Pembrolizumab (urothelial carcinoma, first-line therapy, combination with enfortumab vedotin)

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

EXTRACT

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[1] Translation of Sections I 1 to I 5 of the dossier assessment *Pembrolizumab (Urothelkarzinom, Erstlinientherapie, Kombination mit Enfortumab Vedotin) – Nutzenbewertung gemäß § 35a SGB V*. Please note: This translation is provided as a service by IQWiG to English-language readers. However, solely the German original text is absolutely authoritative and legally binding.

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Medical and scientific advice

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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. for participating in the written exchange about how they experienced the disease and its treatment and about the treatment goals. The respondent and the Selbsthilfe-Bund Blasenkrebs e.V. were not involved in the actual preparation of the dossier assessment.

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Part I: Benefit assessment

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

I List of abbreviations

Abbreviation	Meaning
ACT	appropriate comparator therapy
AUC	area under the curve
BSA	body surface area
CPS	combined positive score
CTCAE	Common Terminology Criteria for Adverse Events
ECOG PS	Eastern Cooperative Oncology Group Performance Status
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)
NYHA	New York Heart Association
PD-L1	programmed cell death ligand 1
PFS	progression-free survival
RCT	randomized controlled trial
SGB	Sozialgesetzbuch (Social Code Book)
SPC	Summary of Product Characteristics
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 pembrolizumab (in combination with enfortumab vedotin). 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 24 September 2024.

Research question

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

The research questions presented in Table 2 result from the ACT specified by the G-BA.

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

Research question	Therapeutic indication	ACT[a]
First-line treatment of adult patients with unresectable or metastatic urothelial carcinoma		
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])
3	For whom cisplatin-based therapy and carboplatin-based therapy are not an option	Individualized treatment[e] selected from ▪ atezolizumab as monotherapy ▪ pembrolizumab as monotherapy ▪ best supportive care[f] taking into account the PD-L1 status and the general condition

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.
e. For the implementation of individualized therapy in a direct comparative study, the investigator is expected as per G-BA to have a selection of several treatment options at disposal to permit an individualized treatment decision taking into account the listed criteria (multicomparator study). A rationale must be provided for the choice and any limitation of treatment options.
f. Best supportive care refers to the therapy which provides the patient with the best possible, individually optimized, supportive treatment to alleviate symptoms and improve the quality of life.

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

On receipt of the dossier, the G-BA adjusted the ACT on 08 October 2024 as presented in Table 2. This does not result in any changes for research questions 1 and 2. Research question 3 has been added as a result of the adjustment, as the approved therapeutic indication for pembrolizumab - unlike the combination partner enfortumab vedotin - does not only relate to patients for whom platinum-containing chemotherapy is an option. Due to the adjustment of the ACT after receipt of the dossier, the information in the company's dossier refer to the original ACT. The present benefit assessment is based on the adjusted ACT.

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 for research questions 1 and 2.

Accordingly, the company did not address research question 3. However, no potentially relevant randomized controlled trial (RCT) was identified for this research question in the search in study registers as part of the dossier assessment, so this has no further consequences.

The assessment was conducted by means of patient-relevant outcomes on the basis of the data provided by the company in the dossier. RCTs were used for the derivation of the added benefit.

Research questions 1 and 2: patients for whom cisplatin-based therapy is suitable (research question 1) and patients for whom cisplatin-based therapy is not suitable (research question 2)

Study pool and study design

The company identified the EV-302/KN-A39 study (SGN22E-003) on the comparison of pembrolizumab + enfortumab vedotin versus platinum-based chemotherapy (cisplatin/carboplatin + gemcitabine). On the basis of this study, the company derived an added benefit of pembrolizumab + enfortumab vedotin 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, since maintenance treatment with avelumab following the study medication was principally possible in the comparator arm, an interpretation of the presented study for research questions 1 and 2 of the present benefit assessment is still potentially possible under certain conditions. However, in its dossier, the company does not provide any information on the proportion of patients in the subpopulations of the study relevant to research questions 1 and 2 for whom maintenance treatment with avelumab would have been an option or how many of these patients actually received maintenance treatment with avelumab. Based on the available data, it is therefore not possible to assess whether the ACT has been implemented for a sufficient proportion of the patients included. Therefore, the data on study EV-302/KN-A39 presented in the company’s dossier are unsuitable for the present benefit assessment.

Study EV-302/KN-A39 is described below and the unsuitability of the data presented in the company's dossier is explained.

Study design

The EV-302/KN-A39 study is an ongoing, multicentre, open-label RCT comparing pembrolizumab + enfortumab vedotin with 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 pembrolizumab + enfortumab vedotin (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.

