Gemeinsamer Bundesausschuss

Resolution

of the Federal Joint Committee on an Amendment on the 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: malignant pleural mesothelioma, first-line, combination with Ipilimumab)

of 16 December 2021

At its session on 16 December 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 by the publication of the resolution of 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 21 October 2021:

Nivolumab

Resolution of: 16 December 2021
Entry into force on: 16 December 2021
Federal Gazette, BAnz AT DD. MM YYYY Bx

New therapeutic indication (according to the marketing authorisation of 1 June 2021):

Opdivo in combination with ipilimumab is indicated for the first-line treatment of adult patients with unresectable malignant pleural mesothelioma.

Therapeutic indication of the resolution (resolution of 16 December 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 malignant pleural mesothelioma and epithelioid tumour histology; first-line therapy

Appropriate comparator therapy:

- Therapy according to doctor's instructions

Extent and probability of the additional benefit of Nivolumab in combination with Ipilimumab compared to the appropriate comparator therapy:

An additional benefit is not proven.

b) Adult patients with unresectable malignant pleural mesothelioma and non-epithelioid tumour histology; first-line therapy

Appropriate comparator therapy:

- Therapy according to doctor's instructions

Extent and probability of the additional benefit of Nivolumab in combination with Ipilimumab compared to the appropriate comparator therapy:

Indication of a considerable additional benefit.

Study results according to endpoints:[1]

a) Adult patients with unresectable malignant pleural mesothelioma and epithelioid tumour histology; first-line therapy

Summary of results for relevant clinical endpoints

Endpoint category	Direction of effect/ risk of bias	Summary
Mortality	↔	No relevant differences for the benefit assessment
Morbidity	↑	Advantage with regard to symptomatology
Health-related quality of life	∅	No data available
Side effects	↓↓	Disadvantage in the endpoint SAE; in detail, advantages and disadvantages 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		

b) Adult patients with unresectable malignant pleural mesothelioma and non-epithelioid tumour histology; first-line therapy

Summary of results for relevant clinical endpoints

Endpoint category	Direction of effect/ risk of bias	Summary
Mortality	↑↑	Advantage in overall survival
Morbidity	↑	Advantages in terms of symptomatology and health status endpoints
Health-related quality of life	∅	No data available
Side effects	↔	No differences relevant for the benefit assessment, in detail, advantages and disadvantages 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		

[1] Data from the dossier assessment of the IQWiG (21-89) and from the addendum (A21-141), unless otherwise indicated.

a) Adult patients with unresectable malignant pleural mesothelioma and epithelioid tumour histology; first-line therapy

and

b) Adult patients with unresectable malignant pleural mesothelioma and non-epithelioid tumour histology; first-line therapy

CA209-743 study: nivolumab + ipilimumab **vs** pemetrexed + cisplatin or pemetrexed + carboplatin

Mortality

Endpoint	**Nivolumab + Ipilimumab**		**Pemetrexed + Cisplatin or Pemetrexed + Carboplatin**		**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 Absolute difference (AD)[a]
Overall survival					
	303	18.07 [16.82; 21.45] 200 (66.0)	302	14.09 [12.45; 16.23] 219 (72.5)	0.74 [0.61; 0.89] 0.002 AD = 3.98 months
Subgroups by tumour histology					
Epithelioid	236	18.73 [17.05; 21.72] 157 (66.5)	235	16.23 [14.09; 19.15] 164 (69.8)	0.85 [0.68; 1.06] 0.151
Non-epithelioid	67	16.89 [11.83; 25.20] 43 (64.2)	67	8.80 [7.62; 11.76] 55 (82.1)	0.46 [0.31; 0.70] < 0.001 AD = 8.09 months
Total					Interaction: p = 0.003

