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: cervical cancer (stage III to IVA), first-line, combination with chemoradiotherapy)

of 15 May 2025

At their session on 15 May 2025, 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 3 April 2025:**

Pembrolizumab

Resolution of: 15 May 2025
Entry into force on: 15 May 2025
Federal Gazette, BAnz AT DD. MM YYYY Bx

New therapeutic indication (according to the marketing authorisation of 21 October 2024):

KEYTRUDA, in combination with chemoradiotherapy (external beam radiation therapy followed by brachytherapy), is indicated for the treatment of FIGO 2014 Stage III - IVA locally advanced cervical cancer in adults who have not received prior definitive therapy.

Therapeutic indication of the resolution (resolution of 15 May 2025):

See new therapeutic indication according to marketing authorisation.

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

Adult patients with FIGO 2014 Stage III - IVA locally advanced cervical cancer who have not received prior definitive therapy

Appropriate comparator therapy:

- Chemoradiotherapy consisting of external beam radiation therapy (EBRT) in combination with cisplatin (monotherapy), followed by brachytherapy

Extent and probability of the additional benefit of pembrolizumab in combination with chemoradiotherapy compared to chemoradiotherapy:

Indication of non-quantifiable additional benefit

Study results according to endpoints:[1]

Adult patients with FIGO 2014 Stage III - IVA locally advanced cervical cancer who have not received prior definitive therapy

Summary of results for relevant clinical endpoints

Endpoint category	Direction of effect/ risk of bias	Summary
Mortality	↑↑	Advantage in overall survival.
Morbidity	↔	No relevant difference for the benefit assessment.
Health-related quality of life	↔	No relevant difference for the benefit assessment.
Side effects	↔	No relevant difference for the benefit assessment; in detail disadvantages 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 A18 study: Pembrolizumab + chemoradiotherapy versus placebo + chemoradiotherapy

Relevant sub-population: Patients in FIGO 2014 Stage III - IVA

Mortality

Endpoint	Pembrolizumab + chemoradiotherapy		Placebo + chemoradiotherapy		Intervention versus 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 (%)*	Hazard ratio [95% CI]; p value[a]
Overall survival					
	296	n.r. *43 (14.5)*	305	n.r. *73 (23.9)*	0.57 [0.39; 0.83][b]; 0.004[c]

[1] Data from the dossier assessment of the IQWiG (A24-110) and from the addendum (A25-43), unless otherwise indicated.

Morbidity

Progression-free survival[d] (presented additionally)					
	296	n.r. *79 (26.7)*	305	n.r. *125 (41.0)*	0.57 [0.43; 0.76]; < 0.001

Endpoint	**Pembrolizumab + chemoradiotherapy**			**Placebo + chemoradiotherapy**			Intervention versus control
	N[e]	Values at the start of the study MV (SD)	Change over the course of the study MV [95%-CI];	N[e]	Values at the start of the study MV (SD)	Change over the course of the study MV [95%-CI];	MD [95% CI]; p value
Symptomatology							
EORTC QLQ-C30[f]							
Fatigue	272	30.4 (24.8)	-7.9 [-11.0; -4.8]	283	30.1 (22.9)	-8.3 [-11.4; -5.2]	0.41 [-3.62; 4.45]; 0.841
Nausea and vomiting	272	8.6 (16.1)	-3.0 [-4.9; -1.1]	283	8.2 (17.6)	-3.7 [-5.7; -1.8]	0.77 [-1.44; 2.99]; 0.492
Pain	272	35.9 (32.1)	-17.1 [-20.6; -13.5]	283	33.3 (28.5)	-14.9 [-18.6; -11.2]	-2.16 [-6.74; 2.41]; 0.353
Dyspnoea	272	10.0 (19.0)	-1.3 [-3.6; 1.1]	283	8.9 (18.0)	-1.6 [-4.0; 0.8]	0.33 [-2.56; 3.22]; 0.822
Insomnia	272	30.8 (30.6)	-12.5 [-16.3; -8.8]	283	31.6 (30.0)	-12.1 [-15.9; -8.2]	-0.45 [-5.19; 4.28]; 0.851
Appetite loss	272	19.3 (25.8)	-9.2 [-12.3; -6.1]	283	21.2 (28.3)	-11.9 [-15.0; -8.7]	2.62 [-0.99; 6.24]; 0.155
Constipation	272	23.4 (29.7)	-13.8 [-17.2; -10.4]	283	24.2 (29.6)	-11.1 [-14.5; -7.6]	-2.72 [-6.75; 1.32]; 0.186
Diarrhoea	272	5.4 (15.9)	4.9 [2.2; 7.6]	283	6.4 (16.5)	1.1 [-1.7; 3.9]	3.83 [0.27; 7.38]; 0.035 SMD: 0.22 [0.02; 0.42]

