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: Head And Neck Squamous Cell Carcinoma, First Line, Combination With Platinum And 5-Fluorouracil (5-FU) Chemotherapy)

of 14 May 2020

At its session on 14 May 2020, 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 resolutions of 19 September 2019, last amended on 28 January 2020 (Federal Gazette, BAnz AT 2 March 2020 B2):

Pembrolizumab

Resolution of: 14 May 2020
Entry into force on: 14 May 2020
Federal Gazette, BAnz AT DD MM YYYY Bx

New therapeutic indication (according to the marketing authorisation of 14 November 2019):

KEYTRUDA, as monotherapy or in combination with platinum and 5-fluorouracil (5-FU) chemotherapy, is indicated for the first-line treatment of metastatic or unresectable recurrent head and neck squamous cell carcinoma in adults whose tumours express PD-L1 with a CPS ≥ 1.

Note:

This assessment relates exclusively to the assessment of the additional benefit of pembrolizumab in combination with platinum and 5-fluorouracil (5-FU) chemotherapy. For the assessment of the additional benefit of pembrolizumab as monotherapy, reference is made to the separate benefit assessment procedure for the monotherapy.

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

Adult patients with metastatic or unresectable recurrent head and neck squamous cell carcinoma (HNSCC) whose tumours express PD-L1 (combined positive score [CPS] ≥ 1); first-line treatment

Appropriate comparator therapy:

- Cetuximab + cisplatin or carboplatin + 5-FU

Extent and probability of the additional benefit of pembrolizumab in combination with platinum and 5-fluorouracil (5-FU) chemotherapy compared with cetuximab in combination with platinum and 5-fluorouracil (5-FU) chemotherapy:

Indication of a minor additional benefit.

Study results according to endpoints:[1]

Adult patients with metastatic or unresectable recurrent head and neck squamous cell carcinoma (HNSCC) whose tumours express PD-L1 (combined positive score [CPS] ≥ 1); first-line treatment

KEYNOTE 048 study: Pembrolizumab vs **pembrolizumab + cisplatin/carboplatin + 5-FU vs cetuximab + cisplatin/carboplatin + 5-FU**

Relevant sub-population: Patients whose tumours express PD-L1 (combined positive score [CPS] ≥ 1)

Mortality

Endpoint	**Pembrolizumab + cisplatin/carboplatin + 5-FU**		**Cetuximab + cisplatin/ carboplatin + 5-FU**		**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]
Overall survival					
	242	13.6 [10.7; 15.5] 177 (73.1)	235	10.4 [9.1; 11.7] 213 (90.6)	0.65 [0.53; 0.80] < 0.001 AD = 3.2 months

Morbidity

Endpoint	**Pembrolizumab + cisplatin/carboplatin + 5-FU**		**Cetuximab + cisplatin/ carboplatin + 5-FU**		**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)[2]					
	242	5.1 [4.7; 6.2] 212 (87.6)	235	5.0 [4.8; 6.0] 221 (94.0)	0.84 [0.69; 1.02] 0.074
Symptomatology (EORTC QLQ-C30 symptom scales)[b]					
Exhaustion	231	7.5 [4.0; n.c.] 93 (40.3)	220	7.9 [4.5; n.c.] 85 (38.6)	1.07 [0.79; 1.44] 0.677

[1] Data from the dossier assessment of the IQWiG (A19-101) unless otherwise indicated.
[2] Data from the dossier on pembrolizumab in combination with carboplatin or cisplatin and 5-FU (Module 4B) of 29 November 2019

