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:

Nivolumab (new therapeutic indication: oesophageal squamous cell carcinoma, PD-L1 expression ≥ 1%, first-line, combination with ipilimumab)

of 20 October 2022

At its session on 20 October 2022, 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 is added after no. 4 to the information on the benefit assessment of nivolumab according to the resolution of 20 October 2022 on the therapeutic indication "...indicated in combination with fluoropyrimidine- and platinum-based combination chemotherapy for the first-line treatment of adults with unresectable advanced, recurrent or metastatic oesophageal squamous cell carcinoma with tumour cell PD-L1 expression ≥ 1%":**

Nivolumab

Resolution of: 20 October 2022
Entry into force on: 20 October 2022
Federal Gazette, BAnz AT DD. MM YYYY Bx

New therapeutic indication (according to the marketing authorisation of 1 April 2022):

Opdivo in combination with ipilimumab is indicated for the first-line treatment of adult patients with unresectable advanced, recurrent or metastatic oesophageal squamous cell carcinoma with tumour cell PD-L1 expression ≥ 1%.

Therapeutic indication of the resolution (resolution of 20 October 2022):

See new therapeutic indication according to marketing authorisation.

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

Adults with advanced, recurrent or metastatic, curatively untreatable oesophageal squamous cell carcinoma with tumour cell PD-L1 expression ≥ 1%; first-line therapy

Appropriate comparator therapy:

- Cisplatin in combination with 5-fluorouracil

Extent and probability of the additional benefit of nivolumab in combination with ipilimumab compared with cisplatin in combination with 5-fluorouracil:

Hint of a considerable additional benefit

Study results according to endpoints:[1]

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	↓	Disadvantage for the endpoint of SAE. In detail, advantages and 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
∅: There are no usable data for the benefit assessment.
n.a.: not assessable

CheckMate 648 study: **Nivolumab + ipilimumab vs** nivolumab + cisplatin + 5-fluorouracil vs **cisplatin + 5-fluorouracil**

Study design: RCT, open-label, ongoing, three-arm

Relevant sub-population: Patients with tumour cell PD-L1 expression ≥ 1%

Data cut-off: 23 August 2021

Mortality

Endpoint	Nivolumab + ipilimumab		Cisplatin + 5-fluorouracil		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] p value[a] Absolute difference (AD)[b]
Overall survival					
	158	13.70 [11.2; 17.4] 119 (75.3)	157	9.07 [7.7; 10.0] 130 (82.8)	0.63 [0.49; 0.82] < 0.001 AD = + 4.63 months

[1] Data from the dossier assessment of the IQWiG (A22-55) and from the addendum (A22-99), unless otherwise indicated.

Morbidity

Endpoint	Nivolumab + ipilimumab		Cisplatin + 5-fluorouracil		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]
Progression-free survival (PFS)[c]					
	158	4.02 [2.66; 4.93] 138 (87.3)	157	4.44 [2.96; 5.78] 143 (91.1)	0.85 [0.67; 1.09] 0.1909
Health status (EQ-5D VAS) – Time to first deterioration[d]					
≥ 15 points	154	6.24 [3.8; 25.1] 70 (45.5)	143	8.25 [5.0; 12.9] 59 (41.3)	0.93 [0.65; 1.32] 0.768

Health-related quality of life

Endpoint	Nivolumab + ipilimumab		Cisplatin + 5-fluorouracil		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]
FACT-E (time to first deterioration)					
≥ 27 points[e]	156	25.07 [12.5; n.c.] 51 (32.7)	140	n.a. [8.5; n.c.] 36 (25.7)	1.11 [0.72; 1.71] 0.401
FACT-G[f] (presented additionally)	156	13.60 [8.7; n.c.] 60 (38.5)	140	15.67 [8.5; n.c.] 40 (28.6)	1.05 [0.70; 1.59] 0.434

(continuation)

PWB (physical well-being)[f]	156	7.03 [5.5; 11.2] 77 (49.4)	141	4.30 [2.8; 5.7] 73 (51.8)	0.64 [0.46; 0.90] 0.019 AD = + 2.73 months
SWB (social well-being)[f]	156	9.72 [5.7; n.c.] 58 (37.2)	141	9.63 [6.7; n.c.] 47 (33.3)	0.89 [0.60; 1.32] 0.902
EWB (emotional well-being)[f]	156	16.39 [8.3; n.c.] 54 (34.6)	141	13.60 [9.0; n.c.] 43 (30.5)	0.90 [0.60; 1.36] 0.740
FWB (functional well-being)[f]	156	4.24 [2.8; 12.5] 79 (50.6)	140	9.53 [4.2; 15.7] 60 (42.9)	1.00 [0.71; 1.41] 0.431
ECS[f] (presented additionally)	156	32.69 [11.2; n.c.] 55 (35.3)	142	14.42 [7.1; 20.5] 51 (35.9)	0.87 [0.59; 1.28] 0.528

