Gemeinsamer Bundesausschuss

Justification

to the Resolution of the Federal Joint Committee (G-BA) 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

Contents

1. Legal basis

According to Section 35a paragraph 1 German Social Code, Book Five (SGB V), the Federal Joint Committee (G-BA) assess the benefit of all reimbursable medicinal products with new active ingredients. This includes in particular the assessment of the additional benefit and its therapeutic significance. The benefit assessment is carried out on the basis of evidence provided by the pharmaceutical company, which must be submitted to the G-BA electronically, including all clinical studies the pharmaceutical company have conducted or commissioned, at the latest at the time of the first placing on the market as well as the marketing authorisation of new therapeutic indications of the medicinal product, and which must contain the following information in particular:

1. approved therapeutic indications,
2. medical benefit,
3. additional medical benefit in relation to the appropriate comparator therapy,
4. number of patients and patient groups for whom there is a therapeutically significant additional benefit,
5. treatment costs for the statutory health insurance funds,
6. requirement for a quality-assured application.

The G-BA may commission the Institute for Quality and Efficiency in Health Care (IQWiG) to carry out the benefit assessment. According to Section 35a, paragraph 2 SGB V, the assessment must be completed within three months of the relevant date for submission of the evidence and published on the internet.

According to Section 35a paragraph 3 SGB V, the G-BA pass a resolution on the benefit assessment within three months of its publication. The resolution is to be published on the internet and is part of the Pharmaceuticals Directive.

2. Key points of the resolution

The pharmaceutical company submitted a dossier for the early benefit assessment for the active ingredient nivolumab (Opdivo) to be assessed for the first time on 24 August 2021. For the resolution of 17 February 2022 made by the G-BA in this procedure, a limitation up to 1 October 2024 was pronounced. At the pharmaceutical company's request, this limitation was extended until 1 July 2025 by the resolution of the G-BA of 2 May 2024.

In accordance with Section 4, paragraph 3, No. 5 Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV) in conjunction with Chapter 5 Section 8, paragraph 1, number 5 VerfO, the procedure for the benefit assessment of the medicinal product Opdivo recommences when the deadline has expired.

The pharmaceutical company submitted the final dossier to the G-BA in accordance with Section 4, paragraph 3, number 5 of the Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV) in conjunction with Chapter 5 Section 8, paragraph 1, number 5 VerfO on 30 June 2025. The G-BA commissioned the IQWiG to carry out the assessment of

the dossier. The benefit assessment was published on 1 October 2025 on the G-BA website (www.g-ba.de), thus initiating the written statement procedure. In addition, an oral hearing was held.

The G-BA came to a resolution on whether an additional benefit of nivolumab compared with the appropriate comparator therapy could be determined on the basis of the dossier of the pharmaceutical company, the dossier assessment prepared by the IQWiG, the statements submitted in the written statement and oral hearing procedure, and the addendum to the benefit assessment prepared by the IQWiG. In order to determine the extent of the additional benefit, the G-BA have evaluated the data justifying the finding of an additional benefit on the basis of their therapeutic relevance (qualitative), in accordance with the criteria laid down in Chapter 5 Section 5, paragraph 7 VerfO. The methodology proposed by the IQWiG in accordance with the General Methods [1] was not used in the benefit assessment of nivolumab.

In the light of the above, and taking into account the statements received and the oral hearing, the G-BA have made the following assessment:

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

2.1.1 Approved therapeutic indication of Nivolumab (Opdivo) in accordance with the product information

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 the approved therapeutic indication

2.1.2 Appropriate comparator therapy

The appropriate comparator therapy was determined as follows:

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

Appropriate comparator therapy for nivolumab as monotherapy:

- Monitoring wait-and-see approach

Criteria according to Chapter 5 Section 6 of the Rules of Procedure of the G-BA and Section 6 paragraph 2 Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV):

The appropriate comparator therapy must be an appropriate therapy in the therapeutic indication in accordance with the generally recognised state of medical knowledge (Section 12 SGB V), preferably a therapy for which endpoint studies are available and which has proven its worth in practical application unless contradicted by the guidelines under Section 92, paragraph 1 SGB V or the principle of economic efficiency.

In determining the appropriate comparator therapy, the following criteria, in particular, must be taken into account as specified in Chapter 5 Section 6, paragraph 3 VerfO:

[1] General Methods, version 7.0 from 19.09.2023. Institute for Quality and Efficiency in Health Care (IQWiG), Cologne.

