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 (new therapeutic indication: unresectable or advanced hepatocellular carcinoma, first-line, combination with ipilimumab)

of 4 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 active ingredient nivolumab (Opdivo) was listed for the first time on 15 July 2015 in the “LAUER-TAXE®”, the extensive German registry of available drugs and their prices.

On 28 November 2024, the pharmaceutical company submitted an application for postponement of the date for the start of the benefit assessment procedure for nivolumab, among others, in the therapeutic indication "First-line treatment of adult patients with unresectable or advanced hepatocellular carcinoma" in accordance with Section 35a paragraph 5b SGB V. The pharmaceutical company expected an extension of the marketing authorisation for the active ingredient nivolumab within the period specified in Section 35a paragraph 5b SGB V for further therapeutic indications.

At their session on 16 January 2025, the G-BA approved the application to postpone the relevant date in accordance with Section 35a paragraph 5b SGB V and postponed the relevant date for the start of the benefit assessment and the submission of a dossier for the benefit assessment for the therapeutic indication in question here to four weeks after the marketing

authorisation of the last therapeutic indication of the therapeutic indications covered by the application, at the latest six months after the first relevant date. All marketing authorisations for the therapeutic indications covered by the application according to Section 35a paragraph 5b SGB V were granted within the 6-month period.

For the therapeutic indication in question here "First-line treatment of adult patients with unresectable or advanced hepatocellular carcinoma", nivolumab received the extension of the marketing authorisation as a major type 2 variation as defined according to Annex 2 No. 2 letter a to Regulation (EC) No. 1234/2008 of the Commission from 24 November 2008 concerning the examination of variations to the terms of marketing authorisations for medicinal products for human use and veterinary medicinal products (OJ L 334, 12.12.2008, p. 7) on 28 February 2025. In accordance with the resolution of 16 January 2025, the benefit assessment of the active ingredient nivolumab in this new therapeutic indication thus began at the latest within four weeks of granting of the last marketing authorisation of nivolumab on 15 May 2025 in the therapeutic indication for the treatment of "non-small cell lung cancer", i.e. at the latest on 12 June 2025.

On 12 June 2025, the pharmaceutical company has submitted a dossier in due time in accordance with Section 4, paragraph 3, number 3 Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV) in conjunction with Chapter 5 Section 8, paragraph 2 of the Rules of Procedure (VerfO) of the G-BA on the active ingredient nivolumab with the therapeutic indication: "First-line treatment of adult patients with unresectable or advanced hepatocellular carcinoma".

The G-BA commissioned the IQWiG to carry out the assessment of the dossier. The benefit assessment was published on 15 September 2025 on the G-BA website (www.g-ba.de), therefore initiating the written statement procedure. In addition, an oral hearing was held.

Based on the dossier of the pharmaceutical company, the dossier assessment prepared by the IQWiG, and the statements submitted in the written statement and oral hearing procedure, the G-BA decided on the question on whether an additional benefit of nivolumab compared with the appropriate comparator therapy could be determined – Annex XII - Resolutions on the benefit assessment of medicinal products with new active ingredients according to Section 35a SGB V. 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 was not used in the benefit assessment of the active ingredient.

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 in combination with ipilimumab is indicated for the first-line treatment of adult patients with unresectable or advanced hepatocellular carcinoma.

Therapeutic indication of the resolution (resolution of 04.12.2025):

See the approved therapeutic indication

2.1.2 Appropriate comparator therapy

The appropriate comparator therapy was determined as follows:

a) Adults with unresectable or advanced hepatocellular carcinoma (HCC) with Child-Pugh A or no liver cirrhosis; first-line therapy

Appropriate comparator therapy for nivolumab in combination with ipilimumab:

- Atezolizumab in combination with bevacizumab

or

- durvalumab in combination with tremelimumab

b) Adults with unresectable or advanced hepatocellular carcinoma (HCC) with Child-Pugh B; first-line therapy

Appropriate comparator therapy for nivolumab in combination with ipilimumab:

- Best supportive care

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. 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.