In the EV-302/KN-A39 study, treatment with pembrolizumab and enfortumab vedotin largely corresponded to the recommendations of the respective Summary of Product Characteristics (SPC).

In the comparator arm, platinum-based chemotherapy was administered in 21-day treatment cycles for a maximum of 6 cycles. Depending on the cisplatin suitability, patients received either cisplatin (70 mg/m² body surface area [BSA]) or carboplatin (4.5 or 5 mg/mL/min area under the curve [AUC]) on Day 1 each in combination with gemcitabine (1000 mg/m² BSA) on Days 1 and 8. Treatment with carboplatin + gemcitabine is not approved for patients for whom cisplatin-based therapy is not suitable. 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 treatment with cisplatin + gemcitabine, however, the SPC for gemcitabine states that treatment should be given in 28-day treatment cycles, with gemcitabine (1000 mg/m² BSA) on Days 1, 8 and additionally on Day 15 of each cycle; according to the SPC, cisplatin is administered at a dose of 70 mg/m² BSA on Day 1 after gemcitabine or on Day 2 of each 28-day treatment cycle. Moreover, the SPC does not specify any fixed upper limit for the number of treatment cycles. A single switch of treatment from cisplatin to carboplatin or from carboplatin to cisplatin was permitted in the study, but is not provided for within the framework of the ACT specified by the G-BA.

Overall, the data presented by the company in its dossier are not suitable to demonstrate whether the ACT, in particular the maintenance therapy with avelumab, is adequately implemented and whether it is therefore possible to interpret the study data for the research questions 1 and 2 presented here. Therefore, the consequences of the deviation in the dosing regimen of cisplatin + gemcitabine are not described further here. 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.

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

The G-BA specified chemotherapy with cisplatin (research question 1) or carboplatin (research question 2), each in combination with gemcitabine, as ACT for adult patients with unresectable or metastatic urothelial carcinoma in first line treatment for whom platinum-

containing therapy 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. 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.

In Module 4 A of its dossier, the company does not address the fact that maintenance treatment with avelumab was not part of the study medication of the EV-302/KN-A39 study, but merely states that treatment with avelumab (800 mg) was administered every 2 weeks, without specifying the conditions under which this treatment was given. Beyond this information, the company does not go into the implementation of maintenance therapy with avelumab in Module 4 A of its dossier. In particular, it does not provide any information on how many patients in the comparator arm of the subpopulations relevant for research questions 1 and 2 would have been eligible for maintenance treatment with avelumab or how many patients received maintenance treatment with avelumab.

The study documents show that in the total population of study EV-302/KN-A39, a total of 135 patients (30%) of the comparator arm received maintenance treatment with avelumab following chemotherapy, although no information is available on how these patients are distributed among the relevant subpopulations of research questions 1 and 2 of the present benefit assessment. In addition, the dossier does not provide any information on the time at which treatment with avelumab took place in these patients, i.e. how many cycles of chemotherapy had been administered before and at what time avelumab therapy was started after the end of chemotherapy. Accordingly, it remains unclear whether treatment with avelumab in these patients was carried out in accordance with the specifications of the SPC for avelumab.

For the remaining 309 patients in the comparator arm, it is not clear from the information in the dossier whether treatment with avelumab would have been indicated according to the ACT. To assess this, it would be necessary to know how many patients in the comparator arm received at least 4 cycles of cisplatin + gemcitabine and were progression-free thereafter. However, the dossier provides no corresponding information. However, the available data on PFS show that in the overall population of the EV-302/KN-A39 study, 213/444 patients (48%) in the comparator arm were still at risk of progression at Month 6 and that maintenance treatment with avelumab would therefore have been indicated for these patients. Assuming that all of the aforementioned 135 patients (30%) in the comparator arm who received

avelumab as maintenance therapy fell into this patient group and were treated according to the specifications of the SPC for avelumab, at least a further 78 (18%) of the patients in the comparator arm should have received treatment with avelumab.

In addition, maintenance treatment with avelumab would also have been potentially indicated for patients with progression events between Month 3 and Month 6 if the progression event had occurred after the end of chemotherapy.

Overall, the information in the company's dossier shows that the actual proportion of patients who would have had to receive maintenance treatment with avelumab in the comparator arm is potentially clearly higher. This is confirmed by the data on the implementation of maintenance treatment with avelumab, which forms the basis of the parallel benefit assessment of A24-98 Enfortumab Vedotin (urothelial carcinoma, first-line therapy, combination with pembrolizumab) commissioned by the G-BA. However, based on the information in the company's dossier relevant for the present benefit assessment, it is not possible to determine for which proportion of patients in the comparator arm of the subpopulations of the EV-302/KN-A39 study relevant for research question 1 and research question 2 the ACT of the G-BA was implemented.

