Nivolumab (new therapeutic indication: non-small cell lung cancer, PD-L1 expression ≥ 1%, neoadjuvant therapy, combination with platinum-based chemotherapy)

Resolution of: 1 February 2024 valid until: unlimited
Entry into force on: 1 February 2024
Federal Gazette, BAnz AT 27. 03 2024 B1

New therapeutic indication (according to the marketing authorisation of 26 June 2023):

Opdivo in combination with platinum-based chemotherapy is indicated for the neoadjuvant treatment of resectable non-small cell lung cancer at high risk of recurrence in adult patients whose tumours have PD-L1 expression ≥ 1%.

Therapeutic indication of the resolution (resolution of 1 February 2024):

See new therapeutic indication according to marketing authorisation.

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

Adults with resectable non-small cell lung cancer with tumour cell PD-L1 expression ≥ 1% at high risk of recurrence; neoadjuvant therapy

Appropriate comparator therapy:

Patient-individual therapy with selection of:

- preoperative (neoadjuvant) systemic chemotherapy with selection of
  - cisplatin in combination with a third-generation cytostatic (vinorelbine or gemcitabine or docetaxel or paclitaxel or pemetrexed)

  and
  - carboplatin in combination with a third-generation cytostatic (vinorelbine or gemcitabine or docetaxel or paclitaxel or pemetrexed) and
- simultaneous radiochemotherapy with platinum-based (cisplatin or carboplatin) combination chemotherapy.

taking into account the tumour stage, the tumour histology, the presence of a Pancoast tumour and the feasibility of an R0 resection, as well as the prerequisites for the use of carboplatin.

Extent and probability of the additional benefit of nivolumab in combination with platinum-based chemotherapy compared to the appropriate comparator therapy:

Hint for a non-quantifiable additional benefit

Study results according to endpoints:[1]

Adults with resectable non-small cell lung cancer with tumour cell PD-L1 expression ≥ 1% at high risk of recurrence; neoadjuvant therapy

Summary of results for relevant clinical endpoints

Endpoint category	Direction of effect/ risk of bias	Summary
Mortality	↑	Advantage in overall survival.
Morbidity	↑	Advantage in the endpoint of failure of the curative therapeutic approach (event rate and event-free survival).
Health-related quality of life	∅	No data available.
Side effects	↑↑	Disadvantage in the endpoint of severe AEs (CTCAE grade ≥ 3). 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 ∅: No data available. n.a.: not assessable		

CheckMate 816 study:

Nivolumab + platinum-based chemotherapy vs platinum-based chemotherapy

Study design: RCT, open-label, ongoing

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

Data cut-off: 3rd data cut-off with database lock on 14.10.2022

1 Data from the dossier assessment of the IQWiG (A23-74) and from the addendum (A23-131), unless otherwise indicated.

Mortality

Endpoint	Nivolumab + platinum-based chemotherapy[a]		Platinum-based chemotherapy[b]		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[c]
Overall survival					
	89	n.r. 13 (14.6)	89	n.r. [45.08; n.c.] 31 (34.8)	0.37 [0.19; 0.71] 0.002

Morbidity

Endpoint	Nivolumab + platinum-based chemotherapy[a]		Platinum-based chemotherapy[b]		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[c]
Failure of the curative approach (event-free survival, EFS)[d]					
	89	n.r. [26.55; n.c.] 37 (41.6)	89	9.05 [4.80; 16.95] 58 (65.2)	0.50 [0.33; 0.75] 0.001 RR [95% CI] p value Absolute difference (AD) 0.64 [0.48; 0.85] 0.002 AD = - 23.6%
Progression of the disease that rules out surgery	89	n.d. 5 (5.6)	89	n.d. 8 (9.0)	n.d.
Locoregional progression	89	n.d. 4 (4.5)	89	n.d. 6 (6.7)	n.d.
Locoregional progression	89	n.d. 1 (1.1)	89	n.d. 2 (2.2)	n.d.

