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 (new therapeutic indication: renal cell carcinoma, adjuvant treatment, monotherapy, pretreated patients)

of 19 January 2023

At its session on 19 January 2023, 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 D 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 15 December 2022:**

Pembrolizumab

Resolution of: 19 January 2023
Entry into force on: 19 January 2023
Federal Gazette, BAnz AT DD. MM YYYY Bx

New therapeutic indication (according to the marketing authorisation of 24 January 2022):

Keytruda as monotherapy is indicated for the adjuvant treatment of adults with renal cell carcinoma at increased risk of recurrence following nephrectomy, or following nephrectomy and resection of metastatic lesions.

Therapeutic indication of the resolution (resolution of 19 January 2023):

See therapeutic indication according to marketing authorisation.

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

Adults with renal cell carcinoma at increased risk of recurrence following nephrectomy or following nephrectomy and resection of metastatic lesions; adjuvant treatment

Appropriate comparator therapy:

Monitoring wait-and-see approach

Extent and probability of the additional benefit of pembrolizumab compared to a monitoring wait-and-see approach:

Hint for a minor additional benefit

Study results according to endpoints:[1]

Adults with renal cell carcinoma at increased risk of recurrence following nephrectomy or following nephrectomy and resection of metastatic lesions; adjuvant treatment

Summary of results for relevant clinical endpoints

Endpoint category	Direction of effect/ risk of bias	Summary
Mortality	↑	Advantage in overall survival.
Morbidity	↑	Advantages in the prevention of recurrences.
Health-related quality of life	↔	No relevant difference for the benefit assessment.
Side effects	↓	Disadvantages in the endpoints of AEs, SAEs and discontinuation due to AEs. In detail, disadvantages in specific AEs.

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.c.: not calculable

KEYNOTE 564 study

Study design: double-blind, randomised, placebo-controlled, phase 3
Comparison: Pembrolizumab **vs** placebo[2]
Data cut-off: 1st data cut-off from 14 December 2020 and 2nd data cut-off from 14 July 2021

Mortality

Endpoint	Pembrolizumab		Placebo		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 (data cut-off of 14 July 2021)					
	496	n.a. *23 (4.6)*	498	n.a. *43 (8.6)*	0.52 [0.31; 0.86] 0.011

[1] Data from the dossier assessment of the IQWiG (A22-71) and from the addendum (A22-128), unless otherwise indicated.
[2] The investigations conducted in the placebo arm of the KEYNOTE 564 study are considered sufficient implementation of the appropriate comparator therapy consisting of the wait-and-see approach.

Morbidity

Endpoint	**Pembrolizumab**		**Placebo**		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
Recurrences (data cut-off from 14 July 2021) (according to the principal investigator)					
Recurrence rate[a]	496	– *114 (23.0)*	498	– 169 (33.9)	RR: 0.68 [0.55; 0.83] < 0.001[b]
Local recurrence	496	– *17 (3.4)*	498	– *32 (6.4)*	–
Remote metastases	496	– *91 (18.3)*	498	– *134 (26.9)*	–
Death	496	– *6 (1.2)*	498	– *3 (0.6)*	–
Disease-free survival	496	n.a. *114 (23.0)*	498	n.a. *169 (33.9)*	0.63 [0.50; 0.80] < 0.001
Recurrences (data cut-off from 14 July 2022) - presented additionally (according to BICR)					
Recurrence rate[a]	477[b]	– *117 (24.5)[b]*	469[b]	– *141 (30.1)[b]*	RR: 0.82 [0.66; 1.01] 0.058[b]
Disease-free survival	496	n.a. *117 (23.6)*	498	n.a. *141 (28.3)*	0.78 [0.61; 0.99] 0.043
Event rate (recurrence/ progression rate)[c]	496[b]	– *133 (26.8)*	498[b]	– *167 (33.5)*	RR: 0.80 [0.66; 0.97] 0.022[b]
Event-free survival	496	– *133 (26.8)*	498	– *167 (33.5)*	0.75 [0.60; 0.94] 0.013

Endpoint	Pembrolizumab			Placebo			Intervention vs control
	N	Values at start of study MV (SD)	Mean change in the course of study MV (SE)	N	Values at start of study MV (SD)	Mean change in the course of study MV (SE)	MD [95% CI] p value
Symptomatology							
FKSI-DRS[d] (data cut-off from 14 December 2020)							
	423	32.86 (3.50)	−1.26 (0.18)	440	32.83 (3.46)	−0.58 (0.18)	-0.68 [-1.06; -0.30] n.d. SMD[b]: -0.24 [-0.37; -0.10]
Symptom scales of the EORTC QLQ-C30[e] (data cut-off from 14 December 2020)							
Exhaustion	426	18.70 (18.98)	6.45 (0.90)	443	18.76 (18.35)	3.86 (0.88)	2.59 [0.71; 4.47] n.d. SMD[b]: 0.18 [0.05; 0.32]
Nausea and vomiting	426	2.03 (7.57)	2.12 (0.45)	443	2.14 (8.53)	0.90 (0.44)	1.23 [0.30; 2.15] n.d. SMD[b]: 0.18 [0.04; 0.31]
Pain	426	15.85 (21.36)	3.48 (0.94)	443	13.96 (17.84)	2.24 (0.92)	1.24 [-0.71; 3.20]; n.d.
Dyspnoea	426	9.00 (18.43)	5.37 (0.89)	443	8.43 (16.91)	2.86 (0.88)	2.51 [0.65; 4.38] n.d. SMD[b]: 0.18 [0.05; 0.31]
Insomnia	426	18.23 (24.92)	3.54 (1.12)	443	21.22 (26.17)	1.82 (1.11)	1.71 [-0.64; 4.06] n.d.
Appetite loss	426	5.56 (15.10)	2.77 (0.74)	443	5.49 (14.27)	-0.28 (0.73)	3.05 [1.51; 4.60] n.d. SMD[b]: 0.26 [0.13; 0.40]

