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 (Reassessment after the deadline (melanoma, adjuvant treatment)

of 16 September 2021

At its session on 16 September 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 TT. Month YYYY (Federal Gazette, BAnz AT DD.MM.YYYY BX), as follows:

I. Annex XII is amended as follows:

1. **The information on nivolumab in the version of the resolution of 21 February 2019 (BAnz AT 29.04.2019 B2) is repealed.**
2. **In Annex XII, the following information shall be added to the information on the benefit assessment of nivolumab in the version of the resolution of 1 July 2021 for the therapeutic indication "[...] for the treatment of adult patients with unresectable advanced, recurrent or metastatic oesophageal squamous cell carcinoma after prior fluoropyrimidine- and platinum-based combination chemotherapy" after number 4:**

nivolumab

Resolution of: 16 September 2021
Entry into force on: 16 September 2021
BAnz AT DD. MM YYYY Bx

Therapeutic indication (according to the marketing authorisation of 30 July 2018):

OPDIVO as monotherapy is indicated for the adjuvant treatment of adults with melanoma with involvement of lymph nodes or metastatic disease who have undergone complete resection (see section 5.1)

Therapeutic indication of the resolution (resolution of 16 September 2021):

see therapeutic indication according to marketing authorisation

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

Adjuvant treatment of adults with melanoma with involvement of lymph nodes or metastatic disease who have undergone complete resection

Appropriate comparator therapy:

- pembrolizumab (only for patients with stage III tumours after complete resection)

or

- dabrafenib in combination with trametinib (only for patients with BRAF V600 mutation-positive melanoma in tumour stage III after complete resection)

or

- monitoring wait-and-see approach

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

Hint of a considerable additional benefit

Study results according to endpoints:[1]

Summary of results for relevant clinical endpoints

Endpoint category	Direction of effect/ risk of bias	Summary
Mortality	n.a.	There are no usable data for the benefit assessment
Morbidity	↑	Advantage in relapses and relapse-free survival
Health-related quality of life	n.a.	There are no usable data for the benefit assessment
Side effects	↓	Disadvantage in case of therapy discontinuation due to AE
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		

<u>Adjusted indirect comparison</u>

Nivolumab vs monitoring wait-and-see approach via the bridge comparator ipilimumab

CA209-238 study: Nivolumab vs ipilimumab; double-blind RCT

CA184-029 study: Ipilimumab vs placebo[2]; double-blind RCT

[1] Data from the dossier assessment of the IQWiG (A21-39) and from the addendum (A21-39), unless otherwise indicated.

[2] The follow-up strategy implemented in study CA184-029 is considered a sufficient approximation to the operationalisation of the monitoring wait-and-see approach.

Mortality

Endpoint	Nivolumab or placebo		Ipilimumab (bridge comparator)		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					
Nivolumab vs ipilimumab (data cut-off from 29 January 2020)					
	368	n.a. 85 (23.1)	367	n.a. 89 (24.3)	0.93 [0.69; 1.25] 0.634
Placebo vs ipilimumab (data cut-off from 13 May 2016)					
	378	59.14 [48.39; n. a.] 189 (50.0)	377	n. a. [79.41; n. a.] 144 (38.2)	1.39 [1.12; 1.72] 0.003
Adjusted indirect comparison via bridge comparators[b]: Nivolumab vs placebo					-[c]

Morbidity

Endpoint	Nivolumab or placebo		Ipilimumab (bridge comparator)		Intervention vs control
	N	Patients with event n (%)	N	Patients with event n (%)	Relative risk [95% CI] p-value Absolute difference (AD)[a]
Relapses					
Nivolumab vs ipilimumab (data cut-off from 29 January 2020)					
Relapse rate	368	166 (45.1)	367	205 (55.9)	0.81 [0.70; 0.93] n.d.
Local relapse	368	32 (8.7)	367	42 (11.4)	-
Regional relapse	368	33 (9.0)	367	39 (10.6)	-

(continuation)

Endpoint	Nivolumab or placebo	Ipilimumab (bridge comparator)	Intervention vs

					control
	N	Patients with event n (%)	N	Patients with event n (%)	Relative risk [95% CI] p-value Absolute difference (AD)[a]
Remote metastasis	368	97 (26.4)	367	111 (30.2)	-
Death	368	3 (0.8)	367	11 (3.0)	-
Placebo vs ipilimumab (data cut-off from 13 May 2016)					
Relapse rate	378	274 (72.5)	377	227 (60.2)	1.20 [1.09; 1.33] n.d.
Local relapse	378	10 (2.6)	377	13 (3.4)	-
In-transit metastases	378	28 (7.4)	377	23 (6.1)	-
Regional relapse	378	57 (15.1)	377	39 (10.3)	-
Remote metastasis	378	170 (45.0)	377	136 (36.1)	-
Death	378	9 (2.4)	377	16 (4.2)	-
Adjusted indirect comparison via bridge comparators[b]: Nivolumab vs placebo					0.67 [0.56; 0.80] < 0.001
	Nivolumab or placebo		**Ipilimumab (bridge comparator)**		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]
Nivolumab vs ipilimumab (data cut-off from 29 January 2020)					
Relapse-free survival	368	52.37 [43.96; n. a.]	367	26.87 [17.08; 38.01]	0.71 [0.58; 0.87] < 0.001

