IQWiG Reports – Commission No. A22-53

Nivolumab (urothelial carcinoma, adjuvant) –

Benefit assessment according to §35a Social Code Book V[1]

Extract

[1] Translation of Sections 2.1 to 2.5 of the dossier assessment *Nivolumab (Urothelkarzinom, adjuvant) – Nutzenbewertung gemäß § 35a SGB V* (Version 1.0; Status: 28 July 2022). Please note: This document was translated by an external translator and is provided as a service by IQWiG to English-language readers. However, solely the German original text is absolutely authoritative and legally binding.

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Patient and family involvement

The questionnaire on the disease and its treatment was answered by one person.

IQWiG thanks the respondent for participating in the written exchange about how they experienced the disease and its treatment and about the treatment goals. The respondent was not involved in the actual preparation of the dossier assessment.

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[2] Table numbers start with “2” as numbering follows that of the full dossier assessment.

List of abbreviations

Abbreviation	Meaning
ACT	appropriate comparator therapy
AE	adverse event
CTCAE	Common Terminology Criteria for Adverse Events
DBL	database lock
DFS	disease-free survival
ECOG-PS	Eastern Cooperative Oncology Group-Performance Status
EORTC	European Organisation for Research and Treatment of Cancer
EQ-5D	European Quality of Life Questionnaire 5 Dimensions
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
MedDRA	Medical Dictionary for Regulatory Activities
MIUC	muscle-invasive urothelial carcinoma
MMRM	mixed model for repeated measures
PD-L1	programmed cell death ligand 1
PT	Preferred Term
QLQ-C30	Quality of Life Questionnaire–Core 30
RCT	randomized controlled trial
SAE	serious adverse event
SGB	Sozialgesetzbuch (Social Code Book)
SOC	System Organ Class
TNM	tumour node metastasis
VAS	visual analogue scale

2 Benefit assessment

2.1 Executive summary of the benefit assessment

Background

In accordance with §35a Social Code Book (SGB) V, the Federal Joint Committee (G-BA) commissioned the Institute for Quality and Efficiency in Health Care (IQWiG) to assess the benefit of the drug nivolumab. The assessment is based on a dossier compiled by the pharmaceutical company (hereinafter referred to as the "company"). The dossier was sent to IQWiG on 2 May 2022.

Research question

The aim of the present report is to assess the added benefit of nivolumab monotherapy in comparison with the appropriate comparator therapy (ACT) for the adjuvant treatment of muscle-invasive urothelial carcinoma (MIUC) with tumour cell programmed cell death ligand 1 (PD-L1) expression ≥ 1% in adult patients with high recurrence risk after radical resection of the MIUC.

The research questions shown in Table 2 were derived from the ACT specified by the G-BA.

Table 2: Research questions of the benefit assessment of nivolumab

Research question	Therapeutic indication	ACT[a]
1	Adult patients with muscle-invasive urothelial carcinoma with tumour cell PD-L1 expression ≥ 1% who are at high risk of recurrence after undergoing radical resection and who are eligible for cisplatin-containing therapy for adjuvant treatment	▪ Cisplatin + gemcitabine or[b] ▪ Cisplatin + methotrexate
2	Adult patients with muscle-invasive urothelial carcinoma with tumour cell PD-L1 expression ≥ 1% who are at high risk of recurrence after undergoing radical resection and who are not eligible for cisplatin-containing therapy, for adjuvant treatment[c]	Watchful waiting

a. Presented is the respective ACT specified by the G-BA.
b. Added benefit can be proven in comparison with one of the cited treatment options; this can typically be achieved in the context of a single-comparator study.
c. According to the G-BA, this includes patients who are generally not eligible for cisplatin chemotherapy (e.g. due to poor general health or renal insufficiency) or who have already received neoadjuvant cisplatin chemotherapy and are therefore not candidates for another round of cisplatin therapy. According to the G-BA, the patient population is therefore heterogeneous.

ACT: appropriate comparator therapy; G-BA: Federal Joint Committee; PD-L1: programmed cell death ligand 1

In the present benefit assessment, the following terms are used for the patient populations of the 2 research questions:

- Research question 1: Patients eligible for cisplatin-containing therapy

- Research question 2: Patients not eligible for cisplatin-containing therapy

The company's dossier presents the research questions in reverse order. This benefit assessment discusses the research questions in the sequence specified by the G-BA (see Table 2).

The company followed the G-BA's specification of the ACT for both research questions.

The assessment is conducted by means of patient-relevant outcomes on the basis of the data provided by the company in the dossier. Randomized controlled trials (RCTs) are used for deriving added benefit. This concurs with the company's inclusion criteria.

Research question 1: Patients eligible for cisplatin-containing therapy

Results

No suitable data are available for assessing the added benefit of nivolumab in comparison with the ACT in patients eligible for cisplatin-containing therapy. This results in no hint of an added benefit of nivolumab in comparison with the ACT; an added benefit is therefore not proven.

Research question 2: Patients not eligible for cisplatin-containing therapy

Study pool and study design

The CA209-274 study was used for the benefit assessment. The CA209-274 study is an ongoing double-blind RCT comparing nivolumab versus placebo. The study enrolled adult patients with MIUC originating in the bladder or upper urinary tract (renal pelvis or ureter) who are at high risk of recurrence following radical MIUC resection. Prerequisite for inclusion was R0 resection ≤ 120 days prior to randomization. Patients who had received neoadjuvant cisplatin chemotherapy had to have the following tumour node metastasis (TNM) status: ypT2-pT4a or ypN+. Patients who had received no neoadjuvant cisplatin chemotherapy and who either were not eligible for or refused adjuvant cisplatin chemotherapy had to have the following status: pT3–pT4a or pN+. Patients with the above TNM statuses are assumed to be at high risk of recurrence. Refusal of cisplatin chemotherapy (by medically eligible patients) had to be thoroughly documented. At enrolment, patients had to be in good general condition corresponding to an Eastern Cooperative Oncology Group-Performance Status (ECOG-PS) of 0 or 1. Patients with an ECOG-PS of 2 were eligible for enrolment if they had not received any neoadjuvant cisplatin chemotherapy and were ineligible for adjuvant cisplatin chemotherapy (ECOG-PS of 2 was deemed a criterion for ineligibility). Patients additionally had to be disease free as documented by a complete physical examination and imaging within 4 weeks prior to randomization.

The CA209-274 study enrolled a total of 709 patients and randomized them in a 1:1 ratio to either nivolumab treatment (N = 353) or to placebo (N = 356). Randomization was stratified by pathological lymph node status (N+ versus N0/x with < 10 removed lymph nodes versus N0 with ≥ 10 removed lymph nodes), PD-L1 tumour expression (≥ 1% versus < 1%, not determined), and the use of cisplatin as neoadjuvant chemotherapy (yes versus no).

Nivolumab treatment in the intervention arm was in compliance with the Summary of Product Characteristics (SPC).

Treatment with the study medication continued until recurrence, unacceptable toxicity, or withdrawal of consent, but for no longer than 1 year. The study did not provide for any switching to the treatment of the other study arm.

The primary outcome of the CA209-274 study was disease-free survival (DFS). Patient-relevant secondary outcomes were outcomes in the mortality, morbidity, health-related quality of life, and adverse events (AEs) categories.

Relevant subpopulation

In accordance with the approved therapeutic indication, only the CA209-274 study's subpopulation of patients with tumour cell PD-L1 expression ≥ 1% is relevant for the benefit assessment. Module 4 R of the company's dossier presents analyses of this subpopulation (140 patients in the nivolumab arm and 142 patients in the placebo arm). Furthermore, the G-BA's research question 2 comprises only patients not eligible for cisplatin-containing therapy. In addition, uncertainties exist as described in the section below.

Research question 2: Patients who are not eligible for cisplatin-containing therapy

The company's dossier states that in the adjuvant treatment of MIUC, cisplatin-containing chemotherapy is generally indicated unless neoadjuvant chemotherapy has already been conducted previously or the patient's general health and comorbidities forbid such therapy. However, the CA209-274 study and hence the relevant subpopulation explicitly included patients who refused adjuvant cisplatin-containing chemotherapy despite being medically eligible for it. The information provided by the company on patients' prior therapy included the reasons why patients did not receive any prior cisplatin-containing chemotherapy. Most of these patients (a total of 36% in the nivolumab arm versus 32% in the placebo arm) did not receive cisplatin-containing chemotherapy due to lack of consent (unwillingness). While the study protocol stipulated for this refusal to be thoroughly documented, the manufacturer's dossier does not provide any further information on this patient population. Likewise, the G-BA does not explicitly identify this patient group. Overall, it remains unclear whether the relatively high percentage of CA209-274 participants who refused cisplatin-containing chemotherapy is consistent with healthcare practice in Germany.

For muscle-invasive urothelial carcinoma, national guidelines recommend either neoadjuvant or adjuvant cisplatin-containing chemotherapy because a metaanalysis found a survival advantage for these therapies. Before treatment start, the treatment concept is to be defined by a multidisciplinary team. The CA209-274 study protocol, however, does not incorporate these recommendations. The information provided in the study's informed consent form likewise does not fully reflect the guideline information and recommendations, and it particularly fails to clearly identify the survival advantage of adjuvant chemotherapy. Therefore, it is conceivable

for patients to not have been fully informed about the advantages and disadvantages of the treatment options available to them.

Overall, it therefore remains unclear, first, whether the relatively high percentage of CA209-274 participants (about one-third) who refused cisplatin-containing chemotherapy is consistent with healthcare practice in Germany. Second, in terms of healthcare practice, it remains unclear whether at least some of these patients would have decided in favour of cisplatin-containing chemotherapy if they had been informed about all relevant aspects cited in the guidelines – and these patients would therefore be allocated to research question 1 rather than 2 (patients eligible for cisplatin-containing therapy).

The benefit assessment used the analyses presented by the company for the CA209-274 study's subpopulation of patients with tumour cell PD-L1 expression ≥ 1%. The assessment of the CA209-274 study results' certainty of conclusions accounts for the uncertainty regarding whether a relevant percentage of patients might have been eligible for adjuvant cisplatin-containing therapy after all.

Available data and data cut-offs

From the CA209-274 study, analyses at various data cut-offs are available for the different outcomes or outcome categories. The 1st data cut-off from August 2020 is the 1st interim analysis of the DFS outcome as prespecified in the study protocol. According to the company, this interim analysis was subsequently deemed the final DFS analysis because the predefined significance level had been reached. For the 1st data cut-off, the company's dossier presents data on all outcomes except overall survival. For the 2nd data cut-off from February 2021, the available documents do not clearly show the reason it was implemented. As part of the marketing authorization procedure, updated data for DFS outcomes were submitted for this data cut-off. The company reports that symptoms, health status, quality of life, and tolerability outcomes were not updated in February 2021. This is because, at the time of the first data cut-off (August 2020), few patients (with tumour cell PD-L1 ≥ 1%) were still being treated (8 in the nivolumab arm versus 5 in the placebo arm), and very little time had passed between the 2 data cut-offs (about 6 months). For the 2nd data cut-off, the company's dossier presents data only for DFS and recurrence rate. Data on overall survival are missing for the 2nd data cut-off as well.

Hence, the manufacturer's dossier does not provide any data on overall survival. The lack of these data is not appropriate in the present situation and is not sufficiently justified by the company. In the present oncological indication, patients' overall survival is of particular importance. The missing data on overall survival represent an uncertainty, which is accounted for in the certainty of results.

As described above for the 2nd data cut-off and in deviation from the dossier template, the company failed to submit any analyses of patient-relevant outcomes except recurrence rate and DFS for the 2nd data cuff. This approach was not sufficiently justified by the company. For the

symptoms, health status, health-related quality of life, and side effects outcomes, the data from the 1st data cut-off are nevertheless deemed sufficient because the time interval between the 2 data cut-offs is relatively short, at about 6 months. At the time of the 1st data cut-off, few patients remained under treatment (8 versus 5 patients), and an estimated maximum of 18% of patients were still under follow-up observation for the outcomes with shortened observation (treatment end plus about 100 days), i.e. symptoms, health-related quality of life, and side effects. For these outcome categories, no relevant amount of additional data would presumably have become available between the 1st and 2nd data cut-offs. The outcome of health status, in contrast, was to be observed for as long as overall survival. Consequently, a potentially relevant amount of data could be added at the 2nd data cut-off for all patients remaining in the study.

