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: mismatch repair deficient (dMMR) or microsatellite instability-high (MSI-H) colorectal cancer, first-line, combination with ipilimumab)

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 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 21 October 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 in question here "First-line treatment of unresectable or metastatic dMMR or MSI-H colorectal cancer" 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 another therapeutic indication (non-small cell lung cancer).

At their session on 5 December 2024, 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.

On 28 November 2024, the pharmaceutical company submitted another application for postponement of the date for the start of the benefit assessment procedure for nivolumab, among others, in the therapeutic indication in question here "First-line treatment of unresectable or metastatic dMMR or MSI-H colorectal cancer" 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 another third therapeutic indication (hepatocellular carcinoma).

At their session on 16 January 2025, the G-BA approved the renewed application to postpone the relevant date - replacing the resolution of 5 December 2024 - 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 unresectable or metastatic dMMR or MSI-H colorectal cancer", 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 19 December 2024. In accordance with the resolution of 5 December 2024, which was subsequently replaced by 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 in due time a dossier 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 new therapeutic indication "First-line treatment of unresectable or metastatic dMMR or MSI-H colorectal cancer".

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.

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 in combination with ipilimumab is indicated for the treatment of adult patients with mismatch repair deficient or microsatellite instability-high colorectal cancer in the following settings:

– First-line treatment of unresectable or metastatic colorectal cancer

Therapeutic indication of the resolution (resolution of 18.12.2025):

See the approved therapeutic indication

2.1.2 Appropriate comparator therapy

The appropriate comparator therapy was determined as follows:

Adults with unresectable or metastatic mismatch repair deficient or microsatellite instability-high colorectal cancer; first-line treatment

– Pembrolizumab as monotherapy

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.

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

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. Medicinal products with the active ingredients capecitabine, 5-fluorouracil, oxaliplatin, calcium folinate, mitomycin, irinotecan, bevacizumab, panitumumab, pembrolizumab and cetuximab are approved in the present therapeutic indication.

On 2. For the patients covered by the present therapeutic indication, it is assumed that treatment with a curative intent or primary resection is not considered. A non-medicinal treatment is not considered as an appropriate comparator therapy.

On 3. Resolutions on the benefit assessment of medicinal products with new active ingredients according to Section 35a SGB V:

- Pembrolizumab (resolution of 16 September 2021)

On 4. The generally recognised state of medical knowledge was illustrated by a systematic search for guidelines as well as 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 indication according to Section 35a paragraph 7 SGB V (see “Information on Appropriate Comparator Therapy”). A joint statement has

been issued in this regard by the Working Group for Internal Oncology (AIO) of the German Cancer Society (DKG), the German Society for Haematology and Medical Oncology (DGHO) and the German Society for Gastroenterology, Digestive and Metabolic Diseases (DGVS).

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 first-line treatment of unresectable or metastatic colorectal cancer, the guidelines recommend the active ingredient pembrolizumab as monotherapy for mismatch repair deficient (dMMR) or microsatellite instability-high (MSI-H) tumours.

The written statements of the scientific-medical societies on the question of comparator therapy also state that treatment with an immune checkpoint inhibitor (pembrolizumab) is a standard in the first-line treatment of unresectable or metastatic dMMR or MSI-H colorectal cancer.

By resolution of 16 September 2021, the G-BA identified in the benefit assessment a hint for a minor additional benefit compared to FOLFOX or FOLFIRI ± cetuximab or bevacizumab for patients who are eligible for intensive therapy.

The guidelines and the written statement of the scientific-medical societies also indicate that cytostatic-based treatment regimens are only recommended for patients who do not have dMMR or MSI-H tumours.

In the overall assessment, the G-BA therefore determined pembrolizumab as monotherapy as the appropriate comparator therapy in the present therapeutic indication.

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 in combination with ipilimumab is assessed as follows:

An additional benefit is not proven.

