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: Pembrolizumab (Reassessment after the deadline: Urothelial carcinoma, CPS ≥ 10, first-line)

of 16 September 2021

At its session on 16 September 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 TT. Month YYYY (Federal Gazette, BAnz AT DD.MM.YYYY BX), as follows:

I. Annex XII is amended as follows:

1. **The information on pembrolizumab in the version of the resolution of 20 June 2019 (BAnz AT 08.08.2019 B3), last modified on 5 March 2020, is repealed.**

2. **In Annex XII, the following information shall be added to the information on the benefit assessment of pembrolizumab in the version of the resolution of 16 September 2021 for the therapeutic indication "[...] monotherapy indicated for the treatment of locally advanced or metastatic urothelial carcinoma in adults who are not eligible for cisplatin-containing chemotherapy and whose tumours express PD-L1 with a combined positive score (CPS) ≥ 10" after number 4:**

Pembrolizumab

Resolution of: 16 September 2021
Entry into force on: 16 September 2021
BAnz AT DD. MM YYYY Bx

Therapeutic indication (according to the marketing authorisation of 6 July 2018):

Urothelial carcinoma

KEYTRUDA as monotherapy is indicated for the treatment of locally advanced or metastatic urothelial carcinoma in adults who have received prior platinum-containing chemotherapy.

KEYTRUDA as monotherapy is indicated for the treatment of locally advanced or metastatic urothelial carcinoma in adults who are not eligible for cisplatin-containing chemotherapy and whose tumours express PD-L1 with a combined positive score (CPS) ≥ 10.

Therapeutic indication of the resolution (resolution from 16.09.2021):

KEYTRUDA as monotherapy is indicated for the treatment of locally advanced or metastatic urothelial carcinoma in adults who are not eligible for cisplatin-containing chemotherapy and whose tumours express PD-L1 with a combined positive score (CPS) ≥ 10.

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

Adults with locally advanced or metastatic urothelial carcinoma who are not eligible for cisplatin-containing chemotherapy and whose tumours express PD-L1 with a combined positive score (CPS) ≥ 10; first-line

Appropriate comparator therapy:

- Carboplatin in combination with gemcitabine (cf. Annex VI concerning Section K of the Pharmaceuticals Directive)

Extent and probability of the additional benefit of pembrolizumab compared to chemotherapy according to the doctor's instructions:

An additional benefit is not proven.

Study results according to endpoints:[1]

Summary of results for relevant clinical endpoints

Endpoint category	Direction of effect/ risk of bias	Summary
Mortality	↔	No relevant difference for the benefit assessment.
Morbidity	↔	No relevant difference for the benefit assessment.
Health-related quality of life	↔	No relevant difference for the benefit assessment.
Side effects	↑	Positive effect in severe AEs, but overall no difference relevant 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		

KEYNOTE 361 study
Study design: randomised, multicentre, active-controlled, open-label
Comparison: Pembrolizumab monotherapy **vs** chemotherapy (cisplatin or carboplatin in combination with gemcitabine)

Relevant sub-population: Adults with PD-L1-expressing tumours (CPS ≥ 10) not eligible for cisplatin-containing therapy

Mortality

Endpoint	Pembrolizumab		Carboplatin + gemcitabine		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 (%)*	HR [95% CI] p-value
Overall survival					
	56	14.5 [8.0; 18.0] *40 (71.4)*	63	12.1 [8.5; 19.2] *49 (77.8)*	0.93 [0.61; 1.42]; 0.740

[1] Data from the dossier assessment of the Institute for Quality and Efficiency in Health Care (IQWiG) (A21-34) unless otherwise indicated.

