Enfortumab vedotin (urothelial carcinoma, first-line therapy, combination with pembrolizumab)

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

EXTRACT

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IQWiG thanks the medical and scientific advisor for his contribution to the dossier assessment. However, the advisor was not involved in the actual preparation of the dossier assessment. The responsibility for the contents of the dossier assessment lies solely with IQWiG.

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. (*Bladder Cancer Self-Help Association*) 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

I Table of contents

I List of tables[2]

Page

[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
BPI-SF	Brief Pain Inventory-Short Form
CPS	combined positive score
CTCAE	Common Terminology Criteria for Adverse Events
ECOG PS	Eastern Cooperative Oncology Group Performance Status
EORTC QLQ-C30	European Organisation for Research and Treatment of Cancer – Quality of Life Questionnaire-Core 30
ESMO	European Society for Medical Oncology
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
GFR	glomerular filtration rate
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care
MedDRA	Medical Dictionary for Regulatory Activities
NYHA	New York Heart Association
PD-1	Programmed Cell Death 1
PD-L1	Programmed Cell Death-Ligand 1
PFS	progression-free survival
RCT	randomized controlled trial
SAE	serious adverse event
SGB	Sozialgesetzbuch (Social Code Book)
SMQ	standardisierte MedDRA-Abfrage
SOC	Systemorganklasse
VAS	visuelle Analogskala
WHO	World Health Organisation

I 1 Executive summary of the benefit assessment

Background

In accordance with § 35a Social Code Book (SGB) V, the Federal Joint Committee (G-BA) commissioned the Institute for Quality and Efficiency in Health Care (IQWiG) to assess the benefit of the drug enfortumab vedotin (in combination with pembrolizumab). 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 23 September 2024.

Research question

The aim of this report is to assess the added benefit of enfortumab vedotin in combination with pembrolizumab (hereinafter referred to as enfortumab vedotin + pembrolizumab) in comparison with the appropriate comparator therapy (ACT) for the first-line treatment of adult patients with unresectable or metastatic urothelial carcinoma who are eligible for platinum-containing chemotherapy.

The research questions presented in Table 4 result from the ACT specified by the G-BA.

Table 2: Research questions of the benefit assessment of enfortumab vedotin + pembrolizumab

Research question	Therapeutic indication	ACT[a]
First-line treatment of adult patients with unresectable or metastatic urothelial carcinoma who are eligible for platinum-containing chemotherapy		
1	For whom cisplatin-based therapy is an option	Cisplatin in combination with gemcitabine followed by avelumab as maintenance therapy (maintenance therapy with avelumab only for progression-free patients[b])
2	For whom cisplatin-based therapy is not an option[c]	Carboplatin in combination with gemcitabine in accordance with Appendix VI to Section K of the Pharmaceutical Directive[d], followed by avelumab as maintenance therapy (maintenance therapy with avelumab only for progression-free patients[b])[b])

a. Presented is the respective ACT specified by the G-BA.
b. According to the G-BA, it is assumed that patients who are not progression-free following platinum-based chemotherapy will not be treated further as part of first-line treatment.
c. According to the G-BA, it is assumed that the patients in question have an increased risk of cisplatin-induced side effects in the context of a combination therapy (e.g. pre-existing neuropathy or relevant hearing impairment, renal insufficiency, heart failure).
d. With regard to the present indication, this is a use in an unapproved therapeutic indication (off-label use). For the present indication, carboplatin in combination with gemcitabine can be prescribed in off-label use, see Appendix VI to Section K of the Pharmaceutical Directive.

ACT: appropriate comparator therapy; G-BA: Federal Joint Committee

The company specified cisplatin in combination with gemcitabine (hereinafter cisplatin + gemcitabine) as ACT for research question 1 and carboplatin in combination with gemcitabine (hereinafter carboplatin + gemcitabine) as ACT for research question 2, in each case followed by avelumab as maintenance therapy (maintenance therapy with avelumab only for progression-free patients), and thus followed the G-BA's specification in each case.

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) are used to derive the added benefit.

Study pool and study design

Relevance of the study EV-302/KN-A39 (presented by the company) for the benefit assessment

For both research questions, the company identified the RCT EV-302/KN-A39 (SGN22E-003) on the comparison of enfortumab vedotin + pembrolizumab versus platinum-based chemotherapy (cisplatin/carboplatin + gemcitabine). The comparator therapy in study EV-302/KN-A39 does not represent a full implementation of the G-BA's ACT, as patients in the comparator arm who were progression-free following chemotherapy were not regularly scheduled for maintenance treatment with avelumab according to the study design. However, the results of the study can be interpreted for the present research questions. This is explained below.

As the included study EV-302/KN-A39 is relevant for both research questions of the present benefit assessment, characteristics across research questions are described in a superordinate manner in the following. Below, research question-specific characteristics are described separately for research question 1 and research question 2.

Study design

The EV-302/KN-A39 study is an ongoing, multicentre, open-label RCT comparing enfortumab vedotin + pembrolizumab versus platinum-based chemotherapy (cisplatin/carboplatin + gemcitabine) in the first-line treatment of adult patients with unresectable or metastatic urothelial carcinoma who are eligible for platinum-based chemotherapy. Patients with histologically confirmed urothelial carcinoma of the urinary bladder, the renal pelvis, the ureter or the urethra were included in the study, whereby squamous or sarcomatoid cell differentiation or mixed cell types were also permitted. On study inclusion, patients had to have an Eastern Cooperative Oncology Group Performance Status (ECOG PS) ≤ 2 and were not allowed to have received prior systemic therapy for the treatment of the advanced or metastatic urothelial carcinoma.

Cisplatin eligibility was assessed prior to randomization. Cisplatin was considered unsuitable for patients who fulfilled at least one of the following criteria:

- Glomerular filtration rate (GFR) < 60 mL/min, but ≥ 30 mL/min
  - at the investigator's discretion, patients could be classified as suitable for cisplatin if they had a GFR ≥ 50 mL/min and did not fulfil any of the other criteria
- ECOG PS or World Health Organisation (WHO) performance status of 2
- Audiometric hearing loss according to Common Terminology Criteria for Adverse Events (CTCAE) grade ≥ 2
- Cardiac failure according to New York Heart Association (NYHA) class III

Patients for whom cisplatin was not suitable according to these criteria were assigned to treatment with carboplatin + gemcitabine in case of randomization to the comparator arm of the study. Patients with persistent sensory or motor neuropathy with CTCAE grade 2 or higher were excluded from the study. Thus, the criteria used to assess cisplatin eligibility in the context of the EV-302/KN-A39 study correspond to the specifications of the current S3 guideline.

The study included a total of 886 patients who were randomly assigned in a 1:1 ratio to treatment with enfortumab vedotin + pembrolizumab (N = 442) or cisplatin/carboplatin + gemcitabine (N = 444). Treatment with cisplatin was assessed as suitable in a total of 482 patients (intervention arm: n = 240, comparator arm: n = 242) and as unsuitable in a total of 404 patients (intervention and comparator arm: n = 202 each). Randomization was stratified by cisplatin eligibility (suitable or unsuitable), programmed cell death ligand 1 (PD-L1) expression (combined positive score [CPS] ≥ 10 or < 10) and liver metastases (present or absent). The stratification factor “cisplatin eligibility” corresponds to the subdivision into the relevant subpopulations for research question 1 (cisplatin suitable) and research question 2 (cisplatin unsuitable) of the present benefit assessment.

Treatment with enfortumab vedotin + pembrolizumab in the intervention arm was largely in compliance with the specifications of the respective Summary of Product Characteristics (SPC).

However, there are various uncertainties regarding the treatment in the comparator arm of the study, which are described in the following sections.

Co-primary outcomes of the EV-302/KN-A39 study were overall survival and progression-free survival (PFS). Other patient-relevant outcomes were outcomes on morbidity, health-related quality of life and side effects.

Treatment in the comparator arm of study EV-302/KN-A39

Treatment with cisplatin/carboplatin + gemcitabine

Treatment with carboplatin + gemcitabine is not approved for patients who are not eligible for cisplatin-based therapy. However, it can be prescribed in accordance with Annex VI to Section K of the Pharmaceutical Directive. The use of carboplatin + gemcitabine essentially complied with the specifications of Annex VI to Section K of the Pharmaceutical Directive. For the treatment with cisplatin + gemcitabine, however, there are deviations from the SPC, which are described below.

Length of treatment cycles with cisplatin + gemcitabine

In the present therapeutic indication, the SPC 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. In accordance with the SPC, 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 EV-302/KN-A39 study, the cycle length was 21 days with administration of 1000 mg/m² gemcitabine on cycle days 1 and 8. The cycle length for cisplatin + gemcitabine therefore does not correspond to the approval. As a result, the dose per cycle or the cumulative dose relating to gemcitabine is lower than stipulated in the approval, while relating to cisplatin, the dose is administered at shorter intervals.

Overall, it is unclear how this deviation affects the results of patient-relevant outcomes. In the present situation, this uncertainty does not fundamentally challenge the relevance of study EV-302/KN-A39 for the present benefit assessment, but contributes to a reduced certainty of conclusions.

Maximum number of treatment cycles with cisplatin + gemcitabine

In the comparator arm of the EV-302/KN-A39 study, treatment with cisplatin + gemcitabine was limited to a maximum treatment duration of 6 cycles, in deviation from the specifications in the SPC. However, the SPC does not specify any fixed upper limit for the number of treatment cycles. The current national S3 guideline does not include a recommendation regarding the duration of treatment with cisplatin + gemcitabine; the guideline of the European Society for Medical Oncology (ESMO) recommends 4 to 6 cycles of platinum-based chemotherapy in this therapeutic indication. Therefore, it is assumed for the present benefit assessment that the limitation of treatment with cisplatin + gemcitabine to a maximum of 6 cycles does not represent a relevant restriction of study EV-302/KN-A39.

Possibility of a single treatment switch between cisplatin and carboplatin

In the comparator arm of study EV-302/KN-A39, a single treatment switch from cisplatin to carboplatin (in the event of acute renal impairment that had not subsided during treatment with cisplatin) or from carboplatin to cisplatin (in the event of improvement in performance status or renal function to such an extent that cisplatin-containing therapy was an option) was permitted at the investigator's discretion. A switch due to lack of response or due to progression of the disease was not permitted in either case.

According to the ACT specified by the G-BA, switching from cisplatin to carboplatin or from carboplatin to cisplatin was not planned. There is no concrete information available on how many patients switched treatment from cisplatin to carboplatin or from carboplatin to cisplatin. In the present situation, however, it is assumed that a corresponding treatment switch occurred in a small proportion of patients at most, so that in the present situation it is not assumed that this represents a relevant deviation from the G-BA's ACT.

Implementation of the ACT: maintenance therapy with avelumab not part of the study medication

The G-BA specified treatment with cisplatin + gemcitabine (research question 1) or carboplatin + gemcitabine (research question 2) as ACT for adult patients with unresectable or metastatic urothelial carcinoma in the first line for whom platinum-containing chemotherapy is an option. As specified by the G-BA, patients who are progression-free after chemotherapy are to receive maintenance treatment with avelumab. In the comparator arm of the EV-302/KN-A39 study, however, maintenance treatment with avelumab was not regularly planned for patients who were progression-free following chemotherapy. However, maintenance therapy with avelumab could be used after completion or discontinuation of platinum-containing chemotherapy according to the investigator's assessment and depending on local availability.

According to the company's information in Module 4 A, only 34.7% (research question 1) or 23.8% (research question 2) of patients in the comparator arm of the respective relevant subpopulation received maintenance treatment with avelumab in the EV-302/KN-A39 study. Overall, this does initially not represent an adequate implementation of the G-BA's ACT.

However, in Module 4 A of its dossier, the company provided further information on the use of avelumab in the EV-302/KN-A39 study. Based on the information provided by the company, a distinction can be made between the following 3 groups of patients:

1) Patients for whom maintenance treatment with avelumab was possible according to the company and who received avelumab
2) Patients for whom maintenance treatment with avelumab was not possible according to the company

3) Patients for whom maintenance treatment with avelumab was possible according to the company and who nevertheless did not receive avelumab

According to the company, the G-BA's ACT had not been implemented in all patients who either received maintenance treatment with avelumab or for whom this was not possible for justified reasons. For research question 1, these are 167/242 (69%) patients, and for research question 2 149/202 (74%) patients of the comparator arm of the respective relevant subpopulation (Institute's calculation based on the company's data). These data are largely appropriate. However, the information provided by the company also shows that a relevant proportion of patients did not receive maintenance treatment with avelumab, although this would have been possible and thus also indicated according to the company's information (research question 1: 69/242 [29%], research question 2: 48/202 [24%]).

In Module 4 A of its dossier, the company argues that the EV-302/KN-A39 study is nevertheless suitable for deriving the added benefit of enfortumab vedotin + pembrolizumab. It cites the following reasons for this:

- Firstly, the chemotherapy component of the ACT in the form of platinum-containing chemotherapy was adequately implemented in the two subpopulations relevant for research questions 1 and 2.
- Secondly, maintenance therapy with avelumab was not excluded from the start of the study in accordance with the study design, although the approval of maintenance therapy with avelumab was only granted during the course of the study. In amendment 4 to the study protocol, it was concretized and specified that maintenance therapy with avelumab could be used after completion or discontinuation of platinum-containing chemotherapy in accordance with the current SPC and depending on the investigator's assessment and local availability.
- In addition, the company subdivided patients for whom maintenance therapy with avelumab was possible and who nevertheless did not receive avelumab into 2 groups: patients who had already died at the present data cut-off and those who survived. According to this, 48/69 (70%) patients in research question 1 and 30/48 (63%) patients in research question 2 in this group were still alive and had thus achieved the best possible result for the outcome of overall survival at this data cut-off according to the company. This means that even with avelumab maintenance therapy, these patients would not have been able to achieve a better result for the outcome of overall survival.

The company's argumentation and its approach of presenting information on the proportion of patients for whom maintenance therapy with avelumab was eligible according to its assessment and in whom it was either implemented or not implemented is basically suitable for assessing the interpretability of the results of the EV-302/KN-A39 study for the benefit

assessment. However, there are several points regarding the subdivision that require comment.

Definition of the possibility of maintenance therapy with avelumab

According to the SPC, freedom from progression after platinum-based chemotherapy is the only prerequisite for maintenance therapy with avelumab. However, the company assumes that maintenance treatment with avelumab was also not possible in patients who had completed < 4 cycles of platinum-based chemotherapy or in whom disease progression or death had occurred within 10 weeks of the last dose of chemotherapy. The company justified this restriction of the possibility of maintenance therapy with avelumab on the basis of the inclusion criteria of the RCT JAVELIN Bladder 100, which was the main evidence on which the approval of avelumab as maintenance therapy in the therapeutic indication was based and which was also used for the benefit assessment of avelumab.

According to the inclusion criteria of the RCT JAVELIN Bladder 100, the following requirements for the use of avelumab applied, which go beyond the specifications of the SPC:

- received 4 to 6 cycles of chemotherapy with cisplatin/carboplatin + gemcitabine
- 4 to 10 weeks have passed since the administration of the last dose of chemotherapy

The use of at least 4 cycles of chemotherapy with cisplatin/carboplatin + gemcitabine before starting maintenance therapy with avelumab is in line with current guideline recommendations.

With regard to the patients in the EV-302/KN-A39 study with disease progression or death within 10 weeks after the last dose of chemotherapy, the company did not provide any information on the time at which the respective events occurred within this time window. The SPC does not specify a time window or point in time after completion of chemotherapy at which maintenance therapy with avelumab is to be started. According to the SPC, it would therefore also be possible to start maintenance treatment with avelumab immediately after completion of platinum-based chemotherapy if there is no progression. The time window in the JAVELIN Bladder 100 approval study was defined as 4 to 10 weeks after receipt of the last dose of chemotherapy, so that even according to this definition a use of avelumab earlier than 10 weeks after the last dose of chemotherapy would have been possible. Due to the fact that the company defined 10 weeks as the maximum possible time for the period of 4 to 10 weeks specified in the JAVELIN Bladder 100 study, it is unclear in how many patients with disease progression or death within 10 weeks of the last dose of chemotherapy would have been able to receive maintenance treatment with avelumab earlier, from which they would have potentially benefited. However, since this criterion of the company only applies to 3.7% of the

subpopulation relevant for research question 1 and 7.4% of the subpopulation relevant for research question 2, this aspect only plays a subordinate role overall.

Lack of information on the use of avelumab

In its argumentation, the company assumes that the G-BA's ACT in the EV-302/KN-A39 study was implemented, among others, in patients in whom maintenance therapy was possible according to the company's criteria and who received avelumab. However, avelumab was not part of the study medication, but could be used after completion or discontinuation of platinum-containing chemotherapy according to the investigator's assessment and depending on local availability. Following the start of the study on 30 March 2020 and the approval of avelumab in the European Union on 21 January 2021, Amendment 4 to the study protocol on 11 November 2021 explicitly described the possibility of maintenance therapy with avelumab (at the investigator's discretion and subject to local availability); Amendment 7 of 30 November 2022 specified that avelumab should be used in accordance with the local SPC. However, there was a lack of specific information on the use of avelumab, particularly prior to the amendment of 30 November 2022. It is unclear whether the requirements of the SPC for avelumab applicable in Germany, for example on dosage, were complied with. Likewise, the time point at which maintenance therapy with avelumab was started after completion of chemotherapy remains unclear. It is therefore also unclear for patients who have received avelumab whether earlier use of maintenance therapy with avelumab would have been possible and whether they would have benefited from it.

Patients who did not receive avelumab and died

With regard to patients for whom maintenance treatment with avelumab was an option according to the company, but who did not receive avelumab and died, the company presented 3 sensitivity analyses to address the consequences of the lack of implementation of the ACT for the outcome of overall survival in these patients. Overall, these analyses were considered appropriate to address this point, so that no additional uncertainty arises.

Conclusion and consequences for the benefit assessment

With regard to maintenance therapy with avelumab, implementation of the ACT was overall incomplete in the EV-302/KN-A39 study, as the information provided by the company shows that only 69% of patients for research question 1 and 74% of patients for research question 2 either received maintenance therapy with avelumab or were not eligible for such therapy. A relevant proportion of patients in the respective relevant subpopulation did not receive maintenance treatment with avelumab, although this would have been possible according to the company's information (research question 1: 69/242 [29%]; research question 2: 48/202 [24%], Institute's calculation). In addition, as described in the previous sections, there are various uncertainties with regard to the data presented by the company.

The results of study EV-302/KN-A39 can be interpreted on the basis of the information presented by the company on the implementation of maintenance therapy with avelumab and the associated sensitivity analyses despite the uncertainties described for research questions 1 and 2 of the present benefit assessment. The consequences resulting from the incomplete implementation of the ACT were examined at outcome level for the benefit assessment.

However, the informative value of the study is limited, particularly due to the incomplete implementation of maintenance therapy with avelumab. In addition, the deviations from the SPC described above for treatment with cisplatin + gemcitabine in the comparator arm contribute to the limitation of the certainty of the results in research question 1. Therefore, at most hints, e.g. of an added benefit, can be determined on the basis of the EV-302/KN-A39 study for research questions 1 and 2 for all outcomes.

Research question 1: Patients for whom cisplatin-based therapy is suitable (cisplatin suitable)

Risk of bias and certainty of conclusions

The outcome-specific risk of bias was also rated as low for the results on “overall survival”, and as high for all other patient-relevant outcomes.

Summary assessment of the certainty of conclusions

In addition to the described aspects of bias, there are uncertainties for the EV-302/KN-A39 study, particularly with regard to the implementation of the ACT. In the present specific data constellation, the results of the study can nevertheless be interpreted for the research questions of the present benefit assessment, but the certainty of the study results for the present assessment is reduced. Based on the EV-302/KN-A39 study, at most hints, e.g. of an added benefit, can be derived for both research questions.

Moreover, for the outcomes in the side effects category, analyses are only available for a significantly shortened period, which in the comparator arm only reflects the treatment with chemotherapy, but not the period of a possible maintenance therapy with avelumab, and in the intervention arm only takes into account the first 6 months of a possibly longer-lasting treatment. This shortened observation in the comparator arm or consideration of recorded data in the intervention arm contributes to a limited certainty of conclusions and additionally justifies the fact that at most hints can be derived.

Results

Mortality

Overall survival

For the outcome of overall survival, a statistically significant difference was found in favour of enfortumab vedotin + pembrolizumab in comparison with cisplatin + gemcitabine. The 3 sensitivity analyses presented by the company, in which patients in the comparator arm for whom maintenance treatment with avelumab would potentially have been indicated and who died without maintenance treatment were accounted for differently, also showed a statistically significant difference in favour of enfortumab vedotin + pembrolizumab compared with cisplatin + gemcitabine in each case. This effect therefore remains even if the maximum situation is assumed that all these patients in the comparator arm have survived to the present data cut-off. In this data constellation, there is a hint of added benefit of enfortumab vedotin + pembrolizumab in comparison with the ACT. However, the results of the main analysis and the 3 sensitivity analyses on overall survival presented by the company differ in terms of their extent. Therefore, the extent of the added benefit for the outcome of overall survival cannot be quantified.

Morbidity

Worst pain (Brief Pain Inventory-Short Form [BPI-SF] item 3)

No statistically significant difference between treatment groups was shown for the outcome of worst pain (recorded using BPI-SF item 3). There is no hint of an added benefit of enfortumab vedotin + pembrolizumab in comparison with the ACT; an added benefit is therefore not proven.

Pain interference (BPI-SF items 9a–g)

No suitable data are available for the outcome "pain interference" (recorded using BPI-SF items 9a-9g). There is no hint of an added benefit of enfortumab vedotin + pembrolizumab in comparison with the ACT; an added benefit is therefore not proven.

Symptoms

Fatigue (recorded with the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30 [EORTC QLQ-C30])

No statistically significant difference between treatment groups was found for the outcome of fatigue. However, there is an effect modification by the characteristic of age. There was a hint of an added benefit of enfortumab vedotin + pembrolizumab versus the ACT for patients < 65 years of age. For patients ≥ 65 years, there was no hint of an added benefit of enfortumab vedotin + pembrolizumab versus the ACT; an added benefit is therefore not proven for patients ≥ 65 years of age.

Nausea and vomiting, constipation (recorded using EORTC QLQ-C30)

For the outcomes of nausea and vomiting as well as constipation, there is a statistically significant difference in favour of enfortumab vedotin + pembrolizumab versus cisplatin + gemcitabine. There is a hint of added benefit of enfortumab vedotin + pembrolizumab in comparison with the ACT.

Pain, dyspnoea, insomnia and diarrhoea (each recorded using the EORTC QLQ-C30)

No statistically significant difference between treatment groups was shown for any of the outcomes of pain, dyspnoea, insomnia, or diarrhoea. There is no hint of an added benefit of enfortumab vedotin + pembrolizumab in comparison with the ACT; an added benefit is therefore not proven.

Appetite loss (recorded with the EORTC QLQ-C30)

For the outcome of appetite loss, a statistically significant difference was found in favour of enfortumab vedotin + pembrolizumab in comparison with cisplatin + gemcitabine. However, the extent of the effect for this outcome in the category of non-serious/non-severe symptoms was no more than marginal. There is no hint of an added benefit of enfortumab vedotin + pembrolizumab in comparison with the ACT; an added benefit is therefore not proven.

Health status (recorded with the EQ-5D visual analogue scale [VAS])

No statistically significant difference between treatment groups was shown for the outcome of health status. There is no hint of an added benefit of enfortumab vedotin + pembrolizumab in comparison with the ACT; an added benefit is therefore not proven.

Health-related quality of life

Global health status, role functioning, emotional functioning and cognitive functioning (each assessed using the EORTC QLQ-C30)

No statistically significant difference between treatment groups was found for any of the outcomes of global health status, role functioning, emotional functioning, and cognitive functioning. In each case, there is no hint of an added benefit of enfortumab vedotin + pembrolizumab in comparison with the ACT; an added benefit is therefore not proven for any case.

Physical functioning (recorded using the EORTC QLQ-C30)

No statistically significant difference between treatment groups was found for the outcome of physical functioning. However, there is an effect modification by the characteristic of age. There is a hint of an added benefit of enfortumab vedotin + pembrolizumab versus the ACT for patients < 65 years of age. For patients ≥ 65 years, there was no hint of an added benefit of enfortumab vedotin + pembrolizumab versus the ACT; an added benefit is therefore not proven for patients ≥ 65 years of age.

Social functioning (recorded using the EORTC QLQ-C30)

No statistically significant difference between treatment groups was found for the outcome of social functioning. There are effect modifications by the characteristics of age and metastases. These effect modifications cannot be assessed without examining for cross-interactions. The added benefit is therefore derived based on the results on the relevant subpopulation. There is no hint of an added benefit of enfortumab vedotin + pembrolizumab in comparison with the ACT; an added benefit is therefore not proven.

Side effects

Serious adverse events (SAEs) and discontinuation due to adverse events (AEs)

No statistically significant difference was found between treatment groups for either of the outcomes of SAEs or discontinuation due to AEs. For each of them, there is no hint of greater or lesser harm from enfortumab vedotin + pembrolizumab in comparison with the ACT; greater or lesser harm is therefore not proven.

Severe AEs

For the outcome of severe AEs, a statistically significant difference was found in favour of enfortumab vedotin + pembrolizumab in comparison with cisplatin + gemcitabine. There is a hint of lesser harm from enfortumab vedotin + pembrolizumab in comparison with the ACT.

Immune-related SAEs, immune-related severe AEs, peripheral neuropathy (AEs), skin reactions (AEs) and severe hyperglycaemia (severe AEs)

For the outcomes of immune-related SAEs, immune-related severe AEs, peripheral neuropathy (AEs), skin reactions (AEs) and severe hyperglycaemia (severe AEs), there was a statistically significant difference to the disadvantage of enfortumab vedotin + pembrolizumab compared to cisplatin + gemcitabine. For each of them, there was a hint of greater harm from enfortumab vedotin + pembrolizumab in comparison with the ACT.

Severe nephrotoxicity (severe AEs)

No statistically significant difference between treatment groups was found for the outcome of severe nephrotoxicity (severe AEs). There is no hint of greater or lesser harm from enfortumab vedotin + pembrolizumab in comparison with the ACT; greater or lesser harm is therefore not proven.

Other specific AEs

Nausea (AEs), vomiting (AEs), blood and lymphatic system disorders (severe AEs), urinary tract infection (severe AEs) and general disorders and administration site conditions (severe AEs)

For the outcomes of nausea (AEs), vomiting (AEs), blood and lymphatic system disorders (severe AEs), urinary tract infection (severe AEs) as well as general disorders and

administration site conditions (severe AEs), there was a statistically significant difference in favour of enfortumab vedotin + pembrolizumab compared to cisplatin + gemcitabine. For each of them, there is a hint of lesser harm from enfortumab vedotin + pembrolizumab in comparison with the ACT.

Eye disorders (AEs), endocrine disorders (AEs), gastrointestinal disorders (SAEs), respiratory, thoracic and mediastinal disorders (SAEs) and diarrhoea (severe AEs)

There was a statistically significant difference to the disadvantage of enfortumab vedotin + pembrolizumab compared to cisplatin + gemcitabine for each of the outcomes of eye disorders (AEs), endocrine disorders (AEs), gastrointestinal disorders (SAEs), respiratory, thoracic and mediastinal disorders (SAEs) and diarrhoea (severe AEs). For each of them, there was a hint of greater harm from enfortumab vedotin + pembrolizumab in comparison with the ACT.

Ear and labyrinth disorders (AE)

For the outcome of ear and labyrinth disorders (AEs), there was a statistically significant difference in favour of enfortumab vedotin + pembrolizumab in comparison with cisplatin + gemcitabine. However, there is an effect modification by the characteristic of age. For both patients < 65 years and patients ≥ 65 years, there is a hint of lesser harm from enfortumab vedotin + pembrolizumab compared with the ACT, although the extent of this harm differs.

Probability and extent of added benefit, patient groups with therapeutically important added benefit (research question 1: cisplatin suitable [3]

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

The overall assessment shows both positive and negative effects with different extents for enfortumab vedotin + pembrolizumab compared with the ACT. For mortality, the observed effects refer to the entire observation period. In particular for the outcomes of side effects, however, the observed effects relate to a shortened period and only represent the roughly first 6 months after randomization and thus in the comparator arm only the period of

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

chemotherapy, but not the period of a possible maintenance therapy with avelumab, and in the intervention arm only the first 6 months of a possibly longer-lasting therapy.

The advantage in overall survival is decisive for the assessment, but its extent cannot be quantified, as the results of the main and sensitivity analyses differ in terms of their extent. In addition, there are advantages for individual outcomes of morbidity and health-related quality of life as well as for outcomes in the side effects category, particularly for the overall rate of severe AEs. On the other hand, there are disadvantages in various specific AEs, especially for severe and serious immune-related AEs.

Thereby, the results on side effects only relate to a shortened period of around 6 months. However, since a high proportion of events already occur during this period, the available results show that the advantage in overall survival is not called into question by the results on side effects.

