

Nivolumab (urothelial carcinoma, adjuvant)

Benefit assessment according to §35a SGB V¹
(expiry of the decision)

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EXTRACT

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No patients or families were involved in this dossier assessment.

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Part I: Benefit assessment

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

I List of abbreviations

Abbreviation	Meaning
ACT	appropriate comparator therapy
AE	adverse event
AESI	AEs of particular interest
CTCAE	Common Terminology Criteria for Adverse Events
DFS	disease-free survival
DGHO	German Society for Haematology and Medical Oncology
ECOG PS	Eastern Cooperative Oncology Group Performance Status
EORTC QLQ-C30	European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
MIUC	muscle invasive urothelial carcinoma
NYHA	New York Heart Association
PD-L1	programmed cell death ligand 1
RCT	randomized controlled trial
SAE	serious adverse event
SGB	Sozialgesetzbuch (Social Code Book)
SmPC	Summary of Product Characteristics
SOC	System Organ Class
TNM	tumour-node-metastasis

I 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 15 December 2025.

The company had already submitted a dossier for a previous benefit assessment of the drug to be assessed. That dossier was sent to IQWiG on 02 May 2022. In that procedure, the G-BA, issued a resolution on 20 October 2022 to limit the period of validity of the resolution to 15 December 2025 for adults for whom cisplatin-based therapy is not suitable or who have already received neoadjuvant treatment with cisplatin. The validity period was limited as further data relevant for the assessment of the added benefit were to be expected from the CA209-274 study, in particularly with regard to overall survival.

Research question

The aim of this report is the assessment of the added benefit of nivolumab as monotherapy compared with watchful waiting as an appropriate comparator therapy (ACT) for adults with muscle invasive urothelial carcinoma (MIUC) with tumour cell programmed cell death ligand 1 (PD-L1) expression ≥ 1% and a high risk of recurrence after undergoing radical resection, for whom cisplatin-containing therapy is not suitable or who have already received neoadjuvant treatment with cisplatin; adjuvant treatment.

The research question shown in Table 2 was defined in accordance with the ACT specified by the G-BA.

Table 2: Research question for the benefit assessment of nivolumab

Therapeutic indication	ACT ^a
Adults with muscle invasive urothelial carcinoma with tumour cell PD-L1 expression ≥ 1% and a high risk of recurrence after undergoing radical resection, for whom cisplatin-containing therapy is not suitable or who have already received neoadjuvant treatment with cisplatin; adjuvant treatment ^b	Watchful waiting
a. Presented is the ACT specified by the G-BA. b. According to the G-BA, this includes patients for whom chemotherapy with cisplatin is generally not an option (e.g. due to poor general health or impaired renal function) or who have already received neoadjuvant chemotherapy with cisplatin and for whom, for this reason, further cisplatin treatment is not an option. 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	

The company followed the G-BA's specification of the ACT.

The assessment was conducted by means of patient-relevant outcomes on the basis of the data provided by the company in the dossier. Randomized controlled trials (RCTs) were used to derive the added benefit. This concurred with the company's inclusion criteria.

Study pool and study design

CA209-274

Concurring with the company, the CA209-274 study was primarily used for the benefit assessment. The CA209-274 study is an ongoing double-blind RCT on the comparison of nivolumab with placebo. The study included adults with MIUC originating in the bladder or the upper urinary tract (renal pelvis or ureter) and a high risk of recurrence after undergoing radical resection of the MIUC. Prerequisite for inclusion was an R0 resection $\leq$ 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 not received neoadjuvant cisplatin chemotherapy and who were not suitable for, or who refused, adjuvant cisplatin chemotherapy had to have the following status: pT3–pT4a or pN+. It is assumed that patients with the described TNM status have a high risk of recurrence. Patients had to be in good general condition at study entry, 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 inclusion in the study if they had not received neoadjuvant cisplatin chemotherapy and if adjuvant cisplatin chemotherapy was unsuitable for them (an ECOG PS of 2 was considered a criterion for unsuitability). Moreover, determination of PD-L1 expression of the tumour tissue was required for study inclusion.

The CA209-274 study included a total of 709 patients, randomized in a 1:1 ratio either to treatment with nivolumab (N = 353) or to placebo (N = 356). Randomization was stratified according to the pathological lymph node status (N+ vs. N0/x with < 10 lymph nodes removed vs. N0 with ≥ 10 lymph nodes removed), PD-L1 tumour expression ($\geq 1\%$ vs. $< 1\%$, indeterminate) and the use of cisplatin as neoadjuvant chemotherapy (yes vs. no).

Treatment with nivolumab in the intervention arm was in compliance with the recommendations of the Summary of Product Characteristics (SmPC). In the comparator arm, a placebo was administered corresponding to the intervention.

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

Relevant subpopulation

In accordance with the approved therapeutic indication, only the subpopulation of patients with tumour cell PD-L1 expression $\geq 1\%$ from the CA209-274 study was relevant for the dossier assessment. In Module 4R of the dossier, the company presents analyses for this subpopulation (140 patients in the nivolumab arm and 142 patients in the placebo arm). Furthermore, this research question only comprises those patients for whom cisplatin-containing therapy is not suitable. There are uncertainties in this regard, which are described in the following section.

Patients for whom treatment with a cisplatin-containing therapy is not an option

In Module 4R, the company names the criteria which, in accordance with the study protocol for study CA209-274, justify a missing suitability of an adjuvant cisplatin treatment. These are creatinine clearance ≤ 60 mL/min, hearing loss on audiometry ($\geq$ grade 2 Common Terminology Criteria for Adverse Events [CTCAE] version 4), peripheral neuropathy ($\geq$ Grade 2 CTCAE Version 4), an ECOG PS of 2, or New York Heart Association (NYHA) class III or IV heart failure. For around 22% of the patients included, cisplatin-containing chemotherapy was not suitable for one of these reasons. In addition, there were around 42% of patients for whom adjuvant cisplatin-containing chemotherapy was not suitable, as they had already received neoadjuvant cisplatin-containing chemotherapy before. According to the currently valid version 3.0 of the S3 guideline this is appropriate.

However, the CA209-274 study and also the relevant subpopulation explicitly included patients who refused adjuvant cisplatin-containing chemotherapy, even though this would have been medically appropriate for them. A lack of willingness (refusal by the patient) was the most common reason following prior neoadjuvant cisplatin-containing chemotherapy (a total of 36% in the nivolumab arm versus 32% in the placebo arm) why adjuvant cisplatin-containing chemotherapy was not an option.

Due to a survival advantage, the current S3 guideline as well as the German Society for Haematology and Medical Oncology (DGHO) recommend neoadjuvant or adjuvant cisplatin-containing chemotherapy for muscle-invasive bladder cancer. In particular, however, the survival benefit of adjuvant cisplatin-containing chemotherapy is not mentioned in the consent form for participation in the CA209-274 study. Consequently, in some cases, patients may not have been fully informed about the advantages and disadvantages of the treatment options available to them.

Overall, it remains unclear whether in the reality of health care, at least some of these patients might have opted for adjuvant cisplatin-containing chemotherapy after having been informed about all relevant aspects set out in the guidelines, and whether these patients were therefore

not covered by the present research question, but should instead be regarded as patients for whom adjuvant cisplatin-containing chemotherapy is appropriate.

The analyses submitted by the company for the subpopulation of patients with tumour cell PD-L1 expression $\geq 1\%$ from the CA209-274 study were used for the benefit assessment. The uncertainty as to whether a relevant proportion of patients might have been suitable for adjuvant cisplatin-containing therapy is taken into account when assessing the certainty of conclusions of the results from the CA209-274 study.

Implementation of the ACT

The G-BA specified watchful waiting as the ACT.

Despite deviations from the guideline recommendations, patients in the CA209-274 study received close and targeted examinations to assess their health status and detect recurrences, so that the examination regimen was overall considered to be a sufficient approximation to the ACT of watchful waiting.

Results on overall survival cannot be interpreted

The use of enfortumab vedotin in combination with pembrolizumab is recommended as the preferred first-line standard for patients in the advanced therapy stage of the bladder carcinoma for whom cisplatin-based therapy is not suitable. The data provided by the company on the first subsequent systemic therapy show that no patient received enfortumab vedotin plus pembrolizumab as their first subsequent line of treatment. It cannot be conclusively assessed to what extent the shortcomings in the subsequent therapies used affect the outcomes on overall survival. Both arms are affected by the inadequate use of the combination therapy comprising enfortumab vedotin and pembrolizumab. Furthermore, unlike in the intervention arm, about half of the patients in the comparator arm had not yet received an immune checkpoint inhibitor, not even in the first line of subsequent therapy. Altogether, the subsequent therapies used in the CA209-274 study only provide an insufficient reflection of the current standard of therapy after recurrence. Against this background, the results regarding overall survival are rated as uninterpretable.

Risk of bias

The results on overall survival are not usable; consequently, the risk of bias is not assessed. The risk of bias for the results on the outcomes failure of the curative treatment approach was rated as low.

The risk of bias in the results on the outcomes symptoms (European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30 [EORTC QLQ-C30]) and health-related quality of life (EORTC QLQ-C30) was rated as high. Here, there are incomplete observations for potentially informative reasons due to the follow-up period linked to the

treatment duration and a possible association between outcome and reason for treatment discontinuation.

According to the company, the outcome health status is recorded using the EQ-5D VAS (unlike the other PRO outcomes) until death, withdrawal of consent, loss to follow-up or end of the study. However, as it is difficult to assess the response rates and the proportion of incomplete observations for potentially informative reasons, a high risk of bias is also assumed for the results on the outcome health status.

The risk of bias of the results on the outcomes serious adverse event (SAEs), severe adverse events (AEs) (overall rates and specific AEs), as well as immune-mediated SAEs/severe AEs was rated as high. For the mentioned outcomes of the category of side effects, there are incomplete observations for potentially informative reasons due to the follow-up period linked to the treatment duration (100 days after the last administration of the study medication) and a possible association between outcome and reason for treatment discontinuation.

Although the risk of bias is low for the results on the outcome of discontinuation due to AEs, the certainty of results is reduced for this outcome. Premature treatment discontinuation for reasons other than AEs is a competing event for the outcome discontinuation due to AEs to be recorded. This means that, although AEs that would have led to discontinuation of therapy may occur after discontinuation for other reasons, the criterion discontinuation is no longer applicable to them. It was impossible to estimate how many AEs this affected.

Summary assessment of the certainty of conclusions

Irrespective of the factors described in relation to the risk of bias, the certainty of conclusions for the study results remained limited due to the uncertainties described regarding the proportion of patients for whom adjuvant cisplatin-containing chemotherapy would have been appropriate. At most hints, e.g. of an added benefit, can be derived from the information available from the CA29-274 study.

Results

Mortality

Overall survival

The results on the outcome overall survival are not interpretable.