Justification:

In the dossier, the pharmaceutical company presented the results of an interim analysis of the label-enabling CA209-8HW study. This three-arm study includes a comparison of nivolumab in combination with ipilimumab with nivolumab versus nivolumab versus chemotherapy according to doctor's instructions. As this study did not include a comparison with the appropriate comparator therapy of pembrolizumab, the pharmaceutical company had used the results in the dossier to present the medical benefit, but not to justify an additional benefit of nivolumab in combination with ipilimumab. In the dossier, the pharmaceutical company refrained from an indirect comparison with the appropriate comparator therapy on the

grounds that no analyses were available for the endpoint of overall survival for the data cut-off of 12 October 2023 considered by them.

With their written statement, the pharmaceutical company submitted an adjusted indirect comparison according to the method of Bucher et al. This includes indirect comparisons of the endpoints of overall survival, PFS, response (overall response rate), SAEs, severe AEs and therapy discontinuation due to AEs. In addition to the CA209-8HW study, the pharmaceutical company includes the KEYNOTE 177 study comparing pembrolizumab versus chemotherapy according to doctor's instructions in this indirect comparison via the bridge comparator of chemotherapy according to doctor's instructions. The data on the endpoint of overall survival from the CA209-8HW study presented in the written statement procedure are based on the results of a current interim analysis with a data cut-off from 30.04.2025. According to information provided by the pharmaceutical company, these data were not yet available at the time of submission of the dossier. However, uncertainties remain as to why evaluations of overall survival were not already conducted for an earlier pre-specified data cut-off of the CA209-8HW study from 28.08.2024, which would have enabled an adjusted indirect comparison in the dossier. For this assessment, the adjusted indirect comparison submitted with the statement is used and assessed as follows:

CA209-8HW study

The CA209-8HW study is an open-label, three-arm, randomised controlled trial that began in 2019 and is currently ongoing to compare nivolumab, nivolumab in combination with ipilimumab versus nivolumab versus chemotherapy according to doctor's instructions. Adult patients with metastatic or recurrent, unresectable dMMR or MSI-H colorectal cancer were enrolled.

A total of 839 patients were enrolled and were randomly assigned in a 2:2:1 ratio either to treatment with nivolumab (N = 353) or nivolumab in combination with ipilimumab (N = 354) or to chemotherapy according to doctor's instructions with selection of folinic acid + 5-fluorouracil (5-FU) + oxaliplatin (modified regimen; mFOLFOX6) or folinic acid + 5-FU + irinotecan (FOLFIRI), each ± bevacizumab or cetuximab (N = 132). Allocation to the chemotherapy arm was restricted to patients who had previously received at most one systemic therapy or none.

The administration of nivolumab in combination with ipilimumab in the intervention arm corresponded to the requirements in the product information. Treatment was given until disease progression, unacceptable toxicity or therapy discontinuation as decided by the doctor or patient. Treatment with nivolumab was limited to a maximum treatment duration of 2 years. If disease progression was confirmed, treatment with nivolumab in combination with ipilimumab was possible as a subsequent therapy in the chemotherapy arm.

The primary endpoints of the CA209-8HW study are progression-free survival (PFS) comparing nivolumab in combination with ipilimumab versus chemotherapy according to doctor's instructions when used in the first-line treatment and comparing nivolumab in combination with ipilimumab versus nivolumab when administered regardless of prior therapy for the metastatic stage. Patient-relevant endpoints on mortality, morbidity, health-related quality of life and adverse events (AEs) were assessed.

Due to the assessed therapeutic indication of nivolumab in combination with ipilimumab in first-line therapy, the pharmaceutical company carried out the presented adjusted indirect comparison using the results of the sub-population of patients who received nivolumab in combination with ipilimumab in comparison with chemotherapy according to doctor's instructions each as first-line therapy (N = 202 vs N = 101).

