

Modul 4A Anhang 4-G

**Dossier zur Nutzenbewertung
gemäß § 35a SGB V**

Dabrafenib (Finlee[®])

Novartis Pharma GmbH

Modul 4 A – Anhang 4-G

*Kombination mit Trametinib zur Behandlung von pädiatrischen
Patienten ab einem Alter von 1 Jahr mit einem LGG mit einer BRAF-
V600E-Mutation, die eine systemische Therapie benötigen*

**Ergänzende Analysen zu der Studie
CDRB436G2201
(Datenschnitt: 28.04.2023)**

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Ergänzende Analysen zur Studie CDRB436G2201 – Gesamtpopulation**1. PROMIS PGH-7+2****1.1. Änderung der T-Scores gegenüber Studienbeginn mittels MMRM-Analyse zu den verschiedenen Erhebungszeitpunkten****1.1.1. Gesamtpopulation****PROMIS Parent Proxy Global Health 7+2 – Repeated measures analysis
Full Analysis Set - L**

Scale: Global Health Scores

Time point	Treatment Groups						Comparison		
	N*	Dabrafenib+Trametinib (N=73)		N*	Carboplatin+Vincristine (N=37)		Difference/ Parameter	[95% CI]	p-value
		LS Means (SE)	[95% CI]		LS Means (SE)	[95% CI]			
Week 5 Day 1	50	0.2 (1.02)	[-1.78, 2.26]	18	-3.2 (1.67)	[-6.52, 0.14]	3.43 ^a	[-0.47, 7.33]	0.084
Week 8 Day 1	53	1.2 (0.97)	[-0.69, 3.17]	18	-4.6 (1.63)	[-7.84, -1.36]	5.84 ^a	[2.07, 9.60]	0.003
Week 16 Day 1	48	1.7 (1.08)	[-0.44, 3.89]	10	-6.1 (2.11)	[-10.35, -1.93]	7.86 ^a	[3.13, 12.59]	0.001
Week 24 Day 1	46	3.1 (1.17)	[0.80, 5.45]	10	-7.3 (2.34)	[-11.96, -2.66]	10.44 ^a	[5.24, 15.64]	<0.001
Week 32 Day 1	47	2.9 (1.06)	[0.77, 4.99]	11	-5.5 (2.03)	[-9.57, -1.46]	8.40 ^a	[3.82, 12.97]	<0.001
Week 48 Day 1	43	2.2 (1.12)	[-0.08, 4.40]	10	-5.4 (2.19)	[-9.71, -1.00]	7.52 ^a	[2.63, 12.42]	0.003
End Of Treatment	50	2.6 (1.29)	[-0.01, 5.12]	14	-3.9 (2.34)	[-8.59, 0.71]	6.49 ^a	[1.18, 11.80]	0.017
Overall treatment effect	60	2.0 (0.88)	[0.23, 3.75]	23	-5.2 (1.55)	[-8.24, -2.06]	7.14 ^b	[3.58, 10.70]	<0.001

Analogous to CSR table 14.2-7.3L.

N*: Number of patients included in the analysis.

MMRM on change from baseline in adjusted for treatment, baseline value, visit and interaction between treatment and visit.

a: LS-Means: difference of Least Squares Means between D+T and C+V group.

b: Parameter displayed for treatment group comparison: "Treatment" effect from the MMRM model.

The analysis only includes assessment time-points where there are at least 10 evaluable subjects on each of the treatment groups.

Patients with baseline scores and at least one non-missing post-baseline assessment are included in the analysis.

MMRM: Mixed Model for Repeated Measures, LS Mean: Least Square Mean, SE: Standard Error, CI: Confidence Interval.

**PROMIS Parent Proxy Global Health 7+2 – Repeated measures analysis
Full Analysis Set - L**

Scale: Pain Scores

Time point	Treatment Groups						Comparison		
	N*	Dabrafenib+Trametinib (N=73)		N*	Carboplatin+Vincristine (N=37)		Difference/ Parameter	[95% CI]	p-value
		LS Means (SE)	[95% CI]		LS Means (SE)	[95% CI]			
Week 5 Day 1	51	-1.5 (0.97)	[-3.45, 0.41]	18	-0.8 (1.63)	[-4.07, 2.42]	-0.69 ^a	[-4.47, 3.09]	0.717
Week 8 Day 1	54	-2.0 (0.89)	[-3.81, -0.25]	18	-1.7 (1.56)	[-4.77, 1.43]	-0.36 ^a	[-3.93, 3.22]	0.844
Week 16 Day 1	48	-1.7 (0.92)	[-3.56, 0.11]	10	-1.0 (1.98)	[-5.01, 2.92]	-0.68 ^a	[-5.05, 3.69]	0.758
Week 24 Day 1	46	-1.5 (1.02)	[-3.51, 0.57]	10	-0.6 (2.06)	[-4.72, 3.49]	-0.86 ^a	[-5.44, 3.72]	0.710
Week 32 Day 1	47	-3.0 (0.93)	[-4.85, -1.11]	11	-2.9 (1.90)	[-6.68, 0.91]	-0.09 ^a	[-4.33, 4.14]	0.965
Week 48 Day 1	43	-2.2 (0.90)	[-3.99, -0.39]	10	-0.7 (1.82)	[-4.38, 2.89]	-1.45 ^a	[-5.51, 2.61]	0.478
End Of Treatment	50	-0.4 (0.94)	[-2.27, 1.48]	14	1.4 (1.76)	[-2.09, 4.92]	-1.81 ^a	[-5.78, 2.16]	0.366
Overall treatment effect	60	-1.8 (0.62)	[-2.99, -0.53]	23	-0.9 (1.13)	[-3.15, 1.33]	-0.85 ^b	[-3.40, 1.71]	0.512

Analogous to CSR table 14.2-7.3L.

N*: Number of patients included in the analysis.

MMRM on change from baseline in adjusted for treatment, baseline value, visit and interaction between treatment and visit.

a: LS-Means: difference of Least Squares Means between D+T and C+V group.

b: Parameter displayed for treatment group comparison: "Treatment" effect from the MMRM model.

The analysis only includes assessment time-points where there are at least 10 evaluable subjects on each of the treatment groups.

Patients with baseline scores and at least one non-missing post-baseline assessment are included in the analysis.

MMRM: Mixed Model for Repeated Measures, LS Mean: Least Square Mean, SE: Standard Error, CI: Confidence Interval.

**PROMIS Parent Proxy Global Health 7+2 – Repeated measures analysis
Full Analysis Set - L**

Scale: Fatigue Scores

Time point	Treatment Groups						Comparison		
	N*	Dabrafenib+Trametinib (N=73)		N*	Carboplatin+Vincristine (N=37)		Difference/ Parameter	[95% CI]	p-value
		LS Means (SE)	[95% CI]		LS Means (SE)	[95% CI]			
Week 5 Day 1	51	0.4 (0.91)	[-1.46, 2.17]	18	2.8 (1.51)	[-0.16, 5.85]	-2.49 ^a	[-6.00, 1.02]	0.162
Week 8 Day 1	54	-0.4 (0.83)	[-2.04, 1.27]	18	4.5 (1.40)	[1.71, 7.28]	-4.88 ^a	[-8.12, -1.64]	0.004
Week 16 Day 1	48	-1.6 (0.86)	[-3.29, 0.13]	10	5.1 (1.73)	[1.61, 8.50]	-6.63 ^a	[-10.48, -2.78]	<0.001
Week 24 Day 1	46	-1.6 (1.02)	[-3.68, 0.42]	10	1.9 (2.11)	[-2.27, 6.16]	-3.57 ^a	[-8.26, 1.12]	0.133
Week 32 Day 1	47	-0.4 (0.87)	[-2.18, 1.28]	11	4.3 (1.74)	[0.83, 7.77]	-4.75 ^a	[-8.63, -0.86]	0.017
Week 48 Day 1	43	-0.8 (1.02)	[-2.82, 1.27]	10	0.6 (2.07)	[-3.53, 4.76]	-1.39 ^a	[-6.02, 3.23]	0.549
End Of Treatment	50	-1.4 (0.91)	[-3.17, 0.46]	14	3.2 (1.70)	[-0.18, 6.59]	-4.56 ^a	[-8.40, -0.72]	0.021
Overall treatment effect	60	-0.8 (0.63)	[-2.08, 0.42]	23	3.2 (1.11)	[1.01, 5.40]	-4.04 ^b	[-6.57, -1.51]	0.002

Analogous to CSR table 14.2-7.3L.

N*: Number of patients included in the analysis.

MMRM on change from baseline in adjusted for treatment, baseline value, visit and interaction between treatment and visit.

a: LS-Means: difference of Least Squares Means between D+T and C+V group.

b: Parameter displayed for treatment group comparison: "Treatment" effect from the MMRM model.

The analysis only includes assessment time-points where there are at least 10 evaluable subjects on each of the treatment groups.

Patients with baseline scores and at least one non-missing post-baseline assessment are included in the analysis.

MMRM: Mixed Model for Repeated Measures, LS Mean: Least Square Mean, SE: Standard Error, CI: Confidence Interval.

1.1.2. Patienten ab 5 Jahren**PROMIS Parent Proxy Global Health 7+2 – Repeated measures analysis for patients aged >= 5 years
Full Analysis Set - L**

Scale: Global Health Scores

Time point	Treatment Groups						Comparison		
	N*	Dabrafenib+Trametinib (N=58)		N*	Carboplatin+Vincristine (N=27)		Difference/ Parameter	[95% CI]	p-value
		LS Means (SE)	[95% CI]		LS Means (SE)	[95% CI]			
Week 5 Day 1	41	-0.7 (1.17)	[-3.06, 1.64]	15	-4.1 (1.96)	[-8.04, -0.22]	3.42 ^a	[-1.14, 7.99]	0.139
Week 8 Day 1	41	0.8 (1.15)	[-1.54, 3.06]	13	-5.6 (1.99)	[-9.56, -1.60]	6.34 ^a	[1.74, 10.94]	0.008
End Of Treatment	41	2.3 (1.54)	[-0.82, 5.36]	12	-4.4 (2.79)	[-9.97, 1.18]	6.66 ^a	[0.29, 13.03]	0.041
Overall treatment effect	47	1.6 (1.04)	[-0.47, 3.70]	17	-6.3 (1.90)	[-10.05, -2.47]	7.88 ^b	[3.55, 12.20]	<0.001

Analogous to CSR table 14.2-7.3L, but for patients aged >= 5 years.

N*: Number of patients included in the analysis.

MMRM on change from baseline in adjusted for treatment, baseline value, visit and interaction between treatment and visit.

a: LS-Means: difference of Least Squares Means between D+T and C+V group.

b: Parameter displayed for treatment group comparison: "Treatment" effect from the MMRM model.

The analysis only includes assessment time-points where there are at least 10 evaluable subjects on each of the treatment groups.

Patients with baseline scores and at least one non-missing post-baseline assessment are included in the analysis.

MMRM: Mixed Model for Repeated Measures, LS Mean: Least Square Mean, SE: Standard Error, CI: Confidence Interval.

**PROMIS Parent Proxy Global Health 7+2 – Repeated measures analysis for patients aged ≥ 5 years
Full Analysis Set - L**

Scale: Pain Scores

Time point	Treatment Groups						Comparison		
	Dabrafenib+Trametinib (N=58)			Carboplatin+Vincristine (N=27)			Difference/ Parameter	[95% CI]	p-value
	N*	LS Means (SE)	[95% CI]	N*	LS Means (SE)	[95% CI]			
Week 5 Day 1	41	-1.8 (1.16)	[-4.07, 0.56]	15	-0.4 (1.91)	[-4.21, 3.44]	-1.37 ^a	[-5.84, 3.11]	0.543
Week 8 Day 1	42	-2.7 (1.04)	[-4.75, -0.60]	13	-2.0 (1.88)	[-5.75, 1.80]	-0.70 ^a	[-5.01, 3.61]	0.746
End Of Treatment	41	-0.5 (1.04)	[-2.62, 1.56]	12	0.2 (1.91)	[-3.61, 4.06]	-0.76 ^a	[-5.12, 3.61]	0.729
Overall treatment effect	47	-2.5 (0.70)	[-3.88, -1.08]	17	-2.0 (1.34)	[-4.64, 0.71]	-0.52 ^b	[-3.54, 2.51]	0.734

Analogous to CSR table 14.2-7.3L, but for patients aged ≥ 5 years.

N*: Number of patients included in the analysis.

MMRM on change from baseline in adjusted for treatment, baseline value, visit and interaction between treatment and visit.

a: LS-Means: difference of Least Squares Means between D+T and C+V group.

b: Parameter displayed for treatment group comparison: "Treatment" effect from the MMRM model.

The analysis only includes assessment time-points where there are at least 10 evaluable subjects on each of the treatment groups.

Patients with baseline scores and at least one non-missing post-baseline assessment are included in the analysis.

MMRM: Mixed Model for Repeated Measures, LS Mean: Least Square Mean, SE: Standard Error, CI: Confidence Interval.

PROMIS Parent Proxy Global Health 7+2 – Repeated measures analysis for patients aged >= 5 years
Full Analysis Set - L

Scale: Fatigue Scores

Time point	Treatment Groups						Comparison		
	Dabrafenib+Trametinib (N=58)			Carboplatin+Vincristine (N=27)			Difference/ Parameter	[95% CI]	p-value
	N*	LS Means (SE)	[95% CI]	N*	LS Means (SE)	[95% CI]			
Week 5 Day 1	41	0.9 (1.00)	[-1.07, 2.92]	15	3.9 (1.65)	[0.57, 7.16]	-2.94 ^a	[-6.79, 0.91]	0.132
Week 8 Day 1	42	-0.2 (1.02)	[-2.28, 1.79]	13	4.3 (1.77)	[0.73, 7.81]	-4.51 ^a	[-8.60, -0.43]	0.031
End Of Treatment	41	-1.6 (1.09)	[-3.78, 0.60]	12	2.7 (2.00)	[-1.32, 6.72]	-4.29 ^a	[-8.87, 0.28]	0.065
Overall treatment effect	47	-1.0 (0.77)	[-2.58, 0.50]	17	2.9 (1.40)	[0.14, 5.74]	-3.98 ^b	[-7.17, -0.78]	0.015

Analogous to CSR table 14.2-7.3L, but for patients aged >= 5 years.

N*: Number of patients included in the analysis.

MMRM on change from baseline in adjusted for treatment, baseline value, visit and interaction between treatment and visit.

a: LS-Means: difference of Least Squares Means between D+T and C+V group.

b: Parameter displayed for treatment group comparison: "Treatment" effect from the MMRM model.

The analysis only includes assessment time-points where there are at least 10 evaluable subjects on each of the treatment groups.

Patients with baseline scores and at least one non-missing post-baseline assessment are included in the analysis.

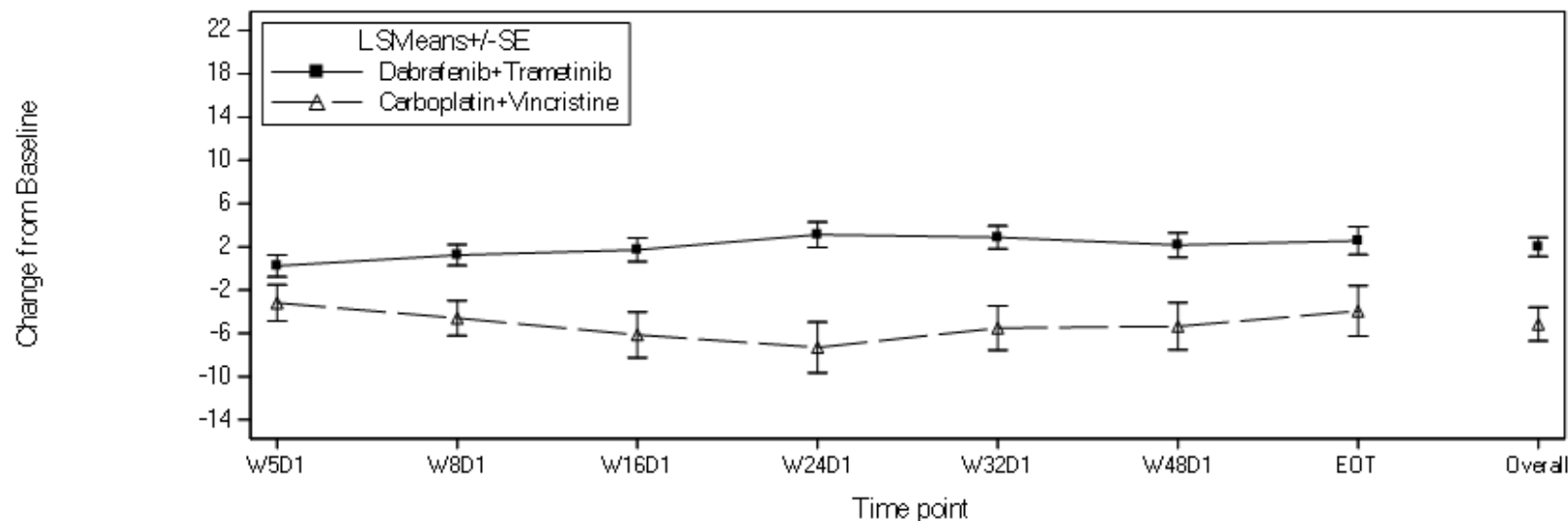
MMRM: Mixed Model for Repeated Measures, LS Mean: Least Square Mean, SE: Standard Error, CI: Confidence Interval.

1.2. Graphische Darstellung der Veränderung der T-Scores gegenüber Studienbeginn mittels MMRM-Analyse zu den verschiedenen Erhebungszeitpunkten

1.2.1. Gesamtpopulation

PROMIS Parent Proxy Global Health 7+2 - Time profile (change from baseline)
(Full Analysis Set - L)

Scale: Global Health Scores



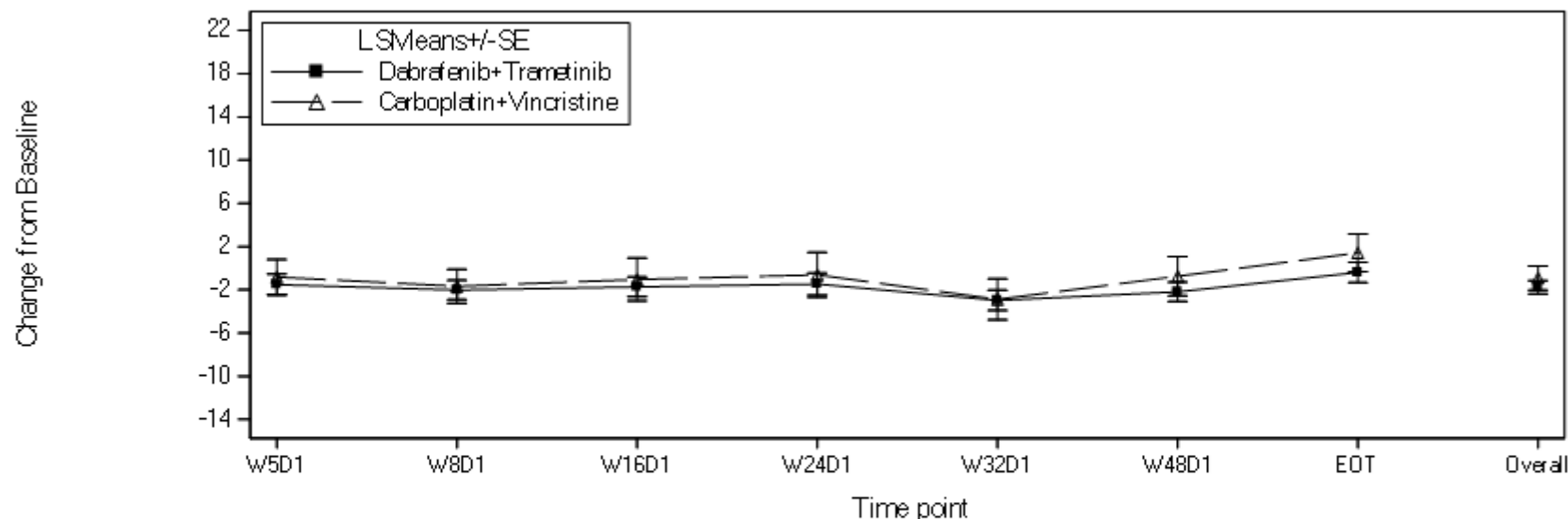
Number of patients with measurement at time point

Dabrafenib+Trametinib	50	53	48	46	47	43	50	60
Carboplatin+Vincristine	18	18	10	10	11	10	14	23

Mixed effects model includes terms for treatment, visit and baseline score as main effects and an interaction term for visit and treatment. The analysis only includes assessment time-points where there are at least 10 evaluable subjects on each of the treatment groups. Baseline is defined as the last assessment on or prior to first treatment date. LS Mean: Least Square Mean, SE: Standard Error, EOT: End Of Treatment.

PROMIS Parent Proxy Global Health 7+2 - Time profile (change from baseline)
(Full Analysis Set - L)

Scale: Pain Scores

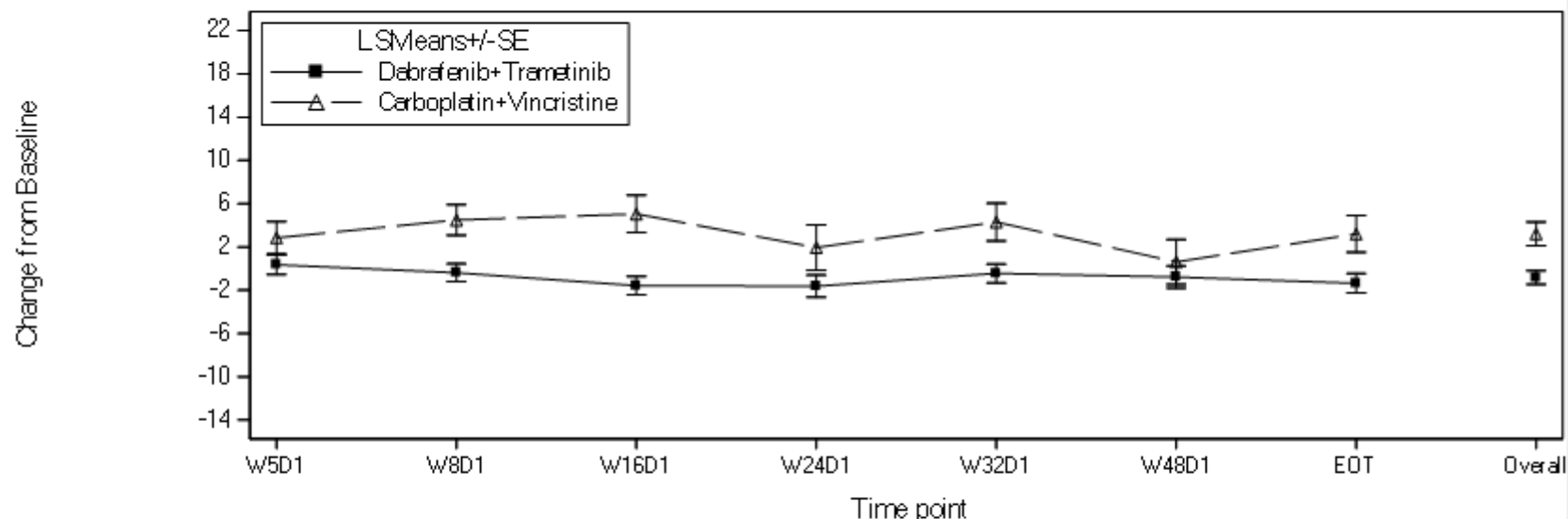


	Number of patients with measurement at time point							
	W5D1	W8D1	W16D1	W24D1	W32D1	W48D1	EOT	Overall
Dabrafenib+Trametinib	51	54	48	46	47	43	50	60
Carboplatin+Vincristine	18	18	10	10	11	10	14	23

Mixed effects model includes terms for treatment, visit and baseline score as main effects and an interaction term for visit and treatment. The analysis only includes assessment time-points where there are at least 10 evaluable subjects on each of the treatment groups. Baseline is defined as the last assessment on or prior to first treatment date. LS Mean: Least Square Mean, SE: Standard Error, EOT: End Of Treatment.

PROMIS Parent Proxy Global Health 7+2 - Time profile (change from baseline)
(Full Analysis Set - L)

Scale: Fatigue Scores



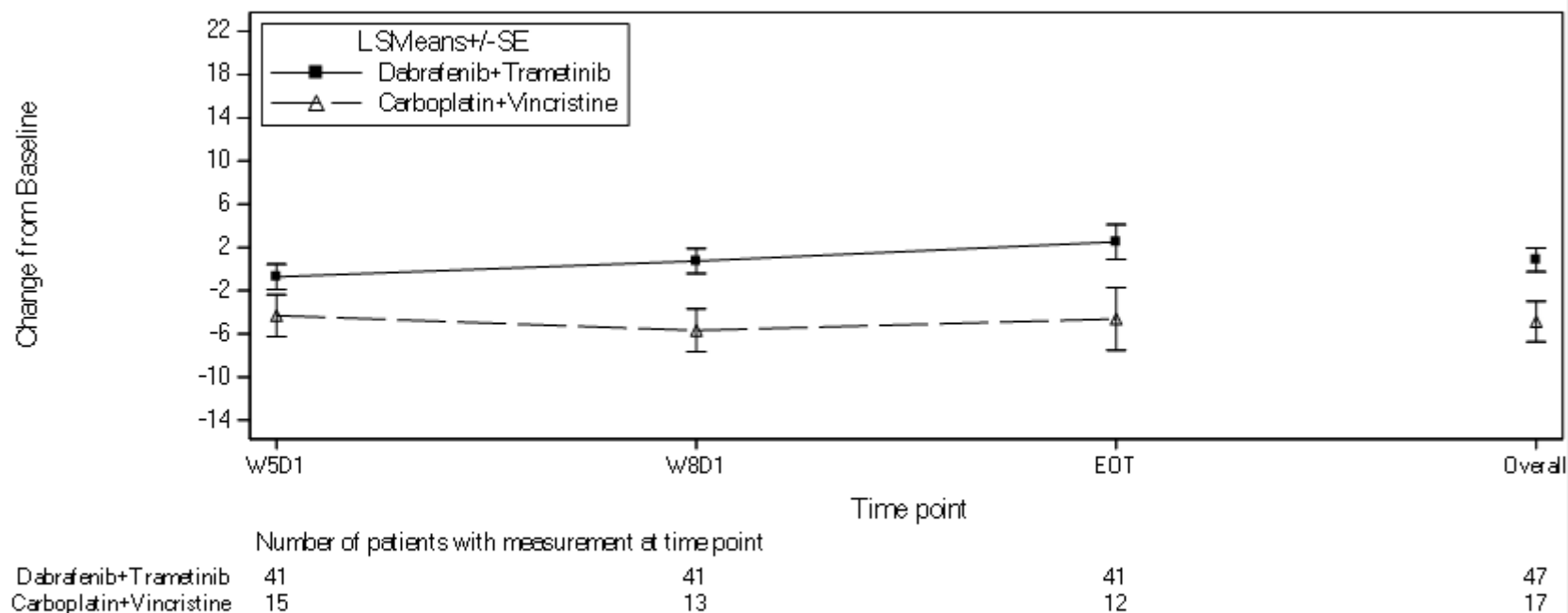
	Number of patients with measurement at time point							
	W5D1	W8D1	W16D1	W24D1	W32D1	W48D1	EOT	Overall
Dabrafenib+Trametinib	51	54	48	46	47	43	50	60
Carboplatin+Vincristine	18	18	10	10	11	10	14	23

Mixed effects model includes terms for treatment, visit and baseline score as main effects and an interaction term for visit and treatment. The analysis only includes assessment time-points where there are at least 10 evaluable subjects on each of the treatment groups. Baseline is defined as the last assessment on or prior to first treatment date. LS Mean: Least Square Mean, SE: Standard Error, EOT: End Of Treatment.

1.2.2. Patienten ab 5 Jahren

FROMISParent Proxy Global Health 7+2 - Time profile (change from baseline) for patients aged >= 5 years (Full Analysis Set - L)

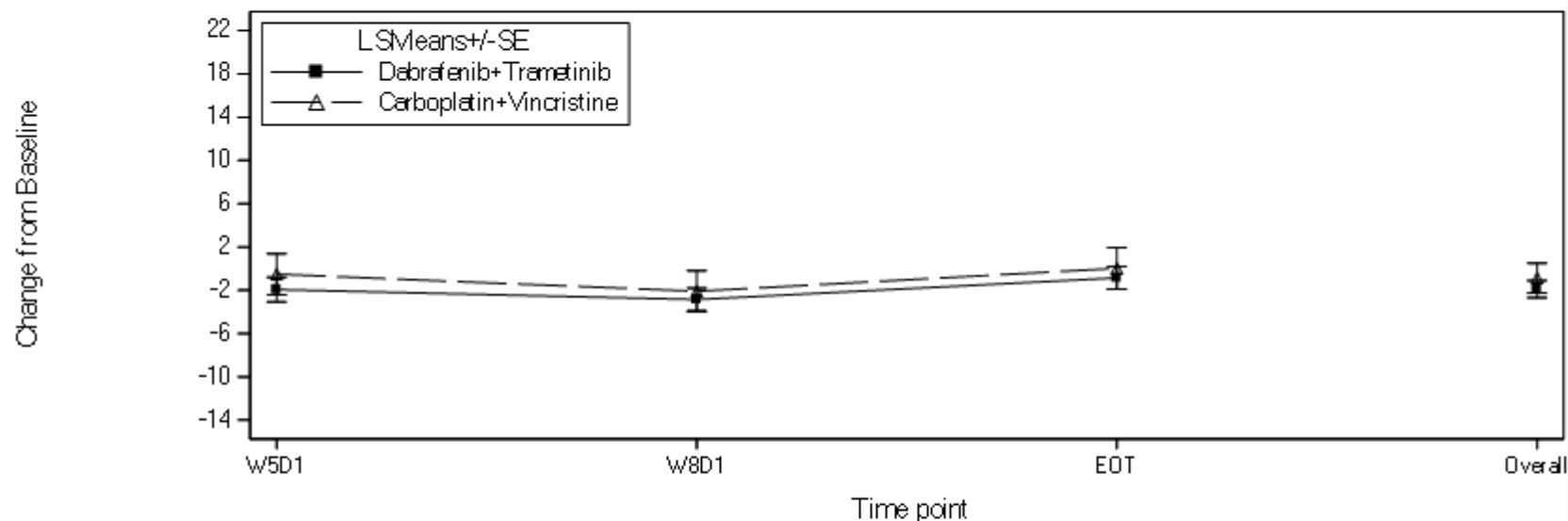
Scale: Global Health Scores



Mixed effects model includes terms for treatment, visit and baseline score as main effects and an interaction term for visit and treatment. The analysis only includes assessment time-points where there are at least 10 evaluable subjects on each of the treatment groups. Baseline is defined as the last assessment on or prior to first treatment date. LS Mean: Least Square Mean, SE: Standard Error, EOT: End Of Treatment.

PROMIS Parent Proxy Global Health 7+2 - Time profile (change from baseline) for patients aged >= 5 years (Full Analysis Set - L)

Scale: Pain Scores

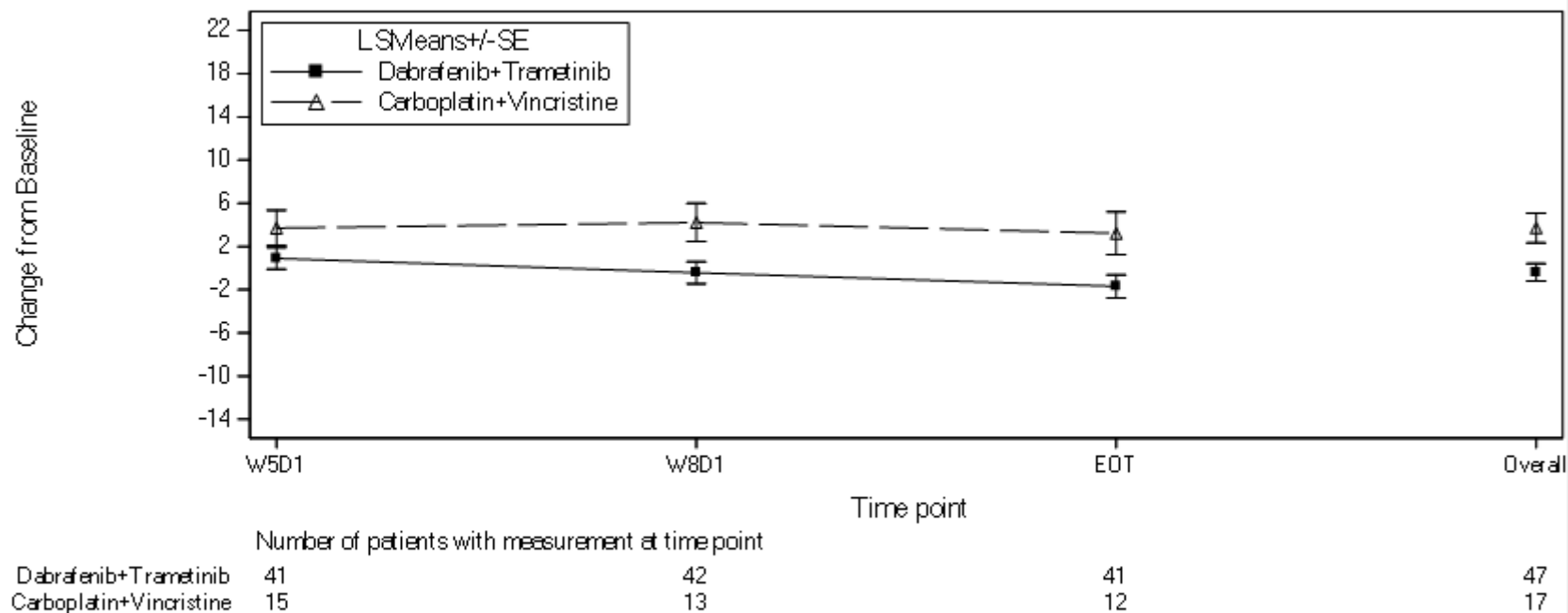


	Number of patients with measurement at time point			
Dabrafenib+Trametinib	41	42	41	47
Carboplatin+Vincristine	15	13	12	17

Mixed effects model includes terms for treatment, visit and baseline score as main effects and an interaction term for visit and treatment. The analysis only includes assessment time-points where there are at least 10 evaluable subjects on each of the treatment groups. Baseline is defined as the last assessment on or prior to first treatment date. LS Mean: Least Square Mean, SE: Standard Error, EOT: End Of Treatment.

FROMISParent Proxy Global Health 7+2 - Time profile (change from baseline) for patients aged ≥ 5 years (Full Analysis Set - L)

Scale: Fatigue Scores



Mixed effects model includes terms for treatment, visit and baseline score as main effects and an interaction term for visit and treatment. The analysis only includes assessment time-points where there are at least 10 evaluable subjects on each of the treatment groups. Baseline is defined as the last assessment on or prior to first treatment date. LS Mean: Least Square Mean, SE: Standard Error, EOT: End Of Treatment.

1.3. Deskriptive Darstellung der T-Scores sowie der Änderung gegenüber Studienbeginn zu den verschiedenen Erhebungszeitpunkten

1.3.1. Gesamtpopulation

PROMIS Parent Proxy Global Health – T-Scores by time point Full Analysis Set - L

Scale: Global Health Scores

Time point	Statistics	Dabrafenib+Trametinib N=73		Carboplatin+Vincristine N=37	
		Raw value	Change from baseline	Raw value	Change from baseline
Baseline	n	61		23	
	Mean (SD)	42.67 (10.068)		42.89 (10.502)	
	Median	41.70		41.70	
	Q1-Q3	37.90 - 49.30		34.60 - 54.50	
	Min-Max	19.4 - 63.2		27.7 - 63.2	
Week 5 Day 1	n	50	50	18	18
	Mean (SD)	42.14 (9.439)	-0.39 (7.960)	39.06 (10.109)	-4.15 (9.529)
	Median	39.70	0.00	36.20	-1.00
	Q1-Q3	36.20 - 49.30	-3.80 - 5.20	32.90 - 45.40	-10.10 - 0.00
	Min-Max	24.4 - 66.1	-21.5 - 22.5	22.7 - 60.2	-24.4 - 10.3
Week 8 Day 1	n	53	53	18	18
	Mean (SD)	43.83 (9.461)	1.61 (8.008)	38.36 (7.759)	-4.77 (10.293)
	Median	41.70	1.70	37.05	-3.40
	Q1-Q3	37.90 - 49.30	-3.80 - 5.70	32.90 - 43.60	-8.50 - 0.00

Baseline is defined as the last assessment on or prior to first treatment date.

PROMIS Parent Proxy Global Health – T-Scores by time point
Full Analysis Set - L

Scale: Global Health Scores

Time point	Statistics	Dabrafenib+Trametinib N=73		Carboplatin+Vincristine N=37	
		Raw value	Change from baseline	Raw value	Change from baseline
	Min-Max	24.4 - 66.1	-16.4 - 20.3	26.1 - 54.5	-28.6 - 10.9
Week 16 Day 1	n	48	48	10	10
	Mean (SD)	44.68 (9.159)	1.87 (8.555)	41.11 (10.798)	-2.99 (9.422)
	Median	44.50	0.85	40.70	-3.80
	Q1-Q3	37.90 - 49.30	-3.30 - 7.50	32.90 - 45.40	-5.00 - 3.50
	Min-Max	24.4 - 66.1	-14.7 - 30.8	24.4 - 63.2	-24.4 - 8.7
Week 24 Day 1	n	46	46	10	10
	Mean (SD)	45.27 (9.168)	3.35 (11.470)	36.57 (6.241)	-5.37 (7.559)
	Median	43.60	0.00	36.25	-2.65
	Q1-Q3	37.90 - 51.80	-1.70 - 6.80	34.60 - 39.70	-5.70 - -1.60
	Min-Max	32.9 - 66.1	-22.3 - 45.1	26.1 - 47.3	-22.7 - 1.7
Week 32 Day 1	n	47	47	11	11
	Mean (SD)	45.46 (8.887)	2.29 (9.291)	40.96 (7.159)	-2.94 (6.539)

Baseline is defined as the last assessment on or prior to first treatment date.

PROMIS Parent Proxy Global Health – T-Scores by time point
Full Analysis Set - L

Scale: Global Health Scores

Time point	Statistics	Dabrafenib+Trametinib N=73		Carboplatin+Vincristine N=37	
		Raw value	Change from baseline	Raw value	Change from baseline
	Median	45.40	2.00	41.70	-3.70
	Q1-Q3	37.90 - 49.30	-2.00 - 5.70	36.20 - 45.40	-5.70 - 1.70
	Min-Max	31.2 - 66.1	-20.5 - 45.1	31.2 - 54.5	-13.7 - 6.8
Week 40 Day 1	n	40	40	7	7
	Mean (SD)	45.37 (9.687)	3.02 (10.195)	38.84 (4.960)	-6.26 (11.903)
	Median	43.60	3.00	37.90	-3.70
	Q1-Q3	38.80 - 49.30	-2.00 - 7.55	36.20 - 41.70	-18.30 - 1.70
	Min-Max	27.7 - 66.1	-17.8 - 45.1	31.2 - 47.3	-26.1 - 8.5
Week 48 Day 1	n	43	43	10	10
	Mean (SD)	44.83 (9.421)	2.51 (10.028)	41.56 (6.953)	-3.11 (8.228)
	Median	43.60	1.90	42.65	-1.85
	Q1-Q3	37.90 - 49.30	-3.80 - 5.90	34.60 - 47.30	-2.70 - 0.00
	Min-Max	27.7 - 66.1	-14.7 - 39.2	32.9 - 51.8	-24.4 - 5.2

Baseline is defined as the last assessment on or prior to first treatment date.

PROMIS Parent Proxy Global Health – T-Scores by time point
Full Analysis Set - L

Scale: Global Health Scores

Time point	Statistics	Dabrafenib+Trametinib N=73		Carboplatin+Vincristine N=37	
		Raw value	Change from baseline	Raw value	Change from baseline
Week 56 Day 1	n	46	46	7	7
	Mean (SD)	44.54 (8.876)	2.29 (7.741)	38.66 (8.851)	-4.91 (8.903)
	Median	43.60	1.90	36.20	-2.70
	Q1-Q3	37.90 - 47.30	-2.00 - 6.80	32.90 - 47.30	-3.70 - -1.60
	Min-Max	31.2 - 66.1	-15.9 - 26.3	26.1 - 51.8	-24.4 - 3.3
Week 72 Day 1	n	40	40	0	0
	Mean (SD)	44.21 (8.967)	2.64 (7.060)		
	Median	44.50	1.85		
	Q1-Q3	37.05 - 49.30	-2.00 - 6.35		
	Min-Max	29.4 - 66.1	-11.4 - 21.1		
Week 88 Day 1	n	38	38	0	0
	Mean (SD)	44.91 (8.847)	2.35 (6.239)		
	Median	43.60	2.90		
	Q1-Q3	37.90 - 49.30	-2.00 - 5.90		

Baseline is defined as the last assessment on or prior to first treatment date.

**PROMIS Parent Proxy Global Health – T-Scores by time point
Full Analysis Set - L**

Scale: Global Health Scores

Time point	Statistics	Dabrafenib+Trametinib N=73		Carboplatin+Vincristine N=37	
		Raw value	Change from baseline	Raw value	Change from baseline
	Min-Max	31.2 - 66.1	-12.9 - 16.6		
Week 104 Day 1	n	39	39	0	0
	Mean (SD)	45.60 (8.231)	2.86 (7.761)		
	Median	45.40	1.80		
	Q1-Q3	39.70 - 49.30	-2.90 - 8.50		
	Min-Max	31.2 - 66.1	-10.9 - 19.6		
Week 120 Day 1	n	33	33	0	0
	Mean (SD)	44.41 (7.317)	2.55 (6.805)		
	Median	45.40	1.70		
	Q1-Q3	37.90 - 47.30	-1.70 - 7.60		
	Min-Max	32.9 - 60.2	-14.8 - 16.1		
Week 136 Day 1	n	24	24	0	0
	Mean (SD)	44.45 (8.074)	1.00 (9.146)		

Baseline is defined as the last assessment on or prior to first treatment date.

**PROMIS Parent Proxy Global Health – T-Scores by time point
Full Analysis Set - L**

Scale: Global Health Scores

Time point	Statistics	Dabrafenib+Trametinib N=73		Carboplatin+Vincristine N=37	
		Raw value	Change from baseline	Raw value	Change from baseline
	Median	43.55	0.85		
	Q1-Q3	37.05 - 49.30	-6.40 - 7.60		
	Min-Max	32.9 - 66.1	-11.4 - 20.7		
Week 152 Day 1	n	17	17	0	0
	Mean (SD)	47.88 (10.534)	5.79 (11.549)		
	Median	47.30	5.00		
	Q1-Q3	39.70 - 54.50	0.00 - 12.70		
	Min-Max	31.2 - 66.1	-11.9 - 28.2		
Week 168 Day 1	n	13	13	0	0
	Mean (SD)	46.48 (9.888)	5.22 (12.687)		
	Median	49.30	8.80		
	Q1-Q3	39.70 - 51.80	-7.10 - 13.60		
	Min-Max	29.4 - 66.1	-12.3 - 28.2		

Baseline is defined as the last assessment on or prior to first treatment date.

PROMIS Parent Proxy Global Health – T-Scores by time point
Full Analysis Set - L

Scale: Global Health Scores

Time point	Statistics	Dabrafenib+Trametinib N=73		Carboplatin+Vincristine N=37	
		Raw value	Change from baseline	Raw value	Change from baseline
End Of Treatment	n	50	50	14	14
	Mean (SD)	44.98 (10.274)	2.90 (11.382)	39.69 (10.536)	-5.21 (13.276)
	Median	45.40	0.80	37.90	-2.75
	Q1-Q3	37.90 - 51.80	-3.80 - 7.50	31.20 - 47.30	-10.00 - 0.00
	Min-Max	27.7 - 66.1	-17.6 - 30.8	26.1 - 63.2	-32.0 - 19.6
Post Treatment Follow-Up 1	n	1	1	4	4
	Mean (SD)	45.40 (NE)	-3.90 (NE)	45.53 (6.288)	-3.95 (6.984)
	Median	45.40	-3.90	48.30	-5.75
	Q1-Q3	45.40 - 45.40	-3.90 - -3.90	41.75 - 49.30	-9.00 - 1.10
	Min-Max	45.4 - 45.4	-3.9 - -3.9	36.2 - 49.3	-10.0 - 5.7
Post Treatment Follow-Up 2	n	1	1	1	1

Baseline is defined as the last assessment on or prior to first treatment date.

PROMIS Parent Proxy Global Health – T-Scores by time point
Full Analysis Set - L

Scale: Global Health Scores

Time point	Statistics	Dabrafenib+Trametinib N=73		Carboplatin+Vincristine N=37	
		Raw value	Change from baseline	Raw value	Change from baseline
	Mean (SD)	27.70 (NE)	-1.70 (NE)	39.70 (NE)	-3.90 (NE)
	Median	27.70	-1.70	39.70	-3.90
	Q1-Q3	27.70 - 27.70	-1.70 - -1.70	39.70 - 39.70	-3.90 - -3.90
	Min-Max	27.7 - 27.7	-1.7 - -1.7	39.7 - 39.7	-3.9 - -3.9
Post Treatment Follow-Up 3	n	1	1	1	1
	Mean (SD)	43.60 (NE)	14.20 (NE)	34.60 (NE)	1.70 (NE)
	Median	43.60	14.20	34.60	1.70
	Q1-Q3	43.60 - 43.60	14.20 - 14.20	34.60 - 34.60	1.70 - 1.70
	Min-Max	43.6 - 43.6	14.2 - 14.2	34.6 - 34.6	1.7 - 1.7
Post Treatment Follow-Up 4	n	1	1	2	2
	Mean (SD)	31.20 (NE)	1.80 (NE)	43.60 (8.061)	-0.90 (1.273)
	Median	31.20	1.80	43.60	-0.90

Baseline is defined as the last assessment on or prior to first treatment date.

PROMIS Parent Proxy Global Health – T-Scores by time point
Full Analysis Set - L

Scale: Global Health Scores

Time point	Statistics	Dabrafenib+Trametinib N=73		Carboplatin+Vincristine N=37	
		Raw value	Change from baseline	Raw value	Change from baseline
	Q1-Q3	31.20 - 31.20	1.80 - 1.80	37.90 - 49.30	-1.80 - 0.00
	Min-Max	31.2 - 31.2	1.8 - 1.8	37.9 - 49.3	-1.8 - 0.0
Post Treatment Follow-Up 5	n	1	1	1	1
	Mean (SD)	29.40 (NE)	0.00 (NE)	37.90 (NE)	5.00 (NE)
	Median	29.40	0.00	37.90	5.00
	Q1-Q3	29.40 - 29.40	0.00 - 0.00	37.90 - 37.90	5.00 - 5.00
	Min-Max	29.4 - 29.4	0.0 - 0.0	37.9 - 37.9	5.0 - 5.0
Post Treatment Follow-Up 6	n	0	0	2	2
	Mean (SD)			36.45 (7.425)	0.15 (2.616)
	Median			36.45	0.15
	Q1-Q3			31.20 - 41.70	-1.70 - 2.00
	Min-Max			31.2 - 41.7	-1.7 - 2.0

Baseline is defined as the last assessment on or prior to first treatment date.

**PROMIS Parent Proxy Global Health – T-Scores by time point
Full Analysis Set - L**

Scale: Global Health Scores

Time point	Statistics	Dabrafenib+Trametinib N=73		Carboplatin+Vincristine N=37	
		Raw value	Change from baseline	Raw value	Change from baseline
Post Treatment	n	0	0	1	1
Follow-Up 8	Mean (SD)			37.90 (NE)	5.00 (NE)
	Median			37.90	5.00
	Q1-Q3			37.90 - 37.90	5.00 - 5.00
	Min-Max			37.9 - 37.9	5.0 - 5.0

Baseline is defined as the last assessment on or prior to first treatment date.

PROMIS Parent Proxy Global Health – T-Scores by time point
Full Analysis Set - L

Scale: Pain Scores

Time point	Statistics	Dabrafenib+Trametinib N=73		Carboplatin+Vincristine N=37	
		Raw value	Change from baseline	Raw value	Change from baseline
Baseline	n	61		23	
	Mean (SD)	52.14 (7.658)		52.64 (7.054)	
	Median	53.05		53.05	
	Q1-Q3	43.25 - 58.51		43.25 - 58.51	
	Min-Max	43.3 - 68.8		43.3 - 63.5	
Week 5 Day 1	n	51	51	18	18
	Mean (SD)	50.11 (7.275)	-1.70 (9.536)	50.97 (6.263)	-0.64 (8.044)
	Median	53.05	0.00	53.05	0.00
	Q1-Q3	43.25 - 53.05	-9.80 - 0.00	43.25 - 53.05	0.00 - 0.00
	Min-Max	43.3 - 68.8	-25.5 - 20.2	43.3 - 63.5	-15.3 - 9.8
Week 8 Day 1	n	54	54	18	18
	Mean (SD)	49.93 (7.727)	-1.58 (7.477)	51.00 (6.037)	-2.61 (9.397)
	Median	43.25	0.00	53.05	0.00
	Q1-Q3	43.25 - 53.05	-5.30 - 0.00	43.25 - 53.05	-9.80 - 0.00

Baseline is defined as the last assessment on or prior to first treatment date.

PROMIS Parent Proxy Global Health – T-Scores by time point
Full Analysis Set - L

Scale: Pain Scores

Time point	Statistics	Dabrafenib+Trametinib N=73		Carboplatin+Vincristine N=37	
		Raw value	Change from baseline	Raw value	Change from baseline
	Min-Max	43.3 - 68.8	-15.3 - 20.2	43.3 - 58.5	-20.2 - 15.3
Week 16 Day 1	n	48	48	10	10
	Mean (SD)	49.72 (7.300)	-1.68 (6.821)	51.75 (6.330)	-2.57 (10.454)
	Median	48.15	0.00	53.05	-2.73
	Q1-Q3	43.25 - 53.05	-5.46 - 0.00	43.25 - 58.51	-9.80 - 5.46
	Min-Max	43.3 - 68.8	-15.7 - 15.3	43.3 - 58.5	-20.2 - 9.8
Week 24 Day 1	n	46	46	10	10
	Mean (SD)	50.65 (7.450)	-1.87 (8.595)	51.81 (7.937)	-0.98 (11.671)
	Median	53.05	0.00	53.05	0.00
	Q1-Q3	43.25 - 53.05	-9.80 - 0.00	43.25 - 58.51	-9.80 - 9.80
	Min-Max	43.3 - 68.8	-20.2 - 20.2	43.3 - 63.5	-20.2 - 15.3
Week 32 Day 1	n	47	47	11	11
	Mean (SD)	48.77 (6.647)	-2.82 (9.350)	49.59 (6.387)	-3.27 (5.749)

Baseline is defined as the last assessment on or prior to first treatment date.

PROMIS Parent Proxy Global Health – T-Scores by time point
Full Analysis Set - L

Scale: Pain Scores

Time point	Statistics	Dabrafenib+Trametinib N=73		Carboplatin+Vincristine N=37	
		Raw value	Change from baseline	Raw value	Change from baseline
	Median	43.25	0.00	53.05	0.00
	Q1-Q3	43.25 - 53.05	-9.80 - 0.00	43.25 - 53.05	-5.46 - 0.00
	Min-Max	43.3 - 63.5	-25.5 - 15.3	43.3 - 58.5	-15.3 - 5.5
Week 40 Day 1	n	40	40	7	7
	Mean (SD)	49.87 (6.389)	-0.89 (8.365)	52.52 (7.402)	2.11 (12.241)
	Median	53.05	0.00	53.05	0.00
	Q1-Q3	43.25 - 53.05	-7.63 - 2.73	43.25 - 58.51	-9.80 - 9.80
	Min-Max	43.3 - 58.5	-15.3 - 15.3	43.3 - 63.5	-15.3 - 20.2
Week 48 Day 1	n	43	43	10	10
	Mean (SD)	49.89 (6.581)	-0.70 (7.395)	51.20 (5.903)	-1.64 (8.947)
	Median	53.05	0.00	53.05	-2.73
	Q1-Q3	43.25 - 58.51	-4.97 - 0.00	43.25 - 53.05	-5.46 - 0.00
	Min-Max	43.3 - 58.5	-15.3 - 15.3	43.3 - 58.5	-15.3 - 15.3

Baseline is defined as the last assessment on or prior to first treatment date.

PROMIS Parent Proxy Global Health – T-Scores by time point
Full Analysis Set - L

Scale: Pain Scores

Time point	Statistics	Dabrafenib+Trametinib N=73		Carboplatin+Vincristine N=37	
		Raw value	Change from baseline	Raw value	Change from baseline
Week 56 Day 1	n	46	46	7	7
	Mean (SD)	48.14 (6.496)	-2.73 (7.606)	53.99 (5.466)	0.62 (8.389)
	Median	43.25	0.00	53.05	0.00
	Q1-Q3	43.25 - 53.05	-9.80 - 0.00	53.05 - 58.51	0.00 - 9.80
	Min-Max	43.3 - 63.5	-20.2 - 20.2	43.3 - 58.5	-15.3 - 9.8
Week 72 Day 1	n	40	40	0	0
	Mean (SD)	49.46 (6.498)	-1.81 (8.164)		
	Median	53.05	0.00		
	Q1-Q3	43.25 - 53.05	-9.80 - 0.00		
	Min-Max	43.3 - 63.5	-15.3 - 15.3		
Week 88 Day 1	n	38	38	0	0
	Mean (SD)	47.82 (6.083)	-2.93 (7.523)		
	Median	43.25	0.00		
	Q1-Q3	43.25 - 53.05	-9.80 - 0.00		

Baseline is defined as the last assessment on or prior to first treatment date.

**PROMIS Parent Proxy Global Health – T-Scores by time point
Full Analysis Set - L**

Scale: Pain Scores

Time point	Statistics	Dabrafenib+Trametinib N=73		Carboplatin+Vincristine N=37	
		Raw value	Change from baseline	Raw value	Change from baseline
	Min-Max	43.3 - 63.5	-15.3 - 15.3		
Week 104 Day 1	n	39	39	0	0
	Mean (SD)	48.74 (6.605)	-2.07 (7.390)		
	Median	43.25	0.00		
	Q1-Q3	43.25 - 53.05	-5.46 - 0.00		
	Min-Max	43.3 - 68.8	-20.2 - 15.7		
Week 120 Day 1	n	33	33	0	0
	Mean (SD)	48.56 (7.583)	-3.01 (7.722)		
	Median	43.25	0.00		
	Q1-Q3	43.25 - 53.05	-9.80 - 0.00		
	Min-Max	43.3 - 68.8	-15.3 - 15.7		
Week 136 Day 1	n	24	24	0	0
	Mean (SD)	46.16 (5.305)	-4.18 (6.730)		

Baseline is defined as the last assessment on or prior to first treatment date.

**PROMIS Parent Proxy Global Health – T-Scores by time point
Full Analysis Set - L**

Scale: Pain Scores

Time point	Statistics	Dabrafenib+Trametinib N=73		Carboplatin+Vincristine N=37	
		Raw value	Change from baseline	Raw value	Change from baseline
	Median	43.25	0.00		
	Q1-Q3	43.25 - 48.15	-9.80 - 0.00		
	Min-Max	43.3 - 58.5	-15.3 - 9.8		
Week 152 Day 1	n	17	17	0	0
	Mean (SD)	47.42 (6.765)	-6.18 (9.598)		
	Median	43.25	-9.80		
	Q1-Q3	43.25 - 53.05	-9.80 - 0.00		
	Min-Max	43.3 - 58.5	-25.5 - 15.3		
Week 168 Day 1	n	13	13	0	0
	Mean (SD)	48.61 (6.298)	-6.62 (5.580)		
	Median	43.25	-5.46		
	Q1-Q3	43.25 - 53.05	-9.80 - 0.00		
	Min-Max	43.3 - 58.5	-15.3 - 0.0		

Baseline is defined as the last assessment on or prior to first treatment date.

**PROMIS Parent Proxy Global Health – T-Scores by time point
Full Analysis Set - L**

Scale: Pain Scores

Time point	Statistics	Dabrafenib+Trametinib N=73		Carboplatin+Vincristine N=37	
		Raw value	Change from baseline	Raw value	Change from baseline
End Of Treatment	n	50	50	14	14
	Mean (SD)	51.46 (6.830)	-1.16 (9.192)	52.87 (6.113)	1.71 (10.164)
	Median	53.05	0.00	53.05	2.48
	Q1-Q3	43.25 - 58.51	-5.46 - 0.00	53.05 - 58.51	-5.46 - 9.80
	Min-Max	43.3 - 63.5	-20.2 - 15.3	43.3 - 63.5	-15.3 - 15.3
Post Treatment Follow-Up 1	n	1	1	4	4
	Mean (SD)	53.05 (NE)	-5.46 (NE)	50.60 (4.900)	-0.28 (12.308)
	Median	53.05	-5.46	53.05	2.17
	Q1-Q3	53.05 - 53.05	-5.46 - -5.46	48.15 - 53.05	-10.36 - 9.80
	Min-Max	53.1 - 53.1	-5.5 - -5.5	43.3 - 53.1	-15.3 - 9.8
Post Treatment Follow-Up 2	n	1	1	1	1

Baseline is defined as the last assessment on or prior to first treatment date.

PROMIS Parent Proxy Global Health – T-Scores by time point
Full Analysis Set - L

Scale: Pain Scores

Time point	Statistics	Dabrafenib+Trametinib N=73		Carboplatin+Vincristine N=37	
		Raw value	Change from baseline	Raw value	Change from baseline
	Mean (SD)	58.51 (NE)	15.26 (NE)	43.25 (NE)	0.00 (NE)
	Median	58.51	15.26	43.25	0.00
	Q1-Q3	58.51 - 58.51	15.26 - 15.26	43.25 - 43.25	0.00 - 0.00
	Min-Max	58.5 - 58.5	15.3 - 15.3	43.3 - 43.3	0.0 - 0.0
Post Treatment	n	1	1	1	1
Follow-Up 3					
	Mean (SD)	53.05 (NE)	9.80 (NE)	43.25 (NE)	0.00 (NE)
	Median	53.05	9.80	43.25	0.00
	Q1-Q3	53.05 - 53.05	9.80 - 9.80	43.25 - 43.25	0.00 - 0.00
	Min-Max	53.1 - 53.1	9.8 - 9.8	43.3 - 43.3	0.0 - 0.0
Post Treatment	n	1	1	2	2
Follow-Up 4					
	Mean (SD)	58.51 (NE)	15.26 (NE)	43.25 (0.000)	-7.63 (10.790)
	Median	58.51	15.26	43.25	-7.63

Baseline is defined as the last assessment on or prior to first treatment date.

PROMIS Parent Proxy Global Health – T-Scores by time point
Full Analysis Set - L

Scale: Pain Scores

Time point	Statistics	Dabrafenib+Trametinib N=73		Carboplatin+Vincristine N=37	
		Raw value	Change from baseline	Raw value	Change from baseline
	Q1-Q3	58.51 - 58.51	15.26 - 15.26	43.25 - 43.25	-15.26 - 0.00
	Min-Max	58.5 - 58.5	15.3 - 15.3	43.3 - 43.3	-15.3 - 0.0
Post Treatment Follow-Up 5	n	1	1	1	1
	Mean (SD)	58.51 (NE)	15.26 (NE)	43.25 (NE)	0.00 (NE)
	Median	58.51	15.26	43.25	0.00
	Q1-Q3	58.51 - 58.51	15.26 - 15.26	43.25 - 43.25	0.00 - 0.00
	Min-Max	58.5 - 58.5	15.3 - 15.3	43.3 - 43.3	0.0 - 0.0
Post Treatment Follow-Up 6	n	0	0	2	2
	Mean (SD)			50.88 (10.790)	-7.63 (10.790)
	Median			50.88	-7.63
	Q1-Q3			43.25 - 58.51	-15.26 - 0.00
	Min-Max			43.3 - 58.5	-15.3 - 0.0

Baseline is defined as the last assessment on or prior to first treatment date.

**PROMIS Parent Proxy Global Health – T-Scores by time point
Full Analysis Set - L**

Scale: Pain Scores

Time point	Statistics	Dabrafenib+Trametinib N=73		Carboplatin+Vincristine N=37	
		Raw value	Change from baseline	Raw value	Change from baseline
Post Treatment	n	0	0	1	1
Follow-Up 8	Mean (SD)			43.25 (NE)	0.00 (NE)
	Median			43.25	0.00
	Q1-Q3			43.25 - 43.25	0.00 - 0.00
	Min-Max			43.3 - 43.3	0.0 - 0.0

Baseline is defined as the last assessment on or prior to first treatment date.

**PROMIS Parent Proxy Global Health – T-Scores by time point
Full Analysis Set - L**

Scale: Fatigue Scores

Time point	Statistics	Dabrafenib+Trametinib N=73		Carboplatin+Vincristine N=37	
		Raw value	Change from baseline	Raw value	Change from baseline
Baseline	n	61		23	
	Mean (SD)	53.30 (6.731)		54.37 (7.981)	
	Median	56.07		56.07	
	Q1-Q3	48.94 - 56.07		48.94 - 62.62	
	Min-Max	40.2 - 68.1		40.2 - 68.1	
Week 5 Day 1	n	51	51	18	18
	Mean (SD)	53.96 (7.588)	0.62 (7.409)	56.88 (6.430)	2.93 (9.025)
	Median	56.07	0.00	56.07	0.00
	Q1-Q3	48.94 - 56.07	-5.50 - 7.13	56.07 - 62.62	0.00 - 7.13
	Min-Max	40.2 - 68.1	-22.5 - 13.7	40.2 - 68.1	-15.9 - 22.5
Week 8 Day 1	n	54	54	18	18
	Mean (SD)	52.68 (6.967)	-0.33 (7.217)	58.10 (4.823)	4.15 (9.204)
	Median	56.07	0.00	56.07	0.00
	Q1-Q3	48.94 - 56.07	0.00 - 0.00	56.07 - 62.62	0.00 - 7.13

Baseline is defined as the last assessment on or prior to first treatment date.

PROMIS Parent Proxy Global Health – T-Scores by time point
Full Analysis Set - L

Scale: Fatigue Scores

Time point	Statistics	Dabrafenib+Trametinib N=73		Carboplatin+Vincristine N=37	
		Raw value	Change from baseline	Raw value	Change from baseline
	Min-Max	40.2 - 68.1	-22.5 - 19.2	48.9 - 68.1	-6.5 - 28.0
Week 16 Day 1	n	48	48	10	10
	Mean (SD)	51.22 (6.983)	-2.11 (7.445)	57.81 (6.193)	2.25 (8.445)
	Median	48.94	0.00	56.07	0.00
	Q1-Q3	48.94 - 56.07	-7.13 - 0.00	56.07 - 62.62	0.00 - 6.55
	Min-Max	40.2 - 68.1	-22.5 - 19.2	48.9 - 68.1	-7.1 - 22.5
Week 24 Day 1	n	46	46	10	10
	Mean (SD)	51.04 (8.005)	-1.96 (7.228)	55.02 (7.248)	-1.92 (9.936)
	Median	48.94	0.00	56.07	0.00
	Q1-Q3	48.94 - 56.07	-7.13 - 0.00	48.94 - 62.62	-6.55 - 0.00
	Min-Max	40.2 - 68.1	-22.5 - 8.8	40.2 - 62.6	-22.5 - 15.9
Week 32 Day 1	n	47	47	11	11
	Mean (SD)	52.49 (7.219)	-0.19 (7.071)	57.66 (5.899)	2.04 (6.424)

Baseline is defined as the last assessment on or prior to first treatment date.

PROMIS Parent Proxy Global Health – T-Scores by time point
Full Analysis Set - L

Scale: Fatigue Scores

Time point	Statistics	Dabrafenib+Trametinib N=73		Carboplatin+Vincristine N=37	
		Raw value	Change from baseline	Raw value	Change from baseline
	Median	56.07	0.00	56.07	0.00
	Q1-Q3	48.94 - 56.07	0.00 - 6.55	56.07 - 62.62	0.00 - 6.55
	Min-Max	40.2 - 68.1	-22.5 - 15.9	48.9 - 68.1	-7.1 - 15.9
Week 40 Day 1	n	40	40	7	7
	Mean (SD)	52.27 (7.450)	-0.29 (7.397)	58.49 (7.072)	4.00 (6.915)
	Median	56.07	0.00	56.07	0.00
	Q1-Q3	48.94 - 56.07	0.00 - 3.27	56.07 - 68.12	0.00 - 12.05
	Min-Max	40.2 - 68.1	-22.5 - 13.7	48.9 - 68.1	0.0 - 15.9
Week 48 Day 1	n	43	43	10	10
	Mean (SD)	51.65 (7.362)	-0.10 (7.826)	53.48 (8.004)	-1.43 (7.242)
	Median	48.94	0.00	56.07	0.00
	Q1-Q3	48.94 - 56.07	-6.55 - 7.13	48.94 - 56.07	0.00 - 0.00
	Min-Max	40.2 - 68.1	-22.5 - 15.9	40.2 - 62.6	-15.9 - 7.1

Baseline is defined as the last assessment on or prior to first treatment date.

PROMIS Parent Proxy Global Health – T-Scores by time point
Full Analysis Set - L

Scale: Fatigue Scores

Time point	Statistics	Dabrafenib+Trametinib N=73		Carboplatin+Vincristine N=37	
		Raw value	Change from baseline	Raw value	Change from baseline
Week 56 Day 1	n	46	46	7	7
	Mean (SD)	50.51 (7.150)	-1.80 (8.090)	57.63 (7.254)	0.94 (2.476)
	Median	48.94	0.00	56.07	0.00
	Q1-Q3	48.94 - 56.07	-7.13 - 0.00	48.94 - 62.62	0.00 - 0.00
	Min-Max	40.2 - 68.1	-22.5 - 13.7	48.9 - 68.1	0.0 - 6.5
Week 72 Day 1	n	40	40	0	0
	Mean (SD)	49.93 (6.910)	-2.58 (7.229)		
	Median	48.94	0.00		
	Q1-Q3	48.94 - 56.07	-7.13 - 0.00		
	Min-Max	40.2 - 62.6	-22.5 - 8.8		
Week 88 Day 1	n	38	38	0	0
	Mean (SD)	50.52 (7.358)	-2.54 (8.325)		
	Median	48.94	0.00		
	Q1-Q3	48.94 - 56.07	-7.13 - 0.00		

Baseline is defined as the last assessment on or prior to first treatment date.

PROMIS Parent Proxy Global Health – T-Scores by time point
Full Analysis Set - L

Scale: Fatigue Scores

Time point	Statistics	Dabrafenib+Trametinib N=73		Carboplatin+Vincristine N=37	
		Raw value	Change from baseline	Raw value	Change from baseline
	Min-Max	40.2 - 68.1	-15.9 - 15.9		
Week 104 Day 1	n	39	39	0	0
	Mean (SD)	51.11 (6.899)	-1.49 (8.005)		
	Median	48.94	0.00		
	Q1-Q3	48.94 - 56.07	-7.13 - 0.00		
	Min-Max	40.2 - 62.6	-22.5 - 15.9		
Week 120 Day 1	n	33	33	0	0
	Mean (SD)	50.40 (7.317)	-3.72 (8.915)		
	Median	48.94	0.00		
	Q1-Q3	48.94 - 56.07	-8.79 - 0.00		
	Min-Max	40.2 - 68.1	-22.5 - 15.9		
Week 136 Day 1	n	24	24	0	0
	Mean (SD)	50.97 (8.667)	-2.25 (9.120)		

Baseline is defined as the last assessment on or prior to first treatment date.

PROMIS Parent Proxy Global Health – T-Scores by time point
Full Analysis Set - L

Scale: Fatigue Scores

Time point	Statistics	Dabrafenib+Trametinib N=73		Carboplatin+Vincristine N=37	
		Raw value	Change from baseline	Raw value	Change from baseline
	Median	48.94	0.00		
	Q1-Q3	40.15 - 56.07	-8.79 - 3.27		
	Min-Max	40.2 - 68.1	-15.9 - 15.9		
Week 152 Day 1	n	17	17	0	0
	Mean (SD)	47.71 (8.037)	-6.56 (10.939)		
	Median	48.94	-7.13		
	Q1-Q3	40.15 - 56.07	-15.92 - 0.00		
	Min-Max	40.2 - 62.6	-22.5 - 15.9		
Week 168 Day 1	n	13	13	0	0
	Mean (SD)	48.21 (8.188)	-6.72 (9.956)		
	Median	48.94	-7.13		
	Q1-Q3	40.15 - 48.94	-15.92 - 0.00		
	Min-Max	40.2 - 62.6	-22.5 - 13.7		

Baseline is defined as the last assessment on or prior to first treatment date.

PROMIS Parent Proxy Global Health – T-Scores by time point
Full Analysis Set - L

Scale: Fatigue Scores

Time point	Statistics	Dabrafenib+Trametinib N=73		Carboplatin+Vincristine N=37	
		Raw value	Change from baseline	Raw value	Change from baseline
End Of Treatment	n	50	50	14	14
	Mean (SD)	52.35 (7.565)	-1.53 (7.395)	56.88 (5.246)	3.49 (9.386)
	Median	56.07	0.00	56.07	0.00
	Q1-Q3	48.94 - 56.07	-7.13 - 0.00	56.07 - 62.62	-5.50 - 7.13
	Min-Max	40.2 - 68.1	-19.2 - 15.9	48.9 - 62.6	-7.1 - 22.5
Post Treatment Follow-Up 1	n	1	1	4	4
	Mean (SD)	48.94 (NE)	8.79 (NE)	52.36 (6.840)	-3.57 (11.904)
	Median	48.94	8.79	48.94	-7.13
	Q1-Q3	48.94 - 48.94	8.79 - 8.79	48.94 - 55.78	-10.41 - 3.27
	Min-Max	48.9 - 48.9	8.8 - 8.8	48.9 - 62.6	-13.7 - 13.7
Post Treatment Follow-Up 2	n	1	1	1	1

Baseline is defined as the last assessment on or prior to first treatment date.

PROMIS Parent Proxy Global Health – T-Scores by time point
Full Analysis Set - L

Scale: Fatigue Scores

Time point	Statistics	Dabrafenib+Trametinib N=73		Carboplatin+Vincristine N=37	
		Raw value	Change from baseline	Raw value	Change from baseline
	Mean (SD)	62.62 (NE)	13.68 (NE)	62.62 (NE)	6.55 (NE)
	Median	62.62	13.68	62.62	6.55
	Q1-Q3	62.62 - 62.62	13.68 - 13.68	62.62 - 62.62	6.55 - 6.55
	Min-Max	62.6 - 62.6	13.7 - 13.7	62.6 - 62.6	6.5 - 6.5
Post Treatment Follow-Up 3	n	1	1	1	1
	Mean (SD)	48.94 (NE)	0.00 (NE)	48.94 (NE)	0.00 (NE)
	Median	48.94	0.00	48.94	0.00
	Q1-Q3	48.94 - 48.94	0.00 - 0.00	48.94 - 48.94	0.00 - 0.00
	Min-Max	48.9 - 48.9	0.0 - 0.0	48.9 - 48.9	0.0 - 0.0
Post Treatment Follow-Up 4	n	1	1	2	2
	Mean (SD)	56.07 (NE)	7.13 (NE)	48.94 (0.000)	0.00 (0.000)
	Median	56.07	7.13	48.94	0.00

Baseline is defined as the last assessment on or prior to first treatment date.

PROMIS Parent Proxy Global Health – T-Scores by time point
Full Analysis Set - L

Scale: Fatigue Scores

Time point	Statistics	Dabrafenib+Trametinib N=73		Carboplatin+Vincristine N=37	
		Raw value	Change from baseline	Raw value	Change from baseline
	Q1-Q3	56.07 - 56.07	7.13 - 7.13	48.94 - 48.94	0.00 - 0.00
	Min-Max	56.1 - 56.1	7.1 - 7.1	48.9 - 48.9	0.0 - 0.0
Post Treatment Follow-Up 5	n	1	1	1	1
	Mean (SD)	62.62 (NE)	13.68 (NE)	48.94 (NE)	0.00 (NE)
	Median	62.62	13.68	48.94	0.00
	Q1-Q3	62.62 - 62.62	13.68 - 13.68	48.94 - 48.94	0.00 - 0.00
	Min-Max	62.6 - 62.6	13.7 - 13.7	48.9 - 48.9	0.0 - 0.0
Post Treatment Follow-Up 6	n	0	0	2	2
	Mean (SD)			55.78 (9.673)	0.00 (0.000)
	Median			55.78	0.00
	Q1-Q3			48.94 - 62.62	0.00 - 0.00
	Min-Max			48.9 - 62.6	0.0 - 0.0

Baseline is defined as the last assessment on or prior to first treatment date.

PROMIS Parent Proxy Global Health – T-Scores by time point
Full Analysis Set - L

Scale: Fatigue Scores

Time point	Statistics	Dabrafenib+Trametinib N=73		Carboplatin+Vincristine N=37	
		Raw value	Change from baseline	Raw value	Change from baseline
Post Treatment	n	0	0	1	1
Follow-Up 8	Mean (SD)			48.94 (NE)	0.00 (NE)
	Median			48.94	0.00
	Q1-Q3			48.94 - 48.94	0.00 - 0.00
	Min-Max			48.9 - 48.9	0.0 - 0.0

Baseline is defined as the last assessment on or prior to first treatment date.

1.3.2. Patienten ab 5 Jahren**PROMIS Parent Proxy Global Health 7+2 – T-Scores by time point for patients aged \geq 5 years
Full Analysis Set - L**

Scale: Global Health Scores

Time point	Statistics	Dabrafenib+Trametinib N=58		Carboplatin+Vincristine N=27	
		Raw value	Change from baseline	Raw value	Change from baseline
Baseline	n	48		17	
	Mean (SD)	42.97 (9.966)		43.89 (10.876)	
	Median	41.70		41.70	
	Q1-Q3	37.90 - 49.30		36.20 - 54.50	
	Min-Max	21.0 - 63.2		29.4 - 63.2	
Week 5 Day 1	n	41	41	15	15
	Mean (SD)	41.42 (9.557)	-1.22 (8.344)	39.81 (10.553)	-5.09 (9.964)
	Median	39.70	-1.70	36.20	-2.00
	Q1-Q3	36.20 - 47.30	-5.50 - 3.30	32.90 - 47.30	-11.90 - 0.00
	Min-Max	24.4 - 66.1	-21.5 - 22.5	22.7 - 60.2	-24.4 - 10.3
Week 8 Day 1	n	41	41	13	13

Analogous to CSR table 14.2-7.2L, but for patients aged \geq 5 years.
Baseline is defined as the last assessment on or prior to first treatment date.
SD: Standard Deviation.

PROMIS Parent Proxy Global Health 7+2 – T-Scores by time point for patients aged >= 5 years
Full Analysis Set - L

Scale: Global Health Scores

Time point	Statistics	Dabrafenib+Trametinib N=58		Carboplatin+Vincristine N=27	
		Raw value	Change from baseline	Raw value	Change from baseline
	Mean (SD)	43.74 (9.666)	0.94 (8.213)	37.63 (7.189)	-5.72 (11.951)
	Median	41.70	0.00	36.20	-3.50
	Q1-Q3	37.90 - 49.30	-3.90 - 5.70	32.90 - 41.70	-12.80 - 0.00
	Min-Max	24.4 - 66.1	-16.4 - 18.7	27.7 - 54.5	-28.6 - 10.9
Week 16 Day 1	n	39	39	7	7
	Mean (SD)	44.52 (9.470)	2.07 (9.202)	39.29 (8.559)	-4.27 (10.379)
	Median	43.60	1.80	39.70	-3.90
	Q1-Q3	37.90 - 49.30	-3.50 - 8.70	32.90 - 45.40	-9.10 - 3.50
	Min-Max	24.4 - 66.1	-14.7 - 30.8	24.4 - 49.3	-24.4 - 5.7
Week 24 Day 1	n	35	35	7	7
	Mean (SD)	45.28 (9.133)	2.79 (11.061)	35.66 (6.948)	-6.37 (8.946)

Analogous to CSR table 14.2-7.2L, but for patients aged >= 5 years.

Baseline is defined as the last assessment on or prior to first treatment date.

SD: Standard Deviation.

**PROMIS Parent Proxy Global Health 7+2 – T-Scores by time point for patients aged \geq 5 years
Full Analysis Set - L**

Scale: Global Health Scores

Time point	Statistics	Dabrafenib+Trametinib N=58		Carboplatin+Vincristine N=27	
		Raw value	Change from baseline	Raw value	Change from baseline
	Median	43.60	0.00	34.60	-3.30
	Q1-Q3	37.90 - 54.50	-2.00 - 8.00	29.40 - 39.70	-14.80 - 0.00
	Min-Max	32.9 - 66.1	-22.3 - 45.1	26.1 - 47.3	-22.7 - 1.7
Week 32 Day 1	n	38	38	7	7
	Mean (SD)	45.61 (9.185)	2.46 (10.290)	40.76 (6.107)	-2.56 (8.221)
	Median	45.40	2.75	41.70	-1.70
	Q1-Q3	37.90 - 49.30	-3.40 - 7.50	36.20 - 45.40	-12.80 - 5.70
	Min-Max	31.2 - 66.1	-20.5 - 45.1	31.2 - 49.3	-13.7 - 6.8
Week 40 Day 1	n	32	32	5	5
	Mean (SD)	45.16 (9.967)	2.56 (11.221)	38.10 (5.830)	-7.24 (14.432)
	Median	43.60	2.00	37.90	-2.00

Analogous to CSR table 14.2-7.2L, but for patients aged \geq 5 years.
Baseline is defined as the last assessment on or prior to first treatment date.
SD: Standard Deviation.

PROMIS Parent Proxy Global Health 7+2 – T-Scores by time point for patients aged \geq 5 years
Full Analysis Set - L

Scale: Global Health Scores

Time point	Statistics	Dabrafenib+Trametinib N=58		Carboplatin+Vincristine N=27	
		Raw value	Change from baseline	Raw value	Change from baseline
	Q1-Q3	37.90 - 49.30	-3.80 - 7.40	36.20 - 37.90	-18.30 - 1.70
	Min-Max	27.7 - 66.1	-17.8 - 45.1	31.2 - 47.3	-26.1 - 8.5
Week 48 Day 1	n	32	32	7	7
	Mean (SD)	45.36 (9.746)	2.22 (10.680)	39.79 (7.118)	-3.53 (10.040)
	Median	43.60	0.95	36.20	0.00
	Q1-Q3	37.90 - 50.55	-4.15 - 6.70	32.90 - 47.30	-7.20 - 3.70
	Min-Max	27.7 - 66.1	-14.7 - 39.2	32.9 - 47.3	-24.4 - 5.2
Week 56 Day 1	n	35	35	5	5
	Mean (SD)	44.41 (9.289)	2.12 (8.483)	35.42 (7.675)	-5.60 (10.804)
	Median	45.40	1.80	34.60	-2.00
	Q1-Q3	36.20 - 47.30	-3.50 - 6.80	32.90 - 36.20	-3.30 - -1.60

Analogous to CSR table 14.2-7.2L, but for patients aged \geq 5 years.
 Baseline is defined as the last assessment on or prior to first treatment date.
 SD: Standard Deviation.

PROMIS Parent Proxy Global Health 7+2 – T-Scores by time point for patients aged >= 5 years
Full Analysis Set - L

Scale: Global Health Scores

Time point	Statistics	Dabrafenib+Trametinib N=58		Carboplatin+Vincristine N=27	
		Raw value	Change from baseline	Raw value	Change from baseline
	Min-Max	31.2 - 66.1	-15.9 - 26.3	26.1 - 47.3	-24.4 - 3.3
Week 72 Day 1	n	30	30	0	0
	Mean (SD)	44.41 (9.776)	2.95 (7.647)		
	Median	44.50	1.85		
	Q1-Q3	36.20 - 49.30	-2.00 - 7.50		
	Min-Max	29.4 - 66.1	-11.4 - 21.1		
Week 88 Day 1	n	32	32	0	0
	Mean (SD)	45.37 (8.960)	2.91 (6.430)		
	Median	43.60	3.75		
	Q1-Q3	38.80 - 49.30	-1.00 - 6.35		
	Min-Max	31.2 - 66.1	-12.9 - 16.6		

Analogous to CSR table 14.2-7.2L, but for patients aged >= 5 years.
 Baseline is defined as the last assessment on or prior to first treatment date.
 SD: Standard Deviation.

**PROMIS Parent Proxy Global Health 7+2 – T-Scores by time point for patients aged \geq 5 years
Full Analysis Set - L**

Scale: Global Health Scores

Time point	Statistics	Dabrafenib+Trametinib N=58		Carboplatin+Vincristine N=27	
		Raw value	Change from baseline	Raw value	Change from baseline
Week 104 Day 1	n	31	31	0	0
	Mean (SD)	46.53 (8.700)	3.55 (8.070)		
	Median	47.30	3.70		
	Q1-Q3	39.70 - 54.50	-3.30 - 9.40		
	Min-Max	31.2 - 66.1	-10.9 - 19.6		
Week 120 Day 1	n	27	27	0	0
	Mean (SD)	44.43 (7.311)	2.32 (7.340)		
	Median	45.40	0.00		
	Q1-Q3	37.90 - 49.30	-2.00 - 8.40		
	Min-Max	32.9 - 60.2	-14.8 - 16.1		

Analogous to CSR table 14.2-7.2L, but for patients aged \geq 5 years.
Baseline is defined as the last assessment on or prior to first treatment date.
SD: Standard Deviation.

PROMIS Parent Proxy Global Health 7+2 – T-Scores by time point for patients aged >= 5 years
Full Analysis Set - L

Scale: Global Health Scores

Time point	Statistics	Dabrafenib+Trametinib N=58		Carboplatin+Vincristine N=27	
		Raw value	Change from baseline	Raw value	Change from baseline
Week 136 Day 1	n	19	19	0	0
	Mean (SD)	43.73 (6.890)	-0.27 (8.983)		
	Median	45.40	-1.80		
	Q1-Q3	36.20 - 49.30	-8.40 - 7.60		
	Min-Max	32.9 - 54.5	-11.4 - 20.7		
Week 152 Day 1	n	13	13	0	0
	Mean (SD)	48.45 (9.820)	6.53 (11.646)		
	Median	47.30	5.20		
	Q1-Q3	41.70 - 54.50	0.00 - 12.70		
	Min-Max	31.2 - 66.1	-10.5 - 28.2		
Week 168 Day 1	n	11	11	0	0

Analogous to CSR table 14.2-7.2L, but for patients aged >= 5 years.
 Baseline is defined as the last assessment on or prior to first treatment date.
 SD: Standard Deviation.

PROMIS Parent Proxy Global Health 7+2 – T-Scores by time point for patients aged >= 5 years
Full Analysis Set - L

Scale: Global Health Scores

Time point	Statistics	Dabrafenib+Trametinib N=58		Carboplatin+Vincristine N=27	
		Raw value	Change from baseline	Raw value	Change from baseline
	Mean (SD)	45.93 (10.149)	4.45 (13.746)		
	Median	49.30	6.40		
	Q1-Q3	39.70 - 51.80	-8.40 - 15.60		
	Min-Max	29.4 - 66.1	-12.3 - 28.2		
End Of Treatment	n	41	41	12	12
	Mean (SD)	44.89 (10.962)	2.59 (11.665)	40.49 (10.598)	-5.52 (14.335)
	Median	43.60	0.00	37.90	-2.75
	Q1-Q3	37.90 - 51.80	-3.80 - 7.50	32.05 - 47.30	-10.00 - 0.00
	Min-Max	27.7 - 66.1	-17.6 - 30.8	27.7 - 63.2	-32.0 - 19.6
Post Treatment	n	0	0	4	4
Follow-Up 1					

Analogous to CSR table 14.2-7.2L, but for patients aged >= 5 years.
 Baseline is defined as the last assessment on or prior to first treatment date.
 SD: Standard Deviation.

