Gemeinsamer Bundesausschuss

Justification

of 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: urothelial carcinoma, PD-L1 expression ≥ 1%, adjuvant treatment)

of 20 October 2022

Contents

1. Legal basis

According to Section 35a paragraph 1 German Social Code, Book Five (SGB V), the Federal Joint Committee (G-BA) assesses the benefit of 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 trials the pharmaceutical company has 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 decides 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 1 April 2022, Opdivo received marketing authorisation for a new therapeutic indication to be classified as a major type 2 variation as defined according to Annex 2 number 2 letter a to Regulation (EC) No. 1234/2008 of the Commission of 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 29 April 2022, i.e. at the latest within four weeks after informing the pharmaceutical company about the approval of a new therapeutic indication, the pharmaceutical company has submitted a dossier in due time in accordance with Section 4, paragraph 3, number 2 Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV) in conjunction with Chapter 5, Section 8, paragraph 1, number 2 of the Rules of Procedure (VerfO) of the G-BA on

the active ingredient nivolumab with the new therapeutic indication (monotherapy for adjunctive treatment of muscle invasive urothelial carcinoma (MIUC) with tumour cell PD-L1 expression ≥ 1% in adults at high risk of recurrence after radical resection of MIUC).

The G-BA commissioned the IQWiG to carry out the assessment of the dossier. The benefit assessment was published on the website of the G-BA (www.g-ba.de) on 1 August 2022, 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 has 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 has come to 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 20.10.2022):

see the approved therapeutic indication

2.1.2 Appropriate comparator therapy

The appropriate comparator therapy was determined as follows:

a) Adults with muscle invasive urothelial carcinoma with tumour cell PD-L1 expression ≥ 1%, who are at high risk of recurrence after undergoing complete resection and are eligible for cisplatin-containing therapy; adjuvant treatment

Appropriate comparator therapy for nivolumab:

- Cisplatin + gemcitabine

or

[1] General Methods, version 6.1 from 24.01.2022. Institute for Quality and Efficiency in Health Care (IQWiG), Cologne.

– Cisplatin + methotrexate

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 and are unsuitable for cisplatin-containing therapy, or have already received neoadjuvant treatment; adjuvant treatment

Appropriate comparator therapy for nivolumab:

– Monitoring wait-and-see approach

Criteria according to Chapter 5, Section 6 of the Rules of Procedure of the G-BA:

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

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

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

Justification based on the criteria set out in Chapter 5, Section 6, paragraph 3 VerfO:

On 1. In addition to nivolumab, medicinal products with the active ingredients cisplatin, doxorubicin, methotrexate and gemcitabine are approved in the present therapeutic indication.

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

On 3. No corresponding resolutions or assessments of the G-BA are available.

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.

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 health care provision.

In current guidelines as well as in the statements of the scientific-medical societies, cisplatin-containing chemotherapy is recommended following radical resection, irrespective of the localisation of the urothelial carcinoma in the case of a high risk of recurrence (≥ pT3 and/or pN+). This recommendation applies to patients who are eligible for cisplatin-containing therapy and did not receive cisplatin-containing therapy in the neoadjuvant treatment setting. This recommendation is based on an advantage of overall survival over radical resection carried out alone. In the statement of the scientific-medical societies, the combination of cisplatin + gemcitabine is used. The recommendation of the S3 guideline of the Association of the Scientific Medical Societies (ASMS), which refers not only to the combination of cisplatin + gemcitabine, but generally to cisplatin-containing combination therapy, is based on a review in which different treatment regimens of adjuvant therapy were compared with resection alone. In addition to the combination therapy cisplatin + gemcitabine, other combinations showed a positive effect compared to resection alone, including the combination therapy cisplatin + methotrexate, which is also eligible according to the authorisation status. Against this background, the combination therapy cisplatin and gemcitabine and the combination therapy cisplatin and methotrexate are determined to be equally appropriate comparator therapies for this patient population.

The current guidelines restrict the recommendations for adjuvant chemotherapy to patients who are suitable for cisplatin-containing therapy (patient group a). For patients who are ineligible for cisplatin-containing therapy (patient group b), there are no recommendations for alternative adjuvant treatment in the current guidelines. For this patient population, a recommendation for tumour follow-up and therapy in the event of a recurrence can be found in the statements of the scientific-medical societies. Accordingly, the monitoring wait-and-see approach is determined as the appropriate comparator therapy for this patient population.

