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)
Durvalumab (new therapeutic indication: biliary tract cancer, first-line, combination with gemcitabine and cisplatin)

of 5 October 2023

At its session on 5 October 2023, 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. 4 to the information on the benefit assessment of Durvalumab in accordance with the resolution of 1 April 2021:**

Durvalumab

Resolution of: 5 October 2023
Entry into force on: 5 October 2023
Federal Gazette, BAnz AT DD. MM YYYY Bx

New therapeutic indication (according to the marketing authorisation of 16 December 2022):

Imfinzi in combination with gemcitabine and cisplatin is indicated for the first-line treatment of adults with unresectable or metastatic biliary tract cancer (BTC)**.**

Therapeutic indication of the resolution (resolution of 5 October 2023):

See new therapeutic indication according to marketing authorisation.

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

Adults with unresectable or metastatic biliary tract cancer (BTC); first-line therapy

Appropriate comparator therapy:

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

Extent and probability of additional benefit of durvalumab 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 unresectable or metastatic biliary tract cancer (BTC); first-line 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 differences for the benefit assessment
Health-related quality of life	↔	No relevant differences for the benefit assessment
Side effects	↔	No relevant differences 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		

TOPAZ-1 study

Comparison: Durvalumab + cisplatin + gemcitabine vs. cisplatin + gemcitabine

Study design: randomised, controlled phase III study

Data cut-offs:

Endpoints of the categories overall survival and side effects:

- global cohort: Data cut-off from 25.02.2022
- China expansion cohort: Data cut-off from 14.10.2022

Endpoints of the categories morbidity and health-related quality of life:

- global cohort: Data cut-off from 11.08.2021
- China expansion cohort: Data cut-off from 14.10.2022

1 Data from the dossier assessment of the IQWiG (A23-26) and from the addendum (A23-83), unless otherwise indicated.

Mortality

Endpoint	**Durvalumab + 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]
Overall survival					
	405	12.6 [11.1; 13.6] 290 (71.6)	405	10.9 [9.7; 11.7] 327 (80.7)	0.77 [0.66; 0.90] < 0.001 AD: + 1.7 months

Morbidity

Endpoint	**Durvalumab + Cisplatin + gemcitabine**		**Cisplatin + gemcitabine**		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][a] p value[b] Absolute difference (AD)[c]
Progression-free survival (PFS)[d]					
PFS according to principal investigator	405	7.2 [6.4; 7.4] 325 (80.2)	405	5.7 [5.4; 5.9] 344 (84.9)	0.76 [0.65; 0.88] 0.0005 AD: + 1.5 months
Symptomatology					
EORTC QLQ-C30 (first deterioration by ≥ 10 points)					
Fatigue	405	1.5 [1.4; 2.1] 183 (45.2)	405	1.8 [1.4; 2.2] 188 (46.4)	1.02 [0.83; 1.26] 0.824
Nausea and vomiting	405	2.2 [1.6; 2.8] 168 (41.5)	405	2.8 [2.1; 3.6] 164 (40.5)	1.07 [0.86; 1.32] 0.641

(continuation)