EORTC QLQ-CX24[f]							
Symptom experience	272	20.6 (14.7)	-10.7 [-12.5; -9.0]	281	21.1 (15.7)	-10.8 [-12.5; -9.1]	0.06 [-2.04; 2.15]; 0.958
Lymphoedema	272	4.0 (12.3)	1.7 [-0.8; 4.1]	281	6.7 (17.7)	1.6 [-0.9; 4.1]	0.06 [-3.16; 3.28]; 0.970
Peripheral neuropathy	272	9.8 (18.1)	7.7 [4.2; 11.2]	281	10.9 (20.9)	4.7 [1.2; 8.3]	2.99 [-1.61; 7.58]; 0.203
Menopausal symptoms	272	16.9 (24.8)	2.6 [-1.4; 6.6]	281	17.0 (24.8)	2.0 [-2.1; 6.0]	0.67 [-4.47; 5.81]; 0.798
Sexual/ vaginal functioning	No suitable data						
Health status							
EQ-5D VAS[g]	272	72.0 (21.3)	9.5 [7.1; 11.9]	281	70.2 (20.1)	7.8 [5.4; 10.2]	1.68 [-1.31; 4.67]; 0.270

Health-related quality of life

EORTC QLQ-C30[g]							
Global health status	272	64.5 (23.7)	10.3 [7.4; 13.2]	283	64.1 (21.9)	9.3 [6.3; 12.2]	1.01 [-2.58; 4.60]; 0.581
Physical functioning	272	83.8 (18.2)	4.8 [2.5; 7.0]	283	83.4 (18.0)	5.2 [2.9; 7.4]	-0.42 [-3.25; 2.42]; 0.772
Role functioning	272	78.7 (27.2)	5.2 [2.0; 8.5]	283	79.1 (26.0)	6.1 [2.8; 9.4]	-0.88 [-5.01; 3.25]; 0.675
Emotional functioning	272	73.4 (21.9)	9.9 [7.1; 12.7]	283	72.8 (21.9)	5.4 [2.6; 8.3]	4.50 [0.78; 8.23]; 0.018 SMD: 0.24 [0.04; 0.43]
Cognitive functioning	272	84.4 (20.9)	-0.1 [-2.9; 2.6]	283	87.4 (18.7)	-2.0 [-4.7; 0.8]	1.83 [-1.71; 5.36]; 0.310
Social functioning	272	80.7 (23.7)	6.1 [3.1; 9.1]	283	78.0 (24.3)	5.8 [2.8; 8.8]	0.34 [-3.43; 4.10]; 0.861

EORTC QLQ-CX24[g]	
Sexual activity	No usable data available[h]
Concern about painful sexual intercourse	No usable data available[h]
Sexual pleasure	No usable data available
Body image	No usable data available[h]

Side effects

Endpoint	**Pembrolizumab + chemoradiotherapy**		**Placebo + chemoradiotherapy**		Intervention versus control
	N	Median time to event in weeks [95% CI] *Patients with event n (%)*	N	Median time to event in weeks [95% CI] *Patients with event n (%)*	Hazard ratio [95% CI]; p value[b,c]
Total adverse events (presented additionally)[i]					
	295	0.6 [0.4; 0.7] *295 (100.0)*	304	0.6 [0.4; 0.6] *302 (99.3)*	–
Serious adverse events (SAE)[i]					
	295	n.r. *100 (33.9)*	304	n.r. *99 (32.6)*	1.03 [0.78; 1.37]; 0.813
Severe adverse events (CTCAE grade 3 or 4)[i]					
	295	5.3 [4.6; 6.0] *232 (78.6)*	304	5.6 [4.9; 6.1] *213 (70.1)*	1.15 [0.95; 1.38]; 0.153
Therapy discontinuation due to adverse events[i]					
	295	n.r. *62 (21.0)*	304	n.r. *46 (15.1)*	1.39 [0.98; 1.96]; 0.063
Specific adverse events					
Immune-mediated severe AEs[j]	295	n.r. *12 (4.1)*	304	n.r. *4 (1.3)*	2.96 [0.95; 9.18]; 0.061
Pneumonia (PT, SAEs)	295	n.r. *13 (4.4)*	304	n.r. *3 (1.0)*	4.40 [1.25; 15.46]; 0.021

