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: oesophageal or gastro-oesophageal junction cancer, pretreated patients, adjuvant treatment)

of 17 February 2022

At its session on 17 February 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 20 January 2022:

Nivolumab

Resolution of: 17 February 2022
Entry into force on: 17 February 2022
Federal Gazette, BAnz AT DD. MM YYYY Bx

New therapeutic indication (according to the marketing authorisation of 28 July 2021):

Opdivo as monotherapy is indicated for the adjuvant treatment of adult patients with oesophageal or gastro-oesophageal junction cancer who have residual pathologic disease following prior neoadjuvant chemoradiotherapy.

Therapeutic indication of the resolution (resolution of 17 February 2022):

See new therapeutic indication according to marketing authorisation.

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

Adults with oesophageal or gastro-oesophageal junction cancer and residual pathologic disease following prior neoadjuvant chemoradiotherapy: 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:

Indication of a non-quantifiable 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	∅	No data available.
Morbidity	↑↑	Advantage in recurrences.
Health-related quality of life	↔	No relevant difference for the benefit assessment.
Side effects	↓↓	Disadvantage in discontinuation due to AEs and in detail disadvantages with 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		

CA209-577 study: Nivolumab vs placebo ("monitoring wait-and-see approach")
Study design: RCT, randomised, double-blind

Mortality

Endpoint	Nivolumab		Placebo ("monitoring wait-and-see approach")		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]
Mortality					
Overall survival	No data available.				

[1] Data from the dossier assessment of the Institute for Quality and Efficiency in Health Care (IQWiG) (A21-108) unless otherwise indicated.

Morbidity

Recurrences					
Recurrence rate [b]	532	– *268 (50.4)*	262	– *171 (65.3)*	RR: 0.77 [0.69; 0.87] [c] < 0.001[d]
Local recurrence	532	– *36 (6.8)*	262	– *23 (8.8)*	–
Regional recurrence	532	– *34 (6.4)*	262	– *25 (9.5)*	–
Remote metastases	532	– *169 (31.8)*	262	– *113 (43.1)*	–
Death without recurrence	532	– *29 (5.5)*	262	– *10 (3.8)*	–
Disease-free survival [b]	532	22.41 [16.95; 33.64] *268 (50.4)*	262	10.35 [8.31; 13.93] *171 (65.3)*	0.67 [0.55; 0.81] < 0.001 AD= 12.06 months
Health status					
EQ-5D VAS (time to permanent deterioration)					
≥ 7 points	532	39.10 [34.46; n.c.] 135 (25.4)	262	n.a. [32.62; n.c.] 62 (23.7)	1.03 [0.76; 1.40] 0.838
≥ 10 points	532	39.10 [34.46; n.c.] 122 (22.9)	262	n.a. [32.62; n.c.] 56 (21.4)	1.05 [0.76; 1.45] 0.762
≥ 15 points	532	39.10 [36.47; n.c.] *85 (16.0)*	262	n.a. [35.61; n.c.] 37 (14.1)	1.11 [0.75; 1.64] 0.607[e]

Health-related quality of life

Time to first deterioration					
FACT-E total score 15 % of the scale range	532	n.a. [n.c.; n.c.] *38 (7.1)*	262	n.a. [n.c.; n.c.] *20 (7.6)*	0.98 [0.57; 1.68]; 0.933 [e]
EWB (presented additionally)	532	16, 95 [16.13; n.c.] *84 (15.8)*	262	n.a. [15.74; n.c.] *36 (13.7)*	1.22 [0.82; 1.81]

SWB (presented additionally)	532	n.a. [n.c.; n.c.] *64 (12.0)*	262	n.a. [15.70; n.c.] *32 (12.2)*	0.98 [0.64; 1.52]
PWB (presented additionally)	532	n.a. [15.90; n.c.] *80 (15.0)*	262	n.a. [15.74; n.c.] *39 (14.9)*	1.07 [0.73; 1.57]
FWB (presented additionally)	532	16.43 [16.13; n.c.] *81 (15.2)*	262	n.a. [16.13; n.c.] *36 (13.7)*	1.09 [0.73; 1.62]
ECS (presented additionally)	no data [f]				

