Durvalumab (urothelial carcinoma, neoadjuvant + adjuvant)

Benefit assessment according to §35a SGB V[1]

EXTRACT

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Patient and family involvement

The questionnaire on the disease and its treatment was answered by Alfred Marenbach.

IQWiG thanks the respondent and the Selbsthilfe-Bund Blasenkrebs e. V. (Self-Help Association, Bladder Cancer) for participating in the written exchange about how he experienced the disease and its treatment and about the treatment goals. The respondent and the Selbsthilfe-Bund Blasenkrebs e. V. were not involved in the actual preparation of the 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
AEPI	AE of possible interest
AESI	AE of special interest
CTCAE	Common Terminology Criteria for Adverse Events
DGHO	German Society for Haematology and Medical Oncology
ECOG PS	Eastern Cooperative Oncology Group – Performance Status
EFS	event-free survival
EORTC QLQ-C30	European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire – Core 30
EQ-5D VAS	European Quality Of Life-5 Dimensions visual analogue scale
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
HR	hazard ratio
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
IVRS	interactive voice response system
MIBC	muscle-invasive bladder cancer
NCCN	National Comprehensive Cancer Network
NYHA	New York Heart Association
pCR	pathological complete response
PD-L1	programmed cell death ligand 1
PGIC	Patient Global Impression of Change
PGIS	Patient Global Impression of Severity
PRO-CTCAE	Patient-Reported Outcomes Version of the Common Terminology Criteria for Adverse Events
RCT	randomized controlled trial
SAE	serious adverse event
SGB	Sozialgesetzbuch (Social Code Book)
SmPC	Summary of Product Characteristics
SOC	System Organ Class

I 1 Executive summary of the benefit assessment

Background

In accordance with § 35a Social Code Book 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 durvalumab in combination with gemcitabine and cisplatin for neoadjuvant therapy followed by durvalumab as monotherapy for adjuvant therapy. 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 29 July 2025.

Research question

The aim of this report is to assess the added benefit of durvalumab in combination with gemcitabine and cisplatin for neoadjuvant therapy followed by durvalumab as monotherapy for adjuvant therapy after radical cystectomy in comparison with the appropriate comparator therapy (ACT) in adults with resectable muscle-invasive bladder cancer (MIBC) for whom platinum-based chemotherapy is suitable.

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

Table 2: Research question of the benefit assessment of durvalumab + gemcitabine + cisplatin (neoadjuvant)/durvalumab (adjuvant)

Therapeutic indication	**ACT**[a]
Adults with resectable muscle-invasive bladder cancer (MIBC) for whom platinum-based chemotherapy is suitable; neoadjuvant and adjuvant therapy after radical cystectomy	A therapy regimen consisting of[b] ▪ neoadjuvant therapy with cisplatin in combination with gemcitabine followed by radical cystectomy and: ▫ watchful waiting or ▫ nivolumab (is only an option for patients with tumour cell programmed cell death ligand 1 (PD-L1) expression ≥ 1% and at high risk of recurrence following radical resection)
a. Presented is the ACT specified by the G-BA. b. The ACT specified here comprises several alternative treatment options. However, individual treatment options only represent a comparator therapy for those members of the patient population who meet the patient and disease characteristics shown in brackets. 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

The NIAGARA study was used to assess the benefit of durvalumab plus gemcitabine plus cisplatin (neoadjuvant) followed by durvalumab as monotherapy (adjuvant). This is an ongoing, open-label RCT comparing durvalumab in combination with gemcitabine + cisplatin (neoadjuvant) followed by durvalumab monotherapy (adjuvant) after radical cystectomy, compared with gemcitabine + cisplatin (neoadjuvant) followed by watchful waiting after radical cystectomy. The study included adult patients with histologically or cytologically confirmed resectable MIBC (tumour stage: T2–T4aN0/1M0) for whom platinum-based chemotherapy is suitable.

The study included patients with an Eastern Cooperative Oncology Group – Performance Status (ECOG PS) ≤ 1 and a creatinine clearance of ≥ 40 mL/min. Patients with New York Heart Association (NYHA) class III or IV heart failure, audiometric hearing loss of CTCAE grade ≥ 2, and peripheral polyneuropathy of CTCAE grade ≥ 2 were excluded. The criteria for assessing suitability for cisplatin, as specified in the inclusion and exclusion criteria, thus comply with the specifications of the current S3 guideline and the recommendations of the German Society for Haematology and Medical Oncology (DGHO).

In addition, prior treatment with systemic chemotherapy or immunotherapy was not allowed for the patients

A total of 1063 patients were included in the study and randomly assigned in a 1:1 ratio either to treatment with durvalumab + gemcitabine + cisplatin (neoadjuvant) followed by durvalumab (adjuvant) (N = 533) or to treatment with gemcitabine + cisplatin (neoadjuvant) followed by watchful waiting (N = 530). Randomization was carried out using an interactive voice response system (IVRS), stratified by clinical tumour status (T2N0 vs. > T2N0), renal function (adequate renal function vs. borderline renal function) and tumour programmed cell death ligand 1 (PD-L1) expression status according to tumour cell score 25/immune cells present+ (high vs. low/negative).

Patients in the intervention arm received 4 therapy cycles with durvalumab + gemcitabine + cisplatin in accordance with the Summary of Product Characteristics (SmPC) in the neoadjuvant treatment phase. For both treatment arms, there are deviations from the SmPC for cisplatin and gemcitabine. For patients in both treatment arms, radical cystectomy should be performed within 14 to 56 days (or up to 70 days in medically justified exceptional cases) following the last dose of the study medication in the neoadjuvant phase. Adjuvant therapy should be initiated 42 to 120 days after radical cystectomy. Patients in the intervention arm

received 8 cycles of SmPC-compliant treatment with durvalumab in the adjuvant treatment phase, while no further active therapy took place in the comparator arm.

In the neoadjuvant phase, treatment in both treatment arms was administered until the completion of the protocol-compliant therapy (4 cycles), disease progression precluding radical cystectomy, unacceptable toxicity, or treatment discontinuation at the physician's discretion or patient decision. In the adjuvant phase, treatment in the intervention arm continued until the completion of the protocol-compliant therapy (8 cycles), disease progression, unacceptable toxicity, or treatment discontinuation at the physician's discretion or patient decision. Patients were not allowed to switch from the intervention arm to the comparator arm.

Co-primary outcomes of the NIAGARA study were pathological complete response (pCR) and event-free survival (EFS). Patient-relevant secondary outcomes included outcomes in the categories of mortality, morbidity, health-related quality of life and side effects.

Implementation of watchful waiting in the adjuvant treatment phase

The G-BA specified a treatment regimen consisting of neoadjuvant therapy with cisplatin in combination with gemcitabine, followed by radical cystectomy and either watchful waiting or nivolumab, as the ACT. In the NIAGARA study presented by the company, patients in the comparator arm did not receive active treatment for their bladder cancer during the adjuvant phase, an approach that corresponds to watchful waiting. The aim in both treatment arms was to provide individually optimized and supportive treatment to alleviate symptoms.

The follow-up examinations performed in the NIAGARA study do 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. Furthermore, imaging in the NIAGARA study was carried out more frequently than recommended. Despite these deviations from guideline recommendations, patients in the NIAGARA study were overall monitored closely with specific examinations to record their health status as well as recurrences, so that watchful waiting in the comparator arm was sufficiently implemented in the adjuvant phase.

Uncertainties in the NIAGARA study

Implementation of the ACT

The use of gemcitabine + cisplatin in patients with T2 tumour stage deviates from the SmPC

According to the SmPC, gemcitabine in combination with cisplatin is approved for the treatment of locally advanced or metastatic bladder cancer. According to the guidelines, advanced bladder cancer is defined as tumour stage T3 or higher. There is no specific

marketing authorization for use in the neoadjuvant setting for bladder cancer. The NIAGARA study included patients with resectable MIBC at tumour stage T2–T4N0/1M0. Neoadjuvant treatment of patients with tumour stage T2 (40% of all patients in both treatment arms) with gemcitabine in combination with cisplatin thus deviated from the marketing authorization. However, neoadjuvant treatment with gemcitabine in combination with cisplatin of patients with MIBC is in line with current guideline recommendations. Consequently, the off-label use of gemcitabine plus cisplatin in patients with tumour stage T2 has no consequences for the benefit assessment.

Length of treatment cycles with gemcitabine + cisplatin deviates from the SmPC

Neoadjuvant treatment with gemcitabine and cisplatin for patients with resectable MIBC is not listed in the relevant SmPC. Information on dosage and cycle length is therefore only available for advanced or metastatic stages. The SmPC for gemcitabine - when combined with cisplatin - specifies a cycle length of 28 days with administration of 1000 mg/m² body surface area of gemcitabine on Cycle days 1, 8 and 15 for the treatment of advanced or metastatic bladder cancer. In accordance with the SmPC, cisplatin is administered at a dose of 70 mg/m² body surface area on Day 1 after gemcitabine or on Day 2 of each 28-day treatment cycle.

In the NIAGARA study, the cycle length was 21 days, with gemcitabine administered at a dose of 1000 mg/m² of body surface area on Cycle days 1 and 8 as part of the neoadjuvant treatment. Cisplatin was administered at a dose of 70 mg/m^2 on Day 1 (alternatively at a dose of 35 mg/m^2 on Days 1 and 8 for patients with impaired renal function) of a 21-day cycle. As a result, the dose per cycle is lower relating to gemcitabine, while in relation to cisplatin, the dose is administered at shorter intervals. The guideline of the National Comprehensive Cancer Network (NCCN) describes that the use of cisplatin in combination with gemcitabine in a 21-day cycle is preferred. Overall, administration over a 21-day cycle is considered adequate. There are thus no consequences for the benefit assessment.

Use of cisplatin as a split dose

In the NIAGARA study, patients with impaired renal function (creatinine clearance ≥ 40 mL/min to < 60 mL/min) were able to receive cisplatin as a split dose in both treatment arms. Instead of a single dose of 70 mg/m^2 body surface area on Day 1, the dose could be split into two doses of 35 mg/m^2 each on Day 1 and Day 8. A dose equivalent to a split dose does not comply with the information in the SmPC, which lists renal function of < 60 mL/min as a contraindication for the use of cisplatin. Under the section on the treatment of locally advanced or metastatic MIBC, the S3 guideline and the recommendations of the DGHO cite the option of a split dose of cisplatin for patients with a creatinine clearance of 40 to 60 mL/min. Furthermore, the EPAR describes that the use of the split dose in patients with impaired renal function was supported by the CHMP in the context of a scientific consultation.

It is assumed that dosing according to the split dose of cisplatin in patients with impaired renal function is standard clinical practice.

Data cut-offs

In Module 4A of the dossier, the company presents analyses for interim analysis 2 for all outcomes (most recent data cut-off date: 29 April 2024). At first, this data cut-off was not prespecified and was only introduced in version 5.0 of the study protocol (1 June 2021). The company justifies the interim analysis 2 on the grounds that the sample size calculation was performed for the entire ITT population, as the original sample size calculation was based on the population of patients with adequate renal function. As interim analysis 1 was conducted on 14 January 2022, and therefore took place after the amendment to the study protocol, there is no indication of a potentially result-driven planning. Therefore, the results from interim analysis 2 were used for the benefit assessment.

Results on overall survival cannot be interpreted

The subsequent therapies used in the NIAGARA 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. As both arms are affected by the insufficient use of the combination therapy of enfortumab vedotin and pembrolizumab, the effect on overall survival may be maintained. However, it is also conceivable that the effect in the comparator arm is offset due to the earlier initiation of an appropriate subsequent therapy following a recurrence. Furthermore, this means that, unlike in the intervention arm, the vast majority of patients in the comparator arm had not yet received an immune checkpoint inhibitor, not even as subsequent therapy. Against this background, the results regarding overall survival are rated as uninterpretable.

Effect estimates for the outcomes on side effects cannot be interpreted

In the current data situation, the effect estimates for the outcomes of the side effects category cannot be interpreted, and the available data allow only for a qualitative classification in the overall assessment. This is justified as follows:

In the intervention arm, patients were followed up for up to 90 days after the last dose of the study medication (usually the last adjuvant study medication) or the date of surgery, whichever occurred later. In the comparator arm, follow-up was planned to continue for up to 90 days after the last dose of neoadjuvant treatment, the date of surgery, or the last adjuvant study visit, whichever occurred later. In both arms, side effects were recorded only up to the first dose of subsequent antineoplastic therapy. In the comparator arm, however, the median observation period for side effects was only 5.3 months and the maximum duration was 8.6 months. The available data do not explain why the median duration of observation was significantly shortened (14.3 months) compared to the intervention arm. It

might be possible that most of the recordings only cover the 90-day period following the last dose of the neoadjuvant study medication, and that only isolated patients in the comparator arm only attended visits during the adjuvant phase. The Kaplan-Meier curves on the various outcomes of the adverse event (AE) category show that there are hardly any patients remaining at risk in the comparator arm after approximately 5 to 6 months, meaning that the adjuvant phase is barely covered. From this point onwards, events in the comparator arm carry significantly more weight than events occurring at the same time in the intervention arm, due to the much shorter observation period. It can also be assumed that, in the comparator arm, the few selected patients still under observation differ significantly from the censored patients.

For both the overall rates of AE outcomes and the specific AEs with statistically significant difference between the treatment arms, the Kaplan-Meier curves are virtually identical up to Month 6 and only begin to diverge from that point onwards. In some cases, there were major effects, such as a hazard ratio (HR) of 0.37 [0.24; 0.57] for the outcome renal and urinary disorders (System Organ Class [SOC], severe AEs), which may be due solely to a small number of late events in the comparator arm. Similar patterns can be observed in other specific AEs, but also, for example, in the overall rates of severe and serious AEs (SAEs). Overall, based on the available Kaplan-Meier curves, it cannot be assumed with sufficient certainty that the proportional hazards assumption is met in each case. Due to uncertainties regarding the shape of the Kaplan-Meier curves and the corresponding effect estimates, these effect estimates for all AEs outcomes cannot be interpreted. As described, it is assumed that, in the comparator arm, almost exclusively events that occur during the neoadjuvant treatment phase are taken into account. To rule out the possibility that the effect estimates of the side effects are predominantly driven by events in the very small number of patients who were still at risk even after Month 5 to 6 in the comparator arm, sensitivity analyses were required in which patients were censored at the time of radical cystectomy. Although this would mean that AEs occurring in the intervention arm during the adjuvant phase would not be included in the analyses, these analyses could be interpreted during the neoadjuvant phase at least for the initial period of the study.

However, based on the trends shown in the Kaplan-Meier curves for the outcomes on side effects, it can generally be assumed that the direction of effect for the respective outcomes will not reverse. In summary, although it is not possible to determine the extent of the outcomes on side effects, the results can be taken into account qualitatively in the overall assessment.

Risk of bias

The risk of bias across outcomes is rated as low for the NIAGARA study.

No suitable data are available for the outcome overall survival; therefore, the risk of bias of the results is not assessed.

The outcome-specific risk of bias is rated as low for the results of the outcome failure of the curative treatment approach.

The outcome-specific risk of bias is rated as high for the results of the outcomes on symptoms (European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire – Core 30 [EORTC QLQ-C30], Patient Global Impression of Severity [PGIS]), on health status (European Quality Of Life-5 Dimensions visual analogue scale [EQ-5D VAS], Patient Global Impression of Change [PGIC]) and on health-related quality of life (EORTC QLQ-C30). This is due to the high proportion of patients not included in the analysis (~20%) and the lack of blinding with subjective recording of outcomes.

The effect estimates for the outcomes in the side effects category cannot be interpreted; consequently, there is no need to assess the risk of bias of the results.