and distant metastasis					
not reported	89	n.d. 0 (0)	89	n.d. 2 (2.2)	n.d.
AE that rules out surgery	89	n.d. 1 (1.1)	89	n.d. 1 (1.1)	n.d.
Other events that rule out surgery	89	n.d. 8 (9.0)	89	n.d. 11 (12.4)	n.d.
Failed R0 resection of the tumour (R1, R2, Rx)	89	n.d. 7 (7.9)	89	n.d. 12 (13.5)	n.d.
Recurrence after successful R0 resection	89	n.d. 14 (15.7)	89	n.d. 21 (23.6)	n.d.
Locoregional recurrence	89	n.d. 8 (9.0)	89	n.d. 11 (12.4)	n.d.
Distant metastasis	89	n.d. 6 (6.7)	89	n.d. 10 (11.2)	n.d.
Recurrence in patients without surgery	89	n.d. 0 (0)	89	n.d. 0 (0)	n.d.
Death from any cause	89	n.d. 2 (2.2)	89	n.d. 5 (5.6)	n.d.
Health status (EQ-5D VAS – time to 1st deterioration)[f]					
	84	34.43 [11.86; 46.95] 44 (52.4)	86	23.46 [16.36; n.c.] 44 (51.2)	0.82 [0.53; 1.25] 0.350

Health-related quality of life

No health-related quality of life data was collected in the CheckMate 816 study.

Side effects

Endpoint	Nivolumab + platinum-based chemotherapy[a]		Platinum-based chemotherapy[b]		Intervention vs control
	N	*Patients with event n (%)*	N	*Patients with event n (%)*	Relative risk [95% CI] p value[e] Absolute difference (AD)
Total adverse events (presented additionally)					
	88	85 (96.6)	89	88 (98.9)	-
Serious adverse events (SAEs)[g]					
	88	25 (28.4)	89	21 (23.6)	1.20 [0.73; 1.98] 0.532
Severe adverse events (CTCAE ≥ 3)[g,]					
	88	39 (44.3)	89	60 (67.4)	0.66 [0.50; 0.87] 0.002 AD = - 23.1%
Therapy discontinuation due to adverse events[i]					
	88	11 (12.5)	89	14 (15.7)	0.79 [0.38; 1.65] 0.573
Specific adverse events					
Immune-mediated AEs (presented additionally)	88	49 (55.7)	89	44 (49.4)	–
Immune-mediated SAEs	88	7 (8.0)	89	3 (3.4)	2.36 [0.63; 8.83] 0.244
Immune-mediated severe AEs[h]	88	9 (10.2)	89	5 (5.6)	1.82 [0.64; 5.22] 0.283
Blood and lymphatic system disorders (SOC, severe AEs)[h]	88	11 (12.5)	89	27 (30.3)	0.41 [0.22; 0.78] 0.004 AD = - 17.8%
Metabolism and nutrition disorders (SOC, severe AEs)[h]	88	2 (2.3)	89	9 (10.1)	0.22 [0.05; 1.01] 0.035[j] AD = - 7.8%

a. Chemotherapy of the principal investigator's choice: cisplatin + gemcitabine (only for squamous histology) or cisplatin + pemetrexed (only for non-squamous histology) or carboplatin + paclitaxel. For patients for whom cisplatin was not (or no longer) suitable and the reason for this was documented, carboplatin could be used instead of cisplatin.
b. Chemotherapy of the principal investigator's choice: cisplatin + gemcitabine (only for squamous histology) or cisplatin + pemetrexed (only for non-squamous histology) or cisplatin + vinorelbine or cisplatin + docetaxel or carboplatin + paclitaxel. For patients for whom cisplatin was not (or no longer) suitable and the reason for this was documented, carboplatin could be used instead of cisplatin.
c. HR and CI: Cox proportional hazards model; p value: log-rank test; each stratified by stage of the disease at start of study (IB/II vs IIIA) and sex (male vs female) according to IRT; for the endpoint of health status (EQ-5D VAS): model with additional adjustment with regard to baseline
d. includes the events: disease progression, AE or any other event that rules out surgery; failed R0 resection of the tumour (R1, R2, Rx); recurrence after successful R0 resection; recurrence in patients without surgery; death from any cause
e. own calculation of RR, CI (asymptotic) and p value (unconditional exact test, CSZ method according to[2]).
f. A decrease in score by ≥ 15 points compared to the start of study is considered clinically relevant deterioration (scale range: 0 to 100).
g. as stated by the pharmaceutical company, excluding events of PT malignant neoplasm progression and PT cancer pain, which are assigned to SOC benign, malignant and unspecified neoplasms (including cysts and polyps)
h. Operationalised as CTCAE grade ≥ 3
i. Operationalised as discontinuation of at least 1 active ingredient component
j. 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; HR: hazard ratio; CI: confidence interval; n.d.: no data available; n: number of patients with event; N: number of patients evaluated; n.c.: not calculable; n.r. = not reached; RCT: randomised controlled trial; RR: relative risk; SOC: system organ class; SAE: serious adverse event; AE: adverse event; VAS: visual analogue scale