PROMIS Parent Proxy Global Health 7+2 – T-Scores by time point for patients aged >= 5 years
Full Analysis Set - L

Scale: Global Health Scores

Time point	Statistics	Dabrafenib+Trametinib N=58		Carboplatin+Vincristine N=27	
		Raw value	Change from baseline	Raw value	Change from baseline
	Mean (SD)			45.53 (6.288)	-3.95 (6.984)
	Median			48.30	-5.75
	Q1-Q3			41.75 - 49.30	-9.00 - 1.10
	Min-Max			36.2 - 49.3	-10.0 - 5.7
Post Treatment	n	1	1	0	0
Follow-Up 2					
	Mean (SD)	27.70 (NE)	-1.70 (NE)		
	Median	27.70	-1.70		
	Q1-Q3	27.70 - 27.70	-1.70 - -1.70		
	Min-Max	27.7 - 27.7	-1.7 - -1.7		
Post Treatment	n	1	1	0	0

Analogous to CSR table 14.2-7.2L, but for patients aged >= 5 years.

Baseline is defined as the last assessment on or prior to first treatment date.

SD: Standard Deviation.

PROMIS Parent Proxy Global Health 7+2 – T-Scores by time point for patients aged >= 5 years
Full Analysis Set - L

Scale: Global Health Scores

Time point	Statistics	Dabrafenib+Trametinib N=58		Carboplatin+Vincristine N=27	
		Raw value	Change from baseline	Raw value	Change from baseline
Follow-Up 3					
	Mean (SD)	43.60 (NE)	14.20 (NE)		
	Median	43.60	14.20		
	Q1-Q3	43.60 - 43.60	14.20 - 14.20		
	Min-Max	43.6 - 43.6	14.2 - 14.2		
Post Treatment	n	1	1	2	2
Follow-Up 4					
	Mean (SD)	31.20 (NE)	1.80 (NE)	43.60 (8.061)	-0.90 (1.273)
	Median	31.20	1.80	43.60	-0.90
	Q1-Q3	31.20 - 31.20	1.80 - 1.80	37.90 - 49.30	-1.80 - 0.00
	Min-Max	31.2 - 31.2	1.8 - 1.8	37.9 - 49.3	-1.8 - 0.0

Analogous to CSR table 14.2-7.2L, but for patients aged >= 5 years.
 Baseline is defined as the last assessment on or prior to first treatment date.
 SD: Standard Deviation.

PROMIS Parent Proxy Global Health 7+2 – T-Scores by time point for patients aged >= 5 years
Full Analysis Set - L

Scale: Global Health Scores

Time point	Statistics	Dabrafenib+Trametinib N=58		Carboplatin+Vincristine N=27	
		Raw value	Change from baseline	Raw value	Change from baseline
Post Treatment	n	1	1	0	0
Follow-Up 5					
	Mean (SD)	29.40 (NE)	0.00 (NE)		
	Median	29.40	0.00		
	Q1-Q3	29.40 - 29.40	0.00 - 0.00		
	Min-Max	29.4 - 29.4	0.0 - 0.0		
Post Treatment	n	0	0	2	2
Follow-Up 6					
	Mean (SD)			36.45 (7.425)	0.15 (2.616)
	Median			36.45	0.15
	Q1-Q3			31.20 - 41.70	-1.70 - 2.00
	Min-Max			31.2 - 41.7	-1.7 - 2.0

Analogous to CSR table 14.2-7.2L, but for patients aged >= 5 years.
 Baseline is defined as the last assessment on or prior to first treatment date.
 SD: Standard Deviation.

**PROMIS Parent Proxy Global Health 7+2 – T-Scores by time point for patients aged \geq 5 years
Full Analysis Set - L**

Scale: Pain Scores

Time point	Statistics	Dabrafenib+Trametinib N=58		Carboplatin+Vincristine N=27	
		Raw value	Change from baseline	Raw value	Change from baseline
Baseline	n	48		17	
	Mean (SD)	51.73 (7.842)		53.90 (6.930)	
	Median	53.05		53.05	
	Q1-Q3	43.25 - 58.51		53.05 - 58.51	
	Min-Max	43.3 - 68.8		43.3 - 63.5	
Week 5 Day 1	n	41	41	15	15
	Mean (SD)	49.98 (7.717)	-1.86 (10.469)	51.86 (6.161)	-1.42 (8.371)
	Median	43.25	0.00	53.05	0.00
	Q1-Q3	43.25 - 53.05	-9.80 - 0.00	43.25 - 53.05	-4.97 - 0.00
	Min-Max	43.3 - 68.8	-25.5 - 20.2	43.3 - 63.5	-15.3 - 9.8
Week 8 Day 1	n	42	42	13	13

Analogous to CSR table 14.2-7.2L, but for patients aged \geq 5 years.

Baseline is defined as the last assessment on or prior to first treatment date.

SD: Standard Deviation.

PROMIS Parent Proxy Global Health 7+2 – T-Scores by time point for patients aged >= 5 years
Full Analysis Set - L

Scale: Pain Scores

Time point	Statistics	Dabrafenib+Trametinib N=58		Carboplatin+Vincristine N=27	
		Raw value	Change from baseline	Raw value	Change from baseline
	Mean (SD)	49.10 (7.885)	-1.91 (8.110)	50.87 (5.644)	-4.04 (8.739)
	Median	43.25	0.00	53.05	-5.46
	Q1-Q3	43.25 - 53.05	-9.80 - 0.00	43.25 - 53.05	-9.80 - 0.00
	Min-Max	43.3 - 68.8	-15.3 - 20.2	43.3 - 58.5	-20.2 - 9.8
Week 16 Day 1	n	39	39	7	7
	Mean (SD)	49.17 (7.607)	-1.80 (7.305)	48.85 (5.238)	-5.23 (11.535)
	Median	43.25	0.00	53.05	-5.46
	Q1-Q3	43.25 - 53.05	-5.46 - 0.00	43.25 - 53.05	-15.26 - 9.80
	Min-Max	43.3 - 68.8	-15.7 - 15.3	43.3 - 53.1	-20.2 - 9.8
Week 24 Day 1	n	35	35	7	7
	Mean (SD)	49.82 (7.220)	-2.62 (8.831)	50.41 (7.059)	-3.67 (12.927)

Analogous to CSR table 14.2-7.2L, but for patients aged >= 5 years.
 Baseline is defined as the last assessment on or prior to first treatment date.
 SD: Standard Deviation.

**PROMIS Parent Proxy Global Health 7+2 – T-Scores by time point for patients aged \geq 5 years
Full Analysis Set - L**

Scale: Pain Scores

Time point	Statistics	Dabrafenib+Trametinib N=58		Carboplatin+Vincristine N=27	
		Raw value	Change from baseline	Raw value	Change from baseline
	Median	53.05	0.00	53.05	-5.46
	Q1-Q3	43.25 - 53.05	-9.80 - 0.00	43.25 - 58.51	-15.26 - 9.80
	Min-Max	43.3 - 68.8	-20.2 - 20.2	43.3 - 58.5	-20.2 - 15.3
Week 32 Day 1	n	38	38	7	7
	Mean (SD)	48.24 (6.713)	-3.21 (9.931)	48.23 (6.472)	-5.14 (5.825)
	Median	43.25	0.00	43.25	-5.46
	Q1-Q3	43.25 - 53.05	-9.80 - 0.00	43.25 - 53.05	-9.80 - 0.00
	Min-Max	43.3 - 63.5	-25.5 - 15.3	43.3 - 58.5	-15.3 - 0.0
Week 40 Day 1	n	32	32	5	5
	Mean (SD)	49.52 (6.661)	-1.09 (9.012)	52.31 (9.054)	0.99 (14.398)
	Median	48.15	0.00	53.05	0.00

Analogous to CSR table 14.2-7.2L, but for patients aged \geq 5 years.
Baseline is defined as the last assessment on or prior to first treatment date.
SD: Standard Deviation.

PROMIS Parent Proxy Global Health 7+2 – T-Scores by time point for patients aged >= 5 years
Full Analysis Set - L

Scale: Pain Scores

Time point	Statistics	Dabrafenib+Trametinib N=58		Carboplatin+Vincristine N=27	
		Raw value	Change from baseline	Raw value	Change from baseline
	Q1-Q3	43.25 - 55.78	-9.80 - 5.46	43.25 - 58.51	-9.80 - 9.80
	Min-Max	43.3 - 58.5	-15.3 - 15.3	43.3 - 63.5	-15.3 - 20.2
Week 48 Day 1	n	32	32	7	7
	Mean (SD)	47.95 (6.393)	-2.05 (7.644)	51.81 (6.337)	-1.56 (10.804)
	Median	43.25	0.00	53.05	-5.46
	Q1-Q3	43.25 - 53.05	-7.63 - 0.00	43.25 - 58.51	-9.80 - 9.80
	Min-Max	43.3 - 58.5	-15.3 - 15.3	43.3 - 58.5	-15.3 - 15.3
Week 56 Day 1	n	35	35	5	5
	Mean (SD)	47.13 (6.488)	-3.29 (7.788)	53.27 (6.233)	0.87 (10.261)
	Median	43.25	0.00	53.05	0.00
	Q1-Q3	43.25 - 53.05	-9.80 - 0.00	53.05 - 58.51	0.00 - 9.80

Analogous to CSR table 14.2-7.2L, but for patients aged >= 5 years.
 Baseline is defined as the last assessment on or prior to first treatment date.
 SD: Standard Deviation.

**PROMIS Parent Proxy Global Health 7+2 – T-Scores by time point for patients aged \geq 5 years
Full Analysis Set - L**

Scale: Pain Scores

Time point	Statistics	Dabrafenib+Trametinib N=58		Carboplatin+Vincristine N=27	
		Raw value	Change from baseline	Raw value	Change from baseline
	Min-Max	43.3 - 63.5	-15.3 - 20.2	43.3 - 58.5	-15.3 - 9.8
Week 72 Day 1	n	30	30	0	0
	Mean (SD)	48.72 (6.356)	-1.91 (8.373)		
	Median	43.25	0.00		
	Q1-Q3	43.25 - 53.05	-9.80 - 0.00		
	Min-Max	43.3 - 63.5	-15.3 - 15.3		
Week 88 Day 1	n	32	32	0	0
	Mean (SD)	47.74 (5.716)	-3.32 (7.921)		
	Median	43.25	-2.48		
	Q1-Q3	43.25 - 53.05	-9.80 - 0.00		
	Min-Max	43.3 - 58.5	-15.3 - 15.3		

Analogous to CSR table 14.2-7.2L, but for patients aged \geq 5 years.
Baseline is defined as the last assessment on or prior to first treatment date.
SD: Standard Deviation.

**PROMIS Parent Proxy Global Health 7+2 – T-Scores by time point for patients aged \geq 5 years
Full Analysis Set - L**

Scale: Pain Scores

Time point	Statistics	Dabrafenib+Trametinib N=58		Carboplatin+Vincristine N=27	
		Raw value	Change from baseline	Raw value	Change from baseline
Week 104 Day 1	n	31	31	0	0
	Mean (SD)	48.22 (6.614)	-2.78 (8.110)		
	Median	43.25	0.00		
	Q1-Q3	43.25 - 53.05	-9.80 - 0.00		
	Min-Max	43.3 - 68.8	-20.2 - 15.7		
Week 120 Day 1	n	27	27	0	0
	Mean (SD)	48.29 (8.088)	-3.12 (8.115)		
	Median	43.25	0.00		
	Q1-Q3	43.25 - 53.05	-9.80 - 0.00		
	Min-Max	43.3 - 68.8	-15.3 - 15.7		

Analogous to CSR table 14.2-7.2L, but for patients aged \geq 5 years.
Baseline is defined as the last assessment on or prior to first treatment date.
SD: Standard Deviation.

PROMIS Parent Proxy Global Health 7+2 – T-Scores by time point for patients aged >= 5 years
Full Analysis Set - L

Scale: Pain Scores

Time point	Statistics	Dabrafenib+Trametinib N=58		Carboplatin+Vincristine N=27	
		Raw value	Change from baseline	Raw value	Change from baseline
Week 136 Day 1	n	19	19	0	0
	Mean (SD)	46.12 (5.060)	-3.73 (6.418)		
	Median	43.25	0.00		
	Q1-Q3	43.25 - 53.05	-9.80 - 0.00		
	Min-Max	43.3 - 58.5	-15.3 - 9.8		
Week 152 Day 1	n	13	13	0	0
	Mean (SD)	47.95 (7.331)	-6.15 (10.836)		
	Median	43.25	-9.80		
	Q1-Q3	43.25 - 58.51	-15.26 - 0.00		
	Min-Max	43.3 - 58.5	-25.5 - 15.3		
Week 168 Day 1	n	11	11	0	0

Analogous to CSR table 14.2-7.2L, but for patients aged >= 5 years.
 Baseline is defined as the last assessment on or prior to first treatment date.
 SD: Standard Deviation.

PROMIS Parent Proxy Global Health 7+2 – T-Scores by time point for patients aged >= 5 years
Full Analysis Set - L

Scale: Pain Scores

Time point	Statistics	Dabrafenib+Trametinib N=58		Carboplatin+Vincristine N=27	
		Raw value	Change from baseline	Raw value	Change from baseline
	Mean (SD)	47.81 (6.553)	-7.83 (5.197)		
	Median	43.25	-9.80		
	Q1-Q3	43.25 - 53.05	-10.27 - -4.97		
	Min-Max	43.3 - 58.5	-15.3 - 0.0		
End Of Treatment	n	41	41	12	12
	Mean (SD)	51.20 (6.967)	-1.02 (9.235)	52.38 (6.404)	-0.09 (9.793)
	Median	53.05	0.00	53.05	-2.48
	Q1-Q3	43.25 - 58.51	-5.46 - 0.00	48.15 - 55.78	-7.63 - 9.80
	Min-Max	43.3 - 63.5	-15.3 - 15.3	43.3 - 63.5	-15.3 - 15.3
Post Treatment	n	0	0	4	4
Follow-Up 1					

Analogous to CSR table 14.2-7.2L, but for patients aged >= 5 years.
 Baseline is defined as the last assessment on or prior to first treatment date.
 SD: Standard Deviation.

PROMIS Parent Proxy Global Health 7+2 – T-Scores by time point for patients aged >= 5 years
Full Analysis Set - L

Scale: Pain Scores

Time point	Statistics	Dabrafenib+Trametinib N=58		Carboplatin+Vincristine N=27	
		Raw value	Change from baseline	Raw value	Change from baseline
	Mean (SD)			50.60 (4.900)	-0.28 (12.308)
	Median			53.05	2.17
	Q1-Q3			48.15 - 53.05	-10.36 - 9.80
	Min-Max			43.3 - 53.1	-15.3 - 9.8
Post Treatment	n	1	1	0	0
Follow-Up 2					
	Mean (SD)	58.51 (NE)	15.26 (NE)		
	Median	58.51	15.26		
	Q1-Q3	58.51 - 58.51	15.26 - 15.26		
	Min-Max	58.5 - 58.5	15.3 - 15.3		
Post Treatment	n	1	1	0	0

Analogous to CSR table 14.2-7.2L, but for patients aged >= 5 years.
 Baseline is defined as the last assessment on or prior to first treatment date.
 SD: Standard Deviation.

PROMIS Parent Proxy Global Health 7+2 – T-Scores by time point for patients aged >= 5 years
Full Analysis Set - L

Scale: Pain Scores

Time point	Statistics	Dabrafenib+Trametinib N=58		Carboplatin+Vincristine N=27	
		Raw value	Change from baseline	Raw value	Change from baseline
Follow-Up 3					
	Mean (SD)	53.05 (NE)	9.80 (NE)		
	Median	53.05	9.80		
	Q1-Q3	53.05 - 53.05	9.80 - 9.80		
	Min-Max	53.1 - 53.1	9.8 - 9.8		
Post Treatment	n	1	1	2	2
Follow-Up 4					
	Mean (SD)	58.51 (NE)	15.26 (NE)	43.25 (0.000)	-7.63 (10.790)
	Median	58.51	15.26	43.25	-7.63
	Q1-Q3	58.51 - 58.51	15.26 - 15.26	43.25 - 43.25	-15.26 - 0.00
	Min-Max	58.5 - 58.5	15.3 - 15.3	43.3 - 43.3	-15.3 - 0.0

Analogous to CSR table 14.2-7.2L, but for patients aged >= 5 years.
 Baseline is defined as the last assessment on or prior to first treatment date.
 SD: Standard Deviation.

PROMIS Parent Proxy Global Health 7+2 – T-Scores by time point for patients aged >= 5 years
Full Analysis Set - L

Scale: Pain Scores

Time point	Statistics	Dabrafenib+Trametinib N=58		Carboplatin+Vincristine N=27	
		Raw value	Change from baseline	Raw value	Change from baseline
Post Treatment	n	1	1	0	0
Follow-Up 5					
	Mean (SD)	58.51 (NE)	15.26 (NE)		
	Median	58.51	15.26		
	Q1-Q3	58.51 - 58.51	15.26 - 15.26		
	Min-Max	58.5 - 58.5	15.3 - 15.3		
Post Treatment	n	0	0	2	2
Follow-Up 6					
	Mean (SD)			50.88 (10.790)	-7.63 (10.790)
	Median			50.88	-7.63
	Q1-Q3			43.25 - 58.51	-15.26 - 0.00
	Min-Max			43.3 - 58.5	-15.3 - 0.0

Analogous to CSR table 14.2-7.2L, but for patients aged >= 5 years.
 Baseline is defined as the last assessment on or prior to first treatment date.
 SD: Standard Deviation.

PROMIS Parent Proxy Global Health 7+2 – T-Scores by time point for patients aged >= 5 years
Full Analysis Set - L

Scale: Fatigue Scores

Time point	Statistics	Dabrafenib+Trametinib N=58		Carboplatin+Vincristine N=27	
		Raw value	Change from baseline	Raw value	Change from baseline
Baseline	n	48		17	
	Mean (SD)	53.81 (6.747)		54.64 (8.795)	
	Median	56.07		56.07	
	Q1-Q3	48.94 - 56.07		48.94 - 62.62	
	Min-Max	40.2 - 68.1		40.2 - 68.1	
Week 5 Day 1	n	41	41	15	15
	Mean (SD)	55.14 (7.342)	1.15 (8.047)	58.11 (5.340)	3.62 (8.395)
	Median	56.07	0.00	56.07	0.00
	Q1-Q3	48.94 - 62.62	-5.50 - 7.13	56.07 - 62.62	0.00 - 6.55
	Min-Max	40.2 - 68.1	-22.5 - 13.7	48.9 - 68.1	-6.5 - 22.5
Week 8 Day 1	n	42	42	13	13

Analogous to CSR table 14.2-7.2L, but for patients aged >= 5 years.
 Baseline is defined as the last assessment on or prior to first treatment date.
 SD: Standard Deviation.

PROMIS Parent Proxy Global Health 7+2 – T-Scores by time point for patients aged >= 5 years
Full Analysis Set - L

Scale: Fatigue Scores

Time point	Statistics	Dabrafenib+Trametinib N=58		Carboplatin+Vincristine N=27	
		Raw value	Change from baseline	Raw value	Change from baseline
	Mean (SD)	53.32 (7.181)	-0.26 (7.992)	58.38 (5.458)	4.65 (9.951)
	Median	56.07	0.00	56.07	0.00
	Q1-Q3	48.94 - 56.07	-5.50 - 6.55	56.07 - 62.62	0.00 - 7.13
	Min-Max	40.2 - 68.1	-22.5 - 19.2	48.9 - 68.1	-6.5 - 28.0
Week 16 Day 1	n	39	39	7	7
	Mean (SD)	51.24 (7.353)	-2.64 (7.978)	57.63 (7.254)	2.19 (10.066)
	Median	48.94	0.00	56.07	0.00
	Q1-Q3	48.94 - 56.07	-7.13 - 0.00	48.94 - 62.62	-6.55 - 6.55
	Min-Max	40.2 - 68.1	-22.5 - 19.2	48.9 - 68.1	-7.1 - 22.5
Week 24 Day 1	n	35	35	7	7
	Mean (SD)	51.27 (8.025)	-2.31 (7.755)	54.65 (7.916)	-1.72 (11.928)

Analogous to CSR table 14.2-7.2L, but for patients aged >= 5 years.

Baseline is defined as the last assessment on or prior to first treatment date.

SD: Standard Deviation.

**PROMIS Parent Proxy Global Health 7+2 – T-Scores by time point for patients aged \geq 5 years
Full Analysis Set - L**

Scale: Fatigue Scores

Time point	Statistics	Dabrafenib+Trametinib N=58		Carboplatin+Vincristine N=27	
		Raw value	Change from baseline	Raw value	Change from baseline
	Median	48.94	0.00	56.07	0.00
	Q1-Q3	48.94 - 56.07	-7.13 - 6.55	48.94 - 62.62	-6.55 - 6.55
	Min-Max	40.2 - 68.1	-22.5 - 8.8	40.2 - 62.6	-22.5 - 15.9
Week 32 Day 1	n	38	38	7	7
	Mean (SD)	52.46 (7.450)	-0.82 (7.542)	56.84 (6.140)	1.41 (7.785)
	Median	56.07	0.00	56.07	0.00
	Q1-Q3	48.94 - 56.07	-6.55 - 5.50	48.94 - 62.62	-5.50 - 6.55
	Min-Max	40.2 - 68.1	-22.5 - 15.9	48.9 - 62.6	-7.1 - 15.9
Week 40 Day 1	n	32	32	5	5
	Mean (SD)	52.21 (8.157)	-0.64 (7.922)	59.46 (8.421)	5.59 (7.781)
	Median	56.07	0.00	56.07	0.00

Analogous to CSR table 14.2-7.2L, but for patients aged \geq 5 years.
Baseline is defined as the last assessment on or prior to first treatment date.
SD: Standard Deviation.

**PROMIS Parent Proxy Global Health 7+2 – T-Scores by time point for patients aged \geq 5 years
Full Analysis Set - L**

Scale: Fatigue Scores

Time point	Statistics	Dabrafenib+Trametinib N=58		Carboplatin+Vincristine N=27	
		Raw value	Change from baseline	Raw value	Change from baseline
	Q1-Q3	48.94 - 56.07	-3.27 - 3.27	56.07 - 68.12	0.00 - 12.05
	Min-Max	40.2 - 68.1	-22.5 - 13.7	48.9 - 68.1	0.0 - 15.9
Week 48 Day 1	n	32	32	7	7
	Mean (SD)	51.09 (7.772)	-1.08 (7.974)	54.65 (7.916)	-0.79 (5.534)
	Median	52.51	0.00	56.07	0.00
	Q1-Q3	44.55 - 56.07	-6.55 - 0.00	48.94 - 62.62	0.00 - 0.00
	Min-Max	40.2 - 68.1	-22.5 - 13.7	40.2 - 62.6	-12.1 - 6.5
Week 56 Day 1	n	35	35	5	5
	Mean (SD)	50.71 (7.399)	-2.35 (8.268)	59.67 (7.364)	1.31 (2.929)
	Median	48.94	0.00	62.62	0.00
	Q1-Q3	48.94 - 56.07	-7.13 - 0.00	56.07 - 62.62	0.00 - 0.00

Analogous to CSR table 14.2-7.2L, but for patients aged \geq 5 years.
Baseline is defined as the last assessment on or prior to first treatment date.
SD: Standard Deviation.

PROMIS Parent Proxy Global Health 7+2 – T-Scores by time point for patients aged \geq 5 years
Full Analysis Set - L

Scale: Fatigue Scores

Time point	Statistics	Dabrafenib+Trametinib N=58		Carboplatin+Vincristine N=27	
		Raw value	Change from baseline	Raw value	Change from baseline
	Min-Max	40.2 - 68.1	-22.5 - 13.7	48.9 - 68.1	0.0 - 6.5
Week 72 Day 1	n	30	30	0	0
	Mean (SD)	49.57 (7.546)	-3.24 (7.695)		
	Median	48.94	0.00		
	Q1-Q3	40.15 - 56.07	-7.13 - 0.00		
	Min-Max	40.2 - 62.6	-22.5 - 8.8		
Week 88 Day 1	n	32	32	0	0
	Mean (SD)	50.00 (7.286)	-3.67 (7.748)		
	Median	48.94	-3.27		
	Q1-Q3	44.55 - 56.07	-7.96 - 0.00		
	Min-Max	40.2 - 68.1	-15.9 - 15.9		

Analogous to CSR table 14.2-7.2L, but for patients aged \geq 5 years.
 Baseline is defined as the last assessment on or prior to first treatment date.
 SD: Standard Deviation.

**PROMIS Parent Proxy Global Health 7+2 – T-Scores by time point for patients aged \geq 5 years
Full Analysis Set - L**

Scale: Fatigue Scores

Time point	Statistics	Dabrafenib+Trametinib N=58		Carboplatin+Vincristine N=27	
		Raw value	Change from baseline	Raw value	Change from baseline
Week 104 Day 1	n	31	31	0	0
	Mean (SD)	51.04 (7.247)	-2.11 (8.820)		
	Median	48.94	0.00		
	Q1-Q3	48.94 - 56.07	-7.13 - 0.00		
	Min-Max	40.2 - 62.6	-22.5 - 15.9		
Week 120 Day 1	n	27	27	0	0
	Mean (SD)	49.93 (7.855)	-4.55 (9.487)		
	Median	48.94	-6.55		
	Q1-Q3	40.15 - 56.07	-12.05 - 0.00		
	Min-Max	40.2 - 68.1	-22.5 - 15.9		

Analogous to CSR table 14.2-7.2L, but for patients aged \geq 5 years.
Baseline is defined as the last assessment on or prior to first treatment date.
SD: Standard Deviation.

**PROMIS Parent Proxy Global Health 7+2 – T-Scores by time point for patients aged \geq 5 years
Full Analysis Set - L**

Scale: Fatigue Scores

Time point	Statistics	Dabrafenib+Trametinib N=58		Carboplatin+Vincristine N=27	
		Raw value	Change from baseline	Raw value	Change from baseline
Week 136 Day 1	n	19	19	0	0
	Mean (SD)	50.49 (8.864)	-2.72 (9.637)		
	Median	48.94	0.00		
	Q1-Q3	40.15 - 56.07	-8.79 - 0.00		
	Min-Max	40.2 - 68.1	-15.9 - 15.9		
Week 152 Day 1	n	13	13	0	0
	Mean (SD)	46.90 (8.300)	-7.35 (12.299)		
	Median	40.15	-15.92		
	Q1-Q3	40.15 - 56.07	-15.92 - 0.00		
	Min-Max	40.2 - 62.6	-22.5 - 15.9		
Week 168 Day 1	n	11	11	0	0

Analogous to CSR table 14.2-7.2L, but for patients aged \geq 5 years.
Baseline is defined as the last assessment on or prior to first treatment date.
SD: Standard Deviation.

PROMIS Parent Proxy Global Health 7+2 – T-Scores by time point for patients aged >= 5 years
Full Analysis Set - L

Scale: Fatigue Scores

Time point	Statistics	Dabrafenib+Trametinib N=58		Carboplatin+Vincristine N=27	
		Raw value	Change from baseline	Raw value	Change from baseline
	Mean (SD)	47.64 (7.269)	-7.73 (9.989)		
	Median	48.94	-7.13		
	Q1-Q3	40.15 - 48.94	-15.92 - 0.00		
	Min-Max	40.2 - 62.6	-22.5 - 13.7		
End Of Treatment	n	41	41	12	12
	Mean (SD)	52.44 (7.985)	-1.74 (7.744)	57.02 (5.691)	3.47 (10.089)
	Median	56.07	0.00	56.07	0.00
	Q1-Q3	48.94 - 56.07	-7.13 - 0.00	52.51 - 62.62	-6.03 - 11.24
	Min-Max	40.2 - 68.1	-19.2 - 15.9	48.9 - 62.6	-7.1 - 22.5
Post Treatment	n	0	0	4	4
Follow-Up 1					

Analogous to CSR table 14.2-7.2L, but for patients aged >= 5 years.
 Baseline is defined as the last assessment on or prior to first treatment date.
 SD: Standard Deviation.

PROMIS Parent Proxy Global Health 7+2 – T-Scores by time point for patients aged >= 5 years
Full Analysis Set - L

Scale: Fatigue Scores

Time point	Statistics	Dabrafenib+Trametinib N=58		Carboplatin+Vincristine N=27	
		Raw value	Change from baseline	Raw value	Change from baseline
	Mean (SD)			52.36 (6.840)	-3.57 (11.904)
	Median			48.94	-7.13
	Q1-Q3			48.94 - 55.78	-10.41 - 3.27
	Min-Max			48.9 - 62.6	-13.7 - 13.7
Post Treatment	n	1	1	0	0
Follow-Up 2					
	Mean (SD)	62.62 (NE)	13.68 (NE)		
	Median	62.62	13.68		
	Q1-Q3	62.62 - 62.62	13.68 - 13.68		
	Min-Max	62.6 - 62.6	13.7 - 13.7		
Post Treatment	n	1	1	0	0

Analogous to CSR table 14.2-7.2L, but for patients aged >= 5 years.
 Baseline is defined as the last assessment on or prior to first treatment date.
 SD: Standard Deviation.

PROMIS Parent Proxy Global Health 7+2 – T-Scores by time point for patients aged >= 5 years
Full Analysis Set - L

Scale: Fatigue Scores

Time point	Statistics	Dabrafenib+Trametinib N=58		Carboplatin+Vincristine N=27	
		Raw value	Change from baseline	Raw value	Change from baseline
Follow-Up 3	Mean (SD)	48.94 (NE)	0.00 (NE)		
	Median	48.94	0.00		
	Q1-Q3	48.94 - 48.94	0.00 - 0.00		
	Min-Max	48.9 - 48.9	0.0 - 0.0		
Post Treatment	n	1	1	2	2
Follow-Up 4	Mean (SD)	56.07 (NE)	7.13 (NE)	48.94 (0.000)	0.00 (0.000)
	Median	56.07	7.13	48.94	0.00
	Q1-Q3	56.07 - 56.07	7.13 - 7.13	48.94 - 48.94	0.00 - 0.00
	Min-Max	56.1 - 56.1	7.1 - 7.1	48.9 - 48.9	0.0 - 0.0

Analogous to CSR table 14.2-7.2L, but for patients aged >= 5 years.
 Baseline is defined as the last assessment on or prior to first treatment date.
 SD: Standard Deviation.

**PROMIS Parent Proxy Global Health 7+2 – T-Scores by time point for patients aged \geq 5 years
Full Analysis Set - L**

Scale: Fatigue Scores

Time point	Statistics	Dabrafenib+Trametinib N=58		Carboplatin+Vincristine N=27	
		Raw value	Change from baseline	Raw value	Change from baseline
Post Treatment	n	1	1	0	0
Follow-Up 5					
	Mean (SD)	62.62 (NE)	13.68 (NE)		
	Median	62.62	13.68		
	Q1-Q3	62.62 - 62.62	13.68 - 13.68		
	Min-Max	62.6 - 62.6	13.7 - 13.7		
Post Treatment	n	0	0	2	2
Follow-Up 6					
	Mean (SD)			55.78 (9.673)	0.00 (0.000)
	Median			55.78	0.00
	Q1-Q3			48.94 - 62.62	0.00 - 0.00
	Min-Max			48.9 - 62.6	0.0 - 0.0

Analogous to CSR table 14.2-7.2L, but for patients aged \geq 5 years.
Baseline is defined as the last assessment on or prior to first treatment date.
SD: Standard Deviation.

2. Verträglichkeit – Spezifische unerwünschte Ereignisse

2.1. Time-to-Event-Analysen zu unerwünschten Ereignissen nach SOC und PT

2.1.1. Unerwünschte Ereignisse nach SOC und PT

**Any AE by SOC and PT: Time to first event
Safety Set – L**

System Preferred Term	Organ	Class	Treatment groups		Comparison		p-value	
			Dabrafenib+Trametinib N=73	Carboplatin+Vincristine N=33	HR (95% CI)			
			n/N* (%)	Median (95% CI)	n/N* (%)	Median (95% CI)		
Blood and lymphatic system disorders			24 / 73 (32.9)	NE (44.0, NE)	25 / 33 (75.8)	1.2 (0.7, 1.9)	0.20 (0.11, 0.36)	<0.001
Anaemia			14 / 73 (19.2)	NE (NE, NE)	20 / 33 (60.6)	1.6 (0.7, NE)	0.16 (0.07, 0.34)	<0.001
Neutropenia			10 / 73 (13.7)	NE (NE, NE)	10 / 33 (30.3)	NE (3.3, NE)	0.31 (0.12, 0.77)	0.008
Thrombocytopenia			1 / 73 (1.4)	NE (NE, NE)	5 / 33 (15.2)	NE (NE, NE)	0.07 (0.01, 0.57)	0.001
Ear and labyrinth disorders			16 / 73 (21.9)	NE (NE, NE)	4 / 33 (12.1)	NE (NE, NE)	0.92 (0.29, 2.91)	0.885
Eye disorders			23 / 73 (31.5)	NE (32.6, NE)	5 / 33 (15.2)	NE (NE, NE)	1.05 (0.38, 2.89)	0.930
Gastrointestinal disorders			59 / 73 (80.8)	2.5 (1.0, 4.7)	27 / 33 (81.8)	0.3 (0.1, 0.8)	0.55 (0.35, 0.88)	0.013
Abdominal pain			15 / 73 (20.5)	NE (NE, NE)	7 / 33 (21.2)	NE (NE, NE)	0.69 (0.28, 1.74)	0.434

Median (time to event) and its 95% CI are generated by KM estimation.

Hazard Ratio (Dabrafenib + Trametinib vs. Carboplatin + Vincristine) estimated by Cox proportional hazards model and two-sided p-value based on a Log-rank test.

Only events are displayed that occurred in at least 10% of patients in at least one of the treatment arms OR in at least 10 patients and in at least 1% of patients in one treatment arm.

CI: Confidence Interval; HR: Hazard Ratio; n: Number of patients with event; N*: Number of patients included in the analysis; PT: Preferred Term; SOC: System Organ Class.

**Any AE by SOC and PT: Time to first event
Safety Set – L**

System Preferred Term	Organ	Class	Treatment groups		Comparison		HR (95% CI)	p-value
			Dabrafenib+Trametinib N=73	Carboplatin+Vincristine N=33	n/N* (%)	Median (95% CI)		
Abdominal pain upper			13 / 73 (17.8)	NE (47.4, NE)	2 / 33 (6.1)	NE (NE, NE)	1.99 (0.44, 9.04)	0.362
Constipation			10 / 73 (13.7)	NE (NE, NE)	12 / 33 (36.4)	NE (1.7, NE)	0.22 (0.09, 0.53)	<0.001
Diarrhoea			27 / 73 (37.0)	46.6 (26.9, NE)	6 / 33 (18.2)	NE (NE, NE)	1.39 (0.56, 3.46)	0.472
Nausea			21 / 73 (28.8)	NE (NE, NE)	17 / 33 (51.5)	4.2 (0.3, NE)	0.31 (0.16, 0.60)	<0.001
Stomatitis			6 / 73 (8.2)	NE (NE, NE)	5 / 33 (15.2)	NE (NE, NE)	0.30 (0.08, 1.12)	0.058
Vomiting			27 / 73 (37.0)	NE (30.0, NE)	17 / 33 (51.5)	4.2 (1.9, NE)	0.47 (0.25, 0.88)	0.016
General disorders and administration site conditions			65 / 73 (89.0)	0.9 (0.5, 2.7)	19 / 33 (57.6)	3.5 (1.0, 10.6)	1.60 (0.95, 2.68)	0.072
Fatigue			25 / 73 (34.2)	NE (NE, NE)	10 / 33 (30.3)	NE (12.5, NE)	1.08 (0.52, 2.27)	0.837
Pyrexia			55 / 73 (75.3)	3.3 (1.5, 9.7)	6 / 33 (18.2)	NE (NE, NE)	4.36 (1.86, 10.18)	<0.001

Median (time to event) and its 95% CI are generated by KM estimation.

Hazard Ratio (Dabrafenib + Trametinib vs. Carboplatin + Vincristine) estimated by Cox proportional hazards model and two-sided p-value based on a Log-rank test.

Only events are displayed that occurred in at least 10% of patients in at least one of the treatment arms OR in at least 10 patients and in at least 1% of patients in one treatment arm.

CI: Confidence Interval; HR: Hazard Ratio; n: Number of patients with event; N*: Number of patients included in the analysis; PT: Preferred Term; SOC: System Organ Class.

Any AE by SOC and PT: Time to first event
Safety Set – L

System Preferred Term	Organ	Class	Treatment groups		Comparison		HR (95% CI)	p-value
			Dabrafenib+Trametinib N=73	Carboplatin+Vincristine N=33	n/N* (%)	Median (95% CI)		
Immune system disorders			4 / 73 (5.5)	NE (NE, NE)	6 / 33 (18.2)	NE (8.3, NE)	0.04 (0.00, 0.33)	<0.001
Hypersensitivity			1 / 73 (1.4)	NE (NE, NE)	6 / 33 (18.2)	NE (8.3, NE)	<0.001 (0.00, NE)	<0.001
Infections and infestations			59 / 73 (80.8)	6.9 (4.6, 12.7)	14 / 33 (42.4)	12.6 (3.5, NE)	1.34 (0.74, 2.44)	0.338
COVID-19			26 / 73 (35.6)	NE (32.9, NE)	0 / 33 (0.0)	NE (NE, NE)	>999.99 (0.00, NE)	0.171
Nasopharyngitis			9 / 73 (12.3)	NE (NE, NE)	2 / 33 (6.1)	NE (NE, NE)	1.29 (0.27, 6.24)	0.754
Paronychia			17 / 73 (23.3)	NE (45.4, NE)	0 / 33 (0.0)	NE (NE, NE)	>999.99 (0.00, NE)	0.097
Rhinitis			7 / 73 (9.6)	NE (NE, NE)	4 / 33 (12.1)	NE (NE, NE)	0.39 (0.10, 1.53)	0.163
Upper respiratory tract infection			16 / 73 (21.9)	NE (NE, NE)	2 / 33 (6.1)	NE (NE, NE)	1.98 (0.44, 8.96)	0.367
Injury, poisoning and procedural complications			30 / 73 (41.1)	NE (20.5, NE)	12 / 33 (36.4)	NE (3.0, NE)	0.58 (0.28, 1.19)	0.130

Median (time to event) and its 95% CI are generated by KM estimation.

Hazard Ratio (Dabrafenib + Trametinib vs. Carboplatin + Vincristine) estimated by Cox proportional hazards model and two-sided p-value based on a Log-rank test.

Only events are displayed that occurred in at least 10% of patients in at least one of the treatment arms OR in at least 10 patients and in at least 1% of patients in one treatment arm.

CI: Confidence Interval; HR: Hazard Ratio; n: Number of patients with event; N*: Number of patients included in the analysis; PT: Preferred Term; SOC: System Organ Class.

**Any AE by SOC and PT: Time to first event
Safety Set – L**

System Preferred Term	Organ	Class	Treatment groups				HR (95% CI)	p-value
			Dabrafenib+Trametinib N=73		Carboplatin+Vincristine N=33			
			n/N* (%)	Median (95% CI)	n/N* (%)	Median (95% CI)		
Infusion related reaction			0 / 73 (0.0)	NE (NE, NE)	5 / 33 (15.2)	NE (NE, NE)	<0.001 (0.00, NE)	<0.001
Investigations			44 / 73 (60.3)	12.7 (7.7, 25.8)	22 / 33 (66.7)	1.6 (0.7, 3.3)	0.44 (0.25, 0.75)	0.002
Alanine aminotransferase increased			10 / 73 (13.7)	NE (NE, NE)	9 / 33 (27.3)	NE (14.0, NE)	0.30 (0.12, 0.76)	0.007
Aspartate aminotransferase increased			9 / 73 (12.3)	NE (NE, NE)	5 / 33 (15.2)	NE (NE, NE)	0.42 (0.13, 1.35)	0.135
Lymphocyte count decreased			5 / 73 (6.8)	NE (NE, NE)	5 / 33 (15.2)	NE (NE, NE)	0.19 (0.04, 0.79)	0.011
Neutrophil count decreased			11 / 73 (15.1)	NE (NE, NE)	16 / 33 (48.5)	NE (1.6, NE)	0.20 (0.09, 0.44)	<0.001
Platelet count decreased			4 / 73 (5.5)	NE (NE, NE)	10 / 33 (30.3)	NE (7.2, NE)	0.12 (0.04, 0.40)	<0.001
Weight decreased			2 / 73 (2.7)	NE (NE, NE)	4 / 33 (12.1)	NE (NE, NE)	0.20 (0.04, 1.11)	0.041
Weight increased			12 / 73 (16.4)	NE (NE, NE)	0 / 33 (0.0)	NE (NE, NE)	>999.99 (0.00, NE)	0.032
White blood cell count decreased			9 / 73 (12.3)	NE (NE, NE)	12 / 33 (36.4)	NE (4.9, NE)	0.18 (0.07, 0.46)	<0.001

Median (time to event) and its 95% CI are generated by KM estimation.

Hazard Ratio (Dabrafenib + Trametinib vs. Carboplatin + Vincristine) estimated by Cox proportional hazards model and two-sided p-value based on a Log-rank test.

Only events are displayed that occurred in at least 10% of patients in at least one of the treatment arms OR in at least 10 patients and in at least 1% of patients in one treatment arm.

CI: Confidence Interval; HR: Hazard Ratio; n: Number of patients with event; N*: Number of patients included in the analysis; PT: Preferred Term; SOC: System Organ Class.

**Any AE by SOC and PT: Time to first event
Safety Set – L**

System Preferred Term	Organ	Class	Treatment groups				Comparison HR (95% CI)	p-value
			Dabrafenib+Trametinib N=73		Carboplatin+Vincristine N=33			
			n/N* (%)	Median (95% CI)	n/N* (%)	Median (95% CI)		
Metabolism and nutrition disorders			17 / 73 (23.3)	NE (NE, NE)	15 / 33 (45.5)	NE (0.5, NE)	0.29 (0.14, 0.60)	<0.001
Decreased appetite			4 / 73 (5.5)	NE (NE, NE)	8 / 33 (24.2)	NE (NE, NE)	0.14 (0.04, 0.54)	<0.001
Hypocalcaemia			2 / 73 (2.7)	NE (NE, NE)	4 / 33 (12.1)	NE (NE, NE)	0.19 (0.03, 1.05)	0.035
Hypokalaemia			3 / 73 (4.1)	NE (NE, NE)	4 / 33 (12.1)	NE (NE, NE)	0.17 (0.03, 0.92)	0.020
Hypomagnesaemia			1 / 73 (1.4)	NE (NE, NE)	6 / 33 (18.2)	NE (NE, NE)	0.05 (0.01, 0.46)	<0.001
Musculoskeletal and connective tissue disorders			31 / 73 (42.5)	NE (13.6, NE)	12 / 33 (36.4)	NE (2.2, NE)	0.77 (0.39, 1.52)	0.464
Arthralgia			9 / 73 (12.3)	NE (NE, NE)	1 / 33 (3.0)	NE (NE, NE)	3.00 (0.37, 24.11)	0.278
Back pain			7 / 73 (9.6)	NE (NE, NE)	4 / 33 (12.1)	NE (NE, NE)	0.56 (0.16, 2.02)	0.374
Pain in extremity			13 / 73 (17.8)	NE (NE, NE)	4 / 33 (12.1)	NE (NE, NE)	0.95 (0.30, 3.01)	0.937

Median (time to event) and its 95% CI are generated by KM estimation.

Hazard Ratio (Dabrafenib + Trametinib vs. Carboplatin + Vincristine) estimated by Cox proportional hazards model and two-sided p-value based on a Log-rank test.

Only events are displayed that occurred in at least 10% of patients in at least one of the treatment arms OR in at least 10 patients and in at least 1% of patients in one treatment arm.

CI: Confidence Interval; HR: Hazard Ratio; n: Number of patients with event; N*: Number of patients included in the analysis; PT: Preferred Term; SOC: System Organ Class.

**Any AE by SOC and PT: Time to first event
Safety Set – L**

System Preferred Term	Organ	Class	Treatment groups		Comparison		HR (95% CI)	p-value
			Dabrafenib+Trametinib N=73	Carboplatin+Vincristine N=33	n/N* (%)	Median (95% CI)		
Pain in jaw			1 / 73 (1.4)	NE (NE, NE)	6 / 33 (18.2)	NE (NE, NE)	<0.001 (0.00, NE)	<0.001
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			15 / 73 (20.5)	NE (NE, NE)	0 / 33 (0.0)	NE (NE, NE)	>999.99 (0.00, NE)	0.064
Skin papilloma			10 / 73 (13.7)	NE (NE, NE)	0 / 33 (0.0)	NE (NE, NE)	>999.99 (0.00, NE)	0.202
Nervous system disorders			49 / 73 (67.1)	5.7 (3.3, 19.1)	22 / 33 (66.7)	2.1 (0.9, 12.5)	0.64 (0.38, 1.08)	0.093
Dizziness			8 / 73 (11.0)	NE (NE, NE)	1 / 33 (3.0)	NE (NE, NE)	2.73 (0.33, 22.26)	0.330
Headache			40 / 73 (54.8)	18.3 (5.7, NE)	9 / 33 (27.3)	NE (9.7, NE)	1.49 (0.71, 3.13)	0.285
Peripheral motor neuropathy			0 / 73 (0.0)	NE (NE, NE)	5 / 33 (15.2)	NE (NE, NE)	<0.001 (0.00, NE)	<0.001
Peripheral sensory neuropathy			0 / 73 (0.0)	NE (NE, NE)	6 / 33 (18.2)	NE (NE, NE)	<0.001 (0.00, NE)	<0.001

Median (time to event) and its 95% CI are generated by KM estimation.

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CI: Confidence Interval; HR: Hazard Ratio; n: Number of patients with event; N*: Number of patients included in the analysis; PT: Preferred Term; SOC: System Organ Class.

**Any AE by SOC and PT: Time to first event
Safety Set – L**

System Preferred Term	Organ	Class	Treatment groups				HR (95% CI)	p-value
			Dabrafenib+Trametinib N=73		Carboplatin+Vincristine N=33			
			n/N* (%)	Median (95% CI)	n/N* (%)	Median (95% CI)		
Psychiatric disorders			10 / 73 (13.7)	NE (NE, NE)	6 / 33 (18.2)	NE (13.3, NE)	0.35 (0.11, 1.05)	0.050
Anxiety			1 / 73 (1.4)	NE (NE, NE)	5 / 33 (15.2)	NE (13.3, NE)	<0.001 (0.00, NE)	<0.001
Renal and urinary disorders			9 / 73 (12.3)	NE (NE, NE)	3 / 33 (9.1)	NE (NE, NE)	0.76 (0.19, 3.09)	0.705
Respiratory, thoracic and mediastinal disorders			34 / 73 (46.6)	34.1 (10.5, NE)	13 / 33 (39.4)	NE (2.8, NE)	0.81 (0.42, 1.56)	0.522
Cough			11 / 73 (15.1)	NE (NE, NE)	4 / 33 (12.1)	NE (NE, NE)	0.67 (0.20, 2.31)	0.527
Epistaxis			17 / 73 (23.3)	NE (NE, NE)	1 / 33 (3.0)	NE (NE, NE)	5.99 (0.79, 45.30)	0.048
Oropharyngeal pain			10 / 73 (13.7)	NE (NE, NE)	7 / 33 (21.2)	NE (NE, NE)	0.41 (0.15, 1.12)	0.074
Rhinorrhoea			2 / 73 (2.7)	NE (NE, NE)	4 / 33 (12.1)	NE (NE, NE)	0.08 (0.01, 0.77)	0.006

Median (time to event) and its 95% CI are generated by KM estimation.

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**Any AE by SOC and PT: Time to first event
Safety Set – L**

System Preferred Term	Organ	Class	Treatment groups				HR (95% CI)	p-value
			Dabrafenib+Trametinib N=73		Carboplatin+Vincristine N=33			
			n/N* (%)	Median (95% CI)	n/N* (%)	Median (95% CI)		
Skin and subcutaneous tissue disorders			64 / 73 (87.7)	1.9 (1.0, 4.0)	17 / 33 (51.5)	9.7 (2.8, NE)	1.83 (1.06, 3.15)	0.028
Acne			10 / 73 (13.7)	NE (NE, NE)	0 / 33 (0.0)	NE (NE, NE)	>999.99 (0.00, NE)	0.145
Alopecia			2 / 73 (2.7)	NE (NE, NE)	9 / 33 (27.3)	NE (NE, NE)	0.07 (0.02, 0.34)	<0.001
Dermatitis acneiform			10 / 73 (13.7)	NE (NE, NE)	0 / 33 (0.0)	NE (NE, NE)	>999.99 (0.00, NE)	0.046
Dry skin			20 / 73 (27.4)	NE (NE, NE)	1 / 33 (3.0)	NE (NE, NE)	6.61 (0.88, 49.94)	0.034
Eczema			13 / 73 (17.8)	NE (NE, NE)	0 / 33 (0.0)	NE (NE, NE)	>999.99 (0.00, NE)	0.049
Erythema			12 / 73 (16.4)	NE (NE, NE)	0 / 33 (0.0)	NE (NE, NE)	>999.99 (0.00, NE)	0.121
Pruritus			9 / 73 (12.3)	NE (NE, NE)	2 / 33 (6.1)	NE (NE, NE)	1.64 (0.35, 7.79)	0.527
Rash			14 / 73 (19.2)	NE (NE, NE)	3 / 33 (9.1)	NE (NE, NE)	2.11 (0.61, 7.37)	0.229
Rash maculo-papular			13 / 73 (17.8)	NE (NE, NE)	0 / 33 (0.0)	NE (NE, NE)	>999.99 (0.00, NE)	0.092

Median (time to event) and its 95% CI are generated by KM estimation.

Hazard Ratio (Dabrafenib + Trametinib vs. Carboplatin + Vincristine) estimated by Cox proportional hazards model and two-sided p-value based on a Log-rank test.

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CI: Confidence Interval; HR: Hazard Ratio; n: Number of patients with event; N*: Number of patients included in the analysis; PT: Preferred Term; SOC: System Organ Class.

**Any AE by SOC and PT: Time to first event
Safety Set – L**

System Preferred Term	Organ	Class	Treatment groups				HR (95% CI)	p-value
			Dabrafenib+Trametinib N=73		Carboplatin+Vincristine N=33			
			n/N* (%)	Median (95% CI)	n/N* (%)	Median (95% CI)		
Vascular disorders			10 / 73 (13.7)	NE (NE, NE)	3 / 33 (9.1)	NE (NE, NE)	0.87 (0.22, 3.41)	0.847

Median (time to event) and its 95% CI are generated by KM estimation.

Hazard Ratio (Dabrafenib + Trametinib vs. Carboplatin + Vincristine) estimated by Cox proportional hazards model and two-sided p-value based on a Log-rank test.

Only events are displayed that occurred in at least 10% of patients in at least one of the treatment arms OR in at least 10 patients and in at least 1% of patients in one treatment arm.

CI: Confidence Interval; HR: Hazard Ratio; n: Number of patients with event; N*: Number of patients included in the analysis; PT: Preferred Term; SOC: System Organ Class.

2.1.2. Schwere unerwünschte Ereignisse (CTCAE-Grad ≥ 3) nach SOC und PT**Grade ≥ 3 AE by SOC and PT: Time to first event
Safety Set – L**

System Preferred Term	Organ	Class	Treatment groups		Comparison		HR (95% CI)	p-value
			Dabrafenib+Trametinib N=73	Median (95% CI)	Carboplatin+Vincristine N=33	Median (95% CI)		
Blood and lymphatic system disorders			7 / 73 (9.6)	NE (NE, NE)	15 / 33 (45.5)	NE (1.9, NE)	0.13 (0.05, 0.33)	<0.001
Anaemia			0 / 73 (0.0)	NE (NE, NE)	8 / 33 (24.2)	NE (NE, NE)	<0.001 (0.00, NE)	<0.001
Neutropenia			7 / 73 (9.6)	NE (NE, NE)	10 / 33 (30.3)	NE (3.3, NE)	0.21 (0.08, 0.58)	0.001
Thrombocytopenia			0 / 73 (0.0)	NE (NE, NE)	4 / 33 (12.1)	NE (NE, NE)	<0.001 (0.00, NE)	<0.001
Gastrointestinal disorders			3 / 73 (4.1)	NE (NE, NE)	4 / 33 (12.1)	NE (NE, NE)	0.16 (0.03, 0.80)	0.012
Diarrhoea			0 / 73 (0.0)	NE (NE, NE)	2 / 33 (6.1)	NE (NE, NE)	<0.001 (0.00, NE)	0.017
General disorders and administration site conditions			10 / 73 (13.7)	NE (NE, NE)	1 / 33 (3.0)	NE (NE, NE)	2.44 (0.29, 20.30)	0.395
Pyrexia			10 / 73 (13.7)	NE (NE, NE)	1 / 33 (3.0)	NE (NE, NE)	2.44 (0.29, 20.30)	0.395

Median (time to event) and its 95% CI are generated by KM estimation.

Hazard Ratio (Dabrafenib + Trametinib vs. Carboplatin + Vincristine) estimated by Cox proportional hazards model and two-sided p-value based on a Log-rank test.

Only events are displayed that occurred in at least 5% of patients in at least one of the treatment arms OR in at least 10 patients and in at least 1% of patients in one treatment arm.

CI: Confidence Interval; HR: Hazard Ratio; n: Number of patients with event; N*: Number of patients included in the analysis; PT: Preferred Term; SOC: System Organ Class.

**Grade >= 3 AE by SOC and PT: Time to first event
Safety Set – L**

System Preferred Term	Organ	Class	Treatment groups		Comparison		HR (95% CI)	p-value
			Dabrafenib+Trametinib N=73	Carboplatin+Vincristine N=33	n/N* (%)	Median (95% CI)		
Infctions and infestations			10 / 73 (13.7)	NE (NE, NE)	3 / 33 (9.1)	NE (NE, NE)	0.81 (0.21, 3.15)	0.757
Injury, poisoning and procedural complications			2 / 73 (2.7)	NE (NE, NE)	2 / 33 (6.1)	NE (NE, NE)	0.31 (0.04, 2.25)	0.221
Investigations			17 / 73 (23.3)	NE (NE, NE)	18 / 33 (54.5)	3.3 (1.6, NE)	0.21 (0.10, 0.42)	<0.001
Alanine aminotransferase increased			4 / 73 (5.5)	NE (NE, NE)	3 / 33 (9.1)	NE (NE, NE)	0.48 (0.11, 2.18)	0.332
Lymphocyte count decreased			0 / 73 (0.0)	NE (NE, NE)	2 / 33 (6.1)	NE (NE, NE)	<0.001 (0.00, NE)	0.005
Neutrophil count decreased			4 / 73 (5.5)	NE (NE, NE)	16 / 33 (48.5)	NE (1.7, NE)	0.08 (0.03, 0.24)	<0.001
Platelet count decreased			0 / 73 (0.0)	NE (NE, NE)	3 / 33 (9.1)	NE (NE, NE)	<0.001 (0.00, NE)	0.002
Weight increased			6 / 73 (8.2)	NE (NE, NE)	0 / 33 (0.0)	NE (NE, NE)	>999.99 (0.00, NE)	0.156
White blood cell count decreased			0 / 73 (0.0)	NE (NE, NE)	5 / 33 (15.2)	NE (NE, NE)	<0.001 (0.00, NE)	<0.001

Median (time to event) and its 95% CI are generated by KM estimation.

Hazard Ratio (Dabrafenib + Trametinib vs. Carboplatin + Vincristine) estimated by Cox proportional hazards model and two-sided p-value based on a Log-rank test.

Only events are displayed that occurred in at least 5% of patients in at least one of the treatment arms OR in at least 10 patients and in at least 1% of patients in one treatment arm.

CI: Confidence Interval; HR: Hazard Ratio; n: Number of patients with event; N*: Number of patients included in the analysis; PT: Preferred Term; SOC: System Organ Class.

**Grade >= 3 AE by SOC and PT: Time to first event
Safety Set – L**

System Preferred Term	Organ	Class	Treatment groups				HR (95% CI)	p-value
			Dabrafenib+Trametinib N=73		Carboplatin+Vincristine N=33			
			n/N* (%)	Median (95% CI)	n/N* (%)	Median (95% CI)		
Metabolism and nutrition disorders			2 / 73 (2.7)	NE (NE, NE)	2 / 33 (6.1)	NE (NE, NE)	0.38 (0.05, 2.76)	0.321
Nervous system disorders			10 / 73 (13.7)	NE (NE, NE)	5 / 33 (15.2)	NE (NE, NE)	0.65 (0.22, 1.95)	0.439
Respiratory, thoracic and mediastinal disorders			4 / 73 (5.5)	NE (NE, NE)	1 / 33 (3.0)	NE (NE, NE)	1.33 (0.14, 12.76)	0.806
Skin and subcutaneous tissue disorders			3 / 73 (4.1)	NE (NE, NE)	2 / 33 (6.1)	NE (NE, NE)	0.35 (0.05, 2.51)	0.274
Vascular disorders			0 / 73 (0.0)	NE (NE, NE)	2 / 33 (6.1)	NE (NE, NE)	<0.001 (0.00, NE)	0.019

Median (time to event) and its 95% CI are generated by KM estimation.

Hazard Ratio (Dabrafenib + Trametinib vs. Carboplatin + Vincristine) estimated by Cox proportional hazards model and two-sided p-value based on a Log-rank test.

Only events are displayed that occurred in at least 5% of patients in at least one of the treatment arms OR in at least 10 patients and in at least 1% of patients in one treatment arm.

CI: Confidence Interval; HR: Hazard Ratio; n: Number of patients with event; N*: Number of patients included in the analysis; PT: Preferred Term; SOC: System Organ Class.

2.1.3. Schwerwiegende unerwünschte Ereignisse nach SOC und PT**SAE by SOC and PT: Time to first event
Safety Set – L**

System Preferred Term	Organ	Class	Treatment groups		Comparison		p-value	
			Dabrafenib+Trametinib N=73	Carboplatin+Vincristine N=33	HR (95% CI)			
			n/N* (%)	Median (95% CI)	n/N* (%)	Median (95% CI)		
Blood and lymphatic system disorders			0 / 73 (0.0)	NE (NE, NE)	2 / 33 (6.1)	NE (NE, NE)	<0.001 (0.00, NE)	0.011
Gastrointestinal disorders			3 / 73 (4.1)	NE (NE, NE)	3 / 33 (9.1)	NE (NE, NE)	0.39 (0.08, 1.93)	0.229
General disorders and administration site conditions			12 / 73 (16.4)	NE (NE, NE)	6 / 33 (18.2)	NE (NE, NE)	0.55 (0.19, 1.56)	0.258
Pyrexia			12 / 73 (16.4)	NE (NE, NE)	6 / 33 (18.2)	NE (NE, NE)	0.55 (0.19, 1.56)	0.258
Infections and infestations			11 / 73 (15.1)	NE (NE, NE)	2 / 33 (6.1)	NE (NE, NE)	1.30 (0.27, 6.17)	0.743
Injury, poisoning and procedural complications			4 / 73 (5.5)	NE (NE, NE)	1 / 33 (3.0)	NE (NE, NE)	1.45 (0.16, 13.18)	0.741

Median (time to event) and its 95% CI are generated by KM estimation.

Hazard Ratio (Dabrafenib + Trametinib vs. Carboplatin + Vincristine) estimated by Cox proportional hazards model and two-sided p-value based on a Log-rank test.

Only events are displayed that occurred in at least 5% of patients in at least one of the treatment arms OR in at least 10 patients and in at least 1% of patients in one treatment arm.

CI: Confidence Interval; HR: Hazard Ratio; n: Number of patients with event; N*: Number of patients included in the analysis; PT: Preferred Term; SOC: System Organ Class.

SAE by SOC and PT: Time to first event
Safety Set – L

System Preferred Term	Organ	Class	Treatment groups				HR (95% CI)	p-value	
			Dabrafenib+Trametinib N=73		Carboplatin+Vincristine N=33				Comparison
			n/N* (%)	Median (95% CI)	n/N* (%)	Median (95% CI)			
Nervous system disorders			8 / 73 (11.0)	NE (NE, NE)	5 / 33 (15.2)	NE (NE, NE)	0.49 (0.15, 1.56)	0.219	
Respiratory, thoracic and mediastinal disorders			5 / 73 (6.8)	NE (NE, NE)	0 / 33 (0.0)	NE (NE, NE)	>999.99 (0.00, NE)	0.184	

Median (time to event) and its 95% CI are generated by KM estimation.

Hazard Ratio (Dabrafenib + Trametinib vs. Carboplatin + Vincristine) estimated by Cox proportional hazards model and two-sided p-value based on a Log-rank test.

Only events are displayed that occurred in at least 5% of patients in at least one of the treatment arms OR in at least 10 patients and in at least 1% of patients in one treatment arm.

CI: Confidence Interval; HR: Hazard Ratio; n: Number of patients with event; N*: Number of patients included in the analysis; PT: Preferred Term; SOC: System Organ Class.

2.2. Time-to-Event-Analysen zu unerwünschten Ereignissen von besonderem Interesse (AESI)**2.2.1. Unerwünschte Ereignisse von besonderem Interesse (AESI)****Time to first AESI
Safety Set – L**

	Treatment groups				Comparison	
	Dabrafenib+Trametinib N=73		Carboplatin+Vincristine N=33		HR (95% CI)	p-value
	n/N* (%)	Median (95% CI)	n/N* (%)	Median (95% CI)		
Bleeding Events	26 / 73 (35.6)	49.3 (45.5, NE)	7 / 33 (21.2)	NE (6.4, NE)	1.02 (0.43, 2.41)	0.971
Cardiac Related Events	2 / 73 (2.7)	NE (NE, NE)	0 / 33 (0.0)	NE (NE, NE)	>999.99 (0.00, NE)	0.495
Hepatic Disorders	17 / 73 (23.3)	NE (NE, NE)	10 / 33 (30.3)	NE (14.0, NE)	0.45 (0.20, 1.02)	0.051
Hyperglycemia	2 / 73 (2.7)	NE (NE, NE)	3 / 33 (9.1)	NE (NE, NE)	0.22 (0.04, 1.38)	0.079
Hypersensitivity	15 / 73 (20.5)	NE (NE, NE)	9 / 33 (27.3)	NE (7.5, NE)	0.37 (0.15, 0.89)	0.021
Hypertension	1 / 73 (1.4)	NE (NE, NE)	1 / 33 (3.0)	NE (NE, NE)	0.34 (0.02, 5.64)	0.434
Neutropenia	20 / 73 (27.4)	NE (40.5, NE)	27 / 33 (81.8)	1.5 (0.9, 1.6)	0.13 (0.07, 0.25)	<0.001
Ocular Events	10 / 73 (13.7)	NE (NE, NE)	1 / 33 (3.0)	NE (NE, NE)	1.77 (0.21, 15.01)	0.598
Pancreatitis	3 / 73 (4.1)	NE (NE, NE)	0 / 33 (0.0)	NE (NE, NE)	>999.99 (0.00, NE)	0.318
Pneumonitis And Interstitial Lung Disease	1 / 73 (1.4)	NE (NE, NE)	0 / 33 (0.0)	NE (NE, NE)	>999.99 (0.00, NE)	0.610
Pyrexia	56 / 73 (76.7)	3.3 (1.5, 9.7)	7 / 33 (21.2)	NE (NE, NE)	3.72 (1.68, 8.23)	<0.001
Skin Toxicity	58 / 73 (79.5)	1.9 (1.0, 4.3)	12 / 33 (36.4)	12.6 (9.7, NE)	2.66 (1.42, 4.99)	0.002

Median (time to event) and its 95% CI are generated by KM estimation.

Hazard Ratio (Dabrafenib + Trametinib vs. Carbaplatin + Vincristine) estimated by Cox proportional hazards model and two-sided p-value based on a Log-rank test.

CI: Confidence Interval, HR: Hazard Ratio, n: Number of patients with event, N*: Number of patients included in the analysis.

**Time to first AESI
Safety Set – L**

	Treatment groups				Comparison	
	Dabrafenib+Trametinib N=73		Carboplatin+Vincristine N=33		HR (95% CI)	p-value
	n/N* (%)	Median (95% CI)	n/N* (%)	Median (95% CI)		
Uveitis	5 / 73 (6.8)	NE (NE, NE)	0 / 33 (0.0)	NE (NE, NE)	>999.99 (0.00, NE)	0.498
Venous Thromboembolism	1 / 73 (1.4)	NE (NE, NE)	1 / 33 (3.0)	NE (NE, NE)	0.46 (0.03, 7.28)	0.568

Median (time to event) and its 95% CI are generated by KM estimation.

Hazard Ratio (Dabrafenib + Trametinib vs. Carbaplatin + Vincristine) estimated by Cox proportional hazards model and two-sided p-value based on a Log-rank test.

CI: Confidence Interval, HR: Hazard Ratio, n: Number of patients with event, N*: Number of patients included in the analysis.

2.2.2. Schwere unerwünschte Ereignisse (CTCAE-Grad ≥ 3) von besonderem Interesse (AESI)**Time to first Grade ≥ 3 AESI
Safety Set – L**

	Treatment groups				Comparison	
	Dabrafenib+Trametinib N=73		Carboplatin+Vincristine N=33		HR (95% CI)	p-value
	n/N* (%)	Median (95% CI)	n/N* (%)	Median (95% CI)		
Hepatic Disorders	5 / 73 (6.8)	NE (NE, NE)	4 / 33 (12.1)	NE (NE, NE)	0.42 (0.11, 1.60)	0.191
Hypersensitivity	1 / 73 (1.4)	NE (NE, NE)	2 / 33 (6.1)	NE (NE, NE)	<0.001 (0.00, NE)	0.017
Hypertension	0 / 73 (0.0)	NE (NE, NE)	1 / 33 (3.0)	NE (NE, NE)	<0.001 (0.00, NE)	0.137
Neutropenia	10 / 73 (13.7)	NE (NE, NE)	25 / 33 (75.8)	1.9 (1.4, 2.1)	0.09 (0.04, 0.19)	<0.001
Pancreatitis	1 / 73 (1.4)	NE (NE, NE)	0 / 33 (0.0)	NE (NE, NE)	>999.99 (0.00, NE)	0.610
Pyrexia	10 / 73 (13.7)	NE (NE, NE)	1 / 33 (3.0)	NE (NE, NE)	2.44 (0.29, 20.30)	0.395
Skin Toxicity	3 / 73 (4.1)	NE (NE, NE)	1 / 33 (3.0)	NE (NE, NE)	0.64 (0.06, 7.19)	0.719
Uveitis	2 / 73 (2.7)	NE (NE, NE)	0 / 33 (0.0)	NE (NE, NE)	1.00 (0.00, NE)	NE

Median (time to event) and its 95% CI are generated by KM estimation.
Hazard Ratio (Dabrafenib + Trametinib vs. Carbaplatin + Vincristine) estimated by Cox proportional hazards model and two-sided p-value based on a Log-rank test.
CI: Confidence Interval, HR: Hazard Ratio, n: Number of patients with event, N*: Number of patients included in the analysis.

2.2.3. Schwerwiegende unerwünschte Ereignisse von besonderem Interesse (AESI)**Time to first Serious AESI
Safety Set – L**

	Treatment groups				Comparison	p-value
	Dabrafenib+Trametinib N=73		Carboplatin+Vincristine N=33			
	n/N* (%)	Median (95% CI)	n/N* (%)	Median (95% CI)		
Bleeding Events	3 / 73 (4.1)	NE (NE, NE)	1 / 33 (3.0)	NE (NE, NE)	1.11 (0.11, 10.77)	0.930
Hypersensitivity	1 / 73 (1.4)	NE (NE, NE)	0 / 33 (0.0)	NE (NE, NE)	1.00 (0.00, NE)	NE
Neutropenia	0 / 73 (0.0)	NE (NE, NE)	1 / 33 (3.0)	NE (NE, NE)	<0.001 (0.00, NE)	0.050
Ocular Events	1 / 73 (1.4)	NE (NE, NE)	0 / 33 (0.0)	NE (NE, NE)	1.00 (0.00, NE)	NE
Pyrexia	12 / 73 (16.4)	NE (NE, NE)	6 / 33 (18.2)	NE (NE, NE)	0.55 (0.19, 1.56)	0.258
Skin Toxicity	1 / 73 (1.4)	NE (NE, NE)	0 / 33 (0.0)	NE (NE, NE)	>999.99 (0.00, NE)	0.501
Venous Thromboembolism	1 / 73 (1.4)	NE (NE, NE)	0 / 33 (0.0)	NE (NE, NE)	>999.99 (0.00, NE)	0.501

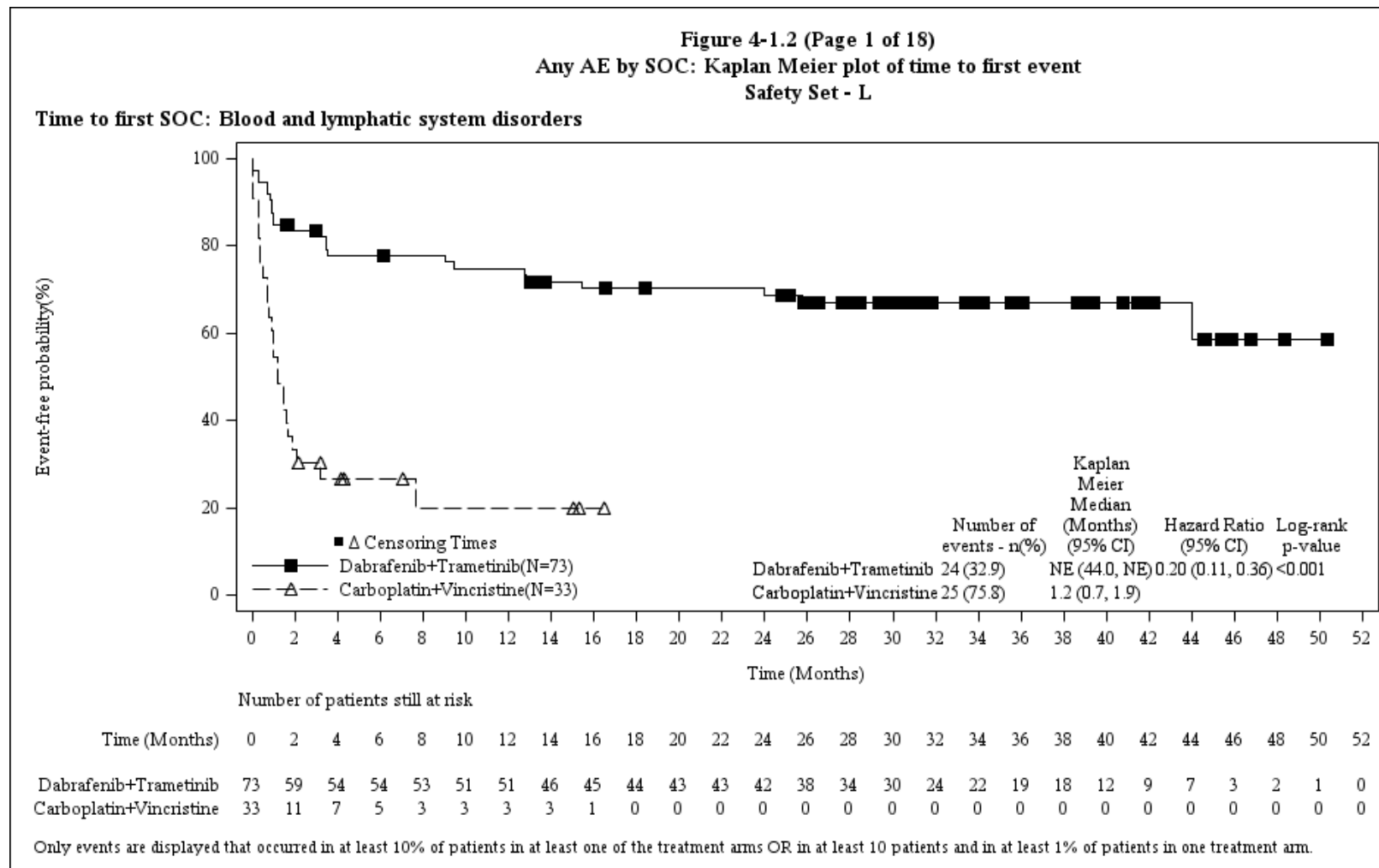
Median (time to event) and its 95% CI are generated by KM estimation.

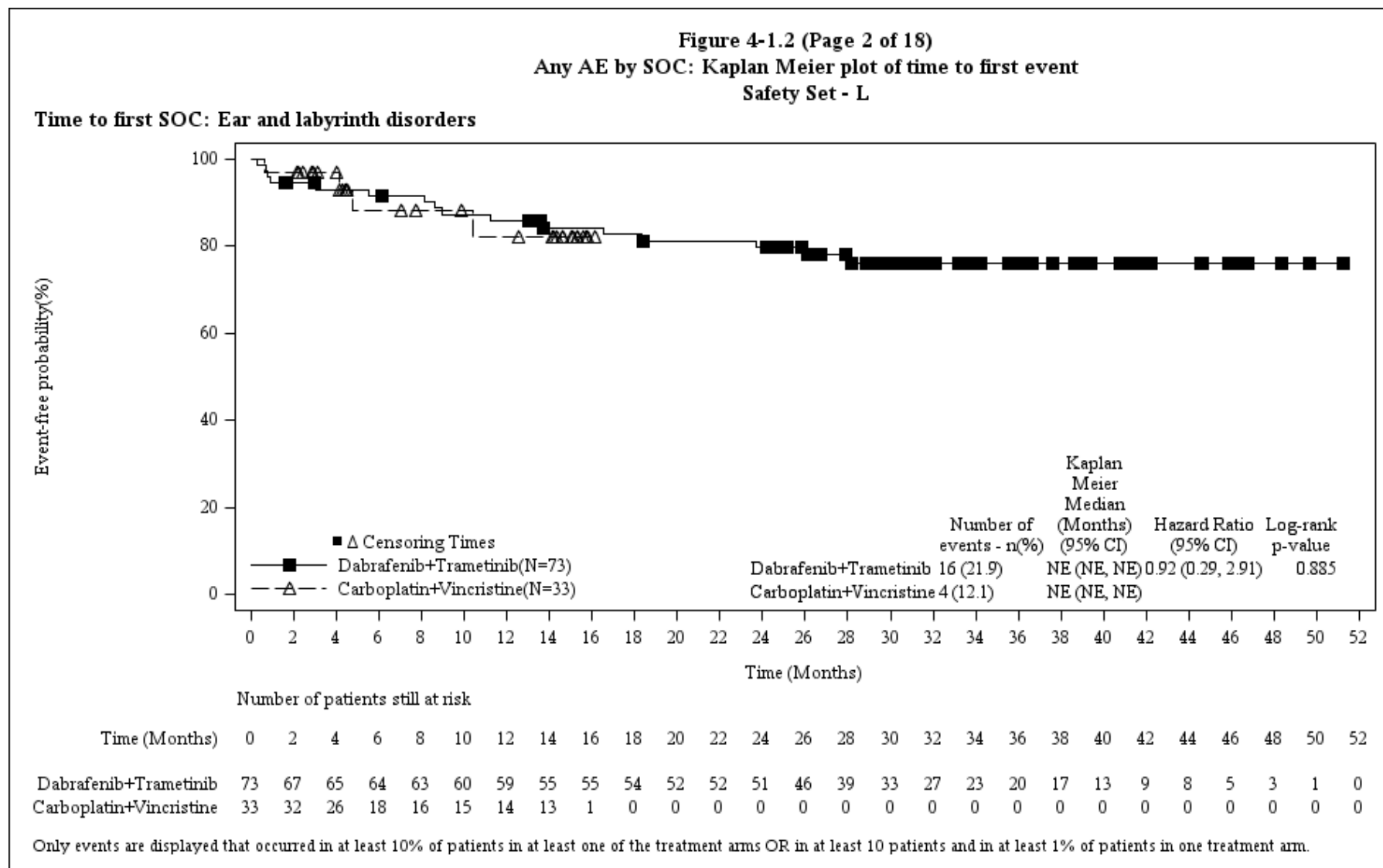
Hazard Ratio (Dabrafenib + Trametinib vs. Carboplatin + Vincristine) estimated by Cox proportional hazards model and two-sided p-value based on a Log-rank test.

CI: Confidence Interval, HR: Hazard Ratio, n: Number of patients with event, N*: Number of patients included in the analysis.

2.3. Kaplan-Meier-Kurven für die Auswertung spezifischer unerwünschter Ereignisse

2.3.1. Unerwünschte Ereignisse nach SOC





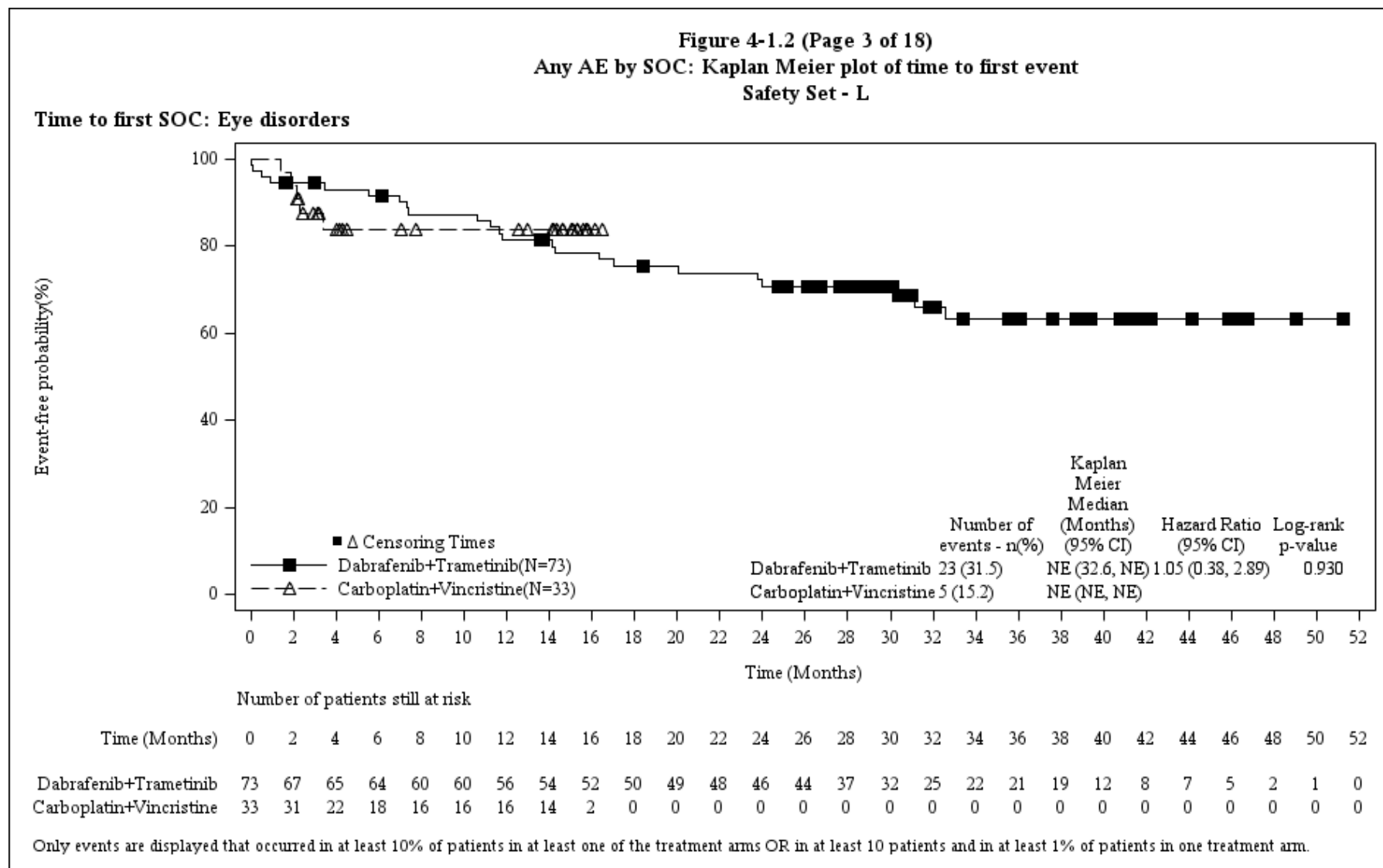
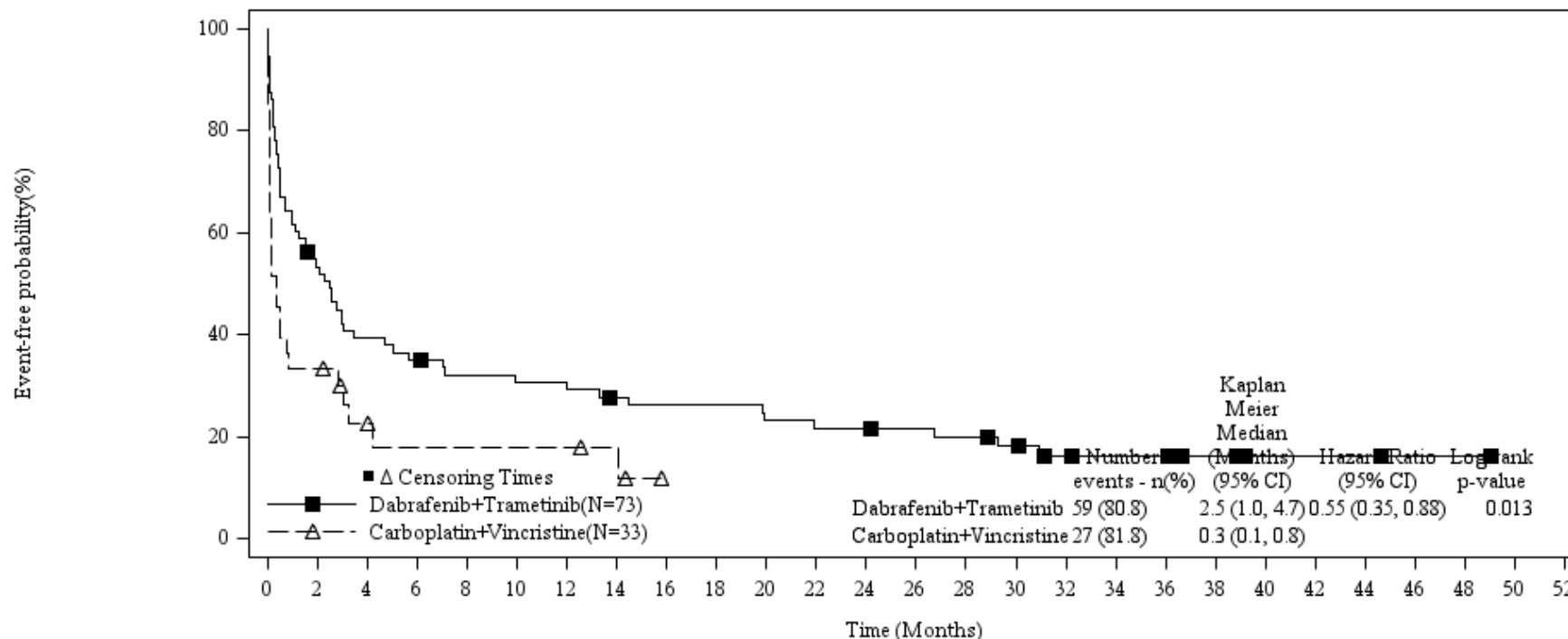


Figure 4-1.2 (Page 4 of 18)
Any AE by SOC: Kaplan Meier plot of time to first event
Safety Set - L

Time to first SOC: Gastrointestinal disorders



Number of patients still at risk

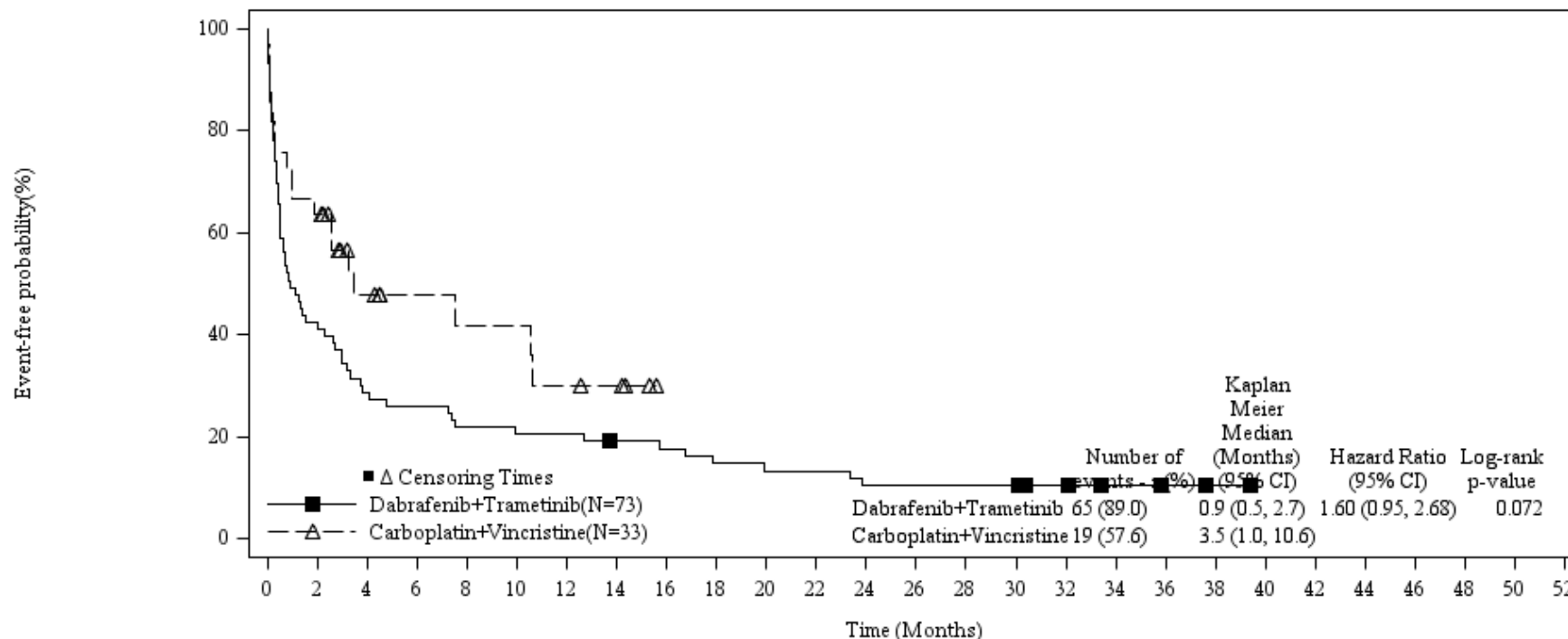
Time (Months)	0	2	4	6	8	10	12	14	16	18	20	22	24	26	28	30	32	34	36	38	40	42	44	46	48	50	52
Dabrafenib+Trametinib	73	38	28	25	22	21	20	18	17	17	15	14	14	13	12	10	7	6	6	4	2	2	2	1	1	0	0
Carboplatin+Vincristine	33	11	6	4	4	4	4	3	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0

Only events are displayed that occurred in at least 10% of patients in at least one of the treatment arms OR in at least 10 patients and in at least 1% of patients in one treatment arm.

