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 Pembrolizumab (new therapeutic indication: non-small cell lung carcinoma, squamous, first line, combination with carboplatin and (nab-) paclitaxel)

of 19 September 2019

At its session on 19 September 2019, the Federal Joint Committee (G-BA) resolved 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 pembrolizumab in accordance with the resolution of 4 April 2019:

Pembrolizumab

Resolution of: 19 September 2019
Entry into force on: 19 September 2019
Federal Gazette, BAnz AT DD MM YYYY Bx

New therapeutic indication (according to the marketing authorisation of 11 March 2019):

KEYTRUDA, in combination with carboplatin and either paclitaxel or nab-paclitaxel, is indicated for the first-line treatment of metastatic squamous NSCLC in adults.

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

a) Adult patients with first-line treatment of metastatic squamous NSCLC whose tumours express PD-L1 with a < 50% tumour proportion score (TPS[1]):

Appropriate comparator therapy:

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

  or

- Carboplatin in combination with a third-generation cytostatic agent (vinorelbine or gemcitabine or docetaxel or paclitaxel; cf Annex VI to Section K of the Pharmaceuticals Directive)

  or

- Carboplatin in combination with nab-paclitaxel

Extent and probability of additional benefit of pembrolizumab in combination with carboplatin and (nab-) paclitaxel versus carboplatin and (nab-) paclitaxel:

Hint for a considerable additional benefit.

b) Adult patients with first-line treatment of metastatic squamous NSCLC whose tumours express PD-L1 with a ≥ 50% tumour proportion score (TPS[1]):

Appropriate comparator therapy:
Pembrolizumab as monotherapy

Extent and probability of additional benefit of pembrolizumab in combination with carboplatin and (nab-) paclitaxel versus carboplatin and (nab-) paclitaxel:

An additional benefit is not proven.

Study results according to endpoints:[2]

[1] TPS: Tumour Proportion Score

[2] Data from the dossier evaluation of the IQWiG (A19-31) and the addendum (A19-62) unless otherwise indicated.

a) Adult patients with first-line treatment of metastatic squamous NSCLC whose tumours express PD-L1 with a < 50% tumour proportion score (TPS):

KEYNOTE 407 study: Pembrolizumab in combination with carboplatin and (nab-) paclitaxel vs carboplatin and (nab-) paclitaxel (data cut-off: 3 April 2018)

Relevant TPC (Treatment of Physician's Choice) sub-population in each case with PD-L1 expression of < 50% (TPS)[1,3]

Mortality

Endpoint	Pembrolizumab + carboplatin-based chemotherapy[a]		Carboplatin-based chemotherapy[a]		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 estimate [95% CI] p value Absolute difference (AD)[b]
Overall survival [g]					
	157	14.4 [13,2; n.c.] 47 (29.9)	153	11.1 [8.9; 13.8] 68 (44.4)	0.56 [0.38; 0.82] 0.003 [h, i] AD: + 3.3 months

Morbidity

Endpoint	Pembrolizumab + carboplatin-based chemotherapy[a]		Carboplatin-based chemotherapy[a]		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 estimate [95% CI] p value Absolute difference (AD)[b]
Progression-free survival (PFS)					
not reported					
Symptomology (EORTC QLQ-C30 symptom scales)[c]					
Dyspnoea	156	8.5 [4.4; n.c.] 61 (39.1)	152	5.6 [3.5; n.c.] 66 (43.4)	0.79 [0.55; 1.13]; 0.191
Fatigue	156	1.9	152	2.1	1.02

[3] The relevant sub-population includes patients with PD-L1 expression < 50% and who were treated according to the results of the pharmaceutical company's TPC survey according to the criteria of the AM-RL for the off-label use of carboplatin (Annex VI to Section K).