Patient group b) includes patients for whom chemotherapy with cisplatin is not an option for medical reasons (e.g., due to a reduced general condition or impaired renal function) or who have already received neoadjuvant chemotherapy with cisplatin and for this reason are ineligible for renewed cisplatin therapy. Thus, a heterogeneous patient population is present.

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

Editorial change to patient group b)

In the original version, the patient group b) was worded 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 and are unsuitable for cisplatin-containing therapy, for adjuvant treatment“.

The following wording is added to the present resolution: "or have already received neoadjuvant treatment".

This does not change the content and does not affect the present assessment.

2.1.3 Extent and probability of the additional benefit

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

a) Adults with muscle invasive urothelial carcinoma with tumour cell PD-L1 expression ≥ 1%, who are at high risk of recurrence after undergoing complete resection and are eligible for cisplatin-containing therapy; adjuvant treatment

An additional benefit is not proven.

Justification:

For the adjuvant treatment of muscle invasive urothelial carcinoma with tumour cell PD-L1 expression ≥ 1% in adults, who are at high risk of recurrence after undergoing radical resection and are suitable for cisplatin-containing therapy, the pharmaceutical company does not submit any data for the assessment of additional benefit. Therefore, an additional benefit is not proven.

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 and are unsuitable for cisplatin-containing therapy, or have already received neoadjuvant treatment; adjuvant treatment

Hint for a non-quantifiable additional benefit

Justification:

For the evidence of additional benefit of nivolumab for the adjuvant treatment of muscle invasive urothelial carcinoma with tumour cell PD-L1 expression ≥ 1% in adults, who are at high risk of recurrence after undergoing radical resection, the pharmaceutical company has submitted the results of the CA209-274 study (CheckMate 274).

The CheckMate 274 study is a multicentre, parallel, double-blind, randomised, controlled phase III study that compares nivolumab to placebo and has been ongoing since March 2016.

The placebo comparison carried out corresponds to an implementation of the appropriate comparator therapy consisting of the monitoring wait-and-see approach.

The study is being conducted in 170 study sites in Asia, Australia, Europe, North and South America.

Adult patients with muscle invasive urothelial carcinoma originating in the bladder or upper urinary tract (renal pelvis or ureter) at a high risk of recurrence after radical resection of the muscle invasive urothelial carcinoma were enrolled in the study. Prerequisite for the enrolment in the study was R0 resection ≤ 120 days prior to randomisation. Patients who received neoadjuvant cisplatin-containing chemotherapy had to have the following tumour lymph node metastasis (TNM) status: ypT2-pT4a or ypN+. Patients who did not receive neoadjuvant cisplatin-containing chemotherapy and who were unsuitable for adjuvant cisplatin-containing chemotherapy or refused the same had to have the following status: pT3-pT4a or pN+. It is assumed that patients with the TNM statuses described were at a high risk of recurrence. Any refusal of cisplatin-containing chemotherapy (despite medical suitability) had to be carefully documented. The patients had to have also a good general condition, with an Eastern Cooperative Oncology Group Performance Status (ECOG-PS) of 0 or 1 (nivolumab arm 97%, placebo arm 97%), and a disease-free status. Patients with an ECOG-PS of 2 could be enrolled in the study if they did not receive neoadjuvant cisplatin-containing chemotherapy and were unsuitable for adjuvant cisplatin chemotherapy (nivolumab arm 2%, placebo arm 3%).

The total of 709 patients enrolled in the study, stratified by pathological lymph node status (N+ vs N0/x with < 10 lymph nodes removed vs N0 with ≥ 10 lymph nodes removed), PD-L1 tumour expression (≥ 1% vs < 1%, indeterminate) and use of cisplatin as neoadjuvant chemotherapy (yes vs no), were randomised 1: 1 to the nivolumab arm (N = 353) or to the placebo arm (N = 356).

Treatment with the study medication continued until recurrence, unacceptable toxicity or withdrawal of consent, but for a maximum of 1 year.