Conclusion

In summary, based on the information provided by the company in the dossier, it remains unclear whether the treatment used in the study represents an adequate implementation of the ACT (including maintenance therapy with avelumab) for the patients in the comparator arm of the subpopulations of the EV-302/KN-A39 study relevant to research question 1 and research question 2. Rather, it can be derived from the information available in the dossier that a relevant proportion of patients did not receive maintenance treatment with avelumab, although this would have been indicated. The analyses on study EV-302/KN-A39 provided in the company’s dossier were therefore not used for the present dossier assessment.

Results on added benefit

In the present situation, as described above, detailed information on the use of maintenance treatment with avelumab in the subpopulations of the EV-302/KN-A39 study relevant to research questions 1 and 2 is required, as without this information it is not possible to assess whether the study results are suitable for deriving an added benefit in the benefit assessment. Corresponding information is not available in the company's dossier, however.

To derive the added benefit, see the following section.

Probability and extent of added benefit, patient groups with therapeutically important added benefit[3] (research questions 1 and 2)

In the present situation, as described above, detailed information on the use of maintenance therapy with avelumab in the subpopulations of study EV-302/KN-A39 relevant to research questions 1 and 2 is required. However, the company's dossier offers no corresponding information.

The G-BA commissioned IQWiG in parallel with the benefit assessments on pembrolizumab (commission A24-99) and enfortumab vedotin (commission A24-98), each in combination with the other drug, in the therapeutic indication of research questions 1 and 2. In both dossiers, the respective companies presented results of the identical study EV-302/KN-A39 at the identical data cut-off. For benefit assessment A24-98 Enfortumab vedotin, however, the company (unlike the company for benefit assessment A24-99 Pembrolizumab) presented detailed information on the implementation of maintenance treatment with avelumab and sensitivity analyses on overall survival in Module 4A of its dossier, which address the incomplete implementation of maintenance treatment with avelumab and on the basis of which it is possible to derive the added benefit of enfortumab vedotin + pembrolizumab compared with the ACT for research questions 1 and 2. In this particular situation, reference is therefore made to the benefit assessment A24-98 Enfortumab vedotin (urothelial carcinoma, first-line therapy, combination with pembrolizumab) for reasons of content for the overall conclusion on the added benefit of pembrolizumab + enfortumab vedotin for research questions 1 and 2.

With reference to benefit assessment A24-98 Enfortumab vedotin (urothelial carcinoma, first-line therapy, combination with pembrolizumab), the results summarize that for adult patients with unresectable or metastatic urothelial carcinoma in first-line therapy for whom cisplatin-based therapy is suitable (research question 1), there is a hint of a non-quantifiable added benefit of pembrolizumab + enfortumab vedotin compared with the ACT.

In summary, for adult patients with unresectable or metastatic urothelial carcinoma in the first-line therapy for whom cisplatin-based therapy is not suitable (research question 2), there is, in summary, a hint of major added benefit of pembrolizumab + enfortumab vedotin compared with the ACT with reference to benefit assessment A24-98.

[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].

Research question 3: Patients not eligible for cisplatin-based and carboplatin-based therapy

Results

On receipt of the dossier, the G-BA adjusted the ACT on 8 October 2024. Research question 3 has been added as a result of the adjustment. Therefore, this research question is not addressed in the company's dossier and the company did not conduct an information retrieval on research question 3.

No RCT potentially relevant to research question 3 was identified by the search in study registers as part of the dossier assessment.

Study EV-302/KN-A39 presented by the company for research question 1 and research question 2 is not relevant for research question 3. This is justified below.

Research question 3 of the present benefit assessment comprises adult patients with unresectable or metastatic urothelial carcinoma in first-line therapy for whom cisplatin-based therapy and carboplatin-based therapy are not suitable. However, only patients for whom cisplatin- or carboplatin-based chemotherapy is suitable were included in the EV-302/KN-A39 study. Accordingly, platinum-based chemotherapy is the study medication in the comparator arm. There are therefore no data available to answer research question 3.

Results on added benefit

Since no relevant study is available for the present research question, there is no hint of added benefit of pembrolizumab + enfortumab vedotin over the ACT; an added benefit is therefore not proven.

Probability and extent of added benefit, patient groups with therapeutically important added benefit (research question 3)

No data are available for the assessment of the added benefit of pembrolizumab + enfortumab vedotin compared with the ACT in adult patients with unresectable or metastatic urothelial carcinoma in first-line therapy for whom cisplatin- and carboplatin-based therapy is not suitable; an added benefit is therefore not proven.

Probability and extent of added benefit – summary

Table 3 shows a summary of the probability and extent of the added benefit of pembrolizumab + enfortumab vedotin. In the present situation, this is based on the parallel benefit assessment on enfortumab vedotin (commission A24-98) for research questions 1 and 2.