Endpoint	Pembrolizumab + carboplatin-based chemotherapy[a]		Carboplatin-based chemotherapy[a]		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 estimate [95% CI] p value Absolute difference (AD)[b]
		[1.4; 2.4] 100 (64.1)		[1.5; 3.3] 93 (61.2)	[0.76; 1.36]; 0.912
Insomnia	156	10.4 [3.6; n.c.] 64 (41.0)	152	4.2 [2.9; n.c.] 69 (45.4)	0.83 [0.58; 1.17]; 0.283
Pain	156	4.4 [3.5; n.c.] 70 (44.9)	152	3.7 [2.6; 4.8] 80 (52.6)	0.72 [0.52; 1.00]; 0.053
Loss of appetite	156	4.0 [3.0; 6.5] 78 (50.0)	152	6.2 [2.8; 6.9] 69 (45.4)	0.99 [0.71; 1.38]; 0.943
Diarrhoea	156	n.a. [5.8; n.c.] 54 (34.6)	152	11.3 [n.c.] 49 (32.2)	1.07 [0.72; 1.59]; 0.742
Nausea and vomiting	156	6.4 [3.4; n.c.] 70 (44.9)	152	4.2 [3.0; n.c.] 70 (46.1)	0.98 [0.69; 1.37]; 0.891
Constipation	156	9.0 [3.7; n.c.] 64 (41.0)	152	11.1 [4.2; 11.1] 54 (35.5)	1.01 [0.70; 1.47]; 0.958
Symptomology (EORTC QLQ-LC13 symptom scales)[c]					
Dyspnoea	156	2.6 [2.0; 3.5] 92 (59.0)	152	2.6 [2.1; 3.7] 88 (57.9)	0.97 [0.72; 1.31]; 0.836
Pain (thorax)	156	n.a. 42 (26.9)	152	7.0 [6.3; n.c.] 55 (36.2)	0.69 [0.46; 1.04]; 0.074
Pain (arm/shoulder)	156	10.4 [6.7; n.c.] 55 (35.3)	152	11.1 [5.7; n.c.] 53 (34.9)	0.85 [0.58; 1.26]; 0.427
Pain (other)	156	3.6 [2.8; 6.7] 77 (49.4)	152	5.7 [3.7; 7.0] 66 (43.4)	1.10 [0.79; 1.54]; 0.569

Endpoint	Pembrolizumab + carboplatin-based chemotherapy[a]		Carboplatin-based chemotherapy[a]		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 estimate [95% CI] p value Absolute difference (AD)[b]
Coughing	156	n.a. [7.3; n.c.] 52 (33.3)	152	n.a. [6.3; n.c.] 47 (30.9)	0.95 [0.63; 1.41]; 0.784
Haemoptysis	156	n.a. 23 (14.7)	152	n.a. 26 (17.1)	0.78 [0.44; 1.39]; 0.402
Alopecia	156	0.8 [0.7; 0.9] 133 (85.3)	152	0.8 [0.7; 0.9] 125 (82.2)	1.09 [0.85; 1.40]; 0.500
Dysphagia	156	n.a. 25 (16.0)	152	n.a. 42 (27.6)	0.52 [0.31; 0.86]; 0.011
Mouth pain	156	n.a. [9.5; n.c.] 42 (26.9)	152	n.a. [8.5; n.c.] 43 (28.3)	0.83 [0.54; 1.29]; 0.417
Peripheral neuropathy	156	2.4 [2.1; 3.5] 89 (57.1)	152	2.6 [2.1; 3.0] 94 (61.8)	0.78 [0.58; 1.05]; 0.098
Health status (EQ-5D VAS) – time until deterioration					
Responder criterion 10 points	156	3.4 [2.3; 6.5] 83 (53.2)	152	3.7 [2.3; 4.2] 84 (55.3)	0.87 [0.64; 1.19] 0.386
Responder criterion 7 points	156	3.0 [2.1; 4.2] 87 (55.8)	152	2.3 [1.9; 3.5] 94 (61.8)	0.81 [0.60; 1.09] 0.157