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

On 1. In addition to nivolumab and ipilimumab, the immune checkpoint inhibitors atezolizumab, durvalumab and tremelimumab, the protein kinase inhibitors lenvatinib and sorafenib and the cytostatic agent mitomycin are approved in the present therapeutic indication.

On 2. A non-medicinal therapy cannot be considered as an appropriate comparator therapy. For the present therapeutic indication, it is assumed that both curative treatment (corresponding to BCLC stages 0 and A) and locoregional therapy in BCLC stage B, in particular transarterial (chemo)embolisation (TACE or TAE), do not (no longer) come into question.

On 3. In the present therapeutic indication, the following resolutions on the benefit assessment of medicinal products with new active ingredients according to Section 35a SGB V are available:

- Durvalumab: resolutions of 5 October 2023 and 6 June 2024
- Tremelimumab: resolution of 5 October 2023
- Atezolizumab: resolution of 20 May 2021
- Lenvatinib: resolution of 22 March 2019

Annex VI to Section K of the Pharmaceuticals Directive – Active ingredients that cannot be prescribed for off-label use:

- octreotide in hepatocellular carcinoma

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. No written opinions were received.

Among the approved active ingredients listed under 1., only certain active ingredients named below will be included in the appropriate comparator therapy, taking into account the evidence on therapeutic benefit, the guideline recommendations and the reality of care.

For use as first-line therapy, it is assumed that both curative treatment (corresponding to BCLC stages 0 and A) and locoregional therapy in BCLC stage B, in particular transarterial (chemo)embolisation (TACE or TAE), are not (no longer) considered.

It is also assumed that patients with stage D BCLC are not eligible for therapy with nivolumab in combination with ipilimumab.

According to the available guidelines, the stage of the disease and the functional capacity of the liver mainly determine the treatment decision for first-line therapy of hepatocellular carcinoma. Against this background, it is considered appropriate to differentiate the determination of the appropriate comparator therapy according to the following patient groups:

a) Adults with unresectable or advanced hepatocellular carcinoma (HCC) with Child-Pugh A or no liver cirrhosis; first-line therapy

According to the generally accepted state of medical knowledge, patients with hepatocellular carcinoma in stage BCLC B or C and with preserved liver function (Child-Pugh score A) are eligible for systemic therapy.

Several substances are available for the treatment of advanced HCC. For first-line therapy, these include the combination therapies atezolizumab + bevacizumab and durvalumab + tremelimumab and monotherapies with durvalumab as well as with the tyrosine kinase inhibitors sorafenib or lenvatinib.

According to the guidelines, the relevant patients should be offered first-line therapy with atezolizumab in combination with bevacizumab or with durvalumab in combination with tremelimumab. According to the recommendations, both combination therapies are equally recommended first-choice therapy options.

In their joint written statement on the present benefit assessment procedure, the Working Group for Internal Oncology of the German Cancer Society (AIO), the German Society for Haematology and Medical Oncology (DGHO) and the German Society for Gastroenterology, Digestive and Metabolic Diseases (DGVS) mention the combination therapies atezolizumab + bevacizumab and durvalumab + tremelimumab as the current therapy standard.

By resolution of 20 May 2021, the G-BA identified an indication of a considerable additional benefit over sorafenib in the benefit assessment of atezolizumab in combination with bevacizumab in patients with Child-Pugh A or no liver cirrhosis who have not received prior systemic treatment.

No additional benefit was identified for the combination therapy durvalumab and tremelimumab for patients with Child-Pugh A or no liver cirrhosis in first-line treatment on the basis of an adjusted indirect comparison with atezolizumab in combination with bevacizumab via the bridge comparator sorafenib (resolutions of 5 October 2023).

According to the guidelines, the monotherapy options with durvalumab, lenvatinib or sorafenib only assume significance as alternatives to first-line therapy in patients with a contraindication to atezolizumab + bevacizumab or durvalumab + tremelimumab. Monotherapy with durvalumab, lenvatinib or sorafenib is therefore not considered as an appropriate comparator therapy.