Morbidity

Failure of the curative treatment approach

For the present benefit assessment, the outcome failure of the curative treatment approach is presented via the occurrence of the event (event rate, effect measure RR) and the time to

event (DFS, effect measure hazard ratio [HR]). A statistically significant difference in favour of nivolumab over placebo was shown for both analyses when considering the total population. However, for the event rate, there is a statistically significant effect modification for the characteristic sex. A statistically significant difference in favour of nivolumab in comparison with placebo was shown for men. For women, however, there was no statistically significant difference between the treatment arms. For the DFS, there is also a significant difference in favour (of nivolumab) for men only; however, there is no statistically significant effect modification for the characteristic sex. For men, there is a hint of added benefit of nivolumab in comparison with the ACT. For women, there is no hint of an added benefit of nivolumab in comparison with the ACT; an added benefit for women is therefore not proven for this outcome.

Symptoms (recorded with the EORTC QLQ-C30)

No statistically significant difference between the treatment arms was shown for any of the outcomes fatigue, nausea and vomiting, pain, dyspnoea, insomnia, appetite loss, constipation and diarrhoea (recorded using the EORTC QLQ-C30). There is no hint of an added benefit of nivolumab over the ACT for any of these outcomes; an added benefit is therefore not proven for these outcomes.

Health status (recorded using the EQ-5D VAS)

For the outcome health status (recorded using the EQ-5D VAS), a statistically significant difference was found in favour of nivolumab in comparison with placebo. This results in a hint of added benefit of nivolumab in comparison with the ACT.

Health-related quality of life

No statistically significant difference between the treatment arms was found for any of the outcomes global health status, physical functioning, role functioning, emotional functioning and social functioning (recorded using the EORTC C30). There is no hint of an added benefit of nivolumab over the ACT for any of these outcomes; an added benefit is therefore not proven for these outcomes.

Side effects

SAEs and severe AEs

There was no statistically significant difference between the treatment arms for the outcomes of SAEs and severe AEs. In each case, there is therefore no hint of greater or lesser harm of nivolumab in comparison with the ACT; 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. However, the extent of the effect

for this outcome in the category of non-serious/non-severe side effects was no more than marginal. There was no hint of greater or lesser harm from nivolumab in comparison with the ACT; greater or lesser harm is therefore not proven.

Immune-mediated SAEs and immune-mediated severe AEs

For each of the outcomes immune-mediated SAEs and immune-mediated severe AEs, a statistically significant difference was found to the disadvantage of nivolumab in comparison with placebo. In each case, this resulted in a hint of greater harm from nivolumab in comparison with the ACT.

Specific AEs

Skin and subcutaneous tissue disorders (AEs), asthenia (AEs), respiratory, thoracic and mediastinal disorders (SAEs), lipase increased (severe AEs)

For the outcomes 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 each to the disadvantage of nivolumab compared with placebo. In each case, this resulted in a hint of greater harm from nivolumab in comparison with the ACT.

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 infections and infestations (SAEs) and gastrointestinal disorders (severe AEs). In each case, this resulted in a hint of lesser harm from nivolumab in comparison with the ACT. However, given the placebo-controlled study design with no active treatment in the comparator arm, it is questionable whether the effect in the outcomes gastrointestinal disorders as well as infections and infestations should actually be assigned to the outcome category of side effects or whether it rather reflects the symptoms of the disease.

Probability and extent of added benefit, patient groups with therapeutically important added benefit³

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:

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].

Overall, both positive and negative effects of nivolumab were shown in comparison with watchful waiting.

On the positive side, there is a hint of minor added benefit for the outcome health status for the total population, as well as a hint of lesser harm in the outcomes infections and infestations (SAEs; extent: considerable) and gastrointestinal disorders (severe AEs; extent: minor). However, given the placebo-controlled study design, it is questionable whether the effect in the outcomes gastrointestinal disorders as well as infections and infestations should actually be assigned to the outcome category of side effects or whether it rather reflects the symptoms of the disease. In addition, for men, there is a hint of considerable added benefit for the outcome failure of the curative treatment approach.

On the side of the negative effects, in contrast, there are hints of greater harm with minor or major extent for the outcome category serious/severe side effects. For non-serious/non-severe side effects, there are hints of greater harm with considerable extent. However, the effects observed in the side effects are based exclusively on the shortened period until the end of treatment plus a maximum of 100 days.

Due to the effect modification in the outcome failure of the curative treatment approach, the added benefit is derived separately for men and women.

In the assessment for men, the positive effect in the outcome failure of the curative treatment approach is decisive in the derivation of the added benefit; however, the negative effects described, particularly in the case of severe or serious immune-mediated AEs, lead to a downgrading of the extent of the added benefit. In summary, there is a hint of minor added benefit of nivolumab compared with the ACT watchful waiting for men with MIUC with tumour cell PD-L1 expression $\geq 1\%$ and a high risk of recurrence after undergoing radical resection, for whom cisplatin-containing therapy is not suitable or who have already received neoadjuvant treatment with cisplatin.

However, due to the effect modification, there is no positive effect in the outcome failure of the curative treatment approach for women. When the remaining positive and negative effects are weighed up, there is thus no added benefit for women. An added benefit of nivolumab in comparison with the ACT watchful waiting is not proven for women with muscle-invasive urothelial carcinoma with tumour cell PD-L1 expression $\geq 1\%$ and a high risk of recurrence after undergoing radical resection, for whom cisplatin-containing therapy is not suitable or who have already received neoadjuvant treatment with cisplatin.

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

Table 3: Nivolumab – probability and extent of added benefit

Therapeutic indication	ACT ^a	Probability and extent of added benefit
Adults with muscle invasive urothelial carcinoma with tumour cell PD-L1 expression $\geq 1\%$ and a high risk of recurrence after undergoing radical resection, for whom cisplatin-containing therapy is not suitable or who have already received neoadjuvant treatment with cisplatin; adjuvant treatment ^b	Watchful waiting	Adults - men: hint of minor added benefit^c - women: added benefit not proven
a. Presented is the ACT specified by the G-BA. b. According to the G-BA, this includes patients for whom chemotherapy with cisplatin is generally not an option (e.g. due to poor general health or impaired renal function) or who have already received neoadjuvant chemotherapy with cisplatin and for whom, for this reason, further cisplatin treatment is not an option. According to the G-BA, the patient population is therefore heterogeneous. c. Only patients with an ECOG PS of 0 or 1 were included in the CA209-274 study. 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 added benefit is a proposal by IQWiG. The G-BA decides on the added benefit.

I 2 Research question

The aim of this report is the assessment of the added benefit of nivolumab as monotherapy compared with watchful waiting as an ACT for adults with MIUC with tumour cell PD-L1 expression $\geq 1\%$ and a high risk of recurrence after undergoing radical resection, for whom cisplatin-containing therapy is not suitable or who have already received neoadjuvant treatment with cisplatin; adjuvant treatment.

The research question shown in Table 4 was defined in accordance with the ACT specified by the G-BA.

Table 4: Research question for the benefit assessment of nivolumab

Therapeutic indication	ACT ^a
Adults with muscle invasive urothelial carcinoma with tumour cell PD-L1 expression $\geq 1\%$ and a high risk of recurrence after undergoing radical resection, for whom cisplatin-containing therapy is not suitable or who have already received neoadjuvant treatment with cisplatin; adjuvant treatment ^b	Watchful waiting
a. Presented is the ACT specified by the G-BA. b. According to the G-BA, this includes patients for whom chemotherapy with cisplatin is generally not an option (e.g. due to poor general health or impaired renal function) or who have already received neoadjuvant chemotherapy with cisplatin and for whom, for this reason, further cisplatin treatment is not an option. 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	

The company followed the G-BA's specification of the ACT.

The assessment was conducted by means of patient-relevant outcomes on the basis of the data provided by the company in the dossier. RCTs were used to derive the added benefit. This concurred with the company's inclusion criteria.

I 3 Information retrieval and study pool

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

Sources used by the company in the dossier:

- Study list on nivolumab (status: 25 September 2025)
- Bibliographical literature search on nivolumab (last search on 25 September 2025)
- Search of trial registries / trial results databases for studies on nivolumab (last search on 20 November 2025)
- Search on the G-BA website for nivolumab (last search on 25 September 2025)

To check the completeness of the study pool:

- Search of trial registries for studies on nivolumab (last search on 08 January 2025); for search strategies, see I Appendix A of the full dossier assessment

The search did not identify any additional relevant studies.

I 3.1 Studies included

The study presented in the following Table 5 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 marketing authorization of the drug to be assessed (yes/no)	Sponsored study ^a (yes/no)	Third-party study (yes/no)	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 [3-6]	Yes [7-9]	Yes [10-16]
a. Study sponsored by the company. 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 referred to by this acronym. G-BA: Federal Joint Committee; RCT: randomized controlled trial						

I 3.2 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 vs. placebo (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 the upper urinary tract (renal pelvis or ureter) and a high risk of recurrence^b after undergoing radical resection^c of the MIUC - ECOG PS ≤ 2^d	Nivolumab (N = 353) placebo (N = 356) relevant subpopulation thereof: nivolumab (n = 140) placebo (n = 142)	Screening: 28 days treatment: until recurrence, unacceptable toxicity or withdrawal of consent, up to a maximum of 1 year follow-up^f: outcome-specific, up to a maximum of 5 years after the primary DFS analysis	170 centres in Argentina, Australia, Austria, Belgium, Brazil, Canada, Chile, China, Colombia, 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 cuts for the relevant sub-population^g: - first data cut (17 July 2020, including erratum of 27 August 2020; final DFS analysis) - second data cut (1 February 2021; first OS interim analysis)^h - third data cut (6 January 2025; second OS interim analysis)ⁱ	Primary: DFS secondary: overall survival, morbidity, health-related quality of life, AEs

Table 6: Characteristics of the study included – RCT, direct comparison: nivolumab vs. placebo (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 taking into account 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 have not received neoadjuvant cisplatin chemotherapy and for whom adjuvant cisplatin chemotherapy is not suitable or who refuse it. According to the study protocol, any refusal of cisplatin chemotherapy (despite suitability) had to be carefully documented. c. R0 resection ≤ 120 days prior to randomization; deviating from the protocol, 8 patients in the relevant subpopulation (tumour cell PD-L1 expression ≥ 1%) were included who had undergone resection > 120 days prior to randomization. d. Patients with an ECOG PS of 2 were eligible for inclusion in the study if they had not received neoadjuvant cisplatin-containing chemotherapy and were unsuitable for adjuvant cisplatin-containing chemotherapy. e. Patients with tumour cell PD-L1 expression ≥ 1%. f. Outcome-specific information is provided in Table 8. g. The study protocol predefined data cuts for both the total population and the subpopulation of patients with tumour cell PD-L1 expression ≥ 1%. Only those data cuts that were relevant for the subpopulation of patients with tumour cell PD-L1 expression ≥ 1% are presented here. h. The first interim analysis for the outcome overall survival (following the occurrence of around 91 events in the outcome overall survival) was linked to the final analysis for DFS. The company states that, the significance threshold for overall survival had not yet been reached at the time of the second data cut (first OS interim analysis). i. With protocol amendment 6 of 28 February 2024, the conduct of the second interim analysis for the outcome overall survival was amended from an event-driven approach to a minimum follow-up duration of 5 years following randomization of the last patient. The final analysis is scheduled after the occurrence 166 events. AE: adverse event; 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; OS: overall survival; 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 vs. placebo

