Gemeinsamer Bundesausschuss

# Justification

for the Resolution of the Federal Joint Committee (G-BA) on an Amendment of the Pharmaceuticals Directive:
Annex XII – Benefit Assessment of Medicinal Products with New Active Ingredients according to Section 35a SGB V
Nivolumab (reassessment after the deadline: urothelial carcinoma, PD-L1 expression ≥ 1%, adjuvant treatment)

From 4 June 2026

**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. requirements 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 decide on the benefit assessment within three months of its publication. The resolution is to be published on the internet and is part of the Pharmaceuticals Directive.

## 2. Key points of the resolution

The pharmaceutical company submitted a dossier for the early benefit assessment of the active ingredient nivolumab (Opdivo) to be assessed for the first time on 29 April 2022. For the resolution of 20 October 2022 adopted by the G-BA in this procedure, a time limit until 15 December 2025 was set for the patient population b) (adults with muscle invasive urothelial carcinoma with tumour cell PD-L1 expression ≥ 1%, who are at high risk of recurrence after undergoing complete resection, are ineligible for cisplatin-based therapy, or have already received neoadjuvant treatment; adjuvant treatment).

In accordance with Section 4, paragraph 3, number 5 of the Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV) in conjunction with Chapter 5, Section 8, paragraph 1, number 5 VerfO, the procedure for the benefit assessment of the medicinal product Opdivo recommences when the deadline has expired.

Pursuant to Section 4, paragraph 3, number 5 of the Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV) in conjunction with Chapter 5, Section 8, paragraph 1, number

5 Rules of Procedure (VerfO), the pharmaceutical company submitted the final dossier to the G-BA on 12 December 2025.

The G-BA commissioned the IQWiG to carry out the assessment of the dossier. The benefit assessment was published on 16 March 2026 on the G-BA website (www.g-ba.de), thus initiating the written statement procedure. In addition, an oral hearing was held.

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

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

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

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

OPDIVO as monotherapy is indicated for the adjuvant treatment of adults with muscle invasive urothelial carcinoma (MIUC) with tumour cell PD-L1 expression ≥ 1%, who are at high risk of recurrence after undergoing radical resection of MIUC.

**Therapeutic indication of the resolution (resolution of 04.06.2026):**

OPDIVO as monotherapy is indicated for the adjuvant treatment of adults with muscle invasive urothelial carcinoma (MIUC) with tumour cell PD-L1 expression ≥ 1%, who are at high risk of recurrence after undergoing radical resection of MIUC, are ineligible for cisplatin-based therapy, or have already received neoadjuvant chemotherapy with cisplatin.

[1] General Methods, version 8.0 from 19.12.2025. Institute for Quality and Efficiency in Health Care (IQWiG), Cologne.

### 2.1.2 Appropriate comparator therapy

The appropriate comparator therapy was determined as follows:

Adults with muscle invasive urothelial carcinoma with tumour cell PD-L1 expression ≥ 1%, who are at high risk of recurrence after undergoing complete resection, are ineligible for cisplatin-based therapy, or have already received neoadjuvant chemotherapy with cisplatin, adjuvant treatment

Appropriate comparator therapy for nivolumab as monotherapy:

- Monitoring wait-and-see approach

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

The appropriate comparator therapy must be an appropriate therapy in the therapeutic indication according to 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 for 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 for 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, medicinal products with the active ingredients cisplatin, doxorubicin, methotrexate and gemcitabine are approved for the present therapeutic indication.

On 2. In the present therapeutic indication, radiotherapy is basically considered as non-medicinal treatment.

On 3. In the present therapeutic indication, the resolution on the benefit assessment of medicinal products with new active ingredients according to Section 35a SGB V for nivolumab dated 20 October 2022 is available, in which the information on patient group b) "Adults with muscle invasive urothelial carcinoma with tumour cell PD-L1 expression ≥ 1%, who are at high risk of recurrence after undergoing complete resection, are ineligible for cisplatin-based therapy, or have already received neoadjuvant chemotherapy with cisplatin, adjuvant treatment" is replaced by the present resolution.