1. To be considered as a comparator therapy, the medicinal product must, principally, have a marketing authorisation for the therapeutic indication.
2. If a non-medicinal treatment is considered as a comparator therapy, this must be available within the framework of the SHI system.
3. As comparator therapy, medicinal products or non-medicinal treatments for which the patient-relevant benefit has already been determined by the G-BA shall be preferred.
4. According to the generally recognised state of medical knowledge, the comparator therapy should be part of the appropriate therapy in the therapeutic indication.

According to Section 6, paragraph 2, sentence 2 Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV), the determination of the appropriate comparator therapy must be based on the actual medical treatment situation as it would be without the medicinal product to be assessed. According to Section 6, paragraph 2, sentence 3 Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV), the G-BA may exceptionally determine the off-label use of medicinal products as an appropriate comparator therapy or as part of the appropriate comparator therapy if they determine by resolution on the benefit assessment according to Section 7, paragraph 4 that, according to the generally recognised state of medical knowledge, this is considered a therapy standard in the therapeutic indication to be assessed or as part of the therapy standard in the medical treatment situation to be taken into account according to sentence 2, and

1. for the first time, a medicinal product approved in the therapeutic indication is available with the medicinal product to be assessed,
2. according to the generally recognised state of medical knowledge, the off-label use is generally preferable to the medicinal products previously approved in the therapeutic indication, or
3. according to the generally recognised state of medical knowledge, the off-label use for relevant patient groups or indication areas is generally preferable to the medicinal products previously approved in the therapeutic indication.

An appropriate comparator therapy may also be non-medicinal therapy, the best possible add-on therapy including symptomatic or palliative treatment, or monitoring wait-and-see approach.

<u>Justification based on the criteria set out in Chapter 5 Section 6, paragraph 3 VerfO and Section 6, paragraph 2 AM-NutzenV:</u>

On 1. Besides nivolumab, there are no approved medicinal products available for the adjuvant treatment of oesophageal or gastro-oesophageal junction cancer.

On 2. A non-medicinal treatment cannot be considered in the planned therapeutic indication.

On 3. In the therapeutic indication "Adjuvant treatment of oesophageal or gastro-oesophageal junction cancer in adults with residual pathologic disease after previous neoadjuvant chemoradiotherapy", the resolution of 17 February 2022 on the benefit assessment of medicinal products with new active ingredients according to Section 35a SGB V is available for nivolumab, which is replaced by the present resolution.

On 4. The generally recognised state of medical knowledge was illustrated by a systematic search for guidelines as well as systematic reviews of clinical studies in the present indication and is presented in the "Research and synopsis of the evidence to determine the appropriate comparator therapy according to Section 35a SGB V".

The scientific-medical societies and the Drugs Commission of the German Medical Association (AkdÄ) were also involved in writing on questions relating to the comparator therapy in the present therapeutic indication according to Section 35a, paragraph 7 SGB V.

The active ingredient nivolumab to be assessed here is the only active ingredient that is explicitly approved for this therapeutic indication.

When determining the appropriate comparator therapy, the actual medical treatment situation as it would be without the medicinal product to be assessed must be taken into account (in accordance with Section 6, paragraph 2, sentence 2 Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV)). A comparison with the active ingredient itself under assessment, specifically a comparison of identical therapies, is ruled out regarding the research question of the benefit assessment.

For patients with oesophageal or gastro-oesophageal junction cancer and residual pathologic disease following prior neoadjuvant chemoradiotherapy, there were no approved medicinal products until the granting of the marketing authorisation for nivolumab and also no recommendations in the guidelines for further adjuvant treatment with or without medicinal products.

This applied to both squamous cell carcinomas and adenocarcinomas, regardless of histology. Since patients in the therapeutic indication were considered disease-free, the recommendations of the guidelines were limited to symptom-oriented after-care with the goals of, among other things, recording functional disorders that affect quality of life and diagnosing recurrences at an early stage.

As part of the statements in the present benefit assessment procedure, the scientific-medical societies state that adjuvant treatment was not recommended post-surgery, as the value of adjuvant systemic chemotherapy was not proven.

Overall, the G-BA therefore determined the "monitoring wait-and-see approach" as the appropriate comparator therapy.

The findings in Annex XII do not restrict the scope of treatment required to fulfil the medical treatment mandate.

A change in the appropriate comparator therapy requires a resolution by the G-BA linked to the prior review of the criteria according to Chapter 5 Section 6, paragraph 3 Rules of Procedure.

2.1.3 Extent and probability of the additional benefit

In summary, the additional benefit of nivolumab is assessed as follows:

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

Hint for a minor additional benefit

Justification:

The pharmaceutical company submitted the data of the CA209-577 study to demonstrate the additional benefit of nivolumab for the adjuvant treatment of oesophageal or gastro-oesophageal junction cancer in adults with residual pathologic disease following prior neoadjuvant chemoradiotherapy.

