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

Addendum to Project A24-98 (dossier assessment)[1]

ADDENDUM

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Table of contents

List of tables

Page

List of figures

Page

List of abbreviations

Abbreviation	Meaning
ACT	appropriate comparator therapy
AE	adverse event
EORTC	European Organisation for Research and Treatment of Cancer
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
PFS	progression-free survival
QLQ-C30	Quality of Life Questionnaire – Core 30
RCT	randomized controlled trial
SAE	serious adverse event
SGB	Sozialgesetzbuch (Social Code Book)
SPC	Summary of Product Characteristics

1 Background

On 11 February 2025, the Federal Joint Committee (G-BA) commissioned the Institute for Quality and Efficiency in Health Care (IQWiG) to conduct supplementary assessments on project A24-98 (enfortumab vedotin – benefit assessment according to §35a Social Code Book V) [1].

The commission comprises the assessment of the analyses of the 2nd data cut-off of the randomized controlled trial (RCT) EV-302/KN-A39 presented by the company in the commenting procedure, including additional analyses such as sensitivity and tipping point analyses [2-5], taking into account the information in the dossier [6].

The responsibility for the present assessment and the assessment result lies exclusively with IQWiG. The assessment is forwarded to the G-BA. The G-BA decides on the added benefit.

2 Assessment

The RCT EV-302/KN-A39 was used for the benefit assessment of enfortumab vedotin within the framework of dossier assessment A24-98 (first-line therapy in adult patients with unresectable or metastatic urothelial carcinoma for whom platinum-containing chemotherapy is an option and for whom cisplatin-based therapy is suitable [research question 1] or not suitable [research question 2]). This study examines the comparison of enfortumab vedotin in combination with pembrolizumab (enfortumab vedotin + pembrolizumab) versus platinum-based chemotherapy (cisplatin/carboplatin + gemcitabine) in the first-line treatment of adult patients with unresectable or metastatic urothelial carcinoma who are eligible for platinum-based chemotherapy.

For the RCT EV-302/KN-A39, the company presented results of the first data cut-off of 08 August 2023 in Module 4 A of its dossier, and this data cut-off was used for the assessment. According to the study design, a second data cut-off was also planned if the results for overall survival had not reached statistical significance at the first data cut-off. This data cut-off was requested by the Food and Drug Administration (FDA) [7] and performed [2].

As part of the commenting procedure, the company presented analyses of the 2nd data cut-off from 8 August 2024 (i.e. conducted 1 year after the 1st data cut-off), including analyses and data on mortality, symptoms, health status and health-related quality of life and on outcomes in the side effects category as well as information on observation durations and subsequent therapies. With regard to the results on mortality, the company presented 3 sensitivity analyses for the 2nd data cut-off analogous to the sensitivity analyses presented in its dossier as well as additional so-called tipping point analyses.

2.1 Study characteristics (aspects across research questions)

A detailed characterisation of study EV-302/KN-A39 can be found in dossier assessment A24-98. The following therefore only describes aspects for which the present addendum yields relevant changes compared with dossier assessment A24-98. As the included study EV-302/KN-A39 is relevant for both research questions of the benefit assessment, only aspects across research questions are initially described. Research question-specific aspects for research question 1 are described in 2.2.1, and those for research question 2 are described in Section 2.3.1.

2.1.1 Limitation of the maximum treatment duration with pembrolizumab to 35 cycles

In study EV-302/KN-A39, treatment with pembrolizumab was limited to a maximum treatment duration of 35 cycles (approx. 24 months), in deviation from the specifications of the Summary of Product Characteristics (SPC), as described in dossier assessment A24-98. According to the SPC, pembrolizumab treatment is to be continued until cancer progression

or the occurrence of unacceptable toxicity [8]. In the intervention arm of the EV-302/KN-A39 study, 16 (6.7%) of the patients in the subpopulation relevant to research question 1 and 14 (6.9%) of the patients in the subpopulation relevant to research question 2 had completed the 35 treatment cycles by the second data cut-off. Due to the small number of affected patients, it is still not assumed that the restriction to a maximum of 35 treatment cycles with pembrolizumab represents a relevant limitation of the treatment.

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

Treatment with cisplatin/carboplatin + gemcitabine

As described in dossier assessment A24-98, the use of carboplatin + gemcitabine essentially complied with the specifications of Annex VI to Section K of the Pharmaceutical Directive. For treatment with cisplatin + gemcitabine, however, there were deviations from the SPC, e.g. with regard to the length of the treatment cycles with cisplatin + gemcitabine. Due to this deviation, the dose per cycle or the cumulative dose relating to gemcitabine is lower than stipulated in the approval, while relating to cisplatin, the dose is administered at shorter intervals.

In the overall view of the available information from publicly available sources [9] and the discussion in the oral hearings on the benefit assessment of nivolumab (A24-70) [10] and on the present benefit assessment of enfortumab vedotin + pembrolizumab (A24-98 and A24-99) [11], it is assumed that no additional uncertainty arises from this deviation in the present situation.

In contrast to dossier assessment A24-98, it is overall assumed for the present addendum that the deviations from the SPC in terms of treatment with cisplatin + gemcitabine in study EV-302/KN-A39 do not contribute to the restriction of the certainty of conclusions in research question 1.

2.1.3 Implementation of the appropriate comparator therapy (ACT): maintenance therapy with avelumab not part of the study medication

As described in dossier assessment A24-98, the ACT in RCT EV-302/KN-A39 was incompletely implemented with regard to maintenance therapy with avelumab, as a relevant proportion of patients did not receive maintenance therapy with avelumab, although this would have been possible according to the company's information.

However, in Module 4 A of its dossier, the company provided further information on the implementation of maintenance therapy with avelumab in the EV-302/KN-A39 study at the 1st data cut-off. As described in dossier assessment A24-98, this information can be used to differentiate between the following 3 groups of patients:

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

With its comments, the company also presented corresponding data on the 2nd data cut-off. These are shown in Table 1 and were supplemented by the Institute's calculation.

Table 1: Information on the implementation of maintenance therapy with avelumab in study EV-302/KN-A39 according to company

Study characteristic category	**Cisplatin + gemcitabine N = 242[a]**	**Carboplatin + gemcitabine N = 202[b]**
EV-302/KN-A39 (2nd data cut-off 08 August 2024)		
Maintenance therapy with avelumab possible according to company and avelumab received[c], n (%)	84 (34.7)	49 (24.3)
Maintenance therapy with avelumab not possible according to the company, n (%)	83 (34.3)[d]	101 (50.0)[d]
Lost to follow-up[e]	1 (0.4)	1 (0.5)
< 4 cycles of platinum-based chemotherapy completed	13 (5.4)	22 (10.9)
Disease progression or death[e], of which	69 (28.5)	78 (38.6)
During chemotherapy[f]	60 (24.8)	63 (31.2)
Within 10 weeks after last dose[f]	9 (3.7)	15 (7.4)
Maintenance therapy with avelumab possible according to company, but nevertheless avelumab not received, n (%)	69 (28.5)[d]	47 (23.3)d
Avelumab not received and alive[g]	34 (14.0)	19 (9.4)
Avelumab not received and deceased	35 (14.5)	28 (13.9)

a. 236 of the 242 (97.5%) patients received platinum-based chemotherapy.
b. 197 of the 202 (97.5%) patients received platinum-based chemotherapy.
c. After completion of chemotherapy.
d. Institute's calculation.
e. During chemotherapy or within 10 weeks after chemotherapy.
f. The company's documents provide no information for the 2nd data cut-off (8 August 2024). It is assumed that there has been no change from the 1st data cut-off (8 August 2023). The information presented refers to the 1st data cut-off.
g. Chemotherapy completed and alive at the time of data cut-off 2 (08 August 2024).
n: number of patients in the category; N: number of randomized patients

The proportions of patients in the 3 groups described above changed only slightly compared to the 2nd data cut-off.

The company's analyses on the proportion of patients for whom it considered maintenance therapy with avelumab to be an option and in whom it was either implemented or not implemented enable an assessment of the interpretability of the results of the 2nd data cut-off of the EV-302/KN-A39 study for the benefit assessment. Further points that were addressed in the context of the implementation of maintenance therapy in the benefit assessment A24-98 are discussed below.

Uncertainties regarding the implementation of maintenance therapy with avelumab remain

The results of RCT EV-302/KN-A39 could be interpreted for the benefit assessment on the basis of the information presented in the company's dossier. However, the informative value of the study was limited, particularly due to the incomplete implementation of maintenance therapy with avelumab. Therefore, in the dossier assessment based on the RCT EV-302/KN-A39, at most hints, e.g. of an added benefit, could be determined for both research questions for all outcomes.

The following three points contributed to the uncertainty due to the incomplete implementation of maintenance therapy with avelumab, as described in the dossier assessment:

- Avelumab was not part of the study medication, but, according to the study design (first description of the possibility of avelumab maintenance therapy with Amendment 4 of the study protocol on 11 November 2021), could be used after completion or discontinuation of platinum-containing chemotherapy according to the investigator's assessment and depending on local availability.
- There is a lack of specific information on the use of avelumab, and it is unclear whether the specifications of the SPC for avelumab applicable in Germany, for example on dosage, were complied with. There is also no information available on the time point at which maintenance therapy with avelumab was started after completion of chemotherapy.
- With regard to patients with disease progression or death within 10 weeks after the last dose of chemotherapy, the company’s dossier did not provide any information on the time at which the respective events occurred within this time window. Therefore, it remains unclear for how many patients with disease progression or death within 10 weeks of the last dose of chemotherapy an earlier use of maintenance therapy with avelumab would have been possible and would have provided them with a potential benefit.

The first point is due to the design of the RCT EV-302/KN-A39 and the fact that avelumab was only approved as a maintenance therapy during the course of the study and therefore cannot be changed retrospectively.

With regard to the second point, the company stated in its comments on the dossier assessment that the administration of avelumab in the EV-302/KN-A39 study took place in experienced study centres, most of which had also participated in the RCT JAVELIN-Bladder 100, on which the approval of avelumab was based. Overall, the appropriate use of maintenance therapy with avelumab in the EV-302 study can therefore be assumed. However, the company does not provide any further information or data on this, such as the dosage used. The company also still provides no data on the length of time from the completion of chemotherapy to the start of maintenance therapy with avelumab.

The third point was not addressed in the context of the commenting procedure, without this being justified by the company.

Overall, the uncertainties described in the dossier assessment with regard to the implementation of maintenance therapy with avelumab therefore continue to exist.

Patients who did not receive avelumab and died

With regard to patients for whom maintenance therapy with avelumab had been an option according to the company, but who did not receive avelumab and died, the company presented 3 sensitivity analyses for both research questions of the benefit assessment at the 2nd data cut-off, analogous to the sensitivity analyses in its dossier submitted for the first data cut-off. As described in the dossier assessment, these sensitivity analyses are overall considered appropriate to address this point in respect of the outcome of overall survival, so that no additional uncertainty arises. In addition, the company presented a so-called tipping point analysis, which is based on sensitivity analysis 2 and is described in Section 2.2.2.1.

Conclusion and consequences for the benefit assessment

As described in dossier assessment A24-98, the informative value of the study is limited, particularly due to the incomplete implementation of maintenance therapy with avelumab. For the present addendum, there are no points that reduce the resulting uncertainty. Overall, at most hints, e.g. of an added benefit, can be determined on the basis of the EV-302/KN-A39 study for both research questions of the dossier assessment for all outcomes.

2.1.4 Planned duration of follow-up observation

Table 2 shows the planned duration of patient follow-up observation for the individual outcomes.

Table 2: Planned duration of follow-up observation – RCT, direct comparison: enfortumab vedotin + pembrolizumab vs. cisplatin/carboplatin + gemcitabine

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

a. According to the study plan, the study was to end at the latest 5 years after the last patient has been included or when no patient remained in the follow-up observation. The sponsor may terminate the study at any time.
b. Presented is the planned duration of follow-up observation according to the study design; patients who had not experienced a first deterioration from baseline before the start of a subsequent antineoplastic therapy were censored on the date of the last available recording of the outcome. This censoring scheme was predefined for the responder analyses on BPI-SF item 3 pre-specified according to the study design and was also applied to the responder analyses conducted post hoc for the dossier.
c. Operationalized as CTCAE grade ≥ 3.

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

Although the outcomes on symptoms, health status and health-related quality of life, as well as overall survival, were to be observed beyond disease progression until the end of the study, patients who had not experienced a first deterioration from baseline before the start of a subsequent antineoplastic therapy were censored on the date of the last available recording of the outcome, as stated in Module 4 A of the dossier. In its comments, the company clarified that this censoring rule was predefined for the responder analyses on Brief Pain Inventory-Short Form (BPI-SF) item 3 pre-specified according to the study design and was also applied to the responder analyses conducted post hoc for the dossier. Recordings that took place after

the start of a subsequent therapy are therefore not included in the analyses. However, in the present data situation, in which the events predominantly took place at an early point in time, this does not limit the interpretability of the present analyses. Further explanations can be found in dossier assessment A24-98. There are therefore no changes with regard to the interpretability of the responder analyses on the patient-reported outcomes on morbidity and health-related quality of life.

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

2.2.1 Study characteristics (specific to research question 1)

For a description of the characteristics across research questions of the EV-302/KN-A39 study, see Section 2.1.

2.2.1.1 Patient characteristics

Table 3 shows the characteristics of the patients in the subpopulation of the included study relevant for research question 1.

Table 3: Characteristics of the study population as well as study/treatment discontinuation – RCT, direct comparison: enfortumab vedotin + pembrolizumab vs. cisplatin + gemcitabine (subpopulation: cisplatin suitable) (multipage table)

Study characteristic category	Enfortumab vedotin + pembrolizumab N = 240	Cisplatin + gemcitabine N = 242
EV-302/KN-A39 (2nd data cut-off 08 August 2024)		
Age [years], mean (SD)	65 (9)	65 (9)
Sex [F/M], %	18/83	24/76
Region		
Europe	98 (41)	102 (42)
North America	57 (24)	51 (21)
Rest of the world[a]	85 (35)	89 (37)
ECOG PS at baseline, n (%)		
0	136 (57)	128 (53)
1	100 (42)	111 (46)
2	4 (2)	2 (1)
Unknown	0 (0)	1 (< 1[b])
Renal function [CrCl in mL/min[c]], n (%)		
Normal [> 90]	78 (33)	82 (34)
Slightly reduced [≥ 60 to < 90]	116 (48)	122 (50)
Moderately reduced [≥ 30 to < 60]	46 (19)	38 (16)
Strongly reduced [≥ 15 to < 30]	0 (0)[b]	0 (0)[b]

Table 3: Characteristics of the study population as well as study/treatment discontinuation – RCT, direct comparison: enfortumab vedotin + pembrolizumab vs. cisplatin + gemcitabine (subpopulation: cisplatin suitable) (multipage table)

Study characteristic category	**Enfortumab vedotin + pembrolizumab N = 240**	**Cisplatin + gemcitabine N = 242**
PD-L1 status at baseline [CPS], n (%)		
< 10	101 (42)	102 (42)
≥ 10	139 (58)	140 (58)
Primary origin of disease[d]		
Upper urinary tract (kidneys, renal pelvis, ureter)	61 (25)	49 (20)
Lower urinary tract (urinary bladder, urethra)	177 (74)	193 (80)
Unknown	2 (1[b])	0 (0)
Disease duration: time between diagnosis of locally advanced or metastatic disease and randomization [months], median [Q1; Q3]	ND[e]	ND[e]
Liver metastases, n (%)	48 (20)	48 (20)
Metastasis category at baseline, n (%)		
Visceral metastases	170 (71)	161 (67)
Exclusively lymph node metastases	60 (25)	67 (28)
No category applicable	10 (4)	14 (6)
Treatment discontinuation, n (%)[f]	187 (78)[b]	90 (37)[b]
Study discontinuation, n (%)[g]	110 (46)	160 (66)

a. Rest of the world includes Argentina, Australia, China, Israel, Japan, Russia, Singapore, South Korea, Taiwan, Thailand and Turkey.
b. Institute's calculation.
c. The CrCl was calculated using the Cockcroft-Gault formula based on the last measured creatinine value prior to taking the first dose of study medication.
d. In relation to the total population of the study, the primary origin of the disease was predominantly the urinary bladder (67% vs. 74%) or the renal pelvis (20% vs. 15%); for the relevant subpopulation, only the summarized data shown in the table are available.
e. Data on the disease duration are not available for the relevant subpopulation; in relation to the total study population, the time between diagnosis of locally advanced or metastatic disease and randomization (median [Q1; Q3]) was 1.6 [1.1; 2.5] months in the intervention arm and 1.6 [1.0; 2.3] months in the comparator arm.
f. Common reasons for treatment discontinuation in the intervention vs. the control arm were the following (percentages based on randomized patients): disease progression (43% versus 13%), adverse event (25% versus 12%). In addition, < 1% vs. 3% of the randomized patients never started treatment; a further 8% vs. 60% of patients completed treatment with the study medication as planned.
g. The figures also include patients who died during the course of the study (intervention arm: 41% vs. control arm: 62%; percentages refer to the randomized patients).

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

A description of the baseline patient characteristics of the EV-302/KN-A39 study can be found in dossier assessment A24-98.

In its comments, the company provided information on the treatment and study discontinuations in the respective subpopulations and on the most frequent reasons for discontinuation. With regard to the 2nd data cut-off, the most common reasons for discontinuation of treatment were disease progression (intervention vs. comparator arm: 43% vs. 13%) or an adverse event (AE) intervention vs. comparator arm: 25% vs. 12%). It should be noted here that for the comparator arm these data only refer to the study medication and thus the chemotherapy with cisplatin/carboplatin + gemcitabine and not to a possible subsequent maintenance therapy with avelumab in progression-free patients, which was not part of the study medication according to the study design. Discontinuation for reasons other than death occurred only sporadically in both treatment arms, in less than 5% of patients in each case (Institute's calculation).

