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: Colorectal cancer with MSI-H or dMMR, 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. **In Annex XII, the following information shall be added after point 4 to the information on the benefit assessment of pembrolizumab in the version of the resolution of 16 September 2021 for the therapeutic indication "[...] for the treatment of adult and paediatric patients aged 3 years and older with relapsed or refractory classical Hodgkin lymphoma who have failed autologous stem cell transplant (ASCT) or following at least two prior therapies when ASCT is not a treatment option":**

Pembrolizumab

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

New therapeutic indication (according to the marketing authorisation of 21 January 2021):

Colorectal cancer (CRC)

KEYTRUDA as monotherapy is indicated for the first-line treatment of metastatic microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) colorectal cancer in adults.

Therapeutic indication of the resolution (resolution of 16 September 2021):

see therapeutic indication according to marketing authorisation

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

a) Adult patients with metastatic microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) colorectal cancer eligible for intensive therapy; first-line treatment

Appropriate comparator therapy:

A patient-individual treatment depending on the all-RAS mutation status, the location of the primary tumour, as well as the risk of bevacizumab-induced toxicity under the selection of

- combination therapy of 5-fluorouracil + folinic acid + oxaliplatin (FOLFOX)

- combination therapy of 5-fluorouracil + folinic acid + irinotecan (FOLFIRI)

- combination therapy of 5-fluorouracil + folinic acid + oxaliplatin (FOLFOX) and an anti-EGFR therapy (cetuximab or panitumumab) - (only for patients with wild-type RAS)

- combination therapy of 5-fluorouracil + folinic acid + irinotecan (FOLFIRI) and an anti-EGFR therapy (cetuximab or panitumumab) - (only for patients with wild-type RAS)

- combination therapy of 5-fluorouracil + folinic acid + oxaliplatin (FOLFOX) and bevacizumab

- combination therapy of 5-fluorouracil + folinic acid + irinotecan (FOLFIRI) and bevacizumab

Extent and probability of the additional benefit of pembrolizumab compared to FOLFOX or FOLFIRI ± cetuximab or bevacizumab

Hint for a minor additional benefit.

b) Adult patients with metastatic microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) colorectal cancer not eligible for intensive therapy; first-line treatment.

Appropriate comparator therapy:

- 5-fluorouracil + folinic acid ± bevacizumab

or

- capecitabine ± bevacizumab

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:[1]

a) Adult patients with metastatic microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) colorectal cancer eligible for intensive therapy; first-line treatment.

[1] Data from the dossier assessment of the IQWiG (A21-36) and from the addendum (A21-105), unless otherwise indicated.

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	n.a.	There are no assessable data.
Health-related quality of life	n.a.	There are no assessable data.
Side effects	↑↑	Advantages in the endpoints severe AEs (CTCAE grade 3 or 4) and serious AEs (SAE)

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 177 study: Pembrolizumab **vs** FOLFOX or FOLFIRI ± cetuximab or bevacizumab (data cut-off 19 February 2020)

Mortality

Endpoint	Pembrolizumab		mFOLFOX6 or FOLFIRI ± cetuximab or bevacizumab		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]
Overall survival					
	153	n.a. 56 (36.6)	154	34.8 [26.3; n. c.] 69 (44.8)	0.77 [0.54; 1.09] 0.140

Morbidity

Progression-free survival (PFS) [i]					
	153	16.5 [5.4; 32.4] 82 (53.6)	154	8.2 [6.1; 10.2] 113 (73.4)	0.60 [0.45; 0.80] < 0.001 AD = 8.3 months
Symptomatology					

Symptomatology (EORTC QLQ-C30)	There are no assessable data.
Symptomatology (EORTC QLQ-CR29)	There are no assessable data.
Health status (EQ-5D VAS)	There are no assessable data.

Health-related quality of life

EORTC QLQ-C30	There are no assessable data.
EORTC QLQ-CR29	There are no assessable data.

Side effects

Endpoint	**Pembrolizumab**		**mFOLFOX6 or FOLFIRI ± cetuximab or bevacizumab**		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][b]; p-value[c] Absolute difference (AD)[a]
Adverse events in total[e]					
	153	0.3 [0.1; 0.5][f] 149 (97.4)	143	0.1 [0.1; 0.1][f] 142 (99.3)	
Serious adverse events (SAE)[e]					
	153	24.6 [14.0; n. c.][f] 62 (40.5)	143	8.0 [3.7; 20.6][f] 75 (52.4)	0.61 [0.43; 0.85]; 0.004 AD = 16.6 months
Severe adverse events (CTCAE grade 3 or 4)[e, g]					
	153	10.8 [6.3; 14.1][f] 86 (56.2)	143	2.1 [1.5; 2.6][f] 111 (77.6)	0.41 [0.31; 0.55]; < 0.001 AD = 8.7 months
Therapy discontinuation due to adverse events					
	153	n.a. 21 (13.7)	143	n. a. [27.5; n. c.][f] 17 (11.9)	0.88 [0.46; 1.70]; 0.710
Immune-mediated SAEs[e,h]					
	153	n. a. 16 (10.5)	143	n. a. 1 (0.7)	12.04 [1.59; 91.28]; 0.016
Immune-mediated severe AEs[e, g, h]					
	153	n. a. 14 (9.2)	143	n. a. 3 (2.1)	3.10 [0.88; 10.95]; 0.079