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

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

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

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

The guidelines derived from the research and synopsis of the evidence recommend cisplatin-based chemotherapy for the present treatment setting for patients who are at high risk of recurrence (≥ pT3 and/or pN+) after undergoing radical resection, regardless of the localisation of the urothelial carcinoma.

The guidelines limit these recommendations on adjuvant chemotherapy to patients who are eligible for cisplatin-based therapy.

The present resolution is based on the patient population that is ineligible for cisplatin-based therapy or has already received neoadjuvant chemotherapy with cisplatin.

The guidelines do not provide any recommendations on alternative adjuvant therapy for patients who are ineligible for cisplatin-based therapy.

The monitoring wait-and-see approach is determined as the appropriate comparator therapy since tumour after-care is considered for the patient population underlying the resolution.

The underlying patient group is heterogeneous, as it includes both patients who are ineligible for chemotherapy with cisplatin for medical reasons (e.g. due to a poor general condition or impaired renal function) as well as those who have already received neoadjuvant chemotherapy with cisplatin, thus not being eligible for renewed cisplatin therapy.

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

Any change to the appropriate comparator therapy requires a decision by the G-BA based on a prior review of the criteria set out in Chapter 5, Section 6, paragraph 3 VerfO.

### 2.1.3 Extent and probability of the additional benefit

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

Adults with muscle invasive urothelial carcinoma with tumour cell PD-L1 expression ≥ 1%, who are at high risk of recurrence after undergoing complete resection, are ineligible for cisplatin-based therapy, or have already received neoadjuvant chemotherapy with cisplatin; adjuvant treatment

Hint for a considerable additional benefit

Justification:

To demonstrate an additional benefit, the pharmaceutical company presented the results of the ongoing, double-blind, randomised, controlled phase III CA209-274 study, comparing nivolumab with the monitoring wait-and-see approach. The study has been conducted at 170 study sites across Europe, North and South America, Australia and Asia since March 2016.

Adult patients with muscle invasive urothelial carcinoma (MIUC) originating in the bladder or upper urinary tract at high risk of recurrence after radical resection of the MIUC were enrolled in the study. Prerequisite for the enrolment in the study was R0 resection ≤ 120 days prior to randomisation. Patients who had received neoadjuvant cisplatin chemotherapy had to have the following tumour-node-metastasis (TNM) status: ypT2-pT4a or ypN+; patients who had not received neoadjuvant cisplatin chemotherapy and who were ineligible for adjuvant cisplatin chemotherapy or refused it had to have the following TNM status: pT3-pT4a or pN+. It is assumed that patients with the TNM status described were at a high risk of recurrence.

The enrolled patients had to have an ECOG-PS of 0 or 1 at the time of enrolment in the study. Patients with an ECOG-PS of 2 could be enrolled, provided that they had not received neoadjuvant cisplatin chemotherapy and were ineligible for adjuvant cisplatin chemotherapy. In addition, they had to have a disease-free status, which had to be documented by a full physical examination and imaging examinations carried out within 4 weeks prior to randomisation.

Determination of the PD-L1 expression in the tumour tissue was a prerequisite for enrolment in the study. The determination of the PD-L1 expression on the tumour cells had to be carried out in a central laboratory and was performed using the PD-L1 IHC 28-8-pharmDx assay. However, patients were enrolled in the study regardless of PD-L1 expression.

Randomisation was stratified according to pathological lymph node status (N+ vs N0/x with < 10 resected lymph nodes vs N0 with ≥ 10 resected lymph nodes), PD-L1 tumour expression (≥ 1% vs < 1%, undetermined) and the use of cisplatin as neoadjuvant chemotherapy (yes vs no).

