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 or gastro-oesophageal junction adenocarcinoma,
PD-L1 expression ≥ 1, HER2+, first-line,
combination with trastuzumab and fluoropyrimidine and platinum-containing chemotherapy)

of 20 June 2024

At its session on 20 June 2024, 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. 5 to the information on the benefit assessment of Pembrolizumab in accordance with the resolution of 2 February 2023:

Pembrolizumab

Resolution of: 20 June 2024
Entry into force on: 20 June 2024
Federal Gazette, BAnz AT DD. MM YYYY Bx

New therapeutic indication (according to the marketing authorisation of 23 August 2023):

KEYTRUDA, in combination with trastuzumab, fluoropyrimidine and platinum-containing chemotherapy, is indicated for the first-line treatment of locally advanced unresectable or metastatic HER2-positive gastric or gastro-oesophageal junction adenocarcinoma in adults whose tumours express PD-L1 with a CPS ≥ 1.

Therapeutic indication of the resolution (resolution of 20 June 2024):

See new therapeutic indication according to marketing authorisation.

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

Adults with locally advanced unresectable or metastatic HER2-positive gastric or gastro-oesophageal junction adenocarcinoma whose tumours express PD-L1 with a CPS ≥ 1; first-line therapy

Appropriate comparator therapy for pembrolizumab, in combination with trastuzumab, fluoropyrimidine and platinum-containing chemotherapy:

- Trastuzumab in combination with capecitabine and cisplatin

  or

- trastuzumab in combination with 5-fluorouracil and cisplatin

Extent and probability of the additional benefit of pembrolizumab, in combination with trastuzumab, fluoropyrimidine and platinum-containing chemotherapy compared with trastuzumab in combination with 5-fluorouracil and cisplatin:

An additional benefit is not proven.

Study results according to endpoints:[1]

Adults with locally advanced unresectable or metastatic HER2-positive gastric or gastro-oesophageal junction adenocarcinoma whose tumours express PD-L1 with a CPS ≥ 1; first-line therapy

An additional benefit is not proven.

[1] Data from the dossier assessment of the Institute for Quality and Efficiency in Health Care (IQWiG) (A24-01) 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	↔	No relevant difference for the benefit assessment in the endpoints of SAEs and severe AEs. No assessable data available for the endpoint of therapy discontinuation due to AEs and for 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 ∅: No data available. n.a.: not assessable		

KEYNOTE-811 study: Pembrolizumab + trastuzumab + fluoropyrimidine and platinum-containing chemotherapy* vs trastuzumab + fluoropyrimidine and platinum-containing chemotherapy*

(* 5-fluorouracil + cisplatin (FP), capecitabine + oxaliplatin (CAPOX) and S-1 (fixed combination of tegafur, gimeracil and oteracil) and oxaliplatin).

Relevant sub-population: Patients with tumours expressing PD-L1 (CPS ≥ 1) and chemotherapy regimen FP: Pembrolizumab + trastuzumab + FP vs trastuzumab + FP.

Mortality

Endpoint	**Pembrolizumab + trastuzumab + chemotherapy**		**trastuzumab + chemotherapy**		Intervention vs control
	N	Median survival time in months [95% CI][a] *Patients with event n (%)*	N	Median survival time in months [95% CI][a] *Patients with event n (%)*	Hazard ratio [95% CI] p value[b]
Overall survival					
	47	16.4 [10.2; 20.1] 40 (85.1)	43	11.2 [8.2; 15.3] 38 (88.4)	0.77 [0.50; 1.21] 0.260

Morbidity

Endpoint	**Pembrolizumab + trastuzumab + chemotherapy**		**trastuzumab + chemotherapy**		Intervention vs control
	N	Median time to event in months [95% CI][a] *Patients with event n (%)*	N	Median time to event in months [95% CI][a] *Patients with event n (%)*	Hazard ratio [95% CI] p value[b]
Symptomatology (EORTC QLQ-C30)					
No suitable data[c]					
Symptomatology (EORTC QLQ-STO22)					
No suitable data[c]					
Health status (EQ-5D VAS)					
No suitable data[c]					

