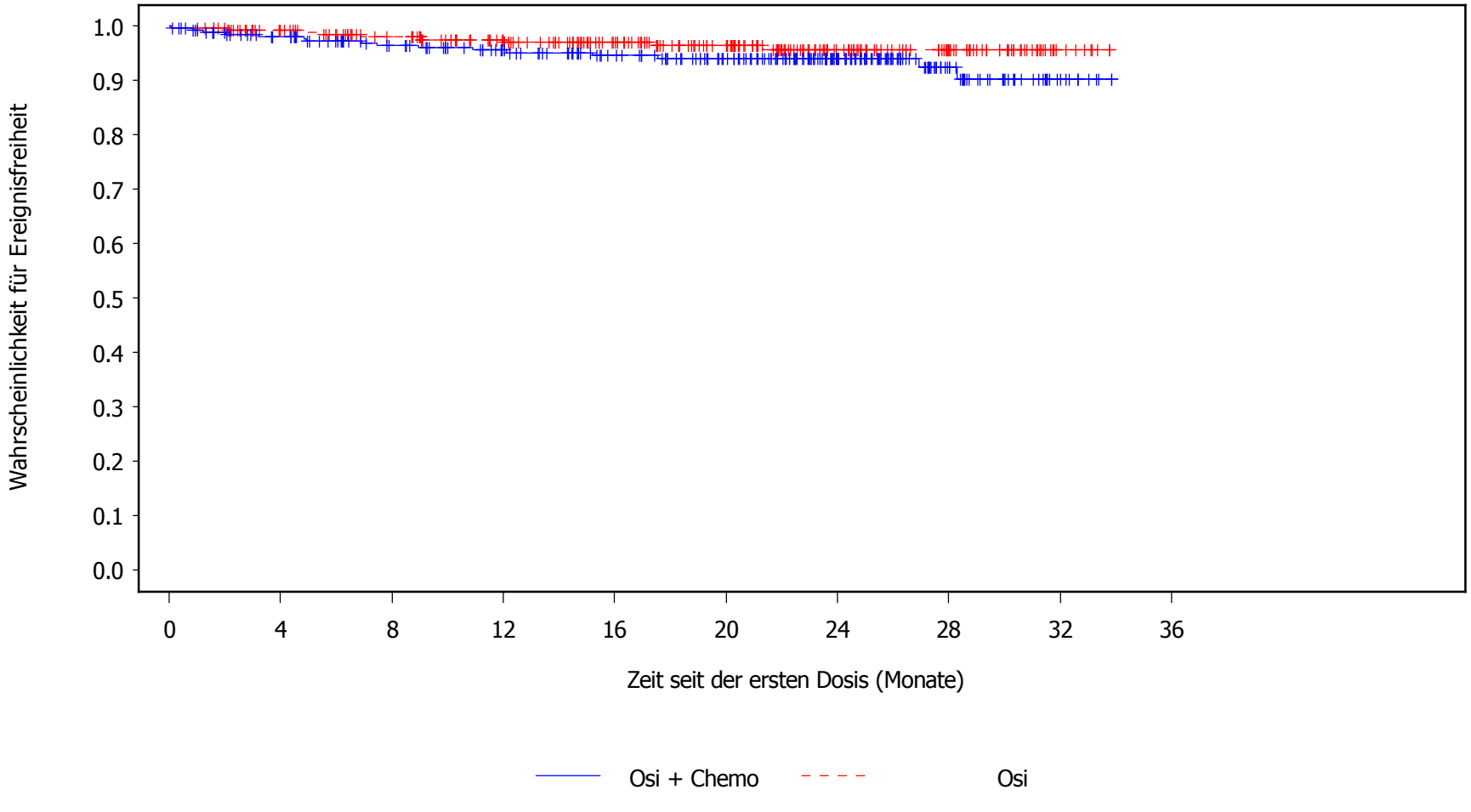


Anzahl an Patienten unter Risiko:

276	233	211	195	173	145	99	41	11	0	Osi + Chemo
275	240	214	186	153	123	72	41	7	0	Osi

root/cdar/d516/payer_germany/ar/d5169c00001_payer_germany/tlf/prod/program/ttemainae.sas gttemainaebcm 24OCT2023:11:33 kvbv306

Figure 3.3.66 FLAURA-2: Kaplan-Meier plot of time to first occurrence of PT: Infektion der oberen Atemwege
Safety Analysis Set, DCO 03APR2023



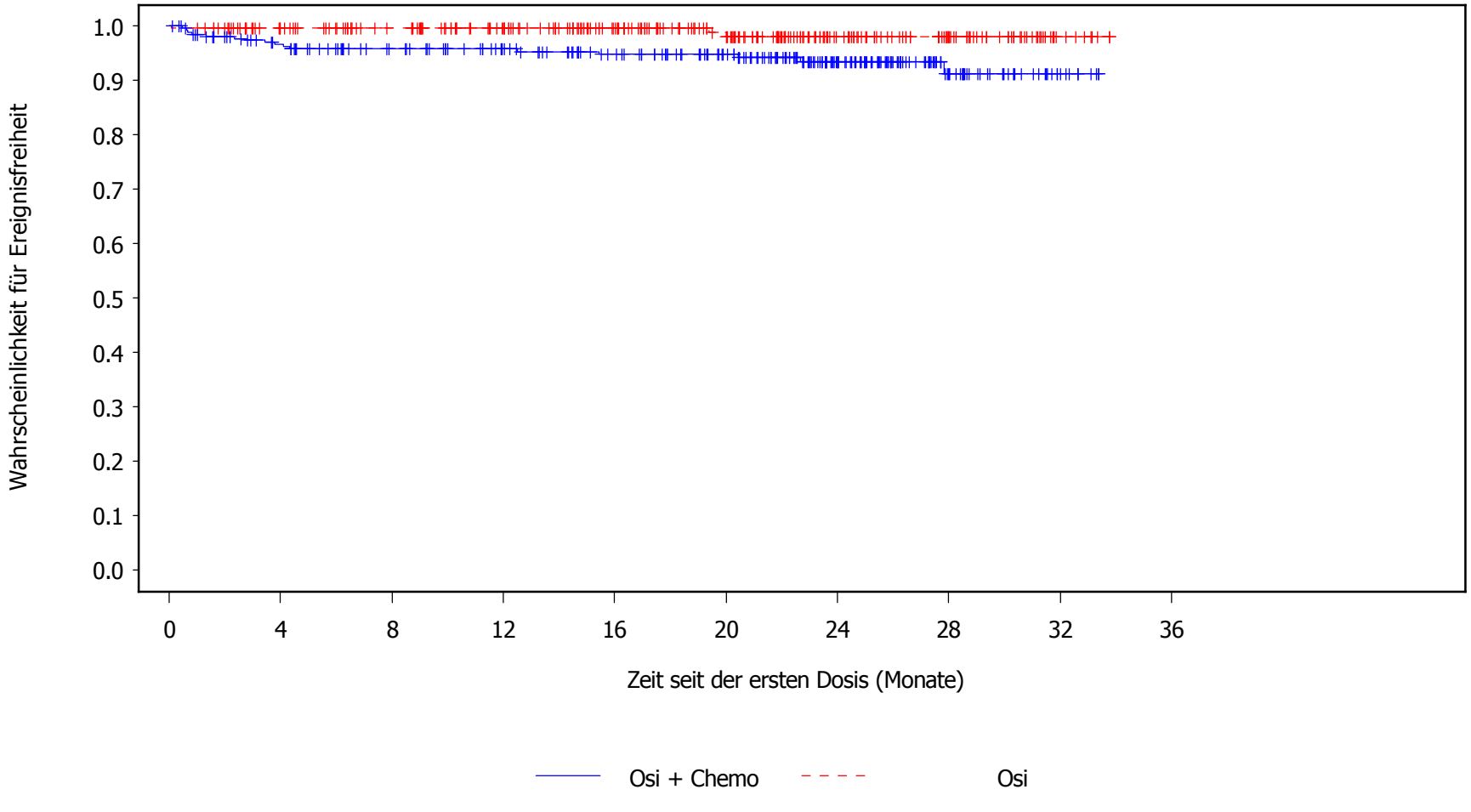
Anzahl an Patienten unter Risiko:

276	251	226	206	182	156	103	43	10	0	Osi + Chemo
275	251	227	201	166	131	78	44	7	0	Osi

root/cdar/d516/payer_germany/ar/d5169c00001_payer_germany/tlf/prod/program/ttemainae.sas gttemainaebcn 24OCT2023:11:33 kvbv306

Nutzenbewertung nach AMNOG Seite 1 von 1

Figure 3.3.67 FLAURA-2: Kaplan-Meier plot of time to first occurrence of PT: Konjunktivitis
Safety Analysis Set, DCO 03APR2023



Anzahl an Patienten unter Risiko:

276	247	224	206	184	159	102	40	9	0	Osi + Chemo
275	252	231	205	170	134	77	42	7	0	Osi

root/cdar/d516/payer_germany/ar/d5169c00001_payer_germany/tlf/prod/program/ttemainae.sas gttemainaebco 24OCT2023:11:33 kvbv306

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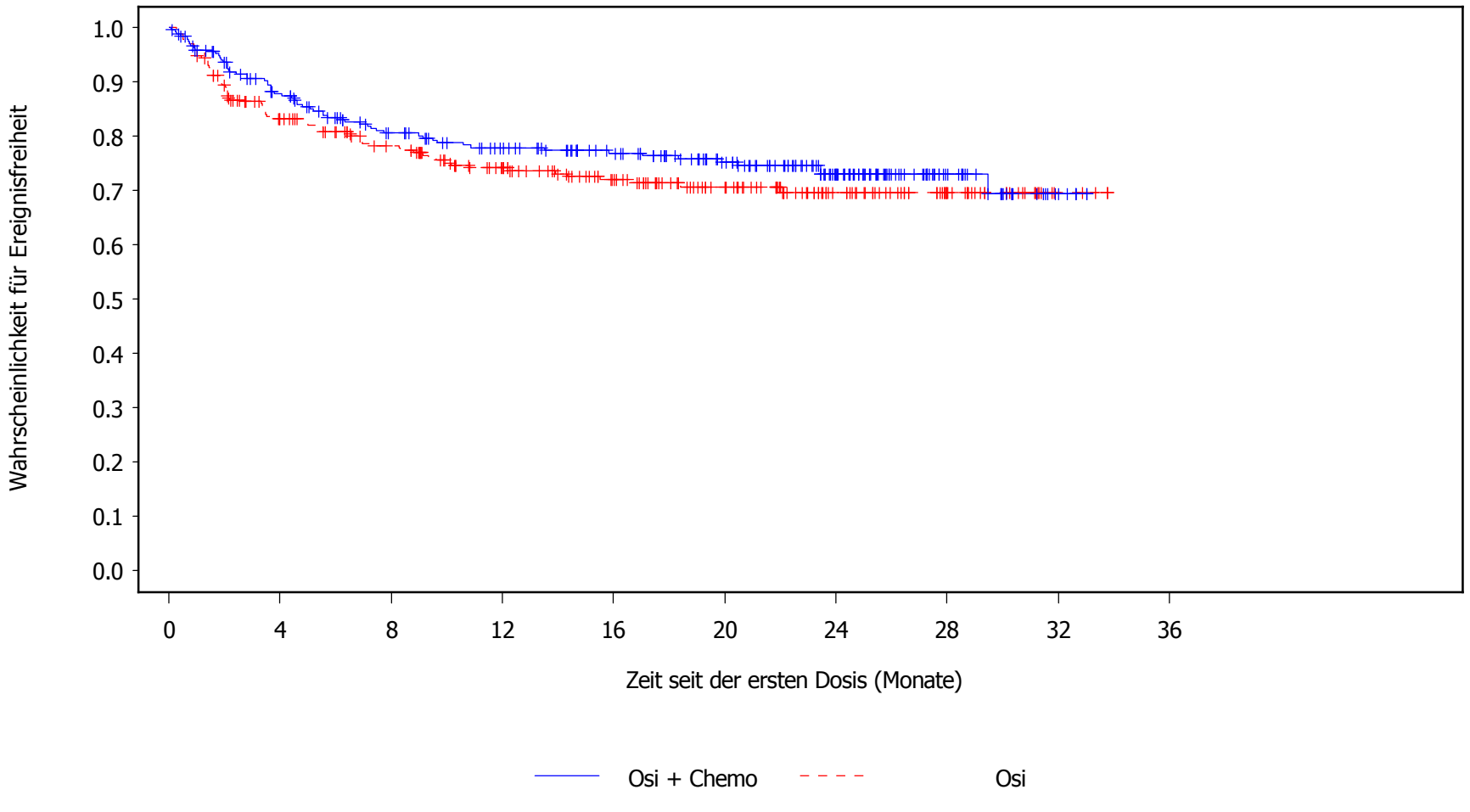
Figure 3.3.68 FLAURA-2: Kaplan-Meier plot of time to first occurrence of PT: Paronychie
Safety Analysis Set, DCO 03APR2023



Anzahl an Patienten unter Risiko:

276	224	189	170	149	122	80	29	6	0	Osi + Chemo
275	210	181	149	121	92	56	27	3	0	Osi

root/cdar/d516/payer_germany/ar/d5169c00001_payer_germany/tlf/prod/program/ttemainae.sas gttemainaebcp 24OCT2023:11:33 kvbv306

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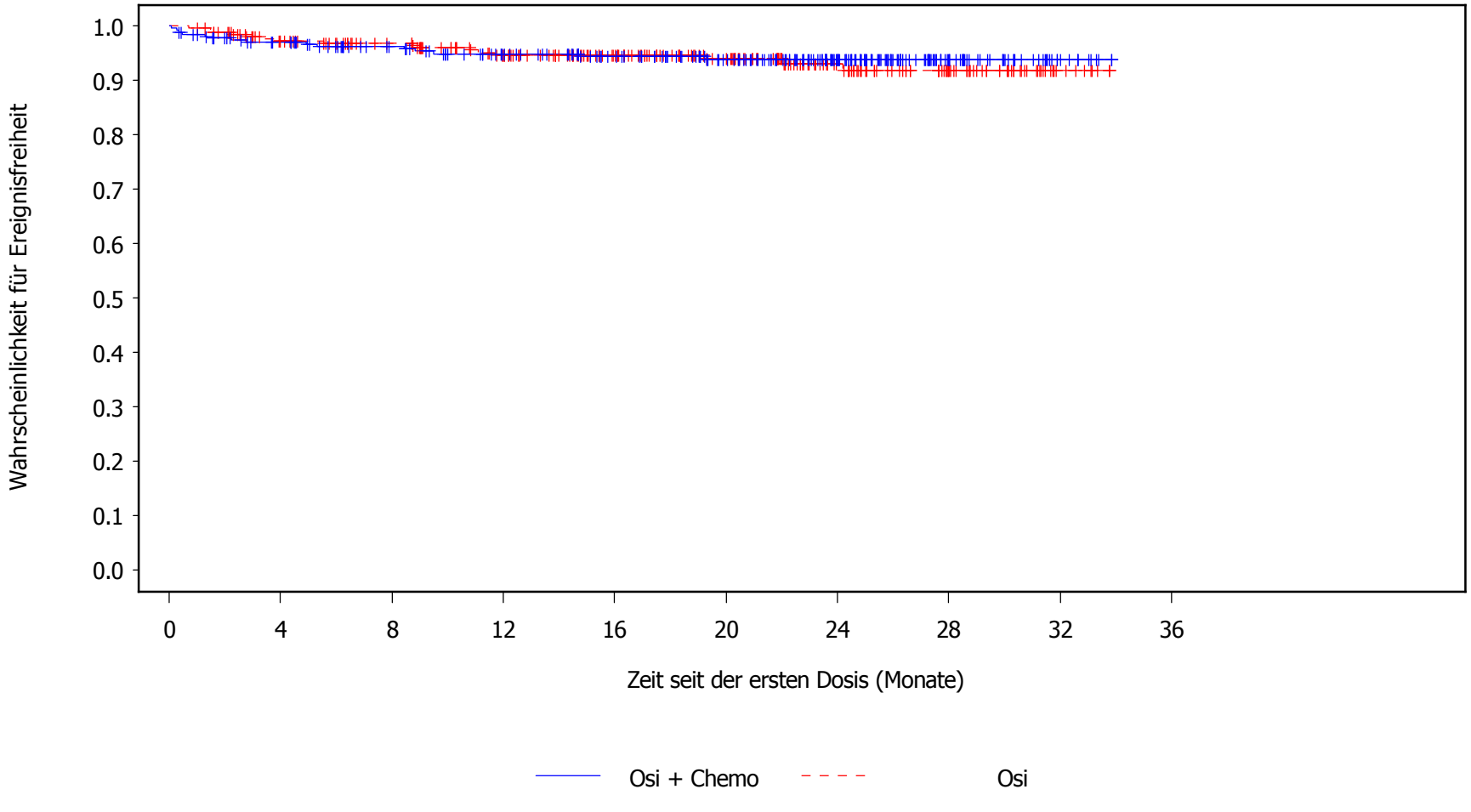
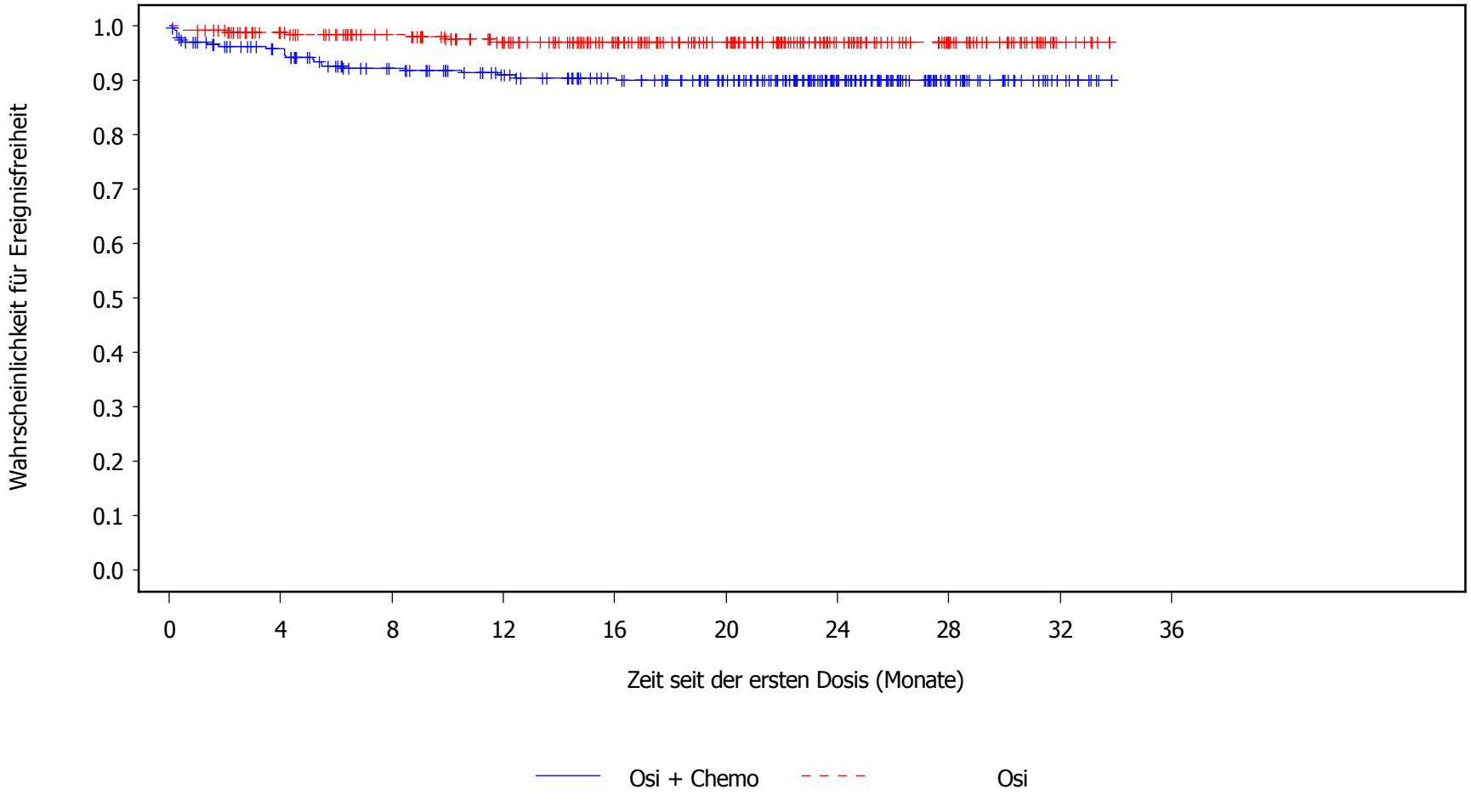
Figure 3.3.69 FLAURA-2: Kaplan-Meier plot of time to first occurrence of PT: Pneumonie
Safety Analysis Set, DCO 03APR2023



root/cdar/d516/payer_germany/ar/d5169c00001_payer_germany/tlf/prod/program/ttemainae.sas gttemainaebcq 24OCT2023:11:33 kvbv306

Figure 3.3.70 FLAURA-2: Kaplan-Meier plot of time to first occurrence of SOC: Leber- und Gallenerkrankungen
Safety Analysis Set, DCO 03APR2023



Anzahl an Patienten unter Risiko:

276	245	217	197	177	153	99	40	10	0	Osi + Chemo
275	250	228	200	166	131	78	43	7	0	Osi

root/cdar/d516/payer_germany/ar/d5169c00001_payer_germany/tlf/prod/program/ttemainae.sas gttemainaebcr 24OCT2023:11:33 kvbv306

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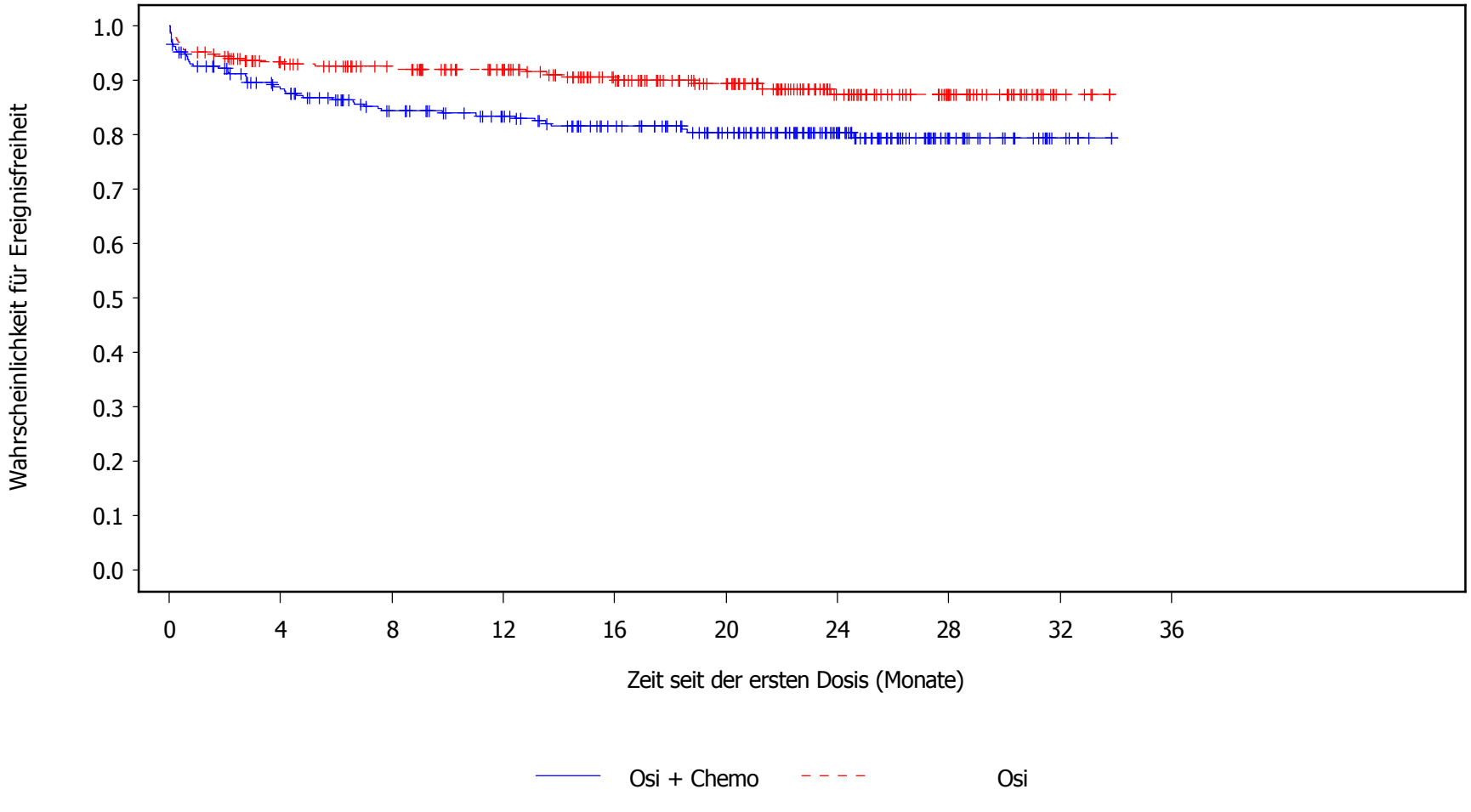
Figure 3.3.71 FLAURA-2: Kaplan-Meier plot of time to first occurrence of SOC: Psychiatrische Erkrankungen
Safety Analysis Set, DCO 03APR2023



Anzahl an Patienten unter Risiko:

276	228	198	182	159	134	85	32	7	0	Osi + Chemo
275	236	216	192	158	127	74	38	5	0	Osi

root/cdar/d516/payer_germany/ar/d5169c00001_payer_germany/tlf/prod/program/ttemainae.sas gttemainaebcs 24OCT2023:11:33 kvbv306

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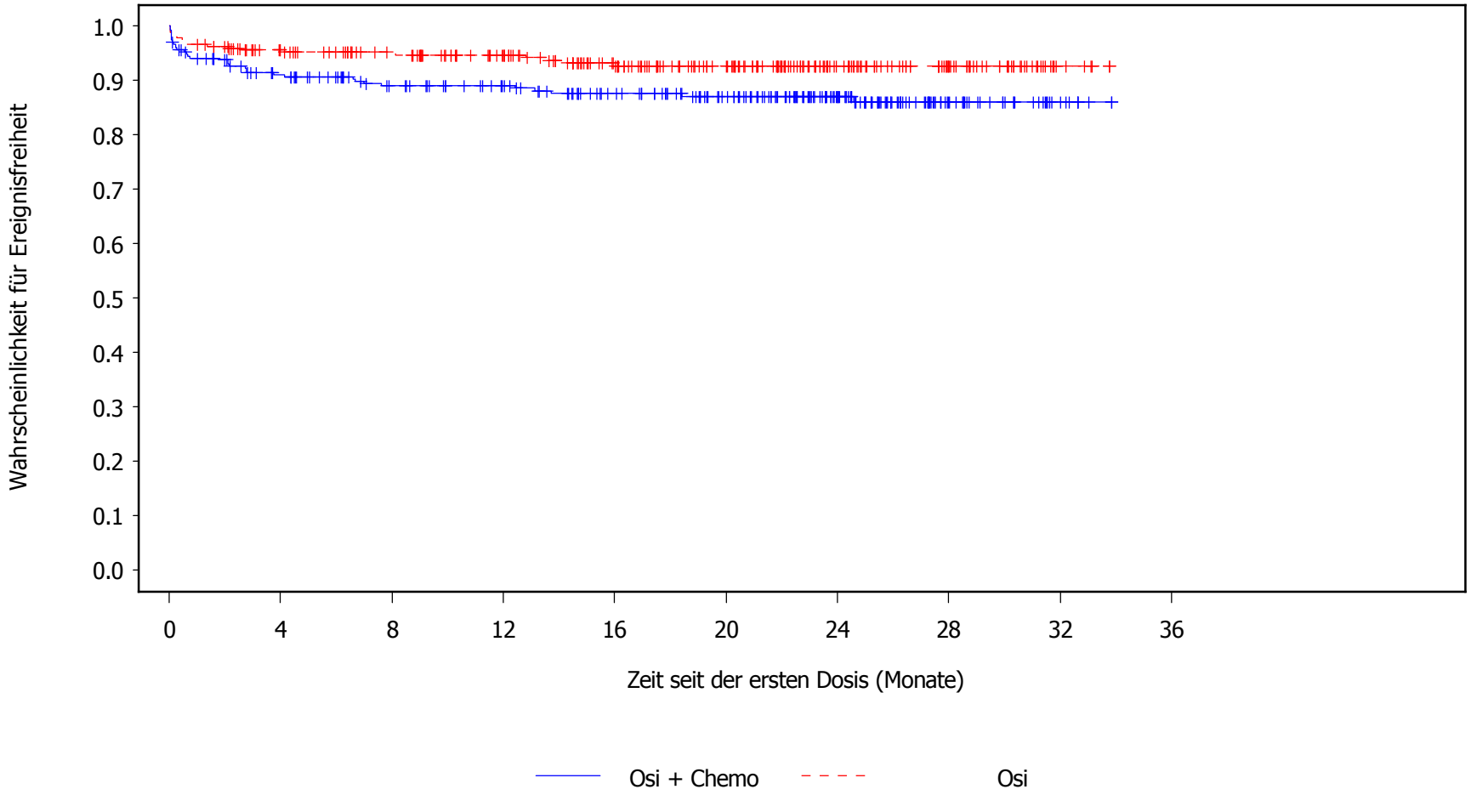
Figure 3.3.72 FLAURA-2: Kaplan-Meier plot of time to first occurrence of PT: Schlaflosigkeit
Safety Analysis Set, DCO 03APR2023



Anzahl an Patienten unter Risiko:

276	234	208	193	170	143	92	33	8	0	Osi + Chemo
275	242	222	197	162	129	76	40	5	0	Osi

root/cdar/d516/payer_germany/ar/d5169c00001_payer_germany/tlf/prod/program/ttemainae.sas gttemainaebct 24OCT2023:11:33 kvbv306

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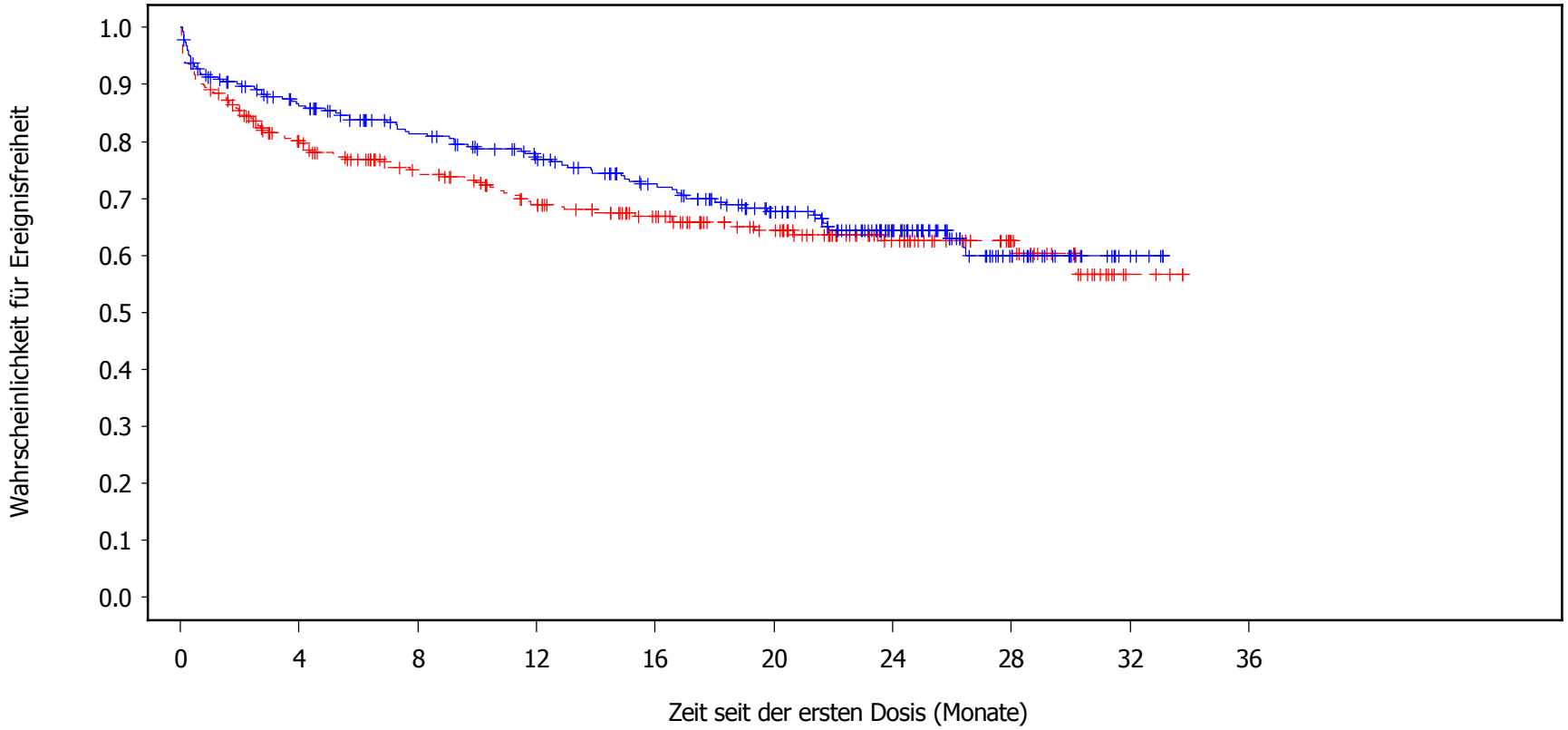
Figure 3.3.73 FLAURA-2: Kaplan-Meier plot of time to first occurrence of SOC: Skelettmuskulatur-, Bindegewebs- und Knochenerkrankungen
Safety Analysis Set, DCO 03APR2023



Anzahl an Patienten unter Risiko:

276	221	190	167	142	113	72	27	5	0	Osi + Chemo
275	201	168	143	120	94	57	29	3	0	Osi

root/cdar/d516/payer_germany/ar/d5169c00001_payer_germany/tlf/prod/program/ttemainae.sas gttemainaebcu 24OCT2023:11:33 kvbv306

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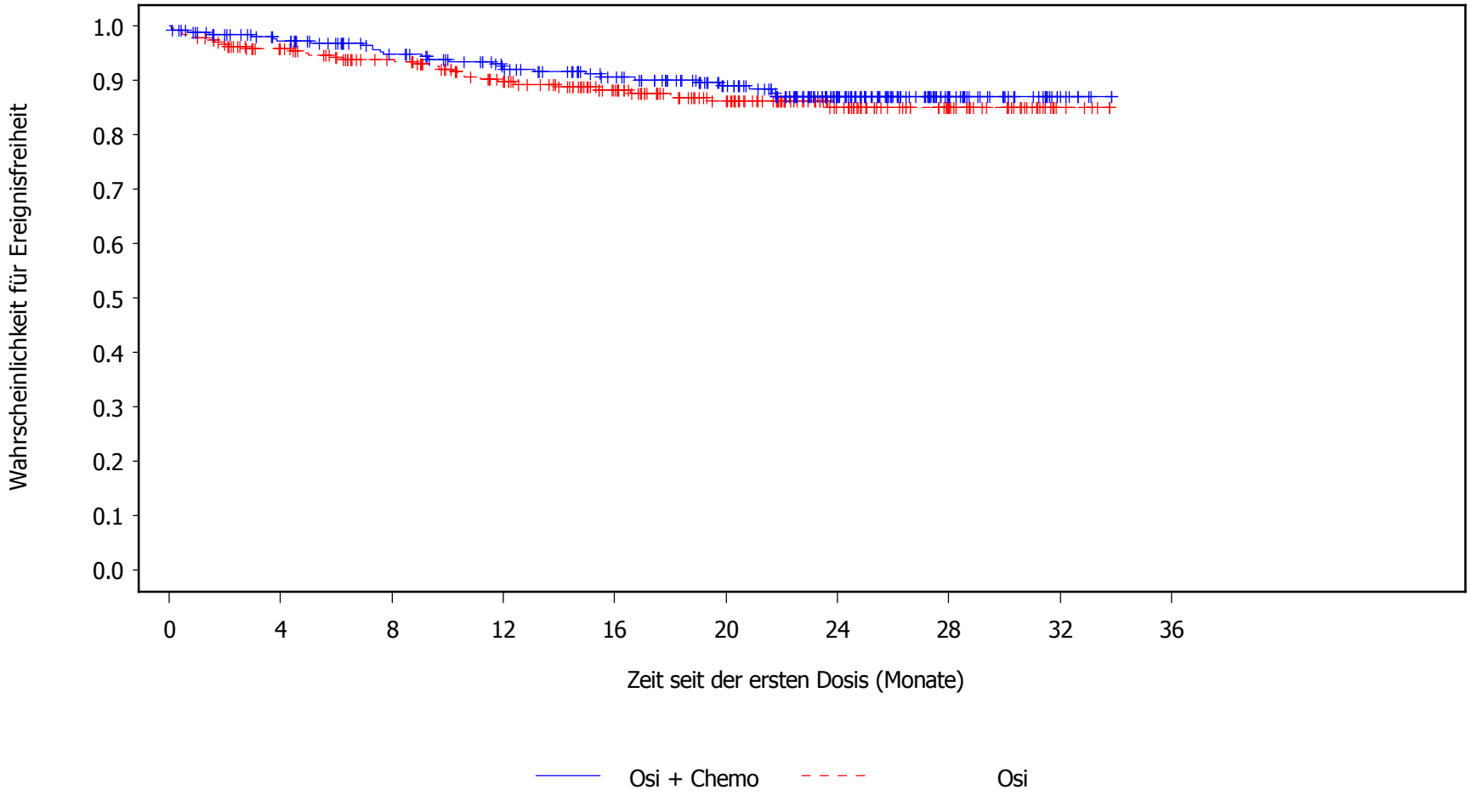
Figure 3.3.74 FLAURA-2: Kaplan-Meier plot of time to first occurrence of PT: Arthralgie
Safety Analysis Set, DCO 03APR2023



root/cdar/d516/payer_germany/ar/d5169c00001_payer_germany/tlf/prod/program/ttemainae.sas gttemainaebcv 24OCT2023:11:33 kvbv306

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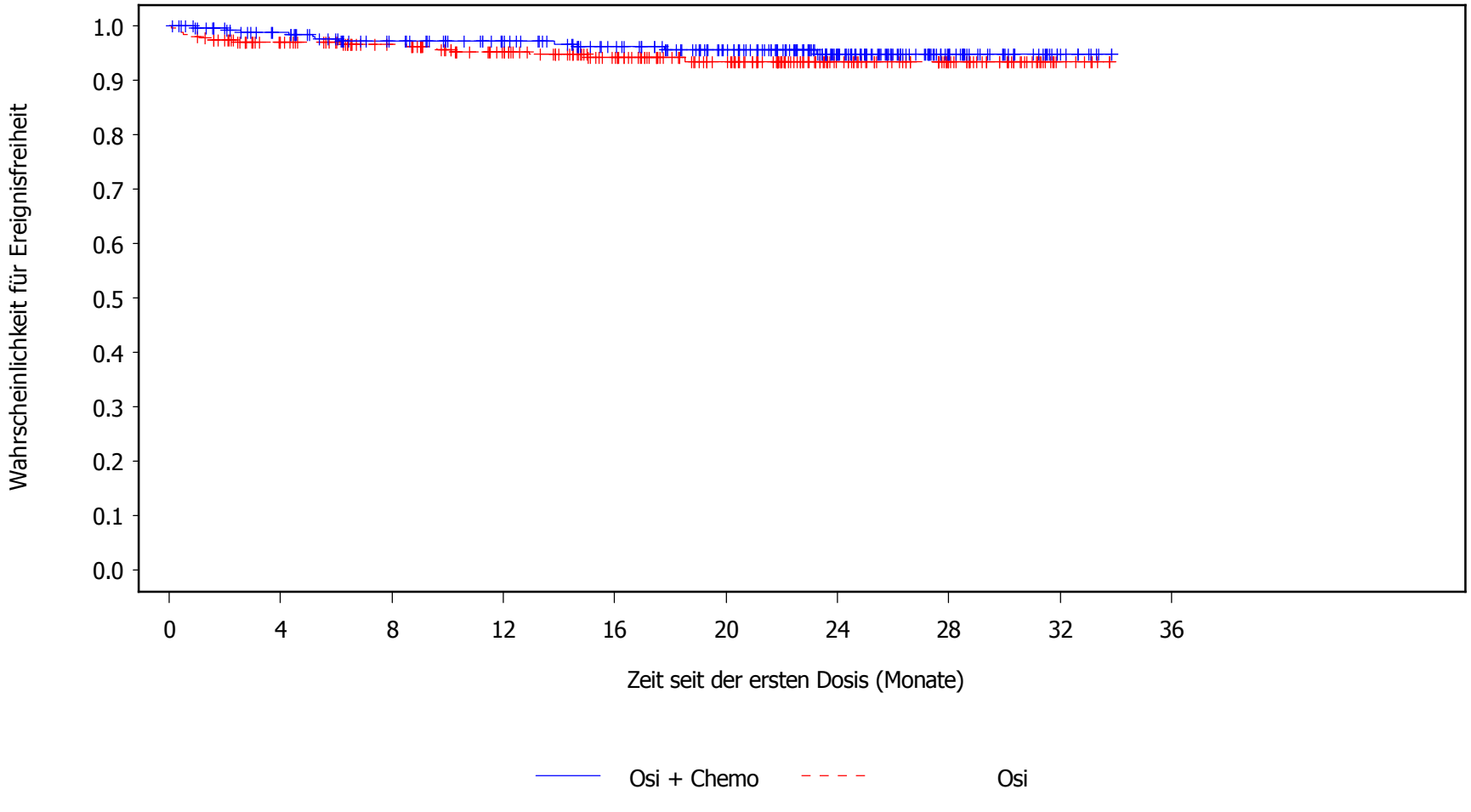
Figure 3.3.75 FLAURA-2: Kaplan-Meier plot of time to first occurrence of PT: Brustschmerzen die Skelettmuskulatur betreffend
Safety Analysis Set, DCO 03APR2023



Anzahl an Patienten unter Risiko:

276	253	228	211	189	160	104	43	10	0	Osi + Chemo
275	245	223	197	164	130	76	43	7	0	Osi

root/cdar/d516/payer_germany/ar/d5169c00001_payer_germany/tlf/prod/program/ttemainae.sas gttemainaebcw 24OCT2023:11:33 kvbv306

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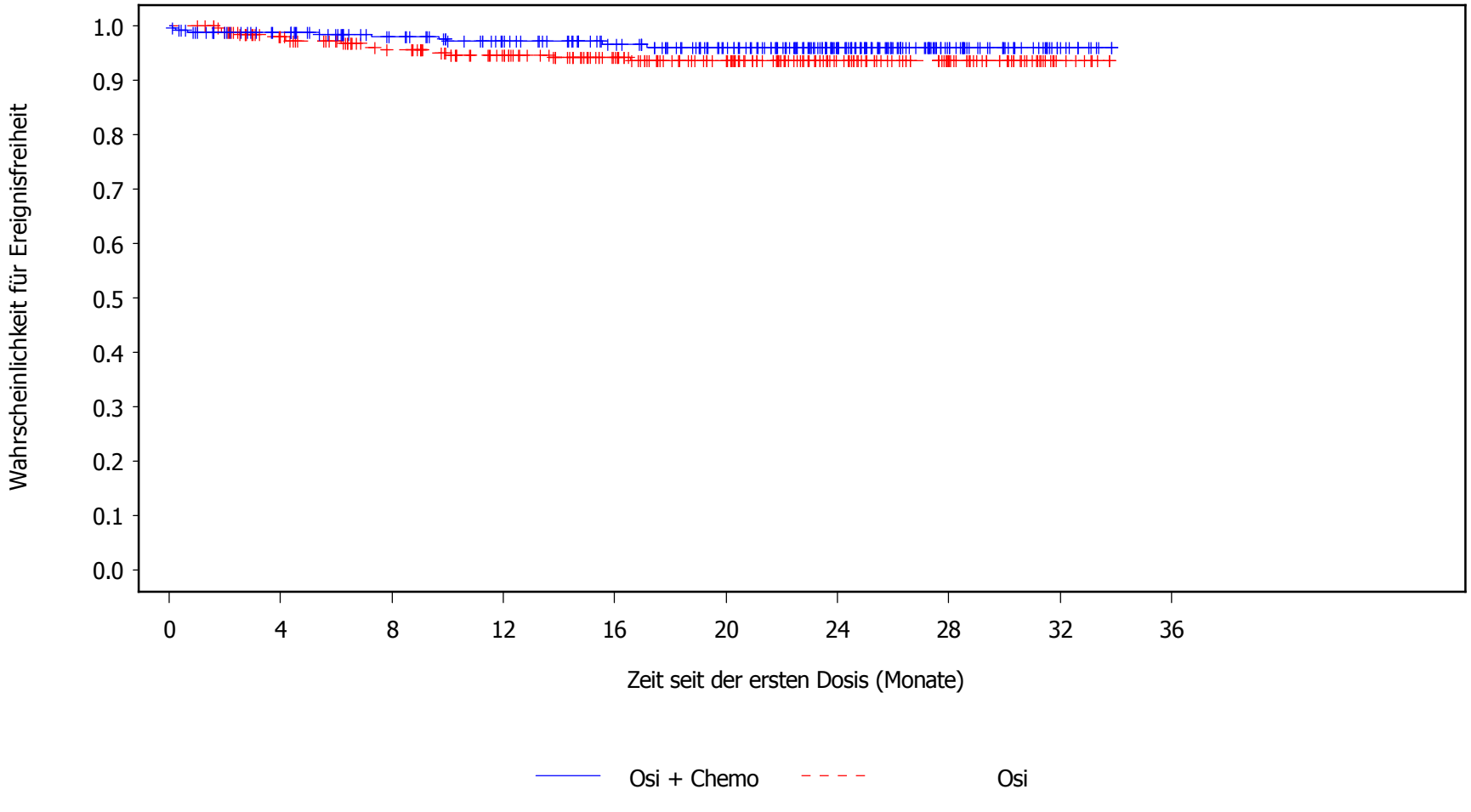
Figure 3.3.76 FLAURA-2: Kaplan-Meier plot of time to first occurrence of PT: Muskelspasmen
Safety Analysis Set, DCO 03APR2023



Anzahl an Patienten unter Risiko:

276	253	230	210	188	160	107	45	11	0	Osi + Chemo
275	248	221	195	162	130	79	44	7	0	Osi

root/cdar/d516/payer_germany/ar/d5169c00001_payer_germany/tlf/prod/program/ttemainae.sas gttemainaebcx 24OCT2023:11:33 kvbv306

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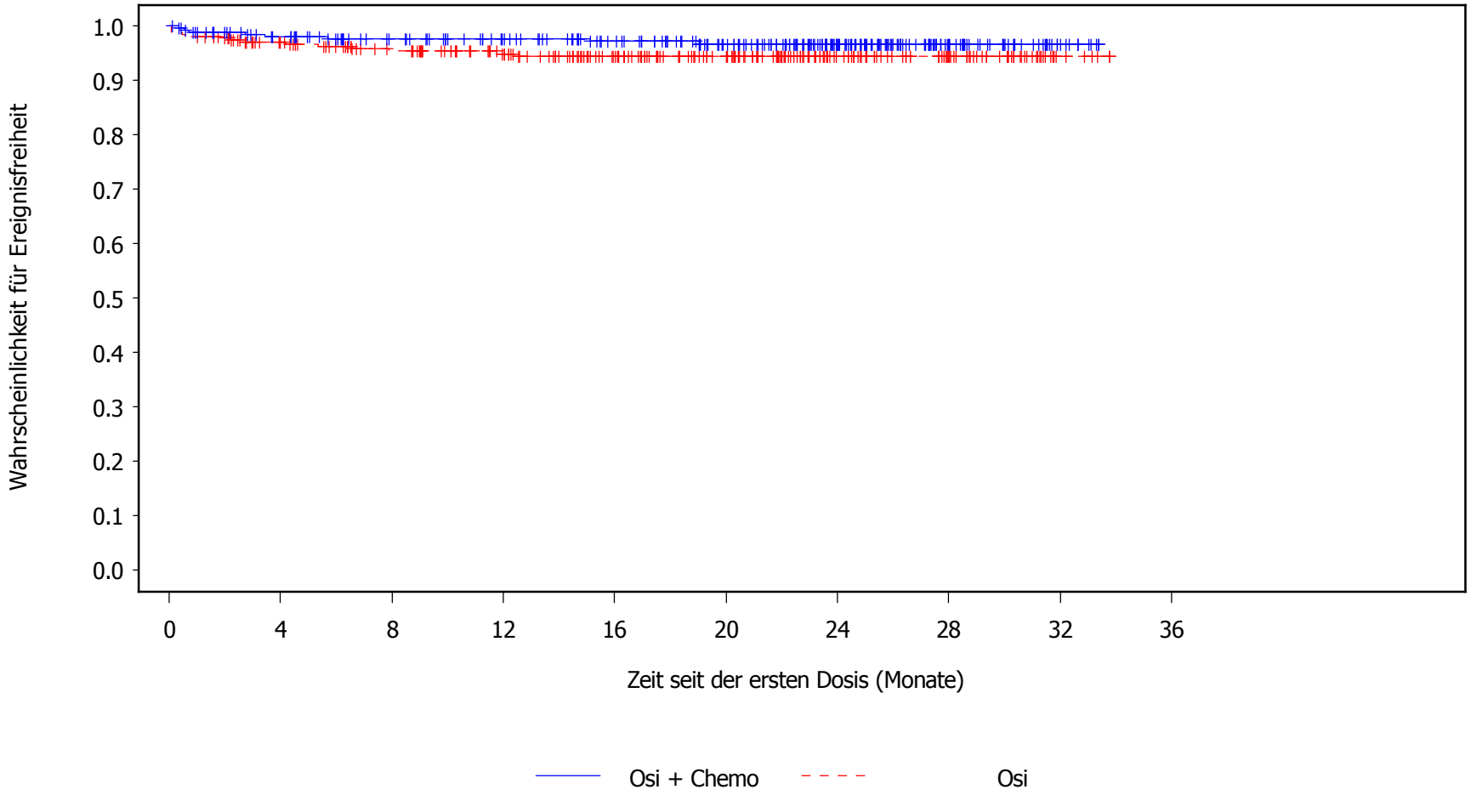
Figure 3.3.77 FLAURA-2: Kaplan-Meier plot of time to first occurrence of PT: Myalgie
Safety Analysis Set, DCO 03APR2023



Anzahl an Patienten unter Risiko:

276	251	229	212	190	161	108	44	10	0	Osi + Chemo
275	245	221	196	161	128	73	40	5	0	Osi

root/cdar/d516/payer_germany/ar/d5169c00001_payer_germany/tlf/prod/program/ttemainae.sas gttemainaebcy 24OCT2023:11:33 kvbv306

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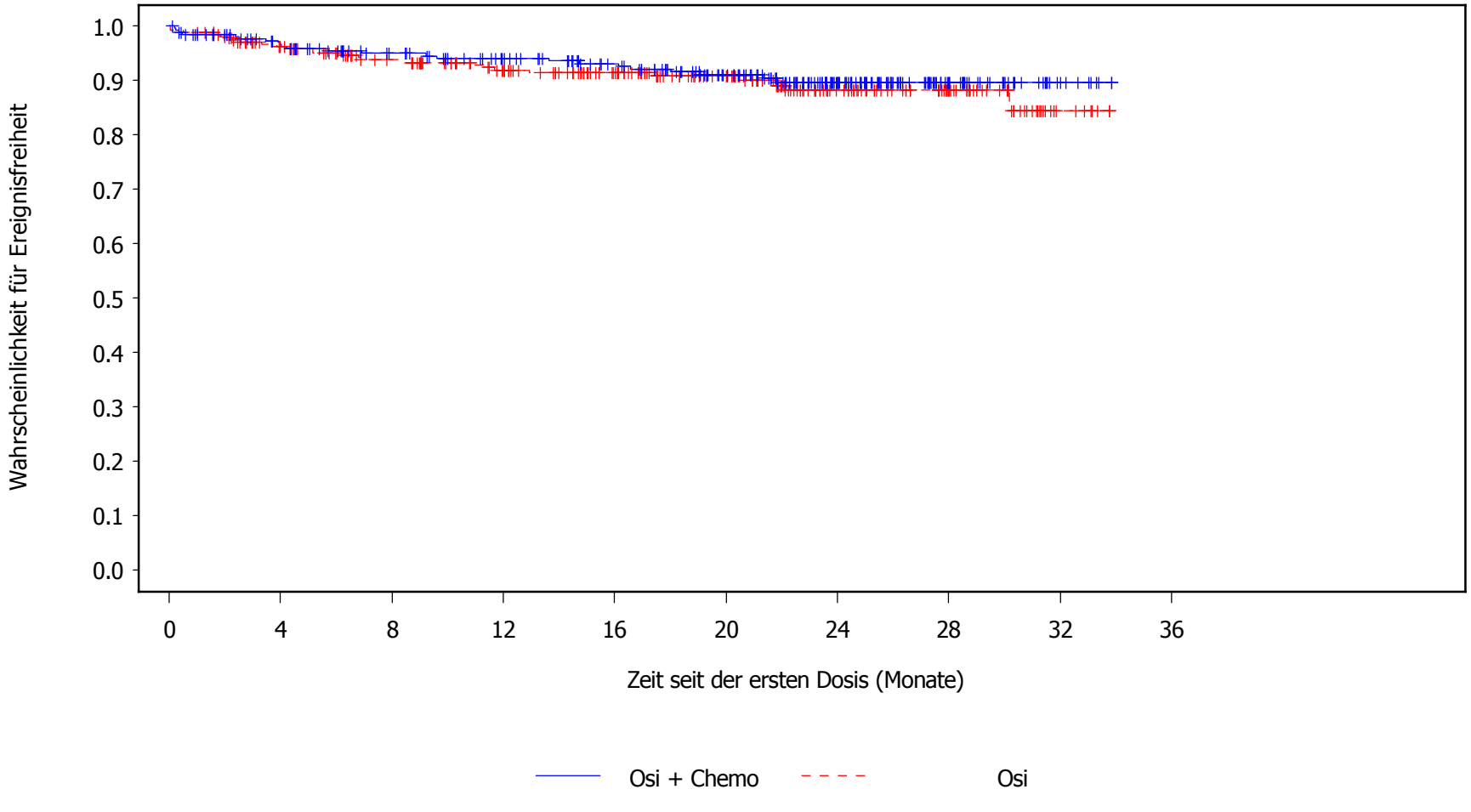
Figure 3.3.78 FLAURA-2: Kaplan-Meier plot of time to first occurrence of PT: Rueckenschmerzen
Safety Analysis Set, DCO 03APR2023



Anzahl an Patienten unter Risiko:

276	248	223	205	183	153	97	38	8	0	Osi + Chemo
275	244	217	189	159	126	73	40	6	0	Osi

root/cdar/d516/payer_germany/ar/d5169c00001_payer_germany/tlf/prod/program/ttemainae.sas gttemainaebcz 24OCT2023:11:33 kvbv306

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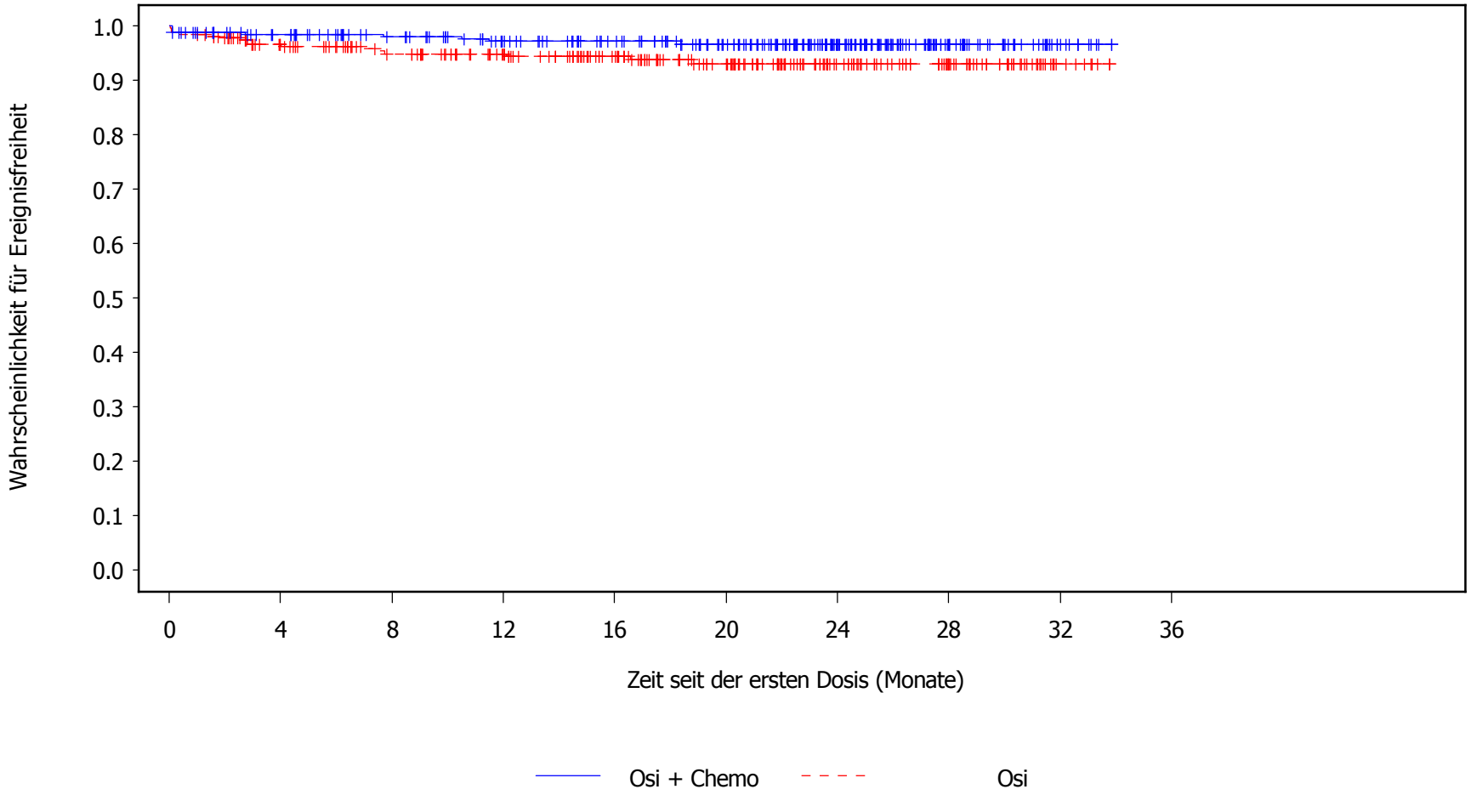
Figure 3.3.79 FLAURA-2: Kaplan-Meier plot of time to first occurrence of PT: Schmerz in einer Extremitaet
Safety Analysis Set, DCO 03APR2023



Anzahl an Patienten unter Risiko:

276	253	232	212	192	164	108	45	11	0	Osi + Chemo
275	244	219	195	164	129	78	44	7	0	Osi

root/cdar/d516/payer_germany/ar/d5169c00001_payer_germany/tlf/prod/program/ttemainae.sas gttemainaebda 24OCT2023:11:33 kvbv306

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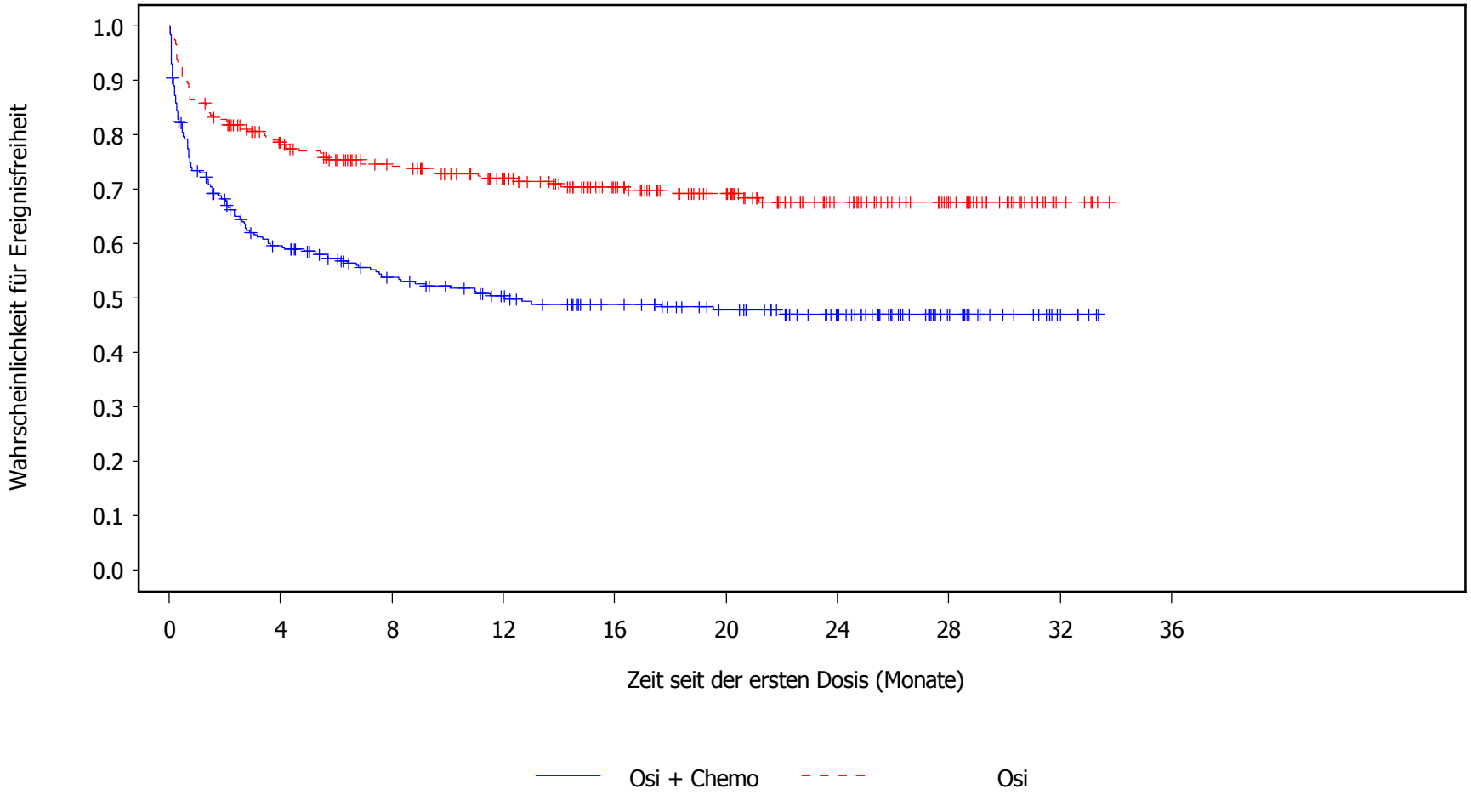
Figure 3.3.80 FLAURA-2: Kaplan-Meier plot of time to first occurrence of SOC: Stoffwechsel- und Ernaehrungsstoerungen
Safety Analysis Set, DCO 03APR2023



Anzahl an Patienten unter Risiko:

276	153	125	107	92	79	58	24	6	0	Osi + Chemo
275	201	174	150	120	95	61	35	6	0	Osi

root/cdar/d516/payer_germany/ar/d5169c00001_payer_germany/tlf/prod/program/ttemainae.sas gttemainaebdb 24OCT2023:11:33 kvbv306

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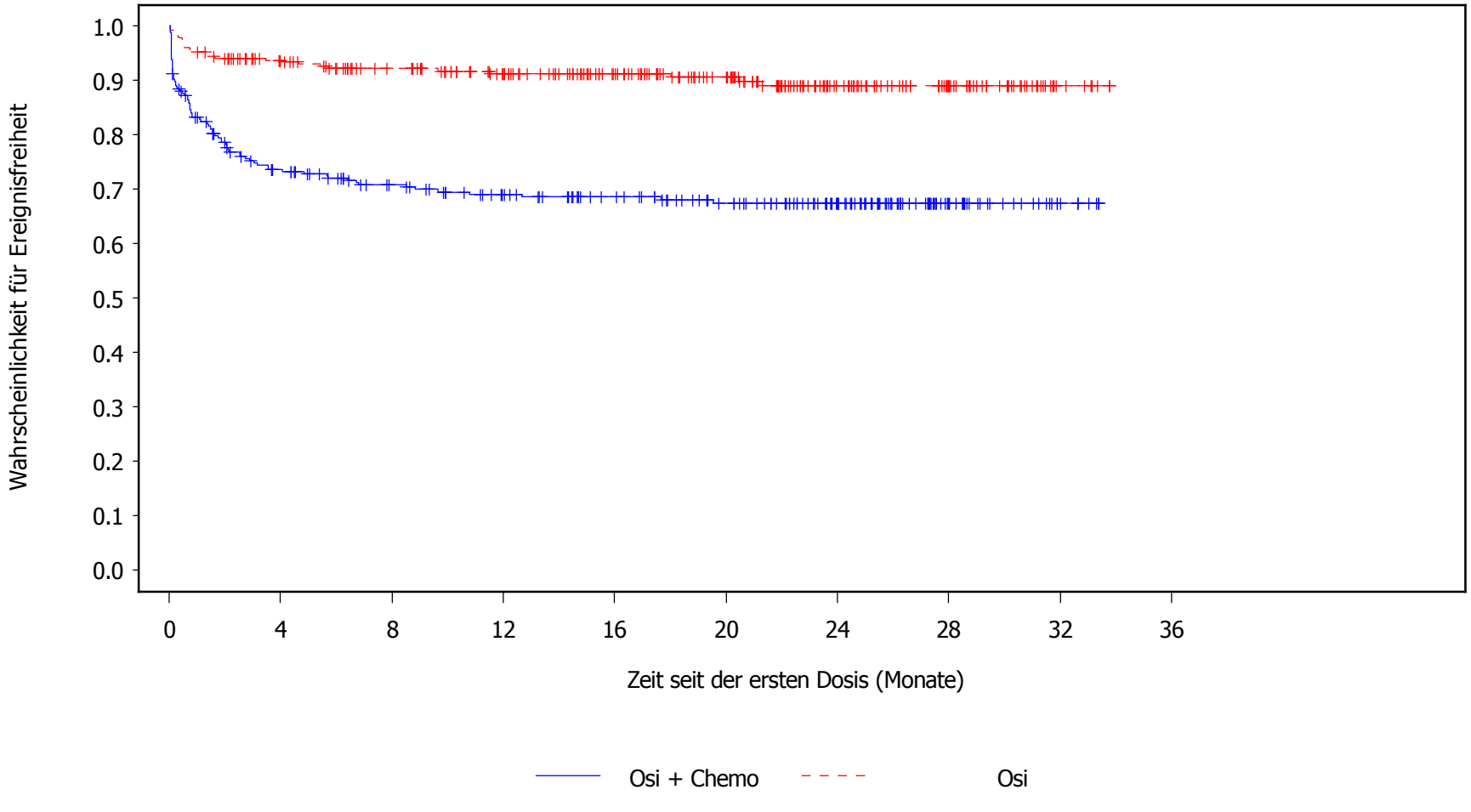
Figure 3.3.81 FLAURA-2: Kaplan-Meier plot of time to first occurrence of PT: Appetit vermindert
Safety Analysis Set, DCO 03APR2023



Anzahl an Patienten unter Risiko:

276	188	164	147	130	112	82	30	7	0	Osi + Chemo
275	239	216	192	160	127	74	40	6	0	Osi

root/cdar/d516/payer_germany/ar/d5169c00001_payer_germany/tlf/prod/program/ttemainae.sas gttemainaebdc 24OCT2023:11:33 kvbv306

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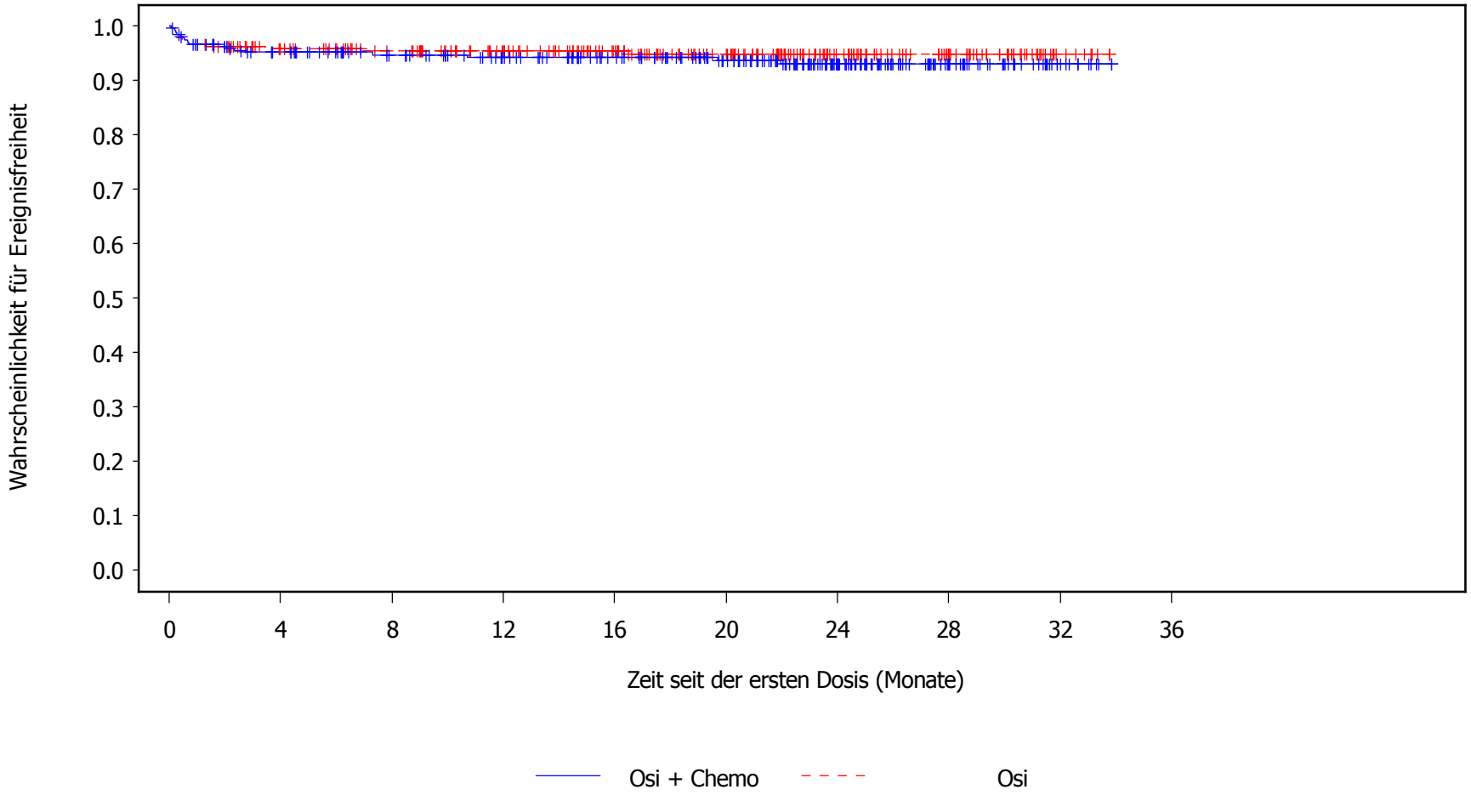
Figure 3.3.82 FLAURA-2: Kaplan-Meier plot of time to first occurrence of PT: Hypalbuminaemie
Safety Analysis Set, DCO 03APR2023



Anzahl an Patienten unter Risiko:

276	245	224	207	185	157	100	44	11	0	Osi + Chemo
275	242	222	197	164	130	77	43	7	0	Osi

root/cdar/d516/payer_germany/ar/d5169c00001_payer_germany/tlf/prod/program/ttemainae.sas gttemainaebdd 24OCT2023:11:33 kvbv306

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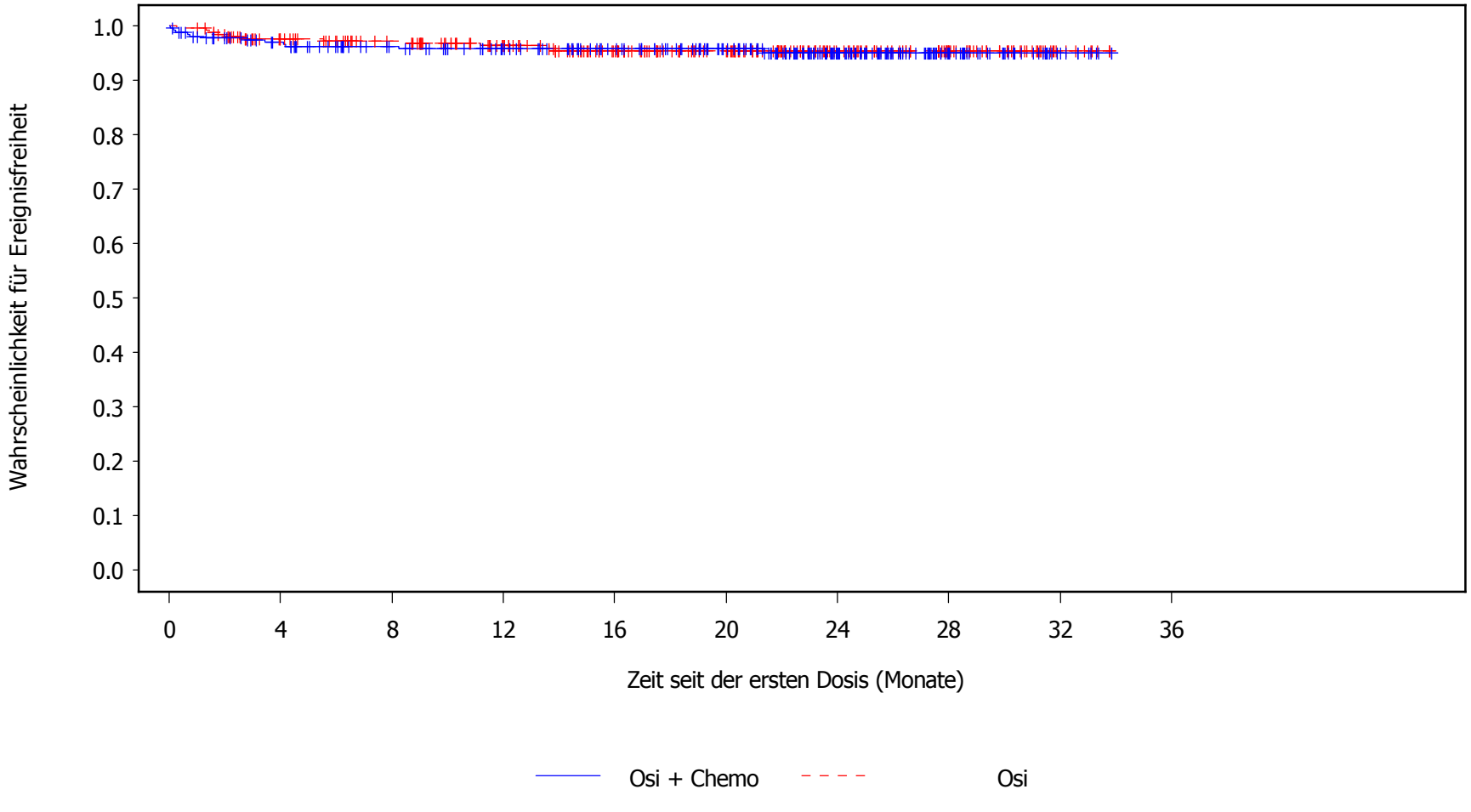
Figure 3.3.83 FLAURA-2: Kaplan-Meier plot of time to first occurrence of PT: Hyperglykaemie
Safety Analysis Set, DCO 03APR2023



Anzahl an Patienten unter Risiko:

276	249	226	209	188	161	104	43	9	0	Osi + Chemo
275	247	225	197	163	131	78	44	7	0	Osi

root/cdar/d516/payer_germany/ar/d5169c00001_payer_germany/tlf/prod/program/ttemainae.sas gttemainaebde 24OCT2023:11:33 kvbv306

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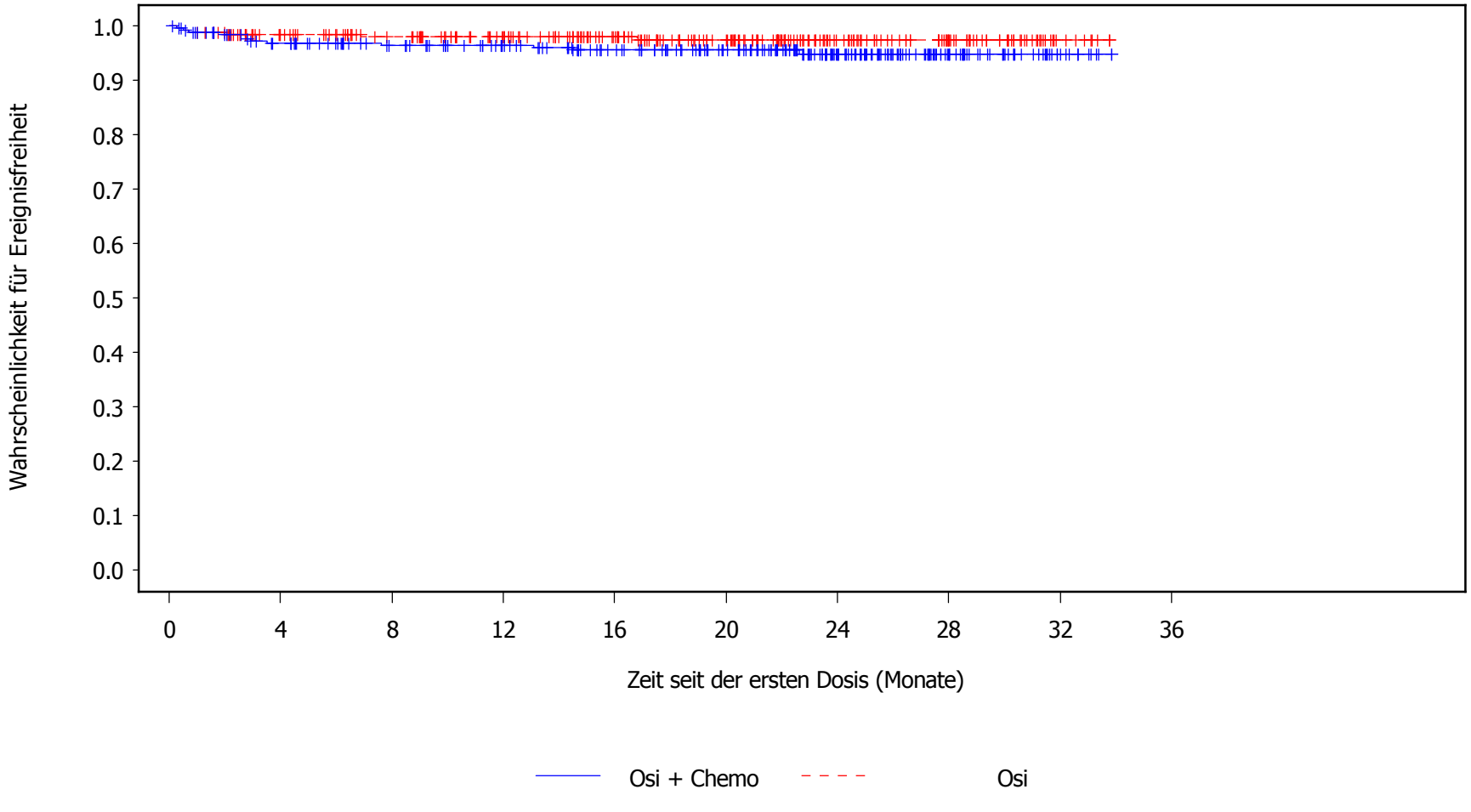
Figure 3.3.84 FLAURA-2: Kaplan-Meier plot of time to first occurrence of PT: Hyperurikaemie
Safety Analysis Set, DCO 03APR2023



Anzahl an Patienten unter Risiko:

276	248	226	208	184	157	103	45	11	0	Osi + Chemo
275	249	227	202	167	131	77	44	7	0	Osi

root/cdar/d516/payer_germany/ar/d5169c00001_payer_germany/tlf/prod/program/ttemainae.sas gttemainaebdf 24OCT2023:11:33 kvbv306

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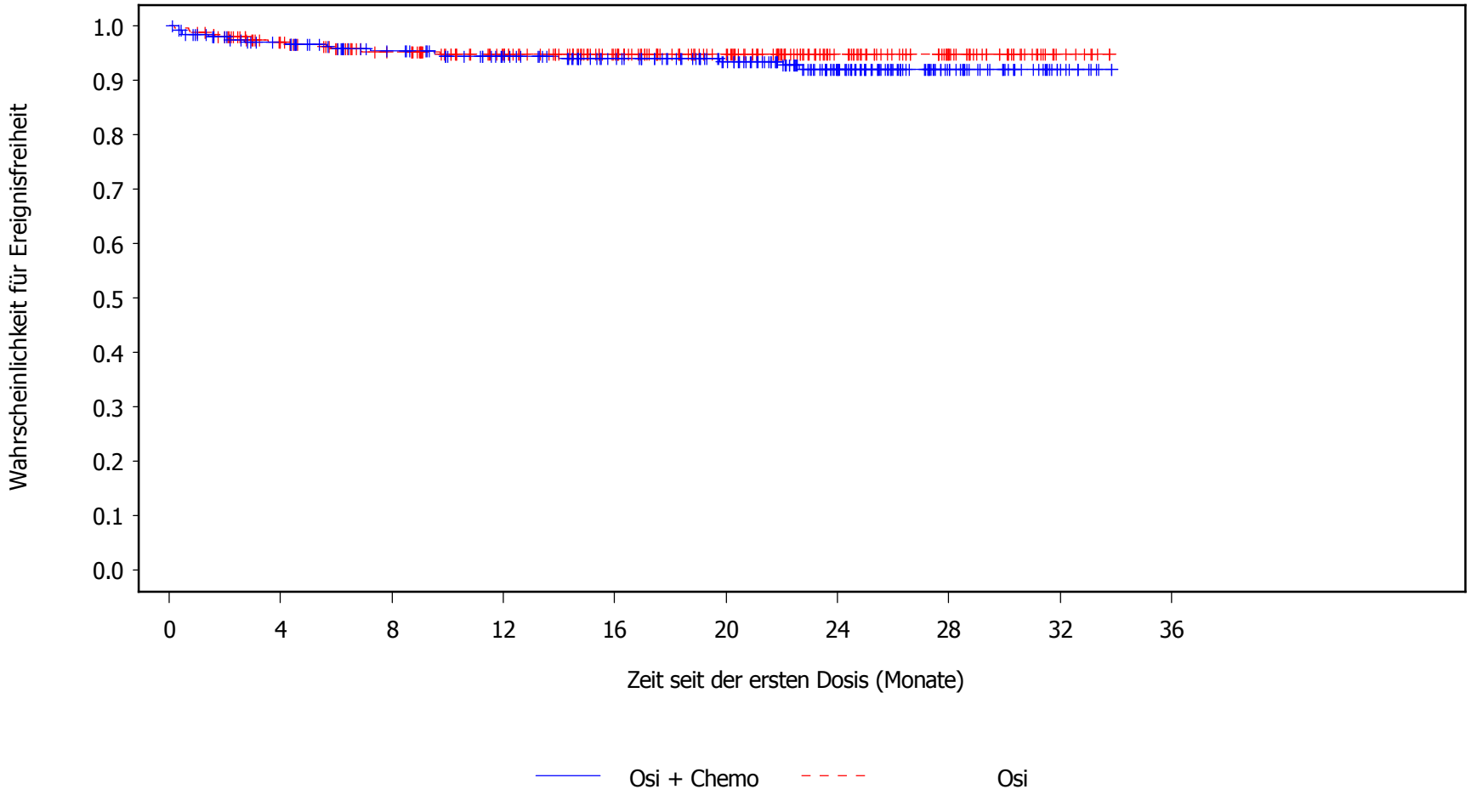
Figure 3.3.85 FLAURA-2: Kaplan-Meier plot of time to first occurrence of PT: Hypokaliaemie
Safety Analysis Set, DCO 03APR2023



Anzahl an Patienten unter Risiko:

276	249	226	207	184	157	103	44	11	0	Osi + Chemo
275	245	221	194	160	127	76	41	7	0	Osi

root/cdar/d516/payer_germany/ar/d5169c00001_payer_germany/tlf/prod/program/ttemainae.sas gttemainaebdg 24OCT2023:11:33 kvbv306

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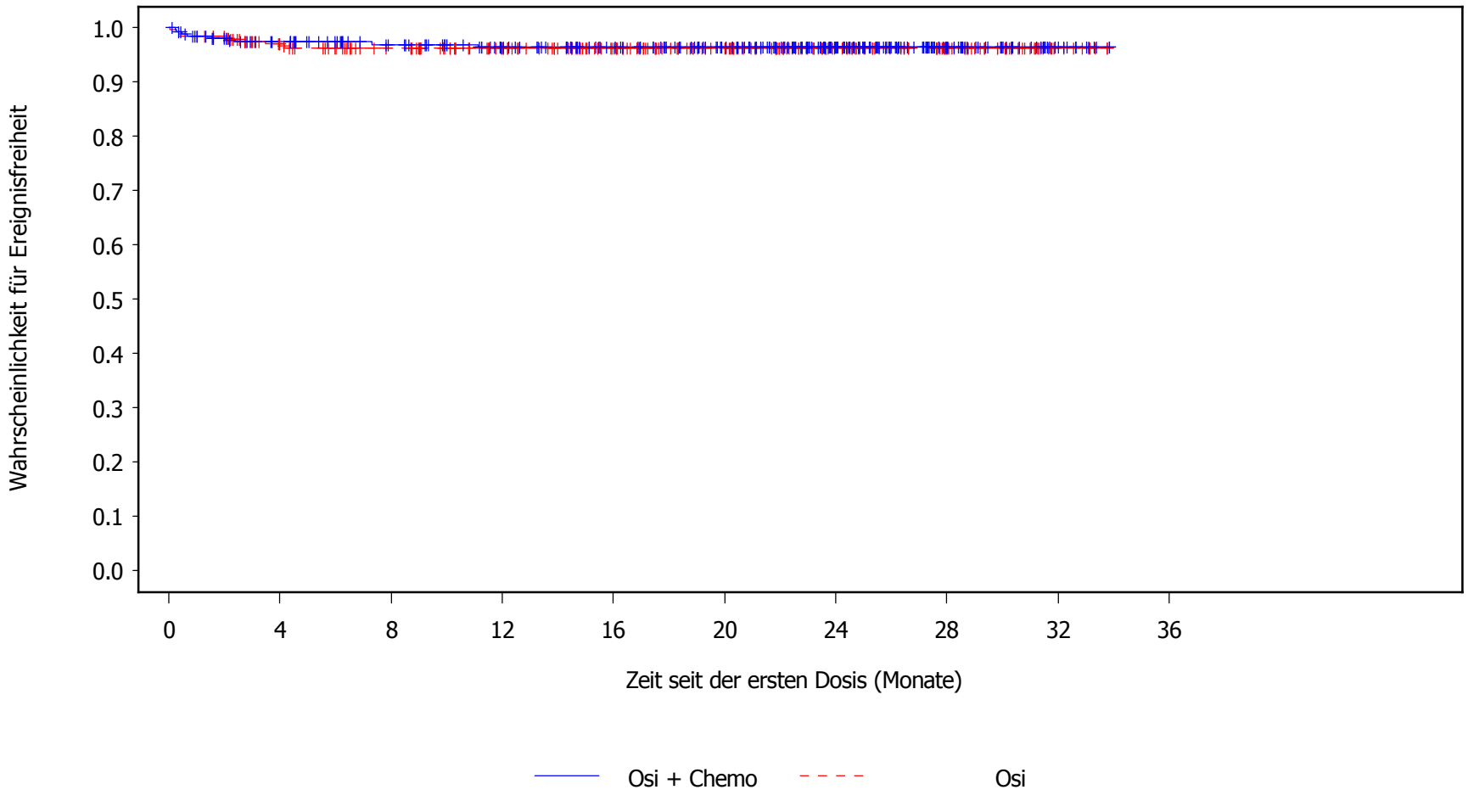
Figure 3.3.86 FLAURA-2: Kaplan-Meier plot of time to first occurrence of PT: Hypokalzaemie
Safety Analysis Set, DCO 03APR2023



Anzahl an Patienten unter Risiko:

276	249	228	209	187	160	107	44	11	0	Osi + Chemo
275	246	225	200	166	131	79	44	7	0	Osi

root/cdar/d516/payer_germany/ar/d5169c00001_payer_germany/tlf/prod/program/ttemainae.sas gttemainaebdh 24OCT2023:11:33 kvbv306

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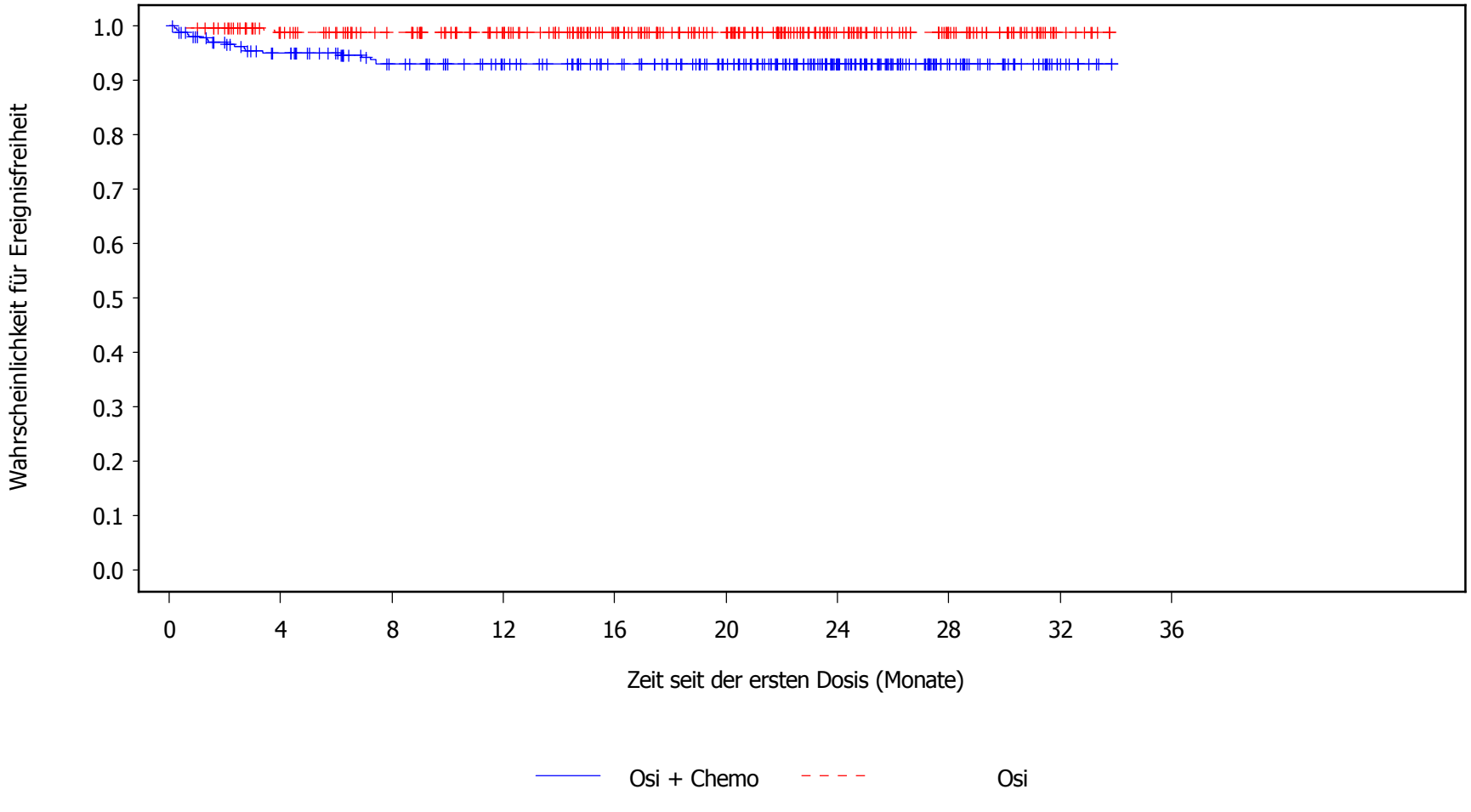
Figure 3.3.87 FLAURA-2: Kaplan-Meier plot of time to first occurrence of PT: Hypomagnesiaemie
Safety Analysis Set, DCO 03APR2023

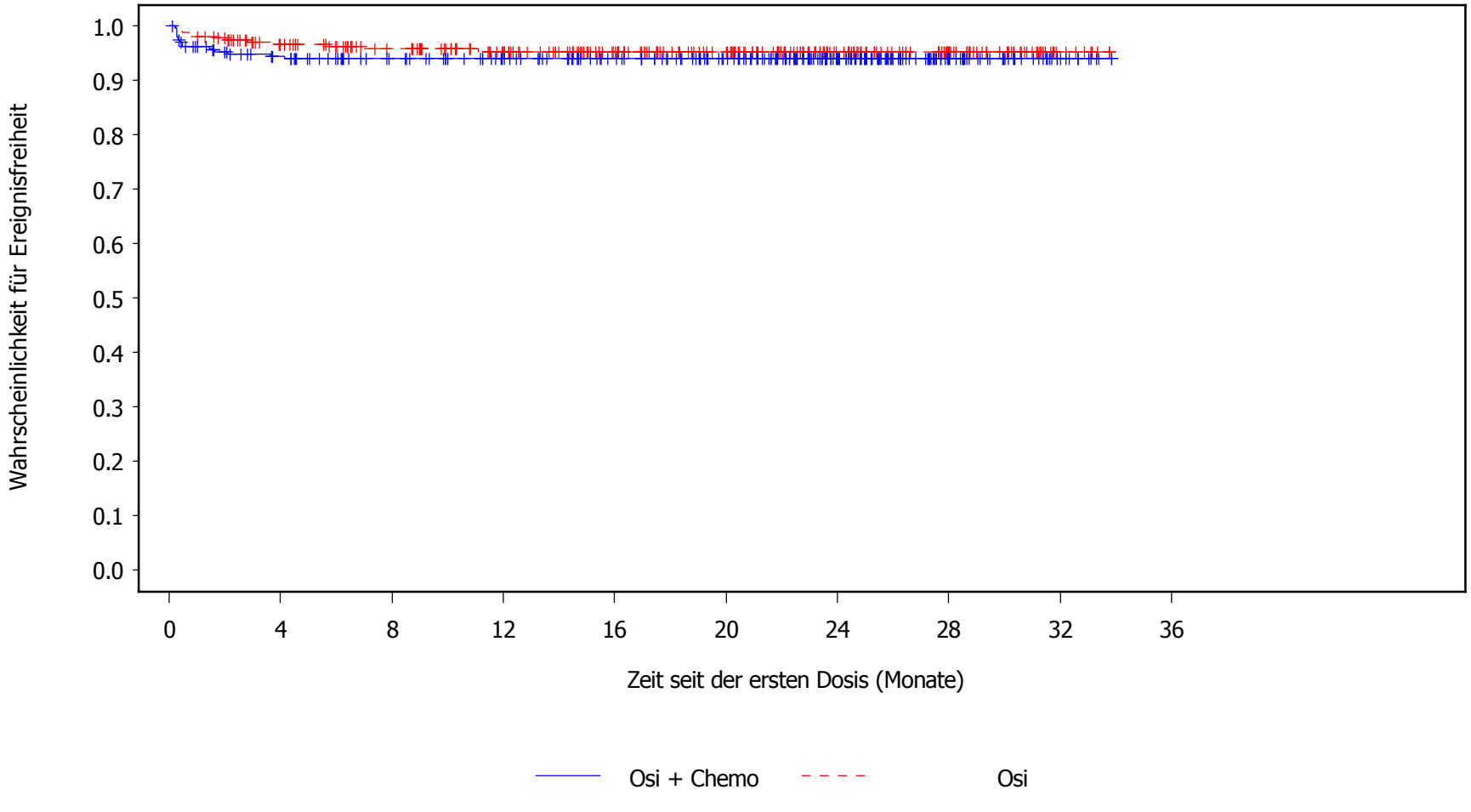


Anzahl an Patienten unter Risiko:

276	243	217	201	181	157	103	43	10	0	Osi + Chemo
275	250	229	204	169	135	79	43	7	0	Osi

root/cdar/d516/payer_germany/ar/d5169c00001_payer_germany/tlf/prod/program/ttemainae.sas gttemainaebdi 24OCT2023:11:33 kvbv306

Figure 3.3.88 FLAURA-2: Kaplan-Meier plot of time to first occurrence of PT: Hyponatriaemie
Safety Analysis Set, DCO 03APR2023



Anzahl an Patienten unter Risiko:

276	242	220	203	182	157	105	44	11	0	Osi + Chemo
275	246	223	197	163	132	79	44	7	0	Osi

root/cdar/d516/payer_germany/ar/d5169c00001_payer_germany/tlf/prod/program/ttemainae.sas gttemainaebdj 24OCT2023:11:33 kvbv306

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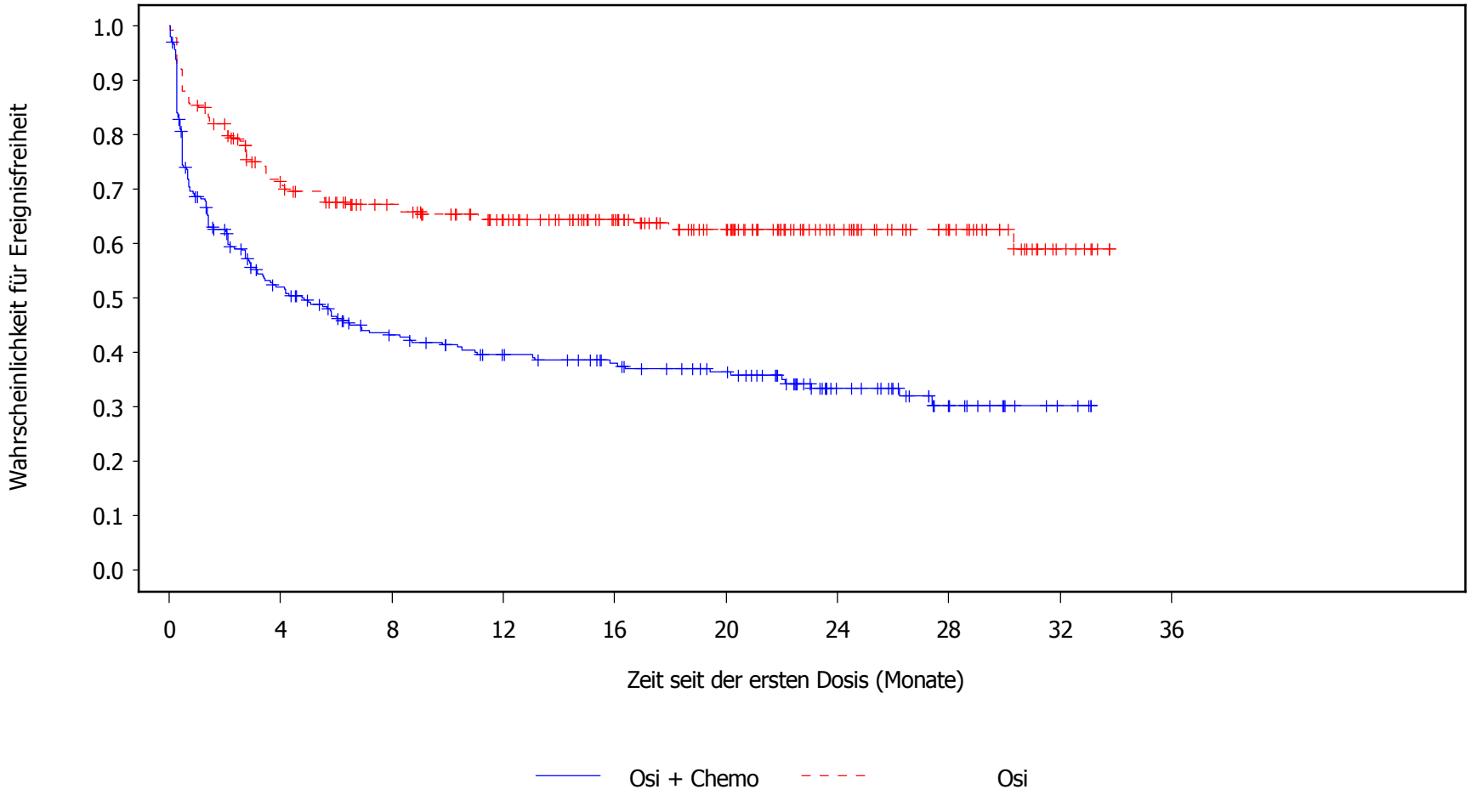
Figure 3.3.89 FLAURA-2: Kaplan-Meier plot of time to first occurrence of SOC: Untersuchungen
Safety Analysis Set, DCO 03APR2023

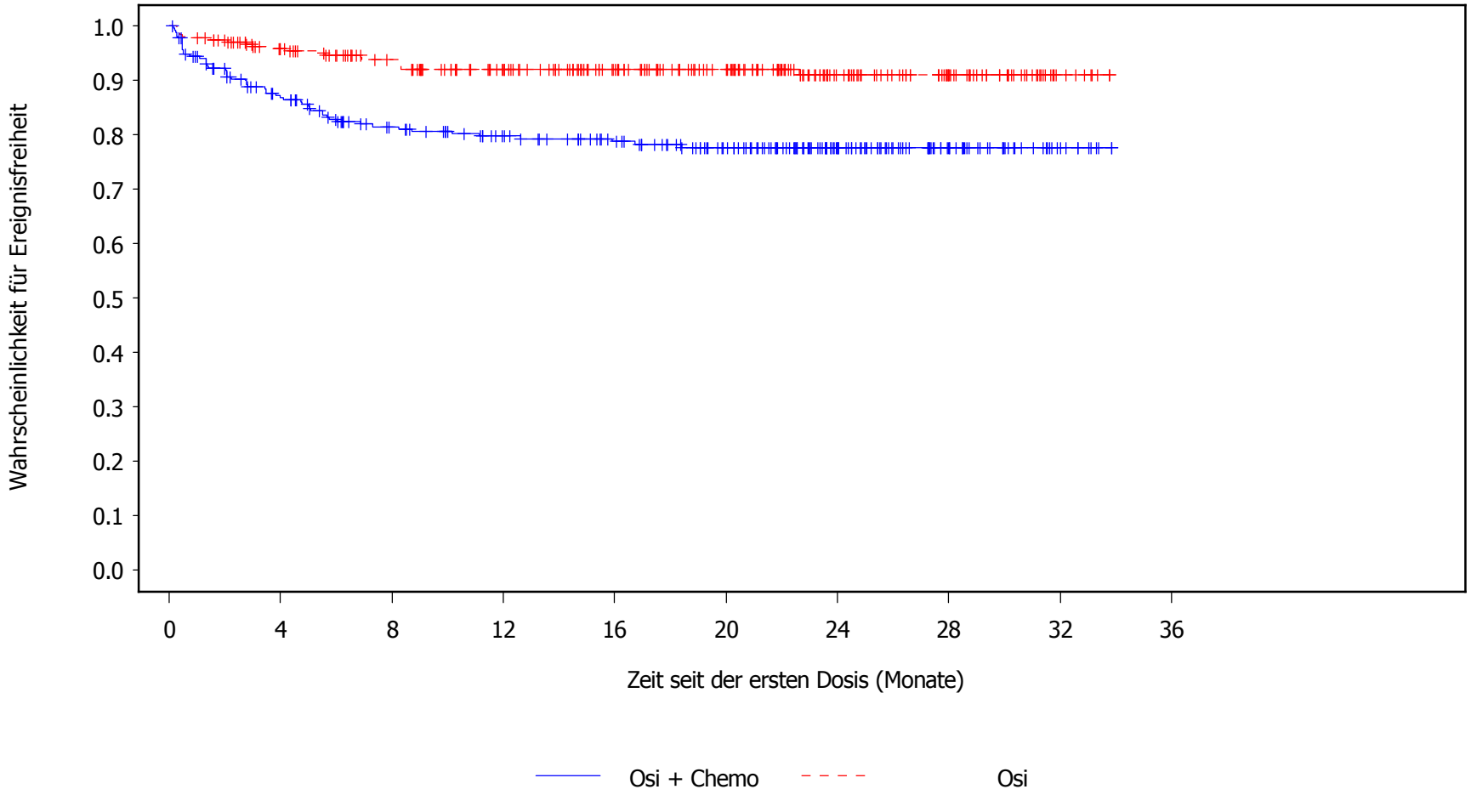


Anzahl an Patienten unter Risiko:

276	130	97	82	71	60	31	14	3	0	Osi + Chemo
275	184	157	132	110	85	51	31	7	0	Osi

root/cdar/d516/payer_germany/ar/d5169c00001_payer_germany/tlf/prod/program/ttemainae.sas gttemainaebdk 24OCT2023:11:33 kvbv306

Figure 3.3.90 FLAURA-2: Kaplan-Meier plot of time to first occurrence of PT: Alaninaminotransferase erhoeht
Safety Analysis Set, DCO 03APR2023



Anzahl an Patienten unter Risiko:

276	222	188	169	151	125	77	37	9	0	Osi + Chemo
275	243	218	189	156	126	73	41	7	0	Osi

root/cdar/d516/payer_germany/ar/d5169c00001_payer_germany/tlf/prod/program/ttemainae.sas gttemainaebdl 24OCT2023:11:33 kvbv306

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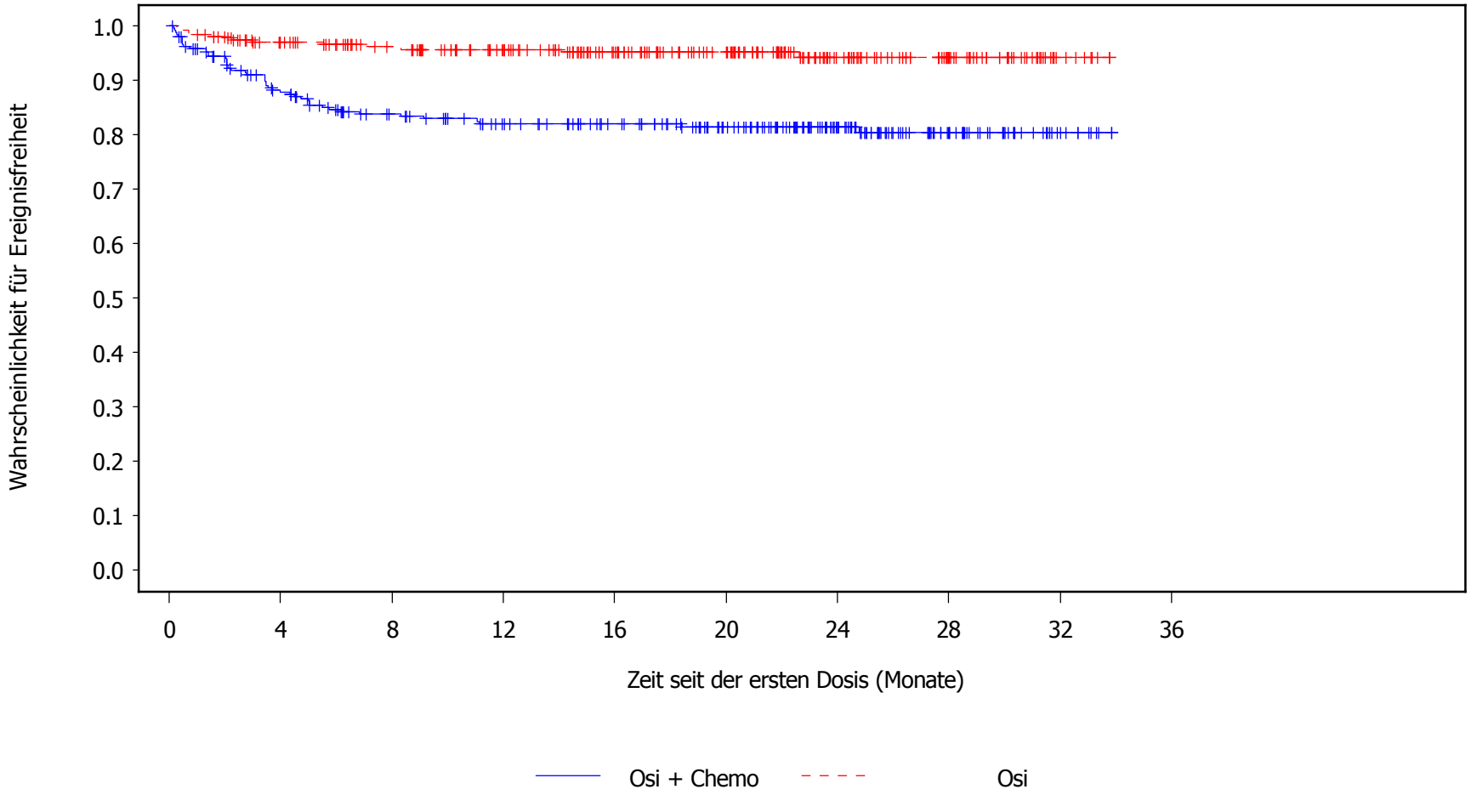
Figure 3.3.91 FLAURA-2: Kaplan-Meier plot of time to first occurrence of PT: Aspartataminotransferase erhoeht
Safety Analysis Set, DCO 03APR2023



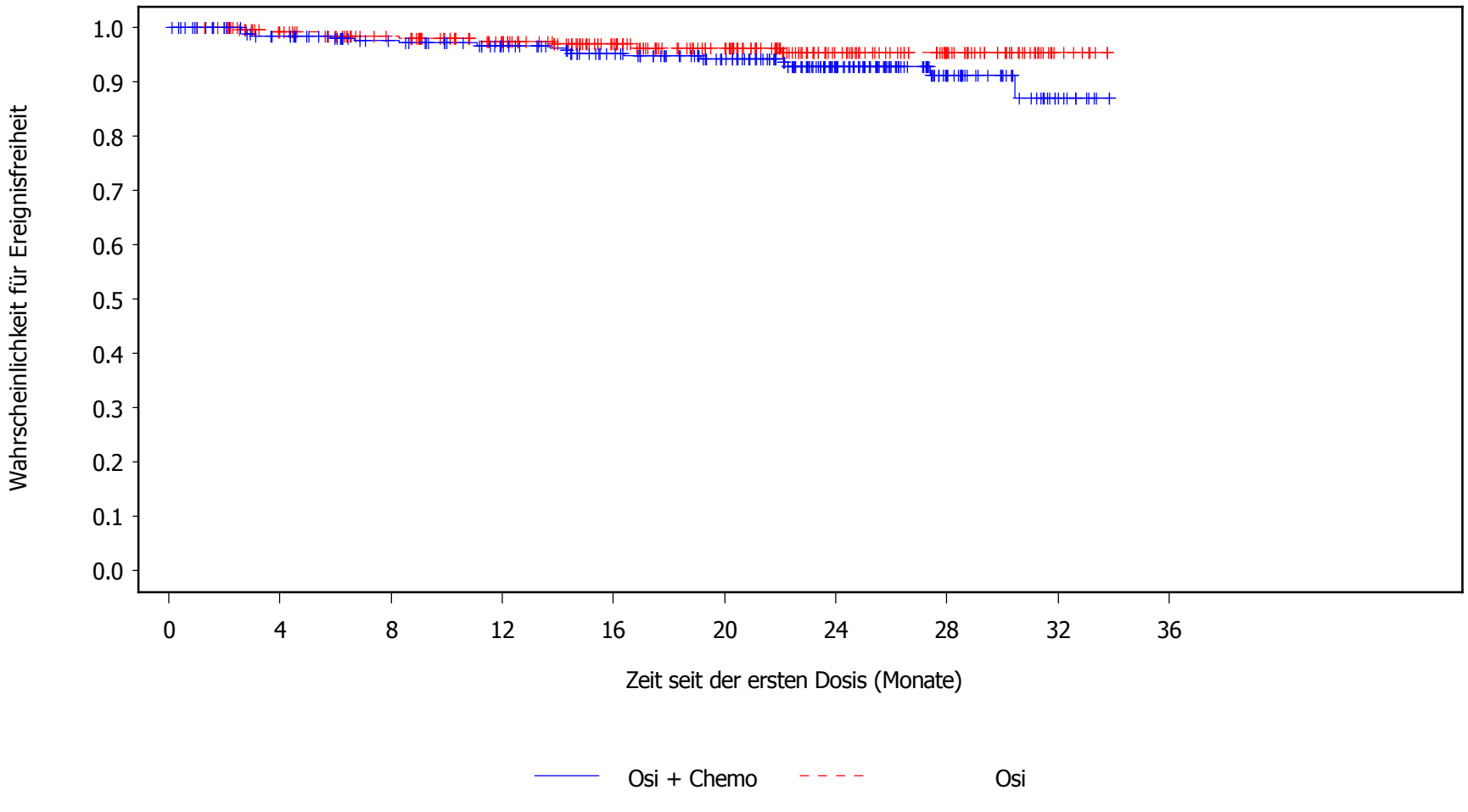
Anzahl an Patienten unter Risiko:

276	225	194	175	157	130	84	39	9	0	Osi + Chemo
275	246	223	197	162	131	75	41	7	0	Osi

root/cdar/d516/payer_germany/ar/d5169c00001_payer_germany/tlf/prod/program/ttemainae.sas gttemainaebdm 24OCT2023:11:33 kvbv306

Nutzenbewertung nach AMNOG Seite 1 von 1

Figure 3.3.92 FLAURA-2: Kaplan-Meier plot of time to first occurrence of PT: Auswurffraktion verkleinert
Safety Analysis Set, DCO 03APR2023



Anzahl an Patienten unter Risiko:

276	252	231	213	190	162	105	43	11	0	Osi + Chemo
275	251	229	201	165	131	77	44	7	0	Osi

root/cdar/d516/payer_germany/ar/d5169c00001_payer_germany/tlf/prod/program/ttemainae.sas gttemainaebdn 24OCT2023:11:33 kvbv306

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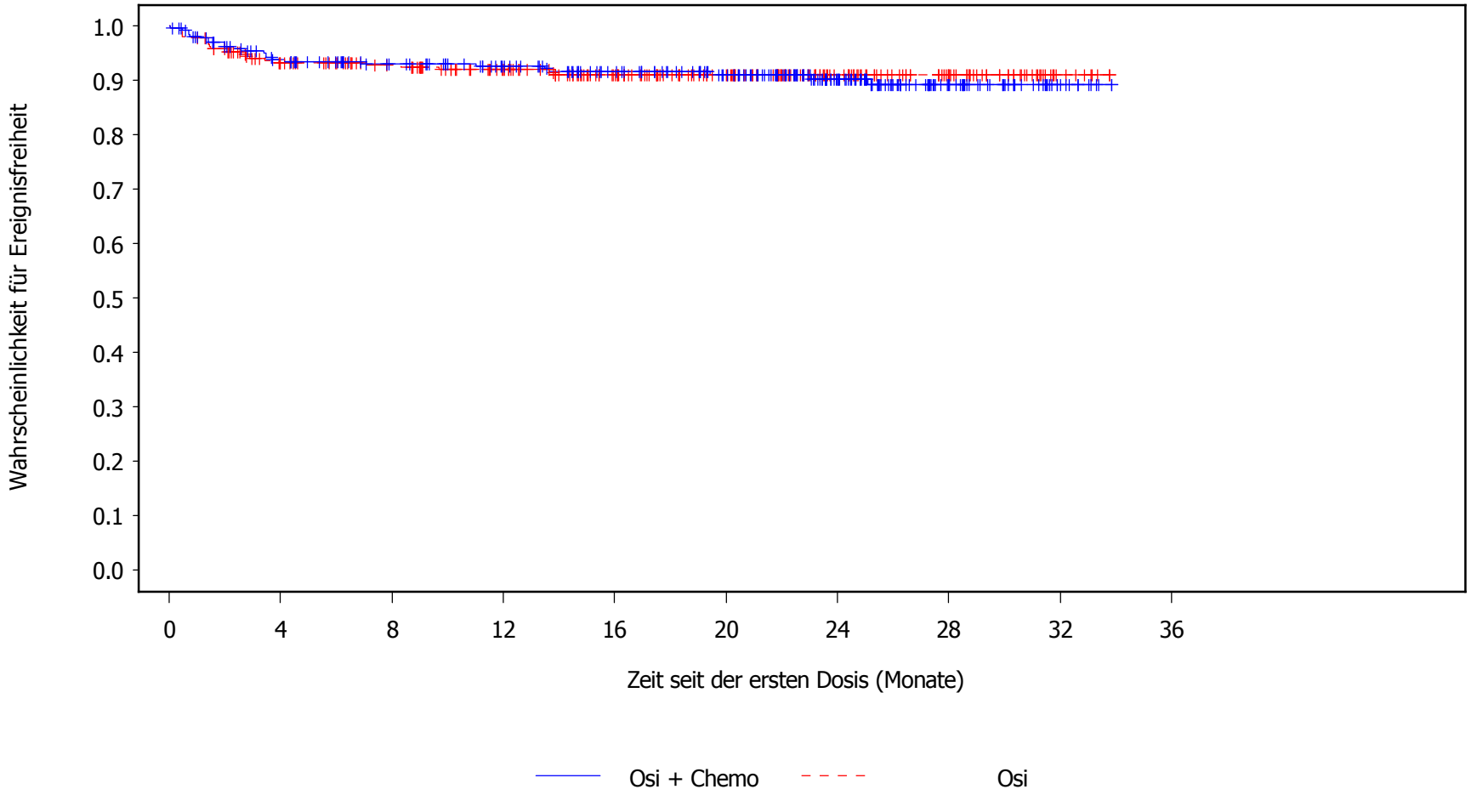
Figure 3.3.93 FLAURA-2: Kaplan-Meier plot of time to first occurrence of PT: Elektrokardiogramm QT verlaengert
Safety Analysis Set, DCO 03APR2023

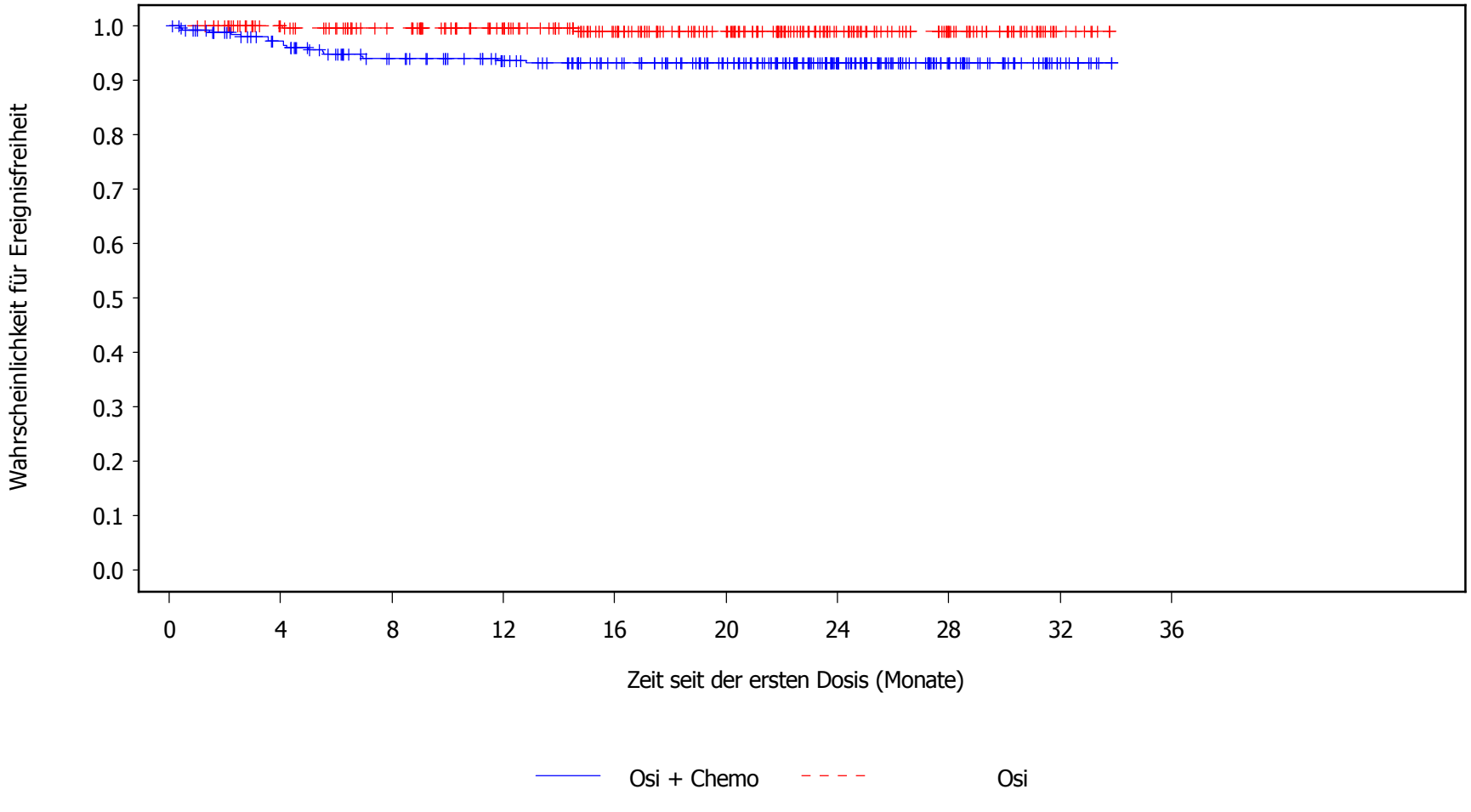


Anzahl an Patienten unter Risiko:

276	240	218	200	177	152	98	44	11	0	Osi + Chemo
275	237	216	190	156	124	75	42	7	0	Osi

root/cdar/d516/payer_germany/ar/d5169c00001_payer_germany/tlf/prod/program/ttemainae.sas gttemainaebdo 24OCT2023:11:33 kvbv306

Figure 3.3.94 FLAURA-2: Kaplan-Meier plot of time to first occurrence of PT: Gamma-Glutamyltransferase erhoeht
Safety Analysis Set, DCO 03APR2023



Anzahl an Patienten unter Risiko:

276	249	220	202	180	153	99	45	11	0	Osi + Chemo
275	253	232	206	171	136	80	44	7	0	Osi

root/cdar/d516/payer_germany/ar/d5169c00001_payer_germany/tlf/prod/program/ttemainae.sas gttemainaebdp 24OCT2023:11:33 kvbv306

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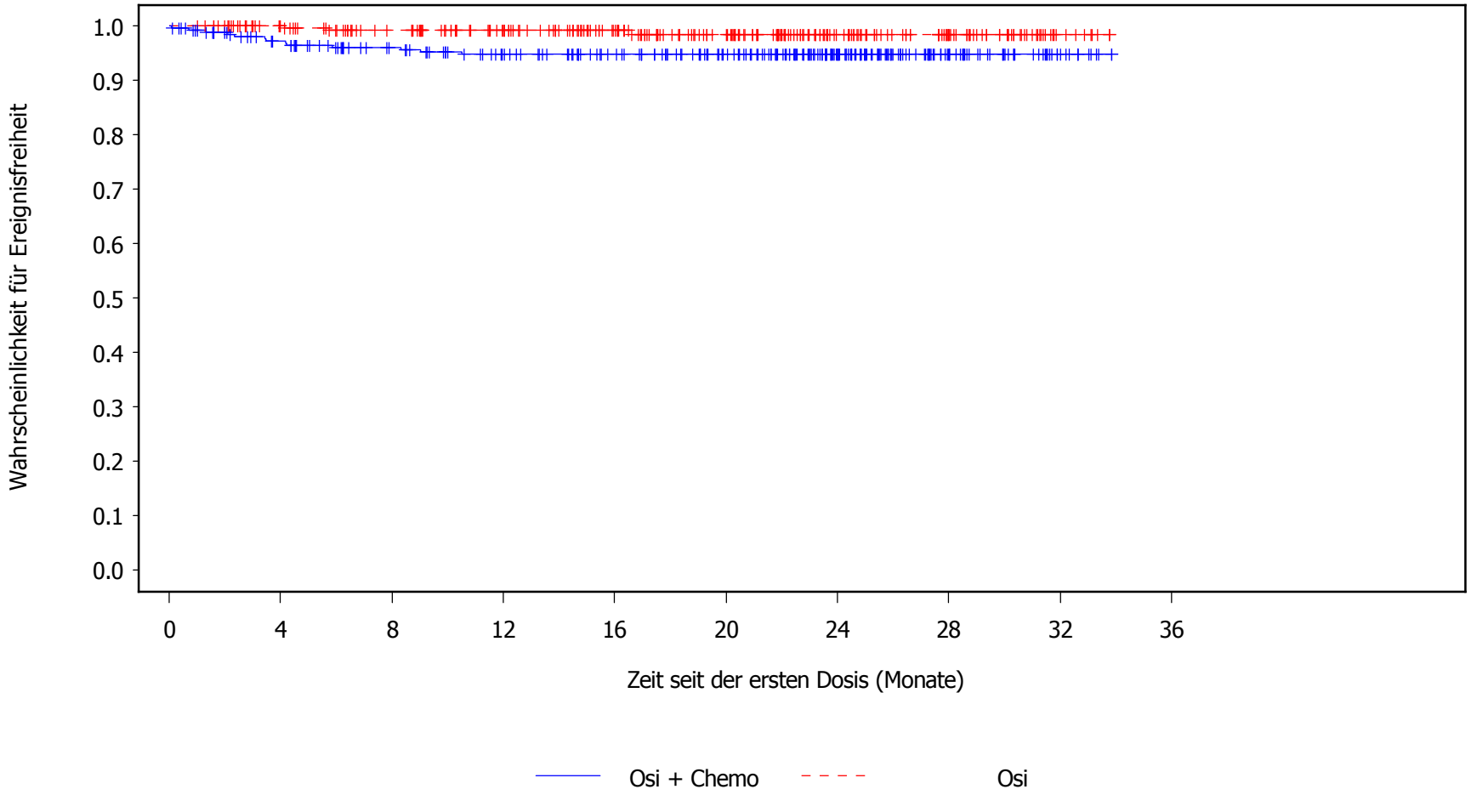
Figure 3.3.95 FLAURA-2: Kaplan-Meier plot of time to first occurrence of PT: Gewicht erhoeht
Safety Analysis Set, DCO 03APR2023

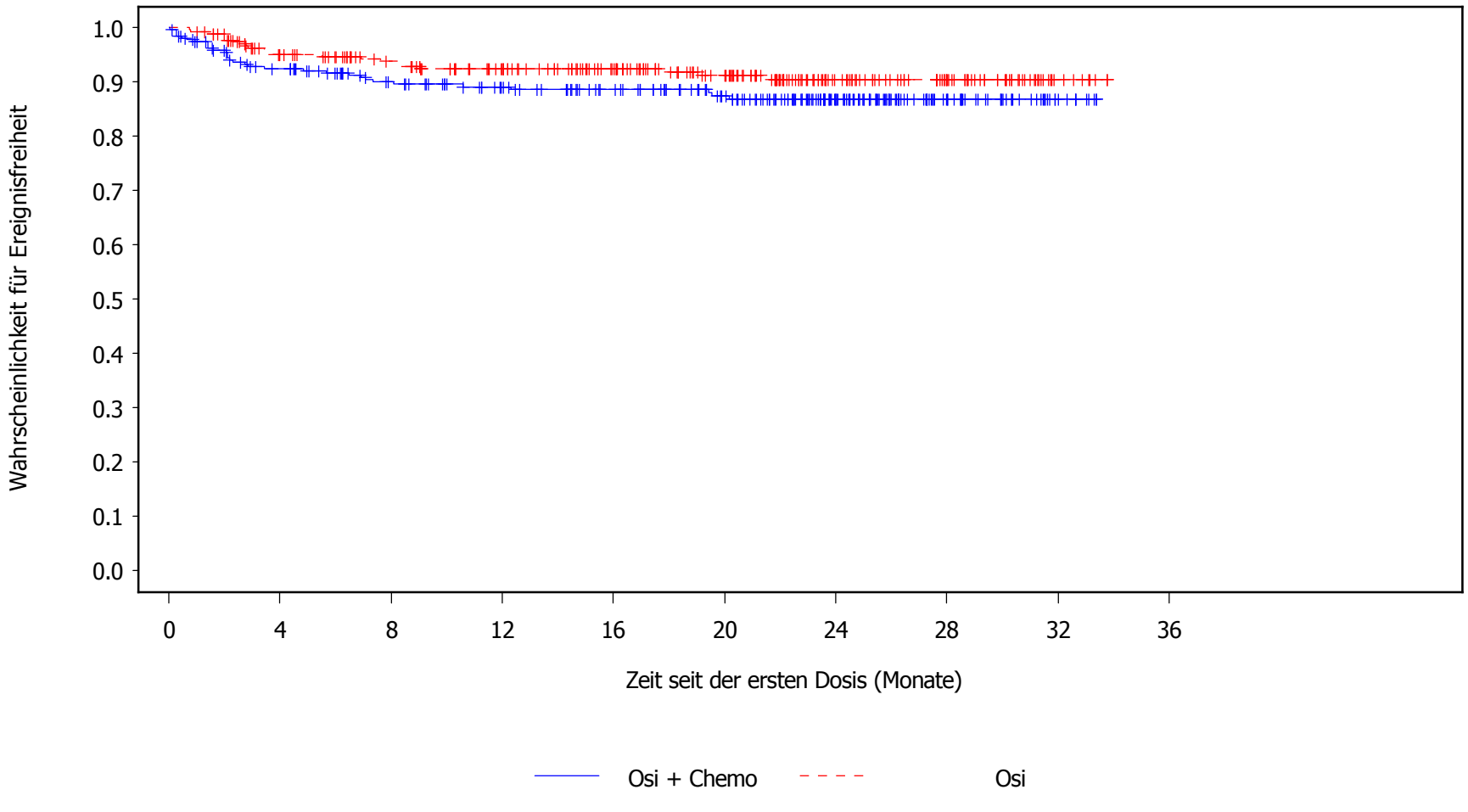


Anzahl an Patienten unter Risiko:

276	249	226	206	184	157	102	43	11	0	Osi + Chemo
275	253	230	204	169	133	79	44	7	0	Osi

root/cdar/d516/payer_germany/ar/d5169c00001_payer_germany/tlf/prod/program/ttemainae.sas gttemainaebdq 24OCT2023:11:33 kvbv306

Figure 3.3.96 FLAURA-2: Kaplan-Meier plot of time to first occurrence of PT: Gewicht erniedrigt
Safety Analysis Set, DCO 03APR2023



Anzahl an Patienten unter Risiko:

276	238	211	192	174	150	97	41	9	0	Osi + Chemo
275	240	217	193	164	130	75	44	7	0	Osi

root/cdar/d516/payer_germany/ar/d5169c00001_payer_germany/tlf/prod/program/ttemainae.sas gttemainaebdr 24OCT2023:11:33 kvbv306

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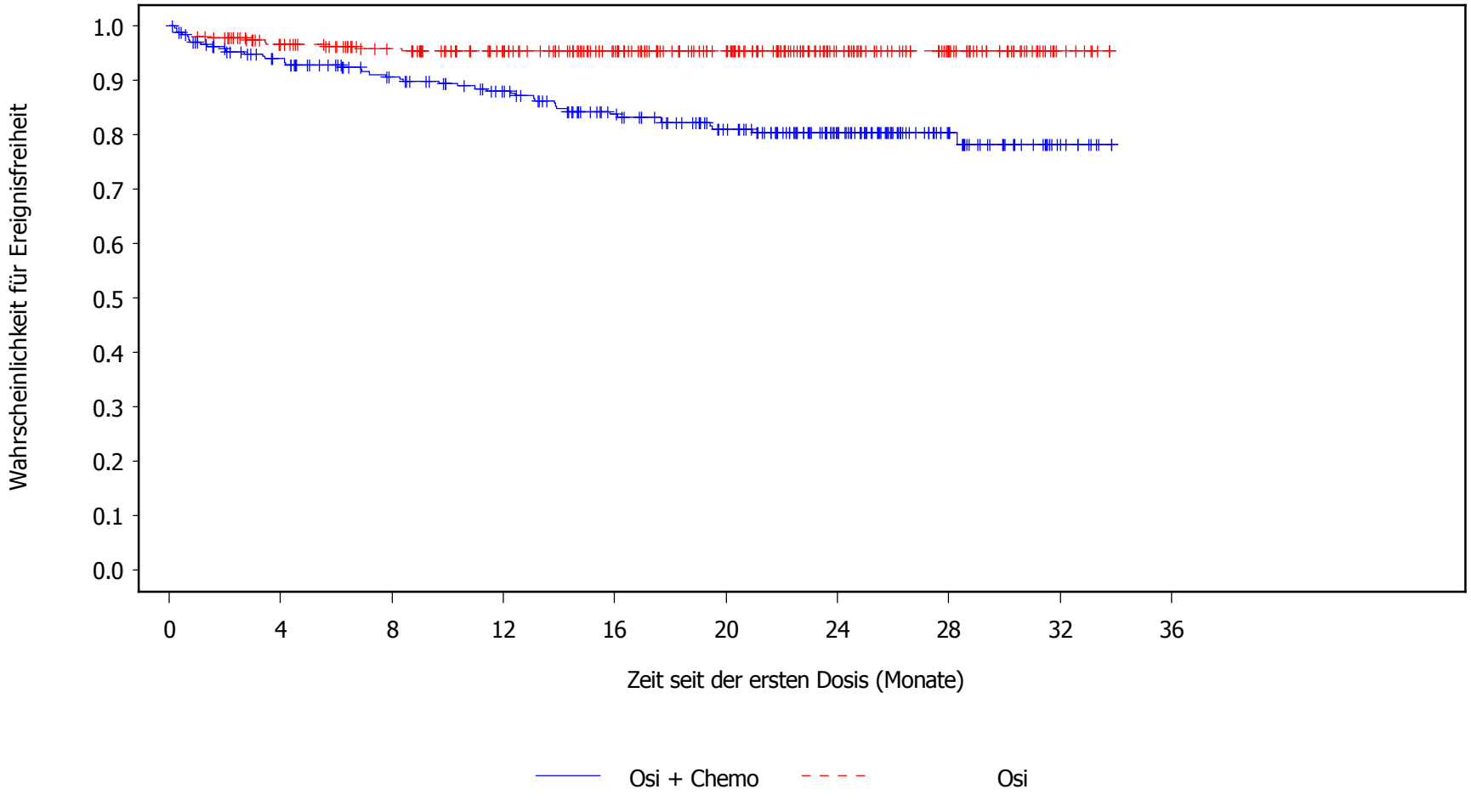
Figure 3.3.97 FLAURA-2: Kaplan-Meier plot of time to first occurrence of PT: Kreatinin im Blut erhoeht
Safety Analysis Set, DCO 03APR2023



Anzahl an Patienten unter Risiko:

276	240	213	193	162	135	90	39	9	0	Osi + Chemo
275	245	222	195	161	127	75	42	7	0	Osi

root/cdar/d516/payer_germany/ar/d5169c00001_payer_germany/tlf/prod/program/ttemainae.sas gttemainaebds 24OCT2023:11:33 kvbv306

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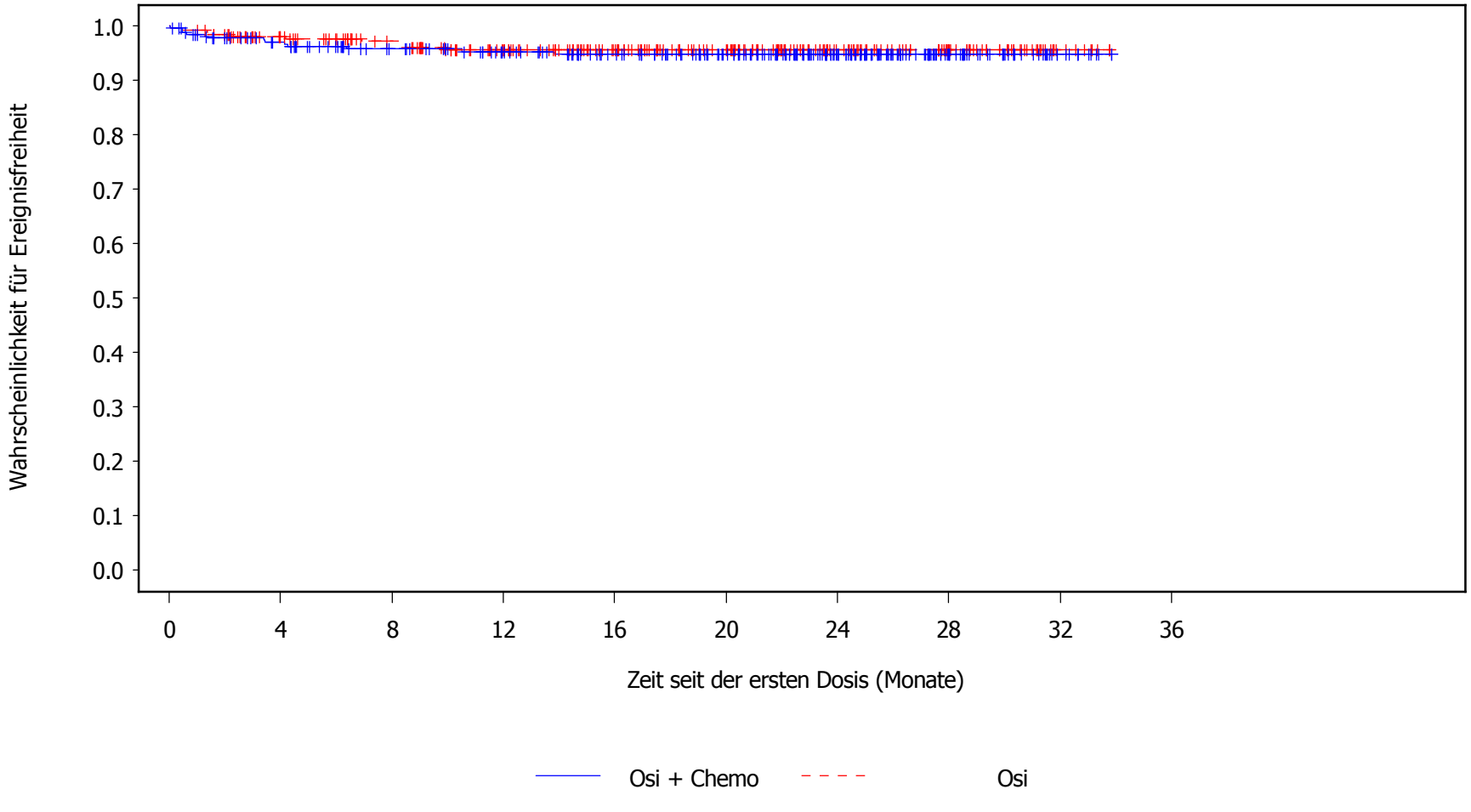
Figure 3.3.98 FLAURA-2: Kaplan-Meier plot of time to first occurrence of PT: Laktatdehydrogenase im Blut erhoeht
Safety Analysis Set, DCO 03APR2023



Anzahl an Patienten unter Risiko:

276	248	224	206	183	155	104	44	10	0	Osi + Chemo
275	249	226	197	162	130	78	43	7	0	Osi

root/cdar/d516/payer_germany/ar/d5169c00001_payer_germany/tlf/prod/program/ttemainae.sas gttemainaebdt 24OCT2023:11:33 kvbv306

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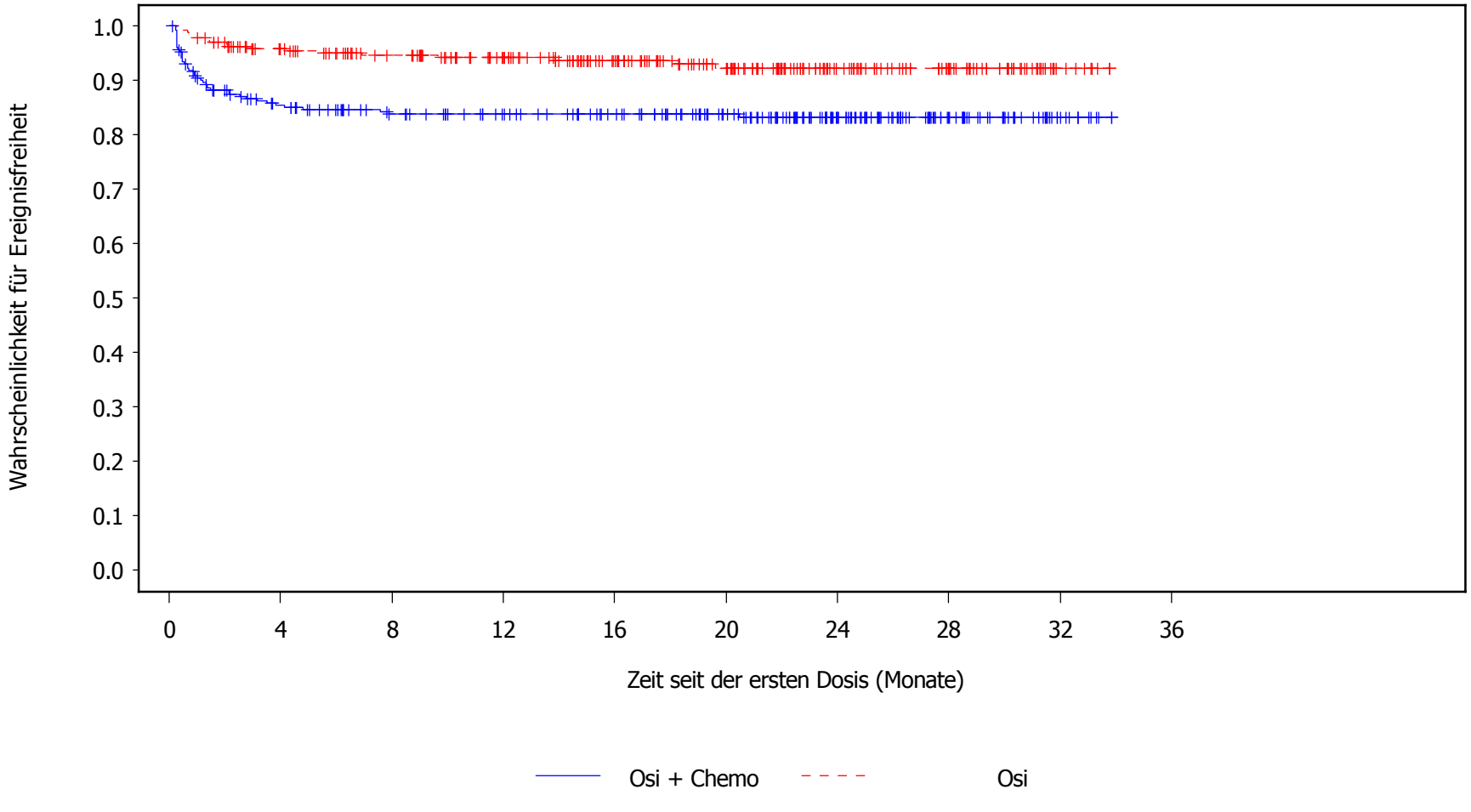
Figure 3.3.99 FLAURA-2: Kaplan-Meier plot of time to first occurrence of PT: Leukozytenzahl erniedrigt
Safety Analysis Set, DCO 03APR2023



Anzahl an Patienten unter Risiko:

276	217	194	180	163	136	89	43	11	0	Osi + Chemo
275	243	219	193	157	122	74	44	7	0	Osi

root/cdar/d516/payer_germany/ar/d5169c00001_payer_germany/tlf/prod/program/ttemainae.sas gttemainaebdu 24OCT2023:11:33 kvbv306

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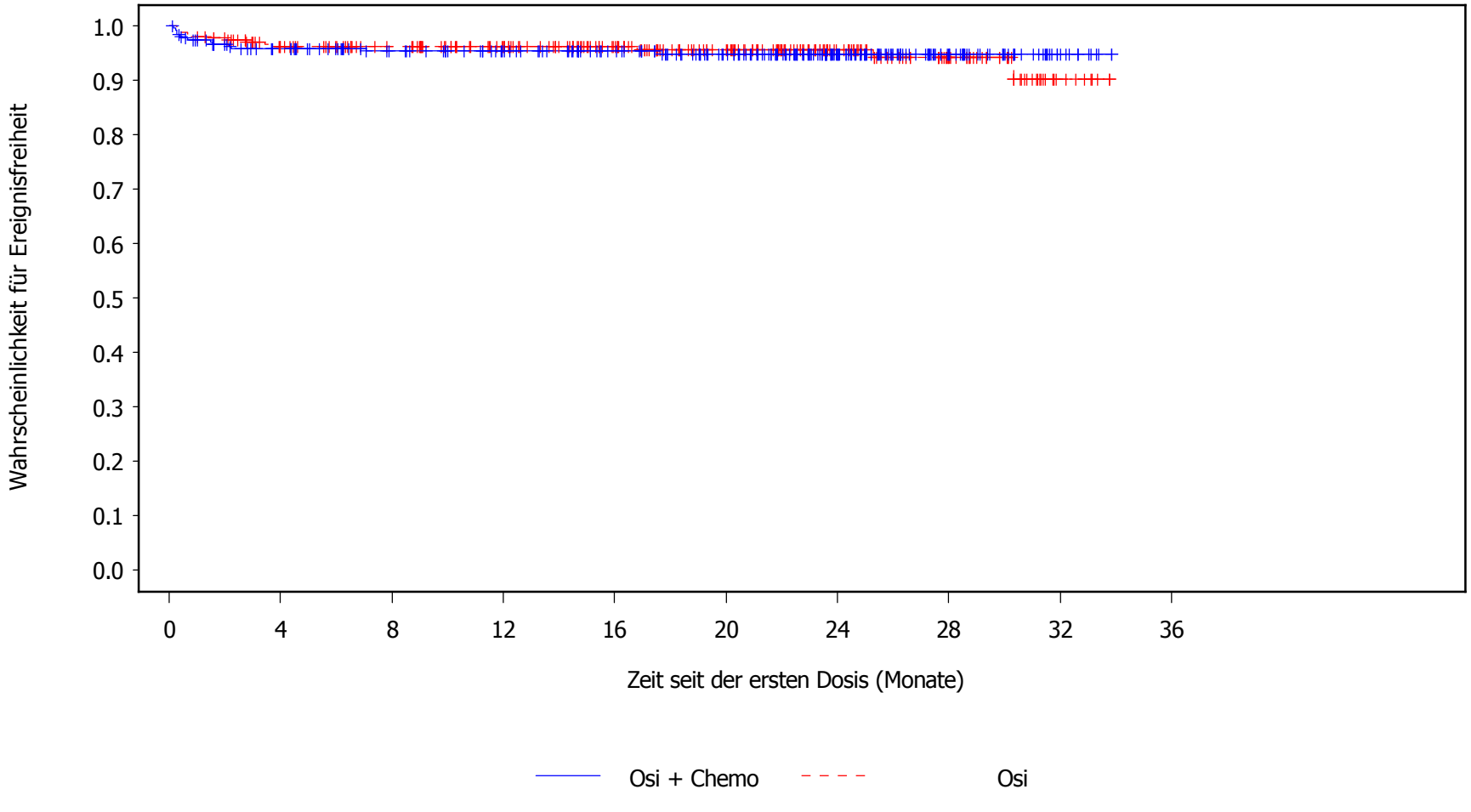
Figure 3.3.100 FLAURA-2: Kaplan-Meier plot of time to first occurrence of PT: Lymphozytenzahl erniedrigt
Safety Analysis Set, DCO 03APR2023



Anzahl an Patienten unter Risiko:

276	245	223	207	185	157	101	45	11	0	Osi + Chemo
275	246	226	201	166	132	80	43	7	0	Osi

root/cdar/d516/payer_germany/ar/d5169c00001_payer_germany/tlf/prod/program/ttemainae.sas gttemainaebdv 24OCT2023:11:33 kvbv306

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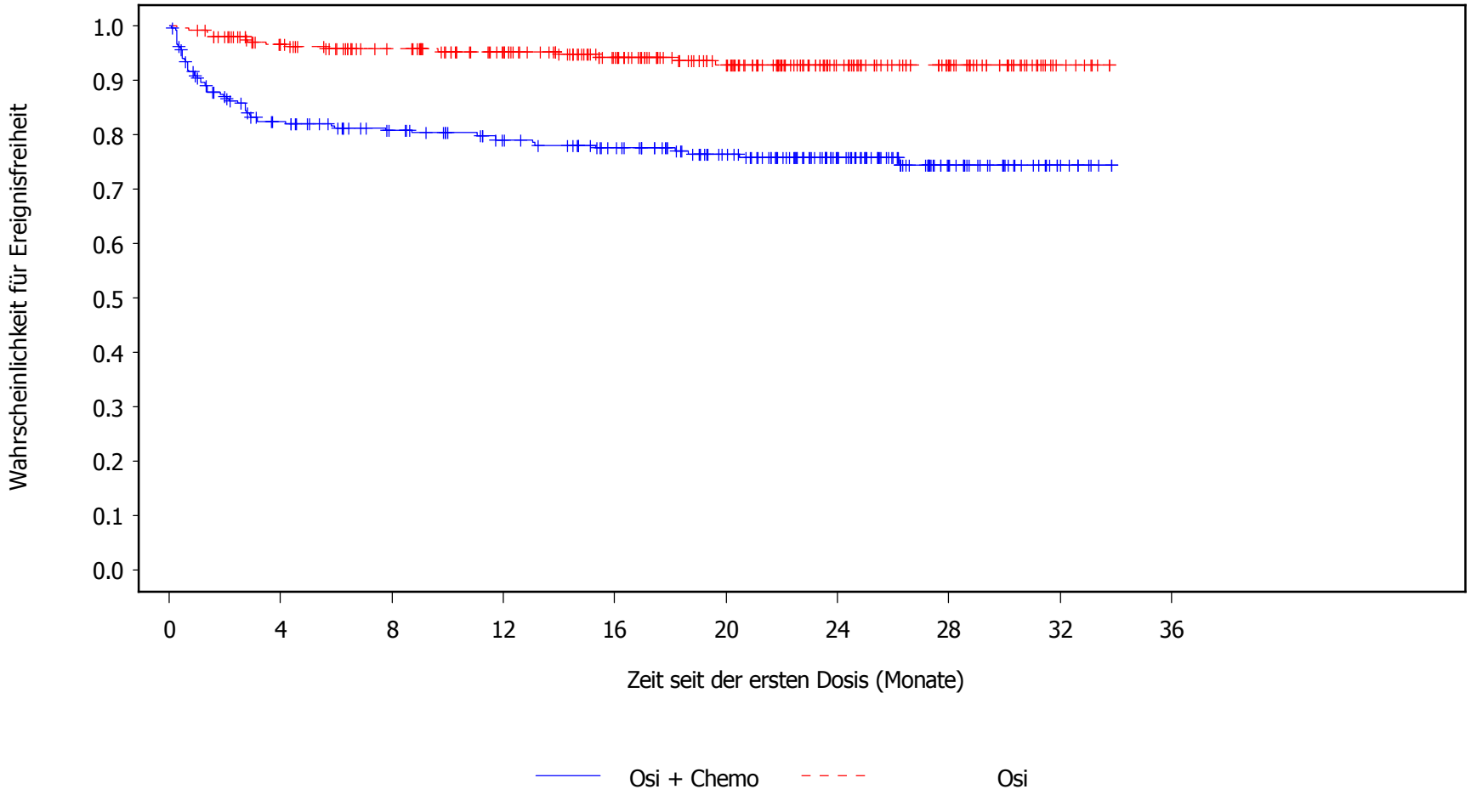
Figure 3.3.101 FLAURA-2: Kaplan-Meier plot of time to first occurrence of PT: Neutrophilenzahl erniedrigt
Safety Analysis Set, DCO 03APR2023



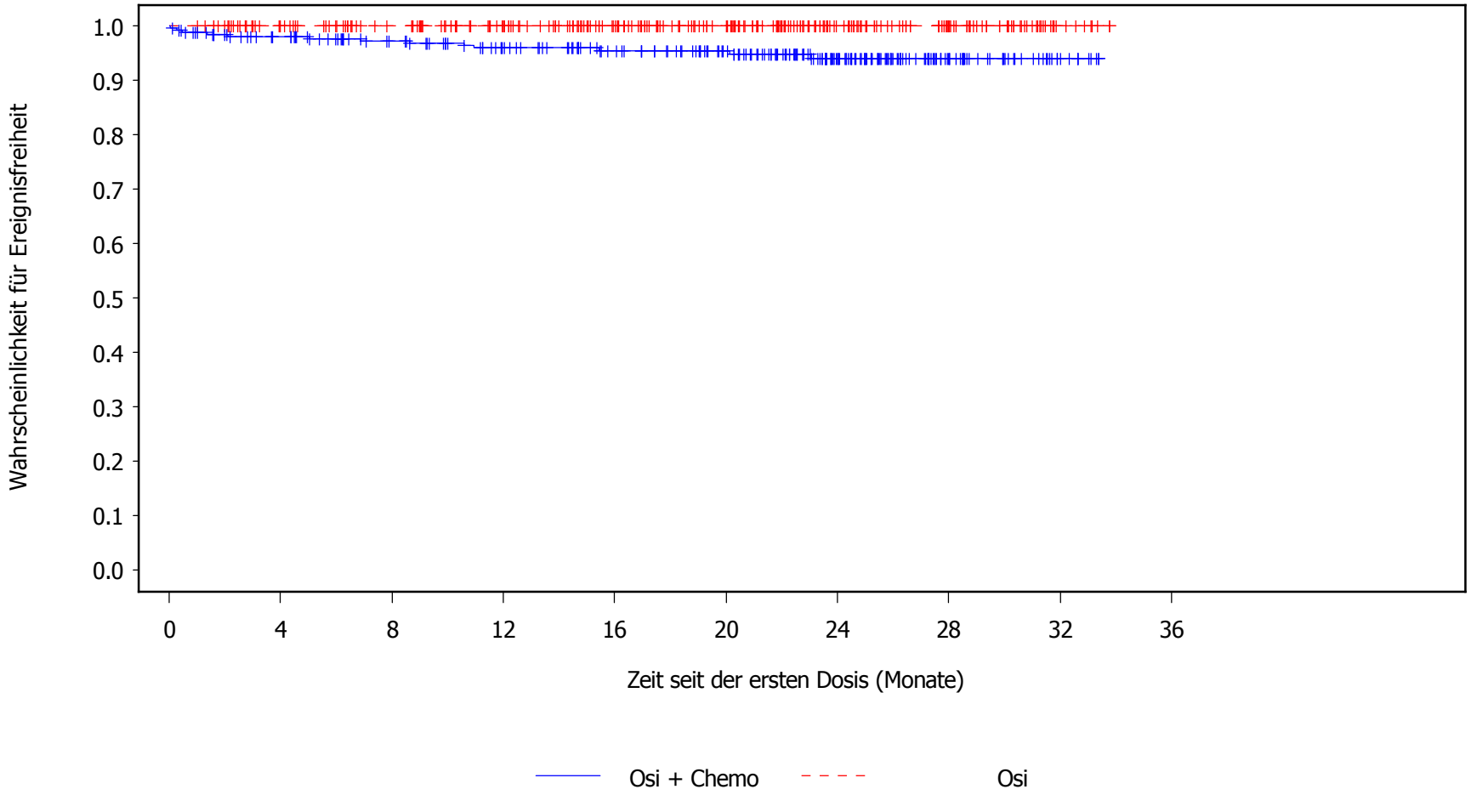
Anzahl an Patienten unter Risiko:

276	209	188	171	154	127	81	35	9	0	Osi + Chemo
275	245	222	196	160	124	73	42	7	0	Osi

root/cdar/d516/payer_germany/ar/d5169c00001_payer_germany/tlf/prod/program/ttemainae.sas gttemainaebdw 24OCT2023:11:33 kvbv306

Nutzenbewertung nach AMNOG Seite 1 von 1

Figure 3.3.102 FLAURA-2: Kaplan-Meier plot of time to first occurrence of PT: Renale Kreatininclearance vermindert
Safety Analysis Set, DCO 03APR2023

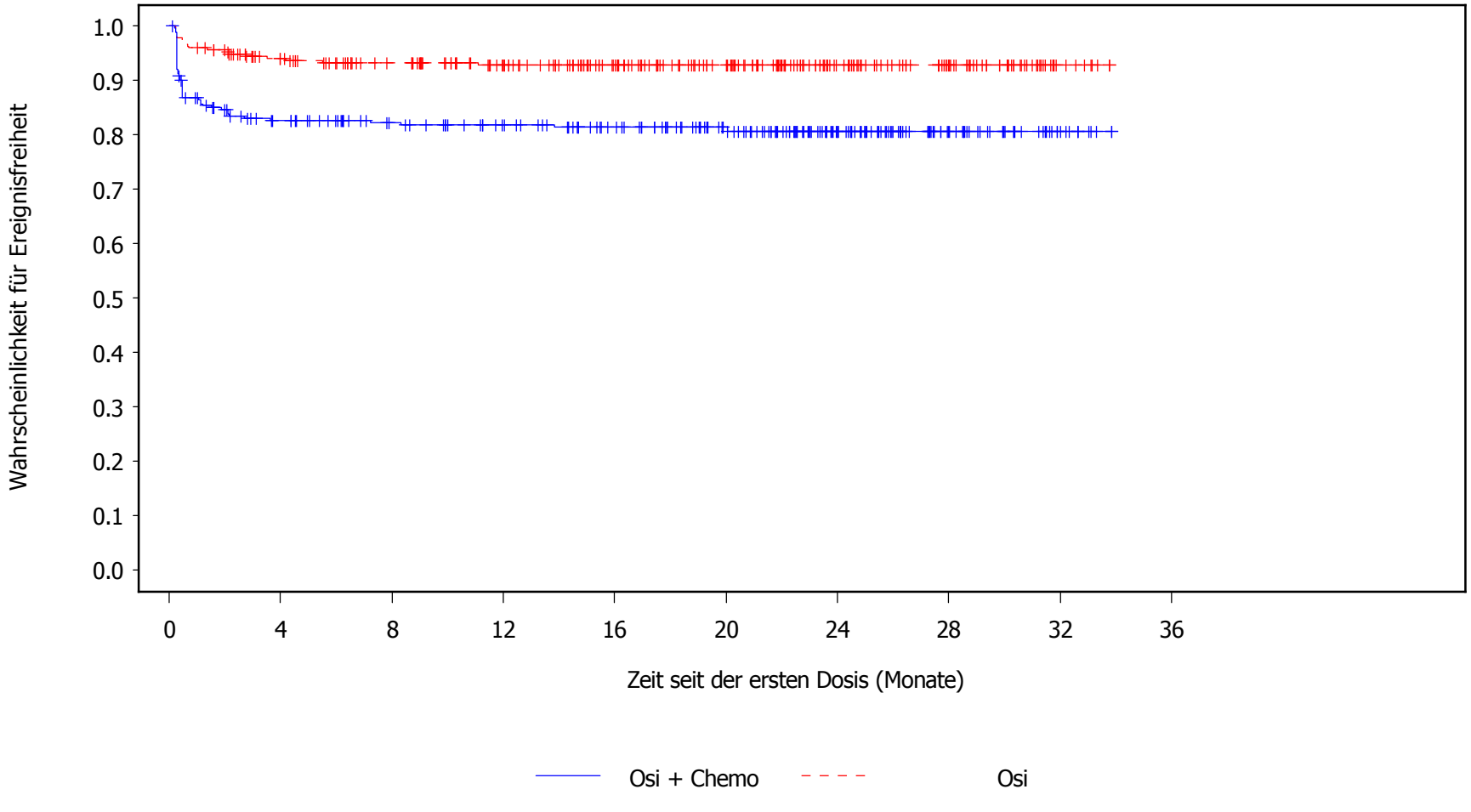


Anzahl an Patienten unter Risiko:

276	251	228	207	184	159	103	40	9	0	Osi + Chemo
275	253	232	206	171	136	80	44	7	0	Osi

root/cdar/d516/payer_germany/ar/d5169c00001_payer_germany/tlf/prod/program/ttemainae.sas gttemainaebdx 24OCT2023:11:33 kvbv306

Figure 3.3.103 FLAURA-2: Kaplan-Meier plot of time to first occurrence of PT: Thrombozytenzahl vermindert
Safety Analysis Set, DCO 03APR2023



Anzahl an Patienten unter Risiko:

276	210	190	176	157	130	83	38	10	0	Osi + Chemo
275	239	216	190	157	124	75	44	7	0	Osi

root/cdar/d516/payer_germany/ar/d5169c00001_payer_germany/tlf/prod/program/ttemainae.sas gttemainaebdy 24OCT2023:11:33 kvbv306

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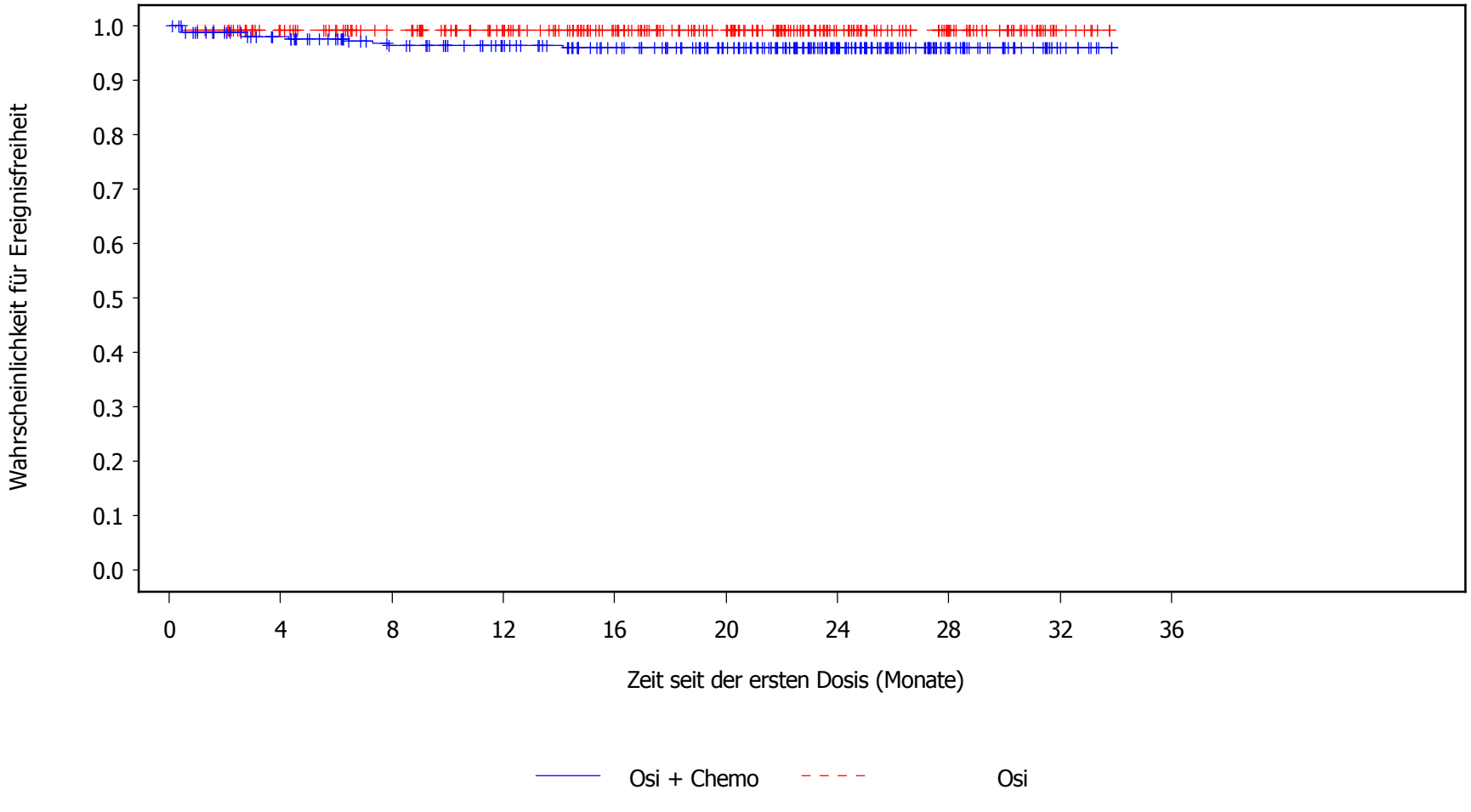
Figure 3.3.104 FLAURA-2: Kaplan-Meier plot of time to first occurrence of PT: Transaminasen erhoeht
Safety Analysis Set, DCO 03APR2023



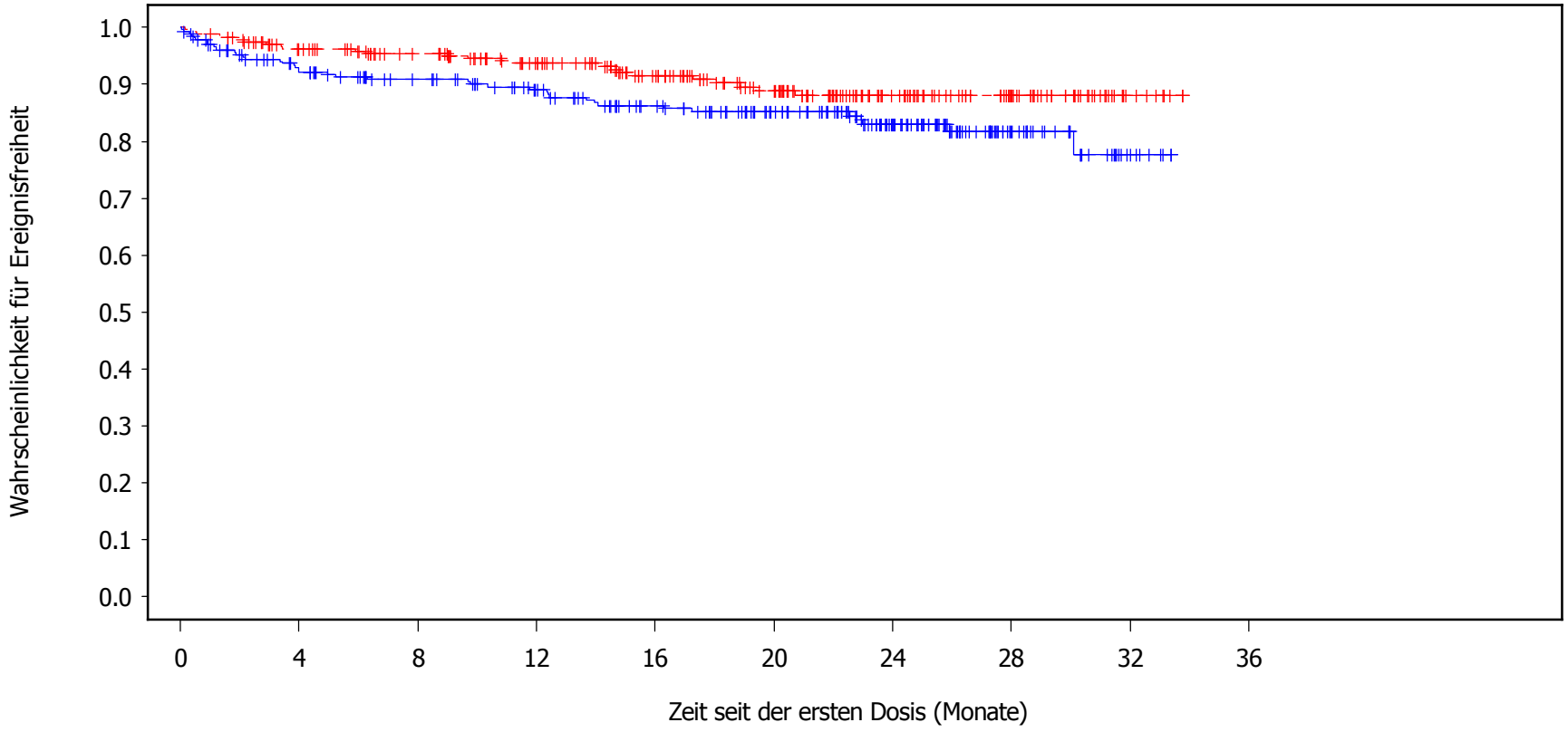
Anzahl an Patienten unter Risiko:

276	251	226	209	187	160	103	41	9	0	Osi + Chemo
275	253	232	206	171	136	80	44	7	0	Osi

root/cdar/d516/payer_germany/ar/d5169c00001_payer_germany/tlf/prod/program/ttemainae.sas gttemainaebdz 24OCT2023:11:33 kvbv306

Nutzenbewertung nach AMNOG Seite 1 von 1

Figure 3.3.105 FLAURA-2: Kaplan-Meier plot of time to first occurrence of SOC: Verletzung, Vergiftung und durch Eingriffe bedingte Komplikationen
Safety Analysis Set, DCO 03APR2023



Anzahl an Patienten unter Risiko:

276	236	214	193	168	140	93	34	7	0	Osi + Chemo
275	247	225	196	160	125	77	41	7	0	Osi

root/cdar/d516/payer_germany/ar/d5169c00001_payer_germany/tlf/prod/program/ttemainae.sas gttemainaebea 24OCT2023:11:33 kvbv306

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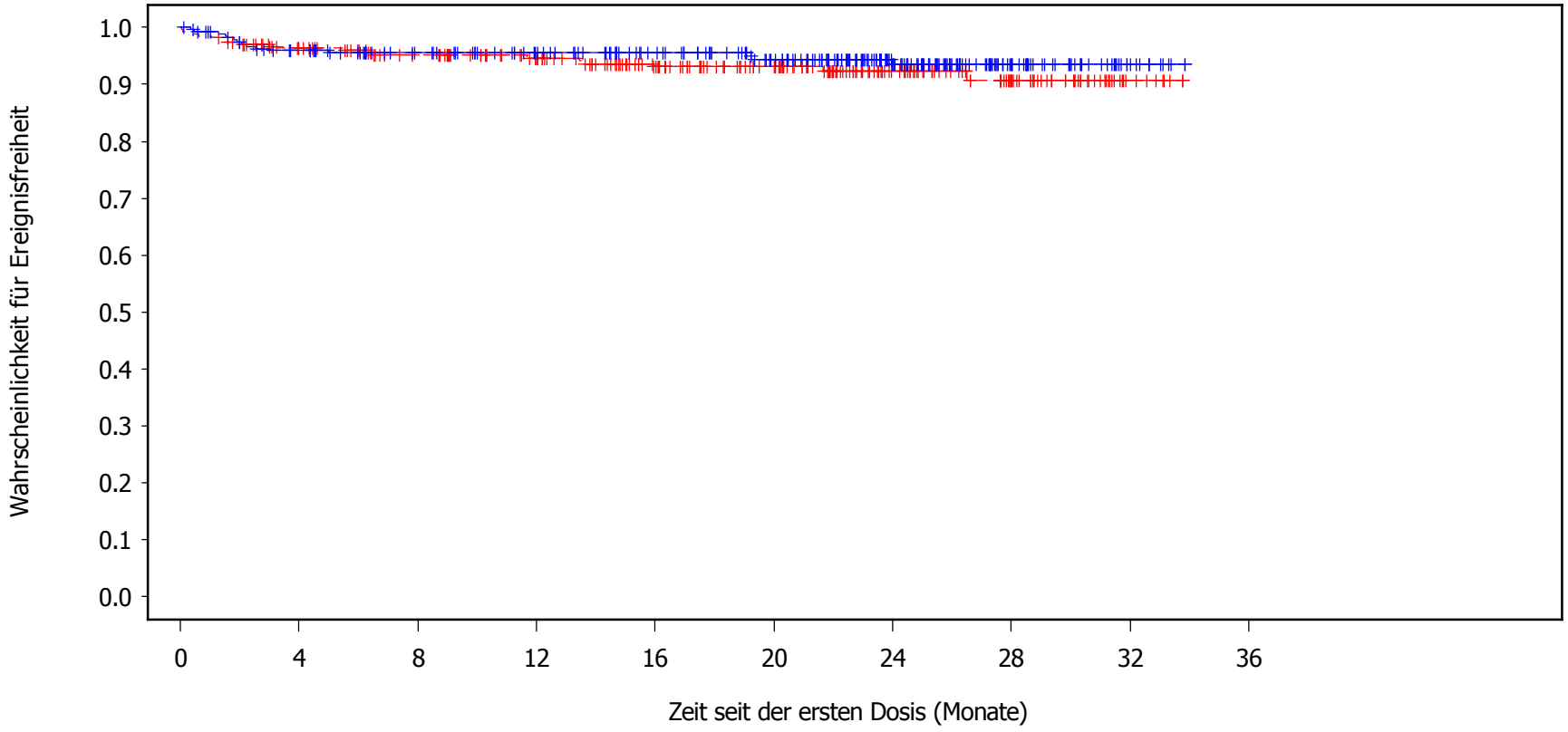
Figure 3.3.107 FLAURA-2: Kaplan-Meier plot of time to first occurrence of SUE SOC: Erkrankungen der Atemwege, des Brustraums und Mediastinums
Safety Analysis Set, DCO 03APR2023



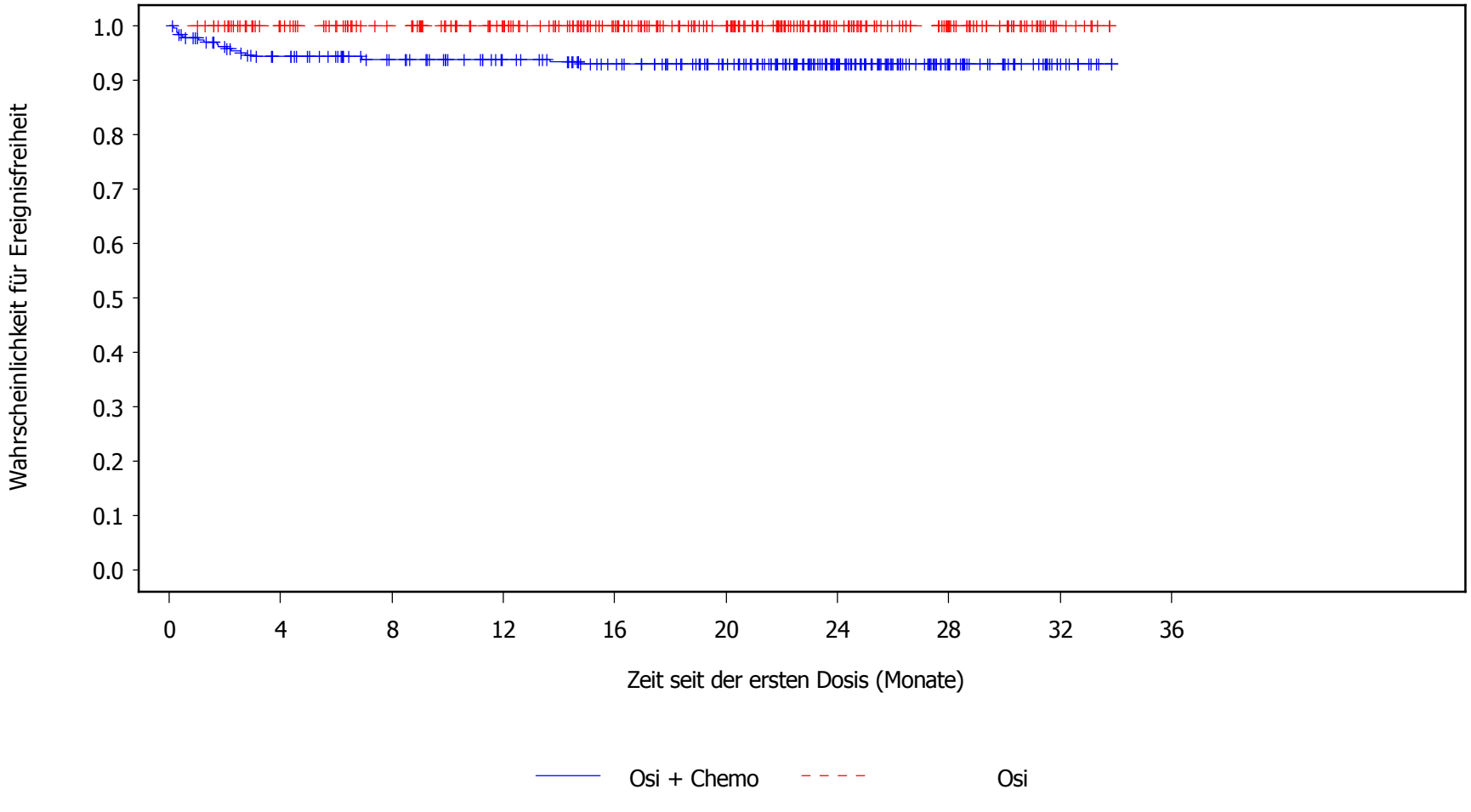
Anzahl an Patienten unter Risiko:

276	252	231	214	192	165	108	45	11	0	Osi + Chemo
275	247	225	201	166	135	80	43	7	0	Osi

root/cdar/d516/payer_germany/ar/d5169c00001_payer_germany/tlf/prod/program/ttemainae.sas gttemainaebec 24OCT2023:11:33 kvbv306

Nutzenbewertung nach AMNOG Seite 1 von 1

Figure 3.3.108 FLAURA-2: Kaplan-Meier plot of time to first occurrence of SUE SOC: Erkrankungen des Blutes und des Lymphsystems
Safety Analysis Set, DCO 03APR2023



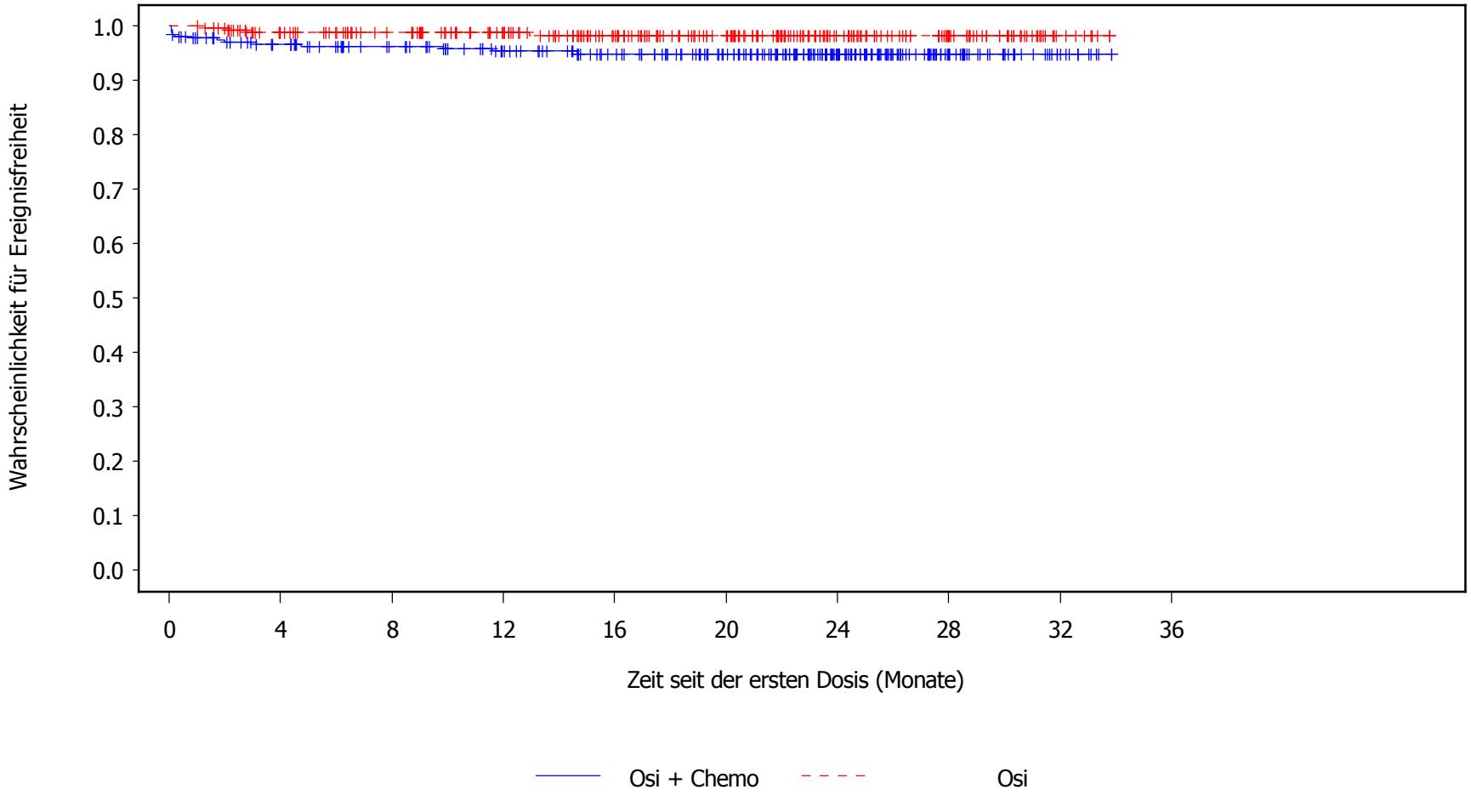
Anzahl an Patienten unter Risiko:

276	241	220	202	182	157	104	44	11	0	Osi + Chemo
275	253	232	206	171	136	80	44	7	0	Osi

root/cdar/d516/payer_germany/ar/d5169c00001_payer_germany/tlf/prod/program/ttemainae.sas gttemainaebed 24OCT2023:11:33 kvbv306

Nutzenbewertung nach AMNOG Seite 1 von 1

Figure 3.3.109 FLAURA-2: Kaplan-Meier plot of time to first occurrence of SUE SOC: Erkrankungen des Gastrointestinaltrakts
Safety Analysis Set, DCO 03APR2023



Anzahl an Patienten unter Risiko:

276	248	228	208	187	159	104	41	11	0	Osi + Chemo
275	250	229	203	168	133	78	42	7	0	Osi

root/cdar/d516/payer_germany/ar/d5169c00001_payer_germany/tlf/prod/program/ttemainae.sas gttemainaebee 24OCT2023:11:33 kvbv306

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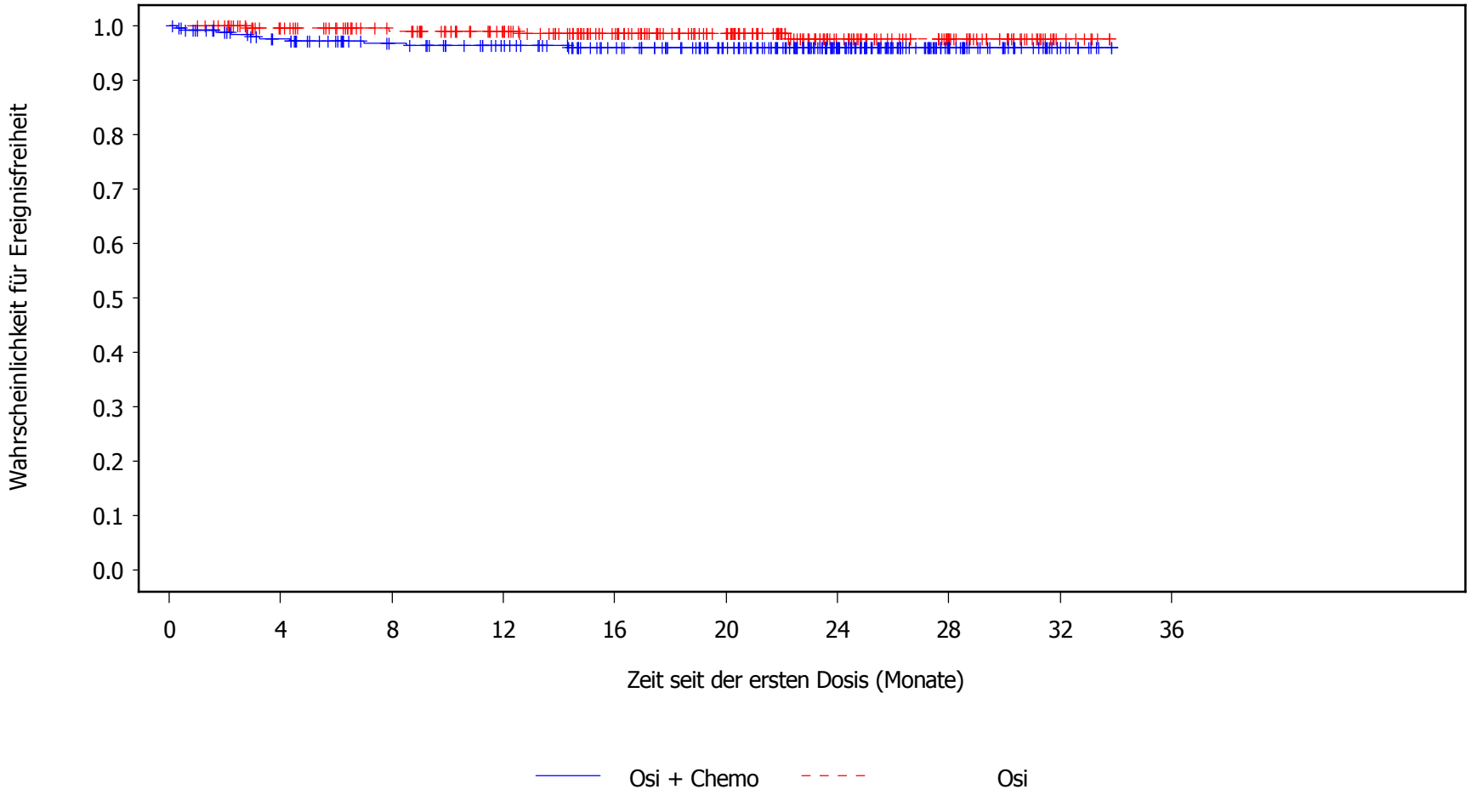
Figure 3.3.110 FLAURA-2: Kaplan-Meier plot of time to first occurrence of SUE SOC: Herzerkrankungen
Safety Analysis Set, DCO 03APR2023



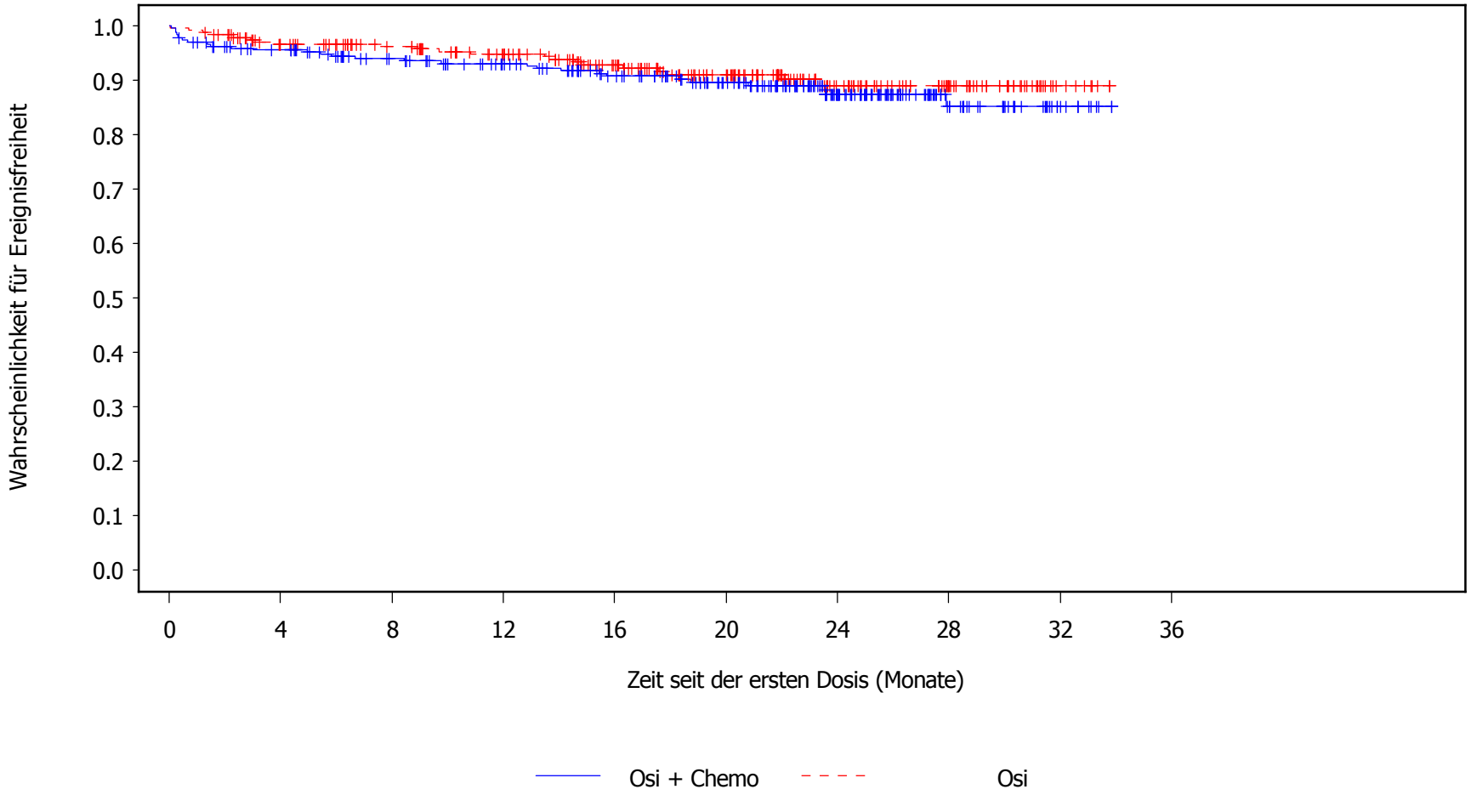
Anzahl an Patienten unter Risiko:

276	251	230	215	192	165	108	45	11	0	Osi + Chemo
275	252	230	205	170	135	79	44	7	0	Osi

root/cdar/d516/payer_germany/ar/d5169c00001_payer_germany/tlf/prod/program/ttemainae.sas gttemainaebef 24OCT2023:11:33 kvbv306

Nutzenbewertung nach AMNOG Seite 1 von 1

Figure 3.3.111 FLAURA-2: Kaplan-Meier plot of time to first occurrence of SUE SOC: Infektionen und parasitaere Erkrankungen
Safety Analysis Set, DCO 03APR2023



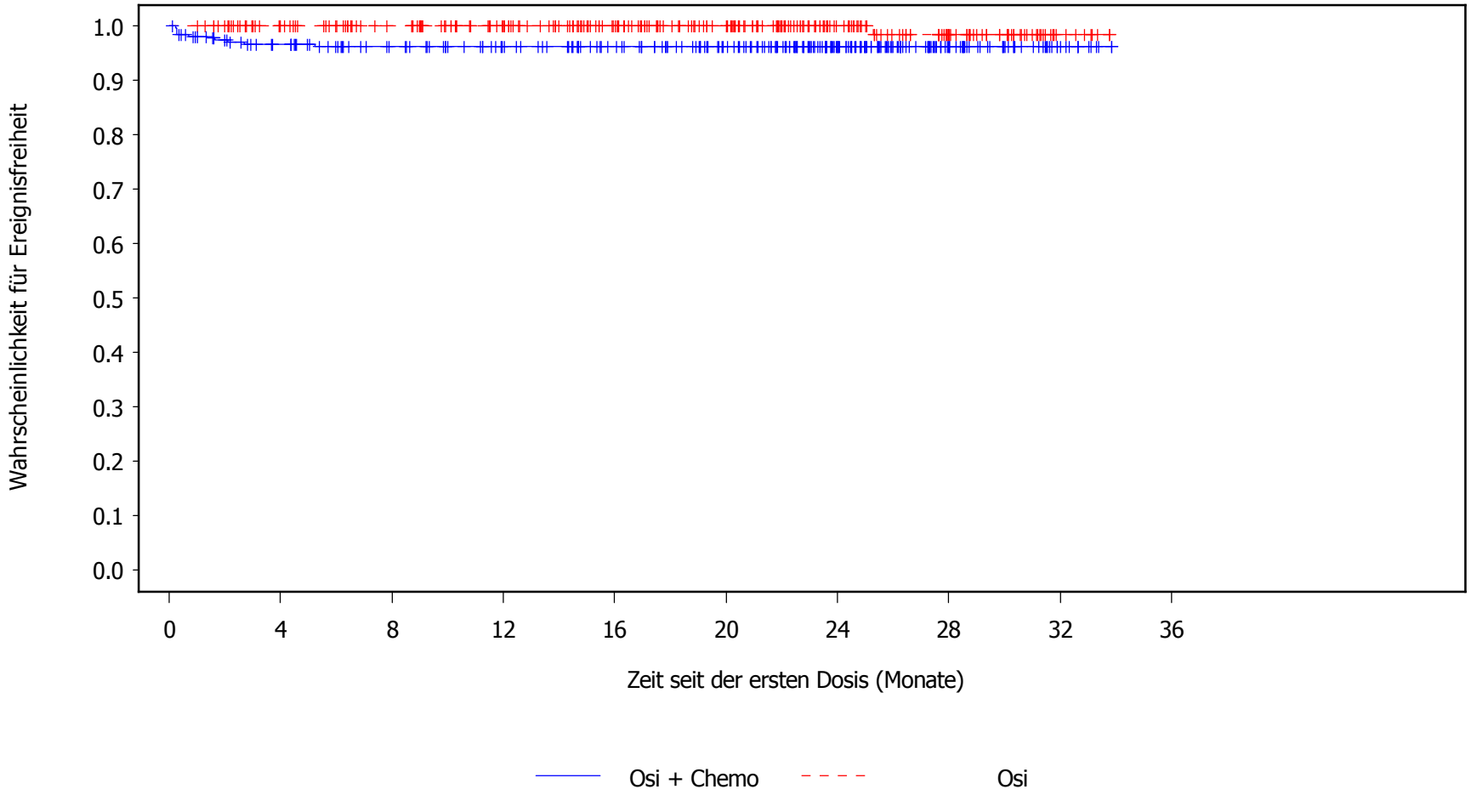
Anzahl an Patienten unter Risiko:

276	251	226	207	181	152	97	37	10	0	Osi + Chemo
275	248	227	204	169	132	77	42	7	0	Osi

root/cdar/d516/payer_germany/ar/d5169c00001_payer_germany/tlf/prod/program/ttemainae.sas gttemainaebeg 24OCT2023:11:33 kvbv306

Nutzenbewertung nach AMNOG Seite 1 von 1

Figure 3.3.112 FLAURA-2: Kaplan-Meier plot of time to first occurrence of SUE SOC: Untersuchungen
Safety Analysis Set, DCO 03APR2023

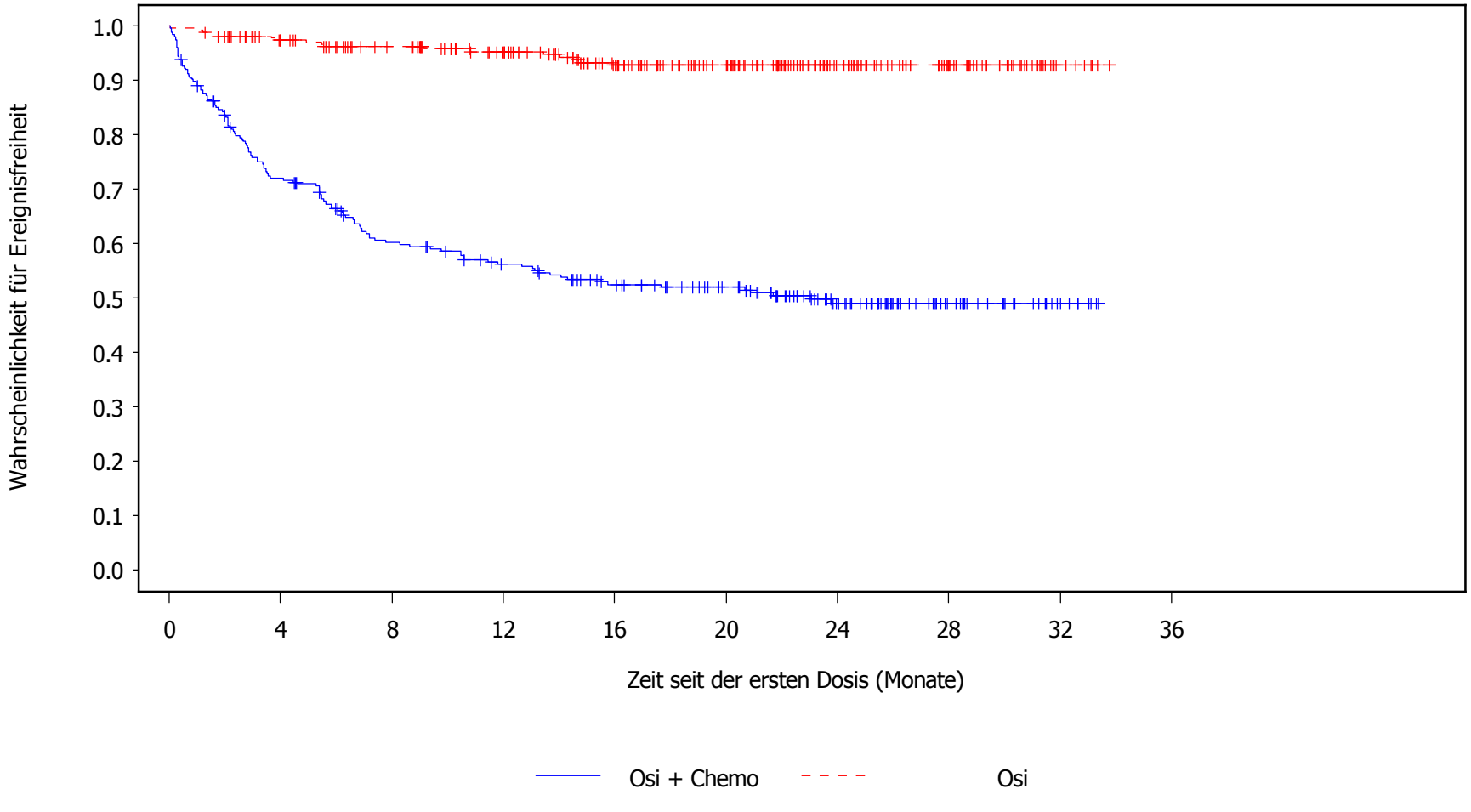


Anzahl an Patienten unter Risiko:

276	247	226	208	188	161	106	45	11	0	Osi + Chemo
275	253	232	206	171	136	80	43	7	0	Osi

root/cdar/d516/payer_germany/ar/d5169c00001_payer_germany/tlf/prod/program/ttemainae.sas gttemainaebeh 24OCT2023:11:33 kvbv306

Figure 3.3.113 FLAURA-2: Kaplan-Meier plot of time to first occurrence of Therapieabbruch aufgrund von UE
Safety Analysis Set, DCO 03APR2023



Anzahl an Patienten unter Risiko:

276	194	155	138	120	103	67	29	8	0	Osi + Chemo
275	251	232	206	170	136	80	44	7	0	Osi

root/cdar/d516/payer_germany/ar/d5169c00001_payer_germany/tlf/prod/program/ttemainae.sas gttemainaebei 24OCT2023:11:33 kvbv306

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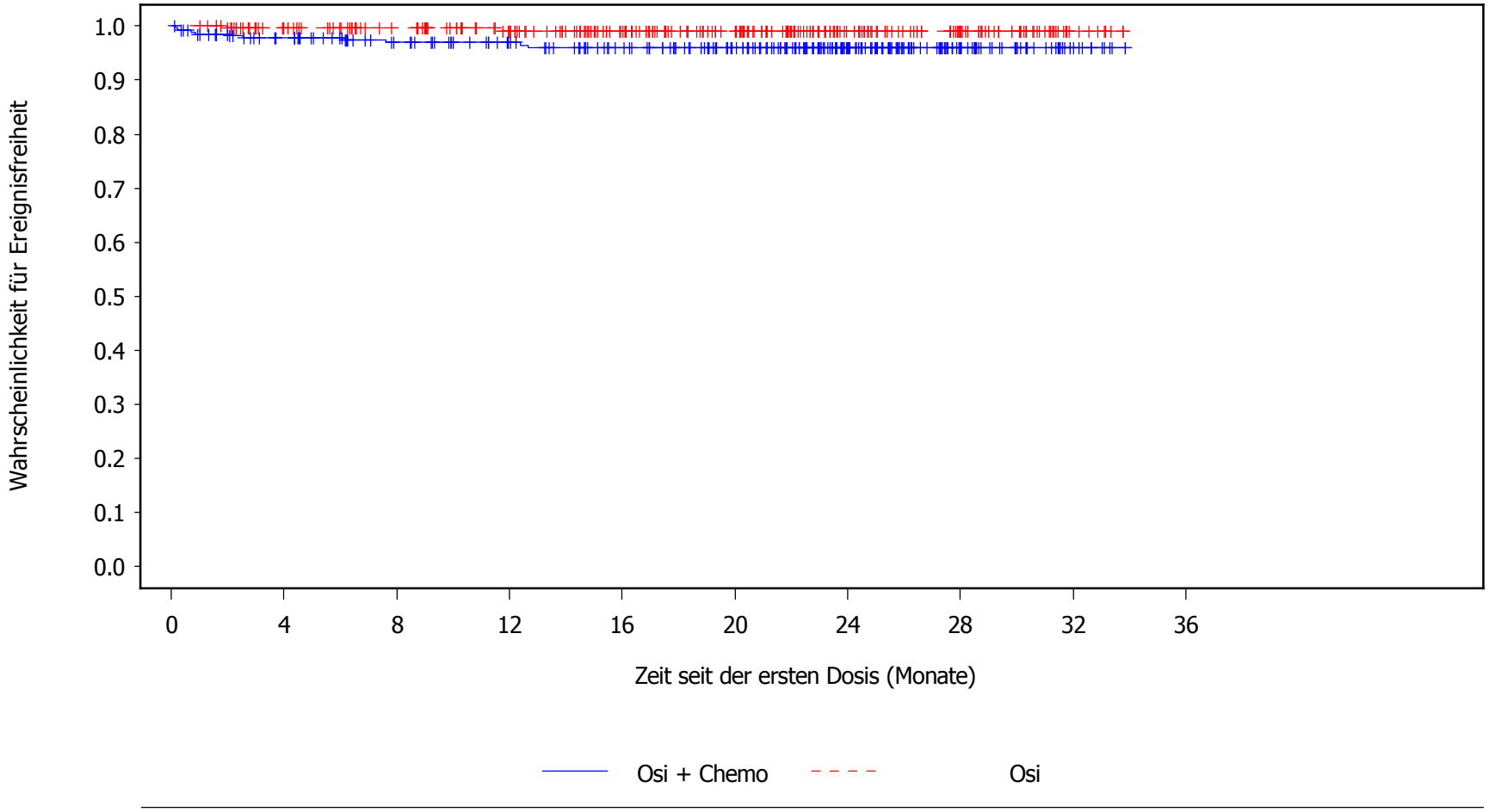
Figure 3.3.115 FLAURA-2: Kaplan-Meier plot of time to first occurrence of G>=3 SOC: Allgemeine Erkrankungen und Beschwerden am Verabreichungsort
Safety Analysis Set, DCO 03APR2023



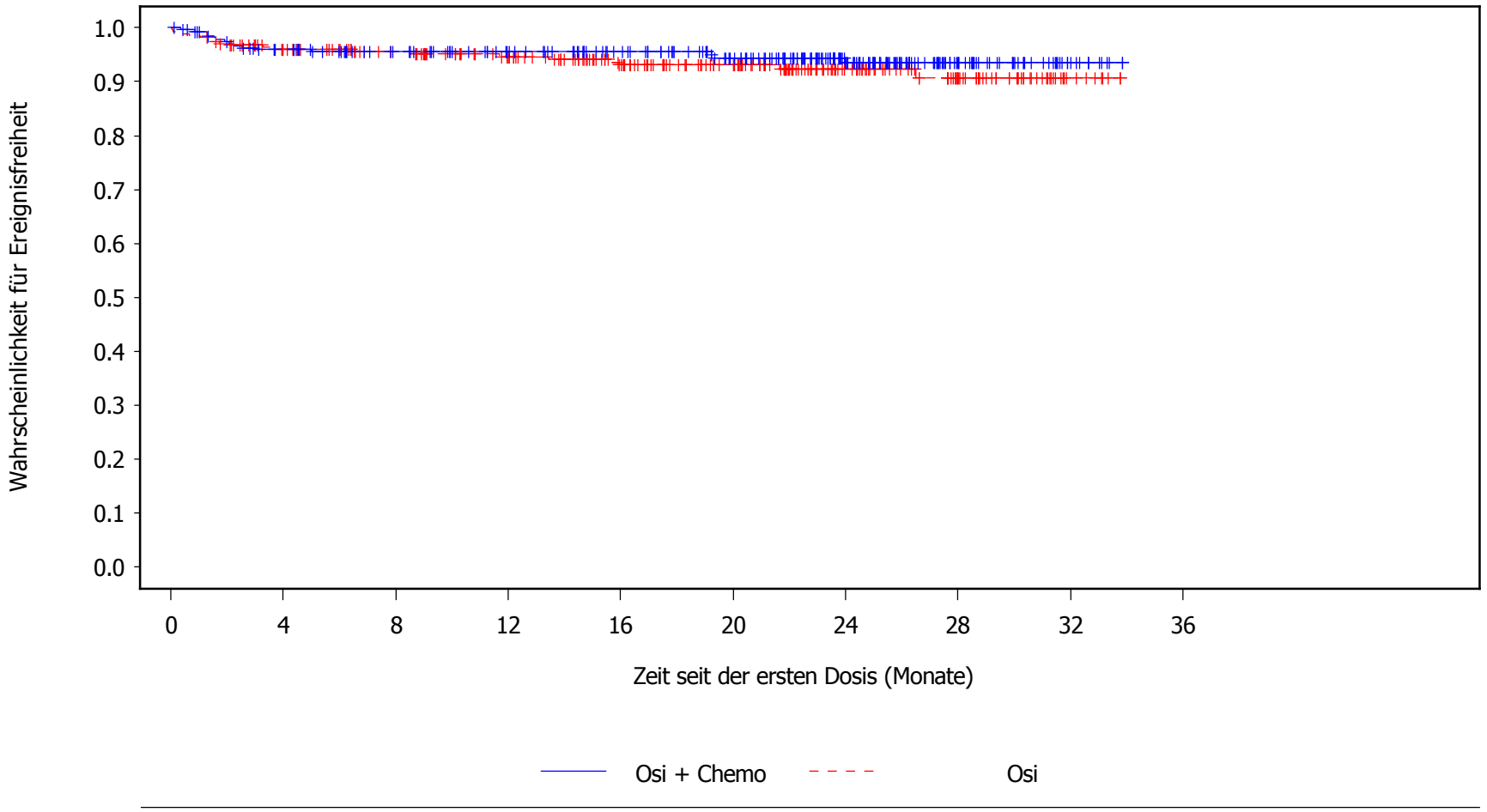
Anzahl an Patienten unter Risiko:

276	251	228	211	191	163	106	45	11	0	Osi + Chemo
275	252	231	206	171	136	80	44	7	0	Osi

root/cdar/d516/payer_germany/ar/d5169c00001_payer_germany/tlf/prod/program/ttemainae.sas gttemainaebek 24OCT2023:11:33 kvbv306

Nutzenbewertung nach AMNOG Seite 1 von 1

Figure 3.3.116 FLAURA-2: Kaplan-Meier plot of time to first occurrence of G>=3 SOC: Erkrankungen der Atemwege, des Brustraums und Mediastinums
Safety Analysis Set, DCO 03APR2023



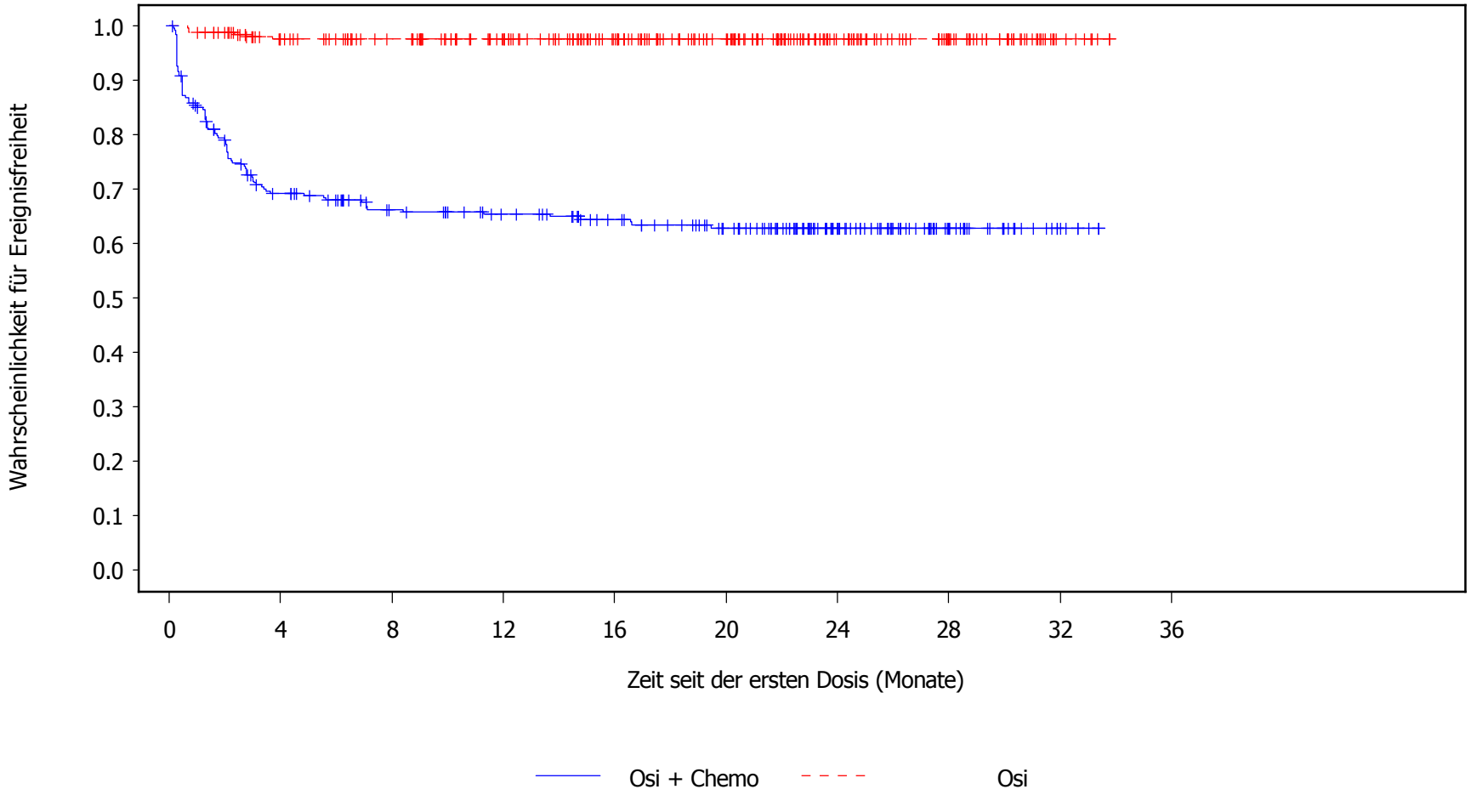
Anzahl an Patienten unter Risiko:

276	251	230	213	192	165	108	45	11	0	Osi + Chemo
275	248	227	203	167	135	80	43	7	0	Osi

root/cdar/d516/payer_germany/ar/d5169c00001_payer_germany/tlf/prod/program/ttemainae.sas gttemainaebel 24OCT2023:11:33 kvbv306

Nutzenbewertung nach AMNOG Seite 1 von 1

Figure 3.3.117 FLAURA-2: Kaplan-Meier plot of time to first occurrence of G>=3 SOC: Erkrankungen des Blutes und des Lymphsystems
Safety Analysis Set, DCO 03APR2023



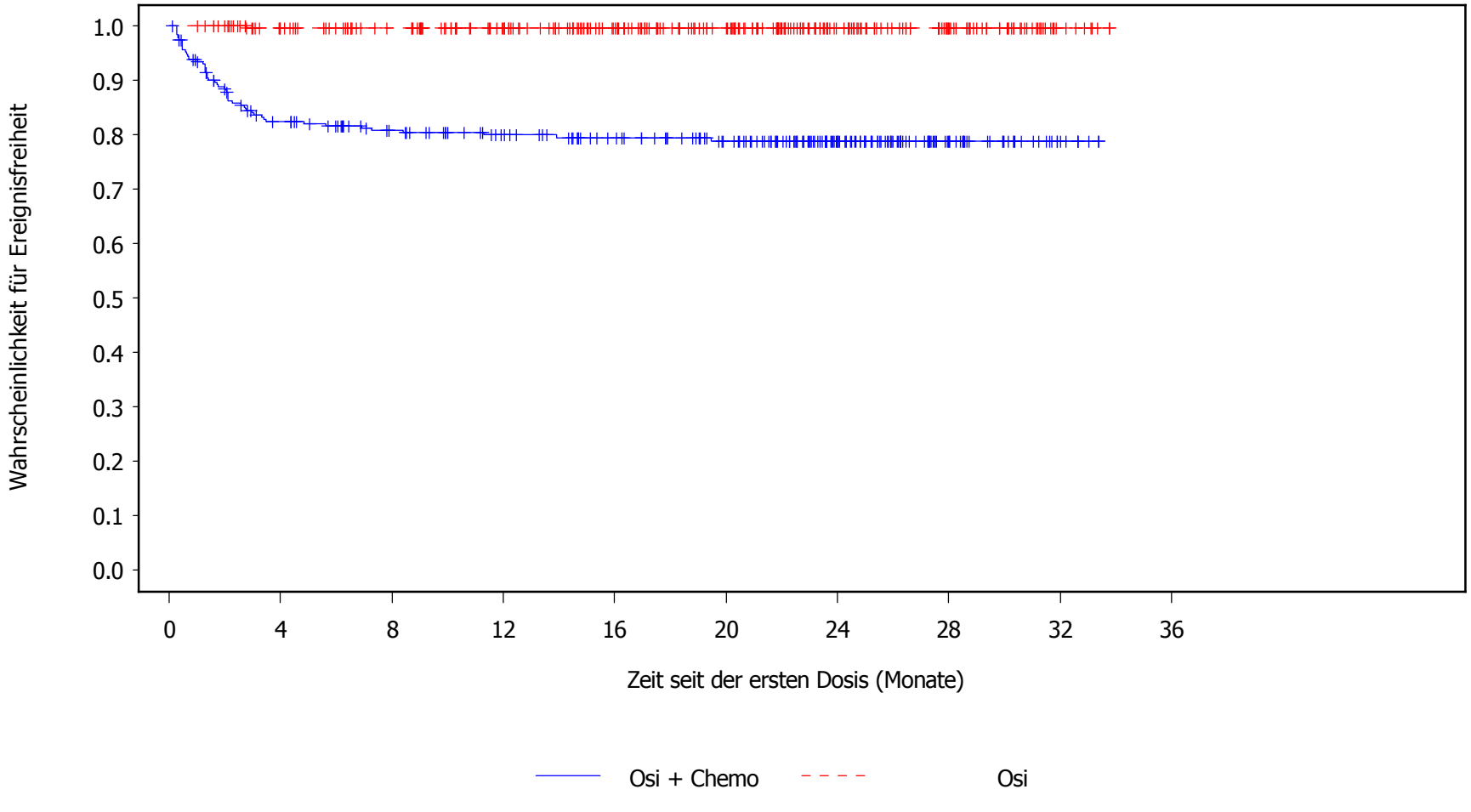
Anzahl an Patienten unter Risiko:

276	179	154	142	126	108	68	29	6	0	Osi + Chemo
275	247	228	202	168	133	78	44	7	0	Osi

root/cdar/d516/payer_germany/ar/d5169c00001_payer_germany/tlf/prod/program/ttemainae.sas gttemainaebem 24OCT2023:11:33 kvbv306

Nutzenbewertung nach AMNOG Seite 1 von 1

Figure 3.3.118 FLAURA-2: Kaplan-Meier plot of time to first occurrence of G>=3 PT: Anaemie
Safety Analysis Set, DCO 03APR2023



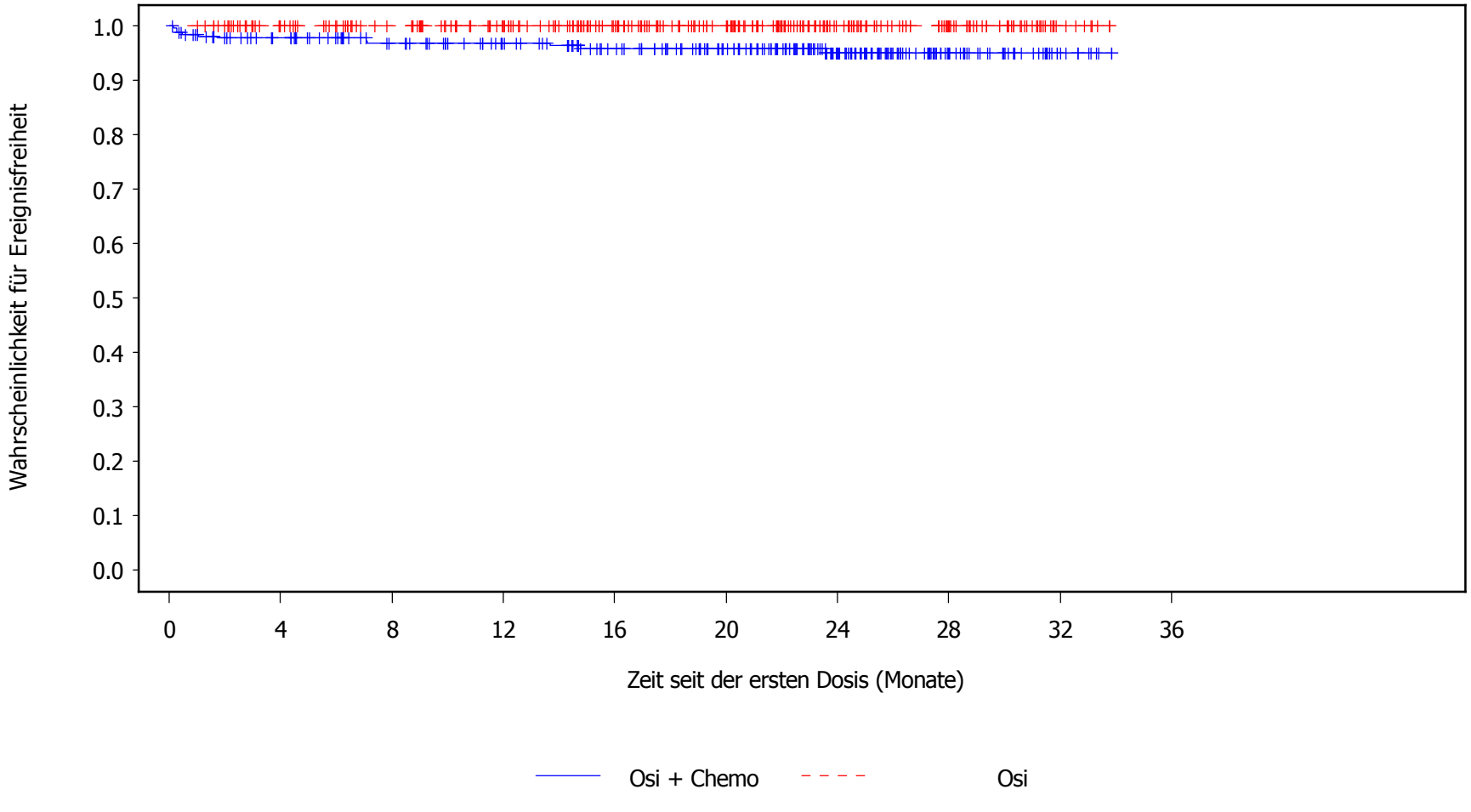
Anzahl an Patienten unter Risiko:

276	213	191	174	156	136	87	34	7	0	Osi + Chemo
275	252	232	206	171	136	80	44	7	0	Osi

root/cdar/d516/payer_germany/ar/d5169c00001_payer_germany/tlf/prod/program/ttemainae.sas gttemainaeben 24OCT2023:11:33 kvbv306

Nutzenbewertung nach AMNOG Seite 1 von 1

Figure 3.3.119 FLAURA-2: Kaplan-Meier plot of time to first occurrence of G>=3 PT: Febrile Neutropenie
Safety Analysis Set, DCO 03APR2023



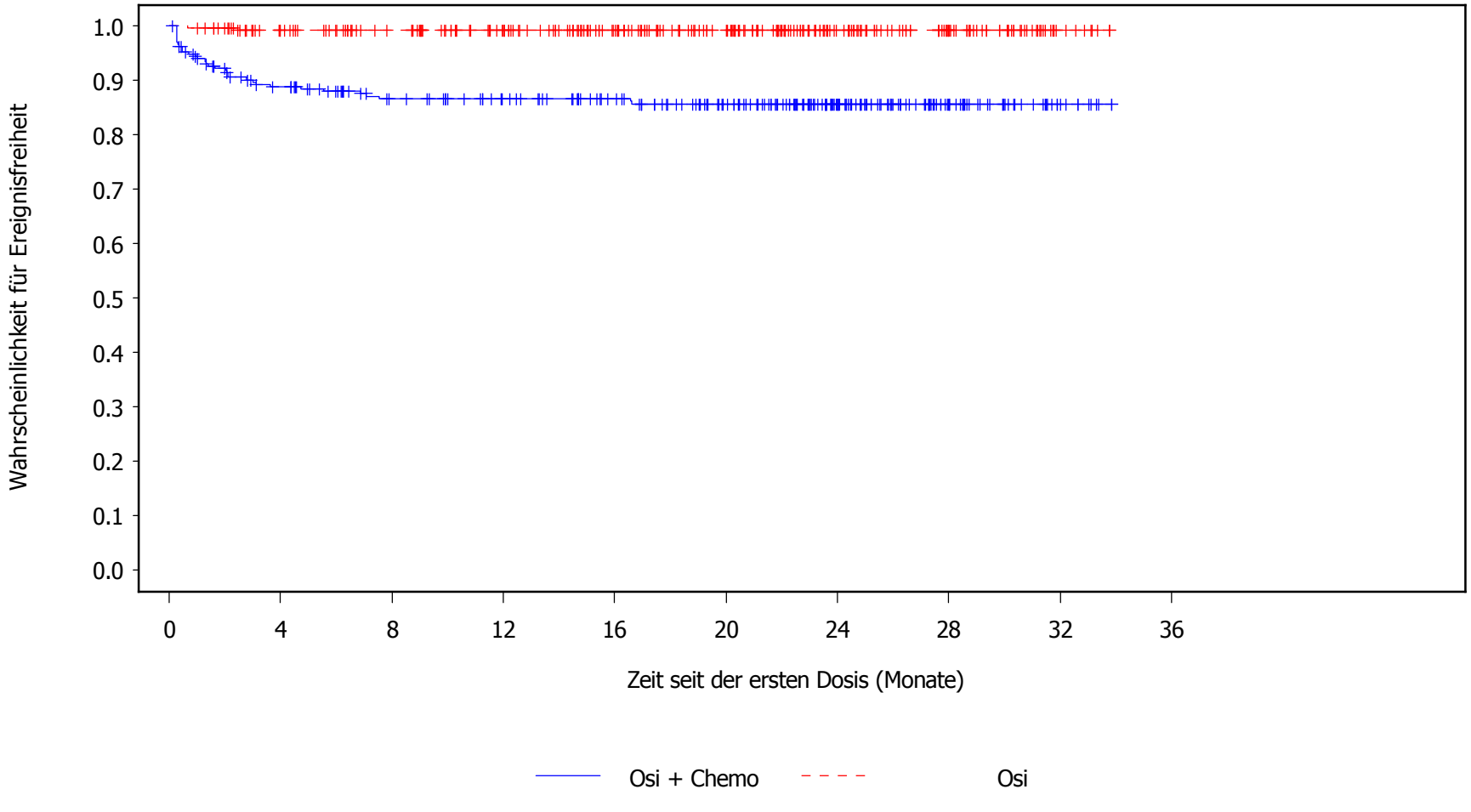
Anzahl an Patienten unter Risiko:

276	250	227	209	187	159	106	42	10	0	Osi + Chemo
275	253	232	206	171	136	80	44	7	0	Osi

root/cdar/d516/payer_germany/ar/d5169c00001_payer_germany/tlf/prod/program/ttemainae.sas gttemainaebeo 24OCT2023:11:33 kvbv306

Nutzenbewertung nach AMNOG Seite 1 von 1

Figure 3.3.120 FLAURA-2: Kaplan-Meier plot of time to first occurrence of G>=3 PT: Neutropenie
Safety Analysis Set, DCO 03APR2023



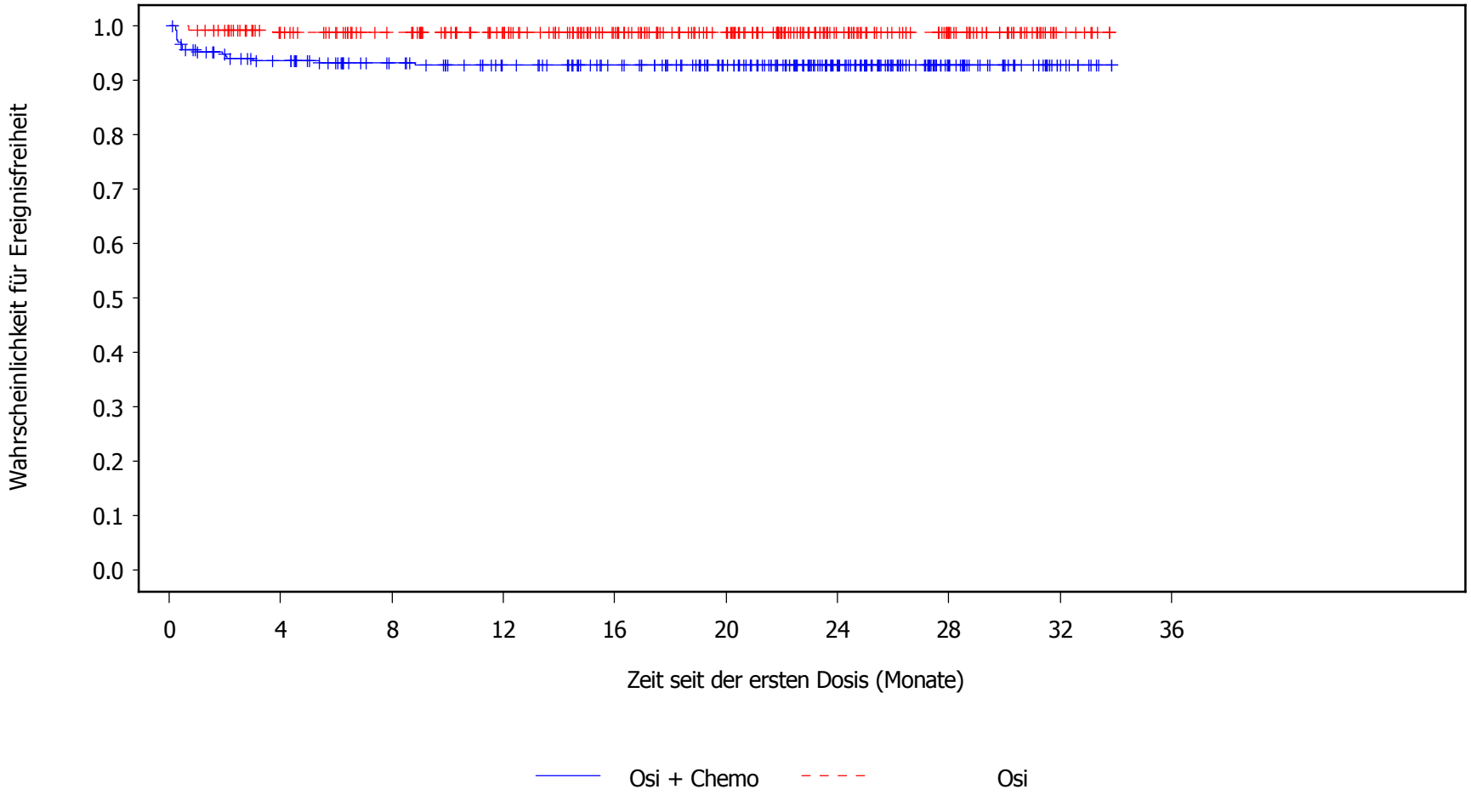
Anzahl an Patienten unter Risiko:

276	227	201	187	168	141	89	39	9	0	Osi + Chemo
275	251	230	204	170	135	80	44	7	0	Osi

root/cdar/d516/payer_germany/ar/d5169c00001_payer_germany/tlf/prod/program/ttemainae.sas gttemainaebep 24OCT2023:11:33 kvbv306

Nutzenbewertung nach AMNOG Seite 1 von 1

Figure 3.3.121 FLAURA-2: Kaplan-Meier plot of time to first occurrence of G>=3 PT: Thrombozytopenie
Safety Analysis Set, DCO 03APR2023



Anzahl an Patienten unter Risiko:

276	242	220	203	184	157	104	44	10	0	Osi + Chemo
275	250	230	204	169	134	78	44	7	0	Osi

root/cdar/d516/payer_germany/ar/d5169c00001_payer_germany/tlf/prod/program/ttemainae.sas gttemainaebeq 24OCT2023:11:33 kvbv306