Side effects

Endpoint	**Nivolumab + ipilimumab**		**Cisplatin + 5-fluorouracil**		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]
Total adverse events (presented additionally)[g]					
	158	0.39 [0.3; 0.5] 157 (99.4)	145	0.10 [0.07; 0.1] 144 (99.3)	-
Serious adverse events (SAEs)[g]					
	158	2.92 [2.0; 3.9] 115 (72.8)	145	6.41 [4.4; 8.2] 77 (53.1)	1.42 [1.06; 1.90] 0.020 AD = - 3.5 months

(continuation)

Severe adverse events (CTCAE grade ≥ 3)[g]					
	158	3.25 [2.3; 3.9] 122 (77.2)	145	2.99 [2.0; 3.8] 108 (74.5)	0.85 [0.65; 1.11] 0.277
Therapy discontinuations due to adverse events[g,h]					
	158	21.19 [12.5; n.c.] 48 (30.4)	145	14.23 [10.1; n.c.] 31.0 (21.4)	1.17 [0.74; 1.87] 0.500
Specific adverse events					
Immune-mediated AEs (presented additionally)[i]					
	158	1.41 [1.0; 1.6] 122 (77.2)	145	5.55 [3.7; 6.4] 79 (54.5)	-
Immune-mediated SAEs[i]					
	158	n.a. [23.1; n.c.] 37 (23.4)	145	n.a. 7 (4.8)	4.82 [2.13; 10.92] < 0.001
Immune-mediated severe AEs (CTCAE grade ≥ 3)[i]					
	158	n.a. [14.6; n.c.] 40 (25.3)	145	n.a. 11 (7.6)	3.41 [1.74; 6.69] < 0.001
Other specific AEs					
Gastrointestinal disorders	158	2.23 [1.6; 3.5] 123 (77.8)	145	0.20 [0.1; 0.2] 132 (91.0)	0.37 [0.28; 0.48] < 0.001 AD = + 2.03 months
Mucosa inflammation	158	n.a. 1 (0.6)	145	n.a. 19 (13.1)	-[j] < 0.001
Alopecia	158	n.a. 8 (5.1)	145	n.a. 21 (14.5)	0.23 [0.09; 0.58] < 0.001
Hiccup	158	n.a. 8 (5.1)	145	n.a. 30 (20.7)	0.23 [0.10; 0.49] < 0.001
Renal and urinary disorders	158	n.a. 12.0 (7.6)	145	n.a. 30 (20.7)	0.32 [0.16; 0.62] < 0.001
Vomiting (SAE)	158	n.a. 3.0 (1.9)	145	n.a. 9.0 (6.2)	0.25 [0.07; 0.96] 0.030

(continuation)

Anaemia (severe AE, CTCAE grade ≥ 3)	158	n.a. 16.0 (10.1)	145	n.a. 26.0 (17.9)	0.49 [0.25; 0.93] 0.027
Neutropenia (severe AE, CTCAE grade ≥ 3)	158	n.a. 4.0 (2.5)	145	n.a. 13.0 (9.0)	0.24 [0.08; 0.746] 0.008
Nervous system disorders (severe AE, CTCAE grade ≥ 3)	158	n.a. 3.0 (1.9)	145	n.a. 8.0 (5.5)	0.28 [0.08; 1.08] 0.0496[k]

a. Hazard ratio and confidence interval from Cox proportional hazards model, with p value from log-rank test, each stratified by ECOG-PS (0, 1) and number of organs with metastases (≤ 1, ≥ 2) according to IRT
b. Indication of absolute difference (AD) only in case of statistically significant difference; own calculation
c. Data from the dossier of the pharmaceutical company (Module 4T) of 29 April 2022
d. A decrease in the score for the EQ-5D VAS by ≥ 15 points compared to the start of the study is considered a clinically relevant deterioration (scale range 0 to 100).
e. A decrease in the score for the FACT-E by ≥ 27 points compared to the start of the study is considered a clinically relevant deterioration (scale range 0 to 176).
f. Shown is a decrease in the score FACT-G by ≥ 17 points, the scores PWB, SWB, FWB and FACT-G7 by ≥ 5 points, the score EWB by ≥ 4 points and the score ECS by ≥ 11 points compared to the start of the study (scale range FATC-G: 0 to 108; PWB, SWB, FWB, FACT-G7: 0 to 28; EWB: 0 to 24; ECS: 0 to 68).
g. Progression events of the underlying disease are not included (multiple PT of SOC "Benign, malignant and unspecified neoplasms (including cysts and polyps)"
h. Discontinuation of at least 1 component
i. The operationalisation of a specific MedDRA PT collection ("select AE") submitted by the pharmaceutical company is used in each case
j. No presentation of effect estimate and confidence interval, as not informative
k. Discrepancy between p value and confidence interval due to different calculation methods

