Gemeinsamer Bundesausschuss

Pembrolizumab (Reassessment due to New Scientific Knowledge: Urothelial Carcinoma)

First Resolution of: 16 March 2018
Entry into force on: 16 March 2018
Federal Gazette, BAnz AT 04 04 2019 B4

Second Resolution of: 2 August 2018
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Federal Gazette, BAnz AT 27 08 2018 B3

Third Resolution of: 20 June 2019 Valid until: 1 July 2020
Entry into force on: 20 June 2019
Federal Gazette, BAnz 08 08 2019 B3

New therapeutic indications (according to the marketing authorisation of 6 July 2018):

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

Keytruda is indicated as monotherapy for the treatment of locally advanced or metastatic urothelial carcinoma after prior platinum-based therapy in adults.

Note:

The resolution of 20 June 2019 relates exclusively to the assessment of the additional benefit of pembrolizumab in the sub-population: a) Urothelial carcinoma; patients who are not eligible for cisplatin-based therapy and whose tumours express PD-L1 with a combined positive score (CPS) ≥ 10 (first line) New therapeutic indications (according to the marketing authorisation of 24 August 2017):

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

a) Urothelial carcinoma; patients who are not eligible for cisplatin-based therapy and whose tumours express PD-L1 with a combined positive score (CPS) ≥ 10 (first line)

Appropriate comparator therapy:

Chemotherapy according to the doctor's instructions

Extent and probability of the additional benefit of pembrolizumab compared to the appropriate comparator therapy:

An additional benefit is not proven.

Study results according to endpoints:

a) Urothelial carcinoma; patients who are not eligible for cisplatin-based therapy and whose tumours express PD-L1 with a combined positive score (CPS) ≥ 10 (first line)

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

b) Patients with prior platinum-containing therapy

Appropriate comparator therapy:

a) For patients with an early relapse (≤ 6 months)

- Vinflunine

b) For patients with a late relapse (> 6 to12 months)

- Vinflunine

or

- Renewed cisplatin-containing chemotherapy (for patients who, depending on the course of the disease, general condition, and tolerability of the first-line therapy, are eligible for it)

Extent and probability of the additional benefit compared with vinflunine:

Indication of a considerable additional benefit.

Study results according to endpoints:

1. Patients who are ineligible for cisplatin-containing therapy (first-line)

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

2. Patients with prior platinum-containing therapy

Results of the KEYNOTE 045 study[1]:

Endpoint category Endpoint		Pembrolizumab		Vinflunine	Pembrolizumab vs vinflunine
	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][a] p value[b]
Mortality					
Overall survival (18 January 2017)[c]	82	10.8 [7.4; 15.0] 54 (65.9)	90	7.4 [5.2; 8.8] 74 (82.2)	0.60 [0.41; 0.87] 0.008
Overall survival (7	82	10.8 [7.4; 15.2]	90	7.4 [5.2; 8.8]	0.65 [0.44; 0.96]

[1] Data from the IQWiG dossier evaluation (A17-46), unless otherwise indicated.