The absence of the described data for the current 2nd data cut-off is not appropriate. Irrespective of this problem, the presented analyses for the symptoms, health status, and health-related quality of life outcomes are unsuitable for the benefit assessment because of (a) the operationalization of definitive deterioration submitted by the company, given the marked between-arm differences in observation durations, and (b) unclear return rates. Due to the longer observation period, data from the 2nd data cut-off were used for DFS and recurrence rate.

Implementation of the ACT

For patients who are not eligible for cisplatin-containing therapy, the G-BA specified the ACT of watchful waiting. The CA209-274 study used placebo as the comparator therapy. Even though the study was not designed for a comparison with watchful waiting, it is nonetheless suitable for such a comparison.

The investigations performed in the CA209-274 study did not fully implement guideline recommendations. In particular, sonography is not discussed despite this procedure being used to detect dysfunction throughout the urinary tract. Additionally, instead of being conducted as a standard test, urine cytology was performed only if clinically indicated. Despite these deviations from guideline recommendations, CA209-274 participants were overall monitored closely with targeted examinations to record their health status as well as recurrences, so that, overall, the examination regimen is deemed to be a sufficient approximation to the ACT of watchful waiting.

Risk of bias

The risk of bias across outcomes was rated as low for the CA209-274 study. The risk of bias for the result on the outcome of recurrence is rated as low. No usable data are available for the outcomes of symptoms (surveyed using the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire–Core 30 [EORTC QLQ-C30]), health status (surveyed with the European Quality of Life Questionnaire 5 Dimensions [EQ-5D] visual analogue scale [VAS]), or health-related quality of life (recorded with the EORTC QLQ-C30). The risk of bias of the results for the outcomes of serious adverse events (SAEs), severe AEs (overall rate and specific AEs), and immune-related SAEs/severe AEs is rated as high. Despite a low risk of bias

for the outcome of discontinuation due to AEs, the certainty of results for this outcome was limited.

Summary assessment of the certainty of conclusions

Irrespective of the aspects described under risk of bias, the certainty of conclusions of the study results is reduced due to (a) the uncertainties in the percentage of patients who might have been eligible for adjuvant cisplatin-containing chemotherapy after all and (b) the lack of data for the outcome of overall survival. Overall, at most hints, e.g. of an added benefit, can therefore be derived on the basis of the CA209-274 study.

Results

Mortality

Overall survival

No data are available on overall survival. According to the company, the significance threshold for overall survival had not been exceeded by the time of the 1st interim analysis (2nd data cut-off, February 2021). The study report and European Public Assessment Report show that the data were not unblinded and no analyses are therefore available. In the present oncological research question, this is not appropriate. In addition, the company's reasoning for foregoing a presentation of the results on overall survival is not completely plausible because – at least for the 1st data cut-off (August 2020) – the study report's analyses of side effects provide data on the number of deceased patients, unblinded per treatment arm. However, it remains unclear whether all deaths which occurred in the study were included in this analysis since according to the footnote, the follow-up observation period was only 30 days. In addition, the event "death for any cause (without prior recurrence)" is included in the analyses of disease-free survival, which means that the number of deaths per treatment arm had to be known. The uncertainties resulting from the missing data on overall survival are taken into account in the certainty of results.

This results in no hint of an added benefit of nivolumab in comparison with watchful waiting; an added benefit is therefore not proven.

Morbidity

Recurrence

For the outcome of recurrence (operationalized as recurrence rate and DFS), a statistically significant difference in favour of nivolumab in comparison with placebo was shown for both operationalizations. This resulted in a hint of an added benefit of nivolumab versus watchful waiting.

Symptoms

There were no usable data for the outcome of symptoms (recorded with the EORTC QLQ-C30). This results in no hint of an added benefit of nivolumab in comparison with watchful waiting; added benefit is therefore not proven.

Health status

No usable data are available for the outcome of health status (recorded using EQ-5D VAS). This results in no hint of an added benefit of nivolumab in comparison with watchful waiting; added benefit is therefore not proven.

Health-related quality of life

No usable data are available for the outcome of health-related quality of life (recorded with the EORTC QLQ-C30). This results in no hint of an added benefit of nivolumab in comparison with watchful waiting; added benefit is therefore not proven.

Side effects

SAEs and severe AEs

No statistically significant between-arm difference was found for either of the outcomes of SAEs or severe AEs. Hence, there was no hint of greater or lesser harm from nivolumab in comparison with watchful waiting for either of them; greater or lesser harm is therefore not proven.

Discontinuation due to AEs

A statistically significant difference to the disadvantage of nivolumab compared with placebo was shown for the outcome of discontinuation due to AEs. This results in a hint of greater harm from nivolumab in comparison with watchful waiting.

Specific AEs

Immune-related SAEs, immune-related severe AEs, diseases of the skin and subcutaneous tissue (AEs), asthenia (AEs), respiratory, thoracic, and mediastinal disorders (SAEs), lipase increased (severe AEs)

For each of the outcomes of immune-related SAEs, immune-related severe AEs, skin and subcutaneous tissue disorders (AEs), asthenia (AEs), respiratory, thoracic, and mediastinal disorders (SAEs), and lipase increased (severe AEs), there was a statistically significant difference to the disadvantage of nivolumab in comparison with placebo. In each case, this results in a hint of greater harm from nivolumab versus watchful waiting.

Infections and infestations (SAEs), gastrointestinal disorders (severe AEs)

A statistically significant difference in favour of nivolumab in comparison with placebo was shown for each of the outcomes of infections and infestations (AEs) and gastrointestinal disorders (severe AEs). In each case, this results in a hint of lesser harm from nivolumab versus watchful waiting. However, given the placebo-controlled study design, it is questionable whether, for the outcomes of gastrointestinal disorders as well as infections and infestations, the effect is actually to be allocated to the outcome category of side effects or whether it rather reflects the symptoms of disease.

Probability and extent of added benefit, patient groups with therapeutically important added benefit[3]

On the basis of the results presented, the probability and extent of the added benefit of the drug nivolumab in comparison with the ACT is assessed as follows:

Research question 1: Patients eligible for cisplatin-containing therapy

Since the company has presented no data for assessing the added benefit of nivolumab in comparison with the ACT in patients eligible for cisplatin-containing therapy, no added benefit is proven.

Research question 2: Patients not eligible for cisplatin-containing therapy

Overall, both favourable and unfavourable effects of nivolumab were found in comparison with the ACT.

On the favourable side, a hint of considerable added benefit was found for the outcome of relapse. Moreover, a hint of lesser harm of minor extent was shown for 2 specific AEs in the outcome category of serious/severe AEs. However, given the placebo-controlled study design, it is questionable whether, for the outcomes of gastrointestinal disorders as well as infections and infestations, the effect is actually to be allocated to the outcome category of side effects or whether it rather reflects the symptoms of disease. On the unfavourable effects side, in contrast, there are hints of greater harm of minor to major extent in the outcome category of serious/severe side effects. For non-serious/non-severe side effects, hints of considerable greater harm were found. However, the effects observed regarding side effects are based exclusively on the shortened period until treatment end plus 100 days.

No data are available on overall survival, and no usable data were found for the symptoms, health status, and health-related quality of life outcomes. For the current 2nd data cut-off dated February 2021, data are available only on the outcome of recurrence. Presumably, the missing or unusable data do not fully call into question the favourable effect in the outcome of recurrence. Nevertheless, the above-described unfavourable effects together with lack of usable data for the symptoms, health status, and health-related quality of life outcomes result in a downgrading of added benefit.

In summary, for patients with MIUC with tumour cell PD-L1 expression ≥ 1% and high risk of recurrence following complete resection who are not eligible for cisplatin-containing therapy,

[3] On the basis of the scientific data analysed, IQWiG draws conclusions on the (added) benefit or harm of an intervention for each patient-relevant outcome. Depending on the number of studies analysed, the certainty of their results, and the direction and statistical significance of treatment effects, conclusions on the probability of (added) benefit or harm are graded into 4 categories: (1) “proof”, (2) “indication”, (3) “hint”, or (4) none of the first 3 categories applies (i.e., no data available or conclusions 1 to 3 cannot be drawn from the available data). The extent of added benefit or harm is graded into 3 categories: (1) major, (2) considerable, (3) minor (in addition, 3 further categories may apply: non-quantifiable extent of added benefit, added benefit not proven, or less benefit). For further details see [1,2].

there is a hint of minor added benefit of nivolumab adjuvant treatment in comparison with the ACT of watchful waiting.

Table 3 shows a summary of the probability and extent of added benefit of nivolumab.

Table 3: Nivolumab – probability and extent of added benefit

Research question	**Therapeutic indication**	**ACT[a]**	**Probability and extent of added benefit**
1	Adult patients with muscle-invasive urothelial carcinoma with tumour cell PD-L1 expression ≥ 1% who are at high risk of recurrence after undergoing radical resection and who are eligible for cisplatin-containing therapy for adjuvant treatment	▪ Cisplatin + gemcitabine or[b] ▪ Cisplatin + methotrexate	Added benefit not proven
2	Adult patients with muscle-invasive urothelial carcinoma with tumour cell PD-L1 expression ≥ 1% who are at high risk of recurrence after undergoing radical resection and who are not eligible for cisplatin-containing therapy, for adjuvant treatment[c]	Watchful waiting	Hint of minor added benefit[d]

a. Presented is the respective ACT specified by the GBA.
b. Added benefit can be proven in comparison to 2 of the cited treatment options; this can typically be achieved in the context of a single-comparator study.
c. According to the G-BA, this includes patients who are either generally ineligible for cisplatin chemotherapy (e.g. due to poor general health or poor renal function) or have already received neoadjuvant cisplatin chemotherapy and are therefore not candidates for another cisplatin therapy. According to the G-BA, the patient population is therefore heterogeneous.
d. The CA209-274 study enrolled predominantly patients with an ECOG-PS of 0 or 1. Only 2.5% of patients from the study's relevant subpopulation had an ECOG-PS of 2. It remains unclear whether the observed effects are transferable to patients with an ECOG PS ≥ 2.

ACT: appropriate comparator therapy; ECOG-PS: Eastern Cooperative Oncology Group Performance Status; G-BA: Federal Joint Committee; PD-L1: programmed cell death ligand 1

The approach for the derivation of an overall conclusion on the added benefit is a proposal by IQWiG. The G-BA decides on the added benefit.

2.2 Research question

The aim of the present report is to assess the added benefit of nivolumab monotherapy in comparison with the ACT for the adjuvant treatment of MIUC with tumour cell PD-L1 expression ≥ 1% in adult patients with high recurrence risk after radical resection of the MIUC.

The research questions shown in Table 4 are derived from the ACT specified by the G-BA.

Table 4: Research questions of the benefit assessment of nivolumab

Research question	Therapeutic indication	ACT[a]
1	Adult patients with muscle-invasive urothelial carcinoma with tumour cell PD-L1 expression ≥ 1% who are at high risk of recurrence after undergoing radical resection and who are eligible for cisplatin-containing therapy for adjuvant treatment	▪ Cisplatin + gemcitabine or[b] ▪ Cisplatin + methotrexate
2	Adult patients with muscle-invasive urothelial carcinoma with tumour cell PD-L1 expression ≥ 1% who are at high risk of recurrence after undergoing radical resection and who are not eligible for cisplatin-containing therapy, for adjuvant treatment[c]	Watchful waiting

a. Presented is the respective ACT specified by the G-BA.
b. Added benefit can be proven in comparison to 2 of the cited treatment options; this can typically be achieved in the context of a single-comparator study.
c. According to the G-BA, this includes patients who are either generally ineligible for cisplatin chemotherapy (e.g. due to poor general health or renal insufficiency) or who have already received neoadjuvant cisplatin chemotherapy and are therefore not candidates for another round of cisplatin therapy. According to the G-BA, the patient population is therefore heterogeneous.

G-BA: Federal Joint Committee; PD-L1: programmed cell death ligand 1

In the present benefit assessment, the following terms are used for the patient populations of the 2 research questions:

- Research question 1: patients eligible for cisplatin-containing therapy
- Research question 2: patients not eligible for cisplatin-containing therapy

The company's dossier presents the research questions in the reverse order. The present benefit assessment discusses the research questions in the sequence specified by the G-BA (see Table 4).

The company followed the G-BA's specification of the ACT for both research questions.

The assessment is conducted by means of patient-relevant outcomes on the basis of the data provided by the company in the dossier. RCTs are used for the derivation of the added benefit. This concurs with the company's inclusion criteria.