2.2.1.2 Information on the course of the study

Table 4 shows the mean and median treatment durations of the patients, and the mean and median observation periods for individual outcomes in the subpopulation relevant to research question 1.

Table 4: Information on the course of the study – RCT, direct comparison: enfortumab vedotin + pembrolizumab vs. cisplatin + gemcitabine (subpopulation: cisplatin suitable)

Study (data cut-off) **duration of the study phase** **outcome category/outcome**	**Enfortumab vedotin + pembrolizumab** **N = 240**	**Cisplatin + gemcitabine** **N = 242**
EV-302/KN-A39 (2nd data cut-off 08 August 2024)		
Treatment duration[a] [months]		
Median [Q1; Q3]	10.0 [4.8; 22.4]	4.1 [3.2; 4.4]
Mean (SD)	12.9 (9.8)	3.6 (1.2)
Observation period [months]		
Overall survival[b]		
Median [Q1; Q3]	23.9 [13.8; 30.1]	18.3 [7.9; 26.6]
Mean (SD)	22.6 (10.4)	18.2 (11.3)
Symptoms (BPI-SF; EORTC QLQ-C30)[c]		
Median [Q1; Q3]	12.1 [5.9; 25.2]	5.9 [2.7; 12.2]
Mean (SD)	15.5 (11.5)	9.2 (9.1)
Health status (EQ-5D VAS)[c]		
Median [Q1; Q3]	12.1 [5.9; 25.2]	5.9 [3.1; 12.2]
Mean (SD)	15.5 (11.4)	9.2 (9.1)
Health-related quality of life (EORTC QLQ-C30)[c]		
Median [Q1; Q3]	12.1 [5.9; 25.2]	5.9 [2.7; 12.2]
Mean (SD)	15.5 (11.5)	9.2 (9.1)
Side effects[d]		
Median [Q1; Q3]	13.5 [7.7; 25.0]	5.6 [4.9; 5.9]
Mean (SD)	15.9 (9.1)	5.2 (1.3)

a. Treatment duration is defined as the time from the first dose of study medication to Day 21 of the last of the 21-day treatment cycles, initiation of subsequent antineoplastic therapy, death, end of study, or time of data cut-off, whichever occurs first.
b. The observation period is defined as the time from randomization to the last time point at which information on overall survival was recorded.
c. The observation period is defined as the time from randomization until the last recording of the outcome; patients who had not experienced a first deterioration since the start of the study before the initiation of subsequent antineoplastic therapy were censored on the date of the last available recording of the outcome.
d. According to company's documents, the observation period is defined as the time from the first study treatment to 90 days after the last study treatment in the intervention arm or 30 days after the last study treatment in the comparator arm. This deviates from the information according to the study design (see dossier assessment A24-98), without this being explained by the company. The information according to the study design is assumed to be true.

N: number of patients; Q1: first quartile; Q3: third quartile; RCT: randomized controlled trial; SD: standard deviation

Within the relevant subpopulation, the patients' median treatment duration was far higher in the intervention arm, at 10.0 months, than in the comparator arm, at 4.1 months. This is due

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

The median observation period for the outcome of overall survival is clearly longer at present 2nd data cut-off (23.9 vs. 18.3 months) than in the 1st data cut-off (14.4 vs. 12.2 months). For the outcomes on symptoms, health status and health-related quality of life as well as for the outcomes on side effects, the observation period for the 2nd data cut-off is only slightly longer than for the 1st data cut-off, while there are no changes for the comparator arm. As described in Section 2.1.4, patients who had not experienced a first deterioration since the start of the study before the initiation of subsequent antineoplastic therapy were censored on the date of the last available recording of the outcome. In the present data situation, it is not assumed that this influences the results to a relevant extent; for an explanation, see Section I 4.2.1 of dossier assessment A24-98.

As described in dossier assessment A24-98, the fixed treatment duration in the comparator arm and the linking of the observation time for side effects to the treatment duration means that the effect estimate only reflects approximately the first 6 months after randomization and thus only the period of chemotherapy in the comparator arm, but not a possible maintenance therapy with avelumab, and only the first 6 months of a possibly longer-lasting therapy in the intervention arm. This has been taken into account in the derivation of the certainty of conclusions for the outcomes on side effects (see Section 2.2.2.2).

2.2.1.3 Subsequent therapies

Table 5 shows the subsequent therapies patients received after discontinuing the study medication in the subpopulation relevant to research question 1.

Table 5: Information on subsequent antineoplastic therapies (≥ 1% of patients in ≥ 1 treatment arm) – RCT, direct comparison: enfortumab vedotin + pembrolizumab versus cisplatin + gemcitabine (subpopulation: cisplatin suitable) (multipage table)

Study **drug class** **therapies** **drug**	**Patients with subsequent therapy, n (%)**	
	enfortumab vedotin + pembrolizumab **N = 240**	**cisplatin + gemcitabine** **N = 242**
Study EV-302/KN-A39 (2nd data cut-off 08 August 2024)		
Subsequent therapy received[a]	103 (42.9)[b]	178 (73.6)[b]
Systemic therapy for progressive disease	87 (36.3)[b]	118 (48.8)[b]
Maintenance therapy	11 (4.6)	92 (38.0)
Avelumab	9 (3.8[b])	86 (35.5[b])
Pembrolizumab	0 (0[b])	5 (2.1[b])
Palliative radiotherapy	33 (13.8)	32 (13.2)
Surgical intervention	9 (3.8)	13 (5.4)
No subsequent therapy received	137 (57.1)	64 (26.4)
No disease progression	101 (42.1[b])	32 (13.2[b])
Still under first-line therapy	32 (13.3)	0 (0)
Study discontinuation	42 (17.5[b])	53 (21.9[b])
Died under first-line therapy	35 (14.6)	46 (19.0)
Other reasons	12 (5.0[b])	5 (2.1[b])
First subsequent systemic therapy after progression under maintenance treatment	10 (4.2[b])	44 (18.2[b])
Platinum-based therapy	8 (3.3[b])	4 (1.7[b])
Cisplatin-based therapy	6 (2.5[b])	2 (0.8[b])
PD-1/-L1-based therapy	0 (0[b])	6 (2.5[b])
Pembrolizumab	0 (0[b])	4 (1.7[b])
Other drugs	2 (0.8[b])	34 (14.0[b])
Enfortumab vedotin	2 (0.8)	20 (8.3[b])
Taxanes	0 (0)	8 (3.3[b])
First subsequent systemic therapy after progression without maintenance treatment	77 (32.1[b])	74 (30.6[b])
Platinum-based therapy	64 (26.7[b])	5 (2.1[b])
Cisplatin-based therapy	38 (15.8[b])	2 (0.8[b])
Carboplatin-based therapy	26 (10.8[b])	3 (1.2[b])
PD-1/-L1-based therapy	3 (1.3[b])	63 (26.0[b])
Atezolizumab	1 (0.4[b])	19 (7.9[b])
Pembrolizumab	2 (0.8[b])	39 (16.1[b])
Other drugs	10 (4.2[b])	6 (2.5[b])
Sacituzumab govitecan	3 (1.3[b])	0 (0[b])
Taxanes	1 (0.4[b])	4 (1.7[b])

Table 5: Information on subsequent antineoplastic therapies (≥ 1% of patients in ≥ 1 treatment arm) – RCT, direct comparison: enfortumab vedotin + pembrolizumab versus cisplatin + gemcitabine (subpopulation: cisplatin suitable) (multipage table)

Study **drug class** **therapies** **drug**	**Patients with subsequent therapy, n (%)**	
	enfortumab vedotin + pembrolizumab **N = 240**	**cisplatin + gemcitabine** **N = 242**
Second subsequent systemic therapy after progression under maintenance treatment	7 (2.9[b])	20 (8.3[b])
Platinum-based therapy	1 (0.4[b])	6 (2.5[b])
Cisplatin-based therapy	0 (0[b])	3 (1.2[b])
Carboplatin-based therapy	1 (0.4[b])	3 (1.2[b])
Other drugs	5 (2.1[b])	14 (5.8[b])
Erdafitinib	0 (0[b])	3 (1.2[b])
Enfortumab vedotin	0 (0[b])	4 (1.7[b])
Sacituzumab govitecan	1 (0.4[b])	5 (2.1[b])
Second subsequent systemic therapy after progression without maintenance treatment	27 (11.3[b])	23 (9.5[b])
Platinum-based therapy	5 (2.1[b])	0 (0[b])
Cisplatin-based therapy	3 (1.3[b])	0 (0[b])
PD-1/-L1-based therapy	5 (2.1[b])	3 (1.2[b])
Pembrolizumab	3 (1.3[b])	0 (0[b])
Other drugs	17 (7.1[b])	20 (8.3[b])
Erdafitinib	6 (2.5[b])	0 (0[b])
Enfortumab vedotin	0 (0[b])	14 (5.8[b])
Sacituzumab govitecan	5 (2.1[b])	2 (0.8[b])
Taxanes	5 (2.1[b])	3 (1.2[b])

a. Including maintenance therapies.
b. Institute's calculation.

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

At the time of dossier assessment A24-98, the data on subsequent systemic antineoplastic therapies in the company's dossier included both systemic therapies for the treatment of progressive disease and maintenance therapies. This is not appropriate. Moreover, it cannot be inferred from the data in the company's dossier, which subsequent therapies were used after disease progression under maintenance treatment with avelumab.

With its comments, the company has now submitted information on subsequent systemic antineoplastic therapies in which systemic therapies for the treatment of progressive disease and maintenance therapies are presented separately and from which it can be seen which subsequent antineoplastic therapies were used after disease progression under maintenance

therapy or after disease progression without maintenance therapy. The reasons why some of the patients did not receive a subsequent therapy are also given.

These data show that in the subpopulation of RCT EV-302/KN-A39 relevant to research question 1, a total of 87 (36%) patients in the intervention arm and 118 (49%) patients in the comparator arm had received at least 1 subsequent systemic therapy for the treatment of progressive disease at the time of the second data cut-off.

In relation to the patients in whom disease progression occurred as a progression-free survival (PFS) event (125 [52.1%] patients in the intervention arm versus 147 [60.7%] patients in the comparator arm), this means that 70% of the patients with disease progression in the intervention arm and 80% in the comparator arm received at least one subsequent therapy for the treatment of progressive disease (Institute's calculation). According to the current S3 guideline, the ability and meaningfulness of second-line therapy must be checked for each patient [12], so that the proportion of patients with subsequent therapy in the subpopulation of the EV-302/KN-A39 study relevant to research question 1 appears appropriate overall.

In the intervention arm, platinum-based chemotherapy was the most common first subsequent therapy after disease progression with enfortumab vedotin + pembrolizumab. This corresponds to current guideline recommendations [13].

Pembrolizumab or atezolizumab is recommended as first-line therapy in case of disease progression under platinum-based chemotherapy [12,13]. In the comparator arm, 16% and 8% of patients in the relevant subpopulation respectively received these agents as first subsequent systemic therapy after disease progression without prior maintenance therapy; this corresponds to 26% and 53% of patients who received subsequent systemic therapy after disease progression without prior maintenance therapy.

In cases of disease progression under maintenance treatment with avelumab following platinum-based chemotherapy as first-line treatment or under second-line treatment with pembrolizumab or atezolizumab, erdafitinib (in certain patients) and enfortumab vedotin are primarily recommended, and sacituzumab govitecan, vinflunine or taxanes [13] are recommended with a lower recommendation grade. Corresponding drugs, particularly enfortumab vedotin, were frequently used in the comparator arm in corresponding situations (see Table 5).

On the basis of the available data and the recommendation of the current S3 guideline, it is assumed that the use of subsequent therapies was predominantly appropriate in the subpopulation of study EV-302/KN-A39 relevant to research question 1 at the second data cut-off.

2.2.1.4 Risk of bias across outcomes (study level)

The risk of bias across outcomes for the EV-302/KN-A39 study was rated as low, as explained in dossier assessment A24-98).

2.2.2 Results on added benefit

2.2.2.1 Outcomes included

Table 6 shows the outcomes for which data for research question 1 are available in the included study.

Table 6: Matrix of outcomes – RCT, direct comparison: enfortumab vedotin + pembrolizumab vs. cisplatin + gemcitabine (subpopulation: cisplatin suitable)

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

a. Severe AEs are operationalized as CTCAE grade ≥ 3.
b. In each case, the operationalization of a specific, predefined MedDRA PT collection from the outcome of AEOSI (Version 27.0) presented by the company is used.
c. Operationalized as skin and subcutaneous tissue disorders (SOC, AEs).
d. Operationalized as renal and urinary disorders (SOC, severe AEs).
e. The following events were considered (MedDRA coding): nausea (PT, AEs), vomiting (PT, AEs), eye disorders (SOC, AEs), ear and labyrinth disorders (SOC, AEs), endocrine disorders (SOC, AEs), gastrointestinal disorders (SOC, SAEs), respiratory, thoracic and mediastinal disorders (SOC, SAEs), blood and lymphatic system disorders (SOC, severe AEs), urinary tract infection (PT, severe AEs), diarrhoea (PT, severe AEs), general disorders and administration site conditions (SOC, severe AEs) and hepatobiliary disorders (SOC, severe AEs).

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

Notes on outcomes

In the following, only aspects are listed for which there is a relevant change compared to dossier assessment A24-98.

Overall survival: tipping point analyses of the company

With regard to patients for whom maintenance therapy with avelumab had been an option according to the company, but who did not receive avelumab and died, the company presented 3 sensitivity analyses for both research questions of the benefit assessment with its comments at the 2nd data cut-off. In their assumptions, these correspond to the sensitivity analyses presented in its dossier for the 1st data cut-off. In addition, the company presented so-called tipping point analyses based on sensitivity analysis 2. As described in dossier assessment A24-98, sensitivity analysis 2 assumes that all patients of group 3 described in Section 2.1.3 (maintenance treatment with avelumab possible according to the company and yet avelumab not received) who died would have survived until the time of the data cut-off presented and thus would have shown the best possible survival in the study instead. In the tipping point analyses, patients who were imputed as survived in sensitivity analysis 2 were successively counted as deceased at their original time of death, while the remaining patients were still included in the analysis as survived [2,4]. According to the company, the death events were categorised as such in ascending order, i.e. patients with a shorter actual survival time were the first to be included in the analysis [11].

The tipping point analyses thus show the proportion of patients imputed as surviving in the sensitivity analysis 2 for which the threshold values for different extents of added benefit for overall survival are exceeded according to the IQWiG General Methods [14].

Since the proportion of patients who would have survived if maintenance therapy with avelumab had actually been implemented is not known, the company further assumes that the expected proportion of deaths among patients in group 3 (maintenance therapy with avelumab possible according to the company and yet no avelumab received) corresponds to the proportion of deaths among patients in group 1 (maintenance therapy with avelumab possible according to the company and avelumab received) if maintenance therapy with avelumab had actually been implemented. The company uses this comparison of the proportions to determine the extent. However, the comparison is based on the assumption that these 2 patient groups are fully comparable, taking into account the treatment decisions after completion of platinum-based chemotherapy. The decision in favour of maintenance treatment with avelumab was based on investigator assessment and depended on local availability, e.g. availability of avelumab was earlier in the EU and the USA than in other countries.

In addition, a further uncertainty arises from the fact that the order of patients to whom the actual time of death is assigned again favours the intervention, i.e. the extent limits are reached more quickly, i.e. with smaller proportions. According to the tipping point analysis in relation to research question 1, the extent threshold for a major added benefit is reached from a proportion of 43% (15/35) of deaths among patients in group 3 (maintenance therapy with avelumab possible according to the company and yet no avelumab received), while the company assumes that the expected proportion of deaths would have been 49% (17/35) in this group if maintenance therapy with avelumab had been fully implemented. However, this difference is ultimately based on only 2 patients. Although the difference between the corresponding proportions is greater in research question 2 (49% vs. 57%), the estimation of the extent is already given there on the basis of the main analysis and the 3 sensitivity analyses.

Overall, the results of the tipping point analyses are not sufficiently certain and are based on unverifiable assumptions, so that they are not suitable for quantifying the extent of the added benefit in addition to the sensitivity analyses presented. Therefore, the results of the tipping point analyses are not used. They are presented as supplementary information in Appendix A.

Outcomes on pain (BPI-SF)

For the outcomes of worst pain (BPI-SF item 3), pain intensity (BPI-SF items 3-6) and pain interference (BPI-SF items 9a-9g) , the company presented responder analyses on the time to the first deterioration by ≥ 2 points (scale range 0 to 10) in its dossier. For the outcomes of pain intensity (BPI-SF items 3-6) and pain interference (BPI-SF items 9a-9g), these responder analyses were not suitable for the benefit assessment, as the response threshold of ≥ 2 points for these outcomes was not predefined and did not correspond to exactly 15% of the scale range, as required by IQWiG's General Methods [14] for post hoc specified responder analyses for the benefit assessment.

In its comments, the company presented responder analyses on the time to first deterioration by ≥ 1.5 points for the outcomes of pain intensity (BPI-SF items 3-6) and impairment due to pain (BPI-SF items 9a-9g), which corresponds to 15% of the scale range and thus to the criteria according to the general methods. The corresponding analyses were used for the benefit assessment.

Discontinuation due to AEs

Module 4 A of the dossier provides no information on whether the outcome was operationalized as discontinuation of at least 1 or all treatment components. Based on the information in the study documents, it is assumed to be operationalized as discontinuation of at least 1 treatment component. This operationalization is appropriate and the outcome is used accordingly for the benefit assessment.

2.2.2.2 Risk of bias

Table 7 describes the risk of bias for the results of the relevant outcomes for research question 1.

