Resolution

Gemeinsamer Bundesausschuss

of the Federal Joint Committee (G-BA) on an Amendment of the Pharmaceuticals Directive (AM-RL): Annex XII – Benefit Assessment of Medicinal Products with New Active Ingredients According to Section 35a SGB V Atezolizumab (New Therapeutic Indication: NSCLC, Non-Squamous, First Line, Combination with Nab-Paclitaxel and Carboplatin)

of 2 April 2020

On 2 April 2020, the Federal Joint Committee (G-BA) resolved by written statement to amend the Directive on the Prescription of Medicinal Products in SHI-accredited Medical Care (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 on 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 June 2019:

Atezolizumab

Resolution of: 2 April 2020
Entry into force on: 2 April 2020
Federal Gazette, BAnz AT DD MM YYYY Bx

New therapeutic indication (according to the marketing authorisation of 3 September 2019):

Tecentriq, in combination with nab-paclitaxel and carboplatin, is indicated for the first line treatment of adult patients with metastatic non-squamous NSCLC who do not have EGFR mutant or ALK-positive NSCLC.

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

a) Adult patients with metastatic non-squamous non-small cell lung cancer and a Tumour Proportion Score [TPS] of ≥ 50% (PD-L1 expression) and without EGFR- or ALK-positive tumour mutations; first-line therapy

Appropriate comparator therapy:

- Pembrolizumab as monotherapy

Extent and probability of the additional benefit of atezolizumab + carboplatin + nab-paclitaxel compared with the appropriate comparator therapy:

An additional benefit is not proven

b) Adult patients with metastatic non-squamous non-small cell lung cancer and a Tumour Proportion Score [TPS] of < 50% (PD-L1 expression) and without EGFR- or ALK-positive tumour mutations; first-line therapy

Appropriate comparator therapy:

- Cisplatin in combination with a third-generation cytostatic agent (vinorelbine or gemcitabine or docetaxel or paclitaxel or pemetrexed)

or

- Carboplatin in combination with a third-generation cytostatic agent (vinorelbine or gemcitabine or docetaxel or paclitaxel or pemetrexed) 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 chemotherapy

Extent and probability of the additional benefit of atezolizumab + carboplatin + nab-paclitaxel compared with carboplatin + nab-paclitaxel:

An additional benefit is not proven.

Study results according to endpoints[1]:

a) Adult patients with metastatic non-squamous non-small cell lung cancer and a Tumour Proportion Score [TPS] of ≥ 50% (PD-L1 expression) and without EGFR- or ALK-positive tumour mutations; first-line therapy

There is no data that would allow for the assessment of the additional benefit.

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:
↑: positive statistically significant and relevant effect with low/unclear reliability of data
↓: negative statistically significant and relevant effect with low/unclear reliability of data
↑↑: positive statistically significant and relevant effect with high reliability of data
↓↓: negative statistically significant and relevant 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 metastatic non-squamous non-small cell lung cancer and a Tumour Proportion Score [TPS] of < 50% (PD-L1 expression) and without EGFR- or ALK-positive tumour mutations; first-line therapy

Study IMpower130: Atezolizumab + nab-paclitaxel + carboplatin vs nab-paclitaxel + carboplatin

Relevant sub-populations:

NEoM population (patients with an approximate PD-L1 expression [TPS] < 50% without EGFR- or ALK-positive tumour mutations)
For side effects endpoints: Wild type population (patients without EGFR or ALK positive tumour mutations; including < 20% patients with PD-L1 expression ≥ 50%)

[1] Data from the dossier evaluation of the IQWiG (A19-84) unless otherwise indicated.