2.3 Research question 1: Patients eligible for cisplatin-containing therapy

2.3.1 Information retrieval and study pool

The study pool of the assessment was compiled on the basis of the following information:

Sources of the company in the dossier:

- study list on nivolumab (status: 20 April 2022)
- bibliographical literature search on nivolumab (last search on 5 April 2022)
- search in trial registries/trial results databases for studies on nivolumab (last search on 5 April 2022)
- search on the G-BA website for nivolumab (last search on 5 April 2022)

To check the completeness of the study pool:

- search in trial registries for studies on nivolumab (last search on 13 May 2022); for search strategies, see Appendix A of the full dossier assessment

Concurring with the company, the check of the completeness of the study pool produced no RCTs directly comparing nivolumab versus the ACT in adult patients eligible for cisplatin-containing therapy.

2.3.2 Results on added benefit

No suitable data are available for assessing the added benefit of nivolumab in comparison with the ACT in patients eligible for cisplatin-containing therapy. This results in no hint of an added benefit of nivolumab in comparison with the ACT; an added benefit is therefore not proven.

2.3.3 Probability and extent of added benefit

No added benefit is proven because the company has presented no data for assessing the added benefit of nivolumab in comparison with the ACT in patients eligible for cisplatin-containing therapy.

The company's dossier likewise claimed no added benefit for this research question.

2.4 Research question 2: Patients not eligible for cisplatin-containing therapy

2.4.1 Information retrieval and study pool

The study pool of the assessment was compiled on the basis of the following information:

Sources of the company in the dossier:

- study list on nivolumab (status: 20 April 2022)
- bibliographical literature search on nivolumab (last search on 5 April 2022)

- search in trial registries/trial results databases for studies on nivolumab (last search on 5 April 2022)
- search on the G-BA website for nivolumab (last search on 5 April 2022)

To check the completeness of the study pool:

- search in trial registries for studies on nivolumab (last search on 13 May 2022); for search strategies, see Appendix A of the full dossier assessment

The check did not identify any additional relevant study.

2.4.1.1 Studies included

The study presented in the following table was included in the benefit assessment.

Table 5: Study pool – RCT, direct comparison: nivolumab versus watchful waiting

Study	Study category			Available sources		
	Study for the approval of the drug to be assessed (yes/no)	Sponsored study[a] (yes/no)	Third-party study (yes/no)	Clinical study report (CSR) (yes/no [citation])	Registry entries[b] (yes/no [citation])	Publication and other sources[c] (yes/no [citation])
CA209-274[d] (CheckMate 274)	Yes	Yes	No	Yes [3,4]	Yes [5-9]	Yes [10-13]

a. Study for which the company was sponsor.
b. Citation of the trial registry entries and, if available, of the reports on study design and/or results listed in the trial registries.
c. Other sources: documents from the search on the G-BA website and other publicly available sources.
d. In the following tables, the study is listed using this designation.

CSR: clinical study report; G-BA: Federal Joint Committee; RCT: randomized controlled trial

The CA209-274 study was used for the benefit assessment. The CA209-274 study used placebo as comparator therapy. While the study was not designed for a comparison with watchful waiting, it is nonetheless suitable for such a comparison (see Section 2.4.1.2). The study pool concurs with that of the company.

2.4.1.2 Study characteristics

Table 6 and Table 7 describe the study used for the benefit assessment.

Table 6: Characteristics of the study included – RCT, direct comparison: nivolumab versus watchful waiting (multipage table)

Study	Study design	Population	Interventions (number of randomized patients)	Study duration	Location and period of study	Primary outcome; secondary outcomes[a]
CA209-274	RCT, double-blind, parallel	Adult patients (≥ 18 years) ▪ with MIUC originating in the bladder or upper urinary tract (renal pelvis or ureter) who are at high risk of recurrence[b] following radical MIUC resection[c]. ▪ ECOG-PS ≤ 2[d]	Nivolumab (N = 353) Placebo (N = 356) Relevant subpopulation thereof[e]: Nivolumab (n = 140) Placebo (n = 142)	Screening: 28 days Treatment: until recurrence, unacceptable toxicity, or withdrawal of consent, but for no longer than 1 year Follow-up observation[f]: outcome-specific, maximum of 5 years after the primary DFS analysis	A total of 170 centres in Argentina, Australia, Austria, Belgium, Brazil, Canada, Chile, China, Columbia, Denmark, France, Germany, Greece, Ireland, Israel, Italy, Japan, Mexico, Netherlands, Peru, Poland, Romania, Russia, South Korea, Spain, Sweden, Switzerland, Taiwan, United Kingdom, United States 03/2016 – ongoing Data cut-offs[g]: 1st data cut-off (August 2020; final DFS analysis): ▪ 17 July 2020 with a DBL of 27 August 2020 ▪ Erratum for DFS outcomes[h]: 27 August 2020 with a DBL of 13 April 2021 2nd data cut-off (February 2021): ▪ 1 February 2021 with a DBL of 19 May 2021	Primary: DFS Secondary: overall survival, morbidity, health-related quality of life, AEs

Table 6: Characteristics of the study included – RCT, direct comparison: nivolumab versus watchful waiting (multipage table)

Study	Study design	Population	Interventions (number of randomized patients)	Study duration	Location and period of study	Primary outcome; secondary outcomes[a]

a. Primary outcomes include information without consideration of the relevance for this benefit assessment. Secondary outcomes only include information on outcomes relevant for this benefit assessment.
b. TNM stage ypT2–pT4a or ypN+ in patients who received neoadjuvant cisplatin chemotherapy; TNM stage pT3–pT4a or pN+ in patients who received no neoadjuvant cisplatin chemotherapy and who are either ineligible for or refuse adjuvant cisplatin chemotherapy. According to the study protocol, refusal of cisplatin chemotherapy (by eligible patients) had to be thoroughly documented.
c. R0 resection; performed ≤ 120 days prior to randomization. In departure from the protocol, the relevant subpopulation (tumour cell PD L1 expression ≥ 1%) included 8 patients who had the resection > 120 days prior to randomization.
d. Patients with an ECOG-PS of 2 were eligible for study enrolment if they had not received any neoadjuvant cisplatin chemotherapy and were not eligible for adjuvant cisplatin-containing chemotherapy.
e. Patients with tumour cell PD-L1 expression ≥ 1%.
f. Outcome-specific information is provided in Table 9.
g. The 1st interim analysis of the DFS outcome was planned to occur after 137 DFS events in patients with a tumour cell PD L1 expression ≥ 1% (348 DFS events in all randomized patients). At the 1st interim analysis, 132 DFS events had occurred in patients with tumour cell PD-L1 expression ≥ 1% (369 DFS events in all randomized patients). At the time of the erratum to the 1st data cut-off, 136 DFS events had occurred in patients with a tumour cell PD-L1 expression ≥ 1% (374 DFS events in all randomized patients). According to the company, this interim analysis was subsequently deemed the final DFS analysis because the predefined significance level had been reached. The 1st interim analysis for the outcome of overall survival (after the occurrence of about 91 events in the outcome of overall survival) was coupled to the final analysis for DFS. The company reports that for overall survival, the significance threshold had not yet been reached by the time of the 2nd data cut-off. A 2nd interim analysis for the outcome of overall survival was planned to occur after 125 events; the final analysis was planned to occur after 166 events. The study report and European Public Assessment Report show that the data were not unblinded and, therefore, no analyses are available (see Section 2.4.2.1 as well as the text below).
h. For the correction of data on DFS outcomes, the database was unlocked. Re-analysed and updated results were presented in an erratum on the study report with a data cut-off from 27 August 2020 (with a DBL of 13 April 2021).

AE: adverse event; DBL: database lock; DFS: disease-free survival; ECOG-PS: Eastern Cooperative Oncology Group – Performance Status; MIUC: muscle-invasive urothelial carcinoma; n: relevant subpopulation; N: number of randomized patients; PD-L1: programmed cell death ligand 1; RCT: randomized controlled trial; TNM: tumour-node-metastasis

Table 7: Characteristics of the intervention – RCT, direct comparison: nivolumab versus watchful waiting

Study	Intervention	Comparison
CA209-274	Nivolumab 240 mg i.v. every 2 weeks	Placebo i.v., every 2 weeks
	Dose adjustment: No dose adjustment allowed; treatment delays of a maximum of 42 days allowed	
	Required pretreatment ▪ R0 resection of the invasive urothelial carcinoma[a] **Non-permitted pretreatment** ▪ Chemotherapy, radiotherapy, anticancer biologics, intravesical therapy, or investigational preparations ≤ 28 days prior to the start of the study medication. ▪ Systemic corticosteroids (> 10 mg prednisone equivalents daily) or other immunosuppressants ≤ 14 days prior to the start of study medication and during the study ▪ Partial cystectomy in primary bladder cancer or partial nephrectomy in primary renal pelvis tumour. ▪ Systemic or radiotherapy in urothelial or prostate carcinoma after radical surgical resection of urothelial carcinoma **Non-permitted concomitant treatment** ▪ Any antineoplastic therapy (i.e. chemotherapy, hormone therapy, immunotherapy, standard or investigational preparations, surgical procedures, or radiotherapy for cancer treatment) ▪ Any intravesical anticancer medications and TUR of the urothelial tract disease except when a recurrence has been documented and the study treatment was completed before the TUR/intravesical therapy[b] **Allowed prior and concomitant treatment** ▪ Corticosteroids in any forms of administration with minimal systemic absorption and < 3 weeks of corticosteroids for prophylaxis or for treatment of non-autoimmune conditions	

a. The resection was to have been conducted within 120 days prior to randomization.
b. Exception: Chemotherapy administered as a single dose intravesically after the resection of a low-risk non-muscle-invasive urothelial carcinoma (standard therapy) is allowed.

i.v.: intravenous; RCT: randomized controlled trial; TUR: transurethral resection

The CA209-274 study is an ongoing double-blind RCT comparing nivolumab versus placebo. The study enrolled adult patients with MIUC originating in the bladder or upper urinary tract (renal pelvis or ureter) who are at high risk of recurrence following radical MIUC resection. Prerequisite for inclusion was R0 resection ≤ 120 days prior to randomization. Patients who had received neoadjuvant cisplatin chemotherapy had to have the following TNM status: ypT2-pT4a or ypN+. Patients who had received no neoadjuvant cisplatin chemotherapy and who either were not eligible for or refused adjuvant cisplatin chemotherapy had to have the following status: pT3–pT4a or pN+. Patients with the above TNM statuses are assumed to be at high risk of recurrence. Refusal of cisplatin chemotherapy (by medically eligible patients) had to be thoroughly documented. At enrolment, patients had to be in good general condition corresponding to an ECOG-PS of 0 or 1. Patients with an ECOG-PS of 2 were eligible for enrolment if they had not received any neoadjuvant cisplatin chemotherapy and were ineligible for adjuvant cisplatin chemotherapy (ECOG-PS of 2 was deemed a criterion for ineligibility). Patients additionally had to be disease free as documented by a complete physical examination and imaging within 4 weeks prior to randomization.

The tumour tissue's PD-L1 expression had to be determined for study inclusion. This test had to be performed in a central laboratory. However, patients were included in the study regardless of their PD-L1 expression. PD-L1 expression on the tumour cells was determined using the PD-L1 IHC 28-8 pharmDx assay.

The CA209-274 study enrolled a total of 709 patients and randomized them in a 1:1 ratio to either nivolumab treatment (N = 353) or to placebo (N = 356). Randomization was stratified by pathological lymph node status (N+ versus N0/x with < 10 removed lymph nodes versus N0 with ≥ 10 removed lymph nodes), PD-L1 tumour expression (≥ 1% versus < 1%, not determined), and the use of cisplatin as neoadjuvant chemotherapy (yes versus no).

Treatment with nivolumab in the intervention arm was in compliance with the recommendations of the SPC [14].

Treatment with the study medication continued until recurrence, unacceptable toxicity, or withdrawal of consent, but for no longer than 1 year. The study did not provide for any switching to the treatment of the other study arm.

The primary outcome of the CA209-274 study was DFS. Patient-relevant secondary outcomes were outcomes in the mortality, morbidity, health-related quality of life, and AE categories.

Relevant subpopulation

In accordance with the approved therapeutic indication, only the CA209-274 study's subpopulation of patients with tumour cell PD-L1 expression ≥ 1% is relevant for the benefit assessment. Module 4 R of the company's dossier presents analyses of this subpopulation (140 patients in the nivolumab arm and 142 patients in the placebo arm). Furthermore, the G-BA's research question 2 comprises only patients not eligible for cisplatin-containing therapy. In addition, uncertainties exist as described in the section below.

