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: biliary tract carcinomas, first-line, combination with gemcitabine and cisplatin)

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 the version of the resolution of 20 June 2024 on the therapeutic indication: "in combination with fluoropyrimidine and platinum-containing chemotherapy, for the first-line treatment of locally advanced unresectable or metastatic HER2-negative gastric or gastro-oesophageal junction adenocarcinoma in adults whose tumours express PD-L1 with a CPS ≥ 1":**

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 11 December 2023):

KEYTRUDA, in combination with gemcitabine and cisplatin, is indicated for the first-line treatment of locally advanced unresectable or metastatic biliary tract carcinoma in adults.

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 biliary tract carcinoma; first-line treatment

Appropriate comparator therapy:

- Cisplatin in combination with gemcitabine (cf. Annex VI to Section K of the Pharmaceuticals Directive)

Extent and probability of the additional benefit of pembrolizumab in combination with gemcitabine and cisplatin compared to cisplatin in combination with gemcitabine (cf. Annex VI to Section K of the Pharmaceuticals Directive):

Indication of a minor additional benefit

Study results according to endpoints:[1]

Adults with locally advanced unresectable or metastatic biliary tract carcinoma; first-line treatment

Summary of results for relevant clinical endpoints

Endpoint category	Direction of effect/ risk of bias	Summary
Mortality	↑↑	Advantage in overall survival
Morbidity	↓↓	Disadvantages in the endpoints of appetite loss, fatigue, jaundice and side effects of treatment
Health-related quality of life	↔	No relevant differences for the benefit assessment
Side effects	↔	No relevant differences for the benefit assessment, in detail, disadvantages and one advantage 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-966 study

- Comparison: Pembrolizumab + cisplatin + gemcitabine vs cisplatin + gemcitabine
- Study design: double-blind, randomised, controlled phase III study
- Results based on the global cohort with the final data cut-off from 15.12.2022

1 Data from the dossier assessment of the Institute for Quality and Efficiency in Health Care (IQWiG) (A24-03) unless otherwise indicated.

Mortality

Endpoint	Pembrolizumab + Cisplatin + gemcitabine		Cisplatin + gemcitabine		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 (%)*	Harzard ratio [95% CI] [a] p value[b] Absolute difference (AD)[c]
Mortality					
Overall survival	533	12.7 [11.5; 13.6] 414 (77.7)	536	10.9 [9.9; 11.6] 443 (82.6)	0.83 [0.72; 0.95] 0.007 AD: + 1.8 months

Morbidity

Endpoint	Pembrolizumab + Cisplatin + gemcitabine		Cisplatin + gemcitabine		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 (%)*	Hazard ratio [95% CI] [a] p value[b] Absolute difference (AD)[c]
Progression-free survival (PFS) [d]					
PFS according to BICR	533	6.5 [5.7; 6.9] 428 (80.3)	536	5.6 [4.9; 6.6] 448 (83.6)	0.87 [0.76; 0.99] 0.035 AD: + 0.9 months
Symptomatology					
EORTC QLQ-C30 (time to first deterioration [e])					
Fatigue	489	1.45 [1.41; 1.64] 364 (74.4)	496	1.48 [1.41; 2.10] 371 (74.8)	1.02 [0.88; 1.18] 0.810
Nausea and vomiting	489	2.60 [2.10; 3.22] 301 (61.6)	496	2.60 [2.14; 3.02] 315 (63.5)	0.95 [0.81; 1.12] 0.570
Pain	489	4.17 [3.48; 5.42] 285 (58.3)	496	3.81 [2.99; 4.40] 304 (61.3)	0.91 [0.77; 1.07] 0.241