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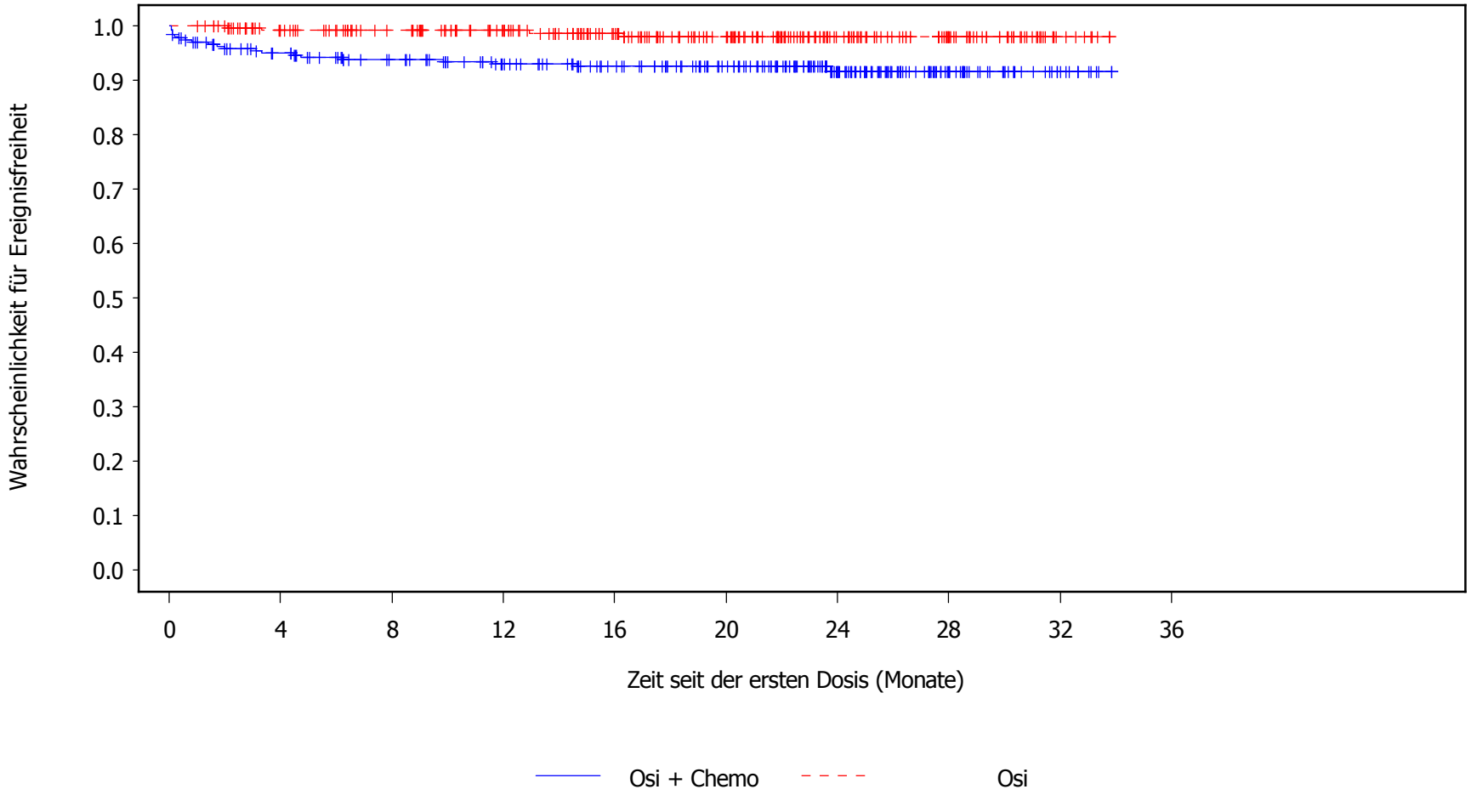
Figure 3.3.122 FLAURA-2: Kaplan-Meier plot of time to first occurrence of G>=3 SOC: Erkrankungen des Gastrointestinaltrakts
Safety Analysis Set, DCO 03APR2023



Anzahl an Patienten unter Risiko:

276	243	221	201	180	154	100	40	11	0	Osi + Chemo
275	251	230	204	169	134	78	42	7	0	Osi

root/cdar/d516/payer_germany/ar/d5169c00001_payer_germany/tlf/prod/program/ttemainae.sas gttemainaeber 24OCT2023:11:33 kvbv306

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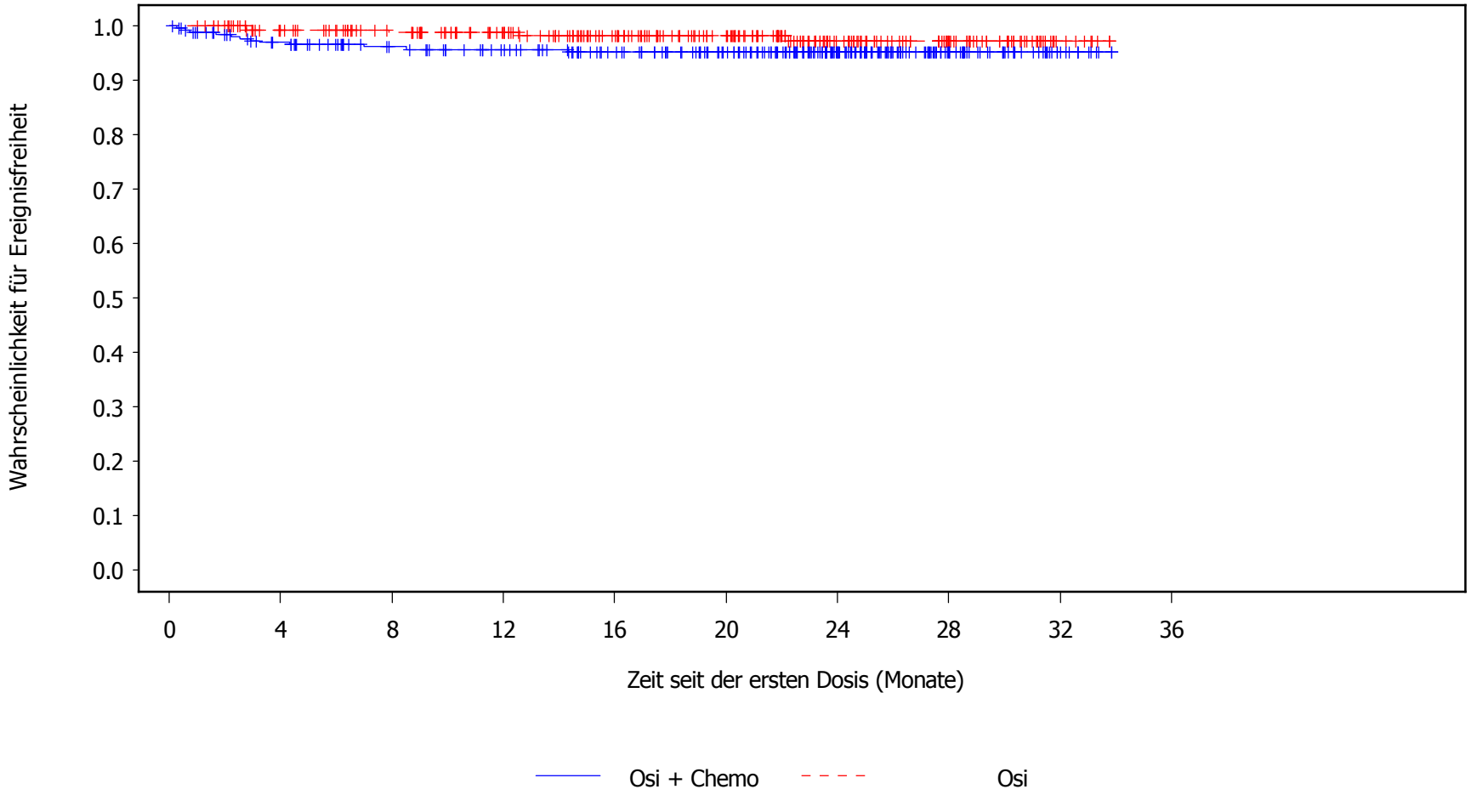
Figure 3.3.123 FLAURA-2: Kaplan-Meier plot of time to first occurrence of G>=3 SOC: Herzerkrankungen
Safety Analysis Set, DCO 03APR2023



Anzahl an Patienten unter Risiko:

276	250	229	215	192	165	108	45	11	0	Osi + Chemo
275	251	230	205	170	135	79	44	7	0	Osi

root/cdar/d516/payer_germany/ar/d5169c00001_payer_germany/tlf/prod/program/ttemainae.sas gttemainaebes 24OCT2023:11:33 kvbv306

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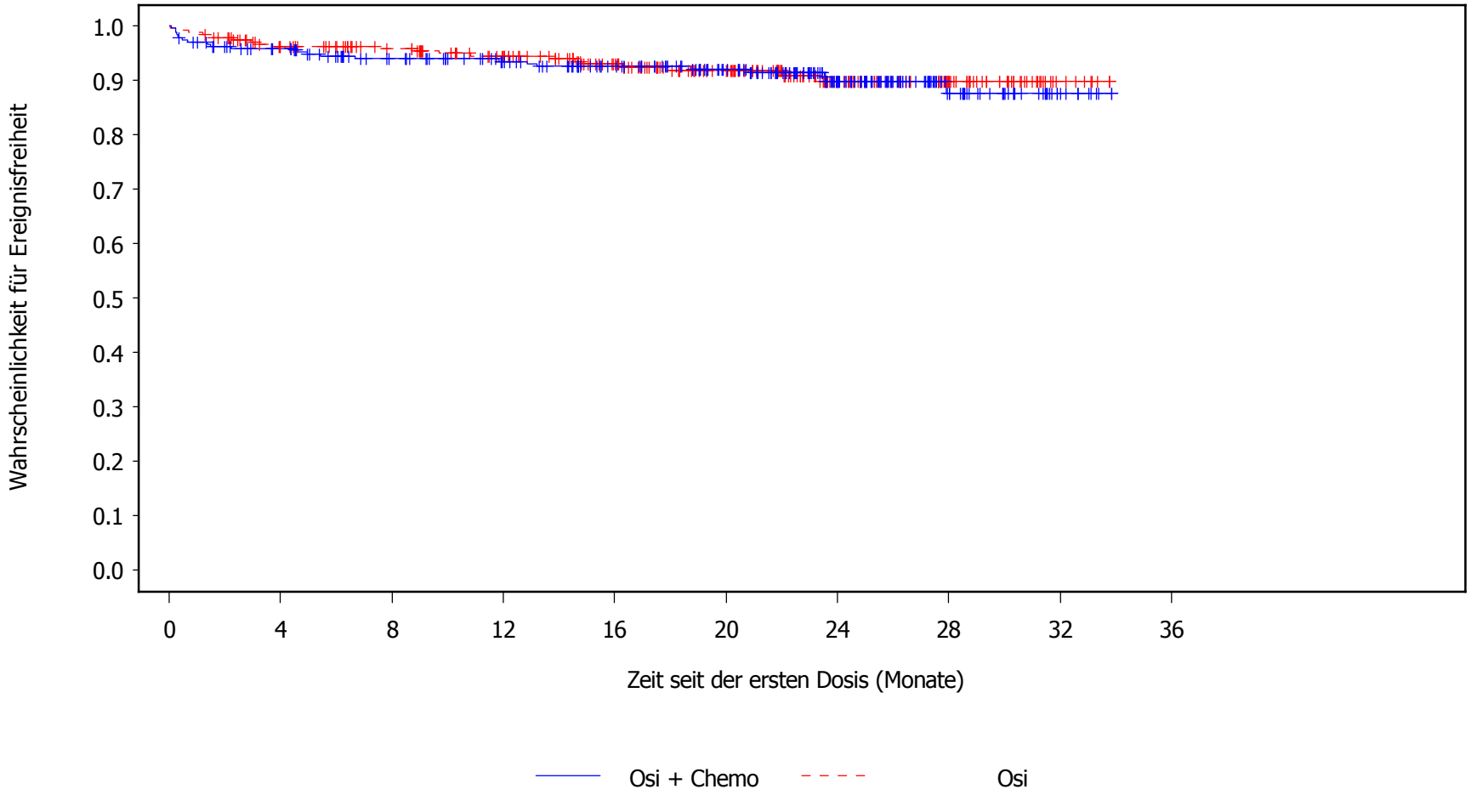
Figure 3.3.124 FLAURA-2: Kaplan-Meier plot of time to first occurrence of G>=3 SOC: Infektionen und parasitaere Erkrankungen
Safety Analysis Set, DCO 03APR2023

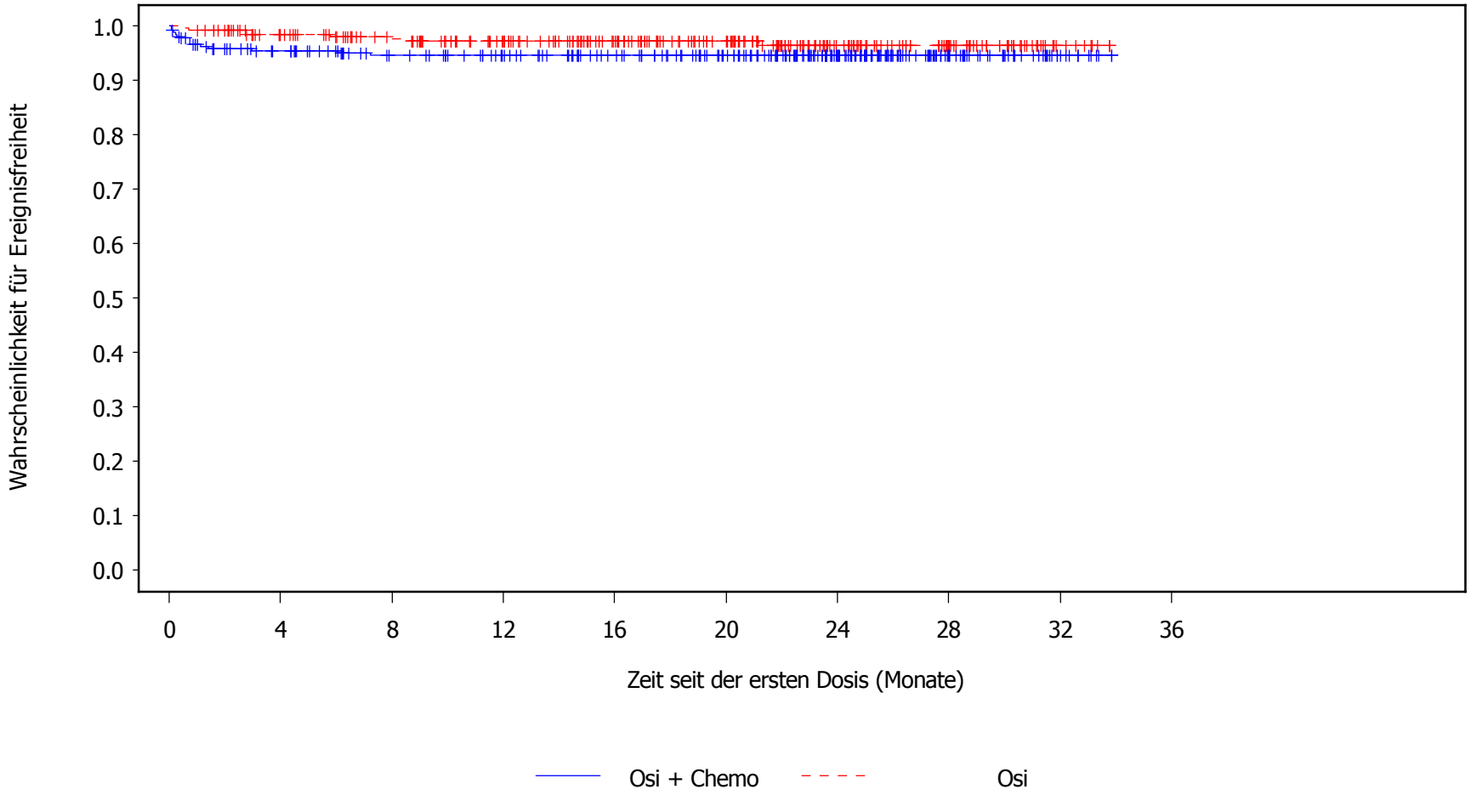


Anzahl an Patienten unter Risiko:

276	251	225	207	184	155	101	40	10	0	Osi + Chemo
275	248	227	204	170	134	78	43	7	0	Osi

root/cdar/d516/payer_germany/ar/d5169c00001_payer_germany/tlf/prod/program/ttemainae.sas gttemainaebet 24OCT2023:11:33 kvbv306

Figure 3.3.125 FLAURA-2: Kaplan-Meier plot of time to first occurrence of G>=3 SOC: Stoffwechsel- und Ernaehrungsstoerungen
Safety Analysis Set, DCO 03APR2023



Anzahl an Patienten unter Risiko:

276	244	221	206	185	159	106	44	11	0	Osi + Chemo
275	250	229	201	167	133	78	42	7	0	Osi

root/cdar/d516/payer_germany/ar/d5169c00001_payer_germany/tlf/prod/program/ttemainae.sas gttemainaebeu 24OCT2023:11:33 kvbv306

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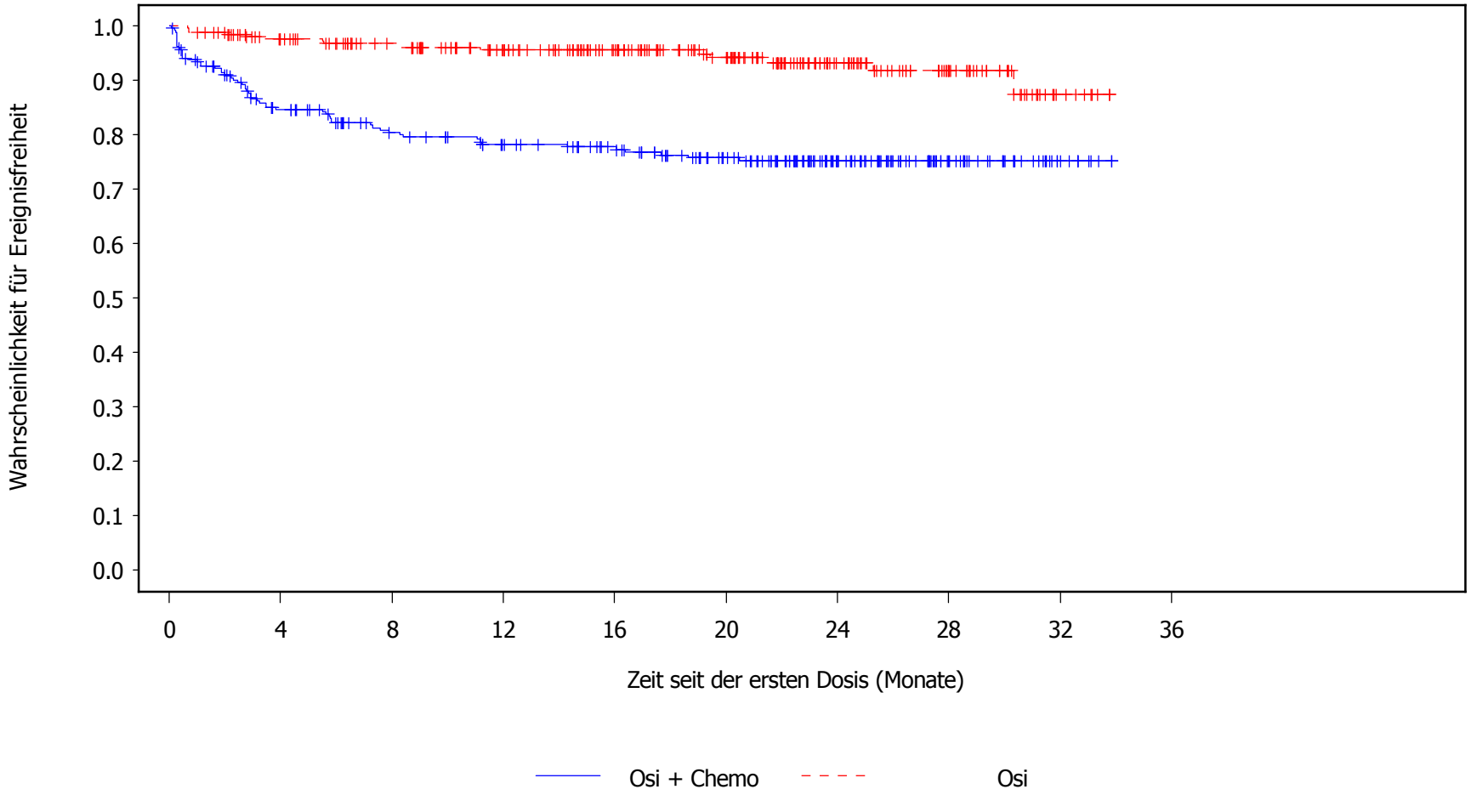
Figure 3.3.126 FLAURA-2: Kaplan-Meier plot of time to first occurrence of G>=3 SOC: Untersuchungen
Safety Analysis Set, DCO 03APR2023

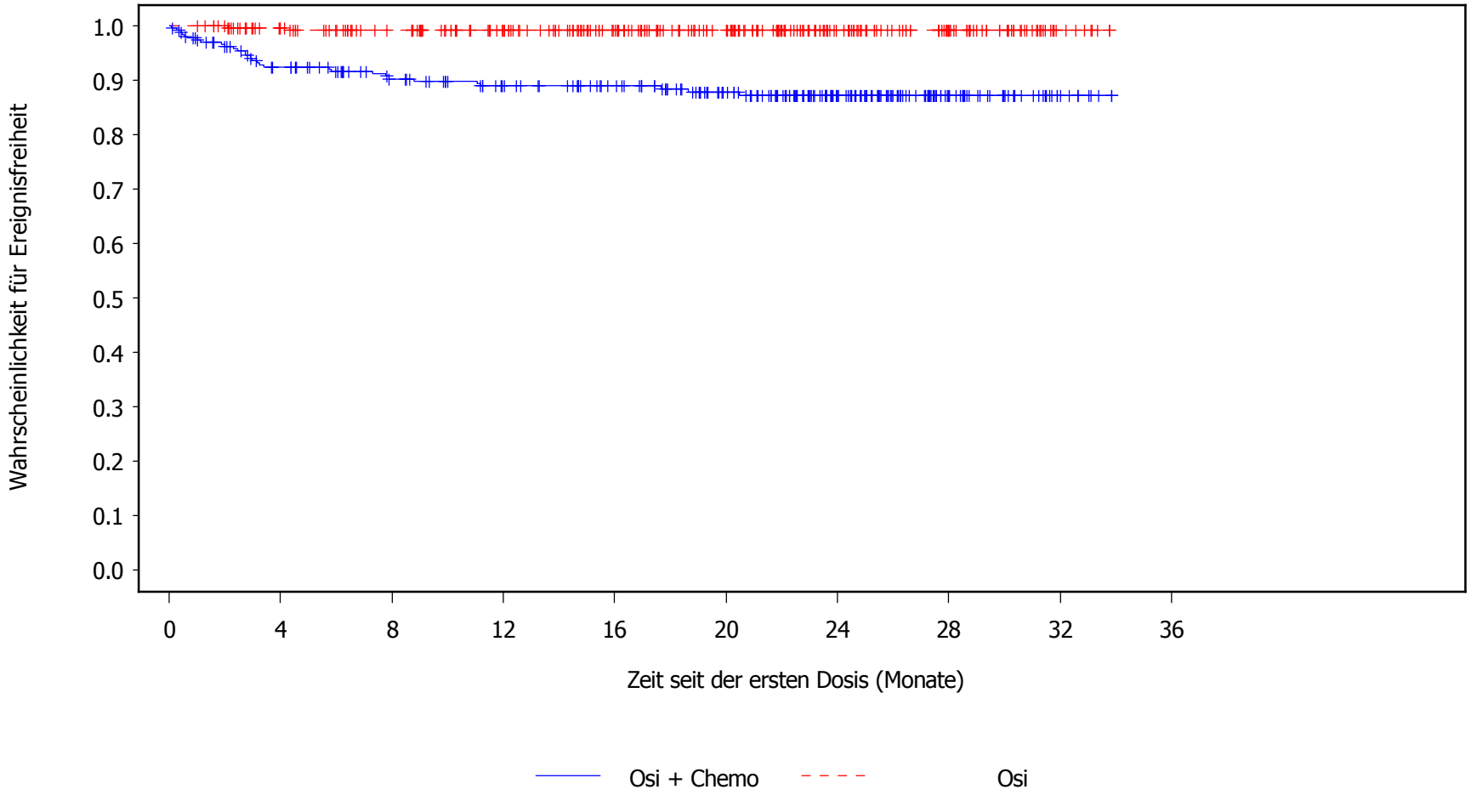


Anzahl an Patienten unter Risiko:

276	216	188	173	158	130	81	37	9	0	Osi + Chemo
275	249	227	199	165	129	76	40	7	0	Osi

root/cdar/d516/payer_germany/ar/d5169c00001_payer_germany/tlf/prod/program/ttemainae.sas gttemainaebev 24OCT2023:11:33 kvbv306

Figure 3.3.127 FLAURA-2: Kaplan-Meier plot of time to first occurrence of G>=3 PT: Neutrophilenzahl erniedrigt
Safety Analysis Set, DCO 03APR2023



Anzahl an Patienten unter Risiko:

276	236	212	194	177	147	95	40	9	0	Osi + Chemo
275	252	230	204	169	134	80	44	7	0	Osi

root/cdar/d516/payer_germany/ar/d5169c00001_payer_germany/tlf/prod/program/ttemainae.sas gttemainaebew 24OCT2023:11:33 kvbv306

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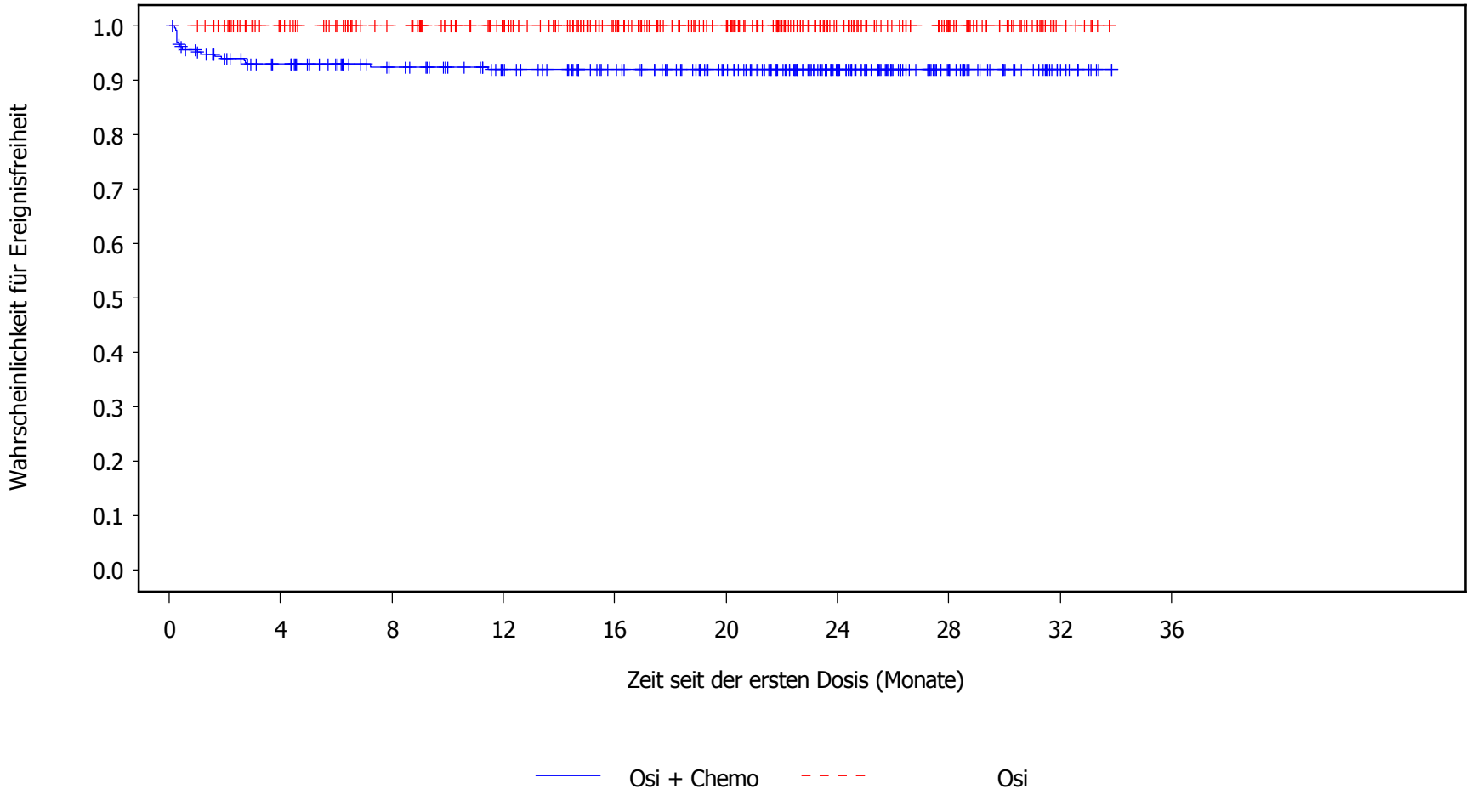
Figure 3.3.128 FLAURA-2: Kaplan-Meier plot of time to first occurrence of G>=3 PT: Thrombozytenzahl vermindert
Safety Analysis Set, DCO 03APR2023

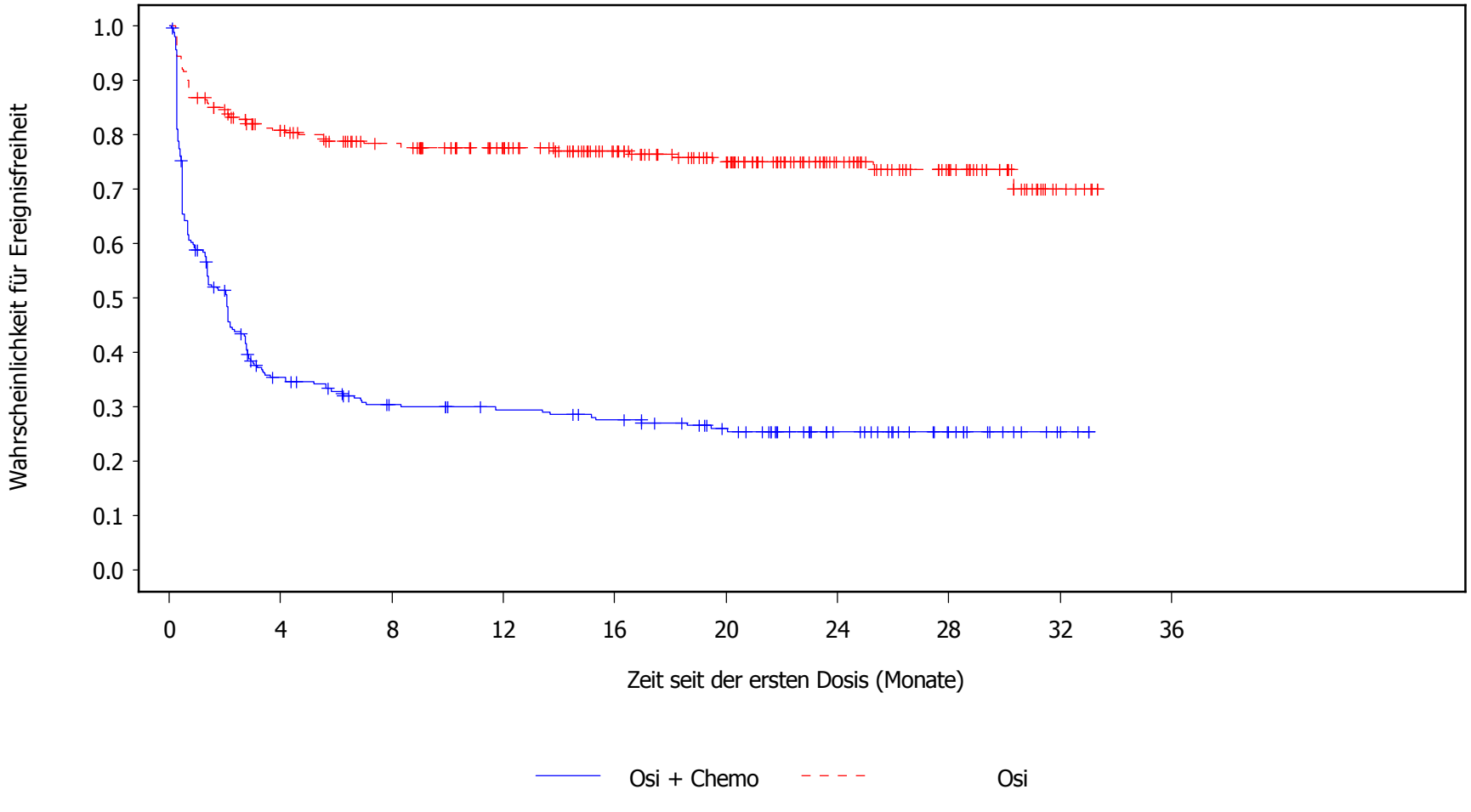


Anzahl an Patienten unter Risiko:

276	238	217	199	180	153	99	43	11	0	Osi + Chemo
275	253	232	206	171	136	80	44	7	0	Osi

root/cdar/d516/payer_germany/ar/d5169c00001_payer_germany/tlf/prod/program/ttemainae.sas gttemainaebex 24OCT2023:11:33 kvbv306

Figure 3.3.129 FLAURA-2: Kaplan-Meier plot of time to first occurrence of UESI GT: Hämatologische Toxizitäten
Safety Analysis Set, DCO 03APR2023



Anzahl an Patienten unter Risiko:

276	89	69	63	57	45	27	14	3	0	Osi + Chemo
275	207	186	162	131	104	63	38	6	0	Osi

root/cdar/d516/payer_germany/ar/d5169c00001_payer_germany/tlf/prod/program/ttemainae.sas gttemainaebey 24OCT2023:11:33 kvbv306

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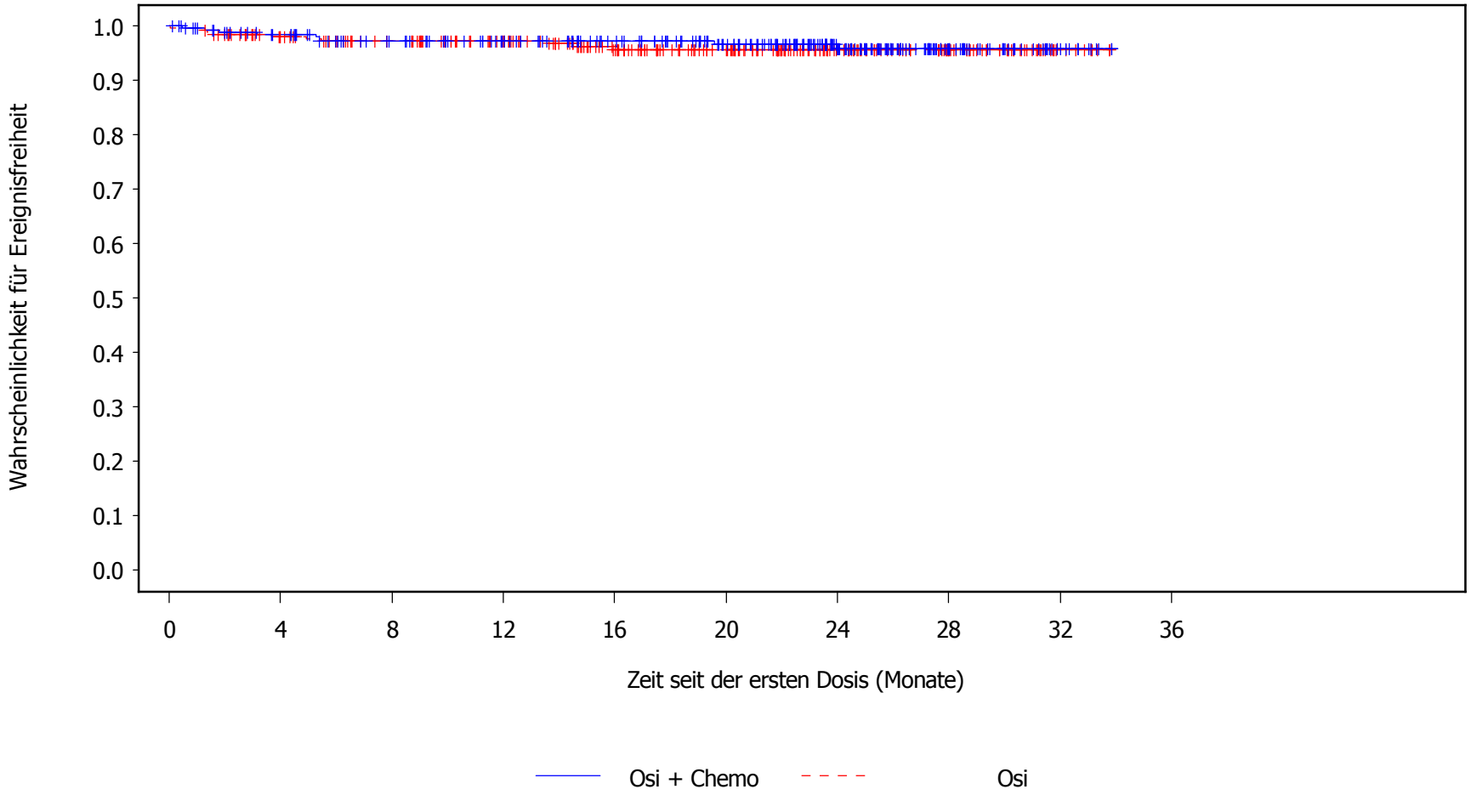
Figure 3.3.130 FLAURA-2: Kaplan-Meier plot of time to first occurrence of UESI GT: ILD und Pneumonitis
Safety Analysis Set, DCO 03APR2023

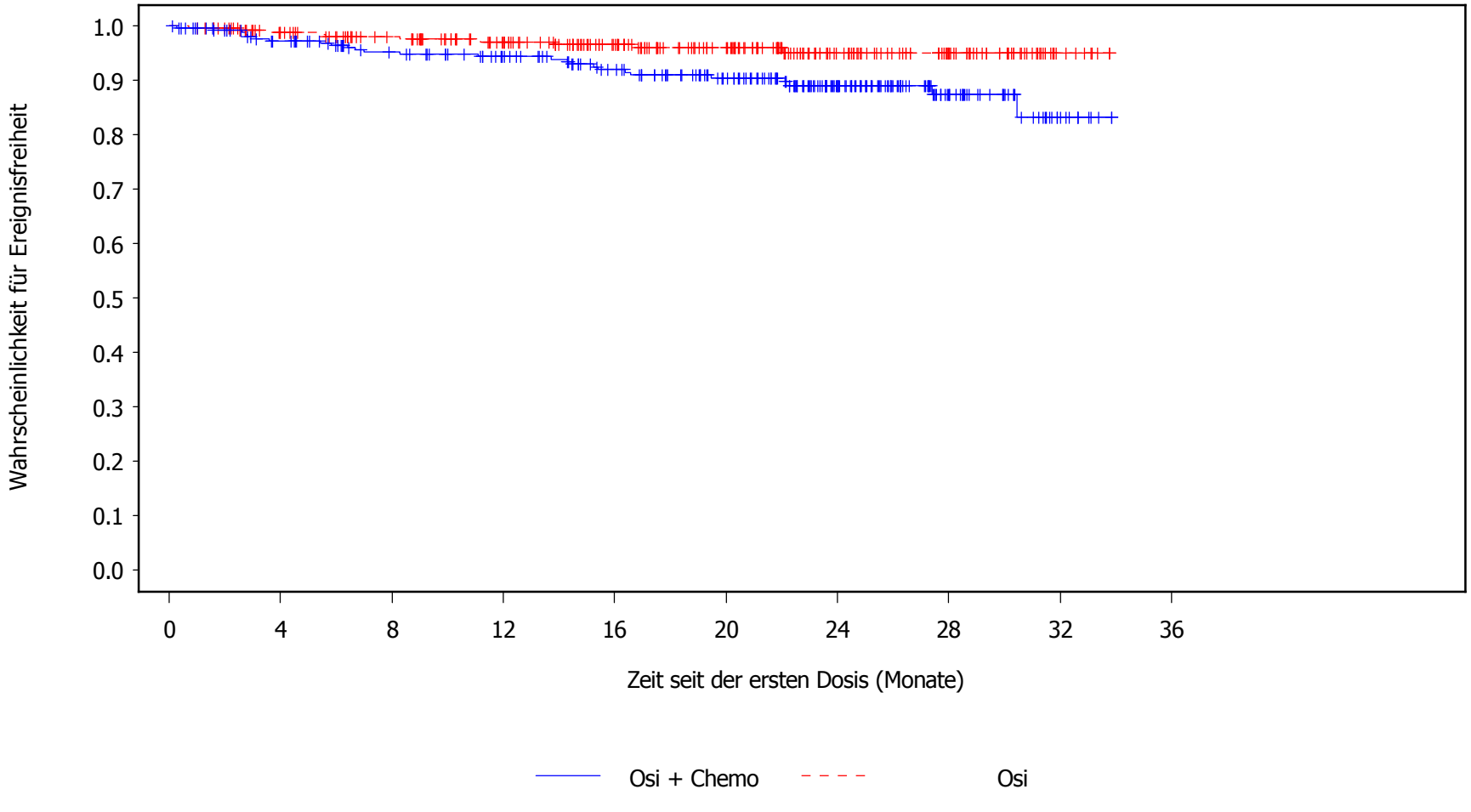


Anzahl an Patienten unter Risiko:

276	255	235	217	195	166	109	45	11	0	Osi + Chemo
275	252	232	206	170	136	80	44	7	0	Osi

root/cdar/d516/payer_germany/ar/d5169c00001_payer_germany/tlf/prod/program/ttemainae.sas gttemainaebez 24OCT2023:11:33 kvbv306

Figure 3.3.131 FLAURA-2: Kaplan-Meier plot of time to first occurrence of UESI GT: Kardiale Effekte (Herzinsuffizienz)
Safety Analysis Set, DCO 03APR2023

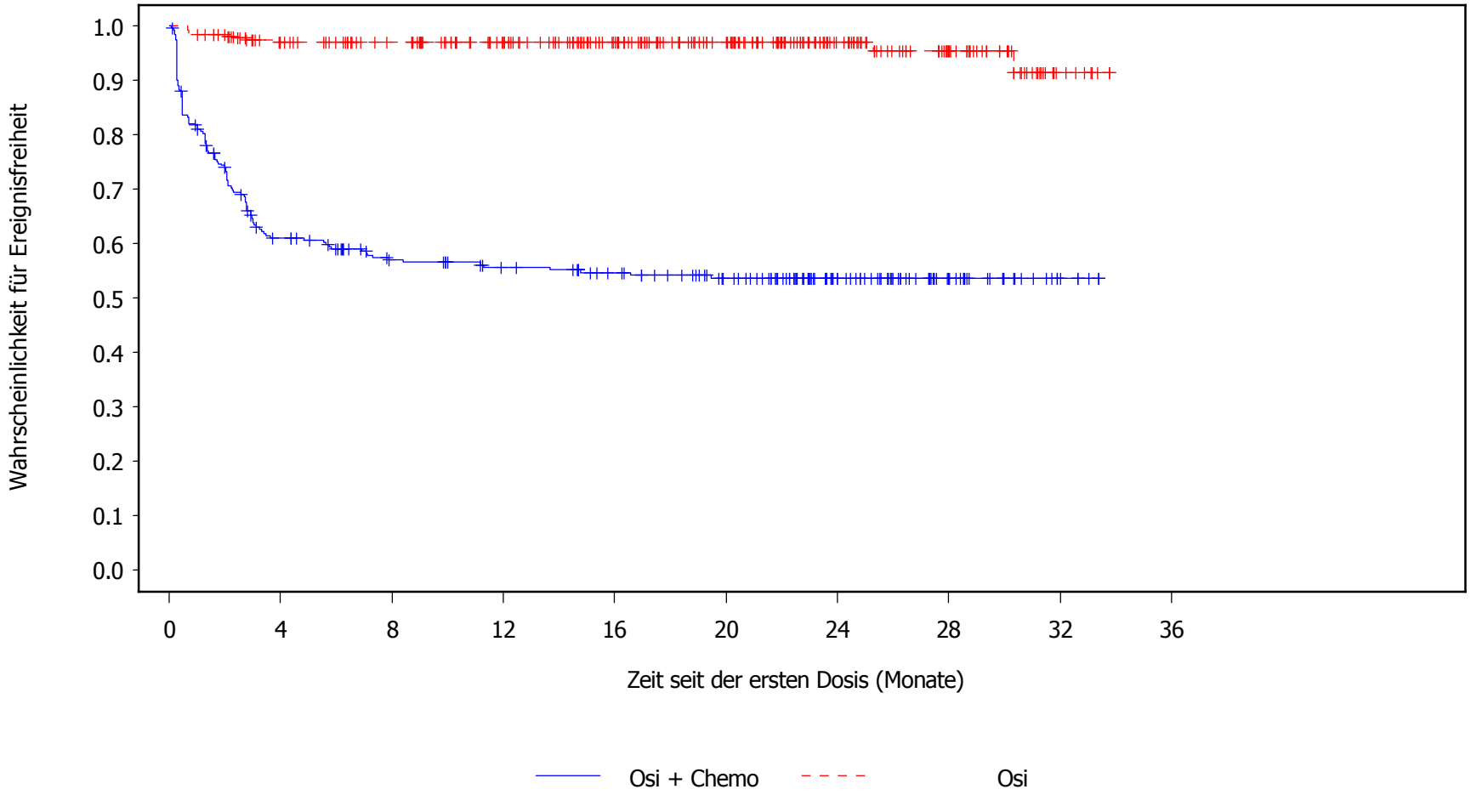


Anzahl an Patienten unter Risiko:

276	250	228	210	186	157	101	42	10	0	Osi + Chemo
275	251	229	201	165	131	77	44	7	0	Osi

root/cdar/d516/payer_germany/ar/d5169c00001_payer_germany/tlf/prod/program/ttemainae.sas gttemainaebfa 24OCT2023:11:33 kvbv306

Figure 3.3.132 FLAURA-2: Kaplan-Meier plot of time to first occurrence of UESI G>=3 GT: Hämatologische Toxizitäten
Safety Analysis Set, DCO 03APR2023



Anzahl an Patienten unter Risiko:

276	158	132	122	111	94	57	26	5	0	Osi + Chemo
275	245	226	200	166	131	78	43	7	0	Osi

root/cdar/d516/payer_germany/ar/d5169c00001_payer_germany/tlf/prod/program/ttemainae.sas gttemainaebfb 24OCT2023:11:33 kvbv306

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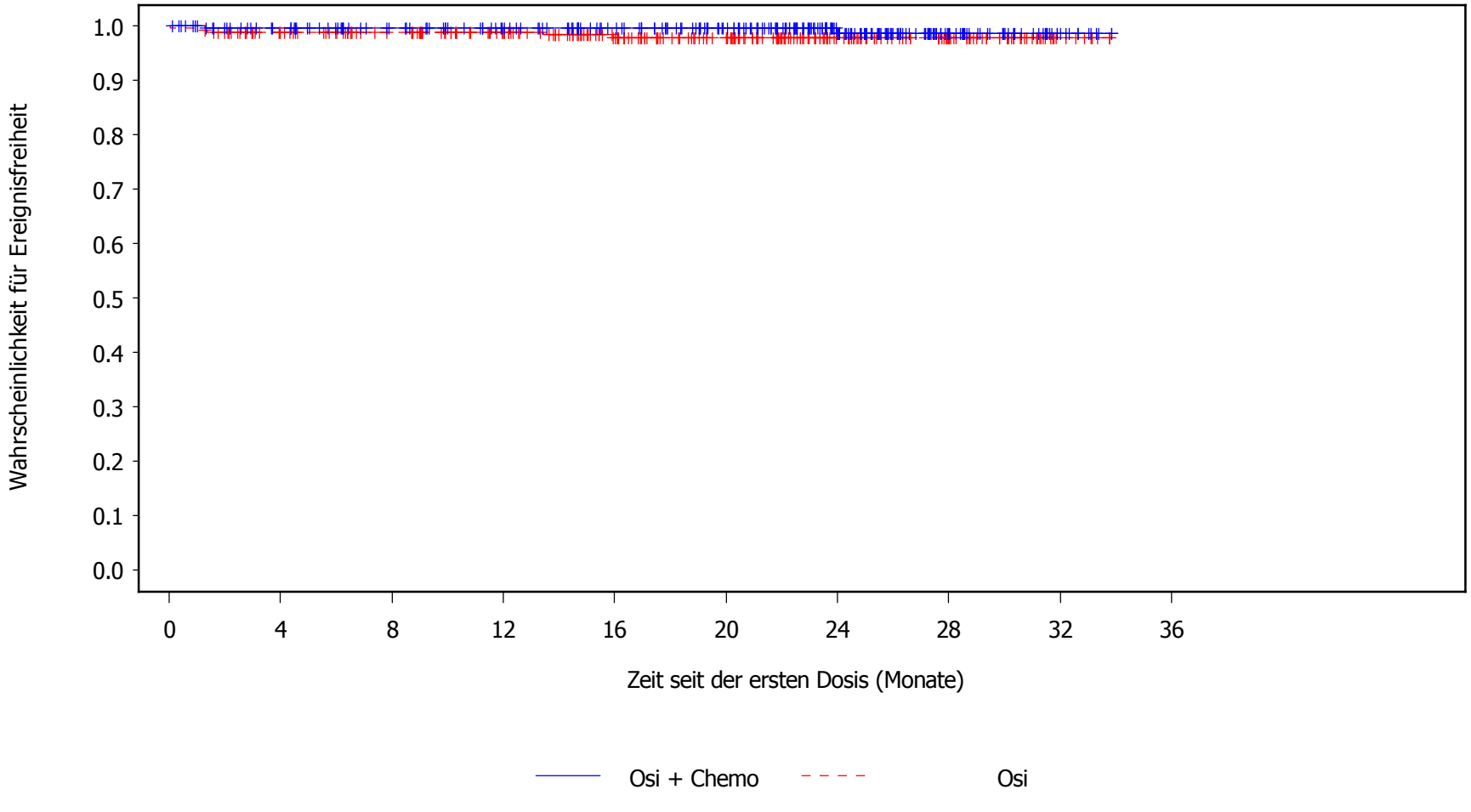
Figure 3.3.133 FLAURA-2: Kaplan-Meier plot of time to first occurrence of UESI G>=3 GT: ILD und Pneumonitis
Safety Analysis Set, DCO 03APR2023



Anzahl an Patienten unter Risiko:

276	256	235	217	195	167	109	45	11	0	Osi + Chemo
275	253	232	206	170	136	80	44	7	0	Osi

root/cdar/d516/payer_germany/ar/d5169c00001_payer_germany/tlf/prod/program/ttemainae.sas gttemainaebfc 24OCT2023:11:33 kvbv306

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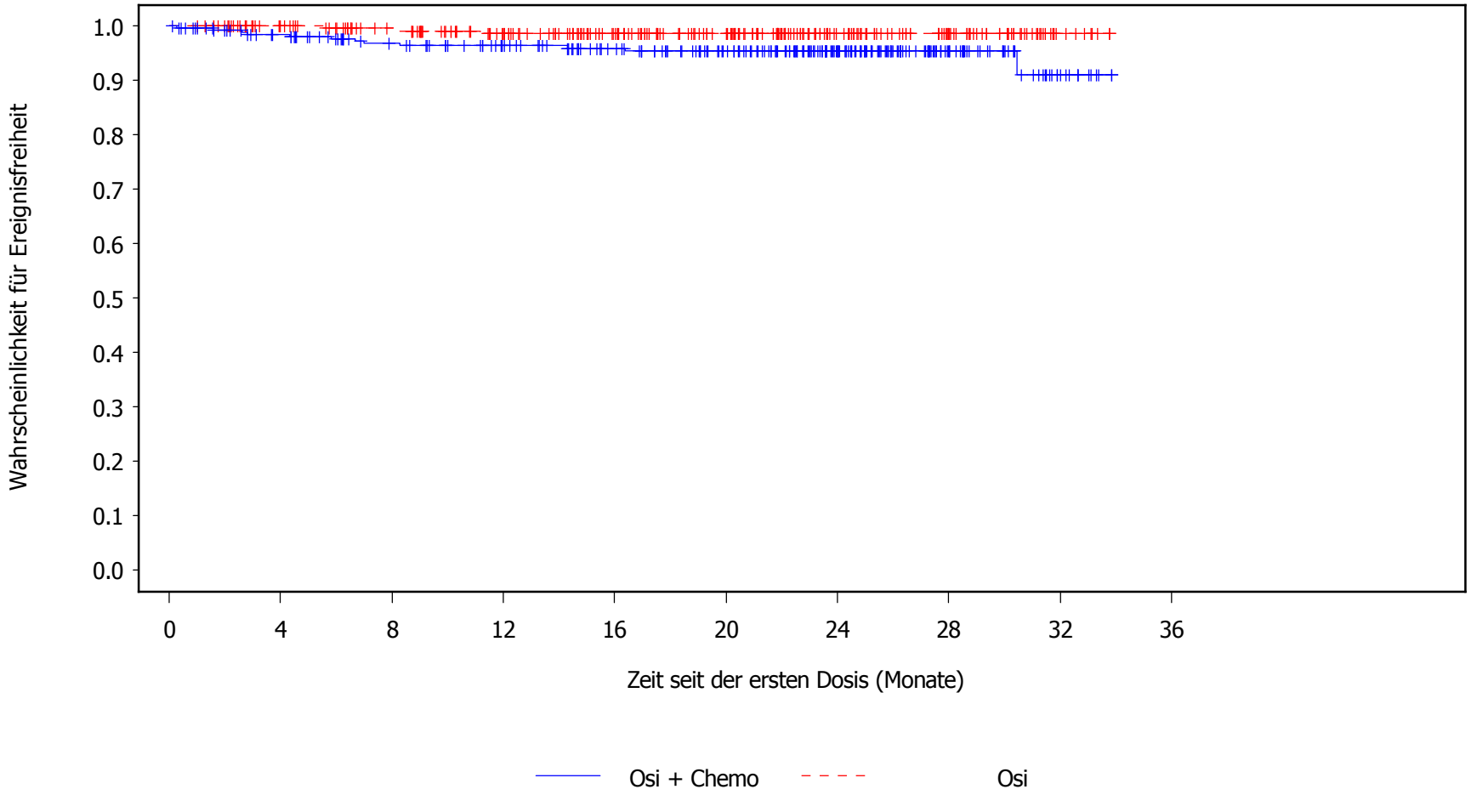
Figure 3.3.134 FLAURA-2: Kaplan-Meier plot of time to first occurrence of UESI G>=3 GT: Kardiale Effekte (Herzinsuffizienz)
Safety Analysis Set, DCO 03APR2023



Anzahl an Patienten unter Risiko:

276	253	231	214	192	164	109	45	11	0	Osi + Chemo
275	253	232	204	169	135	80	44	7	0	Osi

root/cdar/d516/payer_germany/ar/d5169c00001_payer_germany/tlf/prod/program/ttemainae.sas gttemainaebfd 24OCT2023:11:33 kvbv306

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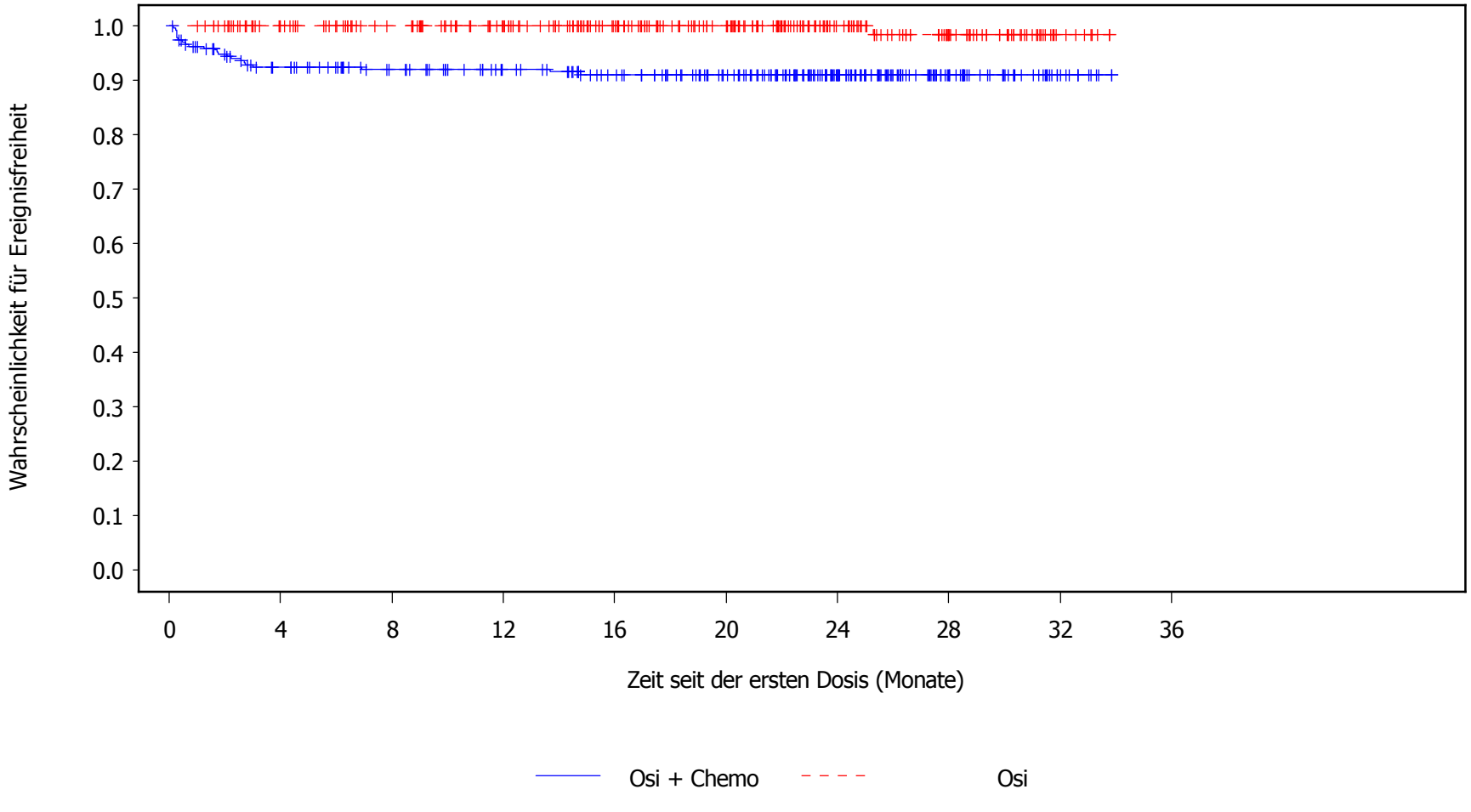
Figure 3.3.135 FLAURA-2: Kaplan-Meier plot of time to first occurrence of SUESI GT: Hämatologische Toxizitäten
Safety Analysis Set, DCO 03APR2023



Anzahl an Patienten unter Risiko:

276	236	215	197	178	153	100	44	11	0	Osi + Chemo
275	253	232	206	171	136	80	43	7	0	Osi

root/cdar/d516/payer_germany/ar/d5169c00001_payer_germany/tlf/prod/program/ttemainae.sas gttemainaebfe 24OCT2023:11:33 kvbv306

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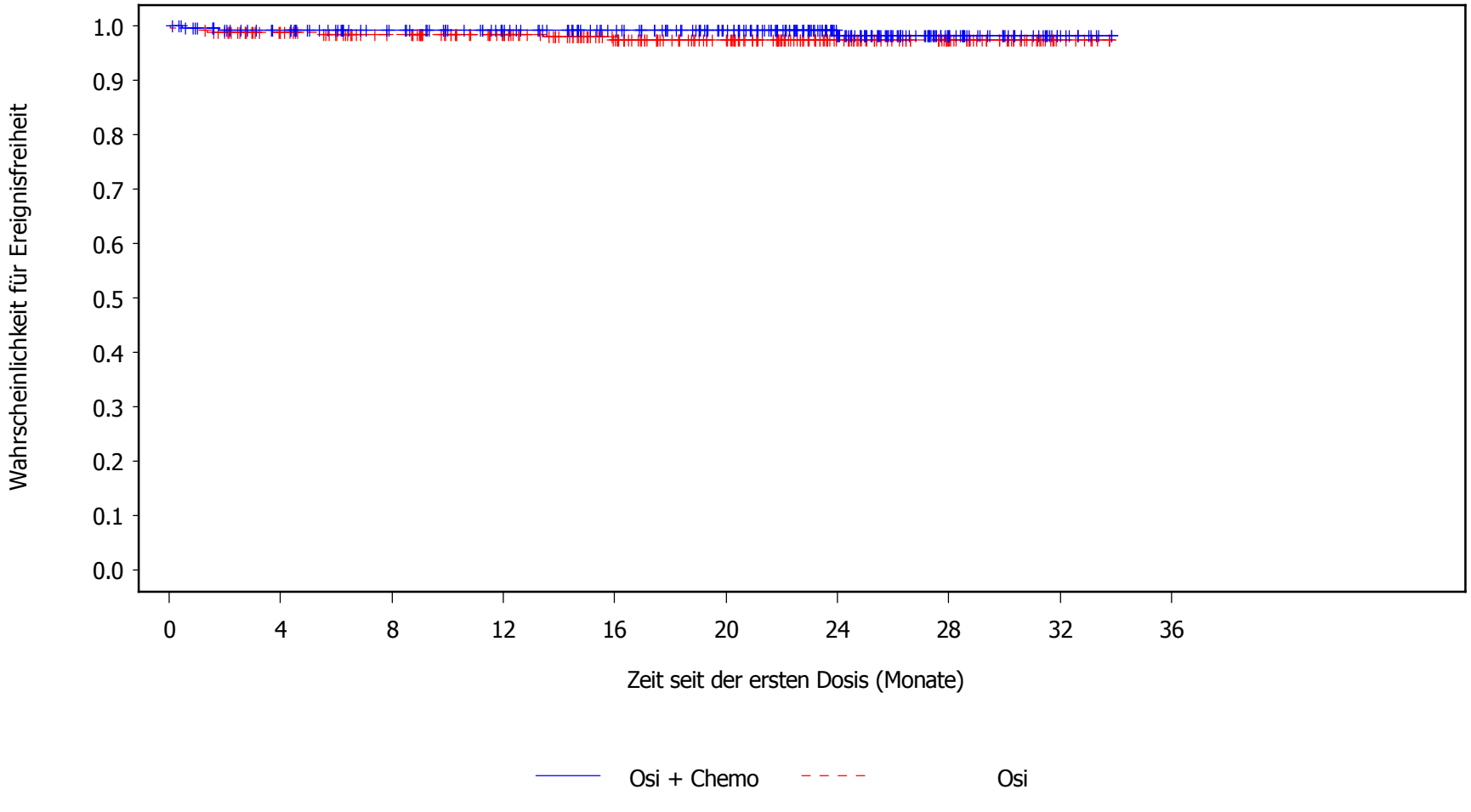
Figure 3.3.136 FLAURA-2: Kaplan-Meier plot of time to first occurrence of SUESI GT: ILD und Pneumonitis
Safety Analysis Set, DCO 03APR2023



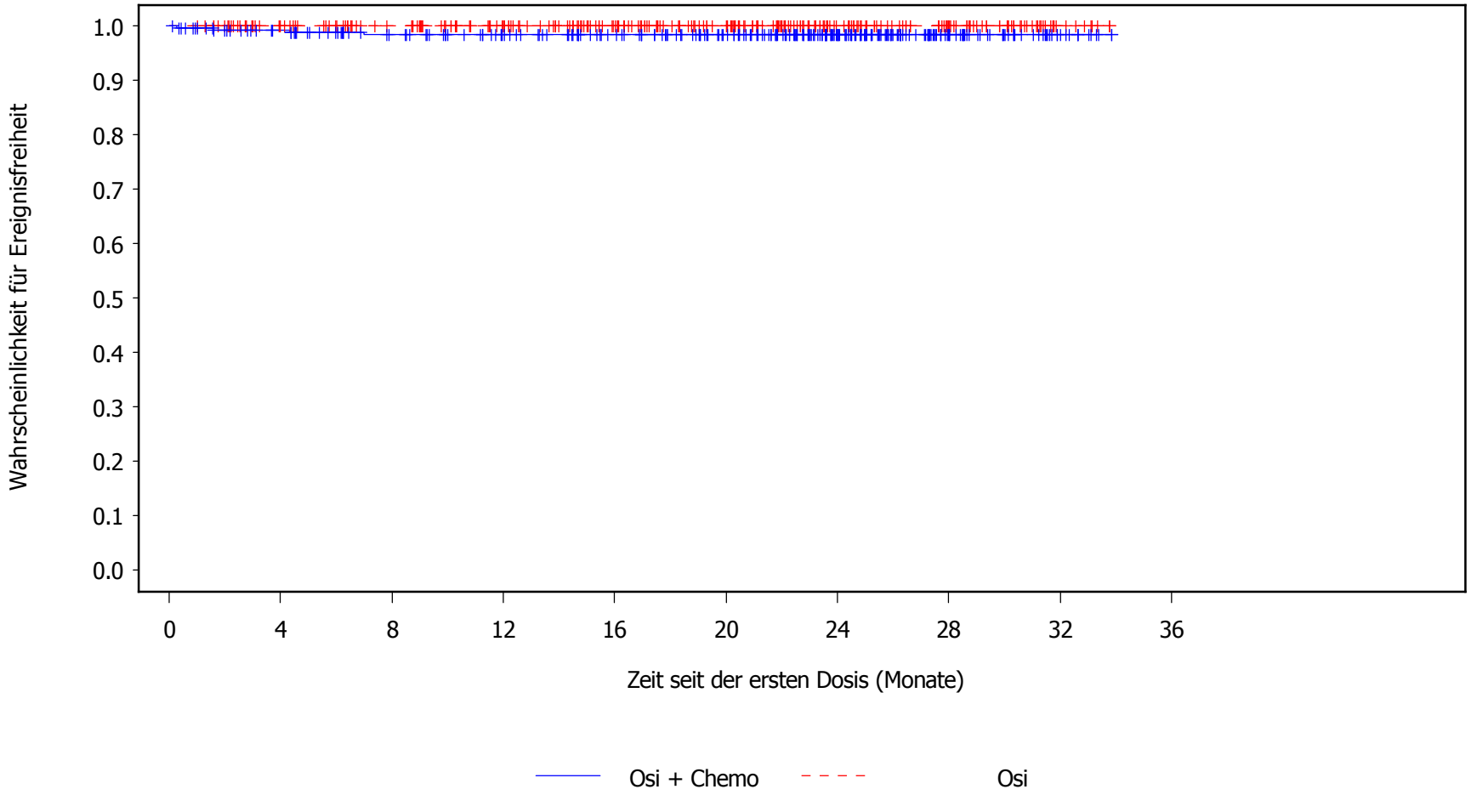
Anzahl an Patienten unter Risiko:

276	256	235	217	195	167	109	45	11	0	Osi + Chemo
275	253	232	206	170	136	80	44	7	0	Osi

root/cdar/d516/payer_germany/ar/d5169c00001_payer_germany/tlf/prod/program/ttemainae.sas gttemainaebff 24OCT2023:11:33 kvbv306

Nutzenbewertung nach AMNOG Seite 1 von 1

Figure 3.3.137 FLAURA-2: Kaplan-Meier plot of time to first occurrence of SUESI GT: Kardiale Effekte (Herzinsuffizienz)
Safety Analysis Set, DCO 03APR2023



Anzahl an Patienten unter Risiko:

276	255	234	216	194	166	109	45	11	0	Osi + Chemo
275	253	232	206	171	136	80	44	7	0	Osi

root/cdar/d516/payer_germany/ar/d5169c00001_payer_germany/tlf/prod/program/ttemainae.sas gttemainaebfg 24OCT2023:11:33 kvbv306

Table 4.1.1.1 FLAURA-2: Summary of subgroup analysis of Gesamtüberleben
Full Analysis Set, DCO 08JAN2024

	Osi + Chemo (N=279)			Osi (N=278)					
Subgruppen	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]	Hazard Ratio [b]	[95%-KI] [b]	2-seitiger p-Wert [b]
Abstammung									
Chinesisch/Asiatisch	71	16 (22,5)	NE [NE; NE]	69	29 (42,0)	NE [NE; NE]	0,49	[0,26; 0,90]	0,0201*
Nicht-chinesisch/ Asiatisch	107	50 (46,7)	38,0 [33,4; NE]	107	48 (44,9)	38,3 [34,3; NE]	1,04	[0,70; 1,55]	0,8543
Nicht-asiatisch	101	34 (33,7)	NE [NE; NE]	102	49 (48,0)	32,5 [27,3; NE]	0,64	[0,41; 0,99]	0,0425*
Interaktion p-Wert									0,0833
Methode zur Gewebeuntersuchung									
zentral	121	44 (36,4)	NE [NE; NE]	119	53 (44,5)	NE [NE; NE]	0,81	[0,54; 1,20]	0,2917
lokal	158	56 (35,4)	NE [NE; NE]	159	73 (45,9)	36,7 [32,6; NE]	0,71	[0,50; 1,002]	0,0515
Interaktion p-Wert									0,6318
WHO Performance-Status									
0	101	30 (29,7)	NE [NE; NE]	102	36 (35,3)	NE [NE; NE]	0,82	[0,50; 1,33]	0,4228
1	178	70 (39,3)	40,5 [36,4; NE]	176	90 (51,1)	33,8 [28,3;38,6]	0,71	[0,52; 0,97]	0,0334*
Interaktion p-Wert									0,6347
Raucherstatus									
Ja	91	33 (36,3)	40,5 [37,1; NE]	97	43 (44,3)	NE [NE; NE]	0,72	[0,45; 1,13]	0,1533
Nein	188	67 (35,6)	NE [NE; NE]	181	83 (45,9)	36,7 [34,1; NE]	0,76	[0,55; 1,05]	0,1000
Interaktion p-Wert									0,8335
Geschlecht									
Maennlich	106	45 (42,5)	38,0 [32,0; NE]	109	55 (50,5)	32,5 [27,0; NE]	0,76	[0,51; 1,12]	0,1676
Weiblich	173	55 (31,8)	NE [NE; NE]	169	71 (42,0)	NE [NE; NE]	0,74	[0,52; 1,05]	0,0895
Interaktion p-Wert									0,9202
Nachweis der EGFR-Mutation durch zentralen ctDNA Cobas Test									
positiv	214	78 (36,4)	NE [NE; NE]	206	101 (49,0)	35,2 [30,1; NE]	0,71	[0,53; 0,95]	0,0233*

OS is defined as the time from the date of randomization until death due to any cause regardless of whether the patient withdraws from study treatment or receives another anti-cancer therapy. Subjects not known to have died at the time of analysis are censored at the last recorded date on which the subject was known to be alive. For certain subgroups there are patients with missing status or belong to a subgroup with too few patients who are therefore not included in the analysis. Analysis is performed if there are >= 10 patients at each subgroup level and >= 10 events in at least one subgroup level combined for both arms.
[a] Median time to event (95% CL) based on the Kaplan Meier estimate. NE=Not estimable (e.g. median is not reached).
[b] Estimated from the main effects of an unstratified Cox proportional hazard model including treatment, subgroup and subgroup-by-treatment interaction. Ties are handled using Efron method and 95% CI derived from profile likelihood estimation. Hazard ratio <1 favours Osimertinib+Chemo. * p<0.05.

root/cdar/d516/payer_germany/ar/d5169c00001_payer_germany/tlf/prod/program/ttesubos.sas gttesubosaa 18MAR2024:10:11 kfrh585

Table 4.1.1.1 FLAURA-2: Summary of subgroup analysis of Gesamtüberleben
Full Analysis Set, DCO 08JAN2024

	Osi + Chemo (N=279)			Osi (N=278)					
Subgruppen	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]	Hazard Ratio [b]	[95%-KI] [b]	2-seitiger p-Wert [b]
negativ	41	11 (26,8)	NE [NE; NE]	40	10 (25,0)	NE [NE; NE]	1,04	[0,44; 2,51]	0,9203
unbekannt	24	11 (45,8)	40,5 [21,3; NE]	32	15 (46,9)	34,5 [20,6; NE]	0,84	[0,37; 1,81]	0,6523
Interaktion p-Wert									0,6792
EGFR-Mutationstyp									
Exon 19 Deletion	172	52 (30,2)	NE [NE; NE]	169	69 (40,8)	NE [NE; NE]	0,74	[0,52; 1,06]	0,1032
Exon 21 (L858R)	106	48 (45,3)	37,7 [34,5; NE]	107	57 (53,3)	32,4 [28,0;37,6]	0,72	[0,49; 1,06]	0,0952
Substitutionsmutation									
Interaktion p-Wert									0,9151
Zentral bestätigte EGFR-Mutation im Gewebe									
positiv	249	93 (37,3)	NE [NE; NE]	240	108 (45,0)	36,7 [33,2; NE]	0,78	[0,59; 1,03]	0,0791
negativ	4	0	NE [NE; NE]	4	1 (25,0)	NE [NE; NE]	NC	[NC]	NC
unbekannt	26	7 (26,9)	NE [NE; NE]	34	17 (50,0)	35,7 [24,7; NE]	0,57	[0,22; 1,32]	0,1963
Interaktion p-Wert									0,4989
ZNS-Metastasen zur Baseline									
Ja	116	44 (37,9)	NE [NE; NE]	110	62 (56,4)	31,0 [26,2;36,7]	0,59	[0,40; 0,87]	0,0075*
Nein	163	56 (34,4)	40,5 [38,0; NE]	168	64 (38,1)	NE [NE; NE]	0,89	[0,62; 1,28]	0,5292
Interaktion p-Wert									0,1292
Zentrale Bestätigung der EGFR-Mutation									
Zentral bestätigte EGFR-Mutation in Gewebe oder ctDNA	266	97 (36,5)	NE [NE; NE]	269	122 (45,4)	35,7 [33,2; NE]	0,76	[0,58; 0,99]	0,0432*
Keine zentrale Bestätigung	13	3 (23,1)	NE [NE; NE]	9	4 (44,4)	38,3 [1,2; NE]	0,49	[0,10; 2,23]	0,3499
Interaktion p-Wert									0,5724
Alter bei Screening									

OS is defined as the time from the date of randomization until death due to any cause regardless of whether the patient withdraws from study treatment or receives another anti-cancer therapy. Subjects not known to have died at the time of analysis are censored at the last recorded date on which the subject was known to be alive. For certain subgroups there are patients with missing status or belong to a subgroup with too few patients who are therefore not included in the analysis. Analysis is performed if there are >= 10 patients at each subgroup level and >= 10 events in at least one subgroup level combined for both arms.
[a] Median time to event (95% CL) based on the Kaplan Meier estimate. NE=Not estimable (e.g. median is not reached).
[b] Estimated from the main effects of an unstratified Cox proportional hazard model including treatment, subgroup and subgroup-by-treatment interaction. Ties are handled using Efron method and 95% CI derived from profile likelihood estimation. Hazard ratio <1 favours Osimertinib+Chemo. * p<0.05.

root/cdar/d516/payer_germany/ar/d5169c00001_payer_germany/tlf/prod/program/ttesubos.sas gttesubosaa 18MAR2024:10:11 kfrh585

Table 4.1.1.1 FLAURA-2: Summary of subgroup analysis of Gesamtüberleben
Full Analysis Set, DCO 08JAN2024

	Osi + Chemo (N=279)			Osi (N=278)					
Subgruppen	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]	Hazard Ratio [b]	[95%-KI] [b]	2-seitiger p-Wert [b]
<65 Jahre	174	52 (29,9)	NE [NE; NE]	166	73 (44,0)	38,6 [33,2; NE]	0,63	[0,44; 0,90]	0,0100*
>=65 Jahre	105	48 (45,7)	37,7 [28,1; NE]	112	53 (47,3)	34,7 [29,5; NE]	0,97	[0,65; 1,43]	0,8629
Interaktion p-Wert									0,1112
Region gPAP									
Asien	170	66 (38,8)	40,5 [37,7; NE]	166	76 (45,8)	38,3 [34,3; NE]	0,81	[0,58; 1,13]	0,2138
Europa	22	9 (40,9)	NE [NE; NE]	23	14 (60,9)	28,8 [15,7; NE]	0,58	[0,24; 1,32]	0,1940
Nordamerika	21	6 (28,6)	NE [NE; NE]	23	6 (26,1)	NE [NE; NE]	1,36	[0,42; 4,34]	0,5964
Rest der Welt	66	19 (28,8)	NE [NE; NE]	66	30 (45,5)	33,8 [28,0; NE]	0,56	[0,31; 0,98]	0,0430*
Interaktion p-Wert									0,4442

OS is defined as the time from the date of randomization until death due to any cause regardless of whether the patient withdraws from study treatment or receives another anti-cancer therapy. Subjects not known to have died at the time of analysis are censored at the last recorded date on which the subject was known to be alive. For certain subgroups there are patients with missing status or belong to a subgroup with too few patients who are therefore not included in the analysis. Analysis is performed if there are >= 10 patients at each subgroup level and >= 10 events in at least one subgroup level combined for both arms.
[a] Median time to event (95% CL) based on the Kaplan Meier estimate. NE=Not estimable (e.g. median is not reached).
[b] Estimated from the main effects of an unstratified Cox proportional hazard model including treatment, subgroup and subgroup-by-treatment interaction. Ties are handled using Efron method and 95% CI derived from profile likelihood estimation. Hazard ratio <1 favours Osimertinib+Chemo. * p<0.05.
root/cdar/d516/payer_germany/ar/d5169c00001_payer_germany/tlf/prod/program/ttesubos.sas gttesubosaa 18MAR2024:10:11 kfrh585

Table 4.1.1.2 FLAURA-2: Summary of subgroup analysis of Progressionsfreies Überleben (nach Prüfarzt)
Full Analysis Set, DCO 03APR2023

	Osi + Chemo (N=279)			Osi (N=278)					
Subgruppen	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]	Hazard Ratio [b]	[95%-KI] [b]	2-seitiger p-Wert [b]
Abstammung									
Chinesisch/Asiatisch	71	26 (36,6)	27,4 [24,9; NE]	69	43 (62,3)	19,4 [16,5;25,0]	0,49	[0,30; 0,80]	0,0040*
Nicht-chinesisch/ Asiatisch	107	54 (50,5)	24,8 [21,9; NE]	107	65 (60,7)	19,3 [13,8;27,6]	0,76	[0,53; 1,09]	0,1302
Nicht-asiatisch	101	40 (39,6)	26,0 [21,0; NE]	102	58 (56,9)	13,8 [11,1;22,1]	0,55	[0,37; 0,83]	0,0037*
Interaktion p-Wert									0,3131
Methode zur Gewebeuntersuchung									
zentral	121	52 (43,0)	25,1 [22,3;27,9]	119	67 (56,3)	17,0 [13,9;28,5]	0,73	[0,50; 1,04]	0,0838
lokal	158	68 (43,0)	27,6 [22,1; NE]	159	99 (62,3)	16,6 [13,7;20,6]	0,55	[0,40; 0,74]	0,0001*
Interaktion p-Wert									0,2397
WHO Performance-Status									
0	101	48 (47,5)	24,7 [22,2;27,6]	102	57 (55,9)	21,3 [14,1;30,3]	0,79	[0,53; 1,16]	0,2269
1	178	72 (40,4)	30,6 [22,3; NE]	176	109 (61,9)	16,6 [13,7;19,4]	0,53	[0,39; 0,72]	<0,0001*
Interaktion p-Wert									0,1149
Raucherstatus									
Ja	91	43 (47,3)	24,8 [21,9;30,6]	97	57 (58,8)	16,5 [13,7;22,3]	0,63	[0,42; 0,93]	0,0215*
Nein	188	77 (41,0)	27,4 [23,8; NE]	181	109 (60,2)	16,9 [13,9;24,6]	0,61	[0,45; 0,82]	0,0008*
Interaktion p-Wert									0,9091
Geschlecht									
Maennlich	106	51 (48,1)	24,7 [21,0; NE]	109	73 (67,0)	14,1 [11,1;19,4]	0,54	[0,37; 0,77]	0,0006*
Weiblich	173	69 (39,9)	27,6 [23,8; NE]	169	93 (55,0)	19,4 [15,4;28,5]	0,67	[0,49; 0,92]	0,0120*
Interaktion p-Wert									0,3542
Nachweis der EGFR-Mutation durch zentralen ctDNA Cobas Test									
positiv	214	96 (44,9)	25,1 [22,0;30,6]	206	130 (63,1)	16,6 [13,8;19,4]	0,62	[0,48; 0,81]	0,0004*

PFS is defined as the time from randomization until the date of objective disease progression or death (by any cause in the absence of progression), regardless of whether the subject withdraws from study treatment or receives another anti-cancer therapy. Subjects who have not progressed or died at the time of analysis will be censored at the time of the latest date of assessment from their last evaluable RECIST assessment. For certain subgroups there are patients with missing status or belong to a subgroup with too few patients who are therefore not included in the analysis. Analysis is performed if there are >= 10 patients at at each subgroup level and >= 10 events in at least one subgroup level combined for both arms. Hazard ratio <1 favours Osimertinib+Chemo. * p<0.05.
[a] Median time to event (95% CL) based on the Kaplan Meier estimate. NE=Not estimable (e.g. median is not reached).
[b] Estimated from the main effects of an unstratified Cox proportional hazard model including treatment, subgroup and subgroup-by-treatment interaction. Ties are handled using Efron method and 95% CI derived from profile likelihood estimation.
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Table 4.1.1.2 FLAURA-2: Summary of subgroup analysis of Progressionsfreies Überleben (nach Prüfarzt)
Full Analysis Set, DCO 03APR2023

	Osi + Chemo (N=279)			Osi (N=278)					
Subgruppen	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]	Hazard Ratio [b]	[95%-KI] [b]	2-seitiger p-Wert [b]
negativ	41	15 (36,6)	25,5 [24,7; NE]	40	15 (37,5)	30,5 [22,2; NE]	0,82	[0,39; 1,70]	0,5866
unbekannt	24	9 (37,5)	26,0 [13,8; NE]	32	21 (65,6)	14,0 [8,4;22,3]	0,42	[0,18; 0,89]	0,0236*
Interaktion p-Wert									0,4670
EGFR-Mutationstyp									
Exon 19 Deletion	172	65 (37,8)	27,9 [25,1; NE]	169	94 (55,6)	19,4 [16,5;27,6]	0,60	[0,44; 0,83]	0,0017*
Exon 21 (L858R) Substitutionsmutation	106	55 (51,9)	24,7 [19,5;27,4]	107	70 (65,4)	13,9 [11,1;19,4]	0,63	[0,44; 0,90]	0,0109*
Interaktion p-Wert									0,8505
Zentral bestätigte EGFR-Mutation im Gewebe									
positiv	249	111 (44,6)	25,1 [23,8;30,6]	240	141 (58,8)	16,9 [15,2;22,2]	0,65	[0,51; 0,84]	0,0007*
negativ	4	0	NE [NE; NE]	4	3 (75,0)	6,9 [0,2; NE]	NC	[NC]	NC
unbekannt	26	9 (34,6)	33,3 [19,3; NE]	34	22 (64,7)	14,1 [11,1;27,6]	0,47	[0,20; 1,01]	0,0546
Interaktion p-Wert									0,4394
ZNS-Metastasen zur Baseline									
Ja	116	52 (44,8)	24,9 [22,0; NE]	110	79 (71,8)	13,8 [11,0;16,7]	0,47	[0,33; 0,66]	<0,0001*
Nein	163	68 (41,7)	27,6 [24,7; NE]	168	87 (51,8)	21,0 [16,7;30,5]	0,75	[0,54; 1,03]	0,0729
Interaktion p-Wert									0,0505
Zentrale Bestätigung der EGFR-Mutation									
Zentral bestätigte EGFR-Mutation in Gewebe oder ctDNA	266	115 (43,2)	25,5 [24,7; NE]	269	158 (58,7)	16,8 [14,2;22,1]	0,64	[0,50; 0,81]	0,0002*
Keine zentrale Bestätigung	13	5 (38,5)	33,3 [19,3; NE]	9	8 (88,9)	8,3 [0,2; NE]	0,25	[0,07; 0,79]	0,0177*
Interaktion p-Wert									0,1156
Alter bei Screening									

PFS is defined as the time from randomization until the date of objective disease progression or death (by any cause in the absence of progression), regardless of whether the subject withdraws from study treatment or receives another anti-cancer therapy. Subjects who have not progressed or died at the time of analysis will be censored at the time of the latest date of assessment from their last evaluable RECIST assessment. For certain subgroups there are patients with missing status or belong to a subgroup with too few patients who are therefore not included in the analysis. Analysis is performed if there are >= 10 patients at at each subgroup level and >= 10 events in at least one subgroup level combined for both arms. Hazard ratio <1 favours Osimertinib+Chemo. * p<0.05.
[a] Median time to event (95% CL) based on the Kaplan Meier estimate. NE=Not estimable (e.g. median is not reached).
[b] Estimated from the main effects of an unstratified Cox proportional hazard model including treatment, subgroup and subgroup-by-treatment interaction. Ties are handled using Efron method and 95% CI derived from profile likelihood estimation.
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Table 4.1.1.2 FLAURA-2: Summary of subgroup analysis of Progressionsfreies Überleben (nach Prüfarzt)
Full Analysis Set, DCO 03APR2023

	Osi + Chemo (N=279)			Osi (N=278)					
Subgruppen	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]	Hazard Ratio [b]	[95%-KI] [b]	2-seitiger p-Wert [b]
<65 Jahre	174	73 (42,0)	27,6 [24,9; NE]	166	97 (58,4)	19,4 [13,9;24,8]	0,59	[0,43; 0,80]	0,0007*
>=65 Jahre	105	47 (44,8)	24,7 [19,3; NE]	112	69 (61,6)	16,6 [13,8;19,4]	0,68	[0,46; 0,98]	0,0365*
Interaktion p-Wert									0,5866
Region gPAP									
Asien	170	79 (46,5)	25,5 [22,3; NE]	166	100 (60,2)	19,4 [16,5;24,8]	0,67	[0,50; 0,91]	0,0089*
Europa	22	8 (36,4)	NE [NE; NE]	23	15 (65,2)	12,2 [5,9; NE]	0,38	[0,15; 0,87]	0,0220*
Nordamerika	21	9 (42,9)	21,9 [10,1; NE]	23	13 (56,5)	14,2 [11,0; NE]	0,87	[0,36; 2,03]	0,7572
Rest der Welt	66	24 (36,4)	26,0 [21,0; NE]	66	38 (57,6)	16,4 [11,1;27,6]	0,51	[0,30; 0,84]	0,0080*
Interaktion p-Wert									0,4125

PFS is defined as the time from randomization until the date of objective disease progression or death (by any cause in the absence of progression), regardless of whether the subject withdraws from study treatment or receives another anti-cancer therapy. Subjects who have not progressed or died at the time of analysis will be censored at the time of the latest date of assessment from their last evaluable RECIST assessment. For certain subgroups there are patients with missing status or belong to a subgroup with too few patients who are therefore not included in the analysis. Analysis is performed if there are >= 10 patients at at each subgroup level and >= 10 events in at least one subgroup level combined for both arms. Hazard ratio <1 favours Osimertinib+Chemo. * p<0.05.
[a] Median time to event (95% CL) based on the Kaplan Meier estimate. NE=Not estimable (e.g. median is not reached).
[b] Estimated from the main effects of an unstratified Cox proportional hazard model including treatment, subgroup and subgroup-by-treatment interaction. Ties are handled using Efron method and 95% CI derived from profile likelihood estimation.
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Table 4.2.3.1 FLAURA-2: Summary of subgroup analysis of change from baseline in EORTC QLQ-C30 Funktionsskala: Körper (mixed model for repeated measures) - average over all visits
Full Analysis Set, DCO 03APR2023

	Osi + Chemo (N=279)			Osi (N=278)			Behandlungseffekt	
Subgruppen	n [a]	Ausgangswert MW (SD) [b]	Veränderung MW (SE)	n [a]	Ausgangswert MW (SD) [b]	Veränderung MW (SE)	MWD [95%-KI]	p-Wert
Abstammung								
Chinesisch/Asiatisch	66	85,86 (12,182)	-1,22 (1,265)	65	83,69 (17,161)	1,00 (1,293)	-2,21 [-5,789; 1,362]	0,2230
Hedges' g SMD							-0,21 [-0,556; 0,131]	0,2250
Nicht-chinesisch/Asiatisch	99	78,52 (19,554)	2,28 (1,410)	101	77,62 (21,325)	5,05 (1,407)	-2,77 [-6,698; 1,163]	0,1664
Hedges' g SMD							-0,20 [-0,474; 0,082]	0,1674
Nicht-asiatisch	88	73,41 (24,185)	4,59 (1,386)	87	68,28 (26,511)	7,63 (1,407)	-3,04 [-6,937; 0,858]	0,1255
Hedges' g SMD							-0,23 [-0,529; 0,066]	0,1267
Int. p-Wert								0,8609
Methode zur Gewebeuntersuchung								
zentral	110	82,97 (16,419)	-0,32 (1,139)	114	80,06 (21,589)	3,18 (1,125)	-3,50 [-6,654; -0,343]	0,0300*
Hedges' g SMD							-0,29 [-0,554; -0,028]	0,0303*
lokal	143	75,34 (22,337)	3,68 (1,105)	139	72,61 (23,763)	5,69 (1,136)	-2,01 [-5,131; 1,108]	0,2055
Hedges' g SMD							-0,15 [-0,385; 0,083]	0,2063
Int. p-Wert								0,4533
WHO Performance-Status								
0	96	86,81 (13,679)	-1,15 (1,090)	94	85,11 (15,159)	2,61 (1,101)	-3,76 [-6,820; -0,707]	0,0161*
Hedges' g SMD							-0,35 [-0,638; -0,064]	0,0164*
1	157	73,67 (22,044)	4,01 (1,090)	159	70,57 (25,183)	6,07 (1,099)	-2,06 [-5,109; 0,980]	0,1831
Hedges' g SMD							-0,15 [-0,371; 0,071]	0,1839
Int. p-Wert								0,7806
Raucherstatus								
Ja	84	78,89 (20,009)	1,96 (1,433)	85	79,61 (21,806)	4,16 (1,438)	-2,20 [-6,211; 1,809]	0,2799
Hedges' g SMD							-0,17 [-0,468; 0,136]	0,2813
Nein	169	78,54 (20,502)	1,90 (0,969)	168	74,13 (23,526)	4,92 (0,983)	-3,02 [-5,735; -0,298]	0,0298*
Hedges' g SMD							-0,24 [-0,452; -0,023]	0,0299*
Int. p-Wert								0,5477

Analysis is performed if there are at least 10 patients in each subgroup level.
[a] = Number of patients with change from baseline used for MMRM analysis at each timepoint. [b] = Mean baseline for patients with change from baseline used for MMRM analysis at each timepoint. Treatment difference is calculated from a mixed model for repeated measures (MMRM) analysis of the change from baseline score with treatment, visit, and treatment by visit interaction as fixed effects, baseline score as a covariate and baseline score by visit interaction. Patient is used as random effect in the model. Only visits where change from baseline is available for at least 25% of patients in both treatment arms are included in the analysis. Toeplitz with heterogeneity covariance matrix is used to model within-subject error. If the MMRM model does not converge the model results are not presented. SMD = standardised mean difference. * p<0.05.
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Table 4.2.3.1 FLAURA-2: Summary of subgroup analysis of change from baseline in EORTC QLQ-C30 Funktionsskala: Körper (mixed model for repeated measures) - average over all visits
Full Analysis Set, DCO 03APR2023

	Osi + Chemo (N=279)			Osi (N=278)			Behandlungseffekt	
Subgruppen	n [a]	Ausgangswert MW (SD) [b]	Veränderung MW (SE)	n [a]	Ausgangswert MW (SD) [b]	Veränderung MW (SE)	MWD [95%-KI]	p-Wert
Geschlecht								
Maennlich	95	80,07 (21,249)	-0,60 (1,383)	94	80,71 (21,407)	1,66 (1,422)	-2,26 [-6,173; 1,646]	0,2547
Hedges' g SMD							-0,17 [-0,451; 0,120]	0,2565
Weiblich	158	77,81 (19,728)	3,50 (0,984)	159	73,17 (23,611)	6,27 (0,982)	-2,76 [-5,504; -0,023]	0,0481*
Hedges' g SMD							-0,22 [-0,444; -0,002]	0,0481*
Int. p-Wert								0,5051
Nachweis der EGFR-Mutation durch zentralen ctDNA Cobas Test								
positiv	192	77,81 (20,342)	2,98 (0,897)	194	75,19 (23,699)	5,65 (0,899)	-2,67 [-5,167; -0,172]	0,0362*
Hedges' g SMD							-0,21 [-0,414; -0,014]	0,0364*
negativ	39	82,05 (21,256)	-1,94 (1,956)	34	81,18 (17,864)	1,68 (2,092)	-3,61 [-9,326; 2,103]	0,2115
Hedges' g SMD							-0,29 [-0,755; 0,170]	0,2148
unbekannt	22	80,00 (18,286)	-0,47 (3,356)	25	74,93 (24,212)	0,83 (3,304)	-1,30 [-10,840; 8,242]	0,7840
Hedges' g SMD							-0,08 [-0,652; 0,494]	0,7870
Int. p-Wert								0,8977
EGFR-Mutationstyp								
Exon 19 Deletion	153	78,30 (21,892)	0,74 (1,055)	156	78,55 (21,636)	4,57 (1,043)	-3,83 [-6,746; -0,915]	0,0102*
Hedges' g SMD							-0,29 [-0,517; -0,069]	0,0104*
Exon 21 (L858R) Substitutionsmutation	100	79,20 (17,684)	3,34 (1,239)	95	71,65 (24,811)	5,05 (1,311)	-1,71 [-5,282; 1,871]	0,3480
Hedges' g SMD							-0,14 [-0,416; 0,146]	0,3464
Int. p-Wert								0,2398
Zentral bestätigte EGFR-Mutation im Gewebe								
positiv	227	78,94 (20,070)	2,15 (0,814)	220	76,64 (22,619)	4,86 (0,837)	-2,71 [-5,003; -0,416]	0,0207*
Hedges' g SMD							-0,22 [-0,405; -0,033]	0,0209*
negativ	3	ID	ID	3	ID	ID	ID	ID
unbekannt	23	74,78 (23,003)	-2,09 (3,276)	30	72,67 (25,870)	4,83 (2,750)	-6,92 [-15,530; 1,686]	0,1126
Hedges' g SMD							-0,44 [-0,995; 0,106]	0,1134

Analysis is performed if there are at least 10 patients in each subgroup level.
[a] = Number of patients with change from baseline used for MMRM analysis at each timepoint. [b] = Mean baseline for patients with change from baseline used for MMRM analysis at each timepoint. Treatment difference is calculated from a mixed model for repeated measures (MMRM) analysis of the change from baseline score with treatment, visit, and treatment by visit interaction as fixed effects, baseline score as a covariate and baseline score by visit interaction. Patient is used as random effect in the model. Only visits where change from baseline is available for at least 25% of patients in both treatment arms are included in the analysis. Toeplitz with heterogeneity covariance matrix is used to model within-subject error. If the MMRM model does not converge the model results are not presented. SMD = standardised mean difference. * p<0.05.
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Table 4.2.3.1 FLAURA-2: Summary of subgroup analysis of change from baseline in EORTC QLQ-C30 Funktionsskala: Körper (mixed model for repeated measures) - average over all visits
Full Analysis Set, DCO 03APR2023

	Osi + Chemo (N=279)			Osi (N=278)			Behandlungseffekt	
Subgruppen	n [a]	Ausgangswert MW (SD) [b]	Veränderung MW (SE)	n [a]	Ausgangswert MW (SD) [b]	Veränderung MW (SE)	MWD [95%-KI]	p-Wert
Int. p-Wert								0,2816
ZNS-Metastasen zur Baseline								
Ja	101	77,23 (19,917)	3,61 (1,275)	101	74,19 (22,601)	4,95 (1,314)	-1,34 [-4,960; 2,273]	0,4645
Hedges' g SMD							-0,10 [-0,379; 0,173]	0,4651
Nein	152	79,61 (20,562)	0,80 (1,029)	152	77,15 (23,368)	4,44 (1,022)	-3,64 [-6,494; -0,790]	0,0125*
Hedges' g SMD							-0,29 [-0,513; -0,061]	0,0127*
Int. p-Wert								0,4991
Zentrale Bestätigung der EGFR-Mutation								
Zentral bestätigte EGFR-Mutation in Gewebe oder ctDNA	241	78,53 (20,227)	2,33 (0,805)	246	76,18 (23,016)	4,84 (0,804)	-2,52 [-4,751; -0,281]	0,0275*
Hedges' g SMD							-0,20 [-0,378; -0,022]	0,0277*
Keine zentrale Bestätigung	12	NC	NC	7	NC	NC	NC	NC
Int. p-Wert								NC
Alter bei Screening								
<65 Jahre	160	79,88 (18,685)	3,90 (0,922)	152	77,81 (21,093)	6,37 (0,955)	-2,48 [-5,088; 0,137]	0,0632
Hedges' g SMD							-0,21 [-0,433; 0,012]	0,0635
>=65 Jahre	93	76,56 (22,770)	-1,72 (1,451)	101	73,20 (25,612)	2,23 (1,401)	-3,95 [-7,926; 0,027]	0,0515
Hedges' g SMD							-0,28 [-0,563; 0,003]	0,0523
Int. p-Wert								0,5643
Region gPAP								
Asien	158	81,77 (16,406)	0,97 (1,007)	160	79,83 (19,950)	2,97 (1,011)	-2,00 [-4,805; 0,814]	0,1633
Hedges' g SMD							-0,16 [-0,377; 0,064]	0,1637
Europa	19	NC	NC	21	NC	NC	NC	NC
Nordamerika	18	NC	NC	17	NC	NC	NC	NC
Rest der Welt	58	77,59 (20,922)	5,69 (1,612)	55	68,73 (28,368)	8,00 (1,718)	-2,31 [-7,020; 2,397]	0,3311

Analysis is performed if there are at least 10 patients in each subgroup level.
[a] = Number of patients with change from baseline used for MMRM analysis at each timepoint. [b] = Mean baseline for patients with change from baseline used for MMRM analysis at each timepoint. Treatment difference is calculated from a mixed model for repeated measures (MMRM) analysis of the change from baseline score with treatment, visit, and treatment by visit interaction as fixed effects, baseline score as a covariate and baseline score by visit interaction. Patient is used as random effect in the model. Only visits where change from baseline is available for at least 25% of patients in both treatment arms are included in the analysis. Toeplitz with heterogeneity covariance matrix is used to model within-subject error. If the MMRM model does not converge the model results are not presented. SMD = standardised mean difference. * p<0.05.
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Table 4.2.3.1 FLAURA-2: Summary of subgroup analysis of change from baseline in EORTC QLQ-C30 Funktionsskala: Körper (mixed model for repeated measures) - average over all visits
Full Analysis Set, DCO 03APR2023

	Osi + Chemo (N=279)			Osi (N=278)			Behandlungseffekt	
Subgruppen	n [a]	Ausgangswert MW (SD) [b]	Veränderung MW (SE)	n [a]	Ausgangswert MW (SD) [b]	Veränderung MW (SE)	MWD [95%-KI]	p-Wert
Hedges' g SMD							-0,18 [-0,553; 0,186]	0,3303
Int. p-Wert								0,6821

Analysis is performed if there are at least 10 patients in each subgroup level.
[a] = Number of patients with change from baseline used for MMRM analysis at each timepoint. [b] = Mean baseline for patients with change from baseline used for MMRM analysis at each timepoint. Treatment difference is calculated from a mixed model for repeated measures (MMRM) analysis of the change from baseline score with treatment, visit, and treatment by visit interaction as fixed effects, baseline score as a covariate and baseline score by visit interaction. Patient is used as random effect in the model. Only visits where change from baseline is available for at least 25% of patients in both treatment arms are included in the analysis. Toeplitz with heterogeneity covariance matrix is used to model within-subject error. If the MMRM model does not converge the model results are not presented. SMD = standardised mean difference. * p<0.05.
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Table 4.2.3.2 FLAURA-2: Summary of subgroup analysis of change from baseline in EORTC QLQ-C30 Funktionsskala: Rolle (mixed model for repeated measures) - average over all visits
Full Analysis Set, DCO 03APR2023

	Osi + Chemo (N=279)			Osi (N=278)			Behandlungseffekt	
Subgruppen	n [a]	Ausgangswert MW (SD) [b]	Veränderung MW (SE)	n [a]	Ausgangswert MW (SD) [b]	Veränderung MW (SE)	MWD [95%-KI]	p-Wert
Abstammung								
Chinesisch/Asiatisch	66	85,61 (20,018)	-3,02 (1,741)	65	84,62 (24,704)	-3,34 (1,770)	0,33 [-4,583; 5,235]	0,8957
Hedges' g SMD							0,02 [-0,320; 0,365]	0,8962
Nicht-chinesisch/Asiatisch	99	76,26 (25,543)	0,52 (1,758)	101	73,93 (25,757)	5,24 (1,757)	-4,72 [-9,621; 0,184]	0,0591
Hedges' g SMD							-0,27 [-0,546; 0,011]	0,0597
Nicht-asiatisch	88	71,21 (28,671)	5,88 (2,025)	87	62,84 (34,729)	8,67 (2,054)	-2,79 [-8,503; 2,925]	0,3366
Hedges' g SMD							-0,15 [-0,442; 0,151]	0,3363
Int. p-Wert								0,5235
Methode zur Gewebeuntersuchung								
zentral	110	82,27 (25,168)	-1,41 (1,536)	114	81,58 (27,190)	1,32 (1,510)	-2,73 [-6,978; 1,512]	0,2059
Hedges' g SMD							-0,17 [-0,431; 0,093]	0,2069
lokal	143	72,84 (25,841)	2,95 (1,443)	139	65,71 (30,414)	6,35 (1,490)	-3,40 [-7,495; 0,692]	0,1030
Hedges' g SMD							-0,19 [-0,429; 0,039]	0,1027
Int. p-Wert								0,9932
WHO Performance-Status								
0	96	84,38 (20,350)	-3,08 (1,558)	94	81,38 (24,424)	0,15 (1,577)	-3,22 [-7,596; 1,149]	0,1476
Hedges' g SMD							-0,21 [-0,495; 0,075]	0,1487
1	157	72,40 (27,909)	3,99 (1,419)	159	67,82 (31,884)	6,61 (1,427)	-2,62 [-6,579; 1,345]	0,1947
Hedges' g SMD							-0,15 [-0,367; 0,075]	0,1951
Int. p-Wert								0,9883
Raucherstatus								
Ja	84	77,58 (25,545)	0,20 (1,736)	85	74,31 (28,931)	3,72 (1,751)	-3,52 [-8,386; 1,351]	0,1556
Hedges' g SMD							-0,22 [-0,521; 0,084]	0,1569
Nein	169	76,63 (26,184)	1,52 (1,330)	168	72,12 (30,601)	4,12 (1,343)	-2,60 [-6,320; 1,120]	0,1701
Hedges' g SMD							-0,15 [-0,363; 0,064]	0,1704
Int. p-Wert								0,8440

Analysis is performed if there are at least 10 patients in each subgroup level.
[a] = Number of patients with change from baseline used for MMRM analysis at each timepoint. [b] = Mean baseline for patients with change from baseline used for MMRM analysis at each timepoint. Treatment difference is calculated from a mixed model for repeated measures (MMRM) analysis of the change from baseline score with treatment, visit, and treatment by visit interaction as fixed effects, baseline score as a covariate and baseline score by visit interaction. Patient is used as random effect in the model. Only visits where change from baseline is available for at least 25% of patients in both treatment arms are included in the analysis. Toeplitz with heterogeneity covariance matrix is used to model within-subject error. If the MMRM model does not converge the model results are not presented. SMD = standardised mean difference. * p<0.05.
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Table 4.2.3.2 FLAURA-2: Summary of subgroup analysis of change from baseline in EORTC QLQ-C30 Funktionsskala: Rolle (mixed model for repeated measures) - average over all visits
Full Analysis Set, DCO 03APR2023

	Osi + Chemo (N=279)			Osi (N=278)			Behandlungseffekt	
Subgruppen	n [a]	Ausgangswert MW (SD) [b]	Veränderung MW (SE)	n [a]	Ausgangswert MW (SD) [b]	Veränderung MW (SE)	MWD [95%-KI]	p-Wert
Geschlecht								
Maennlich	95	76,84 (27,212)	-1,35 (1,709)	94	75,89 (27,826)	1,09 (1,763)	-2,44 [-7,282; 2,399]	0,3209
Hedges' g SMD							-0,14 [-0,430; 0,141]	0,3226
Weiblich	158	77,00 (25,210)	2,72 (1,353)	159	71,07 (31,178)	5,44 (1,350)	-2,72 [-6,485; 1,051]	0,1570
Hedges' g SMD							-0,16 [-0,380; 0,061]	0,1568
Int. p-Wert								0,8932
Nachweis der EGFR-Mutation durch zentralen ctDNA Cobas Test								
positiv	192	76,39 (25,996)	2,61 (1,209)	194	71,74 (30,042)	5,51 (1,211)	-2,90 [-6,267; 0,468]	0,0913
Hedges' g SMD							-0,17 [-0,372; 0,028]	0,0914
negativ	39	79,49 (28,475)	-5,83 (2,739)	34	82,35 (23,189)	-1,13 (2,919)	-4,70 [-12,686; 3,285]	0,2446
Hedges' g SMD							-0,27 [-0,735; 0,190]	0,2478
unbekannt	22	77,27 (20,922)	0,09 (3,896)	25	68,67 (36,107)	-0,23 (3,884)	0,32 [-10,796; 11,432]	0,9542
Hedges' g SMD							0,02 [-0,556; 0,589]	0,9549
Int. p-Wert								0,4192
EGFR-Mutationstyp								
Exon 19 Deletion	153	75,16 (27,514)	0,50 (1,404)	156	73,93 (29,033)	4,79 (1,389)	-4,29 [-8,174; -0,406]	0,0305*
Hedges' g SMD							-0,25 [-0,470; -0,023]	0,0309*
Exon 21 (L858R) Substitutionsmutation	100	79,67 (23,160)	1,74 (1,621)	95	71,05 (31,717)	2,88 (1,703)	-1,14 [-5,794; 3,516]	0,6300
Hedges' g SMD							-0,07 [-0,350; 0,212]	0,6294
Int. p-Wert								0,1155
Zentral bestätigte EGFR-Mutation im Gewebe								
positiv	227	76,80 (26,518)	1,17 (1,089)	220	74,77 (28,998)	3,90 (1,117)	-2,73 [-5,791; 0,339]	0,0812
Hedges' g SMD							-0,17 [-0,351; 0,021]	0,0816
negativ	3	ID	ID	3	ID	ID	ID	ID
unbekannt	23	76,81 (21,165)	-2,61 (4,360)	30	62,22 (33,600)	7,92 (3,626)	-10,53 [-22,102; 1,038]	0,0735
Hedges' g SMD							-0,51 [-1,063; 0,042]	0,0701

Analysis is performed if there are at least 10 patients in each subgroup level.
[a] = Number of patients with change from baseline used for MMRM analysis at each timepoint. [b] = Mean baseline for patients with change from baseline used for MMRM analysis at each timepoint. Treatment difference is calculated from a mixed model for repeated measures (MMRM) analysis of the change from baseline score with treatment, visit, and treatment by visit interaction as fixed effects, baseline score as a covariate and baseline score by visit interaction. Patient is used as random effect in the model. Only visits where change from baseline is available for at least 25% of patients in both treatment arms are included in the analysis. Toeplitz with heterogeneity covariance matrix is used to model within-subject error. If the MMRM model does not converge the model results are not presented. SMD = standardised mean difference. * p<0.05.
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Table 4.2.3.2 FLAURA-2: Summary of subgroup analysis of change from baseline in EORTC QLQ-C30 Funktionsskala: Rolle (mixed model for repeated measures) - average over all visits
Full Analysis Set, DCO 03APR2023

	Osi + Chemo (N=279)			Osi (N=278)			Behandlungseffekt	
Subgruppen	n [a]	Ausgangswert MW (SD) [b]	Veränderung MW (SE)	n [a]	Ausgangswert MW (SD) [b]	Veränderung MW (SE)	MWD [95%-KI]	p-Wert
Int. p-Wert								0,2101
ZNS-Metastasen zur Baseline								
Ja	101	75,25 (24,790)	3,10 (1,657)	101	73,10 (29,625)	4,71 (1,702)	-1,62 [-6,300; 3,069]	0,4973
Hedges' g SMD							-0,10 [-0,371; 0,181]	0,4983
Nein	152	78,07 (26,676)	-0,30 (1,387)	152	72,70 (30,361)	3,69 (1,381)	-3,99 [-7,843; -0,136]	0,0425*
Hedges' g SMD							-0,23 [-0,459; -0,008]	0,0427*
Int. p-Wert								0,2706
Zentrale Bestätigung der EGFR-Mutation								
Zentral bestätigte EGFR-Mutation in Gewebe oder ctDNA	241	76,69 (26,303)	1,65 (1,063)	246	73,37 (29,912)	4,23 (1,061)	-2,57 [-5,524; 0,380]	0,0875
Hedges' g SMD							-0,15 [-0,333; 0,023]	0,0879
Keine zentrale Bestätigung	12	NC	NC	7	NC	NC	NC	NC
Int. p-Wert								NC
Alter bei Screening								
<65 Jahre	160	77,71 (24,649)	3,01 (1,256)	152	73,25 (28,070)	5,44 (1,302)	-2,43 [-5,998; 1,128]	0,1798
Hedges' g SMD							-0,15 [-0,374; 0,070]	0,1799
>=65 Jahre	93	75,63 (28,078)	-2,57 (1,930)	101	72,28 (32,853)	1,86 (1,861)	-4,42 [-9,711; 0,862]	0,1004
Hedges' g SMD							-0,24 [-0,519; 0,046]	0,1015
Int. p-Wert								0,7373
Region gPAP								
Asien	158	80,49 (23,207)	-0,52 (1,286)	160	77,29 (26,665)	1,53 (1,291)	-2,05 [-5,640; 1,532]	0,2605
Hedges' g SMD							-0,13 [-0,346; 0,094]	0,2611
Europa	19	NC	NC	21	NC	NC	NC	NC
Nordamerika	18	NC	NC	17	NC	NC	NC	NC
Rest der Welt	58	75,29 (27,966)	6,58 (2,408)	55	66,06 (37,124)	7,61 (2,527)	-1,03 [-7,975; 5,905]	0,7681

Analysis is performed if there are at least 10 patients in each subgroup level.
[a] = Number of patients with change from baseline used for MMRM analysis at each timepoint. [b] = Mean baseline for patients with change from baseline used for MMRM analysis at each timepoint. Treatment difference is calculated from a mixed model for repeated measures (MMRM) analysis of the change from baseline score with treatment, visit, and treatment by visit interaction as fixed effects, baseline score as a covariate and baseline score by visit interaction. Patient is used as random effect in the model. Only visits where change from baseline is available for at least 25% of patients in both treatment arms are included in the analysis. Toeplitz with heterogeneity covariance matrix is used to model within-subject error. If the MMRM model does not converge the model results are not presented. SMD = standardised mean difference. * p<0.05.
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Table 4.2.3.2 FLAURA-2: Summary of subgroup analysis of change from baseline in EORTC QLQ-C30 Funktionsskala: Rolle (mixed model for repeated measures) - average over all visits
Full Analysis Set, DCO 03APR2023

	Osi + Chemo (N=279)			Osi (N=278)			Behandlungseffekt	
Subgruppen	n [a]	Ausgangswert MW (SD) [b]	Veränderung MW (SE)	n [a]	Ausgangswert MW (SD) [b]	Veränderung MW (SE)	MWD [95%-KI]	p-Wert
Hedges' g SMD							-0,06 [-0,424; 0,314]	0,7683
Int. p-Wert								0,6432

Analysis is performed if there are at least 10 patients in each subgroup level.
[a] = Number of patients with change from baseline used for MMRM analysis at each timepoint. [b] = Mean baseline for patients with change from baseline used for MMRM analysis at each timepoint. Treatment difference is calculated from a mixed model for repeated measures (MMRM) analysis of the change from baseline score with treatment, visit, and treatment by visit interaction as fixed effects, baseline score as a covariate and baseline score by visit interaction. Patient is used as random effect in the model. Only visits where change from baseline is available for at least 25% of patients in both treatment arms are included in the analysis. Toeplitz with heterogeneity covariance matrix is used to model within-subject error. If the MMRM model does not converge the model results are not presented. SMD = standardised mean difference. * p<0.05.
root/cdar/d516/payer_germany/ar/d5169c00001_payer_germany/tlf/prod/program/mmrmsubpra.sas gmmrmsubpraab 04JUN2024:17:59 kvbv306

Table 4.2.3.3 FLAURA-2: Summary of subgroup analysis of change from baseline in EORTC QLQ-C30 Funktionsskala: Kognition (mixed model for repeated measures) - average over all visits
Full Analysis Set, DCO 03APR2023

	Osi + Chemo (N=279)			Osi (N=278)			Behandlungseffekt	
Subgruppen	n [a]	Ausgangswert MW (SD) [b]	Veränderung MW (SE)	n [a]	Ausgangswert MW (SD) [b]	Veränderung MW (SE)	MWD [95%-KI]	p-Wert
Abstammung								
Chinesisch/Asiatisch	66	86,87 (14,767)	-1,95 (1,247)	65	88,46 (18,616)	-1,95 (1,269)	0,00 [-3,522; 3,527]	0,9990
Hedges' g SMD							0,00 [-0,342; 0,343]	0,9990
Nicht-chinesisch/Asiatisch	99	85,02 (15,882)	-1,45 (1,182)	101	83,83 (19,924)	-0,49 (1,181)	-0,96 [-4,257; 2,336]	0,5663
Hedges' g SMD							-0,08 [-0,358; 0,196]	0,5672
Nicht-asiatisch	88	85,42 (17,655)	-4,46 (1,254)	87	85,25 (20,715)	0,98 (1,268)	-5,44 [-8,963; -1,923]	0,0026*
Hedges' g SMD							-0,46 [-0,760; -0,159]	0,0027*
Int. p-Wert								0,1426
Methode zur Gewebeuntersuchung								
zentral	110	89,09 (14,533)	-3,73 (1,099)	114	87,57 (18,920)	-1,46 (1,081)	-2,26 [-5,300; 0,776]	0,1436
Hedges' g SMD							-0,20 [-0,458; 0,067]	0,1445
lokal	143	82,98 (16,954)	-2,01 (0,961)	139	83,81 (20,554)	0,25 (0,985)	-2,27 [-4,975; 0,444]	0,1010
Hedges' g SMD							-0,20 [-0,430; 0,038]	0,1014
Int. p-Wert								0,8849
WHO Performance-Status								
0	96	88,89 (13,608)	-3,46 (1,164)	94	86,70 (18,707)	-1,07 (1,177)	-2,40 [-5,664; 0,872]	0,1498
Hedges' g SMD							-0,21 [-0,494; 0,076]	0,1506
1	157	83,65 (17,344)	-2,20 (0,905)	159	84,80 (20,574)	0,15 (0,910)	-2,36 [-4,884; 0,171]	0,0675
Hedges' g SMD							-0,21 [-0,427; 0,015]	0,0678
Int. p-Wert								0,9316
Raucherstatus								
Ja	84	86,90 (15,752)	-3,66 (1,424)	85	85,69 (20,437)	-2,63 (1,429)	-1,03 [-5,013; 2,957]	0,6112
Hedges' g SMD							-0,08 [-0,380; 0,224]	0,6122
Nein	169	85,01 (16,431)	-2,24 (0,805)	168	85,42 (19,660)	0,66 (0,812)	-2,90 [-5,152; -0,653]	0,0116*
Hedges' g SMD							-0,28 [-0,491; -0,061]	0,0117*
Int. p-Wert								0,4022

Analysis is performed if there are at least 10 patients in each subgroup level.
[a] = Number of patients with change from baseline used for MMRM analysis at each timepoint. [b] = Mean baseline for patients with change from baseline used for MMRM analysis at each timepoint. Treatment difference is calculated from a mixed model for repeated measures (MMRM) analysis of the change from baseline score with treatment, visit, and treatment by visit interaction as fixed effects, baseline score as a covariate and baseline score by visit interaction. Patient is used as random effect in the model. Only visits where change from baseline is available for at least 25% of patients in both treatment arms are included in the analysis. Toeplitz with heterogeneity covariance matrix is used to model within-subject error. If the MMRM model does not converge the model results are not presented. SMD = standardised mean difference. * p<0.05.
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Table 4.2.3.3 FLAURA-2: Summary of subgroup analysis of change from baseline in EORTC QLQ-C30 Funktionsskala: Kognition (mixed model for repeated measures) - average over all visits
Full Analysis Set, DCO 03APR2023

	Osi + Chemo (N=279)			Osi (N=278)			Behandlungseffekt	
Subgruppen	n [a]	Ausgangswert MW (SD) [b]	Veränderung MW (SE)	n [a]	Ausgangswert MW (SD) [b]	Veränderung MW (SE)	MWD [95%-KI]	p-Wert
Geschlecht								
Maennlich	95	87,02 (15,975)	-2,99 (1,305)	94	85,46 (19,436)	-1,64 (1,343)	-1,35 [-5,047; 2,346]	0,4720
Hedges' g SMD							-0,10 [-0,390; 0,181]	0,4730
Weiblich	158	84,81 (16,332)	-2,52 (0,849)	159	85,53 (20,206)	0,21 (0,842)	-2,73 [-5,079; -0,372]	0,0234*
Hedges' g SMD							-0,26 [-0,477; -0,034]	0,0235*
Int. p-Wert								0,6437
Nachweis der EGFR-Mutation durch zentralen ctDNA Cobas Test								
positiv	192	86,28 (15,253)	-2,82 (0,803)	194	85,22 (19,474)	-0,30 (0,803)	-2,52 [-4,754; -0,288]	0,0270*
Hedges' g SMD							-0,23 [-0,426; -0,025]	0,0272*
negativ	39	82,91 (19,303)	-2,11 (1,916)	34	89,22 (19,193)	0,64 (2,060)	-2,74 [-8,390; 2,905]	0,3360
Hedges' g SMD							-0,23 [-0,688; 0,235]	0,3363
unbekannt	22	84,85 (18,480)	-2,66 (2,641)	25	82,67 (23,805)	-2,86 (2,633)	0,20 [-7,323; 7,726]	0,9570
Hedges' g SMD							0,02 [-0,557; 0,588]	0,9578
Int. p-Wert								0,7077
EGFR-Mutationstyp								
Exon 19 Deletion	153	84,97 (16,308)	-3,71 (0,936)	156	85,36 (19,797)	0,54 (0,926)	-4,24 [-6,834; -1,651]	0,0014*
Hedges' g SMD							-0,37 [-0,591; -0,141]	0,0014*
Exon 21 (L858R) Substitutionsmutation	100	86,67 (16,067)	-1,22 (1,094)	95	85,44 (20,229)	-2,11 (1,150)	0,90 [-2,233; 4,029]	0,5724
Hedges' g SMD							0,08 [-0,200; 0,362]	0,5731
Int. p-Wert								0,0309*
Zentral bestätigte EGFR-Mutation im Gewebe								
positiv	227	85,68 (16,499)	-2,31 (0,724)	220	85,15 (20,064)	0,15 (0,743)	-2,46 [-4,498; -0,419]	0,0183*
Hedges' g SMD							-0,22 [-0,410; -0,038]	0,0184*
negativ	3	ID	ID	3	ID	ID	ID	ID
unbekannt	23	84,06 (13,742)	-6,64 (2,948)	30	86,67 (19,278)	-2,83 (2,487)	-3,81 [-11,581; 3,956]	0,3282
Hedges' g SMD							-0,27 [-0,817; 0,275]	0,3300

Analysis is performed if there are at least 10 patients in each subgroup level.
[a] = Number of patients with change from baseline used for MMRM analysis at each timepoint. [b] = Mean baseline for patients with change from baseline used for MMRM analysis at each timepoint. Treatment difference is calculated from a mixed model for repeated measures (MMRM) analysis of the change from baseline score with treatment, visit, and treatment by visit interaction as fixed effects, baseline score as a covariate and baseline score by visit interaction. Patient is used as random effect in the model. Only visits where change from baseline is available for at least 25% of patients in both treatment arms are included in the analysis. Toeplitz with heterogeneity covariance matrix is used to model within-subject error. If the MMRM model does not converge the model results are not presented. SMD = standardised mean difference. * p<0.05.
root/cdar/d516/payer_germany/ar/d5169c00001_payer_germany/tlf/prod/program/mmrmsubpra.sas gmmrmsubpraac 04JUN2024:17:59 kvbv306

Table 4.2.3.3 FLAURA-2: Summary of subgroup analysis of change from baseline in EORTC QLQ-C30 Funktionsskala: Kognition (mixed model for repeated measures) - average over all visits
Full Analysis Set, DCO 03APR2023

	Osi + Chemo (N=279)			Osi (N=278)			Behandlungseffekt	
Subgruppen	n [a]	Ausgangswert MW (SD) [b]	Veränderung MW (SE)	n [a]	Ausgangswert MW (SD) [b]	Veränderung MW (SE)	MWD [95%-KI]	p-Wert
Int. p-Wert								0,7652
ZNS-Metastasen zur Baseline								
Ja	101	83,99 (15,797)	-1,35 (1,094)	101	83,99 (21,203)	0,04 (1,128)	-1,39 [-4,493; 1,705]	0,3762
Hedges' g SMD							-0,12 [-0,400; 0,152]	0,3774
Nein	152	86,73 (16,426)	-3,68 (0,944)	152	86,51 (18,963)	-0,72 (0,934)	-2,97 [-5,580; -0,354]	0,0262*
Hedges' g SMD							-0,26 [-0,481; -0,030]	0,0264*
Int. p-Wert								0,4749
Zentrale Bestätigung der EGFR-Mutation								
Zentral bestätigte EGFR-Mutation in Gewebe oder ctDNA	241	85,62 (16,333)	-2,59 (0,722)	246	85,57 (19,535)	-0,42 (0,719)	-2,17 [-4,170; -0,166]	0,0339*
Hedges' g SMD							-0,19 [-0,371; -0,015]	0,0340*
Keine zentrale Bestätigung	12	NC	NC	7	NC	NC	NC	NC
Int. p-Wert								NC
Alter bei Screening								
<65 Jahre	160	85,83 (16,947)	-1,66 (0,846)	152	85,64 (20,574)	0,88 (0,877)	-2,55 [-4,944; -0,148]	0,0375*
Hedges' g SMD							-0,24 [-0,459; -0,013]	0,0378*
>=65 Jahre	93	85,30 (14,917)	-4,70 (1,269)	101	85,31 (18,898)	-2,35 (1,220)	-2,35 [-5,825; 1,120]	0,1829
Hedges' g SMD							-0,19 [-0,474; 0,091]	0,1841
Int. p-Wert								0,9019
Region gPAP								
Asien	158	86,08 (15,266)	-1,55 (0,891)	160	85,21 (19,604)	-1,11 (0,894)	-0,44 [-2,924; 2,045]	0,7281
Hedges' g SMD							-0,04 [-0,259; 0,181]	0,7285
Europa	19	NC	NC	21	NC	NC	NC	NC
Nordamerika	18	83,33 (17,150)	-3,57 (2,718)	17	88,24 (14,148)	-0,23 (2,761)	-3,34 [-11,277; 4,593]	0,3975
Hedges' g SMD							-0,28 [-0,952; 0,382]	0,4022
Rest der Welt	58	85,34 (18,490)	-3,18 (1,501)	55	85,15 (22,606)	1,77 (1,574)	-4,95 [-9,262; -0,644]	0,0247*

Analysis is performed if there are at least 10 patients in each subgroup level.
[a] = Number of patients with change from baseline used for MMRM analysis at each timepoint. [b] = Mean baseline for patients with change from baseline used for MMRM analysis at each timepoint. Treatment difference is calculated from a mixed model for repeated measures (MMRM) analysis of the change from baseline score with treatment, visit, and treatment by visit interaction as fixed effects, baseline score as a covariate and baseline score by visit interaction. Patient is used as random effect in the model. Only visits where change from baseline is available for at least 25% of patients in both treatment arms are included in the analysis. Toeplitz with heterogeneity covariance matrix is used to model within-subject error. If the MMRM model does not converge the model results are not presented. SMD = standardised mean difference. * p<0.05.
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Table 4.2.3.3 FLAURA-2: Summary of subgroup analysis of change from baseline in EORTC QLQ-C30 Funktionsskala: Kognition (mixed model for repeated measures) - average over all visits
Full Analysis Set, DCO 03APR2023

	Osi + Chemo (N=279)			Osi (N=278)			Behandlungseffekt	
Subgruppen	n [a]	Ausgangswert MW (SD) [b]	Veränderung MW (SE)	n [a]	Ausgangswert MW (SD) [b]	Veränderung MW (SE)	MWD [95%-KI]	p-Wert
Hedges' g SMD							-0,43 [-0,799; -0,053]	0,0252*
Int. p-Wert								0,3087

Analysis is performed if there are at least 10 patients in each subgroup level.
[a] = Number of patients with change from baseline used for MMRM analysis at each timepoint. [b] = Mean baseline for patients with change from baseline used for MMRM analysis at each timepoint. Treatment difference is calculated from a mixed model for repeated measures (MMRM) analysis of the change from baseline score with treatment, visit, and treatment by visit interaction as fixed effects, baseline score as a covariate and baseline score by visit interaction. Patient is used as random effect in the model. Only visits where change from baseline is available for at least 25% of patients in both treatment arms are included in the analysis. Toeplitz with heterogeneity covariance matrix is used to model within-subject error. If the MMRM model does not converge the model results are not presented. SMD = standardised mean difference. * p<0.05.
root/cdar/d516/payer_germany/ar/d5169c00001_payer_germany/tlf/prod/program/mmrmsubpra.sas gmmrmsubpraac 04JUN2024:17:59 kvbv306

Table 4.2.3.4 FLAURA-2: Summary of subgroup analysis of change from baseline in EORTC QLQ-C30 Funktionsskala: Emotionalität (mixed model for repeated measures) - average over all visits
Full Analysis Set, DCO 03APR2023

	Osi + Chemo (N=279)			Osi (N=278)			Behandlungseffekt	
Subgruppen	n [a]	Ausgangswert MW (SD) [b]	Veränderung MW (SE)	n [a]	Ausgangswert MW (SD) [b]	Veränderung MW (SE)	MWD [95%-KI]	p-Wert
Abstammung								
Chinesisch/Asiatisch	66	81,44 (16,264)	4,23 (1,391)	65	80,51 (19,889)	2,85 (1,417)	1,38 [-2,544; 5,306]	0,4877
Hedges' g SMD							0,12 [-0,222; 0,464]	0,4896
Nicht-chinesisch/Asiatisch	99	73,23 (18,644)	7,95 (1,262)	101	72,85 (19,988)	9,30 (1,261)	-1,35 [-4,869; 2,166]	0,4495
Hedges' g SMD							-0,11 [-0,384; 0,171]	0,4507
Nicht-asiatisch	88	71,02 (23,772)	6,06 (1,436)	87	71,84 (24,683)	8,90 (1,456)	-2,83 [-6,870; 1,201]	0,1674
Hedges' g SMD							-0,21 [-0,506; 0,089]	0,1688
Int. p-Wert								0,3797
Methode zur Gewebeuntersuchung								
zentral	110	78,71 (19,700)	3,81 (1,177)	114	78,00 (21,444)	5,64 (1,157)	-1,83 [-5,079; 1,418]	0,2679
Hedges' g SMD							-0,15 [-0,410; 0,115]	0,2695
lokal	143	71,45 (20,424)	8,05 (1,058)	139	71,58 (21,929)	8,76 (1,084)	-0,71 [-3,690; 2,273]	0,6403
Hedges' g SMD							-0,06 [-0,289; 0,178]	0,6408
Int. p-Wert								0,6117
WHO Performance-Status								
0	96	77,17 (18,466)	5,97 (1,176)	94	75,98 (21,091)	7,17 (1,188)	-1,21 [-4,505; 2,089]	0,4707
Hedges' g SMD							-0,10 [-0,389; 0,180]	0,4718
1	157	73,04 (21,395)	6,43 (1,037)	159	73,58 (22,388)	7,85 (1,041)	-1,42 [-4,309; 1,471]	0,3348
Hedges' g SMD							-0,11 [-0,329; 0,112]	0,3357
Int. p-Wert								0,8534
Raucherstatus								
Ja	84	72,42 (22,255)	7,79 (1,413)	85	74,41 (21,199)	6,82 (1,420)	0,98 [-2,978; 4,931]	0,6266
Hedges' g SMD							0,07 [-0,227; 0,376]	0,6276
Nein	169	75,69 (19,382)	5,50 (0,941)	168	74,50 (22,314)	7,73 (0,949)	-2,23 [-4,855; 0,400]	0,0963
Hedges' g SMD							-0,18 [-0,395; 0,033]	0,0969
Int. p-Wert								0,2708

Analysis is performed if there are at least 10 patients in each subgroup level.
[a] = Number of patients with change from baseline used for MMRM analysis at each timepoint. [b] = Mean baseline for patients with change from baseline used for MMRM analysis at each timepoint. Treatment difference is calculated from a mixed model for repeated measures (MMRM) analysis of the change from baseline score with treatment, visit, and treatment by visit interaction as fixed effects, baseline score as a covariate and baseline score by visit interaction. Patient is used as random effect in the model. Only visits where change from baseline is available for at least 25% of patients in both treatment arms are included in the analysis. Toeplitz with heterogeneity covariance matrix is used to model within-subject error. If the MMRM model does not converge the model results are not presented. SMD = standardised mean difference. * p<0.05.
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Table 4.2.3.4 FLAURA-2: Summary of subgroup analysis of change from baseline in EORTC QLQ-C30 Funktionsskala: Emotionalität (mixed model for repeated measures) - average over all visits
Full Analysis Set, DCO 03APR2023

	Osi + Chemo (N=279)			Osi (N=278)			Behandlungseffekt	
Subgruppen	n [a]	Ausgangswert MW (SD) [b]	Veränderung MW (SE)	n [a]	Ausgangswert MW (SD) [b]	Veränderung MW (SE)	MWD [95%-KI]	p-Wert
Geschlecht								
Maennlich	95	77,37 (19,812)	4,05 (1,249)	94	77,57 (21,378)	5,56 (1,283)	-1,51 [-5,040; 2,023]	0,4004
Hedges' g SMD							-0,12 [-0,408; 0,163]	0,4017
Weiblich	158	72,94 (20,621)	7,53 (1,013)	159	72,64 (22,070)	8,51 (1,007)	-0,98 [-3,789; 1,828]	0,4926
Hedges' g SMD							-0,08 [-0,297; 0,143]	0,4936
Int. p-Wert								0,6930
Nachweis der EGFR-Mutation durch zentralen ctDNA Cobas Test								
positiv	192	75,13 (20,314)	6,05 (0,900)	194	73,41 (21,892)	7,99 (0,899)	-1,95 [-4,447; 0,556]	0,1270
Hedges' g SMD							-0,16 [-0,355; 0,044]	0,1275
negativ	39	70,30 (20,925)	8,57 (1,971)	34	80,15 (18,692)	7,48 (2,114)	1,10 [-4,745; 6,940]	0,7092
Hedges' g SMD							0,09 [-0,372; 0,548]	0,7073
unbekannt	22	77,65 (19,985)	2,88 (2,941)	25	75,00 (25,459)	3,62 (2,937)	-0,74 [-9,109; 7,622]	0,8586
Hedges' g SMD							-0,05 [-0,624; 0,522]	0,8610
Int. p-Wert								0,5100
EGFR-Mutationstyp								
Exon 19 Deletion	153	74,24 (20,797)	4,13 (1,072)	156	75,05 (21,325)	7,57 (1,059)	-3,44 [-6,406; -0,479]	0,0230*
Hedges' g SMD							-0,26 [-0,483; -0,035]	0,0232*
Exon 21 (L858R) Substitutionsmutation	100	75,17 (19,854)	9,80 (1,088)	95	73,07 (22,885)	7,46 (1,144)	2,35 [-0,768; 5,463]	0,1389
Hedges' g SMD							0,21 [-0,069; 0,494]	0,1394
Int. p-Wert								0,0316*
Zentral bestätigte EGFR-Mutation im Gewebe								
positiv	227	74,74 (20,388)	5,78 (0,811)	220	75,61 (21,001)	7,74 (0,831)	-1,96 [-4,241; 0,321]	0,0920
Hedges' g SMD							-0,16 [-0,345; 0,026]	0,0923
negativ	3	ID	ID	3	ID	ID	ID	ID
unbekannt	23	72,46 (21,823)	11,19 (2,792)	30	65,56 (26,779)	8,91 (2,359)	2,28 [-5,113; 9,665]	0,5387
Hedges' g SMD							0,17 [-0,373; 0,715]	0,5384

Analysis is performed if there are at least 10 patients in each subgroup level.
[a] = Number of patients with change from baseline used for MMRM analysis at each timepoint. [b] = Mean baseline for patients with change from baseline used for MMRM analysis at each timepoint. Treatment difference is calculated from a mixed model for repeated measures (MMRM) analysis of the change from baseline score with treatment, visit, and treatment by visit interaction as fixed effects, baseline score as a covariate and baseline score by visit interaction. Patient is used as random effect in the model. Only visits where change from baseline is available for at least 25% of patients in both treatment arms are included in the analysis. Toeplitz with heterogeneity covariance matrix is used to model within-subject error. If the MMRM model does not converge the model results are not presented. SMD = standardised mean difference. * p<0.05.
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Table 4.2.3.4 FLAURA-2: Summary of subgroup analysis of change from baseline in EORTC QLQ-C30 Funktionsskala: Emotionalität (mixed model for repeated measures) - average over all visits
Full Analysis Set, DCO 03APR2023

	Osi + Chemo (N=279)			Osi (N=278)			Behandlungseffekt	
Subgruppen	n [a]	Ausgangswert MW (SD) [b]	Veränderung MW (SE)	n [a]	Ausgangswert MW (SD) [b]	Veränderung MW (SE)	MWD [95%-KI]	p-Wert
Int. p-Wert								0,2081
ZNS-Metastasen zur Baseline								
Ja	101	72,52 (19,527)	6,36 (1,307)	101	76,24 (21,647)	7,58 (1,340)	-1,22 [-4,919; 2,471]	0,5144
Hedges' g SMD							-0,09 [-0,368; 0,184]	0,5149
Nein	152	75,99 (20,901)	6,19 (0,980)	152	73,30 (22,065)	7,43 (0,971)	-1,24 [-3,953; 1,479]	0,3709
Hedges' g SMD							-0,10 [-0,328; 0,122]	0,3714
Int. p-Wert								0,8954
Zentrale Bestätigung der EGFR-Mutation								
Zentral bestätigte EGFR-Mutation in Gewebe oder ctDNA	241	74,52 (20,646)	6,01 (0,798)	246	74,73 (21,677)	7,52 (0,795)	-1,50 [-3,717; 0,708]	0,1822
Hedges' g SMD							-0,12 [-0,299; 0,057]	0,1828
Keine zentrale Bestätigung	12	76,39 (15,006)	12,68 (525820)	7	65,48 (29,435)	7,96 (1,48E6)	4,71 [-2,45E7;2,446E7]	1,0000
Hedges' g SMD							0,00 [-0,932; 0,932]	1,0000
Int. p-Wert								0,0931
Alter bei Screening								
<65 Jahre	160	74,22 (20,915)	6,46 (0,985)	152	72,64 (23,026)	8,92 (1,021)	-2,46 [-5,249; 0,331]	0,0838
Hedges' g SMD							-0,20 [-0,419; 0,027]	0,0843
>=65 Jahre	93	75,27 (19,561)	5,86 (1,295)	101	77,23 (19,892)	5,25 (1,243)	0,61 [-2,929; 4,153]	0,7334
Hedges' g SMD							0,05 [-0,233; 0,331]	0,7340
Int. p-Wert								0,1382
Region gPAP								
Asien	158	77,11 (17,844)	6,43 (0,963)	160	75,57 (21,089)	6,38 (0,966)	0,04 [-2,641; 2,728]	0,9746
Hedges' g SMD							0,00 [-0,216; 0,223]	0,9746
Europa	19	NC	NC	21	NC	NC	NC	NC
Nordamerika	18	NC	NC	17	NC	NC	NC	NC
Rest der Welt	58	70,55 (25,277)	7,68 (1,862)	55	70,15 (24,933)	9,76 (1,944)	-2,08 [-7,411; 3,247]	0,4404

Analysis is performed if there are at least 10 patients in each subgroup level.
[a] = Number of patients with change from baseline used for MMRM analysis at each timepoint. [b] = Mean baseline for patients with change from baseline used for MMRM analysis at each timepoint. Treatment difference is calculated from a mixed model for repeated measures (MMRM) analysis of the change from baseline score with treatment, visit, and treatment by visit interaction as fixed effects, baseline score as a covariate and baseline score by visit interaction. Patient is used as random effect in the model. Only visits where change from baseline is available for at least 25% of patients in both treatment arms are included in the analysis. Toeplitz with heterogeneity covariance matrix is used to model within-subject error. If the MMRM model does not converge the model results are not presented. SMD = standardised mean difference. * p<0.05.
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Table 4.2.3.4 FLAURA-2: Summary of subgroup analysis of change from baseline in EORTC QLQ-C30 Funktionsskala: Emotionalität (mixed model for repeated measures) - average over all visits
Full Analysis Set, DCO 03APR2023

	Osi + Chemo (N=279)			Osi (N=278)			Behandlungseffekt	
Subgruppen	n [a]	Ausgangswert MW (SD) [b]	Veränderung MW (SE)	n [a]	Ausgangswert MW (SD) [b]	Veränderung MW (SE)	MWD [95%-KI]	p-Wert
Hedges' g SMD							-0,14 [-0,514; 0,225]	0,4427
Int. p-Wert								0,2793

Analysis is performed if there are at least 10 patients in each subgroup level.
[a] = Number of patients with change from baseline used for MMRM analysis at each timepoint. [b] = Mean baseline for patients with change from baseline used for MMRM analysis at each timepoint. Treatment difference is calculated from a mixed model for repeated measures (MMRM) analysis of the change from baseline score with treatment, visit, and treatment by visit interaction as fixed effects, baseline score as a covariate and baseline score by visit interaction. Patient is used as random effect in the model. Only visits where change from baseline is available for at least 25% of patients in both treatment arms are included in the analysis. Toeplitz with heterogeneity covariance matrix is used to model within-subject error. If the MMRM model does not converge the model results are not presented. SMD = standardised mean difference. * p<0.05.
root/cdar/d516/payer_germany/ar/d5169c00001_payer_germany/tlf/prod/program/mmrmsubpra.sas gmmrmsubpraad 04JUN2024:17:59 kvbv306

Table 4.2.3.5 FLAURA-2: Summary of subgroup analysis of change from baseline in EORTC QLQ-C30 Funktionsskala: Sozial (mixed model for repeated measures) - average over all visits
Full Analysis Set, DCO 03APR2023

	Osi + Chemo (N=279)			Osi (N=278)			Behandlungseffekt	
Subgruppen	n [a]	Ausgangswert MW (SD) [b]	Veränderung MW (SE)	n [a]	Ausgangswert MW (SD) [b]	Veränderung MW (SE)	MWD [95%-KI]	p-Wert
Abstammung								
Chinesisch/Asiatisch	66	77,27 (20,389)	-4,66 (2,046)	65	76,41 (27,934)	0,61 (2,079)	-5,27 [-11,040; 0,493]	0,0728
Hedges' g SMD							-0,31 [-0,659; 0,031]	0,0741
Nicht-chinesisch/Asiatisch	99	73,23 (23,184)	3,34 (1,464)	101	76,40 (24,974)	8,85 (1,466)	-5,51 [-9,596; -1,416]	0,0086*
Hedges' g SMD							-0,37 [-0,654; -0,095]	0,0087*
Nicht-asiatisch	88	77,27 (25,916)	-0,09 (1,821)	87	69,92 (30,694)	5,08 (1,850)	-5,17 [-10,303; -0,028]	0,0488*
Hedges' g SMD							-0,30 [-0,598; -0,002]	0,0488*
Int. p-Wert								0,9904
Methode zur Gewebeuntersuchung								
zentral	110	80,76 (20,342)	-5,48 (1,595)	114	79,97 (24,509)	2,16 (1,567)	-7,64 [-12,043; -3,237]	0,0007*
Hedges' g SMD							-0,46 [-0,721; -0,190]	0,0008*
lokal	143	71,79 (25,038)	4,40 (1,279)	139	69,42 (29,597)	8,02 (1,316)	-3,62 [-7,229; -0,004]	0,0497*
Hedges' g SMD							-0,23 [-0,468; 0,000]	0,0501
Int. p-Wert								0,0993
WHO Performance-Status								
0	96	79,51 (21,829)	-1,22 (1,520)	94	81,03 (25,935)	2,23 (1,536)	-3,45 [-7,717; 0,807]	0,1116
Hedges' g SMD							-0,23 [-0,516; 0,054]	0,1125
1	157	73,35 (24,230)	1,22 (1,323)	159	70,13 (28,257)	7,43 (1,331)	-6,22 [-9,909; -2,524]	0,0010*
Hedges' g SMD							-0,37 [-0,594; -0,149]	0,0011*
Int. p-Wert								0,4356
Raucherstatus								
Ja	84	72,42 (24,061)	3,36 (1,590)	85	74,31 (29,942)	6,80 (1,603)	-3,44 [-7,897; 1,022]	0,1300
Hedges' g SMD							-0,23 [-0,536; 0,069]	0,1310
Nein	169	77,32 (23,109)	-1,39 (1,273)	168	74,11 (26,853)	4,60 (1,284)	-5,99 [-9,545; -2,430]	0,0010*
Hedges' g SMD							-0,36 [-0,575; -0,145]	0,0010*
Int. p-Wert								0,3412

Analysis is performed if there are at least 10 patients in each subgroup level.
[a] = Number of patients with change from baseline used for MMRM analysis at each timepoint. [b] = Mean baseline for patients with change from baseline used for MMRM analysis at each timepoint. Treatment difference is calculated from a mixed model for repeated measures (MMRM) analysis of the change from baseline score with treatment, visit, and treatment by visit interaction as fixed effects, baseline score as a covariate and baseline score by visit interaction. Patient is used as random effect in the model. Only visits where change from baseline is available for at least 25% of patients in both treatment arms are included in the analysis. Toeplitz with heterogeneity covariance matrix is used to model within-subject error. If the MMRM model does not converge the model results are not presented. SMD = standardised mean difference. * p<0.05.
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Table 4.2.3.5 FLAURA-2: Summary of subgroup analysis of change from baseline in EORTC QLQ-C30 Funktionsskala: Sozial (mixed model for repeated measures) - average over all visits
Full Analysis Set, DCO 03APR2023

	Osi + Chemo (N=279)			Osi (N=278)			Behandlungseffekt	
Subgruppen	n [a]	Ausgangswert MW (SD) [b]	Veränderung MW (SE)	n [a]	Ausgangswert MW (SD) [b]	Veränderung MW (SE)	MWD [95%-KI]	p-Wert
Geschlecht								
Maennlich	95	75,79 (23,666)	-0,19 (1,645)	94	73,58 (28,336)	4,84 (1,698)	-5,04 [-9,701; -0,375]	0,0343*
Hedges' g SMD							-0,31 [-0,596; -0,022]	0,0348*
Weiblich	158	75,63 (23,468)	0,23 (1,277)	159	74,53 (27,674)	5,76 (1,269)	-5,54 [-9,076; -1,998]	0,0023*
Hedges' g SMD							-0,34 [-0,566; -0,123]	0,0023*
Int. p-Wert								0,8259
Nachweis der EGFR-Mutation durch zentralen ctDNA Cobas Test								
positiv	192	76,13 (23,911)	0,55 (1,136)	194	72,77 (28,110)	6,52 (1,138)	-5,98 [-9,141; -2,815]	0,0002*
Hedges' g SMD							-0,38 [-0,579; -0,176]	0,0002*
negativ	39	75,64 (20,536)	-2,41 (2,624)	34	85,78 (14,869)	1,09 (2,840)	-3,50 [-11,341; 4,344]	0,3770
Hedges' g SMD							-0,21 [-0,671; 0,251]	0,3718
unbekannt	22	NC	NC	25	NC	NC	NC	NC
Int. p-Wert								0,3807
EGFR-Mutationstyp								
Exon 19 Deletion	153	76,36 (23,306)	-2,49 (1,301)	156	75,32 (27,919)	6,10 (1,287)	-8,59 [-12,192; -4,994]	<0,0001*
Hedges' g SMD							-0,53 [-0,760; -0,306]	<0,0001*
Exon 21 (L858R) Substitutionsmutation	100	74,67 (23,864)	4,14 (1,588)	95	72,11 (27,978)	4,32 (1,668)	-0,19 [-4,730; 4,359]	0,9359
Hedges' g SMD							-0,01 [-0,292; 0,269]	0,9360
Int. p-Wert								0,0048*
Zentral bestätigte EGFR-Mutation im Gewebe								
positiv	227	75,77 (23,368)	0,02 (1,057)	220	74,85 (27,471)	5,84 (1,083)	-5,82 [-8,796; -2,849]	0,0001*
Hedges' g SMD							-0,36 [-0,550; -0,176]	0,0001*
negativ	3	ID	ID	3	ID	ID	ID	ID
unbekannt	23	74,64 (26,049)	-1,02 (3,321)	30	70,56 (31,160)	5,11 (2,788)	-6,13 [-14,867; 2,597]	0,1639
Hedges' g SMD							-0,39 [-0,937; 0,160]	0,1651
Int. p-Wert								0,9661

Analysis is performed if there are at least 10 patients in each subgroup level.
[a] = Number of patients with change from baseline used for MMRM analysis at each timepoint. [b] = Mean baseline for patients with change from baseline used for MMRM analysis at each timepoint. Treatment difference is calculated from a mixed model for repeated measures (MMRM) analysis of the change from baseline score with treatment, visit, and treatment by visit interaction as fixed effects, baseline score as a covariate and baseline score by visit interaction. Patient is used as random effect in the model. Only visits where change from baseline is available for at least 25% of patients in both treatment arms are included in the analysis. Toeplitz with heterogeneity covariance matrix is used to model within-subject error. If the MMRM model does not converge the model results are not presented. SMD = standardised mean difference. * p<0.05.
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Table 4.2.3.5 FLAURA-2: Summary of subgroup analysis of change from baseline in EORTC QLQ-C30 Funktionsskala: Sozial (mixed model for repeated measures) - average over all visits
Full Analysis Set, DCO 03APR2023

	Osi + Chemo (N=279)			Osi (N=278)			Behandlungseffekt	
Subgruppen	n [a]	Ausgangswert MW (SD) [b]	Veränderung MW (SE)	n [a]	Ausgangswert MW (SD) [b]	Veränderung MW (SE)	MWD [95%-KI]	p-Wert
ZNS-Metastasen zur Baseline								
Ja	101	73,93 (23,024)	0,39 (1,610)	101	73,93 (28,128)	6,46 (1,657)	-6,07 [-10,627; -1,519]	0,0092*
Hedges' g SMD							-0,37 [-0,647; -0,090]	0,0094*
Nein	152	76,86 (23,807)	-0,06 (1,295)	152	74,34 (27,788)	4,87 (1,285)	-4,93 [-8,515; -1,336]	0,0073*
Hedges' g SMD							-0,31 [-0,535; -0,083]	0,0074*
Int. p-Wert								0,9301
Zentrale Bestätigung der EGFR-Mutation								
Zentral bestätigte EGFR-Mutation in Gewebe oder ctDNA	241	75,45 (23,768)	0,39 (1,026)	246	74,59 (27,753)	5,72 (1,022)	-5,32 [-8,166; -2,477]	0,0003*
Hedges' g SMD							-0,33 [-0,511; -0,154]	0,0003*
Keine zentrale Bestätigung	12	NC	NC	7	NC	NC	NC	NC
Int. p-Wert								NC
Alter bei Screening								
<65 Jahre	160	75,83 (23,332)	0,24 (1,262)	152	73,90 (28,558)	5,80 (1,308)	-5,56 [-9,143; -1,987]	0,0024*
Hedges' g SMD							-0,35 [-0,570; -0,122]	0,0024*
>=65 Jahre	93	75,45 (23,900)	-0,23 (1,671)	101	74,59 (26,936)	4,91 (1,606)	-5,13 [-9,699; -0,564]	0,0279*
Hedges' g SMD							-0,32 [-0,600; -0,033]	0,0284*
Int. p-Wert								0,9780
Region gPAP								
Asien	158	74,79 (21,997)	0,87 (1,235)	160	75,10 (27,408)	5,75 (1,239)	-4,88 [-8,318; -1,434]	0,0056*
Hedges' g SMD							-0,31 [-0,533; -0,091]	0,0057*
Europa	19	NC	NC	21	NC	NC	NC	NC
Nordamerika	18	NC	NC	17	NC	NC	NC	NC
Rest der Welt	58	80,75 (23,735)	-0,46 (2,189)	55	72,12 (30,941)	3,88 (2,303)	-4,35 [-10,660; 1,970]	0,1755
Hedges' g SMD							-0,26 [-0,626; 0,115]	0,1759
Int. p-Wert								0,8938

Analysis is performed if there are at least 10 patients in each subgroup level.
[a] = Number of patients with change from baseline used for MMRM analysis at each timepoint. [b] = Mean baseline for patients with change from baseline used for MMRM analysis at each timepoint. Treatment difference is calculated from a mixed model for repeated measures (MMRM) analysis of the change from baseline score with treatment, visit, and treatment by visit interaction as fixed effects, baseline score as a covariate and baseline score by visit interaction. Patient is used as random effect in the model. Only visits where change from baseline is available for at least 25% of patients in both treatment arms are included in the analysis. Toeplitz with heterogeneity covariance matrix is used to model within-subject error. If the MMRM model does not converge the model results are not presented. SMD = standardised mean difference. * p<0.05.
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Table 4.2.3.6 FLAURA-2: Summary of subgroup analysis of change from baseline in EORTC QLQ-C30 Fatigue (mixed model for repeated measures) - average over all visits
Full Analysis Set, DCO 03APR2023

	Osi + Chemo (N=279)			Osi (N=278)			Behandlungseffekt	
Subgruppen	n [a]	Ausgangswert MW (SD) [b]	Veränderung MW (SE)	n [a]	Ausgangswert MW (SD) [b]	Veränderung MW (SE)	MWD [95%-KI]	p-Wert
Abstammung								
Chinesisch/Asiatisch	66	24,92 (15,721)	1,58 (1,626)	65	25,98 (24,318)	-2,06 (1,654)	3,64 [-0,941; 8,217]	0,1185
Hedges' g SMD							0,27 [-0,072; 0,617]	0,1206
Nicht-chinesisch/Asiatisch	99	30,75 (20,440)	-0,65 (1,430)	101	32,67 (22,977)	-5,29 (1,429)	4,64 [0,653; 8,627]	0,0228*
Hedges' g SMD							0,32 [0,044; 0,602]	0,0231*
Nicht-asiatisch	88	31,82 (25,280)	-1,00 (1,620)	87	41,89 (30,439)	-4,89 (1,649)	3,90 [-0,682; 8,481]	0,0948
Hedges' g SMD							0,25 [-0,044; 0,552]	0,0943
Int. p-Wert								0,8321
Methode zur Gewebeuntersuchung								
zentral	110	25,86 (20,143)	1,35 (1,373)	114	29,14 (26,541)	-3,27 (1,353)	4,62 [0,826; 8,422]	0,0173*
Hedges' g SMD							0,32 [0,056; 0,583]	0,0176*
lokal	143	32,48 (21,831)	-0,82 (1,151)	139	38,21 (26,284)	-5,13 (1,187)	4,31 [1,044; 7,567]	0,0098*
Hedges' g SMD							0,31 [0,075; 0,544]	0,0098*
Int. p-Wert								0,8786
WHO Performance-Status								
0	96	20,95 (17,724)	5,11 (1,329)	94	24,94 (21,902)	-0,08 (1,344)	5,19 [1,456; 8,923]	0,0067*
Hedges' g SMD							0,40 [0,110; 0,684]	0,0068*
1	157	34,89 (21,662)	-3,24 (1,180)	159	39,55 (27,886)	-7,15 (1,189)	3,92 [0,620; 7,213]	0,0200*
Hedges' g SMD							0,26 [0,041; 0,484]	0,0202*
Int. p-Wert								0,9627
Raucherstatus								
Ja	84	26,85 (21,209)	0,97 (1,558)	85	30,72 (27,626)	-2,01 (1,567)	2,98 [-1,384; 7,343]	0,1794
Hedges' g SMD							0,21 [-0,096; 0,509]	0,1806
Nein	169	30,97 (21,316)	-0,30 (1,091)	168	35,85 (26,184)	-5,36 (1,105)	5,06 [2,004; 8,116]	0,0012*
Hedges' g SMD							0,35 [0,139; 0,569]	0,0013*
Int. p-Wert								0,6573

Analysis is performed if there are at least 10 patients in each subgroup level.
[a] = Number of patients with change from baseline used for MMRM analysis at each timepoint. [b] = Mean baseline for patients with change from baseline used for MMRM analysis at each timepoint. Treatment difference is calculated from a mixed model for repeated measures (MMRM) analysis of the change from baseline score with treatment, visit, and treatment by visit interaction as fixed effects, baseline score as a covariate and baseline score by visit interaction. Patient is used as random effect in the model. Only visits where change from baseline is available for at least 25% of patients in both treatment arms are included in the analysis. Toeplitz with heterogeneity covariance matrix is used to model within-subject error. If the MMRM model does not converge the model results are not presented. SMD = standardised mean difference. * p<0.05.
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Table 4.2.3.6 FLAURA-2: Summary of subgroup analysis of change from baseline in EORTC QLQ-C30 Fatigue (mixed model for repeated measures) - average over all visits
Full Analysis Set, DCO 03APR2023

	Osi + Chemo (N=279)			Osi (N=278)			Behandlungseffekt	
Subgruppen	n [a]	Ausgangswert MW (SD) [b]	Veränderung MW (SE)	n [a]	Ausgangswert MW (SD) [b]	Veränderung MW (SE)	MWD [95%-KI]	p-Wert
Geschlecht								
Maennlich	95	27,13 (21,606)	3,08 (1,412)	94	30,02 (26,914)	-1,50 (1,460)	4,58 [0,579; 8,586]	0,0251*
Hedges' g SMD							0,33 [0,040; 0,614]	0,0256*
Weiblich	158	31,08 (21,088)	-1,70 (1,145)	159	36,55 (26,411)	-5,79 (1,143)	4,09 [0,902; 7,279]	0,0121*
Hedges' g SMD							0,28 [0,062; 0,505]	0,0121*
Int. p-Wert								0,8862
Nachweis der EGFR-Mutation durch zentralen ctDNA Cobas Test								
positiv	192	31,08 (21,768)	-1,96 (1,002)	194	35,80 (26,326)	-6,22 (1,004)	4,25 [1,462; 7,046]	0,0029*
Hedges' g SMD							0,30 [0,104; 0,505]	0,0029*
negativ	39	24,79 (21,245)	7,82 (2,426)	34	24,51 (24,887)	1,05 (2,588)	6,77 [-0,292; 13,834]	0,0600
Hedges' g SMD							0,44 [-0,023; 0,909]	0,0623
unbekannt	22	NC	NC	25	NC	NC	NC	NC
Int. p-Wert								0,6779
EGFR-Mutationstyp								
Exon 19 Deletion	153	31,45 (23,355)	0,71 (1,134)	156	32,05 (26,141)	-4,69 (1,121)	5,40 [2,262; 8,532]	0,0008*
Hedges' g SMD							0,38 [0,159; 0,609]	0,0008*
Exon 21 (L858R) Substitutionsmutation	100	26,78 (17,522)	-0,91 (1,476)	95	37,89 (27,576)	-3,96 (1,568)	3,05 [-1,244; 7,336]	0,1630
Hedges' g SMD							0,20 [-0,080; 0,484]	0,1597
Int. p-Wert								0,6306
Zentral bestätigte EGFR-Mutation im Gewebe								
positiv	227	29,56 (21,911)	0,11 (0,919)	220	32,83 (26,541)	-4,04 (0,945)	4,14 [1,553; 6,730]	0,0018*
Hedges' g SMD							0,30 [0,110; 0,483]	0,0018*
negativ	3	ID	ID	3	ID	ID	ID	ID
unbekannt	23	30,92 (16,051)	3,16 (3,660)	30	41,11 (25,630)	-8,66 (3,060)	11,82 [2,117; 21,532]	0,0179*
Hedges' g SMD							0,68 [0,121; 1,241]	0,0171*
Int. p-Wert								0,3250

Analysis is performed if there are at least 10 patients in each subgroup level.
[a] = Number of patients with change from baseline used for MMRM analysis at each timepoint. [b] = Mean baseline for patients with change from baseline used for MMRM analysis at each timepoint. Treatment difference is calculated from a mixed model for repeated measures (MMRM) analysis of the change from baseline score with treatment, visit, and treatment by visit interaction as fixed effects, baseline score as a covariate and baseline score by visit interaction. Patient is used as random effect in the model. Only visits where change from baseline is available for at least 25% of patients in both treatment arms are included in the analysis. Toeplitz with heterogeneity covariance matrix is used to model within-subject error. If the MMRM model does not converge the model results are not presented. SMD = standardised mean difference. * p<0.05.
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Table 4.2.3.6 FLAURA-2: Summary of subgroup analysis of change from baseline in EORTC QLQ-C30 Fatigue (mixed model for repeated measures) - average over all visits
Full Analysis Set, DCO 03APR2023

	Osi + Chemo (N=279)			Osi (N=278)			Behandlungseffekt	
Subgruppen	n [a]	Ausgangswert MW (SD) [b]	Veränderung MW (SE)	n [a]	Ausgangswert MW (SD) [b]	Veränderung MW (SE)	MWD [95%-KI]	p-Wert
ZNS-Metastasen zur Baseline								
Ja	101	31,35 (20,209)	-1,90 (1,463)	101	36,30 (24,287)	-5,81 (1,508)	3,91 [-0,243; 8,057]	0,0649
Hedges' g SMD							0,26 [-0,016; 0,538]	0,0651
Nein	152	28,44 (22,028)	1,41 (1,117)	152	32,68 (28,226)	-3,51 (1,109)	4,92 [1,822; 8,016]	0,0019*
Hedges' g SMD							0,36 [0,131; 0,584]	0,0020*
Int. p-Wert								0,6567
Zentrale Bestätigung der EGFR-Mutation								
Zentral bestätigte EGFR-Mutation in Gewebe oder ctDNA	241	29,83 (21,565)	-0,30 (0,894)	246	33,74 (26,586)	-4,60 (0,893)	4,30 [1,818; 6,783]	0,0007*
Hedges' g SMD							0,31 [0,129; 0,487]	0,0007*
Keine zentrale Bestätigung	12	NC	NC	7	NC	NC	NC	NC
Int. p-Wert								NC
Alter bei Screening								
<65 Jahre	160	29,58 (20,773)	-1,59 (1,051)	152	33,19 (26,112)	-7,00 (1,091)	5,41 [2,431; 8,395]	0,0004*
Hedges' g SMD							0,40 [0,180; 0,628]	0,0004*
>=65 Jahre	93	29,63 (22,363)	3,22 (1,572)	101	35,53 (27,712)	-0,25 (1,520)	3,47 [-0,849; 7,782]	0,1148
Hedges' g SMD							0,23 [-0,056; 0,509]	0,1156
Int. p-Wert								0,3743
Region gPAP								
Asien	158	27,57 (18,118)	0,25 (1,099)	160	30,63 (23,767)	-3,81 (1,103)	4,06 [0,997; 7,127]	0,0095*
Hedges' g SMD							0,29 [0,071; 0,513]	0,0096*
Europa	19	NC	NC	21	NC	NC	NC	NC
Nordamerika	18	NC	NC	17	NC	NC	NC	NC
Rest der Welt	58	28,93 (23,264)	-2,32 (1,892)	55	41,21 (33,923)	-5,00 (2,007)	2,69 [-2,801; 8,177]	0,3339
Hedges' g SMD							0,18 [-0,187; 0,552]	0,3337
Int. p-Wert								0,8214

Analysis is performed if there are at least 10 patients in each subgroup level.
[a] = Number of patients with change from baseline used for MMRM analysis at each timepoint. [b] = Mean baseline for patients with change from baseline used for MMRM analysis at each timepoint. Treatment difference is calculated from a mixed model for repeated measures (MMRM) analysis of the change from baseline score with treatment, visit, and treatment by visit interaction as fixed effects, baseline score as a covariate and baseline score by visit interaction. Patient is used as random effect in the model. Only visits where change from baseline is available for at least 25% of patients in both treatment arms are included in the analysis. Toeplitz with heterogeneity covariance matrix is used to model within-subject error. If the MMRM model does not converge the model results are not presented. SMD = standardised mean difference. * p<0.05.
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Table 4.2.3.7 FLAURA-2: Summary of subgroup analysis of change from baseline in EORTC QLQ-C30 Schmerzen (mixed model for repeated measures) - average over all visits
Full Analysis Set, DCO 03APR2023

	Osi + Chemo (N=279)			Osi (N=278)			Behandlungseffekt	
Subgruppen	n [a]	Ausgangswert MW (SD) [b]	Veränderung MW (SE)	n [a]	Ausgangswert MW (SD) [b]	Veränderung MW (SE)	MWD [95%-KI]	p-Wert
Abstammung								
Chinesisch/Asiatisch	66	20,96 (16,618)	-5,42 (1,394)	65	23,59 (23,365)	-6,27 (1,422)	0,85 [-3,090; 4,790]	0,6702
Hedges' g SMD							0,07 [-0,268; 0,417]	0,6714
Nicht-chinesisch/Asiatisch	99	30,13 (24,821)	-7,49 (1,437)	101	26,07 (23,853)	-7,79 (1,431)	0,30 [-3,702; 4,306]	0,8817
Hedges' g SMD							0,02 [-0,256; 0,298]	0,8819
Nicht-asiatisch	88	25,95 (27,665)	-11,92 (1,638)	87	38,70 (35,172)	-12,05 (1,659)	0,13 [-4,519; 4,777]	0,9564
Hedges' g SMD							0,01 [-0,288; 0,305]	0,9561
Int. p-Wert								0,9598
Methode zur Gewebeuntersuchung								
zentral	110	25,00 (23,435)	-6,61 (1,332)	114	26,32 (29,071)	-8,24 (1,308)	1,63 [-2,045; 5,311]	0,3826
Hedges' g SMD							0,12 [-0,146; 0,379]	0,3838
lokal	143	27,27 (24,906)	-8,91 (1,143)	139	32,61 (28,366)	-9,25 (1,179)	0,34 [-2,896; 3,584]	0,8346
Hedges' g SMD							0,02 [-0,209; 0,258]	0,8345
Int. p-Wert								0,7132
WHO Performance-Status								
0	96	17,53 (20,286)	-4,15 (1,363)	94	23,58 (25,448)	-5,75 (1,376)	1,60 [-2,229; 5,438]	0,4102
Hedges' g SMD							0,12 [-0,165; 0,404]	0,4098
1	157	31,63 (24,978)	-10,66 (1,121)	159	33,44 (30,090)	-10,89 (1,130)	0,23 [-2,903; 3,360]	0,8860
Hedges' g SMD							0,02 [-0,204; 0,237]	0,8862
Int. p-Wert								0,5717
Raucherstatus								
Ja	84	27,38 (26,211)	-10,60 (1,462)	85	30,59 (29,418)	-10,51 (1,476)	-0,09 [-4,195; 4,014]	0,9652
Hedges' g SMD							-0,01 [-0,308; 0,295]	0,9653
Nein	169	25,74 (23,285)	-6,67 (1,072)	168	29,37 (28,563)	-7,99 (1,082)	1,32 [-1,675; 4,322]	0,3857
Hedges' g SMD							0,09 [-0,119; 0,308]	0,3862
Int. p-Wert								0,6285

Analysis is performed if there are at least 10 patients in each subgroup level.
[a] = Number of patients with change from baseline used for MMRM analysis at each timepoint. [b] = Mean baseline for patients with change from baseline used for MMRM analysis at each timepoint. Treatment difference is calculated from a mixed model for repeated measures (MMRM) analysis of the change from baseline score with treatment, visit, and treatment by visit interaction as fixed effects, baseline score as a covariate and baseline score by visit interaction. Patient is used as random effect in the model. Only visits where change from baseline is available for at least 25% of patients in both treatment arms are included in the analysis. Toeplitz with heterogeneity covariance matrix is used to model within-subject error. If the MMRM model does not converge the model results are not presented. SMD = standardised mean difference. * p<0.05.
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Table 4.2.3.7 FLAURA-2: Summary of subgroup analysis of change from baseline in EORTC QLQ-C30 Schmerzen (mixed model for repeated measures) - average over all visits
Full Analysis Set, DCO 03APR2023

	Osi + Chemo (N=279)			Osi (N=278)			Behandlungseffekt	
Subgruppen	n [a]	Ausgangswert MW (SD) [b]	Veränderung MW (SE)	n [a]	Ausgangswert MW (SD) [b]	Veränderung MW (SE)	MWD [95%-KI]	p-Wert
Geschlecht								
Maennlich	95	25,96 (25,464)	-10,17 (1,374)	94	28,19 (29,434)	-8,22 (1,417)	-1,95 [-5,844; 1,945]	0,3247
Hedges' g SMD							-0,14 [-0,429; 0,142]	0,3259
Weiblich	158	26,48 (23,580)	-6,65 (1,119)	159	30,71 (28,471)	-9,15 (1,114)	2,49 [-0,616; 5,602]	0,1156
Hedges' g SMD							0,18 [-0,044; 0,398]	0,1160
Int. p-Wert								0,0922
Nachweis der EGFR-Mutation durch zentralen ctDNA Cobas Test								
positiv	192	27,43 (24,594)	-9,58 (0,942)	194	30,67 (28,694)	-10,81 (0,943)	1,24 [-1,387; 3,860]	0,3548
Hedges' g SMD							0,09 [-0,105; 0,294]	0,3551
negativ	39	21,37 (24,468)	-2,66 (2,427)	34	19,12 (26,633)	-3,44 (2,587)	0,78 [-6,310; 7,873]	0,8264
Hedges' g SMD							0,05 [-0,409; 0,511]	0,8275
unbekannt	22	25,00 (20,412)	-3,14 (3,535)	25	37,33 (29,768)	-0,83 (3,565)	-2,31 [-12,497; 7,881]	0,6496
Hedges' g SMD							-0,13 [-0,705; 0,442]	0,6532
Int. p-Wert								0,8191
EGFR-Mutationstyp								
Exon 19 Deletion	153	26,03 (24,018)	-7,48 (1,129)	156	30,56 (29,197)	-9,33 (1,118)	1,84 [-1,286; 4,973]	0,2473
Hedges' g SMD							0,13 [-0,092; 0,355]	0,2476
Exon 21 (L858R) Substitutionsmutation	100	26,67 (24,732)	-8,87 (1,377)	95	28,95 (28,373)	-8,13 (1,453)	-0,74 [-4,693; 3,204]	0,7102
Hedges' g SMD							-0,05 [-0,334; 0,228]	0,7107
Int. p-Wert								0,5560
Zentral bestätigte EGFR-Mutation im Gewebe								
positiv	227	27,24 (24,407)	-8,62 (0,884)	220	28,48 (28,029)	-9,34 (0,908)	0,73 [-1,763; 3,215]	0,5669
Hedges' g SMD							0,05 [-0,131; 0,240]	0,5674
negativ	3	ID	ID	3	ID	ID	ID	ID
unbekannt	23	NC	NC	30	NC	NC	NC	NC
Int. p-Wert								NC

Analysis is performed if there are at least 10 patients in each subgroup level.
[a] = Number of patients with change from baseline used for MMRM analysis at each timepoint. [b] = Mean baseline for patients with change from baseline used for MMRM analysis at each timepoint. Treatment difference is calculated from a mixed model for repeated measures (MMRM) analysis of the change from baseline score with treatment, visit, and treatment by visit interaction as fixed effects, baseline score as a covariate and baseline score by visit interaction. Patient is used as random effect in the model. Only visits where change from baseline is available for at least 25% of patients in both treatment arms are included in the analysis. Toeplitz with heterogeneity covariance matrix is used to model within-subject error. If the MMRM model does not converge the model results are not presented. SMD = standardised mean difference. * p<0.05.
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Table 4.2.3.7 FLAURA-2: Summary of subgroup analysis of change from baseline in EORTC QLQ-C30 Schmerzen (mixed model for repeated measures) - average over all visits
Full Analysis Set, DCO 03APR2023

	Osi + Chemo (N=279)			Osi (N=278)			Behandlungseffekt	
Subgruppen	n [a]	Ausgangswert MW (SD) [b]	Veränderung MW (SE)	n [a]	Ausgangswert MW (SD) [b]	Veränderung MW (SE)	MWD [95%-KI]	p-Wert
ZNS-Metastasen zur Baseline								
Ja	101	28,71 (24,166)	-9,12 (1,367)	101	29,87 (27,519)	-9,55 (1,417)	0,43 [-3,453; 4,311]	0,8277
Hedges' g SMD							0,03 [-0,245; 0,306]	0,8282
Nein	152	24,67 (24,260)	-7,12 (1,124)	152	29,71 (29,710)	-8,30 (1,114)	1,17 [-1,944; 4,291]	0,4595
Hedges' g SMD							0,08 [-0,140; 0,310]	0,4596
Int. p-Wert								0,9449
Zentrale Bestätigung der EGFR-Mutation								
Zentral bestätigte EGFR-Mutation in Gewebe oder ctDNA	241	27,11 (24,447)	-8,52 (0,862)	246	29,13 (28,539)	-8,97 (0,861)	0,44 [-1,949; 2,837]	0,7156
Hedges' g SMD							0,03 [-0,145; 0,211]	0,7159
Keine zentrale Bestätigung	12	NC	NC	7	NC	NC	NC	NC
Int. p-Wert								NC
Alter bei Screening								
<65 Jahre	160	28,13 (25,506)	-10,03 (1,078)	152	32,57 (29,048)	-12,65 (1,118)	2,62 [-0,439; 5,684]	0,0929
Hedges' g SMD							0,19 [-0,032; 0,413]	0,0929
>=65 Jahre	93	23,12 (21,707)	-4,48 (1,458)	101	25,58 (28,044)	-2,49 (1,404)	-1,99 [-5,979; 1,998]	0,3261
Hedges' g SMD							-0,14 [-0,423; 0,141]	0,3279
Int. p-Wert								0,1310
Region gPAP								
Asien	158	25,95 (22,057)	-6,66 (1,068)	160	25,63 (24,435)	-6,78 (1,071)	0,12 [-2,851; 3,098]	0,9351
Hedges' g SMD							0,01 [-0,211; 0,229]	0,9353
Europa	19	NC	NC	21	NC	NC	NC	NC
Nordamerika	18	NC	NC	17	NC	NC	NC	NC
Rest der Welt	58	27,30 (27,341)	-13,49 (2,009)	55	39,70 (38,288)	-13,60 (2,105)	0,10 [-5,710; 5,919]	0,9716
Hedges' g SMD							0,01 [-0,362; 0,376]	0,9715
Int. p-Wert								0,6454

Analysis is performed if there are at least 10 patients in each subgroup level.
[a] = Number of patients with change from baseline used for MMRM analysis at each timepoint. [b] = Mean baseline for patients with change from baseline used for MMRM analysis at each timepoint. Treatment difference is calculated from a mixed model for repeated measures (MMRM) analysis of the change from baseline score with treatment, visit, and treatment by visit interaction as fixed effects, baseline score as a covariate and baseline score by visit interaction. Patient is used as random effect in the model. Only visits where change from baseline is available for at least 25% of patients in both treatment arms are included in the analysis. Toeplitz with heterogeneity covariance matrix is used to model within-subject error. If the MMRM model does not converge the model results are not presented. SMD = standardised mean difference. * p<0.05.
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Table 4.2.3.8 FLAURA-2: Summary of subgroup analysis of change from baseline in EORTC QLQ-C30 Übelkeit und Erbrechen (mixed model for repeated measures) - average over all visits
Full Analysis Set, DCO 03APR2023

	Osi + Chemo (N=279)			Osi (N=278)			Behandlungseffekt	
Subgruppen	n [a]	Ausgangswert MW (SD) [b]	Veränderung MW (SE)	n [a]	Ausgangswert MW (SD) [b]	Veränderung MW (SE)	MWD [95%-KI]	p-Wert
Abstammung								
Chinesisch/Asiatisch	66	3,79 (9,150)	2,72 (0,836)	65	2,56 (7,923)	1,54 (0,858)	1,18 [-1,199; 3,552]	0,3287
Hedges' g SMD							0,17 [-0,173; 0,514]	0,3297
Nicht-chinesisch/Asiatisch	99	7,41 (14,720)	-0,67 (0,862)	101	6,93 (17,363)	-1,90 (0,863)	1,24 [-1,167; 3,644]	0,3111
Hedges' g SMD							0,14 [-0,134; 0,421]	0,3124
Nicht-asiatisch	88	6,63 (11,997)	2,29 (0,803)	87	7,47 (15,410)	-1,41 (0,829)	3,70 [1,414; 5,977]	0,0017*
Hedges' g SMD							0,48 [0,181; 0,783]	0,0017*
Int. p-Wert								0,1126
Methode zur Gewebeuntersuchung								
zentral	110	6,21 (13,891)	1,67 (0,837)	114	6,29 (17,654)	-0,84 (0,824)	2,51 [0,195; 4,830]	0,0338*
Hedges' g SMD							0,28 [0,021; 0,548]	0,0340*
lokal	143	6,18 (11,479)	1,31 (0,634)	139	5,76 (12,157)	-1,17 (0,653)	2,47 [0,682; 4,264]	0,0070*
Hedges' g SMD							0,32 [0,088; 0,558]	0,0071*
Int. p-Wert								0,8584
WHO Performance-Status								
0	96	3,13 (6,972)	1,82 (0,747)	94	4,61 (11,569)	0,34 (0,757)	1,48 [-0,627; 3,578]	0,1678
Hedges' g SMD							0,20 [-0,085; 0,486]	0,1682
1	157	8,07 (14,691)	1,09 (0,668)	159	6,81 (16,477)	-1,74 (0,676)	2,82 [0,953; 4,695]	0,0032*
Hedges' g SMD							0,33 [0,111; 0,555]	0,0033*
Int. p-Wert								0,4826
Raucherstatus								
Ja	84	3,77 (8,717)	1,65 (0,912)	85	5,10 (14,553)	0,57 (0,922)	1,08 [-1,484; 3,643]	0,4068
Hedges' g SMD							0,13 [-0,174; 0,429]	0,4079
Nein	169	7,40 (13,951)	1,35 (0,591)	168	6,45 (15,032)	-1,75 (0,597)	3,10 [1,449; 4,753]	0,0003*
Hedges' g SMD							0,40 [0,186; 0,617]	0,0003*
Int. p-Wert								0,2590

Analysis is performed if there are at least 10 patients in each subgroup level.
[a] = Number of patients with change from baseline used for MMRM analysis at each timepoint. [b] = Mean baseline for patients with change from baseline used for MMRM analysis at each timepoint. Treatment difference is calculated from a mixed model for repeated measures (MMRM) analysis of the change from baseline score with treatment, visit, and treatment by visit interaction as fixed effects, baseline score as a covariate and baseline score by visit interaction. Patient is used as random effect in the model. Only visits where change from baseline is available for at least 25% of patients in both treatment arms are included in the analysis. Toeplitz with heterogeneity covariance matrix is used to model within-subject error. If the MMRM model does not converge the model results are not presented. SMD = standardised mean difference. * p<0.05.
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Table 4.2.3.8 FLAURA-2: Summary of subgroup analysis of change from baseline in EORTC QLQ-C30 Übelkeit und Erbrechen (mixed model for repeated measures) - average over all visits
Full Analysis Set, DCO 03APR2023

	Osi + Chemo (N=279)			Osi (N=278)			Behandlungseffekt	
Subgruppen	n [a]	Ausgangswert MW (SD) [b]	Veränderung MW (SE)	n [a]	Ausgangswert MW (SD) [b]	Veränderung MW (SE)	MWD [95%-KI]	p-Wert
Geschlecht								
Maennlich	95	5,09 (12,414)	1,11 (0,808)	94	6,56 (17,830)	-0,90 (0,847)	2,01 [-0,298; 4,324]	0,0874
Hedges' g SMD							0,25 [-0,037; 0,536]	0,0878
Weiblich	158	6,86 (12,637)	1,60 (0,645)	159	5,66 (12,832)	-0,98 (0,640)	2,58 [0,788; 4,367]	0,0049*
Hedges' g SMD							0,32 [0,096; 0,539]	0,0049*
Int. p-Wert								0,6308
Nachweis der EGFR-Mutation durch zentralen ctDNA Cobas Test								
positiv	192	6,60 (13,095)	0,78 (0,561)	194	6,53 (15,560)	-1,62 (0,564)	2,40 [0,834; 3,964]	0,0028*
Hedges' g SMD							0,31 [0,106; 0,507]	0,0028*
negativ	39	4,27 (9,143)	4,18 (1,545)	34	2,94 (6,449)	0,79 (1,643)	3,39 [-1,122; 7,896]	0,1384
Hedges' g SMD							0,35 [-0,115; 0,812]	0,1406
unbekannt	22	NC	NC	25	NC	NC	NC	NC
Int. p-Wert								0,7927
EGFR-Mutationstyp								
Exon 19 Deletion	153	7,41 (14,164)	2,08 (0,698)	156	5,98 (15,021)	-1,20 (0,690)	3,29 [1,355; 5,222]	0,0009*
Hedges' g SMD							0,38 [0,155; 0,605]	0,0009*
Exon 21 (L858R) Substitutionsmutation	100	4,33 (9,362)	0,13 (0,625)	95	5,96 (14,771)	-0,41 (0,671)	0,54 [-1,275; 2,355]	0,5578
Hedges' g SMD							0,08 [-0,197; 0,365]	0,5574
Int. p-Wert								0,1049
Zentral bestätigte EGFR-Mutation im Gewebe								
positiv	227	6,68 (13,048)	1,05 (0,534)	220	6,29 (15,674)	-1,08 (0,550)	2,12 [0,618; 3,630]	0,0058*
Hedges' g SMD							0,26 [0,076; 0,448]	0,0059*
negativ	3	ID	ID	3	ID	ID	ID	ID
unbekannt	23	NC	NC	30	NC	NC	NC	NC
Int. p-Wert								NC

Analysis is performed if there are at least 10 patients in each subgroup level.
[a] = Number of patients with change from baseline used for MMRM analysis at each timepoint. [b] = Mean baseline for patients with change from baseline used for MMRM analysis at each timepoint. Treatment difference is calculated from a mixed model for repeated measures (MMRM) analysis of the change from baseline score with treatment, visit, and treatment by visit interaction as fixed effects, baseline score as a covariate and baseline score by visit interaction. Patient is used as random effect in the model. Only visits where change from baseline is available for at least 25% of patients in both treatment arms are included in the analysis. Toeplitz with heterogeneity covariance matrix is used to model within-subject error. If the MMRM model does not converge the model results are not presented. SMD = standardised mean difference. * p<0.05.
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Table 4.2.3.8 FLAURA-2: Summary of subgroup analysis of change from baseline in EORTC QLQ-C30 Übelkeit und Erbrechen (mixed model for repeated measures) - average over all visits
Full Analysis Set, DCO 03APR2023

	Osi + Chemo (N=279)			Osi (N=278)			Behandlungseffekt	
Subgruppen	n [a]	Ausgangswert MW (SD) [b]	Veränderung MW (SE)	n [a]	Ausgangswert MW (SD) [b]	Veränderung MW (SE)	MWD [95%-KI]	p-Wert
ZNS-Metastasen zur Baseline								
Ja	101	6,93 (12,532)	1,16 (0,922)	101	7,43 (17,397)	-1,03 (0,961)	2,19 [-0,433; 4,821]	0,1011
Hedges' g SMD							0,23 [-0,046; 0,508]	0,1018
Nein	152	5,70 (12,593)	1,51 (0,536)	152	5,04 (12,873)	-0,99 (0,529)	2,50 [1,018; 3,984]	0,0010*
Hedges' g SMD							0,38 [0,153; 0,607]	0,0010*
Int. p-Wert								0,6045
Zentrale Bestätigung der EGFR-Mutation								
Zentral bestätigte EGFR-Mutation in Gewebe oder ctDNA	241	6,36 (12,769)	1,36 (0,519)	246	6,03 (15,013)	-0,93 (0,519)	2,30 [0,854; 3,738]	0,0019*
Hedges' g SMD							0,28 [0,105; 0,462]	0,0019*
Keine zentrale Bestätigung	12	NC	NC	7	NC	NC	NC	NC
Int. p-Wert								NC
Alter bei Screening								
<65 Jahre	160	6,98 (13,540)	1,54 (0,611)	152	5,59 (14,218)	-1,58 (0,639)	3,11 [1,374; 4,854]	0,0005*
Hedges' g SMD							0,40 [0,174; 0,623]	0,0005*
>=65 Jahre	93	4,84 (10,593)	1,09 (0,865)	101	6,60 (15,825)	0,13 (0,832)	0,96 [-1,409; 3,331]	0,4248
Hedges' g SMD							0,11 [-0,167; 0,397]	0,4256
Int. p-Wert								0,0983
Region gPAP								
Asien	158	5,91 (12,907)	0,68 (0,636)	160	5,42 (14,784)	-0,69 (0,640)	1,37 [-0,404; 3,147]	0,1296
Hedges' g SMD							0,17 [-0,050; 0,390]	0,1302
Europa	19	NC	NC	21	NC	NC	NC	NC
Nordamerika	18	NC	NC	17	NC	NC	NC	NC
Rest der Welt	58	7,47 (13,670)	2,76 (0,940)	55	7,27 (17,790)	-0,67 (1,032)	3,44 [0,659; 6,214]	0,0160*
Hedges' g SMD							0,46 [0,087; 0,835]	0,0157*
Int. p-Wert								0,0272*

Analysis is performed if there are at least 10 patients in each subgroup level.
[a] = Number of patients with change from baseline used for MMRM analysis at each timepoint. [b] = Mean baseline for patients with change from baseline used for MMRM analysis at each timepoint. Treatment difference is calculated from a mixed model for repeated measures (MMRM) analysis of the change from baseline score with treatment, visit, and treatment by visit interaction as fixed effects, baseline score as a covariate and baseline score by visit interaction. Patient is used as random effect in the model. Only visits where change from baseline is available for at least 25% of patients in both treatment arms are included in the analysis. Toeplitz with heterogeneity covariance matrix is used to model within-subject error. If the MMRM model does not converge the model results are not presented. SMD = standardised mean difference. * p<0.05.
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Table 4.2.3.9 FLAURA-2: Summary of subgroup analysis of change from baseline in EORTC QLQ-C30 Dyspnoe (mixed model for repeated measures) - average over all visits
Full Analysis Set, DCO 03APR2023

	Osi + Chemo (N=279)			Osi (N=278)			Behandlungseffekt	
Subgruppen	n [a]	Ausgangswert MW (SD) [b]	Veränderung MW (SE)	n [a]	Ausgangswert MW (SD) [b]	Veränderung MW (SE)	MWD [95%-KI]	p-Wert
Abstammung								
Chinesisch/Asiatisch	66	20,71 (20,891)	-6,96 (1,569)	65	23,59 (21,018)	-6,18 (1,601)	-0,79 [-5,223; 3,652]	0,7266
Hedges' g SMD							-0,06 [-0,403; 0,282]	0,7275
Nicht-chinesisch/Asiatisch	99	23,23 (24,951)	-4,95 (1,474)	101	26,40 (27,615)	-7,74 (1,476)	2,79 [-1,321; 6,910]	0,1821
Hedges' g SMD							0,19 [-0,089; 0,467]	0,1831
Nicht-asiatisch	88	29,17 (29,820)	-9,89 (1,705)	87	37,93 (33,400)	-12,24 (1,742)	2,36 [-2,465; 7,182]	0,3358
Hedges' g SMD							0,15 [-0,151; 0,442]	0,3360
Int. p-Wert								0,5259
Methode zur Gewebeuntersuchung								
zentral	110	22,42 (25,586)	-8,08 (1,247)	114	27,78 (27,664)	-9,86 (1,231)	1,78 [-1,676; 5,242]	0,3108
Hedges' g SMD							0,14 [-0,127; 0,398]	0,3110
lokal	143	26,34 (26,197)	-6,21 (1,286)	139	31,18 (29,817)	-7,69 (1,325)	1,48 [-2,153; 5,117]	0,4230
Hedges' g SMD							0,10 [-0,138; 0,329]	0,4236
Int. p-Wert								0,8420
WHO Performance-Status								
0	96	16,67 (20,520)	-4,61 (1,243)	94	22,34 (26,045)	-5,69 (1,261)	1,08 [-2,424; 4,582]	0,5442
Hedges' g SMD							0,09 [-0,196; 0,373]	0,5441
1	157	29,51 (27,727)	-8,43 (1,258)	159	33,96 (29,642)	-10,66 (1,270)	2,23 [-1,286; 5,748]	0,2130
Hedges' g SMD							0,14 [-0,081; 0,361]	0,2138
Int. p-Wert								0,5745
Raucherstatus								
Ja	84	24,21 (25,004)	-6,86 (1,603)	85	26,27 (27,743)	-6,72 (1,619)	-0,15 [-4,645; 4,352]	0,9487
Hedges' g SMD							-0,01 [-0,311; 0,292]	0,9489
Nein	169	24,85 (26,485)	-6,89 (1,122)	168	31,35 (29,342)	-9,78 (1,139)	2,89 [-0,261; 6,038]	0,0721
Hedges' g SMD							0,20 [-0,018; 0,410]	0,0722
Int. p-Wert								0,4886

Analysis is performed if there are at least 10 patients in each subgroup level.
[a] = Number of patients with change from baseline used for MMRM analysis at each timepoint. [b] = Mean baseline for patients with change from baseline used for MMRM analysis at each timepoint. Treatment difference is calculated from a mixed model for repeated measures (MMRM) analysis of the change from baseline score with treatment, visit, and treatment by visit interaction as fixed effects, baseline score as a covariate and baseline score by visit interaction. Patient is used as random effect in the model. Only visits where change from baseline is available for at least 25% of patients in both treatment arms are included in the analysis. Toeplitz with heterogeneity covariance matrix is used to model within-subject error. If the MMRM model does not converge the model results are not presented. SMD = standardised mean difference. * p<0.05.
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Table 4.2.3.9 FLAURA-2: Summary of subgroup analysis of change from baseline in EORTC QLQ-C30 Dyspnoe (mixed model for repeated measures) - average over all visits
Full Analysis Set, DCO 03APR2023

	Osi + Chemo (N=279)			Osi (N=278)			Behandlungseffekt	
Subgruppen	n [a]	Ausgangswert MW (SD) [b]	Veränderung MW (SE)	n [a]	Ausgangswert MW (SD) [b]	Veränderung MW (SE)	MWD [95%-KI]	p-Wert
Geschlecht								
Maennlich	95	23,86 (27,359)	-5,03 (1,503)	94	29,08 (32,141)	-7,29 (1,560)	2,26 [-2,013; 6,539]	0,2977
Hedges' g SMD							0,15 [-0,134; 0,437]	0,2989
Weiblich	158	25,11 (25,150)	-7,98 (1,165)	159	29,98 (26,834)	-9,43 (1,163)	1,46 [-1,788; 4,699]	0,3779
Hedges' g SMD							0,10 [-0,121; 0,319]	0,3781
Int. p-Wert								0,7779
Nachweis der EGFR-Mutation durch zentralen ctDNA Cobas Test								
positiv	192	26,04 (26,290)	-8,47 (1,048)	194	31,27 (28,110)	-10,40 (1,052)	1,93 [-0,995; 4,849]	0,1955
Hedges' g SMD							0,13 [-0,068; 0,332]	0,1956
negativ	39	21,37 (24,765)	-5,03 (2,384)	34	27,45 (31,216)	-6,30 (2,553)	1,26 [-5,722; 8,247]	0,7194
Hedges' g SMD							0,08 [-0,376; 0,544]	0,7207
unbekannt	22	18,18 (24,618)	4,02 (3,227)	25	20,00 (30,429)	2,38 (3,263)	1,64 [-7,601; 10,885]	0,7216
Hedges' g SMD							0,10 [-0,471; 0,676]	0,7265
Int. p-Wert								0,7433
EGFR-Mutationstyp								
Exon 19 Deletion	153	28,10 (27,867)	-7,39 (1,218)	156	27,14 (28,031)	-10,45 (1,204)	3,06 [-0,310; 6,428]	0,0750
Hedges' g SMD							0,20 [-0,021; 0,426]	0,0756
Exon 21 (L858R) Substitutionsmutation	100	19,33 (21,804)	-5,90 (1,381)	95	34,04 (29,964)	-6,33 (1,477)	0,43 [-3,616; 4,470]	0,8351
Hedges' g SMD							0,03 [-0,251; 0,311]	0,8331
Int. p-Wert								0,3148
Zentral bestätigte EGFR-Mutation im Gewebe								
positiv	227	24,67 (26,391)	-7,31 (0,937)	220	29,85 (28,545)	-9,04 (0,966)	1,74 [-0,909; 4,384]	0,1976
Hedges' g SMD							0,12 [-0,064; 0,308]	0,1977
negativ	3	ID	ID	3	ID	ID	ID	ID
unbekannt	23	26,09 (22,375)	-0,45 (4,049)	30	23,33 (26,479)	-4,05 (3,395)	3,59 [-7,019; 14,206]	0,4997
Hedges' g SMD							0,19 [-0,358; 0,731]	0,5014

Analysis is performed if there are at least 10 patients in each subgroup level.
[a] = Number of patients with change from baseline used for MMRM analysis at each timepoint. [b] = Mean baseline for patients with change from baseline used for MMRM analysis at each timepoint. Treatment difference is calculated from a mixed model for repeated measures (MMRM) analysis of the change from baseline score with treatment, visit, and treatment by visit interaction as fixed effects, baseline score as a covariate and baseline score by visit interaction. Patient is used as random effect in the model. Only visits where change from baseline is available for at least 25% of patients in both treatment arms are included in the analysis. Toeplitz with heterogeneity covariance matrix is used to model within-subject error. If the MMRM model does not converge the model results are not presented. SMD = standardised mean difference. * p<0.05.
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Table 4.2.3.9 FLAURA-2: Summary of subgroup analysis of change from baseline in EORTC QLQ-C30 Dyspnoe (mixed model for repeated measures) - average over all visits
Full Analysis Set, DCO 03APR2023

	Osi + Chemo (N=279)			Osi (N=278)			Behandlungseffekt	
Subgruppen	n [a]	Ausgangswert MW (SD) [b]	Veränderung MW (SE)	n [a]	Ausgangswert MW (SD) [b]	Veränderung MW (SE)	MWD [95%-KI]	p-Wert
Int. p-Wert								0,8998
ZNS-Metastasen zur Baseline								
Ja	101	25,41 (26,728)	-8,47 (1,396)	101	30,69 (26,112)	-8,78 (1,454)	0,31 [-3,675; 4,286]	0,8799
Hedges' g SMD							0,02 [-0,255; 0,297]	0,8800
Nein	152	24,12 (25,504)	-5,96 (1,210)	152	28,95 (30,614)	-8,61 (1,204)	2,65 [-0,707; 6,013]	0,1213
Hedges' g SMD							0,18 [-0,047; 0,403]	0,1218
Int. p-Wert								0,4094
Zentrale Bestätigung der EGFR-Mutation								
Zentral bestätigte EGFR-Mutation in Gewebe oder ctDNA	241	24,76 (26,180)	-7,15 (0,921)	246	29,40 (28,379)	-8,60 (0,922)	1,46 [-1,106; 4,019]	0,2646
Hedges' g SMD							0,10 [-0,077; 0,279]	0,2650
Keine zentrale Bestätigung	12	NC	NC	7	NC	NC	NC	NC
Int. p-Wert								NC
Alter bei Screening								
<65 Jahre	160	25,83 (26,422)	-9,79 (1,059)	152	29,17 (28,531)	-10,90 (1,101)	1,11 [-1,902; 4,114]	0,4699
Hedges' g SMD							0,08 [-0,140; 0,304]	0,4703
>=65 Jahre	93	22,58 (25,138)	-1,82 (1,669)	101	30,36 (29,477)	-5,50 (1,618)	3,68 [-0,915; 8,276]	0,1158
Hedges' g SMD							0,23 [-0,056; 0,509]	0,1161
Int. p-Wert								0,2686
Region gPAP								
Asien	158	21,10 (22,684)	-5,73 (1,101)	160	25,83 (25,065)	-7,07 (1,107)	1,33 [-1,745; 4,409]	0,3950
Hedges' g SMD							0,10 [-0,124; 0,315]	0,3950
Europa	19	NC	NC	21	NC	NC	NC	NC
Nordamerika	18	NC	NC	17	NC	NC	NC	NC
Rest der Welt	58	24,71 (28,312)	-11,18 (1,937)	55	38,18 (35,380)	-12,51 (2,060)	1,33 [-4,325; 6,987]	0,6418

Analysis is performed if there are at least 10 patients in each subgroup level.
[a] = Number of patients with change from baseline used for MMRM analysis at each timepoint. [b] = Mean baseline for patients with change from baseline used for MMRM analysis at each timepoint. Treatment difference is calculated from a mixed model for repeated measures (MMRM) analysis of the change from baseline score with treatment, visit, and treatment by visit interaction as fixed effects, baseline score as a covariate and baseline score by visit interaction. Patient is used as random effect in the model. Only visits where change from baseline is available for at least 25% of patients in both treatment arms are included in the analysis. Toeplitz with heterogeneity covariance matrix is used to model within-subject error. If the MMRM model does not converge the model results are not presented. SMD = standardised mean difference. * p<0.05.
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Table 4.2.3.9 FLAURA-2: Summary of subgroup analysis of change from baseline in EORTC QLQ-C30 Dyspnoe (mixed model for repeated measures) - average over all visits
Full Analysis Set, DCO 03APR2023

	Osi + Chemo (N=279)			Osi (N=278)			Behandlungseffekt	
Subgruppen	n [a]	Ausgangswert MW (SD) [b]	Veränderung MW (SE)	n [a]	Ausgangswert MW (SD) [b]	Veränderung MW (SE)	MWD [95%-KI]	p-Wert
Hedges' g SMD							0,09 [-0,281; 0,457]	0,6400
Int. p-Wert								0,5968

Analysis is performed if there are at least 10 patients in each subgroup level.
[a] = Number of patients with change from baseline used for MMRM analysis at each timepoint. [b] = Mean baseline for patients with change from baseline used for MMRM analysis at each timepoint. Treatment difference is calculated from a mixed model for repeated measures (MMRM) analysis of the change from baseline score with treatment, visit, and treatment by visit interaction as fixed effects, baseline score as a covariate and baseline score by visit interaction. Patient is used as random effect in the model. Only visits where change from baseline is available for at least 25% of patients in both treatment arms are included in the analysis. Toeplitz with heterogeneity covariance matrix is used to model within-subject error. If the MMRM model does not converge the model results are not presented. SMD = standardised mean difference. * p<0.05.
root/cdar/d516/payer_germany/ar/d5169c00001_payer_germany/tlf/prod/program/mmrmsubpra.sas gmmrmsubpraai 04JUN2024:17:59 kvbv306

Table 4.2.3.10 FLAURA-2: Summary of subgroup analysis of change from baseline in EORTC QLQ-C30 Schlaflosigkeit (mixed model for repeated measures) - average over all visits
Full Analysis Set, DCO 03APR2023

	Osi + Chemo (N=279)			Osi (N=278)			Behandlungseffekt	
Subgruppen	n [a]	Ausgangswert MW (SD) [b]	Veränderung MW (SE)	n [a]	Ausgangswert MW (SD) [b]	Veränderung MW (SE)	MWD [95%-KI]	p-Wert
Abstammung								
Chinesisch/Asiatisch	66	23,23 (21,854)	-4,12 (1,701)	65	22,56 (27,072)	-6,03 (1,730)	1,91 [-2,883; 6,710]	0,4314
Hedges' g SMD							0,14 [-0,206; 0,480]	0,4333
Nicht-chinesisch/Asiatisch	99	29,29 (22,972)	-9,44 (1,446)	101	31,68 (32,103)	-11,60 (1,449)	2,16 [-1,873; 6,201]	0,2918
Hedges' g SMD							0,15 [-0,129; 0,427]	0,2930
Nicht-asiatisch	88	35,61 (28,943)	-13,23 (1,648)	87	37,93 (33,400)	-14,27 (1,673)	1,05 [-3,587; 5,683]	0,6558
Hedges' g SMD							0,07 [-0,229; 0,364]	0,6568
Int. p-Wert								0,9337
Methode zur Gewebeuntersuchung								
zentral	110	26,36 (25,580)	-6,05 (1,317)	114	24,56 (30,094)	-6,68 (1,293)	0,63 [-3,010; 4,261]	0,7348
Hedges' g SMD							0,05 [-0,217; 0,307]	0,7355
lokal	143	32,63 (24,853)	-11,11 (1,251)	139	37,17 (32,123)	-14,22 (1,289)	3,11 [-0,424; 6,650]	0,0843
Hedges' g SMD							0,21 [-0,028; 0,440]	0,0845
Int. p-Wert								0,3993
WHO Performance-Status								
0	96	27,43 (26,488)	-8,80 (1,371)	94	27,66 (31,162)	-9,29 (1,384)	0,49 [-3,354; 4,329]	0,8026
Hedges' g SMD							0,04 [-0,248; 0,321]	0,8032
1	157	31,42 (24,530)	-9,10 (1,202)	159	33,75 (32,040)	-12,03 (1,213)	2,92 [-0,437; 6,281]	0,0880
Hedges' g SMD							0,19 [-0,029; 0,413]	0,0887
Int. p-Wert								0,2981
Raucherstatus								
Ja	84	28,57 (23,792)	-7,58 (1,540)	85	26,67 (31,623)	-10,10 (1,556)	2,52 [-1,799; 6,844]	0,2509
Hedges' g SMD							0,18 [-0,126; 0,479]	0,2523
Nein	169	30,57 (26,080)	-9,65 (1,118)	168	33,93 (31,691)	-11,47 (1,128)	1,81 [-1,309; 4,939]	0,2540
Hedges' g SMD							0,12 [-0,090; 0,338]	0,2546
Int. p-Wert								0,7733

Analysis is performed if there are at least 10 patients in each subgroup level.
[a] = Number of patients with change from baseline used for MMRM analysis at each timepoint. [b] = Mean baseline for patients with change from baseline used for MMRM analysis at each timepoint. Treatment difference is calculated from a mixed model for repeated measures (MMRM) analysis of the change from baseline score with treatment, visit, and treatment by visit interaction as fixed effects, baseline score as a covariate and baseline score by visit interaction. Patient is used as random effect in the model. Only visits where change from baseline is available for at least 25% of patients in both treatment arms are included in the analysis. Toeplitz with heterogeneity covariance matrix is used to model within-subject error. If the MMRM model does not converge the model results are not presented. SMD = standardised mean difference. * p<0.05.
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Table 4.2.3.10 FLAURA-2: Summary of subgroup analysis of change from baseline in EORTC QLQ-C30 Schlaflosigkeit (mixed model for repeated measures) - average over all visits
Full Analysis Set, DCO 03APR2023

	Osi + Chemo (N=279)			Osi (N=278)			Behandlungseffekt	
Subgruppen	n [a]	Ausgangswert MW (SD) [b]	Veränderung MW (SE)	n [a]	Ausgangswert MW (SD) [b]	Veränderung MW (SE)	MWD [95%-KI]	p-Wert
Geschlecht								
Maennlich	95	26,67 (22,068)	-7,72 (1,345)	94	27,30 (32,040)	-9,52 (1,395)	1,80 [-2,026; 5,618]	0,3551
Hedges' g SMD							0,13 [-0,151; 0,420]	0,3563
Weiblich	158	31,86 (26,958)	-9,74 (1,214)	159	33,96 (31,483)	-11,79 (1,207)	2,06 [-1,311; 5,425]	0,2304
Hedges' g SMD							0,13 [-0,086; 0,355]	0,2313
Int. p-Wert								0,8954
Nachweis der EGFR-Mutation durch zentralen ctDNA Cobas Test								
positiv	192	29,17 (25,411)	-8,86 (1,044)	194	31,62 (31,420)	-12,37 (1,044)	3,51 [0,604; 6,410]	0,0180*
Hedges' g SMD							0,24 [0,041; 0,442]	0,0182*
negativ	39	33,33 (25,363)	-8,88 (2,376)	34	27,45 (30,118)	-4,59 (2,525)	-4,30 [-11,241; 2,645]	0,2210
Hedges' g SMD							-0,29 [-0,750; 0,175]	0,2228
unbekannt	22	30,30 (25,006)	-10,85 (2,813)	25	36,00 (37,168)	-5,97 (2,930)	-4,88 [-13,015; 3,262]	0,2339
Hedges' g SMD							-0,34 [-0,920; 0,235]	0,2448
Int. p-Wert								0,0630
EGFR-Mutationstyp								
Exon 19 Deletion	153	30,28 (27,667)	-9,26 (1,150)	156	30,77 (30,653)	-11,84 (1,138)	2,58 [-0,606; 5,760]	0,1121
Hedges' g SMD							0,18 [-0,043; 0,404]	0,1128
Exon 21 (L858R) Substitutionsmutation	100	29,33 (21,336)	-8,53 (1,473)	95	32,63 (34,028)	-9,56 (1,551)	1,03 [-3,186; 5,245]	0,6306
Hedges' g SMD							0,07 [-0,212; 0,350]	0,6315
Int. p-Wert								0,4436
Zentral bestätigte EGFR-Mutation im Gewebe								
positiv	227	29,52 (25,573)	-8,27 (0,961)	220	30,30 (31,388)	-10,68 (0,987)	2,41 [-0,297; 5,114]	0,0809
Hedges' g SMD							0,17 [-0,021; 0,351]	0,0813
negativ	3	ID	ID	3	ID	ID	ID	ID
unbekannt	23	33,33 (24,618)	-14,35 (3,234)	30	37,78 (33,600)	-13,27 (2,681)	-1,08 [-9,551; 7,388]	0,7979
Hedges' g SMD							-0,07 [-0,614; 0,473]	0,7983

Analysis is performed if there are at least 10 patients in each subgroup level.
[a] = Number of patients with change from baseline used for MMRM analysis at each timepoint. [b] = Mean baseline for patients with change from baseline used for MMRM analysis at each timepoint. Treatment difference is calculated from a mixed model for repeated measures (MMRM) analysis of the change from baseline score with treatment, visit, and treatment by visit interaction as fixed effects, baseline score as a covariate and baseline score by visit interaction. Patient is used as random effect in the model. Only visits where change from baseline is available for at least 25% of patients in both treatment arms are included in the analysis. Toeplitz with heterogeneity covariance matrix is used to model within-subject error. If the MMRM model does not converge the model results are not presented. SMD = standardised mean difference. * p<0.05.
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Table 4.2.3.10 FLAURA-2: Summary of subgroup analysis of change from baseline in EORTC QLQ-C30 Schlaflosigkeit (mixed model for repeated measures) - average over all visits
Full Analysis Set, DCO 03APR2023

	Osi + Chemo (N=279)			Osi (N=278)			Behandlungseffekt	
Subgruppen	n [a]	Ausgangswert MW (SD) [b]	Veränderung MW (SE)	n [a]	Ausgangswert MW (SD) [b]	Veränderung MW (SE)	MWD [95%-KI]	p-Wert
Int. p-Wert								0,2517
ZNS-Metastasen zur Baseline								
Ja	101	28,71 (20,564)	-7,52 (1,412)	101	30,03 (30,370)	-10,45 (1,468)	2,93 [-1,087; 6,944]	0,1519
Hedges' g SMD							0,20 [-0,075; 0,478]	0,1530
Nein	152	30,70 (28,067)	-9,92 (1,191)	152	32,46 (32,765)	-11,31 (1,179)	1,39 [-1,907; 4,685]	0,4077
Hedges' g SMD							0,09 [-0,130; 0,320]	0,4088
Int. p-Wert								0,6814
Zentrale Bestätigung der EGFR-Mutation								
Zentral bestätigte EGFR-Mutation in Gewebe oder ctDNA	241	29,46 (25,345)	-8,73 (0,938)	246	31,17 (31,656)	-10,81 (0,936)	2,09 [-0,515; 4,692]	0,1156
Hedges' g SMD							0,14 [-0,035; 0,320]	0,1161
Keine zentrale Bestätigung	12	NC	NC	7	NC	NC	NC	NC
Int. p-Wert								NC
Alter bei Screening								
<65 Jahre	160	30,00 (24,572)	-9,80 (1,118)	152	32,46 (32,084)	-12,78 (1,161)	2,97 [-0,197; 6,145]	0,0660
Hedges' g SMD							0,21 [-0,014; 0,431]	0,0663
>=65 Jahre	93	29,75 (26,677)	-7,66 (1,573)	101	30,03 (31,448)	-7,92 (1,512)	0,26 [-4,037; 4,559]	0,9049
Hedges' g SMD							0,02 [-0,265; 0,299]	0,9053
Int. p-Wert								0,2796
Region gPAP								
Asien	158	26,16 (22,366)	-7,42 (1,127)	160	29,17 (31,445)	-9,43 (1,133)	2,01 [-1,132; 5,157]	0,2090
Hedges' g SMD							0,14 [-0,079; 0,361]	0,2096
Europa	19	NC	NC	21	NC	NC	NC	NC
Nordamerika	18	42,59 (25,063)	-21,66 (4,916)	17	39,22 (29,428)	-21,31 (5,180)	-0,36 [-15,852; 15,139]	0,9615
Hedges' g SMD							-0,02 [-0,679; 0,646]	0,9610
Rest der Welt	58	33,33 (27,217)	-10,83 (2,097)	55	35,76 (34,459)	-11,06 (2,206)	0,23 [-5,792; 6,249]	0,9402

Analysis is performed if there are at least 10 patients in each subgroup level.
[a] = Number of patients with change from baseline used for MMRM analysis at each timepoint. [b] = Mean baseline for patients with change from baseline used for MMRM analysis at each timepoint. Treatment difference is calculated from a mixed model for repeated measures (MMRM) analysis of the change from baseline score with treatment, visit, and treatment by visit interaction as fixed effects, baseline score as a covariate and baseline score by visit interaction. Patient is used as random effect in the model. Only visits where change from baseline is available for at least 25% of patients in both treatment arms are included in the analysis. Toeplitz with heterogeneity covariance matrix is used to model within-subject error. If the MMRM model does not converge the model results are not presented. SMD = standardised mean difference. * p<0.05.
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Table 4.2.3.10 FLAURA-2: Summary of subgroup analysis of change from baseline in EORTC QLQ-C30 Schlaflosigkeit (mixed model for repeated measures) - average over all visits
Full Analysis Set, DCO 03APR2023

	Osi + Chemo (N=279)			Osi (N=278)			Behandlungseffekt	
Subgruppen	n [a]	Ausgangswert MW (SD) [b]	Veränderung MW (SE)	n [a]	Ausgangswert MW (SD) [b]	Veränderung MW (SE)	MWD [95%-KI]	p-Wert
Hedges' g SMD							0,01 [-0,355; 0,383]	0,9406
Int. p-Wert								0,7320

Analysis is performed if there are at least 10 patients in each subgroup level.
[a] = Number of patients with change from baseline used for MMRM analysis at each timepoint. [b] = Mean baseline for patients with change from baseline used for MMRM analysis at each timepoint. Treatment difference is calculated from a mixed model for repeated measures (MMRM) analysis of the change from baseline score with treatment, visit, and treatment by visit interaction as fixed effects, baseline score as a covariate and baseline score by visit interaction. Patient is used as random effect in the model. Only visits where change from baseline is available for at least 25% of patients in both treatment arms are included in the analysis. Toeplitz with heterogeneity covariance matrix is used to model within-subject error. If the MMRM model does not converge the model results are not presented. SMD = standardised mean difference. * p<0.05.
root/cdar/d516/payer_germany/ar/d5169c00001_payer_germany/tlf/prod/program/mmrmsubpra.sas gmmrmsubpraaj 04JUN2024:17:59 kvbv306

Table 4.2.3.11 FLAURA-2: Summary of subgroup analysis of change from baseline in EORTC QLQ-C30 Appetitverlust (mixed model for repeated measures) - average over all visits
Full Analysis Set, DCO 03APR2023

	Osi + Chemo (N=279)			Osi (N=278)			Behandlungseffekt	
Subgruppen	n [a]	Ausgangswert MW (SD) [b]	Veränderung MW (SE)	n [a]	Ausgangswert MW (SD) [b]	Veränderung MW (SE)	MWD [95%-KI]	p-Wert
Abstammung								
Chinesisch/Asiatisch	66	10,10 (15,436)	7,59 (1,654)	65	15,90 (23,649)	1,56 (1,692)	6,03 [1,329; 10,728]	0,0123*
Hedges' g SMD							0,44 [0,096; 0,789]	0,0124*
Nicht-chinesisch/Asiatisch	99	25,59 (26,440)	-0,01 (1,672)	101	20,79 (28,617)	-2,61 (1,672)	2,60 [-2,076; 7,270]	0,2745
Hedges' g SMD							0,15 [-0,123; 0,432]	0,2746
Nicht-asiatisch	88	23,86 (31,944)	-1,11 (1,778)	87	27,59 (33,798)	-7,02 (1,807)	5,91 [0,889; 10,923]	0,0213*
Hedges' g SMD							0,35 [0,052; 0,649]	0,0213*
Int. p-Wert								0,3689
Methode zur Gewebeuntersuchung								
zentral	110	16,06 (25,031)	5,57 (1,534)	114	19,59 (29,353)	-1,57 (1,508)	7,13 [2,892; 11,374]	0,0011*
Hedges' g SMD							0,44 [0,177; 0,707]	0,0011*
lokal	143	24,71 (27,892)	-0,79 (1,301)	139	23,74 (29,826)	-4,12 (1,346)	3,33 [-0,352; 7,013]	0,0761
Hedges' g SMD							0,21 [-0,023; 0,446]	0,0767
Int. p-Wert								0,1962
WHO Performance-Status								
0	96	15,97 (23,185)	4,26 (1,483)	94	17,02 (26,660)	-3,14 (1,499)	7,40 [3,244; 11,563]	0,0006*
Hedges' g SMD							0,51 [0,218; 0,796]	0,0006*
1	157	23,99 (28,703)	0,48 (1,316)	159	24,74 (30,974)	-3,13 (1,329)	3,60 [-0,075; 7,282]	0,0548
Hedges' g SMD							0,22 [-0,005; 0,437]	0,0554
Int. p-Wert								0,1959
Raucherstatus								
Ja	84	22,22 (26,044)	-1,64 (1,854)	85	23,14 (32,130)	-3,70 (1,869)	2,06 [-3,137; 7,252]	0,4354
Hedges' g SMD							0,12 [-0,182; 0,422]	0,4370
Nein	169	20,32 (27,486)	3,77 (1,186)	168	21,23 (28,356)	-2,71 (1,200)	6,48 [3,163; 9,795]	0,0001*
Hedges' g SMD							0,42 [0,202; 0,633]	0,0001*
Int. p-Wert								0,1927

Analysis is performed if there are at least 10 patients in each subgroup level.
[a] = Number of patients with change from baseline used for MMRM analysis at each timepoint. [b] = Mean baseline for patients with change from baseline used for MMRM analysis at each timepoint. Treatment difference is calculated from a mixed model for repeated measures (MMRM) analysis of the change from baseline score with treatment, visit, and treatment by visit interaction as fixed effects, baseline score as a covariate and baseline score by visit interaction. Patient is used as random effect in the model. Only visits where change from baseline is available for at least 25% of patients in both treatment arms are included in the analysis. Toeplitz with heterogeneity covariance matrix is used to model within-subject error. If the MMRM model does not converge the model results are not presented. SMD = standardised mean difference. * p<0.05.
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Table 4.2.3.11 FLAURA-2: Summary of subgroup analysis of change from baseline in EORTC QLQ-C30 Appetitverlust (mixed model for repeated measures) - average over all visits
Full Analysis Set, DCO 03APR2023

	Osi + Chemo (N=279)			Osi (N=278)			Behandlungseffekt	
Subgruppen	n [a]	Ausgangswert MW (SD) [b]	Veränderung MW (SE)	n [a]	Ausgangswert MW (SD) [b]	Veränderung MW (SE)	MWD [95%-KI]	p-Wert
Geschlecht								
Maennlich	95	17,89 (24,702)	4,02 (1,630)	94	20,92 (29,728)	-2,74 (1,694)	6,76 [2,121; 11,396]	0,0045*
Hedges' g SMD							0,42 [0,128; 0,705]	0,0046*
Weiblich	158	22,78 (28,176)	0,73 (1,241)	159	22,43 (29,648)	-3,21 (1,234)	3,94 [0,496; 7,378]	0,0251*
Hedges' g SMD							0,25 [0,031; 0,473]	0,0254*
Int. p-Wert								0,4539
Nachweis der EGFR-Mutation durch zentralen ctDNA Cobas Test								
positiv	192	21,53 (26,631)	0,31 (1,123)	194	23,20 (30,260)	-4,20 (1,126)	4,51 [1,383; 7,637]	0,0048*
Hedges' g SMD							0,29 [0,088; 0,489]	0,0049*
negativ	39	16,24 (21,456)	9,28 (2,841)	34	10,78 (19,627)	4,18 (3,034)	5,10 [-3,220; 13,416]	0,2258
Hedges' g SMD							0,28 [-0,178; 0,747]	0,2275
unbekannt	22	NC	NC	25	NC	NC	NC	NC
Int. p-Wert								0,7406
EGFR-Mutationstyp								
Exon 19 Deletion	153	22,88 (28,986)	2,36 (1,298)	156	22,65 (30,524)	-4,35 (1,285)	6,70 [3,113; 10,296]	0,0003*
Hedges' g SMD							0,42 [0,191; 0,642]	0,0003*
Exon 21 (L858R) Substitutionsmutation	100	18,00 (23,413)	1,18 (1,533)	95	21,05 (28,373)	-0,77 (1,630)	1,95 [-2,473; 6,365]	0,3860
Hedges' g SMD							0,12 [-0,157; 0,405]	0,3863
Int. p-Wert								0,1547
Zentral bestätigte EGFR-Mutation im Gewebe								
positiv	227	21,15 (27,034)	1,82 (1,055)	220	20,76 (29,168)	-3,05 (1,084)	4,88 [1,906; 7,849]	0,0013*
Hedges' g SMD							0,30 [0,118; 0,491]	0,0014*
negativ	3	ID	ID	3	ID	ID	ID	ID
unbekannt	23	20,29 (27,959)	4,24 (3,438)	30	28,89 (32,440)	-4,00 (2,845)	8,24 [-0,810; 17,291]	0,0732
Hedges' g SMD							0,51 [-0,044; 1,061]	0,0714
Int. p-Wert								0,9303

Analysis is performed if there are at least 10 patients in each subgroup level.
[a] = Number of patients with change from baseline used for MMRM analysis at each timepoint. [b] = Mean baseline for patients with change from baseline used for MMRM analysis at each timepoint. Treatment difference is calculated from a mixed model for repeated measures (MMRM) analysis of the change from baseline score with treatment, visit, and treatment by visit interaction as fixed effects, baseline score as a covariate and baseline score by visit interaction. Patient is used as random effect in the model. Only visits where change from baseline is available for at least 25% of patients in both treatment arms are included in the analysis. Toeplitz with heterogeneity covariance matrix is used to model within-subject error. If the MMRM model does not converge the model results are not presented. SMD = standardised mean difference. * p<0.05.
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Table 4.2.3.11 FLAURA-2: Summary of subgroup analysis of change from baseline in EORTC QLQ-C30 Appetitverlust (mixed model for repeated measures) - average over all visits
Full Analysis Set, DCO 03APR2023

	Osi + Chemo (N=279)			Osi (N=278)			Behandlungseffekt	
Subgruppen	n [a]	Ausgangswert MW (SD) [b]	Veränderung MW (SE)	n [a]	Ausgangswert MW (SD) [b]	Veränderung MW (SE)	MWD [95%-KI]	p-Wert
ZNS-Metastasen zur Baseline								
Ja	101	25,08 (25,563)	-0,71 (1,683)	101	24,09 (30,228)	-5,41 (1,743)	4,69 [-0,084; 9,469]	0,0541
Hedges' g SMD							0,27 [-0,006; 0,549]	0,0548
Nein	152	18,20 (27,621)	3,77 (1,230)	152	20,39 (29,228)	-1,59 (1,217)	5,36 [1,951; 8,760]	0,0021*
Hedges' g SMD							0,35 [0,127; 0,581]	0,0022*
Int. p-Wert								0,5019
Zentrale Bestätigung der EGFR-Mutation								
Zentral bestätigte EGFR-Mutation in Gewebe oder ctDNA	241	21,44 (27,328)	1,62 (1,016)	246	21,68 (29,503)	-3,08 (1,015)	4,70 [1,875; 7,516]	0,0011*
Hedges' g SMD							0,30 [0,117; 0,474]	0,0012*
Keine zentrale Bestätigung	12	11,11 (16,412)	6,95 (4,135)	7	28,57 (35,635)	-0,85 (6,599)	7,80 [-9,611; 25,209]	0,3482
Hedges' g SMD							0,48 [-0,467; 1,428]	0,3204
Int. p-Wert								0,3235
Alter bei Screening								
<65 Jahre	160	21,46 (27,305)	0,38 (1,208)	152	21,71 (28,517)	-6,01 (1,256)	6,39 [2,960; 9,816]	0,0003*
Hedges' g SMD							0,41 [0,190; 0,639]	0,0003*
>=65 Jahre	93	20,07 (26,530)	4,60 (1,682)	101	22,11 (31,368)	1,76 (1,621)	2,84 [-1,762; 7,447]	0,2248
Hedges' g SMD							0,17 [-0,108; 0,456]	0,2264
Int. p-Wert								0,1689
Region gPAP								
Asien	158	18,57 (23,342)	3,21 (1,221)	160	19,79 (27,800)	-0,66 (1,229)	3,87 [0,459; 7,274]	0,0263*
Hedges' g SMD							0,25 [0,029; 0,470]	0,0265*
Europa	19	NC	NC	21	NC	NC	NC	NC
Nordamerika	18	NC	NC	17	NC	NC	NC	NC
Rest der Welt	58	23,56 (30,594)	-0,01 (2,151)	55	26,06 (34,955)	-6,39 (2,269)	6,38 [0,177; 12,582]	0,0439*

Analysis is performed if there are at least 10 patients in each subgroup level.
[a] = Number of patients with change from baseline used for MMRM analysis at each timepoint. [b] = Mean baseline for patients with change from baseline used for MMRM analysis at each timepoint. Treatment difference is calculated from a mixed model for repeated measures (MMRM) analysis of the change from baseline score with treatment, visit, and treatment by visit interaction as fixed effects, baseline score as a covariate and baseline score by visit interaction. Patient is used as random effect in the model. Only visits where change from baseline is available for at least 25% of patients in both treatment arms are included in the analysis. Toeplitz with heterogeneity covariance matrix is used to model within-subject error. If the MMRM model does not converge the model results are not presented. SMD = standardised mean difference. * p<0.05.
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Table 4.2.3.11 FLAURA-2: Summary of subgroup analysis of change from baseline in EORTC QLQ-C30 Appetitverlust (mixed model for repeated measures) - average over all visits
Full Analysis Set, DCO 03APR2023

	Osi + Chemo (N=279)			Osi (N=278)			Behandlungseffekt	
Subgruppen	n [a]	Ausgangswert MW (SD) [b]	Veränderung MW (SE)	n [a]	Ausgangswert MW (SD) [b]	Veränderung MW (SE)	MWD [95%-KI]	p-Wert
Hedges' g SMD							0,38 [0,009; 0,754]	0,0446*
Int. p-Wert								0,2064

Analysis is performed if there are at least 10 patients in each subgroup level.
[a] = Number of patients with change from baseline used for MMRM analysis at each timepoint. [b] = Mean baseline for patients with change from baseline used for MMRM analysis at each timepoint. Treatment difference is calculated from a mixed model for repeated measures (MMRM) analysis of the change from baseline score with treatment, visit, and treatment by visit interaction as fixed effects, baseline score as a covariate and baseline score by visit interaction. Patient is used as random effect in the model. Only visits where change from baseline is available for at least 25% of patients in both treatment arms are included in the analysis. Toeplitz with heterogeneity covariance matrix is used to model within-subject error. If the MMRM model does not converge the model results are not presented. SMD = standardised mean difference. * p<0.05.
root/cdar/d516/payer_germany/ar/d5169c00001_payer_germany/tlf/prod/program/mmrmsubpra.sas gmmrmsubpraak 04JUN2024:17:59 kvbv306

Table 4.2.3.12 FLAURA-2: Summary of subgroup analysis of change from baseline in EORTC QLQ-C30 Verstopfung (mixed model for repeated measures) - average over all visits
Full Analysis Set, DCO 03APR2023

	Osi + Chemo (N=279)			Osi (N=278)			Behandlungseffekt	
Subgruppen	n [a]	Ausgangswert MW (SD) [b]	Veränderung MW (SE)	n [a]	Ausgangswert MW (SD) [b]	Veränderung MW (SE)	MWD [95%-KI]	p-Wert
Abstammung								
Chinesisch/Asiatisch	66	13,64 (18,469)	0,00 (1,301)	65	6,67 (17,873)	-0,21 (1,327)	0,21 [-3,526; 3,936]	0,9134
Hedges' g SMD							0,02 [-0,323; 0,362]	0,9125
Nicht-chinesisch/Asiatisch	99	14,14 (21,344)	0,81 (1,308)	101	17,16 (23,387)	-3,30 (1,311)	4,10 [0,449; 7,761]	0,0280*
Hedges' g SMD							0,31 [0,033; 0,591]	0,0283*
Nicht-asiatisch	88	16,29 (27,679)	-1,75 (1,523)	87	17,24 (28,240)	-4,75 (1,556)	3,00 [-1,303; 7,298]	0,1707
Hedges' g SMD							0,21 [-0,090; 0,504]	0,1716
Int. p-Wert								0,5595
Methode zur Gewebeuntersuchung								
zentral	110	13,03 (21,224)	1,44 (1,213)	114	11,40 (23,394)	-2,20 (1,191)	3,64 [0,290; 6,999]	0,0334*
Hedges' g SMD							0,29 [0,022; 0,549]	0,0336*
lokal	143	16,08 (24,339)	-1,32 (1,063)	139	17,03 (24,856)	-3,76 (1,097)	2,44 [-0,566; 5,447]	0,1112
Hedges' g SMD							0,19 [-0,044; 0,424]	0,1117
Int. p-Wert								0,7515
WHO Performance-Status								
0	96	11,46 (19,840)	-0,87 (1,229)	94	15,25 (26,171)	-2,42 (1,240)	1,55 [-1,896; 4,998]	0,3760
Hedges' g SMD							0,13 [-0,156; 0,413]	0,3766
1	157	16,77 (24,641)	0,38 (1,046)	159	14,05 (23,235)	-3,53 (1,057)	3,91 [0,979; 6,840]	0,0091*
Hedges' g SMD							0,29 [0,073; 0,517]	0,0091*
Int. p-Wert								0,1912
Raucherstatus								
Ja	84	15,87 (22,241)	0,44 (1,368)	85	16,47 (26,036)	-3,93 (1,387)	4,37 [0,525; 8,215]	0,0262*
Hedges' g SMD							0,34 [0,040; 0,647]	0,0267*
Nein	169	14,20 (23,475)	-0,42 (0,975)	168	13,49 (23,425)	-2,76 (0,983)	2,35 [-0,378; 5,069]	0,0912
Hedges' g SMD							0,18 [-0,030; 0,398]	0,0917
Int. p-Wert								0,5423

Analysis is performed if there are at least 10 patients in each subgroup level.
[a] = Number of patients with change from baseline used for MMRM analysis at each timepoint. [b] = Mean baseline for patients with change from baseline used for MMRM analysis at each timepoint. Treatment difference is calculated from a mixed model for repeated measures (MMRM) analysis of the change from baseline score with treatment, visit, and treatment by visit interaction as fixed effects, baseline score as a covariate and baseline score by visit interaction. Patient is used as random effect in the model. Only visits where change from baseline is available for at least 25% of patients in both treatment arms are included in the analysis. Toeplitz with heterogeneity covariance matrix is used to model within-subject error. If the MMRM model does not converge the model results are not presented. SMD = standardised mean difference. * p<0.05.
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Table 4.2.3.12 FLAURA-2: Summary of subgroup analysis of change from baseline in EORTC QLQ-C30 Verstopfung (mixed model for repeated measures) - average over all visits
Full Analysis Set, DCO 03APR2023

	Osi + Chemo (N=279)			Osi (N=278)			Behandlungseffekt	
Subgruppen	n [a]	Ausgangswert MW (SD) [b]	Veränderung MW (SE)	n [a]	Ausgangswert MW (SD) [b]	Veränderung MW (SE)	MWD [95%-KI]	p-Wert
Geschlecht								
Maennlich	95	12,28 (19,481)	0,59 (1,236)	94	13,48 (25,078)	-2,99 (1,284)	3,57 [0,059; 7,091]	0,0463*
Hedges' g SMD							0,29 [0,004; 0,577]	0,0469*
Weiblich	158	16,24 (24,881)	-0,53 (1,050)	159	15,09 (23,925)	-3,15 (1,044)	2,63 [-0,285; 5,540]	0,0769
Hedges' g SMD							0,20 [-0,022; 0,420]	0,0774
Int. p-Wert								0,7733
Nachweis der EGFR-Mutation durch zentralen ctDNA Cobas Test								
positiv	192	14,76 (22,801)	-0,08 (0,868)	194	14,26 (23,200)	-3,33 (0,870)	3,25 [0,836; 5,669]	0,0085*
Hedges' g SMD							0,27 [0,068; 0,469]	0,0086*
negativ	39	14,53 (22,679)	1,92 (2,391)	34	11,76 (23,039)	-1,65 (2,553)	3,58 [-3,402; 10,553]	0,3105
Hedges' g SMD							0,24 [-0,224; 0,699]	0,3137
unbekannt	22	15,15 (26,681)	-6,08 (2,538)	25	20,00 (33,333)	-3,07 (2,586)	-3,01 [-10,382; 4,362]	0,4121
Hedges' g SMD							-0,24 [-0,813; 0,338]	0,4184
Int. p-Wert								0,7004
EGFR-Mutationstyp								
Exon 19 Deletion	153	14,16 (22,843)	0,51 (1,020)	156	14,96 (24,035)	-3,52 (1,009)	4,03 [1,206; 6,853]	0,0053*
Hedges' g SMD							0,32 [0,094; 0,543]	0,0054*
Exon 21 (L858R) Substitutionsmutation	100	15,67 (23,429)	-1,25 (1,301)	95	14,04 (25,067)	-2,33 (1,372)	1,09 [-2,650; 4,822]	0,5671
Hedges' g SMD							0,08 [-0,199; 0,363]	0,5672
Int. p-Wert								0,1455
Zentral bestätigte EGFR-Mutation im Gewebe								
positiv	227	15,12 (23,493)	-0,16 (0,854)	220	14,09 (23,590)	-3,21 (0,878)	3,05 [0,643; 5,458]	0,0131*
Hedges' g SMD							0,24 [0,049; 0,421]	0,0132*
negativ	3	ID	ID	3	ID	ID	ID	ID
unbekannt	23	10,14 (18,627)	-1,13 (2,544)	30	18,89 (29,921)	-1,42 (2,107)	0,29 [-6,408; 6,991]	0,9304
Hedges' g SMD							0,02 [-0,519; 0,568]	0,9301

Analysis is performed if there are at least 10 patients in each subgroup level.
[a] = Number of patients with change from baseline used for MMRM analysis at each timepoint. [b] = Mean baseline for patients with change from baseline used for MMRM analysis at each timepoint. Treatment difference is calculated from a mixed model for repeated measures (MMRM) analysis of the change from baseline score with treatment, visit, and treatment by visit interaction as fixed effects, baseline score as a covariate and baseline score by visit interaction. Patient is used as random effect in the model. Only visits where change from baseline is available for at least 25% of patients in both treatment arms are included in the analysis. Toeplitz with heterogeneity covariance matrix is used to model within-subject error. If the MMRM model does not converge the model results are not presented. SMD = standardised mean difference. * p<0.05.
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Table 4.2.3.12 FLAURA-2: Summary of subgroup analysis of change from baseline in EORTC QLQ-C30 Verstopfung (mixed model for repeated measures) - average over all visits
Full Analysis Set, DCO 03APR2023

	Osi + Chemo (N=279)			Osi (N=278)			Behandlungseffekt	
Subgruppen	n [a]	Ausgangswert MW (SD) [b]	Veränderung MW (SE)	n [a]	Ausgangswert MW (SD) [b]	Veränderung MW (SE)	MWD [95%-KI]	p-Wert
Int. p-Wert								0,4647
ZNS-Metastasen zur Baseline								
Ja	101	11,88 (19,768)	1,22 (1,286)	101	14,85 (24,710)	-2,86 (1,336)	4,08 [0,414; 7,736]	0,0293*
Hedges' g SMD							0,31 [0,031; 0,586]	0,0295*
Nein	152	16,67 (24,862)	-0,94 (1,035)	152	14,25 (24,141)	-3,22 (1,022)	2,28 [-0,581; 5,147]	0,1178
Hedges' g SMD							0,18 [-0,046; 0,405]	0,1182
Int. p-Wert								0,3847
Zentrale Bestätigung der EGFR-Mutation								
Zentral bestätigte EGFR-Mutation in Gewebe oder ctDNA	241	15,08 (23,343)	-0,17 (0,821)	246	13,82 (23,494)	-3,07 (0,819)	2,90 [0,625; 5,182]	0,0126*
Hedges' g SMD							0,23 [0,048; 0,405]	0,0127*
Keine zentrale Bestätigung	12	NC	NC	7	NC	NC	NC	NC
Int. p-Wert								NC
Alter bei Screening								
<65 Jahre	160	15,00 (23,880)	-0,76 (0,938)	152	14,04 (23,811)	-4,53 (0,976)	3,77 [1,104; 6,431]	0,0057*
Hedges' g SMD							0,31 [0,091; 0,538]	0,0058*
>=65 Jahre	93	14,34 (21,646)	1,00 (1,464)	101	15,18 (25,177)	-0,97 (1,406)	1,97 [-2,031; 5,971]	0,3327
Hedges' g SMD							0,14 [-0,143; 0,421]	0,3343
Int. p-Wert								0,4731
Region gPAP								
Asien	158	13,92 (19,984)	0,48 (0,971)	160	13,75 (23,163)	-2,52 (0,977)	3,01 [0,296; 5,714]	0,0298*
Hedges' g SMD							0,24 [0,024; 0,465]	0,0301*
Europa	19	NC	NC	21	NC	NC	NC	NC
Nordamerika	18	NC	NC	17	NC	NC	NC	NC
Rest der Welt	58	16,67 (27,395)	-3,29 (1,825)	55	17,58 (28,584)	-4,16 (1,938)	0,87 [-4,405; 6,146]	0,7440