Endpoint category Endpoint		Pembrolizumab		Vinflunine	Pembrolizumab vs vinflunine
	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][a] p value[b]
September 2016)[c]		48 (58.5)		66 (73.3)	0.032
Morbidity					
Progression-free survival (PFS)					
No data available for the relevant sub-population.					
EORTC QLQ-C30 – symptom scales (time until deterioration – 10 points)					
Fatigue	82	1.4 [0.7; 2.1] 58 (70.7)	86	1.4 [0.8; 1.4] 57 (66.3)	0.77 [0.52; 1.15] 0.200
Nausea and vomiting	82	7.0 [3.8; n.a.] 32 (39.0)	86	2.4 [1.9; 6.2] 37 (43.0)	0.49 [0.28; 0.85] 0.012
Pain	82	2.1 [1.5; 6.8] 43 (52.4)	86	2.1 [1.4; 3.7] 45 (52.3)	0.81 [0.52; 1.26] 0.347
Dyspnoea	82	6.2 [3.8; n.a.] 33 (40.2)	86	3.4 [1.5; 10.3] 38 (44.2)	0.53 [0.31; 0.90] 0.019
Insomnia	82	9.2 [2.1; n.a.] 32 (39.0)	86	5.3 [2.1; n.a.] 29 (33.7)	0.94 [0.56; 1.60] 0.862
Loss of appetite	82	7.8 [4.2; n.a.] 32 (39.0)	86	2.4 [1.4; 3.6] 45 (52.3)	0.53 [0.32; 0.87] 0.012
Constipation	82	9.3 [4.9; n.a.] 27 (32.9)	86	1.6 [1.1; 3.4] 43 (50.0)	0.41 [0.24; 0.70] 0.001
Diarrhoea	82	11.8 [6.3; n.a.] 24 (29.3)	86	5.9 [4.0; n.a.] 25 (29.1)	0.79 [0.43; 1.45] 0.454
Health status (EQ-5D VAS)					
Time until deterioration – 10 points	82	4.9 [2.1; 9.2] 39 (47.6)	86	2.1 [1.5; 3.7] 42 (48.8)	0.66 [0.41; 1.06] 0.088
Time until deterioration – 7 points	82	3.7 [1.9; 7.0] 42 (51.2)	86	1.8 [1.4; 2.3] 48 (55.8)	0.64 [0.41; 1.01] 0.055
Health-related quality of life					
EORTC QLQ-C30 – functional scales (time until deterioration – 10 points)					
Global health status/quality of life	82	3.7 [2.1; 7.0] 41 (50.0)	86	2.4 [1.6; 4.1] 40 (46.5)	0.78 [0.49; 1.26] 0.312
Physical function	82	2.1 [2.0; 9.0] 42 (51.2)	86	2.1 [1.4; 4.1] 44 (51.2)	0.78 [0.50; 1.22] 0.280
Role function	82	2.1 [1.3; 6.2]	86	1.4 [1.0; 1.6]	0.73 [0.47; 1.12]

Endpoint category Endpoint		Pembrolizumab		Vinflunine	Pembrolizumab vs vinflunine
	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][a] p value[b]
		46 (56.1)		51 (59.3)	0.151
Emotional function	82	7.6 [4.8; n.a.] 32 (39.0)	86	3.6 [2.1; 7.1] 36 (41.9)	0.65 [0.39; 1.10] 0.109
Cognitive function	82	4.8 [1.5; 7.6] 41 (50.0)	86	2.1 [1.4; 3.5] 42 (48.8)	0.78 [0.49; 1.25] 0.307
Social function	82	3.5 [2.0; 6.2] 42 (51.2)	86	1.5 [1.0; 2.4] 48 (55.8)	0.76 [0.48; 1.19] 0.227
Side effects					
AE (additionally shown)	82	0.3 [0.2; 0.4][d] 77 (93.9)	87	0.1 [0.0; 0.1][d] 87 (100.0)	–
SAE	82	20.0 [6.0; n.a.][d] 35 (42.7)	87	3.0 [0.9; n.a.][d] 49 (56.3)	0.56 [0.35; 0.90] 0.015
Severe AE (CTCAE grade ≥ 3)	82	5.8 [2.1; 9.0][d] 46 (56.1)	87	0.8 [0.3; 1.4][d] 59 (67.8)	0.52 [0.34; 0.78] 0.002
Discontinuation because of AE	82	7 (8.5)	87	13 (14.9)	RR: 0.57 [0.24; 1.36] 0.245[e]
Specific AE					
Immune mediated AE	No data available for the relevant sub-population				
Immune mediated SAE	No data available for the relevant sub-population				
immune mediated Severe AE (CTCAE grade ≥ 3)	No data available for the relevant sub-population				
Other specific AE	No data available for the relevant sub-population				

a: Cox proportional hazard model stratified by ECOG performance status (0 / 1 vs 2), presence of liver metastases (yes vs no), haemoglobin value (≥ 10 g/dl vs < 10 g/dl), and time since last completed chemotherapy (< 3 months vs ≥ 3 months).
b: Two-sided p value (Wald test)
c: The derivation of the additional benefit is based on the data cut-off of 18 January 2017; the data cut-off of 7 September 2016 is presented additionally.
d: In Module 4 B, the median time to the event is given in weeks; for the sake of clarity, a separate conversion into months was performed.
e: Own calculation of effect, CI (asymptotic), and p value (unconditional exact test, CSZ method).

