Gemeinsamer Bundesausschuss

Resolution

of the Federal Joint Committee on an Amendment of the Pharmaceuticals Directive:
Annex XII – Benefit Assessment of Medicinal Products with New Active Ingredients according to Section 35a SGB V
Osimertinib (new therapeutic indication: non-small cell lung cancer, first-line, combination with pemetrexed and platinum-based chemotherapy)

of 6 February 2025

At its session on 6 February 2025, the Federal Joint Committee (G-BA) resolved to amend the Pharmaceuticals Directive (AM-RL) in the version dated 18 December 2008 / 22 January 2009 (Federal Gazette, BAnz. No. 49a of 31 March 2009), as last amended by the publication of the resolution of D Month YYYY (Federal Gazette, BAnz AT DD.MM.YYYY BX), as follows:

I. In Annex XII, the following information shall be added after No. 5 to the information on the benefit assessment of Osimertinib in accordance with the resolution of 19 December 2024:

Osimertinib

Resolution of: 6 February 2025
Entry into force on: 6 February 2025
Federal Gazette, BAnz AT DD. MM YYYY Bx

New therapeutic indication (according to the marketing authorisation of 28 June 2024):

Tagrisso is indicated in combination with pemetrexed and platinum-based chemotherapy for the first-line treatment of adult patients with advanced NSCLC whose tumours have EGFR exon 19 deletions or exon 21 (L858R) substitution mutations.

Therapeutic indication of the resolution (resolution of 6 February 2025):

See new therapeutic indication according to marketing authorisation.

1. Additional benefit of the medicinal product in relation to the appropriate comparator therapy

Adults with advanced NSCLC whose tumours have EGFR exon 19 deletions or exon 21 (L858R) substitution mutations; first-line treatment

Appropriate comparator therapy for osimertinib in combination with pemetrexed and platinum-based chemotherapy:

- Afatinib (only for patients with the activating EGFR exon 19 deletion mutation)

or

- Osimertinib

Extent and probability of the additional benefit of osimertinib in combination with pemetrexed and platinum-based chemotherapy versus osimertinib:

An additional benefit is not proven.

Study results according to endpoints:[1]

Adults with advanced NSCLC whose tumours have EGFR exon 19 deletions or exon 21 (L858R) substitution mutations; first-line treatment

Summary of results for relevant clinical endpoints

Endpoint category	Direction of effect/ risk of bias	Summary
Mortality	↔	No relevant difference for the benefit assessment
Morbidity	↔	No relevant difference for the benefit assessment
Health-related quality of life	↔	No relevant difference for the benefit assessment
Side effects	↓↓	Disadvantages in severe AEs, SAEs and therapy discontinuation due to AEs. In detail, disadvantages for each of the specific AEs.
Explanations: ↑: statistically significant and relevant positive effect with low/unclear reliability of data ↓: statistically significant and relevant negative effect with low/unclear reliability of data ↑↑: statistically significant and relevant positive effect with high reliability of data ↓↓: statistically significant and relevant negative effect with high reliability of data ↔: no statistically significant or relevant difference ∅: No data available. n.a.: not assessable		

FLAURA-2 study

- RCT, open-label, parallel
- Osimertinib in combination with pemetrexed and platinum-based chemotherapy **vs** osimertinib
- Data cut-offs:
  - 2nd data cut-off from 03.04.2023 (primary PFS analysis; used for endpoints of morbidity, health-related quality of life and side effects)
  - 3rd data cut-off from 08.01.2024 (EMA requirement; endpoint of overall survival; additionally considered for the present assessment)

[1] Data from the dossier assessment of the IQWiG (A24-77) and from the addendum (A24-119), unless otherwise indicated.