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

For the present benefit assessment, the data cut-off from February 2021 is used for the endpoints of recurrence rate and disease-free survival, and the prespecified 1st data cut-off from August 2020 was used for the other endpoints of the categories morbidity, health-related quality of life and adverse events (AEs).

Relevant sub-population of the CheckMate 274 study

For the benefit assessment, the pharmaceutical company uses a sub-population of the CheckMate 274 study. These are patients with tumour cell PD-L1 expression ≥ 1% who are unsuitable for cisplatin-containing therapy or refused the same (nivolumab arm N = 140; placebo arm N = 142).

According to current guidelines, either neoadjuvant or adjuvant cisplatin-containing chemotherapy is recommended for muscle invasive urinary bladder cancer. The therapy concept should be determined in a multidisciplinary manner before the start of treatment. However, these recommendations are not included in the study protocol of the CheckMate 274 study. Also in the patient consent form, the survival benefit of adjuvant cisplatin-containing chemotherapy is not presented in the section on alternative treatment. 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-containing

therapy. In addition, there is uncertainty as to whether the relatively high percentage of patients in the study who refuse cisplatin-containing chemotherapy (36% in the nivolumab arm vs 32% in the placebo arm) reflects the reality of care.

Extent and probability of the additional benefit

Mortality

The pharmaceutical company does not provide any data on overall survival.

The pharmaceutical company justifies its action with the fact that the first interim analysis (2nd data cut-off from February 2021) for overall survival was linked to the interim analysis for the primary endpoint of disease-free survival (DFS) and was dependent on achieving the planned number of DFS events. As the predefined significance level was not reached for the first interim analysis, the data on overall survival were not unblinded for the pharmaceutical company.

According to IQWiG's statements, the failure to unblind the overall survival data is not fully understandable, as at least for the 1st data cut-off (August 2020), information on the number of deceased patients unblinded per treatment arm is available from the evaluations on side effects in the study report. In addition, "death from any cause (without prior recurrence)" is also included as an event in the evaluations of disease-free survival, for which unblinded data per treatment arm are available.

The approach on the part of the pharmaceutical company is therefore viewed critically. Data on overall survival are considered particularly relevant in the assessment of the additional benefit of nivolumab in the treatment settings presented here. However, an assessment of the endpoint is not possible based on the pharmaceutical company's approach.

Morbidity

Recurrences

The endpoint of recurrence, operationalised as recurrence rate, describes the percentage of patients with a recurrence event or death at the corresponding data cut-off (event rate). In the endpoint of disease-free survival (DFS), the time to the event (recurrence or death) is also considered (time-to-event analysis).

The combined endpoint recurrences include the following individual components:

- Local recurrence in the urothelial tract
- Local recurrence outside the urothelial tract
- Remote metastases
- Death of any cause (without previous recurrence)

Recurrences (event rate)

For the recurrence rate, there is a statistically significant difference in the benefit of nivolumab compared to the monitoring wait-and-see approach. The endpoint recurrence rate includes the same individual components and thus the same recurrence events and deaths before recurrence events as other components like the endpoint DFS.

Disease-free survival (DFS)

The time-to-event analysis shows a statistically significant effect in favour of nivolumab compared to the monitoring wait-and-see approach.

The overall assessment of the results on recurrences show a statistically significant advantage of nivolumab compared to the monitoring wait-and-see approach, the extent of which is assessed as a clinical improvement.

Symptomatology (assessed using EORTC QLQ-C30)

The pharmaceutical company submits time-to-event analysis for the symptomatology, collected by means of the EORTC QLQ-C30, for the "time to permanent deterioration". These are defined by the pharmaceutical company as a decrease in the corresponding score by at least the response criterion without subsequent improvement above the response criterion in one of the following assessments.

The durations of observation for the endpoints of symptomatology are systematically shorter than the median overall survival. Moreover, they differ significantly between the treatment arms. This results in uncertainties in the interpretation of the evaluation of the "time to permanent deterioration". Furthermore, sustained deterioration across all follow-up values is potentially more difficult to achieve in the longer observed intervention arm. The time-to-event analysis of the symptom scales of the EORTC QLQ-C30 submitted by the pharmaceutical company in the dossier are therefore not usable.