Table 7: Risk of bias across outcomes and outcome-specific risk of bias – RCT, direct comparison: enfortumab vedotin + pembrolizumab vs. cisplatin + gemcitabine (subpopulation: cisplatin suitable)

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

a. Severe AEs are operationalized as CTCAE grade ≥ 3.
b. In each case, the operationalization of a specific, predefined MedDRA PT collection from the outcome of AEOSI (Version 27.0) presented by the company is used.
c. Operationalized as skin and subcutaneous tissue disorders (SOC, AEs).
d. Operationalized as renal and urinary disorders (SOC, severe AEs).
e. The following events were considered (MedDRA coding): nausea (PT, AEs), vomiting (PT, AEs), eye disorders (SOC, AEs), ear and labyrinth disorders (SOC, AEs), endocrine disorders (SOC, AEs), gastrointestinal disorders (SOC, SAEs), respiratory, thoracic and mediastinal disorders (SOC, SAEs), blood and lymphatic system disorders (SOC, severe AEs), urinary tract infection (PT, severe AEs), diarrhoea (PT, severe AEs), general disorders and administration site conditions (SOC, severe AEs) and hepatobiliary disorders (SOC, severe AEs).
f. Lack of blinding in subjective recording of outcomes, unless severe or serious AEs are involved.
g. Decreasing response to questionnaires in the course of the study; large proportion of patients not included in the analysis (> 10 %) or large difference between the treatment groups (> 5 percentage points).
h. Incomplete observations for potentially informative reasons.
i. Lack of blinding in subjective decision for treatment discontinuation.

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

The outcome-specific risk of bias for the results of the outcome of pain interference (BPI-SF items 9a) is rated as high. The reason therefore is the decreasing response to the questionnaire in the course of the study, the large proportion of patients not considered in the analysis (> 10%) and the large difference between the treatment groups (> 5 percentage points). This is accompanied by the lack of blinding in subjective recording of outcomes.

The outcome-specific risk of bias for all other outcomes is described in dossier assessment A24-98 and has not changed for the present addendum.

Summary assessment of the certainty of conclusions

In addition to the described aspects of bias, there are uncertainties for study EV-302/KN-A39, as described in dossier assessment A24-98 and in Section 2.1.3 of this addendum, particularly in the implementation of the ACT. In the present specific data constellation, the results of the study can nevertheless be interpreted for the research questions of the present benefit assessment, but the certainty of the study results for the present assessment is reduced. The shortened observation in the comparator arm or consideration of data collected in the intervention arm for outcomes in the side effects category also contributes to limited certainty of conclusions. Based on the EV-302/KN-A39 study, at most hints, e.g. of an added benefit, can be derived for both research questions.

2.2.2.3 Results

Table 8 summarizes the results of the comparison of enfortumab vedotin + pembrolizumab with cisplatin + gemcitabine for first-line treatment in adult patients with unresectable or metastatic urothelial carcinoma for whom cisplatin-based therapy is suitable. Where necessary, calculations conducted by the Institute are provided in addition to the data from the company's documents.

Kaplan-Meier curves on the presented time-to-event analyses can be found in Appendix B.1. Results on common AEs, serious AEs (SAEs), severe AEs, and discontinuation due to AEs are presented in Appendix C.1. Results on frequent immune-related AEs, immune-related SAEs and immune-related severe AEs are not available in the company's documents.

Table 8: Results (mortality, morbidity, health-related quality of life, side effects) – RCT, direct comparison: enfortumab vedotin + pembrolizumab vs. cisplatin + gemcitabine (subpopulation: cisplatin suitable) (multipage table)

Study (data cut-off) outcome category outcome	Enfortumab vedotin + pembrolizumab		Cisplatin + gemcitabine		Enfortumab vedotin + pembrolizumab vs. cisplatin + gemcitabine
	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]; p-value
EV-302/KN-A39 (2nd data cut-off 08 August 2024)					
Mortality					
Overall survival	240	36.7 [31.5; NC] 100 (41.7)	242	18.4 [16.4; 21.6] 149 (61.6)	0.54 [0.42; 0.70]; < 0.001[a]
Overall survival (sensitivity analysis 1[b])	240	36.7 [31.5; NC] 100 (41.7)	242	26.5 [19.5; NC] 114 (47.1)	0.71 [0.54; 0.93]; 0.012[a]
Overall survival (sensitivity analysis 2[c])	240	36.7 [31.5; NC] 100 (41.7)	242	28.6 [21.1; NC] 114 (47.1)	0.79 [0.60; 1.03]; 0.077[a]
Overall survival (sensitivity analysis 3[d])	240	36.7 [31.5; NC] 100 (41.7)	242	21.9 [19.5; 26.6] 140 (57.9)	0.61 [0.47; 0.79]; < 0.001[a]
Morbidity					
Worst pain (BPI-SF item 3 - time to first deterioration)[e]	240	2.0 [1.3; 4.5] 132 (55.0)	242	1.8 [1.1; 3.2] 115 (47.5)	0.89 [0.68; 1.17]; 0.410[a]
Pain intensity (BPI-SF items 3–6, time to first deterioration, presented as supplementary information)[f]	*240*	*12.1 [7.3; 28.6]* *99 (41.3)*	*242*	*NA [8,1; NC]* *72 (29,8)*	*1.04 [0.75; 1.46];* *0.802[a]*
Pain interference (BPI-SF items 9a-g – time to first deterioration)[f]	240	2.3 [1.5; 5.2] 137 (57.1)	242	2.0 [1.1; 4.5] 109 (45.0)	0.95 [0.72; 1.26]; 0.726[a]
Symptoms (EORTC QLQ-C30 – time to first deterioration[g])					
Fatigue	240	0.4 [0.4; 0.6] 170 (70.8)	242	0.4 [0.4; 0.6] 158 (65.3)	0.80 [0.63; 1.02]; 0.080[a]
Nausea and vomiting	240	2.0 [1.1; 4.6] 134 (55.8)	242	0.4 [0.4; 0.8] 142 (58.7)	0.56 [0.43; 0.73]; < 0.001[a]
Pain	240	0.7 [0.5; 1.3] 151 (62.9)	242	1.1 [0.6; 1.4] 130 (53.7)	1.04 [0.80; 1.35]; 0.793[a]
Dyspnoea	240	2.4 [1.6; 4.6] 140 (58.3)	242	2.0 [1.7; 3.9] 109 (45.0)	1.04 [0.79; 1.37]; 0.773[a]

Table 8: Results (mortality, morbidity, health-related quality of life, side effects) – RCT, direct comparison: enfortumab vedotin + pembrolizumab vs. cisplatin + gemcitabine (subpopulation: cisplatin suitable) (multipage table)

Study (data cut-off) **outcome category** **outcome**	**Enfortumab vedotin + pembrolizumab**		**Cisplatin + gemcitabine**		**Enfortumab vedotin + pembrolizumab vs. cisplatin + gemcitabine**
	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]; p-value**
Insomnia	240	2.3 [0.9; 4.5] 127 (52.9)	242	2.0 [0.9; 3.8] 116 (47.9)	0.76 [0.58; 1.01]; 0.063[a]
Appetite loss	240	0.9 [0.6; 1.7] 144 (60.0)	242	0.6 [0.4; 0.9] 132 (54.5)	0.75 [0.58; 0.97]; 0.024[a]
Constipation	240	2.2 [1.5; 4.5] 128 (53.3)	242	0.7 [0.4; 1.3] 134 (55.4)	0.59 [0.46; 0.78]; < 0.001[a]
Diarrhoea	240	2.0 [1.3; 3.8] 139 (57.9)	242	3.1 [2.0; 9.3] 98 (40.5)	1.13 [0.86; 1.50]; 0.371[a]
Health status (EQ-5D VAS - time to first deterioration[h])	240	2.5 [1.3; 5.2] 144 (60.0)	242	2.2 [1.5; 3.2] 113 (46.7)	1.02 [0.78; 1.34]; 0.913[a]
Health-related quality of life					
EORTC EORTC-QLQ-C30 – time to first deterioration[i]					
Global health status	240	0.7 [0.6; 1.3] 158 (65.8)	242	0.9 [0.6; 1.1] 133 (55.0)	0.88 [0.68; 1.14]; 0.344[a]
Physical functioning	240	1.1 [0.6; 1.6] 165 (68.8)	242	0.9 [0.6; 1.1] 138 (57.0)	0.92 [0.72; 1.18]; 0.472[a]
Role functioning	240	0.6 [0.4; 0.8] 166 (69.2)	242	0.4 [0.4; 0.9] 140 (57.9)	0.90 [0.70; 1.16]; 0.469[a]
Emotional functioning	240	3.2 [2.0; 10.1] 126 (52.5)	242	3.8 [2.0; 11.4] 96 (39.7)	1.02 [0.76; 1.36]; 0.905[a]
Cognitive functioning	240	1.8 [1.1; 2.3] 148 (61.7)	242	0.9 [0.6; 1.5] 130 (53.7)	0.89 [0.69; 1.16]; 0.408[a]
Social functioning	240	0.7 [0.5; 1.1] 164 (68.3)	242	0.9 [0.6; 1.1] 130 (53.7)	1.16 [0.90; 1.49]; 0.236[a]
Side effects[j]					
AEs (supplementary information)	239	0.2 [0.2; 0.2] 239 (100.0)	236	0.1 [0.1; 0.2] 234 (99.2)	–
SAEs	239	18.0 [9.5; NC] 112 (46.9)	236	NA 83 (35.2)	0.91 [0.67; 1.23]; 0.543[k]
Severe AEs[l]	239	4.2 [3.0; 6.0] 168 (70.3)	236	1.4 [1.0; 1.8] 175 (74.2)	0.52 [0.41; 0.66]; < 0.001[k]

Table 8: Results (mortality, morbidity, health-related quality of life, side effects) – RCT, direct comparison: enfortumab vedotin + pembrolizumab vs. cisplatin + gemcitabine (subpopulation: cisplatin suitable) (multipage table)

Study (data cut-off) **outcome category** **outcome**	**Enfortumab vedotin + pembrolizumab**		**Cisplatin + gemcitabine**		**Enfortumab vedotin + pembrolizumab vs. cisplatin + gemcitabine**
	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]; p-value**
Discontinuation due to AEs[m]	239	12.2 [9.7; 17.9] 110 (46.0)	236	NA 58 (24.6)	0.73 [0.50; 1.06]; 0.095[k]
Immune-related AEs[n] (supplementary information)	*239*	*12.6 [7.2; NC]* *108 (45.2)*	*236*	*NA* *10 (4.2)*	–
Immune-related SAEs[n]	239	NA 36 (15.1)	236	NA 2 (0.8)	11.08 [2.61; 46.92]; < 0.001[k]
Immune-related severe AEs[l, n]	239	NA 51 (21.3)	236	NA 3 (1.3)	11.07 [3.40; 36.11]; < 0.001[k]
Peripheral neuropathy (SMQ, AEs)[o]	239	4.4 [3.5; 5.1] 163 (68.2)	236	NA 43 (18.2)	3.30 [2.33; 4.67]; < 0.001[k]
Skin reactions[p]	239	0.5 [0.4; 0.6] 204 (85.4)	236	NA 61 (25.8)	5.90 [4.40; 7.89]; < 0.001[k]
Severe hyperglycaemia (PT, severe AEs[f])	239	NA 19 (7.9)	236	NA 2 (0.8)	7.70 [1.77; 33.57]; 0.001[k]
Severe nephrotoxicity[l, q]	239	NA 17 (7.1)	236	NA 16 (6.8)	0.69 [0.33; 1.46]; 0.330[k]
Other specific AEs					
Nausea (PT, AEs)	239	NA 63 (26.4)	236	3.3 [2.1; NC] 120 (50.8)	0.36 [0.26; 0.49]; < 0.001[k]
Vomiting (PT, AEs)	239	NA 27 (11.3)	236	NA 42 (17.8)	0.47 [0.28; 0.79]; 0.004[k]
Eye disorders (SOC, AEs)	239	24.6 [12.7; NC] 93 (38.9)	236	NA 14 (5.9)	5.30 [2.98; 9.41]; < 0.001[k]
Ear and labyrinth disorders (SOC, AEs)	239	NA 17 (7.1)	236	NA 33 (14.0)	0.17 [0.07; 0.40]; < 0.001[k]
Endocrine disorders (SOC, AEs)	239	NA 40 (16.7)	236	NA 2 (0.8)	13.47 [3.21; 56.56]; < 0.001[k]
Gastrointestinal disorders (SOC, SAEs)	239	NA 28 (11.7)	236	NA 6 (2.5)	3.22 [1.29; 7.99]; 0.008[k]

Table 8: Results (mortality, morbidity, health-related quality of life, side effects) – RCT, direct comparison: enfortumab vedotin + pembrolizumab vs. cisplatin + gemcitabine (subpopulation: cisplatin suitable) (multipage table)

Study (data cut-off) **outcome category** **outcome**	**Enfortumab vedotin + pembrolizumab**		**Cisplatin + gemcitabine**		**Enfortumab vedotin + pembrolizumab vs. cisplatin + gemcitabine**
	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]; p-value**
Respiratory, thoracic and mediastinal disorders (SOC, SAEs)	239	NA 26 (10.9)	236	NA 4 (1.7)	4.07 [1.37; 12.04]; 0.006[k]
Blood and lymphatic system disorders (SOC, severe AEs)[f]	239	NA 17 (7.1)	236	4.9 [3.0; NC] 110 (46.6)	0.08 [0.05; 0.15]; < 0.001[k]
Diarrhoea (PT, severe AEs)[l]	239	NA 8 (3.3)	236	6.1 [6.1; NC] 19 (8.1)	0.32 [0.13; 0.76]; 0.007[k]
Diarrhoea (PT, severe AEs)l	239	NA 11 (4.6)	236	NA 2 (0.8)	4.34 [0.94; 20.10][f]; 0.040[k]
General disorders and administration site conditions (SOC, severe AEs)[l]	239	NA 17 (7.1)	236	NA 24 (10.2)	0.30 [0.14; 0.68]; 0.002[k]
Hepatobiliary disorders (SOC, severe AEs)[l]	239	NA 11 (4.6)	236	NA 1 (0.4)	7.95 [0.995; 63.60][f]; 0.020

Table 8: Results (mortality, morbidity, health-related quality of life, side effects) – RCT, direct comparison: enfortumab vedotin + pembrolizumab vs. cisplatin + gemcitabine (subpopulation: cisplatin suitable) (multipage table)

Study (data cut-off) **outcome category** **outcome**	**Enfortumab vedotin + pembrolizumab**		**Cisplatin + gemcitabine**		**Enfortumab vedotin + pembrolizumab vs. cisplatin + gemcitabine**
	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]; p-value**

a. HR and CI: Cox proportional hazards model, p-value: log-rank test, each stratified by PD-L1 expression (high vs. low) and liver metastases (present vs. not present).
b. Censoring at the time of death: avelumab-eligible patients who had not received avelumab and died were censored at the time of death.
c. Censoring at data cut-off: avelumab-eligible patients who had not received avelumab and died were censored at the time of data cut-off.
d. Modified time of death: avelumab-eligible patients who had not received avelumab and died were censored with a modified time of death. A simplified assumption was made that the patients would have benefited from treatment with avelumab to the extent shown in the approval study of avelumab (JAVELIN Bladder 100); see dossier assessment A24-98 for explanation.
e. A score increase by ≥ 2 points from baseline is considered a clinically relevant deterioration (scale range: 0 to 10); for explanation, see dossier assessment A24-98.
f. A score increase by ≥ 1.5 points from baseline is considered a clinically relevant deterioration (scale range: 0 to 10); for explanation, see dossier assessment A24-98.
g. An EORTC QLQ-C30 score increase by ≥ 10 points from baseline is considered a clinically relevant deterioration (scale range: 0 to 100).
h. An EQ-5D VAS score decrease by ≥ 15 points from baseline is considered a clinically relevant deterioration (scale range: 0 to 100).
i. An EORTC QLQ-C30 score decrease by ≥ 10 points from baseline is considered a clinically relevant deterioration (scale range: 0 to 100).
j. The terms of disease progression, progression of a disease and progression of a malignant disease as well as similar terms were not taken into account in the assessment of AEs. The fixed treatment duration and the associated discontinuation of observation after the end of study medication in the comparator arm mean that the effect estimate only reflects approximately the first 6 months after randomization.
k. HR and CI: unstratified Cox proportional hazards model; p-value: unstratified log-rank test.
l. Operationalized as CTCAE grade ≥ 3.
m. For the outcome of discontinuation due to AEs, see also Addendum A25-23 [15].
n. In each case, the operationalization of a specific, predefined MedDRA PT collection from the outcome of AESI (Version 27.0) presented by the company is used.
o. The following result is shown for the severe AEs of the SMQ “peripheral neuropathy” included in the results on AEs: 19 (7.9) vs. 0 (0); HR: NC [NC; NC]; p = 0.0512; Kaplan-Meier curve see Figure 36.
p. Operationalized as skin and subcutaneous tissue disorders (SOC, AEs); the following result is shown for the severe AEs of the SOC ”skin and subcutaneous tissue disorders” included in the results on AEs: 40 (16.7) vs. 0 (0); HR: NC [NC; NC]; p < 0.001; Kaplan-Meier curve see Figure 38.
q. Operationalized as renal and urinary disorders (SOC, severe AEs).
r. Discrepancy between CI and p-value due to different calculation methods.

Table 8: Results (mortality, morbidity, health-related quality of life, side effects) – RCT, direct comparison: enfortumab vedotin + pembrolizumab vs. cisplatin + gemcitabine (subpopulation: cisplatin suitable) (multipage table)

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

Based on the available information, at most hints, e.g. of an added benefit, can be determined for all outcomes due to the limited certainty of conclusions (see Section 2.1.3 of this addendum and dossier assessment A24-98).

When interpreting the results on side effects, it should be noted that due to the fixed treatment duration and the associated discontinuation of observation in the comparator arm, the effect estimate only covers approximately the first 6 months after randomization (for reasons, see dossier assessment A24-98).