Mortality

Endpoint	Osimertinib + pemetrexed + platinum-based chemotherapy[b]		Osimertinib		Intervention vs control
	N[c]	Median survival time in months [95% CI] *Patients with event n (%)*	N[c]	Median survival time in months [95% CI] *Patients with event n (%)*	Effect estimator [95% CI] p value[d] Absolute difference (AD)[a]
Overall survival					
	279	n.r. [31.9; n.c.] 71 (25.4)	278	n.r. 78 (28.1)	HR: 0.90 [0.65; 1.24]; 0.524[e]
Data cut-off from 08.01.2024 (presented additionally)	279	n.r. 100 (35.8)	278	36.7 [33.2; n.c.] 126 (45.3)	HR 0.75 [0.57; 0.97]; 0.028

Morbidity

Endpoint	Osimertinib + pemetrexed + platinum-based chemotherapy[b]		Osimertinib		Intervention vs control
	N	Median survival time in months [95% CI] *Patients with event n (%)*	N	Median survival time in months [95% CI] *Patients with event n (%)*	Effect estimator [95% CI] p value
Progression-free survival (PFS) [2]					
	279	25.5 [24.7; n.r.] 120 (43.0)	278	16.7 [14.1; 21.3] 166 (59.7)	HR: 0.62 [0.49; 0.79] < 0.0001

[2] Data on osimertinib from module 4 of the pharmaceutical company from 23.07.2024

Endpoint	Osimertinib + pemetrexed + platinum-based chemotherapy[b]			Osimertinib			Intervention vs control
	N[j]	Values at the start of study MV (SD)	Mean change in the course of study MV[k] (SE)	N[j]	Values at the start of study MV (SD)	Mean change in the course of study MV[k] (SE)	MD [95% CI]; p value
Symptomatology (EORTC-QLQ-30)[l]							
Fatigue	253	29.60 (21.33)	0.13 (0.89)	253	34.12 (26.73)	-4.28 (0.90)	4.40 [1.91; 6.89]; < 0.001 SMD: 0.31 [0.13; 0.48]
Pain	253	26.28 (24.26)	-7.97 (0.87)	253	29.78 (28.80)	-8.78 (0.88)	0.81 [-1.61; 3.23]; 0.511
Nausea and vomiting	253	6.19 (12.56)	1.45 (0.50)	253	5.99 (14.86)	-0.94 (0.51)	2.40 [1.00; 3.80]; < 0.001 SMD: 0.30 [0.12; 0.47]
Dyspnoea	253	24.64 (25.96)	-6.88 (0.92)	253	29.64 (28.86)	-8.68 (0.93)	1.79 [-0.77; 4.36]; 0.170
Insomnia	253	29.91 (25.31)	-8.98 (0.91)	253	31.49 (31.79)	-10.92 (0.92)	1.94 [-0.59; 4.48]; 0.133
Appetite loss	253	20.95 (26.98)	2.01 (0.99)	253	21.87 (29.63)	-3.02 (1.00)	5.04 [2.27; 7.81]; < 0.001 SMD: 0.32 [0.14; 0.49]
Constipation	253	14.76 (23.04)	-0.13 (0.80)	253	14.49 (24.32)	-3.04 (0.81)	2.91 [0.67; 5.15]; 0.011 SMD: 0.23 [0.05; 0.40]
Diarrhoea	253	5.01 (12.30)	9.51 (0.85)	253	6.59 (15.45)	11.00 (0.86)	-1.49 [-3.86; 0.88]; 0.219
Symptomatology (EORTC QLQ-LC13)[l]							
Cough	253	32.41 (27.44)	-12.66 (0.83)	251	31.34 (28.61)	-10.04 (0.84)	-2.62 [-4.94; -0.31]; 0.027 SMD: -0.20 [-0.37; -0.02]
Haemoptysis	253	2.11 (8.66)	-1.94 (0.20)	251	5.58 (16.99)	-1.94 (0.21)	0.00 [-0.57; 0.58]; 0.988

