

Nivolumab (New therapeutic indication: Oesophageal squamous cell carcinoma, pretreated patients)

Resolution of: 1 July 2021
Entry into force on: 1 July 2021
BAnz AT 22 07 2021 B3

Valid until: unlimited

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 |
| <p>Explanations:</p> <p>↑: statistically significant and relevant positive effect with low/unclear reliability of data</p> <p>↓: statistically significant and relevant negative effect with low/unclear reliability of data</p> <p>↑↑: statistically significant and relevant positive effect with high reliability of data</p> <p>↓↓: statistically significant and relevant negative effect with high reliability of data</p> <p>↔: no statistically significant or relevant difference</p> <p>∅: There are no usable data for the benefit assessment.</p> <p>n.a.: not assessable</p> | | |

ATTRACTION-3 study:

Nivolumab vs docetaxel or paclitaxel

Study design: open, randomised, controlled

Mortality

| Endpoint | Nivolumab | | Docetaxel or paclitaxel | | 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> | 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 |

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

Morbidity

| Endpoint | Nivolumab | | Docetaxel or paclitaxel | | 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> | 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] <i>Patients with event n (%)</i> | N | Median time to event in months [95% CI] <i>Patients with event n (%)</i> | 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 |
| <p>^a Indication of absolute difference (AD) only in case of statistically significant difference; own calculation</p> <p>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.</p> | | | | | |

- 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 ↓: 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 | | |

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 |