Study	Intervention	Comparison
CA209-274	Nivolumab 240 mg IV every 2 weeks	Placebo IV every 2 weeks
	Dose adjustment: no dose adjustment permitted; treatment delays of up to 42 days permitted	
	Required prior treatment ▪ R0 resection of invasive urothelial carcinoma^a	
	disallowed prior treatment ▪ chemotherapy, radiotherapy, anti-cancer biologics, intravesical therapy or investigational products ≤ 28 days before the start of the study medication ▪ systemic corticosteroids (> 10 mg prednisone equivalents daily) or other immunosuppressants ≤ 14 days prior to the start of the study medication and during the study ▪ partial cystectomy for primary bladder cancer or partial nephrectomy for a primary tumour of the renal pelvis ▪ systemic therapy or radiotherapy for urothelial carcinoma or prostate cancer following radical surgical resection of a urothelial carcinoma	
	disallowed concomitant treatment ▪ any antineoplastic therapy (i.e. chemotherapy, hormonal therapy, immunotherapy, standard or investigational products, surgical interventions or radiotherapy for the treatment of cancer) ▪ any intravesical anticancer drugs and transurethral resection (TUR) of urothelial tract diseases, unless a recurrence has been documented and the study treatment was completed prior to the TUR or intravesical therapy^b	
	allowed prior and concomitant treatment ▪ corticosteroids in forms of administration with minimal systemic absorption and < 3 weeks of corticosteroids for prophylaxis or for treatment of non-autoimmune conditions	
a. The resection should have been performed within the 120 days prior to randomization.		
b. Exception: intravesical chemotherapy administered as a single dose following the resection of a low-risk, non-muscle invasive urothelial carcinoma (standard treatment) is permitted.		
IV: intravenous; RCT: randomized controlled trial; TUR: transurethral resection		

The CA209-274 study is an ongoing double-blind RCT on the comparison of nivolumab with placebo. The study included adults with MIUC originating in the bladder or the upper urinary tract (renal pelvis or ureter) and a high risk of recurrence after undergoing radical resection of the MIUC. Prerequisite for inclusion was an 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 not received neoadjuvant cisplatin chemotherapy and who were not suitable for, or who refused, adjuvant cisplatin chemotherapy had to have the following TNM status: pT3–pT4a or pN+. It is assumed that patients with the described TNM status have a high risk of recurrence. If cisplatin-based chemotherapy was refused (despite being medically suitable), this had to be carefully documented. Patients had to be in good general condition at study entry, corresponding to an ECOG PS of 0 or 1. Patients with an ECOG PS of 2 were eligible for inclusion in the study if they

had not received neoadjuvant cisplatin chemotherapy and if adjuvant cisplatin chemotherapy was unsuitable for them (an ECOG PS of 2 was considered a criterion for unsuitability). Patients additionally had to have disease-free status documented by a complete physical examination and imaging studies within 4 weeks prior to randomisation.

Determination of PD-L1 expression of the tumour tissue was required 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. The PD-L1 expression on the tumour cells was determined using the PD-L1 IHC 28-8 pharmDx assay.

The CA209-274 study included a total of 709 patients, randomized in a 1:1 ratio either to treatment with nivolumab (N = 353) or to placebo (N = 356). Randomization was stratified according to the pathological lymph node status (N+ vs. N0/x with < 10 lymph nodes removed vs. N0 with ≥ 10 lymph nodes removed), PD-L1 tumour expression (≥ 1% vs. < 1%, indeterminate) and the use of cisplatin as neoadjuvant chemotherapy (yes vs. no).

Treatment with nivolumab in the intervention arm was in compliance with the recommendations of the SPC [17]. In the comparator arm, a placebo was administered corresponding to the intervention.

Treatment with the study medication was continued until recurrence, unacceptable toxicity or withdrawal of consent, however, up to a maximum of 1 year. The study did not provide for any switching between study arms.

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

Relevant subpopulation

In accordance with the approved therapeutic indication, only the subpopulation of patients with tumour cell PD-L1 expression ≥ 1% from the CA209-274 study was relevant for the dossier assessment. In Module 4R of the dossier, the company presents analyses for this subpopulation (140 patients in the nivolumab arm and 142 patients in the placebo arm). Furthermore, this research question only comprises those patients for whom cisplatin-containing therapy is not suitable. There are uncertainties in this regard, which are described in the following section.

Patients for whom treatment with a cisplatin-containing therapy is not an option

In Module 4R, the company names the criteria which, in accordance with the study protocol for study CA209-274, justify a missing suitability of an adjuvant cisplatin treatment. These are creatinine clearance ≤ 60 mL/min, hearing loss on audiometry (≥ grade 2 CTCAE version 4), peripheral neuropathy (≥ grade 2 CTCAE Version 4), an ECOG PS of 2, or NYHA class III or IV

heart failure. For around 22% of the patients included, cisplatin-containing chemotherapy was not suitable for one of these reasons (see also Table 9). In addition, there were around 42% of patients for whom adjuvant cisplatin-containing chemotherapy was not suitable, as they had already received neoadjuvant cisplatin-containing chemotherapy before. According to the currently valid version 3.0 of the S3 guideline this is appropriate [18].

However, the CA209-274 study and also the relevant subpopulation explicitly included patients who refused adjuvant cisplatin-containing chemotherapy, even though this would have been medically appropriate for them. A lack of willingness (refusal by the patient) was the most common reason following prior neoadjuvant cisplatin-containing chemotherapy (a total of 36% in the nivolumab arm versus 32% in the placebo arm) why adjuvant cisplatin-containing chemotherapy was not an option. Although this refusal should be carefully documented in accordance with the study protocol, the company's dossier does not contain any further details regarding this patient population.

The current S3 guideline and the DGHO recommend neoadjuvant or adjuvant cisplatin-containing chemotherapy for muscle invasive bladder cancer [18,19]. Both the S3-guideline and the DGHO describe a survival advantage of neoadjuvant or adjuvant cisplatin-containing chemotherapy. However, these recommendations do not appear in the study protocol for study CA209-274. Nor is the aforementioned survival advantage of adjuvant cisplatin-containing chemotherapy explicitly mentioned in the section on treatment alternatives in the informed consent form for patients. Instead, it states (translated from the study report): Whilst clinical trials have shown contradictory results regarding the benefit of adjuvant chemotherapy, some studies have shown that adjuvant chemotherapy regimens containing cisplatin can delay recurrence. Adjuvant cisplatin-containing chemotherapy may be an option for patients who tolerate cisplatin, depending on factors including, but not limited to, renal function and hearing. This study includes patients who refuse cisplatin chemotherapy or are unable to undergo it. Please discuss this treatment option with your physician before you decide to take part in the trial. The information contained in the consent form for participation in the study therefore does not fully reflect the recommendations set out in the guidelines [18,19], as in particular the survival advantage of adjuvant cisplatin-containing chemotherapy is not clearly stated. Consequently, in some cases, patients may not have been fully informed about the advantages and disadvantages of the treatment options available to them.

Overall, it remains unclear whether in the reality of health care, at least some of these patients might have opted for adjuvant cisplatin-containing chemotherapy after having been informed about all relevant aspects set out in the guidelines, and whether these patients were therefore not covered by the present research question, but should instead be regarded as patients for whom adjuvant cisplatin-containing chemotherapy is appropriate.

The analyses submitted by the company for the subpopulation of patients with tumour cell PD-L1 expression $\geq 1\%$ from the CA209-274 study were used for the benefit assessment. The uncertainty as to whether a relevant proportion of patients might have been suitable for adjuvant cisplatin-containing therapy is taken into account when assessing the certainty of conclusions of the results from the CA209-274 study. A summary assessment of the certainty of conclusions can be found in Section I 4.2.

Available data cut

In Module 4R, the company only presents analyses for the data cut of 06 January 2025 (second OS interim analysis). In accordance with the justification of the decision on the first assessment, analyses of all patient-relevant outcomes at the final data cut, or, if this is not yet available, on a data cut that is no more than 6 months old, must be submitted after expiry of the decision on 15 December 2025 [20]. As it was clear that the planned number of events required to carry out the originally planned data cut for the second OS-interim analysis was not achievable, the company modified the time point of the second OS interim analysis so that it should be carried out once a follow-up period of at least 5 years has been reached for all patients (with protocol Amendment No 6 of 28 February 2024). This has been achieved for all patients as of the data cut of 6 January 2025. The company informed the G-BA, and the G-BA accepted this approach as appropriate. The analyses on the data cut of 6 January 2025 were used for this dossier assessment.

Implementation of the ACT

The G-BA specified watchful waiting as the ACT.

In the CA209-274 study, watchful waiting was operationalized through the following examinations for the assessment of the health and the detection of recurrences:

- Targeted physical examination, recording of weight and ECOG PS, and laboratory parameters during the treatment phase and at the start of each treatment cycle (see Table 7) as well as (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 the occurrence of a recurrence outside the urothelial tract or discontinuation of treatment (whichever occurs later) for a maximum of 5 years
- Cystoscopy in patients with primary tumours of the upper urinary tract in whom the bladder is still intact: every 12 weeks up to Week 48; every 24 weeks from Week 48 to Week 96; thereafter every 48 weeks until the occurrence of a recurrence outside the

urothelial tract or discontinuation of treatment (whichever occurs later) for a maximum of 5 years

According to the S3 guideline, follow-up is to comprise early detection of tumour recurrence, metabolic changes, dysfunction, and psycho-oncological 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 year of follow-up). 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 using imaging to detect tumour recurrence should take place 3 to 6 months after radical cystectomy, every 6 months up to and including the third year of follow-up, and every 12 months in the fourth and fifth year of follow-up [18,21]. The same examinations are recommended for patients in TNM stages ≤ pT2, pN0, and cM0, but imaging was to take place as early as from the third year of follow-up onwards at six-month intervals.

The examinations performed in CA209-274 did not fully represent the 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 deviations from the guideline recommendations, patients in the CA209-274 study received close and targeted examinations to assess their health status and detect recurrences, so that the examination regimen was overall considered to be a sufficient approximation to the ACT watchful waiting.

Table 8 shows the planned duration of patient follow-up for the individual outcomes.