No suitable data are available for the outcome assessed using the Patient-Reported Outcomes Version of the Common Terminology Criteria for Adverse Events (PRO-CTCAE). Therefore, the risk of bias for the corresponding results is not assessed.

Results

Mortality

Overall survival

The results on the outcome overall survival are not interpretable.

Morbidity

Failure of the curative treatment approach

Operationalization

For the present benefit assessment, the outcome failure of the curative treatment approach is presented via the time to event (effect measure HR) and the occurrence of the event (effect measure RR). Both analyses include the following events: first recurrence of the disease following radical cystectomy; radical cystectomy not feasible for medical reasons; refusal of radical cystectomy by the patient, or intraoperative failure of radical cystectomy, and death.

Result

A statistically significant difference in favour of the intervention was shown for the outcome "failure of the curative treatment approach". There was an indication of added benefit of durvalumab + gemcitabine + cisplatin (neoadjuvant) followed by durvalumab (adjuvant) in comparison with gemcitabine + cisplatin (neoadjuvant) followed by watchful waiting.

symptoms (recorded using EORTC QLQ-C30 and PGIS)

EORTC QLQ-C30

No statistically significant difference between the treatment groups was shown for any of the outcomes fatigue, nausea and vomiting, pain, dyspnoea, insomnia, appetite loss, constipation and diarrhoea. There is no hint of an added benefit of durvalumab + gemcitabine + cisplatin (neoadjuvant) followed by durvalumab (adjuvant) in comparison with gemcitabine + cisplatin (neoadjuvant) followed by watchful waiting; an added benefit is therefore not proven in either case.

PGIS

No statistically significant difference between treatment groups was shown for the symptoms recorded using PGIS. There was no hint of an added benefit of durvalumab + gemcitabine + cisplatin (neoadjuvant) followed by durvalumab (adjuvant) in comparison with gemcitabine + cisplatin (neoadjuvant) followed by watchful waiting; an added benefit is therefore not proven.

Health status (recorded using EQ-5D VAS and PGIC)

EQ-5D VAS

No statistically significant difference between treatment groups was shown for health status recorded using EQ-5D VAS. For this outcome, there is an effect modification by the characteristic clinical tumour status at baseline according to IVRS. However, the extent of the effect for this outcome in the category of non-serious/non-severe symptoms/late complications was no more than marginal. For patients with tumour stage T2N0 and > T2N0. there is no hint of an added benefit of durvalumab + gemcitabine + cisplatin (neoadjuvant) followed by durvalumab (adjuvant) in comparison with gemcitabine + cisplatin (neoadjuvant) followed by watchful waiting; an added benefit is therefore not proven.

PGIC

The health status assessed using the PGIC shows a statistically significant difference in favour of the intervention. However, the extent of the effect for this outcome in the category of non-serious/non-severe symptoms/late complications was no more than marginal. There was no hint of an added benefit of durvalumab + gemcitabine + cisplatin (neoadjuvant) followed by durvalumab (adjuvant) in comparison with gemcitabine + cisplatin (neoadjuvant) followed by watchful waiting; an added benefit is therefore not proven.

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

Role functioning and social functioning

No statistically significant difference between the treatment groups was shown for the outcomes role functioning and social functioning respectively. There is an effect modification

by the characteristic sex in these outcomes. For women, there was a hint of lesser benefit of durvalumab + gemcitabine + cisplatin (neoadjuvant) followed by durvalumab (adjuvant) in comparison with gemcitabine + cisplatin (neoadjuvant) followed by watchful waiting for these outcomes. For men, there was no hint of an added benefit of durvalumab + gemcitabine + cisplatin (neoadjuvant) followed by durvalumab (adjuvant) in comparison with gemcitabine + cisplatin (neoadjuvant) followed by watchful waiting for these outcomes; an added benefit is therefore not proven for men.

Global health status, physical functioning, emotional functioning, and cognitive functioning

No statistically significant difference between the treatment groups was shown for any of the following outcomes: global health status, physical functioning, emotional functioning, and cognitive functioning. There was no hint of an added benefit of durvalumab + gemcitabine + cisplatin (neoadjuvant) followed by durvalumab (adjuvant) in comparison with gemcitabine + cisplatin (neoadjuvant) followed by watchful waiting; an added benefit is therefore not proven.

Side effects

SAEs, severe AEs, discontinuation due to AEs, immune-mediated SAEs, immune-mediated severe AEs and further specific AEs

Effect estimates for the outcomes of the side effects category cannot be interpreted. On the basis of the available data and the shapes of the Kaplan-Meier curves, a qualitative assessment of the side effects can be made as part of the overall assessment.

PRO-CTCAE

No suitable data are available for the outcome PRO-CTCAE. There is no hint of greater or lesser harm from durvalumab + gemcitabine + cisplatin (neoadjuvant) followed by durvalumab (adjuvant) in comparison with gemcitabine + cisplatin (neoadjuvant) followed by watchful waiting; greater or lesser harm is therefore not proven for this outcome.

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

On the basis of the results presented, the probability and extent of added benefit of the drug durvalumab + gemcitabine + cisplatin (neoadjuvant)/durvalumab (adjuvant) 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)

In the overall consideration, there were both positive and negative effects of durvalumab + gemcitabine + cisplatin (neoadjuvant) followed by durvalumab (adjuvant) in comparison with gemcitabine + cisplatin (neoadjuvant) followed by watchful waiting. For the outcomes in the health-related quality of life category, these relate exclusively to the shortened period (up to the recurrence of the disease, the start of subsequent therapy or study discontinuation).

In terms of positive effects, there is an indication of considerable added benefit for the outcome failure of the curative treatment approach. In contrast, there are negative effects in two aspects of health-related quality of life, which are shown in the subgroup of women due to effect modification. The effect estimates on the side effects cannot be interpreted. However, as it is assumed on the basis of the available information that the directions of the effects will not reverse, the results regarding side effects can be taken into account qualitatively in the overall assessment. Overall, it is therefore assumed that potential disadvantages in the AEs, such as serious and severe immune-mediated AEs, will not completely call into question the advantage in the outcome failure of the curative treatment approach. However, this uncertainty was taken into account when determining the extent.

In summary, for patients with resectable MIBC for whom platinum-based chemotherapy is suitable, there is an indication of minor added benefit of durvalumab in combination with gemcitabine and cisplatin for neoadjuvant treatment, followed by durvalumab as monotherapy for adjuvant treatment, compared with the ACT.

Table 3 presents a summary of the probability and extent of the added benefit of durvalumab + gemcitabine + cisplatin (neoadjuvant)/durvalumab (adjuvant) in comparison with the ACT .

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].

Table 3: Durvalumab + gemcitabine + cisplatin (neoadjuvant)/durvalumab (adjuvant) – probability and extent of added benefit

Therapeutic indication	**ACT[a]**	**Probability and extent of added benefit**
Adults with resectable muscle-invasive bladder cancer (MIBC) for whom platinum-based chemotherapy is suitable; neoadjuvant and adjuvant therapy after radical cystectomy	A therapy regimen consisting of[b] ▪ neoadjuvant therapy with cisplatin in combination with gemcitabine followed by radical cystectomy and: ▫ watchful waiting or ▫ nivolumab (is only an option for patients with tumour cell programmed cell death ligand 1 (PD-L1) expression ≥ 1% and at high risk of recurrence following radical resection)	Indication of minor added benefit[c]

a. Presented is the ACT specified by the G-BA.
b. The ACT specified here comprises several alternative treatment options. However, individual treatment options only represent a comparator therapy for those members of the patient population who meet the patient and disease characteristics shown in brackets.
c. Only patients with an ECOG PS of 0 or 1 were included in the NIAGARA 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 to assess the added benefit of durvalumab in combination with gemcitabine and cisplatin for neoadjuvant therapy followed by durvalumab as monotherapy for adjuvant therapy after radical cystectomy in comparison with the ACT in adults with resectable MIBC for whom platinum-based chemotherapy is suitable.

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

Table 4: Research question of the benefit assessment of durvalumab + gemcitabine + cisplatin (neoadjuvant)/durvalumab (adjuvant)

Therapeutic indication	**ACT**[a]
Adults with resectable muscle-invasive bladder cancer (MIBC) for whom platinum-based chemotherapy is suitable; neoadjuvant and adjuvant therapy after radical cystectomy	A therapy regimen consisting of[b] ▪ neoadjuvant therapy with cisplatin in combination with gemcitabine followed by radical cystectomy and: ▫ watchful waiting or ▫ nivolumab (is only an option for patients with tumour cell programmed cell death ligand 1 (PD-L1) expression ≥ 1% and at high risk of recurrence following radical resection)
a. Presented is the ACT specified by the G-BA. b. The ACT specified here comprises several alternative treatment options. However, individual treatment options only represent a comparator therapy for those members of the patient population who meet the patient and disease characteristics shown in brackets. 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 durvalumab + gemcitabine + cisplatin (status 05 June 2025)
- Bibliographical literature search on durvalumab + gemcitabine + cisplatin (last search on 28 May 2025)
- Search of trial registries/trial results databases for studies on durvalumab + gemcitabine + cisplatin (last search on 28 May 2025)
- Search on the G-BA website for durvalumab + gemcitabine + cisplatin (last search on 05 June 2025)

To check the completeness of the study pool:

- Search in trial registries for studies on durvalumab + gemcitabine + cisplatin (last search on 13 August 2025); for search strategies, see Appendix I 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: durvalumab + gemcitabine + cisplatin (neoadjuvant)/durvalumab (adjuvant) vs. gemcitabine + cisplatin (neoadjuvant)/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])
D933RC00001 NIAGARA[d]	Yes	Yes	No	Yes [3]	Yes [4-6]	Yes [7,8]

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

The study pool for the present benefit assessment comprises the RCT NIAGARA. This concurs with the company's study pool.

I 3.2 Study characteristics

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

Table 6: Characteristics of the included study – RCT, direct comparison: durvalumab + gemcitabine + cisplatin (neoadjuvant)/durvalumab (adjuvant) vs. gemcitabine + cisplatin (neoadjuvant)/watchful waiting (multipage table)

Study	Study design	Population	Interventions (number of randomized patients)	Study duration	Location and period of study	Primary outcome; secondary outcomes[a]
NIAGARA	RCT, open-label, parallel	Adults with resectable muscle-invasive bladder cancer[b] for whom platinum-based chemotherapy is suitable ▪ TNM stage: T2–T4aN0/1M0[c] ▪ not pretreated with systemic chemotherapy or immunotherapy ▪ ECOG PS ≤ 1	Durvalumab + gemcitabine + cisplatin (neoadjuvant)/durvalumab (adjuvant) (N = 533) gemcitabine + cisplatin (neoadjuvant)/watchful waiting (N = 530)	Screening: 28 days treatment: ▪ neoadjuvant (intervention arm and comparator arm): up to 4 cycles or until disease progression that precludes radical cystectomy, unacceptable toxicity, or discontinuation of treatment following the physician's or patient's decision ▪ radical cystectomy ▪ adjuvant (intervention arm)[d]: ▪ up to 8 cycles or until disease progression, unacceptable toxicity, or treatment discontinuation following the physician's or patient's decision observation[e]: outcome-specific, at most until death, lost to follow-up, withdrawal of consent or end of study	168 study centres in Australia, Belgium, Brazil, Canada, Chile, Czech Republic, France, Germany, Israel, Italy, Japan, Netherlands, Philippines, Poland, Russia, South Korea, Spain, Taiwan, Turkey, United Kingdom, United States and Vietnam 11/2018–ongoing data cut-offs: ▪ 14 January 2022[f] ▪ 29 April 2024[g]	Primary: pCR, EFS secondary: overall survival, morbidity, health-related quality of life, AEs

Table 6: Characteristics of the included study – RCT, direct comparison: durvalumab + gemcitabine + cisplatin (neoadjuvant)/durvalumab (adjuvant) vs. gemcitabine + cisplatin (neoadjuvant)/watchful waiting (multipage table)

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

a. Primary outcomes include information without taking into account the relevance for this benefit assessment. Secondary outcomes only include information on relevant available outcomes for this benefit assessment.
b. Histologically or cytologically confirmed.
c. According to the AJCC classification, 8th edition.
d. Although radical cystectomy is a mandatory part of the study, patients in the intervention arm who, for medical reasons, have undergone only a partial cystectomy are also eligible to receive adjuvant treatment. If patients refuse radical cystectomy, they are allowed to proceed to an extension phase provided that, within 56 days of the last dose of the study medication in the neoadjuvant phase, complete remission has been determined based on a local multimodal examination (at least cystoscopy with biopsy, CT/MRI) and no additional intervention has taken place (since Amendment 2 to the study protocol dated 9 December 2019). Patients in the intervention arm will then also receive durvalumab as monotherapy for up to 8 cycles, whilst patients in the comparator arm will not receive any further study treatment (as in the adjuvant phase following cystectomy).
e. Outcome-specific information is described in Table 8.
f. Prespecified first interim analysis for pCR.
g. Final analysis for the EFS (only introduced with Amendment 4 to the study protocol dated 1 June 2021).

AE: adverse event; AJCC: American Joint Committee on Cancer; CT: computed tomography; ECOG PS: Eastern Cooperative Oncology Group - Performance Status; EFS: event-free survival; MRI: magnetic resonance imaging; N: number of randomized patients; pCR: pathological complete response; RCT: randomized controlled trial; TNM: tumour-node-metastasis

Table 7: Characteristics of the intervention – RCT, direct comparison: durvalumab + gemcitabine + cisplatin (neoadjuvant)/durvalumab (adjuvant) vs. gemcitabine + cisplatin (neoadjuvant)/watchful waiting (multipage table)

Study	Intervention	Comparison
NIAGARA	Neoadjuvant therapy: cycles 1-4 (21 days each) ▪ durvalumab 1500 mg IV on Day 1 ▪ cisplatin 70 mg/m^2 BSA[a] IV on Day 1 ▪ gemcitabine 1000 mg/m^2 BSA IV on Day 1 and Day 8 ▪ ▪ radical cystectomy[b] ▪ ▪ adjuvant therapy[c]: cycles 1-8 (28 days each) ▪ durvalumab 1500 mg IV on Day 1	Neoadjuvant therapy: cycles 1-4 (21 days each) ▪ ▪ cisplatin 70 mg/m^2 BSA[a] IV on Day 1 ▪ gemcitabine 1000 mg/m^2 BSA IV on Day 1 and Day 8 radical cystectomy[b] ▪ adjuvant therapy: ▪ none
	Dose adjustment: ▪ durvalumab: no dose reduction allowed; dose delay[d] and treatment discontinuation are possible in the event of toxicity ▪ cisplatin/gemcitabine: treatment discontinuation and dose delays with subsequent resumption of treatment in accordance with local standards (including the omission of the dose on Day 8) are allowed in the event of toxicity ▪ if a dose of one component (durvalumab or cisplatin/gemcitabine) is delayed, the other component may be continued as planned. ▪ if cisplatin/gemcitabine therapy is discontinued due to toxicity, neoadjuvant treatment with durvalumab should also be discontinued[e] and radical cystectomy should be performed; thereafter, durvalumab may be continued as monotherapy.	