Mortality

Overall survival

For the outcome of overall survival, a statistically significant difference was found in favour of enfortumab vedotin + pembrolizumab in comparison with cisplatin + gemcitabine. The sensitivity analyses 1 and 3 presented by the company, in which patients in the comparator arm for whom maintenance treatment with avelumab would potentially have been indicated and who died without maintenance treatment were accounted for differently (see dossier assessment A24-98), also showed a statistically significant difference in favour of enfortumab vedotin + pembrolizumab compared with cisplatin + gemcitabine in each case. In sensitivity analysis 2, which is based on the maximum assumption that all these patients in the comparator arm would have survived to the present data cut-off, the effect is not retained. Since the probability of this assumption (all patients survive until the data cut-off) decreases with increasing observation duration, i.e. for the 2nd data cut-off compared to the 1st data

cut-off, this does not call into question an added benefit in the present data situation. However, the varying extent of the results of the different analyses(from a lack of statistical significance in sensitivity analysis 2 to major in the main analysis and sensitivity analysis 3) still contributes to the fact that the added benefit cannot be quantified. There is a hint of added benefit of enfortumab vedotin + pembrolizumab in comparison with the ACT, the extent of which cannot be quantified, however (see Section 2.2.3.1).

Morbidity

Worst pain (BPI-SF item 3)

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

Pain interference (BPI-SF items 9a–g)

No statistically significant difference between treatment groups was shown for the outcome of pain interference (recorded using the BPI-SF items 9a–g). There is no hint of an added benefit of enfortumab vedotin + pembrolizumab in comparison with the ACT; an added benefit is therefore not proven.

Symptoms

EORTC QLQ-C30: European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30 (EORTC QLQ-C30)

Fatigue, pain, dyspnoea, insomnia and diarrhoea

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

Nausea and vomiting, constipation

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

Appetite loss

For the outcome of appetite loss, a statistically significant difference was found in favour of enfortumab vedotin + pembrolizumab in comparison with cisplatin + gemcitabine. For this outcome of the non-serious/non-severe symptoms category, however, the extent of the effect was no more than marginal (see Section 2.2.3.1). There is no hint of an added benefit of

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

Health status

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

Health-related quality of life

EORTC QLQ-C30

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

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

Physical functioning

No statistically significant difference between treatment groups was found for the outcome of physical functioning. However, there is an effect modification by the characteristic of age (see Section 2.2.2.4). There was a hint of an added benefit of enfortumab vedotin + pembrolizumab versus the ACT for patients < 65 years of age. For patients ≥ 65 years, there was no hint of an added benefit of enfortumab vedotin + pembrolizumab versus the ACT; an added benefit is therefore not proven for patients ≥ 65 years of age.

Social functioning

No statistically significant difference between treatment groups was found for the outcome of social functioning. There are effect modifications by the characteristics of age and metastases (see Section 2.2.2.4). These effect modifications cannot be assessed without examining for cross-interactions. The added benefit is therefore derived based on the results on the relevant subpopulation. There is no hint of an added benefit of enfortumab vedotin + pembrolizumab in comparison with the ACT; an added benefit is therefore not proven.

Side effects

SAEs and discontinuation due to AEs

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

Severe AEs

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

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

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

Severe nephrotoxicity (severe AEs)

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

Other specific AEs

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

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

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

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

Vomiting (AEs)

For the outcome of vomiting (AEs), a statistically significant difference was found in favour of enfortumab vedotin + pembrolizumab in comparison with cisplatin + gemcitabine. However, there is an effect modification by the characteristic of age (see Section 2.2.2.4). There was a hint of lesser harm from enfortumab vedotin + pembrolizumab versus the ACT for patients < 65 years of age. There was no hint of greater or lesser harm from enfortumab vedotin + pembrolizumab versus the ACT for patients ≥ 65 years; greater or lesser harm is therefore not proven for patients ≥ 65 years.

Ear and labyrinth disorders (AE)

For the outcome of ear and labyrinth disorders (AEs), there was a statistically significant difference in favour of enfortumab vedotin + pembrolizumab in comparison with cisplatin + gemcitabine. However, there is an effect modification by the characteristic of age (see Section 2.2.2.4). For both patients < 65 years and patients ≥ 65 years, there is a hint of lesser harm from enfortumab vedotin + pembrolizumab compared with the ACT; however, the extent of this harm differs (see Section 2.2.3.1).

2.2.2.4 Subgroups and other effect modifiers

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

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

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

Only the results with an effect modification with a statistically significant interaction between treatment and subgroup characteristic (p-value < 0.05) are presented. In addition, subgroup results are presented only if there is a statistically significant and relevant effect in at least one subgroup. Subgroup results where the extent does not differ between subgroups are not presented.

The results are presented in Table 9. The Kaplan-Meier curves on the subgroup results are presented in Appendix B.1.

Table 9: Subgroups (morbidity, health-related quality of life, side effects) – RCT, direct comparison: enfortumab vedotin + pembrolizumab vs. cisplatin + gemcitabine (subpopulation: cisplatin suitable) (multipage table)

Study outcome characteristic subgroup	Enfortumab vedotin + pembrolizumab		Cisplatin + gemcitabine		Enfortumab vedotin + pembrolizumab vs. cisplatin + gemcitabine	
	N	median time to event in months [95 % CI] patients with event n (%)	N	median time to event in months [95 % CI] patients with event n (%)	HR [95% CI][a]	p-value[a]
EV-302/KN-A39 (2nd data cut-off 08 August 2024)						
Health-related quality of life (EORTC QLQ-C30, physical functioning - time to first deterioration[b]						
Age						
< 65 years	105	1.8 [0.9; 7.3] 62 (59.0)	106	0.6 [0.4; 1.2] 61 (57.5)	0.61 [0.41; 0.90]	0.014
≥ 65 years	135	0.6 [0.5; 1.1] 103 (76.3)	136	1.1 [0.7; 1.5] 77 (56.6)	1.20 [0.87; 1.65]	0.283
					Interaction:	0.007[c]
Health-related quality of life (EORTC QLQ-C30, social functioning - time to first deterioration[b]						
Age						
< 65 years	105	2.0 [0.7; 3.9] 68 (64.8)	106	0.6 [0.4; 1.3] 57 (53.8)	0.85 [0.57; 1.26]	0.436
≥ 65 years	135	0.6 [0.4; 0.7] 96 (71.1)	136	0.9 [0.6; 1.1] 73 (53.7)	1.44 [1.03; 2.01]	0.028
					Interaction:	0.033[c]
Metastases						
Visceral metastases	170	0.7 [0.4; 1.1] 114 (67.1)	161	1.1 [0.5; 1.8] 78 (48.4)	1.41 [1.01; 1.96]	0.034
Lymph nodes only	60	0.9 [0.4; 1.3] 43 (71.7)	67	0.6 [0.4; 0.9] 43 (64.2)	0.93 [0.56; 1.56]	0.738
					Interaction:	0.031[c]
Vomiting (PT, AEs)[d]						
Age						
< 65 years	105	NA 11 (10.5)	102	NA 28 (27.5)	0.28 [0.13; 0.59]	< 0.001
≥ 65 years	134	NA 16 (11.9)	134	NA 14 (10.4)	0.85 [0.40; 1.83]	0.680
					Interaction:	0.017[c]
Ear and labyrinth disorders (SOC, AEs)[d]						
Age						
< 65 years	105	NA 5 (4.8)	102	NA 20 (19.6)	0.09 [0.02; 0.37]	< 0.001

Table 9: Subgroups (morbidity, health-related quality of life, side effects) – RCT, direct comparison: enfortumab vedotin + pembrolizumab vs. cisplatin + gemcitabine (subpopulation: cisplatin suitable) (multipage table)

Study outcome characteristic subgroup	Enfortumab vedotin + pembrolizumab		Cisplatin + gemcitabine		Enfortumab vedotin + pembrolizumab vs. cisplatin + gemcitabine	
	N	median time to event in months [95 % CI] patients with event n (%)	N	median time to event in months [95 % CI] patients with event n (%)	HR [95% CI][a]	p-value[a]
≥ 65 years	134	NA 12 (9.0)	134	NA 13 (9.7)	0.30 [0.10; 0.89]	0.022
					Interaction:	0.023[c]

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

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

Morbidity

Health-related quality of life

EORTC QLQ-C30

Physical functioning

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

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

Social functioning

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

Side effects

Specific AEs

Vomiting (AEs)

There was an effect modification by the characteristic of age for the outcome of vomiting (AEs). A statistically significant difference in favour of enfortumab vedotin + pembrolizumab in comparison with cisplatin + gemcitabine was shown for patients < 65 years. There is a hint of lesser harm from enfortumab vedotin + pembrolizumab in comparison with the ACT.

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

Ear and labyrinth disorders (AE)

For the outcome of ear and labyrinth disorders (AEs), there is an effect modification by the characteristic of age. A statistically significant difference in favour of enfortumab vedotin + pembrolizumab in comparison with cisplatin + gemcitabine was shown for both patients < 65 years and patients ≥ 65 years. In each case, there is a hint of lesser harm from enfortumab vedotin + pembrolizumab in comparison with the ACT the extents of which , however, differ(see Section 2.2.3.1).

2.2.3 Probability and extent of added benefit

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

2.2.3.1 Assessment of added benefit at outcome level

The extent of the respective added benefit at outcome level was estimated from the results presented in Section 2.2.2.3 (see Table 10).

Determination of the outcome category for symptom outcomes

For the symptoms outcomes below, the company's documents do not state whether they are serious/severe or non-serious/non-severe. Reasoning is provided for the classification of these outcomes.

Symptoms (EORTC QLQ-C30)

Nausea and vomiting, loss of appetite, and constipation

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

Table 10: Extent of added benefit at outcome level: enfortumab vedotin + pembrolizumab vs. cisplatin + gemcitabine (subpopulation: cisplatin suitable) (multipage table)

Outcome category **outcome** **effect modifier** **subgroup**	**Enfortumab vedotin + pembrolizumab vs. cisplatin + gemcitabine** **median time to event (months) or proportion of events (%)** **effect estimation [95% CI];** **p-value** **probability**[a]	**Derivation of extent**[b]
Outcomes with observation over the entire study duration		
Mortality		
Overall survival Main analysis	36.7 vs. 18.4 months HR: 0.54 [0.42; 0.70]; p < 0.001 probability: "hint"	Outcome category: mortality added benefit, extent: "non-quantifiable"
Sensitivity analysis 1[c]	36.7 vs. 26.5 months HR: 0.71 [0.54; 0.93]; p = 0.012	
Sensitivity analysis 2[d]	36.7 vs. 28.6 months HR: 0.79 [0.60; 1.03]; p = 0.077	
Sensitivity analysis 3[e]	36.7 vs. 21.9 months HR: 0.61 [0.47; 0.79]; p = < 0.001	
Outcomes with shortened observation period		
Morbidity		
Worst pain (BPI-SF item 3 - time to first deterioration)	2.0 vs. 1.8 months HR: 0.89 [0.68; 1.17]; p = 0.410	Lesser/added benefit not proven
Pain interference (BPI-SF items 9a-g – time to first deterioration)	2.3 vs. 2.0 months HR: 0.95 [0.72; 1.26]; p = 0.726	Lesser/added benefit not proven
Symptoms (EORTC QLQ-C30 – time to first deterioration)		
Fatigue	0.4 vs. 0.4 months HR: 0.80 [0.63; 1.02]; p = 0.080	Lesser/added benefit not proven
Nausea and vomiting	2.0 vs. 0.4 months HR: 0.56 [0.43; 0.73]; p < 0.001 probability: "hint"	Outcome category: non-serious/non-severe symptoms/late complications CI_u < 0.80 added benefit; extent: "considerable"

Table 10: Extent of added benefit at outcome level: enfortumab vedotin + pembrolizumab vs. cisplatin + gemcitabine (subpopulation: cisplatin suitable) (multipage table)

Outcome category **outcome** **effect modifier** **subgroup**	**Enfortumab vedotin + pembrolizumab vs. cisplatin + gemcitabine** **median time to event (months) or proportion of events (%)** **effect estimation [95% CI];** **p-value** **probability**[a]	**Derivation of extent**[b]
Pain	0.7 vs. 1.1 months HR: 1.04 [0.80; 1.35]; p = 0.793	Lesser/added benefit not proven
Dyspnoea	2.4 vs. 2.0 months HR: 1.04 [0.79; 1.37]; p = 0.773	Lesser/added benefit not proven
Insomnia	2.3 vs. 2.0 months HR: 0.76 [0.58; 1.01]; p = 0.063	Lesser/added benefit not proven
Appetite loss	0.9 vs. 0.6 months HR: 0.75 [0.58; 0.97]; p = 0.024	Outcome category: non-serious/non-severe symptoms/late complications $0.90 \leq CI_u < 1.00$ lesser/added benefit not proven[f]
Constipation	2.2 vs. 0.7 months HR: 0.59 [0.46; 0.78]; p < 0.001 probability: “hint”	Outcome category: non-serious/non-severe symptoms/late complications $CI_u < 0.80$ added benefit; extent: “considerable”
Diarrhoea	2.0 vs. 3.1 months HR: 1.13 [0.86; 1.50]; p = 0.371	Lesser/added benefit not proven
Health status (EQ-5D VAS, time to first deterioration)	2.5 vs. 2.2 months HR: 1.02 [0.78; 1.34]; p = 0.913	Lesser/added benefit not proven
Health-related quality of life		
EORTC-QLQ C30 – time to first deterioration		
Global health status	0.7 vs. 0.9 months HR: 0.88 [0.68; 1.14]; p = 0.344	Lesser/added benefit not proven
Physical functioning Age		
< 65 years	1.8 vs. 0.6 months HR: 0.61 [0.41; 0.90]; p = 0.014 probability: “hint”	Outcome category: health-related quality of life $0.90 \leq CI_u < 1.00$ added benefit, extent: “minor”

Table 10: Extent of added benefit at outcome level: enfortumab vedotin + pembrolizumab vs. cisplatin + gemcitabine (subpopulation: cisplatin suitable) (multipage table)

Outcome category **outcome** **effect modifier** **subgroup**	**Enfortumab vedotin + pembrolizumab vs. cisplatin + gemcitabine** **median time to event (months) or proportion of events (%)** **effect estimation [95% CI];** **p-value** **probability**[a]	**Derivation of extent**[b]
≥ 65 years	0.6 vs. 1.1 months HR: 1.20 [0.87; 1.65]; p = 0.283	Lesser/added benefit not proven
Role functioning	0.6 vs. 0.4 months HR: 0.90 [0.70; 1.16]; p = 0.469	Lesser/added benefit not proven
Emotional functioning	3.2 vs. 3.8 months HR: 1.02 [0.76; 1.36]; p = 0.905	Lesser/added benefit not proven
Cognitive functioning	1.8 vs. 0.9 months HR: 0.89 [0.69; 1.16]; p = 0.408	Lesser/added benefit not proven
Social functioning	0.7 vs. 0.9 months HR: 1.16 [0.90; 1.49]; p = 0.236	Lesser/added benefit not proven
Side effects[h]		
SAEs	18.0 vs. NA months HR: 0.91 [0.67; 1.23]; p = 0.543	Greater/lesser harm not proven
Severe AEs	4.2 vs. 1.4 months HR: 0.52 [0.41; 0.66]; p < 0.001 probability: “hint”	Outcome category: serious/severe side effects CI_u < 0.75; risk ≥ 5% lesser harm, extent: “major”
Discontinuation due to AEs[f]	12.2 vs. NA months HR: 0.73 [0.50; 1.06]; p = 0.095	Greater/lesser harm not proven
Immune-related SAEs	NA vs. NA months HR: 11.08 [2.61; 46.92] HR: 0.09 [0.02; 0.38][g]; p < 0.001 probability: “hint”	Outcome category: serious/severe side effects CI_u < 0.75; risk ≥ 5% greater harm, extent: “major”

Table 10: Extent of added benefit at outcome level: enfortumab vedotin + pembrolizumab vs. cisplatin + gemcitabine (subpopulation: cisplatin suitable) (multipage table)

Outcome category **outcome** **effect modifier** **subgroup**	**Enfortumab vedotin + pembrolizumab vs. cisplatin + gemcitabine** **median time to event (months) or proportion of events (%)** **effect estimation [95% CI];** **p-value** **probability**[a]	**Derivation of extent**[b]
Immune-related severe AEs	NA vs. NA months HR: 11.07 [3.40; 36.11] HR: 0.09 [0.03; 0.29][g]; p < 0.001 probability: "hint"	Outcome category: serious/severe side effects CI_u < 0.75; risk ≥ 5% greater harm, extent: "major"
peripheral neuropathy (AEs)	4.4 vs. NA months HR: 3.30 [2.33; 4.67] HR: 0.30 [0.21; 0.43][g]; p < 0.001 probability: "hint"	Outcome category: non-serious/non-severe side effects CI_u < 0.80 greater harm, extent: "considerable"
Skin reactions (AEs)	0.5 vs. NA months HR: 5.90 [4.40; 7.89] HR: 0.17 [0.13; 0.23][g]; p < 0.001 probability: "hint"	Outcome category: non-serious/non-severe side effects CI_u < 0.80 greater harm, extent: "considerable"
Severe hyperglycaemia (severe AEs)	NA vs. NA months HR: 7.70 [1.77; 33.57] HR: 0.13 [0.03; 0.57][g]; p = 0.001 probability: "hint"	Outcome category: serious/severe side effects CI_u < 0.75; risk ≥ 5% greater harm, extent: "major"
severe nephrotoxicity (severe AEs)	NA vs. NA months HR: 0.69 [0.33; 1.46]; p = 0.330	Greater/lesser harm not proven
Other specific AEs		
Nausea (AEs)	NA vs. 3.3 months HR: 0.36 [0.26; 0.49]; p < 0.001 probability: "hint"	Outcome category: non-serious/non-severe side effects CI_u < 0.80 lesser harm, extent: "considerable"
Vomiting (AEs) Age		
< 65 years	NA vs. NA months HR: 0.28 [0.13; 0.59]; p < 0.001 probability: "hint"	Outcome category: non-serious/non-severe side effects CI_u < 0.80 lesser harm, extent: "considerable"