Dysphagia	253	5.53 (15.00)	3.07 (0.63)	251	4.78 (14.43)	2.16 (0.64)	0.91 [-0.85; 2.68]; 0.310
Pain (arm/ shoulder)	253	17.79 (22.12)	-3.61 (0.80)	251	18.86 (24.92)	-2.86 (0.81)	-0.75 [-2.99; 1.49]; 0.510
Pain (in other body parts)	253	21.87 (23.67)	-2.47 (0.83)	251	27.09 (29.68)	-3.80 (0.84)	1.34 [-0.98; 3.65]; 0.258
Pain (chest)	253	16.86 (20.49)	-5.82 (0.69)	251	21.25 (25.47)	-5.80 (0.69)	-0.02 [-1.94; 1.90]; 0.980
Wounded mouth	253	3.82 (12.19)	11.12 (0.84)	251	4.78 (14.73)	8.74 (0.84)	2.38 [0.06; 4.71]; 0.045 SMD: 0.18 [0.00; 0.35]
Dyspnoea	253	23.54 (20.58)	-2.52 (0.81)	251	26.69 (24.25)	-4.42 (0.82)	1.90 [-0.36; 4.16]; 0.099
Peripheral neuropathy	253	7.77 (16.70)	9.08 (0.84)	251	7.17 (16.65)	7.84 (0.85)	1.24 [-1.11; 3.58]; 0.301
Alopecia	253	5.67 (16.76)	6.63 (0.84)	251	9.96 (23.53)	6.44 (0.85)	0.19 [-2.17; 2.55]; 0.874
Symptomatology (PGIS)[l]							
	242	1.58 (1.40)	-0.16 (0.05)	248	1.75 (1.47)	-0.24 (0.05)	0.09 [-0.06; 0.23]; 0.230
Health status (EQ-5D VAS)[m]							
	246	71.94 (18.26)	1.26 (0.79)	249	71.28 (19.47)	2.49 (0.79)	-1.23 [-3.42; 0.96]; 0.272

Health-related quality of life

Endpoint	Osimertinib + pemetrexed + platinum-based chemotherapy[b]			Osimertinib			Intervention vs control
	N[j]	Values at the start of study MV (SD)	Mean change in the course of study MV[k] (SE)	N[j]	Values at the start of study MV (SD)	Mean change in the course of study MV[k] (SE)	MD [95% CI]; p value[k]
EORTC-QLQ-30[m]							
Physical functioning	253	78.66 (20.30)	1.91 (0.80)	253	75.97 (23.07)	4.62 (0.81)	-2.71 [-4.94; -0.47]; 0.018 SMD: -0.21 [-0.39; -0.04]
Role functioning	253	76.94 (25.93)	1.09 (1.06)	253	72.86 (30.01)	3.98 (1.07)	-2.89 [-5.86; 0.08]; 0.056
Cognitive functioning	253	85.64 (16.20)	-2.75 (0.72)	253	85.51 (19.88)	-0.43 (0.72)	-2.32 [-4.31; -0.32]; 0.023 SMD: -0.20 [-0.38; -0.03]
Emotional functioning	253	74.60 (20.40)	6.22 (0.78)	253	74.47 (21.90)	7.45 (0.79)	-1.23 [-3.42; 0.95]; 0.268
Social functioning	253	75.69 (23.50)	0.09 (1.01)	253	74.18 (27.87)	5.40 (1.01)	-5.31 [-8.12; -2.51]; < 0.001 SMD: -0.33 [-0.51; -0.16]
Global health status	253	65.91 (19.45)	3.04 (0.80)	253	63.77 (21.56)	5.51 (0.80)	-2.47 [-4.69; -0.25]; 0.029 SMD: -0.19 [-0.37; -0.02]