Figure 4-1.2 (Page 5 of 18)

Any AE by SOC: Kaplan Meier plot of time to first event
Safety Set - L

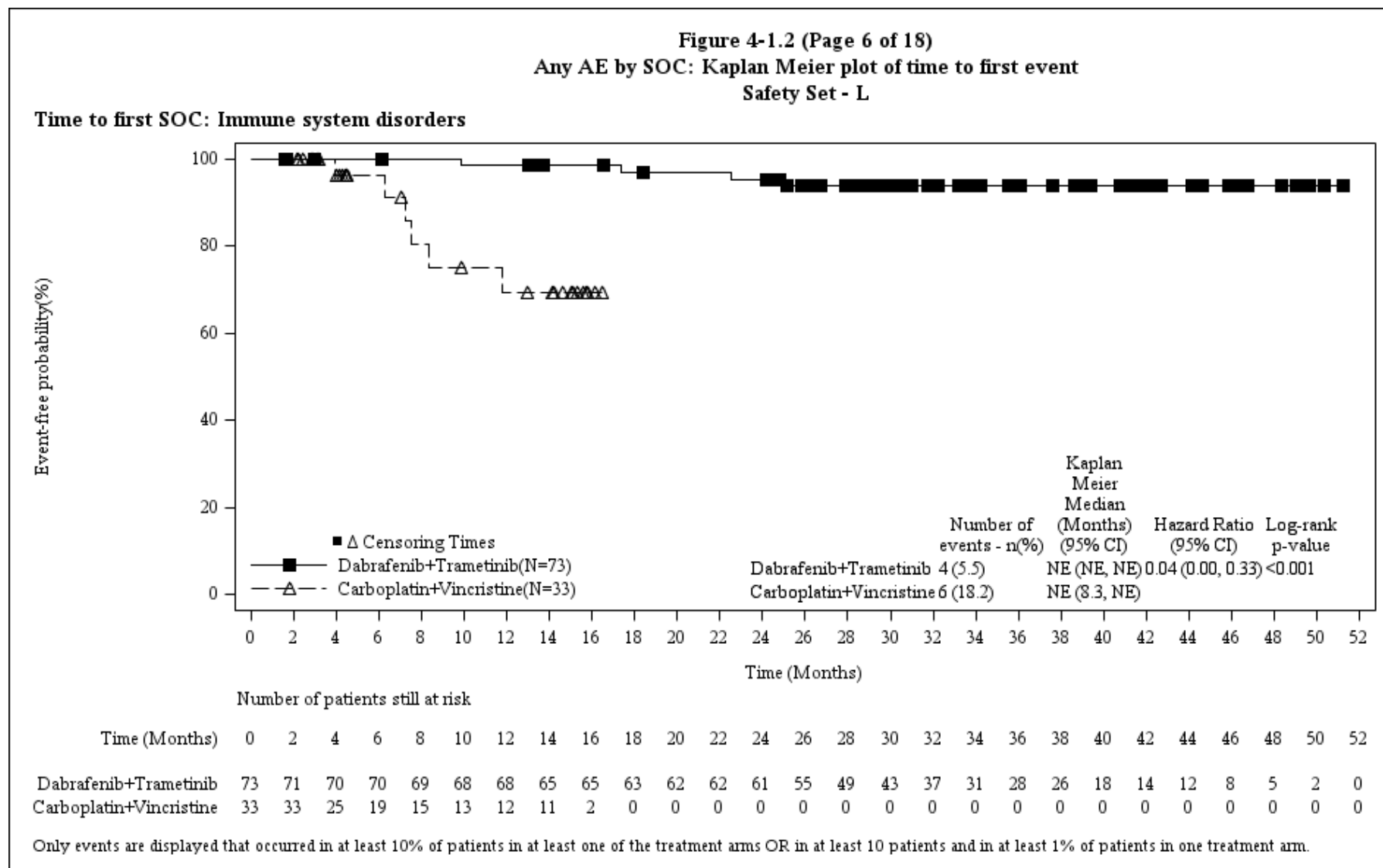
Time to first SOC: General disorders and administration site conditions

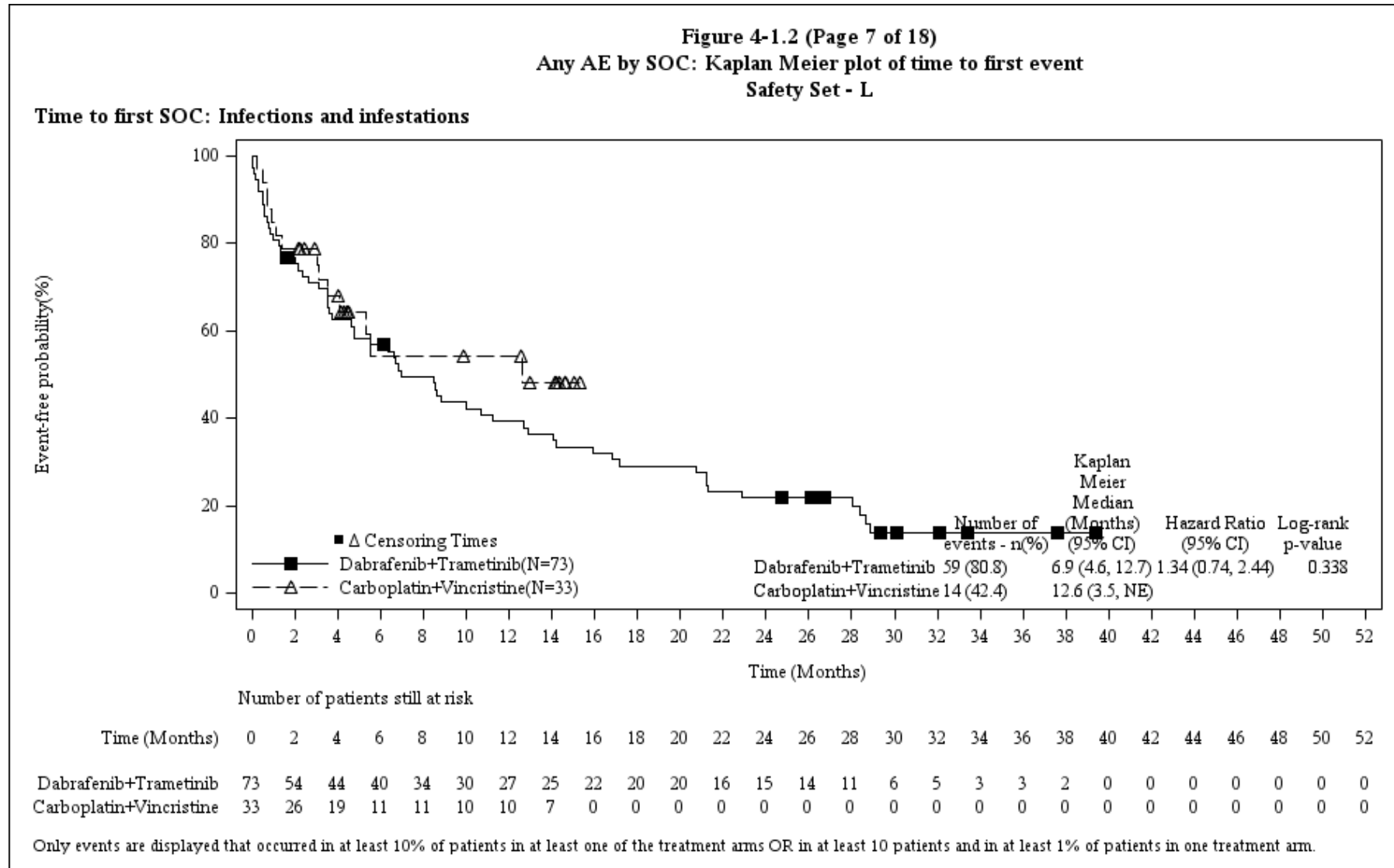


Number of patients still at risk

Time (Months)	0	2	4	6	8	10	12	14	16	18	20	22	24	26	28	30	32	34	36	38	40	42	44	46	48	50	52
Dabrafenib+Trametinib	73	31	21	19	16	15	15	13	12	10	9	9	7	7	7	7	5	3	2	1	0	0	0	0	0	0	0
Carboplatin+Vincristine	33	21	11	8	7	7	5	4	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0

Only events are displayed that occurred in at least 10% of patients in at least one of the treatment arms OR in at least 10 patients and in at least 1% of patients in one treatment arm.





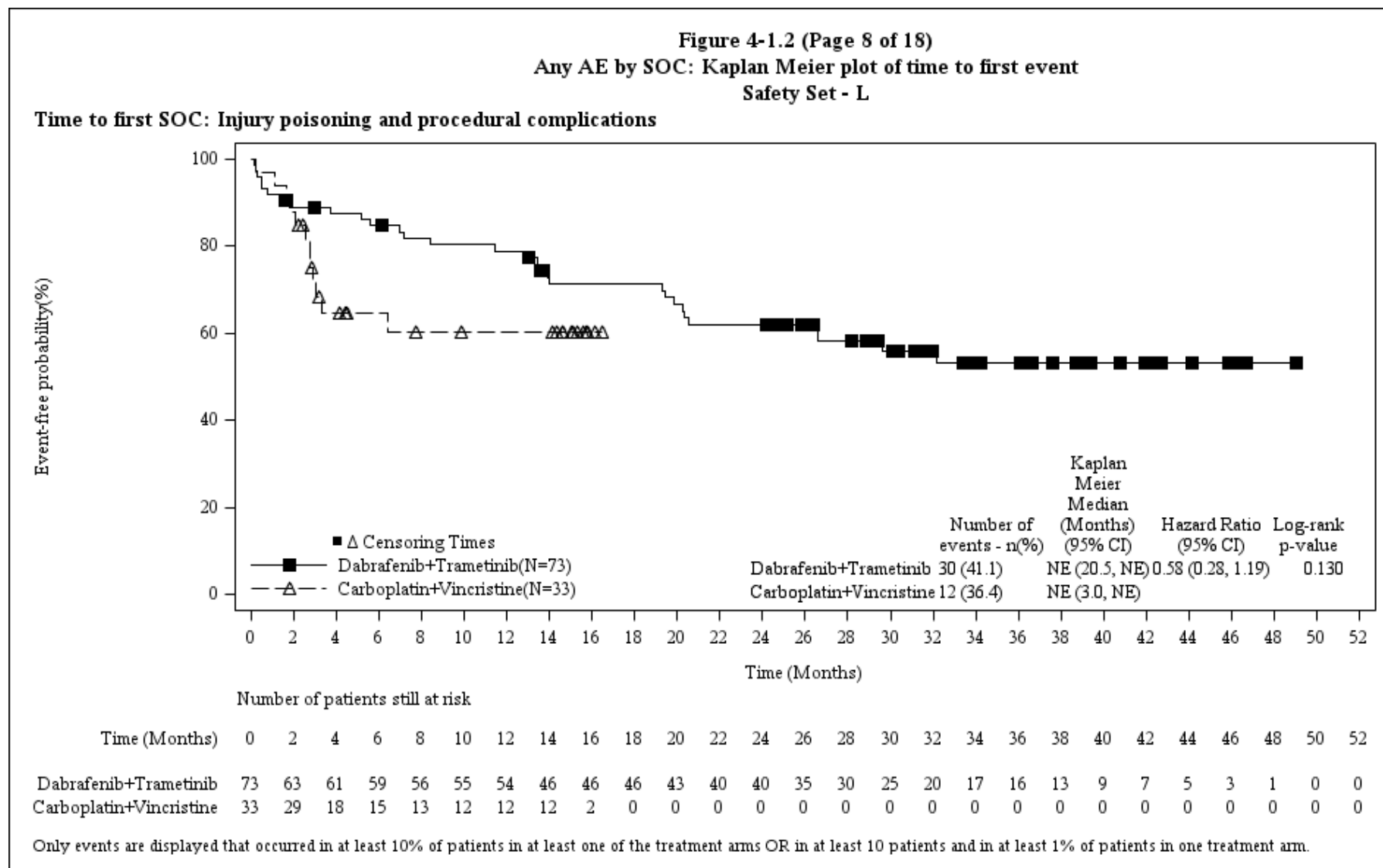
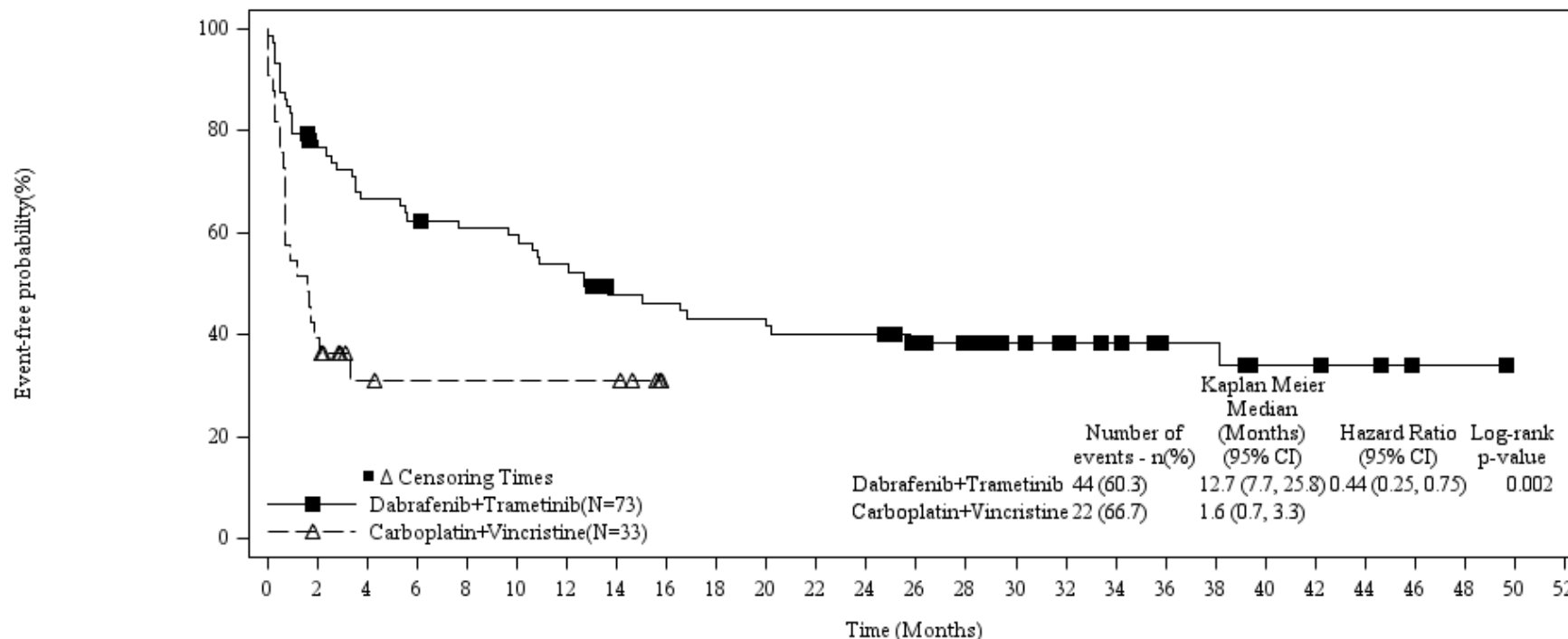


Figure 4-1.2 (Page 9 of 18)
Any AE by SOC: Kaplan Meier plot of time to first event
Safety Set - L

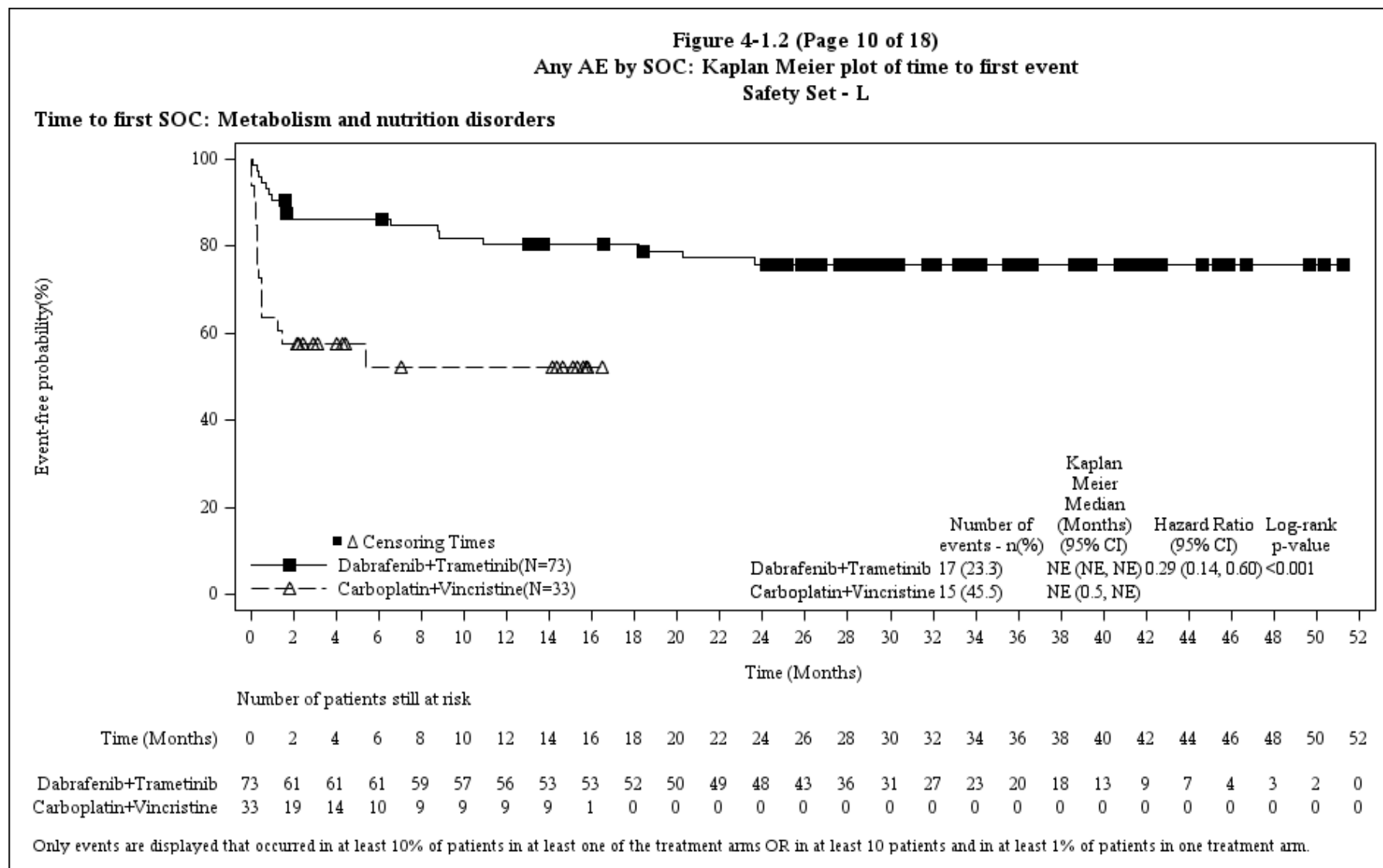
Time to first SOC: Investigations

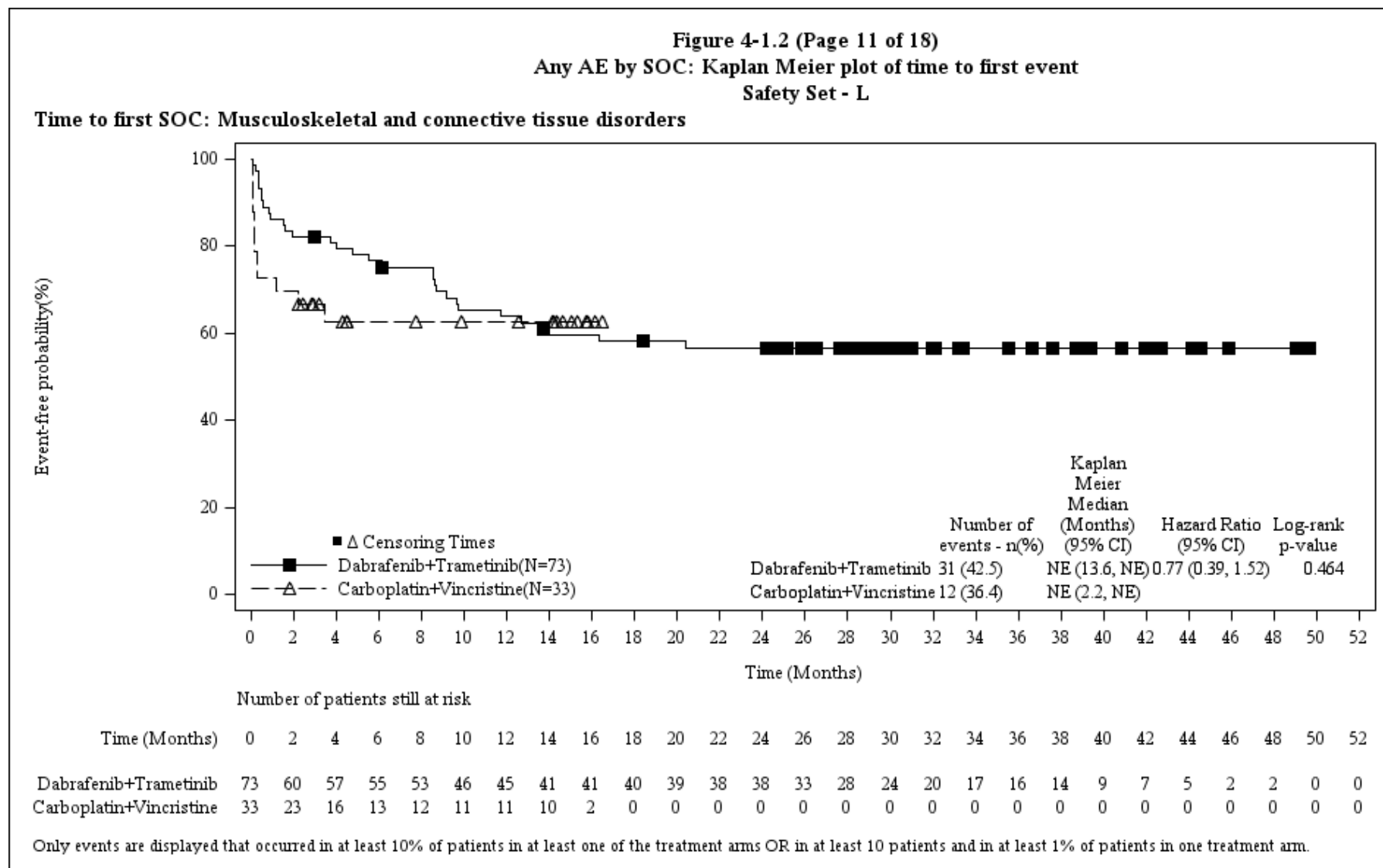


Number of patients still at risk

Time (Months)	0	2	4	6	8	10	12	14	16	18	20	22	24	26	28	30	32	34	36	38	40	42	44	46	48	50	52
Dabrafenib+Trametinib	73	55	47	44	42	41	37	31	30	28	28	26	26	21	19	16	14	12	9	9	4	4	3	1	1	0	0
Carboplatin+Vincristine	33	13	6	5	5	5	5	5	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0

Only events are displayed that occurred in at least 10% of patients in at least one of the treatment arms OR in at least 10 patients and in at least 1% of patients in one treatment arm.





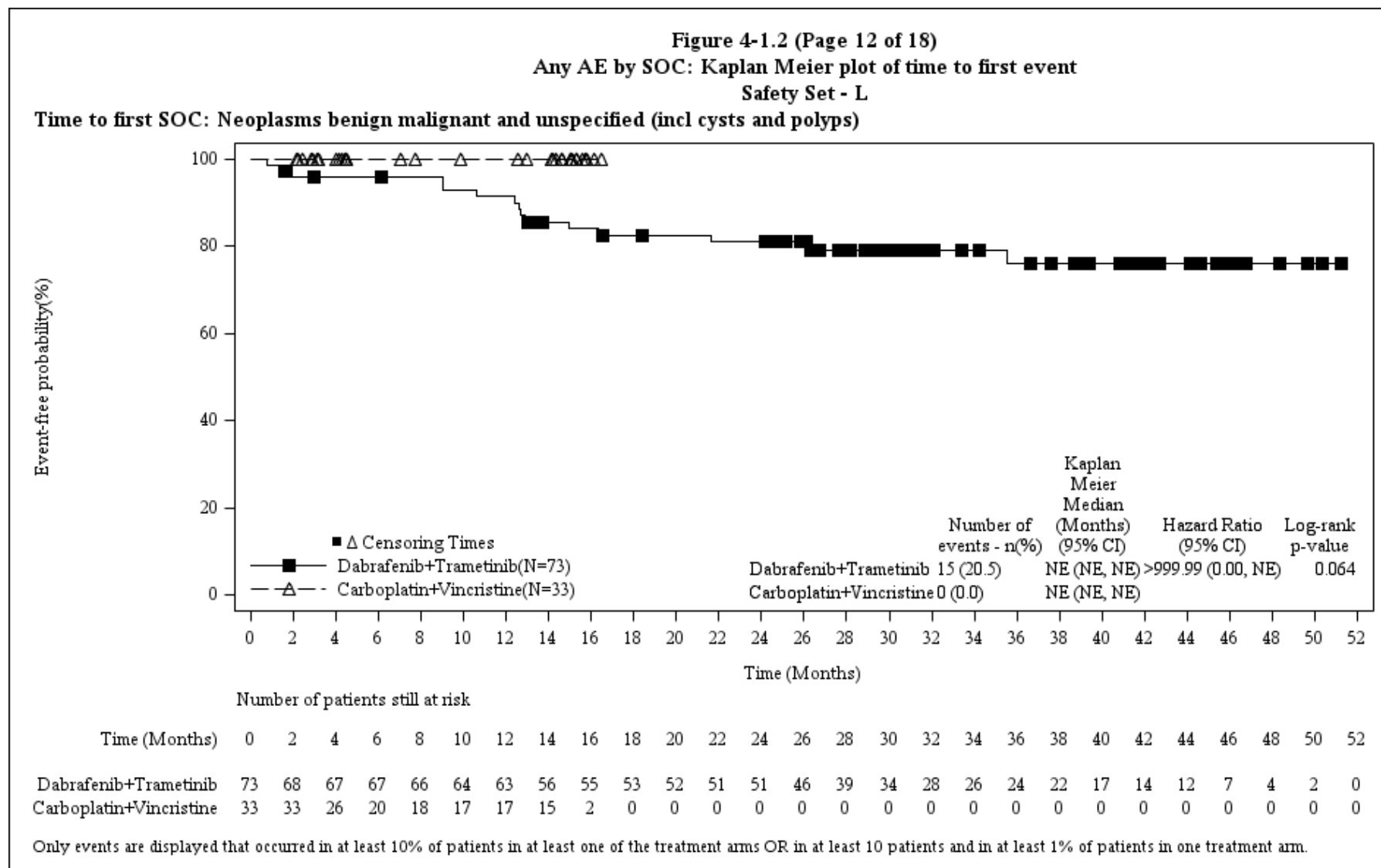
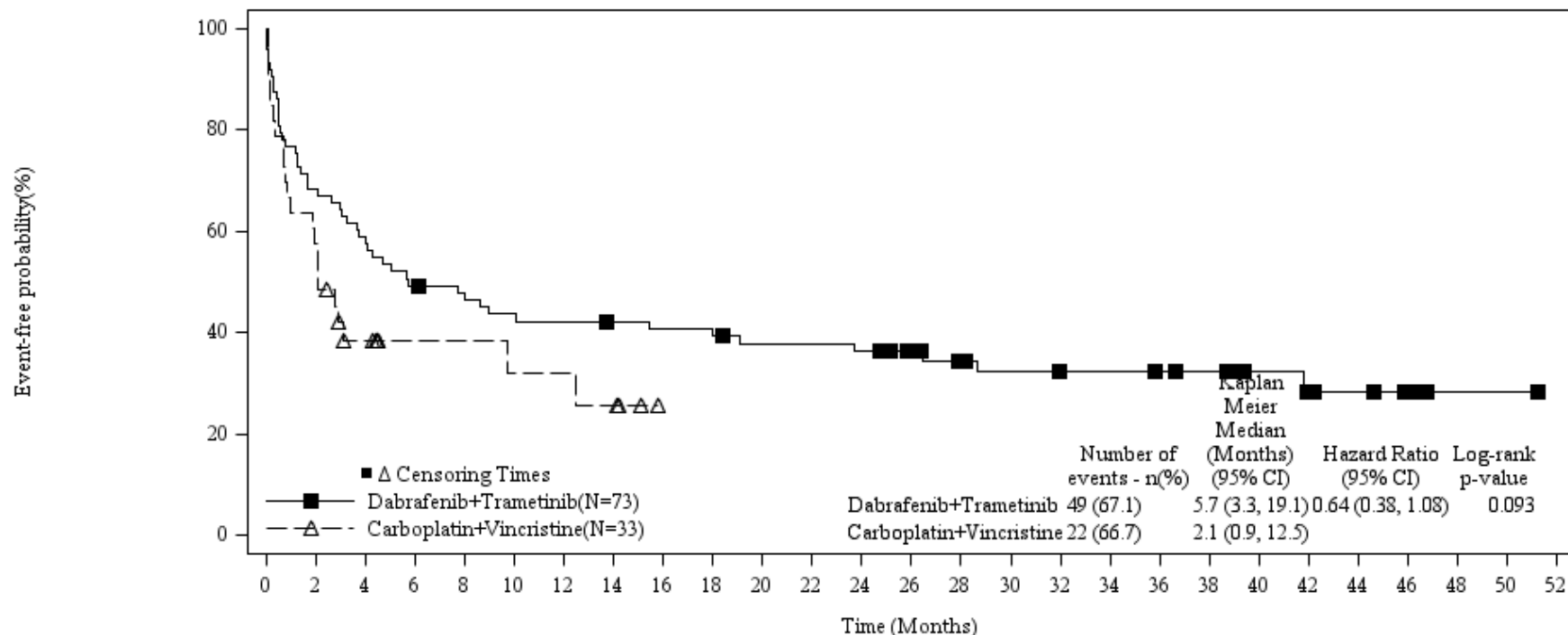


Figure 4-1.2 (Page 13 of 18)
Any AE by SOC: Kaplan Meier plot of time to first event
Safety Set - L

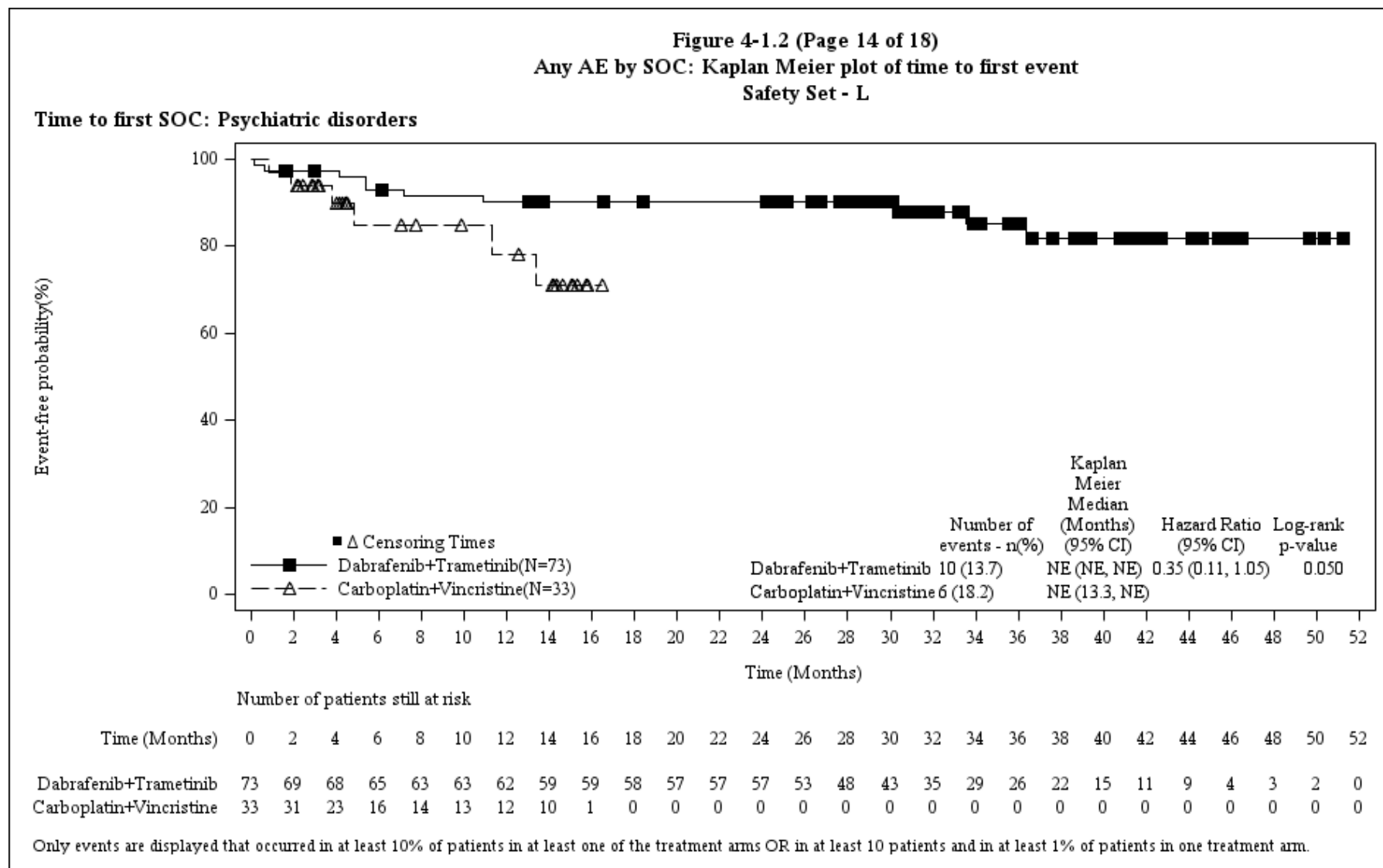
Time to first SOC: Nervous system disorders

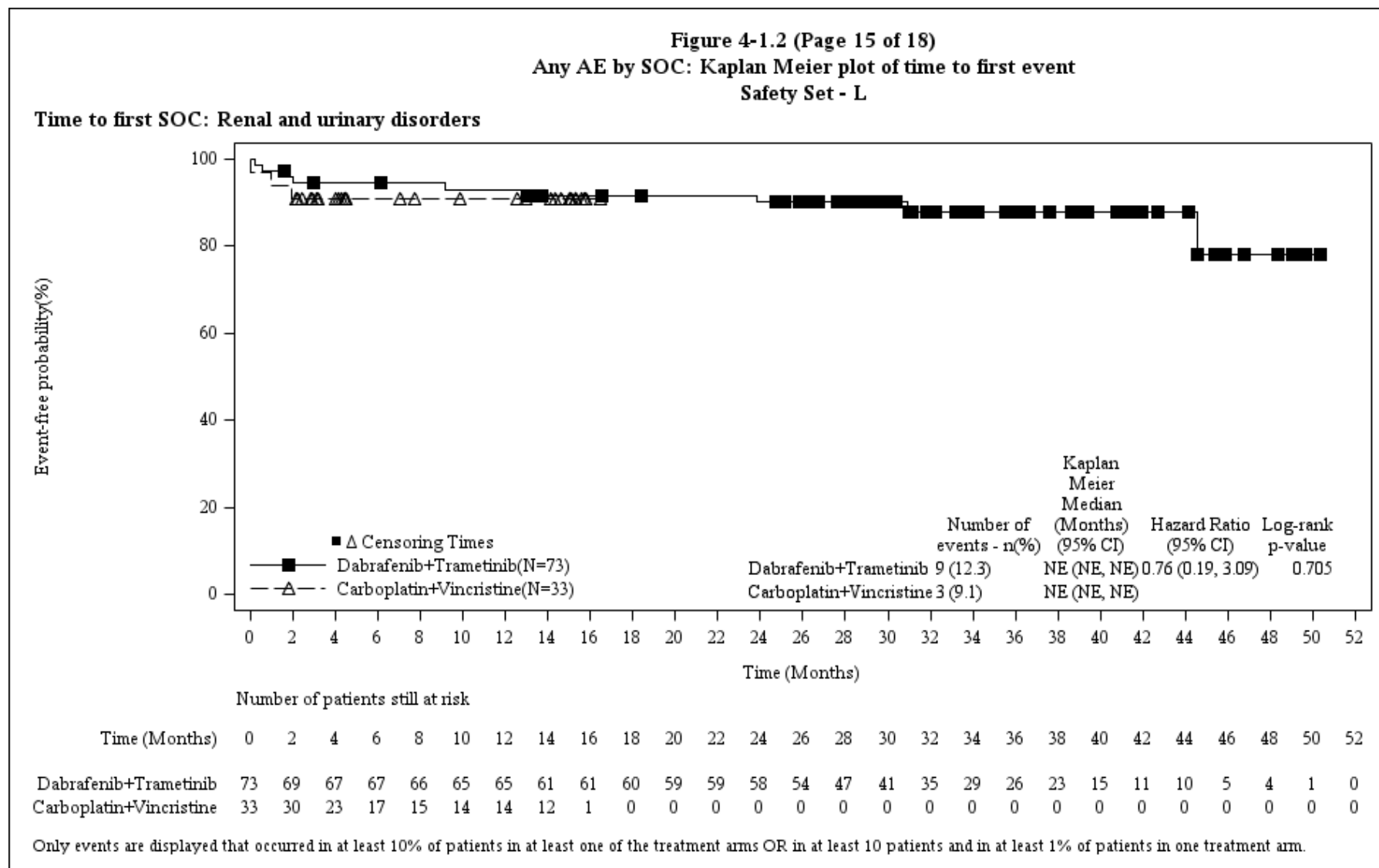


Number of patients still at risk

Time (Months)	0	2	4	6	8	10	12	14	16	18	20	22	24	26	28	30	32	34	36	38	40	42	44	46	48	50	52
Dabrafenib+Trametinib	73	50	42	36	34	31	30	29	28	27	25	25	24	21	18	16	15	15	14	13	8	6	5	3	1	1	0
Carboplatin+Vincristine	33	19	10	6	6	5	5	4	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0

Only events are displayed that occurred in at least 10% of patients in at least one of the treatment arms OR in at least 10 patients and in at least 1% of patients in one treatment arm.





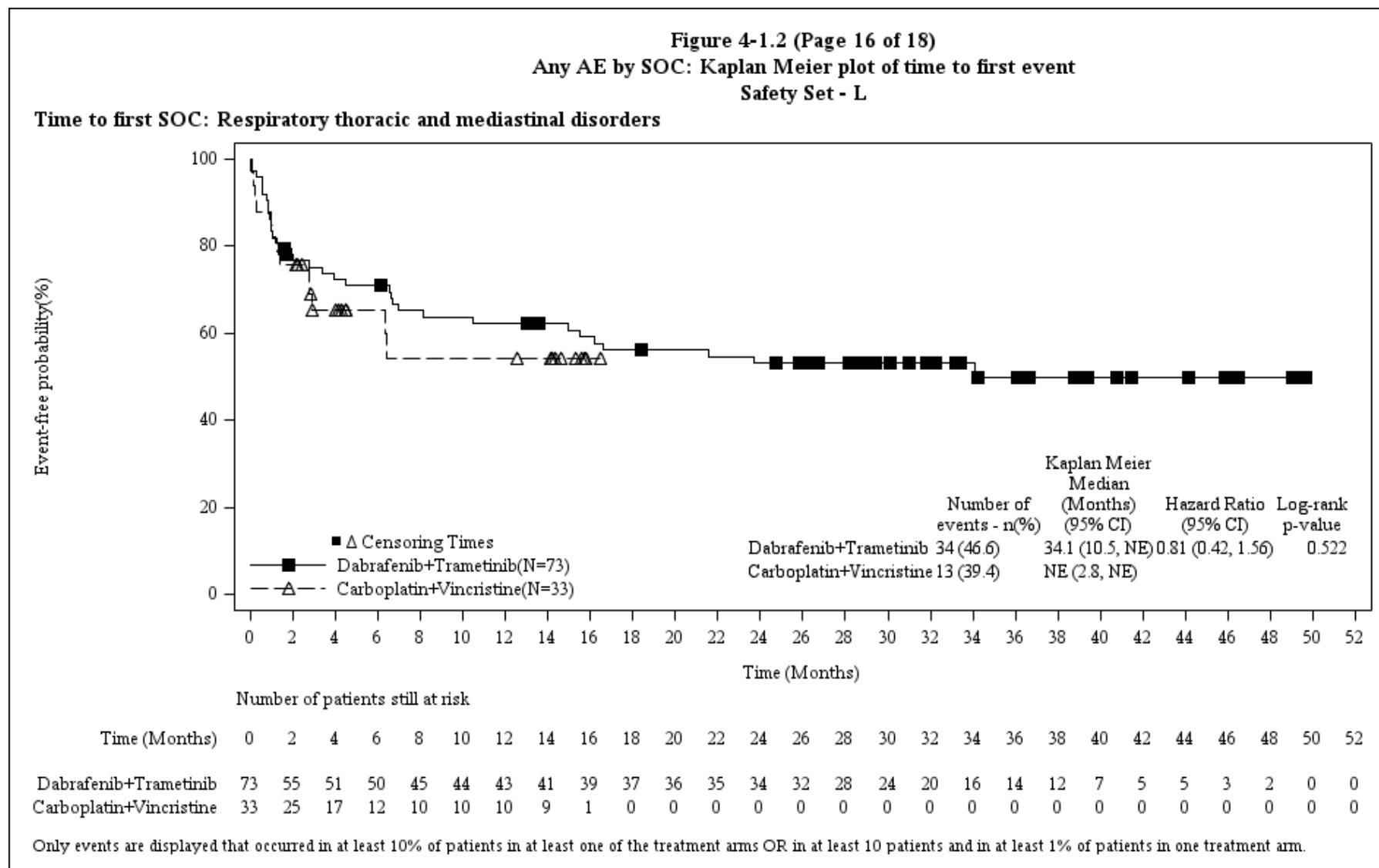
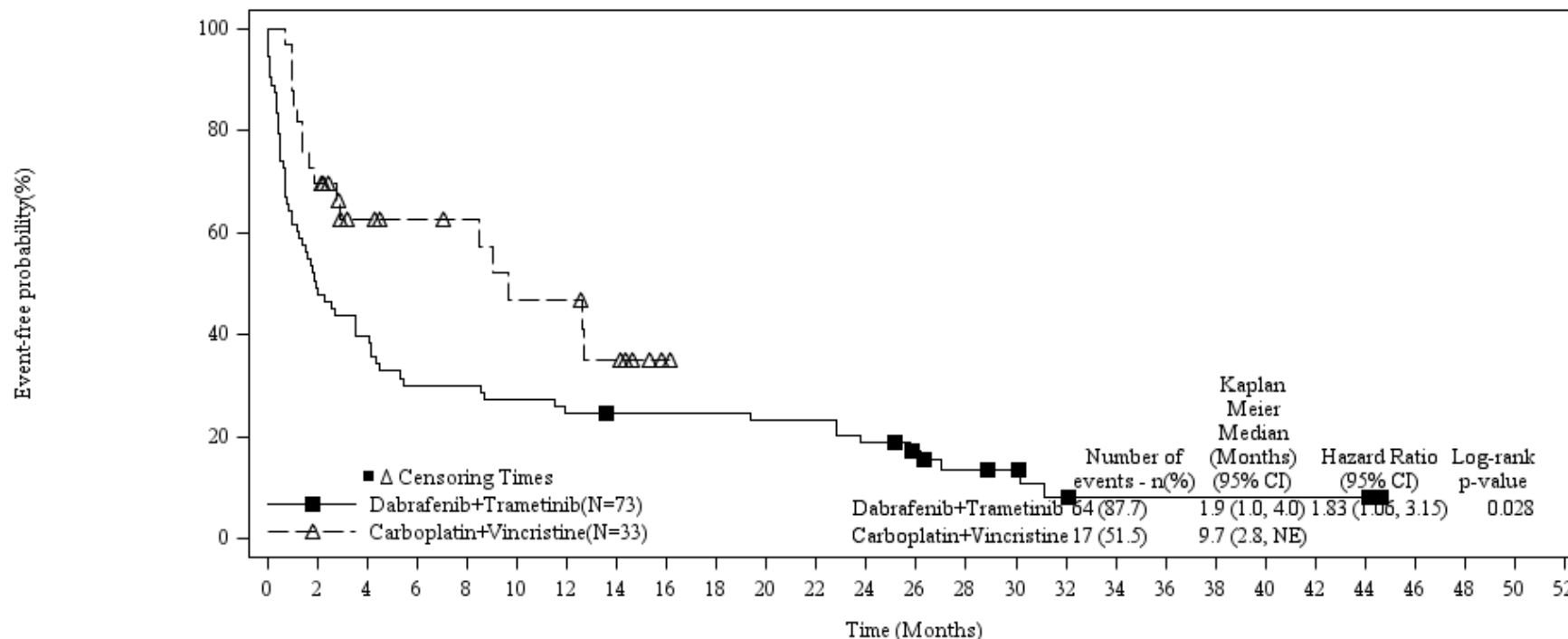


Figure 4-1.2 (Page 17 of 18)

Any AE by SOC: Kaplan Meier plot of time to first event
Safety Set - L

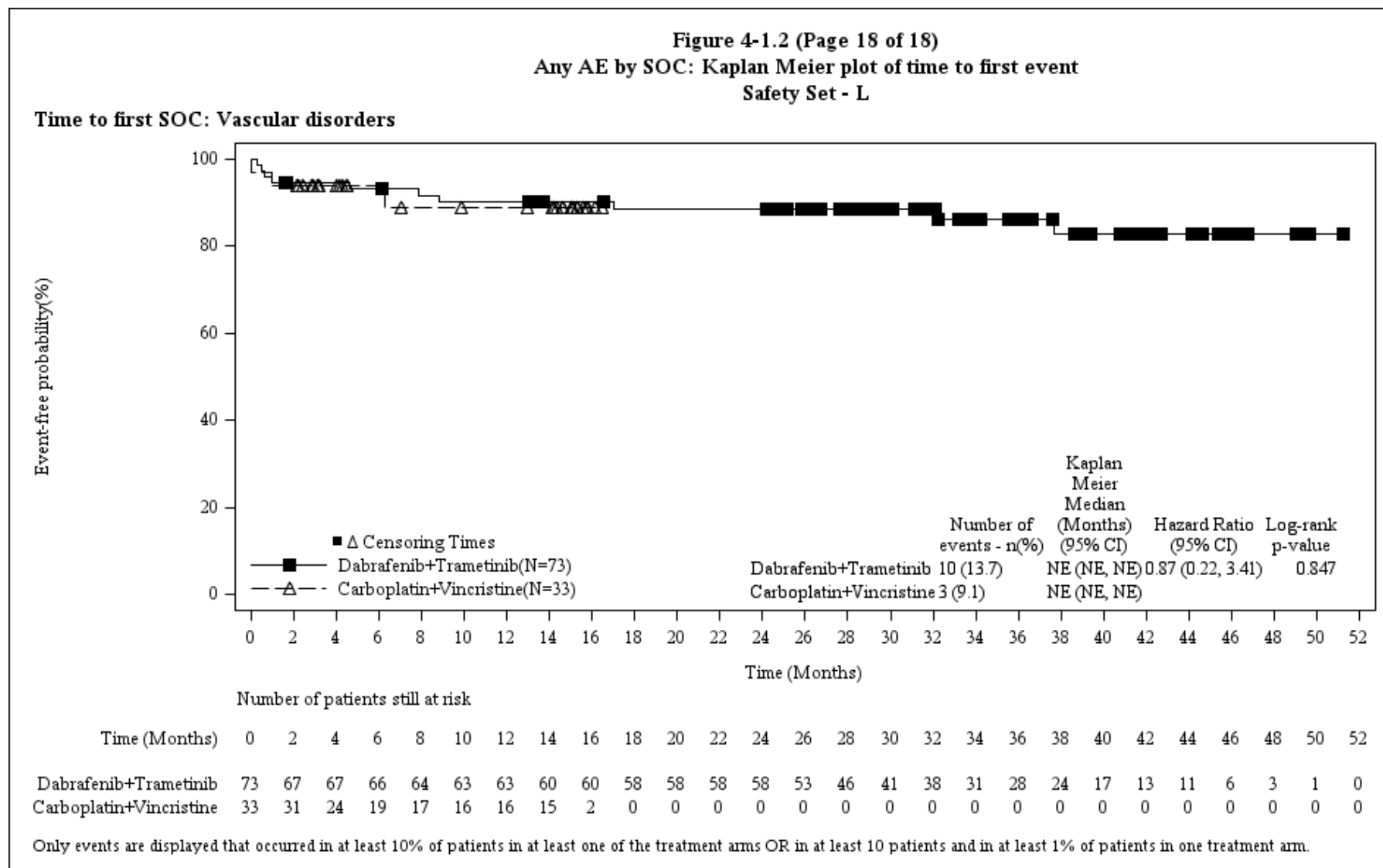
Time to first SOC: Skin and subcutaneous tissue disorders



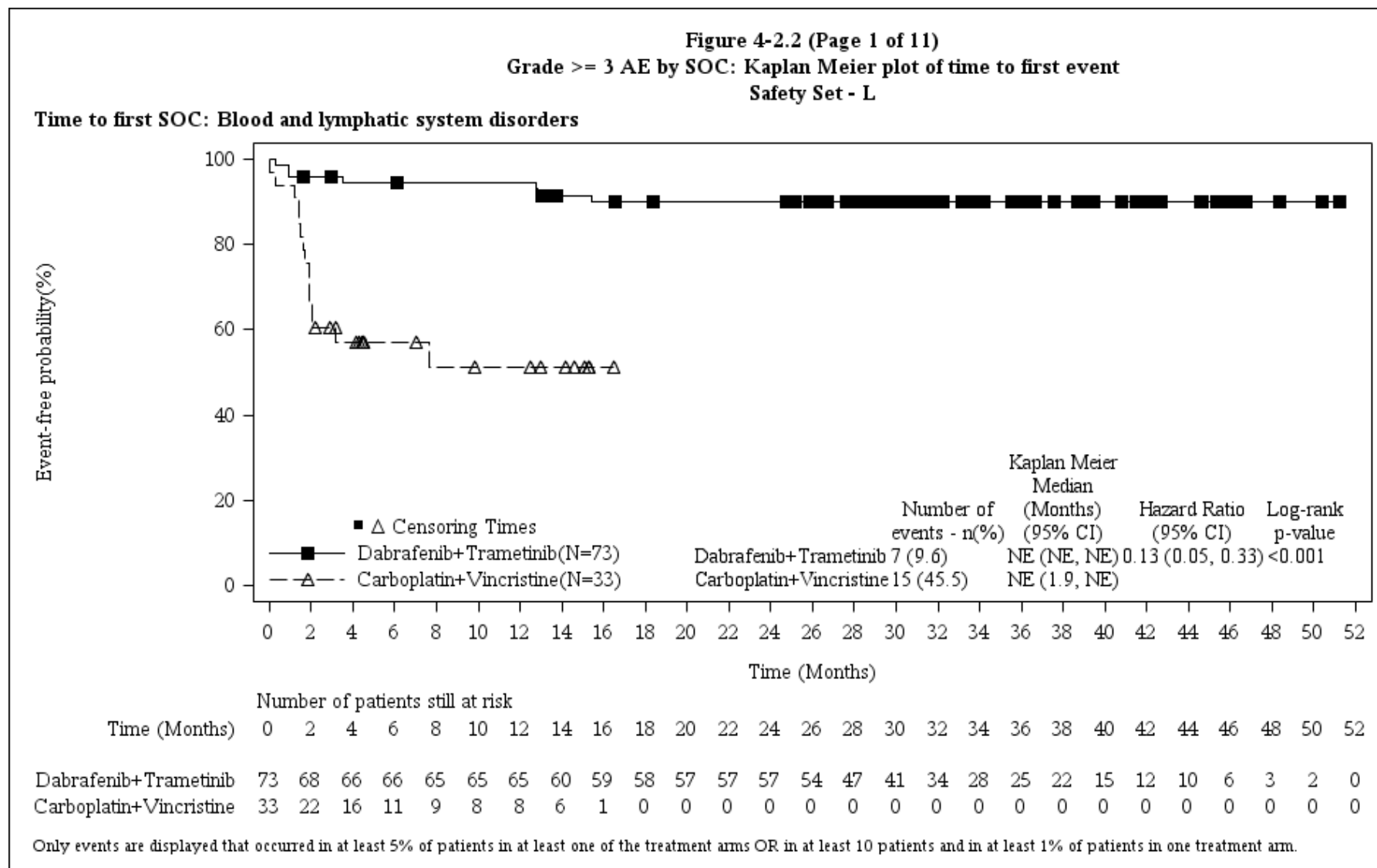
Number of patients still at risk

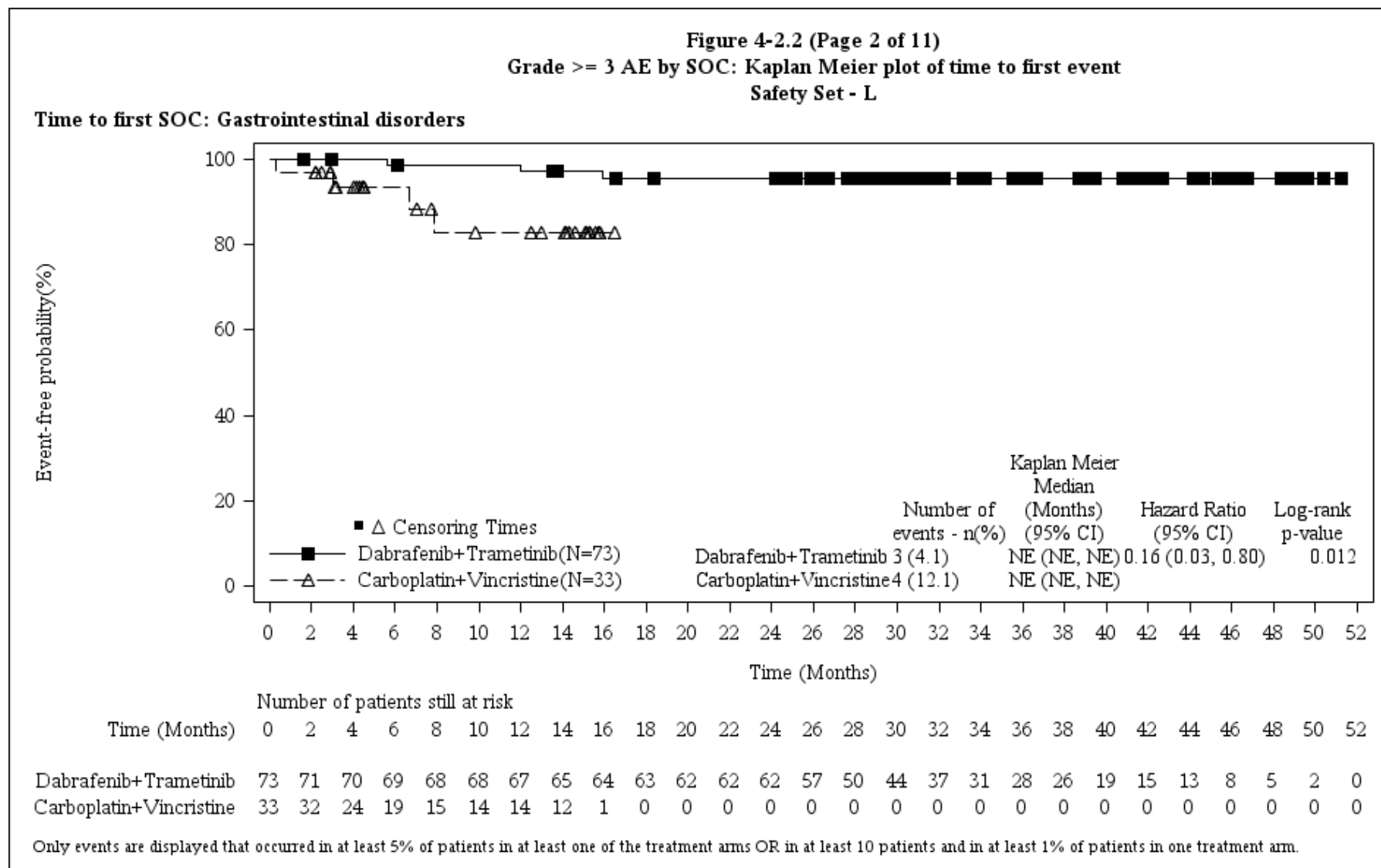
Time (Months)	0	2	4	6	8	10	12	14	16	18	20	22	24	26	28	30	32	34	36	38	40	42	44	46	48	50	52
Dabrafenib+Trametinib	73	36	29	22	22	20	18	17	17	17	16	16	13	10	7	6	3	2	2	2	2	2	2	0	0	0	0
Carboplatin+Vincristine	33	23	15	13	12	9	9	6	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0

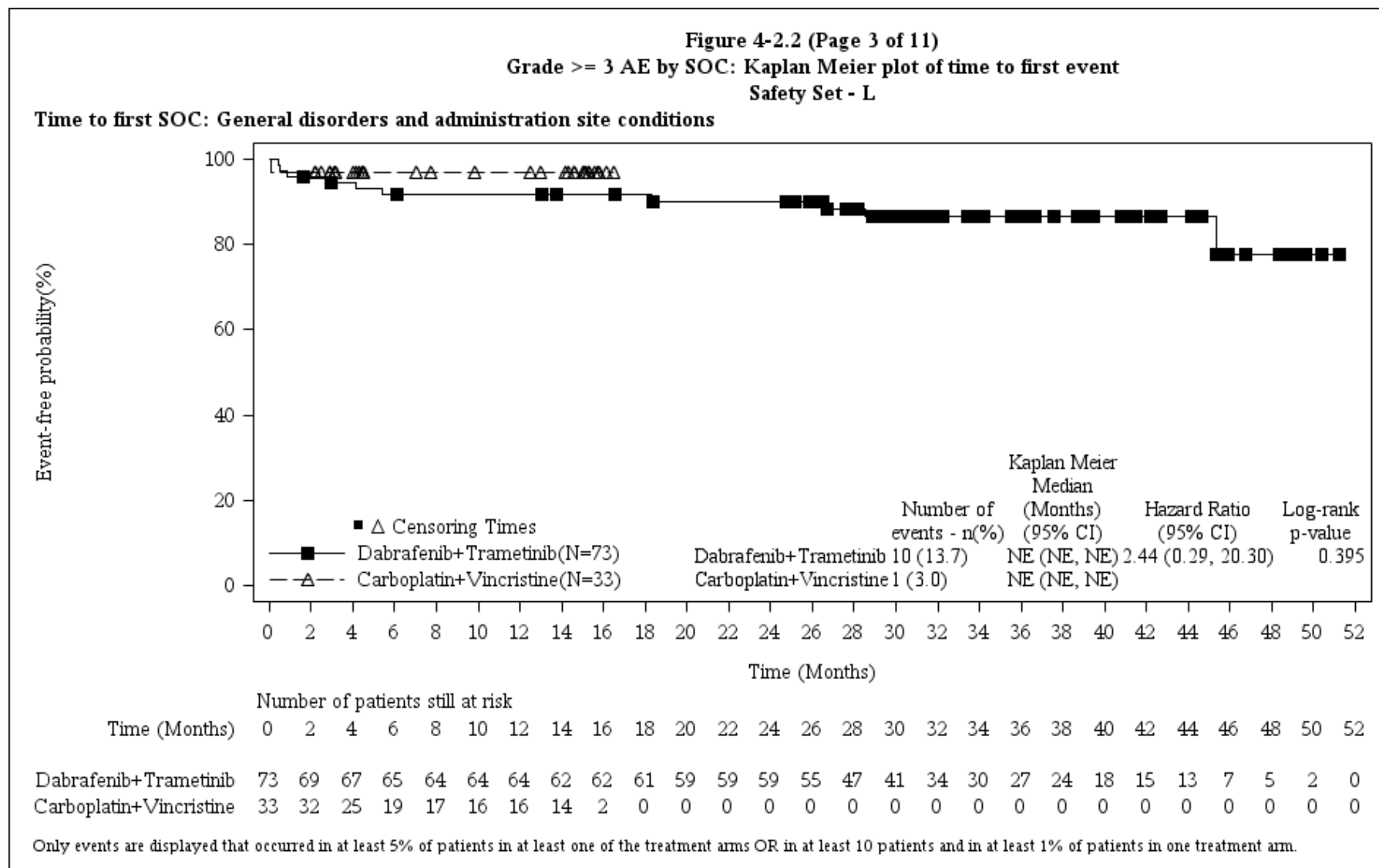
Only events are displayed that occurred in at least 10% of patients in at least one of the treatment arms OR in at least 10 patients and in at least 1% of patients in one treatment arm.

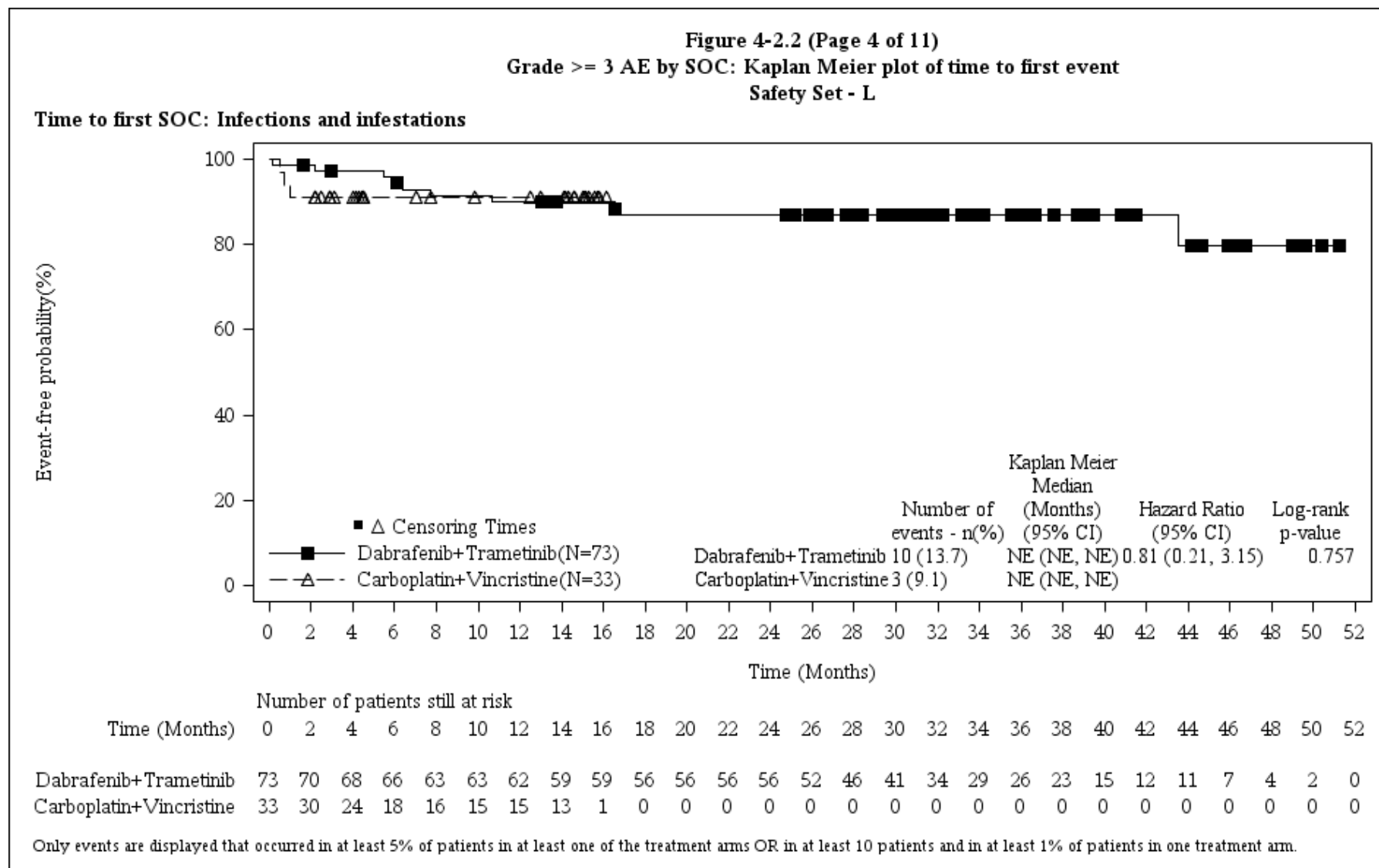


2.3.2. Schwere unerwünschte Ereignisse (CTCAE-Grad ≥ 3) nach SOC









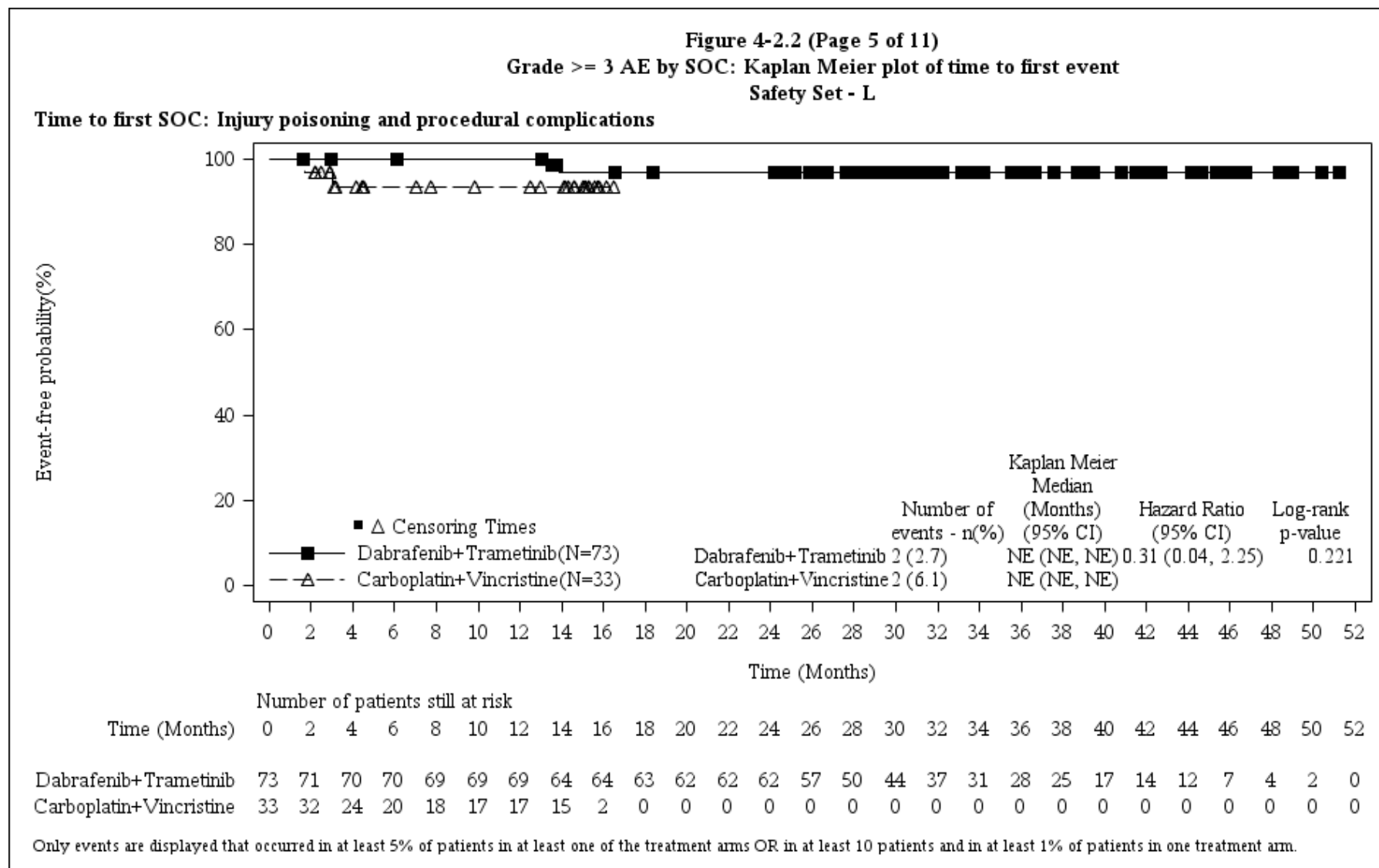
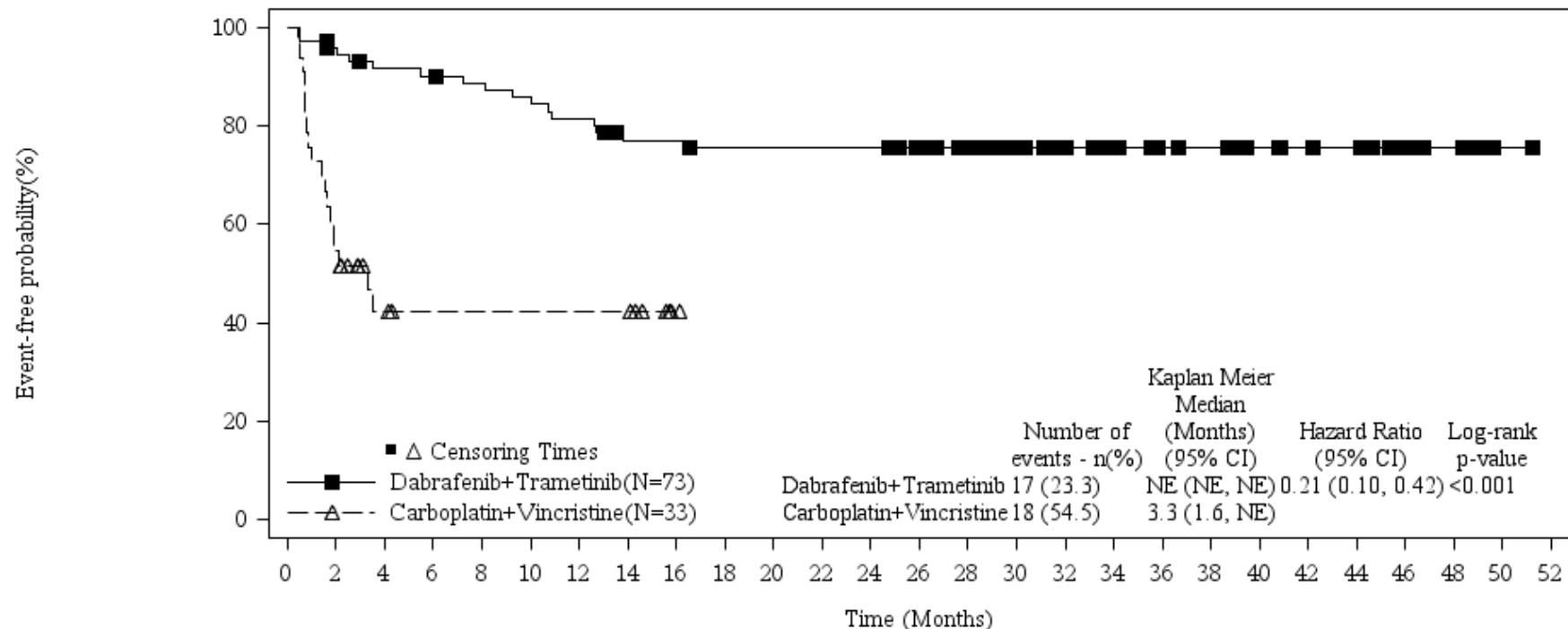


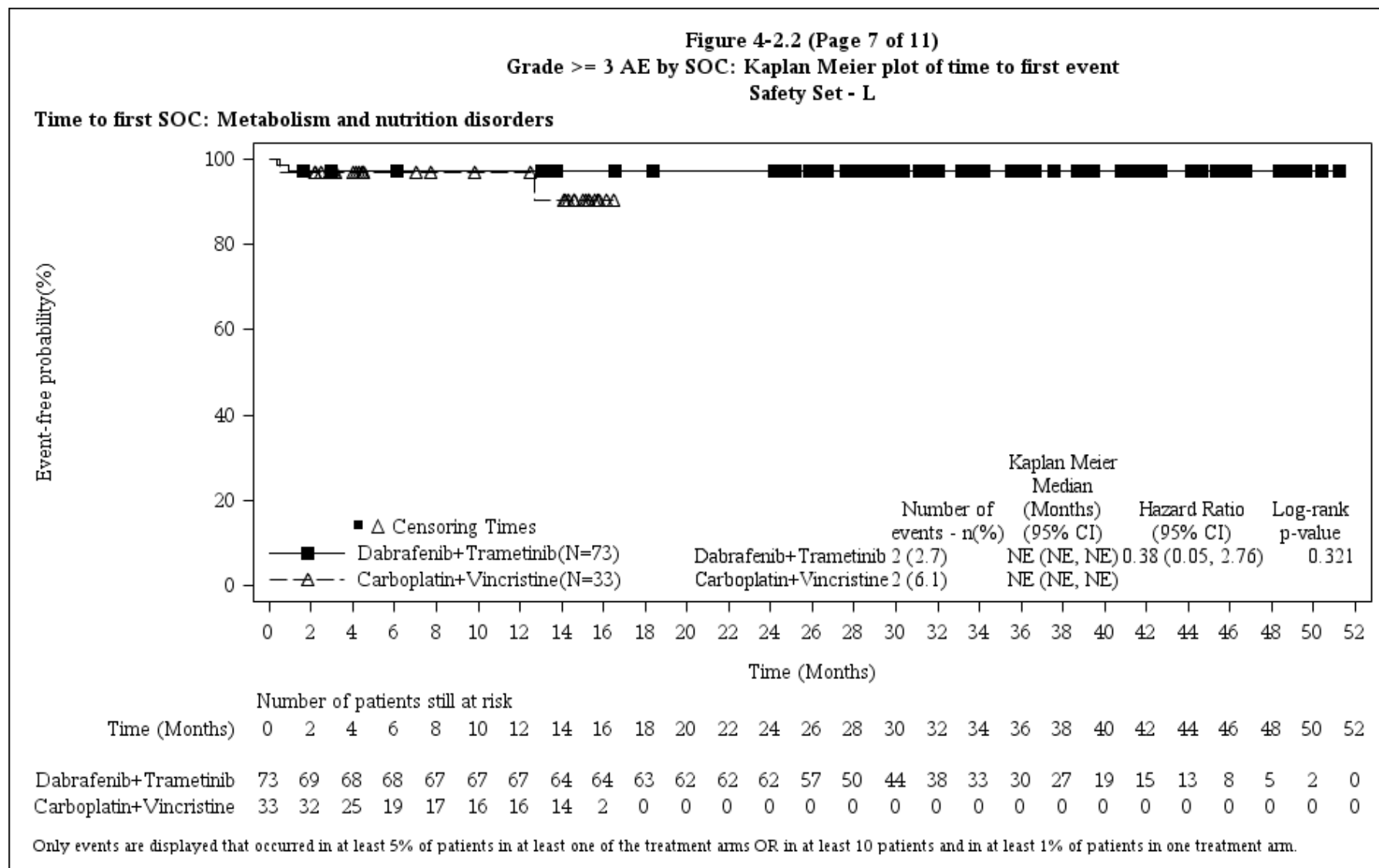
Figure 4-2.2 (Page 6 of 11)
Grade >= 3 AE by SOC: Kaplan Meier plot of time to first event
Safety Set - L

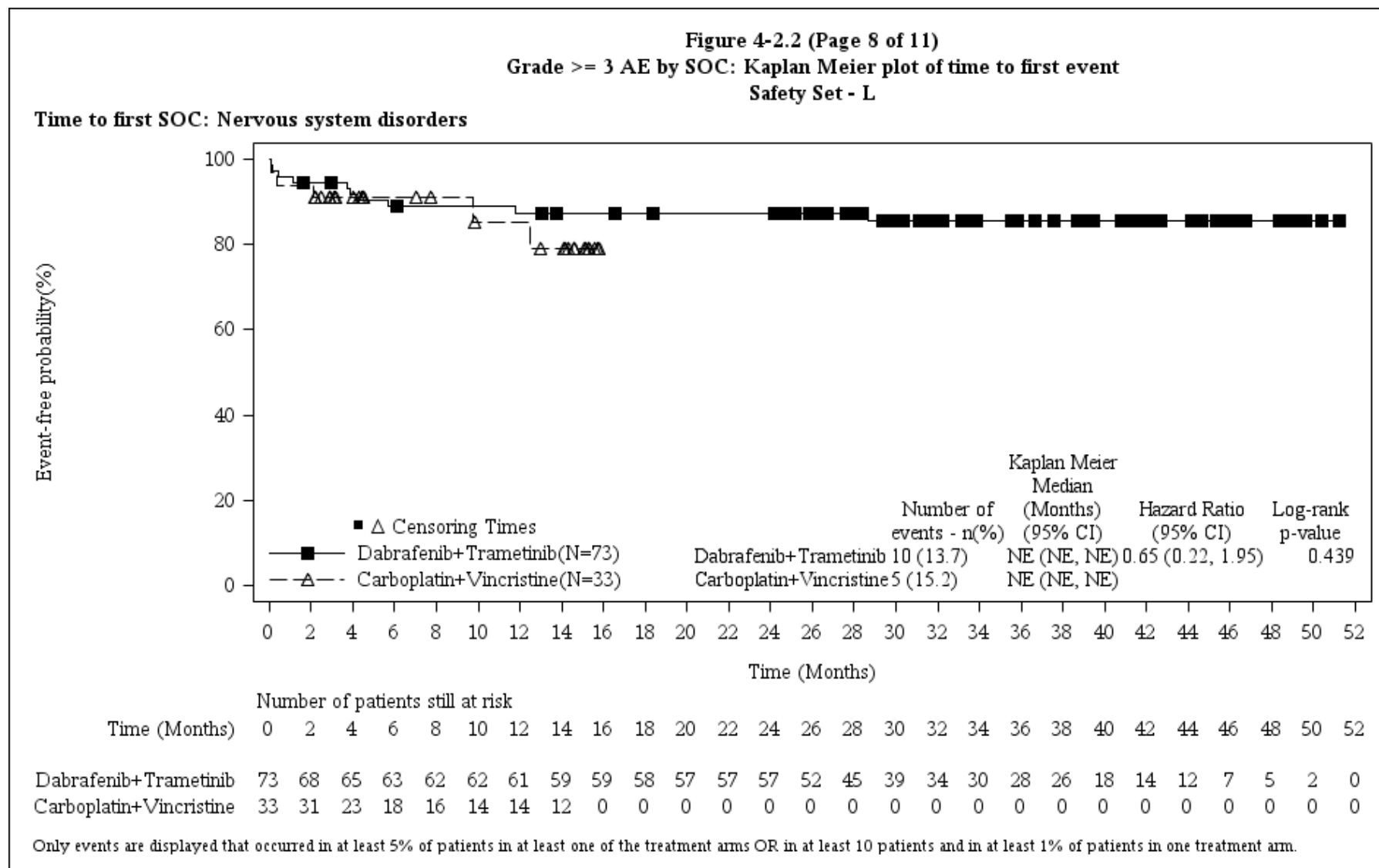
Time to first SOC: Investigations

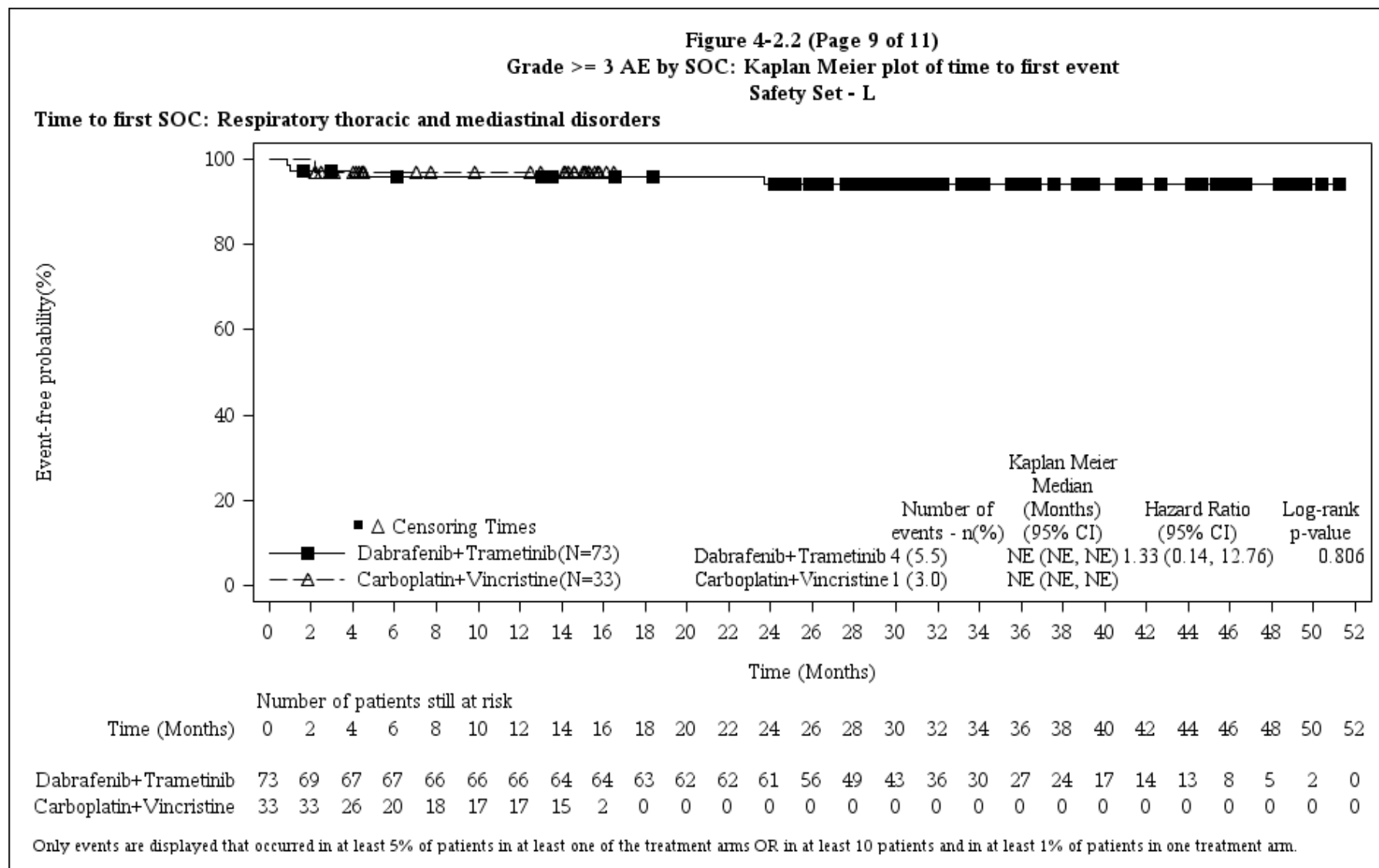


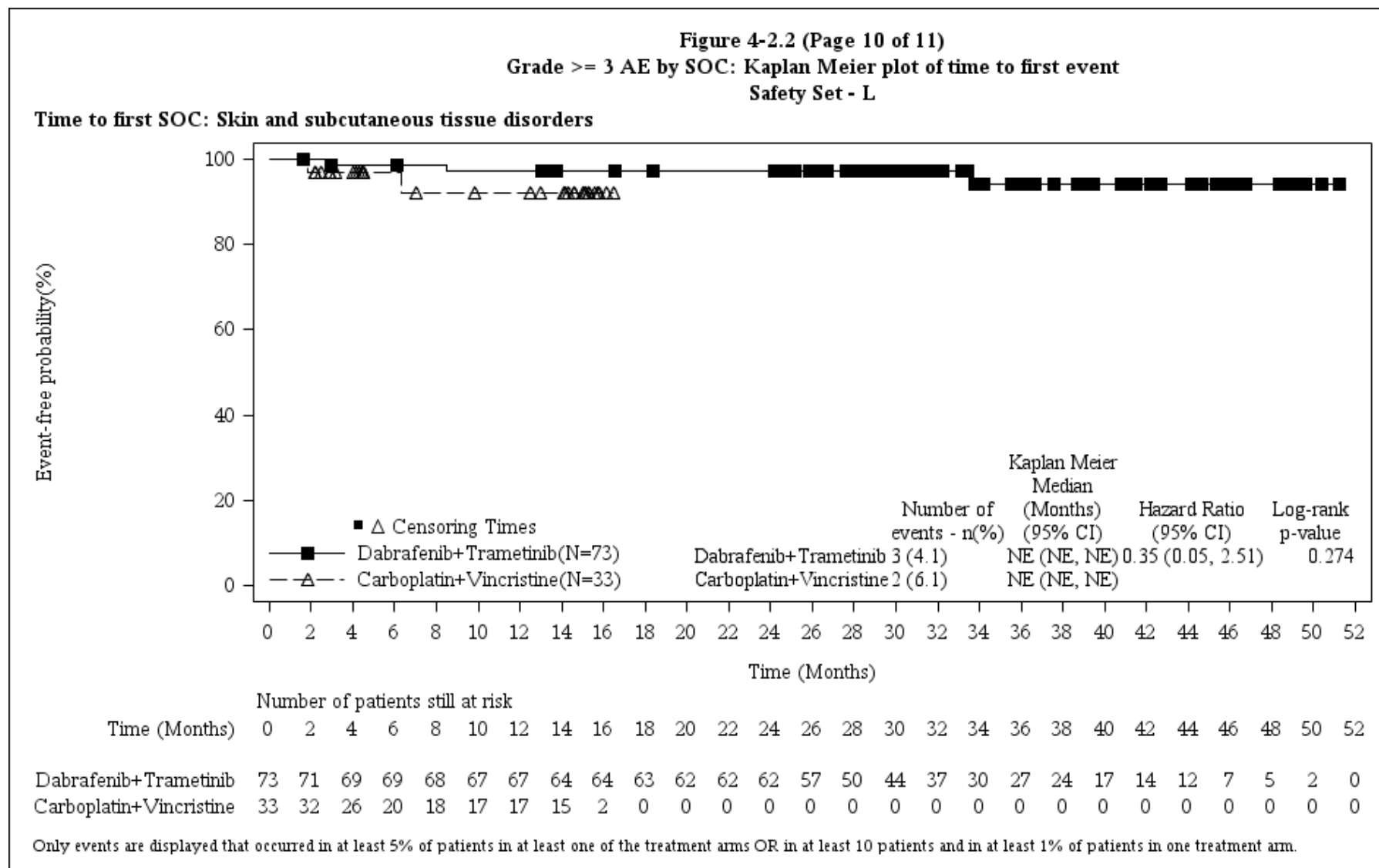
	Number of patients still at risk																										
Time (Months)	0	2	4	6	8	10	12	14	16	18	20	22	24	26	28	30	32	34	36	38	40	42	44	46	48	50	52
Dabrafenib+Trametinib	73	68	64	63	61	59	56	51	51	49	49	49	45	39	33	28	24	21	20	14	12	11	6	4	1	0	
Carboplatin+Vincristine	33	18	9	7	7	7	7	7	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	

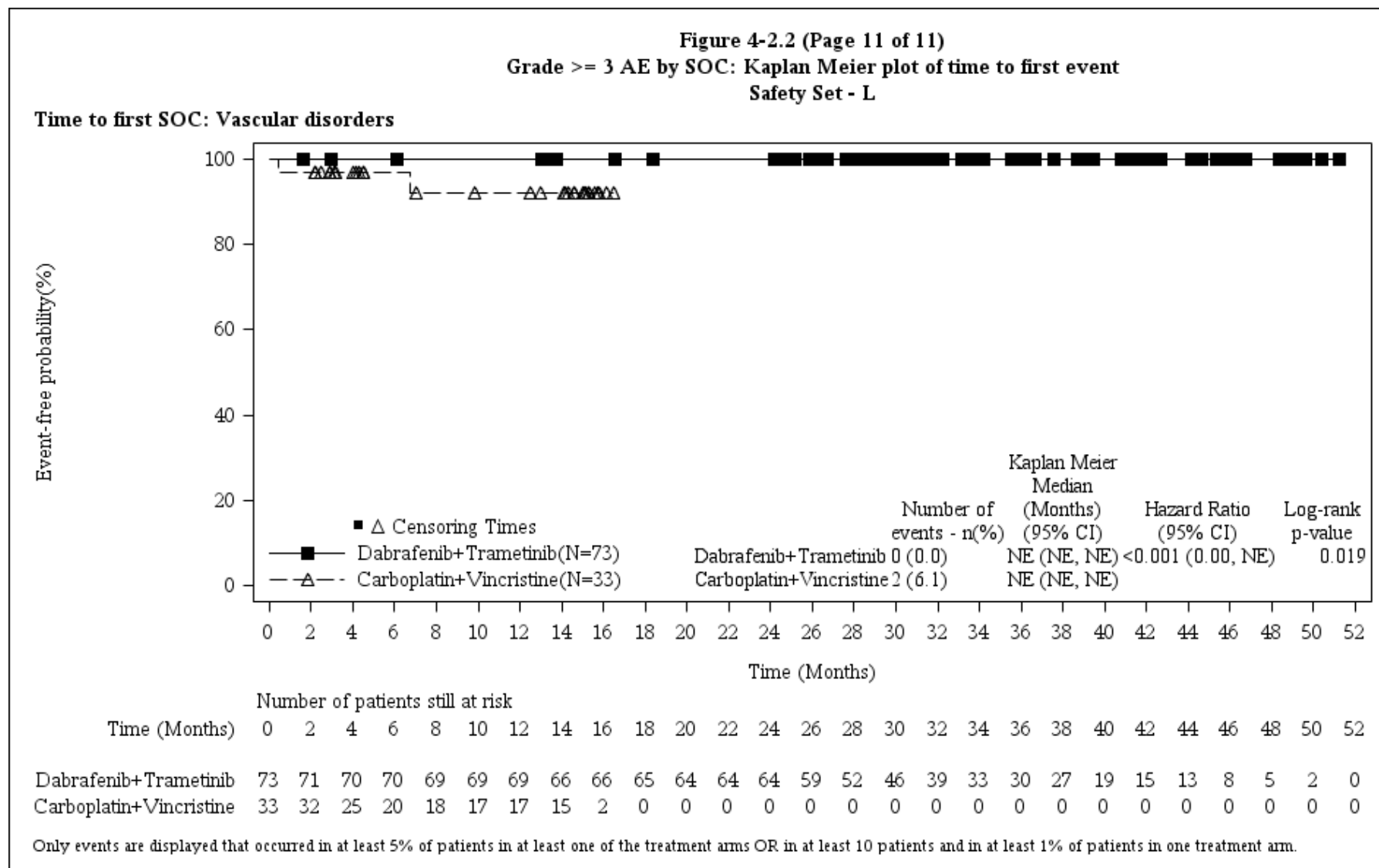
Only events are displayed that occurred in at least 5% of patients in at least one of the treatment arms OR in at least 10 patients and in at least 1% of patients in one treatment arm.