KEYNOTE 177

The KEYNOTE 177 study is a completed, open-label randomised controlled trial comparing pembrolizumab with chemotherapy according to doctor's instructions. The study was conducted between 2015 and 2023.

Adult patients with metastatic colorectal cancer with dMMR or MSI-H tumours were enrolled in the study. Patients were not allowed to have received any previous systemic therapy in the metastatic stage, and previous adjuvant chemotherapy for an earlier stage of colorectal cancer had to have been completed six months before the start of the study.

A total of 307 patients were enrolled and randomly assigned in a 1:1 ratio either to treatment with pembrolizumab (N = 153) or chemotherapy consisting of mFOLFOX6 or FOLFIRI each ± bevacizumab or cetuximab (N = 154).

The treatment with pembrolizumab in the intervention arm was carried out largely according to the requirements in the product information. Overall, in the KEYNOTE 177 study, treatment was given until progression, until the occurrence of unacceptable toxicity or intercurrent diseases that make further treatment impossible, or until the decision of the principal investigator or the patient. If disease progression was confirmed, treatment with pembrolizumab as subsequent therapy in the chemotherapy arm was possible after a washout phase of 30 days.

Co-primary endpoints in the study were overall survival and PFS. In addition, patient-relevant endpoints on morbidity, health-related quality of life and AEs were assessed.

For the endpoint of overall survival, the results included in the indirect comparison are based on the data cut-off from 19.02.2021 and for the endpoints on side effects on the data cut-off from 19.02.2020.

On the adjusted indirect comparison according to Bucher

There are clear differences between the studies with regard to testing of the dMMR or MSI-H status. Patients with locally confirmed dMMR or MSI-H were enrolled in the CA209-8HW study. In addition, centralised testing was carried out after enrolment in the study to confirm the local findings. In contrast, only local testing of the dMMR or MSI-H status was carried out in the KEYNOTE 177 study. There was no central confirmation.

The available data show that the previously locally detected dMMR/ MSI-H status was confirmed centrally for 171 of 202 (85%) patients in the intervention arm of the CA209-8HW study and 84 of 101 (83%) patients in the comparator arm. For patients in the intervention arm, it can be seen that significantly fewer deaths occur in the patient group with centrally confirmed dMMR/ MSI-H status of the tumour than in the patient group without central confirmation (19% vs 71%). For the patient group with centrally confirmed dMMR/ MSI-H status, there was a clear difference in the percentage of deaths between the intervention and control arms (19% vs 43%) in favour of nivolumab in combination with ipilimumab compared to patients without central confirmation (71% vs 82%).

The results of the CA209-8HW study thus clearly show that the fact whether a dMMR/ MSI-H status was confirmed centrally represents a potential effect modifier. On the other hand, it can be assumed on the basis of these data that even a small percentage of patients in whom the mutation was not confirmed could have a relevant influence on the overall result.

Due to the exclusively localised detection in the KEYNOTE 177 study, it is unclear to what extent the patient populations of the KEYNOTE 177 and CA209-8HW studies are similar in terms of the percentage of patients with central confirmation of dMMR or MSI-H status. Nor

can it be assumed with sufficient certainty that there is a percentage of patients in the KEYNOTE 177 study - in comparison to the CA209-8HW study - who would have received central confirmation of the dMMR/ MSI-H status of the tumour if tested by a central laboratory. This is based on the fact that the local test procedures used in the studies differ in a relevant way - according to the information in the study documents. For example, in the CA209-8HW study, testing using NGS was also possible to determine MSI-H status, and more and different loci in the genome were tested to determine MSI-H than with the tests used in the KEYNOTE 177 study. In this regard, it should be noted that the tests used for local detection of the dMMR/ MSI-H status in the CA209-8HW study, which was started four years later, may have better quality criteria than the tests used in the KEYNOTE 177 study. Thus, a larger percentage of patients - in whom local detection would not have been confirmed by a central laboratory - in the KEYNOTE 177 study compared to the CA209-8HW study cannot be ruled out.

