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: Atezolizumab (new therapeutic indication: non-small cell lung cancer, PD-L1 expression ≥ 50% on TC or ≥ 10% on IC, EGFR/ALK-negative, first-line)

of 19 November 2021

At its session on 19 November 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 last amended by the publication of the resolution of DD. 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 atezolizumab in accordance with the resolution of 20 May 2021:**

Atezolizumab

Resolution of: 19 November 2021
Entry into force on: 19 November 2021
Federal Gazette, BAnz AT DD. MM YYYY Bx

New therapeutic indication (according to the marketing authorisation of 30 April 2021):

Tecentriq as monotherapy is indicated for the first-line treatment of adult patients with metastatic NSCLC whose tumours have a PD-L1 expression ≥ 50% tumour cells (TC) or ≥ 10% tumour-infiltrating immune cells (IC) and who do not have EGFR mutant or ALK-positive NSCLC.

Therapeutic indication of the resolution (resolution from 19 November 2021):

see new therapeutic indication according to marketing authorisation

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

a) Adults with metastatic, non-small cell lung cancer (NSCLC), whose tumours have PD-L1 expression ≥ 50% of the tumour cells and who do not have EGFR mutant or ALK-positive NSCLC; first-line

Appropriate comparator therapy:

– Pembrolizumab as monotherapy

Extent and probability of the additional benefit of atezolizumab compared to pembrolizumab:

An additional benefit is not proven.

b) Adults with metastatic, non-small cell lung cancer (NSCLC), whose tumours have PD-L1 expression < 50% of the tumour cells and PD-L1 expression ≥ 10% of the tumour-infiltrating immune cells and who do not have EGFR mutant or ALK-positive NSCLC; first-line

Appropriate comparator therapy:

- Cisplatin in combination with a third-generation cytostatic (vinorelbine or gemcitabine or docetaxel or paclitaxel or pemetrexed (except in the case of predominantly squamous histology))

  or

- Carboplatin in combination with a third-generation cytostatic agent (vinorelbine or gemcitabine or docetaxel or paclitaxel or pemetrexed (except in the case of predominantly squamous histology)) cf. Annex VI to Section K of the Pharmaceuticals Directive

  or

- Carboplatin in combination with nab-paclitaxel

  or

- Pembrolizumab in combination with pemetrexed and platinum-containing chemotherapy (only for adults with non-squamous histology)

  or

- Pembrolizumab in combination with carboplatin and either paclitaxel or nab-paclitaxel (only for adults with squamous histology)

  or

- Monotherapy with gemcitabine or vinorelbine (only for adults with ECOG performance status 2 as an alternative to platinum-based combination treatment)

Extent and probability of the additional benefit of atezolizumab compared to the appropriate comparator therapy:

An additional benefit is not proven.

Study results according to endpoints:[1]

a) Adults with metastatic, non-small cell lung cancer (NSCLC), whose tumours have PD-L1 expression ≥ 50% of the tumour cells and who do not have EGFR mutant or ALK-positive NSCLC; first-line

Summary of results for relevant clinical endpoints

Endpoint category	Direction of effect/ risk of bias	Summary
Mortality	↔	No difference in overall survival.
Morbidity	n.a.	There are no assessable data.
Health-related quality of life	n.a.	There are no assessable data.
Side effects	↔	No relevant difference 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

Adjusted indirect comparison

– *Intervention versus bridge comparator: IMpower110 phase III study (GO29431)*

  Atezolizumab versus platinum-based chemotherapy (pemetrexed + carboplatin or cisplatin (non-squamous only); gemcitabine + carboplatin or cisplatin (squamous only)); data cut-off from 10 September 2018

  Sub-population with a tumour proportion score [TPS] ≥ 50% or PD-L1 expression ≥ 50% of the tumour cells according to the PD-L1 IHC 22C3 test relative to the total IMpower110 study population without ALK or EGFR aberrations

– *Appropriate comparator therapy versus bridge comparator: KEYNOTE 024 and KEYNOTE 042*
  phase III studies

  KEYNOTE 024: Pembrolizumab versus platinum-based chemotherapy (pemetrexed + cisplatin or carboplatin (non-squamous only), gemcitabine + cisplatin or carboplatin, paclitaxel + carboplatin); data cut-off from 9 May 2016

  Only adults with a tumour proportion score [TPS] ≥ 50% or PD-L1 expression ≥ 50% of the tumour cells according to PD-L1 IHC 22C3 test were included in the study.