Table 7: Characteristics of the intervention – RCT, direct comparison: durvalumab + gemcitabine + cisplatin (neoadjuvant)/durvalumab (adjuvant) vs. gemcitabine + cisplatin (neoadjuvant)/watchful waiting (multipage table)

Study	Intervention	Comparison
	Disallowed prior and concomitant treatment[f] in both arms**:** ▪ allogeneic stem cell transplantation prior to the start of the study ▪ immune-mediated therapies (exception: bacille Calmette-Guérin), including, for example, other anti-CTLA-4, anti-PD-1, anti-PD-L1 or anti-PD-L2 antibodies, before and during the study ▪ pelvic radiotherapy ≤ 2 years before randomization and during the study ▪ any chemotherapy, investigational drug, and biological or hormonal therapy[g] as anticancer treatment during the study in the intervention arm: ▪ immunosuppressants ≤ 14 days prior to the first dose and during treatment, including, for example, systemic corticosteroids ≥ 10 mg/day of prednisone or equivalent, methotrexate, azathioprine and TNF-α inhibitors (with the exceptions listed below) ▪ EGFR tyrosine kinase inhibitors during treatment (and to be used with caution for 90 days afterwards) ▪ herbal and natural remedies that may have an immunomodulatory effect during treatment **permitted pretreatment (in both arms) and permitted concomitant treatment in the intervention arm** ▪ intranasal, inhaled, topical steroids, or local steroid injections ▪ steroids ▫ for a short period during combination chemotherapy, if the SmPC specifies the use of steroids in the event of hypersensitivity reactions ▫ if clinically indicated for the treatment of events not related to immunotherapy (e.g. COPD, radiotherapy, nausea) ▪ immunosuppressants ▫ for the treatment of side effects of durvalumab ▫ as premedication in imaging procedures (in patients with contrast medium allergies) **allowed concomitant treatment in both arms** ▪ any other drugs for prophylactic or supportive treatment (e.g. paracetamol or diphenhydramine), if prescribed by the investigator ▪ BSC (including, for example, antibiotics, analgesics, drugs for symptom control)	

a. In patients with impaired renal function (CrCl ≥ 40 mL/min to < 60 mL/min), the cisplatin dose may be reduced to 35 mg/m^2 BSA on Day 1 and 35 mg/m^2 BSA on Day 8.
b. Recommended between 14 and 56 days after the last dose of the study medication in the neoadjuvant phase; a delay of up to 70 days was permitted for medical reasons.
c. Commencing within 120 days of radical cystectomy, but no earlier than 42 days thereafter.
d. In the neoadjuvant treatment, the dose should then be omitted and resumed in the next cycle; in the adjuvant treatment, the cycle intervals may be shortened (but not to less than 21 days).
e. If, in the investigator's opinion, continuing neoadjuvant durvalumab therapy without chemotherapy would be of clinical benefit to the patient, the sponsor may decide to continue neoadjuvant durvalumab therapy.
f. In both arms during treatment with the study medication and in the control arm during study visits in the adjuvant phase.
g. The simultaneous use of hormonal therapy for non-cancer-related conditions is permitted (e.g. hormone replacement therapy).

Table 7: Characteristics of the intervention – RCT, direct comparison: durvalumab + gemcitabine + cisplatin (neoadjuvant)/durvalumab (adjuvant) vs. gemcitabine + cisplatin (neoadjuvant)/watchful waiting (multipage table)

Study	Intervention	Comparison
BSA: body surface area; BSC: best supportive care; COPD: chronic obstructive pulmonary disease; CrCl: creatinine clearance; CTLA-4: cytotoxic T-lymphocyte-associated antigen 4; EGFR: epidermal growth factor receptor; IV: intravenous; PD-1: programmed cell death protein-1; PD-L1/L2: programmed cell death ligand 1/2; RCT: randomized controlled trial		

Study design

The NIAGARA study is an ongoing, open-label RCT comparing durvalumab in combination with gemcitabine + cisplatin (neoadjuvant) followed by durvalumab monotherapy (adjuvant) after radical cystectomy, compared with gemcitabine + cisplatin (neoadjuvant) followed by watchful waiting after radical cystectomy. The study included adult patients with histologically or cytologically confirmed resectable MIBC (tumour stage: T2–T4aN0/1M0) for whom platinum-based chemotherapy is suitable.

According to the S3 guideline and the recommendations of the DGHO [9,10], cisplatin is unsuitable for patients if at least one of the following criteria is met:

- ECOG PS ≥ 2
- creatinine clearance < 40 mL/min
- audiometric hearing loss according to CTCAE grade ≥ 2
- peripheral neuropathy according to CTCAE grade ≥ 2
- cardiac failure according to NYHA class ≥ III

The study included patients with an ECOG PS ≤ 1 and a creatinine clearance of ≥ 40 mL/min. Patients with NYHA class III or IV heart failure, audiometric hearing loss of CTCAE grade ≥ 2, and peripheral polyneuropathy of CTCAE grade ≥ 2 were excluded. The criteria for assessing suitability for cisplatin, as specified in the inclusion and exclusion criteria, thus comply with the specifications of the current S3 guideline and the recommendations of the DGHO.

In addition, prior treatment with systemic chemotherapy or immunotherapy was not allowed for the patients.

A total of 1063 patients were included in the study and randomly assigned in a 1:1 ratio either to treatment with durvalumab + gemcitabine + cisplatin (neoadjuvant) followed by durvalumab (adjuvant) (N = 533) or to treatment with gemcitabine + cisplatin (neoadjuvant) followed by watchful waiting (N = 530). Randomization was carried out using an IVRS, stratified by clinical tumour status (T2N0 vs. > T2N0), renal function (adequate renal function vs.

borderline renal function) and tumour PD-L1 expression status, determined using the VENTANA PD-L1 (SP263) Assay, according to tumour cell score 25/immune cells present+ (high vs. low/negative).

Patients in the intervention arm received 4 cycles of durvalumab + gemcitabine + cisplatin in accordance with the SmPC in the neoadjuvant treatment phase [11]. For both treatment arms, there are deviations from the SmPC for cisplatin and gemcitabine (see section 'Uncertainties in the NIAGARA study') Teva, 02.2025 #28;AqVida, 12.2018 #27}. For patients in both treatment arms, radical cystectomy should be performed within 14 to 56 days (or up to 70 days in medically justified exceptional cases) following the last dose of the study medication in the neoadjuvant phase. Adjuvant therapy should be initiated 42 to 120 days after radical cystectomy. Patients in the intervention arm received 8 cycles of SmPC-compliant treatment with durvalumab [11] in the adjuvant treatment phase, while no further active therapy took place in the comparator arm.

In the neoadjuvant phase, treatment in both treatment arms was administered until the completion of the protocol-compliant therapy (4 cycles), disease progression precluding radical cystectomy, unacceptable toxicity, or treatment discontinuation at the physician's discretion or patient decision. In the adjuvant phase, treatment in the intervention arm continued until the completion of the protocol-compliant therapy (8 cycles), disease progression, unacceptable toxicity, or treatment discontinuation at the physician's discretion or patient decision. Patients were not allowed to switch from the intervention arm to the treatment of the comparator arm.

Co-primary outcomes of the NIAGARA study were pCR and EFS. Patient-relevant secondary outcomes included outcomes in the categories of mortality, morbidity, health-related quality of life and side effects.

Implementation of watchful waiting in the adjuvant treatment phase

The G-BA specified a treatment regimen consisting of neoadjuvant therapy with cisplatin in combination with gemcitabine, followed by radical cystectomy and either watchful waiting or nivolumab, as the ACT. In the NIAGARA study presented by the company, patients in the comparator arm did not receive active treatment for their bladder cancer during the adjuvant phase, an approach that corresponds to watchful waiting. The aim in both treatment arms was to provide individually optimized and supportive treatment to alleviate symptoms.

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

- Targeted, symptom-based physical examination; recording of weight and ECOG PS and recording of laboratory parameters during the adjuvant phase at Weeks 1, 9, 17 and 25,

as well as (with the exception of the targeted physical examination) during follow-up for up to 90 days after the last adjuvant study visit

- Imaging (computed tomography or magnetic resonance imaging) during the adjuvant phase 42 days after radical cystectomy, then every 12 weeks for the first two years, then every 24 weeks for 3 years, then once a year until disease progression, death, withdrawal of consent, a decision by the sponsor or the end of the study (whichever occurs first)

According to the S3 guideline, follow-up is to comprise early detection of tumour recurrence, metabolic changes, dysfunction, and psycho-oncological and social status [9]. Patients with TNM stage > pT3 and/or pN were to receive regular laboratory work and sonography (3 and 6 months after radical cystectomy, then every 6 months, and annually starting from the 5th follow-up year). A stoma exam and anamnesis of continence and sexual function as well as psycho-oncological status were to be performed at the same intervals. Follow-up with imaging for the detection of tumour recurrence was to take place 3 to 6 months after radical cystectomy, every 6 months until the 3rd year of follow-up, and every 12 months in the 4th to 5th year of follow-up [9]. For patients in TNM stage ≤ pT2, pN0, and cM0, the same examinations are recommended, but imaging was to be taken at longer intervals.

The examinations performed in the NIAGARA study do 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. Furthermore, imaging in the NIAGARA study was carried out more frequently than recommended. Despite these deviations from guideline recommendations, patients in the NIAGARA study were overall monitored closely with specific examinations to record their health status as well as recurrences, so that watchful waiting in the comparator arm was sufficiently implemented in the adjuvant phase.

Uncertainties in the NIAGARA study

Implementation of the ACT

The use of gemcitabine + cisplatin in patients with T2 tumour stage deviates from the SmPC

According to the SmPC, gemcitabine in combination with cisplatin is approved for the treatment of locally advanced or metastatic bladder cancer [12]. According to the guidelines, advanced bladder cancer is defined as tumour stage of T3 or higher [9,10]. There is no specific marketing authorization for use in the neoadjuvant setting for bladder cancer. The NIAGARA study included patients with resectable MIBC at tumour stage T2–T4N0/1M0. Neoadjuvant treatment of patients with tumour stage T2 (40% of all patients in both treatment arms) with gemcitabine in combination with cisplatin thus deviated from the marketing authorization.

However, neoadjuvant treatment with gemcitabine in combination with cisplatin for patients with MIBC is in line with the current guideline recommendations [9,10]. Consequently, the off-label use of gemcitabine plus cisplatin in patients with tumour stage T2 has no consequences for the benefit assessment.

Length of treatment cycles with gemcitabine + cisplatin deviates from the SmPC

As described, neoadjuvant treatment of patients with resectable MIBC with gemcitabine and cisplatin is not listed in the respective SmPC. Information on dosage and cycle length is therefore only available for advanced or metastatic stages. The SmPC for gemcitabine - when combined with cisplatin - specifies a cycle length of 28 days with administration of 1000 mg/m² BSA of gemcitabine on Cycle days 1, 8 and 15 for the treatment of advanced or metastatic bladder cancer [12]. In accordance with the SmPC, cisplatin is administered at a dose of 70 mg/m² BSA on Day 1 after gemcitabine or on Day 2 of each 28-day treatment cycle [12].

In the NIAGARA study, the cycle length was 21 days, with gemcitabine administered at a dose of 1000 mg/m² of body surface area on Cycle days 1 and 8 as part of the neoadjuvant treatment. Cisplatin was administered at a dose of 70 mg/m^2 on Day 1 (alternatively at a dose of 35 mg/m^2 on Days 1 and 8 for patients with impaired renal function) of a 21-day cycle. As a result, the dose per cycle is lower relating to gemcitabine, while in relation to cisplatin, the dose is administered at shorter intervals. The guideline of the NCCN describes that the use of cisplatin in combination with gemcitabine in a 21-day cycle is preferred [13]. Overall, administration over a 21-day cycle is considered adequate (see also [14]). There are thus no consequences for the benefit assessment.

Use of cisplatin as a split dose

In the NIAGARA study, patients with impaired renal function (creatinine clearance ≥ 40 mL/min to < 60 mL/min) were able to receive cisplatin as a split dose in both treatment arms. Instead of a single dose of 70 mg/m^2 body surface area on Day 1, the dose could be split into two doses of 35 mg/m^2 each on Day 1 and Day 8. A dose equivalent to a split dose does not comply with the information in the SmPC [15], which lists a renal function of < 60 mL/min as a contraindication for the use of cisplatin. Under the section on the treatment of locally advanced or metastatic MIBC, the S3 guideline and the recommendations of the DGHO cite the option of a split dose of cisplatin for patients with a creatinine clearance of 40 to 60 mL/min [9,10]. Furthermore, the EPAR describes that the use of the split dose in patients with impaired renal function was supported by the CHMP in the context of a scientific consultation [8]. It is assumed that dosing according to the split dose of cisplatin in patients with impaired renal function is standard clinical practice.

Imaging during neoadjuvant therapy

According to the S3 guideline, imaging restaging should be carried out every two cycles during neoadjuvant treatment to rule out any possible progression [9]. In the NIAGARA study, imaging was performed at baseline and following neoadjuvant therapy (after 4 cycles), in accordance with the study protocol. The imaging procedures implemented in the study before and after the neoadjuvant phase are considered sufficiently adequate, meaning that this deviation from the guideline recommendation has no consequences for the benefit assessment.

Time point of radical cystectomy

The guidelines contain varying recommendations regarding the time point of radical cystectomy in patients with resectable MIBC. According to the S3 guideline, radical cystectomy should be performed within 3 months of diagnosis if patients have not received neoadjuvant therapy [9]. According to DGHO guidelines, a radical cystectomy should be performed 4 weeks (28 days) after neoadjuvant treatment [10]. In the NIAGARA study, radical cystectomy was to be performed within 14 to 56 days (or up to 70 days in medically justified exceptional cases) following neoadjuvant treatment. In the NIAGARA study, the median time from randomization to radical cystectomy is 16 weeks in both treatment arms. The third quartile is around 18 weeks in both arms. As neoadjuvant treatment regularly lasts 12 weeks (4 cycles of 21 days each), the median time point of radical cystectomy was 4 weeks after neoadjuvant treatment. The median value is in line with the recommendations of the DGHO; however, some patients underwent the procedure at a later date than that recommended by the DGHO. As the guidelines do not provide any more specific recommendations regarding the appropriate time window for radical cystectomy, the timing of the surgeries carried out in the study is considered appropriate.

Start of adjuvant therapy

The guidelines do not provide any general recommendation regarding the performance of adjuvant therapy following neoadjuvant therapy. The DGHO recommends that adjuvant therapy be administered within 12 to 14 weeks of cystectomy if no prior neoadjuvant therapy has been administered [10]. Accordingly, the guidelines do not specify when adjuvant therapy should be administered following neoadjuvant therapy and cystectomy. In the NIAGARA study, adjuvant therapy was to be initiated 42 to 120 days after cystectomy. However, the study documents do not contain any information on when patients actually started adjuvant therapy. As the guidelines do not provide any recommendations regarding adjuvant therapy following prior neoadjuvant therapy, this uncertainty has no consequences for the benefit assessment.

Data cut-offs

In Module 4A of the dossier, the company presents analyses for interim analysis 2 for all outcomes (most recent data cut-off date: 29 April 2024). At first, this data cut-off was not

prespecified and was only introduced in version 5.0 of the study protocol (1 June 2021). The company justifies the interim analysis 2 on the grounds that the sample size calculation was performed for the entire ITT population, as the original sample size calculation was based on the population of patients with adequate renal function. As interim analysis 1 was conducted on 14 January 2022, and therefore took place after the amendment to the study protocol, there is no indication of a potentially result-driven planning. Therefore, the results from interim analysis 2 were used for the benefit assessment.

Planned duration of follow-up

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

Table 8: Planned duration of follow-up observation – RCT, direct comparison: durvalumab + gemcitabine + cisplatin (neoadjuvant)/durvalumab (adjuvant) vs. gemcitabine + cisplatin (neoadjuvant)/watchful waiting

Study **outcome category** **outcome**	**Planned follow-up observation**
NIAGARA	
Mortality	
Overall survival	until death, lost to follow-up[a], withdrawal of consent[a] or end of study
Morbidity	
Failure of the curative treatment approach (EFS)	until disease progression, death, withdrawal of consent, decision of the sponsor or end of study (whichever occurs first)
Symptoms (EORTC QLQ-C30, PGIS)	until recurrence of the disease, initiation of subsequent therapy or discontinuation of the study (whichever occurs first)
Health status (EQ-5D VAS, PGIC)	until recurrence of the disease, initiation of subsequent therapy or discontinuation of the study (whichever occurs first)
Health-related quality of life (EORTC QLQ-C30)	until recurrence of the disease, initiation of subsequent therapy or discontinuation of the study (whichever occurs first)
Side effects	
PRO-CTCAE	90 days after the last dose of study medication (intervention arm) or after the last adjuvant study visit (comparator arm)
All other outcomes in the side effects category	90 days after the last dose of study medication (intervention arm) or after the last adjuvant study visit (comparator arm)

a. In the event of lost to follow-up, the study staff were able to obtain information on survival status from the patient's hospital file or the records of the attending physician, or by consulting a public register of deaths. It was also possible to make an enquiry via a public register of deaths even if the consent had been withdrawn.