Table 8: Planned duration of follow-up – RCT, direct comparison: nivolumab vs. placebo

Study outcome category outcome	Planned follow-up
CA209-274	
Mortality	
Overall survival	Until death, withdrawal of consent, lost to follow-up, or end of study; up to a maximum of 5 years after primary DFS analysis
Morbidity	
Failure of the curative treatment approach ^a	Until the occurrence of a recurrence outside the urothelial tract or discontinuation of treatment (whichever occurs later); up to a maximum of 5 years
Symptoms (EORTC QLQ-C30)	Approx. 100 days after the last dose of the study medication
Health status (EQ-5D VAS)	Until death, withdrawal of consent, lost to follow-up, or end of study; up to a maximum of 5 years after primary DFS analysis
Health-related quality of life (EORTC QLQ-C30)	Approx. 100 days after the last dose of the study medication
Side effects	
All outcomes in the side effects category	Approx. 100 days after the last dose of the study medication ^b
a. Represented by the event rate and DFS, the events include local recurrence within the urothelial tract, local recurrence outside the urothelial tract, distant metastases and death from any cause (without prior recurrence). b. Following the second follow-up visit (approximately 100 days after the last dose of the study medication), only adverse events assigned to the study treatment were recorded. DFS: disease-free survival; EORTC: European Organisation for Research and Treatment of Cancer; QLQ-C30: Quality of Life Questionnaire-Core 30; RCT: randomized controlled trial; VAS: visual analogue scale	

The observation periods for the outcomes symptoms, health-related quality of life, and for the outcomes of the side effects category were systematically shortened, because they were only recorded for the time period of treatment with the study medication (plus approx. 100 days). For these outcomes, data are therefore available only for the shortened observation period.

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

Table 9 shows the patient characteristics of the included study.

Table 9: Characteristics of the study population as well as study/treatment discontinuation – RCT, direct comparison: nivolumab vs. placebo (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, n (%)		
In the past/currently	96 (69)	101 (71)
Never smoker	42 (30)	40 (28)
Unknown	2 (1)	1 (1)
Family origin, 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 reported	0 (0)	1 (1)
ECOP 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 the initial diagnosis of the disease to randomization		
< 1 year	132 (94)	129 (91)
≥ 1 year	8 (6)	13 (9)
Pathological stage upon 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 reported	0 (0)	1 (1)

Table 9: Characteristics of the study population as well as study/treatment discontinuation – RCT, direct comparison: nivolumab vs. placebo (multipage table)

Study characteristic category	Nivolumab N ^a = 140	Placebo N ^a = 142
Lymph node status and number of lymph nodes removed		
N0/X with < 10 removed lymph nodes	38 (27)	38 (27)
N0/X 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 reported	1 (1)	1 (1)
The reason why adjuvant cisplatin-containing therapy is not an option		
Prior neoadjuvant cisplatin-containing chemotherapy	57 (41)	61 (43)
Lack of willingness (refusal by the patient)	51 (36)	46 (32)
Not suitable due to impaired renal function	19 (14)	22 (16)
Not suitable due to neuropathy	0 (0)	1 (1)
Not suitable due to hearing loss	1 (1)	4 (3)
Not suitable due to poor PS	4 (3)	5 (4)
Not suitable due to impaired cardiac function	3 (2)	2 (1)
Other reasons	4 (3)	0 (0)
Not reported	1 (1)	1 (1)
Time from radical resection to 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}	72 (51 ^d)	88 (62 ^d)
Study discontinuation, n (%) ^{c, e}	76 (54 ^d)	94 (66 ^d)

Table 9: Characteristics of the study population as well as study/treatment discontinuation – RCT, direct comparison: nivolumab vs. placebo (multipage table)

Study characteristic category	Nivolumab N ^a = 140	Placebo N ^a = 142
a. Number of randomized patients who received at least one dose of the respective treatment. Values that are based on other patient numbers are marked in the corresponding line if the deviation is relevant. b. Frequent reasons for premature treatment discontinuation in the nivolumab arm vs. the placebo arm: (percentages refer to randomized patients, Institute's calculation): disease recurrence (24% vs. 42%), toxicity (18% vs. 5%), AEs not associated with the study medication (3% vs. 6%). An additional 1% vs. 2% of randomized patients never started treatment. Furthermore, 48 % vs. 36 % of the patients completed treatment as planned. c. Data cut of 6 January 2025. d. Institute's calculation. e. Frequent reasons for study discontinuation in the nivolumab arm vs. the placebo arm were (percentages refer to randomized patients, Institute's calculation): withdrawal of consent (11% vs. 8%) and lost to follow-up (4% vs. 5%). The data additionally include patients who died during the course of the study (intervention arm: 37% vs. control arm: 51%). AE: adverse event; 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; PS: performance status; RCT: randomized controlled trial; SD: standard deviation		

Both study arms were largely balanced in terms of the demographic and clinical characteristics of the patients in the relevant subpopulation. The mean age of the patients was 65 years. The vast majority of the patient population were men – the proportion of women was slightly higher in the nivolumab arm (28%) than in the placebo arm (21%). The majority of the patient population was of white family origin. The proportion of patients with tumours originating in the bladder was approximately 82%, the proportion of patients with tumours originating in the renal pelvis was approximately 12%, and the proportion of those with tumours originating in the ureter was approximately 7%. Around 42% of patients had received previous cisplatin treatment. 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 10 shows the patients' mean/median treatment duration and the mean/median observation period for individual outcomes.

Table 10: Information on the course of the study – RCT, direct comparison: nivolumab vs. placebo (multipage table)

Study duration of the study phase outcome category / outcome	Nivolumab N = 139	Placebo N = 139
CA209-274 (data cut-off: 06 January 2025)		
Treatment duration [months]		
Median [min; max]	10.6 [0.0; 12.5]	6.5 [0.0; 12.0]
Mean (SD)	7.9 (4.5)	7.0 (4.4)
Observation period [months]		
Overall survival ^{a, b}	52.6 (32.2)	43.6 (33.5)
Median [min; max]	61.2 [0.4; 102.4]	35.84 [0.0; 102.6]
Mean (SD)		
Morbidity		
Failure of the curative treatment approach ^{a, c}		
Median [min; max]	25.8 [0.0; 70.8]	8.0 [0.0; 80.7]
Mean (SD)	31.7 (24.9)	21.2 (23.9)
Symptoms (EORTC QLQ-C30) ^{d, e}		
Median [min; max]	13.8 [1.0; 16.9]	10.2 [1.0; 25.1]
Mean (SD)	11.3 (5.1)	10.3 (5.2)
Health status (EQ-5D VAS) ^{d, f}		
Median [min; max]	46.0 [1.0; 100.4]	33.1 [1.0; 102.6]
Mean (SD)	46.2 (32.0)	41.0 (33.1)
Health-related quality of life (EORTC QLQ-C30) ^{d, e}		
Median [min; max]	13.8 [1.0; 16.9]	10.2 [1.0; 25.1]
Mean (SD)	11.3 (5.1)	10.3 (5.2)
Side effects ^g		
Median [min; max]	13.9 [0.4; 15.8]	9.8 [0.5; 15.4]
Mean (SD)	11.0 (4.7)	10.1 (4.8)
Immune-mediated SAEs/severe AEs ^h	ND	ND
a. The data refer to N = 140 in the nivolumab arm versus N = 142 in the placebo arm. b. The time between randomization and death from any cause or the last known date on which the patient was known to be alive. c. Time between randomization and the DFS event or censoring. d. The data refer to N = 123 in the nivolumab arm versus N = 128 in the placebo arm. e. Time between randomization and the last non-missing EORTC QLQ-C30 documentation. f. Time between randomization and the last non-missing EQ-5D-3L VAS documentation. g. Time between randomization and 100 days after the last dose of study medication or the last date on which the patient was known to be alive (whichever occurs first). h. Severe AEs are operationalised as CTCAE grade ≥ 3.		

Table 10: Information on the course of the study – RCT, direct comparison: nivolumab vs. placebo (multipage table)

Study	Nivolumab N = 139	Placebo N = 139
duration of the study phase		
outcome category / outcome		
AE: adverse event; CTCAE: Common Terminology Criteria for Adverse Events; DFS: disease-free survival; EORTC: European Organisation for Research and Treatment of Cancer; max: maximum; min: minimum; N: number of analysed patients; ND: no data; QLQ-C30: Quality of Life Questionnaire-Core 30; RCT: randomized controlled trial; SD: standard deviation; SAE: serious adverse event; VAS: visual analogue scale		

At the data cut of 6 January 2025, the median duration of treatment for patients in the relevant subpopulation was 10.6 months in the nivolumab arm, which was significantly longer than the median treatment duration in the placebo arm (6.5 months). Consequently, there are also differences in the follow-up period of outcomes whose monitoring is linked to the duration of treatment.

Table 11 shows the first systemic antineoplastic therapies patients received after discontinuing the study medication.

Table 11: Information on the first systemic antineoplastic therapy – RCT, direct comparison: nivolumab versus placebo

Study drug class drug	Patients with subsequent therapy, n (% ^a)	
	nivolumab N = 140	placebo N = 142
CA209-274 (data cut-off: 06 January 2025)		
Patients with at least one subsequent systemic therapy	39 (27.9 ^b)	56 (39.4 ^b)
Immune checkpoint inhibitor	2 (5.1)	29 (51.8)
Atezolizumab	0 (0)	10 (17.9)
Nivolumab	1 (2.6)	2 (3.6)
Nivolumab + ipilimumab	0 (0)	1 (1.8)
Pembrolizumab	0 (0)	15 (26.8)
Pembrolizumab + carboplatin + paclitaxel	1 (2.6)	0 (0)
Pembrolizumab + cisplatin	0 (0)	1 (1.8)
Chemotherapy	36 (92.3)	25 (44.6)
Bevacizumab + gemcitabine	0 (0)	1 (1.8)
Carboplatin + enfortumab vedotin	0 (0)	1 (1.8)
Carboplatin + gemcitabine	11 (28.2)	8 (14.3)
Carboplatin + gemcitabine + paclitaxel	0 (0)	1 (1.8)
Carboplatin + paclitaxel	2 (5.1)	0 (0)
Cisplatin + docetaxel + cetuximab	1 (2.6)	0 (0)
Cisplatin + gemcitabine	11 (28.2)	8 (14.3)
Cisplatin + gemcitabine + guadecitabine	0 (0)	1 (1.8)
Cisplatin + gemcitabine + paclitaxel	0 (0)	1 (1.8)
Docetaxel	2 (5.1)	0 (0)
Gemcitabine	2 (5.1)	0 (0)
Methotrexate + vinblastine + doxorubicin + cisplatin	2 (5.1)	2 (3.6)
Mitomycin	1 (2.6)	0 (0)
Mitomycin + fluorouracil	1 (2.6)	0 (0)
Paclitaxel	2 (5.1)	1 (1.8)
Vinflunine	1 (2.6)	1 (1.8)
Other	1 (2.6)	2 (3.6)
BCG (intravesical)	0 (0)	1 (1.8)
Cabozantinib	1 (2.6)	0 (0)
Chinese medicinal herbs	0 (0)	1 (1.8)
a. Institute's calculation, unless otherwise stated; percentages are based on the number of patients with at least one subsequent systemic therapy.		
b. Institute's calculation; based on the number of analysed patients.		
BCG: bacille Calmette-Guérin; n: number of patients with subsequent therapy; N: number of analysed patients; RCT: randomized controlled trial		

The company presents information on the first subsequent systemic antineoplastic therapy in Annex 4G. The choice of the subsequent antineoplastic therapy was not restricted in the CA209-274 study. After discontinuation of the study medication, 39 (27.9%) patients in the nivolumab arm and 56 patients (39.4%) in the placebo arm received a subsequent therapy at the given data cut. By the given data cut, 57 and 80 patients, respectively, had experienced a recurrence. Based on patients with a recurrence, approximately 68% and 70%, respectively, would have received subsequent systemic therapy. It is assumed that subsequent systemic therapy is not suitable for all patients. It is therefore assumed that most patients with recurrence for whom subsequent therapy was indicated also received it. The majority of patients who received at least one subsequent systemic therapy received chemotherapies (92.3% vs. 44.6%). 5.1% vs. 51.8% received treatment with an immune checkpoint inhibitor.