Health-related quality of life

Endpoint	Pembrolizumab + carboplatin-based chemotherapy[a]		Carboplatin-based chemotherapy[a]		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 estimate [95% CI] p value Absolute difference (AD)[b]
Symptomology (EORTC QLQ-C30 functional scales) [d, e]					
Global health status	156	3.6 [2.2; 6.4] 80 (51.3)	152	3.5 [2.1; 5.1] 79 (52.0)	0.89 [0.65; 1.23]; 0.488
Emotional function	156	n.a. 49 (31.4)	152	n.a. [6,1; n.c.] 53 (34.9)	0.77 [0.52; 1.15]; 0.205
Cognitive function	156	4.1 [3.2; n.c.] 71 (45.5)	152	3.5 [2.3; 6.2] 77 (50.7)	0.83 [0.60; 1.16]; 0.277
Physical function	156	3.5 [2.4; 9.5] 77 (49.4)	152	2.8 [2.1; 4.0] 91 (59.9)	0.71 [0.52; 0.96]; 0.028
Role function	156	3.1 [2.3; 3.7] 91 (58.3)	152	2.8 [1.8; 4.2] 85 (55.9)	0.98 [0.73; 1.32]; 0.896
Social function	156	4.0 [2.8; 7.8] 76 (48.7)	152	2.8 [2.1; 4.2] 81 (53.3)	0.87 [0.63; 1.20]; 0.388

Side effects [f]

Endpoint	Pembrolizumab + carboplatin-based chemotherapy[a]		Carboplatin-based chemotherapy[a]		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 estimate [95% CI] p value Absolute difference (AD)[b]
Adverse events in total					
	157	0.1 [0.1; 0.2] 153 (97.5)	152	0.1 [0.1; 0.2] 151 (99.3)	–
Serious adverse events (SAE)					

Endpoint	Pembrolizumab + carboplatin-based chemotherapy[a]		Carboplatin-based chemotherapy[a]		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 estimate [95% CI] p value Absolute difference (AD)[b]
	No usable evaluations				
Adverse events (CTCAE grade ≥ 3)					
	157	1.9 [1.6; 2.7] 107 (68.2)	152	1.2 [0.7; 1.5] 118 (77.6)	0.69 [0.53; 0.90]; 0.006
Therapy discontinuation because of adverse events					
	157	n.a. [14.4; n.c.] 31 (19.7)	152	n.a. [12.9; n.c.] 19 (12.5)	1.38 [0.78; 2.44]; 0.274
Specific adverse events					
Immune-mediated AEs	157	n.a. 41 (26.1)	152	n.a. 13 (8.6)	3.09 [1.66; 5.77]; < 0.001
Immune-mediated SAEs	No usable evaluations				
Immune-mediated AEs (CTCAE grade ≥ 3)	157	n.a. 19 (12.1)	152	n.a. 8 (5.3)	2.28 [1.00; 5.20]; 0.051

a Consisting of carboplatin in combination with either paclitaxel or nab-paclitaxel

b Absolute difference (AD) given only in the case of a statistically significant difference; own calculation.

c Time to first deterioration; defined as an increase of the score by ≥ 10 points compared with baseline

d Time to first deterioration; defined as a decrease of the score by ≥ 10 points compared with baseline

e Cox proportional hazard model with treatment as covariates, stratified by PD-L1 expression (TPS < 1% vs ≥ 1%), taxane chemotherapy (paclitaxel vs nab-paclitaxel), and region (East Asia vs non-East Asia), 2-sided p value (Wald test)

f Cox proportional hazard model with treatment as covariates; 2-sided p value (Wald test)

g Patients were censored at the time of data cut-off.

h Cox proportional hazard model with treatment as covariates, stratified by PD-L1 expression (TPS < 1% vs ≥ 1%), taxane chemotherapy (paclitaxel vs nab-paclitaxel), and region (East Asia vs non-East Asia)

i 2-sided p value (Wald test)

AD = absolute difference; CTCAE = Common Terminology Criteria for Adverse Events; EORTC: European Organization for Research and Treatment of Cancer; HR = Hazard Ratio; CI = confidence

