IQWiG Reports – Commission No. A22-61

Enfortumab vedotin (urothelial carcinoma) –

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

Extract

[1] Translation of Sections 2.1 to 2.5 of the dossier assessment *Enfortumab Vedotin (*Urothelkarzinom*) – Nutzenbewertung gemäß § 35a SGB V* (Version 1.0; Status: 29 August 2022). 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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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

No feedback of persons concerned or patient organizations was received within the framework of the present dossier assessment.

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Table of contents

List of tables[2]

Page

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

List of abbreviations

Abbreviation	Meaning
ACT	appropriate comparator therapy
AE	adverse event
BSC	best supportive care
CSR	clinical study report
CTCAE	Common Technology 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-C30
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
PD-1	programmed cell death protein 1
PD-L1	programmed cell death ligand 1
PT	Preferred Term
RCT	randomized controlled trial
SAE	serious adverse event
SGB	Sozialgesetzbuch (Social Code Book)
SPC	Summary of Product Characteristics

2 Benefit assessment

2.1 Executive summary of the benefit assessment

Background

In accordance with §35a Social Code Book (SGB) V, the Federal Joint Committee (G-BA) commissioned the Institute for Quality and Efficiency in Health Care (IQWiG) to assess the benefit of the drug 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 25 May 2022.

Research question

The aim of this report is to assess the added benefit of enfortumab vedotin in comparison with the appropriate comparator therapy (ACT) in adult patients with locally advanced or metastatic urothelial cancer, who have received a prior platinum-containing chemotherapy and a programmed cell death protein 1 (PD-1) or programmed cell death ligand 1 (PD-L1) inhibitor.

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

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

Research question	Therapeutic indication	ACT[a]
1	Adults with locally advanced or metastatic urothelial cancer[b] who have previously received a platinum-containing chemotherapy and a PD-1 or PD-L1 inhibitor and for whom chemotherapy is suitable	Vinflunine monotherapy or cisplatin in combination with gemcitabine
2	Adults with locally advanced or metastatic urothelial cancer[b] who have previously received a platinum-containing chemotherapy and a PD-1 or PD-L1 inhibitor and for whom chemotherapy is unsuitable	Best supportive care (BSC)[c]

a. Presented is the respective ACT specified by the G-BA.
b. It is assumed that the intended therapeutic indication includes patients whose locally advanced or metastasised urothelial cancer is inoperable.
c. BSC refers to the therapy that provides the patient with the best possible, individually optimized, supportive treatment to alleviate symptoms and improve the quality of life.

BSC: best supportive care; G-BA: Federal Joint Committee; PD-(L)1: programmed cell death (ligand) 1

For easier presentation and better readability, the present benefit assessment uses the following terms for the research questions:

- Research question 1: patients for whom chemotherapy is suitable
- Research question 2: Patients for whom chemotherapy is unsuitable

The company deviates from the G-BA's specification of the ACT by considering the therapeutic indication of enfortumab vedotin independently of whether chemotherapy is suitable for the patients. Moreover, in departure from the G-BA's specification, the company names treatment of physician's choice taking into account mono- or combination chemotherapies (cisplatin, doxorubicin, methotrexate, gemcitabine, vinblastine, vinflunine, paclitaxel or docetaxel) and best supportive care (BSC) as ACT. The company justified the deviation from the ACT specified by the G-BA by stating that the recommendations of the guidelines and the health care context in Germany were not sufficiently taken into account. Overall, the company's justification for the deviation from the G-BA's ACT was not sufficient. Therefore, the assessment was conducted in comparison with the G-BA's ACT. The deviation of the company has no consequence for the present dossier assessment, since the inclusion criteria for study selection in Module 4 A specify the ACTs of the G-BA and the company presents analyses on enfortumab vedotin versus the GBA's ACT in its dossier (vinflunine subpopulation).

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

Research question 1: patients for whom chemotherapy is suitable

Study pool and study design

The study pool for research question 1 consists of the EV-301 study. EV-301 is a multicentre, open-label RCT on the comparison of enfortumab vedotin with a chemotherapy of physician's choice choosing from vinflunine, paclitaxel and docetaxel, each as monotherapy. The study included adult patients with locally advanced or metastatic urothelial carcinoma pretreated with platinum-based chemotherapy (cisplatin or carboplatin) and a PD-1 or PD-L1 inhibitor for the treatment of the advanced or metastatic disease.

The study included 608 patients who, according to the inclusion criteria, were to be candidates for vinflunine, paclitaxel or docetaxel monotherapy. Prior to randomization, the investigator determined which therapy option each patient was to receive if assigned to the control arm. Patients were randomly allocated in a 1:1 ratio to the intervention arm (n = 301) or the control arm (n = 307).

Paclitaxel and docetaxel are not part of the ACT. Therefore, the only subpopulation relevant for the dossier assessment is the one of 73 (enfortumab vedotin) versus 78 (vinflunine) patients for whom vinflunine was the therapy chosen before they had been allocated to the control arm.

Treatment in both study arms was largely conducted in accordance with the respective Summary of Product Characteristics (SPCs) with a possible third dose adjustment of enfortumab vedotin to 0.50 mg/kg not being cited as an option in the study protocol. Likewise, concomitant treatment with laxatives and dietary measures including oral hydration as constipation prophylaxis, which the SPC recommends in the first 5 to 7 days after each use with vinflunine according to the SPC, is not planned according to the study protocol.

Treatment with the study medication was to be continued until at least one of the following discontinuation criteria occurred: disease progression, initiation of a new anticancer therapy, withdrawal of consent, physician's decision, death or unacceptable toxicity.

Primary outcome of the study was overall survival; patient-relevant secondary outcomes included outcomes on morbidity, health-related quality of life and side effects.

Relevant subpopulation and implementation of the ACT

The EV-301 study is a multicomparator study in which the investigator defined before randomization the chemotherapy to be administered to each individual patient in case of their allocation to the control arm. The choices were paclitaxel, docetaxel and vinflunine.

Since paclitaxel and docetaxel were no ACT options, the subpopulation relevant for the benefit assessment only comprised patients from the enfortumab vedotin or the control arm, who were to receive vinflunine if assigned to the control arm. The company presented related results on all outcomes from additional analyses in the Appendix to its dossier. This is appropriate and leads to the relevant subpopulation comprising 73 of the 301 randomized patients of the intervention arm and 78 of the 307 patients of the control arm.

In the present benefit assessment, the subpopulation formed by the company was used as the relevant population (vinflunine subpopulation).

Risk of bias

The risk of bias across outcomes was rated as low for the EV-301 study. The risk of bias for the outcomes "overall survival", "serious adverse events (SAEs) and severe adverse events (AEs) was rated as low. For all other outcomes, the risk of bias of the results is rated as high.

Results

Mortality

All-cause mortality

There was no statistically significant difference between the treatment arms for the outcome "all-cause mortality". This resulted in no hint of an added benefit of enfortumab vedotin in comparison with the ACT; an added benefit is therefore not proven.

Morbidity

Symptoms (European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-C 30 [EORTC QLQ-C30])

Fatigue, nausea and vomiting, and pain

For each of the outcomes of fatigue, nausea and vomiting, and pain, no statistically significant difference between treatment arms was found. In each case, this resulted in no hint of an added benefit of enfortumab vedotin in comparison with the ACT; an added benefit is therefore not proven.

Dyspnoea

For the outcome of dyspnoea, a statistically significant difference was found in favour of enfortumab vedotin in comparison with vinflunine. This resulted in a hint of added benefit of enfortumab vedotin in comparison with the ACT.

Insomnia

For the outcome of insomnia, a statistically significant difference was found in favour of enfortumab vedotin in comparison with vinflunine. This difference was no more than marginal, however. This resulted in no hint of an added benefit of enfortumab vedotin in comparison with the ACT; an added benefit is therefore not proven.

Diarrhoea

For the outcome of diarrhoea, a statistically significant difference was found to the disadvantage of enfortumab vedotin in comparison with vinflunine. This difference was no more than marginal, however. This resulted in no hint of an added benefit of enfortumab vedotin in comparison with the ACT; an added benefit is therefore not proven.

Appetite loss

No statistically significant difference between the treatment arms was shown for the outcome "appetite loss", but there was an effect modification by the characteristic "age". This results in a hint of an added benefit of enfortumab vedotin versus the ACT for patients < 65 years of age. For patients ≥ 65 years, there was no hint of an added benefit of enfortumab vedotin versus the ACT; an added benefit is therefore not proven for these patients.

Constipation

For the outcome "constipation", no usable data are available for a comparison of enfortumab vedotin with vinflunine. This resulted in no hint of an added benefit of enfortumab vedotin in comparison with the ACT; an added benefit is therefore not proven.

Health status (EQ-5D VAS)

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

Health-related quality of life

EORTC QLQ-C30

Global health status and physical functioning

No statistically significant difference between the treatment arms was shown for each of the outcomes "global health status" and "physical functioning". In each case, this resulted in no hint of an added benefit of enfortumab vedotin in comparison with the ACT; an added benefit is therefore not proven.

Role functioning, emotional functioning and cognitive functioning

No statistically significant difference between the treatment arms was shown for each of the outcomes "role functioning", "emotional functioning" and "cognitive functioning"; however, there was an effect modification by the characteristic "age" in each case. In each case, this results in a hint of an added benefit of enfortumab vedotin versus the ACT for patients < 65 years of age. For patients ≥ 65 years, there was no hint of an added benefit of enfortumab vedotin versus the ACT; an added benefit is therefore not proven for these patients.

Social functioning

For the outcome of social functioning, a statistically significant difference was found in favour of enfortumab vedotin in comparison with vinflunine. This resulted in a hint of added benefit of enfortumab vedotin in comparison with the ACT.

Side effects

SAEs and severe AEs

For each of the outcomes "SAEs" and "severe AEs", a statistically significant difference was found in favour of enfortumab vedotin in comparison with vinflunine. However, in each case, there was an effect modification by the characteristic "liver metastases". In patients without liver metastases, this resulted in an indication of lesser harm from enfortumab vedotin versus the ACT. In each case, there was no hint of greater or lesser harm from enfortumab vedotin versus the ACT for patients with liver metastases; greater or lesser harm is therefore not proven for these patients.

Discontinuation due to AEs

There was no statistically significant difference between the treatment arms for the outcome "discontinuation due to AEs". This resulted in no hint of greater or lesser harm from enfortumab vedotin in comparison with the ACT for the outcome "discontinuation due to AEs"; greater or lesser harm is therefore not proven.

Specific AEs

Peripheral neuropathy (AEs)

For the outcome "peripheral neuropathy (AEs)", a statistically significant difference was found to the disadvantage of enfortumab vedotin in comparison with vinflunine. However, there was an effect modification by the characteristic "age". This results in a hint of greater harm from enfortumab vedotin versus the ACT for patients ≥ 65 years of age. There was no hint of greater or lesser harm from enfortumab vedotin versus the ACT for patients < 65 years; greater or lesser harm is therefore not proven for these patients.

Hyperglycaemia (severe AEs)

There was no statistically significant difference between the treatment arms for the outcome of hyperglycaemia (severe AEs). This resulted in no hint of greater or lesser harm from enfortumab vedotin in comparison with the ACT; greater or lesser harm is therefore not proven.

Constipation

For the outcome "constipation", no usable data are available for a comparison of enfortumab vedotin with vinflunine. This resulted in no hint of greater or lesser harm from enfortumab vedotin versus the ACT; greater or lesser harm is therefore not proven.