(continuation)

Endpoint	Nivolumab or placebo		Ipilimumab (bridge comparator)		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]
Placebo vs ipilimumab (data cut-off from 13 May 2016)					
Relapse-free survival	378	11.63 [10.32; 16.20]	377	21.19 [16.46; 28.12]	1.33 [1.12; 1.59] 0.001
Adjusted indirect comparison via bridge comparators[b]: Nivolumab vs placebo					0.53 [0.41; 0.70] < 0.001
Health status (EQ-5D VAS)	No usable data available				
Symptomatology (EORTC QLQ-C30)	No usable data available				

Health-related quality of life

Functional scales (EORTC QLQ-C30)	No usable data available

Side effects

Endpoint	Nivolumab or placebo		Ipilimumab (bridge comparator)		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]
Total adverse events (AE, presented additionally)					
Nivolumab vs ipilimumab (data cut-off from 29 January 2020)					
	367	0.49 [0.43; 0.56] 360 (98.1)	367	0.33 [0.26; 0.39] 362 (98.6)	-
Placebo vs ipilimumab (data cut-off from 13 May 2016)					
	377	0.82 [0.72; 1.05] 334 (88.6)	373	0.26 [0.26; 0.36] 366 (98.1)	-
Adjusted indirect comparison via bridge comparators[b]: Nivolumab vs placebo					-

Endpoint	Nivolumab or placebo		Ipilimumab (bridge comparator)		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]
Serious adverse events (SAE)					
Nivolumab vs ipilimumab (data cut-off from 29 January 2020)					
	367	n.a. 75 (20.4)	367	n. a. [6.44; n. a.] 172 (46.9)	0.31 [0.23; 0.40] < 0.001
Placebo vs ipilimumab (data cut-off from 13 May 2016)					
	377	n.a. 80 (21.2)	373	9.69 [4.21; 21.22] 200 (53.6)	0.28 [0.22; 0.36] < 0.001
Adjusted indirect comparison via bridge comparators[b]: Nivolumab vs placebo					1.10 [0.75; 1.60] 0.633
Severe adverse events (CTCAE grade ≥ 3)					
Nivolumab vs ipilimumab (data cut-off from 29 January 2020)					
	367	n.a. 111 (30.2)	367	3.25 [2.76; 4.80] 228 (62.1)	0.30 [0.24; 0.38] < 0.001
Placebo vs ipilimumab (data cut-off from 13 May 2016)					
	377	n. a. [38.60; n. a.] 96 (25.5)	373	8.08 [3.29; 14.52] 204 (54.7)	0.33 [0.26; 0.42] < 0.001
Adjusted indirect compare[b]: Nivolumab vs placebo					0.93 [0.66; 1.29] 0.646
Discontinuation because of AEs					
Nivolumab vs ipilimumab (data cut-off from 29 January 2020)					
	367	n.a. 43 (11.7)	367	n. a. [7.85; n. a.] 173 (47.1)	0.18 [0.13; 0.25] < 0.001
Placebo vs ipilimumab (data cut-off from 13 May 2016)					

Endpoint	Nivolumab or placebo		Ipilimumab (bridge comparator)		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]
	377	n.a. 22 (5.8)	373	17.97 [8.31; 28.78] 184 (49.3)	0.09 [0.05; 0.13] < 0.001
Adjusted indirect comparison via bridge comparators[b]: Nivolumab vs placebo					2.07 [1.19; 3.62] 0.010
Immune-mediated AEs	No usable data available				

[a] Absolute difference (AD) is given only in the case of a statistically significant difference; own calculation
[b] Indirect comparison according to Bucher
[c] There are no usable results for the indirect comparison
[d] No presentation of effect estimates due to insufficient certainty of results

Abbreviations used:
AD = Absolute difference; CTCAE = Common Terminology Criteria for Adverse Events; CI = confidence interval; n.d. = no data, N = number of patients evaluated; n = number of patients with (at least one) event; n. a. = not achieved; vs = versus

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

Adjuvant treatment of adults with melanoma with involvement of lymph nodes or metastatic disease who have undergone complete resection

approx. 3450 to 4340 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: 28 May 2021):
https://www.ema.europa.eu/en/documents/product-information/opdivo-epar-product-information_en.pdf

The initiation and monitoring of treatment with nivolumab must be carried out by a specialist experienced in the field of oncology and in the therapy of patients with melanoma (specialist in internal medicine, haematology and oncology, a specialist in skin and venereal diseases as well as 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 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:

Adjuvant treatment of adults with melanoma with involvement of lymph nodes or metastatic disease who have undergone complete resection

Designation of the therapy	Annual treatment costs/ patient
Medicinal product to be assessed:	
nivolumab	€ 79,308.84
Appropriate comparator therapy:	
Pembrolizumab	€ 103,144.32
Dabrafenib + trametinib	
Dabrafenib	€ 70,930.94
Trametinib	€ 53,114.44
Total	€ 124,045.37
Monitoring wait-and-see approach	incalculable

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

Other SHI services:

Designation of 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	13 - 26	€ 923 - € 1,846
Pembrolizumab	Surcharge for the preparation of a parenteral solution containing monoclonal antibodies	€ 71	1	9 - 18	€ 639 - € 1,278

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

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

Berlin, 16 September 2021

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

Prof. Hecken