Analysis is performed if there are at least 10 patients in each subgroup level.
[a] = Number of patients with change from baseline used for MMRM analysis at each timepoint. [b] = Mean baseline for patients with change from baseline used for MMRM analysis at each timepoint. Treatment difference is calculated from a mixed model for repeated measures (MMRM) analysis of the change from baseline score with treatment, visit, and treatment by visit interaction as fixed effects, baseline score as a covariate and baseline score by visit interaction. Patient is used as random effect in the model. Only visits where change from baseline is available for at least 25% of patients in both treatment arms are included in the analysis. Toeplitz with heterogeneity covariance matrix is used to model within-subject error. If the MMRM model does not converge the model results are not presented. SMD = standardised mean difference. * p<0.05.
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Table 4.2.3.12 FLAURA-2: Summary of subgroup analysis of change from baseline in EORTC QLQ-C30 Verstopfung (mixed model for repeated measures) - average over all visits
Full Analysis Set, DCO 03APR2023

	Osi + Chemo (N=279)			Osi (N=278)			Behandlungseffekt	
Subgruppen	n [a]	Ausgangswert MW (SD) [b]	Veränderung MW (SE)	n [a]	Ausgangswert MW (SD) [b]	Veränderung MW (SE)	MWD [95%-KI]	p-Wert
Hedges' g SMD							0,06 [-0,308; 0,430]	0,7453
Int. p-Wert								0,6716

Analysis is performed if there are at least 10 patients in each subgroup level.
[a] = Number of patients with change from baseline used for MMRM analysis at each timepoint. [b] = Mean baseline for patients with change from baseline used for MMRM analysis at each timepoint. Treatment difference is calculated from a mixed model for repeated measures (MMRM) analysis of the change from baseline score with treatment, visit, and treatment by visit interaction as fixed effects, baseline score as a covariate and baseline score by visit interaction. Patient is used as random effect in the model. Only visits where change from baseline is available for at least 25% of patients in both treatment arms are included in the analysis. Toeplitz with heterogeneity covariance matrix is used to model within-subject error. If the MMRM model does not converge the model results are not presented. SMD = standardised mean difference. * p<0.05.
root/cdar/d516/payer_germany/ar/d5169c00001_payer_germany/tlf/prod/program/mmrmsubpra.sas gmmrmsubpraal 04JUN2024:17:59 kvbv306

Table 4.2.3.13 FLAURA-2: Summary of subgroup analysis of change from baseline in EORTC QLQ-C30 Diarrhö (mixed model for repeated measures) - average over all visits
Full Analysis Set, DCO 03APR2023

	Osi + Chemo (N=279)			Osi (N=278)			Behandlungseffekt	
Subgruppen	n [a]	Ausgangswert MW (SD) [b]	Veränderung MW (SE)	n [a]	Ausgangswert MW (SD) [b]	Veränderung MW (SE)	MWD [95%-KI]	p-Wert
Abstammung								
Chinesisch/Asiatisch	66	4,55 (11,527)	9,54 (1,479)	65	5,13 (12,120)	10,88 (1,505)	-1,34 [-5,514; 2,833]	0,5263
Hedges' g SMD							-0,11 [-0,453; 0,232]	0,5279
Nicht-chinesisch/Asiatisch	99	6,06 (13,771)	8,47 (1,366)	101	7,59 (16,919)	11,04 (1,368)	-2,56 [-6,378; 1,250]	0,1865
Hedges' g SMD							-0,19 [-0,465; 0,091]	0,1875
Nicht-asiatisch	88	4,17 (11,087)	10,58 (1,600)	87	6,51 (15,945)	11,41 (1,623)	-0,83 [-5,336; 3,668]	0,7151
Hedges' g SMD							-0,06 [-0,351; 0,241]	0,7157
Int. p-Wert								0,8078
Methode zur Gewebeuntersuchung								
zentral	110	4,55 (11,491)	8,81 (1,281)	114	7,02 (17,999)	9,17 (1,255)	-0,36 [-3,894; 3,182]	0,8431
Hedges' g SMD							-0,03 [-0,288; 0,236]	0,8433
lokal	143	5,36 (12,910)	10,06 (1,142)	139	6,24 (13,045)	12,48 (1,175)	-2,41 [-5,638; 0,811]	0,1418
Hedges' g SMD							-0,18 [-0,409; 0,059]	0,1424
Int. p-Wert								0,4110
WHO Performance-Status								
0	96	4,51 (11,465)	12,54 (1,420)	94	6,03 (13,794)	13,78 (1,436)	-1,24 [-5,224; 2,743]	0,5398
Hedges' g SMD							-0,09 [-0,373; 0,196]	0,5408
1	157	5,31 (12,804)	7,65 (1,044)	159	6,92 (16,380)	9,16 (1,049)	-1,51 [-4,426; 1,402]	0,3082
Hedges' g SMD							-0,11 [-0,335; 0,106]	0,3087
Int. p-Wert								0,9199
Raucherstatus								
Ja	84	5,56 (12,497)	9,92 (1,631)	85	8,24 (16,188)	12,58 (1,648)	-2,66 [-7,246; 1,924]	0,2536
Hedges' g SMD							-0,18 [-0,478; 0,126]	0,2541
Nein	169	4,73 (12,224)	9,39 (0,984)	168	5,75 (15,039)	10,21 (0,989)	-0,83 [-3,574; 1,915]	0,5527
Hedges' g SMD							-0,06 [-0,278; 0,149]	0,5532
Int. p-Wert								0,5263

Analysis is performed if there are at least 10 patients in each subgroup level.
[a] = Number of patients with change from baseline used for MMRM analysis at each timepoint. [b] = Mean baseline for patients with change from baseline used for MMRM analysis at each timepoint. Treatment difference is calculated from a mixed model for repeated measures (MMRM) analysis of the change from baseline score with treatment, visit, and treatment by visit interaction as fixed effects, baseline score as a covariate and baseline score by visit interaction. Patient is used as random effect in the model. Only visits where change from baseline is available for at least 25% of patients in both treatment arms are included in the analysis. Toeplitz with heterogeneity covariance matrix is used to model within-subject error. If the MMRM model does not converge the model results are not presented. SMD = standardised mean difference. * p<0.05.
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Table 4.2.3.13 FLAURA-2: Summary of subgroup analysis of change from baseline in EORTC QLQ-C30 Diarrhö (mixed model for repeated measures) - average over all visits
Full Analysis Set, DCO 03APR2023

	Osi + Chemo (N=279)			Osi (N=278)			Behandlungseffekt	
Subgruppen	n [a]	Ausgangswert MW (SD) [b]	Veränderung MW (SE)	n [a]	Ausgangswert MW (SD) [b]	Veränderung MW (SE)	MWD [95%-KI]	p-Wert
Geschlecht								
Maennlich	95	4,56 (12,501)	8,04 (1,387)	94	8,87 (17,743)	9,90 (1,430)	-1,86 [-5,810; 2,083]	0,3529
Hedges' g SMD							-0,14 [-0,421; 0,150]	0,3519
Weiblich	158	5,27 (12,204)	10,41 (1,078)	159	5,24 (13,797)	11,51 (1,070)	-1,11 [-4,094; 1,883]	0,4673
Hedges' g SMD							-0,08 [-0,302; 0,139]	0,4680
Int. p-Wert								0,7715
Nachweis der EGFR-Mutation durch zentralen ctDNA Cobas Test								
positiv	192	4,86 (12,279)	8,99 (0,953)	194	6,70 (15,393)	10,72 (0,953)	-1,73 [-4,381; 0,922]	0,2005
Hedges' g SMD							-0,13 [-0,330; 0,069]	0,2007
negativ	39	5,98 (12,959)	10,08 (2,460)	34	6,86 (15,953)	13,54 (2,622)	-3,46 [-10,629; 3,708]	0,3390
Hedges' g SMD							-0,22 [-0,685; 0,238]	0,3426
unbekannt	22	4,55 (11,708)	12,50 (2,799)	25	5,33 (15,753)	11,44 (2,813)	1,06 [-6,912; 9,033]	0,7901
Hedges' g SMD							0,08 [-0,497; 0,650]	0,7937
Int. p-Wert								0,6749
EGFR-Mutationstyp								
Exon 19 Deletion	153	5,23 (12,749)	10,53 (1,102)	156	4,91 (14,068)	12,09 (1,089)	-1,56 [-4,607; 1,492]	0,3157
Hedges' g SMD							-0,11 [-0,337; 0,109]	0,3164
Exon 21 (L858R) Substitutionsmutation	100	4,67 (11,625)	7,87 (1,342)	95	9,47 (17,302)	9,23 (1,409)	-1,36 [-5,217; 2,500]	0,4882
Hedges' g SMD							-0,10 [-0,381; 0,181]	0,4868
Int. p-Wert								0,7067
Zentral bestätigte EGFR-Mutation im Gewebe								
positiv	227	4,99 (12,327)	9,23 (0,905)	220	7,12 (16,079)	11,10 (0,928)	-1,87 [-4,422; 0,677]	0,1497
Hedges' g SMD							-0,14 [-0,322; 0,049]	0,1497
negativ	3	ID	ID	3	ID	ID	ID	ID
unbekannt	23	4,35 (11,478)	10,60 (2,832)	30	3,33 (10,171)	10,78 (2,359)	-0,18 [-7,581; 7,226]	0,9617
Hedges' g SMD							-0,01 [-0,556; 0,530]	0,9618

Analysis is performed if there are at least 10 patients in each subgroup level.
[a] = Number of patients with change from baseline used for MMRM analysis at each timepoint. [b] = Mean baseline for patients with change from baseline used for MMRM analysis at each timepoint. Treatment difference is calculated from a mixed model for repeated measures (MMRM) analysis of the change from baseline score with treatment, visit, and treatment by visit interaction as fixed effects, baseline score as a covariate and baseline score by visit interaction. Patient is used as random effect in the model. Only visits where change from baseline is available for at least 25% of patients in both treatment arms are included in the analysis. Toeplitz with heterogeneity covariance matrix is used to model within-subject error. If the MMRM model does not converge the model results are not presented. SMD = standardised mean difference. * p<0.05.
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Table 4.2.3.13 FLAURA-2: Summary of subgroup analysis of change from baseline in EORTC QLQ-C30 Diarrhö (mixed model for repeated measures) - average over all visits
Full Analysis Set, DCO 03APR2023

	Osi + Chemo (N=279)			Osi (N=278)			Behandlungseffekt	
Subgruppen	n [a]	Ausgangswert MW (SD) [b]	Veränderung MW (SE)	n [a]	Ausgangswert MW (SD) [b]	Veränderung MW (SE)	MWD [95%-KI]	p-Wert
Int. p-Wert								0,5413
ZNS-Metastasen zur Baseline								
Ja	101	5,61 (12,534)	6,93 (1,332)	101	9,90 (19,745)	8,70 (1,381)	-1,77 [-5,569; 2,031]	0,3597
Hedges' g SMD							-0,13 [-0,405; 0,147]	0,3587
Nein	152	4,61 (12,161)	11,17 (1,114)	152	4,39 (11,305)	12,34 (1,101)	-1,17 [-4,253; 1,911]	0,4552
Hedges' g SMD							-0,09 [-0,310; 0,139]	0,4559
Int. p-Wert								0,7978
Zentrale Bestätigung der EGFR-Mutation								
Zentral bestätigte EGFR-Mutation in Gewebe oder ctDNA	241	4,98 (12,289)	9,32 (0,873)	246	6,78 (15,626)	11,12 (0,870)	-1,79 [-4,217; 0,631]	0,1468
Hedges' g SMD							-0,13 [-0,309; 0,046]	0,1470
Keine zentrale Bestätigung	12	NC	NC	7	NC	NC	NC	NC
Int. p-Wert								NC
Alter bei Screening								
<65 Jahre	160	5,83 (13,244)	9,32 (1,111)	152	6,36 (15,693)	12,11 (1,151)	-2,79 [-5,939; 0,354]	0,0818
Hedges' g SMD							-0,20 [-0,420; 0,025]	0,0822
>=65 Jahre	93	3,58 (10,382)	9,85 (1,303)	101	6,93 (15,141)	9,41 (1,254)	0,45 [-3,132; 4,024]	0,8060
Hedges' g SMD							0,04 [-0,246; 0,317]	0,8060
Int. p-Wert								0,1387
Region gPAP								
Asien	158	5,49 (12,957)	8,75 (1,034)	160	6,88 (15,458)	10,86 (1,038)	-2,11 [-4,992; 0,777]	0,1515
Hedges' g SMD							-0,16 [-0,381; 0,059]	0,1520
Europa	19	NC	NC	21	NC	NC	NC	NC
Nordamerika	18	1,85 (7,857)	, (,)	17	3,92 (11,070)	, (,)	6,40 [-3,760; 16,561]	0,2097
Hedges' g SMD							, [, ; ,]	
Rest der Welt	58	4,60 (11,595)	8,04 (1,892)	55	6,06 (17,082)	13,71 (1,998)	-5,66 [-11,121; -0,207]	0,0421*

Analysis is performed if there are at least 10 patients in each subgroup level.
[a] = Number of patients with change from baseline used for MMRM analysis at each timepoint. [b] = Mean baseline for patients with change from baseline used for MMRM analysis at each timepoint. Treatment difference is calculated from a mixed model for repeated measures (MMRM) analysis of the change from baseline score with treatment, visit, and treatment by visit interaction as fixed effects, baseline score as a covariate and baseline score by visit interaction. Patient is used as random effect in the model. Only visits where change from baseline is available for at least 25% of patients in both treatment arms are included in the analysis. Toeplitz with heterogeneity covariance matrix is used to model within-subject error. If the MMRM model does not converge the model results are not presented. SMD = standardised mean difference. * p<0.05.
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Table 4.2.3.13 FLAURA-2: Summary of subgroup analysis of change from baseline in EORTC QLQ-C30 Diarrhö (mixed model for repeated measures) - average over all visits
Full Analysis Set, DCO 03APR2023

	Osi + Chemo (N=279)			Osi (N=278)			Behandlungseffekt	
Subgruppen	n [a]	Ausgangswert MW (SD) [b]	Veränderung MW (SE)	n [a]	Ausgangswert MW (SD) [b]	Veränderung MW (SE)	MWD [95%-KI]	p-Wert
Hedges' g SMD							-0,39 [-0,758; -0,013]	0,0427*
Int. p-Wert								0,1468

Analysis is performed if there are at least 10 patients in each subgroup level.
[a] = Number of patients with change from baseline used for MMRM analysis at each timepoint. [b] = Mean baseline for patients with change from baseline used for MMRM analysis at each timepoint. Treatment difference is calculated from a mixed model for repeated measures (MMRM) analysis of the change from baseline score with treatment, visit, and treatment by visit interaction as fixed effects, baseline score as a covariate and baseline score by visit interaction. Patient is used as random effect in the model. Only visits where change from baseline is available for at least 25% of patients in both treatment arms are included in the analysis. Toeplitz with heterogeneity covariance matrix is used to model within-subject error. If the MMRM model does not converge the model results are not presented. SMD = standardised mean difference. * p<0.05.
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Table 4.2.3.14 FLAURA-2: Summary of subgroup analysis of change from baseline in EORTC QLQ-C30 Allgemeine Lebensqualität/Gesundheitsszustand (mixed model for repeated measures) - average over all visits
Full Analysis Set, DCO 03APR2023

	Osi + Chemo (N=279)			Osi (N=278)			Behandlungseffekt	
Subgruppen	n [a]	Ausgangswert MW (SD) [b]	Veränderung MW (SE)	n [a]	Ausgangswert MW (SD) [b]	Veränderung MW (SE)	MWD [95%-KI]	p-Wert
Abstammung								
Chinesisch/Asiatisch	66	70,20 (18,494)	4,85 (1,443)	65	67,05 (21,114)	5,80 (1,473)	-0,95 [-5,036; 3,130]	0,6451
Hedges' g SMD							-0,08 [-0,423; 0,262]	0,6461
Nicht-chinesisch/Asiatisch	99	62,63 (18,225)	2,69 (1,297)	101	64,03 (21,014)	4,19 (1,294)	-1,50 [-5,113; 2,112]	0,4139
Hedges' g SMD							-0,12 [-0,393; 0,162]	0,4151
Nicht-asiatisch	88	66,38 (20,970)	2,37 (1,321)	87	61,02 (22,393)	7,28 (1,337)	-4,91 [-8,626; -1,191]	0,0100*
Hedges' g SMD							-0,39 [-0,692; -0,094]	0,0100*
Int. p-Wert								0,3611
Methode zur Gewebeuntersuchung								
zentral	110	69,85 (17,559)	3,00 (1,147)	114	68,20 (21,994)	6,40 (1,130)	-3,40 [-6,566; -0,224]	0,0360*
Hedges' g SMD							-0,28 [-0,544; -0,018]	0,0366*
lokal	143	62,88 (20,334)	3,16 (1,053)	139	60,13 (20,578)	4,79 (1,081)	-1,63 [-4,606; 1,338]	0,2801
Hedges' g SMD							-0,13 [-0,362; 0,105]	0,2805
Int. p-Wert								0,4413
WHO Performance-Status								
0	96	72,40 (17,535)	-1,59 (1,175)	94	70,57 (21,506)	2,49 (1,186)	-4,08 [-7,374; -0,784]	0,0155*
Hedges' g SMD							-0,35 [-0,640; -0,066]	0,0158*
1	157	61,94 (19,550)	6,09 (1,063)	159	59,75 (20,631)	7,56 (1,069)	-1,48 [-4,441; 1,489]	0,3281
Hedges' g SMD							-0,11 [-0,331; 0,111]	0,3290
Int. p-Wert								0,5365
Raucherstatus								
Ja	84	63,99 (18,798)	4,03 (1,394)	85	65,49 (21,979)	2,51 (1,400)	1,51 [-2,385; 5,415]	0,4443
Hedges' g SMD							0,12 [-0,184; 0,419]	0,4457
Nein	169	66,86 (19,753)	2,63 (0,957)	168	62,90 (21,364)	6,99 (0,967)	-4,37 [-7,045; -1,688]	0,0015*
Hedges' g SMD							-0,35 [-0,564; -0,134]	0,0015*
Int. p-Wert								0,0180*

Analysis is performed if there are at least 10 patients in each subgroup level.
[a] = Number of patients with change from baseline used for MMRM analysis at each timepoint. [b] = Mean baseline for patients with change from baseline used for MMRM analysis at each timepoint. Treatment difference is calculated from a mixed model for repeated measures (MMRM) analysis of the change from baseline score with treatment, visit, and treatment by visit interaction as fixed effects, baseline score as a covariate and baseline score by visit interaction. Patient is used as random effect in the model. Only visits where change from baseline is available for at least 25% of patients in both treatment arms are included in the analysis. Toeplitz with heterogeneity covariance matrix is used to model within-subject error. If the MMRM model does not converge the model results are not presented. SMD = standardised mean difference. * p<0.05.
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Table 4.2.3.14 FLAURA-2: Summary of subgroup analysis of change from baseline in EORTC QLQ-C30 Allgemeine Lebensqualität/Gesundheitsszustand (mixed model for repeated measures) - average over all visits
Full Analysis Set, DCO 03APR2023

	Osi + Chemo (N=279)			Osi (N=278)			Behandlungseffekt	
Subgruppen	n [a]	Ausgangswert MW (SD) [b]	Veränderung MW (SE)	n [a]	Ausgangswert MW (SD) [b]	Veränderung MW (SE)	MWD [95%-KI]	p-Wert
Geschlecht								
Maennlich	95	66,93 (19,655)	1,99 (1,315)	94	67,02 (23,409)	2,53 (1,356)	-0,54 [-4,261; 3,189]	0,7767
Hedges' g SMD							-0,04 [-0,326; 0,244]	0,7773
Weiblich	158	65,30 (19,364)	3,76 (1,006)	159	61,84 (20,226)	7,23 (1,001)	-3,47 [-6,269; -0,680]	0,0150*
Hedges' g SMD							-0,27 [-0,496; -0,053]	0,0151*
Int. p-Wert								0,2797
Nachweis der EGFR-Mutation durch zentralen ctDNA Cobas Test								
positiv	192	65,19 (19,464)	4,54 (0,913)	194	61,94 (22,134)	6,30 (0,914)	-1,76 [-4,301; 0,781]	0,1740
Hedges' g SMD							-0,14 [-0,338; 0,061]	0,1743
negativ	39	69,02 (18,332)	-2,90 (2,105)	34	68,63 (16,547)	1,57 (2,244)	-4,47 [-10,601; 1,661]	0,1504
Hedges' g SMD							-0,34 [-0,801; 0,126]	0,1537
unbekannt	22	66,67 (21,517)	-0,32 (2,358)	25	71,33 (21,120)	5,03 (2,341)	-5,35 [-12,076; 1,372]	0,1156
Hedges' g SMD							-0,46 [-1,042; 0,120]	0,1198
Int. p-Wert								0,7597
EGFR-Mutationstyp								
Exon 19 Deletion	153	65,85 (20,295)	1,33 (0,972)	156	65,76 (21,136)	5,41 (0,960)	-4,08 [-6,769; -1,396]	0,0030*
Hedges' g SMD							-0,34 [-0,564; -0,115]	0,0031*
Exon 21 (L858R) Substitutionsmutation	100	66,00 (18,184)	5,95 (1,401)	95	60,09 (21,809)	5,64 (1,469)	0,31 [-3,711; 4,330]	0,8796
Hedges' g SMD							0,02 [-0,259; 0,303]	0,8793
Int. p-Wert								0,0798
Zentral bestätigte EGFR-Mutation im Gewebe								
positiv	227	65,46 (19,709)	3,70 (0,834)	220	64,05 (21,215)	5,87 (0,855)	-2,18 [-4,522; 0,171]	0,0691
Hedges' g SMD							-0,17 [-0,358; 0,014]	0,0695
negativ	3	ID	ID	3	ID	ID	ID	ID
unbekannt	23	68,48 (17,400)	-4,56 (3,140)	30	61,67 (23,222)	4,17 (2,627)	-8,73 [-17,039; -0,415]	0,0400*
Hedges' g SMD							-0,59 [-1,141; -0,030]	0,0388*

Analysis is performed if there are at least 10 patients in each subgroup level.
[a] = Number of patients with change from baseline used for MMRM analysis at each timepoint. [b] = Mean baseline for patients with change from baseline used for MMRM analysis at each timepoint. Treatment difference is calculated from a mixed model for repeated measures (MMRM) analysis of the change from baseline score with treatment, visit, and treatment by visit interaction as fixed effects, baseline score as a covariate and baseline score by visit interaction. Patient is used as random effect in the model. Only visits where change from baseline is available for at least 25% of patients in both treatment arms are included in the analysis. Toeplitz with heterogeneity covariance matrix is used to model within-subject error. If the MMRM model does not converge the model results are not presented. SMD = standardised mean difference. * p<0.05.
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Table 4.2.3.14 FLAURA-2: Summary of subgroup analysis of change from baseline in EORTC QLQ-C30 Allgemeine Lebensqualität/Gesundheitsszustand (mixed model for repeated measures) - average over all visits
Full Analysis Set, DCO 03APR2023

	Osi + Chemo (N=279)			Osi (N=278)			Behandlungseffekt	
Subgruppen	n [a]	Ausgangswert MW (SD) [b]	Veränderung MW (SE)	n [a]	Ausgangswert MW (SD) [b]	Veränderung MW (SE)	MWD [95%-KI]	p-Wert
Int. p-Wert								0,1780
ZNS-Metastasen zur Baseline								
Ja	101	64,27 (20,184)	5,89 (1,290)	101	62,79 (20,466)	6,27 (1,329)	-0,38 [-4,032; 3,274]	0,8380
Hedges' g SMD							-0,03 [-0,305; 0,247]	0,8384
Nein	152	67,00 (18,937)	1,10 (1,011)	152	64,42 (22,307)	5,11 (1,003)	-4,02 [-6,817; -1,214]	0,0051*
Hedges' g SMD							-0,32 [-0,549; -0,096]	0,0052*
Int. p-Wert								0,1077
Zentrale Bestätigung der EGFR-Mutation								
Zentral bestätigte EGFR-Mutation in Gewebe oder ctDNA	241	65,35 (19,440)	3,69 (0,817)	246	63,52 (21,651)	5,84 (0,815)	-2,15 [-4,414; 0,119]	0,0633
Hedges' g SMD							-0,17 [-0,346; 0,010]	0,0636
Keine zentrale Bestätigung	12	NC	NC	7	NC	NC	NC	NC
Int. p-Wert								NC
Alter bei Screening								
<65 Jahre	160	66,88 (19,781)	4,34 (1,008)	152	63,54 (22,752)	6,45 (1,045)	-2,11 [-4,968; 0,750]	0,1477
Hedges' g SMD							-0,16 [-0,386; 0,058]	0,1480
>=65 Jahre	93	64,25 (18,859)	0,81 (1,284)	101	64,11 (19,746)	4,27 (1,233)	-3,46 [-6,967; 0,052]	0,0534
Hedges' g SMD							-0,28 [-0,561; 0,005]	0,0542
Int. p-Wert								0,5425
Region gPAP								
Asien	158	65,88 (17,741)	3,42 (1,030)	160	64,79 (21,064)	4,53 (1,033)	-1,11 [-3,982; 1,758]	0,4464
Hedges' g SMD							-0,09 [-0,305; 0,135]	0,4472
Europa	19	58,77 (22,986)	-4,71 (3,534)	21	59,13 (21,875)	6,73 (3,253)	-11,44 [-21,377; -1,506]	0,0257*
Hedges' g SMD							-0,74 [-1,384; -0,097]	0,0242*
Nordamerika	18	NC	NC	17	NC	NC	NC	NC
Rest der Welt	58	68,82 (20,446)	3,51 (1,449)	55	62,12 (23,560)	8,29 (1,520)	-4,78 [-8,956; -0,607]	0,0252*

Analysis is performed if there are at least 10 patients in each subgroup level.
[a] = Number of patients with change from baseline used for MMRM analysis at each timepoint. [b] = Mean baseline for patients with change from baseline used for MMRM analysis at each timepoint. Treatment difference is calculated from a mixed model for repeated measures (MMRM) analysis of the change from baseline score with treatment, visit, and treatment by visit interaction as fixed effects, baseline score as a covariate and baseline score by visit interaction. Patient is used as random effect in the model. Only visits where change from baseline is available for at least 25% of patients in both treatment arms are included in the analysis. Toeplitz with heterogeneity covariance matrix is used to model within-subject error. If the MMRM model does not converge the model results are not presented. SMD = standardised mean difference. * p<0.05.
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Table 4.2.3.14 FLAURA-2: Summary of subgroup analysis of change from baseline in EORTC QLQ-C30 Allgemeine Lebensqualität/Gesundheitsszustand (mixed model for repeated measures) - average over all visits
Full Analysis Set, DCO 03APR2023

	Osi + Chemo (N=279)			Osi (N=278)			Behandlungseffekt	
Subgruppen	n [a]	Ausgangswert MW (SD) [b]	Veränderung MW (SE)	n [a]	Ausgangswert MW (SD) [b]	Veränderung MW (SE)	MWD [95%-KI]	p-Wert
Hedges' g SMD							-0,43 [-0,799; -0,053]	0,0253*
Int. p-Wert								0,0747

Analysis is performed if there are at least 10 patients in each subgroup level.
[a] = Number of patients with change from baseline used for MMRM analysis at each timepoint. [b] = Mean baseline for patients with change from baseline used for MMRM analysis at each timepoint. Treatment difference is calculated from a mixed model for repeated measures (MMRM) analysis of the change from baseline score with treatment, visit, and treatment by visit interaction as fixed effects, baseline score as a covariate and baseline score by visit interaction. Patient is used as random effect in the model. Only visits where change from baseline is available for at least 25% of patients in both treatment arms are included in the analysis. Toeplitz with heterogeneity covariance matrix is used to model within-subject error. If the MMRM model does not converge the model results are not presented. SMD = standardised mean difference. * p<0.05.
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Table 4.2.3.15 FLAURA-2: Summary of subgroup analysis of change from baseline in EORTC QLQ-C30 Finanzielle Schwierigkeiten (mixed model for repeated measures) - average over all visits
Full Analysis Set, DCO 03APR2023

	Osi + Chemo (N=279)			Osi (N=278)			Behandlungseffekt	
Subgruppen	n [a]	Ausgangswert MW (SD) [b]	Veränderung MW (SE)	n [a]	Ausgangswert MW (SD) [b]	Veränderung MW (SE)	MWD [95%-KI]	p-Wert
Abstammung								
Chinesisch/Asiatisch	66	36,36 (30,789)	0,07 (2,778)	65	30,77 (31,351)	-5,14 (2,810)	5,21 [-2,617; 13,033]	0,1904
Hedges' g SMD							0,23 [-0,115; 0,573]	0,1916
Nicht-chinesisch/Asiatisch	99	27,27 (27,915)	-4,94 (1,630)	101	27,72 (30,937)	-10,39 (1,628)	5,45 [0,912; 9,996]	0,0188*
Hedges' g SMD							0,33 [0,054; 0,613]	0,0192*
Nicht-asiatisch	88	17,80 (26,236)	2,90 (1,899)	87	24,14 (32,822)	-3,05 (1,921)	5,94 [0,602; 11,284]	0,0294*
Hedges' g SMD							0,33 [0,033; 0,630]	0,0296*
Int. p-Wert								0,9865
Methode zur Gewebeuntersuchung								
zentral	110	32,12 (30,600)	1,75 (1,997)	114	28,36 (31,741)	-5,72 (1,960)	7,47 [1,953; 12,987]	0,0082*
Hedges' g SMD							0,36 [0,092; 0,620]	0,0083*
lokal	143	21,91 (26,861)	-3,71 (1,365)	139	26,38 (31,718)	-7,41 (1,396)	3,70 [-0,147; 7,548]	0,0593
Hedges' g SMD							0,23 [-0,009; 0,459]	0,0594
Int. p-Wert								0,2446
WHO Performance-Status								
0	96	25,00 (28,613)	-3,97 (1,749)	94	25,53 (34,016)	-4,36 (1,766)	0,38 [-4,519; 5,285]	0,8778
Hedges' g SMD							0,02 [-0,262; 0,307]	0,8781
1	157	27,18 (29,192)	0,35 (1,567)	159	28,30 (30,280)	-8,09 (1,566)	8,43 [4,076; 12,794]	0,0002*
Hedges' g SMD							0,43 [0,204; 0,650]	0,0002*
Int. p-Wert								0,0272*
Raucherstatus								
Ja	84	26,59 (30,073)	-2,80 (1,945)	85	27,45 (34,186)	-6,23 (1,950)	3,43 [-2,005; 8,863]	0,2147
Hedges' g SMD							0,19 [-0,112; 0,493]	0,2163
Nein	169	26,23 (28,444)	-0,56 (1,472)	168	27,18 (30,441)	-6,66 (1,479)	6,10 [1,995; 10,202]	0,0037*
Hedges' g SMD							0,32 [0,103; 0,533]	0,0038*
Int. p-Wert								0,3765

Analysis is performed if there are at least 10 patients in each subgroup level.
[a] = Number of patients with change from baseline used for MMRM analysis at each timepoint. [b] = Mean baseline for patients with change from baseline used for MMRM analysis at each timepoint. Treatment difference is calculated from a mixed model for repeated measures (MMRM) analysis of the change from baseline score with treatment, visit, and treatment by visit interaction as fixed effects, baseline score as a covariate and baseline score by visit interaction. Patient is used as random effect in the model. Only visits where change from baseline is available for at least 25% of patients in both treatment arms are included in the analysis. Toeplitz with heterogeneity covariance matrix is used to model within-subject error. If the MMRM model does not converge the model results are not presented. SMD = standardised mean difference. * p<0.05.
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Table 4.2.3.15 FLAURA-2: Summary of subgroup analysis of change from baseline in EORTC QLQ-C30 Finanzielle Schwierigkeiten (mixed model for repeated measures) - average over all visits
Full Analysis Set, DCO 03APR2023

	Osi + Chemo (N=279)			Osi (N=278)			Behandlungseffekt	
Subgruppen	n [a]	Ausgangswert MW (SD) [b]	Veränderung MW (SE)	n [a]	Ausgangswert MW (SD) [b]	Veränderung MW (SE)	MWD [95%-KI]	p-Wert
Geschlecht								
Maennlich	95	28,77 (32,109)	-1,29 (1,861)	94	27,66 (32,291)	-4,05 (1,904)	2,76 [-2,493; 8,011]	0,3015
Hedges' g SMD							0,15 [-0,135; 0,436]	0,3028
Weiblich	158	24,89 (26,851)	-1,37 (1,518)	159	27,04 (31,415)	-8,16 (1,506)	6,79 [2,587; 11,002]	0,0016*
Hedges' g SMD							0,36 [0,134; 0,578]	0,0017*
Int. p-Wert								0,1969
Nachweis der EGFR-Mutation durch zentralen ctDNA Cobas Test								
positiv	192	28,30 (29,797)	-2,08 (1,365)	194	27,84 (30,981)	-8,75 (1,360)	6,67 [2,883; 10,459]	0,0006*
Hedges' g SMD							0,35 [0,151; 0,553]	0,0006*
negativ	39	18,80 (21,350)	0,03 (1,993)	34	21,57 (30,575)	0,68 (2,113)	-0,65 [-6,436; 5,131]	0,8229
Hedges' g SMD							-0,05 [-0,512; 0,408]	0,8243
unbekannt	22	NC	NC	25	NC	NC	NC	NC
Int. p-Wert								0,0374*
EGFR-Mutationstyp								
Exon 19 Deletion	153	26,58 (30,435)	0,65 (1,589)	156	28,85 (32,591)	-7,98 (1,571)	8,63 [4,230; 13,025]	0,0001*
Hedges' g SMD							0,44 [0,212; 0,664]	0,0001*
Exon 21 (L858R) Substitutionsmutation	100	26,00 (26,625)	-4,51 (1,709)	95	25,26 (30,253)	-4,28 (1,788)	-0,23 [-5,105; 4,647]	0,9264
Hedges' g SMD							-0,01 [-0,294; 0,268]	0,9266
Int. p-Wert								0,0128*
Zentral bestätigte EGFR-Mutation im Gewebe								
positiv	227	26,87 (28,522)	-0,38 (1,261)	220	27,12 (31,803)	-6,99 (1,288)	6,61 [3,070; 10,155]	0,0003*
Hedges' g SMD							0,35 [0,160; 0,533]	0,0003*
negativ	3	ID	ID	3	ID	ID	ID	ID
unbekannt	23	21,74 (34,243)	-10,00 (3,131)	30	26,67 (29,556)	-4,92 (2,624)	-5,08 [-13,286; 3,131]	0,2200
Hedges' g SMD							-0,34 [-0,889; 0,206]	0,2216
Int. p-Wert								0,0431*

Analysis is performed if there are at least 10 patients in each subgroup level.
[a] = Number of patients with change from baseline used for MMRM analysis at each timepoint. [b] = Mean baseline for patients with change from baseline used for MMRM analysis at each timepoint. Treatment difference is calculated from a mixed model for repeated measures (MMRM) analysis of the change from baseline score with treatment, visit, and treatment by visit interaction as fixed effects, baseline score as a covariate and baseline score by visit interaction. Patient is used as random effect in the model. Only visits where change from baseline is available for at least 25% of patients in both treatment arms are included in the analysis. Toeplitz with heterogeneity covariance matrix is used to model within-subject error. If the MMRM model does not converge the model results are not presented. SMD = standardised mean difference. * p<0.05.
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Table 4.2.3.15 FLAURA-2: Summary of subgroup analysis of change from baseline in EORTC QLQ-C30 Finanzielle Schwierigkeiten (mixed model for repeated measures) - average over all visits
Full Analysis Set, DCO 03APR2023

	Osi + Chemo (N=279)			Osi (N=278)			Behandlungseffekt	
Subgruppen	n [a]	Ausgangswert MW (SD) [b]	Veränderung MW (SE)	n [a]	Ausgangswert MW (SD) [b]	Veränderung MW (SE)	MWD [95%-KI]	p-Wert
ZNS-Metastasen zur Baseline								
Ja	101	28,05 (27,782)	-2,36 (1,836)	101	29,04 (34,853)	-8,61 (1,883)	6,24 [1,059; 11,429]	0,0185*
Hedges' g SMD							0,33 [0,055; 0,611]	0,0188*
Nein	152	25,22 (29,715)	-0,68 (1,542)	152	26,10 (29,446)	-5,36 (1,529)	4,67 [0,401; 8,944]	0,0322*
Hedges' g SMD							0,25 [0,021; 0,472]	0,0325*
Int. p-Wert								0,5738
Zentrale Bestätigung der EGFR-Mutation								
Zentral bestätigte EGFR-Mutation in Gewebe oder ctDNA	241	26,97 (29,283)	-0,89 (1,211)	246	26,83 (31,344)	-6,95 (1,202)	6,06 [2,703; 9,408]	0,0004*
Hedges' g SMD							0,32 [0,142; 0,500]	0,0004*
Keine zentrale Bestätigung	12	NC	NC	7	NC	NC	NC	NC
Int. p-Wert								NC
Alter bei Screening								
<65 Jahre	160	28,33 (29,484)	-2,54 (1,537)	152	30,92 (33,685)	-6,66 (1,585)	4,12 [-0,222; 8,469]	0,0629
Hedges' g SMD							0,21 [-0,012; 0,434]	0,0632
>=65 Jahre	93	22,94 (27,793)	0,49 (1,796)	101	21,78 (27,663)	-6,25 (1,722)	6,74 [1,832; 11,646]	0,0074*
Hedges' g SMD							0,39 [0,103; 0,672]	0,0075*
Int. p-Wert								0,5613
Region gPAP								
Asien	158	31,43 (28,958)	-2,87 (1,532)	160	28,96 (31,082)	-7,72 (1,532)	4,84 [0,579; 9,108]	0,0261*
Hedges' g SMD							0,25 [0,029; 0,471]	0,0263*
Europa	19	NC	NC	21	NC	NC	NC	NC
Nordamerika	18	NC	NC	17	NC	NC	NC	NC
Rest der Welt	58	18,39 (25,875)	3,37 (2,534)	55	29,09 (36,320)	-3,34 (2,657)	6,70 [-0,613; 14,022]	0,0722
Hedges' g SMD							0,34 [-0,030; 0,713]	0,0717
Int. p-Wert								0,5820

Analysis is performed if there are at least 10 patients in each subgroup level.
[a] = Number of patients with change from baseline used for MMRM analysis at each timepoint. [b] = Mean baseline for patients with change from baseline used for MMRM analysis at each timepoint. Treatment difference is calculated from a mixed model for repeated measures (MMRM) analysis of the change from baseline score with treatment, visit, and treatment by visit interaction as fixed effects, baseline score as a covariate and baseline score by visit interaction. Patient is used as random effect in the model. Only visits where change from baseline is available for at least 25% of patients in both treatment arms are included in the analysis. Toeplitz with heterogeneity covariance matrix is used to model within-subject error. If the MMRM model does not converge the model results are not presented. SMD = standardised mean difference. * p<0.05.
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Table 4.2.3.16 FLAURA-2: Summary of subgroup analysis of change from baseline in EQ-5D-5L Visuelle Analogskala (mixed model for repeated measures) - average over all visits
Full Analysis Set, DCO 03APR2023

	Osi + Chemo (N=279)			Osi (N=278)			Behandlungseffekt	
Subgruppen	n [a]	Ausgangswert MW (SD) [b]	Veränderung MW (SE)	n [a]	Ausgangswert MW (SD) [b]	Veränderung MW (SE)	MWD [95%-KI]	p-Wert
Abstammung								
Chinesisch/Asiatisch	66	77,30 (16,345)	1,83 (1,416)	65	76,31 (18,412)	1,20 (1,439)	0,63 [-3,361; 4,625]	0,7548
Hedges' g SMD							0,05 [-0,288; 0,397]	0,7558
Nicht-chinesisch/Asiatisch	99	69,43 (18,199)	0,95 (1,310)	101	70,18 (19,695)	1,95 (1,305)	-1,00 [-4,648; 2,641]	0,5878
Hedges' g SMD							-0,08 [-0,354; 0,201]	0,5888
Nicht-asiatisch	81	70,64 (19,099)	1,52 (1,337)	83	68,67 (19,489)	4,50 (1,335)	-2,99 [-6,712; 0,735]	0,1150
Hedges' g SMD							-0,25 [-0,553; 0,061]	0,1167
Int. p-Wert								0,7897
Methode zur Gewebeuntersuchung								
zentral	107	76,30 (15,069)	1,33 (1,104)	113	75,15 (18,622)	3,07 (1,079)	-1,73 [-4,771; 1,306]	0,2624
Hedges' g SMD							-0,15 [-0,416; 0,114]	0,2641
lokal	139	68,59 (19,782)	1,27 (1,078)	136	68,06 (19,629)	1,89 (1,101)	-0,63 [-3,657; 2,406]	0,6850
Hedges' g SMD							-0,05 [-0,285; 0,188]	0,6857
Int. p-Wert								0,5260
WHO Performance-Status								
0	93	76,76 (16,425)	-1,36 (1,196)	93	75,82 (19,621)	0,71 (1,197)	-2,06 [-5,402; 1,276]	0,2244
Hedges' g SMD							-0,18 [-0,466; 0,110]	0,2256
1	153	69,01 (18,738)	3,01 (1,041)	156	68,57 (18,919)	3,68 (1,043)	-0,67 [-3,566; 2,226]	0,6493
Hedges' g SMD							-0,05 [-0,275; 0,171]	0,6503
Int. p-Wert								0,6230
Raucherstatus								
Ja	82	72,90 (19,033)	-0,01 (1,434)	83	72,64 (19,267)	-1,31 (1,436)	1,30 [-2,703; 5,305]	0,5221
Hedges' g SMD							0,10 [-0,206; 0,405]	0,5236
Nein	164	71,46 (17,897)	1,92 (0,943)	166	70,60 (19,585)	4,38 (0,944)	-2,46 [-5,086; 0,160]	0,0656
Hedges' g SMD							-0,20 [-0,419; 0,014]	0,0662
Int. p-Wert								0,3232

Analysis is performed if there are at least 10 patients in each subgroup level.
[a] = Number of patients with change from baseline used for MMRM analysis at each timepoint. [b] = Mean baseline for patients with change from baseline used for MMRM analysis at each timepoint. Treatment difference is calculated from a mixed model for repeated measures (MMRM) analysis of the change from baseline score with treatment, visit, and treatment by visit interaction as fixed effects, baseline score as a covariate and baseline score by visit interaction. Patient is used as random effect in the model. Only visits where change from baseline is available for at least 25% of patients in both treatment arms are included in the analysis. Toeplitz with heterogeneity covariance matrix is used to model within-subject error. If the MMRM model does not converge the model results are not presented. SMD = standardised mean difference. * p<0.05.
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Table 4.2.3.16 FLAURA-2: Summary of subgroup analysis of change from baseline in EQ-5D-5L Visuelle Analogskala (mixed model for repeated measures) - average over all visits
Full Analysis Set, DCO 03APR2023

	Osi + Chemo (N=279)			Osi (N=278)			Behandlungseffekt	
Subgruppen	n [a]	Ausgangswert MW (SD) [b]	Veränderung MW (SE)	n [a]	Ausgangswert MW (SD) [b]	Veränderung MW (SE)	MWD [95%-KI]	p-Wert
Geschlecht								
Maennlich	94	73,94 (17,587)	0,29 (1,314)	93	73,09 (19,764)	0,60 (1,351)	-0,31 [-4,029; 3,405]	0,8687
Hedges' g SMD							-0,02 [-0,311; 0,263]	0,8691
Weiblich	152	70,71 (18,609)	1,88 (0,989)	156	70,20 (19,267)	3,62 (0,975)	-1,74 [-4,467; 0,992]	0,2113
Hedges' g SMD							-0,14 [-0,366; 0,081]	0,2126
Int. p-Wert								0,9778
Nachweis der EGFR-Mutation durch zentralen ctDNA Cobas Test								
positiv	186	71,74 (18,279)	2,09 (0,884)	192	69,31 (20,442)	3,33 (0,876)	-1,24 [-3,689; 1,206]	0,3192
Hedges' g SMD							-0,10 [-0,304; 0,099]	0,3198
negativ	38	73,53 (18,143)	-1,40 (2,432)	33	77,30 (13,985)	-2,65 (2,592)	1,25 [-5,856; 8,358]	0,7266
Hedges' g SMD							0,08 [-0,384; 0,549]	0,7280
unbekannt	22	70,91 (18,951)	-1,63 (2,572)	24	78,75 (14,143)	4,13 (2,592)	-5,76 [-13,219; 1,693]	0,1265
Hedges' g SMD							-0,46 [-1,043; 0,130]	0,1270
Int. p-Wert								0,3906
EGFR-Mutationstyp								
Exon 19 Deletion	148	71,14 (19,247)	-0,50 (0,975)	153	73,27 (18,654)	1,57 (0,957)	-2,07 [-4,757; 0,619]	0,1310
Hedges' g SMD							-0,17 [-0,401; 0,052]	0,1317
Exon 21 (L858R) Substitutionsmutation	98	73,16 (16,673)	4,35 (1,335)	94	67,68 (20,321)	3,86 (1,388)	0,50 [-3,321; 4,314]	0,7980
Hedges' g SMD							0,04 [-0,246; 0,320]	0,7974
Int. p-Wert								0,3524
Zentral bestätigte EGFR-Mutation im Gewebe								
positiv	222	71,83 (18,673)	2,03 (0,815)	217	71,70 (18,830)	2,65 (0,831)	-0,63 [-2,913; 1,659]	0,5901
Hedges' g SMD							-0,05 [-0,238; 0,136]	0,5907
negativ	3	ID	ID	3	ID	ID	ID	ID
unbekannt	21	NC	NC	29	NC	NC	NC	NC
Int. p-Wert								NC

Analysis is performed if there are at least 10 patients in each subgroup level.
[a] = Number of patients with change from baseline used for MMRM analysis at each timepoint. [b] = Mean baseline for patients with change from baseline used for MMRM analysis at each timepoint. Treatment difference is calculated from a mixed model for repeated measures (MMRM) analysis of the change from baseline score with treatment, visit, and treatment by visit interaction as fixed effects, baseline score as a covariate and baseline score by visit interaction. Patient is used as random effect in the model. Only visits where change from baseline is available for at least 25% of patients in both treatment arms are included in the analysis. Toeplitz with heterogeneity covariance matrix is used to model within-subject error. If the MMRM model does not converge the model results are not presented. SMD = standardised mean difference. * p<0.05.
root/cdar/d516/payer_germany/ar/d5169c00001_payer_germany/tlf/prod/program/mmrmsubpra.sas gmmrmsubpraap 04JUN2024:17:59 kvbv306

Table 4.2.3.16 FLAURA-2: Summary of subgroup analysis of change from baseline in EQ-5D-5L Visuelle Analogskala (mixed model for repeated measures) - average over all visits
Full Analysis Set, DCO 03APR2023

	Osi + Chemo (N=279)			Osi (N=278)			Behandlungseffekt	
Subgruppen	n [a]	Ausgangswert MW (SD) [b]	Veränderung MW (SE)	n [a]	Ausgangswert MW (SD) [b]	Veränderung MW (SE)	MWD [95%-KI]	p-Wert
ZNS-Metastasen zur Baseline								
Ja	99	70,20 (18,614)	2,75 (1,264)	100	71,30 (18,530)	2,81 (1,287)	-0,06 [-3,612; 3,496]	0,9743
Hedges' g SMD							0,00 [-0,282; 0,273]	0,9744
Nein	147	73,12 (17,982)	0,34 (1,014)	149	71,26 (20,129)	2,32 (1,003)	-1,98 [-4,786; 0,829]	0,1666
Hedges' g SMD							-0,16 [-0,389; 0,067]	0,1673
Int. p-Wert								0,5691
Zentrale Bestätigung der EGFR-Mutation								
Zentral bestätigte EGFR-Mutation in Gewebe oder ctDNA	234	71,50 (18,457)	1,95 (0,800)	242	71,23 (19,550)	2,49 (0,792)	-0,54 [-2,747; 1,674]	0,6335
Hedges' g SMD							-0,04 [-0,223; 0,136]	0,6342
Keine zentrale Bestätigung	12	NC	NC	7	NC	NC	NC	NC
Int. p-Wert								NC
Alter bei Screening								
<65 Jahre	155	71,92 (18,991)	2,91 (1,000)	149	70,03 (21,433)	4,38 (1,030)	-1,47 [-4,298; 1,351]	0,3054
Hedges' g SMD							-0,12 [-0,343; 0,108]	0,3063
>=65 Jahre	91	71,98 (17,037)	-1,49 (1,282)	100	73,13 (16,017)	-0,48 (1,228)	-1,02 [-4,514; 2,484]	0,5678
Hedges' g SMD							-0,08 [-0,367; 0,202]	0,5692
Int. p-Wert								0,9336
Region gPAP								
Asien	158	73,12 (17,034)	1,24 (1,011)	160	72,14 (19,300)	1,30 (1,012)	-0,07 [-2,882; 2,745]	0,9618
Hedges' g SMD							-0,01 [-0,225; 0,214]	0,9619
Europa	18	64,83 (24,052)	-0,99 (2,595)	20	64,65 (19,556)	4,78 (2,439)	-5,76 [-13,012; 1,485]	0,1153
Hedges' g SMD							-0,52 [-1,164; 0,133]	0,1195
Nordamerika	16	NC	NC	15	NC	NC	NC	NC
Rest der Welt	54	72,07 (18,253)	3,02 (1,576)	54	71,81 (21,005)	4,31 (1,598)	-1,29 [-5,730; 3,149]	0,5658

Analysis is performed if there are at least 10 patients in each subgroup level.
[a] = Number of patients with change from baseline used for MMRM analysis at each timepoint. [b] = Mean baseline for patients with change from baseline used for MMRM analysis at each timepoint. Treatment difference is calculated from a mixed model for repeated measures (MMRM) analysis of the change from baseline score with treatment, visit, and treatment by visit interaction as fixed effects, baseline score as a covariate and baseline score by visit interaction. Patient is used as random effect in the model. Only visits where change from baseline is available for at least 25% of patients in both treatment arms are included in the analysis. Toeplitz with heterogeneity covariance matrix is used to model within-subject error. If the MMRM model does not converge the model results are not presented. SMD = standardised mean difference. * p<0.05.
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Table 4.2.3.16 FLAURA-2: Summary of subgroup analysis of change from baseline in EQ-5D-5L Visuelle Analogskala (mixed model for repeated measures) - average over all visits
Full Analysis Set, DCO 03APR2023

	Osi + Chemo (N=279)			Osi (N=278)			Behandlungseffekt	
Subgruppen	n [a]	Ausgangswert MW (SD) [b]	Veränderung MW (SE)	n [a]	Ausgangswert MW (SD) [b]	Veränderung MW (SE)	MWD [95%-KI]	p-Wert
Hedges' g SMD							-0,11 [-0,487; 0,268]	0,5683
Int. p-Wert								0,5602

Analysis is performed if there are at least 10 patients in each subgroup level.
[a] = Number of patients with change from baseline used for MMRM analysis at each timepoint. [b] = Mean baseline for patients with change from baseline used for MMRM analysis at each timepoint. Treatment difference is calculated from a mixed model for repeated measures (MMRM) analysis of the change from baseline score with treatment, visit, and treatment by visit interaction as fixed effects, baseline score as a covariate and baseline score by visit interaction. Patient is used as random effect in the model. Only visits where change from baseline is available for at least 25% of patients in both treatment arms are included in the analysis. Toeplitz with heterogeneity covariance matrix is used to model within-subject error. If the MMRM model does not converge the model results are not presented. SMD = standardised mean difference. * p<0.05.
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Table 4.2.3.17 FLAURA-2: Summary of subgroup analysis of change from baseline in EORTC QLQ-LC13 Husten (mixed model for repeated measures) - average over all visits
Full Analysis Set, DCO 03APR2023

	Osi + Chemo (N=279)			Osi (N=278)			Behandlungseffekt	
Subgruppen	n [a]	Ausgangswert MW (SD) [b]	Veränderung MW (SE)	n [a]	Ausgangswert MW (SD) [b]	Veränderung MW (SE)	MWD [95%-KI]	p-Wert
Abstammung								
Chinesisch/Asiatisch	66	28,79 (23,305)	-13,13 (0,863)	65	25,64 (24,839)	-8,37 (0,895)	-4,76 [-7,215; -2,311]	0,0002*
Hedges' g SMD							-0,67 [-1,018; -0,314]	0,0002*
Nicht-chinesisch/Asiatisch	103	33,01 (24,916)	-12,59 (0,661)	102	29,08 (26,811)	-10,54 (0,687)	-2,05 [-3,928; -0,174]	0,0323*
Hedges' g SMD							-0,30 [-0,575; -0,024]	0,0330*
Nicht-asiatisch	84	34,52 (32,907)	-14,33 (0,972)	84	38,49 (32,103)	-13,48 (1,010)	-0,85 [-3,604; 1,895]	0,5418
Hedges' g SMD							-0,09 [-0,396; 0,209]	0,5442
Int. p-Wert								0,0866
Methode zur Gewebeuntersuchung								
zentral	110	29,39 (25,435)	-13,53 (0,660)	114	27,78 (25,826)	-9,05 (0,660)	-4,49 [-6,319; -2,652]	<0,0001*
Hedges' g SMD							-0,64 [-0,908; -0,371]	<0,0001*
lokal	143	34,73 (28,765)	-13,16 (0,635)	137	34,31 (30,503)	-12,25 (0,680)	-0,90 [-2,729; 0,921]	0,3313
Hedges' g SMD							-0,12 [-0,350; 0,119]	0,3325
Int. p-Wert								0,0064*
WHO Performance-Status								
0	93	27,24 (26,442)	-9,64 (0,746)	93	27,96 (29,196)	-8,45 (0,753)	-1,19 [-3,265; 0,895]	0,2636
Hedges' g SMD							-0,16 [-0,451; 0,125]	0,2662
1	160	35,42 (27,646)	-15,53 (0,596)	158	33,33 (28,154)	-12,44 (0,632)	-3,09 [-4,794; -1,384]	0,0004*
Hedges' g SMD							-0,40 [-0,620; -0,176]	0,0004*
Int. p-Wert								0,1822
Raucherstatus								
Ja	83	33,33 (28,985)	-11,20 (0,829)	84	29,76 (28,818)	-11,46 (0,868)	0,26 [-2,102; 2,614]	0,8313
Hedges' g SMD							0,03 [-0,271; 0,336]	0,8320
Nein	170	31,96 (26,735)	-14,08 (0,558)	167	32,14 (28,551)	-10,61 (0,579)	-3,47 [-5,044; -1,889]	<0,0001*
Hedges' g SMD							-0,47 [-0,685; -0,252]	<0,0001*
Int. p-Wert								0,0221*

Analysis is performed if there are at least 10 patients in each subgroup level.
[a] = Number of patients with change from baseline used for MMRM analysis at each timepoint. [b] = Mean baseline for patients with change from baseline used for MMRM analysis at each timepoint. Treatment difference is calculated from a mixed model for repeated measures (MMRM) analysis of the change from baseline score with treatment, visit, and treatment by visit interaction as fixed effects, baseline score as a covariate and baseline score by visit interaction. Patient is used as random effect in the model. Only visits where change from baseline is available for at least 25% of patients in both treatment arms are included in the analysis. Autoregressive with heterogeneity covariance matrix is used to model within-subject error. If the MMRM model does not converge the model results are not presented. SMD = standardised mean difference. * p<0.05.
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Table 4.2.3.17 FLAURA-2: Summary of subgroup analysis of change from baseline in EORTC QLQ-LC13 Husten (mixed model for repeated measures) - average over all visits
Full Analysis Set, DCO 03APR2023

	Osi + Chemo (N=279)			Osi (N=278)			Behandlungseffekt	
Subgruppen	n [a]	Ausgangswert MW (SD) [b]	Veränderung MW (SE)	n [a]	Ausgangswert MW (SD) [b]	Veränderung MW (SE)	MWD [95%-KI]	p-Wert
Geschlecht								
Maennlich	95	30,18 (26,217)	-11,92 (0,729)	94	32,27 (31,090)	-10,10 (0,793)	-1,82 [-3,932; 0,298]	0,0921
Hedges' g SMD							-0,24 [-0,531; 0,042]	0,0941
Weiblich	158	33,76 (28,151)	-13,96 (0,602)	157	30,79 (27,096)	-11,28 (0,609)	-2,68 [-4,359; -0,995]	0,0018*
Hedges' g SMD							-0,35 [-0,574; -0,129]	0,0020*
Int. p-Wert								0,7769
Nachweis der EGFR-Mutation durch zentralen ctDNA Cobas Test								
positiv	193	32,99 (27,636)	-14,60 (0,511)	193	33,16 (29,755)	-11,79 (0,525)	-2,81 [-4,245; -1,371]	0,0001*
Hedges' g SMD							-0,39 [-0,591; -0,188]	0,0002*
negativ	38	28,95 (27,037)	-9,22 (1,289)	33	29,29 (24,661)	-9,67 (1,396)	0,45 [-3,297; 4,191]	0,8142
Hedges' g SMD							0,06 [-0,411; 0,522]	0,8159
unbekannt	22	33,33 (27,217)	-6,84 (2,121)	25	20,00 (21,517)	-4,56 (2,273)	-2,28 [-8,514; 3,964]	0,4715
Hedges' g SMD							-0,21 [-0,783; 0,366]	0,4769
Int. p-Wert								0,1816
EGFR-Mutationstyp								
Exon 19 Deletion	154	33,55 (28,646)	-13,21 (0,612)	154	30,52 (27,732)	-11,72 (0,618)	-1,49 [-3,200; 0,222]	0,0880
Hedges' g SMD							-0,19 [-0,418; 0,029]	0,0887
Exon 21 (L858R) Substitutionsmutation	99	30,64 (25,500)	-12,96 (0,698)	95	32,98 (30,167)	-9,51 (0,765)	-3,46 [-5,487; -1,426]	0,0009*
Hedges' g SMD							-0,48 [-0,764; -0,193]	0,0010*
Int. p-Wert								0,0582
Zentral bestätigte EGFR-Mutation im Gewebe								
positiv	229	32,17 (27,012)	-13,31 (0,480)	219	30,90 (28,808)	-10,67 (0,509)	-2,64 [-4,010; -1,265]	0,0002*
Hedges' g SMD							-0,36 [-0,543; -0,169]	0,0002*
negativ	3	ID	ID	3	ID	ID	ID	ID
unbekannt	21	36,51 (33,174)	-11,74 (1,939)	29	35,63 (26,624)	-14,24 (1,574)	2,51 [-2,423; 7,433]	0,3166
Hedges' g SMD							0,29 [-0,280; 0,850]	0,3224

Analysis is performed if there are at least 10 patients in each subgroup level.
[a] = Number of patients with change from baseline used for MMRM analysis at each timepoint. [b] = Mean baseline for patients with change from baseline used for MMRM analysis at each timepoint. Treatment difference is calculated from a mixed model for repeated measures (MMRM) analysis of the change from baseline score with treatment, visit, and treatment by visit interaction as fixed effects, baseline score as a covariate and baseline score by visit interaction. Patient is used as random effect in the model. Only visits where change from baseline is available for at least 25% of patients in both treatment arms are included in the analysis. Autoregressive with heterogeneity covariance matrix is used to model within-subject error. If the MMRM model does not converge the model results are not presented. SMD = standardised mean difference. * p<0.05.
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Table 4.2.3.17 FLAURA-2: Summary of subgroup analysis of change from baseline in EORTC QLQ-LC13 Husten (mixed model for repeated measures) - average over all visits
Full Analysis Set, DCO 03APR2023

	Osi + Chemo (N=279)			Osi (N=278)			Behandlungseffekt	
Subgruppen	n [a]	Ausgangswert MW (SD) [b]	Veränderung MW (SE)	n [a]	Ausgangswert MW (SD) [b]	Veränderung MW (SE)	MWD [95%-KI]	p-Wert
Int. p-Wert								0,0504
ZNS-Metastasen zur Baseline								
Ja	103	39,16 (27,387)	-18,55 (0,702)	101	35,97 (28,938)	-14,24 (0,781)	-4,31 [-6,376; -2,248]	<0,0001*
Hedges' g SMD							-0,57 [-0,854; -0,293]	<0,0001*
Nein	150	27,78 (26,593)	-9,74 (0,618)	150	28,22 (28,045)	-8,64 (0,614)	-1,11 [-2,815; 0,598]	0,2028
Hedges' g SMD							-0,15 [-0,373; 0,080]	0,2048
Int. p-Wert								0,0211*
Zentrale Bestätigung der EGFR-Mutation								
Zentral bestätigte EGFR-Mutation in Gewebe oder ctDNA	241	32,37 (27,114)	-13,43 (0,465)	244	31,28 (28,695)	-10,93 (0,478)	-2,50 [-3,809; -1,194]	0,0002*
Hedges' g SMD							-0,34 [-0,520; -0,161]	0,0002*
Keine zentrale Bestätigung	12	NC	NC	7	NC	NC	NC	NC
Int. p-Wert								NC
Alter bei Screening								
<65 Jahre	158	34,81 (27,220)	-15,61 (0,536)	150	30,00 (29,093)	-13,34 (0,579)	-2,28 [-3,828; -0,723]	0,0041*
Hedges' g SMD							-0,33 [-0,553; -0,103]	0,0042*
>=65 Jahre	95	28,42 (27,491)	-8,73 (0,849)	101	33,33 (27,889)	-7,13 (0,830)	-1,59 [-3,927; 0,742]	0,1810
Hedges' g SMD							-0,19 [-0,472; 0,090]	0,1826
Int. p-Wert								0,5652
Region gPAP								
Asien	162	30,45 (23,903)	-12,49 (0,516)	161	27,33 (25,790)	-9,90 (0,535)	-2,59 [-4,053; -1,128]	0,0005*
Hedges' g SMD							-0,39 [-0,607; -0,167]	0,0006*
Europa	18	37,04 (34,087)	-15,51 (1,951)	20	38,33 (27,091)	-13,17 (1,816)	-2,33 [-7,703; 3,034]	0,3902
Hedges' g SMD							-0,28 [-0,919; 0,361]	0,3932
Nordamerika	17	56,86 (32,839)	-20,94 (2,722)	15	37,78 (37,515)	-14,87 (2,807)	-6,07 [-14,127; 1,978]	0,1372
Hedges' g SMD							-0,54 [-1,244; 0,173]	0,1385

Analysis is performed if there are at least 10 patients in each subgroup level.
[a] = Number of patients with change from baseline used for MMRM analysis at each timepoint. [b] = Mean baseline for patients with change from baseline used for MMRM analysis at each timepoint. Treatment difference is calculated from a mixed model for repeated measures (MMRM) analysis of the change from baseline score with treatment, visit, and treatment by visit interaction as fixed effects, baseline score as a covariate and baseline score by visit interaction. Patient is used as random effect in the model. Only visits where change from baseline is available for at least 25% of patients in both treatment arms are included in the analysis. Autoregressive with heterogeneity covariance matrix is used to model within-subject error. If the MMRM model does not converge the model results are not presented. SMD = standardised mean difference. * p<0.05.
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Table 4.2.3.17 FLAURA-2: Summary of subgroup analysis of change from baseline in EORTC QLQ-LC13 Husten (mixed model for repeated measures) - average over all visits
Full Analysis Set, DCO 03APR2023

	Osi + Chemo (N=279)			Osi (N=278)			Behandlungseffekt	
Subgruppen	n [a]	Ausgangswert MW (SD) [b]	Veränderung MW (SE)	n [a]	Ausgangswert MW (SD) [b]	Veränderung MW (SE)	MWD [95%-KI]	p-Wert
Rest der Welt	56	29,17 (29,857)	-13,07 (1,220)	55	38,79 (32,561)	-11,51 (1,313)	-1,57 [-5,115; 1,979]	0,3853
Hedges' g SMD							-0,16 [-0,538; 0,208]	0,3857
Int. p-Wert								0,1835

Analysis is performed if there are at least 10 patients in each subgroup level.
[a] = Number of patients with change from baseline used for MMRM analysis at each timepoint. [b] = Mean baseline for patients with change from baseline used for MMRM analysis at each timepoint. Treatment difference is calculated from a mixed model for repeated measures (MMRM) analysis of the change from baseline score with treatment, visit, and treatment by visit interaction as fixed effects, baseline score as a covariate and baseline score by visit interaction. Patient is used as random effect in the model. Only visits where change from baseline is available for at least 25% of patients in both treatment arms are included in the analysis. Autoregressive with heterogeneity covariance matrix is used to model within-subject error. If the MMRM model does not converge the model results are not presented. SMD = standardised mean difference. * p<0.05.
root/cdar/d516/payer_germany/ar/d5169c00001_payer_germany/tlf/prod/program/mmrmsubprbg.sas gmmrmsubprbgaq 04JUN2024:18:00 kvbv306

Table 4.2.3.18 FLAURA-2: Summary of subgroup analysis of change from baseline in EORTC QLQ-LC13 Hämoptyse (mixed model for repeated measures) - average over all visits
Full Analysis Set, DCO 03APR2023

	Osi + Chemo (N=279)			Osi (N=278)			Behandlungseffekt	
Subgruppen	n [a]	Ausgangswert MW (SD) [b]	Veränderung MW (SE)	n [a]	Ausgangswert MW (SD) [b]	Veränderung MW (SE)	MWD [95%-KI]	p-Wert
Abstammung								
Chinesisch/Asiatisch	66	NC	NC	65	NC	NC	NC	NC
Nicht-chinesisch/Asiatisch	103	0,97 (5,633)	-1,72 (0,169)	102	6,54 (19,922)	-1,91 (0,174)	0,20 [-0,287; 0,677]	0,4266
Hedges' g SMD							0,11 [-0,162; 0,386]	0,4239
Nicht-asiatisch	84	NC	NC	84	NC	NC	NC	NC
Int. p-Wert								NC
Methode zur Gewebeuntersuchung								
zentral	110	3,03 (10,633)	-2,41 (0,199)	114	5,85 (16,738)	-2,43 (0,198)	0,01 [-0,541; 0,564]	0,9677
Hedges' g SMD							0,01 [-0,257; 0,267]	0,9678
lokal	143	1,40 (6,707)	-1,71 (0,114)	137	5,35 (17,261)	-1,81 (0,122)	0,10 [-0,224; 0,430]	0,5375
Hedges' g SMD							0,07 [-0,161; 0,308]	0,5378
Int. p-Wert								0,2351
WHO Performance-Status								
0	93	NC	NC	93	NC	NC	NC	NC
1	160	2,50 (9,568)	-2,13 (0,140)	158	6,33 (18,868)	-2,08 (0,148)	-0,05 [-0,448; 0,354]	0,8186
Hedges' g SMD							-0,03 [-0,246; 0,194]	0,8186
Int. p-Wert								NC
Raucherstatus								
Ja	83	NC	NC	84	NC	NC	NC	NC
Nein	170	2,75 (9,880)	-3,06 (0,117)	167	7,19 (19,402)	-2,73 (0,122)	-0,33 [-0,659; 0,005]	0,0534
Hedges' g SMD							-0,21 [-0,425; 0,004]	0,0540
Int. p-Wert								NC
Geschlecht								
Maennlich	95	1,75 (7,483)	-2,26 (0,249)	94	6,74 (18,665)	-2,29 (0,268)	0,03 [-0,692; 0,753]	0,9345
Hedges' g SMD							0,01 [-0,273; 0,297]	0,9343
Weiblich	158	2,32 (9,305)	-1,86 (0,108)	157	4,88 (15,930)	-1,95 (0,108)	0,09 [-0,213; 0,386]	0,5712

Analysis is performed if there are at least 10 patients in each subgroup level.
[a] = Number of patients with change from baseline used for MMRM analysis at each timepoint. [b] = Mean baseline for patients with change from baseline used for MMRM analysis at each timepoint. Treatment difference is calculated from a mixed model for repeated measures (MMRM) analysis of the change from baseline score with treatment, visit, and treatment by visit interaction as fixed effects, baseline score as a covariate and baseline score by visit interaction. Patient is used as random effect in the model. Only visits where change from baseline is available for at least 25% of patients in both treatment arms are included in the analysis. Autoregressive with heterogeneity covariance matrix is used to model within-subject error. If the MMRM model does not converge the model results are not presented. SMD = standardised mean difference. * p<0.05.
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Table 4.2.3.18 FLAURA-2: Summary of subgroup analysis of change from baseline in EORTC QLQ-LC13 Hämoptyse (mixed model for repeated measures) - average over all visits
Full Analysis Set, DCO 03APR2023

	Osi + Chemo (N=279)			Osi (N=278)			Behandlungseffekt	
Subgruppen	n [a]	Ausgangswert MW (SD) [b]	Veränderung MW (SE)	n [a]	Ausgangswert MW (SD) [b]	Veränderung MW (SE)	MWD [95%-KI]	p-Wert
Hedges' g SMD							0,06 [-0,157; 0,285]	0,5718
Int. p-Wert								0,6104
Nachweis der EGFR-Mutation durch zentralen ctDNA Cobas Test								
positiv	193	1,90 (7,748)	-2,26 (0,123)	193	6,22 (17,887)	-2,41 (0,126)	0,15 [-0,201; 0,494]	0,4072
Hedges' g SMD							0,08 [-0,115; 0,284]	0,4066
negativ	38	NC	NC	33	NC	NC	NC	NC
unbekannt	22	NC	NC	25	NC	NC	NC	NC
Int. p-Wert								NC
EGFR-Mutationstyp								
Exon 19 Deletion	154	1,95 (8,721)	-1,40 (0,140)	154	5,19 (16,227)	-1,79 (0,141)	0,39 [0,001; 0,781]	0,0494*
Hedges' g SMD							0,22 [0,000; 0,448]	0,0503
Exon 21 (L858R) Substitutionsmutation	99	2,36 (8,588)	-3,07 (0,171)	95	6,32 (18,383)	-2,52 (0,189)	-0,55 [-1,054; -0,052]	0,0307*
Hedges' g SMD							-0,31 [-0,594; -0,028]	0,0313*
Int. p-Wert								0,0021*
Zentral bestätigte EGFR-Mutation im Gewebe								
positiv	229	2,33 (9,070)	-1,97 (0,118)	219	5,33 (16,499)	-2,05 (0,124)	0,08 [-0,256; 0,418]	0,6374
Hedges' g SMD							0,04 [-0,141; 0,230]	0,6370
negativ	3	ID	ID	3	ID	ID	ID	ID
unbekannt	21	NC	NC	29	NC	NC	NC	NC
Int. p-Wert								NC
ZNS-Metastasen zur Baseline								
Ja	103	2,91 (10,548)	-2,21 (0,218)	101	5,61 (17,682)	-2,87 (0,238)	0,66 [0,026; 1,297]	0,0412*
Hedges' g SMD							0,29 [0,010; 0,562]	0,0421*
Nein	150	1,56 (7,054)	-1,87 (0,111)	150	5,56 (16,573)	-1,57 (0,110)	-0,30 [-0,606; 0,005]	0,0540
Hedges' g SMD							-0,22 [-0,449; 0,005]	0,0550
Int. p-Wert								0,0091*

Analysis is performed if there are at least 10 patients in each subgroup level.
[a] = Number of patients with change from baseline used for MMRM analysis at each timepoint. [b] = Mean baseline for patients with change from baseline used for MMRM analysis at each timepoint. Treatment difference is calculated from a mixed model for repeated measures (MMRM) analysis of the change from baseline score with treatment, visit, and treatment by visit interaction as fixed effects, baseline score as a covariate and baseline score by visit interaction. Patient is used as random effect in the model. Only visits where change from baseline is available for at least 25% of patients in both treatment arms are included in the analysis. Autoregressive with heterogeneity covariance matrix is used to model within-subject error. If the MMRM model does not converge the model results are not presented. SMD = standardised mean difference. * p<0.05.
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Table 4.2.3.18 FLAURA-2: Summary of subgroup analysis of change from baseline in EORTC QLQ-LC13 Hämoptyse (mixed model for repeated measures) - average over all visits
Full Analysis Set, DCO 03APR2023

	Osi + Chemo (N=279)			Osi (N=278)			Behandlungseffekt	
Subgruppen	n [a]	Ausgangswert MW (SD) [b]	Veränderung MW (SE)	n [a]	Ausgangswert MW (SD) [b]	Veränderung MW (SE)	MWD [95%-KI]	p-Wert
Zentrale Bestätigung der EGFR-Mutation								
Zentral bestätigte EGFR-Mutation in Gewebe oder ctDNA	241	2,21 (8,855)	-1,98 (0,111)	244	5,46 (16,761)	-2,07 (0,114)	0,09 [-0,221; 0,403]	0,5678
Hedges' g SMD							0,05 [-0,126; 0,230]	0,5678
Keine zentrale Bestätigung	12	NC	NC	7	NC	NC	NC	NC
Int. p-Wert								NC
Alter bei Screening								
<65 Jahre	158	NC	NC	150	NC	NC	NC	NC
>=65 Jahre	95	NC	NC	101	NC	NC	NC	NC
Int. p-Wert								NC
Region gPAP								
Asien	162	2,26 (8,412)	-2,04 (0,142)	161	5,80 (17,703)	-2,08 (0,147)	0,04 [-0,365; 0,440]	0,8546
Hedges' g SMD							0,02 [-0,198; 0,239]	0,8545
Europa	18	NC	NC	20	NC	NC	NC	NC
Nordamerika	17	NC	NC	15	NC	NC	NC	NC
Rest der Welt	56	NC	NC	55	NC	NC	NC	NC
Int. p-Wert								NC

Analysis is performed if there are at least 10 patients in each subgroup level.
[a] = Number of patients with change from baseline used for MMRM analysis at each timepoint. [b] = Mean baseline for patients with change from baseline used for MMRM analysis at each timepoint. Treatment difference is calculated from a mixed model for repeated measures (MMRM) analysis of the change from baseline score with treatment, visit, and treatment by visit interaction as fixed effects, baseline score as a covariate and baseline score by visit interaction. Patient is used as random effect in the model. Only visits where change from baseline is available for at least 25% of patients in both treatment arms are included in the analysis. Autoregressive with heterogeneity covariance matrix is used to model within-subject error. If the MMRM model does not converge the model results are not presented. SMD = standardised mean difference. * p<0.05.
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Table 4.2.3.19 FLAURA-2: Summary of subgroup analysis of change from baseline in EORTC QLQ-LC13 Dysphagie (mixed model for repeated measures) - average over all visits
Full Analysis Set, DCO 03APR2023

	Osi + Chemo (N=279)			Osi (N=278)			Behandlungseffekt	
Subgruppen	n [a]	Ausgangswert MW (SD) [b]	Veränderung MW (SE)	n [a]	Ausgangswert MW (SD) [b]	Veränderung MW (SE)	MWD [95%-KI]	p-Wert
Abstammung								
Chinesisch/Asiatisch	66	2,53 (8,888)	5,78 (0,706)	65	2,05 (9,995)	3,59 (0,727)	2,19 [0,198; 4,181]	0,0313*
Hedges' g SMD							0,38 [0,030; 0,721]	0,0332*
Nicht-chinesisch/Asiatisch	103	8,41 (17,907)	0,59 (0,560)	102	7,52 (18,110)	0,68 (0,578)	-0,09 [-1,671; 1,491]	0,9113
Hedges' g SMD							-0,02 [-0,289; 0,258]	0,9116
Nicht-asiatisch	84	4,37 (14,432)	3,58 (0,624)	84	3,57 (11,591)	2,64 (0,649)	0,94 [-0,829; 2,712]	0,2965
Hedges' g SMD							0,16 [-0,142; 0,464]	0,2986
Int. p-Wert								0,2181
Methode zur Gewebeuntersuchung								
zentral	110	5,76 (16,191)	3,61 (0,536)	114	3,51 (13,573)	2,32 (0,531)	1,29 [-0,187; 2,777]	0,0868
Hedges' g SMD							0,23 [-0,034; 0,491]	0,0884
lokal	143	5,36 (14,070)	2,43 (0,482)	137	5,84 (15,069)	1,75 (0,513)	0,69 [-0,697; 2,069]	0,3308
Hedges' g SMD							0,12 [-0,118; 0,351]	0,3308
Int. p-Wert								0,8354
WHO Performance-Status								
0	93	3,94 (11,887)	2,19 (0,556)	93	3,23 (12,103)	2,15 (0,561)	0,04 [-1,508; 1,593]	0,9571
Hedges' g SMD							0,01 [-0,280; 0,295]	0,9573
1	160	6,46 (16,507)	3,41 (0,463)	158	5,70 (15,600)	1,81 (0,485)	1,60 [0,287; 2,921]	0,0171*
Hedges' g SMD							0,27 [0,047; 0,488]	0,0175*
Int. p-Wert								0,2094
Raucherstatus								
Ja	83	4,42 (12,506)	1,15 (0,718)	84	6,35 (15,928)	1,46 (0,747)	-0,31 [-2,354; 1,728]	0,7633
Hedges' g SMD							-0,05 [-0,350; 0,257]	0,7637
Nein	170	6,08 (16,084)	3,81 (0,407)	167	3,99 (13,593)	2,22 (0,417)	1,60 [0,454; 2,741]	0,0062*
Hedges' g SMD							0,30 [0,083; 0,513]	0,0065*
Int. p-Wert								0,1036

Analysis is performed if there are at least 10 patients in each subgroup level.
[a] = Number of patients with change from baseline used for MMRM analysis at each timepoint. [b] = Mean baseline for patients with change from baseline used for MMRM analysis at each timepoint. Treatment difference is calculated from a mixed model for repeated measures (MMRM) analysis of the change from baseline score with treatment, visit, and treatment by visit interaction as fixed effects, baseline score as a covariate and baseline score by visit interaction. Patient is used as random effect in the model. Only visits where change from baseline is available for at least 25% of patients in both treatment arms are included in the analysis. Autoregressive with heterogeneity covariance matrix is used to model within-subject error. If the MMRM model does not converge the model results are not presented. SMD = standardised mean difference. * p<0.05.
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Table 4.2.3.19 FLAURA-2: Summary of subgroup analysis of change from baseline in EORTC QLQ-LC13 Dysphagie (mixed model for repeated measures) - average over all visits
Full Analysis Set, DCO 03APR2023

	Osi + Chemo (N=279)			Osi (N=278)			Behandlungseffekt	
Subgruppen	n [a]	Ausgangswert MW (SD) [b]	Veränderung MW (SE)	n [a]	Ausgangswert MW (SD) [b]	Veränderung MW (SE)	MWD [95%-KI]	p-Wert
Geschlecht								
Maennlich	95	5,61 (14,302)	0,54 (0,586)	94	6,74 (18,014)	-0,47 (0,633)	1,01 [-0,691; 2,703]	0,2446
Hedges' g SMD							0,17 [-0,117; 0,455]	0,2460
Weiblich	158	5,49 (15,448)	4,36 (0,453)	157	3,61 (11,682)	3,34 (0,455)	1,02 [-0,238; 2,278]	0,1120
Hedges' g SMD							0,18 [-0,043; 0,400]	0,1135
Int. p-Wert								0,9956
Nachweis der EGFR-Mutation durch zentralen ctDNA Cobas Test								
positiv	193	6,04 (15,711)	1,95 (0,385)	193	5,35 (15,218)	1,27 (0,394)	0,68 [-0,399; 1,761]	0,2161
Hedges' g SMD							0,13 [-0,074; 0,325]	0,2171
negativ	38	4,39 (13,800)	4,64 (0,839)	33	3,03 (12,812)	2,78 (0,901)	1,87 [-0,556; 4,289]	0,1305
Hedges' g SMD							0,36 [-0,114; 0,827]	0,1371
unbekannt	22	3,03 (9,808)	, (,)	25	2,67 (9,230)	, (,)	1,88 [-3,920; 7,684]	0,5213
Hedges' g SMD							, [, ; ,]	
Int. p-Wert								0,5108
EGFR-Mutationstyp								
Exon 19 Deletion	154	6,06 (15,459)	3,20 (0,444)	154	4,76 (13,966)	1,67 (0,445)	1,52 [0,287; 2,754]	0,0158*
Hedges' g SMD							0,27 [0,050; 0,499]	0,0164*
Exon 21 (L858R) Substitutionsmutation	99	4,71 (14,294)	2,59 (0,612)	95	4,91 (15,351)	2,62 (0,668)	-0,03 [-1,808; 1,758]	0,9778
Hedges' g SMD							0,00 [-0,285; 0,277]	0,9778
Int. p-Wert								0,1557
Zentral bestätigte EGFR-Mutation im Gewebe								
positiv	229	5,82 (15,136)	3,10 (0,373)	219	4,41 (14,128)	2,10 (0,393)	1,00 [-0,066; 2,061]	0,0660
Hedges' g SMD							0,17 [-0,012; 0,359]	0,0666
negativ	3	ID	ID	3	ID	ID	ID	ID
unbekannt	21	3,17 (14,548)	2,16 (1,495)	29	6,90 (16,377)	0,95 (1,199)	1,21 [-2,613; 5,026]	0,5331
Hedges' g SMD							0,18 [-0,384; 0,742]	0,5324

Analysis is performed if there are at least 10 patients in each subgroup level.
[a] = Number of patients with change from baseline used for MMRM analysis at each timepoint. [b] = Mean baseline for patients with change from baseline used for MMRM analysis at each timepoint. Treatment difference is calculated from a mixed model for repeated measures (MMRM) analysis of the change from baseline score with treatment, visit, and treatment by visit interaction as fixed effects, baseline score as a covariate and baseline score by visit interaction. Patient is used as random effect in the model. Only visits where change from baseline is available for at least 25% of patients in both treatment arms are included in the analysis. Autoregressive with heterogeneity covariance matrix is used to model within-subject error. If the MMRM model does not converge the model results are not presented. SMD = standardised mean difference. * p<0.05.
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Table 4.2.3.19 FLAURA-2: Summary of subgroup analysis of change from baseline in EORTC QLQ-LC13 Dysphagie (mixed model for repeated measures) - average over all visits
Full Analysis Set, DCO 03APR2023

	Osi + Chemo (N=279)			Osi (N=278)			Behandlungseffekt	
Subgruppen	n [a]	Ausgangswert MW (SD) [b]	Veränderung MW (SE)	n [a]	Ausgangswert MW (SD) [b]	Veränderung MW (SE)	MWD [95%-KI]	p-Wert
Int. p-Wert								0,5656
ZNS-Metastasen zur Baseline								
Ja	103	5,50 (14,832)	2,90 (0,522)	101	6,93 (18,449)	1,35 (0,577)	1,55 [0,019; 3,089]	0,0472*
Hedges' g SMD							0,28 [0,003; 0,555]	0,0474*
Nein	150	5,56 (15,163)	2,99 (0,491)	150	3,33 (10,751)	2,33 (0,487)	0,66 [-0,697; 2,019]	0,3398
Hedges' g SMD							0,11 [-0,116; 0,337]	0,3406
Int. p-Wert								0,2865
Zentrale Bestätigung der EGFR-Mutation								
Zentral bestätigte EGFR-Mutation in Gewebe oder ctDNA	241	5,53 (14,808)	3,05 (0,366)	244	4,78 (14,500)	2,11 (0,373)	0,93 [-0,091; 1,959]	0,0740
Hedges' g SMD							0,16 [-0,016; 0,340]	0,0748
Keine zentrale Bestätigung	12	NC	NC	7	NC	NC	NC	NC
Int. p-Wert								NC
Alter bei Screening								
<65 Jahre	158	5,06 (13,657)	2,08 (0,409)	150	5,33 (15,486)	0,35 (0,435)	1,73 [0,556; 2,902]	0,0039*
Hedges' g SMD							0,33 [0,104; 0,554]	0,0041*
>=65 Jahre	95	6,32 (17,049)	4,59 (0,668)	101	3,96 (12,725)	4,39 (0,651)	0,19 [-1,639; 2,026]	0,8355
Hedges' g SMD							0,03 [-0,251; 0,310]	0,8360
Int. p-Wert								0,0646
Region gPAP								
Asien	162	6,17 (15,418)	2,80 (0,438)	161	5,38 (15,768)	1,68 (0,450)	1,12 [-0,118; 2,348]	0,0763
Hedges' g SMD							0,20 [-0,022; 0,416]	0,0773
Europa	18	NC	NC	20	NC	NC	NC	NC
Nordamerika	17	3,92 (11,070)	-3,01 (2,062)	15	6,67 (18,687)	0,98 (2,049)	-3,99 [-9,817; 1,836]	0,1756
Hedges' g SMD							-0,47 [-1,177; 0,233]	0,1896
Rest der Welt	56	1,79 (9,888)	, (,)	55	2,42 (8,736)	, (,)	1,15 [-1,128; 3,429]	0,3213

Analysis is performed if there are at least 10 patients in each subgroup level.
[a] = Number of patients with change from baseline used for MMRM analysis at each timepoint. [b] = Mean baseline for patients with change from baseline used for MMRM analysis at each timepoint. Treatment difference is calculated from a mixed model for repeated measures (MMRM) analysis of the change from baseline score with treatment, visit, and treatment by visit interaction as fixed effects, baseline score as a covariate and baseline score by visit interaction. Patient is used as random effect in the model. Only visits where change from baseline is available for at least 25% of patients in both treatment arms are included in the analysis. Autoregressive with heterogeneity covariance matrix is used to model within-subject error. If the MMRM model does not converge the model results are not presented. SMD = standardised mean difference. * p<0.05.
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Table 4.2.3.19 FLAURA-2: Summary of subgroup analysis of change from baseline in EORTC QLQ-LC13 Dysphagie (mixed model for repeated measures) - average over all visits
Full Analysis Set, DCO 03APR2023

	Osi + Chemo (N=279)			Osi (N=278)			Behandlungseffekt	
Subgruppen	n [a]	Ausgangswert MW (SD) [b]	Veränderung MW (SE)	n [a]	Ausgangswert MW (SD) [b]	Veränderung MW (SE)	MWD [95%-KI]	p-Wert
Hedges' g SMD							, [, ; ,]	
Int. p-Wert								0,1726

Analysis is performed if there are at least 10 patients in each subgroup level.
[a] = Number of patients with change from baseline used for MMRM analysis at each timepoint. [b] = Mean baseline for patients with change from baseline used for MMRM analysis at each timepoint. Treatment difference is calculated from a mixed model for repeated measures (MMRM) analysis of the change from baseline score with treatment, visit, and treatment by visit interaction as fixed effects, baseline score as a covariate and baseline score by visit interaction. Patient is used as random effect in the model. Only visits where change from baseline is available for at least 25% of patients in both treatment arms are included in the analysis. Autoregressive with heterogeneity covariance matrix is used to model within-subject error. If the MMRM model does not converge the model results are not presented. SMD = standardised mean difference. * p<0.05.
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Table 4.2.3.20 FLAURA-2: Summary of subgroup analysis of change from baseline in EORTC QLQ-LC13 Schmerzen in Armen oder Schultern (mixed model for repeated measures) - average over all visits
Full Analysis Set, DCO 03APR2023

	Osi + Chemo (N=279)			Osi (N=278)			Behandlungseffekt	
Subgruppen	n [a]	Ausgangswert MW (SD) [b]	Veränderung MW (SE)	n [a]	Ausgangswert MW (SD) [b]	Veränderung MW (SE)	MWD [95%-KI]	p-Wert
Abstammung								
Chinesisch/Asiatisch	66	17,17 (18,713)	-3,45 (0,798)	65	17,44 (22,133)	-2,50 (0,826)	-0,95 [-3,207; 1,306]	0,4080
Hedges' g SMD							-0,14 [-0,487; 0,199]	0,4110
Nicht-chinesisch/Asiatisch	103	20,06 (23,028)	-3,75 (0,738)	102	20,59 (26,135)	-5,41 (0,764)	1,66 [-0,431; 3,741]	0,1197
Hedges' g SMD							0,22 [-0,058; 0,491]	0,1217
Nicht-asiatisch	84	15,48 (23,397)	-3,96 (0,959)	84	17,86 (25,584)	-0,52 (1,001)	-3,44 [-6,167; -0,712]	0,0136*
Hedges' g SMD							-0,38 [-0,686; -0,076]	0,0144*
Int. p-Wert								0,0567
Methode zur Gewebeuntersuchung								
zentral	110	18,48 (22,389)	-4,31 (0,735)	114	20,18 (26,092)	-3,76 (0,729)	-0,55 [-2,582; 1,485]	0,5968
Hedges' g SMD							-0,07 [-0,333; 0,191]	0,5978
lokal	143	17,25 (21,974)	-3,22 (0,628)	137	17,76 (23,932)	-2,73 (0,669)	-0,50 [-2,296; 1,303]	0,5881
Hedges' g SMD							-0,06 [-0,299; 0,170]	0,5889
Int. p-Wert								0,8250
WHO Performance-Status								
0	93	11,83 (19,440)	-1,83 (0,738)	93	19,71 (24,196)	-2,75 (0,742)	0,92 [-1,156; 2,991]	0,3852
Hedges' g SMD							0,13 [-0,160; 0,416]	0,3830
1	160	21,25 (22,890)	-4,68 (0,619)	158	18,35 (25,391)	-3,76 (0,651)	-0,93 [-2,694; 0,840]	0,3035
Hedges' g SMD							-0,12 [-0,335; 0,105]	0,3036
Int. p-Wert								0,3268
Raucherstatus								
Ja	83	17,27 (21,691)	-3,91 (0,797)	84	17,46 (24,531)	-4,44 (0,831)	0,53 [-1,733; 2,789]	0,6465
Hedges' g SMD							0,07 [-0,233; 0,374]	0,6480
Nein	170	18,04 (22,384)	-3,54 (0,583)	167	19,56 (25,149)	-2,62 (0,601)	-0,92 [-2,559; 0,726]	0,2737
Hedges' g SMD							-0,12 [-0,333; 0,095]	0,2749
Int. p-Wert								0,2695

Analysis is performed if there are at least 10 patients in each subgroup level.
[a] = Number of patients with change from baseline used for MMRM analysis at each timepoint. [b] = Mean baseline for patients with change from baseline used for MMRM analysis at each timepoint. Treatment difference is calculated from a mixed model for repeated measures (MMRM) analysis of the change from baseline score with treatment, visit, and treatment by visit interaction as fixed effects, baseline score as a covariate and baseline score by visit interaction. Patient is used as random effect in the model. Only visits where change from baseline is available for at least 25% of patients in both treatment arms are included in the analysis. Autoregressive with heterogeneity covariance matrix is used to model within-subject error. If the MMRM model does not converge the model results are not presented. SMD = standardised mean difference. * p<0.05.
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Table 4.2.3.20 FLAURA-2: Summary of subgroup analysis of change from baseline in EORTC QLQ-LC13 Schmerzen in Armen oder Schultern (mixed model for repeated measures) - average over all visits
Full Analysis Set, DCO 03APR2023

	Osi + Chemo (N=279)			Osi (N=278)			Behandlungseffekt	
Subgruppen	n [a]	Ausgangswert MW (SD) [b]	Veränderung MW (SE)	n [a]	Ausgangswert MW (SD) [b]	Veränderung MW (SE)	MWD [95%-KI]	p-Wert
Geschlecht								
Maennlich	95	16,84 (21,123)	-5,30 (0,763)	94	18,09 (25,242)	-4,25 (0,824)	-1,05 [-3,252; 1,159]	0,3515
Hedges' g SMD							-0,14 [-0,421; 0,150]	0,3536
Weiblich	158	18,35 (22,744)	-2,78 (0,604)	157	19,32 (24,786)	-2,62 (0,608)	-0,16 [-1,837; 1,525]	0,8557
Hedges' g SMD							-0,02 [-0,241; 0,200]	0,8560
Int. p-Wert								0,7229
Nachweis der EGFR-Mutation durch zentralen ctDNA Cobas Test								
positiv	193	17,96 (20,966)	-4,63 (0,507)	193	19,86 (25,513)	-5,45 (0,520)	0,82 [-0,603; 2,247]	0,2578
Hedges' g SMD							0,12 [-0,085; 0,315]	0,2588
negativ	38	16,67 (27,672)	-0,12 (1,316)	33	10,10 (19,516)	2,62 (1,416)	-2,74 [-6,560; 1,088]	0,1599
Hedges' g SMD							-0,33 [-0,803; 0,137]	0,1646
unbekannt	22	18,18 (22,366)	-3,08 (1,987)	25	22,67 (24,944)	7,61 (2,067)	-10,69 [-16,371; -5,009]	0,0003*
Hedges' g SMD							-1,06 [-1,680; -0,449]	0,0007*
Int. p-Wert								<0,0001*
EGFR-Mutationstyp								
Exon 19 Deletion	154	16,67 (21,305)	-3,78 (0,624)	154	20,78 (27,237)	-3,67 (0,627)	-0,11 [-1,842; 1,631]	0,9052
Hedges' g SMD							-0,01 [-0,237; 0,210]	0,9054
Exon 21 (L858R) Substitutionsmutation	99	19,53 (23,333)	-3,78 (0,719)	95	15,79 (20,538)	-2,31 (0,790)	-1,47 [-3,570; 0,630]	0,1697
Hedges' g SMD							-0,20 [-0,479; 0,085]	0,1710
Int. p-Wert								0,2098
Zentral bestätigte EGFR-Mutation im Gewebe								
positiv	229	17,90 (21,958)	-3,82 (0,480)	219	18,42 (24,331)	-3,38 (0,507)	-0,44 [-1,812; 0,927]	0,5266
Hedges' g SMD							-0,06 [-0,245; 0,125]	0,5270
negativ	3	ID	ID	3	ID	ID	ID	ID
unbekannt	21	17,46 (24,987)	-5,03 (2,089)	29	22,99 (29,685)	-4,35 (1,719)	-0,68 [-6,044; 4,683]	0,8020
Hedges' g SMD							-0,07 [-0,633; 0,490]	0,8035

Analysis is performed if there are at least 10 patients in each subgroup level.
[a] = Number of patients with change from baseline used for MMRM analysis at each timepoint. [b] = Mean baseline for patients with change from baseline used for MMRM analysis at each timepoint. Treatment difference is calculated from a mixed model for repeated measures (MMRM) analysis of the change from baseline score with treatment, visit, and treatment by visit interaction as fixed effects, baseline score as a covariate and baseline score by visit interaction. Patient is used as random effect in the model. Only visits where change from baseline is available for at least 25% of patients in both treatment arms are included in the analysis. Autoregressive with heterogeneity covariance matrix is used to model within-subject error. If the MMRM model does not converge the model results are not presented. SMD = standardised mean difference. * p<0.05.
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Table 4.2.3.20 FLAURA-2: Summary of subgroup analysis of change from baseline in EORTC QLQ-LC13 Schmerzen in Armen oder Schultern (mixed model for repeated measures) - average over all visits
Full Analysis Set, DCO 03APR2023

	Osi + Chemo (N=279)			Osi (N=278)			Behandlungseffekt	
Subgruppen	n [a]	Ausgangswert MW (SD) [b]	Veränderung MW (SE)	n [a]	Ausgangswert MW (SD) [b]	Veränderung MW (SE)	MWD [95%-KI]	p-Wert
Int. p-Wert								0,6693
ZNS-Metastasen zur Baseline								
Ja	103	20,06 (21,562)	-4,82 (0,706)	101	19,47 (23,696)	-3,98 (0,783)	-0,85 [-2,918; 1,226]	0,4229
Hedges' g SMD							-0,11 [-0,387; 0,163]	0,4242
Nein	150	16,22 (22,431)	-2,91 (0,633)	150	18,44 (25,773)	-2,75 (0,628)	-0,17 [-1,916; 1,586]	0,8533
Hedges' g SMD							-0,02 [-0,248; 0,205]	0,8535
Int. p-Wert								0,7476
Zentrale Bestätigung der EGFR-Mutation								
Zentral bestätigte EGFR-Mutation in Gewebe oder ctDNA	241	17,98 (22,140)	-3,78 (0,478)	244	18,85 (25,115)	-3,43 (0,488)	-0,35 [-1,689; 0,991]	0,6097
Hedges' g SMD							-0,05 [-0,224; 0,132]	0,6104
Keine zentrale Bestätigung	12	NC	NC	7	NC	NC	NC	NC
Int. p-Wert								NC
Alter bei Screening								
<65 Jahre	158	19,83 (22,896)	-4,46 (0,605)	150	21,33 (24,510)	-5,31 (0,644)	0,86 [-0,877; 2,593]	0,3323
Hedges' g SMD							0,11 [-0,113; 0,334]	0,3331
>=65 Jahre	95	14,39 (20,428)	-2,37 (0,754)	101	15,18 (25,177)	0,14 (0,740)	-2,51 [-4,585; -0,436]	0,0178*
Hedges' g SMD							-0,34 [-0,620; -0,056]	0,0188*
Int. p-Wert								0,0257*
Region gPAP								
Asien	162	18,93 (21,302)	-3,64 (0,553)	161	19,67 (25,131)	-4,57 (0,571)	0,93 [-0,630; 2,490]	0,2422
Hedges' g SMD							0,13 [-0,088; 0,348]	0,2436
Europa	18	NC	NC	20	NC	NC	NC	NC
Nordamerika	17	19,61 (26,507)	-0,66 (2,115)	15	13,33 (21,082)	1,55 (2,041)	-2,20 [-8,063; 3,654]	0,4559
Hedges' g SMD							-0,26 [-0,955; 0,440]	0,4697
Rest der Welt	56	16,07 (24,611)	-5,25 (1,203)	55	16,97 (24,740)	0,50 (1,292)	-5,75 [-9,226; -2,271]	0,0013*

Analysis is performed if there are at least 10 patients in each subgroup level.
[a] = Number of patients with change from baseline used for MMRM analysis at each timepoint. [b] = Mean baseline for patients with change from baseline used for MMRM analysis at each timepoint. Treatment difference is calculated from a mixed model for repeated measures (MMRM) analysis of the change from baseline score with treatment, visit, and treatment by visit interaction as fixed effects, baseline score as a covariate and baseline score by visit interaction. Patient is used as random effect in the model. Only visits where change from baseline is available for at least 25% of patients in both treatment arms are included in the analysis. Autoregressive with heterogeneity covariance matrix is used to model within-subject error. If the MMRM model does not converge the model results are not presented. SMD = standardised mean difference. * p<0.05.
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Table 4.2.3.20 FLAURA-2: Summary of subgroup analysis of change from baseline in EORTC QLQ-LC13 Schmerzen in Armen oder Schultern (mixed model for repeated measures) - average over all visits
Full Analysis Set, DCO 03APR2023

	Osi + Chemo (N=279)			Osi (N=278)			Behandlungseffekt	
Subgruppen	n [a]	Ausgangswert MW (SD) [b]	Veränderung MW (SE)	n [a]	Ausgangswert MW (SD) [b]	Veränderung MW (SE)	MWD [95%-KI]	p-Wert
Hedges' g SMD							-0,61 [-0,995; -0,233]	0,0016*
Int. p-Wert								0,0058*

Analysis is performed if there are at least 10 patients in each subgroup level.
[a] = Number of patients with change from baseline used for MMRM analysis at each timepoint. [b] = Mean baseline for patients with change from baseline used for MMRM analysis at each timepoint. Treatment difference is calculated from a mixed model for repeated measures (MMRM) analysis of the change from baseline score with treatment, visit, and treatment by visit interaction as fixed effects, baseline score as a covariate and baseline score by visit interaction. Patient is used as random effect in the model. Only visits where change from baseline is available for at least 25% of patients in both treatment arms are included in the analysis. Autoregressive with heterogeneity covariance matrix is used to model within-subject error. If the MMRM model does not converge the model results are not presented. SMD = standardised mean difference. * p<0.05.
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Table 4.2.3.21 FLAURA-2: Summary of subgroup analysis of change from baseline in EORTC QLQ-LC13 Schmerzen in anderen Körperteilen (mixed model for repeated measures) - average over all visits
Full Analysis Set, DCO 03APR2023

	Osi + Chemo (N=279)			Osi (N=278)			Behandlungseffekt	
Subgruppen	n [a]	Ausgangswert MW (SD) [b]	Veränderung MW (SE)	n [a]	Ausgangswert MW (SD) [b]	Veränderung MW (SE)	MWD [95%-KI]	p-Wert
Abstammung								
Chinesisch/Asiatisch	66	17,17 (22,828)	-0,40 (0,799)	65	22,05 (27,812)	-2,38 (0,823)	1,98 [-0,274; 4,237]	0,0850
Hedges' g SMD							0,30 [-0,044; 0,645]	0,0877
Nicht-chinesisch/Asiatisch	103	23,30 (21,305)	-3,45 (0,658)	102	27,12 (26,835)	-5,35 (0,681)	1,90 [0,043; 3,765]	0,0449*
Hedges' g SMD							0,28 [0,005; 0,555]	0,0462*
Nicht-asiatisch	84	23,81 (26,672)	-3,66 (0,869)	84	30,95 (33,846)	-3,60 (0,904)	-0,06 [-2,526; 2,400]	0,9599
Hedges' g SMD							-0,01 [-0,310; 0,295]	0,9600
Int. p-Wert								0,5080
Methode zur Gewebeuntersuchung								
zentral	110	20,91 (22,961)	-2,25 (0,685)	114	21,64 (28,389)	-2,25 (0,681)	0,00 [-1,901; 1,894]	0,9970
Hedges' g SMD							0,00 [-0,262; 0,261]	0,9970
lokal	143	22,61 (24,258)	-3,10 (0,577)	137	31,63 (30,066)	-5,35 (0,615)	2,25 [0,587; 3,916]	0,0081*
Hedges' g SMD							0,32 [0,083; 0,555]	0,0081*
Int. p-Wert								0,0607
WHO Performance-Status								
0	93	16,49 (21,210)	1,26 (0,703)	93	21,86 (26,691)	-1,43 (0,708)	2,69 [0,726; 4,648]	0,0073*
Hedges' g SMD							0,39 [0,103; 0,684]	0,0079*
1	160	25,00 (24,515)	-5,14 (0,562)	158	30,17 (30,976)	-5,79 (0,590)	0,64 [-0,957; 2,243]	0,4306
Hedges' g SMD							0,09 [-0,132; 0,308]	0,4312
Int. p-Wert								0,2055
Raucherstatus								
Ja	83	21,69 (25,200)	-6,70 (0,679)	84	32,54 (33,122)	-6,70 (0,709)	0,00 [-1,934; 1,936]	0,9989
Hedges' g SMD							0,00 [-0,303; 0,304]	0,9989
Nein	170	21,96 (22,964)	-0,65 (0,565)	167	24,35 (27,487)	-2,80 (0,581)	2,15 [0,565; 3,745]	0,0079*
Hedges' g SMD							0,29 [0,074; 0,504]	0,0083*
Int. p-Wert								0,1647

Analysis is performed if there are at least 10 patients in each subgroup level.
[a] = Number of patients with change from baseline used for MMRM analysis at each timepoint. [b] = Mean baseline for patients with change from baseline used for MMRM analysis at each timepoint. Treatment difference is calculated from a mixed model for repeated measures (MMRM) analysis of the change from baseline score with treatment, visit, and treatment by visit interaction as fixed effects, baseline score as a covariate and baseline score by visit interaction. Patient is used as random effect in the model. Only visits where change from baseline is available for at least 25% of patients in both treatment arms are included in the analysis. Autoregressive with heterogeneity covariance matrix is used to model within-subject error. If the MMRM model does not converge the model results are not presented. SMD = standardised mean difference. * p<0.05.
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Table 4.2.3.21 FLAURA-2: Summary of subgroup analysis of change from baseline in EORTC QLQ-LC13 Schmerzen in anderen Körperteilen (mixed model for repeated measures) - average over all visits
Full Analysis Set, DCO 03APR2023

	Osi + Chemo (N=279)			Osi (N=278)			Behandlungseffekt	
Subgruppen	n [a]	Ausgangswert MW (SD) [b]	Veränderung MW (SE)	n [a]	Ausgangswert MW (SD) [b]	Veränderung MW (SE)	MWD [95%-KI]	p-Wert
Geschlecht								
Maennlich	95	20,70 (24,398)	-5,48 (0,665)	94	29,43 (30,471)	-5,22 (0,719)	-0,26 [-2,195; 1,669]	0,7891
Hedges' g SMD							-0,04 [-0,324; 0,246]	0,7887
Weiblich	158	22,57 (23,274)	-0,89 (0,575)	157	25,69 (29,204)	-3,26 (0,580)	2,36 [0,761; 3,964]	0,0039*
Hedges' g SMD							0,33 [0,103; 0,548]	0,0041*
Int. p-Wert								0,1005
Nachweis der EGFR-Mutation durch zentralen ctDNA Cobas Test								
positiv	193	22,80 (24,262)	-3,18 (0,489)	193	26,77 (30,096)	-5,16 (0,501)	1,98 [0,611; 3,358]	0,0047*
Hedges' g SMD							0,29 [0,087; 0,489]	0,0049*
negativ	38	19,30 (22,769)	-2,30 (1,174)	33	22,22 (23,074)	-2,84 (1,261)	0,54 [-2,856; 3,934]	0,7549
Hedges' g SMD							0,07 [-0,393; 0,540]	0,7571
unbekannt	22	18,18 (19,860)	1,64 (1,768)	25	36,00 (33,222)	4,22 (1,846)	-2,58 [-7,656; 2,495]	0,3165
Hedges' g SMD							-0,29 [-0,864; 0,288]	0,3270
Int. p-Wert								0,1859
EGFR-Mutationstyp								
Exon 19 Deletion	154	21,86 (23,916)	-0,89 (0,563)	154	25,76 (29,155)	-3,09 (0,566)	2,20 [0,632; 3,765]	0,0060*
Hedges' g SMD							0,31 [0,088; 0,538]	0,0063*
Exon 21 (L858R) Substitutionsmutation	99	21,89 (23,407)	-5,66 (0,706)	95	29,82 (30,548)	-5,54 (0,774)	-0,13 [-2,190; 1,938]	0,9049
Hedges' g SMD							-0,02 [-0,299; 0,264]	0,9047
Int. p-Wert								0,1624
Zentral bestätigte EGFR-Mutation im Gewebe								
positiv	229	22,71 (23,953)	-3,03 (0,453)	219	26,33 (28,941)	-4,34 (0,479)	1,31 [0,014; 2,602]	0,0476*
Hedges' g SMD							0,19 [0,002; 0,373]	0,0482*
negativ	3	ID	ID	3	ID	ID	ID	ID
unbekannt	21	12,70 (19,653)	2,94 (2,046)	29	33,33 (34,503)	-1,43 (1,647)	4,37 [-0,977; 9,711]	0,1085
Hedges' g SMD							0,47 [-0,097; 1,043]	0,1037

Analysis is performed if there are at least 10 patients in each subgroup level.
[a] = Number of patients with change from baseline used for MMRM analysis at each timepoint. [b] = Mean baseline for patients with change from baseline used for MMRM analysis at each timepoint. Treatment difference is calculated from a mixed model for repeated measures (MMRM) analysis of the change from baseline score with treatment, visit, and treatment by visit interaction as fixed effects, baseline score as a covariate and baseline score by visit interaction. Patient is used as random effect in the model. Only visits where change from baseline is available for at least 25% of patients in both treatment arms are included in the analysis. Autoregressive with heterogeneity covariance matrix is used to model within-subject error. If the MMRM model does not converge the model results are not presented. SMD = standardised mean difference. * p<0.05.
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Table 4.2.3.21 FLAURA-2: Summary of subgroup analysis of change from baseline in EORTC QLQ-LC13 Schmerzen in anderen Körperteilen (mixed model for repeated measures) - average over all visits
Full Analysis Set, DCO 03APR2023

	Osi + Chemo (N=279)			Osi (N=278)			Behandlungseffekt	
Subgruppen	n [a]	Ausgangswert MW (SD) [b]	Veränderung MW (SE)	n [a]	Ausgangswert MW (SD) [b]	Veränderung MW (SE)	MWD [95%-KI]	p-Wert
Int. p-Wert								0,4920
ZNS-Metastasen zur Baseline								
Ja	103	22,98 (22,880)	-3,40 (0,716)	101	30,36 (29,851)	-6,10 (0,788)	2,69 [0,595; 4,792]	0,0119*
Hedges' g SMD							0,35 [0,077; 0,630]	0,0123*
Nein	150	21,11 (24,246)	-2,15 (0,560)	150	24,89 (29,459)	-2,70 (0,555)	0,55 [-0,999; 2,095]	0,4872
Hedges' g SMD							0,08 [-0,146; 0,306]	0,4882
Int. p-Wert								0,0606
Zentrale Bestätigung der EGFR-Mutation								
Zentral bestätigte EGFR-Mutation in Gewebe oder ctDNA	241	22,27 (23,906)	-2,98 (0,441)	244	26,78 (29,518)	-4,18 (0,451)	1,19 [-0,046; 2,432]	0,0591
Hedges' g SMD							0,17 [-0,007; 0,350]	0,0597
Keine zentrale Bestätigung	12	NC	NC	7	NC	NC	NC	NC
Int. p-Wert								NC
Alter bei Screening								
<65 Jahre	158	23,21 (24,297)	-3,14 (0,543)	150	27,78 (28,488)	-6,88 (0,579)	3,74 [2,181; 5,299]	<0,0001*
Hedges' g SMD							0,54 [0,309; 0,764]	<0,0001*
>=65 Jahre	95	19,65 (22,542)	-1,76 (0,741)	101	26,07 (31,483)	0,50 (0,724)	-2,26 [-4,291; -0,222]	0,0298*
Hedges' g SMD							-0,31 [-0,592; -0,028]	0,0310*
Int. p-Wert								<0,0001*
Region gPAP								
Asien	162	20,37 (22,058)	-2,13 (0,519)	161	25,67 (27,950)	-4,13 (0,536)	2,00 [0,536; 3,468]	0,0075*
Hedges' g SMD							0,30 [0,079; 0,517]	0,0078*
Europa	18	27,78 (28,583)	-2,26 (2,006)	20	28,33 (34,666)	-1,39 (1,926)	-0,88 [-6,374; 4,622]	0,7526
Hedges' g SMD							-0,10 [-0,737; 0,537]	0,7581
Nordamerika	17	19,61 (20,612)	-1,29 (2,176)	15	28,89 (21,331)	-0,63 (2,177)	-0,66 [-6,905; 5,580]	0,8334
Hedges' g SMD							-0,07 [-0,769; 0,621]	0,8344

Analysis is performed if there are at least 10 patients in each subgroup level.
[a] = Number of patients with change from baseline used for MMRM analysis at each timepoint. [b] = Mean baseline for patients with change from baseline used for MMRM analysis at each timepoint. Treatment difference is calculated from a mixed model for repeated measures (MMRM) analysis of the change from baseline score with treatment, visit, and treatment by visit interaction as fixed effects, baseline score as a covariate and baseline score by visit interaction. Patient is used as random effect in the model. Only visits where change from baseline is available for at least 25% of patients in both treatment arms are included in the analysis. Autoregressive with heterogeneity covariance matrix is used to model within-subject error. If the MMRM model does not converge the model results are not presented. SMD = standardised mean difference. * p<0.05.
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Table 4.2.3.21 FLAURA-2: Summary of subgroup analysis of change from baseline in EORTC QLQ-LC13 Schmerzen in anderen Körperteilen (mixed model for repeated measures) - average over all visits
Full Analysis Set, DCO 03APR2023

	Osi + Chemo (N=279)			Osi (N=278)			Behandlungseffekt	
Subgruppen	n [a]	Ausgangswert MW (SD) [b]	Veränderung MW (SE)	n [a]	Ausgangswert MW (SD) [b]	Veränderung MW (SE)	MWD [95%-KI]	p-Wert
Rest der Welt	56	25,00 (27,155)	-4,89 (1,023)	55	30,30 (34,708)	-5,31 (1,098)	0,42 [-2,532; 3,365]	0,7814
Hedges' g SMD							0,05 [-0,320; 0,424]	0,7828
Int. p-Wert								0,7351

Analysis is performed if there are at least 10 patients in each subgroup level.
[a] = Number of patients with change from baseline used for MMRM analysis at each timepoint. [b] = Mean baseline for patients with change from baseline used for MMRM analysis at each timepoint. Treatment difference is calculated from a mixed model for repeated measures (MMRM) analysis of the change from baseline score with treatment, visit, and treatment by visit interaction as fixed effects, baseline score as a covariate and baseline score by visit interaction. Patient is used as random effect in the model. Only visits where change from baseline is available for at least 25% of patients in both treatment arms are included in the analysis. Autoregressive with heterogeneity covariance matrix is used to model within-subject error. If the MMRM model does not converge the model results are not presented. SMD = standardised mean difference. * p<0.05.
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Table 4.2.3.22 FLAURA-2: Summary of subgroup analysis of change from baseline in EORTC QLQ-LC13 Schmerzen in der Brust (mixed model for repeated measures) - average over all visits
Full Analysis Set, DCO 03APR2023

	Osi + Chemo (N=279)			Osi (N=278)			Behandlungseffekt	
Subgruppen	n [a]	Ausgangswert MW (SD) [b]	Veränderung MW (SE)	n [a]	Ausgangswert MW (SD) [b]	Veränderung MW (SE)	MWD [95%-KI]	p-Wert
Abstammung								
Chinesisch/Asiatisch	66	17,68 (20,439)	-7,00 (0,735)	65	18,97 (22,798)	-4,46 (0,761)	-2,54 [-4,618; -0,453]	0,0171*
Hedges' g SMD							-0,42 [-0,763; -0,070]	0,0185*
Nicht-chinesisch/Asiatisch	103	21,68 (21,241)	-7,29 (0,607)	102	21,90 (25,039)	-8,98 (0,627)	1,69 [-0,027; 3,398]	0,0536
Hedges' g SMD							0,27 [-0,006; 0,544]	0,0554
Nicht-asiatisch	84	10,32 (17,907)	-3,89 (0,687)	84	22,22 (28,024)	-3,58 (0,717)	-0,30 [-2,278; 1,675]	0,7645
Hedges' g SMD							-0,05 [-0,349; 0,256]	0,7625
Int. p-Wert								0,0394*
Methode zur Gewebeuntersuchung								
zentral	110	16,36 (21,055)	-4,57 (0,664)	114	21,05 (25,576)	-5,93 (0,659)	1,37 [-0,472; 3,207]	0,1447
Hedges' g SMD							0,19 [-0,068; 0,457]	0,1461
lokal	143	17,25 (20,114)	-7,26 (0,467)	137	21,41 (25,481)	-6,40 (0,498)	-0,86 [-2,207; 0,478]	0,2065
Hedges' g SMD							-0,15 [-0,386; 0,083]	0,2067
Int. p-Wert								0,0369*
WHO Performance-Status								
0	93	12,54 (18,333)	-5,82 (0,591)	93	19,71 (23,176)	-4,80 (0,596)	-1,03 [-2,686; 0,635]	0,2258
Hedges' g SMD							-0,18 [-0,466; 0,110]	0,2248
1	160	19,38 (21,303)	-6,35 (0,505)	158	22,15 (26,765)	-7,21 (0,530)	0,86 [-0,579; 2,296]	0,2416
Hedges' g SMD							0,13 [-0,089; 0,351]	0,2427
Int. p-Wert								0,0167*
Raucherstatus								
Ja	83	18,88 (20,948)	-8,44 (0,615)	84	19,05 (23,305)	-7,02 (0,641)	-1,41 [-3,157; 0,335]	0,1130
Hedges' g SMD							-0,24 [-0,549; 0,060]	0,1155
Nein	170	15,88 (20,256)	-5,04 (0,491)	167	22,36 (26,496)	-5,90 (0,505)	0,85 [-0,532; 2,241]	0,2268
Hedges' g SMD							0,13 [-0,082; 0,346]	0,2265
Int. p-Wert								0,0199*

Analysis is performed if there are at least 10 patients in each subgroup level.
[a] = Number of patients with change from baseline used for MMRM analysis at each timepoint. [b] = Mean baseline for patients with change from baseline used for MMRM analysis at each timepoint. Treatment difference is calculated from a mixed model for repeated measures (MMRM) analysis of the change from baseline score with treatment, visit, and treatment by visit interaction as fixed effects, baseline score as a covariate and baseline score by visit interaction. Patient is used as random effect in the model. Only visits where change from baseline is available for at least 25% of patients in both treatment arms are included in the analysis. Autoregressive with heterogeneity covariance matrix is used to model within-subject error. If the MMRM model does not converge the model results are not presented. SMD = standardised mean difference. * p<0.05.
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Table 4.2.3.22 FLAURA-2: Summary of subgroup analysis of change from baseline in EORTC QLQ-LC13 Schmerzen in der Brust (mixed model for repeated measures) - average over all visits
Full Analysis Set, DCO 03APR2023

	Osi + Chemo (N=279)			Osi (N=278)			Behandlungseffekt	
Subgruppen	n [a]	Ausgangswert MW (SD) [b]	Veränderung MW (SE)	n [a]	Ausgangswert MW (SD) [b]	Veränderung MW (SE)	MWD [95%-KI]	p-Wert
Geschlecht								
Maennlich	95	16,49 (20,556)	-7,17 (0,607)	94	19,86 (25,550)	-5,57 (0,656)	-1,60 [-3,355; 0,160]	0,0747
Hedges' g SMD							-0,26 [-0,545; 0,027]	0,0762
Weiblich	158	17,09 (20,516)	-5,48 (0,498)	157	22,08 (25,474)	-6,61 (0,502)	1,12 [-0,265; 2,515]	0,1126
Hedges' g SMD							0,18 [-0,042; 0,400]	0,1131
Int. p-Wert								0,0278*
Nachweis der EGFR-Mutation durch zentralen ctDNA Cobas Test								
positiv	193	17,27 (20,154)	-6,12 (0,443)	193	21,59 (25,005)	-7,05 (0,454)	0,93 [-0,319; 2,175]	0,1445
Hedges' g SMD							0,15 [-0,051; 0,348]	0,1448
negativ	38	15,79 (21,556)	-7,07 (0,917)	33	17,17 (23,748)	-3,78 (0,985)	-3,28 [-5,930; -0,631]	0,0154*
Hedges' g SMD							-0,57 [-1,050; -0,098]	0,0182*
unbekannt	22	15,15 (22,366)	-4,84 (1,512)	25	24,00 (31,210)	-2,78 (1,687)	-2,06 [-6,423; 2,308]	0,3529
Hedges' g SMD							-0,26 [-0,834; 0,317]	0,3793
Int. p-Wert								0,0066*
EGFR-Mutationstyp								
Exon 19 Deletion	154	17,10 (20,956)	-5,50 (0,500)	154	21,86 (25,389)	-6,90 (0,503)	1,40 [0,007; 2,791]	0,0489*
Hedges' g SMD							0,22 [0,000; 0,448]	0,0497*
Exon 21 (L858R) Substitutionsmutation	99	16,50 (19,848)	-7,29 (0,601)	95	20,35 (25,863)	-4,94 (0,657)	-2,35 [-4,113; -0,597]	0,0087*
Hedges' g SMD							-0,38 [-0,663; -0,095]	0,0089*
Int. p-Wert								0,0019*
Zentral bestätigte EGFR-Mutation im Gewebe								
positiv	229	16,89 (20,381)	-5,76 (0,410)	219	21,16 (25,015)	-6,00 (0,433)	0,24 [-0,935; 1,409]	0,6921
Hedges' g SMD							0,04 [-0,148; 0,223]	0,6918
negativ	3	ID	ID	3	ID	ID	ID	ID
unbekannt	21	17,46 (22,655)	-11,33 (1,336)	29	24,14 (29,408)	-9,80 (1,074)	-1,53 [-4,918; 1,853]	0,3730
Hedges' g SMD							-0,25 [-0,818; 0,310]	0,3765

Analysis is performed if there are at least 10 patients in each subgroup level.
[a] = Number of patients with change from baseline used for MMRM analysis at each timepoint. [b] = Mean baseline for patients with change from baseline used for MMRM analysis at each timepoint. Treatment difference is calculated from a mixed model for repeated measures (MMRM) analysis of the change from baseline score with treatment, visit, and treatment by visit interaction as fixed effects, baseline score as a covariate and baseline score by visit interaction. Patient is used as random effect in the model. Only visits where change from baseline is available for at least 25% of patients in both treatment arms are included in the analysis. Autoregressive with heterogeneity covariance matrix is used to model within-subject error. If the MMRM model does not converge the model results are not presented. SMD = standardised mean difference. * p<0.05.
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Table 4.2.3.22 FLAURA-2: Summary of subgroup analysis of change from baseline in EORTC QLQ-LC13 Schmerzen in der Brust (mixed model for repeated measures) - average over all visits
Full Analysis Set, DCO 03APR2023

	Osi + Chemo (N=279)			Osi (N=278)			Behandlungseffekt	
Subgruppen	n [a]	Ausgangswert MW (SD) [b]	Veränderung MW (SE)	n [a]	Ausgangswert MW (SD) [b]	Veränderung MW (SE)	MWD [95%-KI]	p-Wert
Int. p-Wert								0,4990
ZNS-Metastasen zur Baseline								
Ja	103	19,09 (21,186)	-6,62 (0,575)	101	17,49 (22,407)	-5,45 (0,644)	-1,17 [-2,864; 0,527]	0,1765
Hedges' g SMD							-0,19 [-0,464; 0,086]	0,1782
Nein	150	15,33 (19,929)	-5,62 (0,516)	150	23,78 (27,126)	-6,86 (0,510)	1,24 [-0,192; 2,671]	0,0897
Hedges' g SMD							0,20 [-0,030; 0,424]	0,0891
Int. p-Wert								0,0334*
Zentrale Bestätigung der EGFR-Mutation								
Zentral bestätigte EGFR-Mutation in Gewebe oder ctDNA	241	16,74 (20,213)	-6,01 (0,399)	244	21,31 (25,505)	-6,19 (0,408)	0,18 [-0,941; 1,300]	0,7535
Hedges' g SMD							0,03 [-0,149; 0,207]	0,7534
Keine zentrale Bestätigung	12	NC	NC	7	NC	NC	NC	NC
Int. p-Wert								NC
Alter bei Screening								
<65 Jahre	158	17,72 (20,836)	-6,54 (0,505)	150	25,11 (27,290)	-8,43 (0,539)	1,89 [0,434; 3,346]	0,0110*
Hedges' g SMD							0,29 [0,067; 0,516]	0,0110*
>=65 Jahre	95	15,44 (19,935)	-5,55 (0,598)	101	15,51 (21,377)	-2,73 (0,586)	-2,82 [-4,462; -1,175]	0,0008*
Hedges' g SMD							-0,48 [-0,763; -0,195]	0,0010*
Int. p-Wert								<0,0001*
Region gPAP								
Asien	162	19,55 (20,567)	-6,94 (0,483)	161	20,70 (24,422)	-6,90 (0,498)	-0,04 [-1,402; 1,321]	0,9534
Hedges' g SMD							-0,01 [-0,225; 0,212]	0,9535
Europa	18	NC	NC	20	NC	NC	NC	NC
Nordamerika	17	13,73 (23,743)	-12,40 (1,614)	15	33,33 (30,861)	-13,62 (1,650)	1,22 [-3,538; 5,975]	0,6126
Hedges' g SMD							0,18 [-0,514; 0,878]	0,6086
Rest der Welt	56	9,52 (17,655)	-2,59 (0,830)	55	21,21 (28,948)	-2,72 (0,890)	0,12 [-2,287; 2,534]	0,9198

Analysis is performed if there are at least 10 patients in each subgroup level.
[a] = Number of patients with change from baseline used for MMRM analysis at each timepoint. [b] = Mean baseline for patients with change from baseline used for MMRM analysis at each timepoint. Treatment difference is calculated from a mixed model for repeated measures (MMRM) analysis of the change from baseline score with treatment, visit, and treatment by visit interaction as fixed effects, baseline score as a covariate and baseline score by visit interaction. Patient is used as random effect in the model. Only visits where change from baseline is available for at least 25% of patients in both treatment arms are included in the analysis. Autoregressive with heterogeneity covariance matrix is used to model within-subject error. If the MMRM model does not converge the model results are not presented. SMD = standardised mean difference. * p<0.05.
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Table 4.2.3.22 FLAURA-2: Summary of subgroup analysis of change from baseline in EORTC QLQ-LC13 Schmerzen in der Brust (mixed model for repeated measures) - average over all visits
Full Analysis Set, DCO 03APR2023

	Osi + Chemo (N=279)			Osi (N=278)			Behandlungseffekt	
Subgruppen	n [a]	Ausgangswert MW (SD) [b]	Veränderung MW (SE)	n [a]	Ausgangswert MW (SD) [b]	Veränderung MW (SE)	MWD [95%-KI]	p-Wert
Hedges' g SMD							0,02 [-0,353; 0,391]	0,9197
Int. p-Wert								0,7664

Analysis is performed if there are at least 10 patients in each subgroup level.
[a] = Number of patients with change from baseline used for MMRM analysis at each timepoint. [b] = Mean baseline for patients with change from baseline used for MMRM analysis at each timepoint. Treatment difference is calculated from a mixed model for repeated measures (MMRM) analysis of the change from baseline score with treatment, visit, and treatment by visit interaction as fixed effects, baseline score as a covariate and baseline score by visit interaction. Patient is used as random effect in the model. Only visits where change from baseline is available for at least 25% of patients in both treatment arms are included in the analysis. Autoregressive with heterogeneity covariance matrix is used to model within-subject error. If the MMRM model does not converge the model results are not presented. SMD = standardised mean difference. * p<0.05.
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Table 4.2.3.23 FLAURA-2: Summary of subgroup analysis of change from baseline in EORTC QLQ-LC13 Wunder Mund (mixed model for repeated measures) - average over all visits
Full Analysis Set, DCO 03APR2023

	Osi + Chemo (N=279)			Osi (N=278)			Behandlungseffekt	
Subgruppen	n [a]	Ausgangswert MW (SD) [b]	Veränderung MW (SE)	n [a]	Ausgangswert MW (SD) [b]	Veränderung MW (SE)	MWD [95%-KI]	p-Wert
Abstammung								
Chinesisch/Asiatisch	66	2,02 (8,014)	13,72 (0,936)	65	4,10 (11,036)	9,05 (0,965)	4,68 [2,021; 7,330]	0,0006*
Hedges' g SMD							0,60 [0,254; 0,955]	0,0007*
Nicht-chinesisch/Asiatisch	103	6,15 (15,302)	11,01 (0,711)	102	6,21 (16,736)	10,82 (0,732)	0,19 [-1,813; 2,193]	0,8524
Hedges' g SMD							0,03 [-0,248; 0,300]	0,8529
Nicht-asiatisch	84	2,38 (10,068)	9,74 (0,739)	84	3,57 (14,652)	5,87 (0,767)	3,87 [1,780; 5,968]	0,0003*
Hedges' g SMD							0,56 [0,250; 0,867]	0,0004*
Int. p-Wert								0,0151*
Methode zur Gewebeuntersuchung								
zentral	110	4,24 (13,628)	10,84 (0,719)	114	4,09 (14,122)	8,42 (0,711)	2,41 [0,430; 4,398]	0,0172*
Hedges' g SMD							0,32 [0,054; 0,582]	0,0181*
lokal	143	3,50 (10,987)	11,85 (0,598)	137	5,35 (15,250)	9,24 (0,635)	2,60 [0,885; 4,316]	0,0030*
Hedges' g SMD							0,36 [0,119; 0,592]	0,0032*
Int. p-Wert								0,7179
WHO Performance-Status								
0	93	2,15 (9,589)	12,24 (0,729)	93	4,30 (15,716)	11,21 (0,733)	1,04 [-0,996; 3,072]	0,3166
Hedges' g SMD							0,15 [-0,141; 0,435]	0,3177
1	160	4,79 (13,400)	10,85 (0,594)	158	5,06 (14,166)	7,21 (0,622)	3,64 [1,949; 5,323]	<0,0001*
Hedges' g SMD							0,47 [0,250; 0,696]	<0,0001*
Int. p-Wert								0,0272*
Raucherstatus								
Ja	83	1,61 (7,183)	10,98 (0,799)	84	4,37 (16,989)	9,83 (0,824)	1,15 [-1,108; 3,414]	0,3169
Hedges' g SMD							0,15 [-0,149; 0,459]	0,3182
Nein	170	4,90 (13,885)	11,56 (0,561)	167	4,99 (13,507)	8,39 (0,577)	3,17 [1,591; 4,750]	<0,0001*
Hedges' g SMD							0,43 [0,212; 0,644]	0,0001*
Int. p-Wert								0,2536

Analysis is performed if there are at least 10 patients in each subgroup level.
[a] = Number of patients with change from baseline used for MMRM analysis at each timepoint. [b] = Mean baseline for patients with change from baseline used for MMRM analysis at each timepoint. Treatment difference is calculated from a mixed model for repeated measures (MMRM) analysis of the change from baseline score with treatment, visit, and treatment by visit interaction as fixed effects, baseline score as a covariate and baseline score by visit interaction. Patient is used as random effect in the model. Only visits where change from baseline is available for at least 25% of patients in both treatment arms are included in the analysis. Autoregressive with heterogeneity covariance matrix is used to model within-subject error. If the MMRM model does not converge the model results are not presented. SMD = standardised mean difference. * p<0.05.
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Table 4.2.3.23 FLAURA-2: Summary of subgroup analysis of change from baseline in EORTC QLQ-LC13 Wunder Mund (mixed model for repeated measures) - average over all visits
Full Analysis Set, DCO 03APR2023

	Osi + Chemo (N=279)			Osi (N=278)			Behandlungseffekt	
Subgruppen	n [a]	Ausgangswert MW (SD) [b]	Veränderung MW (SE)	n [a]	Ausgangswert MW (SD) [b]	Veränderung MW (SE)	MWD [95%-KI]	p-Wert
Geschlecht								
Maennlich	95	2,46 (8,755)	9,40 (0,651)	94	4,26 (14,854)	7,90 (0,703)	1,50 [-0,385; 3,387]	0,1186
Hedges' g SMD							0,23 [-0,059; 0,513]	0,1197
Weiblich	158	4,64 (13,807)	12,53 (0,613)	157	5,10 (14,698)	9,40 (0,616)	3,13 [1,425; 4,834]	0,0003*
Hedges' g SMD							0,40 [0,182; 0,628]	0,0004*
Int. p-Wert								0,4781
Nachweis der EGFR-Mutation durch zentralen ctDNA Cobas Test								
positiv	193	4,32 (13,124)	11,85 (0,510)	193	4,15 (13,397)	7,99 (0,521)	3,86 [2,434; 5,293]	<0,0001*
Hedges' g SMD							0,54 [0,336; 0,742]	<0,0001*
negativ	38	2,63 (9,109)	11,76 (1,392)	33	6,06 (15,489)	13,92 (1,499)	-2,16 [-6,208; 1,887]	0,2940
Hedges' g SMD							-0,25 [-0,717; 0,220]	0,2980
unbekannt	22	1,52 (7,107)	, (,)	25	8,00 (22,111)	, (,)	1,42 [-2,566; 5,409]	0,4826
Hedges' g SMD							, [, ; ,]	
Int. p-Wert								0,0009*
EGFR-Mutationstyp								
Exon 19 Deletion	154	4,98 (13,626)	12,13 (0,570)	154	3,46 (11,540)	8,58 (0,572)	3,55 [1,964; 5,137]	<0,0001*
Hedges' g SMD							0,50 [0,273; 0,726]	<0,0001*
Exon 21 (L858R) Substitutionsmutation	99	2,02 (9,305)	10,05 (0,790)	95	7,02 (18,765)	9,43 (0,862)	0,62 [-1,702; 2,951]	0,5983
Hedges' g SMD							0,08 [-0,205; 0,358]	0,5942
Int. p-Wert								0,0253*
Zentral bestätigte EGFR-Mutation im Gewebe								
positiv	229	4,22 (12,744)	11,38 (0,485)	219	4,72 (15,079)	9,48 (0,510)	1,90 [0,518; 3,280]	0,0071*
Hedges' g SMD							0,25 [0,069; 0,441]	0,0073*
negativ	3	ID	ID	3	ID	ID	ID	ID
unbekannt	21	0,00 (0,000)	8,87 (1,660)	29	5,75 (12,814)	5,24 (1,322)	3,63 [-0,655; 7,909]	0,0963
Hedges' g SMD							0,49 [-0,083; 1,058]	0,0940

Analysis is performed if there are at least 10 patients in each subgroup level.
[a] = Number of patients with change from baseline used for MMRM analysis at each timepoint. [b] = Mean baseline for patients with change from baseline used for MMRM analysis at each timepoint. Treatment difference is calculated from a mixed model for repeated measures (MMRM) analysis of the change from baseline score with treatment, visit, and treatment by visit interaction as fixed effects, baseline score as a covariate and baseline score by visit interaction. Patient is used as random effect in the model. Only visits where change from baseline is available for at least 25% of patients in both treatment arms are included in the analysis. Autoregressive with heterogeneity covariance matrix is used to model within-subject error. If the MMRM model does not converge the model results are not presented. SMD = standardised mean difference. * p<0.05.
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Table 4.2.3.23 FLAURA-2: Summary of subgroup analysis of change from baseline in EORTC QLQ-LC13 Wunder Mund (mixed model for repeated measures) - average over all visits
Full Analysis Set, DCO 03APR2023

	Osi + Chemo (N=279)			Osi (N=278)			Behandlungseffekt	
Subgruppen	n [a]	Ausgangswert MW (SD) [b]	Veränderung MW (SE)	n [a]	Ausgangswert MW (SD) [b]	Veränderung MW (SE)	MWD [95%-KI]	p-Wert
Int. p-Wert								0,0470*
ZNS-Metastasen zur Baseline								
Ja	103	4,21 (12,935)	11,58 (0,768)	101	4,95 (15,192)	7,60 (0,836)	3,98 [1,751; 6,211]	0,0005*
Hedges' g SMD							0,49 [0,211; 0,768]	0,0006*
Nein	150	3,56 (11,680)	11,29 (0,573)	150	4,67 (14,465)	9,57 (0,567)	1,72 [0,141; 3,308]	0,0328*
Hedges' g SMD							0,25 [0,019; 0,473]	0,0336*
Int. p-Wert								0,0564
Zentrale Bestätigung der EGFR-Mutation								
Zentral bestätigte EGFR-Mutation in Gewebe oder ctDNA	241	4,01 (12,456)	11,51 (0,472)	244	4,64 (14,701)	9,06 (0,481)	2,44 [1,122; 3,766]	0,0003*
Hedges' g SMD							0,33 [0,150; 0,508]	0,0003*
Keine zentrale Bestätigung	12	NC	NC	7	NC	NC	NC	NC
Int. p-Wert								NC
Alter bei Screening								
<65 Jahre	158	4,22 (12,888)	11,10 (0,539)	150	4,67 (13,940)	7,99 (0,573)	3,11 [1,567; 4,655]	<0,0001*
Hedges' g SMD							0,45 [0,224; 0,676]	<0,0001*
>=65 Jahre	95	3,16 (10,952)	12,02 (0,840)	101	4,95 (15,907)	10,12 (0,819)	1,90 [-0,409; 4,209]	0,1066
Hedges' g SMD							0,23 [-0,051; 0,512]	0,1081
Int. p-Wert								0,2745
Region gPAP								
Asien	162	4,73 (13,327)	12,43 (0,577)	161	5,18 (14,700)	10,13 (0,593)	2,30 [0,679; 3,926]	0,0055*
Hedges' g SMD							0,31 [0,090; 0,528]	0,0058*
Europa	18	NC	NC	20	NC	NC	NC	NC
Nordamerika	17	NC	NC	15	NC	NC	NC	NC
Rest der Welt	56	2,98 (11,506)	9,03 (0,941)	55	4,85 (17,472)	7,56 (0,998)	1,48 [-1,223; 4,177]	0,2827

Analysis is performed if there are at least 10 patients in each subgroup level.
[a] = Number of patients with change from baseline used for MMRM analysis at each timepoint. [b] = Mean baseline for patients with change from baseline used for MMRM analysis at each timepoint. Treatment difference is calculated from a mixed model for repeated measures (MMRM) analysis of the change from baseline score with treatment, visit, and treatment by visit interaction as fixed effects, baseline score as a covariate and baseline score by visit interaction. Patient is used as random effect in the model. Only visits where change from baseline is available for at least 25% of patients in both treatment arms are included in the analysis. Autoregressive with heterogeneity covariance matrix is used to model within-subject error. If the MMRM model does not converge the model results are not presented. SMD = standardised mean difference. * p<0.05.
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Table 4.2.3.23 FLAURA-2: Summary of subgroup analysis of change from baseline in EORTC QLQ-LC13 Wunder Mund (mixed model for repeated measures) - average over all visits
Full Analysis Set, DCO 03APR2023

	Osi + Chemo (N=279)			Osi (N=278)			Behandlungseffekt	
Subgruppen	n [a]	Ausgangswert MW (SD) [b]	Veränderung MW (SE)	n [a]	Ausgangswert MW (SD) [b]	Veränderung MW (SE)	MWD [95%-KI]	p-Wert
Hedges' g SMD							0,20 [-0,170; 0,576]	0,2859
Int. p-Wert								0,4256

Analysis is performed if there are at least 10 patients in each subgroup level.
[a] = Number of patients with change from baseline used for MMRM analysis at each timepoint. [b] = Mean baseline for patients with change from baseline used for MMRM analysis at each timepoint. Treatment difference is calculated from a mixed model for repeated measures (MMRM) analysis of the change from baseline score with treatment, visit, and treatment by visit interaction as fixed effects, baseline score as a covariate and baseline score by visit interaction. Patient is used as random effect in the model. Only visits where change from baseline is available for at least 25% of patients in both treatment arms are included in the analysis. Autoregressive with heterogeneity covariance matrix is used to model within-subject error. If the MMRM model does not converge the model results are not presented. SMD = standardised mean difference. * p<0.05.
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Table 4.2.3.24 FLAURA-2: Summary of subgroup analysis of change from baseline in EORTC QLQ-LC13 Dyspnoe (mixed model for repeated measures) - average over all visits
Full Analysis Set, DCO 03APR2023

	Osi + Chemo (N=279)			Osi (N=278)			Behandlungseffekt	
Subgruppen	n [a]	Ausgangswert MW (SD) [b]	Veränderung MW (SE)	n [a]	Ausgangswert MW (SD) [b]	Veränderung MW (SE)	MWD [95%-KI]	p-Wert
Abstammung								
Chinesisch/Asiatisch	66	21,38 (16,109)	-3,02 (0,943)	65	20,51 (18,658)	-1,98 (0,965)	-1,04 [-3,697; 1,612]	0,4401
Hedges' g SMD							-0,13 [-0,477; 0,209]	0,4428
Nicht-chinesisch/Asiatisch	103	22,76 (20,069)	-1,38 (0,759)	102	23,75 (23,559)	-4,79 (0,774)	3,41 [1,282; 5,542]	0,0018*
Hedges' g SMD							0,44 [0,161; 0,715]	0,0019*
Nicht-asiatisch	84	26,19 (24,001)	-5,63 (1,033)	84	35,05 (26,748)	-8,50 (1,053)	2,87 [-0,053; 5,795]	0,0543
Hedges' g SMD							0,30 [-0,005; 0,603]	0,0541
Int. p-Wert								0,0235*
Methode zur Gewebeuntersuchung								
zentral	110	22,63 (20,412)	-2,29 (0,729)	114	24,37 (22,990)	-4,82 (0,721)	2,52 [0,510; 4,537]	0,0141*
Hedges' g SMD							0,33 [0,064; 0,591]	0,0149*
lokal	143	24,24 (20,751)	-3,60 (0,725)	137	28,63 (25,162)	-5,39 (0,761)	1,79 [-0,281; 3,855]	0,0902
Hedges' g SMD							0,20 [-0,032; 0,438]	0,0905
Int. p-Wert								0,6794
WHO Performance-Status								
0	93	16,85 (18,434)	-0,57 (0,699)	93	19,35 (20,781)	-1,75 (0,703)	1,19 [-0,761; 3,136]	0,2316
Hedges' g SMD							0,17 [-0,113; 0,463]	0,2337
1	160	27,43 (20,812)	-4,80 (0,701)	158	31,01 (25,146)	-7,27 (0,724)	2,48 [0,499; 4,458]	0,0142*
Hedges' g SMD							0,28 [0,054; 0,496]	0,0145*
Int. p-Wert								0,2510
Raucherstatus								
Ja	83	21,69 (18,356)	-1,13 (0,888)	84	22,75 (21,397)	-3,64 (0,908)	2,51 [0,013; 5,007]	0,0489*
Hedges' g SMD							0,30 [-0,001; 0,610]	0,0505
Nein	170	24,44 (21,575)	-3,95 (0,639)	167	28,68 (25,388)	-5,80 (0,653)	1,85 [0,051; 3,641]	0,0438*
Hedges' g SMD							0,22 [0,005; 0,434]	0,0444*
Int. p-Wert								0,6772

Analysis is performed if there are at least 10 patients in each subgroup level.
[a] = Number of patients with change from baseline used for MMRM analysis at each timepoint. [b] = Mean baseline for patients with change from baseline used for MMRM analysis at each timepoint. Treatment difference is calculated from a mixed model for repeated measures (MMRM) analysis of the change from baseline score with treatment, visit, and treatment by visit interaction as fixed effects, baseline score as a covariate and baseline score by visit interaction. Patient is used as random effect in the model. Only visits where change from baseline is available for at least 25% of patients in both treatment arms are included in the analysis. Autoregressive with heterogeneity covariance matrix is used to model within-subject error. If the MMRM model does not converge the model results are not presented. SMD = standardised mean difference. * p<0.05.
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Table 4.2.3.24 FLAURA-2: Summary of subgroup analysis of change from baseline in EORTC QLQ-LC13 Dyspnoe (mixed model for repeated measures) - average over all visits
Full Analysis Set, DCO 03APR2023

	Osi + Chemo (N=279)			Osi (N=278)			Behandlungseffekt	
Subgruppen	n [a]	Ausgangswert MW (SD) [b]	Veränderung MW (SE)	n [a]	Ausgangswert MW (SD) [b]	Veränderung MW (SE)	MWD [95%-KI]	p-Wert
Geschlecht								
Maennlich	95	20,94 (20,747)	-0,97 (0,849)	94	23,64 (24,181)	-3,83 (0,902)	2,85 [0,420; 5,289]	0,0217*
Hedges' g SMD							0,33 [0,047; 0,621]	0,0226*
Weiblich	158	25,11 (20,383)	-4,27 (0,653)	157	28,52 (24,176)	-5,80 (0,654)	1,53 [-0,288; 3,346]	0,0990
Hedges' g SMD							0,19 [-0,035; 0,407]	0,0996
Int. p-Wert								0,4030
Nachweis der EGFR-Mutation durch zentralen ctDNA Cobas Test								
positiv	193	24,58 (21,098)	-4,10 (0,588)	193	27,58 (24,325)	-6,48 (0,595)	2,38 [0,736; 4,018]	0,0046*
Hedges' g SMD							0,29 [0,088; 0,489]	0,0048*
negativ	38	19,59 (17,978)	0,26 (1,367)	33	24,58 (24,808)	-1,01 (1,472)	1,27 [-2,715; 5,250]	0,5302
Hedges' g SMD							0,15 [-0,318; 0,616]	0,5330
unbekannt	22	21,21 (19,967)	0,27 (1,897)	25	22,67 (23,236)	0,57 (1,993)	-0,29 [-5,744; 5,156]	0,9148
Hedges' g SMD							-0,03 [-0,603; 0,542]	0,9169
Int. p-Wert								0,7644
EGFR-Mutationstyp								
Exon 19 Deletion	154	26,41 (21,969)	-2,81 (0,676)	154	25,32 (23,303)	-6,51 (0,674)	3,70 [1,830; 5,578]	0,0001*
Hedges' g SMD							0,44 [0,215; 0,667]	0,0001*
Exon 21 (L858R) Substitutionsmutation	99	19,08 (17,391)	-3,43 (0,798)	95	29,24 (25,731)	-2,68 (0,860)	-0,74 [-3,070; 1,580]	0,5292
Hedges' g SMD							-0,09 [-0,373; 0,191]	0,5268
Int. p-Wert								0,0055*
Zentral bestätigte EGFR-Mutation im Gewebe								
positiv	229	23,87 (20,669)	-3,28 (0,529)	219	26,13 (23,145)	-4,94 (0,553)	1,66 [0,158; 3,160]	0,0304*
Hedges' g SMD							0,20 [0,019; 0,390]	0,0308*
negativ	3	ID	ID	3	ID	ID	ID	ID
unbekannt	21	21,16 (19,533)	1,75 (2,282)	29	27,97 (30,082)	-7,40 (1,878)	9,15 [3,233; 15,058]	0,0028*
Hedges' g SMD							0,88 [0,288; 1,467]	0,0035*

Analysis is performed if there are at least 10 patients in each subgroup level.
[a] = Number of patients with change from baseline used for MMRM analysis at each timepoint. [b] = Mean baseline for patients with change from baseline used for MMRM analysis at each timepoint. Treatment difference is calculated from a mixed model for repeated measures (MMRM) analysis of the change from baseline score with treatment, visit, and treatment by visit interaction as fixed effects, baseline score as a covariate and baseline score by visit interaction. Patient is used as random effect in the model. Only visits where change from baseline is available for at least 25% of patients in both treatment arms are included in the analysis. Autoregressive with heterogeneity covariance matrix is used to model within-subject error. If the MMRM model does not converge the model results are not presented. SMD = standardised mean difference. * p<0.05.
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Table 4.2.3.24 FLAURA-2: Summary of subgroup analysis of change from baseline in EORTC QLQ-LC13 Dyspnoe (mixed model for repeated measures) - average over all visits
Full Analysis Set, DCO 03APR2023

	Osi + Chemo (N=279)			Osi (N=278)			Behandlungseffekt	
Subgruppen	n [a]	Ausgangswert MW (SD) [b]	Veränderung MW (SE)	n [a]	Ausgangswert MW (SD) [b]	Veränderung MW (SE)	MWD [95%-KI]	p-Wert
Int. p-Wert								0,0014*
ZNS-Metastasen zur Baseline								
Ja	103	25,24 (21,848)	-4,91 (0,777)	101	28,49 (24,110)	-5,67 (0,836)	0,75 [-1,495; 2,998]	0,5111
Hedges' g SMD							0,09 [-0,183; 0,367]	0,5116
Nein	150	22,37 (19,649)	-1,79 (0,700)	150	25,48 (24,341)	-4,65 (0,694)	2,86 [0,927; 4,796]	0,0038*
Hedges' g SMD							0,33 [0,107; 0,562]	0,0040*
Int. p-Wert								0,0941
Zentrale Bestätigung der EGFR-Mutation								
Zentral bestätigte EGFR-Mutation in Gewebe oder ctDNA	241	23,97 (20,762)	-3,38 (0,514)	244	26,50 (23,958)	-5,39 (0,520)	2,00 [0,569; 3,438]	0,0062*
Hedges' g SMD							0,25 [0,070; 0,427]	0,0064*
Keine zentrale Bestätigung	12	NC	NC	7	NC	NC	NC	NC
Int. p-Wert								NC
Alter bei Screening								
<65 Jahre	158	24,82 (21,140)	-5,53 (0,616)	150	26,37 (24,273)	-7,13 (0,647)	1,60 [-0,158; 3,352]	0,0744
Hedges' g SMD							0,20 [-0,021; 0,427]	0,0753
>=65 Jahre	95	21,40 (19,532)	1,51 (0,916)	101	27,17 (24,317)	-1,90 (0,892)	3,41 [0,885; 5,942]	0,0083*
Hedges' g SMD							0,38 [0,097; 0,663]	0,0084*
Int. p-Wert								0,1900
Region gPAP								
Asien	162	21,60 (18,504)	-1,87 (0,599)	161	22,91 (21,861)	-3,62 (0,611)	1,75 [0,072; 3,432]	0,0410*
Hedges' g SMD							0,23 [0,008; 0,446]	0,0418*
Europa	18	29,01 (23,536)	-3,50 (2,132)	20	30,56 (24,149)	-5,55 (2,028)	2,05 [-3,883; 7,986]	0,4928
Hedges' g SMD							0,22 [-0,417; 0,861]	0,4964
Nordamerika	17	35,29 (20,501)	-1,66 (3,264)	15	29,63 (22,090)	-8,24 (3,396)	6,58 [-2,920; 16,084]	0,1702
Hedges' g SMD							0,48 [-0,224; 1,187]	0,1808

Analysis is performed if there are at least 10 patients in each subgroup level.
[a] = Number of patients with change from baseline used for MMRM analysis at each timepoint. [b] = Mean baseline for patients with change from baseline used for MMRM analysis at each timepoint. Treatment difference is calculated from a mixed model for repeated measures (MMRM) analysis of the change from baseline score with treatment, visit, and treatment by visit interaction as fixed effects, baseline score as a covariate and baseline score by visit interaction. Patient is used as random effect in the model. Only visits where change from baseline is available for at least 25% of patients in both treatment arms are included in the analysis. Autoregressive with heterogeneity covariance matrix is used to model within-subject error. If the MMRM model does not converge the model results are not presented. SMD = standardised mean difference. * p<0.05.
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Table 4.2.3.24 FLAURA-2: Summary of subgroup analysis of change from baseline in EORTC QLQ-LC13 Dyspnoe (mixed model for repeated measures) - average over all visits
Full Analysis Set, DCO 03APR2023

	Osi + Chemo (N=279)			Osi (N=278)			Behandlungseffekt	
Subgruppen	n [a]	Ausgangswert MW (SD) [b]	Veränderung MW (SE)	n [a]	Ausgangswert MW (SD) [b]	Veränderung MW (SE)	MWD [95%-KI]	p-Wert
Rest der Welt	56	23,81 (24,105)	-7,26 (1,174)	55	35,56 (29,037)	-8,45 (1,237)	1,19 [-2,194; 4,583]	0,4879
Hedges' g SMD							0,13 [-0,240; 0,505]	0,4870
Int. p-Wert								0,4439

Analysis is performed if there are at least 10 patients in each subgroup level.
[a] = Number of patients with change from baseline used for MMRM analysis at each timepoint. [b] = Mean baseline for patients with change from baseline used for MMRM analysis at each timepoint. Treatment difference is calculated from a mixed model for repeated measures (MMRM) analysis of the change from baseline score with treatment, visit, and treatment by visit interaction as fixed effects, baseline score as a covariate and baseline score by visit interaction. Patient is used as random effect in the model. Only visits where change from baseline is available for at least 25% of patients in both treatment arms are included in the analysis. Autoregressive with heterogeneity covariance matrix is used to model within-subject error. If the MMRM model does not converge the model results are not presented. SMD = standardised mean difference. * p<0.05.
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Table 4.2.3.25 FLAURA-2: Summary of subgroup analysis of change from baseline in EORTC QLQ-LC13 Periphere Neuropathie (mixed model for repeated measures) - average over all visits
Full Analysis Set, DCO 03APR2023

	Osi + Chemo (N=279)			Osi (N=278)			Behandlungseffekt	
Subgruppen	n [a]	Ausgangswert MW (SD) [b]	Veränderung MW (SE)	n [a]	Ausgangswert MW (SD) [b]	Veränderung MW (SE)	MWD [95%-KI]	p-Wert
Abstammung								
Chinesisch/Asiatisch	66	6,06 (14,213)	7,29 (0,847)	65	3,08 (11,370)	7,65 (0,873)	-0,36 [-2,764; 2,036]	0,7658
Hedges' g SMD							-0,05 [-0,395; 0,291]	0,7662
Nicht-chinesisch/Asiatisch	103	8,41 (17,907)	11,50 (0,814)	102	8,17 (17,194)	7,93 (0,837)	3,57 [1,280; 5,867]	0,0023*
Hedges' g SMD							0,43 [0,149; 0,703]	0,0026*
Nicht-asiatisch	84	8,33 (17,064)	7,88 (0,909)	84	9,13 (18,907)	7,52 (0,940)	0,36 [-2,213; 2,930]	0,7843
Hedges' g SMD							0,04 [-0,260; 0,345]	0,7851
Int. p-Wert								0,0612
Methode zur Gewebeuntersuchung								
zentral	110	9,09 (17,434)	6,00 (0,675)	114	7,60 (17,758)	6,10 (0,670)	-0,10 [-1,973; 1,775]	0,9173
Hedges' g SMD							-0,01 [-0,276; 0,248]	0,9172
lokal	143	6,76 (16,098)	11,64 (0,709)	137	6,81 (15,728)	8,90 (0,748)	2,74 [0,715; 4,763]	0,0081*
Hedges' g SMD							0,32 [0,081; 0,553]	0,0084*
Int. p-Wert								0,0387*
WHO Performance-Status								
0	93	5,02 (15,500)	12,11 (0,768)	93	4,30 (14,928)	7,99 (0,773)	4,12 [1,981; 6,260]	0,0002*
Hedges' g SMD							0,55 [0,259; 0,845]	0,0002*
1	160	9,38 (17,202)	7,45 (0,649)	158	8,86 (17,411)	7,56 (0,675)	-0,12 [-1,955; 1,724]	0,9021
Hedges' g SMD							-0,01 [-0,234; 0,206]	0,9022
Int. p-Wert								0,0042*
Raucherstatus								
Ja	83	7,63 (15,897)	9,78 (0,929)	84	6,75 (16,182)	9,97 (0,962)	-0,19 [-2,826; 2,450]	0,8888
Hedges' g SMD							-0,02 [-0,325; 0,282]	0,8888
Nein	170	7,84 (17,122)	8,99 (0,588)	167	7,39 (16,926)	6,76 (0,602)	2,24 [0,588; 3,889]	0,0079*
Hedges' g SMD							0,29 [0,075; 0,504]	0,0082*
Int. p-Wert								0,0973

Analysis is performed if there are at least 10 patients in each subgroup level.
[a] = Number of patients with change from baseline used for MMRM analysis at each timepoint. [b] = Mean baseline for patients with change from baseline used for MMRM analysis at each timepoint. Treatment difference is calculated from a mixed model for repeated measures (MMRM) analysis of the change from baseline score with treatment, visit, and treatment by visit interaction as fixed effects, baseline score as a covariate and baseline score by visit interaction. Patient is used as random effect in the model. Only visits where change from baseline is available for at least 25% of patients in both treatment arms are included in the analysis. Autoregressive with heterogeneity covariance matrix is used to model within-subject error. If the MMRM model does not converge the model results are not presented. SMD = standardised mean difference. * p<0.05.
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Table 4.2.3.25 FLAURA-2: Summary of subgroup analysis of change from baseline in EORTC QLQ-LC13 Periphere Neuropathie (mixed model for repeated measures) - average over all visits
Full Analysis Set, DCO 03APR2023

	Osi + Chemo (N=279)			Osi (N=278)			Behandlungseffekt	
Subgruppen	n [a]	Ausgangswert MW (SD) [b]	Veränderung MW (SE)	n [a]	Ausgangswert MW (SD) [b]	Veränderung MW (SE)	MWD [95%-KI]	p-Wert
Geschlecht								
Maennlich	95	8,77 (16,990)	8,03 (0,877)	94	5,67 (15,176)	8,52 (0,939)	-0,49 [-3,020; 2,047]	0,7060
Hedges' g SMD							-0,05 [-0,340; 0,230]	0,7059
Weiblich	158	7,17 (16,546)	10,04 (0,607)	157	8,07 (17,460)	7,19 (0,608)	2,86 [1,170; 4,541]	0,0009*
Hedges' g SMD							0,37 [0,151; 0,597]	0,0010*
Int. p-Wert								0,0127*
Nachweis der EGFR-Mutation durch zentralen ctDNA Cobas Test								
positiv	193	7,77 (15,684)	8,82 (0,558)	193	5,70 (14,703)	7,79 (0,567)	1,03 [-0,534; 2,598]	0,1965
Hedges' g SMD							0,13 [-0,068; 0,331]	0,1961
negativ	38	2,63 (11,960)	12,84 (1,290)	33	9,09 (17,225)	8,36 (1,394)	4,48 [0,693; 8,257]	0,0206*
Hedges' g SMD							0,55 [0,079; 1,031]	0,0223*
unbekannt	22	16,67 (26,726)	6,26 (2,039)	25	16,00 (25,676)	6,32 (2,180)	-0,05 [-5,957; 5,849]	0,9856
Hedges' g SMD							-0,01 [-0,578; 0,568]	0,9860
Int. p-Wert								0,1824
EGFR-Mutationstyp								
Exon 19 Deletion	154	7,36 (15,361)	9,81 (0,653)	154	7,14 (17,028)	8,29 (0,653)	1,51 [-0,300; 3,327]	0,1017
Hedges' g SMD							0,19 [-0,038; 0,410]	0,1028
Exon 21 (L858R) Substitutionsmutation	99	8,42 (18,653)	8,25 (0,796)	95	7,37 (16,257)	6,83 (0,862)	1,42 [-0,887; 3,728]	0,2270
Hedges' g SMD							0,17 [-0,109; 0,455]	0,2281
Int. p-Wert								0,8952
Zentral bestätigte EGFR-Mutation im Gewebe								
positiv	229	6,99 (14,962)	9,37 (0,514)	219	7,00 (16,018)	8,81 (0,541)	0,57 [-0,897; 2,031]	0,4478
Hedges' g SMD							0,07 [-0,114; 0,257]	0,4481
negativ	3	ID	ID	3	ID	ID	ID	ID
unbekannt	21	15,87 (29,096)	6,74 (2,280)	29	9,20 (21,633)	-1,05 (1,846)	7,79 [1,938; 13,647]	0,0096*
Hedges' g SMD							0,76 [0,173; 1,338]	0,0110*

Analysis is performed if there are at least 10 patients in each subgroup level.
[a] = Number of patients with change from baseline used for MMRM analysis at each timepoint. [b] = Mean baseline for patients with change from baseline used for MMRM analysis at each timepoint. Treatment difference is calculated from a mixed model for repeated measures (MMRM) analysis of the change from baseline score with treatment, visit, and treatment by visit interaction as fixed effects, baseline score as a covariate and baseline score by visit interaction. Patient is used as random effect in the model. Only visits where change from baseline is available for at least 25% of patients in both treatment arms are included in the analysis. Autoregressive with heterogeneity covariance matrix is used to model within-subject error. If the MMRM model does not converge the model results are not presented. SMD = standardised mean difference. * p<0.05.
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Table 4.2.3.25 FLAURA-2: Summary of subgroup analysis of change from baseline in EORTC QLQ-LC13 Periphere Neuropathie (mixed model for repeated measures) - average over all visits
Full Analysis Set, DCO 03APR2023

	Osi + Chemo (N=279)			Osi (N=278)			Behandlungseffekt	
Subgruppen	n [a]	Ausgangswert MW (SD) [b]	Veränderung MW (SE)	n [a]	Ausgangswert MW (SD) [b]	Veränderung MW (SE)	MWD [95%-KI]	p-Wert
Int. p-Wert								0,0134*
ZNS-Metastasen zur Baseline								
Ja	103	10,03 (18,574)	8,68 (0,845)	101	10,56 (19,397)	6,95 (0,921)	1,73 [-0,726; 4,187]	0,1669
Hedges' g SMD							0,19 [-0,082; 0,468]	0,1685
Nein	150	6,22 (15,149)	9,58 (0,619)	150	4,89 (14,130)	8,23 (0,613)	1,35 [-0,365; 3,058]	0,1230
Hedges' g SMD							0,18 [-0,049; 0,405]	0,1240
Int. p-Wert								0,5847
Zentrale Bestätigung der EGFR-Mutation								
Zentral bestätigte EGFR-Mutation in Gewebe oder ctDNA	241	7,47 (15,501)	9,13 (0,504)	244	7,10 (16,413)	8,18 (0,512)	0,95 [-0,456; 2,366]	0,1847
Hedges' g SMD							0,12 [-0,058; 0,299]	0,1852
Keine zentrale Bestätigung	12	NC	NC	7	NC	NC	NC	NC
Int. p-Wert								NC
Alter bei Screening								
<65 Jahre	158	7,17 (14,736)	9,28 (0,632)	150	6,67 (15,923)	7,00 (0,670)	2,28 [0,474; 4,090]	0,0134*
Hedges' g SMD							0,28 [0,058; 0,507]	0,0138*
>=65 Jahre	95	8,77 (19,576)	9,16 (0,821)	101	7,92 (17,732)	8,90 (0,800)	0,26 [-1,995; 2,516]	0,8207
Hedges' g SMD							0,03 [-0,248; 0,312]	0,8210
Int. p-Wert								0,2428
Region gPAP								
Asien	162	7,82 (16,839)	9,81 (0,621)	161	6,42 (15,597)	7,82 (0,637)	1,99 [0,241; 3,734]	0,0258*
Hedges' g SMD							0,25 [0,029; 0,467]	0,0264*
Europa	18	5,56 (12,783)	8,74 (1,876)	20	10,00 (19,041)	5,99 (1,809)	2,75 [-2,475; 7,983]	0,2972
Hedges' g SMD							0,34 [-0,306; 0,978]	0,3051
Nordamerika	17	7,84 (18,743)	, (,)	15	0,00 (0,000)	, (,)	-0,21 [-6,282; 5,857]	0,9445
Hedges' g SMD							, [, ; ,]	

Analysis is performed if there are at least 10 patients in each subgroup level.
[a] = Number of patients with change from baseline used for MMRM analysis at each timepoint. [b] = Mean baseline for patients with change from baseline used for MMRM analysis at each timepoint. Treatment difference is calculated from a mixed model for repeated measures (MMRM) analysis of the change from baseline score with treatment, visit, and treatment by visit interaction as fixed effects, baseline score as a covariate and baseline score by visit interaction. Patient is used as random effect in the model. Only visits where change from baseline is available for at least 25% of patients in both treatment arms are included in the analysis. Autoregressive with heterogeneity covariance matrix is used to model within-subject error. If the MMRM model does not converge the model results are not presented. SMD = standardised mean difference. * p<0.05.
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Table 4.2.3.25 FLAURA-2: Summary of subgroup analysis of change from baseline in EORTC QLQ-LC13 Periphere Neuropathie (mixed model for repeated measures) - average over all visits
Full Analysis Set, DCO 03APR2023

	Osi + Chemo (N=279)			Osi (N=278)			Behandlungseffekt	
Subgruppen	n [a]	Ausgangswert MW (SD) [b]	Veränderung MW (SE)	n [a]	Ausgangswert MW (SD) [b]	Veränderung MW (SE)	MWD [95%-KI]	p-Wert
Rest der Welt	56	8,33 (17,115)	7,15 (1,117)	55	10,30 (20,157)	6,95 (1,196)	0,21 [-3,015; 3,425]	0,9004
Hedges' g SMD							0,02 [-0,348; 0,396]	0,9009
Int. p-Wert								0,7727

Analysis is performed if there are at least 10 patients in each subgroup level.
[a] = Number of patients with change from baseline used for MMRM analysis at each timepoint. [b] = Mean baseline for patients with change from baseline used for MMRM analysis at each timepoint. Treatment difference is calculated from a mixed model for repeated measures (MMRM) analysis of the change from baseline score with treatment, visit, and treatment by visit interaction as fixed effects, baseline score as a covariate and baseline score by visit interaction. Patient is used as random effect in the model. Only visits where change from baseline is available for at least 25% of patients in both treatment arms are included in the analysis. Autoregressive with heterogeneity covariance matrix is used to model within-subject error. If the MMRM model does not converge the model results are not presented. SMD = standardised mean difference. * p<0.05.
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Table 4.2.3.26 FLAURA-2: Summary of subgroup analysis of change from baseline in EORTC QLQ-LC13 Alopezie (mixed model for repeated measures) - average over all visits
Full Analysis Set, DCO 03APR2023

	Osi + Chemo (N=279)			Osi (N=278)			Behandlungseffekt	
Subgruppen	n [a]	Ausgangswert MW (SD) [b]	Veränderung MW (SE)	n [a]	Ausgangswert MW (SD) [b]	Veränderung MW (SE)	MWD [95%-KI]	p-Wert
Abstammung								
Chinesisch/Asiatisch	66	6,57 (13,359)	3,91 (1,174)	65	8,21 (17,708)	6,52 (1,200)	-2,61 [-5,922; 0,702]	0,1218
Hedges' g SMD							-0,27 [-0,614; 0,074]	0,1239
Nicht-chinesisch/Asiatisch	103	3,88 (15,691)	7,85 (0,919)	102	11,44 (25,475)	6,62 (0,933)	1,23 [-1,365; 3,832]	0,3513
Hedges' g SMD							0,13 [-0,143; 0,405]	0,3484
Nicht-asiatisch	84	7,14 (20,088)	6,99 (1,127)	84	9,52 (25,122)	5,55 (1,134)	1,44 [-1,711; 4,582]	0,3700
Hedges' g SMD							0,14 [-0,165; 0,441]	0,3717
Int. p-Wert								0,2359
Methode zur Gewebeuntersuchung								
zentral	110	6,67 (16,154)	4,56 (1,014)	114	12,28 (25,576)	5,99 (0,993)	-1,43 [-4,232; 1,371]	0,3159
Hedges' g SMD							-0,13 [-0,397; 0,128]	0,3156
lokal	143	4,90 (17,224)	8,10 (0,762)	137	8,03 (21,589)	6,80 (0,796)	1,30 [-0,876; 3,469]	0,2417
Hedges' g SMD							0,14 [-0,094; 0,375]	0,2410
Int. p-Wert								0,7044
WHO Performance-Status								
0	93	4,66 (16,733)	6,39 (0,971)	93	7,53 (20,341)	8,81 (0,969)	-2,41 [-5,116; 0,293]	0,0804
Hedges' g SMD							-0,26 [-0,545; 0,032]	0,0813
1	160	6,25 (16,797)	6,56 (0,769)	158	11,39 (25,174)	4,90 (0,789)	1,66 [-0,513; 3,830]	0,1342
Hedges' g SMD							0,17 [-0,052; 0,389]	0,1337
Int. p-Wert								0,0092*
Raucherstatus								
Ja	83	6,43 (20,467)	5,50 (0,950)	84	8,33 (23,641)	2,96 (0,968)	2,54 [-0,126; 5,213]	0,0617
Hedges' g SMD							0,29 [-0,016; 0,594]	0,0633
Nein	170	5,29 (14,665)	7,09 (0,763)	167	10,78 (23,505)	7,98 (0,772)	-0,89 [-3,032; 1,257]	0,4167
Hedges' g SMD							-0,09 [-0,302; 0,125]	0,4150
Int. p-Wert								0,1597

Analysis is performed if there are at least 10 patients in each subgroup level.
[a] = Number of patients with change from baseline used for MMRM analysis at each timepoint. [b] = Mean baseline for patients with change from baseline used for MMRM analysis at each timepoint. Treatment difference is calculated from a mixed model for repeated measures (MMRM) analysis of the change from baseline score with treatment, visit, and treatment by visit interaction as fixed effects, baseline score as a covariate and baseline score by visit interaction. Patient is used as random effect in the model. Only visits where change from baseline is available for at least 25% of patients in both treatment arms are included in the analysis. Autoregressive with heterogeneity covariance matrix is used to model within-subject error. If the MMRM model does not converge the model results are not presented. SMD = standardised mean difference. * p<0.05.
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Table 4.2.3.26 FLAURA-2: Summary of subgroup analysis of change from baseline in EORTC QLQ-LC13 Alopezie (mixed model for repeated measures) - average over all visits
Full Analysis Set, DCO 03APR2023

	Osi + Chemo (N=279)			Osi (N=278)			Behandlungseffekt	
Subgruppen	n [a]	Ausgangswert MW (SD) [b]	Veränderung MW (SE)	n [a]	Ausgangswert MW (SD) [b]	Veränderung MW (SE)	MWD [95%-KI]	p-Wert
Geschlecht								
Maennlich	95	4,21 (13,959)	3,31 (0,747)	94	7,80 (23,149)	1,64 (0,792)	1,67 [-0,473; 3,816]	0,1263
Hedges' g SMD							0,22 [-0,064; 0,508]	0,1274
Weiblich	158	6,54 (18,222)	8,51 (0,820)	157	11,25 (23,737)	9,05 (0,813)	-0,54 [-2,818; 1,737]	0,6415
Hedges' g SMD							-0,05 [-0,273; 0,168]	0,6408
Int. p-Wert								0,1370
Nachweis der EGFR-Mutation durch zentralen ctDNA Cobas Test								
positiv	193	5,87 (17,679)	8,27 (0,706)	193	8,46 (21,858)	6,26 (0,710)	2,00 [0,034; 3,970]	0,0461*
Hedges' g SMD							0,20 [0,003; 0,403]	0,0465*
negativ	38	4,39 (13,800)	2,85 (1,210)	33	10,10 (22,799)	7,23 (1,294)	-4,39 [-7,906; -0,867]	0,0149*
Hedges' g SMD							-0,58 [-1,059; -0,106]	0,0166*
unbekannt	22	6,06 (13,159)	-2,60 (2,062)	25	21,33 (33,166)	6,30 (2,051)	-8,89 [-14,851; -2,935]	0,0039*
Hedges' g SMD							-0,88 [-1,478; -0,273]	0,0044*
Int. p-Wert								<0,0001*
EGFR-Mutationstyp								
Exon 19 Deletion	154	5,84 (18,722)	8,09 (0,810)	154	9,74 (24,677)	6,92 (0,804)	1,17 [-1,079; 3,416]	0,3076
Hedges' g SMD							0,12 [-0,107; 0,340]	0,3076
Exon 21 (L858R) Substitutionsmutation	99	5,39 (13,220)	3,78 (0,883)	95	10,53 (21,887)	5,72 (0,936)	-1,94 [-4,485; 0,606]	0,1349
Hedges' g SMD							-0,22 [-0,498; 0,066]	0,1340
Int. p-Wert								0,2233
Zentral bestätigte EGFR-Mutation im Gewebe								
positiv	229	5,68 (16,276)	6,19 (0,621)	219	10,35 (23,987)	6,24 (0,643)	-0,05 [-1,813; 1,709]	0,9537
Hedges' g SMD							-0,01 [-0,191; 0,180]	0,9535
negativ	3	ID	ID	3	ID	ID	ID	ID
unbekannt	21	6,35 (22,655)	9,46 (2,697)	29	6,90 (20,662)	8,11 (2,224)	1,35 [-5,639; 8,336]	0,7013
Hedges' g SMD							0,11 [-0,453; 0,671]	0,7029

Analysis is performed if there are at least 10 patients in each subgroup level.
[a] = Number of patients with change from baseline used for MMRM analysis at each timepoint. [b] = Mean baseline for patients with change from baseline used for MMRM analysis at each timepoint. Treatment difference is calculated from a mixed model for repeated measures (MMRM) analysis of the change from baseline score with treatment, visit, and treatment by visit interaction as fixed effects, baseline score as a covariate and baseline score by visit interaction. Patient is used as random effect in the model. Only visits where change from baseline is available for at least 25% of patients in both treatment arms are included in the analysis. Autoregressive with heterogeneity covariance matrix is used to model within-subject error. If the MMRM model does not converge the model results are not presented. SMD = standardised mean difference. * p<0.05.
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Table 4.2.3.26 FLAURA-2: Summary of subgroup analysis of change from baseline in EORTC QLQ-LC13 Alopezie (mixed model for repeated measures) - average over all visits
Full Analysis Set, DCO 03APR2023

	Osi + Chemo (N=279)			Osi (N=278)			Behandlungseffekt	
Subgruppen	n [a]	Ausgangswert MW (SD) [b]	Veränderung MW (SE)	n [a]	Ausgangswert MW (SD) [b]	Veränderung MW (SE)	MWD [95%-KI]	p-Wert
Int. p-Wert								0,7760
ZNS-Metastasen zur Baseline								
Ja	103	6,47 (17,501)	5,81 (1,034)	101	13,20 (28,315)	4,16 (1,093)	1,65 [-1,338; 4,631]	0,2788
Hedges' g SMD							0,15 [-0,122; 0,428]	0,2763
Nein	150	5,11 (16,264)	6,80 (0,728)	150	7,78 (19,470)	7,91 (0,719)	-1,11 [-3,124; 0,902]	0,2787
Hedges' g SMD							-0,13 [-0,352; 0,101]	0,2793
Int. p-Wert								0,0102*
Zentrale Bestätigung der EGFR-Mutation								
Zentral bestätigte EGFR-Mutation in Gewebe oder ctDNA	241	5,81 (17,035)	6,68 (0,615)	244	9,56 (23,022)	6,33 (0,617)	0,35 [-1,364; 2,063]	0,6890
Hedges' g SMD							0,04 [-0,142; 0,214]	0,6886
Keine zentrale Bestätigung	12	NC	NC	7	NC	NC	NC	NC
Int. p-Wert								NC
Alter bei Screening								
<65 Jahre	158	5,27 (14,337)	7,06 (0,738)	150	10,89 (24,878)	5,65 (0,769)	1,41 [-0,693; 3,517]	0,1883
Hedges' g SMD							0,15 [-0,073; 0,374]	0,1868
>=65 Jahre	95	6,32 (20,220)	5,60 (1,046)	101	8,58 (21,423)	7,52 (1,015)	-1,92 [-4,786; 0,948]	0,1889
Hedges' g SMD							-0,19 [-0,468; 0,093]	0,1905
Int. p-Wert								0,1272
Region gPAP								
Asien	162	5,14 (15,124)	6,11 (0,720)	161	9,94 (21,999)	6,38 (0,731)	-0,27 [-2,294; 1,754]	0,7935
Hedges' g SMD							-0,03 [-0,247; 0,189]	0,7929
Europa	18	3,70 (10,779)	, (,)	20	0,00 (0,000)	, (,)	2,04 [-3,500; 7,583]	0,4654
Hedges' g SMD							, [, ; ,]	
Nordamerika	17	NC	NC	15	NC	NC	NC	NC
Rest der Welt	56	8,93 (23,347)	5,42 (1,441)	55	13,33 (29,116)	6,56 (1,478)	-1,14 [-5,212; 2,926]	0,5803

Analysis is performed if there are at least 10 patients in each subgroup level.
[a] = Number of patients with change from baseline used for MMRM analysis at each timepoint. [b] = Mean baseline for patients with change from baseline used for MMRM analysis at each timepoint. Treatment difference is calculated from a mixed model for repeated measures (MMRM) analysis of the change from baseline score with treatment, visit, and treatment by visit interaction as fixed effects, baseline score as a covariate and baseline score by visit interaction. Patient is used as random effect in the model. Only visits where change from baseline is available for at least 25% of patients in both treatment arms are included in the analysis. Autoregressive with heterogeneity covariance matrix is used to model within-subject error. If the MMRM model does not converge the model results are not presented. SMD = standardised mean difference. * p<0.05.
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Table 4.2.3.26 FLAURA-2: Summary of subgroup analysis of change from baseline in EORTC QLQ-LC13 Alopezie (mixed model for repeated measures) - average over all visits
Full Analysis Set, DCO 03APR2023

	Osi + Chemo (N=279)			Osi (N=278)			Behandlungseffekt	
Subgruppen	n [a]	Ausgangswert MW (SD) [b]	Veränderung MW (SE)	n [a]	Ausgangswert MW (SD) [b]	Veränderung MW (SE)	MWD [95%-KI]	p-Wert
Hedges' g SMD							-0,10 [-0,477; 0,268]	0,5827
Int. p-Wert								0,3020

Analysis is performed if there are at least 10 patients in each subgroup level.
[a] = Number of patients with change from baseline used for MMRM analysis at each timepoint. [b] = Mean baseline for patients with change from baseline used for MMRM analysis at each timepoint. Treatment difference is calculated from a mixed model for repeated measures (MMRM) analysis of the change from baseline score with treatment, visit, and treatment by visit interaction as fixed effects, baseline score as a covariate and baseline score by visit interaction. Patient is used as random effect in the model. Only visits where change from baseline is available for at least 25% of patients in both treatment arms are included in the analysis. Autoregressive with heterogeneity covariance matrix is used to model within-subject error. If the MMRM model does not converge the model results are not presented. SMD = standardised mean difference. * p<0.05.
root/cdar/d516/payer_germany/ar/d5169c00001_payer_germany/tlf/prod/program/mmrmsubprcg.sas gmmrmsubprcgaz 04JUN2024:18:00 kvbv306

Table 4.2.3.27 FLAURA-2: Summary of subgroup analysis of change from baseline in PGIS (mixed model for repeated measures) - average over all visits
Full Analysis Set, DCO 03APR2023

	Osi + Chemo (N=279)			Osi (N=278)			Behandlungseffekt	
Subgruppen	n [a]	Ausgangswert MW (SD) [b]	Veränderung MW (SE)	n [a]	Ausgangswert MW (SD) [b]	Veränderung MW (SE)	MWD [95%-KI]	p-Wert
Abstammung								
Chinesisch/Asiatisch	65	1,40 (1,209)	0,13 (0,079)	65	1,51 (1,348)	0,08 (0,081)	0,05 [-0,177; 0,271]	0,6797
Hedges' g SMD							0,07 [-0,272; 0,416]	0,6813
Nicht-chinesisch/Asiatisch	99	1,70 (1,501)	-0,23 (0,055)	100	1,74 (1,561)	-0,39 (0,056)	0,16 [0,002; 0,312]	0,0475*
Hedges' g SMD							0,28 [0,002; 0,560]	0,0488*
Nicht-asiatisch	78	1,59 (1,427)	-0,34 (0,066)	83	1,95 (1,447)	-0,38 (0,067)	0,04 [-0,149; 0,223]	0,6948
Hedges' g SMD							0,06 [-0,247; 0,371]	0,6957
Int. p-Wert								0,5748
Methode zur Gewebeuntersuchung								
zentral	105	1,33 (1,182)	-0,03 (0,058)	112	1,53 (1,329)	-0,06 (0,057)	0,03 [-0,132; 0,190]	0,7235
Hedges' g SMD							0,05 [-0,218; 0,314]	0,7247
lokal	137	1,77 (1,529)	-0,27 (0,049)	136	1,93 (1,564)	-0,41 (0,051)	0,15 [0,008; 0,288]	0,0378*
Hedges' g SMD							0,25 [0,013; 0,490]	0,0385*
Int. p-Wert								0,3452
WHO Performance-Status								
0	91	1,24 (1,409)	0,09 (0,061)	93	1,51 (1,494)	-0,26 (0,061)	0,35 [0,183; 0,523]	<0,0001*
Hedges' g SMD							0,60 [0,305; 0,896]	<0,0001*
1	151	1,79 (1,364)	-0,33 (0,046)	155	1,90 (1,447)	-0,25 (0,048)	-0,08 [-0,207; 0,055]	0,2559
Hedges' g SMD							-0,13 [-0,354; 0,095]	0,2578
Int. p-Wert								0,0002*
Raucherstatus								
Ja	82	1,48 (1,476)	-0,20 (0,055)	83	1,61 (1,438)	-0,28 (0,056)	0,08 [-0,072; 0,237]	0,2965
Hedges' g SMD							0,16 [-0,144; 0,468]	0,2989
Nein	160	1,64 (1,367)	-0,15 (0,049)	165	1,82 (1,491)	-0,25 (0,049)	0,10 [-0,036; 0,237]	0,1481
Hedges' g SMD							0,16 [-0,058; 0,378]	0,1493
Int. p-Wert								0,7212

Analysis is performed if there are at least 10 patients in each subgroup level.
[a] = Number of patients with change from baseline used for MMRM analysis at each timepoint. [b] = Mean baseline for patients with change from baseline used for MMRM analysis at each timepoint. Treatment difference is calculated from a mixed model for repeated measures (MMRM) analysis of the change from baseline score with treatment, visit, and treatment by visit interaction as fixed effects, baseline score as a covariate and baseline score by visit interaction. Patient is used as random effect in the model. Only visits where change from baseline is available for at least 25% of patients in both treatment arms are included in the analysis. Autoregressive with heterogeneity covariance matrix is used to model within-subject error. If the MMRM model does not converge the model results are not presented. SMD = standardised mean difference. * p<0.05.
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Table 4.2.3.27 FLAURA-2: Summary of subgroup analysis of change from baseline in PGIS (mixed model for repeated measures) - average over all visits
Full Analysis Set, DCO 03APR2023

	Osi + Chemo (N=279)			Osi (N=278)			Behandlungseffekt	
Subgruppen	n [a]	Ausgangswert MW (SD) [b]	Veränderung MW (SE)	n [a]	Ausgangswert MW (SD) [b]	Veränderung MW (SE)	MWD [95%-KI]	p-Wert
Geschlecht								
Maennlich	92	1,53 (1,346)	-0,12 (0,054)	93	1,75 (1,508)	-0,29 (0,058)	0,17 [0,014; 0,325]	0,0333*
Hedges' g SMD							0,31 [0,023; 0,603]	0,0344*
Weiblich	150	1,61 (1,441)	-0,18 (0,051)	155	1,75 (1,458)	-0,24 (0,050)	0,06 [-0,082; 0,198]	0,4187
Hedges' g SMD							0,09 [-0,132; 0,317]	0,4200
Int. p-Wert								0,3619
Nachweis der EGFR-Mutation durch zentralen ctDNA Cobas Test								
positiv	183	1,61 (1,390)	-0,17 (0,043)	191	1,83 (1,475)	-0,31 (0,043)	0,14 [0,018; 0,259]	0,0243*
Hedges' g SMD							0,23 [0,030; 0,436]	0,0248*
negativ	38	1,24 (1,422)	-0,04 (0,091)	33	1,24 (1,501)	0,00 (0,097)	-0,04 [-0,304; 0,223]	0,7621
Hedges' g SMD							-0,07 [-0,538; 0,395]	0,7640
unbekannt	21	1,95 (1,431)	-0,29 (0,140)	24	1,83 (1,341)	-0,26 (0,145)	-0,04 [-0,439; 0,366]	0,8566
Hedges' g SMD							-0,05 [-0,639; 0,533]	0,8598
Int. p-Wert								0,4726
EGFR-Mutationstyp								
Exon 19 Deletion	146	1,51 (1,391)	-0,05 (0,048)	152	1,72 (1,520)	-0,23 (0,048)	0,18 [0,043; 0,309]	0,0098*
Hedges' g SMD							0,30 [0,071; 0,528]	0,0101*
Exon 21 (L858R) Substitutionsmutation	96	1,69 (1,424)	-0,34 (0,059)	94	1,82 (1,414)	-0,32 (0,064)	-0,01 [-0,183; 0,159]	0,8894
Hedges' g SMD							-0,02 [-0,305; 0,264]	0,8897
Int. p-Wert								0,0511
Zentral bestätigte EGFR-Mutation im Gewebe								
positiv	218	1,56 (1,401)	-0,14 (0,040)	216	1,66 (1,444)	-0,21 (0,041)	0,07 [-0,038; 0,187]	0,1926
Hedges' g SMD							0,12 [-0,063; 0,313]	0,1936
negativ	3	ID	ID	3	ID	ID	ID	ID
unbekannt	21	1,90 (1,480)	-0,37 (0,126)	29	2,28 (1,533)	-0,70 (0,101)	0,33 [0,003; 0,649]	0,0479*
Hedges' g SMD							0,57 [0,001; 1,148]	0,0496*

Analysis is performed if there are at least 10 patients in each subgroup level.
[a] = Number of patients with change from baseline used for MMRM analysis at each timepoint. [b] = Mean baseline for patients with change from baseline used for MMRM analysis at each timepoint. Treatment difference is calculated from a mixed model for repeated measures (MMRM) analysis of the change from baseline score with treatment, visit, and treatment by visit interaction as fixed effects, baseline score as a covariate and baseline score by visit interaction. Patient is used as random effect in the model. Only visits where change from baseline is available for at least 25% of patients in both treatment arms are included in the analysis. Autoregressive with heterogeneity covariance matrix is used to model within-subject error. If the MMRM model does not converge the model results are not presented. SMD = standardised mean difference. * p<0.05.
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Table 4.2.3.27 FLAURA-2: Summary of subgroup analysis of change from baseline in PGIS (mixed model for repeated measures) - average over all visits
Full Analysis Set, DCO 03APR2023

	Osi + Chemo (N=279)			Osi (N=278)			Behandlungseffekt	
Subgruppen	n [a]	Ausgangswert MW (SD) [b]	Veränderung MW (SE)	n [a]	Ausgangswert MW (SD) [b]	Veränderung MW (SE)	MWD [95%-KI]	p-Wert
Int. p-Wert								0,3271
ZNS-Metastasen zur Baseline								
Ja	98	1,69 (1,380)	-0,21 (0,056)	100	1,82 (1,452)	-0,29 (0,060)	0,08 [-0,078; 0,245]	0,3097
Hedges' g SMD							0,14 [-0,135; 0,423]	0,3122
Nein	144	1,51 (1,419)	-0,13 (0,050)	148	1,70 (1,491)	-0,22 (0,049)	0,09 [-0,049; 0,229]	0,2021
Hedges' g SMD							0,15 [-0,081; 0,379]	0,2032
Int. p-Wert								0,7985
Zentrale Bestätigung der EGFR-Mutation								
Zentral bestätigte EGFR-Mutation in Gewebe oder ctDNA	230	1,60 (1,416)	-0,16 (0,038)	241	1,71 (1,462)	-0,25 (0,039)	0,09 [-0,022; 0,192]	0,1185
Hedges' g SMD							0,14 [-0,037; 0,325]	0,1196
Keine zentrale Bestätigung	12	1,25 (1,138)	-0,24 (0,196)	7	3,00 (1,414)	-0,28 (0,415)	0,03 [-0,974; 1,036]	0,9515
Hedges' g SMD							0,03 [-0,897; 0,967]	0,9417
Int. p-Wert								0,3042
Alter bei Screening								
<65 Jahre	152	1,64 (1,383)	-0,29 (0,048)	149	1,95 (1,460)	-0,49 (0,050)	0,20 [0,063; 0,338]	0,0043*
Hedges' g SMD							0,33 [0,103; 0,558]	0,0044*
>=65 Jahre	90	1,48 (1,440)	0,05 (0,059)	99	1,45 (1,452)	0,11 (0,057)	-0,05 [-0,212; 0,109]	0,5277
Hedges' g SMD							-0,09 [-0,377; 0,194]	0,5303
Int. p-Wert								0,0134*
Region gPAP								
Asien	157	1,61 (1,376)	-0,10 (0,047)	159	1,67 (1,499)	-0,20 (0,048)	0,10 [-0,033; 0,232]	0,1423
Hedges' g SMD							0,16 [-0,056; 0,386]	0,1435
Europa	18	1,94 (1,626)	-0,09 (0,134)	20	1,65 (1,424)	-0,11 (0,133)	0,02 [-0,359; 0,391]	0,9322
Hedges' g SMD							0,03 [-0,610; 0,664]	0,9337
Nordamerika	15	1,60 (1,595)	-0,31 (0,159)	15	2,00 (1,069)	-0,82 (0,154)	0,51 [0,065; 0,965]	0,0261*

Analysis is performed if there are at least 10 patients in each subgroup level.
[a] = Number of patients with change from baseline used for MMRM analysis at each timepoint. [b] = Mean baseline for patients with change from baseline used for MMRM analysis at each timepoint. Treatment difference is calculated from a mixed model for repeated measures (MMRM) analysis of the change from baseline score with treatment, visit, and treatment by visit interaction as fixed effects, baseline score as a covariate and baseline score by visit interaction. Patient is used as random effect in the model. Only visits where change from baseline is available for at least 25% of patients in both treatment arms are included in the analysis. Autoregressive with heterogeneity covariance matrix is used to model within-subject error. If the MMRM model does not converge the model results are not presented. SMD = standardised mean difference. * p<0.05.
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Table 4.2.3.27 FLAURA-2: Summary of subgroup analysis of change from baseline in PGIS (mixed model for repeated measures) - average over all visits
Full Analysis Set, DCO 03APR2023

	Osi + Chemo (N=279)			Osi (N=278)			Behandlungseffekt	
Subgruppen	n [a]	Ausgangswert MW (SD) [b]	Veränderung MW (SE)	n [a]	Ausgangswert MW (SD) [b]	Veränderung MW (SE)	MWD [95%-KI]	p-Wert
Hedges' g SMD							0,83 [0,076; 1,576]	0,0308*
Rest der Welt	52	1,37 (1,358)	-0,36 (0,077)	54	1,94 (1,522)	-0,32 (0,081)	-0,04 [-0,265; 0,178]	0,6990
Hedges' g SMD							-0,07 [-0,456; 0,306]	0,6997
Int. p-Wert								0,2389

Analysis is performed if there are at least 10 patients in each subgroup level.
[a] = Number of patients with change from baseline used for MMRM analysis at each timepoint. [b] = Mean baseline for patients with change from baseline used for MMRM analysis at each timepoint. Treatment difference is calculated from a mixed model for repeated measures (MMRM) analysis of the change from baseline score with treatment, visit, and treatment by visit interaction as fixed effects, baseline score as a covariate and baseline score by visit interaction. Patient is used as random effect in the model. Only visits where change from baseline is available for at least 25% of patients in both treatment arms are included in the analysis. Autoregressive with heterogeneity covariance matrix is used to model within-subject error. If the MMRM model does not converge the model results are not presented. SMD = standardised mean difference. * p<0.05.
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Table 4.2.3.28 FLAURA-2: Summary of subgroup analysis of change from baseline in PRO-CTCAE Wunde oder offene Stellen in Mund oder Hals (mixed model for repeated measures) - average over all visits
Full Analysis Set, DCO 03APR2023

	Osi + Chemo (N=279)			Osi (N=278)			Behandlungseffekt	
Subgruppen	n [a]	Ausgangswert MW (SD) [b]	Veränderung MW (SE)	n [a]	Ausgangswert MW (SD) [b]	Veränderung MW (SE)	MWD [95%-KI]	p-Wert
Abstammung								
Chinesisch/Asiatisch	66	1,08 (0,252)	0,40 (0,030)	65	1,14 (0,527)	0,26 (0,030)	0,14 [0,057; 0,223]	0,0010*
Hedges' g SMD							0,58 [0,225; 0,925]	0,0013*
Nicht-chinesisch/Asiatisch	68	1,07 (0,263)	0,37 (0,026)	69	1,11 (0,428)	0,35 (0,027)	0,02 [-0,059; 0,090]	0,6759
Hedges' g SMD							0,07 [-0,264; 0,406]	0,6774
Nicht-asiatisch	79	1,10 (0,427)	0,20 (0,022)	81	1,10 (0,406)	0,12 (0,022)	0,08 [0,017; 0,138]	0,0128*
Hedges' g SMD							0,39 [0,080; 0,706]	0,0139*
Int. p-Wert								0,0533
Methode zur Gewebeuntersuchung								
zentral	86	1,10 (0,308)	0,33 (0,026)	93	1,11 (0,478)	0,23 (0,025)	0,09 [0,023; 0,164]	0,0093*
Hedges' g SMD							0,39 [0,092; 0,684]	0,0101*
lokal	127	1,07 (0,343)	0,32 (0,019)	122	1,11 (0,430)	0,25 (0,020)	0,07 [0,015; 0,123]	0,0121*
Hedges' g SMD							0,32 [0,068; 0,568]	0,0127*
Int. p-Wert								0,5811
WHO Performance-Status								
0	79	1,05 (0,206)	0,32 (0,025)	81	1,09 (0,360)	0,31 (0,025)	0,01 [-0,056; 0,080]	0,7314
Hedges' g SMD							0,05 [-0,256; 0,364]	0,7323
1	134	1,10 (0,383)	0,32 (0,019)	134	1,13 (0,498)	0,19 (0,020)	0,13 [0,072; 0,182]	<0,0001*
Hedges' g SMD							0,56 [0,313; 0,801]	<0,0001*
Int. p-Wert								0,0041*
Raucherstatus								
Ja	75	1,04 (0,214)	0,28 (0,024)	78	1,18 (0,629)	0,21 (0,024)	0,07 [0,001; 0,137]	0,0461*
Hedges' g SMD							0,32 [0,004; 0,642]	0,0471*
Nein	138	1,11 (0,376)	0,34 (0,019)	137	1,08 (0,303)	0,26 (0,020)	0,08 [0,024; 0,133]	0,0051*
Hedges' g SMD							0,34 [0,100; 0,576]	0,0054*
Int. p-Wert								0,7597

Analysis is performed if there are at least 10 patients in each subgroup level.
[a] = Number of patients with change from baseline used for MMRM analysis at each timepoint. [b] = Mean baseline for patients with change from baseline used for MMRM analysis at each timepoint. Treatment difference is calculated from a mixed model for repeated measures (MMRM) analysis of the change from baseline score with treatment, visit, and treatment by visit interaction as fixed effects, baseline score as a covariate and baseline score by visit interaction. Patient is used as random effect in the model. Only visits where change from baseline is available for at least 25% of patients in both treatment arms are included in the analysis. Autoregressive with heterogeneity covariance matrix is used to model within-subject error. If the MMRM model does not converge the model results are not presented. SMD = standardised mean difference. * p<0.05.
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Table 4.2.3.28 FLAURA-2: Summary of subgroup analysis of change from baseline in PRO-CTCAE Wunde oder offene Stellen in Mund oder Hals (mixed model for repeated measures) - average over all visits
Full Analysis Set, DCO 03APR2023

	Osi + Chemo (N=279)			Osi (N=278)			Behandlungseffekt	
Subgruppen	n [a]	Ausgangswert MW (SD) [b]	Veränderung MW (SE)	n [a]	Ausgangswert MW (SD) [b]	Veränderung MW (SE)	MWD [95%-KI]	p-Wert
Geschlecht								
Maennlich	78	1,07 (0,276)	0,28 (0,022)	82	1,10 (0,470)	0,22 (0,023)	0,06 [-0,005; 0,120]	0,0725
Hedges' g SMD							0,28 [-0,029; 0,594]	0,0752
Weiblich	135	1,09 (0,357)	0,35 (0,020)	133	1,12 (0,440)	0,25 (0,021)	0,09 [0,037; 0,151]	0,0012*
Hedges' g SMD							0,39 [0,153; 0,636]	0,0014*
Int. p-Wert								0,4483
Nachweis der EGFR-Mutation durch zentralen ctDNA Cobas Test								
positiv	161	1,09 (0,333)	0,34 (0,017)	163	1,10 (0,404)	0,21 (0,018)	0,13 [0,082; 0,179]	<0,0001*
Hedges' g SMD							0,59 [0,366; 0,811]	<0,0001*
negativ	32	1,08 (0,314)	0,27 (0,044)	30	1,18 (0,533)	0,37 (0,046)	-0,09 [-0,218; 0,035]	0,1558
Hedges' g SMD							-0,36 [-0,861; 0,144]	0,1620
unbekannt	20	1,08 (0,335)	, (,)	22	1,14 (0,640)	, (,)	-0,04 [-0,184; 0,108]	0,6053
Hedges' g SMD							, [, ; ,]	
Int. p-Wert								0,0007*
EGFR-Mutationstyp								
Exon 19 Deletion	126	1,10 (0,381)	0,35 (0,018)	128	1,07 (0,297)	0,24 (0,018)	0,12 [0,065; 0,167]	<0,0001*
Hedges' g SMD							0,56 [0,306; 0,807]	<0,0001*
Exon 21 (L858R) Substitutionsmutation	87	1,06 (0,234)	0,26 (0,026)	85	1,19 (0,612)	0,26 (0,029)	0,00 [-0,073; 0,081]	0,9163
Hedges' g SMD							0,02 [-0,283; 0,315]	0,9159
Int. p-Wert								0,0713
Zentral bestätigte EGFR-Mutation im Gewebe								
positiv	190	1,09 (0,347)	0,33 (0,016)	188	1,11 (0,454)	0,26 (0,017)	0,07 [0,026; 0,119]	0,0021*
Hedges' g SMD							0,32 [0,113; 0,519]	0,0023*
negativ	2	ID	ID	3	ID	ID	ID	ID
unbekannt	21	1,00 (0,000)	0,21 (0,043)	24	1,17 (0,458)	0,17 (0,039)	0,04 [-0,073; 0,161]	0,4583
Hedges' g SMD							0,22 [-0,365; 0,810]	0,4583

Analysis is performed if there are at least 10 patients in each subgroup level.
[a] = Number of patients with change from baseline used for MMRM analysis at each timepoint. [b] = Mean baseline for patients with change from baseline used for MMRM analysis at each timepoint. Treatment difference is calculated from a mixed model for repeated measures (MMRM) analysis of the change from baseline score with treatment, visit, and treatment by visit interaction as fixed effects, baseline score as a covariate and baseline score by visit interaction. Patient is used as random effect in the model. Only visits where change from baseline is available for at least 25% of patients in both treatment arms are included in the analysis. Autoregressive with heterogeneity covariance matrix is used to model within-subject error. If the MMRM model does not converge the model results are not presented. SMD = standardised mean difference. * p<0.05.
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Table 4.2.3.28 FLAURA-2: Summary of subgroup analysis of change from baseline in PRO-CTCAE Wunde oder offene Stellen in Mund oder Hals (mixed model for repeated measures) - average over all visits
Full Analysis Set, DCO 03APR2023

	Osi + Chemo (N=279)			Osi (N=278)			Behandlungseffekt	
Subgruppen	n [a]	Ausgangswert MW (SD) [b]	Veränderung MW (SE)	n [a]	Ausgangswert MW (SD) [b]	Veränderung MW (SE)	MWD [95%-KI]	p-Wert
Int. p-Wert								0,3993
ZNS-Metastasen zur Baseline								
Ja	84	1,11 (0,418)	0,36 (0,024)	85	1,14 (0,521)	0,19 (0,027)	0,17 [0,100; 0,242]	<0,0001*
Hedges' g SMD							0,72 [0,413; 1,036]	<0,0001*
Nein	129	1,07 (0,256)	0,30 (0,019)	130	1,10 (0,399)	0,27 (0,019)	0,02 [-0,029; 0,078]	0,3660
Hedges' g SMD							0,11 [-0,132; 0,356]	0,3675
Int. p-Wert								0,0063*
Zentrale Bestätigung der EGFR-Mutation								
Zentral bestätigte EGFR-Mutation in Gewebe oder ctDNA	201	1,09 (0,338)	0,33 (0,016)	208	1,11 (0,439)	0,25 (0,016)	0,08 [0,032; 0,120]	0,0007*
Hedges' g SMD							0,34 [0,141; 0,531]	0,0007*
Keine zentrale Bestätigung	12	NC	NC	7	NC	NC	NC	NC
Int. p-Wert								NC
Alter bei Screening								
<65 Jahre	127	1,12 (0,392)	0,30 (0,017)	127	1,08 (0,349)	0,22 (0,018)	0,09 [0,036; 0,135]	0,0007*
Hedges' g SMD							0,43 [0,178; 0,675]	0,0008*
>=65 Jahre	86	1,03 (0,193)	0,35 (0,028)	88	1,16 (0,565)	0,27 (0,028)	0,08 [0,003; 0,160]	0,0423*
Hedges' g SMD							0,31 [0,010; 0,608]	0,0426*
Int. p-Wert								0,7831
Region gPAP								
Asien	126	1,08 (0,264)	0,40 (0,020)	128	1,12 (0,481)	0,31 (0,021)	0,09 [0,034; 0,147]	0,0017*
Hedges' g SMD							0,39 [0,145; 0,642]	0,0019*
Europa	18	1,03 (0,118)	, (,)	18	1,03 (0,118)	, (,)	0,14 [0,038; 0,246]	0,0082*
Hedges' g SMD							, [, ; ,]	
Nordamerika	15	NC	NC	15	NC	NC	NC	NC
Rest der Welt	54	1,14 (0,509)	0,19 (0,028)	54	1,10 (0,449)	0,17 (0,030)	0,02 [-0,062; 0,100]	0,6465

Analysis is performed if there are at least 10 patients in each subgroup level.
[a] = Number of patients with change from baseline used for MMRM analysis at each timepoint. [b] = Mean baseline for patients with change from baseline used for MMRM analysis at each timepoint. Treatment difference is calculated from a mixed model for repeated measures (MMRM) analysis of the change from baseline score with treatment, visit, and treatment by visit interaction as fixed effects, baseline score as a covariate and baseline score by visit interaction. Patient is used as random effect in the model. Only visits where change from baseline is available for at least 25% of patients in both treatment arms are included in the analysis. Autoregressive with heterogeneity covariance matrix is used to model within-subject error. If the MMRM model does not converge the model results are not presented. SMD = standardised mean difference. * p<0.05.
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Table 4.2.3.28 FLAURA-2: Summary of subgroup analysis of change from baseline in PRO-CTCAE Wunde oder offene Stellen in Mund oder Hals (mixed model for repeated measures) - average over all visits
Full Analysis Set, DCO 03APR2023

	Osi + Chemo (N=279)			Osi (N=278)			Behandlungseffekt	
Subgruppen	n [a]	Ausgangswert MW (SD) [b]	Veränderung MW (SE)	n [a]	Ausgangswert MW (SD) [b]	Veränderung MW (SE)	MWD [95%-KI]	p-Wert
Hedges' g SMD							0,09 [-0,290; 0,465]	0,6481
Int. p-Wert								0,1987

Analysis is performed if there are at least 10 patients in each subgroup level.
[a] = Number of patients with change from baseline used for MMRM analysis at each timepoint. [b] = Mean baseline for patients with change from baseline used for MMRM analysis at each timepoint. Treatment difference is calculated from a mixed model for repeated measures (MMRM) analysis of the change from baseline score with treatment, visit, and treatment by visit interaction as fixed effects, baseline score as a covariate and baseline score by visit interaction. Patient is used as random effect in the model. Only visits where change from baseline is available for at least 25% of patients in both treatment arms are included in the analysis. Autoregressive with heterogeneity covariance matrix is used to model within-subject error. If the MMRM model does not converge the model results are not presented. SMD = standardised mean difference. * p<0.05.
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Table 4.2.3.29 FLAURA-2: Summary of subgroup analysis of change from baseline in PRO-CTCAE Übelkeit (mixed model for repeated measures) - average over all visits
Full Analysis Set, DCO 03APR2023

	Osi + Chemo (N=279)			Osi (N=278)			Behandlungseffekt	
Subgruppen	n [a]	Ausgangswert MW (SD) [b]	Veränderung MW (SE)	n [a]	Ausgangswert MW (SD) [b]	Veränderung MW (SE)	MWD [95%-KI]	p-Wert
Abstammung								
Chinesisch/Asiatisch	66	1,15 (0,350)	0,37 (0,030)	65	1,15 (0,475)	0,15 (0,030)	0,22 [0,141; 0,307]	<0,0001*
Hedges' g SMD							0,92 [0,560; 1,282]	<0,0001*
Nicht-chinesisch/Asiatisch	68	1,18 (0,447)	0,16 (0,022)	69	1,22 (0,622)	-0,05 (0,023)	0,21 [0,148; 0,274]	<0,0001*
Hedges' g SMD							1,12 [0,762; 1,484]	<0,0001*
Nicht-asiatisch	79	1,34 (0,619)	0,24 (0,029)	81	1,32 (0,598)	-0,05 (0,030)	0,29 [0,212; 0,377]	<0,0001*
Hedges' g SMD							1,11 [0,774; 1,441]	<0,0001*
Int. p-Wert								0,1136
Methode zur Gewebeuntersuchung								
zentral	86	1,19 (0,460)	0,27 (0,024)	93	1,21 (0,528)	0,06 (0,023)	0,20 [0,137; 0,269]	<0,0001*
Hedges' g SMD							0,90 [0,594; 1,210]	<0,0001*
lokal	127	1,26 (0,523)	0,25 (0,021)	122	1,26 (0,607)	-0,02 (0,022)	0,27 [0,216; 0,333]	<0,0001*
Hedges' g SMD							1,16 [0,893; 1,431]	<0,0001*
Int. p-Wert								0,0771
WHO Performance-Status								
0	79	1,16 (0,397)	0,29 (0,027)	81	1,20 (0,459)	0,04 (0,027)	0,25 [0,176; 0,327]	<0,0001*
Hedges' g SMD							1,03 [0,698; 1,359]	<0,0001*
1	134	1,27 (0,547)	0,24 (0,019)	134	1,26 (0,633)	-0,01 (0,020)	0,24 [0,190; 0,299]	<0,0001*
Hedges' g SMD							1,07 [0,817; 1,330]	<0,0001*
Int. p-Wert								0,5737
Raucherstatus								
Ja	75	1,23 (0,502)	0,21 (0,030)	78	1,22 (0,612)	0,06 (0,031)	0,15 [0,068; 0,237]	0,0005*
Hedges' g SMD							0,57 [0,245; 0,892]	0,0006*
Nein	138	1,23 (0,499)	0,28 (0,018)	137	1,25 (0,553)	-0,01 (0,019)	0,29 [0,242; 0,344]	<0,0001*
Hedges' g SMD							1,35 [1,092; 1,616]	<0,0001*
Int. p-Wert								0,0218*

Analysis is performed if there are at least 10 patients in each subgroup level.
[a] = Number of patients with change from baseline used for MMRM analysis at each timepoint. [b] = Mean baseline for patients with change from baseline used for MMRM analysis at each timepoint. Treatment difference is calculated from a mixed model for repeated measures (MMRM) analysis of the change from baseline score with treatment, visit, and treatment by visit interaction as fixed effects, baseline score as a covariate and baseline score by visit interaction. Patient is used as random effect in the model. Only visits where change from baseline is available for at least 25% of patients in both treatment arms are included in the analysis. Autoregressive with heterogeneity covariance matrix is used to model within-subject error. If the MMRM model does not converge the model results are not presented. SMD = standardised mean difference. * p<0.05.
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Table 4.2.3.29 FLAURA-2: Summary of subgroup analysis of change from baseline in PRO-CTCAE Übelkeit (mixed model for repeated measures) - average over all visits
Full Analysis Set, DCO 03APR2023

	Osi + Chemo (N=279)			Osi (N=278)			Behandlungseffekt	
Subgruppen	n [a]	Ausgangswert MW (SD) [b]	Veränderung MW (SE)	n [a]	Ausgangswert MW (SD) [b]	Veränderung MW (SE)	MWD [95%-KI]	p-Wert
Geschlecht								
Maennlich	78	1,22 (0,467)	0,27 (0,026)	82	1,21 (0,578)	0,02 (0,027)	0,25 [0,171; 0,320]	<0,0001*
Hedges' g SMD							1,02 [0,690; 1,350]	<0,0001*
Weiblich	135	1,23 (0,518)	0,25 (0,020)	133	1,26 (0,573)	0,01 (0,020)	0,25 [0,190; 0,300]	<0,0001*
Hedges' g SMD							1,06 [0,808; 1,320]	<0,0001*
Int. p-Wert								0,7333
Nachweis der EGFR-Mutation durch zentralen ctDNA Cobas Test								
positiv	161	1,26 (0,531)	0,23 (0,019)	163	1,26 (0,609)	0,00 (0,019)	0,23 [0,180; 0,284]	<0,0001*
Hedges' g SMD							0,97 [0,743; 1,204]	<0,0001*
negativ	32	1,08 (0,224)	0,36 (0,039)	30	1,10 (0,305)	0,05 (0,040)	0,31 [0,196; 0,415]	<0,0001*
Hedges' g SMD							1,39 [0,829; 1,945]	<0,0001*
unbekannt	20	1,20 (0,523)	0,31 (0,050)	22	1,25 (0,572)	0,07 (0,052)	0,24 [0,099; 0,382]	0,0010*
Hedges' g SMD							1,02 [0,369; 1,663]	0,0021*
Int. p-Wert								0,3665
EGFR-Mutationstyp								
Exon 19 Deletion	126	1,25 (0,543)	0,31 (0,021)	128	1,24 (0,551)	0,00 (0,021)	0,31 [0,253; 0,368]	<0,0001*
Hedges' g SMD							1,33 [1,054; 1,598]	<0,0001*
Exon 21 (L858R) Substitutionsmutation	87	1,19 (0,426)	0,18 (0,024)	85	1,24 (0,615)	0,04 (0,025)	0,13 [0,066; 0,202]	0,0001*
Hedges' g SMD							0,59 [0,285; 0,896]	0,0002*
Int. p-Wert								0,0013*
Zentral bestätigte EGFR-Mutation im Gewebe								
positiv	190	1,23 (0,511)	0,26 (0,017)	188	1,23 (0,581)	0,02 (0,017)	0,24 [0,194; 0,290]	<0,0001*
Hedges' g SMD							1,02 [0,810; 1,239]	<0,0001*
negativ	2	ID	ID	3	ID	ID	ID	ID
unbekannt	21	1,21 (0,405)	0,25 (0,051)	24	1,33 (0,545)	-0,01 (0,046)	0,26 [0,124; 0,397]	0,0003*
Hedges' g SMD							1,11 [0,477; 1,742]	0,0006*

Analysis is performed if there are at least 10 patients in each subgroup level.
[a] = Number of patients with change from baseline used for MMRM analysis at each timepoint. [b] = Mean baseline for patients with change from baseline used for MMRM analysis at each timepoint. Treatment difference is calculated from a mixed model for repeated measures (MMRM) analysis of the change from baseline score with treatment, visit, and treatment by visit interaction as fixed effects, baseline score as a covariate and baseline score by visit interaction. Patient is used as random effect in the model. Only visits where change from baseline is available for at least 25% of patients in both treatment arms are included in the analysis. Autoregressive with heterogeneity covariance matrix is used to model within-subject error. If the MMRM model does not converge the model results are not presented. SMD = standardised mean difference. * p<0.05.
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Table 4.2.3.29 FLAURA-2: Summary of subgroup analysis of change from baseline in PRO-CTCAE Übelkeit (mixed model for repeated measures) - average over all visits
Full Analysis Set, DCO 03APR2023

	Osi + Chemo (N=279)			Osi (N=278)			Behandlungseffekt	
Subgruppen	n [a]	Ausgangswert MW (SD) [b]	Veränderung MW (SE)	n [a]	Ausgangswert MW (SD) [b]	Veränderung MW (SE)	MWD [95%-KI]	p-Wert
Int. p-Wert								0,8350
ZNS-Metastasen zur Baseline								
Ja	84	1,27 (0,546)	0,30 (0,029)	85	1,25 (0,615)	0,02 (0,030)	0,28 [0,196; 0,360]	<0,0001*
Hedges' g SMD							1,02 [0,700; 1,342]	<0,0001*
Nein	129	1,20 (0,466)	0,23 (0,018)	130	1,23 (0,547)	0,01 (0,018)	0,22 [0,174; 0,275]	<0,0001*
Hedges' g SMD							1,07 [0,813; 1,334]	<0,0001*
Int. p-Wert								0,3207
Zentrale Bestätigung der EGFR-Mutation								
Zentral bestätigte EGFR-Mutation in Gewebe oder ctDNA	201	1,24 (0,510)	0,25 (0,016)	208	1,24 (0,577)	0,02 (0,016)	0,24 [0,192; 0,283]	<0,0001*
Hedges' g SMD							1,01 [0,807; 1,219]	<0,0001*
Keine zentrale Bestätigung	12	NC	NC	7	NC	NC	NC	NC
Int. p-Wert								NC
Alter bei Screening								
<65 Jahre	127	1,27 (0,519)	0,30 (0,021)	127	1,25 (0,597)	-0,02 (0,022)	0,32 [0,260; 0,378]	<0,0001*
Hedges' g SMD							1,33 [1,054; 1,598]	<0,0001*
>=65 Jahre	86	1,17 (0,464)	0,19 (0,024)	88	1,23 (0,541)	0,07 (0,023)	0,12 [0,053; 0,183]	0,0004*
Hedges' g SMD							0,54 [0,233; 0,838]	0,0005*
Int. p-Wert								0,0009*
Region gPAP								
Asien	126	1,16 (0,404)	0,26 (0,019)	128	1,20 (0,566)	0,04 (0,020)	0,22 [0,169; 0,277]	<0,0001*
Hedges' g SMD							1,02 [0,756; 1,279]	<0,0001*
Europa	18	NC	NC	18	NC	NC	NC	NC
Nordamerika	15	NC	NC	15	NC	NC	NC	NC
Rest der Welt	54	1,34 (0,643)	0,25 (0,034)	54	1,28 (0,588)	-0,03 (0,036)	0,28 [0,183; 0,379]	<0,0001*

Analysis is performed if there are at least 10 patients in each subgroup level.
[a] = Number of patients with change from baseline used for MMRM analysis at each timepoint. [b] = Mean baseline for patients with change from baseline used for MMRM analysis at each timepoint. Treatment difference is calculated from a mixed model for repeated measures (MMRM) analysis of the change from baseline score with treatment, visit, and treatment by visit interaction as fixed effects, baseline score as a covariate and baseline score by visit interaction. Patient is used as random effect in the model. Only visits where change from baseline is available for at least 25% of patients in both treatment arms are included in the analysis. Autoregressive with heterogeneity covariance matrix is used to model within-subject error. If the MMRM model does not converge the model results are not presented. SMD = standardised mean difference. * p<0.05.
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Table 4.2.3.29 FLAURA-2: Summary of subgroup analysis of change from baseline in PRO-CTCAE Übelkeit (mixed model for repeated measures) - average over all visits
Full Analysis Set, DCO 03APR2023

	Osi + Chemo (N=279)			Osi (N=278)			Behandlungseffekt	
Subgruppen	n [a]	Ausgangswert MW (SD) [b]	Veränderung MW (SE)	n [a]	Ausgangswert MW (SD) [b]	Veränderung MW (SE)	MWD [95%-KI]	p-Wert
Hedges' g SMD							1,08 [0,674; 1,483]	<0,0001*
Int. p-Wert								0,1614

Analysis is performed if there are at least 10 patients in each subgroup level.
[a] = Number of patients with change from baseline used for MMRM analysis at each timepoint. [b] = Mean baseline for patients with change from baseline used for MMRM analysis at each timepoint. Treatment difference is calculated from a mixed model for repeated measures (MMRM) analysis of the change from baseline score with treatment, visit, and treatment by visit interaction as fixed effects, baseline score as a covariate and baseline score by visit interaction. Patient is used as random effect in the model. Only visits where change from baseline is available for at least 25% of patients in both treatment arms are included in the analysis. Autoregressive with heterogeneity covariance matrix is used to model within-subject error. If the MMRM model does not converge the model results are not presented. SMD = standardised mean difference. * p<0.05.
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Table 4.2.3.30 FLAURA-2: Summary of subgroup analysis of change from baseline in PRO-CTCAE Erbrechen (mixed model for repeated measures) - average over all visits
Full Analysis Set, DCO 03APR2023

	Osi + Chemo (N=279)			Osi (N=278)			Behandlungseffekt	
Subgruppen	n [a]	Ausgangswert MW (SD) [b]	Veränderung MW (SE)	n [a]	Ausgangswert MW (SD) [b]	Veränderung MW (SE)	MWD [95%-KI]	p-Wert
Abstammung								
Chinesisch/Asiatisch	66	1,05 (0,210)	0,21 (0,021)	65	1,05 (0,229)	0,13 (0,021)	0,09 [0,030; 0,148]	0,0034*
Hedges' g SMD							0,51 [0,164; 0,861]	0,0039*
Nicht-chinesisch/Asiatisch	68	1,03 (0,170)	0,00 (0,008)	69	1,14 (0,562)	-0,04 (0,008)	0,04 [0,014; 0,060]	0,0015*
Hedges' g SMD							0,54 [0,202; 0,885]	0,0018*
Nicht-asiatisch	79	1,08 (0,311)	0,03 (0,011)	81	1,12 (0,422)	-0,02 (0,011)	0,05 [0,020; 0,081]	0,0013*
Hedges' g SMD							0,51 [0,193; 0,823]	0,0016*
Int. p-Wert								0,5787
Methode zur Gewebeuntersuchung								
zentral	86	1,05 (0,212)	0,14 (0,018)	93	1,11 (0,448)	0,06 (0,017)	0,08 [0,031; 0,129]	0,0014*
Hedges' g SMD							0,48 [0,182; 0,777]	0,0016*
lokal	127	1,06 (0,261)	0,04 (0,007)	122	1,10 (0,416)	-0,02 (0,007)	0,05 [0,034; 0,074]	<0,0001*
Hedges' g SMD							0,67 [0,419; 0,930]	<0,0001*
Int. p-Wert								0,2956
WHO Performance-Status								
0	79	1,04 (0,192)	0,06 (0,012)	81	1,07 (0,342)	0,03 (0,012)	0,03 [-0,004; 0,062]	0,0874
Hedges' g SMD							0,27 [-0,042; 0,581]	0,0895
1	134	1,06 (0,268)	0,09 (0,011)	134	1,13 (0,474)	0,01 (0,012)	0,08 [0,050; 0,114]	<0,0001*
Hedges' g SMD							0,61 [0,365; 0,855]	<0,0001*
Int. p-Wert								0,1165
Raucherstatus								
Ja	75	1,07 (0,251)	0,04 (0,013)	78	1,10 (0,442)	0,00 (0,014)	0,04 [0,002; 0,077]	0,0411*
Hedges' g SMD							0,33 [0,010; 0,648]	0,0435*
Nein	138	1,04 (0,238)	0,10 (0,011)	137	1,11 (0,423)	0,03 (0,011)	0,07 [0,045; 0,105]	<0,0001*
Hedges' g SMD							0,60 [0,354; 0,837]	<0,0001*
Int. p-Wert								0,6754

Analysis is performed if there are at least 10 patients in each subgroup level.
[a] = Number of patients with change from baseline used for MMRM analysis at each timepoint. [b] = Mean baseline for patients with change from baseline used for MMRM analysis at each timepoint. Treatment difference is calculated from a mixed model for repeated measures (MMRM) analysis of the change from baseline score with treatment, visit, and treatment by visit interaction as fixed effects, baseline score as a covariate and baseline score by visit interaction. Patient is used as random effect in the model. Only visits where change from baseline is available for at least 25% of patients in both treatment arms are included in the analysis. Autoregressive with heterogeneity covariance matrix is used to model within-subject error. If the MMRM model does not converge the model results are not presented. SMD = standardised mean difference. * p<0.05.
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Table 4.2.3.30 FLAURA-2: Summary of subgroup analysis of change from baseline in PRO-CTCAE Erbrechen (mixed model for repeated measures) - average over all visits
Full Analysis Set, DCO 03APR2023

	Osi + Chemo (N=279)			Osi (N=278)			Behandlungseffekt	
Subgruppen	n [a]	Ausgangswert MW (SD) [b]	Veränderung MW (SE)	n [a]	Ausgangswert MW (SD) [b]	Veränderung MW (SE)	MWD [95%-KI]	p-Wert
Geschlecht								
Maennlich	78	1,04 (0,194)	0,06 (0,013)	82	1,10 (0,433)	0,01 (0,014)	0,05 [0,013; 0,088]	0,0077*
Hedges' g SMD							0,42 [0,108; 0,735]	0,0084*
Weiblich	135	1,06 (0,267)	0,09 (0,011)	133	1,11 (0,428)	0,02 (0,011)	0,07 [0,040; 0,101]	<0,0001*
Hedges' g SMD							0,55 [0,308; 0,797]	<0,0001*
Int. p-Wert								0,6349
Nachweis der EGFR-Mutation durch zentralen ctDNA Cobas Test								
positiv	161	1,05 (0,245)	0,08 (0,010)	163	1,12 (0,472)	0,01 (0,010)	0,07 [0,039; 0,096]	<0,0001*
Hedges' g SMD							0,52 [0,294; 0,737]	<0,0001*
negativ	32	NC	NC	30	NC	NC	NC	NC
unbekannt	20	NC	NC	22	NC	NC	NC	NC
Int. p-Wert								NC
EGFR-Mutationstyp								
Exon 19 Deletion	126	1,05 (0,248)	0,11 (0,010)	128	1,09 (0,372)	0,03 (0,010)	0,08 [0,047; 0,105]	<0,0001*
Hedges' g SMD							0,65 [0,398; 0,903]	<0,0001*
Exon 21 (L858R) Substitutionsmutation	87	1,06 (0,234)	0,04 (0,015)	85	1,14 (0,508)	0,00 (0,016)	0,04 [-0,003; 0,081]	0,0719
Hedges' g SMD							0,28 [-0,025; 0,576]	0,0725
Int. p-Wert								0,2534
Zentral bestätigte EGFR-Mutation im Gewebe								
positiv	190	1,05 (0,246)	0,08 (0,009)	188	1,11 (0,452)	0,02 (0,009)	0,06 [0,032; 0,083]	<0,0001*
Hedges' g SMD							0,45 [0,245; 0,653]	<0,0001*
negativ	2	ID	ID	3	ID	ID	ID	ID
unbekannt	21	NC	NC	24	NC	NC	NC	NC
Int. p-Wert								NC
ZNS-Metastasen zur Baseline								

Analysis is performed if there are at least 10 patients in each subgroup level.
[a] = Number of patients with change from baseline used for MMRM analysis at each timepoint. [b] = Mean baseline for patients with change from baseline used for MMRM analysis at each timepoint. Treatment difference is calculated from a mixed model for repeated measures (MMRM) analysis of the change from baseline score with treatment, visit, and treatment by visit interaction as fixed effects, baseline score as a covariate and baseline score by visit interaction. Patient is used as random effect in the model. Only visits where change from baseline is available for at least 25% of patients in both treatment arms are included in the analysis. Autoregressive with heterogeneity covariance matrix is used to model within-subject error. If the MMRM model does not converge the model results are not presented. SMD = standardised mean difference. * p<0.05.
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Table 4.2.3.30 FLAURA-2: Summary of subgroup analysis of change from baseline in PRO-CTCAE Erbrechen (mixed model for repeated measures) - average over all visits
Full Analysis Set, DCO 03APR2023

	Osi + Chemo (N=279)			Osi (N=278)			Behandlungseffekt	
Subgruppen	n [a]	Ausgangswert MW (SD) [b]	Veränderung MW (SE)	n [a]	Ausgangswert MW (SD) [b]	Veränderung MW (SE)	MWD [95%-KI]	p-Wert
Ja	84	1,06 (0,284)	0,06 (0,014)	85	1,14 (0,496)	0,00 (0,014)	0,07 [0,026; 0,105]	0,0011*
Hedges' g SMD							0,51 [0,199; 0,812]	0,0012*
Nein	129	1,05 (0,211)	0,09 (0,011)	130	1,08 (0,379)	0,03 (0,011)	0,06 [0,031; 0,092]	<0,0001*
Hedges' g SMD							0,49 [0,242; 0,737]	0,0001*
Int. p-Wert								0,9977
Zentrale Bestätigung der EGFR-Mutation								
Zentral bestätigte EGFR-Mutation in Gewebe oder ctDNA	201	1,05 (0,240)	0,08 (0,009)	208	1,11 (0,436)	0,02 (0,009)	0,06 [0,036; 0,085]	<0,0001*
Hedges' g SMD							0,48 [0,285; 0,679]	<0,0001*
Keine zentrale Bestätigung	12	NC	NC	7	NC	NC	NC	NC
Int. p-Wert								NC
Alter bei Screening								
<65 Jahre	127	1,06 (0,244)	0,10 (0,012)	127	1,11 (0,417)	0,00 (0,012)	0,10 [0,068; 0,133]	<0,0001*
Hedges' g SMD							0,76 [0,504; 1,013]	<0,0001*
>=65 Jahre	86	1,03 (0,240)	0,05 (0,012)	88	1,10 (0,448)	0,05 (0,012)	0,00 [-0,034; 0,034]	0,9911
Hedges' g SMD							0,00 [-0,296; 0,299]	0,9912
Int. p-Wert								0,0002*
Region gPAP								
Asien	126	1,03 (0,176)	0,11 (0,012)	128	1,10 (0,444)	0,04 (0,012)	0,07 [0,037; 0,105]	<0,0001*
Hedges' g SMD							0,51 [0,262; 0,762]	<0,0001*
Europa	18	NC	NC	18	NC	NC	NC	NC
Nordamerika	15	NC	NC	15	NC	NC	NC	NC
Rest der Welt	54	NC	NC	54	NC	NC	NC	NC
Int. p-Wert								NC

Analysis is performed if there are at least 10 patients in each subgroup level.
[a] = Number of patients with change from baseline used for MMRM analysis at each timepoint. [b] = Mean baseline for patients with change from baseline used for MMRM analysis at each timepoint. Treatment difference is calculated from a mixed model for repeated measures (MMRM) analysis of the change from baseline score with treatment, visit, and treatment by visit interaction as fixed effects, baseline score as a covariate and baseline score by visit interaction. Patient is used as random effect in the model. Only visits where change from baseline is available for at least 25% of patients in both treatment arms are included in the analysis. Autoregressive with heterogeneity covariance matrix is used to model within-subject error. If the MMRM model does not converge the model results are not presented. SMD = standardised mean difference. * p<0.05.
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Table 4.2.3.31 FLAURA-2: Summary of subgroup analysis of change from baseline in PRO-CTCAE Weicher oder wässriger Stuhl (mixed model for repeated measures) - average over all visits
Full Analysis Set, DCO 03APR2023

	Osi + Chemo (N=279)			Osi (N=278)			Behandlungseffekt	
Subgruppen	n [a]	Ausgangswert MW (SD) [b]	Veränderung MW (SE)	n [a]	Ausgangswert MW (SD) [b]	Veränderung MW (SE)	MWD [95%-KI]	p-Wert
Abstammung								
Chinesisch/Asiatisch	66	1,29 (0,519)	0,44 (0,035)	65	1,29 (0,631)	0,56 (0,036)	-0,12 [-0,219; -0,023]	0,0153*
Hedges' g SMD							-0,42 [-0,769; -0,077]	0,0167*
Nicht-chinesisch/Asiatisch	68	1,24 (0,694)	0,61 (0,046)	69	1,25 (0,604)	0,74 (0,047)	-0,13 [-0,258; 0,001]	0,0524
Hedges' g SMD							-0,33 [-0,668; 0,007]	0,0549
Nicht-asiatisch	79	1,20 (0,540)	0,55 (0,044)	81	1,28 (0,617)	0,54 (0,045)	0,01 [-0,113; 0,135]	0,8616
Hedges' g SMD							0,03 [-0,282; 0,337]	0,8621
Int. p-Wert								0,1709
Methode zur Gewebeuntersuchung								
zentral	86	1,23 (0,501)	0,51 (0,037)	93	1,32 (0,710)	0,53 (0,036)	-0,02 [-0,117; 0,084]	0,7504
Hedges' g SMD							-0,05 [-0,341; 0,246]	0,7514
lokal	127	1,24 (0,639)	0,56 (0,032)	122	1,24 (0,531)	0,68 (0,034)	-0,12 [-0,212; -0,029]	0,0103*
Hedges' g SMD							-0,33 [-0,576; -0,075]	0,0108*
Int. p-Wert								0,2343
WHO Performance-Status								
0	79	1,15 (0,455)	0,69 (0,043)	81	1,27 (0,592)	0,71 (0,043)	-0,01 [-0,134; 0,106]	0,8200
Hedges' g SMD							-0,04 [-0,346; 0,274]	0,8202
1	134	1,29 (0,647)	0,43 (0,029)	134	1,28 (0,630)	0,55 (0,030)	-0,12 [-0,199; -0,036]	0,0049*
Hedges' g SMD							-0,34 [-0,585; -0,103]	0,0052*
Int. p-Wert								0,1802
Raucherstatus								
Ja	75	1,21 (0,501)	0,61 (0,049)	78	1,28 (0,622)	0,76 (0,050)	-0,15 [-0,287; -0,011]	0,0340*
Hedges' g SMD							-0,34 [-0,662; -0,024]	0,0353*
Nein	138	1,25 (0,629)	0,50 (0,027)	137	1,27 (0,612)	0,53 (0,028)	-0,03 [-0,109; 0,042]	0,3890
Hedges' g SMD							-0,10 [-0,340; 0,133]	0,3903
Int. p-Wert								0,0629

Analysis is performed if there are at least 10 patients in each subgroup level.
[a] = Number of patients with change from baseline used for MMRM analysis at each timepoint. [b] = Mean baseline for patients with change from baseline used for MMRM analysis at each timepoint. Treatment difference is calculated from a mixed model for repeated measures (MMRM) analysis of the change from baseline score with treatment, visit, and treatment by visit interaction as fixed effects, baseline score as a covariate and baseline score by visit interaction. Patient is used as random effect in the model. Only visits where change from baseline is available for at least 25% of patients in both treatment arms are included in the analysis. Autoregressive with heterogeneity covariance matrix is used to model within-subject error. If the MMRM model does not converge the model results are not presented. SMD = standardised mean difference. * p<0.05.
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Table 4.2.3.31 FLAURA-2: Summary of subgroup analysis of change from baseline in PRO-CTCAE Weicher oder wässriger Stuhl (mixed model for repeated measures) - average over all visits
Full Analysis Set, DCO 03APR2023

	Osi + Chemo (N=279)			Osi (N=278)			Behandlungseffekt	
Subgruppen	n [a]	Ausgangswert MW (SD) [b]	Veränderung MW (SE)	n [a]	Ausgangswert MW (SD) [b]	Veränderung MW (SE)	MWD [95%-KI]	p-Wert
Geschlecht								
Maennlich	78	1,21 (0,466)	0,51 (0,039)	82	1,34 (0,652)	0,62 (0,041)	-0,11 [-0,220; 0,002]	0,0535
Hedges' g SMD							-0,31 [-0,617; 0,007]	0,0550
Weiblich	135	1,26 (0,646)	0,55 (0,031)	133	1,23 (0,589)	0,61 (0,031)	-0,05 [-0,139; 0,035]	0,2414
Hedges' g SMD							-0,14 [-0,383; 0,097]	0,2430
Int. p-Wert								0,3546
Nachweis der EGFR-Mutation durch zentralen ctDNA Cobas Test								
positiv	161	1,23 (0,584)	0,53 (0,027)	163	1,26 (0,597)	0,62 (0,028)	-0,08 [-0,158; -0,005]	0,0360*
Hedges' g SMD							-0,23 [-0,451; -0,014]	0,0368*
negativ	32	1,22 (0,553)	0,53 (0,080)	30	1,27 (0,583)	0,76 (0,082)	-0,23 [-0,458; -0,006]	0,0444*
Hedges' g SMD							-0,51 [-1,016; -0,002]	0,0489*
unbekannt	20	1,35 (0,671)	0,57 (0,066)	22	1,36 (0,790)	0,35 (0,070)	0,21 [0,022; 0,401]	0,0287*
Hedges' g SMD							0,66 [0,039; 1,287]	0,0372*
Int. p-Wert								0,0054*
EGFR-Mutationstyp								
Exon 19 Deletion	126	1,24 (0,543)	0,61 (0,032)	128	1,18 (0,442)	0,69 (0,032)	-0,08 [-0,169; 0,010]	0,0801
Hedges' g SMD							-0,22 [-0,466; 0,027]	0,0814
Exon 21 (L858R) Substitutionsmutation	87	1,24 (0,646)	0,42 (0,037)	85	1,41 (0,791)	0,50 (0,040)	-0,07 [-0,181; 0,033]	0,1768
Hedges' g SMD							-0,21 [-0,506; 0,094]	0,1781
Int. p-Wert								0,8752
Zentral bestätigte EGFR-Mutation im Gewebe								
positiv	190	1,24 (0,595)	0,54 (0,026)	188	1,26 (0,613)	0,64 (0,027)	-0,10 [-0,173; -0,025]	0,0087*
Hedges' g SMD							-0,27 [-0,472; -0,067]	0,0091*
negativ	2	ID	ID	3	ID	ID	ID	ID
unbekannt	21	1,24 (0,539)	0,40 (0,070)	24	1,42 (0,654)	0,37 (0,064)	0,03 [-0,161; 0,218]	0,7675
Hedges' g SMD							0,09 [-0,498; 0,674]	0,7693