Neutropenia and febrile neutropenia (each of them being severe AEs)

For each of the outcomes "neutropenia" and "febrile neutropenia" (both being severe AEs), a statistically significant difference was found in favour of enfortumab vedotin in comparison with vinflunine. For each of them, this results in a hint of lesser harm from enfortumab vedotin in comparison with the ACT.

Eye disorders, diarrhoea, conjunctivitis and skin and subcutaneous tissue disorders (in each case AEs) and nervous system disorders (severe AEs)

A statistically significant difference to the disadvantage of enfortumab vedotin in comparison with vinflunine was shown for each of the outcomes of eye disorders, diarrhoea, conjunctivitis and skin and subcutaneous tissue disorders (in each case AEs) and nervous system disorders (severe AEs). For each of them, this results in a hint of greater harm from enfortumab vedotin in comparison with the ACT.

Research question 2: Patients for whom chemotherapy is unsuitable

The company presented no data for the assessment of the added benefit of enfortumab vedotin in comparison with the ACT for adult patients with locally advanced or metastatic urothelial carcinoma who had received prior platinum-containing chemotherapy and a PD-1 or PD-L1 inhibitor and for whom chemotherapy is unsuitable. This resulted in no hint of an added benefit of enfortumab vedotin versus the ACT. An added benefit is therefore not proven.

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

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

For research question 1, the overall assessment shows both positive and negative effects of different extents for enfortumab vedotin in the vinflunine subpopulation. There were also different subgroup effects for the characteristics "age" and "liver metastases"; however, it is

[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].

unclear to what extent the different subgroups overlap. Therefore, the added benefit was not derived separately according to subgroups.

For “symptoms” and “health-related quality of life”, only positive effects of enfortumab vedotin were shown, most of them with the extent “minor”. For patients < 65 years, further advantages with varying extents were shown for these outcome categories. In the outcome category of serious/severe side effects, there is an indication of lesser harm with the extent "considerable" or "major" for patients without liver metastases for the overall rate of severe AEs and SAEs respectively. In addition, for several specific serious/severe side effects, there are hints of lesser harm with the extent “minor” or “non-quantifiable” for the vinflunine subpopulation.

The negative effects are related exclusively to outcomes of the category of side effects; for serious/severe side effects with the extent “non-quantifiable” as well as for various non-serious/non-severe side effects with the extent “considerable”.

The observed effects for symptoms, health-related quality of life, and side effects are based exclusively on the shortened time period until treatment end (plus 30 days).

In summary, there is a hint of minor added benefit of enfortumab vedotin versus the ACT for patients with locally advanced or metastatic urothelial carcinoma who had received prior platinum-containing chemotherapy and a PD-1 or PD-L1 inhibitor and for whom chemotherapy is suitable.

The company presented no data for research question 2. An added benefit of enfortumab vedotin in comparison with the ACT is thus not proven for these patients.

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

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

Research question	Therapeutic indication	ACT[a]	Probability and extent of added benefit
1	Adults with locally advanced or metastatic urothelial carcinoma[b] who have received prior platinum-containing chemotherapy and a PD1 or PD-L1 inhibitor and for whom chemotherapy is suitable	Vinflunine monotherapy or cisplatin in combination with gemcitabine	Hint of minor added benefit[c]
2	Adults with locally advanced or metastatic urothelial carcinoma[b] who have previously received a platinum-containing chemotherapy and a PD-1 or PD-L1 inhibitor and for whom chemotherapy is unsuitable	BSC[d]	Added benefit not proven

a. Presented is the respective ACT specified by the G-BA.
b. It is assumed that the intended therapeutic indication includes patients whose locally advanced or metastatic urothelial carcinoma is inoperable.
c. Only patients with an ECOG PS of 0 or 1 were included in the EV-301 study. It remains unclear whether the observed effects are transferable to patients with an ECOG PS ≥ 2.
d. BSC 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; BSC: best supportive care; ECOG PS: Eastern Cooperative Oncology Group Performance Status; G-BA: Federal Joint Committee; PD-(L)1: programmed cell death (ligand) 1

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

2.2 Research question

The aim of this report is to assess the added benefit of enfortumab vedotin in comparison with the ACT in adult patients with locally advanced or metastatic urothelial carcinoma, who have received a prior platinum-containing chemotherapy and a PD-1 or PD-L1 inhibitor.

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

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

Research question	Therapeutic indication	ACT[a]
1	Adults with locally advanced or metastatic urothelial carcinoma[b] who have received prior platinum-containing chemotherapy and a PD-1 or PD-L1 inhibitor and for whom chemotherapy is suitable	Vinflunine monotherapy or cisplatin in combination with gemcitabine
2	Adults with locally advanced or metastatic urothelial carcinoma[b] who have previously received a platinum-containing chemotherapy and a PD-1 or PD-L1 inhibitor and for whom chemotherapy is unsuitable	Best supportive care (BSC)[c]

a. Presented is the respective ACT specified by the G-BA.
b. It is assumed that the intended therapeutic indication includes patients whose locally advanced or metastatic urothelial carcinoma is inoperable.
c. BSC refers to the therapy that provides the patient with the best possible, individually optimized, supportive treatment to alleviate symptoms and improve the quality of life.

BSC: best supportive care; G-BA: Federal Joint Committee; PD-(L)1: programmed cell death (ligand) 1;

For easier presentation and better readability, the present benefit assessment uses the following terms for the research questions:

- Research question 1: patients for whom chemotherapy is suitable
- Research question 2: Patients for whom chemotherapy is unsuitable

The company deviates from the G-BA's specification of the ACT by considering the therapeutic indication of enfortumab vedotin independently of whether chemotherapy is suitable for the patients. Moreover, in departure from the G-BA's specification, the company names treatment of physician's choice taking into account mono- or combination chemotherapies (cisplatin, doxorubicin, methotrexate, gemcitabine, vinblastine, vinflunine, paclitaxel or docetaxel) and BSC as ACT. The company justified the deviation from the ACT specified by the G-BA by stating that the recommendations of the guidelines [3-5] and the health care context in Germany were not sufficiently taken into account. In order to represent the actual health care setting in Germany, the company uses data from a retrospective analysis of patient records in Germany within the framework of the EVOLVE study conducted by the company [6].

Overall, the company's justification for the deviation from the G-BA's ACT was not sufficient. This is explained as follows:

The German S3 guideline [4] provides a concrete recommendation for patients who have received prior platinum-containing chemotherapy and a PD-(L)1 inhibitor. International guidelines [3,5] primarily name vinflunine and the taxanes (paclitaxel and docetaxel) as possible therapy options. However, unlike vinflunine, the taxanes are not approved for the treatment of urothelial carcinoma.

Moreover, the data from everyday health care in Germany presented by the company are not very informative due to the small sample size (N = 23). In addition, the company itself states that other drugs (including doxorubicin and methotrexate) from the comparator therapy named by it were only rarely used in the EVOLVE study. The company's justification for expanding the comparator therapy to include the drugs doxorubicin, methotrexate, vinblastine, paclitaxel and docetaxel based on an insufficiently considered actual health care setting is not comprehensible on the basis of the data presented by the company. Like the taxanes (paclitaxel and docetaxel), vinblastine is not approved for the treatment of urothelial carcinoma, regardless of the line of treatment.

Accordingly, the present assessment was conducted in comparison with the G-BA's ACT. The deviation of the company has no consequence for the present dossier assessment, since the inclusion criteria for study selection in Module 4 A specify the ACTs of the G-BA and the company presents analyses on enfortumab vedotin in comparison with the GBA's ACT in its dossier (vinflunine subpopulation, see Section 2.3.1.2).

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.

2.3 Research question 1: patients for whom chemotherapy is suitable

2.3.1 Information retrieval and study pool

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

Sources of the company in the dossier:

- study list on enfortumab vedotin (status: 5 April 2022)
- bibliographical literature search on enfortumab vedotin (last search on 5 April 2022)
- search in trial registries/trial results databases for studies on enfortumab vedotin (last search on 5 April 2022)
- search on the G-BA website for enfortumab vedotin (last search on 05 April 2022)

To check the completeness of the study pool:

- search in trial registries for studies on enfortumab vedotin (last search on 15 June 2022); for search strategies, see Appendix A of the full dossier assessment

The check did not identify any additional relevant study.

2.3.1.1 Studies included

The study presented in the following Table 5 is included in the benefit assessment.

Table 5: Study pool – RCT, direct comparison: enfortumab vedotin vs. treatment of physician's choice[a]

Study	Study category			Available sources		
	Approval study for the drug to be assessed (yes/no)	Sponsored study[b] (yes/no)	Third-party study (yes/no)	CSR (yes/no)	Registry entries[c] (yes/no)	Publication (yes/no)
EV-301	Yes	Yes	No	Yes [7,8]	Yes [9,10]	Yes [11]

a. In the EV-301 study, therapy could be chosen from vinflunine, paclitaxel and docetaxel. The option relevant for the dossier assessment is vinflunine.
b. Study for which the company was sponsor.
c. Citation of the study registry entries and, if available, of the reports on study design and/or results listed in the study registries.
RCT: randomized controlled trial

The EV-301 study was used for the benefit assessment. However, a subpopulation was analysed because the study also allowed the administration of therapies going beyond the ACT (see Section 2.3.1.2). Deviating from this, the company considered the total population of the EV-301 study in its dossier and presents the results of the subpopulation as supplementary information in Appendix 4-G3 of its dossier.

2.3.1.2 Study characteristics

Study and intervention characteristics

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 vs. treatment of physician's choice[a] (multipage table)

Study	Study design	Population	Interventions (number of randomized patients)	Study duration	Location and period of study	Primary outcome; secondary outcomes[b]
EV-301	RCT, open-label, parallel-group	Adults with locally advanced or metastatic urothelial carcinoma ▪ prior platinum-containing therapy[c] ▪ disease progression or recurrence during or after treatment with a PD-(L)1 inhibitor in the advanced or metastatic stage ▪ ECOG PS 0 or 1	Enfortumab vedotin (N = 301) chemotherapy[d] (N = 307) relevant subpopulation thereof[e]: enfortumab vedotin (N = 73) vinflunine (n = 78)	Screening: 28 days treatment[f]: until disease progression, initiation of a new anticancer therapy, toxicity, physician's or patient's decision, loss to follow-up or death observation[g]: outcome-specific, at most until death, loss to follow-up, withdrawal of consent or end of study	158 study centres in: Argentina, Australia, Austria, Belgium, Canada, Denmark, France, Germany, Italy, Japan, Netherlands, Portugal, Russia, South Korea, Spain, Switzerland, Taiwan, United Kingdom and United States of America 06/2018–ongoing first data cut-off: 15 July 2020[h] second data cut-off: 30 July 2021[i]	Primary: overall survival secondary: morbidity, health-related quality of life, AEs

Table 6: Characteristics of the included study – RCT, direct comparison: enfortumab vedotin vs. treatment of physician's choice[a] (multipage table)

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

a. In the EV-301 study, therapy could be chosen from vinflunine, paclitaxel and docetaxel. The option relevant for the dossier assessment is vinflunine.
b. Primary outcomes include information without consideration of the relevance for this benefit assessment. Secondary outcomes include only information on relevant available outcomes for this benefit assessment.
c. Treatment with cisplatin or carboplatin in the locally advanced or metastatic stage. Patients with disease progression within 12 months after neoadjuvant or adjuvant platinum therapy could also be included.
d. Docetaxel or vinflunine or paclitaxel, as decided by the treating physician before randomization. The proportion of patients who were to receive vinflunine was limited to 35%.
e. Subpopulation of patients for whom, prior to randomization, vinflunine was chosen as the drug to be administered if they were allocated to the control arm. Patients for whom docetaxel or paclitaxel was chosen are not further considered below.
f. With Amendment 3 of the study protocol of 14 September 2020, patients in the control arm could switch to enfortumab vedotin in the event of a statistically significant effect in the primary analysis of overall survival (first data cut-off: 15 July 2020) (cross-over extension). This was an option for patients who were either still on study treatment or had discontinued it due to intolerance, AEs or disease progression, had not yet started a new systemic anticancer treatment and were still participating in the follow-up phase of the study.
g. Outcome-specific information is provided in Table 8.
h. An interim analysis was planned after 285 deaths (65% of the 439 estimated deaths; Amendment 2, 11 December 2019) and was conducted after 299 actual deaths on 15 July 2020 due to exceeding the efficacy threshold for overall survival. The Independent Data Monitoring Committee (IDMC) recommended stopping the trial for the efficacy outcomes and this analysis was conducted as the primary analysis for overall survival.
i. Originally planned primary data cut-off for the final analysis of overall survival after 439 deaths requested by the Swiss regulatory authority and also submitted to the European Medicines Agency (EMA). For this data cut-off, data are only available for overall survival, PFS1 and safety.