In summary, for adult patients with unresectable or metastatic urothelial carcinoma in the first-line therapy for whom cisplatin-based therapy is suitable, there is a hint of non-quantifiable added benefit of enfortumab vedotin + pembrolizumab compared with the ACT.

Research question 2: Patients for whom cisplatin-based chemotherapy is unsuitable (cisplatin unsuitable)

Risk of bias and certainty of conclusions

The outcome-specific risk of bias was also rated as low for the results on “overall survival”, and as high for all other patient-relevant outcomes.

Summary assessment of the certainty of conclusions

In addition to the described aspects of bias, there are uncertainties for the EV-302/KN-A39 study, particularly with regard to the implementation of the ACT. In the present specific data constellation, the results of the study can nevertheless be interpreted for the research questions of the present benefit assessment, but the certainty of the study results for the present assessment is reduced. Based on the EV-302/KN-A39 study, at most hints, e.g. of an added benefit, can be derived for both research questions.

Moreover, for the outcomes in the side effects category, analyses are only available for a significantly shortened period, which in the comparator arm only reflects the treatment with chemotherapy, but not the period of a possible maintenance therapy with avelumab, and in the intervention arm only takes into account the first 6 months of a possibly longer-lasting treatment. This shortened observation in the comparator arm or consideration of recorded data in the intervention arm contributes to a limited certainty of conclusions and additionally justifies the fact that at most hints can be derived.

Results

Mortality

Overall survival

For the outcome of overall survival, a statistically significant difference was found in favour of enfortumab vedotin + pembrolizumab in comparison with carboplatin + gemcitabine. The 3 sensitivity analyses presented by the company, in which patients in the comparator arm for whom maintenance treatment with avelumab would potentially have been indicated and who died without maintenance treatment were accounted for differently, also showed a statistically significant difference in favour of enfortumab vedotin + pembrolizumab compared with carboplatin + gemcitabine in each case. This effect therefore remains even if the maximum situation is assumed that all these patients in the comparator arm have survived to the present data cut-off. In this data constellation, there is a hint of added benefit of enfortumab vedotin + pembrolizumab in comparison with the ACT. The extent of the added benefit is major both in the main analysis and in all sensitivity analyses.

Morbidity

Worst pain (BPI-SF item 3)

For the outcome of worst pain (recorded using the BPI-SF item 3), a statistically significant difference was found in favour of enfortumab vedotin + pembrolizumab in comparison with carboplatin + gemcitabine. However, there is an effect modification by the characteristic of metastases. For patients with visceral metastases, there was no hint of an added benefit of enfortumab vedotin + pembrolizumab versus the ACT; an added benefit is therefore not proven for this patient group. There was a hint of an added benefit of enfortumab vedotin + pembrolizumab versus the ACT for patients with exclusively lymph node metastases.

Pain interference (BPI-SF item 9a–g)

No suitable data are available for the outcome "pain interference" (recorded using BPI-SF items 9a-9g). There is no hint of an added benefit of enfortumab vedotin + pembrolizumab in comparison with the ACT; an added benefit is therefore not proven.

Symptoms

Fatigue (recorded with the EORTC QLQ-C30)

No statistically significant difference between treatment groups was found for the outcome of fatigue. However, there is an effect modification by the characteristic of sex. For women, there is a hint of added benefit of enfortumab vedotin + pembrolizumab in comparison with the ACT. For men, there is no hint of an added benefit of enfortumab vedotin + pembrolizumab in comparison with the ACT; an added benefit is therefore not proven.

Nausea and vomiting (recorded using EORTC QLQ-C30)

For the outcome of nausea and vomiting, there was a statistically significant difference in favour of enfortumab vedotin + pembrolizumab in comparison with carboplatin + gemcitabine. However, the extent of the effect for this outcome in the category of non-serious/non-severe symptoms was no more than marginal. There is no hint of an added benefit of enfortumab vedotin + pembrolizumab in comparison with the ACT; an added benefit is therefore not proven.

Pain, dyspnoea, insomnia, appetite loss and diarrhoea (each recorded using the EORTC QLQ-C30)

No statistically significant difference between treatment groups was shown for any of the outcomes of pain, dyspnoea, insomnia, appetite loss and diarrhoea. There is no hint of an added benefit of enfortumab vedotin + pembrolizumab in comparison with the ACT; an added benefit is therefore not proven.

Constipation (recorded with the EORTC QLQ-C30)

For the outcome of constipation, a statistically significant difference was found in favour of enfortumab vedotin + pembrolizumab in comparison with carboplatin + gemcitabine. However, there is an effect modification by the characteristic of metastases. For both patients with visceral metastases and patients with exclusively lymph node metastases, there is a hint of added benefit of enfortumab vedotin + pembrolizumab versus the ACT, although the extent differs.

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

No statistically significant difference between treatment groups was shown for the outcome of health status. There is no hint of an added benefit of enfortumab vedotin + pembrolizumab in comparison with the ACT; an added benefit is therefore not proven.

Health-related quality of life

Global health status, physical functioning, cognitive functioning and social functioning (each assessed using the EORTC QLQ-C30)

No statistically significant difference between the treatment groups was shown for any of the outcomes of global health status, physical functioning, cognitive functioning, and social functioning. In each case, there is no hint of an added benefit of enfortumab vedotin + pembrolizumab in comparison with the ACT; an added benefit is therefore not proven for any case.

Role functioning and emotional functioning (recorded using the EORTC QLQ-C30)

A statistically significant difference was neither shown for the outcome of role functioning nor for the outcome of emotional functioning. However, in each case, there is an effect

modification by the characteristic of sex. For women, there is a hint of added benefit of enfortumab vedotin + pembrolizumab in comparison with the ACT. For men, there is no hint of an added benefit of enfortumab vedotin + pembrolizumab in comparison with the ACT; an added benefit is therefore not proven for men.

Side effects

SAEs and discontinuation due to AEs

No statistically significant difference was found between treatment groups for either of the outcomes of SAEs or discontinuation due to AEs. For each of them, there is no hint of greater or lesser harm from enfortumab vedotin + pembrolizumab in comparison with the ACT; greater or lesser harm is therefore not proven.

Severe AEs

For the outcome of severe AEs, a statistically significant difference was found in favour of enfortumab vedotin + pembrolizumab in comparison with carboplatin + gemcitabine. There is a hint of lesser harm from enfortumab vedotin + pembrolizumab in comparison with the ACT.

Immune-related SAEs, immune-related severe AEs, peripheral neuropathy (AEs), skin reactions (AEs) and severe hyperglycaemia (severe AEs)

For each of the outcomes of immune-related SAEs, immune-related severe AEs, peripheral neuropathy (AEs), skin reactions (AEs) and severe hyperglycaemia (severe AEs), a statistically significant difference was found to the disadvantage of enfortumab vedotin + pembrolizumab in comparison with carboplatin + gemcitabine. For each of them, there is a hint of greater harm from enfortumab vedotin + pembrolizumab in comparison with the ACT.

Severe nephrotoxicity (severe AEs)

No statistically significant difference between treatment groups was found for the outcome of severe nephrotoxicity (severe AEs). There is no hint of greater or lesser harm from enfortumab vedotin + pembrolizumab in comparison with the ACT; greater or lesser harm is therefore not proven.

Other specific AEs

Constipation (AEs), blood and lymphatic system disorders (severe AEs)

A statistically significant difference in favour of enfortumab vedotin + pembrolizumab versus carboplatin + gemcitabine was shown for the outcomes of constipation (AEs) and blood and lymphatic system disorders (severe AEs). For each of them, there is a hint of lesser harm from enfortumab vedotin + pembrolizumab in comparison with the ACT.

Diarrhoea (AEs), dysgeusia (AEs), eye disorders (AEs), endocrine disorders (AEs) and acute kidney injury (severe AEs)

A statistically significant difference to the disadvantage of enfortumab vedotin + pembrolizumab versus carboplatin + gemcitabine was shown for each of the outcomes of diarrhoea (AEs), dysgeusia (AEs), eye disorders (AEs), endocrine disorders (AEs) and acute kidney injury (severe AEs). For each of them, there is a hint of greater harm from enfortumab vedotin + pembrolizumab in comparison with the ACT.

Probability and extent of added benefit, patient groups with therapeutically important added benefit (research question 2: cisplatin unsuitable)

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

The overall assessment shows both positive and negative effects with different extents for enfortumab vedotin + pembrolizumab compared with the ACT. For mortality, the observed effects refer to the entire observation period. In particular for the outcomes of side effects, however, the observed effects relate to a shortened period and only represent the roughly first 6 months after randomization and thus in the comparator arm only the period of chemotherapy, but not the period of a possible maintenance therapy with avelumab, and in the intervention arm only the first 6 months of a possibly longer-lasting therapy.

The advantage in overall survival, the extent of which is “major” both in the main analysis and in all sensitivity analyses, is decisive for the assessment. In addition, there are advantages for individual outcomes of morbidity and health-related quality of life as well as for outcomes in the side effects category, particularly for the overall rate of severe AEs. On the other hand, there are disadvantages in various specific AEs, especially for severe and serious immune-related AEs.

Thereby, the results on side effects only relate to a shortened period of around 6 months. However, since a high proportion of events already occur during this period, the available results show that the advantage in overall survival is not called into question by the results on side effects.

In summary, for adult patients with unresectable or metastatic urothelial carcinoma in the first-line therapy for whom cisplatin-based therapy is not suitable, there is a hint of major added benefit of enfortumab vedotin + pembrolizumab compared with the ACT.

Probability and extent of added benefit – summary

Table 3 shows a summary of the probability and extent of the added benefit of enfortumab vedotin + pembrolizumab.

Table 3: Enfortumab vedotin + pembrolizumab – probability and extent of added benefit

Research question	**Therapeutic indication**	**ACT[a]**	**Probability and extent of added benefit**
First-line treatment of adult patients with unresectable or metastatic urothelial carcinoma who are eligible for platinum-containing chemotherapy			
1	For whom cisplatin-based therapy is an option	Cisplatin in combination with gemcitabine followed by avelumab as maintenance therapy (maintenance therapy with avelumab only for progression-free patients[b])	Hint of non-quantifiable added benefit[c]
2	For whom cisplatin-based therapy is not an option[d]	Carboplatin in combination with gemcitabine in accordance with Annex VI to Section K of the Pharmaceutical Directive[e], followed by avelumab as maintenance therapy (maintenance therapy with avelumab only for progression-free patients[b])	Hint of major added benefit[c]

a. Presented is the respective ACT specified by the G-BA.
b. According to the G-BA, it is assumed that patients who are not progression-free following platinum-based chemotherapy will not be treated further as part of first-line treatment.
c. The EV-302/KN-A39 study almost exclusively included patients with an ECOG PS of 0 or 1 (ECOG PS ≥ 2 in the respectively relevant subpopulation: research question 1: 4 [2%] vs. 2 [1%]; research question 2: 11 [5%] vs. 9 [4%]). It remains unclear whether the observed effects are transferable to patients with an ECOG PS ≥ 2.
d. According to the G-BA, it is assumed that the patients in question have an increased risk of cisplatin-induced side effects in the context of a combination therapy (e.g. pre-existing neuropathy or relevant hearing impairment, renal failure, heart failure).
e. With regard to the present indication, this is a use in an unapproved therapeutic indication (off-label use). For the present indication, carboplatin in combination with gemcitabine can be prescribed in off-label use, see Appendix VI to Section K of the Pharmaceutical Directive.

ACT: appropriate comparator therapy; G-BA: Federal Joint Committee

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 enfortumab vedotin in combination with pembrolizumab (hereinafter referred to as enfortumab vedotin + pembrolizumab) in comparison with the ACT for the first-line treatment of adult patients with unresectable or metastatic urothelial carcinoma who are eligible for platinum-containing chemotherapy.

The research questions presented in Table 4 result from the ACT specified by the G-BA.

Table 4: Research questions of the benefit assessment of enfortumab vedotin + pembrolizumab

Research question	Therapeutic indication	ACT[a]
First-line treatment of adult patients with unresectable or metastatic urothelial carcinoma who are eligible for platinum-containing chemotherapy		
1	For whom cisplatin-based therapy is an option	Cisplatin in combination with gemcitabine followed by avelumab as maintenance therapy (maintenance therapy with avelumab only for progression-free patients[b])
2	For whom cisplatin-based therapy is not an option[c]	Carboplatin in combination with gemcitabine in accordance with Appendix VI to Section K of the Pharmaceutical Directive[d], followed by avelumab as maintenance therapy (maintenance therapy with avelumab only for progression-free patients[b])

a. Presented is the respective ACT specified by the G-BA.
b. According to the G-BA, it is assumed that patients who are not progression-free following platinum-based chemotherapy will not be treated further as part of first-line treatment.
c. According to the G-BA, it is assumed that the patients in question have an increased risk of cisplatin-induced side effects in the context of a combination therapy (e.g. pre-existing neuropathy or relevant hearing impairment, renal insufficiency, heart failure).
d. With regard to the present indication, this is a use in an unapproved therapeutic indication (off-label use). For the present indication, carboplatin in combination with gemcitabine can be prescribed in off-label use, see Appendix VI to Section K of the Pharmaceutical Directive.

ACT: appropriate comparator therapy; G-BA: Federal Joint Committee

The company specified cisplatin in combination with gemcitabine (hereinafter cisplatin + gemcitabine) as ACT for research question 1 and carboplatin in combination with gemcitabine (hereinafter carboplatin + gemcitabine) as ACT for research question 2, in each case followed by avelumab as maintenance therapy (maintenance therapy with avelumab only for progression-free patients), and thus followed the G-BA's specification in each case.

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

I 3 Information retrieval and study pool

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

Sources of the company in the dossier:

- study list on enfortumab vedotin (status: 25 July 2024)
- bibliographical literature search on enfortumab vedotin (last search on 25 July 2024)
- search in trial registries/trial results databases for studies on enfortumab vedotin (last search on 22 July 2024)
- search on the G-BA website for enfortumab vedotin (last search on 25 July 2024)

To check the completeness of the study pool:

- search in trial registries for studies on enfortumab vedotin (last search on 17 October 2024); for search strategies, see I Appendix A of the full dossier assessment

The check did not identify any additional relevant study for either question.

Relevance of the study EV-302/KN-A39 (presented by the company) for the benefit assessment

For both research questions, the company identified the RCT EV-302/KN-A39 (SGN22E-003) on the comparison of enfortumab vedotin + pembrolizumab versus platinum-based chemotherapy (cisplatin/carboplatin + gemcitabine). On the basis of this study, the company derived an added benefit of enfortumab vedotin + pembrolizumab versus the ACT.

The comparator therapy in study EV-302/KN-A39 does not represent a full implementation of the G-BA's ACT, as patients in the comparator arm who were progression-free following chemotherapy were not regularly scheduled for maintenance treatment with avelumab according to the study design. However, the results of the study can be interpreted for the present research questions (see Section I 3.2 for an explanation).

I 3.1 Studies included

The study presented in the following Table 5 was included in the benefit assessment for both research questions.

Table 5: Study pool – RCT, direct comparison: enfortumab vedotin + pembrolizumab vs. cisplatin/carboplatin + gemcitabine

Study	Study category			Available sources		
	Study for the approval of the drug to be assessed (yes/no)	Sponsored study[a] (yes/no)	Third-party study (yes/no)	CSR (yes/no [citation])	Registry entries[b] (yes/no [citation])	Publication (yes/no [citation])
SGN22E-003 (EV302/KN-A39[c])	Yes	Yes	No	Yes [3]	Yes [4-6]	Yes [7]

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. In the tables below, the study will be referred to using this acronym.

CSR: clinical study report; RCT: randomized controlled trial

I 3.2 Study characteristics (aspects across research questions)

As the included study EV-302/KN-A39 is relevant for both research questions of the present benefit assessment, characteristics across research questions are described in a superordinate manner in the following. Research question-specific characteristics for research question 1 are described in Section I 5.1, and those for research question 2 are described in Section I 5.1 of the full benefit assessment.

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

Table 6: Characteristics of the included study – RCT, direct comparison: enfortumab vedotin + pembrolizumab vs. cisplatin/carboplatin + gemcitabine (multipage table)

Study	Study design	Population	Interventions (number of randomized patients)	Study duration	Location and period of study	Primary outcome; secondary outcomes[a]
EV-302/ KN-A39	RCT, open-label, parallel	Adult patients (≥ 18 years) with previously untreated[b] unresectable locally advanced or metastatic urothelial carcinoma[c] ▪ patients for whom platinum-based chemotherapy[d] is an option ▪ ECOG PS ≤ 2[e]	Enfortumab vedotin + pembrolizumab (N = 442) cisplatin/carboplatin [d] + gemcitabine (N = 444) pembrolizumab + enfortumab vedotin + cisplatin/carboplatin (N = 11)[f] relevant subpopulations thereof: <u>research question 1 (cisplatin suitable)</u>[g] enfortumab vedotin + pembrolizumab (N = 240) cisplatin + gemcitabine (N = 242) <u>research question 2 (cisplatin unsuitable)</u>[g] enfortumab vedotin + pembrolizumab (N = 202) carboplatin + gemcitabine (N = 202)	Screening: 42 days treatment: until disease progression, unacceptable toxicity, investigator's decision, patient request, start of subsequent therapy, end of study or a maximum of 6 cycles of cisplatin/carboplatin + gemcitabine[h] or 35 cycles of pembrolizumab observation[i]: outcome-specific, at most until death, discontinuation of participation in the study or end of study	183 study centres in Argentina, Australia, Belgium, Canada, China, Czech Republic, Denmark, France, Germany, Hungary, Israel, Italy, Japan, Netherlands, Poland, Russia, Singapore, South Korea, Spain, Switzerland, Taiwan, Thailand, Turkey, United Kingdom, USA 03/2020–ongoing data cut-offs: 08 August 2023 (interim analysis)[j] 06 September 2024 (final OS data cut-off[k]	Primary: overall survival, PFS secondary: morbidity, health-related quality of life, AEs

Table 6: Characteristics of the included study – RCT, direct comparison: enfortumab vedotin + pembrolizumab vs. cisplatin/carboplatin + gemcitabine (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 include only information on relevant available outcomes for this benefit assessment.
b. No previous systemic therapy of locally advanced/metastatic urothelial carcinoma other than adjuvant or neoadjuvant chemotherapy, provided the recurrence occurred > 12 months after completion of this therapy.
c. Histologically confirmed cancer of the urinary bladder, renal pelvis, ureters or urethra; squamous or sarcomatoid differentiation or mixed cell types were permitted. According to the investigator's assessment, the disease had to be measurable in accordance with RECIST v1.1.
d. Prior to randomization, the investigator assessed whether treatment with cisplatin or carboplatin was suitable for a patient on the basis of criteria defined in the protocol.
e. The following criteria had to be met for an ECOG PS of 2: haemoglobin ≥ 10 g/dL, GFR ≥ 50 mL/min and no NYHA class III heart failure.
f. Initially, 3 treatment arms had been planned in the study (arm A: enfortumab vedotin + pembrolizumab; arm B: cisplatin/carboplatin + gemcitabine; arm C: enfortumab vedotin + pembrolizumab + cisplatin/carboplatin). Treatment arm C was terminated with protocol amendment 2 of 12 August 2020 due to new clinical findings. A total of 11 patients had been assigned to treatment with enfortumab vedotin + pembrolizumab + cisplatin/carboplatin before this arm was closed for enrolment. This study arm is not relevant for the benefit assessment and is no longer presented hereinafter.
g. Cisplatin was considered unsuitable for patients who met at least one of the following criteria: (1) GFR < 60 mL/min but ≥ 30 mL/min (as measured by the Cockcroft-Gault formula, MDRD or 24-hour urine; at the investigator's discretion, patients could be rated as eligible for cisplatin if they had a GFR ≥ 50 mL/min and did not fulfil any of the other criteria); (2) ECOG PS of 2; (3) audiometric hearing loss (CTCAE grade ≥ 2); (4) NYHA class III heart failure. Patients with persistent sensory or motor neuropathy with grade 2 or higher were excluded from the study.
h. Following platinum-based chemotherapy, maintenance treatment with avelumab was possible for progression-free patients in accordance with the current SPC and the investigator's assessment, provided the drug was locally available.
i. Outcome-specific information is provided in Table 9.
j. The interim analysis (final PFS analysis) was planned for the time point at which 526 PFS events or 356 deaths had occurred, whichever occurred later. At the time of the data cut-off, 359 OS events had occurred. In the event of statistical significance of the results on overall survival, this data cut-off was pre-specified as the final analysis of overall survival.
k. A final OS analysis was planned for the time point at which 489 deaths had occurred if the OS (final PFS analysis) was not significant in the framework of the interim analysis. Although the results on overall survival had already been significant at the 1st data cut-off, this data cut-off was requested by the FDA [8] and conducted [9]. According to the FDA, the results are expected to be available in April 2025.

AE: adverse event; CTCAE: Common Terminology Criteria for Adverse Events; ECOG PS: Eastern Cooperative Oncology Group Performance Status; GFR: glomerular filtration rate; MDRD: modification of diet in renal disease; n: relevant subpopulation; N: number of randomized patients; NYHA: New York Heart Association; PFS: progression-free survival; RCT: randomized controlled trial; RECIST: Response Evaluation Criteria In Solid Tumours

Table 7: Characteristics of the intervention – RCT, direct comparison: enfortumab vedotin + pembrolizumab vs. cisplatin/carboplatin + gemcitabine (multipage table)

Study	Intervention	Comparison
EV-302/KN-A39	Enfortumab vedotin 1.25 mg/kg (at most 125 mg) IV, on Days 1 and 8 of a 21-day cycle + pembrolizumab 200 mg IV on Day 1 of a 21-day cycle over a maximum of 35 cycles	Platinum-based chemotherapy for a maximum of 6 cycles[a]: cisplatin 70 mg/m^2 BSA, IV, Day 1 of a 21-day cycle, or carboplatin AUC of 4.5 or 5 mg/mL/min, IV, Day 1 of a 21-day cycle + gemcitabine 1000 mg/m^2 BSA, IV, on Days 1 and 8 of a 21-week cycle
	Dose adjustment: ▪ enfortumab vedotin: dose reductionb to 1 mg/kg or 0.75 mg/kg or dose interruption permitted in case of toxicity ▪ pembrolizumab: no dose adjustment allowed; interruption allowed in case of toxicity	▪ platinum-based chemotherapy: dose reduction by 25% or dose interruption permitted in case of toxicity ▪ gemcitabine: dose adjustments allowed according to SPC or institutional standard
	Allowed pretreatment ▪ definitive radiotherapy, provided that measurable disease according to RECIST v1.1 outside the radiotherapy field or clear progression of the disease was present after completion of radiotherapy **disallowed pretreatment** ▪ no previous systemic therapy of locally advanced or metastatic urothelial carcinomac ▪ enfortumab vedotin or other MMAE-based antibody-drug conjugates ▪ PD-1 or PD-L1 inhibitors (including atezolizumab, pembrolizumab, nivolumab, durvalumab, avelumab) for the treatment of any cancer, including early-stage urothelial carcinoma ▪ any therapy targeting another stimulating or co-inhibitory T-cell receptor (including CD137 agonists, CTLA-4 inhibitors or OX-40 agonists) ▪ any anti-cancer therapy with chemotherapeutic agents, biologics or investigational products < 4 weeks before the start of the study **allowed concomitant treatment** ▪ surgical resection with curative intent ▪ antiemetics, G-CSF (from Day 9 of a cycle), insulin, CYP3A4 inhibitors, p-glycoprotein inhibitors, vaccines[d], antimicrobial agents ▪ appropriate pre- and post-hydration in the comparator arm ▪ premedication for the treatment of infusion-related reactions ▪ haematopoietic growth factors and transfusionse ▪ long-term use of prednisone or equivalent (≤ 10 mg/day); long-term use of or topical steroids[f] **disallowed concomitant treatment** ▪ systemic antineoplastic therapyg ▪ any other immunotherapy, chemotherapy, investigational products, radiotherapyh ▪ live vaccinesd	

Table 7: Characteristics of the intervention – RCT, direct comparison: enfortumab vedotin + pembrolizumab vs. cisplatin/carboplatin + gemcitabine (multipage table)

Study	Intervention	Comparison
a. Includes cisplatin-containing or carboplatin-containing chemotherapy. Prior to randomization, the investigator assessed whether treatment with cisplatin was suitable for the patient based on the following criteria defined in the protocol: renal insufficiency (GFR ≥ 30 < 60 mL/min), CTCAE grade ≥ 2 audiometric hearing loss, ECOG PS of 2 and/or NYHA class III heart failure. Patients with persistent sensory or motor neuropathy with grade 2 or higher were excluded from the study. Following platinum-based chemotherapy, maintenance treatment with avelumab was possible for progression-free patients in accordance with the current SPC and the investigator's assessment, provided the drug was locally available. b. After a necessary dose reduction, a re-escalation by one dose level was permitted (i.e. a dose reduction to 0.75 mg/kg permitted re-escalation to 1 mg/kg) provided that the toxicity that occurred did not require interruption of the study medication and this again corresponded to the baseline value or a CTCAE grade ≤ 1. If the toxicity occurred again, a new escalation was not permitted. Re-escalation was not permitted for corneal toxicity with CTCAE grade ≥ 2. c. With the following exceptions: neoadjuvant chemotherapy with recurrence > 12 months after completion of therapy, or adjuvant chemotherapy after a cystectomy with recurrence > 12 months after completion of therapy. d. No live vaccines ≥ 30 days before randomization and up to 90 days after the last dose of the study medication. e. For the treatment of enfortumab vedotin-related toxicity. f. Only for patients in the pembrolizumab arm. An increased dose of prednisone (or equivalent) was permitted provided that its use was limited to the time required to treat an acute condition. g. With the exception of adjuvant hormonal therapy for the treatment of local breast or prostate cancer that has already been definitively treated. h. Palliative radiotherapy for the treatment of stable symptomatic non-target bone lesions was permitted. AUC: area under the curve; BSA: body surface area; CTCAE: Common Terminology Criteria for Adverse Events; CTLA-4: cytotoxic T-lymphocyte-associated protein 4; CYP: cytochrome P450; ECOG PS: Eastern Cooperative Oncology Group - Performance Status; G-CSF: granulocyte colony-stimulating factor; IV: intravenous; MMAE: monomethyl auristatin E; PD-1: programmed cell death 1; PD-L1: programmed cell death ligand 1; RCT: randomized controlled trial; RECIST: Response Evaluation Criteria in Solid Tumours		

I 3.2.1 Study design

The EV-302/KN-A39 study is an ongoing, multicentre, open-label RCT comparing enfortumab vedotin + pembrolizumab versus platinum-based chemotherapy (cisplatin/carboplatin + gemcitabine) in the first-line treatment of adult patients with unresectable or metastatic urothelial carcinoma who are eligible for platinum-based chemotherapy. Patients with histologically confirmed urothelial carcinoma of the urinary bladder, the renal pelvis, the ureter or the urethra were included in the study, whereby squamous or sarcomatoid cell differentiation or mixed cell types were also permitted. On study inclusion, patients had to have an ECOG PS ≤ 2 and were not allowed to have received prior systemic therapy for the treatment of the advanced or metastatic urothelial carcinoma. Prior neoadjuvant chemotherapy or adjuvant chemotherapy after cystectomy each with recurrence > 12 months after completion of the therapy was allowed. Patients with active metastases of the central nervous system were excluded; no data are available for them.

Cisplatin eligibility was assessed prior to randomization. Cisplatin was considered unsuitable for patients who fulfilled at least one of the following criteria:

- GFR < 60 mL/min, but ≥ 30 mL/min
  - at the investigator's discretion, patients could be classified as suitable for cisplatin if they had a GFR ≥ 50 mL/min and did not fulfil any of the other criteria
- ECOG PS or WHO performance status of 2
- audiometric hearing loss according to CTCAE grade ≥ 2
- cardiac failure according to NYHA class III

Patients for whom cisplatin was not suitable according to these criteria were assigned to treatment with carboplatin + gemcitabine in case of randomization to the comparator arm of the study. Patients with persistent sensory or motor neuropathy with CTCAE grade 2 or higher were excluded from the study. Thus, the criteria used to assess cisplatin eligibility in the context of the EV-302/KN-A39 study correspond to the specifications of the current S3 guideline [10].

The study included a total of 886 patients who were randomly assigned in a 1:1 ratio to treatment with enfortumab vedotin + pembrolizumab (N = 442) or cisplatin/carboplatin + gemcitabine (N = 444). Treatment with cisplatin was assessed as suitable in a total of 482 patients (intervention arm: n = 240, comparator arm: n = 242) and as unsuitable in a total of 404 patients (intervention and comparator arm: n = 202 each). Randomization was stratified by cisplatin eligibility (suitable or unsuitable), PD-L1 expression (CPS ≥ 10 or < 10) and liver metastases (present or absent). The stratification factor “cisplatin eligibility” corresponds to the subdivision into the relevant subpopulations for research question 1 (cisplatin suitable) and research question 2 (cisplatin unsuitable) of the present dossier assessment.

