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, EGFR mutations, adjuvant treatment)

of 16 December 2021

At its session on 16 December 2021, 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 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. 4 to the information on the benefit assessment of Osimertinib in accordance with the resolution of 17 January 2019:

Osimertinib

Resolution of: 16 December 2021
Entry into force on: 16 December 2021
Federal Gazette, BAnz AT DD. MM YYYY Bx

New therapeutic indication (according to the marketing authorisation of 21 May 2021):

TAGRISSO as monotherapy is indicated for the adjuvant treatment after complete tumour resection in adult patients with stage IB-IIIA non-small cell lung cancer (NSCLC) whose tumours have epidermal growth factor receptor (EGFR) exon 19 deletions or exon 21 (L858R) substitution mutations.

Therapeutic indication of the resolution (resolution of 16 December 2021):

see therapeutic indication according to marketing authorisation

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

a) Adult patients with stage IB-IIIA non-small cell lung cancer (NSCLC), whose tumours have epidermal growth factor receptor (EGFR) exon 19 deletions or exon 21 (L858R) substitution mutations for adjuvant treatment after complete tumour resection and who are eligible for adjuvant platinum-based chemotherapy.

Appropriate comparator therapy for Osimertinib as monotherapy:

- Monitoring wait-and-see approach (only for adult patients in stage IB)

or

- Systemic antineoplastic medicinal treatment according to doctor's instructions

Extent and probability of the additional benefit of Osimertinib as monotherapy compared to the appropriate comparator therapy:

An additional benefit is not proven.

b) Adult patients with stage IB-IIIA non-small cell lung cancer (NSCLC), whose tumours have epidermal growth factor receptor (EGFR) exon 19 deletions or exon 21 (L858R) substitution mutations for adjuvant treatment after complete tumour resection, after prior adjuvant platinum-based chemotherapy or who are ineligible for these.

Appropriate comparator therapy for Osimertinib as monotherapy:

- Monitoring wait-and-see approach

Extent and probability of the additional benefit of Osimertinib as monotherapy compared to monitoring wait-and-see approach:

Indication of non-quantifiable additional benefit

Study results according to endpoints:[1]

a) Adult patients with stage IB-IIIA non-small cell lung cancer (NSCLC), whose tumours have epidermal growth factor receptor (EGFR) exon 19 deletions or exon 21 (L858R) substitution mutations for adjuvant treatment after complete tumour resection and who are eligible for adjuvant platinum-based chemotherapy.

No data available.

Summary of results for relevant clinical endpoints

Endpoint category	Direction of effect/ risk of bias	Summary
Mortality	∅	There are no usable data for the benefit assessment.
Morbidity	∅	There are no usable data for the benefit assessment.
Health-related quality of life	∅	There are no usable data for the benefit assessment.
Side effects	∅	There are no usable data for the benefit assessment.
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 ∅: There are no usable data for the benefit assessment. n.a.: not assessable		

b) Adult patients with stage IB-IIIA non-small cell lung cancer (NSCLC), whose tumours have epidermal growth factor receptor (EGFR) exon 19 deletions or exon 21 (L858R) substitution mutations for adjuvant treatment after complete tumour resection, after prior adjuvant platinum-based chemotherapy or who are ineligible for these.

[1] Data from the dossier assessment of the Institute for Quality and Efficiency in Health Care (IQWiG) (A21-86) unless otherwise indicated.

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	↑↑	Advantages in the endpoints of recurrence rates and disease-free survival
Health-related quality of life	↓	Disadvantage in the physical component score of the SF-36v2
Side effects	↓↓	Disadvantages in the endpoints severe AEs (CTCAE grade ≥ 3), therapy discontinuation due to AEs, as well as in detail for 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
∅: There are no usable data for the benefit assessment.
n.a.: not assessable

ADAURA study

Study design: randomised, multicentre, double-blind

Comparison: osimertinib **vs** placebo

Mortality

Endpoint	**Osimertinib**		**Placebo**		Osimertinib vs placebo
	N	Median survival time in months [95% CI] *Patients with event n (%)*	N	Median survival time in months [95% CI] *Patients with event n (%)*	HR [95% CI] p-value Absolute
Overall survival					
	339	n.a. *9 (2.7)*	343	- *20 (5.8)*	0.48 [0.23; 1.02] 0.055