The guideline recommendations for the advanced therapy stage of bladder cancer are decisive for the assessment of the administered subsequent therapies in the CA209-274 study. For patients for whom cisplatin-based therapy is not an option, the use of enfortumab vedotin in combination with pembrolizumab is recommended as the preferred first-line standard [19]. Based on IQWiG's assessment of the SGN22E-003 study (in short: EV302/KN-A39), the G-BA has decided that enfortumab vedotin in combination with pembrolizumab offers a considerable added benefit for patients for whom cisplatin-containing therapy is unsuitable [22-24]. Also in the proceedings on erdafitinib [25] and durvalumab [26] for bladder cancer, it became clear during the oral hearing that enfortumab vedotin in combination with pembrolizumab is used as standard first-line treatment for unresectable or metastatic urothelial carcinoma. The data provided by the company on the first subsequent systemic therapy show that no patient received enfortumab vedotin plus pembrolizumab as their first subsequent line of treatment. In Appendix 4G, the company states that in 94.2% of patients with recurrence, this had already occurred prior to the data cut in February 2021. Consequently, the majority of the events occurred long before the marketing authorization of enfortumab vedotin in combination with pembrolizumab, which was issued in August 2024. It is therefore comprehensible that enfortumab vedotin (in combination with pembrolizumab) was not used as subsequent therapy.

In addition to enfortumab vedotin/pembrolizumab, the DGHO also recommends the use of atezolizumab or pembrolizumab, depending on the circumstances [19]. In the comparator arm, however, only 51.8% of patients who received at least one subsequent systemic antineoplastic therapy were treated with immunotherapy in the first subsequent line of therapy. As patients in the comparator arm had not previously received immunotherapy in the perioperative setting, the proportion of immunotherapies used in the comparator arm is to be rated as low against the background of the guideline recommendations.

In summary, the subsequent therapies used in the CA209-274 study only provide an insufficient reflection of the current standard of therapy after recurrence. It cannot be conclusively assessed to what extent the shortcomings in the subsequent therapies used affect the outcomes on overall survival. Both arms are affected by the inadequate use of the combination therapy comprising enfortumab vedotin and pembrolizumab. Furthermore, unlike in the intervention arm, about half of the patients in the comparator arm had not yet received an immune checkpoint inhibitor, not even in the first subsequent line of therapy. Against this background, the results on overall survival were rated as non-interpretable (see also Section I 4.1).

Risk of bias across outcomes (study level)

Table 12 shows the risk of bias across outcomes (risk of bias at study level).

Table 12: Risk of bias across outcomes (study level) – RCT, direct comparison: nivolumab vs. placebo

Study	Adequate random sequence generation	Allocation concealment	Blinding		Reporting independent of the results	Absence of other aspects	Risk of bias at study level
			Patients	Treating staff			
CA209-274	Yes	Yes	Yes	Yes	Yes	Yes	Low
RCT: randomized controlled trial							

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

Transferability of the study results to the German health care context

From the company’s point of view, the results of the CA209-274 study can be transferred to the German health care context without limitations due to the study design and the characteristics of the patient population under investigation. Furthermore, the company states that the use of nivolumab in CA209-274 corresponds to the marketing authorization. In summary, the results of the CA209-274 study are assumed to be completely transferable to German health care context.

The company did not provide any further information on the transferability of the study results to the German health care context. For the transferability of the study results, see also Section I 4.2.

I 4 Results on added benefit

I 4.1 Outcomes included

The following patient-relevant outcomes were to be included in the assessment:

- Mortality
 - overall survival
- Morbidity
 - failure of the curative treatment approach
 - symptoms, assessed using the EORTC QLQ-C30
 - health status, recorded using the EQ-5D VAS
- Health-related quality of life
 - recorded with the EORTC QLQ-C30
- Side effects
 - SAEs
 - severe AEs (CTCAE grade ≥ 3)
 - discontinuation due to AEs
 - immune-mediated SAEs and severe AEs
 - other specific AEs, if any

Table 13 shows for which outcomes data were available in the included study.

Table 13: Matrix of outcomes – RCT, direct comparison: nivolumab vs. placebo

Study	Outcomes										
	Overall survival	Failure of the curative treatment approach ^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-mediated SAEs ^d	Immune-mediated severe AEs ^{c, d}	Further specific AEs ^e
CA209-274	No ^f	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes ^g	Yes ^g	Yes
a. Represented by the event rate and DFS, the events include local recurrence within the urothelial tract, local recurrence outside the urothelial tract, distant metastases and death from any cause (without prior recurrence). b. Excludes progression events of the underlying disease (several PTs of the SOC “neoplasms benign, malignant and unspecified” [including cysts and polyps]” according to the company’s list). c. Operationalised as CTCAE grade ≥ 3. d. The operationalization of a specific MedDRA PT collection (“select AEs”) presented by the company is used in each case. e. The following events (MedDRA coding) are considered: skin and subcutaneous tissue disorders (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. Data not interpretable; for justification, see the section below. g. In Module 4R, there are no data on immune-mediated side effects for the data cut of 6 January 2025. The results from the data cut of 17 July 2020 are used in each case; see the 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; 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											

Results on overall survival not interpretable due to inadequate subsequent therapies

The observation period for overall survival in patients in this therapeutic indication is composed of a phase of DFS until recurrence and the subsequent stage of advanced and/or metastatic urothelial carcinoma.

An observed effect in the outcome of overall survival is not only influenced by the initial study treatment, but also by the subsequent antineoplastic therapies used after disease progression or recurrence [27-29]. In order for an observed effect in the outcome of overall survival to be interpreted meaningfully, adequate guideline-compliant subsequent treatment of patients after progression or recurrence of the disease is therefore necessary, especially in the adjuvant therapy situation.

Based on the available data, however, it is assumed that the subsequent systemic therapies administered do not adequately reflect the current standard of care after recurrence (see Section I 3.2). Thus, the results on overall survival in the CA209-274 study cannot be interpreted overall. The results are presented as supplementary information in I Appendix E of the full dossier assessment.

Failure of the curative treatment approach

In this therapeutic indication, curative therapy is generally possible and the aim of treatment. The occurrence of a relapse after achieved R0 resection means that the curative treatment approach in this line of therapy has failed. Failure of the curative treatment approach is a patient-relevant event in this treatment situation, as it is usually followed by a transition to a palliative treatment situation. Failure of the curative treatment approach was therefore considered a patient-relevant outcome in this assessment.

In the CA209-274 study, failure of the curative treatment approach as an outcome was not directly recorded. As an approximation, the present assessment considers the events that were recorded as part of the composite outcome DFS in the CA209-274 study as operationalization for the outcome. The proportion of patients with event (referred to below as “event rate”) and also the time to the occurrence of an event (DFS) is used for the assessment. The operationalisation of the outcome is explained below.

According to the information in the statistical analysis plan, the outcome DFS was defined as time from randomisation to the first occurrence of one of the following events:

- local recurrence outside the urinary tract
- local recurrence outside the urinary tract
- Distant recurrence
- Death from any cause (without prior recurrence)

In the present data situation, the events recorded in the outcome DFS of the CA209-274 study are suitable for reflecting the failure of the curative treatment approach and are therefore used for the benefit assessment. The Kaplan-Meier curves on DFS are presented in I Appendix B.1.

Compared with the first assessment A22-53 [30], the presently available, more recent data set allows for a significantly longer follow-up period for most patients.

Immune-mediated AEs, severe AEs and SAEs

The outcomes immune-mediated AEs, severe AEs and SAEs are of particular importance for the assessment of an immune checkpoint inhibitor such as nivolumab. The significance of

these AEs specific to immune checkpoint inhibitors is generally acknowledged and is also reflected, for example, in the fact that the Association of the Scientific Medical Societies (AWMF) included a separate chapter on the prevention, diagnosis and treatment of immune-mediated AEs in the current version of its guideline on supportive therapy for oncological patients [31]. Immune-mediated AEs (SAEs and severe AEs) are patient-relevant outcomes for the assessment of immune checkpoint inhibitors, which were routinely used in the past when assessing drugs in this class.

Although, as in the first assessment in this therapeutic indication, the company has previously presented suitable analyses on immune-mediated AEs, SAEs and severe AEs, these are missing in the present dossier. It provided no justification for this. However, it states elsewhere that, in accordance with the G-BA's new Code of Procedure of 17 July 2025 [32], a priori defined AEs of particular interest (AESI) as well as predefined AE analyses across System Organ Classes (SOCs) are not taken into account. This was not appropriate. Analyses of all relevant outcomes must be submitted in accordance with the module template. As outlined, in this therapeutic indication, this also includes analyses on immune-mediated AEs, SAEs and severe AEs. For a complete assessment, these must be presented in an appropriate operationalization, for example as a priori defined AESI.

The first assessment A22-53 contained data on immune-mediated AEs, immune-mediated SAEs and immune-mediated severe AEs for the data cut of 17 July 2020, and these data were used. As the follow-up for all AEs up to 100 days after the last administration of the study medication had already been largely completed at the data cut of 17 July 2020, it was not assumed that any significant number of events will have been added at the given data cut of 6 January 2025. This was also confirmed by a comparison of the number of events of individual SOCs and PTs between the data cuts. Therefore, as an auxiliary measure, the results on the immune-mediated AEs, SAEs and severe AEs at the data cut of 17 July 2020 were used in this assessment.

The operationalization available at the time was regarded as a sufficient approximation for representing the immune-mediated AEs. Operationalization took place using a MedDRA PT collection predefined by the company ('select AEs') [30]. This is a selection of categories and PTs which count among the typical immune-mediated AEs and for which treatment with immunosuppressants (e.g. corticosteroids) of these AEs could be necessary, but did not have to be. The operationalization also includes events recorded as hypersensitivity/infusion-related reactions. However, these events are not relevant for the representation of immune-mediated AEs, as they are not assumed to have an immune-mediated cause. However, due to the low proportion of patients with events this entails no consequences (proportion of patients with serious hypersensitivity events/infusion-related reactions: 1.4% vs. 0.7%;

proportion of patients with severe hypersensitivity events/infusion-related reactions: 0.7% vs. 0.7%; see I Appendix D).