In the control arm, patients were not actively treated for their bladder cancer during the adjuvant treatment phase. The investigations carried out in the CA209-274 study do not fully reflect the guideline recommendations. Nevertheless, all patients in the CA209-274 study were examined closely and selectively to assess their health status and any recurrences, meaning that the investigation regimen is regarded overall as a sufficient approximation of the appropriate comparator therapy of the monitoring wait-and-see approach.

In addition to the primary endpoints of disease-free survival (DFS), endpoints in the categories of mortality (overall survival), morbidity, health-related quality of life and side effects were also assessed.

The results of the 3rd data cut-off from 06.01.2025 were used for the present benefit assessment.

A total of 709 patients were enrolled in the CA209-274 study and randomised in a 1:1 ratio to the intervention arm with nivolumab (N = 353) or the control arm (N = 356). The present benefit assessment only covers the sub-population with tumour cell PD-L1 expression ≥ 1% – 140 patients in the intervention arm and 142 patients in the control arm. Furthermore, this benefit assessment only covers those patients who are ineligible for cisplatin-based therapy. In this regard, relevant uncertainties are described below.

<u>Uncertainties in the CA209-274 study regarding the relevant sub-population that is ineligible for cisplatin-based therapy</u>

Current guidelines recommend either neoadjuvant or adjuvant cisplatin-based chemotherapy for muscle invasive urinary bladder cancer. The therapy concept should be determined multidisciplinarily before the start of treatment. In the CA209-274 study, about 22% of the enrolled patients were not eligible for an adjuvant cisplatin-based chemotherapy, and 42% of the patients had already received a neoadjuvant cisplatin-based chemotherapy, which is why an adjuvant cisplatin-based chemotherapy was not indicated.

The study protocol of the CA209-274 study does not include the recommendations from the guidelines on neoadjuvant or adjuvant cisplatin-based chemotherapy. Also in the patient consent form, the survival benefit of adjuvant cisplatin-based chemotherapy is not presented in the section on alternative treatment. Consequently, patients may not have been fully informed about the advantages and disadvantages of the treatment options available to them. Any refusal of cisplatin-based chemotherapy despite medical suitability had to be carefully documented. This shows that the relevant sub-population for the present benefit assessment also includes patients who refused an adjuvant cisplatin-based chemotherapy despite medical suitability. 36% of patients in the intervention arm and 32% of them in the control arm refused cisplatin-based chemotherapy despite suitability. Thus, there are significant uncertainties as to whether patients were fully informed about the advantages and disadvantages of the treatment options available to them and whether a relevant percentage of patients would not have been suitable for adjuvant cisplatin-based therapy. In addition, there is uncertainty as to whether the relatively high percentage of patients in the study who refuse cisplatin-based chemotherapy (36% in the nivolumab arm vs 32% in the placebo arm) reflects the reality of care.

On the implementation of the time limit requirements

According to the justification for the resolution of 20 October 2022, the limitation was based on the fact that further relevant clinical data for the benefit assessment were expected from the CA209-274 study.

For the benefit reassessment after expiry of the deadline, the results on all patient-relevant endpoints from the CA209-274 study for patient group b) must be presented in the dossier at the final data cut-off.

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

Extent and probability of the additional benefit

Mortality

*Overall survival*

In the CA209-274 study, overall survival is operationalised as the time between randomisation and death from any cause.

For the endpoint of overall survival, there is a statistically significant difference between the treatment groups in favour of nivolumab. The extent of the prolongation achieved in overall survival is assessed as a significant improvement.

The data on subsequent therapies in the CA209-274 study show that no patient received enfortumab vedotin in combination with pembrolizumab. Enfortumab vedotin in combination with pembrolizumab represents a highly effective treatment option and the current therapy standard for patients in first-line therapy of unresectable or metastatic urothelial carcinoma. In view of the fact that the corresponding marketing authorisation of enfortumab vedotin in combination with pembrolizumab was granted only after the 1st data cut-off of the CA209-274 study, it is basically understandable that enfortumab vedotin in combination with pembrolizumab was not used as subsequent therapy. Nevertheless, it should be noted that the subsequent therapies in the CA209-274 study only inadequately reflect the current standard of care.

