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) and Annex XIIa – Combinations of Medicinal Products with New Active Ingredients according to Section 35a SGB V
Pembrolizumab (new therapeutic indication: urothelial carcinoma, unresectable or metastatic, first-line, combination with enfortumab vedotin)

of 3 April 2025

At their session on 3 April 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 20 March 2025:

Pembrolizumab

Resolution of: 3 April 2025
Entry into force on: 3 April 2025
Federal Gazette, BAnz AT DD. MM YYYY Bx

New therapeutic indication (according to the marketing authorisation of 29 August 2024):

KEYTRUDA, in combination with enfortumab vedotin, is indicated for the first-line treatment of unresectable or metastatic urothelial carcinoma in adults.

Therapeutic indication of the resolution (resolution of 3 April 2025):

See new therapeutic indication according to marketing authorisation.

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

a) Adults with unresectable or metastatic urothelial carcinoma who are eligible for a cisplatin-based therapy; first-line treatment

Appropriate comparator therapy:

Cisplatin in combination with gemcitabine followed by avelumab as maintenance treatment (maintenance treatment with avelumab only for patients who are progression-free)

Extent and probability of the additional benefit of pembrolizumab in combination with enfortumab vedotin compared with cisplatin in combination with gemcitabine (if applicable, followed by avelumab maintenance treatment):

Indication of non-quantifiable additional benefit.

b) Adults with unresectable or metastatic urothelial carcinoma who are not eligible for a cisplatin-based therapy; first-line treatment

Appropriate comparator therapy:

Carboplatin in combination with gemcitabine in accordance with Annex VI to Section K of the Pharmaceuticals Directive followed by avelumab as maintenance treatment (maintenance treatment with avelumab only for patients who are progression-free)

Extent and probability of the additional benefit of pembrolizumab in combination with enfortumab vedotin compared with carboplatin in combination with gemcitabine (if applicable, followed by avelumab maintenance treatment):

Indication of a considerable additional benefit.

c) Adults with unresectable or metastatic urothelial carcinoma who are not eligible for a cisplatin and carboplatin-based therapy; first-line treatment

Appropriate comparator therapy:

Individualised therapy with selection of

- atezolizumab as monotherapy,
- pembrolizumab as monotherapy and
- best supportive care

Extent and probability of the additional benefit of pembrolizumab in combination with enfortumab vedotin compared to the appropriate comparator therapy:

An additional benefit is not proven.

Study results according to endpoints:[1]

a) Adults with unresectable or metastatic urothelial carcinoma who are eligible for a cisplatin-based therapy; first-line treatment

Indication of non-quantifiable additional benefit

Summary of results for relevant clinical endpoints

Endpoint category	Direction of effect/ risk of bias	Summary
Mortality	↑↑	Advantage in overall survival
Morbidity	↑	Advantages in the symptom scales "nausea and vomiting", "constipation" and "appetite loss"
Health-related quality of life	↔	No relevant differences for the benefit assessment
Side effects	↑	Advantage for severe AEs; disadvantages and advantages for specific AEs in detail
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		

- EV-302 / KN-A39 study: Enfortumab vedotin + pembrolizumab **vs** cisplatin/ carboplatin + gemcitabine

[1] Data from the dossier assessment of the IQWiG (A24-99) and from the addendum (A25-23), unless otherwise indicated.

- Relevant sub-population: Patients who are eligible for a **cisplatin**-based therapy (n = 282)
- Ongoing, multicentre, open-label, randomised phase III study
- 1st data cut-off from 8 August 2023

Mortality

Endpoint	**Pembrolizumab + enfortumab vedotin**		**Cisplatin + gemcitabine (if applicable, followed by avelumab maintenance treatment)**		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] Absolute difference (AD)[b]
Mortality					
Overall survival	240	31.5 [25.4; n.c.] *69 (28.8)*	242	18.4 [15.6; 27.5] *110 (45.5)*	0.54 [0.40; 0.73] < 0.001 AD = +13.1 months
Overall survival (sensitivity analysis 1[c])	240	31.5 [25.4; n.c.] *69 (28.8)*	242	27.5 [18.4; n.c.] *89 (36.8)*	0.66 [0.48; 0.90] 0.009 AD = + 4 months
Overall survival (sensitivity analysis 2[d])	240	31.5 [25.4; n.c.] *69 (28.8)*	242	n.r. [18.4: n.c.] *89 (36.8)*	0.70 [0.51; 0.97] 0.030
Overall survival (sensitivity analysis 3[e])	240	31.5 [25.4; n.c.] *69 (28.8)*	242	20.4 [17.9; 30.9] *101 (41.7)*	0.61 [0.45; 0.82] 0.001 AD = + 11.4 months