Research question 2: Patients who are not eligible for cisplatin-containing therapy

Regarding subpopulations, Section 4.2.5.2.1 (Module 4 R) of the company's dossier states that in the adjuvant treatment of MIUC, the ACT specified by the G-BA requires the nivolumab target population to be split into 2 groups. The company argues that the split is determined by patients' eligibility or ineligibility for cisplatin-containing chemotherapy. In the adjuvant treatment of MIUC, cisplatin-containing chemotherapy is generally indicated unless neoadjuvant chemotherapy has already been conducted or the patient's general health and comorbidities forbid such therapy. Below, the company lists 5 criteria from the German S3 guideline on bladder cancer [15], in the presence of at least 1 of which patients should not be treated with cisplatin-containing chemotherapy: World Health Organization Performance Status or ECOG-PS ≥ 2 or Karnofsky Performance Status ≤ 70%, creatinine clearance (calculated or measured) ≤ 60 mL/min, hearing loss in audiometry (≥ grade 2 Common Terminology Criteria for Adverse Events [CTCAE] version 4), peripheral neuropathy (≥ grade 2 CTCAE version 4), or heart failure of New York Heart Association (NYHA)

class ≥ III. The company concludes that the inclusion and exclusion criteria of the CA209-274 study relevant for the present benefit assessment is in line with the described specifications of the German S3 guideline.

The company's arguments regarding the patient population relevant for research question 2 are only partially plausible. While the company correctly describes the criteria based on which patients are deemed ineligible for adjuvant cisplatin-containing chemotherapy as per S3 guideline, the company failed to mention that the study and therefore the relevant subpopulation explicitly included patients who refused adjuvant cisplatin-containing chemotherapy despite them being medically indicated for such treatment. The information provided by the company on patients' prior therapies suggests the reasons for which patients did not receive prior cisplatin-containing chemotherapy (also see Table 10). The reason why most of these patients (a total of 36% in the nivolumab arm versus 32% in the placebo arm) received no cisplatin-containing chemotherapy was that they were unwilling to give consent. While the study protocol stipulated that this refusal to be thoroughly documented, the manufacturer's dossier does not provide any further information on this patient population. Likewise, the G-BA does not explicitly identify this patient group. Overall, it remains unclear whether the relatively high percentage of CA209-274 participants who refused cisplatin-containing chemotherapy is consistent with healthcare practice in Germany.

For muscle-invasive urothelial carcinoma, national guidelines recommend either neoadjuvant or adjuvant cisplatin-containing chemotherapy because a metaanalysis found a survival advantage for these therapies [15,16]. Before treatment start, the treatment concept is to be defined by a multidisciplinary team. The CA209-274 study protocol, however, does not incorporate these recommendations. The treatment alternatives section of the patient consent form likewise lists neither the above-mentioned survival advantage of adjuvant cisplatin-containing chemotherapy nor the multidisciplinary treatment concept. Instead, it states (translated from study report): While clinical trials have produced contradictory results on the benefit of adjuvant chemotherapy, some studies have shown that adjuvant chemotherapy regimens containing cisplatin can delay recurrence. Adjuvant cisplatin-containing chemotherapy can be an option for patients who tolerate cisplatin depending on parameters including, but not limited to, renal function and hearing. This study includes patients who refuse or are ineligible for cisplatin chemotherapy. Talk to your physician about this treatment option before deciding to participate in the study. Hence, the information on the study's consent form does not fully cover the information and recommendations provided in the guidelines [15,16], particularly by failing to clearly discuss the survival advantage of adjuvant chemotherapy. Therefore, it is conceivable that patients were not fully informed about the advantages and disadvantages of the treatment options available to them.

Overall, it therefore remains unclear, first, whether the relatively high percentage of CA209-274 participants (about one-third) who refused cisplatin-containing chemotherapy is consistent with healthcare practice in Germany. Second, it remains unclear whether in healthcare practice, at least a portion of these patients would have decided in favour of cisplatin-containing

chemotherapy if they had been informed about all relevant aspects cited in the guidelines – and these patients would therefore be allocated to research question 1 rather than 2 (patients eligible for cisplatin-containing therapy).

The benefit assessment used the analyses presented by the company for the CA209-274 study's subpopulation of patients with tumour cell PD-L1 expression ≥ 1%. The assessment of the CA209-274 study results' certainty of conclusions accounts for the uncertainty regarding whether a relevant percentage of patients might have been eligible for adjuvant cisplatin-containing therapy after all. A summary assessment of the risk of bias can be found in Section 2.4.2.2.

Available data and data cut-offs

In the dossier's Module 4 R, the company presents analyses of various data cut-offs for the different outcomes or outcome categories. Table 8 shows the data cut-offs and the results reported for them by outcome category.

Table 8: Analyses presented by the company for the CA209-274 study for each data cut-off and outcome category

Data cut-off	Mortality[a]	Morbidity	Health-related quality of life	Side effects
1st data cut-off, August 2020[b]: ▪ 17 July 2020 with DBL of 27 August 2020	–	x	x	x
▪ Erratum for DFS outcomes[c]: 27 August 2020 with DBL of 13 April 2021	–	x[d]	–	–
2nd data cut-off, February 2021[e]: ▪ 1 February 2021 with DBL of 19 May 2021	–	x[d]	–	–

a. The first interim analysis for the outcome of overall survival was planned to occur at the same time point as the final analysis for DFS. The company reports that for overall survival, the significance threshold had not yet been reached by the time of the 2nd data cut-off. The study report and European Public Assessment Report show that the data were not unblinded and no analyses are therefore available (see Section 2.4.2.1 as well as the section below).
b. Planned 1st interim analysis of the DFS outcome; according to the company, this interim analysis was later deemed the final DFS analysis because the predefined significance level had been reached by the 1st data cut-off.
c. The database was unlocked for correcting data on DFS outcomes. Re-analysed and updated results were submitted in an erratum to the study report.
d. Only DFS outcomes.
e. As part of the marketing authorization procedure, updated data for DFS outcomes were submitted.

DBL: database lock; DFS: disease-free survival

Results on 2 data cut-offs are available for the CA209-274 study:

- 1st data cut-off, August 2020: The 1st interim analysis of the DFS outcome had been planned to occur after 137 DFS events in patients with tumour cell PD-L1 expression

≥ 1% (348 DFS events in all randomized patients). At the 1st data cut-off, 132 DFS events had occurred in patients with tumour cell PD-L1 expression ≥ 1% (369 DFS events in all randomized patients). At the time of the erratum to the 1st data cut-off, 136 DFS events had occurred in patients with a tumour cell PD-L1 expression ≥ 1% (374 DFS events in all randomized patients). According to the company, this interim analysis was subsequently deemed the final DFS analysis because the predefined significance level had been reached. For the 1st data cut-off, the company's dossier presents data on all outcomes except overall survival.

In the present report, the 1st data cut-off is referred to as the August 2020 data cut-off. This comprises data from both the 17 July 2020 data cut-off with database lock (DBL) on 27 August 2020 and data from the data cut-off for the erratum to the study report from 27 August 2020, with a DBL of 13 April 2021, with data updated only for DFS outcomes.

- Second data cut-off, February 2021: The available documents fail to specify why this data cut-off was implemented. As part of the marketing authorization procedure, updated data for DFS outcomes were submitted for this data cut-off. The company reports that symptoms, health status, quality of life, and tolerability outcomes were not updated in February 2021 because at the time of the first data cut-off (August 2020), few patients (with tumour cell PD-L1 ≥ 1%) remained under treatment (8 in the nivolumab arm versus 5 in the placebo arm), and very little time had passed between the 2 data cut-offs (about 6 months). For the 2nd data cut-off, the company's dossier presents data only for DFS and recurrence rate. Data on overall survival are missing for the 2nd data cut-off as well. No study report is available for the 2nd data cut-off.

According to the company, the 1st interim analysis for the outcome of overall survival was coupled to the final analysis for DFS and was planned to occur after about 91 events in the outcome of overall survival. The company reports that for overall survival, the significance threshold had not yet been reached by the time of the 2nd data cut-off. According to the company, at the time of the 2nd data cut-off, 84 events had been observed for the outcome of overall survival. A 2nd interim analysis of the outcome of overall survival was planned to occur after 125 events with the final analysis to occur after 166 events. The study report and European Public Assessment Report show that the data were not unblinded and no analyses are therefore available.

Hence, the manufacturer's dossier does not provide any data on overall survival. The lack of these data is not appropriate in the present situation and has not been adequately justified by the company. In the present oncological indication, patients' overall survival is of particular importance. The missing data on overall survival represent an uncertainty which is taken into account in the certainty of results (also see Sections 2.4.2.1 and 2.4.2.2).

As described above concerning the 2nd data cut-off and in deviation from the dossier template [17], the company failed to submit any analyses for patient-relevant outcomes except recurrence rate and DFS for the 2nd data cuff. This approach was insufficiently justified by the company.

For the symptoms, health status, health-related quality of life, and side effects outcomes, the data from the 1st data cut-off are nevertheless deemed sufficient because the time interval between the 2 data cut-offs is relatively short, at about 6 months. At the time of the 1st data cut-off, few patients remained under treatment (8 versus 5 patients), and an estimated maximum of 18% of patients were still under follow-up observation for the outcomes with shortened observation period (treatment end plus about 100 days, see Section 2.4.1.2), i.e. symptoms, health-related quality of life, and side effects. For these outcome categories, no relevant amount of additional data would presumably have become available between the 1st and 2nd data cut-offs. The outcome of health status, in contrast, was to be observed for as long as overall survival. Consequently, a potentially relevant amount of data could be added at the 2nd data cut-off for all patients remaining in the study.

The absence of the described data for the current 2nd data cut-off is not appropriate. Irrespective of this, the presented analyses for the outcomes on symptoms, health status, and health-related quality of life are unsuitable for the benefit assessment (see Section 2.4.2.1). Due to the longer observation period, data from the 2nd data cut-off were used for DFS and recurrence rate.

Implementation of the ACT

For patients who are not eligible for cisplatin-containing therapy, the G-BA specified the ACT of watchful waiting.

The CA209-274 study used placebo as comparator therapy. The study was not designed for a comparison with watchful waiting but is nonetheless suitable for such a comparison. This is explained below.

The following examinations were performed for assessing health status or detecting recurrences in the CA209-274 study:

- specific physical examination, determination of weight and ECOG-PS as well as laboratory work during the treatment phase, at the start of each treatment cycle (see Table 7), and (except for ECOG-PS and weight) at follow-up visit 1 (35 days [± 7 days] after the last dose of the study medication) and at follow-up visit 2 (80 days [± 7 days] after follow-up visit 1).
- Imaging (computed tomography or magnetic resonance imaging) every 12 weeks up to Week 96, every 16 weeks from Week 96 to Week 160 and thereafter every 24 weeks until a recurrence outside the urothelial tract or treatment discontinuation (whichever occurs later), for a maximum of 5 years.
- Cystoscopy for patients with primary tumours of the upper urinary tract whose bladder is still intact, to be conducted every 12 weeks up to Week 48, every 24 weeks from Week 48 to Week 96, and thereafter every 48 weeks until a recurrence outside the urothelial tract or treatment discontinuation (whichever occurs later) for a maximum of 5 years.

According to the S3 guideline, the follow-up is to comprise early detection of tumour recurrence, metabolic changes, dysfunction, and psycho-oncological and social status. Patients with TNM stage > pT3 and/or pN+ were to receive regular laboratory work and sonography (3 and 6 months after radical cystectomy, then every 6 months, and annually starting from the 5th follow-up year). A stoma exam and anamnesis of continence and sexual function as well as psycho-oncological status were to be performed at the same intervals. Follow-up with imaging for the detection of tumour recurrence was to take place 3 to 6 months after radical cystectomy, every 6 months until the 3rd year of follow-up, and every 12 months in the 4th to 5th year of follow-up [15]. For patients in TNM stage ≤ pT2, pN0, and cM0, the same examinations are recommended, but imaging was to be taken at longer intervals.

The investigations performed in the CA209-274 study did not fully implement guideline recommendations. In particular, sonography is not discussed despite this procedure being used to detect dysfunction throughout the urinary tract. Additionally, urine cytology was not conducted as a standard test but only when clinically indicated. Despite these deviations from guideline recommendations, CA209-274 participants were overall monitored closely with specific examinations to record their health status as well as recurrences, so that the examination regimen is overall deemed to be a sufficient approximation to the ACT of watchful waiting.

