Resolution

Gemeinsamer Bundesausschuss

of the Federal Joint Committee 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: Renal Cell Carcinoma, First-Line, Combination with Axitinib)

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):

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 26 August 2019):

KEYTRUDA, in combination with axitinib, is indicated for the first-line treatment of advanced renal cell carcinoma in adults (see section 5.1).

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

a) Adult patients with untreated advanced renal cell carcinoma with a favourable or intermediate risk profile (IMDC score 0–2)

Appropriate comparator therapy:

- Bevacizumab in combination with interferon alfa-2a

  or
- Nivolumab in combination with ipilimumab (only for patients with intermediate risk profile)

  or
- Monotherapy with pazopanib

  or
- Monotherapy with sunitinib

Extent and probability of the additional benefit of pembrolizumab in combination with axitinib compared with sunitinib:

Hint for a considerable additional benefit

b) Adult patients with untreated advanced renal cell carcinoma with a poor risk profile (IMDC score ≥ 3)

Appropriate comparator therapy:

- Nivolumab in combination with ipilimumab

  or
- Sunitinib

  or
- Temsirolimus

Extent and probability of the additional benefit of pembrolizumab in combination with axitinib compared with sunitinib:

Indication of a considerable additional benefit

Study results according to endpoints[1]:

KEYNOTE 426 study:

Pembrolizumab + axitinib vs sunitinib

Study design: randomised, open-label, Phase III

Data cut-off: 2 January 2019

a) Adult patients with untreated advanced renal cell carcinoma with a favourable or intermediate risk profile (IMDC score 0–2)

Mortality

Endpoint	**Pembrolizumab + axitinib**		**Sunitinib**		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[a] Absolute difference (AD)[b]
Overall survival					
	376	n.a. *58 (15.4)*	377	n.a. *90 (23.9)*	0.57 [0.41; 0.80] 0.001 AD: n.c.

Morbidity

Progression-free survival (PFS)[c]					
	376	18.0 [15.0; 23.5] *169 (44.9)*	377	12.5 [10.2; 15.2] *193 (51.2)*	0.70 [0.57; 0.86] < 0.001 AD: 5.5 months
Symptomatology					
EORTC QLQ-C30 symptom scales					
No usable data					
FKSI-DRS					
No usable data					
Health status					
EQ-5D VAS					
No usable data					

(Continuation)

[1] Data from the dossier assessment of the IQWiG (A19-99) unless otherwise indicated.

Health-related quality of life

EORTC QLQ-C30 functional scales
No usable data

Side effects

Endpoint	Pembrolizumab + axitinib		Sunitinib		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[a] Absolute difference (AD)[b]
Total adverse events (presented additionally)[d]					
	374	0.2 [0.2; 0.3] *370 (98.9)*	373	0.3 [0.3; 0.4] *373 (100.0)*	-
Serious adverse events (SAE)[d]					
	374	19.2 [15.1; n.c.] *167 (44.7)*	373	24.2 [24.2; n.c.] *123 (33.0)*	1.36 [1.08; 1.72] 0.009 AD: 5.0 months
Severe adverse events (CTCAE grade ≥ 3)[d]					
	374	3.1 [2.8; 3.9] *298 (79.7)*	373	2.4 [2.0; 3.4] *271 (72.7)*	1.02 [0.87; 1.20] 0.801
Therapy discontinuation because of adverse events[d]					
	374	n.a.[e] *127 (34.0)*	373	n.a. *53 (14.2)*	2.40 [1.74; 3.31] < 0.001 AD: n.c.
Specific adverse events					
Immune mediated AE (presented additionally)[f]	374	8.3 [5.7; 12.0] *208 (55.6)*	373	16.5 [12.5; 20.9] *151 (40.5)*	-
Immune mediated SAE	374	n.a. *42 (11.2)*	373	n.a. *5 (1.3)*	7.80 [3.08; 19.71] < 0.001 AD: n.c.

