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: melanoma, adjuvant treatment, ≥ 12 years)

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 19 January 2023: "as monotherapy for the treatment of unresectable or metastatic biliary cancer with MSI-H or a dMMR and disease progression during or after at least one prior therapy":**

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 22 June 2022):

Keytruda as monotherapy is indicated for the adjuvant treatment of adults and adolescents aged 12 years and older with Stage IIB, IIC or III melanoma and who have undergone complete resection.

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

Keytruda as monotherapy is indicated for the adjuvant treatment of adults and adolescents aged 12 years and older with Stage IIB or IIC melanoma and who have undergone complete resection, and adolescents aged 12 years and older in tumour stage III after complete resection.

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

a) Adults and adolescents aged 12 years and older with melanoma in tumour Stage IIB or IIC after complete resection; 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:

Indication of non-quantifiable additional benefit

b) Adolescents aged 12 years and older with melanoma in tumour stage III after complete resection; adjuvant treatment

Appropriate comparator therapy:

Therapy according to 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) Adults and adolescents aged 12 years and older with melanoma in tumour Stage IIB or IIC after complete resection; adjuvant treatment

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	↑↑	Advantage in recurrences and recurrence-free survival
Health-related quality of life	↔	No relevant differences for the benefit assessment.
Side effects	↓↓	Disadvantages in the endpoints of severe AEs (CTCAE grade ≥ 3) 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 716 study: Pembrolizumab **vs** placebo [1, 2]

Study design: randomised, double-blind, two-armed

Mortality

Endpoint	**Pembrolizumab**		**Placebo**		Intervention vs control
	N	Patients with event n (%)	N	Patients with event n (%)	RR [95% CI] p value Absolute difference (AD)[a]
Overall mortality [b]					
	487	25 (5.1)[c]	489	30 (6.1)[c]	0.84 [0.50; 1.40] 0.533[c]

Morbidity

Endpoint	**Pembrolizumab**		**Placebo**		Intervention vs control
	N	Patients with event n (%)	N	Patients with event n (%)	RR [95% CI] p value Absolute difference (AD)[a]
Recurrences					
Recurrence rate[d]	487	95 (19.5)	489	139 (28.4)	0.69 [0.55; 0.86] 0.001[c]
Local recurrence	487	24 (4.9)	489	26 (5.3)	–[f]
Regional recurrence	487	15 (3.1)	489	24 (4.9)	–[f]
locoregional recurrence	487	7 (1.4)	489	6 (1.2)	–[f]
Remote metasta-sation	487	41 (8.4)	489	71 (14.5)	–[f]
Loco-regional recurrence and	487	4 (0.8)	489	6 (1.2)	–[f]

[1] Data from the dossier assessment of the Institute for Quality and Efficiency in Health Care (IQWiG) (A22-72) unless otherwise indicated.

[2] Data cut-off from 04.01.2022

Endpoint	Pembrolizumab		Placebo		Intervention vs control
	N	Patients with event n (%)	N	Patients with event n (%)	RR [95% CI] p value Absolute difference (AD)[a]
remote metasta-sation[e]					
Death without recurrence	487	4 (0.8)	489	6 (1.2)	–[f]
	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]
Recurrence-free survival	487	37.2 [n.c.; n.c.] 95 (19.5)	489	n.a. [n.c.; n.c.] 139 (28.4)	0.64 [0.50; 0.84] < 0.001

Endpoint	Pembrolizumab			Placebo			Intervention vs control
	N[g]	Values at the start of the study MV (SD)	Mean change in the course of the study MV (SE)	N[g]	Values at the start of the study MV (SD)	Mean change in the course of the study MV (SE)	MD [95% CI] p value[d]
Disease symptomatology							
Symptom scales of the EORTC QLQ-C30[h]							
Fatigue	430	12.58 (16.51)	7.67 (0.70)	449	14.40 (18.92)	4.30 (0.69)	3.37 [1.46; 5.27] < 0.001 SMD: 0.18 [0.08; 0.29]
Nausea and vomiting	430	1.12 (5.75)	1.97 (0.30)	449	1.22 (5.26)	1.58 (0.30)	0.40 [-0.42; 1.21] 0.339
Pain	430	11.05 (18.39)	4.48 (0.66)	449	12.58 (19.18)	1.83 (0.65)	2.65 [0.86; 4.44] 0.004