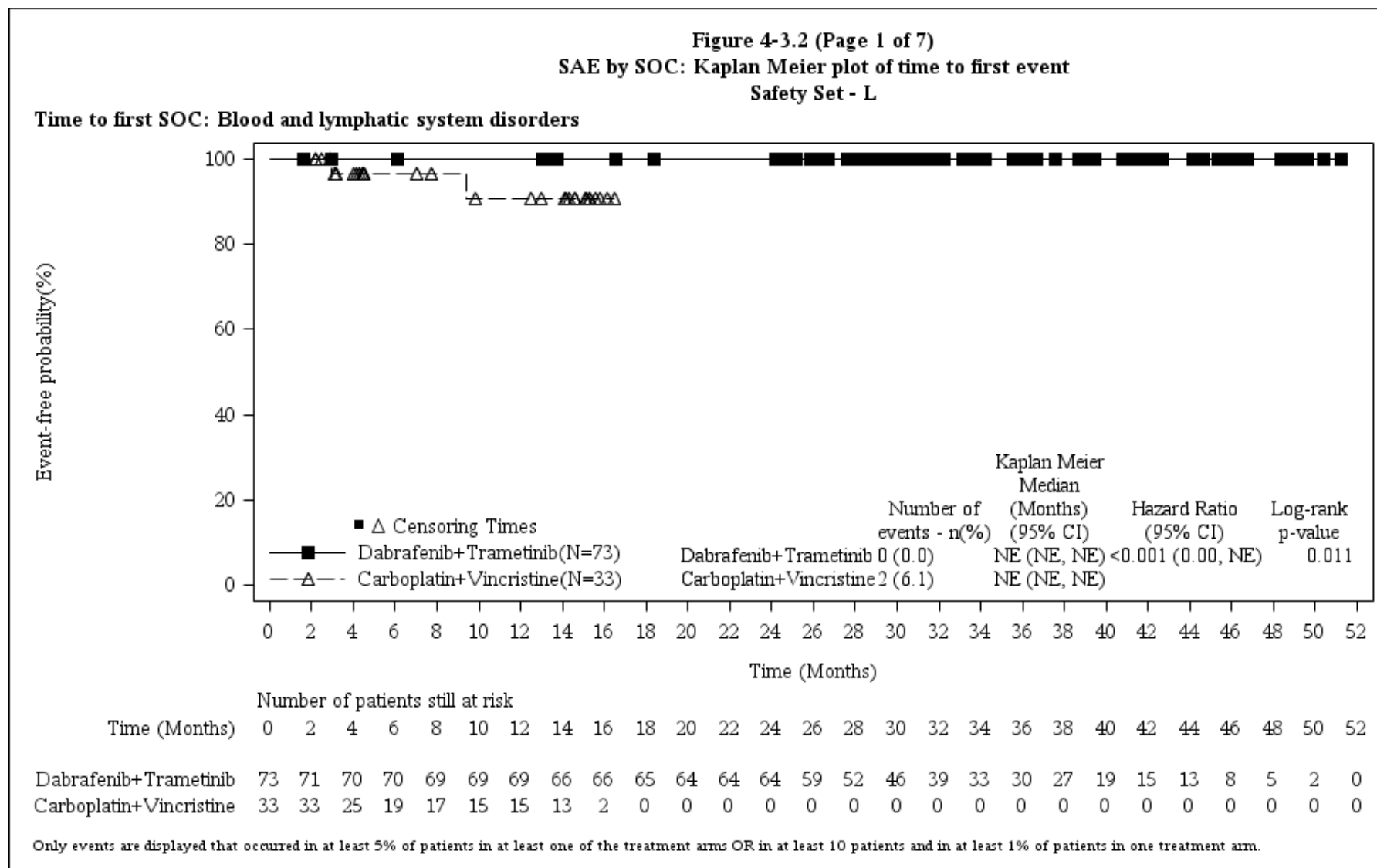


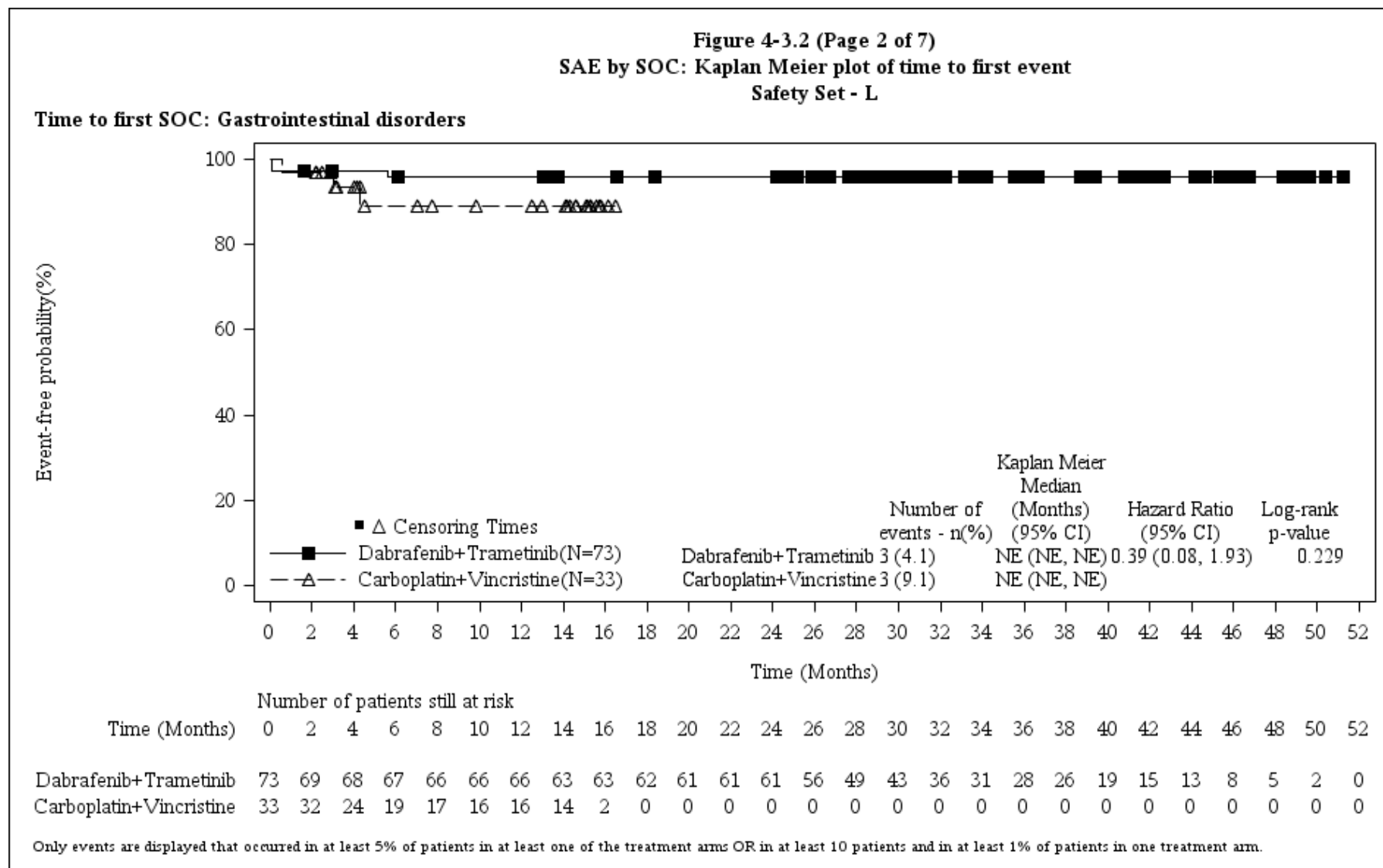


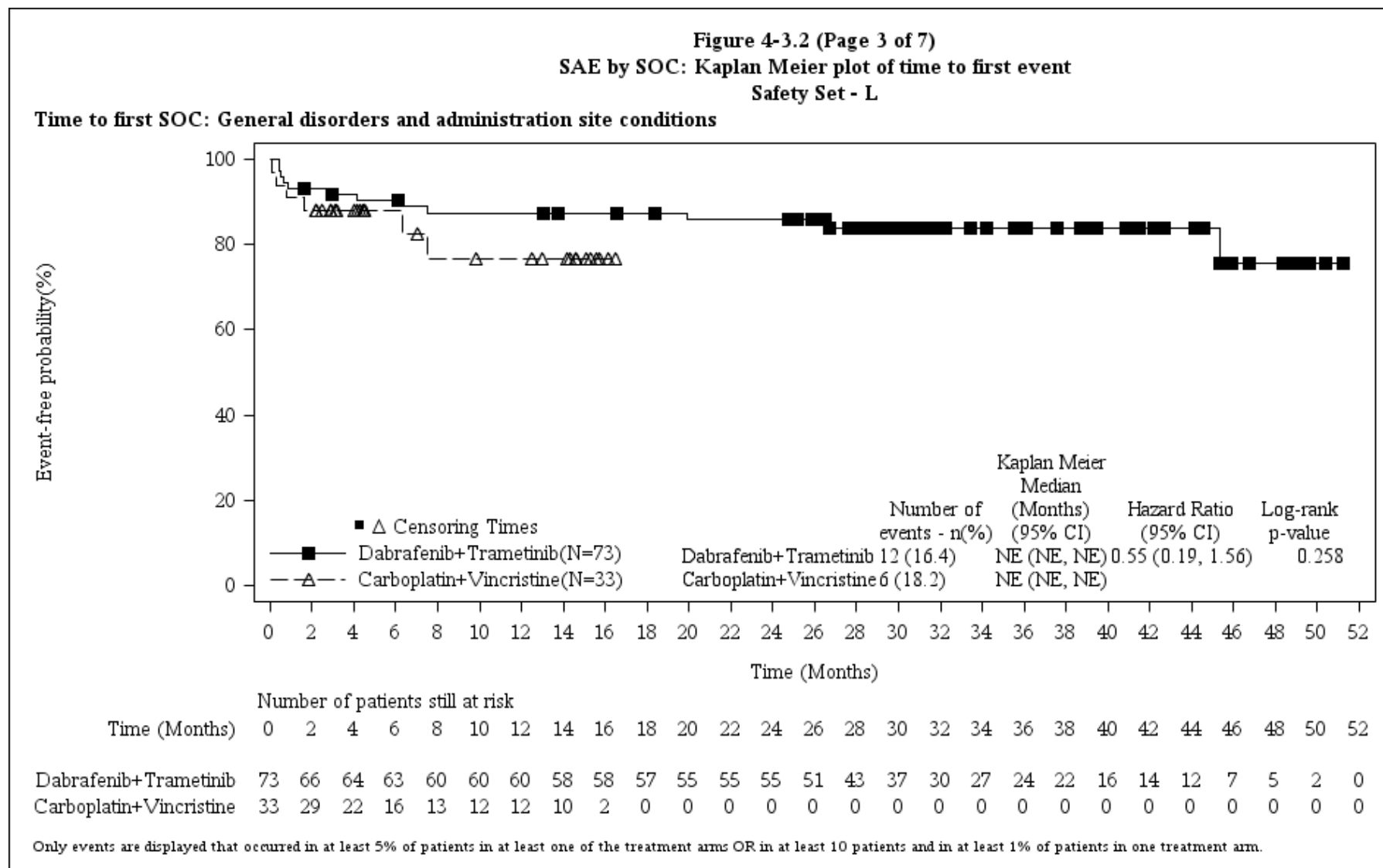


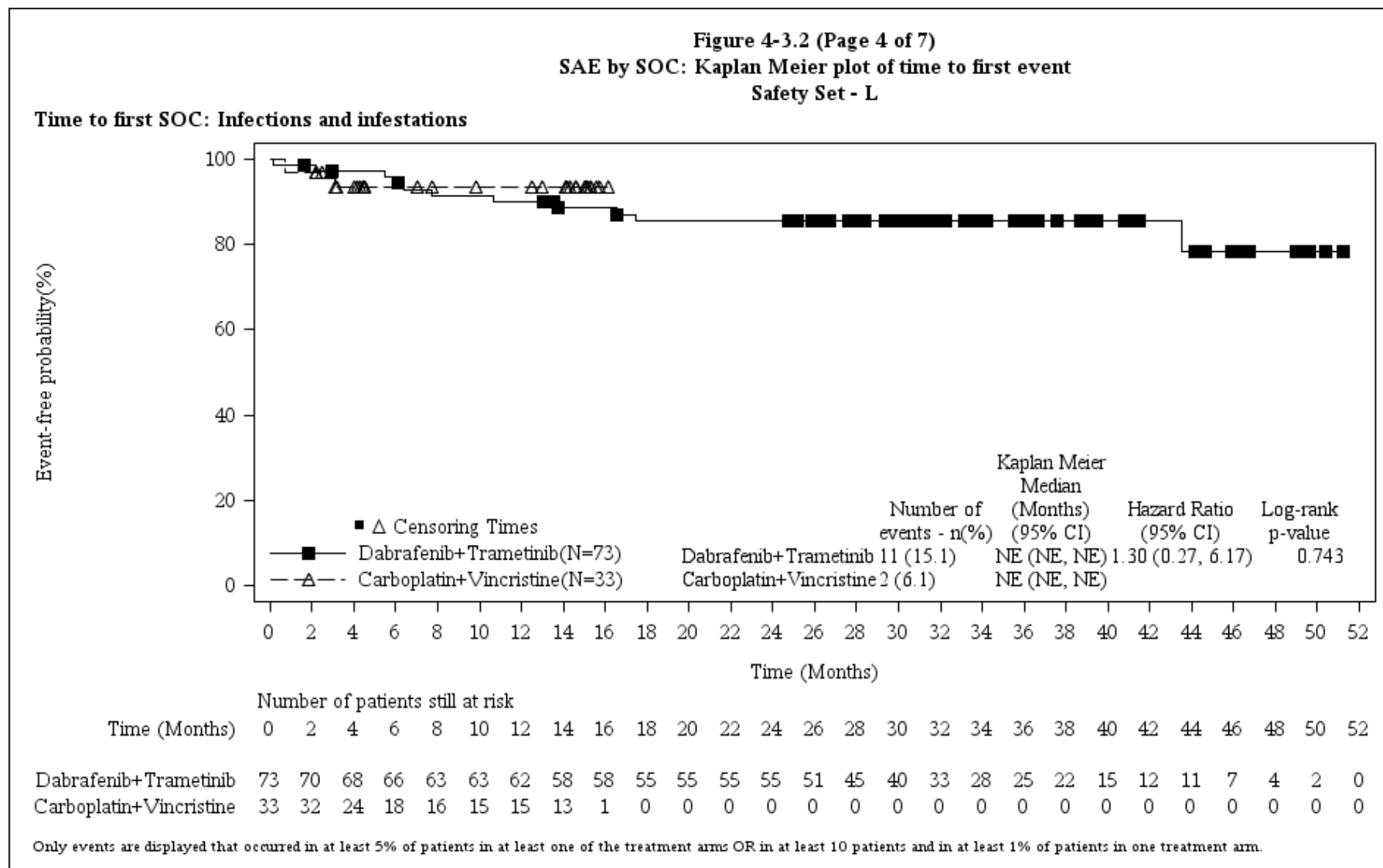


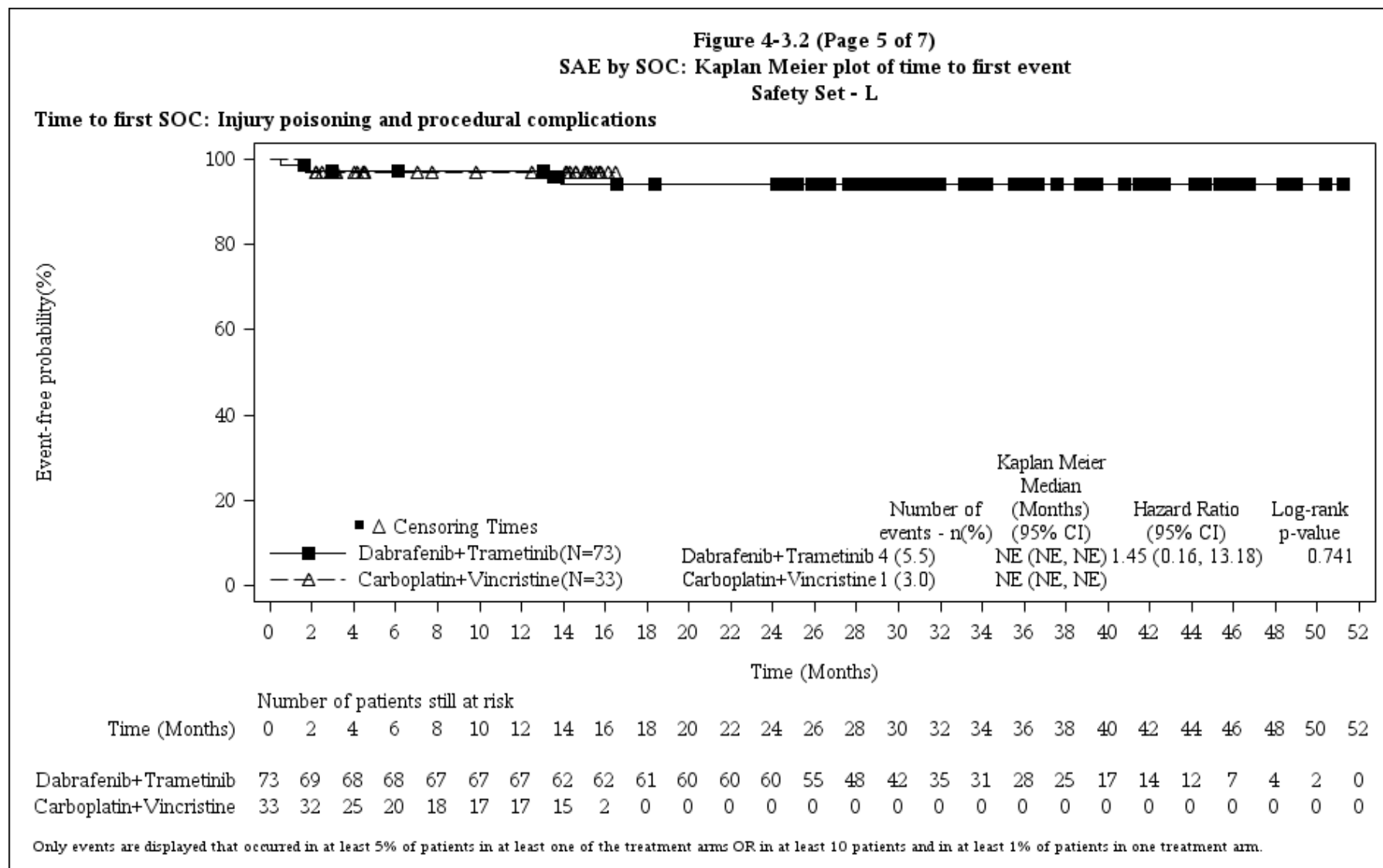
2.3.3. Schwerwiegende unerwünschte Ereignisse nach SOC

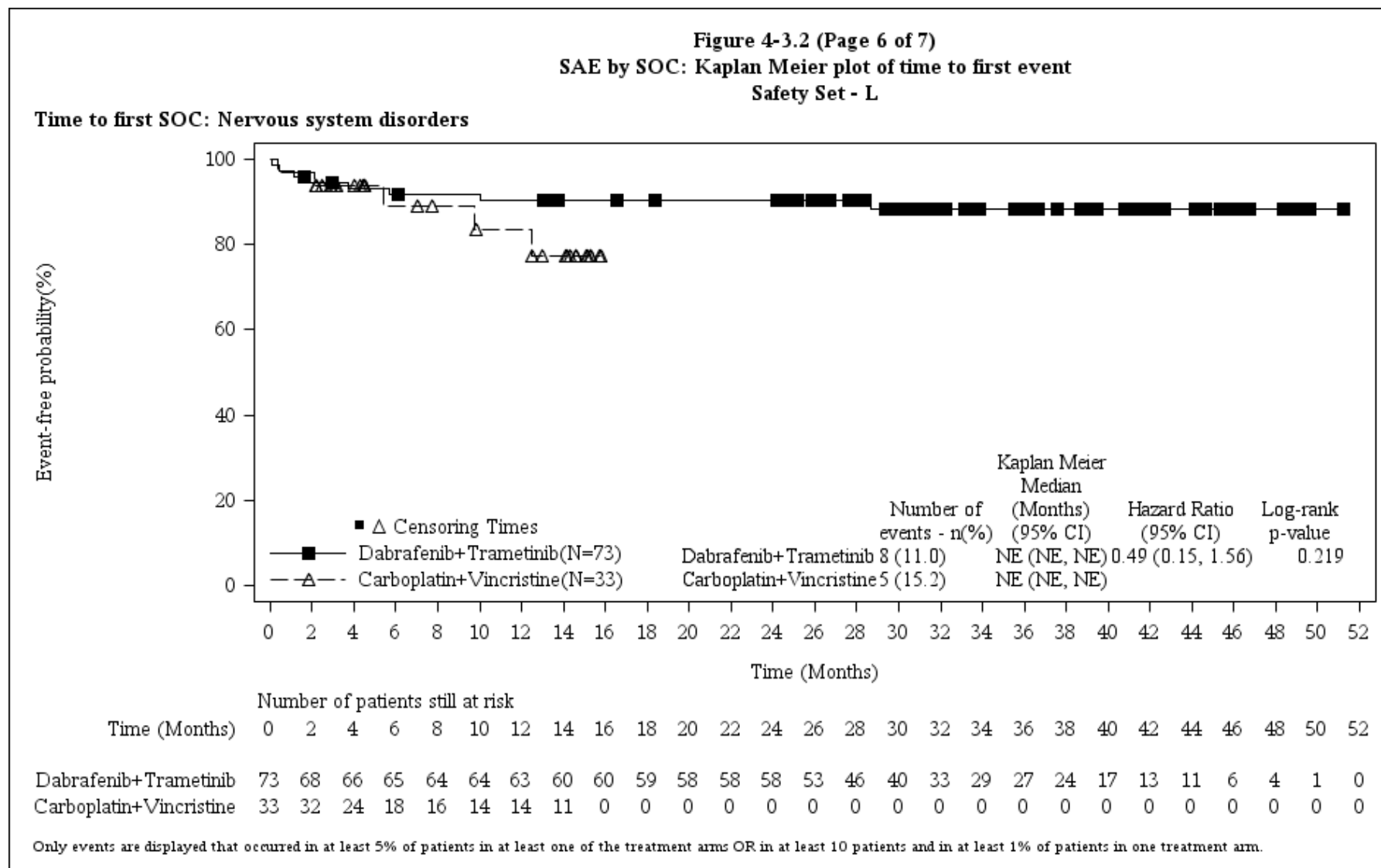


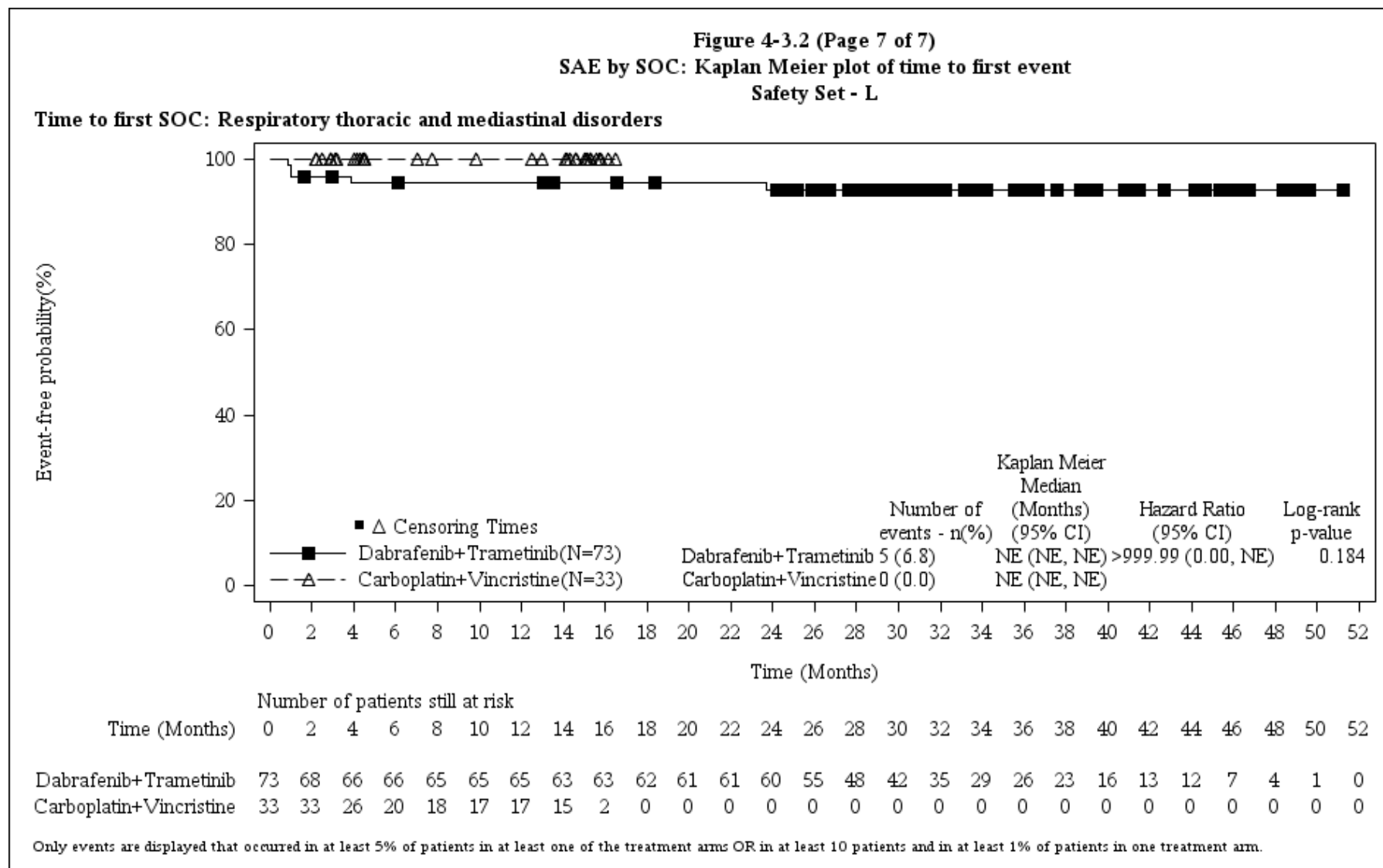




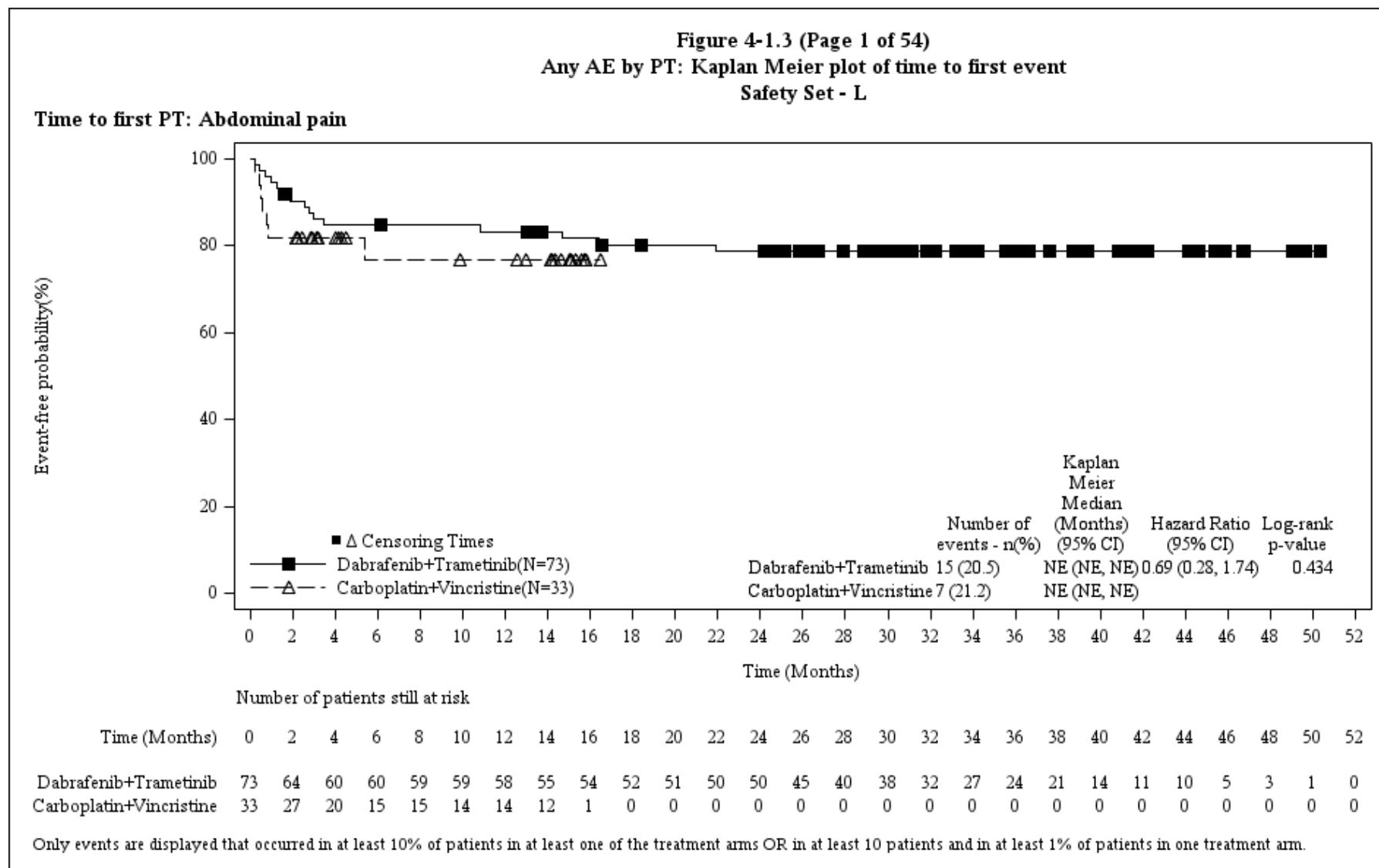


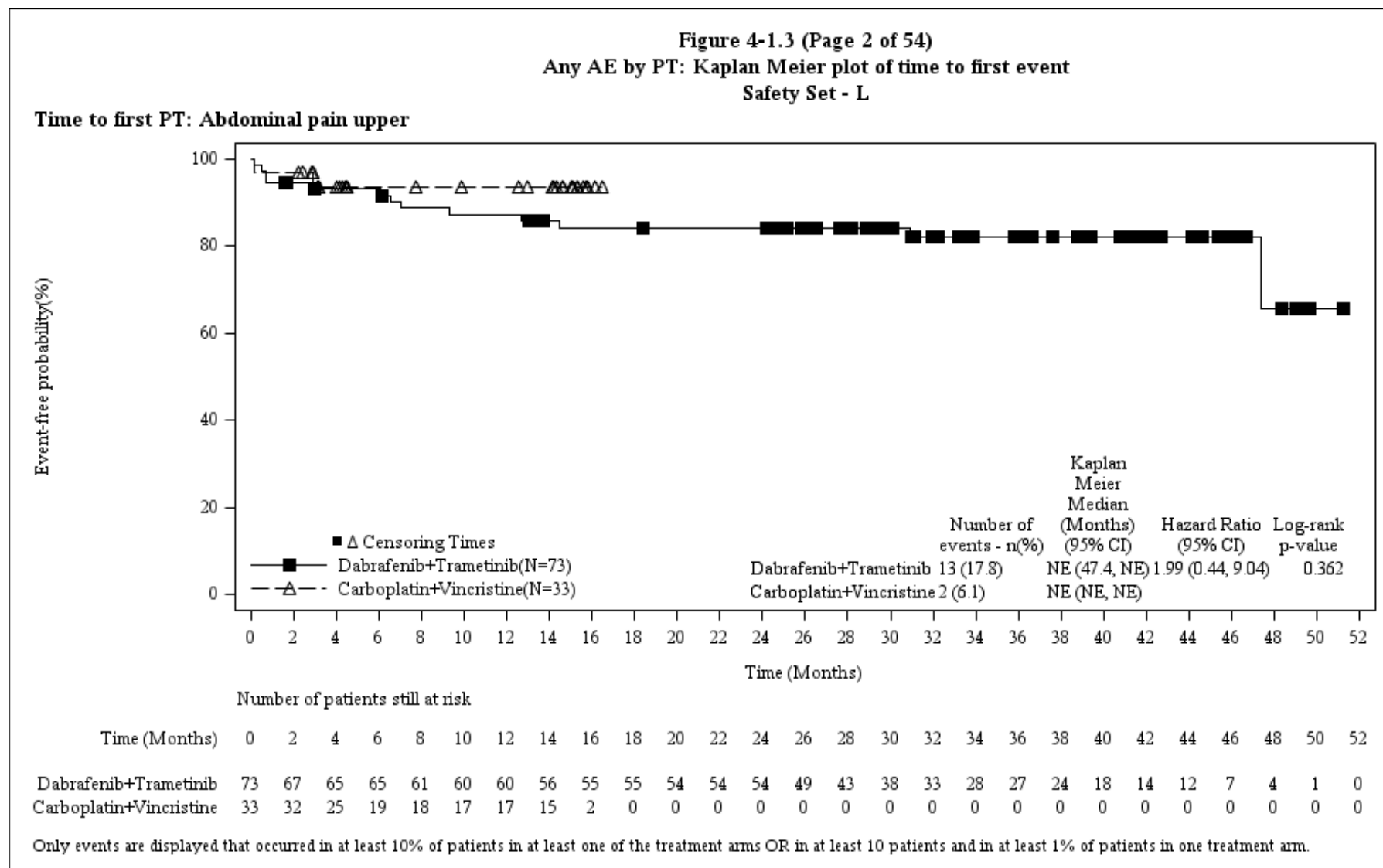


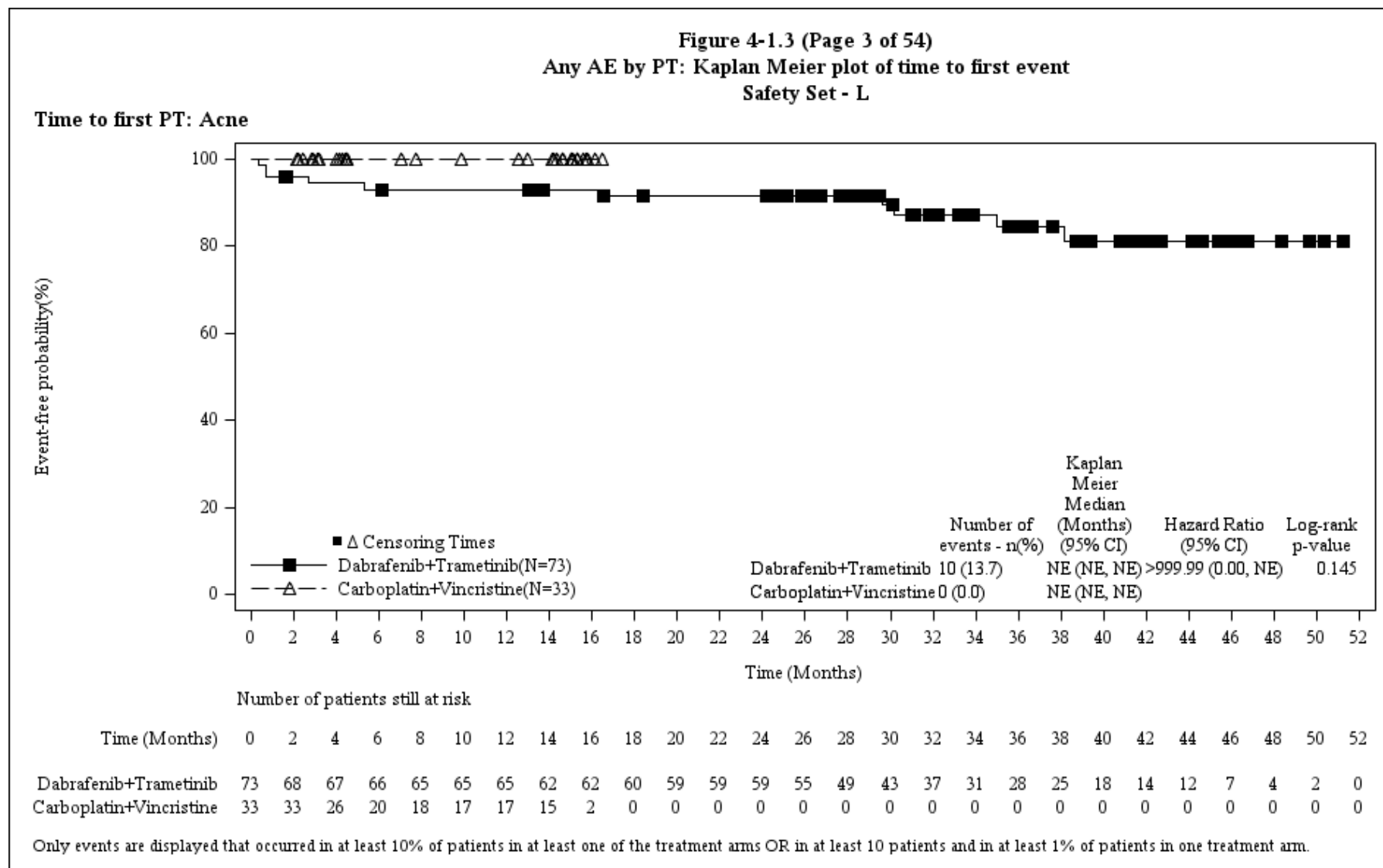


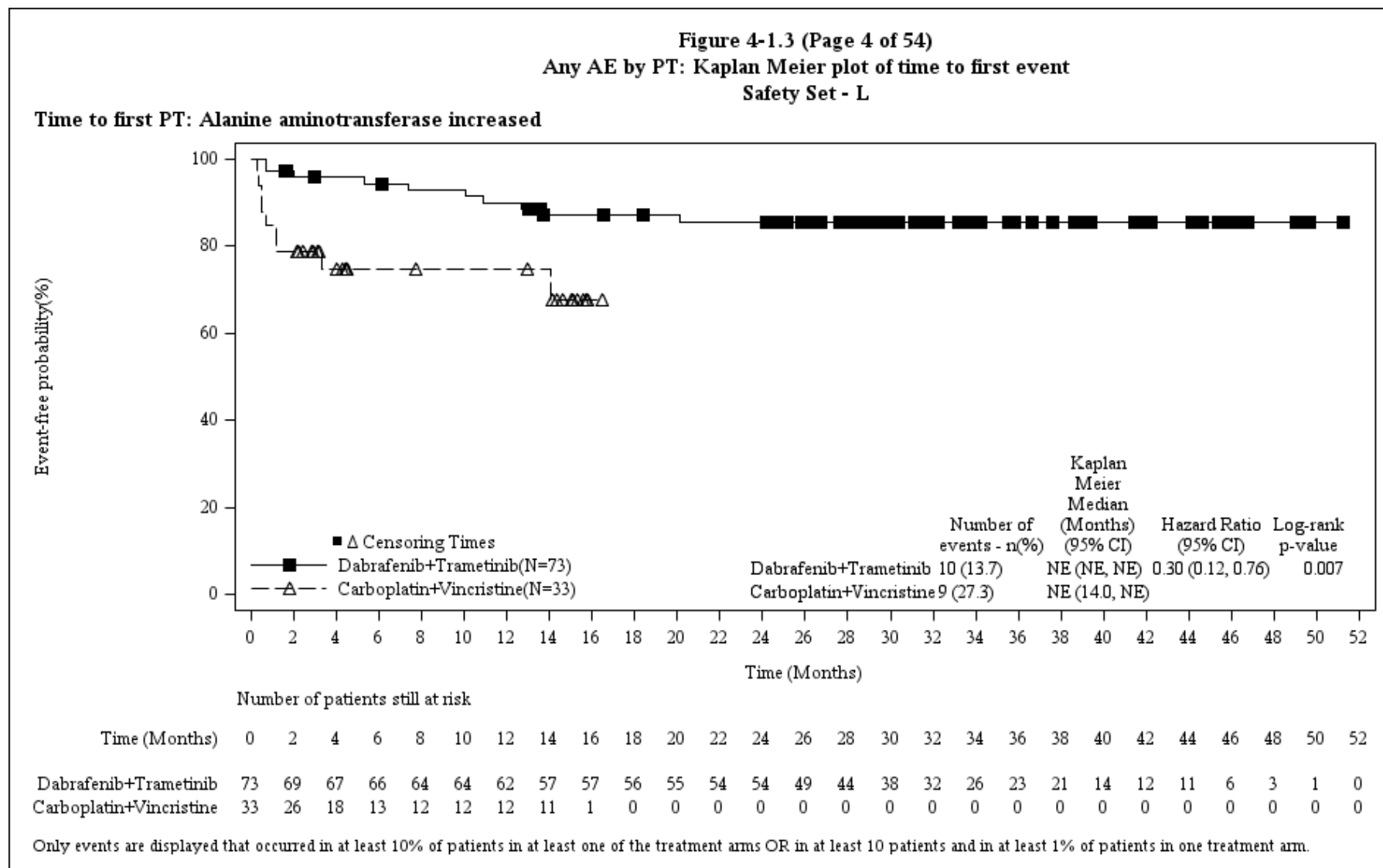


2.3.4. Unerwünschte Ereignisse nach PT









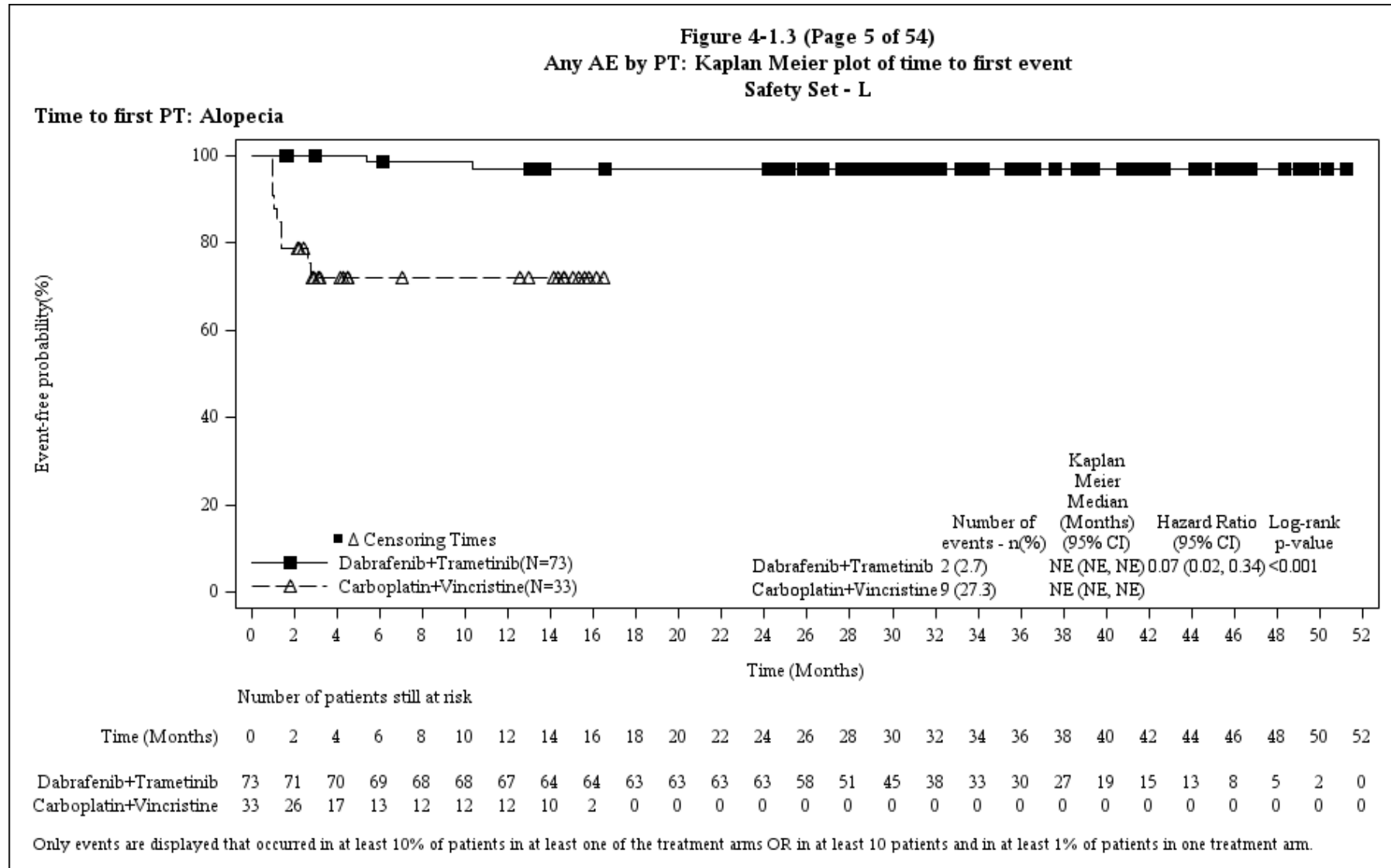
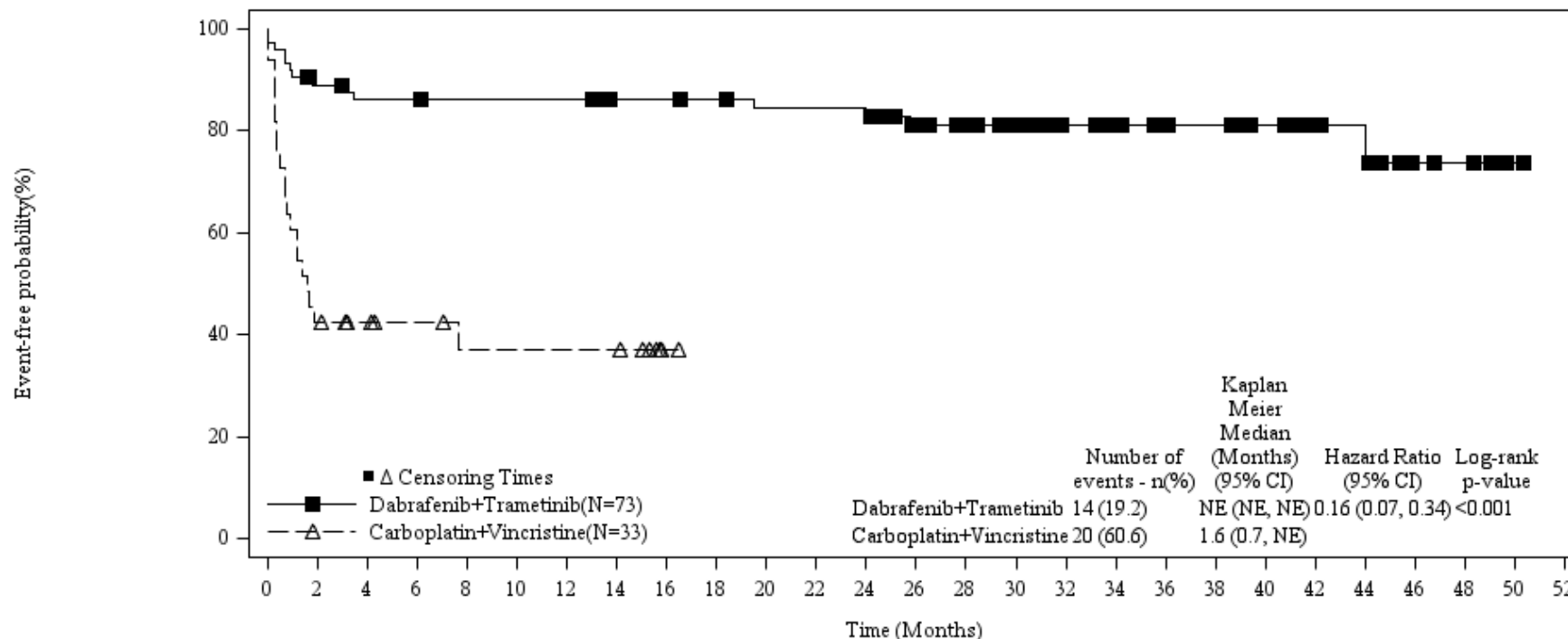


Figure 4-1.3 (Page 6 of 54)
Any AE by PT: Kaplan Meier plot of time to first event
Safety Set - L

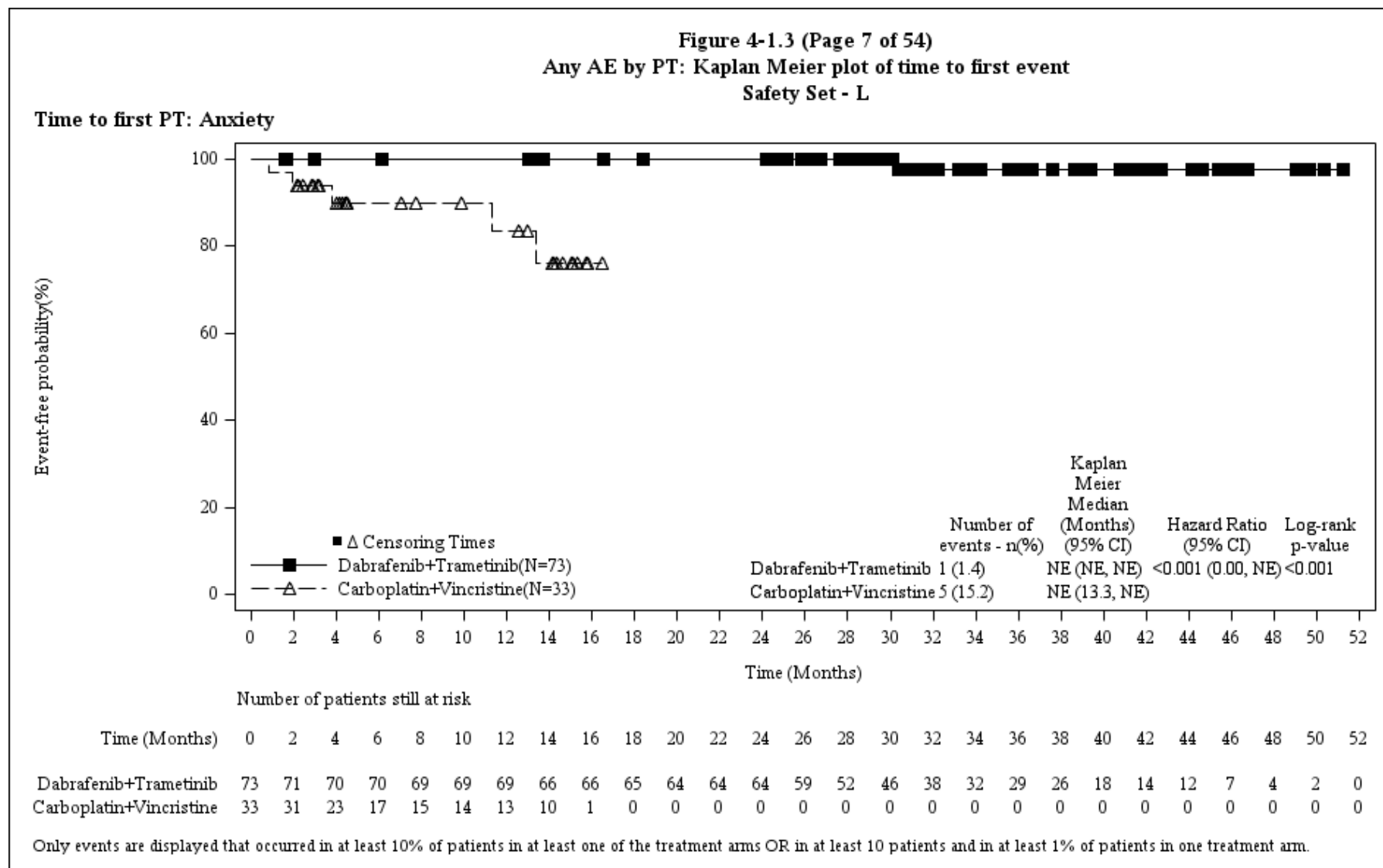
Time to first PT: Anaemia

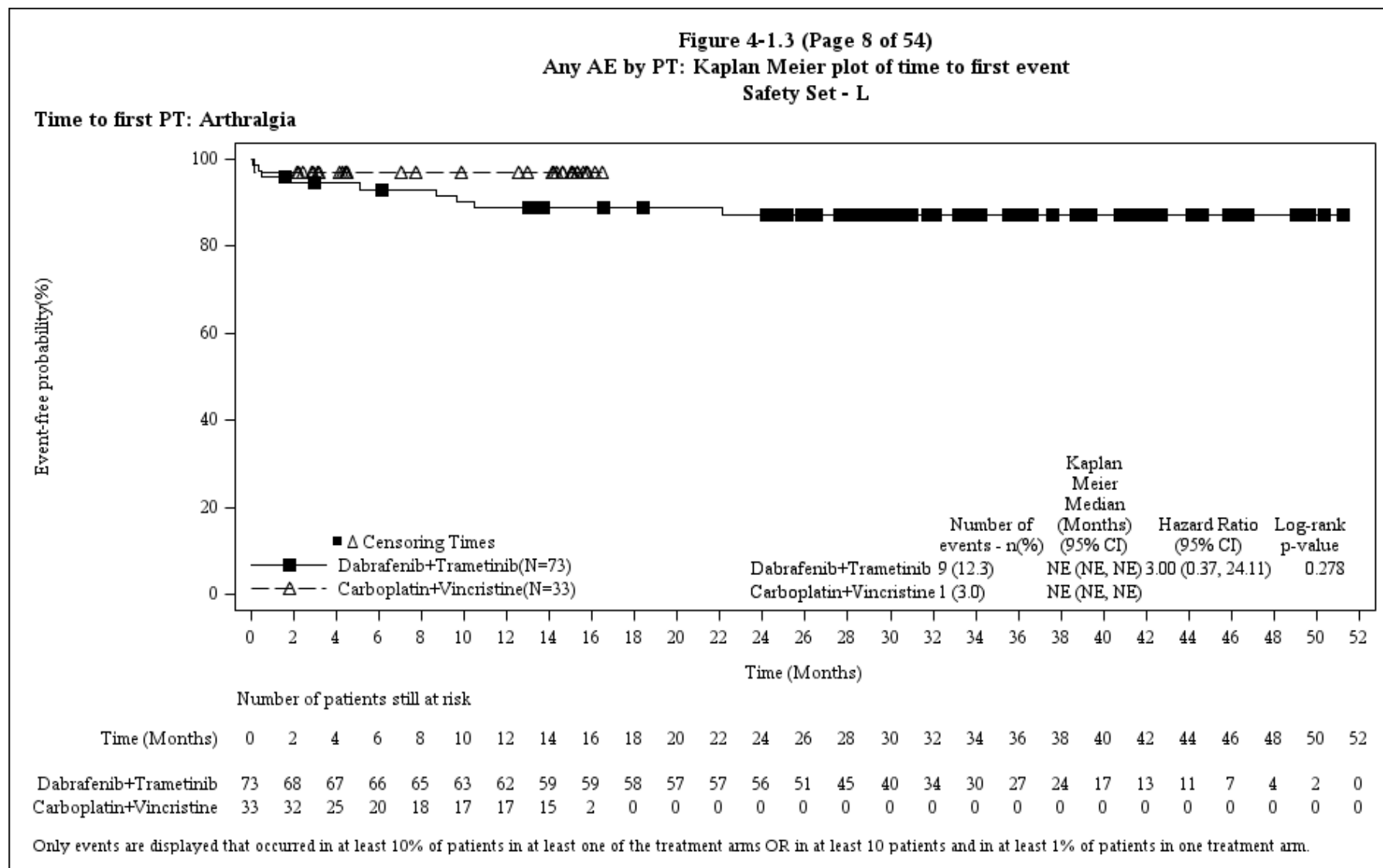


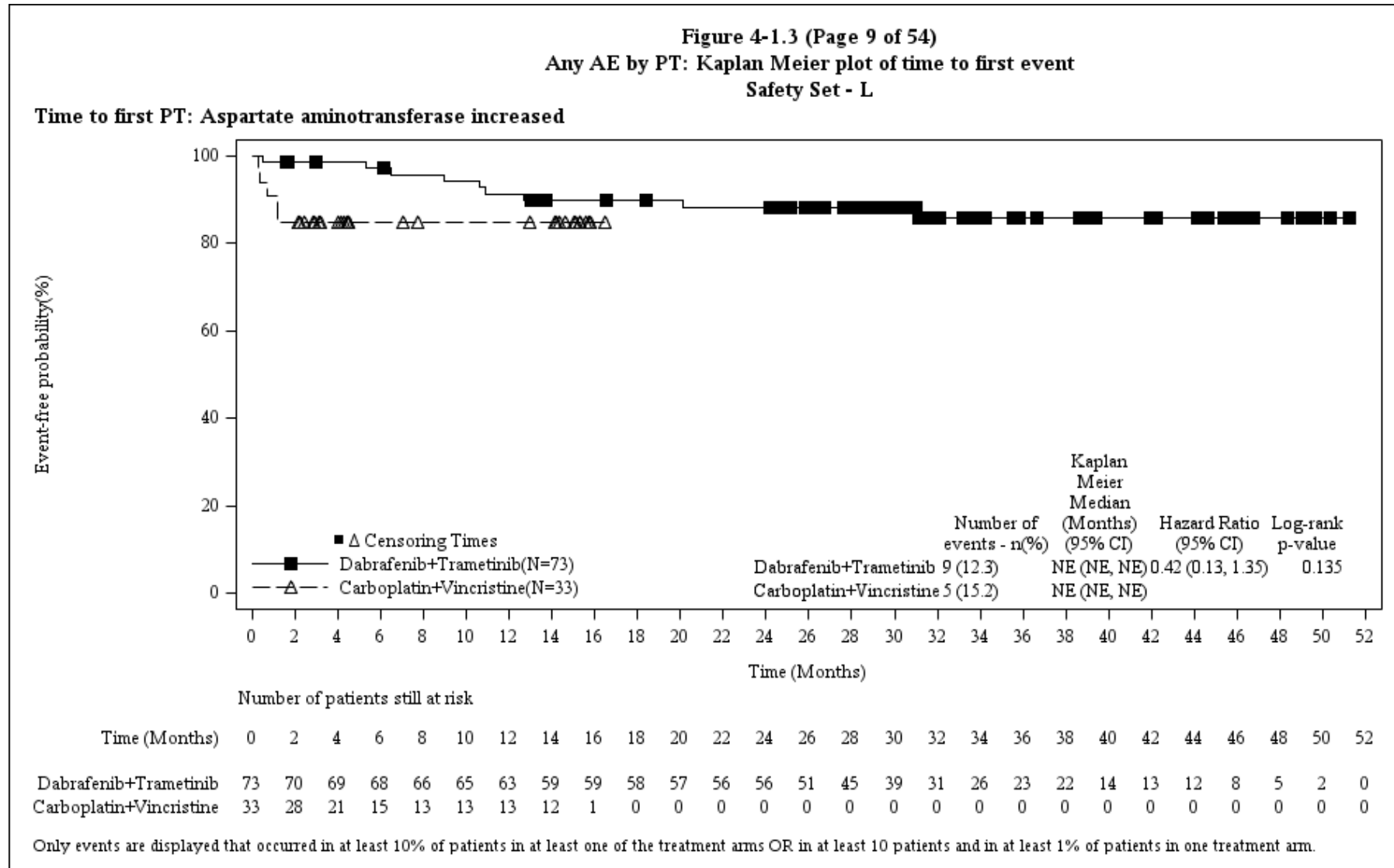
Number of patients still at risk

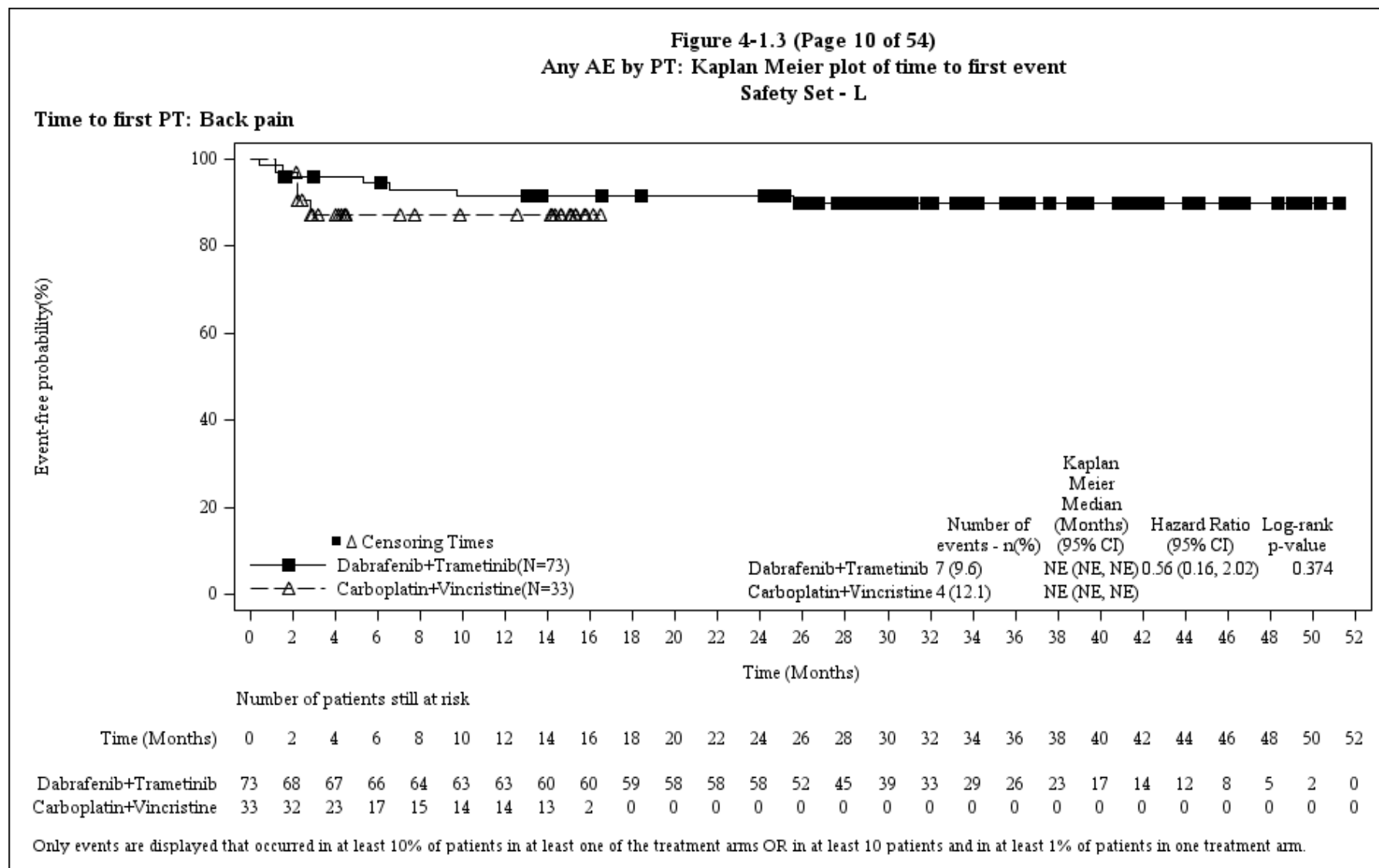
Time (Months)	0	2	4	6	8	10	12	14	16	18	20	22	24	26	28	30	32	34	36	38	40	42	44	46	48	50	52
Dabrafenib+Trametinib	73	63	60	60	59	59	59	56	56	55	53	53	52	46	42	37	31	27	24	23	16	12	10	5	4	1	0
Carboplatin+Vincristine	33	14	11	9	7	7	7	7	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0

Only events are displayed that occurred in at least 10% of patients in at least one of the treatment arms OR in at least 10 patients and in at least 1% of patients in one treatment arm.









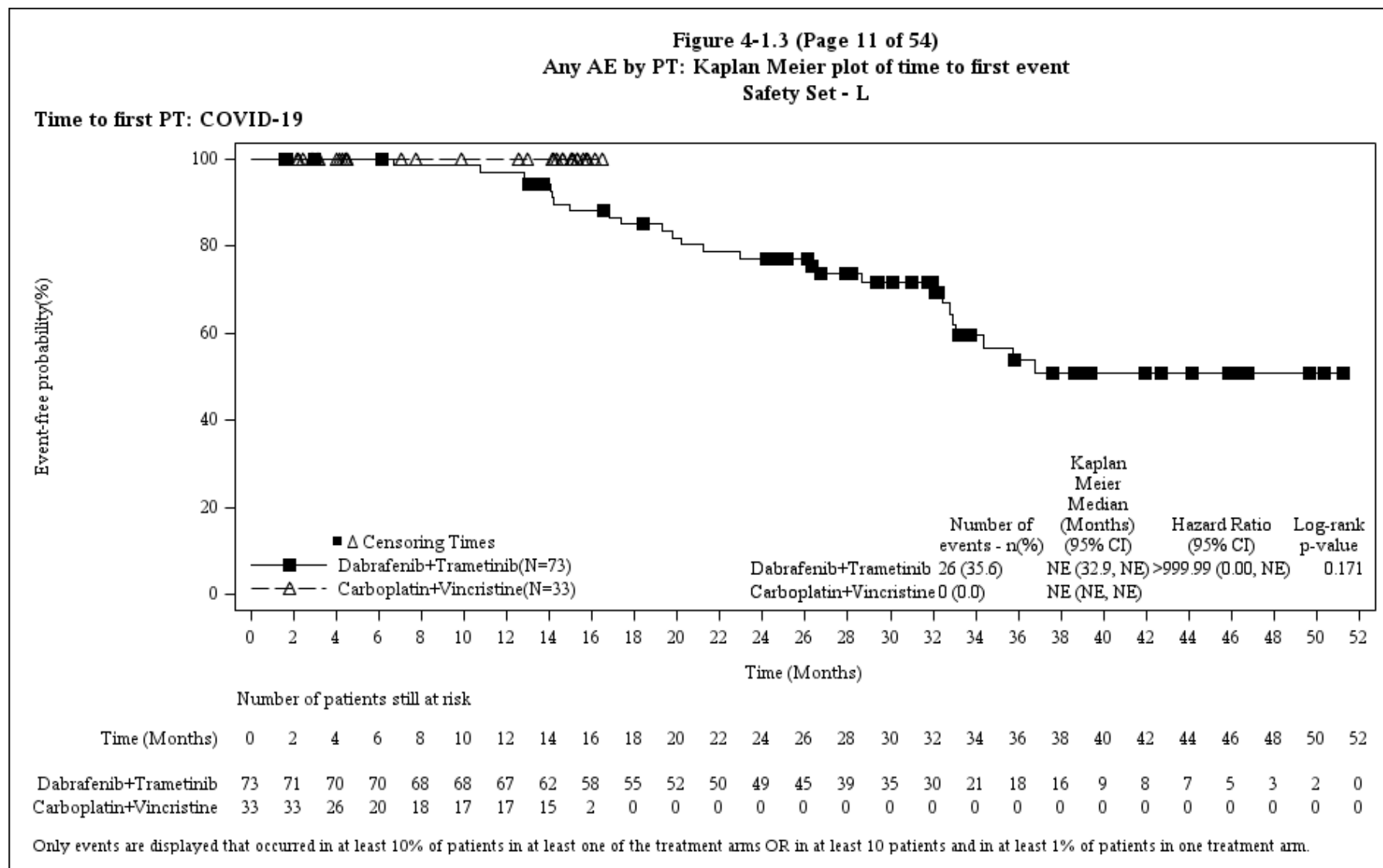
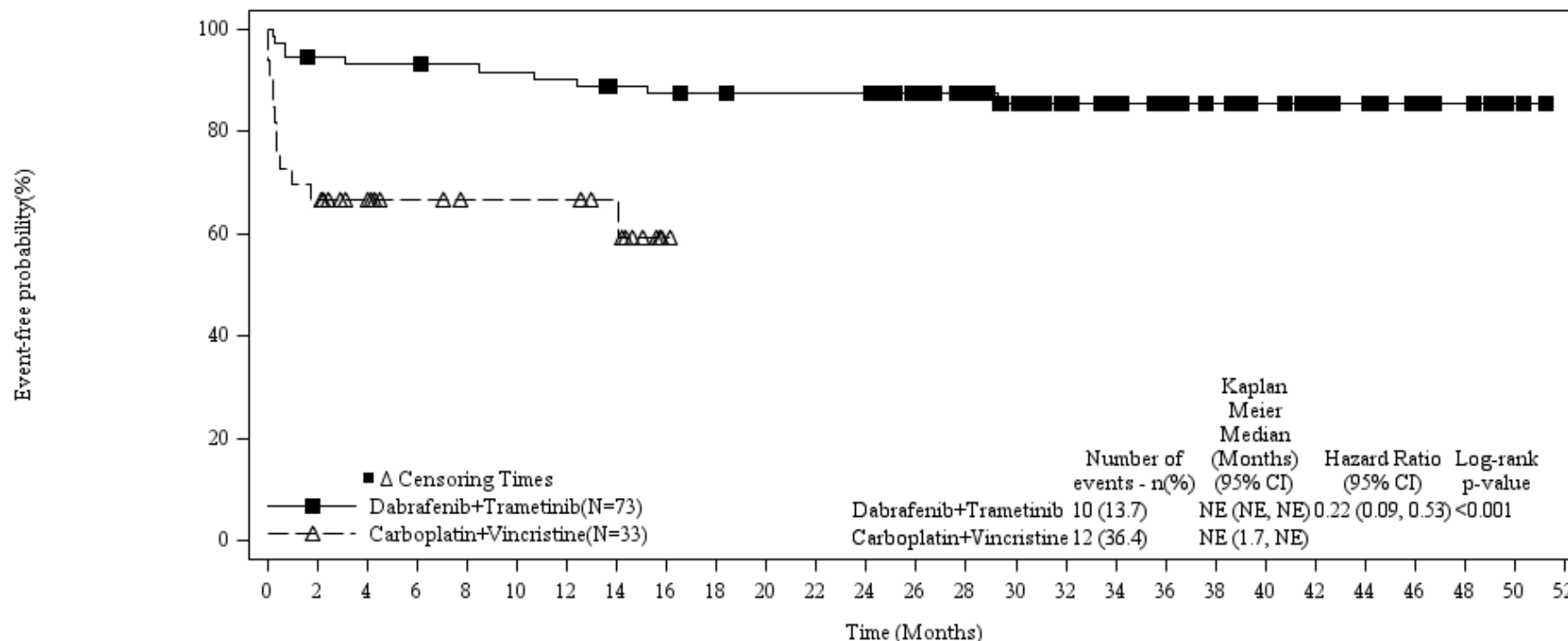


Figure 4-1.3 (Page 12 of 54)
Any AE by PT: Kaplan Meier plot of time to first event
Safety Set - L

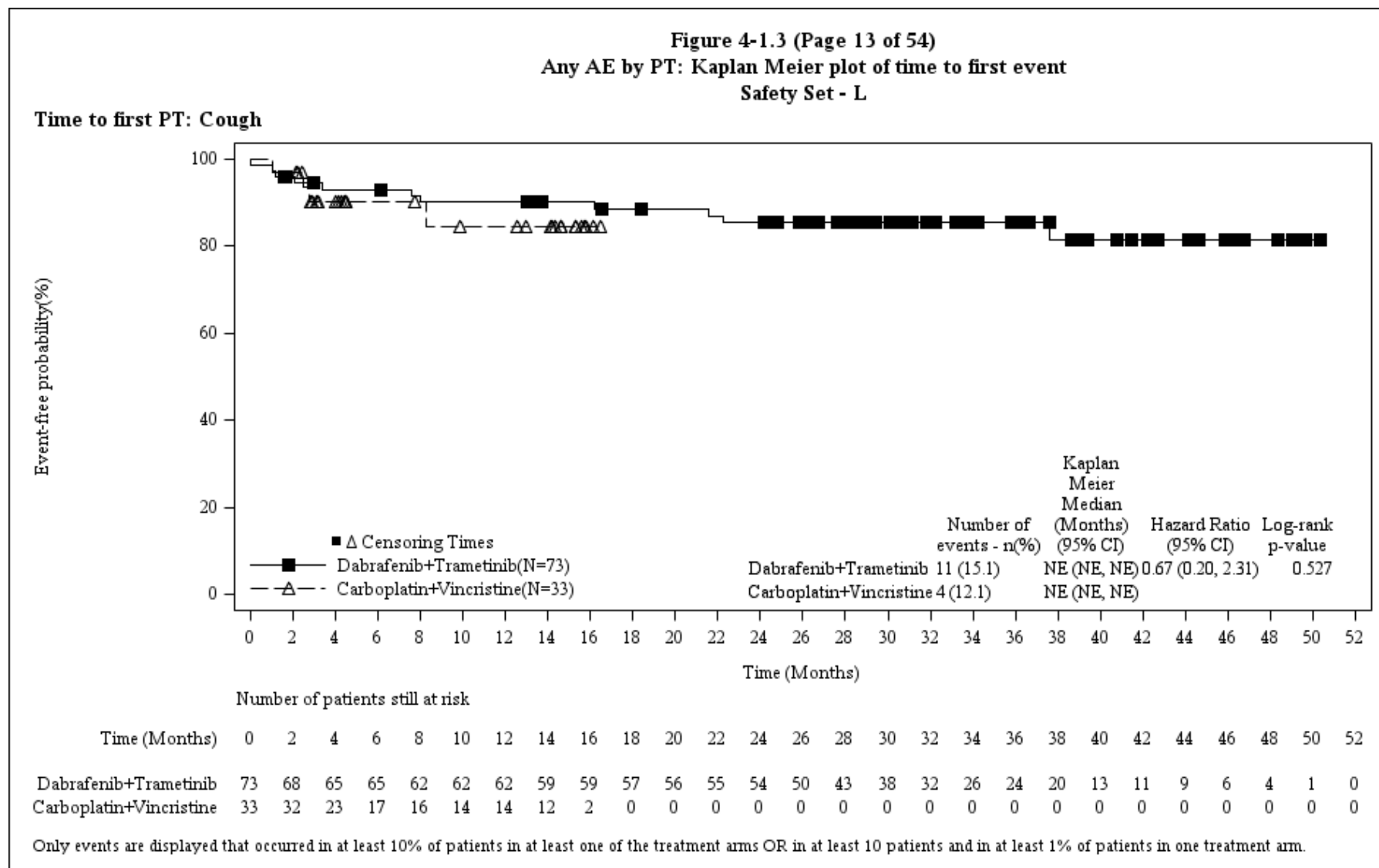
Time to first PT: Constipation

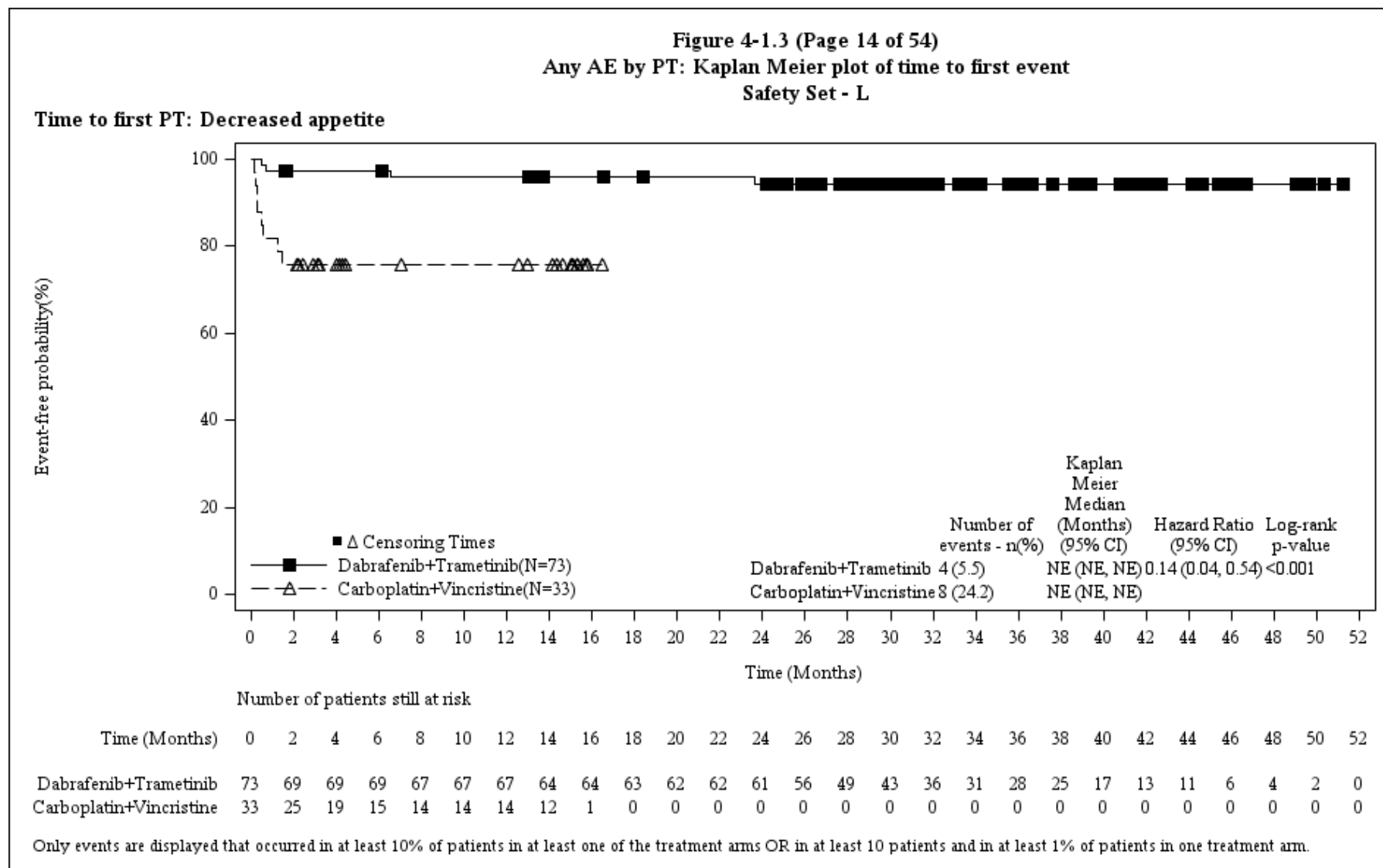


Number of patients still at risk

Time (Months)	0	2	4	6	8	10	12	14	16	18	20	22	24	26	28	30	32	34	36	38	40	42	44	46	48	50	52
Dabrafenib+Trametinib	73	68	67	67	66	65	64	61	60	59	58	58	58	54	47	41	35	31	28	25	17	14	12	8	5	2	0
Carboplatin+Vincristine	33	22	17	13	11	11	11	9	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0

Only events are displayed that occurred in at least 10% of patients in at least one of the treatment arms OR in at least 10 patients and in at least 1% of patients in one treatment arm.