Analysis is performed if there are at least 10 patients in each subgroup level.
[a] = Number of patients with change from baseline used for MMRM analysis at each timepoint. [b] = Mean baseline for patients with change from baseline used for MMRM analysis at each timepoint. Treatment difference is calculated from a mixed model for repeated measures (MMRM) analysis of the change from baseline score with treatment, visit, and treatment by visit interaction as fixed effects, baseline score as a covariate and baseline score by visit interaction. Patient is used as random effect in the model. Only visits where change from baseline is available for at least 25% of patients in both treatment arms are included in the analysis. Autoregressive with heterogeneity covariance matrix is used to model within-subject error. If the MMRM model does not converge the model results are not presented. SMD = standardised mean difference. * p<0.05.
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Table 4.2.3.31 FLAURA-2: Summary of subgroup analysis of change from baseline in PRO-CTCAE Weicher oder wässriger Stuhl (mixed model for repeated measures) - average over all visits
Full Analysis Set, DCO 03APR2023

	Osi + Chemo (N=279)			Osi (N=278)			Behandlungseffekt	
Subgruppen	n [a]	Ausgangswert MW (SD) [b]	Veränderung MW (SE)	n [a]	Ausgangswert MW (SD) [b]	Veränderung MW (SE)	MWD [95%-KI]	p-Wert
Int. p-Wert								0,2054
ZNS-Metastasen zur Baseline								
Ja	84	1,26 (0,642)	0,49 (0,040)	85	1,38 (0,740)	0,61 (0,043)	-0,12 [-0,239; -0,008]	0,0366*
Hedges' g SMD							-0,32 [-0,625; -0,018]	0,0379*
Nein	129	1,22 (0,548)	0,56 (0,031)	130	1,21 (0,509)	0,61 (0,031)	-0,05 [-0,136; 0,034]	0,2403
Hedges' g SMD							-0,15 [-0,390; 0,098]	0,2419
Int. p-Wert								0,4450
Zentrale Bestätigung der EGFR-Mutation								
Zentral bestätigte EGFR-Mutation in Gewebe oder ctDNA	201	1,24 (0,596)	0,53 (0,025)	208	1,28 (0,621)	0,62 (0,025)	-0,09 [-0,161; -0,021]	0,0110*
Hedges' g SMD							-0,25 [-0,446; -0,057]	0,0114*
Keine zentrale Bestätigung	12	1,17 (0,389)	, (,)	7	1,14 (0,378)	, (,)	, [, ; ,]	
Hedges' g SMD							, [, ; ,]	
Int. p-Wert								0,0189*
Alter bei Screening								
<65 Jahre	127	1,27 (0,636)	0,53 (0,033)	127	1,27 (0,597)	0,67 (0,034)	-0,15 [-0,238; -0,054]	0,0018*
Hedges' g SMD							-0,39 [-0,639; -0,143]	0,0020*
>=65 Jahre	86	1,20 (0,505)	0,55 (0,036)	88	1,28 (0,642)	0,52 (0,037)	0,03 [-0,070; 0,133]	0,5463
Hedges' g SMD							0,09 [-0,206; 0,388]	0,5480
Int. p-Wert								0,0087*
Region gPAP								
Asien	126	1,27 (0,625)	0,54 (0,030)	128	1,27 (0,624)	0,66 (0,031)	-0,13 [-0,211; -0,041]	0,0037*
Hedges' g SMD							-0,36 [-0,613; -0,116]	0,0040*
Europa	18	1,33 (0,686)	0,46 (0,108)	18	1,28 (0,575)	0,37 (0,106)	0,10 [-0,204; 0,398]	0,5211
Hedges' g SMD							0,21 [-0,446; 0,865]	0,5305
Nordamerika	15	1,27 (0,594)	0,59 (0,082)	15	1,40 (0,632)	0,34 (0,079)	0,26 [0,029; 0,481]	0,0274*

Analysis is performed if there are at least 10 patients in each subgroup level.
[a] = Number of patients with change from baseline used for MMRM analysis at each timepoint. [b] = Mean baseline for patients with change from baseline used for MMRM analysis at each timepoint. Treatment difference is calculated from a mixed model for repeated measures (MMRM) analysis of the change from baseline score with treatment, visit, and treatment by visit interaction as fixed effects, baseline score as a covariate and baseline score by visit interaction. Patient is used as random effect in the model. Only visits where change from baseline is available for at least 25% of patients in both treatment arms are included in the analysis. Autoregressive with heterogeneity covariance matrix is used to model within-subject error. If the MMRM model does not converge the model results are not presented. SMD = standardised mean difference. * p<0.05.
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Table 4.2.3.31 FLAURA-2: Summary of subgroup analysis of change from baseline in PRO-CTCAE Weicher oder wässriger Stuhl (mixed model for repeated measures) - average over all visits
Full Analysis Set, DCO 03APR2023

	Osi + Chemo (N=279)			Osi (N=278)			Behandlungseffekt	
Subgruppen	n [a]	Ausgangswert MW (SD) [b]	Veränderung MW (SE)	n [a]	Ausgangswert MW (SD) [b]	Veränderung MW (SE)	MWD [95%-KI]	p-Wert
Hedges' g SMD							0,79 [0,046; 1,541]	0,0374*
Rest der Welt	54	1,13 (0,436)	0,54 (0,053)	54	1,24 (0,612)	0,64 (0,055)	-0,10 [-0,248; 0,055]	0,2094
Hedges' g SMD							-0,24 [-0,619; 0,138]	0,2130
Int. p-Wert								0,0110*

Analysis is performed if there are at least 10 patients in each subgroup level.
[a] = Number of patients with change from baseline used for MMRM analysis at each timepoint. [b] = Mean baseline for patients with change from baseline used for MMRM analysis at each timepoint. Treatment difference is calculated from a mixed model for repeated measures (MMRM) analysis of the change from baseline score with treatment, visit, and treatment by visit interaction as fixed effects, baseline score as a covariate and baseline score by visit interaction. Patient is used as random effect in the model. Only visits where change from baseline is available for at least 25% of patients in both treatment arms are included in the analysis. Autoregressive with heterogeneity covariance matrix is used to model within-subject error. If the MMRM model does not converge the model results are not presented. SMD = standardised mean difference. * p<0.05.
root/cdar/d516/payer_germany/ar/d5169c00001_payer_germany/tlf/prod/program/mmrmsubprdg.sas gmmrmsubprdgae 04JUN2024:18:07 kvbv306

Table 4.2.3.32 FLAURA-2: Summary of subgroup analysis of change from baseline in PRO-CTCAE Bauchschmerzen (mixed model for repeated measures) - average over all visits
Full Analysis Set, DCO 03APR2023

	Osi + Chemo (N=279)			Osi (N=278)			Behandlungseffekt	
Subgruppen	n [a]	Ausgangswert MW (SD) [b]	Veränderung MW (SE)	n [a]	Ausgangswert MW (SD) [b]	Veränderung MW (SE)	MWD [95%-KI]	p-Wert
Abstammung								
Chinesisch/Asiatisch	66	1,15 (0,342)	0,25 (0,026)	65	1,16 (0,449)	0,21 (0,026)	0,03 [-0,038; 0,106]	0,3478
Hedges' g SMD							0,16 [-0,180; 0,507]	0,3505
Nicht-chinesisch/Asiatisch	68	1,13 (0,382)	0,27 (0,026)	69	1,16 (0,445)	0,21 (0,027)	0,06 [-0,016; 0,132]	0,1235
Hedges' g SMD							0,26 [-0,074; 0,599]	0,1266
Nicht-asiatisch	79	1,24 (0,539)	0,25 (0,027)	81	1,29 (0,698)	0,12 (0,028)	0,12 [0,047; 0,200]	0,0015*
Hedges' g SMD							0,50 [0,186; 0,816]	0,0018*
Int. p-Wert								0,1667
Methode zur Gewebeuntersuchung								
zentral	86	1,15 (0,378)	0,22 (0,025)	93	1,29 (0,713)	0,15 (0,025)	0,07 [-0,004; 0,135]	0,0666
Hedges' g SMD							0,27 [-0,021; 0,569]	0,0683
lokal	127	1,19 (0,474)	0,28 (0,018)	122	1,15 (0,391)	0,20 (0,020)	0,08 [0,027; 0,132]	0,0033*
Hedges' g SMD							0,37 [0,123; 0,624]	0,0035*
Int. p-Wert								0,8135
WHO Performance-Status								
0	79	1,08 (0,282)	0,28 (0,023)	81	1,25 (0,537)	0,16 (0,023)	0,12 [0,059; 0,189]	0,0002*
Hedges' g SMD							0,59 [0,278; 0,912]	0,0002*
1	134	1,23 (0,499)	0,24 (0,020)	134	1,19 (0,569)	0,19 (0,020)	0,05 [-0,005; 0,106]	0,0748
Hedges' g SMD							0,22 [-0,023; 0,458]	0,0758
Int. p-Wert								0,2576
Raucherstatus								
Ja	75	1,14 (0,368)	0,29 (0,025)	78	1,18 (0,600)	0,23 (0,026)	0,05 [-0,020; 0,121]	0,1631
Hedges' g SMD							0,22 [-0,093; 0,543]	0,1662
Nein	138	1,19 (0,471)	0,24 (0,019)	137	1,23 (0,532)	0,15 (0,019)	0,09 [0,036; 0,142]	0,0010*
Hedges' g SMD							0,40 [0,158; 0,636]	0,0011*
Int. p-Wert								0,3854

Analysis is performed if there are at least 10 patients in each subgroup level.
[a] = Number of patients with change from baseline used for MMRM analysis at each timepoint. [b] = Mean baseline for patients with change from baseline used for MMRM analysis at each timepoint. Treatment difference is calculated from a mixed model for repeated measures (MMRM) analysis of the change from baseline score with treatment, visit, and treatment by visit interaction as fixed effects, baseline score as a covariate and baseline score by visit interaction. Patient is used as random effect in the model. Only visits where change from baseline is available for at least 25% of patients in both treatment arms are included in the analysis. Autoregressive with heterogeneity covariance matrix is used to model within-subject error. If the MMRM model does not converge the model results are not presented. SMD = standardised mean difference. * p<0.05.
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Table 4.2.3.32 FLAURA-2: Summary of subgroup analysis of change from baseline in PRO-CTCAE Bauchschmerzen (mixed model for repeated measures) - average over all visits
Full Analysis Set, DCO 03APR2023

	Osi + Chemo (N=279)			Osi (N=278)			Behandlungseffekt	
Subgruppen	n [a]	Ausgangswert MW (SD) [b]	Veränderung MW (SE)	n [a]	Ausgangswert MW (SD) [b]	Veränderung MW (SE)	MWD [95%-KI]	p-Wert
Geschlecht								
Maennlich	78	1,13 (0,332)	0,30 (0,024)	82	1,16 (0,454)	0,22 (0,026)	0,08 [0,011; 0,149]	0,0236*
Hedges' g SMD							0,36 [0,044; 0,669]	0,0252*
Weiblich	135	1,20 (0,487)	0,23 (0,019)	133	1,24 (0,610)	0,16 (0,019)	0,07 [0,020; 0,127]	0,0071*
Hedges' g SMD							0,33 [0,088; 0,570]	0,0075*
Int. p-Wert								0,8511
Nachweis der EGFR-Mutation durch zentralen ctDNA Cobas Test								
positiv	161	1,17 (0,441)	0,24 (0,016)	163	1,20 (0,587)	0,16 (0,017)	0,08 [0,033; 0,124]	0,0008*
Hedges' g SMD							0,37 [0,152; 0,592]	0,0009*
negativ	32	1,11 (0,301)	0,38 (0,043)	30	1,06 (0,216)	0,26 (0,044)	0,11 [-0,007; 0,237]	0,0644
Hedges' g SMD							0,47 [-0,038; 0,973]	0,0697
unbekannt	20	1,27 (0,578)	0,16 (0,062)	22	1,47 (0,570)	0,21 (0,065)	-0,04 [-0,229; 0,141]	0,6407
Hedges' g SMD							-0,15 [-0,754; 0,459]	0,6340
Int. p-Wert								0,2249
EGFR-Mutationstyp								
Exon 19 Deletion	126	1,19 (0,453)	0,32 (0,018)	128	1,14 (0,434)	0,19 (0,018)	0,13 [0,079; 0,181]	<0,0001*
Hedges' g SMD							0,63 [0,375; 0,879]	<0,0001*
Exon 21 (L858R) Substitutionsmutation	87	1,15 (0,415)	0,16 (0,025)	85	1,32 (0,695)	0,18 (0,028)	-0,02 [-0,093; 0,055]	0,6090
Hedges' g SMD							-0,08 [-0,377; 0,221]	0,6090
Int. p-Wert								0,0006*
Zentral bestätigte EGFR-Mutation im Gewebe								
positiv	190	1,17 (0,435)	0,25 (0,016)	188	1,22 (0,580)	0,18 (0,016)	0,08 [0,032; 0,121]	0,0008*
Hedges' g SMD							0,34 [0,141; 0,547]	0,0009*
negativ	2	ID	ID	3	ID	ID	ID	ID
unbekannt	21	1,24 (0,485)	0,24 (0,049)	24	1,18 (0,368)	0,20 (0,045)	0,04 [-0,089; 0,176]	0,5204
Hedges' g SMD							0,19 [-0,397; 0,777]	0,5253

Analysis is performed if there are at least 10 patients in each subgroup level.
[a] = Number of patients with change from baseline used for MMRM analysis at each timepoint. [b] = Mean baseline for patients with change from baseline used for MMRM analysis at each timepoint. Treatment difference is calculated from a mixed model for repeated measures (MMRM) analysis of the change from baseline score with treatment, visit, and treatment by visit interaction as fixed effects, baseline score as a covariate and baseline score by visit interaction. Patient is used as random effect in the model. Only visits where change from baseline is available for at least 25% of patients in both treatment arms are included in the analysis. Autoregressive with heterogeneity covariance matrix is used to model within-subject error. If the MMRM model does not converge the model results are not presented. SMD = standardised mean difference. * p<0.05.
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Table 4.2.3.32 FLAURA-2: Summary of subgroup analysis of change from baseline in PRO-CTCAE Bauchschmerzen (mixed model for repeated measures) - average over all visits
Full Analysis Set, DCO 03APR2023

	Osi + Chemo (N=279)			Osi (N=278)			Behandlungseffekt	
Subgruppen	n [a]	Ausgangswert MW (SD) [b]	Veränderung MW (SE)	n [a]	Ausgangswert MW (SD) [b]	Veränderung MW (SE)	MWD [95%-KI]	p-Wert
Int. p-Wert								0,4087
ZNS-Metastasen zur Baseline								
Ja	84	1,25 (0,507)	0,21 (0,024)	85	1,30 (0,672)	0,08 (0,026)	0,12 [0,055; 0,191]	0,0004*
Hedges' g SMD							0,54 [0,234; 0,848]	0,0006*
Nein	129	1,13 (0,380)	0,28 (0,019)	130	1,15 (0,459)	0,23 (0,019)	0,05 [-0,003; 0,104]	0,0664
Hedges' g SMD							0,23 [-0,017; 0,472]	0,0677
Int. p-Wert								0,0727
Zentrale Bestätigung der EGFR-Mutation								
Zentral bestätigte EGFR-Mutation in Gewebe oder ctDNA	201	1,17 (0,437)	0,25 (0,015)	208	1,21 (0,559)	0,19 (0,016)	0,06 [0,015; 0,101]	0,0080*
Hedges' g SMD							0,26 [0,067; 0,457]	0,0083*
Keine zentrale Bestätigung	12	1,28 (0,446)	, (,)	7	1,29 (0,488)	, (,)	, [, ; ,]	
Hedges' g SMD							, [, ; ,]	
Int. p-Wert								0,0007*
Alter bei Screening								
<65 Jahre	127	1,20 (0,466)	0,27 (0,019)	127	1,24 (0,624)	0,13 (0,019)	0,13 [0,082; 0,187]	<0,0001*
Hedges' g SMD							0,63 [0,376; 0,880]	<0,0001*
>=65 Jahre	86	1,13 (0,390)	0,24 (0,025)	88	1,17 (0,441)	0,26 (0,025)	-0,02 [-0,088; 0,051]	0,6007
Hedges' g SMD							-0,08 [-0,376; 0,218]	0,6022
Int. p-Wert								0,0008*
Region gPAP								
Asien	126	1,13 (0,363)	0,27 (0,019)	128	1,14 (0,426)	0,22 (0,019)	0,05 [0,001; 0,108]	0,0439*
Hedges' g SMD							0,25 [0,006; 0,499]	0,0451*
Europa	18	1,31 (0,652)	0,26 (0,052)	18	1,13 (0,382)	0,05 (0,051)	0,20 [0,059; 0,350]	0,0064*
Hedges' g SMD							0,92 [0,230; 1,612]	0,0090*
Nordamerika	15	1,11 (0,349)	0,38 (0,052)	15	1,29 (0,434)	0,15 (0,051)	0,24 [0,084; 0,387]	0,0027*

Analysis is performed if there are at least 10 patients in each subgroup level.
[a] = Number of patients with change from baseline used for MMRM analysis at each timepoint. [b] = Mean baseline for patients with change from baseline used for MMRM analysis at each timepoint. Treatment difference is calculated from a mixed model for repeated measures (MMRM) analysis of the change from baseline score with treatment, visit, and treatment by visit interaction as fixed effects, baseline score as a covariate and baseline score by visit interaction. Patient is used as random effect in the model. Only visits where change from baseline is available for at least 25% of patients in both treatment arms are included in the analysis. Autoregressive with heterogeneity covariance matrix is used to model within-subject error. If the MMRM model does not converge the model results are not presented. SMD = standardised mean difference. * p<0.05.
root/cdar/d516/payer_germany/ar/d5169c00001_payer_germany/tlf/prod/program/mmrmsubprdg.sas gmmrmsubprdgaf 04JUN2024:18:07 kvbv306

Table 4.2.3.32 FLAURA-2: Summary of subgroup analysis of change from baseline in PRO-CTCAE Bauchschmerzen (mixed model for repeated measures) - average over all visits
Full Analysis Set, DCO 03APR2023

	Osi + Chemo (N=279)			Osi (N=278)			Behandlungseffekt	
Subgruppen	n [a]	Ausgangswert MW (SD) [b]	Veränderung MW (SE)	n [a]	Ausgangswert MW (SD) [b]	Veränderung MW (SE)	MWD [95%-KI]	p-Wert
Hedges' g SMD							1,15 [0,367; 1,928]	0,0040*
Rest der Welt	54	1,23 (0,521)	0,18 (0,034)	54	1,38 (0,822)	0,14 (0,037)	0,03 [-0,067; 0,131]	0,5224
Hedges' g SMD							0,12 [-0,255; 0,500]	0,5246
Int. p-Wert								0,0736

Analysis is performed if there are at least 10 patients in each subgroup level.
[a] = Number of patients with change from baseline used for MMRM analysis at each timepoint. [b] = Mean baseline for patients with change from baseline used for MMRM analysis at each timepoint. Treatment difference is calculated from a mixed model for repeated measures (MMRM) analysis of the change from baseline score with treatment, visit, and treatment by visit interaction as fixed effects, baseline score as a covariate and baseline score by visit interaction. Patient is used as random effect in the model. Only visits where change from baseline is available for at least 25% of patients in both treatment arms are included in the analysis. Autoregressive with heterogeneity covariance matrix is used to model within-subject error. If the MMRM model does not converge the model results are not presented. SMD = standardised mean difference. * p<0.05.
root/cdar/d516/payer_germany/ar/d5169c00001_payer_germany/tlf/prod/program/mmrmsubprdg.sas gmmrmsubprdgaf 04JUN2024:18:07 kvbv306

Table 4.2.3.33 FLAURA-2: Summary of subgroup analysis of change from baseline in PRO-CTCAE Verlust der Kontrolle über den Stuhlgang (mixed model for repeated measures) - average over all visits
Full Analysis Set, DCO 03APR2023

	Osi + Chemo (N=279)			Osi (N=278)			Behandlungseffekt	
Subgruppen	n [a]	Ausgangswert MW (SD) [b]	Veränderung MW (SE)	n [a]	Ausgangswert MW (SD) [b]	Veränderung MW (SE)	MWD [95%-KI]	p-Wert
Abstammung								
Chinesisch/Asiatisch	66	1,08 (0,398)	0,11 (0,016)	65	1,05 (0,372)	0,12 (0,016)	-0,01 [-0,059; 0,029]	0,5138
Hedges' g SMD							-0,11 [-0,457; 0,229]	0,5147
Nicht-chinesisch/Asiatisch	68	1,03 (0,147)	0,08 (0,016)	69	1,07 (0,346)	0,06 (0,017)	0,03 [-0,021; 0,072]	0,2858
Hedges' g SMD							0,18 [-0,154; 0,518]	0,2881
Nicht-asiatisch	79	1,18 (0,631)	0,04 (0,015)	81	1,12 (0,442)	0,05 (0,015)	-0,01 [-0,048; 0,036]	0,7794
Hedges' g SMD							-0,04 [-0,354; 0,266]	0,7804
Int. p-Wert								0,6069
Methode zur Gewebeuntersuchung								
zentral	86	1,09 (0,410)	0,11 (0,016)	93	1,11 (0,515)	0,10 (0,015)	0,01 [-0,032; 0,054]	0,6221
Hedges' g SMD							0,07 [-0,220; 0,367]	0,6236
lokal	127	1,11 (0,482)	0,06 (0,011)	122	1,06 (0,262)	0,07 (0,012)	-0,01 [-0,038; 0,026]	0,7233
Hedges' g SMD							-0,04 [-0,293; 0,204]	0,7239
Int. p-Wert								0,3406
WHO Performance-Status								
0	79	1,02 (0,125)	0,11 (0,017)	81	1,06 (0,310)	0,11 (0,017)	0,00 [-0,047; 0,048]	0,9821
Hedges' g SMD							0,00 [-0,306; 0,313]	0,9822
1	134	1,15 (0,559)	0,07 (0,011)	134	1,09 (0,434)	0,06 (0,012)	0,01 [-0,022; 0,041]	0,5710
Hedges' g SMD							0,07 [-0,170; 0,309]	0,5718
Int. p-Wert								0,5294
Raucherstatus								
Ja	75	1,06 (0,296)	0,12 (0,017)	78	1,04 (0,304)	0,09 (0,017)	0,03 [-0,016; 0,077]	0,1971
Hedges' g SMD							0,21 [-0,110; 0,526]	0,1998
Nein	138	1,12 (0,519)	0,06 (0,011)	137	1,10 (0,434)	0,07 (0,012)	-0,01 [-0,043; 0,021]	0,5040
Hedges' g SMD							-0,08 [-0,317; 0,156]	0,5051
Int. p-Wert								0,2141

Analysis is performed if there are at least 10 patients in each subgroup level.
[a] = Number of patients with change from baseline used for MMRM analysis at each timepoint. [b] = Mean baseline for patients with change from baseline used for MMRM analysis at each timepoint. Treatment difference is calculated from a mixed model for repeated measures (MMRM) analysis of the change from baseline score with treatment, visit, and treatment by visit interaction as fixed effects, baseline score as a covariate and baseline score by visit interaction. Patient is used as random effect in the model. Only visits where change from baseline is available for at least 25% of patients in both treatment arms are included in the analysis. Autoregressive with heterogeneity covariance matrix is used to model within-subject error. If the MMRM model does not converge the model results are not presented. SMD = standardised mean difference. * p<0.05.
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Table 4.2.3.33 FLAURA-2: Summary of subgroup analysis of change from baseline in PRO-CTCAE Verlust der Kontrolle über den Stuhlgang (mixed model for repeated measures) - average over all visits
Full Analysis Set, DCO 03APR2023

	Osi + Chemo (N=279)			Osi (N=278)			Behandlungseffekt	
Subgruppen	n [a]	Ausgangswert MW (SD) [b]	Veränderung MW (SE)	n [a]	Ausgangswert MW (SD) [b]	Veränderung MW (SE)	MWD [95%-KI]	p-Wert
Geschlecht								
Maennlich	78	1,04 (0,239)	0,12 (0,017)	82	1,05 (0,300)	0,09 (0,018)	0,03 [-0,019; 0,078]	0,2300
Hedges' g SMD							0,19 [-0,122; 0,500]	0,2330
Weiblich	135	1,14 (0,538)	0,06 (0,011)	133	1,10 (0,438)	0,07 (0,011)	-0,01 [-0,043; 0,020]	0,4856
Hedges' g SMD							-0,09 [-0,325; 0,155]	0,4867
Int. p-Wert								0,1725
Nachweis der EGFR-Mutation durch zentralen ctDNA Cobas Test								
positiv	161	1,07 (0,339)	0,11 (0,012)	163	1,07 (0,366)	0,08 (0,012)	0,03 [-0,005; 0,060]	0,0916
Hedges' g SMD							0,19 [-0,031; 0,405]	0,0928
negativ	32	NC	NC	30	NC	NC	NC	NC
unbekannt	20	NC	NC	22	NC	NC	NC	NC
Int. p-Wert								NC
EGFR-Mutationstyp								
Exon 19 Deletion	126	1,12 (0,430)	0,12 (0,012)	128	1,04 (0,210)	0,07 (0,012)	0,05 [0,013; 0,078]	0,0058*
Hedges' g SMD							0,35 [0,099; 0,594]	0,0062*
Exon 21 (L858R) Substitutionsmutation	87	1,08 (0,487)	0,02 (0,016)	85	1,15 (0,562)	0,10 (0,017)	-0,08 [-0,123; -0,033]	0,0007*
Hedges' g SMD							-0,52 [-0,821; -0,213]	0,0009*
Int. p-Wert								<0,0001*
Zentral bestätigte EGFR-Mutation im Gewebe								
positiv	190	1,11 (0,468)	0,08 (0,010)	188	1,07 (0,387)	0,08 (0,011)	0,00 [-0,027; 0,032]	0,8723
Hedges' g SMD							0,02 [-0,185; 0,218]	0,8724
negativ	2	ID	ID	3	ID	ID	ID	ID
unbekannt	21	1,07 (0,327)	, (,)	24	1,15 (0,454)	, (,)	0,00 [-0,074; 0,068]	0,9297
Hedges' g SMD							, [, ; ,]	
Int. p-Wert								0,9107

Analysis is performed if there are at least 10 patients in each subgroup level.
[a] = Number of patients with change from baseline used for MMRM analysis at each timepoint. [b] = Mean baseline for patients with change from baseline used for MMRM analysis at each timepoint. Treatment difference is calculated from a mixed model for repeated measures (MMRM) analysis of the change from baseline score with treatment, visit, and treatment by visit interaction as fixed effects, baseline score as a covariate and baseline score by visit interaction. Patient is used as random effect in the model. Only visits where change from baseline is available for at least 25% of patients in both treatment arms are included in the analysis. Autoregressive with heterogeneity covariance matrix is used to model within-subject error. If the MMRM model does not converge the model results are not presented. SMD = standardised mean difference. * p<0.05.
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Table 4.2.3.33 FLAURA-2: Summary of subgroup analysis of change from baseline in PRO-CTCAE Verlust der Kontrolle über den Stuhlgang (mixed model for repeated measures) - average over all visits
Full Analysis Set, DCO 03APR2023

	Osi + Chemo (N=279)			Osi (N=278)			Behandlungseffekt	
Subgruppen	n [a]	Ausgangswert MW (SD) [b]	Veränderung MW (SE)	n [a]	Ausgangswert MW (SD) [b]	Veränderung MW (SE)	MWD [95%-KI]	p-Wert
ZNS-Metastasen zur Baseline								
Ja	84	1,08 (0,409)	0,09 (0,013)	85	1,09 (0,447)	0,05 (0,014)	0,05 [0,010; 0,084]	0,0120*
Hedges' g SMD							0,39 [0,081; 0,690]	0,0130*
Nein	129	1,11 (0,481)	0,08 (0,013)	130	1,07 (0,353)	0,09 (0,013)	-0,02 [-0,052; 0,020]	0,3816
Hedges' g SMD							-0,11 [-0,352; 0,135]	0,3832
Int. p-Wert								0,0290*
Zentrale Bestätigung der EGFR-Mutation								
Zentral bestätigte EGFR-Mutation in Gewebe oder ctDNA	201	1,11 (0,466)	0,08 (0,010)	208	1,08 (0,392)	0,08 (0,010)	0,00 [-0,030; 0,026]	0,9000
Hedges' g SMD							-0,01 [-0,206; 0,181]	0,9002
Keine zentrale Bestätigung	12	NC	NC	7	NC	NC	NC	NC
Int. p-Wert								NC
Alter bei Screening								
<65 Jahre	127	1,13 (0,523)	0,05 (0,010)	127	1,09 (0,390)	0,04 (0,011)	0,01 [-0,016; 0,043]	0,3763
Hedges' g SMD							0,11 [-0,135; 0,357]	0,3778
>=65 Jahre	86	1,06 (0,324)	0,12 (0,017)	88	1,07 (0,395)	0,14 (0,017)	-0,02 [-0,063; 0,033]	0,5317
Hedges' g SMD							-0,09 [-0,392; 0,203]	0,5341
Int. p-Wert								0,2120
Region gPAP								
Asien	126	1,06 (0,307)	0,09 (0,012)	128	1,06 (0,366)	0,09 (0,012)	0,00 [-0,033; 0,036]	0,9241
Hedges' g SMD							0,01 [-0,234; 0,258]	0,9243
Europa	18	NC	NC	18	NC	NC	NC	NC
Nordamerika	15	1,10 (0,387)	0,13 (0,032)	15	1,17 (0,362)	0,03 (0,031)	0,10 [0,009; 0,185]	0,0314*
Hedges' g SMD							0,78 [0,033; 1,526]	0,0407*
Rest der Welt	54	1,18 (0,681)	0,05 (0,018)	54	1,13 (0,506)	0,09 (0,019)	-0,04 [-0,093; 0,009]	0,1094

Analysis is performed if there are at least 10 patients in each subgroup level.
[a] = Number of patients with change from baseline used for MMRM analysis at each timepoint. [b] = Mean baseline for patients with change from baseline used for MMRM analysis at each timepoint. Treatment difference is calculated from a mixed model for repeated measures (MMRM) analysis of the change from baseline score with treatment, visit, and treatment by visit interaction as fixed effects, baseline score as a covariate and baseline score by visit interaction. Patient is used as random effect in the model. Only visits where change from baseline is available for at least 25% of patients in both treatment arms are included in the analysis. Autoregressive with heterogeneity covariance matrix is used to model within-subject error. If the MMRM model does not converge the model results are not presented. SMD = standardised mean difference. * p<0.05.
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Table 4.2.3.33 FLAURA-2: Summary of subgroup analysis of change from baseline in PRO-CTCAE Verlust der Kontrolle über den Stuhlgang (mixed model for repeated measures) - average over all visits
Full Analysis Set, DCO 03APR2023

	Osi + Chemo (N=279)			Osi (N=278)			Behandlungseffekt	
Subgruppen	n [a]	Ausgangswert MW (SD) [b]	Veränderung MW (SE)	n [a]	Ausgangswert MW (SD) [b]	Veränderung MW (SE)	MWD [95%-KI]	p-Wert
Hedges' g SMD							-0,31 [-0,685; 0,074]	0,1146
Int. p-Wert								0,0132*

Analysis is performed if there are at least 10 patients in each subgroup level.
[a] = Number of patients with change from baseline used for MMRM analysis at each timepoint. [b] = Mean baseline for patients with change from baseline used for MMRM analysis at each timepoint. Treatment difference is calculated from a mixed model for repeated measures (MMRM) analysis of the change from baseline score with treatment, visit, and treatment by visit interaction as fixed effects, baseline score as a covariate and baseline score by visit interaction. Patient is used as random effect in the model. Only visits where change from baseline is available for at least 25% of patients in both treatment arms are included in the analysis. Autoregressive with heterogeneity covariance matrix is used to model within-subject error. If the MMRM model does not converge the model results are not presented. SMD = standardised mean difference. * p<0.05.
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Table 4.2.3.34 FLAURA-2: Summary of subgroup analysis of change from baseline in PRO-CTCAE Trockene Haut (mixed model for repeated measures) - average over all visits
Full Analysis Set, DCO 03APR2023

	Osi + Chemo (N=279)			Osi (N=278)			Behandlungseffekt	
Subgruppen	n [a]	Ausgangswert MW (SD) [b]	Veränderung MW (SE)	n [a]	Ausgangswert MW (SD) [b]	Veränderung MW (SE)	MWD [95%-KI]	p-Wert
Abstammung								
Chinesisch/Asiatisch	66	1,27 (0,482)	0,51 (0,034)	65	1,20 (0,403)	0,54 (0,035)	-0,04 [-0,132; 0,060]	0,4604
Hedges' g SMD							-0,13 [-0,471; 0,214]	0,4625
Nicht-chinesisch/Asiatisch	68	1,35 (0,593)	0,65 (0,032)	69	1,26 (0,634)	0,61 (0,033)	0,03 [-0,057; 0,124]	0,4697
Hedges' g SMD							0,12 [-0,212; 0,458]	0,4720
Nicht-asiatisch	79	1,43 (0,692)	0,63 (0,037)	81	1,36 (0,658)	0,61 (0,037)	0,02 [-0,086; 0,120]	0,7470
Hedges' g SMD							0,05 [-0,259; 0,361]	0,7479
Int. p-Wert								0,7046
Methode zur Gewebeuntersuchung								
zentral	86	1,35 (0,589)	0,55 (0,033)	93	1,28 (0,559)	0,52 (0,032)	0,03 [-0,065; 0,116]	0,5782
Hedges' g SMD							0,08 [-0,210; 0,376]	0,5794
lokal	127	1,36 (0,613)	0,63 (0,025)	122	1,28 (0,607)	0,64 (0,027)	-0,02 [-0,088; 0,057]	0,6722
Hedges' g SMD							-0,05 [-0,302; 0,195]	0,6726
Int. p-Wert								0,2668
WHO Performance-Status								
0	79	1,27 (0,499)	0,63 (0,031)	81	1,21 (0,586)	0,72 (0,031)	-0,09 [-0,176; -0,002]	0,0452*
Hedges' g SMD							-0,32 [-0,628; -0,004]	0,0469*
1	134	1,41 (0,651)	0,57 (0,026)	134	1,32 (0,583)	0,50 (0,027)	0,07 [-0,005; 0,141]	0,0690
Hedges' g SMD							0,22 [-0,018; 0,462]	0,0700
Int. p-Wert								0,0052*
Raucherstatus								
Ja	75	1,32 (0,596)	0,66 (0,037)	78	1,24 (0,585)	0,63 (0,037)	0,03 [-0,068; 0,136]	0,5142
Hedges' g SMD							0,11 [-0,212; 0,422]	0,5160
Nein	138	1,38 (0,607)	0,56 (0,023)	137	1,30 (0,586)	0,57 (0,024)	-0,01 [-0,076; 0,057]	0,7723
Hedges' g SMD							-0,03 [-0,271; 0,202]	0,7727
Int. p-Wert								0,9825

Analysis is performed if there are at least 10 patients in each subgroup level.
[a] = Number of patients with change from baseline used for MMRM analysis at each timepoint. [b] = Mean baseline for patients with change from baseline used for MMRM analysis at each timepoint. Treatment difference is calculated from a mixed model for repeated measures (MMRM) analysis of the change from baseline score with treatment, visit, and treatment by visit interaction as fixed effects, baseline score as a covariate and baseline score by visit interaction. Patient is used as random effect in the model. Only visits where change from baseline is available for at least 25% of patients in both treatment arms are included in the analysis. Autoregressive with heterogeneity covariance matrix is used to model within-subject error. If the MMRM model does not converge the model results are not presented. SMD = standardised mean difference. * p<0.05.
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Table 4.2.3.34 FLAURA-2: Summary of subgroup analysis of change from baseline in PRO-CTCAE Trockene Haut (mixed model for repeated measures) - average over all visits
Full Analysis Set, DCO 03APR2023

	Osi + Chemo (N=279)			Osi (N=278)			Behandlungseffekt	
Subgruppen	n [a]	Ausgangswert MW (SD) [b]	Veränderung MW (SE)	n [a]	Ausgangswert MW (SD) [b]	Veränderung MW (SE)	MWD [95%-KI]	p-Wert
Geschlecht								
Maennlich	78	1,28 (0,556)	0,59 (0,029)	82	1,15 (0,475)	0,51 (0,031)	0,08 [-0,001; 0,165]	0,0522
Hedges' g SMD							0,31 [-0,005; 0,618]	0,0541
Weiblich	135	1,40 (0,625)	0,60 (0,026)	133	1,36 (0,632)	0,64 (0,026)	-0,03 [-0,106; 0,040]	0,3779
Hedges' g SMD							-0,11 [-0,347; 0,132]	0,3789
Int. p-Wert								0,1351
Nachweis der EGFR-Mutation durch zentralen ctDNA Cobas Test								
positiv	161	1,34 (0,580)	0,61 (0,023)	163	1,29 (0,598)	0,58 (0,023)	0,02 [-0,038; 0,088]	0,4411
Hedges' g SMD							0,09 [-0,132; 0,303]	0,4421
negativ	32	1,47 (0,671)	0,52 (0,057)	30	1,27 (0,640)	0,57 (0,058)	-0,05 [-0,210; 0,113]	0,5517
Hedges' g SMD							-0,15 [-0,649; 0,348]	0,5547
unbekannt	20	1,35 (0,671)	0,61 (0,063)	22	1,18 (0,395)	0,70 (0,067)	-0,09 [-0,274; 0,091]	0,3228
Hedges' g SMD							-0,30 [-0,910; 0,309]	0,3340
Int. p-Wert								0,5729
EGFR-Mutationstyp								
Exon 19 Deletion	126	1,38 (0,618)	0,65 (0,026)	128	1,25 (0,575)	0,58 (0,026)	0,06 [-0,012; 0,135]	0,1029
Hedges' g SMD							0,20 [-0,042; 0,452]	0,1033
Exon 21 (L858R) Substitutionsmutation	87	1,32 (0,581)	0,52 (0,030)	85	1,33 (0,605)	0,60 (0,033)	-0,08 [-0,166; 0,010]	0,0825
Hedges' g SMD							-0,26 [-0,565; 0,036]	0,0845
Int. p-Wert								0,0308*
Zentral bestätigte EGFR-Mutation im Gewebe								
positiv	190	1,34 (0,603)	0,60 (0,021)	188	1,24 (0,508)	0,62 (0,022)	-0,03 [-0,085; 0,035]	0,4066
Hedges' g SMD							-0,09 [-0,287; 0,116]	0,4065
negativ	2	ID	ID	3	ID	ID	ID	ID
unbekannt	21	1,52 (0,602)	0,58 (0,067)	24	1,54 (0,932)	0,37 (0,062)	0,21 [0,032; 0,393]	0,0212*
Hedges' g SMD							0,69 [0,081; 1,290]	0,0262*

Analysis is performed if there are at least 10 patients in each subgroup level.
[a] = Number of patients with change from baseline used for MMRM analysis at each timepoint. [b] = Mean baseline for patients with change from baseline used for MMRM analysis at each timepoint. Treatment difference is calculated from a mixed model for repeated measures (MMRM) analysis of the change from baseline score with treatment, visit, and treatment by visit interaction as fixed effects, baseline score as a covariate and baseline score by visit interaction. Patient is used as random effect in the model. Only visits where change from baseline is available for at least 25% of patients in both treatment arms are included in the analysis. Autoregressive with heterogeneity covariance matrix is used to model within-subject error. If the MMRM model does not converge the model results are not presented. SMD = standardised mean difference. * p<0.05.
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Table 4.2.3.34 FLAURA-2: Summary of subgroup analysis of change from baseline in PRO-CTCAE Trockene Haut (mixed model for repeated measures) - average over all visits
Full Analysis Set, DCO 03APR2023

	Osi + Chemo (N=279)			Osi (N=278)			Behandlungseffekt	
Subgruppen	n [a]	Ausgangswert MW (SD) [b]	Veränderung MW (SE)	n [a]	Ausgangswert MW (SD) [b]	Veränderung MW (SE)	MWD [95%-KI]	p-Wert
Int. p-Wert								0,0369*
ZNS-Metastasen zur Baseline								
Ja	84	1,39 (0,640)	0,62 (0,032)	85	1,33 (0,625)	0,55 (0,035)	0,08 [-0,017; 0,170]	0,1074
Hedges' g SMD							0,25 [-0,056; 0,550]	0,1098
Nein	129	1,33 (0,577)	0,58 (0,026)	130	1,25 (0,558)	0,62 (0,026)	-0,04 [-0,115; 0,027]	0,2270
Hedges' g SMD							-0,15 [-0,394; 0,094]	0,2280
Int. p-Wert								0,0279*
Zentrale Bestätigung der EGFR-Mutation								
Zentral bestätigte EGFR-Mutation in Gewebe oder ctDNA	201	1,36 (0,609)	0,58 (0,021)	208	1,27 (0,560)	0,60 (0,021)	-0,01 [-0,070; 0,045]	0,6658
Hedges' g SMD							-0,04 [-0,237; 0,151]	0,6659
Keine zentrale Bestätigung	12	1,33 (0,492)	, (,)	7	1,57 (1,134)	, (,)	, [, ; ,]	
Hedges' g SMD							, [, ; ,]	
Int. p-Wert								0,0193*
Alter bei Screening								
<65 Jahre	127	1,40 (0,608)	0,57 (0,027)	127	1,24 (0,559)	0,58 (0,028)	-0,01 [-0,087; 0,066]	0,7917
Hedges' g SMD							-0,03 [-0,279; 0,213]	0,7916
>=65 Jahre	86	1,29 (0,591)	0,64 (0,030)	88	1,33 (0,620)	0,60 (0,030)	0,03 [-0,051; 0,115]	0,4468
Hedges' g SMD							0,11 [-0,183; 0,412]	0,4490
Int. p-Wert								0,4189
Region gPAP								
Asien	126	1,32 (0,546)	0,57 (0,024)	128	1,23 (0,540)	0,56 (0,024)	0,02 [-0,051; 0,083]	0,6403
Hedges' g SMD							0,06 [-0,187; 0,305]	0,6410
Europa	18	1,67 (0,840)	0,47 (0,093)	18	1,56 (0,856)	0,45 (0,093)	0,02 [-0,247; 0,278]	0,9059
Hedges' g SMD							0,04 [-0,615; 0,692]	0,9076
Nordamerika	15	1,07 (0,258)	0,83 (0,097)	15	1,27 (0,594)	0,64 (0,097)	0,19 [-0,089; 0,469]	0,1775

Analysis is performed if there are at least 10 patients in each subgroup level.
[a] = Number of patients with change from baseline used for MMRM analysis at each timepoint. [b] = Mean baseline for patients with change from baseline used for MMRM analysis at each timepoint. Treatment difference is calculated from a mixed model for repeated measures (MMRM) analysis of the change from baseline score with treatment, visit, and treatment by visit interaction as fixed effects, baseline score as a covariate and baseline score by visit interaction. Patient is used as random effect in the model. Only visits where change from baseline is available for at least 25% of patients in both treatment arms are included in the analysis. Autoregressive with heterogeneity covariance matrix is used to model within-subject error. If the MMRM model does not converge the model results are not presented. SMD = standardised mean difference. * p<0.05.
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Table 4.2.3.34 FLAURA-2: Summary of subgroup analysis of change from baseline in PRO-CTCAE Trockene Haut (mixed model for repeated measures) - average over all visits
Full Analysis Set, DCO 03APR2023

	Osi + Chemo (N=279)			Osi (N=278)			Behandlungseffekt	
Subgruppen	n [a]	Ausgangswert MW (SD) [b]	Veränderung MW (SE)	n [a]	Ausgangswert MW (SD) [b]	Veränderung MW (SE)	MWD [95%-KI]	p-Wert
Hedges' g SMD							0,49 [-0,237; 1,219]	0,1859
Rest der Welt	54	1,43 (0,662)	0,61 (0,042)	54	1,30 (0,571)	0,72 (0,045)	-0,11 [-0,229; 0,014]	0,0823
Hedges' g SMD							-0,33 [-0,714; 0,046]	0,0846
Int. p-Wert								0,0778

Analysis is performed if there are at least 10 patients in each subgroup level.
[a] = Number of patients with change from baseline used for MMRM analysis at each timepoint. [b] = Mean baseline for patients with change from baseline used for MMRM analysis at each timepoint. Treatment difference is calculated from a mixed model for repeated measures (MMRM) analysis of the change from baseline score with treatment, visit, and treatment by visit interaction as fixed effects, baseline score as a covariate and baseline score by visit interaction. Patient is used as random effect in the model. Only visits where change from baseline is available for at least 25% of patients in both treatment arms are included in the analysis. Autoregressive with heterogeneity covariance matrix is used to model within-subject error. If the MMRM model does not converge the model results are not presented. SMD = standardised mean difference. * p<0.05.
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Table 4.2.3.35 FLAURA-2: Summary of subgroup analysis of change from baseline in PRO-CTCAE Haarausfall (mixed model for repeated measures) - average over all visits
Full Analysis Set, DCO 03APR2023

	Osi + Chemo (N=279)			Osi (N=278)			Behandlungseffekt	
Subgruppen	n [a]	Ausgangswert MW (SD) [b]	Veränderung MW (SE)	n [a]	Ausgangswert MW (SD) [b]	Veränderung MW (SE)	MWD [95%-KI]	p-Wert
Abstammung								
Chinesisch/Asiatisch	66	1,18 (0,426)	0,21 (0,038)	65	1,15 (0,364)	0,31 (0,039)	-0,10 [-0,209; 0,006]	0,0632
Hedges' g SMD							-0,32 [-0,669; 0,021]	0,0654
Nicht-chinesisch/Asiatisch	68	1,12 (0,612)	0,21 (0,039)	69	1,32 (0,978)	0,10 (0,039)	0,11 [0,002; 0,219]	0,0468*
Hedges' g SMD							0,34 [0,004; 0,678]	0,0476*
Nicht-asiatisch	79	1,25 (0,688)	0,22 (0,044)	81	1,35 (0,964)	0,20 (0,044)	0,02 [-0,108; 0,139]	0,8072
Hedges' g SMD							0,04 [-0,271; 0,348]	0,8079
Int. p-Wert								0,1932
Methode zur Gewebeuntersuchung								
zentral	86	1,22 (0,540)	0,20 (0,042)	93	1,31 (0,847)	0,24 (0,041)	-0,04 [-0,157; 0,074]	0,4772
Hedges' g SMD							-0,11 [-0,399; 0,187]	0,4789
lokal	127	1,17 (0,627)	0,22 (0,028)	122	1,25 (0,829)	0,18 (0,030)	0,04 [-0,036; 0,126]	0,2795
Hedges' g SMD							0,14 [-0,112; 0,386]	0,2796
Int. p-Wert								0,6795
WHO Performance-Status								
0	79	1,20 (0,648)	0,17 (0,039)	81	1,27 (0,837)	0,23 (0,038)	-0,06 [-0,166; 0,048]	0,2824
Hedges' g SMD							-0,17 [-0,480; 0,141]	0,2842
1	134	1,18 (0,560)	0,23 (0,030)	134	1,28 (0,837)	0,19 (0,031)	0,05 [-0,037; 0,131]	0,2757
Hedges' g SMD							0,13 [-0,107; 0,373]	0,2767
Int. p-Wert								0,0977
Raucherstatus								
Ja	75	1,23 (0,727)	0,16 (0,035)	78	1,23 (0,788)	0,10 (0,035)	0,06 [-0,035; 0,159]	0,2079
Hedges' g SMD							0,20 [-0,115; 0,521]	0,2105
Nein	138	1,17 (0,507)	0,24 (0,031)	137	1,31 (0,862)	0,26 (0,032)	-0,02 [-0,107; 0,068]	0,6584
Hedges' g SMD							-0,05 [-0,290; 0,183]	0,6585
Int. p-Wert								0,3172

Analysis is performed if there are at least 10 patients in each subgroup level.
[a] = Number of patients with change from baseline used for MMRM analysis at each timepoint. [b] = Mean baseline for patients with change from baseline used for MMRM analysis at each timepoint. Treatment difference is calculated from a mixed model for repeated measures (MMRM) analysis of the change from baseline score with treatment, visit, and treatment by visit interaction as fixed effects, baseline score as a covariate and baseline score by visit interaction. Patient is used as random effect in the model. Only visits where change from baseline is available for at least 25% of patients in both treatment arms are included in the analysis. Autoregressive with heterogeneity covariance matrix is used to model within-subject error. If the MMRM model does not converge the model results are not presented. SMD = standardised mean difference. * p<0.05.
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Table 4.2.3.35 FLAURA-2: Summary of subgroup analysis of change from baseline in PRO-CTCAE Haarausfall (mixed model for repeated measures) - average over all visits
Full Analysis Set, DCO 03APR2023

	Osi + Chemo (N=279)			Osi (N=278)			Behandlungseffekt	
Subgruppen	n [a]	Ausgangswert MW (SD) [b]	Veränderung MW (SE)	n [a]	Ausgangswert MW (SD) [b]	Veränderung MW (SE)	MWD [95%-KI]	p-Wert
Geschlecht								
Maennlich	78	1,12 (0,426)	0,14 (0,027)	82	1,18 (0,722)	0,08 (0,029)	0,06 [-0,015; 0,141]	0,1132
Hedges' g SMD							0,25 [-0,062; 0,561]	0,1159
Weiblich	135	1,23 (0,668)	0,25 (0,033)	133	1,34 (0,895)	0,28 (0,033)	-0,03 [-0,117; 0,066]	0,5842
Hedges' g SMD							-0,07 [-0,306; 0,173]	0,5846
Int. p-Wert								0,0659
Nachweis der EGFR-Mutation durch zentralen ctDNA Cobas Test								
positiv	161	1,19 (0,638)	0,29 (0,028)	163	1,17 (0,654)	0,22 (0,028)	0,07 [-0,006; 0,148]	0,0708
Hedges' g SMD							0,20 [-0,018; 0,419]	0,0717
negativ	32	1,16 (0,448)	0,05 (0,043)	30	1,40 (0,968)	0,15 (0,044)	-0,10 [-0,224; 0,019]	0,0981
Hedges' g SMD							-0,42 [-0,924; 0,083]	0,1019
unbekannt	20	1,20 (0,410)	-0,11 (0,075)	22	1,91 (1,411)	0,21 (0,076)	-0,32 [-0,539; -0,100]	0,0049*
Hedges' g SMD							-0,90 [-1,543; -0,265]	0,0055*
Int. p-Wert								<0,0001*
EGFR-Mutationstyp								
Exon 19 Deletion	126	1,20 (0,681)	0,25 (0,033)	128	1,27 (0,876)	0,23 (0,033)	0,02 [-0,072; 0,112]	0,6703
Hedges' g SMD							0,05 [-0,193; 0,299]	0,6709
Exon 21 (L858R) Substitutionsmutation	87	1,17 (0,437)	0,15 (0,032)	85	1,29 (0,784)	0,17 (0,033)	-0,02 [-0,114; 0,068]	0,6151
Hedges' g SMD							-0,08 [-0,376; 0,222]	0,6156
Int. p-Wert								0,9282
Zentral bestätigte EGFR-Mutation im Gewebe								
positiv	190	1,18 (0,557)	0,22 (0,025)	188	1,26 (0,800)	0,21 (0,025)	0,01 [-0,059; 0,079]	0,7747
Hedges' g SMD							0,03 [-0,172; 0,231]	0,7750
negativ	2	ID	ID	3	ID	ID	ID	ID
unbekannt	21	1,24 (0,889)	0,16 (0,086)	24	1,42 (1,060)	0,16 (0,079)	0,01 [-0,230; 0,241]	0,9646
Hedges' g SMD							0,01 [-0,572; 0,599]	0,9648

Analysis is performed if there are at least 10 patients in each subgroup level.
[a] = Number of patients with change from baseline used for MMRM analysis at each timepoint. [b] = Mean baseline for patients with change from baseline used for MMRM analysis at each timepoint. Treatment difference is calculated from a mixed model for repeated measures (MMRM) analysis of the change from baseline score with treatment, visit, and treatment by visit interaction as fixed effects, baseline score as a covariate and baseline score by visit interaction. Patient is used as random effect in the model. Only visits where change from baseline is available for at least 25% of patients in both treatment arms are included in the analysis. Autoregressive with heterogeneity covariance matrix is used to model within-subject error. If the MMRM model does not converge the model results are not presented. SMD = standardised mean difference. * p<0.05.
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Table 4.2.3.35 FLAURA-2: Summary of subgroup analysis of change from baseline in PRO-CTCAE Haarausfall (mixed model for repeated measures) - average over all visits
Full Analysis Set, DCO 03APR2023

	Osi + Chemo (N=279)			Osi (N=278)			Behandlungseffekt	
Subgruppen	n [a]	Ausgangswert MW (SD) [b]	Veränderung MW (SE)	n [a]	Ausgangswert MW (SD) [b]	Veränderung MW (SE)	MWD [95%-KI]	p-Wert
Int. p-Wert								0,0688
ZNS-Metastasen zur Baseline								
Ja	84	1,26 (0,730)	0,17 (0,040)	85	1,33 (0,956)	0,10 (0,042)	0,07 [-0,041; 0,186]	0,2118
Hedges' g SMD							0,19 [-0,110; 0,494]	0,2135
Nein	129	1,14 (0,480)	0,23 (0,028)	130	1,25 (0,748)	0,26 (0,027)	-0,03 [-0,109; 0,044]	0,4087
Hedges' g SMD							-0,10 [-0,346; 0,141]	0,4094
Int. p-Wert								0,0031*
Zentrale Bestätigung der EGFR-Mutation								
Zentral bestätigte EGFR-Mutation in Gewebe oder ctDNA	201	1,19 (0,606)	0,22 (0,024)	208	1,25 (0,776)	0,20 (0,024)	0,02 [-0,046; 0,086]	0,5486
Hedges' g SMD							0,06 [-0,135; 0,253]	0,5492
Keine zentrale Bestätigung	12	NC	NC	7	NC	NC	NC	NC
Int. p-Wert								NC
Alter bei Screening								
<65 Jahre	127	1,18 (0,541)	0,21 (0,030)	127	1,34 (0,919)	0,16 (0,030)	0,05 [-0,035; 0,133]	0,2548
Hedges' g SMD							0,14 [-0,103; 0,389]	0,2546
>=65 Jahre	86	1,20 (0,665)	0,22 (0,039)	88	1,19 (0,692)	0,28 (0,039)	-0,06 [-0,165; 0,052]	0,3038
Hedges' g SMD							-0,16 [-0,453; 0,142]	0,3061
Int. p-Wert								0,0440*
Region gPAP								
Asien	126	1,16 (0,543)	0,21 (0,028)	128	1,22 (0,687)	0,19 (0,029)	0,01 [-0,065; 0,093]	0,7262
Hedges' g SMD							0,04 [-0,202; 0,290]	0,7267
Europa	18	NC	NC	18	NC	NC	NC	NC
Nordamerika	15	NC	NC	15	NC	NC	NC	NC
Rest der Welt	54	1,31 (0,797)	0,17 (0,055)	54	1,43 (1,039)	0,29 (0,056)	-0,12 [-0,272; 0,037]	0,1364

Analysis is performed if there are at least 10 patients in each subgroup level.
[a] = Number of patients with change from baseline used for MMRM analysis at each timepoint. [b] = Mean baseline for patients with change from baseline used for MMRM analysis at each timepoint. Treatment difference is calculated from a mixed model for repeated measures (MMRM) analysis of the change from baseline score with treatment, visit, and treatment by visit interaction as fixed effects, baseline score as a covariate and baseline score by visit interaction. Patient is used as random effect in the model. Only visits where change from baseline is available for at least 25% of patients in both treatment arms are included in the analysis. Autoregressive with heterogeneity covariance matrix is used to model within-subject error. If the MMRM model does not converge the model results are not presented. SMD = standardised mean difference. * p<0.05.
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Table 4.2.3.35 FLAURA-2: Summary of subgroup analysis of change from baseline in PRO-CTCAE Haarausfall (mixed model for repeated measures) - average over all visits
Full Analysis Set, DCO 03APR2023

	Osi + Chemo (N=279)			Osi (N=278)			Behandlungseffekt	
Subgruppen	n [a]	Ausgangswert MW (SD) [b]	Veränderung MW (SE)	n [a]	Ausgangswert MW (SD) [b]	Veränderung MW (SE)	MWD [95%-KI]	p-Wert
Hedges' g SMD							-0,29 [-0,665; 0,094]	0,1399
Int. p-Wert								0,1004

Analysis is performed if there are at least 10 patients in each subgroup level.
[a] = Number of patients with change from baseline used for MMRM analysis at each timepoint. [b] = Mean baseline for patients with change from baseline used for MMRM analysis at each timepoint. Treatment difference is calculated from a mixed model for repeated measures (MMRM) analysis of the change from baseline score with treatment, visit, and treatment by visit interaction as fixed effects, baseline score as a covariate and baseline score by visit interaction. Patient is used as random effect in the model. Only visits where change from baseline is available for at least 25% of patients in both treatment arms are included in the analysis. Autoregressive with heterogeneity covariance matrix is used to model within-subject error. If the MMRM model does not converge the model results are not presented. SMD = standardised mean difference. * p<0.05.
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Table 4.2.3.36 FLAURA-2: Summary of subgroup analysis of change from baseline in PRO-CTCAE Taubheit oder Kribbeln in Händen und Füßen (mixed model for repeated measures) - average over all visits
Full Analysis Set, DCO 03APR2023

	Osi + Chemo (N=279)			Osi (N=278)			Behandlungseffekt	
Subgruppen	n [a]	Ausgangswert MW (SD) [b]	Veränderung MW (SE)	n [a]	Ausgangswert MW (SD) [b]	Veränderung MW (SE)	MWD [95%-KI]	p-Wert
Abstammung								
Chinesisch/Asiatisch	66	1,23 (0,490)	0,12 (0,027)	65	1,23 (0,587)	0,16 (0,027)	-0,04 [-0,115; 0,035]	0,2920
Hedges' g SMD							-0,18 [-0,526; 0,160]	0,2956
Nicht-chinesisch/Asiatisch	68	1,19 (0,405)	0,39 (0,037)	69	1,22 (0,645)	0,21 (0,038)	0,18 [0,071; 0,280]	0,0010*
Hedges' g SMD							0,56 [0,222; 0,905]	0,0012*
Nicht-asiatisch	79	1,16 (0,406)	0,22 (0,030)	81	1,23 (0,638)	0,23 (0,031)	0,00 [-0,087; 0,082]	0,9568
Hedges' g SMD							-0,01 [-0,318; 0,301]	0,9570
Int. p-Wert								0,0027*
Methode zur Gewebeuntersuchung								
zentral	86	1,21 (0,482)	0,15 (0,026)	93	1,30 (0,708)	0,19 (0,025)	-0,04 [-0,111; 0,031]	0,2706
Hedges' g SMD							-0,16 [-0,458; 0,130]	0,2734
lokal	127	1,19 (0,397)	0,31 (0,025)	122	1,18 (0,546)	0,21 (0,026)	0,09 [0,022; 0,165]	0,0108*
Hedges' g SMD							0,32 [0,074; 0,574]	0,0112*
Int. p-Wert								0,0372*
WHO Performance-Status								
0	79	1,11 (0,339)	0,32 (0,031)	81	1,19 (0,573)	0,22 (0,031)	0,10 [0,018; 0,189]	0,0175*
Hedges' g SMD							0,38 [0,063; 0,688]	0,0186*
1	134	1,24 (0,474)	0,20 (0,023)	134	1,26 (0,651)	0,19 (0,024)	0,01 [-0,053; 0,078]	0,7071
Hedges' g SMD							0,05 [-0,194; 0,285]	0,7078
Int. p-Wert								0,0162*
Raucherstatus								
Ja	75	1,23 (0,452)	0,28 (0,034)	78	1,17 (0,527)	0,25 (0,035)	0,03 [-0,063; 0,129]	0,4995
Hedges' g SMD							0,11 [-0,208; 0,426]	0,5010
Nein	138	1,18 (0,422)	0,23 (0,022)	137	1,26 (0,670)	0,18 (0,022)	0,05 [-0,007; 0,115]	0,0840
Hedges' g SMD							0,21 [-0,029; 0,445]	0,0852
Int. p-Wert								0,7017

Analysis is performed if there are at least 10 patients in each subgroup level.
[a] = Number of patients with change from baseline used for MMRM analysis at each timepoint. [b] = Mean baseline for patients with change from baseline used for MMRM analysis at each timepoint. Treatment difference is calculated from a mixed model for repeated measures (MMRM) analysis of the change from baseline score with treatment, visit, and treatment by visit interaction as fixed effects, baseline score as a covariate and baseline score by visit interaction. Patient is used as random effect in the model. Only visits where change from baseline is available for at least 25% of patients in both treatment arms are included in the analysis. Autoregressive with heterogeneity covariance matrix is used to model within-subject error. If the MMRM model does not converge the model results are not presented. SMD = standardised mean difference. * p<0.05.
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Table 4.2.3.36 FLAURA-2: Summary of subgroup analysis of change from baseline in PRO-CTCAE Taubheit oder Kribbeln in Händen und Füßen (mixed model for repeated measures) - average over all visits
Full Analysis Set, DCO 03APR2023

	Osi + Chemo (N=279)			Osi (N=278)			Behandlungseffekt	
Subgruppen	n [a]	Ausgangswert MW (SD) [b]	Veränderung MW (SE)	n [a]	Ausgangswert MW (SD) [b]	Veränderung MW (SE)	MWD [95%-KI]	p-Wert
Geschlecht								
Maennlich	78	1,24 (0,482)	0,23 (0,033)	82	1,12 (0,427)	0,24 (0,034)	-0,01 [-0,101; 0,084]	0,8551
Hedges' g SMD							-0,03 [-0,339; 0,281]	0,8554
Weiblich	135	1,17 (0,401)	0,26 (0,023)	133	1,30 (0,710)	0,18 (0,023)	0,08 [0,015; 0,141]	0,0147*
Hedges' g SMD							0,30 [0,057; 0,539]	0,0153*
Int. p-Wert								0,3984
Nachweis der EGFR-Mutation durch zentralen ctDNA Cobas Test								
positiv	161	1,15 (0,344)	0,24 (0,020)	163	1,21 (0,614)	0,21 (0,020)	0,03 [-0,021; 0,090]	0,2251
Hedges' g SMD							0,13 [-0,083; 0,353]	0,2265
negativ	32	1,22 (0,400)	0,31 (0,043)	30	1,17 (0,330)	0,15 (0,045)	0,15 [0,032; 0,277]	0,0135*
Hedges' g SMD							0,63 [0,116; 1,138]	0,0161*
unbekannt	20	1,53 (0,835)	0,19 (0,088)	22	1,43 (0,917)	0,29 (0,090)	-0,11 [-0,357; 0,146]	0,4038
Hedges' g SMD							-0,25 [-0,862; 0,354]	0,4132
Int. p-Wert								0,3323
EGFR-Mutationstyp								
Exon 19 Deletion	126	1,15 (0,347)	0,29 (0,024)	128	1,18 (0,521)	0,24 (0,024)	0,04 [-0,023; 0,110]	0,1973
Hedges' g SMD							0,16 [-0,085; 0,408]	0,1989
Exon 21 (L858R) Substitutionsmutation	87	1,26 (0,527)	0,19 (0,029)	85	1,31 (0,752)	0,14 (0,031)	0,05 [-0,035; 0,133]	0,2488
Hedges' g SMD							0,18 [-0,124; 0,475]	0,2508
Int. p-Wert								0,7198
Zentral bestätigte EGFR-Mutation im Gewebe								
positiv	190	1,18 (0,424)	0,24 (0,019)	188	1,25 (0,645)	0,21 (0,019)	0,03 [-0,026; 0,078]	0,3312
Hedges' g SMD							0,10 [-0,102; 0,302]	0,3322
negativ	2	ID	ID	3	ID	ID	ID	ID
unbekannt	21	1,31 (0,512)	0,25 (0,082)	24	1,13 (0,448)	0,20 (0,075)	0,05 [-0,177; 0,276]	0,6639
Hedges' g SMD							0,13 [-0,455; 0,717]	0,6617

Analysis is performed if there are at least 10 patients in each subgroup level.
[a] = Number of patients with change from baseline used for MMRM analysis at each timepoint. [b] = Mean baseline for patients with change from baseline used for MMRM analysis at each timepoint. Treatment difference is calculated from a mixed model for repeated measures (MMRM) analysis of the change from baseline score with treatment, visit, and treatment by visit interaction as fixed effects, baseline score as a covariate and baseline score by visit interaction. Patient is used as random effect in the model. Only visits where change from baseline is available for at least 25% of patients in both treatment arms are included in the analysis. Autoregressive with heterogeneity covariance matrix is used to model within-subject error. If the MMRM model does not converge the model results are not presented. SMD = standardised mean difference. * p<0.05.
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Table 4.2.3.36 FLAURA-2: Summary of subgroup analysis of change from baseline in PRO-CTCAE Taubheit oder Kribbeln in Händen und Füßen (mixed model for repeated measures) - average over all visits
Full Analysis Set, DCO 03APR2023

	Osi + Chemo (N=279)			Osi (N=278)			Behandlungseffekt	
Subgruppen	n [a]	Ausgangswert MW (SD) [b]	Veränderung MW (SE)	n [a]	Ausgangswert MW (SD) [b]	Veränderung MW (SE)	MWD [95%-KI]	p-Wert
Int. p-Wert								0,1306
ZNS-Metastasen zur Baseline								
Ja	84	1,19 (0,424)	0,32 (0,034)	85	1,31 (0,740)	0,20 (0,037)	0,11 [0,014; 0,211]	0,0249*
Hedges' g SMD							0,34 [0,041; 0,649]	0,0261*
Nein	129	1,20 (0,439)	0,20 (0,021)	130	1,18 (0,528)	0,20 (0,021)	0,00 [-0,055; 0,062]	0,9055
Hedges' g SMD							0,01 [-0,229; 0,258]	0,9057
Int. p-Wert								0,0813
Zentrale Bestätigung der EGFR-Mutation								
Zentral bestätigte EGFR-Mutation in Gewebe oder ctDNA	201	1,19 (0,420)	0,24 (0,018)	208	1,23 (0,629)	0,21 (0,018)	0,02 [-0,028; 0,073]	0,3811
Hedges' g SMD							0,09 [-0,107; 0,280]	0,3823
Keine zentrale Bestätigung	12	1,33 (0,615)	, (,)	7	1,14 (0,378)	, (,)	, [, ; ,]	
Hedges' g SMD							, [, ; ,]	
Int. p-Wert								0,0001*
Alter bei Screening								
<65 Jahre	127	1,22 (0,453)	0,20 (0,022)	127	1,25 (0,584)	0,15 (0,023)	0,06 [-0,008; 0,118]	0,0883
Hedges' g SMD							0,21 [-0,033; 0,460]	0,0897
>=65 Jahre	86	1,16 (0,400)	0,32 (0,032)	88	1,20 (0,677)	0,29 (0,032)	0,03 [-0,060; 0,116]	0,5348
Hedges' g SMD							0,09 [-0,204; 0,391]	0,5362
Int. p-Wert								0,7990
Region gPAP								
Asien	126	1,23 (0,459)	0,26 (0,025)	128	1,23 (0,598)	0,20 (0,025)	0,06 [-0,005; 0,135]	0,0691
Hedges' g SMD							0,23 [-0,019; 0,474]	0,0705
Europa	18	1,17 (0,343)	0,24 (0,062)	18	1,17 (0,514)	0,22 (0,060)	0,02 [-0,158; 0,190]	0,8554
Hedges' g SMD							0,06 [-0,593; 0,714]	0,8568
Nordamerika	15	1,07 (0,176)	, (,)	15	1,07 (0,258)	, (,)	0,11 [-0,076; 0,302]	0,2336

Analysis is performed if there are at least 10 patients in each subgroup level.
[a] = Number of patients with change from baseline used for MMRM analysis at each timepoint. [b] = Mean baseline for patients with change from baseline used for MMRM analysis at each timepoint. Treatment difference is calculated from a mixed model for repeated measures (MMRM) analysis of the change from baseline score with treatment, visit, and treatment by visit interaction as fixed effects, baseline score as a covariate and baseline score by visit interaction. Patient is used as random effect in the model. Only visits where change from baseline is available for at least 25% of patients in both treatment arms are included in the analysis. Autoregressive with heterogeneity covariance matrix is used to model within-subject error. If the MMRM model does not converge the model results are not presented. SMD = standardised mean difference. * p<0.05.
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Table 4.2.3.36 FLAURA-2: Summary of subgroup analysis of change from baseline in PRO-CTCAE Taubheit oder Kribbeln in Händen und Füßen (mixed model for repeated measures) - average over all visits
Full Analysis Set, DCO 03APR2023

	Osi + Chemo (N=279)			Osi (N=278)			Behandlungseffekt	
Subgruppen	n [a]	Ausgangswert MW (SD) [b]	Veränderung MW (SE)	n [a]	Ausgangswert MW (SD) [b]	Veränderung MW (SE)	MWD [95%-KI]	p-Wert
Hedges' g SMD							, [, ; ,]	
Rest der Welt	54	1,17 (0,445)	0,19 (0,035)	54	1,31 (0,767)	0,21 (0,037)	-0,02 [-0,125; 0,077]	0,6371
Hedges' g SMD							-0,09 [-0,468; 0,287]	0,6394
Int. p-Wert								0,3895

Analysis is performed if there are at least 10 patients in each subgroup level.
[a] = Number of patients with change from baseline used for MMRM analysis at each timepoint. [b] = Mean baseline for patients with change from baseline used for MMRM analysis at each timepoint. Treatment difference is calculated from a mixed model for repeated measures (MMRM) analysis of the change from baseline score with treatment, visit, and treatment by visit interaction as fixed effects, baseline score as a covariate and baseline score by visit interaction. Patient is used as random effect in the model. Only visits where change from baseline is available for at least 25% of patients in both treatment arms are included in the analysis. Autoregressive with heterogeneity covariance matrix is used to model within-subject error. If the MMRM model does not converge the model results are not presented. SMD = standardised mean difference. * p<0.05.
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Table 4.3.1.1 FLAURA-2: Summary of subgroup analysis of time to first UE
Safety Analysis Set, DCO 03APR2023

	Osi + Chemo (N=276)			Osi (N=275)					
Subgruppen	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]	Hazard Ratio [b]	[95%-KI] [b]	2-seitiger p-Wert [b]
Abstammung									
Chinesisch/Asiatisch	68	68 (100)	0,1 [0,1; 0,2]	70	70 (100)	0,3 [0,2; 0,3]	1,90	[1,35; 2,66]	0,0002*
Nicht-chinesisch/ Asiatisch	107	107 (100)	0,1 [0,1; 0,2]	106	105 (99,1)	0,3 [0,2; 0,5]	2,22	[1,68; 2,93]	<0,0001*
Nicht-asiatisch	101	101 (100)	0,1 [0,1; 0,2]	99	93 (93,9)	0,3 [0,2; 0,4]	2,04	[1,53; 2,73]	<0,0001*
Interaktion p-Wert									0,7716
Methode zur Gewebeuntersuchung									
zentral	120	120 (100)	0,2 [0,1; 0,2]	119	116 (97,5)	0,3 [0,3; 0,5]	2,00	[1,54; 2,60]	<0,0001*
lokal	156	156 (100)	0,1 [0,1; 0,1]	156	152 (97,4)	0,2 [0,2; 0,3]	2,20	[1,75; 2,78]	<0,0001*
Interaktion p-Wert									0,5822
WHO Performance-Status									
0	100	100 (100)	0,1 [0,1; 0,1]	100	96 (96,0)	0,3 [0,2; 0,5]	2,34	[1,76; 3,13]	<0,0001*
1	176	176 (100)	0,1 [0,1; 0,2]	175	172 (98,3)	0,3 [0,2; 0,3]	1,91	[1,54; 2,38]	<0,0001*
Interaktion p-Wert									0,2588
Raucherstatus									
Ja	90	90 (100)	0,1 [0,1; 0,2]	96	96 (100)	0,3 [0,2; 0,4]	1,80	[1,35; 2,40]	<0,0001*
Nein	186	186 (100)	0,1 [0,1; 0,2]	179	172 (96,1)	0,3 [0,2; 0,3]	2,23	[1,79; 2,78]	<0,0001*
Interaktion p-Wert									0,2448
Geschlecht									
Maennlich	104	104 (100)	0,1 [0,1; 0,2]	107	105 (98,1)	0,3 [0,2; 0,5]	2,08	[1,58; 2,74]	<0,0001*
Weiblich	172	172 (100)	0,1 [0,1; 0,2]	168	163 (97,0)	0,3 [0,2; 0,3]	2,04	[1,63; 2,55]	<0,0001*
Interaktion p-Wert									0,9121
Nachweis der EGFR-Mutation durch zentralen ctDNA Cobas Test									
positiv	211	211 (100)	0,1 [0,1; 0,2]	204	199 (97,5)	0,3 [0,3; 0,4]	2,07	[1,70; 2,54]	<0,0001*

Time to event of AE is defined as the time from first dose of study treatment to first onset of the respective AE or the time to censoring if the AE has not occurred by 28 days following discontinuation of study treatment, before administration of subsequent cancer therapy or death, whichever comes first. All AEs are coded using MedDRA version 25.1. Includes AEs with onset date on or after the date of first dose and up to and including 28 days following discontinuation of study treatment. Analysis done if >=10 patients at each subgroup level and >=10 events in at least one subgroup level combined for both arms. Analysis done for SOC and PT only if main effect for that SOC or PT is statistically significant at 5% level. [a] Median time to event based on the Kaplan Meier estimate. NE = Not estimable as median (or 95% CLs) is not reached. [b] Estimated from main effects of unstratified Cox proportional hazard model including trt., subgroup and subgroup-by-trt. interaction. Ties handled using Efron method and 95% CI derived from profile likelihood estimation. NC = Not calculable. HR <1 favours Osimertinib+Chemo. * p<0.05.
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Table 4.3.1.1 FLAURA-2: Summary of subgroup analysis of time to first UE
Safety Analysis Set, DCO 03APR2023

	Osi + Chemo (N=276)			Osi (N=275)					
Subgruppen	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]	Hazard Ratio [b]	[95%-KI] [b]	2-seitiger p-Wert [b]
negativ	41	41 (100)	0,1 [0,1; 0,2]	39	38 (97,4)	0,3 [0,1; 0,5]	2,29	[1,46; 3,60]	0,0003*
unbekannt	24	24 (100)	0,1 [0,1; 0,3]	32	31 (96,9)	0,2 [0,1; 0,5]	1,68	[0,98; 2,87]	0,0610
Interaktion p-Wert									0,6784
EGFR-Mutationstyp									
Exon 19 Deletion	172	172 (100)	0,1 [0,1; 0,1]	167	163 (97,6)	0,3 [0,2; 0,3]	2,13	[1,70; 2,66]	<0,0001*
Exon 21 (L858R)	104	104 (100)	0,1 [0,1; 0,2]	106	103 (97,2)	0,3 [0,2; 0,4]	1,99	[1,51; 2,63]	<0,0001*
Substitutionsmutation									
Interaktion p-Wert									0,7094
Zentral bestätigte EGFR-Mutation im Gewebe									
positiv	248	248 (100)	0,1 [0,1; 0,2]	238	233 (97,9)	0,3 [0,3; 0,3]	2,05	[1,70; 2,48]	<0,0001*
negativ	3	3 (100)	0,2 [0,1; NE]	4	4 (100)	0,1 [0,0; NE]	NC	[NC]	NC
unbekannt	25	25 (100)	0,1 [0,1; 0,3]	33	31 (93,9)	0,2 [0,1; 0,7]	2,38	[1,38; 4,05]	0,0020*
Interaktion p-Wert									0,6103
ZNS-Metastasen zur Baseline									
Ja	113	113 (100)	0,1 [0,1; 0,2]	110	109 (99,1)	0,3 [0,2; 0,3]	1,72	[1,32; 2,25]	<0,0001*
Nein	163	163 (100)	0,1 [0,1; 0,2]	165	159 (96,4)	0,3 [0,2; 0,4]	2,33	[1,86; 2,94]	<0,0001*
Interaktion p-Wert									0,0834
Zentrale Bestätigung der EGFR-Mutation									
Zentral bestätigte EGFR-Mutation in Gewebe oder ctDNA	263	263 (100)	0,1 [0,1; 0,1]	266	259 (97,4)	0,3 [0,3; 0,3]	2,08	[1,74; 2,49]	<0,0001*
Keine zentrale Bestätigung	13	13 (100)	0,2 [0,0; 0,3]	9	9 (100)	0,2 [0,0; 1,4]	1,57	[0,68; 3,81]	0,2946
Interaktion p-Wert									0,5295
Alter bei Screening									

Time to event of AE is defined as the time from first dose of study treatment to first onset of the respective AE or the time to censoring if the AE has not occurred by 28 days following discontinuation of study treatment, before administration of subsequent cancer therapy or death, whichever comes first. All AEs are coded using MedDRA version 25.1. Includes AEs with onset date on or after the date of first dose and up to and including 28 days following discontinuation of study treatment. Analysis done if >=10 patients at each subgroup level and >=10 events in at least one subgroup level combined for both arms. Analysis done for SOC and PT only if main effect for that SOC or PT is statistically significant at 5% level. [a] Median time to event based on the Kaplan Meier estimate. NE = Not estimable as median (or 95% CLs) is not reached. [b] Estimated from main effects of unstratified Cox proportional hazard model including trt., subgroup and subgroup-by-trt. interaction. Ties handled using Efron method and 95% CI derived from profile likelihood estimation. NC = Not calculable. HR <1 favours Osimertinib+Chemo. * p<0.05.
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Table 4.3.1.1 FLAURA-2: Summary of subgroup analysis of time to first UE
Safety Analysis Set, DCO 03APR2023

	Osi + Chemo (N=276)			Osi (N=275)					
Subgruppen	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]	Hazard Ratio [b]	[95%-KI] [b]	2-seitiger p-Wert [b]
<65 Jahre	172	172 (100)	0,1 [0,1; 0,1]	164	160 (97,6)	0,3 [0,2; 0,3]	2,07	[1,66; 2,59]	<0,0001*
>=65 Jahre	104	104 (100)	0,1 [0,1; 0,2]	111	108 (97,3)	0,3 [0,2; 0,4]	2,03	[1,54; 2,68]	<0,0001*
Interaktion p-Wert									0,9052
Region gPAP									
Asien	168	168 (100)	0,1 [0,1; 0,2]	166	165 (99,4)	0,3 [0,2; 0,3]	2,12	[1,70; 2,65]	<0,0001*
Europa	22	22 (100)	0,1 [0,0; 0,3]	23	23 (100)	0,3 [0,2; 0,4]	2,08	[1,15; 3,75]	0,0159*
Nordamerika	20	20 (100)	0,1 [0,0; 0,2]	22	22 (100)	0,1 [0,0; 0,2]	1,35	[0,73; 2,48]	0,3348
Rest der Welt	66	66 (100)	0,1 [0,1; 0,2]	64	58 (90,6)	0,4 [0,2; 0,6]	2,29	[1,60; 3,30]	<0,0001*
Interaktion p-Wert									0,5222

Time to event of AE is defined as the time from first dose of study treatment to first onset of the respective AE or the time to censoring if the AE has not occurred by 28 days following discontinuation of study treatment, before administration of subsequent cancer therapy or death, whichever comes first. All AEs are coded using MedDRA version 25.1. Includes AEs with onset date on or after the date of first dose and up to and including 28 days following discontinuation of study treatment. Analysis done if >=10 patients at each subgroup level and >=10 events in at least one subgroup level combined for both arms. Analysis done for SOC and PT only if main effect for that SOC or PT is statistically significant at 5% level. [a] Median time to event based on the Kaplan Meier estimate. NE = Not estimable as median (or 95% CLs) is not reached. [b] Estimated from main effects of unstratified Cox proportional hazard model including trt., subgroup and subgroup-by-trt. interaction. Ties handled using Efron method and 95% CI derived from profile likelihood estimation. NC = Not calculable. HR <1 favours Osimertinib+Chemo. * p<0.05.
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Table 4.3.1.2 FLAURA-2: Summary of subgroup analysis of time to first SOC: Allgemeine Erkrankungen und Beschwerden am Verabreichungsort
Safety Analysis Set, DCO 03APR2023

	Osi + Chemo (N=276)			Osi (N=275)					
Subgruppen	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]	Hazard Ratio [b]	[95%-KI] [b]	2-seitiger p-Wert [b]
Abstammung									
Chinesisch/Asiatisch	68	39 (57,4)	5,3 [2,3; NE]	70	25 (35,7)	NE [NE; NE]	1,94	[1,18; 3,24]	0,0087*
Nicht-chinesisch/ Asiatisch	107	56 (52,3)	20,2 [6,5;27,6]	106	26 (24,5)	NE [NE; NE]	2,74	[1,74; 4,43]	<0,0001*
Nicht-asiatisch	101	72 (71,3)	1,1 [0,7; 2,3]	99	38 (38,4)	NE [NE; NE]	2,84	[1,93; 4,25]	<0,0001*
Interaktion p-Wert									0,4720
Methode zur Gewebeuntersuchung									
zentral	120	57 (47,5)	21,4 [10,3; NE]	119	35 (29,4)	NE [NE; NE]	1,90	[1,25; 2,91]	0,0024*
lokal	156	110 (70,5)	1,5 [0,8; 3,4]	156	54 (34,6)	NE [NE; NE]	3,04	[2,21; 4,25]	<0,0001*
Interaktion p-Wert									0,0837
WHO Performance-Status									
0	100	61 (61,0)	4,7 [0,9;19,2]	100	30 (30,0)	NE [NE; NE]	2,86	[1,87; 4,49]	<0,0001*
1	176	106 (60,2)	4,1 [2,3;10,9]	175	59 (33,7)	NE [NE; NE]	2,29	[1,67; 3,17]	<0,0001*
Interaktion p-Wert									0,4178
Raucherstatus									
Ja	90	52 (57,8)	4,5 [2,1;22,0]	96	28 (29,2)	NE [NE; NE]	2,57	[1,63; 4,12]	<0,0001*
Nein	186	115 (61,8)	4,1 [2,1;10,3]	179	61 (34,1)	NE [NE; NE]	2,44	[1,79; 3,35]	<0,0001*
Interaktion p-Wert									0,8560
Geschlecht									
Maennlich	104	61 (58,7)	7,3 [2,1;21,4]	107	34 (31,8)	29,5 [20,8; NE]	2,36	[1,56; 3,63]	<0,0001*
Weiblich	172	106 (61,6)	3,4 [2,1; 9,1]	168	55 (32,7)	NE [NE; NE]	2,56	[1,86; 3,57]	<0,0001*
Interaktion p-Wert									0,7672
Nachweis der EGFR-Mutation durch zentralen ctDNA Cobas Test									

Time to event of AE is defined as the time from first dose of study treatment to first onset of the respective AE or the time to censoring if the AE has not occurred by 28 days following discontinuation of study treatment, before administration of subsequent cancer therapy or death, whichever comes first. All AEs are coded using MedDRA version 25.1. Includes AEs with onset date on or after the date of first dose and up to and including 28 days following discontinuation of study treatment. Analysis done if >=10 patients at each subgroup level and >=10 events in at least one subgroup level combined for both arms. Analysis done for SOC and PT only if main effect for that SOC or PT is statistically significant at 5% level. [a] Median time to event based on the Kaplan Meier estimate. NE = Not estimable as median (or 95% CLs) is not reached. [b] Estimated from main effects of unstratified Cox proportional hazard model including trt., subgroup and subgroup-by-trt. interaction. Ties handled using Efron method and 95% CI derived from profile likelihood estimation. NC = Not calculable. HR <1 favours Osimertinib+Chemo. * p<0.05.
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Table 4.3.1.2 FLAURA-2: Summary of subgroup analysis of time to first SOC: Allgemeine Erkrankungen und Beschwerden am Verabreichungsort
Safety Analysis Set, DCO 03APR2023

	Osi + Chemo (N=276)			Osi (N=275)					
Subgruppen	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]	Hazard Ratio [b]	[95%-KI] [b]	2-seitiger p-Wert [b]
positiv	211	124 (58,8)	8,1 [2,9;12,9]	204	64 (31,4)	NE [NE; NE]	2,43	[1,80; 3,30]	<0,0001*
negativ	41	28 (68,3)	2,3 [0,4; 5,7]	39	12 (30,8)	NE [NE; NE]	3,69	[1,92; 7,56]	<0,0001*
unbekannt	24	15 (62,5)	2,8 [0,6; NE]	32	13 (40,6)	NE [NE; NE]	1,80	[0,86; 3,85]	0,1206
Interaktion p-Wert									0,3487
EGFR-Mutationstyp									
Exon 19 Deletion	172	106 (61,6)	3,3 [1,6;10,5]	167	53 (31,7)	NE [NE; NE]	2,74	[1,98; 3,83]	<0,0001*
Exon 21 (L858R) Substitutionsmutation	104	61 (58,7)	7,3 [2,8;20,6]	106	35 (33,0)	NE [NE; NE]	2,16	[1,43; 3,30]	0,0002*
Interaktion p-Wert									0,3812
Zentral bestätigte EGFR-Mutation im Gewebe									
positiv	248	145 (58,5)	6,5 [2,9;12,9]	238	71 (29,8)	NE [NE; NE]	2,55	[1,93; 3,41]	<0,0001*
negativ	3	2 (66,7)	0,8 [0,1; NE]	4	2 (50,0)	13,3 [1,0; NE]	NC	[NC]	NC
unbekannt	25	20 (80,0)	1,1 [0,2; 3,2]	33	16 (48,5)	20,8 [9,7; NE]	2,94	[1,52; 5,77]	0,0014*
Interaktion p-Wert									0,6994
ZNS-Metastasen zur Baseline									
Ja	113	64 (56,6)	10,6 [3,4;27,3]	110	35 (31,8)	NE [NE; NE]	2,03	[1,35; 3,10]	0,0006*
Nein	163	103 (63,2)	2,3 [1,4; 6,5]	165	54 (32,7)	NE [NE; NE]	2,86	[2,07; 4,01]	<0,0001*
Interaktion p-Wert									0,2043
Zentrale Bestätigung der EGFR-Mutation									
Zentral bestätigte EGFR-Mutation in Gewebe oder ctDNA	263	156 (59,3)	5,7 [2,9;10,9]	266	84 (31,6)	NE [NE; NE]	2,46	[1,90; 3,23]	<0,0001*
Keine zentrale Bestätigung	13	11 (84,6)	0,9 [0,1; 3,2]	9	5 (55,6)	13,3 [0,8; NE]	2,79	[1,01; 8,86]	0,0475*
Interaktion p-Wert									0,8247

Time to event of AE is defined as the time from first dose of study treatment to first onset of the respective AE or the time to censoring if the AE has not occurred by 28 days following discontinuation of study treatment, before administration of subsequent cancer therapy or death, whichever comes first. All AEs are coded using MedDRA version 25.1. Includes AEs with onset date on or after the date of first dose and up to and including 28 days following discontinuation of study treatment. Analysis done if >=10 patients at each subgroup level and >=10 events in at least one subgroup level combined for both arms. Analysis done for SOC and PT only if main effect for that SOC or PT is statistically significant at 5% level. [a] Median time to event based on the Kaplan Meier estimate. NE = Not estimable as median (or 95% CLs) is not reached. [b] Estimated from main effects of unstratified Cox proportional hazard model including trt., subgroup and subgroup-by-trt. interaction. Ties handled using Efron method and 95% CI derived from profile likelihood estimation. NC = Not calculable. HR <1 favours Osimertinib+Chemo. * p<0.05.
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Table 4.3.1.2 FLAURA-2: Summary of subgroup analysis of time to first SOC: Allgemeine Erkrankungen und Beschwerden am Verabreichungsort
Safety Analysis Set, DCO 03APR2023

	Osi + Chemo (N=276)			Osi (N=275)					
Subgruppen	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]	Hazard Ratio [b]	[95%-KI] [b]	2-seitiger p-Wert [b]
Alter bei Screening									
<65 Jahre	172	105 (61,0)	5,3 [2,1;12,4]	164	59 (36,0)	NE [NE; NE]	2,19	[1,59; 3,03]	<0,0001*
>=65 Jahre	104	62 (59,6)	3,4 [2,1;11,8]	111	30 (27,0)	NE [NE; NE]	3,07	[2,01; 4,82]	<0,0001*
Interaktion p-Wert									0,2135
Region gPAP									
Asien	168	88 (52,4)	12,9 [5,3;27,6]	166	45 (27,1)	NE [NE; NE]	2,40	[1,68; 3,47]	<0,0001*
Europa	22	14 (63,6)	0,8 [0,1; NE]	23	4 (17,4)	NE [NE; NE]	6,09	[2,18; 21,51]	0,0004*
Nordamerika	20	19 (95,0)	0,4 [0,1; 0,8]	22	14 (63,6)	7,7 [0,8; NE]	3,34	[1,68; 6,83]	0,0007*
Rest der Welt	66	46 (69,7)	2,3 [1,1; 6,4]	64	26 (40,6)	NE [NE; NE]	2,44	[1,52; 4,00]	0,0002*
Interaktion p-Wert									0,3481

Time to event of AE is defined as the time from first dose of study treatment to first onset of the respective AE or the time to censoring if the AE has not occurred by 28 days following discontinuation of study treatment, before administration of subsequent cancer therapy or death, whichever comes first. All AEs are coded using MedDRA version 25.1. Includes AEs with onset date on or after the date of first dose and up to and including 28 days following discontinuation of study treatment. Analysis done if >=10 patients at each subgroup level and >=10 events in at least one subgroup level combined for both arms. Analysis done for SOC and PT only if main effect for that SOC or PT is statistically significant at 5% level. [a] Median time to event based on the Kaplan Meier estimate. NE = Not estimable as median (or 95% CLs) is not reached. [b] Estimated from main effects of unstratified Cox proportional hazard model including trt., subgroup and subgroup-by-trt. interaction. Ties handled using Efron method and 95% CI derived from profile likelihood estimation. NC = Not calculable. HR <1 favours Osimertinib+Chemo. * p<0.05.
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Table 4.3.1.3 FLAURA-2: Summary of subgroup analysis of time to first PT: Asthenie
Safety Analysis Set, DCO 03APR2023

	Osi + Chemo (N=276)			Osi (N=275)					
Subgruppen	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]	Hazard Ratio [b]	[95%-KI] [b]	2-seitiger p-Wert [b]
Abstammung									
Chinesisch/Asiatisch	68	3 (4,4)	NE [NE; NE]	70	0	NE [NE; NE]	NC	[NC]	NC
Nicht-chinesisch/ Asiatisch	107	5 (4,7)	NE [NE; NE]	106	0	NE [NE; NE]	NC	[NC]	NC
Nicht-asiatisch	101	18 (17,8)	NE [NE; NE]	99	7 (7,1)	NE [NE; NE]	2,77	[1,21; 7,13]	0,0155*
Interaktion p-Wert									NC
Methode zur Gewebeuntersuchung									
zentral	120	14 (11,7)	NE [NE; NE]	119	3 (2,5)	NE [NE; NE]	4,91	[1,60; 21,30]	0,0040*
lokal	156	12 (7,7)	NE [NE; NE]	156	4 (2,6)	NE [NE; NE]	3,11	[1,08; 11,13]	0,0342*
Interaktion p-Wert									0,5939
WHO Performance-Status									
0	100	9 (9,0)	NE [NE; NE]	100	1 (1,0)	NE [NE; NE]	9,50	[1,79;175,18]	0,0052*
1	176	17 (9,7)	NE [NE; NE]	175	6 (3,4)	NE [NE; NE]	2,94	[1,22; 8,14]	0,0153*
Interaktion p-Wert									0,2649
Raucherstatus									
Ja	90	9 (10,0)	NE [NE; NE]	96	3 (3,1)	NE [NE; NE]	3,32	[0,99; 14,98]	0,0517
Nein	186	17 (9,1)	NE [NE; NE]	179	4 (2,2)	NE [NE; NE]	4,31	[1,59; 14,97]	0,0030*
Interaktion p-Wert									0,7659
Geschlecht									
Maennlich	104	11 (10,6)	NE [NE; NE]	107	1 (0,9)	NE [NE; NE]	11,59	[2,26;211,89]	0,0013*
Weiblich	172	15 (8,7)	NE [NE; NE]	168	6 (3,6)	NE [NE; NE]	2,59	[1,05; 7,27]	0,0376*
Interaktion p-Wert									0,1431
Nachweis der EGFR-Mutation durch zentralen ctDNA Cobas Test									
positiv	211	19 (9,0)	NE [NE; NE]	204	4 (2,0)	NE [NE; NE]	4,86	[1,83; 16,75]	0,0009*

Time to event of AE is defined as the time from first dose of study treatment to first onset of the respective AE or the time to censoring if the AE has not occurred by 28 days following discontinuation of study treatment, before administration of subsequent cancer therapy or death, whichever comes first. All AEs are coded using MedDRA version 25.1. Includes AEs with onset date on or after the date of first dose and up to and including 28 days following discontinuation of study treatment. Analysis done if >=10 patients at each subgroup level and >=10 events in at least one subgroup level combined for both arms. Analysis done for SOC and PT only if main effect for that SOC or PT is statistically significant at 5% level. [a] Median time to event based on the Kaplan Meier estimate. NE = Not estimable as median (or 95% CLs) is not reached. [b] Estimated from main effects of unstratified Cox proportional hazard model including trt., subgroup and subgroup-by-trt. interaction. Ties handled using Efron method and 95% CI derived from profile likelihood estimation. NC = Not calculable. HR <1 favours Osimertinib+Chemo. * p<0.05.
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Table 4.3.1.3 FLAURA-2: Summary of subgroup analysis of time to first PT: Asthenie
Safety Analysis Set, DCO 03APR2023

	Osi + Chemo (N=276)			Osi (N=275)					
Subgruppen	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]	Hazard Ratio [b]	[95%-KI] [b]	2-seitiger p-Wert [b]
negativ	41	7 (17,1)	NE [NE; NE]	39	1 (2,6)	NE [NE; NE]	7,32	[1,30;136,92]	0,0209*
unbekannt	24	0	NE [NE; NE]	32	2 (6,3)	NE [NE; NE]	NC	[NC]	NC
Interaktion p-Wert									0,7250
EGFR-Mutationstyp									
Exon 19 Deletion	172	17 (9,9)	NE [NE; NE]	167	2 (1,2)	NE [NE; NE]	8,82	[2,53; 55,60]	0,0002*
Exon 21 (L858R) Substitutionsmutation	104	9 (8,7)	NE [NE; NE]	106	5 (4,7)	NE [NE; NE]	1,86	[0,64; 6,06]	0,2541
Interaktion p-Wert									0,0793
Zentral bestätigte EGFR-Mutation im Gewebe									
positiv	248	23 (9,3)	NE [NE; NE]	238	5 (2,1)	NE [NE; NE]	4,61	[1,90; 13,73]	0,0004*
negativ	3	0	NE [NE; NE]	4	1 (25,0)	NE [NE; NE]	NC	[NC]	NC
unbekannt	25	3 (12,0)	NE [NE; NE]	33	1 (3,0)	NE [NE; NE]	4,46	[0,57; 90,13]	0,1577
Interaktion p-Wert									0,9791
ZNS-Metastasen zur Baseline									
Ja	113	5 (4,4)	NE [NE; NE]	110	1 (0,9)	NE [NE; NE]	4,82	[0,78; 92,38]	0,0961
Nein	163	21 (12,9)	NE [NE; NE]	165	6 (3,6)	NE [NE; NE]	3,86	[1,65; 10,51]	0,0013*
Interaktion p-Wert									0,8484
Zentrale Bestätigung der EGFR-Mutation									
Zentral bestätigte EGFR-Mutation in Gewebe oder ctDNA	263	25 (9,5)	NE [NE; NE]	266	6 (2,3)	NE [NE; NE]	4,42	[1,94; 11,90]	0,0002*
Keine zentrale Bestätigung	13	1 (7,7)	NE [NE; NE]	9	1 (11,1)	NE [NE; NE]	0,70	[0,03; 17,60]	0,7988
Interaktion p-Wert									0,2356
Alter bei Screening									

Time to event of AE is defined as the time from first dose of study treatment to first onset of the respective AE or the time to censoring if the AE has not occurred by 28 days following discontinuation of study treatment, before administration of subsequent cancer therapy or death, whichever comes first. All AEs are coded using MedDRA version 25.1. Includes AEs with onset date on or after the date of first dose and up to and including 28 days following discontinuation of study treatment. Analysis done if >=10 patients at each subgroup level and >=10 events in at least one subgroup level combined for both arms. Analysis done for SOC and PT only if main effect for that SOC or PT is statistically significant at 5% level. [a] Median time to event based on the Kaplan Meier estimate. NE = Not estimable as median (or 95% CLs) is not reached. [b] Estimated from main effects of unstratified Cox proportional hazard model including trt., subgroup and subgroup-by-trt. interaction. Ties handled using Efron method and 95% CI derived from profile likelihood estimation. NC = Not calculable. HR <1 favours Osimertinib+Chemo. * p<0.05.
root/cdar/d516/payer_germany/ar/d5169c00001_payer_germany/tlf/prod/program/ttesubae.sas gttesubaeaac 22DEC2023:09:13 kfrh585

Table 4.3.1.3 FLAURA-2: Summary of subgroup analysis of time to first PT: Asthenie
Safety Analysis Set, DCO 03APR2023

	Osi + Chemo (N=276)			Osi (N=275)					
Subgruppen	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]	Hazard Ratio [b]	[95%-KI] [b]	2-seitiger p-Wert [b]
<65 Jahre	172	17 (9,9)	NE [NE; NE]	164	3 (1,8)	NE [NE; NE]	5,61	[1,88; 24,03]	0,0011*
>=65 Jahre	104	9 (8,7)	NE [NE; NE]	111	4 (3,6)	NE [NE; NE]	2,56	[0,83; 9,44]	0,1025
Interaktion p-Wert									0,3619
Region gPAP									
Asien	168	8 (4,8)	NE [NE; NE]	166	0	NE [NE; NE]	NC	[NC]	NC
Europa	22	5 (22,7)	NE [NE; NE]	23	1 (4,3)	NE [NE; NE]	6,04	[0,97;115,70]	0,0538
Nordamerika	20	0	NE [NE; NE]	22	0	NE [NE; NE]	NC	[NC]	NC
Rest der Welt	66	13 (19,7)	NE [NE; NE]	64	6 (9,4)	NE [NE; NE]	2,31	[0,91; 6,57]	0,0786
Interaktion p-Wert									0,3935

Time to event of AE is defined as the time from first dose of study treatment to first onset of the respective AE or the time to censoring if the AE has not occurred by 28 days following discontinuation of study treatment, before administration of subsequent cancer therapy or death, whichever comes first. All AEs are coded using MedDRA version 25.1. Includes AEs with onset date on or after the date of first dose and up to and including 28 days following discontinuation of study treatment. Analysis done if >=10 patients at each subgroup level and >=10 events in at least one subgroup level combined for both arms. Analysis done for SOC and PT only if main effect for that SOC or PT is statistically significant at 5% level. [a] Median time to event based on the Kaplan Meier estimate. NE = Not estimable as median (or 95% CLs) is not reached. [b] Estimated from main effects of unstratified Cox proportional hazard model including trt., subgroup and subgroup-by-trt. interaction. Ties handled using Efron method and 95% CI derived from profile likelihood estimation. NC = Not calculable. HR <1 favours Osimertinib+Chemo. * p<0.05.
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Table 4.3.1.4 FLAURA-2: Summary of subgroup analysis of time to first PT: Ermuedung
Safety Analysis Set, DCO 03APR2023

	Osi + Chemo (N=276)			Osi (N=275)					
Subgruppen	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]	Hazard Ratio [b]	[95%-KI] [b]	2-seitiger p-Wert [b]
Abstammung									
Chinesisch/Asiatisch	68	18 (26,5)	NE [NE; NE]	70	6 (8,6)	NE [NE; NE]	3,27	[1,37; 9,02]	0,0067*
Nicht-chinesisch/ Asiatisch	107	15 (14,0)	NE [NE; NE]	106	5 (4,7)	NE [NE; NE]	3,16	[1,23; 9,73]	0,0163*
Nicht-asiatisch	101	43 (42,6)	NE [NE; NE]	99	15 (15,2)	NE [NE; NE]	3,48	[1,98; 6,48]	<0,0001*
Interaktion p-Wert									0,9849
Methode zur Gewebeuntersuchung									
zentral	120	21 (17,5)	NE [NE; NE]	119	4 (3,4)	NE [NE; NE]	5,59	[2,13; 19,17]	0,0002*
lokal	156	55 (35,3)	NE [NE; NE]	156	22 (14,1)	NE [NE; NE]	2,88	[1,78; 4,83]	<0,0001*
Interaktion p-Wert									0,2490
WHO Performance-Status									
0	100	24 (24,0)	NE [NE; NE]	100	9 (9,0)	NE [NE; NE]	2,99	[1,44; 6,80]	0,0028*
1	176	52 (29,5)	NE [NE; NE]	175	17 (9,7)	NE [NE; NE]	3,38	[2,00; 6,03]	<0,0001*
Interaktion p-Wert									0,7984
Raucherstatus									
Ja	90	18 (20,0)	NE [NE; NE]	96	8 (8,3)	NE [NE; NE]	2,52	[1,13; 6,15]	0,0229*
Nein	186	58 (31,2)	NE [NE; NE]	179	18 (10,1)	NE [NE; NE]	3,57	[2,15; 6,23]	<0,0001*
Interaktion p-Wert									0,4954
Geschlecht									
Maennlich	104	28 (26,9)	NE [NE; NE]	107	10 (9,3)	NE [NE; NE]	3,07	[1,54; 6,64]	0,0011*
Weiblich	172	48 (27,9)	NE [NE; NE]	168	16 (9,5)	NE [NE; NE]	3,37	[1,96; 6,12]	<0,0001*
Interaktion p-Wert									0,8433
Nachweis der EGFR-Mutation durch zentralen ctDNA Cobas Test									
positiv	211	51 (24,2)	NE [NE; NE]	204	19 (9,3)	NE [NE; NE]	2,87	[1,72; 4,98]	<0,0001*

Time to event of AE is defined as the time from first dose of study treatment to first onset of the respective AE or the time to censoring if the AE has not occurred by 28 days following discontinuation of study treatment, before administration of subsequent cancer therapy or death, whichever comes first. All AEs are coded using MedDRA version 25.1. Includes AEs with onset date on or after the date of first dose and up to and including 28 days following discontinuation of study treatment. Analysis done if >=10 patients at each subgroup level and >=10 events in at least one subgroup level combined for both arms. Analysis done for SOC and PT only if main effect for that SOC or PT is statistically significant at 5% level. [a] Median time to event based on the Kaplan Meier estimate. NE = Not estimable as median (or 95% CLs) is not reached. [b] Estimated from main effects of unstratified Cox proportional hazard model including trt., subgroup and subgroup-by-trt. interaction. Ties handled using Efron method and 95% CI derived from profile likelihood estimation. NC = Not calculable. HR <1 favours Osimertinib+Chemo. * p<0.05.
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Table 4.3.1.4 FLAURA-2: Summary of subgroup analysis of time to first PT: Ermuedung
Safety Analysis Set, DCO 03APR2023

	Osi + Chemo (N=276)			Osi (N=275)					
Subgruppen	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]	Hazard Ratio [b]	[95%-KI] [b]	2-seitiger p-Wert [b]
negativ	41	14 (34,1)	NE [NE; NE]	39	2 (5,1)	NE [NE; NE]	8,14	[2,27; 51,86]	0,0005*
unbekannt	24	11 (45,8)	27,7 [1,4; NE]	32	5 (15,6)	NE [NE; NE]	3,17	[1,15; 10,08]	0,0249*
Interaktion p-Wert									0,3592
EGFR-Mutationstyp									
Exon 19 Deletion	172	51 (29,7)	NE [NE; NE]	167	16 (9,6)	NE [NE; NE]	3,61	[2,11; 6,53]	<0,0001*
Exon 21 (L858R) Substitutionsmutation	104	25 (24,0)	NE [NE; NE]	106	10 (9,4)	NE [NE; NE]	2,66	[1,32; 5,80]	0,0059*
Interaktion p-Wert									0,5183
Zentral bestätigte EGFR-Mutation im Gewebe									
positiv	248	64 (25,8)	NE [NE; NE]	238	20 (8,4)	NE [NE; NE]	3,39	[2,09; 5,75]	<0,0001*
negativ	3	0	NE [NE; NE]	4	0	NE [NE; NE]	NC	[NC]	NC
unbekannt	25	12 (48,0)	4,7 [1,4; NE]	33	6 (18,2)	NE [NE; NE]	3,54	[1,37; 10,18]	0,0087*
Interaktion p-Wert									0,9395
ZNS-Metastasen zur Baseline									
Ja	113	30 (26,5)	NE [NE; NE]	110	13 (11,8)	NE [NE; NE]	2,39	[1,27; 4,74]	0,0062*
Nein	163	46 (28,2)	NE [NE; NE]	165	13 (7,9)	NE [NE; NE]	4,13	[2,30; 7,96]	<0,0001*
Interaktion p-Wert									0,2327
Zentrale Bestätigung der EGFR-Mutation									
Zentral bestätigte EGFR-Mutation in Gewebe oder ctDNA	263	70 (26,6)	NE [NE; NE]	266	25 (9,4)	NE [NE; NE]	3,15	[2,02; 5,07]	<0,0001*
Keine zentrale Bestätigung	13	6 (46,2)	NE [NE; NE]	9	1 (11,1)	NE [NE; NE]	4,99	[0,85; 94,19]	0,0785
Interaktion p-Wert									0,6622
Alter bei Screening									

Time to event of AE is defined as the time from first dose of study treatment to first onset of the respective AE or the time to censoring if the AE has not occurred by 28 days following discontinuation of study treatment, before administration of subsequent cancer therapy or death, whichever comes first. All AEs are coded using MedDRA version 25.1. Includes AEs with onset date on or after the date of first dose and up to and including 28 days following discontinuation of study treatment. Analysis done if >=10 patients at each subgroup level and >=10 events in at least one subgroup level combined for both arms. Analysis done for SOC and PT only if main effect for that SOC or PT is statistically significant at 5% level. [a] Median time to event based on the Kaplan Meier estimate. NE = Not estimable as median (or 95% CLs) is not reached. [b] Estimated from main effects of unstratified Cox proportional hazard model including trt., subgroup and subgroup-by-trt. interaction. Ties handled using Efron method and 95% CI derived from profile likelihood estimation. NC = Not calculable. HR <1 favours Osimertinib+Chemo. * p<0.05.
root/cdar/d516/payer_germany/ar/d5169c00001_payer_germany/tlf/prod/program/ttesubae.sas gttesubaeaad 22DEC2023:09:13 kfrh585

Table 4.3.1.4 FLAURA-2: Summary of subgroup analysis of time to first PT: Ermuedung
Safety Analysis Set, DCO 03APR2023

	Osi + Chemo (N=276)			Osi (N=275)					
Subgruppen	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]	Hazard Ratio [b]	[95%-KI] [b]	2-seitiger p-Wert [b]
<65 Jahre	172	51 (29,7)	NE [NE; NE]	164	19 (11,6)	NE [NE; NE]	2,82	[1,70; 4,90]	<0,0001*
>=65 Jahre	104	25 (24,0)	NE [NE; NE]	111	7 (6,3)	NE [NE; NE]	4,33	[1,98; 10,87]	0,0001*
Interaktion p-Wert									0,3883
Region gPAP									
Asien	168	27 (16,1)	NE [NE; NE]	166	6 (3,6)	NE [NE; NE]	4,72	[2,08; 12,64]	<0,0001*
Europa	22	7 (31,8)	NE [NE; NE]	23	2 (8,7)	NE [NE; NE]	4,07	[0,98; 27,32]	0,0531
Nordamerika	20	17 (85,0)	0,8 [0,2; 4,1]	22	8 (36,4)	NE [NE; NE]	4,09	[1,81; 10,08]	0,0006*
Rest der Welt	66	25 (37,9)	NE [NE; NE]	64	10 (15,6)	NE [NE; NE]	2,89	[1,43; 6,31]	0,0027*
Interaktion p-Wert									0,8516

Time to event of AE is defined as the time from first dose of study treatment to first onset of the respective AE or the time to censoring if the AE has not occurred by 28 days following discontinuation of study treatment, before administration of subsequent cancer therapy or death, whichever comes first. All AEs are coded using MedDRA version 25.1. Includes AEs with onset date on or after the date of first dose and up to and including 28 days following discontinuation of study treatment. Analysis done if >=10 patients at each subgroup level and >=10 events in at least one subgroup level combined for both arms. Analysis done for SOC and PT only if main effect for that SOC or PT is statistically significant at 5% level. [a] Median time to event based on the Kaplan Meier estimate. NE = Not estimable as median (or 95% CLs) is not reached. [b] Estimated from main effects of unstratified Cox proportional hazard model including trt., subgroup and subgroup-by-trt. interaction. Ties handled using Efron method and 95% CI derived from profile likelihood estimation. NC = Not calculable. HR <1 favours Osimertinib+Chemo. * p<0.05.
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Table 4.3.1.5 FLAURA-2: Summary of subgroup analysis of time to first PT: Fieber
Safety Analysis Set, DCO 03APR2023

	Osi + Chemo (N=276)			Osi (N=275)					
Subgruppen	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]	Hazard Ratio [b]	[95%-KI] [b]	2-seitiger p-Wert [b]
Abstammung									
Chinesisch/Asiatisch	68	8 (11,8)	NE [NE; NE]	70	3 (4,3)	NE [NE; NE]	2,63	[0,76; 12,02]	0,1298
Nicht-chinesisch/ Asiatisch	107	15 (14,0)	NE [NE; NE]	106	10 (9,4)	NE [NE; NE]	1,55	[0,70; 3,56]	0,2785
Nicht-asiatisch	101	8 (7,9)	NE [NE; NE]	99	2 (2,0)	NE [NE; NE]	3,94	[0,99; 26,12]	0,0523
Interaktion p-Wert									0,5039
Methode zur Gewebeuntersuchung									
zentral	120	10 (8,3)	NE [NE; NE]	119	5 (4,2)	NE [NE; NE]	2,00	[0,71; 6,41]	0,1936
lokal	156	21 (13,5)	NE [NE; NE]	156	10 (6,4)	NE [NE; NE]	2,12	[1,02; 4,70]	0,0434*
Interaktion p-Wert									0,9299
WHO Performance-Status									
0	100	16 (16,0)	NE [NE; NE]	100	8 (8,0)	NE [NE; NE]	2,17	[0,95; 5,34]	0,0654
1	176	15 (8,5)	NE [NE; NE]	175	7 (4,0)	NE [NE; NE]	2,06	[0,87; 5,39]	0,1028
Interaktion p-Wert									0,9353
Raucherstatus									
Ja	90	12 (13,3)	NE [NE; NE]	96	8 (8,3)	NE [NE; NE]	1,57	[0,65; 4,01]	0,3168
Nein	186	19 (10,2)	NE [NE; NE]	179	7 (3,9)	NE [NE; NE]	2,67	[1,17; 6,84]	0,0184*
Interaktion p-Wert									0,4027
Geschlecht									
Maennlich	104	13 (12,5)	NE [NE; NE]	107	9 (8,4)	NE [NE; NE]	1,41	[0,61; 3,41]	0,4286
Weiblich	172	18 (10,5)	NE [NE; NE]	168	6 (3,6)	NE [NE; NE]	3,07	[1,29; 8,46]	0,0105*
Interaktion p-Wert									0,2189
Nachweis der EGFR-Mutation durch zentralen ctDNA Cobas Test									
positiv	211	19 (9,0)	NE [NE; NE]	204	11 (5,4)	NE [NE; NE]	1,67	[0,81; 3,63]	0,1695

Time to event of AE is defined as the time from first dose of study treatment to first onset of the respective AE or the time to censoring if the AE has not occurred by 28 days following discontinuation of study treatment, before administration of subsequent cancer therapy or death, whichever comes first. All AEs are coded using MedDRA version 25.1. Includes AEs with onset date on or after the date of first dose and up to and including 28 days following discontinuation of study treatment. Analysis done if >=10 patients at each subgroup level and >=10 events in at least one subgroup level combined for both arms. Analysis done for SOC and PT only if main effect for that SOC or PT is statistically significant at 5% level. [a] Median time to event based on the Kaplan Meier estimate. NE = Not estimable as median (or 95% CLs) is not reached. [b] Estimated from main effects of unstratified Cox proportional hazard model including trt., subgroup and subgroup-by-trt. interaction. Ties handled using Efron method and 95% CI derived from profile likelihood estimation. NC = Not calculable. HR <1 favours Osimertinib+Chemo. * p<0.05.
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Table 4.3.1.5 FLAURA-2: Summary of subgroup analysis of time to first PT: Fieber
Safety Analysis Set, DCO 03APR2023

	Osi + Chemo (N=276)			Osi (N=275)					
Subgruppen	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]	Hazard Ratio [b]	[95%-KI] [b]	2-seitiger p-Wert [b]
negativ	41	8 (19,5)	NE [NE; NE]	39	3 (7,7)	NE [NE; NE]	2,72	[0,79; 12,43]	0,1168
unbekannt	24	4 (16,7)	NE [NE; NE]	32	1 (3,1)	NE [NE; NE]	5,32	[0,79;104,04]	0,0894
Interaktion p-Wert									0,5145
EGFR-Mutationstyp									
Exon 19 Deletion	172	15 (8,7)	NE [NE; NE]	167	8 (4,8)	NE [NE; NE]	1,86	[0,81; 4,63]	0,1451
Exon 21 (L858R) Substitutionsmutation	104	16 (15,4)	NE [NE; NE]	106	6 (5,7)	NE [NE; NE]	2,69	[1,11; 7,50]	0,0285*
Interaktion p-Wert									0,5706
Zentral bestätigte EGFR-Mutation im Gewebe									
positiv	248	27 (10,9)	NE [NE; NE]	238	12 (5,0)	NE [NE; NE]	2,15	[1,11; 4,41]	0,0218*
negativ	3	1 (33,3)	NE [NE; NE]	4	1 (25,0)	NE [NE; NE]	NC	[NC]	NC
unbekannt	25	3 (12,0)	NE [NE; NE]	33	2 (6,1)	NE [NE; NE]	2,30	[0,38; 17,46]	0,3565
Interaktion p-Wert									0,9466
ZNS-Metastasen zur Baseline									
Ja	113	9 (8,0)	NE [NE; NE]	110	3 (2,7)	NE [NE; NE]	2,74	[0,82; 12,35]	0,1059
Nein	163	22 (13,5)	NE [NE; NE]	165	12 (7,3)	NE [NE; NE]	1,96	[0,99; 4,10]	0,0539
Interaktion p-Wert									0,6561
Zentrale Bestätigung der EGFR-Mutation									
Zentral bestätigte EGFR-Mutation in Gewebe oder ctDNA	263	27 (10,3)	NE [NE; NE]	266	14 (5,3)	NE [NE; NE]	1,95	[1,04; 3,83]	0,0369*
Keine zentrale Bestätigung	13	4 (30,8)	NE [NE; NE]	9	1 (11,1)	NE [NE; NE]	3,11	[0,46; 60,74]	0,2643
Interaktion p-Wert									0,6800
Alter bei Screening									

Time to event of AE is defined as the time from first dose of study treatment to first onset of the respective AE or the time to censoring if the AE has not occurred by 28 days following discontinuation of study treatment, before administration of subsequent cancer therapy or death, whichever comes first. All AEs are coded using MedDRA version 25.1. Includes AEs with onset date on or after the date of first dose and up to and including 28 days following discontinuation of study treatment. Analysis done if >=10 patients at each subgroup level and >=10 events in at least one subgroup level combined for both arms. Analysis done for SOC and PT only if main effect for that SOC or PT is statistically significant at 5% level. [a] Median time to event based on the Kaplan Meier estimate. NE = Not estimable as median (or 95% CLs) is not reached. [b] Estimated from main effects of unstratified Cox proportional hazard model including trt., subgroup and subgroup-by-trt. interaction. Ties handled using Efron method and 95% CI derived from profile likelihood estimation. NC = Not calculable. HR <1 favours Osimertinib+Chemo. * p<0.05.
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Table 4.3.1.5 FLAURA-2: Summary of subgroup analysis of time to first PT: Fieber
Safety Analysis Set, DCO 03APR2023

	Osi + Chemo (N=276)			Osi (N=275)					
Subgruppen	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]	Hazard Ratio [b]	[95%-KI] [b]	2-seitiger p-Wert [b]
<65 Jahre	172	15 (8,7)	NE [NE; NE]	164	7 (4,3)	NE [NE; NE]	2,01	[0,85; 5,25]	0,1163
>=65 Jahre	104	16 (15,4)	NE [NE; NE]	111	8 (7,2)	NE [NE; NE]	2,27	[0,997; 5,59]	0,0508
Interaktion p-Wert									0,8455
Region gPAP									
Asien	168	22 (13,1)	NE [NE; NE]	166	13 (7,8)	NE [NE; NE]	1,67	[0,85; 3,40]	0,1377
Europa	22	2 (9,1)	NE [NE; NE]	23	1 (4,3)	NE [NE; NE]	1,88	[0,18; 40,44]	0,5965
Nordamerika	20	3 (15,0)	NE [NE; NE]	22	1 (4,5)	NE [NE; NE]	4,06	[0,52; 82,13]	0,1868
Rest der Welt	66	4 (6,1)	NE [NE; NE]	64	0	NE [NE; NE]	NC	[NC]	NC
Interaktion p-Wert									0,7391

Time to event of AE is defined as the time from first dose of study treatment to first onset of the respective AE or the time to censoring if the AE has not occurred by 28 days following discontinuation of study treatment, before administration of subsequent cancer therapy or death, whichever comes first. All AEs are coded using MedDRA version 25.1. Includes AEs with onset date on or after the date of first dose and up to and including 28 days following discontinuation of study treatment. Analysis done if >=10 patients at each subgroup level and >=10 events in at least one subgroup level combined for both arms. Analysis done for SOC and PT only if main effect for that SOC or PT is statistically significant at 5% level. [a] Median time to event based on the Kaplan Meier estimate. NE = Not estimable as median (or 95% CLs) is not reached. [b] Estimated from main effects of unstratified Cox proportional hazard model including trt., subgroup and subgroup-by-trt. interaction. Ties handled using Efron method and 95% CI derived from profile likelihood estimation. NC = Not calculable. HR <1 favours Osimertinib+Chemo. * p<0.05.
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Table 4.3.1.6 FLAURA-2: Summary of subgroup analysis of time to first PT: Gesichtsoedem
Safety Analysis Set, DCO 03APR2023

	Osi + Chemo (N=276)			Osi (N=275)					
Subgruppen	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]	Hazard Ratio [b]	[95%-KI] [b]	2-seitiger p-Wert [b]
Abstammung									
Chinesisch/Asiatisch	68	5 (7,4)	NE [NE; NE]	70	1 (1,4)	NE [NE; NE]	NC	[NC]	NC
Nicht-chinesisch/ Asiatisch	107	4 (3,7)	NE [NE; NE]	106	0	NE [NE; NE]	NC	[NC]	NC
Nicht-asiatisch	101	1 (1,0)	NE [NE; NE]	99	1 (1,0)	NE [NE; NE]	NC	[NC]	NC
Interaktion p-Wert									NC
Methode zur Gewebeuntersuchung									
zentral	120	5 (4,2)	NE [NE; NE]	119	1 (0,8)	NE [NE; NE]	NC	[NC]	NC
lokal	156	5 (3,2)	NE [NE; NE]	156	1 (0,6)	NE [NE; NE]	NC	[NC]	NC
Interaktion p-Wert									NC
WHO Performance-Status									
0	100	4 (4,0)	NE [NE; NE]	100	0	NE [NE; NE]	NC	[NC]	NC
1	176	6 (3,4)	NE [NE; NE]	175	2 (1,1)	NE [NE; NE]	NC	[NC]	NC
Interaktion p-Wert									NC
Raucherstatus									
Ja	90	0	NE [NE; NE]	96	1 (1,0)	NE [NE; NE]	NC	[NC]	NC
Nein	186	10 (5,4)	NE [NE; NE]	179	1 (0,6)	NE [NE; NE]	9,69	[1,86;177,80]	0,0040*
Interaktion p-Wert									NC
Geschlecht									
Maennlich	104	1 (1,0)	NE [NE; NE]	107	0	NE [NE; NE]	NC	[NC]	NC
Weiblich	172	9 (5,2)	NE [NE; NE]	168	2 (1,2)	NE [NE; NE]	4,51	[1,16; 29,61]	0,0278*
Interaktion p-Wert									NC
Nachweis der EGFR-Mutation durch zentralen ctDNA Cobas Test									
positiv	211	9 (4,3)	NE [NE; NE]	204	1 (0,5)	NE [NE; NE]	8,63	[1,62;159,05]	0,0080*

Time to event of AE is defined as the time from first dose of study treatment to first onset of the respective AE or the time to censoring if the AE has not occurred by 28 days following discontinuation of study treatment, before administration of subsequent cancer therapy or death, whichever comes first. All AEs are coded using MedDRA version 25.1. Includes AEs with onset date on or after the date of first dose and up to and including 28 days following discontinuation of study treatment. Analysis done if >=10 patients at each subgroup level and >=10 events in at least one subgroup level combined for both arms. Analysis done for SOC and PT only if main effect for that SOC or PT is statistically significant at 5% level. [a] Median time to event based on the Kaplan Meier estimate. NE = Not estimable as median (or 95% CLs) is not reached. [b] Estimated from main effects of unstratified Cox proportional hazard model including trt., subgroup and subgroup-by-trt. interaction. Ties handled using Efron method and 95% CI derived from profile likelihood estimation. NC = Not calculable. HR <1 favours Osimertinib+Chemo. * p<0.05.
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Table 4.3.1.6 FLAURA-2: Summary of subgroup analysis of time to first PT: Gesichtsoedem
Safety Analysis Set, DCO 03APR2023

	Osi + Chemo (N=276)			Osi (N=275)					
Subgruppen	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]	Hazard Ratio [b]	[95%-KI] [b]	2-seitiger p-Wert [b]
negativ	41	1 (2,4)	NE [NE; NE]	39	0	NE [NE; NE]	NC	[NC]	NC
unbekannt	24	0	NE [NE; NE]	32	1 (3,1)	NE [NE; NE]	NC	[NC]	NC
Interaktion p-Wert									NC
EGFR-Mutationstyp									
Exon 19 Deletion	172	6 (3,5)	NE [NE; NE]	167	1 (0,6)	NE [NE; NE]	NC	[NC]	NC
Exon 21 (L858R) Substitutionsmutation	104	4 (3,8)	NE [NE; NE]	106	1 (0,9)	NE [NE; NE]	NC	[NC]	NC
Interaktion p-Wert									NC
Zentral bestätigte EGFR-Mutation im Gewebe									
positiv	248	10 (4,0)	NE [NE; NE]	238	1 (0,4)	NE [NE; NE]	9,44	[1,81;173,25]	0,0046*
negativ	3	0	NE [NE; NE]	4	0	NE [NE; NE]	NC	[NC]	NC
unbekannt	25	0	NE [NE; NE]	33	1 (3,0)	NE [NE; NE]	NC	[NC]	NC
Interaktion p-Wert									NC
ZNS-Metastasen zur Baseline									
Ja	113	6 (5,3)	NE [NE; NE]	110	2 (1,8)	NE [NE; NE]	NC	[NC]	NC
Nein	163	4 (2,5)	NE [NE; NE]	165	0	NE [NE; NE]	NC	[NC]	NC
Interaktion p-Wert									NC
Zentrale Bestätigung der EGFR-Mutation									
Zentral bestätigte EGFR-Mutation in Gewebe oder ctDNA	263	10 (3,8)	NE [NE; NE]	266	1 (0,4)	NE [NE; NE]	9,99	[1,91;183,34]	0,0035*
Keine zentrale Bestätigung	13	0	NE [NE; NE]	9	1 (11,1)	NE [NE; NE]	NC	[NC]	NC
Interaktion p-Wert									NC
Alter bei Screening									

Time to event of AE is defined as the time from first dose of study treatment to first onset of the respective AE or the time to censoring if the AE has not occurred by 28 days following discontinuation of study treatment, before administration of subsequent cancer therapy or death, whichever comes first. All AEs are coded using MedDRA version 25.1. Includes AEs with onset date on or after the date of first dose and up to and including 28 days following discontinuation of study treatment. Analysis done if >=10 patients at each subgroup level and >=10 events in at least one subgroup level combined for both arms. Analysis done for SOC and PT only if main effect for that SOC or PT is statistically significant at 5% level. [a] Median time to event based on the Kaplan Meier estimate. NE = Not estimable as median (or 95% CLs) is not reached. [b] Estimated from main effects of unstratified Cox proportional hazard model including trt., subgroup and subgroup-by-trt. interaction. Ties handled using Efron method and 95% CI derived from profile likelihood estimation. NC = Not calculable. HR <1 favours Osimertinib+Chemo. * p<0.05.
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Table 4.3.1.6 FLAURA-2: Summary of subgroup analysis of time to first PT: Gesichtsoedem
Safety Analysis Set, DCO 03APR2023

	Osi + Chemo (N=276)			Osi (N=275)					
Subgruppen	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]	Hazard Ratio [b]	[95%-KI] [b]	2-seitiger p-Wert [b]
<65 Jahre	172	7 (4,1)	NE [NE; NE]	164	1 (0,6)	NE [NE; NE]	NC	[NC]	NC
>=65 Jahre	104	3 (2,9)	NE [NE; NE]	111	1 (0,9)	NE [NE; NE]	NC	[NC]	NC
Interaktion p-Wert									NC
Region gPAP									
Asien	168	8 (4,8)	NE [NE; NE]	166	1 (0,6)	NE [NE; NE]	NC	[NC]	NC
Europa	22	0	NE [NE; NE]	23	0	NE [NE; NE]	NC	[NC]	NC
Nordamerika	20	0	NE [NE; NE]	22	0	NE [NE; NE]	NC	[NC]	NC
Rest der Welt	66	2 (3,0)	NE [NE; NE]	64	1 (1,6)	NE [NE; NE]	NC	[NC]	NC
Interaktion p-Wert									NC

Time to event of AE is defined as the time from first dose of study treatment to first onset of the respective AE or the time to censoring if the AE has not occurred by 28 days following discontinuation of study treatment, before administration of subsequent cancer therapy or death, whichever comes first. All AEs are coded using MedDRA version 25.1. Includes AEs with onset date on or after the date of first dose and up to and including 28 days following discontinuation of study treatment. Analysis done if >=10 patients at each subgroup level and >=10 events in at least one subgroup level combined for both arms. Analysis done for SOC and PT only if main effect for that SOC or PT is statistically significant at 5% level. [a] Median time to event based on the Kaplan Meier estimate. NE = Not estimable as median (or 95% CLs) is not reached. [b] Estimated from main effects of unstratified Cox proportional hazard model including trt., subgroup and subgroup-by-trt. interaction. Ties handled using Efron method and 95% CI derived from profile likelihood estimation. NC = Not calculable. HR <1 favours Osimertinib+Chemo. * p<0.05.
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Table 4.3.1.7 FLAURA-2: Summary of subgroup analysis of time to first PT: Oedem peripher
Safety Analysis Set, DCO 03APR2023

	Osi + Chemo (N=276)			Osi (N=275)					
Subgruppen	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]	Hazard Ratio [b]	[95%-KI] [b]	2-seitiger p-Wert [b]
Abstammung									
Chinesisch/Asiatisch	68	9 (13,2)	NE [NE; NE]	70	1 (1,4)	NE [NE; NE]	8,99	[1,69;165,91]	0,0067*
Nicht-chinesisch/ Asiatisch	107	15 (14,0)	NE [NE; NE]	106	4 (3,8)	NE [NE; NE]	3,90	[1,42; 13,70]	0,0071*
Nicht-asiatisch	101	18 (17,8)	NE [NE; NE]	99	7 (7,1)	NE [NE; NE]	2,56	[1,12; 6,59]	0,0260*
Interaktion p-Wert									0,4639
Methode zur Gewebeuntersuchung									
zentral	120	11 (9,2)	NE [NE; NE]	119	2 (1,7)	NE [NE; NE]	5,43	[1,46; 35,10]	0,0094*
lokal	156	31 (19,9)	NE [NE; NE]	156	10 (6,4)	NE [NE; NE]	3,21	[1,63; 6,91]	0,0005*
Interaktion p-Wert									0,5223
WHO Performance-Status									
0	100	12 (12,0)	NE [NE; NE]	100	1 (1,0)	NE [NE; NE]	12,54	[2,47;228,30]	0,0007*
1	176	30 (17,0)	NE [NE; NE]	175	11 (6,3)	NE [NE; NE]	2,72	[1,40; 5,68]	0,0026*
Interaktion p-Wert									0,1036
Raucherstatus									
Ja	90	15 (16,7)	NE [NE; NE]	96	4 (4,2)	NE [NE; NE]	4,11	[1,49; 14,43]	0,0051*
Nein	186	27 (14,5)	NE [NE; NE]	179	8 (4,5)	NE [NE; NE]	3,30	[1,57; 7,78]	0,0012*
Interaktion p-Wert									0,7491
Geschlecht									
Maennlich	104	14 (13,5)	NE [NE; NE]	107	4 (3,7)	NE [NE; NE]	3,48	[1,25; 12,27]	0,0159*
Weiblich	172	28 (16,3)	NE [NE; NE]	168	8 (4,8)	NE [NE; NE]	3,60	[1,72; 8,47]	0,0004*
Interaktion p-Wert									0,9603
Nachweis der EGFR-Mutation durch zentralen ctDNA Cobas Test									
positiv	211	35 (16,6)	NE [NE; NE]	204	8 (3,9)	NE [NE; NE]	4,36	[2,13; 10,13]	<0,0001*

Time to event of AE is defined as the time from first dose of study treatment to first onset of the respective AE or the time to censoring if the AE has not occurred by 28 days following discontinuation of study treatment, before administration of subsequent cancer therapy or death, whichever comes first. All AEs are coded using MedDRA version 25.1. Includes AEs with onset date on or after the date of first dose and up to and including 28 days following discontinuation of study treatment. Analysis done if >=10 patients at each subgroup level and >=10 events in at least one subgroup level combined for both arms. Analysis done for SOC and PT only if main effect for that SOC or PT is statistically significant at 5% level. [a] Median time to event based on the Kaplan Meier estimate. NE = Not estimable as median (or 95% CLs) is not reached. [b] Estimated from main effects of unstratified Cox proportional hazard model including trt., subgroup and subgroup-by-trt. interaction. Ties handled using Efron method and 95% CI derived from profile likelihood estimation. NC = Not calculable. HR <1 favours Osimertinib+Chemo. * p<0.05.
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Table 4.3.1.7 FLAURA-2: Summary of subgroup analysis of time to first PT: Oedem peripher
Safety Analysis Set, DCO 03APR2023

	Osi + Chemo (N=276)			Osi (N=275)					
Subgruppen	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]	Hazard Ratio [b]	[95%-KI] [b]	2-seitiger p-Wert [b]
negativ	41	6 (14,6)	NE [NE; NE]	39	1 (2,6)	NE [NE; NE]	6,03	[1,03;113,92]	0,0458*
unbekannt	24	1 (4,2)	NE [NE; NE]	32	3 (9,4)	NE [NE; NE]	0,39	[0,02; 3,06]	0,3872
Interaktion p-Wert									0,0829
EGFR-Mutationstyp									
Exon 19 Deletion	172	25 (14,5)	NE [NE; NE]	167	4 (2,4)	NE [NE; NE]	6,26	[2,43; 21,25]	<0,0001*
Exon 21 (L858R) Substitutionsmutation	104	17 (16,3)	NE [NE; NE]	106	8 (7,5)	NE [NE; NE]	2,17	[0,97; 5,33]	0,0607
Interaktion p-Wert									0,1144
Zentral bestätigte EGFR-Mutation im Gewebe									
positiv	248	35 (14,1)	NE [NE; NE]	238	9 (3,8)	NE [NE; NE]	3,78	[1,90; 8,37]	<0,0001*
negativ	3	1 (33,3)	NE [NE; NE]	4	0	NE [NE; NE]	NC	[NC]	NC
unbekannt	25	6 (24,0)	NE [NE; NE]	33	3 (9,1)	NE [NE; NE]	2,97	[0,78; 14,10]	0,1098
Interaktion p-Wert									0,7671
ZNS-Metastasen zur Baseline									
Ja	113	16 (14,2)	NE [NE; NE]	110	4 (3,6)	NE [NE; NE]	3,66	[1,34; 12,76]	0,0098*
Nein	163	26 (16,0)	NE [NE; NE]	165	8 (4,8)	NE [NE; NE]	3,54	[1,68; 8,37]	0,0006*
Interaktion p-Wert									0,9634
Zentrale Bestätigung der EGFR-Mutation									
Zentral bestätigte EGFR-Mutation in Gewebe oder ctDNA	263	39 (14,8)	NE [NE; NE]	266	11 (4,1)	NE [NE; NE]	3,66	[1,94; 7,50]	<0,0001*
Keine zentrale Bestätigung	13	3 (23,1)	NE [NE; NE]	9	1 (11,1)	NE [NE; NE]	2,01	[0,26; 40,55]	0,5257
Interaktion p-Wert									0,6341
Alter bei Screening									

Time to event of AE is defined as the time from first dose of study treatment to first onset of the respective AE or the time to censoring if the AE has not occurred by 28 days following discontinuation of study treatment, before administration of subsequent cancer therapy or death, whichever comes first. All AEs are coded using MedDRA version 25.1. Includes AEs with onset date on or after the date of first dose and up to and including 28 days following discontinuation of study treatment. Analysis done if >=10 patients at each subgroup level and >=10 events in at least one subgroup level combined for both arms. Analysis done for SOC and PT only if main effect for that SOC or PT is statistically significant at 5% level. [a] Median time to event based on the Kaplan Meier estimate. NE = Not estimable as median (or 95% CLs) is not reached. [b] Estimated from main effects of unstratified Cox proportional hazard model including trt., subgroup and subgroup-by-trt. interaction. Ties handled using Efron method and 95% CI derived from profile likelihood estimation. NC = Not calculable. HR <1 favours Osimertinib+Chemo. * p<0.05.
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Table 4.3.1.7 FLAURA-2: Summary of subgroup analysis of time to first PT: Oedem peripher
Safety Analysis Set, DCO 03APR2023

	Osi + Chemo (N=276)			Osi (N=275)					
Subgruppen	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]	Hazard Ratio [b]	[95%-KI] [b]	2-seitiger p-Wert [b]
<65 Jahre	172	25 (14,5)	NE [NE; NE]	164	7 (4,3)	NE [NE; NE]	3,38	[1,54; 8,48]	0,0018*
>=65 Jahre	104	17 (16,3)	NE [NE; NE]	111	5 (4,5)	NE [NE; NE]	3,89	[1,54; 11,82]	0,0033*
Interaktion p-Wert									0,8346
Region gPAP									
Asien	168	23 (13,7)	NE [NE; NE]	166	6 (3,6)	NE [NE; NE]	3,83	[1,66; 10,36]	0,0011*
Europa	22	6 (27,3)	NE [NE; NE]	23	1 (4,3)	NE [NE; NE]	6,60	[1,13;124,60]	0,0349*
Nordamerika	20	4 (20,0)	NE [NE; NE]	22	1 (4,5)	NE [NE; NE]	5,44	[0,80;106,30]	0,0853
Rest der Welt	66	9 (13,6)	NE [NE; NE]	64	4 (6,3)	NE [NE; NE]	2,12	[0,69; 7,82]	0,1944
Interaktion p-Wert									0,7418

Time to event of AE is defined as the time from first dose of study treatment to first onset of the respective AE or the time to censoring if the AE has not occurred by 28 days following discontinuation of study treatment, before administration of subsequent cancer therapy or death, whichever comes first. All AEs are coded using MedDRA version 25.1. Includes AEs with onset date on or after the date of first dose and up to and including 28 days following discontinuation of study treatment. Analysis done if >=10 patients at each subgroup level and >=10 events in at least one subgroup level combined for both arms. Analysis done for SOC and PT only if main effect for that SOC or PT is statistically significant at 5% level. [a] Median time to event based on the Kaplan Meier estimate. NE = Not estimable as median (or 95% CLs) is not reached. [b] Estimated from main effects of unstratified Cox proportional hazard model including trt., subgroup and subgroup-by-trt. interaction. Ties handled using Efron method and 95% CI derived from profile likelihood estimation. NC = Not calculable. HR <1 favours Osimertinib+Chemo. * p<0.05.
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Table 4.3.1.8 FLAURA-2: Summary of subgroup analysis of time to first PT: Unwohlsein
Safety Analysis Set, DCO 03APR2023

	Osi + Chemo (N=276)			Osi (N=275)					
Subgruppen	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]	Hazard Ratio [b]	[95%-KI] [b]	2-seitiger p-Wert [b]
Abstammung									
Chinesisch/Asiatisch	68	5 (7,4)	NE [NE; NE]	70	1 (1,4)	NE [NE; NE]	5,01	[0,81; 95,94]	0,0876
Nicht-chinesisch/ Asiatisch	107	14 (13,1)	NE [NE; NE]	106	2 (1,9)	NE [NE; NE]	7,44	[2,08; 47,37]	0,0010*
Nicht-asiatisch	101	0	NE [NE; NE]	99	0	NE [NE; NE]	NC	[NC]	NC
Interaktion p-Wert									0,7702
Methode zur Gewebeuntersuchung									
zentral	120	5 (4,2)	NE [NE; NE]	119	2 (1,7)	NE [NE; NE]	2,48	[0,53; 17,32]	0,2530
lokal	156	14 (9,0)	NE [NE; NE]	156	1 (0,6)	NE [NE; NE]	14,43	[2,90;261,37]	0,0002*
Interaktion p-Wert									0,1702
WHO Performance-Status									
0	100	8 (8,0)	NE [NE; NE]	100	1 (1,0)	NE [NE; NE]	8,36	[1,53;155,03]	0,0107*
1	176	11 (6,3)	NE [NE; NE]	175	2 (1,1)	NE [NE; NE]	5,48	[1,47; 35,41]	0,0090*
Interaktion p-Wert									0,7435
Raucherstatus									
Ja	90	9 (10,0)	NE [NE; NE]	96	2 (2,1)	NE [NE; NE]	4,90	[1,26; 32,11]	0,0198*
Nein	186	10 (5,4)	NE [NE; NE]	179	1 (0,6)	NE [NE; NE]	9,79	[1,88;179,69]	0,0038*
Interaktion p-Wert									0,5874
Geschlecht									
Maennlich	104	10 (9,6)	NE [NE; NE]	107	2 (1,9)	NE [NE; NE]	5,12	[1,35; 33,28]	0,0143*
Weiblich	172	9 (5,2)	NE [NE; NE]	168	1 (0,6)	NE [NE; NE]	9,08	[1,70;167,32]	0,0064*
Interaktion p-Wert									0,6547
Nachweis der EGFR-Mutation durch zentralen ctDNA Cobas Test									
positiv	211	11 (5,2)	NE [NE; NE]	204	3 (1,5)	NE [NE; NE]	3,57	[1,11; 15,78]	0,0312*

Time to event of AE is defined as the time from first dose of study treatment to first onset of the respective AE or the time to censoring if the AE has not occurred by 28 days following discontinuation of study treatment, before administration of subsequent cancer therapy or death, whichever comes first. All AEs are coded using MedDRA version 25.1. Includes AEs with onset date on or after the date of first dose and up to and including 28 days following discontinuation of study treatment. Analysis done if >=10 patients at each subgroup level and >=10 events in at least one subgroup level combined for both arms. Analysis done for SOC and PT only if main effect for that SOC or PT is statistically significant at 5% level. [a] Median time to event based on the Kaplan Meier estimate. NE = Not estimable as median (or 95% CLs) is not reached. [b] Estimated from main effects of unstratified Cox proportional hazard model including trt., subgroup and subgroup-by-trt. interaction. Ties handled using Efron method and 95% CI derived from profile likelihood estimation. NC = Not calculable. HR <1 favours Osimertinib+Chemo. * p<0.05.
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Table 4.3.1.8 FLAURA-2: Summary of subgroup analysis of time to first PT: Unwohlsein
Safety Analysis Set, DCO 03APR2023

	Osi + Chemo (N=276)			Osi (N=275)					
Subgruppen	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]	Hazard Ratio [b]	[95%-KI] [b]	2-seitiger p-Wert [b]
negativ	41	5 (12,2)	NE [NE; NE]	39	0	NE [NE; NE]	NC	[NC]	NC
unbekannt	24	3 (12,5)	NE [NE; NE]	32	0	NE [NE; NE]	NC	[NC]	NC
Interaktion p-Wert									NC
EGFR-Mutationstyp									
Exon 19 Deletion	172	7 (4,1)	NE [NE; NE]	167	1 (0,6)	NE [NE; NE]	6,99	[1,24;130,69]	0,0246*
Exon 21 (L858R) Substitutionsmutation	104	12 (11,5)	NE [NE; NE]	106	2 (1,9)	NE [NE; NE]	6,13	[1,67; 39,38]	0,0043*
Interaktion p-Wert									0,9197
Zentral bestätigte EGFR-Mutation im Gewebe									
positiv	248	17 (6,9)	NE [NE; NE]	238	3 (1,3)	NE [NE; NE]	5,51	[1,85; 23,59]	0,0012*
negativ	3	2 (66,7)	0,8 [0,1; NE]	4	0	NE [NE; NE]	NC	[NC]	NC
unbekannt	25	0	NE [NE; NE]	33	0	NE [NE; NE]	NC	[NC]	NC
Interaktion p-Wert									NC
ZNS-Metastasen zur Baseline									
Ja	113	7 (6,2)	NE [NE; NE]	110	1 (0,9)	NE [NE; NE]	6,69	[1,19;125,14]	0,0286*
Nein	163	12 (7,4)	NE [NE; NE]	165	2 (1,2)	NE [NE; NE]	6,33	[1,73; 40,68]	0,0036*
Interaktion p-Wert									0,9662
Zentrale Bestätigung der EGFR-Mutation									
Zentral bestätigte EGFR-Mutation in Gewebe oder ctDNA	263	17 (6,5)	NE [NE; NE]	266	3 (1,1)	NE [NE; NE]	5,81	[1,95; 24,90]	0,0008*
Keine zentrale Bestätigung	13	2 (15,4)	NE [NE; NE]	9	0	NE [NE; NE]	NC	[NC]	NC
Interaktion p-Wert									NC
Alter bei Screening									

Time to event of AE is defined as the time from first dose of study treatment to first onset of the respective AE or the time to censoring if the AE has not occurred by 28 days following discontinuation of study treatment, before administration of subsequent cancer therapy or death, whichever comes first. All AEs are coded using MedDRA version 25.1. Includes AEs with onset date on or after the date of first dose and up to and including 28 days following discontinuation of study treatment. Analysis done if >=10 patients at each subgroup level and >=10 events in at least one subgroup level combined for both arms. Analysis done for SOC and PT only if main effect for that SOC or PT is statistically significant at 5% level. [a] Median time to event based on the Kaplan Meier estimate. NE = Not estimable as median (or 95% CLs) is not reached. [b] Estimated from main effects of unstratified Cox proportional hazard model including trt., subgroup and subgroup-by-trt. interaction. Ties handled using Efron method and 95% CI derived from profile likelihood estimation. NC = Not calculable. HR <1 favours Osimertinib+Chemo. * p<0.05.
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Table 4.3.1.8 FLAURA-2: Summary of subgroup analysis of time to first PT: Unwohlsein
Safety Analysis Set, DCO 03APR2023

	Osi + Chemo (N=276)			Osi (N=275)					
Subgruppen	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]	Hazard Ratio [b]	[95%-KI] [b]	2-seitiger p-Wert [b]
<65 Jahre	172	12 (7,0)	NE [NE; NE]	164	1 (0,6)	NE [NE; NE]	11,42	[2,25;208,04]	0,0012*
>=65 Jahre	104	7 (6,7)	NE [NE; NE]	111	2 (1,8)	NE [NE; NE]	3,94	[0,95; 26,42]	0,0592
Interaktion p-Wert									0,4029
Region gPAP									
Asien	168	19 (11,3)	NE [NE; NE]	166	3 (1,8)	NE [NE; NE]	6,45	[2,20; 27,44]	0,0003*
Europa	22	0	NE [NE; NE]	23	0	NE [NE; NE]	NC	[NC]	NC
Nordamerika	20	0	NE [NE; NE]	22	0	NE [NE; NE]	NC	[NC]	NC
Rest der Welt	66	0	NE [NE; NE]	64	0	NE [NE; NE]	NC	[NC]	NC
Interaktion p-Wert									NC

Time to event of AE is defined as the time from first dose of study treatment to first onset of the respective AE or the time to censoring if the AE has not occurred by 28 days following discontinuation of study treatment, before administration of subsequent cancer therapy or death, whichever comes first. All AEs are coded using MedDRA version 25.1. Includes AEs with onset date on or after the date of first dose and up to and including 28 days following discontinuation of study treatment. Analysis done if >=10 patients at each subgroup level and >=10 events in at least one subgroup level combined for both arms. Analysis done for SOC and PT only if main effect for that SOC or PT is statistically significant at 5% level. [a] Median time to event based on the Kaplan Meier estimate. NE = Not estimable as median (or 95% CLs) is not reached. [b] Estimated from main effects of unstratified Cox proportional hazard model including trt., subgroup and subgroup-by-trt. interaction. Ties handled using Efron method and 95% CI derived from profile likelihood estimation. NC = Not calculable. HR <1 favours Osimertinib+Chemo. * p<0.05.
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Table 4.3.1.9 FLAURA-2: Summary of subgroup analysis of time to first SOC: Augenerkrankungen
Safety Analysis Set, DCO 03APR2023

	Osi + Chemo (N=276)			Osi (N=275)					
Subgruppen	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]	Hazard Ratio [b]	[95%-KI] [b]	2-seitiger p-Wert [b]
Abstammung									
Chinesisch/Asiatisch	68	12 (17,6)	NE [NE; NE]	70	6 (8,6)	NE [NE; NE]	1,98	[0,77; 5,68]	0,1604
Nicht-chinesisch/ Asiatisch	107	13 (12,1)	NE [NE; NE]	106	12 (11,3)	NE [NE; NE]	1,09	[0,50; 2,43]	0,8234
Nicht-asiatisch	101	26 (25,7)	NE [NE; NE]	99	11 (11,1)	NE [NE; NE]	2,49	[1,27; 5,26]	0,0077*
Interaktion p-Wert									0,2985
Methode zur Gewebeuntersuchung									
zentral	120	14 (11,7)	NE [NE; NE]	119	7 (5,9)	NE [NE; NE]	1,99	[0,83; 5,26]	0,1246
lokal	156	37 (23,7)	NE [NE; NE]	156	22 (14,1)	NE [NE; NE]	1,75	[1,04; 3,01]	0,0351*
Interaktion p-Wert									0,8034
WHO Performance-Status									
0	100	18 (18,0)	NE [NE; NE]	100	13 (13,0)	NE [NE; NE]	1,43	[0,70; 2,98]	0,3230
1	176	33 (18,8)	NE [NE; NE]	175	16 (9,1)	NE [NE; NE]	2,09	[1,17; 3,89]	0,0125*
Interaktion p-Wert									0,4246
Raucherstatus									
Ja	90	16 (17,8)	NE [NE; NE]	96	10 (10,4)	NE [NE; NE]	1,68	[0,77; 3,83]	0,1933
Nein	186	35 (18,8)	NE [NE; NE]	179	19 (10,6)	NE [NE; NE]	1,85	[1,07; 3,30]	0,0266*
Interaktion p-Wert									0,8388
Geschlecht									
Maennlich	104	20 (19,2)	NE [NE; NE]	107	8 (7,5)	NE [NE; NE]	2,54	[1,16; 6,12]	0,0191*
Weiblich	172	31 (18,0)	NE [NE; NE]	168	21 (12,5)	NE [NE; NE]	1,51	[0,87; 2,66]	0,1408
Interaktion p-Wert									0,2973
Nachweis der EGFR-Mutation durch zentralen ctDNA Cobas Test									
positiv	211	38 (18,0)	NE [NE; NE]	204	22 (10,8)	NE [NE; NE]	1,71	[1,02; 2,94]	0,0411*

Time to event of AE is defined as the time from first dose of study treatment to first onset of the respective AE or the time to censoring if the AE has not occurred by 28 days following discontinuation of study treatment, before administration of subsequent cancer therapy or death, whichever comes first. All AEs are coded using MedDRA version 25.1. Includes AEs with onset date on or after the date of first dose and up to and including 28 days following discontinuation of study treatment. Analysis done if >=10 patients at each subgroup level and >=10 events in at least one subgroup level combined for both arms. Analysis done for SOC and PT only if main effect for that SOC or PT is statistically significant at 5% level. [a] Median time to event based on the Kaplan Meier estimate. NE = Not estimable as median (or 95% CLs) is not reached. [b] Estimated from main effects of unstratified Cox proportional hazard model including trt., subgroup and subgroup-by-trt. interaction. Ties handled using Efron method and 95% CI derived from profile likelihood estimation. NC = Not calculable. HR <1 favours Osimertinib+Chemo. * p<0.05.
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Table 4.3.1.9 FLAURA-2: Summary of subgroup analysis of time to first SOC: Augenerkrankungen
Safety Analysis Set, DCO 03APR2023

	Osi + Chemo (N=276)			Osi (N=275)					
Subgruppen	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]	Hazard Ratio [b]	[95%-KI] [b]	2-seitiger p-Wert [b]
negativ	41	6 (14,6)	NE [NE; NE]	39	4 (10,3)	NE [NE; NE]	1,48	[0,42; 5,80]	0,5378
unbekannt	24	7 (29,2)	NE [NE; NE]	32	3 (9,4)	NE [NE; NE]	3,16	[0,88; 14,68]	0,0787
Interaktion p-Wert									0,6587
EGFR-Mutationstyp									
Exon 19 Deletion	172	37 (21,5)	NE [NE; NE]	167	20 (12,0)	NE [NE; NE]	1,93	[1,13; 3,39]	0,0150*
Exon 21 (L858R) Substitutionsmutation	104	14 (13,5)	NE [NE; NE]	106	9 (8,5)	NE [NE; NE]	1,50	[0,66; 3,60]	0,3365
Interaktion p-Wert									0,6211
Zentral bestätigte EGFR-Mutation im Gewebe									
positiv	248	45 (18,1)	NE [NE; NE]	238	22 (9,2)	NE [NE; NE]	2,02	[1,23; 3,42]	0,0054*
negativ	3	0	NE [NE; NE]	4	0	NE [NE; NE]	NC	[NC]	NC
unbekannt	25	6 (24,0)	NE [NE; NE]	33	7 (21,2)	NE [NE; NE]	1,20	[0,39; 3,62]	0,7415
Interaktion p-Wert									0,3987
ZNS-Metastasen zur Baseline									
Ja	113	20 (17,7)	NE [NE; NE]	110	15 (13,6)	NE [NE; NE]	1,20	[0,62; 2,39]	0,5907
Nein	163	31 (19,0)	NE [NE; NE]	165	14 (8,5)	NE [NE; NE]	2,45	[1,33; 4,75]	0,0037*
Interaktion p-Wert									0,1282
Zentrale Bestätigung der EGFR-Mutation									
Zentral bestätigte EGFR-Mutation in Gewebe oder ctDNA	263	46 (17,5)	NE [NE; NE]	266	27 (10,2)	NE [NE; NE]	1,76	[1,10; 2,86]	0,0177*
Keine zentrale Bestätigung	13	5 (38,5)	NE [NE; NE]	9	2 (22,2)	NE [NE; NE]	1,78	[0,38; 12,40]	0,4769
Interaktion p-Wert									0,9913
Alter bei Screening									

Time to event of AE is defined as the time from first dose of study treatment to first onset of the respective AE or the time to censoring if the AE has not occurred by 28 days following discontinuation of study treatment, before administration of subsequent cancer therapy or death, whichever comes first. All AEs are coded using MedDRA version 25.1. Includes AEs with onset date on or after the date of first dose and up to and including 28 days following discontinuation of study treatment. Analysis done if >=10 patients at each subgroup level and >=10 events in at least one subgroup level combined for both arms. Analysis done for SOC and PT only if main effect for that SOC or PT is statistically significant at 5% level. [a] Median time to event based on the Kaplan Meier estimate. NE = Not estimable as median (or 95% CLs) is not reached. [b] Estimated from main effects of unstratified Cox proportional hazard model including trt., subgroup and subgroup-by-trt. interaction. Ties handled using Efron method and 95% CI derived from profile likelihood estimation. NC = Not calculable. HR <1 favours Osimertinib+Chemo. * p<0.05.
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Table 4.3.1.9 FLAURA-2: Summary of subgroup analysis of time to first SOC: Augenerkrankungen
Safety Analysis Set, DCO 03APR2023

	Osi + Chemo (N=276)			Osi (N=275)					
Subgruppen	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]	Hazard Ratio [b]	[95%-KI] [b]	2-seitiger p-Wert [b]
<65 Jahre	172	31 (18,0)	NE [NE; NE]	164	19 (11,6)	NE [NE; NE]	1,52	[0,87; 2,74]	0,1462
>=65 Jahre	104	20 (19,2)	NE [NE; NE]	111	10 (9,0)	NE [NE; NE]	2,38	[1,14; 5,31]	0,0204*
Interaktion p-Wert									0,3496
Region gPAP									
Asien	168	21 (12,5)	NE [NE; NE]	166	16 (9,6)	NE [NE; NE]	1,28	[0,67; 2,48]	0,4613
Europa	22	5 (22,7)	NE [NE; NE]	23	2 (8,7)	NE [NE; NE]	2,58	[0,56; 18,00]	0,2329
Nordamerika	20	11 (55,0)	6,9 [2,7; NE]	22	6 (27,3)	NE [NE; NE]	2,92	[1,11; 8,50]	0,0301*
Rest der Welt	66	14 (21,2)	NE [NE; NE]	64	5 (7,8)	NE [NE; NE]	2,85	[1,09; 8,83]	0,0317*
Interaktion p-Wert									0,4037

Time to event of AE is defined as the time from first dose of study treatment to first onset of the respective AE or the time to censoring if the AE has not occurred by 28 days following discontinuation of study treatment, before administration of subsequent cancer therapy or death, whichever comes first. All AEs are coded using MedDRA version 25.1. Includes AEs with onset date on or after the date of first dose and up to and including 28 days following discontinuation of study treatment. Analysis done if >=10 patients at each subgroup level and >=10 events in at least one subgroup level combined for both arms. Analysis done for SOC and PT only if main effect for that SOC or PT is statistically significant at 5% level. [a] Median time to event based on the Kaplan Meier estimate. NE = Not estimable as median (or 95% CLs) is not reached. [b] Estimated from main effects of unstratified Cox proportional hazard model including trt., subgroup and subgroup-by-trt. interaction. Ties handled using Efron method and 95% CI derived from profile likelihood estimation. NC = Not calculable. HR <1 favours Osimertinib+Chemo. * p<0.05.
root/cdar/d516/payer_germany/ar/d5169c00001_payer_germany/tlf/prod/program/ttesubae.sas gttesubaeaai 22DEC2023:09:13 kfrh585

Table 4.3.1.10 FLAURA-2: Summary of subgroup analysis of time to first PT: Traenensekretion verstaerkt
Safety Analysis Set, DCO 03APR2023

	Osi + Chemo (N=276)			Osi (N=275)					
Subgruppen	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]	Hazard Ratio [b]	[95%-KI] [b]	2-seitiger p-Wert [b]
Abstammung									
Chinesisch/Asiatisch	68	1 (1,5)	NE [NE; NE]	70	0	NE [NE; NE]	NC	[NC]	NC
Nicht-chinesisch/ Asiatisch	107	3 (2,8)	NE [NE; NE]	106	0	NE [NE; NE]	NC	[NC]	NC
Nicht-asiatisch	101	12 (11,9)	NE [NE; NE]	99	1 (1,0)	NE [NE; NE]	12,46	[2,45;226,84]	0,0007*
Interaktion p-Wert									NC
Methode zur Gewebeuntersuchung									
zentral	120	1 (0,8)	NE [NE; NE]	119	0	NE [NE; NE]	NC	[NC]	NC
lokal	156	15 (9,6)	NE [NE; NE]	156	1 (0,6)	NE [NE; NE]	15,60	[3,16;282,12]	<0,0001*
Interaktion p-Wert									NC
WHO Performance-Status									
0	100	6 (6,0)	NE [NE; NE]	100	0	NE [NE; NE]	NC	[NC]	NC
1	176	10 (5,7)	NE [NE; NE]	175	1 (0,6)	NE [NE; NE]	9,90	[1,90;181,67]	0,0036*
Interaktion p-Wert									NC
Raucherstatus									
Ja	90	5 (5,6)	NE [NE; NE]	96	0	NE [NE; NE]	NC	[NC]	NC
Nein	186	11 (5,9)	NE [NE; NE]	179	1 (0,6)	NE [NE; NE]	10,86	[2,11;198,51]	0,0019*
Interaktion p-Wert									NC
Geschlecht									
Maennlich	104	6 (5,8)	NE [NE; NE]	107	0	NE [NE; NE]	NC	[NC]	NC
Weiblich	172	10 (5,8)	NE [NE; NE]	168	1 (0,6)	NE [NE; NE]	10,20	[1,95;187,08]	0,0031*
Interaktion p-Wert									NC
Nachweis der EGFR-Mutation durch zentralen ctDNA Cobas Test									
positiv	211	11 (5,2)	NE [NE; NE]	204	1 (0,5)	NE [NE; NE]	10,82	[2,10;197,71]	0,0020*

Time to event of AE is defined as the time from first dose of study treatment to first onset of the respective AE or the time to censoring if the AE has not occurred by 28 days following discontinuation of study treatment, before administration of subsequent cancer therapy or death, whichever comes first. All AEs are coded using MedDRA version 25.1. Includes AEs with onset date on or after the date of first dose and up to and including 28 days following discontinuation of study treatment. Analysis done if >=10 patients at each subgroup level and >=10 events in at least one subgroup level combined for both arms. Analysis done for SOC and PT only if main effect for that SOC or PT is statistically significant at 5% level. [a] Median time to event based on the Kaplan Meier estimate. NE = Not estimable as median (or 95% CLs) is not reached. [b] Estimated from main effects of unstratified Cox proportional hazard model including trt., subgroup and subgroup-by-trt. interaction. Ties handled using Efron method and 95% CI derived from profile likelihood estimation. NC = Not calculable. HR <1 favours Osimertinib+Chemo. * p<0.05.
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Table 4.3.1.10 FLAURA-2: Summary of subgroup analysis of time to first PT: Traenensekretion verstaerkt
Safety Analysis Set, DCO 03APR2023

	Osi + Chemo (N=276)			Osi (N=275)					
Subgruppen	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]	Hazard Ratio [b]	[95%-KI] [b]	2-seitiger p-Wert [b]
negativ	41	4 (9,8)	NE [NE; NE]	39	0	NE [NE; NE]	NC	[NC]	NC
unbekannt	24	1 (4,2)	NE [NE; NE]	32	0	NE [NE; NE]	NC	[NC]	NC
Interaktion p-Wert									NC
EGFR-Mutationstyp									
Exon 19 Deletion	172	12 (7,0)	NE [NE; NE]	167	1 (0,6)	NE [NE; NE]	12,21	[2,41;222,43]	0,0008*
Exon 21 (L858R) Substitutionsmutation	104	4 (3,8)	NE [NE; NE]	106	0	NE [NE; NE]	NC	[NC]	NC
Interaktion p-Wert									NC
Zentral bestätigte EGFR-Mutation im Gewebe									
positiv	248	14 (5,6)	NE [NE; NE]	238	0	NE [NE; NE]	NC	[NC]	NC
negativ	3	0	NE [NE; NE]	4	0	NE [NE; NE]	NC	[NC]	NC
unbekannt	25	2 (8,0)	NE [NE; NE]	33	1 (3,0)	NE [NE; NE]	NC	[NC]	NC
Interaktion p-Wert									NC
ZNS-Metastasen zur Baseline									
Ja	113	5 (4,4)	NE [NE; NE]	110	1 (0,9)	NE [NE; NE]	NC	[NC]	NC
Nein	163	11 (6,7)	NE [NE; NE]	165	0	NE [NE; NE]	NC	[NC]	NC
Interaktion p-Wert									NC
Zentrale Bestätigung der EGFR-Mutation									
Zentral bestätigte EGFR-Mutation in Gewebe oder ctDNA	263	14 (5,3)	NE [NE; NE]	266	1 (0,4)	NE [NE; NE]	14,40	[2,90;260,82]	0,0002*
Keine zentrale Bestätigung	13	2 (15,4)	NE [NE; NE]	9	0	NE [NE; NE]	NC	[NC]	NC
Interaktion p-Wert									NC
Alter bei Screening									

Time to event of AE is defined as the time from first dose of study treatment to first onset of the respective AE or the time to censoring if the AE has not occurred by 28 days following discontinuation of study treatment, before administration of subsequent cancer therapy or death, whichever comes first. All AEs are coded using MedDRA version 25.1. Includes AEs with onset date on or after the date of first dose and up to and including 28 days following discontinuation of study treatment. Analysis done if >=10 patients at each subgroup level and >=10 events in at least one subgroup level combined for both arms. Analysis done for SOC and PT only if main effect for that SOC or PT is statistically significant at 5% level. [a] Median time to event based on the Kaplan Meier estimate. NE = Not estimable as median (or 95% CLs) is not reached. [b] Estimated from main effects of unstratified Cox proportional hazard model including trt., subgroup and subgroup-by-trt. interaction. Ties handled using Efron method and 95% CI derived from profile likelihood estimation. NC = Not calculable. HR <1 favours Osimertinib+Chemo. * p<0.05.
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Table 4.3.1.10 FLAURA-2: Summary of subgroup analysis of time to first PT: Traenensekretion verstaerkt
Safety Analysis Set, DCO 03APR2023

	Osi + Chemo (N=276)			Osi (N=275)					
Subgruppen	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]	Hazard Ratio [b]	[95%-KI] [b]	2-seitiger p-Wert [b]
<65 Jahre	172	9 (5,2)	NE [NE; NE]	164	1 (0,6)	NE [NE; NE]	8,31	[1,56;153,22]	0,0094*
>=65 Jahre	104	7 (6,7)	NE [NE; NE]	111	0	NE [NE; NE]	NC	[NC]	NC
Interaktion p-Wert									NC
Region gPAP									
Asien	168	3 (1,8)	NE [NE; NE]	166	0	NE [NE; NE]	NC	[NC]	NC
Europa	22	3 (13,6)	NE [NE; NE]	23	1 (4,3)	NE [NE; NE]	NC	[NC]	NC
Nordamerika	20	6 (30,0)	NE [NE; NE]	22	0	NE [NE; NE]	NC	[NC]	NC
Rest der Welt	66	4 (6,1)	NE [NE; NE]	64	0	NE [NE; NE]	NC	[NC]	NC
Interaktion p-Wert									NC

Time to event of AE is defined as the time from first dose of study treatment to first onset of the respective AE or the time to censoring if the AE has not occurred by 28 days following discontinuation of study treatment, before administration of subsequent cancer therapy or death, whichever comes first. All AEs are coded using MedDRA version 25.1. Includes AEs with onset date on or after the date of first dose and up to and including 28 days following discontinuation of study treatment. Analysis done if >=10 patients at each subgroup level and >=10 events in at least one subgroup level combined for both arms. Analysis done for SOC and PT only if main effect for that SOC or PT is statistically significant at 5% level. [a] Median time to event based on the Kaplan Meier estimate. NE = Not estimable as median (or 95% CLs) is not reached. [b] Estimated from main effects of unstratified Cox proportional hazard model including trt., subgroup and subgroup-by-trt. interaction. Ties handled using Efron method and 95% CI derived from profile likelihood estimation. NC = Not calculable. HR <1 favours Osimertinib+Chemo. * p<0.05.
root/cdar/d516/payer_germany/ar/d5169c00001_payer_germany/tlf/prod/program/ttesubae.sas gttesubaeaaj 22DEC2023:09:13 kfrh585

Table 4.3.1.11 FLAURA-2: Summary of subgroup analysis of time to first PT: Schluckauf
Safety Analysis Set, DCO 03APR2023

	Osi + Chemo (N=276)			Osi (N=275)					
Subgruppen	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]	Hazard Ratio [b]	[95%-KI] [b]	2-seitiger p-Wert [b]
Abstammung									
Chinesisch/Asiatisch	68	0	NE [NE; NE]	70	1 (1,4)	NE [NE; NE]	NC	[NC]	NC
Nicht-chinesisch/ Asiatisch	107	8 (7,5)	NE [NE; NE]	106	0	NE [NE; NE]	NC	[NC]	NC
Nicht-asiatisch	101	3 (3,0)	NE [NE; NE]	99	0	NE [NE; NE]	NC	[NC]	NC
Interaktion p-Wert									NC
Methode zur Gewebeuntersuchung									
zentral	120	2 (1,7)	NE [NE; NE]	119	0	NE [NE; NE]	NC	[NC]	NC
lokal	156	9 (5,8)	NE [NE; NE]	156	1 (0,6)	NE [NE; NE]	9,30	[1,75;171,41]	0,0058*
Interaktion p-Wert									NC
WHO Performance-Status									
0	100	5 (5,0)	NE [NE; NE]	100	0	NE [NE; NE]	NC	[NC]	NC
1	176	6 (3,4)	NE [NE; NE]	175	1 (0,6)	NE [NE; NE]	NC	[NC]	NC
Interaktion p-Wert									NC
Raucherstatus									
Ja	90	6 (6,7)	NE [NE; NE]	96	0	NE [NE; NE]	NC	[NC]	NC
Nein	186	5 (2,7)	NE [NE; NE]	179	1 (0,6)	NE [NE; NE]	NC	[NC]	NC
Interaktion p-Wert									NC
Geschlecht									
Maennlich	104	11 (10,6)	NE [NE; NE]	107	0	NE [NE; NE]	NC	[NC]	NC
Weiblich	172	0	NE [NE; NE]	168	1 (0,6)	NE [NE; NE]	NC	[NC]	NC
Interaktion p-Wert									NC
Nachweis der EGFR-Mutation durch zentralen ctDNA Cobas Test									
positiv	211	6 (2,8)	NE [NE; NE]	204	1 (0,5)	NE [NE; NE]	NC	[NC]	NC

Time to event of AE is defined as the time from first dose of study treatment to first onset of the respective AE or the time to censoring if the AE has not occurred by 28 days following discontinuation of study treatment, before administration of subsequent cancer therapy or death, whichever comes first. All AEs are coded using MedDRA version 25.1. Includes AEs with onset date on or after the date of first dose and up to and including 28 days following discontinuation of study treatment. Analysis done if >=10 patients at each subgroup level and >=10 events in at least one subgroup level combined for both arms. Analysis done for SOC and PT only if main effect for that SOC or PT is statistically significant at 5% level. [a] Median time to event based on the Kaplan Meier estimate. NE = Not estimable as median (or 95% CLs) is not reached. [b] Estimated from main effects of unstratified Cox proportional hazard model including trt., subgroup and subgroup-by-trt. interaction. Ties handled using Efron method and 95% CI derived from profile likelihood estimation. NC = Not calculable. HR <1 favours Osimertinib+Chemo. * p<0.05.
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Table 4.3.1.11 FLAURA-2: Summary of subgroup analysis of time to first PT: Schluckauf
Safety Analysis Set, DCO 03APR2023

	Osi + Chemo (N=276)			Osi (N=275)					
Subgruppen	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]	Hazard Ratio [b]	[95%-KI] [b]	2-seitiger p-Wert [b]
negativ	41	4 (9,8)	NE [NE; NE]	39	0	NE [NE; NE]	NC	[NC]	NC
unbekannt	24	1 (4,2)	NE [NE; NE]	32	0	NE [NE; NE]	NC	[NC]	NC
Interaktion p-Wert									NC
EGFR-Mutationstyp									
Exon 19 Deletion	172	4 (2,3)	NE [NE; NE]	167	1 (0,6)	NE [NE; NE]	NC	[NC]	NC
Exon 21 (L858R) Substitutionsmutation	104	7 (6,7)	NE [NE; NE]	106	0	NE [NE; NE]	NC	[NC]	NC
Interaktion p-Wert									NC
Zentral bestätigte EGFR-Mutation im Gewebe									
positiv	248	9 (3,6)	NE [NE; NE]	238	1 (0,4)	NE [NE; NE]	8,83	[1,66;162,75]	0,0073*
negativ	3	1 (33,3)	NE [NE; NE]	4	0	NE [NE; NE]	NC	[NC]	NC
unbekannt	25	1 (4,0)	NE [NE; NE]	33	0	NE [NE; NE]	NC	[NC]	NC
Interaktion p-Wert									NC
ZNS-Metastasen zur Baseline									
Ja	113	5 (4,4)	NE [NE; NE]	110	0	NE [NE; NE]	NC	[NC]	NC
Nein	163	6 (3,7)	NE [NE; NE]	165	1 (0,6)	NE [NE; NE]	NC	[NC]	NC
Interaktion p-Wert									NC
Zentrale Bestätigung der EGFR-Mutation									
Zentral bestätigte EGFR-Mutation in Gewebe oder ctDNA	263	9 (3,4)	NE [NE; NE]	266	1 (0,4)	NE [NE; NE]	9,30	[1,75;171,37]	0,0058*
Keine zentrale Bestätigung	13	2 (15,4)	NE [NE; NE]	9	0	NE [NE; NE]	NC	[NC]	NC
Interaktion p-Wert									NC
Alter bei Screening									

Time to event of AE is defined as the time from first dose of study treatment to first onset of the respective AE or the time to censoring if the AE has not occurred by 28 days following discontinuation of study treatment, before administration of subsequent cancer therapy or death, whichever comes first. All AEs are coded using MedDRA version 25.1. Includes AEs with onset date on or after the date of first dose and up to and including 28 days following discontinuation of study treatment. Analysis done if >=10 patients at each subgroup level and >=10 events in at least one subgroup level combined for both arms. Analysis done for SOC and PT only if main effect for that SOC or PT is statistically significant at 5% level. [a] Median time to event based on the Kaplan Meier estimate. NE = Not estimable as median (or 95% CLs) is not reached. [b] Estimated from main effects of unstratified Cox proportional hazard model including trt., subgroup and subgroup-by-trt. interaction. Ties handled using Efron method and 95% CI derived from profile likelihood estimation. NC = Not calculable. HR <1 favours Osimertinib+Chemo. * p<0.05.
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Table 4.3.1.11 FLAURA-2: Summary of subgroup analysis of time to first PT: Schluckauf
Safety Analysis Set, DCO 03APR2023

	Osi + Chemo (N=276)			Osi (N=275)					
Subgruppen	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]	Hazard Ratio [b]	[95%-KI] [b]	2-seitiger p-Wert [b]
<65 Jahre	172	6 (3,5)	NE [NE; NE]	164	1 (0,6)	NE [NE; NE]	NC	[NC]	NC
>=65 Jahre	104	5 (4,8)	NE [NE; NE]	111	0	NE [NE; NE]	NC	[NC]	NC
Interaktion p-Wert									NC
Region gPAP									
Asien	168	8 (4,8)	NE [NE; NE]	166	1 (0,6)	NE [NE; NE]	NC	[NC]	NC
Europa	22	0	NE [NE; NE]	23	0	NE [NE; NE]	NC	[NC]	NC
Nordamerika	20	1 (5,0)	NE [NE; NE]	22	0	NE [NE; NE]	NC	[NC]	NC
Rest der Welt	66	2 (3,0)	NE [NE; NE]	64	0	NE [NE; NE]	NC	[NC]	NC
Interaktion p-Wert									NC

Time to event of AE is defined as the time from first dose of study treatment to first onset of the respective AE or the time to censoring if the AE has not occurred by 28 days following discontinuation of study treatment, before administration of subsequent cancer therapy or death, whichever comes first. All AEs are coded using MedDRA version 25.1. Includes AEs with onset date on or after the date of first dose and up to and including 28 days following discontinuation of study treatment. Analysis done if >=10 patients at each subgroup level and >=10 events in at least one subgroup level combined for both arms. Analysis done for SOC and PT only if main effect for that SOC or PT is statistically significant at 5% level. [a] Median time to event based on the Kaplan Meier estimate. NE = Not estimable as median (or 95% CLs) is not reached. [b] Estimated from main effects of unstratified Cox proportional hazard model including trt., subgroup and subgroup-by-trt. interaction. Ties handled using Efron method and 95% CI derived from profile likelihood estimation. NC = Not calculable. HR <1 favours Osimertinib+Chemo. * p<0.05.
root/cdar/d516/payer_germany/ar/d5169c00001_payer_germany/tlf/prod/program/ttesubae.sas gttesubaeaak 22DEC2023:09:13 kfrh585

Table 4.3.1.12 FLAURA-2: Summary of subgroup analysis of time to first PT: Schmerzen im Oropharynx
Safety Analysis Set, DCO 03APR2023

	Osi + Chemo (N=276)			Osi (N=275)					
Subgruppen	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]	Hazard Ratio [b]	[95%-KI] [b]	2-seitiger p-Wert [b]
Abstammung									
Chinesisch/Asiatisch	68	6 (8,8)	NE [NE; NE]	70	2 (2,9)	NE [NE; NE]	2,98	[0,69; 20,36]	0,1502
Nicht-chinesisch/ Asiatisch	107	8 (7,5)	NE [NE; NE]	106	3 (2,8)	NE [NE; NE]	2,69	[0,78; 12,29]	0,1208
Nicht-asiatisch	101	4 (4,0)	NE [NE; NE]	99	2 (2,0)	NE [NE; NE]	1,94	[0,38; 13,98]	0,4319
Interaktion p-Wert									0,9317
Methode zur Gewebeuntersuchung									
zentral	120	5 (4,2)	NE [NE; NE]	119	3 (2,5)	NE [NE; NE]	1,61	[0,40; 7,85]	0,5078
lokal	156	13 (8,3)	NE [NE; NE]	156	4 (2,6)	NE [NE; NE]	3,28	[1,16; 11,66]	0,0239*
Interaktion p-Wert									0,4455
WHO Performance-Status									
0	100	7 (7,0)	NE [NE; NE]	100	4 (4,0)	NE [NE; NE]	1,78	[0,54; 6,79]	0,3487
1	176	11 (6,3)	NE [NE; NE]	175	3 (1,7)	NE [NE; NE]	3,58	[1,12; 15,82]	0,0308*
Interaktion p-Wert									0,4365
Raucherstatus									
Ja	90	2 (2,2)	NE [NE; NE]	96	2 (2,1)	NE [NE; NE]	1,02	[0,12; 8,50]	0,9836
Nein	186	16 (8,6)	NE [NE; NE]	179	5 (2,8)	NE [NE; NE]	3,12	[1,22; 9,55]	0,0161*
Interaktion p-Wert									0,3240
Geschlecht									
Maennlich	104	3 (2,9)	NE [NE; NE]	107	2 (1,9)	NE [NE; NE]	1,43	[0,24; 10,89]	0,6904
Weiblich	172	15 (8,7)	NE [NE; NE]	168	5 (3,0)	NE [NE; NE]	3,04	[1,18; 9,34]	0,0206*
Interaktion p-Wert									0,4811
Nachweis der EGFR-Mutation durch zentralen ctDNA Cobas Test									

Time to event of AE is defined as the time from first dose of study treatment to first onset of the respective AE or the time to censoring if the AE has not occurred by 28 days following discontinuation of study treatment, before administration of subsequent cancer therapy or death, whichever comes first. All AEs are coded using MedDRA version 25.1. Includes AEs with onset date on or after the date of first dose and up to and including 28 days following discontinuation of study treatment. Analysis done if >=10 patients at each subgroup level and >=10 events in at least one subgroup level combined for both arms. Analysis done for SOC and PT only if main effect for that SOC or PT is statistically significant at 5% level. [a] Median time to event based on the Kaplan Meier estimate. NE = Not estimable as median (or 95% CLs) is not reached. [b] Estimated from main effects of unstratified Cox proportional hazard model including trt., subgroup and subgroup-by-trt. interaction. Ties handled using Efron method and 95% CI derived from profile likelihood estimation. NC = Not calculable. HR <1 favours Osimertinib+Chemo. * p<0.05.
root/cdar/d516/payer_germany/ar/d5169c00001_payer_germany/tlf/prod/program/ttesubae.sas gttesubaeaal 22DEC2023:09:13 kfrh585

Table 4.3.1.12 FLAURA-2: Summary of subgroup analysis of time to first PT: Schmerzen im Oropharynx
Safety Analysis Set, DCO 03APR2023

	Osi + Chemo (N=276)			Osi (N=275)					
Subgruppen	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]	Hazard Ratio [b]	[95%-KI] [b]	2-seitiger p-Wert [b]
positiv	211	12 (5,7)	NE [NE; NE]	204	4 (2,0)	NE [NE; NE]	2,87	[1,0004; 10,28]	0,0499*
negativ	41	3 (7,3)	NE [NE; NE]	39	3 (7,7)	NE [NE; NE]	0,95	[0,18; 5,15]	0,9541
unbekannt	24	3 (12,5)	NE [NE; NE]	32	0	NE [NE; NE]	NC	[NC]	NC
Interaktion p-Wert									0,2699
EGFR-Mutationstyp									
Exon 19 Deletion	172	12 (7,0)	NE [NE; NE]	167	3 (1,8)	NE [NE; NE]	3,96	[1,26; 17,37]	0,0171*
Exon 21 (L858R) Substitutionsmutation	104	6 (5,8)	NE [NE; NE]	106	4 (3,8)	NE [NE; NE]	1,47	[0,42; 5,73]	0,5503
Interaktion p-Wert									0,2721
Zentral bestätigte EGFR-Mutation im Gewebe									
positiv	248	16 (6,5)	NE [NE; NE]	238	7 (2,9)	NE [NE; NE]	2,17	[0,93; 5,65]	0,0753
negativ	3	0	NE [NE; NE]	4	0	NE [NE; NE]	NC	[NC]	NC
unbekannt	25	2 (8,0)	NE [NE; NE]	33	0	NE [NE; NE]	NC	[NC]	NC
Interaktion p-Wert									NC
ZNS-Metastasen zur Baseline									
Ja	113	6 (5,3)	NE [NE; NE]	110	2 (1,8)	NE [NE; NE]	2,72	[0,63; 18,56]	0,1900
Nein	163	12 (7,4)	NE [NE; NE]	165	5 (3,0)	NE [NE; NE]	2,52	[0,94; 7,93]	0,0680
Interaktion p-Wert									0,9387
Zentrale Bestätigung der EGFR-Mutation									
Zentral bestätigte EGFR-Mutation in Gewebe oder ctDNA	263	16 (6,1)	NE [NE; NE]	266	7 (2,6)	NE [NE; NE]	2,29	[0,98; 5,97]	0,0563
Keine zentrale Bestätigung	13	2 (15,4)	NE [NE; NE]	9	0	NE [NE; NE]	NC	[NC]	NC
Interaktion p-Wert									NC

Time to event of AE is defined as the time from first dose of study treatment to first onset of the respective AE or the time to censoring if the AE has not occurred by 28 days following discontinuation of study treatment, before administration of subsequent cancer therapy or death, whichever comes first. All AEs are coded using MedDRA version 25.1. Includes AEs with onset date on or after the date of first dose and up to and including 28 days following discontinuation of study treatment. Analysis done if >=10 patients at each subgroup level and >=10 events in at least one subgroup level combined for both arms. Analysis done for SOC and PT only if main effect for that SOC or PT is statistically significant at 5% level. [a] Median time to event based on the Kaplan Meier estimate. NE = Not estimable as median (or 95% CLs) is not reached. [b] Estimated from main effects of unstratified Cox proportional hazard model including trt., subgroup and subgroup-by-trt. interaction. Ties handled using Efron method and 95% CI derived from profile likelihood estimation. NC = Not calculable. HR <1 favours Osimertinib+Chemo. * p<0.05.
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Table 4.3.1.12 FLAURA-2: Summary of subgroup analysis of time to first PT: Schmerzen im Oropharynx
Safety Analysis Set, DCO 03APR2023

	Osi + Chemo (N=276)			Osi (N=275)					
Subgruppen	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]	Hazard Ratio [b]	[95%-KI] [b]	2-seitiger p-Wert [b]
Alter bei Screening									
<65 Jahre	172	12 (7,0)	NE [NE; NE]	164	4 (2,4)	NE [NE; NE]	2,79	[0,97; 9,99]	0,0569
>=65 Jahre	104	6 (5,8)	NE [NE; NE]	111	3 (2,7)	NE [NE; NE]	2,20	[0,58; 10,44]	0,2489
Interaktion p-Wert									0,7958
Region gPAP									
Asien	168	12 (7,1)	NE [NE; NE]	166	4 (2,4)	NE [NE; NE]	2,94	[1,02; 10,51]	0,0449*
Europa	22	0	NE [NE; NE]	23	1 (4,3)	NE [NE; NE]	NC	[NC]	NC
Nordamerika	20	4 (20,0)	NE [NE; NE]	22	1 (4,5)	NE [NE; NE]	5,11	[0,75; 99,87]	0,0986
Rest der Welt	66	2 (3,0)	NE [NE; NE]	64	1 (1,6)	NE [NE; NE]	1,90	[0,18; 40,77]	0,5913
Interaktion p-Wert									0,8277

Time to event of AE is defined as the time from first dose of study treatment to first onset of the respective AE or the time to censoring if the AE has not occurred by 28 days following discontinuation of study treatment, before administration of subsequent cancer therapy or death, whichever comes first. All AEs are coded using MedDRA version 25.1. Includes AEs with onset date on or after the date of first dose and up to and including 28 days following discontinuation of study treatment. Analysis done if >=10 patients at each subgroup level and >=10 events in at least one subgroup level combined for both arms. Analysis done for SOC and PT only if main effect for that SOC or PT is statistically significant at 5% level. [a] Median time to event based on the Kaplan Meier estimate. NE = Not estimable as median (or 95% CLs) is not reached. [b] Estimated from main effects of unstratified Cox proportional hazard model including trt., subgroup and subgroup-by-trt. interaction. Ties handled using Efron method and 95% CI derived from profile likelihood estimation. NC = Not calculable. HR <1 favours Osimertinib+Chemo. * p<0.05.
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Table 4.3.1.13 FLAURA-2: Summary of subgroup analysis of time to first PT: Ausschlag
Safety Analysis Set, DCO 03APR2023

	Osi + Chemo (N=276)			Osi (N=275)					
Subgruppen	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]	Hazard Ratio [b]	[95%-KI] [b]	2-seitiger p-Wert [b]
Abstammung									
Chinesisch/Asiatisch	68	18 (26,5)	NE [NE; NE]	70	19 (27,1)	NE [NE; NE]	0,98	[0,51; 1,87]	0,9401
Nicht-chinesisch/ Asiatisch	107	30 (28,0)	NE [NE; NE]	106	16 (15,1)	NE [NE; NE]	2,06	[1,14; 3,87]	0,0167*
Nicht-asiatisch	101	29 (28,7)	NE [NE; NE]	99	22 (22,2)	NE [NE; NE]	1,43	[0,82; 2,51]	0,2065
Interaktion p-Wert									0,2505
Methode zur Gewebeuntersuchung									
zentral	120	23 (19,2)	NE [NE; NE]	119	22 (18,5)	NE [NE; NE]	1,08	[0,60; 1,94]	0,8073
lokal	156	54 (34,6)	NE [NE; NE]	156	35 (22,4)	NE [NE; NE]	1,72	[1,13; 2,65]	0,0116*
Interaktion p-Wert									0,2044
WHO Performance-Status									
0	100	34 (34,0)	NE [NE; NE]	100	24 (24,0)	NE [NE; NE]	1,63	[0,97; 2,77]	0,0658
1	176	43 (24,4)	NE [NE; NE]	175	33 (18,9)	NE [NE; NE]	1,35	[0,86; 2,14]	0,1926
Interaktion p-Wert									0,5981
Raucherstatus									
Ja	90	30 (33,3)	NE [NE; NE]	96	22 (22,9)	NE [NE; NE]	1,56	[0,90; 2,73]	0,1126
Nein	186	47 (25,3)	NE [NE; NE]	179	35 (19,6)	NE [NE; NE]	1,40	[0,91; 2,19]	0,1282
Interaktion p-Wert									0,7708
Geschlecht									
Maennlich	104	38 (36,5)	NE [NE; NE]	107	19 (17,8)	NE [NE; NE]	2,29	[1,34; 4,06]	0,0023*
Weiblich	172	39 (22,7)	NE [NE; NE]	168	38 (22,6)	NE [NE; NE]	1,06	[0,68; 1,66]	0,7906
Interaktion p-Wert									0,0315*
Nachweis der EGFR-Mutation durch zentralen ctDNA Cobas Test									
positiv	211	55 (26,1)	NE [NE; NE]	204	41 (20,1)	NE [NE; NE]	1,38	[0,92; 2,07]	0,1207

Time to event of AE is defined as the time from first dose of study treatment to first onset of the respective AE or the time to censoring if the AE has not occurred by 28 days following discontinuation of study treatment, before administration of subsequent cancer therapy or death, whichever comes first. All AEs are coded using MedDRA version 25.1. Includes AEs with onset date on or after the date of first dose and up to and including 28 days following discontinuation of study treatment. Analysis done if >=10 patients at each subgroup level and >=10 events in at least one subgroup level combined for both arms. Analysis done for SOC and PT only if main effect for that SOC or PT is statistically significant at 5% level. [a] Median time to event based on the Kaplan Meier estimate. NE = Not estimable as median (or 95% CLs) is not reached. [b] Estimated from main effects of unstratified Cox proportional hazard model including trt., subgroup and subgroup-by-trt. interaction. Ties handled using Efron method and 95% CI derived from profile likelihood estimation. NC = Not calculable. HR <1 favours Osimertinib+Chemo. * p<0.05.
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Table 4.3.1.13 FLAURA-2: Summary of subgroup analysis of time to first PT: Ausschlag
Safety Analysis Set, DCO 03APR2023

	Osi + Chemo (N=276)			Osi (N=275)					
Subgruppen	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]	Hazard Ratio [b]	[95%-KI] [b]	2-seitiger p-Wert [b]
negativ	41	16 (39,0)	NE [NE; NE]	39	12 (30,8)	NE [NE; NE]	1,46	[0,69; 3,15]	0,3204
unbekannt	24	6 (25,0)	NE [NE; NE]	32	4 (12,5)	NE [NE; NE]	2,24	[0,64; 8,75]	0,2062
Interaktion p-Wert									0,7688
EGFR-Mutationstyp									
Exon 19 Deletion	172	51 (29,7)	NE [NE; NE]	167	31 (18,6)	NE [NE; NE]	1,81	[1,17; 2,86]	0,0079*
Exon 21 (L858R) Substitutionsmutation	104	26 (25,0)	NE [NE; NE]	106	25 (23,6)	NE [NE; NE]	1,06	[0,61; 1,84]	0,8366
Interaktion p-Wert									0,1364
Zentral bestätigte EGFR-Mutation im Gewebe									
positiv	248	65 (26,2)	NE [NE; NE]	238	45 (18,9)	NE [NE; NE]	1,49	[1,02; 2,19]	0,0389*
negativ	3	2 (66,7)	0,4 [0,2; NE]	4	1 (25,0)	NE [NE; NE]	NC	[NC]	NC
unbekannt	25	10 (40,0)	NE [NE; NE]	33	11 (33,3)	NE [NE; NE]	1,36	[0,57; 3,22]	0,4848
Interaktion p-Wert									0,8498
ZNS-Metastasen zur Baseline									
Ja	113	29 (25,7)	NE [NE; NE]	110	27 (24,5)	NE [NE; NE]	1,05	[0,62; 1,78]	0,8570
Nein	163	48 (29,4)	NE [NE; NE]	165	30 (18,2)	NE [NE; NE]	1,84	[1,17; 2,93]	0,0080*
Interaktion p-Wert									0,1145
Zentrale Bestätigung der EGFR-Mutation									
Zentral bestätigte EGFR-Mutation in Gewebe oder ctDNA	263	71 (27,0)	NE [NE; NE]	266	55 (20,7)	NE [NE; NE]	1,40	[0,98; 1,99]	0,0626
Keine zentrale Bestätigung	13	6 (46,2)	NE [NE; NE]	9	2 (22,2)	NE [NE; NE]	2,75	[0,63; 18,75]	0,1853
Interaktion p-Wert									0,3967
Alter bei Screening									

Time to event of AE is defined as the time from first dose of study treatment to first onset of the respective AE or the time to censoring if the AE has not occurred by 28 days following discontinuation of study treatment, before administration of subsequent cancer therapy or death, whichever comes first. All AEs are coded using MedDRA version 25.1. Includes AEs with onset date on or after the date of first dose and up to and including 28 days following discontinuation of study treatment. Analysis done if >=10 patients at each subgroup level and >=10 events in at least one subgroup level combined for both arms. Analysis done for SOC and PT only if main effect for that SOC or PT is statistically significant at 5% level. [a] Median time to event based on the Kaplan Meier estimate. NE = Not estimable as median (or 95% CLs) is not reached. [b] Estimated from main effects of unstratified Cox proportional hazard model including trt., subgroup and subgroup-by-trt. interaction. Ties handled using Efron method and 95% CI derived from profile likelihood estimation. NC = Not calculable. HR <1 favours Osimertinib+Chemo. * p<0.05.
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Table 4.3.1.13 FLAURA-2: Summary of subgroup analysis of time to first PT: Ausschlag
Safety Analysis Set, DCO 03APR2023

	Osi + Chemo (N=276)			Osi (N=275)					
Subgruppen	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]	Hazard Ratio [b]	[95%-KI] [b]	2-seitiger p-Wert [b]
<65 Jahre	172	47 (27,3)	NE [NE; NE]	164	37 (22,6)	NE [NE; NE]	1,25	[0,82; 1,94]	0,3010
>=65 Jahre	104	30 (28,8)	NE [NE; NE]	111	20 (18,0)	NE [NE; NE]	1,85	[1,06; 3,31]	0,0304*
Interaktion p-Wert									0,2806
Region gPAP									
Asien	168	45 (26,8)	NE [NE; NE]	166	33 (19,9)	NE [NE; NE]	1,43	[0,92; 2,26]	0,1159
Europa	22	10 (45,5)	NE [NE; NE]	23	9 (39,1)	NE [NE; NE]	1,18	[0,48; 2,97]	0,7176
Nordamerika	20	6 (30,0)	NE [NE; NE]	22	5 (22,7)	NE [NE; NE]	1,76	[0,53; 6,12]	0,3486
Rest der Welt	66	16 (24,2)	NE [NE; NE]	64	10 (15,6)	NE [NE; NE]	1,67	[0,77; 3,80]	0,1988
Interaktion p-Wert									0,9348

Time to event of AE is defined as the time from first dose of study treatment to first onset of the respective AE or the time to censoring if the AE has not occurred by 28 days following discontinuation of study treatment, before administration of subsequent cancer therapy or death, whichever comes first. All AEs are coded using MedDRA version 25.1. Includes AEs with onset date on or after the date of first dose and up to and including 28 days following discontinuation of study treatment. Analysis done if >=10 patients at each subgroup level and >=10 events in at least one subgroup level combined for both arms. Analysis done for SOC and PT only if main effect for that SOC or PT is statistically significant at 5% level. [a] Median time to event based on the Kaplan Meier estimate. NE = Not estimable as median (or 95% CLs) is not reached. [b] Estimated from main effects of unstratified Cox proportional hazard model including trt., subgroup and subgroup-by-trt. interaction. Ties handled using Efron method and 95% CI derived from profile likelihood estimation. NC = Not calculable. HR <1 favours Osimertinib+Chemo. * p<0.05.
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Table 4.3.1.14 FLAURA-2: Summary of subgroup analysis of time to first PT: Nagelerkrankung
Safety Analysis Set, DCO 03APR2023

	Osi + Chemo (N=276)			Osi (N=275)					
Subgruppen	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]	Hazard Ratio [b]	[95%-KI] [b]	2-seitiger p-Wert [b]
Abstammung									
Chinesisch/Asiatisch	68	1 (1,5)	NE [NE; NE]	70	2 (2,9)	NE [NE; NE]	NC	[NC]	NC
Nicht-chinesisch/ Asiatisch	107	1 (0,9)	NE [NE; NE]	106	2 (1,9)	NE [NE; NE]	NC	[NC]	NC
Nicht-asiatisch	101	1 (1,0)	NE [NE; NE]	99	6 (6,1)	NE [NE; NE]	NC	[NC]	NC
Interaktion p-Wert									NC
Methode zur Gewebeuntersuchung									
zentral	120	0	NE [NE; NE]	119	1 (0,8)	NE [NE; NE]	NC	[NC]	NC
lokal	156	3 (1,9)	NE [NE; NE]	156	9 (5,8)	NE [NE; NE]	0,33	[0,07; 1,09]	0,0701
Interaktion p-Wert									NC
WHO Performance-Status									
0	100	1 (1,0)	NE [NE; NE]	100	3 (3,0)	NE [NE; NE]	NC	[NC]	NC
1	176	2 (1,1)	NE [NE; NE]	175	7 (4,0)	NE [NE; NE]	NC	[NC]	NC
Interaktion p-Wert									NC
Raucherstatus									
Ja	90	0	NE [NE; NE]	96	5 (5,2)	NE [NE; NE]	NC	[NC]	NC
Nein	186	3 (1,6)	NE [NE; NE]	179	5 (2,8)	NE [NE; NE]	NC	[NC]	NC
Interaktion p-Wert									NC
Geschlecht									
Maennlich	104	0	NE [NE; NE]	107	3 (2,8)	NE [NE; NE]	NC	[NC]	NC
Weiblich	172	3 (1,7)	NE [NE; NE]	168	7 (4,2)	NE [NE; NE]	0,42	[0,09; 1,53]	0,1939
Interaktion p-Wert									NC
Nachweis der EGFR-Mutation durch zentralen ctDNA Cobas Test									
positiv	211	2 (0,9)	NE [NE; NE]	204	7 (3,4)	NE [NE; NE]	NC	[NC]	NC

Time to event of AE is defined as the time from first dose of study treatment to first onset of the respective AE or the time to censoring if the AE has not occurred by 28 days following discontinuation of study treatment, before administration of subsequent cancer therapy or death, whichever comes first. All AEs are coded using MedDRA version 25.1. Includes AEs with onset date on or after the date of first dose and up to and including 28 days following discontinuation of study treatment. Analysis done if >=10 patients at each subgroup level and >=10 events in at least one subgroup level combined for both arms. Analysis done for SOC and PT only if main effect for that SOC or PT is statistically significant at 5% level. [a] Median time to event based on the Kaplan Meier estimate. NE = Not estimable as median (or 95% CLs) is not reached. [b] Estimated from main effects of unstratified Cox proportional hazard model including trt., subgroup and subgroup-by-trt. interaction. Ties handled using Efron method and 95% CI derived from profile likelihood estimation. NC = Not calculable. HR <1 favours Osimertinib+Chemo. * p<0.05.
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Table 4.3.1.14 FLAURA-2: Summary of subgroup analysis of time to first PT: Nagelerkrankung
Safety Analysis Set, DCO 03APR2023

	Osi + Chemo (N=276)			Osi (N=275)					
Subgruppen	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]	Hazard Ratio [b]	[95%-KI] [b]	2-seitiger p-Wert [b]
negativ	41	0	NE [NE; NE]	39	2 (5,1)	NE [NE; NE]	NC	[NC]	NC
unbekannt	24	1 (4,2)	NE [NE; NE]	32	1 (3,1)	NE [NE; NE]	NC	[NC]	NC
Interaktion p-Wert									NC
EGFR-Mutationstyp									
Exon 19 Deletion	172	2 (1,2)	NE [NE; NE]	167	5 (3,0)	NE [NE; NE]	NC	[NC]	NC
Exon 21 (L858R) Substitutionsmutation	104	1 (1,0)	NE [NE; NE]	106	5 (4,7)	NE [NE; NE]	NC	[NC]	NC
Interaktion p-Wert									NC
Zentral bestätigte EGFR-Mutation im Gewebe									
positiv	248	2 (0,8)	NE [NE; NE]	238	7 (2,9)	NE [NE; NE]	NC	[NC]	NC
negativ	3	0	NE [NE; NE]	4	0	NE [NE; NE]	NC	[NC]	NC
unbekannt	25	1 (4,0)	NE [NE; NE]	33	3 (9,1)	NE [NE; NE]	NC	[NC]	NC
Interaktion p-Wert									NC
ZNS-Metastasen zur Baseline									
Ja	113	1 (0,9)	NE [NE; NE]	110	0	NE [NE; NE]	NC	[NC]	NC
Nein	163	2 (1,2)	NE [NE; NE]	165	10 (6,1)	NE [NE; NE]	0,20	[0,03; 0,76]	0,0157*
Interaktion p-Wert									NC
Zentrale Bestätigung der EGFR-Mutation									
Zentral bestätigte EGFR-Mutation in Gewebe oder ctDNA	263	2 (0,8)	NE [NE; NE]	266	9 (3,4)	NE [NE; NE]	0,22	[0,03; 0,87]	0,0288*
Keine zentrale Bestätigung	13	1 (7,7)	NE [NE; NE]	9	1 (11,1)	NE [NE; NE]	0,58	[0,02; 14,76]	0,7054
Interaktion p-Wert									0,5539
Alter bei Screening									

Time to event of AE is defined as the time from first dose of study treatment to first onset of the respective AE or the time to censoring if the AE has not occurred by 28 days following discontinuation of study treatment, before administration of subsequent cancer therapy or death, whichever comes first. All AEs are coded using MedDRA version 25.1. Includes AEs with onset date on or after the date of first dose and up to and including 28 days following discontinuation of study treatment. Analysis done if >=10 patients at each subgroup level and >=10 events in at least one subgroup level combined for both arms. Analysis done for SOC and PT only if main effect for that SOC or PT is statistically significant at 5% level. [a] Median time to event based on the Kaplan Meier estimate. NE = Not estimable as median (or 95% CLs) is not reached. [b] Estimated from main effects of unstratified Cox proportional hazard model including trt., subgroup and subgroup-by-trt. interaction. Ties handled using Efron method and 95% CI derived from profile likelihood estimation. NC = Not calculable. HR <1 favours Osimertinib+Chemo. * p<0.05.
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Table 4.3.1.14 FLAURA-2: Summary of subgroup analysis of time to first PT: Nagelerkrankung
Safety Analysis Set, DCO 03APR2023

	Osi + Chemo (N=276)			Osi (N=275)					
Subgruppen	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]	Hazard Ratio [b]	[95%-KI] [b]	2-seitiger p-Wert [b]
<65 Jahre	172	2 (1,2)	NE [NE; NE]	164	6 (3,7)	NE [NE; NE]	NC	[NC]	NC
>=65 Jahre	104	1 (1,0)	NE [NE; NE]	111	4 (3,6)	NE [NE; NE]	NC	[NC]	NC
Interaktion p-Wert									NC
Region gPAP									
Asien	168	1 (0,6)	NE [NE; NE]	166	3 (1,8)	NE [NE; NE]	NC	[NC]	NC
Europa	22	0	NE [NE; NE]	23	1 (4,3)	NE [NE; NE]	NC	[NC]	NC
Nordamerika	20	1 (5,0)	NE [NE; NE]	22	5 (22,7)	NE [NE; NE]	NC	[NC]	NC
Rest der Welt	66	1 (1,5)	NE [NE; NE]	64	1 (1,6)	NE [NE; NE]	NC	[NC]	NC
Interaktion p-Wert									NC

Time to event of AE is defined as the time from first dose of study treatment to first onset of the respective AE or the time to censoring if the AE has not occurred by 28 days following discontinuation of study treatment, before administration of subsequent cancer therapy or death, whichever comes first. All AEs are coded using MedDRA version 25.1. Includes AEs with onset date on or after the date of first dose and up to and including 28 days following discontinuation of study treatment. Analysis done if >=10 patients at each subgroup level and >=10 events in at least one subgroup level combined for both arms. Analysis done for SOC and PT only if main effect for that SOC or PT is statistically significant at 5% level. [a] Median time to event based on the Kaplan Meier estimate. NE = Not estimable as median (or 95% CLs) is not reached. [b] Estimated from main effects of unstratified Cox proportional hazard model including trt., subgroup and subgroup-by-trt. interaction. Ties handled using Efron method and 95% CI derived from profile likelihood estimation. NC = Not calculable. HR <1 favours Osimertinib+Chemo. * p<0.05.
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Table 4.3.1.15 FLAURA-2: Summary of subgroup analysis of time to first SOC: Erkrankungen der Nieren und Harnwege
Safety Analysis Set, DCO 03APR2023

	Osi + Chemo (N=276)			Osi (N=275)					
Subgruppen	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]	Hazard Ratio [b]	[95%-KI] [b]	2-seitiger p-Wert [b]
Abstammung									
Chinesisch/Asiatisch	68	17 (25,0)	NE [NE; NE]	70	13 (18,6)	NE [NE; NE]	1,31	[0,64; 2,75]	0,4625
Nicht-chinesisch/ Asiatisch	107	14 (13,1)	NE [NE; NE]	106	3 (2,8)	NE [NE; NE]	4,73	[1,54; 20,53]	0,0050*
Nicht-asiatisch	101	21 (20,8)	NE [NE; NE]	99	10 (10,1)	NE [NE; NE]	2,12	[1,02; 4,70]	0,0430*
Interaktion p-Wert									0,1750
Methode zur Gewebeuntersuchung									
zentral	120	25 (20,8)	NE [NE; NE]	119	11 (9,2)	NE [NE; NE]	2,35	[1,18; 4,97]	0,0139*
lokal	156	27 (17,3)	NE [NE; NE]	156	15 (9,6)	NE [NE; NE]	1,79	[0,96; 3,44]	0,0657
Interaktion p-Wert									0,5729
WHO Performance-Status									
0	100	18 (18,0)	NE [NE; NE]	100	8 (8,0)	NE [NE; NE]	2,34	[1,05; 5,71]	0,0367*
1	176	34 (19,3)	NE [NE; NE]	175	18 (10,3)	NE [NE; NE]	1,87	[1,07; 3,39]	0,0277*
Interaktion p-Wert									0,6610
Raucherstatus									
Ja	90	16 (17,8)	NE [NE; NE]	96	7 (7,3)	NE [NE; NE]	2,46	[1,05; 6,41]	0,0376*
Nein	186	36 (19,4)	NE [NE; NE]	179	19 (10,6)	NE [NE; NE]	1,85	[1,08; 3,29]	0,0259*
Interaktion p-Wert									0,5909
Geschlecht									
Maennlich	104	20 (19,2)	NE [NE; NE]	107	10 (9,3)	NE [NE; NE]	1,97	[0,94; 4,38]	0,0723
Weiblich	172	32 (18,6)	NE [NE; NE]	168	16 (9,5)	NE [NE; NE]	2,05	[1,14; 3,83]	0,0156*
Interaktion p-Wert									0,9320
Nachweis der EGFR-Mutation durch zentralen ctDNA Cobas Test									
positiv	211	36 (17,1)	NE [NE; NE]	204	15 (7,4)	NE [NE; NE]	2,37	[1,32; 4,45]	0,0033*

Time to event of AE is defined as the time from first dose of study treatment to first onset of the respective AE or the time to censoring if the AE has not occurred by 28 days following discontinuation of study treatment, before administration of subsequent cancer therapy or death, whichever comes first. All AEs are coded using MedDRA version 25.1. Includes AEs with onset date on or after the date of first dose and up to and including 28 days following discontinuation of study treatment. Analysis done if >=10 patients at each subgroup level and >=10 events in at least one subgroup level combined for both arms. Analysis done for SOC and PT only if main effect for that SOC or PT is statistically significant at 5% level. [a] Median time to event based on the Kaplan Meier estimate. NE = Not estimable as median (or 95% CLs) is not reached. [b] Estimated from main effects of unstratified Cox proportional hazard model including trt., subgroup and subgroup-by-trt. interaction. Ties handled using Efron method and 95% CI derived from profile likelihood estimation. NC = Not calculable. HR <1 favours Osimertinib+Chemo. * p<0.05.
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Table 4.3.1.15 FLAURA-2: Summary of subgroup analysis of time to first SOC: Erkrankungen der Nieren und Harnwege
Safety Analysis Set, DCO 03APR2023

	Osi + Chemo (N=276)			Osi (N=275)					
Subgruppen	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]	Hazard Ratio [b]	[95%-KI] [b]	2-seitiger p-Wert [b]
negativ	41	10 (24,4)	NE [NE; NE]	39	2 (5,1)	NE [NE; NE]	5,23	[1,38; 34,03]	0,0129*
unbekannt	24	6 (25,0)	NE [NE; NE]	32	9 (28,1)	NE [NE; NE]	0,77	[0,26; 2,13]	0,6126
Interaktion p-Wert									0,0622
EGFR-Mutationstyp									
Exon 19 Deletion	172	32 (18,6)	NE [NE; NE]	167	17 (10,2)	NE [NE; NE]	1,88	[1,06; 3,46]	0,0312*
Exon 21 (L858R) Substitutionsmutation	104	20 (19,2)	NE [NE; NE]	106	9 (8,5)	NE [NE; NE]	2,25	[1,05; 5,19]	0,0358*
Interaktion p-Wert									0,7196
Zentral bestätigte EGFR-Mutation im Gewebe									
positiv	248	45 (18,1)	NE [NE; NE]	238	20 (8,4)	NE [NE; NE]	2,20	[1,32; 3,81]	0,0023*
negativ	3	1 (33,3)	NE [NE; NE]	4	0	NE [NE; NE]	NC	[NC]	NC
unbekannt	25	6 (24,0)	NE [NE; NE]	33	6 (18,2)	NE [NE; NE]	1,38	[0,43; 4,42]	0,5749
Interaktion p-Wert									0,4671
ZNS-Metastasen zur Baseline									
Ja	113	23 (20,4)	NE [NE; NE]	110	13 (11,8)	NE [NE; NE]	1,64	[0,84; 3,33]	0,1485
Nein	163	29 (17,8)	NE [NE; NE]	165	13 (7,9)	NE [NE; NE]	2,38	[1,27; 4,74]	0,0067*
Interaktion p-Wert									0,4357
Zentrale Bestätigung der EGFR-Mutation									
Zentral bestätigte EGFR-Mutation in Gewebe oder ctDNA	263	48 (18,3)	NE [NE; NE]	266	24 (9,0)	NE [NE; NE]	2,05	[1,27; 3,40]	0,0031*
Keine zentrale Bestätigung	13	4 (30,8)	NE [NE; NE]	9	2 (22,2)	NE [NE; NE]	1,33	[0,26; 9,56]	0,7410
Interaktion p-Wert									0,6361
Alter bei Screening									

Time to event of AE is defined as the time from first dose of study treatment to first onset of the respective AE or the time to censoring if the AE has not occurred by 28 days following discontinuation of study treatment, before administration of subsequent cancer therapy or death, whichever comes first. All AEs are coded using MedDRA version 25.1. Includes AEs with onset date on or after the date of first dose and up to and including 28 days following discontinuation of study treatment. Analysis done if >=10 patients at each subgroup level and >=10 events in at least one subgroup level combined for both arms. Analysis done for SOC and PT only if main effect for that SOC or PT is statistically significant at 5% level. [a] Median time to event based on the Kaplan Meier estimate. NE = Not estimable as median (or 95% CLs) is not reached. [b] Estimated from main effects of unstratified Cox proportional hazard model including trt., subgroup and subgroup-by-trt. interaction. Ties handled using Efron method and 95% CI derived from profile likelihood estimation. NC = Not calculable. HR <1 favours Osimertinib+Chemo. * p<0.05.
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Table 4.3.1.15 FLAURA-2: Summary of subgroup analysis of time to first SOC: Erkrankungen der Nieren und Harnwege
Safety Analysis Set, DCO 03APR2023

	Osi + Chemo (N=276)			Osi (N=275)					
Subgruppen	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]	Hazard Ratio [b]	[95%-KI] [b]	2-seitiger p-Wert [b]
<65 Jahre	172	30 (17,4)	NE [NE; NE]	164	17 (10,4)	NE [NE; NE]	1,63	[0,91; 3,02]	0,1013
>=65 Jahre	104	22 (21,2)	NE [NE; NE]	111	9 (8,1)	NE [NE; NE]	2,86	[1,36; 6,55]	0,0051*
Interaktion p-Wert									0,2561
Region gPAP									
Asien	168	30 (17,9)	NE [NE; NE]	166	12 (7,2)	NE [NE; NE]	2,50	[1,31; 5,07]	0,0048*
Europa	22	6 (27,3)	NE [NE; NE]	23	1 (4,3)	NE [NE; NE]	6,23	[1,06;117,73]	0,0415*
Nordamerika	20	5 (25,0)	NE [NE; NE]	22	8 (36,4)	NE [NE; NE]	0,70	[0,21; 2,09]	0,5217
Rest der Welt	66	11 (16,7)	NE [NE; NE]	64	5 (7,8)	NE [NE; NE]	2,19	[0,80; 6,96]	0,1304
Interaktion p-Wert									0,1431

Time to event of AE is defined as the time from first dose of study treatment to first onset of the respective AE or the time to censoring if the AE has not occurred by 28 days following discontinuation of study treatment, before administration of subsequent cancer therapy or death, whichever comes first. All AEs are coded using MedDRA version 25.1. Includes AEs with onset date on or after the date of first dose and up to and including 28 days following discontinuation of study treatment. Analysis done if >=10 patients at each subgroup level and >=10 events in at least one subgroup level combined for both arms. Analysis done for SOC and PT only if main effect for that SOC or PT is statistically significant at 5% level. [a] Median time to event based on the Kaplan Meier estimate. NE = Not estimable as median (or 95% CLs) is not reached. [b] Estimated from main effects of unstratified Cox proportional hazard model including trt., subgroup and subgroup-by-trt. interaction. Ties handled using Efron method and 95% CI derived from profile likelihood estimation. NC = Not calculable. HR <1 favours Osimertinib+Chemo. * p<0.05.
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Table 4.3.1.16 FLAURA-2: Summary of subgroup analysis of time to first SOC: Erkrankungen des Blutes und des Lymphsystems
Safety Analysis Set, DCO 03APR2023

	Osi + Chemo (N=276)			Osi (N=275)					
Subgruppen	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]	Hazard Ratio [b]	[95%-KI] [b]	2-seitiger p-Wert [b]
Abstammung									
Chinesisch/Asiatisch	68	50 (73,5)	1,4 [0,9; 2,8]	70	24 (34,3)	NE [NE; NE]	3,25	[2,02; 5,38]	<0,0001*
Nicht-chinesisch/ Asiatisch	107	60 (56,1)	3,5 [2,6;18,6]	106	10 (9,4)	NE [NE; NE]	8,45	[4,53; 17,55]	<0,0001*
Nicht-asiatisch	101	64 (63,4)	2,8 [1,5; 6,2]	99	14 (14,1)	NE [NE; NE]	6,66	[3,85; 12,37]	<0,0001*
Interaktion p-Wert									0,0418*
Methode zur Gewebeuntersuchung									
zentral	120	91 (75,8)	2,1 [1,4; 2,8]	119	30 (25,2)	NE [NE; NE]	4,82	[3,22; 7,41]	<0,0001*
lokal	156	83 (53,2)	6,9 [2,6; NE]	156	18 (11,5)	NE [NE; NE]	6,40	[3,94; 10,99]	<0,0001*
Interaktion p-Wert									0,3926
WHO Performance-Status									
0	100	56 (56,0)	6,9 [2,8; NE]	100	14 (14,0)	NE [NE; NE]	5,19	[2,97; 9,70]	<0,0001*
1	176	118 (67,0)	2,1 [1,4; 2,8]	175	34 (19,4)	NE [NE; NE]	5,48	[3,78; 8,16]	<0,0001*
Interaktion p-Wert									0,8774
Raucherstatus									
Ja	90	50 (55,6)	3,6 [2,2; NE]	96	16 (16,7)	NE [NE; NE]	4,45	[2,60; 8,07]	<0,0001*
Nein	186	124 (66,7)	2,4 [2,0; 3,4]	179	32 (17,9)	NE [NE; NE]	5,70	[3,91; 8,56]	<0,0001*
Interaktion p-Wert									0,4823
Geschlecht									
Maennlich	104	70 (67,3)	3,3 [2,1; 6,2]	107	14 (13,1)	NE [NE; NE]	7,11	[4,14; 13,17]	<0,0001*
Weiblich	172	104 (60,5)	2,6 [2,0; 5,5]	168	34 (20,2)	NE [NE; NE]	4,51	[3,09; 6,75]	<0,0001*
Interaktion p-Wert									0,1897
Nachweis der EGFR-Mutation durch zentralen ctDNA Cobas Test									
positiv	211	136 (64,5)	2,8 [2,1; 3,4]	204	34 (16,7)	NE [NE; NE]	5,83	[4,05; 8,64]	<0,0001*

Time to event of AE is defined as the time from first dose of study treatment to first onset of the respective AE or the time to censoring if the AE has not occurred by 28 days following discontinuation of study treatment, before administration of subsequent cancer therapy or death, whichever comes first. All AEs are coded using MedDRA version 25.1. Includes AEs with onset date on or after the date of first dose and up to and including 28 days following discontinuation of study treatment. Analysis done if >=10 patients at each subgroup level and >=10 events in at least one subgroup level combined for both arms. Analysis done for SOC and PT only if main effect for that SOC or PT is statistically significant at 5% level. [a] Median time to event based on the Kaplan Meier estimate. NE = Not estimable as median (or 95% CLs) is not reached. [b] Estimated from main effects of unstratified Cox proportional hazard model including trt., subgroup and subgroup-by-trt. interaction. Ties handled using Efron method and 95% CI derived from profile likelihood estimation. NC = Not calculable. HR <1 favours Osimertinib+Chemo. * p<0.05.
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Table 4.3.1.16 FLAURA-2: Summary of subgroup analysis of time to first SOC: Erkrankungen des Blutes und des Lymphsystems
Safety Analysis Set, DCO 03APR2023

	Osi + Chemo (N=276)			Osi (N=275)					
Subgruppen	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]	Hazard Ratio [b]	[95%-KI] [b]	2-seitiger p-Wert [b]
negativ	41	23 (56,1)	5,6 [2,1; NE]	39	8 (20,5)	NE [NE; NE]	3,46	[1,61; 8,26]	0,0011*
unbekannt	24	15 (62,5)	1,7 [0,7; NE]	32	6 (18,8)	NE [NE; NE]	4,89	[1,99; 13,71]	0,0004*
Interaktion p-Wert									0,5262
EGFR-Mutationstyp									
Exon 19 Deletion	172	107 (62,2)	2,8 [2,0; 5,5]	167	26 (15,6)	NE [NE; NE]	5,97	[3,95; 9,36]	<0,0001*
Exon 21 (L858R) Substitutionsmutation	104	67 (64,4)	2,8 [2,1; 6,2]	106	22 (20,8)	NE [NE; NE]	4,37	[2,75; 7,25]	<0,0001*
Interaktion p-Wert									0,3470
Zentral bestätigte EGFR-Mutation im Gewebe									
positiv	248	162 (65,3)	2,7 [2,1; 3,1]	238	40 (16,8)	NE [NE; NE]	5,86	[4,18; 8,40]	<0,0001*
negativ	3	1 (33,3)	NE [NE; NE]	4	0	NE [NE; NE]	NC	[NC]	NC
unbekannt	25	11 (44,0)	NE [NE; NE]	33	8 (24,2)	NE [NE; NE]	2,17	[0,88; 5,60]	0,0933
Interaktion p-Wert									0,0528
ZNS-Metastasen zur Baseline									
Ja	113	70 (61,9)	2,6 [1,4; 6,2]	110	24 (21,8)	NE [NE; NE]	3,99	[2,55; 6,47]	<0,0001*
Nein	163	104 (63,8)	2,8 [2,1; 5,6]	165	24 (14,5)	NE [NE; NE]	6,56	[4,28; 10,48]	<0,0001*
Interaktion p-Wert									0,1290
Zentrale Bestätigung der EGFR-Mutation									
Zentral bestätigte EGFR-Mutation in Gewebe oder ctDNA	263	170 (64,6)	2,8 [2,1; 3,4]	266	46 (17,3)	NE [NE; NE]	5,60	[4,07; 7,85]	<0,0001*
Keine zentrale Bestätigung	13	4 (30,8)	NE [NE; NE]	9	2 (22,2)	NE [NE; NE]	1,26	[0,25; 9,10]	0,7860
Interaktion p-Wert									0,1276
Alter bei Screening									

Time to event of AE is defined as the time from first dose of study treatment to first onset of the respective AE or the time to censoring if the AE has not occurred by 28 days following discontinuation of study treatment, before administration of subsequent cancer therapy or death, whichever comes first. All AEs are coded using MedDRA version 25.1. Includes AEs with onset date on or after the date of first dose and up to and including 28 days following discontinuation of study treatment. Analysis done if >=10 patients at each subgroup level and >=10 events in at least one subgroup level combined for both arms. Analysis done for SOC and PT only if main effect for that SOC or PT is statistically significant at 5% level. [a] Median time to event based on the Kaplan Meier estimate. NE = Not estimable as median (or 95% CLs) is not reached. [b] Estimated from main effects of unstratified Cox proportional hazard model including trt., subgroup and subgroup-by-trt. interaction. Ties handled using Efron method and 95% CI derived from profile likelihood estimation. NC = Not calculable. HR <1 favours Osimertinib+Chemo. * p<0.05.
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Table 4.3.1.16 FLAURA-2: Summary of subgroup analysis of time to first SOC: Erkrankungen des Blutes und des Lymphsystems
Safety Analysis Set, DCO 03APR2023

	Osi + Chemo (N=276)			Osi (N=275)					
Subgruppen	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]	Hazard Ratio [b]	[95%-KI] [b]	2-seitiger p-Wert [b]
<65 Jahre	172	108 (62,8)	2,8 [2,1; 5,6]	164	27 (16,5)	NE [NE; NE]	5,43	[3,61; 8,45]	<0,0001*
>=65 Jahre	104	66 (63,5)	2,8 [1,4; 6,2]	111	21 (18,9)	NE [NE; NE]	5,15	[3,20; 8,62]	<0,0001*
Interaktion p-Wert									0,8714
Region gPAP									
Asien	168	107 (63,7)	2,8 [2,1; 3,5]	166	30 (18,1)	NE [NE; NE]	5,20	[3,51; 7,95]	<0,0001*
Europa	22	16 (72,7)	0,9 [0,3;13,7]	23	3 (13,0)	NE [NE; NE]	9,82	[3,27; 42,21]	<0,0001*
Nordamerika	20	10 (50,0)	19,5 [0,5; NE]	22	3 (13,6)	NE [NE; NE]	4,74	[1,45; 21,15]	0,0089*
Rest der Welt	66	41 (62,1)	3,1 [2,0; 6,9]	64	12 (18,8)	NE [NE; NE]	4,66	[2,53; 9,28]	<0,0001*
Interaktion p-Wert									0,7332

Time to event of AE is defined as the time from first dose of study treatment to first onset of the respective AE or the time to censoring if the AE has not occurred by 28 days following discontinuation of study treatment, before administration of subsequent cancer therapy or death, whichever comes first. All AEs are coded using MedDRA version 25.1. Includes AEs with onset date on or after the date of first dose and up to and including 28 days following discontinuation of study treatment. Analysis done if >=10 patients at each subgroup level and >=10 events in at least one subgroup level combined for both arms. Analysis done for SOC and PT only if main effect for that SOC or PT is statistically significant at 5% level. [a] Median time to event based on the Kaplan Meier estimate. NE = Not estimable as median (or 95% CLs) is not reached. [b] Estimated from main effects of unstratified Cox proportional hazard model including trt., subgroup and subgroup-by-trt. interaction. Ties handled using Efron method and 95% CI derived from profile likelihood estimation. NC = Not calculable. HR <1 favours Osimertinib+Chemo. * p<0.05.
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Table 4.3.1.17 FLAURA-2: Summary of subgroup analysis of time to first PT: Anaemie
Safety Analysis Set, DCO 03APR2023

	Osi + Chemo (N=276)			Osi (N=275)					
Subgruppen	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]	Hazard Ratio [b]	[95%-KI] [b]	2-seitiger p-Wert [b]
Abstammung									
Chinesisch/Asiatisch	68	43 (63,2)	2,1 [1,3;11,1]	70	15 (21,4)	NE [NE; NE]	4,60	[2,61; 8,57]	<0,0001*
Nicht-chinesisch/ Asiatisch	107	43 (40,2)	NE [NE; NE]	106	4 (3,8)	NE [NE; NE]	13,61	[5,51; 45,25]	<0,0001*
Nicht-asiatisch	101	42 (41,6)	NE [NE; NE]	99	3 (3,0)	NE [NE; NE]	17,67	[6,44; 72,94]	<0,0001*
Interaktion p-Wert									0,0388*
Methode zur Gewebeuntersuchung									
zentral	120	68 (56,7)	4,2 [2,8;21,0]	119	19 (16,0)	NE [NE; NE]	5,01	[3,07; 8,57]	<0,0001*
lokal	156	60 (38,5)	NE [NE; NE]	156	3 (1,9)	NE [NE; NE]	25,77	[9,55;105,56]	<0,0001*
Interaktion p-Wert									0,0033*
WHO Performance-Status									
0	100	40 (40,0)	NE [NE; NE]	100	5 (5,0)	NE [NE; NE]	10,06	[4,36; 29,18]	<0,0001*
1	176	88 (50,0)	13,6 [2,8; NE]	175	17 (9,7)	NE [NE; NE]	7,15	[4,37; 12,45]	<0,0001*
Interaktion p-Wert									0,5206
Raucherstatus									
Ja	90	39 (43,3)	NE [NE; NE]	96	7 (7,3)	NE [NE; NE]	7,76	[3,70; 18,99]	<0,0001*
Nein	186	89 (47,8)	21,0 [3,5; NE]	179	15 (8,4)	NE [NE; NE]	7,71	[4,60; 13,87]	<0,0001*
Interaktion p-Wert									0,9881
Geschlecht									
Maennlich	104	49 (47,1)	NE [NE; NE]	107	5 (4,7)	NE [NE; NE]	12,67	[5,56; 36,48]	<0,0001*
Weiblich	172	79 (45,9)	NE [NE; NE]	168	17 (10,1)	NE [NE; NE]	6,30	[3,82; 11,00]	<0,0001*
Interaktion p-Wert									0,1762
Nachweis der EGFR-Mutation durch zentralen ctDNA Cobas Test									
positiv	211	102 (48,3)	17,0 [3,4; NE]	204	16 (7,8)	NE [NE; NE]	8,46	[5,14; 14,88]	<0,0001*

Time to event of AE is defined as the time from first dose of study treatment to first onset of the respective AE or the time to censoring if the AE has not occurred by 28 days following discontinuation of study treatment, before administration of subsequent cancer therapy or death, whichever comes first. All AEs are coded using MedDRA version 25.1. Includes AEs with onset date on or after the date of first dose and up to and including 28 days following discontinuation of study treatment. Analysis done if >=10 patients at each subgroup level and >=10 events in at least one subgroup level combined for both arms. Analysis done for SOC and PT only if main effect for that SOC or PT is statistically significant at 5% level. [a] Median time to event based on the Kaplan Meier estimate. NE = Not estimable as median (or 95% CLs) is not reached. [b] Estimated from main effects of unstratified Cox proportional hazard model including trt., subgroup and subgroup-by-trt. interaction. Ties handled using Efron method and 95% CI derived from profile likelihood estimation. NC = Not calculable. HR <1 favours Osimertinib+Chemo. * p<0.05.
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Table 4.3.1.17 FLAURA-2: Summary of subgroup analysis of time to first PT: Anaemie
Safety Analysis Set, DCO 03APR2023

	Osi + Chemo (N=276)			Osi (N=275)					
Subgruppen	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]	Hazard Ratio [b]	[95%-KI] [b]	2-seitiger p-Wert [b]
negativ	41	16 (39,0)	NE [NE; NE]	39	5 (12,8)	NE [NE; NE]	3,62	[1,42; 11,07]	0,0062*
unbekannt	24	10 (41,7)	NE [NE; NE]	32	1 (3,1)	NE [NE; NE]	17,62	[3,38;323,88]	0,0001*
Interaktion p-Wert									0,2478
EGFR-Mutationstyp									
Exon 19 Deletion	172	76 (44,2)	NE [NE; NE]	167	10 (6,0)	NE [NE; NE]	10,01	[5,43; 20,62]	<0,0001*
Exon 21 (L858R) Substitutionsmutation	104	52 (50,0)	11,1 [2,9; NE]	106	12 (11,3)	NE [NE; NE]	5,77	[3,19; 11,33]	<0,0001*
Interaktion p-Wert									0,2346
Zentral bestätigte EGFR-Mutation im Gewebe									
positiv	248	120 (48,4)	17,0 [3,5; NE]	238	20 (8,4)	NE [NE; NE]	7,84	[5,00; 12,98]	<0,0001*
negativ	3	1 (33,3)	NE [NE; NE]	4	0	NE [NE; NE]	NC	[NC]	NC
unbekannt	25	7 (28,0)	NE [NE; NE]	33	2 (6,1)	NE [NE; NE]	5,41	[1,31; 36,29]	0,0186*
Interaktion p-Wert									0,6664
ZNS-Metastasen zur Baseline									
Ja	113	55 (48,7)	17,0 [2,7; NE]	110	9 (8,2)	NE [NE; NE]	8,12	[4,22; 17,61]	<0,0001*
Nein	163	73 (44,8)	NE [NE; NE]	165	13 (7,9)	NE [NE; NE]	7,48	[4,29; 14,13]	<0,0001*
Interaktion p-Wert									0,8605
Zentrale Bestätigung der EGFR-Mutation									
Zentral bestätigte EGFR-Mutation in Gewebe oder ctDNA	263	125 (47,5)	21,0 [5,2; NE]	266	22 (8,3)	NE [NE; NE]	7,80	[5,06; 12,61]	<0,0001*
Keine zentrale Bestätigung	13	3 (23,1)	NE [NE; NE]	9	0	NE [NE; NE]	NC	[NC]	NC
Interaktion p-Wert									NC
Alter bei Screening									

Time to event of AE is defined as the time from first dose of study treatment to first onset of the respective AE or the time to censoring if the AE has not occurred by 28 days following discontinuation of study treatment, before administration of subsequent cancer therapy or death, whichever comes first. All AEs are coded using MedDRA version 25.1. Includes AEs with onset date on or after the date of first dose and up to and including 28 days following discontinuation of study treatment. Analysis done if >=10 patients at each subgroup level and >=10 events in at least one subgroup level combined for both arms. Analysis done for SOC and PT only if main effect for that SOC or PT is statistically significant at 5% level. [a] Median time to event based on the Kaplan Meier estimate. NE = Not estimable as median (or 95% CLs) is not reached. [b] Estimated from main effects of unstratified Cox proportional hazard model including trt., subgroup and subgroup-by-trt. interaction. Ties handled using Efron method and 95% CI derived from profile likelihood estimation. NC = Not calculable. HR <1 favours Osimertinib+Chemo. * p<0.05.
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Table 4.3.1.17 FLAURA-2: Summary of subgroup analysis of time to first PT: Anaemie
Safety Analysis Set, DCO 03APR2023

	Osi + Chemo (N=276)			Osi (N=275)					
Subgruppen	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]	Hazard Ratio [b]	[95%-KI] [b]	2-seitiger p-Wert [b]
<65 Jahre	172	77 (44,8)	NE [NE; NE]	164	10 (6,1)	NE [NE; NE]	9,58	[5,21; 19,74]	<0,0001*
>=65 Jahre	104	51 (49,0)	13,6 [3,3; NE]	111	12 (10,8)	NE [NE; NE]	6,32	[3,49; 12,44]	<0,0001*
Interaktion p-Wert									0,3696
Region gPAP									
Asien	168	85 (50,6)	11,1 [2,8; NE]	166	19 (11,4)	NE [NE; NE]	6,15	[3,83; 10,43]	<0,0001*
Europa	22	10 (45,5)	NE [NE; NE]	23	0	NE [NE; NE]	NC	[NC]	NC
Nordamerika	20	6 (30,0)	NE [NE; NE]	22	0	NE [NE; NE]	NC	[NC]	NC
Rest der Welt	66	27 (40,9)	NE [NE; NE]	64	3 (4,7)	NE [NE; NE]	11,06	[3,91; 46,32]	<0,0001*
Interaktion p-Wert									0,3485

Time to event of AE is defined as the time from first dose of study treatment to first onset of the respective AE or the time to censoring if the AE has not occurred by 28 days following discontinuation of study treatment, before administration of subsequent cancer therapy or death, whichever comes first. All AEs are coded using MedDRA version 25.1. Includes AEs with onset date on or after the date of first dose and up to and including 28 days following discontinuation of study treatment. Analysis done if >=10 patients at each subgroup level and >=10 events in at least one subgroup level combined for both arms. Analysis done for SOC and PT only if main effect for that SOC or PT is statistically significant at 5% level. [a] Median time to event based on the Kaplan Meier estimate. NE = Not estimable as median (or 95% CLs) is not reached. [b] Estimated from main effects of unstratified Cox proportional hazard model including trt., subgroup and subgroup-by-trt. interaction. Ties handled using Efron method and 95% CI derived from profile likelihood estimation. NC = Not calculable. HR <1 favours Osimertinib+Chemo. * p<0.05.
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Table 4.3.1.18 FLAURA-2: Summary of subgroup analysis of time to first PT: Febrile Neutropenie
Safety Analysis Set, DCO 03APR2023