Endpoint	Pembrolizumab			Placebo			Intervention vs control
	N[g]	Values at the start of the study MV (SD)	Mean change in the course of the study MV (SE)	N[g]	Values at the start of the study MV (SD)	Mean change in the course of the study MV (SE)	MD [95% CI] p value[d]
							SMD: 0.15 [0.05; 0.24]
Dyspnoea	430	7.21 (15.84)	4.81 (0.62)	449	5.86 (14.18)	2.94 (0.61)	1.87 [0.19; 3.56] 0.030 SMD: 0.11 [0.01; 0.21]
Insomnia	430	17.60 (25.20)	1.92 (0.80)	449	17.52 (23.99)	1.38 (0.79)	0.54 [-1.63; 2.71] 0.627
Appetite loss	430	3.10 (10.21)	2.97 (0.52)	449	5.12 (15.14)	1.54 (0.51)	1.44 [0.03; 2.85] 0.045 SMD: 0.10 [0.00; 0.19]
Constipation	430	6.98 (17.12)	0.99 (0.57)	449	7.72 (18.09)	1.16 (0.56)	-0.17 [-1.71; 1.36] 0.824
Diarrhoea	430	6.51 (15.73)	1.62 (0.52)	449	5.49 (14.24)	-0.31 (0.51)	1.92 [0.51; 3.34] 0.008 SMD: 0.12 [0.03; 0.21]
Health status							
EQ-5D VAS[i]							
	437	84.41 (12.72)	-2.29 (0.46)	458	84.97 (12.79)	-0.84 (0.45)	-1.45 [-2.69; -0.21] 0.022 SMD: -0.12 [-0.22; -0.02]

Health-related quality of life

Endpoint	Pembrolizumab			Placebo			Intervention vs control
	N[g]	Values at the start of the study MV (SD)	Mean change in the course of the study MV (SE)	N[g]	Values at the start of the study MV (SD)	Mean change in the course of the study MV (SE)	MD [95% CI] p value[d]
Health-related quality of life							
Functional scales of the EORTC QLQ-C30[i]							
Global health status	430	81.80 (16.28)	-4.53 (0.54)	449	81.16 (16.00)	-2.07 (0.53)	-2.46 [-3.93; -0.98] 0.001 SMD: -0.16 [-0.26; -0.07]
Physical functioning	430	92.05 (12.49)	-2.89 (0.47)	449	91.83 (13.77)	-1.99 (0.46)	-0.90 [-2.18; 0.38] 0.169
Role functioning	430	90.23 (19.25)	-2.90 (0.66)	449	89.01 (20.91)	-0.24 (0.65)	-2.67 [-4.46; -0.87] 0.004 SMD: -0.15 [-0.25; -0.05]
Emotional functioning	430	84.86 (17.71)	0.02 (0.58)	449	84.73 (17.09)	1.18 (0.57)	-1.15 [-2.72; 0.41] 0.149
Cognitive functioning	430	92.79 (13.11)	-3.97 (0.54)	449	92.02 (14.48)	-3.02 (0.53)	-0.96 [-2.41; 0.49] 0.195
Social functioning	430	91.82 (15.72)	-1.60 (0.60)	449	90.05 (19.16)	0.84 (0.59)	-2.44 [-4.06; -0.82] 0.003 SMD: -0.15 [-0.25; -0.05]

Side effects

Endpoint	Pembrolizumab		Placebo		Intervention vs control
	N	Patients with event n (%)	N	Patients with event n (%)	RR [95% CI] p value Absolute difference (AD)[a]
Adverse events (AEs) (presented additionally)					
	483	462 (95.7)	486	445 (91.6)	-
Serious adverse events (SAE)[j]					
	483	103 (21.3)	486	94 (19.3)	1.10 [0.86; 1.42] 0.533[c]
Severe adverse events (CTCAE grade ≥ 3) [j]					
	483	137 (28.4)	486	97 (20.0)	1.42 [1.13; 1.78] 0.002 [c]
Therapy discontinuation due to adverse events[j]					
	483	83 (17.2)	486	22 (4.5)	3.80 [2.41; 5.97] <0.001[c]
Specific adverse events					
Immune-mediated SAE[j, k]	483	36 (7.5)	486	4 (0.8)	9.06 [3.25; 25.25] <0.001[c]
Immune-mediated severe AEs[j, k]	483	51 (10.6)	486	6 (1.2)	8.55 [3.71; 19.74] <0.001[c]
Endocrine disorders (SOC, severe AE[j])	483	10 (2.1)	486	0 (0)	21.13 [1.24; 359.58] 0.001 [c]
Gastrointestinal disorders (SOC, severe AEs[j])	483	23 (4.8)	486	1 (0.2)	23.14 [3.14; 170.69] <0.001[c]
Hepatobiliary disorders (SOC, severe AEs[j])	483	11 (2.3)	486	2 (0.4)	5.53 [1.23; 24.84] 0.012 [c]
Skin and subcutaneous tissue disorders (SOC, severe AE[j])	483	15 (3.1)	486	3 (0.6)	5.03 [1.47; 17.27] 0.004 [c]

