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: urothelial carcinoma, PD-L1 expression ≥ 1%, adjuvant treatment)

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 shall be added after No. 4 to the information on the benefit assessment of Nivolumab in accordance with the resolution of 19 May 2022 last modified on 12 July 2022:

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 as monotherapy is indicated for the adjuvant treatment of adults with muscle invasive urothelial carcinoma (MIUC) with tumour cell PD-L1 expression ≥ 1%, who are at high risk of recurrence after undergoing radical resection of MIUC.

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

a) Adults with muscle invasive urothelial carcinoma with tumour cell PD-L1 expression ≥ 1%, who are at high risk of recurrence after undergoing complete resection and are eligible for cisplatin-containing therapy; adjuvant treatment

Appropriate comparator therapy:

- Cisplatin + gemcitabine

or

- Cisplatin + methotrexate

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

An additional benefit is not proven.

b) Adults with muscle invasive urothelial carcinoma with tumour cell PD-L1 expression ≥ 1%, who are at high risk of recurrence after undergoing complete resection and are unsuitable for cisplatin-containing therapy, or have already received neoadjuvant treatment; adjuvant treatment

Appropriate comparator therapy:

– Monitoring wait-and-see approach

Extent and probability of the additional benefit of nivolumab compared to a monitoring wait-and-see approach:

Hint for a non-quantifiable additional benefit

Study results according to endpoints:[1]

a) Adults with muscle invasive urothelial carcinoma with tumour cell PD-L1 expression ≥ 1%, who are at high risk of recurrence after undergoing complete resection and are eligible for cisplatin-containing therapy; adjuvant treatment

No 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	∅	No data available.
Morbidity	∅	No data available.
Health-related quality of life	∅	No data available.
Side effects	∅	No data available.
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		

b) Adults with muscle invasive urothelial carcinoma with tumour cell PD-L1 expression ≥ 1%, who are at high risk of recurrence after undergoing complete resection and are unsuitable for cisplatin-containing therapy, or have already received neoadjuvant treatment; adjuvant treatment

Summary of results for relevant clinical endpoints

Endpoint category	Direction of effect/ risk of bias	Summary
Mortality	∅	No data available.
Morbidity	↑	Advantages in the endpoints recurrences (recurrence rate and disease-free survival) and health status.

[1] Data from the dossier assessment of the IQWiG (A22-53) and from the addendum (A22-97), unless otherwise indicated.

Endpoint category	Direction of effect/ risk of bias	Summary
Health-related quality of life	↔	No relevant differences for the benefit assessment.
Side effects	↓	Disadvantage in the endpoint of therapy discontinuation due to AE. In detail, advantages and disadvantages in case of specific adverse events.

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

CA209-274 study: Nivolumab vs placebo

Study design: randomised, double-blind

Relevant sub-population: Adults with tumour cell PD-L1 expression ≥ 1% who are unsuitable for cisplatin-containing therapy

Data cut-offs used:

- 1st data cut-off: August 2020 (morbidity (except recurrence rate and disease-free survival), health-related quality of life, side effects)
- 2nd data cut-off: February 2021 (recurrence rate, disease-free survival)

Mortality

Endpoint	Nivolumab		placebo		Nivolumab vs placebo
	N	Median survival time in months [95% CI] *Patients with event n (%)*	N	Median survival time in months [95% CI] *Patients with event n (%)*	HR [95% CI] p value Absolute difference (AD)[a]
No data available.					