Morbidity

*Failure of the curative therapeutic approach (event rate and disease-free survival (DFS))*

In the present therapeutic indication, curative therapy is generally possible and is the treatment objective. Recurrence following an R0 resection means that the curative therapeutic approach has failed in this line of therapy. Based on a curative therapeutic approach, the failure of the potential cure is basically patient-relevant.

In the CA209-274 study, the failure of the curative therapeutic approach was not directly assessed as an endpoint. For the present assessment, the events collected as part of the DFS composite endpoint in the CA209-274 study are considered as an approximation of the operationalisation of the endpoint. The percentage of patients with an event (event rate) as well as the time to event occurrence (DFS) is used for the assessment.

In accordance with the data in the statistical analysis plan, the DFS endpoint was defined as the time from randomisation to the first occurrence of any of the following events:

- local recurrence within the efferent urinary tract
- local recurrence outside the efferent urinary tract
- Distant recurrence
- Death of any cause (without previous recurrence)

Given the present data basis, the events collected for the DFS endpoint from the CA209-274 study are suitable for illustrating the failure of the curative therapeutic approach.

In terms of event rate, there was a statistically significant difference in favour of nivolumab, which showed a significant advantage in preventing the failure of the curative therapeutic approach compared with the monitoring wait-and-see approach. Furthermore, the time-to-event analysis, which also takes into account the time to event occurrence, showed a significant difference to the advantage of nivolumab in terms of disease-free survival (DFS).

The subgroup analyses of the event rate suggest an effect modification for the "sex" characteristic. There was a statistically significant difference to the advantage of nivolumab in male patients. In contrast, there was no statistically significant difference between the treatment groups in female patients. The subgroup analyses of DFS, by contrast, show no effect modification for the "sex" characteristic. The subgroup result for the event rate is considered a relevant result of the present benefit assessment. This is however considered inadequate to derive separate statements on the additional benefit in the overall assessment.

*Symptomatology (assessed using EORTC QLQ-C30)*

Disease symptomatology was surveyed in the CA209-274 study using the EORTC QLQ-C30 questionnaire. Presented responder analyses of the time to 1st deterioration by ≥ 10 points are used for the present benefit assessment.

For the symptomatology surveyed using the EORTC QLQ-C30, there was no statistically significant difference between the treatment arms for each of the endpoints "fatigue", "nausea and vomiting", "pain", "dyspnoea", "insomnia", "appetite loss", "constipation" and "diarrhoea".

*Health status (assessed using EQ-5D VAS)*

In terms of health status, assessed using the EQ-5D visual analogue scale, there was a statistically significant difference to the advantage of nivolumab compared with the monitoring wait-and-see approach.

In summary, in the endpoint category of morbidity, there was a significant advantage of nivolumab in terms of preventing the failure of the curative therapeutic approach, which is associated with a significant difference in disease-free survival (DFS) to the advantage of nivolumab. There was also an advantage in terms of health status. There was no significant difference between the treatment arms in the endpoints on symptomatology.

Quality of life

Health-related quality of life was assessed in the CA209-274 study using the EORTC QLQ-C30 questionnaire. Presented responder analyses of the time to 1st deterioration by ≥ 10 points are used for the present benefit assessment.

For the health-related quality of life surveyed using the EORTC QLQ-C30, there was no statistically significant difference between the treatment arms for each of the endpoints "global health status", "physical functioning", "role functioning", "cognitive functioning", "emotional functioning" and "social functioning".

Overall, neither an advantage nor a disadvantage was thus identified for the endpoint category of health-related quality of life.

Side effects

*Total adverse events (AEs)*

In the CA209-274 study, almost all patients in the control and intervention arms experienced an AE. The results were only presented additionally.