CA209-577 study

The CA209-577 study is a parallel, double-blind, randomised controlled phase III study which compared nivolumab to placebo. The placebo comparison carried out corresponds to an implementation of the appropriate comparator therapy consisting of the "monitoring wait-and-see approach".

The study was conducted in 170 study sites in Europe, North and South America, Asia and Australia between July 2016 and November 2024.

Adults with stage II or III oesophageal or gastro-oesophageal junction cancers (classification according to the 7th edition of the American Joint Committee on Cancer) were enrolled at initial diagnosis. Patients had to have completed neoadjuvant platinum-based chemoradiotherapy followed by resection and there had to be R0 resection with residual pathologic disease (≥ ypT1 or ≥ ypN1).

The patients had to also be in a good general condition with an Eastern Cooperative Oncology Group Performance Status (ECOG-PS) of 0 or 1, and have a disease-free status.

The 794 patients enrolled were randomised in a 2:1 ratio to the nivolumab arm (N = 532) and placebo arm (N = 262), stratified by PD-L1 status (≥ 1 % vs < 1 % or indeterminate/ not evaluable), pathological lymph node status (≥ ypN1 vs ypN0) and histology (squamous cell carcinoma vs adenocarcinoma).

In addition to the primary endpoint of disease-free survival (DFS), endpoints of the categories mortality, morbidity, health-related quality of life and adverse events (AEs) were assessed.

For the CA209-577 study, data from the data cut-offs from 18 March 2024, 4 January 2021, 25 January 2022 and 7 November 2024 are available. The data cut-off from 7 November 2024 (final analysis of overall survival) is used for the present benefit assessment.

<u>On the implementation of the time limit requirements</u>

According to the justification of the resolution of 17 February 2022, the limitation was that further clinical data relevant for the benefit assessment were expected from the CA209-577 study.

For the benefit reassessment after expiry of the deadline, the results on all patient-relevant endpoints from the CA209-577 study must be submitted in the dossier at the final data cut-off.

The pharmaceutical company presented the required evaluations in the dossier, so that the time limit requirements are considered to have been implemented overall.

<u>Extent and probability of the additional benefit</u>

<u>Mortality</u>

In the CA209-577 study, overall survival was defined as the time between randomisation and death from any cause.

For the endpoint of overall survival, there was no statistically significant difference between the treatment arms.

With regard to the available subgroup analyses, the subgroup analyses of the characteristics

- localisation of the disease (oesophageal cancers; gastro-oesophageal junction carcinomas),
- pathological tumour status (ypT0; ypT1/ypT2; ypT3/ypT4) and

- histology (adenocarcinoma; squamous cell carcinoma)

are also considered for the present assessment as these are clinically relevant characteristics, on which the clinical experts also commented in their statements.

Effect modifications are shown here by the characteristics "Localisation of the disease" and "pathological tumour status". In the subgroup of patients with oesophageal cancers, there was a statistically significant difference to the advantage of nivolumab, while there was no statistically significant difference for patients with gastro-oesophageal junction carcinomas. In the subgroup of patients with a pathological tumour status ypT0 and ypT1/ ypT2, there was a statistically significant advantage of nivolumab, while there was no statistically significant difference in the subgroup with a pathological tumour status ypT3/ ypT4. During the oral hearing, the clinical experts also stated that patients with tumours at the gastro-oesophageal junction may benefit less than patients with oesophageal cancer and that this in turn interacts with the histology. However, an effect modification for the "histology" characteristic is not apparent from the subgroup analyses.

For the present assessment, the aforementioned effect modifications are considered clinically relevant results of CA209-577 study and are presented accordingly. Nevertheless, these are not considered to be a sufficient basis for making an overall assessment of the additional benefit for appropriately definable subgroups. It is also taken into account that these effect modifications are not observed in the corresponding subgroup analyses for the endpoint of disease-free survival (DFS).

Morbidity

Recurrences (recurrence rate and disease-free survival (DFS))

Patients in the present therapeutic indication are treated with a curative therapeutic approach. The failure of a curative therapeutic approach is fundamentally patient-relevant. The significance of the endpoints on recurrences depends on the extent to which the selected individual components are suitable for adequately reflecting the failure of potential cure by the present curative therapeutic approach.

In the present benefit assessment, both the recurrence rate and the evaluation as DFS are considered for recurrences. Both evaluations include the following events:

- Local recurrence
- Regional recurrence
- Distant metastases
- Death without recurrence

This operationalisation is considered suitable for depicting a failure of the potential cure through the curative therapeutic approach.