[1] Data from the dossier assessment of the IQWiG (A21-69: version 2.0) and from the addendum (A21-133), unless otherwise indicated.

KEYNOTE 042: Pembrolizumab versus platinum-based chemotherapy (pemetrexed + carboplatin (non-squamous only), paclitaxel + carboplatin); data cut-off from 26 February 2018

Sub-population with a tumour proportion score [TPS] ≥ 50% or PD-L1 expression ≥ 50% of the tumour cells according to PD-L1 IHC 22C3 test.

Mortality

Endpoint	**Atezolizumab (intervention) or pembrolizumab (appropriate comparator therapy)**		**Platinum-based chemotherapy (bridge comparator)**		Group difference
	N	Median survival time in months [95% CI] *Patients with event n (%)*	N	Median survival time in months [95% CI] *Patients with event n (%)*	Hazard ratio [95% CI] p-value
Overall survival					
Intervention versus bridge comparator					
IMpower110	134	20.2 [13.3; n.c.] *53 (39.6)*	126	11.0 [8.8; 16.5] *67 (53.2)*	0.57 [0.39; 0.82] 0.002[a]
Appropriate comparator therapy versus bridge comparator					
KEYNOTE 024	154	n.a. *44 (28.6)*	151	n.a. [9.4; n.c.] *64 (42.4)*	0.60 [0.41; 0.89] 0.010[b]
KEYNOTE 042	299	20.0 [15.4; 24.9] *n.d.*	300	12.2 [10.4; 14.2] *n.d.*	0.69 [0.56; 0.85] < 0.001[c]
Total					0.67 [0.56; 0.80]; < 0.001[d]
Indirect comparison via bridge comparator (according to Bucher): Atezolizumab versus pembrolizumab					0.85 [0.56; 1.29] 0.449[e]

Morbidity

Endpoint	**Atezolizumab (intervention) or pembrolizumab (appropriate comparator therapy)**		**Platinum-based chemotherapy (bridge comparator)**		Group difference
	N	Median time in months [95% CI] *Patients with event n (%)*	N	Median time in months [95% CI] *Patients with event n (%)*	Hazard ratio [95% CI] p-value
Health status (EQ-5D VAS)					
There are no assessable data.[f]					
Symptomatology (EORTC QLQ-C30, EORTC QLQ-LC13)					
There are no assessable data.[f]					

Health-related quality of life

Health-related quality of life (EORTC QLQ-C30, EORTC QLQ-LC13)
There are no assessable data.[f]

Side effects

Endpoint	**Atezolizumab (intervention) or pembrolizumab (appropriate comparator therapy)**		**Platinum-based chemotherapy (bridge comparator)**		Group difference
	N	Median time in months [95% CI] *Patients with event n (%)*	N	Median time in months [95% CI] *Patients with event n (%)*	Hazard ratio [95% CI] p-value
Total adverse events (AE) (presented additionally)					
Intervention versus bridge comparator					
IMpower110	134	n.d. *118 (88.1)*	114	n.d. *104 (91.2)*	-
Appropriate comparator therapy versus bridge comparator					
KEYNOTE 024	154	n.d. *148 (96.1)*	150	n.d. *145 (96.7)*	-
KEYNOTE 042	299	n.d.	300	n.d.	-

(continuation)

Endpoint	Atezolizumab (intervention) or pembrolizumab (appropriate comparator therapy)		Platinum-based chemotherapy (bridge comparator)		Group difference
	N	Median time in months [95% CI] *Patients with event n (%)*	N	Median time in months [95% CI] *Patients with event n (%)*	Hazard ratio [95% CI] p-value
Serious adverse events (SAE)					
Intervention versus bridge comparator					
IMpower110	134	n.d. *39 (29.1)*	114	n.d. *31 (27.2)*	0.87 [0.54; 1.41]; 0.579[g]
Appropriate comparator therapy versus bridge comparator					
KEYNOTE 024	154	n.d. *68 (44.2)*	150	n.d. *66 (44.0)*	1.00 [0.71; 1.41] 0.994[b]
KEYNOTE 042	299	n.d.	300	n.d.	n.d.
Total					-
Indirect comparison via bridge comparator (according to Bucher): Atezolizumab versus pembrolizumab					0.87 [0.48; 1.57] 0.645[e]
Severe adverse events (CTCAE grade ≥ 3)					
Intervention versus bridge comparator					
IMpower110	134	n.d. *43 (32.1)*	114	n.d. *62 (54.4)*	0.37 [0.25; 0.56] < 0.001[g]
Appropriate comparator therapy versus bridge comparator					
KEYNOTE 024	154	n.d. *82 (53.2)*	150	n.d. *109 (72.7)*	0.49 [0.36; 0.66]; < 0.001[b]
KEYNOTE 042	299	n.d.	300	n.d.	n.d.
Indirect comparison via bridge comparator (according to Bucher): Atezolizumab versus pembrolizumab					0.76 [0.46; 1.25] 0.282[e]