Morbidity

Endpoint	Pembrolizumab + enfortumab vedotin		Cisplatin + gemcitabine (if applicable, followed by avelumab maintenance treatment)		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[a] Absolute difference (AD)[b]
Progression-free survival (PFS)[2]					
	240	12.8 [10.4; n.c.] *115 (47.9)*	242	6.5 [6.3; 7.7] *157 (64.9)*	0.48 [0.38; 0.61] < 0.0001 AD = + 6.3 months
Pain (BPI-SF – time to 1st deterioration[f])					
Worst pain (BPI-SF item 3)	210	2.0 [1.3; 4.5] *130 (61.9)*	189	1.8 [1.1; 3.2] *113 (59.8)*	0.93 [0.72; 1.21] 0.601
Impairment due to pain (BPI-SF item 9a–9g)[g]	No suitable data available				
Symptomatology (EORTC QLQ-C30 – time to 1st deterioration[h])					
Fatigue	210	0.4 [0.4; 0.6] *169 (80.5)*	189	0.4 [0.4; 0.6] *157 (83.1)*	0.80 [0.64; 1.00] 0.052
Nausea and vomiting	210	2.0 [1.1; 4.6] *131 (62.4)*	189	0.4 [0.4; 0.8] *142 (75.1)*	0.54 [0.42; 0.69] < 0.001 AD = + 1.6 months
Pain	210	0.7 [0.5; 1.3] *147 (70.0)*	189	1.1 [0.6; 1.4] *130 (68.8)*	0.97 [0.76; 1.23] 0.801
Dyspnoea	210	2.4 [1.6; 4.6] *134 (63.8)*	189	2.0 [1.7; 3.9] *107 (56.6)*	1.00 [0.77; 1.29] 0.973
Insomnia	210	2.3 [0.9; 4.5] *125 (59.5)*	189	2.0 [0.9; 3.8] *113 (59.8)*	0.85 [0.65; 1.09] 0.203
Appetite loss	210	0.9 [0.6; 1.7] *141 (67.1)*	189	0.6 [0.4; 0.9] *130 (68.8)*	0.77 [0.61; 0.98] 0.037 AD = + 0.3 months

[2] Data from Module 4 of the benefit assessment dossier from 20 September 2024

Endpoint	**Pembrolizumab + enfortumab vedotin**		**Cisplatin + gemcitabine (if applicable, followed by avelumab maintenance treatment)**		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[a] Absolute difference (AD)[b]
Constipation	210	2.2 [1.5; 4.5] *125 (59.5)*	189	0.7 [0.4; 1.3] *133 (70.4)*	0.58 [0.45; 0.74] < 0.001 AD = + 1.5 months
Diarrhoea	210	2.0 [1.3; 3.8] *132 (62.9)*	189	3.1 [2.0; 10.1] *96 (50.8)*	1.15 [0.88; 1.51] 0.290
Health status (EQ-5D VAS – time to 1st deterioration[i])					
	210	2.5 [1.3; 5.2] *138 (65.7)*	189	2.2 [1.5; 3.2] *110 (58.2)*	0.99 [0.77; 1.28] 0.948

Health-related quality of life

Endpoint	**Pembrolizumab + enfortumab vedotin**		**Cisplatin + gemcitabine (if applicable, followed by avelumab maintenance treatment)**		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[a] Absolute difference (AD)[b]
EORTC QLQ-C30 – time to 1st deterioration[j]					
Global health status	240	0.7 [0.6; 1.3] *158 (75.2)*	242	0.9 [0.6; 1.1] *132 (69.8)*	0.93 [0.73; 1.17] 0.519
Physical functioning	240	1.1 [0.6; 1.6] *165 (78.6)*	242	0.9 [0.6; 1.1] *136 (72.0)*	0.91 [0.71; 1.17] 0.407
Role functioning	240	0.6 [0.4; 0.8] *164 (78.1)*	242	0.4 [0.4; 0.9] *140 (74.1)*	0.90 [0.71; 1.13] 0.343
Emotional functioning	240	3.2 [2.0; 10.1] *120 (57.1)*	242	3.8 [2.0; n.c.] *93 (49.2)*	1.05 [0.80; 1.37] 0.751
Cognitive functioning	240	1.8 [1.1; 2.3] *143 (68.1)*	242	0.9 [0.6; 1.5] *130 (68.8)*	0.82 [0.64; 1.04] 0.098
Social functioning	240	0.7 [0.5; 1.1] *161 (76.7)*	242	0.9 [0.6; 1.1] *129 (68.3)*	1.08 [0.85; 1.36] 0.526