EORTC: European Organisation for Research and Treatment of Cancer; PGIC: Patient Global Impression of Change; PGIS: Patient Global Impression of Severity; PRO-CTCAE: Patient-Reported Outcomes Version of the Common Terminology Criteria for Adverse Events; QLQ-C30: Quality of Life Questionnaire-Core 30; RCT: randomized controlled trial; VAS: visual analogue scale

The observation periods for the outcomes on symptoms, health status and health-related quality of life are systematically shortened because they were only recorded until disease recurrence, initiation of subsequent therapy or study discontinuation. The observation periods for the outcomes on side effects were also systematically shortened. According to the dossier, the analyses included AEs observed in the intervention arm up to 90 days after the last dose of the study medication (usually the last adjuvant study medication) or the date of surgery, whichever occurred later. In the comparator arm, AEs were considered that occurred up to 90 days after the last dose of neoadjuvant treatment, the date of surgery, or the last adjuvant study visit, whichever occurred later. In both arms, side effects were recorded only up to the first dose of subsequent antineoplastic therapy or until the data cut-off.

Drawing a reliable conclusion on the total study period or the time until patient death would require for the outcomes on symptoms, health status, health-related quality of life, and side effects to be recorded over the total period of time, as was the case for survival or failure of the curative treatment approach.

Characteristics of the study population

Table 9 shows the patient characteristics of the included study.

Table 9: Characteristics of the study population and study/treatment discontinuation – RCT, direct comparison: durvalumab + gemcitabine + cisplatin (neoadjuvant)/durvalumab (adjuvant) vs. gemcitabine + cisplatin (neoadjuvant)/watchful waiting (multipage table)

Study characteristic category	**Durvalumab + gemcitabine + cisplatin/Durvalumab N = 533**	**Gemcitabine + cisplatin/watchful waiting N = 530**
NIAGARA		
Age [years], mean (SD)	64 (9)	65 (9)
Sex [F/M], %	18/82	18/82
Region, n (%)		
Asia	151 (28)	143 (27)
Europe	265 (50)	287 (54)
North America and Australia	66 (12)	62 (12)
South America	51 (10)	38 (7)
Family origin, n (%)		
White	354 (66)	358 (68)
Black or African American	6 (1)	4 (< 1)
Asian	152 (29)	145 (27)
Other	7 (1)	1 (< 1)
Missing	14 (3)	22 (4)
WHO/ECOG PS upon randomization, n (%)		
0	418 (78)	415 (78)
1	115 (22)	115 (22)
Tumour PD-L1 expression according to TC1 score upon randomization, n (%)		
TC ≥ 1%	291 (55)	281 (53)
TC < 1%	242 (45)	249 (47)
Lymph node status, n (%)		
N0	505 (95)	500 (94)
N1	28 (5)	30 (6)
Prior BCG therapy	31 (6)	26 (5)
Removal of all visible tumours during transurethral resection of a bladder tumour (TURBT) prior to the start of the study, n (%)		
Yes	353 (66)	316 (60)
No	173 (33)	210 (40)
Missing	7 (1)	4 (< 1)
Clinical tumour status according to IVRS, n (%)		
T2N0	215 (40)	213 (40)
> T2N0[a]	318 (60)	317 (60)

Table 9: Characteristics of the study population and study/treatment discontinuation – RCT, direct comparison: durvalumab + gemcitabine + cisplatin (neoadjuvant)/durvalumab (adjuvant) vs. gemcitabine + cisplatin (neoadjuvant)/watchful waiting (multipage table)

Study characteristic category	**Durvalumab + gemcitabine + cisplatin/Durvalumab N = 533**	**Gemcitabine + cisplatin/watchful waiting N = 530**
Renal function following IVRS, n (%)		
Adequate renal function	432 (81)	430 (81)
Borderline renal function	101 (19)	100 (19)
Tumour PD-L1 expression status according to tumour cell score 25 (TC25)/ICP+ according to IVRS[b]		
High[c]	389 (73)	388 (73)
Low/negative[d]	144 (27)	142 (27)
Treatment discontinuation during the neoadjuvant phase, n (%)[e]	113 (21[f])	137 (26[f])
Patients who have not undergone a cystectomy[g]	63 (12)	84 (16)
Treatment discontinuation during the adjuvant phase, n (%)[h, i]	95 (18[f])	–
Study discontinuation, n (%)[j]	154 (29)	197 (37)

a. Includes T2N1, T3 and T4a.
b. According to the IVRS, one patient in the durvalumab arm was incorrectly assigned to the group with high tumour PD-L1 expression; however, based on data from the central laboratory, this patient should have been assigned to the group with low tumour PD-L1 expression.
c. The tumour PD-L1 expression status was determined using the VENTANA PD-L1 (SP263) assay. The status was rated as 'high' if any of the following conditions were met: i) ≥ 25% of tumour cells showed PD-L1 membrane staining; ii) ICP > 1% and IC+ ≥ 25%; or iii) ICP = 1% and IC+ = 100%.
d. The status was rated as 'low/negative' if none of the conditions set out under (c) were met.
e. Common reasons for treatment discontinuation during the neoadjuvant phase in the intervention arm versus the comparator arm were the following (percentages based on randomized patients): AEs (15% vs. 15%), patient decision (2% vs. 6%) and other reasons (3% vs. 4%). An additional 3 vs. 4 patients never started treatment.
f. Institute's calculation; based on the randomized patients.
g. Common reasons why cystectomy was not performed in the intervention arm versus the control arm (percentages based on randomized patients): patient decision (6% vs. 7%), disease progression (2% vs. 2%), study discontinuation (<1% vs. 2%). The data additionally include patients who had already died at this time point (intervention arm: 5 [< 1] vs. comparator arm: 8 [2%].
h. Common reasons for treatment discontinuation during the adjuvant phase in the intervention arm were the following (percentages based on randomized patients): AEs (6%), recurrence (6%), patient decision (3%) and other reasons (2%). In addition, 288 (54%) patients completed the adjuvant therapy as planned.
i. In the intervention arm, 383 patients received adjuvant therapy, compared with 0 in the comparator arm.
j. A reason for study discontinuation in the intervention arm was (percentages based on randomized patients): withdrawal of consent (4% vs. 6%). The data additionally include patients who died during the course of the study (intervention arm: 134 [25%] vs. comparator arm: 165 [31%]).

AE: adverse event; BCG: Bacillus Calmette Guérin; ECOG PS: European Cooperative Oncology Group Performance Status; f: female; IC+: immune cells with staining; ICP: immune cells present; IVRS: Interactive Voice Response System; m: male; n: number of patients in the category; N: number of randomized patients; PD-L1: programmed cell death ligand 1; RCT: randomized controlled trial; SD: standard deviation; TC: tumour cell (tumour cell score); TURB: transurethral resection of the bladder tumour; WHO: World Health Organisation

The patient characteristics of the NIAGARA study are largely comparable between the two treatment arms. The mean age of the patients was 65 years; around 52% came from the region of Europe. In both treatment arms, 78% of all patients had an ECOG PS of 0.

Before the start of the study, 66% versus 60% of all patients had had all visible tumours removed during a transurethral resection of the bladder tumour. 60% of patients in both treatment arms had a clinical tumour stage > T2N0 at the start of the study. In addition, 81% of all patients in both treatment arms had an adequate renal function at baseline.

21% of the patients in the intervention arm discontinued treatment in the neoadjuvant phase versus 26% of the patients in the comparator arm. Radical cystectomy was not performed in 12% of patients in the intervention arm and 16% of patients in the comparator arm. In both treatment arms, the main reason for this was patient decision.

Information on the course of the study

Table 10 shows patients' median treatment duration and the median observation period for individual outcomes.

Table 10: Information on the course of the study – RCT, direct comparison: durvalumab + gemcitabine + cisplatin (neoadjuvant)/durvalumab (adjuvant) vs. gemcitabine + cisplatin (neoadjuvant)/watchful waiting (multipage table)

Study **duration of the study phase** **outcome category/outcome**	**Durvalumab + gemcitabine + cisplatin/durvalumab** **N = 533**	**Gemcitabine + cisplatin/watchful waiting** **N = 530**
NIAGARA		
Treatment duration [weeks][a]		
Median [min; max]	Neoadjuvant + adjuvant durvalumab: 44.0 [1; 84] neoadjuvant gemcitabine + cisplatin: 12.2 [1; 23]	Neoadjuvant: 12.0 [1; 27]
Mean (SD)	Neoadjuvant + adjuvant durvalumab: 33.5 (16.3) neoadjuvant gemcitabine + cisplatin: 12.2 (2.4)	Neoadjuvant: 11.6 [3.1]
Observation period [months]		
Overall survival [b]		
Median [min; max]	42.3 [0.3; 64.6]	39.6 [0; 64.7]
Mean (SD)	ND	ND
Failure of the curative treatment approach (EFS)[b]		
Median [min; max]	34.7 [0; 60.7]	27.7 [0; 61.3]
Mean (SD)	ND	ND
Symptoms[c]		
EORTC QLQ-C30		
Median [min; max]	11.6 [0; 63.0]	9.2 [0; 62.8]
Mean (SD)	ND	ND
PGIS		
Median [min; max]	11.4 [0; 63.0]	8.9 [0; 62.8]
Mean (SD)	ND	ND
health status (EQ-5D VAS, PGIC)[c]		
Median [min; max]	11.4 [0; 63.0]	8.9 [0; 62.8]
Mean (SD)	ND	ND
health-related quality of life (EORTC QLQ-C30)[c]		
Median [min; max]	11.6 [0; 63.0]	9.2 [0; 62.8]
Mean (SD)	ND	ND
Side effects[d]		
Median [min; max]	14.3 [0.3; 24.6]	5.3 [0.3; 8.6]
Mean (SD)	ND	ND

Table 10: Information on the course of the study – RCT, direct comparison: durvalumab + gemcitabine + cisplatin (neoadjuvant)/durvalumab (adjuvant) vs. gemcitabine + cisplatin (neoadjuvant)/watchful waiting (multipage table)

Study **duration of the study phase** **outcome category/outcome**	**Durvalumab + gemcitabine + cisplatin/durvalumab** **N = 533**	**Gemcitabine + cisplatin/watchful waiting** **N = 530**
a. Data based on the safety population: N = 530 (intervention) vs. N = 526 (comparator). b. The observation period is defined as the time from randomization until the occurrence of the qualifying event (either death from any cause or an EFS event, depending on the outcome), or, for patients without event, until the last time point of documentation. c. The observation period is defined as the time from randomization to the last PRO survey date or to the data cut-off, whichever occurs first. Patients without a baseline value or post-baseline values are included in the calculation with one day. d. There are discrepancies between the study documents and the dossier (Appendix 4 G) regarding the definition of the observation period. See Section I 3.2 (planned duration of follow-up). EORTC: European Organisation for Research and Treatment of Cancer; EFS: event-free survival; max: maximum; min: minimum; N: number of randomized patients; ND: no data; PGIC: Patient Global Impression of Change; PGIS: Patient Global Impression of Severity; PRO: patient-reported outcome; QLQ-C30: Quality of Life Questionnaire-Core 30; RCT: randomized controlled trial; SD: standard deviation; VAS: visual analogue scale		

The median treatment duration in the neoadjuvant phase is comparable between the two treatment arms (intervention arm: 12.2 weeks; comparator arm: 12.0 weeks). The median observation period for the outcomes of the categories mortality, morbidity and health-related quality of life is slightly shorter in the comparator arm than in the intervention arm.

The median observation period for the outcomes in the side effects category was 14.3 months in the intervention arm and only 5.3 months the comparator arm. The information on the planned duration of follow-up (see Table 8) does not explain why there is such a marked difference in the observation periods between the two arms. The observation period for the comparator arm corresponds to the duration of the neoadjuvant treatment (possibly plus 90 days following the last dose of the neoadjuvant study medication).

Overall, the observation period for the outcomes of the categories morbidity (except failure of the curative treatment approach), health-related quality of life and side effects is shortened compared with the outcomes on mortality and failure of the curative treatment approach, which were recorded over the entire period.

Information on subsequent therapies

Table 11 shows the subsequent therapies patients received after discontinuing the study medication.

Table 11: Information on subsequent antineoplastic therapiesa – RCT, direct comparison: durvalumab + gemcitabine + cisplatin (neoadjuvant)/durvalumab (adjuvant) vs. gemcitabine + cisplatin (neoadjuvant)/watchful waiting (multipage table)

Study **drug class** **drug**	**Patients with subsequent therapy, n (%)**	
	durvalumab + gemcitabine + cisplatin/durvalumab **N = 533**	**gemcitabine + cisplatin/watchful waiting** **N = 530**
NIAGARA		
Total	53 (9.9)	93 (17.5)
Radiotherapy	26 (4.9)	31 (5.8)
Immunotherapy	18 (3.4)	62 (11.7)
Atezolizumab	2 (0.4)	10 (1.9)
Avelumab	3 (0.6)	9 (1.7)
Bintrafusp alfa	0 (0)	1 (0.2)
Blinded therapy	0 (0)	1 (0.2)
Cemiplimab	0 (0)	1 (0.2)
Domvanalimab	0 (0)	1 (0.2)
Durvalumab	0 (0)	1 (0.2)
Enfortumab vedotin	1 (0.2)	0 (0)
Nivolumab	1 (0.2)	4 (0.8)
Pembrolizumab	13 (2.4)	34 (6.4)
SAR439459	0 (0)	1 (0.2)
Zimberelimab	0 (0)	1 (0.2)
Cytotoxic chemotherapy	34 (6.4)	44 (8.3)
Cabozantinib	1 (0.2)	1 (0.2)
Capecitabine	1 (0.2)	0 (0)
Carboplatin	11 (2.1)	15 (2.8)
Cisplatin	10 (1.9)	19 (3.6)
Cisplatin/gemcitabine hydrochloride	0 (0)	1 (0.2)
Docetaxel	5 (0.9)	3 (0.6)
Doxorubicin	1 (0.2)	1 (0.2)
Enfortumab vedotin	1 (0.2)	1 (0.2)
Fluorouracil	1 (0.2)	1 (0.2)
Fluorouracil/glucose	0 (0)	1 (0.2)
Gemcitabine	16 (3.0)	22 (4.2)
Gemcitabine hydrochloride	2 (0.4)	7 (1.3)
Methotrexate	0 (0)	1 (0.2)
Methotrexate sodium	1 (0.2)	0 (0)
Mitomycin	1 (0.2)	1 (0.2)
Nedaplatin	0 (0)	1 (0.2)
Oxaliplatin	1 (0.2)	1 (0.2)

Table 11: Information on subsequent antineoplastic therapiesa – RCT, direct comparison: durvalumab + gemcitabine + cisplatin (neoadjuvant)/durvalumab (adjuvant) vs. gemcitabine + cisplatin (neoadjuvant)/watchful waiting (multipage table)

Study **drug class** **drug**	**Patients with subsequent therapy, n (%)**	
	durvalumab + gemcitabine + cisplatin/durvalumab **N = 533**	**gemcitabine + cisplatin/watchful waiting** **N = 530**
Paclitaxel	10 (1.9)	6 (1.1)
Pemetrexed	1 (0.2)	1 (0.2)
Pirarubicin	0 (0)	1 (0.2)
Tegafur/uracil	1 (0.2)	0 (0)
Vinblastine	1 (0.2)	0 (0)
Vinblastine sulphate	0 (0)	1 (0.2)
Vinflunine	3 (0.6)	2 (0.4)
Targeted therapy	3 (0.6)	7 (1.3)
Enfortumab vedotin	2 (0.4)	4 (0.8)
Enfortumab vedotin-ejfv	0 (0)	1 (0.2)
Niraparib	1 (0.2)	0 (0)
Sacituzumab govitecan	0 (0)	1 (0.2)
Trastuzumab deruxtecan	0 (0)	1 (0.2)
Radiopharmaceuticals	1 (0.2)	0 (0)
(^{90}Y) Yttrium chloride	1 (0.2)	0 (0)
Other	8 (1.5)	6 (1.1)
Enfortumab vedotin	3 (0.6)	2 (0.4)
Enfortumab vedotin-ejfv	3 (0.6)	4 (0.8)
Letrozole	1 (0.2)	0 (0)
Sacituzumab govitecan	1 (0.2)	0 (0)

a. Data taken from the study documents without adjustment.

n: number of patients with subsequent therapy; N: number of analysed patients; RCT: randomized controlled trial

In its dossier, the company does not submit any data on antineoplastic subsequent therapies. The clinical study report (CSR) provides details of the subsequent therapies used for the total population. Data on subsequent antineoplastic therapies related to patients with recurrence, as well as data on the first subsequent therapy, are therefore not available. Based on the information available, it is therefore only possible to assess the subsequent therapies used to a limited extent.