Endpoint	Pembrolizumab + carboplatin-based chemotherapy[a]		Carboplatin-based chemotherapy[a]		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 estimate [95% CI] p value Absolute difference (AD)[b]
interval; N = number of patients evaluated; n = number of patients with (at least one) event; n.c. = not calculable; n.a. = not achieved; vs = versus; QLQ-C30: Quality of Life Questionnaire-Cancer 30; QLQ-LC13: Quality of Life Questionnaire-Lung Cancer 13; RCT: randomised controlled study; SAE: serious adverse event; TPS: Tissue Proportion Score; AE: adverse event; vs: versus					

b) Adult patients with first-line treatment of metastatic squamous NSCLC whose tumours express PD-L1 with a ≥ 50% tumour proportion score (TPS):

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

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

a) Adult patients with first-line treatment of metastatic squamous NSCLC whose tumours express PD-L1 with a < 50% tumour proportion score (TPS):

approx. 3800 to 3960 patients

b) Adult patients with first-line treatment of metastatic squamous NSCLC whose tumours express PD-L1 with a ≥ 50% tumour proportion score (TPS):

approx. 1540 to 1610 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 Keytruda® (active ingredient: pembrolizumab) at the following publicly accessible link (last access: 11 June 2019):

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

Treatment with pembrolizumab should 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 carcinoma.

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 pembrolizumab:

- Training and information material for doctors/medical professionals
- Training and information material for the patient

4. Treatment costs

Annual treatment costs:

a) Adult patients with first-line treatment of metastatic squamous NSCLC whose tumours express PD-L1 with a < 50% tumour proportion score (TPS):

Designation of the therapy	Annual treatment costs/patient
Medicinal product to be assessed:	
Pembrolizumab + carboplatin + nab-paclitaxel	
Pembrolizumab	103,757.46
Carboplatin	€ 8,514.45
nab-paclitaxel	€ 41,219.22
Total:	€ 153,491.13
Pembrolizumab + carboplatin + paclitaxel	
Pembrolizumab	103,757.46
Carboplatin	€ 8,514.45
Paclitaxel	€ 20,269.78
Total:	€ 132,542.03
Additionally required SHI services:	€ 233.55
Appropriate comparator therapy:	
Cisplatin plus docetaxel	
Cisplatin	€ 1,959.42
Docetaxel	€ 20,741.53
Total:	€ 22,700.95
Additionally required SHI services:	€ 324.43–415.33
Cisplatin plus gemcitabine	
Cisplatin	€ 1,959.42–2,427.26
Gemcitabine	€ 7,999.18
Total:	€ 9,958.60–10,426.44
Additionally required SHI services:	€ 324.43–415.33
Cisplatin plus paclitaxel	
Cisplatin	€ 2,216.63
Paclitaxel	€ 20,269.78
Total:	€ 22,486.41
Additionally required SHI services:	€ 557.97–648.87
Cisplatin plus vinorelbine	
Cisplatin	€ 1,959.42–2,427.26

Designation of the therapy	Annual treatment costs/patient
Vinorelbine	€ 4,890.22–6,096.88
Total:	€ 6,849.64–8,524.14
Additionally required SHI services:	€ 324.43–415.33
Carboplatin plus docetaxel	
Carboplatin	€ 8,514.45
Docetaxel	€ 20,741.53
Total:	€ 29,255.98
Carboplatin plus gemcitabine	
Carboplatin	€ 8,514.45
Gemcitabine	€ 7,999.18
Total:	€ 16,513.63
Carboplatin plus paclitaxel	
Carboplatin	€ 8,514.45
Paclitaxel	€ 20,269.78
Total:	€ 28,784.23
Additionally required SHI services:	€ 233.55
Carboplatin plus vinorelbine	
Carboplatin	€ 8,514.45
Vinorelbine	€ 4,890.22–6,096.88
Total:	€ 13,404.67–14,611.33
Carboplatin plus nab-paclitaxel	
Carboplatin	€ 8,514.45
nab-paclitaxel	€ 41,219.22
Total:	€ 49,733.67