Morbidity

Endpoint	Pembrolizumab		Carboplatin + gemcitabine		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 (%)*	HR [95% CI] p-value Absolute difference (AD)[a]
EORTC QLQ-C30 symptom scales[b]					
Exhaustion	50	1.4 [0.8; 2.1] *36 (72.0)*	55	1.4 [0.9; 4.1] *33 (60.0)*	1.10 [0.67; 1.80]; 0.697
Nausea and vomiting	50	8.1 [4.2; n. c.] *18 (36.0)*	55	n. a. [2.4; n. c.] *20 (36.4)*	0.74 [0.37; 1.50]; 0.406
Pain	50	2.3 [0.9; 10.4] *28 (56.0)*	55	4.1 [2.1; n. c.] *24 (43.6)*	1.33 [0.75; 2.34]; 0.327
Dyspnoea	50	8.9 [2.1; n. c.] *20 (40.0)*	55	3.7 [1.6; n. c.] *28 (50.9)*	0.64 [0.35; 1.17]; 0.151
Insomnia	50	9.0 [6.3; n. c.] *19 (38.0)*	55	n. a. [4.7; n. c.] *13 (23.6)*	0.99 [0.45; 2.17]; 0.976
Appetite loss	50	3.9 [1.4; 7.9] *28 (56.0)*	55	6.1 [6.1; n. c.] *17 (30.9)*	1.92 [1.04; 3.55]; 0.038 AD = 2.2 months
Constipation	50	8.1 [2.4; n. c.] *19 (38.0)*	55	n. a. [1.4; n. c.] *21 (38.2)*	0.85 [0.45; 1.61]; 0.626
Diarrhoea	50	n. a. [8.3; n. c.] *13 (26.0)*	55	n. a. [4.7; n. c.] *17 (30.9)*	0.63 [0.29; 1.36]; 0.239
Health status (EQ-5D VAS)					
≥ 7 points	50	2.0 [1.4; 3.9] *33 (66.0)*	55	2.1 [1.4; 4.6] *32 (58.2)*	1.06 [0.64; 1.76]; 0.816
≥ 10 points	50	3.4 [1.4; 6.2] *31 (62.0)*	55	4.1 [2.1; n. c.] *27 (49.1)*	1.01 [0.58; 1.76]; 0.960
Progression-free survival					
no data are presented in the dossier for the relevant sub-population					

Health-related quality of life

Endpoint	**Pembrolizumab**		**Carboplatin + gemcitabine**		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 (%)*	HR [95% CI] p-value
EORTC QLQ-C30 – functional scales[b]					
Global health status	50	5.3 [2.1; 8.1] *28 (56.0)*	55	4.1 [1.4; n. c.] *29 (52.7)*	0.74 [0.42; 1.30]; 0.294
physical functioning	50	3.5 [0.8; 5.3] *32 (64.0)*	55	3.1 [1.4; n. c.] *29 (52.7)*	1.09 [0.64; 1.85]; 0.748
Role functioning	50	2.0 [0.8; 6.8] *30 (60.0)*	55	1.9 [1.4; n. c.] *30 (54.5)*	1.10 [0.65; 1.86]; 0.728
emotional functioning	50	n. a. [2.4; n. c.] *14 (28.0)*	55	n. a. [4.4; n. c.] *14 (25.5)*	1.18 [0.55; 2.52]; 0.669
cognitive functioning	50	5.1 [2.2; 18.4] *24 (48.0)*	55	2.2 [1.4; n. c.] *28 (50.9)*	0.70 [0.40; 1.25]; 0.232
social functioning	50	3.5 [1.4; 6.8] *30 (60.0)*	55	4.4 [1.7; n. c.] *24 (43.6)*	1.23 [0.70; 2.17]; 0.478