Treatment with enfortumab vedotin + pembrolizumab in the intervention arm was largely in compliance with the requirements of the respective SPC [11,12]. Treatment with enfortumab vedotin was not time-limited in the study. Treatment took place until disease progression, the occurrence of further criteria for discontinuation of treatment (e.g. start of a new anti-cancer therapy, unacceptable toxicities, withdrawal of consent) or the end of the study, whichever came first. In contrast, treatment with pembrolizumab was limited to a maximum treatment duration of 35 cycles (approx. 24 months), in deviation from the specifications of the SPC. According to the SPC, pembrolizumab treatment is to be continued until cancer progression or the occurrence of unacceptable toxicity [12]. In the EV-302/KN-A39 study, however, only 8 (2%) patients in the total population in the intervention arm had achieved the 35 treatment cycles at the data cut-off presented. Due to the small number of affected patients, it is not

assumed that the restriction to a maximum of 35 treatment cycles with pembrolizumab represents a relevant limitation of the treatment.

However, there are various uncertainties regarding the treatment in the comparator arm of the study, which are described in the following Section I 3.2.2 and Section I 3.2.3.

Co-primary outcomes of the EV-302/KN-A39 study were overall survival and PFS. Other patient-relevant outcomes were outcomes on morbidity, health-related quality of life and side effects.

I 3.2.2 Treatment in the comparator arm of study EV-302/KN-A39

Treatment with cisplatin/carboplatin + gemcitabine

Treatment in the comparator arm was with cisplatin/carboplatin + gemcitabine according to the regimens described in Table 7. Treatment with carboplatin + gemcitabine is not approved for patients who are not eligible for cisplatin-based therapy. However, it can be prescribed in accordance with Annex VI to Section K of the Pharmaceutical Directive [13]. The use of carboplatin + gemcitabine essentially complied with the specifications of Annex VI to Section K of the Pharmaceutical Directive. For the treatment with cisplatin + gemcitabine, however, there are deviations from the SPC, which are described below.

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

In the present therapeutic indication, the SPC 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 days 1, 8 and 15 of a cycle [14]. In accordance with the SPC, 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 [14].

In the EV-302/KN-A39 study, the cycle length was 21 days with administration of 1000 mg/m² gemcitabine on cycle days 1 and 8. The cycle length for cisplatin + gemcitabine therefore does not correspond to the approval. As a result, the dose per cycle or the cumulative dose relating to gemcitabine is lower than stipulated in the approval, while relating to cisplatin, the dose is administered at shorter intervals.

Overall, it is unclear how this deviation affects the results of patient-relevant outcomes. In the present situation, this uncertainty does not fundamentally challenge the relevance of study EV-302/KN-A39 for the present benefit assessment, but contributes to a reduced certainty of conclusions (see Section I 4.2.3).

Maximum number of treatment cycles with cisplatin + gemcitabine

In the comparator arm of the EV-302/KN-A39 study, treatment with cisplatin + gemcitabine was limited to a maximum treatment duration of 6 cycles, in deviation from the specifications

in the SPC. However, the SPC does not specify any fixed upper limit for the number of treatment cycles [14,15]. In the total population of the EV-302/KN-A39 study, patients in the comparator arm received a median (first quartile [Q1]; third quartile [Q3]) of 6 [4; 6] cycles of cisplatin/carboplatin + gemcitabine. The current national S3 guideline does not include a recommendation regarding the duration of treatment with cisplatin + gemcitabine [10]; the ESMO guideline recommends 4 to 6 cycles of platinum-based chemotherapy in this therapeutic indication [16]. Therefore, it is assumed for the present benefit assessment that the limitation of treatment with cisplatin + gemcitabine to a maximum of 6 cycles does not represent a relevant restriction of study EV-302/KN-A39.

Possibility of a single treatment switch between cisplatin and carboplatin

In the comparator arm of study EV-302/KN-A39, a single treatment switch from cisplatin to carboplatin (in the event of acute renal impairment that had not subsided during treatment with cisplatin) or from carboplatin to cisplatin (in the event of improvement in performance status or renal function to such an extent that cisplatin-containing therapy was an option) was permitted at the investigator's discretion. A switch due to lack of response or due to progression of the disease was not permitted in either case.

According to the ACT specified by the G-BA, switching from cisplatin to carboplatin or from carboplatin to cisplatin was not planned. There is no concrete information available on how many patients switched treatment from cisplatin to carboplatin or from carboplatin to cisplatin. In the present situation, however, it is assumed that a corresponding treatment switch occurred in a small proportion of patients at most, so that in the present situation it is not assumed that this represents a relevant deviation from the G-BA’s ACT.

I 3.2.3 Implementation of the ACT: maintenance therapy with avelumab not part of the study medication

The G-BA specified treatment with cisplatin + gemcitabine (research question 1) or carboplatin + gemcitabine (research question 2) as ACT for adult patients with unresectable or metastatic urothelial carcinoma in the first line for whom platinum-containing chemotherapy is an option. As specified by the G-BA, patients who are progression-free after chemotherapy are to receive maintenance treatment with avelumab. In the comparator arm of the EV-302/KN-A39 study, however, maintenance treatment with avelumab was not regularly planned according to the study design for patients who were progression-free following chemotherapy. However, maintenance therapy with avelumab could be used after completion or discontinuation of platinum-containing chemotherapy according to the investigator's assessment and depending on local availability.

According to the company's information in Module 4 A, only 34.7% (research question 1) or 23.8% (research question 2) of patients in the comparator arm of the respective relevant

subpopulation received maintenance treatment with avelumab in the EV-302/KN-A39 study (see Table 8). Overall, this does initially not represent an adequate implementation of the G-BA's ACT.

However, in Module 4 A of its dossier, the company provided further information on the use of avelumab in the EV-302/KN-A39 study. Based on the information provided by the company, a distinction can be made between the following 3 groups of patients:

1) Patients for whom maintenance treatment with avelumab was possible according to the company and who received avelumab
2) Patients for whom maintenance treatment with avelumab was not possible according to the company
3) Patients for whom maintenance treatment with avelumab was possible according to the company and who nevertheless did not receive avelumab

The company's information on the proportion of these 3 groups of patients in the comparator arm of the respective subpopulation is shown in Table 8 and was supplemented by the Institute's calculations.

Table 8: Information on the implementation of maintenance therapy with avelumab in the EV-302/KN-A39 study (data cut-off 1) according to the company's information in Module 4 A

Study characteristic category	Cisplatin + gemcitabine N = 242[a]	Carboplatin + gemcitabine N = 202[b]
EV-302/KN-A39		
Maintenance therapy with avelumab possible according to company and avelumab received[c], n (%)	84 (34.7)	48 (23.8)
Maintenance therapy with avelumab not possible according to the company, n (%)	83 (34.3)[d]	101 (50.0)[d]
Lost to follow-up	1 (0.4)	1 (0.5)
< 4 cycles of platinum-based chemotherapy completed	13 (5.4)	22 (10.9)
Disease progression or death[e], of which	69 (28.5)	78 (38.6)
During chemotherapy	60 (24.8)	63 (31.2)
Within 10 weeks after last dose	9 (3.7)	15 (7.4)
Maintenance therapy with avelumab possible according to company, but nevertheless avelumab not received, n (%)	69 (28.5)[d]	48 (23.8)[d]
Avelumab not received and alive[f]	48 (19.8)	30 (14.9)
Avelumab not received and deceased	21 (8.7)	18 (8.9)

a. 236 of the 242 (97.5%) patients received platinum-based chemotherapy.
b. 197 of the 202 (97.5%) patients received platinum-based chemotherapy.
c. After completion of chemotherapy.
d. Institute's calculation.
e. During chemotherapy or within 10 weeks after chemotherapy.
f. Chemotherapy completed and alive at the time of data cut-off 1.

n: number of patients in the category; N: number of randomized patients

According to the company, the G-BA's ACT had not been implemented in all patients who either received maintenance treatment with avelumab or for whom this was not possible for justified reasons. According to the company, these are 167/242 (69%) patients for research question 1, and for research question 2 149/202 (74%) patients of the comparator arm of the respective relevant subpopulation (Institute's calculation based on the company's data). These data are largely appropriate. However, the information provided by the company also shows that a relevant proportion of patients did not receive maintenance treatment with avelumab, although this would have been possible and thus also indicated according to the company's information (research question 1: 69/242 [29%], research question 2: 48/202 [24%]).

In Module 4 A of its dossier, the company argues that the EV-302/KN-A39 study is nevertheless suitable for deriving the added benefit of enfortumab vedotin + pembrolizumab. It cites the following reasons for this:

- Firstly, the chemotherapy component of the ACT in the form of platinum-containing chemotherapy was adequately implemented in the two subpopulations relevant for research questions 1 and 2.
- Secondly, maintenance therapy with avelumab was not excluded from the start of the study in accordance with the study design, although the approval of maintenance therapy with avelumab was only granted during the course of the study. In amendment 4 to the study protocol, it was concretized and specified that maintenance therapy with avelumab could be used after completion or discontinuation of platinum-containing chemotherapy in accordance with the current SPC and depending on the investigator's assessment and local availability.
- In addition, the company subdivided patients for whom maintenance therapy with avelumab was possible and who nevertheless did not receive avelumab into 2 groups: patients who had already died at the present data cut-off and those who survived. According to this, 48/69 (70%) patients in research question 1 and 30/48 (63%) patients in research question 2 in this group were still alive and had thus achieved the best possible result for the outcome of overall survival at this data cut-off. This means that even with avelumab maintenance therapy, these patients would not have been able to achieve a better result for the outcome of overall survival.

The company's argumentation and its approach of presenting information on the proportion of patients for whom maintenance therapy with avelumab was eligible according to its assessment and in whom it was either implemented or not implemented is basically suitable for assessing the interpretability of the results of the EV-302/KN-A39 study for the benefit assessment. However, there are several points regarding the subdivision that require comment.

Definition of the possibility of maintenance therapy with avelumab

According to the SPC, freedom from progression after platinum-based chemotherapy is the only prerequisite for maintenance therapy with avelumab [17]. However, the company assumes that maintenance treatment with avelumab was also not possible in patients who had completed < 4 cycles of platinum-based chemotherapy or in whom disease progression or death had occurred within 10 weeks of the last dose of chemotherapy. The company justified this restriction of the possibility of maintenance therapy with avelumab on the basis of the inclusion criteria of the RCT JAVELIN Bladder 100 [18,19], which was the main evidence on which the approval of avelumab as maintenance therapy in the therapeutic indication was based [20] and which was also used for the benefit assessment of avelumab [21].

According to the inclusion criteria of the RCT JAVELIN Bladder 100, the following requirements for the use of avelumab applied, which go beyond the specifications of the SPC:

- received 4 to 6 cycles of chemotherapy with cisplatin/carboplatin + gemcitabine
- 4 to 10 weeks have passed since the administration of the last dose of chemotherapy

The use of at least 4 cycles of chemotherapy with cisplatin/carboplatin + gemcitabine before starting maintenance therapy with avelumab is in line with current guideline recommendations [16].

With regard to the patients in the EV-302/KN-A39 study with disease progression or death within 10 weeks after the last dose of chemotherapy, the company did not provide any information on the time at which the respective events occurred within this time window. The SPC does not specify a time window or point in time after completion of chemotherapy at which maintenance therapy with avelumab is to be started. According to the SPC, it would therefore also be possible to start maintenance treatment with avelumab immediately after completion of platinum-based chemotherapy if there is no progression [17]. The time window in the JAVELIN Bladder 100 approval study was defined as 4 to 10 weeks after receipt of the last dose of chemotherapy, so that even according to this definition a use of avelumab earlier than 10 weeks after the last dose of chemotherapy would have been possible. Due to the fact that the company defined 10 weeks as the maximum possible time for the period of 4 to 10 weeks specified in the JAVELIN Bladder 100 study, it is unclear in how many patients with disease progression or death within 10 weeks of the last dose of chemotherapy would have been able to receive maintenance treatment with avelumab earlier, from which they would have potentially benefited. However, since this criterion of the company only applies to 3.7% of the subpopulation relevant for research question 1 and 7.4% of the subpopulation relevant for research question 2, this aspect only plays a subordinate role overall.

Lack of information on the use of avelumab

In its argumentation, the company assumes that the G-BA's ACT in the EV-302/KN-A39 study was implemented, among others, in patients in whom maintenance therapy was possible according to the company's criteria and who received avelumab. However, avelumab was not part of the study medication, but could be used after completion or discontinuation of platinum-containing chemotherapy according to the investigator's assessment and depending on local availability. Following the start of the study on 30 March 2020 and the approval of avelumab in the European Union on 21 January 2021 [22], Amendment 4 to the study protocol on 11 November 2021 explicitly described the possibility of maintenance therapy with avelumab (at the investigator's discretion and subject to local availability); Amendment 7 of 30 November 2022 specified that avelumab should be used in accordance with the local SPC. However, there was a lack of specific information on the use of avelumab, particularly prior to the amendment of 30 November 2022. It is unclear whether the requirements of the SPC for avelumab applicable in Germany, for example on dosage, were complied with. There is also no information available on the time point at which maintenance therapy with avelumab

was started after completion of chemotherapy. It is therefore also unclear for patients who have received avelumab whether earlier use of maintenance therapy with avelumab would have been possible and whether they would have benefited from it.

Patients who did not receive avelumab and died

With regard to patients for whom maintenance treatment with avelumab was an option according to the company, but who did not receive avelumab and died, the company presented 3 sensitivity analyses to address the consequences of the lack of implementation of the ACT for the outcome of overall survival in these patients. These analyses are described in Section I 5.2.1 and are overall considered appropriate to address this point in respect of the outcome of overall survival, so that no additional uncertainty arises.

Conclusion and consequences for the benefit assessment

With regard to maintenance therapy with avelumab, implementation of the ACT was overall incomplete in the EV-302/KN-A39 study, as the information provided by the company shows that only 69% of patients for research question 1 and 74% of patients for research question 2 either received maintenance therapy with avelumab or were not eligible for such therapy. A relevant proportion of patients in the respective relevant subpopulation did not receive maintenance treatment with avelumab, although this would have been possible according to the company's information (research question 1: 69/242 [29%]; research question 2: 48/202 [24%], see Table 8; Institute's calculation). In addition, as described in the previous sections, there are various uncertainties with regard to the data presented by the company.

The results of study EV-302/KN-A39 can be interpreted on the basis of the information presented by the company on the implementation of maintenance therapy with avelumab and the associated sensitivity analyses on the outcome of overall survival despite the uncertainties described for research questions 1 and 2 of the present benefit assessment. The consequences resulting from the incomplete implementation of the ACT were examined at outcome level and described in Section I 5.2.1.

However, the informative value of the study is limited, particularly due to the incomplete implementation of maintenance therapy with avelumab. In addition, the deviations from the SPC described above for treatment with cisplatin + gemcitabine in the comparator arm contribute to the limitation of the certainty of the results in research question 1. Therefore, at most hints, e.g. of an added benefit, can be determined on the basis of the EV-302/KN-A39 study for both research questions of the present dossier assessment for all outcomes.

I 3.2.4 Relevance of the Chinese cohort

The documents of the EV-302/KN-A39 study presented in the company's dossier comprise the data of 886 globally recruited patients. These patients were recruited in accordance with the

study design and are included in the presented data cut-off. In addition, Protocol Amendment 6 of 12 April 2022 provided for the recruitment of further patients in China, which was to be continued after completion of the recruitment phase for the global cohort. This Chinese cohort was to include a total of 130 patients, 2 of whom were already included in the 886 globally recruited patients. Only the data of these 2 patients were considered in the present benefit assessment. The company did not provide any data on the 128 other patients in the Chinese cohort. The Chinese cohort is to be analysed separately from the global cohort in accordance with the study planning. There is no indication in the company's dossier as to whether the Chinese cohort has already been analysed.

The patients in the Chinese cohort represent a relevant subpopulation for the present benefit assessment. However, the proportion of the additional 128 patients of the Chinese cohort in the total number of both cohorts (1014 patients in total) is only 13%. In addition, in accordance with the study protocol, the recruitment of additional patients into the Chinese cohort should only begin after the end of recruitment into the global cohort. As recruitment to the global cohort was only completed on 5 October 2022 [23], it is assumed that analyses of the Chinese cohort are still pending. Therefore, the non-consideration of the Chinese cohort has no consequences for the present benefit assessment.

I 3.2.5 Data cut-offs

Two data cut-offs were performed for study EV-302/KN-A39:

- 1st data cut-off of 8 August 2023: planned for the time at which 526 PFS events or 356 deaths had occurred, depending on which event occurred later. At the time of the data cut-off, 359 deaths had occurred. If the results on overall survival were statistically significant, this data cut-off was pre-specified as the final analysis of overall survival, otherwise as interim analysis of overall survival.
- 2nd data cut-off of 6 September 2024 (see information in the parallel benefit assessment A24-99 of pembrolizumab in combination with enfortumab vedotin [9]): planned for the time point at which 489 deaths had occurred, provided overall survival was not significant at the time of the 1st data cut-off. Although the results on overall survival had already been significant at the 1st data cut-off, this data cut-off was requested by the FDA [8] and conducted [9]. According to the FDA, the results are expected to be available in April 2025.

For its assessment in Module 4 A, the company used the results of the prespecified first data cut-off dated 8 August 2023. The 2nd data cut-off is not mentioned by the company. However, it can be assumed that no results are currently available for this data cut-off. The data of the first data cut-off were used for the present benefit assessment.

I 3.2.6 Planned duration of follow-up observation

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

Table 9: Planned duration of follow-up observation – RCT, direct comparison: enfortumab vedotin + pembrolizumab vs. cisplatin/carboplatin + gemcitabine

Study **outcome category** **outcome**	**Planned follow-up observation**
EV-302/KN-A39	
Mortality	
Overall survival	Until death, loss to follow-up, withdrawal of consent or end of study[a] (whichever occurred first)
Morbidity	
Symptoms (BPI-SF; EORTC QLQ-C30)	Until death, loss to follow-up, withdrawal of consent or end of study[a] (whichever occurred first)[b]
Health status (EQ-5D VAS)	Until death, loss to follow-up, withdrawal of consent or end of study[a] (whichever occurred first)[b]
Health-related quality of life	
EORTC QLQ-C30	Until death, loss to follow-up, withdrawal of consent or end of study[a] (whichever occurred first)[b]
Side effects	
AEs/severe AEs[c]	30 days after the last study treatment
SAEs	90 days after the last study treatment in the intervention arm or 30 days after the last study treatment in the comparator arm, and in the intervention arm after discontinuation of treatment, if a subsequent antineoplastic therapy was started

a. According to the study plan, the study was to end at the latest 5 years after the last patient has been included or when no patient remained in the follow-up observation. The sponsor may terminate the study at any time.
b. Presented is the planned duration of follow-up observation according to the study design; according to the information in Module 4 A, patients who had not experienced a first deterioration since the start of the study before the initiation of subsequent antineoplastic therapy were censored on the date of the last available recording of the outcome. It is unclear whether this censoring scheme was predefined.
c. Operationalized as CTCAE grade ≥ 3.

AE: adverse event; BPI-SF: Brief Pain Inventory-Short Form; CTCAE: Common Terminology Criteria for Adverse Events; EORTC QLQ-C30: European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30; RCT: randomized controlled trial; SAE: serious adverse event; VAS: visual analogue scale

It is generally positive to note that, in accordance with the study design, the outcomes on symptoms, health status and health-related quality of life in the EV-302/KN-A39 study, as well as overall survival, were to be observed beyond disease progression until the end of the study.
b. However, according to the information in Module 4 A, patients who had not experienced a

first deterioration since the start of the study before the initiation of subsequent antineoplastic therapy were censored on the date of the last available recording of the outcome. There is no information on whether this censoring scheme was predefined. Regardless of the planned observation period, the actual observation periods for these outcomes were shortened (see information on the course of the study in Section I 5.1.2).

The monitoring periods for the outcomes on side effects were systematically shortened, because they were only recorded for the time of treatment with the study medication (plus 30 days, or 90 days for SAEs in the intervention arm).

Drawing a reliable conclusion on the total study period or the time to patient death, however, would require surveying these outcomes for the total period, as was done for survival.

I 4 Research question 1: Patients for whom cisplatin-based therapy is suitable (cisplatin suitable)

I 4.1 Study characteristics (specific to research question 1)

For characteristics across research questions of the EV-302/KN-A39 study, including information on the study design, treatment in the comparator arm, comments on the implementation of the ACT, relevance of the Chinese cohort, data cut-offs and on the planned duration of follow-up observation, see Section I 4.2.

I 4.1.1 Patient characteristics

Table 10 shows the characteristics of the patients in the subpopulation of the included study relevant for research question 1.

Table 10: Characteristics of the study population as well as study/treatment discontinuation – RCT, direct comparison: enfortumab vedotin + pembrolizumab vs. cisplatin + gemcitabine (subpopulation: cisplatin suitable) (multipage table)

Study characteristic category	Enfortumab vedotin + pembrolizumab N = 240	Cisplatin + gemcitabine N = 242
EV-302/KN-A39		
Age [years], mean (SD)	65 (9)	65 (9)
Sex [F/M], %	18/83	24/76
Region		
Europe	98 (41)	102 (42)
North America	57 (24)	51 (21)
Rest of the world[a]	85 (35)	89 (37)
ECOG PS at baseline, n (%)		
0	136 (57)	128 (53)
1	100 (42)	111 (46)
2	4 (2)	2 (1)
Unknown	0 (0)	1 (< 1[b])
Renal function [CrCl in mL/min[c]], n (%)		
Normal [> 90]	78 (33)	82 (34)
Slightly reduced [≥ 60 to < 90]	116 (48)	122 (50)
Moderately reduced [≥ 30 to < 60]	46 (19)	38 (16)
Strongly reduced [≥ 15 to < 30]	0 (0)[b]	0 (0)[b]
PD-L1 status at baseline [CPS], n (%)		
< 10	101 (42)	102 (42)
≥ 10	139 (58)	140 (58)

Table 10: Characteristics of the study population as well as study/treatment discontinuation – RCT, direct comparison: enfortumab vedotin + pembrolizumab vs. cisplatin + gemcitabine (subpopulation: cisplatin suitable) (multipage table)

Study characteristic category	Enfortumab vedotin + pembrolizumab N = 240	Cisplatin + gemcitabine N = 242
Primary origin of disease[d]		
Upper urinary tract (kidneys, renal pelvis, ureter)	61 (25)	49 (20)
Lower urinary tract (urinary bladder, urethra)	177 (74)	193 (80)
Unknown	2 (1[b])	0 (0)
Disease duration: time between diagnosis of locally advanced or metastatic disease and randomization [months], median [Q1; Q3]	ND[e]	ND[e]
Liver metastases, n (%)	48 (20)	48 (20)
Metastasis category at baseline, n (%)		
Visceral metastases	170 (71)	161 (67)
Exclusively lymph node metastases	60 (25)	67 (28)
No category applicable	10 (4)	14 (6)
Treatment discontinuation, n (%)[f]	ND[f]	ND[f]
Study discontinuation, n (%)[g]	ND[g]	ND[g]

a. Rest of the world includes Argentina, Australia, China, Israel, Japan, Russia, Singapore, South Korea, Taiwan, Thailand and Turkey.
b. Institute's calculation.
c. The CrCl was calculated using the Cockcroft-Gault formula based on the last measured creatinine level before intake of the first dose of the study medication.
d. In relation to the total population of the study, the primary origin of the disease was predominantly the urinary bladder (67% vs. 74%) or the renal pelvis (20% vs. 15%); for the relevant subpopulation, only the summarized data shown in the table are available.
e. Data on the disease duration are not available for the relevant subpopulation; in relation to the total study population, the time between diagnosis of locally advanced or metastatic disease and randomization (median [Q1; Q3]) was 1.6 [1.1; 2.5] months in the intervention arm and 1.6 [1.0; 2.3] months in the comparator arm.
f. Data on treatment discontinuations are not available for the relevant subpopulation; in relation to the overall population of the study, a total of 288 (65%) patients in the intervention arm vs. 189 (43%) in the control arm discontinued treatment (Institute's calculation). Common reasons for treatment discontinuation were the following (percentages based on randomized patients): disease progression (35% versus 16%), adverse event (22% versus 14%). In addition, < 1% vs. 3% of the randomized patients never started treatment; a further 2% vs. 55% of patients completed treatment with the study medication as planned.
g. Data on study discontinuations are not available for the relevant subpopulation; in relation to the total study population, a total of 146 (33%) patients in the intervention arm vs. 241 (54%) patients in the control arm discontinued treatment. These figures also include patients who died during the course of the study (intervention arm: 30% vs. control arm: 51%; percentages refer to the randomized patients).

CPS: combined positive score; CrCl: creatinine clearance; ECOG PS: Eastern Cooperative Oncology Group Performance Status; f: female; m: male; n: number of patients in the category; N: number of randomized patients; ND: no data; PD-L1: programmed cell death ligand 1; Q1: 1st quartile; Q3: 3rd quartile; RCT: randomized controlled trial; SD: standard deviation

The patient characteristics for the relevant subpopulation in the EV-302/KN-A39 study are sufficiently comparable between the two treatment arms. The mean age of the patients was 65 years; around 42% came from the region of Europe. Only very few patients in both arms had an ECOG PS of 2 (2% vs. 1%), so it is unclear whether the observed effects can be transferred to patients with an ECOG PS ≥ 2.

In the majority of patients, the origin of the disease was in the lower urinary tract (bladder and urethra), although detailed information on the origin of the disease is only available for the total study population; in this population, the origin of the disease was in the bladder in 67% vs. 74% of patients. At the start of the study, visceral metastases were present in 71% vs. 67% of patients, including liver metastases in 20% in both arms.

Information on common reasons for treatment or study discontinuation is not available for the relevant subpopulation; in relation to the overall study population, the most common reasons for treatment discontinuation were disease progression (35% vs. 16%) or an adverse event (22% vs. 14%). It should be noted here that for the comparator arm these data only refer to the study medication and thus the chemotherapy with cisplatin/carboplatin + gemcitabine and not to a possible subsequent maintenance therapy with avelumab in progression-free patients, which was not part of the study medication according to the study design. In the total study population, discontinuation for reasons other than death occurred only sporadically in both treatment arms, in around 3% of patients in each case (Institute's calculation).

I 4.1.2 Information on the course of the study

Table 11 shows the mean and median treatment durations of the patients, and the mean and median observation periods for individual outcomes in the subpopulation relevant to research question 1.

Table 11: Information on the course of the study – RCT, direct comparison: enfortumab vedotin + pembrolizumab vs. cisplatin + gemcitabine (subpopulation: cisplatin suitable)

Study **duration of the study phase** **outcome category/outcome**	**Enfortumab vedotin + pembrolizumab** **N = 240**	**Cisplatin + gemcitabine** **N = 242**
EV-302/KN-A39		
Treatment duration[a] [months]		
Median [Q1; Q3]	9.6 [4.8; 14.5]	4.1 [3.2; 4.4]
Mean (SD)	10.3 (6.8)	3.6 (1.2)
Observation period [months]		
Overall survival [b]		
Median [Q1; Q3]	14.4 [10.3; 20.1]	12.2 [7.9; 17.7]
Mean (SD)	15.2 (6.8)	13.1 (7.4)
Symptoms (BPI-SF; EORTC QLQ-C30)[c]		
Median [Q1; Q3]	10.1 [5.9; 15.6]	5.9 [2.8; 11.4]
Mean (SD)	11.1 (7.2)	7.5 (6.4)
Health status (EQ-5D VAS)[c]		
Median [Q1; Q3]	10.1 [5.9; 15.6]	5.9 [3.1; 11.4]
Mean (SD)	11.1 (7.2)	7.6 (6.4)
Health-related quality of life (EORTC QLQ-C30)[c]		
Median [Q1; Q3]	10.1 [5.9; 15.6]	5.9 [2.7; 11.4]
Mean (SD)	11.1 (7.2)	7.5 (6.4)
Side effects[d]		
Median [Q1; Q3]	11.6 [7.7; 16.1]	5.6 [4.9; 5.9]
Mean (SD)	12.6 (6.2)	5.2 (1.3)

a. Treatment duration is defined as the time from the first dose of study medication to Day 21 of the last of the 21-day treatment cycles, initiation of subsequent antineoplastic therapy, death, end of study, or time of data cut-off, whichever occurs first.
b. The observation period is defined as the time from randomization to the last time point at which information on overall survival was recorded.
c. The observation period is defined as the time from randomization until the last recording of the outcome; according to the information in Module 4 A, patients who had not experienced a first deterioration since the start of the study before the initiation of subsequent antineoplastic therapy were censored on the date of the last available recording of the outcome.
d. According to Module 4 A, the observation period is defined as the time from the first study treatment to 90 days after the last study treatment in the intervention arm or 30 days after the last study treatment in the comparator arm. This deviates from the information according to the study plan (Table 9), without this being explained in Module 4 A. The information according to the study design is assumed to be true.

BPI-SF: Brief Pain Inventory-Short Form; EORTC QLQ-C30: European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30; N: number of patients; Q1: first quartile; Q3: third quartile; RCT: randomized controlled trial; SD: standard deviation; VAS: visual analogue scale

Within the relevant subpopulation, the patients' median treatment duration was far higher in the intervention arm, at 9.6 months, than in the comparator arm, at 4.1 months. This is due

to the fact that in the intervention arm treatment was planned to be administered until disease progression or the occurrence of unacceptable toxicity (pembrolizumab for a maximum of 35 cycles), while treatment in the comparator arm was limited to a maximum of 6 cycles. The stated treatment duration for the comparator arm does not take into account the duration of a possible maintenance therapy with avelumab.