As part of the written statement procedure, responder analyses on the "time to first deterioration" by 10 points compared to the baseline were submitted by the pharmaceutical company. The responder analyses on "time to first deterioration" are used as a basis for the assessment. These do not show any statistically significant differences.

Thus, for the endpoints of symptomatology, there are no statistically significant differences between the treatment arms.

Health status (assessed by EQ-5D VAS)

The health status was assessed using the visual analogue scale (VAS) of the EQ-5D questionnaire. For the benefit assessment, the pharmaceutical company submitted responder analyses for the "time to permanent deterioration" for this endpoint.

The operationalisation of "time to permanent deterioration" for the endpoint of health status submitted by the pharmaceutical company corresponds to the operationalisation already described for the endpoints of symptomatology. The assessment of the health status should be conducted until death, or until the end of the survival follow-up (maximum 5 years after primary DFS analysis). Based on the information on the returns, conclusions can be drawn that the corresponding percentages decrease after the end of treatment with the study medication in both arms. Whether the return rates were adequately calculated cannot be verified due to the lack of data on overall survival. Against the background that the data on the returns are only available separately for the period under treatment and the period after treatment, and an allocation of the follow-up visits to the corresponding points in time from randomisation (i.e., the temporally corresponding visits) is missing, an assessment of whether the evaluation of the "permanent deterioration" is adequate is not possible. The responder analyses of the EQ-5D VAS on "time to permanent deterioration" submitted by the pharmaceutical company in the dossier are therefore not considered for the assessment.

As part of the written statement procedure, responder analyses on the "time to first deterioration" by 7, 10 and 15 points compared to the baseline were submitted by the pharmaceutical company. The responder analyses on "time to first deterioration" by 15 points are used as a basis for the assessment.

Regarding the endpoint of health status (EQ-5D VAS), there is a statistically significant difference in favour of nivolumab.

Quality of life

Health-related quality of life (assessed using EORTC QLQ-C30)

Health-related quality of life is assessed in the CheckMate 274 study using the functional scales of the cancer-specific questionnaire EORTC QLQ-C30.

In line with the explanations on the endpoints of symptomatology, the responder analyses on the "time to permanent deterioration" submitted by the pharmaceutical company for the health-related quality of life in the dossier are not taken into account for the assessment.

As part of the written statement procedure, responder analyses on the "time to first deterioration" by ≥ 10 points compared to the baseline were submitted by the pharmaceutical company and are used as a basis for the assessment. These analyses do not show any statistically significant differences.

Thus, for the endpoints of global health status, cognitive functioning, social functioning, physical functioning, role functioning and emotional functioning, there is no statistically significant difference between the treatment arms.

Side effects

Adverse events (AEs) in total

Almost all participants in the CheckMate 274 study experienced adverse events. The results for the endpoint "total adverse events" are only presented additionally.

Serious AEs (SAEs), severe AEs (CTCAE grade ≥ 3)

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

Therapy discontinuations due to AEs

For the endpoint of therapy discontinuations due to AEs, there is a statistically significant difference to the disadvantage of nivolumab compared to placebo.

Specific AEs

For the endpoints of immune-mediated SAEs, immune-mediated severe AEs, skin and subcutaneous tissue disorders (AEs), asthenia (AEs), respiratory, thoracic and mediastinal disorders (SAEs) and lipase increased (severe AEs), there is a statistically significant difference in each case to the disadvantage of nivolumab compared to placebo.

Statistically significant differences to the advantage of nivolumab exist with regard to the specific AEs of infections and infestations (SAEs) and gastrointestinal disorders (severe AEs).

The overall assessment of the results on side effects shows a disadvantage for nivolumab in terms of therapy discontinuations due to AEs compared to placebo. In detail, there are advantages as well as disadvantages of nivolumab in terms of the specific adverse events.

Overall assessment

For the assessment of the additional benefit of nivolumab, results on morbidity, quality of life and side effects are available from the CheckMate 274 study in comparison to the monitoring wait-and-see approach.

For the endpoint category of mortality, no data were provided by the pharmaceutical company. However, data on overall survival are considered particularly relevant in the assessment of the additional benefit of nivolumab in the treatment setting presented here.