(Continuation)

Immune mediated severe AE (CTCAE grade ≥ 3)	374	n.a. *47 (12.6)*	373	n.a. *6 (1.6)*	7.10 [3.03; 16.61] < 0.001 AD: n.c.
Respiratory, thoracic, and mediastinal disorders (SOC, AE)	374	5.8 [4.0; 8.3] *233 (62.3)*	373	20.8 [15.0; n.c.] *155 (41.6)*	1.70 [1.38; 2.08] < 0.001 AD: 15.0 months
Endocrine disorders (SOC, SAE)	374	n.a. *12 (3.2)*	373	n.a. *1 (0.3)*	11.02 [1.43; 84.78] 0.021 AD: n.c.
Blood and lymphatic system disorders (SOC, severe AE [CTCAE grade ≥ 3])	374	n.a. *5 (1.3)*	373	n.a. *72 (19.3)*	0.06 [0.02; 0.14] < 0.001 AD: n.c.
Hepatobiliary disorders (SOC, severe AE [CTCAE grade ≥ 3])	374	n.a. *24 (6.4)*	373	n.a. *10 (2.7)*	2.24 [1.07; 4.69] 0.032 AD: n.c.
Infections and infestations (SOC severe AE [CTCAE grade ≥ 3])	374	n.a. *32 (8.6)*	373	n.a. *45 (12.1)*	0.61 [0.39; 0.96] 0.032 AD: n.c.
Renal and urinary disorders (SOC severe AE [CTCAE grade ≥ 3])	374	n.a. *32 (8.6)*	373	n.a. *14 (3.8)*	2.20 [1.17; 4.12] 0.014 AD: n.c.

[a] Hazard ratio, confidence interval (CI), p value: Cox Proportional Hazards Model; stratified by region (North America vs Western Europe vs Rest of the World) for the endpoint overall survival; unstratified for the endpoints of the side effects category
[b] Absolute difference (AD) given only in the case of a statistically significant difference; own calculation.
[c] Information from the dossier of the pharmaceutical company
[d] Evaluation without the PT “Progression of a neoplasm”, “Progression of a malignant neoplasm”, and “Progression of a disease”
[e] It is unclear whether it is the discontinuation of pembrolizumab and/or axitinib.

(Continuation)

[f] In the total population of the study at the time of the 1st data cut-off (24 August 2018), the endpoint is mainly PT hyperthyroidism and hypothyroidism. For hyperthyroidism, 30 (about 55%) patients in the intervention arm vs 13 (about 81%) in the comparison arm reported events based on CTCAE grade 1; for hypothyroidism, this was 49 (32%) vs 55 (41%). CTCAE grade 1 is not patient-relevant for this PT because it is defined as "asymptomatic; only clinical or diagnostic observation; intervention not indicated". Data for the 2nd data cut-off (2 January 2019) are not available.

Abbreviations used:

AD: Absolute difference; CTCAE: Common Terminology Criteria for Adverse Events; EORTC QLQ-C30: European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30; EQ-5D: European Quality of Life Questionnaire – 5 Dimensions; FKSI-DRS: Functional Assessment of Cancer Therapy – Kidney Symptom Index – Disease related Symptoms; CI: confidence interval; n: number of patients with (at least one) event; N: number of patients evaluated; n.c.: not calculable; n.a.: not achieved; PT: preferred term; SOC: system organ class; AE: adverse event; VAS: visual analogue scale; vs: versus

Summary of results for relevant clinical endpoints

Endpoint category	Direction of effect/ Risk of bias	Summary
Mortality	↑	Advantage in overall survival
Morbidity	n.a.	not assessable
Health-related quality of life	n.a.	not assessable
Side effects	↓	Disadvantages in the endpoints serious adverse events (SAE) and discontinuation of therapy because of AE; advantage and disadvantage 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

b) Adult patients with untreated advanced renal cell carcinoma with a poor risk profile (IMDC score ≥ 3)

Mortality

Endpoint	**Pembrolizumab + axitinib**		**Sunitinib**		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[a] Absolute difference (AD)[b]
Overall survival					
	56	21.8 [14.7; 25.2] *26 (46.4)*	52	10.1 [7.0; 17.6] *32 (61.5)*	0.50 [0.29; 0.87] 0.015 AD: 11.7 months