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

Adults with resectable non-small cell lung cancer with tumour cell PD-L1 expression ≥ 1% at high risk of recurrence; neoadjuvant therapy

approx. 110 - 990 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: 2 October 2023):

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

2 Martín Andrés A, Silva Mato A. Choosing the optimal unconditioned test for comparing two independents proportions. Computat Stat Data Anal 1994; 17(5): 555-574. https://dx.doi.org/10.1016/0167-9473(94)90148-1

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 non-small cell lung cancer, as well as specialists in internal medicine and pulmonology or specialists in pulmonary medicine and other doctors from specialist groups participating in the Oncology Agreement.

In accordance with the European Medicines Agency (EMA) requirements regarding additional risk minimisation measures, the pharmaceutical company must provide training material that contains information for medical professionals and patients (incl. patient identification card).

The training material contains, in particular, information and warnings about immune-mediated side effects as well as infusion-related reactions.

4. Treatment costs

Annual treatment costs:

Adults with resectable non-small cell lung cancer with tumour cell PD-L1 expression ≥ 1% at high risk of recurrence; neoadjuvant therapy

Designation of the therapy	Annual treatment costs/ patient
Medicinal product to be assessed: Nivolumab + platinum-based chemotherapy	
Nivolumab + paclitaxel + carboplatin	
Nivolumab	€ 13,139.19
Paclitaxel	€ 2,867.07 - € 3,211.38
Carboplatin	€ 1,088.28 - € 1,295.70
Total:	€ 17,094.54 - € 17,646.27
Nivolumab + pemetrexed + cisplatin	
Nivolumab	€ 13,139.19
Pemetrexed	€ 3,235.32
Cisplatin	€ 342.09
Total:	€ 16,716.60
Nivolumab + cisplatin + gemcitabine	
Nivolumab	€ 13,139.19
Cisplatin	€ 342.09
Gemcitabine	€ 1,101.30 - € 1,413.54
Total:	€ 14,582.58 - € 14,894.82
Appropriate comparator therapy:	
Patient-individual therapy with selection of preoperative (neoadjuvant) systemic chemotherapy with selection of	
Cisplatin in combination with vinorelbine	

Designation of the therapy	Annual treatment costs/ patient
Cisplatin	€ 390.84
Vinorelbine	€ 1,032.78
Total:	€ 1,423.62
Cisplatin in combination with paclitaxel	
Cisplatin	€ 210.82
Paclitaxel	€ 1,911.38
Total:	€ 2,122.20
Cisplatin in combination with gemcitabine	
Cisplatin	€ 342.09 - € 390.84
Gemcitabine	€ 1,413.54
Total:	€ 1,755.63 - € 1,804.38
Cisplatin in combination with docetaxel	
Cisplatin	€ 390.84
Docetaxel	€ 1,469.52
Total:	€ 1,860.36
Cisplatin in combination with pemetrexed	
Cisplatin	€ 342.09
Pemetrexed	€ 3,235.32
Total:	€ 3,577.41
Carboplatin in combination with vinorelbine	
Carboplatin	Not calculable
Vinorelbine	Not calculable
Total:	Not calculable
Carboplatin in combination with paclitaxel	
Carboplatin	€ 1,088.28
Paclitaxel	€ 2,867.07
Total:	€ 3,955.35
Carboplatin in combination with gemcitabine	
Carboplatin	€ 1,182.93
Gemcitabine	€ 1,101.30
Total:	€ 2,284.23
Carboplatin in combination with docetaxel	
Carboplatin	€ 1,295.70
Docetaxel	€ 1,469.52

Designation of the therapy	Annual treatment costs/ patient
Total:	€ 2,765.22
Carboplatin in combination with pemetrexed	
Carboplatin	€ 1,727.60
Pemetrexed	€ 4,313.76
Total:	€ 6,041.36
Simultaneous radio chemotherapy	
Radiotherapy	€ 3,430.39 - € 4,003.24
Chemotherapy	Not calculable
Total:	Not calculable

Costs after deduction of statutory rebates (LAUER-TAXE®) as last revised: 15 January 2024)