Table 10: Extent of added benefit at outcome level: enfortumab vedotin + pembrolizumab vs. cisplatin + gemcitabine (subpopulation: cisplatin suitable) (multipage table)

Outcome category **outcome** **effect modifier** **subgroup**	**Enfortumab vedotin + pembrolizumab vs. cisplatin + gemcitabine** **median time to event (months) or proportion of events (%)** **effect estimation [95% CI];** **p-value** **probability**[a]	**Derivation of extent**[b]
≥ 65 years	NA vs. NA months HR: 0.85 [0.40; 1.83]; p = 0.680	Greater/lesser harm not proven
Eye disorders (AEs)	24.6 vs. NA months HR: 5.30 [2.98; 9.41] HR: 0.19 [0.11; 0.34][g]; p < 0.001 probability: "hint"	Outcome category: non-serious/non-severe side effects $CI_u < 0.80$ greater harm, extent: "considerable"
Ear and labyrinth disorders (AE) Age		
< 65 years	NA vs. NA months HR: 0.09 [0.02; 0.37]; p < 0.001 probability: "hint"	Outcome category: non-serious/non-severe side effects $CI_u < 0.80$ lesser harm, extent: "considerable"
≥ 65 years	NA vs. NA months HR: 0.30 [0.10; 0.89]; p = 0.022 probability: "hint"	Outcome category: non-serious/non-severe side effects $0.80 \leq CI_u < 0.90$ lesser harm, extent: "minor"
Endocrine disorders (AEs)	NA vs. NA months HR: 13.47 [3.21; 56.56] HR: 0.07 [0.02; 0.31][g]; p < 0.001 probability: "hint"	Outcome category: non-serious/non-severe side effects $CI_u < 0.80$ greater harm, extent: "considerable"
Gastrointestinal disorders (SAEs)	NA vs. NA months HR: 3.22 [1.29; 7.99] HR: 0.31 [0.13; 0.77][g]; p = 0.008 probability: "hint"	Outcome category: serious/severe side effects $0.75 \leq CI_u < 0.90$ greater harm, extent: "considerable"
Respiratory, thoracic and mediastinal disorders (SAEs)	NA vs. NA months HR: 4.07 [1.37; 12.04] HR: 0.25 [0.08; 0.73][g]; p = 0.006 probability: "hint"	Outcome category: serious/severe side effects $CI_u < 0.75$; risk ≥ 5% greater harm, extent: "major"

Table 10: Extent of added benefit at outcome level: enfortumab vedotin + pembrolizumab vs. cisplatin + gemcitabine (subpopulation: cisplatin suitable) (multipage table)

Outcome category **outcome** **effect modifier** **subgroup**	**Enfortumab vedotin + pembrolizumab vs. cisplatin + gemcitabine** **median time to event (months) or proportion of events (%)** **effect estimation [95% CI];** **p-value** **probability**[a]	**Derivation of extent**[b]
Blood and lymphatic system disorders (severe AEs)	NA vs. 4.9 months HR: 0.08 [0.05; 0.15]; p < 0.001 probability: “hint”	Outcome category: serious/severe side effects $CI_u < 0.75$; risk ≥ 5% lesser harm, extent: “major”
Urinary tract infection (severe AEs)	NA vs. 6.1 months HR: 0.32 [0.13; 0.76]; p = 0.007 probability: “hint”	Outcome category: serious/severe side effects $0.75 \leq CI_u < 0.90$ lesser harm, extent: “considerable”
Diarrhoea (severe AEs)	NA vs. NA months HR: 4.34 [0.94; 20.10] HR: 0.23 [0.05; 1.07][g]; p = 0.040 probability: “hint”	Outcome category: serious/severe side effects greater harm[j], extent: "minor"[k]
General disorders and administration site conditions (severe AEs)	NA vs. NA months HR: 0.30 [0.14; 0.68]; p = 0.002 probability: “hint”	Outcome category: serious/severe side effects $CI_u < 0.75$; risk ≥ 5% lesser harm, extent: “major”
Hepatobiliary disorders (severe AEs)	NA vs. NA months HR: 7.95 [0.995; 63.60] HR: 0.13 [0.02; 1.01][g]; p = 0.020 probability: “hint”	Outcome category: serious/severe side effects greater harm[j], extent: "minor"[k]

Table 10: Extent of added benefit at outcome level: enfortumab vedotin + pembrolizumab vs. cisplatin + gemcitabine (subpopulation: cisplatin suitable) (multipage table)

Outcome category **outcome** **effect modifier** **subgroup**	**Enfortumab vedotin + pembrolizumab vs. cisplatin + gemcitabine** **median time to event (months) or proportion of events (%)** **effect estimation [95% CI];** **p-value** **probability**[a]	**Derivation of extent**[b]
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. Censoring at the time of death: avelumab-eligible patients who had not received avelumab and died were censored at the time of death. d. Censoring at data cut-off: avelumab-eligible patients who had not received avelumab and died were censored at the time of data cut-off. e. Modified time of death: avelumab-eligible patients who had not received avelumab and died were censored with a modified time of death. A simplified assumption was made that the patients would have benefited from treatment with avelumab to the extent shown in the approval study of avelumab (JAVELIN Bladder 100); see dossier assessment A24-98 for explanation. f. The extent of the effect in this non-serious/non-severe outcome was no more than marginal. g. Institute's calculation; inverse direction of effect to enable use of limits to derive the extent of the added benefit. h. The fixed treatment duration and the associated discontinuation of observation after the end of study medication in the comparator arm mean that the effect estimate only reflects approximately the first 6 months after randomization. i. For the outcome of discontinuation due to AEs, see also Addendum A25-23 [15]. j. The result of the statistical test is decisive for the derivation of the added benefit. k. Discrepancy between CI and p-value due to different calculation methods; the extent is rated as minor. AE: adverse event; BPI-SF: Brief Pain Inventory-Short Form; CI: confidence interval; CI_u: upper limit of confidence interval; EORTC: European Organisation for Research and Treatment of Cancer; HR: hazard ratio; NA: not achieved; QLQ-C30: Quality of Life Questionnaire-Core 30; SAE: serious adverse event; VAS: visual analogue scale		

2.2.3.2 Overall conclusion on added benefit

Table 11 summarizes the results taken into account in the overall conclusion on the extent of added benefit.

Table 11: Positive and negative effects from the assessment of enfortumab vedotin + pembrolizumab in comparison with the ACT (subpopulation: cisplatin unsuitable)

Positive effects	**Negative effects**
Outcomes with observation over the entire study duration	
Mortality ▪ overall survival: hint of an added benefit – extent: “non-quantifiable”	–
Outcomes with shortened observation period[a]	
Health-related quality of life ▪ physical function (each EORTC-QLQ-C30) ▫ age (< 65 years): hint of added benefit – extent: “minor”	–
Non-serious/non-severe symptoms/late complications ▪ nausea and vomiting, constipation (EORTC QLQ-C30): hint of added benefit – extent: "considerable"	–
Serious/severe side effects ▪ severe AEs: hint of lesser harm – extent: “major” ▫ blood and lymphatic system disorders (severe AEs), general disorders and administration site conditions (severe AEs): in each case hint of lesser harm – extent: “major” ▫ urinary tract infection (severe AEs): ▫ hint of lesser harm – extent: “considerable”	Serious/severe side effects ▪ immune-related SAEs, immune-related severe AEs; severe hyperglycaemia (severe AEs), respiratory, thoracic and mediastinal disorders (SAEs): hint of greater harm in each case – extent: “major” ▪ gastrointestinal disorders (SAE): hint of greater harm – extent: “considerable” ▪ diarrhoea (severe AEs), hepatobiliary disorders (severe AEs): hint of greater harm – extent: “minor”
Non-serious/non-severe side effects ▪ nausea (AEs): hint of lesser harm – extent: “considerable” ▪ vomiting (AEs) ▫ age (< 65 years): hint of lesser harm – extent: "considerable" ▪ ear and labyrinth disorders (AE) ▫ age (< 65 years): hint of lesser harm – extent: "considerable" ▫ age (≥ 65 years): hint of lesser harm – extent: "minor"	Non-serious/non-severe side effects ▪ peripheral neuropathy (AEs), skin reactions (AEs), eye disorders (AEs), endocrine disorders (AEs): hint of greater harm each - extent: “considerable”
For the outcome of discontinuation due to AEs, see also Addendum A25-23 [15].	
a. For the side effect outcomes, the fixed treatment duration and the associated discontinuation of observation after the end of study medication in the comparator arm mean that the effect estimate only reflects approximately the first 6 months after randomization. AE: adverse event; EORTC: European Organisation for Research and Treatment of Cancer; QLQ-C30: Quality of Life Questionnaire – Core 30; SAE: serious adverse event	

The overall assessment shows both positive and negative effects with different extents for enfortumab vedotin + pembrolizumab compared with the ACT. For mortality, the observed

effects refer to the entire observation period. In particular for the outcomes of side effects, however, the observed effects relate to a shortened period and only represent the roughly first 6 months after randomization and thus in the comparator arm only the period of chemotherapy, but not the period of a possible maintenance therapy with avelumab, and in the intervention arm only the first 6 months of a possibly longer-lasting therapy.

The advantage in overall survival is decisive for the assessment, but its extent cannot be quantified, as the results of the main and sensitivity analyses differ in terms of their extent. The fact that the benefit is not retained in sensitivity analysis 2, which is based on the maximum assumption that all patients who did not receive avelumab, although this therapy would have been suitable for them, would have survived in the comparator arm up to the present data cut-off, does not call into question an added benefit in the present data situation, but contributes to the fact that it cannot be quantified.

With regard to all other outcomes, there were no changes relevant for the overall assessment compared with dossier assessment A24-98.

For the outcome of discontinuation due to AEs, see also Addendum A25-23 [15].

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

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

2.3 Research question 2: Patients for whom cisplatin-based therapy is not suitable (cisplatin unsuitable)

2.3.1 Study characteristics (specific to research question 2)

2.3.1.1 Patient characteristics

Table 12 shows the characteristics of the patients in the subpopulation of the included study relevant for research question 2.

Table 12: Characteristics of the study population as well as study/treatment discontinuation – RCT, direct comparison: enfortumab vedotin + pembrolizumab vs. carboplatin + gemcitabine (subpopulation: cisplatin unsuitable) (multipage table)

Study characteristic category	**Enfortumab vedotin + pembrolizumab N = 202**	**Carboplatin + gemcitabine N = 202**
EV-302/KN-A39 (2nd data cut-off 08 August 2024)		
Age [years], mean (SD)	71 (8)	72 (8)
Sex [F/M], %	28/72	25/75
Region		
Europe	74 (37)	95 (47)
North America	46 (23)	34 (17)
Rest of the world[a]	82 (41)	73 (36)
ECOG PS at baseline, n (%)		
0	87 (43)	87 (43)
1	104 (51)	105 (52)
2	11 (5)	9 (5)
Unknown	0 (0)	1 (< 1[b])
Renal function [CrCl in mL/min[c]], n (%)		
Normal [> 90]	6 (3)	13 (6)
Slightly reduced [≥ 60 to < 90]	49 (24)	40 (20)
Moderately reduced [≥ 30 to < 60]	140 (69)	141 (70)
Strongly reduced [≥ 15 to < 30]	7 (4)	8 (4)
PD-L1 status at baseline [CPS], n (%)		
< 10	85 (42)	87 (43)
≥ 10	117 (58)	115 (57)
Primary origin of disease[d]		
Upper tract (kidney, renal pelvis, ureter)	74 (37)	55 (27)
Lower tract (urinary bladder, urethra)	128 (63)	146 (72)
Unknown	0 (0)	1 (< 1)
Disease duration: time between diagnosis of locally advanced or metastatic disease and randomization [months], median [Q1; Q3]	ND[e]	ND[e]
Liver metastases, n (%)	50 (25)	50 (25)
Metastasis category at baseline, n (%)		
Visceral metastases	148 (73)	157 (78)
Exclusively lymph node metastases	43 (21)	37 (18)
No category applicable	11 (5)	8 (4)
Reason for unsuitability of cisplatin		
Renal insufficiency [GFR ≥ 30, < 60 ml/min)[f]	164 (81)	163 (81)
Audiometric hearing loss (CTCAE grade ≥ 2)	29 (14)	29 (14)
Poor performance status [ECOG PS 2]	9 (4)	8 (4)

Table 12: Characteristics of the study population as well as study/treatment discontinuation – RCT, direct comparison: enfortumab vedotin + pembrolizumab vs. carboplatin + gemcitabine (subpopulation: cisplatin unsuitable) (multipage table)

Study characteristic category	Enfortumab vedotin + pembrolizumab N = 202	Carboplatin + gemcitabine N = 202
Heart failure [NYHA class III]	4 (2)	7 (3)
Several of the reasons listed above	12 (6)	10 (5)
Not specified	8 (4)[c]	5 (2)[c]
Treatment discontinuation, n (%)[g]	163 (81)[b]	99 (49)[b]
Study discontinuation, n (%)[h]	114 (56)	153 (76)

a. Rest of the world includes Argentina, Australia, China, Israel, Japan, Russia, Singapore, South Korea, Taiwan, Thailand and Turkey.
b. Institute's calculation.
c. The CrCl was calculated using the Cockcroft-Gault formula based on the last measured creatinine value prior to taking the first dose of study medication.
d. In relation to the total population of the study, the primary origin of the disease was predominantly the urinary bladder (67% vs. 74%) or the renal pelvis (20% vs. 15%); for the relevant subpopulation, only the summarized data shown in the table are available.
e. Data on the disease duration are not available for the relevant subpopulation; in relation to the total study population, the time between diagnosis of locally advanced or metastatic disease and randomization (median [Q1; Q3]) was 1.6 [1.1; 2.5] months in the intervention arm and 1.6 [1.0; 2.3] months in the comparator arm.
f. Patients with a GFR ≥ 50 mL/min and no other criteria for unsuitability of cisplatin could be considered cisplatin-suitable according to the investigator's assessment.
g. Common reasons for treatment discontinuation in the intervention vs. the control arm were the following (percentages based on randomized patients): disease progression (38% versus 21%), adverse event (28% versus 17%). In addition, 1% vs. 3% of the randomized patients never started treatment; a further 8% vs. 49% of patients completed treatment with the study medication as planned.
h. The figures include patients who died during the course of the study (intervention arm: 51% vs. control arm: 73%; percentages refer to the randomized patients).

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

A description of the baseline patient characteristics of the EV-302/KN-A39 study can be found in dossier assessment A24-98.

In its comments, the company provided information on the treatment and study discontinuations in the respective subpopulations and on the most frequent reasons for discontinuation. With regard to the 2nd data cut-off, the most common reasons for discontinuation of treatment were disease progression (38% vs. 21%) or an adverse event (28% vs. 17%). It should be noted here that for the comparator arm these data only refer to the study medication and thus the chemotherapy with carboplatin + gemcitabine and not to

a possible subsequent maintenance therapy with avelumab in progression-free patients, which was not part of the study medication according to the study design. Study discontinuation for reasons other than death occurred only sporadically in both treatment arms, in about 3% to 5% of patients (Institute's calculation).

2.3.1.2 Information on the course of the study

Table 13 shows the mean and median treatment durations of the patients, and the mean and median observation periods for individual outcomes in the subpopulation relevant to research question 2.

Table 13: Information on the course of the study – RCT, direct comparison: enfortumab vedotin + pembrolizumab vs. carboplatin + gemcitabine (subpopulation: cisplatin unsuitable)

Study (data cut-off) **duration of the study phase** **outcome category/outcome**	**Enfortumab vedotin + pembrolizumab** **N = 202**	**Carboplatin + gemcitabine** **N = 202**
EV-302/KN-A39 (2nd data cut-off 08 August 2024)		
Treatment duration[a] [months]		
Median [Q1; Q3]	9.2 [4.3; 20.7]	4.1 [2.6; 4.4]
Mean (SD)	12.2 (9.4)	3.4 (1.5)
Observation period [months]		
Overall survival[b]		
Median [Q1; Q3]	22.7 [10.4; 28.7]	12.6 [6.6; 23.5]
Mean (SD)	20.4 (11.0)	15.0 (10.0)
Symptoms (BPI-SF; EORTC QLQ-C30)[c]		
Median [Q1; Q3]	11.1 [3.2; 22.5]	4.6 [2.3; 10.7]
Mean (SD)	13.7 (11.3)	7.8 (8.1)
Health status (EQ-5D VAS)[c]		
Median [Q1; Q3]	11.1 [3.2; 22.5]	4.6 [2.3; 10.7]
Mean (SD)	13.7 (11.3)	7.8 (8.1)
Health-related quality of life (EORTC QLQ-C30)[c]		
Median [Q1; Q3]	11.1 [3.2; 22.5]	4.6 [2.3; 10.7]
Mean (SD)	13.7 (11.3)	7.8 (8.1)
Side effects[d]		
Median [Q1; Q3]	12.9 [7.7; 22.8]	5.4 [3.8; 5.9]
Mean (SD)	15.1 (9.3)	4.9 (1.6)

a. Treatment duration is defined as the time from the first dose of study medication to Day 21 of the last of the 21-day treatment cycles, initiation of subsequent antineoplastic therapy, death, end of study, or time of data cut-off, whichever occurs first.
b. The observation period is calculated as the time from randomization to the last time point at which information on overall survival was recorded.
c. The observation period is defined as the time from randomization until the last recording of the outcome; patients who had not experienced a first deterioration since the start of the study before the initiation of subsequent antineoplastic therapy were censored on the date of the last available recording of the outcome.
d. According to company's documents, the observation period is defined as the time from the first study treatment to 90 days after the last study treatment in the intervention arm or 30 days after the last study treatment in the comparator arm. This deviates from the information according to the study design (see dossier assessment A24-98), without this being explained by the company. The information according to the study design is assumed to be true.