Side effects

Endpoint	Pembrolizumab + enfortumab vedotin		Cisplatin + gemcitabine (if applicable, followed by avelumab maintenance treatment)		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[k] Absolute difference (AD)[b]
Adverse events in total					
	239	0.2 [0.2; 0.2] *239 (100.0)*	236	0.1 [0.1; 0.2] *234 (99.2)*	-
Serious adverse events (SAE)					
	239	n.r. [41.71; n.c.] *107 (44.8)*	236	n.r. *83 (35.2)*	0.93 [0.69; 1.26] 0.639
Severe adverse events (CTCAE grade 3 or 4)					
	239	4.2 [3.0; 6.1] *164 (68.6)*	236	1.4 [1.0; 1.8] *175 (74.2)*	0.51 [0.41; 0.65] < 0.001 AD = + 2.8 months
Therapy discontinuation due to adverse events					
	239	19.3 [12.0; n.c.] *92 (38.5)*	236	n.r. *58 (24.6)*	0.94 [0.65; 1.34] 0.725
Specific adverse events					
Immune-mediated AEs (presented additionally)	*No suitable data available*				
Immune-mediated SAEs[l]	239	n.r. *34 (14.2)*	236	n.r. *2 (0.8)*	11.64 [2.76; 49.11] < 0.001
Immune-mediated severe AEs[l]	239	n.r. *49 (20.5)*	236	n.r. *3 (1.3)*	11.06 [3.39; 36.07] < 0.001
Peripheral neuropathy (SMQ, AEs)	*No suitable data available*				
Skin reactions	239	0.5 [0.4; 0.6] *204 (85.4)*	236	n.r. *61 (25.8)*	5.88 [4.39; 7.87] < 0.001

Endpoint	Pembrolizumab + enfortumab vedotin		Cisplatin + gemcitabine (if applicable, followed by avelumab maintenance treatment)		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[k] Absolute difference (AD)[b]
Severe hyperglycaemia (PT, severe AEs)	239	n.r. *20 (8.4)*	236	n.r. *2 (0.8)*	7.68 [1.76; 33.49] 0.007
Severe nephrotoxicity	239	n.r. *16 (6.7)*	236	n.r. *16 (6.8)*	0.69 [0.33; 1.46] 0.331
Nausea (PT, AEs)	239	n.r. *61 (25.5)*	236	3.1 [2.1; n.c.] *120 (50.8)*	0.35 [0.26; 0.49] < 0.001
Diarrhoea (PT, severe AEs)	239	n.r. [16.4; n.c.] *89 (37.2)*	236	n.r. *40 (16.9)*	1.90 [1.29; 2.79] 0.001
Vomiting (PT, AEs)	239	n.r. *24 (10.0)*	236	n.r. *42 (17.8)*	0.44 [0.26; 0.75] 0.003
Eye disorders (SOC, AEs)	239	19.7 [12.7; n.c.] *88 (36.8)*	236	n.r. *14 (5.9)*	5.30 [2.98; 9.41] < 0.001
Ear and labyrinth disorders (SOC, AEs)	239	n.r. *17 (7.1)*	236	n.r. *33 (14.0)*	0.17 [0.07; 0.40] < 0.001
Endocrine disorder (SOC, SAEs)	239	n.r. *34 (14.2)*	236	n.r. *2 (0.8)*	12.38 [2.94; 52.19] < 0.001
Gastrointestinal disorders (SOC, SAEs)	239	n.r. *24 (10.0)*	236	n.r. *6 (2.5)*	3.21 [1.29; 7.97] 0.012
Respiratory, thoracic and mediastinal disorders (SOC, SAEs)	239	n.r. *25 (10.5)*	236	n.r. *4 (1.7)*	4.26 [1.45; 12.53] 0.009
Blood and lymphatic system disorders (SOC, severe AEs)	239	n.r. *17 (7.1)*	236	4.9 [3.0; n.c.] *110 (46.6)*	0.08 [0.05; 0.15] < 0.001

Endpoint	Pembrolizumab + enfortumab vedotin		Cisplatin + gemcitabine (if applicable, followed by avelumab maintenance treatment)		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[k] Absolute difference (AD)[b]
Urinary tract infection (PT, severe AEs)	239	n.r. *8 (3.3)*	236	6.1 [6.1; n.c.] *19 (8.1)*	0.32 [0.13; 0.76] 0.010
General disorders and administration site conditions (SOC, severe AEs)	239	n.r. *13 (5.4)*	236	n.r. *24 (10.2)*	0.30 [0.14; 0.67] 0.003