The median observation period for the outcome of overall survival is comparable between the study arms.

Observation beyond disease progression up to the end of the study was planned for the outcomes on symptoms, health status and health-related quality of life. Nevertheless, the observation period of these outcomes is shorter compared to the outcome of overall survival (in the intervention arm by approx. 4 months, in the control arm by approx. 6 months). Furthermore, the observation period in the intervention arm is approx. 4 months longer than in the comparator arm. As described in Section I 3.2.6, according to the information in Module 4 A, patients who had not experienced a first deterioration since the start of the study before the initiation of subsequent antineoplastic therapy were censored on the date of the last available recording of the outcome. There is no information available on whether this censoring scheme was predefined and to what extent it affects the stated observation periods.

For the side effects outcomes, the observation period in the intervention arm is approx. 6 months longer than in the comparator arm. In addition, the fixed treatment duration in the comparator arm and the linking of the observation time for side effects to the treatment duration means that the effect estimate only reflects approximately the first 6 months after randomization and thus only the period of chemotherapy in the comparator arm, but not a possible maintenance therapy with avelumab, and only the first 6 months of a possibly longer-lasting therapy in the intervention arm. This has been taken into account in the derivation of the certainty of conclusions for the outcomes on side effects (see Section I 5.2.1).

I 4.1.3 Subsequent therapies

Table 12 shows the subsequent therapies patients received after discontinuing the study medication in the subpopulation relevant to research question 1.

Table 12: Information on subsequent antineoplastic therapies (≥ 1% of patients in ≥ 1 treatment arm) – RCT, direct comparison: enfortumab vedotin + pembrolizumab versus cisplatin + gemcitabine (subpopulation: cisplatin suitable) (multipage table)

Study **drug class** **therapies** **drug**	**Patients with subsequent therapy, n (%)**	
	enfortumab vedotin + pembrolizumab **N = 240**	**cisplatin + gemcitabine** **N = 242**
Study EV-302/KN-A39		
Total[a]	84 (35.0)	174 (71.9)
Palliative radiotherapy	22 (9.2)	25 (10.3)
Non-palliative radiotherapy	4 (1.7)	5 (2.1)
Surgical intervention	5 (2.1)	11 (4.5)
Systemic therapy	81 (33.8)	164 (67.8)
For progressive disease	70 (29.2)	104 (43.0)
As maintenance therapy	7 (2.9)	91 (37.6)
First subsequent systemic therapy	81 (33.8)	164 (67.8)
Platinum-based therapy[b]	71 (29.6)	9 (3.7)
Cisplatin-based therapy	44 (18.3)	5 (2.1)
Carboplatin-based therapy	27 (11.3)	4 (1.7)
PD-1/-L1-based maintenance therapy	0 (0)	88 (36.4)
Avelumab	0 (0)	84 (34.7)
Pembrolizumab	0 (0)	5 (2.1)
Other PD-1/-L1-based therapy	3 (1.3)	62 (25.6)
Atezolizumab	0 (0)	19 (7.9)
Pembrolizumab	3 (1.3)	39 (16.1)
Other drugs	7 (2.9)	5 (2.1)
Second and later subsequent systemic therapies	26 (10.8)[c]	55 (22.7)[c]
Platinum-based therapy[b]	5 (2.1)	7 (2.9)
Cisplatin-based therapy	4 (1.7)	4 (1.7)
Carboplatin-based therapy	1 (0.4)	4 (1.7)
PD-1/-L1-based maintenance therapy	6 (2.5)	3 (1.2)
Avelumab	6 (2.5)	2 (0.8)
Other PD-1/-L1-based therapy	7 (2.9)	7 (2.9)
Pembrolizumab	4 (1.7)	4 (1.7)
Other drugs	20 (8.3)	46 (19.0)
Erdafitinib	7 (2.9)	3 (1.2)
Enfortumab vedotin	0 (0)	31 (12.8)
Sacituzumab govitecan	5 (2.1)	8 (3.3)
Paclitaxel	8 (3.3)	9 (3.7)

Table 12: Information on subsequent antineoplastic therapies (≥ 1% of patients in ≥ 1 treatment arm) – RCT, direct comparison: enfortumab vedotin + pembrolizumab versus cisplatin + gemcitabine (subpopulation: cisplatin suitable) (multipage table)

Study drug class therapies drug	Patients with subsequent therapy, n (%) enfortumab vedotin + pembrolizumab N = 240	 cisplatin + gemcitabine N = 242

a. Including maintenance therapies.
b. If a platinum-based therapy and a PD-1/-L1-based therapy were used in the same line of therapy, the latter was categorized as a platinum-based therapy.
c. Institute's calculation.

n: number of patients with subsequent therapy; N: number of analysed patients; PD-1: programmed cell death 1; PD-L1: programmed cell death ligand 1; RCT: randomized controlled trial

The information on subsequent systemic antineoplastic therapies in the company's dossier includes both systemic therapies for the treatment of progressive disease and maintenance therapies. This is not appropriate, as maintenance therapy is not a subsequent therapy in the sense of a new line of treatment, but a further treatment within the framework of the current line of therapy. The mixing of actual subsequent therapies and maintenance therapy means that for therapies labelled as second and later subsequent systemic therapies, it is unclear whether they were used after systemic therapy for progressive disease or after maintenance therapy. In the second case, this would be the actual first subsequent therapy. In addition, the available data do not show which subsequent therapies were used after disease progression under maintenance treatment with avelumab.

In the EV-302/KN-A39 study, subsequent therapies were permitted without restrictions in both study arms. In the subpopulation relevant to research question 1, a total of 70 (29%) patients in the intervention arm and 104 (43%) patients in the comparator arm received at least 1 subsequent antineoplastic systemic therapy for the treatment of progressive disease. In relation to the patients in whom disease progression occurred as a PFS event (105 patients in the intervention arm versus 141 patients in the comparator arm), this means that 67% of the patients with disease progression in the intervention arm and 74% in the comparator arm received at least one subsequent antineoplastic therapy for the treatment of progressive disease (Institute's calculation). According to the current S3 guideline, the ability and meaningfulness of second-line therapy must be checked for each patient [10], so that the proportion of patients with subsequent therapy in the subpopulation of the EV-302/KN-A39 study relevant to research question 1 appears appropriate overall.

According to current guideline recommendations, platinum-based chemotherapy or, in certain patients, erdafitinib is recommended as a subsequent therapy after disease progression under enfortumab vedotin + pembrolizumab [16]; platinum-based chemotherapy

was the predominant first subsequent therapy in the intervention arm, which 30% of patients received.

Pembrolizumab or atezolizumab is recommended as first-line therapy for disease progression under platinum-based chemotherapy [10,16] In the comparator arm, 16% and 8% of patients respectively received these drugs as the first Programmed Cell Death 1 (PD-1)/PD-L1-based subsequent systemic therapy, which was not a maintenance therapy.

In cases of disease progression under maintenance treatment with avelumab following platinum-based chemotherapy as first-line treatment, erdafitinib (in certain patients) and enfortumab vedotin are primarily recommended, and sacituzumab govitecan, vinflunine or taxanes [16] are recommended with a lower recommendation grade. These drugs, particularly enfortumab vedotin, were frequently used as second and later subsequent systemic therapies in the comparator arm (see Table 12). However, as described above, it is not clear from the information provided by the company whether these drugs were used after disease progression under maintenance therapy or under a previous subsequent therapy for the treatment of a progressive disease and thus in a later line of therapy.

Despite this lack of information, it is assumed on the basis of the available data and the recommendations of the current S3 guideline that implementation of the subsequent therapies was predominantly appropriate in the subpopulation of study EV-302/KN-A39 relevant to research question 1.

I 4.1.4 Risk of bias across outcomes (study level)

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

Table 13: : Risk of bias across outcomes (study level) – RCT, direct comparison: enfortumab vedotin + pembrolizumab vs. cisplatin/carboplatin + gemcitabine

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			
EV-302/KN-A39	Yes	Yes	No	No	Yes	Yes	Low
RCT: randomized controlled trial							

The risk of bias across outcomes for the EV-302/KN-A39 study was rated as low.

Limitations resulting from the open-label study design are described in Section I 5.2.2 under outcome-specific risk of bias.

I 4.1.5 Transferability of the study results to the German health care context

The company states that the study population corresponds to the target population in Germany in terms of demographic and disease-specific characteristics. Furthermore, the study medication with platinum-containing chemotherapy administered in the control arm of the study corresponded to the German standard therapy for unresectable or metastatic urothelial carcinoma prior to the approval of enfortumab vedotin + pembrolizumab. The incipient change in the German therapeutic landscape with the addition of avelumab as a maintenance therapy was also addressed in the study and the application rate of avelumab reflected the German health care context. According to the company, the subsequent therapies used in the event of progression also reflect the German health care context.

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

I 4.2 Results on added benefit

I 4.2.1 Outcomes included

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

- Mortality
  - overall survival
- Morbidity
  - worst pain (Brief Pain Inventory – Short Form [BPI-SF] item 3)
  - pain interference (BPI-SF item 9a–g)
  - symptoms, recorded with the EORTC QLQ-C30
  - health status, recorded using the EQ-5D VAS
- Health-related quality of life
  - recorded with the EORTC QLQ-C30
- Side effects
  - SAEs
  - severe AEs (CTCAE grade ≥ 3)
  - discontinuation due to AEs
  - immune-related SAEs

- Immune-related severe AEs (CTCAE grade ≥ 3)
- peripheral neuropathy (standardized Medical Dictionary for Regulatory Activities (Standardized MedDRA Query [SMQ], AEs)
- skin reactions, operationalized as skin and subcutaneous tissue disorders (System Organ Class [SOC], AEs)
- severe hyperglycaemia (PT, severe AEs)
- severe nephrotoxicity, operationalized as renal and urinary disorders (SOC, severe AEs)
- other specific AEs, if any

The choice of patient-relevant outcomes deviates from that made by the company, which used further outcomes in the dossier (Module 4 A).

Table 14 shows the outcomes for which data for research question 1 are available in the included study.

Table 14: Matrix of outcomes – RCT, direct comparison: enfortumab vedotin + pembrolizumab vs. cisplatin + gemcitabine (subpopulation: cisplatin suitable)

Study	Outcomes															
	Overall survival	Worst pain (BPI-SF item 3)	Pain interference (BPI-SF item 9a–g)	Symptoms (EORTC QLQ-C30)	Health status (EQ-5D VAS)	Health-related quality of life (EORTC-QLQ-C30)	SAEs	Severe AEs[a]	Discontinuation due to AEs	Immune-related SAEs[b]	Immune-related severe AEs[a, b]	Peripheral neuropathy (SMQ, AEs)	Skin reactions[c]	Severe hyperglycaemia (PT, severe AEs[a])	Severe nephrotoxicity[d]	Further specific AEs[a, e]
EV-302/KN-A39	Yes	Yes	No[f]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes

a. Severe AEs are operationalized as CTCAE grade ≥ 3.
b. In each case, the operationalization of a specific, predefined MedDRA PT collection from the outcome of AEOSI (Version 25.0) presented by the company is used.
c. Operationalized as skin and subcutaneous tissue disorders (SOC, AEs).
d. Operationalized as renal and urinary disorders (SOC, severe AEs).
e. The following events were considered (MedDRA coding): nausea (PT, AEs), vomiting (PT, AEs), eye disorders (SOC, AEs), ear and labyrinth disorders (SOC, AEs), endocrine disorders (SOC, AEs), gastrointestinal disorders (SOC, SAEs), respiratory, thoracic and mediastinal disorders (SOC, SAEs), blood and lymphatic system disorders (SOC, severe AEs), urinary tract infection (PT, severe AEs), diarrhoea (PT, severe AEs) and general disorders and administration site conditions (SOC, severe AEs).
f. No suitable data available; for the reasoning, see Section I 5.2.1 of the present dossier assessment.

AE: adverse event; AESI: adverse events of special interest; BPI-SF: Brief Pain Inventory – Short Form; CTCAE: Common Terminology Criteria for Adverse Events; EORTC QLQ-C30: European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30; MedDRA: Medical Dictionary for Regulatory Activities; PT: Preferred Term; RCT: randomized controlled trial; SAE: serious adverse event; SMQ: Standardized MedDRA Query; SOC: System Organ Class; VAS: visual analogue scale

Notes on outcomes

As described in Section I 4.2.3, the ACT was only incompletely implemented in study EV-302/KN-A39, as maintenance therapy with avelumab was not part of the study treatment and not all patients who were eligible for maintenance treatment with avelumab also received it. The consequences for the benefit assessment resulting from this at outcome level are described below together with other aspects.

Overall survival: sensitivity analyses of the company

In order to address the uncertainty for the results on overall survival resulting from the incomplete implementation of the maintenance therapy with avelumab, the company presented 3 sensitivity analyses. In these analyses, patients who had not received avelumab despite suitability according to the company's criteria and who died are considered in different ways.

- In sensitivity analysis 1, patients who had been eligible for maintenance therapy with avelumab and who had not received avelumab and died were censored at the time of death. This means that the observation period of these patients until death is included in the analysis without taking the event itself into account.
- In sensitivity analysis 2, patients who had been eligible for maintenance therapy with avelumab and who had not received avelumab and died were censored at the time of the data cut-off and thus imputed as event-free (i.e. survived) up to the data cut-off.
- In sensitivity analysis 3, patients who had been eligible for maintenance therapy with avelumab and who had not received avelumab and died were imputed with a modified time of death. In this analysis, a simplified assumption was made that the patients would have benefited from treatment with avelumab to an extent that, according to the company's assessment, can be learned from subsequent analyses on prespecified subgroups of the JAVELIN Bladder 100 study [24]. The imputed median benefit in terms of overall survival was 8.8 months for patients who had received cisplatin + gemcitabine and 7.0 months for patients who had received carboplatin + gemcitabine. This median benefit was added to the actually observed time of death and a hypothetical modified date of death was determined and included in the analysis.

Sensitivity analysis 2 represents a maximum assumption, as it assumes that all patients for whom maintenance treatment with avelumab was an option according to the company and who did not receive avelumab and died would instead have survived until the time of the data cut-off presented. It therefore represents the best possible result for these patients in terms of overall survival at the present data cut-off. It is assumed that the actual result for the outcome of overall survival would have ranged between the result of the main analysis (all died) and sensitivity analysis 2 (all alive) if maintenance therapy with avelumab had been fully implemented. Sensitivity analyses 1 and 3 provide supplementary information on this with less extreme assumptions for the imputation or consideration of deaths in this group.

The sensitivity analyses presented by the company are suitable to adequately address the uncertainty due to the incomplete implementation of maintenance therapy with avelumab with regard to those patients who did not receive avelumab despite suitability according to the company's criteria and who died. Taking into account the sensitivity analyses, it is

therefore possible to interpret the results of the outcome of overall survival in the present data constellation.

Morbidity and health-related quality of life

The median time to event for all patient-reported outcomes on morbidity and health-related quality of life, for which there are generally usable data, was a maximum of 4.5 months in both arms (see Table 16 for research question 1 and Table 25 for research question 2) and is thus only sporadically and insignificantly longer than the median duration of treatment with chemotherapy of 4.1 months (see Table 17 for research question 1 and Table 21 for research question 2). However, the Kaplan-Meier curves show that the majority of events for the outcomes of morbidity and health-related quality of life occurred early in the course of the study during the chemotherapy period in the comparator arm (see I Appendix B). In the present data situation, it is therefore assumed that the incomplete implementation of the subsequent maintenance therapy does not have a relevant impact on the results. For this reason, the patient-reported outcomes on morbidity and health-related quality of life were used to derive the added benefit. However, it should be noted that the available results chiefly refer to the first months of observation under treatment and are therefore of limited informative value for the present research question. At the same time, analyses covering a longer period would not be interpretable without corresponding sensitivity analyses due to the incomplete implementation of maintenance therapy.

Further aspects relating to individual morbidity and health-related quality of life outcomes are described below.

Outcomes on pain (BPI-SF)

In the EV-302/KN-A39 study, the BPI-SF questionnaire is used to record pain. In Module 4 A, the company presented analyses on worst pain (BPI-SF item 3), on pain intensity (BPI-SF items 3–6), and pain interference (BPI-SF items 9a-g), It also presents analyses on the introduction of a new opioid medication for the treatment of pain and on pain progression (a composite outcome of worst pain [BPI-SF item 3] and introduction of a new opioid medication).

The outcomes of worst pain (BPI-SF item 3), pain intensity (BPI-SF items 3-6) and pain interference (BPI-SF items 9a-9g) were used for the benefit assessment. Pain intensity is presented as supplementary information.

However, the outcomes of introduction of a new opioid medication and pain progression were not used for the benefit assessment. This is explained below.

Although the introduction of a new opioid medication is linked to the patient-relevant symptom of pain, it only reflects this indirectly. In the present situation, in which a direct patient-reported recording of pain outcomes using BPI-SF was performed at short intervals (3

to 4 days after randomization, weekly until Week 12, at Week 14, and every 3 weeks thereafter) and in which the majority of events for the outcome of worst pain (BPI-SF item 3) occurred within the first 14 weeks (median time to event 2.0 vs. 1.8 months for research question 1 and 3.2 vs. 1.3 months for research question 2, see Table 16 and Table 25), it cannot be assumed that consideration of the introduction of a new opioid medication will lead to the recording of a relevant number of pain progression events that are not recorded by the BPI-SF. This is also shown by the event figures presented in Module 4 A of the dossier for the outcome of pain progression, which correspond to those for the outcome of worst pain (BPI-SF item 3).

For the outcomes of worst pain (BPI-SF item 3), pain intensity (BPI-SF items 3-6) and pain interference (BPI-SF items 9a-9g) , the company presented responder analyses on the time until the first deterioration by ≥ 2 points (scale range 0 to 10). For the benefit assessment, these responder analyses are used for the outcome of worst pain (BPI-SF item 3). For the outcomes of pain intensity (BPI-SF items 3-6) and pain interference (BPI-SF items 9a-9g), however, the responder analyses presented are not suitable for the benefit assessment. This is justified below.

The response threshold of ≥ 2 points was predefined only for item 3 of the BPI-SF and, in accordance with the IQWiG *General Methods* [1], is therefore used for toe outcome of worst pain. No response threshold was predefined for the outcomes of pain intensity (BPI-SF items 3–6), and pain interference (BPI-SF items 9a-g); therefore, the response threshold of ≥ 15% of the scale range is used for the assessment in accordance with the IQWiG *General Methods* [1].

For all individual items and sum scores of the BPI-SF, 1.5 points correspond to of the response threshold of ≥ 15% of the scale range. Only for the individual items (but not for the total scores such as pain intensity [BPI-SF items 3-6] and pain interference [BPI-SF items 9a-9g]) is the response criterion “2 points” identical to 1.5 points, as there is no value between 1 and 2. Therefore, no suitable data are available for the outcomes of pain intensity (BPI-SF items 3-6) and pain interference (BPI-SF items 9a-9g).

Side effects

Only analyses that do not cover the entire observation period of study EV-302/A-39 are available for the side effects outcomes. The fixed treatment duration and the associated discontinuation of observation after the end of study medication in the comparator arm mean that the effect estimate only reflects approximately the first 6 months after randomization. In the comparator arm, this essentially corresponds to the treatment duration with cisplatin/carboplatin + gemcitabine plus 30 days (see Table 9 and Table 11 for research question 1 and Table 21 for research question 2); the period of possible maintenance treatment with avelumab is not shown. For the period of a possible maintenance therapy with

avelumab in progression-free patients, the side effects outcomes were not followed up and events that occur under such therapy are therefore not included in the analyses on side effects presented by the company. Therefore, statements on the full duration of therapy in the sense of the ACT are not possible for the side effects outcomes. Even in the intervention arm, only the first 6 months of a possibly longer-lasting therapy are taken into account. This shortened observation in the comparator arm or consideration of data collected in the intervention arm limits the certainty of conclusions on the results on AEs. The results can nevertheless be used for the assessment in the present data situation. The particular data constellation presented here is taken into account accordingly when weighing up the added benefit.

Immune-related SAEs and immune-related severe AEs

For the outcomes of immune-related SAEs and immune-related severe AEs (defined as AESIs in the EV-302/KN-A39 study), the predefined list (Version 25.0) of PTs, which was presented by the company, is deemed a suitable operationalization and is used within the framework of the present benefit assessment.

I 4.2.2 Risk of bias

Table 15 describes the risk of bias for the results of the relevant outcomes for research question 1.

Table 15: Risk of bias across outcomes and outcome-specific risk of bias – RCT, direct comparison: enfortumab vedotin + pembrolizumab vs. cisplatin + gemcitabine (subpopulation: cisplatin suitable)

Study		Outcomes																
	Study level	Overall survival	Worst pain (BPI-SF item 3)	Pain interference (BPI-SF item 9a–g)	Symptoms (EORTC QLQ-C30)	Health status (EQ-5D VAS)	Health-related quality of life (EORTC-QLQ-C30)	SAEs	Severe AEs[a]	Discontinuation due to AEs	Immune-related SAEs[b]	Immune-related severe AEs[a, b]	Peripheral neuropathy (SMQ, AEs)	Skin reactions[c]	Severe hyperglycaemia (PT, severe AEs[a])	Severe nephrotoxicity[d]	Further specific AEs[a, e]
EV-302/KN-A39	L	L	H[f, g]	–[h]	H[f, g]	H[f, g]	H[f, g]	H[i]	H[i]	H[i, j]	H[i]	H[i]	H[f, i]	H[f, i]	H[i]	H[i]	H[f, i]

a. Severe AEs are operationalized as CTCAE grade ≥ 3.
b. In each case, the operationalization of a specific, predefined MedDRA PT collection from the outcome of AEOSI (Version 25.0) presented by the company is used.
c. Operationalized as skin and subcutaneous tissue disorders (SOC, AEs).
d. Operationalized as renal and urinary disorders (SOC, severe AEs).
e. The following events were considered (MedDRA coding): nausea (PT, AEs), vomiting (PT, AEs), eye disorders (SOC, AEs), ear and labyrinth disorders (SOC, AEs), endocrine disorders (SOC, AEs), gastrointestinal disorders (SOC, SAEs), respiratory, thoracic and mediastinal disorders (SOC, SAEs), blood and lymphatic system disorders (SOC, severe AEs), urinary tract infection (PT, severe AEs), diarrhoea (PT, severe AEs) and general disorders and administration site conditions (SOC, severe AEs).
f. Lack of blinding in the case of subjective recording of outcomes, unless severe or serious AEs are involved.
g. Decreasing response to questionnaires in the course of the study; large proportion of patients not included in the analysis (> 10 %) or large difference between the treatment groups (> 5 percentage points).
h. No suitable data available; for the reasoning, see Section I 5.2.1 of the present dossier assessment.
i. Incomplete observations for potentially informative reasons.
j. Lack of blinding in the presence of subjective decision on treatment discontinuation.

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

The outcome-specific risk of bias was also rated as low for the results on "overall survival", and as high for all other patient-relevant outcomes.

The outcome-specific risk of bias for the results of the outcomes of worst pain (BPI-SF item 3), symptoms (EORTC QLQ-C30), health status (EQ-5D VAS) and health-related quality of life

(EORTC QLQ-C30) is rated as high. The reason therefore is the decreasing response to the respective questionnaire in the course of the study, the large proportion of patients not considered in the analysis (> 10%) and the large difference between the treatment groups (> 5 percentage points). This is accompanied by the lack of blinding in subjective recording of outcomes.

No suitable data are available for the outcome of pain interference (recorded using BPI-SF items 9a-9g) (for reasons, see Section I 5.2.1), thus, the risk of bias is not assessed.

The outcome-specific risk of bias of the results on the outcomes of the side effects category was rated as high. This is due to incomplete observations for potentially informative reasons, as these outcomes were only followed up for 30 and 90 days after the last dose of study medication. Results on non-serious and non-severe specific AEs additionally have a high risk of bias due to the lack of blinding in subjective recording of outcomes. Moreover, the results of the outcome of discontinuation due to AEs have a high risk of bias due to the lack of blinding in the case of a subjective decision on treatment discontinuation.

Summary assessment of the certainty of conclusions

In addition to the described aspects of bias, there are uncertainties for study EV-302/KN-A39, as described in Section I 4.2.2 and Section I 4.2.3, particularly in the implementation of the ACT. In the present specific data constellation, the results of the study can nevertheless be interpreted for the research questions of the present benefit assessment, but the certainty of the study results for the present assessment is reduced. Based on the EV-302/KN-A39 study, at most hints, e.g. of an added benefit, can be derived for both research questions.

Moreover, for the outcomes in the side effects category, analyses are only available for a significantly shortened period, which in the comparator arm only reflects the treatment with chemotherapy, but not the period of a possible maintenance therapy with avelumab, and in the intervention arm only takes into account the first 6 months of a possibly longer-lasting treatment (see Section I 5.2.1). This shortened observation in the comparator arm or consideration of recorded data in the intervention arm contributes to a limited certainty of conclusions and additionally justifies the fact that at most hints can be derived.

I 4.2.3 Results

Table 16 summarizes the results of the comparison of enfortumab vedotin + pembrolizumab with cisplatin + gemcitabine for first-line treatment in adult patients with unresectable or metastatic urothelial carcinoma for whom cisplatin-based therapy is suitable. Where necessary, IQWiG calculations are provided to supplement the data from the company's dossier.

Kaplan-Meier curves on the presented time-to-event analyses can be found in I Appendix B.1 of the full dossier assessment. Results on common AEs, SAEs, severe AEs and discontinuations due to AEs are presented in I Appendix C.1 of the full dossier assessment. Results on frequent immune-related AEs, immune-related SAEs and immune-related severe AEs are not available in the company's dossier.