I 4.2 Risk of bias

Table 14 describes the risk of bias for the results of the relevant outcomes.

Table 14: Risk of bias across outcomes and outcome-specific risk of bias – RCT, direct comparison: nivolumab vs. placebo

Study	Study level	Outcomes										
		Overall survival	Failure of the curative treatment approach ^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-mediated SAEs ^c	Immune-mediated severe AEs ^{b, c}	Further specific AEs ^d
CA209-274	N	– ^e	N	H ^f	H ^f	H ^f	H ^f	H ^f	L ^g	H ^f	H ^f	H ^f

a. Represented by the event rate and DFS, the events include local recurrence within the urothelial tract, local recurrence outside the urothelial tract, distant metastases and death from any cause (without prior recurrence).

b. Severe AEs are operationalised as CTCAE grade ≥ 3 .

c. The operationalization of a specific MedDRA PT collection (“select AEs”) presented by the company is used in each case.

d. The following events (MedDRA coding) are considered: skin and subcutaneous tissue disorders (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 suitable data available; see Section I 4.1 for the reasoning.

f. Incomplete observations for potentially informative reasons.

g. Despite the low risk of bias, the certainty of results for the outcome discontinuation due to AEs is assumed to be limited (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 results on overall survival are not usable (see Section I 4.1); therefore, the risk of bias is not assessed. The risk of bias of the results on the outcome failure of the curative treatment approach was rated as low.

The risk of bias in the results on the outcomes symptoms (EORTC QLQ-C30) and health-related quality of life (EORTC QLQ-C30) was rated as high. Here, there are incomplete observations

for potentially informative reasons due to the follow-up period linked to the treatment duration and a possible association between outcome and reason for treatment discontinuation.

According to the company, the outcome health status is recorded using the EQ-5D VAS (unlike the other PRO outcomes) until death, withdrawal of consent, loss to follow-up or end of the study (see Table 8). As already noted in the first assessment A22-53 and the respective addendum A22-97 [30,33], the follow-up recordings are not assigned to the corresponding visits, which makes it difficult to estimate the response rates. Consequently, it is also not possible to compare the response rates with the data on overall survival. Taking into account the Kaplan-Meier curves (see Figure 10), it can be assumed that by the end of the planned minimum follow-up period at Month 60 (5 years), the censoring rate will be 26% or 27%, whereby the proportion of incomplete observations for potentially informative reasons remains unclear. However, it is assumed that the majority of censorings from Month 60 onwards are administrative censorings (data cut) and therefore not informative censorings. Overall, a high risk of bias is also assumed for the results of the outcome health status.

The risk of bias of the results on the outcomes SAEs, severe AEs (overall rates and specific AEs), as well as immune-mediated SAEs/severe AEs was rated as high. For the mentioned outcomes of the category of side effects, there are incomplete observations for potentially informative reasons due to the follow-up period linked to the treatment duration (100 days after the last administration of the study medication) and a possible association between outcome and reason for treatment discontinuation.

Although the risk of bias is low for the results on the outcome of discontinuation due to AEs, the certainty of results is reduced for this outcome. Premature treatment discontinuation for reasons other than AEs is a competing event for the outcome discontinuation due to AEs to be recorded. This means that, although AEs that would have led to discontinuation of therapy may occur after discontinuation for other reasons, the criterion discontinuation is no longer applicable to them. It was impossible to estimate how many AEs this affected.

Summary assessment of the certainty of conclusions

Irrespective of the factors described in relation to the risk of bias, the certainty of conclusions for the study results remained limited due to the uncertainties described in Section I 3.2 regarding the proportion of patients for whom adjuvant cisplatin-containing chemotherapy would have been appropriate. At most hints, e.g. of an added benefit, can be derived from the information available from the CA29-274 study.

I 4.3 Results

Table 15 summarizes the results of the comparison of nivolumab with watchful waiting in patients with MIUC with tumour cell PD-L1 expression of $\geq 1\%$ and a high risk of recurrence after undergoing radical resection, for whom cisplatin-containing therapy is not suitable or who have already received neoadjuvant treatment. Where necessary, calculations conducted by the Institute are provided in addition to the data from the company's dossier.

The Kaplan-Meier curves for the time-to-event analyses are presented in I Appendix B, the results on common AEs, SAEs, severe AEs and discontinuations due to AEs at the level of SOC and PTs are presented in I Appendix C, and the results on common immune-mediated AEs, SAEs and severe AEs are presented in I Appendix D.

Table 15: Results (mortality, morbidity, health-related quality of life and side effects, time to event) – RCT, direct comparison: nivolumab vs. placebo (multipage table)

Study outcome category	Nivolumab		Placebo		Nivolumab vs. placebo
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 (data cut-off: 06 January 2025)					
Mortality					
Overall survival	No suitable data ^b				
Morbidity					
Failure of the curative treatment approach					
Event rate ^c	140	– 68 (48.6)	142	– 92 (64.8) ^d	RR: 0.75 [0.61; 0.92] ^e ; < 0.006 ^f
Distant recurrence	140	– 46 (32.9)	142	– 55 (38.7)	–
Local recurrence outside the urinary tract	140	– 7 (5.0)	142	– 20 (14.1)	–
Local recurrence outside the urinary tract, invasive	140	– 1 (0.7)	142	– 3 (2.1)	–
Local recurrence outside the urinary tract, non-invasive	140	– 3 (2.1)	142	– 2 (1.4)	–
Death from any cause (without prior recurrence)	140	– 11 (7.9)	142	– 11 (7.7)	–
DFS	140	55.49 [25.79; 66.50] 68 (48.6)	142	8.41 [5.59; 20.04] 92 (64.8)	0.57 [0.42; 0.79]; < 0.001
Symptoms (time to first deterioration)					
EORTC QLQ-C30g					
Fatigue	123	4.90 [2.04; 7.39] 77 (62.6)	128	3.78 [2.50; 5.19] 82 (64.1)	0.97 [0.71; 1.33]; 0.861
Nausea and vomiting	123	NA [15.41; NC] 44 (35.8)	128	NA 35 (27.3)	1.35 [0.86; 2.10]; 0.191
Pain	123	9.69 [5.16; 15.64] 67 (54.5)	128	4.76 [3.25; 7.16] 81 (63.3)	0.75 [0.54; 1.04]; 0.084
Dyspnoea	123	15.93 [8.90; NC] 51 (41.5)	127	NA [12.91; NC] 44 (34.6)	1.17 [0.78; 1.75]; 0.460
Insomnia	123	15.80 [11.07; NC] 49 (39.8)	128	10.61 [5.49; NC] 64 (50.0)	0.72 [0.49; 1.06]; 0.095
Appetite loss	122	15.93 [9.23; NC] 52 (42.6)	128	NA [11.24; NC] 49 (38.3)	1.14 [0.77; 1.71]; 0.510

Table 15: Results (mortality, morbidity, health-related quality of life and side effects, time to event) – RCT, direct comparison: nivolumab vs. placebo (multipage table)

Study outcome category outcome	Nivolumab		Placebo		Nivolumab vs. placebo
	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
Constipation	122	NA 37 (30.3)	127	NA 43 (33.9)	0.88 [0.56; 1.36]; 0.560
Diarrhoea	122	NA [13.83; NC] 41 (33.6)	127	NA 41 (32.3)	0.95 [0.61; 1.47]; 0.821
Health status (time to first deterioration)					
EQ-5D VAS ^h	127	25.13 [12.02; 63.61] 68 (53.5)	129	9.43 [5.88; 17.25] 80 (62.0)	0.63 [0.45; 0.87]; 0.025
Health-related quality of life					
EORTC QLQ-C30 (time to first deterioration ⁱ)					
Global health status	123	9.95 [6.93; NC] 57 (46.3)	127	10.51 [5.59; NC] 64 (50.4)	0.94 [0.66; 1.36]; 0.747
Physical functioning	123	16.43 [8.84; NC] 48 (39.0)	128	NA [9.20; NC] 54 (42.2)	0.84 [0.57; 1.25]; 0.395
Role functioning	123	8.31 [4.63; 12.75] 68 (55.3)	128	5.55 [4.04; 11.73] 70 (54.7)	0.93 [0.66; 1.30]; 0.656
Emotional functioning	123	NA [15.24; NC] 46 (37.4)	127	12.91 [7.16; NC] 55 (43.3)	0.78 [0.53; 1.16]; 0.218
Cognitive functioning	123	7.66 [4.67; 15.77] 64 (52.0)	127	8.61 [4.86; NC] 64 (50.4)	1.01 [0.71; 1.43]; 0.973
Social functioning	122	15.64 [6.47; NC] 55 (45.1)	126	NA [7.56; NC] 52 (41.3)	1.06 [0.72; 1.55]; 0.766
Side effects					
AEs (supplementary information) ^j	139	0.49 [0.33; 0.49] 138 (99.3)	139	0.59 [0.49; 0.85] 133 (95.7)	–
SAEs ^j	139	NA [14.23; NC] 51 (36.7)	139	NA [9.53; NC] 57 (41.0)	0.83 [0.57; 1.21]; 0.327
Severe AEs, ^{j, k}	139	9.49 [6.11; NC] 74 (53.2)	139	15.01 [8.41; NC] 61 (43.9)	1.23 [0.88; 1.73]; 0.235
Discontinuation due to AEs ^j	139	NA 30 (21.6)	139	NA 15 (10.8)	1.94 [1.05; 3.62]; 0.033
Immune-mediated UEs (supplementary information) ^{l, m}	139	1.68 [0.95; 2.33] 108 (77.7)	139	4.53 [2.73; 8.05] 80 (57.6)	–
Immune-mediated SAEs ^{l, m}	139	NA 17 (12.2)	139	NA 6 (4.3)	2.64 [1.04; 6.72]; 0.034

Table 15: Results (mortality, morbidity, health-related quality of life and side effects, time to event) – RCT, direct comparison: nivolumab vs. placebo (multipage table)

Study outcome category outcome	Nivolumab		Placebo		Nivolumab vs. placebo
	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
Immune-mediated severe AEs ^{k, l, m}	139	NA 27 (19.4)	139	NA 9 (6.5)	2.89 [1.36; 6.14]; 0.004
Other specific AEs					
Skin and subcutaneous tissue disorders (SOC, AEs)	139	5.22 [2.50; 10.35] 77 (55.4)	139	NA 45 (32.4)	1.95 [1.35; 2.83]; < 0.001
Asthenia (PT, AEs)	139	NA 19 (13.7)	139	NA 5 (3.6)	3.96 [1.48; 10.60]; 0.003
Infections and infestations (SOC, SAEs)	139	NA 14 (10.1)	139	NA 28 (20.1)	0.47 [0.25; 0.89]; 0.017
Respiratory, thoracic and mediastinal disorders (SOC, SAEs)	139	NA 9 (6.5)	139	NA 1 (0.7)	8.30 [1.05; 65.59]; 0.016
Gastrointestinal disorders (SOC, severe AEs ^k)	139	NA 8 (5.8)	139	NA 17 (12.2)	0.44 [0.19; 1.01]; 0.047
Lipase increased (PT, severe AEs ^k)	139	NA 11 (7.9)	139	NA 1 (0.7)	10.45 [1.35; 81.03]; 0.005
a. HR and CI: Cox proportional hazards model, p-value: log-rank test; each stratified by pathological lymph node status and the use of cisplatin as neoadjuvant chemotherapy. b. See Section I 4.1 for reasons. c. Individual components are presented in the lines below (in each case, only with the qualifying events that are relevant for the formation of the composite outcome; calculation of effect estimates is therefore not meaningful). d. One patient already had measurable disease at baseline. This was included in the analysis as an event. e. Cochran-Mantel-Haenszel method, stratified by pathological lymph node status and the use of cisplatin as neoadjuvant chemotherapy. f. Institute's calculation (unconditional exact test [CSZ method according to [34]]). g. A score increase by ≥ 10 points from baseline is deemed a clinically relevant deterioration (scale range of 0 to 100). h. A score decrease by ≥ 15 points from baseline is deemed a clinically relevant deterioration (scale range of 0 to 100). i. A score decrease by ≥ 10 points from baseline is deemed a clinically relevant deterioration (scale range of 0 to 100). j. Excludes progression events of the underlying disease (several PTs of the SOC "neoplasms benign, malignant and unspecified" [including cysts and polyps]" according to the company's list). k. Operationalized as CTCAE grade ≥ 3. l. Data cut 17 July 2020. m. The operationalization of a specific MedDRA PT collection ("select AEs") presented by the company is used in each case.					