Mortality (data cut-off of 4 September 2018)

Endpoint	Atezolizumab + nab-paclitaxel + carboplatin		Nab-paclitaxel + carboplatin		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 (%)*	Hazard Ratio [95% CI] p value Absolute difference (AD)[a]
Overall survival					
	368	18.2 [14.7; 21.1] *222 (60.3)*	186	13.1 [10.4; 17.7] *123 (66.1)*	0.83 [0.66; 1.03] 0.096

Morbidity (data cut-off of 15 March 2018)

Endpoint	Atezolizumab + nab-paclitaxel + carboplatin		Nab-paclitaxel + carboplatin		Intervention vs Control
	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 (%)*	Hazard Ratio [95% CI] p value Absolute difference (AD)[a]
Progression-free survival (PFS)[b]					
	368	7.1 [6.4;8.2]	186	6.5 [5.5;7.9]	0.79 [0.64; 0.96] 0.0204 AD = 0.6 months
EORTC QLQ-C30 symptom scales (time until 1st deterioration)[c]					
Loss of appetite	368	4.2 [3.0; 7.2] *163 (44.3)*	186	7.7 [5.0; 12.1] *69 (37.1)*	1.18 [0.89; 1.57] 0.246
Diarrhoea	368	5.7 [3.5; 26.5] *143 (38.9)*	186	7.3 [2.8; 11.0] *72 (38.7)*	0.86 [0.65; 1.15] 0.317
Dyspnoea	368	4.0 [2.8; 7.2] *162 (44.0)*	186	6.1 [2.9; 11.3] *72 (38.7)*	1.07 [0.81; 1.41] 0.653
Fatigue	368	1.7 [1.4; 2.2] *218 (59.2)*	186	1.7 [1.4; 2.2] *110 (59.1)*	0.99 [0.78; 1.25] 0.914

(Continuation)

Endpoint	Atezolizumab + nab-paclitaxel + carboplatin		Nab-paclitaxel + carboplatin		Intervention vs Control
	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 (%)*	Hazard Ratio [95% CI] p value Absolute difference (AD)[a]
Insomnia	368	12.7 [5.8; n.c.] *130 (35.3)*	186	8.5 [3.5; n.c.] *63 (33.9)*	0.90 [0.66; 1.22] 0.481
Pain	368	6.0 [4.4; 8.4] *167 (45.4)*	186	6.0 [3.6; 11.4] *72 (38.7)*	0.97 [0.73; 1.28] 0.822
Nausea and vomiting	368	3.1 [2.5; 6.8] *170 (46.2)*	186	3.9 [2.5; 6.9] *80 (43.0)*	0.95 [0.73; 1.25] 0.733
Constipation	368	3.7 [2.4; 5.8] *169 (45.9)*	186	4.1 [2.4; 10.1] *78 (41.9)*	1.00 [0.76; 1.31] 0.982
EORTC QLQ-LC13 symptom scales (time until 1st deterioration)[c]					
Alopecia	368	1.0 [0.9; 1.1] *250 (67.9)*	186	0.9 [0.8; 1.0] *125 (67.2)*	0.85 [0.68; 1.07] 0.160
Haemoptysis	368	n.a. *35 (9.5)*	186	n.a. *19 (10.2)*	0.79 [0.45; 1.38] 0.399
Dyspnoea	368	2.4 [2.1; 3.2] *189 (51.4)*	186	2.1 [1.5; 3.1] *96 (51.6)*	0.84 [0.66; 1.09] 0.187
Coughing	368	15.3 [10.0; n.c.] *123 (33.4)*	186	23.5 [15.3; n.c.] *48 (25.8)*	1.20 [0.85; 1.69] 0.294
Mouth pain	368	12.8 [8.2; 19.1] *127 (34.5)*	186	n.a. [9.9; n.c.] *49 (26.3)*	1.22 [0.87; 1.70] 0.242
Peripheral neuropathy	368	3.5 [3.0; 4.0] *181 (49.2)*	186	2.8 [2.4; 3.4] *91 (48.9)*	0.82 [0.64; 1.06] 0.129
Dysphagia	368	23.0 [15.4; n.c.] *96 (26.1)*	186	n.a. *34 (18.3)*	1.32 [0.89; 1.95] 0.168

(Continuation)