Abbreviations used: CTCAE: Common Terminology Criteria for Adverse Events; EORTC QLQ-C30: European Organization for Research and Treatment of Cancer Quality of Life Questionnaire; EQ-5D: EuroQoL-5 Dimensions; HR: Hazard ratio; CI: confidence interval; n: number of patients with (at least one) event; N: number of patients evaluation; n.a.: not achieved; RCT: randomised controlled trial; SAE: serious adverse event; AE: adverse event; VAS: visual analogue scale; vs: versus

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

a) Urothelial carcinoma; patients who are not eligible for cisplatin-based therapy and whose tumours express PD-L1 with a combined positive score (CPS) ≥ 10 (first line)

Approx. 240–420 patients

b) Patients with prior platinum-containing therapy

Approx. 1,500 to 1,900 patients

3. Requirements for a quality-assured application

The requirements of 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: 27 March 2019):

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

Only specialists in internal medicine, haematology, and oncology with experience treating patients with urothelial carcinoma, specialists in urology, and specialists participating in the Oncology Agreement may initiate and monitor treatment with pembrolizumab.

In accordance with the specifications of the EMA regarding additional measures for risk minimisation, the pharmaceutical company must provide training material and a patient card. Patients are requested to carry their patient cards with them at all times. The training material for health professionals and the patient card shall include, in particular, instructions on how to deal with the potential immune-mediated adverse reactions to pembrolizumab as well as infusion reactions.

4. Treatment costs

a) Urothelial carcinoma; patients who are not eligible for cisplatin-based therapy and whose tumours express PD-L1 with a combined positive score (CPS) ≥ 10 (first line)

Designation of the therapy	Annual treatment costs/patient
Medicinal product to be assessed:	
Pembrolizumab	€ 103,757.46
Appropriate comparator therapy:	
patient-individualized	

Costs after deduction of statutory rebates (LAUER-TAXE®) as last revised: 01 June 2019)

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
Pembrolizumab	a)	€ 71	1	8.5 - 17	€ 603.50 – € 1,207
a) Surcharge for the preparation of a parenteral solution containing monoclonal antibodies"					

Designation of the therapy	Annual treatment costs per patient
Medicinal product to be assessed	
Pembrolizumab	€ 105,010.36
Appropriate comparator therapy	
1. Patients who are ineligible for cisplatin-containing therapy (first-line)	
different for each individual patient	
2. Patients with prior platinum-containing therapy	
Vinflunine	€ 66,446.20
Cisplatin monotherapy[2] (dosing scheme 1) *Additionally required SHI services* Total	€ 928.07 – 3,173.05 *€ 127.06 – 413.74* € 1,055.13 – 3,586.79
Cisplatin monotherapy[2] (dosing scheme 2) *Additionally required SHI services* Total	€ 2,851.55 – 3,728.95 *€ 635.31 – 1,294.34* € 3,486.86 – 5,023.29
Cisplatin + gemcitabine[2] *Additionally required SHI services* Total	€ 6,914.70 *(cisplatin: € 1,498.38, gemcitabine: € 5,416.32)* *€ 245.49 – 316.39* € 7,160.19 – 7,231.09

Costs after deduction of statutory rebates (LAUER-TAXE®) as last revised: 15 February 2018

[2] In accordance with the appropriate comparator therapy, renewed cisplatin-containing chemotherapy can only be considered for patients with relapse after at least 6 – 12 months.

Other services covered by SHI funds:

Designation of the therapy	Type of service	Cost per unit	Number per cycle	Number per patient per year	Cost per patient per year
Type of service: *a = Surcharge for the preparation of a parenteral solution containing monoclonal antibodies* *b = Surcharge for production of a parenteral preparation containing cytostatic agents*					
Medicinal product to be assessed					
Pembrolizumab	a	€ 71	1	17	€ 1,207
Appropriate comparator therapy					
1. Patients who are ineligible for cisplatin-containing therapy (first-line)					
different for each individual patient					
2. Patients with prior platinum-containing therapy					
Vinflunine	b	€ 81	1	17	€ 1,377
Cisplatin monotherapy	b	€ 81	1 – 5	13 – 85	€ 1,053 – 6,885
Cisplatin + gemcitabine					
Cisplatin	b	€ 81	1	13	€ 1,053
Gemcitabine	b	€ 81	3	39	€ 3,159