Table 16: Results (mortality, morbidity, health-related quality of life, side effects) – RCT, direct comparison: enfortumab vedotin + pembrolizumab vs. cisplatin + gemcitabine (subpopulation: cisplatin suitable) (multipage table)

Study **outcome category** **outcome**	**Enfortumab vedotin + pembrolizumab**		**Cisplatin + gemcitabine**		**Enfortumab vedotin + pembrolizumab vs. cisplatin + gemcitabine**
	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**
EV-302/KN-A39					
Mortality					
Overall survival	240	31.5 [25.4; NC] 69 (28.8)	242	18.4 [15.6; 27.5] 110 (45.5)	0.54 [0.40; 0.73]; < 0.001[a]
Overall survival (sensitivity analysis 1[b])	240	31.5 [25.4; NC] 69 (28.8)	242	27.5 [18.4; NC] 89 (36.8)	0.66 [0.48; 0.91]; 0.010[a]
Overall survival (sensitivity analysis 2[c])	240	31.5 [25.4; NC] 69 (28.8)	242	NA [19.7; NC] 89 (36.8)	0.70 [0.51; 0.96]; 0.027[a]
Overall survival (sensitivity analysis 3[d])	240	31.5 [25.4; NC] 69 (28.8)	242	21.3 [18.4; 27.5] 100 (41.3)	0.62 [0.46; 0.85]; 0.002[a]
Morbidity					
Worst pain (BPI-SF item 3 - time to first deterioration)[e]	240	2.0 [1.3; 4.5] 130 (54.2)	242	1.8 [1.1; 3.2] 113 (46.7)	0.89 [0.68; 1.17]; 0.420[a]
Pain intensity (BPI-SF items 3–6, time to first deterioration, presented as supplementary information)[f]			*No suitable data available*[g]		
Pain interference (BPI-SF items 9a-g – time to first deterioration)[f]			No suitable data available[g]		

Table 16: Results (mortality, morbidity, health-related quality of life, side effects) – RCT, direct comparison: enfortumab vedotin + pembrolizumab vs. cisplatin + gemcitabine (subpopulation: cisplatin suitable) (multipage table)

Study outcome category outcome	Enfortumab vedotin + pembrolizumab		Cisplatin + gemcitabine		Enfortumab vedotin + pembrolizumab vs. cisplatin + gemcitabine
	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
Symptoms (EORTC QLQ-C30 – time to first deterioration[h])					
Fatigue	240	0.4 [0.4; 0.6] 169 (70.4)	242	0.4 [0.4; 0.6] 157 (64.9)	0.80 [0.62; 1.02]; 0.079[a]
Nausea and vomiting	240	2.0 [1.1; 4.6] 131 (54.6)	242	0.4 [0.4; 0.8] 142 (58.7)	0.55 [0.42; 0.72]; < 0.001[a]
Pain	240	0.7 [0.5; 1.3] 147 (61.3)	242	1.1 [0.6; 1.4] 130 (53.7)	1.02 [0.79; 1.33]; 0.887[a]
Dyspnoea	240	2.4 [1.6; 4.6] 134 (55.8)	242	2.0 [1.7; 3.9] 108 (44.6)	1.03 [0.78; 1.36]; 0.795[a]
Insomnia	240	2.3 [0.9; 4.5] 125 (52.1)	242	2.0 [0.9; 3.8] 114 (47.1)	0.78 [0.59; 1.04]; 0.091[a]
Appetite loss	240	0.9 [0.6; 1.7] 141 (58.8)	242	0.6 [0.4; 0.9] 130 (53.7)	0.75 [0.58; 0.97]; 0.027[a]
Constipation	240	2.2 [1.5; 4.5] 125 (52.1)	242	0.7 [0.4; 1.3] 133 (55.0)	0.59 [0.46; 0.78]; < 0.001[a]
Diarrhoea	240	2.0 [1.3; 3.8] 132 (55.0)	242	3.1 [2.0; 9.3] 98 (40.5)	1.14 [0.86; 1.51]; 0.345[a]
Health status (EQ-5D VAS - time to first deterioration)[i]	240	2.5 [1.3; 5.2] 138 (57.5)	242	2.2 [1.5; 3.2] 111 (45.9)	1.01 [0.77; 1.33]; 0.963[a]
health-related quality of life					
EORTC-QLQ C30 – time to first deterioration[j]					
Global health status	240	0.7 [0.6; 1.3] 158 (65.8)	242	0.9 [0.6; 1.1] 132 (54.5)	0.89 [0.69; 1.15]; 0.366[a]
Physical functioning	240	1.1 [0.6; 1.6] 164 (68.3)	242	0.9 [0.6; 1.1] 137 (56.6)	0.91 [0.71; 1.17]; 0.454[a]
Role functioning	240	0.6 [0.4; 0.8] 164 (68.3)	242	0.4 [0.4; 0.9] 140 (57.9)	0.90 [0.70; 1.15]; 0.453[a]
Emotional functioning	240	3.2 [2.0; 10.1] 120 (50.0)	242	3.8 [2.0; 11.4] 95 (39.3)	1.00 [0.75; 1.35]; 0.984[a]
Cognitive functioning	240	1.8 [1.1; 2.3] 143 (59.6)	242	0.9 [0.6; 1.5] 130 (53.7)	0.85 [0.66; 1.10]; 0.247[a]
Social functioning	240	0.7 [0.5; 1.1] 161 (67.1)	242	0.9 [0.6; 1.1] 129 (53.3)	1.17 [0.91; 1.51]; 0.210[a]

Table 16: Results (mortality, morbidity, health-related quality of life, side effects) – RCT, direct comparison: enfortumab vedotin + pembrolizumab vs. cisplatin + gemcitabine (subpopulation: cisplatin suitable) (multipage table)

Study outcome category outcome	Enfortumab vedotin + pembrolizumab		Cisplatin + gemcitabine		Enfortumab vedotin + pembrolizumab vs. cisplatin + gemcitabine
	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
Side effects[k]					
AEs (supplementary information)	239	0.2 [0.2; 0.2] 239 (100.0)	236	0.1 [0.1; 0.2] 234 (99.2)	–
SAEs	239	18.0 [9.5; NC] 107 (44.8)	236	NA 83 (35.2)	0.91 [0.67; 1.23]; 0.543[l]
Severe AEs[m]	239	4.2 [3.0; 6.1] 164 (68.6)	236	1.4 [1.0; 1.8] 175 (74.2)	0.51 [0.41; 0.65]; < 0.001[l]
Discontinuation due to AEs	239	14.5 [11.3; NC] 92 (38.5)	236	NA 58 (24.6)	0.70 [0.48; 1.03]; 0.068[l]
Immune-related AEs[n] (supplementary information)	*239*	*12.6 [7.2; NC]* *104 (43.5)*	*236*	*NA* *10 (4.2)*	–
Immune-related SAEs[n]	239	NA 34 (14.2)	236	NA 2 (0.8)	11.08 [2.61; 46.92]; < 0.001[l]
Immune-related severe AEs,[m, n]	239	NA 49 (20.5)	236	NA 3 (1.3)	11.07 [3.40; 36.11]; < 0.001[l]
Peripheral neuropathy (SMQ, AEs)[o]	239	4.4 [3.5; 5.1] 162 (67.8)	236	NA 43 (18.2)	3.30 [2.33; 4.67]; < 0.001[l]
Skin reactions[p]	239	0.5 [0.4; 0.6] 204 (85.4)	236	NA 61 (25.8)	5.90 [4.40; 7.90]; < 0.001[l]
Severe hyperglycaemia (PT, severe AEs[m])	239	NA 20 (8.4)	236	NA 2 (0.8)	7.70 [1.77; 33.57]; 0.001[l]
severe nephrotoxicity[m, q]	239	NA 16 (6.7)	236	NA 16 (6.8)	0.69 [0.33; 1.46]; 0.330[l]
Nausea (PT, AEs)	239	NA 61 (25.5)	236	3.3 [2.1; NC] 120 (50.8)	0.36 [0.26; 0.49]; < 0.001[l]
Vomiting (PT, AEs)	239	NA 24 (10.0)	236	NA 42 (17.8)	0.45 [0.26; 0.76]; 0.002[l]
Eye disorders (SOC, AEs)	239	19.7 [12.7; NC] 88 (36.8)	236	NA 14 (5.9)	5.30 [2.98; 9.41]; < 0.001[l]

Table 16: Results (mortality, morbidity, health-related quality of life, side effects) – RCT, direct comparison: enfortumab vedotin + pembrolizumab vs. cisplatin + gemcitabine (subpopulation: cisplatin suitable) (multipage table)

Study outcome category outcome	Enfortumab vedotin + pembrolizumab		Cisplatin + gemcitabine		Enfortumab vedotin + pembrolizumab vs. cisplatin + gemcitabine
	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
Ear and labyrinth disorders (SOC, AEs)	239	NA 17 (7.1)	236	NA 33 (14.0)	0.17 [0.07; 0.40]; < 0.001[l]
Endocrine disorders (SOC, AEs)	239	NA 34 (14.2)	236	NA 2 (0.8)	12.37 [2.93; 52.16]; < 0.001[l]
Gastrointestinal disorders (SOC, SAEs)	239	NA 24 (10.0)	236	NA 6 (2.5)	3.22 [1.29; 7.99]; 0.008[l]
Respiratory, thoracic and mediastinal disorders (SOC, SAEs)	239	NA 25 (10.5)	236	NA 4 (1.7)	4.07 [1.37; 12.04]; 0.006[l]
Blood and lymphatic system disorders (SOC, severe AEs)[m]	239	NA 17 (7.1)	236	4.9 [3.0; NC] 110 (46.6)	0.08 [0.05; 0.15]; < 0.001[l]
Anaemia (PT, severe AEs)[m]	239	NA 8 (3.3)	236	6.1 [6.1; NC] 19 (8.1)	0.32 [0.13; 0.76]; 0.007[l]
Diarrhoea (PT, severe AEs)[l]	239	NA 10 (4.2)	236	NA 2 (0.8)	4.34 [0.94; 20.10]; 0.040[l]
General disorders and administration site conditions (SOC, severe AEs)[m]	239	NA 13 (5.4)	236	NA 24 (10.2)	0.30 [0.14; 0.68]; 0.002[l]

Table 16: Results (mortality, morbidity, health-related quality of life, side effects) – RCT, direct comparison: enfortumab vedotin + pembrolizumab vs. cisplatin + gemcitabine (subpopulation: cisplatin suitable) (multipage table)

Study outcome category outcome	Enfortumab vedotin + pembrolizumab		Cisplatin + gemcitabine		Enfortumab vedotin + pembrolizumab vs. cisplatin + gemcitabine
	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. HR and CI: Cox proportional hazards model, p-value: log-rank test, each stratified by PD-L1 expression (high vs. low) and liver metastases (present vs. not present).
b. Censoring at the time of death: avelumab-eligible patients who had not received avelumab and died were censored at the time of death.
c. Censoring at data cut-off: avelumab-eligible patients who had not received avelumab and died were censored at the time of data cut-off.
d. Modified time of death: avelumab-eligible patients who had not received avelumab and died were censored with a modified time of death. A simplified assumption was made that the patients would have benefited from treatment with avelumab to the extent shown in the approval study of avelumab (JAVELIN Bladder 100); see Section I 5.2.1 for explanation.
e. A score increase by ≥ 2 points from baseline is considered a clinically relevant deterioration (scale range 0 to 10); for explanation, see Section I 5.2.1.
f. A score increase by ≥ 1.5 points from baseline is considered a clinically relevant deterioration (scale range 0 to 10); for explanation, see Section I 5.2.1.
g. See Section I 5.2.1 for a rationale.
h. An EORTC QLQ-C30 score increase by ≥ 10 points from baseline is considered a clinically relevant deterioration (scale range: 0 to 100).
i. An EQ-5D VAS score decrease by ≥ 15 points from baseline is considered a clinically relevant deterioration (scale range: 0 to 100).
j. An EORTC QLQ-C30 score decrease by ≥ 10 points from baseline is considered a clinically relevant deterioration (scale range: 0 to 100).
k. The terms of disease progression, progression of a disease and progression of a malignant disease as well as similar terms were not taken into account in the assessment of AEs. The fixed treatment duration and the associated discontinuation of observation after the end of study medication in the comparator arm mean that the effect estimate only reflects approximately the first 6 months after randomization.
l. HR and CI: unstratified Cox proportional hazards model; p-value: unstratified log-rank test.
m. Operationalized as CTCAE grade ≥ 3.
n. In each case, the operationalization of a specific, predefined MedDRA PT collection from the outcome of AESI (Version 25.0) presented by the company is used.
o. The following result is shown for the severe AEs of the SMQ “peripheral neuropathy” included in the results on AEs: 17 (7.1) vs. 0 (0); HR: NC [NC; NC]; p = 0.0512; Kaplan-Meier curve see Figure 35.
p. Operationalized as skin and subcutaneous tissue disorders (SOC, AEs); the following result is shown for the severe AEs of the SOC ”skin and subcutaneous tissue disorders” included in the results on AEs: 39 (16.3) vs. 0 (0); HR: NC [NC; NC]; < 0.001; Kaplan-Meier curve see Figure 37.
q. Operationalized as renal and urinary disorders (SOC, severe AEs).

Table 16: Results (mortality, morbidity, health-related quality of life, side effects) – RCT, direct comparison: enfortumab vedotin + pembrolizumab vs. cisplatin + gemcitabine (subpopulation: cisplatin suitable) (multipage table)

Study outcome category outcome	Enfortumab vedotin + pembrolizumab		Cisplatin + gemcitabine		Enfortumab vedotin + pembrolizumab vs. cisplatin + gemcitabine
	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
AE: adverse event; AESI: adverse events of special interest; BPI-SF: Brief Pain Inventory – Short Form; CI: confidence interval; CTCAE: Common Terminology Criteria for Adverse Events; EORTC QLQ-C30: European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30; HR: hazard ratio; n: number of patients with (at least one) event; N: number of analysed patients; NA: not achieved; NC: not calculable; PD-L1: programmed cell death ligand 1; PT: Preferred Term; RCT: randomized controlled trial; SAE: serious adverse event; SOC: System Organ Class; VAS: visual analogue scale					

Based on the available information, at most hints, e.g. of an added benefit, can be determined for all outcomes due to the limited certainty of conclusions (see Section I 4.2.2 and I 4.2.3 for the reasoning).

When interpreting the results on side effects, it should be noted that due to the fixed treatment duration and the associated discontinuation of observation in the comparator arm, the effect estimate only covers approximately the first 6 months after randomization (see Section I 5.1.2).

Mortality

Overall survival

For the outcome of overall survival, a statistically significant difference was found in favour of enfortumab vedotin + pembrolizumab in comparison with cisplatin + gemcitabine. The 3 sensitivity analyses presented by the company, in which patients in the comparator arm for whom maintenance treatment with avelumab would potentially have been indicated and who died without maintenance treatment were accounted for differently (see Section I 5.2.1), also showed a statistically significant difference in favour of enfortumab vedotin + pembrolizumab compared with cisplatin + gemcitabine in each case. This effect remains even if the maximum situation is assumed that all these patients in the comparator arm have survived to the present data cut-off. In this data constellation, there is a hint of added benefit of enfortumab vedotin + pembrolizumab in comparison with the ACT. However, the results of the main analysis and the 3 sensitivity analyses on overall survival presented by the company differ in terms of their

extent (see Section I 5.3.1). Therefore, the extent of the added benefit for the outcome of overall survival cannot be quantified.

Morbidity

Worst pain (BPI-SF item 3)

No statistically significant difference between treatment groups was shown for the outcome of worst pain (recorded using BPI-SF item 3). There is no hint of an added benefit of enfortumab vedotin + pembrolizumab in comparison with the ACT; an added benefit is therefore not proven.

Pain interference (BPI-SF item 9a–g)

No suitable data are available for the outcome of pain interference (recorded using BPI-SF items 9a-9g) (for reasons, see Section I 5.2.1). There is no hint of an added benefit of enfortumab vedotin + pembrolizumab in comparison with the ACT; an added benefit is therefore not proven.

Symptoms

EORTC QLQ-C30

Fatigue

No statistically significant difference between treatment groups was found for the outcome of fatigue. However, there is an effect modification by the characteristic of age, however (see Section I 5.2.4). There is a hint of an added benefit of enfortumab vedotin + pembrolizumab versus the ACT for patients < 65 years of age. For patients ≥ 65 years, there was no hint of an added benefit of enfortumab vedotin + pembrolizumab versus the ACT; an added benefit is therefore not proven for patients ≥ 65 years of age.

Nausea and vomiting, constipation

For the outcomes of nausea and vomiting as well as constipation, there is a statistically significant difference in favour of enfortumab vedotin + pembrolizumab versus cisplatin + gemcitabine. There is a hint of added benefit of enfortumab vedotin + pembrolizumab in comparison with the ACT.

Pain, dyspnoea, insomnia and diarrhoea

No statistically significant difference between treatment groups was shown for any of the outcomes of pain, dyspnoea, insomnia, or diarrhoea. There is no hint of an added benefit of enfortumab vedotin + pembrolizumab in comparison with the ACT; an added benefit is therefore not proven.

Appetite loss

For the outcome of appetite loss, a statistically significant difference was found in favour of enfortumab vedotin + pembrolizumab in comparison with cisplatin + gemcitabine. For this outcome of the non-serious/non-severe symptoms category, however, the extent of the effect was no more than marginal (see Section I 5.3.1). There is no hint of an added benefit of enfortumab vedotin + pembrolizumab in comparison with the ACT; an added benefit is therefore not proven.

Health status

No statistically significant difference between treatment groups was shown for the outcome of health status. There is no hint of an added benefit of enfortumab vedotin + pembrolizumab in comparison with the ACT; an added benefit is therefore not proven.

Health-related quality of life

EORTC QLQ-C30

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

No statistically significant difference between treatment groups was found for any of the outcomes of global health status, role functioning, emotional functioning, and cognitive functioning. In each case, there is no hint of an added benefit of enfortumab vedotin + pembrolizumab in comparison with the ACT; an added benefit is therefore not proven for any case.

Physical functioning

No statistically significant difference between treatment groups was found for the outcome of physical functioning. However, there is an effect modification by the characteristic of age, however (see Section I 5.2.4). There was a hint of an added benefit of enfortumab vedotin + pembrolizumab versus the ACT for patients < 65 years of age. For patients ≥ 65 years, there was no hint of an added benefit of enfortumab vedotin + pembrolizumab versus the ACT; an added benefit is therefore not proven for patients ≥ 65 years of age.

Social functioning

No statistically significant difference between treatment groups was found for the outcome of social functioning. There are effect modifications by the characteristics of age and metastases (see Section I 5.2.4). These effect modifications cannot be assessed without examining for cross-interactions. The added benefit is therefore derived based on the results on the relevant subpopulation. There is no hint of an added benefit of enfortumab vedotin + pembrolizumab in comparison with the ACT; an added benefit is therefore not proven.

Side effects

SAEs and discontinuation due to AEs

No statistically significant difference was found between treatment groups for either of the outcomes of SAEs or discontinuation due to AEs. For each of them, there is no hint of greater or lesser harm from enfortumab vedotin + pembrolizumab in comparison with the ACT; greater or lesser harm is therefore not proven.

Severe AEs

For the outcome of severe AEs, a statistically significant difference was found in favour of enfortumab vedotin + pembrolizumab in comparison with cisplatin + gemcitabine. There is a hint of lesser harm from enfortumab vedotin + pembrolizumab in comparison with the ACT.

Immune-related SAEs, immune-related severe AEs, peripheral neuropathy (AEs), skin reactions (AEs) and severe hyperglycaemia (severe AEs)

For the outcomes of immune-related SAEs, immune-related severe AEs, peripheral neuropathy (AEs), skin reactions (AEs) and severe hyperglycaemia (severe AEs), there was a statistically significant difference to the disadvantage of enfortumab vedotin + pembrolizumab compared to cisplatin + gemcitabine. For each of them, there was a hint of greater harm from enfortumab vedotin + pembrolizumab in comparison with the ACT.

severe nephrotoxicity (severe AEs)

No statistically significant difference between treatment groups was found for the outcome of severe nephrotoxicity (severe AEs). There is no hint of greater or lesser harm from enfortumab vedotin + pembrolizumab in comparison with the ACT; greater or lesser harm is therefore not proven.

Other specific AEs

Nausea (AEs), vomiting (AEs), blood and lymphatic system disorders (severe AEs), urinary tract infection (severe AEs) and general disorders and administration site conditions (severe AEs)

For the outcomes of nausea (AEs), vomiting (AEs), blood and lymphatic system disorders (severe AEs), urinary tract infection (severe AEs) as well as general disorders and administration site conditions (severe AEs), there was a statistically significant difference in favour of enfortumab vedotin + pembrolizumab compared to cisplatin + gemcitabine. For each of them, there is a hint of lesser harm from enfortumab vedotin + pembrolizumab in comparison with the ACT.

Eye disorders (AEs), endocrine disorders (AEs), gastrointestinal disorders (SAEs), respiratory, thoracic and mediastinal disorders (SAEs) and diarrhoea (severe AEs)

There was a statistically significant difference to the disadvantage of enfortumab vedotin + pembrolizumab compared to cisplatin + gemcitabine for each of the outcomes of eye disorders (AEs), endocrine disorders (AEs), gastrointestinal disorders (SAEs), respiratory, thoracic and mediastinal disorders (SAEs) and diarrhoea (severe AEs). For each of them, there was a hint of greater harm from enfortumab vedotin + pembrolizumab in comparison with the ACT.

Ear and labyrinth disorders (AE)

For the outcome of ear and labyrinth disorders (AEs), there was a statistically significant difference in favour of enfortumab vedotin + pembrolizumab in comparison with cisplatin + gemcitabine. However, there is an effect modification by the characteristic of age, however (see Section I 5.2.4). For both patients < 65 years and patients ≥ 65 years, there is a hint of lesser harm from enfortumab vedotin + pembrolizumab compared with the ACT; however, the extent of this harm differs (see Section I 5.3.1).

I 4.2.4 Subgroups and other effect modifiers

The following subgroup characteristics are taken into account in the present benefit assessment:

- age (< 65 years versus ≥ 65 years)
- sex (male versus female)
- Metastases (visceral metastases vs. exclusively lymph node metastases)

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 presented only if there is a statistically significant and relevant effect in at least one subgroup. Subgroup results where the extent does not differ between subgroups are not presented.

The results are presented in Table 17. The Kaplan-Meier curves on the subgroup results are presented in I Appendix B.1 of the full dossier assessment.

Table 17: Subgroups (morbidity, health-related quality of life, side effects) – RCT, direct comparison: enfortumab vedotin + pembrolizumab vs. cisplatin + gemcitabine (subpopulation: cisplatin suitable) (multipage table)

Study outcome characteristic subgroup	Enfortumab vedotin + pembrolizumab		Cisplatin + gemcitabine		Enfortumab vedotin + pembrolizumab vs. cisplatin + gemcitabine	
	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][a]	p-value[a]
EV-302/KN-A39						
Symptoms (EORTC QLQ-C30, fatigue – time to first deterioration[b])						
Age						
< 65 years	105	0.6 [0.4; 1.6] 71 (67.6)	106	0.4 [0.2; 0.6] 71 (67.0)	0.56 [0.38; 0.82]	0.003
≥ 65 years	135	0.4 [0.4; 0.5] 98 (72.6)	136	0.4 [0.4; 0.6] 86 (63.2)	1.02 [0.74; 1.41]	0.800
					Interaction:	0.043[c]
Health-related quality of life (EORTC QLQ-C30, physical functioning - time to first deterioration by ≥ 10 points[d]						
Age						
< 65 years	105	1.8 [0.9; 7.3] 61 (58.1)	106	0.6 [0.4; 1.2] 61 (57.5)	0.59 [0.40; 0.88]	0.009
≥ 65 years	135	0.6 [0.5; 1.1] 103 (76.3)	136	1.1 [0.7; 1.5] 76 (55.9)	1.21 [0.88; 1.67]	0.258
					Interaction:	0.005[c]
Health-related quality of life (EORTC QLQ-C30, social functioning - time to first deterioration[d]						
Age						
< 65 years	105	2.0 [0.7; 3.9] 66 (62.9)	106	0.6 [0.4; 1.3] 57 (53.8)	0.85 [0.57; 1.26]	0.436
≥ 65 years	135	0.6 [0.4; 0.7] 95 (70.4)	136	0.9 [0.6; 1.1] 72 (52.9)	1.47 [1.05; 2.04]	0.022
					Interaction:	0.027[c]
Metastases						
Visceral metastases	170	0.7 [0.4; 1.1] 112 (65.9)	161	1.1 [0.5; 1.8] 78 (48.8)	1.41 [1.01; 1.96]	0.034
Lymph nodes only	60	0.9 [0.4; 1.3] 42 (70.0)	67	0.6 [0.4; 0.9] 42 (62.7)	0.93 [0.56; 1.56]	0.738
					Interaction:	0.043[c]

Table 17: Subgroups (morbidity, health-related quality of life, side effects) – RCT, direct comparison: enfortumab vedotin + pembrolizumab vs. cisplatin + gemcitabine (subpopulation: cisplatin suitable) (multipage table)

Study outcome characteristic subgroup	Enfortumab vedotin + pembrolizumab		Cisplatin + gemcitabine		Enfortumab vedotin + pembrolizumab vs. cisplatin + gemcitabine	
	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][a]	p-value[a]
Ear and labyrinth disorders (SOC, AEs)[e]						
Age						
< 65 years	105	NA 5 (4.8)	102	NA 20 (19.6)	0.09 [0.02; 0.37]	< 0.001
≥ 65 years	134	NA 12 (9.0)	134	NA 13 (9.7)	0.30 [0.10; 0.89]	0.022
					Interaction:	0.020[c]

a. HR and CI: Cox proportional hazards model, p-value: log-rank test, each stratified by age, sex, region, PD-L1 expression and liver metastases as well as subgroup and the interaction term subgroup and treatment.
b. An EORTC QLQ-C30 score increase by ≥ 10 points from baseline is considered a clinically relevant deterioration (scale range: 0 to 100).
c. p-value from Wald test based on Cox proportional hazards model with the variable subgroup and interaction term subgroup and treatment.
d. An EORTC QLQ-C30 score decrease by ≥ 10 points from baseline is considered a clinically relevant deterioration (scale range: 0 to 100).
a. The fixed treatment duration and the associated discontinuation of observation after the end of study medication in the comparator arm mean that the effect estimate only reflects approximately the first 6 months after randomization.

AE: adverse event; CI: confidence interval; EORTC QLQ-C30: European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30; HR: hazard ratio; n: number of patients with (at least 1) event; N: number of analysed patients; NA: not achieved; RCT: randomized controlled trial; SOC: System Organ Class

Morbidity

Symptoms

EORTC QLQ-C30

Fatigue

There is an effect modification by the characteristic of age for the outcome of fatigue. A statistically significant difference in favour of enfortumab vedotin + pembrolizumab in comparison with cisplatin + gemcitabine was shown for patients < 65 years. There was a hint of added benefit of enfortumab vedotin + pembrolizumab in comparison with the ACT for this patient group. However, no statistically significant difference between treatment groups was

found for patients ≥ 65 years. There is no hint of an added benefit of enfortumab vedotin + pembrolizumab in comparison with the ACT for this patient group; an added benefit is therefore not proven.

Health-related quality of life

EORTC QLQ-C30

Physical functioning

There was an effect modification by the characteristic “age" for the outcome **“physical functioning”**. A statistically significant difference in favour of enfortumab vedotin + pembrolizumab in comparison with cisplatin + gemcitabine was shown for patients < 65 years”. There was a hint of added benefit of enfortumab vedotin + pembrolizumab in comparison with the ACT for this patient group.

However, no statistically significant difference between treatment groups was found for patients ≥ 65 years. There is no hint of an added benefit of enfortumab vedotin + pembrolizumab in comparison with the ACT; an added benefit is therefore not proven for this patient group.

Social functioning

There was an effect modification by the characteristics of age and metastases each for the outcome of social functioning. These effect modifications cannot be assessed without examining for cross-interactions. The added benefit is therefore derived based on the results on the relevant subpopulation.

Side effects

Specific AEs

Ear and labyrinth disorders (AE)

For the outcome of ear and labyrinth disorders (AEs), there is an effect modification by the characteristic of age. A statistically significant difference in favour of enfortumab vedotin + pembrolizumab in comparison with cisplatin + gemcitabine was shown for both patients < 65 years and patients ≥ 65 years. In each case, there is a hint of added benefit of enfortumab vedotin + pembrolizumab in comparison with the ACT the extents of which differ; an added benefit is therefore not proven (see Section I 5.3.1).

I 4.3 Probability and extent of added benefit

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

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

I 4.3.1 Assessment of added benefit at outcome level

The extent of the respective added benefit at outcome level is estimated from the results presented in Section I 4.2 (see Table 18).

Determination of the outcome category for symptom outcomes

For the symptom outcomes below, it cannot be inferred from the dossier whether they are serious/severe or non-serious/non-severe. Reasoning is provided for the classification of these outcomes.

Symptoms (EORTC QLQ-C30)

Fatigue, nausea and vomiting, constipation, and appetite loss

For the outcomes of fatigue, nausea and vomiting, constipation as well as appetite loss, each recorded using the EORTC QLQ-C30, there is insufficient information available to classify the severity category as serious/severe. These outcomes are therefore each assigned to the outcome category of non-serious/non-severe symptoms/late complications.