AE: adverse event; ECOG PS: Eastern Cooperative Oncology Group Performance Status; EMA: European Medicines Agency; IDMC: Independent Data Monitoring Center; n: relevant subpopulation; N: number of randomized patients; OS: overall survival; PD-(L)1: programmed cell death (ligand) 1; PFS: progression-free survival; RCT: randomized controlled trial

Table 7: Characteristics of the intervention – RCT, direct comparison: enfortumab vedotin vs. vinflunine

Study	Intervention	Comparison[a]
EV-301	Enfortumab vedotin 1.25 mg/kg BW[b] IV, on days 1, 8 and 15 of a 28-day cycle	Vinflunine 320 mg/m^2 IV[c], on day 1 of a 21-week cycle
	Treatment adjustment dose adjustment or interruption of treatment is possible as needed[b]	
	Pretreatment <u>required</u> ▪ platinum-based chemotherapy (cisplatin or carboplatin) and 1 PD-1 or PD-L1 inhibitor <u>not allowed</u> ▪ enfortumab vedotin or other MMAE-based antibody-drug conjugates (ADCs) ▪ pretreatment with all chemotherapies possible in the comparator arm (docetaxel, vinflunine and paclitaxel) ▪ > 1 chemotherapy in the locally advanced or metastatic stage, including adjuvant or neoadjuvant chemotherapy with recurrence within 12 months after end of treatment ▪ not completed treatment with chemotherapy, biologics, immunotherapies or other investigational drugs ≤ 2 weeks before the first dose of the study medication ▪ radiation or major surgical intervention ≤ 4 weeks before the first dose of the study medication **Concomitant treatment** <u>not allowed</u> ▪ other chemotherapy or anticancer therapy (except endocrine therapy for the adjuvant treatment of breast cancer or drugs for the treatment of bone metastases) ▪ radiation (exception in case of symptomatic singular lesions or at the bones, after consultation with the sponsor	

a. In the EV-301 study, therapy could be chosen from vinflunine, paclitaxel and docetaxel. The option relevant for the dossier assessment is vinflunine.
b. Patients with body weights ≥ 100 kg were administered a maximum dose of 125 mg. The dose was recalculated for all patients on day 1 of each cycle.
c. Recommended dose for patients < 75 years. Deviating dose for the following patient groups:
- 280 mg/m² for patients aged 75 to < 80 years, with moderate kidney dysfunction (40 mL/min ≤ creatinine clearance (CrCl) ≤ 60 mL/min), with ECOG PS 1 and/or with prior radiation of the pelvic area
- 250 mg/m² for patients aged ≥ 80 years, mild liver dysfunction (Child-Pugh grade A) and/or kidney dysfunction (30 mL/min ≤ CrCl < 40 ml/min)

▪ a. Toxicity-related dose adjustments up to treatment discontinuation were made without relevant deviation from the requirements of the SPCs.

ADC: antibody-drug conjugate; CrCl: creatinine clearance; ECOG PS: Eastern Cooperative Oncology Group Performance Status; IV: intravenous; BW: body weight; MMAE: monomethyl auristatin E; PD-(L)1: programmed cell death (ligand) 1; RCT: randomized controlled trial

The EV-301 study is a multicentre, open-label RCT on the comparison of enfortumab vedotin with a chemotherapy of physician's choice choosing from vinflunine, paclitaxel and docetaxel, each as monotherapy. The study included adult patients with locally advanced or metastatic urothelial carcinoma pretreated with platinum-based chemotherapy (cisplatin or carboplatin) and a PD-1 or PD-L1 inhibitor for the treatment of the advanced or metastatic disease. Administration of the platinum-based chemotherapy was allowed in the neoadjuvant or adjuvant setting if disease progression occurred within 12 months of the end of therapy. All

patients had to have an Eastern Cooperative Oncology Group Performance Status (ECOG PS) of 0 or 1.

The study included 608 patients who, according to the inclusion criteria, were to be candidates for vinflunine, paclitaxel or docetaxel monotherapy. Prior to randomization, the investigator determined which therapy option each patient was to receive if assigned to the control arm. Vinflunine was only considered as therapy option in countries where it is approved for the treatment of urothelial carcinoma. Patients were randomly assigned in a 1:1 ratio to the enfortumab vedotin arm (n = 301) or the control arm (n = 307). Stratification factors were "region" (Western Europe vs. United States vs. rest of the world), "ECOG PS" (0 versus 1) and "presence of liver metastases at baseline" (yes vs. no).

Paclitaxel and docetaxel are not part of the ACT. Therefore, the only subpopulation relevant for the dossier assessment is the one of 73 (enfortumab vedotin) versus 78 (vinflunine) patients for whom vinflunine was the therapy chosen before they had been allocated to the control arm (see the section "Relevant subpopulation and implementation of the ACT").

Treatment in both study arms was largely conducted in accordance with the respective SPC [12,13] with a possible third dose adjustment of enfortumab vedotin to 0.50 mg/kg not being cited as an option in the study protocol. Likewise, concomitant treatment with laxatives and dietary measures including oral hydration as constipation prophylaxis, which the SPC recommends in the first 5 to 7 days after each use with vinflunine according to the SPC, is not planned according to the study protocol (see Section 2.3.2.1).

Treatment with the study medication was to be continued until at least one of the following discontinuation criteria occurred: disease progression, initiation of a new anticancer therapy, withdrawal of consent, physician's decision, death or unacceptable toxicity. A switch from treatment of the control arm to the enfortumab vedotin arm (treatment switching) was initially ruled out be the study protocol. However, after the first data cut-off had been conducted (15 July 2020), patients from the control arm were allowed to switch to treatment in the enfortumab vedotin arm according to Amendment 3 of the study protocol of 14 September 2020. At the time point of the second data cut-off (30 July 2021), as many as 4 (5.1%) patients had switched from treatment with vinflunine to treatment with enfortumab vedotin. It is assumed, that this has no relevant influence on the study results due to the small proportion of affected patients.

Primary outcome of the study was overall survival; patient-relevant secondary outcomes included outcomes on morbidity, health-related quality of life and side effects.

Relevant subpopulation and implementation of the ACT

The EV-301 study is a multicomparator study in which the investigator defined before randomization the chemotherapy to be administered to each individual patient in case of their allocation to the control arm. The choices were paclitaxel, docetaxel and vinflunine. Vinflunine

was only considered as therapy option in countries where it is approved for the treatment of urothelial carcinoma.

Since paclitaxel and docetaxel were no ACT options, the subpopulation relevant for the benefit assessment only comprised patients from the enfortumab vedotin or the control arm, who were to receive vinflunine if assigned to the control arm. For this purpose, the company presented results on all outcomes as supplementary information in Appendix 4-G3 to its dossier. This is appropriate and leads to the relevant subpopulation comprising 73 of the 301 randomized patients of the intervention arm and 78 of the 307 patients of the control arm. Studies on enfortumab vedotin in comparison with the other treatment options specified by the G-BA (see Section 2.3.1).

In the present benefit assessment, the subpopulation formed by the company was used as the relevant population (vinflunine subpopulation). For information on the use of an increased significance level in the subpopulation, see Section 2.3.2.1.

Data cut-offs

EV-301 is an ongoing study (start: June 2018) whose recruitment has been completed. Results are available for 2 data cut-offs:

- First data cut-off: 15 July 2020 – predefined interim analysis planned after 285 deaths (approx. 65% of the estimated deaths) and conducted as primary analysis. For this data cut-off, analyses are available on all patient-relevant outcomes (“overall survival”, “morbidity”, “health-related quality of life” and “side effects”).
- Second data cut-off: 30 July 2021 – originally planned final analysis on overall survival after 439 deaths, conducted on request of the Swiss regulatory authority. For this data cut-off, analyses are available on overall survival and side effects.

In the present benefit assessment, the results of the first data cut-off were used for the outcomes on morbidity and health-related quality of life; the results of the second data cut-off were used for overall survival and the outcomes on side effects, as these cover the individual longest available observation periods.

For the outcomes of morbidity and health-related quality of life, the company did not present any analyses on the second data cut-off and did not justify this in the dossier. The company’s approach is not appropriate.

According to the clinical study report (CSR), the study was to be terminated for the efficacy outcomes after the first data cut-off (15 July 2020) on the recommendation of the Independent Data Monitoring Centre. However, the study documents do not suggest that the recording for the outcomes of morbidity and health-related quality of life was actually discontinued after the first data cut. In accordance with the dossier template, analyses for the second data cut-off should thus have been conducted for all outcomes and submitted for the benefit assessment.

The analyses on the first data cut-off were nevertheless considered usable for the following reasons: At the time of the first data cut-off, the majority of patients were no longer receiving treatment (treatment discontinuations: 57 [78%] vs. 68 [87%] patients in the enfortumab vedotin vs. the vinflunine arm, see Table 9). In addition, the outcomes on morbidity and health-related quality of life were to be observed for a maximum of 30 days after the last dose of study medication, so that it can be assumed that for most patients who discontinued treatment before the first data cut-off, all data recorded on these outcomes were available at the first data cut-off. Moreover, there was a sharp decline in the response rate to the EORTC QLQ-C30 and the EQ-5D as early as at the first data cut-off. Therefore, it is not assumed that the results on the outcomes on morbidity and health-related quality of life would change to any relevant extent when considering the second data cut-off.

Planned duration of follow-up observation

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

Table 8: Planned duration of follow-up observation – RCT, direct comparison: enfortumab vedotin vs. vinflunine

Study **outcome category** **outcome**	**Planned follow-up observation**
EV-301	
Mortality	
Overall survival	Until death, lost to follow-up, withdrawal of consent or end of study
Morbidity	
Symptoms (EORTC QLQ-C30), health status (EQ-5D VAS)	Up to 30 days after the last dose of the study medication
Health-related quality of life (EORTC QLQ-C30)	Up to 30 days after the last dose of the study medication
Side effects	
All outcomes in the category of side effects	Up to 30 days after the last dose of the study medication
EORTC QLQ-C30: European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30; RCT: randomized controlled trial; VAS: visual analogue scale	

The observation periods for the outcomes “morbidity”, “health-related quality of life” and “side effects” were systematically shortened because they were only recorded for the time period of treatment with the study medication (plus 30 days). For these outcomes, data are therefore available only for the shortened observation period. However, to be able to draw a reliable conclusion on the total study period or the time to patient death, it would be necessary to record these outcomes as well for the total period, as was done for survival.

Characteristics of the relevant subpopulation

Table 9 shows the characteristics of the patients in the relevant subpopulation of the included study.