Morbidity

Endpoint	Nivolumab		placebo		Nivolumab vs placebo
	N	Median survival time in months [95% CI] *Patients with event n (%)*	N	Median survival time in months [95% CI] *Patients with event n (%)*	HR [95% CI] p value[b] Absolute difference (AD)[a]
Recurrences					
Recurrence rate[c, d]	140	– 56 (40.0)	142	– 85 (59.9)	RR: 0.67 [0.52; 0.85][e] < 0.001[f]
Distant recurrence	140	– 41 (29.3)	142	– 54 (38.0)	-
Local recurrence outside the efferent urinary tract	140	– 7 (5.0)	142	– 20 (14.1)	-
Local recurrence within the efferent urinary tract, invasive	140	– 1 (0.7)	142	– 3 (2.1)	-
Local recurrence within the efferent urinary tract, non-invasive	140	– 2 (1.4)	142	– 2 (1.4)	-
Death of any cause (without previous recurrence)	140	– 5 (3.6)	142	– 6 (4.2)	-
Disease-free survival (DFS)[c]	140	n.a. [22.10; n.c.] 56 (40.0)	142	8.41 [5.59; 20.04] 85 (59.9)	0.53 [0.38; 0.75]; < 0.001
Symptomatology (EORTC QLQ-C30)[g] – Time to first deterioration					
Fatigue	123	4.90 [2.04; 7.39] 77 (62.6)	128	3.78 [2.50; 5.19] 80 (62.5)	0.99 [0.72; 1.36] 0.745
Nausea and vomiting	123	n.a. [15.41; n.c.] 44 (35.8)	128	n.a. 35 (27.3)	1.35 [0.86; 2.11] 0.178
Pain	123	9.69 [5.16; 13.01] 67 (54.5)	128	4.76 [3.25; 7.16] 81 (63.3)	0.75 [0.54; 1.04] 0.079
Dyspnoea	123	15.93 [8.90; n.c.] 51 (41.5)	127	n.a. [12.94; n.c.] 43 (33.9)	1.20 [0.80; 1.80] 0.400

Endpoint	Nivolumab		placebo		Nivolumab vs placebo
	N	Median survival time in months [95% CI] *Patients with event n (%)*	N	Median survival time in months [95% CI] *Patients with event n (%)*	HR [95% CI] p value[b] Absolute difference (AD)[a]
Insomnia	123	n.a. [8.87; n.c.] 48 (39.0)	128	11.04 [5.49; n.c.] 62 (48.4)	0.72 [0.49; 1.06] 0.054
Appetite loss	122	15.90 [9.23; n.c.] 51 (41.8)	128	n.a. [11.73; n.c.] 47 (36.7)	1.21 [0.81; 1.81] 0.614
Constipation	122	n.a. [n.a.; n.c.] 37 (30.3)	127	n.a. 42 (33.1)	0.91 [0.58; 1.42] 0.749
Diarrhoea	122	n.a. [13.83; n.c.] 40 (32.8)	127	n.a. 41 (32.3)	0.94 [0.60; 1.45] 0.739
Health status (EQ 5D VAS)[h] – Time to first deterioration					
	126	18.37 [11.14; n.c.] 59 (46.8)	129	9.00 [5.88; 17.77] 71 (55.0)	0.64 [0.45; 0.91] 0.036 AD = 9.37 months

Health-related quality of life

Endpoint	Nivolumab		placebo		Nivolumab vs placebo
	N	Median survival time in months [95% CI] *Patients with event n (%)*	N	Median survival time in months [95% CI] *Patients with event n (%)*	HR [95% CI] p value Absolute difference (AD)[a]
EORTC QLQ-C30[g] – Time to first deterioration					
Global health status	123	9.95 [6.93; n.c.] 57 (46.3)	127	10.51 [5.59; n.c.] 64 (50.4)	0.95 [0.66; 1.36] 0.529
Physical functioning	123	16.43 [8.84; n.c.] 48 (39.0)	128	n.a. [9.20; n.c.] 54 (42.2)	0.84 [0.57; 1.24] 0.387
Role functioning	123	8.31 [4.63; 12.75] 68 (55.3)	128	5.55 [4.04; n.c.] 68 (53.1)	0.95 [0.67; 1.34] 0.663
Emotional functioning	123	n.a. [15.24; n.c.] 45 (36.6)	127	13.14 [7.16; n.c.] 53 (41.7)	0.80 [0.53; 1.19] 0.258
Cognitive functioning	123	7.66 [4.67; 15.77] 64 (52.0)	127	8.61 [4.86; n.c.] 64 (50.4)	1.01 [0.71; 1.43] 0.946

Endpoint	Nivolumab		placebo		Nivolumab vs placebo
	N	Median survival time in months [95% CI] *Patients with event n (%)*	N	Median survival time in months [95% CI] *Patients with event n (%)*	HR [95% CI] p value Absolute difference (AD)[a]
Social functioning	122	14.06 [6.47; n.c.] 55 (45.1)	126	n.a. [7.56; n.c.] 52 (41.3)	1.06 [0.73; 1.56] 0.621