[a] HR and CI: Cox proportional hazards model, stratified by PD-L1 expression (high vs low) and liver metastases (present vs absent); p value: Wald test
[b] Indication of absolute difference (AD) only in case of statistically significant difference; own calculation
[c] Censoring at the time of death: Avelumab-eligible patients who did not receive avelumab and died were censored at the time of death.
[d] Censoring for the data cut-off: Avelumab-eligible patients who did not receive avelumab and died were censored at the time of the data cut-off
[e] Modified date of death: Avelumab-eligible patients who did not receive avelumab and died were imputed with a modified time of death.
[f] An increase in score by ≥ 2 points compared to the start of the study is considered a clinically relevant deterioration (scale range: 0 to 10)
[g] An increase in score by ≥ 1.5 points compared to the start of the study is considered a clinically relevant deterioration (scale range: 0 to 10)
[h] An increase in EORTC QLQ-C30 score by ≥ 10 points compared to the start of the study is considered a clinically relevant deterioration (scale range: 0 to 100).
[i] A decrease in EQ-5D VAS score by ≥ 15 points compared to the start of study is considered clinically relevant deterioration (scale range: 0 to 100).
[j] A decrease in EORTC QLQ-C30 score by ≥ 10 points compared to the baseline is considered a clinically relevant deterioration (scale range: 0 to 100).
[k] HR and CI: unstratified Cox proportional hazards model, p value: Wald test
[l] In each case, the operationalisation of a specific, predefined MedDRA PT collection from the AEOSI endpoint (PT collection version 25.0, MedDRA version 26.0) presented by the pharmaceutical company is used.

Abbreviations used:
AD = absolute difference; AEOSI = Adverse Events of Special Interest; BPI-SF = Brief Pain Inventory – Short Form; CTCAE = Common Terminology Criteria for Adverse Events; EORTC QLQ-C30 = European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire – Core 30; HR = hazard ratio; CI = confidence interval; N = number of patients evaluated; n = number of patients with (at least one) event; n.c. = not calculable; n.r. = not reached; PD-L1 = Programmed Cell Death-Ligand 1; PT = preferred term; SOC = system organ class; VAS = visual analogue scale; vs = versus

b) Adults with unresectable or metastatic urothelial carcinoma who are not eligible for a cisplatin-based therapy; first-line treatment

Indication of a considerable additional benefit.

Summary of results for relevant clinical endpoints

Endpoint category	Direction of effect/ risk of bias	Summary
Mortality	↑↑	Advantage in overall survival
Morbidity	↑	Advantages for the endpoint "worst pain" and in the symptom scales "nausea and vomiting" and "constipation"; disadvantage in the symptom scale "diarrhoea"; overall advantage
Health-related quality of life	↔	Overall, no relevant differences for the benefit assessment; advantage in the functional scale "role functioning".
Side effects	↔	Advantage for severe AEs, disadvantage for therapy discontinuation due to AEs; disadvantages and advantages for specific AEs in detail
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		

- EV-302 / KN-A39 study: Enfortumab vedotin + pembrolizumab **vs** cisplatin/ carboplatin + gemcitabine
- Relevant sub-population: Patients who are **not** eligible for a **cisplatin**-based therapy (n = 404)
- Ongoing, multicentre, open-label, randomised phase III study
- 1st data cut-off from 8 August 2023

Mortality

Endpoint	**Pembrolizumab + enfortumab vedotin**		**Carboplatin + gemcitabine (if applicable followed by avelumab maintenance treatment)**		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] Absolute difference (AD)[b]
Mortality					
Overall survival	202	n.r. [22.9; n.c.] *64 (31.7)*	202	12.9 [11.4; 15.9] *116 (57.4)*	0.41 [0.30; 0.56] < 0.001
Overall survival (sensitivity analysis 1[c])	202	n.r. [22.9; n.c.] *64 (31.7)*	202	15.1 [12.5; 20.6] *97 (48.0)*	0.49 [0.36; 0.68] < 0.001
Overall survival (sensitivity analysis 2[d])	202	n.r. [22.9; n.c.] *64 (31.7)*	202	16.3 [12.9; n.c.] *97 (48.0)*	0.55 [0.40; 0.76] < 0.001
Overall survival (sensitivity analysis 3[e])	202	n.r. [22.9; n.c.] *64 (31.7)*	202	15.1 [12.9; 17.7] *110 (54.5)*	0.45 [0.33; 0.62] < 0.001