Morbidity

Endpoint	Nivolumab + Ipilimumab		Pemetrexed + Cisplatin or Pemetrexed + Carboplatin		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 Absolute difference (AD)[a]
Symptomatology (LCSS-Meso ASBI) [b]					
	303	n.a. [22.18; n.c.] 64 (21.1)	302	12.22 [8.02; n.c.] 59 (19.5)	0.58 [0.39; 0.86] 0.006
Health status (EQ-5D VAS) [c]					
15 points	303	26.15 [22.64; n.c.] 81 (26.7)	302	16.69 [15.01; 21.75] 99 (32.8)	0.65 [0.49; 0.88] 0.005 AD = 9.46 months
7 points	303	18.89 [16.33; 25.82] 115 (38.0)	302	12.68 [9.95; 15.01] 134 (44.4)	0.67 [0.52; 0.86] 0.002 AD = 6.21 months
Subgroups by tumour histology					
Epithelioid	236	18.33 [15.47; 25.82] 91 (38.6)	235	13.73 [10.32; 18.33] 96 (40.9)	0.80 [0.60; 1.07] 0.134
Non-epithelioid	67	21.52 [9.69; n.c.] 24 (35.8)	67	8.02 [2.33; 10.97] 38 (56.7)	0.37 [0.22; 0.62] < 0.001 AD = 13.50 months
Total					Interaction: p = 0.005
10 points	303	20.14 [18.04; 26.09] 107 (35.3)	302	12.85 [10.32; 15.70] 130 (43.0)	0.63 [0.49; 0.82] < 0.001 AD = 7.29 months

Health-related quality of life

Not surveyed

Side effects [d]

Endpoint	Nivolumab + Ipilimumab		Pemetrexed + Cisplatin or Pemetrexed +Carboplatin		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 Absolute difference (AD)[a]
Total adverse events (presented additionally) [e]					
	300	0.26 [0.20; 0.39] 298 (99.3)	284	0.13 [0.10; 0.20] 276 (97.2)	-
Serious adverse events (SAE) [e]					
	300	9.33 [7.56; 12.52] 163 (54.3)	284	n.a. 77 (27.1)	1.74 [1.31; 2.32] < 0.001
Subgroups by tumour histology					
Epithelioid	233	9.23 [6.37; 12.45] 131 (56.2)	219	n.a. 53 (24.2)	1.98 [1.42; 2.76] < 0.001
Non-epithelioid	67	9.72 [4.37; n.c.] 32 (47.8)	65	n.a. [4.47; n.c.] 24 (36.9)	1.13 [0.65; 1.97] 0.665
Total					Interaction: p = 0.031
Severe adverse events (CTCAE grade ≥ 3) [e]					
	300	7.13 [5.26; 9.79] 178 (59.3)	284	6.77 [3.55; n.c.] 139 (48.9)	0.91 [0.72; 1.15] 0.418
Therapy discontinuations due to adverse events [e,f]					
	300	22.11 [17.58; n.c.] 92 (30.7)	284	n.a. 58 (20.4)	0.99 [0.69; 1.41] 0.935
Specific adverse events [g]					
Immune-mediated AEs (presented additionally)	300	1.48 [1.22; 1.87] 236 (78.7)	284	n.a. 107 (37.7)	-
Immune-mediated SAEs	300	n.a. 66 (22.0)	284	n.a. 7 (2.5)	7.54 [3.42; 16.61] < 0.001