Table 15: Results (mortality, morbidity, health-related quality of life and side effects, time to event) – RCT, direct comparison: nivolumab vs. placebo (multipage table)

Study outcome category outcome	Nivolumab		Placebo		Nivolumab vs. placebo
	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
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; HR: hazard ratio; MedDRA: Medical Dictionary for Regulatory Activities; n: number of patients with (at least one) event; N: number of analysed patients; NA: not achieved; NC: not calculable; 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, no more than hints, e.g. of an added benefit, can be determined for all outcomes.

Mortality

Overall survival

The results for the outcome overall survival are not interpretable (see Section I 4.1).

Morbidity

Failure of the curative treatment approach

For the present benefit assessment, the outcome failure of the curative treatment approach is presented via the occurrence of the event (event rate, effect measure RR) and the time to event (DFS, effect measure HR). A statistically significant difference in favour of nivolumab over placebo was shown for both analyses when considering the total population. However, for the event rate, there is a statistically significant effect modification for the characteristic sex. A statistically significant difference in favour of nivolumab in comparison with placebo was shown for men. For women, however, there was no statistically significant difference between the treatment arms. For the DFS, there is also a significant difference in favour (of nivolumab) for men only; however, there is no statistically significant effect modification for the characteristic sex (see Section I 4.4). For men, there is a hint of added benefit of nivolumab in comparison with the ACT. For women, there is no hint of an added benefit of nivolumab in comparison with the ACT; an added benefit for women is therefore not proven for this outcome.

Symptoms (recorded with the EORTC QLQ-C30)

No statistically significant difference between the treatment arms was shown for any of the outcomes fatigue, nausea and vomiting, pain, dyspnoea, insomnia, appetite loss, constipation and diarrhoea (recorded using the EORTC QLQ-C30). There is no hint of an added benefit of nivolumab over the ACT for any of these outcomes; an added benefit is therefore not proven for these outcomes.

Health status (recorded using the EQ-5D VAS)

For the outcome health status (recorded using the EQ-5D VAS), a statistically significant difference was found in favour of nivolumab in comparison with placebo. This results in a hint of added benefit of nivolumab in comparison with the ACT.

Health-related quality of life

No statistically significant difference between the treatment arms was found for any of the outcomes global health status, physical functioning, role functioning, emotional functioning and social functioning (recorded using the EORTC C30). There is no hint of an added benefit of nivolumab over the ACT for any of these outcomes; an added benefit is therefore not proven for these outcomes.

Side effects

SAEs and severe AEs

There was no statistically significant difference between the treatment arms for the outcomes of SAEs and severe AEs. In each case, there is therefore no hint of greater or lesser harm of nivolumab in comparison with the ACT; 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. However, the extent of the effect for this outcome in the category of non-serious/non-severe side effects was no more than marginal. There was no hint of greater or lesser harm from nivolumab in comparison with the ACT; greater or lesser harm is therefore not proven.

Immune-mediated SAEs and immune-mediated severe AEs

For each of the outcomes immune-mediated SAEs and immune-mediated severe AEs, a statistically significant difference was found to the disadvantage of nivolumab in comparison with placebo. In each case, this resulted in a hint of greater harm from nivolumab in comparison with the ACT.

Specific AEs

Skin and subcutaneous tissue disorders (AEs), asthenia (AEs), respiratory, thoracic and mediastinal disorders (SAEs), lipase increased (severe AEs)

For the outcomes 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 each to the disadvantage of nivolumab compared with placebo. In each case, this resulted in a hint of greater harm from nivolumab in comparison with the ACT.

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 infections and infestations (SAEs) and gastrointestinal disorders (severe AEs). In each case, this resulted in a hint of lesser harm from nivolumab in comparison with the ACT. However, given the placebo-controlled study design with no active treatment in the comparator arm, it is questionable whether the effect in the outcomes gastrointestinal disorders as well as infections and infestations should actually be assigned to the outcome category of side effects or whether it rather reflects the symptoms of the disease.

I 4.4 Subgroups and other effect modifiers

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

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

No subgroup analyses are available in the company's dossier for the operationalization event rate for the outcome failure of the curative treatment approach. These were therefore calculated by the Institute as part of the benefit assessment.

Interaction tests are performed when at least 10 patients per subgroup are included in the analysis. For binary data, there must also be at least 10 events in at least one 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.

The results are presented in Table 16.

Table 16: Subgroups (morbidity, time to event) – RCT, direct comparison: nivolumab vs. placebo

Study outcome characteristic subgroup	Nivolumab		Placebo		Nivolumab vs. placebo	
	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
CA209-274 (data cut-off: 06 January 2025)						
Failure of the curative treatment approach						
Event rate						
Sex						
Men	101	– 47 (46.5)	112	– 78 (69.6)	RR: 0.67 [0.52; 0.85] ^a	< 0.001 ^a
Women	39	– 21 (53.8)	30	– 14 (46.7)	RR: 1.15 [0.71; 1.87] ^a	0.605 ^a
Total					Interaction ^b :	0.047
<i>Presented as supplementary information: DFS</i>						
Sex						
Men	101	55.49 [25.79; NC] 47 (46.5)	112	8.25 [5.19; 17.94] 78 (69.6)	0.50 [0.35; 0.72] ^c	< 0.001 ^c
Women	39	42.55 [5.72; NC] 21 (53.8)	30	28.98 [2.79; NC] 14 (46.7)	0.91 [0.46; 1.80] ^c	0.787 ^c
Total					Interaction ^d :	0.118
a. Institute's calculation, p-value unconditional exact test, (CSZ method according to [34]). b. Institute's calculation of Q test for heterogeneity. c. HR and CI: Cox proportional hazards model, p-value: log-rank test; each unstratified. d. p-value based on the interaction term in the Cox proportional hazards model, adjusted for subgroup and interaction between treatment and subgroup. CI: confidence interval; DFS: disease-free survival; HR: hazard ratio; n: number of patients with (at least one) event; N: number of analysed patients; NC: not calculable; RCT: randomized controlled trial; RR: relative risk						

Morbidity

Failure of the curative treatment approach

There is a statistically significant effect modification for the characteristic sex for the operationalization event rate of the outcome failure of the curative treatment approach. A statistically significant difference in favour of nivolumab in comparison with placebo was shown for men. For men, there is a hint of added benefit of nivolumab in comparison with the ACT. For women, however, there was no statistically significant difference between the treatment arms. For this subgroup, there is no hint of an added benefit of nivolumab in comparison with the ACT; an added benefit for women is therefore not proven for this outcome.

In addition, the results for the subgroups of men and women are presented for the DFS operationalization. There is no significant effect modification for these; however, analogous to the results on the event rate, a significant effect in favour of nivolumab is observed only in men. For women, there was no statistically significant difference between the treatment arms.

I 5 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 *General Methods* of IQWiG [35].

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.

I 5.1 Assessment of added benefit at outcome level

The extent of the respective added benefit at outcome level was assessed based on the results presented in Chapter I 4 (see Table 17).

Determination of the outcome category for the outcomes failure of curative treatment, health status and discontinuation due to AEs

For the following outcomes, it cannot be inferred from the dossier whether they are serious/severe or non-serious/non-severe. The classification of this outcome/these outcomes is justified below.

Failure of the curative treatment approach

The outcome of failure of curative treatment is deemed to be serious/severe. On the one hand, recurrence of 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 death from any cause (without previous recurrence) is a component of the outcome of failure of curative treatment.

Health status (recorded using the EQ-5D VAS)

The company assigned the outcome health status (recorded using the EQ-5D VAS) in Module 4R to the outcome category serious/severe symptoms/late complications, but does not provide any justification for this classification. For the outcome health status (recorded using the EQ-5D VAS), there is insufficient information available to assign the severity category. The outcome health status was therefore assigned to the outcome category non-serious/non-severe symptoms/late complications.

Discontinuation due to AEs

For the relevant subpopulation of the CA209-274 study, information is available on the severities of the AEs due to which treatment was discontinued (including progression events). This shows that in 40.5% of the AEs that led to discontinuation of treatment there was an event of CTCAE grade ≥ 3 . Therefore, the outcome was assigned to the outcome category of non-serious/non-severe side effects.