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

*Therapy discontinuation due to AEs*

In terms of therapy discontinuation due to AEs, there was a statistically significant difference between the treatment arms to the disadvantage of nivolumab compared to the monitoring wait-and-see approach.

*Specific AEs*

*Immune-mediated severe AEs (CTCAE grade ≥ 3) and immune-mediated serious AEs (SAEs) [subject to the addendum]*

For the endpoints of immune-mediated severe AEs and immune-mediated serious AEs (SAEs), there were statistically significant differences between the treatment arms to the disadvantage of nivolumab compared to the monitoring wait-and-see approach.

*Skin and subcutaneous tissue disorders (AEs), asthenia (AE), elevated lipase (severe AE) as well as respiratory, thoracic and mediastinal disorders (SAEs)*

For the endpoints of skin and subcutaneous tissue disorders (AEs), asthenia (AE), elevated lipase (severe AE) as well as respiratory, thoracic and mediastinal disorders (SAEs), there was a statistically significant difference in each case to the disadvantage of nivolumab compared to the monitoring wait-and-see approach.

*Gastrointestinal disorders (severe AEs) as well as infections and infestations (SAEs)*

For the endpoints of gastrointestinal disorders (severe AEs) as well as infections and infestations (SAEs), there was a statistically significant difference in each case to the advantage of nivolumab compared to the monitoring wait-and-see approach.

The overall analysis of the results on side effects showed no statistically significant differences between the treatment arms in terms of SAEs and severe AEs. In terms of therapy discontinuation due to AEs, a disadvantage of nivolumab was observed. In detail, there were advantages and disadvantages in terms of some specific AEs. Overall, a disadvantage of nivolumab compared to the monitoring wait-and-see approach can be identified due to the increase in therapy discontinuation due to AEs.

Overall assessment

Results on mortality, morbidity, health-related quality of life and side effects from the ongoing, double-blind, randomised, controlled phase III CA209-274 study are available for the assessment of the additional benefit of nivolumab as monotherapy for the adjuvant treatment of adults with muscle invasive urothelial carcinoma (MIUC) with tumour cell PD-L1 expression ≥ 1%, who are at high risk of recurrence after undergoing radical resection of MIUC, are ineligible for cisplatin-based therapy, or have already received neoadjuvant chemotherapy with cisplatin.

For the endpoint of overall survival, there was a statistically significant difference to the advantage of nivolumab compared to the monitoring wait-and-see approach. The extent of the prolongation achieved in overall survival is assessed as a significant improvement.

The data on subsequent therapies in the CA209-274 study show that no patient received treatment with enfortumab vedotin in combination with pembrolizumab, which represents a highly effective treatment option and the current therapy standard for patients in first-line therapy for unresectable or metastatic urothelial carcinoma. In view of the fact that the corresponding marketing authorisation of enfortumab vedotin in combination with pembrolizumab was granted only after the 1st data cut-off of the CA209-274 study, it is basically understandable that enfortumab vedotin in combination with pembrolizumab was not used as subsequent therapy. Nevertheless, it should be noted that the subsequent therapies in the CA209-274 study only inadequately reflect the current standard of care.

In the endpoint category of morbidity, the failure of the curative therapeutic approach - represented as the event rate and disease-free survival (DFS) - as well as disease symptomatology (EORTC QLQ-C30) and health status (EQ-5D VAS) were assessed. In summary, in the endpoint category of morbidity, there was a significant advantage of nivolumab in terms of preventing the failure of the curative therapeutic approach, which is associated with a significant difference in disease-free survival (DFS) to the advantage of nivolumab. There was also an advantage in terms of health status. There was no significant difference between the treatment arms in the endpoints on symptomatology.

In terms of health-related quality of life assessed using the EORTC QLQ-C30, neither an advantage nor a disadvantage of nivolumab over the monitoring wait-and-see approach was identified.