Planned duration of follow-up observation

Table 9 shows the planned duration of patient follow-up observation for the individual outcomes.

Table 9: Planned duration of follow-up observation – RCT, direct comparison: nivolumab versus watchful waiting

Study **Outcome category** **Outcome**	**Planned follow-up observation**
CA209-274	
Mortality	
Overall survival	Until death, revocation of consent, lost to follow-up, or study end; maximum of 5 years after the primary DFS analysis
Morbidity	
Recurrence[a]	Until a recurrence outside the urothelial tract or treatment discontinuation (whichever was later); a maximum of up to 5 years
Symptoms (EORTC QLQ-C30)	About 100 days after the last dose of the study medication
Health status (EQ-5D VAS)	Until death, revocation of consent, lost to follow-up, or study end; maximum of 5 years after the primary DFS analysis
Health-related quality of life (EORTC QLQ-C30)	About 100 days after the last dose of the study medication
Side effects	
All outcomes in the side effects category	About 100 days after the last dose of the study medication[b]

a. Presented via recurrence rate and DFS; comprises the events of local recurrence in the urothelial tract, local recurrence outside the urothelial tract, distant metastases, and death for any cause (without prior recurrence).
b. After the 2nd follow-up visit (about 100 days after the last dose of the study medication), only side effects which were deemed to be due to the study therapy were surveyed.

DFS: disease-free survival; EORTC: European Organisation for Research and Treatment of Cancer; EQ-5D: European Quality of Life Questionnaire 5 Dimensions; QLQ-C30: Quality of Life Questionnaire-Core 30; RCT: randomized controlled trial; VAS: visual analogue scale

The observation periods for the outcomes of symptoms, health-related quality of life as well as outcomes of the side effects category were systematically shortened because they were surveyed only for the period of treatment with the study medication (plus about 100 days). For these outcomes, data are therefore available only for the shortened observation period. Data on the entire study duration or until death are missing.

However, to be able to draw a reliable conclusion on the total study period or the time to patient death, it would be necessary to record these outcomes for the total period, as was done for survival.

Characteristics of the study population

Table 10 shows the characteristics of the patients in the included study.

Table 10: Characteristics of the study population as well as study/therapy discontinuation – RCT, direct comparison: nivolumab versus watchful waiting (multipage table)

Study **Characteristic** **Category**	**Nivolumab** **N[a] = 140**	**Placebo** **N[a] = 142**
CA209-274		
Age [years], mean (SD)	64 (10)	66 (8)
Sex [f/m], %	28/72	21/79
Smoking status		
Previous/current	96 (69)	101 (71)
Never smoker	42 (30)	40 (28)
Unknown	2 (1)	1 (1)
Ancestry, n (%)		
White	104 (74)	109 (77)
Black or African American	0 (0)	2 (1)
Asian	33 (24)	28 (20)
Native American or Alaska Native	1 (1)	0 (0)
Other	2 (1)	2 (1)
Not specified	0 (0)	1 (1)
ECOG-PS, n (%)		
0	86 (61)	85 (60)
1	51 (36)	53 (37)
2	3 (2)	4 (3)
Tumour origin		
Urinary bladder	113 (81)	117 (82)
Renal pelvis	19 (14)	14 (10)
Ureter	8 (6)	11 (8)
Time from first disease diagnosis until randomization		
< 1 year	132 (94)	129 (91)
≥ 1 year	8 (6)	13 (9)
Pathological stage at resection		
Tumour stage		
pTx	4 (3)	0 (0)
pT0	3 (2)	3 (2)
pTis	0 (0)	0 (0)
pT1	4 (3)	2 (1)
pT2	19 (14)	26 (18)
pT3	87 (62)	83 (59)
pT4A	23 (16)	27 (19)
Not specified	0 (0)	1 (1)

Table 10: Characteristics of the study population as well as study/therapy discontinuation – RCT, direct comparison: nivolumab versus watchful waiting (multipage table)

Study **Characteristic** **Category**	**Nivolumab** **N[a] = 140**	**Placebo** **N[a] = 142**
Lymph node status and number of removed lymph nodes		
N0/X with < 10 removed lymph nodes	38 (27)	38 (27)
N0 with ≥ 10 removed lymph nodes	42 (30)	38 (27)
N1	29 (21)	33 (23)
N2	28 (20)	26 (18)
N3	3 (2)	7 (5)
PD-L1 tumour cell expression status		
≥ 1% and < 5%	29 (21)	35 (25)
≥ 5%	110 (79)	105 (74)
Not specified	1 (1)	1 (1)
Prior neoadjuvant therapy	61 (44)	62 (44)
Prior cisplatin therapy		
Yes	57 (41)	61 (43)
No	83 (59)	81 (57)
Reason for not having received any prior cisplatin therapy		
Lack of consent (unwilling)	51 (36)	46 (32)
Ineligible due to impaired renal function	19 (14)	22 (16)
Ineligible due to neuropathy	0 (0)	1 (1)
Ineligible due to hearing loss	1 (1)	4 (3)
Ineligible due to impaired PS	4 (3)	5 (4)
Ineligible due to impaired cardiac function	3 (2)	2 (1)
Other reasons	4 (3)	0 (0)
Not specified	1 (1)	1 (1)
Time from radical resection until randomization		
≥ 0 and ≤ 30 days	1 (1)	0 (0)
> 30 and ≤ 60 days	35 (25)	28 (20)
> 60 and ≤ 90 days	57 (41)	66 (47)
> 90 and ≤ 120 days	46 (33)	41 (29)
> 120 days	1 (1)	7 (5)
Treatment discontinuation, n (%)[b, c]	71 (51)	87 (63)
Treatment phase completed[c]	60 (43)	47 (34)
Study discontinuation, n (%)[c,d]	8 (6)	15 (11)

Table 10: Characteristics of the study population as well as study/therapy discontinuation – RCT, direct comparison: nivolumab versus watchful waiting (multipage table)

Study Characteristic Category	Nivolumab N[a] = 140	Placebo N[a] = 142
a. Number of randomized patients. Values which are based on other patient numbers are marked in the corresponding line if the deviation is relevant. b. Common reasons for premature treatment discontinuation (i.e. discontinuation prior to reaching the planned maximum treatment duration of 1 year) in the nivolumab arm versus placebo arm: recurrence of disease (24% versus 42%), toxicity (17% versus 5%), AEs unrelated to the study medication (3% versus 6%). c. 1st data cut-off, August 2020. d. Common reasons for study discontinuation in the intervention arm versus control arm were withdrawal of consent (4% vs. 4%) and death (1% versus 4%). It is unclear why these data differ from the event rates of deaths from the side effects analyses in the study report (21.6% versus 33.8%). ECOG-PS: Eastern Cooperative Oncology Group Performance Status; f: female; m: male; n: number of patients in the category; N: number of randomized patients; PD-L1: programmed cell death ligand 1; RCT: randomized controlled trial; SD: standard deviation		

Both study arms were very similar in terms of the demographic and clinical characteristics of the patients in the relevant subpopulation. The mean patient age was 65 years. A substantial majority of the patient population was male, with the proportion of women being slightly higher in the nivolumab arm at 28% than in the nivolumab arm at 21%. The majority of the patient population was of White ancestry. The tumour originated in the urinary bladder in about 82% of patients, in the renal pelvis in about 12%, and in the ureter in about 7%. About 42% of patients had received prior cisplatin therapy. The most common reason for premature treatment discontinuation was disease recurrence (nivolumab arm: 24%; placebo arm: 42%).

Information on the course of the study

Table 11 shows patients' median/mean treatment durations and the median/mean observation periods for individual outcomes.

Table 11: Information on the course of the study – RCT, direct comparison: nivolumab versus watchful waiting

Study **Duration of the study phase** **Outcome category**	**Nivolumab** **N = 139[a]**	**Placebo** **N = 139[a]**
CA209-274		
Treatment duration [months]		
August 2020 data cut-off		
Median [min; max]	10.1 [0.0; 12.5]	6.5 [0.0; 12.0]
Mean (SD)	7.8 (ND)	7.0 (ND)
February 2021 data cut-off		
Median [min; max]	10.6 [0.0; 12.5]	6.5 [0.0; 12.0]
Mean (SD)	7.9 (ND)	7.0 (ND)
Duration of follow-up observation [months]		
August 2020 data cut-off		
Overall survival[b]		
Median [min; max]	22.1 [0.1; 47.5]	18.7 [0.0; 49.1]
Mean (SD)	22.4 (ND)	20.3 (ND)
Outcomes of the morbidity, health-related quality of life, and side effects categories	ND	ND
February 2021 data cut-off		
Overall survival[b]		
Median [min; max]	25.5 [0.1; 54.3]	22.4 [0.0; 54.6]
Mean (SD)	26.3 (ND)	23.6 (ND)
Outcomes of the morbidity, health-related quality of life, and side effects categories	ND	ND

a. The information provided on observation durations is based on N = 140 in the nivolumab arm versus N = 142 in the placebo arm.
b. No information is available on how the observation period was calculated.

max: maximum; min: minimum; N: number of analysed patients; ND: no data; RCT: randomized controlled trial; SD: standard deviation

At the August 2020 data cut-off, the median treatment duration for patients in the relevant subpopulation was substantially higher in the nivolumab arm, at 10.1 months, than in the placebo arm, at 6.5 months. The company provided information on the observation duration only for the outcome of overall survival. No information on the observation duration was available for the outcomes of the morbidity, health-related quality of life, and side effects categories. While the outcomes of overall survival, recurrence, and health status were to be observed for a maximum of 5 years (after primary DFS analysis for the outcomes of overall survival and health status), the observation duration for the symptoms, health-related quality of life, and side effects outcomes was linked to treatment end (plus about 100 days) (see Table 9). For the latter outcomes, conclusions can therefore be drawn only for the period up to 100 days after treatment. Based on the information on treatment duration plus 100 days, the estimated

maximum median observation period was 13.4 months in the nivolumab arm and 9.8 months in the placebo arm. Hence, the observation durations for these outcomes were shortened in comparison with median overall survival. Data for the entire observation period are missing for these outcomes.

Additionally, the observation durations for the outcomes differ between study arms based on the differences in treatment durations. This data situation influences the interpretability of the outcomes with shorter observation period (see Section 2.4.2.1).

Information on subsequent therapies

Table 12 shows the subsequent therapies patients received after discontinuing the study medication.

Table 12: Information on subsequent antineoplastic therapies – RCT, direct comparison: nivolumab versus watchful waiting (CA209-274)

Study **Drug class** **Drug**	**Patients with subsequent therapy n (%)**	
	Nivolumab **N = 140**	**Placebo** **N = 142**
CA209-274		
Total[a,b]	39 (27.9)	54 (38.0)
Radiotherapy	7 (5.0)	11 (7.7)
Surgery	1 (0.7)	4 (2.8)
Systemic treatment	36 (25.7)	50 (35.2)
Immunotherapy	8 (5.7)	31 (21.8)
Nivolumab	0 (0)	5 (3.5)
Pembrolizumab	4 (2.9)	17 (12.0)
Atezolizumab	4 (2.9)	9 (6.3)
Ipilimumab	1 (0.7)	2 (1.4)
BCG intravesical	0 (0)	1 (0.7)
Platinum-containing chemotherapy	27 (19.3)	25 (17.6)
Carboplatin	14 (10.0)	12 (8.5)
Carboplatin + Taxol	1 (0.7)	0 (0)
Cisplatin	12 (8.6)	13 (9.2)
Cisplatin + doxorubicin, methotrexate + vinblastine	1 (0.7)	0 (0)
Oxaliplatin	1 (0.7)	0 (0)
VEGFR inhibitors (bevacizumab)	0 (0)	1 (0.7)
Further chemotherapeutics (docetaxel, gemcitabine, paclitaxel, methotrexate, etc.)	35 (25.0)	32 (22.5)

a. It was possible for patients to receive more than 1 subsequent therapy.
b. August 2020 data cut-off.

BCG: Bacillus Calmette Guerin; n: number of patients with subsequent therapy; N: number of analysed patients; RCT: randomized controlled trial; VEGF: vascular endothelial growth factor

With regard to subsequent therapies, the study protocol specified no limitations. After discontinuation of the study medication, 28% of the patients in the nivolumab arm and 38% of patients in the placebo arm received subsequent therapy. In both study arms, the subsequent therapy was predominantly systemic therapy. The majority of patients received other chemotherapies, some of them in combination with carboplatin or cisplatin. Additionally, 22% of patients in the placebo arm received immunotherapy (nivolumab arm: 6%).