Health-related quality of life

Endpoint	**Pembrolizumab + trastuzumab + chemotherapy**		**trastuzumab + chemotherapy**		Intervention vs control
	N	Median time to event in months [95% CI][a] *Patients with event n (%)*	N	Median time to event in months [95% CI][a] *Patients with event n (%)*	Hazard ratio [95% CI] p value[b]
EORTC QLQ-C30					
No suitable data[c]					

Side effects

Endpoint	Pembrolizumab + trastuzumab + chemotherapy		trastuzumab + chemotherapy		Intervention vs control
	N	Median time to event in months [95% CI][a] *Patients with event n (%)*	N	Median time to event in months [95% CI][a] *Patients with event n (%)*	Hazard ratio [95% CI] p value[b]
Total adverse events (presented additionally)					
	47	0.1 [0.1; 0.3][d] 46 (97.9)	42	0.2 [0.1; 0.3][d] 42 (100.0)	-
Serious adverse events (SAE)					
	47	13.3 [5.3; n.c.][d] 23 (48.9)	42	12.6 [4.5; n.c.][d] 79 (56.4)	0.88 [0.48; 1.60] 0.673
Severe adverse events (CTCAE grade ≥ 3)					
	47	2.3 [1.1; 3.7][d] 39 (83.0)	A42	2.4 [1.4; 6.7][d] 28 (66.7)	1.37 [0.84; 2.22] 0.209
Therapy discontinuation due to adverse events					
No suitable data[e]					
Specific adverse events					
Cardiac disorders (SOC, severe AE; CTCAE grade ≥ 3)					
	n.d.	n.d.	n.d.	n.d.	n.d.
Immune-mediated AEs (presented additionally)[f]					
	n.d.	n.d.	n.d.	n.d.	-
Immune-mediated SAEs (PT collection)[f]					
	n.d.	n.d.	n.d.	n.d.	n.d.
Immune-mediated severe AEs (PT collection; CTCAE grade ≥ 3)[f]					
	n.d.	n.d.	n.d.	n.d.	n.d.
Other specific AEs					
No suitable data[g]					

a. Kaplan-Meier estimate
b. HR, CI and p value: Cox proportional hazards model with Wald CI and two-tailed Wald test, unstratified
c. For these evaluations, the pharmaceutical company only provides information in the dossier on the return numbers of the questionnaires for the patient population it is considering. This includes all patients with PD-L1 CPS ≥ 1 regardless of the therapy received. As the assessment-relevant sub-population (CPS ≥ 1 and FP treatment) only accounts for around 15% of this population, the available information on the returns for

the relevant sub-population is not significant. It is therefore not possible to estimate the percentage of missing values for the assessment-relevant sub-population.

d. Conversion from weeks to months; IQWiG calculation
e. For the endpoint of therapy discontinuation due to AEs, it is not clear from the information provided by the pharmaceutical company in Module 4 A whether these are evaluations of the time until discontinuation of all active ingredient components or until discontinuation of at least 1 active ingredient component. After discontinuation of individual active ingredients, patients were able to continue treatment with the remaining active ingredients in accordance with the study protocol. In the present data basis (4 active ingredient components in the intervention arm and 3 active ingredient components in the comparator arm), an evaluation of the discontinuation of all active ingredient components alone cannot be interpreted meaningfully.
f. In each case, the operationalisation of the pharmaceutical company-specific MedDRA PT collection from the endpoint of adverse events of special interest (AEOSI, version 23) is used.
g. Suitable evaluations (time-to-event analyses) of AEs according to PT and SOC are not fully available for the relevant sub-population, so it is not possible to select specific AEs.

Abbreviations used:
AEOSI = Adverse Events of Special Interest; 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 Organisation for Research and Treatment of Cancer Quality of Life Questionnaire – Gastric Cancer 22; EQ-5D = European Quality of Life-5 Dimensions; FP = 5-fluorouracil + cisplatin; HR = hazard ratio; n.d. = no data available; CI = confidence interval; MedDRA = Medical Dictionary for Regulatory Activities; N = number of patients evaluated; n = number of patients with (at least one) event; n.c. = not calculable; PT = preferred term; SOC = system organ class; 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

Adults with locally advanced unresectable or metastatic HER2-positive gastric or gastro-oesophageal junction adenocarcinoma whose tumours express PD-L1 with a CPS ≥ 1; first-line therapy

Approx. 70 to 710 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: 12 June 2024):

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 or gastro-oesophageal junction carcinomas.