Side effects

Endpoint	Osimertinib + pemetrexed + platinum-based chemotherapy		Osimertinib		Intervention vs control
	N[c]	Median in months [95% CI] *Patients with event n (%)*	N[c]	Median in months [95% CI] *Patients with event n (%)*	RR [95% CI] p value[d] Absolute difference (AD)[a]
Adverse events in total					
	276	– 276 (100)	275	– 268 (97.5)	–
Serious adverse events (SAE)					
	276	– 104 (37.7)	275	– 53 (19.3)	1.96 [1.47; 2.60]; < 0.001
Severe adverse events[f]					
	276	– 176 (63.8)	275	– 75 (27.3)	2.34 [1.89; 2.89]; < 0.001
Therapy discontinuation due to adverse events[g]					
	276	– 132 (47.8)	275	– 17 (6.2)	7.74 [4.80; 12.46]; < 0.001
PRO-CTCAE	No suitable data				
Specific adverse events					
Skin and subcutaneous tissue disorders (SOC, AEs)	276	– 191 (69.2)	275	– 184 (66.9)	1.03 [0.92; 1.16]; 0.602
ILD and pneumonitis[h] (PTs, severe AEs[f])	276	– 2 (0.7)	275	– 5 (1.8)	0.40 [0.08; 2.04]; 0.268
Cardiac effects[i] (SMQs, severe AEs[f])	276	– 12 (4.3)	275	– 3 (1.1)	3.99 [1.14; 13.97]; 0.020
Loss of appetite (PT, AEs)	276	– 85 (30.8)	275	– 26 (9.5)	3.26 [2.17; 4.89]; < 0.001
General disorders and administration site conditions (SOC, severe AEs[f])	276	– 10 (3.6)	275	– 2 (0.7)	4.98 [1.10; 22.53]; 0.021

Blood and lymphatic system disorders (SOC, SAEs)	276	– 18 (6.5)	275	– 0 (0.0)	36.87 [2.23; 608.72]; < 0.001
Gastrointestinal disorders (SOC, severe AEs[f])	276	– 20 (7.2)	275	– 4 (1.5)	4.98 [1.73; 14.39]; < 0.001
Investigations (SOC, SAEs)	276	– 10 (3.6)	275	– 1 (0.4)	9.96 [1.28; 77.31]; 0.006

a. Indication of absolute difference (AD) only in case of statistically significant difference; own calculation
b. Cisplatin/ carboplatin
c. Mortality data refer to the number of randomised patients. Data on side effects refer to the number of randomised patients in the intervention vs control arm who received at least 1 dose of study treatment (276 vs 275 patients).
d. For the endpoints of the side effects category: own calculation of RR, 95% CI and p value (unconditional exact test, CSZ method according to [22])
e. Analysis by log-rank test, stratified by descent (Chinese/ Asian vs non-Chinese/ Asian vs non-Asian), WHO PS (0 vs 1) and method of tissue testing (central vs local).
f. Operationalised as CTCAE grade ≥ 3
g. Discontinuation of at least one component
h. PT collection of the pharmaceutical company (PTs included: acute interstitial pneumonitis, alveolitis, diffuse alveolar damage, idiopathic pulmonary fibrosis, interstitial lung disease, lung disease, organising pneumonia, pneumonitis, pulmonary toxicity and pulmonary fibrosis; of which the following PTs occurred: interstitial lung disease, pneumonitis, organising pneumonia)
i. Operationalised via the SMQs heart failure and cardiomyopathy
j. Number of patients who were taken into account in the evaluation for calculating the effect estimate; the values at start of study can be based on other patient numbers.
k. MMRM (contains data at all survey time points up to and including week 100) with treatment, visit and interaction from treatment and visit as fixed effects as well as baseline value as covariate and interaction between baseline and visit
l. Lower (decreasing) values mean better symptomatology; negative effects (intervention minus comparison) mean an advantage for the intervention (scale range: 0 to 100).
m. Higher (increasing) values mean better health status/ better health-related quality of life; positive effects (intervention minus comparison) mean an advantage for the intervention (scale range: 0 to 100).
n. Number of patients with event

AD = absolute difference; CTCAE = Common Terminology Criteria for Adverse Events; HR = hazard ratio; CI = confidence interval; N = number of patients evaluated; n = number of patients with (at least one) event; n.c. = not calculable; n.r. = not reached; vs = versus

2. Number of patients or demarcation of patient groups eligible for treatment

<u>Adults with advanced NSCLC whose tumours have EGFR exon 19 deletions or exon 21 (L858R) substitution mutations; first-line treatment</u>

Approx. 840 – 2,720 patients

3. Requirements for a quality-assured application

The requirements in the product information are to be taken into account. The European Medicines Agency (EMA) provides the contents of the product information (summary of

product characteristics, SmPC) for Tagrisso (active ingredient: osimertinib) at the following publicly accessible link (last access: 4 October 2024):

https://wyww.ema.europa.eu/en/documents/product-information/tagrisso-epar-product-information_en.pdf

Treatment with osimertinib may only be initiated and monitored by specialists in internal medicine, haematology and oncology who are experienced in the treatment of patients with non-small cell lung cancer, as well as specialists in internal medicine and pulmonology or specialists in pulmonary medicine and doctors from other specialist groups participating in the Oncology Agreement.