Morbidity

Endpoint	Pembrolizumab + enfortumab vedotin		Carboplatin + gemcitabine (if applicable followed by avelumab maintenance treatment)		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)[b]
Progression-free survival (PFS)[3]					
	202	10.6 [8.3; 15.3] *108 (53.5)*	202	6.1 [5.8; 6.2] *150 (74.3)*	0.42 [0.33; 0.54] < 0.0001 AD = + 4.5 months
Pain (BPI-SF – time to 1st deterioration[f])					
Worst pain (BPI-SF item 3)	166	3.2 [1.6; 10.7] *85 (51.2)*	166	1.3 [0.7; 2.2] *104 (62.7)*	0.67 [0.50; 0.89] 0.006 AD = + 1.9 months
Impairment due to pain (BPI-SF item 9a–9g)[g]	No suitable data available				
Symptomatology (EORTC QLQ-C30 – time to 1st deterioration[h])					
Fatigue	166	0.6 [0.4; 0.8] *130 (78.3)*	166	0.4 [0.4; 0.6] *131 (78.9)*	0.84 [0.65; 1.07] 0.152
Nausea and vomiting	166	1.8 [1.1; 2.7] *103 (62.0)*	166	0.9 [0.4; 1.5] *117 (70.5)*	0.71 [0.54; 0.92] 0.011 AD = + 0.9 months
Pain	166	1.1 [0.7; 1.8] *106 (63.9)*	166	0.9 [0.5; 1.3] *117 (70.5)*	0.78 [0.60; 1.02] 0.069
Dyspnoea	166	2.0 [1.3; 2.7] *101 (60.8)*	166	1.5 [1.1; 2.2] 103 (62.0)	0.87 [0.66; 1.15] 0.336
Insomnia	166	1.5 [1.1; 2.2] *101 (60.8)*	166	1.3 [0.9; 2.2] *92 (55.4)*	0.96 [0.72; 1.28] 0.793
Appetite loss	166	0.9 [0.7; 1.3] *116 (69.9)*	166	1.1 [0.6; 1.5] *110 (66.3)*	0.94 [0.72; 1.23] 0.664

[3] Data from Module 4 of the benefit assessment dossier from 20 September 2024

Endpoint	**Pembrolizumab + enfortumab vedotin**		**Carboplatin + gemcitabine (if applicable followed by avelumab maintenance treatment)**		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)[b]
Constipation	166	2.2 [1.5; 3.1] *93 (56.0)*	166	0.4 [0.4; 0.9] *112 (67.5)*	0.51 [0.39; 0.68] < 0.001 AD = + 1.8 months
Diarrhoea	166	2.0 [1.3; 3.2] *101 (60.8)*	166	4.5 [2.0; 11.0] *77 (46.4)*	1.37 [1.02; 1.85] 0.037 AD = - 2.5 months
Health status (EQ-5D VAS – time to 1st deterioration[i])					
	166	1.5 [1.0; 3.2] *105 (63.3)*	166	1.3 [0.9; 2.0] *110 (66.3)*	0.84 [0.64; 1.10] 0.202

Health-related quality of life

Endpoint	Pembrolizumab + enfortumab vedotin		Carboplatin + gemcitabine (if applicable followed by avelumab maintenance treatment)		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[a] Absolute difference (AD)[b]
EORTC-QLQ-C30 – Time to 1st deterioration[j]					
Global health status	166	1.1 [0.6; 1.6] *117 (70.5)*	166	0.9 [0.6; 1.3] *113 (68.1)*	0.97 [0.74; 1.26] 0.803
Physical functioning	166	1.1 [0.7; 1.6] *121 (72.9)*	166	0.7 [0.4; 1.1] *124 (74.7)*	0.78 [0.61; 1.01] 0.062
Role functioning	166	0.7 [0.5; 1.1] *125 (75.3)*	166	0.4 [0.4; 0.6] *136 (81.9)*	0.69 [0.54; 0.89] 0.004 AD = + 0.3 months
Emotional functioning	166	4.5 [2.1; 9.4] *90 (54.2)*	166	2.0 [1.1; 3.2] *94 (56.6)*	0.77 [0.58; 1.04] 0.088
Cognitive functioning	166	1.5 [1.1; 1.8] *112 (67.5)*	166	0.9 [0.6; 1.5] *114 (68.7)*	0.83 [0.64; 1.08] 0.173
Social functioning	166	0.9 [0.6; 1.3] *118 (71.1)*	166	0.9 [0.4; 1.1] *111 (66.9)*	0.98 [0.75; 1.28] 0.877