N: number of patients; Q1: first quartile; Q3: third quartile; RCT: randomized controlled trial; SD: standard deviation

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

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

The median observation period for the outcome of overall survival in the intervention arm is clearly longer at the present 2nd data cut-off (22.7 vs. 12.6 months) than at the 1st data cut-off (13.7 vs. 10.7 months). For the outcomes on symptoms, health status and health-related quality of life as well as for the outcomes on side effects, the observation period for the 2nd data cut-off is only slightly longer than for the 1st data cut-off, while there are no changes for the comparator arm. As described in Section 2.1.4, patients who had not experienced a first deterioration since the start of the study before the initiation of subsequent antineoplastic therapy were censored on the date of the last available recording of the outcome. In the present data situation, it is not assumed that this influences the results to a relevant extent; for an explanation, see Section I 4.2.3 of dossier assessment A24-98.

As described in dossier assessment A24-98, the fixed treatment duration in the comparator arm and the linking of the observation time for side effects to the treatment duration means that the effect estimate only reflects approximately the first 6 months after randomization and thus only the period of chemotherapy in the comparator arm, but not a possible maintenance therapy with avelumab, and only the first 6 months of a possibly longer-lasting therapy in the intervention arm. This has been taken into account in the derivation of the certainty of conclusions for the outcomes on side effects (see Section 2.3.2.2).

2.3.1.3 Subsequent therapies

Table 14 shows the subsequent therapies patients received after discontinuing the study medication in the subpopulation relevant to research question 2.

Table 14: Information on subsequent antineoplastic therapies (≥ 1% of patients in ≥ 1 treatment arm) – RCT, direct comparison: enfortumab vedotin + pembrolizumab versus carboplatin + gemcitabine (subpopulation: cisplatin unsuitable) (multipage table)

Study **drug class** **therapies** **drug**	**Patients with subsequent therapy, n (%)**	
	enfortumab vedotin + pembrolizumab **N = 202**	**cisplatin + gemcitabine** **N = 202**
Study EV-302/KN-A39 (2nd data cut-off 08 August 2024)		
Subsequent therapy received[a]	71 (35.1)[b]	143 (70.8)[b]
Systemic therapy for progressive disease	55 (27.2)[b]	101 (50.0)[b]
Maintenance therapy	3 (1.5)	57 (28.2)
Atezolizumab	0 (0[b])	2 (1.0[b])
Avelumab	3 (1.5[b])	53 (26.2[b])
Pembrolizumab	0 (0[b])	4 (2.0[b])
Other drugs	0 (0[b])	3 (1.5[b])
Palliative radiotherapy	16 (7.9)	25 (12.4)
Surgical intervention	5 (2.5)	5 (2.5)
No subsequent therapy received	131 (64.9)	59 (29.2)
No disease progression	92 (45.5[b])	35 (17.3[b])
Still under first-line therapy	22 (10.9)	0 (0)
Study discontinuation	71 (35.1[b])	50 (24.8[b])
Died under first-line therapy	62 (30.7)	46 (22.8)
Other reasons	9 (4.5[b])	2 (1.0[b])
First subsequent systemic therapy after progression under maintenance therapy	3 (1.5[b])	30 (14.9[b])
Platinum-based therapy	3 (1.5[b])	3 (1.5[b])
Carboplatin-based therapy	2 (1.0[b])	2 (1.0[b])
PD-1/-L1-based therapy	0 (0[b])	2 (1.0[b])
Other drugs	0 (0[b])	25 (12.4[b])
Enfortumab vedotin	0 (0[b])	15 (7.4[b])
Taxanes	0 (0[b])	7 (3.5[b])
First subsequent systemic therapy after progression without maintenance therapy	52 (25.7[b])	71 (35.1[b])
Platinum-based therapy	46 (22.8[b])	6 (3.0[b])
Cisplatin-based therapy	9 (4.5[b])	2 (1.0[b])
Carboplatin-based therapy	36 (17.8[b])	3 (1.5[b])
PD-1/-L1-based therapy	3 (1.5[b])	55 (27.2[b])
Atezolizumab	0 (0[b])	24 (11.9[b])
Pembrolizumab	2 (1.0[b])	30 (14.9[b])
Other drugs	3 (1.5[b])	10 (5.0[b])

Table 14: Information on subsequent antineoplastic therapies (≥ 1% of patients in ≥ 1 treatment arm) – RCT, direct comparison: enfortumab vedotin + pembrolizumab versus carboplatin + gemcitabine (subpopulation: cisplatin unsuitable) (multipage table)

Study **drug class** **therapies** **drug**	**Patients with subsequent therapy, n (%)**	
	enfortumab vedotin + pembrolizumab **N = 202**	**cisplatin + gemcitabine** **N = 202**
Erdafitinib	0 (0[b])	2 (1.0[b])
Taxanes	0 (0[b])	5 (2.5[b])
Second subsequent systemic therapy after progression under maintenance therapy	0 (0[b])	12 (5.9[b])
Other drugs	0 (0[b])	11 (5.4[b])
Enfortumab vedotin	0 (0[b])	5 (2.5[b])
Sacituzumab govitecan	0 (0[b])	3 (1.5[b])
Second subsequent systemic therapy after progression without maintenance therapy	13 (6.4[b])	23 (11.4[b])
Platinum-based therapy	3 (1.5[b])	1 (0.5[b])
Carboplatin-based therapy	2 (1.0[b])	1 (0.5[b])
PD-1/-L1-based therapy	2 (1.0[b])	4 (2.0[b])
Pembrolizumab	1 (0.5[b])	2 (1.0[b])
Other drugs	8 (4.0[b])	18 (8.9[b])
Enfortumab vedotin	0 (0[b])	10 (5.0[b])
Sacituzumab govitecan	2 (1.0[b])	1 (0.5[b])
Taxanes	4 (2.0[b])	5 (2.5[b])

a. Including maintenance therapies.
b. Institute's calculation.

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

At the time of dossier assessment A24-98, the data on subsequent systemic antineoplastic therapies in the company's dossier included both systemic therapies for the treatment of progressive disease and maintenance therapies. This is not appropriate. Moreover, it cannot be inferred from the data in the company's dossier, which subsequent therapies were used after disease progression under maintenance treatment with avelumab.

With its comments, the company has now submitted information on subsequent systemic antineoplastic therapies in which systemic therapies for the treatment of progressive disease and maintenance therapies are presented separately and from which it can be seen which subsequent antineoplastic therapies were used after disease progression under maintenance

therapy or after disease progression without maintenance therapy. The reasons why some of the patients did not receive a subsequent therapy are also given.

These data show that in the subpopulation of RCT EV-302/KN-A39 relevant to research question 2, a total of 55 (27%) patients in the intervention arm and 101 (50%) patients in the comparator arm had received at least 1 subsequent systemic therapy for the treatment of progressive disease at the time of the second data cut-off.

In relation to the patients in whom disease progression occurred as a PFS event (99 [49.0%] patients in the intervention arm versus 136 [67.3%] patients in the comparator arm), this means that 56% of the patients with disease progression in the intervention arm and 74% in the comparator arm received at least one subsequent therapy for the treatment of progressive disease (Institute's calculation). According to the current S3 guideline, the ability and meaningfulness of second-line therapy must be checked for each patient [12], so that the proportion of patients with subsequent therapy in the subpopulation of the EV-302/KN-A39 study relevant to research question 2 appears appropriate overall.

In the intervention arm, platinum-based chemotherapy was the most common first subsequent therapy after disease progression with enfortumab vedotin + pembrolizumab. This corresponds to current guideline recommendations [13].

Pembrolizumab or atezolizumab is recommended as first-line therapy in case of disease progression under platinum-based chemotherapy [12,13]. In the comparator arm, 15% and 12% of patients in the relevant subpopulation respectively received these agents as first subsequent systemic therapy after disease progression without prior maintenance therapy; this corresponds to 34% and 42% of patients who received subsequent systemic therapy after disease progression without prior maintenance therapy.

In cases of disease progression under maintenance treatment with avelumab following platinum-based chemotherapy as first-line treatment or under second-line treatment with pembrolizumab or atezolizumab, erdafitinib (in certain patients) and enfortumab vedotin are primarily recommended, and sacituzumab govitecan, vinflunine or taxanes [13] are recommended with a lower recommendation grade. Corresponding drugs, particularly enfortumab vedotin, were frequently used in the comparator arm in corresponding situations (see Table 14).

On the basis of the available data and the recommendation of the current S3 guideline, it is assumed that the use of subsequent therapies was predominantly appropriate in the subpopulation of study EV-302/KN-A39 relevant to research question 2 at the second data cut-off.

2.3.2 Results on added benefit

2.3.2.1 Outcomes included

Table 15 shows the outcomes for which data for research question 2 are available in the included study.

Table 15: Matrix of outcomes – RCT, direct comparison: enfortumab vedotin + pembrolizumab vs. carboplatin + gemcitabine (subpopulation: cisplatin unsuitable)

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

a. Severe AEs are operationalized as CTCAE grade ≥ 3.
b. In each case, the operationalization of a specific, predefined MedDRA PT collection from the outcome of AEOSI (Version 27.0) presented by the company is used.
c. Operationalized as skin and subcutaneous tissue disorders (SOC, AEs).
d. Operationalized as renal and urinary disorders (SOC, severe AEs).
e. The following events were considered (MedDRA coding): constipation (PT, AEs), diarrhoea (PT, AEs), dysgeusia (PT, AEs), eye disorders (SOC, AEs), endocrine disorders (SOC, AEs), blood and lymphatic system disorders (SOC, severe AEs) and acute kidney injury (PT, severe AEs).

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

Notes on outcomes

Aspects for which there is a relevant change compared to dossier assessment A24-98 are described in Section 2.2.2.1.

Overall survival: tipping point analyses of the company

A detailed description of the tipping point analyses presented by the company during the commenting procedure can be found in Section 2.2.2.1. As described there, the results of the tipping point analyses were not used because they were not sufficiently reliable and were based on unverifiable assumptions. With regard to research question 2 of the benefit assessment, the assessment of the extent is already given on the basis of the main analysis and the 3 sensitivity analyses, so that the attempt to quantify the extent by means of further analyses is not necessary.

2.3.2.2 Risk of bias

Table 16 describes the risk of bias for the results of the relevant outcomes for research question 2.

Table 16: Risk of bias across outcomes and outcome-specific risk of bias – RCT, direct comparison: enfortumab vedotin + pembrolizumab vs. carboplatin + gemcitabine (subpopulation: cisplatin unsuitable)

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

a. Severe AEs are operationalized as CTCAE grade ≥ 3.
b. In each case, the operationalization of a specific, predefined MedDRA PT collection from the outcome of AEOSI (Version 27.0) presented by the company is used.
c. Operationalized as skin and subcutaneous tissue disorders (SOC, AEs).
d. Operationalized as renal and urinary disorders (SOC, severe AEs).
e. The following events were considered (MedDRA coding): constipation (PT, AEs), diarrhoea (PT, AEs), dysgeusia (PT, AEs), eye disorders (SOC, AEs), endocrine disorders (SOC, AEs), blood and lymphatic system disorders (SOC, severe AEs) and acute kidney injury (PT, severe AEs).
f. Lack of blinding in subjective recording of outcomes, unless severe or serious AEs are involved.
g. Decreasing response to questionnaires in the course of the study; large proportion of patients not included in the analysis (> 10 %) or large difference between the treatment groups (> 5 percentage points).
h. Incomplete observations for potentially informative reasons.
i. Lack of blinding in subjective decision for treatment discontinuation.

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

The outcome-specific risk of bias does not differ between research question 1 and research question 2. More detailed information can therefore be found in Section 2.2.2.2. and in dossier assessment A24-98.

Summary assessment of the certainty of conclusions

In addition to the described aspects of bias, there are uncertainties for study EV-302/KN-A39, as described in dossier assessment A24-98 and in Section 2.1.3 of this addendum, particularly

in the implementation of the ACT. In the present specific data constellation, the results of the study can nevertheless be interpreted for the research questions of the present benefit assessment, but the certainty of the study results for the present assessment is reduced. The shortened observation in the comparator arm or consideration of data collected in the intervention arm for outcomes in the side effects category also contributes to limited certainty of conclusions. Based on the EV-302/KN-A39 study, at most hints, e.g. of an added benefit, can be derived for both research questions.

2.3.2.3 Results

Table 17 summarizes the results of the comparison of enfortumab vedotin + pembrolizumab with carboplatin + gemcitabine for first-line treatment in adult patients with unresectable or metastatic urothelial carcinoma for whom cisplatin-based therapy is not suitable. Where necessary, calculations conducted by the Institute are provided in addition to the data from the company's documents.

Kaplan-Meier curves on the presented time-to-event analyses can be found in Appendix B.2. Results on common AEs, SAEs, severe AEs, and discontinuation due to AEs are presented in Appendix C.2. Results on frequent immune-related AEs, immune-related SAEs and immune-related severe AEs are not available in the company's documents.

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

Study (data cut-off) outcome category outcome	Enfortumab vedotin + pembrolizumab		Carboplatin + gemcitabine		Enfortumab vedotin + pembrolizumab vs. carboplatin + gemcitabine
	N	median time to event in months [95% CI] patients with event n (%)	N	median time to event in months [95% CI] patients with event n (%)	HR [95% CI]; p-value
EV-302/KN-A39 (08 August 2024)					
Mortality					
Overall survival	202	25.6 [23.0; 36.3] 103 (51.0)	202	12.9 [11.3; 15.0] 148 (73.3)	0.49 [0.38; 0.63]; < 0.001[a]
Overall survival (sensitivity analysis 1[b])	202	25.6 [23.0; 36.3] 103 (51.0)	202	15.0 [12.2; 20.0] 120 (59.4)	0.61 [0.47; 0.80]; < 0.001[a]
Overall survival (sensitivity analysis 2[c])	202	25.6 [23.0; 36.3] 103 (51.0)	202	15.9 [12.5; 21.2] 120 (59.4)	0.71 [0.55; 0.93]; 0.011[a]
Overall survival (sensitivity analysis 3[d])	202	25.6 [23.0; 36.3] 103 (51.0)	202	14.7 [12.5; 18.3] 143 (70.8)	0.54 [0.42; 0.70]; < 0.001[a]
Morbidity					
Worst pain (BPI-SF item 3 - time to first deterioration)[e]	202	3.2 [1.6; 13.5] 88 (43.6)	202	1.3 [0.7; 2.2] 107 (53.0)	0.67 [0.49; 0.92]; 0.013[a]
Pain intensity (BPI-SF items 3–6, time to first deterioration, presented as supplementary information)[f]	*202*	*19.7 [10.8; NC]* *69 (34.2)*	*202*	*5.9 [2.4; 8.0]* *86 (42.6)*	*0.61 [0.42; 0.88]; 0.008*[a]
Pain interference (BPI-SF items 9a-g – time to first deterioration)[f]	202	2.7 [1.3; 10.8] 90 (44.6)	202	1.3 [0.8; 2.0] 112 (55.4)	0.74 [0.54; 1.02]; 0.069[a]
Symptoms (EORTC QLQ-C30 – time to first deterioration[g])					
Fatigue	202	0.6 [0.4; 0.8] 131 (64.9)	202	0.4 [0.4; 0.6] 132 (65.3)	0.77 [0.58; 1.02]; 0.068[a]
Nausea and vomiting	202	1.8 [1.1; 2.7] 105 (52.0)	202	1.1 [0.4; 1.5] 118 (58.4)	0.72 [0.54; 0.97]; 0.037[a]
Pain	202	1.1 [0.7; 2.0] 110 (54.5)	202	0.9 [0.5; 1.3] 120 (59.4)	0.79 [0.59; 1.06]; 0.110[a]
Dyspnoea	202	2.0 [1.5; 3.1] 104 (51.5)	202	1.5 [1.1; 2.2] 108 (53.5)	0.85 [0.62; 1.15]; 0.300[a]
Insomnia	202	1.6 [1.1; 2.2] 102 (50.5)	202	1.3 [0.9; 2.2] 96 (47.5)	0.87 [0.64; 1.20]; 0.409[a]