In the endpoint category of morbidity, nivolumab shows a relevant advantage over the monitoring wait-and-see approach with regard to the avoidance of recurrences. The avoidance of recurrences is a significant therapeutic goal in view of the present fundamentally curative therapy claim.

With regard to symptomatology, there is no statistically significant difference between the treatment arms.

Regarding the endpoint of health status (EQ-5D VAS), there is a statistically significant difference in favour of nivolumab.

For the endpoint category of health-related quality of life, there is no statistically significant difference between the treatment arms.

In terms of side effects, for the endpoint of therapy discontinuation due to AEs, a disadvantage of nivolumab compared to the monitoring wait-and-see approach is observed. In detail, there are also advantages and disadvantages of nivolumab in terms of the specific AEs. Thus, in the category of side effects, there is a disadvantageous effect of nivolumab compared to the monitoring wait-and-see approach overall.

In the overall analysis, the positive effect on recurrences and the health status is offset by a disadvantage in terms of side effects.

However, against the background that no data on overall survival are available, the extent of the additional benefit cannot be quantified in the overall assessment. Thus, a non-quantifiable additional benefit is identified for nivolumab for the adjuvant treatment of adults with muscle invasive urothelial carcinoma and tumour cell PD-L1 expression ≥ 1%, who are at high risk of recurrence after radical resection.

Reliability of data (probability of additional benefit)

The present assessment is based on the results of a double-blind, randomised, multicentre, placebo-controlled study.

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

However, 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 adjuvant cisplatin-containing therapy and the study results are thus transferable to the reality of care.

In addition, the reliability of data for the overall assessment of the additional benefit is limited by the fact that no data are available for the endpoint of overall survival.

Therefore, in the overall assessment, the reliability of data for the additional benefit determined is classified in the category “hint”.

2.1.4 Limitation of the period of validity of the resolution

The limitation of the period of validity of the resolution on the present benefit assessment of nivolumab finds its legal basis in Section 35a paragraph 3 sentence 4 SGB V. Thereafter, the G-BA may limit the validity of the resolution on the benefit assessment of a medicinal product. In the present case, the limitation is justified by objective reasons consistent with the purpose of the benefit assessment pursuant to Section 35a paragraph 1 SGB V.

Due to the lack of results on overall survival for patient population b), the significance is limited and uncertainties remain.

Since further clinical data from the CheckMate 274 study are expected, which are relevant for the benefit assessment of the medicinal product, it is justified to limit the validity of the present resolution for patient population b).

Conditions of the limitation:

For the new benefit assessment of nivolumab after the deadline, the results on all patient-relevant endpoints from the CheckMate 274 study must be submitted in the dossier by 15 December 2025. By the time the limitation expires, the data from the final data cut-off after the occurrence of 166 events in overall survival should be submitted. If the final data are not yet available at the time of the expiry of the limitation, the data from a data cut-off at a time point that is not older than 6 months before the expiry of the limitation, on all patient-relevant endpoints from the CheckMate 274 study must be submitted to the G-BA.

A time limit on the validity of the resolution for patient group b) until 15 December 2025 is considered appropriate.

A change in the limitation can generally be granted if it is justified and clearly demonstrated that the limitation period is too long.

In accordance with Section 3, No. 7 AM-NutzenV in conjunction with Chapter 5 Section 1, paragraph 2, No. 6 VerfO, the procedure for the benefit assessment of the medicinal product nivolumab recommences when the deadline has expired. For this purpose, the pharmaceutical company must submit a dossier to the G-BA at the latest on the date of expiry to prove the extent of the additional benefit of nivolumab in comparison with the appropriate comparator therapy (Section 4, paragraph 3, number 5 AM-NutzenV in conjunction with Chapter 5 Section 8, number 5 VerfO). The possibility that a benefit assessment for the medicinal product nivolumab can be carried out at an earlier point in time due to other reasons (cf. Chapter 5, Section 1 paragraph 2, nos. 2 – 4 VerfO) remains unaffected hereof.

2.1.5 Summary of the assessment

The present assessment is the benefit assessment of a new therapeutic indication for the active ingredient nivolumab. The therapeutic indication assessed here is as follows: "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."