Pain	405	3.6 [2.9; 4.9] 147 (36.6)	405	4.9 [3.5; 6.2] 144 (35.6)	1.11 [0.88; 1.39] 0.378
Dyspnoea	405	4.4 [3.5; 8.7] 123 (30.4)	405	5.5 [3.5; 9.8] 121 (29.9)	1.04 [0.81; 1.34] 0.815
Insomnia	405	5.0 [4.2; 6.7] 124 (30.6)	405	5.8 [3.7; 9.4] 121 (29.9)	1.00 [0.78; 1.29] 0.853
Appetite loss	405	3.9 [2.9; 5.1] 142 (35.1)	405	3.5 [2.4; 5.6] 145 (35.8)	0.97 [0.77; 1.22] 0.759
Constipation	405	4.2 [2.2; 9.2] 135 (33.3)	405	3.5 [2.5; 9.2] 139 (34.3)	0.97 [0.76; 1.23] 0.711
Diarrhoea	405	n.r. 81 (20.0)	405	11.0 [9.2; n.c.] 84 (20.7)	0.95 [0.70, 1.29] 0.899
EORTC QLQ-BIL21 (first deterioration by ≥ 10 points)					
Pain	405	n.r. 86 (21.2)	405	8.5 [6.6; n.c.] 92 (22.7)	0.98 [0.73; 1.32] 0.885
Fatigue	405	1.5 [1.4; 2.1] 165 (40.7)	405	2.2 [1.5; 2.9] 166 (41.0)	1.16 [0.93; 1.44] 0.188
Jaundice	405	5.6 [3.6; 7.5] 119 (29.4)	405	4.8 [3.9; 7.5] 123 (30.4)	0.98 [0.76; 1.26] 0.913
Difficulties with food intake	405	3.9 [2.8; 4.9] 133 (32.8)	405	5.7 [3.9; 9.2] 116 (28.6)	1.22 [0.95; 1.57] 0.124
Side effects of the treatment	405	1.5 [1.4; 2.1] 173 (42.7)	405	2.3 [1.6; 2.9] 172 (42.5)	1.16 [0.93; 1.43] 0.236
Difficulties with drainage	405	n.r. 49 (12.1)	405	n.r. 31 (7.7)	1.67 [1.07; 2.65] 0.024

(continuation)

PGIS (first deterioration to 5 points or 6 points)					
	405	n.r. 27 (6.7)	405	n.r. 19 (4.7)	1.38 [0.77; 2.51] 0.316
Health status					
EQ-5D VAS (first deterioration ≥ 15 points)					
	405	8.8 [5.6; n.c.] 104 (25.7)	405	7.7 [5.8; 10.2] 109 (26.9)	0.90 [0.69; 1.18] 0.421

Health-related quality of life

Endpoint	**Durvalumab + Cisplatin + gemcitabine**		**Cisplatin + gemcitabine**		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][a] p value[b] Absolute difference (AD)[c]
EORTC QLQ-C30 (first deterioration by ≥ 10 points)					
Global health status	405	4.3 [2.8; 6.3] 145 (35.8)	405	4.2 [2.4; 6.7] 145 (35.8)	0.96 [0.76; 1.21] 0.746
Physical functioning	405	3.5 [2.8; 6.5] 141 (34.8)	405	4.2 [3.2; 6.5] 138 (34.1)	1.02 [0.80; 1.29] 0.839
Role functioning	405	2.2 [2.1; 2.9] 166 (41.0)	405	2.6 [2.1; 3.5] 171 (42.2)	1.03 [0.83; 1.28] 0.740
Emotional functioning	405	12.2 [5.8; n.c.] 100 (24.7)	405	6.8 [4.3; n.c.] 111 (27.4)	0.85 [0.65; 1.11] 0.228
Cognitive functioning	405	3.0 [2.8; 3.6] 158 (39.0)	405	3.8 [2.8; 5.4] 142 (35.1)	1.12 [0.89; 1.41] 0.283

(continuation)

Social functioning	405	3.1 [2.1; 4.5] 152 (37.5)	405	3.7 [2.7; 5.6] 142 (35.1)	1.08 [0.86; 1.35] 0.450
EORTC QLQ-BIL21 (first deterioration by ≥ 10 points)					
Anxiety	405	11.1 [6.7; n.c.] 91 (22.5)	405	n.r. 92 (22.7)	0.96 [0.71; 1.28] 0.670
Concern about weight loss	405	9.3 [6.3; n.c.] 97 (24.0)	405	17.5 [9.2; n.c.] 85 (21.0)	1.22 [0.91; 1.64] 0.185

Side effects

Endpoint	**Durvalumab + Cisplatin + gemcitabine**		**Cisplatin + gemcitabine**		Intervention vs control
	N	*Patients with event n (%)*	N	*Patients with event n (%)*	Relative risk [95% CI] p value[e]
Total adverse events (presented additionally)					
	402	399 (99.3)	403	399 (99.0)	-
Serious adverse events (SAE)					
	402	190 (47.3)	403	171 (42.4)	1.11 [0.96; 1.30] 0.212
Severe adverse events (CTCAE grade ≥ 3)					
	402	313 (77.9)	403	315 (78.2)	0.98 [0.70; 1.39] 0.956
Therapy discontinuation due to adverse events					
	402	56 (13.9)	403	57 (14.1)	1.00 [0.93; 1.07] 0.948