Endpoint	Nivolumab + Ipilimumab		Pemetrexed + Cisplatin or Pemetrexed +Carboplatin		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 Absolute difference (AD)[a]
Immune-mediated severe AEs	300	n.a. [21.68; n.c.] 74 (24.7)	284	n.a. 11 (3.9)	4.62 [2.40; 8.87] < 0.001
Diarrhoea (PT, AEs)	300	21.49 [15.11; n.c.] 98 (32.7)	284	n.a. 34 (12.0)	2.22 [1.48; 3.33] < 0.001
Nausea (PT, AEs)	300	n.a. 76 (25.3)	284	n.a. [4.53; n.c.] 124 (43.7)	0.37 [0.28; 0.51] < 0.001
Renal and urinary disorders (SOC, SAEs)	300	n.a. 13 (4.3)	284	n.a. 3 (1.1)	3.68 [1.03; 13.19] 0.032
Subgroups by tumour histology					
Epithelioid	233	n.a. 12 (5.2)	219	n.a. 1 (0.5)	10.03 [1.28; 78.39] 0.007
Non-epithelioid	67	n.a. 1 (1.5)	65	n.a. 2 (3.1)	0.50 [0.05; 5.55] 0.567
Total					Interaction: p = 0.049
Endocrine disorders (SOC, SAEs)	300	n.a. 10 (3.3)	284	n.a. 1 (0.4)	7.76 [0.97; 62.03] 0.022
Asthenia (PT, severe AEs)	300	n.a. 4 (1.3)	284	n.a. 13 (4.6)	0.23 [0.07; 0.77] 0.010
Lipase elevated (PT, severe AEs)	300	n.a. 17 (5.7)	284	n.a. 1 (0.4)	11.72 [1.52; 90.15] 0.003
Anaemia (PT, severe AEs)	300	n.a. 10 (3.3)	284	n.a. 39 (13.7)	0.17 [0.08; 0.37] < 0.001
Neutropoenia (PT, severe AEs)	300	n.a. 4 (1.3)	284	n.a. 45 (15.8)	0.04 [0.01; 0.16] < 0.001
Thrombocytopenia (PT, severe AEs)	300	n.a. 4 (1.3)	284	n.a. 11 (3.9)	0.17 [0.04; 0.78] 0.010

Endpoint	Nivolumab + Ipilimumab		Pemetrexed + Cisplatin or Pemetrexed +Carboplatin		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 Absolute difference (AD)[a]
Hepatobiliary disorders (SOC, severe AEs)	300	n.a. 20 (6.7)	284	n.a. 0 (0)	n.a. < 0.001
Nervous system disorders (SOC, severe AEs)	300	n.a. 15 (5.0)	284	n.a. 3 (1.1)	3.57 [0.99; 12.79] 0.037
Skin and subcutaneous tissue disorders (SOC, severe AEs)	300	n.a. 14 (4.7)	284	n.a. 1 (0.4)	8.67 [1.10; 68.44] 0.014
Musculoskeletal and connective tissue disorders (SOC, severe AEs)	300	n.a. 13 (4.3)	284	n.a. 2 (0.7)	4.42 [0.96; 20.45] 0.037

[a] Indication of absolute difference (AD) only in case of statistically significant difference; own calculation
[b] Calculated as the mean of the 5 symptom scales of the LCSS-Meso (loss of appetite, fatigue, cough, dyspnoea, and pain). Time to permanent deterioration; defined as a decrease of ≥ 15 points compared to the start of study
[c] Time to permanent deterioration; defined as a decrease in score by the response threshold with no improvement below the response threshold in any of the following surveys
[d] When interpreting the results on side effects, it should be noted that the significantly shorter planned treatment duration and the associated discontinuation of observation in the comparator arm mean that the hazard ratio only represents approximately the first 8 months after randomisation.
[e] Without detection of progression of the underlying disease
[f] Operationalised as discontinuation of at least one active ingredient component
[g] Selection according to the methodology of the IQWiG; selection using events occurred in the study, based on frequency and differences between treatment arms, and taking into account patient relevance

Abbreviations used:
AD = absolute difference; ASBI = Average Symptom Burden Index; CTCAE = Common Terminology Criteria for Adverse Events; HR = hazard ratio; CI = confidence interval; 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; SOC = system organ class; VAS = visual analogue scale; vs = versus

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

a) Adult patients with unresectable malignant pleural mesothelioma and epithelioid tumour histology; first-line therapy

and

b) Adult patients with unresectable malignant pleural mesothelioma and non-epithelioid tumour histology; first-line therapy

approx. 160 patients in total

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: 10 November 2021):

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

Treatment with nivolumab in combination with ipilimumab may only be initiated and monitored by specialists in internal medicine, haematology and oncology who are experienced in the treatment of adult patients with lung cancer or malignant pleural mesothelioma, as well as specialists in internal medicine and pulmonology or specialists in pulmonary medicine and doctors from other specialist groups 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 doctor must discuss the risks of therapy with nivolumab with the patient. The patient card should be made available to the patient.