Endpoint	Pembrolizumab + cisplatin/carboplatin + 5-FU		Cetuximab + cisplatin/ carboplatin + 5-FU		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]
Nausea and vomiting	231	n.a. [12.4; n.c.] 67 (29.0)	220	n.a. 54 (24.5)	1.18 [0.83; 1.70] 0.359
Pain	231	n.a. [10.6; n.c.] 61 (26.4)	220	n.a. 44 (20.0)	1.36 [0.92; 2.02] 0.125
Dyspnoea	231	n.a. 54 (23.4)	220	n.a. 33 (15.0)	1.55 [1.00; 2.40] 0.051
Insomnia	231	n.a. 48 (20.8)	220	n.a. 28 (12.7)	1.65 [1.03; 2.65] 0.036
Loss of appetite	231	n.a. [12.2; n.c.] 64 (27.7)	220	n.a. [10.6; n.c.] 56 (25.5)	1.11 [0.77; 1.60] 0.564
Constipation	231	n.a. [10.6; n.c.] 63 (27.3)	220	n.a. 46 (20.9)	1.21 [0.82; 1.77] 0.340
Diarrhoea	231	n.a. 26 (11.3)	220	n.a. 33 (15.0)	0.66 [0.40; 1.12] 0.125
Symptomatology (EORTC QLQ-H&N35 symptom scales)[b]					
Pain[c]	230	n.a. 57 (24.8)	220	n.a. 39 (17.7)	1.43 [0.95; 2.16] 0.088
Difficulties swallowing[d]	230	n.a. 45 (19.6)	220	n.a. [10.6; n.c.] 42 (19.1)	0.94 [0.61; 1.45] 0.791
Emotional disorders	230	n.a. [9.9; n.c.] 73 (31.7)	220	n.a. 60 (27.3)	1.14 [0.81; 1.61] 0.455
Speech disorders	230	n.a. 57 (24.8)	220	n.a. 56 (25.5)	0.92 [0.63; 1.34] 0.663
Teeth problems	230	n.a. [23.7; n.c.] 35 (15.2)	220	n.a. 35 (15.9)	0.83 [0.51; 1.34] 0.444
Problems	230	n.a.	220	n.a.	0.80

Endpoint	Pembrolizumab + cisplatin/carboplatin + 5-FU		Cetuximab + cisplatin/ carboplatin + 5-FU		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]
opening the mouth		38 (16.5)		41 (18.6)	[0.51; 1.26] 0.337
Xerostomia	230	n.a. 45 (19.6)	220	n.a. 52 (23.6)	0.75 [0.50; 1.12] 0.163
Sticky saliva	230	n.a. 50 (21.7)	220	n.a. 45 (20.5)	1.10 [0.73; 1.65] 0.659
Coughing	230	n.a. 41 (17.8)	220	n.a. 40 (18.2)	0.91 [0.59; 1.42] 0.685
Feelings of illness	230	n.a. 48 (20.9)	220	n.a. 36 (16.4)	1.22 [0.79; 1.89] 0.372
Health status (EQ-5D VAS) [e]					
MID: 7 points	232	n.a. [12.0; n.c.] 62 (26.7)	220	n.a. 62 (28.2)	0.91 [0.64; 1.29] 0.591
MID: 10 points	232	n.a. 54 (23.3)	220	n.a. 52 (23.6)	0.94 [0.64; 1.38] 0.746

Endpoint	Pembrolizumab + cisplatin/carboplatin + 5-FU		Cetuximab + cisplatin/ carboplatin + 5-FU		Intervention vs control
	N	Values at start of study MV (SD) Value at Week 9 MV (SD)	N	Values at start of study MV (SD) Value at Week 9 MV (SD)	Mean difference [95% CI] p value
Health status (EQ-5D VAS) (presented as a supplement)					
	182	68 (19.6) 72.9 (16.9)	170	67.1 (19.6) 72.9 (15.9)	0.20 [−3.30; 3.70] 0.910