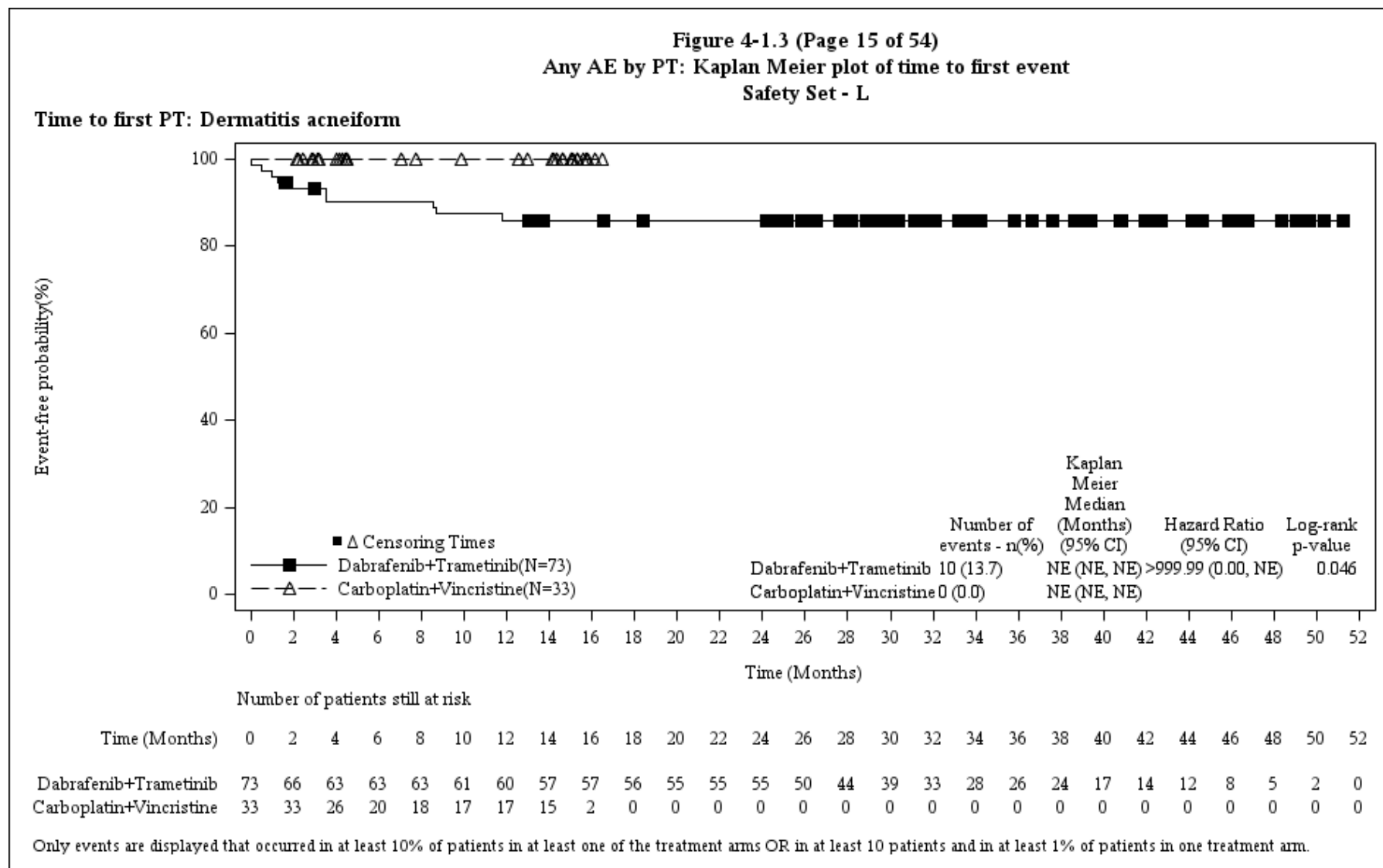
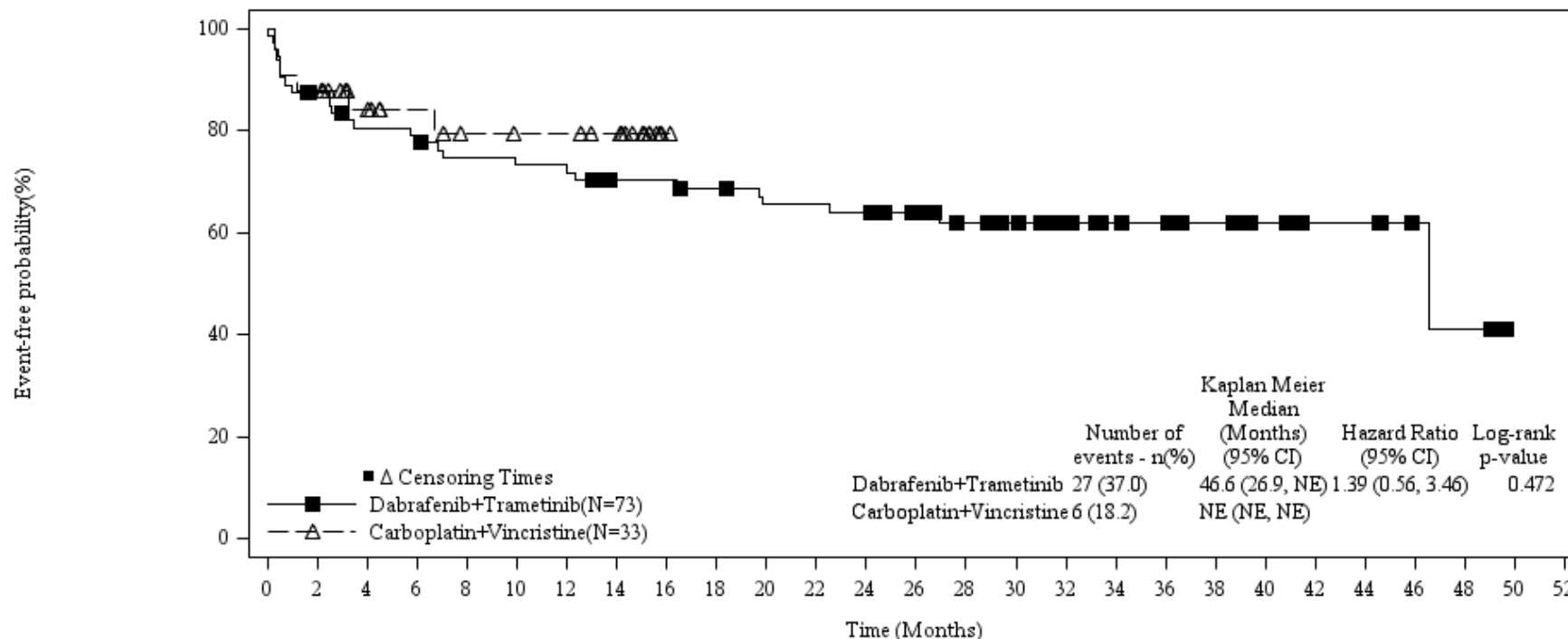


Figure 4-1.3 (Page 16 of 54)
Any AE by PT: Kaplan Meier plot of time to first event
Safety Set - L

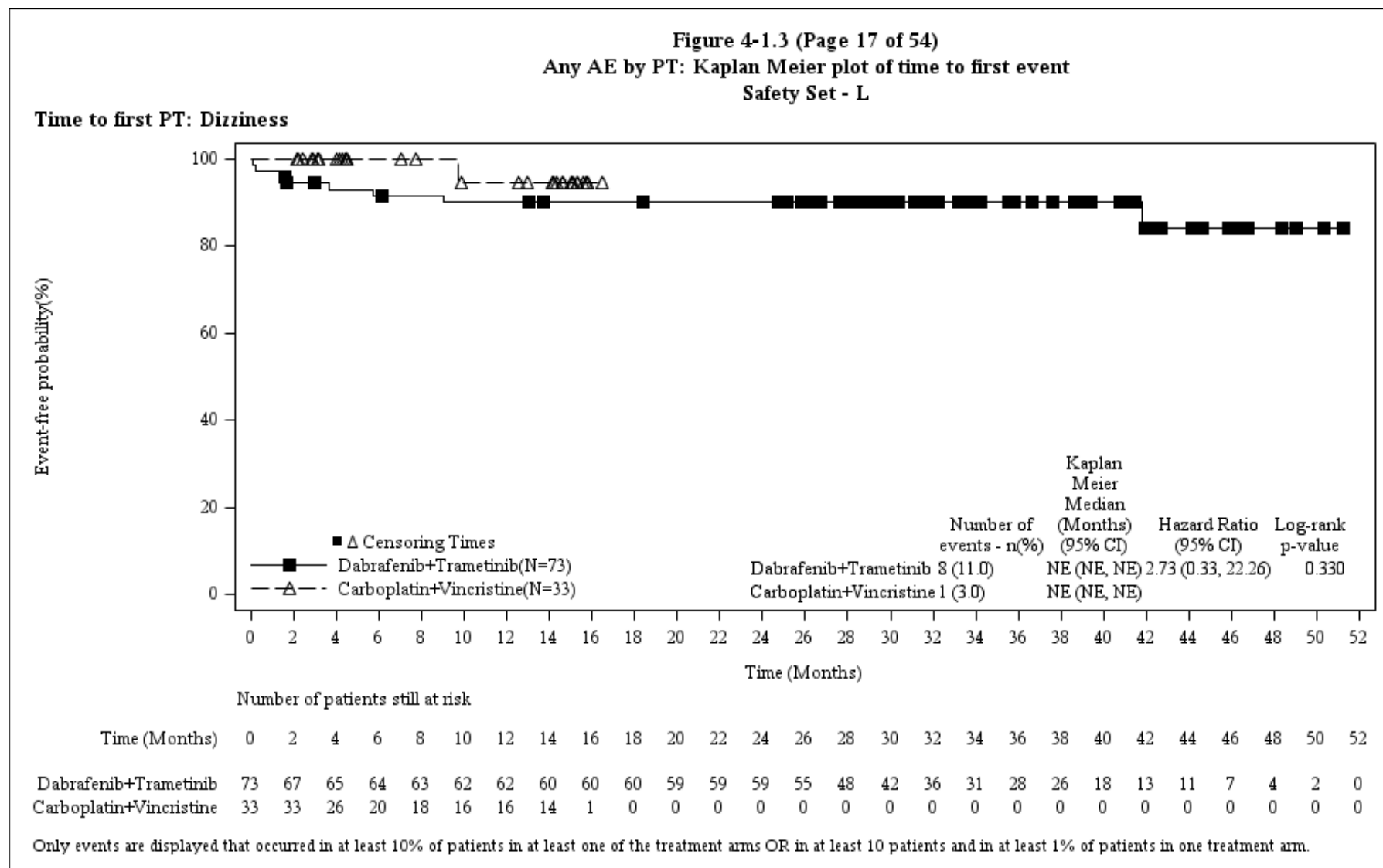
Time to first PT: Diarrhoea

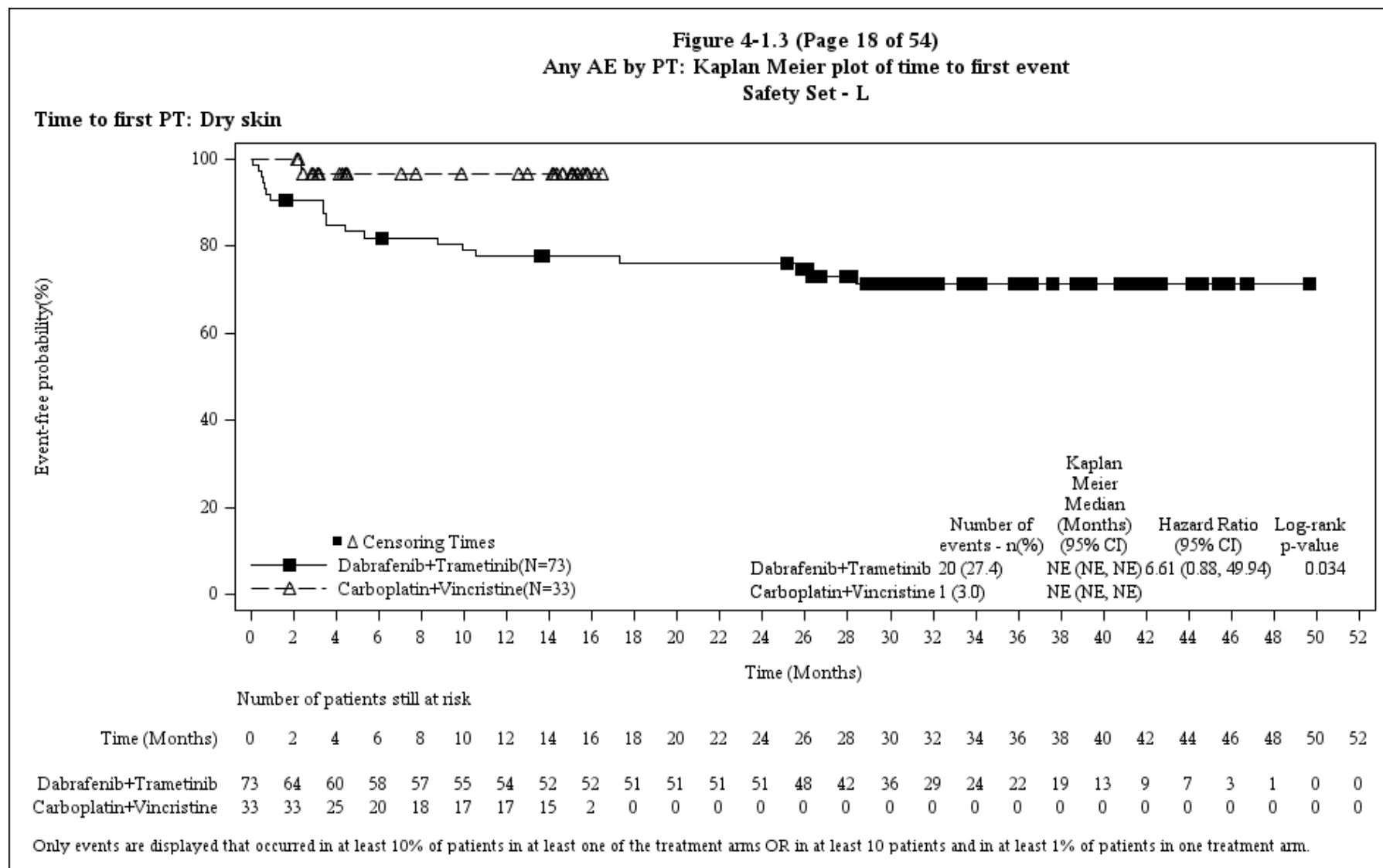


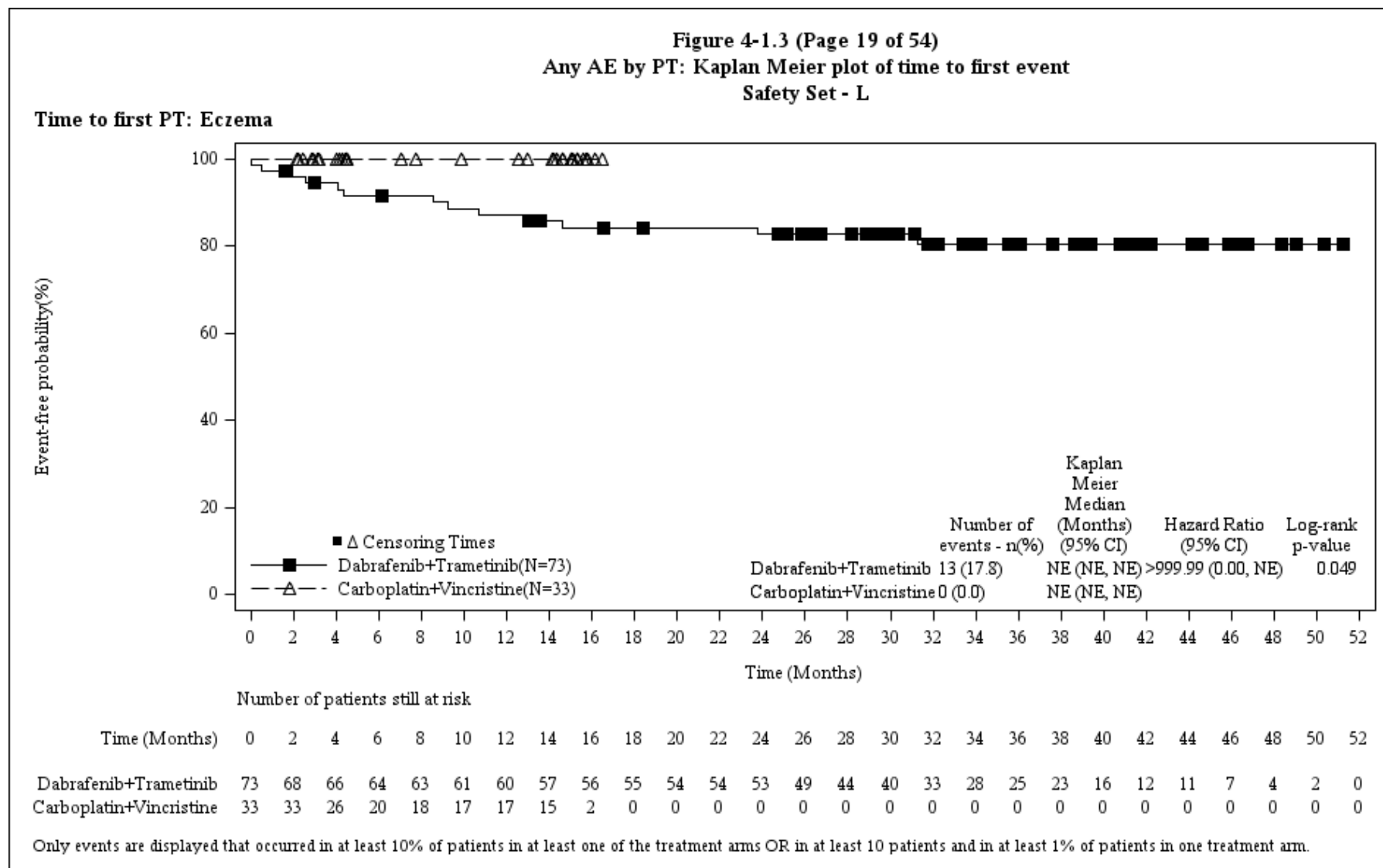
Number of patients still at risk

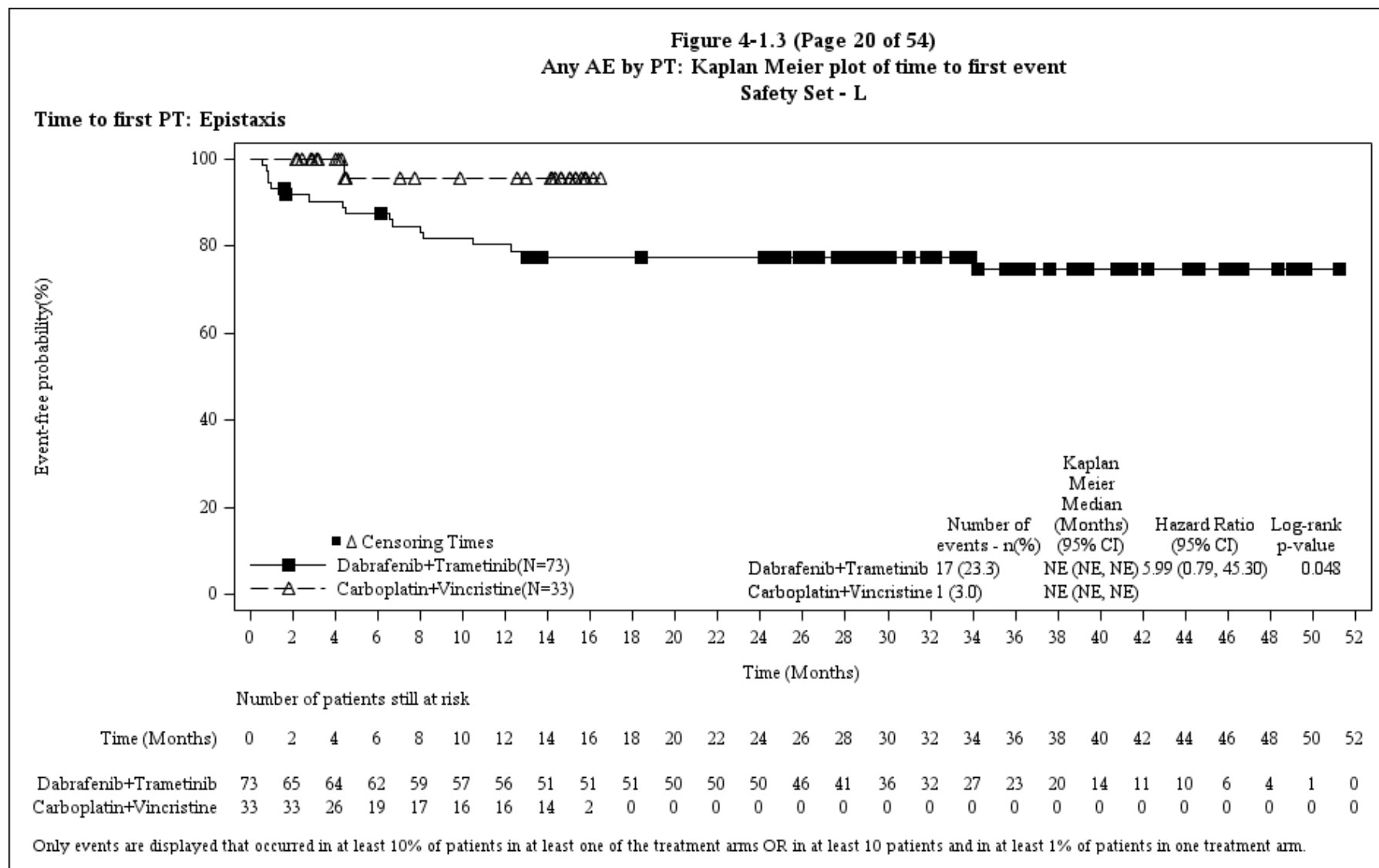
Time (Months)	0	2	4	6	8	10	12	14	16	18	20	22	24	26	28	30	32	34	36	38	40	42	44	46	48	50	52
Dabrafenib+Trametinib	73	62	56	54	51	50	49	45	45	43	40	40	39	36	30	27	22	18	17	15	8	6	6	3	2	0	0
Carboplatin+Vincristine	33	29	22	18	15	14	14	12	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0

Only events are displayed that occurred in at least 10% of patients in at least one of the treatment arms OR in at least 10 patients and in at least 1% of patients in one treatment arm.









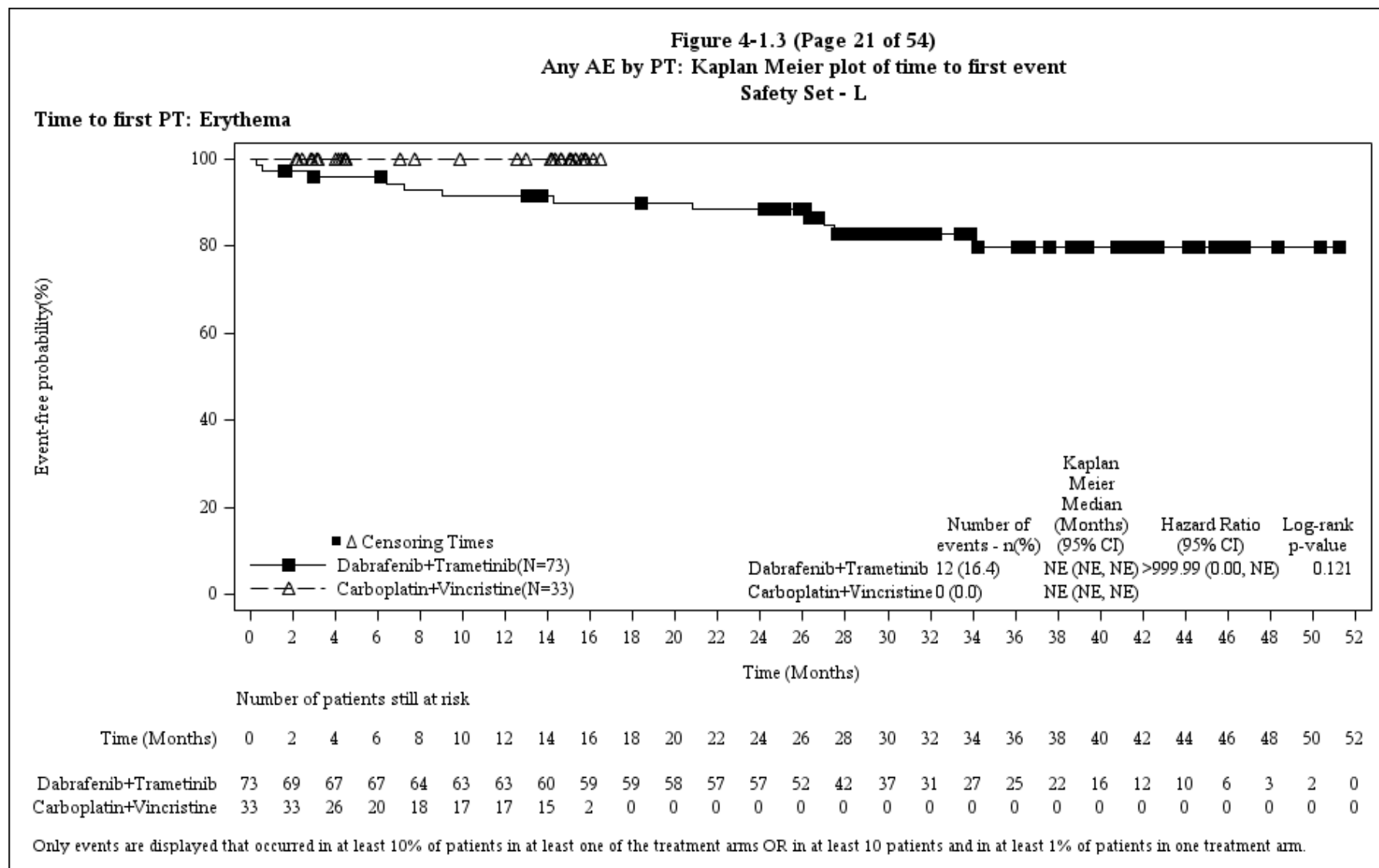
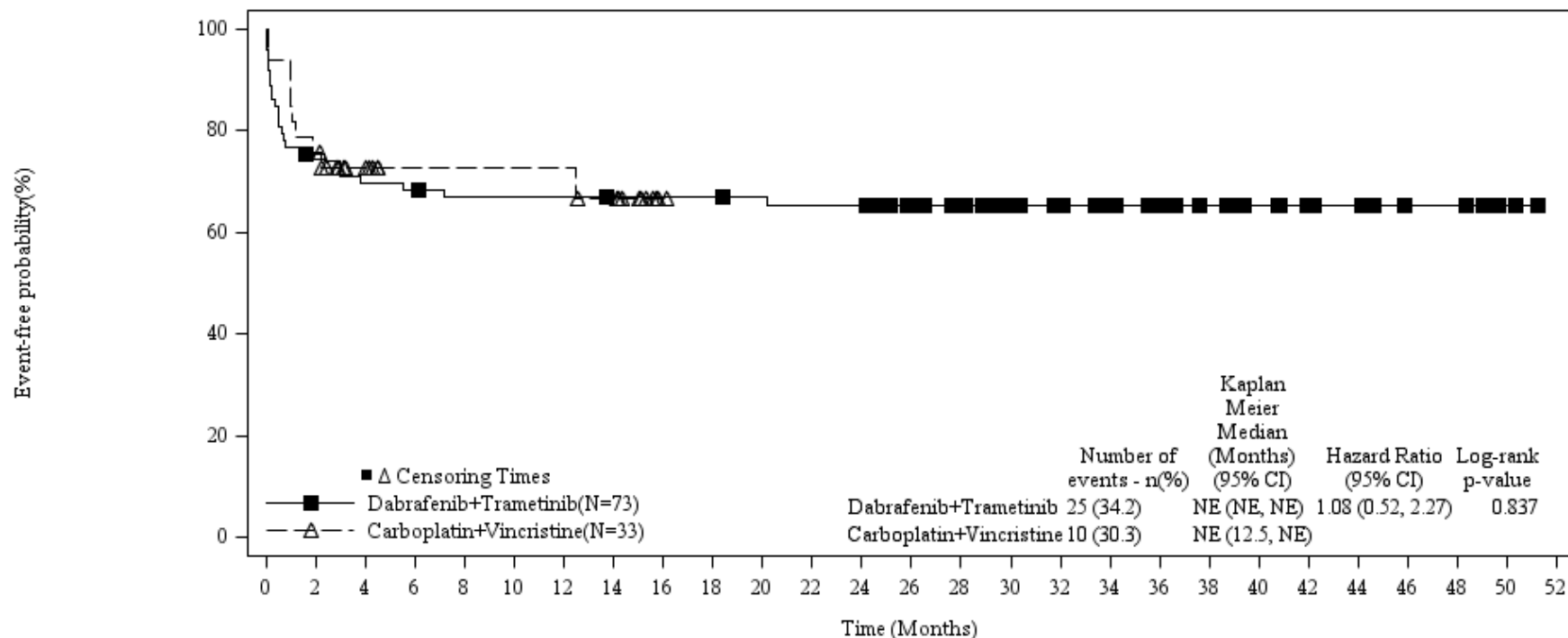


Figure 4-1.3 (Page 22 of 54)
Any AE by PT: Kaplan Meier plot of time to first event
Safety Set - L

Time to first PT: Fatigue



	Number of events - n(%)	Kaplan Meier Median (Months) (95% CI)	Hazard Ratio (95% CI)	Log-rank p-value
Dabrafenib+Trametinib	25 (34.2)	NE (NE, NE)	1.08 (0.52, 2.27)	0.837
Carboplatin+Vincristine	10 (30.3)	NE (12.5, NE)		

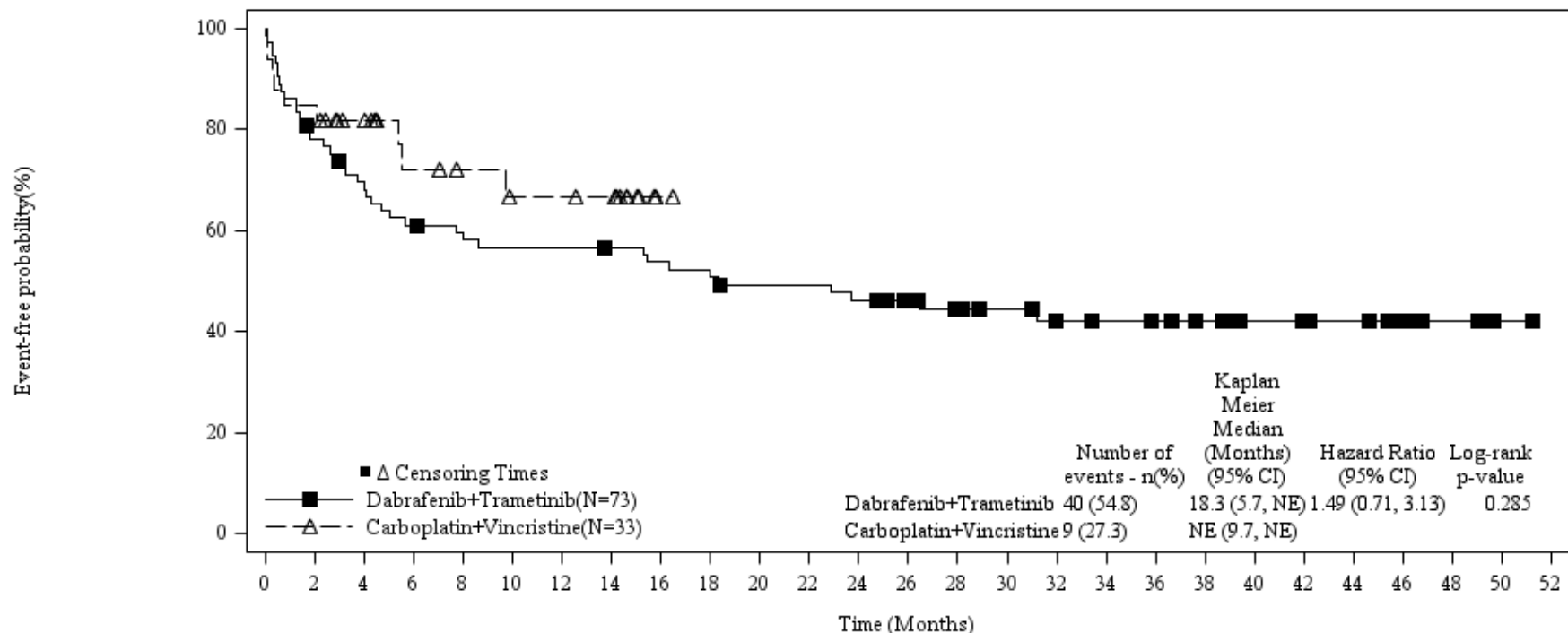
Number of patients still at risk

Time (Months)	0	2	4	6	8	10	12	14	16	18	20	22	24	26	28	30	32	34	36	38	40	42	44	46	48	50	52
Dabrafenib+Trametinib	73	54	50	49	47	47	47	46	46	46	45	44	44	40	35	30	26	23	20	17	12	9	8	5	5	2	0
Carboplatin+Vincristine	33	25	17	12	12	12	12	10	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0

Only events are displayed that occurred in at least 10% of patients in at least one of the treatment arms OR in at least 10 patients and in at least 1% of patients in one treatment arm.

Figure 4-1.3 (Page 23 of 54)
Any AE by PT: Kaplan Meier plot of time to first event
Safety Set - L

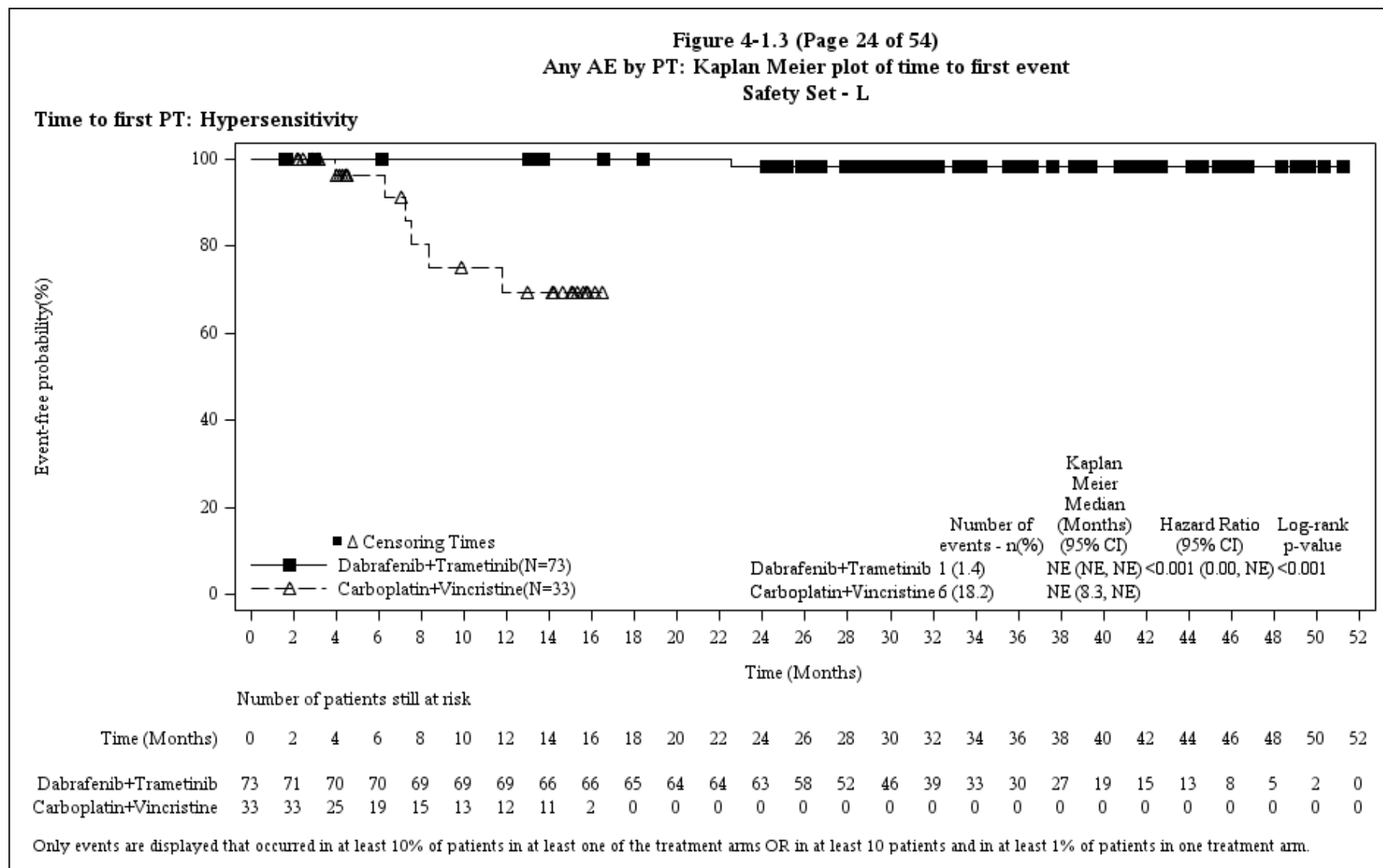
Time to first PT: Headache

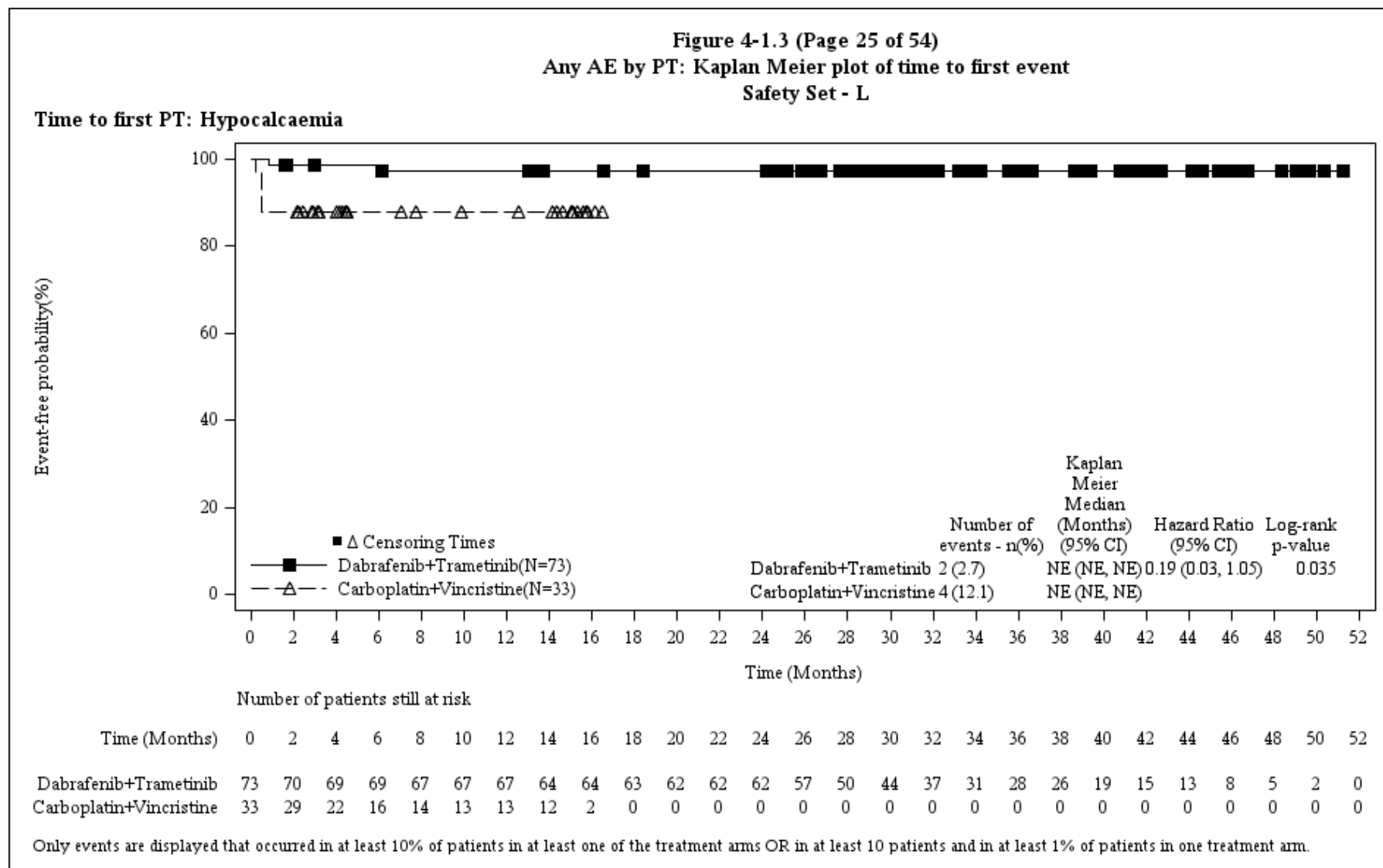


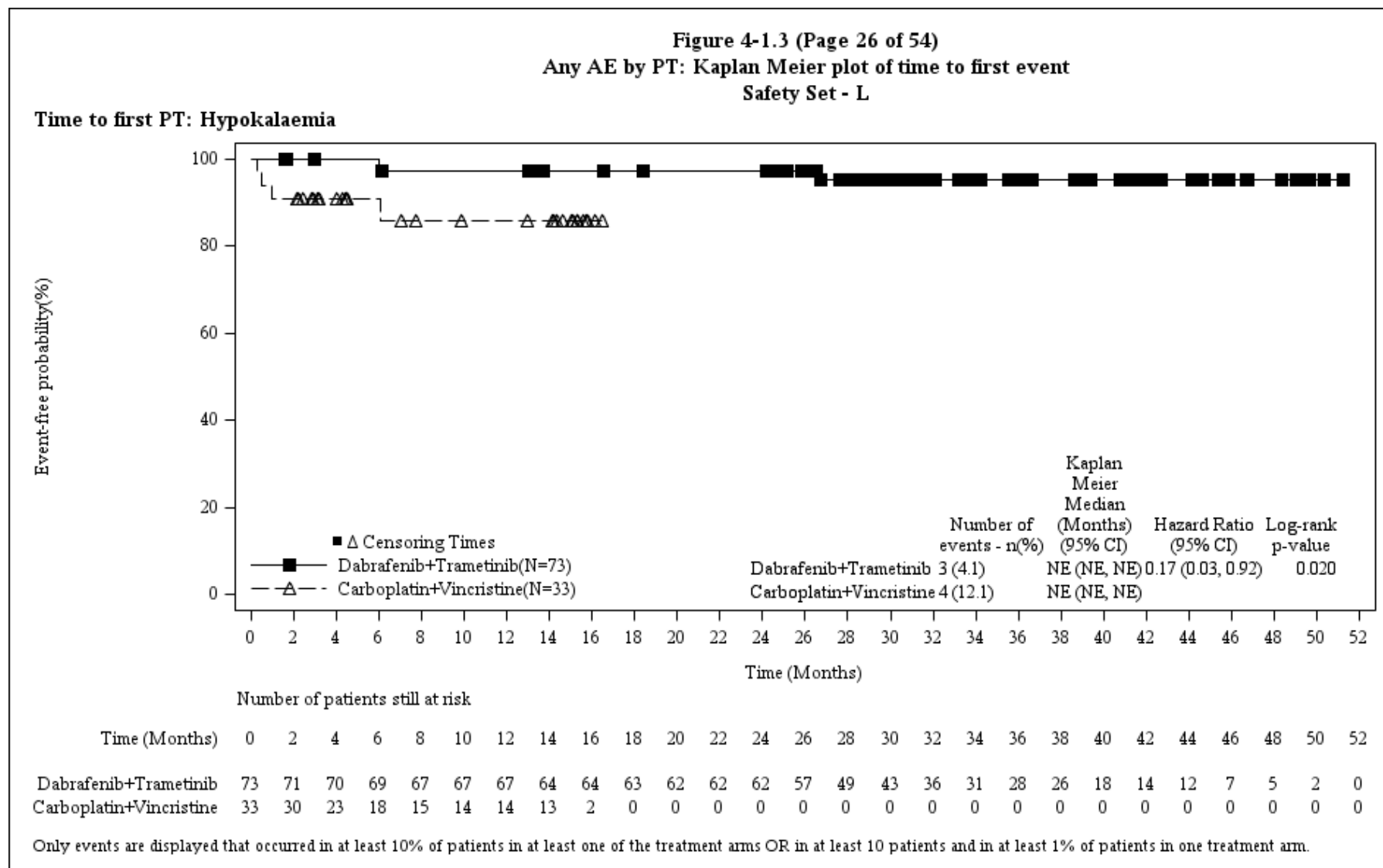
Number of patients still at risk

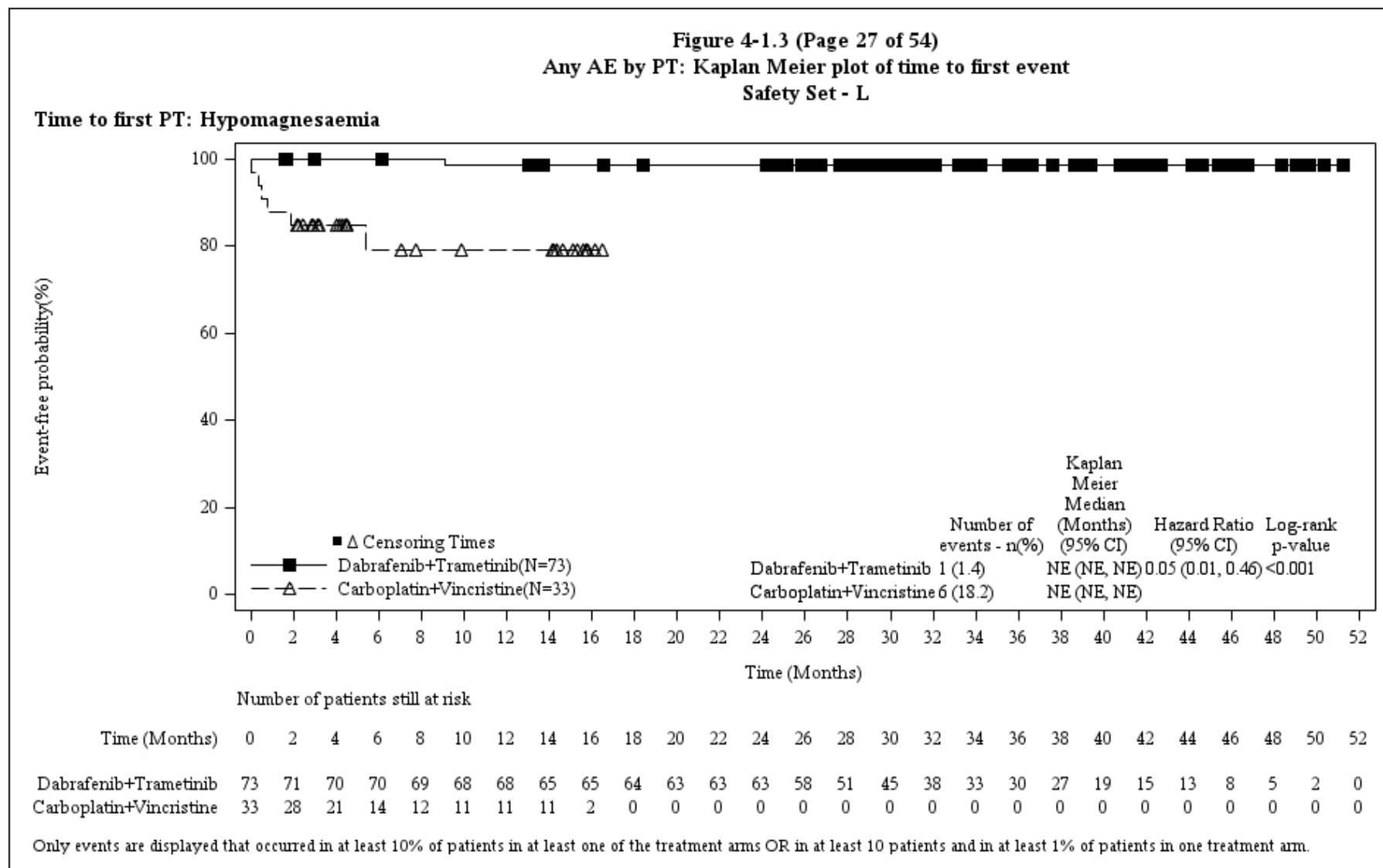
Time (Months)	0	2	4	6	8	10	12	14	16	18	20	22	24	26	28	30	32	34	36	38	40	42	44	46	48	50	52
Dabrafenib+Trametinib	73	56	48	43	41	39	39	38	36	34	32	32	30	27	24	22	19	18	17	15	10	9	8	5	3	1	0
Carboplatin+Vincristine	33	28	22	15	13	11	11	10	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0

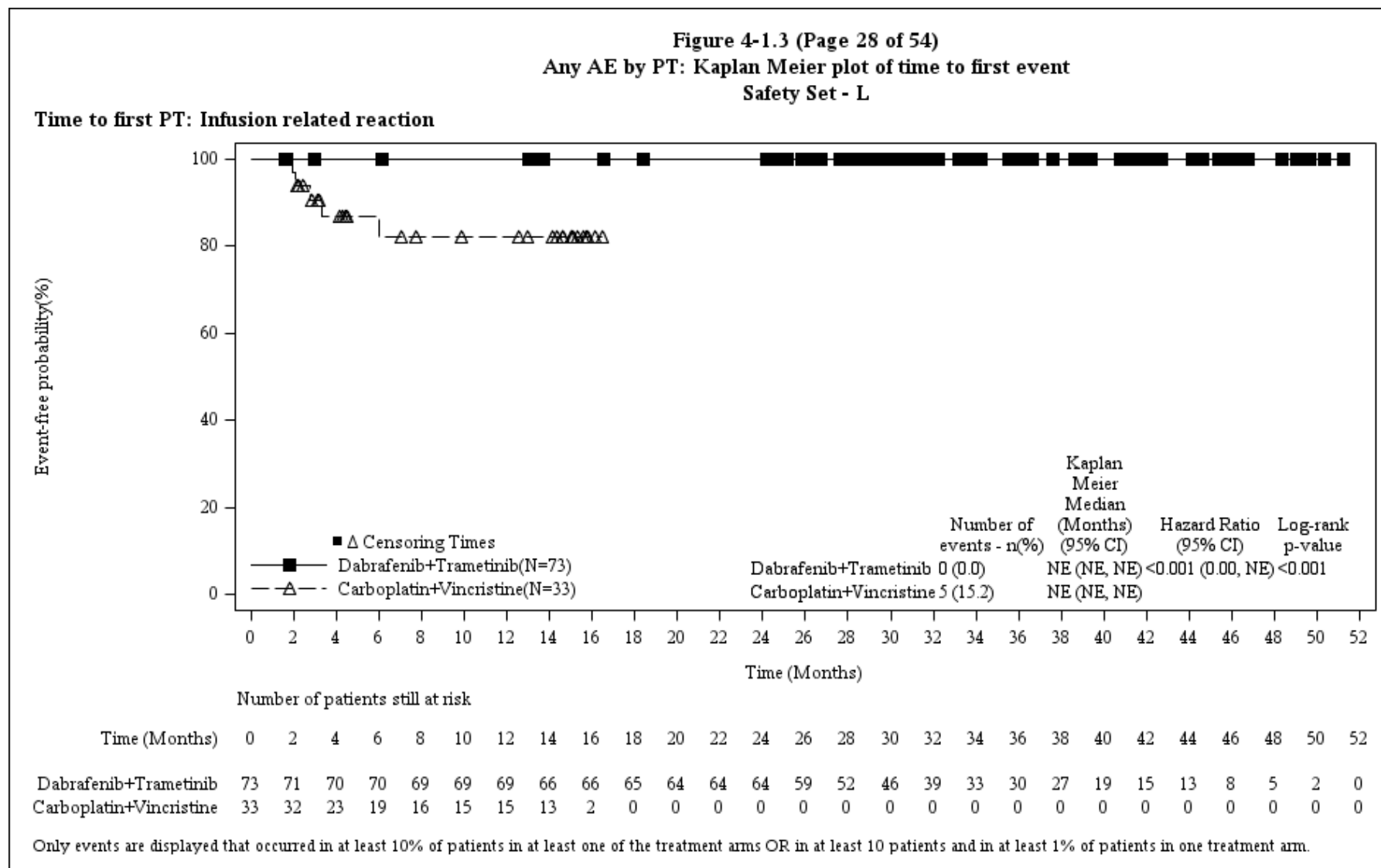
Only events are displayed that occurred in at least 10% of patients in at least one of the treatment arms OR in at least 10 patients and in at least 1% of patients in one treatment arm.

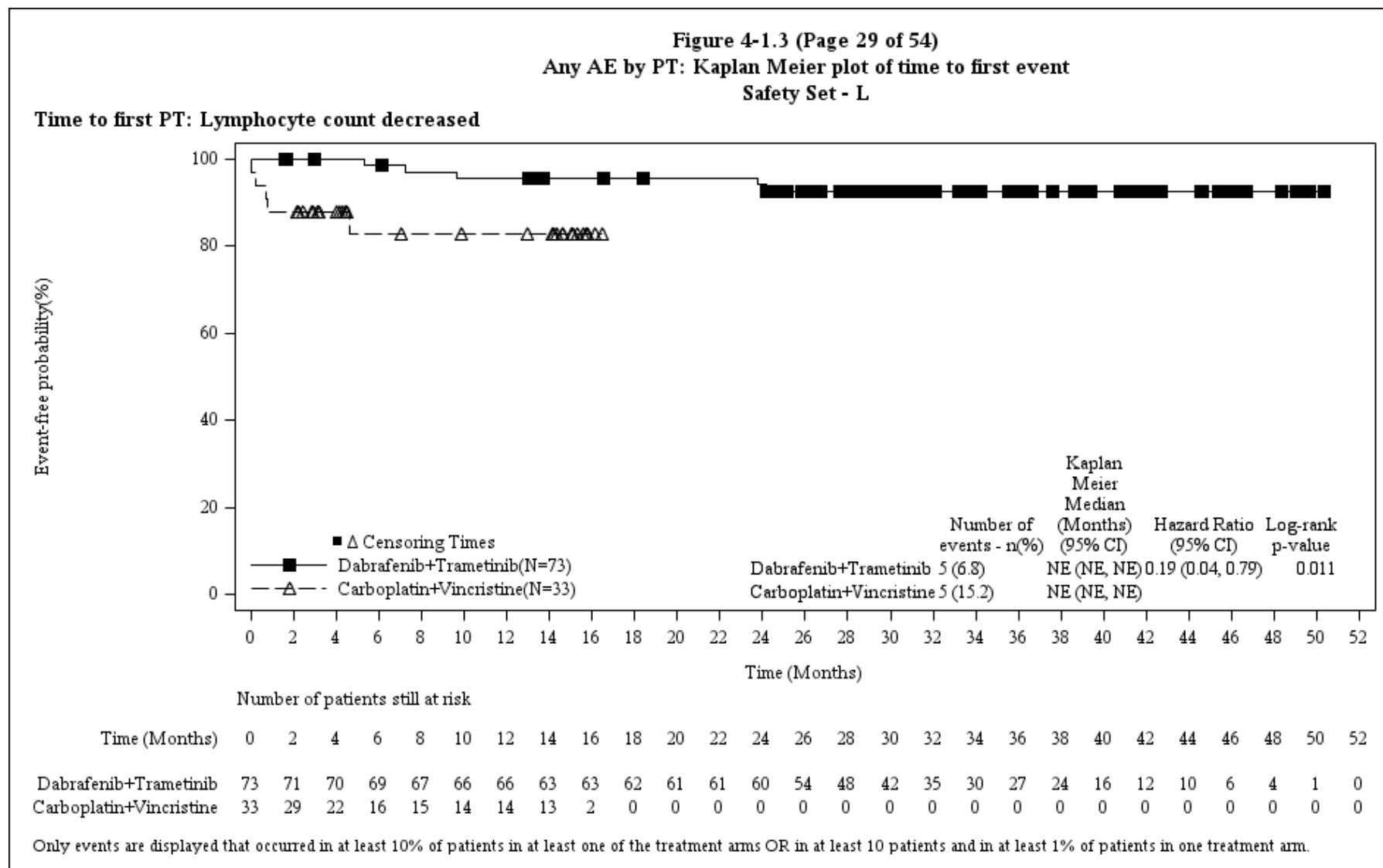












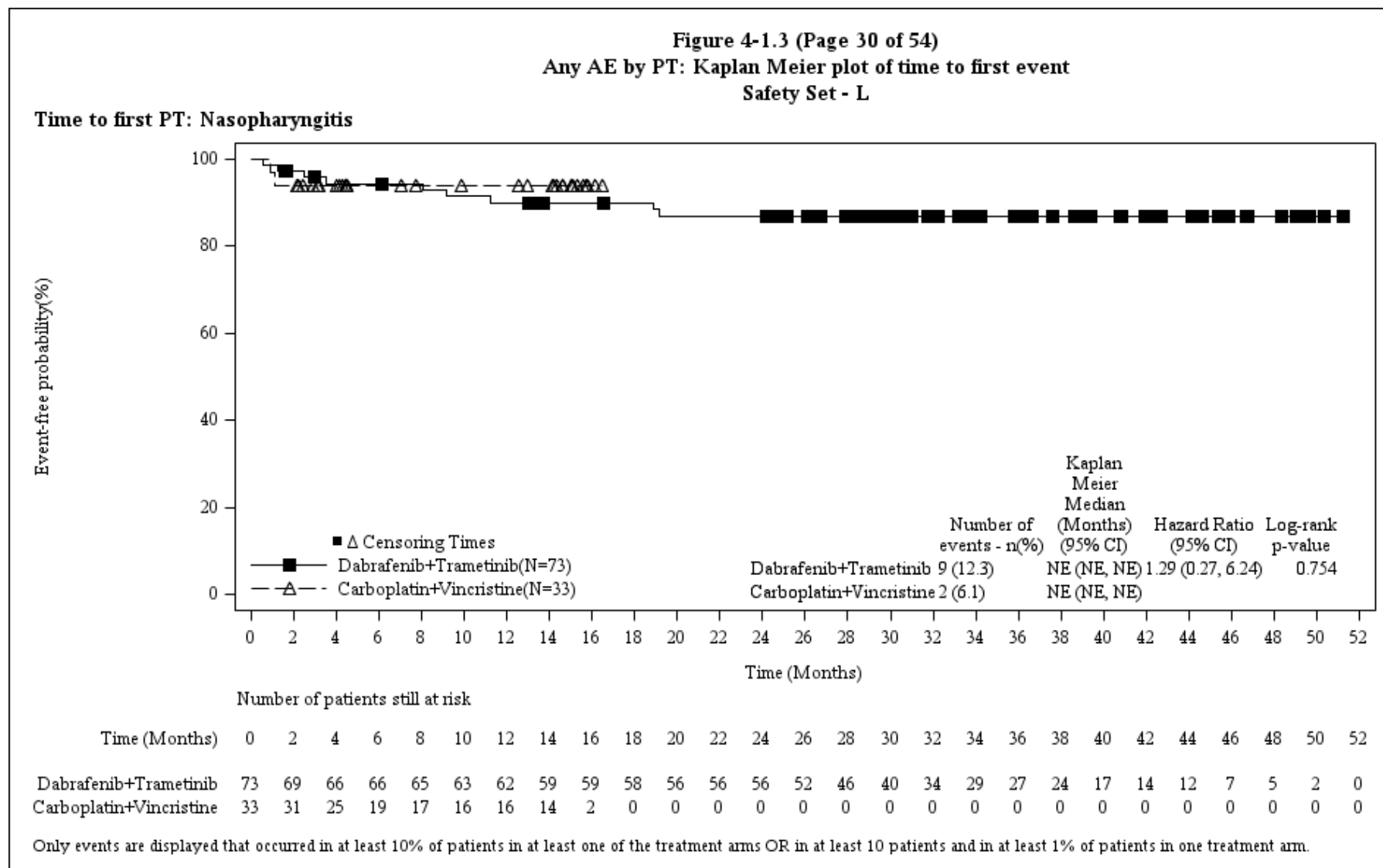
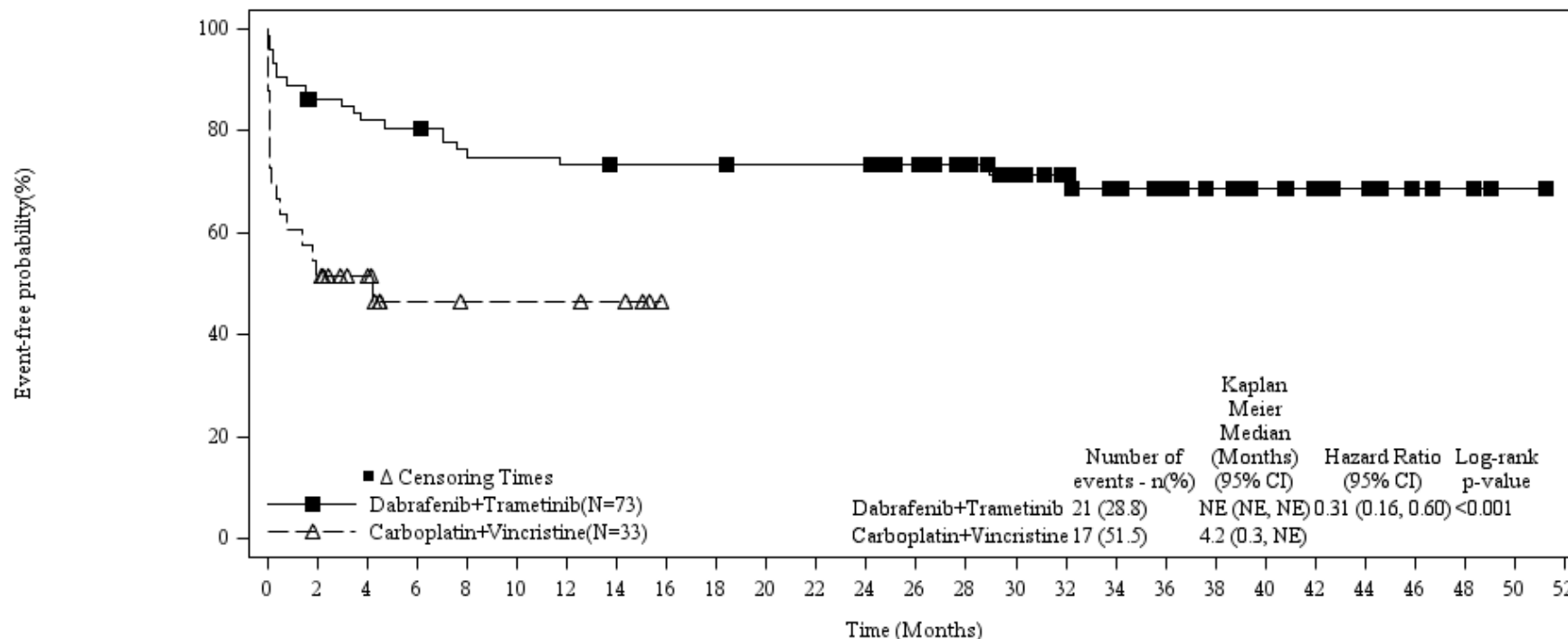


Figure 4-1.3 (Page 31 of 54)
Any AE by PT: Kaplan Meier plot of time to first event
Safety Set - L

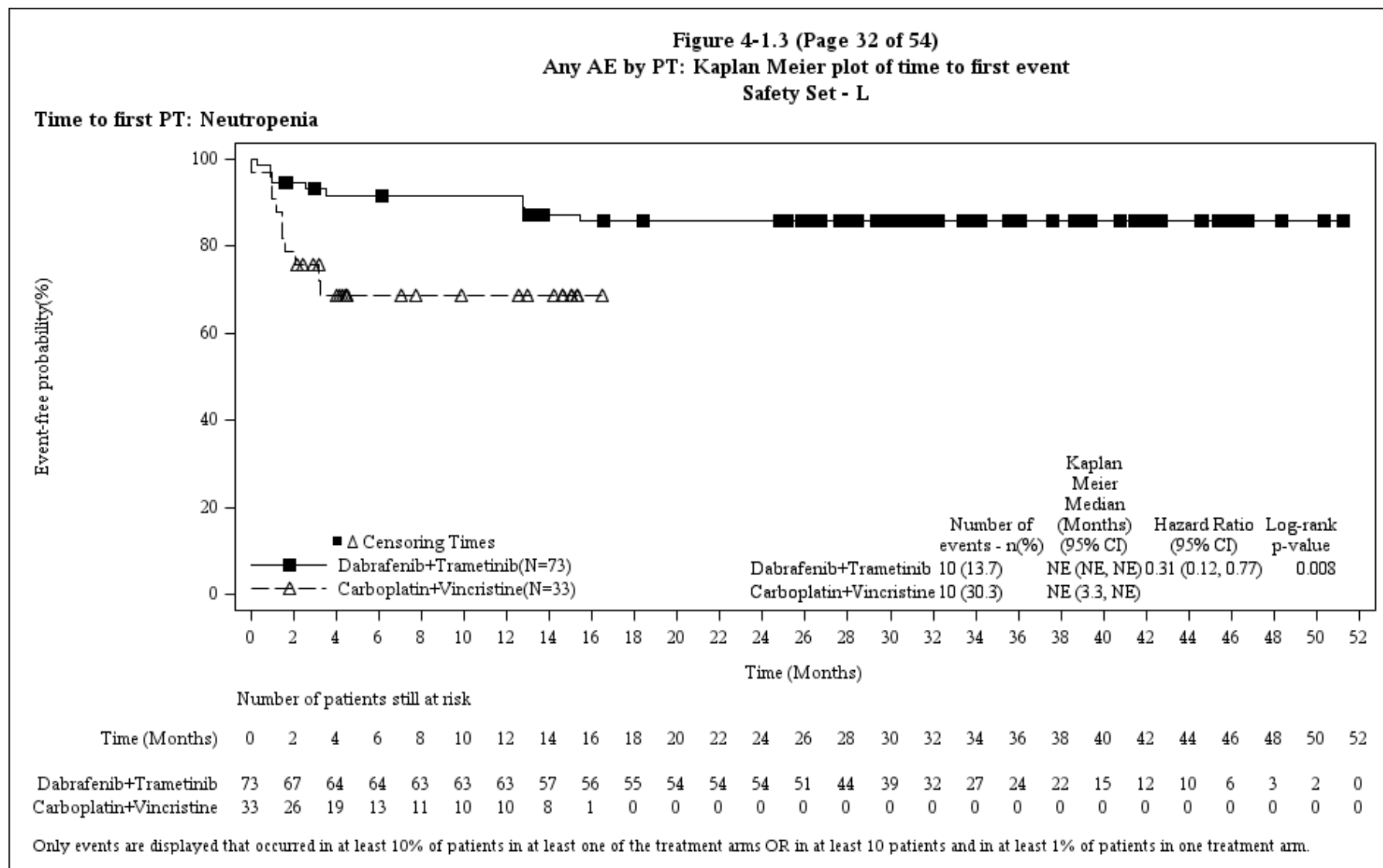
Time to first PT: Nausea

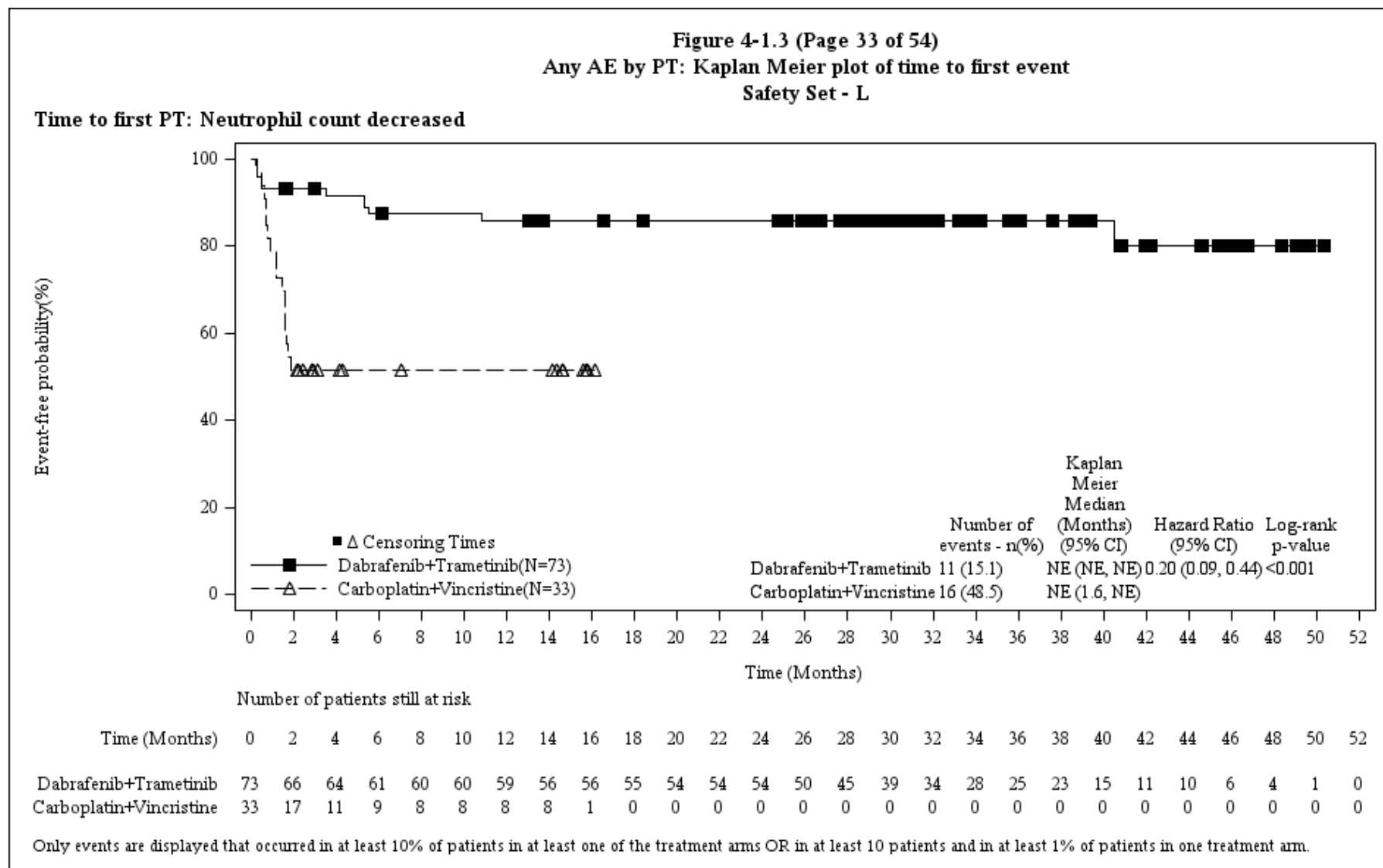


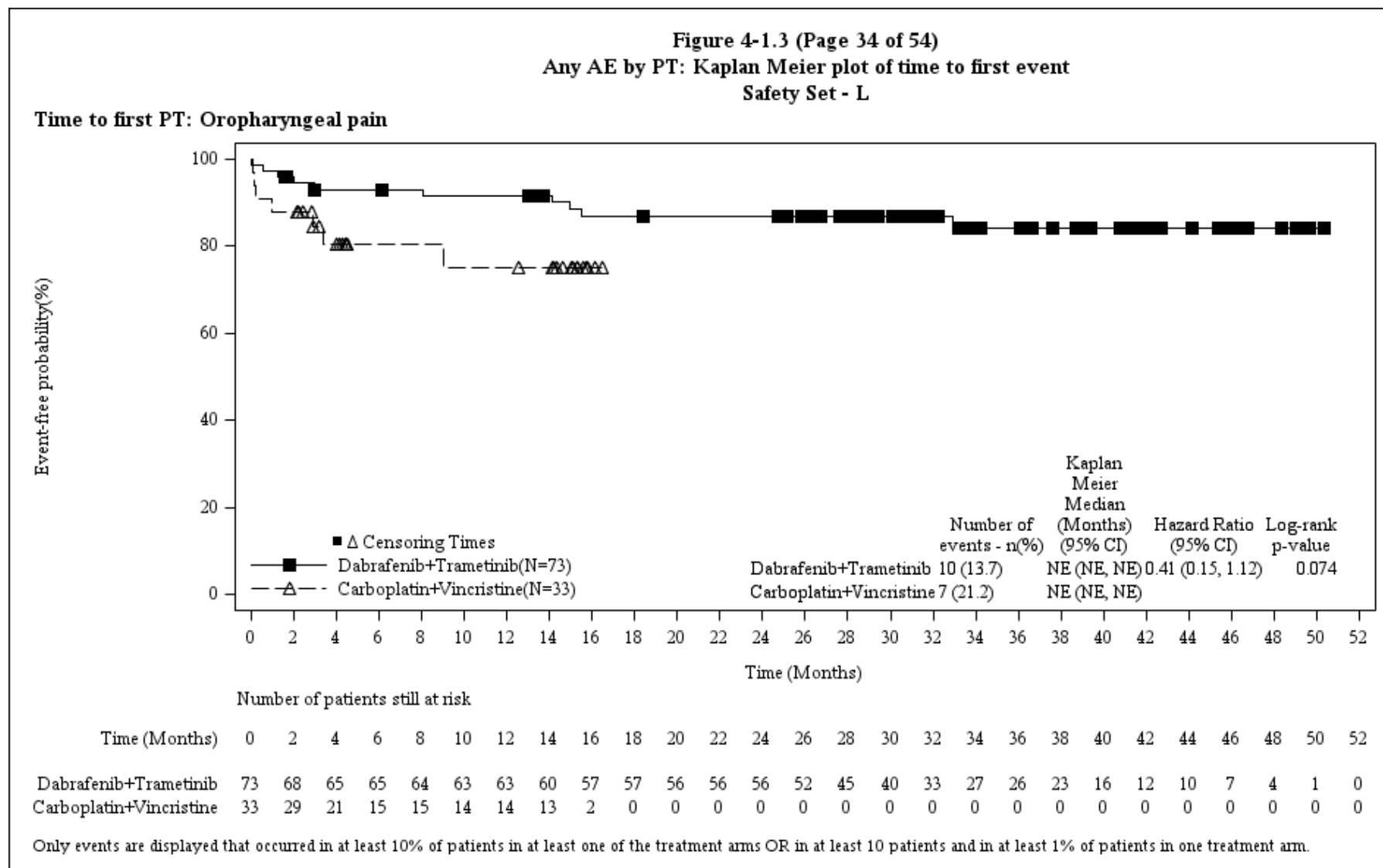
Number of patients still at risk

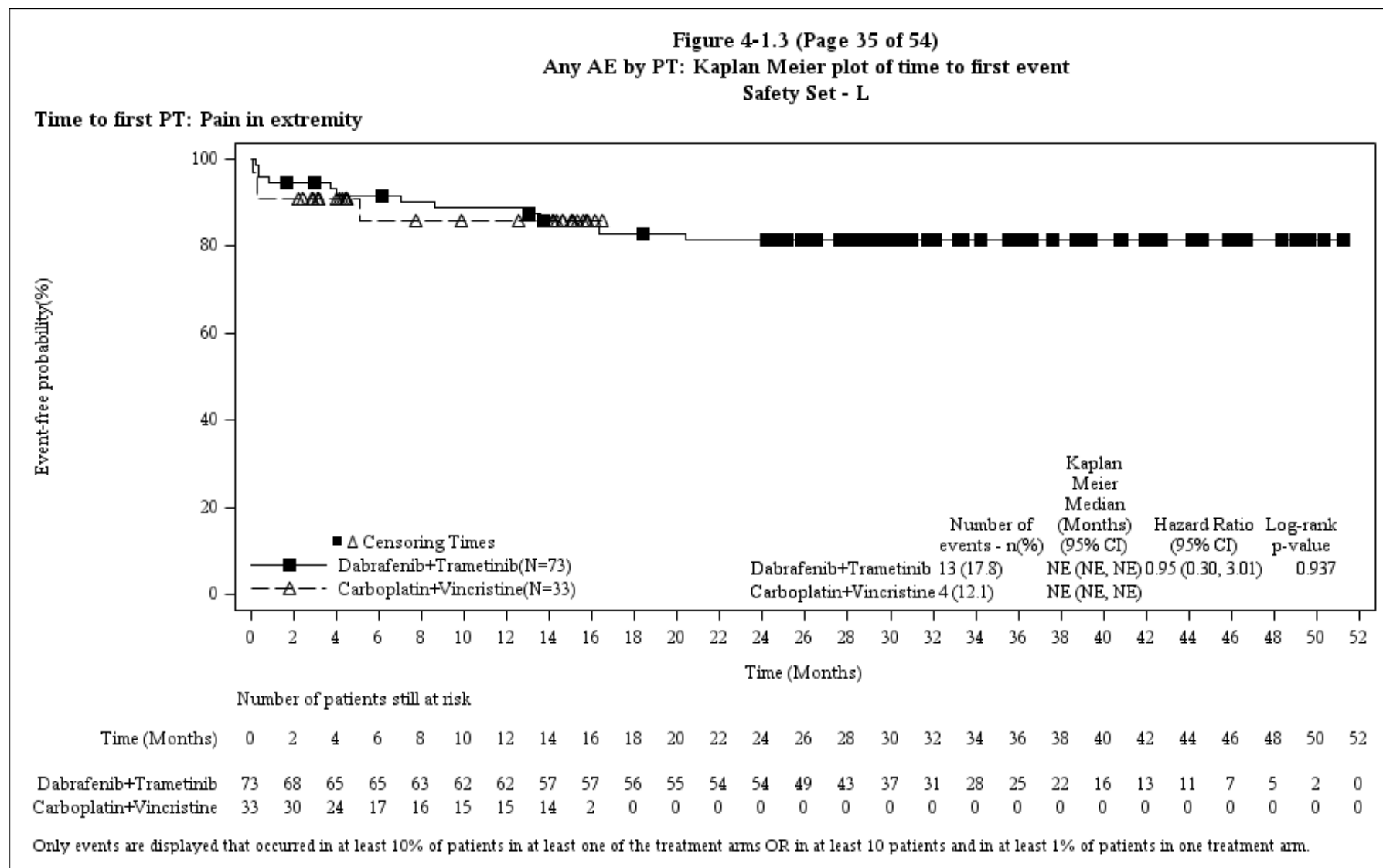
Time (Months)	0	2	4	6	8	10	12	14	16	18	20	22	24	26	28	30	32	34	36	38	40	42	44	46	48	50	52
Dabrafenib+Trametinib	73	61	58	57	53	52	51	50	50	50	49	49	49	45	38	32	27	23	21	18	12	9	7	4	3	1	0
Carboplatin+Vincristine	33	17	12	6	5	5	5	4	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0

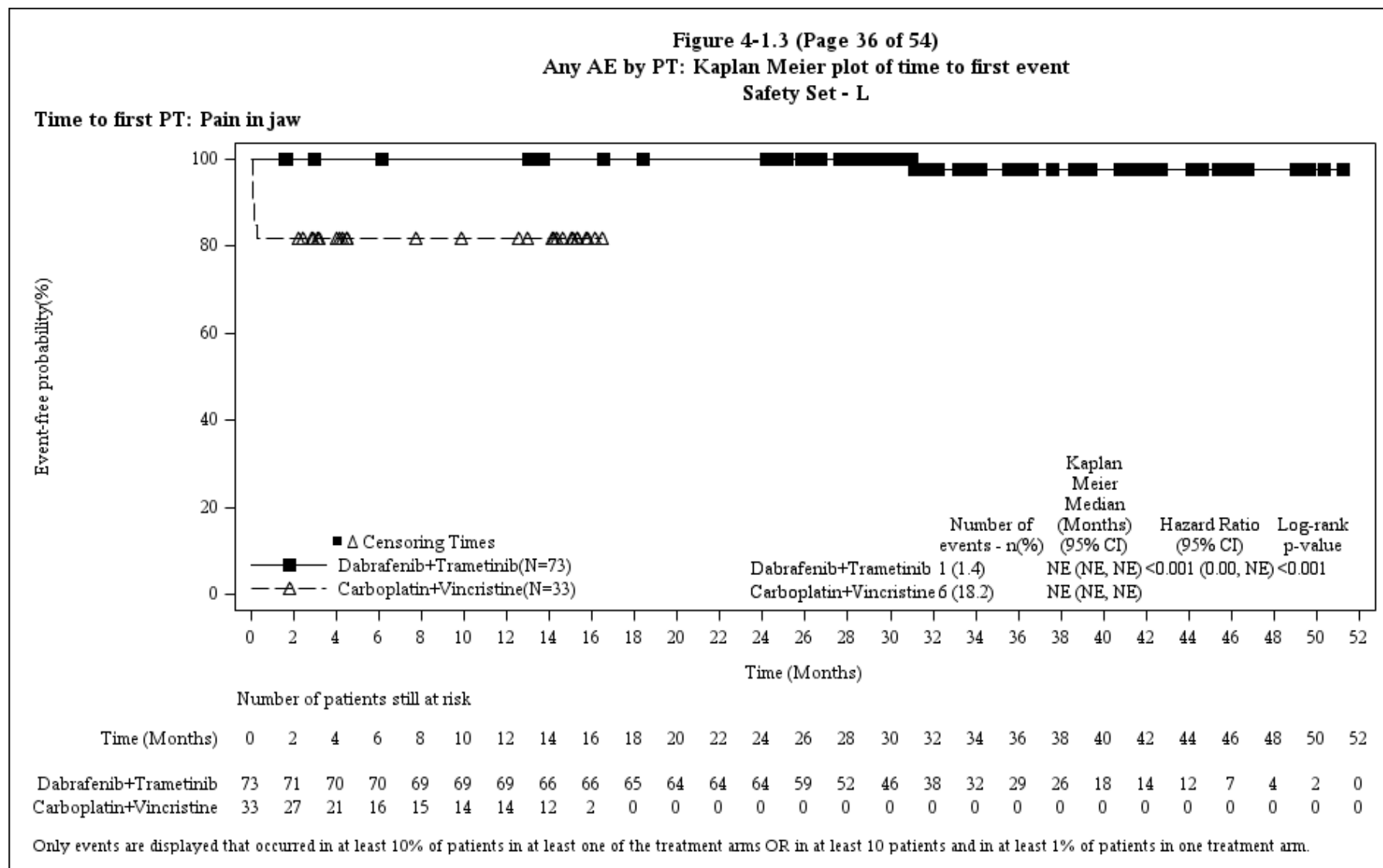
Only events are displayed that occurred in at least 10% of patients in at least one of the treatment arms OR in at least 10 patients and in at least 1% of patients in one treatment arm.