Pain (arm/shoulder)	368	8.4 [6.9; 12.9] *133 (36.1)*	186	9.7 [6.9; 24.4] *56 (30.1)*	1.02 [0.74; 1.39] 0.925
Pain (thorax)	368	19.1 [9.3; n.c.] *118 (32.1)*	186	15.2 [6.7; n.c.] *53 (28.5)*	0.99 [0.71; 1.37] 0.943
Pain (other)	368	7.2 [5.5; 11.1] *139 (37.8)*	186	6.9 [3.4; 12.3] *71 (38.2)*	0.84 [0.63; 1.12] 0.227
Health EQ-5D VAS (time until 1st deterioration)[d,e]					
≥ 10 points	368	3.2 [2.6; 4.4] 172 (46.7)	186	2.6 [2.1; 5.4] 80 (43.0)	0.95 [0.72; 1.24] 0.683

Health-related quality of life (data cut-off of 15 March 2018)

	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 (%)*	Hazard Ratio [95% CI] p value Absolute difference (AD)[a]
EORTC QLQ-C30 functional scales (time until 1st deterioration)[e]					
Global health status	368	2.6 [2.2; 3.3] *196 (53.3)*	186	3.3 [2.2; 5.9] *83 (44.6)*	1.17 [0.90; 1.52]; 0.233
Emotional function	368	17.3 [8.2; 21.5] *126 (34.2)*	186	n.a. [11.0; n.c.] *45 (24.2)*	1.24 [0.88; 1.75]; 0.215
Cognitive function	368	4.2 [3.3; 6.9] *171 (46.5)*	186	3.9 [2.8; 5.9] *85 (45.7)*	0.91 [0.70; 1.18]; 0.478
Physical function	368	2.8 [2.2; 4.2] *178 (48.4)*	186	2.6 [2.1; 5.8] *87 (46.8)*	0.93 [0.72; 1.21]; 0.601
Role function	368	2.4 [2.2; 3.1] *196 (53.3)*	186	2.1 [1.5; 2.6] *97 (52.2)*	0.89 [0.70; 1.14]; 0.360
Social function	368	2.1 [1.6; 2.4] *209 (56.8)*	186	1.7 [1.4; 2.4] *104 (55.9)*	0.90 [0.70; 1.14]; 0.373

Side effects[f] (data cut-off of 15 March 2018, induction and maintenance phase)

Endpoint	Atezolizumab + nab-paclitaxel + carboplatin		Nab-paclitaxel + carboplatin		Intervention vs Control
	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 (%)*	Hazard Ratio [95% CI] p value Absolute difference (AD)[a]
Adverse events (presented additionally)					
	447	no data available *445 (99.6)*	223	no data available *221 (99.1)*	-
Serious adverse events (SAE)					
	No usable evaluations				
Severe adverse events (CTCAE grade 3 or 4)					
	447	no data available *380 (85.0)*	223	no data available *166 (74.4)*	1.24 [1.03; 1.49] 0.026
Therapy discontinuation because of adverse events					
	447	no data available *120 (26.8)*	223	no data available *50 (22.4)*	1.01 [0.72; 1.40] 0.968
Immune mediated AE					
	No usable evaluations				
Immune mediated SAE					
	No usable evaluations				
Immune mediated severe AE (CTCAE grade 3–4)					
	No usable evaluations				
Other specific AE (severe AE with CTCAE grade 3–4)					
Blood and lymphatic system disorders (SOC)					
	447	no data available *256 (57.3)*	223	no data available *105 (47.1)*	1.27 [1.01; 1.60] 0.038
Investigations (SOC)					
	447	no data available *102 (22.8)*	223	no data available *34 (15.2)*	1.50 [1.01; 2.21] 0.042
Syncope (PT)					
	447	no data available *13 (2.9)*	223	no data available *0 (0)*	n.c. 0.037

(Continuation)

Dyspnoea (PT)					
	447	no data available *20 (4.5)*	223	no data available *1 (0.4)*	7.89 [1.05; 59.01] 0.017

[a] Absolute difference (AD) given only in the case of a statistically significant difference; own calculation
[b] Information from the dossier (Module 4, p. 121, NEoM population, evaluation by independent review committee)
[c] Defined as an increase of the score by ≥ 10 points compared with baseline
[d] Information from dossier evaluation of the IQWiG (A19-84) Annex D
[e] Defined as a decrease of the score by ≥ 10 points compared with baseline
[f] Wild type population; survey in accordance with protocol without recording events related to the underlying disease

