Gemeinsamer Bundesausschuss

Resolution

of the Federal Joint Committee on an Amendment of the Pharmaceuticals Directive (AM-RL)

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, pretreated patients)

of 1 July 2021

At its session on 1 July 2021, 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 on DD. 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 nivolumab in accordance with the resolution of 3 June 2021:

Nivolumab

Resolution of: 1 July 2021
Entry into force on: 1 July 2021
BAnz AT DD. MM YYYY Bx

New therapeutic indication (according to the marketing authorisation of 20 November 2020):

OPDIVO as monotherapy is indicated for the treatment of adult patients with unresectable advanced, recurrent or metastatic oesophageal squamous cell carcinoma after prior fluoropyrimidine- and platinum-based combination chemotherapy.

Therapeutic indication of the resolution (resolution of 1 July 2021):

see new therapeutic indication according to marketing authorisation

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

a) Adult patients with unresectable advanced, recurrent or metastatic oesophageal squamous cell carcinoma after prior fluoropyrimidine- and platinum-based combination chemotherapy, for whom chemotherapy is an appropriate treatment option:

Appropriate comparator therapy:

- Chemotherapy according to the doctor's instructions

Extent and probability of the additional benefit of nivolumab compared to chemotherapy according to the doctor's instructions:

Hint for a minor additional benefit.

b) adult patients with unresectable advanced, recurrent or metastatic oesophageal squamous cell carcinoma after prior fluoropyrimidine- and platinum-based chemotherapy, for whom chemotherapy is not an appropriate treatment option:

Appropriate comparator therapy:

- Best supportive care

Extent and probability of the additional benefit of nivolumab compared to the appropriate comparator therapy:

An additional benefit is not proven

Study results according to endpoints:[1]

a) Adult patients with unresectable advanced, recurrent or metastatic oesophageal squamous cell carcinoma after prior fluoropyrimidine- and platinum-based combination chemotherapy, for whom chemotherapy is an appropriate treatment option:

Summary of results for relevant clinical endpoints

Endpoint category	Direction of effect/ Risk of bias	Summary
Mortality	↑↑	Advantage in overall survival
Morbidity	n.c.	There are no assessable data.
Health-related quality of life	∅	There are no usable data for the benefit assessment.
Side effects	↑	Advantage for severe AEs and in detail 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
∅: There are no usable data for the benefit assessment.
n.a.: not assessable

ATTRACTION-3 study:

Nivolumab **vs** docetaxel or paclitaxel

Study design: open, randomised, controlled

[1] Data from the dossier assessment of the IQWiG (A20-121) and from the addendum (A21-62), unless otherwise indicated.

Mortality

Endpoint	Nivolumab		Docetaxel or paclitaxel		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)[a]
Overall survival					
	210	10.91 [9.23; 13.34] *160 (76.2)*	209	8.38 [7.20; 9.86] *173 (82.8)*	0.77 [0.62; 0.96]; 0.019 AD: 2.53 months

Morbidity

Endpoint	Nivolumab		Docetaxel or paclitaxel		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)[a]
Progression-free survival (PFS)					
	210	1.68 [1.51; 2.79] *194 (92.4)*	209	4.04 [3.02; 4.21] *196 (93.8)*	4.04 [3.02; 4.21] 0.3315
Health status (EQ-5D VAS)					
	No usable data available.				

Health-related quality of life

Health-related quality of life was not examined in the study.

Side effects

Endpoint	Nivolumab		Docetaxel or paclitaxel		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 (%)*	Effect estimator [95% CI] p value Absolute difference (AD)[a]
Adverse events (presented additionally)					
	209	0.46 [0.30; 0.53] *190 (90.9)*	208	0.26 [0.20; 0.26] *206 (99.0)*	-
Serious adverse events (SAEs)					
	209	20.34 [8.11; n. a.] *79 (37.8)*	208	11.10 [6.93; n. a.] *88 (42.3)*	0.79 [0.58; 1.07]; 0.123
Severe adverse events (CTCAE grade 3 or 4)					
	209	7.62 [5.39; n. a.] *99 (47.4)*	208	0.71 [0.49; 0.99] *159 (76.4)*	0.36 [0.28; 0.47]; < 0.001
Therapy discontinuation due to adverse events					
	209	n.a. *30 (14.4)*	208	n.a. *33 (15.9)*	0.84 [0.51; 1.38]; 0.485
Specific adverse events					
Immune-mediated AEs	No usable data available.				
Stomatitis (PT, AEs)	209	n.a. *9 (4.3)*	208	n.a. *26 (12.5)*	0.32 [0.15; 0.68]; 0.002
General disorders and administration site conditions (SOC, AEs)	209	12.06 [7.06; n. a.] *86 (41.1)*	208	1.41 [1.02; 2.46] *138 (66.3)*	0.46 [0.35; 0.60]; < 0.001
Decreased appetite (PT, AEs)	209	n.a. *44 (21.1)*	208	n.a. *72 (34.6)*	0.03 [< 0.01; 0.07]; 0.001
Alopecia (PT, AEs)	209	n.a. *5 (2.4)*	208	n. a. [0.95; n. c.] *100 (48.1)*	0.03 [< 0.01; 0.07]; 0.001
Musculoskeletal and connective tissue disorders and bone and joint injuries (SOC, AEs)	209	22.57 [15.31; 22.57] *38 (18.2)*	208	n.a. *59 (28.4)*	0.51 [0.33; 0.77]; 0.001