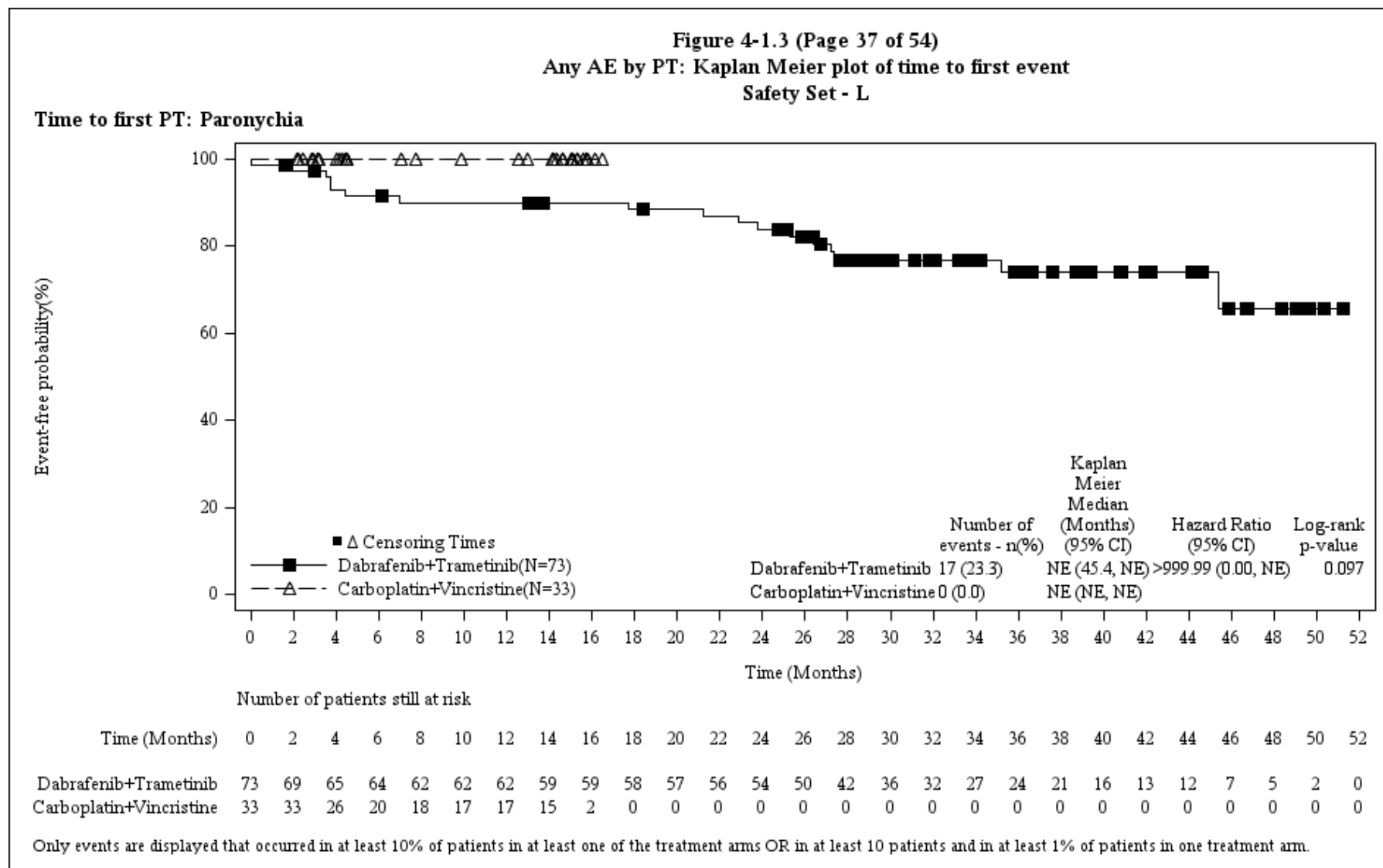


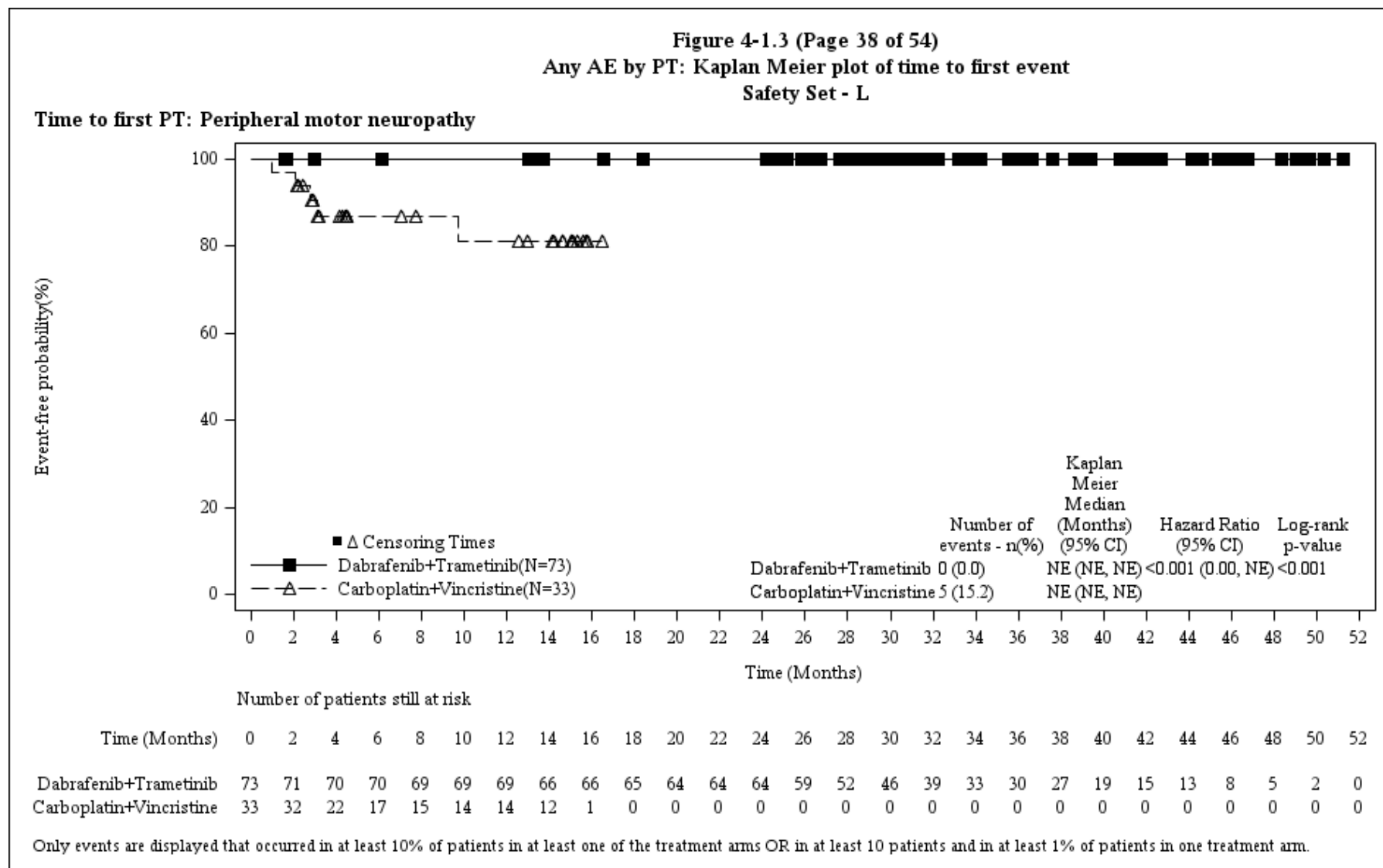


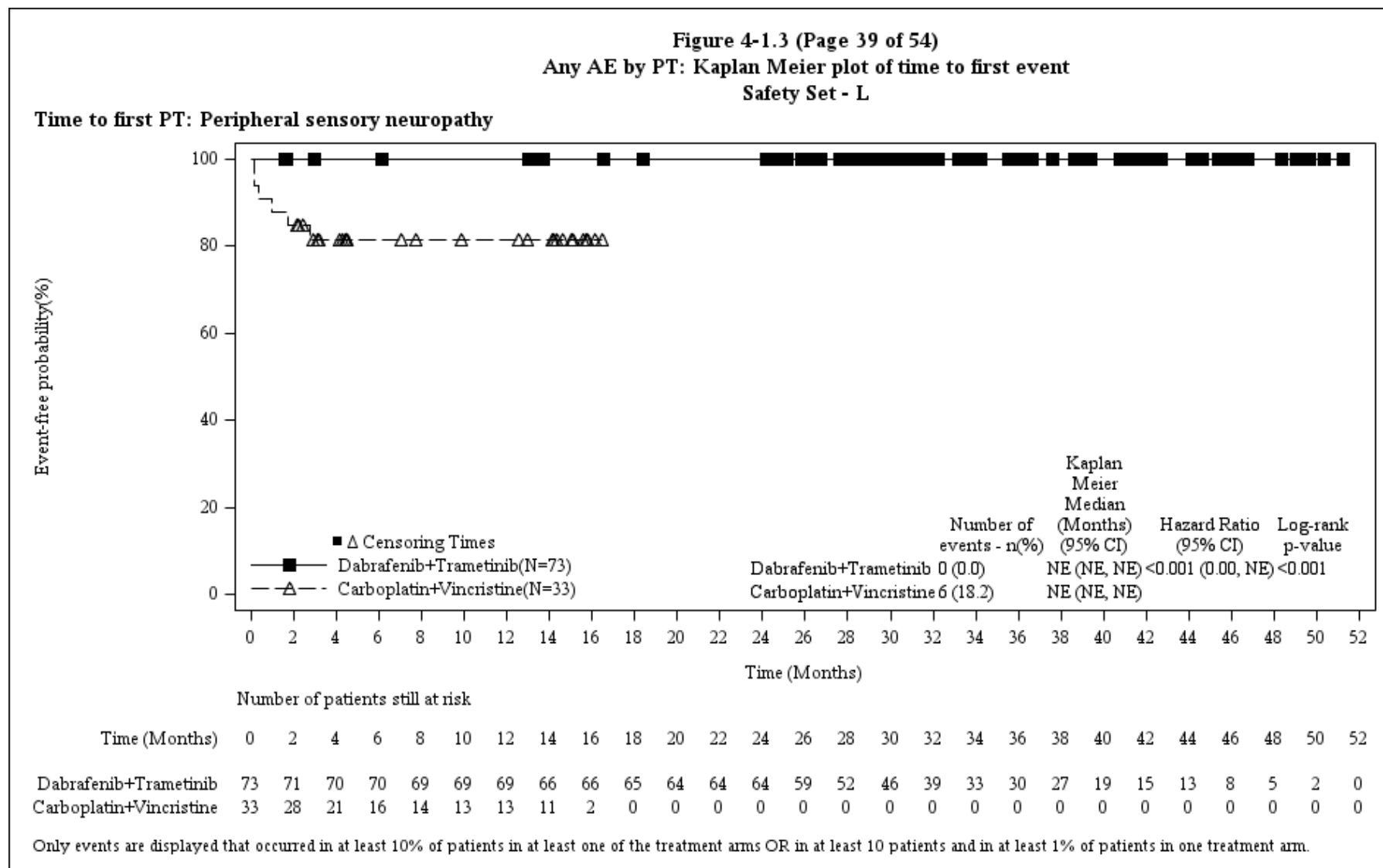


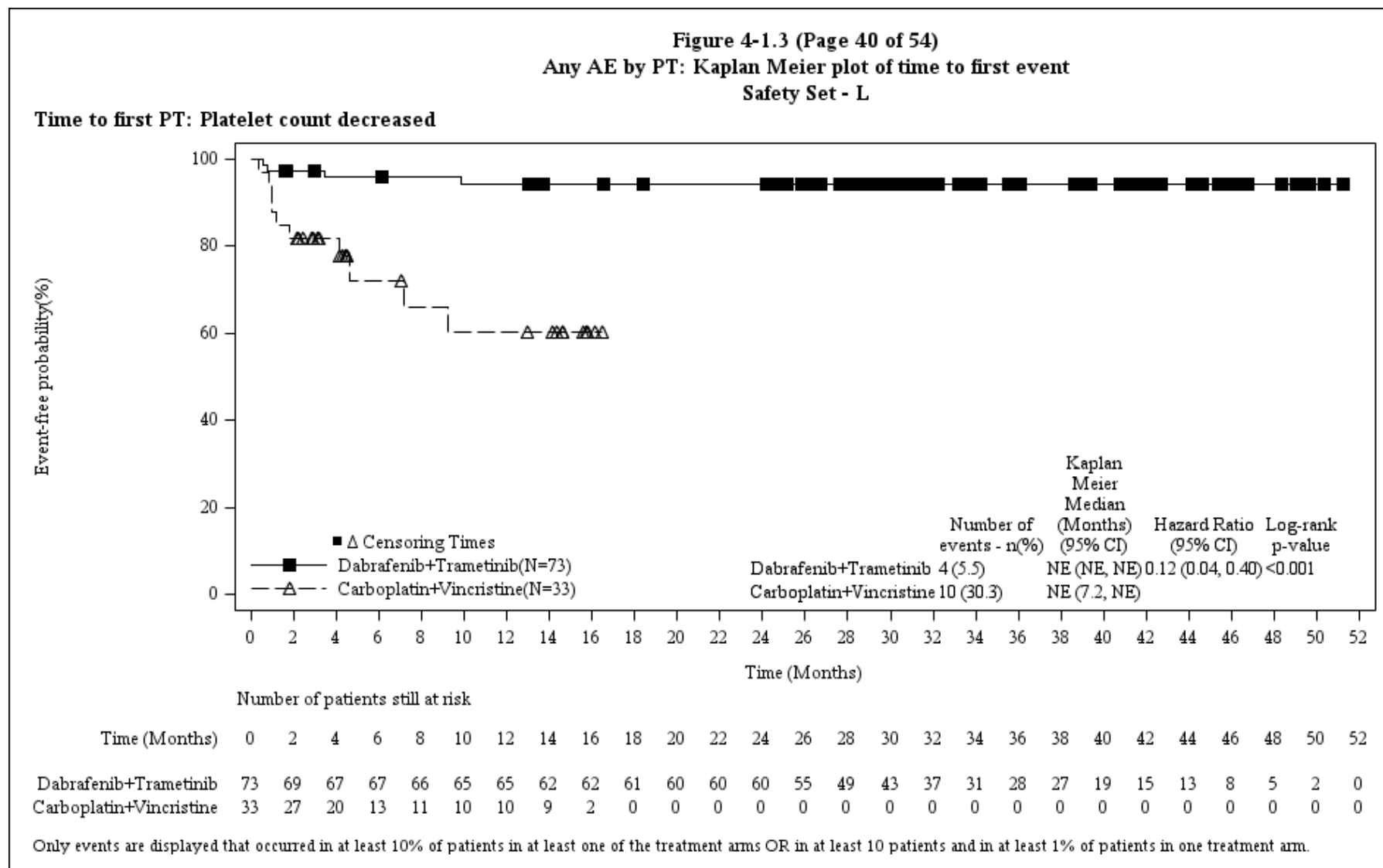












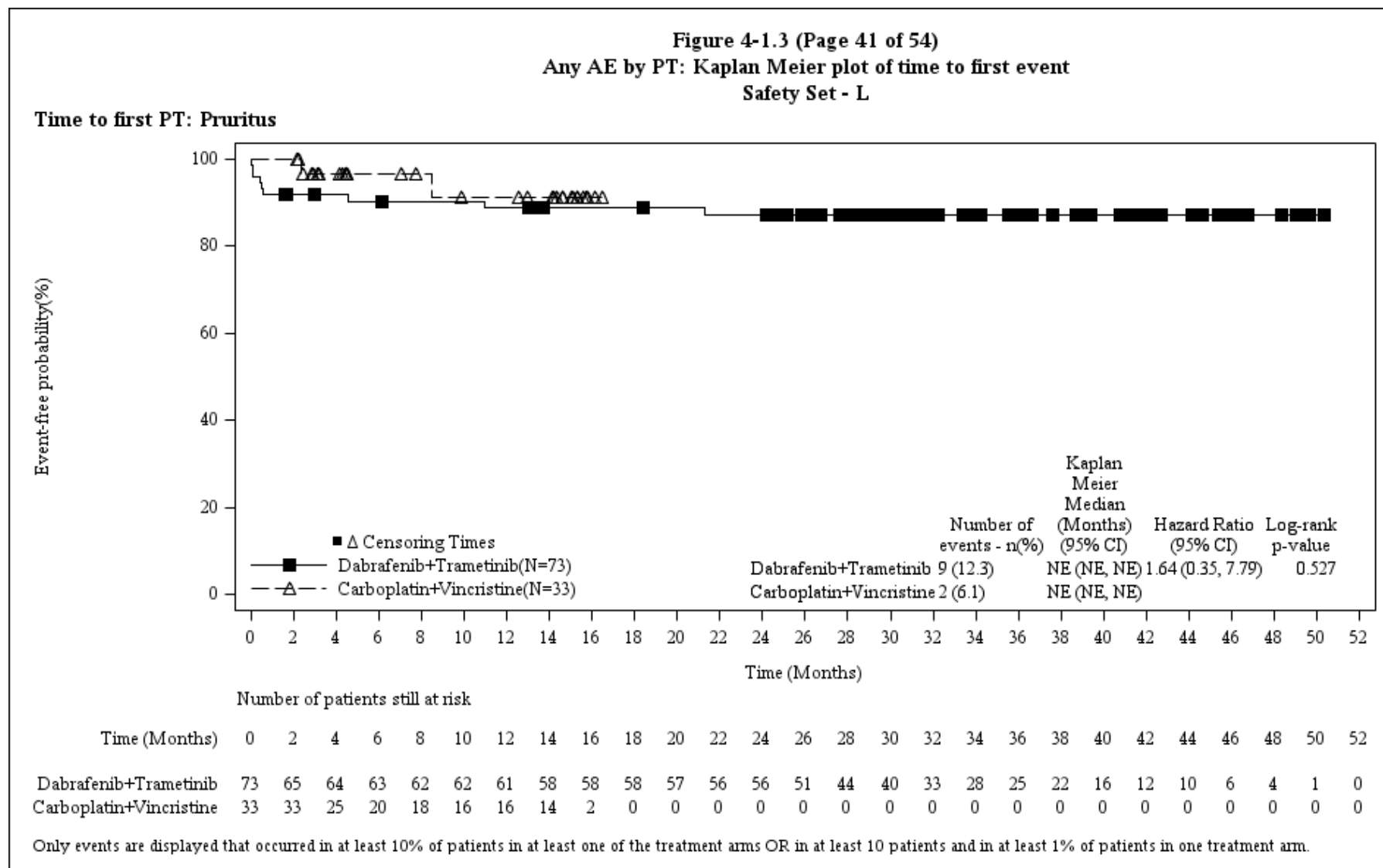
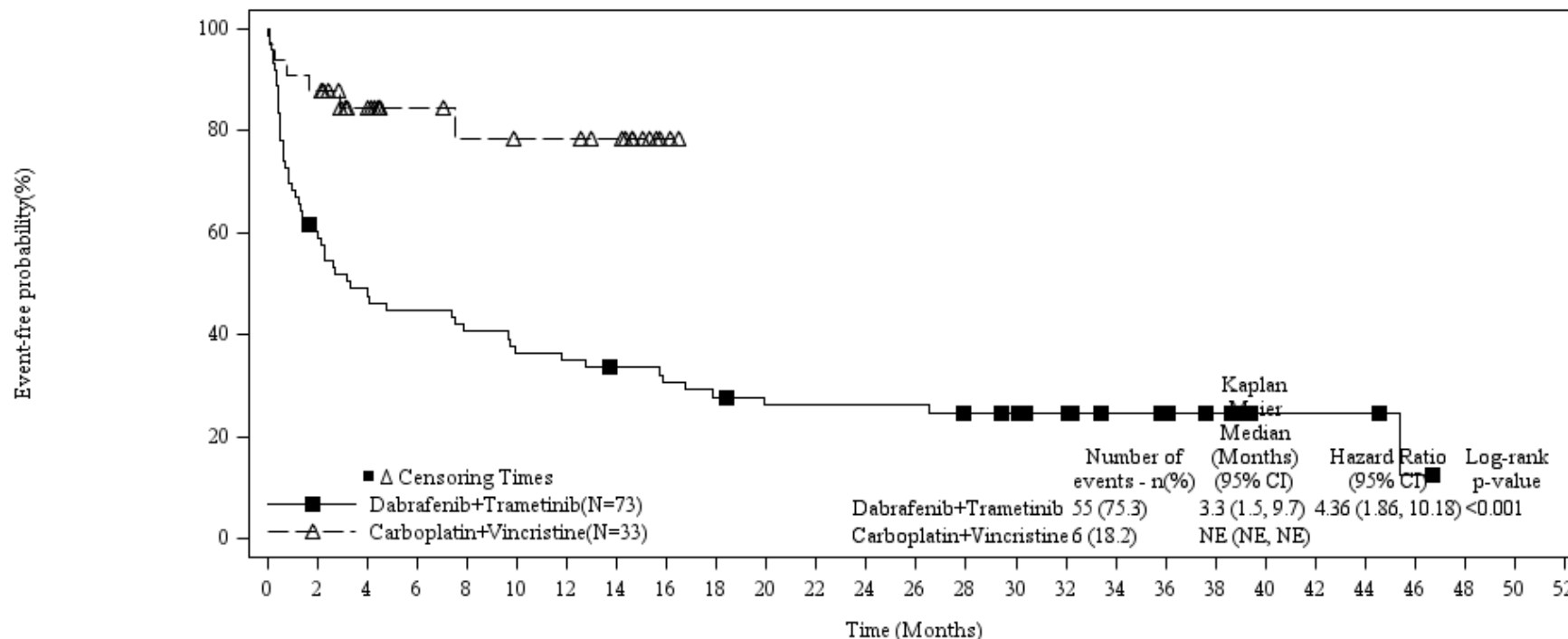


Figure 4-1.3 (Page 42 of 54)
Any AE by PT: Kaplan Meier plot of time to first event
Safety Set - L

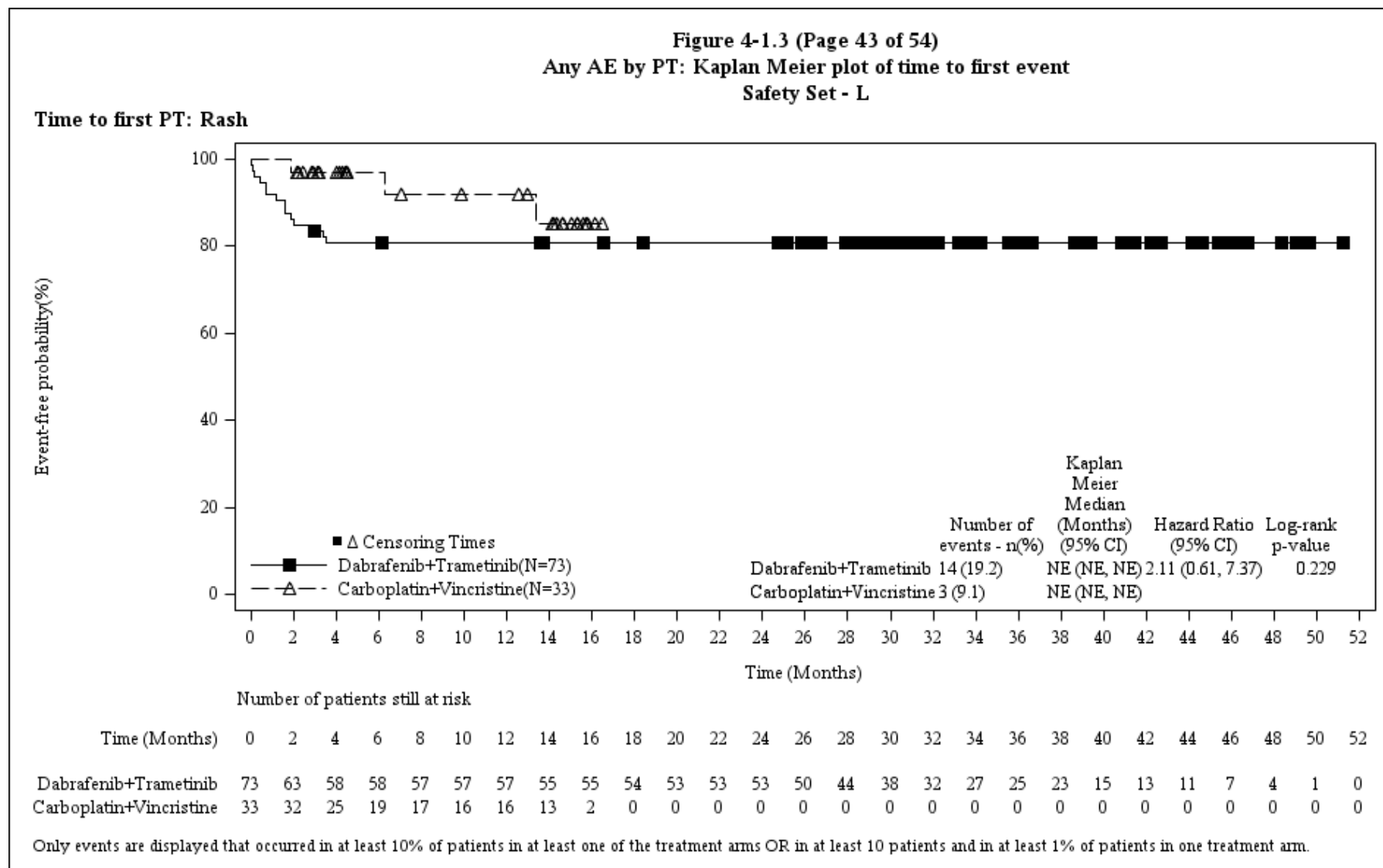
Time to first PT: Pyrexia

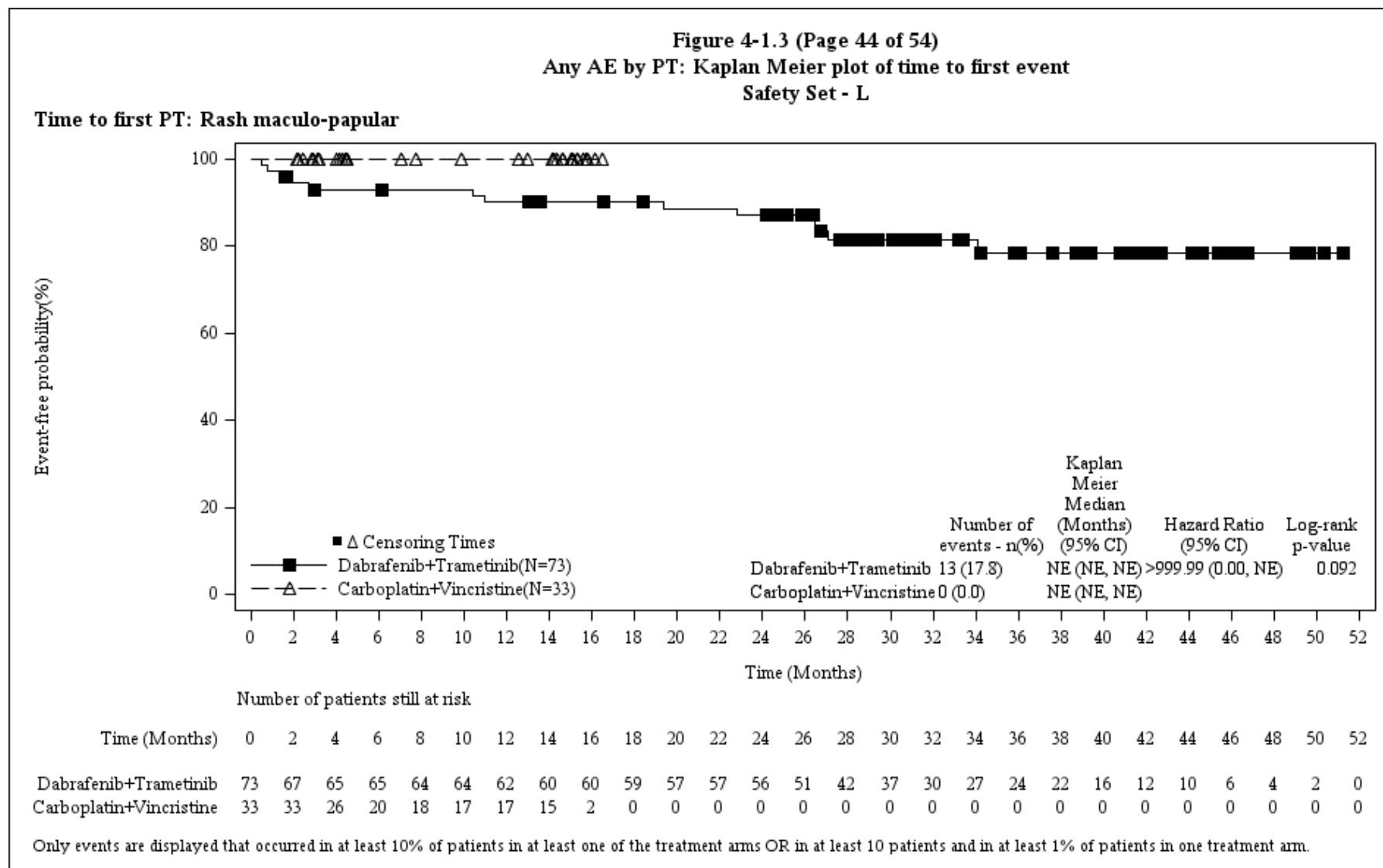


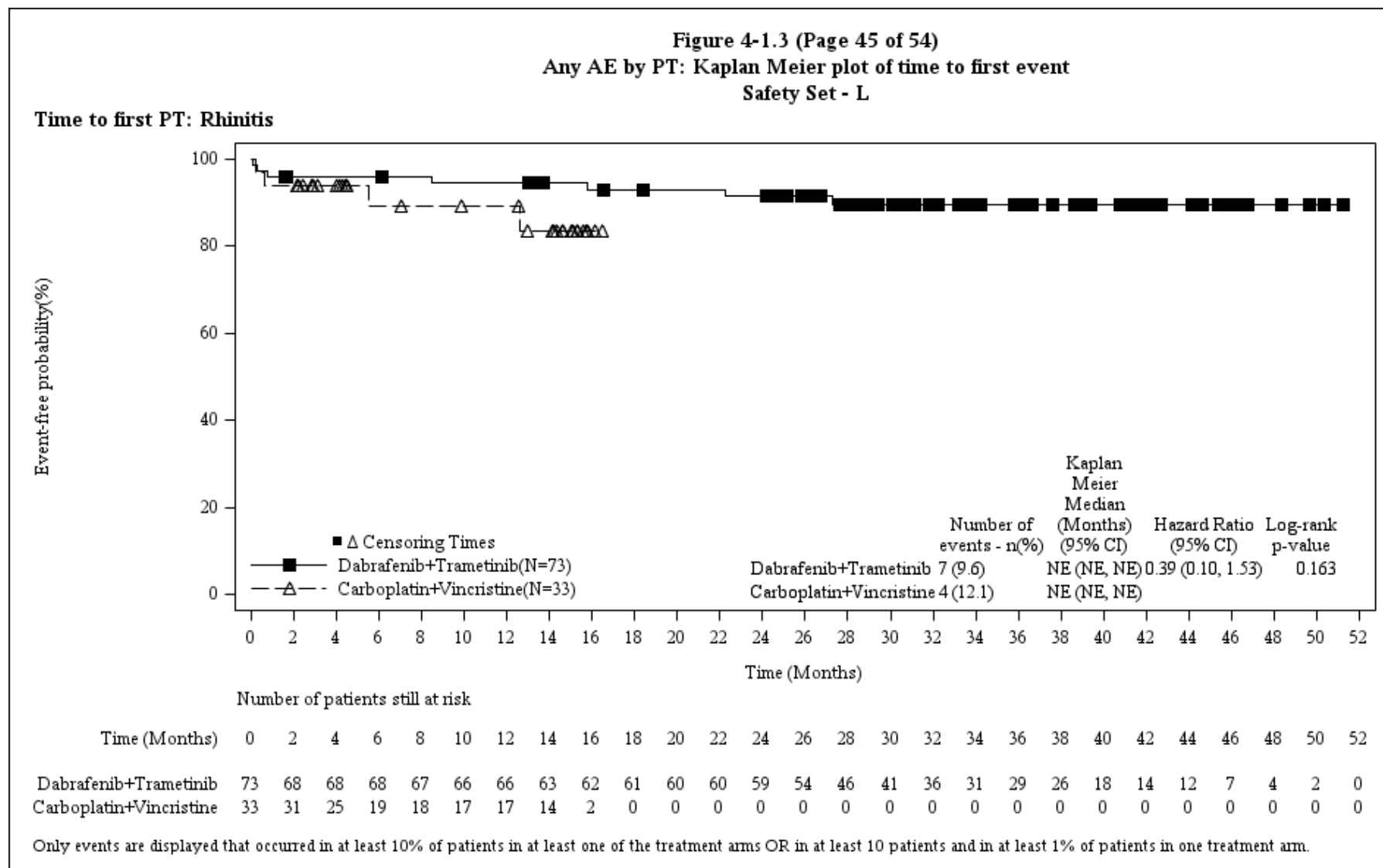
Number of patients still at risk

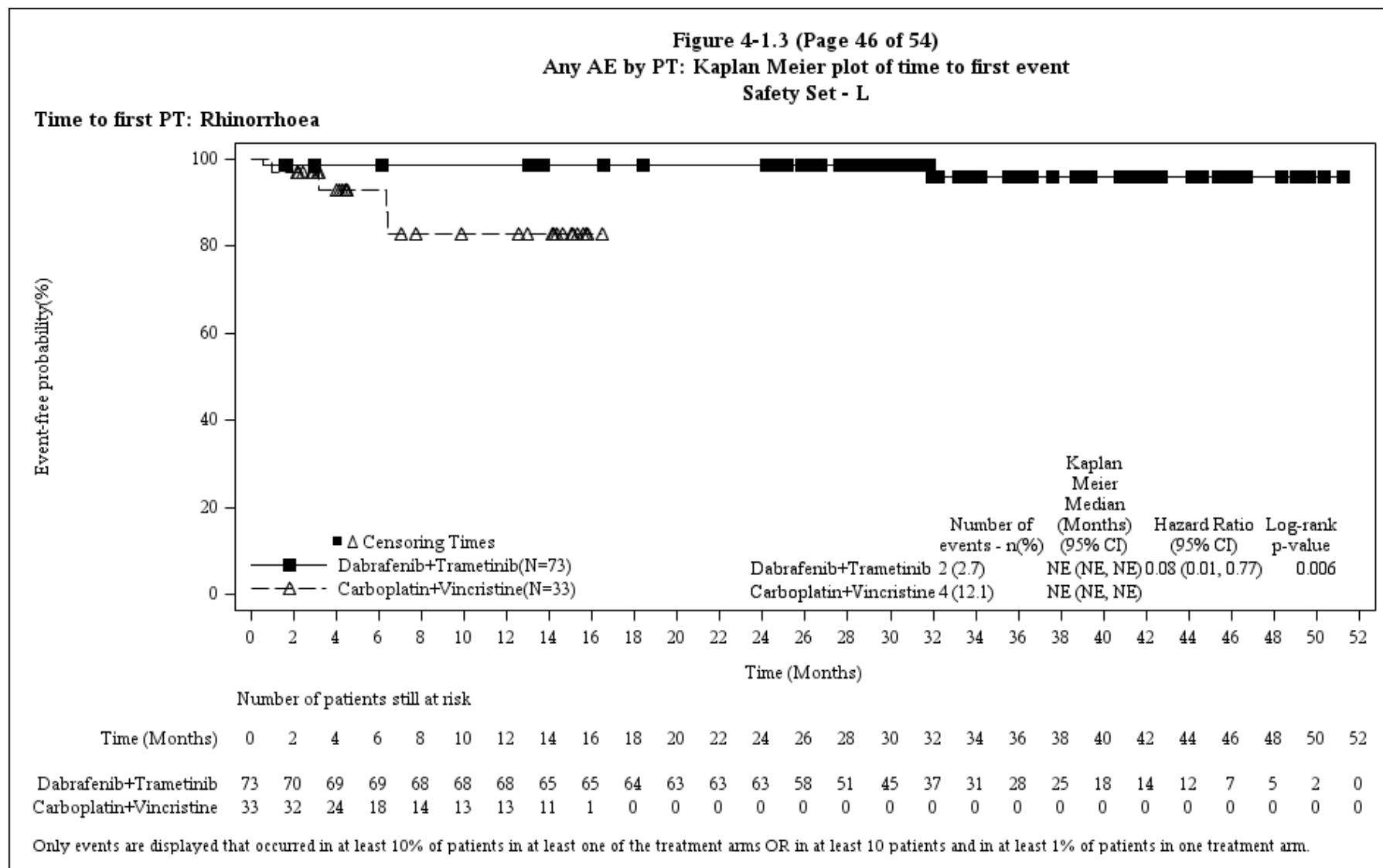
Time (Months)	0	2	4	6	8	10	12	14	16	18	20	22	24	26	28	30	32	34	36	38	40	42	44	46	48	50	52
Dabrafenib+Trametinib	73	43	35	32	29	26	25	23	21	19	17	17	17	17	15	14	12	9	8	6	3	3	3	1	0	0	0
Carboplatin+Vincristine	33	29	21	15	13	12	12	10	2	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	

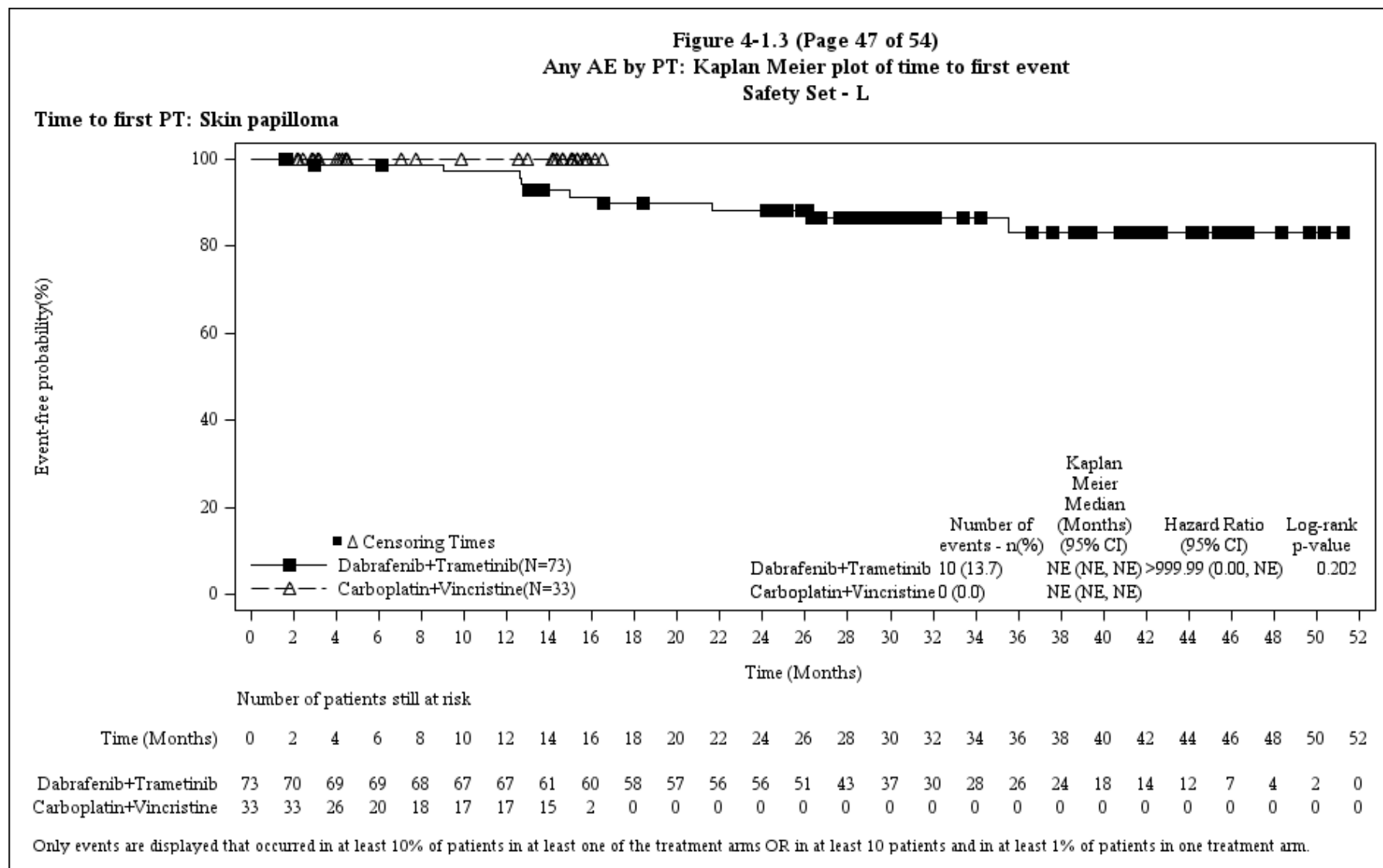
Only events are displayed that occurred in at least 10% of patients in at least one of the treatment arms OR in at least 10 patients and in at least 1% of patients in one treatment arm.

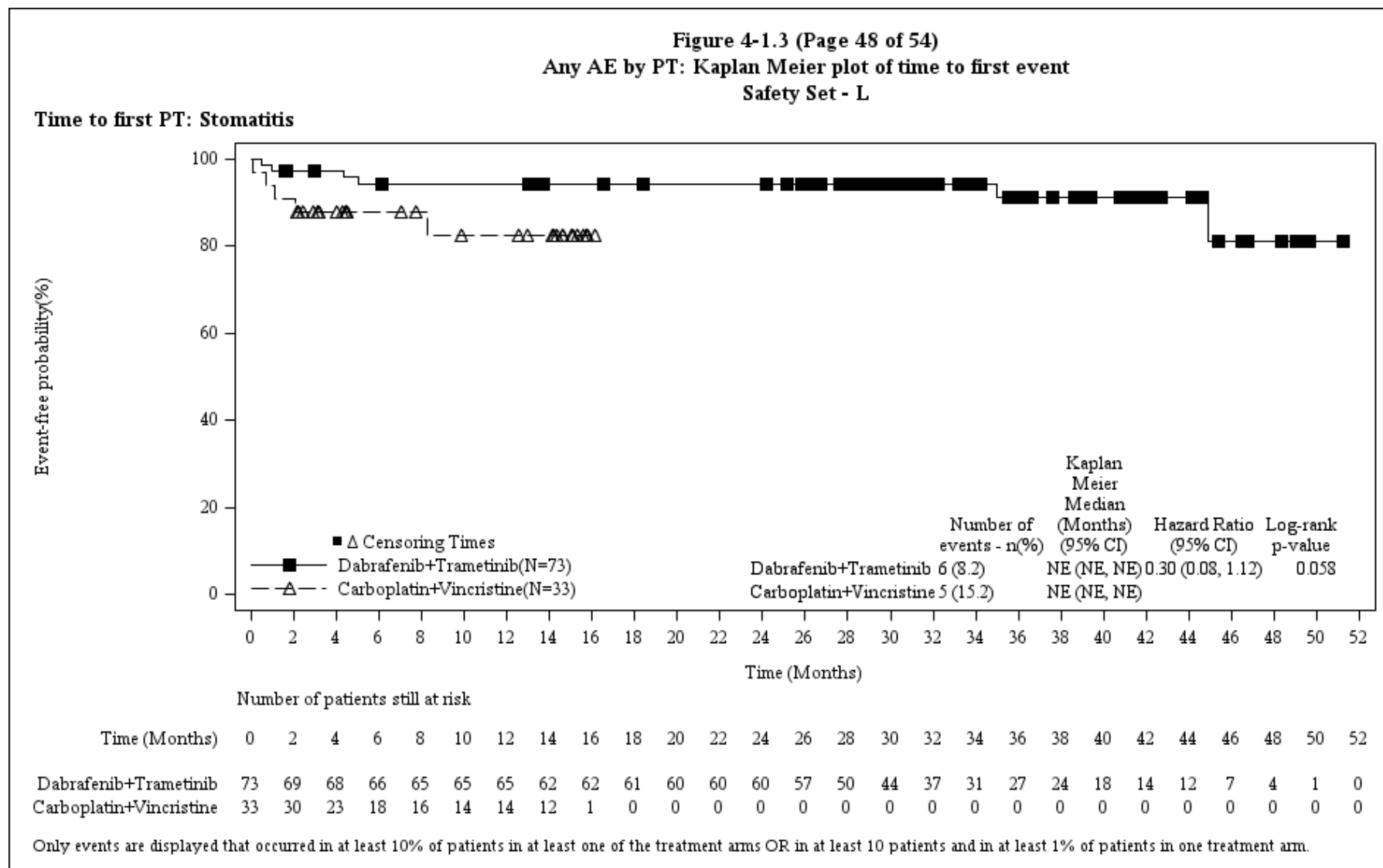


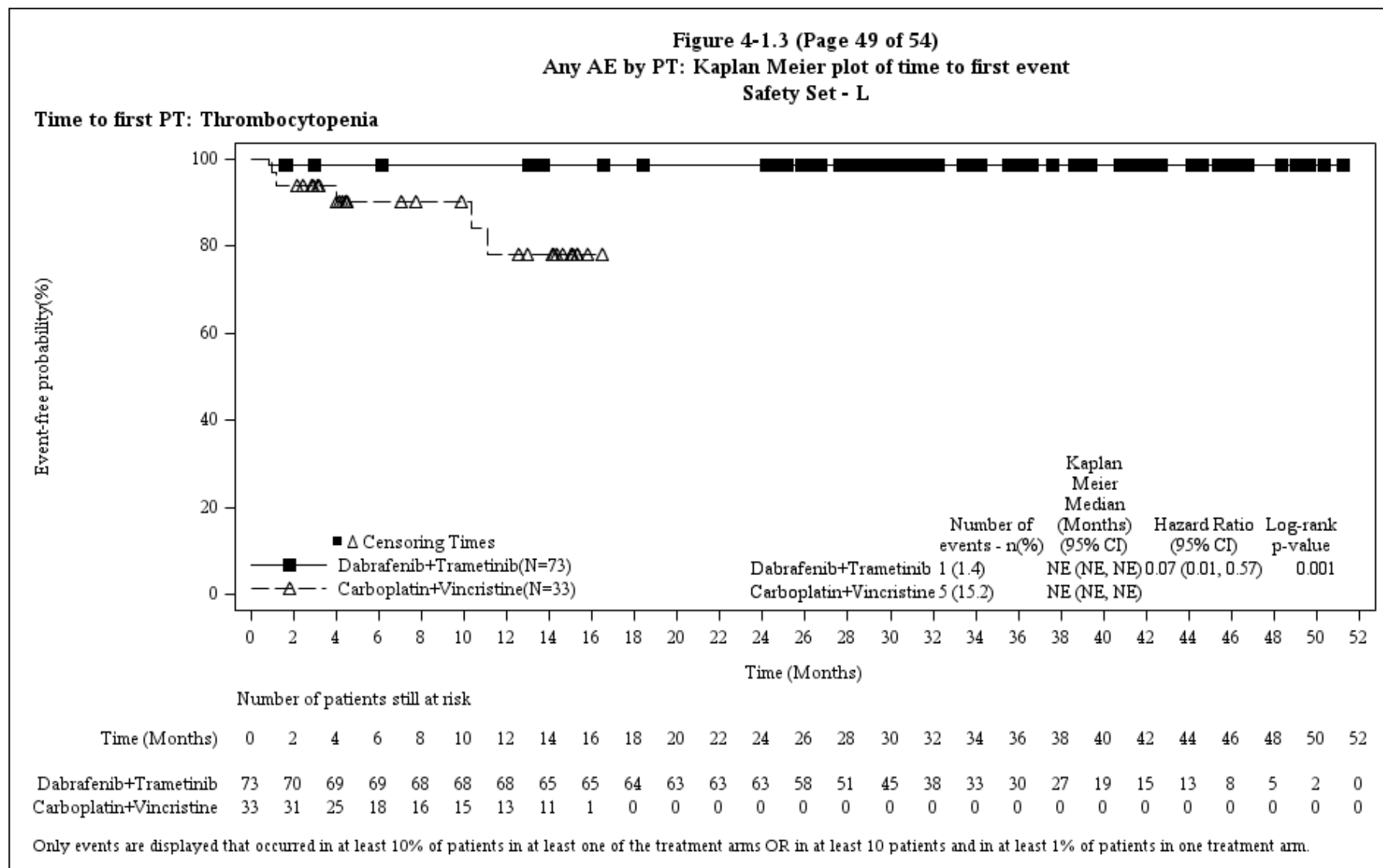












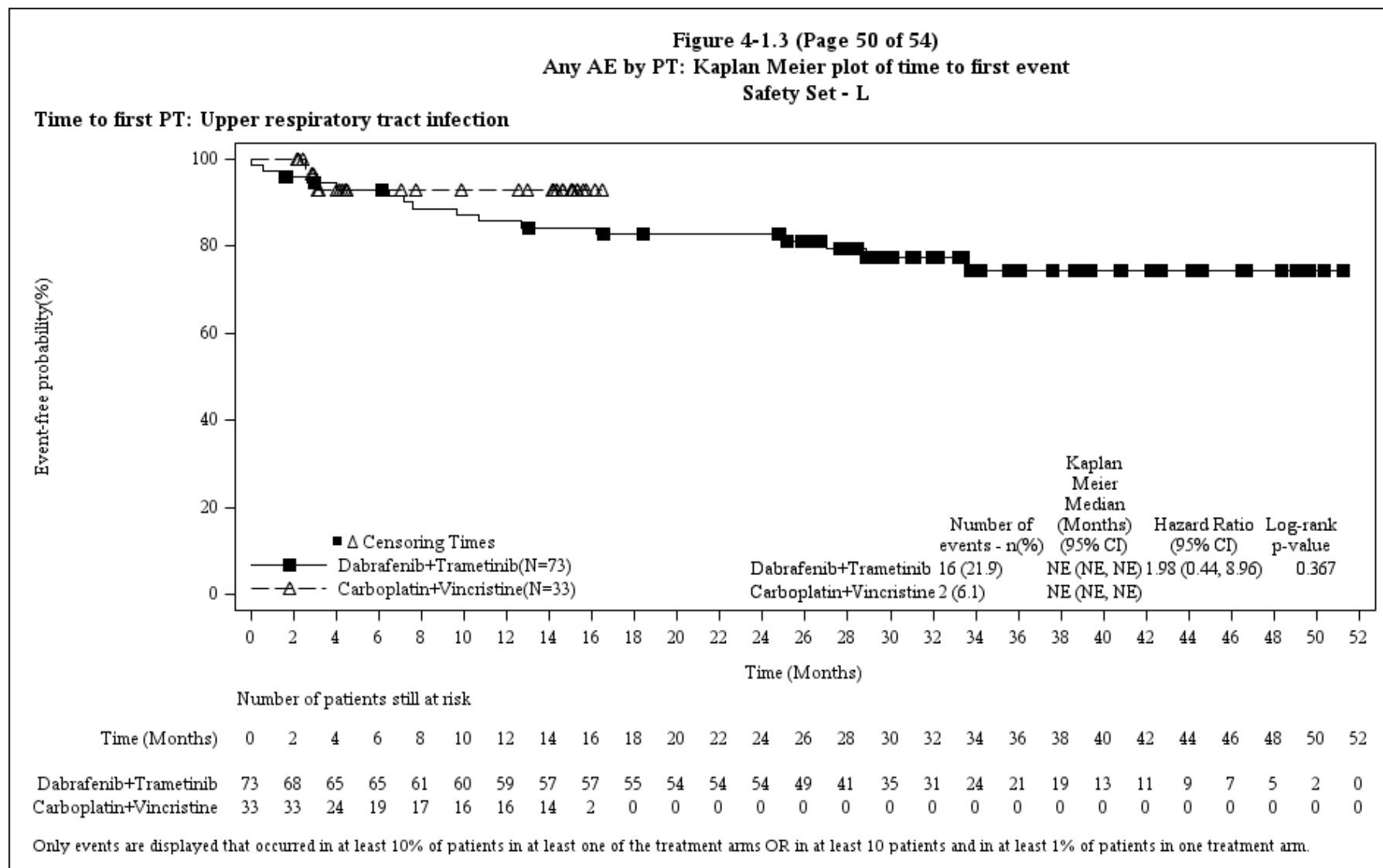
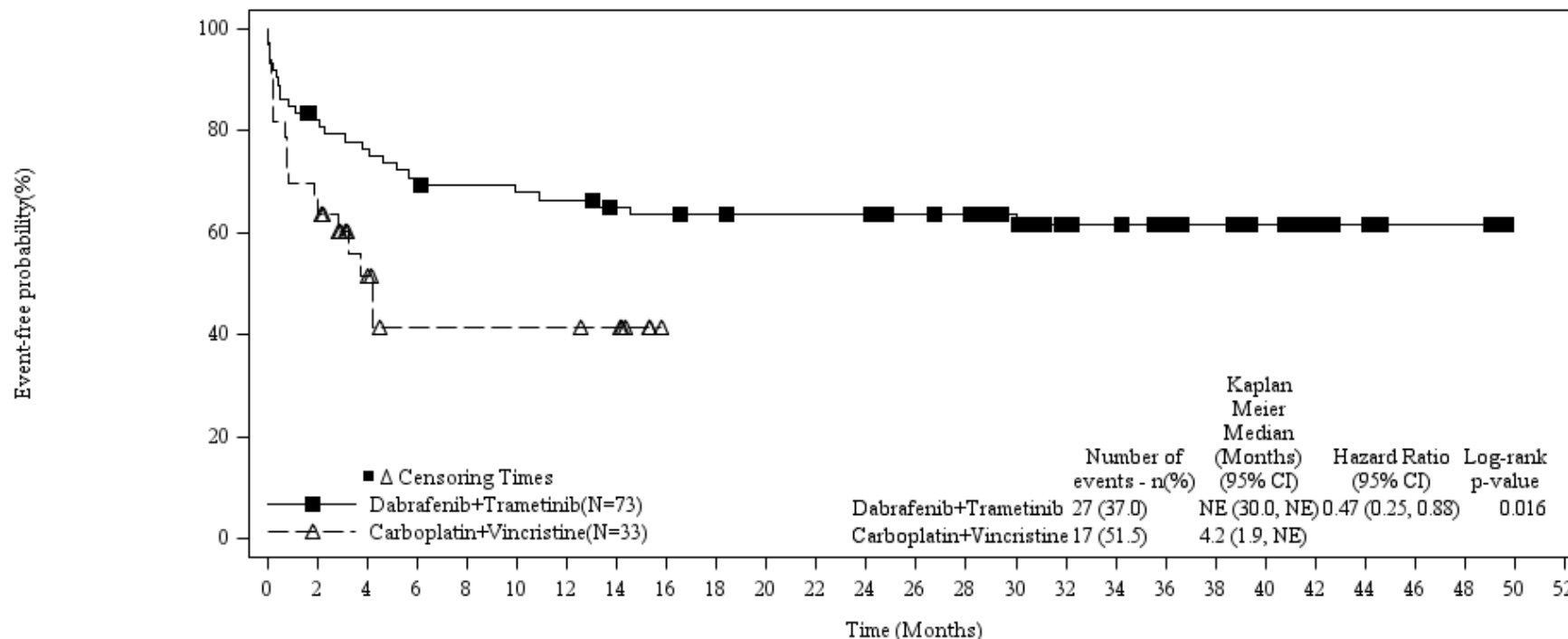


Figure 4-1.3 (Page 51 of 54)
Any AE by PT: Kaplan Meier plot of time to first event
Safety Set - L

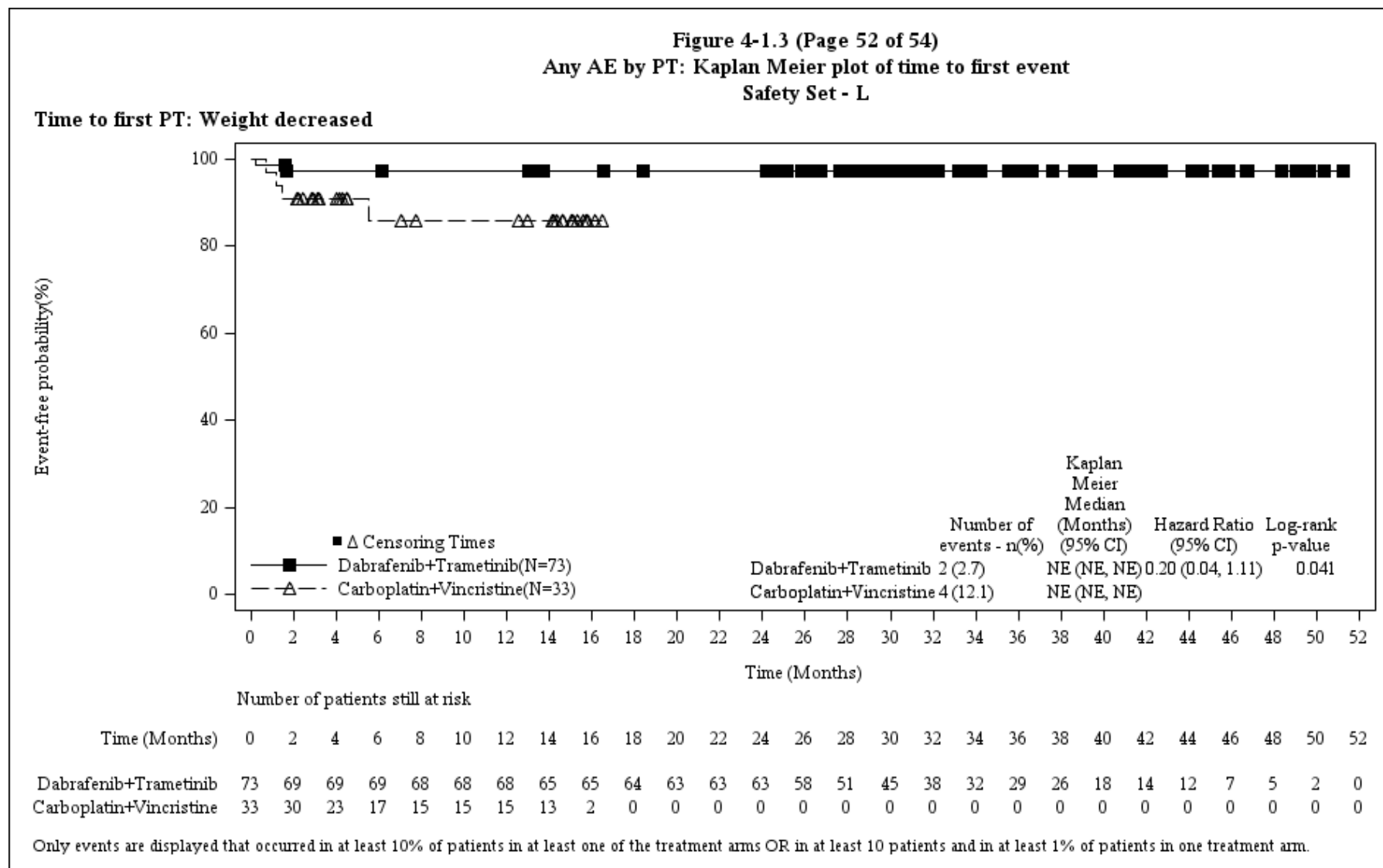
Time to first PT: Vomiting

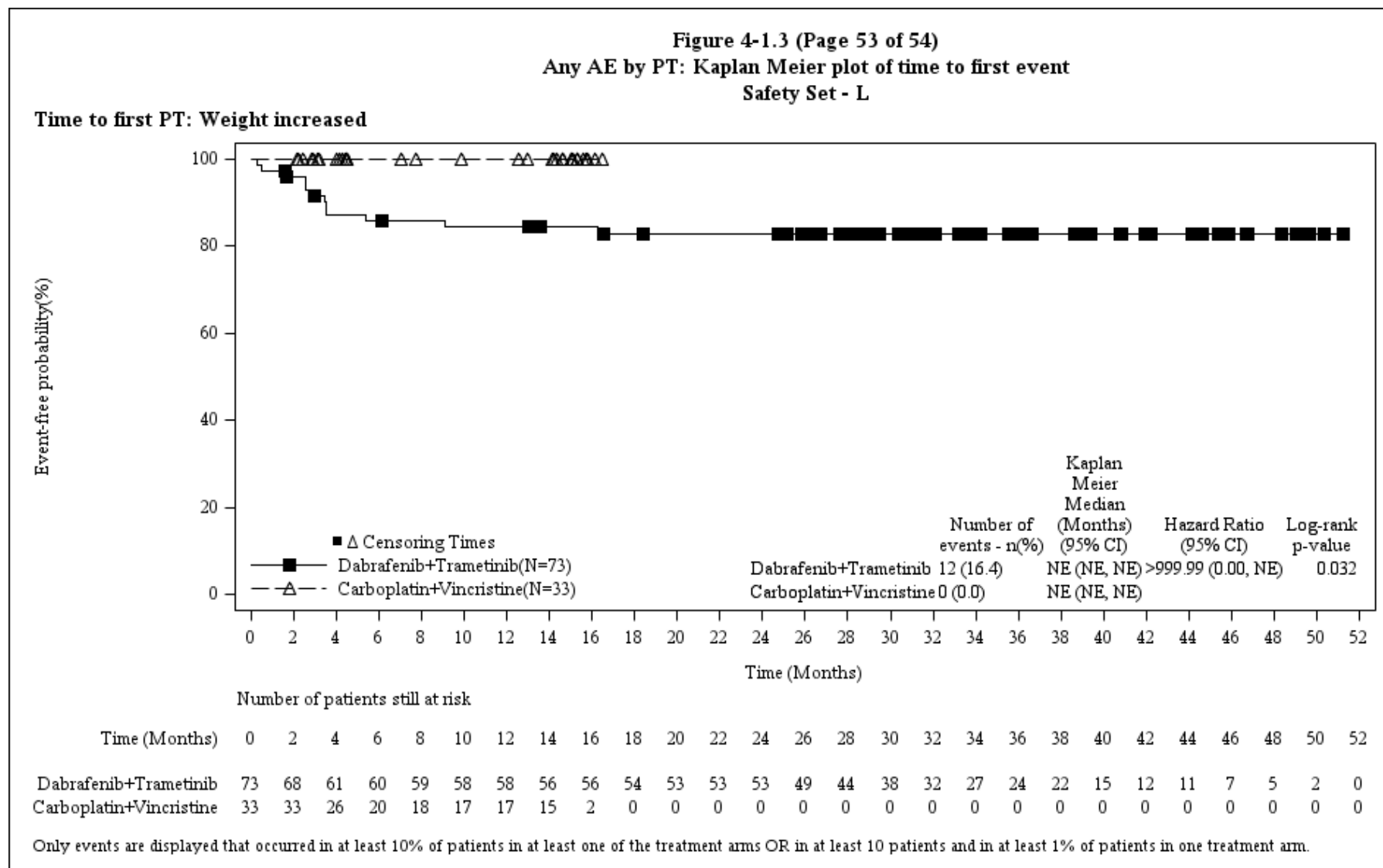


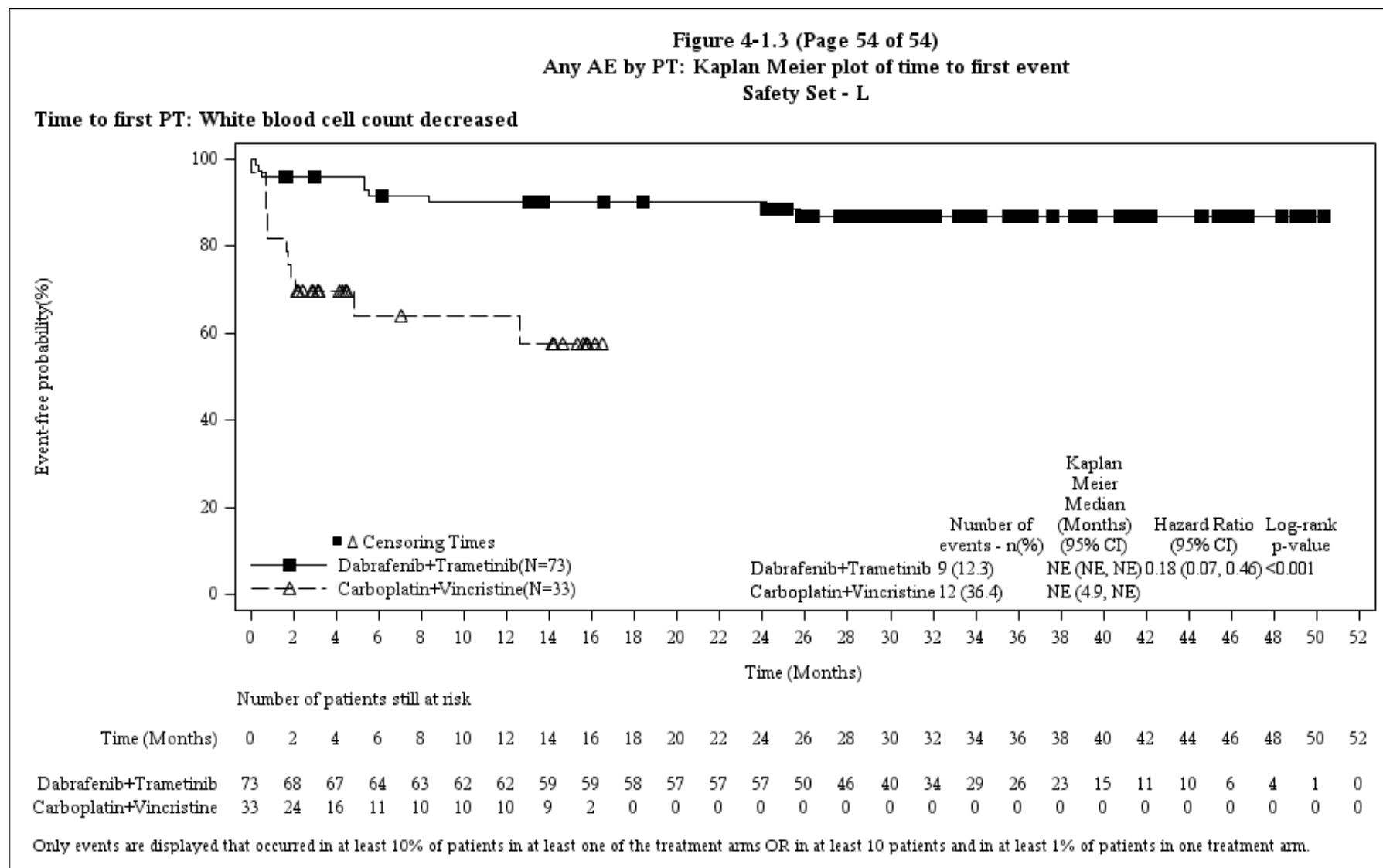
Number of patients still at risk

Time (Months)	0	2	4	6	8	10	12	14	16	18	20	22	24	26	28	30	32	34	36	38	40	42	44	46	48	50	52
Dabrafenib+Trametinib	73	58	54	49	48	47	46	43	42	41	40	40	40	37	36	31	24	22	19	17	11	7	5	2	2	0	0
Carboplatin+Vincristine	33	22	12	7	7	7	7	6	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0

Only events are displayed that occurred in at least 10% of patients in at least one of the treatment arms OR in at least 10 patients and in at least 1% of patients in one treatment arm.







2.3.5. Schwere unerwünschte Ereignisse (CTCAE-Grad ≥ 3) nach PT

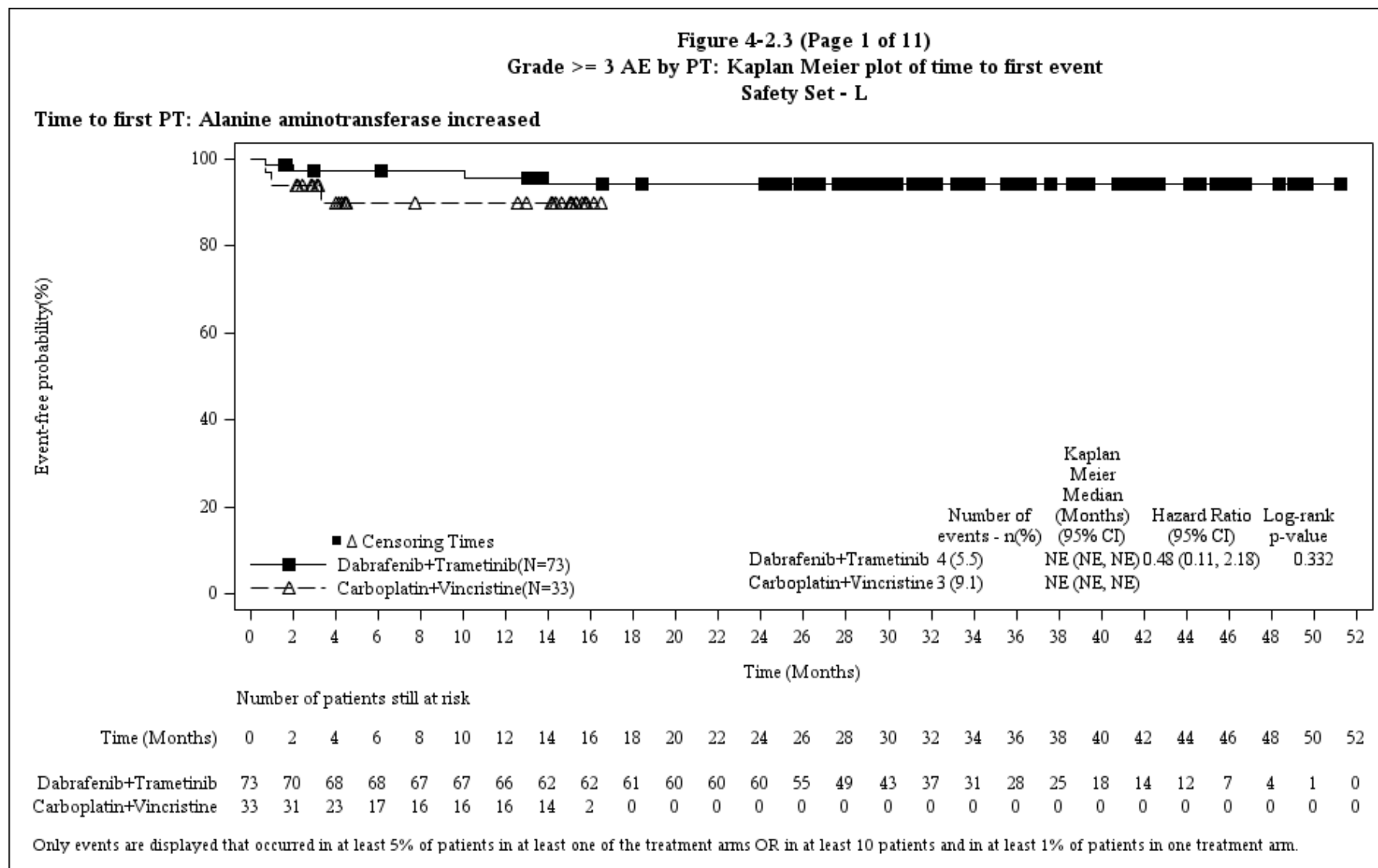
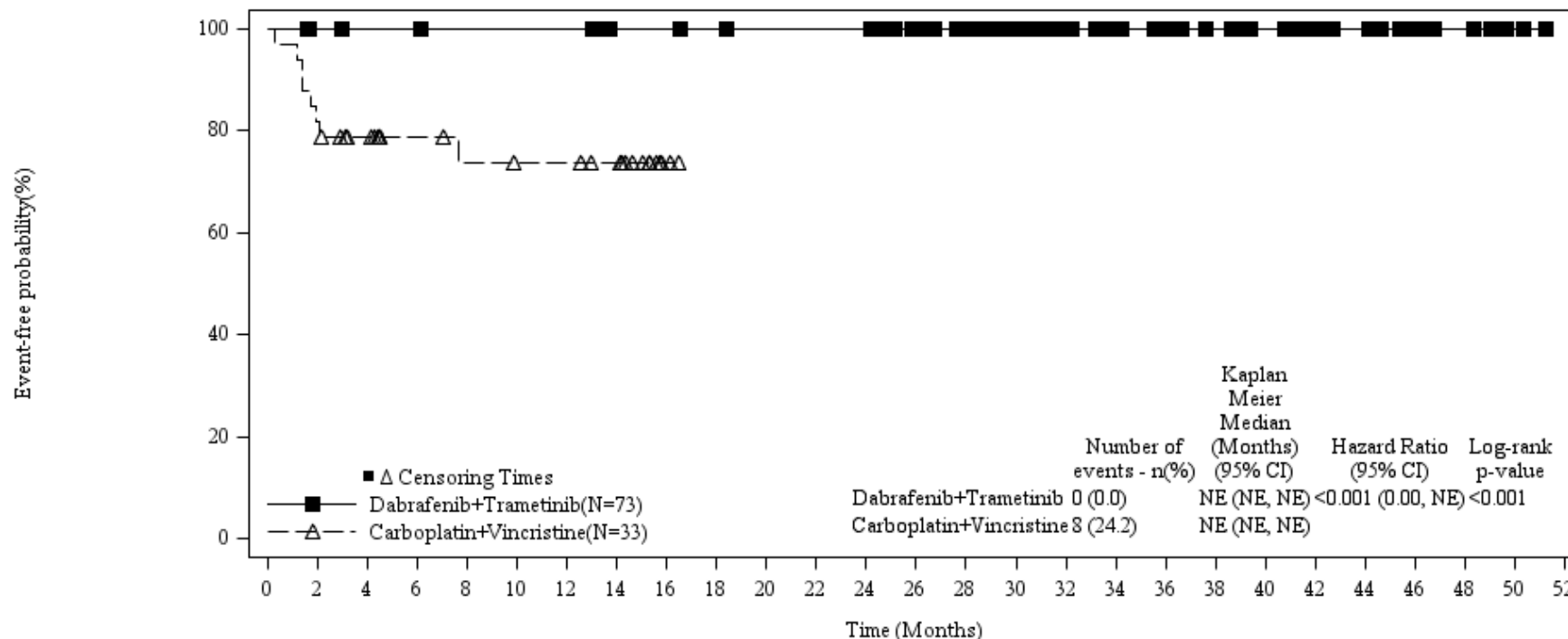


Figure 4-2.3 (Page 2 of 11)
Grade >= 3 AE by PT: Kaplan Meier plot of time to first event
Safety Set - L

Time to first PT: Anaemia



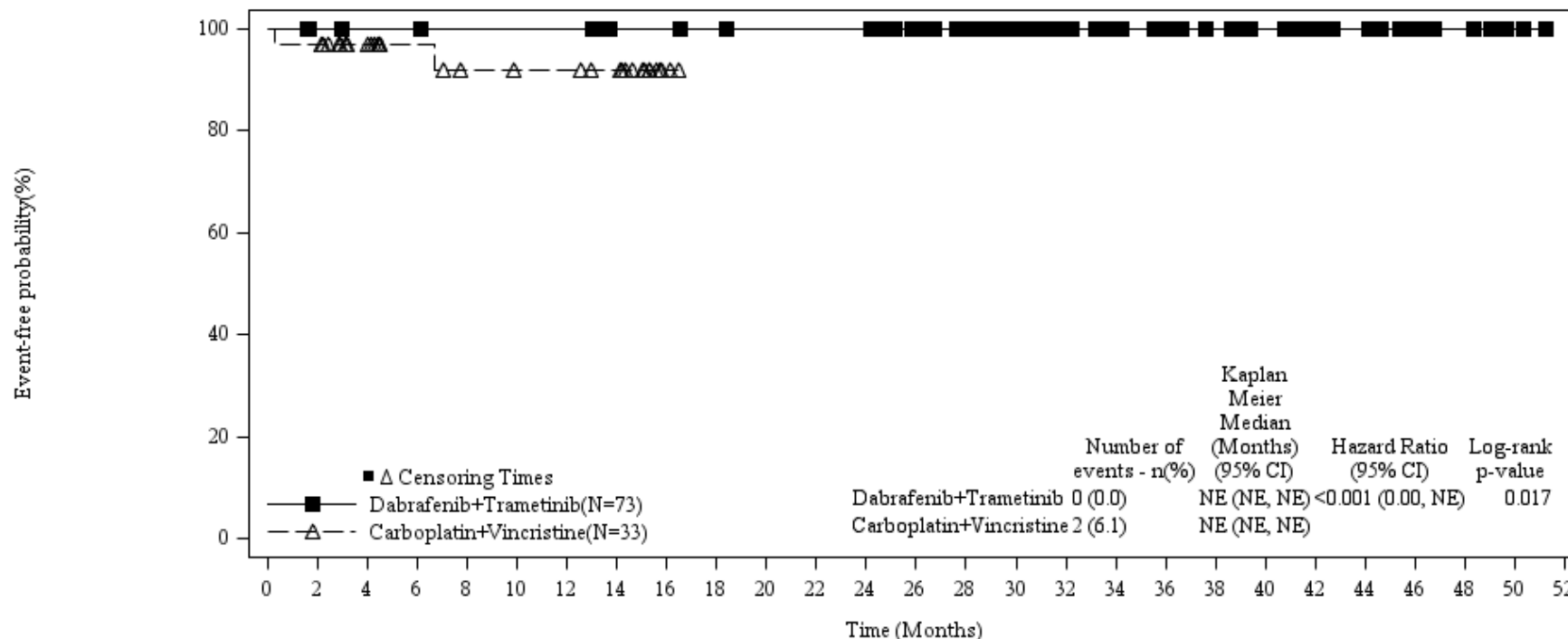
Number of patients still at risk

Time (Months)	0	2	4	6	8	10	12	14	16	18	20	22	24	26	28	30	32	34	36	38	40	42	44	46	48	50	52
Dabrafenib+Trametinib	73	71	70	70	69	69	69	66	66	65	64	64	64	59	52	46	39	33	30	27	19	15	13	8	5	2	0
Carboplatin+Vincristine	33	27	22	17	15	14	14	12	2	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0

Only events are displayed that occurred in at least 5% of patients in at least one of the treatment arms OR in at least 10 patients and in at least 1% of patients in one treatment arm.

Figure 4-2.3 (Page 3 of 11)
Grade >= 3 AE by PT: Kaplan Meier plot of time to first event
Safety Set - L

Time to first PT: Diarrhoea



Number of patients still at risk

Time (Months)	0	2	4	6	8	10	12	14	16	18	20	22	24	26	28	30	32	34	36	38	40	42	44	46	48	50	52
Dabrafenib+Trametinib	73	71	70	70	69	69	69	66	66	65	64	64	64	59	52	46	39	33	30	27	19	15	13	8	5	2	0
Carboplatin+Vincristine	33	32	25	19	16	15	15	13	2	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0

Only events are displayed that occurred in at least 5% of patients in at least one of the treatment arms OR in at least 10 patients and in at least 1% of patients in one treatment arm.