The choice of the subsequent antineoplastic therapies was not restricted in the NIAGARA study. Based on the total population, 9.9% of patients in the intervention arm and 17.5% in the comparator arm received at least one subsequent antineoplastic therapy. Based on the

data on the outcome failure of the curative treatment approach, a qualifying event (except deaths) occurred in 22% of patients in the intervention arm and 30% in the comparator arm. Assuming that these patients were generally eligible for subsequent antineoplastic therapy, only 45% of these patients in the intervention arm and 58% in the comparator arm received at least one subsequent therapy.

The guideline recommendations for the advanced therapy stage of bladder cancer are decisive for the assessment of the administered subsequent therapies in the NIAGARA study. The choice of systemic therapy for advanced or metastatic bladder cancer depends on whether and which platinum-based therapy is suitable for the patient [10]. For patients for whom platinum-based therapy is suitable, the use of enfortumab vedotin in combination with pembrolizumab is recommended as the preferred first-line treatment. Based on IQWiG's assessment of the SGN22E-003 study (in short: EV302/KN-A39), the G-BA has decided that this treatment option offers a non-quantifiable added benefit for patients for whom cisplatin-based therapy is suitable, or a considerable added benefit for patients for whom cisplatin-containing therapy is not suitable [14,16,17]. In the oral hearing involved in the procedure on erdafitinib in bladder cancer [18], it also became clear that enfortumab vedotin in combination with pembrolizumab is used as standard first-line therapy for unresectable or metastatic urothelial carcinoma. The data on subsequent therapies presented by the company show that a maximum of 8% of patients in the intervention arm and a maximum of 8% of patients in the comparator arm—for whom subsequent therapy would, in principle, have been an option—received subsequent therapy with enfortumab vedotin. It is not clear from the information provided whether this was a combination therapy with pembrolizumab. Furthermore, it is unclear whether enfortumab vedotin was administered as part of the first subsequent therapy, as recommended by the guidelines. The low use of enfortumab vedotin in combination with pembrolizumab in the subsequent therapy and the resulting unclear impact on overall survival, is also addressed in the publication on the NIAGARA study [7].

In the control arm, moreover, a maximum of 39% of patients for whom subsequent therapy would have been indicated received immunotherapy. In addition to enfortumab vedotin/pembrolizumab, the guidelines also recommend, depending on the patient's circumstances, the use of nivolumab in combination with cisplatin/gemcitabine or maintenance therapy with avelumab following platinum-based chemotherapy [10]. Hence, the proportion of immunotherapies used can be considered low in light of the recommendations set out in the guidelines.

Altogether, the subsequent therapies used in the NIAGARA 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. As both arms are affected by the insufficient use of the

combination therapy of enfortumab vedotin and pembrolizumab, the effect on overall survival may be maintained. However, it is also conceivable that the effect in the comparator arm is offset due to the earlier initiation of an appropriate subsequent therapy following a recurrence. Furthermore, this means that, unlike in the intervention arm, the vast majority of patients in the comparator arm had not yet received an immune checkpoint inhibitor, not even as subsequent 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) for – RCT, direct comparison: durvalumab + gemcitabine + cisplatin (neoadjuvant)/durvalumab (adjuvant) vs. gemcitabine + cisplatin (neoadjuvant)/watchful waiting

Study	Adequate random sequence generation	Allocation concealment	Blinding		Reporting independent of the results	No additional aspects	Risk of bias at study level
			Patients	Treating staff			
NIAGARA	Yes	Yes	No	No	Yes	Yes	Low
RCT: randomized controlled trial							

The risk of bias across outcomes is rated as low for the NIAGARA study.

Limitations resulting from the open-label study design are described in Section I 4.2 under outcome-specific risk of bias.

Transferability of the study results to the German health care context

From the company's perspective, the findings of the NIAGARA study could be transferred to the German health care context, as the patients included were comparable to the corresponding patient population in Germany in terms of their epidemiological characteristics.

In addition, the company stated that the majority of patients included in both arms were male (82% in both treatment arms), which is roughly in line with the sex ratio of patients with MIBC in Germany. Moreover, the median age in the NIAGARA study—65 years in the intervention arm and 66 years in the comparator arm—is slightly below the median for the German patient population. In 2020, the median age at disease onset for patients with MIBC was 75 years for men and 77 years for women. In the NIAGARA study, just over half of the patients in both

study arms had tumour PD-L1 expressions of TC ≥ 1. The company assumes that this corresponds to the proportion of PD-L1 expression in the German population, even though the PD-L1 status is not determined on a regular basis in Germany and no data on PD-L1 status are available for patients in the therapeutic indication.

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

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 (represented via EFS)
  - symptoms
    - recorded using the EORTC QLQ-C30
    - recorded using the PGIS
  - health status
    - recorded using the EQ-5D VAS
    - recorded using the PGIC
- Health-related quality of life
  - recorded using the EORTC QLQ-C30
- Side effects
  - SAEs
  - severe AEs (CTCAE grade ≥ 3)
  - discontinuation due to AEs
  - PRO-CTCAE
  - immune-mediated SAEs
  - immune-related severe AEs (CTCAE grade ≥ 3)
  - Other specific AEs, if any

The selection of patient-relevant outcomes deviated from that of the company, which used further outcomes in the dossier (Module 4A).

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

Table 13: Matrix of outcomes – RCT, direct comparison: durvalumab + gemcitabine + cisplatin (neoadjuvant)/durvalumab (adjuvant) vs. gemcitabine + cisplatin (neoadjuvant)/watchful waiting

Study	Outcomes											
	Overall survival	Failure of the curative treatment approach[a]	Symptoms (EORTC QLQ-C30, PGIS)	Health status (EQ-5D VAS, PGIC)	Health-related quality of life (EORTC QLQ-C30)	SAEs	Severe AEs[b]	Discontinuation due to AEs	PRO-CTCAE	Immune-mediated SAEs[c]	Immune-mediated severe AEs[b, c]	Other specific AEs[b]
NIAGARA	No[d]	Yes	Yes	Yes	Yes	No[e]	No[e]	No[e]	No[f]	No[e]	No[e]	No[e]

a. Presented via EFS; includes the following events: first recurrence of the disease following radical cystectomy; radical cystectomy not feasible for medical reasons; refusal of radical cystectomy by the patient, or intraoperative failure of radical cystectomy, and death.
b. Severe AEs are operationalized as CTCAE grade ≥ 3.
c. The predefined operationalization of AEs of special interest is used in each case.
d. Data not interpretable; for justification, see body of text below.
e. Effect estimation not interpretable. See the following running text for reasons.
f. No suitable data available; for the reasoning, see Section I 4.1 of the present dossier assessment.

AE: adverse event; CTCAE: Common Terminology Criteria for Adverse Events; EORTC: European Organisation for Research and Treatment of Cancer; PGIC: Patient Global Impression of Change; PGIS: Patient Global Impression of Severity; PRO-CTCAE: Patient-Reported Outcomes Version of the Common Terminology Criteria for Adverse Events; PRO-CTCAE: Patient-Reported Outcomes version of the Common Terminology Criteria for Adverse Events; QLQ-C30: Quality of Life Questionnaire-Core 30; RCT: randomized controlled trial; SAE: serious adverse event; VAS: visual analogue scale

Notes on outcomes

Results on overall survival not interpretable due to inadequate subsequent therapies

The observation period for overall survival in patients in the present 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 [19-21]. 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 (neo-)adjuvant treatment setting.

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 NIAGARA 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 infeasibility of the planned surgery or recurrence after R0 remission 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 NIAGARA study, failure of the curative treatment approach was not directly recorded as an outcome. As an approximation, the present assessment considers the events that were recorded as part of the primary outcome of the NIAGARA study, i.e. the composite outcome of EFS, 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 (EFS) is used for the assessment. The operationalization of the outcome is explained below.

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

- Recurrence of the disease following radical cystectomy
- Disease progression in patients for whom radical cystectomy is not an option
- Refusal or non-performance of radical cystectomy in patients with residual disease
- death from any cause

In the NIAGARA study, an EFS event was recorded both by a blinded independent central review (BICR) and by the investigator’s decision. The decision was made independently as to whether an EFS event had occurred. The findings of both the independent central review and the investigator were not shared with one another. The decision on further treatment was based on the investigator’s assessment.

In its dossier, the company presents post-hoc analyses of EFS, along with the respective reasons within the components. Here, EFS was defined as time from randomization to the first occurrence of one of the following events:

- First recurrence of the disease following radical cystectomy

- Radical cystectomy not feasible for medical reasons
  - not suitable for surgery (e.g. reduced ECOG PS)
  - progression of the disease
  - AE
  - physician's decision
- Refusal of radical cystectomy by the patient or intraoperative failure of radical cystectomy
  - patients who refuse radical cystectomy
  - patients in whom radical cystectomy was not successful (R1 resection, intraoperative decision)
  - patients who discontinued the study after the expected date of cystectomy
  - death
- Death from any cause

In Module 4A, the company describes that the individual components of the dossier were prepared in accordance with the G-BA's requirements. It is clear from the minutes of the G-BA that the EFS analysis should include a list of the individual events relating to the individual components specified in the study protocol. The company complied with this requirement. However, there are discrepancies between the information in the results table and the flowchart in Module 4A and the CSR. According to the flowchart, 32 out of 36 patients did not undergo a cystectomy due to patient decision. In the list of qualifying events, 1 versus 5 patients are listed in the individual component 'patients who refused radical cystectomy'. The total number of events corresponds to the figures given in the CSR. Moreover, the assignment to the four main components of the composite outcome is comprehensible, taking into account the different operationalizations between the dossier and the CSR. The data in Module 4A also show that 25 patients in the intervention arm and 35 patients in the comparator arm discontinued the study after the expected date of cystectomy, which ultimately means that cystectomy did not take place in these cases either (see Table 16). Even if the discrepant data do not fully match, they are considered to be sufficiently plausible. Therefore, this discrepancy does not mean that the data on the EFS are considered unsuitable. The results from Module 4A are therefore used for this benefit assessment.

In the present data situation, the outcome of EFS is suitable for depicting the failure of curative treatment approach and is therefore used for the benefit assessment. Recurrence in this situation means that the attempt at cure by the curative treatment approach was not successful. In addition to the occurrence of the event (effect measure: relative risk [RR]), the

time to the occurrence of an event (EFS, effect measure: HR) is also relevant for the assessment.

Patient-reported outcomes on symptoms, health status and health-related quality of life

Operationalization of the instruments EORTC QLQ-C30 and EQ-5D VAS

In its dossier, the company presents post hoc analyses for the outcomes morbidity and health-related quality of life for the time to first deterioration by 10 points (EORTC QLQ-C30) and by 15 points (EQ-5D VAS). Given the differences in observation periods between the treatment arms, it is appropriate to submit responder analyses for the time to first deterioration, and these are used in this benefit assessment (see Table 10).

Recording time points for the instruments EORTC QLQ-C30, EQ-5D VAS, and EQ-5D and PGIS

According to the study protocol and the dossier, the EORTC QLQ-C30, EQ-5D VAS and PGIS should be recorded during the neoadjuvant phase at baseline and then every 4 weeks until radical cystectomy. However, the study protocol and the dossier report different recording dates for the subsequent adjuvant phase. According to the dossier, recordings were to take place every four weeks following a radical cystectomy. In contrast, the study protocol provided for the first recording following radical cystectomy to take place on Day 1 of Cycle 1 and every 4 weeks thereafter. However, according to the study design, the period between radical cystectomy and the first cycle of the adjuvant phase may vary from 42 to 120 days depending on the individual patient and depending on the initiation of the adjuvant phase. This would mean that the time points of recording for patients following radical cystectomy are not consistent. This approach is not appropriate. Based on the discrepancies between the dossier and the study documents, it is unclear how the recordings were conducted in the NIAGARA study. In addition, once the study medication had been discontinued, the patients entered a follow-up period during which recordings were initially carried out monthly and, from Month 6 onwards, every 8 weeks. The proportions (21% vs. 26%) of patients who discontinued the study medication during the neoadjuvant phase is comparable between the treatment arms. In the analyses of patient-reported outcomes relating to morbidity and health-related quality of life, most events occur early on in the period up to radical cystectomy (see, for example, Figure 6, Figure 10). Given the current data, it is therefore assumed that even a potentially inappropriate survey during the adjuvant treatment phase, or the extension of survey intervals following discontinuation of the study medication, will not have any impact on the results of the morbidity outcomes, as assessed using the EORTC QLQ-C30, EQ-5D VAS and PGIS.

Symptoms recorded using the PGIS

The PGIS consists of a single question asking the patients to rate their cancer symptoms over the past 7 days. The respective specific question is set out in the study documents for the NIAGARA studies and is face valid. There are 6 possible responses (“no symptoms”, “very

mild", "mild", "moderate", "severe", "very severe"). The company converted the PGIS scale into numerical values from 0 to 5, where 0 means that the patient has no symptoms and 5 means that the patient has very severe symptoms. The recording of symptoms by means of a PGIS is regarded as patient relevant. In Module 4A, the company presented post hoc time-to-event analyses on the first deterioration, defining a deterioration as an increase by ≥ 1 point from baseline. An increase by ≥ 1 point from baseline is considered a deterioration that is sufficiently certain to reflect a noticeable change for the patients. The time-to-event analyses on the first deterioration presented by the company were used for the present benefit assessment.

Health status assessed using PGIC

The PGIC consists of a single question asking the patients to rate the change in their health status compared with the time before starting the study medication. The respective specific question is set out in the study documents for the NIAGARA studies and is face valid. There are 7 possible responses ('much improved', 'a little improved', 'minimally improved', 'no change', 'minimally worse', 'a little worse', 'much worse'). The recording of health status by means of a PGIC is regarded as patient relevant. In Module 4A, the company presents post hoc time-to-event analyses on the first deterioration, defining only the responses "minimally worse", "a little worse" or "much worse" as an event. This analysis shows a change perceived by patients and thus a patient-relevant change; consequently, the time-to-event analyses on the first deterioration presented by the company were used for the present benefit assessment.