With regard to the endpoints of recurrence rate and disease-free survival, there was a statistically significant advantage of nivolumab compared to the monitoring wait-and-see approach.

Health status

The health status was assessed using the visual analogue scale (VAS) of the EQ-5D questionnaire. For the benefit assessment, the pharmaceutical company submitted evaluations of the "time to deterioration", which is operationalised as a combination of one-off and confirmed deterioration.

There was no statistically significant difference between the treatment arms.

The subgroup analysis showed an effect modification by the "Sex" characteristic. For female subjects, there was a statistically significant difference to the advantage of nivolumab, while for male subjects there was a statistically significant disadvantage of nivolumab. These subgroup results are considered a relevant outcome of the present benefit assessment. However, they are considered inadequate to derive separate statements on the additional benefit in the overall assessment. Furthermore, this effect modification is not evident for other patient-relevant endpoints.

Quality of life

FACT-E

Health-related quality of life was assessed in the CA209-577 study using the FACT-E questionnaire. However, as only the FACT-G7 and the oesophageal cancer-specific subscale, but no longer the full FACT-E, were collected in the survival follow-up, the responder analyses of the FACT-E total score, operationalised as a combination of one-off and confirmed deterioration, are used for the present benefit assessment.

For the endpoint FACT-E , there was no statistically significant difference.

Side effects

Adverse events (AEs) in total

In the CA209-577 study, 96.8% of patients in the intervention arm experienced an adverse event, compared to 92.7% of patients in the comparator arm. The results are only presented additionally.

Serious adverse events (SAEs) and severe AEs (CTCAE grade 3 or 4)

For the endpoints of SAEs and severe AEs (CTCAE grade ≥ 3), there were no statistically significant differences between the treatment groups.

Therapy discontinuation due to AEs

For the endpoint on therapy discontinuation due to an AE, there was a statistically significant difference to the disadvantage of nivolumab.

Specific AEs

In detail, there were disadvantages of nivolumab in the following endpoints on specific AEs: immune-mediated SAEs, skin and subcutaneous tissue disorders, infections and infestations as well as blood and lymphatic system disorders. For the endpoint of immune-mediated severe AEs, there was no statistically significant difference between the treatment arms.

In the overall analysis of the results on side effects, a disadvantage of nivolumab was found overall due to the disadvantage in therapy discontinuation and in detail in the specific AEs.

Overall assessment

For the reassessment after expiry of the deadline for nivolumab for the adjuvant treatment of oesophageal or gastro-oesophageal junction carcinomas in adults with residual pathologic disease after previous neoadjuvant chemoradiotherapy, results on mortality, morbidity, quality of life and side effects are available from the CA209-577 study in comparison with the monitoring wait-and-see approach.

With regard to the endpoint of overall survival, there was no statistically significant difference between the treatment arms. The subgroup analysis showed an effect modification by the characteristics "Localisation of the disease" and "Pathological tumour status". For patients

with oesophageal cancers, there was a statistically significant advantage of nivolumab, while there was no statistically significant difference for patients with gastro-oesophageal junction carcinomas. For patients with a pathological tumour status ypT0 and ypT1/ ypT2, there was a statistically significant advantage of nivolumab, while there was no statistically significant difference in the subgroup with a pathological tumour status ypT3/ ypT4. These results are not considered to be a sufficient basis for making an overall assessment of the additional benefit for appropriately definable subgroups.

For the endpoints of recurrence rate and disease-free survival, there was a statistically significant advantage of nivolumab compared to the monitoring wait-and-see approach. In the present curative treatment setting, the avoidance of recurrences is an essential therapeutic goal.

With regard to the health status (EQ-5D VAS), there was no statistically significant difference between the treatment arms. The subgroup analysis showed an effect modification by the "Sex" characteristic. For female subjects, there was a statistically significant advantage of nivolumab, while for male subjects there was a statistically significant disadvantage thereof. These subgroup results are considered inadequate to derive separate statements on the additional benefit in the overall assessment.

For the endpoint FACT-E total score, there was no statistically significant difference.

In terms of side effects, a disadvantage of nivolumab was found for the endpoint of therapy discontinuation due to AEs. In detail, there were also disadvantages of nivolumab in the specific AEs. For SAEs and severe AEs, there were no statistically significant differences. In the category of side effects, a disadvantage of nivolumab compared to the monitoring wait-and-see approach was derived overall.

Overall, the positive effect on recurrences is offset by a disadvantage in terms of side effects. Although the positive effect with regard to the prevention of recurrences is not supported by further advantages in other patient-relevant endpoints, the disadvantage does not affect the positive effect with regard to the prevention of recurrences. Overall, the extent of improvement in therapeutic benefit is rated as a relevant improvement, but no more than a minor improvement.