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Dyspnoea	489	4.83 [3.78; 5.65] 264 (54.0)	496	4.40 [3.45; 6.21] 273 (55.0)	0.95 [0.80; 1.12] 0.534
Insomnia	489	5.29 [3.94; 6.93] 251 (51.3)	496	5.78 [4.63; 8.77] 242 (48.8)	1.08 [0.90; 1.29] 0.407
Appetite loss	489	3.71 [2.79; 4.44] 286 (58.5)	496	4.40 [3.88; 5.62] 264 (53.2)	1.19 [1.00; 1.40] 0.047 AD: - 0.7 months
Constipation	489	3.15 [2.73; 4.17] 273 (55.8)	496	3.06 [2.33; 4.80] 276 (55.6)	1.0 [0.86; 1.20] 0.846
Diarrhoea	489	10.65 [7.62; 14.78] 195 (39.9)	496	11.93 [8.77; 18.17] 191 (38.5)	1.03 [0.84; 1.26] 0.804
EORTC QLQ-BIL21 (time to first deterioration [e])					
Pain	482	8.58 [6.47; 10.74] 212 (44.0)	490	9.17 [6.97; 11.93] 212 (43.3)	1.02 [0.84; 1.24] 0.838
Fatigue	482	1.51 [1.41; 2.07] 350 (72.6)	490	2.10 [1.64; 2.69] 338 (69.0)	1.18 [1.01; 1.37] 0.033 AD: - 0.6 months
Jaundice	482	4.17 [3.38; 5.32] 275 (57.1)	490	5.13 [3.65; 6.74] 246 (50.2)	1.22 [1.02; 1.45] 0.027 AD: - 1.0 months
Difficulties with food intake	482	3.78 [3.48; 4.93] 282 (58.5)	490	4.37 [3.48; 5.32] 269 (54.9)	1.10 [0.93; 1.30] 0.288
Side effect of the treatment	482	1.41 [1.35; 1.68] 342 (71.0)	490	1.84 [1.45; 2.27] 329 (67.1)	1.17 [1.01; 1.37] 0.039 AD: - 0.4 months
Difficulties with drainage	482	n.r. 105 (21.8)	490	n.r. [24.41; n.r.] 109 (22.2)	1.00 [0.76; 1.31] 0.995

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Health status					
EQ-5D VAS (time to first deterioration [f])					
	491	6.51 [4.86; 9.43] 231 (47.0)	500	8.31 [6.44; 9.36] 234 (46.8)	1.07 [0.89; 1.29] 0.453

Health-related quality of life

Endpoint	**Pembrolizumab + Cisplatin + gemcitabine**		**Cisplatin + gemcitabine**		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 (%)*	Hazard ratio [95% CI] [a] p value[b] Absolute difference (AD)[c]
EORTC QLQ-C30 (time to first deterioration [g])					
Global health status	489	3.52 [2.79; 4.40] 297 (60.7)	469	2.99 [2.50; 3.71] 310 (62.5)	0.91 [0.77; 1.06] 0.227
Physical functioning	489	3.48 [2.83; 3.94] 320 (65.4)	469	2.92 [2.69; 3.48] 325 (65.5)	0.97 [0.83; 1.14] 0.733
Role functioning	489	2.33 [2.07; 2.79] 328 (67.1)	496	2.20 [1.87; 2.73] 346 (69.8)	0.93 [0.80; 1.08] 0.361
Emotional functioning	489	5.55 [4.27; 8.12] 245 (50.1)	496	6.47 [5.26; 9.89] 225 (45.4)	1.20 [1.00; 1.44] 0.052
Cognitive functioning	489	3.25 [2.56; 3.71] 294 (60.1)	496	3.09 [2.76; 3.52] 316 (63.7)	0.93 [0.79; 1.09] 0.363
Social functioning	489	2.17 [2.07; 2.79] 327 (66.9)	496	2.27 [2.10; 2.79] 328 (66.1)	0.99 [0.85; 1.15] 0.891
EORTC QLQ-BIL21 (time to first deterioration [e])					
Anxiety [h]	482	5.62 [4.83; 7.59] 253 (52.5)	490	8.12 [5.62; 9.79] 227 (46.3)	1.18 [0.99; 1.42] 0.069

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Concern about weight loss [h]	482	11.24 [7.56; n.r.] 199 (41.3)	490	10.61 [7.56; 15.70] 205 (41.8)	1.02 [0.84; 1.25] 0.808

Side effects [i]

Endpoint	**Pembrolizumab + Cisplatin + gemcitabine**		**Cisplatin + gemcitabine**		Intervention vs control
	N	*Patients with event n (%)*	N	*Patients with event n (%)*	Relative risk [95% CI] p value [j]
Total adverse events (presented additionally)					
	529	524 (99.1)	534	532 (99.6)	-
Serious adverse events (SAE)					
	529	276 (52.2)	534	263 (49.3)	1.06 [0.94; 1.19] 0.530
Severe adverse events (CTCAE grade ≥ 3)					
	529	451 (85.3)	534	449 (84.1)	1.01 [0.96; 1.07] 0.683
Therapy discontinuation due to adverse events					
	529	138 (26.1)	534	122 (22.8)	1.14 [0.92; 1.41] 0.248
Specific adverse events					
Immune-mediated AEs (presented additionally)	529	117 (22.1)	534	69 (12.9)	-
Immune-mediated SAEs	529	31 (5.9)	534	18 (3.4)	1.74 [0.98; 3.07] 0.054
Immune-mediated severe AEs [k]	529	38 (7.2)	534	21 (3.9)	1.83 [1.09; 3.07] 0.021
Rash (PT, AE)	529	90 (17.0)	534	49 (9.2)	1.85 [1.34; 2.57] < 0.001