Side effects

Endpoint	Pembrolizumab		Carboplatin + gemcitabine		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 (%)*	HR [95% CI] p-value Absolute difference (AD)[a]
Total adverse events (presented additionally)					
	55	0.6 [0.2; 0.7] *53 (96.4)*	62	0.2 [0.1; 0.3] *62 (100.0)*	-
Serious adverse events (SAE)					
	55	4.9 [3.1; n. c.] *30 (54.5)*	62	n. a. [3.1; n. c.] *25 (40.3)*	1.24 [0.72; 2.14]; 0.431
Severe adverse events (CTCAE grade 3 or 4)					
	55	3.6 [1.9; 5.3] *40 (72.7)*	62	1.1 [0.7; 1.9] *55 (88.7)*	0.36 [0.23; 0.58]; < 0.001 AD = 2.5 months
Therapy discontinuation due to adverse events					
	55	n.a. *11 (20.0)*	62	n.a. *7 (11.3)*	1.32 [0.48; 3.63]; 0.597
Immune-mediated serious adverse events					
	55	n.a. *3 (5.5)*	62	n.a. *0 (0)*	n.c.; 0.052
Immune-mediated severe adverse events					
	55	n.a. *4 (7.3)*	62	n.a. *1 (1.6)*	3.56 [0.37; 34.19]; 0.272

Endpoint	Pembrolizumab		Carboplatin + gemcitabine		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 (%)*	HR [95% CI] p-value Absolute difference (AD)[a]
Specific adverse events					
Gastrointestinal disorders (SOC, severe AE)	55	5.6 [2.3; 8.0] *30 (54.5)*	62	0.9 [0.3; 1.6] *44 (71.0)*	0.39 [0.23; 0.64]; < 0.001 AD = 4.7 months
Blood and lymphatic system disorders (SOC, severe AE)	55	n.a. *9 (16.4)*	62	2.1 [1.4; 2.6] *49 (79.0)*	0.13 [0.06; 0.27]f; < 0.001
Metabolism and nutrition disorders (SOC, severe AE)	55	n.a. *11 (20.0)*	62	n.a. *4 (6.5)*	3.40 [1.08; 10.67]f; 0.036
Vascular diseases (SOC, severe AE)	55	n.a. *5 (9.1)*	62	n.a. *0 (0)*	n. d.f, h; 0.029

[a] Data on absolute difference (AD) only in the case of statistically significant difference; own calculation
[b] Time to deterioration; defined as an increase in score by ≥ 10 points (for symptom scales) or decrease in score by ≥ 10 points (for functional scales) compared with baseline; scale range 0-100 points

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; vs = versus

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

approx. 225 – 380 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: 2 September 2021):

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

Treatment with pembrolizumab should only be initiated and monitored by specialists in internal medicine, haematology, and oncology and urology, and specialists participating in the Oncology Agreement experienced in the treatment of adults with urothelial carcinoma.

In accordance with the EMA requirements regarding additional risk minimisation measures, the pharmaceutical company must provide training material and a patient card. The training material for health professionals and the patient card contains, in particular, instructions on the management of immune-mediated side effects potentially occurring with pembrolizumab as well as on infusion-related reactions. The prescribing doctor must discuss with the patient the risks of therapy with KEYTRUDA. The patient card should be made available to the patient.

4. Treatment costs

Annual treatment costs:

Designation of the therapy	Annual treatment costs/ patient
Medicinal product to be assessed:	
Pembrolizumab	€ 99 597.03
Appropriate comparator therapy:	
Carboplatin in combination with gemcitabine	
Carboplatin	€ 746.96 € - € 1 120.44
Gemcitabine	€ 1 468.08 - € 2 202.12
Total costs	€ 2 215.04 - € 3 322.56

Costs after deduction of statutory rebates (LAUER-TAXE® as last revised: 1 September 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
Pembrolizumab	Surcharge for the preparation of a parenteral solution containing monoclonal antibodies	€ 71	1	8.7 – 17.4	€ 617.02 - € 1 234.05
Carboplatin in combination with gemcitabine	Surcharge for the preparation of a parenteral preparation containing cytostatic agents	€ 81	2	8-12	€ 648.00 - € 972.00

II. The resolution will enter into force on the day of its publication on the website of the G-BA on 16 September 2021.

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

Berlin, 16 September 2021

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

Prof. Hecken