Although the pharmaceutical company bases the indirect comparison on the patient population with local testing on both sides, the influence on the estimate of the endpoint of overall survival in the indirect comparison will be correspondingly larger or smaller depending on the test-quality-dependent percentage value without central confirmation of the dMMR or MSI-H status and the magnitude of the potential effect modification in the KEYNOTE 177 study. Due to this uncertainty, only a sufficiently large effect on overall survival could be interpreted, but this is not the case. The data for overall survival from the adjusted indirect comparison show an effect estimator (HR) of 0.59 and a 95% confidence interval between 0.36 and 0.99 (p = 0.046) and thus a result that is only of minor statistical significance. In view of the uncertainties described above, particularly with regard to the similarity of the two study populations in connection with the central confirmation of the dMMR or MSI-H status, the data on overall survival from the adjusted indirect comparison are not assessed as being suitable for making statements on the additional benefit.

Conclusion

A core requirement for the consideration of studies in the adjusted indirect comparison via a bridge comparator is the similarity between the studies. In this regard, there are clear differences between the CA209-8HW and KEYNOTE 177 studies in terms of the testing of the dMMR or MSI-H status. The data on overall survival are therefore not suitable for making statements on the additional benefit, given that the result is only of minor statistical significance. Based on the core significance of data on overall survival in the present therapeutic indication and for the relevant proof of an additional benefit by indirect comparisons, the adjusted indirect comparison is assessed overall as being unsuitable for making statements on the additional benefit, taking into account the limited data basis on patient-relevant endpoints.

No data are thus available in the overall assessment to allow an assessment of the additional benefit. An additional benefit of nivolumab in combination with ipilimumab versus the appropriate comparator therapy is therefore 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:

"OPDIVO in combination with ipilimumab is indicated for the treatment of adult patients with mismatch repair deficient or microsatellite instability-high colorectal cancer in the following settings:

– First-line treatment of unresectable or metastatic colorectal cancer"

Pembrolizumab was determined to be the appropriate comparator therapy.

The pharmaceutical company submitted data on the label-enabling CA209-8HW study in the dossier. This three-arm study includes a comparison of nivolumab in combination with ipilimumab with nivolumab versus nivolumab versus chemotherapy according to doctor's instructions, therefore not allowing a comparison with the appropriate comparator therapy of pembrolizumab.

With their written statement, the pharmaceutical company submitted an adjusted indirect comparison according to the method of Bucher et al. including KEYNOTE 177 for the comparison of pembrolizumab versus chemotherapy according to doctor's instructions. A core requirement for the consideration of studies in the adjusted indirect comparison via a bridge comparator is the similarity between the studies. In this regard, there are clear differences between the CA209-8HW and KEYNOTE 177 studies in terms of the testing of the dMMR or MSI-H status. The data on overall survival are therefore not suitable for making statements on the additional benefit, given that the result is only of minor statistical significance. Based on the core significance of data on overall survival in the present therapeutic indication and for the relevant proof of an additional benefit by indirect comparisons, the adjusted indirect comparison is assessed overall as being unsuitable for making statements on the additional benefit, taking into account the limited data basis on patient-relevant endpoints.

No data are thus available in the overall assessment to allow an assessment of the additional benefit. An additional benefit of nivolumab in combination with ipilimumab versus the appropriate comparator therapy is therefore not proven.

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 resolution is based on the information from the dossier assessment of the IQWiG.