Specific adverse events					
Mucosa inflammation (PT, AEs)	153	n. a. 7 (4.6)	143	n. a. 27 (18.9)	0.19 [0.08; 0.44]; < 0.001
Decreased appetite (PT, AEs)	153	n. a. 36 (23.5)	143	14.9 [6.9; n. c.][f] 58 (40.6)	0.49 [0.32; 0.74]; < 0.001
Arthralgia (PT, AEs)	153	n. a. 28 (18.3)	143	n. a. 7 (4.9)	3.12 [1.35; 7.19]; 0.008
Peripheral neuropathy (PT, AE)	153	n. a. 1 (0.7)	143	n. a. 27 (18.9)	0.03 [0.00; 0.22]; < 0.001
Peripheral sensory neuropathy (PT, AEs)	153	n. a. 3 (2.0)	143	n. a. 31 (21.7)	0.07 [0.02; 0.22]; < 0.001
Epistaxis (PT, AEs)	153	n. a. 2 (1.3)	143	n. a. 23 (16.1)	0.07 [0.02; 0.28]; < 0.001
Alopecia (PT, AEs)	153	n. a. 11 (7.2)	143	n. a. 29 (20.3)	0.29 [0.14; 0.59]; < 0.001
palmar-plantar erythrodysesthesia syndrome (PT, AEs)	153	n. a. 1 (0.7)	143	n. a. [17,0: n. c.][f] 25 (17.5)	0.03 [0.00; 0.19]; < 0.001
Blood and lymphatic system disorders (SOC, severe AEs[g])	153	n. a. 12 (7.8)	143	n. a. 39 (27.3)	0.24 [0.12; 0.46]; < 0.001
Gastrointestinal disorders (SOC, severe AEs[g])	153	n. a. 31 (20.3)	143	n. a. [9,5: n. c.][f] 52 (36.4)	0.40 [0.25; 0.63]; < 0.001
Fatigue (PT, severe AEs[g])	153	n. a. 6 (3.9)	143	n. a. 13 (9.1)	0.32 [0.12; 0.86]; 0.024
Infections and infestations (SOC, severe AEs[g])	153	n. a. 14 (9.2)	143	n. a. 23 (16.1)	0.51 [0.26; 0.99]; 0.046

a. Indication of absolute difference (AD) only in case of statistically significant difference; own calculation
b. HR and CI: Cox-Proportional-Hazards-Model
c. p-value: Wald test
d. no usable data available; for justification, see section 2.3.2.1 of the present dossier assessment
e. Overall rate excluding AEs attributed to progression of the underlying disease, defined as the MedDRA terms "neoplasm progression", "malignant neoplasm progression", and "disease progression."
f. own conversion from weeks to months
g. operationalised as CTCAE grade ≥ 3
h. predefined PT list of the pharmaceutical company (version 17.1)
i. Data from the dossier of the pharmaceutical company; BICR (Blinded Independent Central Review), primary analysis

Abbreviations used:
5-FU: 5-Fluorouracil; 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-Cancer 30; EORTC-QLQ-CR29: European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Colorectal 29; EQ-5D: European Quality of Life-5 Dimensions; FOLFIRI: Folinic acid + 5-FU + irinotecan; HR: Hazard ratio; CI: Confidence interval; mFOLFOX6: Folinic acid + 5-FU + oxaliplatin (modified regimen); MedDRA: Medical Dictionary for Regulatory Activities; n: number of patients with event; N: Number

of patients evaluated; n. c.: not calculable; n. a.: not achieved; PT: preferred term; RCT: randomised controlled trial; SOC: System organ class; SAE: serious adverse event; AE: adverse event; VAS: visual analogue scale; vs: versus

b) Adult patients with metastatic microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) colorectal cancer not eligible for intensive therapy; first-line 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.a.: not assessable

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

a) Adult patients with metastatic microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) colorectal cancer eligible for intensive therapy; first-line treatment:

approx. 320 – 830 patients

b) Adult patients with metastatic microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) colorectal cancer not eligible for intensive therapy; first-line treatment.

approx. 50 – 125 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: 15 August 2021):
https://www.ema.europa.eu/en/documents/product-information/keytruda-epar-product-information_en.pdf

Treatment with pembrolizumab should only be initiated in patients with metastatic colorectal cancer and monitored by specialists in internal medicine, haematology, oncology, gastroenterology specialists, and specialists participating in the Oncology Agreement.

Before initiation of therapy with pembrolizumab, the presence of microsatellite instability-high (MSI-H) or mismatch repair deficiency (dMMR) should be confirmed by a validated test in a tumour sample.