(continuation)

Endpoint	Pembrolizumab			Placebo			Intervention vs control
	N	Values at start of study MV (SD)	Mean change in the course of study MV (SE)	N	Values at start of study MV (SD)	Mean change in the course of study MV (SE)	MD [95% CI] p value
Constipation	426	8.61 (17.68)	0.95 (0.84)	443	7.98 (16.68)	0.69 (0.82)	0.27 [-1.48; 2.01]; n.d.
Diarrhoea	426	4.30 (11.87)	3.97 (0.78)	443	3.99 (11.06)	3.37 (0.76)	0.60 [-1.01; 2.22]; n.d.
Health status (data cut-off from 14 December 2020)							
EQ-5D-5L VAS[c]	436	84.07 (13.99)	-3.52 (0.66)	454	83.22 (14.48)	-2.44 (0.65)	-1.08 [-2.47; 0.30] n.d.

Health-related quality of life

Endpoint	Pembrolizumab			Placebo			Intervention vs control
	N	Values at start of study MV (SD)	Mean change in the course of study MV (SE)	N	Values at start of study MV (SD)	Mean change in the course of study MV (SE)	MD [95% CI] p value
Functional scales of the EORTC QLQ-C30[d] (data cut-off from 14 December 2020)							
Global health status	426	79.28 (18.56)	-5.52 (0.84)	443	77.29 (17.36)	-2.07 (0.83)	-3.45 [-5.20; -1.69] n.d. SMD[b]: -0.26 [-0.39; -0.13]
Physical functioning	426	88.69 (14.89)	-2.91 (0.61)	443	88.88 (13.82)	-1.45 (0.60)	-1.46 [-2.73; -0.18] n.d. SMD[b]: -0.15 [-0.29; -0.02]

(continuation)

Endpoint	Pembrolizumab			Placebo			Intervention vs control
	N	Values at start of study MV (SD)	Mean change in the course of study MV (SE)	N	Values at start of study MV (SD)	Mean change in the course of study MV (SE)	MD [95% CI] p value
Role functioning	426	87.95 (19.92)	-4.42 (0.92)	443	87.92 (19.07)	-2.11 (0.90)	-2.31 [-4.22; -0.39]; n.d. SMD[b]: -0.16 [-0.29; -0.03]
Emotional functioning	426	85.04 (17.60)	-3.10 (0.83)	443	84.41 (17.83)	-0.99 (0.82)	-2.11 [-3.86; -0.37] n.d. SMD[b]: -0.16 [-0.29; -0.03]
Cognitive functioning	426	91.67 (13.44)	-4.55 (0.78)	443	90.44 (14.80)	-2.72 (0.77)	-1.83 [-3.46; -0.19] n.d. SMD[b]: -0.15 [-0.28; -0.02]
Social functioning	426	90.26 (17.14)	-4.34 (0.88)	443	88.68 (18.90)	-1.01 (0.86)	-3.33 [-5.17; -1.50] n.d. SMD[b]: -0.24 [-0.37; -0.11]

Side effects
(data cut-off from 14 July 2021)

Endpoint	Pembrolizumab		Placebo		Intervention vs control
	N	*Patients with event n (%)*	N	*Patients with event n (%)*	Relative risk [95% CI] p value[b]
Adverse events (AEs)[f] (presented additionally)					
	488	470 (96.3)	496	453 (91.3)	–

(continuation)

Endpoint	Pembrolizumab		Placebo		Intervention vs control
	N	*Patients with event n (%)*	N	*Patients with event n (%)*	Relative risk [95% CI] p value[b]
Serious adverse events (SAE)[f]					
	488	101 (20.7)	496	57 (11.5)	1.80 [1.33; 2.43] < 0.001
Severe adverse events (CTCAE grade ≥ 3)[f]					
	488	157 (32.2)	496	88 (17.7)	1.81 [1.44; 2.28] <0.001
Therapy discontinuation due to adverse events[f]					
	488	103 (21.1)	496	11 (2.2)	9.52 [5.18; 17.50] < 0.001
Specific adverse events					
Immune-mediated AEs (presented additionally)	488	n.d.	496	n.d.	–
Immune-mediated SAEs	488	42 (8.6)	496	1 (0.2)	42.69 [5.90; 308.94] <0.001
Immune-mediated severe AEs	488	45 (9.2)	496	3 (0.6)	15.25 [4.77; 48.73] < 0.001
Endocrine disorders (severe AE, SOC)	488	12 (2.5)	496	1 (0.2)	12.20 [1.59; 93.44] 0.002
Skin and subcutaneous tissue disorders (severe AE, SOC)	488	10 (2.0)	496	2 (0.4)	5.08 [1.12; 23.07] 0.019
Gastrointestinal disorders (severe AE, SOC)	488	24 (4.9)	496	9 (1.8)	2.71 [1.27; 5.77] 0.010