In the overall analysis, according to the generally recognised state of medical knowledge, first-line therapy with atezolizumab in combination with bevacizumab or durvalumab in combination with tremelimumab represents the current therapy standard for patients with Child-Pugh A or no liver cirrhosis and is determined to be the appropriate comparator therapy.

The appropriate comparator therapy determined here includes several therapeutic alternatives. These therapeutic alternatives are equally appropriate for the comparator therapy. The additional benefit can be demonstrated compared to one of the therapeutic alternatives mentioned.

b) Adults with unresectable or advanced hepatocellular carcinoma (HCC) with Child-Pugh B; first-line therapy

According to the generally accepted state of medical knowledge, antineoplastic systemic therapy is generally only recommended for patients in Child-Pugh score A. The guidelines recommend offering systemic therapy with sorafenib, lenvatinib or an anti-PD-1 antibody also in Child-Pugh score B (up to 8 points) only in individual cases. This is only an open recommendation (recommendation grade 0). Sorafenib, lenvatinib and anti-PD-1 antibody are therefore not considered as an appropriate comparator therapy.

Best supportive care for patients with Child-Pugh score B is determined as the appropriate comparator therapy. Best supportive care is defined as the therapy that provides the best possible, patient-individual, optimised supportive treatment to alleviate symptoms and improve quality of life.

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:

a) Adults with unresectable or advanced hepatocellular carcinoma (HCC) with Child-Pugh A or no liver cirrhosis; first-line therapy

An additional benefit is not proven.

b) Adults with unresectable or advanced hepatocellular carcinoma (HCC) with Child-Pugh B; first-line therapy

An additional benefit is not proven.

Justification:

The pharmaceutical company did not present any direct comparator study of nivolumab in combination with ipilimumab versus the appropriate comparator therapy for the benefit assessment. Furthermore, no indirect comparison was submitted.

The pharmaceutical company referred to the label-enabling CA209-9DW study in the dossier. This is an ongoing, open-label, randomised, multicentre phase III study comparing nivolumab in combination with ipilimumab with a therapy according to doctor's instructions with selection of sorafenib and lenvatinib. The study has been conducted in 210 study sites in Europe, North and South America, Asia and Australia since November 2019.

Adult patients with advanced hepatocellular carcinoma and a Child-Pugh score 5-6 (corresponding to Child-Pugh A) and an ECOG-PS 0-1 without previous systemic therapy were enrolled in the study.

Overall, 335 patients were randomly assigned to treatment with nivolumab in combination with ipilimumab and 333 patients to treatment with sorafenib/ lenvatinib. Stratification factors during randomisation were the aetiology, the occurrence of macrovascular invasion and extrahepatic spread and the initial alpha-fetoprotein concentration.

In addition to the primary endpoint of overall survival, endpoints in the categories of mortality, morbidity, health-related quality of life and side effects were collected.

Assessment:

The data from the CA209-9DW study are unsuitable for the assessment of the additional benefit. Patients with advanced hepatocellular carcinoma and Child-Pugh A were enrolled in the study (patient group a). In the comparator arm, patients were treated with sorafenib or lenvatinib. This does not correspond to the appropriate comparator therapy for patient group a. Furthermore, no patients with Child-Pugh B (patient group b) were enrolled in the study. Thus, no comparison with the respective appropriate comparator therapy is possible for both patient groups.

In the overall assessment, no suitable data that would allow an assessment of the additional benefit of nivolumab in combination with ipilimumab are therefore available for patient group a, and no such data are available for patient group b. An additional benefit of nivolumab in combination with ipilimumab versus the appropriate comparator therapy is thus not proven.

2.1.4 Summary of the assessment

The present assessment is the benefit assessment of a new therapeutic indication for the active ingredient nivolumab.