Risk of bias across outcomes (study level)

Table 13 shows the risk of bias across outcomes (risk of bias at study level).

Table 13: Risk of bias across outcomes (study level) – RCT, direct comparison: nivolumab versus watchful waiting

Study	Adequate random sequence generation	Allocation concealment	Blinding		Nonselective reporting	No additional aspects	Risk of bias at study level
			Patients	Treatment providers			
CA209-274	Yes	Yes	Yes	Yes	Yes	Yes	Low
RCT: randomized controlled trial							

The risk of bias across outcomes was rated as low for the CA209-274 study.

Transferability of the study results to the German health care context

In the company's view, the results of the CA209-274 study are fully transferable to the German health care context due to the study design as well as the characteristics of the investigated patient population. Additionally, the company reports that the use of nivolumab in the CA209-274 study is in line with approval. In summary, the CA209-274 study results are reportedly fully transferable to the German healthcare context.

The company did not provide any further information on the transferability of the study results to the German health care context.

2.4.2 Results on added benefit

2.4.2.1 Outcomes included

The following patient-relevant outcomes were to be taken into account in the assessment:

- Mortality
  - overall survival
- Morbidity

- recurrence
- symptoms, surveyed using the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire – Core 30 (EORTC QLQ-C30)
- health status, surveyed using the EQ-5D VAS

- Health-related quality of life
  - surveyed with the EORTC QLQ-C30
- Side effects
  - SAEs
  - severe AEs (CTCAE grade ≥ 3)
  - discontinuation due to AEs
  - immune-related SAEs
  - immune-related severe AEs
  - further specific AEs, if any

Table 14 shows the outcomes for which data were available in the included study.

Table 14: Matrix of outcomes – RCT, direct comparison: nivolumab versus watchful waiting

Study	Outcomes										
	Overall survival	Recurrences[a]	Symptoms (EORTC QLQ-C30)	Health status (EQ-5D VAS)	Health-related quality of life (EORTC QLQ-C30)	SAEs[b]	Severe AEs[b, c]	Discontinuation due to AEs[b]	Immune-related SAEs[d]	Immune-related severe AEs[c, d]	Further specific AEs[e]
CA209-274	No[f]	Yes	No[g]	No[g]	No[g]	Yes	Yes	Yes	Yes	Yes	Yes

a. Presented via recurrence rate and DFS; comprises the events of local recurrence in the urothelial tract, local recurrence outside the urothelial tract, distant metastases, and death for any cause (without prior recurrence).
b. Excludes progression events of the underlying disease (according to the company's list, several PTs of the SOC "benign, malignant and unspecified [including cysts and polyps]").
c. Severe AEs are operationalized as CTCAE grade ≥ 3.
d. The operationalization of a specific MedDRA PT collection ("select AE") presented by the company was used in each case.
e. Analysed were the following events (MedDRA coded): diseases of the skin and subcutaneous tissue (SOC, AEs), asthenia (PT, AEs), infections and infestations (SOC, SAEs), respiratory, thoracic and mediastinal disorders (SOC, SAEs), gastrointestinal disorders (SOC, severe AEs), lipase increased (PT, severe AEs).
f. No data are available on overall survival (see Section 2.4.1.2 and the section below in this dossier assessment).
g. No usable data available; for reasoning, see the section below in this dossier assessment.

AE: adverse event; CTCAE: Common Terminology Criteria for Adverse Events; DFS: disease-free survival; EORTC: European Organisation for Research and Treatment of Cancer; EQ-5D: European Quality of Life Questionnaire 5 Dimensions; MedDRA: Medical Dictionary for Regulatory Activities; PT: Preferred Term; QLQ-C30: Quality of Life Questionnaire-Core 30; RCT: randomized controlled trial; SAE: serious adverse event; SOC: System Organ Class; VAS: visual analogue scale

Notes on outcomes

Analyses on overall survival

No data are available on overall survival (see Section 2.4.1.2 of this dossier assessment). In the present oncological research question, this is not appropriate. In addition, the company's justification for foregoing a presentation of results on overall survival is not entirely plausible because – at least for the 1st data cut-off (August 2020) – the study report's analyses of side effects provide data on the number of deceased patients, unblinded per treatment arm (see Table 16). However, it remains unclear whether all deaths which occurred in the study were included in this analysis since according to the footnote, the follow-up observation period was only 30 days. In addition, the event "death for any cause (without prior recurrence)" is included in the analyses of disease-free survival, which means that the number of deaths per treatment arm had to be known. The uncertainties resulting from the lack of data on overall survival are taken into account in the certainty of results (see Section 2.4.2.2).

Analyses on patient-reported outcomes of the morbidity and health-related quality of life categories

The analyses of the patient-reported outcomes are unsuitable for the benefit assessment. This is described in the following section.

Response criteria for the EORTC QLQ-C30 and EQ-5D VAS scales

For the EORTC QLQ-C30, the company's dossier presents responder analyses of the proportion of patients with a change by ≥ 10 points of the scale range (respective scale range 0–100). As explained in the *General Methods* of the Institute [1,18], for a response criterion to reflect with sufficient certainty a patient-noticeable change, it should correspond to a predefined value of at least 15% of the scale range of an instrument (in post hoc analyses exactly 15% of the scale range). For the EORTC QLQ-C30 and its supplementary modules, the analysis with a response threshold of 10 points is deemed a sufficient approximation to an analysis with a 15% threshold (15 points) [19].

For the analyses of EQ-5D VAS, the company uses the threshold of 15 points, among others. This corresponds to 15% of the instrument's scale range.

The response criteria used by the company are therefore appropriate.

Unusable time-to-event analyses of the EORTC QLQ-C30 scales

For patient-reported outcomes, the company presents time-to-event analyses in the categories of symptoms and health-related quality of life, surveyed with EORTC QLQ-C30. These were operationalized as time to "definitive deterioration". "Definitive deterioration" was defined as a decrease of the corresponding score by at least the response criterion without subsequent improvement above the response criterion in one of the following recordings.

As described in Section 2.4.1.2, the follow-up duration for the outcomes on symptoms and health-related quality of life were (a) systematically shortened compared to the median overall survival and (b) substantially differed between treatment arms (see Table 9 and Table 11). This makes it difficult to interpret the analysis of time to definitive deterioration; among other things, lasting deterioration across all subsequent values is potentially more difficult to reach in the intervention arm observed for a longer period (nivolumab treatment). In this situation, analyses of time to first deterioration are needed. The EORTC QLQ-C30 scales' time-to-event analyses are therefore unusable.

Unusable time-to-event analyses of EQ-5D VAS

The company's presented operationalization of time to definitive deterioration for the outcome of health status (EQ-5D VAS) corresponds to the above-described operationalization for the outcomes of the symptoms and health-related quality of life categories. Unlike EORTC QLQ-30, health status (EQ-5D VAS) should be surveyed until the end of the survival follow-up (a maximum of 5 years after primary DFS analysis). However, the information provided on return rates shows that, in both arms, the corresponding percentages decreased after the end of

treatment with the study medication. Due to the missing data on overall survival, it is impossible to determine whether the return rates were calculated correctly. It is impossible to determine whether definitive deterioration has been adequately analysed because (a) return rate data are available only separately for the period on treatment and the period after treatment and (b) follow-up visits were not allocated to the corresponding time points after randomization (i.e. the corresponding visits occurring at that time). The company did not present any information on the actual (e.g. median) duration of follow-up observation (see Table 11 and Section 2.4.1.2). In addition, no subgroup analyses are available on the response criterion relevant for the benefit assessment, 15 points. In the present scenario with unclear data, the analyses of definitive deterioration of the EQ-5D VAS were therefore disregarded.

Unusable mixed model for repeated measures (MMRM) analyses on the EORTC QLQ-C30 scales and EQ-5D VAS

As sensitivity analyses of the EORTC QLQ-C30 scales and EQ-5D VAS, the company additionally submitted analyses of change since study start using an MMRM. However, it remains unclear whether and, if so, how the surveys after treatment end were taken into account (2 subsequent surveys were conducted for EORTC QLQ-C30: follow-up visit 1 at about Day 35 and follow-up visit 2 at about Day 100; after these 2 follow-up visits, EQ-5D VAS was further followed up for a maximum of 5 years after the primary DFS analysis). The change over time curves presented in Module 4 R contain no data after treatment end. The benefit assessment requires for the entire observation period to be included in the analyses. Values collected after treatment end must be included in the analyses for the benefit assessment, and in case of premature treatment end, they must be transparently matched to the corresponding times from randomization (i.e. the visits at the corresponding times). Due to these deficiencies, the available MMRM analyses are likewise unsuitable for the benefit assessment and were therefore disregarded therein.

Summary on patient-reported outcomes of the categories of morbidity and health-related quality of life

The analyses presented on health-related quality of life, symptoms, and health status cannot be interpreted without further information and analyses. Hence, no suitable analyses on patient-reported outcomes are available for the benefit assessment.

Analyses on the outcomes of the category of side effects

The company submitted Kaplan-Meier curves for the overall rates of AEs (AEs, SAEs, severe AEs, discontinuation due to AEs), but not for analyses at the level of the System Organ Class (SOC) or Preferred Terms (PTs) of the Medical Dictionary for Regulatory Activities (MedDRA). This approach is inadequate but remains of no consequence for the present benefit assessment.

For the outcomes of immune-related AEs, immune-related severe AEs, and immune-related SAEs, the operationalization deemed relevant is a specific MedDRA PT collection ("select

AE") presented by the company. The latter is a selection of categories and PTs which represent typical immune-related AEs; immunosuppressant (e.g. corticosteroid) treatment of these AEs may have been required, but not necessarily so. This operationalization is deemed a sufficient approximation of immune-related AEs.

2.4.2.2 Risk of bias

Table 15 presents the risk of bias for the results of the relevant outcomes.

Table 15: Risk of bias across outcomes and outcome-specific risk of bias – RCT, direct comparison: nivolumab versus watchful waiting

Study	Study level	Outcomes										
		Overall survival	Recurrences[a]	Symptoms (EORTC QLQ-C30)	Health status (EQ-5D VAS)	Health-related quality of life (EORTC QLQ-C30)	SAEs	Severe AEs[b]	Discontinuation due to AEs	Immune-related SAEs[c]	Immune-related severe AEs[b, c]	Further specific AEs[d]
CA209-274	L	–[e]	L	–[f]	–[f]	–[f]	H[g]	H[g]	L[h]	H[g]	H[g]	H[g]

a. Presented via recurrence rate and DFS; comprises the events of local recurrence in the urothelial tract, local recurrence outside the urothelial tract, distant metastases, and death for any cause (without prior recurrence).
b. Severe AEs are operationalized as CTCAE grade ≥ 3.
c. In each case, the operationalization of a specific MedDRA PT collection presented by the company ("select AEs") was used.
d. Analysed were the following events (MedDRA coded): diseases of the skin and subcutaneous tissue (SOC, AEs), asthenia (PT, AEs), infections and infestations (SOC, SAEs), respiratory, thoracic and mediastinal disorders (SOC, SAEs), gastrointestinal disorders (SOC, severe AEs), lipase increased (PT, severe AEs).
e. No data are available on overall survival (see Sections 2.4.1.2 and 2.4.2.1 of this dossier assessment).
f. No usable data available; for reasons, see Section 2.4.2.1 of this dossier assessment.
g. Incomplete observations for potentially informative reasons.
h. Despite a low risk of bias, the certainty of results for the outcome of discontinuation due to AEs is assumed to be reduced (see section below).

AE: adverse event; CTCAE: Common Terminology Criteria for Adverse Events; DFS: disease-free survival; EORTC: European Organisation for Research and Treatment of Cancer; H: high; L: low; MedDRA: Medical Dictionary for Regulatory Activities; PT: Preferred Term; QLQ-C30: Quality of Life Questionnaire–Core 30; RCT: randomized controlled trial; SAE: serious adverse event; SOC: System Organ Class; VAS: visual analogue scale

The risk of bias for the result on the outcome of recurrence is rated as low. No usable data are available for the outcomes of symptoms (EORTC QLQ-C30), health status (EQ-5D VAS), or health-related quality of life (EORTC QLQ-C30) (see Section 2.4.2.1).