Morbidity

Progression-free survival (PFS)[c]					
	56	4.9 [2.9; 12.6] *38 (67.9)*	52	2.9 [2.7; 4.2] *39 (75.0)*	0.57 [0.35; 0.92] 0.022 AD: 3.0 months
Symptomatology					
EORTC QLQ-C30 symptom scales					
No usable data					
FKSI-DRS					
No usable data					
Health status					
EQ-5D VAS					
No usable data					

Health-related quality of life

EORTC QLQ-C30 functional scales
No usable data

(Continuation)

Side effects

Endpoint	Pembrolizumab + axitinib		Sunitinib		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[a] Absolute difference (AD)[b]
Total adverse events (presented additionally)[d]					
	55	0.2 [0.1; 0.5] *52 (94.5)*	52	0.3 [0.2; 0.3] *52 (100.0)*	-
Serious adverse events (SAE)[d]					
	55	9.3 [3.0; n.c.] *29 (52.7)*	52	9.8 [1.9; n.c.] *25 (48.1)*	0.88 [0.51; 1.51] 0.644
Severe adverse events (CTCAE grade ≥ 3)[d]					
	55	2.7 [1.6; 4.4] *42 (76.4)*	52	1.0 [0.6; 2.2] *44 (84.6)*	0.60 [0.39; 0.93] 0.022 AD: 1.7 months
Therapy discontinuation because of adverse events[d]					
	55	n.a. [10.7; n.a.][e] *15 (27.3)*	52	n.a. 10 (19.2)	1.15 [0.51; 2.59] 0.728
Specific adverse events					
Immune mediated AE (presented additionally)[f]	55	8.3 [5.5; 12.5] *24 (43.6)*	52	n.a. [4.5; n.c.] *15 (28.8)*	-
Immune mediated SAE	55	n.a. *6 (10.9)*	52	n.a. *1 (1.9)*	4.08 [0.48; 34.58] 0.198
Immune mediated severe AE (CTCAE grade ≥ 3)	55	n.a. [19.5; n.c.] *6 (10.9)*	52	n.a. *2 (3.8)*	1.88 [0.37; 9.56] 0.448

(Continuation)

Nervous system disorders (SOC, AE)	55	16.9 [8.9; n.c.] *21 (38.2)*	52	3.6 [0.9; n.c.] *27 (51.9)*	0.39 [0.21; 0.72] 0.003 AD: 13.3 months
Blood and lymphatic system disorders (SOC, severe AE [CTCAE grade ≥ 3])	55	n.a. *2 (3.6)*	52	n.a. [19.7; n.c.] *11 (21.2)*	0.12 [0.03; 0.56] 0.007 AD: n.c.
General disorders and administration site conditions (SOC, severe AE [CTCAE grade ≥ 3])	55	n.a. *3 (5.5)*	52	n.a. *12 (23.1)*	0.17 [0.05; 0.62] 0.007 AD: n.c.
Metabolism and nutrition disorders (SOC severe AE [CTCAE grade ≥ 3])	55	n.a. *7 (12.7)*	52	n.a. [6.0; n.c.] *16 (30.8)*	0.28 [0.11; 0.70] 0.006 AD: n.c.

[a] Hazard ratio, confidence interval (CI), p value: Cox Proportional Hazards Model; stratified by region (North America vs Western Europe vs Rest of the World) for the endpoint overall survival; unstratified for the endpoints of the side effects category

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

[c] Information from the dossier of the pharmaceutical company

[d] Evaluation without the PT “Progression of a neoplasm”, “Progression of a malignant neoplasm”, and “Progression of a disease”

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Health-related quality of life	n.a.	not assessable
Side effects	↑	Advantage in the endpoint severe adverse events (CTCAE grade ≥ 3); advantages in individual specific AE

Explanations:
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↔: 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 untreated advanced renal cell carcinoma with a favourable or intermediate risk profile (IMDC score 0–2)

approx. 2,700 patients

b) Adult patients with untreated advanced renal cell carcinoma with a poor risk profile (IMDC score ≥ 3)

approx. 800 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: 5 May 2020):

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

Treatment with pembrolizumab in combination with axitinib may only be initiated and monitored by specialists in internal medicine, haematology, and oncology, specialists in internal medicine and nephrology, and other specialists participating in the Oncology Agreement who are experienced in the treatment of patients with renal cell 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

The KEYNOTE 426 study exclusively investigated patients with renal cell carcinoma with clear cell histology. No data are available for patients with non-clear-cell renal cell carcinoma.