Table 9: Characteristics of the relevant subpopulation as well as discontinuation of the study/treatment – RCT, direct comparison: enfortumab vedotin vs. vinflunine (multipage table)

Study characteristic category	Enfortumab vedotin N[a] = 73	Vinflunine N[a] = 78
EV-301		
Age [years], mean (SD)	66 (11)	68 (10)
Sex [F/M], %	19/81	18/82
Family origin, n (%)		
White	52 (71)	51 (65)
Asian	1 (1)	0 (0)
Unknown	20 (27)	27 (35)
Region, n (%)		
Western Europe	67 (92)	74 (95)
United States	0 (0)	0 (0)
Rest of the world	6 (8)	4 (5)
ECOG PS, n (%)		
0	25 (34)	25 (32)
1	48 (66)	53 (68)
Liver metastases, n (%)		
Yes	27 (37)	28 (36)
No	46 (63)	50 (64)
Visceral metastases, n (%)		
Yes	60 (82)	64 (82)
No	13 (18)	14 (18)
Primary origin of the disease		
Upper tract	17 (23)	22 (28)
Bladder/other	56 (77)	56 (72)
Present extent of disease, n (%)		
Metastatic	70 (96)	73 (94)
Locally advanced	3 (4)	5 (6)
Number of prior lines of treatment, n (%)		
1	12 (16)[b]	11 (14)[b]
2	55 (75)	58 (74)
≥ 3	6 (8)	9 (12)
Treatment discontinuation first data cut-off 15 July 2020, n (%)[c]	57 (78)	68 (87)
Study discontinuation first data cut-off 15 July 2020, n (%)[d]	32 (44)	45 (58)

Table 9: Characteristics of the relevant subpopulation as well as discontinuation of the study/treatment – RCT, direct comparison: enfortumab vedotin vs. vinflunine (multipage table)

Study characteristic category	Enfortumab vedotin N[a] = 73	Vinflunine N[a] = 78
Treatment discontinuation second data cut-off 30 July 2021, n (%)[e]	69 (95)	75 (96)
Study discontinuation second data cut-off 30 July 2021, n (%)[f]	50 (69)	64 (82)

a. Number of randomized patients.
b. Within the framework of a clinical study, patients with only one prior line of treatment received a combination therapy of a platinum-containing chemotherapy and a PD-(L)1 inhibitor.
c. Common reasons for treatment discontinuation in the intervention versus the control arm were: disease progression (51% vs. 55%), AEs (21% vs. 17%), withdrawal of consent (4% vs. 6 %).
d. Common reasons for study discontinuation in the intervention versus the control arm were: death (41% vs. 53%) and withdrawal of consent (3% vs. 4%).
e. Common reasons for treatment discontinuation in the intervention versus the control arm were: disease progression (62% vs. 62%), AEs (25% vs. 18%), withdrawal of consent (4% vs. 6%).
f. Common reasons for study discontinuation in the intervention versus the control arm were: death (66% vs. 77%), withdrawal of consent (3% vs. 4 %).

AE: adverse event; ECOG PS: Eastern Cooperative Oncology Group Performance Status; F: female; M: male; n: number of patients in the category; N: number of randomized patients; PD-(L)1: programmed cell death (ligand) 1; RCT: randomized controlled trial; SD: standard deviation

The patient characteristics between the treatment groups in the vinflunine subpopulation of the EV-301 study were comparable. Most patients were white; the mean age was 67 years. In both study arms, the proportion of men (about 81%) was higher than the proportion of women (about 19%). According to the inclusion criteria, all patients had already received at least 1 platinum-based chemotherapy and a PD-1 or PD-L1 inhibitor for the treatment of urothelial carcinoma prior to study inclusion, of which approx. 10% had been pretreated with 3 or more therapies. More than 90% of the patients included were in the metastatic stage of the disease upon study inclusion; approx. 37% of them had liver metastases.

At both data cut-offs, there were differences between the treatment arms regarding treatment and study discontinuation, with higher discontinuation rates in the vinflunine arm in each case.

Treatment duration and observation period as well as subsequent therapies

Table 10 shows the mean and median treatment duration of the patients as well as the mean and median observation period for individual outcomes.

Table 10: Information on the course of the study – RCT, direct comparison: enfortumab vedotin vs. vinflunine

Study **duration of the study phase** **outcome category**	**Enfortumab vedotin** **N[a] = 73**	**Vinflunine** **N[a] = 78**
EV-301		
Treatment duration, first data cut-off 15 July 2020 [months][b]	n = 71	n = 75
Median [min; max]	5.4 [0.5; 14.1]	3.9 [0.2; 13.9]
Mean (SD)	5.3 (3.6)	4.6 (3.4)
Treatment duration, second data cut-off 30 July 2021 [months][b]		
Median [min; max]	5.4 [0.5; 25.7]	3.9 [0.2; 26.4]
Mean (SD)	6.6 (6.1)	5.4 (5.3)
Observation period [months][b]	n = 73	n = 78
Overall survival, second data cut-off 30 July 2021		
Median [min; max][c]	12.3 [0.5; 29.5]	8.7 [0.1; 31.9]
Mean (SD)[c]	12.7 (8.6)	11.1 (8.3)
Morbidity (EORTC QLQ-C30 and EQ-5D VAS) and health-related quality of life (EORTC QLQ-C30), first data cut-off 15 July 2020	n = 73	n = 78
Median [min; max]	5.7 [0.0; 15.1]	4.2 [0.0; 14.0]
Mean (SD)	5.4 (3.7)	4.6 (3.6)
Side effects (second data cut-off 30 July 2021)	n = 71	n = 75
Median [min; max]	6.1 [1.0; 25.9]	4.4 [1.0; 26.4]
Mean (SD)	7.2 (6.0)	6.2 (5.9)

a. Number of randomized patients.
b. Institute's calculation from data in days.
c. Information on how the observation period was calculated is not available.

EORTC QLQ-C30: European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30; max: maximum; min: minimum; n: number of analysed patients; N: number of analysed patients; RCT: randomized controlled trial; SD: standard deviation; VAS: visual analogue scale

The median treatment duration at both data cut-offs was longer in the intervention (5.4 months) than in the control arm (3.9 months).

The median follow-up duration for overall survival was 12.3 months in the intervention arm and 8.7 months in the control arm. For the morbidity, health-related quality of life, and side effects outcomes, whose follow-up duration was linked to treatment end (see Table 8); the follow-up durations were markedly shorter in comparison. For these outcomes, conclusions can therefore be drawn only regarding the time under treatment (plus 30 days); the median treatment time in both treatment arms was approximately half of the median observation time for overall survival (Table 10). Data for the entire observation period are missing for these outcomes.

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

Table 11: Information on subsequent antineoplastic therapies - RCT, direct comparison: enfortumab vedotin vs. vinflunine, second data cut-off: 30 July 2021

Study drug	Patients with subsequent therapy n (%)	
	enfortumab vedotin N = 73	vinflunine N = 78
EV-301		
Total[a]	29 (39.7)	35 (44.9)
Radiotherapy	5 (6.8)	8 (10.3)
Paclitaxel	4 (5.5)	9 (11.5)
Vinflunine	8 (11.0)	0 (0)
Enfortumab vedotin	0 (0)	5 (6.4)[b]
Docetaxel	2 (2.7)	1 (1.3)
Pembrolizumab	1 (1.4)	2 (2.6)
Abemaciclib	1 (1.4)	1 (1.3)
Carboplatin + gemcitabine	1 (1.4)	1 (1.3)
Cisplatin	2 (2.7)	0 (0)
Cisplatin + gemcitabine	1 (1.4)	1 (1.3)
Erdafitinib	1 (1.4)	1 (1.3)
Sacituzumab govitecan	0 (0)	2 (2.6)
Carboplatin + paclitaxel	0 (0)	1 (1.3)
Durvalumab	1 (1.4)	0 (0)
Gemcitabine + paclitaxel	0 (0)	1 (1.3)
Ibrutinib	0 (0)	1 (1.3)
Pemigatinib	0 (0)	1 (1.3)
Cancer vaccines, therapeutic	1 (1.4)	0 (0)
Any other therapeutic products	1 (1.4)	0 (0)

a. Patients with at least one subsequent antineoplastic therapy; subsequent data on the specific therapies only refer to the first subsequent therapy.
b. According to Amendment 3 of the study protocol of 14 September 2020 after the first data cut-off (15 July 2020), a switch from the vinflunine arm to treatment of the intervention arm with enfortumab vedotin was possible. This has occurred in 4 (5.1%) patients by the second data cut-off. 1 other patient received enfortumab vedotin outside the framework of the described treatment switch.

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

At the time point of the second data cut-off, approx. 40% of the patients in the enfortumab vedotin arm and approx. 45% of the patients in the vinflunine arm had received subsequent therapy. The most common subsequent therapy in the enfortumab vedotin arm was vinflunine, followed by radiotherapy and paclitaxel. The most common subsequent therapy in the vinflunine arm was paclitaxel, followed by radiotherapy and enfortumab vedotin. Subsequent therapy with paclitaxel was twice as common in the vinflunine arm than in the enfortumab vedotin arm.

Risk of bias across outcomes (study level)

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

Table 12: Risk of bias across outcomes (study level) – RCT, direct comparison: enfortumab vedotin vs. vinflunine

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-301	Yes	Yes	No	No	Yes	Yes	Low
RCT: randomized controlled trial							

The risk of bias across outcomes was rated as low for the EV-301 study.

Limitations resulting from the open-label study design are described in Section 2.3.2 with the outcome-specific risk of bias.

Transferability of the study results to the German health care context

The company stated that the study population was transferable to the German health care context with regard to sex, age, body weight and ECOG PS. For this purpose, the company used retrospective analyses of the non-interventional EVOLVE study [6] for comparison, which, according to the company, included a representative German patient population. The company also stated that in both treatment arms, almost half of the patients were located in Western Europe and half of the patients were of white family origin. According to the company, men in Germany are four times more likely to develop urothelial carcinoma than women. This was reflected in the characteristics of the study population. Overall, the company considers the results obtained from the EV-301 study to be generally transferable to the German healthcare context.

However, the information provided by the company refers to the total population of the EV-301 study. For the vinflunine subpopulation, the company did not provide any information on the transferability of the study results to the German healthcare context.

2.3.2 Results on added benefit

2.3.2.1 Outcomes included

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

- Mortality
  - overall survival

- Morbidity
  - symptoms measured with the EORTC QLQ-C30 symptom scales
  - health status measured using the EQ-5D VAS
- Health-related quality of life
  - measured with the EORTC QLQ-C30 functional scales
- Side effects
  - serious AEs (SAEs)
  - severe AEs (Common Terminology Criteria for Adverse Events [CTCAE] grade ≥ 3)
  - discontinuation due to AEs
  - peripheral neuropathy (standardized MedDRA query [SMQ], AE)
  - hyperglycaemia (Preferred Term [PT], severe AEs)
  - constipation
  - neutropenia (PT, severe AEs)
  - febrile neutropenia (PT, severe AEs)
  - further specific AEs, if any

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

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

Table 13: Matrix of outcomes – RCT, direct comparison: enfortumab vedotin vs. vinflunine

Study	Outcomes											
	Overall survival	Symptoms (EORTC QLQ-C30 symptom scales)	Health status (EQ-5D VAS)	Health-related quality of life (EORTC QLQ-C30 functional scales)	SAEs	Severe AEs[a]	Discontinuation due to AEs	Peripheral neuropathy (SMQ, AEs)	Hyperglycaemia (PT, severe AEs[a])	Constipation	Neutropenia[b]	Further specific AEs[c]
EV-301	Yes	Yes[d]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No[e]	Yes	Yes

a. Operationalized as CTCAE grade ≥ 3.
b. Operationalized as neutropenia (PT, severe AEs) and febrile neutropenia (PT, severe AEs).
c. The following events are considered (MedDRA coding): eye disorders (SOC, AEs), diarrhoea (PT, AEs), conjunctivitis (PT, AEs), skin and subcutaneous tissue disorders (SOC, AEs) and nervous system disorders (SOC, severe AEs).
d. Does not apply to the symptom scale "constipation", for which no usable data are available; for justification see running text below.
e. No usable data available; for justification see running text below.