Side effects

Endpoint	Nivolumab		placebo		Nivolumab vs placebo
	N	Median in months [95% CI] *Patients with event n (%)*	N	Median in months [95% CI] *Patients with event n (%)*	HR [95% CI] p value
Total adverse events (presented additionally)[i,j]					
	139	0.49 [0.33; 0.49] 137 (98.6)	139	0.59 [0.49; 0.85] 133 (95.7)	-
Serious adverse events (SAEs) [i,j]					
	139	n.a. [13.80; n.c.] 51 (36.7)	139	n.a. [8.77; n.c.] 56 (40.3)	0.84 [0.58; 1.23] 0.380
Severe adverse events (CTCAE grade ≥ 3) [i,j]					
	139	0.84 [0.58; 1.23]; 0.380	139	n.a. [8.41; n.c.] 59 (42.4)	1.28 [0.91; 1.81] 0.154
Therapy discontinuations due to adverse events [i,j]					
	139	n.a. 28 (20.1)	139	n.a. 14 (10.1)	1.94 [1.02; 3.70] 0.039
Immune-mediated adverse events					
Immune-mediated AEs (presented additionally)[i,l]	139	1.68 [0.95; 2.33] 108 (77.7)	139	4.53 [2.73; 8.05] 80 (57.6)	-
Immune-mediated SAEs [i,l]	139	n.a. 17 (12.2)	139	n.a. 6 (4.3)	2.64 [1.04; 6.72] 0.034
Immune-mediated severe	139	n.a. 27 (19.4)	139	n.a. 9 (6.5)	2.89 [1.36; 6.14] 0.004

Endpoint	Nivolumab		placebo		Nivolumab vs placebo
	N	Median in months [95% CI] *Patients with event n (%)*	N	Median in months [95% CI] *Patients with event n (%)*	HR [95% CI] p value
AEs (CTCAE grade ≥ 3) [i,l]					
Specific adverse events[i]					
Skin and subcutaneous tissue disorders (SOC, AE)	139	5.36 [2.79; 10.48] 76 (54.7)	139	n.a. 45 (32.4)	1.89 [1.30; 2.74] 0.001
Asthenia (PT, AE)	139	n.a. 18 (12.9)	139	n.a. 5 (3.6)	3.70 [1.37; 9.97] 0.006
Infections and infestations (SOC, SAE)	139	n.a. 14 (10.1)	139	n.a. 27 (19.4)	0.48 [0.25; 0.92] 0.024
Respiratory, thoracic and mediastinal disorders (SOC, SAE)	139	n.a. 9 (6.5)	139	n.a. 1 (0.7)	8.38 [1.06; 66.20] 0.016
Gastrointestinal disorders (SOC, severe AEs)	139	n.a. 8 (5.8)	139	n.a. 17 (12.2)	0.44 [0.19; 1.01] 0.047
Lipase elevated (PT, severe AE)	139	n.a. 11 (7.9)	139	n.a. 1 (0.7)	10.50 [1.35; 81.42] 0.005

[a] Absolute difference (AD) given only in the case of a statistically significant difference; own calculation
[b] HR and CI from stratified Cox model with treatment as sole covariate, p value from log-rank test, each stratified by pathological lymph node status and use of cisplatin as neoadjuvant chemotherapy
[c] Data cut-off from February 2021
[d] Percentage of patients, individual components are shown in the rows below (in each case only with the qualifying events that come into play in the formation of the combined endpoint; calculation of effect estimators therefore not meaningful)
[e] Cochran-Mantel-Haenszel method stratified by pathological lymph node status and use of cisplatin as neoadjuvant chemotherapy
[f] IQWiG calculation (unconditional exact test (CSZ method according to Martín Andrés A, Silva Mato A. Choosing the optimal unconditioned test for comparing two independent proportions. Computat Stat Data Anal 1994;
17(5): 555-574.)
[g] Time to first deterioration. An increase in the score by ≥ 10 points compared to the start of the study is considered a clinically relevant deterioration (scale range 0 to 100).
[h] Time to first deterioration. A decrease in the score by ≥ 15 points compared to the start of the study is considered a clinically relevant deterioration (scale range 0 to 100).
[i] Data cut-off from August 2020
[j] Progression events of the underlying disease are not included (multiple PTs of SOC "Benign, malignant and unspecified neoplasms [including cysts and polyps]" according to the list of the pharmaceutical company).