In the overall assessment, a minor additional benefit of nivolumab over the monitoring wait-and-see approach is therefore identified for the adjuvant treatment of oesophageal or gastro-oesophageal junction cancer in adults with residual pathologic disease following prior neoadjuvant chemoradiotherapy.

Reliability of data (probability of additional benefit)

The present assessment is based on the results of the CA209-577 study. This study compared nivolumab to placebo in a randomised, controlled, double-blind comparison.

The risk of bias at study level is rated as low.

The endpoint-specific risk of bias for the endpoints of overall survival and recurrences is rated as low. The reliability of data for the endpoint of therapy discontinuation due to AEs is limited, as premature therapy discontinuation for reasons other than AEs represents a competing event. This means that the "Therapy discontinuation" criterion can no longer be assessed for AEs that may still occur after discontinuation for reasons other than AEs.

In addition, there were effect modifications by the characteristics "Location of the disease" and "Pathological tumour status" in the endpoint of overall survival and by the "Sex" characteristic in the endpoint of health status (EQ-5D VAS). Due to the effect modifications,

there was a relevant uncertainty regarding the reliability of data for the total patient population.

Overall, the available data basis is therefore subject to uncertainty, which is why the reliability of data regarding the additional benefit identified is classified in the hint category.

2.1.4 Summary of the assessment

The present assessment is a new benefit assessment of the active ingredient nivolumab due to the expiry of the limitation of the resolution on 2 May 2024.

The therapeutic indication assessed here is as follows: 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.

The monitoring wait-and-see approach was determined as the appropriate comparator therapy.

The pharmaceutical company presented data on mortality, morbidity, quality of life and side effects from the CA209-577 study.

With regard to overall survival, there was no statistically significant difference.

For the endpoints of recurrence rate and disease-free survival, there was a statistically significant advantage of nivolumab compared to the monitoring wait-and-see approach. In the present curative treatment setting, the avoidance of recurrences is an essential therapeutic goal.

With regard to the health status (EQ-5D VAS), there was no statistically significant difference.

For the endpoint of FACT-E total score, there was no statistically significant difference.

In terms of side effects, a disadvantage of nivolumab was found for the endpoint of therapy discontinuation due to AEs. In detail, there were also disadvantages in the specific AEs. For SAEs and severe AEs, there were no statistically significant differences. In the category of side effects, a disadvantage of nivolumab compared to the monitoring wait-and-see approach was derived overall.

Overall, the positive effect on recurrences is offset by a disadvantage in terms of side effects. Although the positive effect with regard to the prevention of recurrences is not supported by further advantages in other patient-relevant endpoints, the disadvantage does not affect the positive effect with regard to the prevention of recurrences. Overall, the extent of improvement in therapeutic benefit is rated as a relevant improvement, but no more than a minor improvement.

In the overall assessment, a hint for a minor additional benefit of nivolumab compared with the monitoring wait-and-see approach is therefore identified.

Due to uncertainties caused by effect modifications, a hint for the reliability of data is derived overall.

2.2 Number of patients or demarcation of patient groups eligible for treatment

The information on the number of patients is based on the target population in statutory health insurance (SHI).

The G-BA take into account the patient numbers stated in the pharmaceutical company's dossier, which are subject to uncertainties. For example, it is uncertain to what extent the

percentage for neoadjuvant chemoradiotherapy and resection deviate if patients are also taken into account for whom no information on treatment is yet available and to what extent they deviate for the year 2025 compared to the year 2018 due to another therapy event. Furthermore, the range includes an unknown number of patients with ≥ R1 resection who are not included in the therapeutic indication.

2.3 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.

2.4 Treatment costs

The treatment costs are based on the contents of the product information and the information listed in the LAUER-TAXE® (last revised: 15 October 2025). The calculation of treatment costs is generally based on the last revised LAUER-TAXE® version following the publication of the benefit assessment.

Treatment period:

If no maximum treatment duration is specified in the product information, the treatment duration is assumed to be one year (365 days), even if the actual treatment duration is different from patient to patient and/or is shorter on average. The time unit "days" is used to calculate the "number of treatments/ patient/ year", time intervals between individual treatments and for the maximum treatment duration, if specified in the product information.

The use of nivolumab as adjuvant treatment is limited to 12 months.