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

4. Treatment costs

Annual treatment costs:

a) Adult patients with metastatic microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) colorectal cancer eligible for intensive therapy; first-line treatment

Designation of the therapy	Annual treatment costs/ patient
Medicinal product to be assessed:	
Pembrolizumab	€ 99,706.18
Appropriate comparator therapy:	
FOLFOX (5-fluorouracil + folinic acid + oxaliplatin) ± bevacizumab or cetuximab or panitumumab	
FOLFOX 4	
Oxaliplatin	€ 4,546.44
Folinic acid	€ 4,315.92
5-fluorouracil	€ 495.18
Total:	€ 9,357.54
Bevacizumab	€ 38,259.21

Designation of the therapy	Annual treatment costs/ patient
FOLFOX 4 + bevacizumab	€ 47,616.75
Cetuximab	€ 74,604.89
FOLFOX 4 + cetuximab	€ 83,962.43
Panitumumab	€ 79,772.56
FOLFOX 4 + Panitumumab	€ 89,130.10
FOLFOX 6	
Oxaliplatin	€ 4,546.44
Folinic acid	€ 3,317.64
5-fluorouracil	€ 495.18
Total:	€ 8,359.26
FOLFIRI (5-fluorouracil + folinic acid + irinotecan) ± bevacizumab or cetuximab or panitumumab	
FOLFIRI	
Irinotecan	€ 16,938.12
Folinic acid	€ 7,200.52
5-fluorouracil	€ 1,044.21
Total:	€ 25,182.85
Bevacizumab	€ 38,259.21
FOLFIRI + bevacizumab	€ 63,442.06
Cetuximab	€ 74,604.89
FOLFIRI + cetuximab	€ 99,787.74
Panitumumab	€ 79,772.56
FOLFIRI + panitumumab	€ 104,995.41

Costs after deduction of statutory rebates (LAUER-TAXE® as last revised: 1 September 2021)

Costs for additionally required SHI services: None

Other SHI services:

Designation of 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 containing monoclonal antibodies	€ 71	1	8.7 – 17.4	€ 617.70 - € 1,235.40
Appropriate comparator therapy:					

FOLFOX 4					
Oxaliplatin	Surcharge for the preparation of a parenteral preparation containing cytostatic agents	€ 81	1	12	€ 972
Folinic acid	Surcharge for production of a parenteral calcium folinate solution	€ 39	2	24	€ 936
5-fluorouracil	Surcharge for the preparation of a parenteral preparation containing cytostatic agents	€ 81	2	24	€ 1,944
FOLFOX 6					
Oxaliplatin	Surcharge for the preparation of a parenteral preparation containing cytostatic agents	€ 81	1	12	€ 972
Folinic acid	Surcharge for production of a parenteral calcium folinate solution	€ 39	1	12	€ 468
5-fluorouracil	Surcharge for the preparation of a parenteral preparation containing cytostatic agents	€ 81	1	12	€ 972
FOLFIRI					
Irinotecan	Surcharge for the preparation of a parenteral preparation containing cytostatic agents	€ 81	1	26.1	€ 2,114.10
Folinic acid	Surcharge for production of a parenteral calcium folinate solution	€ 39	1	26.1	€ 1,017.90
5-fluorouracil	Surcharge for the preparation of a parenteral preparation containing cytostatic agents	€ 81	1	26.1	€ 2,114.10

Combination therapies					
Bevacizumab (14-day cycle)	Surcharge for the preparation of parenteral solutions containing monoclonal antibodies	€ 71	1	26.1	€ 1,853.10
Cetuximab	Surcharge for the preparation of parenteral solutions containing monoclonal antibodies	€ 71	1	52.1	€ 3,699.10
Panitumumab	Surcharge for the preparation of parenteral solutions containing monoclonal antibodies	€ 71	1	26.1	€ 1,853.10

b) Adult patients with metastatic microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) colorectal cancer not eligible for intensive therapy; first-line treatment.

Designation of the therapy	Annual treatment costs/ patient
Medicinal product to be assessed:	
Pembrolizumab	€ 99,706.18
Appropriate comparator therapy:	
5-fluorouracil ± bevacizumab	
Folinic acid	€ 9,286.48
5-fluorouracil	€ 1,044.21
5-fluorouracil + folinic acid	€ 10,330.69
Bevacizumab	€ 38,259.21
5-fluorouracil + folinic acid + bevacizumab	€ 48,589.90
Capecitabine ± bevacizumab	
Capecitabine	€ 2,777.53
Bevacizumab	€ 38,508.46
Capecitabine + bevacizumab	€ 41,285.99

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
Medicinal product to be assessed:					
Pembrolizumab	Surcharge for the preparation of parenteral solutions containing monoclonal antibodies	€ 71	1	8.7 – 17.4	€ 617.70 - € 1,235.40
Appropriate comparator therapy:					
Folinic acid	Surcharge for production of a parenteral calcium folinate solution	€ 39	2	52.2	€ 2,035.80
5-fluorouracil	Surcharge for the preparation of a parenteral preparation containing cytostatic agents	€ 81	2	52.2	€ 4,228.20
Bevacizumab (14-day cycle)	Surcharge for the preparation of parenteral solutions containing monoclonal antibodies	€ 71	1	26.1	€ 1,853.10
Bevacizumab (21-day cycle)	Surcharge for the preparation of parenteral solutions containing monoclonal antibodies	€ 71	1	17.4	€ 1,235.40

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