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

Study (data cut-off) outcome category outcome	Enfortumab vedotin + pembrolizumab		Carboplatin + gemcitabine		Enfortumab vedotin + pembrolizumab vs. carboplatin + gemcitabine
	N	median time to event in months [95% CI] patients with event n (%)	N	median time to event in months [95% CI] patients with event n (%)	HR [95% CI]; p-value
Appetite loss	202	0.9 [0.6; 1.3] 118 (58.4)	202	1.1 [0.6; 1.5] 110 (54.5)	0.96 [0.71; 1.30]; 0.859[a]
Constipation	202	2.2 [1.5; 3.1] 97 (48.0)	202	0.4 [0.4; 0.9] 113 (55.9)	0.49 [0.36; 0.68]; < 0.001[a]
Diarrhoea	202	2.0 [1.3; 3.1] 104 (51.5)	202	4.6 [2.0; 11.0] 79 (39.1)	1.33 [0.96; 1.85]; 0.075[a]
Health status (EQ-5D VAS - time to first deterioration[h])	202	1.5 [1.0; 3.2] 110 (54.5)	202	1.3 [0.9; 2.0] 111 (55.0)	0.89 [0.66; 1.21]; 0.508[a]
health-related quality of life					
EORTC-QLQ-C30 – time to first deterioration[i]					
Global health status	202	1.1 [0.6; 1.5] 123 (60.9)	202	0.9 [0.6; 1.1] 116 (57.4)	0.96 [0.71; 1.30]; 0.841[a]
Physical functioning	202	1.1 [0.7; 1.7] 126 (62.4)	202	0.7 [0.4; 1.1] 126 (62.4)	0.82 [0.61; 1.09]; 0.168[a]
Role functioning	202	0.7 [0.5; 1.1] 126 (62.4)	202	0.4 [0.4; 0.6] 137 (67.8)	0.76 [0.56; 1.01]; 0.063[a]
Emotional functioning	202	4.5 [2.5; 9.4] 92 (45.5)	202	2.0 [1.1; 3.2] 96 (47.5)	0.74 [0.53; 1.04]; 0.087[a]
Cognitive functioning	202	1.5 [1.1; 2.0] 114 (56.4)	202	0.9 [0.6; 1.5] 117 (57.9)	0.80 [0.59; 1.07]; 0.140[a]
Social functioning	202	0.9 [0.6; 1.3] 122 (60.4)	202	0.9 [0.4; 1.1] 114 (56.4)	1.04 [0.77; 1.41]; 0.752[a]
Side effects[j]					
AEs (supplementary information)	201	0.3 [0.2; 0.3] 200 (99.5)	197	0.2 [0.1; 0.2] 193 (98.0)	–
SAEs	201	7.9 [5.3; 13.1] 122 (60.7)	197	5.4 [4.2; NC] 86 (43.7)	0.87 [0.64; 1.18]; 0.365[k]
Severe AEs[l]	201	2.6 [2.0; 4.0] 163 (81.1)	197	0.7 [0.5; 0.9] 166 (84.3)	0.46 [0.36; 0.58]; < 0.001[k]
Discontinuation due to AEs[m]	201	11.5 [8.9; 15.0] 102 (50.7)	197	NA 35 (17.8)	1.35 [0.88; 2.06]; 0.169[k]

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

Study (data cut-off) outcome category outcome	**Enfortumab vedotin + pembrolizumab**		**Carboplatin + gemcitabine**		**Enfortumab vedotin + pembrolizumab vs. carboplatin + gemcitabine**
	N	**median time to event in months [95% CI] patients with event n (%)**	**N**	**median time to event in months [95% CI] patients with event n (%)**	**HR [95% CI]; p-value**
Immune-related AEs[n] (supplementary information)	*201*	*11.0 [6.9; 23.9] 93 (46.3)*	*197*	*NA 11 (5.6)*	–
Immune-related SAEs[n]	201	NA 24 (11.9)	197	NA 2 (1.0)	6.93 [1.58; 30.31]; 0.003[k]
Immune-related severe AE [l, n]	201	NA 45 (22.4)	197	NA 2 (1.0)	15.92 [3.82; 66.38]; < 0.001[k]
Peripheral neuropathy (SMQ, AEs)[o]	201	4.5 [3.7; 5.1] 133 (66.2)	197	NA 17 (8.6)	6.41 [3.83; 10.73]; < 0.001[k]
Skin reactions[p]	201	0.6 [0.5; 0.7] 163 (81.1)	197	NA 51 (25.9)	4.95 [3.60; 6.81]; < 0.001[k]
Severe hyperglycaemia (PT, severe AEs[f])	201	NA 12 (6.0)	197	NA 1 (0.5)	10.71 [1.38; 82.92]; 0.005[k]
Severe nephrotoxicity[l, q]	201	NA 28 (13.9)	197	NA 15 (7.6)	1.12 [0.57; 2.23]; 0.736[k]
Other specific AEs					
Constipation (PT, AEs)	201	NA 50 (24.9)	197	NA 71 (36.0)	0.45 [0.30; 0.66]; < 0.001[k]
Diarrhoea (PT, AEs)	201	23.9 [11.1; NC] 80 (39.8)	197	NA 29 (14.7)	2.30 [1.48; 3.56]; < 0.001[k]
Dysgeusia (PT, AEs)	201	NA 46 (22.9)	197	NA 9 (4.6)	4.83 [2.35; 9.92]; < 0.001[k]
Eye disorders (SOC, AEs)	201	27.9 [17.5; NC] 66 (32.8)	197	NA 12 (6.1)	3.85 [2.04; 7.26]; < 0.001[k]
Endocrine disorders (SOC, AEs)	201	NA 39 (19.4)	197	NA 4 (2.0)	5.47 [1.90; 15.79]; < 0.001[k]
Blood and lymphatic system disorders (SOC, severe AEs)[f]	201	NA 47 (23.4)	197	1.3 [1.0; 1.6] 135 (68.5)	0.14 [0.09; 0.20]; < 0.001[k]
Acute kidney injury (PT, severe AEs)[l]	201	NA 16 (8.0)	197	NA 4 (2.0)	3.05 [0.99; 9.36]f; 0.041[k]

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

Study (data cut-off) outcome category outcome	Enfortumab vedotin + pembrolizumab		Carboplatin + gemcitabine		Enfortumab vedotin + pembrolizumab vs. carboplatin + gemcitabine
	N	median time to event in months [95% CI] patients with event n (%)	N	median time to event in months [95% CI] patients with event n (%)	HR [95% CI]; p-value

a. HR and CI: Cox proportional hazards model, p-value: log-rank test, each stratified by PD-L1 expression (high vs. low) and liver metastases (present vs. not present).
b. Censoring at the time of death: avelumab-eligible patients who had not received avelumab and died were censored at the time of death.
c. Censoring at data cut-off: avelumab-eligible patients who had not received avelumab and died were censored at the time of data cut-off.
d. Modified time of death: avelumab-eligible patients who had not received avelumab and died were censored with a modified time of death. A simplified assumption was made that the patients would have benefited from treatment with avelumab to the extent shown in the approval study of avelumab (JAVELIN Bladder 100); see dossier assessment A24-98 for explanation.
e. A score increase by ≥ 2 points from baseline is considered a clinically relevant deterioration (scale range: 0 to 10); for explanation, see dossier assessment A24-98.
f. A score increase by ≥ 1.5 points from baseline is considered a clinically relevant deterioration (scale range: 0 to 10); for explanation, see dossier assessment A24-98.
g. An EORTC QLQ-C30 score increase by ≥ 10 points from baseline is considered a clinically relevant deterioration (scale range: 0 to 100).
h. An EQ-5D VAS score decrease by ≥ 15 points from baseline is considered a clinically relevant deterioration (scale range: 0 to 100).
i. An EORTC QLQ-C30 score decrease by ≥ 10 points from baseline is considered a clinically relevant deterioration (scale range: 0 to 100).
j. The terms of disease progression, progression of a disease and progression of a malignant disease as well as similar terms were not taken into account in the assessment of AEs. The fixed treatment duration and the associated discontinuation of observation after the end of study medication in the comparator arm mean that the effect estimate only reflects approximately the first 6 months after randomization.
k. HR and CI: unstratified Cox proportional hazards model; p-value: unstratified log-rank test.
l. Operationalized as CTCAE grade ≥ 3.
m. For the outcome of discontinuation due to AEs, see also Addendum A25-23 [15].
n. In each case, the operationalization of a specific, predefined MedDRA PT collection from the outcome of AESI (Version 27.0) presented by the company is used.
o. The following result is shown for the severe AEs of the SMQ “peripheral neuropathy” included in the results on AEs: 18 (9.0) vs. 0 (0); HR: NC [NC; NC]; p = 0.0407; Kaplan-Meier curve see Figure 94.
p. Operationalized as skin and subcutaneous tissue disorders (SOC, AEs); the following result is shown for the severe AEs of the SOC ”skin and subcutaneous tissue disorders” included in the results on AEs: 41 (20.4) vs. 2 (1.0); HR: 15.28 [3.66; 63.84]; p < 0.001; Kaplan-Meier curve see Figure 96.
q. Operationalized as renal and urinary disorders (SOC, severe AEs).
r. Discrepancy between CI and p-value due to different calculation methods.

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

Study (data cut-off) outcome category outcome	Enfortumab vedotin + pembrolizumab		Carboplatin + gemcitabine		Enfortumab vedotin + pembrolizumab vs. carboplatin + gemcitabine
	N	median time to event in months [95% CI] patients with event n (%)	N	median time to event in months [95% CI] patients with event n (%)	HR [95% CI]; p-value

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

Based on the available information, at most hints, e.g. of an added benefit, can be determined for all outcomes due to the limited certainty of conclusions (see Section 2.1.3 of this addendum and dossier assessment A24-98).

When interpreting the results on side effects, it should be noted that due to the fixed treatment duration and the associated discontinuation of observation in the comparator arm, the effect estimate only covers approximately the first 6 months after randomization (for reasons, see dossier assessment A24-98).

Mortality

Overall survival

For the outcome of overall survival, a statistically significant difference was found in favour of enfortumab vedotin + pembrolizumab in comparison with carboplatin + gemcitabine. The 3 sensitivity analyses presented by the company, in which patients in the comparator arm for whom maintenance treatment with avelumab would potentially have been indicated and who died without maintenance treatment were accounted for differently (see dossier assessment A24-98), also showed a statistically significant difference in favour of enfortumab vedotin + pembrolizumab compared with cisplatin + gemcitabine in each case. This effect is also retained in sensitivity analysis 2, which is based on the maximum assumption that all these patients in the comparator arm would have survived to the present data cut-off. However, the effect size and the associated extent are smaller in this analysis than in the sensitivity analyses 1 and 3 and in the main analysis. Since the extreme assumption underlying sensitivity analysis 2, namely that all patients in the comparator arm who did not receive maintenance treatment

with avelumab, although this would have been possible, survive until the end of observation, is even more relevant for the present 2nd data cut-off with a correspondingly longer observation period than for the 1st data cut-off, this does not call into question the extent of the added benefit in the present data situation. There is a hint of added benefit of enfortumab vedotin + pembrolizumab in comparison with the ACT. The extent of the added benefit is major both in the main analysis and in sensitivity analyses 1 and 3 (see Section 2.3.3.1).

Morbidity

Worst pain (BPI-SF item 3)

For the outcome of worst pain (recorded using the BPI-SF item 3), a statistically significant difference was found in favour of enfortumab vedotin + pembrolizumab in comparison with carboplatin + gemcitabine. However, there is an effect modification by the characteristic of metastases (see Section 2.3.2.4). For patients with visceral metastases, there was no hint of an added benefit of enfortumab vedotin + pembrolizumab versus the ACT; an added benefit is therefore not proven for this patient group. There was a hint of an added benefit of enfortumab vedotin + pembrolizumab versus the ACT for patients with exclusively lymph node metastases.

Pain interference (BPI-SF items 9a–g)

No statistically significant difference between treatment groups was shown for the outcome of pain interference (recorded using the BPI-SF items 9a–g). There is no hint of an added benefit of enfortumab vedotin + pembrolizumab in comparison with the ACT; an added benefit is therefore not proven.

Symptoms

EORTC QLQ-C30

Fatigue

No statistically significant difference between treatment groups was found for the outcome of fatigue. However, there is an effect modification by the characteristic of sex (see Section 2.3.2.4). For women, there is a hint of added benefit of enfortumab vedotin + pembrolizumab in comparison with the ACT. For men, there is no hint of an added benefit of enfortumab vedotin + pembrolizumab in comparison with the ACT; an added benefit is therefore not proven for men.

Nausea and vomiting

For the outcome of nausea and vomiting, there was a statistically significant difference in favour of enfortumab vedotin + pembrolizumab in comparison with carboplatin + gemcitabine. For this outcome of the non-serious/non-severe symptoms category, however, the extent of the effect was no more than marginal (see Section 2.3.3.1).

There is no hint of an added benefit of enfortumab vedotin + pembrolizumab in comparison with the ACT; an added benefit is therefore not proven.

Pain, dyspnoea, insomnia, appetite loss and diarrhoea

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

Constipation

For the outcome of constipation, a statistically significant difference was found in favour of enfortumab vedotin + pembrolizumab in comparison with carboplatin + gemcitabine. However, there is an effect modification by the characteristic of metastases (see Section 2.3.2.4). For both patients with visceral metastases and patients with exclusively lymph node metastases, there is a hint of added benefit of enfortumab vedotin + pembrolizumab versus the ACT, however, with a differing extent (see Section 2.3.3.1).

Health status

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

Health-related quality of life

EORTC QLQ-C30

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

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

Role functioning and emotional functioning

A statistically significant difference was neither shown for the outcome of role functioning nor for the outcome of emotional functioning. However, there is an effect modification by the characteristic of sex in each case (see Section 2.3.2.4). For women, there is a hint of added benefit of enfortumab vedotin + pembrolizumab in comparison with the ACT. For men, there is no hint of an added benefit of enfortumab vedotin + pembrolizumab in comparison with the ACT; an added benefit is therefore not proven for men.

Side effects

SAEs and discontinuation due to AEs

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

Severe AEs

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

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

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

Severe nephrotoxicity (severe AEs)

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

Other specific AEs

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

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

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

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

2.3.2.4 Subgroups and other effect modifiers

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

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

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

Only the results with an effect modification with a statistically significant interaction between treatment and subgroup characteristic (p-value < 0.05) are presented. In addition, subgroup results are presented only if there is a statistically significant and relevant effect in at least one subgroup. Subgroup results where the extent does not differ between subgroups are not presented.

The results are presented in Table 18. The Kaplan-Meier curves on the subgroup results are presented in Appendix C.2.

Table 18: Subgroups (morbidity, health-related quality of life) – RCT, direct comparison: enfortumab vedotin + pembrolizumab vs. carboplatin + gemcitabine (subpopulation: cisplatin unsuitable) (multipage table)

Study outcome characteristic subgroup	Enfortumab vedotin + pembrolizumab		Carboplatin + gemcitabine		Enfortumab vedotin + pembrolizumab vs. carboplatin + gemcitabine	
	N	median time to event in months [95 % CI] patients with event n (%)	N	median time to event in months [95 % CI] patients with event n (%)	HR [95% CI][a]	p-value[a]
EV-302/KN-A39 (2nd data cut-off 08 August 2024)						
Worst pain (BPI-SF item 3 - time to first deterioration[b])						
Metastases						
Visceral metastases	148	2.8 [1.1; 5.9] 69 (46.6)	157	1.7 [0.8; 2.4] 81 (51.6)	0.89 [0.60; 1.30]	0.509
Lymph nodes only	43	34.2 [1.5; NC] 17 (39.5)	37	0.5 [0.2; 2.4] 22 (59.5)	0.32 [0.14; 0.73]	0.006
					Interaction:	0.029[c]

Table 18: Subgroups (morbidity, health-related quality of life) – RCT, direct comparison: enfortumab vedotin + pembrolizumab vs. carboplatin + gemcitabine (subpopulation: cisplatin unsuitable) (multipage table)

Study outcome characteristic subgroup	Enfortumab vedotin + pembrolizumab		Carboplatin + gemcitabine		Enfortumab vedotin + pembrolizumab vs. carboplatin + gemcitabine	
	N	median time to event in months [95 % CI] patients with event n (%)	N	median time to event in months [95 % CI] patients with event n (%)	HR [95% CI][a]	p-value[a]
Symptoms (EORTC QLQ-C30, fatigue – time to first deterioration[d])						
Sex						
Female	56	0.7 [0.4; 2.2] 31 (55.4)	51	0.4 [0.2; 0.6] 35 (68.6)	0.21 [0.09; 0.48]	< 0.001
Male	146	0.5 [0.4; 0.7] 100 (68.5)	151	0.4 [0.4; 0.6] 97 (64.2)	0.97 [0.72; 1.32]	0.859
					Interaction:	0.030[c]
Symptoms (EORTC QLQ-C30, constipation – time to first deterioration[d])						
Metastases						
Visceral metastases	148	2.0 [0.9; 3.1] 74 (50.0)	157	0.6 [0.4; 1.7] 80 (51.0)	0.59 [0.41; 0.88]	0.010
Lymph nodes only	43	2.1 [0.6; NC] 20 (46.5)	37	0.3 [0.2; 0.5] 25 (67.6)	0.33 [0.14; 0.78]	0.008
					Interaction:	0.017[c]
Health-related quality of life (EORTC QLQ-C30, role functioning – time to first deterioration[e])						
Sex						
Female	56	0.7 [0.4; 1.1] 35 (62.5)	51	0.2 [0.2; 0.4] 37 (72.5)	0.52 [0.28; 0.97]	0.031
Male	146	0.7 [0.4; 1.1] 91 (62.3)	151	0.4 [0.4; 0.8] 100 (66.2)	0.85 [0.61; 1.19]	0.356
					Interaction:	0.021[c]
Health-related quality of life (EORTC QLQ-C30, emotional functioning - time to first deterioration[e])						
Sex						
Female	56	10.7 [1.8; NC] 20 (35.7)	51	0.9 [0.4; 1.1] 27 (52.9)	0.36 [0.17; 0.79]	0.010
Male	146	3.2 [1.7; 9.4] 72 (49.3)	151	2.7 [1.3; 5.9] 69 (45.7)	0.89 [0.61; 1.31]	0.574
					Interaction:	0.012[c]

Table 18: Subgroups (morbidity, health-related quality of life) – RCT, direct comparison: enfortumab vedotin + pembrolizumab vs. carboplatin + gemcitabine (subpopulation: cisplatin unsuitable) (multipage table)

Study outcome characteristic subgroup	Enfortumab vedotin + pembrolizumab		Carboplatin + gemcitabine		Enfortumab vedotin + pembrolizumab vs. carboplatin + gemcitabine	
	N	median time to event in months [95 % CI] patients with event n (%)	N	median time to event in months [95 % CI] patients with event n (%)	HR [95% CI][a]	p-value[a]

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

BPI-SF: Brief Pain Inventory – Short Form; CI: confidence interval; EORTC QLQ-C30: European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30; HR: hazard ratio; n: number of patients with (at least 1) event; N: number of analysed patients; NA: not achieved; NC: not calculable; RCT: randomized controlled trial

Morbidity

Worst pain (BPI-SF item 3)

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

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

Symptoms

EORTC QLQ-C30

Fatigue

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

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

Constipation

There was an effect modification by the characteristic of metastases for the outcome of constipation. A statistically significant difference in favour of enfortumab vedotin + pembrolizumab in comparison with carboplatin + gemcitabine was shown both for patients with visceral metastases and patients with exclusively lymph node metastases. In each case, there is a hint of added benefit of enfortumab vedotin + pembrolizumab in comparison with the ACT the extents of which, however, differ (see Section 2.3.3.1).