Designation of the therapy	Treatment mode	Number of treatments/ patient/ year	Treatment duration/ treatment (days)	Treatment days/ patient/ year
Medicinal product to be assessed				
Nivolumab				
Initial treatment (week 1-16)	1 x per 14-day cycle	8.0	1	8.0
	or			
	1 x per 28-day cycle	4.0	1	4.0
Follow-up treatment (from week 17)	1 x per 28-day cycle	9.0	1	9.0
Appropriate comparator therapy				
Monitoring wait-and-see approach	Not calculable			

Consumption:

For the cost representation, only the dosages of the general case are considered. Patient-individual dose adjustments (e.g. because of side effects or co-morbidities) are not taken into account when calculating the annual treatment costs.

Designation of the therapy	Dosage/ application	Dose/ patient/ treatment days	Consumption by potency/ treatment day	Treatment days/ patient/ year	Average annual consumption by potency
Medicinal product to be assessed					
Nivolumab					
Initial treatment (week 1-16)	240 mg	240 mg	2 x 120 mg	8.0	16 x 120 mg
	or				
	480 mg	480 mg	4 x 120 mg	4.0	16 x 120 mg
Follow-up treatment (from week 17)	480 mg	480 mg	4 x 120 mg	9.0	36 x 120 mg
Appropriate comparator therapy					
Monitoring wait-and-see approach	Not calculable				

Costs:

In order to improve comparability, the costs of the medicinal products were approximated both on the basis of the pharmacy sales price level and also deducting the statutory rebates in accordance with Section 130 and Section 130a SGB V. To calculate the annual treatment costs, the required number of packs of a particular potency was first determined on the basis of consumption. Having determined the number of packs of a particular potency, the costs of the medicinal products were then calculated on the basis of the costs per pack after deduction of the statutory rebates. Any reference prices shown in the cost representation may not represent the cheapest available alternative.

Costs of the medicinal products:

Designation of the therapy	Packaging size	Costs (pharmacy sales price)	Rebate Section 130 SGB V	Rebate Section 130a SGB V	Costs after deduction of statutory rebates
Medicinal product to be assessed					
Nivolumab 120 mg	1 CIS	€ 1,539.71	€ 1.77	€ 84.64	€ 1,453.30
Appropriate comparator therapy					
Monitoring wait-and-see approach	Not calculable				
Abbreviations: CIS = concentrate for the preparation of an infusion solution					

LAUER-TAXE® last revised: 15 October 2025

Costs for additionally required SHI services:

Only costs directly related to the use of the medicinal product are taken into account. If there are regular differences in the necessary use of medical treatment or in the prescription of other services in the use of the medicinal product to be evaluated and the appropriate comparator therapy in accordance with the product information, the costs incurred for this must be taken into account as costs for additionally required SHI services.

Medical treatment costs, medical fee services, and costs incurred for routine examinations (e.g. regular laboratory services such as blood count tests) that do not exceed the standard expenditure in the course of the treatment are not shown.

Because there are no regular differences in the necessary use of medical treatment or in the prescription of other services in the use of the medicinal product to be evaluated and the appropriate comparator therapy in accordance with the product information, no costs for additionally required SHI services had to be taken into account.

Other SHI services:

The special agreement on contractual unit costs of retail pharmacist services (Hilfstaxe) (Sections 4 and 5 of the Pharmaceutical Price Ordinance) from 1 October 2009 is not fully used to calculate costs. Alternatively, the pharmacy sales price publicly accessible in the directory services according to Section 131 paragraph 4 SGB V is a suitable basis for a standardised calculation.

According to the currently valid version of the special agreement on contractual unit costs of retail pharmacist services (Hilfstaxe), surcharges for the production of parenteral preparations containing cytostatic agents a maximum amount of € 100 per ready-to-use preparation, and

for the production of parenteral solutions containing monoclonal antibodies a maximum of € 100 per ready-to-use unit are to be payable. These additional other costs are not added to the pharmacy sales price but rather follow the rules for calculating in the Hilfstaxe. The cost representation is based on the pharmacy retail price and the maximum surcharge for the preparation and is only an approximation of the treatment costs. This presentation does not take into account, for example, the rebates on the pharmacy purchase price of the active ingredient, the invoicing of discards, the calculation of application containers, and carrier solutions in accordance with the regulations in Annex 3 of the special agreement on contractual unit costs of retail pharmacist services (Hilfstaxe).

2.5 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

According to Section 35a, paragraph 3, sentence 4, the G-BA designate all medicinal products with new active ingredients that can be used in a combination therapy with the assessed medicinal product for the therapeutic indication to be assessed on the basis of the marketing authorisation under Medicinal Products Act.