Abbreviations used: CTCAE: Common Terminology Criteria for Adverse Events; HR: hazard ratio; EORTC: European Organisation for Research and Treatment of Cancer; CI: confidence interval; n: number of patients with (at least 1) event; N: number of patients evaluated; n.c.: not calculable; n.a.: not achieved; PT: preferred term; QLQ-C30: Quality of Life Questionnaire – Cancer 30; QLQ-LC13: Quality of Life Questionnaire – Lung Cancer 13; RCT: randomised controlled study; SOC: system organ class; SAE: serious adverse event; AE: adverse event

Summary of results for relevant clinical endpoints

Endpoint category	Direction of effect/ Risk of bias	Summary
Mortality	↔	no statistically significant or relevant difference
Morbidity	↔	no statistically significant or relevant difference
Health-related quality of life	↔	no statistically significant or relevant difference
Side effects	↓	statistically significant disadvantages for severe AE (CTCAE grade 3–4)

Explanations:
↑: positive statistically significant and relevant effect with low/unclear reliability of data
↓: negative statistically significant and relevant effect with low/unclear reliability of data
↑↑: positive statistically significant and relevant effect with high reliability of data
↓↓: negative statistically significant and relevant 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) Adult patients with metastatic non-squamous non-small cell lung cancer and a Tumour Proportion Score [TPS] of ≥ 50% (PD-L1 expression) and without EGFR- or ALK-positive tumour mutations; first-line therapy

approx. 2,320 to 2,640 patients

b) Adult patients with metastatic non-squamous non-small cell lung cancer and a Tumour Proportion Score [TPS] of < 50% (PD-L1 expression) and without EGFR- or ALK-positive tumour mutations; first-line therapy

approx. 5,700 to 6,480 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: 11 February 2020):

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

Treatment with atezolizumab may only be initiated and monitored by specialists in internal medicine, haematology, and oncology, specialists in internal medicine and pneumology, specialists in pulmonary medicine, and specialists participating in the Oncology Agreement who are experienced in the treatment of patients with non-small cell lung cancer.

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 includes, in particular, instructions on how to deal with the immune mediated side effects potentially occurring under atezolizumab treatment as well as infusion-related reactions.

4. Treatment costs

Annual treatment costs:

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

a) Adult patients with metastatic non-squamous non-small cell lung cancer and a Tumour Proportion Score [TPS] of ≥ 50% (PD-L1 expression) and without EGFR- or ALK-positive tumour mutations; first-line therapy

Designation of the therapy	Annual treatment costs/patient
Medicinal product to be assessed:	
Induction therapy	
Atezolizumab	€ 17,702.36 – 26,553.54
Carboplatin	€ 2,003.88 – 3,005.82
Nab-paclitaxel	€ 8,985.84 – 13,478.76
Maintenance treatment	
Atezolizumab	€ 50,451.73 – 59,302.91
Total:	€ 87,994.99 – 93,489.85
Appropriate comparator therapy:	
Pembrolizumab	€ 101,243.99

Costs after deduction of statutory rebates (LAUER-TAXE®) as last revised: 15 March 2020

Other services covered by SHI funds:

Designation of the 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	17.4	€ 1,235.40
Carboplatin	Surcharge for production of a parenteral preparation containing cytostatic agents	€ 81	1	4–6	€ 324 – 486
Nab-paclitaxel	Surcharge for production of a parenteral preparation containing cytostatic agents	€ 81	3	12–18	€ 972 – 1,458
Appropriate comparator therapy:					
Pembrolizumab	Surcharge for the preparation of a parenteral solution containing monoclonal antibodies	€ 71	1	17.4	€ 1,235.40

b) Adult patients with metastatic non-squamous non-small cell lung cancer and a Tumour Proportion Score [TPS] of < 50% (PD-L1 expression) and without EGFR- or ALK-positive tumour mutations; first-line therapy