(continuation)

Specific adverse events					
Immune-mediated SAEs[f]	402	15 (3.7)	403	14 (3.5)	1.07 [0.57; 2.20] 0.902
Immune-mediated severe AEs[f,g]	402	15 (3.7)	403	14 (3.5)	1.07 [0.57; 2.20] 0.902
Skin and subcutaneous tissue disorders (SOC, AEs)	402	158 (39.3)	403	102 (25.3)	1.55 [1.26; 1.91] < 0.001
Fever (PT, SAE)	402	18 (3.7)	403	8 (2.0)	2.26 [0.99; 5.13][h] 0.048[h]
Anaemia (PT, SAEs)	402	14 (3.5)	403	5 (1.2)	2.81 [1.02; 7.72] 0.039
Cholangitis (PT, severe AEs[f])	402	23 (5.7)	403	11 (2.7)	2.10 [1.04; 4.24] 0.039

[a] Effect and CI: Stratified Cox proportional hazards model adjusted for disease status and primary tumour location
[b] Stratified log-rank test adjusted for disease status and primary tumour location
[c] Indication of absolute difference (AD) only in case of statistically significant difference; own calculation
[d] Information from the dossier of the pharmaceutical company
[e] Unconditional exact test, CSZ method according to Andrés AM, Mato AS. Choosing the optimal unconditioned test for comparing two independent proportions. Computational Statistics & Data Analysis 1994; 17(5): 555-574. https://dx.doi.org/10.1016/0167-9473(94)90148-1.
[f] Pooled analysis without consideration of SMQs
[g] Operationalised as CTCAE grade ≥ 3
[h] Discrepancy between p value (exact) and CI (asymptotic) due to different calculation methods

Abbreviations used:
AD = absolute difference; CTCAE = Common Terminology Criteria for Adverse Events; EORTC = European Organisation for Research and Treatment of Cancer; EQ-5D = European Quality of Life Questionnaire – 5 Dimensions; 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; PGIS = Patient's Global Impression of Severity; PT = preferred term; QLQ-BIL21 = Quality of Life Questionnaire – Cholangiocarcinoma and Gallbladder Cancer Specific Module 21; QLQ-C30 = Quality of Life Questionnaire-Core 30; SMQ = standardised MEDRA query; SOC = system organ class; AE = adverse event; VAS = visual analogue scale; vs = versus

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

Adults with unresectable or metastatic biliary tract cancer (BTC); first-line therapy

approx. 1,800 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 Imfinzi (active ingredient: durvalumab) at the following publicly accessible link (last access: 20 September 2023):

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

Treatment with durvalumab 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 cancer.

4. Treatment costs

Annual treatment costs:

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

Adults with unresectable or metastatic biliary tract cancer (BTC); first-line therapy

Designation of the therapy	Annual treatment costs/ patient
Medicinal product to be assessed:	
Durvalumab in combination with gemcitabine and cisplatin	
Durvalumab	€ 88,147.35
Gemcitabine	€ 2,936.80
Cisplatin	€ 657.92
Total:	€ 91,742.07
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

Costs after deduction of statutory rebates (LAUER-TAXE®) as last revised: 15 September 2023

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:					
Durvalumab in combination with gemcitabine and cisplatin					
Durvalumab	Surcharge for the preparation of a parenteral solution containing monoclonal antibodies	€ 100	1	1st year 15.0	1st year € 1,500.00
Cisplatin	Surcharge for production of a parenteral preparation containing cytostatic agents	€ 100	2	16.0	€ 1,600
Gemcitabine	Surcharge for production of a parenteral preparation containing cytostatic agents	€ 100	2	16.0	€ 1,600
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	16.0	€ 1,600
Gemcitabine	Surcharge for production of a parenteral preparation containing cytostatic agents	€ 100	2	16.0	€ 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:

<u>Adults with unresectable or metastatic biliary tract cancer (BTC); first-line therapy</u>

- No medicinal product with new active ingredients that can be used in a combination therapy that 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 5 October 2023.

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

Berlin, 5 October 2023

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

Prof. Hecken