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

of 18 December 2025

At their session on 18 December 2025, 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 information on the active ingredient Nivolumab in the version of the resolution of 17 February 2022 (Federal Gazette, BAnz AT 21.03.2022 B3) shall be replaced by the following information:

Nivolumab

Resolution of: 18 December 2025
Entry into force on: 18 December 2025
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 18 December 2025):

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:

Hint for a minor additional benefit

Study results according to endpoints:[1]

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

[1] Data from the dossier assessment of the IQWiG (A25-88) and from the addendum (A25-142), unless otherwise indicated.

Summary of results for relevant clinical endpoints

Endpoint category	Direction of effect/ risk of bias	Summary
Mortality	↔	No relevant difference for the benefit assessment.
Morbidity	↑↑	Advantage in recurrences.
Health-related quality of life	↔	No relevant difference for the benefit assessment.
Side effects	↓	Disadvantage in the endpoint of discontinuation due to AEs. In detail, disadvantages 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

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

Mortality

Endpoint	Nivolumab		Monitoring wait-and-see approach		Intervention versus 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					
	532	51.71 [41.03; 61.63] *299 (56.2)*	262	35.25 [30.72; 48.76] *162 (61.8)*	0.85 [0.70; 1.03]; 0.106[b]
Effect modification by the characteristic "Localisation of the disease"					
Oesophageal cancers	314	49.5 [36.6; 65.4] *177 (56.4)*	153	31.4 [24.4; 36.6] *105 (68.6)*	0.69 [0.55; 0.88]; 0.003
Gastro-oesophageal junction carcinomas	218	54.9 [39.2; 78.6] *122 (56.0)*	109	64.2 [35.2; n.c.] *57 (52.3)*	1.14 [0.83; 1.56]; 0.418
					Interaction 0.015

Effect modification by the characteristic "Pathological tumour status"[c]					
ypT0	29	78.8 (34.0; n.r.) *13 (44.8)*	16	20.1 (8.3; 47.9) *13 (81.3)*	0.39 (0.18; 0.84); 0.0132
ypT1/ypT2	205	78.6 (50.7; n.r.) *99 (48.3)*	106	34.8 (26.2; 56.7) *65 (61.3)*	0.68 (0.50; 0.94); 0.0170
ypT3/ypT4	296	39.1 (31.1; 50.0) *186 (62.8)*	140	42.4 (31.7; 62.9) *84 (60.0)*	1.07 (0.83; 1.39); 0.5875
					Interaction 0.0065

Morbidity

Recurrences					
Recurrence rate	532	– *334 (62.8)*[d]	*262*	– *185 (70.6)*[d]	Relative risk: 0.89 [0.81; 0.98][e]; 0.030
Local recurrence	532	– *39 (7.3)*	*262*	– *15 (5.7)*	–
Regional recurrence	532	– *41 (7.7)*[d]	*262*	– *27 (10.3)*	–
Distant metastases	532	– *205 (38.5)*[d]	*262*	– *127 (48.5)*[d]	–
Death without recurrence	532	– *49 (9.2)*[d]	*262*	– *16 (6.1)*[d]	–
Disease-free survival	532	21.3 [16.62; 29.50] *334 (62.8)*[d]	262	10.8 [8.31; 14.32] *185 (70.6)*[d]	0.76 [0.63; 0.91]; 0.003[b] AD = 10.5 months
Health status					
EQ-5D VAS (time to deterioration[f])					
	497	n.r. [50.92; n.c.] *106 (21.3)*	247	n.r. *40 (16.2)*	1.30 [0.90; 1.88]; 0.160[b]
Effect modification by the "Sex" characteristic					
Male	418	n.r. [50.63; n.c.] *97 (23.2)*	212	n.r. *29 (13.7)*	1.77 [1.17; 2.68]; 0.008
Female	79	n.r. [48.66; n.c.] *9 (11.4)*	35	n.r. [27.01; n.c.] *11 (31.4)*	0.31 [0.13; 0.75]; 0.014
					Interaction < 0.001

Health-related quality of life

FACT-E (time to deterioration[f])					
Total score	484	n.r. 40 (8.3)	248	n.r. 20 (8.1)	1.02 [0.60; 1.75][b]; 0.956[g]
Physical well-being	495	n.r. 80 (16.2)	250	n.r. 38 (15.2)	1.14 [0.77; 1.68][b]
Social/ family well-being	495	18.00 [16.85; n.c.] 65 (13.1)	250	n.r. [15.90; n.c.] 31 (12.4)	1.03 [0.67; 1.60][b]
Emotional well-being	492	n.r. [16.16; n.c.] 85 (17.3)	249	n.r. 37 (14.9)	1.20 [0.81; 1.77][b]
Functional well-being	493	16.46 [16.16; n.c.] 87 (17.6)	249	n.r. [16.13; n.c.] 35 (14.1)	1.22 [0.82; 1.82][b]
Oesophageal cancer-specific subscale	494	n.r. 59 (11.9)	249	n.r. [57.10; n.c.] 32 (12.9)	1.01 [0.65; 1.57][b]

