

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 \geq 1%, first-line,
combination with fluoropyrimidine and platinum-based
chemotherapy)

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 in accordance with the resolution of 20 October 2022
on the therapeutic indication "...indicated as monotherapy for the adjuvant treatment of
adults with muscle invasive urothelial carcinoma (MIUC) with tumour cell PD-L1
expression \geq 1%, who are at high risk of recurrence after undergoing radical resection of
MIUC":

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 fluoropyrimidine- and platinum-based combination chemotherapy 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 $\geq 1\%$.

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 $\geq 1\%$; first-line therapy

Appropriate comparator therapy:

- Cisplatin in combination with 5-fluorouracil

Extent and probability of the additional benefit of nivolumab in combination with fluoropyrimidine- and platinum-based chemotherapy compared with cisplatin in combination with 5-fluorouracil:

Indication 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 therapy discontinuation due to AE. In detail, advantages 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 + Cisplatin + 5-fluorouracil		Cisplatin + 5-fluorouracil		Intervention vs control
	N	Median survival time in months [95% CI] <i>Patients with event n (%)</i>	N	Median survival time in months [95% CI] <i>Patients with event n (%)</i>	Hazard ratio [95% CI] p value ^a Absolute difference (AD) ^b
Overall survival					
	158	15.05 [11.9; 18.6] 118 (74.7)	157	9.07 [7.7; 10.0] 130 (82.8)	0.59 [0.46; 0.76] < 0.001 AD = + 5.98 months

¹ Data from the dossier assessment of the IQWiG (A22-54) and from the addendum (A22-98), unless otherwise indicated.

Morbidity

Endpoint	Nivolumab + Cisplatin + 5-fluorouracil		Cisplatin + 5-fluorouracil		Intervention vs control
	N	Median time to event in months [95% CI] <i>Patients with event n (%)</i>	N	Median time to event in months [95% CI] <i>Patients with event n (%)</i>	Hazard ratio [95% CI] p value ^a Absolute difference (AD) ^b
Progression-free survival (PFS)^c					
	158	6.83 [5.65; 8.28] 143 (90.5)	157	4.44 [2.96; 5.78] 143 (91.1)	0.68 [0.53; 0.85] 0.0009 AD = + 2.39 months
Health status (EQ-5D VAS) – Time to first deterioration^d					
≥ 15% points	155	11.43 [7.6; 18.27] 65 (41.9)	143	8.25 [5.0; 12.9] 59 (41.3)	0.72 [0.50; 1.04] 0.165

Health-related quality of life

Endpoint	Nivolumab + Cisplatin + 5-fluorouracil		Cisplatin + 5-fluorouracil		Intervention vs control
	N	Median time to event in months [95% CI] <i>Patients with event n (%)</i>	N	Median time to event in months [95% CI] <i>Patients with event n (%)</i>	Hazard ratio [95% CI] p value
FACT-E (time to first deterioration)					
≥ 27 points ^e	152	n.a. 38 (25.0)	140	n.a. [8.5; n.c.] 36 (25.7)	0.72 [0.45; 1.14] 0.202
FACT-G ^f (presented additionally)	153	n.a. [12.6; n.c.] 47 (30.7)	140	15.67 [8.5; n.c.] 40 (28.6)	0.78 [0.50; 1.20] 0.227
PWB (physical well-being) ^f	155	6.97 [4.0; 7.7] 86 (55.5)	141	4.30 [2.8; 5.7] 73 (51.8)	0.85 [0.62; 1.17] 0.252

(continuation)

SWB (social well-being) ^f	155	16.8 [10.7; n.c.] 55 (35.5)	141	9.63 [6.7; n.c.] 47 (33.3)	0.67 [0.44; 1.00] 0.190
EWB (emotional well-being) ^f	154	20.76 [7.0; n.c.] 62 (40.3)	141	13.60 [9.0; n.c.] 43 (30.5)	1.16 [0.78; 1.72] 0.628
FWB (functional well-being) ^f	153	7.72 [5.6; 12.6] 74 (48.4)	140	9.53 [4.2; 15.7] 60 (42.9)	0.82 [0.58; 1.17] 0.548
ECS ^f (presented additionally)	154	32.26 [19.8; n.c.] 44 (28.6)	142	14.42 [7.1; 20.5] 51 (35.9)	0.49 [0.32; 0.75] 0.003