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Cardiac disorders (SOC, SAE)	529	19 (3.6)	534	7 (1.3)	2.74 [1.16; 6.46] 0.017
Fever (PT, SAE)	529	30 (5.7)	534	12 (2.2)	2.52 [1.31; 4.88] 0.004
Neutropenia (PT, SAE)	529	11 (2.1)	534	1 (0.2)	11.10 [1.44; 85.70] 0.004
Liver abscess (PT, severe AE [k])	529	4 (0.8)	534	12 (2.2)	0.34 [0.11; 1.04] 0.047

[a] Effect estimator and CI: Cox proportional hazards model with treatment as a covariate, stratified by region (Asia or not), disease status (metastatic or locally advanced) and site of origin (hepatic, extrahepatic and gall bladder). In the strata for locally advanced disease status, the characteristic manifestations for the site of origin "gallbladder" and "extrahepatic" were summarised.
[b] Wald test
[c] Information on absolute difference (AD) only in case of statistically significant difference; own calculation
[d] Information from the dossier of the pharmaceutical company
[e] An increase by ≥ 10 points compared to the start of study is considered a clinically relevant deterioration (scale range 0 to 100)
[f] A decrease by ≥ 15 points compared to the start of study is considered a clinically relevant deterioration (scale range 0 to 100)
[g] A decrease by ≥ 10 points compared to the start of study is considered a clinically relevant deterioration (scale range 0 to 100)
[h] In deviation from the pharmaceutical company's procedure, this scale was not assigned to symptomatology but to health-related quality of life
[i] The MedDRA terms (PTs) of neoplasm progression, malignant neoplasm progression and disease progression were not included in the evaluation.
[j] Unconditional exact test (CSZ method according to Martín Andrés A, Silva Mato A. Choosing the optimal unconditional test for comparing two independent proportions. Computat Stat Data Anal 1994; 17(5): 555-574. https://doi.org/10.1016/0167-9473(94)90148-1). Discrepancy between p value (exact) and CI (asymptotic) due to different calculation methods
[k] Operationalised as CTCAE grade ≥ 3

Abbreviations used:
AD = absolute difference; CTCAE = Common Terminology Criteria for Adverse Events; EORTC = European Organisation for Research and Treatment of Cancer; HR = hazard ratio; CI = confidence interval; N = number of patients evaluated; n = number of patients with (at least one) event; n.r. = not reached; PT = preferred term; QLQ-BIL21 = Quality of life Questionnaire – Cholangiocarcinoma and Gall Bladder specific Module 21; QLQ-C30 = Quality of life Questionnaire - Core 30; RCT = randomised controlled trial; RR = relative risk; 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 biliary tract carcinoma; first-line treatment

Approx. 1480 to 2180 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: 29 May 2024):

https://www.ema.europa.eu/en/documents/overview/keytruda-epar-medicine-overview_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 biliary tract 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:

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

Adults with locally advanced unresectable or metastatic biliary tract carcinoma; first-line treatment

Designation of the therapy	Annual treatment costs/ patient
Medicinal product to be assessed:	
Pembrolizumab in combination with gemcitabine and cisplatin	
Pembrolizumab	€ 97,656.46
Gemcitabine	€ 6,387.54
Cisplatin	€ 1,430.98
Total:	€ 105,474.97
Additionally required SHI costs	€ 657.16 - € 843.24
Appropriate comparator therapy:	
Cisplatin in combination with gemcitabine (cf. Annex VI to Section K of the Pharmaceuticals Directive)	
Gemcitabine	€ 2,936.80
Cisplatin	€ 657.92
Total:	€ 3,594.72
Additionally required SHI costs	€ 345.10 - € 442.84

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 gemcitabine and cisplatin					
Pembrolizumab	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	34.8	€ 3,480
Gemcitabine	Surcharge for production of a parenteral preparation containing cytostatic agents	€ 100	1	34.8	€ 3,480
Appropriate comparator therapy					
Cisplatin in combination with gemcitabine (cf. Annex VI to Section K of the Pharmaceuticals Directive)					
Cisplatin	Surcharge for production of a parenteral preparation containing cytostatic agents	€ 100	2	16	€ 1,600
Gemcitabine	Surcharge for production of a parenteral preparation containing cytostatic agents	€ 100	2	16	€ 1,600

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:

Adults with locally advanced unresectable or metastatic biliary tract carcinoma; first-line 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.

III. 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