(continuation)

Endpoint	Pembrolizumab		Placebo		Intervention vs control
	N	*Patients with event n (%)*	N	*Patients with event n (%)*	Relative risk [95% CI] p value[b]
Examinations (severe AE, SOC)	488	27 (5.5)	496	4 (0.8)	6.86 [2.42; 19.46] < 0.001
Metabolism and nutrition disorders (severe AE, SOC)	488	26 (5.3)	496	14 (2.8)	1.89 [1.00; 3.57] 0.047

[a] Individual components - if available - are shown in the rows below; since only the qualifying events are included in the recurrence rate (total), effect estimators of the individual components are not shown

[b] IQWiG calculation (RR, CI, p value, SMD)

[c] The endpoint event-free survival is based on the assessments of a BICR. It includes the events of recurrence (local recurrence or remote metastases) in patients who were tumour-free at baseline or disease progression in patients who were assessed as tumour-free at baseline by the principal investigator but not by the BICR, or death of any cause. The assessment of disease status at baseline was based on baseline scans.

[d] Higher (increasing) values mean better symptomatology / health-related quality of life; positive effects (intervention minus control) mean an advantage for the intervention (scale range EORTC QLQ-C30 functional scales and global health status 0 to 100, EQ- 5D VAS 0 to 100, FKSI-DRS 0 to 36).

[e] Lower (decreasing) values mean better symptomatology; negative effects (intervention minus control) mean an advantage for the intervention (scale range 0 to 100).

[f] Progression events of the underlying disease are not included (PTs "Neoplasm progression", "Malignant neoplasm progression" and "Disease progression").

Abbreviations used:
BICR = Blinded Independent Central Review; CTCAE = Common Terminology Criteria for Adverse Events; HR = hazard ratio; n.d. = no data available; CI = confidence interval; MD = mean difference; MedDRA = Medical Dictionary for Regulatory Activities; MMRM = Mixed Model with Repeated Measures; MV = mean value;; N = number of patients evaluated; n = number of patients with (at least one) event; n. c. = not calculable; n. a. = not achieved; OS = overall survival; PT = preferred term; RR = relative risk; SD = standard deviation; SE = standard error; SMD = standardised mean difference (Hedges' g); SOC = system organ class; vs = versus

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

Adults with renal cell carcinoma at increased risk of recurrence following nephrectomy or following nephrectomy and resection of metastatic lesions; adjuvant treatment

approx. 1,518 - 1,973 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: 3 January 2023):

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 as well as specialists in internal medicine and nephrology and other specialists participating in the Oncology Agreement, all of whom are experienced in the treatment of patients with renal cell carcinoma.

In accordance with the EMA requirements regarding additional risk minimisation measures, the pharmaceutical company must provide training material that contains information for medical professionals and patients. The training material contains, in particular, instructions on the management of immune-mediated side effects potentially occurring with pembrolizumab as well as on infusion-related reactions.

4. Treatment costs

Annual treatment costs:

Adults with renal cell carcinoma at increased risk of recurrence following nephrectomy or following nephrectomy and resection of metastatic lesions; adjuvant treatment

Designation of the therapy	Annual treatment costs/ patient
Medicinal product to be assessed:	
Pembrolizumab	€ 85,997.44 - € 91,372.28
Appropriate comparator therapy:	
Monitoring wait-and-see approach	incalculable

Costs after deduction of statutory rebates (LAUER-TAXE® as last revised: 1 January 2023)

Costs for additionally required SHI services: not applicable

Other SHI services:

Designation of the 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	€ 100	1	8 - 17	€ 800 - € 1,700

5. Medicinal products with new active ingredients according to Section 35a, paragraph 3, sentence 4 SGB V that can be used in a combination therapy with pembrolizumab

Medicinal products with new active ingredients pursuant to Section 35a, paragraph 3, sentence 4 SGB V are medicinal products with the following new active ingredients which, on the basis of the marketing authorisation under Medicinal Products Act, can be used in a combination therapy with pembrolizumab for the adjuvant treatment of renal cell carcinoma with increased risk of recurrence after nephrectomy or after nephrectomy and resection of metastatic lesions in adults:

Adults with renal cell carcinoma at increased risk of recurrence following nephrectomy or following nephrectomy and resection of metastatic lesions; adjuvant treatment

- No active ingredient that can be used in a combination therapy that fulfils the requirements of Section 35a, paragraph 3, sentence 4 SGB V.

II. The resolution will enter into force on the day of its publication on the website of the G-BA on 19 January 2023.

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

Berlin, 19 January 2023

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

Prof. Hecken