Side effects

Endpoint	**Nivolumab**		**Placebo ("monitoring wait-and-see approach")**		Intervention vs control
	N	Patients with event n (%)	N	Patients with event n (%)	RR [95 % CI] p value [g]
Total adverse events (presented additionally)					
	532	511 (96.1)	260	241 (92.7)	–
Serious adverse events (SAE)					
	532	173 (32.5)	260	81 (31.2)	0.99 [0.82; 1.21] 0.961
Severe adverse events (CTCAE grade 3 or 4)					
	532	214 (40.2)	260	94 (36.2)	1.04 [0.87; 1.23] 0.736
Therapy discontinuation due to adverse events					
	532	73 (13.7)	260	15 (5.8)	2.38 [1.39; 4.06] < 0.001

Specific adverse events					
Immune-mediated AEs (presented additionally)	532	375 (70.5)	260	142 (54.6)	–
Immune-mediated SAEs	532	34 (6.4)	260	8 (3.1)	2.08 [0.98; 4.42] 0.052
Immune-mediated severe AEs	532	48 (9.0)	260	14 (5.4)	1.68 [0.94; 2.98] 0.078
Infections and infestations (SOC, severe AEs)	532	40 (7.5)	260	8 (3.1)	2.44 [1.16; 5.14] 0.014
Blood and lymphatic system disorders (SOC, severe AEs)	532	17 (3.2)	260	2 (0.8)	4.15 [0.97; 17.85] 0.037

a Indication of absolute difference (AD) only in case of statistically significant difference; own calculation
b The data of the 2nd data cut-off (18.02.2021) are used
c Based on Cochran-Mantel-Haenszel method stratified by PD-L1 status (≥ 1 %, < 1 % or undetermined/not evaluable), pathological lymph node status (positive [≥ ypN1], negative [ypN0]) and histology (squamous cell carcinoma, adenocarcinoma) according to IRT
d. IQWiG calculation (unconditional exact test [CSZ method])
e p-value from Cox model stratified by PD-L1 status (≥ 1 %, < 1 % or indeterminate/not evaluable), pathological lymph node status (positive (≥ ypN1), negative (ypN0)) and histology (squamous cell carcinoma, adenocarcinoma) with baseline value as covariate
f The pharmaceutical company does not provide any evaluations for this subscale concerning the 2nd follow-up visit
g IQWiG calculation of RR, CI (asymptotic) and p value (unconditional exact test, CSZ method). 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; ECS = Esophageal Cancer Subscale; EWB = Emotional Well-Being; FACT-E = Functional Assessment of Cancer Therapy - Esophageal; FWB = Functional Well-Being; HR = Hazard Ratio; IRT = Interactive Response Technology; n.d. = no data available; 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; RR = relative risk; PWB = Physical Well-Being; SOC = System Organ Class; SWB = Social Well-Being; SAE = serious adverse event; AE = adverse event; vs = versus

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

approx. 590 - 860 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 February 2022):

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

Treatment with nivolumab should only be initiated and monitored by specialists in internal medicine, haematology, oncology and gastroenterology, and specialists participating in the Oncology Agreement experienced in the treatment of adults with oesophageal carcinoma.

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

Annual treatment costs:

Designation of the therapy	Annual treatment costs[2]/ patient
Medicinal product to be assessed:	
Nivolumab	
Initial treatment (week 1-16)	€ 23,361.76
Follow-up treatment (from week 17)	€ 52,563.96
Initial treatment + follow-up treatment total	€ 75,925.72
Appropriate comparator therapy:	
Monitoring wait-and-see approach	incalculable

Costs after deduction of statutory rebates (LAUER-TAXE®) as last revised: 1 March 2022)

Costs for additionally required SHI services: not applicable

[2] In order to maintain consistency regarding old procedures with nivolumab, a distinction was made between initial and follow-up treatment when calculating the annual treatment costs.

Other SHI services:

Designation of the therapy	Type of service	Costs/ unit	Number/ cycle	Number/ patient/ year	Costs/ patient/ year
Nivolumab (Initial treatment in a 14-day cycle)	Surcharge for the preparation of a parenteral solution containing monoclonal antibodies	€ 71	1	8.0	€ 568.00
Nivolumab (Initial treatment in a 28-day cycle)	Surcharge for the preparation of a parenteral solution containing monoclonal antibodies	€ 71	1	4.0	€ 284.00
Nivolumab (Follow-up treatment in a 28-day cycle)	Surcharge for the preparation of a parenteral solution containing monoclonal antibodies	€ 71	1	9.0	€ 639.00
Total					€ 923.00 - € 1,207

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 17 February 2022.**
2. **The period of validity of the resolution is limited to 1 October 2024.**

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

Berlin, 17 February 2022

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

Prof. Hecken