Table 3: Pembrolizumab + enfortumab vedotin – 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			
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]
3	For whom cisplatin-based therapy and carboplatin-based therapy are not an option	Individualized treatment[f] selected from ▪ atezolizumab as monotherapy ▪ pembrolizumab as monotherapy ▪ best supportive care[g] taking into account the PD-L1 status and the general condition	Added benefit not proven

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.
f. For the implementation of individualized therapy in a direct comparative study, the investigator is expected as per G-BA to have a selection of several treatment options at disposal to permit an individualized treatment decision taking into account the listed criteria (multicomparator study). A rationale must be provided for the choice and any limitation of treatment options.
g. Best supportive care refers to the therapy which provides the patient with the best possible, individually optimized, supportive treatment to alleviate symptoms and improve the quality of life.

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

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

I 2 Research question

The aim of this report was to assess the added benefit of pembrolizumab in combination with enfortumab vedotin (hereinafter referred to as pembrolizumab + enfortumab vedotin) in comparison with the ACT for the first-line treatment of adult patients with unresectable or metastatic urothelial carcinoma.

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 pembrolizumab + enfortumab vedotin

Research question	Therapeutic indication	ACT[a]
First-line treatment of adult patients with unresectable or metastatic urothelial carcinoma		
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])
3	For whom cisplatin-based therapy and carboplatin-based therapy are not an option	Individualized treatment[e] selected from ▪ atezolizumab as monotherapy ▪ pembrolizumab as monotherapy ▪ best supportive care[f] taking into account the PD-L1 status and the general condition

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.
e. For the implementation of individualized therapy in a direct comparative study, the investigator is expected as per G-BA to have a selection of several treatment options at disposal to permit an individualized treatment decision taking into account the listed criteria (multicomparator study). A rationale must be provided for the choice and any limitation of treatment options.
f. Best supportive care refers to the therapy which provides the patient with the best possible, individually optimized, supportive treatment to alleviate symptoms and improve the quality of life.

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

On receipt of the dossier, the G-BA adjusted the ACT on 8 October 2024 in as presented in Table 4 [3]. This does not result in any changes for research questions 1 and 2. Research

question 3 has been added as a result of the adjustment, as the approved therapeutic indication for pembrolizumab - unlike the combination partner enfortumab vedotin - does not only relate to patients for whom platinum-containing chemotherapy is an option. Due to the adjustment of the ACT after receipt of the dossier, the information in the company's dossier refer to the original ACT. The present benefit assessment is based on the adjusted ACT.

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 for research questions 1 and 2.

Accordingly, the company did not address research question 3. However, the search in study registers as part of the dossier assessment did not identify any potentially relevant RCT for this research question (see Chapter I 4), so this has no further consequences.

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

I 3 Research questions 1 and 2: patients for whom cisplatin-based therapy is suitable (research question 1) and patients for whom cisplatin-based therapy is not suitable (research question 2)

I 3.1 Information retrieval and study pool

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

Sources of the company in the dossier:

- study list on pembrolizumab (status: 17 July 2024)
- bibliographical literature search on pembrolizumab (last search on 9 July 2024)
- search in trial registries / trial results databases for studies on pembrolizumab (last search on 12 July 2024)
- search on the G-BA website for pembrolizumab (last search on 12 July 2024)

To check the completeness of the study pool:

- search in trial registries for studies on pembrolizumab (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.

The company identified the study EV-302/KN-A39 (SGN22E-003) [4-8] on the comparison of pembrolizumab + enfortumab vedotin versus platinum-based chemotherapy (cisplatin/carboplatin + gemcitabine). On the basis of this study, the company derived an added benefit of pembrolizumab + enfortumab vedotin 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, since maintenance treatment with avelumab following the study medication was principally possible in the comparator arm, an interpretation of the presented study for research questions 1 and 2 of the present benefit assessment is still potentially possible under certain conditions. However, in its dossier, the company does not provide any information on the proportion of patients in the subpopulations of the study relevant to research questions 1 and 2 for whom maintenance treatment with avelumab would have been an option or how many of these patients actually received maintenance treatment with avelumab. Based on the available data, it is therefore not possible to assess whether the ACT has been implemented for a sufficient proportion of the patients included. Therefore, the data on study EV-302/KN-

A39 presented in the company's dossier are unsuitable for the present benefit assessment. Study EV-302/KN-A39 is described below and the unsuitability of the data presented in the company's dossier is explained.

Evidence provided by the company

Design of the EV-302/KN-A39 study

The tables on the characterisation of the EV-302/KN-A39 study, on the interventions used and on the characterisation of the patients included are also shown in I Appendix B.1.