Side effects

Endpoint	Pembrolizumab + enfortumab vedotin		Carboplatin + gemcitabine (if applicable followed by avelumab maintenance treatment)		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[k] Absolute difference (AD)[b]
Adverse events in total					
	201	0.3 [0.2; 0.3] *200 (99.5)*	197	0.2 [0.1; 0.2] *193 (98.0)*	-
Serious adverse events (SAE)					
	201	7.6 [4.8; 13.1] *113 (56.2)*	197	5.4 [4.2; n.c.] *86 (43.7)*	0.91 [0.67; 1.22] 0.525
Severe adverse events (CTCAE grade 3 or 4)					
	201	2.6 [2.0; 4.0] *157 (78.1)*	197	0.7 [0.5; 0.9] *166 (84.3)*	0.46 [0.36; 0.58] < 0.001 AD = + 1.9 months
Therapy discontinuation due to adverse events					
	201	20.3 [9.9; n.c.] *83 (41.3)*	197	n.r. *35 (17.8)*	1.77 [1.17; 2.66] 0.007
Specific adverse events					
Immune-mediated AEs (presented additionally)[l]	*No suitable data available*				
Immune-mediated SAEs[l]	201	n.r. *20 (10.0)*	197	n.r. *2 (1.0)*	7.16 [1.64; 31.21] 0.009
Immune-mediated severe AEs[l]	201	n.r. *42 (20.9)*	197	n.r. *2 (1.0)*	15.91 [3.82; 66.35] < 0.001
Peripheral neuropathy (SMQ, AEs)	No suitable data available				
Skin reactions	201	0.6 [0.5; 0.7] *162 (80.6)*	197	n.r. *51 (25.9)*	4.95 [3.60; 6.81] < 0.001

Endpoint	**Pembrolizumab + enfortumab vedotin**		**Carboplatin + gemcitabine (if applicable followed by avelumab maintenance treatment)**		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[k] Absolute difference (AD)[b]
Severe hyperglycaemia (PT, severe AEs)[m]	201	n.r. *12 (6.0)*	197	n.r. *1 (0.5)*	10.71 [1.38; 82.93] 0.023
Severe nephrotoxicity	201	n.r. *25 (12.4)*	197	n.r. *15 (7.6)*	1.12 [0.57; 2.23] 0.736
Constipation (PT, AEs)	201	n.r. *49 (24.4)*	197	n.r. *71 (36.0)*	0.45 [0.30; 0.66] < 0.001
Diarrhoea (PT, AEs)	201	n.r. [11.1; n.c.] *77 (38.3)*	197	n.r. *29 (14.7)*	2.30 [1.48; 3.56] < 0.001
Dysgeusia (PT, AEs)	201	n.r. *46 (22.9)*	197	n.r. *9 (4.6)*	4.83 [2.35; 9.92] < 0.001
Eye disorders (SOC, AEs)	201	n.r. [16.6; n.c.] *64 (31.8)*	197	n.r. *12 (6.1)*	3.85 [2.04; 7.26] < 0.001
Endocrine disorder (SOC, SAEs)	201	n.r. *36 (17.9)*	197	n.r. *4 (2.0)*	5.47 [1.90; 15.79] 0.002
Blood and lymphatic system disorders (SOC, severe AEs)	201	n.r. *43 (21.4)*	197	1.3 [1.0; 1.6] *135 (68.5)*	0.14 [0.09; 0.20] < 0.001

Endpoint	Pembrolizumab + enfortumab vedotin		Carboplatin + gemcitabine (if applicable followed by avelumab maintenance treatment)		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[k] Absolute difference (AD)[b]

[a] HR and CI: Cox proportional hazards model, stratified by PD-L1 expression (high vs low) and liver metastases (present vs absent); p value: Wald test

[b] Indication of absolute difference (AD) only in case of statistically significant difference; own calculation

[c] Censoring at the time of death: Avelumab-eligible patients who did not receive avelumab and died were censored at the time of death.

[d] Censoring for the data cut-off: Avelumab-eligible patients who did not receive avelumab and died were censored at the time of the data cut-off

[e] Modified date of death: Avelumab-eligible patients who did not receive avelumab and died were imputed with a modified time of death.

[f] An increase in score by ≥ 2 points compared to the start of the study is considered a clinically relevant deterioration (scale range: 0 to 10)

[g] An increase in score by ≥ 1.5 points compared to the start of the study is considered a clinically relevant deterioration (scale range: 0 to 10)

[h] An increase in EORTC QLQ-C30 score by ≥ 10 points compared to the start of the study is considered a clinically relevant deterioration (scale range: 0 to 100).

[i] A decrease in EQ-5D VAS score by ≥ 15 points compared to the start of study is considered clinically relevant deterioration (scale range: 0 to 100).

[j] A decrease in EORTC QLQ-C30 score by ≥ 10 points compared to the baseline is considered a clinically relevant deterioration (scale range: 0 to 100).

[k] HR and CI: unstratified Cox proportional hazards model, p value: Wald test

[l] In each case, the operationalisation of a specific, predefined MedDRA PT collection from the AEOSI endpoint (PT collection version 25.0, MedDRA version 26.0) presented by the pharmaceutical company is used.