4. Treatment costs

Annual treatment costs:

a) Adult patients with untreated advanced renal cell carcinoma with a favourable or intermediate risk profile (IMDC score 0–2)

Designation of the therapy	Annual treatment costs/patient
Medicinal product to be assessed:	
Pembrolizumab in combination with axitinib	
Pembrolizumab	€ 101,243.99
Axitinib	€ 46,868.22
Total	€ 148,112.21
Appropriate comparator therapy:	
Bevacizumab in combination with interferon alfa-2a	
Bevacizumab	€ 83,251.69
Interferon alfa-2a	€ 15,508.68
Total	€ 98,760.37
Nivolumab in combination with ipilimumab	
Initial treatment	
Nivolumab	€ 12,201.36
Ipilimumab	€ 29,046.08
Total	€ 41,247.44
Follow-up treatment	
Nivolumab	€ 56,736.32 – 61,311.83
Initial treatment + total follow-up treatment	€ 102,559.27 – 97,983.76
Monotherapies	
Pazopanib	€ 54,403.13
Sunitinib	€ 55,245.07

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

Costs for additionally required SHI services: not applicable

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
Appropriate comparator therapy:					
Bevacizumab	Surcharge for the preparation of parenteral solutions with monoclonal antibodies	€ 71	1	26.1	€ 1,853.10
Nivolumab in combination with ipilimumab					
Nivolumab (follow-up treatment with nivolumab in 14-day cycle)	Surcharge for the preparation of parenteral solutions with monoclonal antibodies	€ 71	1	24.1	€ 1,711.10
Nivolumab (follow-up treatment with nivolumab in 28-day cycle)	Surcharge for the preparation of parenteral solutions with monoclonal antibodies	€ 71	1	13.3	€ 944.30
Ipilimumab	Surcharge for the preparation of parenteral solutions with monoclonal antibodies	€ 71	1	4	€ 284.00
Total					€ 1,228.30 – 1,995.10

b) Adult patients with untreated advanced renal cell carcinoma with a poor risk profile (IMDC score ≥ 3)

Designation of the therapy	Annual treatment costs/patient
Medicinal product to be assessed:	
Pembrolizumab in combination with axitinib	
Pembrolizumab	€ 101,243.99
Axitinib	€ 46,868.22
Total	€ 148,112.21
Appropriate comparator therapy:	
Nivolumab in combination with ipilimumab	
Initial treatment	
Nivolumab	€ 12,201.36
Ipilimumab	€ 29,046.08
Total	€ 41,247.44
Follow-up treatment	
Nivolumab	€ 56,736.32 – 61,311.83
Initial treatment + total follow-up treatment	€ 102,559.27 – 97,983.76
Monotherapies	
Sunitinib	€ 55,245.07
Temsirolimus	€ 58,154.54

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

Costs for additionally required SHI services: not applicable

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

(Continuation)

Appropriate comparator therapy:					
Nivolumab in combination with ipilimumab					
Nivolumab (follow-up treatment with nivolumab in 14-day cycle)	Surcharge for the preparation of parenteral solutions with monoclonal antibodies	€ 71	1	24.1	€ 1,711.10
Nivolumab (follow-up treatment with nivolumab in 28-day cycle)	Surcharge for the preparation of parenteral solutions with monoclonal antibodies	€ 71	1	13.3	€ 944.30
Ipilimumab	Surcharge for the preparation of parenteral solutions with monoclonal antibodies	€ 71	1	4	€ 284.00
Total					€ 1,228.30 – 1,995.10
Temsirolimus	Surcharge for production of a parenteral preparation containing cytostatic agents	€ 81	1	52.1	€ 4,220.10

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