The EV-302/KN-A39 study is an ongoing, multicentre, open-label RCT comparing pembrolizumab + enfortumab vedotin with 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 from the study; 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 [9].

The study included a total of 886 patients who were randomly assigned in a 1:1 ratio to treatment with pembrolizumab + enfortumab vedotin (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 benefit assessment.

Treatment with pembrolizumab + enfortumab vedotin in the intervention arm was largely in compliance with the requirements of the respective SPC [10,11]. Treatment duration with enfortumab vedotin was not restricted in the study beyond the criteria of disease progression and unacceptable toxicity. 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 [10].

In the comparator arm, platinum-based chemotherapy was administered in 21-day treatment cycles for a maximum of 6 cycles. Depending on the cisplatin suitability, patients received either cisplatin (70 mg/m² BSA) or carboplatin (4.5 or 5 mg/mL/min AUC) on Day 1 each in combination with gemcitabine (1000 mg/m² BSA) on Days 1 and 8. Treatment with carboplatin + gemcitabine is not approved for patients for whom cisplatin-based therapy is not suitable. However, it can be prescribed in accordance with Annex VI to Section K of the Pharmaceutical Directive [12]. The use of carboplatin + gemcitabine essentially complied with the specifications of Annex VI to Section K of the Pharmaceutical Directive.

For treatment with cisplatin + gemcitabine, however, the SPC for gemcitabine states that treatment should be given in 28-day treatment cycles, with gemcitabine (1000 mg/m² BSA) on Days 1, 8 and additionally on Day 15 of each cycle; according to the SPC, cisplatin is administered at a dose of 70 mg/m² BSA on Day 1 after gemcitabine or on Day 2 of each 28-day treatment cycle [13]. Moreover, the SPC does not specify any fixed upper limit for the number of treatment cycles. A single switch of treatment from cisplatin to carboplatin or from carboplatin to cisplatin was permitted in the study, but is not provided for within the framework of the ACT specified by the G-BA.

Overall, the data presented by the company in its dossier are not suitable to demonstrate whether the ACT, in particular the maintenance therapy with avelumab, is adequately implemented and whether it is therefore possible to interpret the study data for the research questions 1 and 2 presented here. Therefore, the consequences of the deviation in the dosing

regimen of cisplatin + gemcitabine are not described further here. A comprehensive description of the implementation of the ACT can be found in benefit assessment A24-98 Enfortumab vedotin (urothelial carcinoma, first-line therapy, combination with pembrolizumab) [14], which was commissioned in parallel by the G-BA . 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.

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 events for PFS 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: planned for the time at which 489 deaths had occurred, provided that overall survival had not been 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 [15]. According to the company, the data cut-off was carried out on 6 September 2024, but these data were not yet available at the time of dossier submission. 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.

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

The G-BA specified chemotherapy with cisplatin (research question 1) or carboplatin (research question 2), each in combination with gemcitabine, as ACT for adult patients with unresectable or metastatic urothelial carcinoma in first line treatment for whom platinum-containing therapy 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. Following the start of the study on 30 March 2020 and the approval of avelumab in the European Union on 21 January 2021 [16], 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.

In Module 4 A of its dossier, the company does not address the fact that maintenance treatment with avelumab was not part of the study medication of the EV-302/KN-A39 study, but merely states that treatment with avelumab (800 mg) was administered every 2 weeks, without specifying the conditions under which this treatment was given. Beyond this information, the company does not go into the implementation of maintenance therapy with avelumab in Module 4 A of its dossier. In particular, it does not provide any information on how many patients in the comparator arm of the subpopulations relevant for research questions 1 and 2 would have been eligible for maintenance treatment with avelumab and how many patients received maintenance treatment with avelumab.

The study documents show that in the total population of study EV-302/KN-A39, a total of 135 patients (30%) of the comparator arm received maintenance treatment with avelumab following chemotherapy, although no information is available on how these patients are distributed among the relevant subpopulations of research questions 1 and 2 of the present benefit assessment. In addition, the dossier does not provide any information on the time at which treatment with avelumab took place in these patients, i.e. how many cycles of chemotherapy had been administered before and at what time avelumab therapy was started after the end of chemotherapy. Accordingly, it remains unclear whether treatment with avelumab in these patients was carried out in accordance with the specifications of the SPC for avelumab.