	Osi + Chemo (N=276)			Osi (N=275)					
Subgruppen	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]	Hazard Ratio [b]	[95%-KI] [b]	2-seitiger p-Wert [b]
Abstammung									
Chinesisch/Asiatisch	68	3 (4,4)	NE [NE; NE]	70	0	NE [NE; NE]	NC	[NC]	NC
Nicht-chinesisch/ Asiatisch	107	7 (6,5)	NE [NE; NE]	106	0	NE [NE; NE]	NC	[NC]	NC
Nicht-asiatisch	101	1 (1,0)	NE [NE; NE]	99	0	NE [NE; NE]	NC	[NC]	NC
Interaktion p-Wert									NC
Methode zur Gewebeuntersuchung									
zentral	120	4 (3,3)	NE [NE; NE]	119	0	NE [NE; NE]	NC	[NC]	NC
lokal	156	7 (4,5)	NE [NE; NE]	156	0	NE [NE; NE]	NC	[NC]	NC
Interaktion p-Wert									NC
WHO Performance-Status									
0	100	3 (3,0)	NE [NE; NE]	100	0	NE [NE; NE]	NC	[NC]	NC
1	176	8 (4,5)	NE [NE; NE]	175	0	NE [NE; NE]	NC	[NC]	NC
Interaktion p-Wert									NC
Raucherstatus									
Ja	90	1 (1,1)	NE [NE; NE]	96	0	NE [NE; NE]	NC	[NC]	NC
Nein	186	10 (5,4)	NE [NE; NE]	179	0	NE [NE; NE]	NC	[NC]	NC
Interaktion p-Wert									NC
Geschlecht									
Maennlich	104	5 (4,8)	NE [NE; NE]	107	0	NE [NE; NE]	NC	[NC]	NC
Weiblich	172	6 (3,5)	NE [NE; NE]	168	0	NE [NE; NE]	NC	[NC]	NC
Interaktion p-Wert									NC
Nachweis der EGFR-Mutation durch zentralen ctDNA Cobas Test									
positiv	211	10 (4,7)	NE [NE; NE]	204	0	NE [NE; NE]	NC	[NC]	NC

Time to event of AE is defined as the time from first dose of study treatment to first onset of the respective AE or the time to censoring if the AE has not occurred by 28 days following discontinuation of study treatment, before administration of subsequent cancer therapy or death, whichever comes first. All AEs are coded using MedDRA version 25.1. Includes AEs with onset date on or after the date of first dose and up to and including 28 days following discontinuation of study treatment. Analysis done if >=10 patients at each subgroup level and >=10 events in at least one subgroup level combined for both arms. Analysis done for SOC and PT only if main effect for that SOC or PT is statistically significant at 5% level. [a] Median time to event based on the Kaplan Meier estimate. NE = Not estimable as median (or 95% CLs) is not reached. [b] Estimated from main effects of unstratified Cox proportional hazard model including trt., subgroup and subgroup-by-trt. interaction. Ties handled using Efron method and 95% CI derived from profile likelihood estimation. NC = Not calculable. HR <1 favours Osimertinib+Chemo. * p<0.05.
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Table 4.3.1.18 FLAURA-2: Summary of subgroup analysis of time to first PT: Febrile Neutropenie
Safety Analysis Set, DCO 03APR2023

	Osi + Chemo (N=276)			Osi (N=275)					
Subgruppen	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]	Hazard Ratio [b]	[95%-KI] [b]	2-seitiger p-Wert [b]
negativ	41	1 (2,4)	NE [NE; NE]	39	0	NE [NE; NE]	NC	[NC]	NC
unbekannt	24	0	NE [NE; NE]	32	0	NE [NE; NE]	NC	[NC]	NC
Interaktion p-Wert									NC
EGFR-Mutationstyp									
Exon 19 Deletion	172	7 (4,1)	NE [NE; NE]	167	0	NE [NE; NE]	NC	[NC]	NC
Exon 21 (L858R) Substitutionsmutation	104	4 (3,8)	NE [NE; NE]	106	0	NE [NE; NE]	NC	[NC]	NC
Interaktion p-Wert									NC
Zentral bestätigte EGFR-Mutation im Gewebe									
positiv	248	10 (4,0)	NE [NE; NE]	238	0	NE [NE; NE]	NC	[NC]	NC
negativ	3	0	NE [NE; NE]	4	0	NE [NE; NE]	NC	[NC]	NC
unbekannt	25	1 (4,0)	NE [NE; NE]	33	0	NE [NE; NE]	NC	[NC]	NC
Interaktion p-Wert									NC
ZNS-Metastasen zur Baseline									
Ja	113	4 (3,5)	NE [NE; NE]	110	0	NE [NE; NE]	NC	[NC]	NC
Nein	163	7 (4,3)	NE [NE; NE]	165	0	NE [NE; NE]	NC	[NC]	NC
Interaktion p-Wert									NC
Zentrale Bestätigung der EGFR-Mutation									
Zentral bestätigte EGFR-Mutation in Gewebe oder ctDNA	263	11 (4,2)	NE [NE; NE]	266	0	NE [NE; NE]	NC	[NC]	NC
Keine zentrale Bestätigung	13	0	NE [NE; NE]	9	0	NE [NE; NE]	NC	[NC]	NC
Interaktion p-Wert									NC
Alter bei Screening									

Time to event of AE is defined as the time from first dose of study treatment to first onset of the respective AE or the time to censoring if the AE has not occurred by 28 days following discontinuation of study treatment, before administration of subsequent cancer therapy or death, whichever comes first. All AEs are coded using MedDRA version 25.1. Includes AEs with onset date on or after the date of first dose and up to and including 28 days following discontinuation of study treatment. Analysis done if >=10 patients at each subgroup level and >=10 events in at least one subgroup level combined for both arms. Analysis done for SOC and PT only if main effect for that SOC or PT is statistically significant at 5% level. [a] Median time to event based on the Kaplan Meier estimate. NE = Not estimable as median (or 95% CLs) is not reached. [b] Estimated from main effects of unstratified Cox proportional hazard model including trt., subgroup and subgroup-by-trt. interaction. Ties handled using Efron method and 95% CI derived from profile likelihood estimation. NC = Not calculable. HR <1 favours Osimertinib+Chemo. * p<0.05.
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Table 4.3.1.18 FLAURA-2: Summary of subgroup analysis of time to first PT: Febrile Neutropenie
Safety Analysis Set, DCO 03APR2023

	Osi + Chemo (N=276)			Osi (N=275)					
Subgruppen	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]	Hazard Ratio [b]	[95%-KI] [b]	2-seitiger p-Wert [b]
<65 Jahre	172	8 (4,7)	NE [NE; NE]	164	0	NE [NE; NE]	NC	[NC]	NC
>=65 Jahre	104	3 (2,9)	NE [NE; NE]	111	0	NE [NE; NE]	NC	[NC]	NC
Interaktion p-Wert									NC
Region gPAP									
Asien	168	10 (6,0)	NE [NE; NE]	166	0	NE [NE; NE]	NC	[NC]	NC
Europa	22	1 (4,5)	NE [NE; NE]	23	0	NE [NE; NE]	NC	[NC]	NC
Nordamerika	20	0	NE [NE; NE]	22	0	NE [NE; NE]	NC	[NC]	NC
Rest der Welt	66	0	NE [NE; NE]	64	0	NE [NE; NE]	NC	[NC]	NC
Interaktion p-Wert									NC

Time to event of AE is defined as the time from first dose of study treatment to first onset of the respective AE or the time to censoring if the AE has not occurred by 28 days following discontinuation of study treatment, before administration of subsequent cancer therapy or death, whichever comes first. All AEs are coded using MedDRA version 25.1. Includes AEs with onset date on or after the date of first dose and up to and including 28 days following discontinuation of study treatment. Analysis done if >=10 patients at each subgroup level and >=10 events in at least one subgroup level combined for both arms. Analysis done for SOC and PT only if main effect for that SOC or PT is statistically significant at 5% level. [a] Median time to event based on the Kaplan Meier estimate. NE = Not estimable as median (or 95% CLs) is not reached. [b] Estimated from main effects of unstratified Cox proportional hazard model including trt., subgroup and subgroup-by-trt. interaction. Ties handled using Efron method and 95% CI derived from profile likelihood estimation. NC = Not calculable. HR <1 favours Osimertinib+Chemo. * p<0.05.
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Table 4.3.1.19 FLAURA-2: Summary of subgroup analysis of time to first PT: Leukopenie
Safety Analysis Set, DCO 03APR2023

	Osi + Chemo (N=276)			Osi (N=275)					
Subgruppen	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]	Hazard Ratio [b]	[95%-KI] [b]	2-seitiger p-Wert [b]
Abstammung									
Chinesisch/Asiatisch	68	16 (23,5)	NE [NE; NE]	70	7 (10,0)	NE [NE; NE]	2,50	[1,07; 6,50]	0,0346*
Nicht-chinesisch/ Asiatisch	107	7 (6,5)	NE [NE; NE]	106	1 (0,9)	NE [NE; NE]	7,34	[1,31;137,20]	0,0207*
Nicht-asiatisch	101	12 (11,9)	NE [NE; NE]	99	3 (3,0)	NE [NE; NE]	4,23	[1,34; 18,58]	0,0120*
Interaktion p-Wert									0,5522
Methode zur Gewebeuntersuchung									
zentral	120	25 (20,8)	NE [NE; NE]	119	9 (7,6)	NE [NE; NE]	3,04	[1,47; 6,90]	0,0022*
lokal	156	10 (6,4)	NE [NE; NE]	156	2 (1,3)	NE [NE; NE]	5,20	[1,37; 33,80]	0,0133*
Interaktion p-Wert									0,5235
WHO Performance-Status									
0	100	11 (11,0)	NE [NE; NE]	100	5 (5,0)	NE [NE; NE]	2,34	[0,85; 7,42]	0,1012
1	176	24 (13,6)	NE [NE; NE]	175	6 (3,4)	NE [NE; NE]	4,25	[1,85; 11,47]	0,0004*
Interaktion p-Wert									0,4003
Raucherstatus									
Ja	90	10 (11,1)	NE [NE; NE]	96	3 (3,1)	NE [NE; NE]	3,64	[1,11; 16,23]	0,0317*
Nein	186	25 (13,4)	NE [NE; NE]	179	8 (4,5)	NE [NE; NE]	3,28	[1,54; 7,76]	0,0016*
Interaktion p-Wert									0,8914
Geschlecht									
Maennlich	104	14 (13,5)	NE [NE; NE]	107	2 (1,9)	NE [NE; NE]	7,33	[2,05; 46,65]	0,0011*
Weiblich	172	21 (12,2)	NE [NE; NE]	168	9 (5,4)	NE [NE; NE]	2,50	[1,18; 5,76]	0,0159*
Interaktion p-Wert									0,1786
Nachweis der EGFR-Mutation durch zentralen ctDNA Cobas Test									
positiv	211	30 (14,2)	NE [NE; NE]	204	8 (3,9)	NE [NE; NE]	3,93	[1,89; 9,21]	0,0001*

Time to event of AE is defined as the time from first dose of study treatment to first onset of the respective AE or the time to censoring if the AE has not occurred by 28 days following discontinuation of study treatment, before administration of subsequent cancer therapy or death, whichever comes first. All AEs are coded using MedDRA version 25.1. Includes AEs with onset date on or after the date of first dose and up to and including 28 days following discontinuation of study treatment. Analysis done if >=10 patients at each subgroup level and >=10 events in at least one subgroup level combined for both arms. Analysis done for SOC and PT only if main effect for that SOC or PT is statistically significant at 5% level. [a] Median time to event based on the Kaplan Meier estimate. NE = Not estimable as median (or 95% CLs) is not reached. [b] Estimated from main effects of unstratified Cox proportional hazard model including trt., subgroup and subgroup-by-trt. interaction. Ties handled using Efron method and 95% CI derived from profile likelihood estimation. NC = Not calculable. HR <1 favours Osimertinib+Chemo. * p<0.05.
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Table 4.3.1.19 FLAURA-2: Summary of subgroup analysis of time to first PT: Leukopenie
Safety Analysis Set, DCO 03APR2023

	Osi + Chemo (N=276)			Osi (N=275)					
Subgruppen	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]	Hazard Ratio [b]	[95%-KI] [b]	2-seitiger p-Wert [b]
negativ	41	4 (9,8)	NE [NE; NE]	39	2 (5,1)	NE [NE; NE]	2,02	[0,40; 14,60]	0,4016
unbekannt	24	1 (4,2)	NE [NE; NE]	32	1 (3,1)	NE [NE; NE]	1,25	[0,05; 31,70]	0,8727
Interaktion p-Wert									0,6223
EGFR-Mutationstyp									
Exon 19 Deletion	172	20 (11,6)	NE [NE; NE]	167	7 (4,2)	NE [NE; NE]	2,99	[1,32; 7,63]	0,0075*
Exon 21 (L858R) Substitutionsmutation	104	15 (14,4)	NE [NE; NE]	106	4 (3,8)	NE [NE; NE]	4,01	[1,45; 14,06]	0,0061*
Interaktion p-Wert									0,6803
Zentral bestätigte EGFR-Mutation im Gewebe									
positiv	248	35 (14,1)	NE [NE; NE]	238	9 (3,8)	NE [NE; NE]	4,04	[2,03; 8,94]	<0,0001*
negativ	3	0	NE [NE; NE]	4	0	NE [NE; NE]	NC	[NC]	NC
unbekannt	25	0	NE [NE; NE]	33	2 (6,1)	NE [NE; NE]	NC	[NC]	NC
Interaktion p-Wert									NC
ZNS-Metastasen zur Baseline									
Ja	113	17 (15,0)	NE [NE; NE]	110	4 (3,6)	NE [NE; NE]	4,44	[1,64; 15,42]	0,0024*
Nein	163	18 (11,0)	NE [NE; NE]	165	7 (4,2)	NE [NE; NE]	2,77	[1,20; 7,11]	0,0157*
Interaktion p-Wert									0,5024
Zentrale Bestätigung der EGFR-Mutation									
Zentral bestätigte EGFR-Mutation in Gewebe oder ctDNA	263	35 (13,3)	NE [NE; NE]	266	11 (4,1)	NE [NE; NE]	3,46	[1,81; 7,14]	<0,0001*
Keine zentrale Bestätigung	13	0	NE [NE; NE]	9	0	NE [NE; NE]	NC	[NC]	NC
Interaktion p-Wert									NC
Alter bei Screening									

Time to event of AE is defined as the time from first dose of study treatment to first onset of the respective AE or the time to censoring if the AE has not occurred by 28 days following discontinuation of study treatment, before administration of subsequent cancer therapy or death, whichever comes first. All AEs are coded using MedDRA version 25.1. Includes AEs with onset date on or after the date of first dose and up to and including 28 days following discontinuation of study treatment. Analysis done if >=10 patients at each subgroup level and >=10 events in at least one subgroup level combined for both arms. Analysis done for SOC and PT only if main effect for that SOC or PT is statistically significant at 5% level. [a] Median time to event based on the Kaplan Meier estimate. NE = Not estimable as median (or 95% CLs) is not reached. [b] Estimated from main effects of unstratified Cox proportional hazard model including trt., subgroup and subgroup-by-trt. interaction. Ties handled using Efron method and 95% CI derived from profile likelihood estimation. NC = Not calculable. HR <1 favours Osimertinib+Chemo. * p<0.05.
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Table 4.3.1.19 FLAURA-2: Summary of subgroup analysis of time to first PT: Leukopenie
Safety Analysis Set, DCO 03APR2023

	Osi + Chemo (N=276)			Osi (N=275)					
Subgruppen	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]	Hazard Ratio [b]	[95%-KI] [b]	2-seitiger p-Wert [b]
<65 Jahre	172	23 (13,4)	NE [NE; NE]	164	6 (3,7)	NE [NE; NE]	3,86	[1,67; 10,45]	0,0010*
>=65 Jahre	104	12 (11,5)	NE [NE; NE]	111	5 (4,5)	NE [NE; NE]	2,79	[1,03; 8,75]	0,0428*
Interaktion p-Wert									0,6433
Region gPAP									
Asien	168	24 (14,3)	NE [NE; NE]	166	8 (4,8)	NE [NE; NE]	3,14	[1,47; 7,47]	0,0025*
Europa	22	3 (13,6)	NE [NE; NE]	23	0	NE [NE; NE]	NC	[NC]	NC
Nordamerika	20	2 (10,0)	NE [NE; NE]	22	1 (4,5)	NE [NE; NE]	2,31	[0,22; 49,66]	0,4799
Rest der Welt	66	6 (9,1)	NE [NE; NE]	64	2 (3,1)	NE [NE; NE]	3,17	[0,73; 21,63]	0,1278
Interaktion p-Wert									0,9719

Time to event of AE is defined as the time from first dose of study treatment to first onset of the respective AE or the time to censoring if the AE has not occurred by 28 days following discontinuation of study treatment, before administration of subsequent cancer therapy or death, whichever comes first. All AEs are coded using MedDRA version 25.1. Includes AEs with onset date on or after the date of first dose and up to and including 28 days following discontinuation of study treatment. Analysis done if >=10 patients at each subgroup level and >=10 events in at least one subgroup level combined for both arms. Analysis done for SOC and PT only if main effect for that SOC or PT is statistically significant at 5% level. [a] Median time to event based on the Kaplan Meier estimate. NE = Not estimable as median (or 95% CLs) is not reached. [b] Estimated from main effects of unstratified Cox proportional hazard model including trt., subgroup and subgroup-by-trt. interaction. Ties handled using Efron method and 95% CI derived from profile likelihood estimation. NC = Not calculable. HR <1 favours Osimertinib+Chemo. * p<0.05.
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Table 4.3.1.20 FLAURA-2: Summary of subgroup analysis of time to first PT: Neutropenie
Safety Analysis Set, DCO 03APR2023

	Osi + Chemo (N=276)			Osi (N=275)					
Subgruppen	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]	Hazard Ratio [b]	[95%-KI] [b]	2-seitiger p-Wert [b]
Abstammung									
Chinesisch/Asiatisch	68	19 (27,9)	NE [NE; NE]	70	1 (1,4)	NE [NE; NE]	21,52	[4,47;386,46]	<0,0001*
Nicht-chinesisch/ Asiatisch	107	14 (13,1)	NE [NE; NE]	106	2 (1,9)	NE [NE; NE]	7,53	[2,10; 47,95]	0,0009*
Nicht-asiatisch	101	35 (34,7)	NE [NE; NE]	99	6 (6,1)	NE [NE; NE]	7,04	[3,19; 18,61]	<0,0001*
Interaktion p-Wert									0,5258
Methode zur Gewebeuntersuchung									
zentral	120	38 (31,7)	NE [NE; NE]	119	4 (3,4)	NE [NE; NE]	10,97	[4,41; 36,59]	<0,0001*
lokal	156	30 (19,2)	NE [NE; NE]	156	5 (3,2)	NE [NE; NE]	6,71	[2,84; 19,67]	<0,0001*
Interaktion p-Wert									0,4889
WHO Performance-Status									
0	100	22 (22,0)	NE [NE; NE]	100	5 (5,0)	NE [NE; NE]	4,81	[1,97; 14,38]	0,0003*
1	176	46 (26,1)	NE [NE; NE]	175	4 (2,3)	NE [NE; NE]	13,30	[5,41; 44,13]	<0,0001*
Interaktion p-Wert									0,1571
Raucherstatus									
Ja	90	21 (23,3)	NE [NE; NE]	96	4 (4,2)	NE [NE; NE]	6,20	[2,36; 21,25]	<0,0001*
Nein	186	47 (25,3)	NE [NE; NE]	179	5 (2,8)	NE [NE; NE]	10,43	[4,57; 30,06]	<0,0001*
Interaktion p-Wert									0,4748
Geschlecht									
Maennlich	104	23 (22,1)	NE [NE; NE]	107	2 (1,9)	NE [NE; NE]	12,87	[3,81; 80,20]	<0,0001*
Weiblich	172	45 (26,2)	NE [NE; NE]	168	7 (4,2)	NE [NE; NE]	7,34	[3,53; 17,82]	<0,0001*
Interaktion p-Wert									0,4875
Nachweis der EGFR-Mutation durch zentralen ctDNA Cobas Test									
positiv	211	52 (24,6)	NE [NE; NE]	204	7 (3,4)	NE [NE; NE]	8,19	[3,98; 19,79]	<0,0001*

Time to event of AE is defined as the time from first dose of study treatment to first onset of the respective AE or the time to censoring if the AE has not occurred by 28 days following discontinuation of study treatment, before administration of subsequent cancer therapy or death, whichever comes first. All AEs are coded using MedDRA version 25.1. Includes AEs with onset date on or after the date of first dose and up to and including 28 days following discontinuation of study treatment. Analysis done if >=10 patients at each subgroup level and >=10 events in at least one subgroup level combined for both arms. Analysis done for SOC and PT only if main effect for that SOC or PT is statistically significant at 5% level. [a] Median time to event based on the Kaplan Meier estimate. NE = Not estimable as median (or 95% CLs) is not reached. [b] Estimated from main effects of unstratified Cox proportional hazard model including trt., subgroup and subgroup-by-trt. interaction. Ties handled using Efron method and 95% CI derived from profile likelihood estimation. NC = Not calculable. HR <1 favours Osimertinib+Chemo. * p<0.05.
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Table 4.3.1.20 FLAURA-2: Summary of subgroup analysis of time to first PT: Neutropenie
Safety Analysis Set, DCO 03APR2023

	Osi + Chemo (N=276)			Osi (N=275)					
Subgruppen	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]	Hazard Ratio [b]	[95%-KI] [b]	2-seitiger p-Wert [b]
negativ	41	11 (26,8)	NE [NE; NE]	39	1 (2,6)	NE [NE; NE]	12,09	[2,35;220,96]	0,0011*
unbekannt	24	5 (20,8)	NE [NE; NE]	32	1 (3,1)	NE [NE; NE]	7,22	[1,16;138,27]	0,0323*
Interaktion p-Wert									0,9253
EGFR-Mutationstyp									
Exon 19 Deletion	172	44 (25,6)	NE [NE; NE]	167	7 (4,2)	NE [NE; NE]	6,98	[3,36; 16,97]	<0,0001*
Exon 21 (L858R) Substitutionsmutation	104	24 (23,1)	NE [NE; NE]	106	2 (1,9)	NE [NE; NE]	13,78	[4,09; 85,77]	<0,0001*
Interaktion p-Wert									0,3966
Zentral bestätigte EGFR-Mutation im Gewebe									
positiv	248	63 (25,4)	NE [NE; NE]	238	8 (3,4)	NE [NE; NE]	8,61	[4,38; 19,47]	<0,0001*
negativ	3	0	NE [NE; NE]	4	0	NE [NE; NE]	NC	[NC]	NC
unbekannt	25	5 (20,0)	NE [NE; NE]	33	1 (3,0)	NE [NE; NE]	7,77	[1,25;148,74]	0,0259*
Interaktion p-Wert									0,9300
ZNS-Metastasen zur Baseline									
Ja	113	24 (21,2)	NE [NE; NE]	110	5 (4,5)	NE [NE; NE]	5,07	[2,10; 15,07]	0,0001*
Nein	163	44 (27,0)	NE [NE; NE]	165	4 (2,4)	NE [NE; NE]	13,06	[5,30; 43,38]	<0,0001*
Interaktion p-Wert									0,1866
Zentrale Bestätigung der EGFR-Mutation									
Zentral bestätigte EGFR-Mutation in Gewebe oder ctDNA	263	66 (25,1)	NE [NE; NE]	266	9 (3,4)	NE [NE; NE]	8,48	[4,46; 18,26]	<0,0001*
Keine zentrale Bestätigung	13	2 (15,4)	NE [NE; NE]	9	0	NE [NE; NE]	NC	[NC]	NC
Interaktion p-Wert									NC
Alter bei Screening									

Time to event of AE is defined as the time from first dose of study treatment to first onset of the respective AE or the time to censoring if the AE has not occurred by 28 days following discontinuation of study treatment, before administration of subsequent cancer therapy or death, whichever comes first. All AEs are coded using MedDRA version 25.1. Includes AEs with onset date on or after the date of first dose and up to and including 28 days following discontinuation of study treatment. Analysis done if >=10 patients at each subgroup level and >=10 events in at least one subgroup level combined for both arms. Analysis done for SOC and PT only if main effect for that SOC or PT is statistically significant at 5% level. [a] Median time to event based on the Kaplan Meier estimate. NE = Not estimable as median (or 95% CLs) is not reached. [b] Estimated from main effects of unstratified Cox proportional hazard model including trt., subgroup and subgroup-by-trt. interaction. Ties handled using Efron method and 95% CI derived from profile likelihood estimation. NC = Not calculable. HR <1 favours Osimertinib+Chemo. * p<0.05.
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Table 4.3.1.20 FLAURA-2: Summary of subgroup analysis of time to first PT: Neutropenie
Safety Analysis Set, DCO 03APR2023

	Osi + Chemo (N=276)			Osi (N=275)					
Subgruppen	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]	Hazard Ratio [b]	[95%-KI] [b]	2-seitiger p-Wert [b]
<65 Jahre	172	46 (26,7)	NE [NE; NE]	164	5 (3,0)	NE [NE; NE]	9,89	[4,33; 28,53]	<0,0001*
>=65 Jahre	104	22 (21,2)	NE [NE; NE]	111	4 (3,6)	NE [NE; NE]	6,78	[2,60; 23,19]	<0,0001*
Interaktion p-Wert									0,6024
Region gPAP									
Asien	168	32 (19,0)	NE [NE; NE]	166	2 (1,2)	NE [NE; NE]	17,31	[5,25;106,79]	<0,0001*
Europa	22	9 (40,9)	NE [NE; NE]	23	1 (4,3)	NE [NE; NE]	12,69	[2,38;234,04]	0,0013*
Nordamerika	20	3 (15,0)	NE [NE; NE]	22	2 (9,1)	NE [NE; NE]	1,77	[0,29; 13,48]	0,5246
Rest der Welt	66	24 (36,4)	NE [NE; NE]	64	4 (6,3)	NE [NE; NE]	7,13	[2,75; 24,27]	<0,0001*
Interaktion p-Wert									0,2736

Time to event of AE is defined as the time from first dose of study treatment to first onset of the respective AE or the time to censoring if the AE has not occurred by 28 days following discontinuation of study treatment, before administration of subsequent cancer therapy or death, whichever comes first. All AEs are coded using MedDRA version 25.1. Includes AEs with onset date on or after the date of first dose and up to and including 28 days following discontinuation of study treatment. Analysis done if >=10 patients at each subgroup level and >=10 events in at least one subgroup level combined for both arms. Analysis done for SOC and PT only if main effect for that SOC or PT is statistically significant at 5% level. [a] Median time to event based on the Kaplan Meier estimate. NE = Not estimable as median (or 95% CLs) is not reached. [b] Estimated from main effects of unstratified Cox proportional hazard model including trt., subgroup and subgroup-by-trt. interaction. Ties handled using Efron method and 95% CI derived from profile likelihood estimation. NC = Not calculable. HR <1 favours Osimertinib+Chemo. * p<0.05.
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Table 4.3.1.21 FLAURA-2: Summary of subgroup analysis of time to first PT: Thrombozytopenie
Safety Analysis Set, DCO 03APR2023

	Osi + Chemo (N=276)			Osi (N=275)					
Subgruppen	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]	Hazard Ratio [b]	[95%-KI] [b]	2-seitiger p-Wert [b]
Abstammung									
Chinesisch/Asiatisch	68	17 (25,0)	NE [NE; NE]	70	7 (10,0)	NE [NE; NE]	2,54	[1,10; 6,56]	0,0293*
Nicht-chinesisch/ Asiatisch	107	13 (12,1)	NE [NE; NE]	106	1 (0,9)	NE [NE; NE]	13,72	[2,73;249,13]	0,0003*
Nicht-asiatisch	101	21 (20,8)	NE [NE; NE]	99	4 (4,0)	NE [NE; NE]	5,84	[2,22; 20,04]	0,0001*
Interaktion p-Wert									0,1896
Methode zur Gewebeuntersuchung									
zentral	120	28 (23,3)	NE [NE; NE]	119	8 (6,7)	NE [NE; NE]	3,76	[1,80; 8,85]	0,0003*
lokal	156	23 (14,7)	NE [NE; NE]	156	4 (2,6)	NE [NE; NE]	6,16	[2,37; 21,01]	<0,0001*
Interaktion p-Wert									0,4578
WHO Performance-Status									
0	100	14 (14,0)	NE [NE; NE]	100	1 (1,0)	NE [NE; NE]	14,92	[3,00;270,31]	0,0002*
1	176	37 (21,0)	NE [NE; NE]	175	11 (6,3)	NE [NE; NE]	3,62	[1,91; 7,46]	<0,0001*
Interaktion p-Wert									0,1302
Raucherstatus									
Ja	90	10 (11,1)	NE [NE; NE]	96	5 (5,2)	NE [NE; NE]	2,17	[0,77; 6,95]	0,1452
Nein	186	41 (22,0)	NE [NE; NE]	179	7 (3,9)	NE [NE; NE]	6,25	[2,99; 15,25]	<0,0001*
Interaktion p-Wert									0,1282
Geschlecht									
Maennlich	104	18 (17,3)	NE [NE; NE]	107	6 (5,6)	NE [NE; NE]	3,15	[1,32; 8,70]	0,0086*
Weiblich	172	33 (19,2)	NE [NE; NE]	168	6 (3,6)	NE [NE; NE]	5,97	[2,69; 15,84]	<0,0001*
Interaktion p-Wert									0,3253
Nachweis der EGFR-Mutation durch zentralen ctDNA Cobas Test									
positiv	211	41 (19,4)	NE [NE; NE]	204	8 (3,9)	NE [NE; NE]	5,42	[2,68; 12,47]	<0,0001*

Time to event of AE is defined as the time from first dose of study treatment to first onset of the respective AE or the time to censoring if the AE has not occurred by 28 days following discontinuation of study treatment, before administration of subsequent cancer therapy or death, whichever comes first. All AEs are coded using MedDRA version 25.1. Includes AEs with onset date on or after the date of first dose and up to and including 28 days following discontinuation of study treatment. Analysis done if >=10 patients at each subgroup level and >=10 events in at least one subgroup level combined for both arms. Analysis done for SOC and PT only if main effect for that SOC or PT is statistically significant at 5% level. [a] Median time to event based on the Kaplan Meier estimate. NE = Not estimable as median (or 95% CLs) is not reached. [b] Estimated from main effects of unstratified Cox proportional hazard model including trt., subgroup and subgroup-by-trt. interaction. Ties handled using Efron method and 95% CI derived from profile likelihood estimation. NC = Not calculable. HR <1 favours Osimertinib+Chemo. * p<0.05.
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Table 4.3.1.21 FLAURA-2: Summary of subgroup analysis of time to first PT: Thrombozytopenie
Safety Analysis Set, DCO 03APR2023

	Osi + Chemo (N=276)			Osi (N=275)					
Subgruppen	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]	Hazard Ratio [b]	[95%-KI] [b]	2-seitiger p-Wert [b]
negativ	41	8 (19,5)	NE [NE; NE]	39	3 (7,7)	NE [NE; NE]	2,60	[0,75; 11,87]	0,1351
unbekannt	24	2 (8,3)	NE [NE; NE]	32	1 (3,1)	NE [NE; NE]	2,72	[0,26; 58,58]	0,3961
Interaktion p-Wert									0,6069
EGFR-Mutationstyp									
Exon 19 Deletion	172	32 (18,6)	NE [NE; NE]	167	6 (3,6)	NE [NE; NE]	5,68	[2,56; 15,09]	<0,0001*
Exon 21 (L858R) Substitutionsmutation	104	19 (18,3)	NE [NE; NE]	106	6 (5,7)	NE [NE; NE]	3,37	[1,42; 9,24]	0,0049*
Interaktion p-Wert									0,4180
Zentral bestätigte EGFR-Mutation im Gewebe									
positiv	248	48 (19,4)	NE [NE; NE]	238	11 (4,6)	NE [NE; NE]	4,52	[2,44; 9,17]	<0,0001*
negativ	3	0	NE [NE; NE]	4	0	NE [NE; NE]	NC	[NC]	NC
unbekannt	25	3 (12,0)	NE [NE; NE]	33	1 (3,0)	NE [NE; NE]	4,26	[0,55; 86,17]	0,1711
Interaktion p-Wert									0,9612
ZNS-Metastasen zur Baseline									
Ja	113	18 (15,9)	NE [NE; NE]	110	5 (4,5)	NE [NE; NE]	3,70	[1,48; 11,22]	0,0043*
Nein	163	33 (20,2)	NE [NE; NE]	165	7 (4,2)	NE [NE; NE]	5,20	[2,44; 12,82]	<0,0001*
Interaktion p-Wert									0,6062
Zentrale Bestätigung der EGFR-Mutation									
Zentral bestätigte EGFR-Mutation in Gewebe oder ctDNA	263	49 (18,6)	NE [NE; NE]	266	12 (4,5)	NE [NE; NE]	4,45	[2,45; 8,77]	<0,0001*
Keine zentrale Bestätigung	13	2 (15,4)	NE [NE; NE]	9	0	NE [NE; NE]	NC	[NC]	NC
Interaktion p-Wert									NC
Alter bei Screening									

Time to event of AE is defined as the time from first dose of study treatment to first onset of the respective AE or the time to censoring if the AE has not occurred by 28 days following discontinuation of study treatment, before administration of subsequent cancer therapy or death, whichever comes first. All AEs are coded using MedDRA version 25.1. Includes AEs with onset date on or after the date of first dose and up to and including 28 days following discontinuation of study treatment. Analysis done if >=10 patients at each subgroup level and >=10 events in at least one subgroup level combined for both arms. Analysis done for SOC and PT only if main effect for that SOC or PT is statistically significant at 5% level. [a] Median time to event based on the Kaplan Meier estimate. NE = Not estimable as median (or 95% CLs) is not reached. [b] Estimated from main effects of unstratified Cox proportional hazard model including trt., subgroup and subgroup-by-trt. interaction. Ties handled using Efron method and 95% CI derived from profile likelihood estimation. NC = Not calculable. HR <1 favours Osimertinib+Chemo. * p<0.05.
root/cdar/d516/payer_germany/ar/d5169c00001_payer_germany/tlf/prod/program/ttesubae.sas gttesubaeaau 22DEC2023:09:13 kfrh585

Table 4.3.1.21 FLAURA-2: Summary of subgroup analysis of time to first PT: Thrombozytopenie
Safety Analysis Set, DCO 03APR2023

	Osi + Chemo (N=276)			Osi (N=275)					
Subgruppen	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]	Hazard Ratio [b]	[95%-KI] [b]	2-seitiger p-Wert [b]
<65 Jahre	172	29 (16,9)	NE [NE; NE]	164	7 (4,3)	NE [NE; NE]	4,13	[1,91; 10,24]	0,0002*
>=65 Jahre	104	22 (21,2)	NE [NE; NE]	111	5 (4,5)	NE [NE; NE]	5,33	[2,19; 15,92]	0,0001*
Interaktion p-Wert									0,6926
Region gPAP									
Asien	168	30 (17,9)	NE [NE; NE]	166	8 (4,8)	NE [NE; NE]	3,88	[1,87; 9,08]	0,0002*
Europa	22	10 (45,5)	NE [NE; NE]	23	2 (8,7)	NE [NE; NE]	6,76	[1,78; 44,01]	0,0035*
Nordamerika	20	2 (10,0)	NE [NE; NE]	22	0	NE [NE; NE]	NC	[NC]	NC
Rest der Welt	66	9 (13,6)	NE [NE; NE]	64	2 (3,1)	NE [NE; NE]	4,78	[1,23; 31,36]	0,0219*
Interaktion p-Wert									0,8015

Time to event of AE is defined as the time from first dose of study treatment to first onset of the respective AE or the time to censoring if the AE has not occurred by 28 days following discontinuation of study treatment, before administration of subsequent cancer therapy or death, whichever comes first. All AEs are coded using MedDRA version 25.1. Includes AEs with onset date on or after the date of first dose and up to and including 28 days following discontinuation of study treatment. Analysis done if >=10 patients at each subgroup level and >=10 events in at least one subgroup level combined for both arms. Analysis done for SOC and PT only if main effect for that SOC or PT is statistically significant at 5% level. [a] Median time to event based on the Kaplan Meier estimate. NE = Not estimable as median (or 95% CLs) is not reached. [b] Estimated from main effects of unstratified Cox proportional hazard model including trt., subgroup and subgroup-by-trt. interaction. Ties handled using Efron method and 95% CI derived from profile likelihood estimation. NC = Not calculable. HR <1 favours Osimertinib+Chemo. * p<0.05.
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Table 4.3.1.22 FLAURA-2: Summary of subgroup analysis of time to first SOC: Erkrankungen des Gastrointestinaltrakts
Safety Analysis Set, DCO 03APR2023

	Osi + Chemo (N=276)			Osi (N=275)					
Subgruppen	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]	Hazard Ratio [b]	[95%-KI] [b]	2-seitiger p-Wert [b]
Abstammung									
Chinesisch/Asiatisch	68	52 (76,5)	0,3 [0,2; 0,8]	70	40 (57,1)	4,1 [0,9; NE]	1,96	[1,30; 2,98]	0,0013*
Nicht-chinesisch/ Asiatisch	107	93 (86,9)	0,3 [0,1; 0,4]	106	72 (67,9)	1,4 [0,9; 2,6]	2,01	[1,48; 2,75]	<0,0001*
Nicht-asiatisch	101	81 (80,2)	0,3 [0,2; 1,1]	99	59 (59,6)	6,0 [1,9;13,8]	2,19	[1,56; 3,07]	<0,0001*
Interaktion p-Wert									0,9062
Methode zur Gewebeuntersuchung									
zentral	120	82 (68,3)	1,0 [0,4; 2,0]	119	61 (51,3)	13,8 [3,4; NE]	1,86	[1,34; 2,60]	0,0002*
lokal	156	144 (92,3)	0,2 [0,1; 0,3]	156	110 (70,5)	1,4 [1,0; 2,1]	2,37	[1,85; 3,05]	<0,0001*
Interaktion p-Wert									0,2521
WHO Performance-Status									
0	100	84 (84,0)	0,3 [0,1; 0,4]	100	65 (65,0)	1,4 [1,0; 8,3]	1,98	[1,44; 2,75]	<0,0001*
1	176	142 (80,7)	0,3 [0,2; 0,5]	175	106 (60,6)	3,3 [1,6; 6,3]	2,10	[1,63; 2,71]	<0,0001*
Interaktion p-Wert									0,7893
Raucherstatus									
Ja	90	77 (85,6)	0,3 [0,1; 0,4]	96	63 (65,6)	1,8 [1,1; 4,1]	2,10	[1,51; 2,94]	<0,0001*
Nein	186	149 (80,1)	0,3 [0,2; 0,5]	179	108 (60,3)	3,4 [1,4; 8,4]	2,05	[1,60; 2,63]	<0,0001*
Interaktion p-Wert									0,9057
Geschlecht									
Maennlich	104	86 (82,7)	0,3 [0,2; 0,7]	107	66 (61,7)	3,4 [1,5; 9,4]	2,02	[1,47; 2,79]	<0,0001*
Weiblich	172	140 (81,4)	0,3 [0,2; 0,4]	168	105 (62,5)	1,9 [1,2; 5,4]	2,08	[1,61; 2,68]	<0,0001*
Interaktion p-Wert									0,8919
Nachweis der EGFR-Mutation durch zentralen ctDNA Cobas Test									
positiv	211	169 (80,1)	0,3 [0,2; 0,4]	204	127 (62,3)	2,5 [1,3; 6,0]	2,00	[1,59; 2,52]	<0,0001*

Time to event of AE is defined as the time from first dose of study treatment to first onset of the respective AE or the time to censoring if the AE has not occurred by 28 days following discontinuation of study treatment, before administration of subsequent cancer therapy or death, whichever comes first. All AEs are coded using MedDRA version 25.1. Includes AEs with onset date on or after the date of first dose and up to and including 28 days following discontinuation of study treatment. Analysis done if >=10 patients at each subgroup level and >=10 events in at least one subgroup level combined for both arms. Analysis done for SOC and PT only if main effect for that SOC or PT is statistically significant at 5% level. [a] Median time to event based on the Kaplan Meier estimate. NE = Not estimable as median (or 95% CLs) is not reached. [b] Estimated from main effects of unstratified Cox proportional hazard model including trt., subgroup and subgroup-by-trt. interaction. Ties handled using Efron method and 95% CI derived from profile likelihood estimation. NC = Not calculable. HR <1 favours Osimertinib+Chemo. * p<0.05.
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Table 4.3.1.22 FLAURA-2: Summary of subgroup analysis of time to first SOC: Erkrankungen des Gastrointestinaltrakts
Safety Analysis Set, DCO 03APR2023

	Osi + Chemo (N=276)			Osi (N=275)					
Subgruppen	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]	Hazard Ratio [b]	[95%-KI] [b]	2-seitiger p-Wert [b]
negativ	41	35 (85,4)	0,3 [0,1; 0,8]	39	26 (66,7)	1,5 [0,3; 8,4]	1,94	[1,17; 3,26]	0,0097*
unbekannt	24	22 (91,7)	0,5 [0,1; 1,1]	32	18 (56,3)	5,3 [1,4; NE]	2,73	[1,47; 5,16]	0,0017*
Interaktion p-Wert									0,6322
EGFR-Mutationstyp									
Exon 19 Deletion	172	133 (77,3)	0,3 [0,2; 0,5]	167	99 (59,3)	3,7 [1,4;13,6]	2,09	[1,61; 2,72]	<0,0001*
Exon 21 (L858R) Substitutionsmutation	104	93 (89,4)	0,3 [0,2; 0,6]	106	70 (66,0)	1,5 [1,3; 3,4]	2,03	[1,49; 2,78]	<0,0001*
Interaktion p-Wert									0,8797
Zentral bestätigte EGFR-Mutation im Gewebe									
positiv	248	199 (80,2)	0,3 [0,2; 0,4]	238	149 (62,6)	2,1 [1,4; 5,4]	1,95	[1,58; 2,42]	<0,0001*
negativ	3	3 (100)	0,2 [0,1; NE]	4	3 (75,0)	5,4 [0,1; NE]	NC	[NC]	NC
unbekannt	25	24 (96,0)	0,3 [0,1; 1,3]	33	19 (57,6)	3,9 [1,0; NE]	2,98	[1,63; 5,51]	0,0004*
Interaktion p-Wert									0,1936
ZNS-Metastasen zur Baseline									
Ja	113	90 (79,6)	0,3 [0,2; 0,8]	110	71 (64,5)	1,7 [1,0; 3,5]	1,73	[1,27; 2,37]	0,0005*
Nein	163	136 (83,4)	0,3 [0,2; 0,4]	165	100 (60,6)	3,7 [1,4;13,3]	2,31	[1,79; 3,01]	<0,0001*
Interaktion p-Wert									0,1610
Zentrale Bestätigung der EGFR-Mutation									
Zentral bestätigte EGFR-Mutation in Gewebe oder ctDNA	263	214 (81,4)	0,3 [0,2; 0,4]	266	166 (62,4)	2,1 [1,4; 4,1]	2,02	[1,64; 2,47]	<0,0001*
Keine zentrale Bestätigung	13	12 (92,3)	0,4 [0,1; 3,2]	9	5 (55,6)	21,6 [0,1; NE]	3,28	[1,22; 10,31]	0,0184*
Interaktion p-Wert									0,3567
Alter bei Screening									

Time to event of AE is defined as the time from first dose of study treatment to first onset of the respective AE or the time to censoring if the AE has not occurred by 28 days following discontinuation of study treatment, before administration of subsequent cancer therapy or death, whichever comes first. All AEs are coded using MedDRA version 25.1. Includes AEs with onset date on or after the date of first dose and up to and including 28 days following discontinuation of study treatment. Analysis done if >=10 patients at each subgroup level and >=10 events in at least one subgroup level combined for both arms. Analysis done for SOC and PT only if main effect for that SOC or PT is statistically significant at 5% level. [a] Median time to event based on the Kaplan Meier estimate. NE = Not estimable as median (or 95% CLs) is not reached. [b] Estimated from main effects of unstratified Cox proportional hazard model including trt., subgroup and subgroup-by-trt. interaction. Ties handled using Efron method and 95% CI derived from profile likelihood estimation. NC = Not calculable. HR <1 favours Osimertinib+Chemo. * p<0.05.
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Table 4.3.1.22 FLAURA-2: Summary of subgroup analysis of time to first SOC: Erkrankungen des Gastrointestinaltrakts
Safety Analysis Set, DCO 03APR2023

	Osi + Chemo (N=276)			Osi (N=275)					
Subgruppen	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]	Hazard Ratio [b]	[95%-KI] [b]	2-seitiger p-Wert [b]
<65 Jahre	172	145 (84,3)	0,3 [0,2; 0,4]	164	101 (61,6)	2,5 [1,4; 5,3]	2,15	[1,67; 2,78]	<0,0001*
>=65 Jahre	104	81 (77,9)	0,3 [0,2; 0,7]	111	70 (63,1)	2,6 [1,2;13,3]	1,91	[1,38; 2,63]	<0,0001*
Interaktion p-Wert									0,5642
Region gPAP									
Asien	168	138 (82,1)	0,3 [0,2; 0,4]	166	105 (63,3)	1,5 [1,0; 3,4]	1,93	[1,50; 2,49]	<0,0001*
Europa	22	17 (77,3)	0,2 [0,1; 6,4]	23	11 (47,8)	14,7 [1,4; NE]	3,02	[1,43; 6,64]	0,0038*
Nordamerika	20	19 (95,0)	0,1 [0,1; 0,3]	22	19 (86,4)	1,1 [0,2; 2,3]	2,17	[1,14; 4,14]	0,0184*
Rest der Welt	66	52 (78,8)	0,5 [0,2; 1,8]	64	36 (56,3)	6,3 [2,6; NE]	2,26	[1,48; 3,48]	0,0002*
Interaktion p-Wert									0,6937

Time to event of AE is defined as the time from first dose of study treatment to first onset of the respective AE or the time to censoring if the AE has not occurred by 28 days following discontinuation of study treatment, before administration of subsequent cancer therapy or death, whichever comes first. All AEs are coded using MedDRA version 25.1. Includes AEs with onset date on or after the date of first dose and up to and including 28 days following discontinuation of study treatment. Analysis done if >=10 patients at each subgroup level and >=10 events in at least one subgroup level combined for both arms. Analysis done for SOC and PT only if main effect for that SOC or PT is statistically significant at 5% level. [a] Median time to event based on the Kaplan Meier estimate. NE = Not estimable as median (or 95% CLs) is not reached. [b] Estimated from main effects of unstratified Cox proportional hazard model including trt., subgroup and subgroup-by-trt. interaction. Ties handled using Efron method and 95% CI derived from profile likelihood estimation. NC = Not calculable. HR <1 favours Osimertinib+Chemo. * p<0.05.
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Table 4.3.1.23 FLAURA-2: Summary of subgroup analysis of time to first PT: Erbrechen
Safety Analysis Set, DCO 03APR2023

	Osi + Chemo (N=276)			Osi (N=275)					
Subgruppen	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]	Hazard Ratio [b]	[95%-KI] [b]	2-seitiger p-Wert [b]
Abstammung									
Chinesisch/Asiatisch	68	20 (29,4)	NE [NE; NE]	70	3 (4,3)	NE [NE; NE]	7,77	[2,66; 32,96]	<0,0001*
Nicht-chinesisch/ Asiatisch	107	24 (22,4)	NE [NE; NE]	106	9 (8,5)	NE [NE; NE]	2,92	[1,41; 6,65]	0,0035*
Nicht-asiatisch	101	29 (28,7)	NE [NE; NE]	99	5 (5,1)	NE [NE; NE]	6,50	[2,74; 19,10]	<0,0001*
Interaktion p-Wert									0,2751
Methode zur Gewebeuntersuchung									
zentral	120	27 (22,5)	NE [NE; NE]	119	5 (4,2)	NE [NE; NE]	6,01	[2,52; 17,74]	<0,0001*
lokal	156	46 (29,5)	NE [NE; NE]	156	12 (7,7)	NE [NE; NE]	4,33	[2,37; 8,55]	<0,0001*
Interaktion p-Wert									0,5691
WHO Performance-Status									
0	100	24 (24,0)	NE [NE; NE]	100	8 (8,0)	NE [NE; NE]	3,35	[1,57; 7,98]	0,0014*
1	176	49 (27,8)	NE [NE; NE]	175	9 (5,1)	NE [NE; NE]	6,12	[3,16; 13,33]	<0,0001*
Interaktion p-Wert									0,2736
Raucherstatus									
Ja	90	17 (18,9)	NE [NE; NE]	96	8 (8,3)	NE [NE; NE]	2,46	[1,09; 6,03]	0,0291*
Nein	186	56 (30,1)	NE [NE; NE]	179	9 (5,0)	NE [NE; NE]	6,87	[3,58; 14,89]	<0,0001*
Interaktion p-Wert									0,0690
Geschlecht									
Maennlich	104	23 (22,1)	NE [NE; NE]	107	5 (4,7)	NE [NE; NE]	5,09	[2,10; 15,15]	0,0001*
Weiblich	172	50 (29,1)	NE [NE; NE]	168	12 (7,1)	NE [NE; NE]	4,72	[2,60; 9,29]	<0,0001*
Interaktion p-Wert									0,8974
Nachweis der EGFR-Mutation durch zentralen ctDNA Cobas Test									
positiv	211	56 (26,5)	NE [NE; NE]	204	12 (5,9)	NE [NE; NE]	5,15	[2,86; 10,08]	<0,0001*

Time to event of AE is defined as the time from first dose of study treatment to first onset of the respective AE or the time to censoring if the AE has not occurred by 28 days following discontinuation of study treatment, before administration of subsequent cancer therapy or death, whichever comes first. All AEs are coded using MedDRA version 25.1. Includes AEs with onset date on or after the date of first dose and up to and including 28 days following discontinuation of study treatment. Analysis done if >=10 patients at each subgroup level and >=10 events in at least one subgroup level combined for both arms. Analysis done for SOC and PT only if main effect for that SOC or PT is statistically significant at 5% level. [a] Median time to event based on the Kaplan Meier estimate. NE = Not estimable as median (or 95% CLs) is not reached. [b] Estimated from main effects of unstratified Cox proportional hazard model including trt., subgroup and subgroup-by-trt. interaction. Ties handled using Efron method and 95% CI derived from profile likelihood estimation. NC = Not calculable. HR <1 favours Osimertinib+Chemo. * p<0.05.
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Table 4.3.1.23 FLAURA-2: Summary of subgroup analysis of time to first PT: Erbrechen
Safety Analysis Set, DCO 03APR2023

	Osi + Chemo (N=276)			Osi (N=275)					
Subgruppen	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]	Hazard Ratio [b]	[95%-KI] [b]	2-seitiger p-Wert [b]
negativ	41	13 (31,7)	NE [NE; NE]	39	3 (7,7)	NE [NE; NE]	4,60	[1,48; 20,07]	0,0067*
unbekannt	24	4 (16,7)	NE [NE; NE]	32	2 (6,3)	NE [NE; NE]	2,74	[0,53; 19,74]	0,2279
Interaktion p-Wert									0,8003
EGFR-Mutationstyp									
Exon 19 Deletion	172	43 (25,0)	NE [NE; NE]	167	10 (6,0)	NE [NE; NE]	4,77	[2,50; 10,06]	<0,0001*
Exon 21 (L858R) Substitutionsmutation	104	30 (28,8)	NE [NE; NE]	106	6 (5,7)	NE [NE; NE]	5,66	[2,53; 15,08]	<0,0001*
Interaktion p-Wert									0,7638
Zentral bestätigte EGFR-Mutation im Gewebe									
positiv	248	64 (25,8)	NE [NE; NE]	238	16 (6,7)	NE [NE; NE]	4,30	[2,55; 7,70]	<0,0001*
negativ	3	2 (66,7)	0,8 [0,1; NE]	4	0	NE [NE; NE]	NC	[NC]	NC
unbekannt	25	7 (28,0)	NE [NE; NE]	33	1 (3,0)	NE [NE; NE]	10,62	[1,89;198,60]	0,0049*
Interaktion p-Wert									0,3696
ZNS-Metastasen zur Baseline									
Ja	113	27 (23,9)	NE [NE; NE]	110	7 (6,4)	NE [NE; NE]	4,09	[1,88; 10,19]	0,0002*
Nein	163	46 (28,2)	NE [NE; NE]	165	10 (6,1)	NE [NE; NE]	5,36	[2,82; 11,26]	<0,0001*
Interaktion p-Wert									0,6236
Zentrale Bestätigung der EGFR-Mutation									
Zentral bestätigte EGFR-Mutation in Gewebe oder ctDNA	263	66 (25,1)	NE [NE; NE]	266	17 (6,4)	NE [NE; NE]	4,38	[2,64; 7,71]	<0,0001*
Keine zentrale Bestätigung	13	7 (53,8)	8,4 [0,8; NE]	9	0	NE [NE; NE]	NC	[NC]	NC
Interaktion p-Wert									NC
Alter bei Screening									

Time to event of AE is defined as the time from first dose of study treatment to first onset of the respective AE or the time to censoring if the AE has not occurred by 28 days following discontinuation of study treatment, before administration of subsequent cancer therapy or death, whichever comes first. All AEs are coded using MedDRA version 25.1. Includes AEs with onset date on or after the date of first dose and up to and including 28 days following discontinuation of study treatment. Analysis done if >=10 patients at each subgroup level and >=10 events in at least one subgroup level combined for both arms. Analysis done for SOC and PT only if main effect for that SOC or PT is statistically significant at 5% level. [a] Median time to event based on the Kaplan Meier estimate. NE = Not estimable as median (or 95% CLs) is not reached. [b] Estimated from main effects of unstratified Cox proportional hazard model including trt., subgroup and subgroup-by-trt. interaction. Ties handled using Efron method and 95% CI derived from profile likelihood estimation. NC = Not calculable. HR <1 favours Osimertinib+Chemo. * p<0.05.
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Table 4.3.1.23 FLAURA-2: Summary of subgroup analysis of time to first PT: Erbrechen
Safety Analysis Set, DCO 03APR2023

	Osi + Chemo (N=276)			Osi (N=275)					
Subgruppen	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]	Hazard Ratio [b]	[95%-KI] [b]	2-seitiger p-Wert [b]
<65 Jahre	172	45 (26,2)	NE [NE; NE]	164	7 (4,3)	NE [NE; NE]	6,88	[3,31; 16,70]	<0,0001*
>=65 Jahre	104	28 (26,9)	NE [NE; NE]	111	10 (9,0)	NE [NE; NE]	3,40	[1,71; 7,35]	0,0004*
Interaktion p-Wert									0,1944
Region gPAP									
Asien	168	43 (25,6)	NE [NE; NE]	166	11 (6,6)	NE [NE; NE]	4,33	[2,32; 8,83]	<0,0001*
Europa	22	6 (27,3)	NE [NE; NE]	23	1 (4,3)	NE [NE; NE]	6,85	[1,17;129,37]	0,0310*
Nordamerika	20	6 (30,0)	NE [NE; NE]	22	3 (13,6)	NE [NE; NE]	2,52	[0,67; 11,96]	0,1751
Rest der Welt	66	18 (27,3)	NE [NE; NE]	64	2 (3,1)	NE [NE; NE]	10,02	[2,89; 63,02]	<0,0001*
Interaktion p-Wert									0,5412

Time to event of AE is defined as the time from first dose of study treatment to first onset of the respective AE or the time to censoring if the AE has not occurred by 28 days following discontinuation of study treatment, before administration of subsequent cancer therapy or death, whichever comes first. All AEs are coded using MedDRA version 25.1. Includes AEs with onset date on or after the date of first dose and up to and including 28 days following discontinuation of study treatment. Analysis done if >=10 patients at each subgroup level and >=10 events in at least one subgroup level combined for both arms. Analysis done for SOC and PT only if main effect for that SOC or PT is statistically significant at 5% level. [a] Median time to event based on the Kaplan Meier estimate. NE = Not estimable as median (or 95% CLs) is not reached. [b] Estimated from main effects of unstratified Cox proportional hazard model including trt., subgroup and subgroup-by-trt. interaction. Ties handled using Efron method and 95% CI derived from profile likelihood estimation. NC = Not calculable. HR <1 favours Osimertinib+Chemo. * p<0.05.
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Table 4.3.1.24 FLAURA-2: Summary of subgroup analysis of time to first PT: Gastrooesophageale Refluxerkrankung
Safety Analysis Set, DCO 03APR2023

	Osi + Chemo (N=276)			Osi (N=275)					
Subgruppen	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]	Hazard Ratio [b]	[95%-KI] [b]	2-seitiger p-Wert [b]
Abstammung									
Chinesisch/Asiatisch	68	5 (7,4)	NE [NE; NE]	70	2 (2,9)	NE [NE; NE]	2,53	[0,54; 17,66]	0,2430
Nicht-chinesisch/ Asiatisch	107	3 (2,8)	NE [NE; NE]	106	2 (1,9)	NE [NE; NE]	1,54	[0,26; 11,71]	0,6314
Nicht-asiatisch	101	14 (13,9)	NE [NE; NE]	99	3 (3,0)	NE [NE; NE]	4,91	[1,60; 21,31]	0,0040*
Interaktion p-Wert									0,5580
Methode zur Gewebeuntersuchung									
zentral	120	1 (0,8)	NE [NE; NE]	119	1 (0,8)	NE [NE; NE]	1,03	[0,04; 25,95]	0,9851
lokal	156	21 (13,5)	NE [NE; NE]	156	6 (3,8)	NE [NE; NE]	3,63	[1,55; 9,89]	0,0022*
Interaktion p-Wert									0,4071
WHO Performance-Status									
0	100	7 (7,0)	NE [NE; NE]	100	5 (5,0)	NE [NE; NE]	1,47	[0,47; 4,97]	0,5076
1	176	15 (8,5)	NE [NE; NE]	175	2 (1,1)	NE [NE; NE]	7,67	[2,16; 48,65]	0,0007*
Interaktion p-Wert									0,0681
Raucherstatus									
Ja	90	7 (7,8)	NE [NE; NE]	96	3 (3,1)	NE [NE; NE]	2,47	[0,69; 11,46]	0,1704
Nein	186	15 (8,1)	NE [NE; NE]	179	4 (2,2)	NE [NE; NE]	3,82	[1,39; 13,42]	0,0082*
Interaktion p-Wert									0,6254
Geschlecht									
Maennlich	104	7 (6,7)	NE [NE; NE]	107	4 (3,7)	NE [NE; NE]	1,71	[0,52; 6,54]	0,3827
Weiblich	172	15 (8,7)	NE [NE; NE]	168	3 (1,8)	NE [NE; NE]	5,33	[1,76; 23,03]	0,0020*
Interaktion p-Wert									0,1991
Nachweis der EGFR-Mutation durch zentralen ctDNA Cobas Test									
positiv	211	16 (7,6)	NE [NE; NE]	204	4 (2,0)	NE [NE; NE]	4,08	[1,50; 14,24]	0,0048*

Time to event of AE is defined as the time from first dose of study treatment to first onset of the respective AE or the time to censoring if the AE has not occurred by 28 days following discontinuation of study treatment, before administration of subsequent cancer therapy or death, whichever comes first. All AEs are coded using MedDRA version 25.1. Includes AEs with onset date on or after the date of first dose and up to and including 28 days following discontinuation of study treatment. Analysis done if >=10 patients at each subgroup level and >=10 events in at least one subgroup level combined for both arms. Analysis done for SOC and PT only if main effect for that SOC or PT is statistically significant at 5% level. [a] Median time to event based on the Kaplan Meier estimate. NE = Not estimable as median (or 95% CLs) is not reached. [b] Estimated from main effects of unstratified Cox proportional hazard model including trt., subgroup and subgroup-by-trt. interaction. Ties handled using Efron method and 95% CI derived from profile likelihood estimation. NC = Not calculable. HR <1 favours Osimertinib+Chemo. * p<0.05.
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Table 4.3.1.24 FLAURA-2: Summary of subgroup analysis of time to first PT: Gastrooesophageale Refluxerkrankung
Safety Analysis Set, DCO 03APR2023

	Osi + Chemo (N=276)			Osi (N=275)					
Subgruppen	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]	Hazard Ratio [b]	[95%-KI] [b]	2-seitiger p-Wert [b]
negativ	41	2 (4,9)	NE [NE; NE]	39	1 (2,6)	NE [NE; NE]	1,93	[0,18; 41,47]	0,5812
unbekannt	24	4 (16,7)	NE [NE; NE]	32	2 (6,3)	NE [NE; NE]	2,57	[0,50; 18,57]	0,2593
Interaktion p-Wert									0,8154
EGFR-Mutationstyp									
Exon 19 Deletion	172	16 (9,3)	NE [NE; NE]	167	4 (2,4)	NE [NE; NE]	4,30	[1,58; 15,03]	0,0034*
Exon 21 (L858R) Substitutionsmutation	104	6 (5,8)	NE [NE; NE]	106	3 (2,8)	NE [NE; NE]	1,90	[0,50; 9,02]	0,3507
Interaktion p-Wert									0,3715
Zentral bestätigte EGFR-Mutation im Gewebe									
positiv	248	19 (7,7)	NE [NE; NE]	238	6 (2,5)	NE [NE; NE]	3,10	[1,31; 8,52]	0,0089*
negativ	3	0	NE [NE; NE]	4	0	NE [NE; NE]	NC	[NC]	NC
unbekannt	25	3 (12,0)	NE [NE; NE]	33	1 (3,0)	NE [NE; NE]	4,87	[0,62; 98,66]	0,1346
Interaktion p-Wert									0,7110
ZNS-Metastasen zur Baseline									
Ja	113	8 (7,1)	NE [NE; NE]	110	4 (3,6)	NE [NE; NE]	1,93	[0,61; 7,25]	0,2678
Nein	163	14 (8,6)	NE [NE; NE]	165	3 (1,8)	NE [NE; NE]	5,03	[1,64; 21,81]	0,0034*
Interaktion p-Wert									0,2759
Zentrale Bestätigung der EGFR-Mutation									
Zentral bestätigte EGFR-Mutation in Gewebe oder ctDNA	263	21 (8,0)	NE [NE; NE]	266	7 (2,6)	NE [NE; NE]	3,13	[1,40; 7,96]	0,0048*
Keine zentrale Bestätigung	13	1 (7,7)	NE [NE; NE]	9	0	NE [NE; NE]	NC	[NC]	NC
Interaktion p-Wert									NC
Alter bei Screening									

Time to event of AE is defined as the time from first dose of study treatment to first onset of the respective AE or the time to censoring if the AE has not occurred by 28 days following discontinuation of study treatment, before administration of subsequent cancer therapy or death, whichever comes first. All AEs are coded using MedDRA version 25.1. Includes AEs with onset date on or after the date of first dose and up to and including 28 days following discontinuation of study treatment. Analysis done if >=10 patients at each subgroup level and >=10 events in at least one subgroup level combined for both arms. Analysis done for SOC and PT only if main effect for that SOC or PT is statistically significant at 5% level. [a] Median time to event based on the Kaplan Meier estimate. NE = Not estimable as median (or 95% CLs) is not reached. [b] Estimated from main effects of unstratified Cox proportional hazard model including trt., subgroup and subgroup-by-trt. interaction. Ties handled using Efron method and 95% CI derived from profile likelihood estimation. NC = Not calculable. HR <1 favours Osimertinib+Chemo. * p<0.05.
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Table 4.3.1.24 FLAURA-2: Summary of subgroup analysis of time to first PT: Gastrooesophageale Refluxerkrankung
Safety Analysis Set, DCO 03APR2023

	Osi + Chemo (N=276)			Osi (N=275)					
Subgruppen	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]	Hazard Ratio [b]	[95%-KI] [b]	2-seitiger p-Wert [b]
<65 Jahre	172	14 (8,1)	NE [NE; NE]	164	5 (3,0)	NE [NE; NE]	2,71	[1,04; 8,39]	0,0417*
>=65 Jahre	104	8 (7,7)	NE [NE; NE]	111	2 (1,8)	NE [NE; NE]	4,61	[1,16; 30,57]	0,0292*
Interaktion p-Wert									0,5670
Region gPAP									
Asien	168	5 (3,0)	NE [NE; NE]	166	3 (1,8)	NE [NE; NE]	1,66	[0,41; 8,08]	0,4818
Europa	22	4 (18,2)	NE [NE; NE]	23	0	NE [NE; NE]	NC	[NC]	NC
Nordamerika	20	6 (30,0)	NE [NE; NE]	22	1 (4,5)	NE [NE; NE]	8,70	[1,48;164,43]	0,0140*
Rest der Welt	66	7 (10,6)	NE [NE; NE]	64	3 (4,7)	NE [NE; NE]	2,42	[0,67; 11,23]	0,1804
Interaktion p-Wert									0,3798

Time to event of AE is defined as the time from first dose of study treatment to first onset of the respective AE or the time to censoring if the AE has not occurred by 28 days following discontinuation of study treatment, before administration of subsequent cancer therapy or death, whichever comes first. All AEs are coded using MedDRA version 25.1. Includes AEs with onset date on or after the date of first dose and up to and including 28 days following discontinuation of study treatment. Analysis done if >=10 patients at each subgroup level and >=10 events in at least one subgroup level combined for both arms. Analysis done for SOC and PT only if main effect for that SOC or PT is statistically significant at 5% level. [a] Median time to event based on the Kaplan Meier estimate. NE = Not estimable as median (or 95% CLs) is not reached. [b] Estimated from main effects of unstratified Cox proportional hazard model including trt., subgroup and subgroup-by-trt. interaction. Ties handled using Efron method and 95% CI derived from profile likelihood estimation. NC = Not calculable. HR <1 favours Osimertinib+Chemo. * p<0.05.
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Table 4.3.1.25 FLAURA-2: Summary of subgroup analysis of time to first PT: Mundtrockenheit
Safety Analysis Set, DCO 03APR2023

	Osi + Chemo (N=276)			Osi (N=275)					
Subgruppen	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]	Hazard Ratio [b]	[95%-KI] [b]	2-seitiger p-Wert [b]
Abstammung									
Chinesisch/Asiatisch	68	1 (1,5)	NE [NE; NE]	70	0	NE [NE; NE]	NC	[NC]	NC
Nicht-chinesisch/ Asiatisch	107	2 (1,9)	NE [NE; NE]	106	3 (2,8)	NE [NE; NE]	0,68	[0,09; 4,13]	0,6736
Nicht-asiatisch	101	12 (11,9)	NE [NE; NE]	99	1 (1,0)	NE [NE; NE]	12,42	[2,45;226,17]	0,0008*
Interaktion p-Wert									0,0211*
Methode zur Gewebeuntersuchung									
zentral	120	4 (3,3)	NE [NE; NE]	119	0	NE [NE; NE]	NC	[NC]	NC
lokal	156	11 (7,1)	NE [NE; NE]	156	4 (2,6)	NE [NE; NE]	2,81	[0,96; 10,12]	0,0601
Interaktion p-Wert									NC
WHO Performance-Status									
0	100	4 (4,0)	NE [NE; NE]	100	3 (3,0)	NE [NE; NE]	1,38	[0,31; 7,03]	0,6685
1	176	11 (6,3)	NE [NE; NE]	175	1 (0,6)	NE [NE; NE]	11,08	[2,15;202,53]	0,0017*
Interaktion p-Wert									0,0823
Raucherstatus									
Ja	90	3 (3,3)	NE [NE; NE]	96	2 (2,1)	NE [NE; NE]	1,58	[0,26; 12,03]	0,6104
Nein	186	12 (6,5)	NE [NE; NE]	179	2 (1,1)	NE [NE; NE]	6,00	[1,64; 38,59]	0,0049*
Interaktion p-Wert									0,2648
Geschlecht									
Maennlich	104	4 (3,8)	NE [NE; NE]	107	1 (0,9)	NE [NE; NE]	4,07	[0,60; 79,60]	0,1594
Weiblich	172	11 (6,4)	NE [NE; NE]	168	3 (1,8)	NE [NE; NE]	3,74	[1,17; 16,53]	0,0251*
Interaktion p-Wert									0,9473
Nachweis der EGFR-Mutation durch zentralen ctDNA Cobas Test									
positiv	211	8 (3,8)	NE [NE; NE]	204	2 (1,0)	NE [NE; NE]	3,94	[0,99; 26,14]	0,0522

Time to event of AE is defined as the time from first dose of study treatment to first onset of the respective AE or the time to censoring if the AE has not occurred by 28 days following discontinuation of study treatment, before administration of subsequent cancer therapy or death, whichever comes first. All AEs are coded using MedDRA version 25.1. Includes AEs with onset date on or after the date of first dose and up to and including 28 days following discontinuation of study treatment. Analysis done if >=10 patients at each subgroup level and >=10 events in at least one subgroup level combined for both arms. Analysis done for SOC and PT only if main effect for that SOC or PT is statistically significant at 5% level. [a] Median time to event based on the Kaplan Meier estimate. NE = Not estimable as median (or 95% CLs) is not reached. [b] Estimated from main effects of unstratified Cox proportional hazard model including trt., subgroup and subgroup-by-trt. interaction. Ties handled using Efron method and 95% CI derived from profile likelihood estimation. NC = Not calculable. HR <1 favours Osimertinib+Chemo. * p<0.05.
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Table 4.3.1.25 FLAURA-2: Summary of subgroup analysis of time to first PT: Mundtrockenheit
Safety Analysis Set, DCO 03APR2023

	Osi + Chemo (N=276)			Osi (N=275)					
Subgruppen	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]	Hazard Ratio [b]	[95%-KI] [b]	2-seitiger p-Wert [b]
negativ	41	2 (4,9)	NE [NE; NE]	39	1 (2,6)	NE [NE; NE]	1,97	[0,19; 42,38]	0,5685
unbekannt	24	5 (20,8)	NE [NE; NE]	32	1 (3,1)	NE [NE; NE]	7,04	[1,13;134,75]	0,0349*
Interaktion p-Wert									0,7413
EGFR-Mutationstyp									
Exon 19 Deletion	172	14 (8,1)	NE [NE; NE]	167	2 (1,2)	NE [NE; NE]	7,19	[2,01; 45,77]	0,0012*
Exon 21 (L858R) Substitutionsmutation	104	1 (1,0)	NE [NE; NE]	106	2 (1,9)	NE [NE; NE]	0,49	[0,02; 5,16]	0,5539
Interaktion p-Wert									0,0518
Zentral bestätigte EGFR-Mutation im Gewebe									
positiv	248	12 (4,8)	NE [NE; NE]	238	4 (1,7)	NE [NE; NE]	2,90	[1,01; 10,38]	0,0478*
negativ	3	0	NE [NE; NE]	4	0	NE [NE; NE]	NC	[NC]	NC
unbekannt	25	3 (12,0)	NE [NE; NE]	33	0	NE [NE; NE]	NC	[NC]	NC
Interaktion p-Wert									NC
ZNS-Metastasen zur Baseline									
Ja	113	6 (5,3)	NE [NE; NE]	110	2 (1,8)	NE [NE; NE]	2,92	[0,67; 19,90]	0,1595
Nein	163	9 (5,5)	NE [NE; NE]	165	2 (1,2)	NE [NE; NE]	4,73	[1,22; 31,04]	0,0229*
Interaktion p-Wert									0,6690
Zentrale Bestätigung der EGFR-Mutation									
Zentral bestätigte EGFR-Mutation in Gewebe oder ctDNA	263	14 (5,3)	NE [NE; NE]	266	4 (1,5)	NE [NE; NE]	3,61	[1,30; 12,75]	0,0127*
Keine zentrale Bestätigung	13	1 (7,7)	NE [NE; NE]	9	0	NE [NE; NE]	NC	[NC]	NC
Interaktion p-Wert									NC
Alter bei Screening									

Time to event of AE is defined as the time from first dose of study treatment to first onset of the respective AE or the time to censoring if the AE has not occurred by 28 days following discontinuation of study treatment, before administration of subsequent cancer therapy or death, whichever comes first. All AEs are coded using MedDRA version 25.1. Includes AEs with onset date on or after the date of first dose and up to and including 28 days following discontinuation of study treatment. Analysis done if >=10 patients at each subgroup level and >=10 events in at least one subgroup level combined for both arms. Analysis done for SOC and PT only if main effect for that SOC or PT is statistically significant at 5% level. [a] Median time to event based on the Kaplan Meier estimate. NE = Not estimable as median (or 95% CLs) is not reached. [b] Estimated from main effects of unstratified Cox proportional hazard model including trt., subgroup and subgroup-by-trt. interaction. Ties handled using Efron method and 95% CI derived from profile likelihood estimation. NC = Not calculable. HR <1 favours Osimertinib+Chemo. * p<0.05.
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Table 4.3.1.25 FLAURA-2: Summary of subgroup analysis of time to first PT: Mundtrockenheit
Safety Analysis Set, DCO 03APR2023

	Osi + Chemo (N=276)			Osi (N=275)					
Subgruppen	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]	Hazard Ratio [b]	[95%-KI] [b]	2-seitiger p-Wert [b]
<65 Jahre	172	7 (4,1)	NE [NE; NE]	164	2 (1,2)	NE [NE; NE]	3,35	[0,81; 22,50]	0,0987
>=65 Jahre	104	8 (7,7)	NE [NE; NE]	111	2 (1,8)	NE [NE; NE]	4,52	[1,13; 29,96]	0,0315*
Interaktion p-Wert									0,7905
Region gPAP									
Asien	168	0	NE [NE; NE]	166	3 (1,8)	NE [NE; NE]	NC	[NC]	NC
Europa	22	2 (9,1)	NE [NE; NE]	23	0	NE [NE; NE]	NC	[NC]	NC
Nordamerika	20	6 (30,0)	NE [NE; NE]	22	0	NE [NE; NE]	NC	[NC]	NC
Rest der Welt	66	7 (10,6)	NE [NE; NE]	64	1 (1,6)	NE [NE; NE]	NC	[NC]	NC
Interaktion p-Wert									NC

Time to event of AE is defined as the time from first dose of study treatment to first onset of the respective AE or the time to censoring if the AE has not occurred by 28 days following discontinuation of study treatment, before administration of subsequent cancer therapy or death, whichever comes first. All AEs are coded using MedDRA version 25.1. Includes AEs with onset date on or after the date of first dose and up to and including 28 days following discontinuation of study treatment. Analysis done if >=10 patients at each subgroup level and >=10 events in at least one subgroup level combined for both arms. Analysis done for SOC and PT only if main effect for that SOC or PT is statistically significant at 5% level. [a] Median time to event based on the Kaplan Meier estimate. NE = Not estimable as median (or 95% CLs) is not reached. [b] Estimated from main effects of unstratified Cox proportional hazard model including trt., subgroup and subgroup-by-trt. interaction. Ties handled using Efron method and 95% CI derived from profile likelihood estimation. NC = Not calculable. HR <1 favours Osimertinib+Chemo. * p<0.05.
root/cdar/d516/payer_germany/ar/d5169c00001_payer_germany/tlf/prod/program/ttesubae.sas gttesubaeaay 22DEC2023:09:13 kfrh585

Table 4.3.1.26 FLAURA-2: Summary of subgroup analysis of time to first PT: Obstipation
Safety Analysis Set, DCO 03APR2023

	Osi + Chemo (N=276)			Osi (N=275)					
Subgruppen	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]	Hazard Ratio [b]	[95%-KI] [b]	2-seitiger p-Wert [b]
Abstammung									
Chinesisch/Asiatisch	68	18 (26,5)	NE [NE; NE]	70	4 (5,7)	NE [NE; NE]	5,16	[1,92; 17,86]	0,0006*
Nicht-chinesisch/ Asiatisch	107	37 (34,6)	NE [NE; NE]	106	13 (12,3)	NE [NE; NE]	3,42	[1,86; 6,68]	<0,0001*
Nicht-asiatisch	101	26 (25,7)	NE [NE; NE]	99	11 (11,1)	NE [NE; NE]	2,57	[1,31; 5,43]	0,0059*
Interaktion p-Wert									0,5525
Methode zur Gewebeuntersuchung									
zentral	120	16 (13,3)	NE [NE; NE]	119	9 (7,6)	NE [NE; NE]	1,82	[0,82; 4,31]	0,1412
lokal	156	65 (41,7)	NE [NE; NE]	156	19 (12,2)	NE [NE; NE]	4,31	[2,64; 7,39]	<0,0001*
Interaktion p-Wert									0,0866
WHO Performance-Status									
0	100	30 (30,0)	NE [NE; NE]	100	10 (10,0)	NE [NE; NE]	3,56	[1,80; 7,67]	0,0002*
1	176	51 (29,0)	NE [NE; NE]	175	18 (10,3)	NE [NE; NE]	3,18	[1,89; 5,58]	<0,0001*
Interaktion p-Wert									0,8012
Raucherstatus									
Ja	90	26 (28,9)	NE [NE; NE]	96	12 (12,5)	NE [NE; NE]	2,63	[1,36; 5,40]	0,0039*
Nein	186	55 (29,6)	NE [NE; NE]	179	16 (8,9)	NE [NE; NE]	3,83	[2,25; 6,90]	<0,0001*
Interaktion p-Wert									0,4066
Geschlecht									
Maennlich	104	27 (26,0)	NE [NE; NE]	107	14 (13,1)	NE [NE; NE]	2,17	[1,16; 4,25]	0,0155*
Weiblich	172	54 (31,4)	NE [NE; NE]	168	14 (8,3)	NE [NE; NE]	4,47	[2,55; 8,36]	<0,0001*
Interaktion p-Wert									0,1054
Nachweis der EGFR-Mutation durch zentralen ctDNA Cobas Test									
positiv	211	59 (28,0)	NE [NE; NE]	204	21 (10,3)	NE [NE; NE]	3,11	[1,92; 5,24]	<0,0001*

Time to event of AE is defined as the time from first dose of study treatment to first onset of the respective AE or the time to censoring if the AE has not occurred by 28 days following discontinuation of study treatment, before administration of subsequent cancer therapy or death, whichever comes first. All AEs are coded using MedDRA version 25.1. Includes AEs with onset date on or after the date of first dose and up to and including 28 days following discontinuation of study treatment. Analysis done if >=10 patients at each subgroup level and >=10 events in at least one subgroup level combined for both arms. Analysis done for SOC and PT only if main effect for that SOC or PT is statistically significant at 5% level. [a] Median time to event based on the Kaplan Meier estimate. NE = Not estimable as median (or 95% CLs) is not reached. [b] Estimated from main effects of unstratified Cox proportional hazard model including trt., subgroup and subgroup-by-trt. interaction. Ties handled using Efron method and 95% CI derived from profile likelihood estimation. NC = Not calculable. HR <1 favours Osimertinib+Chemo. * p<0.05.
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Table 4.3.1.26 FLAURA-2: Summary of subgroup analysis of time to first PT: Obstipation
Safety Analysis Set, DCO 03APR2023

	Osi + Chemo (N=276)			Osi (N=275)					
Subgruppen	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]	Hazard Ratio [b]	[95%-KI] [b]	2-seitiger p-Wert [b]
negativ	41	13 (31,7)	NE [NE; NE]	39	3 (7,7)	NE [NE; NE]	5,00	[1,61; 21,80]	0,0041*
unbekannt	24	9 (37,5)	NE [NE; NE]	32	4 (12,5)	NE [NE; NE]	3,28	[1,07; 12,10]	0,0380*
Interaktion p-Wert									0,7754
EGFR-Mutationstyp									
Exon 19 Deletion	172	46 (26,7)	NE [NE; NE]	167	17 (10,2)	NE [NE; NE]	3,03	[1,77; 5,43]	<0,0001*
Exon 21 (L858R) Substitutionsmutation	104	35 (33,7)	NE [NE; NE]	106	11 (10,4)	NE [NE; NE]	3,72	[1,96; 7,69]	<0,0001*
Interaktion p-Wert									0,6411
Zentral bestätigte EGFR-Mutation im Gewebe									
positiv	248	68 (27,4)	NE [NE; NE]	238	25 (10,5)	NE [NE; NE]	2,95	[1,89; 4,75]	<0,0001*
negativ	3	3 (100)	0,2 [0,1; NE]	4	1 (25,0)	NE [NE; NE]	NC	[NC]	NC
unbekannt	25	10 (40,0)	NE [NE; NE]	33	2 (6,1)	NE [NE; NE]	8,73	[2,30; 56,82]	0,0008*
Interaktion p-Wert									0,1426
ZNS-Metastasen zur Baseline									
Ja	113	36 (31,9)	NE [NE; NE]	110	12 (10,9)	NE [NE; NE]	3,36	[1,80; 6,73]	<0,0001*
Nein	163	45 (27,6)	NE [NE; NE]	165	16 (9,7)	NE [NE; NE]	3,27	[1,89; 5,96]	<0,0001*
Interaktion p-Wert									0,9525
Zentrale Bestätigung der EGFR-Mutation									
Zentral bestätigte EGFR-Mutation in Gewebe oder ctDNA	263	76 (28,9)	NE [NE; NE]	266	26 (9,8)	NE [NE; NE]	3,39	[2,20; 5,39]	<0,0001*
Keine zentrale Bestätigung	13	5 (38,5)	NE [NE; NE]	9	2 (22,2)	NE [NE; NE]	2,01	[0,43; 14,02]	0,3848
Interaktion p-Wert									0,5597
Alter bei Screening									

Time to event of AE is defined as the time from first dose of study treatment to first onset of the respective AE or the time to censoring if the AE has not occurred by 28 days following discontinuation of study treatment, before administration of subsequent cancer therapy or death, whichever comes first. All AEs are coded using MedDRA version 25.1. Includes AEs with onset date on or after the date of first dose and up to and including 28 days following discontinuation of study treatment. Analysis done if >=10 patients at each subgroup level and >=10 events in at least one subgroup level combined for both arms. Analysis done for SOC and PT only if main effect for that SOC or PT is statistically significant at 5% level. [a] Median time to event based on the Kaplan Meier estimate. NE = Not estimable as median (or 95% CLs) is not reached. [b] Estimated from main effects of unstratified Cox proportional hazard model including trt., subgroup and subgroup-by-trt. interaction. Ties handled using Efron method and 95% CI derived from profile likelihood estimation. NC = Not calculable. HR <1 favours Osimertinib+Chemo. * p<0.05.
root/cdar/d516/payer_germany/ar/d5169c00001_payer_germany/tlf/prod/program/ttesubae.sas gttesubaeaaz 22DEC2023:09:13 kfrh585

Table 4.3.1.26 FLAURA-2: Summary of subgroup analysis of time to first PT: Obstipation
Safety Analysis Set, DCO 03APR2023

	Osi + Chemo (N=276)			Osi (N=275)					
Subgruppen	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]	Hazard Ratio [b]	[95%-KI] [b]	2-seitiger p-Wert [b]
<65 Jahre	172	49 (28,5)	NE [NE; NE]	164	15 (9,1)	NE [NE; NE]	3,48	[2,00; 6,43]	<0,0001*
>=65 Jahre	104	32 (30,8)	NE [NE; NE]	111	13 (11,7)	NE [NE; NE]	3,18	[1,71; 6,27]	0,0002*
Interaktion p-Wert									0,8351
Region gPAP									
Asien	168	50 (29,8)	NE [NE; NE]	166	14 (8,4)	NE [NE; NE]	4,09	[2,33; 7,69]	<0,0001*
Europa	22	5 (22,7)	NE [NE; NE]	23	1 (4,3)	NE [NE; NE]	5,34	[0,86;102,21]	0,0747
Nordamerika	20	10 (50,0)	11,6 [0,7; NE]	22	6 (27,3)	NE [NE; NE]	2,37	[0,88; 6,96]	0,0885
Rest der Welt	66	16 (24,2)	NE [NE; NE]	64	7 (10,9)	NE [NE; NE]	2,51	[1,07; 6,54]	0,0335*
Interaktion p-Wert									0,6887

Time to event of AE is defined as the time from first dose of study treatment to first onset of the respective AE or the time to censoring if the AE has not occurred by 28 days following discontinuation of study treatment, before administration of subsequent cancer therapy or death, whichever comes first. All AEs are coded using MedDRA version 25.1. Includes AEs with onset date on or after the date of first dose and up to and including 28 days following discontinuation of study treatment. Analysis done if >=10 patients at each subgroup level and >=10 events in at least one subgroup level combined for both arms. Analysis done for SOC and PT only if main effect for that SOC or PT is statistically significant at 5% level. [a] Median time to event based on the Kaplan Meier estimate. NE = Not estimable as median (or 95% CLs) is not reached. [b] Estimated from main effects of unstratified Cox proportional hazard model including trt., subgroup and subgroup-by-trt. interaction. Ties handled using Efron method and 95% CI derived from profile likelihood estimation. NC = Not calculable. HR <1 favours Osimertinib+Chemo. * p<0.05.
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Table 4.3.1.27 FLAURA-2: Summary of subgroup analysis of time to first PT: Schmerzen Oberbauch
Safety Analysis Set, DCO 03APR2023

	Osi + Chemo (N=276)			Osi (N=275)					
Subgruppen	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]	Hazard Ratio [b]	[95%-KI] [b]	2-seitiger p-Wert [b]
Abstammung									
Chinesisch/Asiatisch	68	10 (14,7)	NE [NE; NE]	70	1 (1,4)	NE [NE; NE]	10,14	[1,94;185,95]	0,0032*
Nicht-chinesisch/ Asiatisch	107	5 (4,7)	NE [NE; NE]	106	2 (1,9)	NE [NE; NE]	2,50	[0,54; 17,44]	0,2495
Nicht-asiatisch	101	5 (5,0)	NE [NE; NE]	99	4 (4,0)	NE [NE; NE]	1,17	[0,31; 4,75]	0,8102
Interaktion p-Wert									0,1554
Methode zur Gewebeuntersuchung									
zentral	120	8 (6,7)	NE [NE; NE]	119	3 (2,5)	NE [NE; NE]	2,59	[0,75; 11,83]	0,1367
lokal	156	12 (7,7)	NE [NE; NE]	156	4 (2,6)	NE [NE; NE]	2,97	[1,03; 10,62]	0,0429*
Interaktion p-Wert									0,8787
WHO Performance-Status									
0	100	10 (10,0)	NE [NE; NE]	100	2 (2,0)	NE [NE; NE]	5,30	[1,40; 34,49]	0,0121*
1	176	10 (5,7)	NE [NE; NE]	175	5 (2,9)	NE [NE; NE]	1,87	[0,67; 6,02]	0,2389
Interaktion p-Wert									0,2564
Raucherstatus									
Ja	90	6 (6,7)	NE [NE; NE]	96	2 (2,1)	NE [NE; NE]	3,13	[0,72; 21,34]	0,1327
Nein	186	14 (7,5)	NE [NE; NE]	179	5 (2,8)	NE [NE; NE]	2,67	[1,02; 8,27]	0,0449*
Interaktion p-Wert									0,8700
Geschlecht									
Maennlich	104	8 (7,7)	NE [NE; NE]	107	0	NE [NE; NE]	NC	[NC]	NC
Weiblich	172	12 (7,0)	NE [NE; NE]	168	7 (4,2)	NE [NE; NE]	1,69	[0,68; 4,55]	0,2602
Interaktion p-Wert									NC
Nachweis der EGFR-Mutation durch zentralen ctDNA Cobas Test									
positiv	211	12 (5,7)	NE [NE; NE]	204	5 (2,5)	NE [NE; NE]	2,26	[0,84; 7,11]	0,1094

Time to event of AE is defined as the time from first dose of study treatment to first onset of the respective AE or the time to censoring if the AE has not occurred by 28 days following discontinuation of study treatment, before administration of subsequent cancer therapy or death, whichever comes first. All AEs are coded using MedDRA version 25.1. Includes AEs with onset date on or after the date of first dose and up to and including 28 days following discontinuation of study treatment. Analysis done if >=10 patients at each subgroup level and >=10 events in at least one subgroup level combined for both arms. Analysis done for SOC and PT only if main effect for that SOC or PT is statistically significant at 5% level. [a] Median time to event based on the Kaplan Meier estimate. NE = Not estimable as median (or 95% CLs) is not reached. [b] Estimated from main effects of unstratified Cox proportional hazard model including trt., subgroup and subgroup-by-trt. interaction. Ties handled using Efron method and 95% CI derived from profile likelihood estimation. NC = Not calculable. HR <1 favours Osimertinib+Chemo. * p<0.05.
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Table 4.3.1.27 FLAURA-2: Summary of subgroup analysis of time to first PT: Schmerzen Oberbauch
Safety Analysis Set, DCO 03APR2023

	Osi + Chemo (N=276)			Osi (N=275)					
Subgruppen	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]	Hazard Ratio [b]	[95%-KI] [b]	2-seitiger p-Wert [b]
negativ	41	4 (9,8)	NE [NE; NE]	39	1 (2,6)	NE [NE; NE]	3,95	[0,58; 77,26]	0,1691
unbekannt	24	4 (16,7)	NE [NE; NE]	32	1 (3,1)	NE [NE; NE]	5,36	[0,79;104,73]	0,0880
Interaktion p-Wert									0,7296
EGFR-Mutationstyp									
Exon 19 Deletion	172	11 (6,4)	NE [NE; NE]	167	5 (3,0)	NE [NE; NE]	2,13	[0,78; 6,77]	0,1452
Exon 21 (L858R) Substitutionsmutation	104	9 (8,7)	NE [NE; NE]	106	2 (1,9)	NE [NE; NE]	4,44	[1,14; 29,16]	0,0297*
Interaktion p-Wert									0,4275
Zentral bestätigte EGFR-Mutation im Gewebe									
positiv	248	16 (6,5)	NE [NE; NE]	238	4 (1,7)	NE [NE; NE]	3,74	[1,37; 13,04]	0,0086*
negativ	3	1 (33,3)	NE [NE; NE]	4	1 (25,0)	NE [NE; NE]	NC	[NC]	NC
unbekannt	25	3 (12,0)	NE [NE; NE]	33	2 (6,1)	NE [NE; NE]	2,22	[0,37; 16,87]	0,3758
Interaktion p-Wert									0,6302
ZNS-Metastasen zur Baseline									
Ja	113	5 (4,4)	NE [NE; NE]	110	3 (2,7)	NE [NE; NE]	1,46	[0,36; 7,14]	0,5979
Nein	163	15 (9,2)	NE [NE; NE]	165	4 (2,4)	NE [NE; NE]	3,96	[1,44; 13,91]	0,0065*
Interaktion p-Wert									0,2854
Zentrale Bestätigung der EGFR-Mutation									
Zentral bestätigte EGFR-Mutation in Gewebe oder ctDNA	263	17 (6,5)	NE [NE; NE]	266	5 (1,9)	NE [NE; NE]	3,37	[1,33; 10,26]	0,0091*
Keine zentrale Bestätigung	13	3 (23,1)	NE [NE; NE]	9	2 (22,2)	NE [NE; NE]	1,06	[0,18; 8,06]	0,9478
Interaktion p-Wert									0,2837
Alter bei Screening									

Time to event of AE is defined as the time from first dose of study treatment to first onset of the respective AE or the time to censoring if the AE has not occurred by 28 days following discontinuation of study treatment, before administration of subsequent cancer therapy or death, whichever comes first. All AEs are coded using MedDRA version 25.1. Includes AEs with onset date on or after the date of first dose and up to and including 28 days following discontinuation of study treatment. Analysis done if >=10 patients at each subgroup level and >=10 events in at least one subgroup level combined for both arms. Analysis done for SOC and PT only if main effect for that SOC or PT is statistically significant at 5% level. [a] Median time to event based on the Kaplan Meier estimate. NE = Not estimable as median (or 95% CLs) is not reached. [b] Estimated from main effects of unstratified Cox proportional hazard model including trt., subgroup and subgroup-by-trt. interaction. Ties handled using Efron method and 95% CI derived from profile likelihood estimation. NC = Not calculable. HR <1 favours Osimertinib+Chemo. * p<0.05.
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Table 4.3.1.27 FLAURA-2: Summary of subgroup analysis of time to first PT: Schmerzen Oberbauch
Safety Analysis Set, DCO 03APR2023

	Osi + Chemo (N=276)			Osi (N=275)					
Subgruppen	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]	Hazard Ratio [b]	[95%-KI] [b]	2-seitiger p-Wert [b]
<65 Jahre	172	17 (9,9)	NE [NE; NE]	164	3 (1,8)	NE [NE; NE]	5,24	[1,76; 22,45]	0,0018*
>=65 Jahre	104	3 (2,9)	NE [NE; NE]	111	4 (3,6)	NE [NE; NE]	0,82	[0,16; 3,70]	0,7895
Interaktion p-Wert									0,0528
Region gPAP									
Asien	168	15 (8,9)	NE [NE; NE]	166	3 (1,8)	NE [NE; NE]	4,90	[1,62; 21,15]	0,0036*
Europa	22	3 (13,6)	NE [NE; NE]	23	0	NE [NE; NE]	NC	[NC]	NC
Nordamerika	20	0	NE [NE; NE]	22	0	NE [NE; NE]	NC	[NC]	NC
Rest der Welt	66	2 (3,0)	NE [NE; NE]	64	4 (6,3)	NE [NE; NE]	0,44	[0,06; 2,26]	0,3289
Interaktion p-Wert									0,0180*

Time to event of AE is defined as the time from first dose of study treatment to first onset of the respective AE or the time to censoring if the AE has not occurred by 28 days following discontinuation of study treatment, before administration of subsequent cancer therapy or death, whichever comes first. All AEs are coded using MedDRA version 25.1. Includes AEs with onset date on or after the date of first dose and up to and including 28 days following discontinuation of study treatment. Analysis done if >=10 patients at each subgroup level and >=10 events in at least one subgroup level combined for both arms. Analysis done for SOC and PT only if main effect for that SOC or PT is statistically significant at 5% level. [a] Median time to event based on the Kaplan Meier estimate. NE = Not estimable as median (or 95% CLs) is not reached. [b] Estimated from main effects of unstratified Cox proportional hazard model including trt., subgroup and subgroup-by-trt. interaction. Ties handled using Efron method and 95% CI derived from profile likelihood estimation. NC = Not calculable. HR <1 favours Osimertinib+Chemo. * p<0.05.
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Table 4.3.1.28 FLAURA-2: Summary of subgroup analysis of time to first PT: Uebelkeit
Safety Analysis Set, DCO 03APR2023

	Osi + Chemo (N=276)			Osi (N=275)					
Subgruppen	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]	Hazard Ratio [b]	[95%-KI] [b]	2-seitiger p-Wert [b]
Abstammung									
Chinesisch/Asiatisch	68	25 (36,8)	NE [NE; NE]	70	3 (4,3)	NE [NE; NE]	10,38	[3,64; 43,59]	<0,0001*
Nicht-chinesisch/ Asiatisch	107	42 (39,3)	NE [NE; NE]	106	9 (8,5)	NE [NE; NE]	6,30	[3,21; 13,82]	<0,0001*
Nicht-asiatisch	101	52 (51,5)	6,9 [1,8; NE]	99	16 (16,2)	NE [NE; NE]	4,25	[2,48; 7,69]	<0,0001*
Interaktion p-Wert									0,3346
Methode zur Gewebeuntersuchung									
zentral	120	32 (26,7)	NE [NE; NE]	119	7 (5,9)	NE [NE; NE]	5,16	[2,42; 12,73]	<0,0001*
lokal	156	87 (55,8)	2,8 [0,9;26,4]	156	21 (13,5)	NE [NE; NE]	6,21	[3,93; 10,28]	<0,0001*
Interaktion p-Wert									0,7039
WHO Performance-Status									
0	100	39 (39,0)	NE [NE; NE]	100	14 (14,0)	NE [NE; NE]	3,64	[2,02; 6,94]	<0,0001*
1	176	80 (45,5)	NE [NE; NE]	175	14 (8,0)	NE [NE; NE]	7,45	[4,37; 13,74]	<0,0001*
Interaktion p-Wert									0,0927
Raucherstatus									
Ja	90	38 (42,2)	NE [NE; NE]	96	13 (13,5)	NE [NE; NE]	4,09	[2,24; 7,98]	<0,0001*
Nein	186	81 (43,5)	NE [NE; NE]	179	15 (8,4)	NE [NE; NE]	6,81	[4,05; 12,29]	<0,0001*
Interaktion p-Wert									0,2353
Geschlecht									
Maennlich	104	41 (39,4)	NE [NE; NE]	107	9 (8,4)	NE [NE; NE]	5,97	[3,04; 13,12]	<0,0001*
Weiblich	172	78 (45,3)	NE [NE; NE]	168	19 (11,3)	NE [NE; NE]	5,34	[3,31; 9,08]	<0,0001*
Interaktion p-Wert									0,8028
Nachweis der EGFR-Mutation durch zentralen ctDNA Cobas Test									
positiv	211	87 (41,2)	NE [NE; NE]	204	21 (10,3)	NE [NE; NE]	5,24	[3,32; 8,66]	<0,0001*

Time to event of AE is defined as the time from first dose of study treatment to first onset of the respective AE or the time to censoring if the AE has not occurred by 28 days following discontinuation of study treatment, before administration of subsequent cancer therapy or death, whichever comes first. All AEs are coded using MedDRA version 25.1. Includes AEs with onset date on or after the date of first dose and up to and including 28 days following discontinuation of study treatment. Analysis done if >=10 patients at each subgroup level and >=10 events in at least one subgroup level combined for both arms. Analysis done for SOC and PT only if main effect for that SOC or PT is statistically significant at 5% level. [a] Median time to event based on the Kaplan Meier estimate. NE = Not estimable as median (or 95% CLs) is not reached. [b] Estimated from main effects of unstratified Cox proportional hazard model including trt., subgroup and subgroup-by-trt. interaction. Ties handled using Efron method and 95% CI derived from profile likelihood estimation. NC = Not calculable. HR <1 favours Osimertinib+Chemo. * p<0.05.
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Table 4.3.1.28 FLAURA-2: Summary of subgroup analysis of time to first PT: Uebelkeit
Safety Analysis Set, DCO 03APR2023

	Osi + Chemo (N=276)			Osi (N=275)					
Subgruppen	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]	Hazard Ratio [b]	[95%-KI] [b]	2-seitiger p-Wert [b]
negativ	41	19 (46,3)	NE [NE; NE]	39	4 (10,3)	NE [NE; NE]	6,16	[2,32; 21,26]	0,0001*
unbekannt	24	13 (54,2)	4,2 [0,8; NE]	32	3 (9,4)	NE [NE; NE]	7,28	[2,34; 31,75]	0,0003*
Interaktion p-Wert									0,8687
EGFR-Mutationstyp									
Exon 19 Deletion	172	77 (44,8)	NE [NE; NE]	167	17 (10,2)	NE [NE; NE]	6,17	[3,74; 10,78]	<0,0001*
Exon 21 (L858R) Substitutionsmutation	104	42 (40,4)	NE [NE; NE]	106	11 (10,4)	NE [NE; NE]	4,59	[2,45; 9,37]	<0,0001*
Interaktion p-Wert									0,4962
Zentral bestätigte EGFR-Mutation im Gewebe									
positiv	248	102 (41,1)	NE [NE; NE]	238	24 (10,1)	NE [NE; NE]	5,28	[3,45; 8,43]	<0,0001*
negativ	3	1 (33,3)	NE [NE; NE]	4	1 (25,0)	NE [NE; NE]	NC	[NC]	NC
unbekannt	25	16 (64,0)	2,1 [0,3; NE]	33	3 (9,1)	NE [NE; NE]	11,03	[3,67; 47,47]	<0,0001*
Interaktion p-Wert									0,2425
ZNS-Metastasen zur Baseline									
Ja	113	49 (43,4)	NE [NE; NE]	110	12 (10,9)	NE [NE; NE]	5,13	[2,83; 10,11]	<0,0001*
Nein	163	70 (42,9)	NE [NE; NE]	165	16 (9,7)	NE [NE; NE]	5,86	[3,49; 10,45]	<0,0001*
Interaktion p-Wert									0,7566
Zentrale Bestätigung der EGFR-Mutation									
Zentral bestätigte EGFR-Mutation in Gewebe oder ctDNA	263	111 (42,2)	NE [NE; NE]	266	27 (10,2)	NE [NE; NE]	5,41	[3,61; 8,41]	<0,0001*
Keine zentrale Bestätigung	13	8 (61,5)	2,1 [0,1; NE]	9	1 (11,1)	NE [NE; NE]	8,31	[1,52;154,17]	0,0110*
Interaktion p-Wert									0,6767
Alter bei Screening									

Time to event of AE is defined as the time from first dose of study treatment to first onset of the respective AE or the time to censoring if the AE has not occurred by 28 days following discontinuation of study treatment, before administration of subsequent cancer therapy or death, whichever comes first. All AEs are coded using MedDRA version 25.1. Includes AEs with onset date on or after the date of first dose and up to and including 28 days following discontinuation of study treatment. Analysis done if >=10 patients at each subgroup level and >=10 events in at least one subgroup level combined for both arms. Analysis done for SOC and PT only if main effect for that SOC or PT is statistically significant at 5% level. [a] Median time to event based on the Kaplan Meier estimate. NE = Not estimable as median (or 95% CLs) is not reached. [b] Estimated from main effects of unstratified Cox proportional hazard model including trt., subgroup and subgroup-by-trt. interaction. Ties handled using Efron method and 95% CI derived from profile likelihood estimation. NC = Not calculable. HR <1 favours Osimertinib+Chemo. * p<0.05.
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Table 4.3.1.28 FLAURA-2: Summary of subgroup analysis of time to first PT: Uebelkeit
Safety Analysis Set, DCO 03APR2023

	Osi + Chemo (N=276)			Osi (N=275)					
Subgruppen	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]	Hazard Ratio [b]	[95%-KI] [b]	2-seitiger p-Wert [b]
<65 Jahre	172	78 (45,3)	NE [NE; NE]	164	15 (9,1)	NE [NE; NE]	6,83	[4,05; 12,34]	<0,0001*
>=65 Jahre	104	41 (39,4)	NE [NE; NE]	111	13 (11,7)	NE [NE; NE]	4,08	[2,25; 7,92]	<0,0001*
Interaktion p-Wert									0,2282
Region gPAP									
Asien	168	62 (36,9)	NE [NE; NE]	166	10 (6,0)	NE [NE; NE]	7,85	[4,22; 16,28]	<0,0001*
Europa	22	11 (50,0)	6,4 [0,2; NE]	23	2 (8,7)	NE [NE; NE]	8,23	[2,21; 53,16]	0,0009*
Nordamerika	20	13 (65,0)	0,6 [0,1; NE]	22	7 (31,8)	NE [NE; NE]	3,17	[1,30; 8,45]	0,0112*
Rest der Welt	66	33 (50,0)	8,5 [1,8; NE]	64	9 (14,1)	NE [NE; NE]	4,65	[2,32; 10,34]	<0,0001*
Interaktion p-Wert									0,4014

Time to event of AE is defined as the time from first dose of study treatment to first onset of the respective AE or the time to censoring if the AE has not occurred by 28 days following discontinuation of study treatment, before administration of subsequent cancer therapy or death, whichever comes first. All AEs are coded using MedDRA version 25.1. Includes AEs with onset date on or after the date of first dose and up to and including 28 days following discontinuation of study treatment. Analysis done if >=10 patients at each subgroup level and >=10 events in at least one subgroup level combined for both arms. Analysis done for SOC and PT only if main effect for that SOC or PT is statistically significant at 5% level. [a] Median time to event based on the Kaplan Meier estimate. NE = Not estimable as median (or 95% CLs) is not reached. [b] Estimated from main effects of unstratified Cox proportional hazard model including trt., subgroup and subgroup-by-trt. interaction. Ties handled using Efron method and 95% CI derived from profile likelihood estimation. NC = Not calculable. HR <1 favours Osimertinib+Chemo. * p<0.05.
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Table 4.3.1.29 FLAURA-2: Summary of subgroup analysis of time to first SOC: Erkrankungen des Nervensystems
Safety Analysis Set, DCO 03APR2023

	Osi + Chemo (N=276)			Osi (N=275)					
Subgruppen	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]	Hazard Ratio [b]	[95%-KI] [b]	2-seitiger p-Wert [b]
Abstammung									
Chinesisch/Asiatisch	68	22 (32,4)	NE [NE; NE]	70	15 (21,4)	NE [NE; NE]	1,47	[0,77; 2,89]	0,2473
Nicht-chinesisch/ Asiatisch	107	39 (36,4)	NE [NE; NE]	106	27 (25,5)	NE [NE; NE]	1,69	[1,04; 2,79]	0,0339*
Nicht-asiatisch	101	42 (41,6)	NE [NE; NE]	99	33 (33,3)	NE [NE; NE]	1,35	[0,86; 2,14]	0,1974
Interaktion p-Wert									0,8006
Methode zur Gewebeuntersuchung									
zentral	120	23 (19,2)	NE [NE; NE]	119	27 (22,7)	NE [NE; NE]	0,82	[0,47; 1,44]	0,4950
lokal	156	80 (51,3)	13,8 [5,5; NE]	156	48 (30,8)	NE [NE; NE]	2,01	[1,41; 2,89]	<0,0001*
Interaktion p-Wert									0,0081*
WHO Performance-Status									
0	100	39 (39,0)	NE [NE; NE]	100	31 (31,0)	NE [NE; NE]	1,45	[0,91; 2,35]	0,1181
1	176	64 (36,4)	NE [NE; NE]	175	44 (25,1)	NE [NE; NE]	1,52	[1,04; 2,25]	0,0301*
Interaktion p-Wert									0,8809
Raucherstatus									
Ja	90	33 (36,7)	NE [NE; NE]	96	25 (26,0)	NE [NE; NE]	1,51	[0,90; 2,56]	0,1206
Nein	186	70 (37,6)	NE [NE; NE]	179	50 (27,9)	NE [NE; NE]	1,48	[1,03; 2,14]	0,0318*
Interaktion p-Wert									0,9643
Geschlecht									
Maennlich	104	41 (39,4)	NE [NE; NE]	107	27 (25,2)	NE [NE; NE]	1,69	[1,05; 2,78]	0,0312*
Weiblich	172	62 (36,0)	NE [NE; NE]	168	48 (28,6)	NE [NE; NE]	1,38	[0,95; 2,02]	0,0940
Interaktion p-Wert									0,5093
Nachweis der EGFR-Mutation durch zentralen ctDNA Cobas Test									
positiv	211	70 (33,2)	NE [NE; NE]	204	53 (26,0)	NE [NE; NE]	1,36	[0,96; 1,95]	0,0880

Time to event of AE is defined as the time from first dose of study treatment to first onset of the respective AE or the time to censoring if the AE has not occurred by 28 days following discontinuation of study treatment, before administration of subsequent cancer therapy or death, whichever comes first. All AEs are coded using MedDRA version 25.1. Includes AEs with onset date on or after the date of first dose and up to and including 28 days following discontinuation of study treatment. Analysis done if >=10 patients at each subgroup level and >=10 events in at least one subgroup level combined for both arms. Analysis done for SOC and PT only if main effect for that SOC or PT is statistically significant at 5% level. [a] Median time to event based on the Kaplan Meier estimate. NE = Not estimable as median (or 95% CLs) is not reached. [b] Estimated from main effects of unstratified Cox proportional hazard model including trt., subgroup and subgroup-by-trt. interaction. Ties handled using Efron method and 95% CI derived from profile likelihood estimation. NC = Not calculable. HR <1 favours Osimertinib+Chemo. * p<0.05.
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Table 4.3.1.29 FLAURA-2: Summary of subgroup analysis of time to first SOC: Erkrankungen des Nervensystems
Safety Analysis Set, DCO 03APR2023

	Osi + Chemo (N=276)			Osi (N=275)					
Subgruppen	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]	Hazard Ratio [b]	[95%-KI] [b]	2-seitiger p-Wert [b]
negativ	41	15 (36,6)	NE [NE; NE]	39	9 (23,1)	NE [NE; NE]	1,96	[0,87; 4,66]	0,1052
unbekannt	24	18 (75,0)	3,0 [0,8;18,5]	32	13 (40,6)	NE [NE; NE]	2,13	[1,05; 4,45]	0,0359*
Interaktion p-Wert									0,4524
EGFR-Mutationstyp									
Exon 19 Deletion	172	62 (36,0)	NE [NE; NE]	167	46 (27,5)	NE [NE; NE]	1,46	[0,998; 2,15]	0,0510
Exon 21 (L858R) Substitutionsmutation	104	41 (39,4)	NE [NE; NE]	106	29 (27,4)	NE [NE; NE]	1,51	[0,95; 2,46]	0,0846
Interaktion p-Wert									0,9041
Zentral bestätigte EGFR-Mutation im Gewebe									
positiv	248	86 (34,7)	NE [NE; NE]	238	65 (27,3)	NE [NE; NE]	1,34	[0,97; 1,86]	0,0714
negativ	3	1 (33,3)	NE [NE; NE]	4	0	NE [NE; NE]	NC	[NC]	NC
unbekannt	25	16 (64,0)	2,7 [1,3;18,7]	33	10 (30,3)	NE [NE; NE]	3,38	[1,55; 7,72]	0,0022*
Interaktion p-Wert									0,0320*
ZNS-Metastasen zur Baseline									
Ja	113	37 (32,7)	NE [NE; NE]	110	35 (31,8)	NE [NE; NE]	1,03	[0,65; 1,64]	0,9075
Nein	163	66 (40,5)	NE [NE; NE]	165	40 (24,2)	NE [NE; NE]	1,93	[1,31; 2,88]	0,0009*
Interaktion p-Wert									0,0419*
Zentrale Bestätigung der EGFR-Mutation									
Zentral bestätigte EGFR-Mutation in Gewebe oder ctDNA	263	94 (35,7)	NE [NE; NE]	266	72 (27,1)	NE [NE; NE]	1,41	[1,04; 1,93]	0,0261*
Keine zentrale Bestätigung	13	9 (69,2)	2,3 [0,2; NE]	9	3 (33,3)	30,5 [0,7; NE]	3,52	[1,05; 15,88]	0,0415*
Interaktion p-Wert									0,1596
Alter bei Screening									

Time to event of AE is defined as the time from first dose of study treatment to first onset of the respective AE or the time to censoring if the AE has not occurred by 28 days following discontinuation of study treatment, before administration of subsequent cancer therapy or death, whichever comes first. All AEs are coded using MedDRA version 25.1. Includes AEs with onset date on or after the date of first dose and up to and including 28 days following discontinuation of study treatment. Analysis done if >=10 patients at each subgroup level and >=10 events in at least one subgroup level combined for both arms. Analysis done for SOC and PT only if main effect for that SOC or PT is statistically significant at 5% level. [a] Median time to event based on the Kaplan Meier estimate. NE = Not estimable as median (or 95% CLs) is not reached. [b] Estimated from main effects of unstratified Cox proportional hazard model including trt., subgroup and subgroup-by-trt. interaction. Ties handled using Efron method and 95% CI derived from profile likelihood estimation. NC = Not calculable. HR <1 favours Osimertinib+Chemo. * p<0.05.
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Table 4.3.1.29 FLAURA-2: Summary of subgroup analysis of time to first SOC: Erkrankungen des Nervensystems
Safety Analysis Set, DCO 03APR2023

	Osi + Chemo (N=276)			Osi (N=275)					
Subgruppen	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]	Hazard Ratio [b]	[95%-KI] [b]	2-seitiger p-Wert [b]
<65 Jahre	172	69 (40,1)	NE [NE; NE]	164	49 (29,9)	NE [NE; NE]	1,39	[0,97; 2,02]	0,0735
>=65 Jahre	104	34 (32,7)	NE [NE; NE]	111	26 (23,4)	NE [NE; NE]	1,66	[0,997; 2,79]	0,0513
Interaktion p-Wert									0,5895
Region gPAP									
Asien	168	54 (32,1)	NE [NE; NE]	166	37 (22,3)	NE [NE; NE]	1,56	[1,03; 2,39]	0,0355*
Europa	22	9 (40,9)	NE [NE; NE]	23	2 (8,7)	NE [NE; NE]	5,23	[1,35; 34,32]	0,0149*
Nordamerika	20	15 (75,0)	1,4 [0,5; 3,1]	22	15 (68,2)	5,5 [1,3; NE]	1,65	[0,80; 3,41]	0,1749
Rest der Welt	66	25 (37,9)	NE [NE; NE]	64	21 (32,8)	NE [NE; NE]	1,22	[0,68; 2,20]	0,5004
Interaktion p-Wert									0,2961

Time to event of AE is defined as the time from first dose of study treatment to first onset of the respective AE or the time to censoring if the AE has not occurred by 28 days following discontinuation of study treatment, before administration of subsequent cancer therapy or death, whichever comes first. All AEs are coded using MedDRA version 25.1. Includes AEs with onset date on or after the date of first dose and up to and including 28 days following discontinuation of study treatment. Analysis done if >=10 patients at each subgroup level and >=10 events in at least one subgroup level combined for both arms. Analysis done for SOC and PT only if main effect for that SOC or PT is statistically significant at 5% level. [a] Median time to event based on the Kaplan Meier estimate. NE = Not estimable as median (or 95% CLs) is not reached. [b] Estimated from main effects of unstratified Cox proportional hazard model including trt., subgroup and subgroup-by-trt. interaction. Ties handled using Efron method and 95% CI derived from profile likelihood estimation. NC = Not calculable. HR <1 favours Osimertinib+Chemo. * p<0.05.
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Table 4.3.1.30 FLAURA-2: Summary of subgroup analysis of time to first PT: Periphere sensorische Neuropathie
Safety Analysis Set, DCO 03APR2023

	Osi + Chemo (N=276)			Osi (N=275)					
Subgruppen	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]	Hazard Ratio [b]	[95%-KI] [b]	2-seitiger p-Wert [b]
Abstammung									
Chinesisch/Asiatisch	68	1 (1,5)	NE [NE; NE]	70	0	NE [NE; NE]	NC	[NC]	NC
Nicht-chinesisch/ Asiatisch	107	7 (6,5)	NE [NE; NE]	106	0	NE [NE; NE]	NC	[NC]	NC
Nicht-asiatisch	101	3 (3,0)	NE [NE; NE]	99	1 (1,0)	NE [NE; NE]	NC	[NC]	NC
Interaktion p-Wert									NC
Methode zur Gewebeuntersuchung									
zentral	120	0	NE [NE; NE]	119	0	NE [NE; NE]	NC	[NC]	NC
lokal	156	11 (7,1)	NE [NE; NE]	156	1 (0,6)	NE [NE; NE]	11,06	[2,15;202,13]	0,0018*
Interaktion p-Wert									NC
WHO Performance-Status									
0	100	3 (3,0)	NE [NE; NE]	100	1 (1,0)	NE [NE; NE]	NC	[NC]	NC
1	176	8 (4,5)	NE [NE; NE]	175	0	NE [NE; NE]	NC	[NC]	NC
Interaktion p-Wert									NC
Raucherstatus									
Ja	90	6 (6,7)	NE [NE; NE]	96	0	NE [NE; NE]	NC	[NC]	NC
Nein	186	5 (2,7)	NE [NE; NE]	179	1 (0,6)	NE [NE; NE]	NC	[NC]	NC
Interaktion p-Wert									NC
Geschlecht									
Maennlich	104	3 (2,9)	NE [NE; NE]	107	0	NE [NE; NE]	NC	[NC]	NC
Weiblich	172	8 (4,7)	NE [NE; NE]	168	1 (0,6)	NE [NE; NE]	NC	[NC]	NC
Interaktion p-Wert									NC
Nachweis der EGFR-Mutation durch zentralen ctDNA Cobas Test									
positiv	211	7 (3,3)	NE [NE; NE]	204	1 (0,5)	NE [NE; NE]	NC	[NC]	NC

Time to event of AE is defined as the time from first dose of study treatment to first onset of the respective AE or the time to censoring if the AE has not occurred by 28 days following discontinuation of study treatment, before administration of subsequent cancer therapy or death, whichever comes first. All AEs are coded using MedDRA version 25.1. Includes AEs with onset date on or after the date of first dose and up to and including 28 days following discontinuation of study treatment. Analysis done if >=10 patients at each subgroup level and >=10 events in at least one subgroup level combined for both arms. Analysis done for SOC and PT only if main effect for that SOC or PT is statistically significant at 5% level. [a] Median time to event based on the Kaplan Meier estimate. NE = Not estimable as median (or 95% CLs) is not reached. [b] Estimated from main effects of unstratified Cox proportional hazard model including trt., subgroup and subgroup-by-trt. interaction. Ties handled using Efron method and 95% CI derived from profile likelihood estimation. NC = Not calculable. HR <1 favours Osimertinib+Chemo. * p<0.05.
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Table 4.3.1.30 FLAURA-2: Summary of subgroup analysis of time to first PT: Periphere sensorische Neuropathie
Safety Analysis Set, DCO 03APR2023

	Osi + Chemo (N=276)			Osi (N=275)					
Subgruppen	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]	Hazard Ratio [b]	[95%-KI] [b]	2-seitiger p-Wert [b]
negativ	41	1 (2,4)	NE [NE; NE]	39	0	NE [NE; NE]	NC	[NC]	NC
unbekannt	24	3 (12,5)	NE [NE; NE]	32	0	NE [NE; NE]	NC	[NC]	NC
Interaktion p-Wert									NC
EGFR-Mutationstyp									
Exon 19 Deletion	172	7 (4,1)	NE [NE; NE]	167	1 (0,6)	NE [NE; NE]	NC	[NC]	NC
Exon 21 (L858R) Substitutionsmutation	104	4 (3,8)	NE [NE; NE]	106	0	NE [NE; NE]	NC	[NC]	NC
Interaktion p-Wert									NC
Zentral bestätigte EGFR-Mutation im Gewebe									
positiv	248	8 (3,2)	NE [NE; NE]	238	1 (0,4)	NE [NE; NE]	NC	[NC]	NC
negativ	3	1 (33,3)	NE [NE; NE]	4	0	NE [NE; NE]	NC	[NC]	NC
unbekannt	25	2 (8,0)	NE [NE; NE]	33	0	NE [NE; NE]	NC	[NC]	NC
Interaktion p-Wert									NC
ZNS-Metastasen zur Baseline									
Ja	113	6 (5,3)	NE [NE; NE]	110	0	NE [NE; NE]	NC	[NC]	NC
Nein	163	5 (3,1)	NE [NE; NE]	165	1 (0,6)	NE [NE; NE]	NC	[NC]	NC
Interaktion p-Wert									NC
Zentrale Bestätigung der EGFR-Mutation									
Zentral bestätigte EGFR-Mutation in Gewebe oder ctDNA	263	9 (3,4)	NE [NE; NE]	266	1 (0,4)	NE [NE; NE]	8,93	[1,68;164,71]	0,0069*
Keine zentrale Bestätigung	13	2 (15,4)	NE [NE; NE]	9	0	NE [NE; NE]	NC	[NC]	NC
Interaktion p-Wert									NC
Alter bei Screening									

Time to event of AE is defined as the time from first dose of study treatment to first onset of the respective AE or the time to censoring if the AE has not occurred by 28 days following discontinuation of study treatment, before administration of subsequent cancer therapy or death, whichever comes first. All AEs are coded using MedDRA version 25.1. Includes AEs with onset date on or after the date of first dose and up to and including 28 days following discontinuation of study treatment. Analysis done if >=10 patients at each subgroup level and >=10 events in at least one subgroup level combined for both arms. Analysis done for SOC and PT only if main effect for that SOC or PT is statistically significant at 5% level. [a] Median time to event based on the Kaplan Meier estimate. NE = Not estimable as median (or 95% CLs) is not reached. [b] Estimated from main effects of unstratified Cox proportional hazard model including trt., subgroup and subgroup-by-trt. interaction. Ties handled using Efron method and 95% CI derived from profile likelihood estimation. NC = Not calculable. HR <1 favours Osimertinib+Chemo. * p<0.05.
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Table 4.3.1.30 FLAURA-2: Summary of subgroup analysis of time to first PT: Periphere sensorische Neuropathie
Safety Analysis Set, DCO 03APR2023

	Osi + Chemo (N=276)			Osi (N=275)					
Subgruppen	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]	Hazard Ratio [b]	[95%-KI] [b]	2-seitiger p-Wert [b]
<65 Jahre	172	8 (4,7)	NE [NE; NE]	164	1 (0,6)	NE [NE; NE]	NC	[NC]	NC
>=65 Jahre	104	3 (2,9)	NE [NE; NE]	111	0	NE [NE; NE]	NC	[NC]	NC
Interaktion p-Wert									NC
Region gPAP									
Asien	168	6 (3,6)	NE [NE; NE]	166	0	NE [NE; NE]	NC	[NC]	NC
Europa	22	0	NE [NE; NE]	23	0	NE [NE; NE]	NC	[NC]	NC
Nordamerika	20	3 (15,0)	NE [NE; NE]	22	1 (4,5)	NE [NE; NE]	NC	[NC]	NC
Rest der Welt	66	2 (3,0)	NE [NE; NE]	64	0	NE [NE; NE]	NC	[NC]	NC
Interaktion p-Wert									NC

Time to event of AE is defined as the time from first dose of study treatment to first onset of the respective AE or the time to censoring if the AE has not occurred by 28 days following discontinuation of study treatment, before administration of subsequent cancer therapy or death, whichever comes first. All AEs are coded using MedDRA version 25.1. Includes AEs with onset date on or after the date of first dose and up to and including 28 days following discontinuation of study treatment. Analysis done if >=10 patients at each subgroup level and >=10 events in at least one subgroup level combined for both arms. Analysis done for SOC and PT only if main effect for that SOC or PT is statistically significant at 5% level. [a] Median time to event based on the Kaplan Meier estimate. NE = Not estimable as median (or 95% CLs) is not reached. [b] Estimated from main effects of unstratified Cox proportional hazard model including trt., subgroup and subgroup-by-trt. interaction. Ties handled using Efron method and 95% CI derived from profile likelihood estimation. NC = Not calculable. HR <1 favours Osimertinib+Chemo. * p<0.05.
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Table 4.3.1.31 FLAURA-2: Summary of subgroup analysis of time to first PT: Schwindelgefuehl
Safety Analysis Set, DCO 03APR2023

	Osi + Chemo (N=276)			Osi (N=275)					
Subgruppen	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]	Hazard Ratio [b]	[95%-KI] [b]	2-seitiger p-Wert [b]
Abstammung									
Chinesisch/Asiatisch	68	10 (14,7)	NE [NE; NE]	70	5 (7,1)	NE [NE; NE]	1,89	[0,67; 6,08]	0,2314
Nicht-chinesisch/ Asiatisch	107	9 (8,4)	NE [NE; NE]	106	4 (3,8)	NE [NE; NE]	2,35	[0,76; 8,66]	0,1393
Nicht-asiatisch	101	13 (12,9)	NE [NE; NE]	99	7 (7,1)	NE [NE; NE]	1,75	[0,72; 4,65]	0,2238
Interaktion p-Wert									0,9262
Methode zur Gewebeuntersuchung									
zentral	120	5 (4,2)	NE [NE; NE]	119	6 (5,0)	NE [NE; NE]	0,80	[0,23; 2,66]	0,7113
lokal	156	27 (17,3)	NE [NE; NE]	156	10 (6,4)	NE [NE; NE]	2,70	[1,35; 5,86]	0,0044*
Interaktion p-Wert									0,0855
WHO Performance-Status									
0	100	17 (17,0)	NE [NE; NE]	100	9 (9,0)	NE [NE; NE]	1,97	[0,90; 4,64]	0,0903
1	176	15 (8,5)	NE [NE; NE]	175	7 (4,0)	NE [NE; NE]	2,03	[0,86; 5,32]	0,1098
Interaktion p-Wert									0,9643
Raucherstatus									
Ja	90	5 (5,6)	NE [NE; NE]	96	5 (5,2)	NE [NE; NE]	0,99	[0,27; 3,55]	0,9819
Nein	186	27 (14,5)	NE [NE; NE]	179	11 (6,1)	NE [NE; NE]	2,41	[1,23; 5,06]	0,0100*
Interaktion p-Wert									0,2212
Geschlecht									
Maennlich	104	11 (10,6)	NE [NE; NE]	107	3 (2,8)	NE [NE; NE]	3,57	[1,12; 15,80]	0,0310*
Weiblich	172	21 (12,2)	NE [NE; NE]	168	13 (7,7)	NE [NE; NE]	1,59	[0,81; 3,27]	0,1805
Interaktion p-Wert									0,2577
Nachweis der EGFR-Mutation durch zentralen ctDNA Cobas Test									
positiv	211	20 (9,5)	NE [NE; NE]	204	11 (5,4)	NE [NE; NE]	1,73	[0,84; 3,73]	0,1377

Time to event of AE is defined as the time from first dose of study treatment to first onset of the respective AE or the time to censoring if the AE has not occurred by 28 days following discontinuation of study treatment, before administration of subsequent cancer therapy or death, whichever comes first. All AEs are coded using MedDRA version 25.1. Includes AEs with onset date on or after the date of first dose and up to and including 28 days following discontinuation of study treatment. Analysis done if >=10 patients at each subgroup level and >=10 events in at least one subgroup level combined for both arms. Analysis done for SOC and PT only if main effect for that SOC or PT is statistically significant at 5% level. [a] Median time to event based on the Kaplan Meier estimate. NE = Not estimable as median (or 95% CLs) is not reached. [b] Estimated from main effects of unstratified Cox proportional hazard model including trt., subgroup and subgroup-by-trt. interaction. Ties handled using Efron method and 95% CI derived from profile likelihood estimation. NC = Not calculable. HR <1 favours Osimertinib+Chemo. * p<0.05.
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Table 4.3.1.31 FLAURA-2: Summary of subgroup analysis of time to first PT: Schwindelgefuehl
Safety Analysis Set, DCO 03APR2023

	Osi + Chemo (N=276)			Osi (N=275)					
Subgruppen	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]	Hazard Ratio [b]	[95%-KI] [b]	2-seitiger p-Wert [b]
negativ	41	6 (14,6)	NE [NE; NE]	39	2 (5,1)	NE [NE; NE]	3,05	[0,70; 20,81]	0,1417
unbekannt	24	6 (25,0)	NE [NE; NE]	32	3 (9,4)	NE [NE; NE]	2,45	[0,64; 11,59]	0,1909
Interaktion p-Wert									0,7718
EGFR-Mutationstyp									
Exon 19 Deletion	172	16 (9,3)	NE [NE; NE]	167	10 (6,0)	NE [NE; NE]	1,55	[0,71; 3,53]	0,2730
Exon 21 (L858R) Substitutionsmutation	104	16 (15,4)	NE [NE; NE]	106	6 (5,7)	NE [NE; NE]	2,64	[1,09; 7,37]	0,0314*
Interaktion p-Wert									0,3878
Zentral bestätigte EGFR-Mutation im Gewebe									
positiv	248	24 (9,7)	NE [NE; NE]	238	14 (5,9)	NE [NE; NE]	1,59	[0,83; 3,15]	0,1616
negativ	3	0	NE [NE; NE]	4	0	NE [NE; NE]	NC	[NC]	NC
unbekannt	25	8 (32,0)	NE [NE; NE]	33	2 (6,1)	NE [NE; NE]	6,74	[1,68; 44,78]	0,0058*
Interaktion p-Wert									0,0693
ZNS-Metastasen zur Baseline									
Ja	113	13 (11,5)	NE [NE; NE]	110	3 (2,7)	NE [NE; NE]	3,98	[1,28; 17,35]	0,0152*
Nein	163	19 (11,7)	NE [NE; NE]	165	13 (7,9)	NE [NE; NE]	1,50	[0,75; 3,12]	0,2533
Interaktion p-Wert									0,1647
Zentrale Bestätigung der EGFR-Mutation									
Zentral bestätigte EGFR-Mutation in Gewebe oder ctDNA	263	26 (9,9)	NE [NE; NE]	266	16 (6,0)	NE [NE; NE]	1,60	[0,87; 3,05]	0,1340
Keine zentrale Bestätigung	13	6 (46,2)	NE [NE; NE]	9	0	NE [NE; NE]	NC	[NC]	NC
Interaktion p-Wert									NC
Alter bei Screening									

Time to event of AE is defined as the time from first dose of study treatment to first onset of the respective AE or the time to censoring if the AE has not occurred by 28 days following discontinuation of study treatment, before administration of subsequent cancer therapy or death, whichever comes first. All AEs are coded using MedDRA version 25.1. Includes AEs with onset date on or after the date of first dose and up to and including 28 days following discontinuation of study treatment. Analysis done if >=10 patients at each subgroup level and >=10 events in at least one subgroup level combined for both arms. Analysis done for SOC and PT only if main effect for that SOC or PT is statistically significant at 5% level. [a] Median time to event based on the Kaplan Meier estimate. NE = Not estimable as median (or 95% CLs) is not reached. [b] Estimated from main effects of unstratified Cox proportional hazard model including trt., subgroup and subgroup-by-trt. interaction. Ties handled using Efron method and 95% CI derived from profile likelihood estimation. NC = Not calculable. HR <1 favours Osimertinib+Chemo. * p<0.05.
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Table 4.3.1.31 FLAURA-2: Summary of subgroup analysis of time to first PT: Schwindelgefuehl
Safety Analysis Set, DCO 03APR2023

	Osi + Chemo (N=276)			Osi (N=275)					
Subgruppen	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]	Hazard Ratio [b]	[95%-KI] [b]	2-seitiger p-Wert [b]
<65 Jahre	172	23 (13,4)	NE [NE; NE]	164	9 (5,5)	NE [NE; NE]	2,31	[1,10; 5,27]	0,0256*
>=65 Jahre	104	9 (8,7)	NE [NE; NE]	111	7 (6,3)	NE [NE; NE]	1,46	[0,54; 4,09]	0,4496
Interaktion p-Wert									0,4748
Region gPAP									
Asien	168	18 (10,7)	NE [NE; NE]	166	7 (4,2)	NE [NE; NE]	2,55	[1,11; 6,55]	0,0269*
Europa	22	2 (9,1)	NE [NE; NE]	23	1 (4,3)	NE [NE; NE]	1,81	[0,17; 39,00]	0,6180
Nordamerika	20	6 (30,0)	NE [NE; NE]	22	4 (18,2)	NE [NE; NE]	1,99	[0,57; 7,80]	0,2814
Rest der Welt	66	6 (9,1)	NE [NE; NE]	64	4 (6,3)	NE [NE; NE]	1,35	[0,39; 5,30]	0,6354
Interaktion p-Wert									0,8839

Time to event of AE is defined as the time from first dose of study treatment to first onset of the respective AE or the time to censoring if the AE has not occurred by 28 days following discontinuation of study treatment, before administration of subsequent cancer therapy or death, whichever comes first. All AEs are coded using MedDRA version 25.1. Includes AEs with onset date on or after the date of first dose and up to and including 28 days following discontinuation of study treatment. Analysis done if >=10 patients at each subgroup level and >=10 events in at least one subgroup level combined for both arms. Analysis done for SOC and PT only if main effect for that SOC or PT is statistically significant at 5% level. [a] Median time to event based on the Kaplan Meier estimate. NE = Not estimable as median (or 95% CLs) is not reached. [b] Estimated from main effects of unstratified Cox proportional hazard model including trt., subgroup and subgroup-by-trt. interaction. Ties handled using Efron method and 95% CI derived from profile likelihood estimation. NC = Not calculable. HR <1 favours Osimertinib+Chemo. * p<0.05.
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Table 4.3.1.32 FLAURA-2: Summary of subgroup analysis of time to first PT: Konjunktivitis
Safety Analysis Set, DCO 03APR2023

	Osi + Chemo (N=276)			Osi (N=275)					
Subgruppen	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]	Hazard Ratio [b]	[95%-KI] [b]	2-seitiger p-Wert [b]
Abstammung									
Chinesisch/Asiatisch	68	3 (4,4)	NE [NE; NE]	70	0	NE [NE; NE]	NC	[NC]	NC
Nicht-chinesisch/ Asiatisch	107	7 (6,5)	NE [NE; NE]	106	3 (2,8)	NE [NE; NE]	2,33	[0,65; 10,83]	0,2003
Nicht-asiatisch	101	6 (5,9)	NE [NE; NE]	99	0	NE [NE; NE]	NC	[NC]	NC
Interaktion p-Wert									NC
Methode zur Gewebeuntersuchung									
zentral	120	4 (3,3)	NE [NE; NE]	119	0	NE [NE; NE]	NC	[NC]	NC
lokal	156	12 (7,7)	NE [NE; NE]	156	3 (1,9)	NE [NE; NE]	3,79	[1,20; 16,63]	0,0215*
Interaktion p-Wert									NC
WHO Performance-Status									
0	100	5 (5,0)	NE [NE; NE]	100	2 (2,0)	NE [NE; NE]	2,54	[0,55; 17,75]	0,2405
1	176	11 (6,3)	NE [NE; NE]	175	1 (0,6)	NE [NE; NE]	10,36	[2,01;189,41]	0,0025*
Interaktion p-Wert									0,2772
Raucherstatus									
Ja	90	6 (6,7)	NE [NE; NE]	96	1 (1,0)	NE [NE; NE]	6,26	[1,07;118,29]	0,0410*
Nein	186	10 (5,4)	NE [NE; NE]	179	2 (1,1)	NE [NE; NE]	4,68	[1,23; 30,47]	0,0213*
Interaktion p-Wert									0,8250
Geschlecht									
Maennlich	104	8 (7,7)	NE [NE; NE]	107	0	NE [NE; NE]	NC	[NC]	NC
Weiblich	172	8 (4,7)	NE [NE; NE]	168	3 (1,8)	NE [NE; NE]	2,52	[0,73; 11,52]	0,1494
Interaktion p-Wert									NC
Nachweis der EGFR-Mutation durch zentralen ctDNA Cobas Test									
positiv	211	13 (6,2)	NE [NE; NE]	204	3 (1,5)	NE [NE; NE]	4,14	[1,33; 18,07]	0,0122*

Time to event of AE is defined as the time from first dose of study treatment to first onset of the respective AE or the time to censoring if the AE has not occurred by 28 days following discontinuation of study treatment, before administration of subsequent cancer therapy or death, whichever comes first. All AEs are coded using MedDRA version 25.1. Includes AEs with onset date on or after the date of first dose and up to and including 28 days following discontinuation of study treatment. Analysis done if >=10 patients at each subgroup level and >=10 events in at least one subgroup level combined for both arms. Analysis done for SOC and PT only if main effect for that SOC or PT is statistically significant at 5% level. [a] Median time to event based on the Kaplan Meier estimate. NE = Not estimable as median (or 95% CLs) is not reached. [b] Estimated from main effects of unstratified Cox proportional hazard model including trt., subgroup and subgroup-by-trt. interaction. Ties handled using Efron method and 95% CI derived from profile likelihood estimation. NC = Not calculable. HR <1 favours Osimertinib+Chemo. * p<0.05.
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Table 4.3.1.32 FLAURA-2: Summary of subgroup analysis of time to first PT: Konjunktivitis
Safety Analysis Set, DCO 03APR2023

	Osi + Chemo (N=276)			Osi (N=275)					
Subgruppen	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]	Hazard Ratio [b]	[95%-KI] [b]	2-seitiger p-Wert [b]
negativ	41	3 (7,3)	NE [NE; NE]	39	0	NE [NE; NE]	NC	[NC]	NC
unbekannt	24	0	NE [NE; NE]	32	0	NE [NE; NE]	NC	[NC]	NC
Interaktion p-Wert									NC
EGFR-Mutationstyp									
Exon 19 Deletion	172	10 (5,8)	NE [NE; NE]	167	2 (1,2)	NE [NE; NE]	4,91	[1,29; 31,93]	0,0173*
Exon 21 (L858R)	104	6 (5,8)	NE [NE; NE]	106	1 (0,9)	NE [NE; NE]	5,62	[0,96;106,21]	0,0564
Substitutionsmutation									
Interaktion p-Wert									0,9179
Zentral bestätigte EGFR-Mutation im Gewebe									
positiv	248	15 (6,0)	NE [NE; NE]	238	3 (1,3)	NE [NE; NE]	4,60	[1,52; 19,88]	0,0054*
negativ	3	0	NE [NE; NE]	4	0	NE [NE; NE]	NC	[NC]	NC
unbekannt	25	1 (4,0)	NE [NE; NE]	33	0	NE [NE; NE]	NC	[NC]	NC
Interaktion p-Wert									NC
ZNS-Metastasen zur Baseline									
Ja	113	4 (3,5)	NE [NE; NE]	110	1 (0,9)	NE [NE; NE]	3,50	[0,52; 68,48]	0,2138
Nein	163	12 (7,4)	NE [NE; NE]	165	2 (1,2)	NE [NE; NE]	6,22	[1,70; 39,97]	0,0040*
Interaktion p-Wert									0,6783
Zentrale Bestätigung der EGFR-Mutation									
Zentral bestätigte EGFR-Mutation in Gewebe oder ctDNA	263	16 (6,1)	NE [NE; NE]	266	3 (1,1)	NE [NE; NE]	5,25	[1,75; 22,59]	0,0020*
Keine zentrale Bestätigung	13	0	NE [NE; NE]	9	0	NE [NE; NE]	NC	[NC]	NC
Interaktion p-Wert									NC
Alter bei Screening									

Time to event of AE is defined as the time from first dose of study treatment to first onset of the respective AE or the time to censoring if the AE has not occurred by 28 days following discontinuation of study treatment, before administration of subsequent cancer therapy or death, whichever comes first. All AEs are coded using MedDRA version 25.1. Includes AEs with onset date on or after the date of first dose and up to and including 28 days following discontinuation of study treatment. Analysis done if >=10 patients at each subgroup level and >=10 events in at least one subgroup level combined for both arms. Analysis done for SOC and PT only if main effect for that SOC or PT is statistically significant at 5% level. [a] Median time to event based on the Kaplan Meier estimate. NE = Not estimable as median (or 95% CLs) is not reached. [b] Estimated from main effects of unstratified Cox proportional hazard model including trt., subgroup and subgroup-by-trt. interaction. Ties handled using Efron method and 95% CI derived from profile likelihood estimation. NC = Not calculable. HR <1 favours Osimertinib+Chemo. * p<0.05.
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Table 4.3.1.32 FLAURA-2: Summary of subgroup analysis of time to first PT: Konjunktivitis
Safety Analysis Set, DCO 03APR2023

	Osi + Chemo (N=276)			Osi (N=275)					
Subgruppen	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]	Hazard Ratio [b]	[95%-KI] [b]	2-seitiger p-Wert [b]
<65 Jahre	172	13 (7,6)	NE [NE; NE]	164	2 (1,2)	NE [NE; NE]	5,91	[1,63; 37,83]	0,0047*
>=65 Jahre	104	3 (2,9)	NE [NE; NE]	111	1 (0,9)	NE [NE; NE]	3,26	[0,42; 65,95]	0,2690
Interaktion p-Wert									0,6739
Region gPAP									
Asien	168	9 (5,4)	NE [NE; NE]	166	3 (1,8)	NE [NE; NE]	2,79	[0,83; 12,58]	0,0998
Europa	22	2 (9,1)	NE [NE; NE]	23	0	NE [NE; NE]	NC	[NC]	NC
Nordamerika	20	0	NE [NE; NE]	22	0	NE [NE; NE]	NC	[NC]	NC
Rest der Welt	66	5 (7,6)	NE [NE; NE]	64	0	NE [NE; NE]	NC	[NC]	NC
Interaktion p-Wert									NC

Time to event of AE is defined as the time from first dose of study treatment to first onset of the respective AE or the time to censoring if the AE has not occurred by 28 days following discontinuation of study treatment, before administration of subsequent cancer therapy or death, whichever comes first. All AEs are coded using MedDRA version 25.1. Includes AEs with onset date on or after the date of first dose and up to and including 28 days following discontinuation of study treatment. Analysis done if >=10 patients at each subgroup level and >=10 events in at least one subgroup level combined for both arms. Analysis done for SOC and PT only if main effect for that SOC or PT is statistically significant at 5% level. [a] Median time to event based on the Kaplan Meier estimate. NE = Not estimable as median (or 95% CLs) is not reached. [b] Estimated from main effects of unstratified Cox proportional hazard model including trt., subgroup and subgroup-by-trt. interaction. Ties handled using Efron method and 95% CI derived from profile likelihood estimation. NC = Not calculable. HR <1 favours Osimertinib+Chemo. * p<0.05.
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Table 4.3.1.33 FLAURA-2: Summary of subgroup analysis of time to first SOC: Leber- und Gallenerkrankungen
Safety Analysis Set, DCO 03APR2023

	Osi + Chemo (N=276)			Osi (N=275)					
Subgruppen	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]	Hazard Ratio [b]	[95%-KI] [b]	2-seitiger p-Wert [b]
Abstammung									
Chinesisch/Asiatisch	68	6 (8,8)	NE [NE; NE]	70	4 (5,7)	NE [NE; NE]	1,48	[0,42; 5,80]	0,5369
Nicht-chinesisch/ Asiatisch	107	10 (9,3)	NE [NE; NE]	106	2 (1,9)	NE [NE; NE]	5,21	[1,37; 33,92]	0,0131*
Nicht-asiatisch	101	9 (8,9)	NE [NE; NE]	99	1 (1,0)	NE [NE; NE]	9,36	[1,76;172,52]	0,0056*
Interaktion p-Wert									0,2196
Methode zur Gewebeuntersuchung									
zentral	120	12 (10,0)	NE [NE; NE]	119	5 (4,2)	NE [NE; NE]	2,45	[0,91; 7,71]	0,0769
lokal	156	13 (8,3)	NE [NE; NE]	156	2 (1,3)	NE [NE; NE]	6,70	[1,85; 42,86]	0,0022*
Interaktion p-Wert									0,2607
WHO Performance-Status									
0	100	4 (4,0)	NE [NE; NE]	100	1 (1,0)	NE [NE; NE]	4,15	[0,61; 81,21]	0,1529
1	176	21 (11,9)	NE [NE; NE]	175	6 (3,4)	NE [NE; NE]	3,57	[1,53; 9,74]	0,0025*
Interaktion p-Wert									0,9000
Raucherstatus									
Ja	90	8 (8,9)	NE [NE; NE]	96	3 (3,1)	NE [NE; NE]	2,88	[0,83; 13,16]	0,0965
Nein	186	17 (9,1)	NE [NE; NE]	179	4 (2,2)	NE [NE; NE]	4,26	[1,58; 14,81]	0,0032*
Interaktion p-Wert									0,6570
Geschlecht									
Maennlich	104	12 (11,5)	NE [NE; NE]	107	4 (3,7)	NE [NE; NE]	3,01	[1,05; 10,78]	0,0399*
Weiblich	172	13 (7,6)	NE [NE; NE]	168	3 (1,8)	NE [NE; NE]	4,51	[1,45; 19,69]	0,0075*
Interaktion p-Wert									0,6379
Nachweis der EGFR-Mutation durch zentralen ctDNA Cobas Test									
positiv	211	21 (10,0)	NE [NE; NE]	204	4 (2,0)	NE [NE; NE]	5,31	[2,02; 18,21]	0,0003*

Time to event of AE is defined as the time from first dose of study treatment to first onset of the respective AE or the time to censoring if the AE has not occurred by 28 days following discontinuation of study treatment, before administration of subsequent cancer therapy or death, whichever comes first. All AEs are coded using MedDRA version 25.1. Includes AEs with onset date on or after the date of first dose and up to and including 28 days following discontinuation of study treatment. Analysis done if >=10 patients at each subgroup level and >=10 events in at least one subgroup level combined for both arms. Analysis done for SOC and PT only if main effect for that SOC or PT is statistically significant at 5% level. [a] Median time to event based on the Kaplan Meier estimate. NE = Not estimable as median (or 95% CLs) is not reached. [b] Estimated from main effects of unstratified Cox proportional hazard model including trt., subgroup and subgroup-by-trt. interaction. Ties handled using Efron method and 95% CI derived from profile likelihood estimation. NC = Not calculable. HR <1 favours Osimertinib+Chemo. * p<0.05.
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Table 4.3.1.33 FLAURA-2: Summary of subgroup analysis of time to first SOC: Leber- und Gallenerkrankungen
Safety Analysis Set, DCO 03APR2023

	Osi + Chemo (N=276)			Osi (N=275)					
Subgruppen	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]	Hazard Ratio [b]	[95%-KI] [b]	2-seitiger p-Wert [b]
negativ	41	2 (4,9)	NE [NE; NE]	39	2 (5,1)	NE [NE; NE]	0,98	[0,12; 8,13]	0,9804
unbekannt	24	2 (8,3)	NE [NE; NE]	32	1 (3,1)	NE [NE; NE]	2,49	[0,24; 53,63]	0,4398
Interaktion p-Wert									0,3273
EGFR-Mutationstyp									
Exon 19 Deletion	172	18 (10,5)	NE [NE; NE]	167	5 (3,0)	NE [NE; NE]	3,68	[1,47; 11,16]	0,0044*
Exon 21 (L858R) Substitutionsmutation	104	7 (6,7)	NE [NE; NE]	106	2 (1,9)	NE [NE; NE]	3,56	[0,86; 23,87]	0,0821
Interaktion p-Wert									0,9704
Zentral bestätigte EGFR-Mutation im Gewebe									
positiv	248	25 (10,1)	NE [NE; NE]	238	7 (2,9)	NE [NE; NE]	3,56	[1,62; 8,91]	0,0011*
negativ	3	0	NE [NE; NE]	4	0	NE [NE; NE]	NC	[NC]	NC
unbekannt	25	0	NE [NE; NE]	33	0	NE [NE; NE]	NC	[NC]	NC
Interaktion p-Wert									NC
ZNS-Metastasen zur Baseline									
Ja	113	8 (7,1)	NE [NE; NE]	110	3 (2,7)	NE [NE; NE]	2,50	[0,72; 11,41]	0,1529
Nein	163	17 (10,4)	NE [NE; NE]	165	4 (2,4)	NE [NE; NE]	4,65	[1,72; 16,16]	0,0017*
Interaktion p-Wert									0,4830
Zentrale Bestätigung der EGFR-Mutation									
Zentral bestätigte EGFR-Mutation in Gewebe oder ctDNA	263	25 (9,5)	NE [NE; NE]	266	7 (2,6)	NE [NE; NE]	3,75	[1,71; 9,39]	0,0007*
Keine zentrale Bestätigung	13	0	NE [NE; NE]	9	0	NE [NE; NE]	NC	[NC]	NC
Interaktion p-Wert									NC
Alter bei Screening									

Time to event of AE is defined as the time from first dose of study treatment to first onset of the respective AE or the time to censoring if the AE has not occurred by 28 days following discontinuation of study treatment, before administration of subsequent cancer therapy or death, whichever comes first. All AEs are coded using MedDRA version 25.1. Includes AEs with onset date on or after the date of first dose and up to and including 28 days following discontinuation of study treatment. Analysis done if >=10 patients at each subgroup level and >=10 events in at least one subgroup level combined for both arms. Analysis done for SOC and PT only if main effect for that SOC or PT is statistically significant at 5% level. [a] Median time to event based on the Kaplan Meier estimate. NE = Not estimable as median (or 95% CLs) is not reached. [b] Estimated from main effects of unstratified Cox proportional hazard model including trt., subgroup and subgroup-by-trt. interaction. Ties handled using Efron method and 95% CI derived from profile likelihood estimation. NC = Not calculable. HR <1 favours Osimertinib+Chemo. * p<0.05.
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Table 4.3.1.33 FLAURA-2: Summary of subgroup analysis of time to first SOC: Leber- und Gallenerkrankungen
Safety Analysis Set, DCO 03APR2023

	Osi + Chemo (N=276)			Osi (N=275)					
Subgruppen	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]	Hazard Ratio [b]	[95%-KI] [b]	2-seitiger p-Wert [b]
<65 Jahre	172	18 (10,5)	NE [NE; NE]	164	7 (4,3)	NE [NE; NE]	2,46	[1,07; 6,32]	0,0336*
>=65 Jahre	104	7 (6,7)	NE [NE; NE]	111	0	NE [NE; NE]	NC	[NC]	NC
Interaktion p-Wert									NC
Region gPAP									
Asien	168	15 (8,9)	NE [NE; NE]	166	6 (3,6)	NE [NE; NE]	2,50	[1,02; 7,01]	0,0459*
Europa	22	0	NE [NE; NE]	23	0	NE [NE; NE]	NC	[NC]	NC
Nordamerika	20	1 (5,0)	NE [NE; NE]	22	1 (4,5)	NE [NE; NE]	1,21	[0,05; 30,69]	0,8911
Rest der Welt	66	9 (13,6)	NE [NE; NE]	64	0	NE [NE; NE]	NC	[NC]	NC
Interaktion p-Wert									0,6313

Time to event of AE is defined as the time from first dose of study treatment to first onset of the respective AE or the time to censoring if the AE has not occurred by 28 days following discontinuation of study treatment, before administration of subsequent cancer therapy or death, whichever comes first. All AEs are coded using MedDRA version 25.1. Includes AEs with onset date on or after the date of first dose and up to and including 28 days following discontinuation of study treatment. Analysis done if >=10 patients at each subgroup level and >=10 events in at least one subgroup level combined for both arms. Analysis done for SOC and PT only if main effect for that SOC or PT is statistically significant at 5% level. [a] Median time to event based on the Kaplan Meier estimate. NE = Not estimable as median (or 95% CLs) is not reached. [b] Estimated from main effects of unstratified Cox proportional hazard model including trt., subgroup and subgroup-by-trt. interaction. Ties handled using Efron method and 95% CI derived from profile likelihood estimation. NC = Not calculable. HR <1 favours Osimertinib+Chemo. * p<0.05.
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Table 4.3.1.34 FLAURA-2: Summary of subgroup analysis of time to first SOC: Psychiatrische Erkrankungen
Safety Analysis Set, DCO 03APR2023

	Osi + Chemo (N=276)			Osi (N=275)					
Subgruppen	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]	Hazard Ratio [b]	[95%-KI] [b]	2-seitiger p-Wert [b]
Abstammung									
Chinesisch/Asiatisch	68	15 (22,1)	NE [NE; NE]	70	6 (8,6)	NE [NE; NE]	2,57	[1,04; 7,20]	0,0399*
Nicht-chinesisch/ Asiatisch	107	15 (14,0)	NE [NE; NE]	106	8 (7,5)	NE [NE; NE]	1,93	[0,84; 4,79]	0,1240
Nicht-asiatisch	101	20 (19,8)	NE [NE; NE]	99	14 (14,1)	NE [NE; NE]	1,44	[0,73; 2,90]	0,2955
Interaktion p-Wert									0,6057
Methode zur Gewebeuntersuchung									
zentral	120	15 (12,5)	NE [NE; NE]	119	9 (7,6)	NE [NE; NE]	1,67	[0,74; 3,98]	0,2151
lokal	156	35 (22,4)	NE [NE; NE]	156	19 (12,2)	NE [NE; NE]	1,91	[1,10; 3,40]	0,0206*
Interaktion p-Wert									0,7986
WHO Performance-Status									
0	100	19 (19,0)	NE [NE; NE]	100	8 (8,0)	NE [NE; NE]	2,55	[1,15; 6,18]	0,0199*
1	176	31 (17,6)	NE [NE; NE]	175	20 (11,4)	NE [NE; NE]	1,53	[0,88; 2,73]	0,1313
Interaktion p-Wert									0,3140
Raucherstatus									
Ja	90	14 (15,6)	NE [NE; NE]	96	11 (11,5)	NE [NE; NE]	1,32	[0,60; 2,98]	0,4887
Nein	186	36 (19,4)	NE [NE; NE]	179	17 (9,5)	NE [NE; NE]	2,14	[1,22; 3,91]	0,0073*
Interaktion p-Wert									0,3328
Geschlecht									
Maennlich	104	15 (14,4)	NE [NE; NE]	107	8 (7,5)	NE [NE; NE]	1,86	[0,81; 4,61]	0,1476
Weiblich	172	35 (20,3)	NE [NE; NE]	168	20 (11,9)	NE [NE; NE]	1,82	[1,06; 3,21]	0,0294*
Interaktion p-Wert									0,9684
Nachweis der EGFR-Mutation durch zentralen ctDNA Cobas Test									
positiv	211	38 (18,0)	NE [NE; NE]	204	22 (10,8)	NE [NE; NE]	1,71	[1,02; 2,93]	0,0420*

Time to event of AE is defined as the time from first dose of study treatment to first onset of the respective AE or the time to censoring if the AE has not occurred by 28 days following discontinuation of study treatment, before administration of subsequent cancer therapy or death, whichever comes first. All AEs are coded using MedDRA version 25.1. Includes AEs with onset date on or after the date of first dose and up to and including 28 days following discontinuation of study treatment. Analysis done if >=10 patients at each subgroup level and >=10 events in at least one subgroup level combined for both arms. Analysis done for SOC and PT only if main effect for that SOC or PT is statistically significant at 5% level. [a] Median time to event based on the Kaplan Meier estimate. NE = Not estimable as median (or 95% CLs) is not reached. [b] Estimated from main effects of unstratified Cox proportional hazard model including trt., subgroup and subgroup-by-trt. interaction. Ties handled using Efron method and 95% CI derived from profile likelihood estimation. NC = Not calculable. HR <1 favours Osimertinib+Chemo. * p<0.05.
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Table 4.3.1.34 FLAURA-2: Summary of subgroup analysis of time to first SOC: Psychiatrische Erkrankungen
Safety Analysis Set, DCO 03APR2023

	Osi + Chemo (N=276)			Osi (N=275)					
Subgruppen	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]	Hazard Ratio [b]	[95%-KI] [b]	2-seitiger p-Wert [b]
negativ	41	6 (14,6)	NE [NE; NE]	39	2 (5,1)	NE [NE; NE]	2,98	[0,69; 20,31]	0,1511
unbekannt	24	6 (25,0)	NE [NE; NE]	32	4 (12,5)	NE [NE; NE]	2,06	[0,59; 8,04]	0,2578
Interaktion p-Wert									0,7864
EGFR-Mutationstyp									
Exon 19 Deletion	172	34 (19,8)	NE [NE; NE]	167	18 (10,8)	NE [NE; NE]	1,92	[1,10; 3,47]	0,0217*
Exon 21 (L858R) Substitutionsmutation	104	16 (15,4)	NE [NE; NE]	106	10 (9,4)	NE [NE; NE]	1,61	[0,74; 3,68]	0,2282
Interaktion p-Wert									0,7284
Zentral bestätigte EGFR-Mutation im Gewebe									
positiv	248	48 (19,4)	NE [NE; NE]	238	22 (9,2)	NE [NE; NE]	2,18	[1,33; 3,68]	0,0017*
negativ	3	0	NE [NE; NE]	4	1 (25,0)	NE [NE; NE]	NC	[NC]	NC
unbekannt	25	2 (8,0)	NE [NE; NE]	33	5 (15,2)	NE [NE; NE]	0,51	[0,07; 2,37]	0,4037
Interaktion p-Wert									0,0796
ZNS-Metastasen zur Baseline									
Ja	113	22 (19,5)	NE [NE; NE]	110	11 (10,0)	NE [NE; NE]	1,89	[0,94; 4,05]	0,0767
Nein	163	28 (17,2)	NE [NE; NE]	165	17 (10,3)	NE [NE; NE]	1,77	[0,98; 3,30]	0,0592
Interaktion p-Wert									0,8913
Zentrale Bestätigung der EGFR-Mutation									
Zentral bestätigte EGFR-Mutation in Gewebe oder ctDNA	263	49 (18,6)	NE [NE; NE]	266	27 (10,2)	NE [NE; NE]	1,89	[1,19; 3,06]	0,0067*
Keine zentrale Bestätigung	13	1 (7,7)	NE [NE; NE]	9	1 (11,1)	NE [NE; NE]	0,64	[0,03; 16,08]	0,7505
Interaktion p-Wert									0,4586
Alter bei Screening									

Time to event of AE is defined as the time from first dose of study treatment to first onset of the respective AE or the time to censoring if the AE has not occurred by 28 days following discontinuation of study treatment, before administration of subsequent cancer therapy or death, whichever comes first. All AEs are coded using MedDRA version 25.1. Includes AEs with onset date on or after the date of first dose and up to and including 28 days following discontinuation of study treatment. Analysis done if >=10 patients at each subgroup level and >=10 events in at least one subgroup level combined for both arms. Analysis done for SOC and PT only if main effect for that SOC or PT is statistically significant at 5% level. [a] Median time to event based on the Kaplan Meier estimate. NE = Not estimable as median (or 95% CLs) is not reached. [b] Estimated from main effects of unstratified Cox proportional hazard model including trt., subgroup and subgroup-by-trt. interaction. Ties handled using Efron method and 95% CI derived from profile likelihood estimation. NC = Not calculable. HR <1 favours Osimertinib+Chemo. * p<0.05.
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Table 4.3.1.34 FLAURA-2: Summary of subgroup analysis of time to first SOC: Psychiatrische Erkrankungen
Safety Analysis Set, DCO 03APR2023

	Osi + Chemo (N=276)			Osi (N=275)					
Subgruppen	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]	Hazard Ratio [b]	[95%-KI] [b]	2-seitiger p-Wert [b]
<65 Jahre	172	33 (19,2)	NE [NE; NE]	164	18 (11,0)	NE [NE; NE]	1,75	[0,999; 3,18]	0,0505
>=65 Jahre	104	17 (16,3)	NE [NE; NE]	111	10 (9,0)	NE [NE; NE]	1,94	[0,90; 4,39]	0,0907
Interaktion p-Wert									0,8395
Region gPAP									
Asien	168	27 (16,1)	NE [NE; NE]	166	12 (7,2)	NE [NE; NE]	2,27	[1,18; 4,65]	0,0138*
Europa	22	3 (13,6)	NE [NE; NE]	23	2 (8,7)	NE [NE; NE]	1,50	[0,25; 11,42]	0,6515
Nordamerika	20	5 (25,0)	NE [NE; NE]	22	4 (18,2)	NE [NE; NE]	1,52	[0,40; 6,15]	0,5309
Rest der Welt	66	15 (22,7)	NE [NE; NE]	64	10 (15,6)	NE [NE; NE]	1,50	[0,68; 3,45]	0,3171
Interaktion p-Wert									0,8601

Time to event of AE is defined as the time from first dose of study treatment to first onset of the respective AE or the time to censoring if the AE has not occurred by 28 days following discontinuation of study treatment, before administration of subsequent cancer therapy or death, whichever comes first. All AEs are coded using MedDRA version 25.1. Includes AEs with onset date on or after the date of first dose and up to and including 28 days following discontinuation of study treatment. Analysis done if >=10 patients at each subgroup level and >=10 events in at least one subgroup level combined for both arms. Analysis done for SOC and PT only if main effect for that SOC or PT is statistically significant at 5% level. [a] Median time to event based on the Kaplan Meier estimate. NE = Not estimable as median (or 95% CLs) is not reached. [b] Estimated from main effects of unstratified Cox proportional hazard model including trt., subgroup and subgroup-by-trt. interaction. Ties handled using Efron method and 95% CI derived from profile likelihood estimation. NC = Not calculable. HR <1 favours Osimertinib+Chemo. * p<0.05.
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Table 4.3.1.35 FLAURA-2: Summary of subgroup analysis of time to first PT: Schlaflosigkeit
Safety Analysis Set, DCO 03APR2023

	Osi + Chemo (N=276)			Osi (N=275)					
Subgruppen	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]	Hazard Ratio [b]	[95%-KI] [b]	2-seitiger p-Wert [b]
Abstammung									
Chinesisch/Asiatisch	68	13 (19,1)	NE [NE; NE]	70	6 (8,6)	NE [NE; NE]	2,22	[0,88; 6,32]	0,0931
Nicht-chinesisch/ Asiatisch	107	11 (10,3)	NE [NE; NE]	106	6 (5,7)	NE [NE; NE]	1,87	[0,71; 5,42]	0,2083
Nicht-asiatisch	101	10 (9,9)	NE [NE; NE]	99	6 (6,1)	NE [NE; NE]	1,67	[0,62; 4,92]	0,3116
Interaktion p-Wert									0,9218
Methode zur Gewebeuntersuchung									
zentral	120	12 (10,0)	NE [NE; NE]	119	8 (6,7)	NE [NE; NE]	1,51	[0,63; 3,86]	0,3590
lokal	156	22 (14,1)	NE [NE; NE]	156	10 (6,4)	NE [NE; NE]	2,24	[1,09; 4,95]	0,0278*
Interaktion p-Wert									0,5094
WHO Performance-Status									
0	100	12 (12,0)	NE [NE; NE]	100	5 (5,0)	NE [NE; NE]	2,51	[0,93; 7,88]	0,0698
1	176	22 (12,5)	NE [NE; NE]	175	13 (7,4)	NE [NE; NE]	1,69	[0,86; 3,44]	0,1286
Interaktion p-Wert									0,5290
Raucherstatus									
Ja	90	9 (10,0)	NE [NE; NE]	96	4 (4,2)	NE [NE; NE]	2,39	[0,78; 8,84]	0,1296
Nein	186	25 (13,4)	NE [NE; NE]	179	14 (7,8)	NE [NE; NE]	1,77	[0,93; 3,49]	0,0811
Interaktion p-Wert									0,6565
Geschlecht									
Maennlich	104	11 (10,6)	NE [NE; NE]	107	5 (4,7)	NE [NE; NE]	2,20	[0,80; 7,00]	0,1280
Weiblich	172	23 (13,4)	NE [NE; NE]	168	13 (7,7)	NE [NE; NE]	1,81	[0,93; 3,67]	0,0812
Interaktion p-Wert									0,7570
Nachweis der EGFR-Mutation durch zentralen ctDNA Cobas Test									
positiv	211	25 (11,8)	NE [NE; NE]	204	14 (6,9)	NE [NE; NE]	1,74	[0,92; 3,44]	0,0892

Time to event of AE is defined as the time from first dose of study treatment to first onset of the respective AE or the time to censoring if the AE has not occurred by 28 days following discontinuation of study treatment, before administration of subsequent cancer therapy or death, whichever comes first. All AEs are coded using MedDRA version 25.1. Includes AEs with onset date on or after the date of first dose and up to and including 28 days following discontinuation of study treatment. Analysis done if >=10 patients at each subgroup level and >=10 events in at least one subgroup level combined for both arms. Analysis done for SOC and PT only if main effect for that SOC or PT is statistically significant at 5% level. [a] Median time to event based on the Kaplan Meier estimate. NE = Not estimable as median (or 95% CLs) is not reached. [b] Estimated from main effects of unstratified Cox proportional hazard model including trt., subgroup and subgroup-by-trt. interaction. Ties handled using Efron method and 95% CI derived from profile likelihood estimation. NC = Not calculable. HR <1 favours Osimertinib+Chemo. * p<0.05.
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Table 4.3.1.35 FLAURA-2: Summary of subgroup analysis of time to first PT: Schlaflosigkeit
Safety Analysis Set, DCO 03APR2023

	Osi + Chemo (N=276)			Osi (N=275)					
Subgruppen	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]	Hazard Ratio [b]	[95%-KI] [b]	2-seitiger p-Wert [b]
negativ	41	4 (9,8)	NE [NE; NE]	39	2 (5,1)	NE [NE; NE]	1,96	[0,38; 14,14]	0,4237
unbekannt	24	5 (20,8)	NE [NE; NE]	32	2 (6,3)	NE [NE; NE]	3,59	[0,77; 25,08]	0,1039
Interaktion p-Wert									0,7096
EGFR-Mutationstyp									
Exon 19 Deletion	172	20 (11,6)	NE [NE; NE]	167	13 (7,8)	NE [NE; NE]	1,53	[0,77; 3,15]	0,2291
Exon 21 (L858R) Substitutionsmutation	104	14 (13,5)	NE [NE; NE]	106	5 (4,7)	NE [NE; NE]	2,89	[1,11; 8,95]	0,0295*
Interaktion p-Wert									0,3029
Zentral bestätigte EGFR-Mutation im Gewebe									
positiv	248	32 (12,9)	NE [NE; NE]	238	15 (6,3)	NE [NE; NE]	2,10	[1,16; 3,99]	0,0141*
negativ	3	0	NE [NE; NE]	4	0	NE [NE; NE]	NC	[NC]	NC
unbekannt	25	2 (8,0)	NE [NE; NE]	33	3 (9,1)	NE [NE; NE]	0,87	[0,11; 5,25]	0,8782
Interaktion p-Wert									0,3549
ZNS-Metastasen zur Baseline									
Ja	113	15 (13,3)	NE [NE; NE]	110	7 (6,4)	NE [NE; NE]	2,02	[0,85; 5,29]	0,1130
Nein	163	19 (11,7)	NE [NE; NE]	165	11 (6,7)	NE [NE; NE]	1,84	[0,89; 4,01]	0,0998
Interaktion p-Wert									0,8789
Zentrale Bestätigung der EGFR-Mutation									
Zentral bestätigte EGFR-Mutation in Gewebe oder ctDNA	263	33 (12,5)	NE [NE; NE]	266	18 (6,8)	NE [NE; NE]	1,89	[1,08; 3,42]	0,0263*
Keine zentrale Bestätigung	13	1 (7,7)	NE [NE; NE]	9	0	NE [NE; NE]	NC	[NC]	NC
Interaktion p-Wert									NC
Alter bei Screening									

Time to event of AE is defined as the time from first dose of study treatment to first onset of the respective AE or the time to censoring if the AE has not occurred by 28 days following discontinuation of study treatment, before administration of subsequent cancer therapy or death, whichever comes first. All AEs are coded using MedDRA version 25.1. Includes AEs with onset date on or after the date of first dose and up to and including 28 days following discontinuation of study treatment. Analysis done if >=10 patients at each subgroup level and >=10 events in at least one subgroup level combined for both arms. Analysis done for SOC and PT only if main effect for that SOC or PT is statistically significant at 5% level. [a] Median time to event based on the Kaplan Meier estimate. NE = Not estimable as median (or 95% CLs) is not reached. [b] Estimated from main effects of unstratified Cox proportional hazard model including trt., subgroup and subgroup-by-trt. interaction. Ties handled using Efron method and 95% CI derived from profile likelihood estimation. NC = Not calculable. HR <1 favours Osimertinib+Chemo. * p<0.05.
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Table 4.3.1.35 FLAURA-2: Summary of subgroup analysis of time to first PT: Schlaflosigkeit
Safety Analysis Set, DCO 03APR2023

	Osi + Chemo (N=276)			Osi (N=275)					
Subgruppen	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]	Hazard Ratio [b]	[95%-KI] [b]	2-seitiger p-Wert [b]
<65 Jahre	172	21 (12,2)	NE [NE; NE]	164	10 (6,1)	NE [NE; NE]	1,99	[0,96; 4,42]	0,0639
>=65 Jahre	104	13 (12,5)	NE [NE; NE]	111	8 (7,2)	NE [NE; NE]	1,84	[0,78; 4,66]	0,1662
Interaktion p-Wert									0,8956
Region gPAP									
Asien	168	22 (13,1)	NE [NE; NE]	166	10 (6,0)	NE [NE; NE]	2,21	[1,07; 4,88]	0,0309*
Europa	22	0	NE [NE; NE]	23	0	NE [NE; NE]	NC	[NC]	NC
Nordamerika	20	2 (10,0)	NE [NE; NE]	22	1 (4,5)	NE [NE; NE]	2,40	[0,23; 51,57]	0,4602
Rest der Welt	66	10 (15,2)	NE [NE; NE]	64	7 (10,9)	NE [NE; NE]	1,43	[0,55; 3,93]	0,4678
Interaktion p-Wert									0,7685

Time to event of AE is defined as the time from first dose of study treatment to first onset of the respective AE or the time to censoring if the AE has not occurred by 28 days following discontinuation of study treatment, before administration of subsequent cancer therapy or death, whichever comes first. All AEs are coded using MedDRA version 25.1. Includes AEs with onset date on or after the date of first dose and up to and including 28 days following discontinuation of study treatment. Analysis done if >=10 patients at each subgroup level and >=10 events in at least one subgroup level combined for both arms. Analysis done for SOC and PT only if main effect for that SOC or PT is statistically significant at 5% level. [a] Median time to event based on the Kaplan Meier estimate. NE = Not estimable as median (or 95% CLs) is not reached. [b] Estimated from main effects of unstratified Cox proportional hazard model including trt., subgroup and subgroup-by-trt. interaction. Ties handled using Efron method and 95% CI derived from profile likelihood estimation. NC = Not calculable. HR <1 favours Osimertinib+Chemo. * p<0.05.
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Table 4.3.1.36 FLAURA-2: Summary of subgroup analysis of time to first SOC: Stoffwechsel- und Ernaehrungsstoerungen
Safety Analysis Set, DCO 03APR2023

	Osi + Chemo (N=276)			Osi (N=275)					
Subgruppen	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]	Hazard Ratio [b]	[95%-KI] [b]	2-seitiger p-Wert [b]
Abstammung									
Chinesisch/Asiatisch	68	38 (55,9)	9,2 [2,1; NE]	70	36 (51,4)	11,2 [3,5; NE]	1,12	[0,71; 1,76]	0,6388
Nicht-chinesisch/ Asiatisch	107	53 (49,5)	12,7 [2,4; NE]	106	22 (20,8)	NE [NE; NE]	3,24	[2,00; 5,43]	<0,0001*
Nicht-asiatisch	101	46 (45,5)	NE [NE; NE]	99	23 (23,2)	NE [NE; NE]	2,29	[1,41; 3,85]	0,0008*
Interaktion p-Wert									0,0059*
Methode zur Gewebeuntersuchung									
zentral	120	53 (44,2)	NE [NE; NE]	119	38 (31,9)	NE [NE; NE]	1,57	[1,04; 2,39]	0,0334*
lokal	156	84 (53,8)	8,8 [3,5; NE]	156	43 (27,6)	NE [NE; NE]	2,45	[1,71; 3,57]	<0,0001*
Interaktion p-Wert									0,1135
WHO Performance-Status									
0	100	53 (53,0)	8,8 [2,6; NE]	100	25 (25,0)	NE [NE; NE]	2,81	[1,77; 4,60]	<0,0001*
1	176	84 (47,7)	19,5 [7,4; NE]	175	56 (32,0)	NE [NE; NE]	1,69	[1,21; 2,38]	0,0021*
Interaktion p-Wert									0,0841
Raucherstatus									
Ja	90	47 (52,2)	11,5 [2,1; NE]	96	33 (34,4)	NE [NE; NE]	1,87	[1,20; 2,95]	0,0053*
Nein	186	90 (48,4)	13,0 [6,4; NE]	179	48 (26,8)	NE [NE; NE]	2,14	[1,52; 3,06]	<0,0001*
Interaktion p-Wert									0,6413
Geschlecht									
Maennlich	104	56 (53,8)	10,1 [3,1; NE]	107	35 (32,7)	NE [NE; NE]	1,96	[1,29; 3,02]	0,0014*
Weiblich	172	81 (47,1)	22,0 [6,2; NE]	168	46 (27,4)	NE [NE; NE]	2,07	[1,45; 3,00]	<0,0001*
Interaktion p-Wert									0,8502
Nachweis der EGFR-Mutation durch zentralen ctDNA Cobas Test									
positiv	211	101 (47,9)	17,7 [6,8; NE]	204	55 (27,0)	NE [NE; NE]	2,16	[1,56; 3,02]	<0,0001*

Time to event of AE is defined as the time from first dose of study treatment to first onset of the respective AE or the time to censoring if the AE has not occurred by 28 days following discontinuation of study treatment, before administration of subsequent cancer therapy or death, whichever comes first. All AEs are coded using MedDRA version 25.1. Includes AEs with onset date on or after the date of first dose and up to and including 28 days following discontinuation of study treatment. Analysis done if >=10 patients at each subgroup level and >=10 events in at least one subgroup level combined for both arms. Analysis done for SOC and PT only if main effect for that SOC or PT is statistically significant at 5% level. [a] Median time to event based on the Kaplan Meier estimate. NE = Not estimable as median (or 95% CLs) is not reached. [b] Estimated from main effects of unstratified Cox proportional hazard model including trt., subgroup and subgroup-by-trt. interaction. Ties handled using Efron method and 95% CI derived from profile likelihood estimation. NC = Not calculable. HR <1 favours Osimertinib+Chemo. * p<0.05.
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Table 4.3.1.36 FLAURA-2: Summary of subgroup analysis of time to first SOC: Stoffwechsel- und Ernaehrungsstoerungen
Safety Analysis Set, DCO 03APR2023

	Osi + Chemo (N=276)			Osi (N=275)					
Subgruppen	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]	Hazard Ratio [b]	[95%-KI] [b]	2-seitiger p-Wert [b]
negativ	41	26 (63,4)	3,5 [1,1;19,5]	39	13 (33,3)	NE [NE; NE]	2,53	[1,32; 5,08]	0,0047*
unbekannt	24	10 (41,7)	NE [NE; NE]	32	13 (40,6)	NE [NE; NE]	0,97	[0,41; 2,20]	0,9353
Interaktion p-Wert									0,1566
EGFR-Mutationstyp									
Exon 19 Deletion	172	78 (45,3)	NE [NE; NE]	167	47 (28,1)	NE [NE; NE]	1,88	[1,31; 2,71]	0,0005*
Exon 21 (L858R) Substitutionsmutation	104	59 (56,7)	7,2 [2,6;13,0]	106	34 (32,1)	NE [NE; NE]	2,24	[1,48; 3,45]	0,0001*
Interaktion p-Wert									0,5321
Zentral bestätigte EGFR-Mutation im Gewebe									
positiv	248	122 (49,2)	12,7 [7,2; NE]	238	67 (28,2)	NE [NE; NE]	2,12	[1,58; 2,88]	<0,0001*
negativ	3	2 (66,7)	0,8 [0,8; NE]	4	3 (75,0)	6,6 [0,3; NE]	NC	[NC]	NC
unbekannt	25	13 (52,0)	6,7 [1,1; NE]	33	11 (33,3)	NE [NE; NE]	1,74	[0,78; 3,97]	0,1752
Interaktion p-Wert									0,6498
ZNS-Metastasen zur Baseline									
Ja	113	56 (49,6)	13,0 [3,5; NE]	110	32 (29,1)	NE [NE; NE]	1,98	[1,29; 3,09]	0,0016*
Nein	163	81 (49,7)	11,0 [6,2; NE]	165	49 (29,7)	NE [NE; NE]	2,05	[1,44; 2,94]	<0,0001*
Interaktion p-Wert									0,9073
Zentrale Bestätigung der EGFR-Mutation									
Zentral bestätigte EGFR-Mutation in Gewebe oder ctDNA	263	131 (49,8)	12,1 [6,4; NE]	266	76 (28,6)	NE [NE; NE]	2,11	[1,59; 2,81]	<0,0001*
Keine zentrale Bestätigung	13	6 (46,2)	NE [NE; NE]	9	5 (55,6)	12,5 [0,2; NE]	0,85	[0,26; 2,95]	0,7901
Interaktion p-Wert									0,1557
Alter bei Screening									

Time to event of AE is defined as the time from first dose of study treatment to first onset of the respective AE or the time to censoring if the AE has not occurred by 28 days following discontinuation of study treatment, before administration of subsequent cancer therapy or death, whichever comes first. All AEs are coded using MedDRA version 25.1. Includes AEs with onset date on or after the date of first dose and up to and including 28 days following discontinuation of study treatment. Analysis done if >=10 patients at each subgroup level and >=10 events in at least one subgroup level combined for both arms. Analysis done for SOC and PT only if main effect for that SOC or PT is statistically significant at 5% level. [a] Median time to event based on the Kaplan Meier estimate. NE = Not estimable as median (or 95% CLs) is not reached. [b] Estimated from main effects of unstratified Cox proportional hazard model including trt., subgroup and subgroup-by-trt. interaction. Ties handled using Efron method and 95% CI derived from profile likelihood estimation. NC = Not calculable. HR <1 favours Osimertinib+Chemo. * p<0.05.
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Table 4.3.1.36 FLAURA-2: Summary of subgroup analysis of time to first SOC: Stoffwechsel- und Ernaehrungsstoerungen
Safety Analysis Set, DCO 03APR2023

	Osi + Chemo (N=276)			Osi (N=275)					
Subgruppen	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]	Hazard Ratio [b]	[95%-KI] [b]	2-seitiger p-Wert [b]
<65 Jahre	172	81 (47,1)	NE [NE; NE]	164	41 (25,0)	NE [NE; NE]	2,23	[1,54; 3,28]	<0,0001*
>=65 Jahre	104	56 (53,8)	7,2 [2,4; NE]	111	40 (36,0)	NE [NE; NE]	1,86	[1,24; 2,81]	0,0025*
Interaktion p-Wert									0,5205
Region gPAP									
Asien	168	86 (51,2)	9,2 [2,8; NE]	166	53 (31,9)	NE [NE; NE]	1,99	[1,41; 2,81]	<0,0001*
Europa	22	10 (45,5)	NE [NE; NE]	23	4 (17,4)	NE [NE; NE]	3,06	[1,03; 11,18]	0,0449*
Nordamerika	20	8 (40,0)	NE [NE; NE]	22	11 (50,0)	NE [NE; NE]	0,78	[0,30; 1,93]	0,5916
Rest der Welt	66	33 (50,0)	12,1 [4,1; NE]	64	13 (20,3)	NE [NE; NE]	2,95	[1,59; 5,80]	0,0005*
Interaktion p-Wert									0,1035

Time to event of AE is defined as the time from first dose of study treatment to first onset of the respective AE or the time to censoring if the AE has not occurred by 28 days following discontinuation of study treatment, before administration of subsequent cancer therapy or death, whichever comes first. All AEs are coded using MedDRA version 25.1. Includes AEs with onset date on or after the date of first dose and up to and including 28 days following discontinuation of study treatment. Analysis done if >=10 patients at each subgroup level and >=10 events in at least one subgroup level combined for both arms. Analysis done for SOC and PT only if main effect for that SOC or PT is statistically significant at 5% level. [a] Median time to event based on the Kaplan Meier estimate. NE = Not estimable as median (or 95% CLs) is not reached. [b] Estimated from main effects of unstratified Cox proportional hazard model including trt., subgroup and subgroup-by-trt. interaction. Ties handled using Efron method and 95% CI derived from profile likelihood estimation. NC = Not calculable. HR <1 favours Osimertinib+Chemo. * p<0.05.
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Table 4.3.1.37 FLAURA-2: Summary of subgroup analysis of time to first PT: Appetit vermindert
Safety Analysis Set, DCO 03APR2023

	Osi + Chemo (N=276)			Osi (N=275)					
Subgruppen	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]	Hazard Ratio [b]	[95%-KI] [b]	2-seitiger p-Wert [b]
Abstammung									
Chinesisch/Asiatisch	68	14 (20,6)	NE [NE; NE]	70	5 (7,1)	NE [NE; NE]	3,07	[1,17; 9,50]	0,0213*
Nicht-chinesisch/ Asiatisch	107	42 (39,3)	NE [NE; NE]	106	12 (11,3)	NE [NE; NE]	4,37	[2,37; 8,68]	<0,0001*
Nicht-asiatisch	101	29 (28,7)	NE [NE; NE]	99	9 (9,1)	NE [NE; NE]	3,56	[1,75; 7,98]	0,0003*
Interaktion p-Wert									0,8288
Methode zur Gewebeuntersuchung									
zentral	120	25 (20,8)	NE [NE; NE]	119	6 (5,0)	NE [NE; NE]	4,56	[2,00; 12,28]	0,0002*
lokal	156	60 (38,5)	NE [NE; NE]	156	20 (12,8)	NE [NE; NE]	3,62	[2,22; 6,15]	<0,0001*
Interaktion p-Wert									0,6529
WHO Performance-Status									
0	100	34 (34,0)	NE [NE; NE]	100	9 (9,0)	NE [NE; NE]	4,56	[2,28; 10,12]	<0,0001*
1	176	51 (29,0)	NE [NE; NE]	175	17 (9,7)	NE [NE; NE]	3,37	[1,99; 6,00]	<0,0001*
Interaktion p-Wert									0,5136
Raucherstatus									
Ja	90	33 (36,7)	NE [NE; NE]	96	15 (15,6)	NE [NE; NE]	2,79	[1,54; 5,29]	0,0006*
Nein	186	52 (28,0)	NE [NE; NE]	179	11 (6,1)	NE [NE; NE]	5,21	[2,83; 10,53]	<0,0001*
Interaktion p-Wert									0,1675
Geschlecht									
Maennlich	104	34 (32,7)	NE [NE; NE]	107	12 (11,2)	NE [NE; NE]	3,34	[1,78; 6,72]	0,0001*
Weiblich	172	51 (29,7)	NE [NE; NE]	168	14 (8,3)	NE [NE; NE]	4,14	[2,36; 7,78]	<0,0001*
Interaktion p-Wert									0,6319
Nachweis der EGFR-Mutation durch zentralen ctDNA Cobas Test									
positiv	211	59 (28,0)	NE [NE; NE]	204	18 (8,8)	NE [NE; NE]	3,68	[2,22; 6,42]	<0,0001*

Time to event of AE is defined as the time from first dose of study treatment to first onset of the respective AE or the time to censoring if the AE has not occurred by 28 days following discontinuation of study treatment, before administration of subsequent cancer therapy or death, whichever comes first. All AEs are coded using MedDRA version 25.1. Includes AEs with onset date on or after the date of first dose and up to and including 28 days following discontinuation of study treatment. Analysis done if >=10 patients at each subgroup level and >=10 events in at least one subgroup level combined for both arms. Analysis done for SOC and PT only if main effect for that SOC or PT is statistically significant at 5% level. [a] Median time to event based on the Kaplan Meier estimate. NE = Not estimable as median (or 95% CLs) is not reached. [b] Estimated from main effects of unstratified Cox proportional hazard model including trt., subgroup and subgroup-by-trt. interaction. Ties handled using Efron method and 95% CI derived from profile likelihood estimation. NC = Not calculable. HR <1 favours Osimertinib+Chemo. * p<0.05.
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Table 4.3.1.37 FLAURA-2: Summary of subgroup analysis of time to first PT: Appetit vermindert
Safety Analysis Set, DCO 03APR2023

	Osi + Chemo (N=276)			Osi (N=275)					
Subgruppen	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]	Hazard Ratio [b]	[95%-KI] [b]	2-seitiger p-Wert [b]
negativ	41	19 (46,3)	NE [NE; NE]	39	4 (10,3)	NE [NE; NE]	5,64	[2,12; 19,46]	0,0003*
unbekannt	24	7 (29,2)	NE [NE; NE]	32	4 (12,5)	NE [NE; NE]	2,36	[0,71; 9,01]	0,1604
Interaktion p-Wert									0,5703
EGFR-Mutationstyp									
Exon 19 Deletion	172	47 (27,3)	NE [NE; NE]	167	15 (9,0)	NE [NE; NE]	3,49	[2,00; 6,46]	<0,0001*
Exon 21 (L858R)	104	38 (36,5)	NE [NE; NE]	106	11 (10,4)	NE [NE; NE]	4,14	[2,19; 8,50]	<0,0001*
Substitutionsmutation									
Interaktion p-Wert									0,7074
Zentral bestätigte EGFR-Mutation im Gewebe									
positiv	248	72 (29,0)	NE [NE; NE]	238	22 (9,2)	NE [NE; NE]	3,63	[2,29; 5,98]	<0,0001*
negativ	3	2 (66,7)	0,8 [0,8; NE]	4	0	NE [NE; NE]	NC	[NC]	NC
unbekannt	25	11 (44,0)	NE [NE; NE]	33	4 (12,1)	NE [NE; NE]	4,31	[1,47; 15,54]	0,0070*
Interaktion p-Wert									0,7846
ZNS-Metastasen zur Baseline									
Ja	113	33 (29,2)	NE [NE; NE]	110	9 (8,2)	NE [NE; NE]	4,04	[2,02; 8,98]	<0,0001*
Nein	163	52 (31,9)	NE [NE; NE]	165	17 (10,3)	NE [NE; NE]	3,64	[2,15; 6,48]	<0,0001*
Interaktion p-Wert									0,8232
Zentrale Bestätigung der EGFR-Mutation									
Zentral bestätigte EGFR-Mutation in Gewebe oder ctDNA	263	80 (30,4)	NE [NE; NE]	266	26 (9,8)	NE [NE; NE]	3,60	[2,34; 5,71]	<0,0001*
Keine zentrale Bestätigung	13	5 (38,5)	NE [NE; NE]	9	0	NE [NE; NE]	NC	[NC]	NC
Interaktion p-Wert									NC
Alter bei Screening									

Time to event of AE is defined as the time from first dose of study treatment to first onset of the respective AE or the time to censoring if the AE has not occurred by 28 days following discontinuation of study treatment, before administration of subsequent cancer therapy or death, whichever comes first. All AEs are coded using MedDRA version 25.1. Includes AEs with onset date on or after the date of first dose and up to and including 28 days following discontinuation of study treatment. Analysis done if >=10 patients at each subgroup level and >=10 events in at least one subgroup level combined for both arms. Analysis done for SOC and PT only if main effect for that SOC or PT is statistically significant at 5% level. [a] Median time to event based on the Kaplan Meier estimate. NE = Not estimable as median (or 95% CLs) is not reached. [b] Estimated from main effects of unstratified Cox proportional hazard model including trt., subgroup and subgroup-by-trt. interaction. Ties handled using Efron method and 95% CI derived from profile likelihood estimation. NC = Not calculable. HR <1 favours Osimertinib+Chemo. * p<0.05.
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Table 4.3.1.37 FLAURA-2: Summary of subgroup analysis of time to first PT: Appetit vermindert
Safety Analysis Set, DCO 03APR2023

	Osi + Chemo (N=276)			Osi (N=275)					
Subgruppen	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]	Hazard Ratio [b]	[95%-KI] [b]	2-seitiger p-Wert [b]
<65 Jahre	172	44 (25,6)	NE [NE; NE]	164	14 (8,5)	NE [NE; NE]	3,35	[1,88; 6,34]	<0,0001*
>=65 Jahre	104	41 (39,4)	NE [NE; NE]	111	12 (10,8)	NE [NE; NE]	4,52	[2,45; 8,99]	<0,0001*
Interaktion p-Wert									0,5046
Region gPAP									
Asien	168	55 (32,7)	NE [NE; NE]	166	14 (8,4)	NE [NE; NE]	4,61	[2,64; 8,62]	<0,0001*
Europa	22	6 (27,3)	NE [NE; NE]	23	1 (4,3)	NE [NE; NE]	7,14	[1,22;134,91]	0,0271*
Nordamerika	20	5 (25,0)	NE [NE; NE]	22	7 (31,8)	NE [NE; NE]	0,80	[0,24; 2,52]	0,7069
Rest der Welt	66	19 (28,8)	NE [NE; NE]	64	4 (6,3)	NE [NE; NE]	5,22	[1,96; 18,01]	0,0005*
Interaktion p-Wert									0,0431*

Time to event of AE is defined as the time from first dose of study treatment to first onset of the respective AE or the time to censoring if the AE has not occurred by 28 days following discontinuation of study treatment, before administration of subsequent cancer therapy or death, whichever comes first. All AEs are coded using MedDRA version 25.1. Includes AEs with onset date on or after the date of first dose and up to and including 28 days following discontinuation of study treatment. Analysis done if >=10 patients at each subgroup level and >=10 events in at least one subgroup level combined for both arms. Analysis done for SOC and PT only if main effect for that SOC or PT is statistically significant at 5% level. [a] Median time to event based on the Kaplan Meier estimate. NE = Not estimable as median (or 95% CLs) is not reached. [b] Estimated from main effects of unstratified Cox proportional hazard model including trt., subgroup and subgroup-by-trt. interaction. Ties handled using Efron method and 95% CI derived from profile likelihood estimation. NC = Not calculable. HR <1 favours Osimertinib+Chemo. * p<0.05.
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Table 4.3.1.38 FLAURA-2: Summary of subgroup analysis of time to first PT: Hypomagnesiaemie
Safety Analysis Set, DCO 03APR2023

	Osi + Chemo (N=276)			Osi (N=275)					
Subgruppen	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]	Hazard Ratio [b]	[95%-KI] [b]	2-seitiger p-Wert [b]
Abstammung									
Chinesisch/Asiatisch	68	4 (5,9)	NE [NE; NE]	70	0	NE [NE; NE]	NC	[NC]	NC
Nicht-chinesisch/ Asiatisch	107	4 (3,7)	NE [NE; NE]	106	1 (0,9)	NE [NE; NE]	4,12	[0,61; 80,48]	0,1558
Nicht-asiatisch	101	10 (9,9)	NE [NE; NE]	99	2 (2,0)	NE [NE; NE]	5,18	[1,37; 33,73]	0,0134*
Interaktion p-Wert									0,8665
Methode zur Gewebeuntersuchung									
zentral	120	7 (5,8)	NE [NE; NE]	119	0	NE [NE; NE]	NC	[NC]	NC
lokal	156	11 (7,1)	NE [NE; NE]	156	3 (1,9)	NE [NE; NE]	3,78	[1,18; 16,69]	0,0240*
Interaktion p-Wert									NC
WHO Performance-Status									
0	100	5 (5,0)	NE [NE; NE]	100	2 (2,0)	NE [NE; NE]	2,60	[0,56; 18,11]	0,2296
1	176	13 (7,4)	NE [NE; NE]	175	1 (0,6)	NE [NE; NE]	13,35	[2,66;242,52]	0,0004*
Interaktion p-Wert									0,2026
Raucherstatus									
Ja	90	5 (5,6)	NE [NE; NE]	96	1 (1,0)	NE [NE; NE]	5,44	[0,88;104,16]	0,0711
Nein	186	13 (7,0)	NE [NE; NE]	179	2 (1,1)	NE [NE; NE]	6,53	[1,80; 41,74]	0,0026*
Interaktion p-Wert									0,8918
Geschlecht									
Maennlich	104	4 (3,8)	NE [NE; NE]	107	1 (0,9)	NE [NE; NE]	4,05	[0,60; 79,20]	0,1609
Weiblich	172	14 (8,1)	NE [NE; NE]	168	2 (1,2)	NE [NE; NE]	7,30	[2,04; 46,51]	0,0011*
Interaktion p-Wert									0,6700
Nachweis der EGFR-Mutation durch zentralen ctDNA Cobas Test									
positiv	211	15 (7,1)	NE [NE; NE]	204	3 (1,5)	NE [NE; NE]	5,05	[1,67; 21,81]	0,0029*

Time to event of AE is defined as the time from first dose of study treatment to first onset of the respective AE or the time to censoring if the AE has not occurred by 28 days following discontinuation of study treatment, before administration of subsequent cancer therapy or death, whichever comes first. All AEs are coded using MedDRA version 25.1. Includes AEs with onset date on or after the date of first dose and up to and including 28 days following discontinuation of study treatment. Analysis done if >=10 patients at each subgroup level and >=10 events in at least one subgroup level combined for both arms. Analysis done for SOC and PT only if main effect for that SOC or PT is statistically significant at 5% level. [a] Median time to event based on the Kaplan Meier estimate. NE = Not estimable as median (or 95% CLs) is not reached. [b] Estimated from main effects of unstratified Cox proportional hazard model including trt., subgroup and subgroup-by-trt. interaction. Ties handled using Efron method and 95% CI derived from profile likelihood estimation. NC = Not calculable. HR <1 favours Osimertinib+Chemo. * p<0.05.
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Table 4.3.1.38 FLAURA-2: Summary of subgroup analysis of time to first PT: Hypomagnesiaemie
Safety Analysis Set, DCO 03APR2023

	Osi + Chemo (N=276)			Osi (N=275)					
Subgruppen	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]	Hazard Ratio [b]	[95%-KI] [b]	2-seitiger p-Wert [b]
negativ	41	2 (4,9)	NE [NE; NE]	39	0	NE [NE; NE]	NC	[NC]	NC
unbekannt	24	1 (4,2)	NE [NE; NE]	32	0	NE [NE; NE]	NC	[NC]	NC
Interaktion p-Wert									NC
EGFR-Mutationstyp									
Exon 19 Deletion	172	11 (6,4)	NE [NE; NE]	167	2 (1,2)	NE [NE; NE]	5,56	[1,49; 35,96]	0,0083*
Exon 21 (L858R)	104	7 (6,7)	NE [NE; NE]	106	1 (0,9)	NE [NE; NE]	7,32	[1,30;136,77]	0,0209*
Substitutionsmutation									
Interaktion p-Wert									0,8336
Zentral bestätigte EGFR-Mutation im Gewebe									
positiv	248	17 (6,9)	NE [NE; NE]	238	2 (0,8)	NE [NE; NE]	8,54	[2,45; 53,85]	0,0002*
negativ	3	0	NE [NE; NE]	4	0	NE [NE; NE]	NC	[NC]	NC
unbekannt	25	1 (4,0)	NE [NE; NE]	33	1 (3,0)	NE [NE; NE]	1,28	[0,05; 32,38]	0,8609
Interaktion p-Wert									0,2485
ZNS-Metastasen zur Baseline									
Ja	113	4 (3,5)	NE [NE; NE]	110	1 (0,9)	NE [NE; NE]	3,91	[0,58; 76,48]	0,1725
Nein	163	14 (8,6)	NE [NE; NE]	165	2 (1,2)	NE [NE; NE]	7,48	[2,09; 47,66]	0,0009*
Interaktion p-Wert									0,6400
Zentrale Bestätigung der EGFR-Mutation									
Zentral bestätigte EGFR-Mutation in Gewebe oder ctDNA	263	17 (6,5)	NE [NE; NE]	266	3 (1,1)	NE [NE; NE]	5,96	[2,00; 25,54]	0,0007*
Keine zentrale Bestätigung	13	1 (7,7)	NE [NE; NE]	9	0	NE [NE; NE]	NC	[NC]	NC
Interaktion p-Wert									NC
Alter bei Screening									

Time to event of AE is defined as the time from first dose of study treatment to first onset of the respective AE or the time to censoring if the AE has not occurred by 28 days following discontinuation of study treatment, before administration of subsequent cancer therapy or death, whichever comes first. All AEs are coded using MedDRA version 25.1. Includes AEs with onset date on or after the date of first dose and up to and including 28 days following discontinuation of study treatment. Analysis done if >=10 patients at each subgroup level and >=10 events in at least one subgroup level combined for both arms. Analysis done for SOC and PT only if main effect for that SOC or PT is statistically significant at 5% level. [a] Median time to event based on the Kaplan Meier estimate. NE = Not estimable as median (or 95% CLs) is not reached. [b] Estimated from main effects of unstratified Cox proportional hazard model including trt., subgroup and subgroup-by-trt. interaction. Ties handled using Efron method and 95% CI derived from profile likelihood estimation. NC = Not calculable. HR <1 favours Osimertinib+Chemo. * p<0.05.
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Table 4.3.1.38 FLAURA-2: Summary of subgroup analysis of time to first PT: Hypomagnesiaemie
Safety Analysis Set, DCO 03APR2023

	Osi + Chemo (N=276)			Osi (N=275)					
Subgruppen	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]	Hazard Ratio [b]	[95%-KI] [b]	2-seitiger p-Wert [b]
<65 Jahre	172	10 (5,8)	NE [NE; NE]	164	2 (1,2)	NE [NE; NE]	4,89	[1,29; 31,82]	0,0175*
>=65 Jahre	104	8 (7,7)	NE [NE; NE]	111	1 (0,9)	NE [NE; NE]	9,00	[1,65;166,85]	0,0079*
Interaktion p-Wert									0,6357
Region gPAP									
Asien	168	7 (4,2)	NE [NE; NE]	166	1 (0,6)	NE [NE; NE]	NC	[NC]	NC
Europa	22	3 (13,6)	NE [NE; NE]	23	1 (4,3)	NE [NE; NE]	NC	[NC]	NC
Nordamerika	20	2 (10,0)	NE [NE; NE]	22	1 (4,5)	NE [NE; NE]	NC	[NC]	NC
Rest der Welt	66	6 (9,1)	NE [NE; NE]	64	0	NE [NE; NE]	NC	[NC]	NC
Interaktion p-Wert									NC

Time to event of AE is defined as the time from first dose of study treatment to first onset of the respective AE or the time to censoring if the AE has not occurred by 28 days following discontinuation of study treatment, before administration of subsequent cancer therapy or death, whichever comes first. All AEs are coded using MedDRA version 25.1. Includes AEs with onset date on or after the date of first dose and up to and including 28 days following discontinuation of study treatment. Analysis done if >=10 patients at each subgroup level and >=10 events in at least one subgroup level combined for both arms. Analysis done for SOC and PT only if main effect for that SOC or PT is statistically significant at 5% level. [a] Median time to event based on the Kaplan Meier estimate. NE = Not estimable as median (or 95% CLs) is not reached. [b] Estimated from main effects of unstratified Cox proportional hazard model including trt., subgroup and subgroup-by-trt. interaction. Ties handled using Efron method and 95% CI derived from profile likelihood estimation. NC = Not calculable. HR <1 favours Osimertinib+Chemo. * p<0.05.
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Table 4.3.1.39 FLAURA-2: Summary of subgroup analysis of time to first SOC: Untersuchungen
Safety Analysis Set, DCO 03APR2023

	Osi + Chemo (N=276)			Osi (N=275)					
Subgruppen	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]	Hazard Ratio [b]	[95%-KI] [b]	2-seitiger p-Wert [b]
Abstammung									
Chinesisch/Asiatisch	68	60 (88,2)	0,5 [0,3; 0,6]	70	44 (62,9)	3,5 [2,1; 8,3]	2,66	[1,81; 3,96]	<0,0001*
Nicht-chinesisch/ Asiatisch	107	52 (48,6)	22,0 [6,5; NE]	106	26 (24,5)	NE [NE; NE]	2,42	[1,52; 3,93]	0,0001*
Nicht-asiatisch	101	58 (57,4)	6,9 [3,8;19,4]	99	28 (28,3)	NE [NE; NE]	2,43	[1,56; 3,87]	<0,0001*
Interaktion p-Wert									0,9362
Methode zur Gewebeuntersuchung									
zentral	120	78 (65,0)	2,9 [0,9; 5,8]	119	57 (47,9)	NE [NE; NE]	1,83	[1,30; 2,58]	0,0005*
lokal	156	92 (59,0)	6,9 [3,4;16,4]	156	41 (26,3)	NE [NE; NE]	2,80	[1,95; 4,09]	<0,0001*
Interaktion p-Wert									0,0939
WHO Performance-Status									
0	100	59 (59,0)	6,5 [3,1;20,2]	100	31 (31,0)	NE [NE; NE]	2,39	[1,56; 3,74]	<0,0001*
1	176	111 (63,1)	3,7 [2,0; 6,9]	175	67 (38,3)	NE [NE; NE]	2,15	[1,59; 2,92]	<0,0001*
Interaktion p-Wert									0,6861
Raucherstatus									
Ja	90	56 (62,2)	5,8 [2,1;13,1]	96	33 (34,4)	NE [NE; NE]	2,17	[1,42; 3,36]	0,0003*
Nein	186	114 (61,3)	4,2 [2,8; 7,2]	179	65 (36,3)	NE [NE; NE]	2,25	[1,66; 3,06]	<0,0001*
Interaktion p-Wert									0,8941
Geschlecht									
Maennlich	104	67 (64,4)	4,2 [1,4;11,0]	107	37 (34,6)	NE [NE; NE]	2,34	[1,58; 3,53]	<0,0001*
Weiblich	172	103 (59,9)	5,1 [3,0; 8,3]	168	61 (36,3)	NE [NE; NE]	2,15	[1,57; 2,96]	<0,0001*
Interaktion p-Wert									0,7351
Nachweis der EGFR-Mutation durch zentralen ctDNA Cobas Test									
positiv	211	136 (64,5)	4,2 [2,7; 6,2]	204	67 (32,8)	NE [NE; NE]	2,68	[2,00; 3,61]	<0,0001*

Time to event of AE is defined as the time from first dose of study treatment to first onset of the respective AE or the time to censoring if the AE has not occurred by 28 days following discontinuation of study treatment, before administration of subsequent cancer therapy or death, whichever comes first. All AEs are coded using MedDRA version 25.1. Includes AEs with onset date on or after the date of first dose and up to and including 28 days following discontinuation of study treatment. Analysis done if >=10 patients at each subgroup level and >=10 events in at least one subgroup level combined for both arms. Analysis done for SOC and PT only if main effect for that SOC or PT is statistically significant at 5% level. [a] Median time to event based on the Kaplan Meier estimate. NE = Not estimable as median (or 95% CLs) is not reached. [b] Estimated from main effects of unstratified Cox proportional hazard model including trt., subgroup and subgroup-by-trt. interaction. Ties handled using Efron method and 95% CI derived from profile likelihood estimation. NC = Not calculable. HR <1 favours Osimertinib+Chemo. * p<0.05.
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Table 4.3.1.39 FLAURA-2: Summary of subgroup analysis of time to first SOC: Untersuchungen
Safety Analysis Set, DCO 03APR2023

	Osi + Chemo (N=276)			Osi (N=275)					
Subgruppen	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]	Hazard Ratio [b]	[95%-KI] [b]	2-seitiger p-Wert [b]
negativ	41	22 (53,7)	3,4 [2,2; NE]	39	18 (46,2)	NE [NE; NE]	1,37	[0,74; 2,59]	0,3174
unbekannt	24	12 (50,0)	19,4 [2,1; NE]	32	13 (40,6)	NE [NE; NE]	1,16	[0,52; 2,55]	0,7137
Interaktion p-Wert									0,0401*
EGFR-Mutationstyp									
Exon 19 Deletion	172	105 (61,0)	5,5 [3,0;10,5]	167	56 (33,5)	NE [NE; NE]	2,38	[1,72; 3,31]	<0,0001*
Exon 21 (L858R) Substitutionsmutation	104	65 (62,5)	3,6 [2,1; 9,8]	106	40 (37,7)	30,3 [30,3; NE]	2,08	[1,41; 3,11]	0,0002*
Interaktion p-Wert									0,6118
Zentral bestätigte EGFR-Mutation im Gewebe									
positiv	248	156 (62,9)	4,3 [2,9; 6,9]	238	86 (36,1)	NE [NE; NE]	2,27	[1,75; 2,96]	<0,0001*
negativ	3	2 (66,7)	1,4 [0,5; NE]	4	3 (75,0)	8,3 [1,1; NE]	NC	[NC]	NC
unbekannt	25	12 (48,0)	20,2 [2,1; NE]	33	9 (27,3)	NE [NE; NE]	1,97	[0,83; 4,84]	0,1212
Interaktion p-Wert									0,7636
ZNS-Metastasen zur Baseline									
Ja	113	73 (64,6)	2,9 [1,4; 6,5]	110	46 (41,8)	30,3 [9,1; NE]	1,90	[1,32; 2,77]	0,0005*
Nein	163	97 (59,5)	6,0 [3,4;13,1]	165	52 (31,5)	NE [NE; NE]	2,49	[1,78; 3,51]	<0,0001*
Interaktion p-Wert									0,2962
Zentrale Bestätigung der EGFR-Mutation									
Zentral bestätigte EGFR-Mutation in Gewebe oder ctDNA	263	164 (62,4)	4,8 [3,0; 6,9]	266	94 (35,3)	NE [NE; NE]	2,29	[1,78; 2,96]	<0,0001*
Keine zentrale Bestätigung	13	6 (46,2)	NE [NE; NE]	9	4 (44,4)	8,3 [0,4; NE]	1,01	[0,29; 3,96]	0,9855
Interaktion p-Wert									0,2313
Alter bei Screening									

Time to event of AE is defined as the time from first dose of study treatment to first onset of the respective AE or the time to censoring if the AE has not occurred by 28 days following discontinuation of study treatment, before administration of subsequent cancer therapy or death, whichever comes first. All AEs are coded using MedDRA version 25.1. Includes AEs with onset date on or after the date of first dose and up to and including 28 days following discontinuation of study treatment. Analysis done if >=10 patients at each subgroup level and >=10 events in at least one subgroup level combined for both arms. Analysis done for SOC and PT only if main effect for that SOC or PT is statistically significant at 5% level. [a] Median time to event based on the Kaplan Meier estimate. NE = Not estimable as median (or 95% CLs) is not reached. [b] Estimated from main effects of unstratified Cox proportional hazard model including trt., subgroup and subgroup-by-trt. interaction. Ties handled using Efron method and 95% CI derived from profile likelihood estimation. NC = Not calculable. HR <1 favours Osimertinib+Chemo. * p<0.05.
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Table 4.3.1.39 FLAURA-2: Summary of subgroup analysis of time to first SOC: Untersuchungen
Safety Analysis Set, DCO 03APR2023

	Osi + Chemo (N=276)			Osi (N=275)					
Subgruppen	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]	Hazard Ratio [b]	[95%-KI] [b]	2-seitiger p-Wert [b]
<65 Jahre	172	112 (65,1)	3,7 [2,1; 7,9]	164	60 (36,6)	NE [NE; NE]	2,30	[1,69; 3,16]	<0,0001*
>=65 Jahre	104	58 (55,8)	5,7 [3,2;27,4]	111	38 (34,2)	NE [NE; NE]	2,07	[1,38; 3,14]	0,0004*
Interaktion p-Wert									0,6917
Region gPAP									
Asien	168	108 (64,3)	3,1 [1,4; 6,5]	166	66 (39,8)	NE [NE; NE]	2,19	[1,62; 2,99]	<0,0001*
Europa	22	13 (59,1)	4,9 [2,1; NE]	23	4 (17,4)	NE [NE; NE]	4,28	[1,51; 15,20]	0,0052*
Nordamerika	20	12 (60,0)	6,2 [0,5; NE]	22	9 (40,9)	NE [NE; NE]	1,58	[0,67; 3,86]	0,2996
Rest der Welt	66	37 (56,1)	7,9 [3,4; NE]	64	19 (29,7)	NE [NE; NE]	2,29	[1,33; 4,06]	0,0025*
Interaktion p-Wert									0,5580

Time to event of AE is defined as the time from first dose of study treatment to first onset of the respective AE or the time to censoring if the AE has not occurred by 28 days following discontinuation of study treatment, before administration of subsequent cancer therapy or death, whichever comes first. All AEs are coded using MedDRA version 25.1. Includes AEs with onset date on or after the date of first dose and up to and including 28 days following discontinuation of study treatment. Analysis done if >=10 patients at each subgroup level and >=10 events in at least one subgroup level combined for both arms. Analysis done for SOC and PT only if main effect for that SOC or PT is statistically significant at 5% level. [a] Median time to event based on the Kaplan Meier estimate. NE = Not estimable as median (or 95% CLs) is not reached. [b] Estimated from main effects of unstratified Cox proportional hazard model including trt., subgroup and subgroup-by-trt. interaction. Ties handled using Efron method and 95% CI derived from profile likelihood estimation. NC = Not calculable. HR <1 favours Osimertinib+Chemo. * p<0.05.
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Table 4.3.1.40 FLAURA-2: Summary of subgroup analysis of time to first PT: Alaninaminotransferase erhoeht
Safety Analysis Set, DCO 03APR2023

	Osi + Chemo (N=276)			Osi (N=275)					
Subgruppen	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]	Hazard Ratio [b]	[95%-KI] [b]	2-seitiger p-Wert [b]
Abstammung									
Chinesisch/Asiatisch	68	36 (52,9)	11,1 [4,7; NE]	70	11 (15,7)	NE [NE; NE]	4,39	[2,31; 9,05]	<0,0001*
Nicht-chinesisch/ Asiatisch	107	8 (7,5)	NE [NE; NE]	106	3 (2,8)	NE [NE; NE]	2,70	[0,78; 12,30]	0,1204
Nicht-asiatisch	101	12 (11,9)	NE [NE; NE]	99	7 (7,1)	NE [NE; NE]	1,76	[0,71; 4,72]	0,2282
Interaktion p-Wert									0,2948
Methode zur Gewebeuntersuchung									
zentral	120	40 (33,3)	NE [NE; NE]	119	11 (9,2)	NE [NE; NE]	4,33	[2,30; 8,87]	<0,0001*
lokal	156	16 (10,3)	NE [NE; NE]	156	10 (6,4)	NE [NE; NE]	1,61	[0,74; 3,68]	0,2292
Interaktion p-Wert									0,0625
WHO Performance-Status									
0	100	19 (19,0)	NE [NE; NE]	100	8 (8,0)	NE [NE; NE]	2,55	[1,16; 6,19]	0,0197*
1	176	37 (21,0)	NE [NE; NE]	175	13 (7,4)	NE [NE; NE]	3,08	[1,68; 6,02]	0,0002*
Interaktion p-Wert									0,7240
Raucherstatus									
Ja	90	14 (15,6)	NE [NE; NE]	96	10 (10,4)	NE [NE; NE]	1,47	[0,66; 3,40]	0,3505
Nein	186	42 (22,6)	NE [NE; NE]	179	11 (6,1)	NE [NE; NE]	4,18	[2,23; 8,54]	<0,0001*
Interaktion p-Wert									0,0510
Geschlecht									
Maennlich	104	17 (16,3)	NE [NE; NE]	107	8 (7,5)	NE [NE; NE]	2,18	[0,97; 5,33]	0,0603
Weiblich	172	39 (22,7)	NE [NE; NE]	168	13 (7,7)	NE [NE; NE]	3,34	[1,83; 6,51]	<0,0001*
Interaktion p-Wert									0,4254
Nachweis der EGFR-Mutation durch zentralen ctDNA Cobas Test									
positiv	211	50 (23,7)	NE [NE; NE]	204	10 (4,9)	NE [NE; NE]	5,52	[2,93; 11,56]	<0,0001*

Time to event of AE is defined as the time from first dose of study treatment to first onset of the respective AE or the time to censoring if the AE has not occurred by 28 days following discontinuation of study treatment, before administration of subsequent cancer therapy or death, whichever comes first. All AEs are coded using MedDRA version 25.1. Includes AEs with onset date on or after the date of first dose and up to and including 28 days following discontinuation of study treatment. Analysis done if >=10 patients at each subgroup level and >=10 events in at least one subgroup level combined for both arms. Analysis done for SOC and PT only if main effect for that SOC or PT is statistically significant at 5% level. [a] Median time to event based on the Kaplan Meier estimate. NE = Not estimable as median (or 95% CLs) is not reached. [b] Estimated from main effects of unstratified Cox proportional hazard model including trt., subgroup and subgroup-by-trt. interaction. Ties handled using Efron method and 95% CI derived from profile likelihood estimation. NC = Not calculable. HR <1 favours Osimertinib+Chemo. * p<0.05.
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Table 4.3.1.40 FLAURA-2: Summary of subgroup analysis of time to first PT: Alaninaminotransferase erhoeht
Safety Analysis Set, DCO 03APR2023

	Osi + Chemo (N=276)			Osi (N=275)					
Subgruppen	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]	Hazard Ratio [b]	[95%-KI] [b]	2-seitiger p-Wert [b]
negativ	41	4 (9,8)	NE [NE; NE]	39	5 (12,8)	NE [NE; NE]	0,76	[0,19; 2,86]	0,6768
unbekannt	24	2 (8,3)	NE [NE; NE]	32	6 (18,8)	NE [NE; NE]	0,37	[0,05; 1,62]	0,1957
Interaktion p-Wert									0,0004*
EGFR-Mutationstyp									
Exon 19 Deletion	172	34 (19,8)	NE [NE; NE]	167	14 (8,4)	NE [NE; NE]	2,55	[1,40; 4,91]	0,0019*
Exon 21 (L858R) Substitutionsmutation	104	22 (21,2)	NE [NE; NE]	106	6 (5,7)	NE [NE; NE]	4,06	[1,75; 11,02]	0,0007*
Interaktion p-Wert									0,3993
Zentral bestätigte EGFR-Mutation im Gewebe									
positiv	248	55 (22,2)	NE [NE; NE]	238	18 (7,6)	NE [NE; NE]	3,22	[1,93; 5,64]	<0,0001*
negativ	3	0	NE [NE; NE]	4	0	NE [NE; NE]	NC	[NC]	NC
unbekannt	25	1 (4,0)	NE [NE; NE]	33	3 (9,1)	NE [NE; NE]	0,44	[0,02; 3,41]	0,4468
Interaktion p-Wert									0,0653
ZNS-Metastasen zur Baseline									
Ja	113	30 (26,5)	NE [NE; NE]	110	10 (9,1)	NE [NE; NE]	3,14	[1,59; 6,76]	0,0007*
Nein	163	26 (16,0)	NE [NE; NE]	165	11 (6,7)	NE [NE; NE]	2,60	[1,32; 5,49]	0,0053*
Interaktion p-Wert									0,7157
Zentrale Bestätigung der EGFR-Mutation									
Zentral bestätigte EGFR-Mutation in Gewebe oder ctDNA	263	55 (20,9)	NE [NE; NE]	266	21 (7,9)	NE [NE; NE]	2,89	[1,78; 4,88]	<0,0001*
Keine zentrale Bestätigung	13	1 (7,7)	NE [NE; NE]	9	0	NE [NE; NE]	NC	[NC]	NC
Interaktion p-Wert									NC
Alter bei Screening									

Time to event of AE is defined as the time from first dose of study treatment to first onset of the respective AE or the time to censoring if the AE has not occurred by 28 days following discontinuation of study treatment, before administration of subsequent cancer therapy or death, whichever comes first. All AEs are coded using MedDRA version 25.1. Includes AEs with onset date on or after the date of first dose and up to and including 28 days following discontinuation of study treatment. Analysis done if >=10 patients at each subgroup level and >=10 events in at least one subgroup level combined for both arms. Analysis done for SOC and PT only if main effect for that SOC or PT is statistically significant at 5% level. [a] Median time to event based on the Kaplan Meier estimate. NE = Not estimable as median (or 95% CLs) is not reached. [b] Estimated from main effects of unstratified Cox proportional hazard model including trt., subgroup and subgroup-by-trt. interaction. Ties handled using Efron method and 95% CI derived from profile likelihood estimation. NC = Not calculable. HR <1 favours Osimertinib+Chemo. * p<0.05.
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Table 4.3.1.40 FLAURA-2: Summary of subgroup analysis of time to first PT: Alaninaminotransferase erhoeht
Safety Analysis Set, DCO 03APR2023

	Osi + Chemo (N=276)			Osi (N=275)					
Subgruppen	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]	Hazard Ratio [b]	[95%-KI] [b]	2-seitiger p-Wert [b]
<65 Jahre	172	47 (27,3)	NE [NE; NE]	164	15 (9,1)	NE [NE; NE]	3,28	[1,88; 6,06]	<0,0001*
>=65 Jahre	104	9 (8,7)	NE [NE; NE]	111	6 (5,4)	NE [NE; NE]	1,70	[0,61; 5,07]	0,3080
Interaktion p-Wert									0,2848
Region gPAP									
Asien	168	43 (25,6)	NE [NE; NE]	166	14 (8,4)	NE [NE; NE]	3,35	[1,88; 6,35]	<0,0001*
Europa	22	2 (9,1)	NE [NE; NE]	23	0	NE [NE; NE]	NC	[NC]	NC
Nordamerika	20	3 (15,0)	NE [NE; NE]	22	3 (13,6)	NE [NE; NE]	1,15	[0,21; 6,21]	0,8647
Rest der Welt	66	8 (12,1)	NE [NE; NE]	64	4 (6,3)	NE [NE; NE]	2,07	[0,65; 7,74]	0,2222
Interaktion p-Wert									0,4184

Time to event of AE is defined as the time from first dose of study treatment to first onset of the respective AE or the time to censoring if the AE has not occurred by 28 days following discontinuation of study treatment, before administration of subsequent cancer therapy or death, whichever comes first. All AEs are coded using MedDRA version 25.1. Includes AEs with onset date on or after the date of first dose and up to and including 28 days following discontinuation of study treatment. Analysis done if >=10 patients at each subgroup level and >=10 events in at least one subgroup level combined for both arms. Analysis done for SOC and PT only if main effect for that SOC or PT is statistically significant at 5% level. [a] Median time to event based on the Kaplan Meier estimate. NE = Not estimable as median (or 95% CLs) is not reached. [b] Estimated from main effects of unstratified Cox proportional hazard model including trt., subgroup and subgroup-by-trt. interaction. Ties handled using Efron method and 95% CI derived from profile likelihood estimation. NC = Not calculable. HR <1 favours Osimertinib+Chemo. * p<0.05.
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Table 4.3.1.41 FLAURA-2: Summary of subgroup analysis of time to first PT: Aspartataminotransferase erhoeht
Safety Analysis Set, DCO 03APR2023

	Osi + Chemo (N=276)			Osi (N=275)					
Subgruppen	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]	Hazard Ratio [b]	[95%-KI] [b]	2-seitiger p-Wert [b]
Abstammung									
Chinesisch/Asiatisch	68	35 (51,5)	18,4 [4,5; NE]	70	8 (11,4)	NE [NE; NE]	5,68	[2,77; 13,19]	<0,0001*
Nicht-chinesisch/ Asiatisch	107	5 (4,7)	NE [NE; NE]	106	1 (0,9)	NE [NE; NE]	5,09	[0,82; 97,40]	0,0843
Nicht-asiatisch	101	8 (7,9)	NE [NE; NE]	99	4 (4,0)	NE [NE; NE]	2,01	[0,63; 7,55]	0,2389
Interaktion p-Wert									0,3808
Methode zur Gewebeuntersuchung									
zentral	120	36 (30,0)	NE [NE; NE]	119	7 (5,9)	NE [NE; NE]	5,93	[2,81; 14,54]	<0,0001*
lokal	156	12 (7,7)	NE [NE; NE]	156	6 (3,8)	NE [NE; NE]	2,02	[0,79; 5,81]	0,1462
Interaktion p-Wert									0,1017
WHO Performance-Status									
0	100	15 (15,0)	NE [NE; NE]	100	6 (6,0)	NE [NE; NE]	2,65	[1,08; 7,42]	0,0337*
1	176	33 (18,8)	NE [NE; NE]	175	7 (4,0)	NE [NE; NE]	5,06	[2,38; 12,48]	<0,0001*
Interaktion p-Wert									0,3120
Raucherstatus									
Ja	90	11 (12,2)	NE [NE; NE]	96	7 (7,3)	NE [NE; NE]	1,63	[0,64; 4,44]	0,3044
Nein	186	37 (19,9)	NE [NE; NE]	179	6 (3,4)	NE [NE; NE]	6,68	[3,04; 17,61]	<0,0001*
Interaktion p-Wert									0,0309*
Geschlecht									
Maennlich	104	15 (14,4)	NE [NE; NE]	107	3 (2,8)	NE [NE; NE]	5,12	[1,69; 22,10]	0,0027*
Weiblich	172	33 (19,2)	NE [NE; NE]	168	10 (6,0)	NE [NE; NE]	3,62	[1,85; 7,75]	<0,0001*
Interaktion p-Wert									0,6274
Nachweis der EGFR-Mutation durch zentralen ctDNA Cobas Test									
positiv	211	42 (19,9)	NE [NE; NE]	204	7 (3,4)	NE [NE; NE]	6,46	[3,10; 15,73]	<0,0001*

Time to event of AE is defined as the time from first dose of study treatment to first onset of the respective AE or the time to censoring if the AE has not occurred by 28 days following discontinuation of study treatment, before administration of subsequent cancer therapy or death, whichever comes first. All AEs are coded using MedDRA version 25.1. Includes AEs with onset date on or after the date of first dose and up to and including 28 days following discontinuation of study treatment. Analysis done if >=10 patients at each subgroup level and >=10 events in at least one subgroup level combined for both arms. Analysis done for SOC and PT only if main effect for that SOC or PT is statistically significant at 5% level. [a] Median time to event based on the Kaplan Meier estimate. NE = Not estimable as median (or 95% CLs) is not reached. [b] Estimated from main effects of unstratified Cox proportional hazard model including trt., subgroup and subgroup-by-trt. interaction. Ties handled using Efron method and 95% CI derived from profile likelihood estimation. NC = Not calculable. HR <1 favours Osimertinib+Chemo. * p<0.05.
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Table 4.3.1.41 FLAURA-2: Summary of subgroup analysis of time to first PT: Aspartataminotransferase erhoeht
Safety Analysis Set, DCO 03APR2023

	Osi + Chemo (N=276)			Osi (N=275)					
Subgruppen	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]	Hazard Ratio [b]	[95%-KI] [b]	2-seitiger p-Wert [b]
negativ	41	3 (7,3)	NE [NE; NE]	39	3 (7,7)	NE [NE; NE]	0,97	[0,18; 5,22]	0,9656
unbekannt	24	3 (12,5)	NE [NE; NE]	32	3 (9,4)	NE [NE; NE]	1,18	[0,22; 6,38]	0,8396
Interaktion p-Wert									0,0397*
EGFR-Mutationstyp									
Exon 19 Deletion	172	27 (15,7)	NE [NE; NE]	167	7 (4,2)	NE [NE; NE]	4,03	[1,85; 10,05]	0,0002*
Exon 21 (L858R) Substitutionsmutation	104	21 (20,2)	NE [NE; NE]	106	6 (5,7)	NE [NE; NE]	3,81	[1,63; 10,38]	0,0014*
Interaktion p-Wert									0,9292
Zentral bestätigte EGFR-Mutation im Gewebe									
positiv	248	48 (19,4)	NE [NE; NE]	238	11 (4,6)	NE [NE; NE]	4,56	[2,46; 9,24]	<0,0001*
negativ	3	0	NE [NE; NE]	4	0	NE [NE; NE]	NC	[NC]	NC
unbekannt	25	0	NE [NE; NE]	33	2 (6,1)	NE [NE; NE]	NC	[NC]	NC
Interaktion p-Wert									NC
ZNS-Metastasen zur Baseline									
Ja	113	24 (21,2)	NE [NE; NE]	110	7 (6,4)	NE [NE; NE]	3,52	[1,60; 8,85]	0,0013*
Nein	163	24 (14,7)	NE [NE; NE]	165	6 (3,6)	NE [NE; NE]	4,38	[1,91; 11,83]	0,0003*
Interaktion p-Wert									0,7272
Zentrale Bestätigung der EGFR-Mutation									
Zentral bestätigte EGFR-Mutation in Gewebe oder ctDNA	263	48 (18,3)	NE [NE; NE]	266	13 (4,9)	NE [NE; NE]	4,04	[2,26; 7,77]	<0,0001*
Keine zentrale Bestätigung	13	0	NE [NE; NE]	9	0	NE [NE; NE]	NC	[NC]	NC
Interaktion p-Wert									NC
Alter bei Screening									

Time to event of AE is defined as the time from first dose of study treatment to first onset of the respective AE or the time to censoring if the AE has not occurred by 28 days following discontinuation of study treatment, before administration of subsequent cancer therapy or death, whichever comes first. All AEs are coded using MedDRA version 25.1. Includes AEs with onset date on or after the date of first dose and up to and including 28 days following discontinuation of study treatment. Analysis done if >=10 patients at each subgroup level and >=10 events in at least one subgroup level combined for both arms. Analysis done for SOC and PT only if main effect for that SOC or PT is statistically significant at 5% level. [a] Median time to event based on the Kaplan Meier estimate. NE = Not estimable as median (or 95% CLs) is not reached. [b] Estimated from main effects of unstratified Cox proportional hazard model including trt., subgroup and subgroup-by-trt. interaction. Ties handled using Efron method and 95% CI derived from profile likelihood estimation. NC = Not calculable. HR <1 favours Osimertinib+Chemo. * p<0.05.
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Table 4.3.1.41 FLAURA-2: Summary of subgroup analysis of time to first PT: Aspartataminotransferase erhoeht
Safety Analysis Set, DCO 03APR2023

	Osi + Chemo (N=276)			Osi (N=275)					
Subgruppen	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]	Hazard Ratio [b]	[95%-KI] [b]	2-seitiger p-Wert [b]
<65 Jahre	172	39 (22,7)	NE [NE; NE]	164	10 (6,1)	NE [NE; NE]	3,99	[2,07; 8,45]	<0,0001*
>=65 Jahre	104	9 (8,7)	NE [NE; NE]	111	3 (2,7)	NE [NE; NE]	3,44	[1,03; 15,49]	0,0453*
Interaktion p-Wert									0,8449
Region gPAP									
Asien	168	39 (23,2)	NE [NE; NE]	166	9 (5,4)	NE [NE; NE]	4,69	[2,38; 10,34]	<0,0001*
Europa	22	0	NE [NE; NE]	23	0	NE [NE; NE]	NC	[NC]	NC
Nordamerika	20	3 (15,0)	NE [NE; NE]	22	2 (9,1)	NE [NE; NE]	1,82	[0,30; 13,85]	0,5048
Rest der Welt	66	6 (9,1)	NE [NE; NE]	64	2 (3,1)	NE [NE; NE]	3,04	[0,70; 20,76]	0,1427
Interaktion p-Wert									0,6103

Time to event of AE is defined as the time from first dose of study treatment to first onset of the respective AE or the time to censoring if the AE has not occurred by 28 days following discontinuation of study treatment, before administration of subsequent cancer therapy or death, whichever comes first. All AEs are coded using MedDRA version 25.1. Includes AEs with onset date on or after the date of first dose and up to and including 28 days following discontinuation of study treatment. Analysis done if >=10 patients at each subgroup level and >=10 events in at least one subgroup level combined for both arms. Analysis done for SOC and PT only if main effect for that SOC or PT is statistically significant at 5% level. [a] Median time to event based on the Kaplan Meier estimate. NE = Not estimable as median (or 95% CLs) is not reached. [b] Estimated from main effects of unstratified Cox proportional hazard model including trt., subgroup and subgroup-by-trt. interaction. Ties handled using Efron method and 95% CI derived from profile likelihood estimation. NC = Not calculable. HR <1 favours Osimertinib+Chemo. * p<0.05.
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Table 4.3.1.42 FLAURA-2: Summary of subgroup analysis of time to first PT: Gamma-Glutamyltransferase erhoeht
Safety Analysis Set, DCO 03APR2023

	Osi + Chemo (N=276)			Osi (N=275)					
Subgruppen	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]	Hazard Ratio [b]	[95%-KI] [b]	2-seitiger p-Wert [b]
Abstammung									
Chinesisch/Asiatisch	68	16 (23,5)	NE [NE; NE]	70	1 (1,4)	NE [NE; NE]	17,55	[3,58;316,85]	<0,0001*
Nicht-chinesisch/ Asiatisch	107	1 (0,9)	NE [NE; NE]	106	0	NE [NE; NE]	NC	[NC]	NC
Nicht-asiatisch	101	0	NE [NE; NE]	99	1 (1,0)	NE [NE; NE]	NC	[NC]	NC
Interaktion p-Wert									NC
Methode zur Gewebeuntersuchung									
zentral	120	15 (12,5)	NE [NE; NE]	119	1 (0,8)	NE [NE; NE]	15,78	[3,20;285,12]	<0,0001*
lokal	156	2 (1,3)	NE [NE; NE]	156	1 (0,6)	NE [NE; NE]	2,00	[0,19; 42,93]	0,5609
Interaktion p-Wert									0,2119
WHO Performance-Status									
0	100	3 (3,0)	NE [NE; NE]	100	0	NE [NE; NE]	NC	[NC]	NC
1	176	14 (8,0)	NE [NE; NE]	175	2 (1,1)	NE [NE; NE]	7,06	[1,97; 44,97]	0,0014*
Interaktion p-Wert									NC
Raucherstatus									
Ja	90	5 (5,6)	NE [NE; NE]	96	1 (1,0)	NE [NE; NE]	5,29	[0,85;101,27]	0,0764
Nein	186	12 (6,5)	NE [NE; NE]	179	1 (0,6)	NE [NE; NE]	12,04	[2,37;219,22]	0,0009*
Interaktion p-Wert									0,5893
Geschlecht									
Maennlich	104	8 (7,7)	NE [NE; NE]	107	0	NE [NE; NE]	NC	[NC]	NC
Weiblich	172	9 (5,2)	NE [NE; NE]	168	2 (1,2)	NE [NE; NE]	4,65	[1,20; 30,47]	0,0247*
Interaktion p-Wert									NC
Nachweis der EGFR-Mutation durch zentralen ctDNA Cobas Test									
positiv	211	15 (7,1)	NE [NE; NE]	204	1 (0,5)	NE [NE; NE]	15,18	[3,08;274,52]	0,0001*

Time to event of AE is defined as the time from first dose of study treatment to first onset of the respective AE or the time to censoring if the AE has not occurred by 28 days following discontinuation of study treatment, before administration of subsequent cancer therapy or death, whichever comes first. All AEs are coded using MedDRA version 25.1. Includes AEs with onset date on or after the date of first dose and up to and including 28 days following discontinuation of study treatment. Analysis done if >=10 patients at each subgroup level and >=10 events in at least one subgroup level combined for both arms. Analysis done for SOC and PT only if main effect for that SOC or PT is statistically significant at 5% level. [a] Median time to event based on the Kaplan Meier estimate. NE = Not estimable as median (or 95% CLs) is not reached. [b] Estimated from main effects of unstratified Cox proportional hazard model including trt., subgroup and subgroup-by-trt. interaction. Ties handled using Efron method and 95% CI derived from profile likelihood estimation. NC = Not calculable. HR <1 favours Osimertinib+Chemo. * p<0.05.
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Table 4.3.1.42 FLAURA-2: Summary of subgroup analysis of time to first PT: Gamma-Glutamyltransferase erhoeht
Safety Analysis Set, DCO 03APR2023

	Osi + Chemo (N=276)			Osi (N=275)					
Subgruppen	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]	Hazard Ratio [b]	[95%-KI] [b]	2-seitiger p-Wert [b]
negativ	41	0	NE [NE; NE]	39	0	NE [NE; NE]	NC	[NC]	NC
unbekannt	24	2 (8,3)	NE [NE; NE]	32	1 (3,1)	NE [NE; NE]	2,44	[0,23; 52,45]	0,4511
Interaktion p-Wert									0,2654
EGFR-Mutationstyp									
Exon 19 Deletion	172	9 (5,2)	NE [NE; NE]	167	2 (1,2)	NE [NE; NE]	4,50	[1,16; 29,52]	0,0281*
Exon 21 (L858R) Substitutionsmutation	104	8 (7,7)	NE [NE; NE]	106	0	NE [NE; NE]	NC	[NC]	NC
Interaktion p-Wert									NC
Zentral bestätigte EGFR-Mutation im Gewebe									
positiv	248	17 (6,9)	NE [NE; NE]	238	1 (0,4)	NE [NE; NE]	16,87	[3,47;304,15]	<0,0001*
negativ	3	0	NE [NE; NE]	4	0	NE [NE; NE]	NC	[NC]	NC
unbekannt	25	0	NE [NE; NE]	33	1 (3,0)	NE [NE; NE]	NC	[NC]	NC
Interaktion p-Wert									NC
ZNS-Metastasen zur Baseline									
Ja	113	9 (8,0)	NE [NE; NE]	110	2 (1,8)	NE [NE; NE]	4,33	[1,12; 28,41]	0,0329*
Nein	163	8 (4,9)	NE [NE; NE]	165	0	NE [NE; NE]	NC	[NC]	NC
Interaktion p-Wert									NC
Zentrale Bestätigung der EGFR-Mutation									
Zentral bestätigte EGFR-Mutation in Gewebe oder ctDNA	263	17 (6,5)	NE [NE; NE]	266	1 (0,4)	NE [NE; NE]	17,75	[3,65;319,97]	<0,0001*
Keine zentrale Bestätigung	13	0	NE [NE; NE]	9	1 (11,1)	NE [NE; NE]	NC	[NC]	NC
Interaktion p-Wert									NC
Alter bei Screening									