Abbreviations used:
AD = absolute difference; CTCAE = Common Terminology Criteria for Adverse Events; ECOG-PS = Eastern Cooperative Oncology Group Performance Status; ECS = esophageal cancer-specific subscale; EWB = emotional well-being;
EQ-5D = European Quality of Life-5 Dimensions; FACT-E = Functional Assessment of Cancer Therapy - Esophageal; FACT-G = Functional Assessment of Cancer Therapy - General; FACT-G7 = Functional Assessment of Cancer Therapy - General 7-item version; FWB = functional well-being; IRT = interactive response technology; CI =confidence interval; MedDRA = Medical Dictionary for Regulatory Activities; N = number of patients evaluated; n = number of patients with (at least one) event; n.c. = not calculable; n.a. = not achieved; PT = preferred term; PWB = physical well-being; SOC = system organ class; SAE = serious adverse event; SWB = social well-being; AE = adverse event; VAS = visual analogue scale; vs = versus

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

approx. 920 – 1580 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 Opdivo (active ingredient: nivolumab) at the following publicly accessible link (last access: 29 September 2022):

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

Treatment with nivolumab should only be initiated and monitored by specialists in internal medicine, haematology and oncology, who are experienced in the treatment of patients with oesophageal cancer, as well as specialists in internal medicine and gastroenterology and other specialists participating in the Oncology Agreement.

In accordance with the Medicines Agency requirements regarding additional risk minimisation measures, the pharmaceutical company must provide healthcare professionals and patients with a patient card. The patient card contains, in particular, instructions on the management of immune-mediated side effects potentially occurring with nivolumab as well as on infusion-related reactions. The prescribing doctors must discuss the risks of therapy with nivolumab with the patients.

4. Treatment costs

Adults with advanced, recurrent or metastatic, curatively untreatable oesophageal squamous cell carcinoma with tumour cell PD-L1 expression ≥ 1%; first-line therapy

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

Annual treatment costs:

Designation of the therapy	Annual treatment costs/ patient
Medicinal product to be assessed:	
Nivolumab in combination with ipilimumab	
Nivolumab	€ 76,217.74
Ipilimumab	€ 57,271.23
Total	€ 133,488.97
Appropriate comparator therapy:	
Cisplatin in combination with 5-fluorouracil	
Cisplatin	€ 1,706.51 - € 2,284.10
5-fluorouracil	€ 1,878.50 - € 2,514.30
Total	€ 3,585.01 - € 4,798.40
Additionally required SHI services	€ 242.72 - € 416.67

Costs after deduction of statutory rebates (LAUER-TAXE®) as last revised: 1 October 2022)

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					
Nivolumab in combination with ipilimumab					
Nivolumab (cycle every 2 weeks)	Surcharge for the preparation of a parenteral solution containing monoclonal antibodies	€ 71	1	26.1	€ 1,853.10
Nivolumab (cycle every 3 weeks)	Surcharge for the preparation of a parenteral solution containing monoclonal antibodies	€ 71	1	17.4	€ 1235.40
Ipilimumab (cycle every 6 weeks)	Surcharge for the preparation of a parenteral solution containing monoclonal antibodies	€ 71	1	8.7	€ 617.70
Appropriate comparator therapy					
Cisplatin in combination with 5-fluorouracil					
Cisplatin	Surcharge for production of a parenteral preparation containing cytostatic agents	€ 81	1	13 - 17.4	€ 1,053.00 - € 1,409.40
5-fluorouracil	Surcharge for production of a parenteral preparation containing cytostatic agents	€ 81	5	65 - 87	€ 5,265.00 - € 7,047.00

II. The resolution will enter into force on the day of its publication on the website of the G-BA on 20 October 2022.

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

Berlin, 20 October 2022

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

Prof. Hecken