For the remaining 309 patients in the comparator arm, it is not clear from the information in the dossier whether treatment with avelumab would have been indicated according to the ACT. To assess this, it would be necessary to know how many patients in the comparator arm received at least 4 cycles of cisplatin + gemcitabine and were progression-free thereafter. However, the dossier provides no corresponding information. However, the Kaplan-Meier curve on PFS (see I Appendix B.2) shows that in the total population of the EV-302/KN-A39 study, 213/444 patients (48%) in the comparator arm were still at risk of progression at Month 6 and that maintenance treatment with avelumab would therefore have been indicated for these patients. Assuming that all of the aforementioned 135 patients (30%) in the comparator arm who received avelumab as maintenance therapy fell into this patient group and were treated according to the specifications of the SPC for avelumab, at least a further 78 (18%) of the patients in the comparator arm should have received treatment with avelumab.

In addition, maintenance treatment with avelumab would also have been potentially indicated for patients with progression events between Month 3 and Month 6 if the progression event had occurred after the end of chemotherapy. On the one hand, treatment with chemotherapy was already completed at Week 18 (corresponding to around 4 months) due to the 21-day treatment cycle in the comparator arm of the study, so that avelumab could have been used in patients without progression at this time point. On the other hand,

maintenance treatment with avelumab would also have been possible after 4 cycles of chemotherapy (corresponding to around Month 3) in accordance with the specifications of the SPC if treatment in the comparator arm was discontinued prematurely without progression or the patient having died.

Overall, the information in the company's dossier shows that the actual proportion of patients who would have had to receive maintenance treatment with avelumab in the comparator arm is potentially clearly higher. This is confirmed by the data on the implementation of maintenance treatment with avelumab, which forms the basis of the parallel benefit assessment of A24-98 Enfortumab Vedotin (urothelial carcinoma, first-line therapy, combination with pembrolizumab) commissioned by the G-BA [14]. However, based on the information in the company's dossier relevant for the present benefit assessment, it is not possible to determine for which proportion of patients in the comparator arm of the subpopulations of the EV-302/KN-A39 study relevant for research question 1 and research question 2 the ACT of the G-BA was implemented.

Conclusion

In summary, based on the information provided by the company in the dossier, it remains unclear whether the treatment used in the study represents an adequate implementation of the ACT (including maintenance therapy with avelumab) for the patients in the comparator arm of the subpopulations of the EV-302/KN-A39 study relevant to research question 1 and research question 2. Rather, it can be derived from the information available in the dossier that a relevant proportion of patients did not receive maintenance treatment with avelumab, although this would have been indicated. The analyses on study EV-302/KN-A39 provided in the company’s dossier were therefore not used for the present dossier assessment.

I 3.2 Results on added benefit

In the present situation, as described above, detailed information on the use of maintenance treatment with avelumab in the subpopulations of the EV-302/KN-A39 study relevant to research questions 1 and 2 is required, as without this information it is not possible to assess whether the study results are suitable for deriving an added benefit in the benefit assessment. Corresponding information is not available in the company's dossier, however.

To derive the added benefit, see the following section.

I 3.3 Probability and extent of added benefit

In the present situation, as described above, detailed information on the use of maintenance therapy with avelumab in the subpopulations of study EV-302/KN-A39 relevant to research questions 1 and 2 is required. However, the company's dossier offers no corresponding information.

The G-BA commissioned IQWiG in parallel with the benefit assessments on pembrolizumab (commission A24-99) and enfortumab vedotin (commission A24-98), each in combination with the other drug, in the therapeutic indication of research questions 1 and 2. In both dossiers, the respective companies presented results of the identical study EV-302/KN-A39 for the identical data cut-off [17,18]. For benefit assessment A24-98 Enfortumab vedotin, however, the company (unlike the company for benefit assessment A24-99 Pembrolizumab) presented detailed information on the implementation of maintenance treatment with avelumab and sensitivity analyses on overall survival in Module 4A of its dossier, which address the incomplete implementation of maintenance treatment with avelumab and on the basis of which it is possible to derive the added benefit of enfortumab vedotin + pembrolizumab compared with the ACT for research questions 1 and 2 [18]. In this particular situation, reference is therefore made to the benefit assessment A24-98 Enfortumab vedotin (urothelial carcinoma, first-line therapy, combination with pembrolizumab) [14] for reasons of content for the overall conclusion on the added benefit of pembrolizumab + enfortumab vedotin for research questions 1 and 2.

With reference to benefit assessment A24-98 Enfortumab vedotin (urothelial carcinoma, first-line therapy, combination with pembrolizumab) [14], the results summarize that for adult patients with unresectable or metastatic urothelial carcinoma in first-line therapy for whom cisplatin-based therapy is suitable (research question 1), there is a hint of a non-quantifiable added benefit of pembrolizumab + enfortumab vedotin compared with the ACT.

In summary, for adult patients with unresectable or metastatic urothelial carcinoma in the first-line therapy for whom cisplatin-based therapy is not suitable (research question 2), there is, in summary, a hint of major added benefit of pembrolizumab + enfortumab vedotin compared with the ACT with reference to benefit assessment A24-98 [14].