Side effects

Effect estimates for the outcomes in the side effects category cannot be interpreted

In the current data situation, the effect estimates for the outcomes of the side effects category cannot be interpreted, and the available data allow only for a qualitative classification in the overall assessment. This is justified as follows:

In the intervention arm, patients were followed up for up to 90 days after the last dose of the study medication (usually the last adjuvant study medication) or the date of surgery, whichever occurred later. In the comparator arm, follow-up was planned to continue for up to 90 days after the last dose of neoadjuvant treatment, the date of surgery, or the last adjuvant study visit, whichever occurred later. In both arms, side effects were recorded only up to the first dose of subsequent antineoplastic therapy. In the comparator arm, however, the median observation period for side effects was only 5.3 months and the maximum duration was 8.6 months (see Table 10). The available data do not explain why the median duration of observation was significantly shortened (14.3 months) compared to the intervention arm. It might be possible that most of the recordings only cover the 90-day period following the last dose of the neoadjuvant study medication, and that only isolated patients

in the comparator arm only attended visits during the adjuvant phase. The Kaplan-Meier curves on the various outcomes of the AE category show that there are hardly any patients remaining at risk in the comparator arm after approximately 5 to 6 months, meaning that the adjuvant phase is barely covered. From this point onwards, events in the comparator arm carry significantly more weight than events occurring at the same time in the intervention arm, due to the much shorter observation period. It can also be assumed that, in the comparator arm, the few selected patients still under observation differ significantly from the censored patients.

For both the overall rates of AE outcomes and the specific AEs with statistically significant difference between the treatment arms, the Kaplan-Meier curves are virtually identical up to Month 6 and only begin to diverge from that point onwards. In some cases, there were large effects, such as an HR of 0.37 [0.24; 0.57] for the outcome renal and urinary disorders (SOC, severe AEs) (see Figure 31), which may be based only on a small number of late events in the comparator arm. Similar patterns can be observed in other specific AEs, but also, for example, in the overall rates of severe and SAEs (see I Appendix F). Overall, based on the available Kaplan-Meier curves, it cannot be assumed with sufficient certainty that the proportional hazards assumption is met in each case. Due to uncertainties regarding the shape of the Kaplan-Meier curves and the corresponding effect estimates, these effect estimates for all AE outcomes cannot be interpreted. As described, it is assumed that, in the comparator arm, almost exclusively events that occur during the neoadjuvant treatment phase are taken into account. To rule out the possibility that the effect estimates of the side effects are predominantly driven by events in the very small number of patients who were still at risk even after Month 5 to 6 in the comparator arm, sensitivity analyses were required in which patients were censored at the time of radical cystectomy. Although this would mean that AEs occurring in the intervention arm during the adjuvant phase would not be included in the analyses, these analyses could be interpreted during the neoadjuvant phase at least for the initial period of the study.

However, based on the trends shown in the Kaplan-Meier curves for the outcomes on side effects, it can generally be assumed that the direction of effect for the respective outcomes will not reverse. In summary, although it is not possible to determine the extent of the outcomes on side effects, the results can be taken into account qualitatively in the overall assessment (see Section I 5.2). The results are presented as supplementary information in I Appendix F of the full dossier assessment.

Recording of the progression of the underlying disease

According to the study protocol, events in the NIAGARA study that were clearly attributable to the progression of the underlying disease were not to be documented as an AE by the investigator. The available information on the documented AEs provides no evidence that

these contain AEs attributable to the progression of the underlying disease to a relevant extent (see I Appendix C of the full dossier assessment). It was not easily possible to distinguish individual AEs that occurred in the study, e.g. hydronephrosis, from events related to the underlying disease. When interpreting the results, it must be noted that these may be due to a combination of side effects and symptoms or late complications of the disease.

PRO-CTCAE

As per the study protocol, side effects were also recorded with the PRO-CTCAE instrument in NIAGARA. However, the dossier did not provide any analysis of this in the dossier. The PRO-CTCAE was only recorded in countries where a linguistically validated version of the questionnaire was available. Overall, the PRO-CTCAE system is a valuable addition to the usual survey and analysis of AEs. The system comprises a total of 81 symptomatic AEs of the CTCAE system, which are compiled into a questionnaire adapted to the respective study situation. The selection process is to be planned a priori and carried out transparently. The selection of the individual symptomatic AEs must be transparent, e.g. the recording of all important potential AEs of the drugs in the intervention and the comparator arm. For a comprehensive description of the PRO-CTCAE system, see the corresponding explanations in benefit assessment A20-87 [22].

According to the study documents, the following symptomatic AEs of the PRO-CTCAE system were recorded in NIAGARA:

- Changes in taste when eating or drinking
- Loss of appetite
- Nausea
- Vomiting
- Constipation
- Diarrhoea
- Shortness of breath
- Cough
- Rash
- Itching
- Numbness or tingling in the hands or feet
- Dizziness
- Muscle pain
- Joint pain

- Fatigue, exhaustion or a lack of energy
- Chills

According to the study documentation, side effects of durvalumab and gemcitabine + cisplatin were considered in the selection of symptomatic AEs of the PRO-CTCAE system, based on the literature. Symptoms associated with immune-mediated AEs were also taken into account, which were described in five package inserts for immunotherapeutics and for which an FDA recommendation for monitoring in clinical trials is available. Items that were considered too general (e.g. abdominal pain and headache) as well as symptomatic AEs not considered specific to the treatment were not chosen in order to minimize the burden on patients during the survey.

The selection process for AEs from the PRO-CTCAE system used in the NIAGRA study appeared generally appropriate, but was not tested further because the data submitted by the company were not suitable for the PRO-CTCAE outcome. The study data show that, at baseline, only around 57% of patients were included in the analysis, and that this figure rose to a maximum of 68% over the course of the study. Furthermore, only descriptive analyses of the response category across the individual measurement points are available, but no analyses comparing the treatment arms. Overall, the data presented are not suitable to assess the added benefit of durvalumab + gemcitabine + cisplatin (neoadjuvant), followed by durvalumab (adjuvant), compared with the ACT.

Immune-mediated AEs

Immune-mediated AEs are a relevant aspect of the side effect profile of PD-L1 inhibitors such as durvalumab. In the NIAGARA study, AEs of special interest (AESIs) assumed to be potentially caused by an inflammatory or immune-mediated reaction and which may require more frequent monitoring and/or interventions such as steroids, immunosuppressants and/or endocrine therapy were recorded for durvalumab. Infusion-related reactions and hypersensitivity reactions were also included under the AESI. In addition, AEs of possible interest (adverse events of possible interest [AEPIs]) were recorded that may potentially have been caused by an inflammatory or immune-mediated reaction, but the likelihood of cause is considered to be low. The AEs identified under the AESI and AEPI are listed in the study documentation.

The NIAGARA study also directly recorded immune-mediated AEs. According to the study protocol of the NIAGARA study, these were defined as AEs identified within the framework of the AESIs and AEPIs (except for infusion-related reactions and hypersensitivity/anaphylactic reactions) and which required an intervention with steroids, immunosuppressants and/or endocrine therapy. The operationalization of immune-mediated AEs without taking into account infusion-related reactions and hypersensitivity/anaphylactic reactions is appropriate;

however, linking immune-mediated AEs to a treatment is not appropriate. These data on directly recorded immune-mediated AEs are therefore not suitable for the present benefit assessment.

In its dossier, the company presents analyses of AESIs for durvalumab. Unlike the immune-mediated AEs, these AESIs, minus infusion-related reactions and hypersensitivity/anaphylactic reactions, could in principle be used to represent immune-mediated AEs, as the underlying categories or PTs included in them are considered to be a sufficient approximation. However, the company does not state in its dossier whether infusion-related reactions and hypersensitivity/anaphylactic reactions were subtracted from the AESI analyses. However, as the dossier contains fewer events than the analyses in the CSR, it is assumed that the infusion-related reactions and hypersensitivity/anaphylactic reactions were subtracted from the dossier's analysis of the AESIs. However, as described, the effect estimates for the outcomes in the side effects category cannot be interpreted. For this reason, there are no suitable data available for immune-mediated AEs either.

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: durvalumab + gemcitabine + cisplatin (neoadjuvant)/durvalumab (adjuvant) vs. gemcitabine + cisplatin (neoadjuvant)/watchful waiting

Study		Outcomes											
	Study level	Overall survival	Failure of the curative treatment approach[a]	Symptoms (EORTC QLQ-C30, PGIS)	Health status (EQ-5D VAS, PGIC)	Health-related quality of life (EORTC QLQ-C30)	SAEs	Severe AEs[b]	Discontinuation due to AEs	PRO-CTCAE	Immune-mediated SAEs[c]	Immune-mediated severe AEs[b, c]	Other specific AEs[b]
NIAGARA	L	–[d]	L	H[e, f]	H[e, f]	H[e, f]	–[g]	–[g]	–[g]	–[d]	–[g]	–[g]	–[g]

a. Presented via EFS; includes the following events: first recurrence of the disease following radical cystectomy; radical cystectomy not feasible for medical reasons; refusal of radical cystectomy by the patient, or intraoperative failure of radical cystectomy, and death.
b. Severe AEs are operationalized as CTCAE grade ≥ 3.
c. The predefined operationalization of AEs of special interest is used in each case.
d. No suitable data available; see Section I 4.1 for the reasoning.
e. High proportion of patients not included in the analysis (~20 %).
f. Lack of blinding in subjective recording of outcomes.
g. Effect estimation not interpretable. See Section I 4.1 for reasons.

AE: adverse event; CTCAE: Common Terminology Criteria for Adverse Events; EORTC: European Organisation for Research and Treatment of Cancer; PGIC: Patient Global Impression of Change; PGIS: Patient Global Impression of Severity; PRO-CTCAE: Patient-Reported Outcomes Version of the Common Terminology Criteria for Adverse Events; PRO-CTCAE: Patient-Reported Outcomes version of the Common Terminology Criteria for Adverse Events; QLQ-C30: Quality of Life Questionnaire-Core 30; RCT: randomized controlled trial; SAE: serious adverse event; VAS: visual analogue scale

No suitable data are available for the outcome of overall survival (for reasons, see Section I 4.1); therefore, the risk of bias of the results is not assessed.

The outcome-specific risk of bias is rated as low for the results of the outcome failure of the curative treatment approach.

The outcome-specific risk of bias is rated as high for the results relating to symptoms (EORTC QLQ-C30, PGIS), health status (EQ-5D VAS, PGIC) and health-related quality of life (EORTC QLQ-C30). This is due to the high proportion of patients not included in the analysis (~20%) and the lack of blinding with subjective recording of outcomes.

The effect estimates for the outcomes in the side effects category cannot be interpreted (see Section I 4.1 for reasons); consequently, there is no need to assess the risk of bias of the results.

No suitable data are available for the outcome recorded using PRO-CTCAE (for reasoning, see Section I 4.1). Therefore, the risk of bias for the corresponding results is not assessed.

I 4.3 Results

Table 15 and Table 16 summarize the results on the comparison of durvalumab in combination with gemcitabine + cisplatin (neoadjuvant) followed by durvalumab (adjuvant) versus gemcitabine + cisplatin (neoadjuvant) and watchful waiting in adults with resectable MIBC. Where necessary, calculations conducted by the Institute are provided in addition to the data from the company's dossier.

Kaplan-Meier curves on the presented event time analyses can be found in I Appendix B of the full dossier assessment. Results on common AEs, SAEs, severe AEs, and discontinuations due to AEs are presented in I Appendix C of the full dossier assessment. Results on common immune-mediated AEs, immune-mediated SAEs, and immune-mediated severe AEs are presented in I Appendix D.

Table 15: Results (mortality, morbidity, health-related quality of life, side effects, time to event) – RCT, direct comparison: durvalumab + gemcitabine + cisplatin (neoadjuvant)/durvalumab (adjuvant) vs. gemcitabine + cisplatin (neoadjuvant)/watchful waiting (multipage table)

Study **outcome category** **outcome**	**Durvalumab + gemcitabine + cisplatin/durvalumab**		**Gemcitabine + cisplatin/watchful waiting**		**Durvalumab + gemcitabine + cisplatin/durvalumab vs. gemcitabine + cisplatin/watchful waiting**
	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]**
NIAGARA					
Mortality					
Overall survival	No suitable data[b]				
Morbidity					
Symptoms (time to first deterioration)					
EORTC QLQ-C30[c, d]					
Fatigue	ND[e]	1.0 [1.0; 1.0] 385 (72.2[f])	ND[e]	1.0 [1.0; 1.1] 360 (67.9[f])	1.12 [0.97; 1.30]; 0.140
Nausea and vomiting	ND[e]	1.8 [1.1; 1.8] 322 (60.4[f])	ND[e]	1.8 [1.1; 1.8] 296 (55.8[f])	1.09 [0.93; 1.28]; 0.304
Pain	ND[e]	2.9 [2.7; 3.6] 309 (58.0[f])	ND[e]	2.7 [1.9; 3.6] 310 (58.5[f])	0.94 [0.81; 1.11]; 0.469
Dyspnoea	ND[e]	2.8 [2.7; 2.9] 290 (54.4[f])	ND[e]	2.8 [2.7; 3.2] 252 (47.5[f])	1.04 [0.87; 1.23]; 0.688
Insomnia	ND[e]	3.7 [2.9; 3.8] 259 (48.6[f])	ND[e]	3.8 [3.6; 4.6] 239 (45.1[f])	1.07 [0.90; 1.28]; 0.455
Appetite loss	ND[e]	1.8 [1.8; 1.9] 319 (59.8[f])	ND[e]	1.8 [1.6; 1.8] 309 (58.3[f])	0.97 [0.83; 1.14]; 0.678
Constipation	ND[e]	1.9 [1.8; 2.7] 287 (53.8[f])	ND[e]	1.8 [1.8; 2.4] 290 (54.7[f])	0.90 [0.76; 1.06]; 0.222
Diarrhoea	ND[e]	4.7 [4.5; 5.7] 220 (41.3[f])	ND[e]	5.5 [4.6; 6.0] 198 (37.4[f])	1.13 [0.93; 1.37]; 0.239
PGIS[d, g]	ND[e]	4.8 [3.7; 5.7] 182 (34.1[f])	ND[e]	4.9 [3.6; 5.7] 185 (34.9[f])	0.96 [0.78; 1.18]; 0.689
Health status (time to first deterioration)					
EQ-5D VAS[d, h]	ND[e]	3.7 [2.9; 4.3] 256 (48.0[f])	ND[e]	2.9 [2.7; 3.7] 239 (45.1[f])	0.97 [0.81; 1.16]; 0.707
PGIC[i]	ND[e]	5.3 [4.6; 7.3] 227 (42.6[f])	ND[e]	4.2 [2.9; 5.0] 246 (46.4[f])	0.82 [0.69; 0.99]; 0.037

Table 15: Results (mortality, morbidity, health-related quality of life, side effects, time to event) – RCT, direct comparison: durvalumab + gemcitabine + cisplatin (neoadjuvant)/durvalumab (adjuvant) vs. gemcitabine + cisplatin (neoadjuvant)/watchful waiting (multipage table)