Two patient populations are differentiated in terms of suitability for cisplatin-containing chemotherapy:

a) Adults with muscle invasive urothelial carcinoma with tumour cell PD-L1 expression ≥ 1%, who are at high risk of recurrence after undergoing complete resection and are eligible for cisplatin-containing therapy; adjuvant treatment

The G-BA determined the combination chemotherapy cisplatin and gemcitabine or the combination chemotherapy cisplatin + methotrexate as the appropriate comparator therapy.

No data were submitted by the pharmaceutical company that would allow an assessment of the additional benefit. An additional benefit is not proven.

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 and are unsuitable for cisplatin-containing therapy, or have already received neoadjuvant treatment; adjuvant treatment

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

For the benefit assessment of nivolumab, data on morbidity, quality of life and side effects are available from the CheckMate 274 study.

No data were presented for the endpoint of overall survival. However, these are considered to be particularly relevant in the assessment of the additional benefit in the treatment setting presented here.

In the endpoint category of morbidity, nivolumab shows a relevant advantage over the monitoring wait-and-see approach with regard to the avoidance of recurrences. The avoidance of recurrences is a significant therapeutic goal in view of the present fundamentally curative therapy claim.

Regarding the endpoint of health status (EQ-5D VAS), there is a statistically significant difference in favour of nivolumab.

With regard to symptomatology and health-related quality of life, there are no statistically significant differences between the treatment arms.

In the endpoint category of side effects, there is an overall disadvantageous effect of nivolumab compared to the monitoring wait-and-see approach.

In the overall analysis, the positive effect on recurrences and the health status is offset by a disadvantage in terms of side effects.

However, against the background that no data on overall survival are available, the extent of the additional benefit cannot be quantified in the overall assessment. Thus, a hint for a non-quantifiable additional benefit of nivolumab compared with the monitoring wait-and-see approach is found.

The validity period of the resolution is limited for this patient group until 15 December 2025, as further clinical data from the CheckMate 274 study are expected.

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

a) Adults with muscle invasive urothelial carcinoma with tumour cell PD-L1 expression ≥ 1%, who are at high risk of recurrence after undergoing complete resection and are eligible for cisplatin-containing therapy; adjuvant treatment

and

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 and are unsuitable for cisplatin-containing therapy, or have already received neoadjuvant treatment; adjuvant treatment

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

The G-BA bases its resolution on the information from the dossier of the pharmaceutical company. The following should be noted:

The pharmaceutical company bases the derivation of the patient numbers on a high percentage of cases with unknown stage at initial diagnosis as well as operationalisation criteria of patients at a high risk of recurrence, which are subject to uncertainties.

There is also uncertainty about the percentage of patients for whom adjuvant cisplatin-containing therapy is unsuitable. Only patients with urinary bladder cancer are taken into account. Furthermore, patients who received neoadjuvant treatment are excluded from the population for the determination of the percentage values.

A further uncertainty arises from the pharmaceutical company's operationalisation of the patients for whom cisplatin-containing therapy is suitable or unsuitable via the percentage of those who do or do not receive adjuvant therapy. In the studies used to determine the number of patients, not all patients are treated with cisplatin as part of adjuvant treatment.

In addition, there are uncertainties related to the percentage of patients with tumour cell PD-L1 expression ≥ 1%. This is especially due to the limited transferability of the percentage values from the marketing authorisation studies used.

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 September 2022):

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 specialists participating in the Oncology Agreement.

In accordance with the Medicines Agency 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 October 2022).

Treatment period:

If no maximum treatment duration is specified in the product information, the treatment duration is assumed to be one year (365 days), even if the actual treatment duration is patient-individual 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 cisplatin in combination with methotrexate, a treatment duration of 3 cycles is assumed, even if the actual treatment duration may differ from patient to patient.