The assessment described above deviates from that of the company, which derived an indication of major added benefit for both research questions.

I 4 Research question 3: Patients not eligible for cisplatin-based and carboplatin-based therapy

I 4.1 Information retrieval and study pool

On receipt of the dossier, the G-BA adjusted the ACT on 8 October 2024 in as presented in Table 4 [3]. Research question 3 has been added as a result of the adjustment. Therefore, this research question is not addressed in the company's dossier and the company did not conduct an information retrieval on research question 3.

No RCT potentially relevant to research question 3 was identified by the search in study registers as part of the dossier assessment (see Section I 3.1).

The study EV-302/KN-A39 presented by the company for research question 1 and research question 2 of the present benefit assessment is not relevant for research question 3. This is justified below. For a description of the EV-302/KN-A39 study, see Section I 3.1.

Research question 3 of the present benefit assessment comprises adult patients with unresectable or metastatic urothelial carcinoma in first-line therapy for whom cisplatin-based therapy and carboplatin-based therapy are not suitable. However, only patients for whom cisplatin- or carboplatin-based chemotherapy is suitable were included in the EV-302/KN-A39 study. Accordingly, platinum-based chemotherapy is the study medication in the comparator arm. There are therefore no data available to answer research question 3.

I 4.2 Results on added benefit

No data are available for the assessment of the added benefit of pembrolizumab + enfortumab vedotin compared with the ACT in adult patients with unresectable or metastatic urothelial carcinoma in first-line therapy for whom cisplatin- and carboplatin-based therapy is not suitable. This resulted in no hint of an added benefit of pembrolizumab + enfortumab vedotin in comparison with the ACT; an added benefit is therefore not proven.

I 4.3 Probability and extent of added benefit

No data are available for the assessment of the added benefit of pembrolizumab + enfortumab vedotin compared with the ACT in adult patients with unresectable or metastatic urothelial carcinoma in first-line therapy for whom cisplatin- and carboplatin-based therapy is not suitable; an added benefit is therefore not proven.

This assessment differs from that of the company insofar as the latter does not address the present research question, as this research question was only included after the adjustment of the ACT following the receipt of the dossier.

I 5 Probability and extent of added benefit – summary

Table 5 summarizes the result of the assessment of the added benefit of pembrolizumab + enfortumab vedotin in comparison with the ACT. In the present situation, this is based on the parallel benefit assessment on enfortumab vedotin (commission A24-98, see also Section I 3.3) for research questions 1 and 2.

Table 5: Pembrolizumab + enfortumab vedotin – 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			
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]
3	For whom cisplatin-based therapy and carboplatin-based therapy are not an option	Individualized treatment[f] selected from ▪ atezolizumab as monotherapy ▪ pembrolizumab as monotherapy ▪ best supportive care[g] taking into account the PD-L1 status and the general condition	Added benefit not proven

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.
f. For the implementation of individualized therapy in a direct comparative study, the investigator is expected as per G-BA to have a selection of several treatment options at disposal to permit an individualized treatment decision taking into account the listed criteria (multicomparator study). A rationale must be provided for the choice and any limitation of treatment options.
g. Best supportive care refers to the therapy which provides the patient with the best possible, individually optimized, supportive treatment to alleviate symptoms and improve the quality of life.

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

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

I 6 References for English extract

Please see full dossier assessment for full reference list.

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

1. Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen. Allgemeine Methoden; Version 7.0 [online]. 2023 [Accessed: 02.09.2024]. URL: https://www.iqwig.de/methoden/allgemeine-methoden_version-7-0.pdf.

2. Skipka G, Wieseler B, Kaiser T et al. Methodological approach to determine minor, considerable, and major treatment effects in the early benefit assessment of new drugs. Biom J 2016; 58(1): 43-58. https://doi.org/10.1002/bimj.201300274.

3. Gemeinsamer Bundesausschuss. Nutzenbewertungsverfahren zum Wirkstoff Pembrolizumab (Neues Anwendungsgebiet: Urothelkarzinom, nicht resezierbar oder metastasiert, Erstlinie, Kombination mit Enfortumab Vedotin); zweckmäßige Vergleichstherapie. [Soon available under: https://www.g-ba.de/bewertungsverfahren/nutzenbewertung/1132/#zweckmaessige-vergleichstherapie].

4. Seagen. Studienbericht KEYNOTE A39: An Open-Label, Randomized, Controlled Phase 3 Study of Enfortumab Vedotin in Combination with Pembrolizumab Versus Chemotherapy Alone in Previously Untreated Locally Advanced or Metastatic Urothelial Cancer [unpublished]. 2023.