Costs after deduction of statutory rebates (LAUER-TAXE®) as last revised: 1 September 2019)

Other services covered by SHI funds:

Designation of the therapy	Type of service	Cost per unit	Number per cycle	Number per patient per year[4]	Cost per patient per year
Medicinal product to be assessed:					
Pembrolizumab	Surcharge for the preparation of a parenteral solution containing monoclonal antibodies	€ 71	1	17	€ 1,207
Carboplatin	Surcharge for production of a parenteral preparation containing cytostatic agents	€ 81	1	17	€ 1,377
Paclitaxel	Surcharge for production of a parenteral preparation containing cytostatic agents	€ 81	1	17	€ 1,377
nab-paclitaxel	Surcharge for production of a parenteral preparation containing cytostatic agents	€ 81	1	51	€ 4,131
Appropriate comparator therapy:					
Carboplatin	Surcharge for production of a parenteral preparation containing cytostatic agents	€ 81	1	17	€ 1,377
Cisplatin	Surcharge for production of a parenteral preparation containing cytostatic agents	€ 81	1	17	€ 1,377
Vinorelbine	Surcharge for production of a parenteral preparation containing cytostatic agents	€ 81	2	34	€ 2,754
Gemcitabine	Surcharge for production of a parenteral preparation containing cytostatic agents	€ 81	2	34	€ 2,754
Docetaxel	Surcharge for production of a parenteral preparation containing cytostatic agents	€ 81	1	17	€ 1,377
Paclitaxel	Surcharge for production of a parenteral preparation containing cytostatic agents	€ 81	1	17	€ 1,377
nab-paclitaxel	Surcharge for production of a parenteral preparation containing	€ 81	1	51	€ 4,131

[4] calculated and standardised for one year

	cytostatic agents				
Pemetrexed	Surcharge for production of a parenteral preparation containing cytostatic agents	€ 81	1	17	€ 1,377

b) Adult patients with first-line treatment of metastatic squamous NSCLC whose tumours express PD-L1 with a ≥ 50% tumour proportion score (TPS):

Designation of the therapy	Annual treatment costs/patient
Medicinal product to be assessed:	
Pembrolizumab + carboplatin + nab-paclitaxel	
Pembrolizumab	103,757.46
Carboplatin	€ 8,514.45
nab-paclitaxel	€ 41,219.22
Total:	€ 153,491.13
Pembrolizumab + carboplatin + paclitaxel	
Pembrolizumab	103,757.46
Carboplatin	€ 8,514.45
Paclitaxel	€ 20,269.78
Total:	€ 132,542.03
Additionally required SHI services:	€ 233.55
Appropriate comparator therapy:	
Pembrolizumab	103,757.46

Costs after deduction of statutory rebates (LAUER-TAXE®) as last revised: 1 September 2019)

Other services covered by SHI funds:

Designation of the therapy	Type of service	Cost per unit	Number per cycle	Number per patient per year[5]	Cost per patient per year
Medicinal product to be assessed:					
Pembrolizumab	Surcharge for the preparation of a parenteral solution containing monoclonal antibodies	€ 71	1	17	€ 1,207
Carboplatin	Surcharge for production of a parenteral preparation containing cytostatic agents	€ 81	1	17	€ 1,377

[5] calculated and standardised for one year

Paclitaxel	Surcharge for production of a parenteral preparation containing cytostatic agents	€ 81	1	17	€ 1,377
nab-paclitaxel	Surcharge for production of a parenteral preparation containing cytostatic agents	€ 81	1	51	€ 4,131
Appropriate comparator therapy:					
Pembrolizumab	Surcharge for the preparation of a parenteral solution containing monoclonal antibodies	€ 71	1	17	€ 1,207

II. The resolution will enter into force on the day of its publication on the internet on the website of the G-BA on 19 September 2019.

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

Berlin, 19 September 2019

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

Prof Hecken