Basic principles of the assessed medicinal product

A designation in accordance with Section 35a, paragraph 3, sentence 4 SGB V requires that it is examined based on the product information for the assessed medicinal product whether it can be used in a combination therapy with other medicinal products in the assessed therapeutic indication. In the first step, the examination is carried out on the basis of all sections of the currently valid product information for the assessed medicinal product.

If the assessed medicinal product contains an active ingredient or a fixed combination of active ingredients in the therapeutic indication of the resolution (assessed therapeutic indication) and is approved exclusively for use in monotherapy, a combination therapy is not considered due to the marketing authorisation under Medicinal Products Act, which is why no designation is made.

A designation is also not considered if the G-BA have decided on an exemption as a reserve antibiotic for the assessed medicinal product in accordance with Section 35a, paragraph 1c, sentence 1 SGB V. The additional benefit is deemed to be proven if the G-BA have decided on an exemption for a reserve antibiotic in accordance with Section 35a, paragraph 1c, sentence 1 SGB V; the extent of the additional benefit and its therapeutic significance are not to be assessed by the G-BA. Due to the lack of an assessment mandate by the G-BA following the resolution on an exemption according to Section 35a, paragraph 1c, sentence 1 SGB V with regard to the extent of the additional benefit and the therapeutic significance of the reserve antibiotic to be assessed, there is a limitation due to the procedural privileging of the pharmaceutical companies to the effect that neither the proof of an existing nor an expected at least considerable additional benefit is possible for exempted reserve antibiotics in the procedures according to Section 35a paragraph 1 or 6 SGB V and Section 35a paragraph 1d SGB V. The procedural privileging of the reserve antibiotics exempted according to Section 35a, paragraph 1c, sentence 1 SGB V must therefore also be taken into account at the level of designation according to Section 35a, paragraph 3, sentence 4 SGB V in order to avoid valuation contradictions.

With regard to the further examination steps, a differentiation is made between a "determined" or "undetermined" combination, which may also be the basis for a designation.

A "determined combination" exists if one or more individual active ingredients which can be

used in combination with the assessed medicinal product in the assessed therapeutic indication are specifically named.

An "undetermined combination" exists if there is information on a combination therapy, but no specific active ingredients are named. An undetermined combination may be present if the information on a combination therapy:

- names a product class or group from which some active ingredients not specified in detail can be used in combination therapy with the assessed medicinal product, or
- does not name any active ingredients, product classes or groups, but the assessed medicinal product is used in addition to a therapeutic indication described in more detail in the relevant product information, which, however, does not include information on active ingredients within the scope of this therapeutic indication.

Concomitant active ingredient

The concomitant active ingredient is a medicinal product with new active ingredients that can be used in combination therapy with the assessed medicinal product for the therapeutic indication to be assessed.

For a medicinal product to be considered as a concomitant active ingredient, it must be classified as a medicinal product with new active ingredients according to Section 2 paragraph 1 Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV) in conjunction with the corresponding regulations in Chapter 5 of the Rules of Procedure of the G-BA as of the date of the present resolution. In addition, the medicinal product must be approved in the assessed therapeutic indication, whereby a marketing authorisation is sufficient only for a sub-area of the assessed therapeutic indication.

Based on an "undetermined combination", the concomitant active ingredient must be attributable to the information on the product class or group or the therapeutic indication according to the product information of the assessed medicinal product in the assessed therapeutic indication, whereby the definition of a product class or group is based on the corresponding requirements in the product information of the assessed medicinal product.

In addition, there must be no reasons for exclusion of the concomitant active ingredient from a combination therapy with the assessed medicinal product, in particular no exclusive marketing authorisation as monotherapy.

In addition, all sections of the currently valid product information of the eligible concomitant active ingredient are checked to see whether there is any information that excludes its use in combination therapy with the assessed medicinal product in the assessed therapeutic indication under marketing authorisation regulations. Corresponding information can be, for example, dosage information or warnings. In the event that the medicinal product is used as part of a determined or undetermined combination which does not include the assessed medicinal product, a combination with the assessed medicinal product shall be excluded.

Furthermore, the product information of the assessed medicinal product must not contain any specific information that excludes its use in combination therapy with the eligible concomitant active ingredient in the assessed therapeutic indication under marketing authorisation regulations.

Medicinal products with new active ingredients for which the G-BA have decided on an exemption as a reserve antibiotic in accordance with Section 35a, paragraph 1c, sentence 1 SGB V are ineligible as concomitant active ingredients. The procedural privileging of the reserve antibiotics exempted according to Section 35a, paragraph 1c, sentence 1 SGB V also applies accordingly to the medicinal product eligible as a concomitant active ingredient.