Health-related quality of life

Endpoint	Pembrolizumab + cisplatin/carboplatin + 5-FU		Cetuximab + cisplatin/ carboplatin + 5-FU		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]
EORTC QLQ-C30 functional scales [b]					
Global health status [f]	231	n.a. 62 (26.8)	220	13.4 [13.4; n.c.] 46 (20.9)	1.31 [0.89; 1.93] 0.168
Physical function	231	n.a. [6.9; n.c.] 79 (34.2)	220	n.a. [10.9; n.c.] 61 (27.7)	1.28 [0.91; 1.79] 0.156
Role function	231	n.a. 75 (32.5)	220	n.a. [4.9; n.c.] 79 (35.9)	0.92 [0.66; 1.26] 0.590
Emotional function	231	n.a. 36 (15.6)	220	n.a. 32 (14.5)	1.03 [0.63; 1.66] 0.913
Cognitive function	231	n.a. [23.7; n.c.] 65 (28.1)	220	n.a. [10.6; n.c.] 55 (25.0)	1.06 [0.73; 1.53] 0.762
Social function	231	n.a. [12.2; n.c.] 62 (26.8)	220	n.a. [6.5; n.c.] 72 (32.7)	0.77 [0.55; 1.09] 0.141
EORTC QLQ-H&N35 functional scales [b]					
Problems eating in public	230	n.a. [12.9; n.c.] 55 (23.9)	220	n.a. 41 (18.6)	1.19 [0.79; 1.79] 0.416
Problems with social contacts	230	n.a. 46 (20.0)	220	n.a. [10.9; n.c.] 49 (22.3)	0.82 [0.54; 1.23] 0.334
Reduced sexuality	229	n.a. 65 (28.4)	220	n.a. [9.1; n.c.] 67 (30.5)	0.86 [0.61; 1.22] 0.404

Side effects

Endpoint	Pembrolizumab + cisplatin/carboplatin + 5-FU		Cetuximab + cisplatin/ carboplatin + 5-FU		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]
Total adverse events (presented additionally)					
	237	0.1 [0.1; 0.1] 233 (98.3)	245	0.1 [0.1; 0.1] 244 (99.6)	-
Serious adverse events (SAE)					
	237	3.1 [2.4; 4.4] 150 (63.3)	245	10.6 [5.1; n.c.] 121 (49.4)	1.39 [1.09; 1.77] 0.007 AD = 7.5 months
Severe adverse events (CTCAE grade ≥ 3)					
	237	1.1 [0.7; 1.4] 203 (85.7)	245	0.9 [0.7; 1.2] 203 (82.9)	1.03 [0.85; 1.26] 0.744
Therapy discontinuation because of adverse events					
	237	n.a. [12.6; n.c.] 82 (34.6)	245	39.3 [39.3; n.c.] 67 (27.3)	1.24 [0.90; 1.71] 0.196
Specific adverse events[g]					
Immune-mediated AEs (presented additionally)	237	n.a. [22.2; n.c.] 63 (26.6)	245	n.a. 59 (24.1)	-
Immune-mediated SAE	237	n.a. 12 (5.1)	245	n.a. 10 (4.1)	1.20 [0.52; 2.78] 0.671
Immune-mediated severe AEs (CTCAE grade ≥ 3)	237	n.a. 14 (5.9)	245	n.a. 27 (11.0)	0.44 [0.23; 0.86] 0.015
Paronychia (PT, AEs)	237	no data available 0 (0)	245	no data available 30 (12.2)	RR: 0.02 [0.00; 0.28] < 0.001
Skin and subcutaneous tissue disorders (SOC severe AEs [CTCAE grade ≥ 3])	237	n.a. 7 (3.0)	245	n.a. 24 (9.8)	0.26 [0.11; 0.61] 0.002

Endpoint	Pembrolizumab + cisplatin/carboplatin + 5-FU		Cetuximab + cisplatin/ carboplatin + 5-FU		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]
Anaemia (PT, AEs ([CTCAE grade ≥ 3])	237	no data available 57 (24.1)	245	no data available 36 (14.7)	RR: 1.64 [1.12; 2.39] 0.010
Stomatitis (PT, AEs [CTCAE grade ≥ 3])	237	no data available 20 (8.4)	245	no data available 9 (3.7)	RR: 2.30 [1.07; 4.94] 0.028
Mucosa inflammation (PT, AEs [CTCAE grade ≥ 3])	237	no data available 25 (10.5)	245	no data available 13 (5.3)	RR: 1.99 [1.04; 3.79] 0.034
Respiratory, thoracic, and mediastinal disorders (SOC, AEs [CTCAE grade ≥ 3])	237	n.a. 35 (14.8)	245	n.a. 18 (7.3)	1.91 [1.08; 3.38] 0.027