(continuation)

Endpoint	Atezolizumab (intervention) or pembrolizumab (appropriate comparator therapy)		Platinum-based chemotherapy (bridge comparator)		Group difference
	N	Median time in months [95% CI] *Patients with event n (%)*	N	Median time in months [95% CI] *Patients with event n (%)*	Hazard ratio [95% CI] p-value
Therapy discontinuations due to AE					
Intervention versus bridge comparator					
IMpower110	134	n.d. *5 (3.7)*	114	n.d. *25 (21.9)*	0.12 [0.05; 0.32] < 0.001[g]
Appropriate comparator therapy versus bridge comparator					
KEYNOTE 024	154	n.d. *14 (9.1)*	150	n.d. *21 (14)*	0.60 [0.31; 1.19] 0.144[b]
KEYNOTE 042	299	n.d.	300	n.d.	n.d.
Indirect comparison via bridge comparator (according to Bucher): Atezolizumab versus pembrolizumab					0.20 [0.06; 0.63] 0.0007[e]
Immune-mediated AEs					
No usable data available					

a HR and 95% CI: Cox regression model, stratified by sex and baseline ECOG-PS, p-value from log-rank test
b HR and 95% CI: Cox regression model, stratified by geographic region, ECOG-PS and histology, p-value from Wald test
c HR and 95% CI: Cox regression model, stratified by geographic region, ECOG-PS and histology, p-value from log-rank test
d IQWiG calculation; fixed-effect meta-analysis (inverse variance)
e IQWiG calculations
f No adjusted indirect comparison feasible as no results are available for at least 1 edge of the indirect comparison.
g HR and 95% CI: unstratified analysis, p-value from log-rank test

Abbreviations used:
AD = Absolute Difference; CTCAE = Common Terminology Criteria for Adverse Events; EORTC: European Organisation for Research and Treatment of Cancer; EQ-5D: European Quality of Life Questionnaire 5 Dimensions; HR = hazard ratio; n.d.: no data available; CI = confidence interval; N = number of patients evaluated; n = number of patients with (at least one) event; n.c. = not calculable; n.a. = not achieved; QLQ-C30: Quality of Life Questionnaire – Cancer 30; QLQ-LC13: Quality of Life Questionnaire – Lung Cancer 13; VAS: visual analogue scale; vs = versus

b) Adults with metastatic, non-small cell lung cancer (NSCLC), whose tumours have PD-L1 expression < 50% of the tumour cells and PD-L1 expression ≥ 10% of the tumour-infiltrating immune cells and who do not have EGFR mutant or ALK-positive NSCLC; first-line

No data are available to allow an assessment of the additional benefit.

Summary of results for relevant clinical endpoints

Endpoint category	Direction of effect/ risk of bias	Summary
Mortality	∅	No data available.
Morbidity	∅	No data available.
Health-related quality of life	∅	No data available.
Side effects	∅	No data available.

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

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

a) Adults with metastatic, non-small cell lung cancer (NSCLC), whose tumours have PD-L1 expression ≥ 50 % of the tumour cells and who do not have EGFR mutation or ALK-positive NSCLC; first-line

approx. 3,940 – 4,430 patients

b) Adults with metastatic, non-small cell lung cancer (NSCLC), whose tumours have PD-L1 expression < 50% of the tumour cells and PD-L1 expression ≥ 10% of the tumour-infiltrating immune cells and who do not have EGFR mutant or ALK-positive NSCLC; first-line

approx. 580 – 650 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 Tecentriq (active ingredient: atezolizumab) at the following publicly accessible link (last access: 2 September 2021):

https://www.ema.europa.eu/en/documents/product-information/tecentriq-epar-product-information_en.pdf

Treatment with atezolizumab may only be initiated and monitored by specialists in internal medicine, haematology and oncology who are experienced in the treatment of adult 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.