AE: adverse event; 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

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

In its dossier, the company presented responder analyses for the proportion of patients with a deterioration by ≥ 7 points, ≥ 10 points and ≥ 15 points (respective scale range 0 to 100) for the EQ-5D VAS. As explained in the *General Methods* of the Institute [14], for a response criterion to reflect with sufficient certainty a patient-noticeable change, it should correspond to at least 15% of the scale range of an instrument if prespecified (in post-hoc analyses exactly 15% of the scale range). The analysis with a response threshold of 15 points (corresponds to 15% of the scale range) is therefore used for the benefit assessment.

For the EORTC QLQ-C30, the company presented responder analyses for the proportion of patients with a deterioration by ≥ 10 points and ≥ 15 points (respective scale range 0 to 100). The analysis with a response threshold of 10 points is considered a sufficient approximation to an analysis with a 15% threshold (15 points) and is used for the benefit assessment (for explanation see [15]).

Note on outcomes of the side effects category

Overall rates SAEs and severe AEs

In addition to analyses on the overall rates of SAEs and severe AEs, the company also presented non-prespecified analyses in the dossier excluding SOCs and PTs that, in its view, were due to progression of the underlying disease. However, the company's choice also included events that were not clearly attributable to the progression of the underlying disease (e.g. haematuria [PT]). Therefore, the prespecified analyses were used for the benefit assessment.

Constipation

According to the SPC, concomitant treatment with laxatives and dietary measures, including oral hydration, is recommended as constipation prophylaxis during treatment with vinflunine. This was to be used in the first 5 to 7 days after each use with vinflunine. In the EV-301 study, constipation prophylaxis was not envisaged according to the study protocol. According to information from the CSR, at the time of the first data cut-off, two thirds of the patients in the total population were taking drugs for constipation. However, it is not clear from the study documents whether this was in the context of constipation prophylaxis or constipation treatment. Information on the subpopulation is not available. It is therefore unclear to what extent the partly severe cases of constipation that occurred in the study could have been avoided by prophylaxis. The results on the AE "constipation" as well as on the constipation symptom scale (EORTC QLQ-C30) are therefore not usable. It is also unclear to what extent the omission of prophylaxis has an impact on other outcomes.

Prerequisites for testing with an increased significance level are not completely fulfilled

For the benefit assessment of enfortumab vedotin compared to vinflunine, the company conducted tests with an increased significance level for the results of all outcomes of the vinflunine subpopulation in Appendix 4-G3 of its dossier. It justified this by stating that the consideration of a subpopulation was usually associated with a loss of power. A non-statistically significant advantage due to too little power could be compensated by the test with an increased significance level.

Irrespective of the statistical requirements, particularly clinical/content requirements must be met for a discussion of a test of the treatment effect at an increased significance level.

One prerequisite is the demonstration that, from a clinical/content perspective, the results of the subpopulation from the total population of the EV-301 study not relevant to the benefit assessment (taxane subpopulation) are sufficiently transferable to the subpopulation relevant to the benefit assessment (vinflunine subpopulation). In Module 3 A, the company explains that vinflunine, docetaxel and paclitaxel have a similar median overall survival. For this purpose, the company compared the effects of the individual drugs from the EV-301 study descriptively. It also presents the results of a network meta-analysis of the studies EV-301, KEYNOTE-045 [16] and IMvigor211 [17], which show no statistically significant difference in overall survival between vinflunine and the taxanes. However, the company neither presents an information

retrieval for the network meta-analysis, nor does it describe the studies KEYNOTE-045 and IMvigor211 in its dossier. It is therefore unclear, whether the study pool for the network meta-analysis is complete, and whether the studies are sufficiently similar for a comparison, for example with regard to the investigated study population. Furthermore, there is no information on the heterogeneity of the results. On the basis of the information provided by the company, it can therefore not be assessed with sufficient certainty that the effects of vinflunine and the taxanes on overall survival are comparable.

Moreover, the following aspects question the transferability: in principle, different effects are observed between the relevant vinflunine subpopulation and the total population. For example, there are significant effects in both the symptom scales (dyspnoea, insomnia and diarrhoea) and the domains (social functioning) of the EORTC QLQ-C30 and in the outcomes of severe AEs and SAEs of the subpopulation, which are not reflected in the results of the total population. Furthermore, due to the different range of side effects of the taxanes compared to vinflunine, impacts on the effects on the outcomes on morbidity and side effects cannot be excluded [13,18,19]. Overall, taxanes show a more neurotoxic spectrum of side effects, as does enfortumab vedotin, while vinflunine rather causes haematotoxic side effects [4].

Overall, the results of the vinflunine subpopulation are therefore used without testing with an increased significance level and without transferring the results of the total population; this approach deviates from that of the company.

2.3.2.2 Risk of bias

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

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

Study		Outcomes												
	Study level	Overall survival	Symptoms (EORTC QLQ-C30 symptom scales)	Health status (EQ-5D VAS)	Health-related quality of life (EORTC QLQ-C30 functional scales)	SAEs	Severe AEs[a]	Discontinuation due to AEs	Peripheral neuropathy (SMQ, AEs)	Hyperglycaemia (PT, severe AEs[a])	Constipation	Neutropenia[b]	Further specific AEs[c]
EV-301	L	L	H[d, e, f]	H[d, e]	H[d, e]	L	L	H[d]	H[d, g]	H[g]	-[h]	H[g]	H[d, g]

a. Operationalized as CTCAE grade ≥ 3.
b. Operationalized as neutropenia (PT, severe AEs) and febrile neutropenia (PT, severe AEs).
c. The following events are considered (MedDRA coding): eye disorders (SOC, AEs), diarrhoea (PT, AEs), conjunctivitis (PT, AEs), skin and subcutaneous tissue disorders (SOC, AEs) and nervous system disorders (SOC, severe AEs).
d. Subjectively influenced outcome in the absence of blinding (except specific AEs with CTCAE grade ≥ 3).
e. Strong decrease in response rates to the questionnaires over the course of the study.
f. Does not apply to the symptom scale "constipation", for which no usable data are available; for justification see Section 2.3.2.1 of the present benefit assessment.
g. Incomplete observations for potentially informative reasons (AEs were only observed until 30 days after treatment discontinuation).
h. No usable data available; for reasons, see Section 2.3.2.1 of the present benefit assessment.

AE: adverse event; 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; SOC: System Organ Class; VAS: visual analogue scale

The risk of bias for the outcomes "overall survival", "SAEs" and severe AEs was rated as low.

For the results of the outcomes of symptoms and health-related quality of life, the risk of bias was rated as high due to the study's open-label design with subjective recording of outcomes and strongly decreasing return rates of the questionnaires in the course of the study.

For the outcomes on side effects, the risk of bias of the results due to incomplete observations for potentially informative reasons (all outcomes except for SAEs and severe AEs) and due to lack of blinding in subjective recording of outcomes (all outcomes except for severe AEs and SAEs) was rated as high.

2.3.2.3 Results

Table 15 summarizes the results on the comparison of enfortumab vedotin with vinflunine in patients with locally advanced or metastatic urothelial carcinoma, who had received prior

platinum-containing chemotherapy and a PD-1 or PD-L1 inhibitor and for whom chemotherapy is suitable. Where necessary, calculations conducted by the Institute are provided in addition to the data from the company's dossier. The Kaplan-Meier curves on the included outcomes are presented in Appendix B of the full dossier assessment, and the results on common AEs, SAEs, severe AEs, and discontinuations due to AEs can be found in Appendix C of the full dossier assessment.

Table 15: Results (mortality, morbidity, health-related quality of life, side effects) – RCT, direct comparison: enfortumab vedotin vs. vinflunine (multipage table)

Study outcome category outcome	Enfortumab vedotin L	Enfortumab vedotin median time to event in months [95% CI] patients with event n (%)	Vinflunine L	Vinflunine median time to event in months [95% CI] patients with event n (%)	Enfortumab vedotin vs. vinflunine HR [95% CI][a]; p-value[b]
EV-301					
Mortality					
Overall survival (second data cut-off 30 July 2021)	73	12.81 [8.38; 17.18] 48 (65.8)	78	9.46 [7.85; 13.11] 60 (76.9)	0.75 [0.51; 1.09]; 0.129
Morbidity					
EORTC QLQ-C30 (first data cut-off: 15 July 2020)[c]					
Fatigue	73	0.85 [0.53; 1.28] 43 (58.9)	78	0.72 [0.43; 0.99] 44 (56.4)	0.89 [0.59; 1.36]; 0.598
Nausea and vomiting	73	1.68 [0.99; NC] 31 (42.5)	78	1.74 [0.99; NC] 29 (37.2)	0.99 [0.60; 1.64]; 0.963
Pain	73	2.14 [0.85; 6.21] 32 (43.8)	78	1.15 [0.53; 1.51] 38 (48.7)	0.68 [0.42; 1.08]; 0.101
Dyspnoea	73	NA [1.68; NC] 20 (27.4)	78	1.71 [0.79; 3.19] 34 (43.6)	0.51 [0.29; 0.89]; 0.014
Insomnia	73	5.42 [1.28; 9.07] 28 (38.4)	78	1.02 [0.53; 1.77] 35 (44.9)	0.61 [0.37; 0.997]; 0.048
Appetite loss	73	1.51 [0.79; 5.32] 34 (46.6)	78	1.08 [0.56; 1.77] 36 (46.2)	0.84 [0.52; 1.34]; 0.451
Constipation	No usable data[d]				
Diarrhoea	73	6.83 [0.79; 9.33] 29 (39.7)	78	NA [2.17; NC] 19 (24.4)	1.91 [1.07; 3.43]; 0.026
Health status (EQ-5D VAS, first data cut-off: 15 July 2020)[e]	73	2.14 [0.92; 6.83] 35 (47.9)	78	1.61 [0.99; 2.14] 35 (44.9)	0.81 [0.51; 1.29]; 0.377

Table 15: Results (mortality, morbidity, health-related quality of life, side effects) – RCT, direct comparison: enfortumab vedotin vs. vinflunine (multipage table)