Abbreviations used:
AD = absolute difference; AEOSI = Adverse Events of Special Interest; BPI-SF = Brief Pain Inventory – Short Form; CTCAE = Common Terminology Criteria for Adverse Events; EORTC QLQ-C30 = European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire – Core 30; HR = hazard ratio; CI = confidence interval; N = number of patients evaluated; n = number of patients with (at least one) event; n.c. = not calculable; n.r. = not reached; PD-L1 = Programmed Cell Death-Ligand 1; PT = preferred term; SOC = system organ class; VAS = visual analogue scale; vs = versus

c) Adults with unresectable or metastatic urothelial carcinoma who are not eligible for a cisplatin and carboplatin-based therapy; first-line treatment

No data available.

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
∅: No data available.
n.a.: not assessable

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

a) Adults with unresectable or metastatic urothelial carcinoma who are eligible for a cisplatin-based therapy; first-line treatment

Approx. 510 to 1,260 patients

b) Adults with unresectable or metastatic urothelial carcinoma who are not eligible for a cisplatin-based therapy; first-line treatment

Approx. 410 to 1020 patients

c) Adults with unresectable or metastatic urothelial carcinoma who are not eligible for a cisplatin and carboplatin-based therapy; first-line treatment

Approx. 130 to 321 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: 25 March 2025):

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

Treatment with enfortumab vedotin should only be initiated and monitored by specialists in internal medicine, haematology, and oncology and urology, and specialists participating in the Oncology Agreement experienced in the treatment of adults with urothelial carcinoma.

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:

The annual treatment costs shown refer to the first year of treatment.

a) Adults with unresectable or metastatic urothelial carcinoma who are eligible for a cisplatin-based therapy; first-line treatment

Designation of the therapy	Annual treatment costs/ patient
Medicinal product to be assessed:	
Pembrolizumab in combination with enfortumab vedotin	
Pembrolizumab	€ 90,059.96
Enfortumab vedotin	€ 91,404.29
Total	€ 181,464.25
Appropriate comparator therapy:	
Cisplatin in combination with gemcitabine followed by avelumab as maintenance treatment (maintenance treatment with avelumab only for patients who are progression-free)	
Cisplatin	€ 463.72 – € 695.58
Gemcitabine	€ 2,159.04 – € 3,238.56
Total	€ 2,622.76 – € 3,934.14
Maintenance treatment with avelumab	
Avelumab	€ 44,412.74 (after 6 cycles of induction therapy) – € 57,012.10 (after 4 cycles of induction therapy)
Cisplatin and gemcitabine including subsequent maintenance treatment with avelumab	
Total	€ 48,346.88 (after 6 cycles of induction therapy) – € 59,634.86 (after 4 cycles of induction therapy)
Additionally required SHI services	€ 105.70 – € 110.55

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

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 enfortumab vedotin					
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)
Enfortumab vedotin	Surcharge for the preparation of a parenteral solution containing monoclonal antibodies	€ 100	2	34.8	€ 3,480
Appropriate comparator therapy					
Cisplatin in combination with gemcitabine					
Cisplatin	Surcharge for production of a parenteral preparation containing cytostatic agents	€ 100	1	4.0 – 6.0	€ 400 – € 600
Gemcitabine	Surcharge for production of a parenteral preparation containing cytostatic agents	€ 100	3	12.0 – 18.0	€ 1,200 – € 1,800
Maintenance treatment with avelumab					
Avelumab	Surcharge for the preparation of a parenteral solution containing monoclonal antibodies	€ 100	1	14.1 – 18.1	€ 1,410 – € 1,810

b) Adults with unresectable or metastatic urothelial carcinoma who are not eligible for a cisplatin-based therapy; first-line treatment

Designation of the therapy	Annual treatment costs/ patient
Medicinal product to be assessed:	
Pembrolizumab in combination with enfortumab vedotin	
Pembrolizumab	€ 90,059.96
Enfortumab vedotin	€ 91,404.29
Total	€ 181,464.25
Appropriate comparator therapy:	
Carboplatin in combination with gemcitabine in accordance with Annex VI to Section K of the Pharmaceuticals Directive followed by avelumab as maintenance treatment (maintenance treatment with avelumab only for patients who are progression-free)	
Carboplatin	€ 1,268.44 – € 1,902.66
Gemcitabine	€ 1,470.24 – € 2,205.36
Total	€ 2,738.68 – € 4,108.02
Maintenance treatment with avelumab	
Avelumab	€ 53,862.26 (after 6 cycles of induction therapy) – € 63,311.78 (after 4 cycles of induction therapy)
Carboplatin and gemcitabine including subsequent maintenance treatment with avelumab	
Total	€ 57,970.28 (after 6 cycles of induction therapy) – € 66,050.46 (after 4 cycles of induction therapy)

