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: gastric cancer with MSI-H or dMMR, pretreated)

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 advanced or recurrent endometrial carcinoma with MSI-H or a dMMR, and with disease progression on or following prior treatment with a platinum-containing therapy in any setting when curative surgery or radiation is not an option":**

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 25 April 2022):

Keytruda as monotherapy is indicated for the treatment of the following MSI-H or dMMR tumours in adults with:

- unresectable or metastatic gastric, small intestine, or biliary cancer, who have disease progression on or following at least one prior therapy.

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

Keytruda as monotherapy is indicated for the treatment of the following MSI-H or dMMR tumours in adults with:

- unresectable or metastatic gastric cancer, who have disease progression on or following at least one prior therapy.

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

a) Adults with unresectable or metastatic gastric cancer with microsatellite instability-high (MSI-H) or with mismatch repair deficiency (dMMR) and disease progression on or following one prior therapy

Appropriate comparator therapy:

Therapy according to doctor's instructions

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

Hint for a non-quantifiable additional benefit

b) Adults with unresectable or metastatic gastric cancer with microsatellite instability-high (MSI-H) or with mismatch repair deficiency (dMMR) and disease progression on or following at least two prior therapies

Appropriate comparator therapy:

Trifluridine/tipiracil

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) Adults with unresectable or metastatic gastric cancer with microsatellite instability-high (MSI-H) or with mismatch repair deficiency (dMMR) and disease progression on or following one prior therapy

Summary of results for relevant clinical endpoints

Endpoint category	Direction of effect/ risk of bias	Summary
Mortality	↑	Advantage in overall survival.
Morbidity	n.c.	There are no assessable data.
Health-related quality of life	n.c.	There are no assessable data.
Side effects	↔	No relevant differences 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.c.: not calculable		

KEYNOTE 061 study: Pembrolizumab vs paclitaxel

Study design: randomised, open-label

Relevant sub-population: Patients with unresectable or metastatic gastric cancer with MSI-H or dMMR and with progression of the disease

Data cut-off used: 10 June 2021

[1] Data from the dossier assessment of the Institute for Quality and Efficiency in Health Care (IQWiG) (A22-77) unless otherwise indicated.

Mortality

Endpoint	**Pembrolizumab**		**Paclitaxel**		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[a]
Overall survival					
	11	n.a. [6.1; n.c.] 5 (45.5)	10	8.9 [1.6; 16.7] 9 (90.0)	0.25 [0.08; 0.80] 0.020

Morbidity

Endpoint	**Pembrolizumab**		**Paclitaxel**		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
Progression-free survival (PFS)[b,c]					
	11[d]	18.3[e] [1.1; -] 8 (72.7)	10[d]	3.6[e] [1.6; 16.7] 9 (90.0)	0.44 [0.16; 1.19][f] 0.105[f,g]
Symptomatology (EORTC QLQ-C30)[h]					
No usable data available					
Symptomatology (EORTC QLQ-STO22)[h]					
No usable data available					
Health status (EQ-5D VAS)[h]					
No usable data available					

Health-related quality of life

EORTC QLQ-C30[h]
No usable data available

Side effects

Endpoint	Pembrolizumab		Paclitaxel		Intervention vs control
	N	Median in months [95% CI] *Patients with event n (%)*	N	Median in months [95% CI] *Patients with event n (%)*	HR [95% CI] P value[a]
Total adverse events (presented additionally)					
	11	0.9 [0.1; 10.7] 11 (100)	10	2.2 [0.1; 6.0] 9 (90.0)	-
Serious adverse events (SAE)					
	11	n.a. [3.3; n.c.] 5 (45.5)	10	n.a. [9.4; n.c.] 2 (20.0)	2.59 [0.50; 13.41] 0.256
Severe adverse events (CTCAE grade ≥ 3)					
	11	n.a. [2.1; n.c.] 5 (45.5)	10	n.a. [1.0; n.c.] 3 (30.0)	1.60 [0.38; 6.68] 0.523
Therapy discontinuation due to adverse events					
	11	n.a. 0 (0)	10	n.a. [12.3; n.c.] 1 (10.0)	–; 0.289
specific AEs					
No usable data available					

[a] HR, CI and p value: Cox proportional hazards model (unstratified, unadjusted); in case of 0 events in a treatment arm score test.
[b] Data from: Dossier on pembrolizumab Module 4C of 18.07.2022.
[c] Primary analysis according to BIRC.
[d] Number of patients: Intention-to-treat population with MSI-H gastric cancer and prior therapy.
[e] Product-limit (Kaplan-Meier) method for censored data.
[f] Cox proportional hazard model with treatment as a covariate.
[g] Two-sided p value (Wald test; score test in case of zero events in one of the study arms).
[h] Evaluations are only available for the data cut-off of 26.10.2017.