Study outcome category outcome	Enfortumab vedotin L	Enfortumab vedotin median time to event in months [95% CI] patients with event n (%)	Vinflunine L	Vinflunine median time to event in months [95% CI] patients with event n (%)	Enfortumab vedotin vs. vinflunine HR [95% CI][a]; p-value[b]
Health-related quality of life					
EORTC QLQ-C30 (first data cut-off: 15 July 2020)[f]					
Global health status	73	1.74 [0.95; 5.95] 34 (46.6)	78	0.99 [0.56; 1.77] 37 (47.4)	0.77 [0.48; 1.23]; 0.278
Physical functioning	73	2.43 [1.25; 5.52] 31 (42.5)	78	1.51 [0.79; 2.73] 33 (42.3)	0.83 [0.51; 1.36]; 0.466
Role functioning	73	1.28 [0.79; 2.79] 40 (54.8)	78	0.79 [0.53; 1.38] 40 (51.3)	0.83 [0.54; 1.29]; 0.421
Emotional functioning	73	5.95 [2.14; NC] 22 (30.1)	78	1.97 [0.99; 4.34] 33 (42.3)	0.59 [0.34; 1.01]; 0.051
Cognitive functioning	73	5.95 [1.45; NC] 26 (35.6)	78	1.28 [0.76; NC] 32 (41.0)	0.71 [0.42; 1.19]; 0.190
Social functioning	73	1.74 [0.95; 6.83] 32 (43.8)	78	0.82 [0.53; 1.51] 42 (53.8)	0.60 [0.38; 0.95]; 0.028
Side effects (second data cut-off 30 July 2021)[g]					
AEs (supplementary information)	71	0.20 [0.13; 0.26] 69 (97.2)	75	0.07 [0.07; 0.13] 74 (98.7)	–
SAEs	71	8.51 [1.84; NC] 37 (52.1)	75	1.94 [0.56; 6.60] 49 (65.3)	0.62 [0.41; 0.96]; 0.030
Severe AEs[h]	71	2.10 [1.25; 4.93] 51 (71.8)	75	0.46 [0.30; 1.25] 58 (77.3)	0.64 [0.44; 0.93]; 0.020
Discontinuation due to AEs	71	NA [11.53; NC] 25 (35.2)	75	NA 20 (26.7)	1.27 [0.71; 2.29]; 0.420
Peripheral neuropathy (SMQ, AEs)	71	5.78 [2.89; 10.84] 36 (50.7)	75	NA [NC; NC] 14 (18.7)	3.53 [1.90; 6.57]; < 0.001
Hyperglycaemia (PT, severe AEs[h])	71	NA 6 (8.5)	75	NA 2 (2.7)	3.18 [0.64; 15.76]; 0.135
Constipation	No usable data[d]				
Neutropenia (PTs, severe AEs[h])	71	NA 3 (4.2)	75	NA 11 (14.7)	0.26 [0.07; 0.93] 0.025
Febrile neutropenia (PT, severe AEs[h])	71	NA 0 (0)	75	NA 6 (8.0)	NC 0.015
Eye disorders (SOC, AEs)	71	NA [7.39; NA] 25 (35.2)	75	NA 3 (4.0)	10.73 [3.24; 35.58]; < 0.001
Diarrhoea (PT, AEs)	71	NA [2.40; NA] 32 (45.1)	75	NA 15 (20)	2.71 [1.47; 5.01]; < 0.001
Conjunctivitis (PT, AEs)	71	NA 11 (15.5)	75	NA 2 (2.7)	6.07 [1.35; 27.40]; 0.008

Table 15: Results (mortality, morbidity, health-related quality of life, side effects) – RCT, direct comparison: enfortumab vedotin vs. vinflunine (multipage table)

Study outcome category outcome	Enfortumab vedotin		Vinflunine		Enfortumab vedotin vs. vinflunine
	L	median time to event in months [95% CI] patients with event n (%)	L	median time to event in months [95% CI] patients with event n (%)	HR [95% CI][a]; p-value[b]
Skin and subcutaneous tissue disorders (SOC, AEs)[i]	71	0.95 [0.62; 1.18] 53 (74.6)	75	NA [12.22; NC] 25 (33.3)	3.40 [2.10; 5.52]; < 0.001
Nervous system disorders (SOC, severe AEs[h])[j]	71	NA 9 (12.7)	75	NA 0 (0)	NC [NC; NC]; 0.002

a. Effect and CI: Cox proportional hazards model, unstratified.
b. p-value from 2-sided log rank test, unstratified.
c. Time to first deterioration; a score increase by ≥ 10 points from baseline is defined as a clinically relevant deterioration (scale range 0 to 100).
d. For reasons, see Section 2.3.2.1.
e. Time to first deterioration; a score increase by ≥ 15 points from baseline is defined as a clinically relevant deterioration (scale range 0 to 100).
f. Time to first deterioration; a score decrease by ≥ 10 points from baseline is defined as a clinically relevant deterioration (scale range 0 to 100).
g. Including events caused by progression of the underlying disease.
h. Operationalized as CTCAE grade ≥ 3.
i. Including the PTs "alopecia", "dry skin", "itching" and "skin rash" as the most common manifestations.
j. Including “peripheral sensory neuropathy“ as most common manifestation.

AE: adverse event; 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 1) event; N: number of analysed patients; NC: not calculable; NA: not achieved; 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 indications, e.g. of an added benefit, can be determined for the outcomes “overall survival”, “severe AEs” and “SAEs”, and at most hints can be determined for all other outcomes due to the high risk of bias.

Mortality

All-cause mortality

There was no statistically significant difference between the treatment arms for the outcome "all-cause mortality". This resulted in no hint of an added benefit of enfortumab vedotin in comparison with the ACT; an added benefit is therefore not proven.

Morbidity

Symptoms (EORTC QLQ-C30)

Fatigue, nausea and vomiting, and pain

For each of the outcomes of fatigue, nausea and vomiting, and pain, no statistically significant difference between treatment arms was found. In each case, this resulted in no hint of an added benefit of enfortumab vedotin in comparison with the ACT; an added benefit is therefore not proven.

Dyspnoea

For the outcome of dyspnoea, a statistically significant difference was found in favour of enfortumab vedotin in comparison with vinflunine. This resulted in a hint of added benefit of enfortumab vedotin in comparison with the ACT.

Insomnia

For the outcome of insomnia, a statistically significant difference was found in favour of enfortumab vedotin in comparison with vinflunine. This difference was no more than marginal, however (see Section 2.3.3.1). This resulted in no hint of an added benefit of enfortumab vedotin in comparison with the ACT; an added benefit is therefore not proven.

Diarrhoea

For the outcome of diarrhoea, a statistically significant difference was found to the disadvantage of enfortumab vedotin in comparison with vinflunine. This difference was no more than marginal, however (see Section 2.3.2.4). This resulted in no hint of an added benefit of enfortumab vedotin in comparison with the ACT; an added benefit is therefore not proven.

Appetite loss

No statistically significant difference between the treatment arms was shown for the outcome "appetite loss", but there was an effect modification by the characteristic "age" (see Section 2.3.2.4). This results in a hint of an added benefit of enfortumab vedotin versus the ACT for patients < 65 years of age. For patients ≥ 65 years, there was no hint of an added benefit of enfortumab vedotin versus the ACT; an added benefit is therefore not proven for these patients.

Constipation

For the outcome "constipation", no usable data are available for a comparison of enfortumab vedotin with vinflunine. This resulted in no hint of an added benefit of enfortumab vedotin in comparison with the ACT; an added benefit is therefore not proven.

Health status (EQ-5D VAS)

No statistically significant difference between the treatment arms was shown for the outcome "health status". This resulted in no hint of an added benefit of enfortumab vedotin in comparison with the ACT; an added benefit is therefore not proven.

Health-related quality of life

EORTC QLQ-C30

Global health status and physical functioning

No statistically significant difference between the treatment arms was shown for each of the outcomes "global health status" and "physical functioning". In each case, this resulted in no hint of an added benefit of enfortumab vedotin in comparison with the ACT; an added benefit is therefore not proven.

Role functioning, emotional functioning and cognitive functioning

For the outcomes of role functioning, emotional functioning and cognitive functioning, there is no statistically significant difference between the treatment arms; however, there is an effect modification by the characteristic “age” (see Section 2.3.2.4). In each case, this results in a hint of an added benefit of enfortumab vedotin versus the ACT for patients < 65 years of age. For patients ≥ 65 years, there was no hint of an added benefit of enfortumab vedotin versus the ACT; an added benefit is therefore not proven for these patients.

Social functioning

For the outcome of social functioning, a statistically significant difference was found in favour of enfortumab vedotin in comparison with vinflunine. This resulted in a hint of added benefit of enfortumab vedotin in comparison with the ACT.

Side effects

SAEs and severe AEs

For each of the outcomes “SAEs” and “severe AEs”, a statistically significant difference was found in favour of enfortumab vedotin in comparison with vinflunine. However, in each case, there was an effect modification by the characteristic “liver metastases” (see Section 2.3.2.4). In patients without liver metastases, this resulted in an indication of lesser harm from enfortumab vedotin versus the ACT. In each case, there was no hint of greater or lesser harm from enfortumab vedotin versus the ACT for patients with liver metastases; greater or lesser harm is therefore not proven for these patients.

Discontinuation due to AEs

There was no statistically significant difference between the treatment arms for the outcome “discontinuation due to AEs”. This resulted in no hint of greater or lesser harm from enfortumab vedotin in comparison with the ACT for the outcome “discontinuation due to AEs”; greater or lesser harm is therefore not proven.

Specific AEs

Peripheral neuropathy (AEs)

For the outcome “peripheral neuropathy (AEs)”, a statistically significant difference was found to the disadvantage of enfortumab vedotin in comparison with vinflunine. However, there was

an effect modification by the characteristic "age" (see Section 2.3.2.4). This results in a hint of greater harm from enfortumab vedotin versus the ACT for patients ≥ 65 years of age. There was no hint of greater or lesser harm from enfortumab vedotin versus the ACT for patients < 65 years; greater or lesser harm is therefore not proven for these patients.

Hyperglycaemia (severe AEs)

There was no statistically significant difference between the treatment arms for the outcome of hyperglycaemia (severe AEs). This resulted in no hint of greater or lesser harm from enfortumab vedotin in comparison with the ACT; greater or lesser harm is therefore not proven.

Constipation

For the outcome "constipation", no usable data are available for a comparison of enfortumab vedotin with vinflunine. This resulted in no hint of greater or lesser harm from enfortumab vedotin versus the ACT; greater or lesser harm is therefore not proven.

Neutropenia and febrile neutropenia (each of them being severe AEs)

For each of the outcomes "neutropenia" and "febrile neutropenia" (both being severe AEs), a statistically significant difference was found in favour of enfortumab vedotin in comparison with vinflunine. For each of them, this results in a hint of lesser harm from enfortumab vedotin in comparison with the ACT.

Eye disorders, diarrhoea, conjunctivitis and skin and subcutaneous tissue disorders (in each case AEs) and nervous system disorders (severe AEs)

A statistically significant difference to the disadvantage of enfortumab vedotin in comparison with vinflunine was shown for each of the outcomes of eye disorders, diarrhoea, conjunctivitis and skin and subcutaneous tissue disorders (in each case AEs) and nervous system disorders (severe AEs). For each of them, this results in a hint of greater harm from enfortumab vedotin in comparison with the ACT.

2.3.2.4 Subgroups and other effect modifiers

The following subgroup characteristics were considered to be relevant for the present benefit assessment:

- age (< 65 years versus ≥ 65 years)
- sex (female versus male)
- liver metastases (yes versus no)

The characteristics mentioned were prespecified.

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

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

The results are presented in Table 16. The Kaplan-Meier curves on the subgroup results are presented in Appendix B of the full dossier assessment.