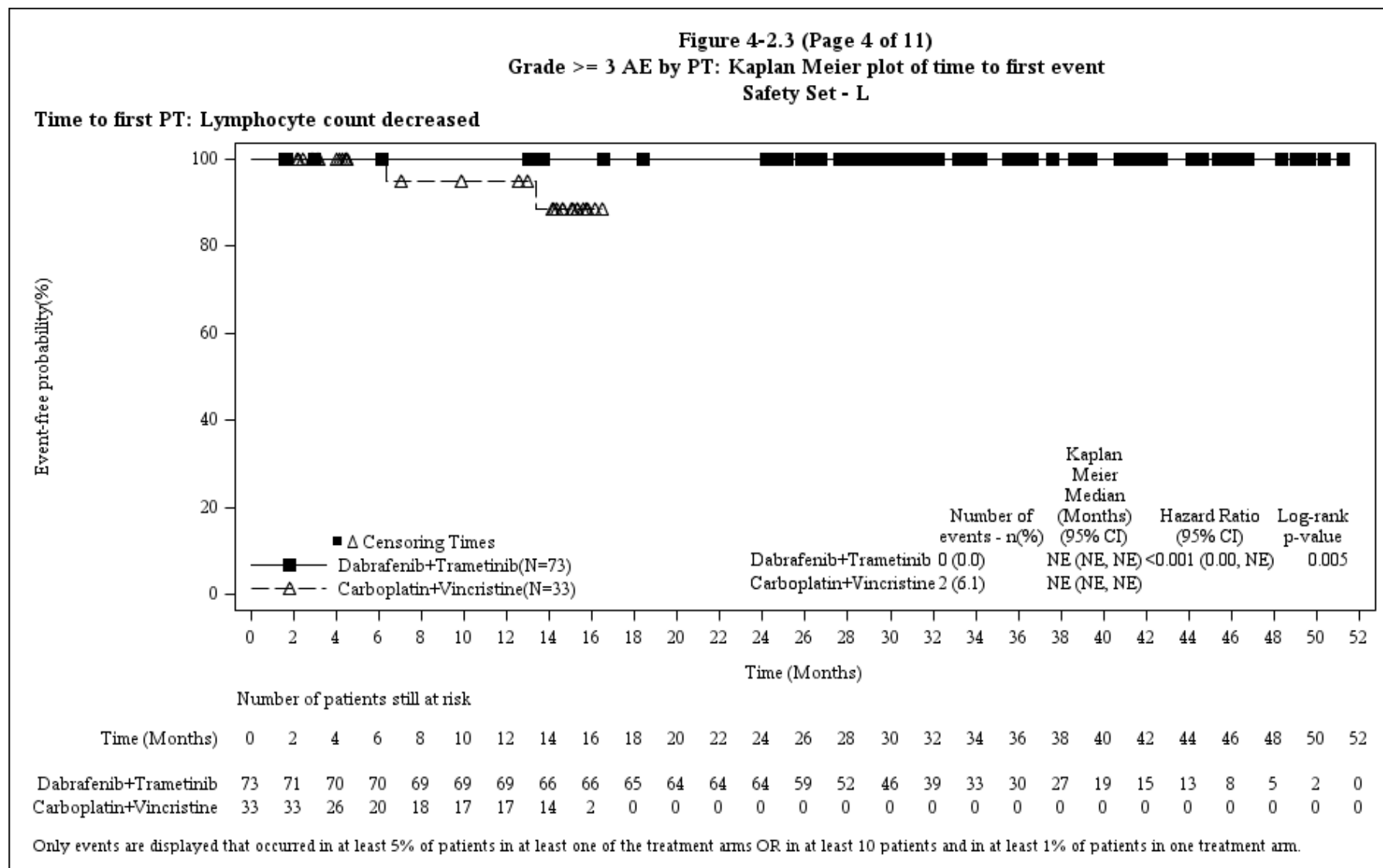
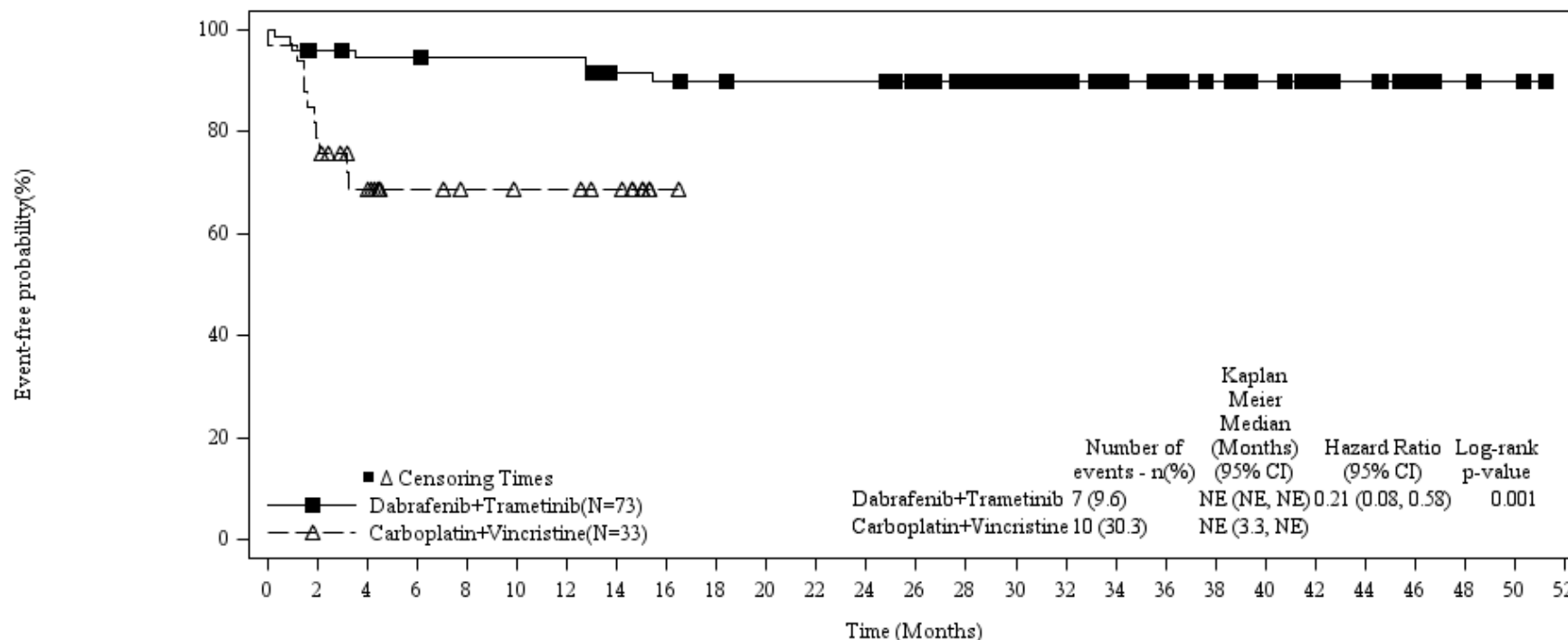


Figure 4-2.3 (Page 5 of 11)
Grade >= 3 AE by PT: Kaplan Meier plot of time to first event
Safety Set - L

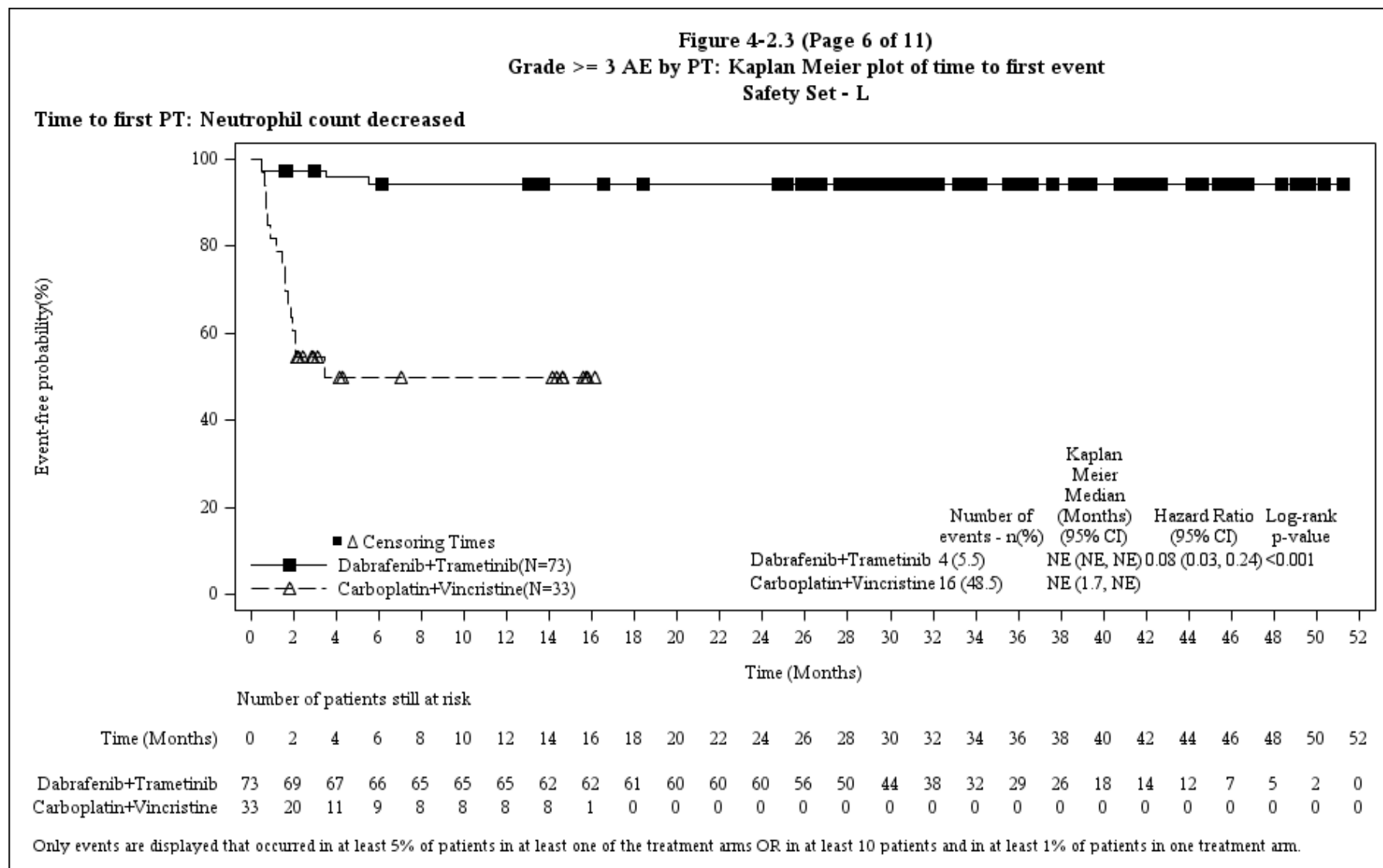
Time to first PT: Neutropenia



Number of patients still at risk

Time (Months)	0	2	4	6	8	10	12	14	16	18	20	22	24	26	28	30	32	34	36	38	40	42	44	46	48	50	52
Dabrafenib+Trametinib	73	68	66	66	65	65	65	60	59	58	57	57	57	54	47	41	34	28	25	22	15	12	10	6	3	2	0
Carboplatin+Vincristine	33	26	19	13	11	10	10	8	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0

Only events are displayed that occurred in at least 5% of patients in at least one of the treatment arms OR in at least 10 patients and in at least 1% of patients in one treatment arm.



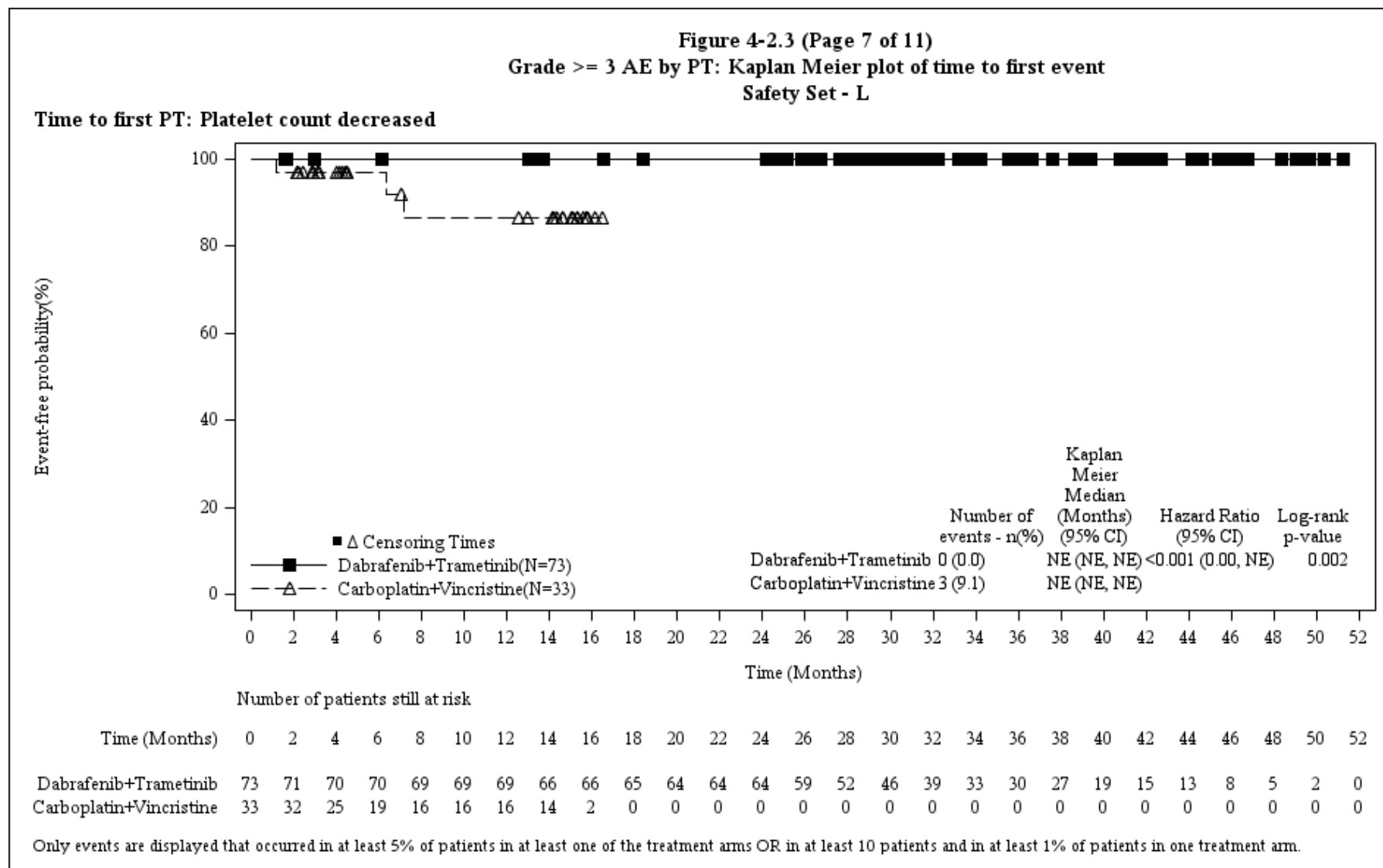
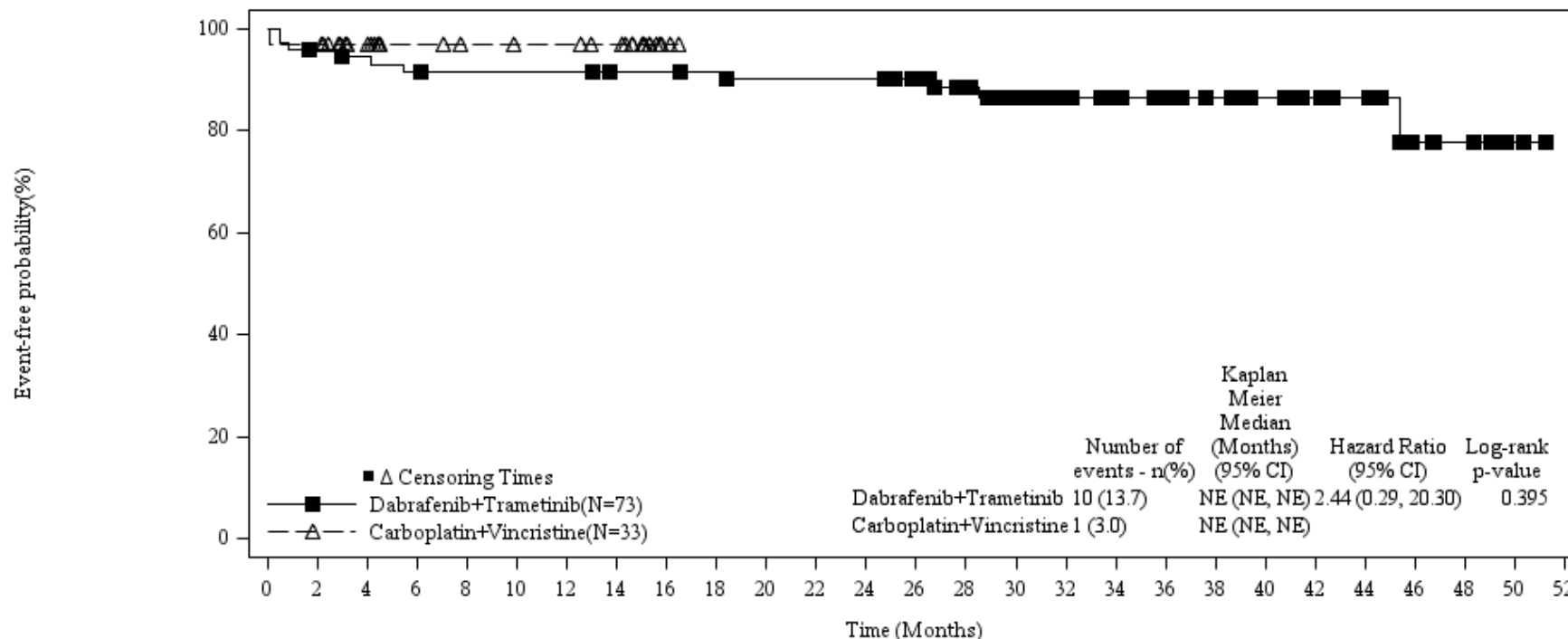


Figure 4-2.3 (Page 8 of 11)
Grade >= 3 AE by PT: Kaplan Meier plot of time to first event
Safety Set - L

Time to first PT: Pyrexia



Number of patients still at risk

Time (Months)	0	2	4	6	8	10	12	14	16	18	20	22	24	26	28	30	32	34	36	38	40	42	44	46	48	50	52
Dabrafenib+Trametinib	73	69	67	65	64	64	64	62	62	61	59	59	59	55	47	41	34	30	27	24	18	15	13	7	5	2	0
Carboplatin+Vincristine	33	32	25	19	17	16	16	14	2	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0

Only events are displayed that occurred in at least 5% of patients in at least one of the treatment arms OR in at least 10 patients and in at least 1% of patients in one treatment arm.

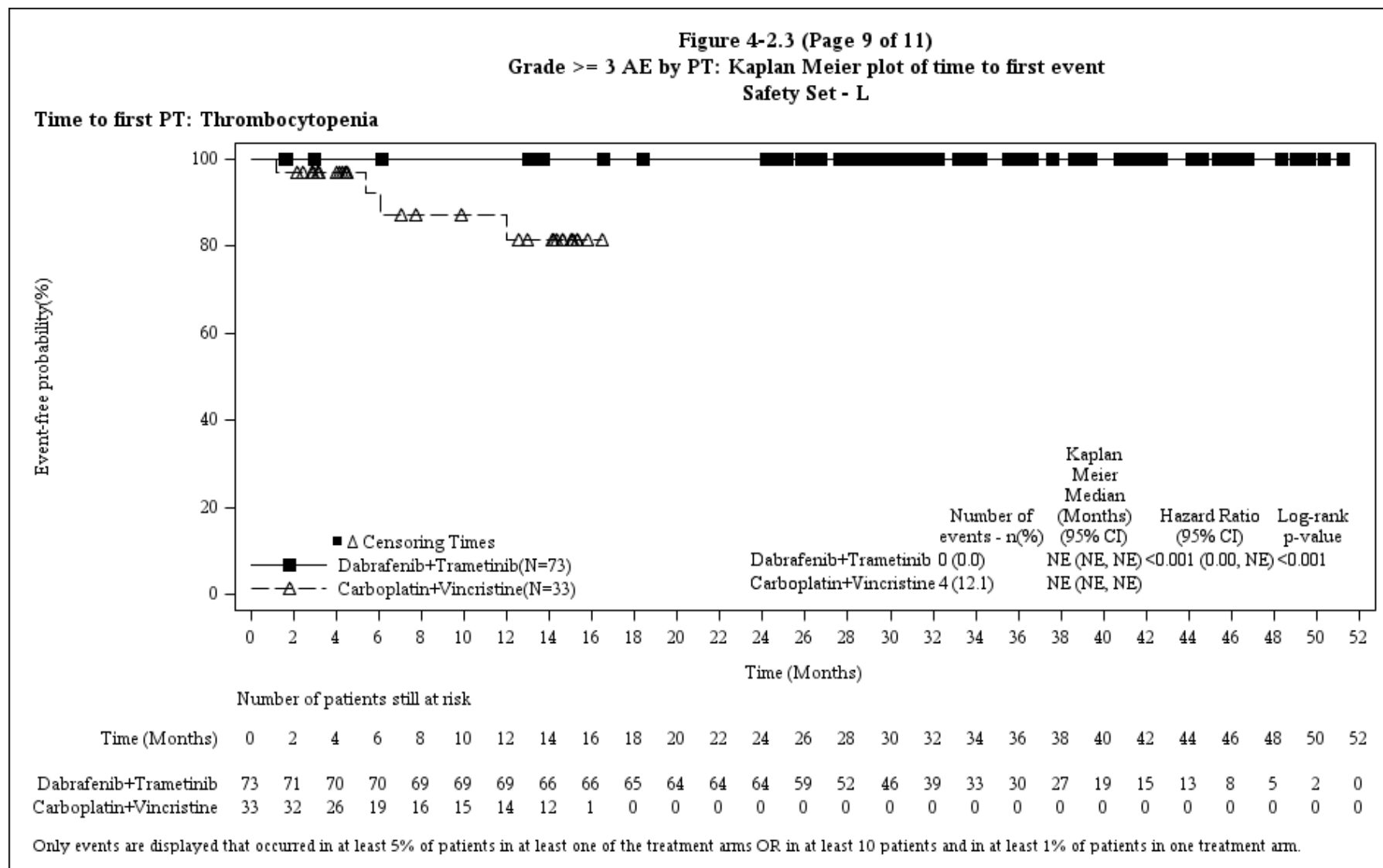
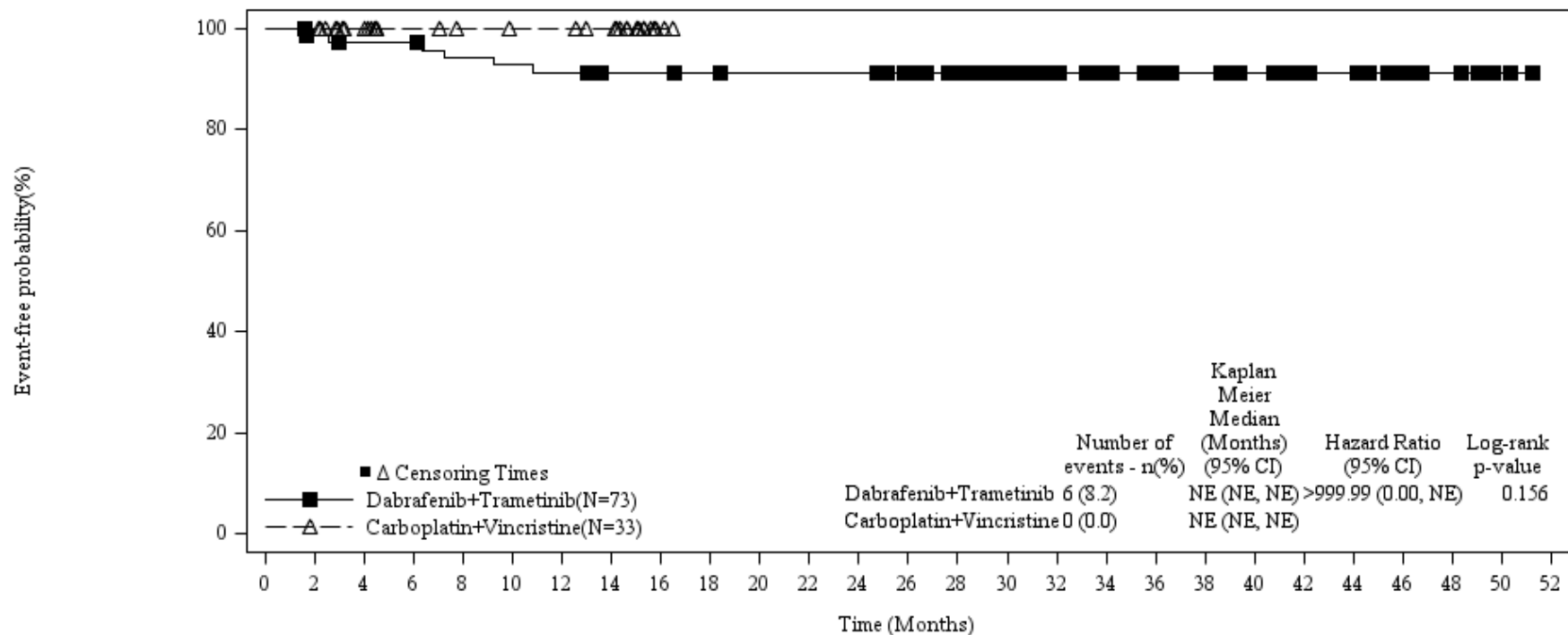


Figure 4-2.3 (Page 10 of 11)
Grade >= 3 AE by PT: Kaplan Meier plot of time to first event
Safety Set - L

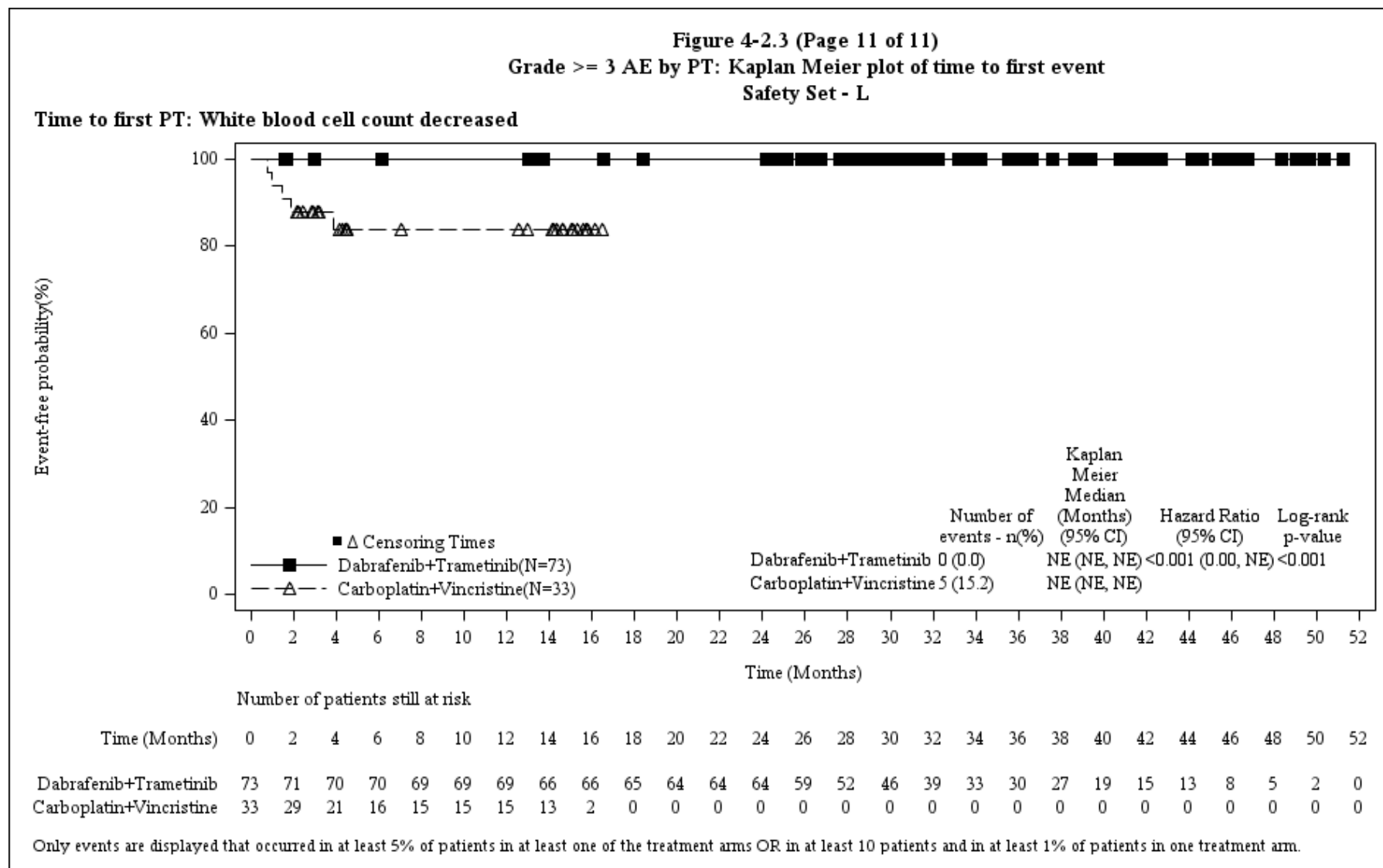
Time to first PT: Weight increased



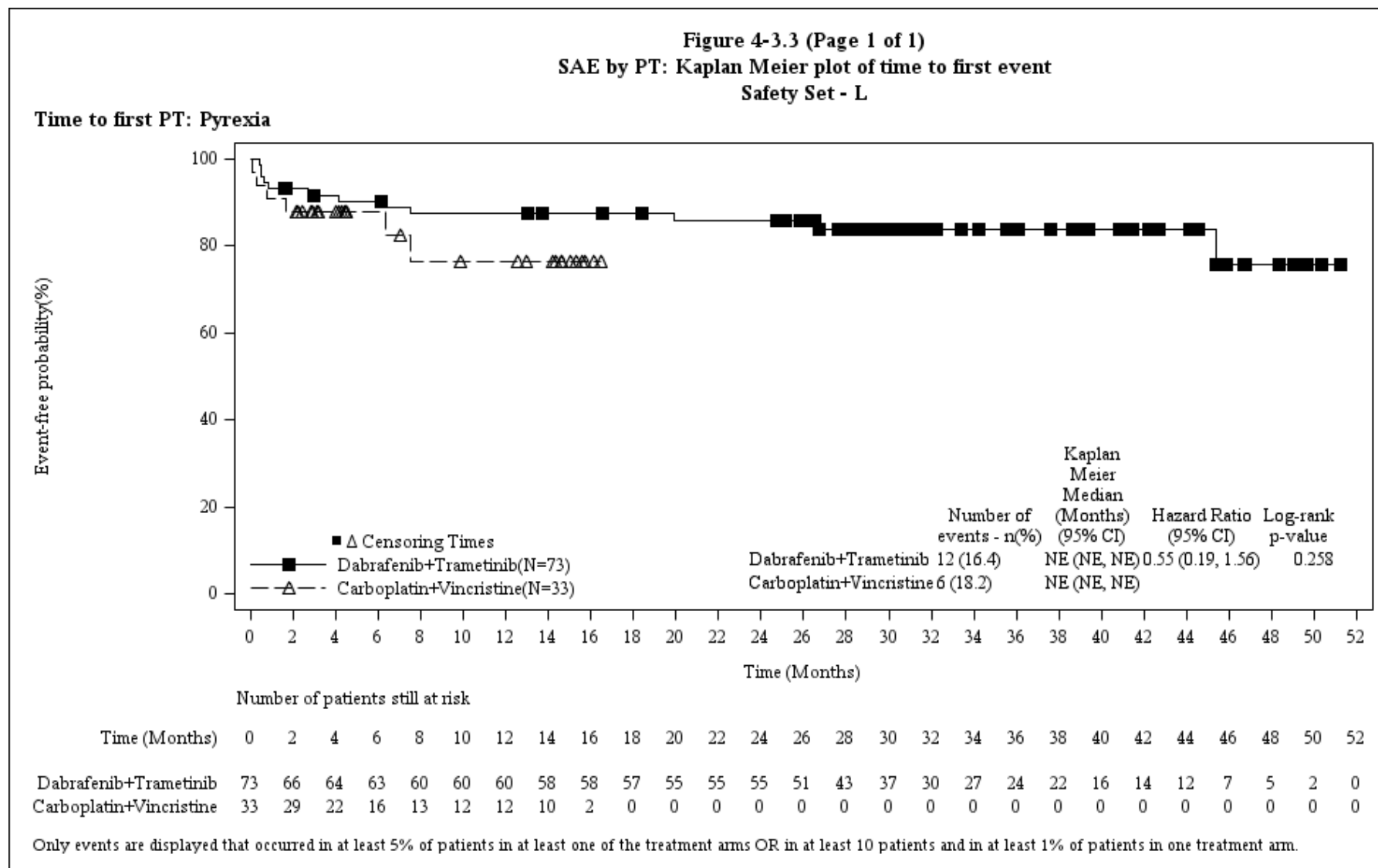
Number of patients still at risk

Time (Months)	0	2	4	6	8	10	12	14	16	18	20	22	24	26	28	30	32	34	36	38	40	42	44	46	48	50	52
Dabrafenib+Trametinib	73	70	68	68	65	64	63	61	61	60	59	59	59	55	48	42	35	30	27	25	18	14	13	8	5	2	0
Carboplatin+Vincristine	33	33	26	20	18	17	17	15	2	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0

Only events are displayed that occurred in at least 5% of patients in at least one of the treatment arms OR in at least 10 patients and in at least 1% of patients in one treatment arm.

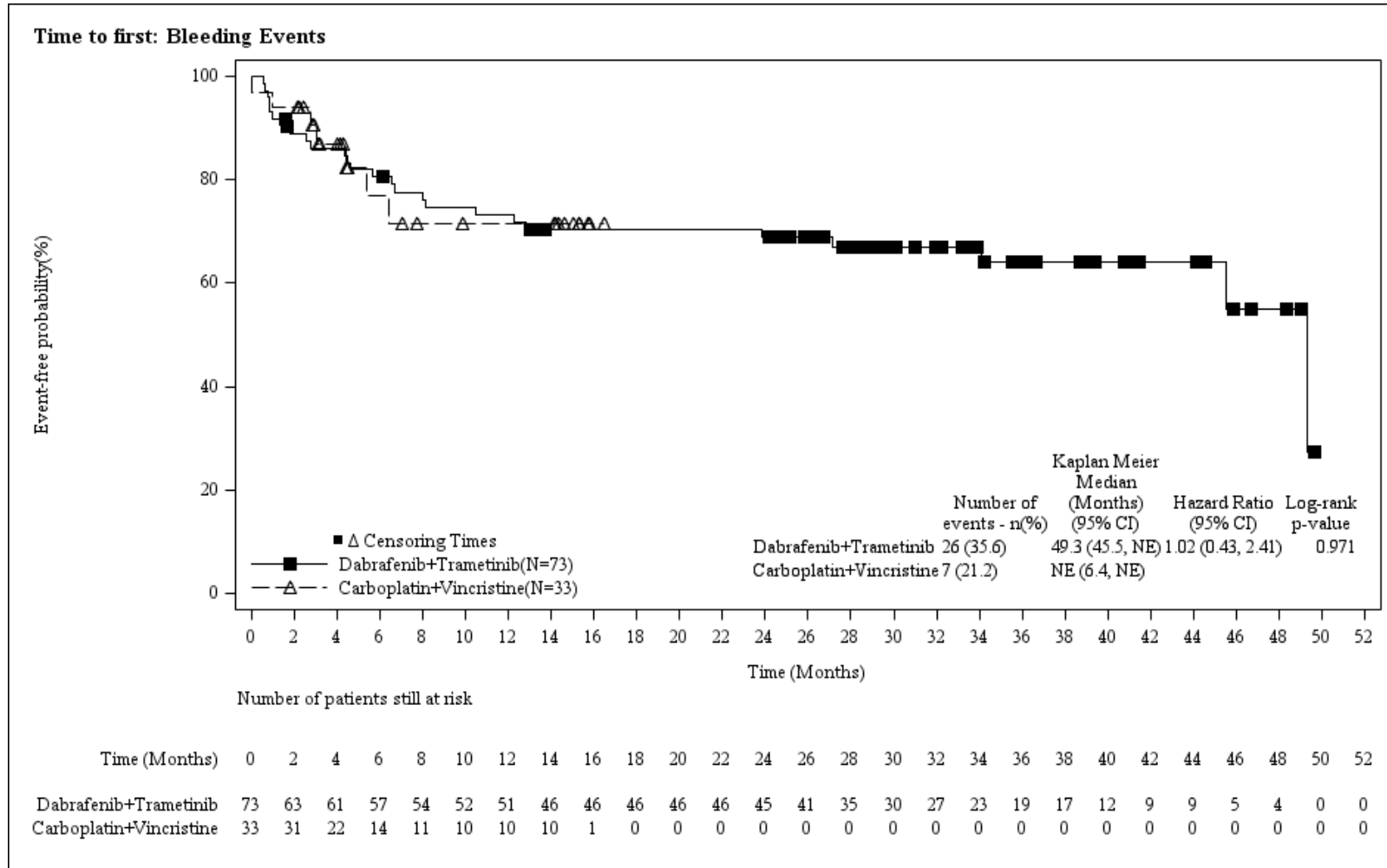


2.3.6. Schwerwiegende unerwünschte Ereignisse nach PT

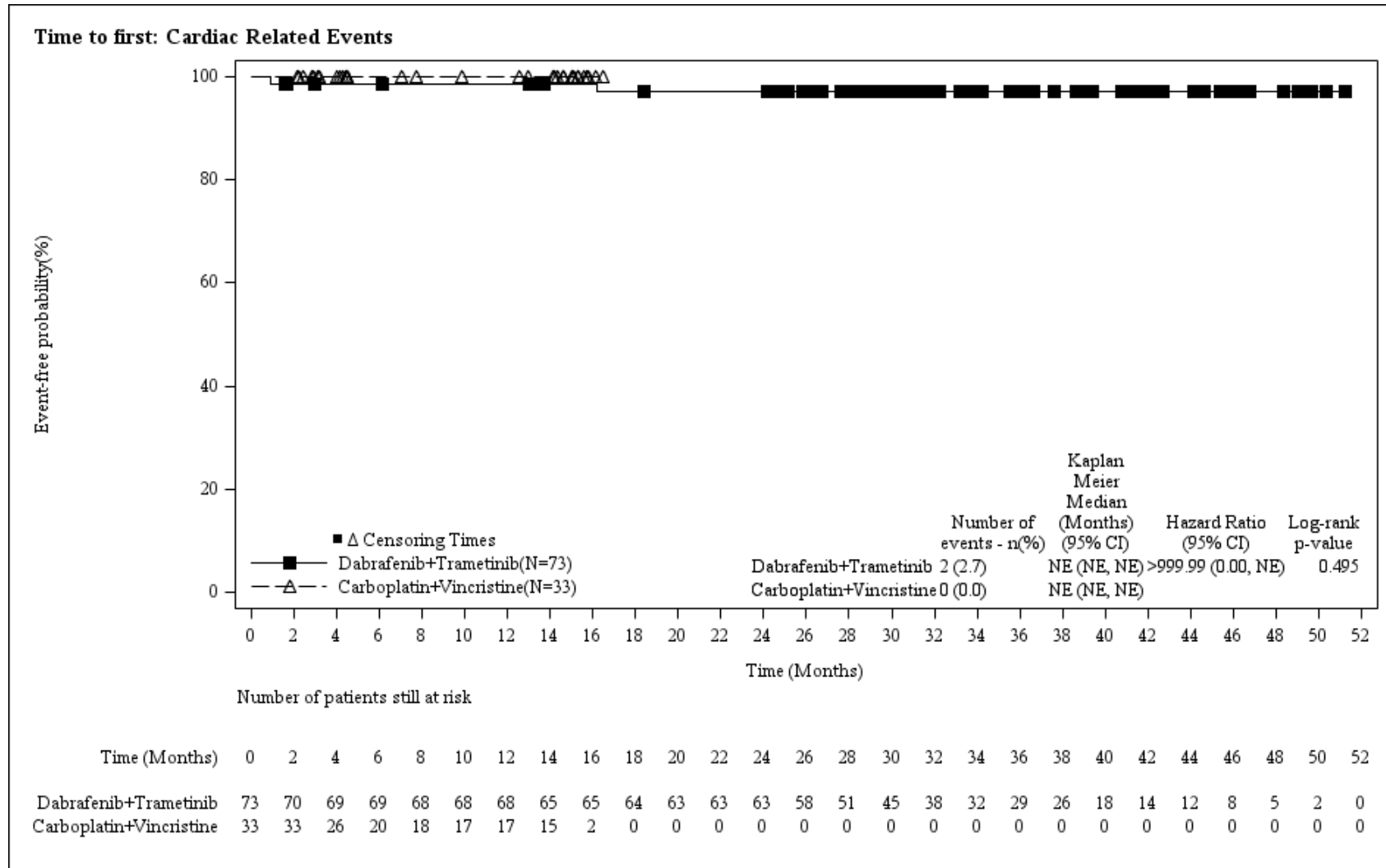


2.3.7. Unerwünschte Ereignisse von besonderem Interesse (AESI)

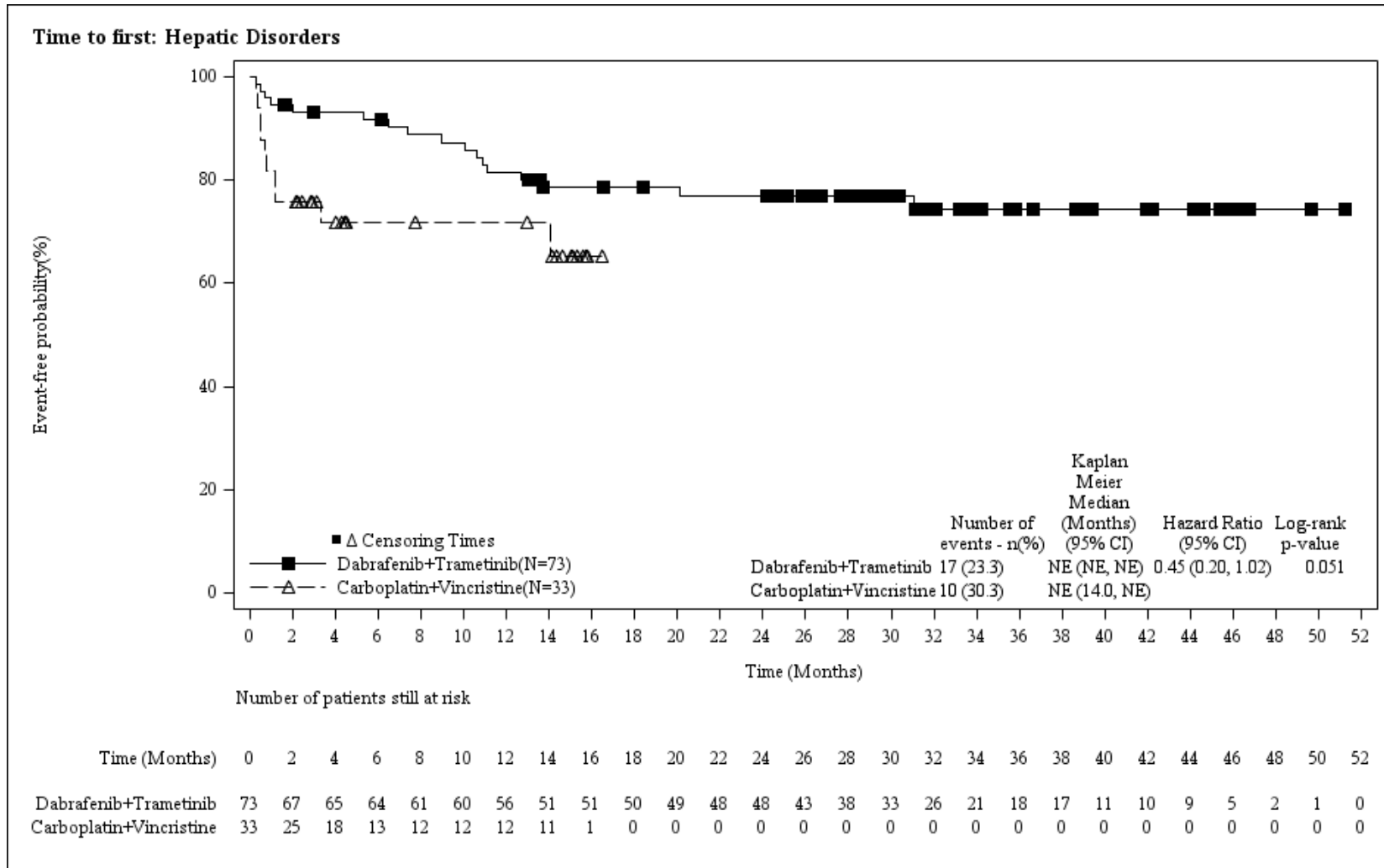
AESI: Kaplan Meier plot of time to first event
Safety Set – L



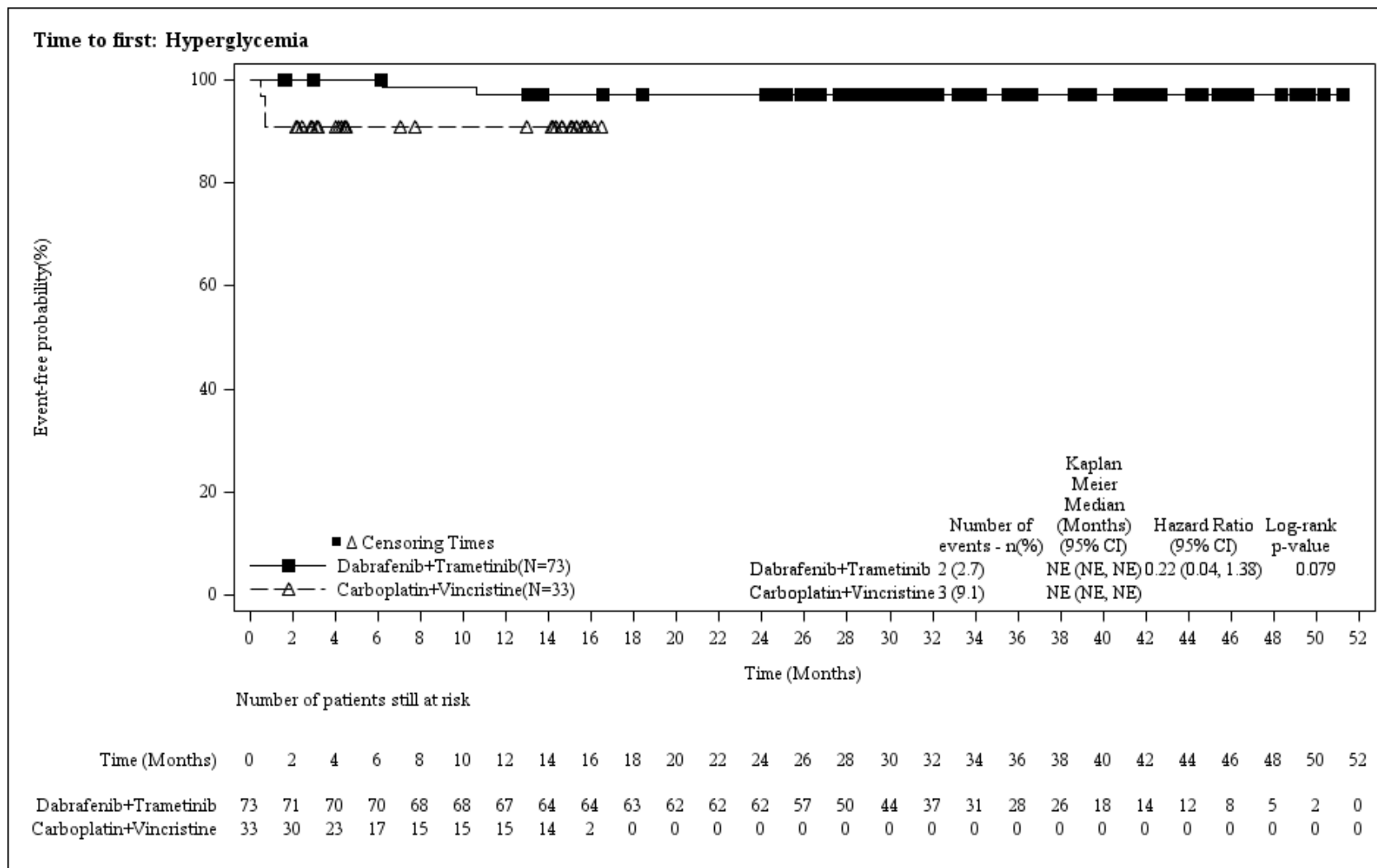
**AESI: Kaplan Meier plot of time to first event
Safety Set – L**



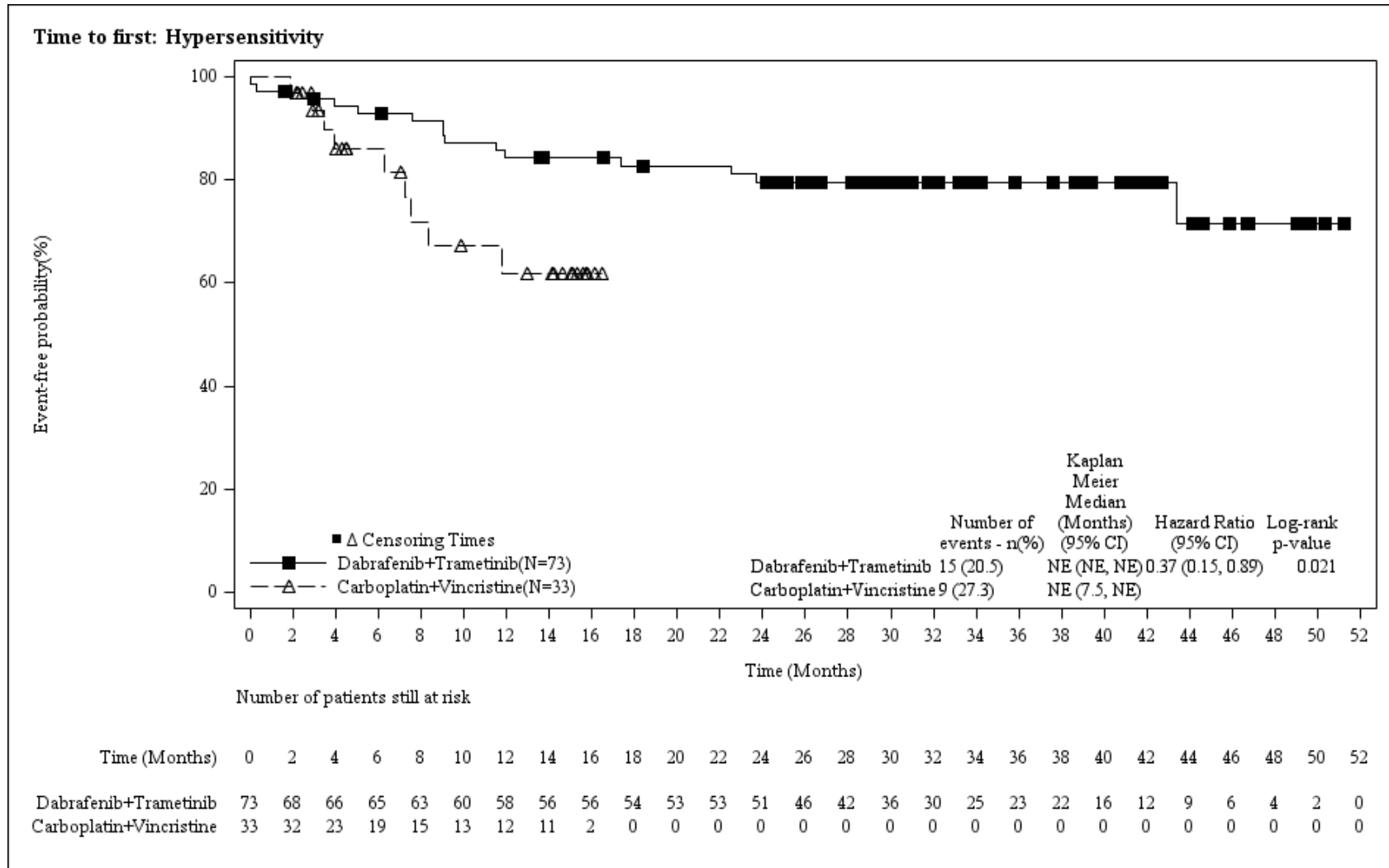
**AESI: Kaplan Meier plot of time to first event
Safety Set – L**



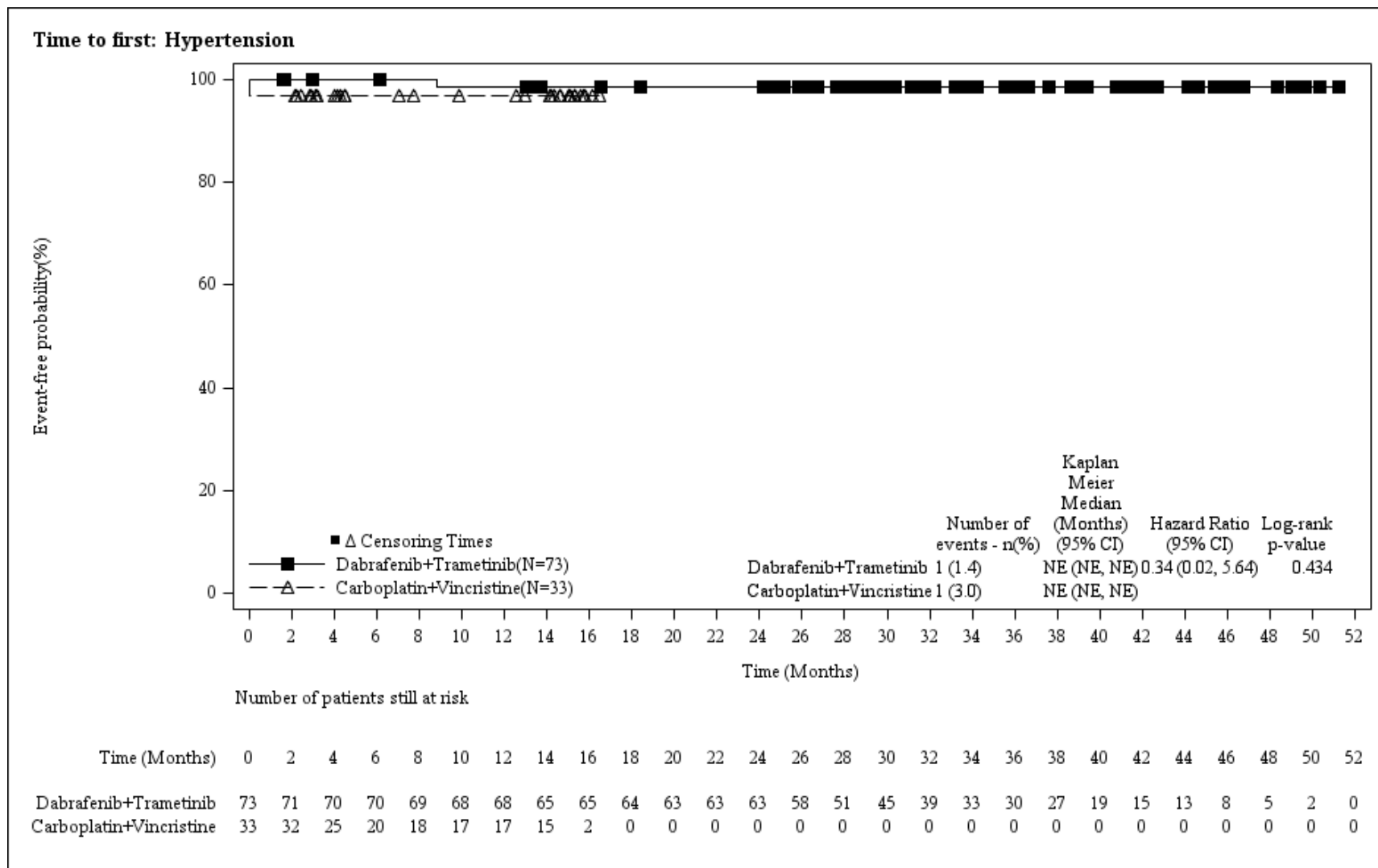
**AESI: Kaplan Meier plot of time to first event
Safety Set – L**



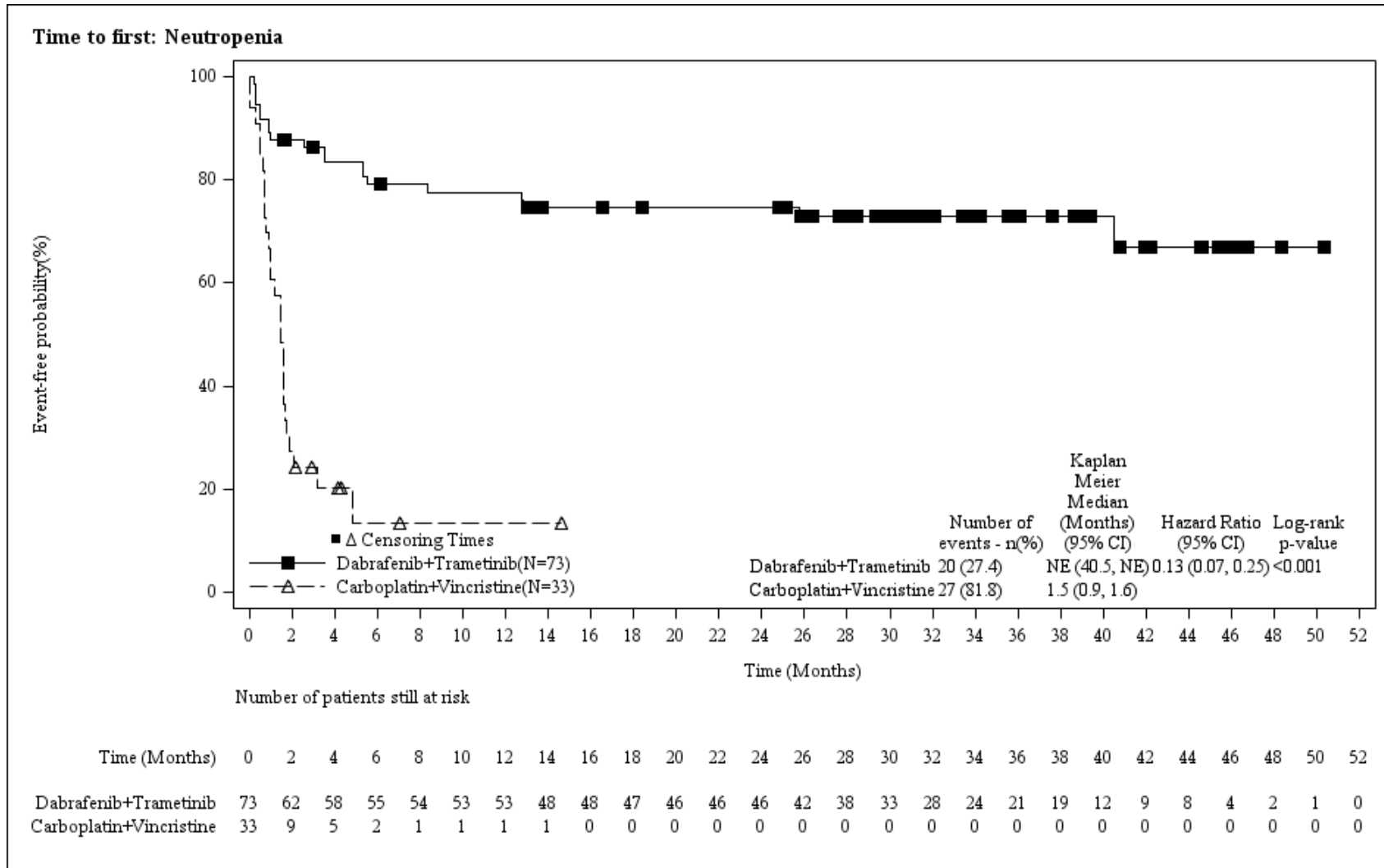
**AESI: Kaplan Meier plot of time to first event
Safety Set – L**



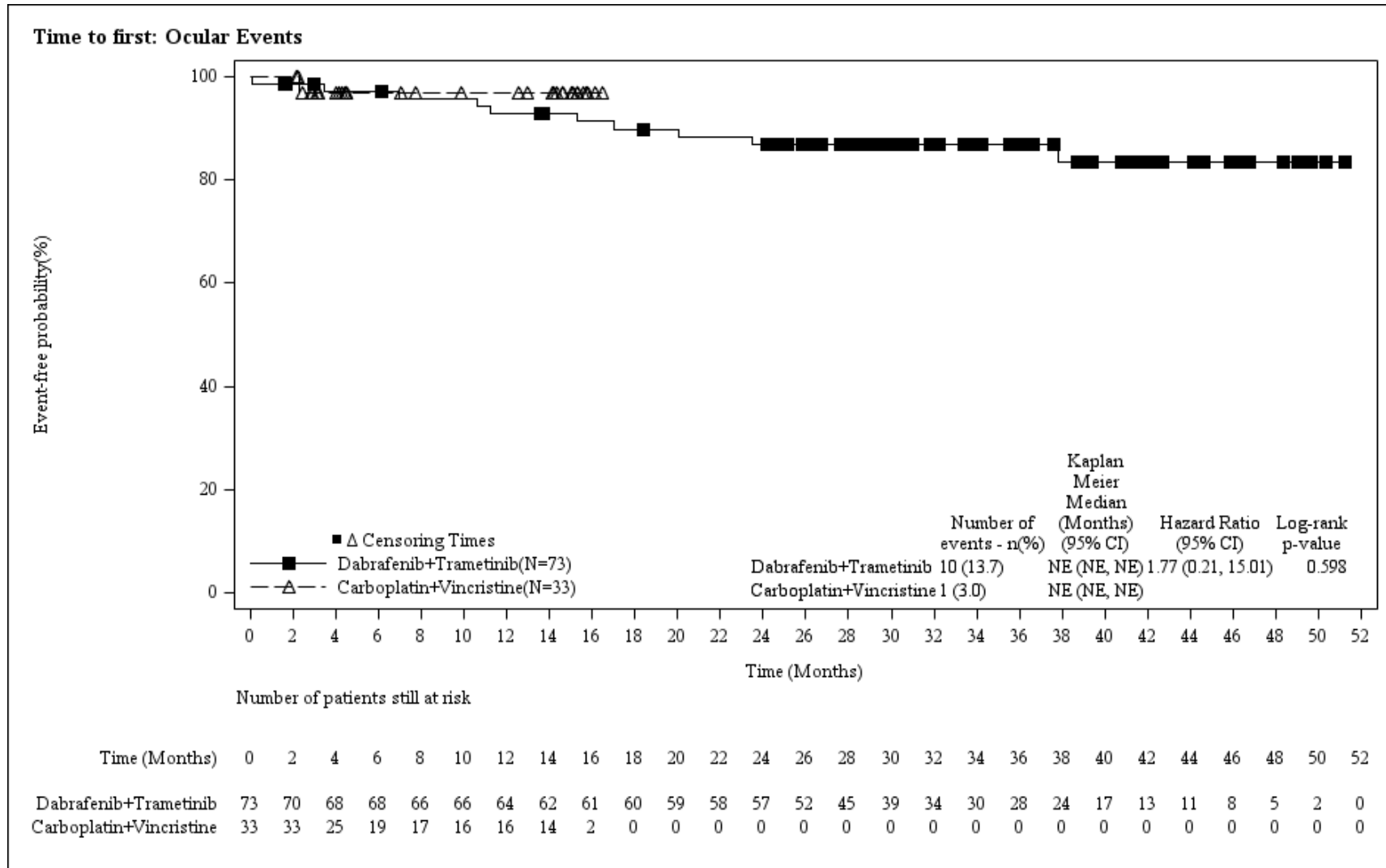
**AESI: Kaplan Meier plot of time to first event
Safety Set – L**



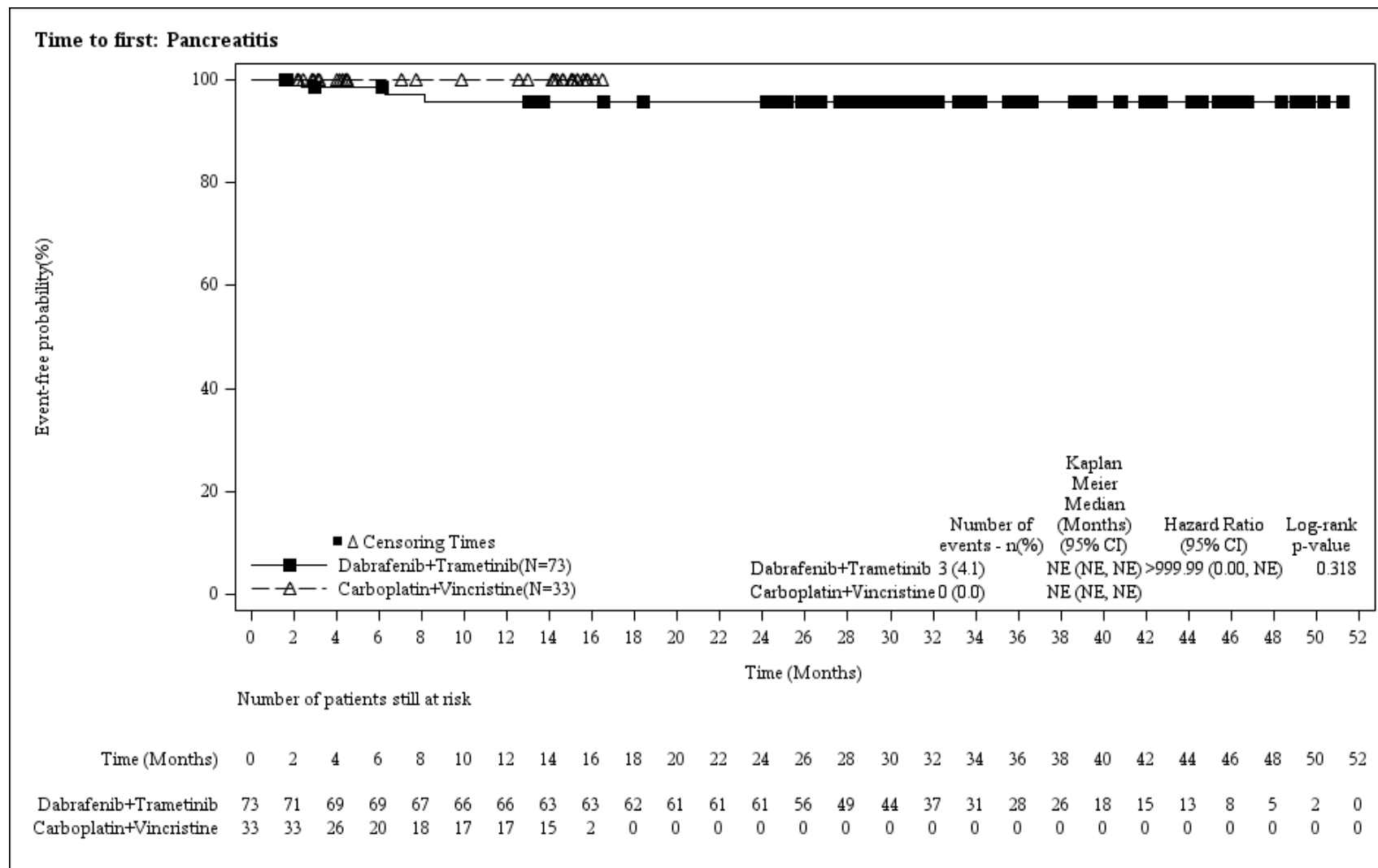
**AESI: Kaplan Meier plot of time to first event
Safety Set – L**



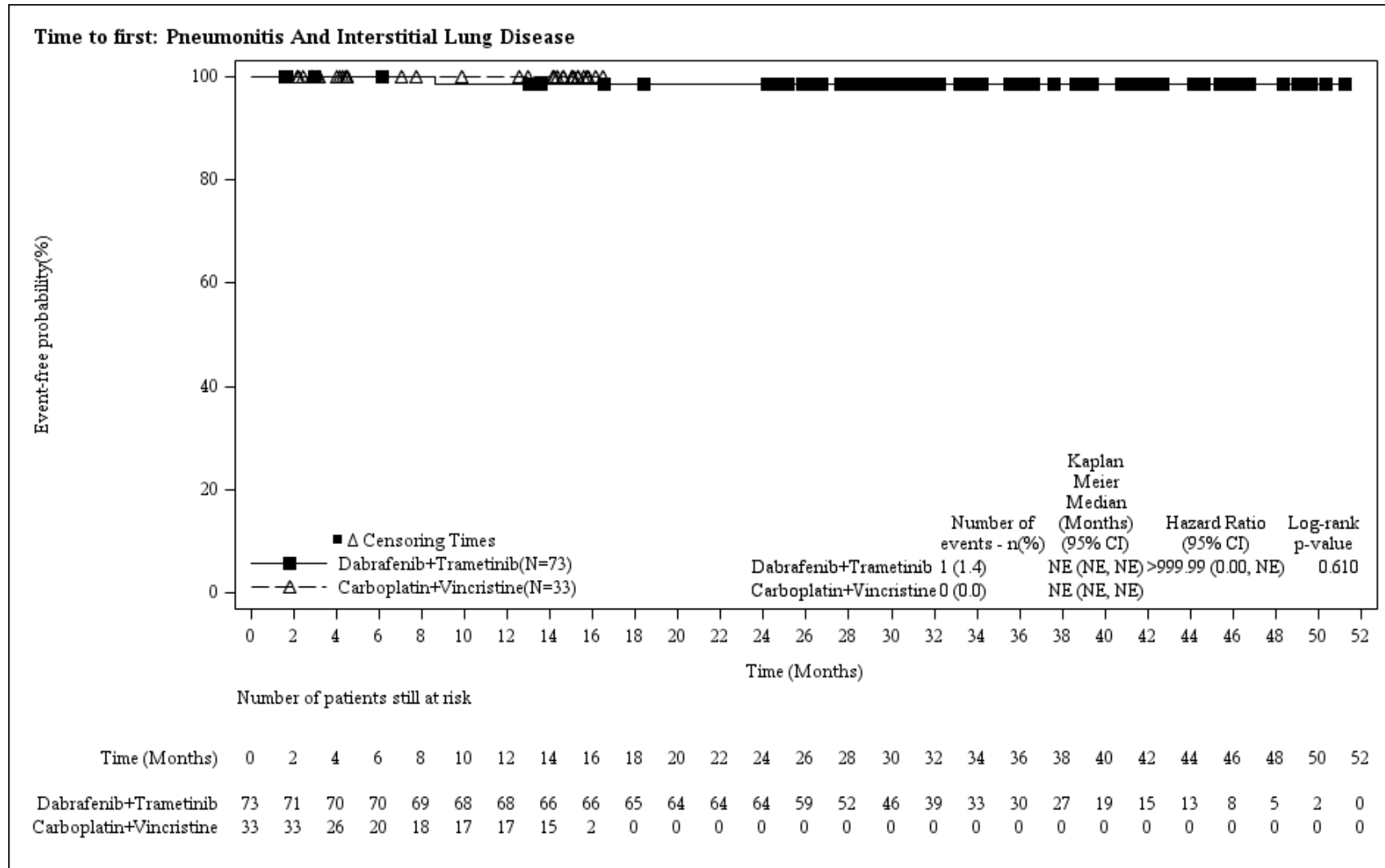
**AESI: Kaplan Meier plot of time to first event
Safety Set – L**



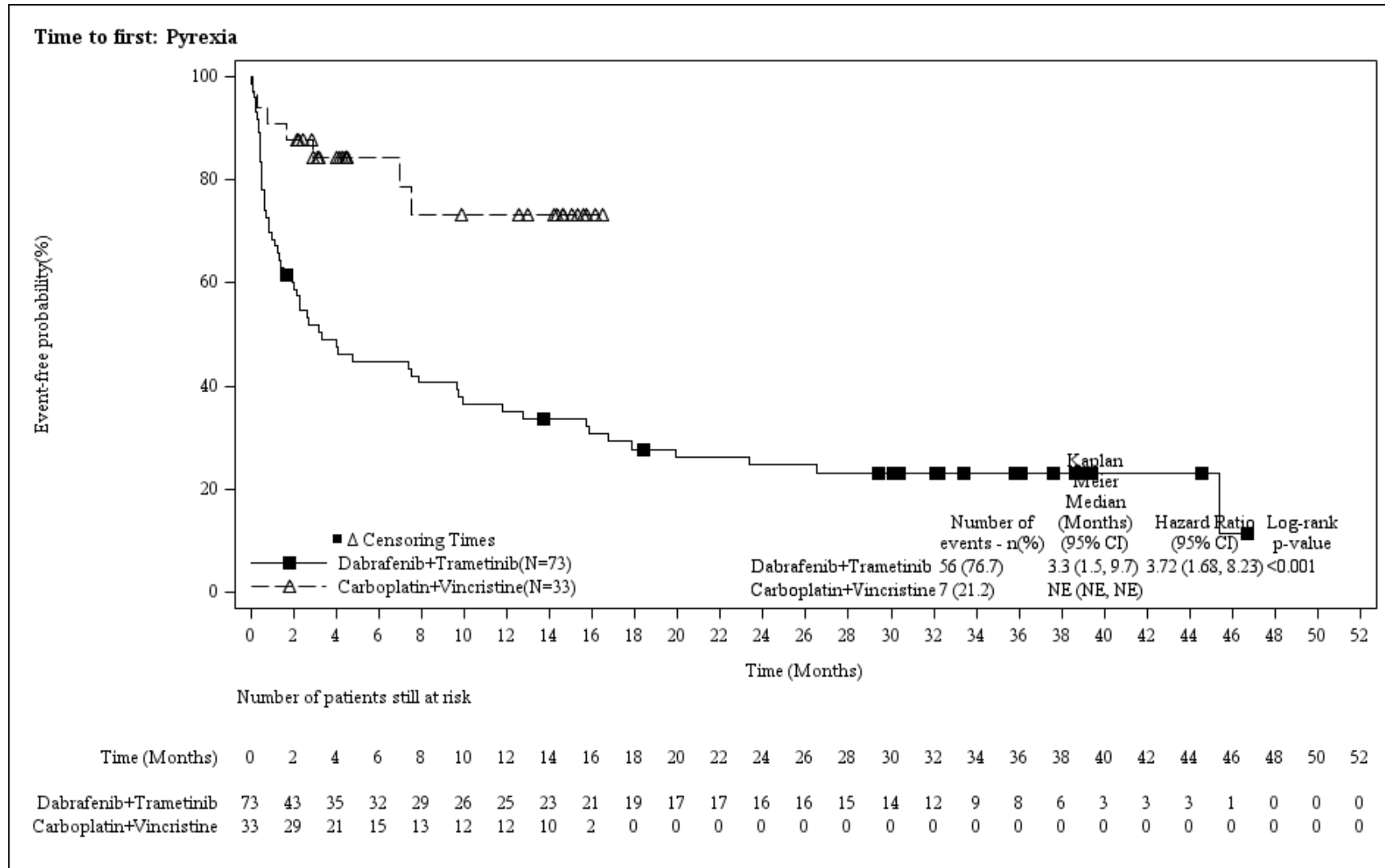
**AESI: Kaplan Meier plot of time to first event
Safety Set – L**



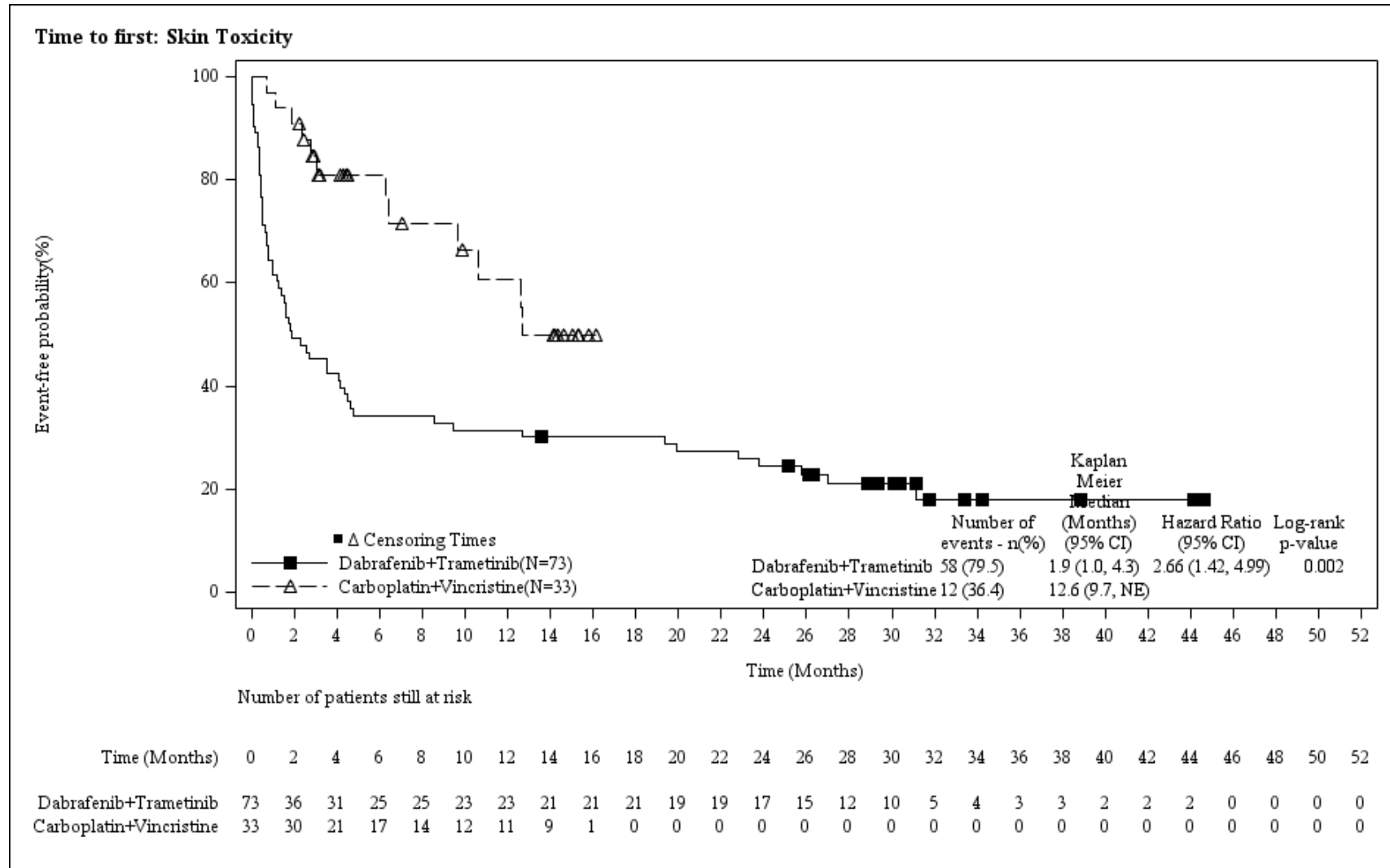
**AESI: Kaplan Meier plot of time to first event
Safety Set – L**



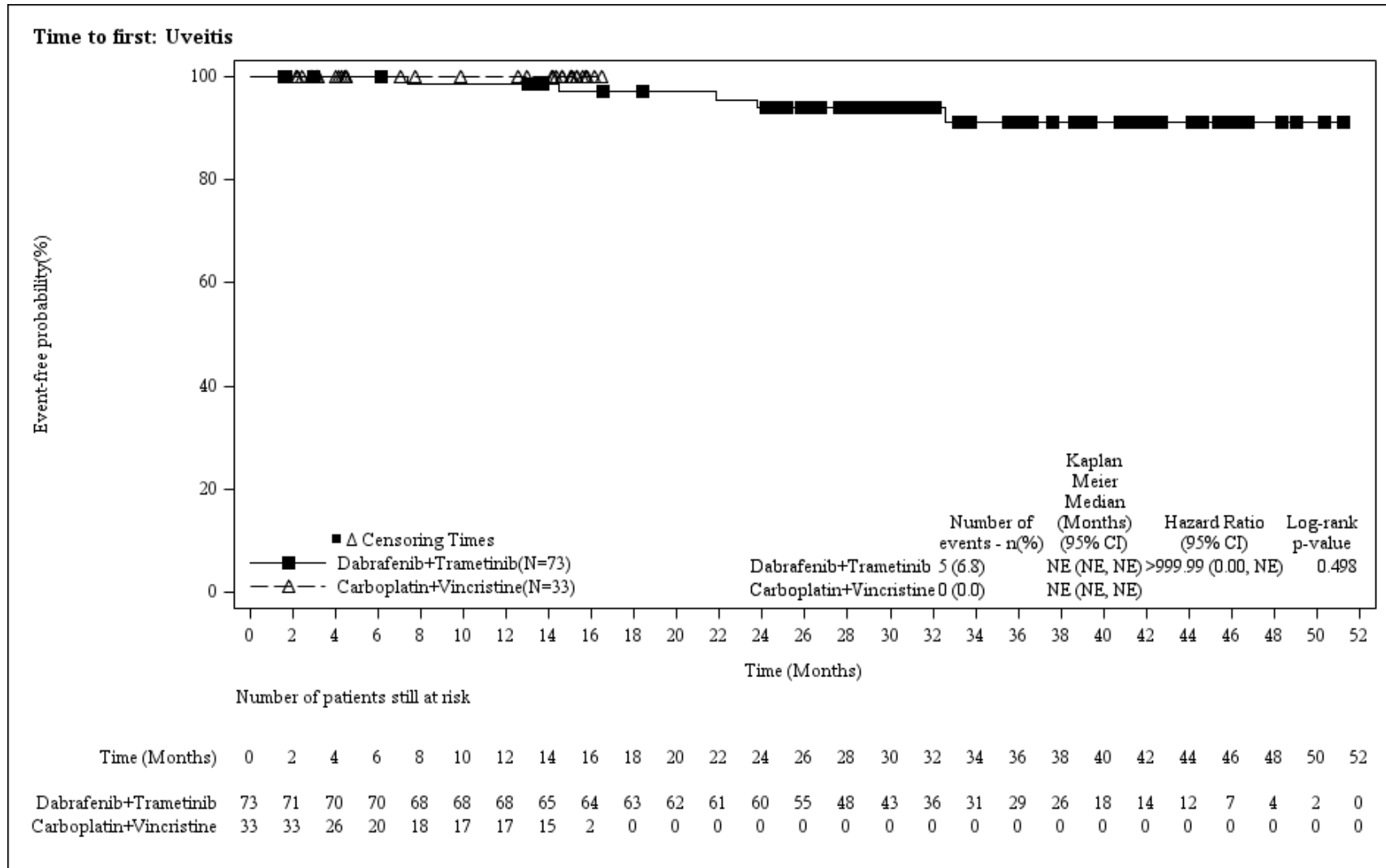
**AESI: Kaplan Meier plot of time to first event
Safety Set – L**



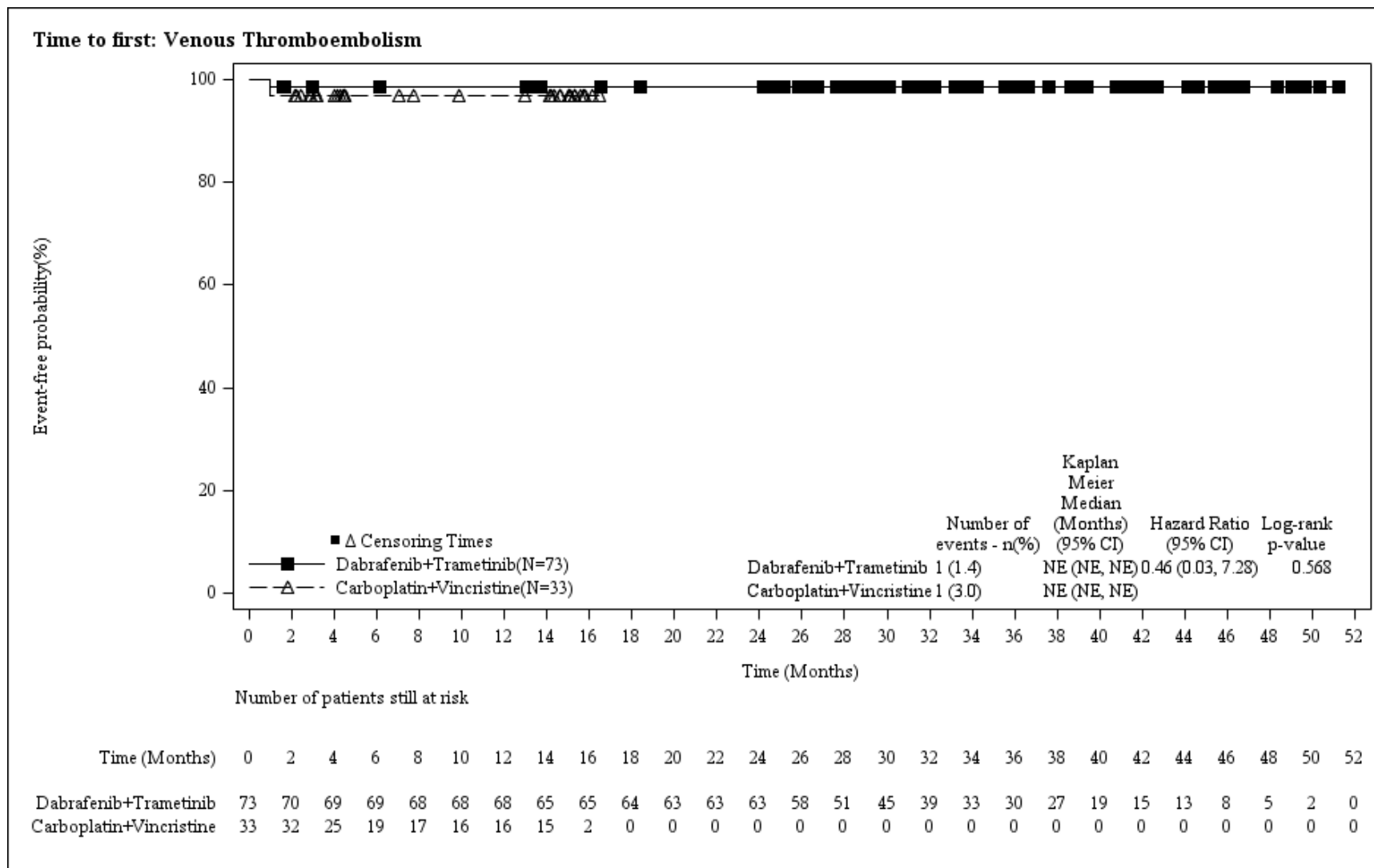
**AESI: Kaplan Meier plot of time to first event
Safety Set – L**