Designation

The medicinal products which have been determined as concomitant active ingredients in accordance with the above points of examination are named by indicating the relevant active ingredient and the invented name. The designation may include several active ingredients, provided that several medicinal products with new active ingredients may be used in the same combination therapy with the assessed medicinal product or different combinations with different medicinal products with new active ingredients form the basis of the designation.

If the present resolution on the assessed medicinal product in the assessed therapeutic indication contains several patient groups, the designation of concomitant active ingredients shall be made separately for each of the patient groups.

Exception to the designation

The designation excludes combination therapies for which - patient group-related - a considerable or major additional benefit has been determined by resolution according to Section 35a, paragraph 3, sentence 1 SGB V or it has been determined according to Section 35a, paragraph 1d, sentence 1 SGB V that at least considerable additional benefit of the combination can be expected. In this context, the combination therapy that is excluded from the designation must, as a rule, be identical to the combination therapy on which the preceding findings were based.

In the case of designations based on undetermined combinations, only those concomitant active ingredients - based on a resolution according to Section 35a, paragraph 3, sentence 1 SGB V on the assessed medicinal product in which a considerable or major additional benefit had been determined - which were approved at the time of this resolution are excluded from the designation.

Legal effects of the designation

The designation of combinations is carried out in accordance with the legal requirements according to Section 35a, paragraph 3, sentence 4 and is used exclusively to implement the combination discount according to Section 130e SGB V between health insurance funds and pharmaceutical companies. The designation is not associated with a statement as to the extent to which a therapy with the assessed medicinal products in combination with the designated medicinal products corresponds to the generally recognised state of medical knowledge. The examination was carried out exclusively on the basis of the possibility under Medicinal Products Act to use the medicinal products in combination therapy in the assessed therapeutic indication based on the product information; the generally recognised state of medical knowledge or the use of the medicinal products in the reality of care were not the subject of the examination due to the lack of an assessment mandate of the G-BA within the framework of Section 35a, paragraph 3, sentence 4 SGB V.

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.

Justification for the findings on designation in the present resolution:

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.

3. Bureaucratic costs calculation

The proposed resolution does not create any new or amended information obligations for care providers within the meaning of Annex II to Chapter 1 VerfO and, accordingly, no bureaucratic costs.

4. Process sequence

At their session on 27 May 2025, the Subcommittee on Medicinal Products determined the appropriate comparator therapy.

On 30 June 2025 the pharmaceutical company submitted a dossier for the benefit assessment of nivolumab to the G-BA in due time in accordance with Chapter 5 Section 8, paragraph 1, number 5 VerfO.

By letter dated 01 July 2025 in conjunction with the resolution of the G-BA of 1 August 2011 concerning the commissioning of the IQWiG to assess the benefits of medicinal products with new active ingredients in accordance with Section 35a SGB V, the G-BA commissioned the IQWiG to assess the dossier concerning the active ingredient nivolumab.

The dossier assessment by the IQWiG was submitted to the G-BA on 25 September 2025, and the written statement procedure was initiated with publication on the G-BA website on 1 October 2025. The deadline for submitting statements was 22 October 2025.

The oral hearing was held on 10 November 2025.

By letter dated 12 November 2025, the IQWiG was commissioned with a supplementary assessment. The addendum prepared by IQWiG was submitted to the G-BA on 28 November 2025.

In order to prepare a recommendation for a resolution, the Subcommittee on Medicinal Products commissioned a working group (Section 35a) consisting of the members nominated by the leading organisations of the care providers, the members nominated by the SHI umbrella organisation, and representatives of the patient organisations. Representatives of the IQWiG also participate in the sessions.

The evaluation of the written statements received and the oral hearing was discussed at the session of the Subcommittee on 9 December 2025, and the proposed draft resolution was approved.

At their session on 18 December 2025, the plenum adopted a resolution to amend the Pharmaceuticals Directive.

Chronological course of consultation

Session	Date	Subject of consultation
Subcommittee on Medicinal Products	27 May 2025	Determination of the appropriate comparator therapy
Working group Section 35a	5 November 2025	Information on written statements received; preparation of the oral hearing
Subcommittee on Medicinal Products	10 November 2025	Conduct of the oral hearing, commissioning of the IQWiG with the supplementary assessment of documents
Working group Section 35a	19 November 2025 3 December 2025	Consultation on the dossier evaluation by the IQWiG and evaluation of the written statement procedure
Subcommittee on Medicinal Products	9 December 2025	Concluding discussion of the draft resolution
Plenum	18 December 2025	Adoption of the resolution on the amendment of the Pharmaceuticals Directive

Berlin, 18 December 2025

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

Prof. Hecken