Table 16: Subgroups (morbidity, health-related quality of life, side effects) – RCT, direct comparison: enfortumab vedotin vs. vinflunine (multipage table)

Study outcome characteristic subgroup	Enfortumab vedotin N	Enfortumab vedotin median time to event in months [95 % CI] patients with event n (%)	Vinflunine N	Vinflunine median time to event in months [95 % CI] patients with event n (%)	Enfortumab vedotin vs. vinflunine HR [95% CI]	Enfortumab vedotin vs. vinflunine p-value[a]
EV-301						
Morbidity						
EORTC QLQ-C30 (first data cut-off 15 July 2020)[b]						
Appetite loss						
Age						
< 65 years	26	1.91 [0.59; NC] 13 (50.0)	23	0.53 [0.30; 0.76] 13 (56.5)	0.37 [0.17; 0.80]	0.010
≥ 65 years	47	0.89 [0.53; 2.14] 21 (44.7)	55	1.64 [0.66; NC] 23 (41.8)	1.22 [0.67; 2.21]	0.583
Total					Interaction:	0.018[c]
Health-related quality of life						
EORTC QLQ-C30 (first data cut-off 15 July 2020)[d]						
Role functioning						
Age						
< 65 years	26	5.42 [0.92; 6.21] 14 (53.8)	23	0.53 [0.30; 0.76] 13 (56.5)	0.35 [0.16; 0.75]	0.003
≥ 65 years	47	0.85 [0.39; 1.45] 26 (55.3)	55	1.18 [0.72; 1.97] 27 (49.1)	1.29 [0.75; 2.20]	0.349
Total					Interaction:	0.006[c]
Emotional functioning						
Age						
< 65 years	26	NA [5.52; NC] 6 (23.1)	23	0.76 [0.30; 2.83] 11 (47.8)	0.21 [0.08; 0.58]	0.001
≥ 65 years	47	3.32 [1.05; NC] 16 (34.0)	55	2.23 [1.18; NC] 22 (40.0)	0.97 [0.51; 1.85]	0.903
Total					Interaction:	0.013[c]
Cognitive functioning						
Age						
< 65 years	26	8.18 [2.14; NC] 8 (30.8)	23	0.76 [0.33; NC] 10 (43.5)	0.33 [0.13; 0.83]	0.014
≥ 65 years	47	1.74 [0.69; NC] 18 (38.3)	55	1.61 [0.79; NC] 22 (40.0)	1.04 [0.56; 1.94]	0.937
Total					Interaction:	0.044[c]

Table 16: Subgroups (morbidity, health-related quality of life, side effects) – RCT, direct comparison: enfortumab vedotin vs. vinflunine (multipage table)

Study outcome characteristic subgroup	Enfortumab vedotin N	Enfortumab vedotin median time to event in months [95 % CI] patients with event n (%)	Vinflunine N	Vinflunine median time to event in months [95 % CI] patients with event n (%)	Enfortumab vedotin vs. vinflunine HR [95% CI]	Enfortumab vedotin vs. vinflunine p-value[a]
Side effects (second data cut-off 30 July 2021)						
SAEs						
Liver metastases						
Yes	26	1.72 [0.62; 5.55] 19 (73.1)	25	2.79 [0.30; NC] 15 (60.0)	1.14 [0.58; 2.24]	0.761
No	45	NA [5.45; NC] 18 (40.0)	50	1.71 [0.53; 6.60] 34 (68.0)	0.42 [0.24; 0.75]	0.003
Total					Interaction:	0.028[c]
Severe AEs						
Liver metastases						
Yes	26	1.23 [0.43; 3.42] 21 (80.8)	25	1.64 [0.30; NC] 16 (64.0)	1.24 [0.65; 2.38]	0.593
No	45	3.45 [1.35; 10.05] 30 (66.7)	50	0.43 [0.26; 1.18] 42 (84.0)	0.45 [0.28; 0.71]	0.001
Total					Interaction:	0.013[c]
Peripheral neuropathy (SMQ, AEs)						
Age						
< 65 years	26	8.80 [4.40; NA] 12 (46.2)	22	NA [2.79; NA] 6 (27.3)	1.54 [0.58; 4.11]	0.335
≥ 65 years	45	3.15 [1.87; NA] 24 (53.3)	53	NA 8 (15.1)	5.80 [2.59; 13.02]	< 0.001
Total					Interaction:	0.041[c]

a. p-value from 2-sided log rank test, unstratified.
b. Time to first deterioration; a score increase by ≥ 10 points from baseline is defined as a clinically relevant deterioration (scale range 0 to 100).
c. p-value: Cox proportional hazards model, unstratified, adjusted for subgroup effect and interaction of treatment and subgroup effect.
d. Time to first deterioration; a score decrease by ≥ 10 points from baseline is defined as a clinically relevant deterioration (scale range 0 to 100).

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 event; N: number of analysed patients; NA: not achieved; NC: not calculable; RCT: randomized controlled trial; SAE: serious adverse event; SMQ: Standardized MedDRA Query; SOC: System Organ Class

Morbidity

Symptoms (EORTC QLQ-C30)

Appetite loss

There was an effect modification by the characteristic “age" for the outcome “appetite loss”.

A statistically significant difference in favour of enfortumab vedotin in comparison with vinflunine was shown for patients aged < 65 years. This resulted in a hint of an added benefit of enfortumab vedotin versus the ACT.

There was no statistically significant difference between the treatment arms for patients ≥ 65 years. For this outcome, this resulted in no hint of an added benefit of enfortumab vedotin versus the ACT; an added benefit is therefore not proven for these patients.

Health-related quality of life

EORTC QLQ-C30

Role functioning, emotional functioning and cognitive functioning

There was an effect modification by the characteristic of age for each of the outcomes “role functioning”, “emotional functioning” and “cognitive functioning”.

A statistically significant difference in favour of enfortumab vedotin in comparison with vinflunine was shown in each case for patients aged < 65 years. In each case, this resulted in a hint of an added benefit of enfortumab vedotin versus the ACT.

There was no statistically significant difference between the treatment arms for patients ≥ 65 years. For each of these outcomes, this resulted in no hint of an added benefit of enfortumab vedotin versus the ACT; an added benefit is therefore not proven for these patients.

Side effects

SAEs and severe AEs

There was an effect modification by the characteristic “liver metastases" for the outcome “SAEs” and “severe AEs”.

A statistically significant difference in favour of enfortumab vedotin in comparison with vinflunine was shown in each case for patients without liver metastases. In each case, this resulted in an indication of lesser harm from enfortumab vedotin versus the ACT.

In each case, there was no hint of greater or lesser harm from enfortumab vedotin versus the ACT for patients with liver metastases; greater or lesser harm is therefore not proven for these patients.

Specific AEs

Peripheral neuropathy

There was an effect modification by the characteristic “age" for the outcome “peripheral neuropathy (AEs)”.

For patients ≥ 65 years, a statistically significant difference was shown to the disadvantage of enfortumab vedotin in comparison with vinflunine. This resulted in a hint of greater harm from enfortumab vedotin versus the ACT.

There was no statistically significant difference between the treatment arms for patients < 65 years. This resulted in no hint of greater or lesser harm from enfortumab vedotin versus the ACT; greater or lesser harm is therefore not proven for these patients.

2.3.3 Probability and extent of added benefit

Probability and extent of added benefit for research question 1 (adult patients for whom chemotherapy is suitable) are derived at outcome level below, taking into account the different outcome categories and effect sizes. The methods used for this purpose are explained in the *General Methods* of IQWiG [14].

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

2.3.3.1 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 2.3.2 (see Table 17).

Determination of the outcome category for symptom outcomes

For the following outcomes on symptoms, the classification of whether they are serious/severe or non-serious/non-severe is justified as follows.

Symptoms

Dyspnoea, insomnia, appetite loss, constipation and diarrhoea (EORTC QLQ-C30)

No information is available which would justify classifying the outcomes of dyspnoea, insomnia, appetite loss, constipation and diarrhoea as serious/severe symptoms/late complications. Therefore, these outcomes were assigned to the outcome category of non-serious/non-severe symptoms/late complications. This concurs with the company’s approach.

Table 17: Extent of added benefit at outcome level: enfortumab vedotin vs. vinflunine (multipage table)

Observation period **outcome category** **outcome** **effect modifier** **subgroup**	**Enfortumab vedotin vs. vinflunine** **median time to event (months)** **effect estimation [95% CI];** **p-value** **probability**[a]	**Derivation of the extent**[b]
Total observation period		
Mortality		
Overall survival	12.81 vs. 9.46 HR: 0.75 [0.51; 1.09] p = 0.129	Lesser benefit/added benefit not proven
Shortened observation period		
Morbidity		
Symptoms (EORTC QLQ-C30, deterioration ≥ 10 points)		
Fatigue	0.85 vs. 0.72 HR: 0.89 [0.59; 1.36] p = 0.598	Lesser benefit/added benefit not proven
Nausea and vomiting	1.68 vs. 1.74 HR: 0.99 [0.60; 1.64] p = 0.963	Lesser benefit/added benefit not proven
Pain	2.14 vs. 1.15 HR: 0.68 [0.42; 1.08] p = 0.101	Lesser benefit/added benefit not proven
Dyspnoea	NA vs. 1.71 HR: 0.51 [0.29; 0.89] p = 0.014 probability: "hint"	Outcome category: non-serious/non-severe symptoms/late complications $0.80 \leq CI_u < 0.90$ added benefit, extent: "minor"
Insomnia	5.42 vs. 1.02 HR: 0.61 [0.37; 0.997] p = 0.048	Outcome category: non-serious/non-severe symptoms/late complications $0.90 \leq CI_u < 1.00$ lesser benefit/added benefit not proven[c]
Appetite loss Age < 65 years	1.91 vs. 0.53 HR: 0.37 [0.17; 0.80] p = 0.010 probability: "hint"	Outcome category: non-serious/non-severe symptoms/late complications $0.80 \leq CI_u < 0.90$ added benefit, extent: "minor"
≥ 65 years	0.89 vs. 1.64 HR: 1.22 [0.67; 2.21] p = 0.583	Lesser benefit/added benefit not proven

Table 17: Extent of added benefit at outcome level: enfortumab vedotin vs. vinflunine (multipage table)

Observation period **outcome category** **outcome** **effect modifier** **subgroup**	**Enfortumab vedotin vs. vinflunine** **median time to event (months)** **effect estimation [95% CI];** **p-value** **probability**[a]	**Derivation of the extent**[b]
Constipation	No usable data	Lesser benefit/added benefit not proven
Diarrhoea	6.83 vs. NA HR: 1.91 [1.07; 3.43] HR: 0.52 [0.29; 0.93][d] p = 0.026	Outcome category: non-serious/non-severe symptoms/late complications $0.90 \leq CI_u < 1.00$ lesser benefit/added benefit not proven[c]
Health status (EQ-5D VAS (deterioration by ≥ 15 points)		
EQ-5D VAS	2.14 vs. 1.61 HR: 0.81 [0.51; 1.29] p = 0.377	Lesser benefit/added benefit not proven
Health-related quality of life (EORTC QLQ-C30, deterioration ≥ 10 points)		
Global health status	1.74 vs. 0.99 HR: 0.77 [0.48; 1.23] p = 0.278	Lesser benefit/added benefit not proven
Physical functioning	2.43 vs. 1.51 HR: 0.83 [0.51; 1.36] p = 0.466	Lesser benefit/added benefit not proven
Role functioning Age		
< 65 years	5.42 vs. 0.53 HR: 0.35 [0.16; 0.75] p = 0.003 probability: hint	Outcome category: health-related quality of life $0.75 \leq CI_u < 0.90$ added benefit; extent: considerable
≥ 65 years	0.85 vs. 1.18 HR: 1.29 [0.75; 2.20] p = 0.349	Lesser benefit/added benefit not proven
Emotional functioning Age		
< 65 years	NA vs. 0.76 HR: 0.21 [0.08; 0.58] p = 0.001 probability: hint	Outcome category: health-related quality of life $CI_u < 0.75$, risk ≥ 5% added benefit, extent: “major”
≥ 65 years	3.32 vs. 2.23 HR: 0.97 [0.51; 1.85] p = 0.903	Lesser benefit/added benefit not proven

Table 17: Extent of added benefit at outcome level: enfortumab vedotin vs. vinflunine (multipage table)