Patients are to be selected for treatment with atezolizumab as monotherapy on the basis of tumour PD-L1 expression, confirmed by a validated test.

According to the requirements for risk minimisation activities in the EPAR (European Public Assessment Report), the pharmaceutical company must provide the following information material on atezolizumab:

- training material for health professionals
- patient pass

The training material contains, in particular, instructions on the management of immune-mediated side effects potentially occurring with atezolizumab as well as on infusion-related reactions.

4. Treatment costs

Annual treatment costs:

a) Adults with metastatic, non-small cell lung cancer (NSCLC), whose tumours have PD-L1 expression ≥ 50% of the tumour cells and who do not have EGFR mutant or ALK-positive NSCLC; first-line

Designation of the therapy	Annual treatment costs/ patient
Medicinal product to be assessed:	
Atezolizumab	€ 67,766.91 - € 71,590.73
Appropriate comparator therapy:	
Pembrolizumab	€ 99,706.18

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

Costs for additionally required SHI services: not applicable

Other SHI services:

Designation of therapy	Type of service	Costs/ unit	Number/ cycle	Number/ patient/ year	Costs/ patient/ year
Medicinal product to be assessed:					
Atezolizumab	Surcharge for the preparation of a parenteral solution containing monoclonal antibodies	€ 71	1	13 – 26.1	€ 923 - € 1,853.10
Appropriate comparator therapy:					
Pembrolizumab	Surcharge for the preparation of a parenteral solution containing monoclonal antibodies	€ 71	1	8.7 - 17.4	€ 617.70 - € 1,235.40

b) <u>Adults with metastatic, non-small cell lung cancer (NSCLC), whose tumours have PD-L1 expression < 50% of the tumour cells and PD-L1 expression ≥ 10% of the tumour-infiltrating immune cells and who do not have EGFR mutant or ALK-positive NSCLC; first-line</u>

Designation of the therapy	Annual treatment costs/ patient
Medicinal product to be assessed:	
Atezolizumab	€ 67,766.91 - € 71,590.73
Appropriate comparator therapy:	
Cisplatin in combination with a third-generation cytostatic (vinorelbine or gemcitabine or docetaxel or paclitaxel or pemetrexed (except in the case of predominantly squamous histology))	
Cisplatin + docetaxel	
Cisplatin	€ 2,007.44
Docetaxel	€ 21,230.61
Total:	€ 23,238.05
Additionally required SHI costs	€ 328.58 - € 421.62
Cisplatin + gemcitabine	
Cisplatin	€ 2,007.44 - € 2,486.11
Gemcitabine	€ 8,193.66
Total:	€ 10,201.10 - € 10,679.77

Designation of the therapy	Annual treatment costs/ patient
Additionally required SHI costs	€ 328.58 - € 421.62
Cisplatin + paclitaxel	
Cisplatin	€ 2,271.74
Paclitaxel	€ 17,473.78
Total:	€ 19,745.52
Additionally required SHI costs	€ 582.78 - € 675.82
Cisplatin + pemetrexed	
Cisplatin	€ 2,007.44
Pemetrexed	€ 9,213.30
Total:	€ 11,220.74
Additionally required SHI costs	€ 455.34 - € 595.97
Cisplatin + vinorelbine	
Cisplatin	€ 2,007.44 - € 2,486.11
Vinorelbine	€ 4,716.97 - € 5,686.32
Total:	€ 6,724.40 - € 8,172.43
Additionally required SHI costs	€ 328.58 - € 421.62
Carboplatin in combination with a third-generation cytostatic agent (vinorelbine or gemcitabine or docetaxel or paclitaxel or pemetrexed (except in the case of predominantly squamous histology)) cf. Annex VI to Section K of the Pharmaceuticals Directive	
Carboplatin + docetaxel	
Carboplatin	€ 8,209,32
Docetaxel	€ 21,230.61
Total:	€ 29,439.93
Carboplatin + gemcitabine	
Carboplatin	€ 8,209,32
Gemcitabine	€ 8,193.66
Total:	€ 16,402.98
Carboplatin + paclitaxel	
Carboplatin	€ 8,209,32
Paclitaxel	€ 17,473.78
Total:	€ 25,683.10
Additionally required SHI costs	€ 254.20
Carboplatin + pemetrexed	
Carboplatin	€ 8,209,32
Pemetrexed	€ 9,213.30
Total:	€ 17,422.62