Endpoint	Pembrolizumab		Placebo		Intervention vs control
	N	Patients with event n (%)	N	Patients with event n (%)	RR [95% CI] p value Absolute difference (AD)[a]

[a] Indication of absolute difference (AD) only in case of statistically significant difference; own calculation.
[b] In the KEYNOTE 716 study, no evaluations of overall survival were planned in the data cut-offs to date. In the study report, however, information on the number of deceased patients is available within the scope of the information on the course of the study and the patient flow, which is used as overall mortality.
[c] IQWiG calculation
[d] The individual components are shown in the lines below.
[e] Both local, regional or locoregional recurrence and remote metastases diagnosed within 30 days of each other
[f] No calculation of effect estimations. The events shown do not fully represent the endpoint. Only the events that come into play in the formation of the combined endpoint are shown.
[g] Number of patients who were taken into account in the evaluation for calculating the effect estimate; the values at start of study can be based on other patient numbers.
[h] Lower (decreasing) values mean better symptomatology; negative effects (intervention minus control) mean an advantage for the intervention.
[i] Higher (increasing) values mean better health status/quality of life; positive effects (intervention minus control) mean an advantage for the intervention.
[j] According to the study protocol, progression events and recurrences were not recorded as AEs.
[k] The operationalisation of a specific MedDRA PT collection submitted by the pharmaceutical company (referred to by the company as "AEOSI" [adverse events of special interest]) is used in each case.

Abbreviations used:
AD = absolute difference; 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

b) Adolescents aged 12 years and older with melanoma in tumour stage III after complete resection; adjuvant treatment

No data are available to allow an assessment of the additional benefit.

Summary of results for relevant clinical endpoints

Endpoint category	Direction of effect/ risk of bias	Summary
Mortality	∅	No data available.
Morbidity	∅	No data available.
Health-related quality of life	∅	No data available.
Side effects	∅	No data available.

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

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

a) Adults and adolescents aged 12 years and older with melanoma in tumour Stage IIB or IIC after complete resection; adjuvant treatment

approx. 1,620 – 2,310 patients

b) Adolescents aged 12 years and older with melanoma in tumour stage III after complete resection; adjuvant treatment

approx. 1 - 4 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 who are experienced in the treatment of

patients with melanoma, as well as specialists in skin and sexually transmitted diseases, and specialists in paediatrics and adolescent medicine with specialisation in paediatric haematology and oncology, and other specialists participating in the Oncology Agreement.

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:

a) Adults and adolescents aged 12 years and older with melanoma in tumour Stage IIB or IIC after complete resection; adjuvant treatment

Designation of the therapy	Annual treatment costs/ patient
Medicinal product to be assessed:	
Pembrolizumab	€ 45,686.14 - € 91,372.28
Appropriate comparator therapy:	
Monitoring wait-and-see approach	incalculable

b) Adolescents aged 12 years and older with melanoma in tumour stage III after complete resection; adjuvant treatment

Designation of the therapy	Annual treatment costs/ patient
Medicinal product to be assessed:	
Pembrolizumab	€ 45,686.14 - € 91,372.28
Appropriate comparator therapy:	
Therapy according to doctor's instructions[3]	

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

Costs for additionally required SHI services: not applicable

[3] The treatment options dabrafenib in combination with trametinib (only for patients with BRAF V600 mutation-positive melanoma in tumour stage III after complete resection) and nivolumab are suitable comparators for the present benefit assessment in the context of therapy according to doctor's instructions. However, these medicinal products are not approved in the present therapeutic indication, and therefore, no costs are presented for these medicinal products.

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 adults and adolescents aged12 years and older with Stage IIB, IIC or III melanoma and who have undergone complete resection:

a) Adults and adolescents aged 12 years and older with melanoma in tumour Stage IIB or IIC after complete resection; 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.

b) Adolescents aged 12 years and older with melanoma in tumour stage III after complete resection; 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