Study outcome category outcome	Durvalumab + gemcitabine + cisplatin/durvalumab		Gemcitabine + cisplatin/watchful waiting		Durvalumab + gemcitabine + cisplatin/durvalumab vs. gemcitabine + cisplatin/watchful waiting
	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]
Health-related quality of life					
EORTC QLQ-C30 (time to first deterioration)[d, j]					
Global health status	ND[e]	1.8 [1.8; 1.9] 326 (61.2[f])	ND[e]	1.8 [1.8; 1.9] 312 (58.9[f])	1.01 [0.86; 1.18]; 0.943
Physical functioning	ND[e]	2.7 [1.9; 2.7] 346 (64.9[f])	ND[e]	1.9 [1.8; 2.7] 339 (64.0[f])	0.96 [0.82; 1.12]; 0.598
Role functioning	ND[e]	1.8 [1.1; 1.8] 356 (66.8[f])	ND[e]	1.8 [1.8; 1.8] 337 (63.6[f])	1.05 [0.90; 1.22]; 0.543
Emotional functioning	ND[e]	3.8 [3.6; 4.7] 251 (47.1[f])	ND[e]	4.0 [3.6; 4.6] 243 (45.8[f])	1.00 [0.83; 1.19]; 0.965
Cognitive functioning	ND[e]	2.3 [1.8; 2.8] 320 (60.0[f])	ND[e]	2.7 [2.0; 2.9] 280 (52.8[f])	1.16 [0.99; 1.36]; 0.079
Social functioning	ND[e]	1.9 [1.8; 2.7] 322 (60.4[f])	ND[e]	1.9 [1.8; 2.8] 313 (59.1[f])	1.00 [0.86; 1.17]; 0.991
Side effects					
AEs (supplementary information)	No suitable data[k]				
SAEs	No suitable data[k]				
Severe AEs[l]	No suitable data[k]				
Discontinuation due to AEs	No suitable data[k]				
PRO-CTCAE	No suitable data[b]				
Immune-mediated AEs (supplementary information)	No suitable data[k]				
Immune-mediated SAEs	No suitable data[k]				
Immune-mediated severe AEs[l]	No suitable data[k]				
Other specific AEs	No suitable data[k]				

Table 15: Results (mortality, morbidity, health-related quality of life, side effects, time to event) – RCT, direct comparison: durvalumab + gemcitabine + cisplatin (neoadjuvant)/durvalumab (adjuvant) vs. gemcitabine + cisplatin (neoadjuvant)/watchful waiting (multipage table)

Study outcome category outcome	Durvalumab + gemcitabine + cisplatin/durvalumab		Gemcitabine + cisplatin/watchful waiting		Durvalumab + gemcitabine + cisplatin/durvalumab vs. gemcitabine + cisplatin/watchful waiting
	N	median time to event in months [95% CI] patients with event n (%)	N	median time to event in months [95% CI] patients with event n (%)	HR [95% CI]; p-value[a]

a. HR and CI from Cox proportional hazards model; p-value from log-rank test. Each stratified by clinical tumour status [T2N0 vs. > T2N0a], renal function [adequate renal function vs. borderline renal function] and tumour PD-L1 expression status [high vs. low/negative]).
b. See Section I 4.1 for reasons.
c. A score increase by ≥ 10 points from baseline is considered a clinically relevant deterioration (scale range 0 to 100).
d. Patients for whom no analysable assessment or baseline data were available at the time point of analysis were censored on Day 1. Patients who did not experience a deterioration and who died within two visits of the last recording were censored at the date of the last recording. In cases where two or more visits were missed (regardless of whether this was followed by a deterioration or death), censoring took place at the time of the last recording prior to the two missed visits. For patients who could not deteriorate due to a baseline value that was too low, the reason for censoring did not include a deterioration.
e. According to the company, all randomized patients were included in the analysis. At the same time the company stated that patients with no baseline value or no value in the course of the study were censored on Day 1. Thus, no times of these patients were actually included in the analysis. It is not possible to state the exact number of these patients; the proportion is approximately 20%.
f. Percentage refers to the number of patients randomized into this arm.
g. An increase by ≥ 1 point from baseline is considered a clinically relevant deterioration (6-point scale).
h. A score decrease by ≥ 15 points from baseline is considered a clinically relevant deterioration (scale range: 0 to 100).
i. Deterioration to the levels 'minimally worse (-1)', 'a little worse (-2)' or 'much worse (-3)' compared with Day 1 of the first cycle.
j. A score decrease by ≥ 10 points from baseline is considered a clinically relevant deterioration (scale range: 0 to 100).
k. Effect estimate not interpretable; see Section I 4.1 for reasons.
l. Operationalized as CTCAE grade ≥ 3.

AE: adverse event; CI: confidence interval; CTCAE: Common Terminology Criteria for Adverse Events; EORTC: European Organisation for Research and Treatment of Cancer; HR: hazard ratio; n: number of patients with (at least one) event; N: number of analysed patients; PD-L1: programmed cell death ligand 1; PGIC: Patient Global Impression of Change; PGIS: Patient Global Impression of Severity; PRO-CTCAE: Patient-Reported Outcomes version of the Common Terminology Criteria for Adverse Events; PT: Preferred Term; QLQ-C30: Quality of Life Questionnaire-Core 30; RCT: randomized controlled trial; SAE: serious adverse event; VAS: visual analogue scale

Table 16: Results (morbidity, dichotomous) – RCT, direct comparison: durvalumab + gemcitabine + cisplatin (neoadjuvant)/durvalumab (adjuvant) vs. gemcitabine + cisplatin (neoadjuvant)/watchful waiting (multipage table)

Study outcome category outcome	Durvalumab + gemcitabine + cisplatin/durvalumab		Gemcitabine + cisplatin/watchful waiting		Durvalumab + gemcitabine + cisplatin/durvalumab vs. gemcitabine + cisplatin/watchful waiting
	N	patients with event n (%)	N	patients with event n (%)	RR [95% CI]; p-value
NIAGARA					
Morbidity					
Failure of the curative treatment approach					
Event rate	533	187 (35.1)	530	246 (46.4)	0, 76 [0.65; 0.87]; < 0.001[a]
Recurrence following radical cystectomy	533	69 (12.9)	530	87 (16.4)	–
No cystectomy (for medical reasons)	533	20 (3.8)	530	27 (5.1)	–
Unresectable	533	2 (0.4)	530	6 (1.1)	–
Progression of the disease	533	8 (1.5)	530	9 (1.7)	–
AE	533	6 (1.1)	530	7 (1.3)	–
Physician's decision	533	4 (0.8)	530	5 (0.9)	–
Refusal of cystectomy or intraoperative failure[b]	533	28 (5.3)	530	42 (7.9)	–
Refusal	533	1 (0.2)	530	5 (0.9)	–
Unsuccessful	533	1 (0.2)	530	0 (0)	–
Study discontinuation	533	25 (4.7)	530	35 (6.6)	–
Death	533	1 (0.2)	530	2 (0.4)	–
Death	533	68 (12.8)[c]	530	85 (16.0)	–
Event-free survival	533	Median time to event [months]: NA	530	Median time to event [months]: 46.1 [32.2; NC]	HR[d]: 0.68 [0.56; 0.82]; < 0.001

Table 16: Results (morbidity, dichotomous) – RCT, direct comparison: durvalumab + gemcitabine + cisplatin (neoadjuvant)/durvalumab (adjuvant) vs. gemcitabine + cisplatin (neoadjuvant)/watchful waiting (multipage table)

Study outcome category outcome	Durvalumab + gemcitabine + cisplatin/durvalumab		Gemcitabine + cisplatin/watchful waiting		Durvalumab + gemcitabine + cisplatin/durvalumab vs. gemcitabine + cisplatin/watchful waiting
	N	patients with event n (%)	N	patients with event n (%)	RR [95% CI]; p-value

a. Institute's calculation, unconditional exact test (CSZ method according to [23]).
b. In addition to the listed events, the study also reported events on medically unjustified partial cystectomy (intervention arm: 1 patient [0.2%]; comparator arm: 5 patients [0.9%]) and on the non-performance of delayed cystectomy (intervention arm: 1 patient [0.2%]; comparator arm: 0 patients [0%]). These are included in the overall rate.
c. Discrepancies between Module 4 and the CSR; in the CSR: 67 (12.6).
d. HR and CI from Cox proportional hazards model; p-value from log-rank test. Each stratified by clinical tumour status [T2N0 vs. > T2N0a], renal function [adequate renal function vs. borderline renal function] and tumour PD-L1 expression status [high vs. low/negative]).

AE: adverse event; CI: confidence interval; CSR: clinical study report; HR: hazard ratio; n: number of patients with (at least one) event; N: number of analysed patients; NA: not achieved; ND: not calculable; PD-L1: programmed cell death ligand 1; RCT: randomized controlled trial; RR: tumour cells; vs.: versus

Based on the available information, at most indications, e.g. of an added benefit, can be determined for the outcome failure of the curative treatment approach, and at most hints can be determined for all other outcomes (see Section I 4.2).

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

Operationalization

For the present benefit assessment, the outcome of failure of the curative treatment approach is presented via the time to event (effect measure HR) and the occurrence of the event (effect measure RR). Both analyses include the following events: first recurrence of the disease following radical cystectomy; radical cystectomy not feasible for medical reasons; refusal of radical cystectomy by the patient, or intraoperative failure of radical cystectomy, and death.

Result

A statistically significant difference in favour of the intervention was shown for the outcome "failure of the curative treatment approach". There was an indication of added benefit of

durvalumab + gemcitabine + cisplatin (neoadjuvant) followed by durvalumab (adjuvant) in comparison with gemcitabine + cisplatin (neoadjuvant) followed by watchful waiting.

Symptoms (recorded using EORTC QLQ-C30 and PGIS)

EORTC QLQ-C30

No statistically significant difference between the treatment groups was shown for any of the outcomes fatigue, nausea and vomiting, pain, dyspnoea, insomnia, appetite loss, constipation and diarrhoea. There is no hint of an added benefit of durvalumab + gemcitabine + cisplatin (neoadjuvant) followed by durvalumab (adjuvant) in comparison with gemcitabine + cisplatin (neoadjuvant) followed by watchful waiting; an added benefit is therefore not proven in either case.

PGIS

No statistically significant difference between treatment groups was shown for the symptoms recorded using PGIS. There was no hint of an added benefit of durvalumab + gemcitabine + cisplatin (neoadjuvant) followed by durvalumab (adjuvant) in comparison with gemcitabine + cisplatin (neoadjuvant) followed by watchful waiting; an added benefit is therefore not proven.

Health status (recorded using EQ-5D VAS and PGIC)

EQ-5D VAS

No statistically significant difference between treatment groups was shown for health status recorded using EQ-5D VAS. For this outcome, there is an effect modification by the characteristic clinical tumour status at baseline according to IVRS (see Section I 4.4). However, the extent of the effect for this outcome in the category of non-serious/non-severe symptoms/late complications was no more than marginal. For patients with tumour stage T2N0 and > T2N0. there is no hint of an added benefit of durvalumab + gemcitabine + cisplatin (neoadjuvant) followed by durvalumab (adjuvant) in comparison with gemcitabine + cisplatin (neoadjuvant) followed by watchful waiting; an added benefit is therefore not proven.

PGIC

The health status assessed using the PGIC shows a statistically significant difference in favour of the intervention. However, the extent of the effect for this outcome in the category of non-serious/non-severe symptoms/late complications was no more than marginal. There was no hint of an added benefit of durvalumab + gemcitabine + cisplatin (neoadjuvant) followed by durvalumab (adjuvant) in comparison with gemcitabine + cisplatin (neoadjuvant) followed by watchful waiting; an added benefit is therefore not proven.

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

Role functioning and social functioning

No statistically significant difference between the treatment groups was shown for the outcomes role functioning and social functioning respectively. There is an effect modification by the characteristic sex for these outcomes (see Section I 4.4). For women, there was a hint of lesser benefit of durvalumab + gemcitabine + cisplatin (neoadjuvant) followed by durvalumab (adjuvant) in comparison with gemcitabine + cisplatin (neoadjuvant) followed by watchful waiting for these outcomes. For men, there was no hint of lesser benefit or added benefit of durvalumab + gemcitabine + cisplatin (neoadjuvant) followed by durvalumab (adjuvant) in comparison with gemcitabine + cisplatin (neoadjuvant) followed by watchful waiting for these outcomes; an added benefit is therefore not proven for men.

Global health status, physical functioning, emotional functioning, and cognitive functioning

No statistically significant difference between the treatment groups was shown for any of the following outcomes: global health status, physical functioning, emotional functioning, and cognitive functioning. There was no hint of an added benefit of durvalumab + gemcitabine + cisplatin (neoadjuvant) followed by durvalumab (adjuvant) in comparison with gemcitabine + cisplatin (neoadjuvant) followed by watchful waiting; an added benefit is therefore not proven.

Side effects

SAEs, severe AEs, discontinuation due to AEs, immune-mediated SAEs, immune-mediated severe AEs and further specific AEs

Effect estimates for the outcomes of the side effects category cannot be interpreted (see Section I 4.1). On the basis of the available data and the shapes of the Kaplan-Meier curves, a qualitative assessment of the side effects can be made as part of the overall assessment. The results and the related Kaplan-Meier curves can be found in I Appendix F.

PRO-CTCAE

There are no suitable data for the outcome PRO-CTCAE (for reasoning, see Section I 4.1). There is no hint of greater or lesser harm from durvalumab + gemcitabine + cisplatin (neoadjuvant) followed by durvalumab (adjuvant) in comparison with gemcitabine + cisplatin (neoadjuvant) followed by watchful waiting; greater or lesser harm is therefore not proven for this outcome.

I 4.4 Subgroups and other effect modifiers

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

- Age (< 65 years versus ≥ 65 years)

- Sex (male versus female)
- Clinical tumour status at baseline according to IVRS (T2N0 vs. > T2N0)

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 17. The Kaplan-Meier curves on the subgroup results are presented in I Appendix B.3 of the full dossier assessment.

Table 17: Subgroups (morbidity, health-related quality of life) – RCT, direct comparison: durvalumab + gemcitabine + cisplatin (neoadjuvant)/durvalumab (adjuvant) vs. gemcitabine + cisplatin (neoadjuvant)/watchful waiting (multipage table)

Study outcome characteristic subgroup	Durvalumab + gemcitabine + cisplatin/durvalumab		Gemcitabine + cisplatin/watchful waiting		Durvalumab + gemcitabine + cisplatin/durvalumab vs. gemcitabine + cisplatin/watchful waiting	
	N[a]	median time to event in months [95 % CI] patients with event n (%)	N[a]	median time to event in months [95 % CI] patients with event n (%)	HR [95% CI][b]	p-value[b]
NIAGARA						
Morbidity (health status, EQ-5D VAS – time to first deterioration[c, d])						
Clinical tumour status at baseline according to IVRS						
T2N0	ND	2.8 [2.0; 3.7] 125 (58.1)	ND	3.6 [2.7; 4.5] 95 (44.6)	1.29 [0.99; 1.69]	0.062
> T2N0	ND	4.5 [3.6; 4.8] 131 (41.2)	ND	2.8 [1.9; 3.7] 144 (45.4)	0.77 [0.61; 0.97]	0.029
Total					Interaction:	0.005[e]
Health-related quality of life (EORTC QLQ-C30, role functioning - time to first deterioration[d, f])						
Sex						
Male	ND	1.8 [1.8; 1.9] 287 (65.7)	ND	1.8 [1.8; 1.9] 277 (64.0)	0.96 [0.81; 1.13]	0.630
Female	ND	1.0 [1.0; 1.8] 69 (71.9)	ND	1.8 [1.0; 1.9] 60 (61.9)	1.48 [1.04; 2.09]	0.027
Total					Interaction:	0.028[e]
Health-related quality of life (EORTC QLQ-C30, social functioning - time to first deterioration[d, f]						
Sex						
Male	ND	2.0 [1.8; 2.8] 255 (58.4)	ND	2.0 [1.8; 2.8] 253 (58.4)	0.92 [0.77; 1.10]	0.361
Female	ND	1.8 [1.0; 1.9] 67 (69.8)	ND	1.8 [1.8; 2.7] 60 (61.9)	1.45 [1.02; 2.06]	0.036
Total					Interaction:	0.023[e]

Table 17: Subgroups (morbidity, health-related quality of life) – RCT, direct comparison: durvalumab + gemcitabine + cisplatin (neoadjuvant)/durvalumab (adjuvant) vs. gemcitabine + cisplatin (neoadjuvant)/watchful waiting (multipage table)

Study outcome characteristic subgroup	Durvalumab + gemcitabine + cisplatin/durvalumab		Gemcitabine + cisplatin/watchful waiting		Durvalumab + gemcitabine + cisplatin/durvalumab vs. gemcitabine + cisplatin/watchful waiting	
	N[a]	median time to event in months [95 % CI] patients with event n (%)	N[a]	median time to event in months [95 % CI] patients with event n (%)	HR [95% CI][b]	p-value[b]

a. Number of randomized patients. According to the company, all randomized patients were included in the analysis. At the same time the company stated that patients with no baseline value or no value in the course of the study were censored on Day 1. Thus, no times of these patients were actually included in the analysis. It is not possible to state the exact number of these patients or their distribution across the subgroups; the total proportion is approximately 20%.
b. Effect, CI and p-value from unstratified Cox model.
c. A score decrease by ≥ 15 points from baseline is considered a clinically relevant deterioration (scale range: 0 to 100).
d. Patients for whom no analysable assessment or baseline data were available at the time point of analysis were censored on Day 1. Patients who did not experience a deterioration and who died within two visits of the last recording were censored at the date of the last recording. In cases where two or more visits were missed (regardless of whether this was followed by a deterioration or death), censoring took place at the time of the last recording prior to the two missed visits. For patients who could not deteriorate due to a baseline value that was too low, the reason for censoring did not include a deterioration.
e. Interaction term from Cox proportional hazards model with treatment, subgroup characteristic and the interaction between treatment and subgroup as covariates.
f. A score decrease by ≥ 10 points from baseline is considered a clinically relevant deterioration (scale range: 0 to 100).