Table 18: Extent of added benefit at outcome level: enfortumab vedotin + pembrolizumab vs. cisplatin + gemcitabine (subpopulation: cisplatin suitable) (multipage table)

Outcome category **outcome** **effect modifier** **subgroup**	**Enfortumab vedotin + pembrolizumab vs. cisplatin + gemcitabine** **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		Outcome category: mortality added benefit, extent: "non-quantifiable"
Main analysis	31.5 vs. 18.4 months HR: 0.54 [0.40; 0.73]; p < 0.001 probability: "hint"	
Sensitivity analysis 1[c]	31.5 vs. 27.5 months HR: 0.66 [0.48; 0.91]; p = 0.010	
Sensitivity analysis 2[d]	31.5 vs. NA months HR: 0.70 [0.51; 0.96]; p = 0.027	
Sensitivity analysis 3[e]	31.5 vs. 21.3 months HR: 0.62 [0.46; 0.85]; p = 0.002	
Outcomes with shortened observation period		
Morbidity		
Worst pain (BPI-SF item 3 - time to first deterioration)	2.0 vs. 1.8 months HR: 0.89 [0.68; 1.17]; p = 0.420	Lesser/added benefit not proven
Pain interference (BPI-SF items 9a–g)	No suitable data[f]	Lesser/added benefit not proven
Symptoms (EORTC QLQ-C30 – time to first deterioration)		
Fatigue Age		
< 65 years	0.6 vs. 0.4 months HR: 0.56 [0.38; 0.82]; p = 0.003 probability: "hint"	Outcome category: non-serious/non-severe symptoms/late complications $0.80 \leq CI_u < 0.90$ added benefit, extent: "minor"
≥ 65 years	0.4 vs. 0.4 months HR: 1.02 [0.74; 1.41]; p = 0.800	Lesser/added benefit not proven

Table 18: Extent of added benefit at outcome level: enfortumab vedotin + pembrolizumab vs. cisplatin + gemcitabine (subpopulation: cisplatin suitable) (multipage table)

Outcome category **outcome** **effect modifier** **subgroup**	**Enfortumab vedotin + pembrolizumab vs. cisplatin + gemcitabine** **median time to event (months)** **effect estimation [95% CI];** **p-value** **probability**[a]	**Derivation of extent**[b]
Nausea and vomiting	2.0 vs. 0.4 months HR: 0.55 [0.42; 0.72]; p < 0.001 probability: “hint”	Outcome category: non-serious/non-severe symptoms/late complications CI_u < 0.80 added benefit; extent: “considerable”
Pain	0.7 vs. 1.1 months HR: 1.02 [0.79; 1.33]; p = 0.887	Lesser/added benefit not proven
Dyspnoea	2.4 vs. 2.0 months HR: 1.03 [0.78; 1.36]; p = 0.795	Lesser/added benefit not proven
Insomnia	2.3 vs. 2.0 months HR: 0.78 [0.59; 1.04]; p = 0.091	Lesser/added benefit not proven
Appetite loss	0.9 vs. 0.6 months HR: 0.75 [0.58; 0.97]; p = 0.027	Outcome category: non-serious/non-severe symptoms/late complications 0.90 ≤ CI_u < 1.00 lesser benefit/added benefit not proven[g]
Constipation	2.2 vs. 0.7 months HR: 0.59 [0.46; 0.78]; p < 0.001 probability: “hint”	Outcome category "non-serious/non-severe symptoms/late complications" CI_u < 0.80 added benefit; extent: “considerable”
Diarrhoea	2.0 vs. 3.1 months HR: 1.14 [0.86; 1.51]; p = 0.345	Lesser/added benefit not proven
Health status (EQ-5D VAS, time to first deterioration)	2.5 vs. 2.2 months HR: 1.01 [0.77; 1.33]; p = 0.963	Lesser/added benefit not proven
Health-related quality of life		
EORTC-QLQ C30 – time to first deterioration		
Global health status	0.7 vs. 0.9 months HR: 0.89 [0.69; 1.15]; p = 0.366	Lesser/added benefit not proven
Physical functioning Age		

Table 18: Extent of added benefit at outcome level: enfortumab vedotin + pembrolizumab vs. cisplatin + gemcitabine (subpopulation: cisplatin suitable) (multipage table)

Outcome category **outcome** **effect modifier** **subgroup**	**Enfortumab vedotin + pembrolizumab vs. cisplatin + gemcitabine** **median time to event (months)** **effect estimation [95% CI];** **p-value** **probability**[a]	**Derivation of extent**[b]
< 65 years	1.8 vs. 0.6 months HR: 0.59 [0.40; 0.88]; p = 0.009 probability: "hint"	Outcome category: health-related quality of life $0.75 \leq CI_u < 0.90$ added benefit; extent: "considerable"
≥ 65 years	0.6 vs. 1.1 months HR: 1.21 [0.88; 1.67]; p = 0.258	Lesser/added benefit not proven
Role functioning	0.6 vs. 0.4 months HR: 0.90 [0.70; 1.15]; p = 0.453	Lesser/added benefit not proven
Emotional functioning	3.2 vs. 3.8 months HR: 1.00 [0.75; 1.35]; p = 0.984	Lesser/added benefit not proven
Cognitive functioning	1.8 vs. 0.9 months HR: 0.85 [0.66; 1.10]; p = 0.247	Lesser/added benefit not proven
Social functioning	0.7 vs. 0.9 months HR: 1.17 [0.91; 1.51] p = 0.210	Lesser/added benefit not proven
Side effects[i]		
SAEs	18.0 vs. NA months HR: 0.91 [0.67; 1.23]; p = 0.543	Greater/lesser harm not proven
Severe AEs	4.2 vs. 1.4 months HR: 0.51 [0.41; 0.65]; p < 0.001 probability: "hint"	Outcome category: serious/severe side effects $CI_u < 0.75$; risk ≥ 5% lesser harm, extent: "major"
Discontinuation due to AEs	14.5 vs. NA months HR: 0.70 [0.48; 1.03]; p = 0.068	Greater/lesser harm not proven
Immune-related SAEs	NA vs. NA months HR: 11.08 [2.61; 46.92] HR: 0.09 [0.02; 0.38][h]; p < 0.001 probability: "hint"	Outcome category: serious/severe side effects $CI_u < 0.75$; risk ≥ 5% greater harm, extent: "major"

Table 18: Extent of added benefit at outcome level: enfortumab vedotin + pembrolizumab vs. cisplatin + gemcitabine (subpopulation: cisplatin suitable) (multipage table)

Outcome category **outcome** **effect modifier** **subgroup**	**Enfortumab vedotin + pembrolizumab vs. cisplatin + gemcitabine** **median time to event (months)** **effect estimation [95% CI];** **p-value** **probability**[a]	**Derivation of extent**[b]
Immune-related severe AEs	NA vs. NA months HR: 11.07 [3.40; 36.11] HR: 0.09 [0.03; 0.29][h]; p < 0.001 probability: "hint"	Outcome category: serious/severe side effects CI_u < 0.75; risk ≥ 5% greater harm, extent: "major"
Peripheral neuropathy (AEs)	4.4 vs. NA months HR: 3.30 [2.33; 4.67] HR: 0.30 [0.21; 0.43][h]; p < 0.001 probability: "hint"	Outcome category: non-serious/non-severe side effects CI_u < 0.80 greater harm, extent: "considerable"
Skin reactions (AEs)	0.5 vs. NA months HR: 5.90 [4.40; 7.90] HR: 0.17 [0.13; 0.23][h]; p < 0.001 probability: "hint"	Outcome category: non-serious/non-severe side effects CI_u < 0.80 greater harm, extent: "considerable"
Hyperglycaemia (severe AEs)	NA vs. NA months HR: 7.70 [1.77; 33.57] HR: 0.13 [0.03; 0.57][h]; p = 0.001 probability: "hint"	Outcome category: serious/severe side effects CI_u < 0.75; risk ≥ 5% greater harm, extent: "major"
Severe nephrotoxicity (severe AEs)	NA vs. NA months HR: 0.69 [0.33; 1.46]; p = 0.330	Greater/lesser harm not proven
Other specific AEs		
Nausea (AEs)	NA vs. 3.3 months HR: 0.36 [0.26; 0.49]; p < 0.001 probability: "hint"	Outcome category: non-serious/non-severe side effects CI_u < 0.80 lesser harm, extent: "considerable"
Vomiting (AEs)	NA vs. NA months HR: 0.45 [0.26; 0.76]; p = 0.002 probability: "hint"	Outcome category: non-serious/non-severe side effects CI_u < 0.80 lesser harm, extent: "considerable"

Table 18: Extent of added benefit at outcome level: enfortumab vedotin + pembrolizumab vs. cisplatin + gemcitabine (subpopulation: cisplatin suitable) (multipage table)

Outcome category **outcome** **effect modifier** **subgroup**	**Enfortumab vedotin + pembrolizumab vs. cisplatin + gemcitabine** **median time to event (months)** **effect estimation [95% CI];** **p-value** **probability**[a]	**Derivation of extent**[b]
Eye disorders (AEs)	19.7 vs. NA months HR: 5.30 [2.98; 9.41] HR: 0.19 [0.11; 0.34][h]; p < 0.001 probability: “hint”	Outcome category: non-serious/non-severe side effects $CI_u < 0.80$ greater harm, extent: “considerable”
Ear and labyrinth disorders (AE) Age		
< 65 years	NA vs. NA months HR: 0.09 [0.02; 0.37]; p < 0.001 probability: “hint”	Outcome category: non-serious/non-severe side effects $CI_u < 0.80$ lesser harm, extent: “considerable”
≥ 65 years	NA vs. NA months HR: 0.30 [0.10; 0.89]; p = 0.022 probability: “hint”	Outcome category: non-serious/non-severe side effects $0.80 \leq CI_u < 0.90$ Lesser harm, extent: “minor”
Endocrine disorders (AEs)	NA vs. NA months HR: 12.37 [2.93; 52.16] HR: 0.08 [0.02; 0.34][h]; p < 0.001 probability: “hint”	Outcome category: non-serious/non-severe side effects $CI_u < 0.80$ greater harm, extent: “considerable”
Gastrointestinal disorders (SAEs)	NA vs. NA months HR: 3.22 [1.29; 7.99] HR: 0.31 [0.13; 0.77][h]; p = 0.008 probability: “hint”	Outcome category: serious/severe side effects $0.75 \leq CI_u < 0.90$ greater harm, extent: “considerable”
Respiratory, thoracic and mediastinal disorders (SAEs)	NA vs. NA months HR: 4.07 [1.37; 12.04] HR: 0.25 [0.08; 0.73][h]; p = 0.006 probability: “hint”	Outcome category: serious/severe side effects $CI_u < 0.75$; risk ≥ 5% greater harm, extent: “major”
Blood and lymphatic system disorders (severe AEs)	NA vs. 4.9 months HR: 0.08 [0.05; 0.15]; p < 0.001 probability: “hint”	Outcome category: serious/severe side effects $CI_u < 0.75$; risk ≥ 5% lesser harm, extent: “major”

Table 18: Extent of added benefit at outcome level: enfortumab vedotin + pembrolizumab vs. cisplatin + gemcitabine (subpopulation: cisplatin suitable) (multipage table)

Outcome category **outcome** **effect modifier** **subgroup**	**Enfortumab vedotin + pembrolizumab vs. cisplatin + gemcitabine** **median time to event (months)** **effect estimation [95% CI];** **p-value** **probability**[a]	**Derivation of extent**[b]
Urinary tract infection (severe AEs)	NA vs. 6.1 months HR: 0.32 [0.13; 0.76]; p = 0.007 probability: “hint”	Outcome category: serious/severe side effects $0.75 \leq CI_u < 0.90$ lesser harm, extent: “considerable”
Diarrhoea (severe AEs)	NA vs. NA months HR: 4.34 [0.94; 20.10] HR: 0.23 [0.05; 1.07][h]; p = 0.040 probability: “hint”	Outcome category: serious/severe side effects greater harm[j], extent: "minor"[k]
General disorders and administration site conditions (severe AEs)	NA vs. NA months HR: 0.30 [0.14; 0.68]; p = 0.002 probability: “hint”	Outcome category: serious/severe side effects $CI_u < 0.75$; risk ≥ 5% lesser harm, extent: “major”

a. Probability provided if there is a statistically significant and relevant effect.
b. Depending on the outcome category, the effect size is estimated using different limits based on the upper limit of the confidence interval (CI_u).
c. Censoring at the time of death: avelumab-eligible patients who had not received avelumab and died were censored at the time of death.
d. Censoring at data cut-off: avelumab-eligible patients who had not received avelumab and died were censored at the time of data cut-off.
e. Modified time of death: avelumab-eligible patients who had not received avelumab and died were censored with a modified time of death. A simplified assumption was made that the patients would have benefited from treatment with avelumab to the extent shown in the approval study of avelumab (JAVELIN Bladder 100); see Section I 5.2.1 for explanation.
f. See Section I 5.2.1 of the present dossier assessment for the reasoning.
g. The extent of the effect in this non-serious/non-severe outcome was no more than marginal.
h. Institute’s calculation; reversed direction of effect to enable use of limits to derive the extent of the added benefit.
i. The fixed treatment duration and the associated discontinuation of observation after the end of study medication in the comparator arm mean that the effect estimate only reflects approximately the first 6 months after randomization.
j. The result of the statistical test is decisive for the derivation of the added benefit.
k. Discrepancy between CI and p-value due to different calculation methods; the extent is rated as minor.

AE: adverse event; BPI-SF: Brief Pain Inventory-Short Form; CI: confidence interval; CI_u: upper limit of confidence interval; EORTC: European Organisation for Research and Treatment of Cancer; HR: hazard ratio; NA: not achieved; QLQ-C30: Quality of Life Questionnaire-Core 30; SAE: serious adverse event; VAS: visual analogue scale

I 4.3.2 Overall conclusion on added benefit

Table 19 summarizes the results taken into account in the overall conclusion on the extent of added benefit.

Table 19: Positive and negative effects from the assessment of enfortumab vedotin + pembrolizumab in comparison with the ACT (subpopulation: cisplatin unsuitable)

Positive effects	**Negative effects**
Outcomes with observation over the entire study duration	
Mortality ▪ overall survival: hint of an added benefit – extent: “non-quantifiable”	–
Outcomes with shortened observation period[a]	
Health-related quality of life ▪ physical function (each EORTC-QLQ-C30) ▫ age (< 65 years): hint of added benefit – extent: "considerable"	–
Non-serious/non-severe symptoms/late complications ▪ nausea and vomiting, constipation (EORTC QLQ-C30): hint of added benefit – extent: "considerable" ▪ fatigue (EORTC QLQ-C30) ▫ age (< 65 years): hint of added benefit – extent: “minor”	–
Serious/severe side effects ▪ severe AEs: hint of lesser harm – extent: “major” ▫ blood and lymphatic system disorders (severe AEs), general disorders and administration site conditions (severe AEs): in each case hint of lesser harm – extent: “major” ▫ urinary tract infection (severe AEs): ▫ hint of lesser harm – extent: “considerable”	Serious/severe side effects ▪ immune-related SAEs, immune-related severe AEs; severe hyperglycaemia (severe AEs), respiratory, thoracic and mediastinal disorders (SAEs): hint of greater harm in each case – extent: “major” ▪ gastrointestinal disorders (SAE): hint of greater harm – extent: “considerable” ▪ diarrhoea (severe AEs): hint of greater harm – extent: “minor”
Non-serious/non-severe side effects ▪ nausea (AEs), vomiting (AEs): hint of lesser harm each – extent: “considerable” ▪ ear and labyrinth disorders (AE) ▫ age (< 65 years): hint of lesser harm – extent: "considerable" ▫ age (≥ 65 years): hint of lesser harm – extent: "minor"	Non-serious/non-severe side effects ▪ peripheral neuropathy (AEs), skin reactions (AEs), eye disorders (AEs), endocrine disorders (AEs): hint of greater harm each - extent: “considerable”
No suitable data are available for the outcome "pain interference" (BPI-SF items 9a-9g).	
a. For the side effect outcomes, the fixed treatment duration and the associated discontinuation of observation after the end of study medication in the comparator arm mean that the effect estimate only reflects approximately the first 6 months after randomization. AE: adverse event; EORTC: European Organisation for Research and Treatment of Cancer; QLQ-C30: Quality of Life Questionnaire – Core 30; SAE: serious adverse event	

The overall assessment shows both positive and negative effects with different extents for enfortumab vedotin + pembrolizumab compared with the ACT. For mortality, the observed effects refer to the entire observation period. In particular for the outcomes of side effects, however, the observed effects relate to a shortened period and only represent the roughly first 6 months after randomization and thus in the comparator arm only the period of chemotherapy, but not the period of a possible maintenance therapy with avelumab, and in the intervention arm only the first 6 months of a possibly longer-lasting therapy.

The advantage in overall survival is decisive for the assessment, but its extent cannot be quantified, as the results of the main and sensitivity analyses differ in terms of their extent. In addition, there are advantages for individual outcomes of morbidity and health-related quality of life as well as for outcomes in the side effects category, particularly for the overall rate of severe AEs. On the other hand, there are disadvantages in various specific AEs, especially for severe and serious immune-related AEs.

The results on side effects only relate to a shortened period of around 6 months. However, since a high proportion of events already occur during this period, the available results show that the advantage in overall survival is not called into question by the results on side effects.

In summary, for adult patients with unresectable or metastatic urothelial carcinoma in the first-line therapy for whom cisplatin-based therapy is suitable, there is a hint of non-quantifiable added benefit of enfortumab vedotin + pembrolizumab compared with the ACT.

The assessment described above deviates from that by the company, which derived an indication of major added benefit.

I 5 Research question 2: Patients for whom cisplatin-based chemotherapy is unsuitable (cisplatin unsuitable)

I 5.1 Study characteristics (specific to research question 2)

For characteristics across research questions of the EV-302/KN-A39 study, including information on the study design, treatment in the comparator arm, comments on the implementation of the ACT, relevance of the Chinese cohort, data cut-offs and on the planned duration of follow-up observation, see Section I 4.2.

I 5.1.1 Patient characteristics

Table 20 shows the characteristics of the patients in the subpopulation of the included study relevant for research question 2.

Table 20: Characteristics of the study population as well as study/treatment discontinuation – RCT, direct comparison: enfortumab vedotin + pembrolizumab vs. carboplatin + gemcitabine (subpopulation: cisplatin unsuitable) (multipage table)

Study characteristic category	Enfortumab vedotin + pembrolizumab N = 202	Carboplatin + gemcitabine N = 202
EV-302/KN-A39		
Age [years], mean (SD)	71 (8)	72 (8)
Sex [F/M], %	28/72	25/75
Region		
Europe	74 (37)	95 (47)
North America	46 (23)	34 (17)
Rest of the world[a]	82 (41)	73 (36)
ECOG PS at baseline, n (%)		
0	87 (43)	87 (43[b])
1	104 (51)	105 (52[b])
2	11 (5)	9 (4[b])
Unknown	0 (0)	1 (< 1[b])
Renal function [CrCl in mL/min[c]], n (%)		
Normal [> 90]	6 (3)	13 (6)
Slightly reduced [≥ 60 to < 90]	49 (24)	40 (20)
Moderately reduced [≥ 30 to < 60]	140 (69)	141 (70)
Strongly reduced [≥ 15 to < 30]	7 (3)	8 (4)
PD-L1 status at baseline [CPS], n (%)		
< 10	85 (42)	87 (43)
≥ 10	117 (58)	115 (57)
Primary origin[d]		
Upper tract (kidney, renal pelvis, ureter)	74 (37)	55 (27)
Lower tract (urinary bladder, urethra)	128 (63)	146 (72)
Unknown	0 (0)	1 (< 1)
Disease duration: time between diagnosis of locally advanced or metastatic disease and randomization [months], median [Q1; Q3]	ND[e]	ND[e]
Liver metastases, n (%)	50 (25)	50 (25)
Metastasis category at baseline, n (%)		
Visceral metastases	148 (73)	157 (78)
Exclusively lymph node metastases	43 (21)	37 (18)
No category applicable	11 (5)	8 (4)
Reason for unsuitability of cisplatin		
Renal insufficiency [GFR ≥ 30, < 60 ml/min)[f]	164 (81)	163 (81)
Audiometric hearing loss (CTCAE grade ≥ 2)	29 (14)	29 (14)
Poor performance status [ECOG PS 2]	9 (4)	8 (4)

Table 20: Characteristics of the study population as well as study/treatment discontinuation – RCT, direct comparison: enfortumab vedotin + pembrolizumab vs. carboplatin + gemcitabine (subpopulation: cisplatin unsuitable) (multipage table)

Study characteristic category	Enfortumab vedotin + pembrolizumab N = 202	Carboplatin + gemcitabine N = 202
Heart failure [NYHA class III]	4 (2)	7 (3)
several of the reasons listed above	12 (6)	10 (5)
Not specified	8 (4)[c]	5 (2)[c]
Treatment discontinuation, n (%)[g]	ND[g]	ND[g]
Study discontinuation, n (%)[h]	ND[h]	ND[h]

a. Rest of the world includes Argentina, Australia, China, Israel, Japan, Russia, Singapore, South Korea, Taiwan, Thailand and Turkey.
b. Institute's calculation.
c. The CrCl was calculated using the Cockcroft-Gault formula based on the last measured creatinine value prior to taking the first dose of study medication.
d. In relation to the total population of the study, the primary origin of the disease was predominantly the urinary bladder (67% vs. 74%) or the renal pelvis (20% vs. 15%); for the relevant subpopulation, only the summarized data shown in the table are available.
e. Data on the disease duration are not available for the relevant subpopulation; in relation to the total study population, the time between diagnosis of locally advanced or metastatic disease and randomization (median [Q1; Q3]) was 1.6 [1.1; 2.5] months in the intervention arm and 1.6 [1.0; 2.3] months in the comparator arm.
f. Patients with a GFR ≥ 50 mL/min and no other criteria for unsuitability of cisplatin could be considered cisplatin-suitable according to the investigator's assessment.
g. Data on treatment discontinuations are not available for the relevant subpopulation; in relation to the total study population, a total of 288 (65%) patients in the intervention arm vs. 189 (43%) in the control arm discontinued treatment (Institute's calculation). Common reasons for treatment discontinuation were the following (percentages based on randomized patients): disease progression (35% versus 16%), adverse event (22% versus 14%). In addition, < 1% vs. 3% of the randomized patients never started treatment; a further 2% and 55% of patients completed treatment with the study medication as planned.
h. Data on study discontinuations are not available for the relevant subpopulation; in relation to the total study population, a total of 146 (33%) patients in the intervention arm vs. 241 (54%) patients in the control arm discontinued treatment. These figures also include patients who died during the course of the study (intervention arm: 30% vs. control arm: 51%; percentages refer to the randomized patients).

CPS: combined positive score; CrCl: creatinine clearance; CTCAE: Common Terminology Criteria for Adverse Events; ECOG PS: Eastern Cooperative Oncology Group Performance Status; f: female; GFR: glomerular filtration rate; m: male; n: number of patients in the category; N: number of randomized patients; ND: no data; NYHA: New York Heart Association; PD-L1: programmed cell death ligand 1; Q1: 1st quartile; Q3: 3rd quartile; RCT: randomized controlled trial; SD: standard deviation

The patient characteristics for the relevant subpopulation in the EV-302/KN-A39 study are sufficiently comparable between the two treatment arms. The mean age of the patients was 71 vs. 72 years; in the intervention arm, less patients were from the European region (37%) compared to (47%) the comparator arm. Only very few patients in both arms had an ECOG PS of 2 (5% vs. 4%), so it is unclear whether the observed effects can be transferred to patients with an ECOG PS ≥ 2.

In the majority of patients, the origin of the disease was in the lower urinary tract (bladder and urethra), although detailed information on the origin of the disease is only available for the total study population; in this population, the origin of the disease was in the bladder in 67% vs. 74% of patients.

At the start of the study, visceral metastases were present in 73% vs. 78% of patients, including liver metastases in 25% in both arms.

The most common reason for the unsuitability of cisplatin in both treatment arms was renal insufficiency (81% in each case).

Information on common reasons for treatment or study discontinuation is not available for the relevant subpopulation; in relation to the overall study population, the most common reasons for treatment discontinuation were disease progression (35% vs. 16%) or an adverse event (22% vs. 14%). It should be noted here that for the comparator arm these data only refer to the study medication and thus the chemotherapy with cisplatin/carboplatin + gemcitabine and not to a possible subsequent maintenance therapy with avelumab in progression-free patients, which was not part of the study medication according to the study design. In the total study population, discontinuation for reasons other than death occurred only sporadically in both treatment arms, in around 3% of patients in each case (Institute's calculation).

I 5.1.2 Information on the course of the study

Table 21 shows the mean and median treatment durations of the patients, and the mean and median observation periods for individual outcomes in the subpopulation relevant to research question 2.

Table 21: Information on the course of the study – RCT, direct comparison: enfortumab vedotin + pembrolizumab vs. carboplatin + gemcitabine (subpopulation: cisplatin unsuitable

Study **duration of the study phase** **outcome category/outcome**	**Enfortumab vedotin + pembrolizumab** **N = 202**	**Carboplatin + gemcitabine** **N = 202**
EV-302/KN-A39		
Treatment duration[a] [months]		
Median [Q1; Q3]	9.2 [4.3; 14.7]	4.1 [2.6; 4.4]
Mean (SD)	10.0 (6.8)	3.4 (1.5)
Observation period [months]		
Overall survival[b]		
Median [Q1; Q3]	13.7 [9.4; 19.4]	10.7 [6.6; 15.3]
Mean (SD)	14.0 (7.0)	11.3 (6.3)
Symptoms (BPI-SF; EORTC QLQ-C30)[c]		
Median [Q1; Q3]	9.4 [3.2; 15.6]	4.6 [2.2; 10.1]
Mean (SD)	10.2 (7.6)	6.6 (5.9)
Health status (EQ-5D VAS)[c]		
Median [Q1; Q3]	9.4 [3.2; 15.6]	4.6 [2.2; 10.1]
Mean (SD)	10.2 (7.5)	6.6 (5.9)
Health-related quality of life (EORTC QLQ-C30)[c]		
Median [Q1; Q3]	9.4 [3.2; 15.6]	4.6 [2.2; 10.1]
Mean (SD)	10.2 (7.6)	6.6 (5.9)
Side effects[d]		
Median [Q1; Q3]	11.3 [7.66; 16.26]	5.4 [3.81; 5.91]
Mean (SD)	12.1 (6.4)	4.9 (1.6)

a. Treatment duration is defined as the time from the first dose of study medication to Day 21 of the last of the 21-day treatment cycles, initiation of subsequent antineoplastic therapy, death, end of study, or time of data cut-off, whichever occurs first.
b. The observation period is defined as the time from randomization to the last time point at which information on overall survival was recorded.
c. The observation period is defined as the time from randomization until the last recording of the outcome; according to the information in Module 4 A, patients who had not experienced a first deterioration since the start of the study before the initiation of subsequent antineoplastic therapy were censored on the date of the last available recording of the outcome.
d. According to Module 4 A, the observation period is defined as the time from the first study treatment to 90 days after the last study treatment in the intervention arm or 30 days after the last study treatment in the comparator arm. This deviates from the information according to the study plan (Table 9), without this being explained in Module 4 A. The information according to the study design is assumed to be true.

BPI-SF: Brief Pain Inventory-Short Form; EORTC QLQ-C30: European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30; N: number of patients; Q1: first quartile; Q3: third quartile; RCT: randomized controlled trial; SD: standard deviation; VAS: visual analogue scale

Within the relevant subpopulation, the patients' median treatment duration was far higher in the intervention arm, at 9.2 months, than in the comparator arm, at 4.1 months. This is due

to the fact that in the intervention arm treatment was planned to be administered until disease progression or the occurrence of unacceptable toxicity, whereas in the comparator arm, while treatment in the comparator arm was limited to a maximum of 6 cycles. The stated treatment duration for the comparator arm does not take into account the duration of a possible maintenance therapy with avelumab.

The median observation period for the outcome of overall survival is comparable between the study arms.

Observation beyond disease progression up to the end of the study was planned for the outcomes on symptoms, health status and health-related quality of life. Nevertheless, the observation period of these outcomes is shorter compared to the outcome of overall survival (in the intervention arm by approx. 4 months, in the control arm by approx. 6 months). Furthermore, the observation period in the intervention arm is approx. 5 months longer than in the comparator arm. As described in Section I 3.2.6, according to the information in Module 4 A, patients who had not experienced a first deterioration since the start of the study before the initiation of subsequent antineoplastic therapy were censored on the date of the last recording of the outcome. There is no information available on whether this censoring scheme was predefined and to what extent it affected the observation periods.

For the side effects outcomes, the observation period in the intervention arm is approx. 6 months longer than in the comparator arm. In addition, the fixed treatment duration in the comparator arm and the linking of the observation time for side effects to the treatment duration means that the effect estimate only reflects approximately the first 6 months after randomization and thus only the period of chemotherapy in the comparator arm, but not a possible maintenance therapy with avelumab and only the first 6 months of a possibly longer-lasting therapy in the intervention arm. This has been taken into account in the derivation of the certainty of conclusions for the outcomes on side effects (see Section I 5.2.1).

I 5.1.3 Subsequent therapies

Table 22 shows the subsequent therapies patients received after discontinuing the study medication in the subpopulation relevant to research question 2.

Table 22: Information on subsequent antineoplastic therapies (≥ 1% of patients in ≥ 1 treatment arm) – RCT, direct comparison: enfortumab vedotin + pembrolizumab versus carboplatin + gemcitabine (subpopulation: cisplatin unsuitable) (multipage table)

Study **drug class** **therapies** **drug**	**Patients with subsequent therapy, n (%)** **enfortumab vedotin + pembrolizumab** **N = 202**	 **carboplatin + gemcitabine** **N = 202**
Study EV-302/KN-A39		
Total[a]	56 (27.7)	139 (68.8)
Palliative radiotherapy	10 (5.0)	17 (8.4)
Non-palliative radiotherapy	2 (1.0)	1 (0.5)
Surgical intervention	3 (1.5)	3 (1.5)
Systemic therapy	47 (23.3)	130 (64.4)
For progressive disease	43 (21.3)	89 (44.1)
As maintenance therapy	2 (1.0)	57 (28.2)
First subsequent systemic therapy	39 (19.3)	87 (43.1)
Platinum-based therapy[b]	39 (19.3)	8 (4.0)
Cisplatin-based therapy	9 (4.5)	3 (1.5)
Carboplatin-based therapy	29 (14.4)	4 (2.0)
PD-1/-L1-based maintenance therapy	0 (0)	55 (27.2)
Avelumab	0 (0)	51 (25.2)
Pembrolizumab	0 (0)	2 (1.0)
Other PD-1/-L1-based therapy	4 (2.0)	55 (27.2)
Atezolizumab	0 (0)	23 (11.4)
Pembrolizumab	4 (2.0)	31 (15.3)
Other drugs	4 (2.0)	12 (5.9)
Erdafitinib	0 (0)	2 (1.0)
Enfortumab vedotin	1 (0.5)	2 (1.0)
Gemcitabine	1 (0.5)	2 (1.0)
Paclitaxel	0 (0)	3 (1.5)
Second and later subsequent systemic therapies	8 (4.0)[c]	43 (21.3)[c]
Pplatinum-based therapy[b]	3 (1.5)	3 (1.5)
Carboplatin-based therapy	2 (1.0)	4 (2.0)
PD-1/-L1-based maintenance therapy	2 (1.0)	3 (1.2)
Avelumab	2 (1.0)	1 (0.5)
Pembrolizumab	0 (0)	2 (1.0)
Other PD-1/-L1-based therapy	0 (0)	5 (2.5)
Pembrolizumab	0 (0)	4 (2.0)
Other drugs	4 (2.0)	36 (17.8)
Erdafitinib	0 (0)	2 (1.0)
Enfortumab vedotin	0 (0)	23 (11.4)

Table 22: Information on subsequent antineoplastic therapies (≥ 1% of patients in ≥ 1 treatment arm) – RCT, direct comparison: enfortumab vedotin + pembrolizumab versus carboplatin + gemcitabine (subpopulation: cisplatin unsuitable) (multipage table)

Study	**Patients with subsequent therapy, n (%)**	
drug class **therapies** **drug**	**enfortumab vedotin + pembrolizumab** **N = 202**	**carboplatin + gemcitabine** **N = 202**
Sacituzumab govitecan	1 (0.5)	3 (1.5)
Paclitaxel	2 (1.0)	10 (5.0)

a. Including maintenance therapies.
b. If a platinum-based therapy and a PD-1/-L1-based therapy were used in the same line of therapy, the latter was categorized as a platinum-based therapy.
c. Institute's calculation.

n: number of patients with subsequent therapy; N: number of analysed patients; PD-1: programmed cell death 1; PD-L1: programmed cell death ligand 1; RCT: randomized controlled trial

As described in Section I 5.3.1, the data on subsequent systemic antineoplastic therapies in the company's dossier include both systemic therapies for the treatment of progressive disease and maintenance therapies. This is not appropriate. It cannot be inferred from the available data which subsequent therapies were used after disease progression under maintenance treatment with avelumab.