The overall analysis of the results on side effects showed no statistically significant differences between the treatment arms in terms of SAEs and severe AEs. In terms of therapy discontinuation due to AEs, a disadvantage of nivolumab was observed. In detail, there were advantages and disadvantages in terms of some specific AEs. Overall, a disadvantage of nivolumab compared to the monitoring wait-and-see approach can be identified due to the increase in therapy discontinuation due to AEs.

In the overall analysis, the significant advantages in terms of overall survival, prevention of the failure of the curative therapeutic approach and improvement in the health status are offset only by a single disadvantage due to the increase in therapy discontinuation due to AEs.

Overall, the G-BA therefore conclude the presence of a considerable additional benefit of nivolumab as monotherapy for the adjuvant treatment of adults with muscle invasive urothelial carcinoma (MIUC) with tumour cell PD-L1 expression ≥ 1%, who are at high risk of recurrence after undergoing radical resection of MIUC, are ineligible for cisplatin-based therapy, or have already received neoadjuvant chemotherapy with cisplatin.

Reliability of data (probability of additional benefit)

The present benefit assessment is based on the results of the randomised, double-blind, multicentre, controlled CA209-274 study.

The cross-endpoint risk of bias of the CA209-274 study is estimated to be low.

The risk of bias is classified as low in the endpoints of overall survival, the results for the endpoint of failure of the curative therapeutic approach and discontinuation due to AEs.

There is an increased risk of bias in the results on the endpoints of symptomatology (EORTC QLQ-C30), health-related quality of life (EORTC QLQ-C30) as well as the endpoints of SAEs, severe AEs (overall rates and specific AEs) and immune-mediated SAEs and immune-mediated severe AEs.

A high risk of bias in the results on the endpoint of health status is assumed, as an assignment of the follow-up surveys to the concurring clinic visits is missing, which makes it difficult to estimate the return rates.

There are significant uncertainties as to the extent to which a relevant percentage of the patients enrolled in the study would have been suitable for an adjuvant cisplatin-based therapy, thus the study results being transferable to the reality of care.

In summary, the reliability of data for the additional benefit identified is classified in the "hint" category.

### 2.1.4 Summary of the assessment

The present assessment is the new benefit assessment of the active ingredient nivolumab due to the expiry of the limitation of the resolution on 20 October 2022.

The assessment refers exclusively to the following patient population: Adults with muscle invasive urothelial carcinoma with tumour cell PD-L1 expression ≥ 1%, who are at high risk of recurrence after undergoing complete resection, are ineligible for cisplatin-based therapy, or have already received neoadjuvant chemotherapy with cisplatin, adjuvant treatment.

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

The pharmaceutical company presented results from the ongoing double-blind phase III CA209-274 RCT to demonstrate the additional benefit.

For the endpoint of overall survival, there is a statistically significant difference between the treatment groups in favour of nivolumab. The extent of the prolongation achieved in overall survival is assessed as a significant improvement.
The data on subsequent therapies in the CA209-274 study show that no patient received treatment with enfortumab vedotin in combination with pembrolizumab, which represents a highly effective treatment option and the current therapy standard for patients in first-line therapy for unresectable or metastatic urothelial carcinoma. In view of the fact that the corresponding marketing authorisation of enfortumab vedotin in combination with pembrolizumab was granted only after the 1st data cut-off of the CA209-274 study, it is basically understandable that enfortumab vedotin in combination with pembrolizumab was

not used as subsequent therapy. Nevertheless, it should be noted that the subsequent therapies in the CA209-274 study only inadequately reflect the current standard of care.

In the endpoint category of morbidity, the failure of the curative therapeutic approach - represented as the event rate and disease-free survival (DFS) - as well as disease symptomatology (EORTC QLQ-C30) and health status (EQ-5D VAS) were assessed. In summary, in the endpoint category of morbidity, there was a significant advantage of nivolumab in terms of preventing the failure of the curative therapeutic approach, which is associated with a significant difference in disease-free survival (DFS) to the advantage of nivolumab. There was also an advantage in terms of health status. There was no significant difference between the treatment arms in the endpoints on symptomatology.