Nervous system disorders (SOC, AEs)	209	n.a. *27 (12.9)*	208	3.48 [2.17; 14.29] *107 (51.4)*	0.18 [0.12; 0.28]; < 0.001
Febrile neutropenia (PT, SAEs)	209	n.a. *2 (1.0)*	208	n.a. *17 (8.2)*	0.11 [0.03; 0.48]; < 0.001
Hyponatremia (PT, severe AEs)	209	n.a. *3 (1.4)*	208	n.a. *11 (5.3)*	0.28 [0.08; 1.00]; 0.037
Physical examination procedures (SOC, severe AEs)	209	n.a. *25 (12.0)*	208	n. a. [7.39; n. c.] *79 (38.0)*	0.23 [0.15; 0.36]; < 0.001
Blood and lymphatic system disorders (SOC, severe AEs)	209	n.a. *22 (10.5)*	208	n.a. *70 (33.7)*	0.25 [0.15; 0.40]; < 0.001

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

Abbreviations used:
AD = absolute difference; CTCAE = Common Terminology Criteria for Adverse Events; EQ-5D = European Quality of Life Questionnaire - 5 Dimensions; HR = hazard ratio; CI = confidence interval; N = number of patients evaluated; n = number of patients with (at least one) event; n. b. = not calculable; n. a. = not achieved; PT = preferred term; SAE = serious adverse event; AE = adverse event; VAS = visual analogue scale; vs = versus.

b) adult patients with unresectable advanced, recurrent or metastatic oesophageal squamous cell carcinoma after prior fluoropyrimidine- and platinum-based chemotherapy, for whom chemotherapy is not an appropriate treatment option:

No adequate data are available to allow an assessment of the additional benefit.

Summary of results for relevant clinical endpoints

Endpoint category	Direction of effect/ Risk of bias	Summary
Mortality	∅	There are no usable data for the benefit assessment.
Morbidity	∅	There are no usable data for the benefit assessment.
Health-related quality of life	∅	There are no usable data for the benefit assessment.
Side effects	∅	There are no usable data for the benefit assessment.

Explanations:
↑: statistically significant and relevant positive effect with low/unclear reliability of data
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2. Number of patients or demarcation of patient groups eligible for treatment

a) Adult patients with unresectable advanced, recurrent or metastatic oesophageal squamous cell carcinoma after prior fluoropyrimidine- and platinum-based combination chemotherapy, for whom chemotherapy is an appropriate treatment option:

approx. 250 – 750 patients

b) Adult patients with unresectable advanced, recurrent or metastatic oesophageal squamous cell carcinoma after prior fluoropyrimidine- and platinum-based combination chemotherapy, for whom chemotherapy is not an appropriate treatment option:

approx. 490 – 1310 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: 14 April 2021):

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

Treatment with nivolumab should only be initiated and monitored by specialists in internal medicine, haematology, and oncology, specialists in gastroenterology, and specialists participating in the Oncology Agreement who are experienced in the treatment of adult patients with oesophageal squamous cell carcinoma.

According to the requirements for risk minimisation activities in the EPAR (European Public Assessment Report), the pharmaceutical company must provide a patient card.

4. Treatment costs

Annual treatment costs:

a) Adult patients with unresectable advanced, recurrent or metastatic oesophageal squamous cell carcinoma after prior fluoropyrimidine- and platinum-based combination chemotherapy, for whom chemotherapy is an appropriate treatment option:

Designation of the therapy	Annual treatment costs/patient
Medicinal product to be assessed:	
Nivolumab	€ 79,613.87
Appropriate comparator therapy:	
Chemotherapy according to the doctor's instructions	For the present benefit assessment, paclitaxel and docetaxel are appropriate comparators in the context of therapy according to the doctor's instructions. However, these medicinal products are not approved in the present therapeutic indication, and therefore no costs are presented for these medicinal products.

b) adult patients with unresectable advanced, recurrent or metastatic oesophageal squamous cell carcinoma after prior fluoropyrimidine- and platinum-based chemotherapy, for whom chemotherapy is not an appropriate treatment option:

Designation of the therapy	Annual treatment costs/patient
Medicinal product to be assessed:	
Nivolumab	€ 79,613.87
Best supportive care	patient-individual
Appropriate comparator therapy:	
Best supportive care	patient-individual

Costs after deduction of statutory rebates (LAUER-TAXE®, as last revised: 15 June 2021)

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
Nivolumab	Surcharge for the preparation of a parenteral solution containing monoclonal antibodies	€ 71	1	26.1	€ 1,853.10

II. The resolution will enter into force on the day of its publication on the internet on the G-BA website on 1 July 2021.

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

Berlin, 1 July 2021

Federal Joint Committee
in accordance with Section 91 SGB V
The Chair

Prof. Hecken