Time to event of AE is defined as the time from first dose of study treatment to first onset of the respective AE or the time to censoring if the AE has not occurred by 28 days following discontinuation of study treatment, before administration of subsequent cancer therapy or death, whichever comes first. All AEs are coded using MedDRA version 25.1. Includes AEs with onset date on or after the date of first dose and up to and including 28 days following discontinuation of study treatment. Analysis done if >=10 patients at each subgroup level and >=10 events in at least one subgroup level combined for both arms. Analysis done for SOC and PT only if main effect for that SOC or PT is statistically significant at 5% level. [a] Median time to event based on the Kaplan Meier estimate. NE = Not estimable as median (or 95% CLs) is not reached. [b] Estimated from main effects of unstratified Cox proportional hazard model including trt., subgroup and subgroup-by-trt. interaction. Ties handled using Efron method and 95% CI derived from profile likelihood estimation. NC = Not calculable. HR <1 favours Osimertinib+Chemo. * p<0.05.
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Table 4.3.1.42 FLAURA-2: Summary of subgroup analysis of time to first PT: Gamma-Glutamyltransferase erhoeht
Safety Analysis Set, DCO 03APR2023

	Osi + Chemo (N=276)			Osi (N=275)					
Subgruppen	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]	Hazard Ratio [b]	[95%-KI] [b]	2-seitiger p-Wert [b]
<65 Jahre	172	17 (9,9)	NE [NE; NE]	164	2 (1,2)	NE [NE; NE]	8,26	[2,37; 52,08]	0,0003*
>=65 Jahre	104	0	NE [NE; NE]	111	0	NE [NE; NE]	NC	[NC]	NC
Interaktion p-Wert									NC
Region gPAP									
Asien	168	17 (10,1)	NE [NE; NE]	166	1 (0,6)	NE [NE; NE]	17,36	[3,57;312,95]	<0,0001*
Europa	22	0	NE [NE; NE]	23	0	NE [NE; NE]	NC	[NC]	NC
Nordamerika	20	0	NE [NE; NE]	22	0	NE [NE; NE]	NC	[NC]	NC
Rest der Welt	66	0	NE [NE; NE]	64	1 (1,6)	NE [NE; NE]	NC	[NC]	NC
Interaktion p-Wert									NC

Time to event of AE is defined as the time from first dose of study treatment to first onset of the respective AE or the time to censoring if the AE has not occurred by 28 days following discontinuation of study treatment, before administration of subsequent cancer therapy or death, whichever comes first. All AEs are coded using MedDRA version 25.1. Includes AEs with onset date on or after the date of first dose and up to and including 28 days following discontinuation of study treatment. Analysis done if >=10 patients at each subgroup level and >=10 events in at least one subgroup level combined for both arms. Analysis done for SOC and PT only if main effect for that SOC or PT is statistically significant at 5% level. [a] Median time to event based on the Kaplan Meier estimate. NE = Not estimable as median (or 95% CLs) is not reached. [b] Estimated from main effects of unstratified Cox proportional hazard model including trt., subgroup and subgroup-by-trt. interaction. Ties handled using Efron method and 95% CI derived from profile likelihood estimation. NC = Not calculable. HR <1 favours Osimertinib+Chemo. * p<0.05.
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Table 4.3.1.43 FLAURA-2: Summary of subgroup analysis of time to first PT: Gewicht erhoeht
Safety Analysis Set, DCO 03APR2023

	Osi + Chemo (N=276)			Osi (N=275)					
Subgruppen	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]	Hazard Ratio [b]	[95%-KI] [b]	2-seitiger p-Wert [b]
Abstammung									
Chinesisch/Asiatisch	68	5 (7,4)	NE [NE; NE]	70	1 (1,4)	NE [NE; NE]	NC	[NC]	NC
Nicht-chinesisch/ Asiatisch	107	3 (2,8)	NE [NE; NE]	106	1 (0,9)	NE [NE; NE]	NC	[NC]	NC
Nicht-asiatisch	101	5 (5,0)	NE [NE; NE]	99	1 (1,0)	NE [NE; NE]	NC	[NC]	NC
Interaktion p-Wert									NC
Methode zur Gewebeuntersuchung									
zentral	120	5 (4,2)	NE [NE; NE]	119	3 (2,5)	NE [NE; NE]	NC	[NC]	NC
lokal	156	8 (5,1)	NE [NE; NE]	156	0	NE [NE; NE]	NC	[NC]	NC
Interaktion p-Wert									NC
WHO Performance-Status									
0	100	5 (5,0)	NE [NE; NE]	100	2 (2,0)	NE [NE; NE]	NC	[NC]	NC
1	176	8 (4,5)	NE [NE; NE]	175	1 (0,6)	NE [NE; NE]	NC	[NC]	NC
Interaktion p-Wert									NC
Raucherstatus									
Ja	90	2 (2,2)	NE [NE; NE]	96	0	NE [NE; NE]	NC	[NC]	NC
Nein	186	11 (5,9)	NE [NE; NE]	179	3 (1,7)	NE [NE; NE]	3,62	[1,13; 16,02]	0,0290*
Interaktion p-Wert									NC
Geschlecht									
Maennlich	104	6 (5,8)	NE [NE; NE]	107	0	NE [NE; NE]	NC	[NC]	NC
Weiblich	172	7 (4,1)	NE [NE; NE]	168	3 (1,8)	NE [NE; NE]	2,37	[0,66; 11,02]	0,1899
Interaktion p-Wert									NC
Nachweis der EGFR-Mutation durch zentralen ctDNA Cobas Test									
positiv	211	10 (4,7)	NE [NE; NE]	204	1 (0,5)	NE [NE; NE]	9,87	[1,89;181,11]	0,0037*

Time to event of AE is defined as the time from first dose of study treatment to first onset of the respective AE or the time to censoring if the AE has not occurred by 28 days following discontinuation of study treatment, before administration of subsequent cancer therapy or death, whichever comes first. All AEs are coded using MedDRA version 25.1. Includes AEs with onset date on or after the date of first dose and up to and including 28 days following discontinuation of study treatment. Analysis done if >=10 patients at each subgroup level and >=10 events in at least one subgroup level combined for both arms. Analysis done for SOC and PT only if main effect for that SOC or PT is statistically significant at 5% level. [a] Median time to event based on the Kaplan Meier estimate. NE = Not estimable as median (or 95% CLs) is not reached. [b] Estimated from main effects of unstratified Cox proportional hazard model including trt., subgroup and subgroup-by-trt. interaction. Ties handled using Efron method and 95% CI derived from profile likelihood estimation. NC = Not calculable. HR <1 favours Osimertinib+Chemo. * p<0.05.
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Table 4.3.1.43 FLAURA-2: Summary of subgroup analysis of time to first PT: Gewicht erhoeht
Safety Analysis Set, DCO 03APR2023

	Osi + Chemo (N=276)			Osi (N=275)					
Subgruppen	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]	Hazard Ratio [b]	[95%-KI] [b]	2-seitiger p-Wert [b]
negativ	41	2 (4,9)	NE [NE; NE]	39	1 (2,6)	NE [NE; NE]	1,94	[0,19; 41,80]	0,5765
unbekannt	24	1 (4,2)	NE [NE; NE]	32	1 (3,1)	NE [NE; NE]	1,23	[0,05; 31,14]	0,8825
Interaktion p-Wert									0,3870
EGFR-Mutationstyp									
Exon 19 Deletion	172	11 (6,4)	NE [NE; NE]	167	2 (1,2)	NE [NE; NE]	5,55	[1,49; 35,87]	0,0084*
Exon 21 (L858R)	104	2 (1,9)	NE [NE; NE]	106	1 (0,9)	NE [NE; NE]	1,97	[0,19; 42,40]	0,5682
Substitutionsmutation									
Interaktion p-Wert									0,4876
Zentral bestätigte EGFR-Mutation im Gewebe									
positiv	248	13 (5,2)	NE [NE; NE]	238	3 (1,3)	NE [NE; NE]	4,23	[1,36; 18,43]	0,0108*
negativ	3	0	NE [NE; NE]	4	0	NE [NE; NE]	NC	[NC]	NC
unbekannt	25	0	NE [NE; NE]	33	0	NE [NE; NE]	NC	[NC]	NC
Interaktion p-Wert									NC
ZNS-Metastasen zur Baseline									
Ja	113	5 (4,4)	NE [NE; NE]	110	0	NE [NE; NE]	NC	[NC]	NC
Nein	163	8 (4,9)	NE [NE; NE]	165	3 (1,8)	NE [NE; NE]	2,78	[0,81; 12,71]	0,1084
Interaktion p-Wert									NC
Zentrale Bestätigung der EGFR-Mutation									
Zentral bestätigte EGFR-Mutation in Gewebe oder ctDNA	263	13 (4,9)	NE [NE; NE]	266	3 (1,1)	NE [NE; NE]	4,46	[1,44; 19,43]	0,0081*
Keine zentrale Bestätigung	13	0	NE [NE; NE]	9	0	NE [NE; NE]	NC	[NC]	NC
Interaktion p-Wert									NC
Alter bei Screening									

Time to event of AE is defined as the time from first dose of study treatment to first onset of the respective AE or the time to censoring if the AE has not occurred by 28 days following discontinuation of study treatment, before administration of subsequent cancer therapy or death, whichever comes first. All AEs are coded using MedDRA version 25.1. Includes AEs with onset date on or after the date of first dose and up to and including 28 days following discontinuation of study treatment. Analysis done if >=10 patients at each subgroup level and >=10 events in at least one subgroup level combined for both arms. Analysis done for SOC and PT only if main effect for that SOC or PT is statistically significant at 5% level. [a] Median time to event based on the Kaplan Meier estimate. NE = Not estimable as median (or 95% CLs) is not reached. [b] Estimated from main effects of unstratified Cox proportional hazard model including trt., subgroup and subgroup-by-trt. interaction. Ties handled using Efron method and 95% CI derived from profile likelihood estimation. NC = Not calculable. HR <1 favours Osimertinib+Chemo. * p<0.05.
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Table 4.3.1.43 FLAURA-2: Summary of subgroup analysis of time to first PT: Gewicht erhoeht
Safety Analysis Set, DCO 03APR2023

	Osi + Chemo (N=276)			Osi (N=275)					
Subgruppen	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]	Hazard Ratio [b]	[95%-KI] [b]	2-seitiger p-Wert [b]
<65 Jahre	172	11 (6,4)	NE [NE; NE]	164	3 (1,8)	NE [NE; NE]	3,47	[1,08; 15,33]	0,0355*
>=65 Jahre	104	2 (1,9)	NE [NE; NE]	111	0	NE [NE; NE]	NC	[NC]	NC
Interaktion p-Wert									NC
Region gPAP									
Asien	168	8 (4,8)	NE [NE; NE]	166	2 (1,2)	NE [NE; NE]	3,91	[0,98; 25,90]	0,0538
Europa	22	1 (4,5)	NE [NE; NE]	23	0	NE [NE; NE]	NC	[NC]	NC
Nordamerika	20	1 (5,0)	NE [NE; NE]	22	0	NE [NE; NE]	NC	[NC]	NC
Rest der Welt	66	3 (4,5)	NE [NE; NE]	64	1 (1,6)	NE [NE; NE]	3,04	[0,39; 61,39]	0,3007
Interaktion p-Wert									0,8580

Time to event of AE is defined as the time from first dose of study treatment to first onset of the respective AE or the time to censoring if the AE has not occurred by 28 days following discontinuation of study treatment, before administration of subsequent cancer therapy or death, whichever comes first. All AEs are coded using MedDRA version 25.1. Includes AEs with onset date on or after the date of first dose and up to and including 28 days following discontinuation of study treatment. Analysis done if >=10 patients at each subgroup level and >=10 events in at least one subgroup level combined for both arms. Analysis done for SOC and PT only if main effect for that SOC or PT is statistically significant at 5% level. [a] Median time to event based on the Kaplan Meier estimate. NE = Not estimable as median (or 95% CLs) is not reached. [b] Estimated from main effects of unstratified Cox proportional hazard model including trt., subgroup and subgroup-by-trt. interaction. Ties handled using Efron method and 95% CI derived from profile likelihood estimation. NC = Not calculable. HR <1 favours Osimertinib+Chemo. * p<0.05.
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Table 4.3.1.44 FLAURA-2: Summary of subgroup analysis of time to first PT: Kreatinin im Blut erhoeht
Safety Analysis Set, DCO 03APR2023

	Osi + Chemo (N=276)			Osi (N=275)					
Subgruppen	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]	Hazard Ratio [b]	[95%-KI] [b]	2-seitiger p-Wert [b]
Abstammung									
Chinesisch/Asiatisch	68	21 (30,9)	NE [NE; NE]	70	7 (10,0)	NE [NE; NE]	3,04	[1,36; 7,73]	0,0061*
Nicht-chinesisch/ Asiatisch	107	12 (11,2)	NE [NE; NE]	106	3 (2,8)	NE [NE; NE]	4,07	[1,29; 17,85]	0,0149*
Nicht-asiatisch	101	13 (12,9)	NE [NE; NE]	99	2 (2,0)	NE [NE; NE]	6,52	[1,80; 41,67]	0,0026*
Interaktion p-Wert									0,6605
Methode zur Gewebeuntersuchung									
zentral	120	21 (17,5)	NE [NE; NE]	119	7 (5,9)	NE [NE; NE]	2,95	[1,32; 7,49]	0,0077*
lokal	156	25 (16,0)	NE [NE; NE]	156	5 (3,2)	NE [NE; NE]	5,16	[2,15; 15,29]	<0,0001*
Interaktion p-Wert									0,3911
WHO Performance-Status									
0	100	16 (16,0)	NE [NE; NE]	100	4 (4,0)	NE [NE; NE]	4,21	[1,55; 14,71]	0,0039*
1	176	30 (17,0)	NE [NE; NE]	175	8 (4,6)	NE [NE; NE]	3,70	[1,78; 8,65]	0,0003*
Interaktion p-Wert									0,8482
Raucherstatus									
Ja	90	9 (10,0)	NE [NE; NE]	96	5 (5,2)	NE [NE; NE]	1,86	[0,64; 6,04]	0,2575
Nein	186	37 (19,9)	NE [NE; NE]	179	7 (3,9)	NE [NE; NE]	5,29	[2,51; 12,97]	<0,0001*
Interaktion p-Wert									0,1371
Geschlecht									
Maennlich	104	19 (18,3)	NE [NE; NE]	107	6 (5,6)	NE [NE; NE]	3,09	[1,31; 8,48]	0,0092*
Weiblich	172	27 (15,7)	NE [NE; NE]	168	6 (3,6)	NE [NE; NE]	4,64	[2,05; 12,45]	0,0001*
Interaktion p-Wert									0,5311
Nachweis der EGFR-Mutation durch zentralen ctDNA Cobas Test									
positiv	211	41 (19,4)	NE [NE; NE]	204	9 (4,4)	NE [NE; NE]	4,58	[2,33; 10,06]	<0,0001*

Time to event of AE is defined as the time from first dose of study treatment to first onset of the respective AE or the time to censoring if the AE has not occurred by 28 days following discontinuation of study treatment, before administration of subsequent cancer therapy or death, whichever comes first. All AEs are coded using MedDRA version 25.1. Includes AEs with onset date on or after the date of first dose and up to and including 28 days following discontinuation of study treatment. Analysis done if >=10 patients at each subgroup level and >=10 events in at least one subgroup level combined for both arms. Analysis done for SOC and PT only if main effect for that SOC or PT is statistically significant at 5% level. [a] Median time to event based on the Kaplan Meier estimate. NE = Not estimable as median (or 95% CLs) is not reached. [b] Estimated from main effects of unstratified Cox proportional hazard model including trt., subgroup and subgroup-by-trt. interaction. Ties handled using Efron method and 95% CI derived from profile likelihood estimation. NC = Not calculable. HR <1 favours Osimertinib+Chemo. * p<0.05.
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Table 4.3.1.44 FLAURA-2: Summary of subgroup analysis of time to first PT: Kreatinin im Blut erhoeht
Safety Analysis Set, DCO 03APR2023

	Osi + Chemo (N=276)			Osi (N=275)					
Subgruppen	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]	Hazard Ratio [b]	[95%-KI] [b]	2-seitiger p-Wert [b]
negativ	41	3 (7,3)	NE [NE; NE]	39	2 (5,1)	NE [NE; NE]	1,39	[0,23; 10,54]	0,7170
unbekannt	24	2 (8,3)	NE [NE; NE]	32	1 (3,1)	NE [NE; NE]	2,41	[0,23; 51,72]	0,4585
Interaktion p-Wert									0,4731
EGFR-Mutationstyp									
Exon 19 Deletion	172	20 (11,6)	NE [NE; NE]	167	6 (3,6)	NE [NE; NE]	3,30	[1,40; 9,02]	0,0052*
Exon 21 (L858R) Substitutionsmutation	104	26 (25,0)	NE [NE; NE]	106	6 (5,7)	NE [NE; NE]	4,48	[1,97; 12,03]	0,0002*
Interaktion p-Wert									0,6379
Zentral bestätigte EGFR-Mutation im Gewebe									
positiv	248	46 (18,5)	NE [NE; NE]	238	11 (4,6)	NE [NE; NE]	4,08	[2,20; 8,30]	<0,0001*
negativ	3	0	NE [NE; NE]	4	0	NE [NE; NE]	NC	[NC]	NC
unbekannt	25	0	NE [NE; NE]	33	1 (3,0)	NE [NE; NE]	NC	[NC]	NC
Interaktion p-Wert									NC
ZNS-Metastasen zur Baseline									
Ja	113	20 (17,7)	NE [NE; NE]	110	7 (6,4)	NE [NE; NE]	2,55	[1,13; 6,51]	0,0235*
Nein	163	26 (16,0)	NE [NE; NE]	165	5 (3,0)	NE [NE; NE]	5,70	[2,38; 16,84]	<0,0001*
Interaktion p-Wert									0,2177
Zentrale Bestätigung der EGFR-Mutation									
Zentral bestätigte EGFR-Mutation in Gewebe oder ctDNA	263	46 (17,5)	NE [NE; NE]	266	12 (4,5)	NE [NE; NE]	3,96	[2,17; 7,82]	<0,0001*
Keine zentrale Bestätigung	13	0	NE [NE; NE]	9	0	NE [NE; NE]	NC	[NC]	NC
Interaktion p-Wert									NC
Alter bei Screening									

Time to event of AE is defined as the time from first dose of study treatment to first onset of the respective AE or the time to censoring if the AE has not occurred by 28 days following discontinuation of study treatment, before administration of subsequent cancer therapy or death, whichever comes first. All AEs are coded using MedDRA version 25.1. Includes AEs with onset date on or after the date of first dose and up to and including 28 days following discontinuation of study treatment. Analysis done if >=10 patients at each subgroup level and >=10 events in at least one subgroup level combined for both arms. Analysis done for SOC and PT only if main effect for that SOC or PT is statistically significant at 5% level. [a] Median time to event based on the Kaplan Meier estimate. NE = Not estimable as median (or 95% CLs) is not reached. [b] Estimated from main effects of unstratified Cox proportional hazard model including trt., subgroup and subgroup-by-trt. interaction. Ties handled using Efron method and 95% CI derived from profile likelihood estimation. NC = Not calculable. HR <1 favours Osimertinib+Chemo. * p<0.05.
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Table 4.3.1.44 FLAURA-2: Summary of subgroup analysis of time to first PT: Kreatinin im Blut erhoeht
Safety Analysis Set, DCO 03APR2023

	Osi + Chemo (N=276)			Osi (N=275)					
Subgruppen	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]	Hazard Ratio [b]	[95%-KI] [b]	2-seitiger p-Wert [b]
<65 Jahre	172	27 (15,7)	NE [NE; NE]	164	5 (3,0)	NE [NE; NE]	5,02	[2,10; 14,81]	0,0001*
>=65 Jahre	104	19 (18,3)	NE [NE; NE]	111	7 (6,3)	NE [NE; NE]	3,19	[1,40; 8,16]	0,0051*
Interaktion p-Wert									0,4870
Region gPAP									
Asien	168	31 (18,5)	NE [NE; NE]	166	9 (5,4)	NE [NE; NE]	3,41	[1,69; 7,61]	0,0004*
Europa	22	2 (9,1)	NE [NE; NE]	23	0	NE [NE; NE]	NC	[NC]	NC
Nordamerika	20	4 (20,0)	NE [NE; NE]	22	1 (4,5)	NE [NE; NE]	5,48	[0,81;107,15]	0,0837
Rest der Welt	66	9 (13,6)	NE [NE; NE]	64	2 (3,1)	NE [NE; NE]	4,44	[1,14; 29,11]	0,0298*
Interaktion p-Wert									0,8900

Time to event of AE is defined as the time from first dose of study treatment to first onset of the respective AE or the time to censoring if the AE has not occurred by 28 days following discontinuation of study treatment, before administration of subsequent cancer therapy or death, whichever comes first. All AEs are coded using MedDRA version 25.1. Includes AEs with onset date on or after the date of first dose and up to and including 28 days following discontinuation of study treatment. Analysis done if >=10 patients at each subgroup level and >=10 events in at least one subgroup level combined for both arms. Analysis done for SOC and PT only if main effect for that SOC or PT is statistically significant at 5% level. [a] Median time to event based on the Kaplan Meier estimate. NE = Not estimable as median (or 95% CLs) is not reached. [b] Estimated from main effects of unstratified Cox proportional hazard model including trt., subgroup and subgroup-by-trt. interaction. Ties handled using Efron method and 95% CI derived from profile likelihood estimation. NC = Not calculable. HR <1 favours Osimertinib+Chemo. * p<0.05.
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Table 4.3.1.45 FLAURA-2: Summary of subgroup analysis of time to first PT: Leukozytenzahl erniedrigt
Safety Analysis Set, DCO 03APR2023

	Osi + Chemo (N=276)			Osi (N=275)					
Subgruppen	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]	Hazard Ratio [b]	[95%-KI] [b]	2-seitiger p-Wert [b]
Abstammung									
Chinesisch/Asiatisch	68	41 (60,3)	2,6 [1,1; NE]	70	17 (24,3)	NE [NE; NE]	3,43	[1,98; 6,21]	<0,0001*
Nicht-chinesisch/ Asiatisch	107	2 (1,9)	NE [NE; NE]	106	1 (0,9)	NE [NE; NE]	2,02	[0,19; 43,39]	0,5548
Nicht-asiatisch	101	1 (1,0)	NE [NE; NE]	99	0	NE [NE; NE]	NC	[NC]	NC
Interaktion p-Wert									0,6821
Methode zur Gewebeuntersuchung									
zentral	120	39 (32,5)	NE [NE; NE]	119	16 (13,4)	NE [NE; NE]	2,91	[1,66; 5,36]	0,0001*
lokal	156	5 (3,2)	NE [NE; NE]	156	2 (1,3)	NE [NE; NE]	2,48	[0,54; 17,34]	0,2526
Interaktion p-Wert									0,8599
WHO Performance-Status									
0	100	15 (15,0)	NE [NE; NE]	100	5 (5,0)	NE [NE; NE]	3,22	[1,25; 9,89]	0,0147*
1	176	29 (16,5)	NE [NE; NE]	175	13 (7,4)	NE [NE; NE]	2,38	[1,26; 4,73]	0,0068*
Interaktion p-Wert									0,6200
Raucherstatus									
Ja	90	11 (12,2)	NE [NE; NE]	96	1 (1,0)	NE [NE; NE]	12,45	[2,42;227,43]	0,0009*
Nein	186	33 (17,7)	NE [NE; NE]	179	17 (9,5)	NE [NE; NE]	2,01	[1,14; 3,70]	0,0158*
Interaktion p-Wert									0,0414*
Geschlecht									
Maennlich	104	16 (15,4)	NE [NE; NE]	107	5 (4,7)	NE [NE; NE]	3,47	[1,36; 10,62]	0,0082*
Weiblich	172	28 (16,3)	NE [NE; NE]	168	13 (7,7)	NE [NE; NE]	2,28	[1,21; 4,55]	0,0108*
Interaktion p-Wert									0,4859
Nachweis der EGFR-Mutation durch zentralen ctDNA Cobas Test									
positiv	211	39 (18,5)	NE [NE; NE]	204	11 (5,4)	NE [NE; NE]	3,79	[2,01; 7,76]	<0,0001*

Time to event of AE is defined as the time from first dose of study treatment to first onset of the respective AE or the time to censoring if the AE has not occurred by 28 days following discontinuation of study treatment, before administration of subsequent cancer therapy or death, whichever comes first. All AEs are coded using MedDRA version 25.1. Includes AEs with onset date on or after the date of first dose and up to and including 28 days following discontinuation of study treatment. Analysis done if >=10 patients at each subgroup level and >=10 events in at least one subgroup level combined for both arms. Analysis done for SOC and PT only if main effect for that SOC or PT is statistically significant at 5% level. [a] Median time to event based on the Kaplan Meier estimate. NE = Not estimable as median (or 95% CLs) is not reached. [b] Estimated from main effects of unstratified Cox proportional hazard model including trt., subgroup and subgroup-by-trt. interaction. Ties handled using Efron method and 95% CI derived from profile likelihood estimation. NC = Not calculable. HR <1 favours Osimertinib+Chemo. * p<0.05.
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Table 4.3.1.45 FLAURA-2: Summary of subgroup analysis of time to first PT: Leukozytenzahl erniedrigt
Safety Analysis Set, DCO 03APR2023

	Osi + Chemo (N=276)			Osi (N=275)					
Subgruppen	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]	Hazard Ratio [b]	[95%-KI] [b]	2-seitiger p-Wert [b]
negativ	41	2 (4,9)	NE [NE; NE]	39	5 (12,8)	NE [NE; NE]	0,37	[0,05; 1,70]	0,2066
unbekannt	24	3 (12,5)	NE [NE; NE]	32	2 (6,3)	NE [NE; NE]	2,03	[0,34; 15,38]	0,4332
Interaktion p-Wert									0,0220*
EGFR-Mutationstyp									
Exon 19 Deletion	172	21 (12,2)	NE [NE; NE]	167	11 (6,6)	NE [NE; NE]	1,96	[0,97; 4,22]	0,0628
Exon 21 (L858R) Substitutionsmutation	104	23 (22,1)	NE [NE; NE]	106	7 (6,6)	NE [NE; NE]	3,68	[1,66; 9,28]	0,0010*
Interaktion p-Wert									0,2657
Zentral bestätigte EGFR-Mutation im Gewebe									
positiv	248	44 (17,7)	NE [NE; NE]	238	17 (7,1)	NE [NE; NE]	2,70	[1,57; 4,85]	0,0002*
negativ	3	0	NE [NE; NE]	4	0	NE [NE; NE]	NC	[NC]	NC
unbekannt	25	0	NE [NE; NE]	33	1 (3,0)	NE [NE; NE]	NC	[NC]	NC
Interaktion p-Wert									NC
ZNS-Metastasen zur Baseline									
Ja	113	21 (18,6)	NE [NE; NE]	110	6 (5,5)	NE [NE; NE]	3,64	[1,56; 9,91]	0,0022*
Nein	163	23 (14,1)	NE [NE; NE]	165	12 (7,3)	NE [NE; NE]	2,09	[1,06; 4,34]	0,0335*
Interaktion p-Wert									0,3353
Zentrale Bestätigung der EGFR-Mutation									
Zentral bestätigte EGFR-Mutation in Gewebe oder ctDNA	263	44 (16,7)	NE [NE; NE]	266	17 (6,4)	NE [NE; NE]	2,84	[1,65; 5,10]	0,0001*
Keine zentrale Bestätigung	13	0	NE [NE; NE]	9	1 (11,1)	NE [NE; NE]	NC	[NC]	NC
Interaktion p-Wert									NC
Alter bei Screening									

Time to event of AE is defined as the time from first dose of study treatment to first onset of the respective AE or the time to censoring if the AE has not occurred by 28 days following discontinuation of study treatment, before administration of subsequent cancer therapy or death, whichever comes first. All AEs are coded using MedDRA version 25.1. Includes AEs with onset date on or after the date of first dose and up to and including 28 days following discontinuation of study treatment. Analysis done if >=10 patients at each subgroup level and >=10 events in at least one subgroup level combined for both arms. Analysis done for SOC and PT only if main effect for that SOC or PT is statistically significant at 5% level. [a] Median time to event based on the Kaplan Meier estimate. NE = Not estimable as median (or 95% CLs) is not reached. [b] Estimated from main effects of unstratified Cox proportional hazard model including trt., subgroup and subgroup-by-trt. interaction. Ties handled using Efron method and 95% CI derived from profile likelihood estimation. NC = Not calculable. HR <1 favours Osimertinib+Chemo. * p<0.05.
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Table 4.3.1.45 FLAURA-2: Summary of subgroup analysis of time to first PT: Leukozytenzahl erniedrigt
Safety Analysis Set, DCO 03APR2023

	Osi + Chemo (N=276)			Osi (N=275)					
Subgruppen	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]	Hazard Ratio [b]	[95%-KI] [b]	2-seitiger p-Wert [b]
<65 Jahre	172	33 (19,2)	NE [NE; NE]	164	14 (8,5)	NE [NE; NE]	2,40	[1,31; 4,62]	0,0042*
>=65 Jahre	104	11 (10,6)	NE [NE; NE]	111	4 (3,6)	NE [NE; NE]	3,18	[1,09; 11,48]	0,0340*
Interaktion p-Wert									0,6666
Region gPAP									
Asien	168	43 (25,6)	NE [NE; NE]	166	17 (10,2)	NE [NE; NE]	2,82	[1,64; 5,08]	0,0001*
Europa	22	1 (4,5)	NE [NE; NE]	23	0	NE [NE; NE]	NC	[NC]	NC
Nordamerika	20	0	NE [NE; NE]	22	1 (4,5)	NE [NE; NE]	NC	[NC]	NC
Rest der Welt	66	0	NE [NE; NE]	64	0	NE [NE; NE]	NC	[NC]	NC
Interaktion p-Wert									NC

Time to event of AE is defined as the time from first dose of study treatment to first onset of the respective AE or the time to censoring if the AE has not occurred by 28 days following discontinuation of study treatment, before administration of subsequent cancer therapy or death, whichever comes first. All AEs are coded using MedDRA version 25.1. Includes AEs with onset date on or after the date of first dose and up to and including 28 days following discontinuation of study treatment. Analysis done if >=10 patients at each subgroup level and >=10 events in at least one subgroup level combined for both arms. Analysis done for SOC and PT only if main effect for that SOC or PT is statistically significant at 5% level. [a] Median time to event based on the Kaplan Meier estimate. NE = Not estimable as median (or 95% CLs) is not reached. [b] Estimated from main effects of unstratified Cox proportional hazard model including trt., subgroup and subgroup-by-trt. interaction. Ties handled using Efron method and 95% CI derived from profile likelihood estimation. NC = Not calculable. HR <1 favours Osimertinib+Chemo. * p<0.05.
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Table 4.3.1.46 FLAURA-2: Summary of subgroup analysis of time to first PT: Neutrophilenzahl erniedrigt
Safety Analysis Set, DCO 03APR2023

	Osi + Chemo (N=276)			Osi (N=275)					
Subgruppen	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]	Hazard Ratio [b]	[95%-KI] [b]	2-seitiger p-Wert [b]
Abstammung									
Chinesisch/Asiatisch	68	44 (64,7)	2,8 [1,3;11,7]	70	13 (18,6)	NE [NE; NE]	5,20	[2,88; 10,07]	<0,0001*
Nicht-chinesisch/ Asiatisch	107	14 (13,1)	NE [NE; NE]	106	3 (2,8)	NE [NE; NE]	4,83	[1,58; 20,95]	0,0044*
Nicht-asiatisch	101	4 (4,0)	NE [NE; NE]	99	0	NE [NE; NE]	NC	[NC]	NC
Interaktion p-Wert									0,9179
Methode zur Gewebeuntersuchung									
zentral	120	41 (34,2)	NE [NE; NE]	119	13 (10,9)	NE [NE; NE]	3,86	[2,13; 7,50]	<0,0001*
lokal	156	21 (13,5)	NE [NE; NE]	156	3 (1,9)	NE [NE; NE]	7,16	[2,47; 30,30]	<0,0001*
Interaktion p-Wert									0,3539
WHO Performance-Status									
0	100	22 (22,0)	NE [NE; NE]	100	4 (4,0)	NE [NE; NE]	6,18	[2,37; 21,13]	<0,0001*
1	176	40 (22,7)	NE [NE; NE]	175	12 (6,9)	NE [NE; NE]	3,61	[1,95; 7,19]	<0,0001*
Interaktion p-Wert									0,3851
Raucherstatus									
Ja	90	13 (14,4)	NE [NE; NE]	96	0	NE [NE; NE]	NC	[NC]	NC
Nein	186	49 (26,3)	NE [NE; NE]	179	16 (8,9)	NE [NE; NE]	3,31	[1,93; 6,01]	<0,0001*
Interaktion p-Wert									NC
Geschlecht									
Maennlich	104	20 (19,2)	NE [NE; NE]	107	3 (2,8)	NE [NE; NE]	7,28	[2,50; 30,90]	<0,0001*
Weiblich	172	42 (24,4)	NE [NE; NE]	168	13 (7,7)	NE [NE; NE]	3,56	[1,97; 6,91]	<0,0001*
Interaktion p-Wert									0,2814
Nachweis der EGFR-Mutation durch zentralen ctDNA Cobas Test									
positiv	211	53 (25,1)	NE [NE; NE]	204	10 (4,9)	NE [NE; NE]	5,84	[3,11; 12,20]	<0,0001*

Time to event of AE is defined as the time from first dose of study treatment to first onset of the respective AE or the time to censoring if the AE has not occurred by 28 days following discontinuation of study treatment, before administration of subsequent cancer therapy or death, whichever comes first. All AEs are coded using MedDRA version 25.1. Includes AEs with onset date on or after the date of first dose and up to and including 28 days following discontinuation of study treatment. Analysis done if >=10 patients at each subgroup level and >=10 events in at least one subgroup level combined for both arms. Analysis done for SOC and PT only if main effect for that SOC or PT is statistically significant at 5% level. [a] Median time to event based on the Kaplan Meier estimate. NE = Not estimable as median (or 95% CLs) is not reached. [b] Estimated from main effects of unstratified Cox proportional hazard model including trt., subgroup and subgroup-by-trt. interaction. Ties handled using Efron method and 95% CI derived from profile likelihood estimation. NC = Not calculable. HR <1 favours Osimertinib+Chemo. * p<0.05.
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Table 4.3.1.46 FLAURA-2: Summary of subgroup analysis of time to first PT: Neutrophilenzahl erniedrigt
Safety Analysis Set, DCO 03APR2023

	Osi + Chemo (N=276)			Osi (N=275)					
Subgruppen	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]	Hazard Ratio [b]	[95%-KI] [b]	2-seitiger p-Wert [b]
negativ	41	3 (7,3)	NE [NE; NE]	39	5 (12,8)	NE [NE; NE]	0,55	[0,11; 2,25]	0,4069
unbekannt	24	6 (25,0)	NE [NE; NE]	32	1 (3,1)	NE [NE; NE]	8,50	[1,45;160,60]	0,0150*
Interaktion p-Wert									0,0098*
EGFR-Mutationstyp									
Exon 19 Deletion	172	31 (18,0)	NE [NE; NE]	167	9 (5,4)	NE [NE; NE]	3,64	[1,81; 8,12]	0,0002*
Exon 21 (L858R) Substitutionsmutation	104	31 (29,8)	NE [NE; NE]	106	7 (6,6)	NE [NE; NE]	5,12	[2,39; 12,66]	<0,0001*
Interaktion p-Wert									0,5440
Zentral bestätigte EGFR-Mutation im Gewebe									
positiv	248	62 (25,0)	NE [NE; NE]	238	15 (6,3)	NE [NE; NE]	4,44	[2,60; 8,10]	<0,0001*
negativ	3	0	NE [NE; NE]	4	0	NE [NE; NE]	NC	[NC]	NC
unbekannt	25	0	NE [NE; NE]	33	1 (3,0)	NE [NE; NE]	NC	[NC]	NC
Interaktion p-Wert									NC
ZNS-Metastasen zur Baseline									
Ja	113	28 (24,8)	NE [NE; NE]	110	7 (6,4)	NE [NE; NE]	4,18	[1,93; 10,40]	0,0001*
Nein	163	34 (20,9)	NE [NE; NE]	165	9 (5,5)	NE [NE; NE]	4,29	[2,15; 9,51]	<0,0001*
Interaktion p-Wert									0,9651
Zentrale Bestätigung der EGFR-Mutation									
Zentral bestätigte EGFR-Mutation in Gewebe oder ctDNA	263	62 (23,6)	NE [NE; NE]	266	15 (5,6)	NE [NE; NE]	4,66	[2,73; 8,50]	<0,0001*
Keine zentrale Bestätigung	13	0	NE [NE; NE]	9	1 (11,1)	NE [NE; NE]	NC	[NC]	NC
Interaktion p-Wert									NC
Alter bei Screening									

Time to event of AE is defined as the time from first dose of study treatment to first onset of the respective AE or the time to censoring if the AE has not occurred by 28 days following discontinuation of study treatment, before administration of subsequent cancer therapy or death, whichever comes first. All AEs are coded using MedDRA version 25.1. Includes AEs with onset date on or after the date of first dose and up to and including 28 days following discontinuation of study treatment. Analysis done if >=10 patients at each subgroup level and >=10 events in at least one subgroup level combined for both arms. Analysis done for SOC and PT only if main effect for that SOC or PT is statistically significant at 5% level. [a] Median time to event based on the Kaplan Meier estimate. NE = Not estimable as median (or 95% CLs) is not reached. [b] Estimated from main effects of unstratified Cox proportional hazard model including trt., subgroup and subgroup-by-trt. interaction. Ties handled using Efron method and 95% CI derived from profile likelihood estimation. NC = Not calculable. HR <1 favours Osimertinib+Chemo. * p<0.05.
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Table 4.3.1.46 FLAURA-2: Summary of subgroup analysis of time to first PT: Neutrophilenzahl erniedrigt
Safety Analysis Set, DCO 03APR2023

	Osi + Chemo (N=276)			Osi (N=275)					
Subgruppen	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]	Hazard Ratio [b]	[95%-KI] [b]	2-seitiger p-Wert [b]
<65 Jahre	172	46 (26,7)	NE [NE; NE]	164	11 (6,7)	NE [NE; NE]	4,39	[2,36; 8,93]	<0,0001*
>=65 Jahre	104	16 (15,4)	NE [NE; NE]	111	5 (4,5)	NE [NE; NE]	3,78	[1,48; 11,55]	0,0046*
Interaktion p-Wert									0,8065
Region gPAP									
Asien	168	56 (33,3)	NE [NE; NE]	166	15 (9,0)	NE [NE; NE]	4,34	[2,52; 7,96]	<0,0001*
Europa	22	1 (4,5)	NE [NE; NE]	23	0	NE [NE; NE]	NC	[NC]	NC
Nordamerika	20	3 (15,0)	NE [NE; NE]	22	1 (4,5)	NE [NE; NE]	3,66	[0,47; 73,98]	0,2233
Rest der Welt	66	2 (3,0)	NE [NE; NE]	64	0	NE [NE; NE]	NC	[NC]	NC
Interaktion p-Wert									0,8874

Time to event of AE is defined as the time from first dose of study treatment to first onset of the respective AE or the time to censoring if the AE has not occurred by 28 days following discontinuation of study treatment, before administration of subsequent cancer therapy or death, whichever comes first. All AEs are coded using MedDRA version 25.1. Includes AEs with onset date on or after the date of first dose and up to and including 28 days following discontinuation of study treatment. Analysis done if >=10 patients at each subgroup level and >=10 events in at least one subgroup level combined for both arms. Analysis done for SOC and PT only if main effect for that SOC or PT is statistically significant at 5% level. [a] Median time to event based on the Kaplan Meier estimate. NE = Not estimable as median (or 95% CLs) is not reached. [b] Estimated from main effects of unstratified Cox proportional hazard model including trt., subgroup and subgroup-by-trt. interaction. Ties handled using Efron method and 95% CI derived from profile likelihood estimation. NC = Not calculable. HR <1 favours Osimertinib+Chemo. * p<0.05.
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Table 4.3.1.47 FLAURA-2: Summary of subgroup analysis of time to first PT: Renale Kreatininclearance vermindert
Safety Analysis Set, DCO 03APR2023

	Osi + Chemo (N=276)			Osi (N=275)					
Subgruppen	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]	Hazard Ratio [b]	[95%-KI] [b]	2-seitiger p-Wert [b]
Abstammung									
Chinesisch/Asiatisch	68	2 (2,9)	NE [NE; NE]	70	0	NE [NE; NE]	NC	[NC]	NC
Nicht-chinesisch/ Asiatisch	107	8 (7,5)	NE [NE; NE]	106	0	NE [NE; NE]	NC	[NC]	NC
Nicht-asiatisch	101	3 (3,0)	NE [NE; NE]	99	0	NE [NE; NE]	NC	[NC]	NC
Interaktion p-Wert									NC
Methode zur Gewebeuntersuchung									
zentral	120	4 (3,3)	NE [NE; NE]	119	0	NE [NE; NE]	NC	[NC]	NC
lokal	156	9 (5,8)	NE [NE; NE]	156	0	NE [NE; NE]	NC	[NC]	NC
Interaktion p-Wert									NC
WHO Performance-Status									
0	100	1 (1,0)	NE [NE; NE]	100	0	NE [NE; NE]	NC	[NC]	NC
1	176	12 (6,8)	NE [NE; NE]	175	0	NE [NE; NE]	NC	[NC]	NC
Interaktion p-Wert									NC
Raucherstatus									
Ja	90	5 (5,6)	NE [NE; NE]	96	0	NE [NE; NE]	NC	[NC]	NC
Nein	186	8 (4,3)	NE [NE; NE]	179	0	NE [NE; NE]	NC	[NC]	NC
Interaktion p-Wert									NC
Geschlecht									
Maennlich	104	4 (3,8)	NE [NE; NE]	107	0	NE [NE; NE]	NC	[NC]	NC
Weiblich	172	9 (5,2)	NE [NE; NE]	168	0	NE [NE; NE]	NC	[NC]	NC
Interaktion p-Wert									NC
Nachweis der EGFR-Mutation durch zentralen ctDNA Cobas Test									
positiv	211	12 (5,7)	NE [NE; NE]	204	0	NE [NE; NE]	NC	[NC]	NC

Time to event of AE is defined as the time from first dose of study treatment to first onset of the respective AE or the time to censoring if the AE has not occurred by 28 days following discontinuation of study treatment, before administration of subsequent cancer therapy or death, whichever comes first. All AEs are coded using MedDRA version 25.1. Includes AEs with onset date on or after the date of first dose and up to and including 28 days following discontinuation of study treatment. Analysis done if >=10 patients at each subgroup level and >=10 events in at least one subgroup level combined for both arms. Analysis done for SOC and PT only if main effect for that SOC or PT is statistically significant at 5% level. [a] Median time to event based on the Kaplan Meier estimate. NE = Not estimable as median (or 95% CLs) is not reached. [b] Estimated from main effects of unstratified Cox proportional hazard model including trt., subgroup and subgroup-by-trt. interaction. Ties handled using Efron method and 95% CI derived from profile likelihood estimation. NC = Not calculable. HR <1 favours Osimertinib+Chemo. * p<0.05.
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Table 4.3.1.47 FLAURA-2: Summary of subgroup analysis of time to first PT: Renale Kreatininclearance vermindert
Safety Analysis Set, DCO 03APR2023

	Osi + Chemo (N=276)			Osi (N=275)					
Subgruppen	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]	Hazard Ratio [b]	[95%-KI] [b]	2-seitiger p-Wert [b]
negativ	41	0	NE [NE; NE]	39	0	NE [NE; NE]	NC	[NC]	NC
unbekannt	24	1 (4,2)	NE [NE; NE]	32	0	NE [NE; NE]	NC	[NC]	NC
Interaktion p-Wert									NC
EGFR-Mutationstyp									
Exon 19 Deletion	172	6 (3,5)	NE [NE; NE]	167	0	NE [NE; NE]	NC	[NC]	NC
Exon 21 (L858R) Substitutionsmutation	104	7 (6,7)	NE [NE; NE]	106	0	NE [NE; NE]	NC	[NC]	NC
Interaktion p-Wert									NC
Zentral bestätigte EGFR-Mutation im Gewebe									
positiv	248	12 (4,8)	NE [NE; NE]	238	0	NE [NE; NE]	NC	[NC]	NC
negativ	3	1 (33,3)	NE [NE; NE]	4	0	NE [NE; NE]	NC	[NC]	NC
unbekannt	25	0	NE [NE; NE]	33	0	NE [NE; NE]	NC	[NC]	NC
Interaktion p-Wert									NC
ZNS-Metastasen zur Baseline									
Ja	113	8 (7,1)	NE [NE; NE]	110	0	NE [NE; NE]	NC	[NC]	NC
Nein	163	5 (3,1)	NE [NE; NE]	165	0	NE [NE; NE]	NC	[NC]	NC
Interaktion p-Wert									NC
Zentrale Bestätigung der EGFR-Mutation									
Zentral bestätigte EGFR-Mutation in Gewebe oder ctDNA	263	13 (4,9)	NE [NE; NE]	266	0	NE [NE; NE]	NC	[NC]	NC
Keine zentrale Bestätigung	13	0	NE [NE; NE]	9	0	NE [NE; NE]	NC	[NC]	NC
Interaktion p-Wert									NC
Alter bei Screening									

Time to event of AE is defined as the time from first dose of study treatment to first onset of the respective AE or the time to censoring if the AE has not occurred by 28 days following discontinuation of study treatment, before administration of subsequent cancer therapy or death, whichever comes first. All AEs are coded using MedDRA version 25.1. Includes AEs with onset date on or after the date of first dose and up to and including 28 days following discontinuation of study treatment. Analysis done if >=10 patients at each subgroup level and >=10 events in at least one subgroup level combined for both arms. Analysis done for SOC and PT only if main effect for that SOC or PT is statistically significant at 5% level. [a] Median time to event based on the Kaplan Meier estimate. NE = Not estimable as median (or 95% CLs) is not reached. [b] Estimated from main effects of unstratified Cox proportional hazard model including trt., subgroup and subgroup-by-trt. interaction. Ties handled using Efron method and 95% CI derived from profile likelihood estimation. NC = Not calculable. HR <1 favours Osimertinib+Chemo. * p<0.05.
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Table 4.3.1.47 FLAURA-2: Summary of subgroup analysis of time to first PT: Renale Kreatininclearance vermindert
Safety Analysis Set, DCO 03APR2023

	Osi + Chemo (N=276)			Osi (N=275)					
Subgruppen	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]	Hazard Ratio [b]	[95%-KI] [b]	2-seitiger p-Wert [b]
<65 Jahre	172	10 (5,8)	NE [NE; NE]	164	0	NE [NE; NE]	NC	[NC]	NC
>=65 Jahre	104	3 (2,9)	NE [NE; NE]	111	0	NE [NE; NE]	NC	[NC]	NC
Interaktion p-Wert									NC
Region gPAP									
Asien	168	10 (6,0)	NE [NE; NE]	166	0	NE [NE; NE]	NC	[NC]	NC
Europa	22	0	NE [NE; NE]	23	0	NE [NE; NE]	NC	[NC]	NC
Nordamerika	20	1 (5,0)	NE [NE; NE]	22	0	NE [NE; NE]	NC	[NC]	NC
Rest der Welt	66	2 (3,0)	NE [NE; NE]	64	0	NE [NE; NE]	NC	[NC]	NC
Interaktion p-Wert									NC

Time to event of AE is defined as the time from first dose of study treatment to first onset of the respective AE or the time to censoring if the AE has not occurred by 28 days following discontinuation of study treatment, before administration of subsequent cancer therapy or death, whichever comes first. All AEs are coded using MedDRA version 25.1. Includes AEs with onset date on or after the date of first dose and up to and including 28 days following discontinuation of study treatment. Analysis done if >=10 patients at each subgroup level and >=10 events in at least one subgroup level combined for both arms. Analysis done for SOC and PT only if main effect for that SOC or PT is statistically significant at 5% level. [a] Median time to event based on the Kaplan Meier estimate. NE = Not estimable as median (or 95% CLs) is not reached. [b] Estimated from main effects of unstratified Cox proportional hazard model including trt., subgroup and subgroup-by-trt. interaction. Ties handled using Efron method and 95% CI derived from profile likelihood estimation. NC = Not calculable. HR <1 favours Osimertinib+Chemo. * p<0.05.
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Table 4.3.1.48 FLAURA-2: Summary of subgroup analysis of time to first PT: Thrombozytenzahl vermindert
Safety Analysis Set, DCO 03APR2023

	Osi + Chemo (N=276)			Osi (N=275)					
Subgruppen	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]	Hazard Ratio [b]	[95%-KI] [b]	2-seitiger p-Wert [b]
Abstammung									
Chinesisch/Asiatisch	68	41 (60,3)	1,2 [0,5; NE]	70	15 (21,4)	NE [NE; NE]	3,86	[2,18; 7,21]	<0,0001*
Nicht-chinesisch/ Asiatisch	107	6 (5,6)	NE [NE; NE]	106	2 (1,9)	NE [NE; NE]	3,10	[0,71; 21,16]	0,1355
Nicht-asiatisch	101	4 (4,0)	NE [NE; NE]	99	2 (2,0)	NE [NE; NE]	1,98	[0,39; 14,29]	0,4162
Interaktion p-Wert									0,7693
Methode zur Gewebeuntersuchung									
zentral	120	39 (32,5)	NE [NE; NE]	119	14 (11,8)	NE [NE; NE]	3,23	[1,79; 6,15]	<0,0001*
lokal	156	12 (7,7)	NE [NE; NE]	156	5 (3,2)	NE [NE; NE]	2,47	[0,92; 7,77]	0,0745
Interaktion p-Wert									0,6691
WHO Performance-Status									
0	100	15 (15,0)	NE [NE; NE]	100	5 (5,0)	NE [NE; NE]	3,22	[1,25; 9,89]	0,0147*
1	176	36 (20,5)	NE [NE; NE]	175	14 (8,0)	NE [NE; NE]	2,79	[1,54; 5,35]	0,0006*
Interaktion p-Wert									0,8125
Raucherstatus									
Ja	90	17 (18,9)	NE [NE; NE]	96	6 (6,3)	NE [NE; NE]	3,16	[1,31; 8,75]	0,0094*
Nein	186	34 (18,3)	NE [NE; NE]	179	13 (7,3)	NE [NE; NE]	2,78	[1,50; 5,46]	0,0009*
Interaktion p-Wert									0,8231
Geschlecht									
Maennlich	104	24 (23,1)	NE [NE; NE]	107	10 (9,3)	NE [NE; NE]	2,64	[1,30; 5,79]	0,0067*
Weiblich	172	27 (15,7)	NE [NE; NE]	168	9 (5,4)	NE [NE; NE]	3,20	[1,56; 7,21]	0,0011*
Interaktion p-Wert									0,7200
Nachweis der EGFR-Mutation durch zentralen ctDNA Cobas Test									
positiv	211	39 (18,5)	NE [NE; NE]	204	15 (7,4)	NE [NE; NE]	2,73	[1,54; 5,11]	0,0005*

Time to event of AE is defined as the time from first dose of study treatment to first onset of the respective AE or the time to censoring if the AE has not occurred by 28 days following discontinuation of study treatment, before administration of subsequent cancer therapy or death, whichever comes first. All AEs are coded using MedDRA version 25.1. Includes AEs with onset date on or after the date of first dose and up to and including 28 days following discontinuation of study treatment. Analysis done if >=10 patients at each subgroup level and >=10 events in at least one subgroup level combined for both arms. Analysis done for SOC and PT only if main effect for that SOC or PT is statistically significant at 5% level. [a] Median time to event based on the Kaplan Meier estimate. NE = Not estimable as median (or 95% CLs) is not reached. [b] Estimated from main effects of unstratified Cox proportional hazard model including trt., subgroup and subgroup-by-trt. interaction. Ties handled using Efron method and 95% CI derived from profile likelihood estimation. NC = Not calculable. HR <1 favours Osimertinib+Chemo. * p<0.05.
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Table 4.3.1.48 FLAURA-2: Summary of subgroup analysis of time to first PT: Thrombozytenzahl vermindert
Safety Analysis Set, DCO 03APR2023

	Osi + Chemo (N=276)			Osi (N=275)					
Subgruppen	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]	Hazard Ratio [b]	[95%-KI] [b]	2-seitiger p-Wert [b]
negativ	41	10 (24,4)	NE [NE; NE]	39	2 (5,1)	NE [NE; NE]	5,30	[1,40; 34,48]	0,0121*
unbekannt	24	2 (8,3)	NE [NE; NE]	32	2 (6,3)	NE [NE; NE]	1,36	[0,16; 11,34]	0,7581
Interaktion p-Wert									0,5257
EGFR-Mutationstyp									
Exon 19 Deletion	172	23 (13,4)	NE [NE; NE]	167	10 (6,0)	NE [NE; NE]	2,39	[1,17; 5,25]	0,0164*
Exon 21 (L858R) Substitutionsmutation	104	28 (26,9)	NE [NE; NE]	106	9 (8,5)	NE [NE; NE]	3,52	[1,73; 7,91]	0,0004*
Interaktion p-Wert									0,4707
Zentral bestätigte EGFR-Mutation im Gewebe									
positiv	248	47 (19,0)	NE [NE; NE]	238	17 (7,1)	NE [NE; NE]	2,89	[1,69; 5,17]	<0,0001*
negativ	3	0	NE [NE; NE]	4	0	NE [NE; NE]	NC	[NC]	NC
unbekannt	25	4 (16,0)	NE [NE; NE]	33	2 (6,1)	NE [NE; NE]	2,79	[0,55; 20,14]	0,2186
Interaktion p-Wert									0,9704
ZNS-Metastasen zur Baseline									
Ja	113	24 (21,2)	NE [NE; NE]	110	11 (10,0)	NE [NE; NE]	2,25	[1,13; 4,78]	0,0207*
Nein	163	27 (16,6)	NE [NE; NE]	165	8 (4,8)	NE [NE; NE]	3,75	[1,79; 8,85]	0,0003*
Interaktion p-Wert									0,3430
Zentrale Bestätigung der EGFR-Mutation									
Zentral bestätigte EGFR-Mutation in Gewebe oder ctDNA	263	48 (18,3)	NE [NE; NE]	266	17 (6,4)	NE [NE; NE]	3,10	[1,82; 5,55]	<0,0001*
Keine zentrale Bestätigung	13	3 (23,1)	NE [NE; NE]	9	2 (22,2)	NE [NE; NE]	1,02	[0,17; 7,74]	0,9837
Interaktion p-Wert									0,2662
Alter bei Screening									

Time to event of AE is defined as the time from first dose of study treatment to first onset of the respective AE or the time to censoring if the AE has not occurred by 28 days following discontinuation of study treatment, before administration of subsequent cancer therapy or death, whichever comes first. All AEs are coded using MedDRA version 25.1. Includes AEs with onset date on or after the date of first dose and up to and including 28 days following discontinuation of study treatment. Analysis done if >=10 patients at each subgroup level and >=10 events in at least one subgroup level combined for both arms. Analysis done for SOC and PT only if main effect for that SOC or PT is statistically significant at 5% level. [a] Median time to event based on the Kaplan Meier estimate. NE = Not estimable as median (or 95% CLs) is not reached. [b] Estimated from main effects of unstratified Cox proportional hazard model including trt., subgroup and subgroup-by-trt. interaction. Ties handled using Efron method and 95% CI derived from profile likelihood estimation. NC = Not calculable. HR <1 favours Osimertinib+Chemo. * p<0.05.
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Table 4.3.1.48 FLAURA-2: Summary of subgroup analysis of time to first PT: Thrombozytenzahl vermindert
Safety Analysis Set, DCO 03APR2023

	Osi + Chemo (N=276)			Osi (N=275)					
Subgruppen	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]	Hazard Ratio [b]	[95%-KI] [b]	2-seitiger p-Wert [b]
<65 Jahre	172	34 (19,8)	NE [NE; NE]	164	12 (7,3)	NE [NE; NE]	2,91	[1,55; 5,85]	0,0007*
>=65 Jahre	104	17 (16,3)	NE [NE; NE]	111	7 (6,3)	NE [NE; NE]	2,84	[1,23; 7,35]	0,0142*
Interaktion p-Wert									0,9669
Region gPAP									
Asien	168	47 (28,0)	NE [NE; NE]	166	16 (9,6)	NE [NE; NE]	3,31	[1,92; 6,03]	<0,0001*
Europa	22	1 (4,5)	NE [NE; NE]	23	1 (4,3)	NE [NE; NE]	1,00	[0,04; 25,38]	0,9974
Nordamerika	20	1 (5,0)	NE [NE; NE]	22	1 (4,5)	NE [NE; NE]	1,16	[0,05; 29,20]	0,9184
Rest der Welt	66	2 (3,0)	NE [NE; NE]	64	1 (1,6)	NE [NE; NE]	1,96	[0,19; 42,22]	0,5706
Interaktion p-Wert									0,7426

Time to event of AE is defined as the time from first dose of study treatment to first onset of the respective AE or the time to censoring if the AE has not occurred by 28 days following discontinuation of study treatment, before administration of subsequent cancer therapy or death, whichever comes first. All AEs are coded using MedDRA version 25.1. Includes AEs with onset date on or after the date of first dose and up to and including 28 days following discontinuation of study treatment. Analysis done if >=10 patients at each subgroup level and >=10 events in at least one subgroup level combined for both arms. Analysis done for SOC and PT only if main effect for that SOC or PT is statistically significant at 5% level. [a] Median time to event based on the Kaplan Meier estimate. NE = Not estimable as median (or 95% CLs) is not reached. [b] Estimated from main effects of unstratified Cox proportional hazard model including trt., subgroup and subgroup-by-trt. interaction. Ties handled using Efron method and 95% CI derived from profile likelihood estimation. NC = Not calculable. HR <1 favours Osimertinib+Chemo. * p<0.05.
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Table 4.3.1.49 FLAURA-2: Summary of subgroup analysis of time to first PT: Transaminasen erhoeht
Safety Analysis Set, DCO 03APR2023

	Osi + Chemo (N=276)			Osi (N=275)					
Subgruppen	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]	Hazard Ratio [b]	[95%-KI] [b]	2-seitiger p-Wert [b]
Abstammung									
Chinesisch/Asiatisch	68	3 (4,4)	NE [NE; NE]	70	1 (1,4)	NE [NE; NE]	NC	[NC]	NC
Nicht-chinesisch/ Asiatisch	107	4 (3,7)	NE [NE; NE]	106	0	NE [NE; NE]	NC	[NC]	NC
Nicht-asiatisch	101	3 (3,0)	NE [NE; NE]	99	1 (1,0)	NE [NE; NE]	NC	[NC]	NC
Interaktion p-Wert									NC
Methode zur Gewebeuntersuchung									
zentral	120	4 (3,3)	NE [NE; NE]	119	2 (1,7)	NE [NE; NE]	NC	[NC]	NC
lokal	156	6 (3,8)	NE [NE; NE]	156	0	NE [NE; NE]	NC	[NC]	NC
Interaktion p-Wert									NC
WHO Performance-Status									
0	100	6 (6,0)	NE [NE; NE]	100	0	NE [NE; NE]	NC	[NC]	NC
1	176	4 (2,3)	NE [NE; NE]	175	2 (1,1)	NE [NE; NE]	NC	[NC]	NC
Interaktion p-Wert									NC
Raucherstatus									
Ja	90	2 (2,2)	NE [NE; NE]	96	2 (2,1)	NE [NE; NE]	NC	[NC]	NC
Nein	186	8 (4,3)	NE [NE; NE]	179	0	NE [NE; NE]	NC	[NC]	NC
Interaktion p-Wert									NC
Geschlecht									
Maennlich	104	2 (1,9)	NE [NE; NE]	107	2 (1,9)	NE [NE; NE]	NC	[NC]	NC
Weiblich	172	8 (4,7)	NE [NE; NE]	168	0	NE [NE; NE]	NC	[NC]	NC
Interaktion p-Wert									NC
Nachweis der EGFR-Mutation durch zentralen ctDNA Cobas Test									
positiv	211	9 (4,3)	NE [NE; NE]	204	1 (0,5)	NE [NE; NE]	8,85	[1,66;163,13]	0,0072*

Time to event of AE is defined as the time from first dose of study treatment to first onset of the respective AE or the time to censoring if the AE has not occurred by 28 days following discontinuation of study treatment, before administration of subsequent cancer therapy or death, whichever comes first. All AEs are coded using MedDRA version 25.1. Includes AEs with onset date on or after the date of first dose and up to and including 28 days following discontinuation of study treatment. Analysis done if >=10 patients at each subgroup level and >=10 events in at least one subgroup level combined for both arms. Analysis done for SOC and PT only if main effect for that SOC or PT is statistically significant at 5% level. [a] Median time to event based on the Kaplan Meier estimate. NE = Not estimable as median (or 95% CLs) is not reached. [b] Estimated from main effects of unstratified Cox proportional hazard model including trt., subgroup and subgroup-by-trt. interaction. Ties handled using Efron method and 95% CI derived from profile likelihood estimation. NC = Not calculable. HR <1 favours Osimertinib+Chemo. * p<0.05.
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Table 4.3.1.49 FLAURA-2: Summary of subgroup analysis of time to first PT: Transaminasen erhoeht
Safety Analysis Set, DCO 03APR2023

	Osi + Chemo (N=276)			Osi (N=275)					
Subgruppen	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]	Hazard Ratio [b]	[95%-KI] [b]	2-seitiger p-Wert [b]
negativ	41	1 (2,4)	NE [NE; NE]	39	0	NE [NE; NE]	NC	[NC]	NC
unbekannt	24	0	NE [NE; NE]	32	1 (3,1)	NE [NE; NE]	NC	[NC]	NC
Interaktion p-Wert									NC
EGFR-Mutationstyp									
Exon 19 Deletion	172	5 (2,9)	NE [NE; NE]	167	1 (0,6)	NE [NE; NE]	NC	[NC]	NC
Exon 21 (L858R) Substitutionsmutation	104	5 (4,8)	NE [NE; NE]	106	1 (0,9)	NE [NE; NE]	NC	[NC]	NC
Interaktion p-Wert									NC
Zentral bestätigte EGFR-Mutation im Gewebe									
positiv	248	9 (3,6)	NE [NE; NE]	238	2 (0,8)	NE [NE; NE]	4,35	[1,12; 28,55]	0,0322*
negativ	3	0	NE [NE; NE]	4	0	NE [NE; NE]	NC	[NC]	NC
unbekannt	25	1 (4,0)	NE [NE; NE]	33	0	NE [NE; NE]	NC	[NC]	NC
Interaktion p-Wert									NC
ZNS-Metastasen zur Baseline									
Ja	113	3 (2,7)	NE [NE; NE]	110	0	NE [NE; NE]	NC	[NC]	NC
Nein	163	7 (4,3)	NE [NE; NE]	165	2 (1,2)	NE [NE; NE]	NC	[NC]	NC
Interaktion p-Wert									NC
Zentrale Bestätigung der EGFR-Mutation									
Zentral bestätigte EGFR-Mutation in Gewebe oder ctDNA	263	10 (3,8)	NE [NE; NE]	266	2 (0,8)	NE [NE; NE]	5,11	[1,35; 33,24]	0,0143*
Keine zentrale Bestätigung	13	0	NE [NE; NE]	9	0	NE [NE; NE]	NC	[NC]	NC
Interaktion p-Wert									NC
Alter bei Screening									

Time to event of AE is defined as the time from first dose of study treatment to first onset of the respective AE or the time to censoring if the AE has not occurred by 28 days following discontinuation of study treatment, before administration of subsequent cancer therapy or death, whichever comes first. All AEs are coded using MedDRA version 25.1. Includes AEs with onset date on or after the date of first dose and up to and including 28 days following discontinuation of study treatment. Analysis done if >=10 patients at each subgroup level and >=10 events in at least one subgroup level combined for both arms. Analysis done for SOC and PT only if main effect for that SOC or PT is statistically significant at 5% level. [a] Median time to event based on the Kaplan Meier estimate. NE = Not estimable as median (or 95% CLs) is not reached. [b] Estimated from main effects of unstratified Cox proportional hazard model including trt., subgroup and subgroup-by-trt. interaction. Ties handled using Efron method and 95% CI derived from profile likelihood estimation. NC = Not calculable. HR <1 favours Osimertinib+Chemo. * p<0.05.
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Table 4.3.1.49 FLAURA-2: Summary of subgroup analysis of time to first PT: Transaminasen erhoeht
Safety Analysis Set, DCO 03APR2023

	Osi + Chemo (N=276)			Osi (N=275)					
Subgruppen	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]	Hazard Ratio [b]	[95%-KI] [b]	2-seitiger p-Wert [b]
<65 Jahre	172	6 (3,5)	NE [NE; NE]	164	2 (1,2)	NE [NE; NE]	NC	[NC]	NC
>=65 Jahre	104	4 (3,8)	NE [NE; NE]	111	0	NE [NE; NE]	NC	[NC]	NC
Interaktion p-Wert									NC
Region gPAP									
Asien	168	7 (4,2)	NE [NE; NE]	166	1 (0,6)	NE [NE; NE]	NC	[NC]	NC
Europa	22	0	NE [NE; NE]	23	0	NE [NE; NE]	NC	[NC]	NC
Nordamerika	20	0	NE [NE; NE]	22	0	NE [NE; NE]	NC	[NC]	NC
Rest der Welt	66	3 (4,5)	NE [NE; NE]	64	1 (1,6)	NE [NE; NE]	NC	[NC]	NC
Interaktion p-Wert									NC

Time to event of AE is defined as the time from first dose of study treatment to first onset of the respective AE or the time to censoring if the AE has not occurred by 28 days following discontinuation of study treatment, before administration of subsequent cancer therapy or death, whichever comes first. All AEs are coded using MedDRA version 25.1. Includes AEs with onset date on or after the date of first dose and up to and including 28 days following discontinuation of study treatment. Analysis done if >=10 patients at each subgroup level and >=10 events in at least one subgroup level combined for both arms. Analysis done for SOC and PT only if main effect for that SOC or PT is statistically significant at 5% level. [a] Median time to event based on the Kaplan Meier estimate. NE = Not estimable as median (or 95% CLs) is not reached. [b] Estimated from main effects of unstratified Cox proportional hazard model including trt., subgroup and subgroup-by-trt. interaction. Ties handled using Efron method and 95% CI derived from profile likelihood estimation. NC = Not calculable. HR <1 favours Osimertinib+Chemo. * p<0.05.
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Table 4.3.1.50 FLAURA-2: Summary of subgroup analysis of time to first SOC: Verletzung, Vergiftung und durch Eingriffe bedingte Komplikationen
Safety Analysis Set, DCO 03APR2023

	Osi + Chemo (N=276)			Osi (N=275)					
Subgruppen	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]	Hazard Ratio [b]	[95%-KI] [b]	2-seitiger p-Wert [b]
Abstammung									
Chinesisch/Asiatisch	68	7 (10,3)	NE [NE; NE]	70	4 (5,7)	NE [NE; NE]	1,65	[0,50; 6,29]	0,4174
Nicht-chinesisch/ Asiatisch	107	19 (17,8)	NE [NE; NE]	106	8 (7,5)	NE [NE; NE]	2,57	[1,16; 6,22]	0,0189*
Nicht-asiatisch	101	15 (14,9)	NE [NE; NE]	99	13 (13,1)	NE [NE; NE]	1,11	[0,53; 2,37]	0,7834
Interaktion p-Wert									0,3269
Methode zur Gewebeuntersuchung									
zentral	120	11 (9,2)	NE [NE; NE]	119	5 (4,2)	NE [NE; NE]	2,18	[0,79; 6,92]	0,1335
lokal	156	30 (19,2)	NE [NE; NE]	156	20 (12,8)	NE [NE; NE]	1,51	[0,87; 2,71]	0,1465
Interaktion p-Wert									0,5467
WHO Performance-Status									
0	100	17 (17,0)	NE [NE; NE]	100	7 (7,0)	NE [NE; NE]	2,61	[1,13; 6,75]	0,0247*
1	176	24 (13,6)	NE [NE; NE]	175	18 (10,3)	NE [NE; NE]	1,28	[0,70; 2,39]	0,4272
Interaktion p-Wert									0,1855
Raucherstatus									
Ja	90	18 (20,0)	NE [NE; NE]	96	11 (11,5)	NE [NE; NE]	1,77	[0,85; 3,87]	0,1290
Nein	186	23 (12,4)	NE [NE; NE]	179	14 (7,8)	NE [NE; NE]	1,59	[0,83; 3,16]	0,1669
Interaktion p-Wert									0,8297
Geschlecht									
Maennlich	104	11 (10,6)	NE [NE; NE]	107	7 (6,5)	NE [NE; NE]	1,51	[0,59; 4,11]	0,3883
Weiblich	172	30 (17,4)	NE [NE; NE]	168	18 (10,7)	NE [NE; NE]	1,71	[0,97; 3,13]	0,0661
Interaktion p-Wert									0,8236
Nachweis der EGFR-Mutation durch zentralen ctDNA Cobas Test									

Time to event of AE is defined as the time from first dose of study treatment to first onset of the respective AE or the time to censoring if the AE has not occurred by 28 days following discontinuation of study treatment, before administration of subsequent cancer therapy or death, whichever comes first. All AEs are coded using MedDRA version 25.1. Includes AEs with onset date on or after the date of first dose and up to and including 28 days following discontinuation of study treatment. Analysis done if >=10 patients at each subgroup level and >=10 events in at least one subgroup level combined for both arms. Analysis done for SOC and PT only if main effect for that SOC or PT is statistically significant at 5% level. [a] Median time to event based on the Kaplan Meier estimate. NE = Not estimable as median (or 95% CLs) is not reached. [b] Estimated from main effects of unstratified Cox proportional hazard model including trt., subgroup and subgroup-by-trt. interaction. Ties handled using Efron method and 95% CI derived from profile likelihood estimation. NC = Not calculable. HR <1 favours Osimertinib+Chemo. * p<0.05.
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Table 4.3.1.50 FLAURA-2: Summary of subgroup analysis of time to first SOC: Verletzung, Vergiftung und durch Eingriffe bedingte Komplikationen
Safety Analysis Set, DCO 03APR2023

	Osi + Chemo (N=276)			Osi (N=275)					
Subgruppen	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]	Hazard Ratio [b]	[95%-KI] [b]	2-seitiger p-Wert [b]
positiv	211	25 (11,8)	NE [NE; NE]	204	19 (9,3)	NE [NE; NE]	1,27	[0,70; 2,33]	0,4319
negativ	41	11 (26,8)	NE [NE; NE]	39	2 (5,1)	NE [NE; NE]	5,76	[1,55; 37,20]	0,0070*
unbekannt	24	5 (20,8)	NE [NE; NE]	32	4 (12,5)	NE [NE; NE]	1,59	[0,42; 6,44]	0,4871
Interaktion p-Wert									0,1249
EGFR-Mutationstyp									
Exon 19 Deletion	172	21 (12,2)	NE [NE; NE]	167	13 (7,8)	NE [NE; NE]	1,62	[0,82; 3,32]	0,1653
Exon 21 (L858R) Substitutionsmutation	104	20 (19,2)	NE [NE; NE]	106	12 (11,3)	NE [NE; NE]	1,64	[0,81; 3,45]	0,1696
Interaktion p-Wert									0,9830
Zentral bestätigte EGFR-Mutation im Gewebe									
positiv	248	38 (15,3)	NE [NE; NE]	238	21 (8,8)	NE [NE; NE]	1,74	[1,03; 3,02]	0,0378*
negativ	3	2 (66,7)	9,8 [3,9; NE]	4	0	NE [NE; NE]	NC	[NC]	NC
unbekannt	25	1 (4,0)	NE [NE; NE]	33	4 (12,1)	NE [NE; NE]	0,35	[0,02; 2,33]	0,2958
Interaktion p-Wert									0,1155
ZNS-Metastasen zur Baseline									
Ja	113	14 (12,4)	NE [NE; NE]	110	11 (10,0)	NE [NE; NE]	1,13	[0,51; 2,55]	0,7636
Nein	163	27 (16,6)	NE [NE; NE]	165	14 (8,5)	NE [NE; NE]	2,09	[1,11; 4,10]	0,0212*
Interaktion p-Wert									0,2373
Zentrale Bestätigung der EGFR-Mutation									
Zentral bestätigte EGFR-Mutation in Gewebe oder ctDNA	263	38 (14,4)	NE [NE; NE]	266	24 (9,0)	NE [NE; NE]	1,60	[0,97; 2,71]	0,0668
Keine zentrale Bestätigung	13	3 (23,1)	NE [NE; NE]	9	1 (11,1)	NE [NE; NE]	2,29	[0,29; 46,24]	0,4476
Interaktion p-Wert									0,7583

Time to event of AE is defined as the time from first dose of study treatment to first onset of the respective AE or the time to censoring if the AE has not occurred by 28 days following discontinuation of study treatment, before administration of subsequent cancer therapy or death, whichever comes first. All AEs are coded using MedDRA version 25.1. Includes AEs with onset date on or after the date of first dose and up to and including 28 days following discontinuation of study treatment. Analysis done if >=10 patients at each subgroup level and >=10 events in at least one subgroup level combined for both arms. Analysis done for SOC and PT only if main effect for that SOC or PT is statistically significant at 5% level. [a] Median time to event based on the Kaplan Meier estimate. NE = Not estimable as median (or 95% CLs) is not reached. [b] Estimated from main effects of unstratified Cox proportional hazard model including trt., subgroup and subgroup-by-trt. interaction. Ties handled using Efron method and 95% CI derived from profile likelihood estimation. NC = Not calculable. HR <1 favours Osimertinib+Chemo. * p<0.05.
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Table 4.3.1.50 FLAURA-2: Summary of subgroup analysis of time to first SOC: Verletzung, Vergiftung und durch Eingriffe bedingte Komplikationen
Safety Analysis Set, DCO 03APR2023

	Osi + Chemo (N=276)			Osi (N=275)					
Subgruppen	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]	Hazard Ratio [b]	[95%-KI] [b]	2-seitiger p-Wert [b]
Alter bei Screening									
<65 Jahre	172	22 (12,8)	NE [NE; NE]	164	12 (7,3)	NE [NE; NE]	1,67	[0,84; 3,48]	0,1464
>=65 Jahre	104	19 (18,3)	NE [NE; NE]	111	13 (11,7)	NE [NE; NE]	1,75	[0,87; 3,62]	0,1171
Interaktion p-Wert									0,9269
Region gPAP									
Asien	168	25 (14,9)	NE [NE; NE]	166	12 (7,2)	NE [NE; NE]	2,07	[1,06; 4,28]	0,0319*
Europa	22	3 (13,6)	NE [NE; NE]	23	3 (13,0)	NE [NE; NE]	0,95	[0,18; 5,14]	0,9509
Nordamerika	20	4 (20,0)	NE [NE; NE]	22	5 (22,7)	NE [NE; NE]	1,04	[0,26; 3,92]	0,9560
Rest der Welt	66	9 (13,6)	NE [NE; NE]	64	5 (7,8)	NE [NE; NE]	1,73	[0,60; 5,64]	0,3149
Interaktion p-Wert									0,7128

Time to event of AE is defined as the time from first dose of study treatment to first onset of the respective AE or the time to censoring if the AE has not occurred by 28 days following discontinuation of study treatment, before administration of subsequent cancer therapy or death, whichever comes first. All AEs are coded using MedDRA version 25.1. Includes AEs with onset date on or after the date of first dose and up to and including 28 days following discontinuation of study treatment. Analysis done if >=10 patients at each subgroup level and >=10 events in at least one subgroup level combined for both arms. Analysis done for SOC and PT only if main effect for that SOC or PT is statistically significant at 5% level. [a] Median time to event based on the Kaplan Meier estimate. NE = Not estimable as median (or 95% CLs) is not reached. [b] Estimated from main effects of unstratified Cox proportional hazard model including trt., subgroup and subgroup-by-trt. interaction. Ties handled using Efron method and 95% CI derived from profile likelihood estimation. NC = Not calculable. HR <1 favours Osimertinib+Chemo. * p<0.05.
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Table 4.3.2.1 FLAURA-2: Summary of subgroup analysis of time to first SUE
Safety Analysis Set, DCO 03APR2023

	Osi + Chemo (N=276)			Osi (N=275)					
Subgruppen	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]	Hazard Ratio [b]	[95%-KI] [b]	2-seitiger p-Wert [b]
Abstammung									
Chinesisch/Asiatisch	68	21 (30,9)	NE [NE; NE]	70	11 (15,7)	NE [NE; NE]	2,02	[0,995; 4,36]	0,0516
Nicht-chinesisch/ Asiatisch	107	52 (48,6)	23,6 [11,1; NE]	106	18 (17,0)	NE [NE; NE]	3,62	[2,16; 6,36]	<0,0001*
Nicht-asiatisch	101	31 (30,7)	NE [NE; NE]	99	24 (24,2)	NE [NE; NE]	1,25	[0,74; 2,16]	0,4026
Interaktion p-Wert									0,0208*
Methode zur Gewebeuntersuchung									
zentral	120	50 (41,7)	27,9 [18,3; NE]	119	16 (13,4)	NE [NE; NE]	3,68	[2,14; 6,67]	<0,0001*
lokal	156	54 (34,6)	NE [NE; NE]	156	37 (23,7)	NE [NE; NE]	1,51	[0,999; 2,32]	0,0503
Interaktion p-Wert									0,0112*
WHO Performance-Status									
0	100	32 (32,0)	31,9 [27,9; NE]	100	11 (11,0)	NE [NE; NE]	3,29	[1,71; 6,84]	0,0002*
1	176	72 (40,9)	NE [NE; NE]	175	42 (24,0)	NE [NE; NE]	1,84	[1,26; 2,71]	0,0014*
Interaktion p-Wert									0,1360
Raucherstatus									
Ja	90	35 (38,9)	NE [NE; NE]	96	23 (24,0)	NE [NE; NE]	1,76	[1,05; 3,03]	0,0322*
Nein	186	69 (37,1)	31,9 [27,9; NE]	179	30 (16,8)	NE [NE; NE]	2,45	[1,61; 3,81]	<0,0001*
Interaktion p-Wert									0,3454
Geschlecht									
Maennlich	104	41 (39,4)	NE [NE; NE]	107	21 (19,6)	NE [NE; NE]	2,11	[1,26; 3,63]	0,0042*
Weiblich	172	63 (36,6)	31,9 [27,9; NE]	168	32 (19,0)	NE [NE; NE]	2,17	[1,43; 3,36]	0,0002*
Interaktion p-Wert									0,9333
Nachweis der EGFR-Mutation durch zentralen ctDNA Cobas Test									
positiv	211	77 (36,5)	NE [NE; NE]	204	42 (20,6)	NE [NE; NE]	1,95	[1,34; 2,86]	0,0004*

Time to event of AE is defined as the time from first dose of study treatment to first onset of the respective AE or the time to censoring if the AE has not occurred by 28 days following discontinuation of study treatment, before administration of subsequent cancer therapy or death, whichever comes first. All AEs are coded using MedDRA version 25.1. Includes AEs with onset date on or after the date of first dose and up to and including 28 days following discontinuation of study treatment. Analysis done if >=10 patients at each subgroup level and >=10 events in at least one subgroup level combined for both arms. Analysis done for SOC and PT only if main effect for that SOC or PT is statistically significant at 5% level. [a] Median time to event based on the Kaplan Meier estimate. NE = Not estimable as median (or 95% CLs) is not reached. [b] Estimated from main effects of unstratified Cox proportional hazard model including trt., subgroup and subgroup-by-trt. interaction. Ties handled using Efron method and 95% CI derived from profile likelihood estimation. NC = Not calculable. HR <1 favours Osimertinib+Chemo. * p<0.05.
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Table 4.3.2.1 FLAURA-2: Summary of subgroup analysis of time to first SUE
Safety Analysis Set, DCO 03APR2023

	Osi + Chemo (N=276)			Osi (N=275)					
Subgruppen	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]	Hazard Ratio [b]	[95%-KI] [b]	2-seitiger p-Wert [b]
negativ	41	21 (51,2)	27,9 [6,4; NE]	39	3 (7,7)	NE [NE; NE]	8,48	[2,92; 35,93]	<0,0001*
unbekannt	24	6 (25,0)	NE [NE; NE]	32	8 (25,0)	NE [NE; NE]	0,88	[0,29; 2,53]	0,8122
Interaktion p-Wert									0,0073*
EGFR-Mutationstyp									
Exon 19 Deletion	172	61 (35,5)	NE [NE; NE]	167	28 (16,8)	NE [NE; NE]	2,42	[1,56; 3,84]	<0,0001*
Exon 21 (L858R) Substitutionsmutation	104	43 (41,3)	31,9 [23,1; NE]	106	25 (23,6)	NE [NE; NE]	1,80	[1,11; 2,99]	0,0173*
Interaktion p-Wert									0,3838
Zentral bestätigte EGFR-Mutation im Gewebe									
positiv	248	94 (37,9)	NE [NE; NE]	238	40 (16,8)	NE [NE; NE]	2,51	[1,75; 3,68]	<0,0001*
negativ	3	1 (33,3)	NE [NE; NE]	4	1 (25,0)	NE [NE; NE]	NC	[NC]	NC
unbekannt	25	9 (36,0)	NE [NE; NE]	33	12 (36,4)	NE [NE; NE]	1,00	[0,41; 2,37]	0,9983
Interaktion p-Wert									0,0536
ZNS-Metastasen zur Baseline									
Ja	113	40 (35,4)	NE [NE; NE]	110	20 (18,2)	NE [NE; NE]	1,99	[1,18; 3,48]	0,0095*
Nein	163	64 (39,3)	31,9 [23,6; NE]	165	33 (20,0)	NE [NE; NE]	2,26	[1,49; 3,48]	<0,0001*
Interaktion p-Wert									0,7212
Zentrale Bestätigung der EGFR-Mutation									
Zentral bestätigte EGFR-Mutation in Gewebe oder ctDNA	263	98 (37,3)	NE [NE; NE]	266	50 (18,8)	NE [NE; NE]	2,19	[1,57; 3,10]	<0,0001*
Keine zentrale Bestätigung	13	6 (46,2)	NE [NE; NE]	9	3 (33,3)	NE [NE; NE]	1,31	[0,35; 6,21]	0,6981
Interaktion p-Wert									0,4940
Alter bei Screening									

Time to event of AE is defined as the time from first dose of study treatment to first onset of the respective AE or the time to censoring if the AE has not occurred by 28 days following discontinuation of study treatment, before administration of subsequent cancer therapy or death, whichever comes first. All AEs are coded using MedDRA version 25.1. Includes AEs with onset date on or after the date of first dose and up to and including 28 days following discontinuation of study treatment. Analysis done if >=10 patients at each subgroup level and >=10 events in at least one subgroup level combined for both arms. Analysis done for SOC and PT only if main effect for that SOC or PT is statistically significant at 5% level. [a] Median time to event based on the Kaplan Meier estimate. NE = Not estimable as median (or 95% CLs) is not reached. [b] Estimated from main effects of unstratified Cox proportional hazard model including trt., subgroup and subgroup-by-trt. interaction. Ties handled using Efron method and 95% CI derived from profile likelihood estimation. NC = Not calculable. HR <1 favours Osimertinib+Chemo. * p<0.05.
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Table 4.3.2.1 FLAURA-2: Summary of subgroup analysis of time to first SUE
Safety Analysis Set, DCO 03APR2023

	Osi + Chemo (N=276)			Osi (N=275)					
Subgruppen	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]	Hazard Ratio [b]	[95%-KI] [b]	2-seitiger p-Wert [b]
<65 Jahre	172	64 (37,2)	NE [NE; NE]	164	23 (14,0)	NE [NE; NE]	2,87	[1,81; 4,72]	<0,0001*
>=65 Jahre	104	40 (38,5)	NE [NE; NE]	111	30 (27,0)	NE [NE; NE]	1,61	[1,01; 2,61]	0,0463*
Interaktion p-Wert									0,0907
Region gPAP									
Asien	168	72 (42,9)	31,9 [23,6; NE]	166	29 (17,5)	NE [NE; NE]	2,83	[1,86; 4,43]	<0,0001*
Europa	22	5 (22,7)	NE [NE; NE]	23	9 (39,1)	21,7 [14,8; NE]	0,51	[0,16; 1,48]	0,2174
Nordamerika	20	5 (25,0)	NE [NE; NE]	22	5 (22,7)	NE [NE; NE]	1,27	[0,35; 4,56]	0,7069
Rest der Welt	66	22 (33,3)	NE [NE; NE]	64	10 (15,6)	NE [NE; NE]	2,19	[1,06; 4,83]	0,0329*
Interaktion p-Wert									0,0251*

Time to event of AE is defined as the time from first dose of study treatment to first onset of the respective AE or the time to censoring if the AE has not occurred by 28 days following discontinuation of study treatment, before administration of subsequent cancer therapy or death, whichever comes first. All AEs are coded using MedDRA version 25.1. Includes AEs with onset date on or after the date of first dose and up to and including 28 days following discontinuation of study treatment. Analysis done if >=10 patients at each subgroup level and >=10 events in at least one subgroup level combined for both arms. Analysis done for SOC and PT only if main effect for that SOC or PT is statistically significant at 5% level. [a] Median time to event based on the Kaplan Meier estimate. NE = Not estimable as median (or 95% CLs) is not reached. [b] Estimated from main effects of unstratified Cox proportional hazard model including trt., subgroup and subgroup-by-trt. interaction. Ties handled using Efron method and 95% CI derived from profile likelihood estimation. NC = Not calculable. HR <1 favours Osimertinib+Chemo. * p<0.05.
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Table 4.3.2.2 FLAURA-2: Summary of subgroup analysis of time to first SUE SOC: Erkrankungen des Blutes und des Lymphsystems
Safety Analysis Set, DCO 03APR2023

	Osi + Chemo (N=276)			Osi (N=275)					
Subgruppen	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]	Hazard Ratio [b]	[95%-KI] [b]	2-seitiger p-Wert [b]
Abstammung									
Chinesisch/Asiatisch	68	4 (5,9)	NE [NE; NE]	70	0	NE [NE; NE]	NC	[NC]	NC
Nicht-chinesisch/ Asiatisch	107	11 (10,3)	NE [NE; NE]	106	0	NE [NE; NE]	NC	[NC]	NC
Nicht-asiatisch	101	3 (3,0)	NE [NE; NE]	99	0	NE [NE; NE]	NC	[NC]	NC
Interaktion p-Wert									NC
Methode zur Gewebeuntersuchung									
zentral	120	11 (9,2)	NE [NE; NE]	119	0	NE [NE; NE]	NC	[NC]	NC
lokal	156	7 (4,5)	NE [NE; NE]	156	0	NE [NE; NE]	NC	[NC]	NC
Interaktion p-Wert									NC
WHO Performance-Status									
0	100	2 (2,0)	NE [NE; NE]	100	0	NE [NE; NE]	NC	[NC]	NC
1	176	16 (9,1)	NE [NE; NE]	175	0	NE [NE; NE]	NC	[NC]	NC
Interaktion p-Wert									NC
Raucherstatus									
Ja	90	5 (5,6)	NE [NE; NE]	96	0	NE [NE; NE]	NC	[NC]	NC
Nein	186	13 (7,0)	NE [NE; NE]	179	0	NE [NE; NE]	NC	[NC]	NC
Interaktion p-Wert									NC
Geschlecht									
Maennlich	104	9 (8,7)	NE [NE; NE]	107	0	NE [NE; NE]	NC	[NC]	NC
Weiblich	172	9 (5,2)	NE [NE; NE]	168	0	NE [NE; NE]	NC	[NC]	NC
Interaktion p-Wert									NC
Nachweis der EGFR-Mutation durch zentralen ctDNA Cobas Test									
positiv	211	15 (7,1)	NE [NE; NE]	204	0	NE [NE; NE]	NC	[NC]	NC

Time to event of AE is defined as the time from first dose of study treatment to first onset of the respective AE or the time to censoring if the AE has not occurred by 28 days following discontinuation of study treatment, before administration of subsequent cancer therapy or death, whichever comes first. All AEs are coded using MedDRA version 25.1. Includes AEs with onset date on or after the date of first dose and up to and including 28 days following discontinuation of study treatment. Analysis done if >=10 patients at each subgroup level and >=10 events in at least one subgroup level combined for both arms. Analysis done for SOC and PT only if main effect for that SOC or PT is statistically significant at 5% level. [a] Median time to event based on the Kaplan Meier estimate. NE = Not estimable as median (or 95% CLs) is not reached. [b] Estimated from main effects of unstratified Cox proportional hazard model including trt., subgroup and subgroup-by-trt. interaction. Ties handled using Efron method and 95% CI derived from profile likelihood estimation. NC = Not calculable. HR <1 favours Osimertinib+Chemo. * p<0.05.
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Table 4.3.2.2 FLAURA-2: Summary of subgroup analysis of time to first SUE SOC: Erkrankungen des Blutes und des Lymphsystems
Safety Analysis Set, DCO 03APR2023

	Osi + Chemo (N=276)			Osi (N=275)					
Subgruppen	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]	Hazard Ratio [b]	[95%-KI] [b]	2-seitiger p-Wert [b]
negativ	41	2 (4,9)	NE [NE; NE]	39	0	NE [NE; NE]	NC	[NC]	NC
unbekannt	24	1 (4,2)	NE [NE; NE]	32	0	NE [NE; NE]	NC	[NC]	NC
Interaktion p-Wert									NC
EGFR-Mutationstyp									
Exon 19 Deletion	172	14 (8,1)	NE [NE; NE]	167	0	NE [NE; NE]	NC	[NC]	NC
Exon 21 (L858R) Substitutionsmutation	104	4 (3,8)	NE [NE; NE]	106	0	NE [NE; NE]	NC	[NC]	NC
Interaktion p-Wert									NC
Zentral bestätigte EGFR-Mutation im Gewebe									
positiv	248	17 (6,9)	NE [NE; NE]	238	0	NE [NE; NE]	NC	[NC]	NC
negativ	3	0	NE [NE; NE]	4	0	NE [NE; NE]	NC	[NC]	NC
unbekannt	25	1 (4,0)	NE [NE; NE]	33	0	NE [NE; NE]	NC	[NC]	NC
Interaktion p-Wert									NC
ZNS-Metastasen zur Baseline									
Ja	113	6 (5,3)	NE [NE; NE]	110	0	NE [NE; NE]	NC	[NC]	NC
Nein	163	12 (7,4)	NE [NE; NE]	165	0	NE [NE; NE]	NC	[NC]	NC
Interaktion p-Wert									NC
Zentrale Bestätigung der EGFR-Mutation									
Zentral bestätigte EGFR-Mutation in Gewebe oder ctDNA	263	18 (6,8)	NE [NE; NE]	266	0	NE [NE; NE]	NC	[NC]	NC
Keine zentrale Bestätigung	13	0	NE [NE; NE]	9	0	NE [NE; NE]	NC	[NC]	NC
Interaktion p-Wert									NC
Alter bei Screening									

Time to event of AE is defined as the time from first dose of study treatment to first onset of the respective AE or the time to censoring if the AE has not occurred by 28 days following discontinuation of study treatment, before administration of subsequent cancer therapy or death, whichever comes first. All AEs are coded using MedDRA version 25.1. Includes AEs with onset date on or after the date of first dose and up to and including 28 days following discontinuation of study treatment. Analysis done if >=10 patients at each subgroup level and >=10 events in at least one subgroup level combined for both arms. Analysis done for SOC and PT only if main effect for that SOC or PT is statistically significant at 5% level. [a] Median time to event based on the Kaplan Meier estimate. NE = Not estimable as median (or 95% CLs) is not reached. [b] Estimated from main effects of unstratified Cox proportional hazard model including trt., subgroup and subgroup-by-trt. interaction. Ties handled using Efron method and 95% CI derived from profile likelihood estimation. NC = Not calculable. HR <1 favours Osimertinib+Chemo. * p<0.05.
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Table 4.3.2.2 FLAURA-2: Summary of subgroup analysis of time to first SUE SOC: Erkrankungen des Blutes und des Lymphsystems
Safety Analysis Set, DCO 03APR2023

	Osi + Chemo (N=276)			Osi (N=275)					
Subgruppen	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]	Hazard Ratio [b]	[95%-KI] [b]	2-seitiger p-Wert [b]
<65 Jahre	172	15 (8,7)	NE [NE; NE]	164	0	NE [NE; NE]	NC	[NC]	NC
>=65 Jahre	104	3 (2,9)	NE [NE; NE]	111	0	NE [NE; NE]	NC	[NC]	NC
Interaktion p-Wert									NC
Region gPAP									
Asien	168	16 (9,5)	NE [NE; NE]	166	0	NE [NE; NE]	NC	[NC]	NC
Europa	22	1 (4,5)	NE [NE; NE]	23	0	NE [NE; NE]	NC	[NC]	NC
Nordamerika	20	0	NE [NE; NE]	22	0	NE [NE; NE]	NC	[NC]	NC
Rest der Welt	66	1 (1,5)	NE [NE; NE]	64	0	NE [NE; NE]	NC	[NC]	NC
Interaktion p-Wert									NC

Time to event of AE is defined as the time from first dose of study treatment to first onset of the respective AE or the time to censoring if the AE has not occurred by 28 days following discontinuation of study treatment, before administration of subsequent cancer therapy or death, whichever comes first. All AEs are coded using MedDRA version 25.1. Includes AEs with onset date on or after the date of first dose and up to and including 28 days following discontinuation of study treatment. Analysis done if >=10 patients at each subgroup level and >=10 events in at least one subgroup level combined for both arms. Analysis done for SOC and PT only if main effect for that SOC or PT is statistically significant at 5% level. [a] Median time to event based on the Kaplan Meier estimate. NE = Not estimable as median (or 95% CLs) is not reached. [b] Estimated from main effects of unstratified Cox proportional hazard model including trt., subgroup and subgroup-by-trt. interaction. Ties handled using Efron method and 95% CI derived from profile likelihood estimation. NC = Not calculable. HR <1 favours Osimertinib+Chemo. * p<0.05.
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Table 4.3.2.3 FLAURA-2: Summary of subgroup analysis of time to first SUE SOC: Erkrankungen des Gastrointestinaltrakts
Safety Analysis Set, DCO 03APR2023

	Osi + Chemo (N=276)			Osi (N=275)					
Subgruppen	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]	Hazard Ratio [b]	[95%-KI] [b]	2-seitiger p-Wert [b]
Abstammung									
Chinesisch/Asiatisch	68	0	NE [NE; NE]	70	0	NE [NE; NE]	NC	[NC]	NC
Nicht-chinesisch/ Asiatisch	107	9 (8,4)	NE [NE; NE]	106	3 (2,8)	NE [NE; NE]	3,15	[0,94; 14,18]	0,0640
Nicht-asiatisch	101	4 (4,0)	NE [NE; NE]	99	1 (1,0)	NE [NE; NE]	3,91	[0,58; 76,52]	0,1723
Interaktion p-Wert									0,8654
Methode zur Gewebeuntersuchung									
zentral	120	5 (4,2)	NE [NE; NE]	119	1 (0,8)	NE [NE; NE]	4,97	[0,80; 95,20]	0,0893
lokal	156	8 (5,1)	NE [NE; NE]	156	3 (1,9)	NE [NE; NE]	2,70	[0,78; 12,34]	0,1192
Interaktion p-Wert									0,6267
WHO Performance-Status									
0	100	6 (6,0)	NE [NE; NE]	100	2 (2,0)	NE [NE; NE]	NC	[NC]	NC
1	176	7 (4,0)	NE [NE; NE]	175	2 (1,1)	NE [NE; NE]	NC	[NC]	NC
Interaktion p-Wert									NC
Raucherstatus									
Ja	90	7 (7,8)	NE [NE; NE]	96	2 (2,1)	NE [NE; NE]	NC	[NC]	NC
Nein	186	6 (3,2)	NE [NE; NE]	179	2 (1,1)	NE [NE; NE]	NC	[NC]	NC
Interaktion p-Wert									NC
Geschlecht									
Maennlich	104	4 (3,8)	NE [NE; NE]	107	3 (2,8)	NE [NE; NE]	1,33	[0,29; 6,74]	0,7100
Weiblich	172	9 (5,2)	NE [NE; NE]	168	1 (0,6)	NE [NE; NE]	9,10	[1,71;167,81]	0,0063*
Interaktion p-Wert									0,1116
Nachweis der EGFR-Mutation durch zentralen ctDNA Cobas Test									

Time to event of AE is defined as the time from first dose of study treatment to first onset of the respective AE or the time to censoring if the AE has not occurred by 28 days following discontinuation of study treatment, before administration of subsequent cancer therapy or death, whichever comes first. All AEs are coded using MedDRA version 25.1. Includes AEs with onset date on or after the date of first dose and up to and including 28 days following discontinuation of study treatment. Analysis done if >=10 patients at each subgroup level and >=10 events in at least one subgroup level combined for both arms. Analysis done for SOC and PT only if main effect for that SOC or PT is statistically significant at 5% level. [a] Median time to event based on the Kaplan Meier estimate. NE = Not estimable as median (or 95% CLs) is not reached. [b] Estimated from main effects of unstratified Cox proportional hazard model including trt., subgroup and subgroup-by-trt. interaction. Ties handled using Efron method and 95% CI derived from profile likelihood estimation. NC = Not calculable. HR <1 favours Osimertinib+Chemo. * p<0.05.
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Table 4.3.2.3 FLAURA-2: Summary of subgroup analysis of time to first SUE SOC: Erkrankungen des Gastrointestinaltrakts
Safety Analysis Set, DCO 03APR2023

	Osi + Chemo (N=276)			Osi (N=275)					
Subgruppen	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]	Hazard Ratio [b]	[95%-KI] [b]	2-seitiger p-Wert [b]
positiv	211	10 (4,7)	NE [NE; NE]	204	3 (1,5)	NE [NE; NE]	3,27	[1,001; 14,60]	0,0497*
negativ	41	1 (2,4)	NE [NE; NE]	39	0	NE [NE; NE]	NC	[NC]	NC
unbekannt	24	2 (8,3)	NE [NE; NE]	32	1 (3,1)	NE [NE; NE]	2,51	[0,24; 54,01]	0,4362
Interaktion p-Wert									0,8500
EGFR-Mutationstyp									
Exon 19 Deletion	172	9 (5,2)	NE [NE; NE]	167	1 (0,6)	NE [NE; NE]	8,96	[1,68;165,25]	0,0068*
Exon 21 (L858R) Substitutionsmutation	104	4 (3,8)	NE [NE; NE]	106	3 (2,8)	NE [NE; NE]	1,34	[0,29; 6,79]	0,7022
Interaktion p-Wert									0,1161
Zentral bestätigte EGFR-Mutation im Gewebe									
positiv	248	13 (5,2)	NE [NE; NE]	238	2 (0,8)	NE [NE; NE]	6,31	[1,74; 40,35]	0,0032*
negativ	3	0	NE [NE; NE]	4	0	NE [NE; NE]	NC	[NC]	NC
unbekannt	25	0	NE [NE; NE]	33	2 (6,1)	NE [NE; NE]	NC	[NC]	NC
Interaktion p-Wert									NC
ZNS-Metastasen zur Baseline									
Ja	113	4 (3,5)	NE [NE; NE]	110	2 (1,8)	NE [NE; NE]	1,88	[0,37; 13,55]	0,4545
Nein	163	9 (5,5)	NE [NE; NE]	165	2 (1,2)	NE [NE; NE]	4,73	[1,22; 31,05]	0,0229*
Interaktion p-Wert									0,4299
Zentrale Bestätigung der EGFR-Mutation									
Zentral bestätigte EGFR-Mutation in Gewebe oder ctDNA	263	13 (4,9)	NE [NE; NE]	266	4 (1,5)	NE [NE; NE]	3,33	[1,18; 11,82]	0,0222*
Keine zentrale Bestätigung	13	0	NE [NE; NE]	9	0	NE [NE; NE]	NC	[NC]	NC
Interaktion p-Wert									NC

Time to event of AE is defined as the time from first dose of study treatment to first onset of the respective AE or the time to censoring if the AE has not occurred by 28 days following discontinuation of study treatment, before administration of subsequent cancer therapy or death, whichever comes first. All AEs are coded using MedDRA version 25.1. Includes AEs with onset date on or after the date of first dose and up to and including 28 days following discontinuation of study treatment. Analysis done if >=10 patients at each subgroup level and >=10 events in at least one subgroup level combined for both arms. Analysis done for SOC and PT only if main effect for that SOC or PT is statistically significant at 5% level. [a] Median time to event based on the Kaplan Meier estimate. NE = Not estimable as median (or 95% CLs) is not reached. [b] Estimated from main effects of unstratified Cox proportional hazard model including trt., subgroup and subgroup-by-trt. interaction. Ties handled using Efron method and 95% CI derived from profile likelihood estimation. NC = Not calculable. HR <1 favours Osimertinib+Chemo. * p<0.05.
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Table 4.3.2.3 FLAURA-2: Summary of subgroup analysis of time to first SUE SOC: Erkrankungen des Gastrointestinaltrakts
Safety Analysis Set, DCO 03APR2023

	Osi + Chemo (N=276)			Osi (N=275)					
Subgruppen	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]	Hazard Ratio [b]	[95%-KI] [b]	2-seitiger p-Wert [b]
Alter bei Screening									
<65 Jahre	172	8 (4,7)	NE [NE; NE]	164	2 (1,2)	NE [NE; NE]	3,75	[0,94; 24,86]	0,0621
>=65 Jahre	104	5 (4,8)	NE [NE; NE]	111	2 (1,8)	NE [NE; NE]	2,82	[0,61; 19,65]	0,1911
Interaktion p-Wert									0,8030
Region gPAP									
Asien	168	9 (5,4)	NE [NE; NE]	166	3 (1,8)	NE [NE; NE]	3,01	[0,90; 13,56]	0,0757
Europa	22	1 (4,5)	NE [NE; NE]	23	0	NE [NE; NE]	NC	[NC]	NC
Nordamerika	20	1 (5,0)	NE [NE; NE]	22	0	NE [NE; NE]	NC	[NC]	NC
Rest der Welt	66	2 (3,0)	NE [NE; NE]	64	1 (1,6)	NE [NE; NE]	1,93	[0,18; 41,41]	0,5821
Interaktion p-Wert									0,7527

Time to event of AE is defined as the time from first dose of study treatment to first onset of the respective AE or the time to censoring if the AE has not occurred by 28 days following discontinuation of study treatment, before administration of subsequent cancer therapy or death, whichever comes first. All AEs are coded using MedDRA version 25.1. Includes AEs with onset date on or after the date of first dose and up to and including 28 days following discontinuation of study treatment. Analysis done if >=10 patients at each subgroup level and >=10 events in at least one subgroup level combined for both arms. Analysis done for SOC and PT only if main effect for that SOC or PT is statistically significant at 5% level. [a] Median time to event based on the Kaplan Meier estimate. NE = Not estimable as median (or 95% CLs) is not reached. [b] Estimated from main effects of unstratified Cox proportional hazard model including trt., subgroup and subgroup-by-trt. interaction. Ties handled using Efron method and 95% CI derived from profile likelihood estimation. NC = Not calculable. HR <1 favours Osimertinib+Chemo. * p<0.05.
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Table 4.3.2.4 FLAURA-2: Summary of subgroup analysis of time to first SUE SOC: Untersuchungen
Safety Analysis Set, DCO 03APR2023

	Osi + Chemo (N=276)			Osi (N=275)					
Subgruppen	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]	Hazard Ratio [b]	[95%-KI] [b]	2-seitiger p-Wert [b]
Abstammung									
Chinesisch/Asiatisch	68	6 (8,8)	NE [NE; NE]	70	1 (1,4)	NE [NE; NE]	NC	[NC]	NC
Nicht-chinesisch/ Asiatisch	107	3 (2,8)	NE [NE; NE]	106	0	NE [NE; NE]	NC	[NC]	NC
Nicht-asiatisch	101	1 (1,0)	NE [NE; NE]	99	0	NE [NE; NE]	NC	[NC]	NC
Interaktion p-Wert									NC
Methode zur Gewebeuntersuchung									
zentral	120	6 (5,0)	NE [NE; NE]	119	1 (0,8)	NE [NE; NE]	NC	[NC]	NC
lokal	156	4 (2,6)	NE [NE; NE]	156	0	NE [NE; NE]	NC	[NC]	NC
Interaktion p-Wert									NC
WHO Performance-Status									
0	100	0	NE [NE; NE]	100	0	NE [NE; NE]	NC	[NC]	NC
1	176	10 (5,7)	NE [NE; NE]	175	1 (0,6)	NE [NE; NE]	10,07	[1,93;184,76]	0,0034*
Interaktion p-Wert									NC
Raucherstatus									
Ja	90	3 (3,3)	NE [NE; NE]	96	1 (1,0)	NE [NE; NE]	NC	[NC]	NC
Nein	186	7 (3,8)	NE [NE; NE]	179	0	NE [NE; NE]	NC	[NC]	NC
Interaktion p-Wert									NC
Geschlecht									
Maennlich	104	2 (1,9)	NE [NE; NE]	107	1 (0,9)	NE [NE; NE]	NC	[NC]	NC
Weiblich	172	8 (4,7)	NE [NE; NE]	168	0	NE [NE; NE]	NC	[NC]	NC
Interaktion p-Wert									NC
Nachweis der EGFR-Mutation durch zentralen ctDNA Cobas Test									
positiv	211	9 (4,3)	NE [NE; NE]	204	1 (0,5)	NE [NE; NE]	8,83	[1,66;162,85]	0,0073*

Time to event of AE is defined as the time from first dose of study treatment to first onset of the respective AE or the time to censoring if the AE has not occurred by 28 days following discontinuation of study treatment, before administration of subsequent cancer therapy or death, whichever comes first. All AEs are coded using MedDRA version 25.1. Includes AEs with onset date on or after the date of first dose and up to and including 28 days following discontinuation of study treatment. Analysis done if >=10 patients at each subgroup level and >=10 events in at least one subgroup level combined for both arms. Analysis done for SOC and PT only if main effect for that SOC or PT is statistically significant at 5% level. [a] Median time to event based on the Kaplan Meier estimate. NE = Not estimable as median (or 95% CLs) is not reached. [b] Estimated from main effects of unstratified Cox proportional hazard model including trt., subgroup and subgroup-by-trt. interaction. Ties handled using Efron method and 95% CI derived from profile likelihood estimation. NC = Not calculable. HR <1 favours Osimertinib+Chemo. * p<0.05.
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Table 4.3.2.4 FLAURA-2: Summary of subgroup analysis of time to first SUE SOC: Untersuchungen
Safety Analysis Set, DCO 03APR2023

	Osi + Chemo (N=276)			Osi (N=275)					
Subgruppen	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]	Hazard Ratio [b]	[95%-KI] [b]	2-seitiger p-Wert [b]
negativ	41	0	NE [NE; NE]	39	0	NE [NE; NE]	NC	[NC]	NC
unbekannt	24	1 (4,2)	NE [NE; NE]	32	0	NE [NE; NE]	NC	[NC]	NC
Interaktion p-Wert									NC
EGFR-Mutationstyp									
Exon 19 Deletion	172	4 (2,3)	NE [NE; NE]	167	1 (0,6)	NE [NE; NE]	NC	[NC]	NC
Exon 21 (L858R) Substitutionsmutation	104	6 (5,8)	NE [NE; NE]	106	0	NE [NE; NE]	NC	[NC]	NC
Interaktion p-Wert									NC
Zentral bestätigte EGFR-Mutation im Gewebe									
positiv	248	10 (4,0)	NE [NE; NE]	238	1 (0,4)	NE [NE; NE]	9,67	[1,85;177,53]	0,0041*
negativ	3	0	NE [NE; NE]	4	0	NE [NE; NE]	NC	[NC]	NC
unbekannt	25	0	NE [NE; NE]	33	0	NE [NE; NE]	NC	[NC]	NC
Interaktion p-Wert									NC
ZNS-Metastasen zur Baseline									
Ja	113	4 (3,5)	NE [NE; NE]	110	0	NE [NE; NE]	NC	[NC]	NC
Nein	163	6 (3,7)	NE [NE; NE]	165	1 (0,6)	NE [NE; NE]	NC	[NC]	NC
Interaktion p-Wert									NC
Zentrale Bestätigung der EGFR-Mutation									
Zentral bestätigte EGFR-Mutation in Gewebe oder ctDNA	263	10 (3,8)	NE [NE; NE]	266	1 (0,4)	NE [NE; NE]	10,22	[1,96;187,59]	0,0031*
Keine zentrale Bestätigung	13	0	NE [NE; NE]	9	0	NE [NE; NE]	NC	[NC]	NC
Interaktion p-Wert									NC
Alter bei Screening									

Time to event of AE is defined as the time from first dose of study treatment to first onset of the respective AE or the time to censoring if the AE has not occurred by 28 days following discontinuation of study treatment, before administration of subsequent cancer therapy or death, whichever comes first. All AEs are coded using MedDRA version 25.1. Includes AEs with onset date on or after the date of first dose and up to and including 28 days following discontinuation of study treatment. Analysis done if >=10 patients at each subgroup level and >=10 events in at least one subgroup level combined for both arms. Analysis done for SOC and PT only if main effect for that SOC or PT is statistically significant at 5% level. [a] Median time to event based on the Kaplan Meier estimate. NE = Not estimable as median (or 95% CLs) is not reached. [b] Estimated from main effects of unstratified Cox proportional hazard model including trt., subgroup and subgroup-by-trt. interaction. Ties handled using Efron method and 95% CI derived from profile likelihood estimation. NC = Not calculable. HR <1 favours Osimertinib+Chemo. * p<0.05.
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Table 4.3.2.4 FLAURA-2: Summary of subgroup analysis of time to first SUE SOC: Untersuchungen
Safety Analysis Set, DCO 03APR2023

	Osi + Chemo (N=276)			Osi (N=275)					
Subgruppen	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]	Hazard Ratio [b]	[95%-KI] [b]	2-seitiger p-Wert [b]
<65 Jahre	172	8 (4,7)	NE [NE; NE]	164	1 (0,6)	NE [NE; NE]	NC	[NC]	NC
>=65 Jahre	104	2 (1,9)	NE [NE; NE]	111	0	NE [NE; NE]	NC	[NC]	NC
Interaktion p-Wert									NC
Region gPAP									
Asien	168	9 (5,4)	NE [NE; NE]	166	1 (0,6)	NE [NE; NE]	9,05	[1,70;166,92]	0,0065*
Europa	22	0	NE [NE; NE]	23	0	NE [NE; NE]	NC	[NC]	NC
Nordamerika	20	0	NE [NE; NE]	22	0	NE [NE; NE]	NC	[NC]	NC
Rest der Welt	66	1 (1,5)	NE [NE; NE]	64	0	NE [NE; NE]	NC	[NC]	NC
Interaktion p-Wert									NC

Time to event of AE is defined as the time from first dose of study treatment to first onset of the respective AE or the time to censoring if the AE has not occurred by 28 days following discontinuation of study treatment, before administration of subsequent cancer therapy or death, whichever comes first. All AEs are coded using MedDRA version 25.1. Includes AEs with onset date on or after the date of first dose and up to and including 28 days following discontinuation of study treatment. Analysis done if >=10 patients at each subgroup level and >=10 events in at least one subgroup level combined for both arms. Analysis done for SOC and PT only if main effect for that SOC or PT is statistically significant at 5% level. [a] Median time to event based on the Kaplan Meier estimate. NE = Not estimable as median (or 95% CLs) is not reached. [b] Estimated from main effects of unstratified Cox proportional hazard model including trt., subgroup and subgroup-by-trt. interaction. Ties handled using Efron method and 95% CI derived from profile likelihood estimation. NC = Not calculable. HR <1 favours Osimertinib+Chemo. * p<0.05.
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Nutzenbewertung nach AMNOG Seite 1 von 3

Table 4.3.3.1 FLAURA-2: Summary of subgroup analysis of time to first Therapieabbruch aufgrund von UE
Safety Analysis Set, DCO 03APR2023

	Osi + Chemo (N=276)			Osi (N=275)					
Subgruppen	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]	Hazard Ratio [b]	[95%-KI] [b]	2-seitiger p-Wert [b]
Abstammung									
Chinesisch/Asiatisch	68	20 (29,4)	NE [NE; NE]	70	3 (4,3)	NE [NE; NE]	7,44	[2,55; 31,59]	<0,0001*
Nicht-chinesisch/ Asiatisch	107	57 (53,3)	13,1 [6,9; NE]	106	8 (7,5)	NE [NE; NE]	9,66	[4,89; 21,93]	<0,0001*
Nicht-asiatisch	101	55 (54,5)	12,7 [6,2; NE]	99	6 (6,1)	NE [NE; NE]	11,78	[5,50; 30,62]	<0,0001*
Interaktion p-Wert									0,8302
Methode zur Gewebeuntersuchung									
zentral	120	52 (43,3)	NE [NE; NE]	119	6 (5,0)	NE [NE; NE]	10,49	[4,89; 27,31]	<0,0001*
lokal	156	80 (51,3)	15,5 [7,1; NE]	156	11 (7,1)	NE [NE; NE]	9,45	[5,26; 18,79]	<0,0001*
Interaktion p-Wert									0,8444
WHO Performance-Status									
0	100	54 (54,0)	13,1 [6,8; NE]	100	2 (2,0)	NE [NE; NE]	36,73	[11,44;224,35]	<0,0001*
1	176	78 (44,3)	NE [NE; NE]	175	15 (8,6)	NE [NE; NE]	6,26	[3,71; 11,31]	<0,0001*
Interaktion p-Wert									0,0062*
Raucherstatus									
Ja	90	41 (45,6)	23,8 [7,2; NE]	96	10 (10,4)	NE [NE; NE]	5,46	[2,85; 11,53]	<0,0001*
Nein	186	91 (48,9)	20,9 [10,6; NE]	179	7 (3,9)	NE [NE; NE]	15,94	[7,95; 37,92]	<0,0001*
Interaktion p-Wert									0,0402*
Geschlecht									
Maennlich	104	47 (45,2)	NE [NE; NE]	107	10 (9,3)	NE [NE; NE]	5,65	[2,98; 11,85]	<0,0001*
Weiblich	172	85 (49,4)	17,7 [7,2; NE]	168	7 (4,2)	NE [NE; NE]	15,74	[7,83; 37,50]	<0,0001*
Interaktion p-Wert									0,0489*
Nachweis der EGFR-Mutation durch zentralen ctDNA Cobas Test									

Time to event of AE is defined as the time from first dose of study treatment to first onset of the respective AE or the time to censoring if the AE has not occurred by 28 days following discontinuation of study treatment, before administration of subsequent cancer therapy or death, whichever comes first. All AEs are coded using MedDRA version 25.1. Includes AEs with onset date on or after the date of first dose and up to and including 28 days following discontinuation of study treatment. Analysis done if >=10 patients at each subgroup level and >=10 events in at least one subgroup level combined for both arms.
[a] Median time to event based on the Kaplan Meier estimate. NE = Not estimable as median (or 95% CLs) is not reached.
[b] Estimated from main effects of unstratified Cox proportional hazard model including trt., subgroup and subgroup-by-trt. interaction. Ties handled using Efron method and 95% CI derived from profile likelihood estimation. NC = Not calculable.
HR <1 favours Osimertinib+Chemo. * p<0.05.

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Table 4.3.3.1 FLAURA-2: Summary of subgroup analysis of time to first Therapieabbruch aufgrund von UE
Safety Analysis Set, DCO 03APR2023

	Osi + Chemo (N=276)			Osi (N=275)					
Subgruppen	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]	Hazard Ratio [b]	[95%-KI] [b]	2-seitiger p-Wert [b]
positiv	211	99 (46,9)	NE [NE; NE]	204	12 (5,9)	NE [NE; NE]	10,03	[5,74; 19,24]	<0,0001*
negativ	41	21 (51,2)	21,7 [4,5; NE]	39	1 (2,6)	NE [NE; NE]	28,38	[5,94;508,58]	<0,0001*
unbekannt	24	12 (50,0)	12,7 [6,7; NE]	32	4 (12,5)	NE [NE; NE]	4,47	[1,56; 15,98]	0,0047*
Interaktion p-Wert									0,2100
EGFR-Mutationstyp									
Exon 19 Deletion	172	83 (48,3)	21,7 [9,8; NE]	167	11 (6,6)	NE [NE; NE]	9,62	[5,36; 19,10]	<0,0001*
Exon 21 (L858R) Substitutionsmutation	104	49 (47,1)	23,1 [10,5; NE]	106	6 (5,7)	NE [NE; NE]	9,91	[4,60; 25,85]	<0,0001*
Interaktion p-Wert									0,9550
Zentral bestätigte EGFR-Mutation im Gewebe									
positiv	248	118 (47,6)	23,8 [12,7; NE]	238	13 (5,5)	NE [NE; NE]	11,01	[6,46; 20,51]	<0,0001*
negativ	3	2 (66,7)	0,8 [0,5; NE]	4	1 (25,0)	NE [NE; NE]	NC	[NC]	NC
unbekannt	25	12 (48,0)	NE [NE; NE]	33	3 (9,1)	NE [NE; NE]	6,79	[2,16; 29,82]	0,0007*
Interaktion p-Wert									0,5098
ZNS-Metastasen zur Baseline									
Ja	113	51 (45,1)	NE [NE; NE]	110	7 (6,4)	NE [NE; NE]	8,35	[4,05; 20,18]	<0,0001*
Nein	163	81 (49,7)	20,7 [7,2; NE]	165	10 (6,1)	NE [NE; NE]	10,87	[5,92; 22,36]	<0,0001*
Interaktion p-Wert									0,6170
Zentrale Bestätigung der EGFR-Mutation									
Zentral bestätigte EGFR-Mutation in Gewebe oder ctDNA	263	125 (47,5)	23,8 [13,1; NE]	266	16 (6,0)	NE [NE; NE]	9,96	[6,11; 17,42]	<0,0001*
Keine zentrale Bestätigung	13	7 (53,8)	10,5 [2,1; NE]	9	1 (11,1)	NE [NE; NE]	6,32	[1,12;118,13]	0,0346*
Interaktion p-Wert									0,6947

Time to event of AE is defined as the time from first dose of study treatment to first onset of the respective AE or the time to censoring if the AE has not occurred by 28 days following discontinuation of study treatment, before administration of subsequent cancer therapy or death, whichever comes first. All AEs are coded using MedDRA version 25.1. Includes AEs with onset date on or after the date of first dose and up to and including 28 days following discontinuation of study treatment. Analysis done if >=10 patients at each subgroup level and >=10 events in at least one subgroup level combined for both arms.
[a] Median time to event based on the Kaplan Meier estimate. NE = Not estimable as median (or 95% CLs) is not reached.
[b] Estimated from main effects of unstratified Cox proportional hazard model including trt., subgroup and subgroup-by-trt. interaction. Ties handled using Efron method and 95% CI derived from profile likelihood estimation. NC = Not calculable.
HR <1 favours Osimertinib+Chemo. * p<0.05.

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Table 4.3.3.1 FLAURA-2: Summary of subgroup analysis of time to first Therapieabbruch aufgrund von UE
Safety Analysis Set, DCO 03APR2023

	Osi + Chemo (N=276)			Osi (N=275)					
Subgruppen	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]	Hazard Ratio [b]	[95%-KI] [b]	2-seitiger p-Wert [b]
Alter bei Screening									
<65 Jahre	172	68 (39,5)	NE [NE; NE]	164	7 (4,3)	NE [NE; NE]	10,82	[5,34; 25,92]	<0,0001*
>=65 Jahre	104	64 (61,5)	6,6 [4,1;13,1]	111	10 (9,0)	NE [NE; NE]	10,18	[5,47; 21,10]	<0,0001*
Interaktion p-Wert									0,9060
Region gPAP									
Asien	168	72 (42,9)	NE [NE; NE]	166	11 (6,6)	NE [NE; NE]	7,92	[4,39; 15,81]	<0,0001*
Europa	22	14 (63,6)	6,8 [2,1; NE]	23	3 (13,0)	NE [NE; NE]	6,51	[2,12; 28,26]	0,0006*
Nordamerika	20	13 (65,0)	7,2 [3,0; NE]	22	0	NE [NE; NE]	NC	[NC]	NC
Rest der Welt	66	33 (50,0)	15,8 [6,1; NE]	64	3 (4,7)	NE [NE; NE]	13,65	[4,90; 56,76]	<0,0001*
Interaktion p-Wert									0,6349

Time to event of AE is defined as the time from first dose of study treatment to first onset of the respective AE or the time to censoring if the AE has not occurred by 28 days following discontinuation of study treatment, before administration of subsequent cancer therapy or death, whichever comes first. All AEs are coded using MedDRA version 25.1. Includes AEs with onset date on or after the date of first dose and up to and including 28 days following discontinuation of study treatment. Analysis done if >=10 patients at each subgroup level and >=10 events in at least one subgroup level combined for both arms.
[a] Median time to event based on the Kaplan Meier estimate. NE = Not estimable as median (or 95% CLs) is not reached.
[b] Estimated from main effects of unstratified Cox proportional hazard model including trt., subgroup and subgroup-by-trt. interaction. Ties handled using Efron method and 95% CI derived from profile likelihood estimation. NC = Not calculable.
HR <1 favours Osimertinib+Chemo. * p<0.05.

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Table 4.3.4.1 FLAURA-2: Summary of subgroup analysis of time to first UE mit CTCAE Grad >=3
Safety Analysis Set, DCO 03APR2023

	Osi + Chemo (N=276)			Osi (N=275)					
Subgruppen	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]	Hazard Ratio [b]	[95%-KI] [b]	2-seitiger p-Wert [b]
Abstammung									
Chinesisch/Asiatisch	68	49 (72,1)	2,5 [1,3; 6,7]	70	19 (27,1)	NE [NE; NE]	4,03	[2,41; 7,01]	<0,0001*
Nicht-chinesisch/ Asiatisch	107	67 (62,6)	3,0 [1,7;14,4]	106	23 (21,7)	NE [NE; NE]	4,43	[2,80; 7,27]	<0,0001*
Nicht-asiatisch	101	60 (59,4)	5,8 [2,8;23,1]	99	33 (33,3)	NE [NE; NE]	2,36	[1,56; 3,65]	<0,0001*
Interaktion p-Wert									0,1132
Methode zur Gewebeuntersuchung									
zentral	120	83 (69,2)	2,8 [1,9; 4,1]	119	29 (24,4)	NE [NE; NE]	4,42	[2,93; 6,87]	<0,0001*
lokal	156	93 (59,6)	5,8 [2,8;18,2]	156	46 (29,5)	NE [NE; NE]	2,79	[1,97; 4,00]	<0,0001*
Interaktion p-Wert									0,0976
WHO Performance-Status									
0	100	59 (59,0)	7,3 [2,8;23,5]	100	16 (16,0)	NE [NE; NE]	5,40	[3,19; 9,71]	<0,0001*
1	176	117 (66,5)	2,8 [1,9; 4,1]	175	59 (33,7)	NE [NE; NE]	2,85	[2,09; 3,92]	<0,0001*
Interaktion p-Wert									0,0416*
Raucherstatus									
Ja	90	58 (64,4)	3,0 [2,0; 6,9]	96	29 (30,2)	NE [NE; NE]	2,99	[1,93; 4,74]	<0,0001*
Nein	186	118 (63,4)	3,3 [2,1; 8,5]	179	46 (25,7)	NE [NE; NE]	3,64	[2,61; 5,17]	<0,0001*
Interaktion p-Wert									0,4942
Geschlecht									
Maennlich	104	58 (55,8)	8,5 [2,7; NE]	107	33 (30,8)	NE [NE; NE]	2,34	[1,54; 3,63]	<0,0001*
Weiblich	172	118 (68,6)	2,8 [2,1; 4,6]	168	42 (25,0)	NE [NE; NE]	4,28	[3,03; 6,15]	<0,0001*
Interaktion p-Wert									0,0340*
Nachweis der EGFR-Mutation durch zentralen ctDNA Cobas Test									
positiv	211	134 (63,5)	3,0 [2,2; 7,3]	204	54 (26,5)	NE [NE; NE]	3,52	[2,58; 4,87]	<0,0001*

Time to event of AE is defined as the time from first dose of study treatment to first onset of the respective AE or the time to censoring if the AE has not occurred by 28 days following discontinuation of study treatment, before administration of subsequent cancer therapy or death, whichever comes first. All AEs are coded using MedDRA version 25.1. Includes AEs with onset date on or after the date of first dose and up to and including 28 days following discontinuation of study treatment. Analysis done if >=10 patients at each subgroup level and >=10 events in at least one subgroup level combined for both arms. Analysis done for SOC and PT only if main effect for that SOC or PT is statistically significant at 5% level. [a] Median time to event based on the Kaplan Meier estimate. NE = Not estimable as median (or 95% CLs) is not reached. [b] Estimated from main effects of unstratified Cox proportional hazard model including trt., subgroup and subgroup-by-trt. interaction. Ties handled using Efron method and 95% CI derived from profile likelihood estimation. NC = Not calculable. HR <1 favours Osimertinib+Chemo. * p<0.05.
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Table 4.3.4.1 FLAURA-2: Summary of subgroup analysis of time to first UE mit CTCAE Grad >=3
Safety Analysis Set, DCO 03APR2023

	Osi + Chemo (N=276)			Osi (N=275)					
Subgruppen	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]	Hazard Ratio [b]	[95%-KI] [b]	2-seitiger p-Wert [b]
negativ	41	28 (68,3)	4,6 [1,4;14,0]	39	10 (25,6)	NE [NE; NE]	4,13	[2,07; 8,94]	<0,0001*
unbekannt	24	14 (58,3)	6,0 [1,3; NE]	32	11 (34,4)	NE [NE; NE]	2,07	[0,94; 4,67]	0,0694
Interaktion p-Wert									0,4082
EGFR-Mutationstyp									
Exon 19 Deletion	172	105 (61,0)	4,6 [2,8;14,7]	167	46 (27,5)	NE [NE; NE]	3,18	[2,26; 4,53]	<0,0001*
Exon 21 (L858R) Substitutionsmutation	104	71 (68,3)	2,8 [1,4; 5,6]	106	29 (27,4)	NE [NE; NE]	3,72	[2,44; 5,82]	<0,0001*
Interaktion p-Wert									0,5745
Zentral bestätigte EGFR-Mutation im Gewebe									
positiv	248	158 (63,7)	3,0 [2,3; 6,9]	238	61 (25,6)	NE [NE; NE]	3,67	[2,74; 4,97]	<0,0001*
negativ	3	3 (100)	0,4 [0,3; NE]	4	2 (50,0)	NE [NE; NE]	NC	[NC]	NC
unbekannt	25	15 (60,0)	12,8 [1,4; NE]	33	12 (36,4)	NE [NE; NE]	2,02	[0,95; 4,40]	0,0694
Interaktion p-Wert									0,1560
ZNS-Metastasen zur Baseline									
Ja	113	69 (61,1)	3,0 [1,7;18,2]	110	29 (26,4)	NE [NE; NE]	3,15	[2,06; 4,93]	<0,0001*
Nein	163	107 (65,6)	3,3 [2,2; 6,7]	165	46 (27,9)	NE [NE; NE]	3,56	[2,54; 5,09]	<0,0001*
Interaktion p-Wert									0,6635
Zentrale Bestätigung der EGFR-Mutation									
Zentral bestätigte EGFR-Mutation in Gewebe oder ctDNA	263	168 (63,9)	3,1 [2,5; 6,9]	266	70 (26,3)	NE [NE; NE]	3,55	[2,70; 4,72]	<0,0001*
Keine zentrale Bestätigung	13	8 (61,5)	5,6 [0,3; NE]	9	5 (55,6)	8,3 [0,0; NE]	1,24	[0,41; 4,09]	0,7085
Interaktion p-Wert									0,0883
Alter bei Screening									

Time to event of AE is defined as the time from first dose of study treatment to first onset of the respective AE or the time to censoring if the AE has not occurred by 28 days following discontinuation of study treatment, before administration of subsequent cancer therapy or death, whichever comes first. All AEs are coded using MedDRA version 25.1. Includes AEs with onset date on or after the date of first dose and up to and including 28 days following discontinuation of study treatment. Analysis done if >=10 patients at each subgroup level and >=10 events in at least one subgroup level combined for both arms. Analysis done for SOC and PT only if main effect for that SOC or PT is statistically significant at 5% level. [a] Median time to event based on the Kaplan Meier estimate. NE = Not estimable as median (or 95% CLs) is not reached. [b] Estimated from main effects of unstratified Cox proportional hazard model including trt., subgroup and subgroup-by-trt. interaction. Ties handled using Efron method and 95% CI derived from profile likelihood estimation. NC = Not calculable. HR <1 favours Osimertinib+Chemo. * p<0.05.
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Table 4.3.4.1 FLAURA-2: Summary of subgroup analysis of time to first UE mit CTCAE Grad >=3
Safety Analysis Set, DCO 03APR2023

	Osi + Chemo (N=276)			Osi (N=275)					
Subgruppen	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]	Hazard Ratio [b]	[95%-KI] [b]	2-seitiger p-Wert [b]
<65 Jahre	172	105 (61,0)	3,8 [2,7;14,7]	164	37 (22,6)	NE [NE; NE]	3,74	[2,60; 5,51]	<0,0001*
>=65 Jahre	104	71 (68,3)	2,8 [1,4; 5,8]	111	38 (34,2)	NE [NE; NE]	3,18	[2,16; 4,76]	<0,0001*
Interaktion p-Wert									0,5564
Region gPAP									
Asien	168	113 (67,3)	2,8 [2,0; 5,8]	166	40 (24,1)	NE [NE; NE]	4,28	[3,01; 6,21]	<0,0001*
Europa	22	11 (50,0)	12,8 [0,3; NE]	23	10 (43,5)	15,9 [8,0; NE]	1,41	[0,60; 3,39]	0,4297
Nordamerika	20	11 (55,0)	8,5 [0,8; NE]	22	6 (27,3)	NE [NE; NE]	2,55	[0,97; 7,41]	0,0576
Rest der Welt	66	41 (62,1)	3,4 [2,1;23,1]	64	19 (29,7)	NE [NE; NE]	2,93	[1,73; 5,16]	<0,0001*
Interaktion p-Wert									0,1087

Time to event of AE is defined as the time from first dose of study treatment to first onset of the respective AE or the time to censoring if the AE has not occurred by 28 days following discontinuation of study treatment, before administration of subsequent cancer therapy or death, whichever comes first. All AEs are coded using MedDRA version 25.1. Includes AEs with onset date on or after the date of first dose and up to and including 28 days following discontinuation of study treatment. Analysis done if >=10 patients at each subgroup level and >=10 events in at least one subgroup level combined for both arms. Analysis done for SOC and PT only if main effect for that SOC or PT is statistically significant at 5% level. [a] Median time to event based on the Kaplan Meier estimate. NE = Not estimable as median (or 95% CLs) is not reached. [b] Estimated from main effects of unstratified Cox proportional hazard model including trt., subgroup and subgroup-by-trt. interaction. Ties handled using Efron method and 95% CI derived from profile likelihood estimation. NC = Not calculable. HR <1 favours Osimertinib+Chemo. * p<0.05.
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Table 4.3.4.2 FLAURA-2: Summary of subgroup analysis of time to first G>=3 SOC: Allgemeine Erkrankungen und Beschwerden am Verabreichungsort
Safety Analysis Set, DCO 03APR2023

	Osi + Chemo (N=276)			Osi (N=275)					
Subgruppen	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]	Hazard Ratio [b]	[95%-KI] [b]	2-seitiger p-Wert [b]
Abstammung									
Chinesisch/Asiatisch	68	1 (1,5)	NE [NE; NE]	70	0	NE [NE; NE]	NC	[NC]	NC
Nicht-chinesisch/ Asiatisch	107	2 (1,9)	NE [NE; NE]	106	1 (0,9)	NE [NE; NE]	NC	[NC]	NC
Nicht-asiatisch	101	7 (6,9)	NE [NE; NE]	99	1 (1,0)	NE [NE; NE]	NC	[NC]	NC
Interaktion p-Wert									NC
Methode zur Gewebeuntersuchung									
zentral	120	4 (3,3)	NE [NE; NE]	119	0	NE [NE; NE]	NC	[NC]	NC
lokal	156	6 (3,8)	NE [NE; NE]	156	2 (1,3)	NE [NE; NE]	NC	[NC]	NC
Interaktion p-Wert									NC
WHO Performance-Status									
0	100	3 (3,0)	NE [NE; NE]	100	0	NE [NE; NE]	NC	[NC]	NC
1	176	7 (4,0)	NE [NE; NE]	175	2 (1,1)	NE [NE; NE]	NC	[NC]	NC
Interaktion p-Wert									NC
Raucherstatus									
Ja	90	2 (2,2)	NE [NE; NE]	96	1 (1,0)	NE [NE; NE]	NC	[NC]	NC
Nein	186	8 (4,3)	NE [NE; NE]	179	1 (0,6)	NE [NE; NE]	NC	[NC]	NC
Interaktion p-Wert									NC
Geschlecht									
Maennlich	104	4 (3,8)	NE [NE; NE]	107	1 (0,9)	NE [NE; NE]	NC	[NC]	NC
Weiblich	172	6 (3,5)	NE [NE; NE]	168	1 (0,6)	NE [NE; NE]	NC	[NC]	NC
Interaktion p-Wert									NC
Nachweis der EGFR-Mutation durch zentralen ctDNA Cobas Test									

Time to event of AE is defined as the time from first dose of study treatment to first onset of the respective AE or the time to censoring if the AE has not occurred by 28 days following discontinuation of study treatment, before administration of subsequent cancer therapy or death, whichever comes first. All AEs are coded using MedDRA version 25.1. Includes AEs with onset date on or after the date of first dose and up to and including 28 days following discontinuation of study treatment. Analysis done if >=10 patients at each subgroup level and >=10 events in at least one subgroup level combined for both arms. Analysis done for SOC and PT only if main effect for that SOC or PT is statistically significant at 5% level. [a] Median time to event based on the Kaplan Meier estimate. NE = Not estimable as median (or 95% CLs) is not reached. [b] Estimated from main effects of unstratified Cox proportional hazard model including trt., subgroup and subgroup-by-trt. interaction. Ties handled using Efron method and 95% CI derived from profile likelihood estimation. NC = Not calculable. HR <1 favours Osimertinib+Chemo. * p<0.05.
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Table 4.3.4.2 FLAURA-2: Summary of subgroup analysis of time to first G>=3 SOC: Allgemeine Erkrankungen und Beschwerden am Verabreichungsort
Safety Analysis Set, DCO 03APR2023

	Osi + Chemo (N=276)			Osi (N=275)					
Subgruppen	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]	Hazard Ratio [b]	[95%-KI] [b]	2-seitiger p-Wert [b]
positiv	211	6 (2,8)	NE [NE; NE]	204	1 (0,5)	NE [NE; NE]	NC	[NC]	NC
negativ	41	4 (9,8)	NE [NE; NE]	39	0	NE [NE; NE]	NC	[NC]	NC
unbekannt	24	0	NE [NE; NE]	32	1 (3,1)	NE [NE; NE]	NC	[NC]	NC
Interaktion p-Wert									NC
EGFR-Mutationstyp									
Exon 19 Deletion	172	6 (3,5)	NE [NE; NE]	167	1 (0,6)	NE [NE; NE]	NC	[NC]	NC
Exon 21 (L858R) Substitutionsmutation	104	4 (3,8)	NE [NE; NE]	106	1 (0,9)	NE [NE; NE]	NC	[NC]	NC
Interaktion p-Wert									NC
Zentral bestätigte EGFR-Mutation im Gewebe									
positiv	248	8 (3,2)	NE [NE; NE]	238	1 (0,4)	NE [NE; NE]	NC	[NC]	NC
negativ	3	0	NE [NE; NE]	4	0	NE [NE; NE]	NC	[NC]	NC
unbekannt	25	2 (8,0)	NE [NE; NE]	33	1 (3,0)	NE [NE; NE]	NC	[NC]	NC
Interaktion p-Wert									NC
ZNS-Metastasen zur Baseline									
Ja	113	6 (5,3)	NE [NE; NE]	110	0	NE [NE; NE]	NC	[NC]	NC
Nein	163	4 (2,5)	NE [NE; NE]	165	2 (1,2)	NE [NE; NE]	NC	[NC]	NC
Interaktion p-Wert									NC
Zentrale Bestätigung der EGFR-Mutation									
Zentral bestätigte EGFR-Mutation in Gewebe oder ctDNA	263	9 (3,4)	NE [NE; NE]	266	2 (0,8)	NE [NE; NE]	4,61	[1,19; 30,27]	0,0254*
Keine zentrale Bestätigung	13	1 (7,7)	NE [NE; NE]	9	0	NE [NE; NE]	NC	[NC]	NC
Interaktion p-Wert									NC

Time to event of AE is defined as the time from first dose of study treatment to first onset of the respective AE or the time to censoring if the AE has not occurred by 28 days following discontinuation of study treatment, before administration of subsequent cancer therapy or death, whichever comes first. All AEs are coded using MedDRA version 25.1. Includes AEs with onset date on or after the date of first dose and up to and including 28 days following discontinuation of study treatment. Analysis done if >=10 patients at each subgroup level and >=10 events in at least one subgroup level combined for both arms. Analysis done for SOC and PT only if main effect for that SOC or PT is statistically significant at 5% level. [a] Median time to event based on the Kaplan Meier estimate. NE = Not estimable as median (or 95% CLs) is not reached. [b] Estimated from main effects of unstratified Cox proportional hazard model including trt., subgroup and subgroup-by-trt. interaction. Ties handled using Efron method and 95% CI derived from profile likelihood estimation. NC = Not calculable. HR <1 favours Osimertinib+Chemo. * p<0.05.
root/cdar/d516/payer_germany/ar/d5169c00001_payer_germany/tlf/prod/program/ttesubae.sas gttesubaedab 22DEC2023:09:13 kfrh585

Table 4.3.4.2 FLAURA-2: Summary of subgroup analysis of time to first G>=3 SOC: Allgemeine Erkrankungen und Beschwerden am Verabreichungsort
Safety Analysis Set, DCO 03APR2023

	Osi + Chemo (N=276)			Osi (N=275)					
Subgruppen	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]	Hazard Ratio [b]	[95%-KI] [b]	2-seitiger p-Wert [b]
Alter bei Screening									
<65 Jahre	172	4 (2,3)	NE [NE; NE]	164	1 (0,6)	NE [NE; NE]	NC	[NC]	NC
>=65 Jahre	104	6 (5,8)	NE [NE; NE]	111	1 (0,9)	NE [NE; NE]	NC	[NC]	NC
Interaktion p-Wert									NC
Region gPAP									
Asien	168	3 (1,8)	NE [NE; NE]	166	1 (0,6)	NE [NE; NE]	NC	[NC]	NC
Europa	22	2 (9,1)	NE [NE; NE]	23	0	NE [NE; NE]	NC	[NC]	NC
Nordamerika	20	1 (5,0)	NE [NE; NE]	22	0	NE [NE; NE]	NC	[NC]	NC
Rest der Welt	66	4 (6,1)	NE [NE; NE]	64	1 (1,6)	NE [NE; NE]	NC	[NC]	NC
Interaktion p-Wert									NC

Time to event of AE is defined as the time from first dose of study treatment to first onset of the respective AE or the time to censoring if the AE has not occurred by 28 days following discontinuation of study treatment, before administration of subsequent cancer therapy or death, whichever comes first. All AEs are coded using MedDRA version 25.1. Includes AEs with onset date on or after the date of first dose and up to and including 28 days following discontinuation of study treatment. Analysis done if >=10 patients at each subgroup level and >=10 events in at least one subgroup level combined for both arms. Analysis done for SOC and PT only if main effect for that SOC or PT is statistically significant at 5% level. [a] Median time to event based on the Kaplan Meier estimate. NE = Not estimable as median (or 95% CLs) is not reached. [b] Estimated from main effects of unstratified Cox proportional hazard model including trt., subgroup and subgroup-by-trt. interaction. Ties handled using Efron method and 95% CI derived from profile likelihood estimation. NC = Not calculable. HR <1 favours Osimertinib+Chemo. * p<0.05.
root/cdar/d516/payer_germany/ar/d5169c00001_payer_germany/tlf/prod/program/ttesubae.sas gttesubaedab 22DEC2023:09:13 kfrh585

Table 4.3.4.3 FLAURA-2: Summary of subgroup analysis of time to first G>=3 SOC: Erkrankungen des Blutes und des Lymphsystems
Safety Analysis Set, DCO 03APR2023

	Osi + Chemo (N=276)			Osi (N=275)					
Subgruppen	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]	Hazard Ratio [b]	[95%-KI] [b]	2-seitiger p-Wert [b]
Abstammung									
Chinesisch/Asiatisch	68	23 (33,8)	NE [NE; NE]	70	1 (1,4)	NE [NE; NE]	27,73	[5,85;496,00]	<0,0001*
Nicht-chinesisch/ Asiatisch	107	37 (34,6)	NE [NE; NE]	106	2 (1,9)	NE [NE; NE]	22,54	[6,90;138,63]	<0,0001*
Nicht-asiatisch	101	37 (36,6)	NE [NE; NE]	99	3 (3,0)	NE [NE; NE]	15,02	[5,43; 62,23]	<0,0001*
Interaktion p-Wert									0,8396
Methode zur Gewebeuntersuchung									
zentral	120	42 (35,0)	NE [NE; NE]	119	5 (4,2)	NE [NE; NE]	10,06	[4,37; 29,11]	<0,0001*
lokal	156	55 (35,3)	NE [NE; NE]	156	1 (0,6)	NE [NE; NE]	67,57	[14,88;1194,4]	<0,0001*
Interaktion p-Wert									0,0458*
WHO Performance-Status									
0	100	23 (23,0)	NE [NE; NE]	100	1 (1,0)	NE [NE; NE]	26,00	[5,48;465,05]	<0,0001*
1	176	74 (42,0)	NE [NE; NE]	175	5 (2,9)	NE [NE; NE]	18,87	[8,45; 53,77]	<0,0001*
Interaktion p-Wert									0,7679
Raucherstatus									
Ja	90	31 (34,4)	NE [NE; NE]	96	1 (1,0)	NE [NE; NE]	39,29	[8,45;699,21]	<0,0001*
Nein	186	66 (35,5)	NE [NE; NE]	179	5 (2,8)	NE [NE; NE]	15,69	[6,99; 44,83]	<0,0001*
Interaktion p-Wert									0,3701
Geschlecht									
Maennlich	104	32 (30,8)	NE [NE; NE]	107	3 (2,8)	NE [NE; NE]	12,43	[4,45; 51,71]	<0,0001*
Weiblich	172	65 (37,8)	NE [NE; NE]	168	3 (1,8)	NE [NE; NE]	27,06	[10,06;110,73]	<0,0001*
Interaktion p-Wert									0,3616
Nachweis der EGFR-Mutation durch zentralen ctDNA Cobas Test									

Time to event of AE is defined as the time from first dose of study treatment to first onset of the respective AE or the time to censoring if the AE has not occurred by 28 days following discontinuation of study treatment, before administration of subsequent cancer therapy or death, whichever comes first. All AEs are coded using MedDRA version 25.1. Includes AEs with onset date on or after the date of first dose and up to and including 28 days following discontinuation of study treatment. Analysis done if >=10 patients at each subgroup level and >=10 events in at least one subgroup level combined for both arms. Analysis done for SOC and PT only if main effect for that SOC or PT is statistically significant at 5% level. [a] Median time to event based on the Kaplan Meier estimate. NE = Not estimable as median (or 95% CLs) is not reached. [b] Estimated from main effects of unstratified Cox proportional hazard model including trt., subgroup and subgroup-by-trt. interaction. Ties handled using Efron method and 95% CI derived from profile likelihood estimation. NC = Not calculable. HR <1 favours Osimertinib+Chemo. * p<0.05.
root/cdar/d516/payer_germany/ar/d5169c00001_payer_germany/tlf/prod/program/ttesubae.sas gttesubaedac 22DEC2023:09:13 kfrh585

Table 4.3.4.3 FLAURA-2: Summary of subgroup analysis of time to first G>=3 SOC: Erkrankungen des Blutes und des Lymphsystems
Safety Analysis Set, DCO 03APR2023

	Osi + Chemo (N=276)			Osi (N=275)					
Subgruppen	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]	Hazard Ratio [b]	[95%-KI] [b]	2-seitiger p-Wert [b]
positiv	211	74 (35,1)	NE [NE; NE]	204	5 (2,5)	NE [NE; NE]	17,49	[7,83; 49,86]	<0,0001*
negativ	41	14 (34,1)	NE [NE; NE]	39	0	NE [NE; NE]	NC	[NC]	NC
unbekannt	24	9 (37,5)	NE [NE; NE]	32	1 (3,1)	NE [NE; NE]	14,42	[2,71;265,84]	0,0006*
Interaktion p-Wert									0,8687
EGFR-Mutationstyp									
Exon 19 Deletion	172	63 (36,6)	NE [NE; NE]	167	2 (1,2)	NE [NE; NE]	38,24	[11,98;233,03]	<0,0001*
Exon 21 (L858R) Substitutionsmutation	104	34 (32,7)	NE [NE; NE]	106	4 (3,8)	NE [NE; NE]	10,16	[4,05; 34,02]	<0,0001*
Interaktion p-Wert									0,1229
Zentral bestätigte EGFR-Mutation im Gewebe									
positiv	248	87 (35,1)	NE [NE; NE]	238	6 (2,5)	NE [NE; NE]	17,07	[8,13; 43,85]	<0,0001*
negativ	3	1 (33,3)	NE [NE; NE]	4	0	NE [NE; NE]	NC	[NC]	NC
unbekannt	25	9 (36,0)	NE [NE; NE]	33	0	NE [NE; NE]	NC	[NC]	NC
Interaktion p-Wert									NC
ZNS-Metastasen zur Baseline									
Ja	113	36 (31,9)	NE [NE; NE]	110	4 (3,6)	NE [NE; NE]	10,30	[4,12; 34,45]	<0,0001*
Nein	163	61 (37,4)	NE [NE; NE]	165	2 (1,2)	NE [NE; NE]	38,58	[12,07;235,21]	<0,0001*
Interaktion p-Wert									0,1243
Zentrale Bestätigung der EGFR-Mutation									
Zentral bestätigte EGFR-Mutation in Gewebe oder ctDNA	263	93 (35,4)	NE [NE; NE]	266	6 (2,3)	NE [NE; NE]	19,23	[9,18; 49,34]	<0,0001*
Keine zentrale Bestätigung	13	4 (30,8)	NE [NE; NE]	9	0	NE [NE; NE]	NC	[NC]	NC

Time to event of AE is defined as the time from first dose of study treatment to first onset of the respective AE or the time to censoring if the AE has not occurred by 28 days following discontinuation of study treatment, before administration of subsequent cancer therapy or death, whichever comes first. All AEs are coded using MedDRA version 25.1. Includes AEs with onset date on or after the date of first dose and up to and including 28 days following discontinuation of study treatment. Analysis done if >=10 patients at each subgroup level and >=10 events in at least one subgroup level combined for both arms. Analysis done for SOC and PT only if main effect for that SOC or PT is statistically significant at 5% level. [a] Median time to event based on the Kaplan Meier estimate. NE = Not estimable as median (or 95% CLs) is not reached. [b] Estimated from main effects of unstratified Cox proportional hazard model including trt., subgroup and subgroup-by-trt. interaction. Ties handled using Efron method and 95% CI derived from profile likelihood estimation. NC = Not calculable. HR <1 favours Osimertinib+Chemo. * p<0.05.
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Table 4.3.4.3 FLAURA-2: Summary of subgroup analysis of time to first G>=3 SOC: Erkrankungen des Blutes und des Lymphsystems
Safety Analysis Set, DCO 03APR2023

	Osi + Chemo (N=276)			Osi (N=275)					
Subgruppen	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]	Hazard Ratio [b]	[95%-KI] [b]	2-seitiger p-Wert [b]
Interaktion p-Wert									NC
Alter bei Screening									
<65 Jahre	172	61 (35,5)	NE [NE; NE]	164	4 (2,4)	NE [NE; NE]	17,25	[7,11; 56,83]	<0,0001*
>=65 Jahre	104	36 (34,6)	NE [NE; NE]	111	2 (1,8)	NE [NE; NE]	24,59	[7,51;151,29]	<0,0001*
Interaktion p-Wert									0,6865
Region gPAP									
Asien	168	59 (35,1)	NE [NE; NE]	166	2 (1,2)	NE [NE; NE]	35,56	[11,12;216,93]	<0,0001*
Europa	22	10 (45,5)	NE [NE; NE]	23	0	NE [NE; NE]	NC	[NC]	NC
Nordamerika	20	5 (25,0)	NE [NE; NE]	22	1 (4,5)	NE [NE; NE]	6,19	[0,998; 118,59]	0,0502
Rest der Welt	66	23 (34,8)	NE [NE; NE]	64	3 (4,7)	NE [NE; NE]	9,23	[3,21; 38,90]	<0,0001*
Interaktion p-Wert									0,2395

Time to event of AE is defined as the time from first dose of study treatment to first onset of the respective AE or the time to censoring if the AE has not occurred by 28 days following discontinuation of study treatment, before administration of subsequent cancer therapy or death, whichever comes first. All AEs are coded using MedDRA version 25.1. Includes AEs with onset date on or after the date of first dose and up to and including 28 days following discontinuation of study treatment. Analysis done if >=10 patients at each subgroup level and >=10 events in at least one subgroup level combined for both arms. Analysis done for SOC and PT only if main effect for that SOC or PT is statistically significant at 5% level. [a] Median time to event based on the Kaplan Meier estimate. NE = Not estimable as median (or 95% CLs) is not reached. [b] Estimated from main effects of unstratified Cox proportional hazard model including trt., subgroup and subgroup-by-trt. interaction. Ties handled using Efron method and 95% CI derived from profile likelihood estimation. NC = Not calculable. HR <1 favours Osimertinib+Chemo. * p<0.05.
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Table 4.3.4.4 FLAURA-2: Summary of subgroup analysis of time to first G>=3 PT: Anaemie
Safety Analysis Set, DCO 03APR2023

	Osi + Chemo (N=276)			Osi (N=275)					
Subgruppen	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]	Hazard Ratio [b]	[95%-KI] [b]	2-seitiger p-Wert [b]
Abstammung									
Chinesisch/Asiatisch	68	12 (17,6)	NE [NE; NE]	70	0	NE [NE; NE]	NC	[NC]	NC
Nicht-chinesisch/ Asiatisch	107	26 (24,3)	NE [NE; NE]	106	0	NE [NE; NE]	NC	[NC]	NC
Nicht-asiatisch	101	17 (16,8)	NE [NE; NE]	99	1 (1,0)	NE [NE; NE]	17,98	[3,69;324,09]	<0,0001*
Interaktion p-Wert									NC
Methode zur Gewebeuntersuchung									
zentral	120	20 (16,7)	NE [NE; NE]	119	1 (0,8)	NE [NE; NE]	21,68	[4,52;388,96]	<0,0001*
lokal	156	35 (22,4)	NE [NE; NE]	156	0	NE [NE; NE]	NC	[NC]	NC
Interaktion p-Wert									NC
WHO Performance-Status									
0	100	12 (12,0)	NE [NE; NE]	100	0	NE [NE; NE]	NC	[NC]	NC
1	176	43 (24,4)	NE [NE; NE]	175	1 (0,6)	NE [NE; NE]	49,31	[10,77;874,25]	<0,0001*
Interaktion p-Wert									NC
Raucherstatus									
Ja	90	20 (22,2)	NE [NE; NE]	96	0	NE [NE; NE]	NC	[NC]	NC
Nein	186	35 (18,8)	NE [NE; NE]	179	1 (0,6)	NE [NE; NE]	37,39	[8,09;664,23]	<0,0001*
Interaktion p-Wert									NC
Geschlecht									
Maennlich	104	19 (18,3)	NE [NE; NE]	107	0	NE [NE; NE]	NC	[NC]	NC
Weiblich	172	36 (20,9)	NE [NE; NE]	168	1 (0,6)	NE [NE; NE]	40,43	[8,76;718,03]	<0,0001*
Interaktion p-Wert									NC
Nachweis der EGFR-Mutation durch zentralen ctDNA Cobas Test									

Time to event of AE is defined as the time from first dose of study treatment to first onset of the respective AE or the time to censoring if the AE has not occurred by 28 days following discontinuation of study treatment, before administration of subsequent cancer therapy or death, whichever comes first. All AEs are coded using MedDRA version 25.1. Includes AEs with onset date on or after the date of first dose and up to and including 28 days following discontinuation of study treatment. Analysis done if >=10 patients at each subgroup level and >=10 events in at least one subgroup level combined for both arms. Analysis done for SOC and PT only if main effect for that SOC or PT is statistically significant at 5% level. [a] Median time to event based on the Kaplan Meier estimate. NE = Not estimable as median (or 95% CLs) is not reached. [b] Estimated from main effects of unstratified Cox proportional hazard model including trt., subgroup and subgroup-by-trt. interaction. Ties handled using Efron method and 95% CI derived from profile likelihood estimation. NC = Not calculable. HR <1 favours Osimertinib+Chemo. * p<0.05.
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Table 4.3.4.4 FLAURA-2: Summary of subgroup analysis of time to first G>=3 PT: Anaemie
Safety Analysis Set, DCO 03APR2023

	Osi + Chemo (N=276)			Osi (N=275)					
Subgruppen	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]	Hazard Ratio [b]	[95%-KI] [b]	2-seitiger p-Wert [b]
positiv	211	41 (19,4)	NE [NE; NE]	204	1 (0,5)	NE [NE; NE]	44,40	[9,68;787,40]	<0,0001*
negativ	41	9 (22,0)	NE [NE; NE]	39	0	NE [NE; NE]	NC	[NC]	NC
unbekannt	24	5 (20,8)	NE [NE; NE]	32	0	NE [NE; NE]	NC	[NC]	NC
Interaktion p-Wert									NC
EGFR-Mutationstyp									
Exon 19 Deletion	172	34 (19,8)	NE [NE; NE]	167	0	NE [NE; NE]	NC	[NC]	NC
Exon 21 (L858R) Substitutionsmutation	104	21 (20,2)	NE [NE; NE]	106	1 (0,9)	NE [NE; NE]	23,48	[4,92;420,75]	<0,0001*
Interaktion p-Wert									NC
Zentral bestätigte EGFR-Mutation im Gewebe									
positiv	248	48 (19,4)	NE [NE; NE]	238	1 (0,4)	NE [NE; NE]	51,65	[11,33;915,18]	<0,0001*
negativ	3	1 (33,3)	NE [NE; NE]	4	0	NE [NE; NE]	NC	[NC]	NC
unbekannt	25	6 (24,0)	NE [NE; NE]	33	0	NE [NE; NE]	NC	[NC]	NC
Interaktion p-Wert									NC
ZNS-Metastasen zur Baseline									
Ja	113	19 (16,8)	NE [NE; NE]	110	0	NE [NE; NE]	NC	[NC]	NC
Nein	163	36 (22,1)	NE [NE; NE]	165	1 (0,6)	NE [NE; NE]	41,22	[8,93;732,01]	<0,0001*
Interaktion p-Wert									NC
Zentrale Bestätigung der EGFR-Mutation									
Zentral bestätigte EGFR-Mutation in Gewebe oder ctDNA	263	52 (19,8)	NE [NE; NE]	266	1 (0,4)	NE [NE; NE]	58,88	[12,96;1043,0]	<0,0001*
Keine zentrale Bestätigung	13	3 (23,1)	NE [NE; NE]	9	0	NE [NE; NE]	NC	[NC]	NC
Interaktion p-Wert									NC

Time to event of AE is defined as the time from first dose of study treatment to first onset of the respective AE or the time to censoring if the AE has not occurred by 28 days following discontinuation of study treatment, before administration of subsequent cancer therapy or death, whichever comes first. All AEs are coded using MedDRA version 25.1. Includes AEs with onset date on or after the date of first dose and up to and including 28 days following discontinuation of study treatment. Analysis done if >=10 patients at each subgroup level and >=10 events in at least one subgroup level combined for both arms. Analysis done for SOC and PT only if main effect for that SOC or PT is statistically significant at 5% level. [a] Median time to event based on the Kaplan Meier estimate. NE = Not estimable as median (or 95% CLs) is not reached. [b] Estimated from main effects of unstratified Cox proportional hazard model including trt., subgroup and subgroup-by-trt. interaction. Ties handled using Efron method and 95% CI derived from profile likelihood estimation. NC = Not calculable. HR <1 favours Osimertinib+Chemo. * p<0.05.
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Table 4.3.4.4 FLAURA-2: Summary of subgroup analysis of time to first G>=3 PT: Anaemie
Safety Analysis Set, DCO 03APR2023

	Osi + Chemo (N=276)			Osi (N=275)					
Subgruppen	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]	Hazard Ratio [b]	[95%-KI] [b]	2-seitiger p-Wert [b]
Alter bei Screening									
<65 Jahre	172	30 (17,4)	NE [NE; NE]	164	0	NE [NE; NE]	NC	[NC]	NC
>=65 Jahre	104	25 (24,0)	NE [NE; NE]	111	1 (0,9)	NE [NE; NE]	31,82	[6,75;568,19]	<0,0001*
Interaktion p-Wert									NC
Region gPAP									
Asien	168	38 (22,6)	NE [NE; NE]	166	0	NE [NE; NE]	NC	[NC]	NC
Europa	22	6 (27,3)	NE [NE; NE]	23	0	NE [NE; NE]	NC	[NC]	NC
Nordamerika	20	2 (10,0)	NE [NE; NE]	22	0	NE [NE; NE]	NC	[NC]	NC
Rest der Welt	66	9 (13,6)	NE [NE; NE]	64	1 (1,6)	NE [NE; NE]	9,63	[1,81;177,51]	0,0049*
Interaktion p-Wert									NC

Time to event of AE is defined as the time from first dose of study treatment to first onset of the respective AE or the time to censoring if the AE has not occurred by 28 days following discontinuation of study treatment, before administration of subsequent cancer therapy or death, whichever comes first. All AEs are coded using MedDRA version 25.1. Includes AEs with onset date on or after the date of first dose and up to and including 28 days following discontinuation of study treatment. Analysis done if >=10 patients at each subgroup level and >=10 events in at least one subgroup level combined for both arms. Analysis done for SOC and PT only if main effect for that SOC or PT is statistically significant at 5% level. [a] Median time to event based on the Kaplan Meier estimate. NE = Not estimable as median (or 95% CLs) is not reached. [b] Estimated from main effects of unstratified Cox proportional hazard model including trt., subgroup and subgroup-by-trt. interaction. Ties handled using Efron method and 95% CI derived from profile likelihood estimation. NC = Not calculable. HR <1 favours Osimertinib+Chemo. * p<0.05.
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Table 4.3.4.5 FLAURA-2: Summary of subgroup analysis of time to first G>=3 PT: Febrile Neutropenie
Safety Analysis Set, DCO 03APR2023

	Osi + Chemo (N=276)			Osi (N=275)					
Subgruppen	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]	Hazard Ratio [b]	[95%-KI] [b]	2-seitiger p-Wert [b]
Abstammung									
Chinesisch/Asiatisch	68	3 (4,4)	NE [NE; NE]	70	0	NE [NE; NE]	NC	[NC]	NC
Nicht-chinesisch/ Asiatisch	107	7 (6,5)	NE [NE; NE]	106	0	NE [NE; NE]	NC	[NC]	NC
Nicht-asiatisch	101	1 (1,0)	NE [NE; NE]	99	0	NE [NE; NE]	NC	[NC]	NC
Interaktion p-Wert									NC
Methode zur Gewebeuntersuchung									
zentral	120	4 (3,3)	NE [NE; NE]	119	0	NE [NE; NE]	NC	[NC]	NC
lokal	156	7 (4,5)	NE [NE; NE]	156	0	NE [NE; NE]	NC	[NC]	NC
Interaktion p-Wert									NC
WHO Performance-Status									
0	100	3 (3,0)	NE [NE; NE]	100	0	NE [NE; NE]	NC	[NC]	NC
1	176	8 (4,5)	NE [NE; NE]	175	0	NE [NE; NE]	NC	[NC]	NC
Interaktion p-Wert									NC
Raucherstatus									
Ja	90	1 (1,1)	NE [NE; NE]	96	0	NE [NE; NE]	NC	[NC]	NC
Nein	186	10 (5,4)	NE [NE; NE]	179	0	NE [NE; NE]	NC	[NC]	NC
Interaktion p-Wert									NC
Geschlecht									
Maennlich	104	5 (4,8)	NE [NE; NE]	107	0	NE [NE; NE]	NC	[NC]	NC
Weiblich	172	6 (3,5)	NE [NE; NE]	168	0	NE [NE; NE]	NC	[NC]	NC
Interaktion p-Wert									NC
Nachweis der EGFR-Mutation durch zentralen ctDNA Cobas Test									
positiv	211	10 (4,7)	NE [NE; NE]	204	0	NE [NE; NE]	NC	[NC]	NC

Time to event of AE is defined as the time from first dose of study treatment to first onset of the respective AE or the time to censoring if the AE has not occurred by 28 days following discontinuation of study treatment, before administration of subsequent cancer therapy or death, whichever comes first. All AEs are coded using MedDRA version 25.1. Includes AEs with onset date on or after the date of first dose and up to and including 28 days following discontinuation of study treatment. Analysis done if >=10 patients at each subgroup level and >=10 events in at least one subgroup level combined for both arms. Analysis done for SOC and PT only if main effect for that SOC or PT is statistically significant at 5% level. [a] Median time to event based on the Kaplan Meier estimate. NE = Not estimable as median (or 95% CLs) is not reached. [b] Estimated from main effects of unstratified Cox proportional hazard model including trt., subgroup and subgroup-by-trt. interaction. Ties handled using Efron method and 95% CI derived from profile likelihood estimation. NC = Not calculable. HR <1 favours Osimertinib+Chemo. * p<0.05.
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Table 4.3.4.5 FLAURA-2: Summary of subgroup analysis of time to first G>=3 PT: Febrile Neutropenie
Safety Analysis Set, DCO 03APR2023

	Osi + Chemo (N=276)			Osi (N=275)					
Subgruppen	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]	Hazard Ratio [b]	[95%-KI] [b]	2-seitiger p-Wert [b]
negativ	41	1 (2,4)	NE [NE; NE]	39	0	NE [NE; NE]	NC	[NC]	NC
unbekannt	24	0	NE [NE; NE]	32	0	NE [NE; NE]	NC	[NC]	NC
Interaktion p-Wert									NC
EGFR-Mutationstyp									
Exon 19 Deletion	172	7 (4,1)	NE [NE; NE]	167	0	NE [NE; NE]	NC	[NC]	NC
Exon 21 (L858R) Substitutionsmutation	104	4 (3,8)	NE [NE; NE]	106	0	NE [NE; NE]	NC	[NC]	NC
Interaktion p-Wert									NC
Zentral bestätigte EGFR-Mutation im Gewebe									
positiv	248	10 (4,0)	NE [NE; NE]	238	0	NE [NE; NE]	NC	[NC]	NC
negativ	3	0	NE [NE; NE]	4	0	NE [NE; NE]	NC	[NC]	NC
unbekannt	25	1 (4,0)	NE [NE; NE]	33	0	NE [NE; NE]	NC	[NC]	NC
Interaktion p-Wert									NC
ZNS-Metastasen zur Baseline									
Ja	113	4 (3,5)	NE [NE; NE]	110	0	NE [NE; NE]	NC	[NC]	NC
Nein	163	7 (4,3)	NE [NE; NE]	165	0	NE [NE; NE]	NC	[NC]	NC
Interaktion p-Wert									NC
Zentrale Bestätigung der EGFR-Mutation									
Zentral bestätigte EGFR-Mutation in Gewebe oder ctDNA	263	11 (4,2)	NE [NE; NE]	266	0	NE [NE; NE]	NC	[NC]	NC
Keine zentrale Bestätigung	13	0	NE [NE; NE]	9	0	NE [NE; NE]	NC	[NC]	NC
Interaktion p-Wert									NC
Alter bei Screening									

Time to event of AE is defined as the time from first dose of study treatment to first onset of the respective AE or the time to censoring if the AE has not occurred by 28 days following discontinuation of study treatment, before administration of subsequent cancer therapy or death, whichever comes first. All AEs are coded using MedDRA version 25.1. Includes AEs with onset date on or after the date of first dose and up to and including 28 days following discontinuation of study treatment. Analysis done if >=10 patients at each subgroup level and >=10 events in at least one subgroup level combined for both arms. Analysis done for SOC and PT only if main effect for that SOC or PT is statistically significant at 5% level. [a] Median time to event based on the Kaplan Meier estimate. NE = Not estimable as median (or 95% CLs) is not reached. [b] Estimated from main effects of unstratified Cox proportional hazard model including trt., subgroup and subgroup-by-trt. interaction. Ties handled using Efron method and 95% CI derived from profile likelihood estimation. NC = Not calculable. HR <1 favours Osimertinib+Chemo. * p<0.05.
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Table 4.3.4.5 FLAURA-2: Summary of subgroup analysis of time to first G>=3 PT: Febrile Neutropenie
Safety Analysis Set, DCO 03APR2023

	Osi + Chemo (N=276)			Osi (N=275)					
Subgruppen	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]	Hazard Ratio [b]	[95%-KI] [b]	2-seitiger p-Wert [b]
<65 Jahre	172	8 (4,7)	NE [NE; NE]	164	0	NE [NE; NE]	NC	[NC]	NC
>=65 Jahre	104	3 (2,9)	NE [NE; NE]	111	0	NE [NE; NE]	NC	[NC]	NC
Interaktion p-Wert									NC
Region gPAP									
Asien	168	10 (6,0)	NE [NE; NE]	166	0	NE [NE; NE]	NC	[NC]	NC
Europa	22	1 (4,5)	NE [NE; NE]	23	0	NE [NE; NE]	NC	[NC]	NC
Nordamerika	20	0	NE [NE; NE]	22	0	NE [NE; NE]	NC	[NC]	NC
Rest der Welt	66	0	NE [NE; NE]	64	0	NE [NE; NE]	NC	[NC]	NC
Interaktion p-Wert									NC

Time to event of AE is defined as the time from first dose of study treatment to first onset of the respective AE or the time to censoring if the AE has not occurred by 28 days following discontinuation of study treatment, before administration of subsequent cancer therapy or death, whichever comes first. All AEs are coded using MedDRA version 25.1. Includes AEs with onset date on or after the date of first dose and up to and including 28 days following discontinuation of study treatment. Analysis done if >=10 patients at each subgroup level and >=10 events in at least one subgroup level combined for both arms. Analysis done for SOC and PT only if main effect for that SOC or PT is statistically significant at 5% level. [a] Median time to event based on the Kaplan Meier estimate. NE = Not estimable as median (or 95% CLs) is not reached. [b] Estimated from main effects of unstratified Cox proportional hazard model including trt., subgroup and subgroup-by-trt. interaction. Ties handled using Efron method and 95% CI derived from profile likelihood estimation. NC = Not calculable. HR <1 favours Osimertinib+Chemo. * p<0.05.
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Table 4.3.4.6 FLAURA-2: Summary of subgroup analysis of time to first G>=3 PT: Neutropenie
Safety Analysis Set, DCO 03APR2023

	Osi + Chemo (N=276)			Osi (N=275)					
Subgruppen	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]	Hazard Ratio [b]	[95%-KI] [b]	2-seitiger p-Wert [b]
Abstammung									
Chinesisch/Asiatisch	68	11 (16,2)	NE [NE; NE]	70	0	NE [NE; NE]	NC	[NC]	NC
Nicht-chinesisch/ Asiatisch	107	7 (6,5)	NE [NE; NE]	106	1 (0,9)	NE [NE; NE]	7,22	[1,29;135,02]	0,0219*
Nicht-asiatisch	101	19 (18,8)	NE [NE; NE]	99	1 (1,0)	NE [NE; NE]	20,93	[4,34;375,86]	<0,0001*
Interaktion p-Wert									0,4802
Methode zur Gewebeuntersuchung									
zentral	120	19 (15,8)	NE [NE; NE]	119	1 (0,8)	NE [NE; NE]	20,39	[4,23;366,24]	<0,0001*
lokal	156	18 (11,5)	NE [NE; NE]	156	1 (0,6)	NE [NE; NE]	19,18	[3,96;344,93]	<0,0001*
Interaktion p-Wert									0,9663
WHO Performance-Status									
0	100	9 (9,0)	NE [NE; NE]	100	1 (1,0)	NE [NE; NE]	9,44	[1,77;174,02]	0,0054*
1	176	28 (15,9)	NE [NE; NE]	175	1 (0,6)	NE [NE; NE]	30,28	[6,47;539,64]	<0,0001*
Interaktion p-Wert									0,4362
Raucherstatus									
Ja	90	10 (11,1)	NE [NE; NE]	96	0	NE [NE; NE]	NC	[NC]	NC
Nein	186	27 (14,5)	NE [NE; NE]	179	2 (1,1)	NE [NE; NE]	14,14	[4,24; 87,64]	<0,0001*
Interaktion p-Wert									NC
Geschlecht									
Maennlich	104	7 (6,7)	NE [NE; NE]	107	2 (1,9)	NE [NE; NE]	NC	[NC]	NC
Weiblich	172	30 (17,4)	NE [NE; NE]	168	0	NE [NE; NE]	NC	[NC]	NC
Interaktion p-Wert									NC
Nachweis der EGFR-Mutation durch zentralen ctDNA Cobas Test									
positiv	211	30 (14,2)	NE [NE; NE]	204	1 (0,5)	NE [NE; NE]	31,37	[6,73;558,41]	<0,0001*

Time to event of AE is defined as the time from first dose of study treatment to first onset of the respective AE or the time to censoring if the AE has not occurred by 28 days following discontinuation of study treatment, before administration of subsequent cancer therapy or death, whichever comes first. All AEs are coded using MedDRA version 25.1. Includes AEs with onset date on or after the date of first dose and up to and including 28 days following discontinuation of study treatment. Analysis done if >=10 patients at each subgroup level and >=10 events in at least one subgroup level combined for both arms. Analysis done for SOC and PT only if main effect for that SOC or PT is statistically significant at 5% level. [a] Median time to event based on the Kaplan Meier estimate. NE = Not estimable as median (or 95% CLs) is not reached. [b] Estimated from main effects of unstratified Cox proportional hazard model including trt., subgroup and subgroup-by-trt. interaction. Ties handled using Efron method and 95% CI derived from profile likelihood estimation. NC = Not calculable. HR <1 favours Osimertinib+Chemo. * p<0.05.
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Table 4.3.4.6 FLAURA-2: Summary of subgroup analysis of time to first G>=3 PT: Neutropenie
Safety Analysis Set, DCO 03APR2023

	Osi + Chemo (N=276)			Osi (N=275)					
Subgruppen	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]	Hazard Ratio [b]	[95%-KI] [b]	2-seitiger p-Wert [b]
negativ	41	4 (9,8)	NE [NE; NE]	39	0	NE [NE; NE]	NC	[NC]	NC
unbekannt	24	3 (12,5)	NE [NE; NE]	32	1 (3,1)	NE [NE; NE]	4,14	[0,53; 83,67]	0,1804
Interaktion p-Wert									0,2080
EGFR-Mutationstyp									
Exon 19 Deletion	172	25 (14,5)	NE [NE; NE]	167	1 (0,6)	NE [NE; NE]	26,60	[5,64;475,03]	<0,0001*
Exon 21 (L858R) Substitutionsmutation	104	12 (11,5)	NE [NE; NE]	106	1 (0,9)	NE [NE; NE]	12,69	[2,50;231,12]	0,0007*
Interaktion p-Wert									0,6148
Zentral bestätigte EGFR-Mutation im Gewebe									
positiv	248	34 (13,7)	NE [NE; NE]	238	2 (0,8)	NE [NE; NE]	17,58	[5,36;108,43]	<0,0001*
negativ	3	0	NE [NE; NE]	4	0	NE [NE; NE]	NC	[NC]	NC
unbekannt	25	3 (12,0)	NE [NE; NE]	33	0	NE [NE; NE]	NC	[NC]	NC
Interaktion p-Wert									NC
ZNS-Metastasen zur Baseline									
Ja	113	14 (12,4)	NE [NE; NE]	110	2 (1,8)	NE [NE; NE]	7,18	[2,00; 45,73]	0,0013*
Nein	163	23 (14,1)	NE [NE; NE]	165	0	NE [NE; NE]	NC	[NC]	NC
Interaktion p-Wert									NC
Zentrale Bestätigung der EGFR-Mutation									
Zentral bestätigte EGFR-Mutation in Gewebe oder ctDNA	263	36 (13,7)	NE [NE; NE]	266	2 (0,8)	NE [NE; NE]	19,63	[6,00;120,79]	<0,0001*
Keine zentrale Bestätigung	13	1 (7,7)	NE [NE; NE]	9	0	NE [NE; NE]	NC	[NC]	NC
Interaktion p-Wert									NC
Alter bei Screening									

Time to event of AE is defined as the time from first dose of study treatment to first onset of the respective AE or the time to censoring if the AE has not occurred by 28 days following discontinuation of study treatment, before administration of subsequent cancer therapy or death, whichever comes first. All AEs are coded using MedDRA version 25.1. Includes AEs with onset date on or after the date of first dose and up to and including 28 days following discontinuation of study treatment. Analysis done if >=10 patients at each subgroup level and >=10 events in at least one subgroup level combined for both arms. Analysis done for SOC and PT only if main effect for that SOC or PT is statistically significant at 5% level. [a] Median time to event based on the Kaplan Meier estimate. NE = Not estimable as median (or 95% CLs) is not reached. [b] Estimated from main effects of unstratified Cox proportional hazard model including trt., subgroup and subgroup-by-trt. interaction. Ties handled using Efron method and 95% CI derived from profile likelihood estimation. NC = Not calculable. HR <1 favours Osimertinib+Chemo. * p<0.05.
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Table 4.3.4.6 FLAURA-2: Summary of subgroup analysis of time to first G>=3 PT: Neutropenie
Safety Analysis Set, DCO 03APR2023

	Osi + Chemo (N=276)			Osi (N=275)					
Subgruppen	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]	Hazard Ratio [b]	[95%-KI] [b]	2-seitiger p-Wert [b]
<65 Jahre	172	27 (15,7)	NE [NE; NE]	164	2 (1,2)	NE [NE; NE]	13,69	[4,11; 84,90]	<0,0001*
>=65 Jahre	104	10 (9,6)	NE [NE; NE]	111	0	NE [NE; NE]	NC	[NC]	NC
Interaktion p-Wert									NC
Region gPAP									
Asien	168	17 (10,1)	NE [NE; NE]	166	0	NE [NE; NE]	NC	[NC]	NC
Europa	22	3 (13,6)	NE [NE; NE]	23	0	NE [NE; NE]	NC	[NC]	NC
Nordamerika	20	3 (15,0)	NE [NE; NE]	22	1 (4,5)	NE [NE; NE]	3,47	[0,44; 70,21]	0,2433
Rest der Welt	66	14 (21,2)	NE [NE; NE]	64	1 (1,6)	NE [NE; NE]	15,75	[3,17;285,36]	0,0001*
Interaktion p-Wert									0,3409

Time to event of AE is defined as the time from first dose of study treatment to first onset of the respective AE or the time to censoring if the AE has not occurred by 28 days following discontinuation of study treatment, before administration of subsequent cancer therapy or death, whichever comes first. All AEs are coded using MedDRA version 25.1. Includes AEs with onset date on or after the date of first dose and up to and including 28 days following discontinuation of study treatment. Analysis done if >=10 patients at each subgroup level and >=10 events in at least one subgroup level combined for both arms. Analysis done for SOC and PT only if main effect for that SOC or PT is statistically significant at 5% level. [a] Median time to event based on the Kaplan Meier estimate. NE = Not estimable as median (or 95% CLs) is not reached. [b] Estimated from main effects of unstratified Cox proportional hazard model including trt., subgroup and subgroup-by-trt. interaction. Ties handled using Efron method and 95% CI derived from profile likelihood estimation. NC = Not calculable. HR <1 favours Osimertinib+Chemo. * p<0.05.
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Table 4.3.4.7 FLAURA-2: Summary of subgroup analysis of time to first G>=3 PT: Thrombozytopenie
Safety Analysis Set, DCO 03APR2023

	Osi + Chemo (N=276)			Osi (N=275)					
Subgruppen	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]	Hazard Ratio [b]	[95%-KI] [b]	2-seitiger p-Wert [b]
Abstammung									
Chinesisch/Asiatisch	68	6 (8,8)	NE [NE; NE]	70	1 (1,4)	NE [NE; NE]	6,19	[1,06;116,98]	0,0423*
Nicht-chinesisch/ Asiatisch	107	4 (3,7)	NE [NE; NE]	106	1 (0,9)	NE [NE; NE]	4,07	[0,60; 79,60]	0,1593
Nicht-asiatisch	101	9 (8,9)	NE [NE; NE]	99	1 (1,0)	NE [NE; NE]	9,53	[1,79;175,77]	0,0051*
Interaktion p-Wert									0,8579
Methode zur Gewebeuntersuchung									
zentral	120	10 (8,3)	NE [NE; NE]	119	3 (2,5)	NE [NE; NE]	3,46	[1,06; 15,45]	0,0392*
lokal	156	9 (5,8)	NE [NE; NE]	156	0	NE [NE; NE]	NC	[NC]	NC
Interaktion p-Wert									NC
WHO Performance-Status									
0	100	3 (3,0)	NE [NE; NE]	100	0	NE [NE; NE]	NC	[NC]	NC
1	176	16 (9,1)	NE [NE; NE]	175	3 (1,7)	NE [NE; NE]	5,57	[1,85; 23,93]	0,0013*
Interaktion p-Wert									NC
Raucherstatus									
Ja	90	0	NE [NE; NE]	96	1 (1,0)	NE [NE; NE]	NC	[NC]	NC
Nein	186	19 (10,2)	NE [NE; NE]	179	2 (1,1)	NE [NE; NE]	9,71	[2,82; 60,93]	<0,0001*
Interaktion p-Wert									NC
Geschlecht									
Maennlich	104	4 (3,8)	NE [NE; NE]	107	1 (0,9)	NE [NE; NE]	4,18	[0,62; 81,74]	0,1509
Weiblich	172	15 (8,7)	NE [NE; NE]	168	2 (1,2)	NE [NE; NE]	7,73	[2,18; 49,04]	0,0006*
Interaktion p-Wert									0,6568
Nachweis der EGFR-Mutation durch zentralen ctDNA Cobas Test									
positiv	211	16 (7,6)	NE [NE; NE]	204	3 (1,5)	NE [NE; NE]	5,40	[1,80; 23,24]	0,0016*

Time to event of AE is defined as the time from first dose of study treatment to first onset of the respective AE or the time to censoring if the AE has not occurred by 28 days following discontinuation of study treatment, before administration of subsequent cancer therapy or death, whichever comes first. All AEs are coded using MedDRA version 25.1. Includes AEs with onset date on or after the date of first dose and up to and including 28 days following discontinuation of study treatment. Analysis done if >=10 patients at each subgroup level and >=10 events in at least one subgroup level combined for both arms. Analysis done for SOC and PT only if main effect for that SOC or PT is statistically significant at 5% level. [a] Median time to event based on the Kaplan Meier estimate. NE = Not estimable as median (or 95% CLs) is not reached. [b] Estimated from main effects of unstratified Cox proportional hazard model including trt., subgroup and subgroup-by-trt. interaction. Ties handled using Efron method and 95% CI derived from profile likelihood estimation. NC = Not calculable. HR <1 favours Osimertinib+Chemo. * p<0.05.
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Table 4.3.4.7 FLAURA-2: Summary of subgroup analysis of time to first G>=3 PT: Thrombozytopenie
Safety Analysis Set, DCO 03APR2023

	Osi + Chemo (N=276)			Osi (N=275)					
Subgruppen	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]	Hazard Ratio [b]	[95%-KI] [b]	2-seitiger p-Wert [b]
negativ	41	2 (4,9)	NE [NE; NE]	39	0	NE [NE; NE]	NC	[NC]	NC
unbekannt	24	1 (4,2)	NE [NE; NE]	32	0	NE [NE; NE]	NC	[NC]	NC
Interaktion p-Wert									NC
EGFR-Mutationstyp									
Exon 19 Deletion	172	11 (6,4)	NE [NE; NE]	167	1 (0,6)	NE [NE; NE]	11,23	[2,18;205,21]	0,0016*
Exon 21 (L858R) Substitutionsmutation	104	8 (7,7)	NE [NE; NE]	106	2 (1,9)	NE [NE; NE]	4,17	[1,04; 27,59]	0,0428*
Interaktion p-Wert									0,4353
Zentral bestätigte EGFR-Mutation im Gewebe									
positiv	248	16 (6,5)	NE [NE; NE]	238	3 (1,3)	NE [NE; NE]	5,31	[1,77; 22,85]	0,0018*
negativ	3	0	NE [NE; NE]	4	0	NE [NE; NE]	NC	[NC]	NC
unbekannt	25	3 (12,0)	NE [NE; NE]	33	0	NE [NE; NE]	NC	[NC]	NC
Interaktion p-Wert									NC
ZNS-Metastasen zur Baseline									
Ja	113	8 (7,1)	NE [NE; NE]	110	2 (1,8)	NE [NE; NE]	4,02	[1,01; 26,61]	0,0489*
Nein	163	11 (6,7)	NE [NE; NE]	165	1 (0,6)	NE [NE; NE]	11,64	[2,26;212,77]	0,0013*
Interaktion p-Wert									0,4019
Zentrale Bestätigung der EGFR-Mutation									
Zentral bestätigte EGFR-Mutation in Gewebe oder ctDNA	263	17 (6,5)	NE [NE; NE]	266	3 (1,1)	NE [NE; NE]	5,95	[2,00; 25,51]	0,0007*
Keine zentrale Bestätigung	13	2 (15,4)	NE [NE; NE]	9	0	NE [NE; NE]	NC	[NC]	NC
Interaktion p-Wert									NC
Alter bei Screening									

Time to event of AE is defined as the time from first dose of study treatment to first onset of the respective AE or the time to censoring if the AE has not occurred by 28 days following discontinuation of study treatment, before administration of subsequent cancer therapy or death, whichever comes first. All AEs are coded using MedDRA version 25.1. Includes AEs with onset date on or after the date of first dose and up to and including 28 days following discontinuation of study treatment. Analysis done if >=10 patients at each subgroup level and >=10 events in at least one subgroup level combined for both arms. Analysis done for SOC and PT only if main effect for that SOC or PT is statistically significant at 5% level. [a] Median time to event based on the Kaplan Meier estimate. NE = Not estimable as median (or 95% CLs) is not reached. [b] Estimated from main effects of unstratified Cox proportional hazard model including trt., subgroup and subgroup-by-trt. interaction. Ties handled using Efron method and 95% CI derived from profile likelihood estimation. NC = Not calculable. HR <1 favours Osimertinib+Chemo. * p<0.05.
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Table 4.3.4.7 FLAURA-2: Summary of subgroup analysis of time to first G>=3 PT: Thrombozytopenie
Safety Analysis Set, DCO 03APR2023

	Osi + Chemo (N=276)			Osi (N=275)					
Subgruppen	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]	Hazard Ratio [b]	[95%-KI] [b]	2-seitiger p-Wert [b]
<65 Jahre	172	10 (5,8)	NE [NE; NE]	164	2 (1,2)	NE [NE; NE]	4,85	[1,28; 31,57]	0,0181*
>=65 Jahre	104	9 (8,7)	NE [NE; NE]	111	1 (0,9)	NE [NE; NE]	10,36	[1,95;191,19]	0,0035*
Interaktion p-Wert									0,5518
Region gPAP									
Asien	168	10 (6,0)	NE [NE; NE]	166	2 (1,2)	NE [NE; NE]	5,04	[1,33; 32,79]	0,0153*
Europa	22	4 (18,2)	NE [NE; NE]	23	0	NE [NE; NE]	NC	[NC]	NC
Nordamerika	20	1 (5,0)	NE [NE; NE]	22	0	NE [NE; NE]	NC	[NC]	NC
Rest der Welt	66	4 (6,1)	NE [NE; NE]	64	1 (1,6)	NE [NE; NE]	4,17	[0,62; 81,58]	0,1516
Interaktion p-Wert									0,8902

Time to event of AE is defined as the time from first dose of study treatment to first onset of the respective AE or the time to censoring if the AE has not occurred by 28 days following discontinuation of study treatment, before administration of subsequent cancer therapy or death, whichever comes first. All AEs are coded using MedDRA version 25.1. Includes AEs with onset date on or after the date of first dose and up to and including 28 days following discontinuation of study treatment. Analysis done if >=10 patients at each subgroup level and >=10 events in at least one subgroup level combined for both arms. Analysis done for SOC and PT only if main effect for that SOC or PT is statistically significant at 5% level. [a] Median time to event based on the Kaplan Meier estimate. NE = Not estimable as median (or 95% CLs) is not reached. [b] Estimated from main effects of unstratified Cox proportional hazard model including trt., subgroup and subgroup-by-trt. interaction. Ties handled using Efron method and 95% CI derived from profile likelihood estimation. NC = Not calculable. HR <1 favours Osimertinib+Chemo. * p<0.05.
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Table 4.3.4.8 FLAURA-2: Summary of subgroup analysis of time to first G>=3 SOC: Erkrankungen des Gastrointestinaltrakts
Safety Analysis Set, DCO 03APR2023

	Osi + Chemo (N=276)			Osi (N=275)					
Subgruppen	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]	Hazard Ratio [b]	[95%-KI] [b]	2-seitiger p-Wert [b]
Abstammung									
Chinesisch/Asiatisch	68	1 (1,5)	NE [NE; NE]	70	1 (1,4)	NE [NE; NE]	0,96	[0,04; 24,39]	0,9799
Nicht-chinesisch/ Asiatisch	107	12 (11,2)	NE [NE; NE]	106	2 (1,9)	NE [NE; NE]	6,47	[1,76; 41,55]	0,0032*
Nicht-asiatisch	101	7 (6,9)	NE [NE; NE]	99	1 (1,0)	NE [NE; NE]	6,80	[1,21;127,03]	0,0271*
Interaktion p-Wert									0,4893
Methode zur Gewebeuntersuchung									
zentral	120	6 (5,0)	NE [NE; NE]	119	2 (1,7)	NE [NE; NE]	2,95	[0,68; 20,15]	0,1544
lokal	156	14 (9,0)	NE [NE; NE]	156	2 (1,3)	NE [NE; NE]	7,20	[2,01; 45,87]	0,0012*
Interaktion p-Wert									0,4259
WHO Performance-Status									
0	100	7 (7,0)	NE [NE; NE]	100	0	NE [NE; NE]	NC	[NC]	NC
1	176	13 (7,4)	NE [NE; NE]	175	4 (2,3)	NE [NE; NE]	3,16	[1,12; 11,21]	0,0294*
Interaktion p-Wert									NC
Raucherstatus									
Ja	90	9 (10,0)	NE [NE; NE]	96	2 (2,1)	NE [NE; NE]	4,95	[1,27; 32,46]	0,0190*
Nein	186	11 (5,9)	NE [NE; NE]	179	2 (1,1)	NE [NE; NE]	5,32	[1,43; 34,41]	0,0104*
Interaktion p-Wert									0,9466
Geschlecht									
Maennlich	104	7 (6,7)	NE [NE; NE]	107	3 (2,8)	NE [NE; NE]	2,33	[0,65; 10,83]	0,1997
Weiblich	172	13 (7,6)	NE [NE; NE]	168	1 (0,6)	NE [NE; NE]	13,18	[2,63;239,52]	0,0004*
Interaktion p-Wert									0,1342
Nachweis der EGFR-Mutation durch zentralen ctDNA Cobas Test									
positiv	211	13 (6,2)	NE [NE; NE]	204	3 (1,5)	NE [NE; NE]	4,31	[1,39; 18,80]	0,0097*

Time to event of AE is defined as the time from first dose of study treatment to first onset of the respective AE or the time to censoring if the AE has not occurred by 28 days following discontinuation of study treatment, before administration of subsequent cancer therapy or death, whichever comes first. All AEs are coded using MedDRA version 25.1. Includes AEs with onset date on or after the date of first dose and up to and including 28 days following discontinuation of study treatment. Analysis done if >=10 patients at each subgroup level and >=10 events in at least one subgroup level combined for both arms. Analysis done for SOC and PT only if main effect for that SOC or PT is statistically significant at 5% level. [a] Median time to event based on the Kaplan Meier estimate. NE = Not estimable as median (or 95% CLs) is not reached. [b] Estimated from main effects of unstratified Cox proportional hazard model including trt., subgroup and subgroup-by-trt. interaction. Ties handled using Efron method and 95% CI derived from profile likelihood estimation. NC = Not calculable. HR <1 favours Osimertinib+Chemo. * p<0.05.
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Table 4.3.4.8 FLAURA-2: Summary of subgroup analysis of time to first G>=3 SOC: Erkrankungen des Gastrointestinaltrakts
Safety Analysis Set, DCO 03APR2023

	Osi + Chemo (N=276)			Osi (N=275)					
Subgruppen	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]	Hazard Ratio [b]	[95%-KI] [b]	2-seitiger p-Wert [b]
negativ	41	4 (9,8)	NE [NE; NE]	39	1 (2,6)	NE [NE; NE]	3,97	[0,59; 77,70]	0,1672
unbekannt	24	3 (12,5)	NE [NE; NE]	32	0	NE [NE; NE]	NC	[NC]	NC
Interaktion p-Wert									0,9499
EGFR-Mutationstyp									
Exon 19 Deletion	172	11 (6,4)	NE [NE; NE]	167	1 (0,6)	NE [NE; NE]	10,92	[2,12;199,59]	0,0019*
Exon 21 (L858R) Substitutionsmutation	104	9 (8,7)	NE [NE; NE]	106	3 (2,8)	NE [NE; NE]	3,06	[0,91; 13,79]	0,0714
Interaktion p-Wert									0,2743
Zentral bestätigte EGFR-Mutation im Gewebe									
positiv	248	18 (7,3)	NE [NE; NE]	238	3 (1,3)	NE [NE; NE]	5,84	[1,98; 24,93]	0,0007*
negativ	3	1 (33,3)	NE [NE; NE]	4	0	NE [NE; NE]	NC	[NC]	NC
unbekannt	25	1 (4,0)	NE [NE; NE]	33	1 (3,0)	NE [NE; NE]	1,33	[0,05; 33,65]	0,8397
Interaktion p-Wert									0,3499
ZNS-Metastasen zur Baseline									
Ja	113	4 (3,5)	NE [NE; NE]	110	1 (0,9)	NE [NE; NE]	3,66	[0,54; 71,56]	0,1965
Nein	163	16 (9,8)	NE [NE; NE]	165	3 (1,8)	NE [NE; NE]	5,75	[1,92; 24,72]	0,0010*
Interaktion p-Wert									0,7313
Zentrale Bestätigung der EGFR-Mutation									
Zentral bestätigte EGFR-Mutation in Gewebe oder ctDNA	263	19 (7,2)	NE [NE; NE]	266	4 (1,5)	NE [NE; NE]	4,87	[1,83; 16,80]	0,0009*
Keine zentrale Bestätigung	13	1 (7,7)	NE [NE; NE]	9	0	NE [NE; NE]	NC	[NC]	NC
Interaktion p-Wert									NC
Alter bei Screening									

Time to event of AE is defined as the time from first dose of study treatment to first onset of the respective AE or the time to censoring if the AE has not occurred by 28 days following discontinuation of study treatment, before administration of subsequent cancer therapy or death, whichever comes first. All AEs are coded using MedDRA version 25.1. Includes AEs with onset date on or after the date of first dose and up to and including 28 days following discontinuation of study treatment. Analysis done if >=10 patients at each subgroup level and >=10 events in at least one subgroup level combined for both arms. Analysis done for SOC and PT only if main effect for that SOC or PT is statistically significant at 5% level. [a] Median time to event based on the Kaplan Meier estimate. NE = Not estimable as median (or 95% CLs) is not reached. [b] Estimated from main effects of unstratified Cox proportional hazard model including trt., subgroup and subgroup-by-trt. interaction. Ties handled using Efron method and 95% CI derived from profile likelihood estimation. NC = Not calculable. HR <1 favours Osimertinib+Chemo. * p<0.05.
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Table 4.3.4.8 FLAURA-2: Summary of subgroup analysis of time to first G>=3 SOC: Erkrankungen des Gastrointestinaltrakts
Safety Analysis Set, DCO 03APR2023

	Osi + Chemo (N=276)			Osi (N=275)					
Subgruppen	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]	Hazard Ratio [b]	[95%-KI] [b]	2-seitiger p-Wert [b]
<65 Jahre	172	12 (7,0)	NE [NE; NE]	164	1 (0,6)	NE [NE; NE]	11,20	[2,21;204,06]	0,0014*
>=65 Jahre	104	8 (7,7)	NE [NE; NE]	111	3 (2,7)	NE [NE; NE]	3,07	[0,89; 14,00]	0,0778
Interaktion p-Wert									0,2665
Region gPAP									
Asien	168	12 (7,1)	NE [NE; NE]	166	3 (1,8)	NE [NE; NE]	4,02	[1,28; 17,64]	0,0158*
Europa	22	2 (9,1)	NE [NE; NE]	23	0	NE [NE; NE]	NC	[NC]	NC
Nordamerika	20	1 (5,0)	NE [NE; NE]	22	0	NE [NE; NE]	NC	[NC]	NC
Rest der Welt	66	5 (7,6)	NE [NE; NE]	64	1 (1,6)	NE [NE; NE]	4,81	[0,77; 92,10]	0,0970
Interaktion p-Wert									0,8868

Time to event of AE is defined as the time from first dose of study treatment to first onset of the respective AE or the time to censoring if the AE has not occurred by 28 days following discontinuation of study treatment, before administration of subsequent cancer therapy or death, whichever comes first. All AEs are coded using MedDRA version 25.1. Includes AEs with onset date on or after the date of first dose and up to and including 28 days following discontinuation of study treatment. Analysis done if >=10 patients at each subgroup level and >=10 events in at least one subgroup level combined for both arms. Analysis done for SOC and PT only if main effect for that SOC or PT is statistically significant at 5% level. [a] Median time to event based on the Kaplan Meier estimate. NE = Not estimable as median (or 95% CLs) is not reached. [b] Estimated from main effects of unstratified Cox proportional hazard model including trt., subgroup and subgroup-by-trt. interaction. Ties handled using Efron method and 95% CI derived from profile likelihood estimation. NC = Not calculable. HR <1 favours Osimertinib+Chemo. * p<0.05.
root/cdar/d516/payer_germany/ar/d5169c00001_payer_germany/tlf/prod/program/ttesubae.sas gttesubaedah 22DEC2023:09:13 kfrh585

Table 4.3.4.9 FLAURA-2: Summary of subgroup analysis of time to first G>=3 SOC: Untersuchungen
Safety Analysis Set, DCO 03APR2023

	Osi + Chemo (N=276)			Osi (N=275)					
Subgruppen	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]	Hazard Ratio [b]	[95%-KI] [b]	2-seitiger p-Wert [b]
Abstammung									
Chinesisch/Asiatisch	68	32 (47,1)	NE [NE; NE]	70	7 (10,0)	NE [NE; NE]	5,80	[2,72; 14,33]	<0,0001*
Nicht-chinesisch/ Asiatisch	107	19 (17,8)	NE [NE; NE]	106	4 (3,8)	NE [NE; NE]	5,12	[1,93; 17,68]	0,0006*
Nicht-asiatisch	101	11 (10,9)	NE [NE; NE]	99	5 (5,1)	NE [NE; NE]	2,22	[0,81; 7,04]	0,1246
Interaktion p-Wert									0,3680
Methode zur Gewebeuntersuchung									
zentral	120	32 (26,7)	NE [NE; NE]	119	8 (6,7)	NE [NE; NE]	4,57	[2,21; 10,66]	<0,0001*
lokal	156	30 (19,2)	NE [NE; NE]	156	8 (5,1)	NE [NE; NE]	3,96	[1,91; 9,28]	0,0001*
Interaktion p-Wert									0,7992
WHO Performance-Status									
0	100	22 (22,0)	NE [NE; NE]	100	3 (3,0)	NE [NE; NE]	8,19	[2,84; 34,59]	<0,0001*
1	176	40 (22,7)	NE [NE; NE]	175	13 (7,4)	NE [NE; NE]	3,32	[1,82; 6,45]	<0,0001*
Interaktion p-Wert									0,1664
Raucherstatus									
Ja	90	20 (22,2)	NE [NE; NE]	96	4 (4,2)	NE [NE; NE]	5,68	[2,15; 19,55]	0,0002*
Nein	186	42 (22,6)	NE [NE; NE]	179	12 (6,7)	NE [NE; NE]	3,75	[2,04; 7,44]	<0,0001*
Interaktion p-Wert									0,5047
Geschlecht									
Maennlich	104	22 (21,2)	NE [NE; NE]	107	7 (6,5)	NE [NE; NE]	3,35	[1,50; 8,48]	0,0025*
Weiblich	172	40 (23,3)	NE [NE; NE]	168	9 (5,4)	NE [NE; NE]	4,92	[2,50; 10,83]	<0,0001*
Interaktion p-Wert									0,5027
Nachweis der EGFR-Mutation durch zentralen ctDNA Cobas Test									
positiv	211	51 (24,2)	NE [NE; NE]	204	10 (4,9)	NE [NE; NE]	5,58	[2,96; 11,66]	<0,0001*

Time to event of AE is defined as the time from first dose of study treatment to first onset of the respective AE or the time to censoring if the AE has not occurred by 28 days following discontinuation of study treatment, before administration of subsequent cancer therapy or death, whichever comes first. All AEs are coded using MedDRA version 25.1. Includes AEs with onset date on or after the date of first dose and up to and including 28 days following discontinuation of study treatment. Analysis done if >=10 patients at each subgroup level and >=10 events in at least one subgroup level combined for both arms. Analysis done for SOC and PT only if main effect for that SOC or PT is statistically significant at 5% level. [a] Median time to event based on the Kaplan Meier estimate. NE = Not estimable as median (or 95% CLs) is not reached. [b] Estimated from main effects of unstratified Cox proportional hazard model including trt., subgroup and subgroup-by-trt. interaction. Ties handled using Efron method and 95% CI derived from profile likelihood estimation. NC = Not calculable. HR <1 favours Osimertinib+Chemo. * p<0.05.
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Table 4.3.4.9 FLAURA-2: Summary of subgroup analysis of time to first G>=3 SOC: Untersuchungen
Safety Analysis Set, DCO 03APR2023

	Osi + Chemo (N=276)			Osi (N=275)					
Subgruppen	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]	Hazard Ratio [b]	[95%-KI] [b]	2-seitiger p-Wert [b]
negativ	41	7 (17,1)	NE [NE; NE]	39	3 (7,7)	NE [NE; NE]	2,33	[0,65; 10,80]	0,2012
unbekannt	24	4 (16,7)	NE [NE; NE]	32	3 (9,4)	NE [NE; NE]	1,67	[0,37; 8,46]	0,5012
Interaktion p-Wert									0,2536
EGFR-Mutationstyp									
Exon 19 Deletion	172	32 (18,6)	NE [NE; NE]	167	12 (7,2)	NE [NE; NE]	2,84	[1,50; 5,75]	0,0010*
Exon 21 (L858R) Substitutionsmutation	104	30 (28,8)	NE [NE; NE]	106	4 (3,8)	NE [NE; NE]	8,39	[3,31; 28,28]	<0,0001*
Interaktion p-Wert									0,0710
Zentral bestätigte EGFR-Mutation im Gewebe									
positiv	248	56 (22,6)	NE [NE; NE]	238	13 (5,5)	NE [NE; NE]	4,53	[2,56; 8,66]	<0,0001*
negativ	3	1 (33,3)	NE [NE; NE]	4	1 (25,0)	NE [NE; NE]	NC	[NC]	NC
unbekannt	25	5 (20,0)	NE [NE; NE]	33	2 (6,1)	NE [NE; NE]	3,64	[0,78; 25,39]	0,1006
Interaktion p-Wert									0,8071
ZNS-Metastasen zur Baseline									
Ja	113	30 (26,5)	NE [NE; NE]	110	7 (6,4)	NE [NE; NE]	4,47	[2,08; 11,08]	<0,0001*
Nein	163	32 (19,6)	NE [NE; NE]	165	9 (5,5)	NE [NE; NE]	4,00	[1,99; 8,91]	<0,0001*
Interaktion p-Wert									0,8440
Zentrale Bestätigung der EGFR-Mutation									
Zentral bestätigte EGFR-Mutation in Gewebe oder ctDNA	263	61 (23,2)	NE [NE; NE]	266	14 (5,3)	NE [NE; NE]	4,88	[2,81; 9,08]	<0,0001*
Keine zentrale Bestätigung	13	1 (7,7)	NE [NE; NE]	9	2 (22,2)	NE [NE; NE]	0,29	[0,01; 3,03]	0,2940
Interaktion p-Wert									0,0235*
Alter bei Screening									

Time to event of AE is defined as the time from first dose of study treatment to first onset of the respective AE or the time to censoring if the AE has not occurred by 28 days following discontinuation of study treatment, before administration of subsequent cancer therapy or death, whichever comes first. All AEs are coded using MedDRA version 25.1. Includes AEs with onset date on or after the date of first dose and up to and including 28 days following discontinuation of study treatment. Analysis done if >=10 patients at each subgroup level and >=10 events in at least one subgroup level combined for both arms. Analysis done for SOC and PT only if main effect for that SOC or PT is statistically significant at 5% level. [a] Median time to event based on the Kaplan Meier estimate. NE = Not estimable as median (or 95% CLs) is not reached. [b] Estimated from main effects of unstratified Cox proportional hazard model including trt., subgroup and subgroup-by-trt. interaction. Ties handled using Efron method and 95% CI derived from profile likelihood estimation. NC = Not calculable. HR <1 favours Osimertinib+Chemo. * p<0.05.
root/cdar/d516/payer_germany/ar/d5169c00001_payer_germany/tlf/prod/program/ttesubae.sas gttesubaedai 22DEC2023:09:13 kfrh585

Table 4.3.4.9 FLAURA-2: Summary of subgroup analysis of time to first G>=3 SOC: Untersuchungen
Safety Analysis Set, DCO 03APR2023

	Osi + Chemo (N=276)			Osi (N=275)					
Subgruppen	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]	Hazard Ratio [b]	[95%-KI] [b]	2-seitiger p-Wert [b]
<65 Jahre	172	38 (22,1)	NE [NE; NE]	164	8 (4,9)	NE [NE; NE]	4,85	[2,39; 11,20]	<0,0001*
>=65 Jahre	104	24 (23,1)	NE [NE; NE]	111	8 (7,2)	NE [NE; NE]	3,66	[1,72; 8,71]	0,0006*
Interaktion p-Wert									0,6186
Region gPAP									
Asien	168	49 (29,2)	NE [NE; NE]	166	10 (6,0)	NE [NE; NE]	5,51	[2,92; 11,55]	<0,0001*
Europa	22	1 (4,5)	NE [NE; NE]	23	2 (8,7)	NE [NE; NE]	0,49	[0,02; 5,12]	0,5490
Nordamerika	20	4 (20,0)	NE [NE; NE]	22	1 (4,5)	NE [NE; NE]	5,20	[0,77;101,65]	0,0943
Rest der Welt	66	8 (12,1)	NE [NE; NE]	64	3 (4,7)	NE [NE; NE]	2,67	[0,77; 12,19]	0,1242
Interaktion p-Wert									0,2258

Time to event of AE is defined as the time from first dose of study treatment to first onset of the respective AE or the time to censoring if the AE has not occurred by 28 days following discontinuation of study treatment, before administration of subsequent cancer therapy or death, whichever comes first. All AEs are coded using MedDRA version 25.1. Includes AEs with onset date on or after the date of first dose and up to and including 28 days following discontinuation of study treatment. Analysis done if >=10 patients at each subgroup level and >=10 events in at least one subgroup level combined for both arms. Analysis done for SOC and PT only if main effect for that SOC or PT is statistically significant at 5% level. [a] Median time to event based on the Kaplan Meier estimate. NE = Not estimable as median (or 95% CLs) is not reached. [b] Estimated from main effects of unstratified Cox proportional hazard model including trt., subgroup and subgroup-by-trt. interaction. Ties handled using Efron method and 95% CI derived from profile likelihood estimation. NC = Not calculable. HR <1 favours Osimertinib+Chemo. * p<0.05.
root/cdar/d516/payer_germany/ar/d5169c00001_payer_germany/tlf/prod/program/ttesubae.sas gttesubaedai 22DEC2023:09:13 kfrh585

Table 4.3.4.10 FLAURA-2: Summary of subgroup analysis of time to first G>=3 PT: Neutrophilenzahl erniedrigt
Safety Analysis Set, DCO 03APR2023

	Osi + Chemo (N=276)			Osi (N=275)					
Subgruppen	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]	Hazard Ratio [b]	[95%-KI] [b]	2-seitiger p-Wert [b]
Abstammung									
Chinesisch/Asiatisch	68	23 (33,8)	NE [NE; NE]	70	2 (2,9)	NE [NE; NE]	13,05	[3,86; 81,30]	<0,0001*
Nicht-chinesisch/ Asiatisch	107	7 (6,5)	NE [NE; NE]	106	0	NE [NE; NE]	NC	[NC]	NC
Nicht-asiatisch	101	1 (1,0)	NE [NE; NE]	99	0	NE [NE; NE]	NC	[NC]	NC
Interaktion p-Wert									NC
Methode zur Gewebeuntersuchung									
zentral	120	20 (16,7)	NE [NE; NE]	119	1 (0,8)	NE [NE; NE]	21,50	[4,48;385,66]	<0,0001*
lokal	156	11 (7,1)	NE [NE; NE]	156	1 (0,6)	NE [NE; NE]	11,06	[2,15;202,00]	0,0017*
Interaktion p-Wert									0,6518
WHO Performance-Status									
0	100	12 (12,0)	NE [NE; NE]	100	0	NE [NE; NE]	NC	[NC]	NC
1	176	19 (10,8)	NE [NE; NE]	175	2 (1,1)	NE [NE; NE]	9,78	[2,84; 61,37]	<0,0001*
Interaktion p-Wert									NC
Raucherstatus									
Ja	90	7 (7,8)	NE [NE; NE]	96	0	NE [NE; NE]	NC	[NC]	NC
Nein	186	24 (12,9)	NE [NE; NE]	179	2 (1,1)	NE [NE; NE]	12,16	[3,61; 75,68]	<0,0001*
Interaktion p-Wert									NC
Geschlecht									
Maennlich	104	9 (8,7)	NE [NE; NE]	107	1 (0,9)	NE [NE; NE]	9,06	[1,70;167,03]	0,0065*
Weiblich	172	22 (12,8)	NE [NE; NE]	168	1 (0,6)	NE [NE; NE]	23,10	[4,86;414,12]	<0,0001*
Interaktion p-Wert									0,5290
Nachweis der EGFR-Mutation durch zentralen ctDNA Cobas Test									
positiv	211	27 (12,8)	NE [NE; NE]	204	0	NE [NE; NE]	NC	[NC]	NC

Time to event of AE is defined as the time from first dose of study treatment to first onset of the respective AE or the time to censoring if the AE has not occurred by 28 days following discontinuation of study treatment, before administration of subsequent cancer therapy or death, whichever comes first. All AEs are coded using MedDRA version 25.1. Includes AEs with onset date on or after the date of first dose and up to and including 28 days following discontinuation of study treatment. Analysis done if >=10 patients at each subgroup level and >=10 events in at least one subgroup level combined for both arms. Analysis done for SOC and PT only if main effect for that SOC or PT is statistically significant at 5% level. [a] Median time to event based on the Kaplan Meier estimate. NE = Not estimable as median (or 95% CLs) is not reached. [b] Estimated from main effects of unstratified Cox proportional hazard model including trt., subgroup and subgroup-by-trt. interaction. Ties handled using Efron method and 95% CI derived from profile likelihood estimation. NC = Not calculable. HR <1 favours Osimertinib+Chemo. * p<0.05.
root/cdar/d516/payer_germany/ar/d5169c00001_payer_germany/tlf/prod/program/ttesubae.sas gttesubaedaj 22DEC2023:09:13 kfrh585

Table 4.3.4.10 FLAURA-2: Summary of subgroup analysis of time to first G>=3 PT: Neutrophilenzahl erniedrigt
Safety Analysis Set, DCO 03APR2023

	Osi + Chemo (N=276)			Osi (N=275)					
Subgruppen	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]	Hazard Ratio [b]	[95%-KI] [b]	2-seitiger p-Wert [b]
negativ	41	2 (4,9)	NE [NE; NE]	39	1 (2,6)	NE [NE; NE]	NC	[NC]	NC
unbekannt	24	2 (8,3)	NE [NE; NE]	32	1 (3,1)	NE [NE; NE]	NC	[NC]	NC
Interaktion p-Wert									NC
EGFR-Mutationstyp									
Exon 19 Deletion	172	14 (8,1)	NE [NE; NE]	167	1 (0,6)	NE [NE; NE]	14,18	[2,85;256,90]	0,0002*
Exon 21 (L858R) Substitutionsmutation	104	17 (16,3)	NE [NE; NE]	106	1 (0,9)	NE [NE; NE]	17,89	[3,68;322,22]	<0,0001*
Interaktion p-Wert									0,8737
Zentral bestätigte EGFR-Mutation im Gewebe									
positiv	248	31 (12,5)	NE [NE; NE]	238	1 (0,4)	NE [NE; NE]	31,14	[6,69;554,18]	<0,0001*
negativ	3	0	NE [NE; NE]	4	0	NE [NE; NE]	NC	[NC]	NC
unbekannt	25	0	NE [NE; NE]	33	1 (3,0)	NE [NE; NE]	NC	[NC]	NC
Interaktion p-Wert									NC
ZNS-Metastasen zur Baseline									
Ja	113	16 (14,2)	NE [NE; NE]	110	1 (0,9)	NE [NE; NE]	15,92	[3,25;287,28]	<0,0001*
Nein	163	15 (9,2)	NE [NE; NE]	165	1 (0,6)	NE [NE; NE]	15,90	[3,22;287,57]	<0,0001*
Interaktion p-Wert									<0,0001*
Zentrale Bestätigung der EGFR-Mutation									
Zentral bestätigte EGFR-Mutation in Gewebe oder ctDNA	263	31 (11,8)	NE [NE; NE]	266	1 (0,4)	NE [NE; NE]	32,80	[7,05;583,57]	<0,0001*
Keine zentrale Bestätigung	13	0	NE [NE; NE]	9	1 (11,1)	NE [NE; NE]	NC	[NC]	NC
Interaktion p-Wert									NC
Alter bei Screening									

Time to event of AE is defined as the time from first dose of study treatment to first onset of the respective AE or the time to censoring if the AE has not occurred by 28 days following discontinuation of study treatment, before administration of subsequent cancer therapy or death, whichever comes first. All AEs are coded using MedDRA version 25.1. Includes AEs with onset date on or after the date of first dose and up to and including 28 days following discontinuation of study treatment. Analysis done if >=10 patients at each subgroup level and >=10 events in at least one subgroup level combined for both arms. Analysis done for SOC and PT only if main effect for that SOC or PT is statistically significant at 5% level. [a] Median time to event based on the Kaplan Meier estimate. NE = Not estimable as median (or 95% CLs) is not reached. [b] Estimated from main effects of unstratified Cox proportional hazard model including trt., subgroup and subgroup-by-trt. interaction. Ties handled using Efron method and 95% CI derived from profile likelihood estimation. NC = Not calculable. HR <1 favours Osimertinib+Chemo. * p<0.05.
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Table 4.3.4.10 FLAURA-2: Summary of subgroup analysis of time to first G>=3 PT: Neutrophilenzahl erniedrigt
Safety Analysis Set, DCO 03APR2023

	Osi + Chemo (N=276)			Osi (N=275)					
Subgruppen	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]	Hazard Ratio [b]	[95%-KI] [b]	2-seitiger p-Wert [b]
<65 Jahre	172	20 (11,6)	NE [NE; NE]	164	2 (1,2)	NE [NE; NE]	9,58	[2,79; 59,97]	<0,0001*
>=65 Jahre	104	11 (10,6)	NE [NE; NE]	111	0	NE [NE; NE]	NC	[NC]	NC
Interaktion p-Wert									NC
Region gPAP									
Asien	168	29 (17,3)	NE [NE; NE]	166	1 (0,6)	NE [NE; NE]	30,41	[6,51;541,70]	<0,0001*
Europa	22	1 (4,5)	NE [NE; NE]	23	0	NE [NE; NE]	NC	[NC]	NC
Nordamerika	20	1 (5,0)	NE [NE; NE]	22	1 (4,5)	NE [NE; NE]	1,18	[0,05; 29,85]	0,9064
Rest der Welt	66	0	NE [NE; NE]	64	0	NE [NE; NE]	NC	[NC]	NC
Interaktion p-Wert									0,0730

Time to event of AE is defined as the time from first dose of study treatment to first onset of the respective AE or the time to censoring if the AE has not occurred by 28 days following discontinuation of study treatment, before administration of subsequent cancer therapy or death, whichever comes first. All AEs are coded using MedDRA version 25.1. Includes AEs with onset date on or after the date of first dose and up to and including 28 days following discontinuation of study treatment. Analysis done if >=10 patients at each subgroup level and >=10 events in at least one subgroup level combined for both arms. Analysis done for SOC and PT only if main effect for that SOC or PT is statistically significant at 5% level. [a] Median time to event based on the Kaplan Meier estimate. NE = Not estimable as median (or 95% CLs) is not reached. [b] Estimated from main effects of unstratified Cox proportional hazard model including trt., subgroup and subgroup-by-trt. interaction. Ties handled using Efron method and 95% CI derived from profile likelihood estimation. NC = Not calculable. HR <1 favours Osimertinib+Chemo. * p<0.05.
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Table 4.3.4.11 FLAURA-2: Summary of subgroup analysis of time to first G>=3 PT: Thrombozytenzahl vermindert
Safety Analysis Set, DCO 03APR2023

	Osi + Chemo (N=276)			Osi (N=275)					
Subgruppen	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]	Hazard Ratio [b]	[95%-KI] [b]	2-seitiger p-Wert [b]
Abstammung									
Chinesisch/Asiatisch	68	16 (23,5)	NE [NE; NE]	70	0	NE [NE; NE]	NC	[NC]	NC
Nicht-chinesisch/ Asiatisch	107	4 (3,7)	NE [NE; NE]	106	0	NE [NE; NE]	NC	[NC]	NC
Nicht-asiatisch	101	1 (1,0)	NE [NE; NE]	99	0	NE [NE; NE]	NC	[NC]	NC
Interaktion p-Wert									NC
Methode zur Gewebeuntersuchung									
zentral	120	15 (12,5)	NE [NE; NE]	119	0	NE [NE; NE]	NC	[NC]	NC
lokal	156	6 (3,8)	NE [NE; NE]	156	0	NE [NE; NE]	NC	[NC]	NC
Interaktion p-Wert									NC
WHO Performance-Status									
0	100	6 (6,0)	NE [NE; NE]	100	0	NE [NE; NE]	NC	[NC]	NC
1	176	15 (8,5)	NE [NE; NE]	175	0	NE [NE; NE]	NC	[NC]	NC
Interaktion p-Wert									NC
Raucherstatus									
Ja	90	5 (5,6)	NE [NE; NE]	96	0	NE [NE; NE]	NC	[NC]	NC
Nein	186	16 (8,6)	NE [NE; NE]	179	0	NE [NE; NE]	NC	[NC]	NC
Interaktion p-Wert									NC
Geschlecht									
Maennlich	104	9 (8,7)	NE [NE; NE]	107	0	NE [NE; NE]	NC	[NC]	NC
Weiblich	172	12 (7,0)	NE [NE; NE]	168	0	NE [NE; NE]	NC	[NC]	NC
Interaktion p-Wert									NC
Nachweis der EGFR-Mutation durch zentralen ctDNA Cobas Test									
positiv	211	19 (9,0)	NE [NE; NE]	204	0	NE [NE; NE]	NC	[NC]	NC

Time to event of AE is defined as the time from first dose of study treatment to first onset of the respective AE or the time to censoring if the AE has not occurred by 28 days following discontinuation of study treatment, before administration of subsequent cancer therapy or death, whichever comes first. All AEs are coded using MedDRA version 25.1. Includes AEs with onset date on or after the date of first dose and up to and including 28 days following discontinuation of study treatment. Analysis done if >=10 patients at each subgroup level and >=10 events in at least one subgroup level combined for both arms. Analysis done for SOC and PT only if main effect for that SOC or PT is statistically significant at 5% level. [a] Median time to event based on the Kaplan Meier estimate. NE = Not estimable as median (or 95% CLs) is not reached. [b] Estimated from main effects of unstratified Cox proportional hazard model including trt., subgroup and subgroup-by-trt. interaction. Ties handled using Efron method and 95% CI derived from profile likelihood estimation. NC = Not calculable. HR <1 favours Osimertinib+Chemo. * p<0.05.
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Table 4.3.4.11 FLAURA-2: Summary of subgroup analysis of time to first G>=3 PT: Thrombozytenzahl vermindert
Safety Analysis Set, DCO 03APR2023

	Osi + Chemo (N=276)			Osi (N=275)					
Subgruppen	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]	Hazard Ratio [b]	[95%-KI] [b]	2-seitiger p-Wert [b]
negativ	41	1 (2,4)	NE [NE; NE]	39	0	NE [NE; NE]	NC	[NC]	NC
unbekannt	24	1 (4,2)	NE [NE; NE]	32	0	NE [NE; NE]	NC	[NC]	NC
Interaktion p-Wert									NC
EGFR-Mutationstyp									
Exon 19 Deletion	172	10 (5,8)	NE [NE; NE]	167	0	NE [NE; NE]	NC	[NC]	NC
Exon 21 (L858R) Substitutionsmutation	104	11 (10,6)	NE [NE; NE]	106	0	NE [NE; NE]	NC	[NC]	NC
Interaktion p-Wert									NC
Zentral bestätigte EGFR-Mutation im Gewebe									
positiv	248	19 (7,7)	NE [NE; NE]	238	0	NE [NE; NE]	NC	[NC]	NC
negativ	3	0	NE [NE; NE]	4	0	NE [NE; NE]	NC	[NC]	NC
unbekannt	25	2 (8,0)	NE [NE; NE]	33	0	NE [NE; NE]	NC	[NC]	NC
Interaktion p-Wert									NC
ZNS-Metastasen zur Baseline									
Ja	113	9 (8,0)	NE [NE; NE]	110	0	NE [NE; NE]	NC	[NC]	NC
Nein	163	12 (7,4)	NE [NE; NE]	165	0	NE [NE; NE]	NC	[NC]	NC
Interaktion p-Wert									NC
Zentrale Bestätigung der EGFR-Mutation									
Zentral bestätigte EGFR-Mutation in Gewebe oder ctDNA	263	20 (7,6)	NE [NE; NE]	266	0	NE [NE; NE]	NC	[NC]	NC
Keine zentrale Bestätigung	13	1 (7,7)	NE [NE; NE]	9	0	NE [NE; NE]	NC	[NC]	NC
Interaktion p-Wert									NC
Alter bei Screening									

Time to event of AE is defined as the time from first dose of study treatment to first onset of the respective AE or the time to censoring if the AE has not occurred by 28 days following discontinuation of study treatment, before administration of subsequent cancer therapy or death, whichever comes first. All AEs are coded using MedDRA version 25.1. Includes AEs with onset date on or after the date of first dose and up to and including 28 days following discontinuation of study treatment. Analysis done if >=10 patients at each subgroup level and >=10 events in at least one subgroup level combined for both arms. Analysis done for SOC and PT only if main effect for that SOC or PT is statistically significant at 5% level. [a] Median time to event based on the Kaplan Meier estimate. NE = Not estimable as median (or 95% CLs) is not reached. [b] Estimated from main effects of unstratified Cox proportional hazard model including trt., subgroup and subgroup-by-trt. interaction. Ties handled using Efron method and 95% CI derived from profile likelihood estimation. NC = Not calculable. HR <1 favours Osimertinib+Chemo. * p<0.05.
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Table 4.3.4.11 FLAURA-2: Summary of subgroup analysis of time to first G>=3 PT: Thrombozytenzahl vermindert
Safety Analysis Set, DCO 03APR2023

	Osi + Chemo (N=276)			Osi (N=275)					
Subgruppen	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]	Hazard Ratio [b]	[95%-KI] [b]	2-seitiger p-Wert [b]
<65 Jahre	172	14 (8,1)	NE [NE; NE]	164	0	NE [NE; NE]	NC	[NC]	NC
>=65 Jahre	104	7 (6,7)	NE [NE; NE]	111	0	NE [NE; NE]	NC	[NC]	NC
Interaktion p-Wert									NC
Region gPAP									
Asien	168	20 (11,9)	NE [NE; NE]	166	0	NE [NE; NE]	NC	[NC]	NC
Europa	22	0	NE [NE; NE]	23	0	NE [NE; NE]	NC	[NC]	NC
Nordamerika	20	1 (5,0)	NE [NE; NE]	22	0	NE [NE; NE]	NC	[NC]	NC
Rest der Welt	66	0	NE [NE; NE]	64	0	NE [NE; NE]	NC	[NC]	NC
Interaktion p-Wert									NC

Time to event of AE is defined as the time from first dose of study treatment to first onset of the respective AE or the time to censoring if the AE has not occurred by 28 days following discontinuation of study treatment, before administration of subsequent cancer therapy or death, whichever comes first. All AEs are coded using MedDRA version 25.1. Includes AEs with onset date on or after the date of first dose and up to and including 28 days following discontinuation of study treatment. Analysis done if >=10 patients at each subgroup level and >=10 events in at least one subgroup level combined for both arms. Analysis done for SOC and PT only if main effect for that SOC or PT is statistically significant at 5% level. [a] Median time to event based on the Kaplan Meier estimate. NE = Not estimable as median (or 95% CLs) is not reached. [b] Estimated from main effects of unstratified Cox proportional hazard model including trt., subgroup and subgroup-by-trt. interaction. Ties handled using Efron method and 95% CI derived from profile likelihood estimation. NC = Not calculable. HR <1 favours Osimertinib+Chemo. * p<0.05.
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Table 4.3.5.1 FLAURA-2: Summary of subgroup analysis of time to first UESI GT: Hämatologische Toxizitäten
Safety Analysis Set, DCO 03APR2023

	Osi + Chemo (N=276)			Osi (N=275)					
Subgruppen	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]	Hazard Ratio [b]	[95%-KI] [b]	2-seitiger p-Wert [b]
Abstammung									
Chinesisch/Asiatisch	68	60 (88,2)	0,5 [0,4; 0,5]	70	37 (52,9)	13,9 [2,1; NE]	3,42	[2,27; 5,22]	<0,0001*
Nicht-chinesisch/ Asiatisch	107	67 (62,6)	2,9 [2,2; 6,6]	106	14 (13,2)	NE [NE; NE]	6,86	[3,98; 12,73]	<0,0001*
Nicht-asiatisch	101	70 (69,3)	2,1 [1,4; 3,4]	99	15 (15,2)	NE [NE; NE]	7,00	[4,13; 12,72]	<0,0001*
Interaktion p-Wert									0,0524
Methode zur Gewebeuntersuchung									
zentral	120	100 (83,3)	0,7 [0,5; 1,5]	119	44 (37,0)	NE [NE; NE]	4,04	[2,84; 5,83]	<0,0001*
lokal	156	97 (62,2)	2,8 [2,1; 6,9]	156	22 (14,1)	NE [NE; NE]	6,34	[4,07; 10,33]	<0,0001*
Interaktion p-Wert									0,1253
WHO Performance-Status									
0	100	67 (67,0)	2,8 [2,1; 5,6]	100	18 (18,0)	NE [NE; NE]	5,38	[3,27; 9,33]	<0,0001*
1	176	130 (73,9)	1,4 [0,6; 2,1]	175	48 (27,4)	NE [NE; NE]	4,36	[3,15; 6,14]	<0,0001*
Interaktion p-Wert									0,5021
Raucherstatus									
Ja	90	55 (61,1)	2,8 [1,4;13,4]	96	21 (21,9)	NE [NE; NE]	3,78	[2,32; 6,39]	<0,0001*
Nein	186	142 (76,3)	1,4 [0,7; 2,1]	179	45 (25,1)	NE [NE; NE]	5,04	[3,63; 7,14]	<0,0001*
Interaktion p-Wert									0,3543
Geschlecht									
Maennlich	104	76 (73,1)	2,3 [0,9; 3,6]	107	26 (24,3)	NE [NE; NE]	4,19	[2,72; 6,67]	<0,0001*
Weiblich	172	121 (70,3)	1,7 [1,2; 2,1]	168	40 (23,8)	NE [NE; NE]	4,87	[3,43; 7,06]	<0,0001*
Interaktion p-Wert									0,6106
Nachweis der EGFR-Mutation durch zentralen ctDNA Cobas Test									
positiv	211	151 (71,6)	1,8 [0,9; 2,6]	204	50 (24,5)	NE [NE; NE]	4,59	[3,35; 6,39]	<0,0001*

Time to event of AE is defined as the time from first dose of study treatment to first onset of the respective AE or the time to censoring if the AE has not occurred by 28 days following discontinuation of study treatment, before administration of subsequent cancer therapy or death, whichever comes first. All AEs are coded using MedDRA version 25.1. Includes AEs with onset date on or after the date of first dose and up to and including 28 days following discontinuation of study treatment. Analysis done if >=10 patients at each subgroup level and >=10 events in at least one subgroup level combined for both arms.
[a] Median time to event based on the Kaplan Meier estimate. NE = Not estimable as median (or 95% CLs) is not reached.
[b] Estimated from main effects of unstratified Cox proportional hazard model including trt., subgroup and subgroup-by-trt. interaction. Ties handled using Efron method and 95% CI derived from profile likelihood estimation. NC = Not calculable.
HR <1 favours Osimertinib+Chemo. * p<0.05.

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Table 4.3.5.1 FLAURA-2: Summary of subgroup analysis of time to first UESI GT: Hämatologische Toxizitäten
Safety Analysis Set, DCO 03APR2023

	Osi + Chemo (N=276)			Osi (N=275)					
Subgruppen	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]	Hazard Ratio [b]	[95%-KI] [b]	2-seitiger p-Wert [b]
negativ	41	29 (70,7)	2,8 [1,7; 6,2]	39	10 (25,6)	NE [NE; NE]	3,78	[1,90; 8,16]	<0,0001*
unbekannt	24	17 (70,8)	1,4 [0,5; 2,8]	32	6 (18,8)	NE [NE; NE]	6,28	[2,61; 17,42]	<0,0001*
Interaktion p-Wert									0,6940
EGFR-Mutationstyp									
Exon 19 Deletion	172	121 (70,3)	2,1 [1,3; 2,8]	167	35 (21,0)	NE [NE; NE]	5,29	[3,67; 7,83]	<0,0001*
Exon 21 (L858R) Substitutionsmutation	104	76 (73,1)	2,1 [0,5; 2,8]	106	31 (29,2)	30,3 [30,3; NE]	3,73	[2,48; 5,75]	<0,0001*
Interaktion p-Wert									0,2254
Zentral bestätigte EGFR-Mutation im Gewebe									
positiv	248	181 (73,0)	2,0 [1,3; 2,2]	238	59 (24,8)	NE [NE; NE]	4,65	[3,48; 6,31]	<0,0001*
negativ	3	1 (33,3)	NE [NE; NE]	4	0	NE [NE; NE]	NC	[NC]	NC
unbekannt	25	15 (60,0)	5,6 [0,5; NE]	33	7 (21,2)	NE [NE; NE]	3,80	[1,60; 9,96]	0,0022*
Interaktion p-Wert									0,6785
ZNS-Metastasen zur Baseline									
Ja	113	80 (70,8)	1,4 [0,8; 2,6]	110	35 (31,8)	NE [NE; NE]	3,18	[2,16; 4,79]	<0,0001*
Nein	163	117 (71,8)	2,1 [1,4; 2,8]	165	31 (18,8)	NE [NE; NE]	6,19	[4,21; 9,37]	<0,0001*
Interaktion p-Wert									0,0201*
Zentrale Bestätigung der EGFR-Mutation									
Zentral bestätigte EGFR-Mutation in Gewebe oder ctDNA	263	190 (72,2)	2,0 [1,3; 2,3]	266	64 (24,1)	NE [NE; NE]	4,71	[3,56; 6,31]	<0,0001*
Keine zentrale Bestätigung	13	7 (53,8)	5,6 [0,3; NE]	9	2 (22,2)	NE [NE; NE]	2,68	[0,65; 17,98]	0,1842
Interaktion p-Wert									0,5107
Alter bei Screening									

Time to event of AE is defined as the time from first dose of study treatment to first onset of the respective AE or the time to censoring if the AE has not occurred by 28 days following discontinuation of study treatment, before administration of subsequent cancer therapy or death, whichever comes first. All AEs are coded using MedDRA version 25.1. Includes AEs with onset date on or after the date of first dose and up to and including 28 days following discontinuation of study treatment. Analysis done if >=10 patients at each subgroup level and >=10 events in at least one subgroup level combined for both arms.
[a] Median time to event based on the Kaplan Meier estimate. NE = Not estimable as median (or 95% CLs) is not reached.
[b] Estimated from main effects of unstratified Cox proportional hazard model including trt., subgroup and subgroup-by-trt. interaction. Ties handled using Efron method and 95% CI derived from profile likelihood estimation. NC = Not calculable.
HR <1 favours Osimertinib+Chemo. * p<0.05.

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Table 4.3.5.1 FLAURA-2: Summary of subgroup analysis of time to first UESI GT: Hämatologische Toxizitäten
Safety Analysis Set, DCO 03APR2023

	Osi + Chemo (N=276)			Osi (N=275)					
Subgruppen	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]	Hazard Ratio [b]	[95%-KI] [b]	2-seitiger p-Wert [b]
<65 Jahre	172	125 (72,7)	2,1 [1,4; 2,6]	164	43 (26,2)	NE [NE; NE]	4,16	[2,96; 5,96]	<0,0001*
>=65 Jahre	104	72 (69,2)	2,0 [0,6; 2,9]	111	23 (20,7)	NE [NE; NE]	5,40	[3,43; 8,83]	<0,0001*
Interaktion p-Wert									0,3783
Region gPAP									
Asien	168	124 (73,8)	1,4 [0,7; 2,1]	166	48 (28,9)	NE [NE; NE]	4,13	[2,97; 5,82]	<0,0001*
Europa	22	17 (77,3)	0,9 [0,3; 6,9]	23	4 (17,4)	NE [NE; NE]	7,59	[2,81; 26,37]	<0,0001*
Nordamerika	20	12 (60,0)	6,2 [0,5; NE]	22	3 (13,6)	NE [NE; NE]	5,92	[1,88; 26,01]	0,0017*
Rest der Welt	66	44 (66,7)	2,8 [1,5; 6,2]	64	11 (17,2)	NE [NE; NE]	5,54	[2,97; 11,29]	<0,0001*
Interaktion p-Wert									0,6227

Time to event of AE is defined as the time from first dose of study treatment to first onset of the respective AE or the time to censoring if the AE has not occurred by 28 days following discontinuation of study treatment, before administration of subsequent cancer therapy or death, whichever comes first. All AEs are coded using MedDRA version 25.1. Includes AEs with onset date on or after the date of first dose and up to and including 28 days following discontinuation of study treatment. Analysis done if >=10 patients at each subgroup level and >=10 events in at least one subgroup level combined for both arms.
[a] Median time to event based on the Kaplan Meier estimate. NE = Not estimable as median (or 95% CLs) is not reached.
[b] Estimated from main effects of unstratified Cox proportional hazard model including trt., subgroup and subgroup-by-trt. interaction. Ties handled using Efron method and 95% CI derived from profile likelihood estimation. NC = Not calculable.
HR <1 favours Osimertinib+Chemo. * p<0.05.