Side effects

Endpoint	Nivolumab + Cisplatin + 5-fluorouracil		Cisplatin + 5-fluorouracil		Intervention vs control
	N	Median time to event in months [95% CI] <i>Patients with event n (%)</i>	N	Median time to event in months [95% CI] <i>Patients with event n (%)</i>	Hazard ratio [95% CI] p value ^a Absolute difference (AD) ^b
Total adverse events (presented additionally)^g					
	155	0.10 [0.07; 0.1] 155 (100.0)	145	0.10 [0.07; 0.1] 144 (99.3)	-
Serious adverse events (SAEs)^g					
	155	6.05 [4.3; 8.0] 98 (63.2)	145	6.41 [4.4; 8.2] 77 (53.1)	0.94 [0.69; 1.27] 0.678
Severe adverse events (CTCAE grade ≥ 3)^g					
	155	2.79 [1.9; 3.7] 122 (78.7)	145	2.99 [2.0; 3.8] 108 (74.5)	0.92 [0.71; 1.20] 0.534

(continuation)

Therapy discontinuations due to adverse events ^{g,h}					
	155	9.43 [7.1; 15.2] 71 (45.8)	145	14.23 [10.1; n.c.] 31.0 (21.4)	1.74 [1.13; 2.67] 0.011 AD = - 4.80 months
Specific adverse events					
Immune-mediated AEs (presented additionally) ⁱ					
	155	1.41 [1.1; 2.3] 121 (78.1)	145	5.55 [3.7; 6.4] 79 (54.5)	-
Immune-mediated SAEs ⁱ					
	155	n.a. 20 (12.9)	145	n.a. 7 (4.8)	2.11 [0.88; 5.07] 0.088
Immune-mediated severe AEs (CTCAE grade ≥ 3) ⁱ					
	155	n.a. 28 (18.1)	145	n.a. 11 (7.6)	1.92 [0.94; 3.90] 0.067
Other specific AEs					
Vomiting (PT, severe AEs, (CTCAE grade ≥ 3))	155	n.a. 2 (1.3)	145	n.a. 8 (5.5)	0.2 [0.04; 0.95] 0.025
Pneumonia (CTCAE grade ≥ 3)	155	n.a. 7 (4.5)	145	n.a. 11 (7.6)	0.38 [0.14; 1.03] 0.048 ^j
<p>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</p> <p>b. Indication of absolute difference (AD) only in case of statistically significant difference; own calculation</p> <p>c. Data from the dossier of the pharmaceutical company (Module 4S) of 29 April 2022</p> <p>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 EQ-5D VAS: 0 to 10).</p> <p>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).</p> <p>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 FACT-G: 0 to 108; PWB, SWB, FWB, FACT-G7: 0 to 28; EWB: 0 to 24; ECS: 0 to 68).</p> <p>g. Progression events of the underlying disease are not included (multiple PT of SOC "Benign, malignant and unspecified neoplasms (including cysts and polyps)")</p> <p>h. Discontinuation of at least 1 component</p> <p>i. The operationalisation of a specific MedDRA PT collection ("select AE") submitted by the pharmaceutical company is used in each case</p> <p>j. Discrepancy between p value and confidence interval due to different calculation methods</p> <p>Abbreviations used: AD = absolute difference; CTCAE = Common Terminology Criteria for Adverse Events; ECOG-PS = Eastern Cooperative Oncology Group Performance Status; EQ-5D = European Quality of Life-5 Dimensions; FACT-E = Functional Assessment of Cancer Therapy - Esophageal; IRT = interactive response technology; CI = confidence interval; MedDRA = Medical Dictionary for Regulatory Activities; N = number of patients evaluated; n = number</p>					

of patients with (at least one) event; n.c. = not calculable; n.a. = not achieved; PT = preferred term; 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

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 \geq 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 cisplatin and 5-fluorouracil	
Nivolumab	€ 75,925.72 - € 76,217.74
Cisplatin	€ 1,706.51 - € 2,284.10
5-fluorouracil	€ 1,878.50 - € 2,514.30
Total	€ 79,510.73 - € 81,016.14
Additionally required SHI services	€ 242.72 - € 416.67
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 cisplatin and 5-fluorouracil					
Nivolumab (cycle every 14 days)	Surcharge for the preparation of a parenteral solution containing monoclonal antibodies	€ 71	1	26.1	€ 1,853.10
Nivolumab (cycle every 28 days)	Surcharge for the preparation of a parenteral solution	€ 71	1	13	€ 923.00

	containing monoclonal antibodies				
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	1	65 - 87	€ 5,265.00 € 7,047.40
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 - € 7,047.40

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