Morbidity

Endpoint	**Osimertinib**		**Placebo**		Osimertinib vs placebo
	N	Median time to event in months [95% CI] *Patients with event n (%)*	N	Median time to event in months [95% CI] *Patients with event n (%)*	HR [95% CI] p-value Absolute difference (AD)[a]
Recurrences					
Recurrence rate	339	– *37 (10.9)*	343	– *159 (46.4)*	RR: 0.24 [0.17; 0.32] < 0.001
Local / regional	339	– *23 (6.8)*	343	– *61 (17.8)*	–
Remote recurrence	339	– *10 (2.9)*	343	– *78 (22.7)*	–
CNS recurrences	339	– *4 (1.2)*	343	– *33 (9.6)*	–
Local / regional and remote recurrence	339	– *4 (1.2)*	343	– *18 (5.2)*	–
Death	339	– *0 (0)*	343	– *2 (0.6)*	–
Disease-free survival	339	n.a. *37 (10.9)*	343	27.5 [22.0; 35.0] *159 (46.4)*	0.20 [0.15; 0.27] < 0.001

Health-related quality of life

Endpoint	**Osimertinib**		**Placebo**		Osimertinib vs placebo
	N	Median time to event in months [95% CI] *Patients with event n (%)*	N	Median time to event in months [95% CI] *Patients with event n (%)*	HR [95% CI] p-value Absolute difference (AD)[a]
SF-36v2					
Physical component score (PCS)	339	n.a. *19 (5.6)*	343	n.a. *8 (2.3)*	2.21 [1.04; 4.70] 0.040
Mental component score (MCS)	339	n.a. *30 (8.8)*	343	n.a. *27 (7.9)*	1.02 [0.60; 1.71] 0.950

Side effects

Endpoint	**Osimertinib**		**Placebo**		Osimertinib vs placebo
	N	Median time to event in months [95% CI] *Patients with event n (%)*	N	Median time to event in months [95% CI] *Patients with event n (%)*	Effect estimator [95% CI] p-value Absolute difference (AD)[a]
Adverse events (presented additionally)					
	337	0.4 [0.3; 0.5] *329 (97.6)*	343	1.0 [0.7; 1.1] *306 (89.2)*	
Serious adverse events (SAEs)					
	337	n.a. *54 (16.0)*	343	n.a. *42 (12.2)*	1.21 [0.81; 1.81] 0.343
Severe adverse events (CTCAE grade ≥ 3)					
	337	n.a. *68 (20.2)*	343	n.a. *46 (13.4)*	1.46 [1.01; 2.10] 0.045
Discontinuation due to AEs					
	337	n.a. *37 (11.0)*	343	n.a. *10 (2.9)*	3.08 [1.73; 5.45] < 0.001

Endpoint	Osimertinib		Placebo		Osimertinib vs placebo
	N	Median time to event in months [95% CI] *Patients with event n (%)*	N	Median time to event in months [95% CI] *Patients with event n (%)*	Effect estimator [95% CI] p-value Absolute difference (AD)[a]
Specific adverse events					
Skin and subcutaneous tissue disorders (SOC, AEs)	337	2.8 [1.9; 5.3] *238 (70.6)*	343	n.a. *122 (35.6)*	2.72 [2.20; 3.36] < 0.001
ILD and pneumonitis[c] (PT, SAEs)	337	n.a. *1 (0.3)*	343	n.a. *0 (0)*	n.d.
Cardiac events[d] (severe AEs[e])	337	n.a. *3 (0.9)*	343	n.a. *1 (0.3)*	2.53 [0.35; 18.05] 0.355
Gastrointestinal disorders (SOC, AEs)	337	1.9 [1.1; 2.6] *239 (70.9)*	343	26,9 [19,2; n.c.] *149 (43.4)*	2.29 [1.87; 2.81]; < 0.001 AD: - 25 months
Included therein:					
Diarrhoea (PT, AEs)	337	34,9 [14,3; n.c.] *156 (46.3)*	343	n.a. *68 (19.8)*	2.69 [2.07; 3.50] < 0.001
Mouth ulcer (PT, AEs)	337	n.a. *39 (11.6)*	343	n.a. *8 (2.3)*	3.88 [2.19; 6.88] < 0.001
Stomatitis (PT, AEs)	337	n.a. *59 (17.5)*	343	n.a. *14 (4.1)*	3.73 [2.36; 5.90] < 0.001
Gastrointestinal disorders (SOC, severe AEs)	337	n.a. *17 (5.0)*	343	n.a. *3 (0.9)*	4.12 [1.71; 9.90] 0.002
Paronychia (PT, AEs)	337	n.a. *85 (25.2)*	343	n.a. *5 (1.5)*	6.79 [4.49; 10.27] < 0.001
Decreased appetite (PT, AEs)	337	n.a. *44 (13.1)*	343	n.a. *13 (3.8)*	3.12 [1.85; 5.24] < 0.001