The therapeutic indication assessed here is as follows: Nivolumab (Opdivo) in combination with ipilimumab is indicated for the first-line treatment of adult patients with unresectable or advanced hepatocellular carcinoma.

In the therapeutic indication to be considered, two patient groups were distinguished:

a) Adults with unresectable or advanced hepatocellular carcinoma (HCC) with Child-Pugh A or no liver cirrhosis; first-line therapy

b) Adults with unresectable or advanced hepatocellular carcinoma (HCC) with Child-Pugh B; first-line therapy

The pharmaceutical company did not submit any direct comparator study of nivolumab in combination with ipilimumab versus the appropriate comparator therapy. Furthermore, no indirect comparison was submitted. In the dossier, the pharmaceutical company referred to the label-enabling CA209-9DW study, which compared nivolumab in combination with ipilimumab with a selection of sorafenib and lenvatinib in adults with Child-Pugh A.

Patient group a

The G-BA determined the appropriate comparator therapy to be atezolizumab + bevacizumab or durvalumab + tremelimumab. There are no suitable data available for an assessment of the additional benefit of nivolumab. An additional benefit is not proven.

Patient group b

The G-BA determined the appropriate comparator therapy to be Best Supportive Care (BSC). No data are available for patients with Child-Pugh B. An additional benefit is not proven.

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

a) Adults with unresectable or advanced hepatocellular carcinoma (HCC) with Child-Pugh A or no liver cirrhosis; first-line therapy

and

b) Adults with unresectable or advanced hepatocellular carcinoma (HCC) with Child-Pugh B; first-line therapy

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

The pharmaceutical company calculated the patient numbers using data from the JADE registry. This calculation results in a lower range of patient numbers compared to the patient numbers from the resolution of 6 June 2024 on durvalumab for first-line treatment of hepatocellular carcinoma. However, the pharmaceutical company's approach of calculating the patient numbers using the JADE registry leads to a result that is subject to uncertainty. On the one hand, the JADE registry does not include patients who were treated exclusively with best supportive care, and on the other, the number of patients included in the JADE registry is lower than in the sources used in the resolution on durvalumab.

This resolution is therefore based on the data from the resolution of 6 June 2024 on durvalumab for the first-line treatment of hepatocellular carcinoma.

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: 27 November 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 participating in the Oncology Agreement, all of whom are experienced in the treatment of patients with hepatocellular carcinoma.

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: 1 October 2025). The calculation of treatment costs is generally based on the last revised LAUER-TAXE® version following the publication of the benefit assessment.

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 varies 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.

Treatment with nivolumab is limited to a maximum duration of 24 months according to the product information.

The treatment costs for best supportive care are different from patient to patient. Because best supportive care has been determined as an appropriate comparator therapy, this is also reflected in the medicinal product to be assessed. The type and scope of best supportive care can vary depending on the medicinal product to be assessed and the comparator therapy.

Treatment period:

a) Adults with unresectable or advanced hepatocellular carcinoma (HCC) with Child-Pugh A or no liver cirrhosis; first-line therapy

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 in combination with ipilimumab				
First year of treatment				
Initial treatment (week 1 – 12)				
Nivolumab	1 x per 21-day cycle	4	1	4
Ipilimumab	1 x per 21-day cycle	4	1	4
Follow-up treatment (from week 13)				
Nivolumab	1 x per 14-day cycle	20	1	20
	or			
	1 x per 28-day cycle	10	1	10
Second year of treatment				

Designation of the therapy	Treatment mode	Number of treatments/ patient/ year	Treatment duration/ treatment (days)	Treatment days/ patient/ year
Nivolumab	1 x per 14-day cycle	26	1	26
	or			
	1 x per 28-day cycle	13	1	13
Appropriate comparator therapy				
Atezolizumab in combination with bevacizumab				
First year of treatment and subsequent years				
Atezolizumab	1 x per 21-day cycle	17.4	1	17.4
Bevacizumab	1 x per 21-day cycle	17.4	1	17.4
Durvalumab in combination with tremelimumab				
First year of treatment				
Durvalumab	1 x per 28-day cycle	13	1	13
Tremelimumab	Single dose on day 1 in cycle 1	1	1	1
Subsequent years				
Durvalumab	1 x per 28-day cycle	13	1	13

b) Adults with unresectable or advanced hepatocellular carcinoma (HCC) with Child-Pugh B; first-line therapy

