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: non-small cell lung carcinoma, adjuvant treatment, after prior chemotherapy)

of 17 October 2024

At its session on 17 October 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 20 June 2024:

Pembrolizumab

Resolution of: 17 October 2024
Entry into force on: 17 October 2024
Federal Gazette, BAnz AT DD. MM YYYY Bx

New therapeutic indication (according to the marketing authorisation of 12 October 2023):

Keytruda as monotherapy is indicated for the adjuvant treatment of adults with non-small cell lung carcinoma who are at high risk of recurrence following complete resection and platinum-based chemotherapy.

Therapeutic indication of the resolution (resolution of 17 October 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 non-small cell lung carcinoma at high risk of recurrence following complete resection and platinum-based chemotherapy; 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:

An additional benefit is not proven.

Study results according to endpoints:[1]

Adults with non-small cell lung carcinoma at high risk of recurrence following complete resection and platinum-based chemotherapy; 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	↑	Advantages in the prevention of recurrences.
Health-related quality of life	↔	No relevant difference for the benefit assessment.
Side effects	↓↓	Disadvantages in the endpoints of serious adverse events (SAE), 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
∅: No data available.
n.a.: not assessable

KEYNOTE 091 study

- Comparison: Pembrolizumab vs placebo[2]
- Study design: triple-blinded, randomised, controlled phase III study
- Relevant sub-population of the KEYNOTE 091 study: Patients with prior chemotherapy
- Results based on the third data cut-off from 24.01.2023

[1] Data from the dossier assessment of the Institute for Quality and Efficiency in Health Care (IQWiG) (A24-47) unless otherwise indicated.
[2] The investigations conducted in the placebo arm of the KEYNOTE 091 study are considered sufficient implementation of the appropriate comparator therapy consisting of the wait-and-see approach.

Mortality

Endpoint	Pembrolizumab		Placebo		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 (%)*	Hazard ratio [95% CI] p value [a] Absolute difference (AD) [b]
Mortality					
Overall survival	506	n.r. 113 (22.3)	504	n.r. 138 (27.4)	0.79 [0.62; 1.01] 0.064

Morbidity

Recurrences					
Recurrence rate	506	- 225 (44.5)	504	- 262 (52.0)	RR: 0.86 [0.75; 0.97] [c] 0.018 AD: - 7.5%
Death	506	- 30 (5.9)	504	- 18 (3.6)	-
Distant metastases	506	- 74 (14.6)	504	- 96 (19.0)	-
Locoregional recurrence	506	- 51 (10.1)	504	- 72 (14.3)	-
Locoregional recurrence and distant metastases	506	- 31 (6.1)	504	- 40 (7.9)	-
New malignancy	506	- 34 (6.7)	504	- 32 (6.3)	-
Not disease-free at the start of the study	506	- 5 (1.0)	504	- 4 (0.8)	-
Disease-free survival [d]	506	53.8 [46.2; 70.4] 225 (44.5)	504	40.5 [32.9; 47.4] 262 (52.0)	0.76 [0.64; 0.91] 0.003 AD: + 13.3 months

Endpoint	Pembrolizumab			Placebo			Intervention vs control
	N [e]	Values at the start of the study MV (SD)	Change over the course of the study MV [f] (SE)	N [e]	Values at the start of the study MV (SD)	Change over the course of the study MV [f] (SE)	MD [95% CI] [f]
Symptomatology							
EORTC QLQ-C30 [g]							
Fatigue	472	30.0 (22.6)	-3.7 (1.1)	492	30.5 (22.1)	-5.0 (1.1)	1.21 [-0.69; 3.12]
Nausea and vomiting	472	6.0 (14.1)	-2.0 (0.5)	492	6.7 (14.8)	-2.7 (0.5)	0.68 [-0.25; 1.60]
Pain	473	15.6 (20.2)	0.5 (1.1)	493	16.2 (20.5)	0.4 (1.2)	0.09 [-1.93; 2.10]
Dyspnoea	466	29.3 (26.6)	-5.0 (1.2)	490	32.0 (28.2)	-6.1 (1.2)	1.05 [-1.11; 3.21]
Insomnia	471	19.5 (26.2)	-0.0 (1.2)	492	20.1 (27.1)	0.3 (1.3)	-0.29 [-2.48; 1.90]
Appetite loss	469	10.7 (19.5)	-2.3 (1.0)	489	14.1 (23.1)	-4.5 (1.0)	2.23 [0.45; 4.00] SMD: 0.11 [0.02; 0.20]
Constipation	473	13.7 (24.3)	-2.6 (1.0)	492	12.0 (22.0)	-3.6 (1.0)	0.98 [-0.76; 2.72]
Diarrhoea	468	6.4 (15.8)	2.3 (0.8)	490	5.9 (15.2)	1.1 (0.9)	1.25 [-0.25; 2.75]
EORTC QLQ-LC13 [g]							
Dyspnoea	465	24.0 (19.0)	-1.5 (0.9)	484	24.9 (20.1)	-2.2 (0.9)	0.75 [-0.89; 2.39]
Cough	471	26.3 (23.9)	-3.6 (1.1)	488	26.9 (23.5)	-3.7 (1.1)	0.16 [-1.79; 2.11]
Haemoptysis	470	0.3 (3.8)	0.2 (0.2)	488	0.6 (5.8)	0.1 (0.2)	0.09 [-0.29; 0.47]