Abbreviations used:
BICR = Blinded Independent Central Review; CTCAE = Common Terminology Criteria for Adverse Events; EORTC QLQ-C30 = European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30; EORTC QLQ-STO22 = European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Stomach 22; EQ-5D = EuroQoL-5 Dimensions; HR = hazard ratio; n.d. = no data available; 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; PT = preferred term; VAS = visual analogue scale; vs = versus

b) <u>Adults with unresectable or metastatic gastric cancer with microsatellite instability-high (MSI-H) or with mismatch repair deficiency (dMMR) and disease progression on or following at least two prior therapies</u>

No adequate 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	n.c.	There are no assessable data.
Morbidity	n.c.	There are no assessable data.
Health-related quality of life	n.c.	There are no assessable data.
Side effects	n.c.	There are no assessable data.
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 with unresectable or metastatic gastric cancer with microsatellite instability-high (MSI-H) or with mismatch repair deficiency (dMMR) and disease progression on or following one prior therapy

approx. 60 – 80 patients

b) Adults with unresectable or metastatic gastric cancer with microsatellite instability-high (MSI-H) or with mismatch repair deficiency (dMMR) and disease progression on or following at least two prior therapies

approx. 20 – 30 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 gastroenterology and other specialists participating in the Oncology Agreement, all of whom are experienced in the treatment of patients with gastric cancer.

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 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 with unresectable or metastatic gastric cancer with microsatellite instability-high (MSI-H) or with mismatch repair deficiency (dMMR) and disease progression on or following one prior therapy

Designation of the therapy	Annual treatment costs/ patient
Medicinal product to be assessed:	
Pembrolizumab	€ 93,522.22
Appropriate comparator therapy:	
Therapy according to doctor's instructions[2]	
Designation of the therapy	Annual treatment costs/ patient
Ramucirumab - combination with paclitaxel	
Ramucirumab	€ 71,049.68
Paclitaxel	€ 18,195.84
Total	€ 89,245.52
Additionally required SHI services	€ 479.61

[2]In the context of a clinical study, the all following treatment options are considered suitable comparators for therapy according to doctor's instructions: Irinotecan, docetaxel, paclitaxel, ramucirumab in combination with paclitaxel. Irinotecan, docetaxel and paclitaxel (monotherapy), however, are not approved in the therapeutic indication, which is why these costs are not presented.

Ramucirumab - monotherapy	
Ramucirumab	€ 71,322.95

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

b) Adults with unresectable or metastatic gastric cancer with microsatellite instability-high (MSI-H) or with mismatch repair deficiency (dMMR) and disease progression on or following at least two prior therapies

Designation of the therapy	Annual treatment costs/ patient
Medicinal product to be assessed:	
Pembrolizumab	€ 93,522.22
Appropriate comparator therapy:	
Trifluridine/ tipiracil	€ 42,234.96

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
Medicinal product to be assessed:					
Pembrolizumab	Surcharge for the preparation of a parenteral solution containing monoclonal antibodies	€ 100	1	8.7 - 17.4	€ 870 - € 1,740
Appropriate comparator therapy:					
Paclitaxel	Surcharge for production of a parenteral preparation containing cytostatic agents	€ 100	3	39.0	€ 3,900
Ramucirumab	Surcharge for the preparation of a parenteral solution containing monoclonal antibodies	€ 100	1 - 2	26.0 - 26.1	€ 2,600 - € 2,610

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 that can be used in a combination therapy with pembrolizumab for the treatment of unresectable or metastatic gastric cancer with microsatellite instability-high (MSI-H) or with a mismatch repair deficiency (dMMR) and progression of the disease on or following at least one previous therapy:

a) Adults with unresectable or metastatic gastric cancer with microsatellite instability-high (MSI-H) or with mismatch repair deficiency (dMMR) and disease progression on or following one prior therapy

- 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) Adults with unresectable or metastatic gastric cancer with microsatellite instability-high (MSI-H) or with mismatch repair deficiency (dMMR) and disease progression on or following at least two prior therapies

- 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