Designation of the therapy	Annual treatment costs/patient
Medicinal product to be assessed:	
Induction therapy	
Atezolizumab	€ 17,702.36 – 26,553.54
Carboplatin	€ 2,003.88 – 3,005.82
Nab-paclitaxel	€ 8,985.84 – 13,478.76
Maintenance treatment	
Atezolizumab	€ 50,451.73 – 59,302.91
Total:	€ 87,994.99 – 93,489.85
Appropriate comparator therapy:	
Cisplatin in combination with a third-generation cytostatic agent (docetaxel or gemcitabine or paclitaxel or pemetrexed or vinorelbine)	
Cisplatin plus docetaxel	
Cisplatin	€ 2,007.44
Docetaxel	€ 21,230.61
Total	€ 23,238.05
Additionally required SHI service	€ 328.58 – 421.62
Cisplatin plus gemcitabine	
Cisplatin	€ 2,007.44 – 2,486.11
Gemcitabine	€ 8,193.66
Total	€ 10,201.10 – 10,679.77
Additionally required SHI service	€ 328.58 – 421.62
Cisplatin plus paclitaxel	
Cisplatin	€ 2,271.74
Paclitaxel	€ 20,749.85
Total	€ 23,021.59
Additionally required SHI service	€ 559.12 – 652.16
Cisplatin plus pemetrexed	
Cisplatin	€ 2,007.44
Pemetrexed	€ 68,656.57
Total	€ 70,664.01
Additionally required SHI service	€ 454.67 – 594.50
Cisplatin plus vinorelbine	
Cisplatin	€ 2,007.44 – 2,486.11

Designation of the therapy	Annual treatment costs/patient
Vinorelbine	€ 4,716.97 – 5,686.32
Total	€ 6,724.41 – 8,172.43
Additionally required SHI service	€ 328.58 – 421.62
Carboplatin plus docetaxel	
Carboplatin	€ 8,716.88
Docetaxel	€ 21,230.61
Total	€ 29,947.49
Carboplatin plus gemcitabine	
Carboplatin	€ 8,716.88
Gemcitabine	€ 8,193.66
Total	€ 16,910.54
Carboplatin plus paclitaxel	
Carboplatin	€ 8,716.88
Paclitaxel	€ 20,749.85
Total	€ 29,466.73
Additionally required SHI service	€ 230.54
Carboplatin plus pemetrexed	
Carboplatin	€ 8,716.88
Pemetrexed	€ 68,656.57
Total	€ 77,373.45
Additionally required SHI service	€ 126.09 – 172.88
Carboplatin plus vinorelbine	
Carboplatin	€ 8,716.88
Vinorelbine	€ 4,716.97 – 5,686.32
Total	€ 13,433.85 – 14,403.20
Carboplatin in combination with nab-paclitaxel	
Carboplatin	€ 8,716.88
Nab-paclitaxel	€ 39,088.40
Total	€ 47,805.28

Costs after deduction of statutory rebates (LAUER-TAXE®) as last revised: 15 March 2020

Other services covered by SHI funds:

Designation of the 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	17.4	€ 1,235.40
Carboplatin	Surcharge for production of a parenteral preparation containing cytostatic agents	€ 81	1	4–6	€ 324 – 486
Nab-paclitaxel	Surcharge for production of a parenteral preparation containing cytostatic agents	€ 81	3	12–18	€ 972 – 1,458
Appropriate comparator therapy:					
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

(Continuation)

Designation of the therapy	Type of service	Costs/ unit	Number / cycle	Number/ patient/ year	Costs/ patient/ year
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
nab-paclitaxel	Surcharge for production of a parenteral preparation containing cytostatic agents	€ 81	1	52.2	€ 4,228.20
Pemetrexed	Surcharge for production of a parenteral preparation containing cytostatic agents	€ 81	1	17.4	€ 1,409.40

II. The resolution will enter into force on the day of its publication on the internet on the website of the G-BA on 2 April 2020.

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

Berlin, 2 April 2020

Federal Joint Committee
in accordance with Section 91 SGB V
The Chair

Prof. Hecken