Hypokalaemia (PT, severe AEs[j])	295	n.r. 22 (7.5)	304	n.r. 10 (3.3)	2.28 [1.08; 4.81]; 0.031

a For the endpoints in the categories of morbidity and side effects: IQWiG calculation of RR, 95% CI and p value (unconditional exact test, CSZ method)
b Cox proportional hazards model
c Wald test (two-tailed)
d Information from the dossier of the pharmaceutical company
e Number of patients who were taken into account in the effect estimate; the values at the start and over the course of the study can be based on other patient numbers.
f Lower (decreasing) values mean better symptomatology; negative effects (intervention minus comparison) mean an advantage for the intervention (scale range: 0 to 100)
g Higher (increasing) values mean better health status/ health-related quality of life; positive effects (intervention minus comparison) mean an advantage for the intervention (scale range: 0 to 100)
h Presented analyses of the sexual activity scale are not plausible: The pharmaceutical company states in Module 4 A that only a few patients were sexually active. However, the data presented indicate a high level of sexual activity. The analyses of the scales "concern about painful sexual intercourse" and "body image" are also considered implausible. Regardless of this, there were no significant differences between the study arms.
i Progression events of the underlying disease are not included (PTs "Neoplasm progression", "Malignant neoplasm progression" and "Disease progression")
j Operationalised as CTCAE grade ≥ 3

Abbreviations used:
AD = absolute difference; CTCAE = Common Terminology Criteria for Adverse Events; EORTC QLQ-CX24 = European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire – Cervical Cancer Module; EORTC QLQ-C30 = European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire – Core 30; HR = hazard ratio; CI = confidence interval; MD = mean difference; MV = mean value; N = number of patients evaluated; n = number of patients with (at least one) event; n.c. = not calculable; n.r. = not reached; RR = relative risk; SD = standard deviation; SMD = standardised mean difference; SAE = serious adverse event; PT = preferred term; AE= adverse event; VAS = visual analogue scale;

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

Adult patients with FIGO 2014 Stage III - IVA locally advanced cervical cancer who have not received prior definitive therapy

Approx. 750 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: 21 February 2025):

https://www.ema.europa.eu/en/documents/product-information/keytruda-epar-product-information_en.pdf

Therapy with pembrolizumab should only be initiated and monitored by specialists in internal medicine, haematology, and oncology, specialists in obstetrics and gynaecology, and other specialists participating in the Oncology Agreement, all of whom are experienced in the treatment of patients with cervical cancer.

4. Treatment costs

Annual treatment costs:

Adult patients with FIGO 2014 Stage III - IVA locally advanced cervical cancer who have not received prior definitive therapy

Designation of the therapy	Annual treatment costs/ patient
Medicinal product to be assessed:	
Pembrolizumab in combination with chemoradiotherapy (external beam radiation therapy followed by brachytherapy)	
Pembrolizumab	€ 90,059.96
Cisplatin	€ 358.60 – € 430.32
External beam radiation therapy	€ 3,800.64 – € 4,157.58
Brachytherapy[2]	€ 1,985.92 – € 7,426.00
Total	€ 96,205.12 – € 102,073.86
Appropriate comparator therapy:	
Chemoradiotherapy consisting of external beam radiation therapy (EBRT) in combination with cisplatin (monotherapy), followed by brachytherapy	
Cisplatin	€ 430.32
External beam radiation therapy	€ 3,800.64 – € 4,157.58
Brachytherapie[2]	€ 1,985.92 – € 7,426.00
Total	€ 6,216.88 – € 12,013.90

Costs after deduction of statutory rebates (LAUER-TAXE®) as last revised: 15 April 2025)

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 in combination with chemoradiotherapy (external beam radiation therapy followed by brachytherapy)					
Pembrolizumab	Surcharge for the preparation of a parenteral solution containing monoclonal antibodies	€ 100	1	17.4 (21-day) or 8.7 (42-day)	€ 1,740 (21-day) or € 870 (42-day)

[2] The lower range results from the consideration of intracavitary brachytherapy as the sole therapy. The upper range results from the combination of intracavitary and interstitial brachytherapy.

Cisplatin	Surcharge for production of a parenteral preparation containing cytostatic agents	€ 100	1	5.0 – 6.0	€ 500 – € 600
Appropriate comparator therapy					
Chemoradiotherapy consisting of external beam radiation therapy (EBRT) in combination with cisplatin (monotherapy), followed by brachytherapy					
Cisplatin	Surcharge for production of a parenteral preparation containing cytostatic agents	€ 100	1	6.0	€ 600

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:

Adult patients with FIGO 2014 Stage III - IVA locally advanced cervical cancer who have not received prior definitive 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 15 May 2025.

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

Berlin, 15 May 2025

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

Prof. Hecken