Observation period **outcome category** **outcome** **effect modifier** **subgroup**	**Enfortumab vedotin vs. vinflunine** **median time to event (months)** **effect estimation [95% CI];** **p-value** **probability**[a]	**Derivation of the extent**[b]
Cognitive functioning		
Age		
< 65 years	8.18 vs. 0.76 HR: 0.33 [0.13; 0.83] p = 0.014 probability: “hint”	Outcome category: health-related quality of life $0.75 \leq CI_u < 0.90$ added benefit; extent: considerable
≥ 65 years	1.74 vs. 1.61 HR: 1.04 [0.56; 1.94] p = 0.937	Lesser benefit/added benefit not proven
Social functioning	1.74 vs. 0.82 HR: 0.60 [0.38; 0.95] p = 0.028 probability: hint	Outcome category: health-related quality of life $0.90 \leq CI_u < 1.00$ added benefit, extent: “minor”
Side effects		
SAEs		
Liver metastases		
Yes	1.72 vs. 2.79 HR: 1.14 [0.58; 2.24] p = 0.761	Greater/lesser harm not proven
No	NA vs. 1.71 HR: 0.42 [0.24; 0.75] p = 0.003 probability: "indication”	Outcome category: serious/severe side effects $0.75 \leq CI_u < 0.90$ lesser harm, extent: considerable
Severe AEs		
Liver metastases		
Yes	1.23 vs. 1.64 HR: 1.24 [0.65; 2.38] p = 0.593	Greater/lesser harm not proven
No	3.45 vs. 0.43 HR: 0.45 [0.28; 0.71] p = 0.001 probability: “indication”	Outcome category: serious/severe side effects $CI_u < 0.75$, risk ≥ 5% lesser harm; extent: major
Discontinuation due to AEs	NA vs. NA HR: 1.27 [0.71; 2.29] p = 0.420	Greater/lesser harm not proven

Table 17: Extent of added benefit at outcome level: enfortumab vedotin vs. vinflunine (multipage table)

Observation period **outcome category** **outcome** **effect modifier** **subgroup**	**Enfortumab vedotin vs. vinflunine** **median time to event (months)** **effect estimation [95% CI];** **p-value** **probability**[a]	**Derivation of the extent**[b]
peripheral neuropathy (AEs) Age < 65 years	8.80 vs. NA HR: 1.54 [0.58; 4.11] p = 0.335	Greater/lesser harm not proven
≥ 65 years	3.15 vs. NA HR: 5.80 [2.59; 13.02] HR: 0.17 [0.08; 0.39][d] 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 HR: 3.18 [0.64; 15.76] p = 0.135	Greater/lesser harm not proven
Constipation (severe AEs)	No usable data	Lesser benefit/added benefit not proven
Neutropenia (severe AEs)	NA vs. NA HR: 0.26 [0.07; 0.93] p = 0.025 probability: hint	Outcome category: serious/severe side effects $0.90 \leq CI_u < 1.00$ lesser harm; extent: minor
Febrile neutropenia (severe AEs)	NA vs. NA proportions of events: 0 (0%) vs. 6 (8.0) HR: NC p = 0.015 probability: hint	Outcome category: serious/severe side effects lesser harm, extent: "non-quantifiable"
Eye disorders (AEs)	NA vs. NA HR: 10.73 [3.24; 35.58] HR: 0.09 [0.03; 0.31][d] p < 0.001 probability: “hint”	Outcome category: non-serious/non-severe side effects $CI_u < 0.80$ greater harm, extent: “considerable”
Diarrhoea (AEs)	NA vs. NA HR: 2.71 [1.47; 5.01] HR: 0.37 [0.20; 0.68][d] p < 0.001 probability: hint	Outcome category: non-serious/non-severe side effects $CI_u < 0.80$ greater harm, extent: “considerable”
Conjunctivitis (AEs)	NA vs. NA HR: 6.07 [1.35; 27.40] HR: 0.16 [0.04; 0.74][d] p = 0.008 probability: hint	Outcome category: non-serious/non-severe side effects $CI_u < 0.80$ greater harm, extent: “considerable”

Table 17: Extent of added benefit at outcome level: enfortumab vedotin vs. vinflunine (multipage table)

Observation period **outcome category** **outcome** **effect modifier** **subgroup**	**Enfortumab vedotin vs. vinflunine** **median time to event (months)** **effect estimation [95% CI];** **p-value** **probability**[a]	**Derivation of the extent**[b]
Skin and subcutaneous tissue disorders (AEs)	0.95 vs. NA HR: 3.40 [2.10; 5.52] HR: 0.29 [0.18; 0.48][d] p < 0.001 probability: "hint"	Outcome category: non-serious/non-severe side effects CI_u < 0.80 greater harm, extent: "considerable"
Nervous system disorders (severe AEs)	NA vs. NA proportions of events: 9 (12.7 %) vs. 0 (0 %) HR: NC p = 0.002 probability: hint	Outcome category: serious/severe side effects greater harm, extent "non-quantifiable"

a. Probability provided if there is a statistically significant and relevant effect.
b. Depending on the outcome category, estimations of effect size are made with different limits based on the upper limit of the confidence interval (CI_u).
c. The extent of the effect in this non-serious/non-severe outcome was no more than marginal.
d. Institute's calculation; reversed direction of effect to enable use of limits to derive the extent of the added benefit.

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

2.3.3.2 Overall conclusion on added benefit

Table 18 summarizes the results included in the overall conclusion on the extent of added benefit.

Table 18: Positive and negative effects from the assessment of enfortumab vedotin in comparison with vinflunine

Positive effects	Negative effects
Shortened observation period	
Non-serious/non-severe symptoms/late complications ▪ symptoms (EORTC QLQ-C30) ▫ dyspnoea: hint of an added benefit – extent: “minor” ▫ appetite loss - age (< 65 years): hint of added benefit – extent: "minor"	-
Health-related quality of life (EORTC QLQ-C30) ▪ role functioning and cognitive functioning ▫ age (< 65 years): hint of added benefit – extent: "considerable" ▪ emotional functioning ▫ age (< 65 years): hint of added benefit – extent: "major" ▪ social functioning: hint of an added benefit – extent: "minor"	-
Serious/severe side effects ▪ SAEs ▫ liver metastases (no): Indication of lesser harm – extent: “considerable” ▪ severe AEs ▫ liver metastases (no): indication of lesser harm – extent: "major" ▪ febrile neutropenia (severe AEs): hint of lesser harm – extent: “non-quantifiable” ▪ neutropenia (severe AEs): hint of lesser harm – extent: “minor”	Serious/severe side effects ▪ nervous system disorders (severe AEs): hint of greater harm – extent: “non-quantifiable”
-	Non-serious/non-severe side effects ▪ eye disorders, diarrhoea, conjunctivitis, skin and subcutaneous tissue disorders (AEs): hint of greater harm – extent: "considerable" ▪ peripheral neuropathy (AEs) ▫ age (≥ 65 years): hint of greater harm – extent: “considerable”
AE: adverse event; EORTC QLQ-C30: European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire – Core 30; SAE: serious adverse event	

The overall assessment shows both positive and negative effects of different extents for enfortumab vedotin versus vinflunine in the vinflunine subpopulation. There were also different subgroup effects for the characteristics “age” and “liver metastases”; however, it is unclear to what extent the different subgroups overlap. Therefore, the added benefit was not derived separately according to subgroups.

For “symptoms” and “health-related quality of life”, only positive effects of enfortumab vedotin were shown, most of them with the extent “minor”. For patients < 65 years, further advantages with varying extents were shown for these outcome categories. In the outcome category of serious/severe side effects, there is an indication of lesser harm with the extent "considerable" or "major" for patients without liver metastases for the overall rate of severe AEs and SAEs respectively. In addition, for several specific serious/severe side effects, there are hints of lesser harm with the extent “minor” or “non-quantifiable” for the vinflunine subpopulation.

The negative effects are related exclusively to outcomes of the category of side effects; for serious/severe side effects with the extent “non-quantifiable” as well as for various non-serious/non-severe side effects with the extent “considerable”.

The observed effects for symptoms, health-related quality of life, and side effects are based exclusively on the shortened time period until treatment end (plus 30 days).

In summary, there is a hint of minor added benefit of enfortumab vedotin versus the ACT for patients with locally advanced or metastatic urothelial carcinoma who had received prior platinum-containing chemotherapy and a PD-1 or PD-L1 inhibitor and for whom chemotherapy is suitable.

The assessment described above deviates from that of the company, which derived an indication of an considerable added benefit of enfortumab vedotin for the total population of the EV-301 study.

2.4 Research question 2: Patients for whom chemotherapy is unsuitable

2.4.1 Information retrieval and study pool

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

Sources of the company in the dossier:

- study list on enfortumab vedotin (status: 5 April 2022)
- bibliographical literature search on enfortumab vedotin (last search on 5 April 2022)
- search in trial registries/trial results databases for studies on enfortumab vedotin (last search on 5 April 2022)
- search on the G-BA website for enfortumab vedotin (last search on 05 April 2022)

To check the completeness of the study pool:

- search in trial registries for studies on enfortumab vedotin (last search on 15 June 2022); for search strategies, see Appendix A of the full dossier assessment

No relevant study was identified from the check. This differs from the assessment of the company, which considers the therapeutic application of enfortumab vedotin independently of

whether chemotherapy is suitable for the patients and identifies the RCT EV-301 for the entire therapeutic indication of enfortumab vedotin. However, this study is only relevant for research question 1 (patients for whom chemotherapy is suitable) (see Section 2.3).

2.4.2 Results on added benefit

The company presented no data for the assessment of the added benefit of enfortumab vedotin in comparison with the ACT for adult patients with locally advanced or metastatic urothelial carcinoma who had received prior platinum-containing chemotherapy and a PD-1 or PD-L1 inhibitor and for whom chemotherapy is unsuitable. This resulted in no hint of an added benefit of enfortumab vedotin versus the ACT. An added benefit is therefore not proven.

2.4.3 Probability and extent of added benefit

The company did not provide any data for the assessment of the added benefit of enfortumab vedotin in adult patients with locally advanced or metastatic urothelial carcinoma who have received prior platinum-containing chemotherapy and a PD-1 or PD-L1 inhibitor and for whom chemotherapy is unsuitable. An added benefit of enfortumab vedotin in comparison with the ACT is thus not proven for these patients.

2.5 Probability and extent of added benefit – summary

Table 19 summarizes the result of the assessment of the added benefit of enfortumab vedotin in comparison with the ACT.

Table 19: Enfortumab vedotin – probability and extent of added benefit

Research question	Therapeutic indication	ACT[a]	Probability and extent of added benefit
1	Adults with locally advanced or metastatic urothelial carcinoma[b] who have received prior platinum-containing chemotherapy and a PD1 or PD-L1 inhibitor and for whom chemotherapy is suitable.	Vinflunine monotherapy or cisplatin in combination with gemcitabine	Hint of minor added benefit[c]
2	Adults with locally advanced or metastatic urothelial carcinoma[b] who have previously received a platinum-containing chemotherapy and a PD-1 or PD-L1 inhibitor and for whom chemotherapy is unsuitable	BSC[d]	Added benefit not proven

a. Presented is the respective ACT specified by the G-BA.
b. It is assumed that the intended therapeutic indication includes patients whose locally advanced or metastatic urothelial carcinoma is inoperable.
c. Only patients with an ECOG PS of 0 or 1 were included in the EV-301 study. It remains unclear whether the observed effects are transferable to patients with an ECOG PS ≥ 2.
d. BSC 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; BSC: best supportive care; ECOG PS: Eastern Cooperative Oncology Group Performance Status; G-BA: Federal Joint Committee; PD-(L)1: programmed cell death (ligand) 1

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

References for English extract

Please see full dossier assessment for full reference list.

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

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