[a] Absolute difference (AD) given only in the case of a statistically significant difference; own calculation
[b] Time to the first confirmed clinically relevant deterioration, defined as an increase of the score by at least 10 points compared with baseline confirmed at the next survey.
[C] Conflicting information in the study report: Patients with event: 49 (21.3) vs. 37 (16.8); HR = 1.30 [0.84; 2.00]; p = 0.885 (one sided)
[d] Conflicting information in the study report: Patients with event: 39 (17.0) vs. 36 (16.4); HR = 0.94 [0.59; 1.50]; p = 0.402 (one sided)
[e] Time to the first confirmed clinically relevant deterioration, defined as an increase of the score by at least 7 or 10 points compared with baseline confirmed at the next survey.
[f] Conflicting information in the study report: Patients with event: 55 (23.8) vs. 36 (16.4); HR = 1.50 [0.98; 2.29]; p = 0.970 (one sided)
[g] Selection in accordance with IQWiG methodology; selection based on those identified in the study Events based on frequency and differences between treatment arms and taking into account patient relevance.

Abbreviations used:
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.a. = not achieved; RR = relative risk; vs = versus

Summary of results for relevant clinical endpoints

Endpoint category	Direction of effect/ Risk of bias	Summary
Mortality	↑↑	Advantage in overall survival.
Morbidity	↔	No differences relevant for the benefit assessment.

Health-related quality of life	↔	No differences relevant for the benefit assessment.
Side effects	↓	Disadvantages in the endpoint serious AE; predominantly disadvantages in individual specific AE.

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

approx. 4,950–5,370 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: 8 April 2020):

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

Treatment with pembrolizumab may only be initiated and monitored by specialists in internal medicine, haematology, and oncology, specialists in otorhinolaryngology, and other specialists participating in the Oncology Agreement who are experienced in the treatment of patients with head and neck tumours. 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:

Designation of the therapy	Annual treatment costs/patient
Medicinal product to be assessed:	

Designation of the therapy	Annual treatment costs/patient
Pembrolizumab + 5-fluorouracil + cisplatin	
Pembrolizumab	€ 101,243.99
+ 5-fluorouracil	€ 928.19
+ cisplatin	€ 2,486.11
Total:	€ 104,658.29
Additionally required SHI service	€ 328.58 – 421.62
Pembrolizumab + 5-fluorouracil + carboplatin	
Pembrolizumab	€ 101,243.99
+ 5-fluorouracil	€ 928.19
+ carboplatin	€ 6,858.73
Total:	€ 109,030.91
Appropriate comparator therapy:	
Cisplatin + 5-fluorouracil + cetuximab	
Cisplatin	€ 2,486.11
+ 5-fluorouracil	€ 928.19
+ cetuximab	€ 73,218.36
Total:	€ 76,632.66
Additionally required SHI service	€ 328.58 – 421.62
Carboplatin + 5-fluorouracil + cetuximab	
Carboplatin	€ 6,858.73
+ 5-fluorouracil	€ 928.19
+ cetuximab	€ 73,218.36
Total:	€ 81,005.28

Costs after deduction of statutory rebates (LAUER-TAXE®) as last revised: 15 April 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					
Pembrolizumab	Surcharge for the preparation of parenteral solutions with monoclonal antibodies	€ 71	1	17.4	€ 1,235.40
5-fluorouracil	Surcharge for production of a parenteral preparation containing cytostatic agents	€ 81	4	69.6	€ 5637.60
Cisplatin or Carboplatin	Surcharge for production of a parenteral preparation containing cytostatic agents	€ 81	1	17.4	€ 1,409.40
Appropriate comparator therapy					
Cisplatin + 5-fluorouracil + cetuximab or carboplatin + 5-fluorouracil + cetuximab					
Cisplatin or Carboplatin	Surcharge for production of a parenteral preparation containing cytostatic agents	€ 81	1	17.4	€ 1,409.40
5-fluorouracil	Surcharge for production of a parenteral preparation containing cytostatic agents	€ 81	4	69.6	€ 5637.60
Cetuximab	Surcharge for the preparation of parenteral solutions with monoclonal antibodies	€ 71	1	52.1	€ 3,699.10

II. The resolution will enter into force with effect from the day of its publication on the internet on the website of the G-BA on 14 May 2020.

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

Berlin, 14 May 2020

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

Prof. Hecken