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	26.1	1	26.1
	or			
	1 x per 28-day cycle	13	1	13
Appropriate comparator therapy				
a) Adults with muscle invasive urothelial carcinoma with tumour cell PD-L1 expression ≥ 1%, who are at high risk of recurrence after undergoing complete resection and are eligible for cisplatin-containing therapy; adjuvant treatment				
Cisplatin in combination with gemcitabine				
Cisplatin	1x on day 1 or day 2 per 28-day cycle	13	1	13

Designation of the therapy	Treatment mode	Number of treatments/ patient/ year	Treatment duration/ treatment (days)	Treatment days/ patient/ year
Gemcitabine	1x on day 1, 8 and 15 per 28-day cycle	13	3	39
Cisplatin in combination with methotrexate				
Cisplatin[2]	1x on day 1 per 21-day cycle	3	1	3
Methotrexate[2]	1x on day 8 and 15 of a 21-day cycle	3	2	6
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 and are unsuitable for cisplatin-containing therapy, or have already received neoadjuvant treatment; adjuvant treatment				
Monitoring wait-and-see approach	incalculable			

Consumption:

For dosages depending on body weight (BW) or body surface area (BSA), the average body measurements were applied (average height: 1,72 m; average body weight: 77 kg). This results in a body surface area of 1.90 m² (calculated according to Du Bois 1916).

Designation of the therapy	Dosage/ application	Dose/ patient/ treatment days	Consumption by potency/ treatment day	Treatment days/ patient/ year	Average annual consumption by potency
Medicinal product to be assessed					
Nivolumab	240 mg	240 mg	2 x 120 mg	26.1	52.2 x 120 mg
	or				
	480 mg	480 mg	4 x 120 mg	13	52.0 x 120 mg
Appropriate comparator therapy					

[2] Lehmann J, Retz M, Wiemers C, Beck J, Thüroff J, Weining C, et al. Adjuvant cisplatin plus methotrexate versus methotrexate, vinblastine, epirubicin, and cisplatin in locally advanced bladder cancer: results of a randomised, multicenter, phase III trial (AUO-AB 05/95). J Clin Oncol 2005;23:4963-4974.

Designation of the therapy	Dosage/ application	Dose/ patient/ treatment days	Consumption by potency/ treatment day	Treatment days/ patient/ year	Average annual consumption by potency
a) Adults with muscle invasive urothelial carcinoma with tumour cell PD-L1 expression ≥ 1%, who are at high risk of recurrence after undergoing complete resection and are eligible for cisplatin-containing therapy; adjuvant treatment					
Cisplatin in combination with gemcitabine					
Cisplatin	70 mg/m² BSA = 133 mg	133 mg	1 x 100 mg 1 x 50 mg	13	13 x 100 mg 13 x 50 mg
Gemcitabine	1,000 mg/m² BSA = 1,900 mg	1900 mg	2 x 1000 mg	39	78 x 1000 mg
Cisplatin in combination with methotrexate					
Cisplatin	70 mg/m² BSA = 133 mg	133 mg	1 x 100 mg 1 x 50 mg	3	3 x 100 mg 3 x 50 mg
Methotrexate	40 mg/m² BSA = 76 mg	76 mg	2 x 50 mg	6	12 x 50 mg
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 and are unsuitable for cisplatin-containing therapy, or have already received neoadjuvant treatment; adjuvant treatment					
Monitoring wait-and-see approach	incalculable				

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.

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	12 ml CIS	€ 1,546.93	€ 1.77	€ 85.05	€ 1,460.11
Appropriate comparator therapy					
a) Adults with muscle invasive urothelial carcinoma with tumour cell PD-L1 expression ≥ 1%, who are at high risk of recurrence after undergoing complete resection and are eligible for cisplatin-containing therapy; adjuvant treatment					
Cisplatin in combination with gemcitabine					
Cisplatin 100 mg	100 ml CIS	€ 76.55	€ 1.77	€ 3.10	€ 71.68
Cisplatin 50 mg	50 ml CIS	€ 47.67	€ 1.77	€ 1.73	€ 44.17
Gemcitabine 1000 mg	1000 mg PIS	€ 102.32	€ 1.77	€ 10.62	€ 89.93
Cisplatin in combination with methotrexate					
Cisplatin 100 mg	100 ml CIS	€ 76.55	€ 1.77	€ 3.10	€ 71.68
Cisplatin 50 mg	50 ml CIS	€ 47.67	€ 1.77	€ 1.73	€ 44.17
Methotrexate[3] 50 mg	2 ml SFI	€ 49.14	€ 1.77	€ 2.99	€ 44.38
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 and are unsuitable for cisplatin-containing therapy, or have already received neoadjuvant treatment; adjuvant treatment					
Monitoring wait-and-see approach	incalculable				
Abbreviations: CIS = concentrate for the preparation of an infusion solution; SFI = solution for injection; PIS = powder 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

[3] Fixed reimbursement rate

expenditure in the course of the treatment are not shown.