In the EV-302/KN-A39 study, subsequent therapies were permitted without restrictions in both study arms. In the subpopulation relevant to research question 2, a total of 43 (21%) patients in the intervention arm and 89 (44%) patients in the comparator arm received at least 1 subsequent antineoplastic systemic therapy for the treatment of progressive disease. In relation to the patients in whom disease progression occurred as a PFS event (85 patients in the intervention arm versus 132 patients in the comparator arm), this means that 51% of the patients with disease progression in the intervention arm and 67% in the comparator arm received at least one subsequent antineoplastic therapy for the treatment of progressive disease (Institute's calculation). According to the current S3 guideline, the ability and meaningfulness of second-line therapy must be checked for each patient [10], so that the proportion of patients with subsequent therapy in the subpopulation of the EV-302/KN-A39 study relevant to research question 2 appears appropriate overall.

According to current guideline recommendations, platinum-based chemotherapy or, in certain patients, erdafitinib is recommended as a subsequent therapy after disease progression under enfortumab vedotin + pembrolizumab [16]; platinum-based chemotherapy was the predominant first subsequent therapy in the intervention arm, which 19% of patients received.

Pembrolizumab or atezolizumab is recommended as first-line therapy for disease progression under platinum-based chemotherapy [10,16]. In the comparator arm, 15% and 11% of patients respectively received these drugs as the first PD-1/PD-L1-based subsequent systemic therapy, which was not a maintenance therapy.

In cases of disease progression under maintenance treatment with avelumab following platinum-based chemotherapy as first-line treatment, erdafitinib (in certain patients) and enfortumab vedotin are primarily recommended, and sacituzumab govitecan, vinflunine or taxanes [16] are recommended with a lower recommendation grade. These drugs, particularly enfortumab vedotin, were frequently used as second and later subsequent systemic therapies in the comparator arm (see Table 22). However, as described above, it is not clear from the information provided by the company whether these drugs were used after disease progression under maintenance therapy or under a previous subsequent therapy for the treatment of a progressive disease and thus in a later line of therapy.

Despite this lack of information, it is assumed on the basis of the available data and the recommendations of the current S3 guideline that implementation of the subsequent therapies was predominantly appropriate in the subpopulation of study EV-302/KN-A39 relevant to research question 2.

I 5.1.4 Risk of bias across outcomes (study level)

The risk of bias across outcomes (risk of bias at study level) is described in Table 13 in Section I 5.1.4 and was rated as low.

Limitations resulting from the open-label study design are described in Section I 5.2.2 under the outcome-specific risk of bias and apply equally to research questions 1 and 2.

I 5.1.5 Transferability of the study results to the German health care context

The company's assessment regarding the transferability of the study results to the German health care context is described in Section I 5.1.5.

I 5.2 Results on added benefit

I 5.2.1 Outcomes included

The patient-relevant outcomes that were to be included in the assessment are identical for research questions 1 and 2 can be found in Section I 5.2.1.

Table 23 shows the outcomes for which data for research question 2 are available in the included study.

Table 23: Matrix of outcomes – RCT, direct comparison: enfortumab vedotin + pembrolizumab vs. carboplatin + gemcitabine (subpopulation: cisplatin unsuitable)

Study	Outcomes															
	Overall survival	Worst pain (BPI-SF item 3)	Pain interference (BPI-SF item 9a–g)	Symptoms (EORTC QLQ-C30)	Health status (EQ-5D VAS)	Health-related quality of life (EORTC-QLQ-C30)	SAEs	Severe AEs[a]	Discontinuation due to AEs	Immune-related SAEs[b]	Immune-related severe AEs[a, b]	Peripheral neuropathy (SMQ, AEs)	Skin reactions[c]	Severe hyperglycaemia (PT, severe AEs[a])	Severe nephrotoxicity[d]	Further specific AEs[a, e]
EV-302/KN-A39	Yes	Yes	No[f]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes

a. Severe AEs are operationalized as CTCAE grade ≥ 3.
b. In each case, the operationalization of a specific, predefined MedDRA PT collection from the outcome of AEOSI (Version 25.0) presented by the company is used.
c. Operationalized as skin and subcutaneous tissue disorders (SOC, AEs).
d. Operationalized as renal and urinary disorders (SOC, severe AEs).
e. The following events were considered (MedDRA coding): constipation (PT, AEs), diarrhoea (PT, AEs), dysgeusia (PT, AEs), eye disorders (SOC, AEs), endocrine disorders (SOC, AEs), blood and lymphatic system disorders (SOC, severe AEs) and acute kidney injury (PT, severe AEs).
f. No suitable data available; for the reasoning, see Section I 5.2.1 of the present dossier assessment.

AE: adverse event; AESI: adverse events of special interest; BPI-SF: Brief Pain Inventory – Short Form; CTCAE: Common Terminology Criteria for Adverse Events; EORTC QLQ-C30: European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30; MedDRA: Medical Dictionary for Regulatory Activities; PT: Preferred Term; RCT: randomized controlled trial; SAE: serious adverse event; SMQ: Standardized MedDRA Query; SOC: System Organ Class; VAS: visual analogue scale

Notes on outcomes

As described in Section I 4.2.3, the ACT was only incompletely implemented in study EV-302/KN-A39, as maintenance therapy with avelumab was not part of the study treatment and not all patients who were eligible for maintenance treatment with avelumab also received it. The consequences for the benefit assessment resulting from this at outcome level can be found in Section I 5.2.1, together with further aspects on the outcomes, such as in particular the company's sensitivity analyses on the outcome of overall survival.

I 5.2.2 Risk of bias

Table 24 describes the risk of bias for the results of the relevant outcomes for research question 2.

Table 24: Risk of bias across outcomes and outcome-specific risk of bias – RCT, direct comparison: enfortumab vedotin + pembrolizumab vs. carboplatin + gemcitabine (subpopulation: cisplatin unsuitable)

Study		Outcomes															
	Study level	Overall survival	Worst pain (BPI-SF item 3)	Pain interference (BPI-SF items 9a–g)	Symptoms (EORTC QLQ-C30)	Health status (EQ-5D VAS)	Health-related quality of life (EORTC-QLQ-C30)	SAEs	Severe AEs[a]	Discontinuation due to AEs	Immune-related SAEs[b]	Immune-related severe AEs[a, b]	Peripheral neuropathy (SMQ, AEs)	Skin reactions[c]	Severe hyperglycaemia (PT, severe AEs[a])	Severe nephrotoxicity[d]	Further specific AEs[a, e]
EV-302/KN-A39	L	L	H[f, g]	–[h]	H[f, g]	H[f, g]	H[f, g]	H[i]	H[i]	H[i, j]	H[i]	H[i]	H[f, i]	H[f, i]	H[i]	H[i]	H[f, i]

a. Severe AEs are operationalized as CTCAE grade ≥ 3.
b. In each case, the operationalization of a specific, predefined MedDRA PT collection from the outcome of AEOSI (Version 25.0) presented by the company is used.
c. Operationalized as skin and subcutaneous tissue disorders (SOC, AEs).
d. Operationalized as renal and urinary disorders (SOC, severe AEs).
e. The following events are considered (MedDRA coding): constipation (PT, AEs), diarrhoea (PT, AEs), dysgeusia (PT, AEs), eye disorders (SOC, AEs), endocrine disorders (SOC, AEs), blood and lymphatic system disorders (SOC, severe AEs) and acute kidney injury (PT, severe AEs).
f. Lack of blinding in the case of subjective recording of outcomes, unless severe or serious AEs are involved.
g. Decreasing response to questionnaires in the course of the study; large proportion of patients not included in the analysis (> 10 %) or large difference between the treatment groups (> 5 percentage points).
h. No suitable data available; see Section I 5.2.1 for reasons.
i. Incomplete observations for potentially informative reasons.
j. Lack of blinding in the presence of subjective decision on treatment discontinuation.

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

The outcome-specific risk of bias does not differ between research question 1 and research question 2 and can therefore be found in Section I 5.2.2.

Summary assessment of the certainty of conclusions

In addition to the described aspects of bias, there are uncertainties for study EV-302/KN-A39, as described in Section I 4.2.2 and Section I 4.2.3, particularly in the implementation of the ACT. In the present specific data constellation, the results of the study can nevertheless be interpreted for the research questions of the present benefit assessment, but the certainty of the study results for the present assessment is reduced. Based on the EV-302/KN-A39 study, at most hints, e.g. of an added benefit, can be derived for both research questions.

Moreover, for the outcomes in the side effects category, analyses are only available for a significantly shortened period, which in the comparator arm only reflects the treatment with chemotherapy, but not the period of a possible maintenance therapy with avelumab, and in the intervention arm only takes into account the first 6 months of a possibly longer-lasting treatment (see Section I 5.2.1). This shortened observation in the comparator arm or consideration of recorded data in the intervention arm contributes to a limited certainty of conclusions and additionally justifies the fact that at most hints can be derived.

I 5.2.3 Results

Table 25 summarizes the results of the comparison of enfortumab vedotin + pembrolizumab with carboplatin + gemcitabine for first-line treatment in adult patients with unresectable or metastatic urothelial carcinoma for whom cisplatin-based therapy is unsuitable. Where necessary, IQWiG calculations are provided to supplement the data from the company’s dossier.

Kaplan-Meier curves on the presented time-to-event analyses can be found in I Appendix B.2 of the full dossier assessment. Results on common AEs, SAEs, severe AEs and discontinuations due to AEs are presented in I Appendix C.2 of the full dossier assessment. The company's dossier does not provide a list of the categories of immune-related AEs, immune-related SAEs and immune-related severe AEs that occurred.

Table 25: Results (mortality, morbidity, health-related quality of life, side effects) – RCT, direct comparison: enfortumab vedotin + pembrolizumab vs. carboplatin + gemcitabine (subpopulation: cisplatin unsuitable) (multipage table)

Study outcome category outcome	Enfortumab vedotin + pembrolizumab		Carboplatin + gemcitabine		Enfortumab vedotin + pembrolizumab vs. carboplatin + gemcitabine
	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
EV-302/KN-A39					
Mortality					
Overall survival	202	NA [22.9; NC] 64 (31.7)	202	12.9 [11.4; 15.9] 116 (57.4)	0.41 [0.30; 0.56]; < 0.001[a]
Overall survival (sensitivity analysis 1[b])	202	NA [22.9; NC] 64 (31.7)	202	15.9 [12.2; 20.6] 98 (48.5)	0.49 [0.35; 0.68]; < 0.001[a]
Overall survival (sensitivity analysis 2[c])	202	NA [22.9; NC] 64 (31.7)	202	17.4 [12.5; 22.0] 98 (48.5)	0.54 [0.39; 0.74]; < 0.001[a]
Overall survival (sensitivity analysis 3[d])	202	NA [22.9; NC] 64 (31.7)	202	15.7 [12.5; 18.4] 111 (55.0)	0.45 [0.32; 0.61]; < 0.001[a]
Morbidity					
Worst pain (BPI-SF item 3 - time to first deterioration)[e]	202	3.2 [1.6; 10.7] 85 (42.1)	202	1.3 [0.7; 2.2] 105 (52.0)	0.68 [0.50; 0.94]; 0.016[a]
Pain intensity (BPI-SF items 3–6, time to first deterioration, presented as supplementary information)[f]			*No suitable data available*[g]		
Pain interference (BPI-SF items 9a-g – time to first deterioration)[f]			No suitable data available[g]		
Symptoms (EORTC QLQ-C30 – time to first deterioration[h])					
Fatigue	202	0.6 [0.4; 0.8] 130 (64.4)	202	0.4 [0.4; 0.6] 131 (64.9)	0.78 [0.59; 1.03]; 0.074[a]
Nausea and vomiting	202	1.8 [1.1; 2.7] 102 (50.5)	202	0.9 [0.4; 1.5] 118 (58.4)	0.71 [0.53; 0.96]; 0.028[a]
Pain	202	1.1 [0.7; 1.8] 106 (52.5)	202	0.9 [0.5; 1.3] 118 (58.4)	0.78 [0.58; 1.05]; 0.100[a]
Dyspnoea	202	2.0 [1.3; 2.7] 101 (50.0)	202	1.5 [1.1; 2.2] 104 (51.5)	0.86 [0.63; 1.18]; 0.351[a]
Insomnia	202	1.5 [1.1; 2.2] 101 (50.0)	202	1.3 [0.9; 2.2] 92 (45.5)	0.90 [0.65; 1.24]; 0.544[a]
Appetite loss	202	0.9 [0.7; 1.3] 116 (57.4)	202	1.1 [0.6; 1.5] 110 (54.5)	0.94 [0.69; 1.28]; 0.748[a]

Table 25: Results (mortality, morbidity, health-related quality of life, side effects) – RCT, direct comparison: enfortumab vedotin + pembrolizumab vs. carboplatin + gemcitabine (subpopulation: cisplatin unsuitable) (multipage table)

Study outcome category outcome	Enfortumab vedotin + pembrolizumab		Carboplatin + gemcitabine		Enfortumab vedotin + pembrolizumab vs. carboplatin + gemcitabine
	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
Constipation	202	2.2 [1.5; 3.1] 94 (46.5)	202	0.4 [0.4; 0.9] 112 (55.4)	0.49 [0.36; 0.67]; < 0.001[a]
Diarrhoea	202	2.0 [1.3; 3.2] 101 (50.0)	202	4.5 [2.0; 11.0] 78 (38.6)	1.34 [0.97; 1.87]; 0.070[a]
Health status (EQ-5D VAS - time to first deterioration[i])	202	1.5 [1.0; 3.2] 107 (53.0)	202	1.3 [0.9; 2.0] 110 (54.5)	0.88 [0.65; 1.20]; 0.468[a]
health-related quality of life					
EORTC-QLQ C30 – time to first deterioration[j]					
Global health status	202	1.1 [0.6; 1.6] 118 (58.4)	202	0.9 [0.6; 1.3] 114 (56.4)	0.95 [0.70; 1.29]; 0.788[a]
Physical functioning	202	1.1 [0.7; 1.6] 121 (59.9)	202	0.7 [0.4; 1.1] 124 (61.4)	0.80 [0.60; 1.07]; 0.129[a]
Role functioning	202	0.7 [0.5; 1.1] 125 (61.9)	202	0.4 [0.4; 0.6] 136 (67.3)	0.76 [0.56; 1.02]; 0.063[a]
Emotional functioning	202	4.5 [2.1; 9.4] 90 (44.6)	202	2.0 [1.1; 3.2] 94 (46.5)	0.73 [0.52; 1.03]; 0.080[a]
Cognitive functioning	202	1.5 [1.1; 1.8] 112 (55.4)	202	0.9 [0.6; 1.5] 114 (56.4)	0.80 [0.60; 1.08]; 0.151[a]
Social functioning	202	0.9 [0.6; 1.3] 118 (58.4)	202	0.9 [0.4; 1.1] 111 (55.0)	1.06 [0.78; 1.43]; 0.700[a]
Side effects[k]					
AEs (supplementary information)	201	0.3 [0.2; 0.3] 200 (99.5)	197	0.2 [0.1; 0.2] 193 (98.0)	–
SAEs	201	7.9 [5.3; 12.9] 113 (56.2)	197	5.4 [4.2; NC] 86 (43.7)	0.87 [0.64; 1.18]; 0.365[l]
Severe AEs[m]	201	2.6 [2.0; 4.0] 157 (78.1)	197	0.7 [0.5; 0.9] 166 (84.3)	0.46 [0.36; 0.58]; < 0.001[l]
Discontinuation due to AEs	201	14.0 [10.3; NC] 83 (41.3)	197	NA 35 (17.8)	1.30 [0.85; 2.00]; 0.228[l]
Immune-related AEsn (supplementary information)	*201*	*11.5 [6.9; NC]* *89 (44.3)*	*197*	*NA* *11 (5.6)*	–

Table 25: Results (mortality, morbidity, health-related quality of life, side effects) – RCT, direct comparison: enfortumab vedotin + pembrolizumab vs. carboplatin + gemcitabine (subpopulation: cisplatin unsuitable) (multipage table)

Study outcome category outcome	Enfortumab vedotin + pembrolizumab		Carboplatin + gemcitabine		Enfortumab vedotin + pembrolizumab vs. carboplatin + gemcitabine
	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
Immune-related SAEsn	201	NA 20 (10.0)	197	NA 2 (1.0)	6.93 [1.58; 30.31]; 0.003[l]
Immune-related severe AEs,[m, n]	201	NA 42 (20.9)	197	NA 2 (1.0)	15.92 [3.82; 66.38]; < 0.001[l]
Peripheral neuropathy (SMQ, AEs)[o]	201	4.5 [3.7; 5.1] 131 (65.2)	197	NA 17 (8.6)	6.41 [3.83; 10.73]; < 0.001[l]
Skin reactions[p]	201	0.6 [0.5; 0.7] 162 (80.6)	197	NA 51 (25.9)	4.95 [3.60; 6.81]; < 0.001[l]
Severe hyperglycaemia (PT, severe AEs[m])	201	NA 12 (6.0)	197	NA 1 (0.5)	10.71 [1.38; 82.92]; 0.005[l]
Severe nephrotoxicity[m, q]	201	NA 25 (12.4)	197	NA 15 (7.6)	1.12 [0.57; 2.23]; 0.736[l]
Constipation (PT, AEs)	201	NA [24,5; NC] 49 (24,4)	197	NA 71 (36.0)	0.45 [0.30; 0.66]; < 0.001[l]
Diarrhoea (PT, AEs)	201	NA [11,1; NC] 77 (38,3)	197	NA 29 (14.7)	2.30 [1.48; 3.56]; < 0.001[l]
Dysgeusia (PT, AEs)	201	NA 46 (22.9)	197	NA 9 (4.6)	4.83 [2.35; 9.92]; < 0.001[l]
Eye disorders (SOC, AEs)	201	NA [16,6; NC] 64 (31,8)	197	NA 12 (6.1)	3.85 [2.04; 7.26]; < 0.001[l]
Endocrine disorders (SOC, AEs)	201	NA 36 (17.9)	197	NA 4 (2.0)	5.47 [1.90; 15.79]; < 0.001[l]
Blood and lymphatic system disorders (SOC, severe AEs)[m]	201	NA 43 (21.4)	197	1.3 [1.0; 1.6] 135 (68.5)	0.14 [0.09; 0.20]; < 0.001[l]
Acute kidney injury (PT, severe AEs)[m]	201	NA 14 (7.0)	197	NA 4 (2.0)	3.05 [0.99; 9.36]; 0.041[l]

Table 25: Results (mortality, morbidity, health-related quality of life, side effects) – RCT, direct comparison: enfortumab vedotin + pembrolizumab vs. carboplatin + gemcitabine (subpopulation: cisplatin unsuitable) (multipage table)

Study outcome category outcome	Enfortumab vedotin + pembrolizumab		Carboplatin + gemcitabine		Enfortumab vedotin + pembrolizumab vs. carboplatin + gemcitabine
	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. HR and CI: Cox proportional hazards model, p-value: log-rank test, each stratified by PD-L1 expression (high vs. low) and liver metastases (present vs. not present).
b. Censoring at the time of death: avelumab-eligible patients who had not received avelumab and died were censored at the time of death.
c. Censoring at data cut-off: avelumab-eligible patients who had not received avelumab and died were censored at the time of data cut-off.
d. Modified time of death: avelumab-eligible patients who had not received avelumab and died were censored with a modified time of death. A simplified assumption was made that the patients would have benefited from treatment with avelumab to the extent shown in the approval study of avelumab (JAVELIN Bladder 100); see Section I 5.2.1 for explanation.
e. A score increase by ≥ 2 points from baseline is considered a clinically relevant deterioration (scale range 0 to 10); for explanation, see Section I 5.2.1.
f. A score increase by ≥ 1.5 points from baseline is considered a clinically relevant deterioration (scale range 0 to 10); for explanation, see Section I 5.2.1.
g. See Section I 5.2.1 for a rationale.
h. An EORTC QLQ-C30 score increase by ≥ 10 points from baseline is considered a clinically relevant deterioration (scale range: 0 to 100).
i. An EQ-5D VAS score decrease by ≥ 15 points from baseline is considered a clinically relevant deterioration (scale range: 0 to 100).
j. An EORTC QLQ-C30 score decrease by ≥ 10 points from baseline is considered a clinically relevant deterioration (scale range: 0 to 100).
k. The terms of disease progression, progression of a disease and progression of a malignant disease as well as similar terms were not taken into account in the assessment of AEs. The fixed treatment duration and the associated discontinuation of observation after the end of study medication in the comparator arm mean that the effect estimate only reflects approximately the first 6 months after randomization.
l. HR and CI: unstratified Cox proportional hazards model; p-value: unstratified log-rank test.
m. Operationalized as CTCAE grade ≥ 3.
n. In each case, the operationalization of a specific, predefined MedDRA PT collection from the outcome of AESI (Version 25.0) presented by the company is used.
o. The following result is shown for the severe AEs of the SMQ “peripheral neuropathy” included in the results on AEs: 17 (8.5) vs. 0 (0); HR: NC [NC; NC]; p = 0.0407; Kaplan-Meier curve see Figure 89.
p. Operationalized as skin and subcutaneous tissue disorders (SOC, AEs); the following result is shown for the severe AEs of the SOC ”skin and subcutaneous tissue disorders” included in the results on AEs: 39 (19.4) vs. 2 (1.0); HR: NC [NC; NC]; < 0.001; Kaplan-Meier curve see Figure 91.
q. Operationalized as renal and urinary disorders (SOC, severe AEs).

Table 25: Results (mortality, morbidity, health-related quality of life, side effects) – RCT, direct comparison: enfortumab vedotin + pembrolizumab vs. carboplatin + gemcitabine (subpopulation: cisplatin unsuitable) (multipage table)

Study outcome category outcome	Enfortumab vedotin + pembrolizumab		Carboplatin + gemcitabine		Enfortumab vedotin + pembrolizumab vs. carboplatin + gemcitabine
	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

AE: adverse event; AESI: adverse events of special interest; BPI-SF: Brief Pain Inventory – Short Form; CI: confidence interval; CTCAE: Common Terminology Criteria for Adverse Events; EORTC QLQ-C30: European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30; HR: hazard ratio; n: number of patients with (at least one) event; N: number of analysed patients; NA: not achieved; NC: not calculable; PD-L1: programmed cell death ligand 1; PT: Preferred Term; RCT: randomized controlled trial; SAE: serious adverse event; SOC: System Organ Class; VAS: visual analogue scale

Based on the available information, at most hints, e.g. of an added benefit, can be determined for all outcomes due to the limited certainty of conclusions (see Section I 4.2 and Section I 5.2.2 for the reasoning).

When interpreting the results on side effects, it should be noted that due to the fixed treatment duration and the associated discontinuation of observation in the comparator arm, the effect estimate only covers approximately the first 6 months after randomization (see Section I 5.1.2).

Mortality

Overall survival

For the outcome of overall survival, a statistically significant difference was found in favour of enfortumab vedotin + pembrolizumab in comparison with carboplatin + gemcitabine. The 3 sensitivity analyses presented by the company, in which patients in the comparator arm for whom maintenance treatment with avelumab would potentially have been indicated and who died without maintenance treatment were accounted for differently (see Section I 5.2.1), also showed a statistically significant difference in favour of enfortumab vedotin + pembrolizumab compared with carboplatin + gemcitabine in each case. This effect therefore remains even if the maximum situation is assumed that all these patients in the comparator arm have survived to the present data cut-off. In this data constellation, there is a hint of added benefit of enfortumab vedotin + pembrolizumab in comparison with the ACT. The extent of the added benefit is major both in the main analysis and in all sensitivity analyses (see Section I 5.3.1).

Morbidity

Worst pain (BPI-SF item 3)

For the outcome of worst pain (recorded using the BPI-SF item 3), a statistically significant difference was found in favour of enfortumab vedotin + pembrolizumab in comparison with carboplatin + gemcitabine. However, there is an effect modification by the characteristic of metastases (see Section I 5.2.4). For patients with visceral metastases, there was no hint of an added benefit of enfortumab vedotin + pembrolizumab versus the ACT; an added benefit is therefore not proven for this patient group. There was a hint of an added benefit of enfortumab vedotin + pembrolizumab versus the ACT for patients with exclusively lymph node metastases.

Pain interference (BPI-SF items 9a–g)

No suitable data are available for the outcome of pain interference (recorded using BPI-SF items 9a-9g) (for reasons, see Section I 5.2.1). There is no hint of an added benefit of enfortumab vedotin + pembrolizumab in comparison with the ACT; an added benefit is therefore not proven.

Symptoms

EORTC QLQ-C30

Fatigue

No statistically significant difference between treatment groups was found for the outcome of fatigue. However, there is an effect modification by the characteristic of sex (see Section I 5.2.4). For women, there is a hint of added benefit of enfortumab vedotin + pembrolizumab in comparison with the ACT. For men, there is no hint of an added benefit of enfortumab vedotin + pembrolizumab in comparison with the ACT; an added benefit is therefore not proven for men.

Nausea and vomiting

For the outcome of nausea and vomiting, there was a statistically significant difference in favour of enfortumab vedotin + pembrolizumab in comparison with carboplatin + gemcitabine. For this outcome of the non-serious/non-severe symptoms category, however, the extent of the effect was no more than marginal (see Section I 5.3.1). There is no hint of an added benefit of enfortumab vedotin + pembrolizumab in comparison with the ACT; an added benefit is therefore not proven.

Pain, dyspnoea, insomnia, appetite loss and diarrhoea

No statistically significant difference between treatment groups was shown for any of the outcomes of pain, dyspnoea, insomnia, appetite loss and diarrhoea. There is no hint of an

added benefit of enfortumab vedotin + pembrolizumab in comparison with the ACT; an added benefit is therefore not proven.

Constipation

For the outcome of constipation, a statistically significant difference was found in favour of enfortumab vedotin + pembrolizumab in comparison with carboplatin + gemcitabine. However, there is an effect modification by the characteristic of metastases (see Section I 5.2.4). For both patients with visceral metastases and patients with exclusively lymph node metastases, there is a hint of added benefit of enfortumab vedotin + pembrolizumab versus the ACT, however, with a differing extent (see Section I 5.3.1).

Health status

No statistically significant difference between treatment groups was shown for the outcome of health status. There is no hint of an added benefit of enfortumab vedotin + pembrolizumab in comparison with the ACT; an added benefit is therefore not proven.

Health-related quality of life

EORTC QLQ-C30

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

No statistically significant difference between the treatment groups was shown for any of the outcomes of global health status, physical functioning, cognitive functioning, and social functioning. In each case, there is no hint of an added benefit of enfortumab vedotin + pembrolizumab in comparison with the ACT; an added benefit is therefore not proven for any case.

Role functioning and emotional functioning

A statistically significant difference was neither shown for the outcome of role functioning nor for the outcome of emotional functioning. In each case, there is an effect modification by the characteristic of sex, however (see Section I 5.2.4). For women, there is a hint of added benefit of enfortumab vedotin + pembrolizumab in comparison with the ACT. For men, there is no hint of an added benefit of enfortumab vedotin + pembrolizumab in comparison with the ACT; an added benefit is therefore not proven.

Side effects

SAEs and discontinuation due to AEs

No statistically significant difference was found between treatment groups for either of the outcomes of SAEs or discontinuation due to AEs. For each of them, there is no hint of greater or lesser harm from enfortumab vedotin + pembrolizumab in comparison with the ACT; greater or lesser harm is therefore not proven.

Severe AEs

For the outcome of severe AEs, a statistically significant difference was found in favour of enfortumab vedotin + pembrolizumab in comparison with carboplatin + gemcitabine. There is a hint of lesser harm from enfortumab vedotin + pembrolizumab in comparison with the ACT.