[a] Indication of absolute difference (AD) only in case of statistically significant difference; own calculation
[b] Information by the pharmaceutical entrepreneur, dossier dated 18.06.2021, module 4 A

Endpoint	Osimertinib		Placebo		Osimertinib vs placebo
	N	Median time to event in months [95% CI] *Patients with event n (%)*	N	Median time to event in months [95% CI] *Patients with event n (%)*	Effect estimator [95% CI] p-value Absolute difference (AD)[a]

[c] PT collection of the pharmaceutical company (PTs included: interstitial lung disease, pneumonitis, acute interstitial pneumonitis, alveolitis, diffuse alveolar damage, idiopathic pulmonary fibrosis, lung disease, pulmonary toxicity and pulmonary fibrosis).
[d] Operationalised via the SMQ cardiac insufficiency and the SMQ cardiomyopathy.
[e] Operationalised as CTCAE grade ≥ 3.

Abbreviations used:

AD = absolute difference; CTCAE = Common Terminology Criteria for Adverse Events; HR = hazard ratio; ILD: interstitial lung disease; CI = confidence interval; MCS: mental component score; N = number of patients evaluated; n = number of patients with (at least one) event; n.c. = not calculable; n.a. = not achieved; NE = not estimable; PT = preferred term; PCS = physical component score; RR = relative risk; SF-36v2 = short form-36 health survey version 2; SMQ = standardised MedDRA query; SOC = system organ class; SAE = serious adverse event; AE = adverse event; vs = versus; CNS = central nervous system

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

a) Adult patients with stage IB-IIIA non-small cell lung cancer (NSCLC), whose tumours have epidermal growth factor receptor (EGFR) exon 19 deletions or exon 21 (L858R) substitution mutations for adjuvant treatment after complete tumour resection and who are eligible for adjuvant platinum-based chemotherapy.

approx. 640 - 930 patients

b) Adult patients with stage IB-IIIA non-small cell lung cancer (NSCLC), whose tumours have epidermal growth factor receptor (EGFR) exon 19 deletions or exon 21 (L858R) substitution mutations for adjuvant treatment after complete tumour resection, after prior adjuvant platinum-based chemotherapy or who are ineligible for these.

approx. 640 - 930 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: 22 September 2021):
https://www.ema.europa.eu/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:

a) Adult patients with stage IB-IIIA non-small cell lung cancer (NSCLC), whose tumours have epidermal growth factor receptor (EGFR) exon 19 deletions or exon 21 (L858R) substitution mutations for adjuvant treatment after complete tumour resection and who are eligible for adjuvant platinum-based chemotherapy.

Designation of the therapy	Annual treatment costs/ patient
Medicinal product to be assessed:	
Osimertinib	€ 70,637.96
Appropriate comparator therapy:	
Monitoring wait-and-see approach (only for adult patients in stage IB)	incalculable
Systemic antineoplastic medicinal treatment according to doctor's instructions	different from patient to patient

Costs after deduction of statutory rebates (LAUER-TAXE® as last revised: 1 December 2021)

Costs for additionally required SHI services: not applicable

b) Adult patients with stage IB-IIIA non-small cell lung cancer (NSCLC), whose tumours have epidermal growth factor receptor (EGFR) exon 19 deletions or exon 21 (L858R) substitution mutations for adjuvant treatment after complete tumour resection, after prior adjuvant platinum-based chemotherapy or who are ineligible for these.

Designation of the therapy	Annual treatment costs/ patient
Medicinal product to be assessed:	
Osimertinib	€ 70,637.96
Appropriate comparator therapy:	
Monitoring wait-and-see approach	incalculable

Costs after deduction of statutory rebates (LAUER-TAXE® as last revised: 1 December 2021)

Costs for additionally required SHI services: not applicable

II. Entry into force

1. **The resolution will enter into force on the day of its publication on the website of the G-BA on 16 December 2021.**
2. **The period of validity of the resolution is limited to 1 July 2024.**

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

Berlin, 16 December 2021

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

Prof. Hecken