If the use of osimertinib is considered, EGFR mutational status must be determined using a validated assay.

4. Treatment costs

Annual treatment costs:

The annual treatment costs shown refer to the first year of treatment.

Adults with advanced NSCLC whose tumours have EGFR exon 19 deletions or exon 21 (L858R) substitution mutations; first-line treatment

Designation of the therapy	Annual treatment costs/ patient
Medicinal product to be assessed: Osimertinib in combination with pemetrexed and platinum-based chemotherapy	
Osimertinib + pemetrexed + cisplatin	
Osimertinib	€ 66,095.17
Pemetrexed	€ 18,617.48
Cisplatin	€ 461.88
Total	€ 85,174.53
Additionally required SHI services	€ 264.62 - € 323.03
Osimertinib + pemetrexed + carboplatin	
Osimertinib	€ 66,095.17
Pemetrexed	€ 18,617.48
Carboplatin	€ 1,451.04
Total	€ 86,163.69
Additionally required SHI services	€ 133.64 - € 186.93
Appropriate comparator therapy:	
Afatinib (only for patients with the activating EGFR exon 19 deletion mutation)	
Afatinib	€ 30,932.71
Osimertinib as monotherapy	

Designation of the therapy	Annual treatment costs/ patient
Osimertinib	€ 66,095.17

Costs after deduction of statutory rebates (LAUER-TAXE®) as last revised: 1 January 2025

Other SHI services:

Designation of the therapy	Type of service	Costs/ unit	Number/ cycle	Number/ patient/ year	Costs/ patient/ year
Medicinal product to be assessed: Osimertinib in combination with pemetrexed and platinum-based chemotherapy					
Osimertinib + pemetrexed + cisplatin					
Pemetrexed	Surcharge for production of a parenteral preparation containing cytostatic agents	€ 100	1	17.4	€ 1,740
Cisplatin	Surcharge for production of a parenteral preparation containing cytostatic agents	€ 100	1	4	€ 400
Osimertinib + pemetrexed + carboplatin					
Pemetrexed	Surcharge for production of a parenteral preparation containing cytostatic agents	€ 100	1	17.4	€ 1,740
Carboplatin	Surcharge for production of a parenteral preparation containing cytostatic agents	€ 100	1	4	€ 400

5. Designation of medicinal products with new active ingredients according to Section 35a, paragraph 3, sentence 4 SGB V that can be used in a combination therapy with the assessed medicinal product

In the context of the designation of medicinal products with new active ingredients pursuant to Section 35a, paragraph 3, sentence 4 SGB V, the following findings are made:

Adults with advanced NSCLC whose tumours have EGFR exon 19 deletions or exon 21 (L858R) substitution mutations; first-line treatment

- No medicinal product with new active ingredients that can be used in a combination therapy and fulfils the requirements of Section 35a, paragraph 3, sentence 4 SGB V.

The designation of combinations exclusively serves the implementation of the combination discount according to Section 130e SGB V between health insurance funds and pharmaceutical companies. The findings made neither restrict the scope of treatment required to fulfil the medical treatment mandate, nor do they make statements about expediency or economic feasibility.

II. The resolution will enter into force on the day of its publication on the website of the G-BA on 6 February 2025.

The justification to this resolution will be published on the website of the G-BA at www.g-ba.de.

Berlin, 6 February 2025

Federal Joint Committee (G-BA)
in accordance with Section 91 SGB V
The Chair

Prof. Hecken