CI: confidence interval; EORTC: European Organisation for Research and Treatment of Cancer; HR: hazard ratio; IVRS = interactive voice response system; n: number of patients with event; N = number of analysed patients; QLQ-C30: Quality of Life Questionnaire-Core 30; RCT: randomized controlled trial; VAS: visual analogue scale

Morbidity

health status (recorded with the EQ-5D VAS)

For the health status assessed using the EQ-5D VAS, there is a statistically significant effect modification for the characteristic clinical tumour status at baseline according to the IVRS. A statistically significant difference in favour of the intervention was shown for patients with a tumour status > T2N0. However, the extent of the effect for this outcome in the category of non-serious/non-severe symptoms/late complications was no more than marginal. There was no statistically significant difference between the treatment groups for patients with tumour stage T2N0. For patients with tumour stage T2N0 and > T2N0. there is no hint of an added benefit of durvalumab + gemcitabine + cisplatin (neoadjuvant) followed by durvalumab

(adjuvant) in comparison with gemcitabine + cisplatin (neoadjuvant) followed by watchful waiting; an added benefit is therefore not proven.

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

Role functioning and social functioning

There was a statistically significant effect modification by the characteristic sex for the outcomes role functioning and social functioning. For women, there was a statistically significant difference to the disadvantage of the intervention in each case. For women, there was a hint of lesser benefit of durvalumab + gemcitabine + cisplatin (neoadjuvant) followed by durvalumab (adjuvant) in comparison with gemcitabine + cisplatin (neoadjuvant) followed by watchful waiting for these outcomes. For men, no statistically significant difference was shown between treatment groups. For men, there was no hint of an added benefit of durvalumab + gemcitabine + cisplatin (neoadjuvant) followed by durvalumab (adjuvant) in comparison with gemcitabine + cisplatin (neoadjuvant) followed by watchful waiting for these outcomes; an added benefit is therefore not proven for men.

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 IQWiG *General Methods* [1].

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

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 18).

Determination of the outcome category for the morbidity outcomes

For the morbidity outcomes below, it could not be inferred from the dossier whether they were serious/severe or non-serious/non-severe. Reasoning is provided for the classification of these outcomes.

Failure of the curative treatment approach

The outcome of failure of curative treatment is deemed to be serious/severe. On the one hand, a recurrence of the cancer can be life-threatening, on the other hand, death from any cause (without prior recurrence) is included as a component in the outcome.

Health status (recorded using EQ-5D VAS and PGIC)

For the outcome health status (EQ-5D VAS and PGIC), insufficient information was available to allow a severity category classification of serious or severe. The outcome health status was therefore assigned to the outcome category non-serious/non-severe symptoms/late complications.

Table 18: Extent of added benefit at outcome level: durvalumab + gemcitabine + cisplatin (neoadjuvant)/durvalumab (adjuvant) vs. gemcitabine + cisplatin (neoadjuvant)/watchful waiting (multipage table)

Outcome category **outcome** **effect modifier** **subgroup**	**Durvalumab + gemcitabine + cisplatin/durvalumab vs. gemcitabine + cisplatin/watchful waiting** **median time to event (months)** **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/added benefit not proven
Morbidity		
Failure of the curative treatment approach		
Event rate	35.1% vs. 46.4% RR: 0.76 [0.65; 0.87] p < 0.001 probability: “indication”	Outcome category: serious/severe symptoms/late complications $0.75 \leq CI_u < 0.90$ added benefit, extent: “considerable”
Event-free survival	NA vs. 46.1 HR: 0.68 [0.56; 0.82] p < 0.001 probability: “indication”	
Outcomes with shortened observation period		
Morbidity		
Symptoms (EORTC QLQ-C30 – time to first deterioration)		
Fatigue	1.0 vs. 1.0 HR: 1.12 [0.97; 1.30] p = 0.140	Lesser benefit/added benefit not proven
Nausea and vomiting	1.8 vs. 1.8 HR: 1.09 [0.93; 1.28] p = 0.304	Lesser benefit/added benefit not proven
Pain	2.9 vs. 2.7 HR: 0.94 [0.81; 1.11] p = 0.469	Lesser benefit/added benefit not proven
Dyspnoea	2.8 vs. 2.8 HR: 1.04 [0.87; 1.23] p = 0.688	Lesser benefit/added benefit not proven
Insomnia	3.7 vs. 3.8 HR: 1.07 [0.90; 1.28] p = 0.455	Lesser benefit/added benefit not proven

Table 18: Extent of added benefit at outcome level: durvalumab + gemcitabine + cisplatin (neoadjuvant)/durvalumab (adjuvant) vs. gemcitabine + cisplatin (neoadjuvant)/watchful waiting (multipage table)

Outcome category **outcome** **effect modifier** **subgroup**	**Durvalumab + gemcitabine + cisplatin/durvalumab vs. gemcitabine + cisplatin/watchful waiting** **median time to event (months)** **effect estimation [95% CI];** **p-value** **probability**[a]	**Derivation of extent**[b]
Appetite loss	1.8 vs. 1.8 HR: 0.97 [0.83; 1.14] p = 0.678	Lesser benefit/added benefit not proven
Constipation	1.9 vs. 1.8 HR: 0.90 [0.76; 1.06] p = 0.222	Lesser benefit/added benefit not proven
diarrhoea	4.7 vs. 5.5 HR: 1.13 [0.93; 1.37] p = 0.239	Lesser benefit/added benefit not proven
Symptoms (PGIS – time to first deterioration)	4.8 vs. 4.9 HR: 0.96 [0.78; 1.18] p = 0.689	Lesser benefit/added benefit not proven
Health status (EQ-5D VAS - time to first deterioration)		
Clinical tumour status at baseline according to IVRS		
T2N0	2.8 vs. 3.6 HR: 1.29 [0.99; 1.69] p = 0.062	Lesser benefit/added benefit not proven
> T2N0	4.5 vs. 2.8 HR: 0.77 [0.61; 0.97] p = 0.029	Outcome category: non-serious/non-severe symptoms/late complications $0.90 \leq CI_u < 1.00$ Lesser benefit/added benefit not proven[d]
Health status (PGIC - time to first deterioration)	5.3 vs. 4.2 HR: 0.82 [0.69; 0.99] p = 0.037	Outcome category: non-serious/non-severe symptoms/late complications $0.90 \leq CI_u < 1.00$ Lesser benefit/added benefit not proven[d]
Health-related quality of life		
EORTC QLQ-C30 – time to first deterioration		
Global health status	1.8 vs. 1.8 HR: 1.01 [0.86; 1.18] p = 0.943	Lesser benefit/added benefit not proven

Table 18: Extent of added benefit at outcome level: durvalumab + gemcitabine + cisplatin (neoadjuvant)/durvalumab (adjuvant) vs. gemcitabine + cisplatin (neoadjuvant)/watchful waiting (multipage table)

Outcome category **outcome** **effect modifier** **subgroup**	**Durvalumab + gemcitabine + cisplatin/durvalumab vs. gemcitabine + cisplatin/watchful waiting** **median time to event (months)** **effect estimation [95% CI];** **p-value** **probability**[a]	**Derivation of extent**[b]
Physical functioning	2.7 vs. 1.9 HR: 0.96 [0.82; 1.12] p = 0.598	Lesser benefit/added benefit not proven
Role functioning Sex Male	1.8 vs. 1.8 HR: 0.96 [0.81; 1.13] p = 0.630	Lesser benefit/added benefit not proven
Female	1.0 vs. 1.8 HR: 1.48 [1.04; 2.09] HR: 0.68 [0.48; 0.96][e] p = 0.027 Probability: hint	Outcome category: health-related quality of life $0.90 \leq CI_u < 1.00$ Lesser benefit, extent: “minor”
Emotional functioning	3.8 vs. 4.0 HR: 1.00 [0.83; 1.19] p = 0.965	Lesser benefit/added benefit not proven
Cognitive functioning	2.3 vs. 2.7 HR: 1.16 [0.99; 1.36] p = 0.079	Lesser benefit/added benefit not proven
Social functioning Sex Male	2.0 vs. 2.0 HR: 0.92 [0.77; 1.10] p = 0.361	Lesser benefit/added benefit not proven
Female	1.8 vs. 1.8 HR: 1.45 [1.02; 2.06] HR: 0.69 [0.49; 0.98][e] p = 0.036 Probability: hint	Outcome category: health-related quality of life $0.90 \leq CI_u < 1.00$ lesser benefit, extent: “minor”
Side effects		
SAEs	No suitable data[f]	Greater/lesser harm not proven
Severe AEs	No suitable data[f]	Greater/lesser harm not proven
Discontinuation due to AEs	No suitable data[f]	Greater/lesser harm not proven
PRO-CTCAE	No suitable data[c]	Greater/lesser harm not proven

Table 18: Extent of added benefit at outcome level: durvalumab + gemcitabine + cisplatin (neoadjuvant)/durvalumab (adjuvant) vs. gemcitabine + cisplatin (neoadjuvant)/watchful waiting (multipage table)

Outcome category **outcome** **effect modifier** **subgroup**	**Durvalumab + gemcitabine + cisplatin/durvalumab vs. gemcitabine + cisplatin/watchful waiting** **median time to event (months)** **effect estimation [95% CI];** **p-value** **probability**[a]	**Derivation of extent**[b]
Immune-mediated SAEs	No suitable data[f]	Greater/lesser harm not proven
Immune-mediated severe AEs	No suitable data[f]	Greater/lesser harm not proven
Other specific AEs	No suitable data[f]	Greater/lesser harm not proven

a. Probability provided if there is a statistically significant and relevant effect.
b. Depending on the outcome category, estimations of effect size are made with different limits based on the upper limit of the confidence interval (CI_u).
c. See Section I 4.1 for reasons.
d. The extent of the effect in this non-serious/non-severe outcome was no more than marginal.
e. Institute's calculation; inverse direction of effect to enable use of limits to derive the extent of the added benefit.
f. Effect estimation not interpretable. See Section I 4.1 for reasons.

AE: adverse event; CI: confidence interval; CI_u: upper limit of the confidence interval; EORTC: European Organisation for Research and Treatment of Cancer; HR: hazard ratio; IVRS: interactive voice response system; NA: not achieved; NC: not calculable; PGIC: Patient Global Impression of Change; PGIS: Patient Global Impression of Severity; PRO-CTCAE: Patient-Reported Outcomes Version of the Common Terminology Criteria for Adverse Events; 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 19 summarizes the results taken into account for the overall conclusion on the extent of the added benefit.

Table 19: Positive and negative effects from the assessment of durvalumab + gemcitabine + cisplatin (neoadjuvant)/durvalumab (adjuvant) in comparison with the ACT

Positive effects	**Negative effects**
Outcomes with observation over the entire study duration	
Morbidity serious/severe symptoms/late complications ▪ failure of the curative treatment approach: indication of an added benefit – extent: "considerable"	–
Outcomes with shortened observation period	
–	Health-related quality of life EORTC QLQ-C30: ▪ role functioning ▫ female: hint of lesser benefit – extent: "minor" ▪ social functioning ▫ Female: hint of lesser benefit – extent: "minor"
No suitable data are available for the outcomes overall survival and PRO-CTCAE. The effect estimates for the outcomes in the side effects category cannot be interpreted and are taken into account in the assessment solely on a qualitative basis.	
EORTC: European Organisation for Research and Treatment of Cancer; PRO-CTCAE: Patient-Reported Outcomes version of the Common Terminology Criteria for Adverse Events; QLQ-C30: Quality of Life Questionnaire-Core 30	

In the overall consideration, there were both positive and negative effects of durvalumab + gemcitabine + cisplatin (neoadjuvant) followed by durvalumab (adjuvant) in comparison with gemcitabine + cisplatin (neoadjuvant) followed by watchful waiting. For the outcomes in the health-related quality of life category, these relate exclusively to the shortened period (up to the recurrence of the disease, the start of subsequent therapy or study discontinuation).

In terms of positive effects, there is an indication of considerable added benefit for the outcome failure of the curative treatment approach. In contrast, there are negative effects in two aspects of health-related quality of life, which are shown in the subgroup of women due to effect modification. The effect estimates on the side effects cannot be interpreted. However, as it is assumed on the basis of the available information that the directions of the effects will not reverse, the results regarding side effects can be taken into account qualitatively in the overall assessment. Overall, it is therefore assumed that potential disadvantages in the AEs, such as serious and severe immune-mediated AEs, will not completely call into question the advantage in the outcome failure of the curative treatment approach. However, this uncertainty was taken into account when determining the extent.

In summary, for patients with resectable MIBC for whom platinum-based chemotherapy is suitable, there is an indication of minor added benefit of durvalumab in combination with

gemcitabine and cisplatin for neoadjuvant treatment, followed by durvalumab as monotherapy for adjuvant treatment, compared with the ACT.

Table 20 summarizes the result of the assessment of the added benefit of durvalumab + gemcitabine + cisplatin (neoadjuvant)/durvalumab (adjuvant) in comparison with the ACT.

Table 20: Durvalumab + gemcitabine + cisplatin (neoadjuvant)/durvalumab (adjuvant) – probability and extent of added benefit

Therapeutic indication	**ACT[a]**	**Probability and extent of added benefit**
Adults with resectable MIBC (MIBC) for whom platinum-based chemotherapy is suitable; neoadjuvant and adjuvant therapy after radical cystectomy	A therapy regimen consisting of[b] ▪ neoadjuvant therapy with cisplatin in combination with gemcitabine followed by radical cystectomy and: ▫ watchful waiting or ▫ nivolumab (is only an option for patients with tumour cell programmed cell death ligand 1 (PD-L1) expression ≥ 1% and at high risk of recurrence following radical resection)	Indication of minor added benefit[c]

a. Presented is the ACT specified by the G-BA.
b. The ACT specified here comprises several alternative treatment options. However, individual treatment options only represent a comparator therapy for those members of the patient population who meet the patient and disease characteristics shown in brackets.
c. Only patients with an ECOG PS of 0 or 1 were included in the NIAGARA 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 deviates from that of the company, which derived an indication of considerable added benefit in its dossier.

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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