Immune-related SAEs, immune-related severe AEs, peripheral neuropathy (AEs), skin reactions (AEs) and severe hyperglycaemia (severe AEs)

For each of the outcomes of immune-related SAEs, immune-related severe AEs, peripheral neuropathy (AEs), skin reactions (AEs) and severe hyperglycaemia (severe AEs), a statistically significant difference was found to the disadvantage of enfortumab vedotin + pembrolizumab in comparison with carboplatin + gemcitabine. For each of them, there is a hint of greater harm from enfortumab vedotin + pembrolizumab in comparison with the ACT.

Severe nephrotoxicity (severe AEs)

No statistically significant difference between treatment groups was found for the outcome of severe nephrotoxicity (severe AEs). There is no hint of greater or lesser harm from enfortumab vedotin + pembrolizumab in comparison with the ACT; greater or lesser harm is therefore not proven.

Other specific AEs

Constipation (AEs), blood and lymphatic system disorders (severe AEs)

A statistically significant difference in favour of enfortumab vedotin + pembrolizumab versus carboplatin + gemcitabine was shown for the outcomes of constipation (AEs) and blood and lymphatic system disorders (severe AEs). For each of them, there is a hint of lesser harm from enfortumab vedotin + pembrolizumab in comparison with the ACT.

Diarrhoea (AEs), dysgeusia (AEs), eye disorders (AEs), endocrine disorders (AEs) and acute kidney injury (severe AEs)

A statistically significant difference to the disadvantage of enfortumab vedotin + pembrolizumab versus carboplatin + gemcitabine was shown for each of the outcomes of diarrhoea (AEs), dysgeusia (AEs), eye disorders (AEs), endocrine disorders (AEs) and acute kidney injury (severe AEs). For each of them, there is a hint of greater harm from enfortumab vedotin + pembrolizumab in comparison with the ACT.

I 5.2.4 Subgroups and other effect modifiers

The following subgroup characteristics are taken into account in the present benefit assessment:

- Age (< 65 years versus ≥ 65 years)

- Sex (male versus female)
- Metastases (visceral metastases vs. exclusively lymph node metastases)

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 presented only if there is a statistically significant and relevant effect in at least one subgroup. Subgroup results where the extent does not differ between subgroups are not presented.

The results are presented in Table 26. The Kaplan-Meier curves on the subgroup results are presented in I Appendix B.2 of the full dossier assessment.

Table 26: Subgroups (morbidity, health-related quality of life) – RCT, direct comparison: enfortumab vedotin + pembrolizumab vs. carboplatin + gemcitabine (subpopulation: cisplatin unsuitable) (multipage table)

Study outcome characteristic subgroup	Enfortumab vedotin + pembrolizumab		Carboplatin + gemcitabine		Enfortumab vedotin + pembrolizumab vs. carboplatin + gemcitabine	
	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][a]	p-value[a]
EV-302/KN-A39						
Worst pain (BPI-SF item 3 - time to first deterioration[b])						
Metastases						
Visceral metastases	148	2.7 [1.1; 4.5] 67 (45.3)	157	1.7 [0.8; 2.5] 79 (50.3)	0.92 [0.62; 1.35]	0.622
Lymph nodes only	43	NA [1.5; NC] 16 (37.2)	37	0.5 [0.2; 2.4] 22 (59.5)	0.32 [0.14; 0.73]	0.006
					Interaction:	0.021[c]

Table 26: Subgroups (morbidity, health-related quality of life) – RCT, direct comparison: enfortumab vedotin + pembrolizumab vs. carboplatin + gemcitabine (subpopulation: cisplatin unsuitable) (multipage table)

Study outcome characteristic subgroup	Enfortumab vedotin + pembrolizumab		Carboplatin + gemcitabine		Enfortumab vedotin + pembrolizumab vs. carboplatin + gemcitabine	
	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][a]	p-value[a]
Symptoms (EORTC QLQ-C30, fatigue – time to first deterioration[d])						
Sex						
Female	56	0.7 [0.4; 2.2] 30 (53.6)	51	0.4 [0.2; 0.6] 33 (68.6)	0.21 [0.09; 0.48]	< 0.001
Male	146	0.5 [0.4; 0.7] 100 (68.5)	151	0.4 [0.4; 0.6] 96 (63.6)	0.98 [0.72; 1.33]	0.898
					Interaction:	0.027[c]
Symptoms (EORTC QLQ-C30, constipation – time to first deterioration[d])						
Metastases						
Visceral metastases	148	2.0 [0.9; 3.1] 71 (48.0)	157	0.6 [0.4; 1.7] 79 (50.3)	0.59 [0.40; 0.87]	0.008
Lymph nodes only	43	2.1 [0.6; NC] 20 (46.5)	37	0.3 [0.2; 0.5] 25 (67.6)	0.33 [0.14; 0.78]	0.008
					Interaction:	0.019[c]
Health-related quality of life (EORTC QLQ-C30, role functioning – time to first deterioration[e])						
Sex						
Female	56	0.7 [0.4; 1.1] 34 (60.7)	51	0.2 [0.2; 0.4] 37 (72.5)	0.52 [0.28; 0.97]	0.031
Male	146	0.7 [0.4; 1.1] 91 (62.3)	151	0.5 [0.4; 0.9] 99 (65.6)	0.85 [0.61; 1.19]	0.360
					Interaction:	0.025[c]
Health-related quality of life (EORTC QLQ-C30, emotional functioning - time to first deterioration[e]						
Sex						
Female	56	10.7 [1.8; NC] 20 (35.7)	51	0.9 [0.4; 1.1] 27 (52.9)	0.36 [0.17; 0.79]	0.010
Male	146	3.2 [1.7; 9.4] 70 (47.9)	151	2.7 [1.3; 5.9] 67 (44.4)	0.89 [0.60; 1.30]	0.549
					Interaction:	0.014[c]

Table 26: Subgroups (morbidity, health-related quality of life) – RCT, direct comparison: enfortumab vedotin + pembrolizumab vs. carboplatin + gemcitabine (subpopulation: cisplatin unsuitable) (multipage table)

Study outcome characteristic subgroup	Enfortumab vedotin + pembrolizumab		Carboplatin + gemcitabine		Enfortumab vedotin + pembrolizumab vs. carboplatin + gemcitabine	
	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][a]	p-value[a]

a. HR and CI: Cox proportional hazards model, p-value: log-rank test, each stratified by age, sex, region, PD-L1 expression and liver metastases as well as subgroup and the interaction term subgroup and treatment.
b. A score increase by ≥ 2 points from baseline is considered a clinically relevant deterioration (scale range 0 to 10).
c. p-value from Wald test based on Cox proportional hazards model with the variable subgroup and interaction term subgroup and treatment.
d. An EORTC QLQ-C30 score increase by ≥ 10 points from baseline is considered a clinically relevant deterioration (scale range: 0 to 100).
e. An EORTC QLQ-C30 score decrease by ≥ 10 points from baseline is considered a clinically relevant deterioration (scale range: 0 to 100).

CI: confidence interval; EORTC QLQ-C30: European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30; HR: hazard ratio; n: number of patients with (at least one) event; N: number of analysed patients; NA: not achieved; NC: not calculable; PT: Preferred Term; RCT: randomized controlled trial; SOC: System Organ Class

Morbidity

Worst pain (BPI-SF item 3)

There is an effect modification by the characteristic of metastases for the outcome of worst pain (BPI-SF item 3). There was no statistically significant difference between the treatment groups for patients with visceral metastases. There is no hint of an added benefit of enfortumab vedotin + pembrolizumab in comparison with the ACT for this patient group; an added benefit is therefore not proven.

A statistically significant difference in favour of enfortumab vedotin + pembrolizumab in comparison with carboplatin + gemcitabine was shown for patients with exclusively lymph node metastases. There was a hint of added benefit of enfortumab vedotin + pembrolizumab in comparison with the ACT for this patient group.

Symptoms

EORTC QLQ-C30

Fatigue

There was an effect modification by the characteristic of sex for the outcome of fatigue. For women, a statistically significant difference was shown in favour of enfortumab vedotin + pembrolizumab in comparison with carboplatin + gemcitabine. There was a hint of added benefit of enfortumab vedotin + pembrolizumab in comparison with the ACT for this patient group.

For men, however, no statistically significant difference was shown between treatment groups. There is no hint of an added benefit of enfortumab vedotin + pembrolizumab in comparison with the ACT; an added benefit is therefore not proven for this patient group.

Constipation

There was an effect modification by the characteristic of metastases for the outcome of constipation. A statistically significant difference in favour of enfortumab vedotin + pembrolizumab in comparison with carboplatin + gemcitabine was shown both for patients with visceral metastases and patients with exclusively lymph node metastases. In each case, there is a hint of added benefit of enfortumab vedotin + pembrolizumab in comparison with the ACT the extents of which differ; an added benefit is therefore not proven (see Section I 5.3.1).

Health-related quality of life

EORTC QLQ-C30

Role functioning and emotional functioning

There was an effect modification by the characteristic of sex for each of the outcomes “role functioning” and “emotional functioning”. For women, a statistically significant difference was shown in favour of enfortumab vedotin + pembrolizumab in comparison with carboplatin + gemcitabine. In each case, there was a hint of added benefit of enfortumab vedotin + pembrolizumab in comparison with the ACT for this patient group.

For men, however, no statistically significant difference was shown between treatment groups. There is no hint of an added benefit of enfortumab vedotin + pembrolizumab in comparison with the ACT for this patient group; an added benefit is therefore not proven.

I 5.3 Probability and extent of added benefit

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

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

I 5.3.1 Assessment of added benefit at outcome level

The extent of the respective added benefit at outcome level is estimated from the results presented in Section I 5.2 (see Table 27).

Determination of the outcome category for symptom outcomes

For the symptom outcomes below, it cannot be inferred from the dossier whether they are serious/severe or non-serious/non-severe. Reasoning is provided for the classification of these outcomes.

Worst pain (BPI-SF item 3)

At the start of the study, the patients showed low values on average (approx. 3 points; this corresponds to mild pain) for “worst pain within the last 24 hours” (BPI-SF item 3), which hardly changed over the course of the study. The company provided no information on what proportion of patients had which BPI-SF item 3 score at the start of the study. In addition, the company provided no information on what values the patients had after the onset of deterioration in the outcome of worst pain. However, the mean values at baseline hardly changed over the course of the study. Therefore, the outcome of worst pain (BPI-SF item 3) was assigned to the outcome category of non-serious/non-severe symptoms/late complications.

Symptoms (EORTC QLQ-C30)

fatigue, nausea and vomiting, and constipation

For the outcomes of fatigue, nausea and vomiting as well as constipation, recorded using the EORTC QLQ-C30, there is insufficient information available to classify the severity category as serious/severe. These outcomes are therefore each assigned to the outcome category of non-serious/non-severe symptoms/late complications.

Table 27: Extent of added benefit at outcome level: enfortumab vedotin + pembrolizumab vs. carboplatin + gemcitabine (subpopulation: cisplatin unsuitable) (multipage table)

Outcome category **outcome** **effect modifier** **subgroup**	**Enfortumab vedotin + pembrolizumab vs. carboplatin + gemcitabine** **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		Outcome category: mortality $CI_u < 0.85$ added benefit; extent: “major”
Main analysis	NA vs. 12.1 months HR: 0.41 [0.30; 0.56]; p < 0.001 probability: “hint”	
Sensitivity analysis 1[c]	NA vs. 15.9 months HR: 0.49 [0.35; 0.68]; p < 0.001	
Sensitivity analysis 2[d]	NA vs. 17.4 months HR: 0.54 [0.39; 0.74]; p < 0.001	
Sensitivity analysis 3[e]	NA vs. 15.7 months HR: 0.45 [0.32; 0.61]; p < 0.001	
Outcomes with shortened observation period		
Morbidity		
Worst pain (BPI-SF item 3 - time to first deterioration)		
Metastases		
Visceral metastases	2.7 vs. 1.7 months HR: 0.92 [0.62; 1.35]; p = 0.622	Lesser/added benefit not proven
Lymph nodes only	NA vs. 0.5 months HR: 0.32 [0.14; 0.73]; p = 0.006 probability: “hint”	Outcome category "non-serious/non-severe symptoms/late complications" $CI_u < 0.80$ added benefit; extent: “considerable”
Pain interference (BPI-SF items 9a–g)	No suitable data[f]	Lesser/added benefit not proven
Symptoms (EORTC QLQ-C30 – time to first deterioration)		
Fatigue		
Sex		

Table 27: Extent of added benefit at outcome level: enfortumab vedotin + pembrolizumab vs. carboplatin + gemcitabine (subpopulation: cisplatin unsuitable) (multipage table)

Outcome category **outcome** **effect modifier** **subgroup**	**Enfortumab vedotin + pembrolizumab vs. carboplatin + gemcitabine** **median time to event (months)** **effect estimation [95% CI];** **p-value** **probability**[a]	**Derivation of extent**[b]
Female	0.7 vs. 0.4 months HR: 0.21 [0.09; 0.48]; p < 0.001 probability: “hint”	Outcome category "non-serious/non-severe symptoms/late complications" CI_u < 0.80 added benefit; extent: “considerable”
Male	0.5 vs. 0.4 months HR: 0.98 [0.72; 1.33]; p = 0.898	Lesser/added benefit not proven
Nausea and vomiting	1.8 vs. 0.9 months HR: 0.71 [0.53; 0.96]; p = 0.028 probability: “hint”	Outcome category: non-serious/non-severe symptoms/late complications 0.90 ≤ CI_u < 1.00 lesser benefit/added benefit not proven[g]
Pain	1.1 vs. 0.9 months HR: 0.78 [0.58; 1.05]; p = 0.100	Lesser/added benefit not proven
Dyspnoea	2.0 vs. 1.5 months HR: 0.86 [0.63; 1.18]; p = 0.351	Lesser/added benefit not proven
Insomnia	1.5 vs. 1.3 months HR: 0.90 [0.65; 1.24]; p = 0.544	Lesser/added benefit not proven
Appetite loss	0.9 vs. 1.1 months HR: 0.94 [0.69; 1.28]; p = 0.748	Lesser/added benefit not proven
Constipation		
Metastases		
Visceral metastases	0.7 vs. 0.4 months HR: 0.59 [0.40; 0.87]; p = 0.008 probability: “hint”	Outcome category: non-serious/non-severe symptoms/late complications 0.80 ≤ CI_u < 0.90 added benefit, extent: “minor”
Lymph nodes only	2.1 vs. 0.3 months HR: 0.33 [0.14; 0.78]; p = 0.008 probability: “hint”	Outcome category "non-serious/non-severe symptoms/late complications" CI_u < 0.80 added benefit; extent: “considerable”

Table 27: Extent of added benefit at outcome level: enfortumab vedotin + pembrolizumab vs. carboplatin + gemcitabine (subpopulation: cisplatin unsuitable) (multipage table)

Outcome category **outcome** **effect modifier** **subgroup**	**Enfortumab vedotin + pembrolizumab vs. carboplatin + gemcitabine** **median time to event (months)** **effect estimation [95% CI];** **p-value** **probability**[a]	**Derivation of extent**[b]
Diarrhoea	2.0 vs. 4.5 months HR: 1.34 [0.97; 1.87]; p = 0.070	Lesser/added benefit not proven
Health status (EQ-5D VAS, time to first deterioration)	1.5 vs. 1.3 months HR: 0.88 [0.65; 1.20]; p = 0.468	Lesser/added benefit not proven
Health-related quality of life		
EORTC-QLQ C30 – time to first deterioration		
Global health status	1.1 vs. 0.9 months HR: 0.95 [0.70; 1.29]; p = 0.788	Lesser/added benefit not proven
Physical functioning	1.1 vs. 0.7 months HR: 0.80 [0.60; 1.07]; p = 0.129	Lesser/added benefit not proven
Role functioning Sex		
Female	0.7 vs. 0.2 months HR: 0.52 [0.28; 0.97]; p = 0.031 probability: “hint”	Outcome category: health-related quality of life $0.90 \leq CI_u < 1.00$ added benefit, extent: “minor”
Male	0.7 vs. 0.5 months HR: 0.85 [0.61; 1.19]; p = 0.360	Lesser/added benefit not proven
Emotional functioning Sex		
Female	10.7 vs. 0.9 months HR: 0.36 [0.17; 0.79]; p = 0.010 probability: “hint”	Outcome category: health-related quality of life $0.90 \leq CI_u < 1.00$ added benefit, extent: “minor”
Male	3.2 vs. 2.7 months HR: 0.89 [0.60; 1.30]; p = 0.549	Lesser/added benefit not proven
Cognitive functioning	1.5 vs. 0.9 months HR: 0.80 [0.60; 1.08]; p = 0.151	Lesser/added benefit not proven

Table 27: Extent of added benefit at outcome level: enfortumab vedotin + pembrolizumab vs. carboplatin + gemcitabine (subpopulation: cisplatin unsuitable) (multipage table)

Outcome category **outcome** **effect modifier** **subgroup**	**Enfortumab vedotin + pembrolizumab vs. carboplatin + gemcitabine** **median time to event (months)** **effect estimation [95% CI];** **p-value** **probability**[a]	**Derivation of extent**[b]
Social functioning	0.9 vs. 0.9 months HR: 1.06 [0.78; 1.43]; p = 0.700	Lesser/added benefit not proven
Side effects[h]		
SAEs	7.9 vs. 5.4 months HR: 0.87 [0.64; 1.18]; p = 0.365	Greater/lesser harm not proven
Severe AEs	2.6 vs. 0.7 months HR: 0.46 [0.36; 0.58]; p < 0.001 probability: “hint”	Outcome category: serious/severe side effects CI_u < 0.75; risk ≥ 5% lesser harm, extent: “major”
Discontinuation due to AEs	14.0 vs. NA months HR: 1.30 [0.85; 2.00]; p = 0.228	Greater/lesser harm not proven
Immune-related SAEs	NA vs. NA months HR: 6.93 [1.58; 30.31] HR: 0.14 [0.03; 0.63][i]; p = 0.003 probability: “hint”	Outcome category: serious/severe side effects CI_u < 0.75; risk ≥ 5% Greater harm, extent: “major”
Immune-related severe AEs	NA vs. NA months HR: 15.92 [3.82; 66.38] HR: 0.06 [0.02; 0.26][i]; p < 0.001 probability: “hint”	Outcome category: serious/severe side effects CI_u < 0.75; risk ≥ 5% greater harm, extent: “major”
Peripheral neuropathy (AEs)	4.5 vs. NA months HR: 6.41 [3.83; 10.73] HR: 0.16 [0.09; 0.26][i]; p < 0.001 probability: “hint”	Outcome category: non-serious/non-severe side effects CI_u < 0.80 greater harm, extent: “considerable”
Skin reactions (AEs)	0.6 vs. NA months HR: 4.95 [3.60; 6.81] HR: 0.20 [0.15; 0.28][i]; p < 0.001 probability: “hint”	Outcome category: non-serious/non-severe side effects CI_u < 0.80 greater harm, extent: “considerable”

Table 27: Extent of added benefit at outcome level: enfortumab vedotin + pembrolizumab vs. carboplatin + gemcitabine (subpopulation: cisplatin unsuitable) (multipage table)

Outcome category **outcome** **effect modifier** **subgroup**	**Enfortumab vedotin + pembrolizumab vs. carboplatin + gemcitabine** **median time to event (months)** **effect estimation [95% CI];** **p-value** **probability**[a]	**Derivation of extent**[b]
Severe hyperglycaemia (severe AEs)	NA vs. NA months HR: 10.71 [1.38; 82.92] HR: 0.09 [0.01; 0.72][i]; p = 0.005 probability: “hint”	Outcome category: serious/severe side effects CI_u < 0.75; risk ≥ 5% greater harm, extent: “major”
Severe nephrotoxicity, (severe AEs)	NA vs. NA months HR: 1.12 [0.57; 2.23]; p = 0.736	Greater/lesser harm not proven
Other specific AEs		
Constipation (AEs)	NA vs. NA months HR: 0.45 [0.30; 0.66]; p < 0.001 probability: “hint”	Outcome category: non-serious/non-severe side effects CI_u < 0.80 lesser harm, extent: “considerable”
Diarrhoea (AEs)	NA vs. NA months HR: 2.30 [1.48; 3.56] HR: 0.43 [0.28; 0.67][i]; p < 0.001 probability: “hint”	Outcome category: non-serious/non-severe side effects CI_u < 0.80 greater harm, extent: “considerable”
Dysgeusia (AEs)	NA vs. NA months HR: 4.83 [2.35; 9.92] HR: 0.21 [0.10; 0.43][i]; p < 0.001 probability: “hint”	Outcome category: non-serious/non-severe side effects CI_u < 0.80 greater harm, extent: “considerable”
Eye disorders (AEs)	NA vs. NA months HR: 3.85 [2.04; 7.26] HR: 0.26 [0.14; 0.49][i]; p < 0.001 probability: “hint”	Outcome category: non-serious/non-severe side effects CI_u < 0.80 greater harm, extent: “considerable”
Endocrine disorders (AEs)	NA vs. NA months HR: 5.47 [1.90; 15.79] HR: 0.18 [0.06; 0.53][i]; p < 0.001 probability: “hint”	Outcome category: non-serious/non-severe side effects CI_u < 0.80 greater harm, extent: “considerable”

Table 27: Extent of added benefit at outcome level: enfortumab vedotin + pembrolizumab vs. carboplatin + gemcitabine (subpopulation: cisplatin unsuitable) (multipage table)

Outcome category **outcome** **effect modifier** **subgroup**	**Enfortumab vedotin + pembrolizumab vs. carboplatin + gemcitabine** **median time to event (months)** **effect estimation [95% CI];** **p-value** **probability**[a]	**Derivation of extent**[b]
Blood and lymphatic system disorders (severe AEs)	NA vs. 1.3 months HR: 0.14 [0.09; 0.20]; p < 0.001 probability: “hint”	Outcome category: serious/severe side effects CI_u < 0.75; risk ≥ 5% lesser harm, extent: “major”
acute kidney injury (severe AEs)	NA vs. NA months HR: 3.05 [0.99; 9.36]; p = 0.041 probability: “hint”	Outcome category: serious/severe side effects greater harm[j], extent: "minor"[k]

a. Probability provided if there is a statistically significant and relevant effect.
b. Depending on the outcome category, the effect size is estimated using different limits based on the upper limit of the confidence interval (CI_u).
c. Censoring at the time of death: avelumab-eligible patients who had not received avelumab and died were censored at the time of death.
d. Censoring at data cut-off: avelumab-eligible patients who had not received avelumab and died were censored at the time of data cut-off.
e. Modified time of death: avelumab-eligible patients who had not received avelumab and died were censored with a modified time of death. A simplified assumption was made that the patients would have benefited from treatment with avelumab to the extent shown in the approval study of avelumab (JAVELIN Bladder 100); see Section I 5.2.1 for explanation.
f. See Section I 5.2.1 for a rationale.
g. The extent of the effect in this non-serious/non-severe outcome was no more than marginal.
h. The fixed treatment duration and the associated discontinuation of observation after the end of study medication in the comparator arm mean that the effect estimate only reflects approximately the first 6 months after randomization.
i. Institute's calculation; reversed direction of effect to enable use of limits to derive the extent of the added benefit.
j. The result of the statistical test is decisive for the derivation of the added benefit.
k. Discrepancy between CI and p-value due to different calculation methods; the extent is rated as minor.

AE: adverse event; BPI-SF: Brief Pain Inventory-Short Form; CI: confidence interval; CI_u: upper limit of confidence interval; EORTC: European Organisation for Research and Treatment of Cancer; HR: hazard ratio; NA: not achieved; NC: not calculable; QLQ-C30: Quality of Life Questionnaire-Core 30; SAE: serious adverse event; VAS: visual analogue scale

I 5.3.2 Overall conclusion on added benefit

Table 28 summarizes the results taken into account in the overall conclusion on the extent of added benefit.

Table 28: Positive and negative effects from the assessment of enfortumab vedotin + pembrolizumab in comparison with the ACT (subpopulation: cisplatin unsuitable) (multipage table)

Positive effects	**Negative effects**
Outcomes with observation over the entire study duration	
Mortality ▪ overall survival: hint of an added benefit – extent: “major”	–
Outcomes with shortened observation period[a]	
Health-related quality of life ▪ role functioning, emotional functioning (per EORTC-QLQ-C30) ▫ sex (female): hint of an added benefit in each case – extent: “minor”	–
Non-serious/non-severe symptoms/late complications ▪ worst pain (BPI-SF item 3) ▫ metastases (lymph nodes only): hint of added benefit – extent: “considerable” ▪ fatigue (EORTC QLQ-C30) ▫ sex (female): hint of an added benefit extent: “considerable” ▪ constipation (EORTC QLQ-C30) ▫ metastases (visceral metastases): hint of added benefit – extent: “minor” ▫ metastases (lymph nodes only): hint of added benefit – extent: “considerable”	–
Serious/severe side effects ▪ severe AEs: hint of lesser harm – extent: “major” ▫ blood and lymphatic system disorders (severe AEs): hint of lesser harm – extent: "major"	Serious/severe side effects ▪ immune-related SAEs, immune-related severe AEs, severe hyperglycaemia (severe AEs): each hint of greater harm – extent: “major” ▪ acute kidney injury (severe AEs): hint of greater harm – extent: “minor”
Non-serious/non-severe side effects ▪ constipation (AEs): hint of lesser harm – extent: “considerable”	Non-serious/non-severe side effects ▪ peripheral neuropathy (AEs), skin reactions (AEs), diarrhoea (AEs), dysgeusia (AEs), eye disorders (AEs), endocrine disorder (AEs): hint of greater harm in each case - extent: “considerable”
No suitable data are available for the outcome "pain interference" (BPI-SF items 9a-9g).	
a. For the side effect outcomes, the fixed treatment duration and the associated discontinuation of observation after the end of study medication in the comparator arm mean that the effect estimate only reflects approximately the first 6 months after randomization. AE: adverse event; BPI-SF: Brief Pain Inventory-Short Form; EORTC: European Organisation for Research and Treatment of Cancer; QLQ-C30: Quality of Life Questionnaire – Core 30; SAE: serious adverse event	

The overall assessment shows both positive and negative effects with different extents for enfortumab vedotin + pembrolizumab compared with the ACT. In particular for the outcomes of side effects, however, the observed effects relate to a shortened period and only represent the roughly first 6 months after randomization and thus in the comparator arm only the period of chemotherapy, but not the period of a possible maintenance therapy with avelumab, and in the intervention arm only the first 6 months of a possibly longer-lasting therapy.

The advantage in overall survival, the extent of which is “major” both in the main analysis and in all sensitivity analyses, is decisive for the assessment. In addition, there are advantages for individual outcomes of morbidity and health-related quality of life as well as for outcomes in the side effects category, particularly for the overall rate of severe AEs. On the other hand, there are disadvantages in various specific AEs, especially for severe and serious immune-related AEs.

The results on side effects only relate to a shortened period of around 6 months. However, since a high proportion of events already occur during this period, the available results show that the advantage in overall survival is not called into question by the results on side effects.

In summary, for adult patients with unresectable or metastatic urothelial carcinoma in the first-line therapy for whom cisplatin-based therapy is not suitable, there is a hint of major added benefit of enfortumab vedotin + pembrolizumab compared with the ACT.

The assessment described above deviates from that by the company, which derived an indication of major added benefit.

I 6 Probability and extent of added benefit – summary

Table 29 summarizes the result of the assessment of the added benefit of enfortumab vedotin + pembrolizumab in comparison with the ACT.

Table 29: Enfortumab vedotin + pembrolizumab – probability and extent of added benefit

Research question	Therapeutic indication	ACT[a]	Probability and extent of added benefit
First-line treatment of adult patients with unresectable or metastatic urothelial carcinoma who are eligible for platinum-containing chemotherapy			
1	For whom cisplatin-based therapy is an option	Cisplatin in combination with gemcitabine followed by avelumab as maintenance therapy (maintenance therapy with avelumab only for progression-free patients[b])	Hint of non-quantifiable added benefit[c]
2	For whom cisplatin-based therapy is not an option[d]	Carboplatin in combination with gemcitabine in accordance with Annex VI to Section K of the Pharmaceutical Directive[e], followed by avelumab as maintenance therapy (maintenance therapy with avelumab only for progression-free patients[b])	Hint of major added benefit[c]

a. Presented is the respective ACT specified by the G-BA.
b. According to the G-BA, it is assumed that patients who are not progression-free following platinum-based chemotherapy will not be treated further as part of first-line treatment.
c. The EV-302/KN-A39 study almost exclusively included patients with an ECOG PS of 0 or 1 (ECOG PS ≥ 2 in the respectively relevant subpopulation: research question 1: 4 [2%] vs. 2 [1%]; research question 2: 11 [5%] vs. 9 [4%]). It remains unclear whether the observed effects are transferable to patients with an ECOG PS ≥ 2.
d. According to the G-BA, it is assumed that the patients in question have an increased risk of cisplatin-induced side effects in the context of a combination therapy (e.g. pre-existing neuropathy or relevant hearing impairment, renal failure, heart failure).
e. With regard to the present indication, this is a use in an unapproved therapeutic indication (off-label use). For the present indication, carboplatin in combination with gemcitabine can be prescribed in off-label use, see Appendix VI to Section K of the Pharmaceutical Directive.

ACT: appropriate comparator therapy; G-BA: Federal Joint Committee

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 7 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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