Side effects

Endpoint	**Nivolumab**		**Monitoring wait-and-see approach**		Intervention versus control
	N	Patients with event n (%)	N	Patients with event n (%)	Relative risk [95% CI]; p value
Total adverse events (presented additionally)					
	532	515 (96.8)	260	241 (92.7)	
Serious adverse events (SAE)					
	532	175 (32.9)	260	82 (31.5)	1.04 [0.84; 1.30]; 0.736
Severe adverse events (CTCAE grade 3 or 4)					
	532	220 (41.4)	260	95 (36.5)	1.13 [0.94; 1.37]; 0.196
Therapy discontinuation due to adverse events					
	532	74 (13.9)	260	16 (6.2)	2.26 [1.34; 3.81]; 0.001
Specific adverse events					
Immune-mediated AEs (presented additionally)	532	379 (71.2)	260	144 (55.4)	–
Immune-mediated SAEs	532	36 (6.8)	260	8 (3.1)	2.20 [1.04; 4.66]; 0.034

Immune-mediated severe AEs	532	48 (9.0)	260	14 (5.4)	1.68 [0.94; 2.98]; 0.090
Skin and subcutaneous tissue disorders (SOC, AEs)	532	209 (39.3)	260	62 (23.8)	1.65 [1.29; 2.10]; < 0.001
Infections and infestations (SOC, severe AEs)	532	45 (8.5)	260	10 (3.8)	2.20 [1.13; 4.30]; 0.017
Blood and lymphatic system disorders (SOC, severe AEs)	532	20 (3.8)	260	2 (0.8)	4.89 [1.15; 20.75][h]; 0.017

[a] Indication of absolute difference (AD) only in case of statistically significant difference; own calculation
[b] HR and CI from stratified Cox model, p value from log-rank test, 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
[c] Information from the dossier module 4 of the pharmaceutical company
[d] Discrepancy between information in the pharmaceutical company's dossier. The deviations have no impact on the effect estimate of disease-free survival. Information in the study report: Recurrence rate 329 (61.8%) vs 183 (69.8%), regional recurrence rate 39 vs 27, distant metastases 204 vs 126, death without recurrence 47 vs 15
[e] 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
[f] The operationalisation represents a combination of one-off deterioration and confirmed deterioration
[g] 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

Abbreviations used:
AD = absolute difference; CTCAE = Common Terminology Criteria for Adverse Events; FACT-E = Functional Assessment of Cancer Therapy – Esophageal; IRT = Interactive Response Technology; 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.r. = not reached; ypN = pathological lymph node status after neoadjuvant treatment

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

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

Approx. 580 to 910 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: 01 September 2025):

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 and oncology as well as specialists in gastroenterology and other specialists from other specialist groups participating in the Oncology Agreement, all of whom are experienced in the treatment of patients with oesophageal cancer or gastro-oesophageal junction cancer.

In accordance with the EMA requirements regarding additional risk minimisation measures, the pharmaceutical company must provide training material that contains information for medical professionals and patients (including 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 oesophageal or gastro-oesophageal junction cancer and residual pathologic disease following prior neoadjuvant chemoradiotherapy; adjuvant treatment

Designation of the therapy	Annual treatment costs[2]/ patient
Medicinal product to be assessed:	
Nivolumab	
Initial treatment (week 1-16)	€ 23,252.80
Follow-up treatment (from week 17)	€ 52,318.80
Initial treatment + follow-up treatment in total	€ 75,571.60
Appropriate comparator therapy:	
Monitoring wait-and-see approach	Not calculable

Costs after deduction of statutory rebates (LAUER-TAXE® as last revised: 15 October 2025)

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	€ 100	1	8.0	€ 800
Nivolumab (Initial treatment in a 28-day cycle)	Surcharge for the preparation of a parenteral solution containing monoclonal antibodies	€ 100	1	4.0	€ 400
Nivolumab (Follow-up treatment in a 28-day cycle)	Surcharge for the preparation of a parenteral solution containing monoclonal antibodies	€ 100	1	9.0	€ 900
Total					€ 1,300 – € 1,700

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 oesophageal or gastro-oesophageal junction cancer and residual pathologic disease following prior neoadjuvant chemoradiotherapy; adjuvant treatment

- No designation of medicinal products with new active ingredients that can be used in combination therapy pursuant to Section 35a, paragraph 3, sentence 4 SGB V, as the active ingredient to be assessed is an active ingredient authorised in monotherapy.

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.

II. **The resolution will enter into force on the day of its publication on the website of the G-BA on 18 December 2025.**

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

Berlin, 18 December 2025

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

Prof. Hecken