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	Treatment days/ year	Cost/ patient/ year
Appropriate comparator therapy							
a) Adults with muscle invasive urothelial carcinoma with tumour cell PD-L1 expression ≥ 1%, who are at high risk of recurrence after undergoing complete resection and are eligible for cisplatin-containing therapy, for adjuvant treatment							
Cisplatin							
Antiemetic treatment							
In clinical practice, an appropriate antiemetic treatment is established before and/or after administration of cisplatin. The product information does not provide any specific information why the necessary costs cannot be quantified.							
Hydration/ diuresis							
Cisplatin in combination with gemcitabine							
Mannitol 10% infusion solution, 37.5 g/day	10 x 500 ml INF	€ 106.22	€ 5.31	€ 9.81	€ 91.10	13	€ 118.43
Sodium chloride 0.9% infusion solution, 3 l - 4.4 l/day	10 x 1000 ml INF	€ 34.68	€ 1.73	€ 1.08	€ 31.87	13	€ 124.29 - € 192.88
	10 x 500 ml INF	€ 22.72	€ 1.14	€ 0.69	€ 20.89		
Cisplatin in combination with methotrexate							
Mannitol 10% infusion solution, 37.5 g/day	10 x 500 ml INF	€ 106.22	€ 5.31	€ 9.81	€ 91.10	3	€ 27.33
Sodium chloride 0.9% infusion solution, 3 l - 4.4 l/day	10 x 1000 ml INF	€ 34.68	€ 1.73	€ 1.08	€ 31.87	3	€ 9.56 - € 44.51
	10 x 500 ml INF	€ 22.72	€ 1.14	€ 0.69	€ 20.89		
Abbreviation: INF = infusion solution							

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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 drugs a maximum amount of € 81 per ready-to-use preparation, and for the production of parenteral solutions containing monoclonal antibodies a maximum of € 71 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.

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 its session on 22 September 2020, the Subcommittee on Medicinal Products determined the appropriate comparator therapy.

After the positive opinion was issued, the appropriate comparator therapy determined by the G-BA was reviewed. The Subcommittee on Medicinal Products determined the appropriate comparator therapy at its session on 16 March 2022.

On 29 April 2022 the pharmaceutical company submitted a dossier for the benefit assessment of nivolumab to the G-BA in due time in accordance with Chapter 5, Section 8, paragraph 1, number 2 VerfO.

By letter dated 2 May 2022 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 28 July 2022, and the written statement procedure was initiated with publication on the website of the G-BA on 1 August 2022. The deadline for submitting written statements was 22 August 2022.

The oral hearing was held on 5 September 2022.

By letter dated 6 September 2022, the IQWiG was commissioned with a supplementary assessment. The addendum prepared by IQWiG was submitted to the G-BA on 27 September 2022.

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 11 October 2022, and the proposed resolution was approved.

At its session on 20 October 2022, the plenum adopted a resolution to amend the Pharmaceuticals Directive.

Chronological course of consultation

Session	Date	Subject of consultation
Subcommittee Medicinal products	22 September 2020	Determination of the appropriate comparator therapy
Subcommittee Medicinal products	16 March 2022	New determination of the appropriate comparator therapy
Working group Section 35a	30 August 2022	Information on written statements received; preparation of the oral hearing
Subcommittee Medicinal products	5 September 2022 6 September 2022	Conduct of the oral hearing, Commissioning of the IQWiG with the supplementary assessment of documents
Working group Section 35a	13 September 2022 20 September 2022 4 October 2022	Consultation on the dossier assessment by the IQWiG, assessment of the written statement procedure
Subcommittee Medicinal products	11 October 2022	Concluding discussion of the draft resolution
Plenum	20 October 2022	Adoption of the resolution on the amendment of Annex XII AM-RL

Berlin, 20 October 2022

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

Prof. Hecken