The risk of bias of the results for the outcomes of SAEs, severe AEs (overall rate and specific AEs) as well as immune-related SAEs / severe AEs is rated as high. For the mentioned

outcomes of the side effects category, observations are incomplete for potentially informative reasons due to (a) the follow-up duration being linked to treatment duration (100 days after the last administration of the study medication) and (b) the outcomes being potentially linked to the grounds for treatment discontinuation.

Although the risk of bias was low for the outcome of discontinuation due to AEs, the certainty of results for this outcome was reduced. Premature treatment discontinuation for reasons other than AEs is a competing event for the outcome to be recorded, discontinuation due to AEs. This means that after discontinuation for other reasons, AEs which would have led to treatment discontinuation may have occurred, but the criterion of discontinuation could then no longer be applied to them. It is impossible to estimate how many AEs are affected by this issue.

Summary assessment of the certainty of conclusions

Irrespective of the aspects described under risk of bias, the certainty of conclusions of the study results is reduced due to the uncertainties described in Section 2.4.1.2 regarding (a) the percentage of patients who might have been eligible for adjuvant cisplatin-containing chemotherapy after all and (b) the lack of data for the outcome of overall survival. Overall, at most hints, e.g. of an added benefit, can therefore be derived on the basis of the CA209-274 study.

2.4.2.3 Results

Table 16 summarizes the results for the comparison of nivolumab versus watchful waiting in patients who are not eligible for cisplatin-containing chemotherapy. Where necessary, calculations conducted by the Institute are provided in addition to the data from the company's dossier.

Tables on common AEs, SAEs, severe AEs, and discontinuation due to AEs are presented in Appendix B of the full dossier assessment. For information purposes, a list of the categories of immune-related AEs, immune-related SAEs, and severe immune-related AEs in which events occurred is presented in Appendix C of the full dossier assessment. The available Kaplan-Meier curves on the presented time-to-event analyses can be found in Appendix D of the full dossier assessment. The company did not submit any Kaplan-Meier curves for the further specific AEs.

Table 16: Results (mortality, morbidity, health-related quality of life, side effects) – RCT, direct comparison: nivolumab versus watchful waiting (multipage table)

Study	Nivolumab		Placebo		Nivolumab vs. placebo
Outcome category **Outcome**	**N**	**Median time to event in months [95% CI]** **Patients with event n (%)**	**N**	**Median time to event in months [95% CI]** **Patients with event n (%)**	**HR [95% CI]; p-value[a]**
CA209-274					
Mortality					
Overall survival[b]				ND[c]	
Morbidity					
Recurrence					
Recurrence rate[d, e]	140	– 56 (40.0)	142	– 85 (59.9)	RR: 0.67 [0.52; 0.85][f]; < 0.001[g]
Distant recurrence	140	– 41 (29.3)	142	– 54 (38.0)	–
Local recurrence outside the excretory urinary tract	140	– 7 (5.0)	142	– 20 (14.1)	–
Local recurrence within the excretory urinary tract, invasive	140	– 1 (0.7)	142	– 3 (2.1)	–
Local recurrence within the excretory urinary tract, noninvasive	140	– 2 (1.4)	142	– 2 (1.4)	–
Death for any cause (without prior recurrence)	140	– 5 (3.6)	140	– 6 (4.2)	–
DFS[d]	140	NR [22.10; NC] 56 (40.0)	142	8.41 [5.59; 20.04] 85 (59.9)	0.53 [0.38; 0.75]; < 0.001
Symptoms (EORTC QLQ-C30)				No usable data[h]	
Health status (EQ-5D VAS)				No usable data[h]	
Health-related quality of life					
EORTC QLQ-C30				No usable data[h]	

Table 16: Results (mortality, morbidity, health-related quality of life, side effects) – RCT, direct comparison: nivolumab versus watchful waiting (multipage table)

Study	Nivolumab		Placebo		Nivolumab vs. placebo
Outcome category Outcome	N	Median time to event in months [95% CI] Patients with event n (%)	N	Median time to event in months [95% CI] Patients with event n (%)	HR [95% CI]; p-value[a]
Side effects					
AEs (supplementary information)[i,j]	139	0.49 [0.33; 0.49] 137 (98.6)	139	0.59 [0.49; 0.85] 133 (95.7)	–
SAEs[i, j]	139	NR [13.80; NC] 51 (36.7)	139	NR [8.77; NC] 56 (40.3)	0.84 [0.58; 1.23]; 0.380
Severe AEs[i,j,k]	139	9.49 [6.11; 13.80] 74 (53.2)	139	NR [8.41; NC] 59 (42.4)	1.28 [0.91; 1.81]; 0.154
Discontinuation due to AEs[i,j]	139	NR 28 (20.1)	139	NR 14 (10.1)	1.94 [1.02; 3.70]; 0.039
Immune-related AEs (supplementary information)[i,l]	*139*	*1.68 [0.95; 2.33]* *108 (77.7)*	*139*	*4.53 [2.73; 8.05]* *80 (57.6)*	–
Immune-related SAEs[i, l]	139	NR 17 (12.2)	139	NR 6 (4.3)	2.64 [1.04; 6.72]; 0.034
Immune-related severe AEs[i, k, l]	139	NR 27 (19.4)	139	NR 9 (6.5)	2.89 [1.36; 6.14]; 0.004
Specific AEs[i]					
Skin and subcutaneous tissue disorders (SOC, AEs)	139	5.36 [2.79; 10.48] 76 (54.7)	139	NR 45 (32.4)	1.89 [1.30; 2.74]; 0.001
Asthenia (PT, AEs)	139	NR 18 (12.9)	139	NR 5 (3.6)	3.70 [1.37; 9.97]; 0.006
Infections and infestations (SOC, SAEs)	139	NR 14 (10.1)	139	NR 27 (19.4)	0.48 [0.25; 0.92]; 0.024
Respiratory, thoracic and mediastinal disorders (SOC, SAEs)	139	NR 9 (6.5)	139	NR 1 (0.7)	8.38 [1.06; 66.20]; 0.016
Gastrointestinal disorders (SOC, severe AEs[k])	139	NR 8 (5.8)	139	NR 17 (12.2)	0.44 [0.19; 1.01]; 0.047
Lipase increased (PT, severe AEs[k])	139	NR 11 (7.9)	139	NR 1 (0.7)	10.50 [1.35; 81.42]; 0.005

Table 16: Results (mortality, morbidity, health-related quality of life, side effects) – RCT, direct comparison: nivolumab versus watchful waiting (multipage table)

Study	Nivolumab		Placebo		Nivolumab vs. placebo
Outcome category Outcome	N	Median time to event in months [95% CI] Patients with event n (%)	N	Median time to event in months [95% CI] Patients with event n (%)	HR [95% CI]; p-value[a]

a. HR and CI from stratified Cox model with treatment as the sole covariate; p-value from log-rank test, each stratified by pathological lymph node status and use of cisplatin as neoadjuvant chemotherapy.
b. No data are available on overall survival (see Section 2.4.1.2 and 2.4.2.1 of this dossier assessment).
c. For the August 2020 data cut-off, the study report's analyses of side effects listed 30 deaths (21.6%) for the nivolumab arm and 47 deaths (33.8%) for the placebo arm. However, it remains unclear whether all deaths which occurred in the study were included in this analysis (see Section 2.4.2.1).
d. February 2021 data cut-off.
e. Percentage of patients; individual components are presented in the rows below (each only with the qualifying events which are relevant for the combined outcome; calculating effect estimators is therefore not meaningful).
f. Cochran-Mantel-Haenszel method stratified by pathological lymph node status and use of cisplatin as neoadjuvant chemotherapy.
g. IQWiG calculation, (unconditional exact test [CSZ method according to [20]]).
h. For reasoning, see Section 2.4.2.1 of this dossier assessment.
i. August 2020 data cut-off.
j. Excluding progression events of the underlying disease (several PTs of the SOC "benign, malignant and unspecified [including cysts and polyps]" according to the company's list).
k. Operationalized as CTCAE grade ≥ 3.
l. In each case, the operationalization of a specific MedDRA PT collection submitted by the company ("select AE") was used.

AE: adverse event; CI: confidence interval; CTCAE: Common Terminology Criteria for Adverse Events; DFS: disease-free survival; EORTC: European Organisation for Research and Treatment of Cancer; EQ-5D: European Quality of Life Questionnaire 5 Dimension; HR: hazard ratio; MedDRA: Medical Dictionary for Regulatory Activities; n: number of patients with (at least one) event; N: number of analysed patients; NC: not calculable; ND: no data; NR: not reached; PT: Preferred Term; QLQ-C30: Quality of Life Questionnaire–Core 30; RCT: randomized controlled trial; RR: relative risk; SAE: serious adverse event; SOC: System Organ Class; VAS: visual analogue scale

On the basis of the available information, at most hints, e.g. of an added benefit, can be determined for all outcomes (see Section 2.4.2.2).

Mortality

No data are available on overall survival (for justification, see Section 2.4.1.2 and 2.4.2.1 of this dossier assessment). This results in no hint of an added benefit of nivolumab in comparison with watchful waiting; an added benefit is therefore not proven.

Morbidity

Recurrence

Operationalization

For the present benefit assessment, the outcome of recurrence was operationalized as the proportion of patients with recurrence and, additionally, as time to recurrence of the disease. For the outcome of DFS, the operationalization presented by the company is used without censoring of the patients who started a subsequent therapy.

Result

For the outcome of recurrence (operationalized as recurrence rate and DFS), a statistically significant difference in favour of nivolumab in comparison with placebo was shown for both operationalizations. This results in a hint of an added benefit of nivolumab versus watchful waiting.

Symptoms

No usable data were available for the outcome of symptoms, recorded with the EORTC QLQ-C30 (for reasons, see Section 2.4.2.1). This results in no hint of an added benefit of nivolumab in comparison with watchful waiting; added benefit is therefore not proven.

Health status

No usable data are available for the outcome of health status (surveyed with EQ-5D VAS) (for reasons, see Section 2.4.2.1). This results in no hint of an added benefit of nivolumab in comparison with watchful waiting; added benefit is therefore not proven.

Health-related quality of life

No usable data are available for the outcome of health-related quality of life (surveyed with the EORTC QLQ-C30) (for reasons, see Section 2.4.2.1). This results in no hint of an added benefit of nivolumab in comparison with watchful waiting; added benefit is therefore not proven.

Side effects

SAEs and severe AEs

There was no statistically significant difference between the treatment arms for either of the outcomes of SAEs or severe AEs. Hence, there was no hint of greater or lesser harm from nivolumab in comparison with watchful waiting for either of them; greater or lesser harm is therefore not proven.

Discontinuation due to AEs

A statistically significant difference to the disadvantage of nivolumab compared with placebo was shown for the outcome of discontinuation due to AEs. This results in a hint of greater harm from nivolumab in comparison with watchful waiting.

Specific AEs

Immune-related SAEs, immune-related severe AEs, diseases of the skin and subcutaneous tissue (AEs), asthenia (AEs), respiratory, thoracic, and mediastinal disorders (SAEs), lipase increased (severe AEs)

For each of the outcomes of immune-related SAEs, immune-related severe AEs, skin and subcutaneous tissue disorders (AEs), asthenia (AEs), respiratory, thoracic, and mediastinal disorders (SAEs), and lipase increased (severe AEs), there was a statistically significant difference to the disadvantage of nivolumab in comparison with placebo. In each case, this results in a hint of greater harm from nivolumab versus watchful waiting.

Infections and infestations (SAEs), gastrointestinal disorders (severe AEs)

A statistically significant difference in favour of nivolumab in comparison with placebo was shown for each of the outcomes of infections and infestations (AEs) and gastrointestinal disorders (severe AEs). In each case, this results in a hint of lesser harm from nivolumab versus watchful waiting. However, given the placebo-controlled study design, it is questionable whether, for the outcomes of gastrointestinal disorders as well as infections and infestations, the effect is actually to be allocated to the outcome category of side effects or whether it rather reflects the symptoms of disease.

2.4.2.4 Subgroups and other effect modifiers

The following subgroup characteristics were taken into account for the present benefit assessment:

- age (< 65/≥ 65)
- sex (female versus male)
- pathological lymph node status (N+ versus N0/x with < 10 lymph nodes removed versus N0 with ≥ 10 lymph nodes removed)

The company's dossier contains no subgroup analyses for the outcome of recurrence rate. Therefore, they were calculated by IQWiG as part of the benefit assessment.

Interaction tests are performed if at least 10 patients per subgroup are included in the analysis. Moreover, for binary data, there had to be at least 10 events in at least 1 subgroup.