5. Astellas Pharma Global Development. Enfortumab Vedotin and Pembrolizumab vs. Chemotherapy Alone in Untreated Locally Advanced or Metastatic Urothelial Cancer (EV-302) [online]. 2024 [Accessed: 18.11.2024]. URL: https://clinicaltrials.gov/study/NCT04223856.

6. Seagen. An open-label, randomized, controlled phase 3 study of enfortumab vedotin in combination with pembrolizumab versus chemotherapy alone in previously untreated locally advanced or metastatic urothelial cancer [online]. 2024 [Accessed: 18.11.2024]. URL: https://euclinicaltrials.eu/search-for-clinical-trials/?lang=en&EUCT=2023-503421-19-00.

7. Seattle Genetics. An open-label, randomized, controlled phase 3 study of enfortumab vedotin in combination with pembrolizumab with or without chemotherapy, versus chemotherapy alone in previously untreated locally advanced or metastatic urothelial cancer [online]. [Accessed: 18.11.2024]. URL: https://www.clinicaltrialsregister.eu/ctr-search/search?query=eudract_number:2019-004542-15.

8. Powles T, Valderrama BP, Gupta S et al. Enfortumab Vedotin and Pembrolizumab in Untreated Advanced Urothelial Cancer. N Engl J Med 2024; 390(10): 875-888. https://doi.org/10.1056/NEJMoa2312117.

9. Leitlinienprogramm Onkologie. S3-Leitlinie Früherkennung, Diagnose, Therapie und Nachsorge des Harnblasenkarzinoms [online]. 2020 [Accessed: 01.10.2024]. URL: https://www.leitlinienprogramm-onkologie.de/fileadmin/user_upload/Downloads/Leitlinien/Blasenkarzinom/Version_2.0/LL_Harnblasenkarzinom_Langversion_2.0.pdf.

10. Merck Sharp & Dohme. KEYTRUDA 25 mg/ml Konzentrat zur Herstellung einer Infusionslösung [online]. 2024 [Accessed: 24.09.2024]. URL: https://www.fachinfo.de/.

11. Astellas Pharma Europe. Padcev 20 mg / 30 mg Pulver für ein Konzentrat zur Herstellung einer Infusionslösung [online]. 2024 [Accessed: 24.09.2024]. URL: https://www.fachinfo.de/.

12. Gemeinsamer Bundesausschuss. Beschluss des Gemeinsamen Bundesausschusses über eine Änderung der Arzneimittel-Richtlinie: Anlage VI (Off-Label-Use) – Carboplatin in Kombination mit Gemcitabin zur Behandlung von Patientinnen und Patienten mit inoperablem lokal fortgeschrittenem oder metastasiertem Urothelkarzinom, wenn eine CisplatinTherapie nicht infrage kommt [online]. 2021 [Accessed: 03.12.2024]. URL: https://www.g-ba.de/downloads/39-261-4850/2021-05-20_AM-RL-VI_Carboplatin-Gemcitabin-Urothelkarzinom_BAnz.pdf.

13. Hexal. Gemcitabin HEXAL 40 mg/ml Konzentrat zur Herstellung einer Infusionslösung [online]. 2023 [Accessed: 24.09.2024]. URL: https://www.fachinfo.de/.

14. Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen. Enfortumab Vedotin (Urothelkarzinom, Erstlinientherapie, Kombination mit Pembrolizumab) – Nutzenbewertung gemäß § 35a SGB V; Dossierbewertung [online]. 2024. URL: https://www.iqwig.de/projekte/a24-98.html.

15. Food and Drug Administration. Supplement Approval/Fulfillment Of Postmarketing Requirement [online]. 2023 [Accessed: 29.10.2024]. URL: https://www.accessdata.fda.gov/drugsatfda_docs/appletter/2023/761137Orig1s024;%20s025ltr.pdf.

16. European Medicines Agency. Bavencio; Procedural steps taken and scientific information after authorisation [online]. 2024 [Accessed: 11.11.2024]. URL: https://www.ema.europa.eu/en/documents/procedural-steps-after/bavencio-epar-procedural-steps-taken-scientific-information-after-authorisation_en.pdf.

17. MSD Sharp & Dohme. Pembrolizumab (KEYTRUDA); Dossier zur Nutzenbewertung gemäß § 35a SGB V. [Soon available under: https://www.g-ba.de/bewertungsverfahren/nutzenbewertung/1132/#dossier].

18. Astellas Pharma. Enfortumab Vedotin (PADCEV); Dossier zur Nutzenbewertung gemäß § 35a SGB V. [Soon available under: https://www.g-ba.de/bewertungsverfahren/nutzenbewertung/1133/#dossier].

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