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 in combination with ipilimumab				
First year of treatment				
Initial treatment (week 1 – 12)				
Nivolumab	1 x per 21-day cycle	4	1	4
Ipilimumab	1 x per 21-day cycle	4	1	4
Follow-up treatment (from week 13)				

Designation of the therapy	Treatment mode	Number of treatments/ patient/ year	Treatment duration/ treatment (days)	Treatment days/ patient/ year
Nivolumab	1 x per 14-day cycle	20	1	20
	or			
	1 x per 28-day cycle	10	1	10
Best supportive care	Different from patient to patient			
Second year of treatment				
Nivolumab	1 x per 14-day cycle	26	1	26
	or			
	1 x per 28-day cycle	13	1	13
Best supportive care	Different from patient to patient			
Appropriate comparator therapy				
First year of treatment and subsequent years				
Best supportive care	Different from patient to patient			

Consumption:

For dosages depending on body weight (BW), the average body measurements from the official representative statistics "Microcensus 2021 – body measurements of the population" were used as a basis (average body weight: 77.7 kg)[1].

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.

a) Adults with unresectable or advanced hepatocellular carcinoma (HCC) with Child-Pugh A or no liver cirrhosis; first-line therapy

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 in combination with ipilimumab					
First year of treatment					

[1] Federal Health Reporting. Average body measurements of the population (2021, both sexes, 15 years and older), www.gbe-bund.de

Designation of the therapy	Dosage/ application	Dose/ patient/ treatment days	Consumption by potency/ treatment day	Treatment days/ patient/ year	Average annual consumption by potency
Initial treatment (week 1 – 12)					
Nivolumab	1 mg/ kg body weight	77.7 mg	2 x 40 mg	4	8 x 40 mg
Ipilimumab	3 mg/ kg body weight	233.1 mg	1 x 200 mg + 1 x 50 mg	4	4 x 200 mg + 4 x 50 mg
Follow-up treatment (from week 13)					
Nivolumab	240 mg	240 mg	2 x 120 mg	20	40 x 120 mg
	or				
	480 mg	480 mg	4 x 120 mg	10	40 x 120 mg
Second year of treatment					
Nivolumab	240 mg	240 mg	2 x 120 mg	26	52 x 120 mg
	or				
	480 mg	480 mg	4 x 120 mg	13	52 x 120 mg
Appropriate comparator therapy					
Atezolizumab in combination with bevacizumab					
First year of treatment and subsequent years					
Atezolizumab	1,875 mg	1,875 mg	1 x 1,875 mg	17.4	17.4 x 1,875 mg
Bevacizumab	15 mg/ kg body weight	1,166 mg	3 x 400 mg	17.4	52.2 x 400 mg
Durvalumab in combination with tremelimumab					
First year of treatment					
Durvalumab	1,500 mg	1,500 mg	3 x 500 mg	13	39 x 500 mg
Tremelimumab	300 mg	300 mg	1 x 300 mg	1	1 x 300 mg
Subsequent years					
Durvalumab	1,500 mg	1,500 mg	3 x 500 mg	13.0	39 x 500 mg

b) Adults with unresectable or advanced hepatocellular carcinoma (HCC) with Child-Pugh B; first-line therapy

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 in combination with ipilimumab					