Mouth pain	470	4.2 (13.9)	0.3 (0.6)	488	5.1 (15.1)	-0.5 (0.7)	0.76 [-0.38; 1.90]
Dysphagia	470	4.4 (13.6)	0.3 (0.6)	487	3.7 (12.3)	0.1 (0.6)	0.21 [-0.80; 1.22]
Peripheral neuropathy	469	14.7 (23.6)	3.9 (1.3)	484	16.9 (27.2)	3.1 (1.4)	0.84 [-1.56; 3.25]
Alopecia	466	26.4 (33.0)	-19.9 (0.8)	484	26.5 (33.0)	-20.6 (0.8)	0.65 [-0.74; 2.05]
(Chest) pain	467	13.6 (20.9)	-2.9 (0.9)	485	13.8 (22.3)	-2.6 (0.9)	-0.21 [-1.85; 1.42]
(Arm/ shoulder) pain	466	10.3 (19.9)	4.0 (1.1)	486	12.3 (21.2)	2.9 (1.1)	1.04 [-0.88; 2.95]
(Other) pain	450	14.0 (22.6)	2.0 (1.2)	466	16.8 (26.3)	1.3 (1.3)	0.69 [-1.54; 2.92]
Health status							
EQ-5D VAS [h]							
	457	74.6 (17.0)	0.5 (0.9)	472	72.8 (16.4)	1.3 (0.9)	-0.82 [-2.41; 0.76]

Health-related quality of life

EORTC QLQ-C30 [h]							
Global health status	467	68.9 (18.9)	1.8 (0.9)	492	66.0 (19.8)	3.3 (1.0)	-1.57 [-3.25; 0.11]
Physical functioning	472	80.6 (16.3)	1.0 (0.8)	494	79.7 (16.7)	0.8 (0.9)	0.22 [-1.27; 1.71]
Role functioning	471	78.2 (25.1)	1.7 (1.2)	493	77.3 (25.0)	3.4 (1.2)	-1.66 [-3.80; 0.47]
Emotional functioning	471	82.8 (19.7)	2.4 (0.9)	491	81.7 (20.6)	2.5 (0.9)	− 0.03 [-1.69; 1.63]
Cognitive functioning	471	88.9 (17.2)	-1.3 (0.8)	492	87.1 (18.3)	-1.1 (0.9)	-0.14 [-1.65; 1.38]

Social functioning	471	82.1 (23.7)	4.3 (1.1)	492	81.5 (22.9)	6.4 (1.2)	-2.07 [-4.14; -0.01] SMD: -0.10 [-0.20; 0.00]

Side effects

Endpoint	**Pembrolizumab**		**Placebo**		Intervention vs control
	N	*Patients with event n (%)*	N	*Patients with event n (%)*	Relative risk [95% CI] p value [c] Absolute difference (AD) [b]
Total adverse events (presented additionally) [i]					
	495	475 (95.8)	499	454 (91.0)	-
Serious adverse events (SAE) [i]					
	496	127 (25.6)	499	76 (15.2)	1.68 [1.30; 2.17] < 0.001 AD: + 10,4%
Severe adverse events (CTCAE grade ≥ 3) [i,j]					
	496	170 (34.3)	499	128 (25.7)	1.34 [1.10; 1.62] 0.003 AD: + 8,6%
Therapy discontinuation due to adverse events [i]					
	496	103 (20.8)	499	29 (5.8)	3.57 [2.41; 5.29] < 0.001 AD: + 15%
Specific adverse events					
Immune-mediated AEs (presented additionally) [j]	496	n.d.	499	n.d.	-
Immune-mediated SAEs [j]	496	44 (8.9)	499	8 (1.6)	5.53 [2.63; 11.63] < 0.001
Immune-mediated severe AEs [j, k]	496	42 (8.5)	499	10 (2.0)	4.23 [2.14; 8.33] < 0.001