Only the results with an effect modification with a statistically significant interaction between treatment and subgroup characteristic (p-value < 0.05) are presented. In addition, subgroup results are only presented if there is a statistically significant and relevant effect in at least one subgroup.

Using the methods described above, the available subgroup analyses do not reveal any effect modifications.

2.4.3 Probability and extent of added benefit

The probability and extent of added benefit at outcome level are derived below, taking into account the different outcome categories and effect sizes. The methods used for this purpose are explained in the IQWiG General Methods [1].

The approach for deriving an overall conclusion on the added benefit based on the aggregation of conclusions derived at outcome level is a proposal by IQWiG. The G-BA decides on the added benefit.

2.4.3.1 Assessment of the added benefit at outcome level

The extent of the respective added benefit at outcome level is estimated from the results presented in Section 2.4.2 (see Table 17).

Determination of the outcome category for outcomes on morbidity and side effects

It cannot be inferred from the dossier for the outcomes of recurrence and discontinuation due to AEs whether they are serious/severe or non-serious/non-severe. The classification for these outcomes is justified.

Recurrence

The outcome of recurrence is deemed to be serious/severe. On the one hand, recurrence of the cancer can be life-threatening, and a recurrence shows that the attempt to cure a potentially life-threatening disease with the curative therapy approach has not been successful. On the other hand, the event of death for any cause (without prior recurrence) is a component of the outcome of recurrence.

Discontinuation due to AEs

For the relevant subpopulation of the CA209-274 study, information is available on the severity degrees of the AEs due to which discontinuation took place (including progression events). This shows that more than 50% of the AEs which led to treatment discontinuation were CTCAE grade ≥ 3 events. Therefore, the outcome was assigned to the outcome category of serious/severe side effects.

Table 17: Extent of added benefit at outcome level: nivolumab versus watchful waiting (multipage table)

Observation period **Outcome category** **Outcome**	**Nivolumab vs. placebo** **Median time to event (months) or proportion of events (%)** **Effect estimation [95% CI];** **p-value** **Probability**[a]	**Derivation of extent**[b]
Total observation period		
Mortality		
Overall survival	ND[c]	Lesser/added benefit not proven
Morbidity		
Recurrence		Outcome category: serious/severe symptoms / late complications $0.75 \leq CI_u < 0.90$ Added benefit, extent: considerable
Recurrence rate	40.0% vs. 59.9% RR: 0.67 [0.52; 0.85]; < 0.001 Probability: hint	
Disease-free survival	NR vs. 8.41 months HR: 0.53 [0.38; 0.75]; < 0.001 Probability: hint	
Shortened observation period		
Morbidity		
Symptoms (EORTC QLQ-C30)	No usable data[d]	Lesser/added benefit not proven
Health status (EQ-5D VAS)	No usable data[d]	Lesser/added benefit not proven
Health-related quality of life		
EORTC QLQ-C30	No usable data[d]	Lesser/added benefit not proven
Side effects		
SAEs	NR vs. NR HR: 0.84 [0.58; 1.23]; 0.380	Greater/lesser harm not proven
Severe AEs	9.49 vs. NR months HR: 1.28 [0.91; 1.81]; 0.154	Greater/lesser harm not proven
Discontinuation due to AEs	NR vs. NR HR: 1.94 [1.02; 3.70]; HR: 0.52 [0.27; 0.98][e] 0.039 Probability: hint	Outcome category: serious/severe side effects $0.90 \leq CI_u < 1.00$ Greater harm, extent: minor
Immune-related SAEs	NR vs. NR HR: 2.64 [1.04; 6.72]; HR: 0.38 [0.15; 0.96][e] 0.034 Probability: hint	Outcome category: serious/severe side effects $0.90 \leq CI_u < 1.00$ Greater harm; extent: minor

Table 17: Extent of added benefit at outcome level: nivolumab versus watchful waiting (multipage table)

Observation period **Outcome category** **Outcome**	**Nivolumab vs. placebo** **Median time to event (months) or proportion of events (%)** **Effect estimation [95% CI];** **p-value** **Probability[a]**	**Derivation of extent[b]**
Immune-related severe AEs	NR vs. NR HR: 2.89 [1.36; 6.14]; HR: 0.35 [0.16; 0.74][e] 0.004 Probability: hint	Outcome category: serious/severe side effects $CI_u < 0.75$, risk ≥ 5% Greater harm, extent: major
Skin and subcutaneous tissue disorders (AEs)	5.36 vs. NR months HR: 1.89 [1.30; 2.74]; HR: 0.53 [0.36; 0.77][e] 0.001 Probability: hint	Outcome category: non-serious/non-severe side effects $CI_u < 0.80$ Greater harm, extent: considerable
Asthenia (AEs)	NR vs. NR HR: 3.70 [1.37; 9.97]; HR: 0.27 [0.10; 0.73][e] 0.006 Probability: hint	Outcome category: non-serious/non-severe side effects $CI_u < 0.80$ Greater harm, extent: considerable
Infections and infestations (SAEs)	NR vs. NR HR: 0.48 [0.25; 0.92]; 0.024 Probability: hint	Outcome category: serious/severe side effects $0.90 \leq CI_u < 1.00$ Lesser harm; extent: minor
Respiratory, thoracic, and mediastinal disorders (SAEs)	NR vs. NR HR: 8.38 [1.06; 66.20]; HR: 0.12 [0.02; 0.94][e] 0.016 Probability: hint	Outcome category: serious/severe side effects $0.90 \leq CI_u < 1.00$ Greater harm; extent: minor
Gastrointestinal disorders (severe AEs)	NR vs. NR HR: 0.44 [0.19; 1.01]; 0.047 Probability: hint	Outcome category: serious/severe side effects Lesser harm[f]; extent: minor[g]
Lipase increased (severe AEs)	NR vs. NR HR: 10.50 [1.35; 81.42]; HR: 0.10 [0.01; 0.74][e] 0.005 Probability: hint	Outcome category: serious/severe side effects $CI_u < 0.75$, risk ≥ 5% Greater harm, extent: major

Table 17: Extent of added benefit at outcome level: nivolumab versus watchful waiting (multipage table)

Observation period **Outcome category** **Outcome**	**Nivolumab vs. placebo** **Median time to event (months) or proportion of events (%)** **Effect estimation [95% CI];** **p-value** **Probability**[a]	**Derivation of extent**[b]
a. Probability provided if there is a statistically significant and relevant effect. b. Depending on the outcome category, estimations of effect size are made with different limits based on the upper limit of the confidence interval (CI_u). c. No data are available on overall survival (for reasoning, see Sections 2.4.1.2 and 2.4.2.1 of this dossier assessment). d. For reasons, see Section 2.4.2.1. e. Institute's calculation; inverse direction of effect to enable use of limits to derive the extent of the added benefit. f. The result of the statistical test is decisive for the derivation of added benefit. g. Discrepancy between CI and p-value; the extent is rated as minor. AE: adverse event; CI: confidence interval; CI_u: upper limit of confidence interval; EORTC: European Organisation for Research and Treatment of Cancer; HR: hazard ratio; ND: no data; NR: not reached; QLQ-C30: Quality of Life Questionnaire–Core 30; RR: relative risk; SAE: serious adverse event; VAS: visual analogue scale		

2.4.3.2 Overall conclusion on added benefit

Table 18 summarizes the results taken into account in the overall conclusion on the extent of added benefit.

Table 18: Favourable and unfavourable effects from the assessment of nivolumab in comparison with watchful waiting

Favourable effects	Unfavourable effects
Total observation period	
Morbidity Serious/severe symptoms/late complications ▪ Recurrences: hint of an added benefit – extent: considerable	–
Shortened observation period	
Serious/severe side effects ▪ Gastrointestinal disorders (severe AEs), infections and infestations (SAEs): for each, hint of lesser harm – extent: minor[a]	Serious/severe side effects ▪ Immune-related severe AEs, lipase increased (severe AEs): each hint of greater harm – extent: major ▪ Discontinuation due to AEs, immune-related SAEs, respiratory, thoracic, and mediastinal disorders (AEs): each hint of greater harm – extent: minor
–	Non-serious/non-severe side effects ▪ Skin and subcutaneous tissue disorders (AEs), asthenia (AEs): each hint of greater harm – extent: considerable
There are no data on overall survival. For the current 2nd data cut-off dated February 2021, results are available only on the outcome of recurrence. No usable data are available for the outcomes of symptoms (EORTC QLQ-C30), health status (EQ-5D VAS), and health-related quality of life (EORTC QLQ-C30).	
a. It is questionable whether the effect is in fact attributable to the outcome category of AEs or rather reflects the symptoms of the disease. AE: adverse event; EORTC: European Organisation for Research and Treatment of Cancer; EQ-5D: European Quality of Life Questionnaire 5 Dimensions; QLQ-C30: Quality of Life Questionnaire-Core 30; SAE: serious adverse event; VAS: visual analogue scale	

Overall, both favourable and unfavourable effects of nivolumab were found in comparison with the ACT.

On the favourable side, a hint of considerable added benefit was found for the outcome of relapse. Moreover, a hint of lesser harm of minor extent was shown for 2 specific AEs in the outcome category of serious/severe AEs. However, given the placebo-controlled study design, it is questionable whether, for the outcomes of gastrointestinal disorders as well as infections and infestations, the effect is actually to be allocated to the outcome category of side effects or whether it rather reflects the symptoms of disease. On the unfavourable effects side, in contrast, there are hints of greater harm of minor to major extent in the outcome category of serious/severe side effects. For non-serious/non-severe side effects, hints of considerable greater harm were found. However, the effects observed regarding side effects are based exclusively on the shortened period until treatment end plus 100 days.

No data are available on overall survival, and no usable data were found for the symptoms, health status, and health-related quality of life outcomes. For the current 2nd data cut-off dated February 2021, data are available only on the outcome of recurrence. Presumably, the missing

or unusable data do not fully call into question the favourable effect in the outcome of recurrence. Nevertheless, the above-described unfavourable effects together with lack of usable data for the symptoms, health status, and health-related quality of life outcomes result in a downgrading of added benefit.

In summary, for patients with MIUC with tumour cell PD-L1 expression ≥ 1% and high risk of recurrence following complete resection who are not eligible for cisplatin-containing therapy, there is a hint of minor added benefit of nivolumab adjuvant treatment in comparison with the ACT of watchful waiting.

The assessment described above departs from that by the company, which used the results of the CA209-274 study to derive an indication of considerable added benefit for patients who are not eligible for cisplatin-containing therapy.

2.5 Probability and extent of added benefit – summary

The result of the assessment of the added benefit of nivolumab in comparison with the ACT is summarized in Table 19.

Table 19: Nivolumab – probability and extent of added benefit

Research question	Therapeutic indication	ACT[a]	Probability and extent of added benefit
1	Adult patients with muscle-invasive urothelial carcinoma with tumour cell PD-L1 expression ≥ 1% who are at high risk of recurrence after undergoing radical resection and who are eligible for cisplatin-containing therapy for adjuvant treatment	▪ Cisplatin + gemcitabine or[b] ▪ Cisplatin + methotrexate	Added benefit not proven
2	Adult patients with muscle-invasive urothelial carcinoma with tumour cell PD-L1 expression ≥ 1% who are at high risk of recurrence after undergoing radical resection and who are not eligible for cisplatin-containing therapy, for adjuvant treatment[c]	Watchful waiting	Hint of minor added benefit[d]

a. Presented is the respective ACT specified by the G-BA.
b. The added benefit can be proven in comparison with 2 of the cited treatment options; this can typically be achieved in the context of a single-comparator study.
c. According to the G-BA, this includes patients who are either generally ineligible for cisplatin chemotherapy (e.g. due to poor general health or poor renal function) or have already received neoadjuvant cisplatin chemotherapy and are therefore not candidates for another cisplatin therapy. According to the G-BA, the patient population is therefore heterogeneous.
d. The CA209-274 study enrolled predominantly patients with an ECOG-PS of 0 or 1. Only 2.5% of patients from the study's relevant subpopulation had an ECOG-PS of 2. It remains unclear whether the observed effects are transferable to patients with an ECOG PS ≥ 2.

ACT: appropriate comparator therapy; ECOG-PS: Eastern Cooperative Oncology Group Performance Status; G-BA: Federal Joint Committee; PD-L1: programmed cell death ligand 1

The approach for the derivation of an overall conclusion on the added benefit is a proposal by IQWiG. The G-BA decides on the added benefit.

References for English extract

Please see full dossier assessment for full reference list.

The reference list contains citations provided by the company in which bibliographical information may be missing.

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