Designation of the therapy	Annual treatment costs/ patient
Additionally required SHI costs	€ 126.76 - € 174.35
Carboplatin + vinorelbine	
Carboplatin	€ 8,209,32
Vinorelbine	€ 4,716.97 - € 5,686.32
Total:	€ 12,926.29 - € 13,895.64
Carboplatin in combination with nab-paclitaxel	
Carboplatin	€ 8,209.32
nab-paclitaxel	€ 39,088.40
Total	€ 47,297.72
Pembrolizumab in combination with pemetrexed and platinum-containing chemotherapy (only for adults with non-squamous histology)	
Pembrolizumab + pemetrexed + cisplatin	
Pembrolizumab	€ 99,706.18
Pemetrexed	€ 9,213.30
Cisplatin	€ 2,007.44
Total:	€ 110,926.91
Additionally required SHI costs	€ 455.34 - € 595.97
Pembrolizumab + pemetrexed + carboplatin	
Pembrolizumab	€ 99,706.18
Pemetrexed	€ 9,213.30
Carboplatin	€ 8,209.32
Total:	€ 117,128.80
Additionally required SHI costs	€ 126.76 - € 174.34
Pembrolizumab in combination with carboplatin and either paclitaxel or nab-paclitaxel (only for adults with squamous histology)	
Pembrolizumab + carboplatin + paclitaxel	
Pembrolizumab	€ 99,706.18
Carboplatin	€ 8,209,32
Paclitaxel	€ 17,473.78
Total:	€ 125,389.28
Additionally required SHI costs	€ 254.20
Pembrolizumab + carboplatin + nab-paclitaxel	
Pembrolizumab	€ 99,706.18
Carboplatin	€ 8,209.32
nab-paclitaxel	€ 39,088.40
Total:	€ 147,003.90

Designation of the therapy	Annual treatment costs/ patient
Monotherapy with gemcitabine or vinorelbine (only for adults with ECOG performance status 2 as an alternative to platinum-based combination treatment)	
Vinorelbine	€ 7,061.89 - € 8,513.14
Gemcitabine	€ 7,156.89

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

Other SHI services:

Designation of therapy	Type of service	Costs/ unit	Number/ cycle	Number/ patient/ year	Costs/ patient/ year
Medicinal product to be assessed:					
Atezolizumab	Surcharge for the preparation of a parenteral solution containing monoclonal antibodies	€ 71	1	13 – 26.1	€ 923 - € 1,853.10
Appropriate comparator therapy:					
Pembrolizumab	Surcharge for the preparation of a parenteral solution containing monoclonal antibodies	€ 71	1	8.7 - 17.4	€ 617.70 - € 1,235.40
Carboplatin	Surcharge for production of a parenteral preparation containing cytostatic agents	€ 81	1	17.4	€ 1,409.40
Cisplatin	Surcharge for production of a parenteral preparation containing cytostatic agents	€ 81	1	17.4	€ 1,409.40
Vinorelbine	Surcharge for production of a parenteral preparation containing cytostatic agents	€ 81	2	34.8	€ 2,818.80
Gemcitabine	Surcharge for production of a parenteral preparation containing cytostatic agents	€ 81	2	34.8	€ 2,818.80
Docetaxel	Surcharge for production of a parenteral preparation containing cytostatic agents	€ 81	1	17.4	€ 1,409.40
Paclitaxel	Surcharge for production of a parenteral preparation containing cytostatic agents	€ 81	1	17.4	€ 1,409.40

Designation of therapy	Type of service	Costs/ unit	Number/ cycle	Number/ patient/ year	Costs/ patient/ year
Pemetrexed	Surcharge for production of a parenteral preparation containing cytostatic agents	€ 81	1	17.4	€ 1,409.40
nab-paclitaxel	Surcharge for production of a parenteral preparation containing cytostatic agents	€ 81	1	52.2	€ 4,228.20
Vinorelbine monotherapy	Surcharge for production of a parenteral preparation containing cytostatic agents	€ 81	2	52.1	€ 4,220.10
Gemcitabine monotherapy	Surcharge for production of a parenteral preparation containing cytostatic agents	€ 81	2	39	€ 3,159.00

II. The resolution will enter into force on the day of its publication on the website of the G-BA on 19 November 2021.

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

Berlin, 19 November 2021

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

Prof. Hecken