**AESI: Kaplan Meier plot of time to first event
Safety Set – L**

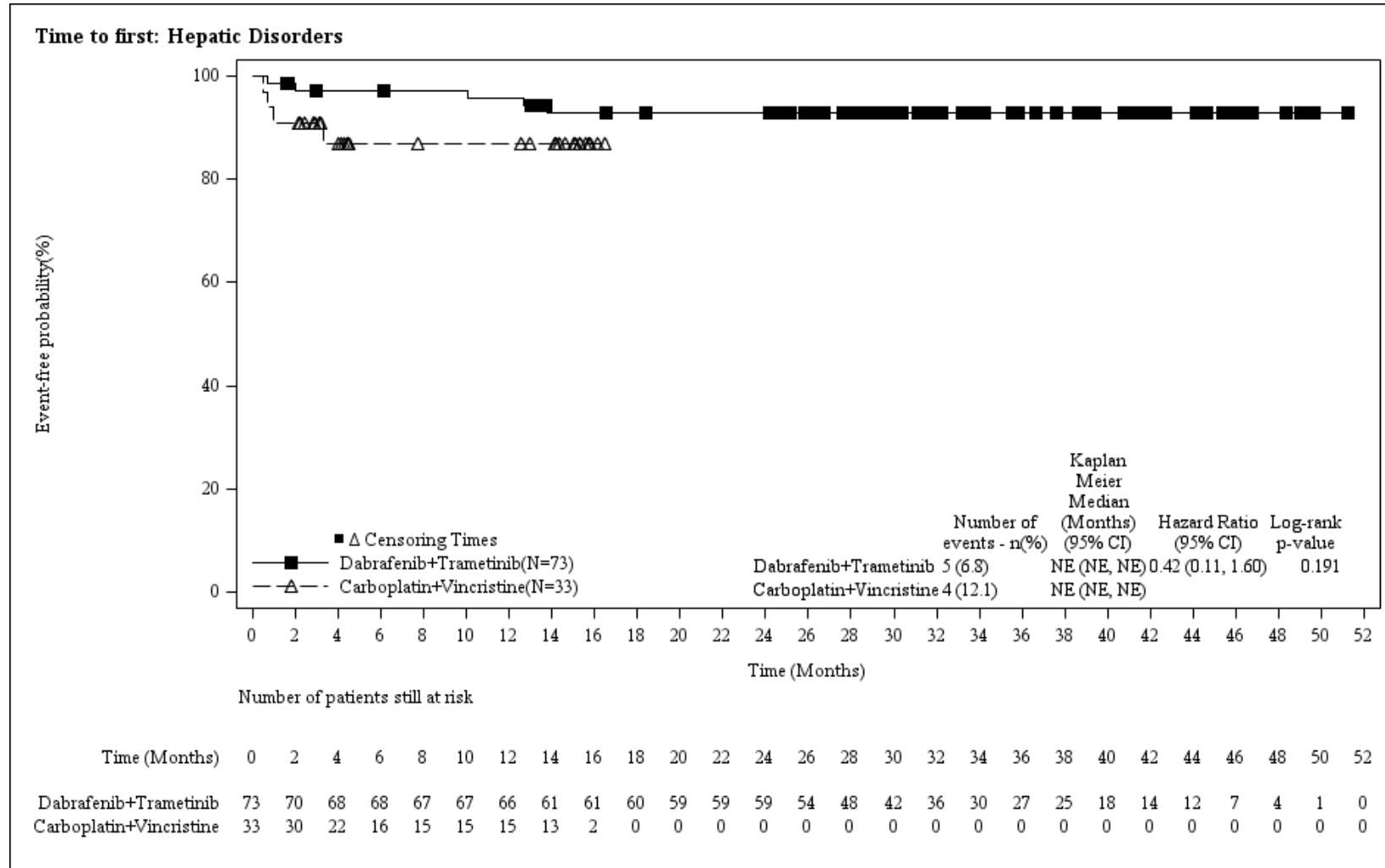


**AESI: Kaplan Meier plot of time to first event
Safety Set – L**

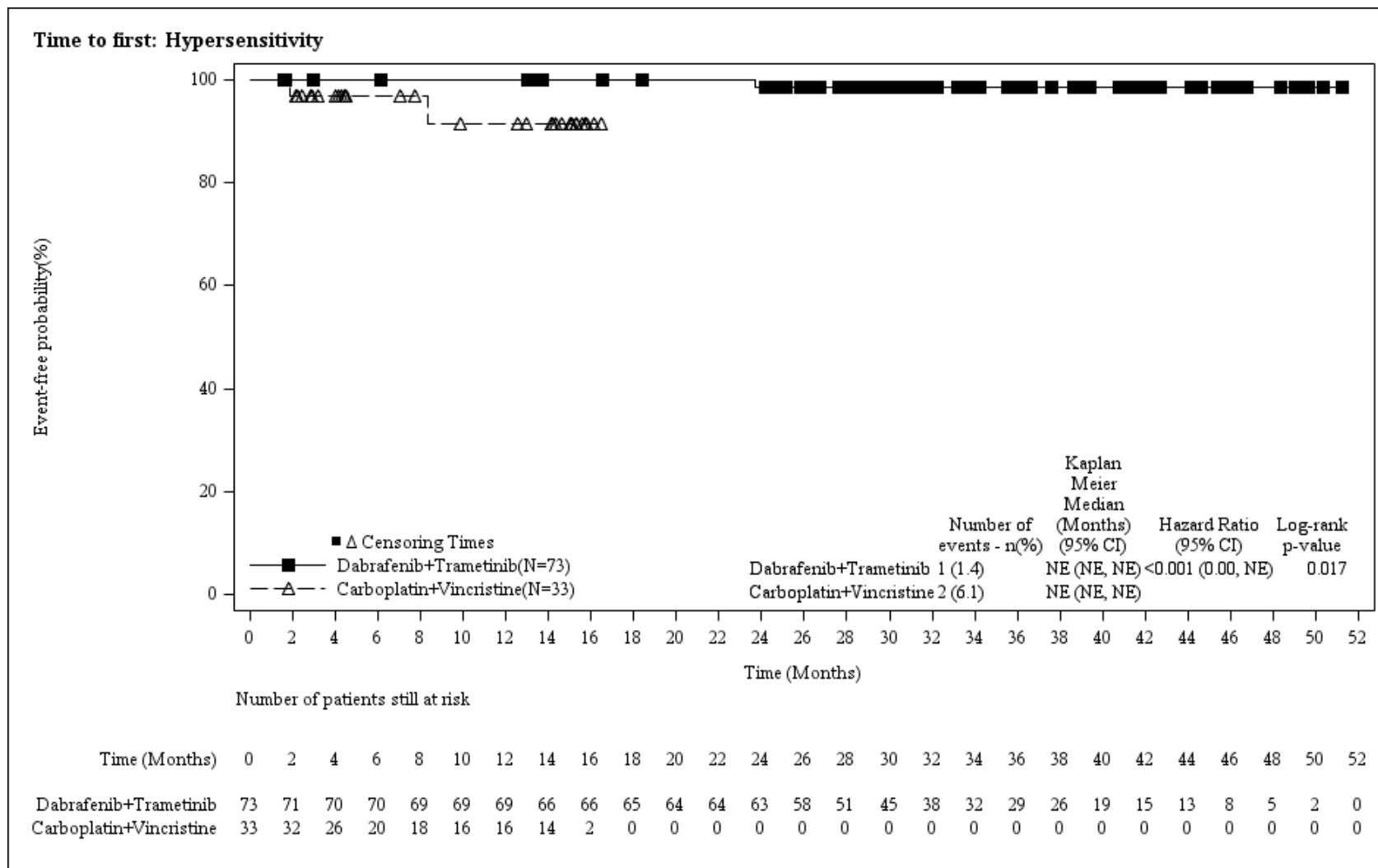


2.3.8. Schwere unerwünschte Ereignisse (CTCAE-Grad ≥ 3) von besonderem Interesse (AESI)

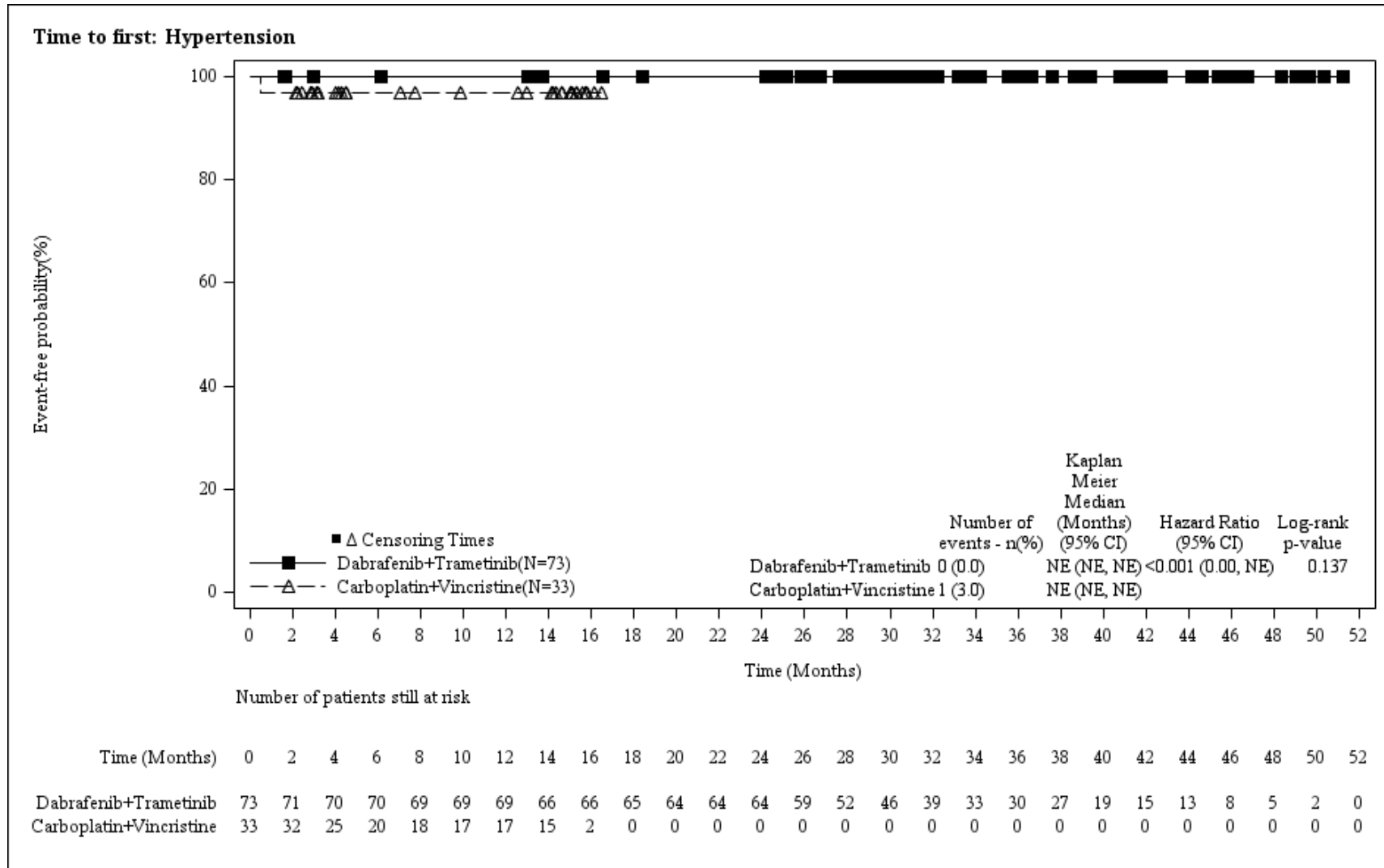
**Grade >= 3 AESI: Kaplan Meier plot of time to first event
Safety Set – L**



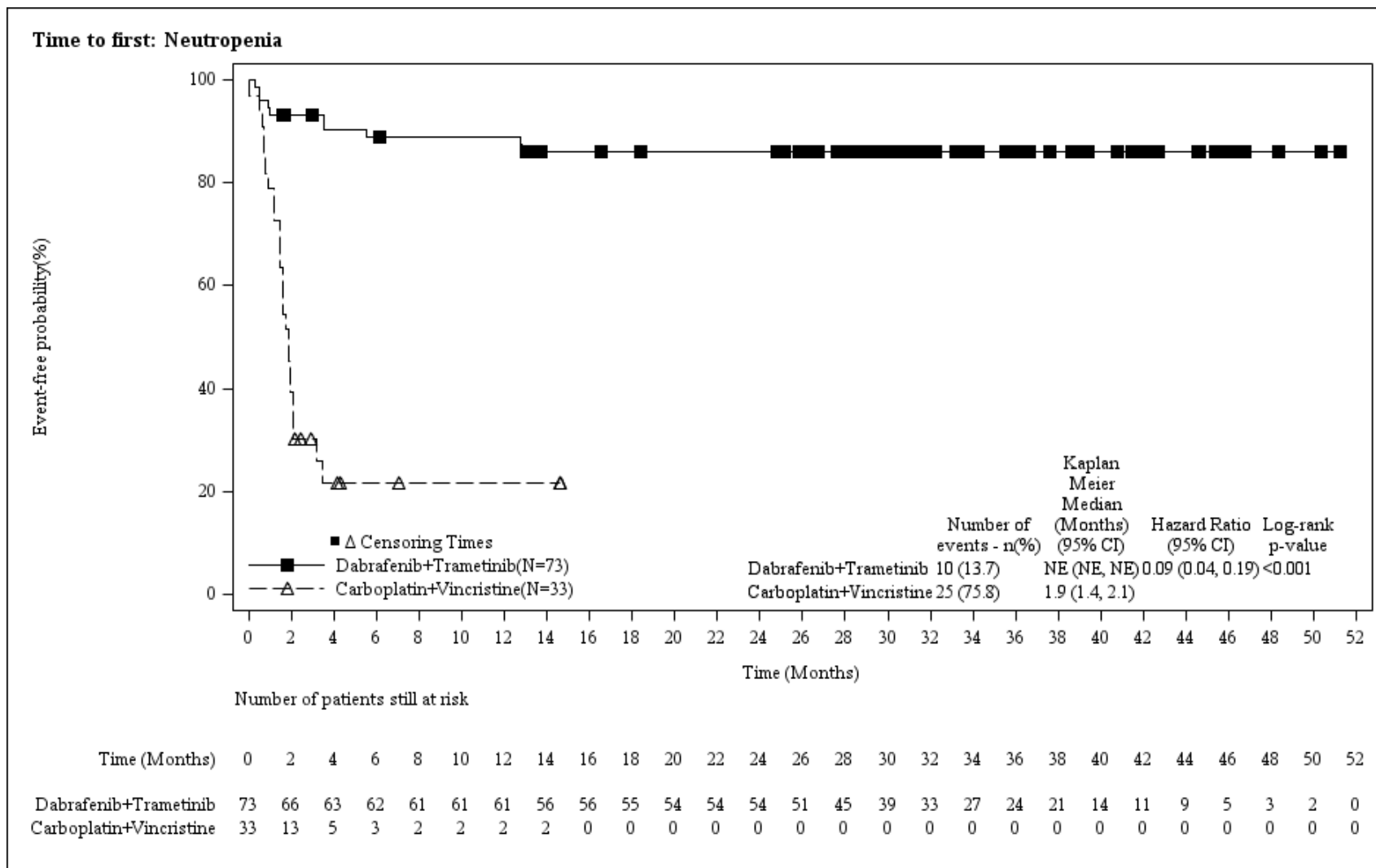
Grade >= 3 AESI: Kaplan Meier plot of time to first event
Safety Set – L



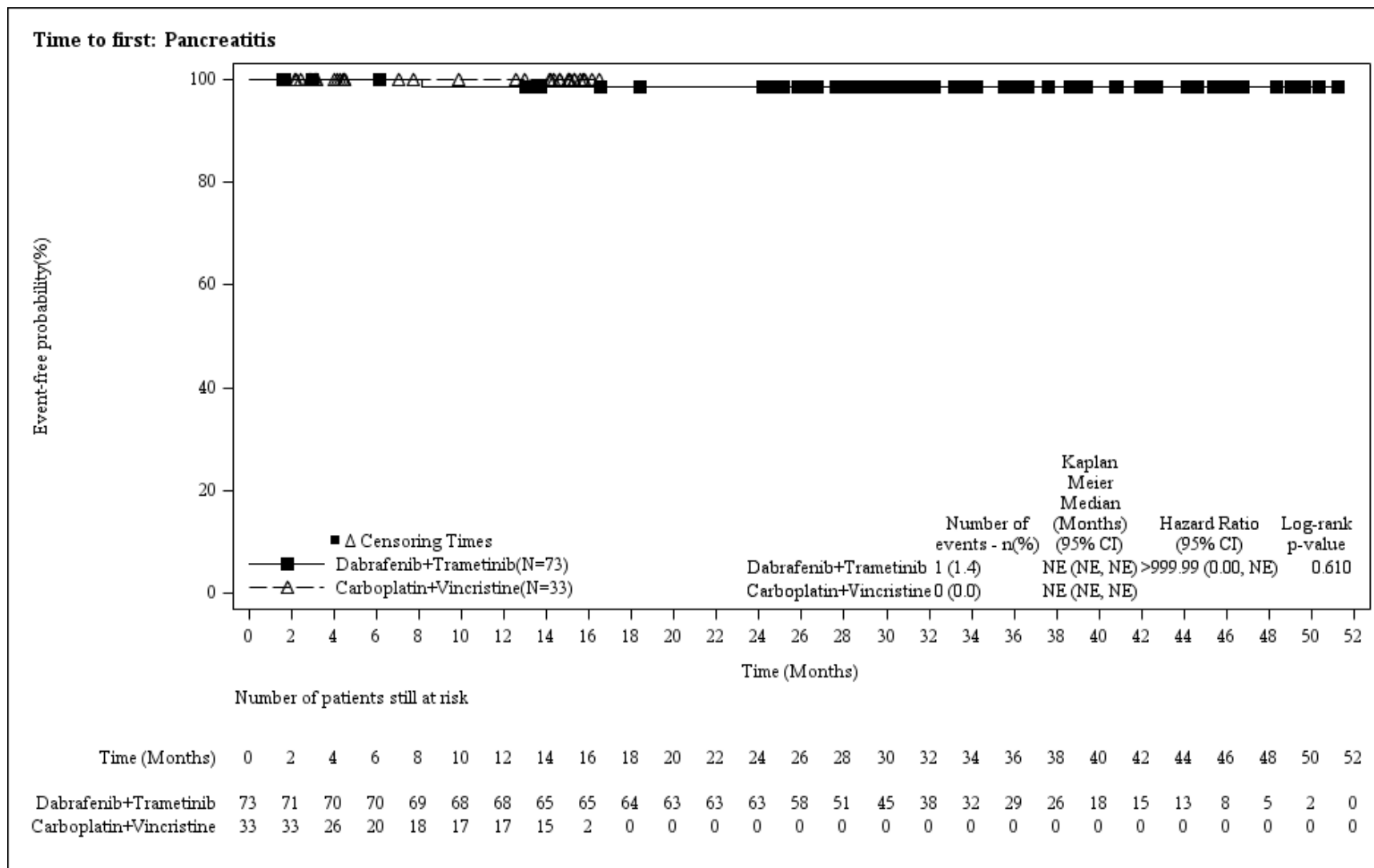
Grade >= 3 AESI: Kaplan Meier plot of time to first event
Safety Set – L



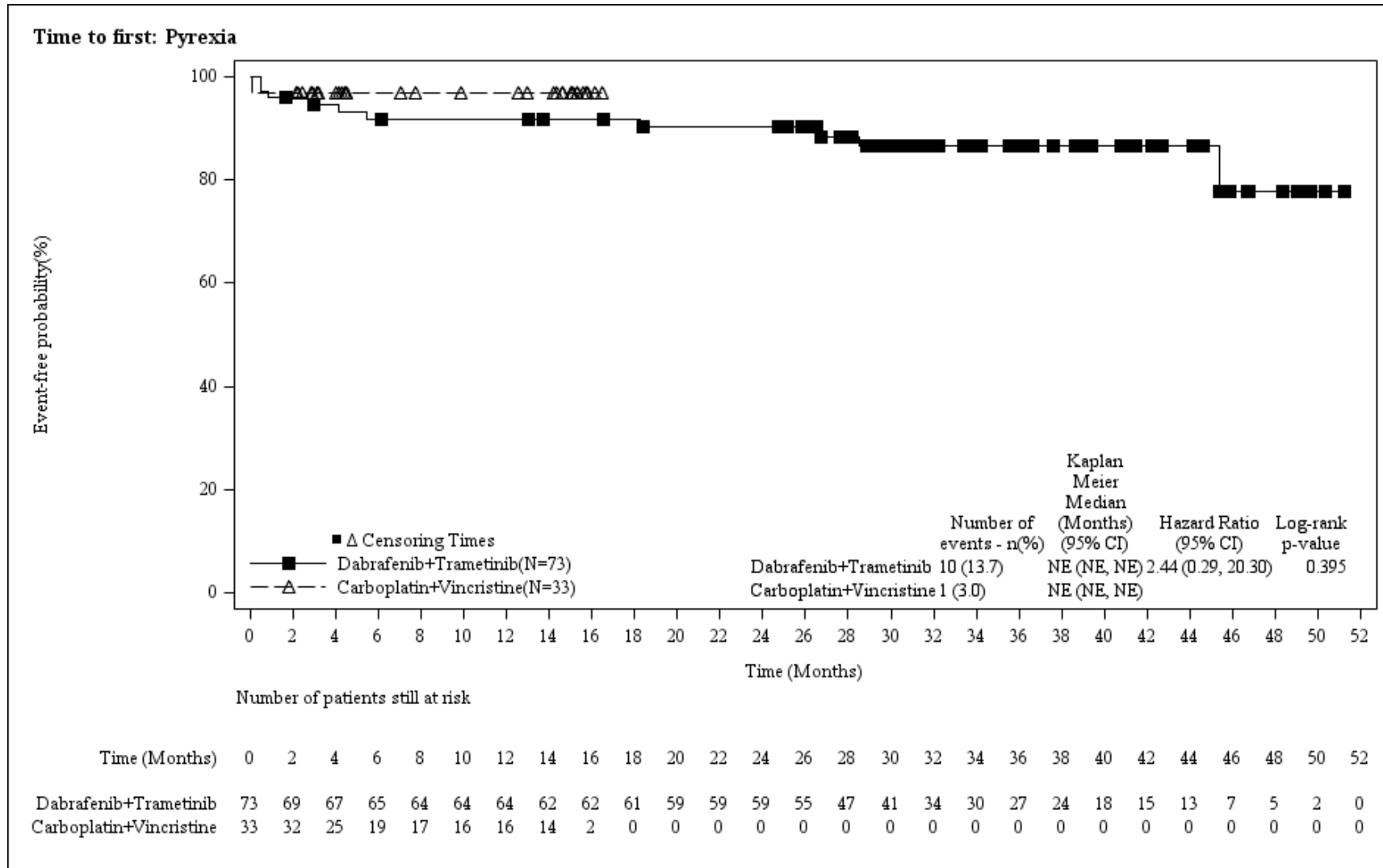
Grade >= 3 AESI: Kaplan Meier plot of time to first event
Safety Set – L



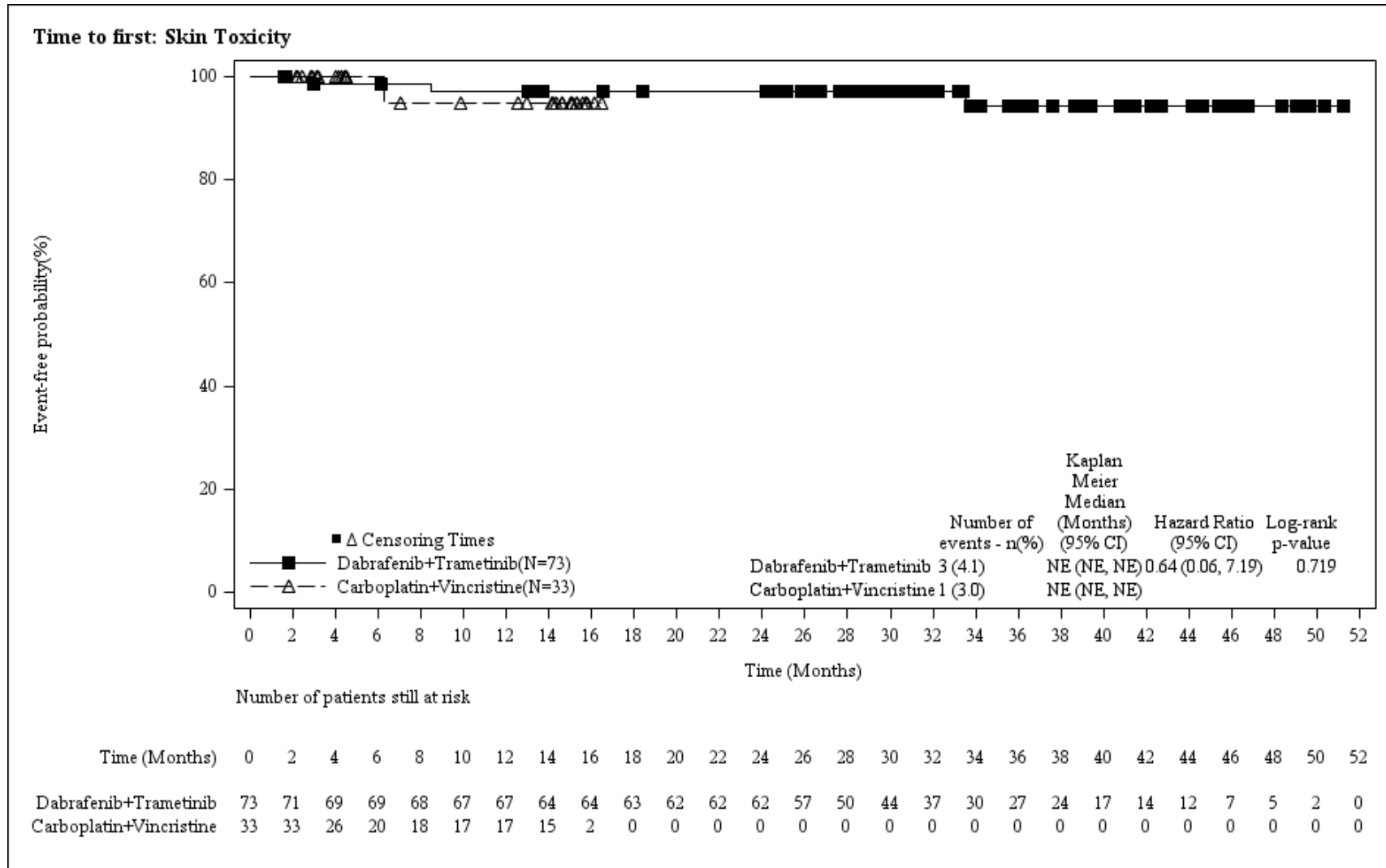
**Grade >= 3 AESI: Kaplan Meier plot of time to first event
Safety Set – L**



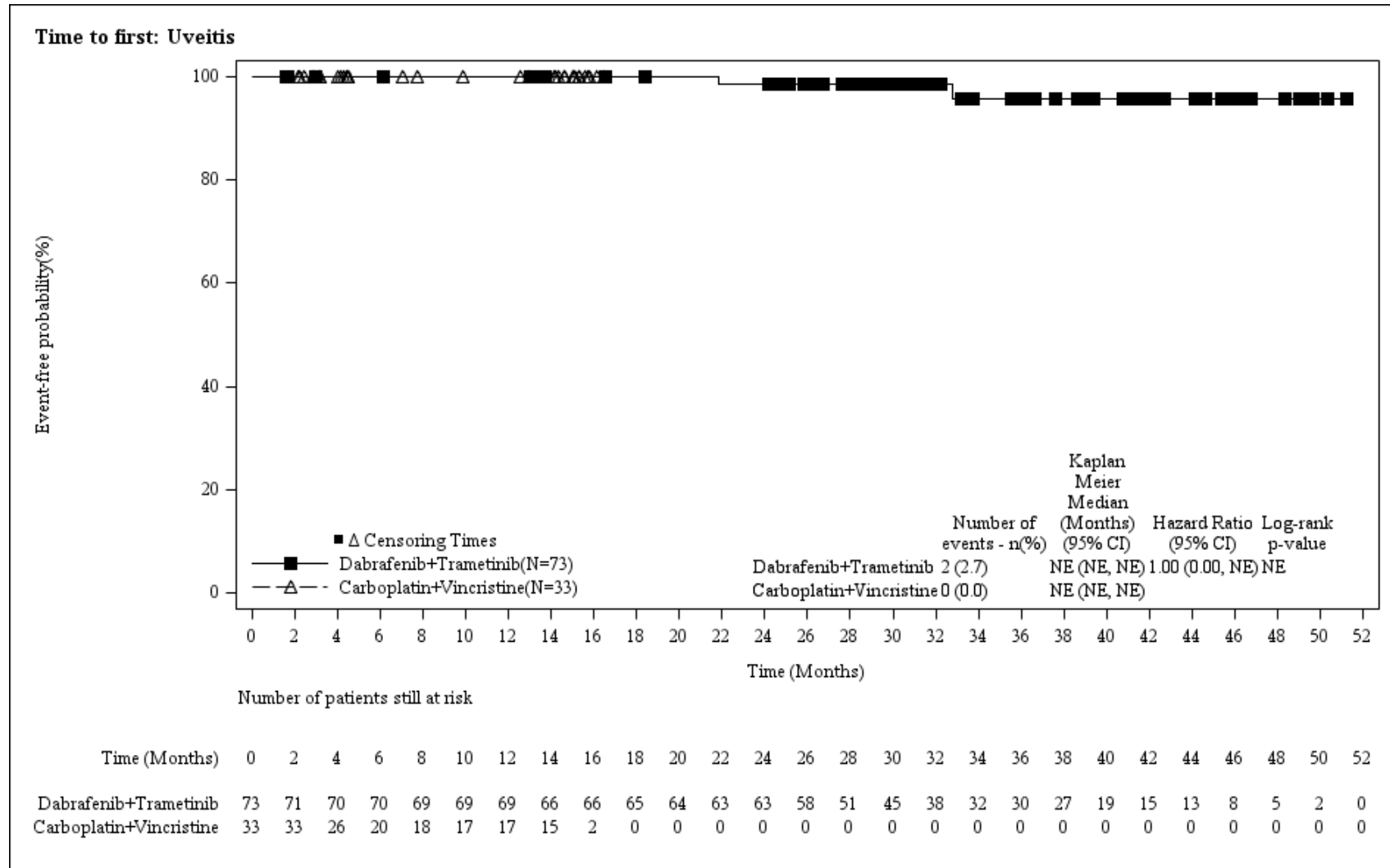
Grade >= 3 AESI: Kaplan Meier plot of time to first event
Safety Set – L



Grade >= 3 AESI: Kaplan Meier plot of time to first event
Safety Set – L

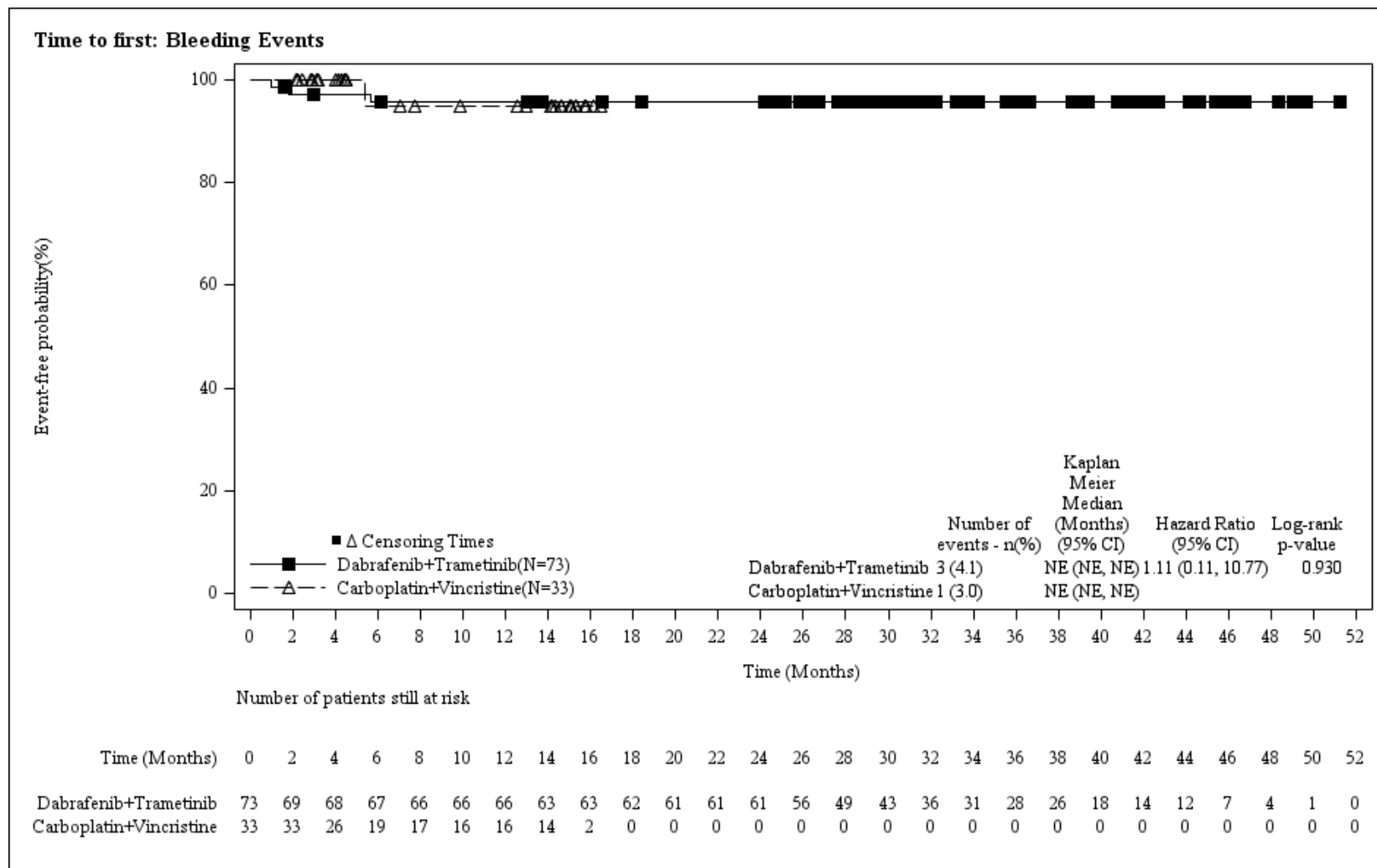


Grade >= 3 AESI: Kaplan Meier plot of time to first event
Safety Set – L

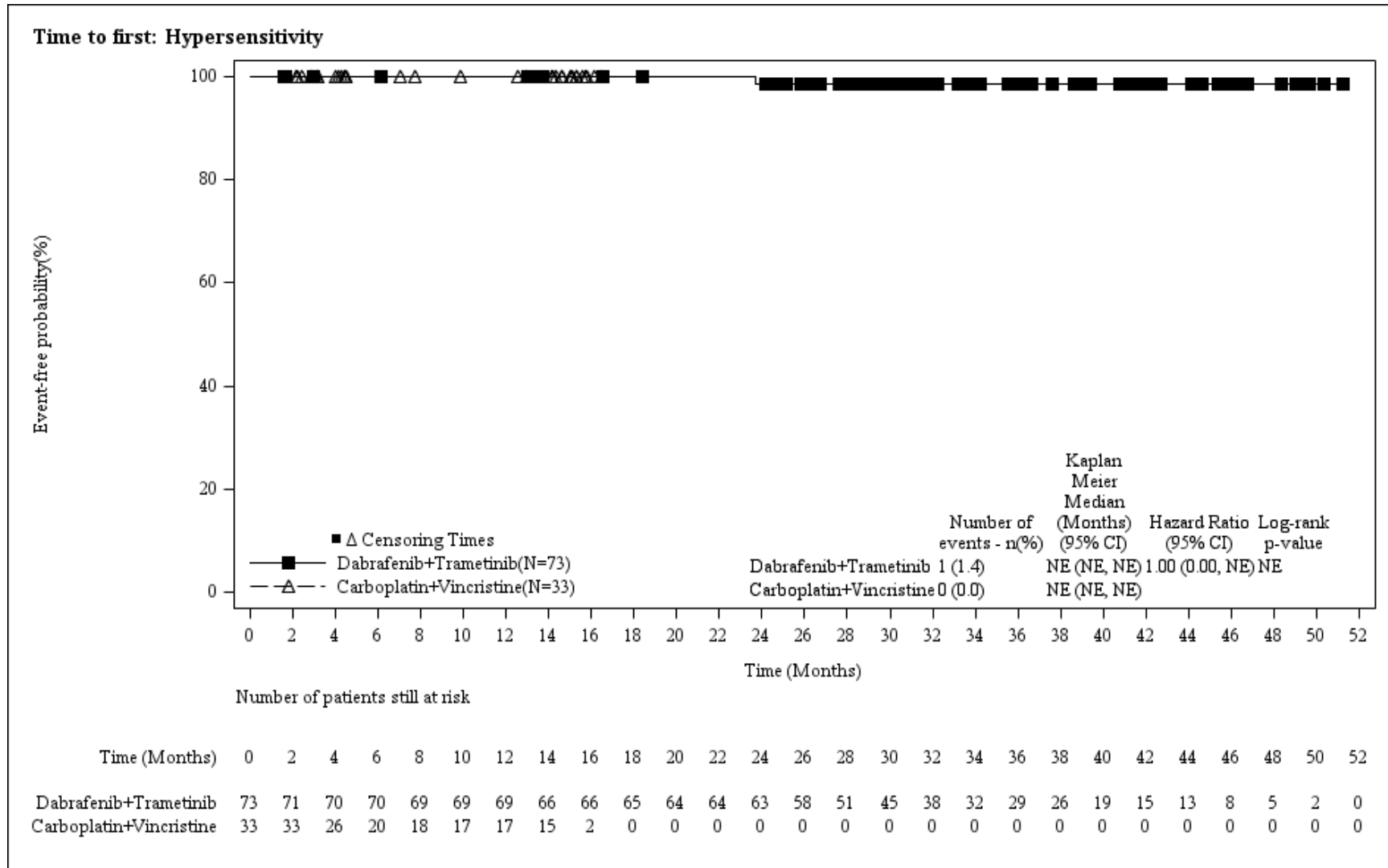


2.3.9. Schwerwiegende unerwünschte Ereignisse von besonderem Interesse (AESI)

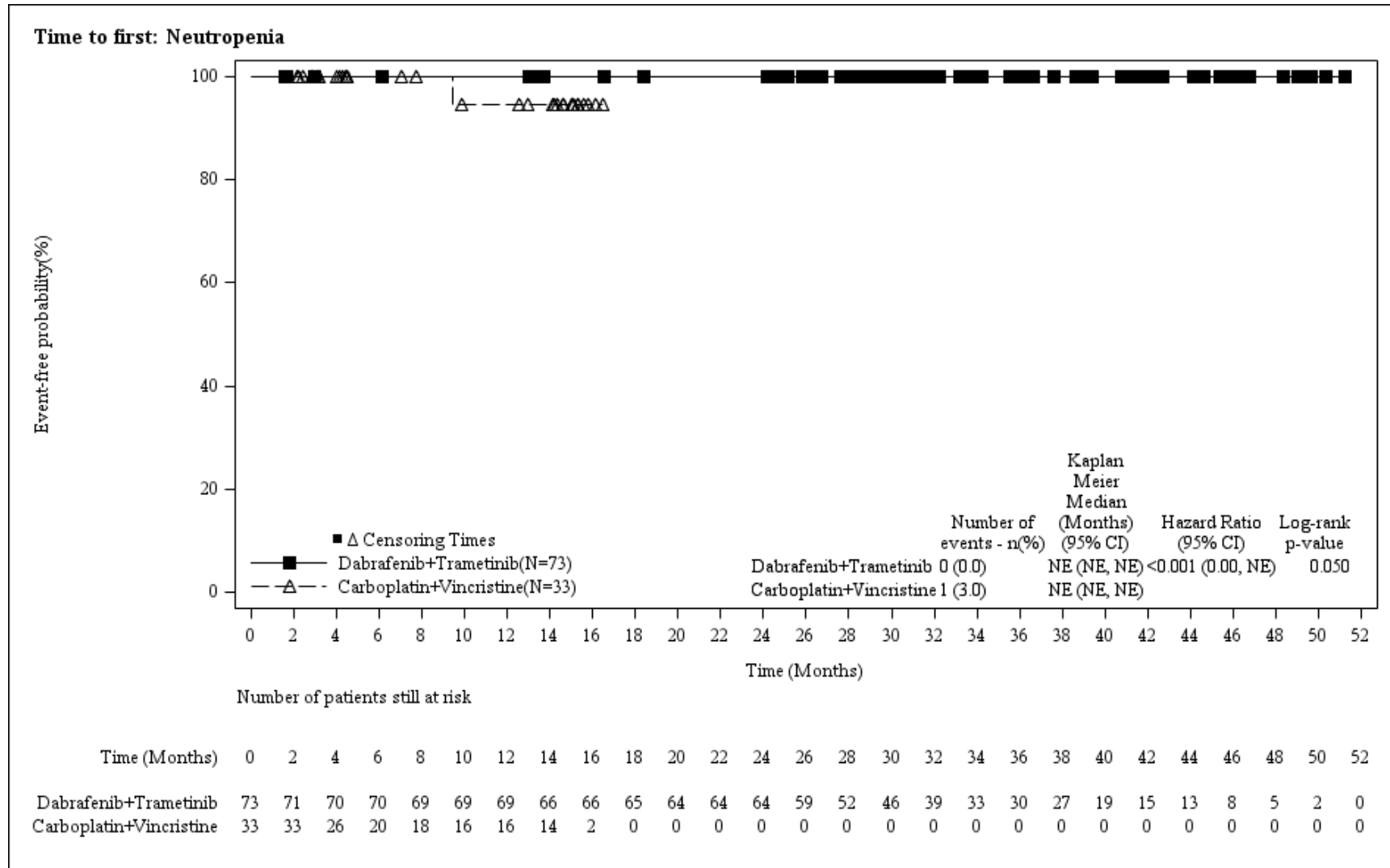
**Serious AESI: Kaplan Meier plot of time to first event
Safety Set – L**



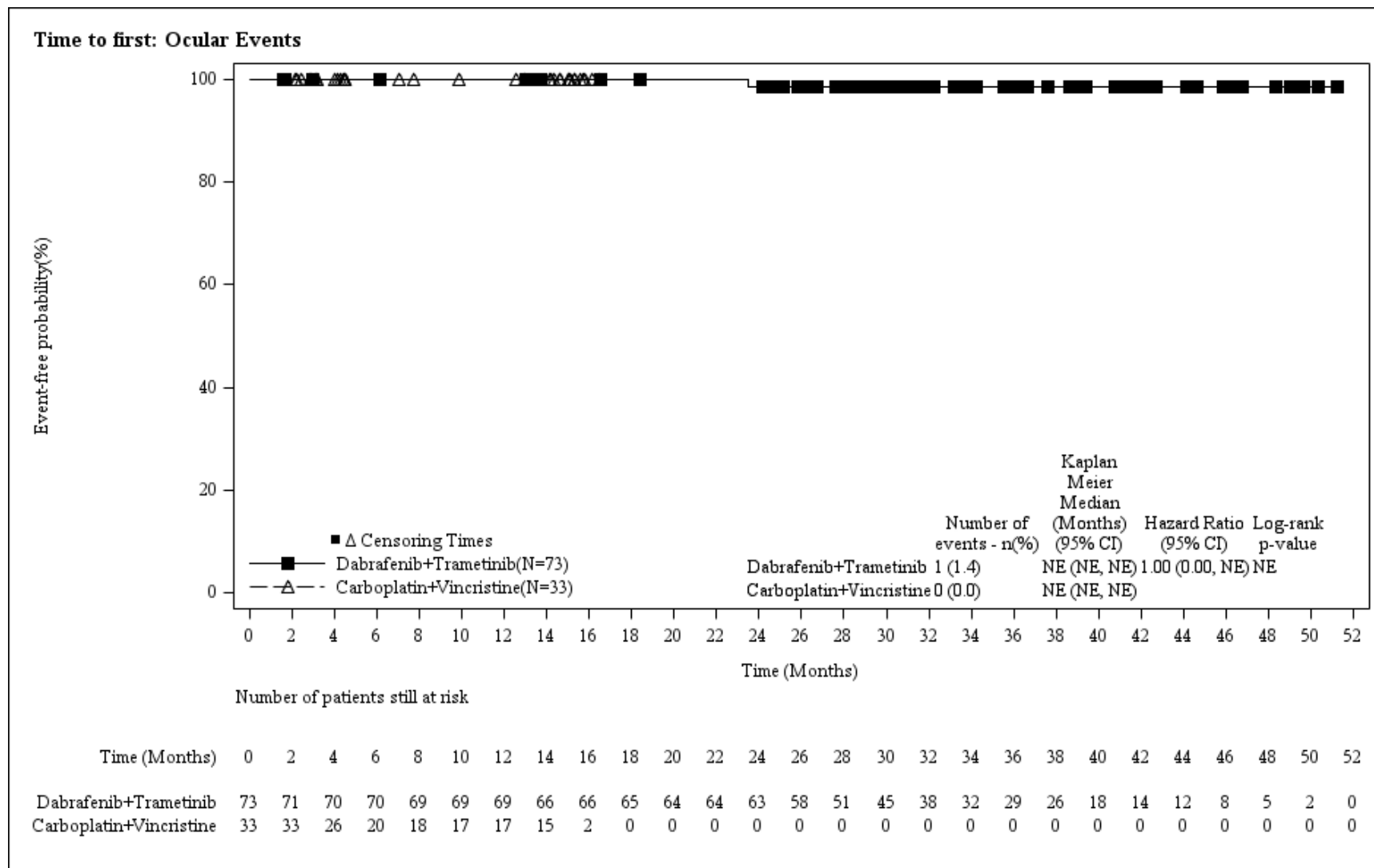
**Serious AESI: Kaplan Meier plot of time to first event
Safety Set – L**



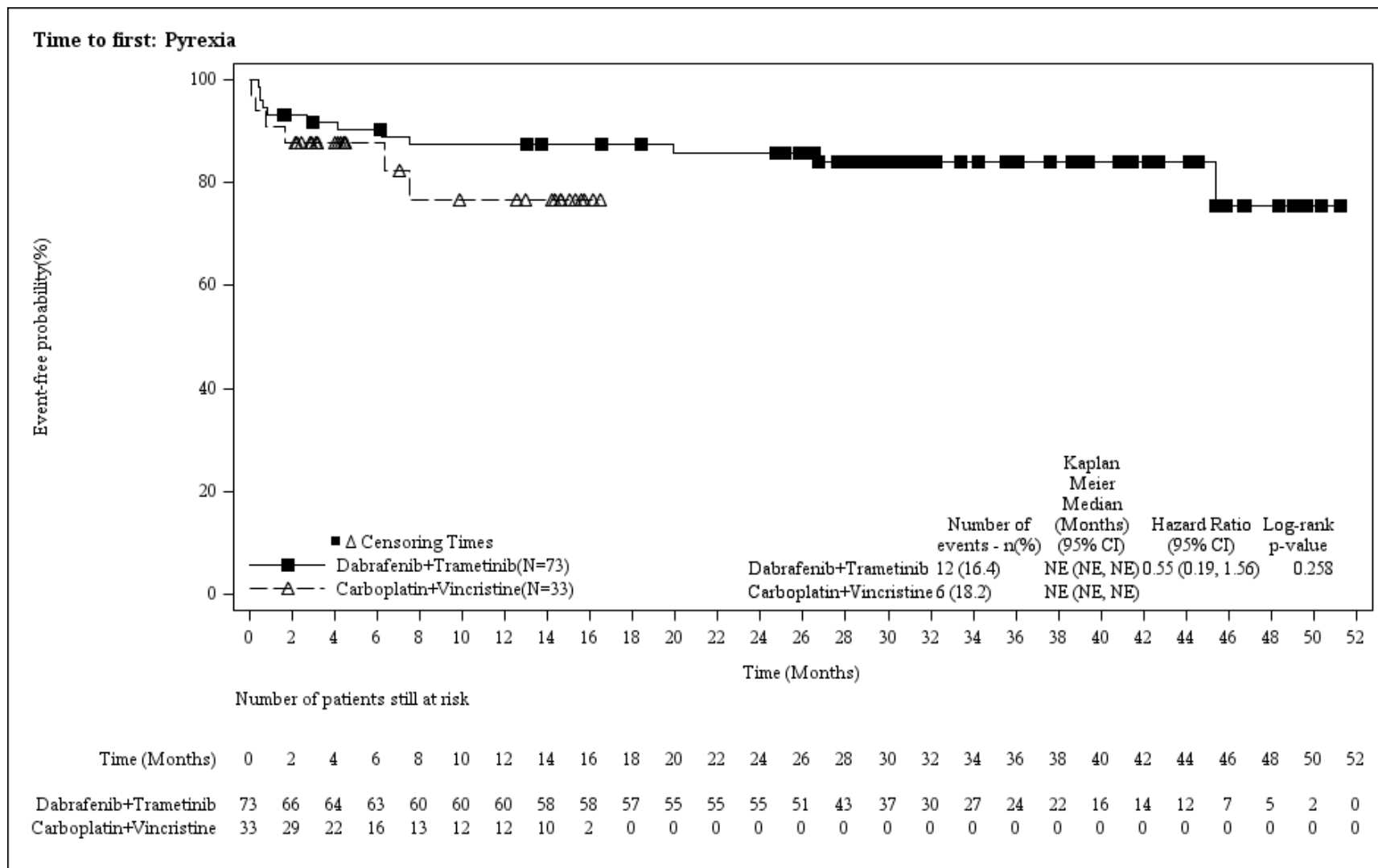
**Serious AESI: Kaplan Meier plot of time to first event
Safety Set – L**



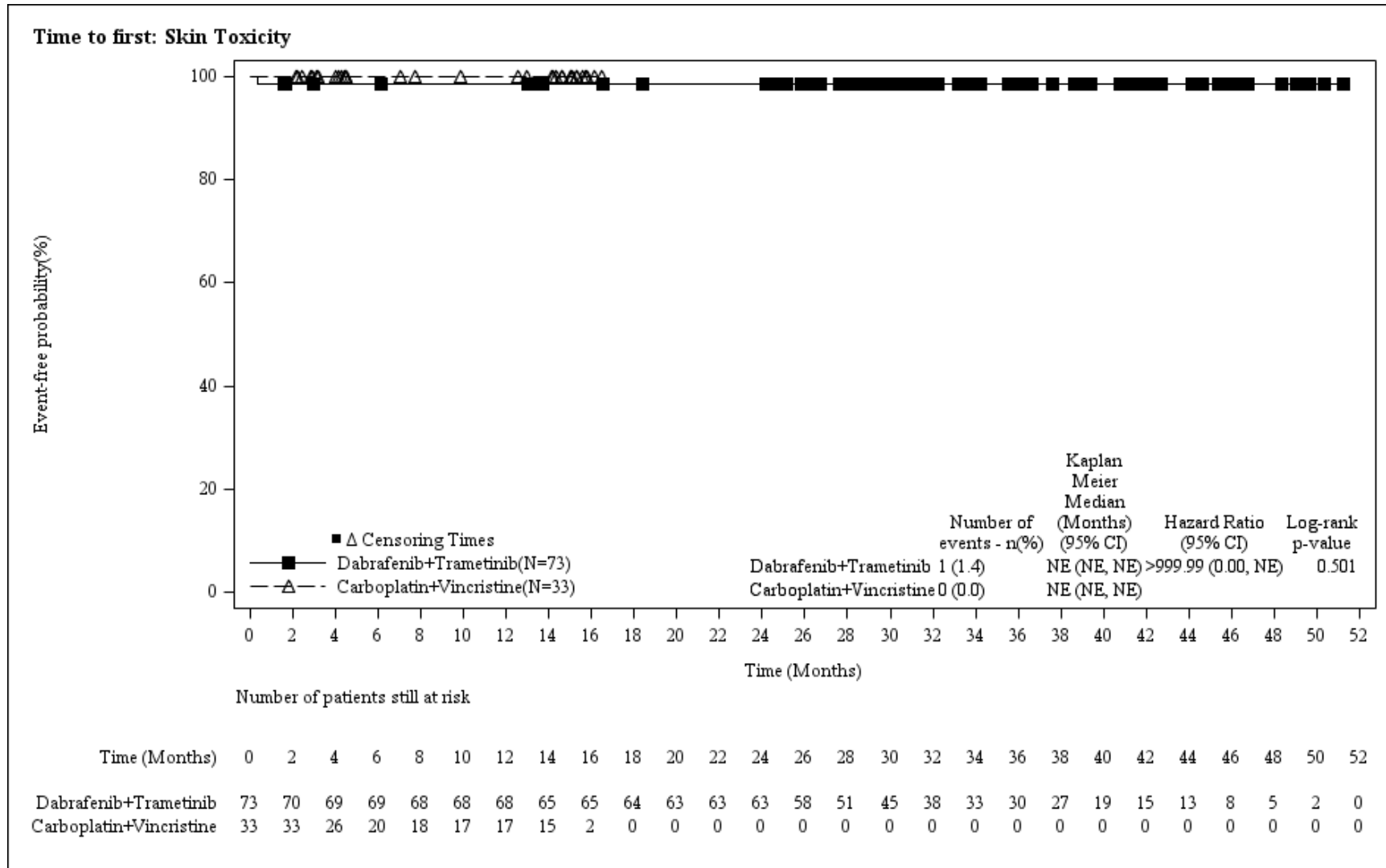
**Serious AESI: Kaplan Meier plot of time to first event
Safety Set – L**



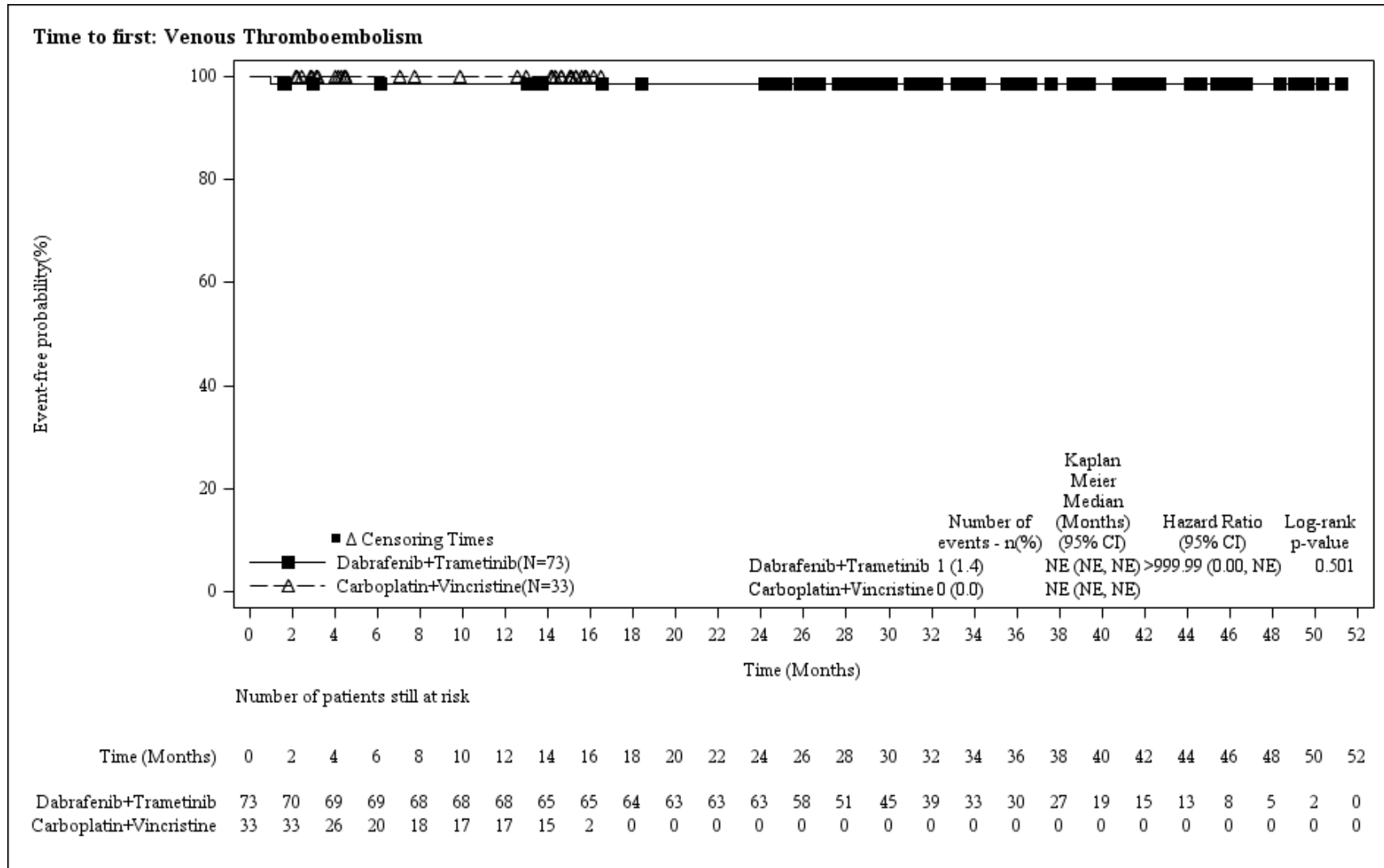
**Serious AESI: Kaplan Meier plot of time to first event
Safety Set – L**



**Serious AESI: Kaplan Meier plot of time to first event
Safety Set – L**



Serious AESI: Kaplan Meier plot of time to first event
Safety Set – L



2.4. Abbrüche wegen unerwünschter Ereignisse nach SOC und PT**AE leading to discontinuation by SOC and PT: Number and percentage of patients with event
Safety Set – L**

Primary system organ class Preferred term	Dabrafenib+Trametinib N=73		Carboplatin+Vincristine N=33	
	All grades n (%)	Grade >=3 n (%)	All grades n (%)	Grade >=3 n (%)
Number of subjects with at least one event n(%)	4 (5.5)	3 (4.1)	8 (24.2)	3 (9.1)
Blood and lymphatic system disorders	0	0	1 (3.0)	1 (3.0)
Neutropenia	0	0	1 (3.0)	1 (3.0)
Eye disorders	0	0	1 (3.0)	0
Eyelid ptosis	0	0	1 (3.0)	0
Gastrointestinal disorders	0	0	1 (3.0)	0
Nausea	0	0	1 (3.0)	0
General disorders and administration site conditions	3 (4.1)	2 (2.7)	0	0
Pyrexia	2 (2.7)	2 (2.7)	0	0
Chills	1 (1.4)	0	0	0
Fatigue	1 (1.4)	0	0	0
Immune system disorders	0	0	2 (6.1)	0
Hypersensitivity	0	0	2 (6.1)	0
Injury, poisoning and procedural complications	0	0	2 (6.1)	0

Numbers (n) represent counts of subjects.

A subject with multiple severity grades for an AE is only counted under the maximum grade.

MedDRA version 26.0, CTCAE version 4.03.

**AE leading to discontinuation by SOC and PT: Number and percentage of patients with event
Safety Set - L**

Primary system organ class Preferred term	Dabrafenib+Trametinib N=73		Carboplatin+Vincristine N=33	
	All grades n (%)	Grade >=3 n (%)	All grades n (%)	Grade >=3 n (%)
Infusion related reaction	0	0	2 (6.1)	0
Investigations	1 (1.4)	1 (1.4)	0	0
Weight increased	1 (1.4)	1 (1.4)	0	0
Nervous system disorders	1 (1.4)	0	2 (6.1)	1 (3.0)
Headache	1 (1.4)	0	1 (3.0)	1 (3.0)
Dizziness	0	0	1 (3.0)	1 (3.0)
Neuropathy peripheral	0	0	1 (3.0)	0
Peripheral motor neuropathy	0	0	1 (3.0)	1 (3.0)
Skin and subcutaneous tissue disorders	0	0	1 (3.0)	1 (3.0)
Urticaria	0	0	1 (3.0)	1 (3.0)

Numbers (n) represent counts of subjects.

A subject with multiple severity grades for an AE is only counted under the maximum grade.

MedDRA version 26.0, CTCAE version 4.03.

Ergänzende Analysen zur Studie CDRB436G2201 – Subgruppenanalysen**3. Subgruppenanalysen zum Tumoransprechen****3.1. Gesamtansprechrates****ORR based on Independent Reviewer assessment per RANO criteria - subgroup analysis
Full Analysis Set - L**

	Treatment groups		RR	Comparison	
	Dabrafenib+ Trametinib N=73 n/N* (%)	Carboplatin+ Vincristine N=37 n/N* (%)		[95% CI]	p-value
Radiographic progression as indication to treatment					
Yes	23/44 (52.3)	3/15 (20.0)	2.61	[0.91, 7.47]	0.031
No	17/29 (58.6)	3/22 (13.6)	4.30	[1.44, 12.85]	<0.001

Risk Ratio (Dabrafenib + Trametinib vs. Carboplatin + Vincristine) with corresponding 95% CI and two-sided p-value were estimated using the Cochran-Mantel-Haenszel method.

RR: Risk Ratio; CI: Confidence Interval; n: Number of patients with event; N*: Number of patients included in the analysis.

4. Subgruppenanalysen zur Verträglichkeit

4.1. Gesamtraten unerwünschter Ereignisse

Any AE: Time to first event - subgroup analysis
Safety Set - L

Parameter: Any AE

	Treatment groups				Comparison	
	Dabrafenib+Trametinib N=73		Carboplatin+Vincristine N=33		HR (95% CI)	p-value
	n/N* (%)	Median (95% CI)	n/N* (%)	Median (95% CI)		
Age						
< 6 Years	20 / 20 (100)	0.3 (0.1, 0.8)	13 / 13 (100)	0.1 (0.0, 0.3)	0.59 (0.28, 1.21)	0.144
6 - <12 Years	25 / 25 (100)	0.2 (0.1, 0.5)	9 / 9 (100)	0.1 (0.0, 0.8)	0.78 (0.35, 1.72)	0.544
12 - <18 Years	28 / 28 (100)	0.3 (0.1, 0.5)	11 / 11 (100)	0.1 (0.0, 0.5)	0.91 (0.44, 1.88)	0.821

Subgroups which contain at least 10 events in one subgroup are displayed, regardless of whether they are significant for interactions or not.

Median (time to event) and its 95% CI are generated by KM estimation.

Hazard Ratio (Dabrafenib + Trametinib vs. Carboplatin + Vincristine) estimated by Cox proportional hazards model.

Two-sided p-value based on a Log-rank test.

AE: Adverse Event; CI: Confidence Interval; HR: Hazard Ratio; n: Number of patients with event; N*: Number of patients included in the analysis.

Grade >= 3 AE: Time to first event - subgroup analysis
Safety Set - L

Parameter: Grade >=3 AE

	Treatment groups				Comparison	
	Dabrafenib+Trametinib N=73		Carboplatin+Vincristine N=33		HR (95% CI)	p-value
	n/N* (%)	Median (95% CI)	n/N* (%)	Median (95% CI)		
Age						
< 6 Years	12 / 20 (60.0)	11.9 (3.5, NE)	12 / 13 (92.3)	0.9 (0.3, 1.7)	0.15 (0.06, 0.39)	<0.001
6 - <12 Years	12 / 25 (48.0)	NE (1.6, NE)	8 / 9 (88.9)	1.6 (0.5, 2.1)	0.31 (0.11, 0.84)	0.014
12 - <18 Years	15 / 28 (53.6)	33.5 (8.1, NE)	11 / 11 (100)	0.8 (0.3, 1.9)	0.12 (0.04, 0.33)	<0.001

Subgroups which contain at least 10 events in one subgroup are displayed, regardless of whether they are significant for interactions or not.

Median (time to event) and its 95% CI are generated by KM estimation.

Hazard Ratio (Dabrafenib + Trametinib vs. Carboplatin + Vincristine) estimated by Cox proportional hazards model.

Two-sided p-value based on a Log-rank test.

AE: Adverse Event; CI: Confidence Interval; HR: Hazard Ratio; n: Number of patients with event; N*: Number of patients included in the analysis.

SAE: Time to first event - subgroup analysis
Safety Set - L

Parameter: Any SAE

	Treatment groups				Comparison	
	Dabrafenib+Trametinib N=73		Carboplatin+Vincristine N=33		HR (95% CI)	p-value
	n/N* (%)	Median (95% CI)	n/N* (%)	Median (95% CI)		
Age						
< 6 Years	13 / 20 (65.0)	10.6 (1.1, NE)	5 / 13 (38.5)	6.3 (3.0, NE)	1.12 (0.39, 3.23)	0.839
6 - <12 Years	10 / 25 (40.0)	44.6 (13.9, NE)	2 / 9 (22.2)	NE (2.1, NE)	1.09 (0.22, 5.41)	0.912
12 - <18 Years	11 / 28 (39.3)	43.5 (7.5, NE)	7 / 11 (63.6)	5.4 (0.6, NE)	0.35 (0.13, 0.98)	0.035

Subgroups which contain at least 10 events in one subgroup are displayed, regardless of whether they are significant for interactions or not.

Median (time to event) and its 95% CI are generated by KM estimation.

Hazard Ratio (Dabrafenib + Trametinib vs. Carboplatin + Vincristine) estimated by Cox proportional hazards model.

Two-sided p-value based on a Log-rank test.

AE: Adverse Event; CI: Confidence Interval; HR: Hazard Ratio; n: Number of patients with event; N*: Number of patients included in the analysis.

4.2. Unerwünschte Ereignisse nach SOC und PT**4.2.1. Unerwünschte Ereignisse nach SOC****Any AE by SOC: Time to first event - subgroup analysis
Safety Set - L**

Parameter: SOC - Blood and lymphatic system disorders

	Treatment groups				Comparison	
	Dabrafenib+Trametinib N=73		Carboplatin+Vincristine N=33		HR (95% CI)	p-value
	n/N* (%)	Median (months) (95% CI)	n/N* (%)	Median (months) (95% CI)		
Age						
< 6 Years	9 / 20 (45.0)	NE (3.5, NE)	11 / 13 (84.6)	0.5 (0.3, 3.2)	0.17 (0.06, 0.46)	<0.001
6 - <12 Years	6 / 25 (24.0)	NE (NE, NE)	7 / 9 (77.8)	1.2 (0.8, NE)	0.19 (0.06, 0.61)	0.002
12 - <18 Years	9 / 28 (32.1)	NE (15.4, NE)	7 / 11 (63.6)	1.9 (0.3, NE)	0.26 (0.09, 0.75)	0.007

Median (time to event) and its 95% CI are generated by KM estimation.

Hazard Ratio (Dabrafenib + Trametinib vs. Carboplatin + Vincristine) estimated by Cox proportional hazards model.

Two-sided p-value based on a Log-rank test.

Events in at least 10% of patients in at least one of the treatment arms OR events in at least 10 patients and in at least 1% of patients in one treatment arm.

Results are only given for SOCs that are significant in the main analysis.

AE: Adverse Event; CI: Confidence Interval; HR: Hazard Ratio; n: Number of patients with event; N*: Number of patients included in the analysis.

Any AE by SOC: Time to first event - subgroup analysis
Safety Set - L

Parameter: SOC - Gastrointestinal disorders

	Treatment groups				Comparison	p-value
	Dabrafenib+Trametinib N=73		Carboplatin+Vincristine N=33			
	n/N* (%)	Median (months) (95% CI)	n/N* (%)	Median (months) (95% CI)		
Age						
< 6 Years	18 / 20 (90.0)	4.0 (0.4, 12.0)	11 / 13 (84.6)	0.5 (0.1, 4.2)	0.60 (0.28, 1.31)	0.200
6 - <12 Years	20 / 25 (80.0)	1.6 (0.3, 2.5)	6 / 9 (66.7)	0.3 (0.0, NE)	0.84 (0.33, 2.13)	0.726
12 - <18 Years	21 / 28 (75.0)	2.9 (0.7, 13.3)	10 / 11 (90.9)	0.1 (0.0, 2.8)	0.36 (0.16, 0.79)	0.008

Median (time to event) and its 95% CI are generated by KM estimation.

Hazard Ratio (Dabrafenib + Trametinib vs. Carboplatin + Vincristine) estimated by Cox proportional hazards model.

Two-sided p-value based on a Log-rank test.

Events in at least 10% of patients in at least one of the treatment arms OR events in at least 10 patients and in at least 1% of patients in one treatment arm.

Results are only given for SOCs that are significant in the main analysis.

AE: Adverse Event; CI: Confidence Interval; HR: Hazard Ratio; n: Number of patients with event; N*: Number of patients included in the analysis.

Any AE by SOC: Time to first event - subgroup analysis
Safety Set - L

Parameter: SOC – Investigations

	Treatment groups				Comparison	p-value
	Dabrafenib+Trametinib N=73		Carboplatin+Vincristine N=33			
	n/N* (%)	Median (months) (95% CI)	n/N* (%)	Median (months) (95% CI)		
Age						
< 6 Years	14 / 20 (70.0)	13.1 (5.6, 25.8)	8 / 13 (61.5)	1.6 (0.5, NE)	0.43 (0.17, 1.09)	0.068
6 - <12 Years	13 / 25 (52.0)	20.0 (5.3, NE)	6 / 9 (66.7)	1.6 (0.3, NE)	0.21 (0.06, 0.75)	0.008
12 - <18 Years	17 / 28 (60.7)	3.2 (1.0, NE)	8 / 11 (72.7)	0.7 (0.0, NE)	0.59 (0.25, 1.37)	0.226

Median (time to event) and its 95% CI are generated by KM estimation.

Hazard Ratio (Dabrafenib + Trametinib vs. Carboplatin + Vincristine) estimated by Cox proportional hazards model.

Two-sided p-value based on a Log-rank test.

Events in at least 10% of patients in at least one of the treatment arms OR events in at least 10 patients and in at least 1% of patients in one treatment arm.

Results are only given for SOC's that are significant in the main analysis.

AE: Adverse Event; CI: Confidence Interval; HR: Hazard Ratio; n: Number of patients with event; N*: Number of patients included in the analysis.

Any AE by SOC: Time to first event - subgroup analysis
Safety Set - L

Parameter: SOC - Metabolism and nutrition disorders

	Treatment groups				Comparison	p-value
	Dabrafenib+Trametinib N=73		Carboplatin+Vincristine N=33			
	n/N* (%)	Median (months) (95% CI)	n/N* (%)	Median (months) (95% CI)		
Age						
< 6 Years	4 / 20 (20.0)	NE (NE, NE)	5 / 13 (38.5)	NE (0.2, NE)	0.37 (0.10, 1.41)	0.132
6 - <12 Years	5 / 25 (20.0)	NE (NE, NE)	5 / 9 (55.6)	1.2 (0.3, NE)	0.15 (0.04, 0.61)	0.003
12 - <18 Years	8 / 28 (28.6)	NE (23.7, NE)	5 / 11 (45.5)	NE (0.2, NE)	0.35 (0.11, 1.17)	0.075

Median (time to event) and its 95% CI are generated by KM estimation.

Hazard Ratio (Dabrafenib + Trametinib vs. Carboplatin + Vincristine) estimated by Cox proportional hazards model.

Two-sided p-value based on a Log-rank test.

Events in at least 10% of patients in at least one of the treatment arms OR events in at least 10 patients and in at least 1% of patients in one treatment arm.

Results are only given for SOC's that are significant in the main analysis.

AE: Adverse Event; CI: Confidence Interval; HR: Hazard Ratio; n: Number of patients with event; N*: Number of patients included in the analysis.

Any AE by SOC: Time to first event - subgroup analysis
Safety Set - L

Parameter: SOC - Skin and subcutaneous tissue disorders

	Treatment groups				Comparison	p-value
	Dabrafenib+Trametinib N=73		Carboplatin+Vincristine N=33			
	n/N* (%)	Median (months) (95% CI)	n/N* (%)	Median (months) (95% CI)		
Age						
< 6 Years	17 / 20 (85.0)	2.2 (0.7, 4.5)	5 / 13 (38.5)	NE (1.0, NE)	2.48 (0.92, 6.74)	0.063
6 - <12 Years	22 / 25 (88.0)	2.3 (1.3, 22.8)	4 / 9 (44.4)	9.0 (1.0, NE)	1.61 (0.54, 4.85)	0.391
12 - <18 Years	25 / 28 (89.3)	0.9 (0.5, 4.0)	8 / 11 (72.7)	9.7 (1.1, NE)	1.60 (0.71, 3.61)	0.262

Median (time to event) and its 95% CI are generated by KM estimation.

Hazard Ratio (Dabrafenib + Trametinib vs. Carboplatin + Vincristine) estimated by Cox proportional hazards model.

Two-sided p-value based on a Log-rank test.

Events in at least 10% of patients in at least one of the treatment arms OR events in at least 10 patients and in at least 1% of patients in one treatment arm.

Results are only given for SOCs that are significant in the main analysis.

AE: Adverse Event; CI: Confidence Interval; HR: Hazard Ratio; n: Number of patients with event; N*: Number of patients included in the analysis.

4.2.2. Schwere unerwünschte Ereignisse (CTCAE-Grad ≥ 3) nach SOC**Grade ≥ 3 AE by SOC: Time to first event - subgroup analysis
Safety Set - L**

Parameter: SOC – Investigations

	Treatment groups				Comparison	p-value
	Dabrafenib+Trametinib N=73		Carboplatin+Vincristine N=33			
	n/N* (%)	Median (months) (95% CI)	n/N* (%)	Median (months) (95% CI)		
Age						
< 6 Years	7 / 20 (35.0)	NE (12.6, NE)	7 / 13 (53.8)	1.9 (0.7, NE)	0.26 (0.08, 0.81)	0.014
6 - <12 Years	4 / 25 (16.0)	NE (NE, NE)	3 / 9 (33.3)	NE (0.6, NE)	0.30 (0.06, 1.42)	0.110
12 - <18 Years	6 / 28 (21.4)	NE (NE, NE)	8 / 11 (72.7)	1.9 (0.7, NE)	0.15 (0.05, 0.44)	<0.001

Median (time to event) and its 95% CI are generated by KM estimation.

Hazard Ratio (Dabrafenib + Trametinib vs. Carboplatin + Vincristine) estimated by Cox proportional hazards model.

Two-sided p-value based on a Log-rank test.

Events in at least 5% of patients in at least one of the treatment arms OR events in at least 10 patients and in at least 1% of patients in one treatment arm.

Results are only given for SOC that are significant in the main analysis.

AE: Adverse Event; CI: Confidence Interval; HR: Hazard Ratio; n: Number of patients with event; N*: Number of patients included in the analysis.

4.2.3. Unerwünschte Ereignisse nach PT**Any AE by PT: Time to first event - subgroup analysis
Safety Set - L**

Parameter: PT - Alanine aminotransferase increased

	Treatment groups				Comparison	
	Dabrafenib+Trametinib N=73		Carboplatin+Vincristine N=33		HR (95% CI)	p-value
	n/N* (%)	Median (months) (95% CI)	n/N* (%)	Median (months) (95% CI)		
Age						
< 6 Years	3 / 20 (15.0)	NE (NE, NE)	1 / 13 (7.7)	NE (NE, NE)	1.03 (0.10, 10.27)	0.982
6 - <12 Years	2 / 25 (8.0)	NE (NE, NE)	3 / 9 (33.3)	NE (0.3, NE)	0.07 (0.01, 0.75)	0.005
12 - <18 Years	5 / 28 (17.9)	NE (NE, NE)	5 / 11 (45.5)	NE (0.5, NE)	0.30 (0.09, 1.06)	0.046

Median (time to event) and its 95% CI are generated by KM estimation.

Hazard Ratio (Dabrafenib + Trametinib vs. Carboplatin + Vincristine) estimated by Cox proportional hazards model.

Two-sided p-value based on a Log-rank test.

Events in at least 10% of patients in at least one of the treatment arms OR events in at least 10 patients and in at least 1% of patients in one treatment arm.

Results are only given for PTs that are significant in the main analysis.

AE: Adverse Event; CI: Confidence Interval; HR: Hazard Ratio; n: Number of patients with event; N*: Number of patients included in the analysis.

Any AE by PT: Time to first event - subgroup analysis
Safety Set - L

Parameter: PT – Anaemia

	Treatment groups				Comparison	p-value
	Dabrafenib+Trametinib N=73		Carboplatin+Vincristine N=33			
	n/N* (%)	Median (months) (95% CI)	n/N* (%)	Median (months) (95% CI)		
Age						
< 6 Years	7 / 20 (35.0)	NE (3.5, NE)	9 / 13 (69.2)	0.5 (0.3, NE)	0.21 (0.07, 0.64)	0.003
6 - <12 Years	3 / 25 (12.0)	NE (NE, NE)	6 / 9 (66.7)	1.6 (0.8, NE)	0.10 (0.02, 0.48)	<0.001
12 - <18 Years	4 / 28 (14.3)	NE (44.0, NE)	5 / 11 (45.5)	NE (0.3, NE)	0.18 (0.04, 0.76)	0.009

Median (time to event) and its 95% CI are generated by KM estimation.

Hazard Ratio (Dabrafenib + Trametinib vs. Carboplatin + Vincristine) estimated by Cox proportional hazards model.

Two-sided p-value based on a Log-rank test.

Events in at least 10% of patients in at least one of the treatment arms OR events in at least 10 patients and in at least 1% of patients in one treatment arm.

Results are only given for PTs that are significant in the main analysis.

AE: Adverse Event; CI: Confidence Interval; HR: Hazard Ratio; n: Number of patients with event; N*: Number of patients included in the analysis.

Any AE by PT: Time to first event - subgroup analysis
Safety Set - L

Parameter: PT - Dry skin

	Treatment groups				Comparison	
	Dabrafenib+Trametinib N=73		Carboplatin+Vincristine N=33			
	n/N* (%)	Median (months) (95% CI)	n/N* (%)	Median (months) (95% CI)	HR (95% CI)	p-value
Age						
< 6 Years	3 / 20 (15.0)	NE (NE, NE)	1 / 13 (7.7)	NE (NE, NE)	1.54 (0.16, 15.03)	0.707
6 - <12 Years	6 / 25 (24.0)	NE (NE, NE)	0 / 9 (0.0)	NE (NE, NE)	>999.99 (0.00, NE)	0.290
12 - <18 Years	11 / 28 (39.3)	NE (10.0, NE)	0 / 11 (0.0)	NE (NE, NE)	>999.99 (0.00, NE)	0.047

Median (time to event) and its 95% CI are generated by KM estimation.

Hazard Ratio (Dabrafenib + Trametinib vs. Carboplatin + Vincristine) estimated by Cox proportional hazards model.

Two-sided p-value based on a Log-rank test.

Events in at least 10% of patients in at least one of the treatment arms OR events in at least 10 patients and in at least 1% of patients in one treatment arm.

Results are only given for PTs that are significant in the main analysis.

AE: Adverse Event; CI: Confidence Interval; HR: Hazard Ratio; n: Number of patients with event; N*: Number of patients included in the analysis.

Any AE by PT: Time to first event - subgroup analysis
Safety Set - L

Parameter: PT – Nausea

	Treatment groups				Comparison	p-value
	Dabrafenib+Trametinib N=73		Carboplatin+Vincristine N=33			
	n/N* (%)	Median (months) (95% CI)	n/N* (%)	Median (months) (95% CI)		
Age						
< 6 Years	3 / 20 (15.0)	NE (28.9, NE)	5 / 13 (38.5)	NE (1.4, NE)	0.22 (0.04, 1.15)	0.050
6 - <12 Years	8 / 25 (32.0)	NE (7.6, NE)	4 / 9 (44.4)	NE (0.0, NE)	0.34 (0.10, 1.23)	0.087
12 - <18 Years	10 / 28 (35.7)	NE (8.0, NE)	8 / 11 (72.7)	0.1 (0.0, NE)	0.23 (0.09, 0.60)	0.001

Median (time to event) and its 95% CI are generated by KM estimation.

Hazard Ratio (Dabrafenib + Trametinib vs. Carboplatin + Vincristine) estimated by Cox proportional hazards model.

Two-sided p-value based on a Log-rank test.

Events in at least 10% of patients in at least one of the treatment arms OR events in at least 10 patients and in at least 1% of patients in one treatment arm.

Results are only given for PTs that are significant in the main analysis.

AE: Adverse Event; CI: Confidence Interval; HR: Hazard Ratio; n: Number of patients with event; N*: Number of patients included in the analysis.

Any AE by PT: Time to first event - subgroup analysis
Safety Set - L

Parameter: PT - Neutrophil count decreased

	Treatment groups				Comparison	p-value
	Dabrafenib+Trametinib N=73		Carboplatin+Vincristine N=33			
	n/N* (%)	Median (months) (95% CI)	n/N* (%)	Median (months) (95% CI)		
Age						
< 6 Years	1 / 20 (5.0)	NE (NE, NE)	7 / 13 (53.8)	1.7 (0.7, NE)	0.06 (0.01, 0.47)	<0.001
6 - <12 Years	5 / 25 (20.0)	NE (NE, NE)	3 / 9 (33.3)	NE (0.6, NE)	0.39 (0.09, 1.73)	0.199
12 - <18 Years	5 / 28 (17.9)	NE (40.5, NE)	6 / 11 (54.5)	1.9 (1.2, NE)	0.22 (0.06, 0.80)	0.012

Median (time to event) and its 95% CI are generated by KM estimation.

Hazard Ratio (Dabrafenib + Trametinib vs. Carboplatin + Vincristine) estimated by Cox proportional hazards model.

Two-sided p-value based on a Log-rank test.

Events in at least 10% of patients in at least one of the treatment arms OR events in at least 10 patients and in at least 1% of patients in one treatment arm.

Results are only given for PTs that are significant in the main analysis.

AE: Adverse Event; CI: Confidence Interval; HR: Hazard Ratio; n: Number of patients with event; N*: Number of patients included in the analysis.

Any AE by PT: Time to first event - subgroup analysis
Safety Set - L

Parameter: PT – Pyrexia

	Treatment groups				Comparison	p-value
	Dabrafenib+Trametinib N=73		Carboplatin+Vincristine N=33			
	n/N* (%)	Median (months) (95% CI)	n/N* (%)	Median (months) (95% CI)		
Age						
< 6 Years	14 / 20 (70.0)	5.4 (1.0, 16.8)	4 / 13 (30.8)	NE (2.9, NE)	2.05 (0.66, 6.33)	0.203
6 - <12 Years	20 / 25 (80.0)	4.1 (0.7, 15.7)	0 / 9 (0.0)	NE (NE, NE)	>999.99 (0.00, NE)	0.008
12 - <18 Years	21 / 28 (75.0)	2.5 (0.7, 11.8)	2 / 11 (18.2)	NE (0.8, NE)	4.79 (1.12, 20.58)	0.020

Median (time to event) and its 95% CI are generated by KM estimation.

Hazard Ratio (Dabrafenib + Trametinib vs. Carboplatin + Vincristine) estimated by Cox proportional hazards model.

Two-sided p-value based on a Log-rank test.

Events in at least 10% of patients in at least one of the treatment arms OR events in at least 10 patients and in at least 1% of patients in one treatment arm.

Results are only given for PTs that are significant in the main analysis.

AE: Adverse Event; CI: Confidence Interval; HR: Hazard Ratio; n: Number of patients with event; N*: Number of patients included in the analysis.

Any AE by PT: Time to first event - subgroup analysis
Safety Set - L

Parameter: PT – Vomiting

	Treatment groups				Comparison	p-value
	Dabrafenib+Trametinib N=73		Carboplatin+Vincristine N=33			
	n/N* (%)	Median (months) (95% CI)	n/N* (%)	Median (months) (95% CI)		
Age						
< 6 Years	10 / 20 (50.0)	30.0 (1.9, NE)	5 / 13 (38.5)	NE (0.8, NE)	0.96 (0.32, 2.88)	0.943
6 - <12 Years	8 / 25 (32.0)	NE (5.2, NE)	3 / 9 (33.3)	NE (0.7, NE)	0.67 (0.17, 2.68)	0.565
12 - <18 Years	9 / 28 (32.1)	NE (14.6, NE)	9 / 11 (81.8)	2.0 (0.2, 4.2)	0.20 (0.08, 0.53)	<0.001

Median (time to event) and its 95% CI are generated by KM estimation.

Hazard Ratio (Dabrafenib + Trametinib vs. Carboplatin + Vincristine) estimated by Cox proportional hazards model.

Two-sided p-value based on a Log-rank test.

Events in at least 10% of patients in at least one of the treatment arms OR events in at least 10 patients and in at least 1% of patients in one treatment arm.

Results are only given for PTs that are significant in the main analysis.

AE: Adverse Event; CI: Confidence Interval; HR: Hazard Ratio; n: Number of patients with event; N*: Number of patients included in the analysis.