Designation of the therapy	Dosage/ application	Dose/ patient/ treatment days	Consumption by potency/ treatment day	Treatment days/ patient/ year	Average annual consumption by potency
First year of treatment					
Initial treatment (week 1 – 12)					
Nivolumab	1 mg/ kg body weight	77.7 mg	2 x 40 mg	4	8 x 40 mg
Ipilimumab	3 mg/ kg body weight	233.1 mg	1 x 200 mg + 1 x 50 mg	4	4 x 200 mg + 4 x 50 mg
Follow-up treatment (from week 13)					
Nivolumab	240 mg	240 mg	2 x 120 mg	20	40 x 120 mg
	or				
	480 mg	480 mg	4 x 120 mg	10	40 x 120 mg
Best supportive care	Different from patient to patient				
Second year of treatment					
Nivolumab	240 mg	240 mg	2 x 120 mg	26	52 x 120 mg
	or				
	480 mg	480 mg	4 x 120 mg	13	52 x 120 mg
Appropriate comparator therapy					
First year of treatment and subsequent years					
Best supportive care	Different from patient to patient				

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					

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
Nivolumab 40 mg	1 CIS	€ 520.90	€ 1.77	€ 28.21	€ 490.92
Nivolumab 120 mg	1 CIS	€ 1,539.71	€ 1.77	€ 84.64	€ 1,453.30
Ipilimumab 50 mg	1 CIS	€ 3,489.23	€ 1.77	€ 195.98	€ 3,291.48
Ipilimumab 200 mg	1 CIS	€ 13,783.97	€ 1.77	€ 783.91	€ 12,998.29
Appropriate comparator therapy					
Atezolizumab 1,875 mg	1 SFI	€ 4,129.23	€ 1.77	€ 232.53	€ 3,894.93
Bevacizumab 400 mg	1 CIS	€ 671.80	€ 1.77	€ 36.57	€ 633.46
Durvalumab 500 mg	1 CIS	€ 2,105.19	€ 1.77	€ 116.94	€ 1,986.48
Tremelimumab 300 mg	1 CIS	€ 20,725.25	€ 1.77	€ 1,180.33	€ 19,543.15
Abbreviations: CIS = concentrate for the preparation of an infusion solution, SFI = solution for injection					

LAUER-TAXE® last revised: 1 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 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:

a) Adults with unresectable or advanced hepatocellular carcinoma (HCC) with Child-Pugh A or no liver cirrhosis; first-line therapy patient group

No medicinal product with new active ingredients that can be used in a combination therapy that fulfils the requirements of Section 35a, paragraph 3, sentence 4 SGB V.

References:
Product information for nivolumab (Opdivo); Opdivo 10 mg/ml concentrate for the preparation of an infusion solution; last revised: May 2025

b) Adults with unresectable or advanced hepatocellular carcinoma (HCC) with Child-Pugh B; first-line therapy

No medicinal product with new active ingredients that can be used in a combination therapy, for which the requirements of Section 35a, paragraph 3, sentence 4 SGB V are fulfilled.

References:
Product information for nivolumab (Opdivo); Opdivo 10 mg/ml concentrate for the preparation of an infusion solution; last revised: May 2025

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 28 January 2025, the Subcommittee on Medicinal Products determined the appropriate comparator therapy.

On 12 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 2 VerfO.

By letter dated 13 June 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 11 September 2025, and the written statement procedure was initiated with publication on the G-BA website on 15 September 2025. The deadline for submitting statements was 6 October 2025.

The oral hearing was held on 27 October 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 25 November 2025, and the proposed draft resolution was approved.

At their session on 4 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	28 January 2025	Determination of the appropriate comparator therapy
Working group Section 35a	15 October 2025	Information on written statements received; preparation of the oral hearing
Subcommittee on Medicinal Products	27 October 2025	Conduct of the oral hearing
Working group Section 35a	5 November 2025 19 November 2025	Consultation on the dossier evaluation by the IQWiG and evaluation of the written statement procedure
Subcommittee on Medicinal Products	25 November 2025	Concluding discussion of the draft resolution
Plenum	4 December 2025	Adoption of the resolution on the amendment of the Pharmaceuticals Directive

Berlin, 4 December 2025

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

Prof. Hecken