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

Outcome category outcome effect modifier subgroup	Nivolumab vs. placebo median time to event (months) or proportion of events (%) effect estimation [95% CI]; p-value probability ^a	Derivation of extent ^b
Outcomes with observation over the entire study duration		
Mortality		
Overall survival	No suitable data ^c	Lesser benefit not proven / added benefit not proven
Morbidity		
Failure of the curative treatment approach		
Event rate		
Sex		
Men	46.5% vs. 69.6% RR: 0.67 [0.52; 0.85]; p < 0.001 probability: hint	Outcome category: serious/severe symptoms/late complications 0.75 ≤ CI _u < 0.90 added benefit, extent: considerable
Women	53.8% vs. 46.7% RR: 1.15 [0.71; 1.87]; p = 0.605	Lesser benefit not proven / added benefit not proven
DFS	55.49 vs. 8.41 months HR: 0.57 [0.42; 0.79]; p < 0.001 probability: hint	
Outcomes with shortened observation period		
Morbidity		
Symptoms (EORTC QLQ-C30– time to first deterioration)		
Fatigue	4.90 vs. 3.78 months HR: 0.97 [0.71; 1.33]; p = 0.861	Lesser benefit not proven / added benefit not proven
Nausea and vomiting	NA vs. NA months HR: 1.35 [0.86; 2.10]; p = 0.191	Lesser benefit not proven / added benefit not proven
Pain	9.69 vs. 4.76 months HR: 0.75 [0.54; 1.04]; p = 0.084	Lesser benefit not proven / added benefit not proven
Dyspnoea	15.93 vs. NA months HR: 1.17 [0.78; 1.75]; p = 0.460	Lesser benefit not proven / added benefit not proven

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

Outcome category outcome effect modifier subgroup	Nivolumab vs. placebo median time to event (months) or proportion of events (%) effect estimation [95% CI]; p-value probability ^a	Derivation of extent ^b
Insomnia	15.80 vs. 10.61 months HR: 0.72 [0.49; 1.06]; p = 0.095	Lesser benefit not proven / added benefit not proven
Appetite loss	15.93 vs. NA months HR: 1.14 [0.77; 1.71]; p = 0.510	Lesser benefit not proven / added benefit not proven
Constipation	NA vs. NA months HR: 0.88 [0.56; 1.36]; p = 0.560	Lesser benefit not proven / added benefit not proven
Diarrhoea	NA vs. NA months HR: 0.95 [0.61; 1.47]; p = 0.821	Lesser benefit not proven / added benefit not proven
Health status (EQ-5D VAS – time to first deterioration)	25.13 vs. 9.43 HR: 0.63 [0.45; 0.87]; p = 0.025 probability: hint	Outcome category: non-serious / non- severe symptoms / late complications 0.80 ≤ CI _u < 0.90 added benefit, extent: minor
Health-related quality of life		
EORTC QLQ-C30 – time to first deterioration		
Global health status	9.95 vs. 10.51 months HR: 0.94 [0.66; 1.36]; p = 0.747	Lesser benefit not proven / added benefit not proven
Physical functioning	16.43 vs. NA months HR: 0.84 [0.57; 1.25]; p = 0.395	Lesser benefit not proven / added benefit not proven
Role functioning	8.31 vs. 5.55 months HR: 0.93 [0.66; 1.30]; p = 0.656	Lesser benefit not proven / added benefit not proven
Emotional functioning	NA vs. 12.91 months HR: 0.78 [0.53; 1.16]; p = 0.218	Lesser benefit not proven / added benefit not proven
Cognitive functioning	7.66 vs. 8.61 months HR: 1.01 [0.71; 1.43]; p = 0.973	Lesser benefit not proven / added benefit not proven
Social functioning	15.64 vs. NA months HR: 1.06 [0.72; 1.55]; p = 0.766	Lesser benefit not proven / added benefit not proven

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

Outcome category outcome effect modifier subgroup	Nivolumab vs. placebo median time to event (months) or proportion of events (%) effect estimation [95% CI]; p-value probability ^a	Derivation of extent ^b
Side effects		
SAEs	NA vs. NA months HR: 0.83 [0.57; 1.21]; p = 0.327	Greater/lesser harm not proven
Severe AEs	9.49 vs. 15.01 months HR: 1.23 [0.88; 1.73]; p = 0.235	Greater/lesser harm not proven
Discontinuation due to AEs	NA vs. NA months HR: 1.94 [1.05; 3.62] HR: 0.52 [0.28; 0.95]d; p = 0.033	Outcome category: non-serious/non-severe side effects $0.90 \leq Cl_u < 1.00$ greater/lesser harm not proven ^e
Immune-mediated SAEs	NA vs. NA months HR: 2.64 [1.04; 6.72] HR: 0.38 [0.15; 0.96]d; p = 0.034 probability: hint	Outcome category: serious/severe side effects $0.90 \leq Cl_u < 1.00$ greater harm, extent: minor
Immune-mediated severe AEs	NA vs. NA months HR: 2.89 [1.36; 6.14] HR: 0.35 [0.16; 0.74]d; p = 0.004 probability: hint	Outcome category: serious/severe side effects $Cl_u < 0.75$, risk $\geq 5\%$ greater harm, extent: major
Skin and subcutaneous tissue disorders (AEs)	5.22 vs. NA months HR: 1.95 [1.35; 2.83] HR: 0.51 [0.35; 0.74]d; p < 0.001 probability: hint	Outcome category: non-serious/non-severe side effects $Cl_u < 0.80$ greater harm, extent: considerable
Asthenia (AEs)	NA vs. NA months HR: 3.96 [1.48; 10.60] HR: 0.25 [0.09; 0.68]d; p = 0.003 probability: hint	Outcome category: non-serious/non-severe side effects $Cl_u < 0.80$ greater harm, extent: considerable
Infections and infestations (SAEs)	NA vs. NA months HR: 0.47 [0.25; 0.89]; p = 0.017 probability: hint	Outcome category: serious/severe side effects $0.75 \leq Cl_u < 0.90$ lesser harm, extent: considerable

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

Outcome category outcome effect modifier subgroup	Nivolumab vs. placebo median time to event (months) or proportion of events (%) effect estimation [95% CI]; p-value probability ^a	Derivation of extent ^b
Respiratory, thoracic and mediastinal disorders (SAEs)	NA vs. NA months HR: 8.30 [1.05; 65.59] HR: 0.12 [0.02; 0.95] ^d ; p = 0.016 probability: hint	Outcome category: serious/severe side effects 0.90 ≤ Cl _u < 1.00 greater harm, extent: minor
Gastrointestinal disorders (severe AEs)	NA vs. NA months HR: 0.44 [0.19; 1.01]; p = 0.047 probability: hint	Outcome category: serious/severe side effects Greater harm ^f , extent: minor ^g
Lipase increased (severe AEs)	NA vs. NA months HR: 10.45 [1.35; 81.03] HR: 0.10 [0.01; 0.74] ^d p = 0.005 probability: hint	Outcome category: serious/severe side effects Cl _u < 0.75, risk ≥ 5% greater harm, extent: major
a. Probability provided if there is a statistically significant and relevant effect. b. Depending on the outcome category, the effect size is estimated using different limits based on the upper limit of the confidence interval (Cl_u). c. See Section I 4.1 for reasons. d. Institute's calculation; reversed direction of effect to enable the use of limits to derive the extent of added benefit. e. The extent of the effect in this non-serious/non-severe outcome was no more than marginal. f. The result of the statistical test is decisive for the derivation of the added benefit. g. Discrepancy between CI and p-value; the extent is rated as minor. AE: adverse event; CI: confidence interval; Cl_u: upper limit of confidence interval; DFS: disease-free survival; EORTC: European Organisation for Research and Treatment of Cancer; HR: hazard ratio; NA: not achieved; QLQ-C30: Quality of Life Questionnaire – Core 30; RR: relative risk; SAE: serious adverse event; VAS: visual analogue scale		

I 5.2 Overall conclusion on added benefit

Table 18 summarises the results taken into account for the overall conclusion on the extent of the added benefit.

Table 18: Positive and negative effects from the assessment of nivolumab in comparison with watchful waiting

Positive effects	Negative effects
Outcomes with observation over the entire study duration	
Morbidity serious/severe symptoms/late complications - failure of the curative treatment approach - sex (men): hint of an added benefit – extent: considerable non-serious/non-severe symptoms/late complications - health status: hint of added benefit – extent: minor	–
Outcomes with shortened observation period	
Serious/severe side effects - infections and infestations (SAEs): hint of lesser harm – extent: considerable^a - gastrointestinal disorders (severe AEs): hint of lesser harm – extent: minor	Serious/severe side effects - immune-mediated severe AEs, lipase increased (severe AEs): in each case hint of greater harm - extent: major - immune-mediated SAEs, respiratory, thoracic and mediastinal disorders (SAEs): in each case hint of greater harm – extent: minor
	Non-serious/non-severe side effects skin and subcutaneous tissue disorders (AEs), asthenia (AEs): in each case hint of greater harm – extent: considerable
No suitable data are available for the outcome of overall survival.	
a. It is questionable whether the effect is actually to be allocated to the outcome category side effects or whether it rather reflects the symptoms of the disease. AE: adverse event; SAE: serious adverse event	

Overall, both positive and negative effects of nivolumab were shown in comparison with watchful waiting.

On the positive side, there is a hint of minor added benefit for the outcome health status for the total population, as well as a hint of lesser harm in the outcomes infections and infestations (SAEs; extent: considerable) and gastrointestinal disorders (severe AEs; extent: minor). However, given the placebo-controlled study design, it is questionable whether the effect in the outcomes gastrointestinal disorders as well as infections and infestations should actually be assigned to the outcome category of side effects or whether it rather reflects the symptoms of the disease. In addition, for men, there is a hint of considerable added benefit for the outcome failure of the curative treatment approach.

On the side of the negative effects, in contrast, there are hints of greater harm with minor or major extent for the outcome category serious/severe side effects. For non-serious/non-severe side effects, there are hints of greater harm with considerable extent. However, the

effects observed in the side effects are based exclusively on the shortened period until the end of treatment plus a maximum of 100 days.

Due to the effect modification in the outcome failure of the curative treatment approach, the added benefit is derived separately for men and women.

In the assessment for men, the positive effect in the outcome failure of the curative treatment approach is decisive in the derivation of the added benefit; however, the negative effects described, particularly in the case of severe or serious immune-mediated AEs, lead to a downgrading of the extent of the added benefit. In summary, there is a hint of minor added benefit of nivolumab compared with the ACT watchful waiting for men with MIUC with tumour cell PD-L1 expression $\geq 1\%$ and a high risk of recurrence after undergoing radical resection, for whom cisplatin-containing therapy is not suitable or who have already received neoadjuvant treatment with cisplatin.

However, due to the effect modification, there is no positive effect in the outcome failure of the curative treatment approach for women. When the remaining positive and negative effects are weighed up, there is thus no added benefit for women. An added benefit of nivolumab in comparison with the ACT watchful waiting is not proven for women with muscle-invasive urothelial carcinoma with tumour cell PD-L1 expression $\geq 1\%$ and a high risk of recurrence after undergoing radical resection, for whom cisplatin-containing therapy is not suitable or who have already received neoadjuvant treatment with cisplatin.

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

Therapeutic indication	ACT ^a	Probability and extent of added benefit
Adults with muscle invasive urothelial carcinoma with tumour cell PD-L1 expression $\geq 1\%$ and a high risk of recurrence after undergoing radical resection, for whom cisplatin-containing therapy is not suitable or who have already received neoadjuvant treatment with cisplatin; adjuvant treatment ^b	Watchful waiting	Adults ^c - men: hint of minor added benefit - women: added benefit not proven
a. Presented is the ACT specified by the G-BA. b. According to the G-BA, this includes patients for whom chemotherapy with cisplatin is generally not an option (e.g. due to poor general health or impaired renal function) or who have already received neoadjuvant chemotherapy with cisplatin and for whom, for this reason, further cisplatin treatment is not an option. According to the G-BA, the patient population is therefore heterogeneous. c. Only patients with an ECOG PS of 0 or 1 were included in the CA209-274 study. 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 assessment described above differs from that of the company, which derived an indication of considerable added benefit.

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

I 6 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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