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Table 4.3.5.2 FLAURA-2: Summary of subgroup analysis of time to first UESI GT: ILD und Pneumonitis
Safety Analysis Set, DCO 03APR2023

	Osi + Chemo (N=276)			Osi (N=275)					
Subgruppen	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]	Hazard Ratio [b]	[95%-KI] [b]	2-seitiger p-Wert [b]
Abstammung									
Chinesisch/Asiatisch	68	0	NE [NE; NE]	70	3 (4,3)	NE [NE; NE]	NC	[NC]	NC
Nicht-chinesisch/ Asiatisch	107	7 (6,5)	NE [NE; NE]	106	4 (3,8)	NE [NE; NE]	1,73	[0,52; 6,60]	0,3739
Nicht-asiatisch	101	2 (2,0)	NE [NE; NE]	99	3 (3,0)	NE [NE; NE]	0,62	[0,08; 3,73]	0,5941
Interaktion p-Wert									0,3469
Methode zur Gewebeuntersuchung									
zentral	120	1 (0,8)	NE [NE; NE]	119	2 (1,7)	NE [NE; NE]	0,48	[0,02; 5,01]	0,5363
lokal	156	8 (5,1)	NE [NE; NE]	156	8 (5,1)	NE [NE; NE]	0,96	[0,35; 2,61]	0,9357
Interaktion p-Wert									0,5915
WHO Performance-Status									
0	100	4 (4,0)	NE [NE; NE]	100	2 (2,0)	NE [NE; NE]	2,01	[0,39; 14,50]	0,4061
1	176	5 (2,8)	NE [NE; NE]	175	8 (4,6)	NE [NE; NE]	0,58	[0,18; 1,75]	0,3370
Interaktion p-Wert									0,2199
Raucherstatus									
Ja	90	2 (2,2)	NE [NE; NE]	96	7 (7,3)	NE [NE; NE]	0,29	[0,04; 1,18]	0,0861
Nein	186	7 (3,8)	NE [NE; NE]	179	3 (1,7)	NE [NE; NE]	2,19	[0,61; 10,18]	0,2354
Interaktion p-Wert									0,0389*
Geschlecht									
Maennlich	104	4 (3,8)	NE [NE; NE]	107	6 (5,6)	NE [NE; NE]	0,62	[0,16; 2,19]	0,4611
Weiblich	172	5 (2,9)	NE [NE; NE]	168	4 (2,4)	NE [NE; NE]	1,22	[0,32; 4,91]	0,7700
Interaktion p-Wert									0,4713
Nachweis der EGFR-Mutation durch zentralen ctDNA Cobas Test									
positiv	211	7 (3,3)	NE [NE; NE]	204	8 (3,9)	NE [NE; NE]	0,82	[0,29; 2,29]	0,7025

Time to event of AE is defined as the time from first dose of study treatment to first onset of the respective AE or the time to censoring if the AE has not occurred by 28 days following discontinuation of study treatment, before administration of subsequent cancer therapy or death, whichever comes first. All AEs are coded using MedDRA version 25.1. Includes AEs with onset date on or after the date of first dose and up to and including 28 days following discontinuation of study treatment. Analysis done if >=10 patients at each subgroup level and >=10 events in at least one subgroup level combined for both arms.
[a] Median time to event based on the Kaplan Meier estimate. NE = Not estimable as median (or 95% CLs) is not reached.
[b] Estimated from main effects of unstratified Cox proportional hazard model including trt., subgroup and subgroup-by-trt. interaction. Ties handled using Efron method and 95% CI derived from profile likelihood estimation. NC = Not calculable.
HR <1 favours Osimertinib+Chemo. * p<0.05.

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Table 4.3.5.2 FLAURA-2: Summary of subgroup analysis of time to first UESI GT: ILD und Pneumonitis
Safety Analysis Set, DCO 03APR2023

	Osi + Chemo (N=276)			Osi (N=275)					
Subgruppen	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]	Hazard Ratio [b]	[95%-KI] [b]	2-seitiger p-Wert [b]
negativ	41	2 (4,9)	NE [NE; NE]	39	1 (2,6)	NE [NE; NE]	1,88	[0,18; 40,37]	0,5970
unbekannt	24	0	NE [NE; NE]	32	1 (3,1)	NE [NE; NE]	NC	[NC]	NC
Interaktion p-Wert									0,5233
EGFR-Mutationstyp									
Exon 19 Deletion	172	2 (1,2)	NE [NE; NE]	167	6 (3,6)	NE [NE; NE]	0,32	[0,05; 1,38]	0,1316
Exon 21 (L858R) Substitutionsmutation	104	7 (6,7)	NE [NE; NE]	106	4 (3,8)	NE [NE; NE]	1,66	[0,50; 6,35]	0,4101
Interaktion p-Wert									0,0919
Zentral bestätigte EGFR-Mutation im Gewebe									
positiv	248	9 (3,6)	NE [NE; NE]	238	7 (2,9)	NE [NE; NE]	1,18	[0,44; 3,32]	0,7364
negativ	3	0	NE [NE; NE]	4	1 (25,0)	NE [NE; NE]	NC	[NC]	NC
unbekannt	25	0	NE [NE; NE]	33	2 (6,1)	NE [NE; NE]	NC	[NC]	NC
Interaktion p-Wert									NC
ZNS-Metastasen zur Baseline									
Ja	113	3 (2,7)	NE [NE; NE]	110	5 (4,5)	NE [NE; NE]	0,53	[0,11; 2,17]	0,3795
Nein	163	6 (3,7)	NE [NE; NE]	165	5 (3,0)	NE [NE; NE]	1,21	[0,37; 4,21]	0,7495
Interaktion p-Wert									0,3805
Zentrale Bestätigung der EGFR-Mutation									
Zentral bestätigte EGFR-Mutation in Gewebe oder ctDNA	263	9 (3,4)	NE [NE; NE]	266	9 (3,4)	NE [NE; NE]	0,98	[0,38; 2,50]	0,9584
Keine zentrale Bestätigung	13	0	NE [NE; NE]	9	1 (11,1)	NE [NE; NE]	NC	[NC]	NC
Interaktion p-Wert									NC
Alter bei Screening									

Time to event of AE is defined as the time from first dose of study treatment to first onset of the respective AE or the time to censoring if the AE has not occurred by 28 days following discontinuation of study treatment, before administration of subsequent cancer therapy or death, whichever comes first. All AEs are coded using MedDRA version 25.1. Includes AEs with onset date on or after the date of first dose and up to and including 28 days following discontinuation of study treatment. Analysis done if >=10 patients at each subgroup level and >=10 events in at least one subgroup level combined for both arms.
[a] Median time to event based on the Kaplan Meier estimate. NE = Not estimable as median (or 95% CLs) is not reached.
[b] Estimated from main effects of unstratified Cox proportional hazard model including trt., subgroup and subgroup-by-trt. interaction. Ties handled using Efron method and 95% CI derived from profile likelihood estimation. NC = Not calculable.
HR <1 favours Osimertinib+Chemo. * p<0.05.

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Table 4.3.5.2 FLAURA-2: Summary of subgroup analysis of time to first UESI GT: ILD und Pneumonitis
Safety Analysis Set, DCO 03APR2023

	Osi + Chemo (N=276)			Osi (N=275)					
Subgruppen	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]	Hazard Ratio [b]	[95%-KI] [b]	2-seitiger p-Wert [b]
<65 Jahre	172	1 (0,6)	NE [NE; NE]	164	5 (3,0)	NE [NE; NE]	0,18	[0,01; 1,09]	0,0638
>=65 Jahre	104	8 (7,7)	NE [NE; NE]	111	5 (4,5)	NE [NE; NE]	1,76	[0,59; 5,82]	0,3145
Interaktion p-Wert									0,0355*
Region gPAP									
Asien	168	7 (4,2)	NE [NE; NE]	166	7 (4,2)	NE [NE; NE]	0,97	[0,33; 2,84]	0,9557
Europa	22	0	NE [NE; NE]	23	3 (13,0)	NE [NE; NE]	NC	[NC]	NC
Nordamerika	20	1 (5,0)	NE [NE; NE]	22	0	NE [NE; NE]	NC	[NC]	NC
Rest der Welt	66	1 (1,5)	NE [NE; NE]	64	0	NE [NE; NE]	NC	[NC]	NC
Interaktion p-Wert									NC

Time to event of AE is defined as the time from first dose of study treatment to first onset of the respective AE or the time to censoring if the AE has not occurred by 28 days following discontinuation of study treatment, before administration of subsequent cancer therapy or death, whichever comes first. All AEs are coded using MedDRA version 25.1. Includes AEs with onset date on or after the date of first dose and up to and including 28 days following discontinuation of study treatment. Analysis done if >=10 patients at each subgroup level and >=10 events in at least one subgroup level combined for both arms.
[a] Median time to event based on the Kaplan Meier estimate. NE = Not estimable as median (or 95% CLs) is not reached.
[b] Estimated from main effects of unstratified Cox proportional hazard model including trt., subgroup and subgroup-by-trt. interaction. Ties handled using Efron method and 95% CI derived from profile likelihood estimation. NC = Not calculable. HR <1 favours Osimertinib+Chemo. * p<0.05.

root/cdar/d516/payer_germany/ar/d5169c00001_payer_germany/tlf/prod/program/ttesubae.sas gttesubaeeab 22DEC2023:09:13 kfrh585

Table 4.3.5.3 FLAURA-2: Summary of subgroup analysis of time to first UESI GT: Kardiale Effekte (Herzinsuffizienz)
Safety Analysis Set, DCO 03APR2023

	Osi + Chemo (N=276)			Osi (N=275)					
Subgruppen	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]	Hazard Ratio [b]	[95%-KI] [b]	2-seitiger p-Wert [b]
Abstammung									
Chinesisch/Asiatisch	68	7 (10,3)	NE [NE; NE]	70	4 (5,7)	NE [NE; NE]	1,55	[0,47; 5,94]	0,4746
Nicht-chinesisch/ Asiatisch	107	10 (9,3)	NE [NE; NE]	106	1 (0,9)	NE [NE; NE]	10,28	[1,97;188,58]	0,0030*
Nicht-asiatisch	101	9 (8,9)	NE [NE; NE]	99	5 (5,1)	NE [NE; NE]	1,64	[0,57; 5,35]	0,3659
Interaktion p-Wert									0,1544
Methode zur Gewebeuntersuchung									
zentral	120	12 (10,0)	NE [NE; NE]	119	6 (5,0)	NE [NE; NE]	1,92	[0,74; 5,51]	0,1818
lokal	156	14 (9,0)	NE [NE; NE]	156	4 (2,6)	NE [NE; NE]	3,31	[1,18; 11,67]	0,0211*
Interaktion p-Wert									0,4676
WHO Performance-Status									
0	100	10 (10,0)	NE [NE; NE]	100	4 (4,0)	NE [NE; NE]	2,55	[0,85; 9,31]	0,0953
1	176	16 (9,1)	NE [NE; NE]	175	6 (3,4)	NE [NE; NE]	2,42	[0,996; 6,76]	0,0511
Interaktion p-Wert									0,9458
Raucherstatus									
Ja	90	12 (13,3)	NE [NE; NE]	96	3 (3,1)	NE [NE; NE]	3,98	[1,26; 17,45]	0,0168*
Nein	186	14 (7,5)	NE [NE; NE]	179	7 (3,9)	NE [NE; NE]	1,86	[0,77; 4,91]	0,1687
Interaktion p-Wert									0,3277
Geschlecht									
Maennlich	104	14 (13,5)	NE [NE; NE]	107	5 (4,7)	NE [NE; NE]	2,53	[0,97; 7,83]	0,0590
Weiblich	172	12 (7,0)	NE [NE; NE]	168	5 (3,0)	NE [NE; NE]	2,35	[0,87; 7,38]	0,0938
Interaktion p-Wert									0,9193
Nachweis der EGFR-Mutation durch zentralen ctDNA Cobas Test									
positiv	211	19 (9,0)	NE [NE; NE]	204	7 (3,4)	NE [NE; NE]	2,51	[1,10; 6,43]	0,0279*

Time to event of AE is defined as the time from first dose of study treatment to first onset of the respective AE or the time to censoring if the AE has not occurred by 28 days following discontinuation of study treatment, before administration of subsequent cancer therapy or death, whichever comes first. All AEs are coded using MedDRA version 25.1. Includes AEs with onset date on or after the date of first dose and up to and including 28 days following discontinuation of study treatment. Analysis done if >=10 patients at each subgroup level and >=10 events in at least one subgroup level combined for both arms.
[a] Median time to event based on the Kaplan Meier estimate. NE = Not estimable as median (or 95% CLs) is not reached.
[b] Estimated from main effects of unstratified Cox proportional hazard model including trt., subgroup and subgroup-by-trt. interaction. Ties handled using Efron method and 95% CI derived from profile likelihood estimation. NC = Not calculable.
HR <1 favours Osimertinib+Chemo. * p<0.05.

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Table 4.3.5.3 FLAURA-2: Summary of subgroup analysis of time to first UESI GT: Kardiale Effekte (Herzinsuffizienz)
Safety Analysis Set, DCO 03APR2023

	Osi + Chemo (N=276)			Osi (N=275)					
Subgruppen	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]	Hazard Ratio [b]	[95%-KI] [b]	2-seitiger p-Wert [b]
negativ	41	6 (14,6)	NE [NE; NE]	39	3 (7,7)	NE [NE; NE]	1,98	[0,52; 9,36]	0,3217
unbekannt	24	1 (4,2)	NE [NE; NE]	32	0	NE [NE; NE]	NC	[NC]	NC
Interaktion p-Wert									0,7758
EGFR-Mutationstyp									
Exon 19 Deletion	172	18 (10,5)	NE [NE; NE]	167	3 (1,8)	NE [NE; NE]	5,92	[2,00; 25,28]	0,0006*
Exon 21 (L858R) Substitutionsmutation	104	8 (7,7)	NE [NE; NE]	106	7 (6,6)	NE [NE; NE]	1,01	[0,36; 2,87]	0,9922
Interaktion p-Wert									0,0222*
Zentral bestätigte EGFR-Mutation im Gewebe									
positiv	248	24 (9,7)	NE [NE; NE]	238	9 (3,8)	NE [NE; NE]	2,40	[1,16; 5,46]	0,0181*
negativ	3	0	NE [NE; NE]	4	1 (25,0)	NE [NE; NE]	NC	[NC]	NC
unbekannt	25	2 (8,0)	NE [NE; NE]	33	0	NE [NE; NE]	NC	[NC]	NC
Interaktion p-Wert									NC
ZNS-Metastasen zur Baseline									
Ja	113	13 (11,5)	NE [NE; NE]	110	5 (4,5)	NE [NE; NE]	2,19	[0,83; 6,84]	0,1182
Nein	163	13 (8,0)	NE [NE; NE]	165	5 (3,0)	NE [NE; NE]	2,67	[1,01; 8,32]	0,0484*
Interaktion p-Wert									0,7913
Zentrale Bestätigung der EGFR-Mutation									
Zentral bestätigte EGFR-Mutation in Gewebe oder ctDNA	263	26 (9,9)	NE [NE; NE]	266	9 (3,4)	NE [NE; NE]	2,79	[1,36; 6,31]	0,0046*
Keine zentrale Bestätigung	13	0	NE [NE; NE]	9	1 (11,1)	NE [NE; NE]	NC	[NC]	NC
Interaktion p-Wert									NC
Alter bei Screening									

Time to event of AE is defined as the time from first dose of study treatment to first onset of the respective AE or the time to censoring if the AE has not occurred by 28 days following discontinuation of study treatment, before administration of subsequent cancer therapy or death, whichever comes first. All AEs are coded using MedDRA version 25.1. Includes AEs with onset date on or after the date of first dose and up to and including 28 days following discontinuation of study treatment. Analysis done if >=10 patients at each subgroup level and >=10 events in at least one subgroup level combined for both arms.
[a] Median time to event based on the Kaplan Meier estimate. NE = Not estimable as median (or 95% CLs) is not reached.
[b] Estimated from main effects of unstratified Cox proportional hazard model including trt., subgroup and subgroup-by-trt. interaction. Ties handled using Efron method and 95% CI derived from profile likelihood estimation. NC = Not calculable.
HR <1 favours Osimertinib+Chemo. * p<0.05.

root/cdar/d516/payer_germany/ar/d5169c00001_payer_germany/tlf/prod/program/ttesubae.sas gttesubaeeac 22DEC2023:09:13 kfrh585

Table 4.3.5.3 FLAURA-2: Summary of subgroup analysis of time to first UESI GT: Kardiale Effekte (Herzinsuffizienz)
Safety Analysis Set, DCO 03APR2023

	Osi + Chemo (N=276)			Osi (N=275)					
Subgruppen	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]	Hazard Ratio [b]	[95%-KI] [b]	2-seitiger p-Wert [b]
<65 Jahre	172	15 (8,7)	NE [NE; NE]	164	4 (2,4)	NE [NE; NE]	3,30	[1,20; 11,57]	0,0197*
>=65 Jahre	104	11 (10,6)	NE [NE; NE]	111	6 (5,4)	NE [NE; NE]	2,00	[0,76; 5,81]	0,1616
Interaktion p-Wert									0,5068
Region gPAP									
Asien	168	16 (9,5)	NE [NE; NE]	166	5 (3,0)	NE [NE; NE]	3,00	[1,18; 9,18]	0,0205*
Europa	22	0	NE [NE; NE]	23	2 (8,7)	NE [NE; NE]	NC	[NC]	NC
Nordamerika	20	3 (15,0)	NE [NE; NE]	22	0	NE [NE; NE]	NC	[NC]	NC
Rest der Welt	66	7 (10,6)	NE [NE; NE]	64	3 (4,7)	NE [NE; NE]	2,06	[0,57; 9,55]	0,2778
Interaktion p-Wert									0,6624

Time to event of AE is defined as the time from first dose of study treatment to first onset of the respective AE or the time to censoring if the AE has not occurred by 28 days following discontinuation of study treatment, before administration of subsequent cancer therapy or death, whichever comes first. All AEs are coded using MedDRA version 25.1. Includes AEs with onset date on or after the date of first dose and up to and including 28 days following discontinuation of study treatment. Analysis done if >=10 patients at each subgroup level and >=10 events in at least one subgroup level combined for both arms.
[a] Median time to event based on the Kaplan Meier estimate. NE = Not estimable as median (or 95% CLs) is not reached.
[b] Estimated from main effects of unstratified Cox proportional hazard model including trt., subgroup and subgroup-by-trt. interaction. Ties handled using Efron method and 95% CI derived from profile likelihood estimation. NC = Not calculable.
HR <1 favours Osimertinib+Chemo. * p<0.05.

root/cdar/d516/payer_germany/ar/d5169c00001_payer_germany/tlf/prod/program/ttesubae.sas gttesubaeeac 22DEC2023:09:13 kfrh585

Table 4.3.6.1 FLAURA-2: Summary of subgroup analysis of time to first UESI G>=3 GT: Hämatologische Toxizitäten
Safety Analysis Set, DCO 03APR2023

	Osi + Chemo (N=276)			Osi (N=275)					
Subgruppen	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]	Hazard Ratio [b]	[95%-KI] [b]	2-seitiger p-Wert [b]
Abstammung									
Chinesisch/Asiatisch	68	42 (61,8)	3,3 [2,1;11,2]	70	4 (5,7)	NE [NE; NE]	15,39	[6,22; 51,21]	<0,0001*
Nicht-chinesisch/ Asiatisch	107	42 (39,3)	NE [NE; NE]	106	3 (2,8)	NE [NE; NE]	17,70	[6,45; 73,08]	<0,0001*
Nicht-asiatisch	101	38 (37,6)	NE [NE; NE]	99	3 (3,0)	NE [NE; NE]	15,70	[5,69; 65,00]	<0,0001*
Interaktion p-Wert									0,9828
Methode zur Gewebeuntersuchung									
zentral	120	59 (49,2)	11,2 [3,1; NE]	119	7 (5,9)	NE [NE; NE]	11,25	[5,50; 27,06]	<0,0001*
lokal	156	63 (40,4)	NE [NE; NE]	156	3 (1,9)	NE [NE; NE]	26,73	[9,93;109,43]	<0,0001*
Interaktion p-Wert									0,2069
WHO Performance-Status									
0	100	33 (33,0)	NE [NE; NE]	100	1 (1,0)	NE [NE; NE]	39,66	[8,56;705,60]	<0,0001*
1	176	89 (50,6)	11,2 [3,0; NE]	175	9 (5,1)	NE [NE; NE]	13,53	[7,21; 28,90]	<0,0001*
Interaktion p-Wert									0,2541
Raucherstatus									
Ja	90	37 (41,1)	NE [NE; NE]	96	2 (2,1)	NE [NE; NE]	24,60	[7,53;151,31]	<0,0001*
Nein	186	85 (45,7)	NE [NE; NE]	179	8 (4,5)	NE [NE; NE]	13,62	[7,03; 30,56]	<0,0001*
Interaktion p-Wert									0,4458
Geschlecht									
Maennlich	104	40 (38,5)	NE [NE; NE]	107	5 (4,7)	NE [NE; NE]	9,83	[4,26; 28,49]	<0,0001*
Weiblich	172	82 (47,7)	16,6 [3,5; NE]	168	5 (3,0)	NE [NE; NE]	22,07	[9,91; 62,79]	<0,0001*
Interaktion p-Wert									0,2256
Nachweis der EGFR-Mutation durch zentralen ctDNA Cobas Test									
positiv	211	96 (45,5)	NE [NE; NE]	204	7 (3,4)	NE [NE; NE]	17,71	[8,85; 42,08]	<0,0001*

Time to event of AE is defined as the time from first dose of study treatment to first onset of the respective AE or the time to censoring if the AE has not occurred by 28 days following discontinuation of study treatment, before administration of subsequent cancer therapy or death, whichever comes first. All AEs are coded using MedDRA version 25.1. Includes AEs with onset date on or after the date of first dose and up to and including 28 days following discontinuation of study treatment. Analysis done if >=10 patients at each subgroup level and >=10 events in at least one subgroup level combined for both arms.
[a] Median time to event based on the Kaplan Meier estimate. NE = Not estimable as median (or 95% CLs) is not reached.
[b] Estimated from main effects of unstratified Cox proportional hazard model including trt., subgroup and subgroup-by-trt. interaction. Ties handled using Efron method and 95% CI derived from profile likelihood estimation. NC = Not calculable.
HR <1 favours Osimertinib+Chemo. * p<0.05.

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Table 4.3.6.1 FLAURA-2: Summary of subgroup analysis of time to first UESI G>=3 GT: Hämatologische Toxizitäten
Safety Analysis Set, DCO 03APR2023

	Osi + Chemo (N=276)			Osi (N=275)					
Subgruppen	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]	Hazard Ratio [b]	[95%-KI] [b]	2-seitiger p-Wert [b]
negativ	41	15 (36,6)	NE [NE; NE]	39	1 (2,6)	NE [NE; NE]	17,29	[3,51;313,00]	<0,0001*
unbekannt	24	11 (45,8)	NE [NE; NE]	32	2 (6,3)	NE [NE; NE]	9,05	[2,43; 58,46]	0,0005*
Interaktion p-Wert									0,7569
EGFR-Mutationstyp									
Exon 19 Deletion	172	74 (43,0)	NE [NE; NE]	167	4 (2,4)	NE [NE; NE]	23,94	[9,94; 78,56]	<0,0001*
Exon 21 (L858R) Substitutionsmutation	104	48 (46,2)	NE [NE; NE]	106	6 (5,7)	NE [NE; NE]	10,25	[4,75; 26,76]	<0,0001*
Interaktion p-Wert									0,2010
Zentral bestätigte EGFR-Mutation im Gewebe									
positiv	248	110 (44,4)	NE [NE; NE]	238	8 (3,4)	NE [NE; NE]	17,27	[8,99; 38,54]	<0,0001*
negativ	3	1 (33,3)	NE [NE; NE]	4	0	NE [NE; NE]	NC	[NC]	NC
unbekannt	25	11 (44,0)	NE [NE; NE]	33	2 (6,1)	NE [NE; NE]	9,40	[2,52; 60,72]	0,0004*
Interaktion p-Wert									0,4953
ZNS-Metastasen zur Baseline									
Ja	113	46 (40,7)	NE [NE; NE]	110	6 (5,5)	NE [NE; NE]	9,33	[4,31; 24,37]	<0,0001*
Nein	163	76 (46,6)	NE [NE; NE]	165	4 (2,4)	NE [NE; NE]	25,77	[10,71; 84,53]	<0,0001*
Interaktion p-Wert									0,1257
Zentrale Bestätigung der EGFR-Mutation									
Zentral bestätigte EGFR-Mutation in Gewebe oder ctDNA	263	117 (44,5)	NE [NE; NE]	266	9 (3,4)	NE [NE; NE]	17,23	[9,27; 36,59]	<0,0001*
Keine zentrale Bestätigung	13	5 (38,5)	NE [NE; NE]	9	1 (11,1)	NE [NE; NE]	3,79	[0,61; 72,59]	0,1663
Interaktion p-Wert									0,2553
Alter bei Screening									

Time to event of AE is defined as the time from first dose of study treatment to first onset of the respective AE or the time to censoring if the AE has not occurred by 28 days following discontinuation of study treatment, before administration of subsequent cancer therapy or death, whichever comes first. All AEs are coded using MedDRA version 25.1. Includes AEs with onset date on or after the date of first dose and up to and including 28 days following discontinuation of study treatment. Analysis done if >=10 patients at each subgroup level and >=10 events in at least one subgroup level combined for both arms.
[a] Median time to event based on the Kaplan Meier estimate. NE = Not estimable as median (or 95% CLs) is not reached.
[b] Estimated from main effects of unstratified Cox proportional hazard model including trt., subgroup and subgroup-by-trt. interaction. Ties handled using Efron method and 95% CI derived from profile likelihood estimation. NC = Not calculable.
HR <1 favours Osimertinib+Chemo. * p<0.05.

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Table 4.3.6.1 FLAURA-2: Summary of subgroup analysis of time to first UESI G>=3 GT: Hämatologische Toxizitäten
Safety Analysis Set, DCO 03APR2023

	Osi + Chemo (N=276)			Osi (N=275)					
Subgruppen	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]	Hazard Ratio [b]	[95%-KI] [b]	2-seitiger p-Wert [b]
<65 Jahre	172	76 (44,2)	NE [NE; NE]	164	7 (4,3)	NE [NE; NE]	13,23	[6,55; 31,59]	<0,0001*
>=65 Jahre	104	46 (44,2)	NE [NE; NE]	111	3 (2,7)	NE [NE; NE]	22,05	[8,08; 90,93]	<0,0001*
Interaktion p-Wert									0,4623
Region gPAP									
Asien	168	82 (48,8)	14,8 [3,5; NE]	166	5 (3,0)	NE [NE; NE]	21,91	[9,84; 62,32]	<0,0001*
Europa	22	10 (45,5)	NE [NE; NE]	23	0	NE [NE; NE]	NC	[NC]	NC
Nordamerika	20	7 (35,0)	NE [NE; NE]	22	2 (9,1)	NE [NE; NE]	4,53	[1,09; 30,37]	0,0365*
Rest der Welt	66	23 (34,8)	NE [NE; NE]	64	3 (4,7)	NE [NE; NE]	9,30	[3,24; 39,22]	<0,0001*
Interaktion p-Wert									0,2180

Time to event of AE is defined as the time from first dose of study treatment to first onset of the respective AE or the time to censoring if the AE has not occurred by 28 days following discontinuation of study treatment, before administration of subsequent cancer therapy or death, whichever comes first. All AEs are coded using MedDRA version 25.1. Includes AEs with onset date on or after the date of first dose and up to and including 28 days following discontinuation of study treatment. Analysis done if >=10 patients at each subgroup level and >=10 events in at least one subgroup level combined for both arms.
[a] Median time to event based on the Kaplan Meier estimate. NE = Not estimable as median (or 95% CLs) is not reached.
[b] Estimated from main effects of unstratified Cox proportional hazard model including trt., subgroup and subgroup-by-trt. interaction. Ties handled using Efron method and 95% CI derived from profile likelihood estimation. NC = Not calculable.
HR <1 favours Osimertinib+Chemo. * p<0.05.

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Table 4.3.6.2 FLAURA-2: Summary of subgroup analysis of time to first UESI G>=3 GT: ILD und Pneumonitis
Safety Analysis Set, DCO 03APR2023

	Osi + Chemo (N=276)			Osi (N=275)					
Subgruppen	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]	Hazard Ratio [b]	[95%-KI] [b]	2-seitiger p-Wert [b]
Abstammung									
Chinesisch/Asiatisch	68	0	NE [NE; NE]	70	1 (1,4)	NE [NE; NE]	NC	[NC]	NC
Nicht-chinesisch/ Asiatisch	107	1 (0,9)	NE [NE; NE]	106	2 (1,9)	NE [NE; NE]	NC	[NC]	NC
Nicht-asiatisch	101	1 (1,0)	NE [NE; NE]	99	2 (2,0)	NE [NE; NE]	NC	[NC]	NC
Interaktion p-Wert									NC
Methode zur Gewebeuntersuchung									
zentral	120	0	NE [NE; NE]	119	0	NE [NE; NE]	NC	[NC]	NC
lokal	156	2 (1,3)	NE [NE; NE]	156	5 (3,2)	NE [NE; NE]	NC	[NC]	NC
Interaktion p-Wert									NC
WHO Performance-Status									
0	100	0	NE [NE; NE]	100	1 (1,0)	NE [NE; NE]	NC	[NC]	NC
1	176	2 (1,1)	NE [NE; NE]	175	4 (2,3)	NE [NE; NE]	NC	[NC]	NC
Interaktion p-Wert									NC
Raucherstatus									
Ja	90	1 (1,1)	NE [NE; NE]	96	4 (4,2)	NE [NE; NE]	NC	[NC]	NC
Nein	186	1 (0,5)	NE [NE; NE]	179	1 (0,6)	NE [NE; NE]	NC	[NC]	NC
Interaktion p-Wert									NC
Geschlecht									
Maennlich	104	1 (1,0)	NE [NE; NE]	107	2 (1,9)	NE [NE; NE]	NC	[NC]	NC
Weiblich	172	1 (0,6)	NE [NE; NE]	168	3 (1,8)	NE [NE; NE]	NC	[NC]	NC
Interaktion p-Wert									NC
Nachweis der EGFR-Mutation durch zentralen ctDNA Cobas Test									
positiv	211	1 (0,5)	NE [NE; NE]	204	4 (2,0)	NE [NE; NE]	NC	[NC]	NC

Time to event of AE is defined as the time from first dose of study treatment to first onset of the respective AE or the time to censoring if the AE has not occurred by 28 days following discontinuation of study treatment, before administration of subsequent cancer therapy or death, whichever comes first. All AEs are coded using MedDRA version 25.1. Includes AEs with onset date on or after the date of first dose and up to and including 28 days following discontinuation of study treatment. Analysis done if >=10 patients at each subgroup level and >=10 events in at least one subgroup level combined for both arms.
[a] Median time to event based on the Kaplan Meier estimate. NE = Not estimable as median (or 95% CLs) is not reached.
[b] Estimated from main effects of unstratified Cox proportional hazard model including trt., subgroup and subgroup-by-trt. interaction. Ties handled using Efron method and 95% CI derived from profile likelihood estimation. NC = Not calculable.
HR <1 favours Osimertinib+Chemo. * p<0.05.

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Table 4.3.6.2 FLAURA-2: Summary of subgroup analysis of time to first UESI G>=3 GT: ILD und Pneumonitis
Safety Analysis Set, DCO 03APR2023

	Osi + Chemo (N=276)			Osi (N=275)					
Subgruppen	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]	Hazard Ratio [b]	[95%-KI] [b]	2-seitiger p-Wert [b]
negativ	41	1 (2,4)	NE [NE; NE]	39	1 (2,6)	NE [NE; NE]	NC	[NC]	NC
unbekannt	24	0	NE [NE; NE]	32	0	NE [NE; NE]	NC	[NC]	NC
Interaktion p-Wert									NC
EGFR-Mutationstyp									
Exon 19 Deletion	172	0	NE [NE; NE]	167	2 (1,2)	NE [NE; NE]	NC	[NC]	NC
Exon 21 (L858R) Substitutionsmutation	104	2 (1,9)	NE [NE; NE]	106	3 (2,8)	NE [NE; NE]	NC	[NC]	NC
Interaktion p-Wert									NC
Zentral bestätigte EGFR-Mutation im Gewebe									
positiv	248	2 (0,8)	NE [NE; NE]	238	3 (1,3)	NE [NE; NE]	NC	[NC]	NC
negativ	3	0	NE [NE; NE]	4	1 (25,0)	NE [NE; NE]	NC	[NC]	NC
unbekannt	25	0	NE [NE; NE]	33	1 (3,0)	NE [NE; NE]	NC	[NC]	NC
Interaktion p-Wert									NC
ZNS-Metastasen zur Baseline									
Ja	113	1 (0,9)	NE [NE; NE]	110	2 (1,8)	NE [NE; NE]	NC	[NC]	NC
Nein	163	1 (0,6)	NE [NE; NE]	165	3 (1,8)	NE [NE; NE]	NC	[NC]	NC
Interaktion p-Wert									NC
Zentrale Bestätigung der EGFR-Mutation									
Zentral bestätigte EGFR-Mutation in Gewebe oder ctDNA	263	2 (0,8)	NE [NE; NE]	266	4 (1,5)	NE [NE; NE]	NC	[NC]	NC
Keine zentrale Bestätigung	13	0	NE [NE; NE]	9	1 (11,1)	NE [NE; NE]	NC	[NC]	NC
Interaktion p-Wert									NC
Alter bei Screening									

Time to event of AE is defined as the time from first dose of study treatment to first onset of the respective AE or the time to censoring if the AE has not occurred by 28 days following discontinuation of study treatment, before administration of subsequent cancer therapy or death, whichever comes first. All AEs are coded using MedDRA version 25.1. Includes AEs with onset date on or after the date of first dose and up to and including 28 days following discontinuation of study treatment. Analysis done if >=10 patients at each subgroup level and >=10 events in at least one subgroup level combined for both arms.
[a] Median time to event based on the Kaplan Meier estimate. NE = Not estimable as median (or 95% CLs) is not reached.
[b] Estimated from main effects of unstratified Cox proportional hazard model including trt., subgroup and subgroup-by-trt. interaction. Ties handled using Efron method and 95% CI derived from profile likelihood estimation. NC = Not calculable.
HR <1 favours Osimertinib+Chemo. * p<0.05.

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Table 4.3.6.2 FLAURA-2: Summary of subgroup analysis of time to first UESI G>=3 GT: ILD und Pneumonitis
Safety Analysis Set, DCO 03APR2023

	Osi + Chemo (N=276)			Osi (N=275)					
Subgruppen	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]	Hazard Ratio [b]	[95%-KI] [b]	2-seitiger p-Wert [b]
<65 Jahre	172	0	NE [NE; NE]	164	2 (1,2)	NE [NE; NE]	NC	[NC]	NC
>=65 Jahre	104	2 (1,9)	NE [NE; NE]	111	3 (2,7)	NE [NE; NE]	NC	[NC]	NC
Interaktion p-Wert									NC
Region gPAP									
Asien	168	1 (0,6)	NE [NE; NE]	166	3 (1,8)	NE [NE; NE]	NC	[NC]	NC
Europa	22	0	NE [NE; NE]	23	2 (8,7)	NE [NE; NE]	NC	[NC]	NC
Nordamerika	20	0	NE [NE; NE]	22	0	NE [NE; NE]	NC	[NC]	NC
Rest der Welt	66	1 (1,5)	NE [NE; NE]	64	0	NE [NE; NE]	NC	[NC]	NC
Interaktion p-Wert									NC

Time to event of AE is defined as the time from first dose of study treatment to first onset of the respective AE or the time to censoring if the AE has not occurred by 28 days following discontinuation of study treatment, before administration of subsequent cancer therapy or death, whichever comes first. All AEs are coded using MedDRA version 25.1. Includes AEs with onset date on or after the date of first dose and up to and including 28 days following discontinuation of study treatment.
Analysis done if >=10 patients at each subgroup level and >=10 events in at least one subgroup level combined for both arms.
[a] Median time to event based on the Kaplan Meier estimate. NE = Not estimable as median (or 95% CLs) is not reached.
[b] Estimated from main effects of unstratified Cox proportional hazard model including trt., subgroup and subgroup-by-trt. interaction. Ties handled using Efron method and 95% CI derived from profile likelihood estimation. NC = Not calculable.
HR <1 favours Osimertinib+Chemo. * p<0.05.

root/cdar/d516/payer_germany/ar/d5169c00001_payer_germany/tlf/prod/program/ttesubae.sas gttesubaefab 22DEC2023:09:13 kfrh585

Table 4.3.6.3 FLAURA-2: Summary of subgroup analysis of time to first UESI G>=3 GT: Kardiale Effekte (Herzinsuffizienz)
Safety Analysis Set, DCO 03APR2023

	Osi + Chemo (N=276)			Osi (N=275)					
Subgruppen	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]	Hazard Ratio [b]	[95%-KI] [b]	2-seitiger p-Wert [b]
Abstammung									
Chinesisch/Asiatisch	68	1 (1,5)	NE [NE; NE]	70	0	NE [NE; NE]	NC	[NC]	NC
Nicht-chinesisch/ Asiatisch	107	6 (5,6)	NE [NE; NE]	106	0	NE [NE; NE]	NC	[NC]	NC
Nicht-asiatisch	101	5 (5,0)	NE [NE; NE]	99	3 (3,0)	NE [NE; NE]	NC	[NC]	NC
Interaktion p-Wert									NC
Methode zur Gewebeuntersuchung									
zentral	120	5 (4,2)	NE [NE; NE]	119	0	NE [NE; NE]	NC	[NC]	NC
lokal	156	7 (4,5)	NE [NE; NE]	156	3 (1,9)	NE [NE; NE]	2,19	[0,61; 10,20]	0,2367
Interaktion p-Wert									NC
WHO Performance-Status									
0	100	4 (4,0)	NE [NE; NE]	100	0	NE [NE; NE]	NC	[NC]	NC
1	176	8 (4,5)	NE [NE; NE]	175	3 (1,7)	NE [NE; NE]	2,55	[0,74; 11,63]	0,1443
Interaktion p-Wert									NC
Raucherstatus									
Ja	90	7 (7,8)	NE [NE; NE]	96	0	NE [NE; NE]	NC	[NC]	NC
Nein	186	5 (2,7)	NE [NE; NE]	179	3 (1,7)	NE [NE; NE]	NC	[NC]	NC
Interaktion p-Wert									NC
Geschlecht									
Maennlich	104	8 (7,7)	NE [NE; NE]	107	2 (1,9)	NE [NE; NE]	3,65	[0,91; 24,24]	0,0689
Weiblich	172	4 (2,3)	NE [NE; NE]	168	1 (0,6)	NE [NE; NE]	4,13	[0,61; 80,74]	0,1551
Interaktion p-Wert									0,9284
Nachweis der EGFR-Mutation durch zentralen ctDNA Cobas Test									
positiv	211	10 (4,7)	NE [NE; NE]	204	2 (1,0)	NE [NE; NE]	4,88	[1,29; 31,79]	0,0176*

Time to event of AE is defined as the time from first dose of study treatment to first onset of the respective AE or the time to censoring if the AE has not occurred by 28 days following discontinuation of study treatment, before administration of subsequent cancer therapy or death, whichever comes first. All AEs are coded using MedDRA version 25.1. Includes AEs with onset date on or after the date of first dose and up to and including 28 days following discontinuation of study treatment. Analysis done if >=10 patients at each subgroup level and >=10 events in at least one subgroup level combined for both arms.
[a] Median time to event based on the Kaplan Meier estimate. NE = Not estimable as median (or 95% CLs) is not reached.
[b] Estimated from main effects of unstratified Cox proportional hazard model including trt., subgroup and subgroup-by-trt. interaction. Ties handled using Efron method and 95% CI derived from profile likelihood estimation. NC = Not calculable.
HR <1 favours Osimertinib+Chemo. * p<0.05.

root/cdar/d516/payer_germany/ar/d5169c00001_payer_germany/tlf/prod/program/ttesubae.sas gttesubaefac 22DEC2023:09:13 kfrh585

Table 4.3.6.3 FLAURA-2: Summary of subgroup analysis of time to first UESI G>=3 GT: Kardiale Effekte (Herzinsuffizienz)
Safety Analysis Set, DCO 03APR2023

	Osi + Chemo (N=276)			Osi (N=275)					
Subgruppen	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]	Hazard Ratio [b]	[95%-KI] [b]	2-seitiger p-Wert [b]
negativ	41	2 (4,9)	NE [NE; NE]	39	1 (2,6)	NE [NE; NE]	1,90	[0,18; 40,96]	0,5885
unbekannt	24	0	NE [NE; NE]	32	0	NE [NE; NE]	NC	[NC]	NC
Interaktion p-Wert									0,5270
EGFR-Mutationstyp									
Exon 19 Deletion	172	9 (5,2)	NE [NE; NE]	167	2 (1,2)	NE [NE; NE]	4,67	[1,20; 30,72]	0,0246*
Exon 21 (L858R)	104	3 (2,9)	NE [NE; NE]	106	1 (0,9)	NE [NE; NE]	2,68	[0,34; 54,34]	0,3630
Substitutionsmutation									
Interaktion p-Wert									0,6971
Zentral bestätigte EGFR-Mutation im Gewebe									
positiv	248	10 (4,0)	NE [NE; NE]	238	2 (0,8)	NE [NE; NE]	4,67	[1,23; 30,42]	0,0214*
negativ	3	0	NE [NE; NE]	4	1 (25,0)	NE [NE; NE]	NC	[NC]	NC
unbekannt	25	2 (8,0)	NE [NE; NE]	33	0	NE [NE; NE]	NC	[NC]	NC
Interaktion p-Wert									NC
ZNS-Metastasen zur Baseline									
Ja	113	7 (6,2)	NE [NE; NE]	110	1 (0,9)	NE [NE; NE]	NC	[NC]	NC
Nein	163	5 (3,1)	NE [NE; NE]	165	2 (1,2)	NE [NE; NE]	NC	[NC]	NC
Interaktion p-Wert									NC
Zentrale Bestätigung der EGFR-Mutation									
Zentral bestätigte EGFR-Mutation in Gewebe oder ctDNA	263	12 (4,6)	NE [NE; NE]	266	2 (0,8)	NE [NE; NE]	6,01	[1,64; 38,61]	0,0048*
Keine zentrale Bestätigung	13	0	NE [NE; NE]	9	1 (11,1)	NE [NE; NE]	NC	[NC]	NC
Interaktion p-Wert									NC
Alter bei Screening									

Time to event of AE is defined as the time from first dose of study treatment to first onset of the respective AE or the time to censoring if the AE has not occurred by 28 days following discontinuation of study treatment, before administration of subsequent cancer therapy or death, whichever comes first. All AEs are coded using MedDRA version 25.1. Includes AEs with onset date on or after the date of first dose and up to and including 28 days following discontinuation of study treatment. Analysis done if >=10 patients at each subgroup level and >=10 events in at least one subgroup level combined for both arms.
[a] Median time to event based on the Kaplan Meier estimate. NE = Not estimable as median (or 95% CLs) is not reached.
[b] Estimated from main effects of unstratified Cox proportional hazard model including trt., subgroup and subgroup-by-trt. interaction. Ties handled using Efron method and 95% CI derived from profile likelihood estimation. NC = Not calculable.
HR <1 favours Osimertinib+Chemo. * p<0.05.

root/cdar/d516/payer_germany/ar/d5169c00001_payer_germany/tlf/prod/program/ttesubae.sas gttesubaefac 22DEC2023:09:13 kfrh585

Table 4.3.6.3 FLAURA-2: Summary of subgroup analysis of time to first UESI G>=3 GT: Kardiale Effekte (Herzinsuffizienz)
Safety Analysis Set, DCO 03APR2023

	Osi + Chemo (N=276)			Osi (N=275)					
Subgruppen	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]	Hazard Ratio [b]	[95%-KI] [b]	2-seitiger p-Wert [b]
<65 Jahre	172	5 (2,9)	NE [NE; NE]	164	1 (0,6)	NE [NE; NE]	NC	[NC]	NC
>=65 Jahre	104	7 (6,7)	NE [NE; NE]	111	2 (1,8)	NE [NE; NE]	NC	[NC]	NC
Interaktion p-Wert									NC
Region gPAP									
Asien	168	6 (3,6)	NE [NE; NE]	166	0	NE [NE; NE]	NC	[NC]	NC
Europa	22	0	NE [NE; NE]	23	2 (8,7)	NE [NE; NE]	NC	[NC]	NC
Nordamerika	20	2 (10,0)	NE [NE; NE]	22	0	NE [NE; NE]	NC	[NC]	NC
Rest der Welt	66	4 (6,1)	NE [NE; NE]	64	1 (1,6)	NE [NE; NE]	NC	[NC]	NC
Interaktion p-Wert									NC

Time to event of AE is defined as the time from first dose of study treatment to first onset of the respective AE or the time to censoring if the AE has not occurred by 28 days following discontinuation of study treatment, before administration of subsequent cancer therapy or death, whichever comes first. All AEs are coded using MedDRA version 25.1. Includes AEs with onset date on or after the date of first dose and up to and including 28 days following discontinuation of study treatment. Analysis done if >=10 patients at each subgroup level and >=10 events in at least one subgroup level combined for both arms.
[a] Median time to event based on the Kaplan Meier estimate. NE = Not estimable as median (or 95% CLs) is not reached.
[b] Estimated from main effects of unstratified Cox proportional hazard model including trt., subgroup and subgroup-by-trt. interaction. Ties handled using Efron method and 95% CI derived from profile likelihood estimation. NC = Not calculable.
HR <1 favours Osimertinib+Chemo. * p<0.05.

root/cdar/d516/payer_germany/ar/d5169c00001_payer_germany/tlf/prod/program/ttesubae.sas gttesubaefac 22DEC2023:09:13 kfrh585

Table 4.3.7.1 FLAURA-2: Summary of subgroup analysis of time to first SUESI GT: Hämatologische Toxizitäten
Safety Analysis Set, DCO 03APR2023

	Osi + Chemo (N=276)			Osi (N=275)					
Subgruppen	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]	Hazard Ratio [b]	[95%-KI] [b]	2-seitiger p-Wert [b]
Abstammung									
Chinesisch/Asiatisch	68	9 (13,2)	NE [NE; NE]	70	1 (1,4)	NE [NE; NE]	9,43	[1,77;173,89]	0,0055*
Nicht-chinesisch/ Asiatisch	107	11 (10,3)	NE [NE; NE]	106	0	NE [NE; NE]	NC	[NC]	NC
Nicht-asiatisch	101	3 (3,0)	NE [NE; NE]	99	0	NE [NE; NE]	NC	[NC]	NC
Interaktion p-Wert									NC
Methode zur Gewebeuntersuchung									
zentral	120	16 (13,3)	NE [NE; NE]	119	1 (0,8)	NE [NE; NE]	17,04	[3,48;307,56]	<0,0001*
lokal	156	7 (4,5)	NE [NE; NE]	156	0	NE [NE; NE]	NC	[NC]	NC
Interaktion p-Wert									NC
WHO Performance-Status									
0	100	2 (2,0)	NE [NE; NE]	100	0	NE [NE; NE]	NC	[NC]	NC
1	176	21 (11,9)	NE [NE; NE]	175	1 (0,6)	NE [NE; NE]	21,90	[4,58;392,44]	<0,0001*
Interaktion p-Wert									NC
Raucherstatus									
Ja	90	7 (7,8)	NE [NE; NE]	96	1 (1,0)	NE [NE; NE]	NC	[NC]	NC
Nein	186	16 (8,6)	NE [NE; NE]	179	0	NE [NE; NE]	NC	[NC]	NC
Interaktion p-Wert									NC
Geschlecht									
Maennlich	104	11 (10,6)	NE [NE; NE]	107	1 (0,9)	NE [NE; NE]	11,21	[2,18;204,89]	0,0016*
Weiblich	172	12 (7,0)	NE [NE; NE]	168	0	NE [NE; NE]	NC	[NC]	NC
Interaktion p-Wert									NC
Nachweis der EGFR-Mutation durch zentralen ctDNA Cobas Test									
positiv	211	19 (9,0)	NE [NE; NE]	204	1 (0,5)	NE [NE; NE]	19,10	[3,97;343,10]	<0,0001*

Time to event of AE is defined as the time from first dose of study treatment to first onset of the respective AE or the time to censoring if the AE has not occurred by 28 days following discontinuation of study treatment, before administration of subsequent cancer therapy or death, whichever comes first. All AEs are coded using MedDRA version 25.1. Includes AEs with onset date on or after the date of first dose and up to and including 28 days following discontinuation of study treatment. Analysis done if >=10 patients at each subgroup level and >=10 events in at least one subgroup level combined for both arms.
[a] Median time to event based on the Kaplan Meier estimate. NE = Not estimable as median (or 95% CLs) is not reached.
[b] Estimated from main effects of unstratified Cox proportional hazard model including trt., subgroup and subgroup-by-trt. interaction. Ties handled using Efron method and 95% CI derived from profile likelihood estimation. NC = Not calculable.
HR <1 favours Osimertinib+Chemo. * p<0.05.

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Table 4.3.7.1 FLAURA-2: Summary of subgroup analysis of time to first SUESI GT: Hämatologische Toxizitäten
Safety Analysis Set, DCO 03APR2023

	Osi + Chemo (N=276)			Osi (N=275)					
Subgruppen	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]	Hazard Ratio [b]	[95%-KI] [b]	2-seitiger p-Wert [b]
negativ	41	2 (4,9)	NE [NE; NE]	39	0	NE [NE; NE]	NC	[NC]	NC
unbekannt	24	2 (8,3)	NE [NE; NE]	32	0	NE [NE; NE]	NC	[NC]	NC
Interaktion p-Wert									NC
EGFR-Mutationstyp									
Exon 19 Deletion	172	16 (9,3)	NE [NE; NE]	167	1 (0,6)	NE [NE; NE]	16,30	[3,33;294,29]	<0,0001*
Exon 21 (L858R) Substitutionsmutation	104	7 (6,7)	NE [NE; NE]	106	0	NE [NE; NE]	NC	[NC]	NC
Interaktion p-Wert									NC
Zentral bestätigte EGFR-Mutation im Gewebe									
positiv	248	22 (8,9)	NE [NE; NE]	238	1 (0,4)	NE [NE; NE]	22,07	[4,64;395,03]	<0,0001*
negativ	3	0	NE [NE; NE]	4	0	NE [NE; NE]	NC	[NC]	NC
unbekannt	25	1 (4,0)	NE [NE; NE]	33	0	NE [NE; NE]	NC	[NC]	NC
Interaktion p-Wert									NC
ZNS-Metastasen zur Baseline									
Ja	113	8 (7,1)	NE [NE; NE]	110	0	NE [NE; NE]	NC	[NC]	NC
Nein	163	15 (9,2)	NE [NE; NE]	165	1 (0,6)	NE [NE; NE]	16,01	[3,25;289,58]	<0,0001*
Interaktion p-Wert									NC
Zentrale Bestätigung der EGFR-Mutation									
Zentral bestätigte EGFR-Mutation in Gewebe oder ctDNA	263	23 (8,7)	NE [NE; NE]	266	1 (0,4)	NE [NE; NE]	24,27	[5,12;433,98]	<0,0001*
Keine zentrale Bestätigung	13	0	NE [NE; NE]	9	0	NE [NE; NE]	NC	[NC]	NC
Interaktion p-Wert									NC
Alter bei Screening									

Time to event of AE is defined as the time from first dose of study treatment to first onset of the respective AE or the time to censoring if the AE has not occurred by 28 days following discontinuation of study treatment, before administration of subsequent cancer therapy or death, whichever comes first. All AEs are coded using MedDRA version 25.1. Includes AEs with onset date on or after the date of first dose and up to and including 28 days following discontinuation of study treatment. Analysis done if >=10 patients at each subgroup level and >=10 events in at least one subgroup level combined for both arms.
[a] Median time to event based on the Kaplan Meier estimate. NE = Not estimable as median (or 95% CLs) is not reached.
[b] Estimated from main effects of unstratified Cox proportional hazard model including trt., subgroup and subgroup-by-trt. interaction. Ties handled using Efron method and 95% CI derived from profile likelihood estimation. NC = Not calculable.
HR <1 favours Osimertinib+Chemo. * p<0.05.

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Table 4.3.7.1 FLAURA-2: Summary of subgroup analysis of time to first SUESI GT: Hämatologische Toxizitäten
Safety Analysis Set, DCO 03APR2023

	Osi + Chemo (N=276)			Osi (N=275)					
Subgruppen	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]	Hazard Ratio [b]	[95%-KI] [b]	2-seitiger p-Wert [b]
<65 Jahre	172	20 (11,6)	NE [NE; NE]	164	1 (0,6)	NE [NE; NE]	19,78	[4,12;354,83]	<0,0001*
>=65 Jahre	104	3 (2,9)	NE [NE; NE]	111	0	NE [NE; NE]	NC	[NC]	NC
Interaktion p-Wert									NC
Region gPAP									
Asien	168	21 (12,5)	NE [NE; NE]	166	1 (0,6)	NE [NE; NE]	22,09	[4,62;395,76]	<0,0001*
Europa	22	1 (4,5)	NE [NE; NE]	23	0	NE [NE; NE]	NC	[NC]	NC
Nordamerika	20	0	NE [NE; NE]	22	0	NE [NE; NE]	NC	[NC]	NC
Rest der Welt	66	1 (1,5)	NE [NE; NE]	64	0	NE [NE; NE]	NC	[NC]	NC
Interaktion p-Wert									NC

Time to event of AE is defined as the time from first dose of study treatment to first onset of the respective AE or the time to censoring if the AE has not occurred by 28 days following discontinuation of study treatment, before administration of subsequent cancer therapy or death, whichever comes first. All AEs are coded using MedDRA version 25.1. Includes AEs with onset date on or after the date of first dose and up to and including 28 days following discontinuation of study treatment. Analysis done if >=10 patients at each subgroup level and >=10 events in at least one subgroup level combined for both arms.
[a] Median time to event based on the Kaplan Meier estimate. NE = Not estimable as median (or 95% CLs) is not reached.
[b] Estimated from main effects of unstratified Cox proportional hazard model including trt., subgroup and subgroup-by-trt. interaction. Ties handled using Efron method and 95% CI derived from profile likelihood estimation. NC = Not calculable. HR <1 favours Osimertinib+Chemo. * p<0.05.

root/cdar/d516/payer_germany/ar/d5169c00001_payer_germany/tlf/prod/program/ttesubae.sas gttesubaegaa 22DEC2023:09:13 kfrh585

Table 4.3.7.2 FLAURA-2: Summary of subgroup analysis of time to first SUESI GT: ILD und Pneumonitis
Safety Analysis Set, DCO 03APR2023

	Osi + Chemo (N=276)			Osi (N=275)					
Subgruppen	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]	Hazard Ratio [b]	[95%-KI] [b]	2-seitiger p-Wert [b]
Abstammung									
Chinesisch/Asiatisch	68	0	NE [NE; NE]	70	2 (2,9)	NE [NE; NE]	NC	[NC]	NC
Nicht-chinesisch/ Asiatisch	107	2 (1,9)	NE [NE; NE]	106	2 (1,9)	NE [NE; NE]	NC	[NC]	NC
Nicht-asiatisch	101	1 (1,0)	NE [NE; NE]	99	2 (2,0)	NE [NE; NE]	NC	[NC]	NC
Interaktion p-Wert									NC
Methode zur Gewebeuntersuchung									
zentral	120	0	NE [NE; NE]	119	1 (0,8)	NE [NE; NE]	NC	[NC]	NC
lokal	156	3 (1,9)	NE [NE; NE]	156	5 (3,2)	NE [NE; NE]	NC	[NC]	NC
Interaktion p-Wert									NC
WHO Performance-Status									
0	100	2 (2,0)	NE [NE; NE]	100	1 (1,0)	NE [NE; NE]	NC	[NC]	NC
1	176	1 (0,6)	NE [NE; NE]	175	5 (2,9)	NE [NE; NE]	NC	[NC]	NC
Interaktion p-Wert									NC
Raucherstatus									
Ja	90	1 (1,1)	NE [NE; NE]	96	5 (5,2)	NE [NE; NE]	NC	[NC]	NC
Nein	186	2 (1,1)	NE [NE; NE]	179	1 (0,6)	NE [NE; NE]	NC	[NC]	NC
Interaktion p-Wert									NC
Geschlecht									
Maennlich	104	2 (1,9)	NE [NE; NE]	107	3 (2,8)	NE [NE; NE]	NC	[NC]	NC
Weiblich	172	1 (0,6)	NE [NE; NE]	168	3 (1,8)	NE [NE; NE]	NC	[NC]	NC
Interaktion p-Wert									NC
Nachweis der EGFR-Mutation durch zentralen ctDNA Cobas Test									
positiv	211	2 (0,9)	NE [NE; NE]	204	5 (2,5)	NE [NE; NE]	NC	[NC]	NC

Time to event of AE is defined as the time from first dose of study treatment to first onset of the respective AE or the time to censoring if the AE has not occurred by 28 days following discontinuation of study treatment, before administration of subsequent cancer therapy or death, whichever comes first. All AEs are coded using MedDRA version 25.1. Includes AEs with onset date on or after the date of first dose and up to and including 28 days following discontinuation of study treatment. Analysis done if >=10 patients at each subgroup level and >=10 events in at least one subgroup level combined for both arms.
[a] Median time to event based on the Kaplan Meier estimate. NE = Not estimable as median (or 95% CLs) is not reached.
[b] Estimated from main effects of unstratified Cox proportional hazard model including trt., subgroup and subgroup-by-trt. interaction. Ties handled using Efron method and 95% CI derived from profile likelihood estimation. NC = Not calculable.
HR <1 favours Osimertinib+Chemo. * p<0.05.

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Table 4.3.7.2 FLAURA-2: Summary of subgroup analysis of time to first SUESI GT: ILD und Pneumonitis
Safety Analysis Set, DCO 03APR2023

	Osi + Chemo (N=276)			Osi (N=275)					
Subgruppen	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]	Hazard Ratio [b]	[95%-KI] [b]	2-seitiger p-Wert [b]
negativ	41	1 (2,4)	NE [NE; NE]	39	1 (2,6)	NE [NE; NE]	NC	[NC]	NC
unbekannt	24	0	NE [NE; NE]	32	0	NE [NE; NE]	NC	[NC]	NC
Interaktion p-Wert									NC
EGFR-Mutationstyp									
Exon 19 Deletion	172	0	NE [NE; NE]	167	3 (1,8)	NE [NE; NE]	NC	[NC]	NC
Exon 21 (L858R) Substitutionsmutation	104	3 (2,9)	NE [NE; NE]	106	3 (2,8)	NE [NE; NE]	NC	[NC]	NC
Interaktion p-Wert									NC
Zentral bestätigte EGFR-Mutation im Gewebe									
positiv	248	3 (1,2)	NE [NE; NE]	238	4 (1,7)	NE [NE; NE]	NC	[NC]	NC
negativ	3	0	NE [NE; NE]	4	1 (25,0)	NE [NE; NE]	NC	[NC]	NC
unbekannt	25	0	NE [NE; NE]	33	1 (3,0)	NE [NE; NE]	NC	[NC]	NC
Interaktion p-Wert									NC
ZNS-Metastasen zur Baseline									
Ja	113	0	NE [NE; NE]	110	3 (2,7)	NE [NE; NE]	NC	[NC]	NC
Nein	163	3 (1,8)	NE [NE; NE]	165	3 (1,8)	NE [NE; NE]	NC	[NC]	NC
Interaktion p-Wert									NC
Zentrale Bestätigung der EGFR-Mutation									
Zentral bestätigte EGFR-Mutation in Gewebe oder ctDNA	263	3 (1,1)	NE [NE; NE]	266	5 (1,9)	NE [NE; NE]	NC	[NC]	NC
Keine zentrale Bestätigung	13	0	NE [NE; NE]	9	1 (11,1)	NE [NE; NE]	NC	[NC]	NC
Interaktion p-Wert									NC
Alter bei Screening									

Time to event of AE is defined as the time from first dose of study treatment to first onset of the respective AE or the time to censoring if the AE has not occurred by 28 days following discontinuation of study treatment, before administration of subsequent cancer therapy or death, whichever comes first. All AEs are coded using MedDRA version 25.1. Includes AEs with onset date on or after the date of first dose and up to and including 28 days following discontinuation of study treatment. Analysis done if >=10 patients at each subgroup level and >=10 events in at least one subgroup level combined for both arms.
[a] Median time to event based on the Kaplan Meier estimate. NE = Not estimable as median (or 95% CLs) is not reached.
[b] Estimated from main effects of unstratified Cox proportional hazard model including trt., subgroup and subgroup-by-trt. interaction. Ties handled using Efron method and 95% CI derived from profile likelihood estimation. NC = Not calculable.
HR <1 favours Osimertinib+Chemo. * p<0.05.

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Table 4.3.7.2 FLAURA-2: Summary of subgroup analysis of time to first SUESI GT: ILD und Pneumonitis
Safety Analysis Set, DCO 03APR2023

	Osi + Chemo (N=276)			Osi (N=275)					
Subgruppen	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]	Hazard Ratio [b]	[95%-KI] [b]	2-seitiger p-Wert [b]
<65 Jahre	172	0	NE [NE; NE]	164	3 (1,8)	NE [NE; NE]	NC	[NC]	NC
>=65 Jahre	104	3 (2,9)	NE [NE; NE]	111	3 (2,7)	NE [NE; NE]	NC	[NC]	NC
Interaktion p-Wert									NC
Region gPAP									
Asien	168	2 (1,2)	NE [NE; NE]	166	4 (2,4)	NE [NE; NE]	NC	[NC]	NC
Europa	22	0	NE [NE; NE]	23	2 (8,7)	NE [NE; NE]	NC	[NC]	NC
Nordamerika	20	0	NE [NE; NE]	22	0	NE [NE; NE]	NC	[NC]	NC
Rest der Welt	66	1 (1,5)	NE [NE; NE]	64	0	NE [NE; NE]	NC	[NC]	NC
Interaktion p-Wert									NC

Time to event of AE is defined as the time from first dose of study treatment to first onset of the respective AE or the time to censoring if the AE has not occurred by 28 days following discontinuation of study treatment, before administration of subsequent cancer therapy or death, whichever comes first. All AEs are coded using MedDRA version 25.1. Includes AEs with onset date on or after the date of first dose and up to and including 28 days following discontinuation of study treatment. Analysis done if >=10 patients at each subgroup level and >=10 events in at least one subgroup level combined for both arms.
[a] Median time to event based on the Kaplan Meier estimate. NE = Not estimable as median (or 95% CLs) is not reached.
[b] Estimated from main effects of unstratified Cox proportional hazard model including trt., subgroup and subgroup-by-trt. interaction. Ties handled using Efron method and 95% CI derived from profile likelihood estimation. NC = Not calculable. HR <1 favours Osimertinib+Chemo. * p<0.05.

root/cdar/d516/payer_germany/ar/d5169c00001_payer_germany/tlf/prod/program/ttesubae.sas gttesubaegab 22DEC2023:09:13 kfrh585

Table 4.3.7.3 FLAURA-2: Summary of subgroup analysis of time to first SUESI GT: Kardiale Effekte (Herzinsuffizienz)
Safety Analysis Set, DCO 03APR2023

	Osi + Chemo (N=276)			Osi (N=275)					
Subgruppen	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]	Hazard Ratio [b]	[95%-KI] [b]	2-seitiger p-Wert [b]
Abstammung									
Chinesisch/Asiatisch	68	1 (1,5)	NE [NE; NE]	70	0	NE [NE; NE]	NC	[NC]	NC
Nicht-chinesisch/ Asiatisch	107	1 (0,9)	NE [NE; NE]	106	0	NE [NE; NE]	NC	[NC]	NC
Nicht-asiatisch	101	2 (2,0)	NE [NE; NE]	99	0	NE [NE; NE]	NC	[NC]	NC
Interaktion p-Wert									NC
Methode zur Gewebeuntersuchung									
zentral	120	3 (2,5)	NE [NE; NE]	119	0	NE [NE; NE]	NC	[NC]	NC
lokal	156	1 (0,6)	NE [NE; NE]	156	0	NE [NE; NE]	NC	[NC]	NC
Interaktion p-Wert									NC
WHO Performance-Status									
0	100	1 (1,0)	NE [NE; NE]	100	0	NE [NE; NE]	NC	[NC]	NC
1	176	3 (1,7)	NE [NE; NE]	175	0	NE [NE; NE]	NC	[NC]	NC
Interaktion p-Wert									NC
Raucherstatus									
Ja	90	1 (1,1)	NE [NE; NE]	96	0	NE [NE; NE]	NC	[NC]	NC
Nein	186	3 (1,6)	NE [NE; NE]	179	0	NE [NE; NE]	NC	[NC]	NC
Interaktion p-Wert									NC
Geschlecht									
Maennlich	104	2 (1,9)	NE [NE; NE]	107	0	NE [NE; NE]	NC	[NC]	NC
Weiblich	172	2 (1,2)	NE [NE; NE]	168	0	NE [NE; NE]	NC	[NC]	NC
Interaktion p-Wert									NC
Nachweis der EGFR-Mutation durch zentralen ctDNA Cobas Test									
positiv	211	4 (1,9)	NE [NE; NE]	204	0	NE [NE; NE]	NC	[NC]	NC

Time to event of AE is defined as the time from first dose of study treatment to first onset of the respective AE or the time to censoring if the AE has not occurred by 28 days following discontinuation of study treatment, before administration of subsequent cancer therapy or death, whichever comes first. All AEs are coded using MedDRA version 25.1. Includes AEs with onset date on or after the date of first dose and up to and including 28 days following discontinuation of study treatment. Analysis done if >=10 patients at each subgroup level and >=10 events in at least one subgroup level combined for both arms.
[a] Median time to event based on the Kaplan Meier estimate. NE = Not estimable as median (or 95% CLs) is not reached.
[b] Estimated from main effects of unstratified Cox proportional hazard model including trt., subgroup and subgroup-by-trt. interaction. Ties handled using Efron method and 95% CI derived from profile likelihood estimation. NC = Not calculable.
HR <1 favours Osimertinib+Chemo. * p<0.05.

root/cdar/d516/payer_germany/ar/d5169c00001_payer_germany/tlf/prod/program/ttesubae.sas gttesubaegac 22DEC2023:09:13 kfrh585

Table 4.3.7.3 FLAURA-2: Summary of subgroup analysis of time to first SUESI GT: Kardiale Effekte (Herzinsuffizienz)
Safety Analysis Set, DCO 03APR2023

	Osi + Chemo (N=276)			Osi (N=275)					
Subgruppen	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]	Hazard Ratio [b]	[95%-KI] [b]	2-seitiger p-Wert [b]
negativ	41	0	NE [NE; NE]	39	0	NE [NE; NE]	NC	[NC]	NC
unbekannt	24	0	NE [NE; NE]	32	0	NE [NE; NE]	NC	[NC]	NC
Interaktion p-Wert									NC
EGFR-Mutationstyp									
Exon 19 Deletion	172	3 (1,7)	NE [NE; NE]	167	0	NE [NE; NE]	NC	[NC]	NC
Exon 21 (L858R) Substitutionsmutation	104	1 (1,0)	NE [NE; NE]	106	0	NE [NE; NE]	NC	[NC]	NC
Interaktion p-Wert									NC
Zentral bestätigte EGFR-Mutation im Gewebe									
positiv	248	4 (1,6)	NE [NE; NE]	238	0	NE [NE; NE]	NC	[NC]	NC
negativ	3	0	NE [NE; NE]	4	0	NE [NE; NE]	NC	[NC]	NC
unbekannt	25	0	NE [NE; NE]	33	0	NE [NE; NE]	NC	[NC]	NC
Interaktion p-Wert									NC
ZNS-Metastasen zur Baseline									
Ja	113	2 (1,8)	NE [NE; NE]	110	0	NE [NE; NE]	NC	[NC]	NC
Nein	163	2 (1,2)	NE [NE; NE]	165	0	NE [NE; NE]	NC	[NC]	NC
Interaktion p-Wert									NC
Zentrale Bestätigung der EGFR-Mutation									
Zentral bestätigte EGFR-Mutation in Gewebe oder ctDNA	263	4 (1,5)	NE [NE; NE]	266	0	NE [NE; NE]	NC	[NC]	NC
Keine zentrale Bestätigung	13	0	NE [NE; NE]	9	0	NE [NE; NE]	NC	[NC]	NC
Interaktion p-Wert									NC
Alter bei Screening									

Time to event of AE is defined as the time from first dose of study treatment to first onset of the respective AE or the time to censoring if the AE has not occurred by 28 days following discontinuation of study treatment, before administration of subsequent cancer therapy or death, whichever comes first. All AEs are coded using MedDRA version 25.1. Includes AEs with onset date on or after the date of first dose and up to and including 28 days following discontinuation of study treatment. Analysis done if >=10 patients at each subgroup level and >=10 events in at least one subgroup level combined for both arms.
[a] Median time to event based on the Kaplan Meier estimate. NE = Not estimable as median (or 95% CLs) is not reached.
[b] Estimated from main effects of unstratified Cox proportional hazard model including trt., subgroup and subgroup-by-trt. interaction. Ties handled using Efron method and 95% CI derived from profile likelihood estimation. NC = Not calculable.
HR <1 favours Osimertinib+Chemo. * p<0.05.

root/cdar/d516/payer_germany/ar/d5169c00001_payer_germany/tlf/prod/program/ttesubae.sas gttesubaegac 22DEC2023:09:13 kfrh585

Table 4.3.7.3 FLAURA-2: Summary of subgroup analysis of time to first SUESI GT: Kardiale Effekte (Herzinsuffizienz)
Safety Analysis Set, DCO 03APR2023

	Osi + Chemo (N=276)			Osi (N=275)					
Subgruppen	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]	n	Anzahl (%) der Patienten mit Ereignis	Mediane Zeit [95%-KI] (Monate) [a]	Hazard Ratio [b]	[95%-KI] [b]	2-seitiger p-Wert [b]
<65 Jahre	172	1 (0,6)	NE [NE; NE]	164	0	NE [NE; NE]	NC	[NC]	NC
>=65 Jahre	104	3 (2,9)	NE [NE; NE]	111	0	NE [NE; NE]	NC	[NC]	NC
Interaktion p-Wert									NC
Region gPAP									
Asien	168	2 (1,2)	NE [NE; NE]	166	0	NE [NE; NE]	NC	[NC]	NC
Europa	22	0	NE [NE; NE]	23	0	NE [NE; NE]	NC	[NC]	NC
Nordamerika	20	0	NE [NE; NE]	22	0	NE [NE; NE]	NC	[NC]	NC
Rest der Welt	66	2 (3,0)	NE [NE; NE]	64	0	NE [NE; NE]	NC	[NC]	NC
Interaktion p-Wert									NC

Time to event of AE is defined as the time from first dose of study treatment to first onset of the respective AE or the time to censoring if the AE has not occurred by 28 days following discontinuation of study treatment, before administration of subsequent cancer therapy or death, whichever comes first. All AEs are coded using MedDRA version 25.1. Includes AEs with onset date on or after the date of first dose and up to and including 28 days following discontinuation of study treatment. Analysis done if >=10 patients at each subgroup level and >=10 events in at least one subgroup level combined for both arms.
[a] Median time to event based on the Kaplan Meier estimate. NE = Not estimable as median (or 95% CLs) is not reached.
[b] Estimated from main effects of unstratified Cox proportional hazard model including trt., subgroup and subgroup-by-trt. interaction. Ties handled using Efron method and 95% CI derived from profile likelihood estimation. NC = Not calculable. HR <1 favours Osimertinib+Chemo. * p<0.05.

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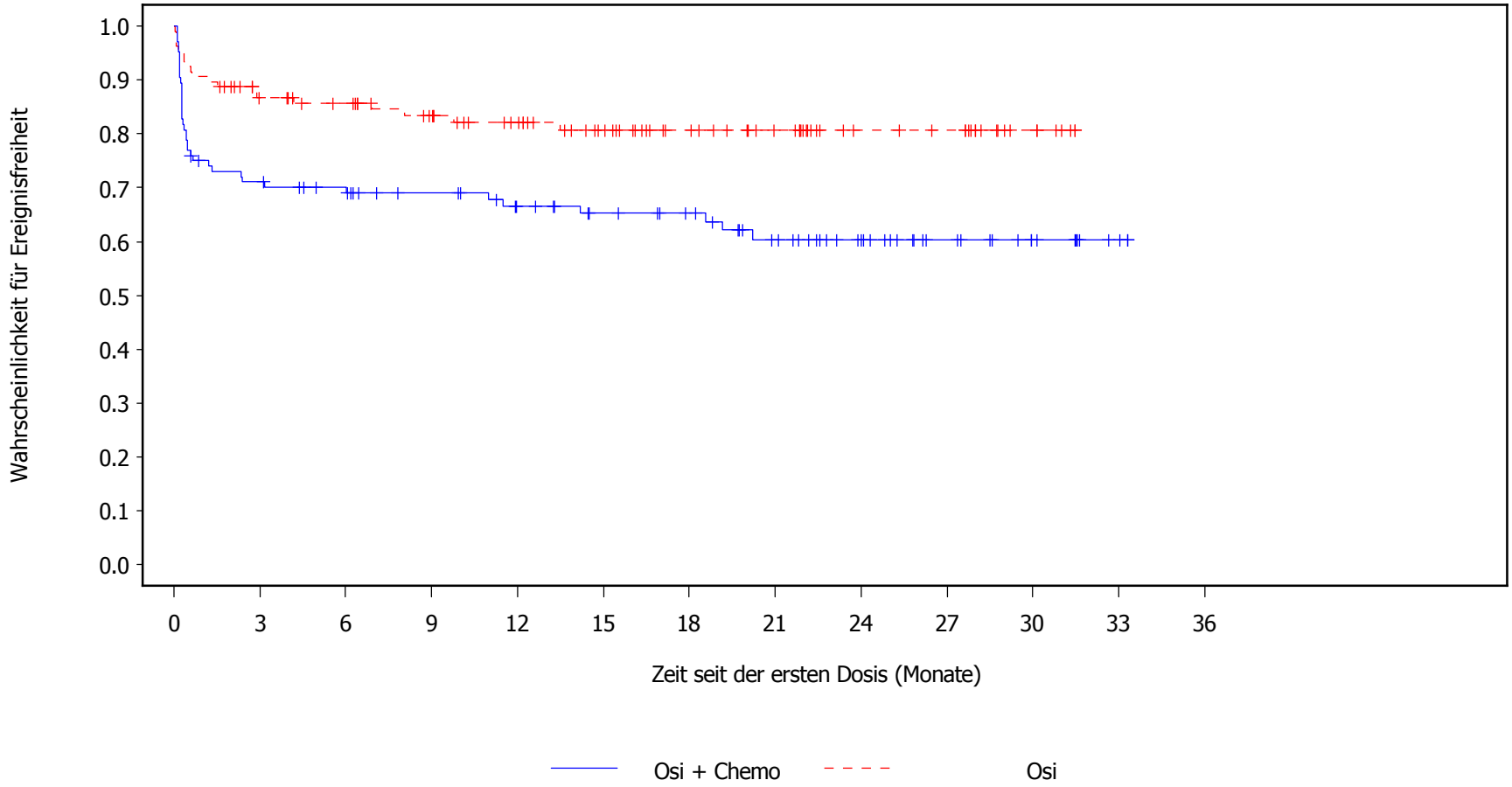
Figure 4.4.1.1 FLAURA-2 Subgroup Analysis: Kaplan-Meier plot of PT: Ausschlag for Geschlecht=Maennlich
Safety Analysis Set, DCO 03APR2023



Anzahl an Patienten unter Risiko:

104	72	67	60	53	47	43	34	24	15	8	2	0	Osi + Chemo
107	85	79	70	61	50	39	31	19	17	6	0	0	Osi

Kaplan-Meier plot is presented only if the interaction term in Cox regression model with treatment, subgroup and treatment-by-subgroup interaction is statistically significant at 5% level.
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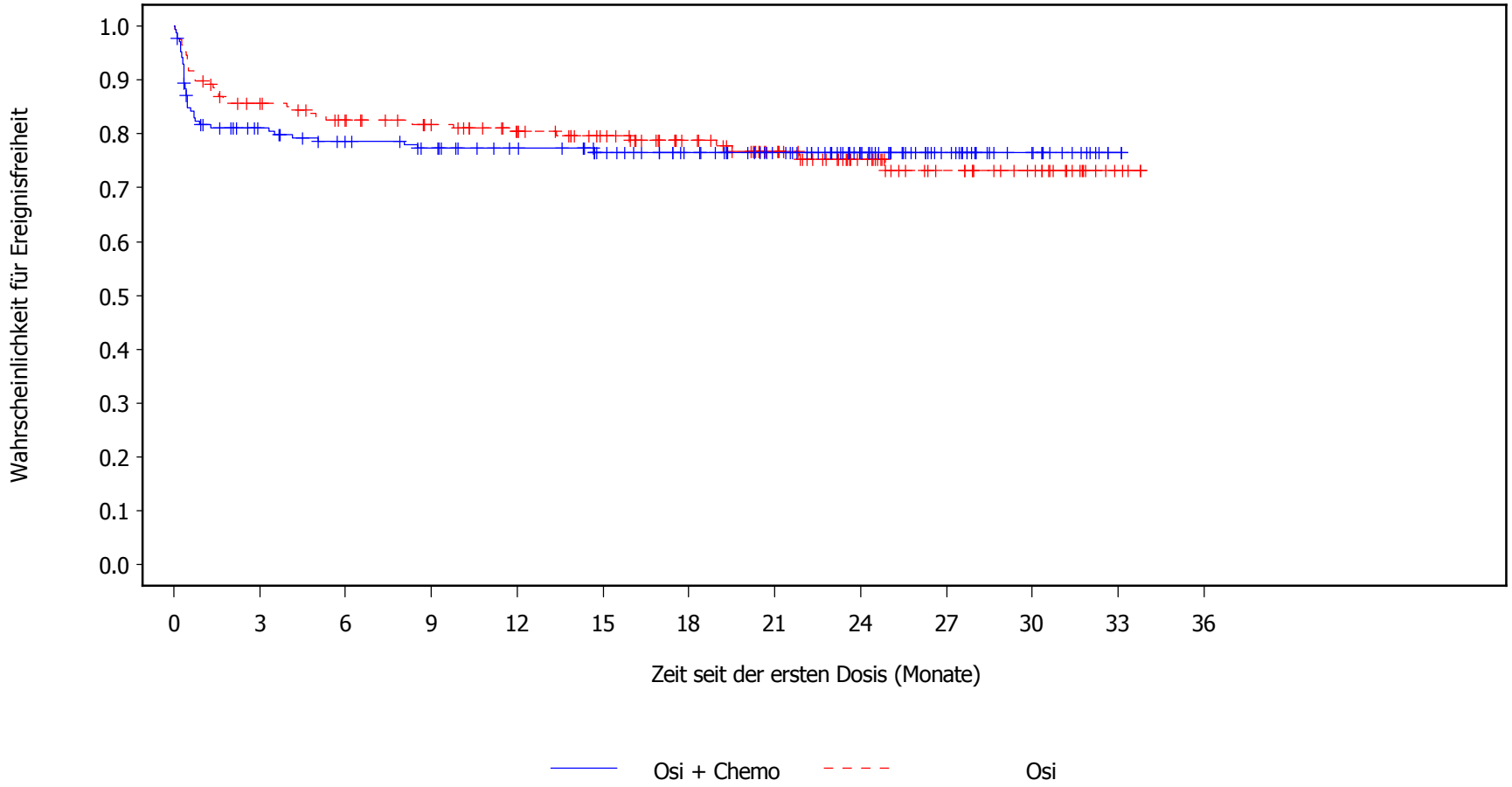
Nutzenbewertung nach AMNOG Seite 1 von 1

Figure 4.4.1.2 FLAURA-2 Subgroup Analysis: Kaplan-Meier plot of PT: Ausschlag for Geschlecht=Weiblich
Safety Analysis Set, DCO 03APR2023



Anzahl an Patienten unter Risiko:

172	128	118	112	104	94	83	71	52	31	15	1	0	Osi + Chemo
168	139	127	119	107	96	80	64	44	28	19	3	0	Osi

Kaplan-Meier plot is presented only if the interaction term in Cox regression model with treatment, subgroup and treatment-by-subgroup interaction is statistically significant at 5% level.
root/cdar/d516/payer_germany/ar/d5169c00001_payer_germany/tlf/prod/program/ttesubae.sas gttesubaehab 22DEC2023:09:13 kfrh585

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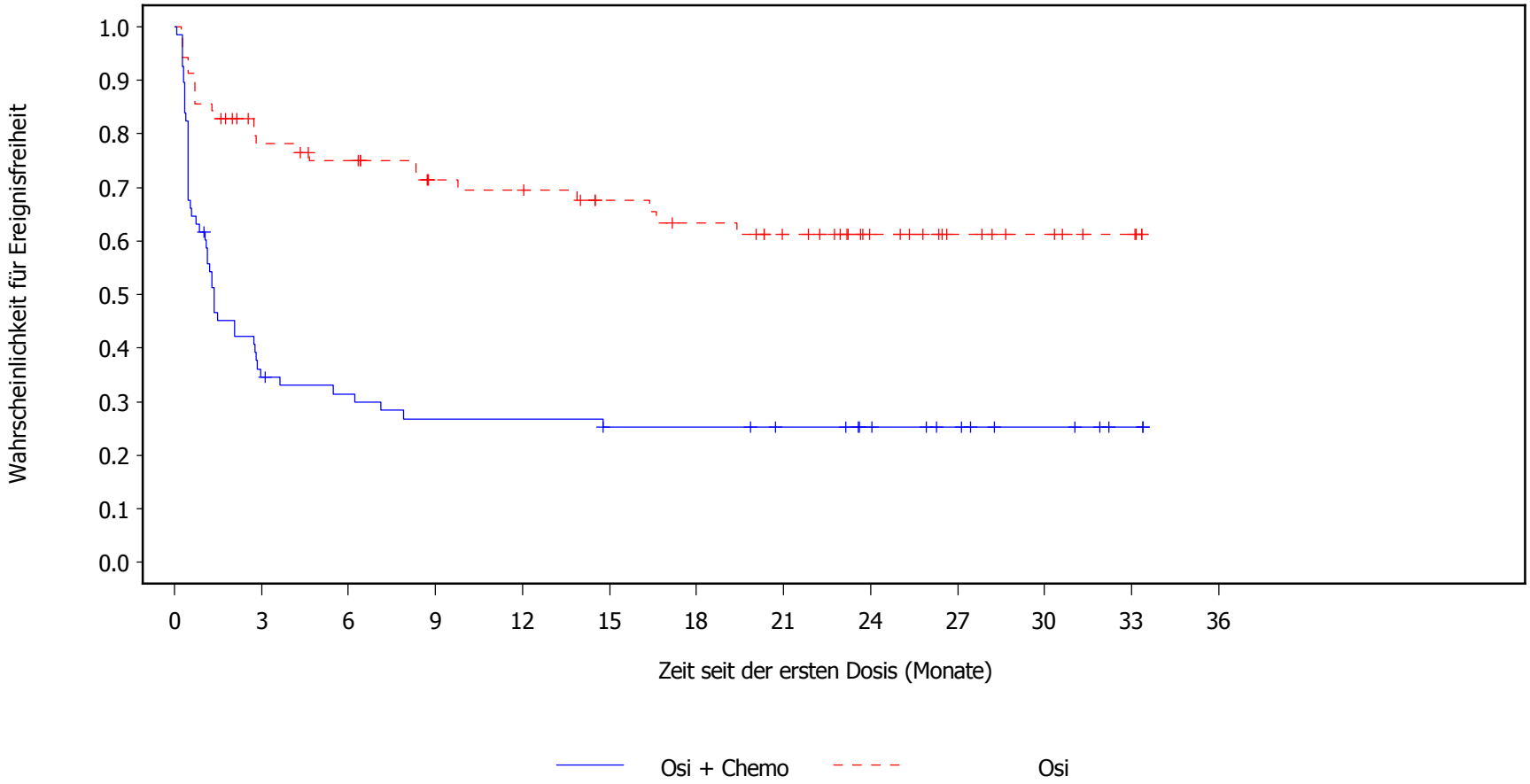
Figure 4.4.1.3 FLAURA-2 Subgroup Analysis: Kaplan-Meier plot of SOC: Erkrankungen des Blutes und des Lymphsystems for Abstammung=Chinesisch/Asiatisch
Safety Analysis Set, DCO 03APR2023



Anzahl an Patienten unter Risiko:

68	23	20	17	17	15	15	13	10	7	4	1	0	Osi + Chemo
70	50	46	38	37	32	29	24	15	9	6	3	0	Osi

Kaplan-Meier plot is presented only if the interaction term in Cox regression model with treatment, subgroup and treatment-by-subgroup interaction is statistically significant at 5% level.
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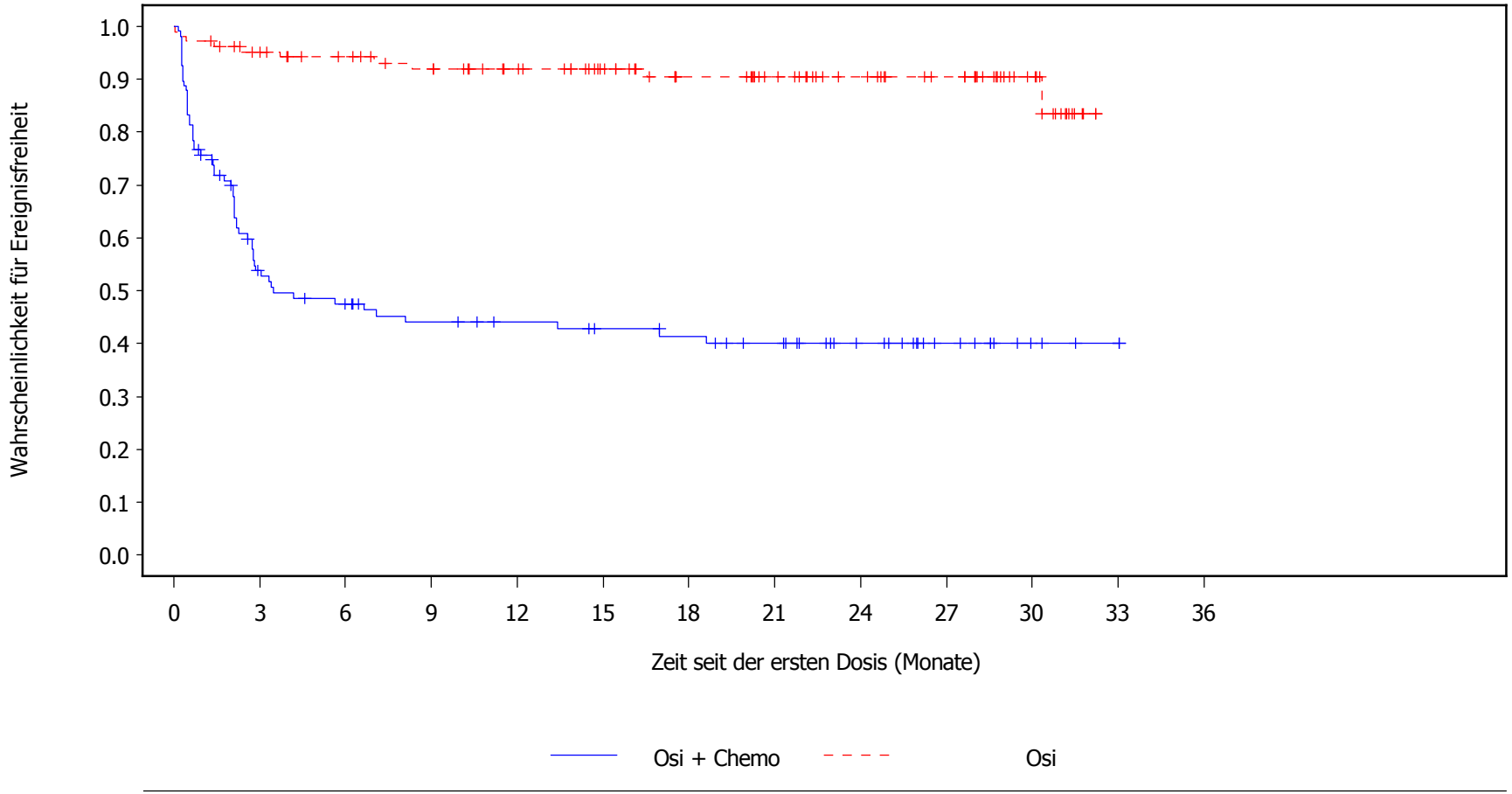
Figure 4.4.1.4 FLAURA-2 Subgroup Analysis: Kaplan-Meier plot of SOC: Erkrankungen des Blutes und des Lymphsystems for Abstammung=Nicht-chinesisch/Asiatisch
Safety Analysis Set, DCO 03APR2023



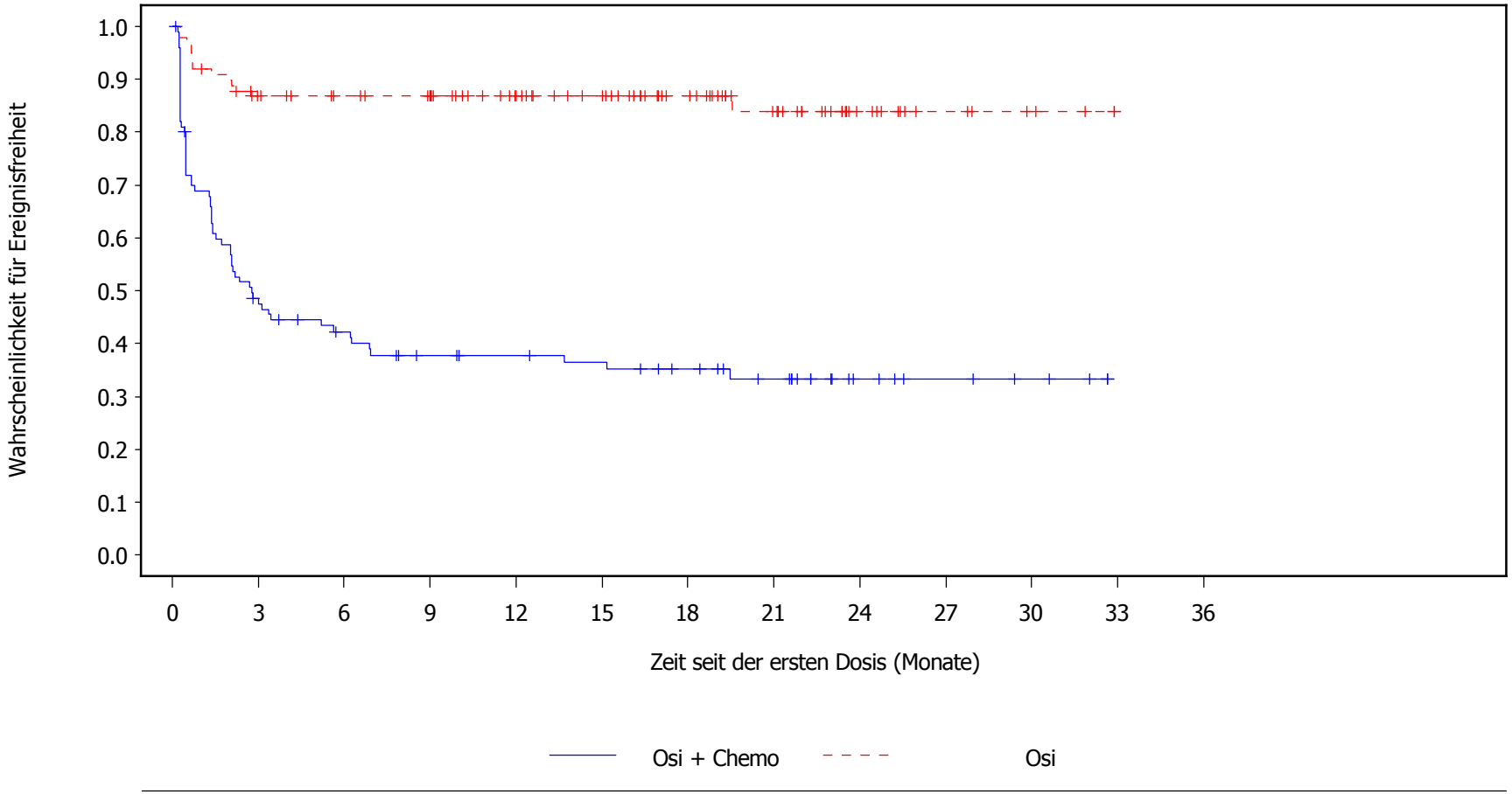
Anzahl an Patienten unter Risiko:

107	52	44	38	35	32	30	26	18	10	3	1	0	Osi + Chemo
106	96	89	83	75	65	54	47	38	31	16	0	0	Osi

Kaplan-Meier plot is presented only if the interaction term in Cox regression model with treatment, subgroup and treatment-by-subgroup interaction is statistically significant at 5% level.
root/cdar/d516/payer_germany/ar/d5169c00001_payer_germany/tlf/prod/program/ttesubae.sas gttesubaehad 22DEC2023:09:13 kfrh585

Nutzenbewertung nach AMNOG Seite 1 von 1

Figure 4.4.1.5 FLAURA-2 Subgroup Analysis: Kaplan-Meier plot of SOC: Erkrankungen des Blutes und des Lymphsystems for Abstammung=Nicht-asiatisch
Safety Analysis Set, DCO 03APR2023

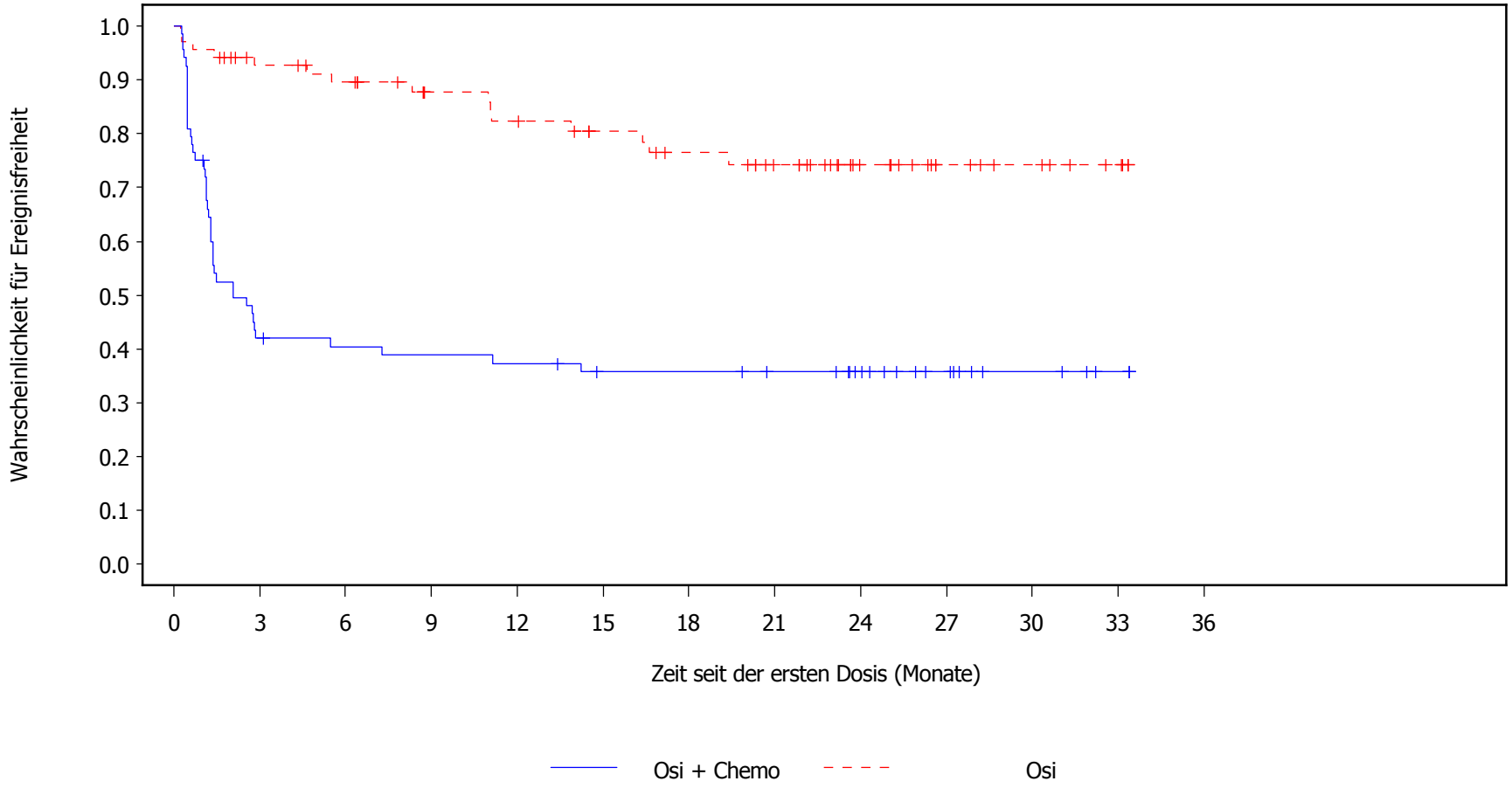


Anzahl an Patienten unter Risiko:

101	47	38	31	29	27	23	18	8	5	3	0	0	Osi + Chemo
99	81	76	73	60	53	40	28	13	6	3	0	0	Osi

Kaplan-Meier plot is presented only if the interaction term in Cox regression model with treatment, subgroup and treatment-by-subgroup interaction is statistically significant at 5% level.
root/cdar/d516/payer_germany/ar/d5169c00001_payer_germany/tlf/prod/program/ttesubae.sas gttesubaehae 22DEC2023:09:13 kfrh585

Figure 4.4.1.6 FLAURA-2 Subgroup Analysis: Kaplan-Meier plot of PT: Anaemie for Abstammung=Chinesisch/Asiatisch
Safety Analysis Set, DCO 03APR2023



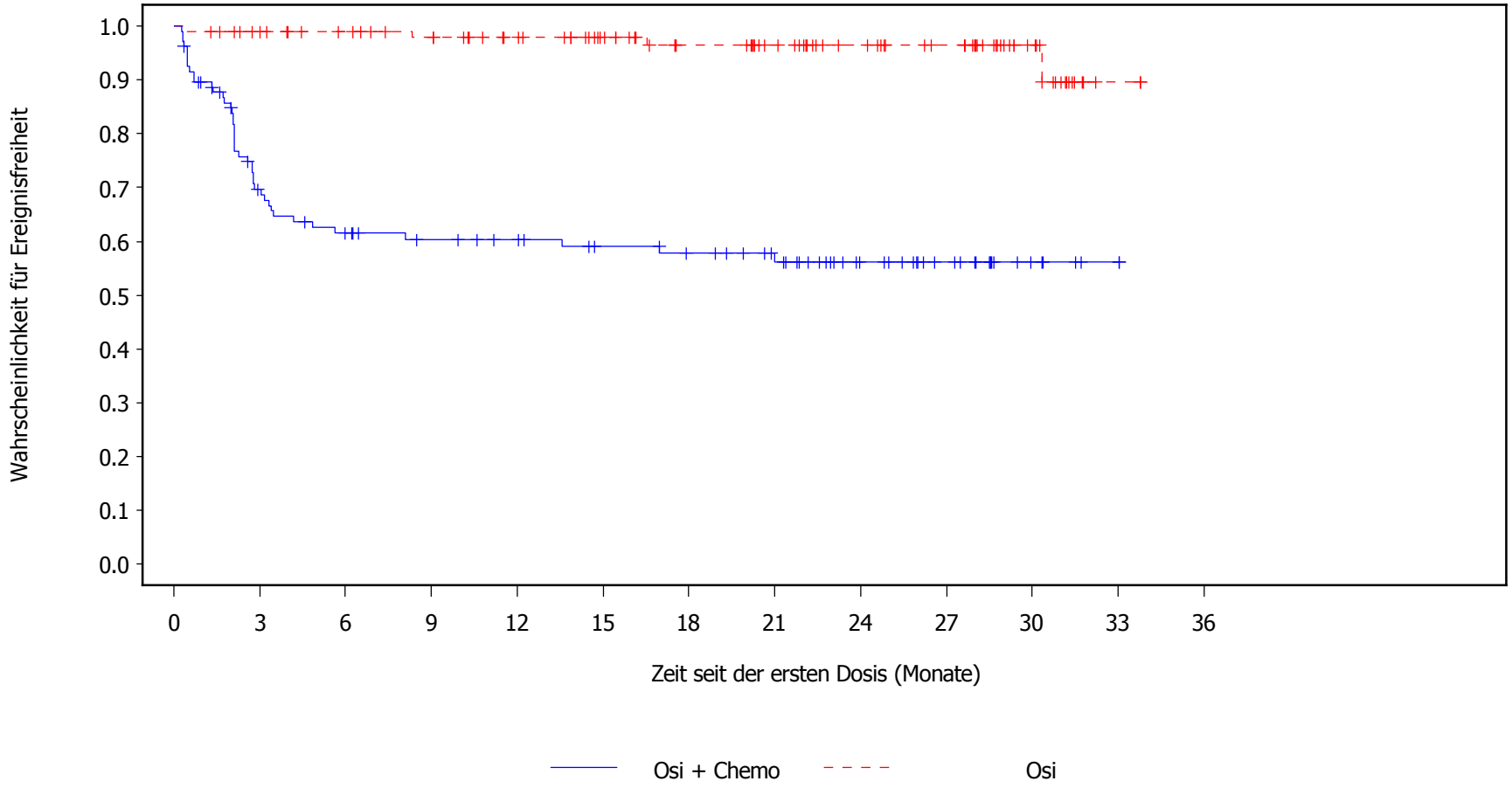
Anzahl an Patienten unter Risiko:

68	28	26	25	24	21	21	19	15	9	4	1	0	Osi + Chemo
70	60	56	48	45	40	36	30	18	10	7	3	0	Osi

Kaplan-Meier plot is presented only if the interaction term in Cox regression model with treatment, subgroup and treatment-by-subgroup interaction is statistically significant at 5% level.
root/cdar/d516/payer_germany/ar/d5169c00001_payer_germany/tlf/prod/program/ttesubae.sas gttesubaehaf 22DEC2023:09:13 kfrh585

Nutzenbewertung nach AMNOG Seite 1 von 1

Figure 4.4.1.7 FLAURA-2 Subgroup Analysis: Kaplan-Meier plot of PT: Anaemie for Abstammung=Nicht-chinesisch/Asiatisch
Safety Analysis Set, DCO 03APR2023



Anzahl an Patienten unter Risiko:

107	68	58	53	50	45	42	36	24	16	5	1	0	Osi + Chemo
106	100	94	89	81	70	59	52	42	35	17	1	0	Osi

Kaplan-Meier plot is presented only if the interaction term in Cox regression model with treatment, subgroup and treatment-by-subgroup interaction is statistically significant at 5% level.

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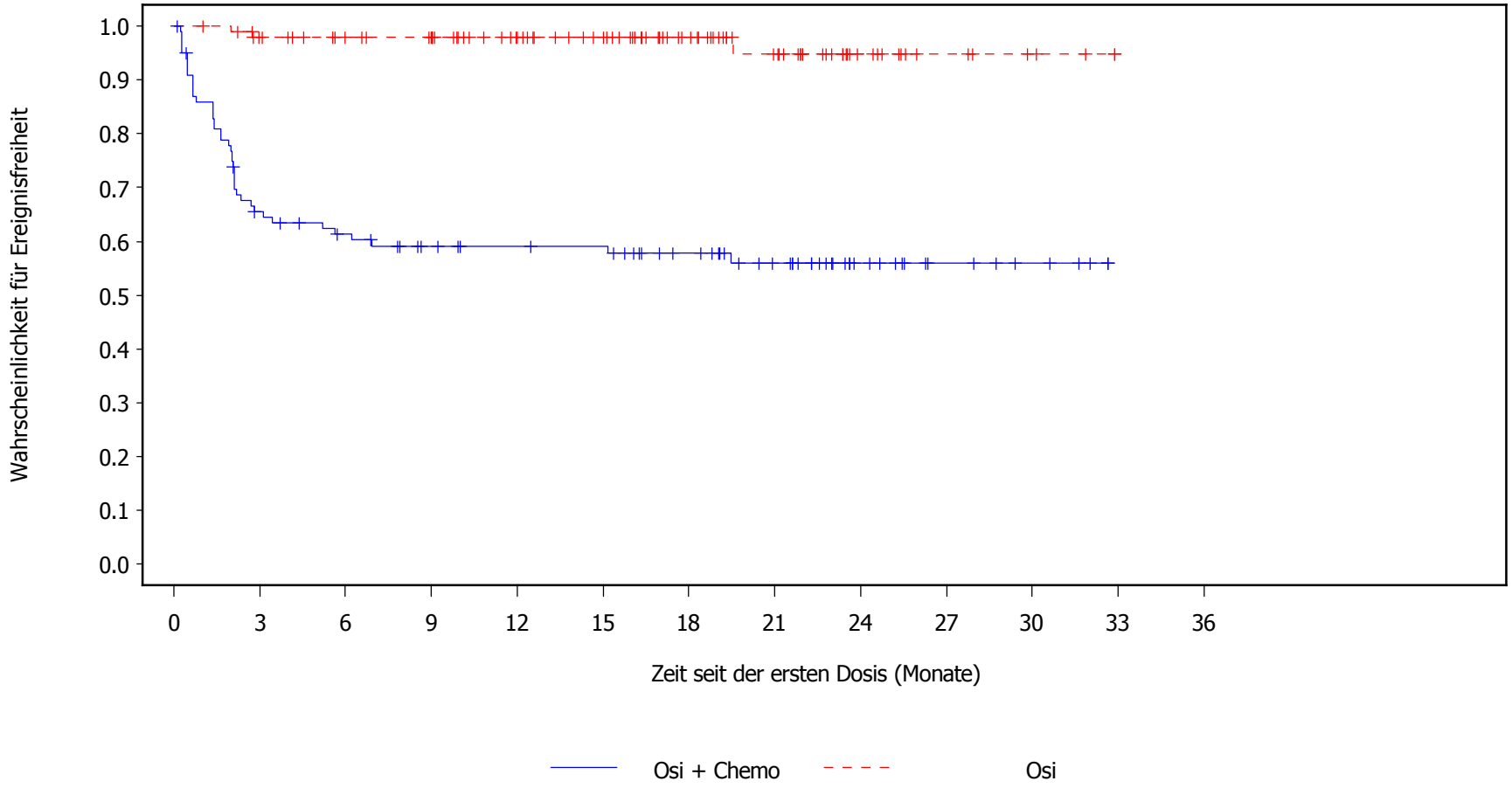
Figure 4.4.1.8 FLAURA-2 Subgroup Analysis: Kaplan-Meier plot of PT: Anaemie for Abstammung=Nicht-asiatisch
Safety Analysis Set, DCO 03APR2023



Anzahl an Patienten unter Risiko:

101	63	56	49	46	45	37	28	14	7	4	0	0	Osi + Chemo
99	92	85	82	68	60	43	30	13	6	3	0	0	Osi

Kaplan-Meier plot is presented only if the interaction term in Cox regression model with treatment, subgroup and treatment-by-subgroup interaction is statistically significant at 5% level.

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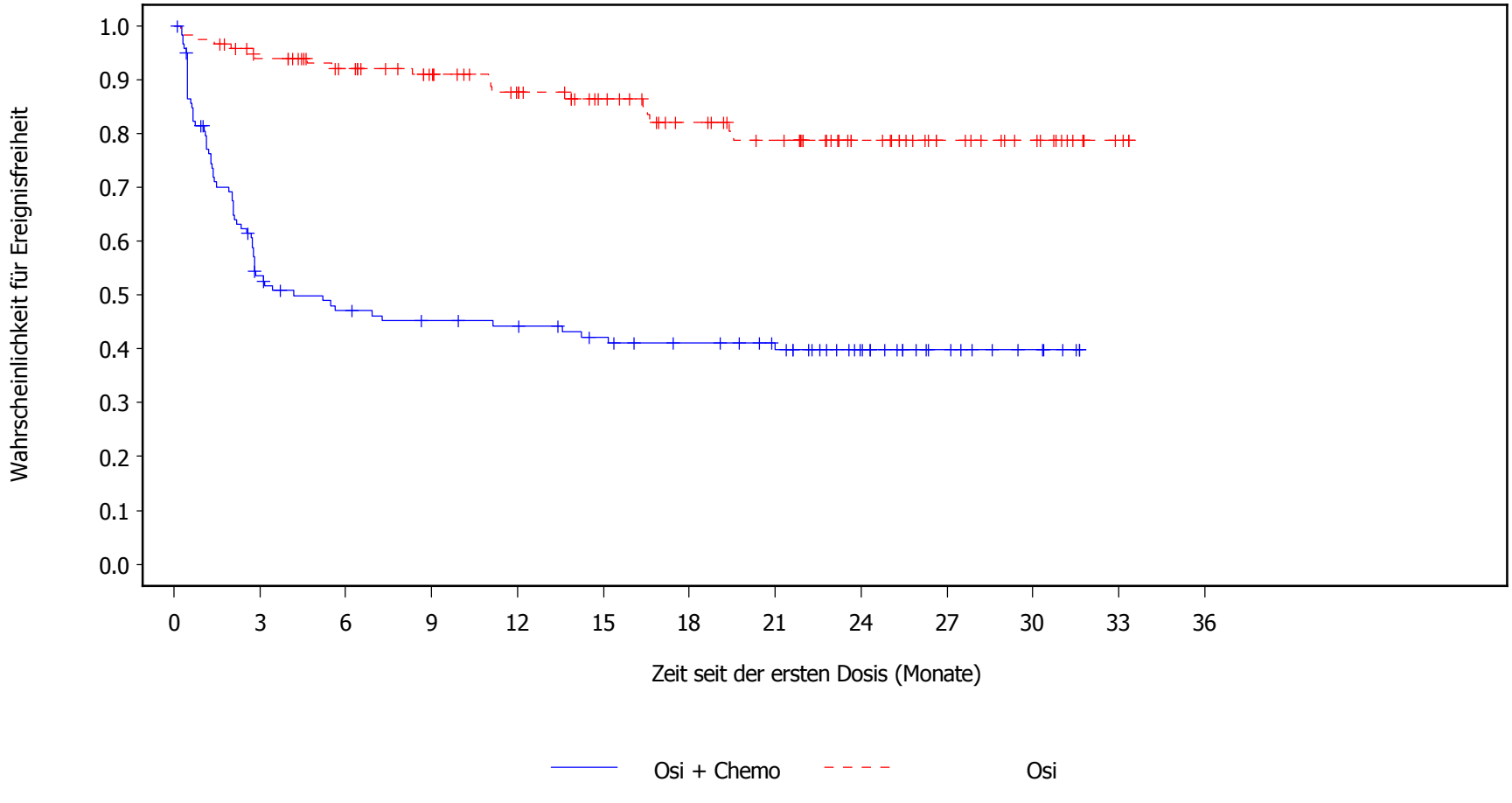
Figure 4.4.1.9 FLAURA-2 Subgroup Analysis: Kaplan-Meier plot of PT: Anaemie for Methode zur Gewebeuntersuchung=zentral
Safety Analysis Set, DCO 03APR2023



Anzahl an Patienten unter Risiko:

120	60	51	47	45	40	36	31	20	10	5	0	0	Osi + Chemo
119	107	96	86	75	64	53	46	29	18	12	2	0	Osi

Kaplan-Meier plot is presented only if the interaction term in Cox regression model with treatment, subgroup and treatment-by-subgroup interaction is statistically significant at 5% level.
root/cdar/d516/payer_germany/ar/d5169c00001_payer_germany/tlf/prod/program/ttesubae.sas gttesubaehai 22DEC2023:09:13 kfrh585

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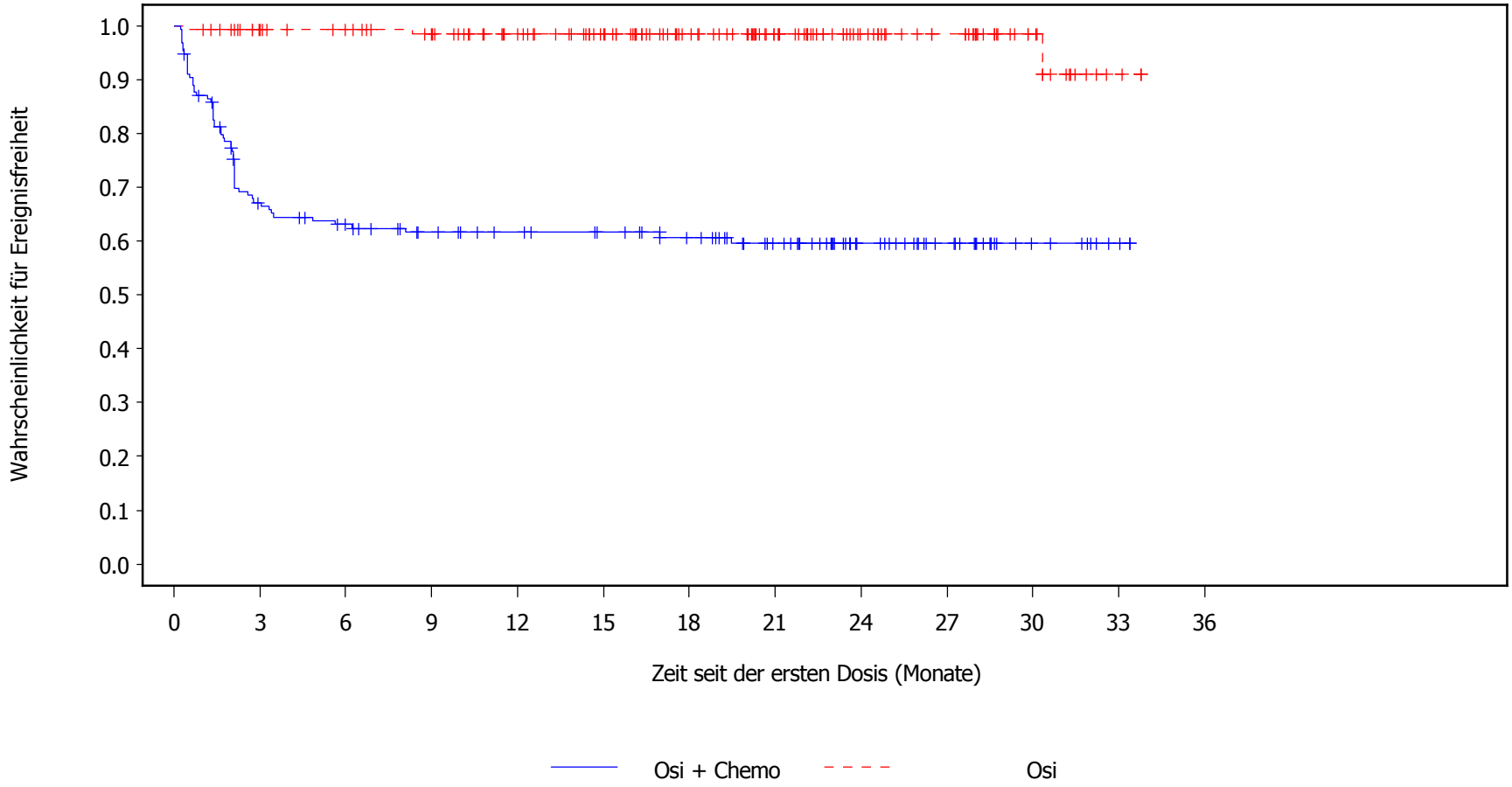
Figure 4.4.1.10 FLAURA-2 Subgroup Analysis: Kaplan-Meier plot of PT: Anaemie for Methode zur Gewebeuntersuchung=lokal
Safety Analysis Set, DCO 03APR2023



Anzahl an Patienten unter Risiko:

156	99	89	80	75	71	64	52	33	22	8	2	0	Osi + Chemo
156	145	139	133	119	106	85	66	44	33	15	2	0	Osi

Kaplan-Meier plot is presented only if the interaction term in Cox regression model with treatment, subgroup and treatment-by-subgroup interaction is statistically significant at 5% level.

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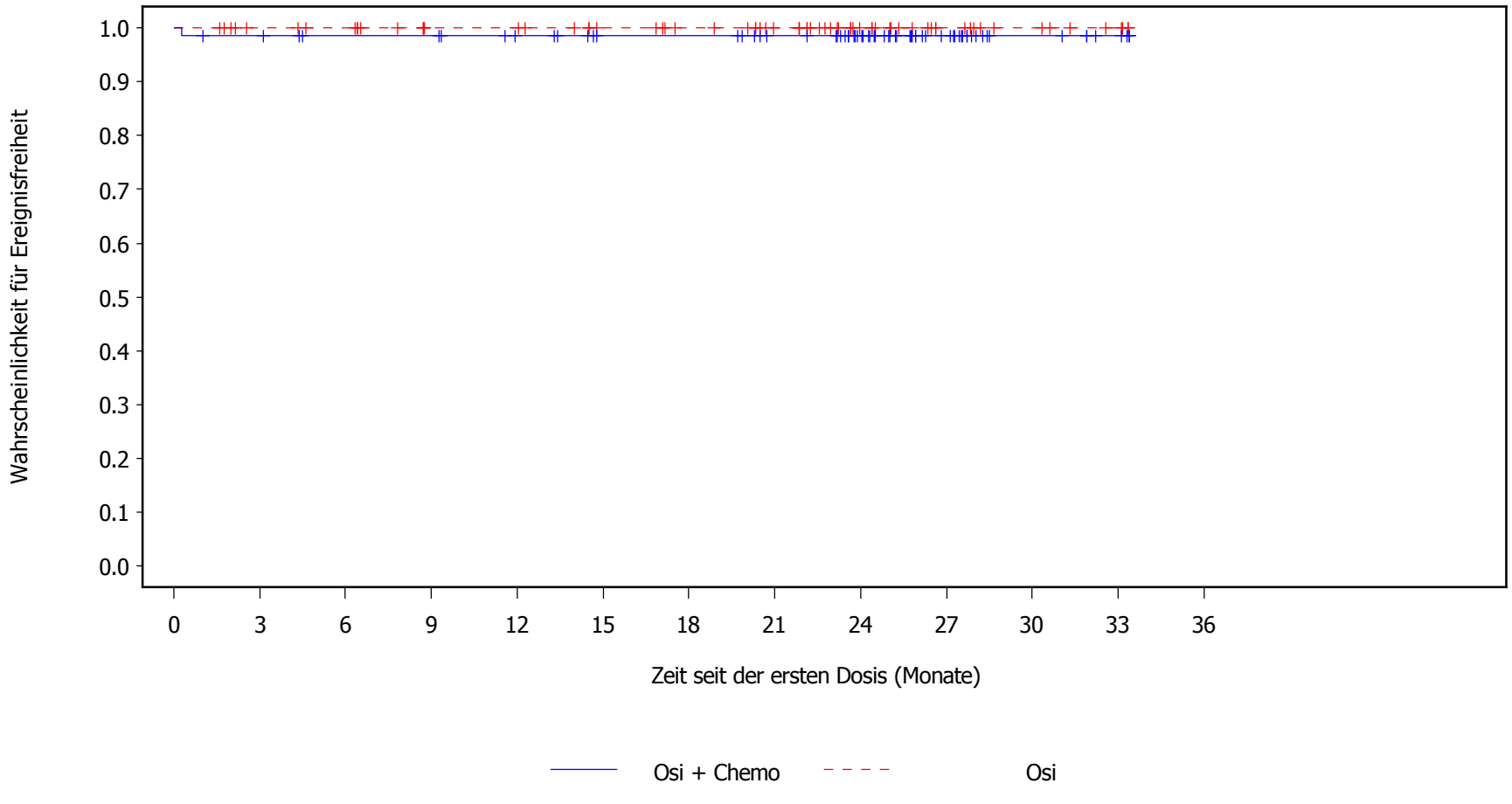
Figure 4.4.1.11 FLAURA-2 Subgroup Analysis: Kaplan-Meier plot of PT: Mundtrockenheit for Abstammung=Chinesisch/Asiatisch
Safety Analysis Set, DCO 03APR2023



Anzahl an Patienten unter Risiko:

68	66	63	63	59	54	54	49	39	20	7	3	0	Osi + Chemo
70	65	63	55	55	49	45	38	23	12	7	3	0	Osi

Kaplan-Meier plot is presented only if the interaction term in Cox regression model with treatment, subgroup and treatment-by-subgroup interaction is statistically significant at 5% level.

root/cdar/d516/payer_germany/ar/d5169c00001_payer_germany/tlf/prod/program/ttesubae.sas gttesubaehak 22DEC2023:09:13 kfrh585

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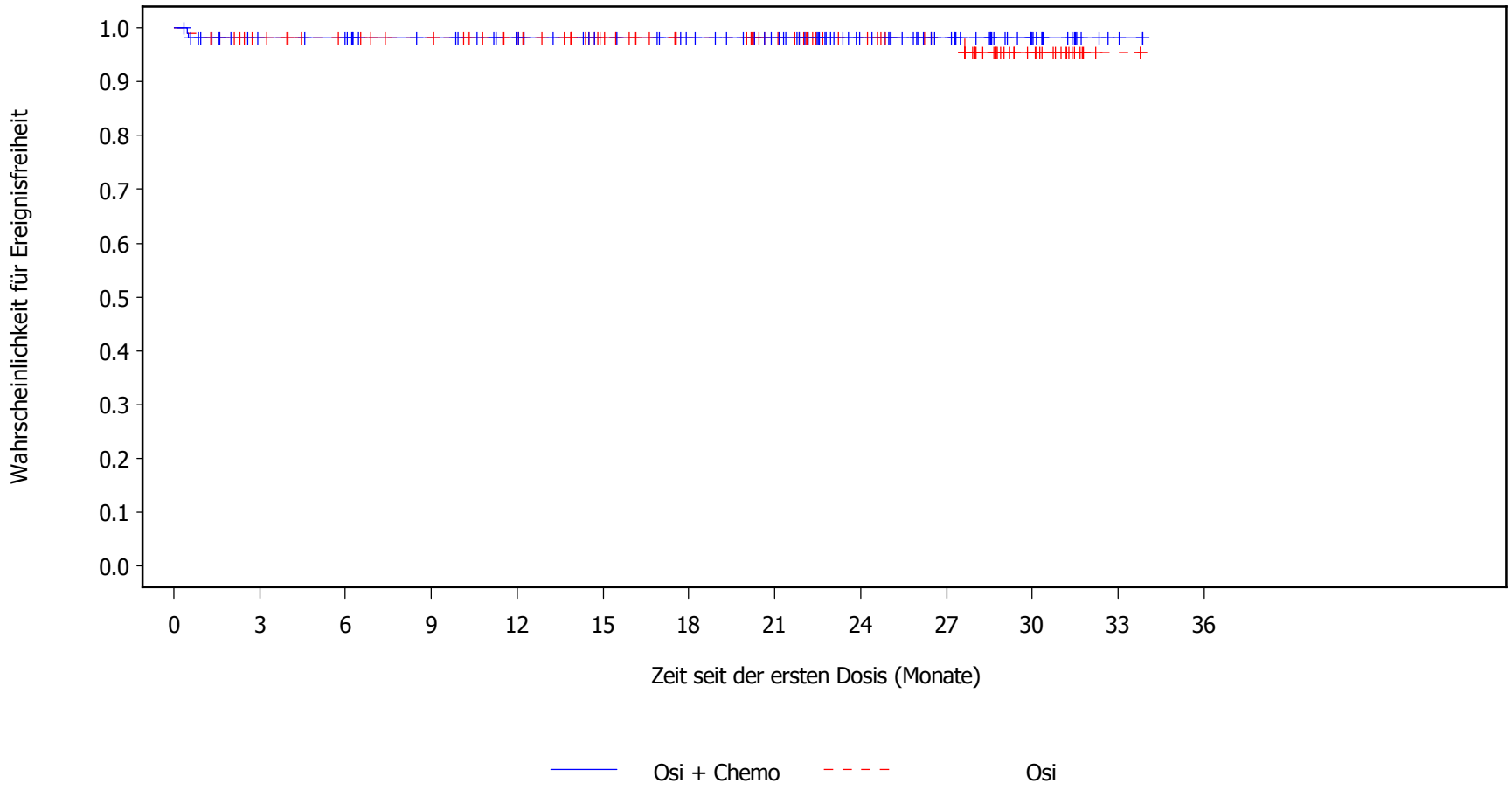
Figure 4.4.1.12 FLAURA-2 Subgroup Analysis: Kaplan-Meier plot of PT: Mundtrockenheit for Abstammung=Nicht-chinesisch/Asiatisch
Safety Analysis Set, DCO 03APR2023



Anzahl an Patienten unter Risiko:

107	95	93	87	80	74	69	62	44	32	15	2	0	Osi + Chemo
106	98	93	90	82	70	60	53	43	36	17	1	0	Osi

Kaplan-Meier plot is presented only if the interaction term in Cox regression model with treatment, subgroup and treatment-by-subgroup interaction is statistically significant at 5% level.
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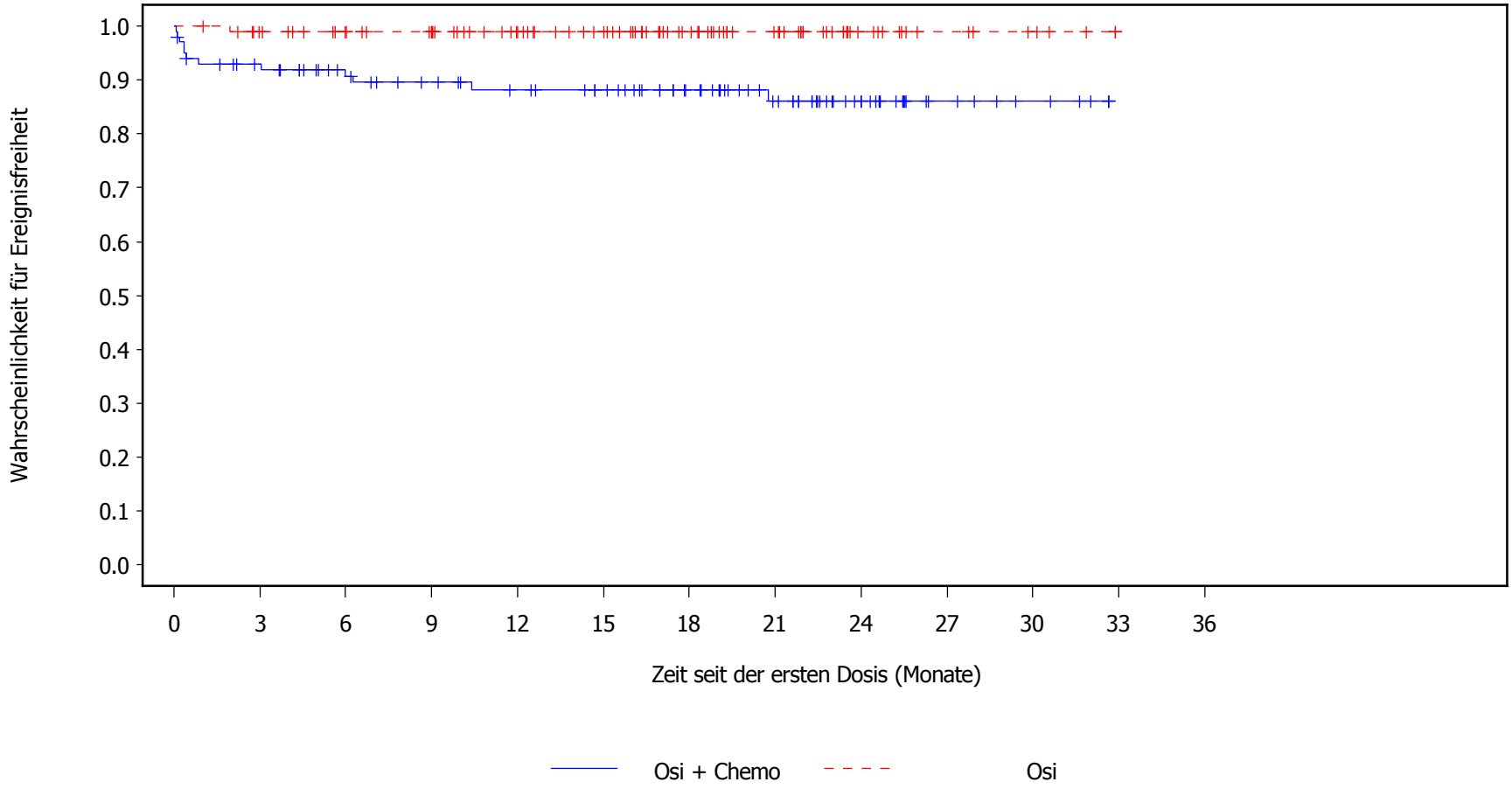
Figure 4.4.1.13 FLAURA-2 Subgroup Analysis: Kaplan-Meier plot of PT: Mundtrockenheit for Abstammung=Nicht-asiatisch
Safety Analysis Set, DCO 03APR2023



Anzahl an Patienten unter Risiko:

101	88	77	71	66	61	49	37	21	9	5	0	0	Osi + Chemo
99	93	86	82	69	61	44	31	14	7	4	0	0	Osi

Kaplan-Meier plot is presented only if the interaction term in Cox regression model with treatment, subgroup and treatment-by-subgroup interaction is statistically significant at 5% level.

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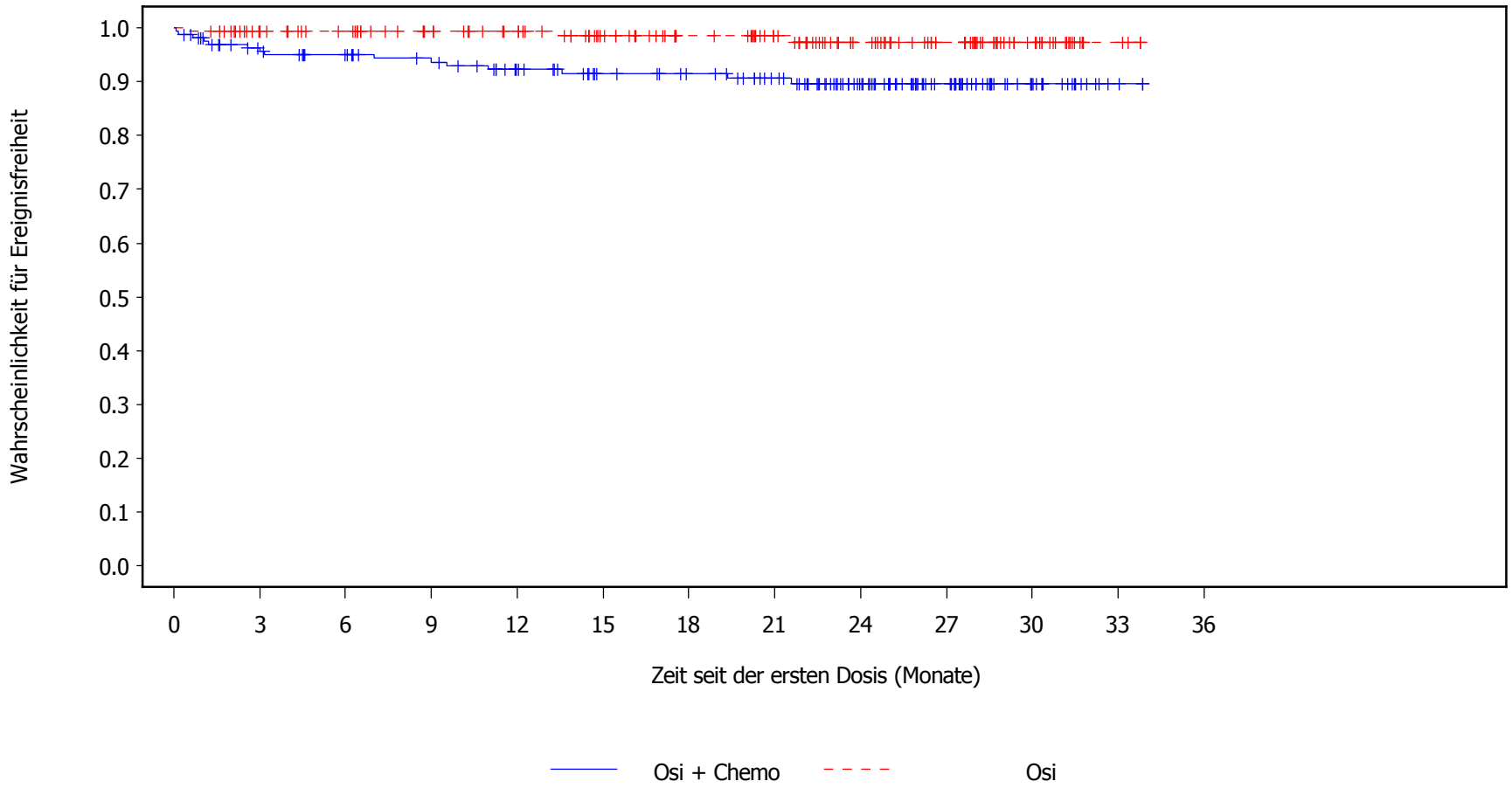
Figure 4.4.1.14 FLAURA-2 Subgroup Analysis: Kaplan-Meier plot of PT: Schmerzen Oberbauch for Region gPAP=Asien
Safety Analysis Set, DCO 03APR2023



Anzahl an Patienten unter Risiko:

168	151	143	136	124	112	107	97	72	45	17	2	0	Osi + Chemo
166	153	145	133	125	108	94	83	60	44	20	3	0	Osi

Kaplan-Meier plot is presented only if the interaction term in Cox regression model with treatment, subgroup and treatment-by-subgroup interaction is statistically significant at 5% level.
root/cdar/d516/payer_germany/ar/d5169c00001_payer_germany/tlf/prod/program/ttesubae.sas gttesubaehan 22DEC2023:09:13 kfrh585

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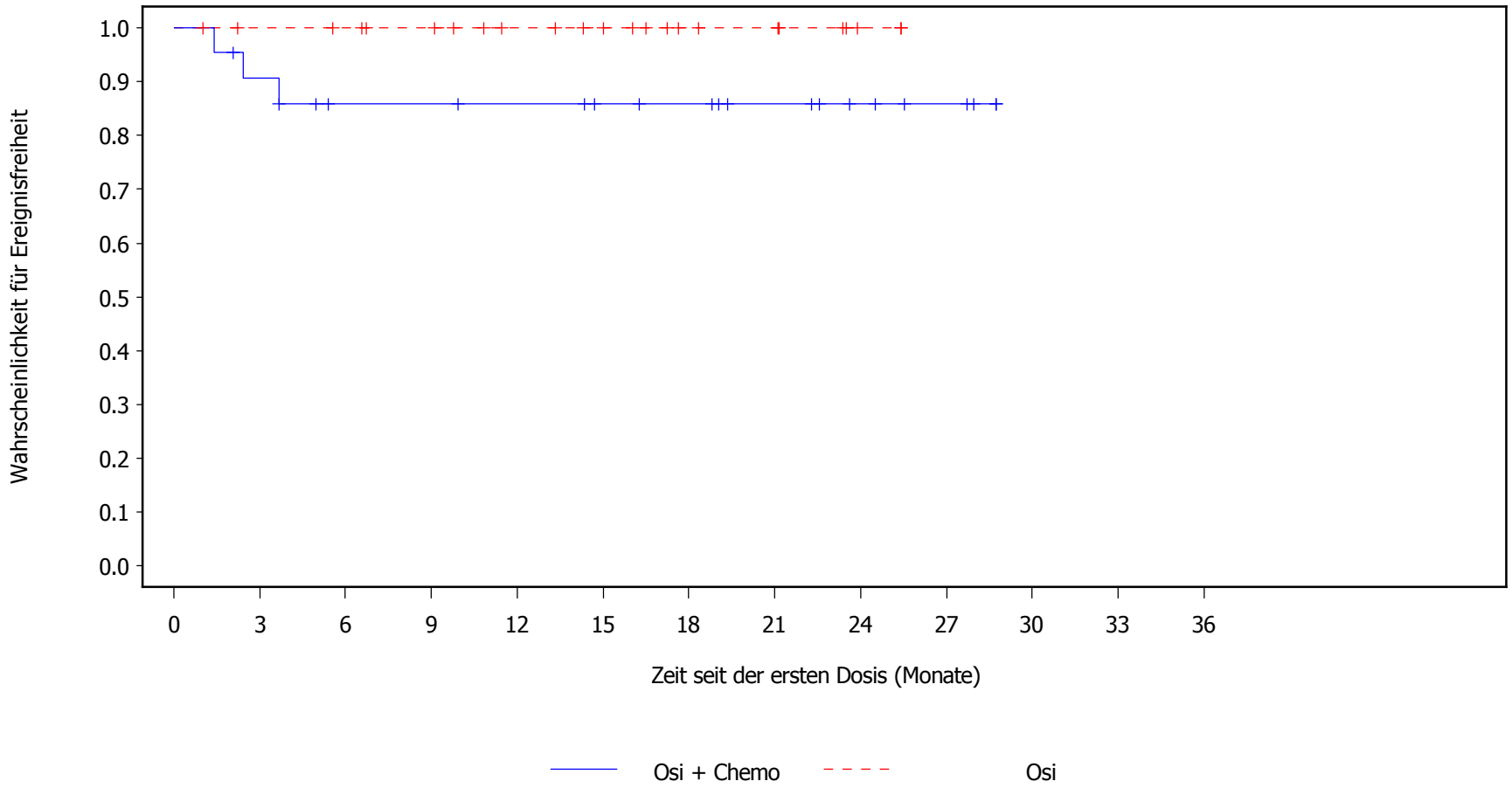
Figure 4.4.1.15 FLAURA-2 Subgroup Analysis: Kaplan-Meier plot of PT: Schmerzen Oberbauch for Region gPAP=Europa
Safety Analysis Set, DCO 03APR2023



Anzahl an Patienten unter Risiko:

22	19	15	15	14	12	11	8	5	3	0	0	0	Osi + Chemo
23	21	20	18	14	12	7	6	1	0	0	0	0	Osi

Kaplan-Meier plot is presented only if the interaction term in Cox regression model with treatment, subgroup and treatment-by-subgroup interaction is statistically significant at 5% level.

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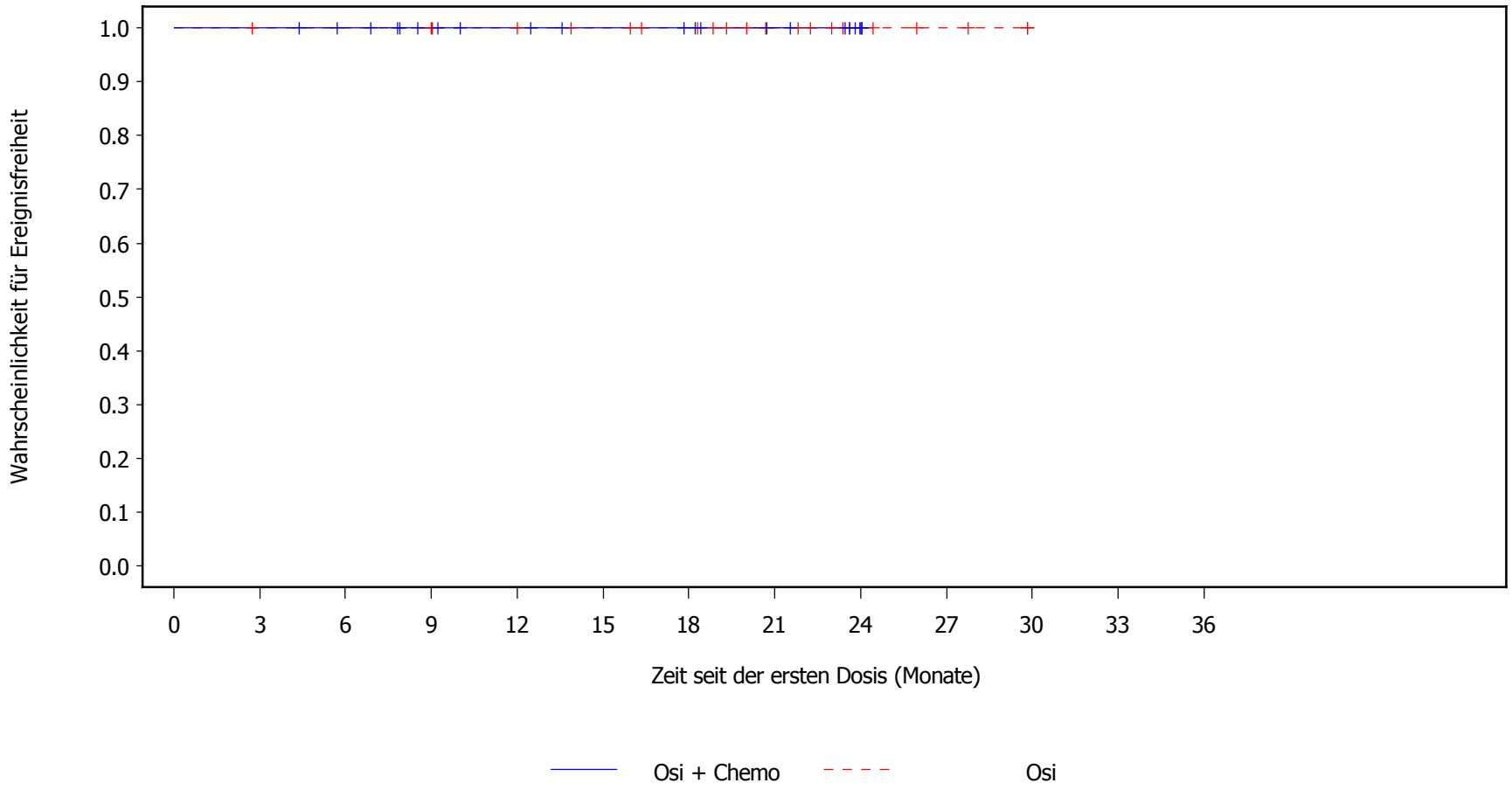
Figure 4.4.1.16 FLAURA-2 Subgroup Analysis: Kaplan-Meier plot of PT: Schmerzen Oberbauch for Region gPAP=Nordamerika
Safety Analysis Set, DCO 03APR2023



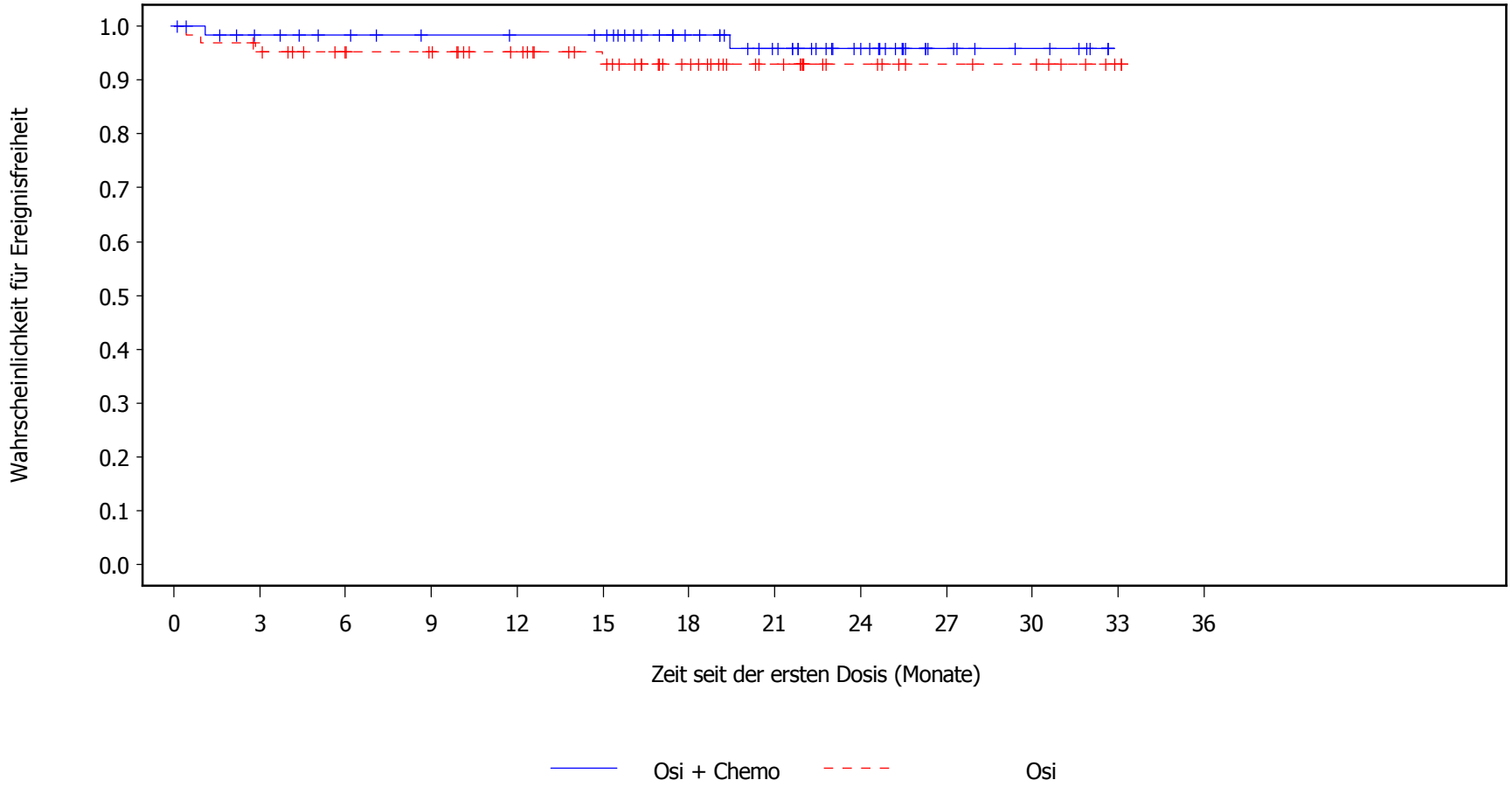
Anzahl an Patienten unter Risiko:

20	20	18	14	12	10	9	6	2	0	0	0	0	Osi + Chemo
22	21	21	21	18	17	15	10	4	2	0	0	0	Osi

Kaplan-Meier plot is presented only if the interaction term in Cox regression model with treatment, subgroup and treatment-by-subgroup interaction is statistically significant at 5% level.

root/cdar/d516/payer_germany/ar/d5169c00001_payer_germany/tlf/prod/program/ttesubae.sas gttesubaehap 22DEC2023:09:13 kfrh585

Figure 4.4.1.17 FLAURA-2 Subgroup Analysis: Kaplan-Meier plot of PT: Schmerzen Oberbauch for Region gPAP=Rest der Welt
Safety Analysis Set, DCO 03APR2023



Anzahl an Patienten unter Risiko:

66	60	57	54	53	52	42	34	22	10	6	0	0	Osi + Chemo
64	60	54	52	46	39	29	20	12	8	7	1	0	Osi

Kaplan-Meier plot is presented only if the interaction term in Cox regression model with treatment, subgroup and treatment-by-subgroup interaction is statistically significant at 5% level.
root/cdar/d516/payer_germany/ar/d5169c00001_payer_germany/tlf/prod/program/ttesubae.sas gttesubaehaq 22DEC2023:09:13 kfrh585

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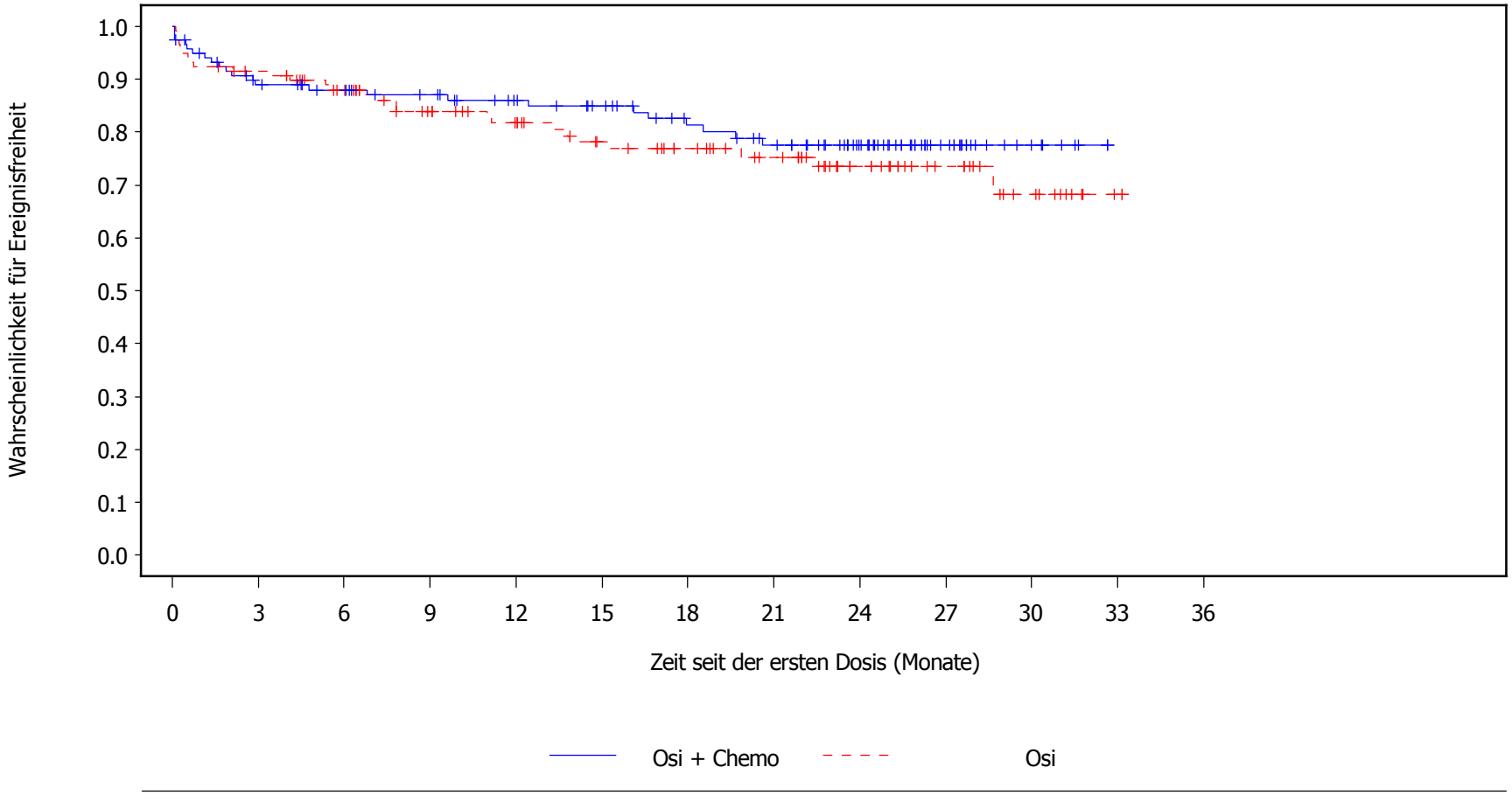
Figure 4.4.1.18 FLAURA-2 Subgroup Analysis: Kaplan-Meier plot of SOC: Erkrankungen des Nervensystems for Methode zur Gewebeuntersuchung=zentral
Safety Analysis Set, DCO 03APR2023



Anzahl an Patienten unter Risiko:

120	101	95	89	81	75	65	59	43	20	6	0	0	Osi + Chemo
119	106	94	80	72	62	55	47	30	19	10	1	0	Osi

Kaplan-Meier plot is presented only if the interaction term in Cox regression model with treatment, subgroup and treatment-by-subgroup interaction is statistically significant at 5% level.
root/cdar/d516/payer_germany/ar/d5169c00001_payer_germany/tlf/prod/program/ttesubae.sas gttesubaehar 22DEC2023:09:13 kfrh585

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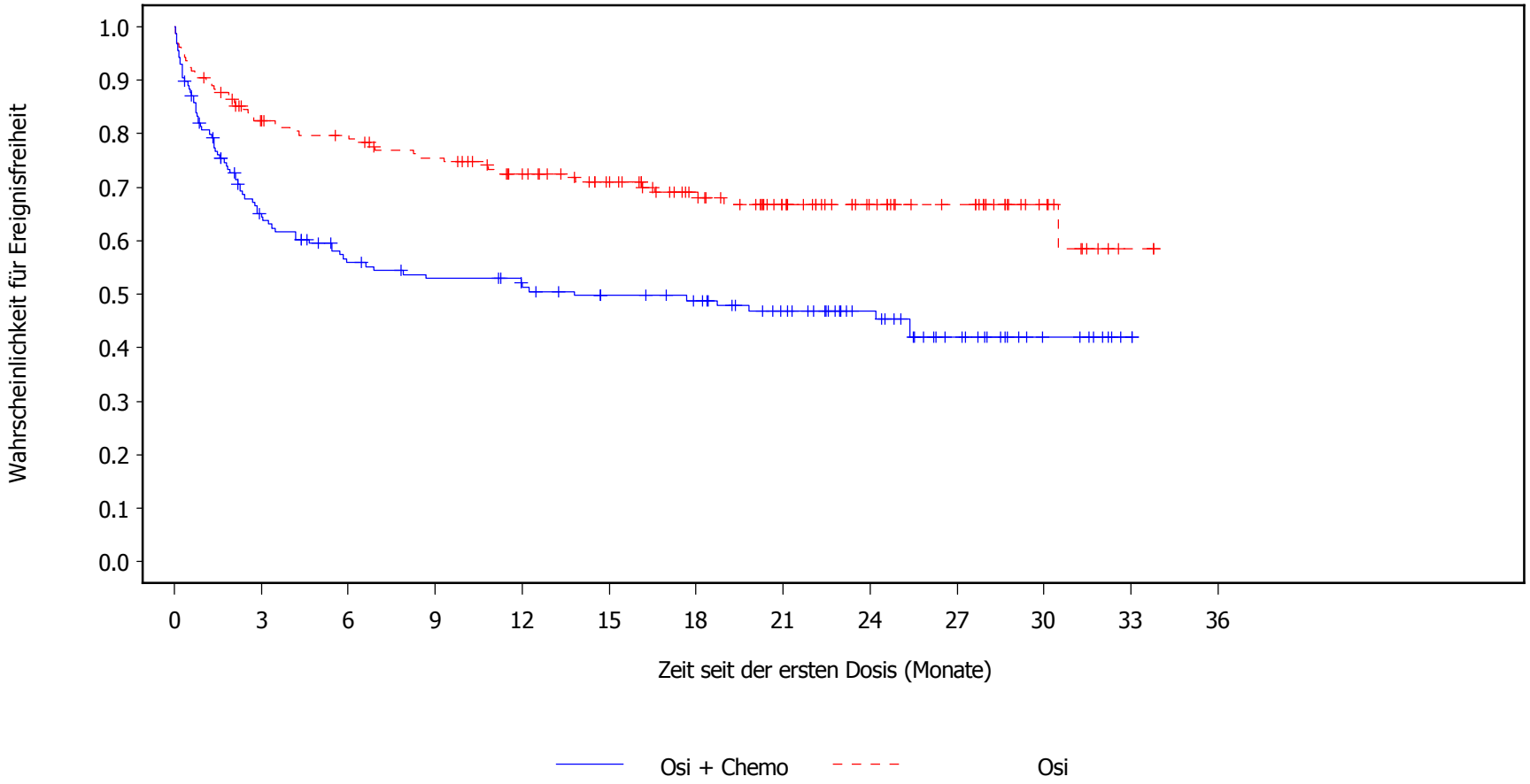
Figure 4.4.1.19 FLAURA-2 Subgroup Analysis: Kaplan-Meier plot of SOC: Erkrankungen des Nervensystems for Methode zur Gewebeuntersuchung=lokal
Safety Analysis Set, DCO 03APR2023



Anzahl an Patienten unter Risiko:

156	94	76	70	65	58	54	44	32	19	8	1	0	Osi + Chemo
156	122	115	106	93	81	65	49	34	26	11	1	0	Osi

Kaplan-Meier plot is presented only if the interaction term in Cox regression model with treatment, subgroup and treatment-by-subgroup interaction is statistically significant at 5% level.
root/cdar/d516/payer_germany/ar/d5169c00001_payer_germany/tlf/prod/program/ttesubae.sas gttesubaehas 22DEC2023:09:13 kfrh585

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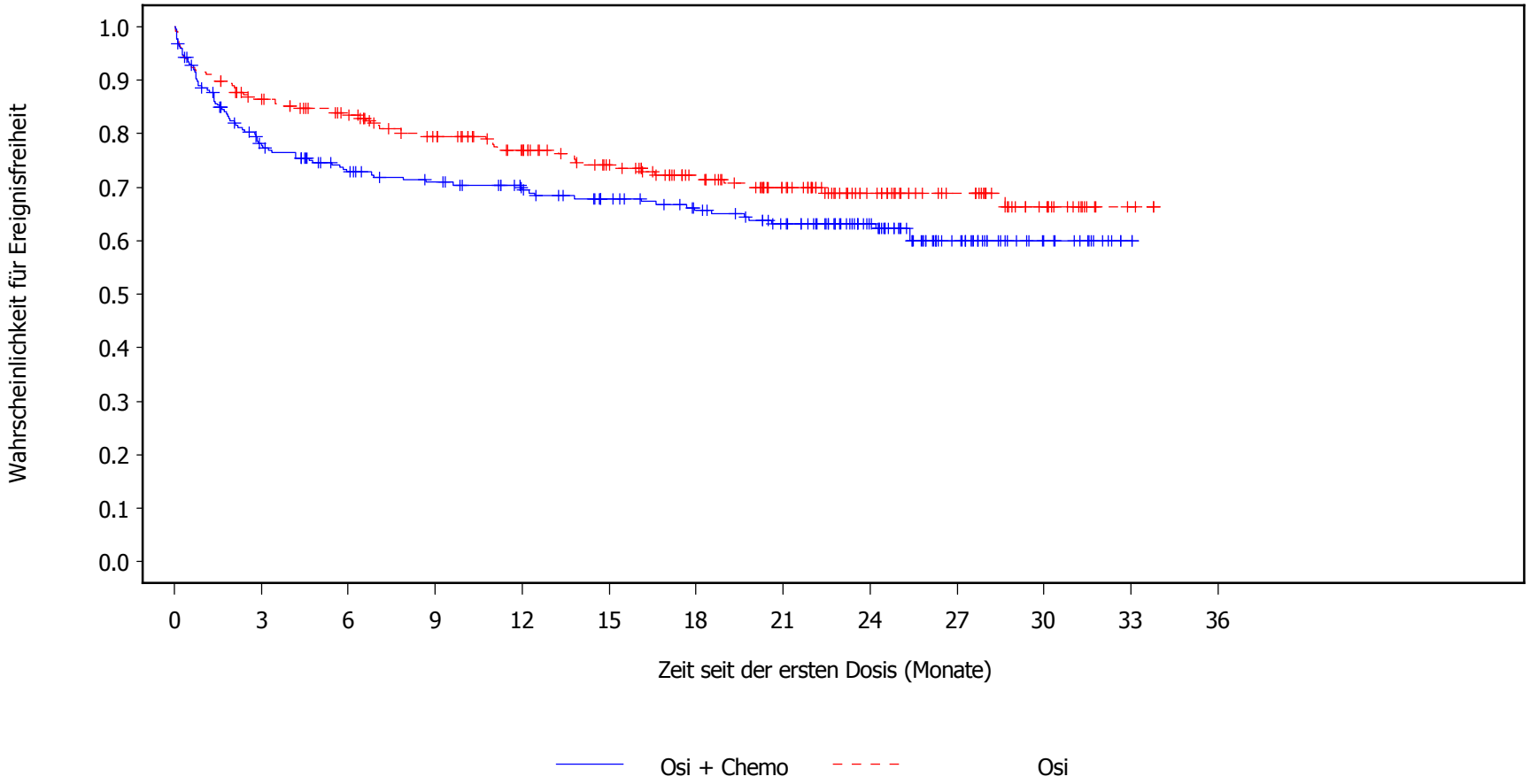
Figure 4.4.1.20 FLAURA-2 Subgroup Analysis: Kaplan-Meier plot of SOC: Erkrankungen des Nervensystems for Zentral bestätigte EGFR-Mutation im Gewebe=positiv
Safety Analysis Set, DCO 03APR2023



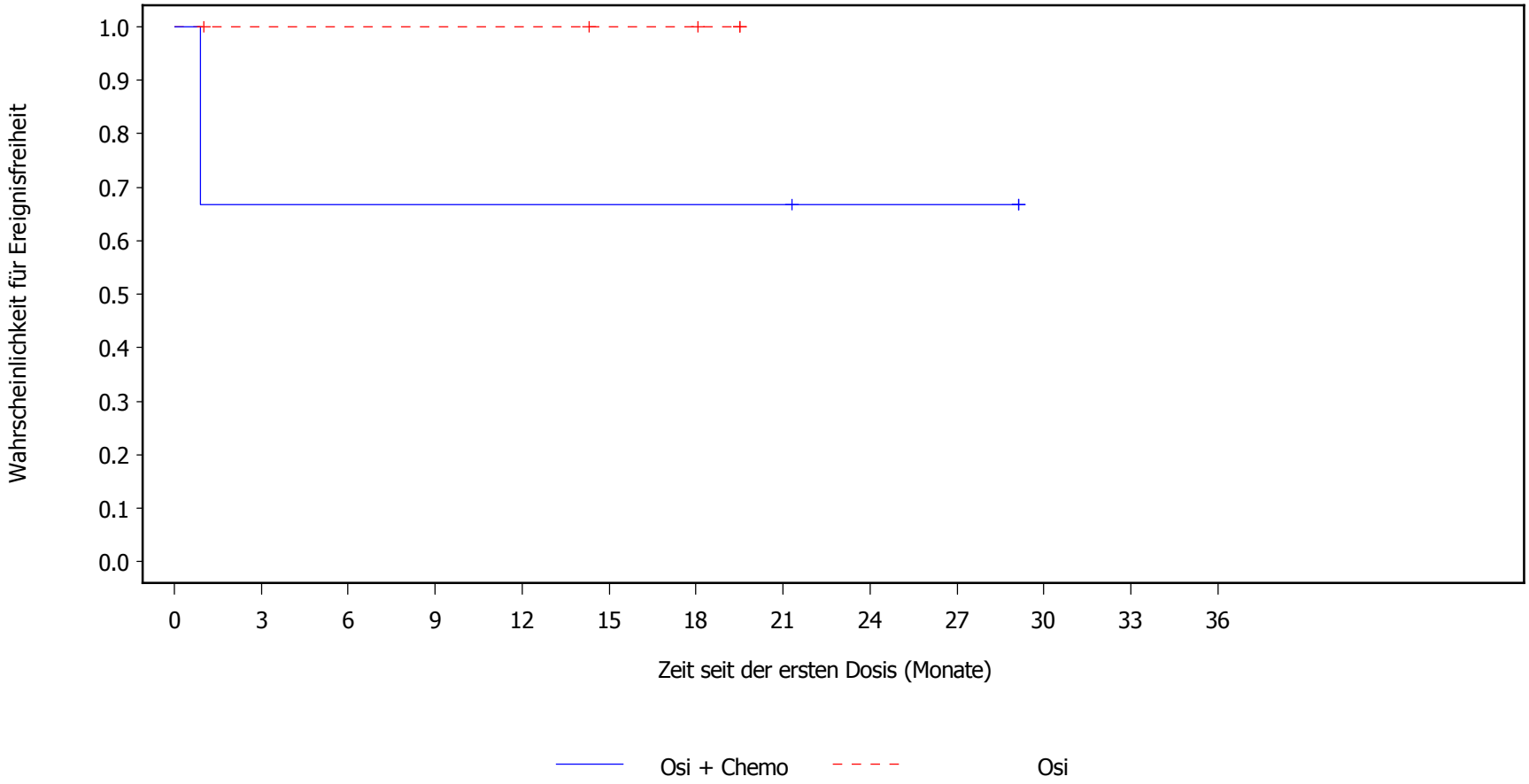
Anzahl an Patienten unter Risiko:

248	182	160	150	137	124	112	99	72	38	14	1	0	Osi + Chemo
238	200	183	162	143	124	102	81	53	36	17	2	0	Osi

Kaplan-Meier plot is presented only if the interaction term in Cox regression model with treatment, subgroup and treatment-by-subgroup interaction is statistically significant at 5% level.
root/cdar/d516/payer_germany/ar/d5169c00001_payer_germany/tlf/prod/program/ttesubae.sas gttesubaehat 22DEC2023:09:13 kfrh585

Nutzenbewertung nach AMNOG Seite 1 von 1

Figure 4.4.1.21 FLAURA-2 Subgroup Analysis: Kaplan-Meier plot of SOC: Erkrankungen des Nervensystems for Zentral bestätigte EGFR-Mutation im Gewebe=negativ
Safety Analysis Set, DCO 03APR2023



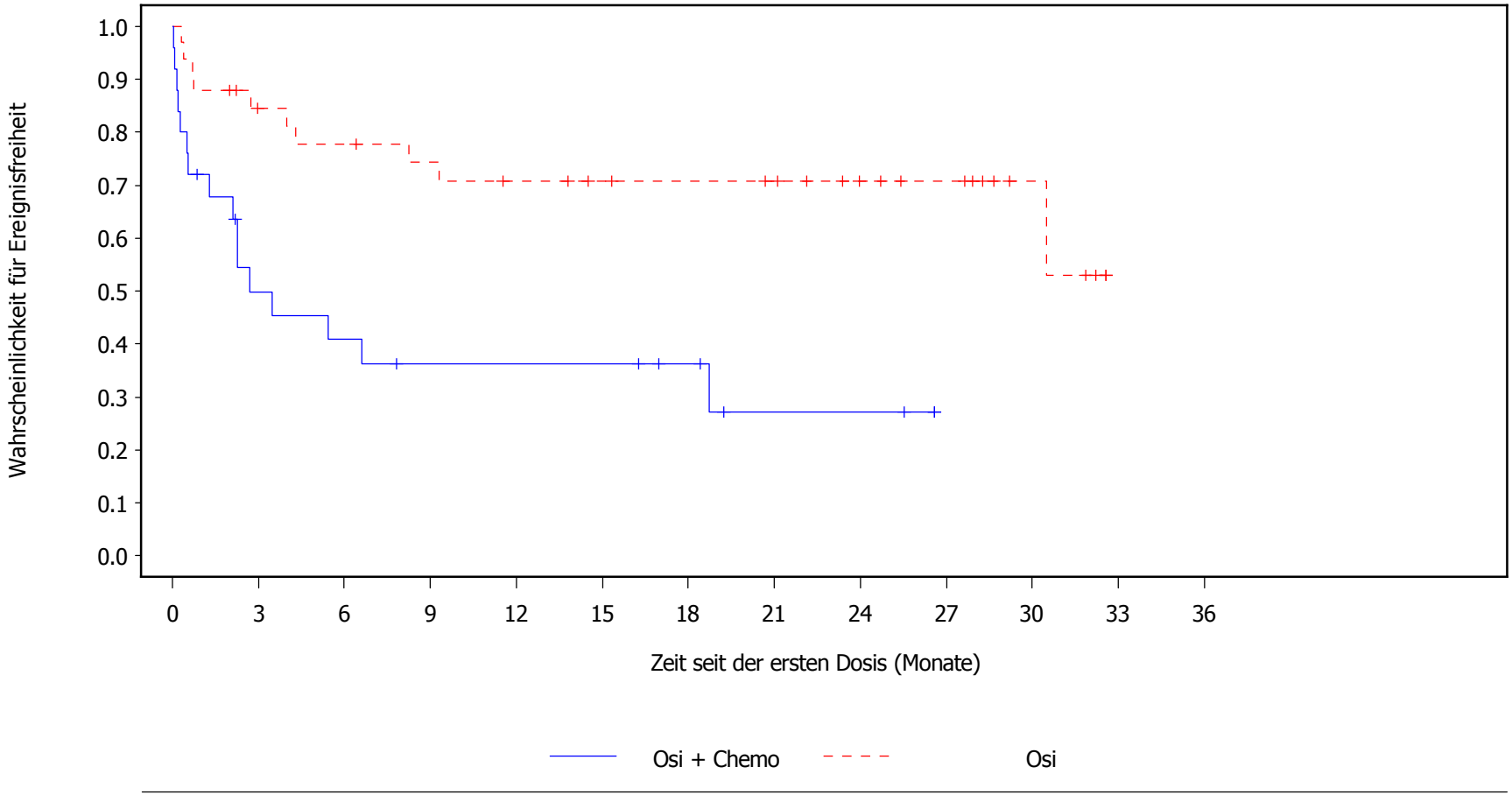
Anzahl an Patienten unter Risiko:

3	2	2	2	2	2	2	2	1	1	0	0	0	Osi + Chemo
4	3	3	3	3	2	2	0	0	0	0	0	0	Osi

Kaplan-Meier plot is presented only if the interaction term in Cox regression model with treatment, subgroup and treatment-by-subgroup interaction is statistically significant at 5% level.
root/cdar/d516/payer_germany/ar/d5169c00001_payer_germany/tlf/prod/program/ttesubae.sas gttesubaehau 22DEC2023:09:13 kfrh585

Nutzenbewertung nach AMNOG Seite 1 von 1

Figure 4.4.1.22 FLAURA-2 Subgroup Analysis: Kaplan-Meier plot of SOC: Erkrankungen des Nervensystems for Zentral bestätigte EGFR-Mutation im Gewebe=unbekannt
Safety Analysis Set, DCO 03APR2023



Anzahl an Patienten unter Risiko:

25	11	9	7	7	7	5	2	2	0	0	0	0	Osi + Chemo
33	25	23	21	19	17	16	15	11	9	4	0	0	Osi

Kaplan-Meier plot is presented only if the interaction term in Cox regression model with treatment, subgroup and treatment-by-subgroup interaction is statistically significant at 5% level.
root/cdar/d516/payer_germany/ar/d5169c00001_payer_germany/tlf/prod/program/ttesubae.sas gttesubaehav 22DEC2023:09:13 kfrh585

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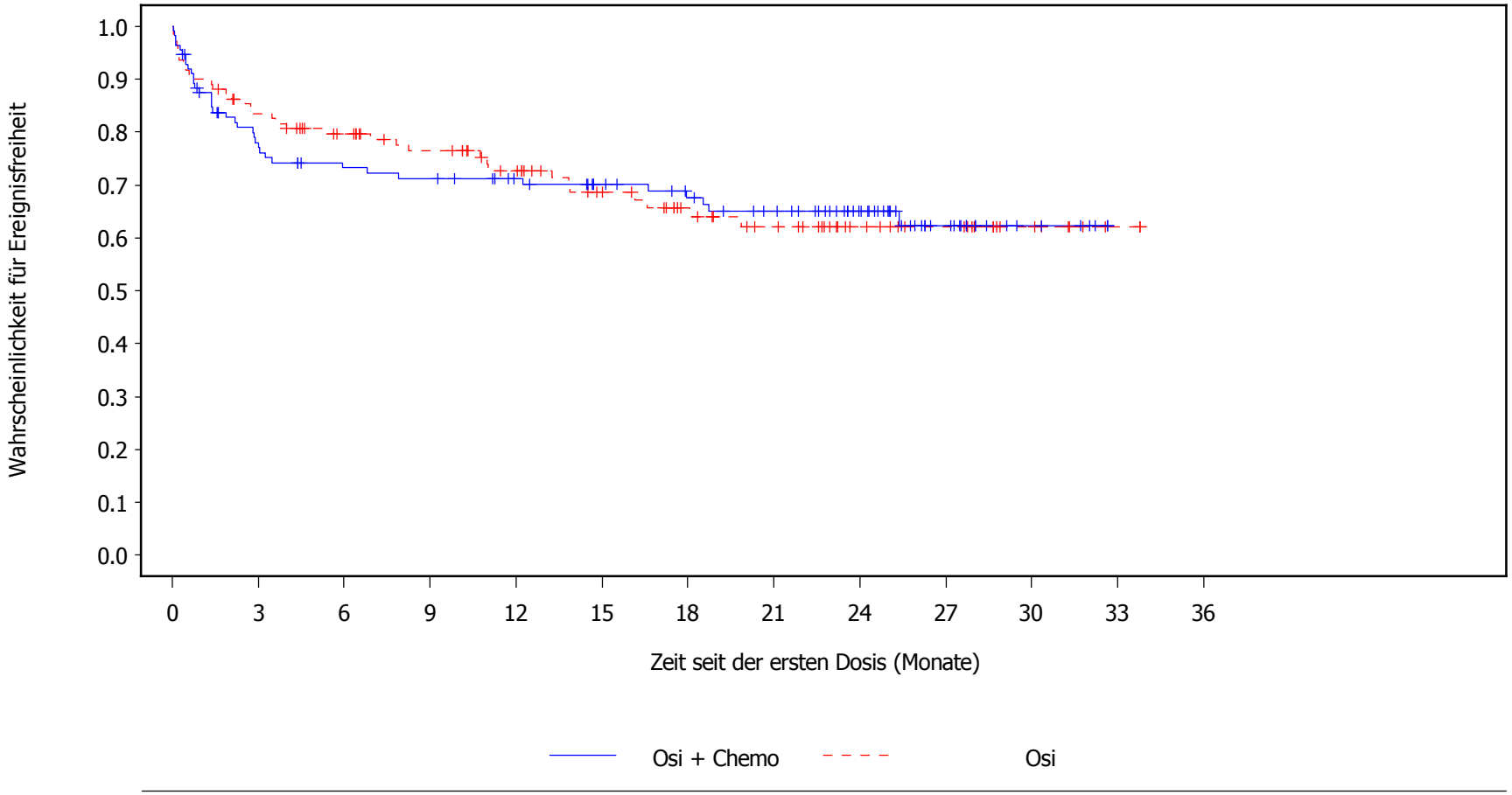
Figure 4.4.1.23 FLAURA-2 Subgroup Analysis: Kaplan-Meier plot of SOC: Erkrankungen des Nervensystems for ZNS-Metastasen zur Baseline=Ja
Safety Analysis Set, DCO 03APR2023



Anzahl an Patienten unter Risiko:

113	82	74	72	66	59	53	47	34	16	5	0	0	Osi + Chemo
110	89	78	69	59	48	38	31	20	15	7	1	0	Osi

Kaplan-Meier plot is presented only if the interaction term in Cox regression model with treatment, subgroup and treatment-by-subgroup interaction is statistically significant at 5% level.
root/cdar/d516/payer_germany/ar/d5169c00001_payer_germany/tlf/prod/program/ttesubae.sas gttesubaehaw 22DEC2023:09:13 kfrh585

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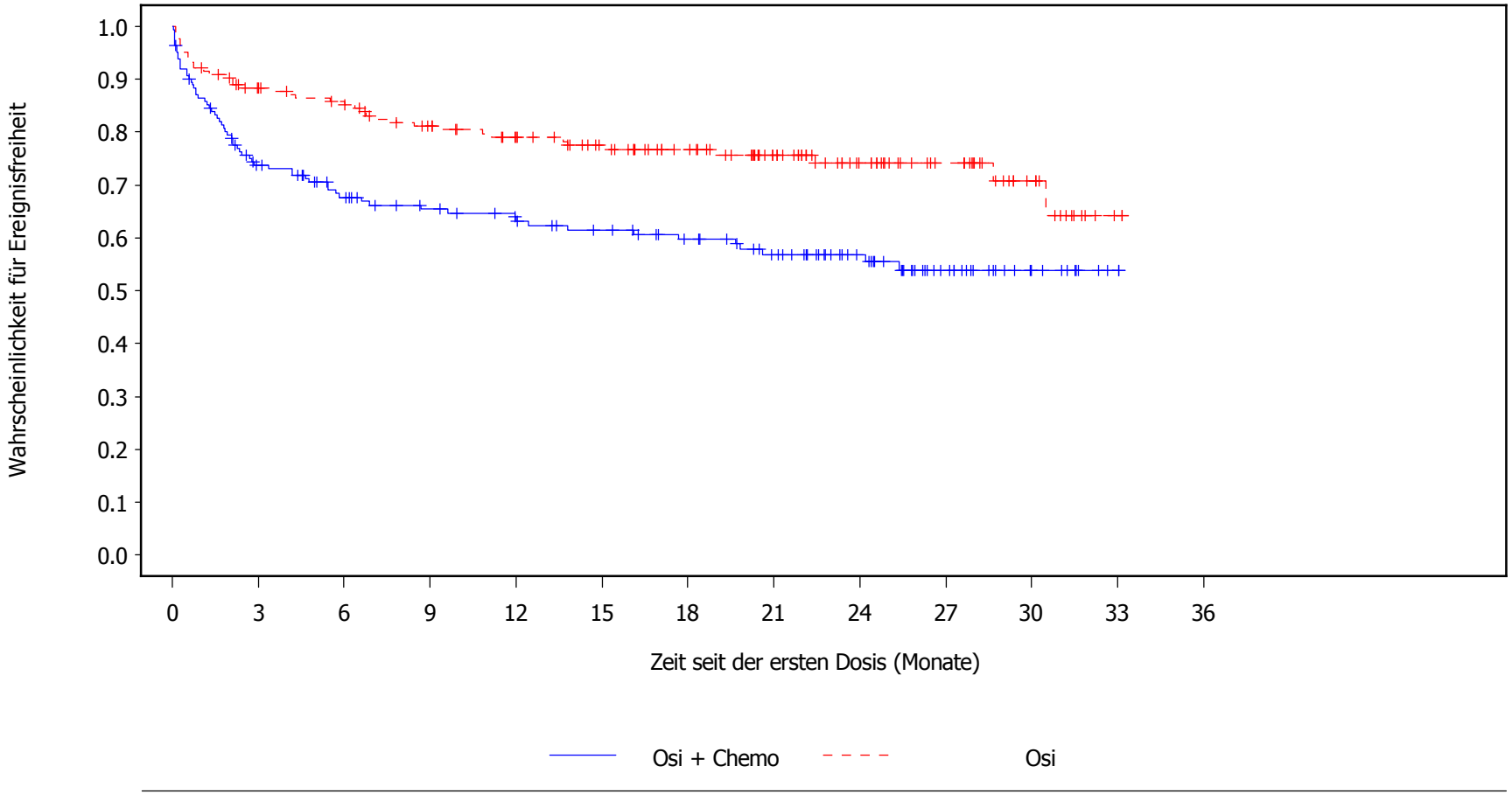
Figure 4.4.1.24 FLAURA-2 Subgroup Analysis: Kaplan-Meier plot of SOC: Erkrankungen des Nervensystems for ZNS-Metastasen zur Baseline=Nein
Safety Analysis Set, DCO 03APR2023

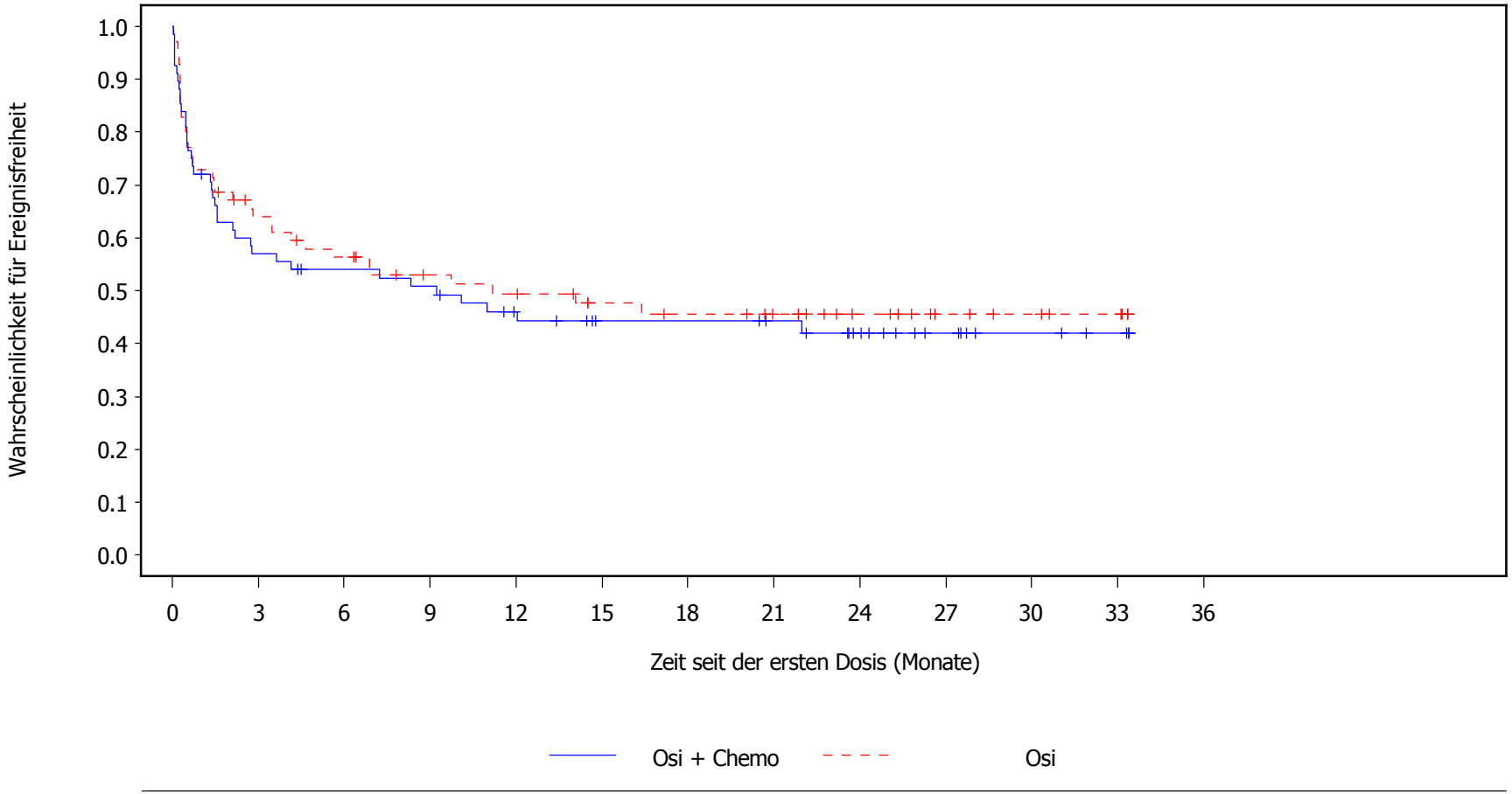


Anzahl an Patienten unter Risiko:

163	113	97	87	80	74	66	56	41	23	9	1	0	Osi + Chemo
165	139	131	117	106	95	82	65	44	30	14	1	0	Osi

Kaplan-Meier plot is presented only if the interaction term in Cox regression model with treatment, subgroup and treatment-by-subgroup interaction is statistically significant at 5% level.
root/cdar/d516/payer_germany/ar/d5169c00001_payer_germany/tlf/prod/program/ttesubae.sas gttesubaehax 22DEC2023:09:13 kfrh585

Figure 4.4.1.25 FLAURA-2 Subgroup Analysis: Kaplan-Meier plot of SOC: Stoffwechsel- und Ernaehrungsstoerungen for Abstammung=Chinesisch/Asiatisch
Safety Analysis Set, DCO 03APR2023



Anzahl an Patienten unter Risiko:

68	38	34	32	26	21	21	19	14	8	4	2	0	Osi + Chemo
70	42	36	30	28	23	21	18	12	7	5	3	0	Osi

Kaplan-Meier plot is presented only if the interaction term in Cox regression model with treatment, subgroup and treatment-by-subgroup interaction is statistically significant at 5% level.
root/cdar/d516/payer_germany/ar/d5169c00001_payer_germany/tlf/prod/program/ttesubae.sas gttesubaehay 22DEC2023:09:13 kfrh585

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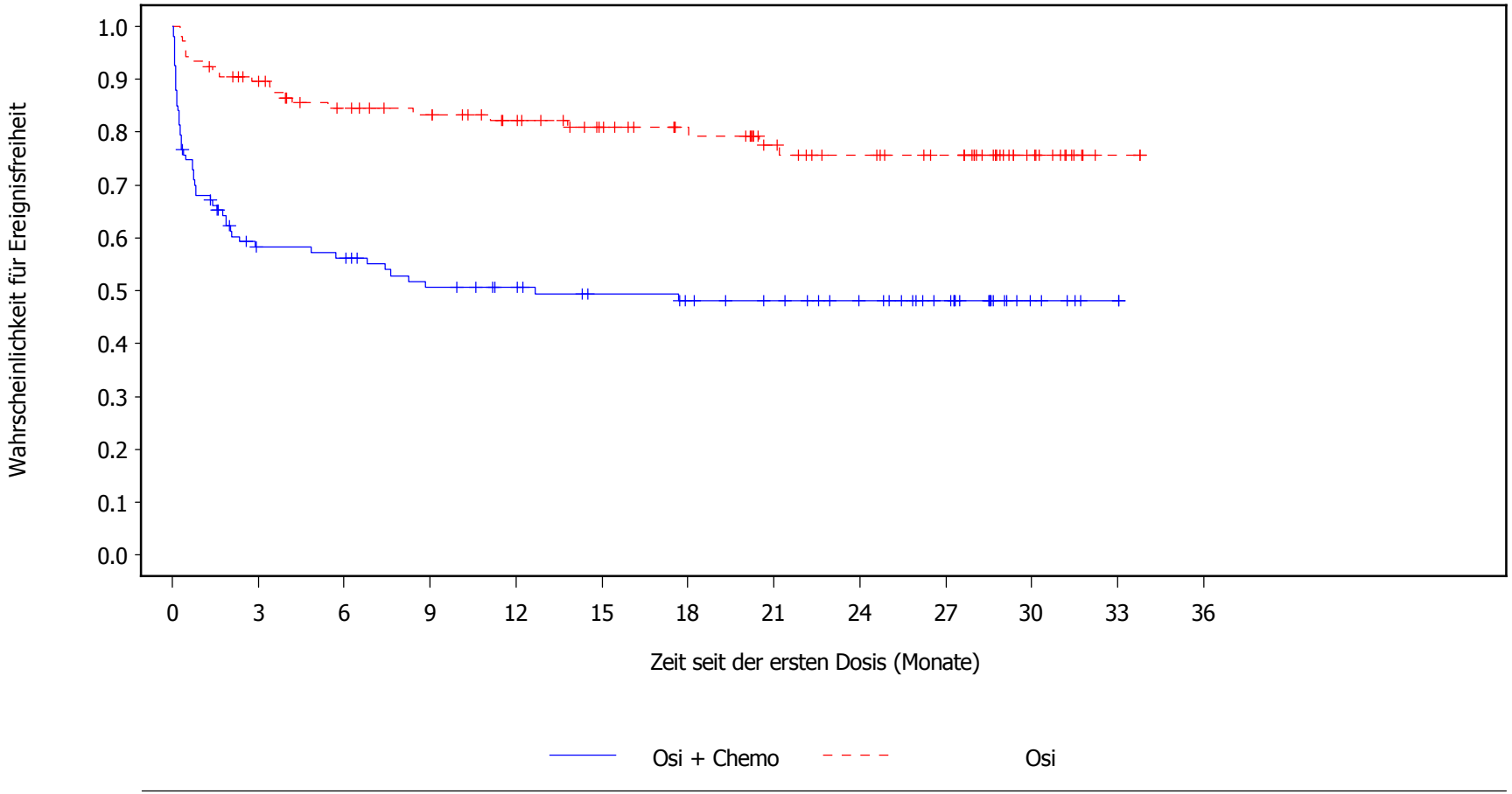
Figure 4.4.1.26 FLAURA-2 Subgroup Analysis: Kaplan-Meier plot of SOC: Stoffwechsel- und Ernaehrungsstoerungen for Abstammung=Nicht-chinesisch/Asiatisch
Safety Analysis Set, DCO 03APR2023



Anzahl an Patienten unter Risiko:

107	56	54	46	42	37	34	31	26	19	5	1	0	Osi + Chemo
106	91	80	75	67	58	51	42	36	31	13	1	0	Osi

Kaplan-Meier plot is presented only if the interaction term in Cox regression model with treatment, subgroup and treatment-by-subgroup interaction is statistically significant at 5% level.
root/cdar/d516/payer_germany/ar/d5169c00001_payer_germany/tlf/prod/program/ttesubae.sas gttesubaehaz 22DEC2023:09:13 kfrh585

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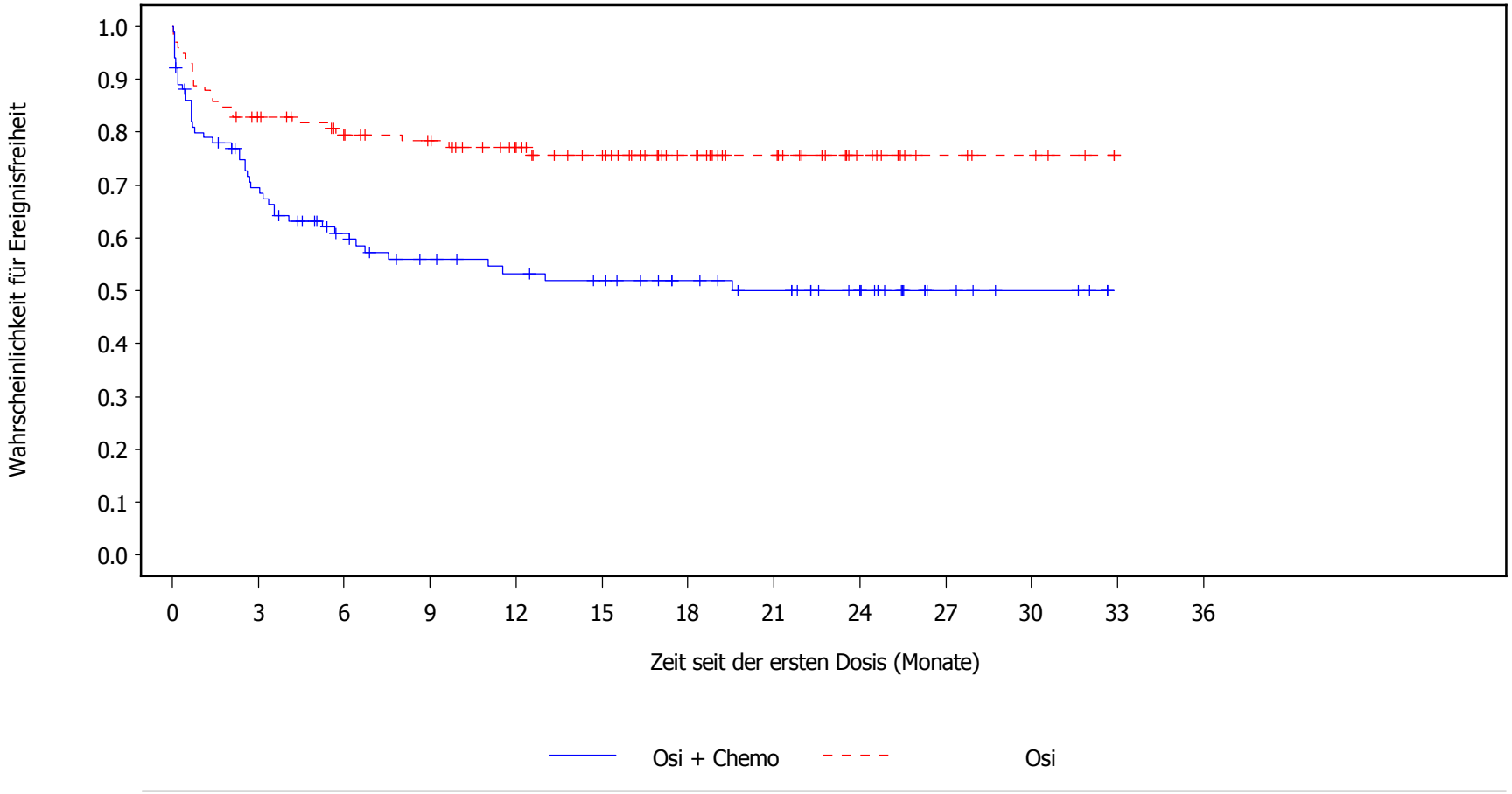
Figure 4.4.1.27 FLAURA-2 Subgroup Analysis: Kaplan-Meier plot of SOC: Stoffwechsel- und Ernaehrungsstoerungen for Abstammung=Nicht-asiatisch
Safety Analysis Set, DCO 03APR2023

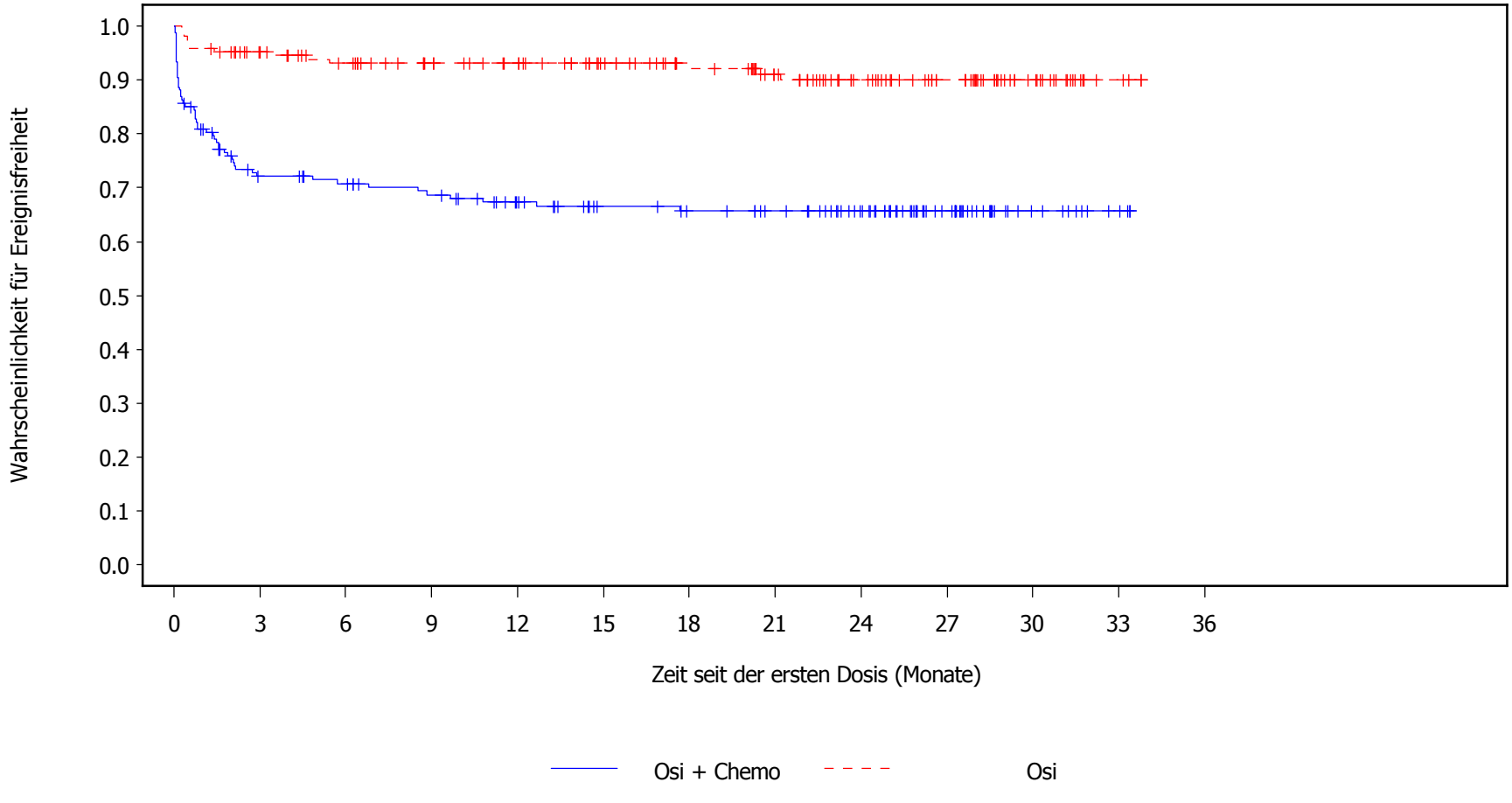


Anzahl an Patienten unter Risiko:

101	66	51	43	39	36	30	26	18	7	4	0	0	Osi + Chemo
99	79	70	65	55	47	32	24	13	6	4	0	0	Osi

Kaplan-Meier plot is presented only if the interaction term in Cox regression model with treatment, subgroup and treatment-by-subgroup interaction is statistically significant at 5% level.
root/cdar/d516/payer_germany/ar/d5169c00001_payer_germany/tlf/prod/program/ttesubae.sas gttesubaehba 22DEC2023:09:13 kfrh585

Figure 4.4.1.28 FLAURA-2 Subgroup Analysis: Kaplan-Meier plot of PT: Appetit vermindert for Region gPAP=Asien
Safety Analysis Set, DCO 03APR2023

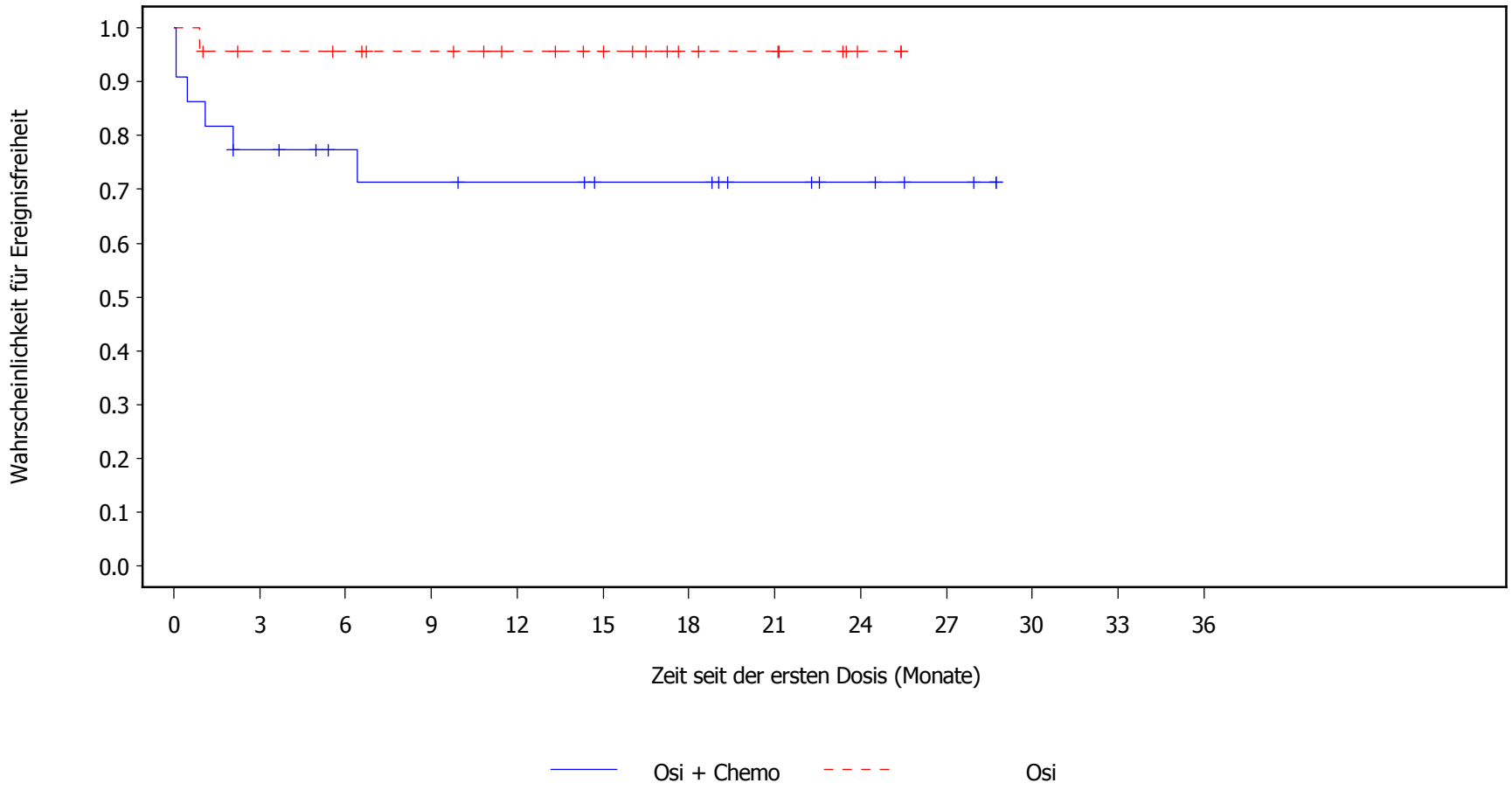


Anzahl an Patienten unter Risiko:

168	112	107	100	89	78	74	69	57	33	10	3	0	Osi + Chemo
166	149	138	127	120	106	93	80	59	43	19	3	0	Osi

Kaplan-Meier plot is presented only if the interaction term in Cox regression model with treatment, subgroup and treatment-by-subgroup interaction is statistically significant at 5% level.
root/cdar/d516/payer_germany/ar/d5169c00001_payer_germany/tlf/prod/program/ttesubae.sas gttesubaehbb 22DEC2023:09:13 kfrh585

Figure 4.4.1.29 FLAURA-2 Subgroup Analysis: Kaplan-Meier plot of PT: Appetit vermindert for Region gPAP=Europa
Safety Analysis Set, DCO 03APR2023

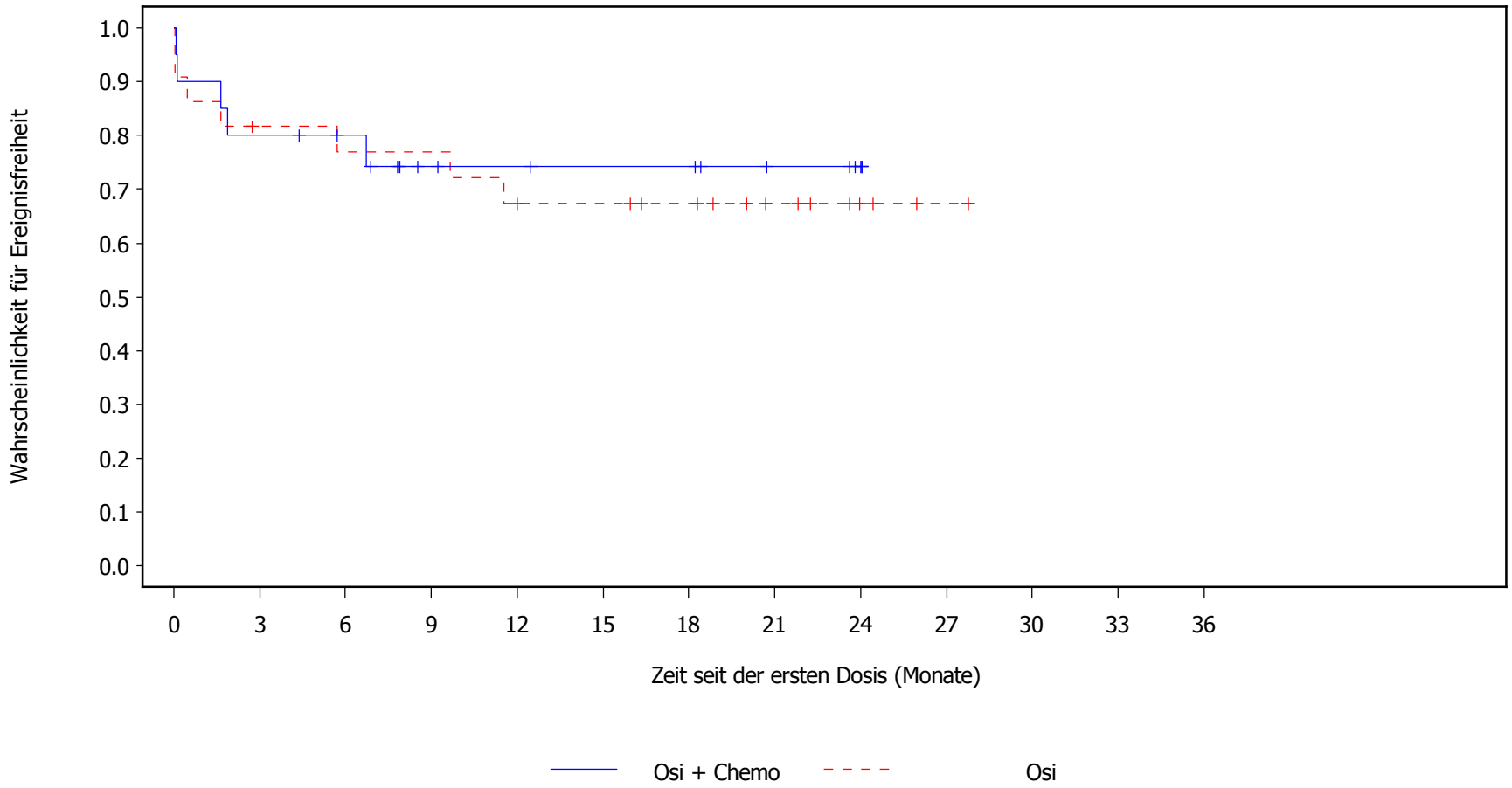


Anzahl an Patienten unter Risiko:

22	16	13	12	11	9	9	6	4	2	0	0	0	Osi + Chemo
23	20	19	17	14	12	7	6	1	0	0	0	0	Osi

Kaplan-Meier plot is presented only if the interaction term in Cox regression model with treatment, subgroup and treatment-by-subgroup interaction is statistically significant at 5% level.
root/cdar/d516/payer_germany/ar/d5169c00001_payer_germany/tlf/prod/program/ttesubae.sas gttesubaehbc 22DEC2023:09:13 kfrh585

Figure 4.4.1.30 FLAURA-2 Subgroup Analysis: Kaplan-Meier plot of PT: Appetit vermindert for Region gPAP=Nordamerika
Safety Analysis Set, DCO 03APR2023

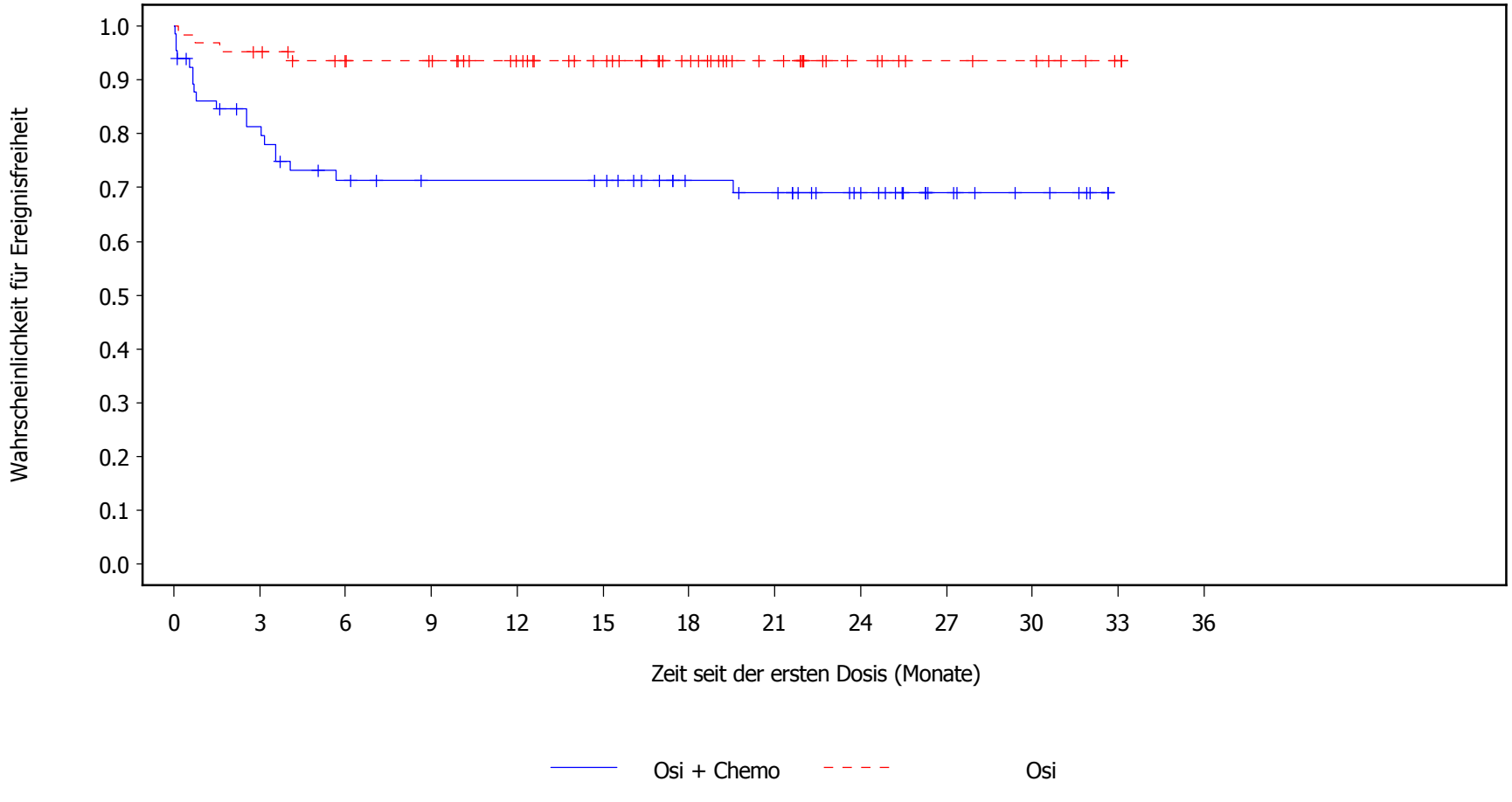


Anzahl an Patienten unter Risiko:

20	16	14	9	8	7	7	4	2	0	0	0	0	Osi + Chemo
22	17	16	16	13	13	11	7	3	1	0	0	0	Osi

Kaplan-Meier plot is presented only if the interaction term in Cox regression model with treatment, subgroup and treatment-by-subgroup interaction is statistically significant at 5% level.
root/cdar/d516/payer_germany/ar/d5169c00001_payer_germany/tlf/prod/program/ttesubae.sas gttesubaehbd 22DEC2023:09:13 kfrh585

Figure 4.4.1.31 FLAURA-2 Subgroup Analysis: Kaplan-Meier plot of PT: Appetit vermindert for Region gPAP=Rest der Welt
Safety Analysis Set, DCO 03APR2023



Anzahl an Patienten unter Risiko:

66	50	42	39	39	38	30	28	19	10	6	0	0	Osi + Chemo
64	60	54	52	45	38	29	20	11	7	6	1	0	Osi

Kaplan-Meier plot is presented only if the interaction term in Cox regression model with treatment, subgroup and treatment-by-subgroup interaction is statistically significant at 5% level.
root/cdar/d516/payer_germany/ar/d5169c00001_payer_germany/tlf/prod/program/ttesubae.sas gttesubaehbe 22DEC2023:09:13 kfrh585

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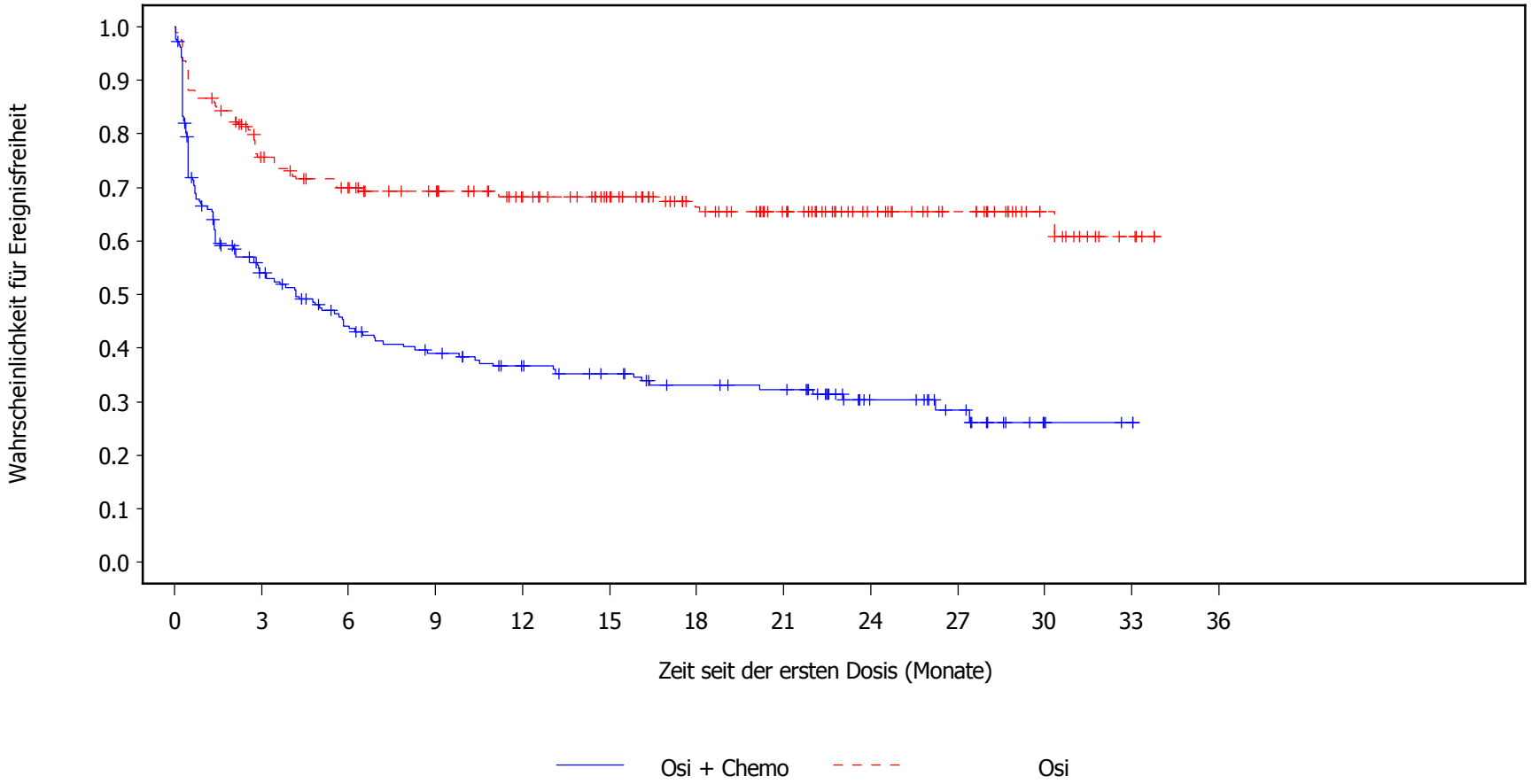
Figure 4.4.1.32 FLAURA-2 Subgroup Analysis: Kaplan-Meier plot of SOC: Untersuchungen for Nachweis der EGFR-Mutation durch zentralen ctDNA Cobas Test=positiv
Safety Analysis Set, DCO 03APR2023



Anzahl an Patienten unter Risiko:

211	103	79	67	57	51	43	40	21	14	3	1	0	Osi + Chemo
204	147	130	120	104	92	72	59	40	29	14	4	0	Osi

Kaplan-Meier plot is presented only if the interaction term in Cox regression model with treatment, subgroup and treatment-by-subgroup interaction is statistically significant at 5% level.
root/cdar/d516/payer_germany/ar/d5169c00001_payer_germany/tlf/prod/program/ttesubae.sas gttesubaehbf 22DEC2023:09:13 kfrh585

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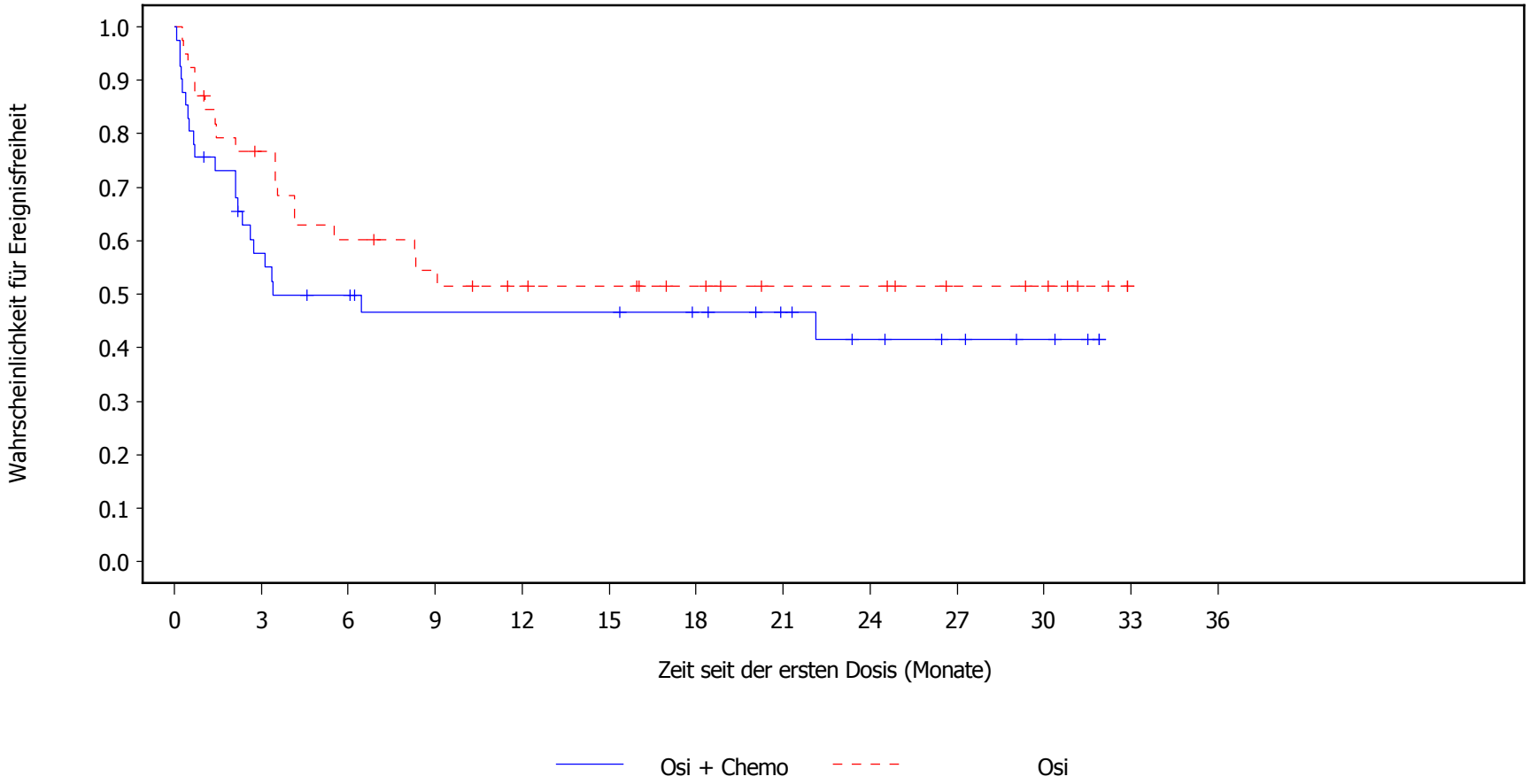
Figure 4.4.1.33 FLAURA-2 Subgroup Analysis: Kaplan-Meier plot of SOC: Untersuchungen for Nachweis der EGFR-Mutation durch zentralen ctDNA Cobas Test=negativ
Safety Analysis Set, DCO 03APR2023



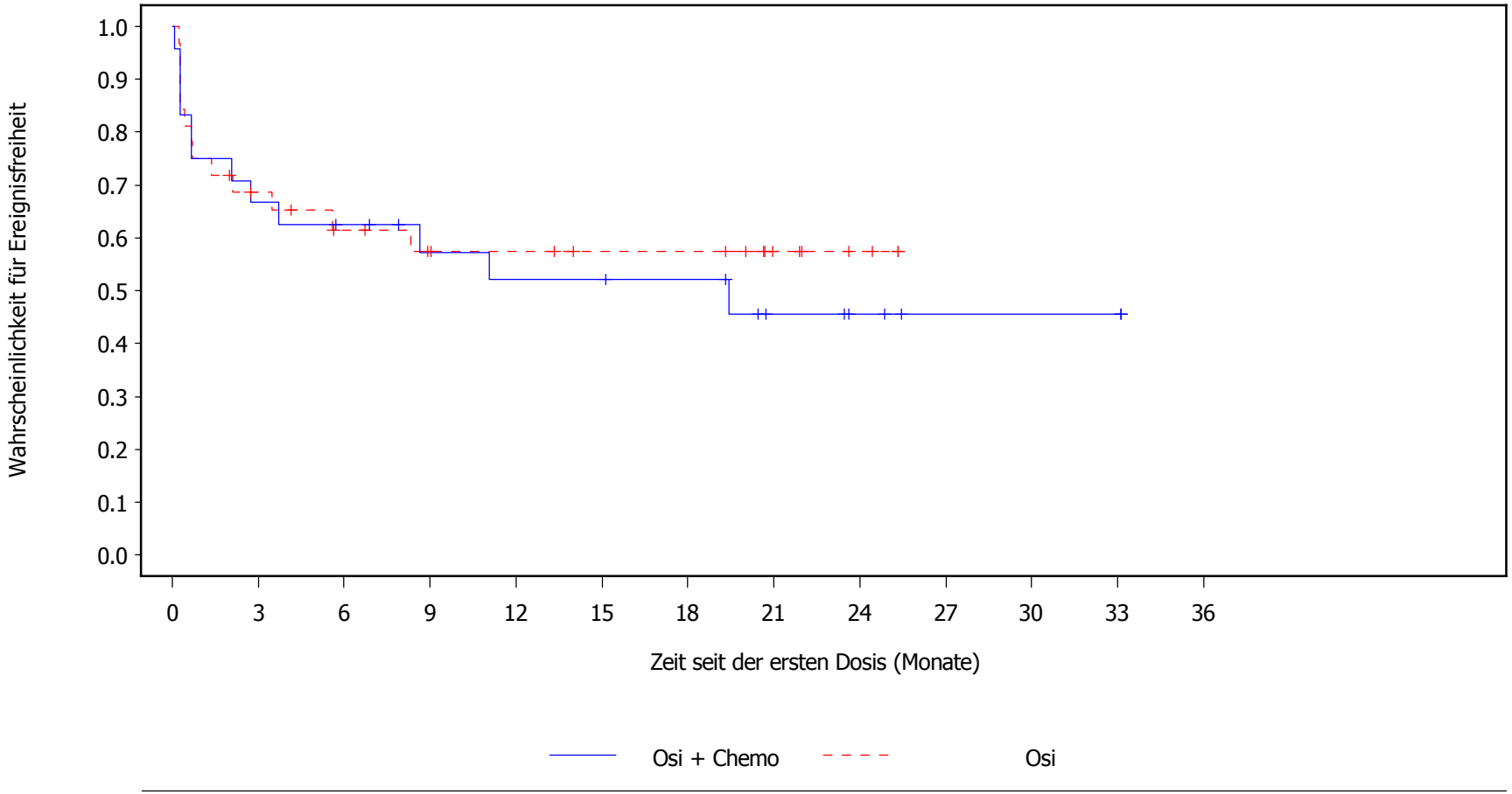
Anzahl an Patienten unter Risiko:

41	22	18	15	15	15	13	10	7	5	3	0	0	Osi + Chemo
39	28	22	19	16	15	12	9	9	6	5	0	0	Osi

Kaplan-Meier plot is presented only if the interaction term in Cox regression model with treatment, subgroup and treatment-by-subgroup interaction is statistically significant at 5% level.
root/cdar/d516/payer_germany/ar/d5169c00001_payer_germany/tlf/prod/program/ttesubae.sas gttesubaehbg 22DEC2023:09:13 kfrh585

Nutzenbewertung nach AMNOG Seite 1 von 1

Figure 4.4.1.34 FLAURA-2 Subgroup Analysis: Kaplan-Meier plot of SOC: Untersuchungen for Nachweis der EGFR-Mutation durch zentralen ctDNA Cobas Test=unbekannt
Safety Analysis Set, DCO 03APR2023



Anzahl an Patienten unter Risiko:

24	16	14	11	10	10	9	5	3	1	1	1	0	Osi + Chemo
32	20	16	13	12	10	10	5	2	0	0	0	0	Osi

Kaplan-Meier plot is presented only if the interaction term in Cox regression model with treatment, subgroup and treatment-by-subgroup interaction is statistically significant at 5% level.
root/cdar/d516/payer_germany/ar/d5169c00001_payer_germany/tlf/prod/program/ttesubae.sas gttesubaehbh 22DEC2023:09:13 kfrh585

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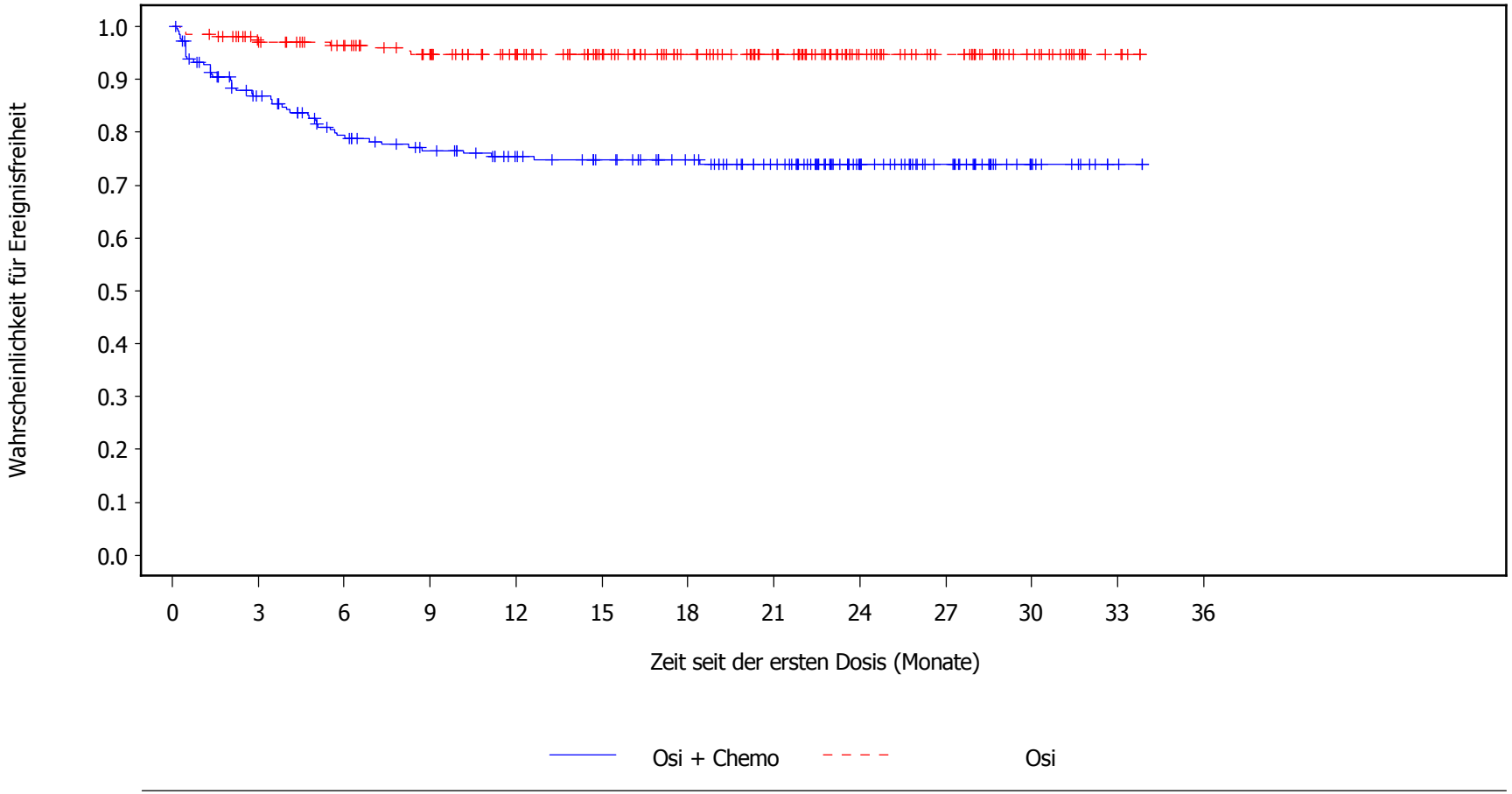
Figure 4.4.1.35 FLAURA-2 Subgroup Analysis: Kaplan-Meier plot of PT: Alaninaminotransferase erhoeht for Nachweis der EGFR-Mutation durch zentralen ctDNA Cobas Test=positiv
Safety Analysis Set, DCO 03APR2023



Anzahl an Patienten unter Risiko:

211	169	145	132	119	110	99	83	50	33	12	2	0	Osi + Chemo
204	189	176	161	143	123	101	84	54	39	19	4	0	Osi

Kaplan-Meier plot is presented only if the interaction term in Cox regression model with treatment, subgroup and treatment-by-subgroup interaction is statistically significant at 5% level.

root/cdar/d516/payer_germany/ar/d5169c00001_payer_germany/tlf/prod/program/ttesubae.sas gttesubaehbi 22DEC2023:09:13 kfrh585