In terms of health-related quality of life assessed using the EORTC QLQ-C30, neither an advantage nor a disadvantage of nivolumab over the monitoring wait-and-see approach was identified.

The overall analysis of the results on side effects showed no statistically significant differences between the treatment arms in terms of SAEs and severe AEs. In terms of therapy discontinuation due to AEs, a disadvantage of nivolumab was observed. In detail, there were advantages and disadvantages in terms of some specific AEs. Overall, a disadvantage of nivolumab compared to the monitoring wait-and-see approach can be identified due to the increase in therapy discontinuation due to AEs.

In the overall analysis, the significant advantages in terms of overall survival, prevention of the failure of the curative therapeutic approach and improvement in the health status are offset only by a single disadvantage due to the increase in therapy discontinuation due to AEs.

Overall, the G-BA therefore conclude the presence of a considerable additional benefit of nivolumab as monotherapy for the adjuvant treatment of adults with muscle invasive urothelial carcinoma (MIUC) with tumour cell PD-L1 expression ≥ 1%, who are at high risk of recurrence after undergoing radical resection of MIUC, are ineligible for cisplatin-based therapy, or have already received neoadjuvant chemotherapy with cisplatin.

The reliability of data of the additional benefit identified is classified in the "hint" category.

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

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

The G-BA base their resolution on the information provided by the pharmaceutical company. The pharmaceutical company submitted data from more recent studies than those cited in the resolution of 20 October 2022. These data are considered to be an improvement of the information basis overall.

## 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: 17 March 2026):

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

Therapy with nivolumab should only be initiated and monitored by specialists in internal medicine, haematology, and oncology, who are experienced in the treatment of patients with urothelial carcinoma as well as specialists in urology, and other doctors from other specialist groups participating in the Oncology Agreement.

In accordance with the regulatory authority's requirements regarding additional risk minimisation measures, the pharmaceutical company must provide healthcare professionals and patients with a patient card. The patient card contains, in particular, instructions on the management of immune-mediated side effects potentially occurring with nivolumab as well as on infusion-related reactions. The prescribing doctors must discuss the risks of therapy with nivolumab with the patients.

## 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 April 2026).

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 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.

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

The annual treatment costs shown refer to the first year of treatment.

Based on the requirements in the product information, the treatment duration for adjuvant treatment with nivolumab is limited to 12 months, but may be shorter on a patient-individual basis. Against this background, therefore, only the completed cycles in the treatment year are considered for nivolumab.

Treatment period:

Adults with muscle invasive urothelial carcinoma with tumour cell PD-L1 expression ≥ 1%, who are at high risk of recurrence after undergoing complete resection, are ineligible for cisplatin-based therapy, or have already received neoadjuvant chemotherapy with cisplatin; adjuvant treatment

| 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 | 1 x per 14-day cycle | 26.0 | 1 | 26.0 |
| | or | | | |

| Designation of the therapy | Treatment mode | Number of treatments/ patient/ year | Treatment duration/ treatment (days) | Treatment days/ patient/ year |
|---|---|---|---|---|
| | 1 x per 28-day cycle | 13.0 | 1 | 13.0 |
| Appropriate comparator therapy | | | | |
| Monitoring wait-and-see approach | Not calculable | | | |

Consumption:

Adults with muscle invasive urothelial carcinoma with tumour cell PD-L1 expression ≥ 1%, who are at high risk of recurrence after undergoing complete resection, are ineligible for cisplatin-based therapy, or have already received neoadjuvant chemotherapy with cisplatin; adjuvant treatment

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

The (daily) doses recommended in the product information were used as the calculation basis.

For dosages depending on body weight (BW) or body surface area (BSA), the average body measurements from the official representative statistics "Microcensus 2017 – body measurements of the population" were applied (average body height: 1.72 m; average body weight: 77.7 kg). This results in a body surface area of 1.91 m² (calculated according to Du Bois 1916)[2].