4. Treatment costs

Annual treatment costs:

a) Adult patients with unresectable malignant pleural mesothelioma and epithelioid tumour histology; first-line therapy

Designation of the therapy	Annual treatment costs/ patient
Medicinal product to be assessed:	
Nivolumab	€ 79,855.56
+ Ipilimumab	€ 63,175.22
Total	€ 143,030.78
Appropriate comparator therapy:	
Therapy according to doctor's instructions: - cisplatin in combination with pemetrexed[2]	
Cisplatin	€ 2,007.44

[2] Costs are presented only for cisplatin in combination with pemetrexed. In addition, carboplatin in combination with pemetrexed and cisplatin in combination with pemetrexed and bevacizumab are also suitable comparators for the present benefit assessment in the context of therapy according to doctor's instructions. However, carboplatin and bevacizumab are not approved in the present therapeutic indication and therefore no costs are represented for these regimens.

Designation of the therapy	Annual treatment costs/ patient
Pemetrexed	€ 9,213.30
Total	€ 11,220.74
Additionally required SHI services	€ 455.34 - € 595.97

Costs after deduction of statutory rebates (LAUER-TAXE® as last revised: 1 December 2021)

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	Preparation for parenteral solutions with monoclonal antibodies	€ 71	1	17.4	€ 1,235.40
Ipilimumab	Preparation for parenteral solutions with monoclonal antibodies	€ 71	1	8.7	€ 617.70
Appropriate comparator therapy					
Cisplatin	Surcharge for production of a parenteral preparation containing cytostatic agents	€ 81	1	17.4	€ 1,409.40
Pemetrexed	Surcharge for production of a parenteral preparation containing cytostatic agents	€ 81	1	17.4	€ 1,409.40

b) <u>Adult patients with unresectable malignant pleural mesothelioma and non-epithelioid tumour histology; first-line therapy</u>

Designation of the therapy	Annual treatment costs/ patient
Medicinal product to be assessed:	
Nivolumab	€ 79,855.56
+ Ipilimumab	€ 63,175.22
Total	€ 143,030.78
Appropriate comparator therapy:	
Therapy according to doctor's instructions: - Cisplatin in combination with pemetrexed[2]	
Cisplatin	€ 2,007.44
Pemetrexed	€ 9,213.30
Total	€ 11,220.74

Designation of the therapy	Annual treatment costs/ patient
Additionally required SHI services	€ 455.34 - € 595.97

Costs after deduction of statutory rebates (LAUER-TAXE® as last revised: 1 December 2021)

Other SHI services:

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Medicinal product to be assessed:					
Nivolumab	Preparation for parenteral solutions with monoclonal antibodies	€ 71	1	17.4	€ 1,235.40
Ipilimumab	Preparation for parenteral solutions with monoclonal antibodies	€ 71	1	8.7	€ 617.70
Appropriate comparator therapy					
Cisplatin	Surcharge for production of a parenteral preparation containing cytostatic agents	€ 81	1	17.4	€ 1,409.40
Pemetrexed	Surcharge for production of a parenteral preparation containing cytostatic agents	€ 81	1	17.4	€ 1,409.40

II. The resolution will enter into force on the day of its publication on the website of the G-BA on 16 December 2021.

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

Berlin, 16 December 2021

Federal Joint Committee (G-BA)
in accordance with Section 91 SGB V
The Chair

Prof. Hecken