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 locally advanced unresectable or metastatic HER2-positive gastric or gastro-oesophageal junction adenocarcinoma whose tumours express PD-L1 with a CPS ≥ 1; first-line therapy

Designation of the therapy	Annual treatment costs/ patient
Medicinal product to be assessed:	
Pembrolizumab in combination with trastuzumab, 5-fluorouracil and cisplatin	
Pembrolizumab	€ 97,656.46
Trastuzumab	€ 42,462.20
5-fluorouracil	€ 1,794.81
Cisplatin	€ 2,274.18
Total	€ 144,187.65
Appropriate comparator therapy:	
Trastuzumab in combination with capecitabine and cisplatin	
Trastuzumab	€ 42,462.20
Capecitabine	€ 2,085.66
Cisplatin	€ 2,274.18
Total	€ 46,822.04
Trastuzumab in combination with 5-fluorouracil and cisplatin	
Trastuzumab	€ 42,462.20
5-fluorouracil	€ 1,794.81
Cisplatin	€ 2,274.18
Total	€ 46,531.19

Costs after deduction of statutory rebates (LAUER-TAXE®) as last revised: 1 June 2024)

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 in combination with trastuzumab, 5-fluorouracil and cisplatin					
Pembrolizumab	Surcharge for the preparation of a parenteral solution containing monoclonal antibodies	€ 100	1	8.7 - 17.4	€ 870 - € 1,740
Trastuzumab	Surcharge for the preparation of a parenteral solution containing monoclonal antibodies	€ 100	1	17.4	€ 1,740
5-fluorouracil	Surcharge for production of a parenteral preparation containing cytostatic agents	€ 100	5	87	€ 8,700
Cisplatin	Surcharge for production of a parenteral preparation containing cytostatic agents	€ 100	1	17.4	€ 1,740
Appropriate comparator therapy:					
Trastuzumab in combination with capecitabine and cisplatin					
Trastuzumab	Surcharge for the preparation of a parenteral solution containing monoclonal antibodies	€ 100	1	17.4	€ 1,740
Cisplatin	Surcharge for production of a parenteral preparation containing cytostatic agents	€ 100	1	17.4	€ 1,740

Designation of the therapy	Type of service	Costs/ unit	Number/ cycle	Number/ patient year	Costs/ patient year
Trastuzumab in combination with 5-fluorouracil and cisplatin					
Trastuzumab	Surcharge for the preparation of a parenteral solution containing monoclonal antibodies	€ 100	1	17.4	€ 1,740
5-fluorouracil	Surcharge for production of a parenteral preparation containing cytostatic agents	€ 100	5	87	€ 8,700
Cisplatin	Surcharge for production of a parenteral preparation containing cytostatic agents	€ 100	1	17.4	€ 1,740

5. Designation of 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 the assessed medicinal product

In the context of the designation of medicinal products with new active ingredients pursuant to Section 35a, paragraph 3, sentence 4 SGB V, the following findings are made:

Adults with locally advanced unresectable or metastatic HER2-positive gastric or gastro-oesophageal junction adenocarcinoma whose tumours express PD-L1 with a CPS ≥ 1; first-line therapy

– No medicinal product with new active ingredients that can be used in a combination therapy and fulfils the requirements of Section 35a, paragraph 3, sentence 4 SGB V.

The designation of combinations exclusively serves the implementation of the combination discount according to Section 130e SGB V between health insurance funds and pharmaceutical companies. The findings made neither restrict the scope of treatment required to fulfil the medical treatment mandate, nor do they make statements about expediency or economic feasibility.

II. The resolution will enter into force on the day of its publication on the website of the G-BA on 20 June 2024.

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

Berlin, 20 June 2024

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

Prof. Hecken