As it is not always possible to achieve the exact target dose per day with the commercially available dosage strengths, in these cases rounding up or down to the next higher or lower available dose that can be achieved with the commercially available dosage strengths as well as the scalability of the respective dosage form.

The maximum duration of adjuvant treatment with nivolumab is 12 months.

| 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: | | | | | |
| | 600 mg | 600 mg | 1 x 600 mg | 26.0 | 26.0 x 600 mg |
| | or | | | | |

[2] 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 |
|---|---|---|---|---|---|
| | 1,200 mg | 1,200 mg | 2 x 600 mg | 13.0 | 26.0 x 600 mg |
| Appropriate comparator therapy | | | | | |
| Monitoring wait-and-see approach | Not calculable | | | | |

Costs:

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

**Costs of the medicinal products:**

Adults with muscle invasive urothelial carcinoma with tumour cell PD-L1 expression ≥ 1%, who are at high risk of recurrence after undergoing complete resection, are ineligible for cisplatin-based therapy, or have already received neoadjuvant chemotherapy with cisplatin, adjuvant treatment

| 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 600 mg | 1 SFI | € 3,021.74 | € 1.77 | € 169.28 | € 2,850.69 |
| Appropriate comparator therapy | | | | | |
| Monitoring wait-and-see approach | Not calculable | | | | |
| Abbreviations: CIS = concentrate for the preparation of an infusion solution | | | | | |

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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 01.10.2009 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-apply 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 data from the product 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 statutory 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 muscle invasive urothelial carcinoma with tumour cell PD-L1 expression ≥ 1%, who are at high risk of recurrence after undergoing complete resection, are ineligible for cisplatin-based therapy, or have already received neoadjuvant chemotherapy with cisplatin; adjuvant treatment

No medicinal product with new active ingredients for use in combination therapy in compliance with the requirements of Section 35a, paragraph 3, sentence 4 SGB V.

Reference:
Product information for nivolumab (Opdivo); Opdivo 600 mg solution for injection; last revised: November 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 8 April 2025, the Subcommittee on Medicinal Products determined the appropriate comparator therapy.

On 11 December 2025, the pharmaceutical company submitted a dossier for the benefit assessment of nivolumab to the G-BA in due time in accordance with Chapter 5, Section 8, paragraph 1, number 5 VerfO.

By letter dated 15 December 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 March 2026, and the written statement procedure was initiated with publication on the G-BA website on 16 March 2026. The deadline for submitting written statements was 7 April 2026.

The oral hearing was held on 27 April 2026.

By letter dated 29 April 2026, the IQWiG was commissioned with a supplementary assessment of data submitted in the written statement procedure. The addendum prepared by the IQWiG was submitted to the G-BA on 13 May 2026.

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 were discussed at the Subcommittee's session on 26 May 2026, and deliberation of the draft resolution was concluded.

At their session on 4 June 2026, the plenum adopted a resolution to amend the Pharmaceuticals Directive.

**Chronological course of consultation**

| Session | Date | Subject of consultation |
|---|---|---|
| Subcommittee on Medicinal Products | 8 April 2025 | Determination of the appropriate comparator therapy |
| Working group Section 35a | 15 April 2026 | Information on written statements received; preparation of the oral hearing |
| Subcommittee on Medicinal Products | 27 April 2026 | Conduct of the oral hearing, commissioning of the IQWiG with the supplementary assessment of documents |
| Working group Section 35a | 6 May 2026<br>20 May 2026 | Consultation on the dossier assessment by the IQWiG and evaluation of the written statement procedure |
| Subcommittee on Medicinal Products | 26 May 2026 | Concluding discussion of the draft resolution |
| Plenum | 4 June 2026 | Adoption of the resolution on the amendment of the Pharmaceuticals Directive |

Berlin, 4 June 2026

Federal Joint Committee
in accordance with Section 91 SGB V
The Chair

Prof. Hecken