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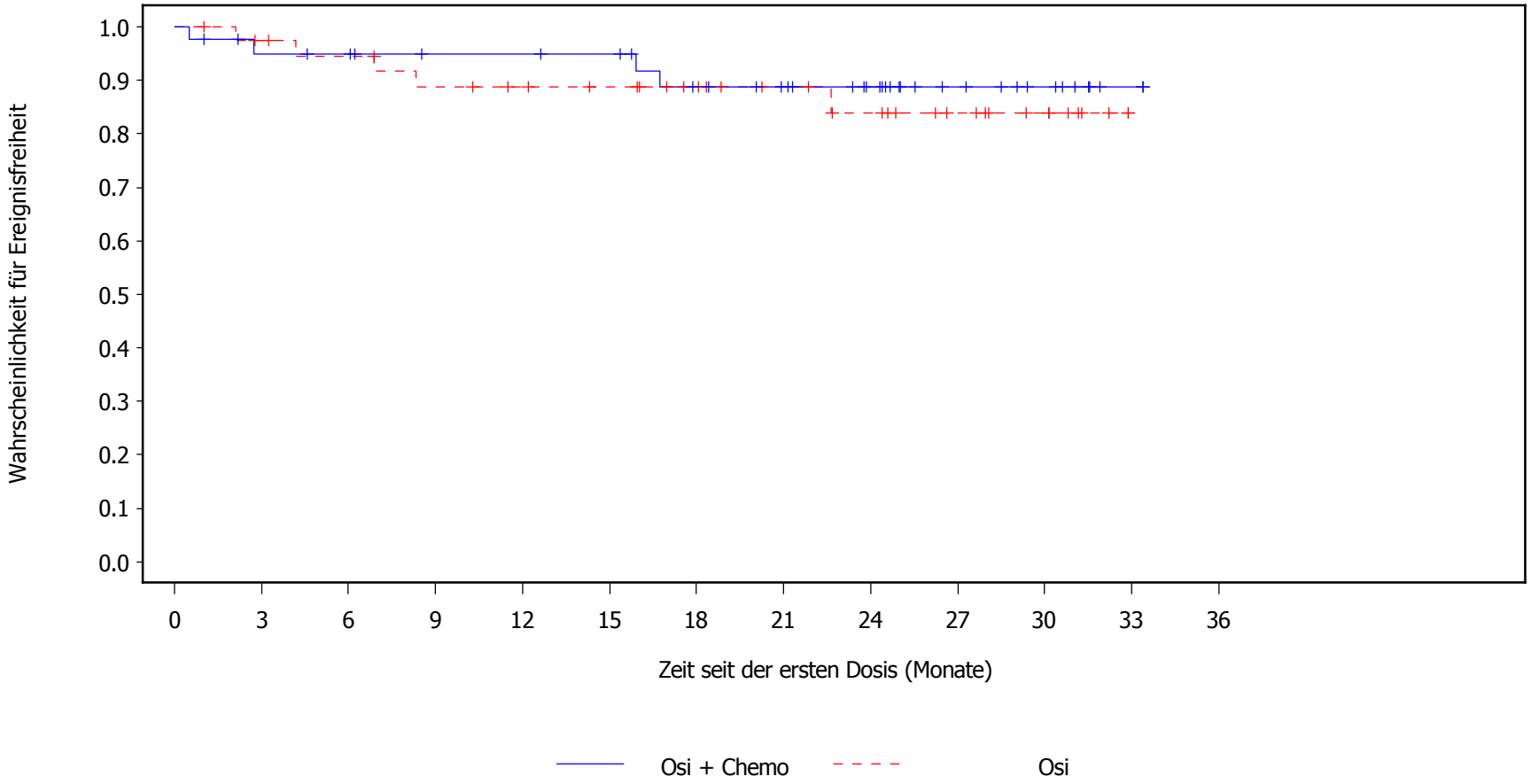
Figure 4.4.1.36 FLAURA-2 Subgroup Analysis: Kaplan-Meier plot of PT: Alaninaminotransferase erhoeht for Nachweis der EGFR-Mutation durch zentralen ctDNA Cobas Test=negativ
Safety Analysis Set, DCO 03APR2023



Anzahl an Patienten unter Risiko:

41	37	36	33	33	32	27	24	19	11	7	1	0	Osi + Chemo
39	36	34	31	29	27	23	19	16	11	7	0	0	Osi

Kaplan-Meier plot is presented only if the interaction term in Cox regression model with treatment, subgroup and treatment-by-subgroup interaction is statistically significant at 5% level.
root/cdar/d516/payer_germany/ar/d5169c00001_payer_germany/tlf/prod/program/ttesubae.sas gttesubaehbj 22DEC2023:09:13 kfrh585

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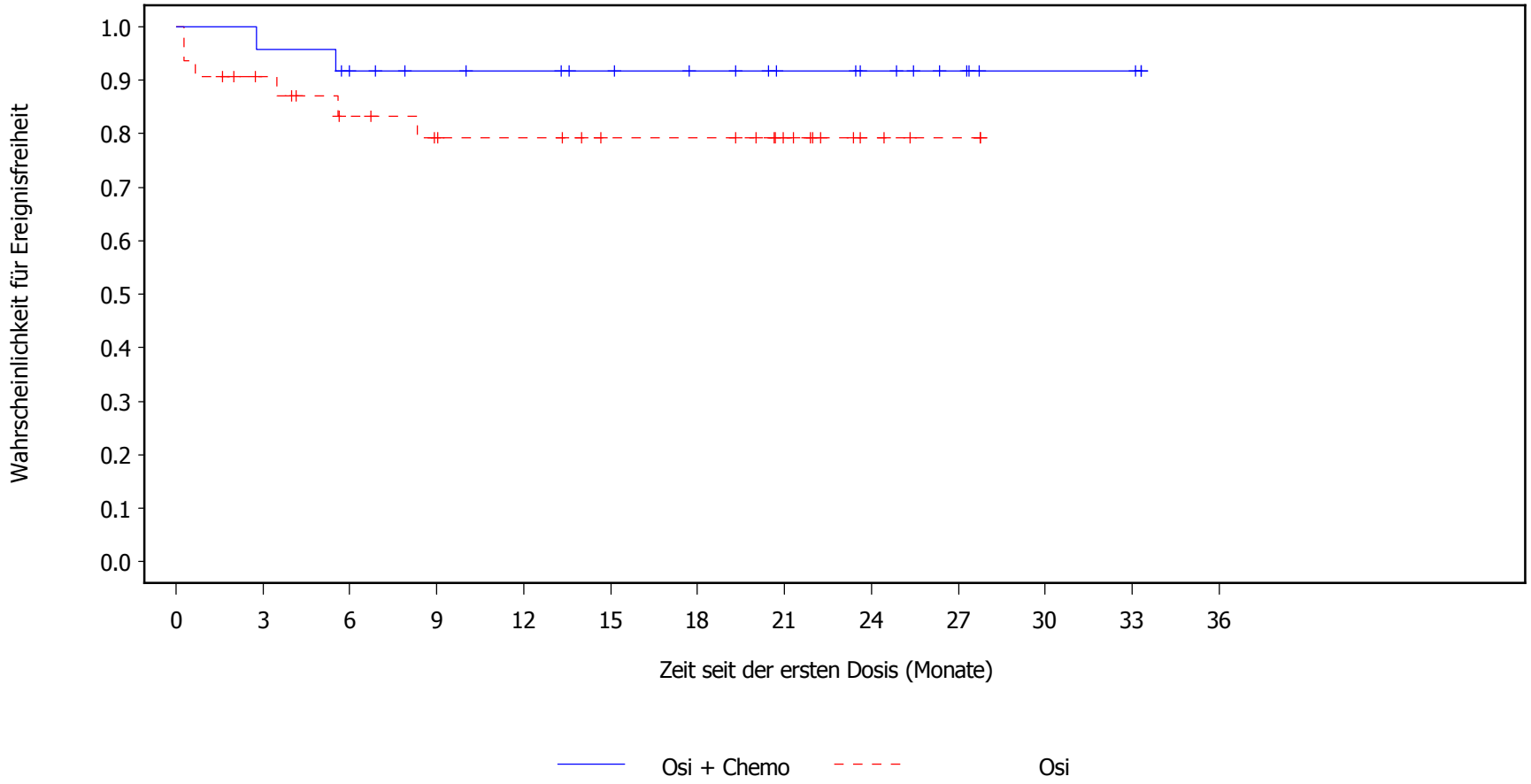
Figure 4.4.1.37 FLAURA-2 Subgroup Analysis: Kaplan-Meier plot of PT: Alaninaminotransferase erhoeht for Nachweis der EGFR-Mutation durch zentralen ctDNA Cobas Test=unbekannt
Safety Analysis Set, DCO 03APR2023



Anzahl an Patienten unter Risiko:

24	23	20	18	17	15	13	10	8	5	2	2	0	Osi + Chemo
32	26	21	18	17	14	14	9	3	1	0	0	0	Osi

Kaplan-Meier plot is presented only if the interaction term in Cox regression model with treatment, subgroup and treatment-by-subgroup interaction is statistically significant at 5% level.
root/cdar/d516/payer_germany/ar/d5169c00001_payer_germany/tlf/prod/program/ttesubae.sas gttesubaehbk 22DEC2023:09:13 kfrh585

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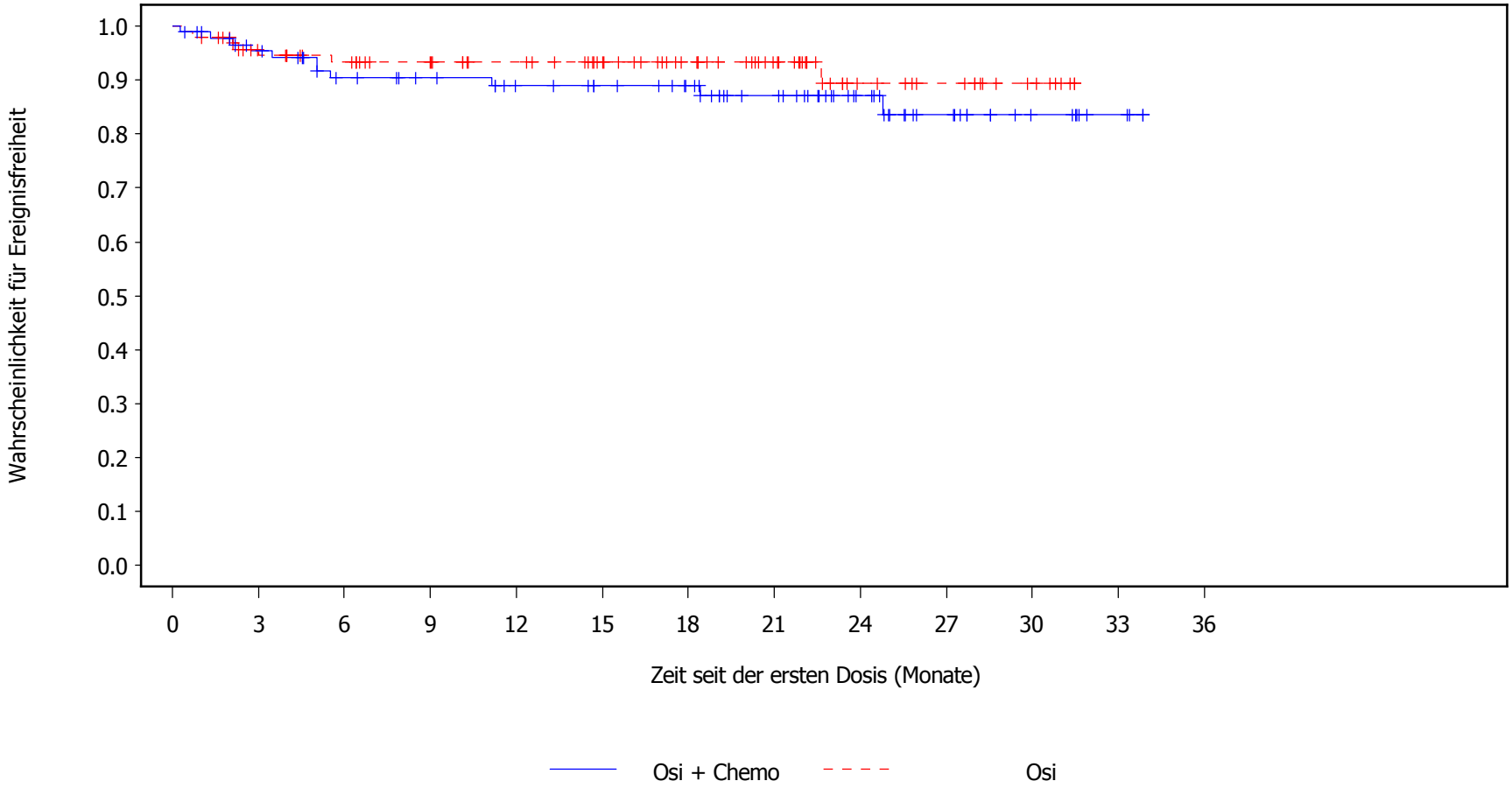
Figure 4.4.1.38 FLAURA-2 Subgroup Analysis: Kaplan-Meier plot of PT: Aspartataminotransferase erhoeht for Raucherstatus=Ja
Safety Analysis Set, DCO 03APR2023



Anzahl an Patienten unter Risiko:

90	80	70	66	60	56	51	41	28	17	8	3	0	Osi + Chemo
96	83	76	70	63	55	45	34	17	13	6	0	0	Osi

Kaplan-Meier plot is presented only if the interaction term in Cox regression model with treatment, subgroup and treatment-by-subgroup interaction is statistically significant at 5% level.

root/cdar/d516/payer_germany/ar/d5169c00001_payer_germany/tlf/prod/program/ttesubae.sas gttesubaehbl 22DEC2023:09:13 kfrh585

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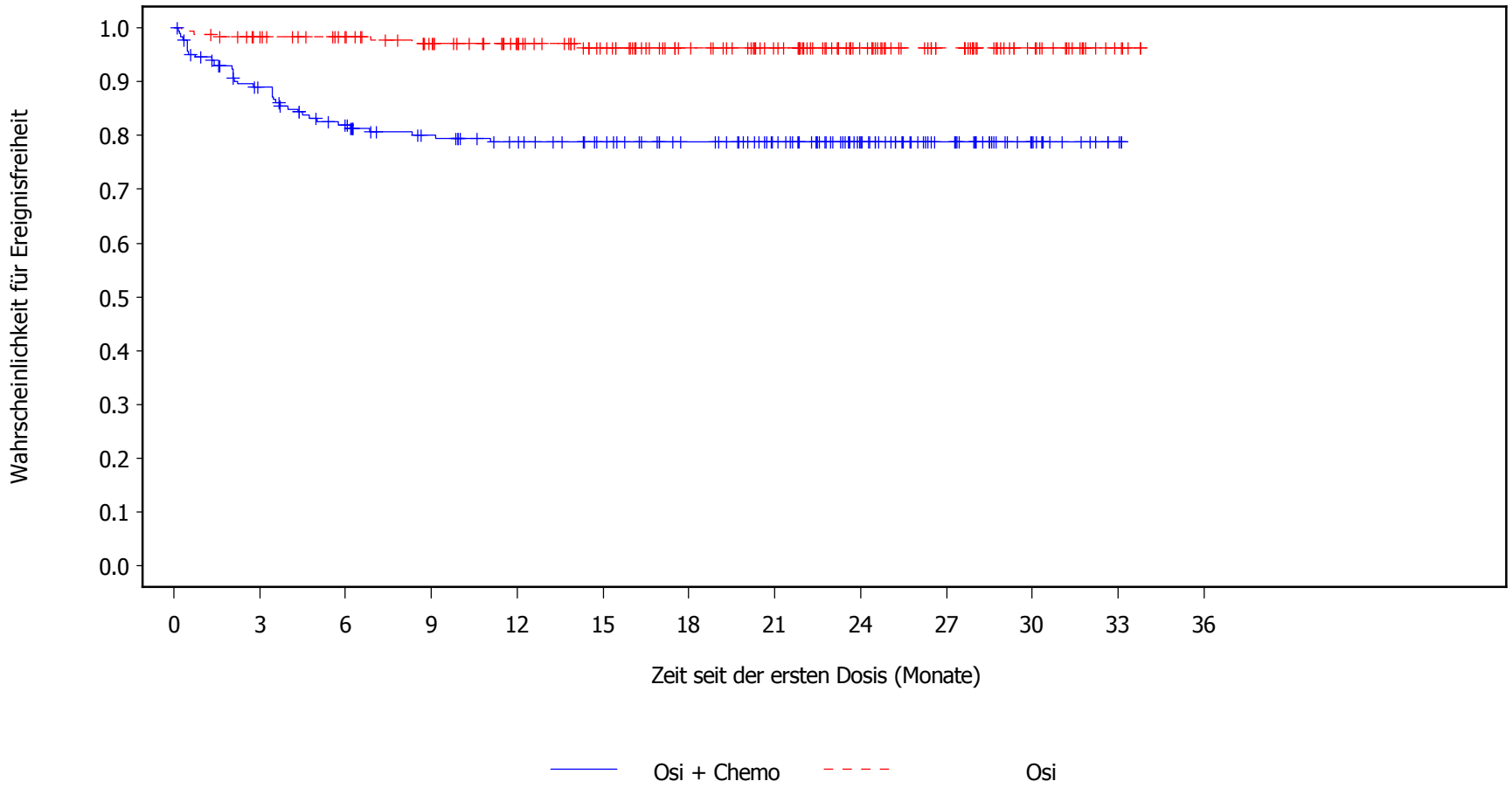
Figure 4.4.1.39 FLAURA-2 Subgroup Analysis: Kaplan-Meier plot of PT: Aspartataminotransferase erhoeht for Raucherstatus=Nein
Safety Analysis Set, DCO 03APR2023



Anzahl an Patienten unter Risiko:

186	155	136	124	115	106	95	82	56	33	14	2	0	Osi + Chemo
179	170	160	148	134	116	97	83	58	39	20	4	0	Osi

Kaplan-Meier plot is presented only if the interaction term in Cox regression model with treatment, subgroup and treatment-by-subgroup interaction is statistically significant at 5% level.
root/cdar/d516/payer_germany/ar/d5169c00001_payer_germany/tlf/prod/program/ttesubae.sas gttesubaehbm 22DEC2023:09:13 kfrh585

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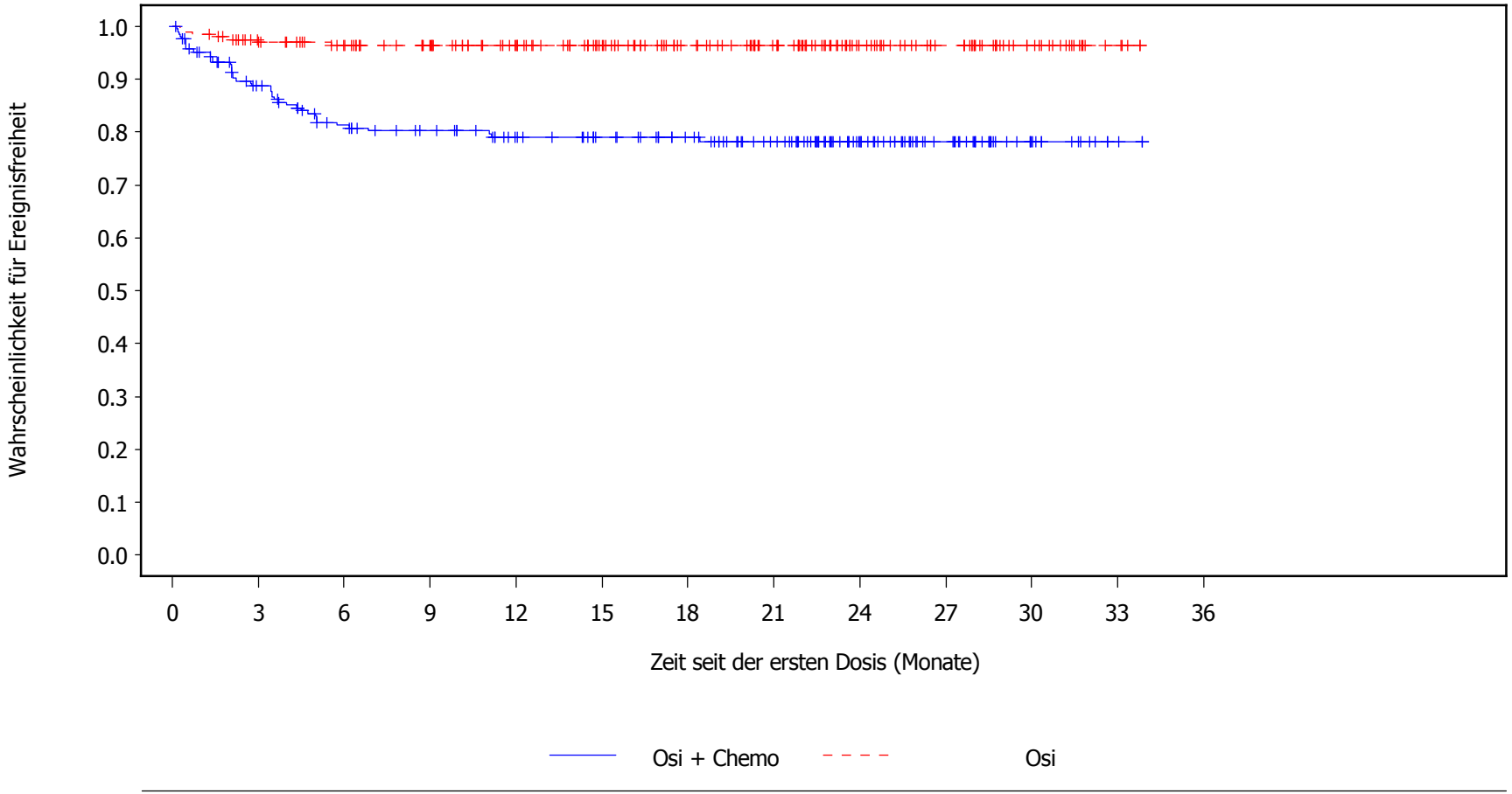
Figure 4.4.1.40 FLAURA-2 Subgroup Analysis: Kaplan-Meier plot of PT: Aspartataminotransferase erhoeht for Nachweis der EGFR-Mutation durch zentralen ctDNA Cobas Test=positiv
Safety Analysis Set, DCO 03APR2023



Anzahl an Patienten unter Risiko:

211	173	149	139	126	116	105	89	57	35	13	2	0	Osi + Chemo
204	189	176	163	145	125	102	86	56	40	19	4	0	Osi

Kaplan-Meier plot is presented only if the interaction term in Cox regression model with treatment, subgroup and treatment-by-subgroup interaction is statistically significant at 5% level.
root/cdar/d516/payer_germany/ar/d5169c00001_payer_germany/tlf/prod/program/ttesubae.sas gttesubaehbn 22DEC2023:09:13 kfrh585

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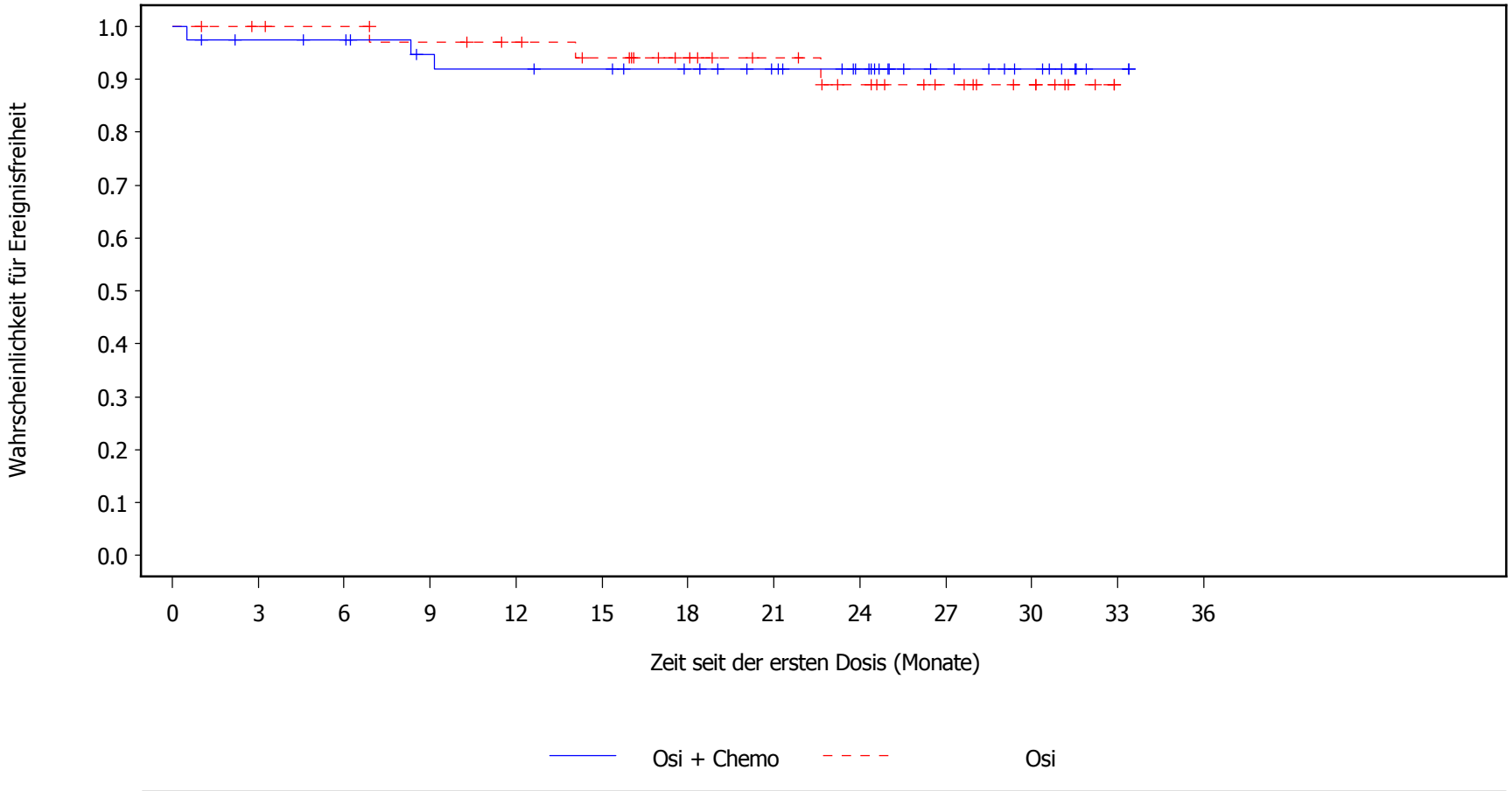
Figure 4.4.1.41 FLAURA-2 Subgroup Analysis: Kaplan-Meier plot of PT: Aspartataminotransferase erhoeht for Nachweis der EGFR-Mutation durch zentralen ctDNA Cobas Test=negativ
Safety Analysis Set, DCO 03APR2023

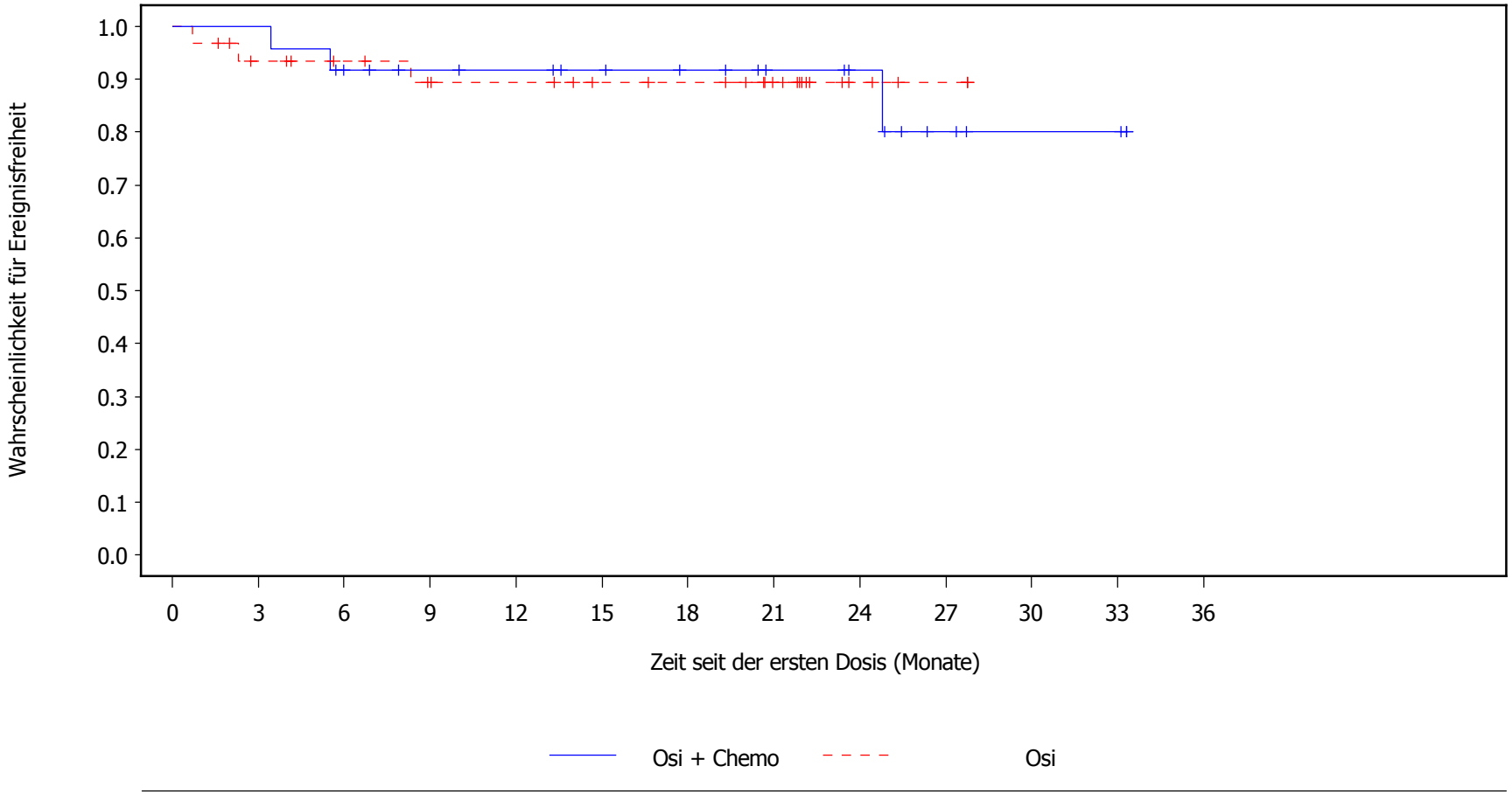


Anzahl an Patienten unter Risiko:

41	38	37	33	32	31	28	24	19	11	7	1	0	Osi + Chemo
39	37	36	34	32	29	24	20	16	11	7	0	0	Osi

Kaplan-Meier plot is presented only if the interaction term in Cox regression model with treatment, subgroup and treatment-by-subgroup interaction is statistically significant at 5% level.
root/cdar/d516/payer_germany/ar/d5169c00001_payer_germany/tlf/prod/program/ttesubae.sas gttesubaehbo 22DEC2023:09:13 kfrh585

Figure 4.4.1.42 FLAURA-2 Subgroup Analysis: Kaplan-Meier plot of PT: Aspartataminotransferase erhoeht for Nachweis der EGFR-Mutation durch zentralen ctDNA Cobas Test=unbekannt
Safety Analysis Set, DCO 03APR2023

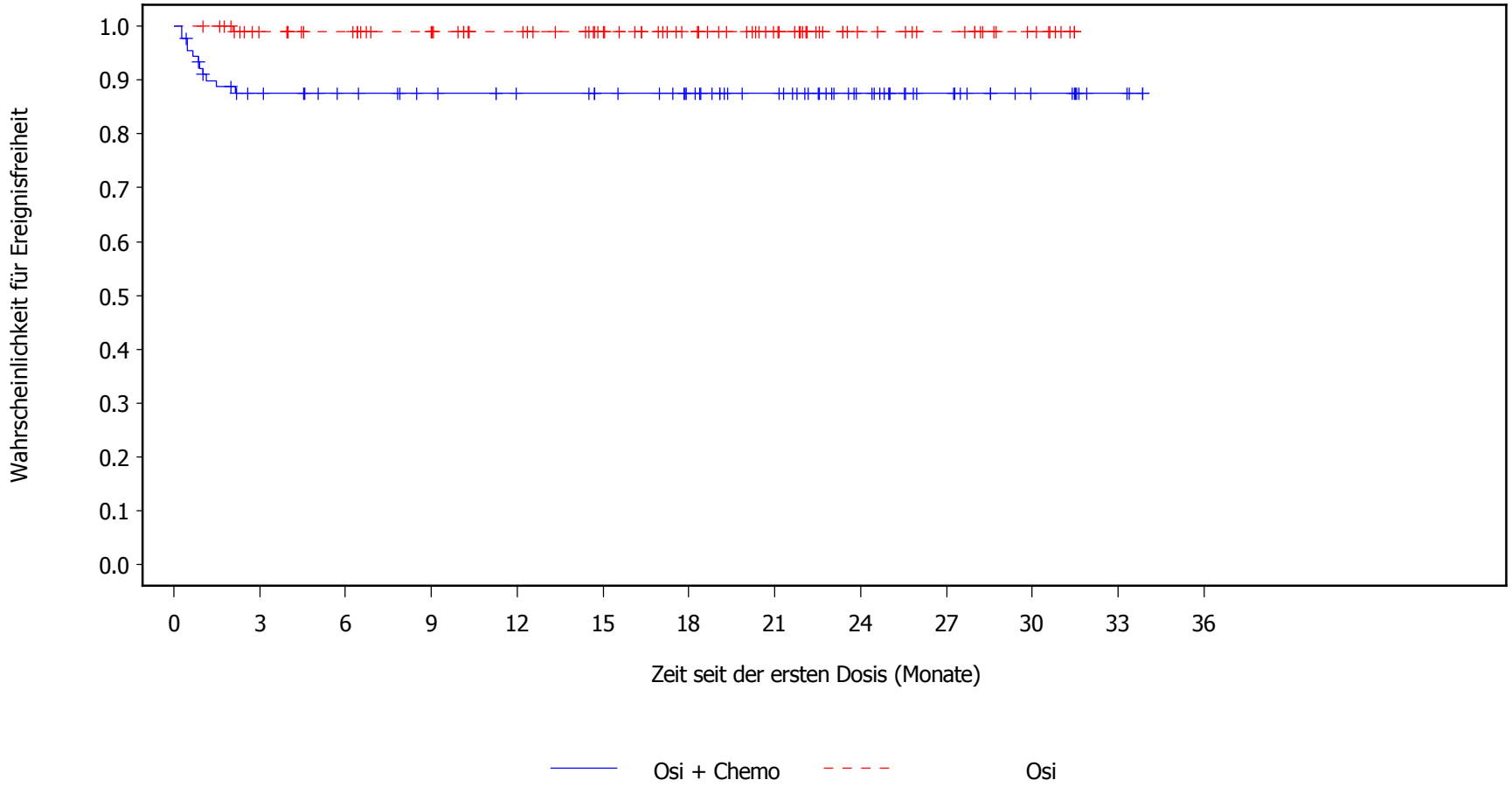


Anzahl an Patienten unter Risiko:

24	24	20	18	17	15	13	10	8	4	2	2	0	Osi + Chemo
32	27	24	21	20	17	16	11	3	1	0	0	0	Osi

Kaplan-Meier plot is presented only if the interaction term in Cox regression model with treatment, subgroup and treatment-by-subgroup interaction is statistically significant at 5% level.
root/cdar/d516/payer_germany/ar/d5169c00001_payer_germany/tlf/prod/program/ttesubae.sas gttesubaehbp 22DEC2023:09:13 kfrh585

Figure 4.4.1.43 FLAURA-2 Subgroup Analysis: Kaplan-Meier plot of PT: Leukozytenzahl erniedrigt for Raucherstatus=Ja
Safety Analysis Set, DCO 03APR2023



Anzahl an Patienten unter Risiko:

90	73	68	64	60	57	51	42	28	17	9	3	0	Osi + Chemo
96	86	81	75	67	58	47	35	19	15	7	0	0	Osi

Kaplan-Meier plot is presented only if the interaction term in Cox regression model with treatment, subgroup and treatment-by-subgroup interaction is statistically significant at 5% level.

root/cdar/d516/payer_germany/ar/d5169c00001_payer_germany/tlf/prod/program/ttesubae.sas gttesubaehbq 22DEC2023:09:13 kfrh585

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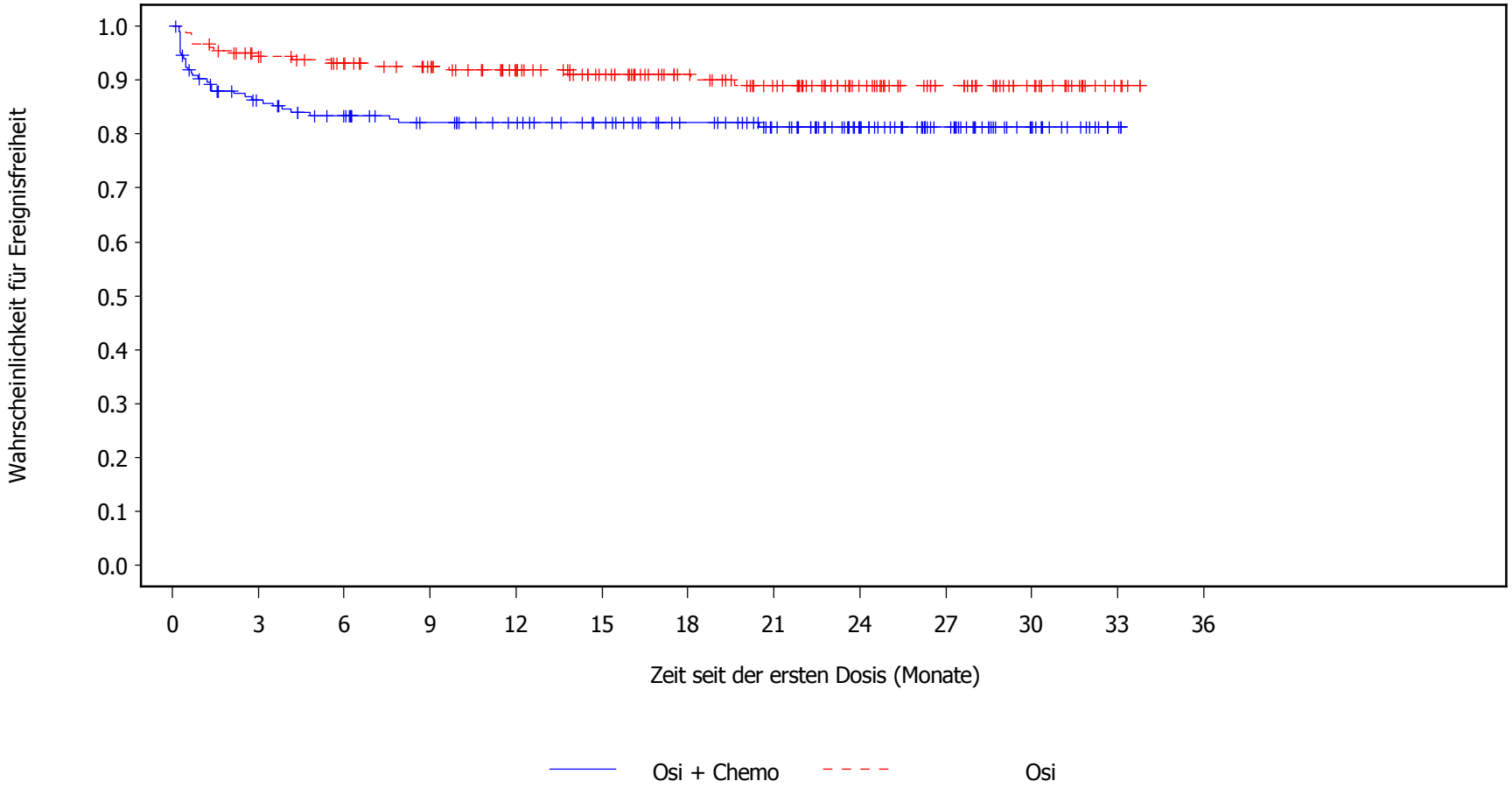
Figure 4.4.1.44 FLAURA-2 Subgroup Analysis: Kaplan-Meier plot of PT: Leukozytenzahl erniedrigt for Raucherstatus=Nein
Safety Analysis Set, DCO 03APR2023



Anzahl an Patienten unter Risiko:

186	150	138	127	120	111	99	86	61	39	18	2	0	Osi + Chemo
179	162	151	141	126	108	89	75	55	37	21	4	0	Osi

Kaplan-Meier plot is presented only if the interaction term in Cox regression model with treatment, subgroup and treatment-by-subgroup interaction is statistically significant at 5% level.

root/cdar/d516/payer_germany/ar/d5169c00001_payer_germany/tlf/prod/program/ttesubae.sas gttesubaehbr 22DEC2023:09:13 kfrh585

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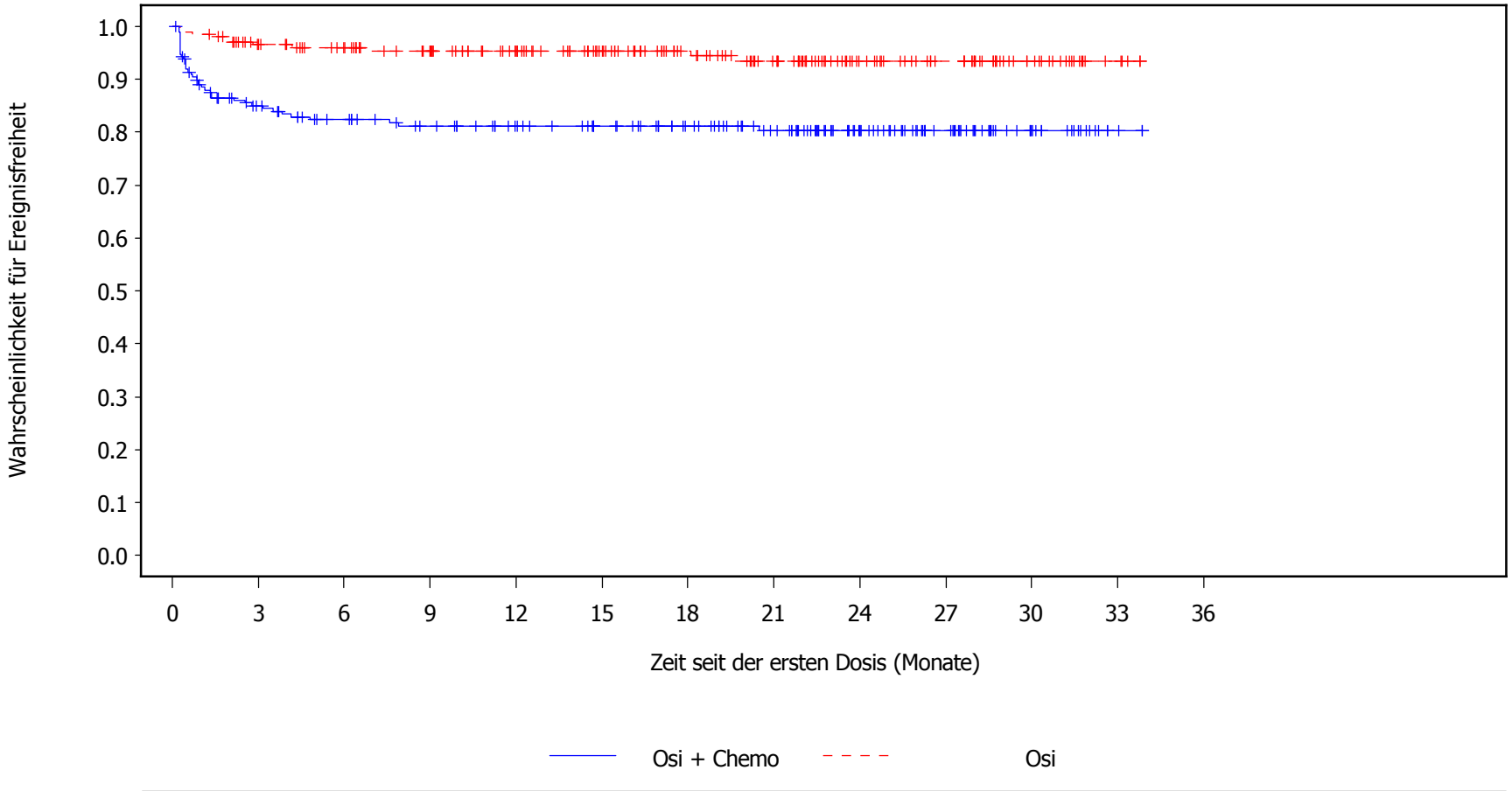
Figure 4.4.1.45 FLAURA-2 Subgroup Analysis: Kaplan-Meier plot of PT: Leukozytenzahl erniedrigt for Nachweis der EGFR-Mutation durch zentralen ctDNA Cobas Test=positiv
Safety Analysis Set, DCO 03APR2023



Anzahl an Patienten unter Risiko:

211	165	151	141	131	121	108	93	62	40	17	2	0	Osi + Chemo
204	186	174	161	143	122	98	81	54	40	19	4	0	Osi

Kaplan-Meier plot is presented only if the interaction term in Cox regression model with treatment, subgroup and treatment-by-subgroup interaction is statistically significant at 5% level.
root/cdar/d516/payer_germany/ar/d5169c00001_payer_germany/tlf/prod/program/ttesubae.sas gttesubaehbs 22DEC2023:09:13 kfrh585

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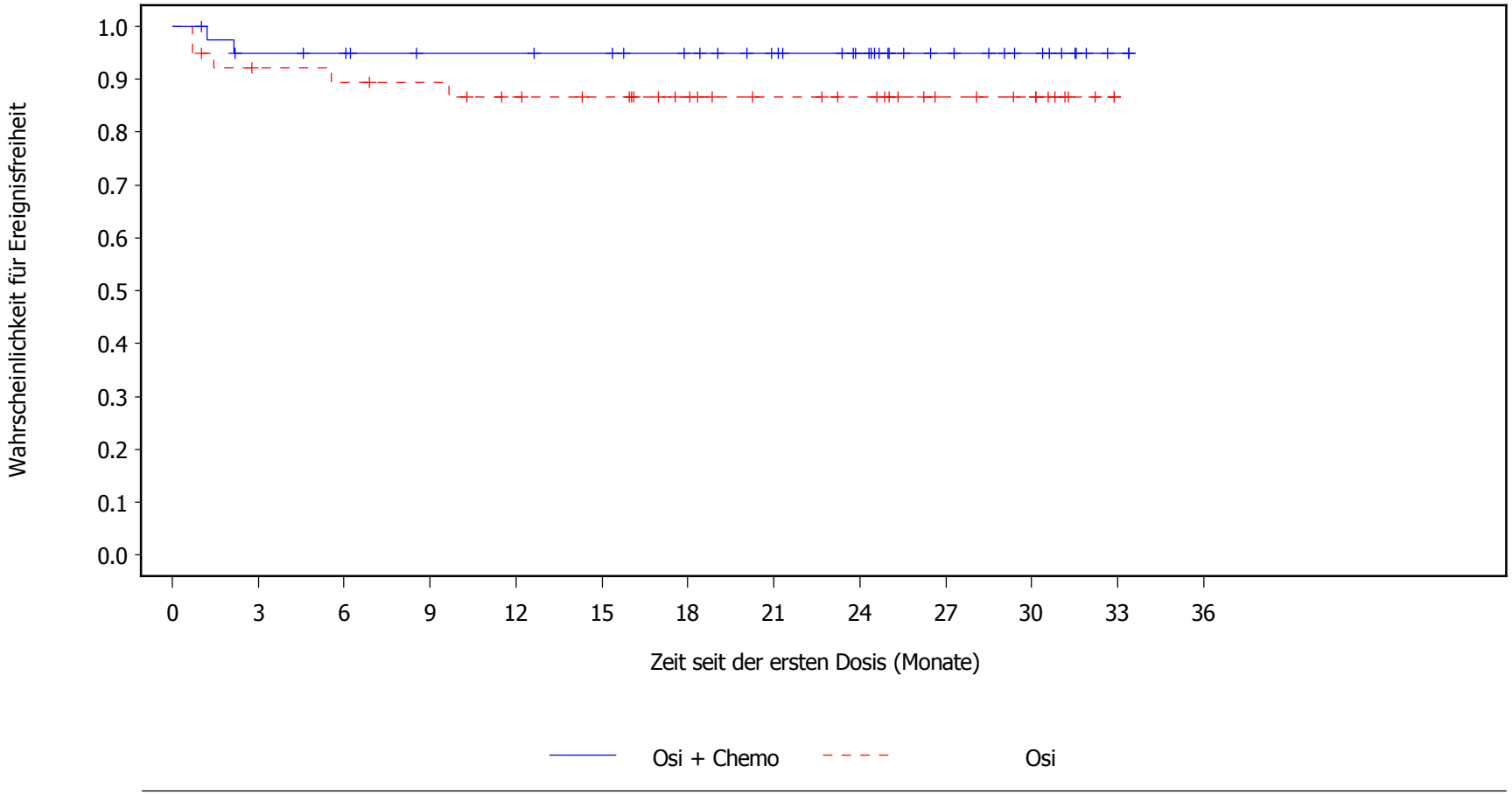
Figure 4.4.1.46 FLAURA-2 Subgroup Analysis: Kaplan-Meier plot of PT: Leukozytenzahl erniedrigt for Nachweis der EGFR-Mutation durch zentralen ctDNA Cobas Test=negativ
Safety Analysis Set, DCO 03APR2023



Anzahl an Patienten unter Risiko:

41	37	36	33	33	32	29	25	20	12	8	1	0	Osi + Chemo
39	34	33	32	29	27	22	18	16	10	8	0	0	Osi

Kaplan-Meier plot is presented only if the interaction term in Cox regression model with treatment, subgroup and treatment-by-subgroup interaction is statistically significant at 5% level.
root/cdar/d516/payer_germany/ar/d5169c00001_payer_germany/tlf/prod/program/ttesubae.sas gttesubaehbt 22DEC2023:09:13 kfrh585

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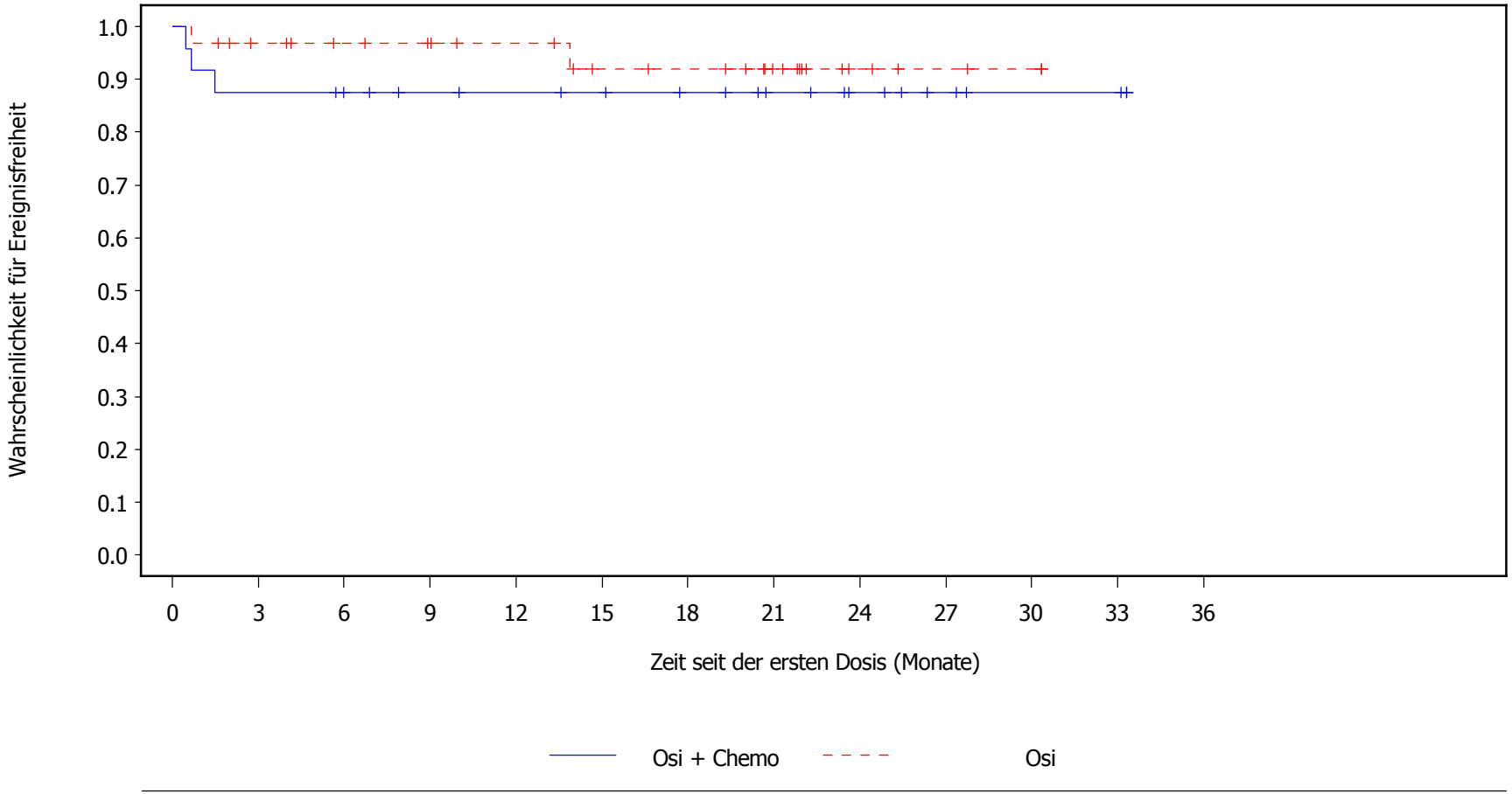
Figure 4.4.1.47 FLAURA-2 Subgroup Analysis: Kaplan-Meier plot of PT: Leukozytenzahl erniedrigt for Nachweis der EGFR-Mutation durch zentralen ctDNA Cobas Test=unbekannt
Safety Analysis Set, DCO 03APR2023



Anzahl an Patienten unter Risiko:

24	21	19	17	16	15	13	10	7	4	2	2	0	Osi + Chemo
32	28	25	23	21	17	16	11	4	2	1	0	0	Osi

Kaplan-Meier plot is presented only if the interaction term in Cox regression model with treatment, subgroup and treatment-by-subgroup interaction is statistically significant at 5% level.
root/cdar/d516/payer_germany/ar/d5169c00001_payer_germany/tlf/prod/program/ttesubae.sas gttesubaehbu 22DEC2023:09:13 kfrh585

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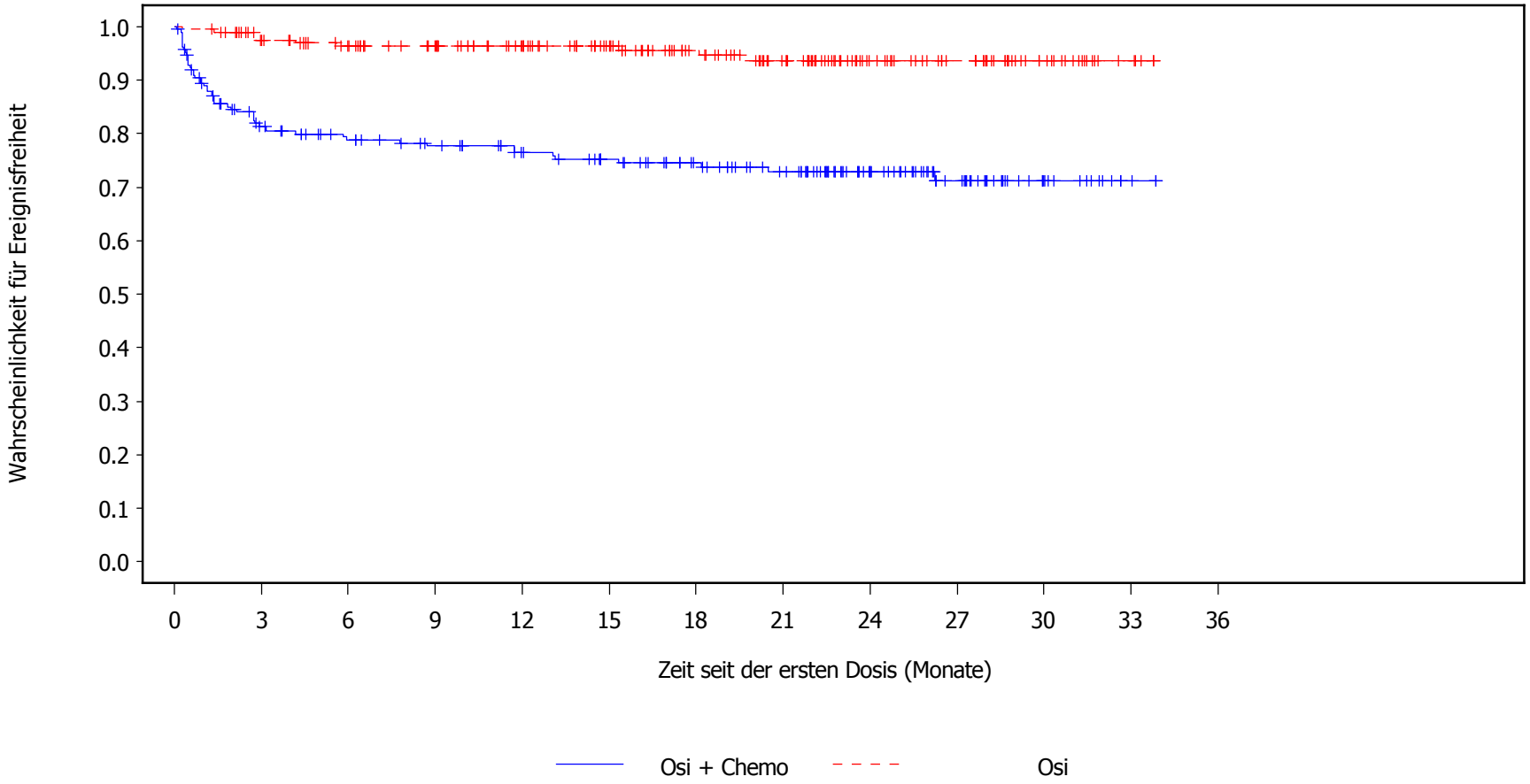
Figure 4.4.1.48 FLAURA-2 Subgroup Analysis: Kaplan-Meier plot of PT: Neutrophilenzahl erniedrigt for Nachweis der EGFR-Mutation durch zentralen ctDNA Cobas Test=positiv
Safety Analysis Set, DCO 03APR2023



Anzahl an Patienten unter Risiko:

211	158	144	135	124	114	100	87	56	34	13	2	0	Osi + Chemo
204	188	175	163	145	125	100	82	53	39	18	4	0	Osi

Kaplan-Meier plot is presented only if the interaction term in Cox regression model with treatment, subgroup and treatment-by-subgroup interaction is statistically significant at 5% level.
root/cdar/d516/payer_germany/ar/d5169c00001_payer_germany/tlf/prod/program/ttesubae.sas gttesubaehbv 22DEC2023:09:13 kfrh585

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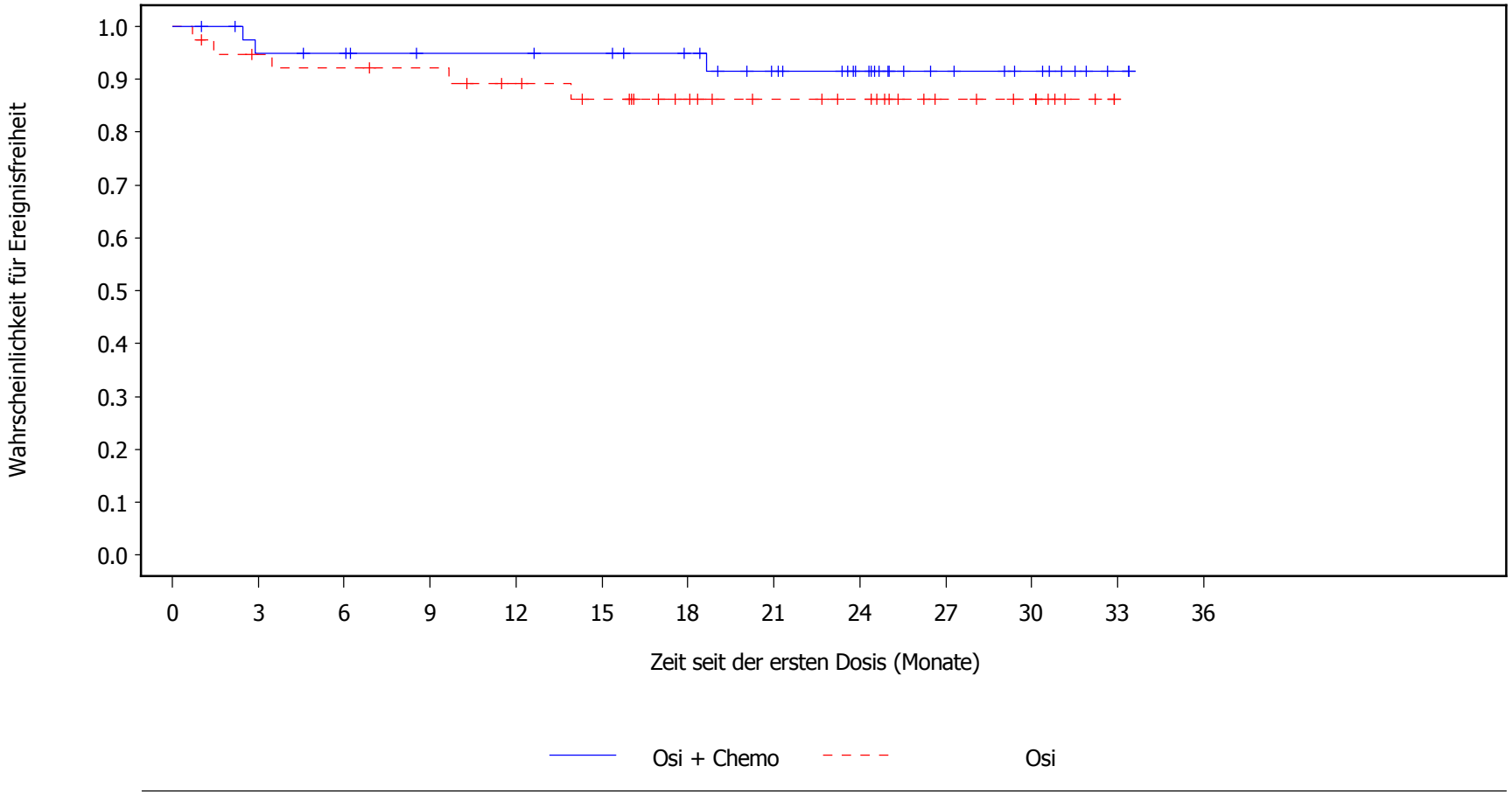
Figure 4.4.1.49 FLAURA-2 Subgroup Analysis: Kaplan-Meier plot of PT: Neutrophilenzahl erniedrigt for Nachweis der EGFR-Mutation durch zentralen ctDNA Cobas Test=negativ
Safety Analysis Set, DCO 03APR2023



Anzahl an Patienten unter Risiko:

41	37	36	33	33	32	29	24	18	10	7	1	0	Osi + Chemo
39	35	34	33	30	27	22	18	16	9	7	0	0	Osi

Kaplan-Meier plot is presented only if the interaction term in Cox regression model with treatment, subgroup and treatment-by-subgroup interaction is statistically significant at 5% level.
root/cdar/d516/payer_germany/ar/d5169c00001_payer_germany/tlf/prod/program/ttesubae.sas gttesubaehbw 22DEC2023:09:13 kfrh585

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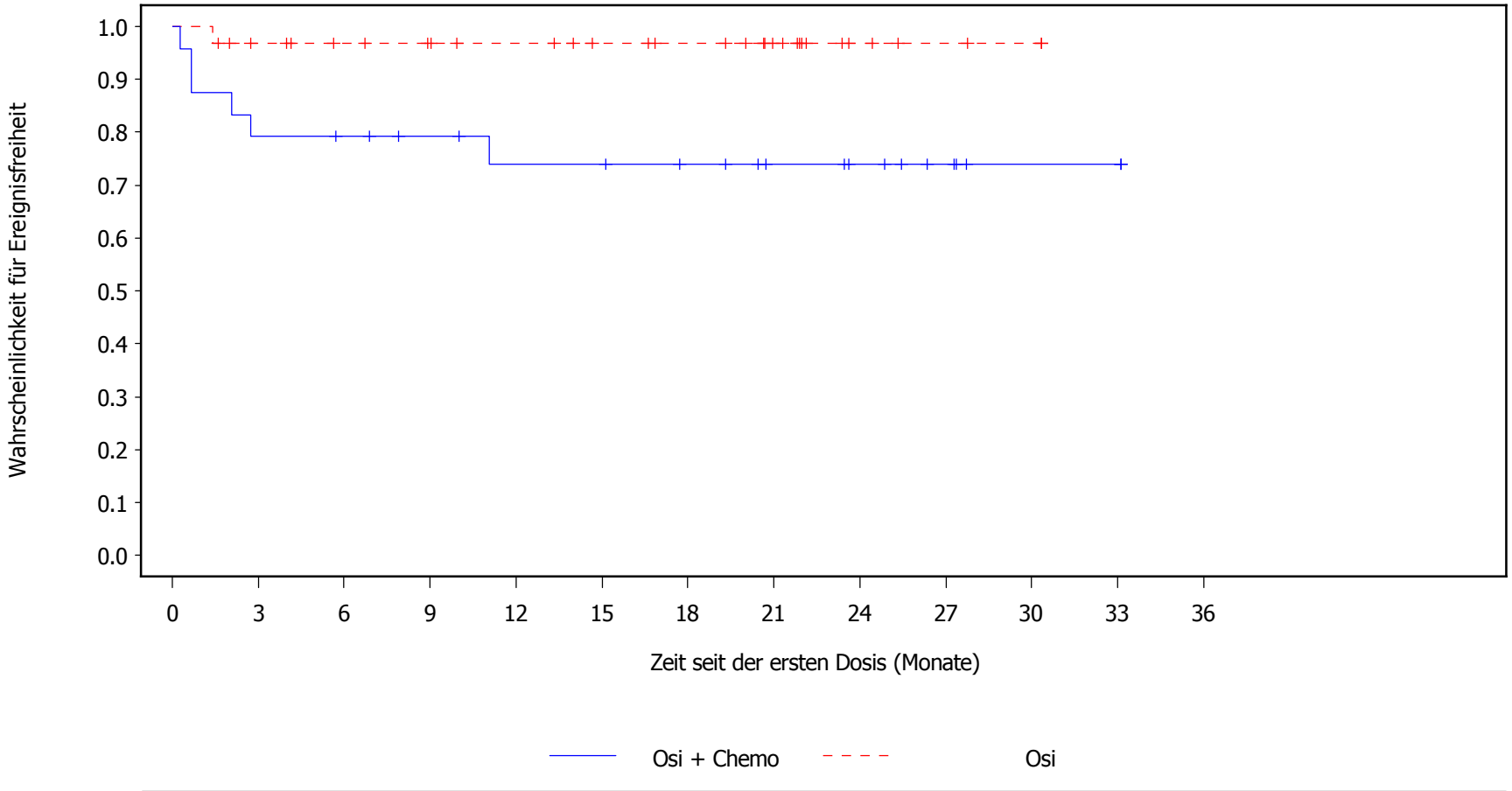
Figure 4.4.1.50 FLAURA-2 Subgroup Analysis: Kaplan-Meier plot of PT: Neutrophilenzahl erniedrigt for Nachweis der EGFR-Mutation durch zentralen ctDNA Cobas Test=unbekannt
Safety Analysis Set, DCO 03APR2023



Anzahl an Patienten unter Risiko:

24	19	18	16	14	14	12	9	7	4	1	1	0	Osi + Chemo
32	28	25	23	21	18	16	11	4	2	1	0	0	Osi

Kaplan-Meier plot is presented only if the interaction term in Cox regression model with treatment, subgroup and treatment-by-subgroup interaction is statistically significant at 5% level.
root/cdar/d516/payer_germany/ar/d5169c00001_payer_germany/tlf/prod/program/ttesubae.sas gttesubaehbx 22DEC2023:09:13 kfrh585

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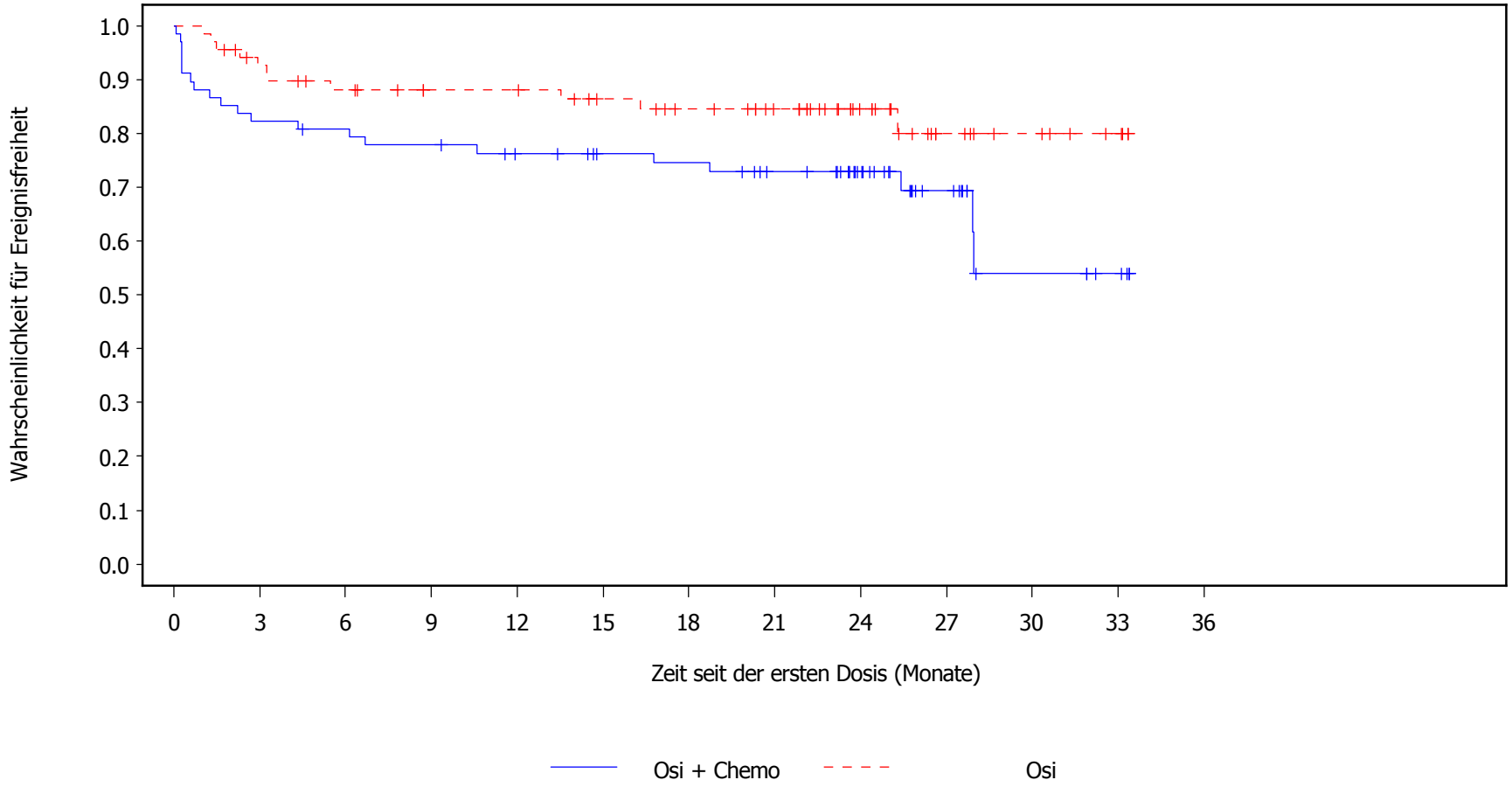
Figure 4.4.2.1 FLAURA-2 Subgroup Analysis: Kaplan-Meier plot of SUE for Abstammung=Chinesisch/Asiatisch
Safety Analysis Set, DCO 03APR2023

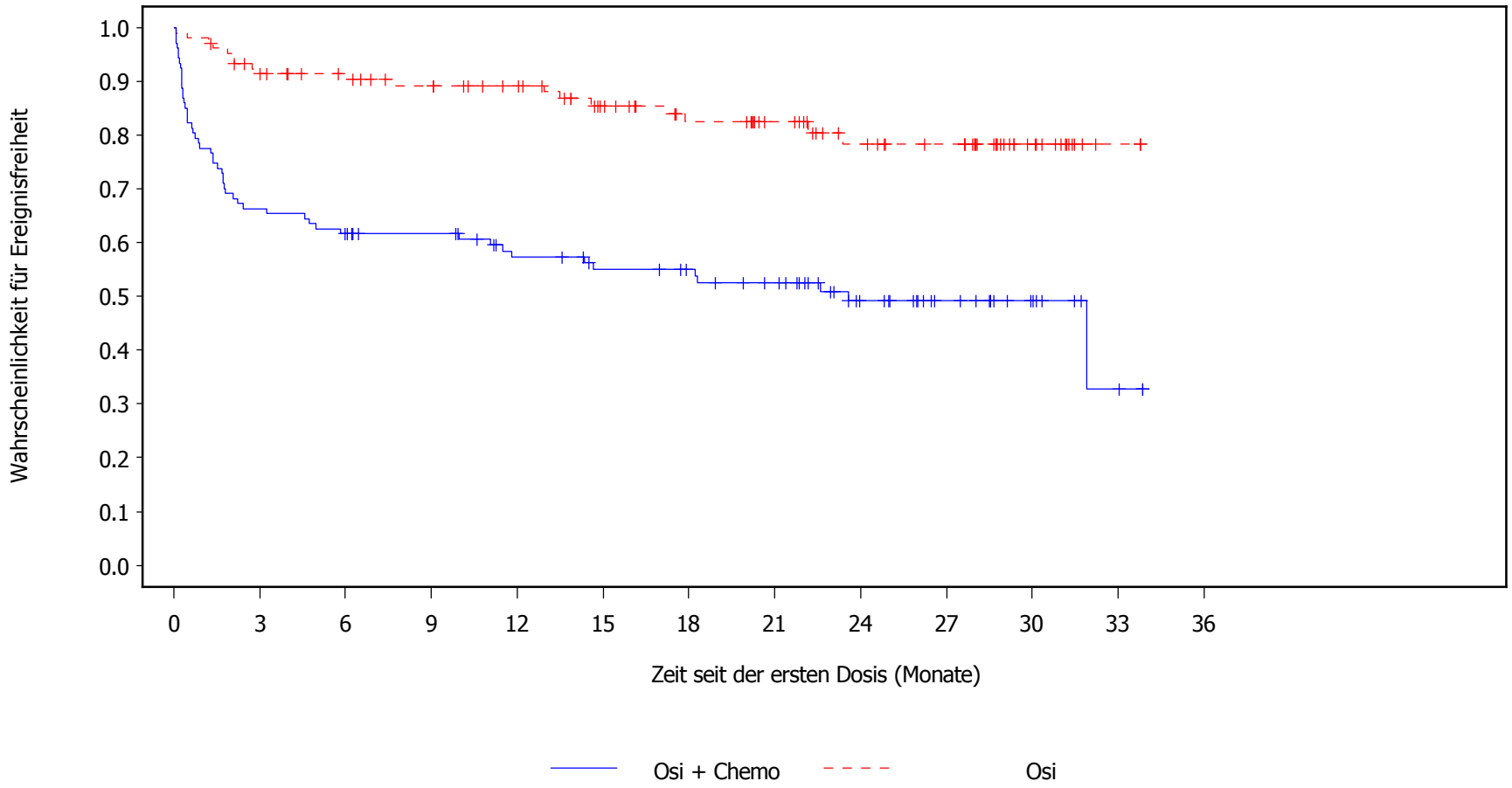


Anzahl an Patienten unter Risiko:

68	56	54	52	48	44	43	38	28	15	6	3	0	Osi + Chemo
70	62	57	52	52	47	43	37	23	11	7	3	0	Osi

Kaplan-Meier plot is presented only if the interaction term in Cox regression model with treatment, subgroup and treatment-by-subgroup interaction is statistically significant at 5% level.
root/cdar/d516/payer_germany/ar/d5169c00001_payer_germany/tlf/prod/program/ttesubae.sas gttesubaeiaa 22DEC2023:09:13 kfrh585

Figure 4.4.2.2 FLAURA-2 Subgroup Analysis: Kaplan-Meier plot of SUE for Abstammung=Nicht-chinesisch/Asiatisch
Safety Analysis Set, DCO 03APR2023

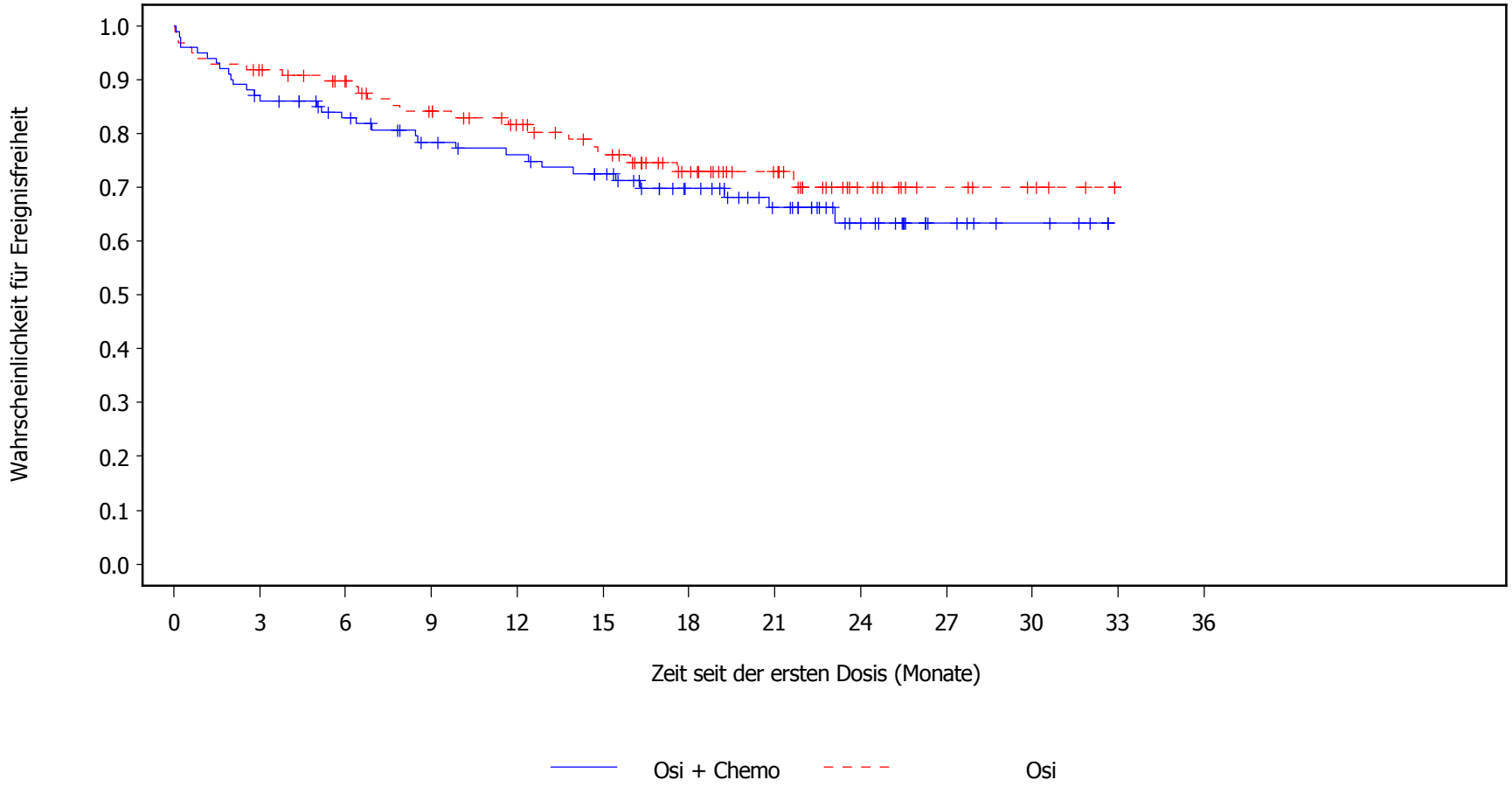


Anzahl an Patienten unter Risiko:

107	71	65	61	52	47	44	39	25	16	8	2	0	Osi + Chemo
106	94	88	82	76	63	53	46	36	31	13	1	0	Osi

Kaplan-Meier plot is presented only if the interaction term in Cox regression model with treatment, subgroup and treatment-by-subgroup interaction is statistically significant at 5% level.
root/cdar/d516/payer_germany/ar/d5169c00001_payer_germany/tlf/prod/program/ttesubae.sas gttesubaeiab 22DEC2023:09:13 kfrh585

Figure 4.4.2.3 FLAURA-2 Subgroup Analysis: Kaplan-Meier plot of SUE for Abstammung=Nicht-asiatisch
Safety Analysis Set, DCO 03APR2023



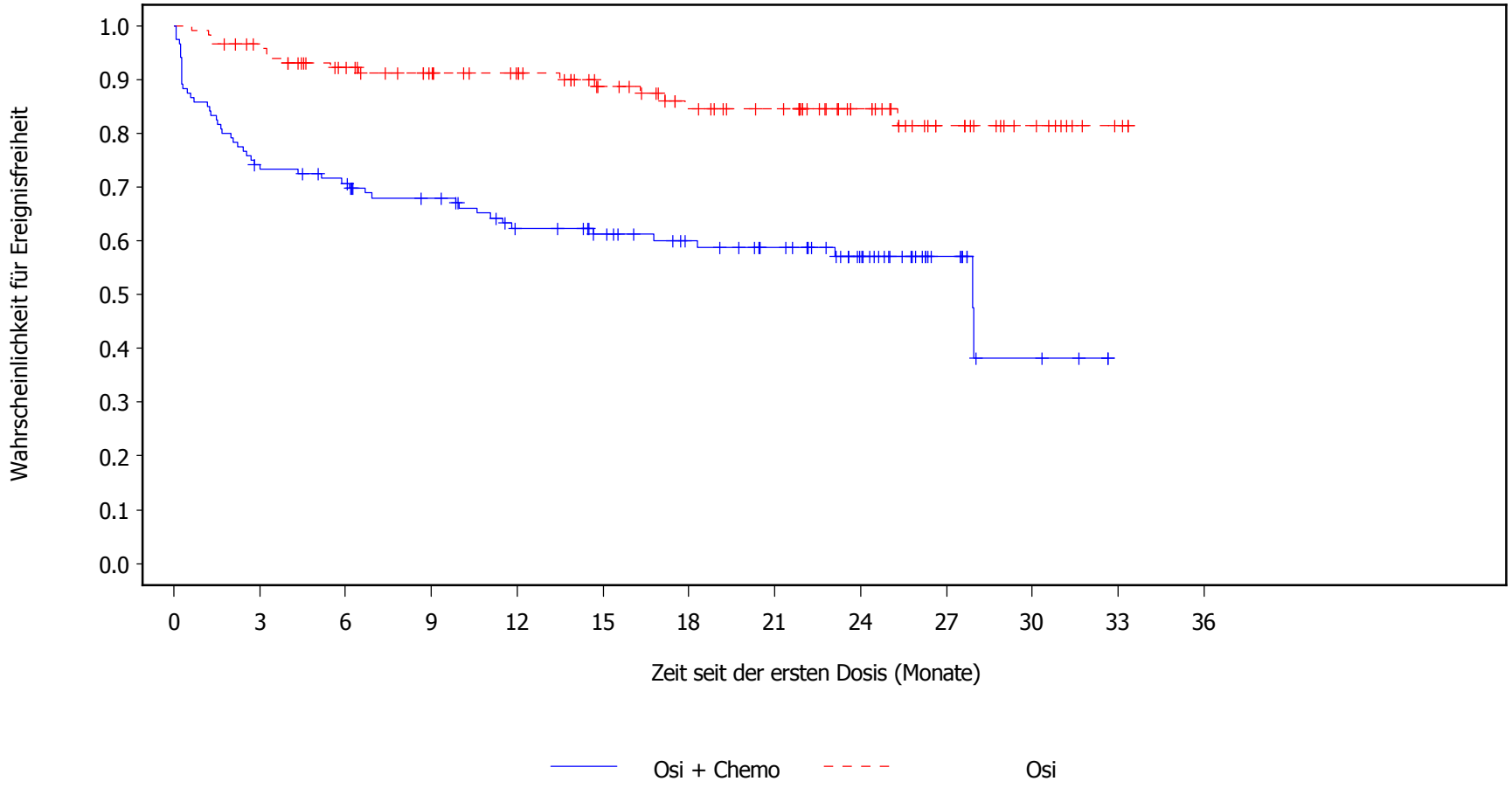
Anzahl an Patienten unter Risiko:

101	87	77	68	64	58	45	34	21	9	5	0	0	Osi + Chemo
99	89	81	72	63	54	40	29	14	7	4	0	0	Osi

Kaplan-Meier plot is presented only if the interaction term in Cox regression model with treatment, subgroup and treatment-by-subgroup interaction is statistically significant at 5% level.

root/cdar/d516/payer_germany/ar/d5169c00001_payer_germany/tlf/prod/program/ttesubae.sas gttesubaeiac 22DEC2023:09:13 kfrh585

Figure 4.4.2.4 FLAURA-2 Subgroup Analysis: Kaplan-Meier plot of SUE for Methode zur Gewebeuntersuchung=zentral
Safety Analysis Set, DCO 03APR2023



Anzahl an Patienten unter Risiko:

120	88	82	74	62	56	48	42	28	11	3	0	0	Osi + Chemo
119	110	98	88	81	68	57	51	33	18	10	2	0	Osi

Kaplan-Meier plot is presented only if the interaction term in Cox regression model with treatment, subgroup and treatment-by-subgroup interaction is statistically significant at 5% level.

root/cdar/d516/payer_germany/ar/d5169c00001_payer_germany/tlf/prod/program/ttesubae.sas gttesubaeiad 22DEC2023:09:13 kfrh585

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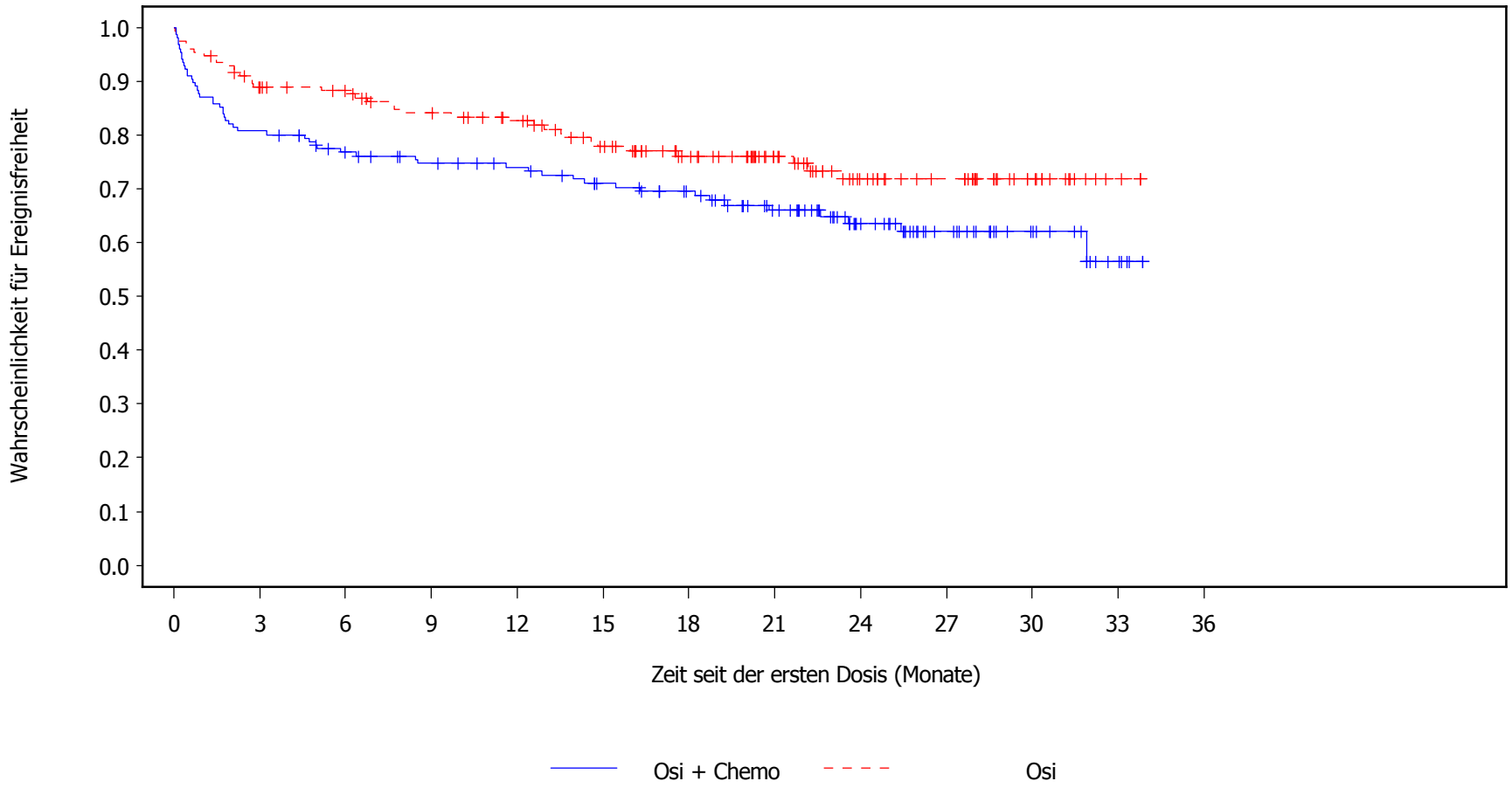
Figure 4.4.2.5 FLAURA-2 Subgroup Analysis: Kaplan-Meier plot of SUE for Methode zur Gewebeuntersuchung=lokal
Safety Analysis Set, DCO 03APR2023

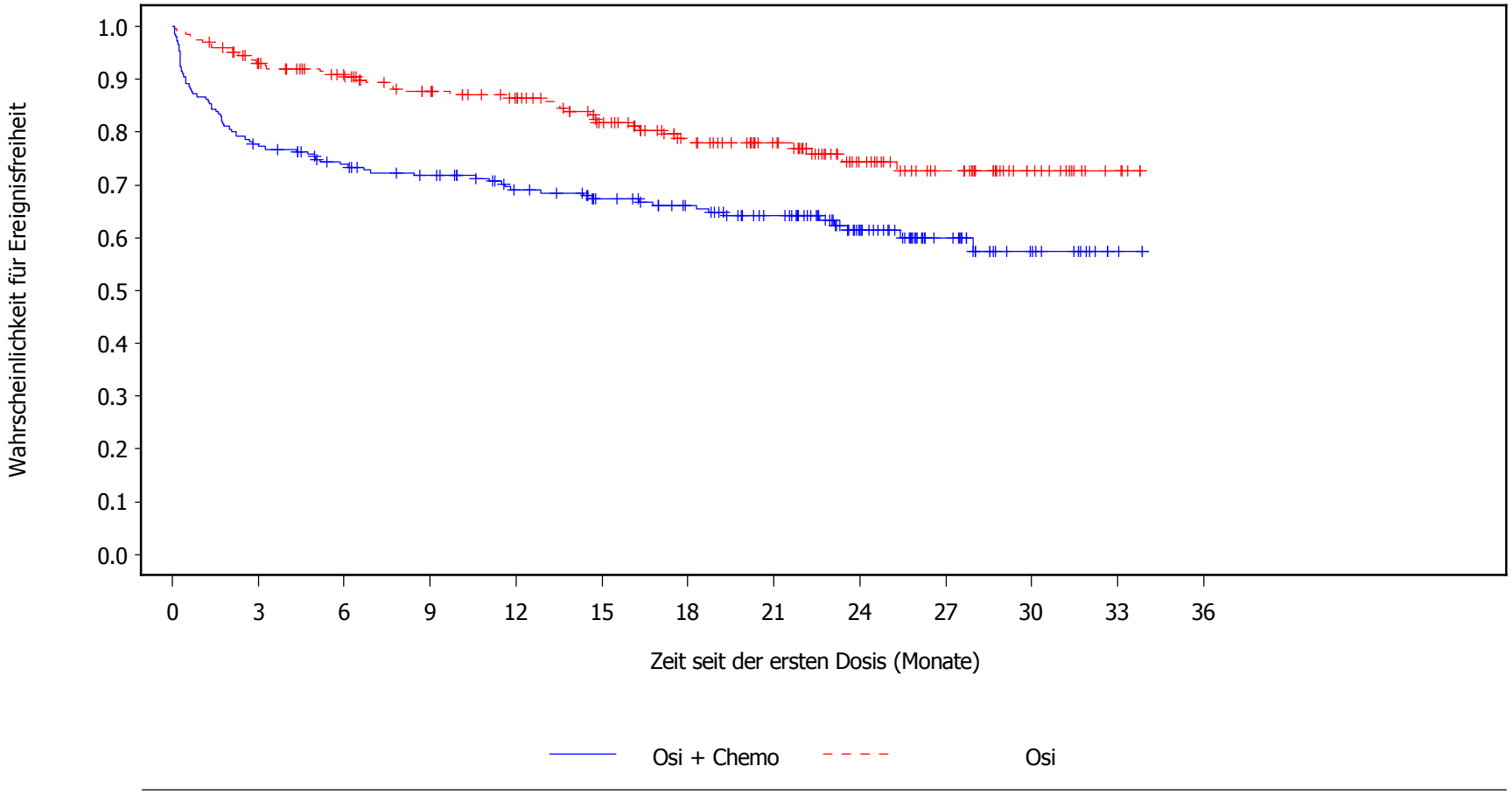


Anzahl an Patienten unter Risiko:

156	126	114	107	102	93	84	69	46	29	16	5	0	Osi + Chemo
156	135	128	118	110	96	79	61	40	31	14	2	0	Osi

Kaplan-Meier plot is presented only if the interaction term in Cox regression model with treatment, subgroup and treatment-by-subgroup interaction is statistically significant at 5% level.
root/cdar/d516/payer_germany/ar/d5169c00001_payer_germany/tlf/prod/program/ttesubae.sas gttesubaeiae 22DEC2023:09:13 kfrh585

Figure 4.4.2.6 FLAURA-2 Subgroup Analysis: Kaplan-Meier plot of SUE for Nachweis der EGFR-Mutation durch zentralen ctDNA Cobas Test=positiv
Safety Analysis Set, DCO 03APR2023

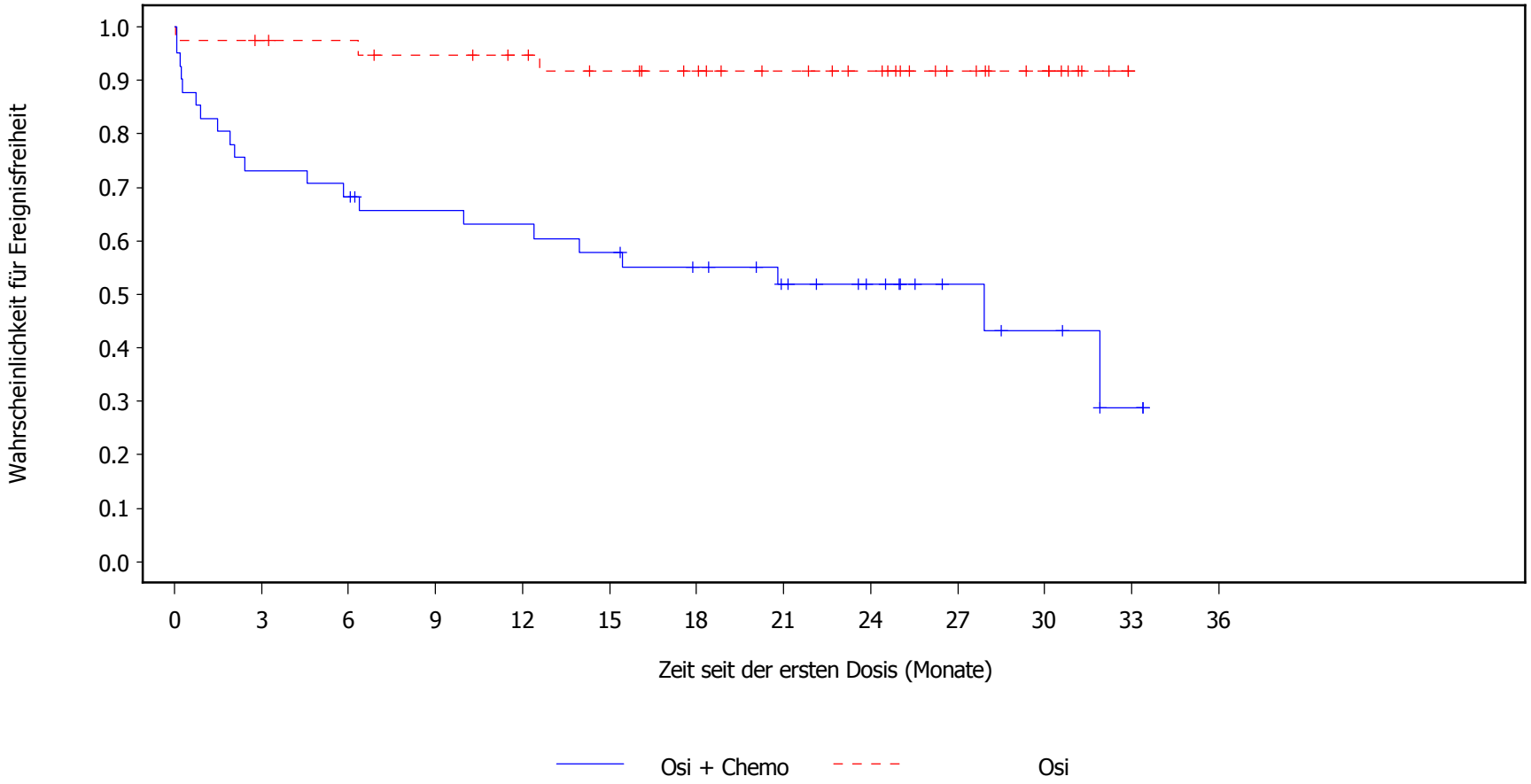


Anzahl an Patienten unter Risiko:

211	163	148	139	124	112	100	86	56	30	13	2	0	Osi + Chemo
204	183	168	152	140	118	94	79	50	35	15	4	0	Osi

Kaplan-Meier plot is presented only if the interaction term in Cox regression model with treatment, subgroup and treatment-by-subgroup interaction is statistically significant at 5% level.
root/cdar/d516/payer_germany/ar/d5169c00001_payer_germany/tlf/prod/program/ttesubae.sas gttesubaeiaf 22DEC2023:09:13 kfrh585

Figure 4.4.2.7 FLAURA-2 Subgroup Analysis: Kaplan-Meier plot of SUE for Nachweis der EGFR-Mutation durch zentralen ctDNA Cobas Test=negativ
Safety Analysis Set, DCO 03APR2023



Anzahl an Patienten unter Risiko:

41	30	28	25	24	22	19	15	11	6	4	1	0	Osi + Chemo
39	37	36	34	32	29	26	22	19	12	8	0	0	Osi

Kaplan-Meier plot is presented only if the interaction term in Cox regression model with treatment, subgroup and treatment-by-subgroup interaction is statistically significant at 5% level.
root/cdar/d516/payer_germany/ar/d5169c00001_payer_germany/tlf/prod/program/ttesubae.sas gttesubaeiag 22DEC2023:09:13 kfrh585

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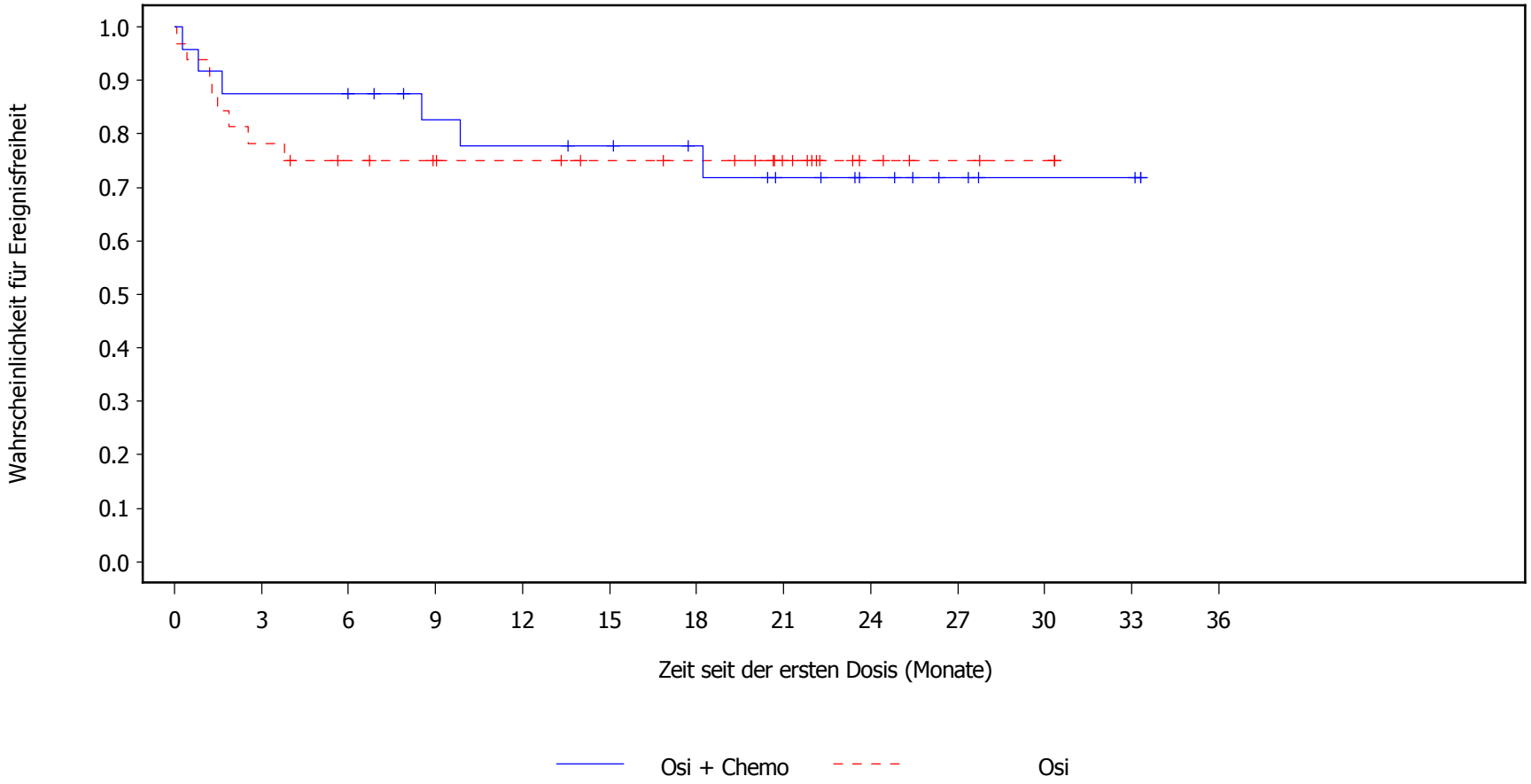
Figure 4.4.2.8 FLAURA-2 Subgroup Analysis: Kaplan-Meier plot of SUE for Nachweis der EGFR-Mutation durch zentralen ctDNA Cobas Test=unbekannt
Safety Analysis Set, DCO 03APR2023



Anzahl an Patienten unter Risiko:

24	21	20	17	16	15	13	10	7	4	2	2	0	Osi + Chemo
32	25	22	20	19	17	16	11	4	2	1	0	0	Osi

Kaplan-Meier plot is presented only if the interaction term in Cox regression model with treatment, subgroup and treatment-by-subgroup interaction is statistically significant at 5% level.
root/cdar/d516/payer_germany/ar/d5169c00001_payer_germany/tlf/prod/program/ttesubae.sas gttesubaeiah 22DEC2023:09:13 kfrh585

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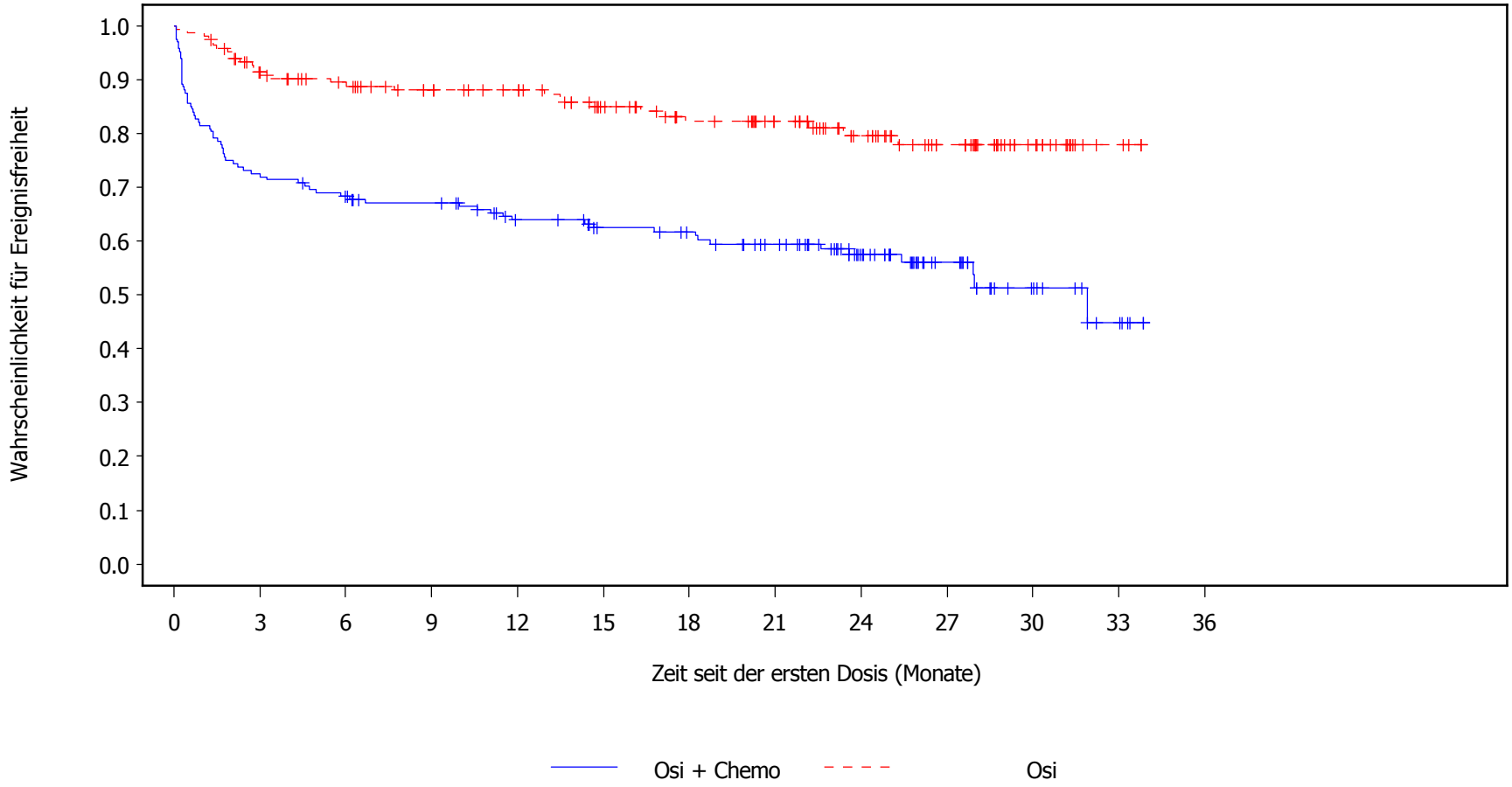
Figure 4.4.2.9 FLAURA-2 Subgroup Analysis: Kaplan-Meier plot of SUE for Region gPAP=Asien
Safety Analysis Set, DCO 03APR2023



Anzahl an Patienten unter Risiko:

168	122	113	107	94	86	82	73	51	29	13	5	0	Osi + Chemo
166	145	134	123	117	101	87	77	56	39	17	3	0	Osi

Kaplan-Meier plot is presented only if the interaction term in Cox regression model with treatment, subgroup and treatment-by-subgroup interaction is statistically significant at 5% level.
root/cdar/d516/payer_germany/ar/d5169c00001_payer_germany/tlf/prod/program/ttesubae.sas gttesubaeiai 22DEC2023:09:13 kfrh585

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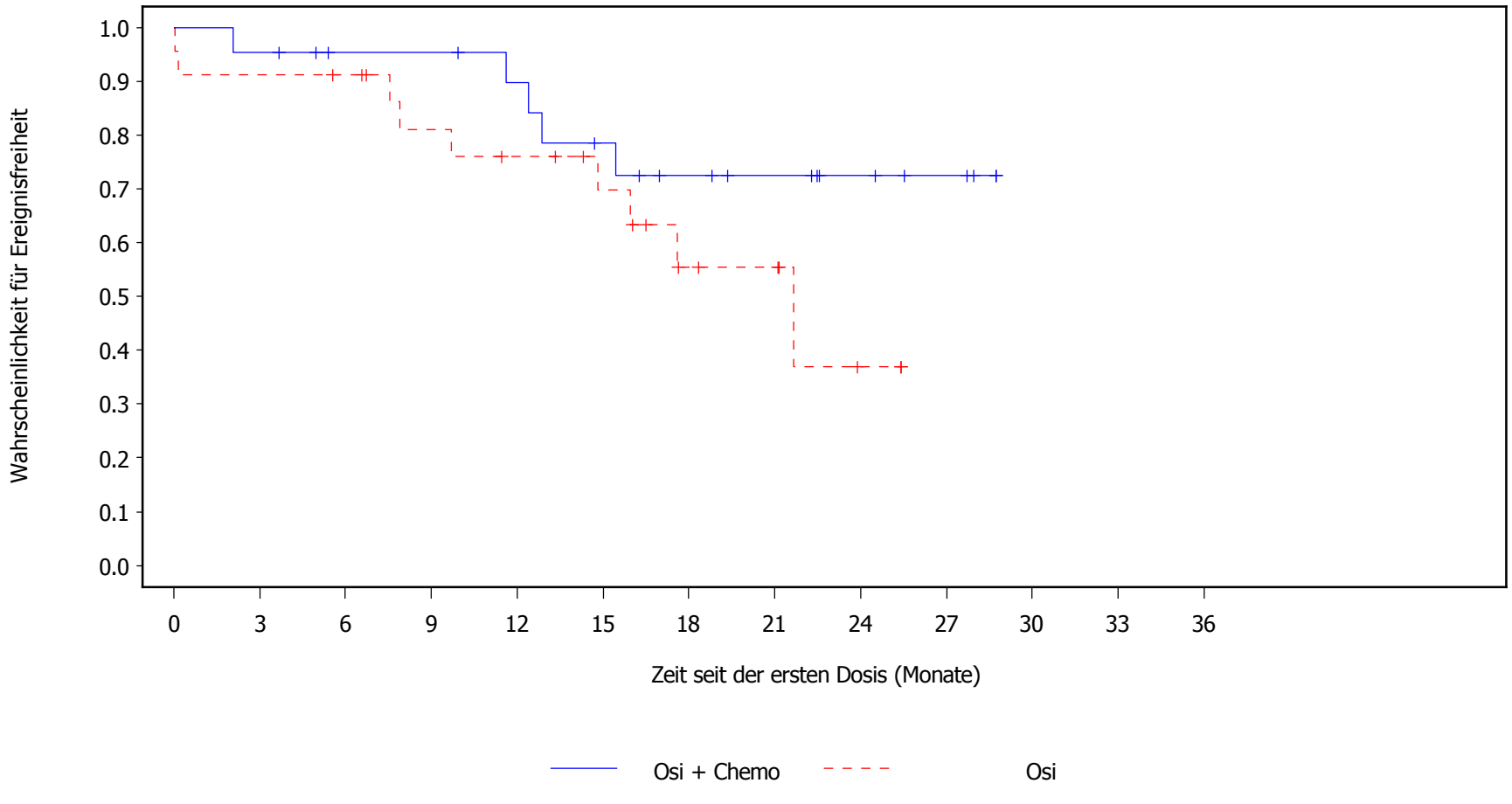
Figure 4.4.2.10 FLAURA-2 Subgroup Analysis: Kaplan-Meier plot of SUE for Region gPAP=Europa
Safety Analysis Set, DCO 03APR2023



Anzahl an Patienten unter Risiko:

22	21	18	18	16	13	10	8	5	3	0	0	0	Osi + Chemo
23	21	20	16	14	11	6	5	1	0	0	0	0	Osi

Kaplan-Meier plot is presented only if the interaction term in Cox regression model with treatment, subgroup and treatment-by-subgroup interaction is statistically significant at 5% level.

root/cdar/d516/payer_germany/ar/d5169c00001_payer_germany/tlf/prod/program/ttesubae.sas gttesubaeiaj 22DEC2023:09:13 kfrh585

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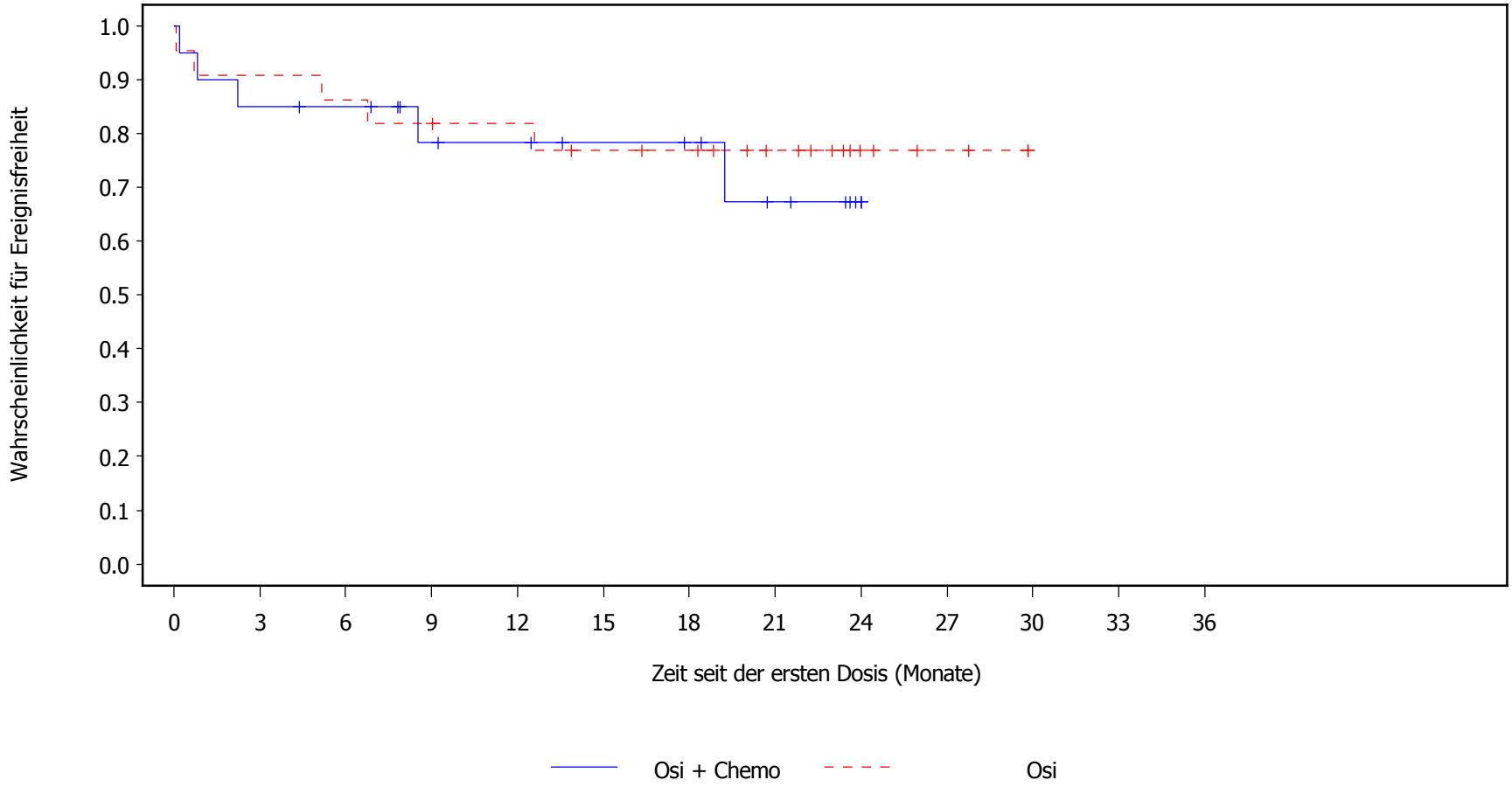
Figure 4.4.2.11 FLAURA-2 Subgroup Analysis: Kaplan-Meier plot of SUE for Region gPAP=Nordamerika
Safety Analysis Set, DCO 03APR2023



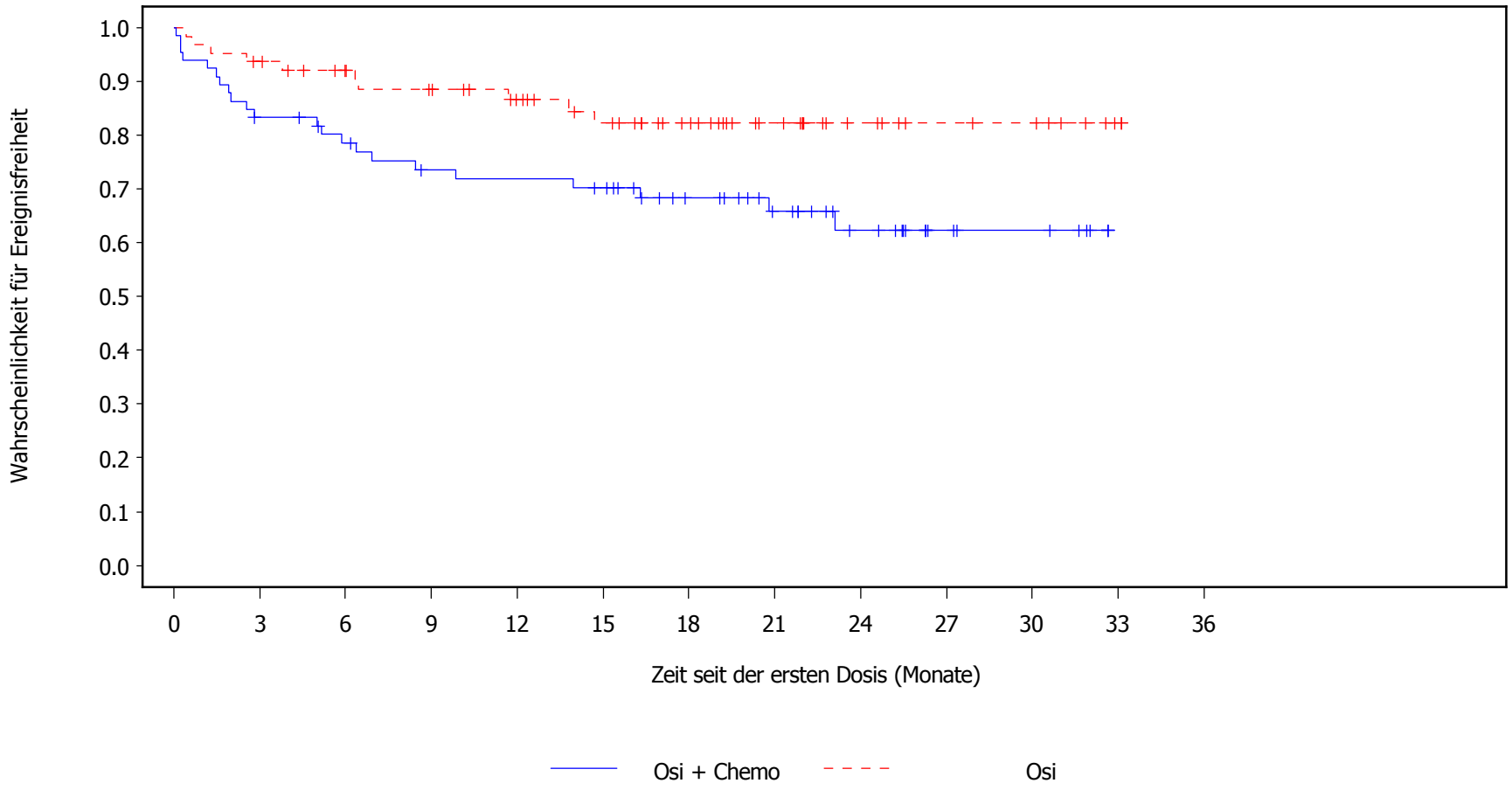
Anzahl an Patienten unter Risiko:

20	17	16	12	11	9	8	5	1	0	0	0	0	Osi + Chemo
22	20	19	18	17	15	14	10	4	2	0	0	0	Osi

Kaplan-Meier plot is presented only if the interaction term in Cox regression model with treatment, subgroup and treatment-by-subgroup interaction is statistically significant at 5% level.

root/cdar/d516/payer_germany/ar/d5169c00001_payer_germany/tlf/prod/program/ttesubae.sas gttesubaeiak 22DEC2023:09:13 kfrh585

Figure 4.4.2.12 FLAURA-2 Subgroup Analysis: Kaplan-Meier plot of SUE for Region gPAP=Rest der Welt
Safety Analysis Set, DCO 03APR2023



Anzahl an Patienten unter Risiko:

66	54	49	44	43	41	32	25	17	8	6	0	0	Osi + Chemo
64	59	53	49	43	37	29	20	12	8	7	1	0	Osi

Kaplan-Meier plot is presented only if the interaction term in Cox regression model with treatment, subgroup and treatment-by-subgroup interaction is statistically significant at 5% level.

root/cdar/d516/payer_germany/ar/d5169c00001_payer_germany/tlf/prod/program/ttesubae.sas gttesubaeial 22DEC2023:09:13 kfrh585

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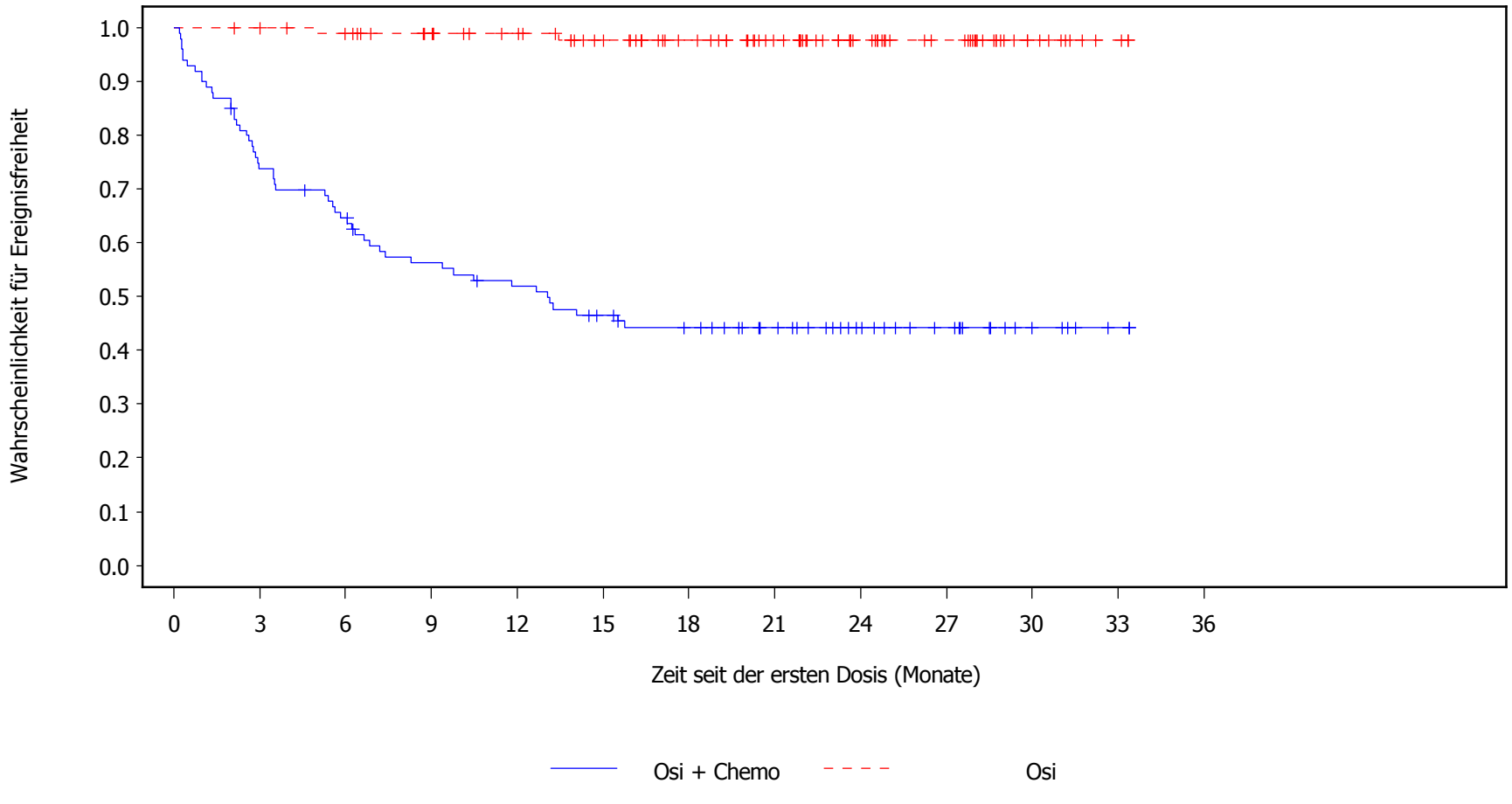
Figure 4.4.3.1 FLAURA-2 Subgroup Analysis: Kaplan-Meier plot of Therapieabbruch aufgrund von UE for WHO Performance-Status=0
Safety Analysis Set, DCO 03APR2023



Anzahl an Patienten unter Risiko:

100	73	63	53	48	41	36	29	20	14	5	1	0	Osi + Chemo
100	99	95	89	83	74	63	51	35	25	9	2	0	Osi

Kaplan-Meier plot is presented only if the interaction term in Cox regression model with treatment, subgroup and treatment-by-subgroup interaction is statistically significant at 5% level.

root/cdar/d516/payer_germany/ar/d5169c00001_payer_germany/tlf/prod/program/ttesubae.sas gttesubaejaa 22DEC2023:09:13 kfrh585

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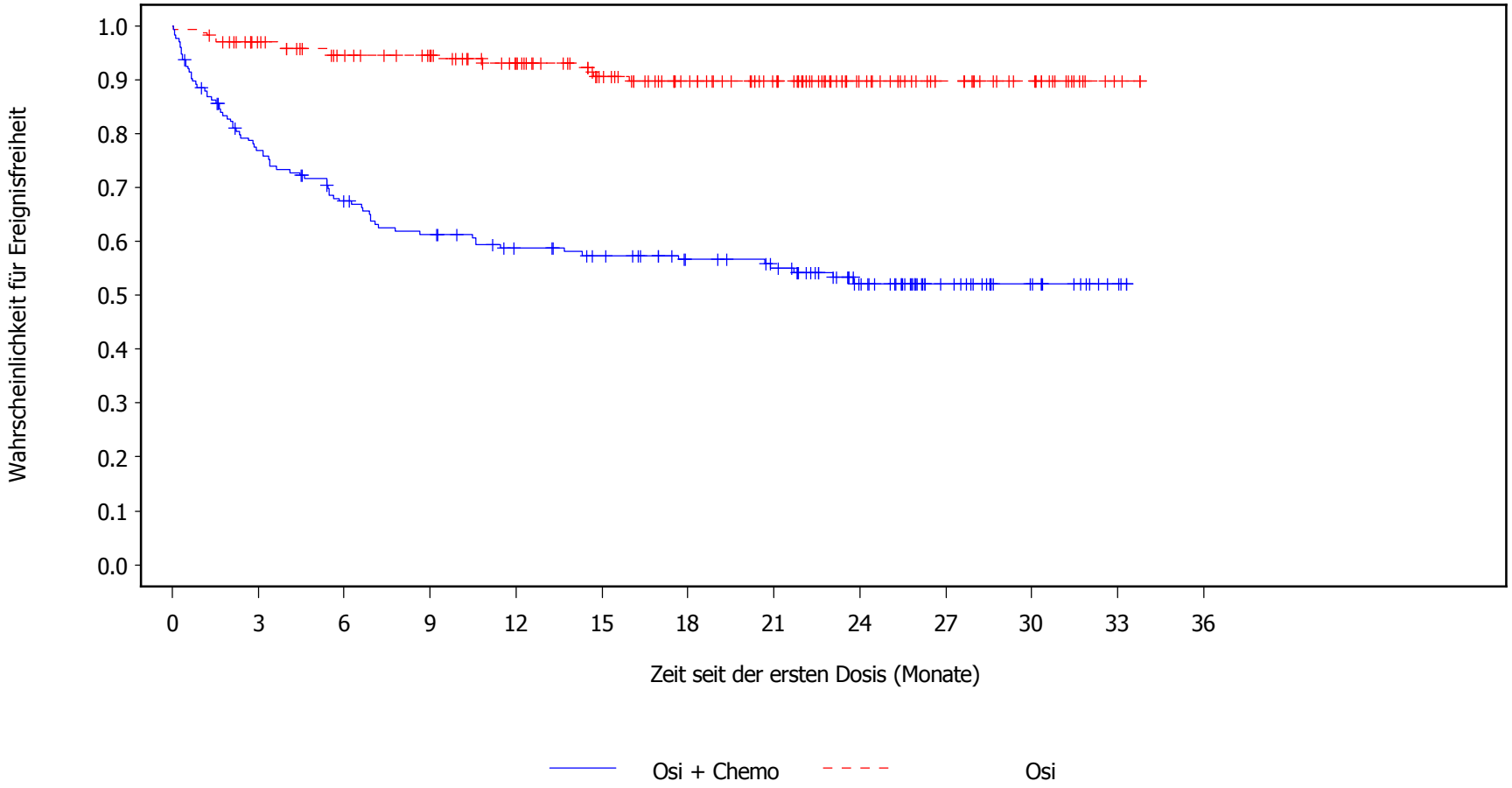
Figure 4.4.3.2 FLAURA-2 Subgroup Analysis: Kaplan-Meier plot of Therapieabbruch aufgrund von UE for WHO Performance-Status=1
Safety Analysis Set, DCO 03APR2023



Anzahl an Patienten unter Risiko:

176	131	111	100	90	84	74	68	47	24	13	3	0	Osi + Chemo
175	160	146	139	123	104	86	71	45	30	19	2	0	Osi

Kaplan-Meier plot is presented only if the interaction term in Cox regression model with treatment, subgroup and treatment-by-subgroup interaction is statistically significant at 5% level.

root/cdar/d516/payer_germany/ar/d5169c00001_payer_germany/tlf/prod/program/ttesubae.sas gttesubaejab 22DEC2023:09:13 kfrh585

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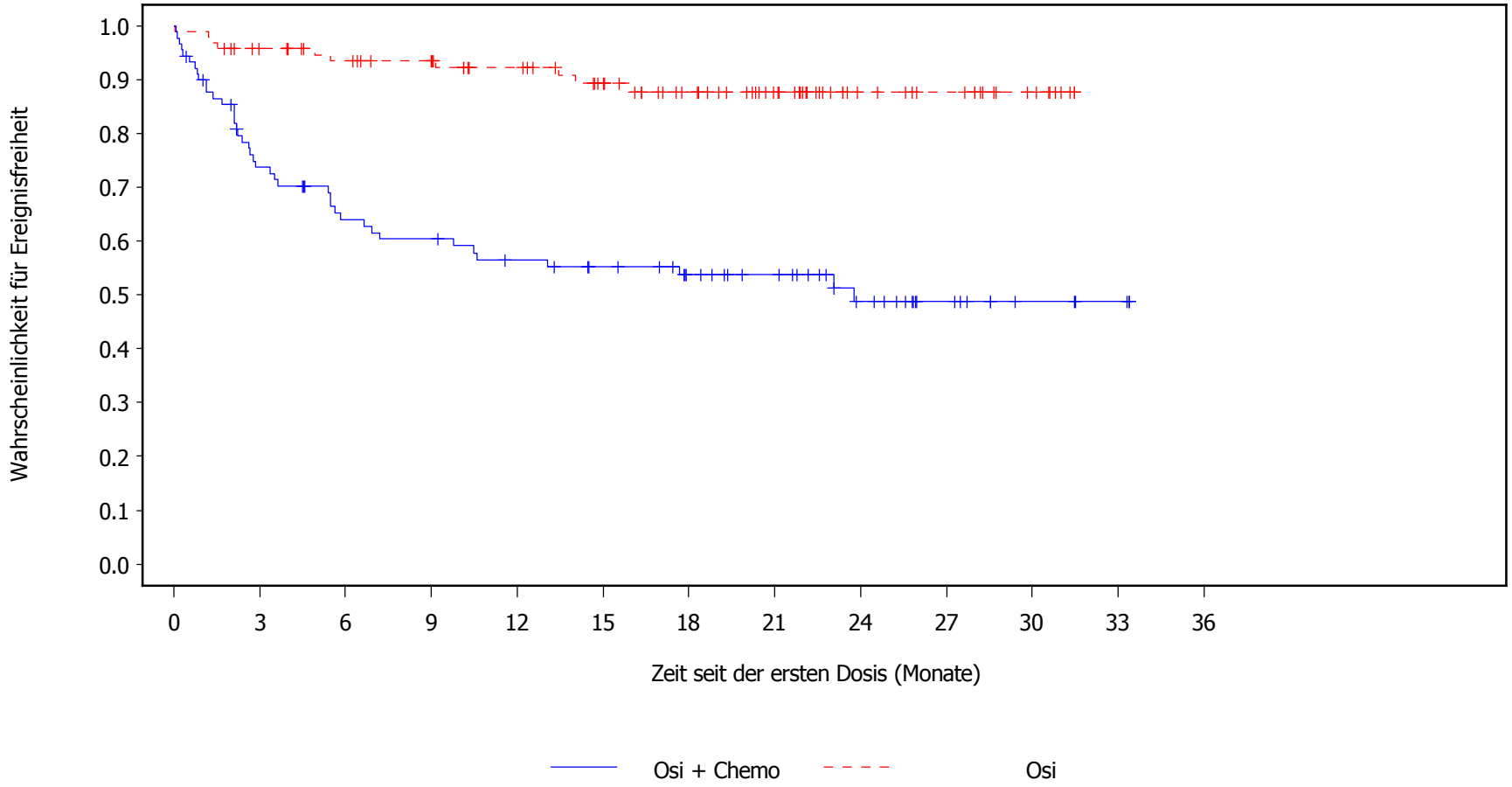
Figure 4.4.3.3 FLAURA-2 Subgroup Analysis: Kaplan-Meier plot of Therapieabbruch aufgrund von UE for Raucherstatus=Ja
Safety Analysis Set, DCO 03APR2023



Anzahl an Patienten unter Risiko:

90	63	52	49	44	40	33	28	18	10	4	2	0	Osi + Chemo
96	87	80	76	68	59	48	36	19	15	7	0	0	Osi

Kaplan-Meier plot is presented only if the interaction term in Cox regression model with treatment, subgroup and treatment-by-subgroup interaction is statistically significant at 5% level.
root/cdar/d516/payer_germany/ar/d5169c00001_payer_germany/tlf/prod/program/ttesubae.sas gttesubaejac 22DEC2023:09:13 kfrh585

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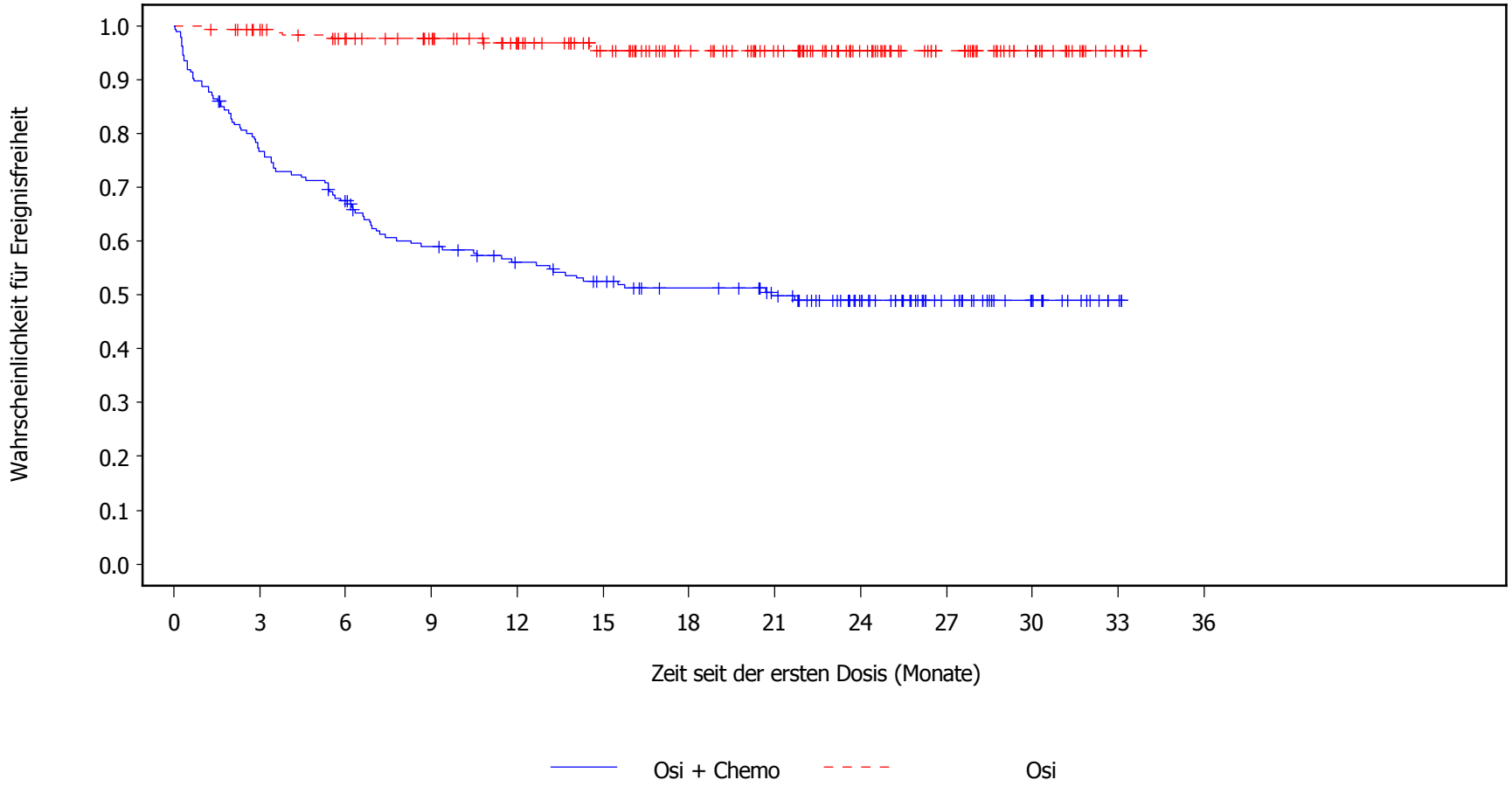
Figure 4.4.3.4 FLAURA-2 Subgroup Analysis: Kaplan-Meier plot of Therapieabbruch aufgrund von UE for Raucherstatus=Nein
Safety Analysis Set, DCO 03APR2023



Anzahl an Patienten unter Risiko:

186	141	122	104	94	85	77	69	49	28	14	2	0	Osi + Chemo
179	172	161	152	138	119	101	86	61	40	21	4	0	Osi

Kaplan-Meier plot is presented only if the interaction term in Cox regression model with treatment, subgroup and treatment-by-subgroup interaction is statistically significant at 5% level.

root/cdar/d516/payer_germany/ar/d5169c00001_payer_germany/tlf/prod/program/ttesubae.sas gttesubaejad 22DEC2023:09:13 kfrh585

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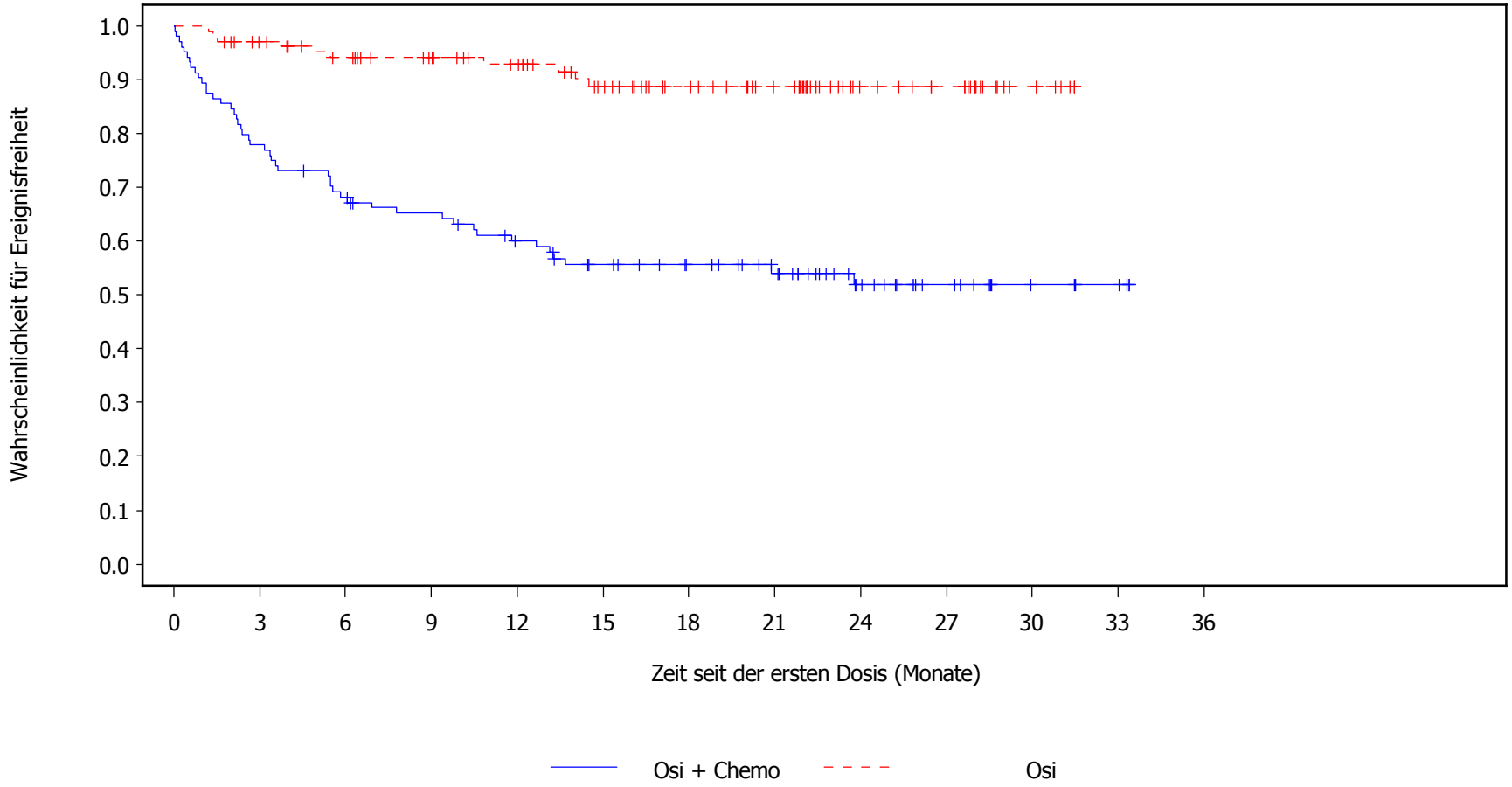
Figure 4.4.3.5 FLAURA-2 Subgroup Analysis: Kaplan-Meier plot of Therapieabbruch aufgrund von UE for Geschlecht=Maennlich
Safety Analysis Set, DCO 03APR2023

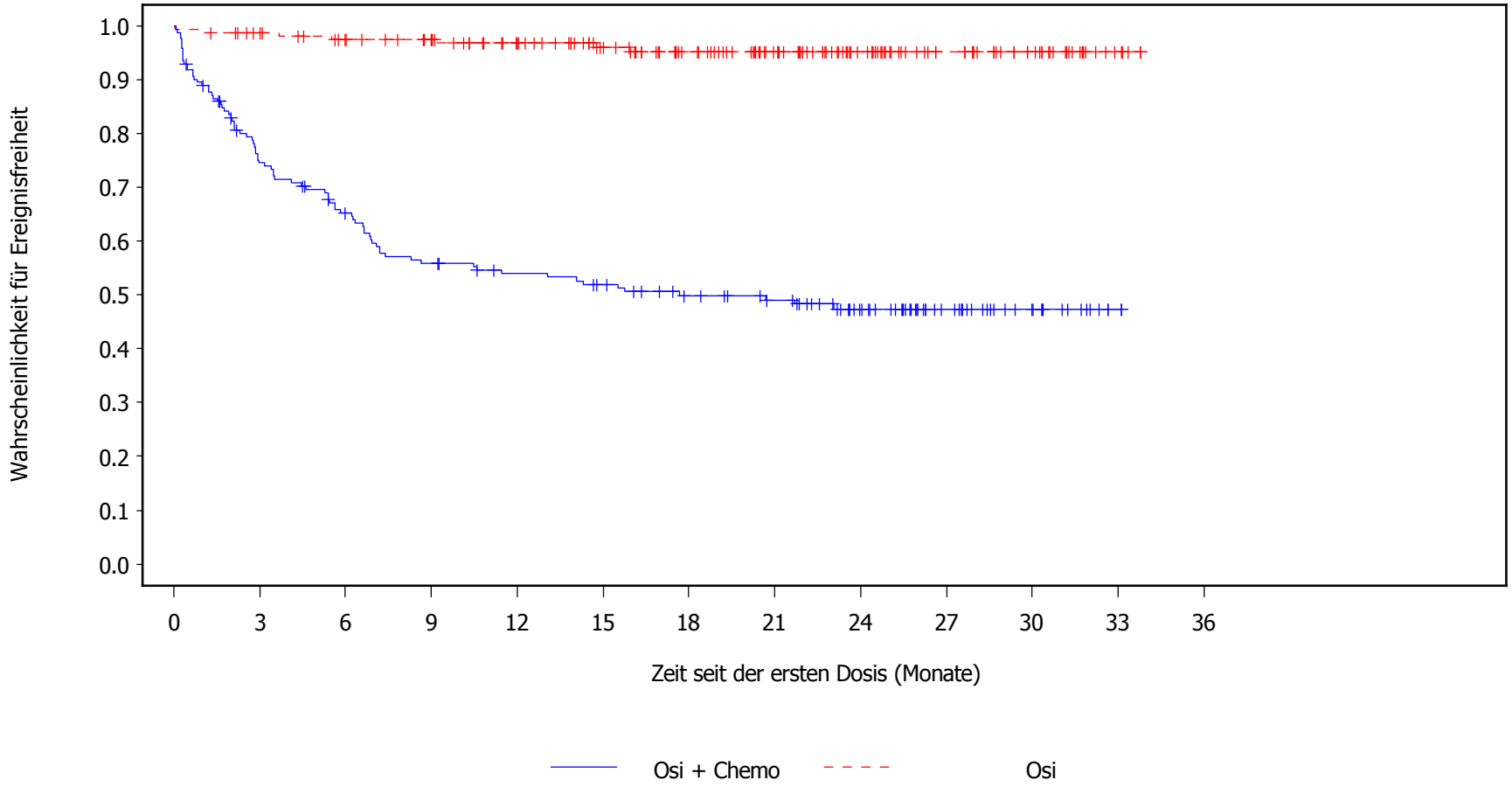


Anzahl an Patienten unter Risiko:

104	81	70	64	56	48	42	35	21	12	5	3	0	Osi + Chemo
107	98	89	82	74	62	51	42	24	19	6	0	0	Osi

Kaplan-Meier plot is presented only if the interaction term in Cox regression model with treatment, subgroup and treatment-by-subgroup interaction is statistically significant at 5% level.
root/cdar/d516/payer_germany/ar/d5169c00001_payer_germany/tlf/prod/program/ttesubae.sas gttesubaejae 22DEC2023:09:13 kfrh585

Figure 4.4.3.6 FLAURA-2 Subgroup Analysis: Kaplan-Meier plot of Therapieabbruch aufgrund von UE for Geschlecht=Weiblich
Safety Analysis Set, DCO 03APR2023



Anzahl an Patienten unter Risiko:

172	123	104	89	82	77	68	62	46	26	13	1	0	Osi + Chemo
168	161	152	146	132	116	98	80	56	36	22	4	0	Osi

Kaplan-Meier plot is presented only if the interaction term in Cox regression model with treatment, subgroup and treatment-by-subgroup interaction is statistically significant at 5% level.

root/cdar/d516/payer_germany/ar/d5169c00001_payer_germany/tlf/prod/program/ttesubae.sas gttesubaejaf 22DEC2023:09:13 kfrh585

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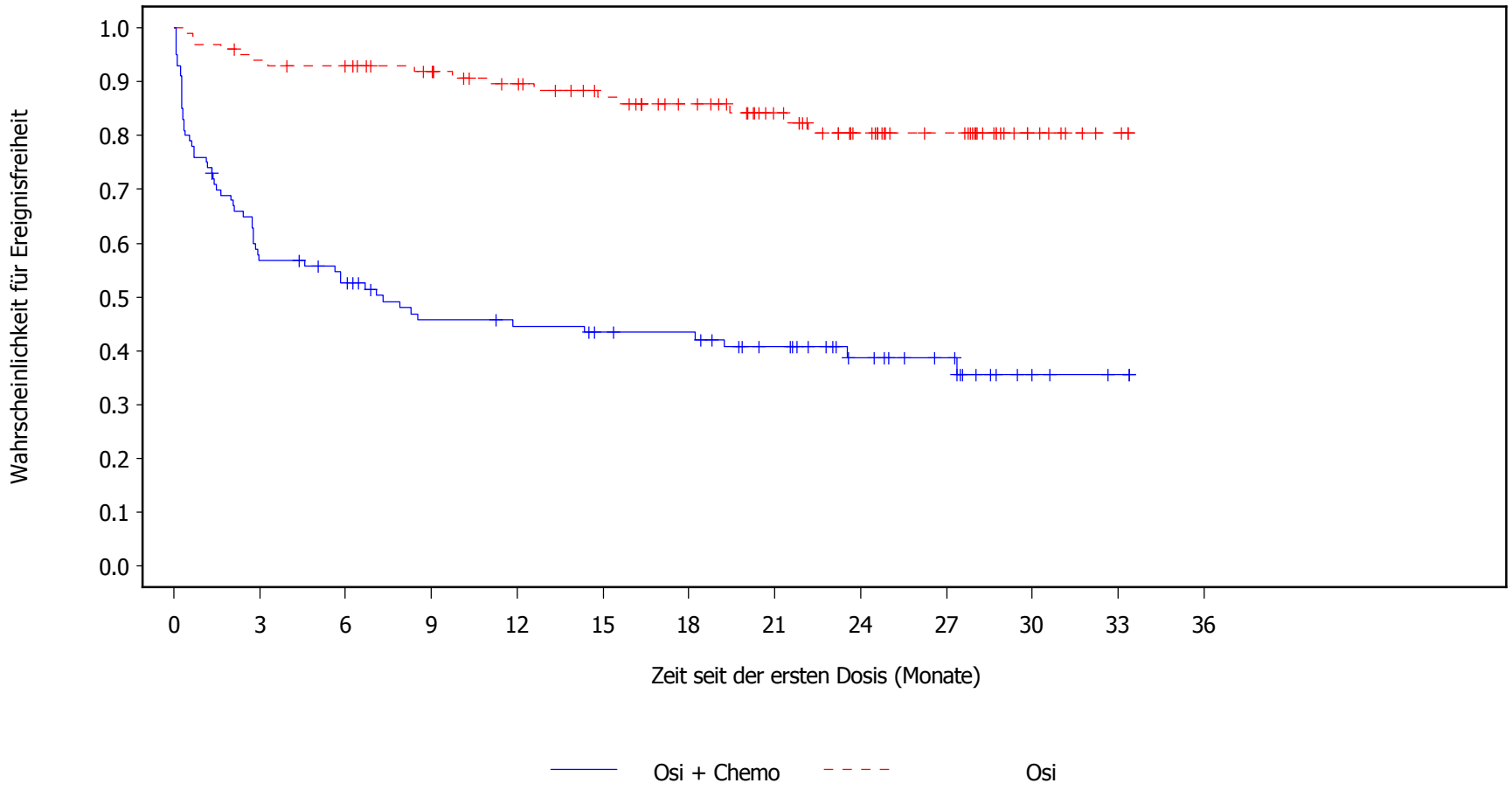
Figure 4.4.4.1 FLAURA-2 Subgroup Analysis: Kaplan-Meier plot of UE mit CTCAE Grad >=3 for WHO Performance-Status=0
Safety Analysis Set, DCO 03APR2023



Anzahl an Patienten unter Risiko:

100	56	50	40	38	35	34	27	18	13	3	1	0	Osi + Chemo
100	93	90	84	76	68	59	47	33	24	8	2	0	Osi

Kaplan-Meier plot is presented only if the interaction term in Cox regression model with treatment, subgroup and treatment-by-subgroup interaction is statistically significant at 5% level.
root/cdar/d516/payer_germany/ar/d5169c00001_payer_germany/tlf/prod/program/ttesubae.sas gttesubaekaa 22DEC2023:09:13 kfrh585

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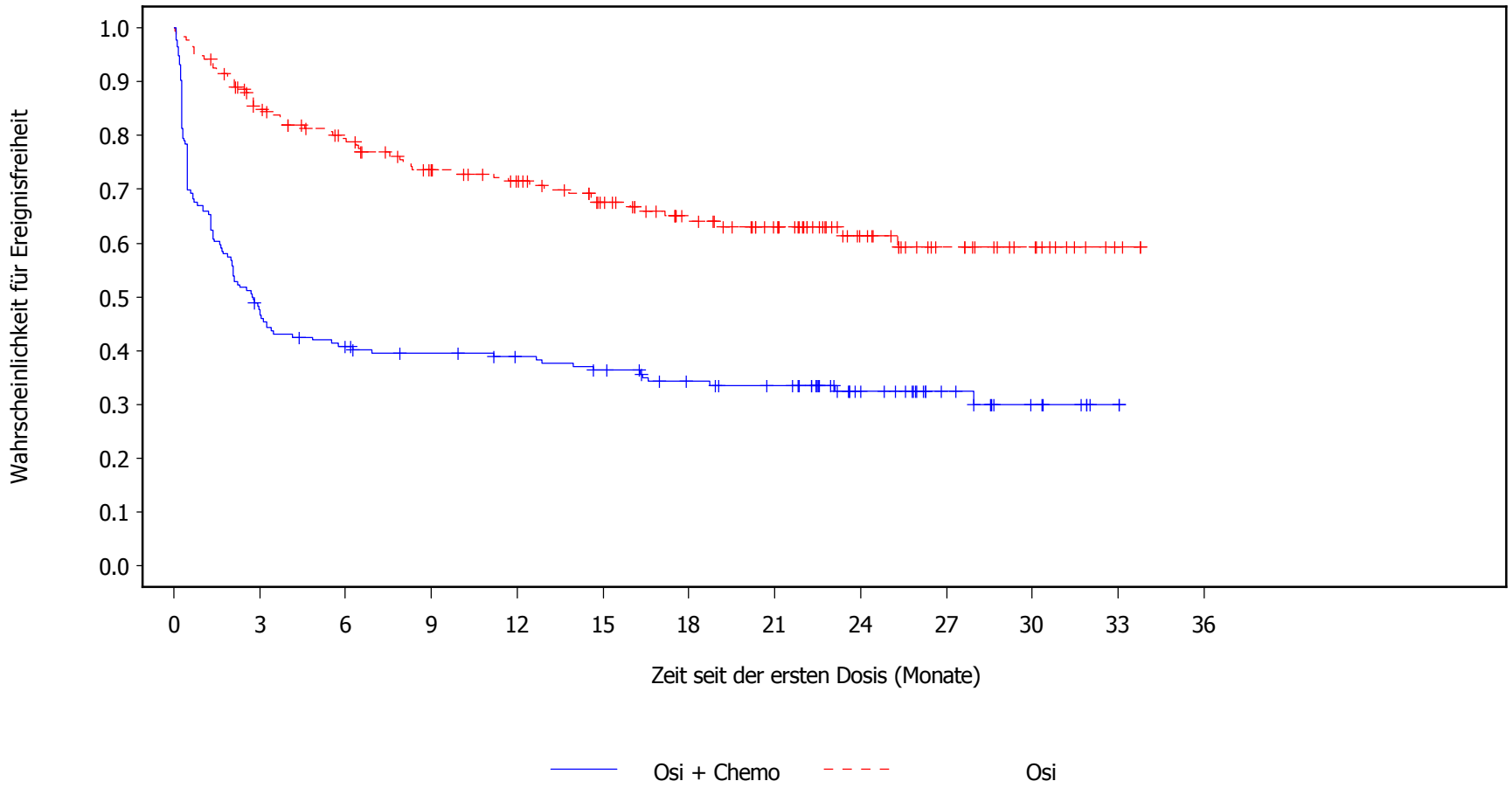
Figure 4.4.4.2 FLAURA-2 Subgroup Analysis: Kaplan-Meier plot of UE mit CTCAE Grad >=3 for WHO Performance-Status=1
Safety Analysis Set, DCO 03APR2023



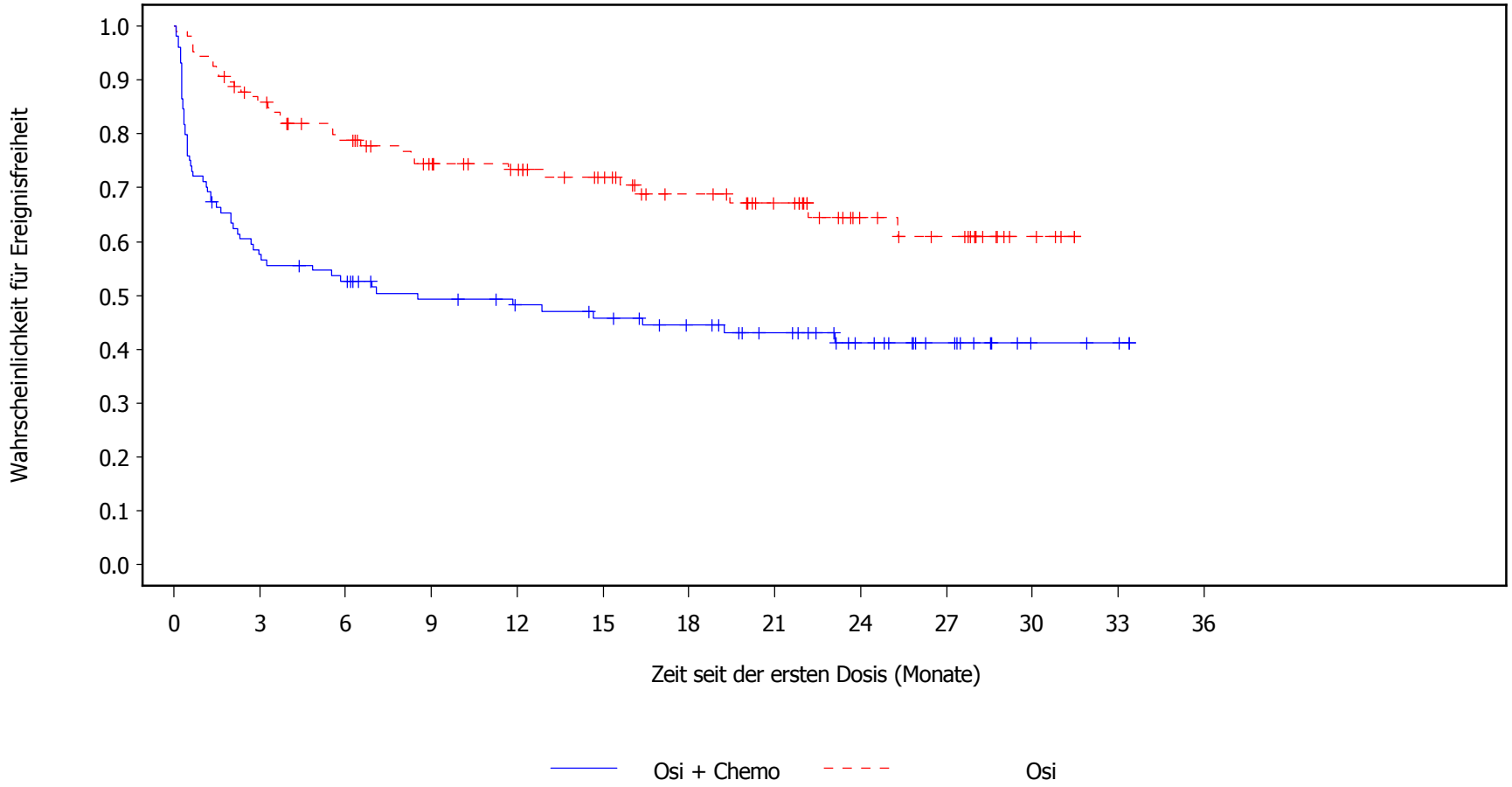
Anzahl an Patienten unter Risiko:

176	83	69	64	60	55	47	43	26	14	7	1	0	Osi + Chemo
175	142	125	109	99	84	67	55	33	20	12	2	0	Osi

Kaplan-Meier plot is presented only if the interaction term in Cox regression model with treatment, subgroup and treatment-by-subgroup interaction is statistically significant at 5% level.

root/cdar/d516/payer_germany/ar/d5169c00001_payer_germany/tlf/prod/program/ttesubae.sas gttesubaekab 22DEC2023:09:13 kfrh585

Figure 4.4.4.3 FLAURA-2 Subgroup Analysis: Kaplan-Meier plot of UE mit CTCAE Grad >=3 for Geschlecht=Maennlich
Safety Analysis Set, DCO 03APR2023



Anzahl an Patienten unter Risiko:

104	59	53	45	41	38	33	27	18	11	3	2	0	Osi + Chemo
107	89	77	66	59	51	41	33	19	15	4	0	0	Osi

Kaplan-Meier plot is presented only if the interaction term in Cox regression model with treatment, subgroup and treatment-by-subgroup interaction is statistically significant at 5% level.
root/cdar/d516/payer_germany/ar/d5169c00001_payer_germany/tlf/prod/program/ttesubae.sas gttesubaekac 22DEC2023:09:13 kfrh585

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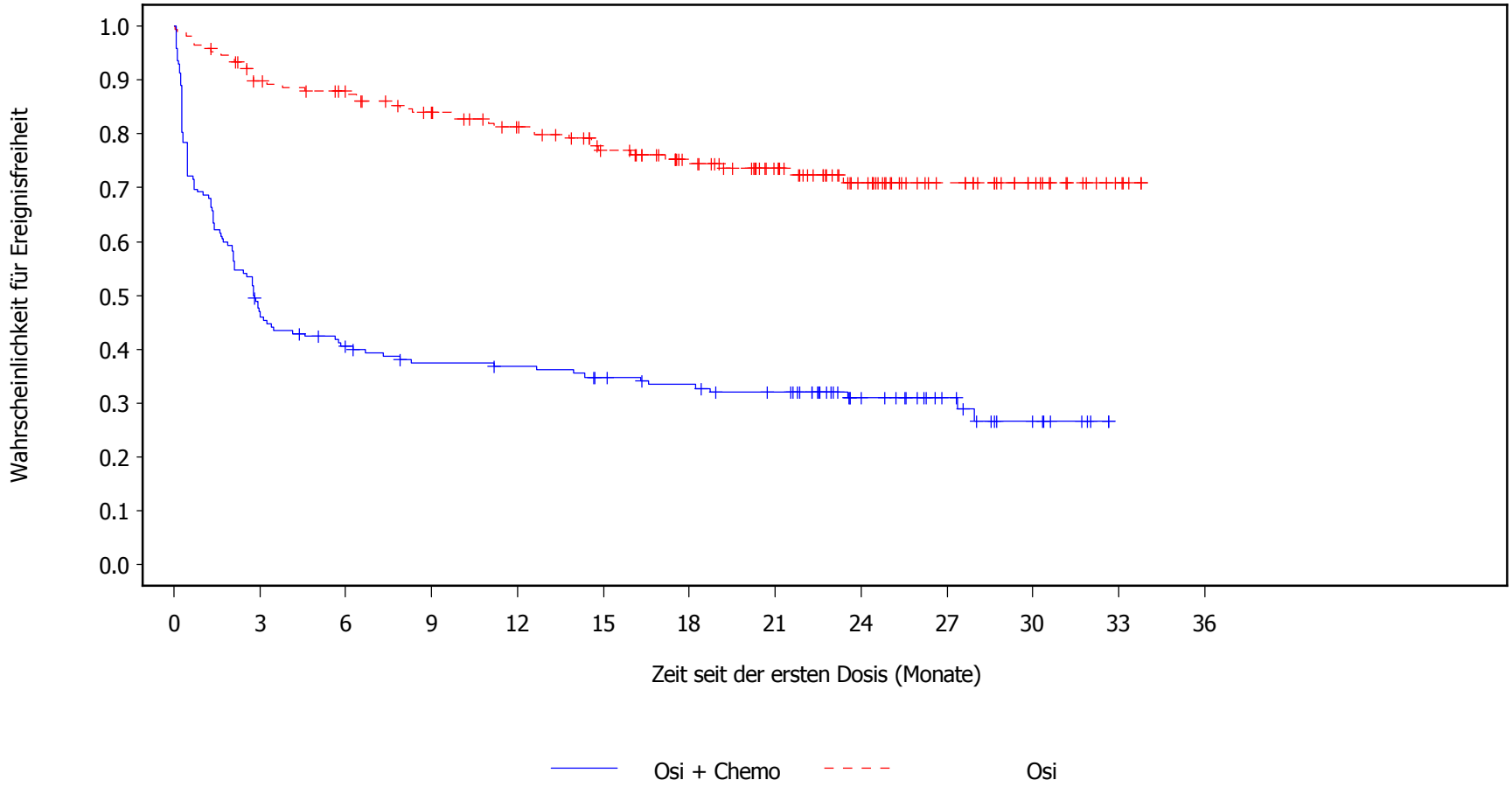
Figure 4.4.4.4 FLAURA-2 Subgroup Analysis: Kaplan-Meier plot of UE mit CTCAE Grad >=3 for Geschlecht=Weiblich
Safety Analysis Set, DCO 03APR2023



Anzahl an Patienten unter Risiko:

172	80	66	59	57	52	48	43	26	16	7	0	0	Osi + Chemo
168	146	138	127	116	101	85	69	47	29	16	4	0	Osi

Kaplan-Meier plot is presented only if the interaction term in Cox regression model with treatment, subgroup and treatment-by-subgroup interaction is statistically significant at 5% level.
root/cdar/d516/payer_germany/ar/d5169c00001_payer_germany/tlf/prod/program/ttesubae.sas gttesubaekad 22DEC2023:09:13 kfrh585

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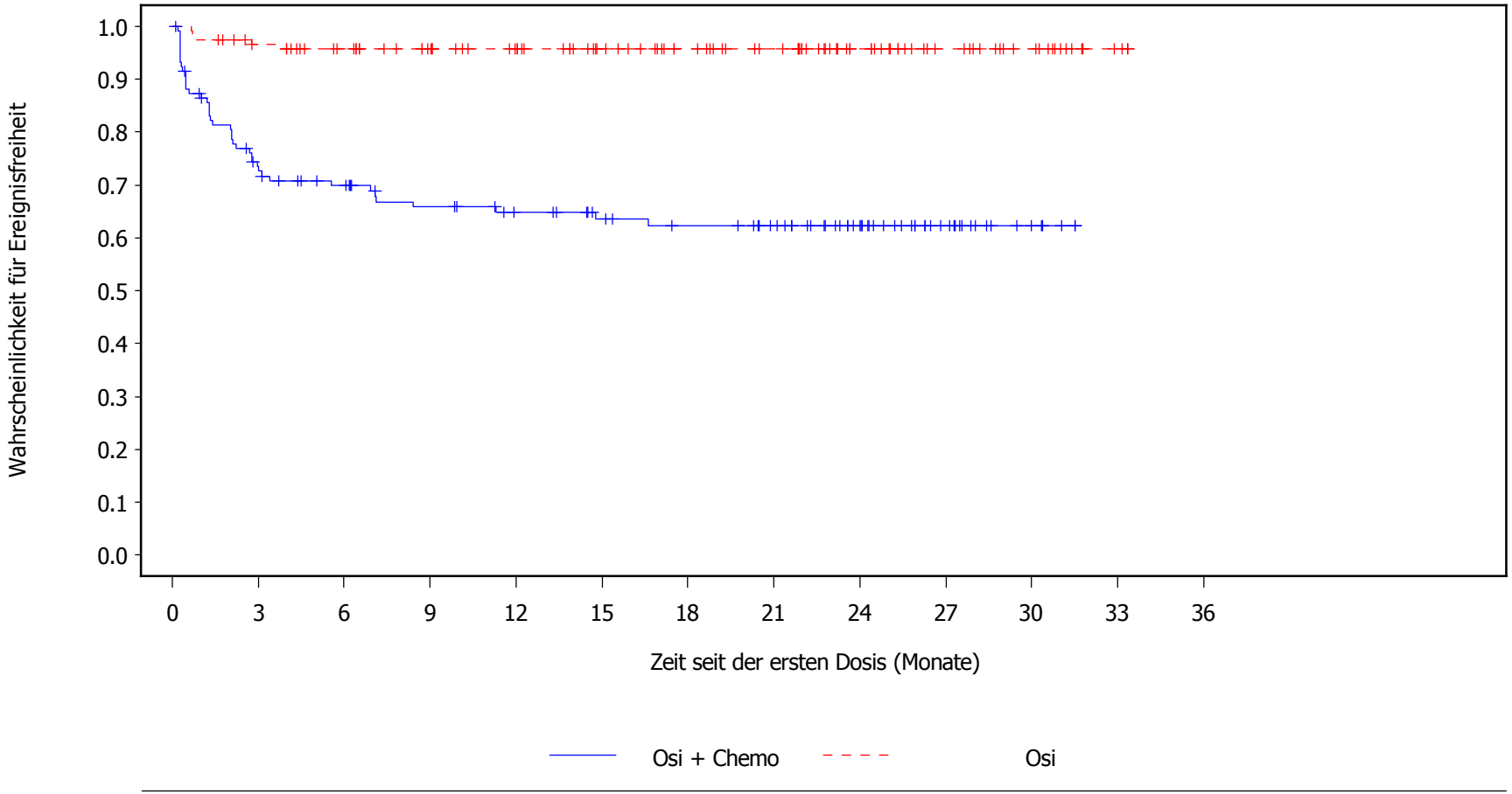
Figure 4.4.4.5 FLAURA-2 Subgroup Analysis: Kaplan-Meier plot of G>=3 SOC: Erkrankungen des Blutes und des Lymphsystems for Methode zur Gewebeuntersuchung=zentral
Safety Analysis Set, DCO 03APR2023



Anzahl an Patienten unter Risiko:

120	83	74	65	59	53	49	44	30	15	4	0	0	Osi + Chemo
119	110	101	91	83	71	61	53	34	21	13	2	0	Osi

Kaplan-Meier plot is presented only if the interaction term in Cox regression model with treatment, subgroup and treatment-by-subgroup interaction is statistically significant at 5% level.
root/cdar/d516/payer_germany/ar/d5169c00001_payer_germany/tlf/prod/program/ttesubae.sas gttesubaekae 22DEC2023:09:13 kfrh585

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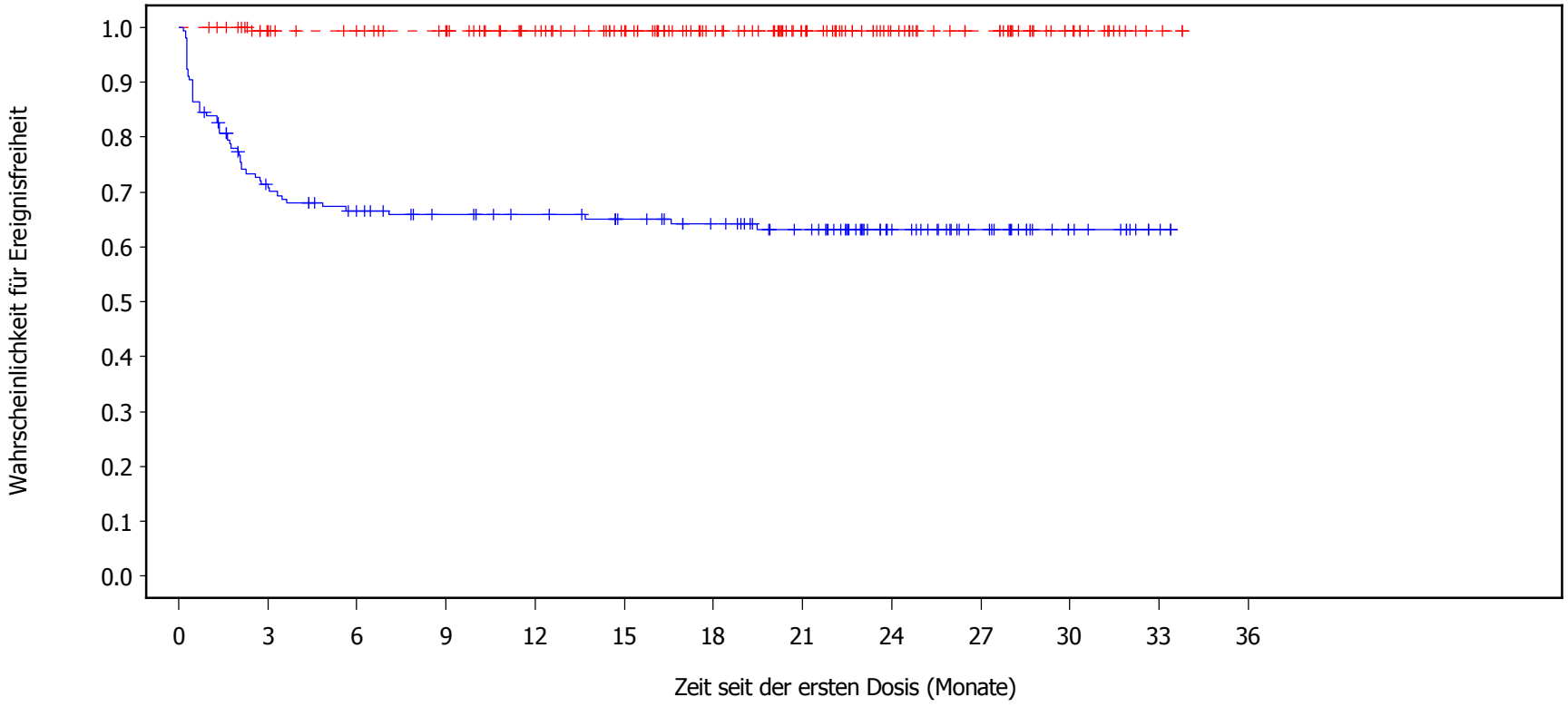
Figure 4.4.4.6 FLAURA-2 Subgroup Analysis: Kaplan-Meier plot of G>=3 SOC: Erkrankungen des Blutes und des Lymphsystems for Methode zur Gewebeuntersuchung=lokal
Safety Analysis Set, DCO 03APR2023



Anzahl an Patienten unter Risiko:

156	106	94	87	83	76	69	59	38	25	11	2	0	Osi + Chemo
156	144	138	133	119	106	85	66	44	33	15	2	0	Osi

Kaplan-Meier plot is presented only if the interaction term in Cox regression model with treatment, subgroup and treatment-by-subgroup interaction is statistically significant at 5% level.
root/cdar/d516/payer_germany/ar/d5169c00001_payer_germany/tlf/prod/program/ttesubae.sas gttesubaekaf 22DEC2023:09:13 kfrh585

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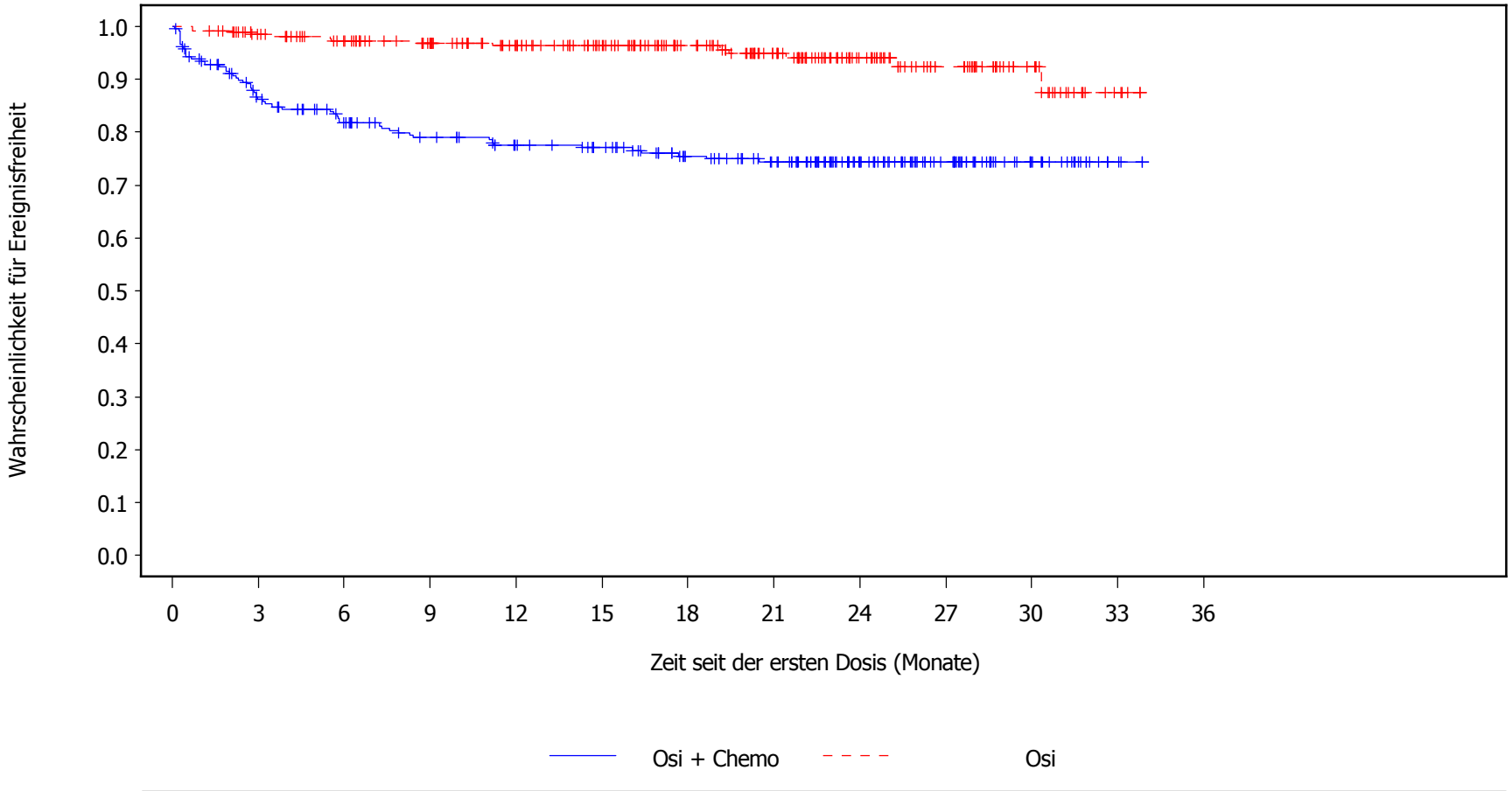
Figure 4.4.4.7 FLAURA-2 Subgroup Analysis: Kaplan-Meier plot of G>=3 SOC: Untersuchungen for Zentrale Bestätigung der EGFR-Mutation=Zentral bestätigte EGFR-Mutation in Gewebe oder ctDNA
Safety Analysis Set, DCO 03APR2023



Anzahl an Patienten unter Risiko:

263	213	190	174	162	153	132	118	79	50	22	3	0	Osi + Chemo
266	249	233	216	194	171	140	113	74	48	23	4	0	Osi

Kaplan-Meier plot is presented only if the interaction term in Cox regression model with treatment, subgroup and treatment-by-subgroup interaction is statistically significant at 5% level.
root/cdar/d516/payer_germany/ar/d5169c00001_payer_germany/tlf/prod/program/ttesubae.sas gttesubaekag 22DEC2023:09:13 kfrh585

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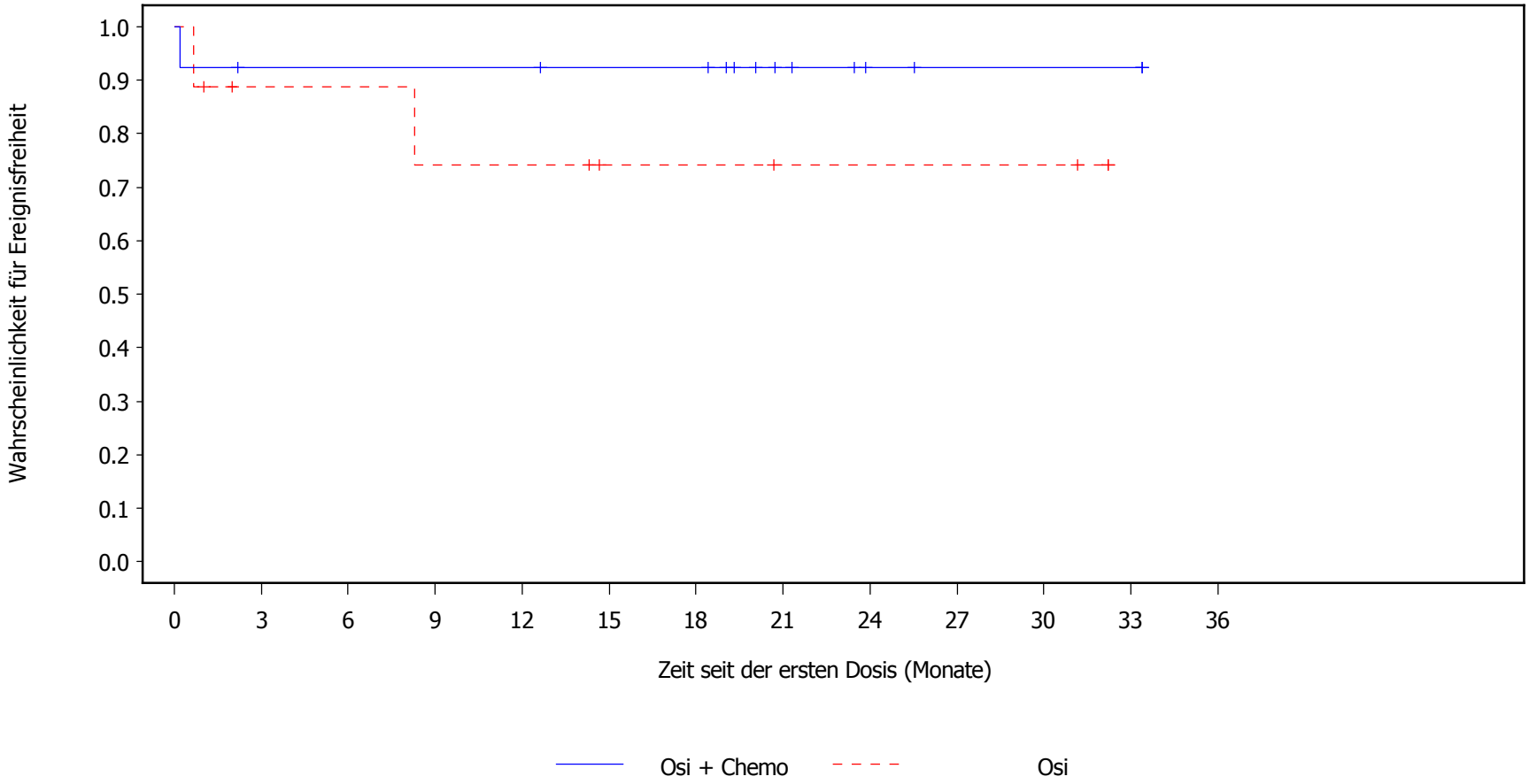
Figure 4.4.4.8 FLAURA-2 Subgroup Analysis: Kaplan-Meier plot of G>=3 SOC: Untersuchungen for Zentrale Bestätigung der EGFR-Mutation=Keine zentrale Bestätigung
Safety Analysis Set, DCO 03APR2023



Anzahl an Patienten unter Risiko:

13	11	11	11	11	10	10	5	2	1	1	1	0	Osi + Chemo
9	6	6	5	5	3	3	2	2	2	2	0	0	Osi

Kaplan-Meier plot is presented only if the interaction term in Cox regression model with treatment, subgroup and treatment-by-subgroup interaction is statistically significant at 5% level.
root/cdar/d516/payer_germany/ar/d5169c00001_payer_germany/tlf/prod/program/ttesubae.sas gttesubaekah 22DEC2023:09:13 kfrh585

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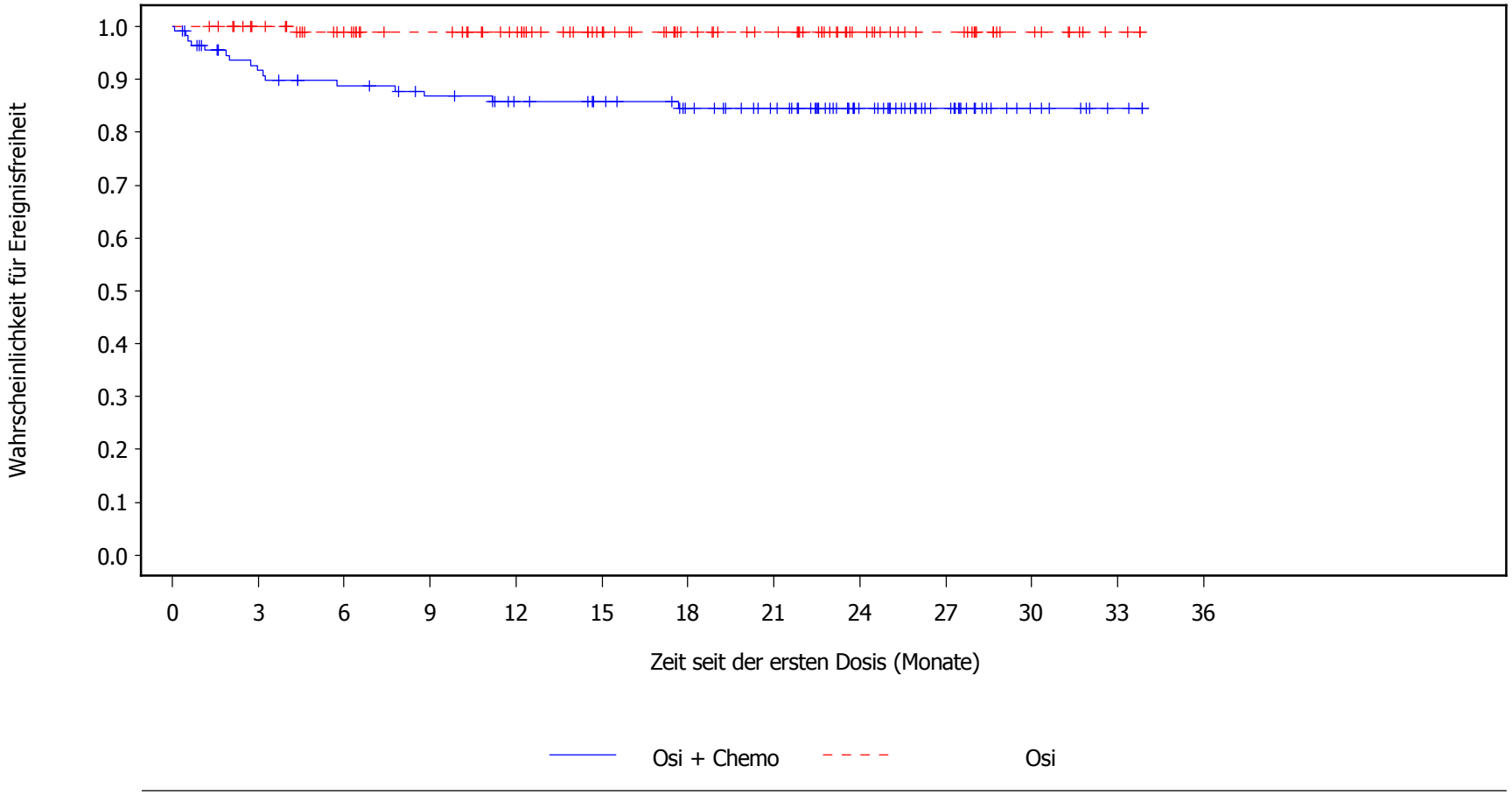
Figure 4.4.4.9 FLAURA-2 Subgroup Analysis: Kaplan-Meier plot of G>=3 PT: Neutrophilenzahl erniedrigt for ZNS-Metastasen zur Baseline=Ja
Safety Analysis Set, DCO 03APR2023



Anzahl an Patienten unter Risiko:

113	96	90	85	79	74	67	59	38	23	8	2	0	Osi + Chemo
110	102	91	84	75	61	49	43	27	19	9	2	0	Osi

Kaplan-Meier plot is presented only if the interaction term in Cox regression model with treatment, subgroup and treatment-by-subgroup interaction is statistically significant at 5% level.

root/cdar/d516/payer_germany/ar/d5169c00001_payer_germany/tlf/prod/program/ttesubae.sas gttesubaekai 22DEC2023:09:13 kfrh585

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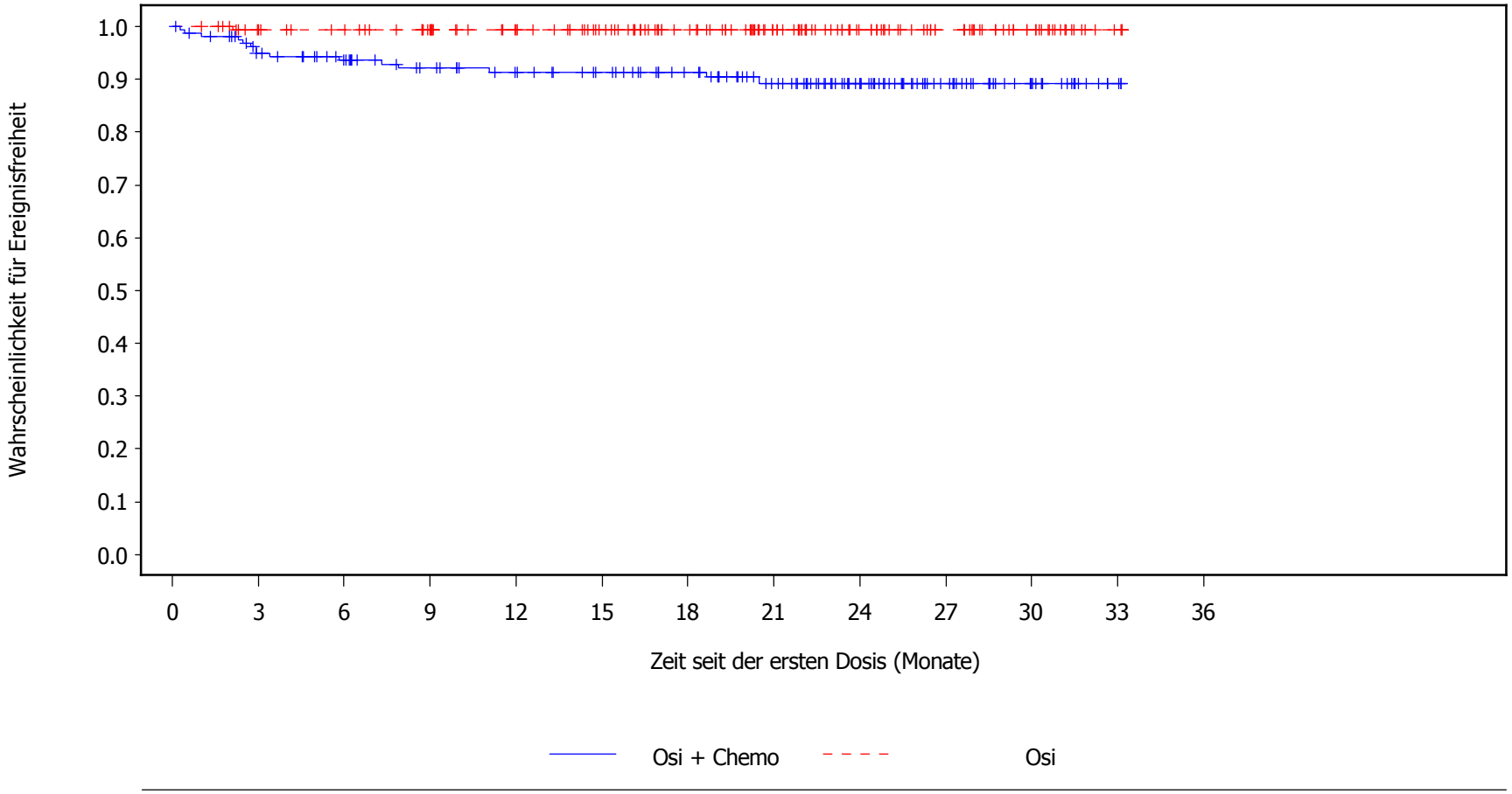
Figure 4.4.4.10 FLAURA-2 Subgroup Analysis: Kaplan-Meier plot of G>=3 PT: Neutrophilenzahl erniedrigt for ZNS-Metastasen zur Baseline=Nein
Safety Analysis Set, DCO 03APR2023

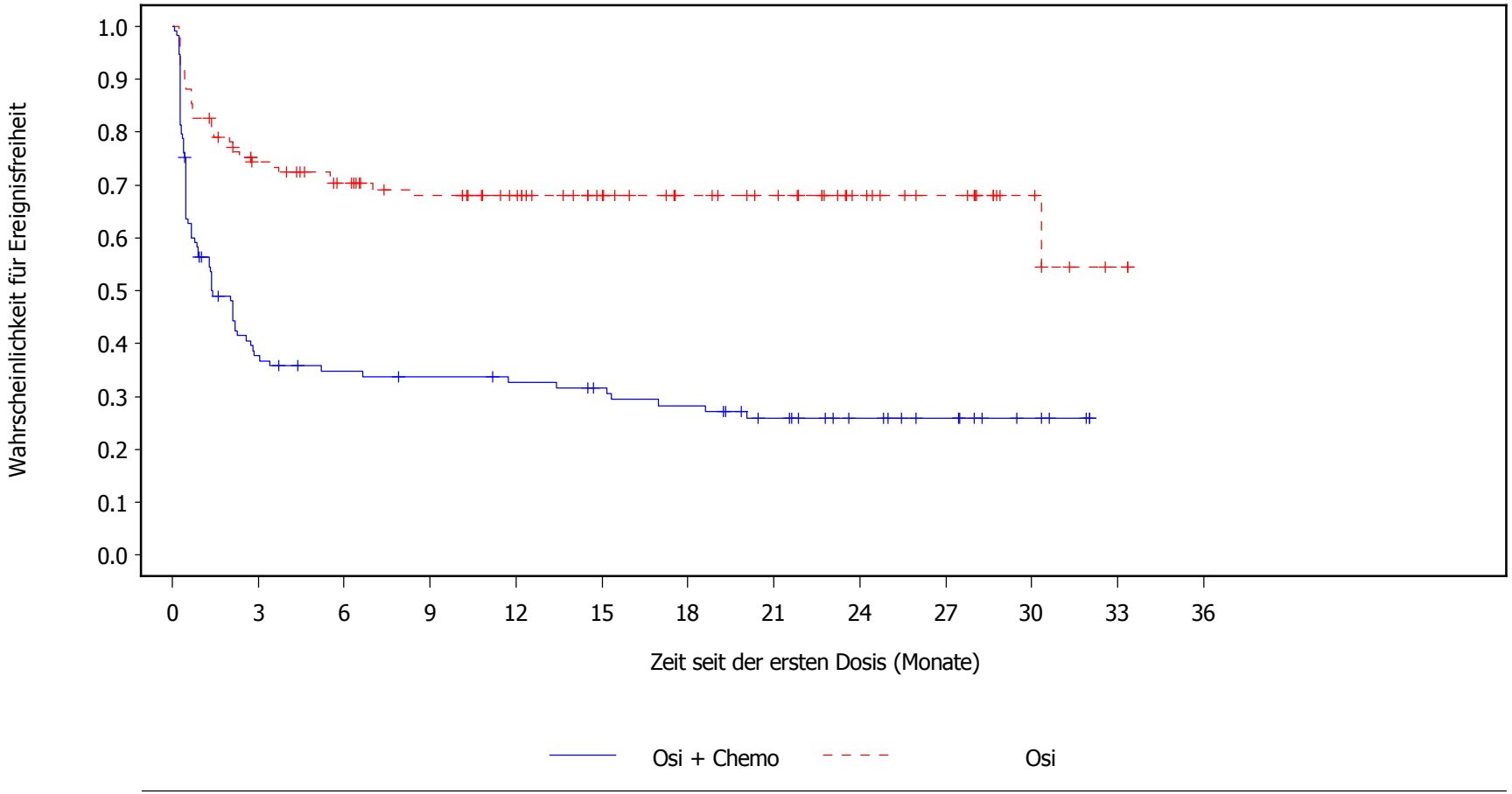


Anzahl an Patienten unter Risiko:

163	146	135	123	115	108	96	80	57	34	16	2	0	Osi + Chemo
165	156	151	142	129	117	98	77	53	36	19	2	0	Osi

Kaplan-Meier plot is presented only if the interaction term in Cox regression model with treatment, subgroup and treatment-by-subgroup interaction is statistically significant at 5% level.
root/cdar/d516/payer_germany/ar/d5169c00001_payer_germany/tlf/prod/program/ttesubae.sas gttesubaekaj 22DEC2023:09:13 kfrh585

Figure 4.4.5.1 FLAURA-2 Subgroup Analysis: Kaplan-Meier plot of UESI GT: Hämatologische Toxizitäten for ZNS-Metastasen zur Baseline=Ja
Safety Analysis Set, DCO 03APR2023

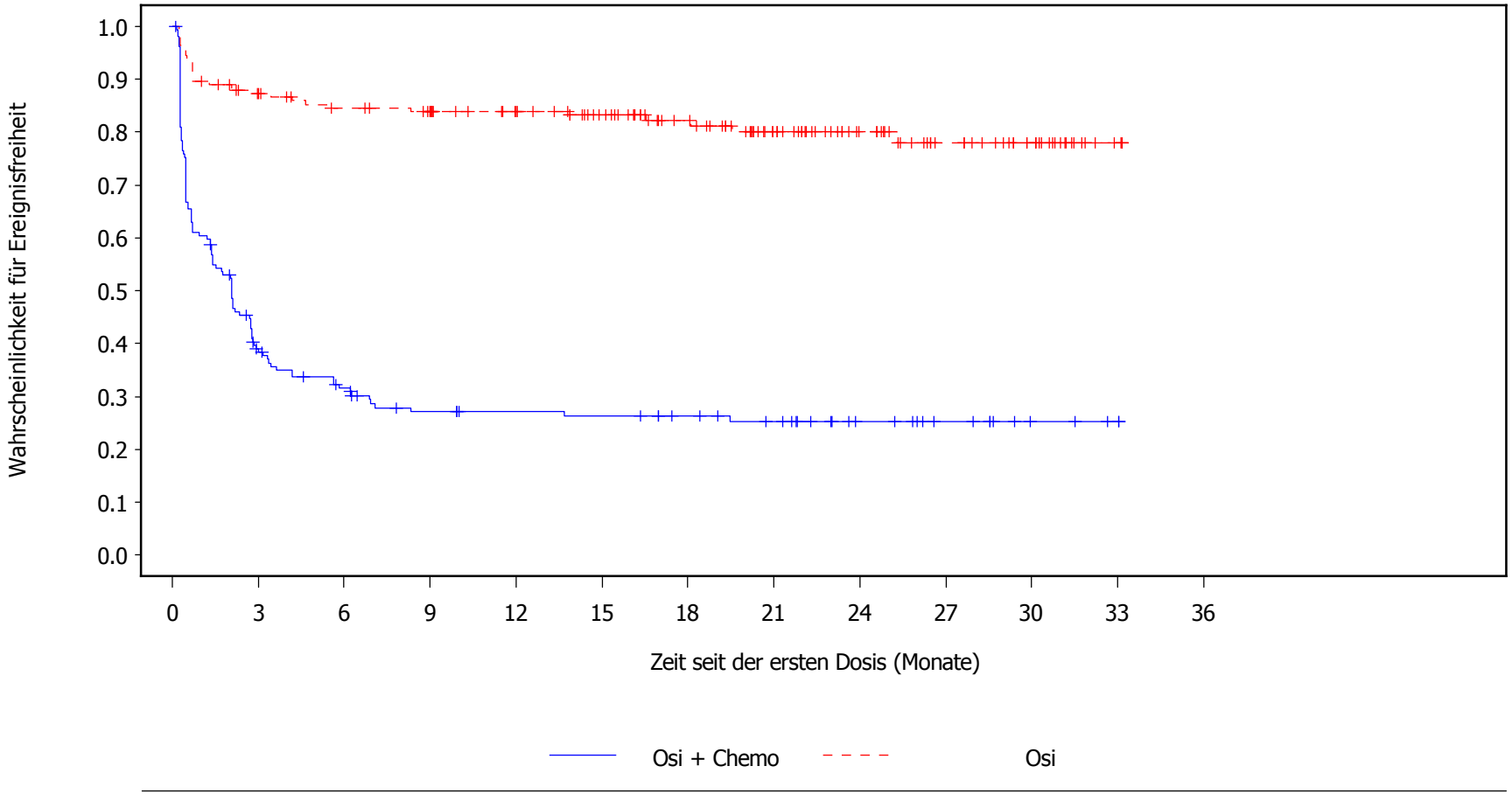


Anzahl an Patienten unter Risiko:

113	40	35	33	31	28	25	19	13	9	4	0	0	Osi + Chemo
110	76	66	58	50	40	33	29	19	14	6	1	0	Osi

Kaplan-Meier plot is presented only if the interaction term in Cox regression model with treatment, subgroup and treatment-by-subgroup interaction is statistically significant at 5% level.
root/cdar/d516/payer_germany/ar/d5169c00001_payer_germany/tlf/prod/program/ttesubae.sas gttesubaelaa 22DEC2023:09:13 kfrh585

Figure 4.4.5.2 FLAURA-2 Subgroup Analysis: Kaplan-Meier plot of UESI GT: Hämatologische Toxizitäten for ZNS-Metastasen zur Baseline=Nein
Safety Analysis Set, DCO 03APR2023



Anzahl an Patienten unter Risiko:

163	59	45	35	32	31	27	23	14	9	3	1	0	Osi + Chemo
165	138	129	124	112	100	83	63	44	29	18	2	0	Osi

Kaplan-Meier plot is presented only if the interaction term in Cox regression model with treatment, subgroup and treatment-by-subgroup interaction is statistically significant at 5% level.
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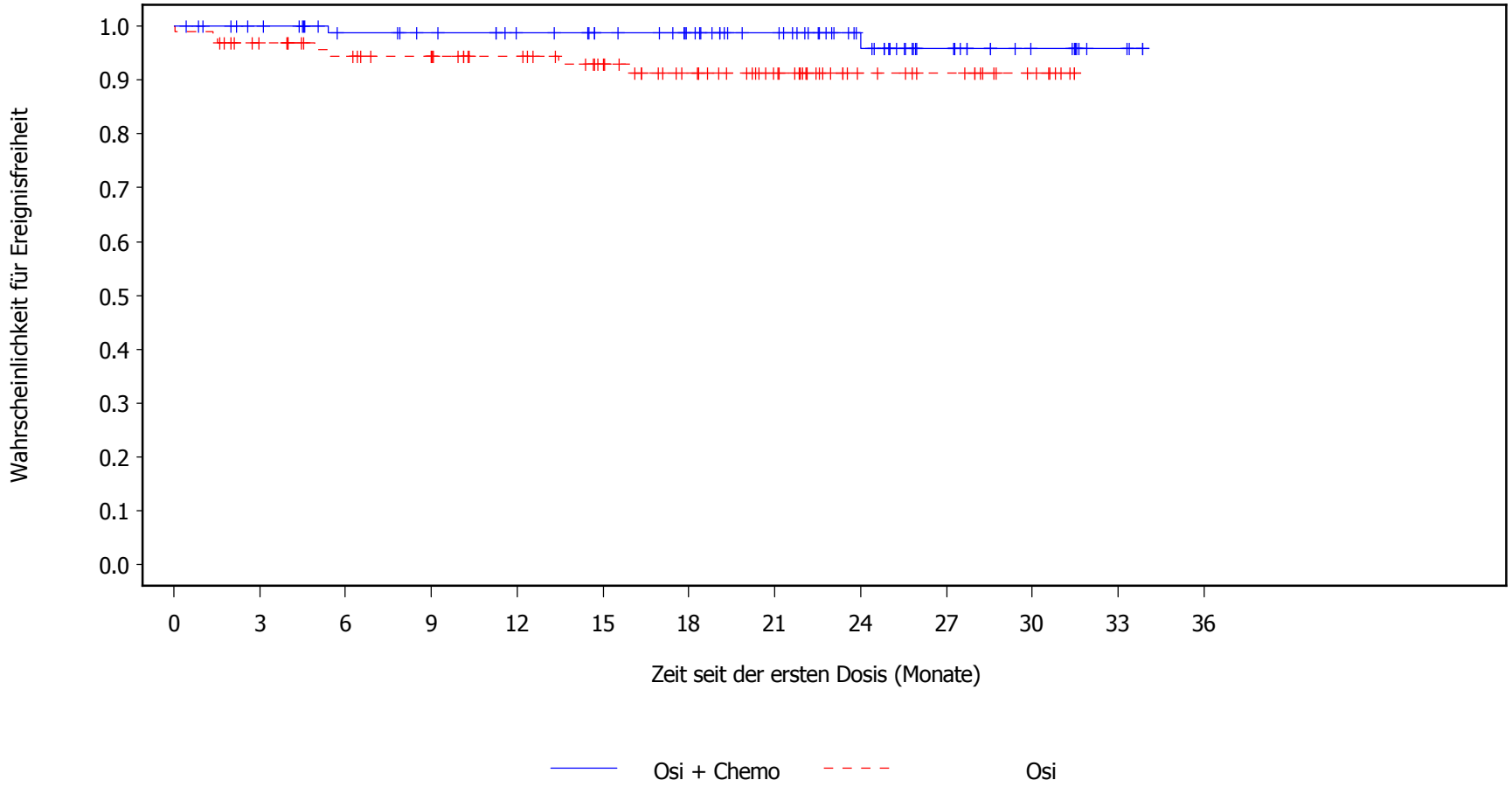
Nutzenbewertung nach AMNOG Seite 1 von 1

Figure 4.4.5.3 FLAURA-2 Subgroup Analysis: Kaplan-Meier plot of UESI GT: ILD und Pneumonitis for Raucherstatus=Ja
Safety Analysis Set, DCO 03APR2023



Anzahl an Patienten unter Risiko:

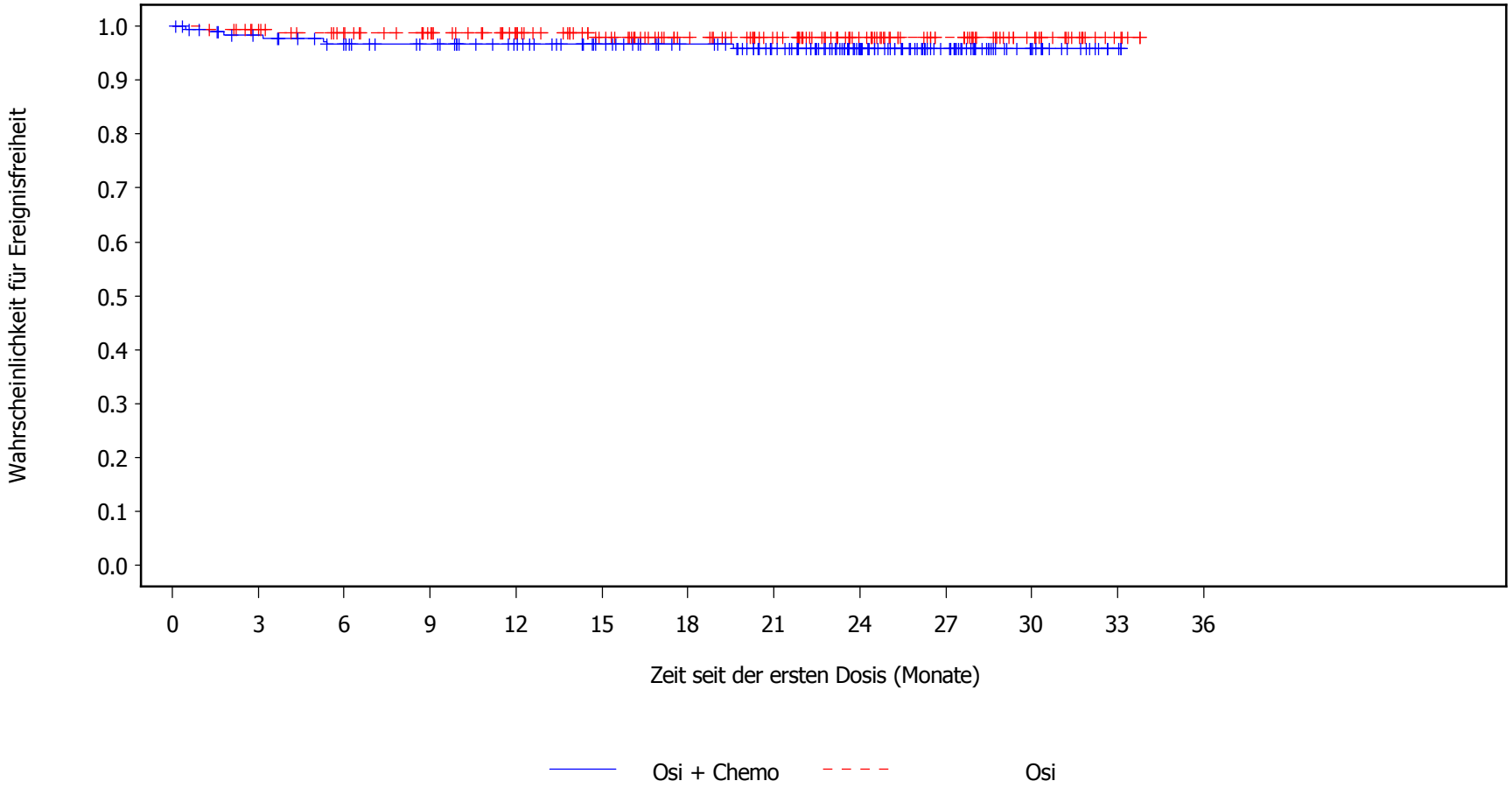
90	84	76	73	68	63	57	48	33	19	9	3	0	Osi + Chemo
96	87	80	76	68	59	48	36	19	15	7	0	0	Osi

Kaplan-Meier plot is presented only if the interaction term in Cox regression model with treatment, subgroup and treatment-by-subgroup interaction is statistically significant at 5% level.

root/cdar/d516/payer_germany/ar/d5169c00001_payer_germany/tlf/prod/program/ttesubae.sas gttesubaelac 22DEC2023:09:13 kfrh585

Nutzenbewertung nach AMNOG Seite 1 von 1

Figure 4.4.5.4 FLAURA-2 Subgroup Analysis: Kaplan-Meier plot of UESI GT: ILD und Pneumonitis for Raucherstatus=Nein
Safety Analysis Set, DCO 03APR2023



Anzahl an Patienten unter Risiko:

186	175	166	159	149	137	125	110	76	44	18	2	0	Osi + Chemo
179	172	162	152	138	120	101	86	61	40	21	4	0	Osi

Kaplan-Meier plot is presented only if the interaction term in Cox regression model with treatment, subgroup and treatment-by-subgroup interaction is statistically significant at 5% level.

root/cdar/d516/payer_germany/ar/d5169c00001_payer_germany/tlf/prod/program/ttesubae.sas gttesubaelad 22DEC2023:09:13 kfrh585

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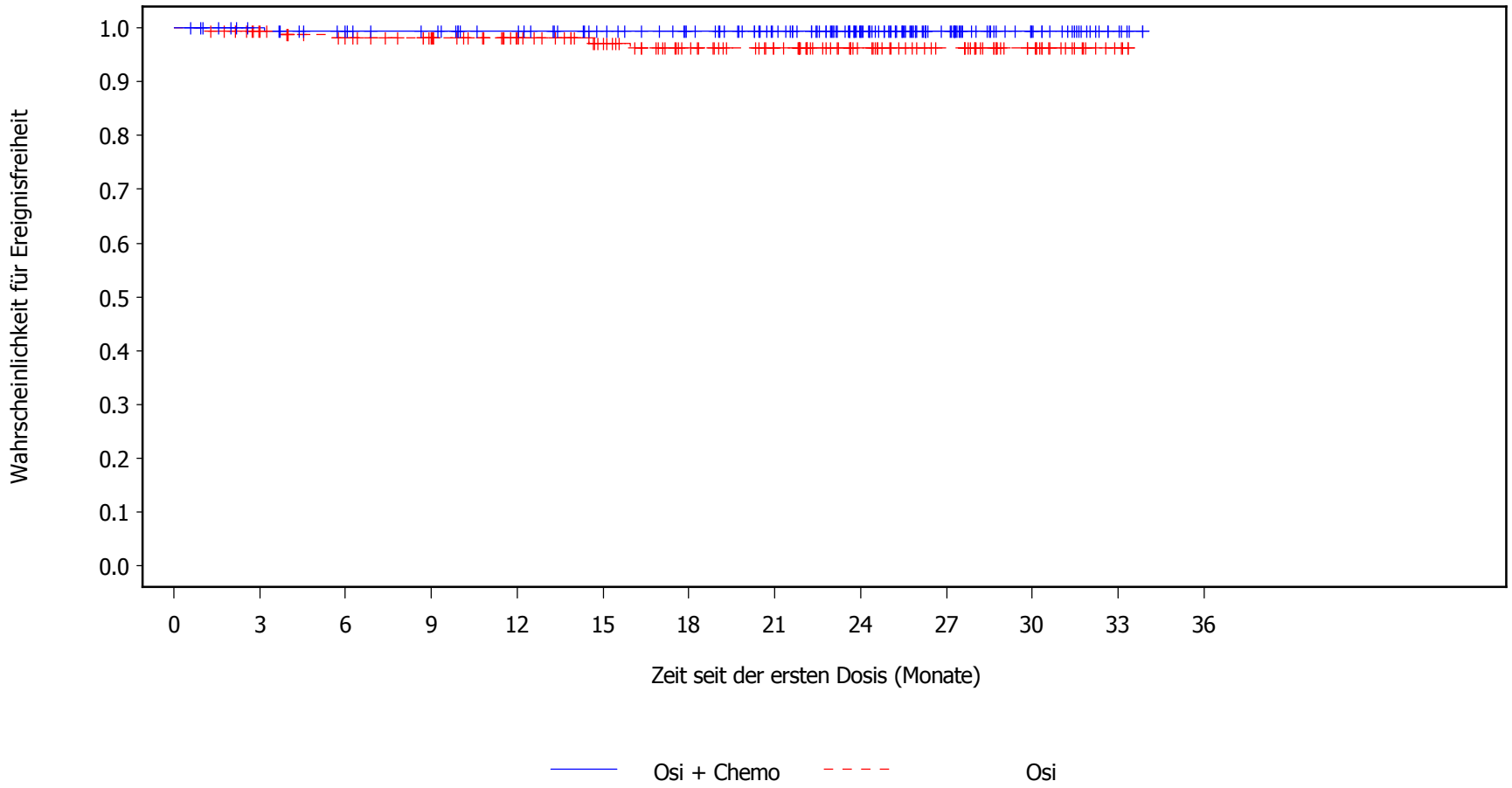
Figure 4.4.5.5 FLAURA-2 Subgroup Analysis: Kaplan-Meier plot of UESI GT: ILD und Pneumonitis for Alter bei Screening=<65 Jahre
Safety Analysis Set, DCO 03APR2023



Anzahl an Patienten unter Risiko:

172	165	158	154	147	137	128	113	83	46	22	5	0	Osi + Chemo
164	156	146	138	123	109	92	78	55	40	21	3	0	Osi

Kaplan-Meier plot is presented only if the interaction term in Cox regression model with treatment, subgroup and treatment-by-subgroup interaction is statistically significant at 5% level.
root/cdar/d516/payer_germany/ar/d5169c00001_payer_germany/tlf/prod/program/ttesubae.sas gttesubaelae 22DEC2023:09:13 kfrh585

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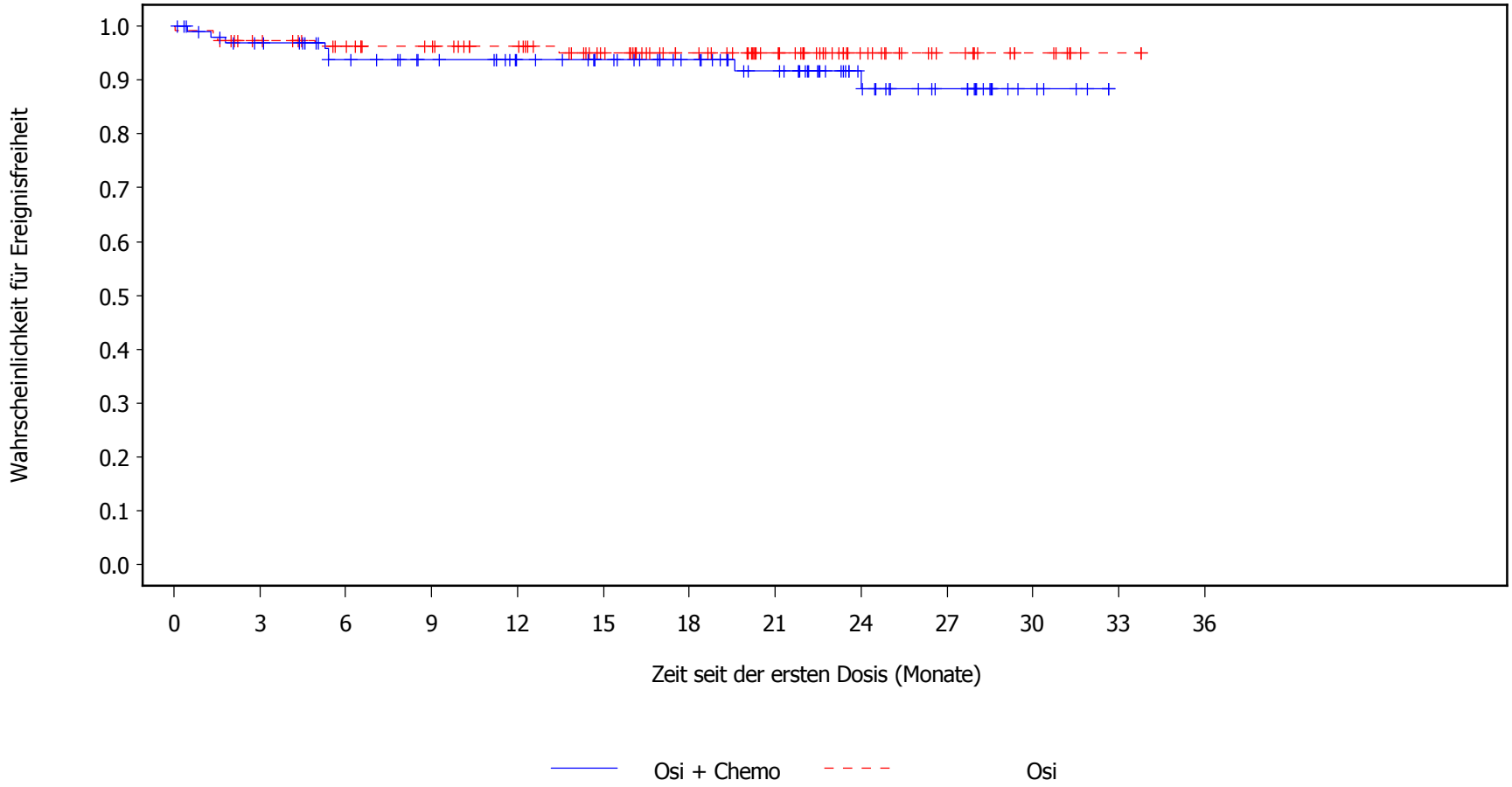
Figure 4.4.5.6 FLAURA-2 Subgroup Analysis: Kaplan-Meier plot of UESI GT: ILD und Pneumonitis for Alter bei Screening=>=65 Jahre
Safety Analysis Set, DCO 03APR2023



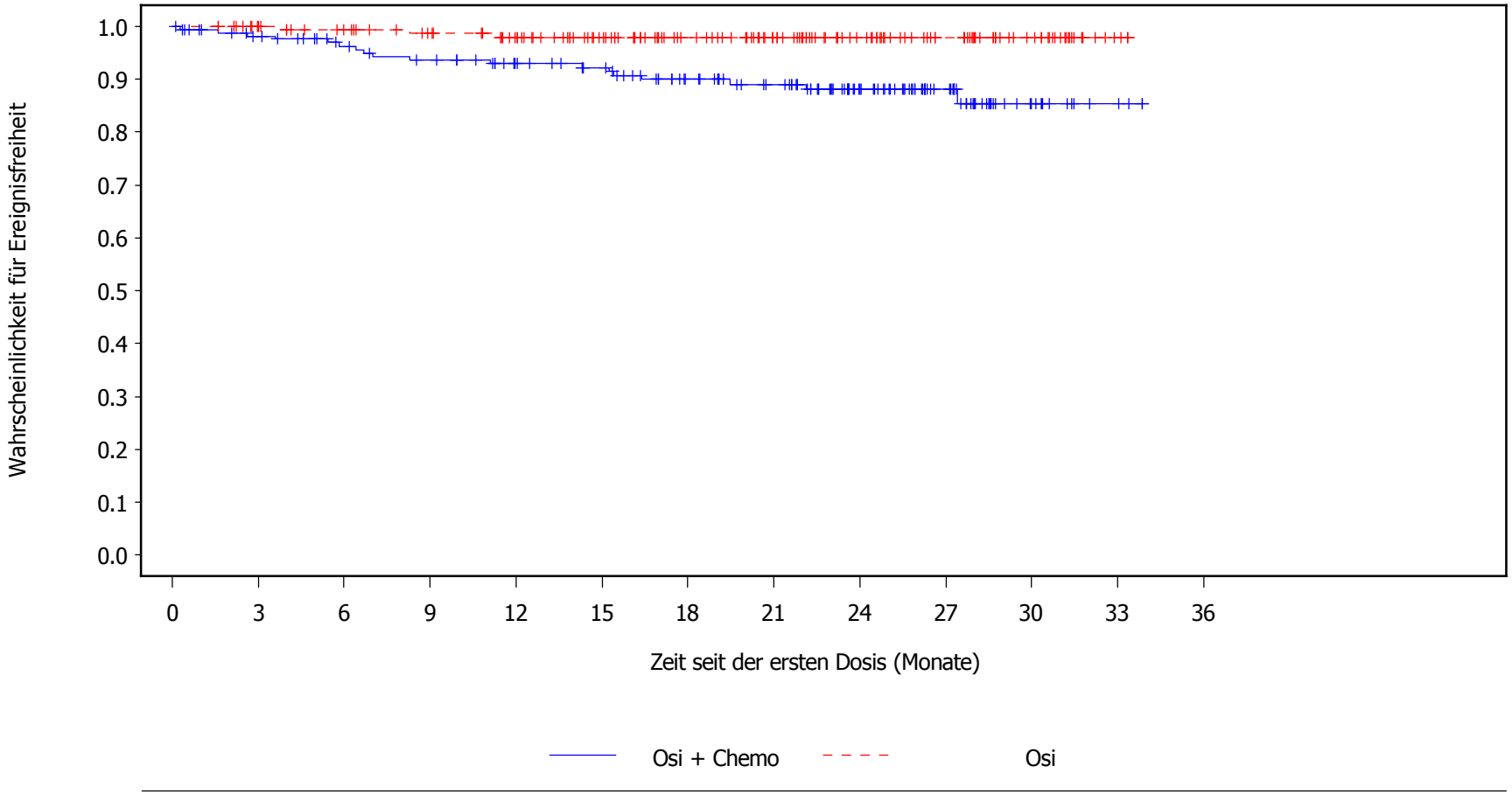
Anzahl an Patienten unter Risiko:

104	94	84	78	70	63	54	45	26	17	5	0	0	Osi + Chemo
111	103	96	90	83	70	57	44	25	15	7	1	0	Osi

Kaplan-Meier plot is presented only if the interaction term in Cox regression model with treatment, subgroup and treatment-by-subgroup interaction is statistically significant at 5% level.

root/cdar/d516/payer_germany/ar/d5169c00001_payer_germany/tlf/prod/program/ttesubae.sas gttesubaelaf 22DEC2023:09:13 kfrh585

Figure 4.4.5.7 FLAURA-2 Subgroup Analysis: Kaplan-Meier plot of UESI GT: Kardiale Effekte (Herzinsuffizienz) for EGFR-Mutationstyp=Exon 19 Deletion
Safety Analysis Set, DCO 03APR2023

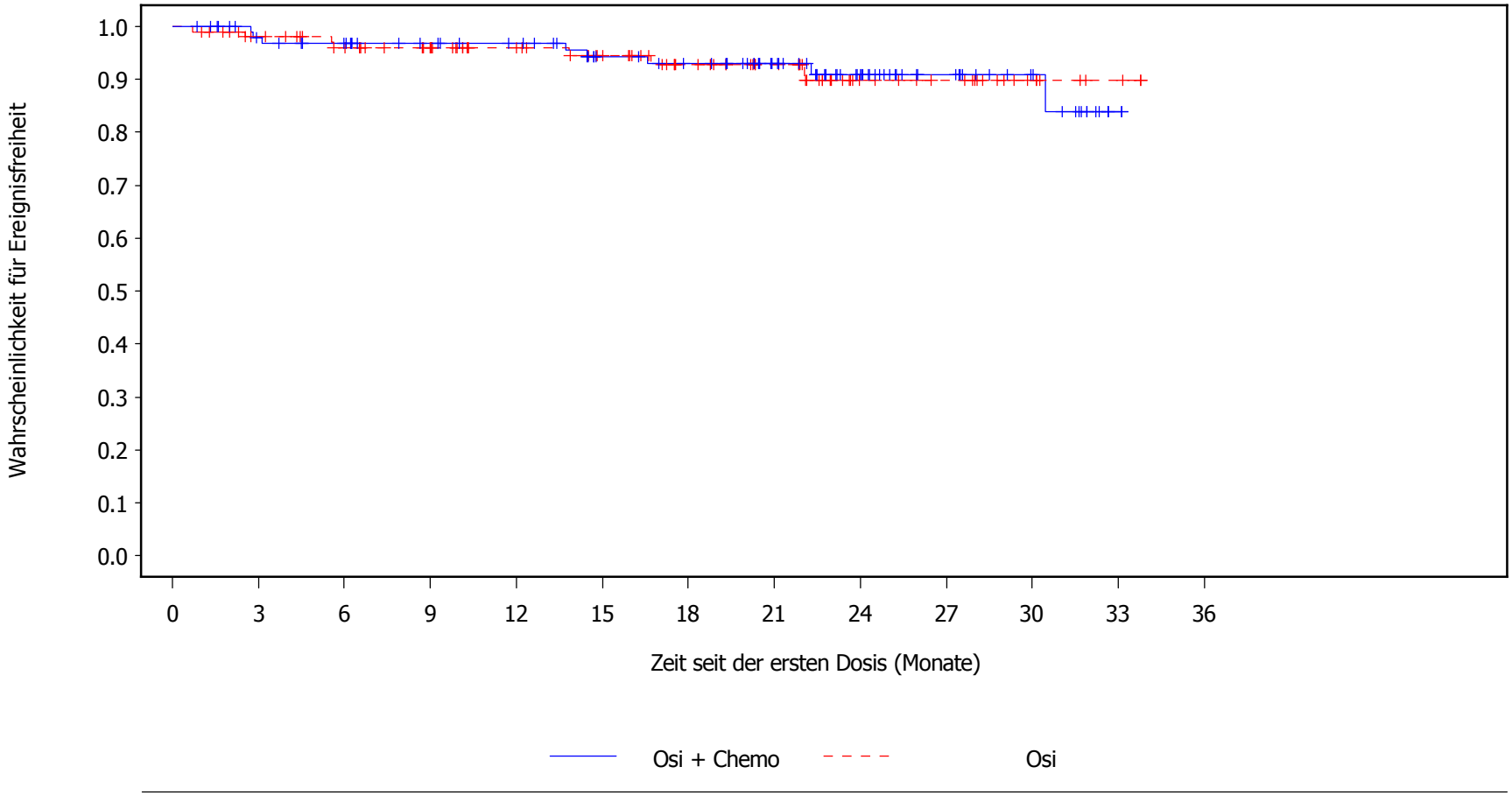


Anzahl an Patienten unter Risiko:

172	160	149	142	131	124	107	95	66	39	12	3	0	Osi + Chemo
167	159	150	142	132	114	94	78	57	39	21	2	0	Osi

Kaplan-Meier plot is presented only if the interaction term in Cox regression model with treatment, subgroup and treatment-by-subgroup interaction is statistically significant at 5% level.
root/cdar/d516/payer_germany/ar/d5169c00001_payer_germany/tlf/prod/program/ttesubae.sas gttesubaelag 22DEC2023:09:13 kfrh585

Figure 4.4.5.8 FLAURA-2 Subgroup Analysis: Kaplan-Meier plot of UESI GT: Kardiale Effekte (Herzinsuffizienz) for EGFR-Mutationstyp=Exon 21 (L858R) Substitutionsmutation
Safety Analysis Set, DCO 03APR2023



Anzahl an Patienten unter Risiko:

104	95	90	83	79	68	64	53	35	22	14	1	0	Osi + Chemo
106	97	89	81	68	60	48	39	20	16	7	2	0	Osi

Kaplan-Meier plot is presented only if the interaction term in Cox regression model with treatment, subgroup and treatment-by-subgroup interaction is statistically significant at 5% level.
root/cdar/d516/payer_germany/ar/d5169c00001_payer_germany/tlf/prod/program/ttesubae.sas gttesubaelah 22DEC2023:09:13 kfrh585