The range of approximately 380 – 930 patients derived by the pharmaceutical company in the dossier in a mathematically comprehensible manner is assumed to be an underestimate. This is due in particular to the fact that the pharmaceutical company's derivation incompletely takes into account patients without an indication of the stage in the lower limits in the target population by not including these patients in the percentage value (i.e. in the counter) for those in stage IV or those in stages I to III. In addition, the percentage of patients with dMMR/ MSI-H in the upper limit may be higher than the range of 3% - 5% estimated by the pharmaceutical company. In addition to data from Germany, which show a percentage value of 9.7% and were already taken into account in an earlier resolution[2], but are subject to methodological limitations, this is supported by data from a retrospective database analysis

[2] 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 Pembrolizumab (new therapeutic indication: dMMR or MSI-H colorectal cancer, after fluoropyrimidine-based combination therapy) from 19 January 2023; BAnz AT 23.03.2023 B3

of the US National Cancer Database, which the pharmaceutical company stated in the dossier and describe a percentage of 7.3%.

Overall, the number of patients determined by IQWiG is subject to uncertainty, which is reflected in the correspondingly large range. In the overall analysis, the G-BA come to the conclusion that the uncertainty regarding the percentage of patients with dMMR/ MSI-H can be taken into account to a greater extent by estimating a correspondingly wide range of patients in the SHI target population.

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: 29 October 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, internal medicine and gastroenterology, and specialists participating in the Oncology Agreement experienced in the treatment of patients with colorectal cancer.

Before initiation of therapy with pembrolizumab, the presence of microsatellite instability-high (MSI-H) or mismatch repair deficiency (dMMR) should be confirmed by a validated test in a tumour sample.

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 based on the LAUER-TAXE® rate valid at the time of the oral hearing.

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.

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

Treatment period

Designation of the therapy	Treatment mode	Number of treatments/ patient/ year	Treatment duration/ treatment (days)	Treatment days/ patient/ year
Medicinal product to be assessed				
First year of treatment				
Initial treatment				
Nivolumab	1 x per 21-day cycle	4	1	4
Ipilimumab	1 x per 21-day cycle	4	1	4
Follow-up treatment				
Nivolumab	1 x per 14-day cycle	20	1	20
	or			
	1 x per 28-day cycle	10	1	10
Second year of treatment				
Nivolumab	1 x per 14-day cycle	26	1	26
	or			
	1 x per 28-day cycle	13	1	13
Appropriate comparator therapy				
First year of treatment and subsequent years				
Pembrolizumab	1 x per 21-day cycle	17.4	1	17.4
	or			
	1 x per 42-day cycle	8.7	1	8.7

Consumption:

For dosages depending on body weight (BW) or body surface area (BSA), the average body measurements from the official representative statistics "Microcensus 2021 – body measurements of the population" were applied (average body height: 1.72 m; average body weight: 77.7 kg).[3]

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					
First year of treatment					
Initial treatment					
Nivolumab	240 mg	240 mg	2 x 120 mg	4	8 x 120 mg
Ipilimumab	1 mg/kg BW	77.7 mg	2 x 50 mg	4	8 x 50 mg
Follow-up treatment					
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					
First year of treatment and subsequent years					
Pembrolizumab	200 mg	200 mg	2 x 100 mg	17.4	34.8 x 100 mg
	or				
	400 mg	400 mg	4 x 100 mg	8.7	34.8 x 100 mg

[3] Federal Health Reporting. Average body measurements of the population (2021, both sexes, from 15 years: https://www.gbe-bund.de/gbe/

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
Ipilimumab 50 mg	1 CIS	€ 3,489.23	€ 1.77	€ 195.98	€ 3,291.48
Appropriate comparator therapy					
Pembrolizumab 100 mg	2 CIS	€ 4,962.26	€ 1.77	€ 280.10	€ 4,680.39
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 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 unresectable or metastatic mismatch repair deficient or microsatellite instability-high colorectal cancer; first-line treatment

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

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 3 May 2023, 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 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 08 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 06 October 2025.

The oral hearing was held on 27 October 2025.

By letter dated 28 October 2025, the IQWiG was commissioned with a supplementary assessment of data submitted in the written statement procedure. The addendum prepared by IQWiG was submitted to the G-BA on 05 December 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	3 May 2023	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, commissioning of the IQWiG with the supplementary assessment of documents
Working group Section 35a	5 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