Costs after deduction of statutory rebates (LAUER-TAXE®) as last revised: 15 March 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 enfortumab vedotin					
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)
Enfortumab vedotin	Surcharge for the preparation of a parenteral solution containing monoclonal antibodies	€ 100	2	34.8	€ 3,480
Appropriate comparator therapy					
Carboplatin in combination with gemcitabine					
Carboplatin	Surcharge for production of a parenteral preparation containing cytostatic agents	€ 100	1	4.0 – 6.0	€ 400 – € 600
Gemcitabine	Surcharge for production of a parenteral preparation containing cytostatic agents	€ 100	2	8.0 – 12.0	€ 800 – € 1,200
Maintenance treatment with avelumab					
Avelumab	Surcharge for the preparation of a parenteral solution containing monoclonal antibodies	€ 100	1	17.1 – 20.1	€ 1,710 – € 2,010

c) Adults with unresectable or metastatic urothelial carcinoma who are not eligible for a cisplatin and carboplatin-based therapy; first-line treatment

Designation of the therapy	Annual treatment costs/ patient
Medicinal product to be assessed:	
Pembrolizumab in combination with enfortumab vedotin	
Pembrolizumab	€ 90,059.96
Enfortumab vedotin	€ 91,404.29
Total	€ 181,464.25
Appropriate comparator therapy:	
Individualised therapy with selection of	
atezolizumab as monotherapy	
Atezolizumab	€ 67,771.78
Pembrolizumab as monotherapy	
Pembrolizumab	€ 90,059.96
Best supportive care	
Best supportive care[4]	Different from patient to patient

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

Costs for additionally required SHI services: not applicable

[4] When comparing pembrolizumab in combination with enfortumab vedotin versus best supportive care, the costs of best supportive care must also be additionally considered for the medicinal product assessed.

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 enfortumab vedotin					
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)
Enfortumab vedotin	Surcharge for the preparation of a parenteral solution containing monoclonal antibodies	€ 100	2	34.8	€ 3,480
Appropriate comparator therapy					
Pembrolizumab as monotherapy					
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)

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:

a) Adults with unresectable or metastatic urothelial carcinoma who are eligible for a cisplatin-based therapy; first-line treatment

The following medicinal products with new active ingredients that can be used in a combination therapy with pembrolizumab in the therapeutic indication of the resolution on the basis of the marketing authorisation under Medicinal Products Act are named (active ingredients and invented names) in accordance with Section 35a, paragraph 3, sentence 4 SGB V:

– Enfortumab vedotin (Padcev)

b) Adults with unresectable or metastatic urothelial carcinoma who are not eligible for a cisplatin-based therapy; first-line treatment

The following medicinal products with new active ingredients that can be used in a combination therapy with the assessed medicinal product in the therapeutic indication of the present resolution on the basis of the marketing authorisation under Medicinal Products Act are excluded from the designation, as the G-BA has identified at least considerable additional benefit for the combination with the assessed medicinal product in the present resolution:

– Enfortumab vedotin (Padcev)

c) Adults with unresectable or metastatic urothelial carcinoma who are not eligible for a cisplatin and carboplatin-based therapy; first-line treatment

The following medicinal products with new active ingredients that can be used in a combination therapy with pembrolizumab in the therapeutic indication of the resolution on the basis of the marketing authorisation under Medicinal Products Act are named (active ingredients and invented names) in accordance with Section 35a, paragraph 3, sentence 4 SGB V:

– Enfortumab vedotin (Padcev)

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. **In Annex XIIa of the Pharmaceuticals Directive, the following information shall be added in alphabetical order:**

"Active ingredient of the assessed medicinal product

Pembrolizumab

Resolution according to Section 35a paragraph 3 SGB V from

3 April 2025

Therapeutic indication of the resolution

KEYTRUDA, in combination with enfortumab vedotin, is indicated for the first-line treatment of unresectable or metastatic urothelial carcinoma in adults.

Patient group a

Adults with unresectable or metastatic urothelial carcinoma who are eligible for a cisplatin-based therapy; first-line treatment

Naming of medicinal products with new active ingredients according to Section 35a, paragraph 3, sentence 4 SGB V (active ingredients and invented names[2])

Enfortumab vedotin (Padcev)

Period of validity of the designation

Since 3 April 2025

Patient group c

Adults with unresectable or metastatic urothelial carcinoma who are not eligible for a cisplatin and carboplatin-based therapy; first-line treatment

Naming of medicinal products with new active ingredients according to Section 35a, paragraph 3, sentence 4 SGB V (active ingredients and invented names[2])

Enfortumab vedotin (Padcev)

Period of validity of the designation

Since 3 April 2025

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.

III. The resolution will enter into force on the day of its publication on the website of the G-BA on 3 April 2025.

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

Berlin, 3 April 2025

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

Prof. Hecken