Endpoint	Nivolumab		placebo		Nivolumab vs placebo
	N	Median in months [95% CI] *Patients with event n (%)*	N	Median in months [95% CI] *Patients with event n (%)*	HR [95% CI] p value

[l] In each case, the operationalisation of a specific MedDRA PT-collection presented by the pharmaceutical company ("select AE") is used.

Abbreviations used:
AD = absolute difference; CTCAE = Common Terminology Criteria for Adverse Events; DFS = disease-free survival; EORTC = European Organisation for Research and Treatment of Cancer; HR = hazard ratio; 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; PC = pharmaceutical company; RR = relative risk; 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

a) Adults with muscle invasive urothelial carcinoma with tumour cell PD-L1 expression ≥ 1%, who are at high risk of recurrence after undergoing complete resection and are eligible for cisplatin-containing therapy; adjuvant treatment

approx. 350 – 460 patients

b) Adults with muscle invasive urothelial carcinoma with tumour cell PD-L1 expression ≥ 1%, who are at high risk of recurrence after undergoing complete resection and are unsuitable for cisplatin-containing therapy, or have already received neoadjuvant treatment; adjuvant treatment

approx. 680 – 830 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

Therapy 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 urothelial carcinoma as well as specialists in urology, 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

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	€ 75,925.72 - € 76,217.74
Appropriate comparator therapy:	
a) Adults with muscle invasive urothelial carcinoma with tumour cell PD-L1 expression ≥ 1%, who are at high risk of recurrence after undergoing complete resection and are eligible for cisplatin-containing therapy; adjuvant treatment	
Cisplatin in combination with gemcitabine	
Cisplatin	€ 1,506.05
Gemcitabine	€ 7,014.54
Total:	€ 8,520.59
Additionally required SHI costs	€ 242.72 - € 311.31
Cisplatin in combination with methotrexate	
Cisplatin	€ 347.55
Methotrexate	€ 532.56
Total:	€ 880.11
Additionally required SHI costs	€ 9.56 – € 44.51
b) Adults with muscle invasive urothelial carcinoma with tumour cell PD-L1 expression ≥ 1%, who are at high risk of recurrence after undergoing complete resection and are unsuitable for cisplatin-containing therapy, or have already received neoadjuvant treatment; adjuvant treatment	
Monitoring wait-and-see approach	incalculable

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
Nivolumab (cycle every 14 days)	Preparation for parenteral solution containing monoclonal antibodies	€ 71	1	26.1	€ 1,853.10
Nivolumab (cycle every 28 days)	Preparation for parenteral solution containing monoclonal antibodies	€ 71	1	13	€ 923.00
Cisplatin (in combination with gemcitabine)	Surcharge for production of a parenteral preparation containing cytostatic agents	€ 81	1	13	€ 1,053.00
Cisplatin (in combination with methotrexate)	Surcharge for production of a parenteral preparation containing cytostatic agents	€ 81	1	3	€ 243.00
Gemcitabine	Surcharge for production of a parenteral preparation containing cytostatic agents	€ 81	3	39	€ 3,159.00
Methotrexate	Surcharge for production of a parenteral preparation containing cytostatic agents	€ 81	2	6	€ 486.00

II. Entry into force

1. **The resolution will enter into force on the day of its publication on the website of the G-BA on 20 October 2022.**
2. **The period of validity of the resolution is limited in accordance with the following regulations:**

   The statements made for the patient group

   b) adults with muscle invasive urothelial carcinoma with tumour cell PD-L1 expression ≥ 1%, who are at high risk of recurrence after undergoing complete resection and are unsuitable for cisplatin-containing therapy, or have already received neoadjuvant treatment; adjuvant treatment

   in numbers 1, 2, 3 and 4 are limited until 15 December 2025.

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