Endocrine disorders (SOC, SAEs)	496	10 (2.0)	499	0 (0)	21.13 [1.24; 359.55] 0.002
Respiratory, thoracic and mediastinal disorders (SOC, SAEs)	496	27 (5.4)	499	11 (2.2)	2.47 [1.24; 4.92] 0.008
Hepatobiliary disorders (SOC, severe AEs) [k]	496	14 (2.8)	499	1 (0.2)	14.08 [1.86; 106.70] < 0.001
Infections and infestations (SOC, severe AEs) [k]	496	34 (6.9)	499	19 (3.8)	1.80 [1.04; 3.11] 0.033

[a.] Cox proportional hazards model, stratified by tumour stage (IB vs II vs IIIA), PD-L1 status (< 1% vs 1-49% vs ≥ 50%), region (Western Europe vs Eastern Europe vs rest of the world vs Asia), histology (squamous vs non-squamous) and smoking status (non-smoker vs former/current smoker)
[b.] Indication of absolute difference (AD) only in case of statistically significant difference; own calculation
[c.] 95% CI: asymptotic, p value: unconditional exact test, CSZ method according to Martin Andres et al., 1994
[d.] operationalised as the time from the day of randomisation up to 1st occurrence of an event, individual components see recurrence rate
[e.] 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.
[f.] MMRM of change at the start of the study adjusted for value at the start of the study, tumour stage (IB vs II vs IIIA), PD-L1 status (< 1% vs 1-49% vs ≥ 50%), region (Western Europe vs Eastern Europe vs rest of the world vs Asia), histology (squamous vs non-squamous) and smoking status (non-smoker vs former/current smoker). The survey time points are continuously included in the model. For the MDs, the pharmaceutical company did not submit the p values required by the dossier template.
[g.] Lower (decreasing) values mean better symptomatology; negative effects (intervention minus comparison) mean an advantage for the intervention (scale range 0 to 100).
[h.] Higher (increasing) values mean a better health status or better health-related quality of life; positive effects (intervention minus comparison) mean an advantage for the intervention (scale range 0 to 100).
[i.] Progression events of the underlying disease are not included (PTs "Neoplasm progression", "Malignant neoplasm progression" and "Disease progression").
[j.] The MedDRA PT collection "Adverse Events Of Special Interest" ("AEOSI, version 23.1") defined by the pharmaceutical company is used.
[k.] Operationalised as CTCAE grade ≥ 3

Abbreviations used:
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 – Core 30; EORTC QLQ-LC13 = European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire – Lung Cancer 13; EQ-5D VAS = EQ-5D visual analogue scale; HR = hazard ratio; n.d.: no data available; CI = confidence interval; MD = mean difference; MMRM = mixed model for repeated measures; MV = mean value; N = number of patients evaluated; n = number of patients with (at least 1) event; n.r. = not reached; RR = relative risk; SD = standard deviation; SE = standard error; SMD = standardised mean difference; SAE = serious adverse event; AE = adverse event; vs = versus

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

Adults with non-small cell lung carcinoma at high risk of recurrence following complete resection and platinum-based chemotherapy; adjuvant treatment

Approx. 2,690 to 3,200 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 September 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 who are experienced in the treatment of patients with non-small cell lung carcinoma, as well as specialists in internal medicine and pulmonology or specialists in pulmonary medicine and other doctors from specialist groups 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:

Adults with non-small cell lung carcinoma at high risk of recurrence following complete resection and platinum-based chemotherapy; adjuvant treatment

Designation of the therapy	Annual treatment costs/ patient
Medicinal product to be assessed:	
Pembrolizumab	€ 82,806.40 - € 87,981.80
Appropriate comparator therapy:	
Monitoring wait-and-see approach	Not calculable

Costs after deduction of statutory rebates (LAUER-TAXE®) as last revised: 15 September 2024)

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
Pembrolizumab	Surcharge for the preparation of a parenteral solution containing monoclonal antibodies	€ 100	1	8-17	€ 800 - € 1,700

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 non-small cell lung carcinoma at high risk of recurrence following complete resection and platinum-based chemotherapy; adjuvant treatment

- 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 17 October 2024.

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

Berlin, 17 October 2024

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

Prof. Hecken