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 + paclitaxel + carboplatin					
Nivolumab	Surcharge for the preparation of a parenteral solution containing monoclonal antibodies	€ 100	1	3	€ 300
Paclitaxel	Surcharge for production of a parenteral preparation containing cytostatic agents	€ 100	1	3	€ 300
Carboplatin	Surcharge for production of a parenteral preparation containing cytostatic agents	€ 100	1	3	€ 300
Nivolumab + pemetrexed + cisplatin					
Nivolumab	Surcharge for the preparation of a	€ 100	1	3	€ 300

Designation of the therapy	Type of service	Costs/ unit	Number/ cycle	Number/ patient/ year	Costs/ patient/ year
	parenteral solution containing monoclonal antibodies				
Pemetrexed	Surcharge for production of a parenteral preparation containing cytostatic agents	€ 100	1	3	€ 300
Cisplatin	Surcharge for production of a parenteral preparation containing cytostatic agents	€ 100	1	3	€ 300
Nivolumab + cisplatin + gemcitabine					
Nivolumab	Surcharge for the preparation of a parenteral solution containing monoclonal antibodies	€ 100	1	3	€ 300
Cisplatin	Surcharge for production of a parenteral preparation containing cytostatic agents	€ 100	1	3	€ 300
Gemcitabine	Surcharge for production of a parenteral preparation containing cytostatic agents	€ 100	2	6	€ 600
Appropriate comparator therapy:					
Cisplatin in combination with vinorelbine					
Cisplatin	Surcharge for production of a parenteral	€ 100	1	3	€ 300

Designation of the therapy	Type of service	Costs/ unit	Number/ cycle	Number/ patient/ year	Costs/ patient/ year
	preparation containing cytostatic agents				
Vinorelbine	Surcharge for production of a parenteral preparation containing cytostatic agents	€ 100	2	6	€ 600
Cisplatin in combination with paclitaxel					
Cisplatin	Surcharge for production of a parenteral preparation containing cytostatic agents	€ 100	1	2	€ 200
Paclitaxel	Surcharge for production of a parenteral preparation containing cytostatic agents	€ 100	1	2	€ 200
Cisplatin in combination with gemcitabine					
Cisplatin	Surcharge for production of a parenteral preparation containing cytostatic agents	€ 100	1	3	€ 300
Gemcitabine	Surcharge for production of a parenteral preparation containing cytostatic agents	€ 100	2	6	€ 600
Cisplatin in combination with docetaxel					
Cisplatin	Surcharge for production of a parenteral preparation containing cytostatic agents	€ 100	1	3	€ 300

Designation of the therapy	Type of service	Costs/ unit	Number/ cycle	Number/ patient/ year	Costs/ patient/ year
Docetaxel	Surcharge for production of a parenteral preparation containing cytostatic agents	€ 100	1	3	€ 300
Cisplatin in combination with pemetrexed					
Cisplatin	Surcharge for production of a parenteral preparation containing cytostatic agents	€ 100	1	3	€ 300
Pemetrexed	Surcharge for production of a parenteral preparation containing cytostatic agents	€ 100	1	3	€ 300
Carboplatin in combination with paclitaxel					
Carboplatin	Surcharge for production of a parenteral preparation containing cytostatic agents	€ 100	1	3	€ 300
Paclitaxel	Surcharge for production of a parenteral preparation containing cytostatic agents	€ 100	1	3	€ 300
Carboplatin in combination with gemcitabine					
Carboplatin	Surcharge for production of a parenteral preparation containing cytostatic agents	€ 100	1	3	€ 300
Gemcitabine	Surcharge for production of a parenteral	€ 100	2	6	€ 600

Designation of the therapy	Type of service	Costs/ unit	Number/ cycle	Number/ patient/ year	Costs/ patient/ year
	preparation containing cytostatic agents				
Carboplatin in combination with docetaxel					
Carboplatin	Surcharge for production of a parenteral preparation containing cytostatic agents	€ 100	1	3	€ 300
Docetaxel	Surcharge for production of a parenteral preparation containing cytostatic agents	€ 100	1	3	€ 300
Carboplatin in combination with pemetrexed					
Carboplatin	Surcharge for production of a parenteral preparation containing cytostatic agents	€ 100	1	4	€ 400
Pemetrexed	Surcharge for production of a parenteral preparation containing cytostatic agents	€ 100	1	4	€ 400

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:

Adults with resectable non-small cell lung cancer with tumour cell PD-L1 expression ≥ 1% at high risk of recurrence; neoadjuvant therapy

- No medicinal product with new active ingredients that can be used in a combination therapy and 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.+