Health-related quality of life

EORTC QLQ-C30

Role functioning and emotional functioning

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

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

2.3.3 Probability and extent of added benefit

The probability and extent of added benefit at outcome level are derived below, taking into account the different outcome categories and effect sizes. The methods used for this purpose are explained in the *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 was estimated from the results presented in Section 2.3.2.3 (see Table 19).

Determination of the outcome category for symptom outcomes

For the symptoms outcomes below, the company's documents do not state whether they are serious/severe or non-serious/non-severe. Reasoning is provided for the classification of these outcomes.

Worst pain (BPI-SF item 3)

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

Symptoms (EORTC QLQ-C30)

Fatigue, nausea and vomiting as well as constipation

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

Table 19: Extent of added benefit at outcome level: enfortumab vedotin + pembrolizumab vs. carboplatin + gemcitabine (subpopulation: cisplatin unsuitable) (multipage table)

Outcome category **outcome** **effect modifier** **subgroup**	**Enfortumab vedotin + pembrolizumab vs. carboplatin + gemcitabine** **median time to event (months) or proportion of events (%)** **effect estimation [95% CI];** **p-value** **probability**[a]	**Derivation of extent**[b]
Outcomes with observation over the entire study duration		
Mortality		
Overall survival		Outcome category: mortality $CI_u < 0.85$ added benefit; extent: “major”
Main analysis	25.6 vs. 12.9 months HR: 0.49 [0.38; 0.63]; p < 0.001 probability: “hint”	
Sensitivity analysis 1[c]	25.6 vs. 15.0 months HR: 0.61 [0.47; 0.80]; p < 0.001	
Sensitivity analysis 2[d]	25.6 vs. 15.9 months HR: 0.71 [0.55; 0.93]; p = 0.011	
Sensitivity analysis 3[e]	25.6 vs. 14.7 months HR: 0.54 [0.42; 0.70]; p < 0.001	
Outcomes with shortened observation period		
Morbidity		
Worst pain (BPI-SF item 3 - time to first deterioration)		
Metastases		
Visceral metastases	2.8 vs. 1.7 months HR: 0.89 [0.60; 1.30]; p = 0.509	Lesser/added benefit not proven
Lymph nodes only	34.2 vs. 0.5 months HR: 0.32 [0.14; 0.73]; p = 0.006 probability: “hint”	Outcome category "non-serious/non-severe symptoms/late complications" $CI_u < 0.80$ added benefit; extent: “considerable”
Pain interference (BPI-SF items 9a-g – time to first deterioration)	2.7 vs. 1.3 months HR: 0.74 [0.54; 1.02]; p = 0.069	Lesser/added benefit not proven
Symptoms (EORTC QLQ-C30 – time to first deterioration)		
Fatigue		
Sex		

Table 19: Extent of added benefit at outcome level: enfortumab vedotin + pembrolizumab vs. carboplatin + gemcitabine (subpopulation: cisplatin unsuitable) (multipage table)

Outcome category **outcome** **effect modifier** **subgroup**	**Enfortumab vedotin + pembrolizumab vs. carboplatin + gemcitabine** **median time to event (months) or proportion of events (%)** **effect estimation [95% CI];** **p-value** **probability[a]**	**Derivation of extent[b]**
Female	0.7 vs. 0.4 months HR: 0.21 [0.09; 0.48]; p < 0.001 probability: “hint”	Outcome category "non-serious/non-severe symptoms/late complications" CI_u < 0.80 added benefit; extent: “considerable”
Male	0.5 vs. 0.4 months HR: 0.97 [0.72; 1.32]; p = 0.859	Lesser/added benefit not proven
Nausea and vomiting	1.8 vs. 1.1 months HR: 0.72 [0.54; 0.97]; p = 0.037 probability: “hint”	Outcome category: non-serious/non-severe symptoms/late complications 0.90 ≤ CI_u < 1.00 lesser/added benefit not proven[f]
Pain	1.1 vs. 0.9 months HR: 0.79 [0.59; 1.06]; p = 0.110	Lesser/added benefit not proven
Dyspnoea	2.0 vs. 1.5 months HR: 0.85 [0.62; 1.15]; p = 0.300	Lesser/added benefit not proven
Insomnia	1.6 vs. 1.3 months HR: 0.87 [0.64; 1.20]; p = 0.409	Lesser/added benefit not proven
Appetite loss	0.9 vs. 1.1 months HR: 0.96 [0.71; 1.30]; p = 0.859	Lesser/added benefit not proven
Constipation		
Metastases		
Visceral metastases	2.0 vs. 0.6 months HR: 0.59 [0.41; 0.88]; p = 0.010 probability: “hint”	Outcome category: non-serious/non-severe symptoms/late complications 0.80 ≤ CI_u < 0.90 added benefit, extent: “minor”
Lymph nodes only	2.1 vs. 0.3 months HR: 0.33 [0.14; 0.78]; p = 0.008 probability: “hint”	Outcome category "non-serious/non-severe symptoms/late complications" CI_u < 0.80 added benefit; extent: “considerable”
Diarrhoea	2.0 vs. 4.6 months HR: 1.33 [0.96; 1.85]; p = 0.075	Lesser/added benefit not proven

Table 19: Extent of added benefit at outcome level: enfortumab vedotin + pembrolizumab vs. carboplatin + gemcitabine (subpopulation: cisplatin unsuitable) (multipage table)

Outcome category **outcome** **effect modifier** **subgroup**	**Enfortumab vedotin + pembrolizumab vs. carboplatin + gemcitabine** **median time to event (months) or proportion of events (%)** **effect estimation [95% CI];** **p-value** **probability**[a]	**Derivation of extent**[b]
Health status (EQ-5D VAS, time to first deterioration)	1.5 vs. 1.3 months HR: 0.89 [0.66; 1.21]; p = 0.508	Lesser/added benefit not proven
Health-related quality of life		
EORTC-QLQ C30 – time to first deterioration		
Global health status	1.1 vs. 0.9 months HR: 0.96 [0.71; 1.30]; p = 0.841	Lesser/added benefit not proven
Physical functioning	1.1 vs. 0.7 months HR: 0.82 [0.61; 1.09]; p = 0.168	Lesser/added benefit not proven
Role functioning Sex		
Female	0.7 vs. 0.2 months HR: 0.52 [0.28; 0.97]; p = 0.031 probability: “hint”	Outcome category: health-related quality of life $0.90 \leq CI_u < 1.00$ added benefit, extent: “minor”
Male	0.7 vs. 0.4 months HR: 0.85 [0.61; 1.19]; p = 0.356	Lesser/added benefit not proven
Emotional functioning Sex		
Female	10.7 vs. 0.9 months HR: 0.36 [0.17; 0.79]; p = 0.010 probability: “hint”	Outcome category: health-related quality of life $0.75 \leq CI_u < 0.90$ added benefit; extent: “considerable”
Male	3.2 vs. 2.7 months HR: 0.89 [0.61; 1.31]; p = 0.574	Lesser/added benefit not proven
Cognitive functioning	1.5 vs. 0.9 months HR: 0.80 [0.59; 1.07]; p = 0.140	Lesser/added benefit not proven
Social functioning	0.9 vs. 0.9 months HR: 1.04 [0.77; 1.41]; p = 0.752	Lesser/added benefit not proven

Table 19: Extent of added benefit at outcome level: enfortumab vedotin + pembrolizumab vs. carboplatin + gemcitabine (subpopulation: cisplatin unsuitable) (multipage table)

Outcome category **outcome** **effect modifier** **subgroup**	**Enfortumab vedotin + pembrolizumab vs. carboplatin + gemcitabine** **median time to event (months) or proportion of events (%)** **effect estimation [95% CI];** **p-value** **probability**[a]	**Derivation of extent**[b]
Side effects[g]		
SAEs	7.9 vs. 5.4 months HR: 0.87 [0.64; 1.18]; p = 0.365	Greater/lesser harm not proven
Severe AEs	2.6 vs. 0.7 months HR: 0.46 [0.36; 0.58]; p < 0.001 probability: “hint”	Outcome category: serious/severe side effects CI_u < 0.75; risk ≥ 5% lesser harm, extent: “major”
Discontinuation due to AEs[h]	11.5 vs. NA months HR: 1.35 [0.88; 2.06]; p = 0.169	Greater/lesser harm not proven
Immune-related SAEs	NA vs. NA months HR: 6.93 [1.58; 30.31] HR: 0.14 [0.03; 0.63][i]; p = 0.003 probability: “hint”	Outcome category: serious/severe side effects CI_u < 0.75; risk ≥ 5% greater harm, extent: “major”
Immune-related severe AEs	NA vs. NA months HR: 15.92 [3.82; 66.38] HR: 0.06 [0.02; 0.26][i]; p < 0.001 probability: “hint”	Outcome category: serious/severe side effects CI_u < 0.75; risk ≥ 5% greater harm, extent: “major”
peripheral neuropathy (AEs)	4.5 vs. NA months HR: 6.41 [3.83; 10.73] HR: 0.16 [0.09; 0.26][i]; p < 0.001 probability: “hint”	Outcome category: non-serious/non-severe side effects CI_u < 0.80 greater harm, extent: “considerable”
Skin reactions (AEs)	0.6 vs. NA months HR: 4.95 [3.60; 6.81] HR: 0.20 [0.15; 0.28][i]; p < 0.001 probability: “hint”	Outcome category: non-serious/non-severe side effects CI_u < 0.80 greater harm, extent: “considerable”
Severe hyperglycaemia (severe AEs)	NA vs. NA months HR: 10.71 [1.38; 82.92] HR: 0.09 [0.01; 0.72][i]; p = 0.005 probability: “hint”	Outcome category: serious/severe side effects CI_u < 0.75; risk ≥ 5% greater harm, extent: “major”

Table 19: Extent of added benefit at outcome level: enfortumab vedotin + pembrolizumab vs. carboplatin + gemcitabine (subpopulation: cisplatin unsuitable) (multipage table)

Outcome category **outcome** **effect modifier** **subgroup**	**Enfortumab vedotin + pembrolizumab vs. carboplatin + gemcitabine** **median time to event (months) or proportion of events (%)** **effect estimation [95% CI];** **p-value** **probability**[a]	**Derivation of extent**[b]
severe nephrotoxicity, (severe AEs)	NA vs. NA months HR: 1.12 [0.57; 2.23]; p = 0.736	Greater/lesser harm not proven
Other specific AEs		
Constipation (AEs)	NA vs. NA months HR: 0.45 [0.30; 0.66]; p < 0.001 probability: “hint”	Outcome category: non-serious/non-severe side effects CI_u < 0.80 lesser harm, extent: “considerable”
Diarrhoea (AEs)	23.9 vs. NA months HR: 2.30 [1.48; 3.56] HR: 0.43 [0.28; 0.67][i]; p < 0.001 probability: “hint”	Outcome category: non-serious/non-severe side effects CI_u < 0.80 greater harm, extent: “considerable”
Dysgeusia (AEs)	NA vs. NA months HR: 4.83 [2.35; 9.92] HR: 0.21 [0.10; 0.43][i]; p < 0.001 probability: “hint”	Outcome category: non-serious/non-severe side effects CI_u < 0.80 greater harm, extent: “considerable”
Eye disorders (AEs)	27.9 vs. NA months HR: 3.85 [2.04; 7.26] HR: 0.26 [0.14; 0.49][i]; p < 0.001 probability: “hint”	Outcome category: non-serious/non-severe side effects CI_u < 0.80 greater harm, extent: “considerable”
Endocrine disorders (AEs)	NA vs. NA months HR: 5.47 [1.90; 15.79] HR: 0.18 [0.06; 0.53][i]; p < 0.001 probability: “hint”	Outcome category: non-serious/non-severe side effects CI_u < 0.80 greater harm, extent: “considerable”
Blood and lymphatic system disorders (severe AEs)	NA vs. 1.3 months HR: 0.14 [0.09; 0.20]; p < 0.001 probability: “hint”	Outcome category: serious/severe side effects CI_u < 0.75; risk ≥ 5% lesser harm, extent: “major”

Table 19: Extent of added benefit at outcome level: enfortumab vedotin + pembrolizumab vs. carboplatin + gemcitabine (subpopulation: cisplatin unsuitable) (multipage table)

Outcome category **outcome** **effect modifier** **subgroup**	**Enfortumab vedotin + pembrolizumab vs. carboplatin + gemcitabine** **median time to event (months) or proportion of events (%)** **effect estimation [95% CI];** **p-value** **probability**[a]	**Derivation of extent**[b]
acute kidney injury (severe AEs)	NA vs. NA months HR: 3.05 [0.99; 9.36] HR: 0.33 [0.11; 1.01][i]; p = 0.041 probability: “hint”	Outcome category: serious/severe side effects greater harm[j], extent: "minor"[k]

a. Probability provided if there is a statistically significant and relevant effect.
b. Depending on the outcome category, estimations of effect size are made with different limits based on the upper limit of the confidence interval (CI_u).
c. Censoring at the time of death: avelumab-eligible patients who had not received avelumab and died were censored at the time of death.
d. Censoring at data cut-off: avelumab-eligible patients who had not received avelumab and died were censored at the time of data cut-off.
e. Modified time of death: avelumab-eligible patients who had not received avelumab and died were censored with a modified time of death. A simplified assumption was made that the patients would have benefited from treatment with avelumab to the extent shown in the approval study of avelumab (JAVELIN Bladder 100); see dossier assessment A24-98 for explanation.
f. The extent of the effect in this non-serious/non-severe outcome was no more than marginal.
g. The fixed treatment duration and the associated discontinuation of observation after the end of study medication in the comparator arm mean that the effect estimate only reflects approximately the first 6 months after randomization.
h. For the outcome of discontinuation due to AEs, see also Addendum A25-23 [15].
i. Institute's calculation; reversed direction of effect to enable use of limits to derive the extent of the added benefit.
j. The result of the statistical test is decisive for the derivation of the added benefit.
k. Discrepancy between CI and p-value due to different calculation methods; the extent is rated as minor.

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

2.3.3.2 Overall conclusion on added benefit

Table 20 summarizes the results taken into account in the overall conclusion on the extent of added benefit.

Table 20: Positive and negative effects from the assessment of enfortumab vedotin + pembrolizumab in comparison with the ACT (subpopulation: cisplatin unsuitable) (multipage table)

Positive effects	**Negative effects**
Outcomes with observation over the entire study duration	
Mortality ▪ overall survival: hint of an added benefit – extent: "major"	–
Outcomes with shortened observation period[a]	
Health-related quality of life ▪ emotional functioning (EORTC QLQ-C30) ▫ sex (female): hint of an added benefit extent: "considerable" ▪ role functioning (EORTC-QLQ-C30) ▫ sex (female): hint of added benefit - extent: "minor"	–
Non-serious/non-severe symptoms/late complications ▪ worst pain (BPI-SF Item 3) ▫ metastases (lymph nodes only): hint of added benefit – extent: "considerable" ▪ fatigue (EORTC QLQ-C30) ▫ sex (female): hint of an added benefit extent: "considerable" ▪ constipation (EORTC QLQ-C30) ▫ metastases (visceral metastases): hint of added benefit – extent: "minor" ▫ metastases (lymph nodes only): hint of added benefit – extent: "considerable"	–
Serious/severe side effects ▪ severe AEs: hint of lesser harm – extent: "major" ▫ blood and lymphatic system disorders (severe AEs): hint of lesser harm – extent: "major"	Serious/severe side effects ▪ immune-related SAEs, immune-related severe AEs, severe hyperglycaemia (severe AEs): each hint of greater harm – extent: "major" ▪ acute kidney injury (severe AEs): hint of greater harm – extent: "minor"
Non-serious/non-severe side effects ▪ constipation (AEs): hint of lesser harm – extent: "considerable"	Non-serious/non-severe side effects ▪ peripheral neuropathy (AEs), skin reactions (AEs), diarrhoea (AEs), dysgeusia (AEs), eye disorders (AEs), endocrine disorder (AEs): hint of greater harm in each case - extent: "considerable"
For the outcome of discontinuation due to AEs, see also Addendum A25-23 [15].	
a. For the side effect outcomes, the fixed treatment duration and the associated discontinuation of observation after the end of study medication in the comparator arm mean that the effect estimate only reflects approximately the first 6 months after randomization. AE: adverse event; BPI-SF: Brief Pain Inventory-Short Form; EORTC: European Organisation for Research and Treatment of Cancer; QLQ-C30: Quality of Life Questionnaire – Core 30; SAE: serious adverse event	

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

The advantage in overall survival, the extent of which is "major" both in the main analysis and in the sensitivity analyses 1 and 3 presented by the company, is decisive for the assessment. The fact that the extent of the benefit in sensitivity analysis 2, which represents the maximum assumption that all patients in the comparator arm who did not receive avelumab, although this therapy would have been suitable for them, would have survived to the present data cut-off, is not major, but only considerable, does overall not call into question the major extent of the added benefit in the present data situation.

With regard to all other outcomes, there were no changes relevant for the overall assessment compared with dossier assessment A24-98.

For the outcome of discontinuation due to AEs, see also Addendum A25-23 [15].

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

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

2.4 Summary

The data subsequently submitted by the company in the commenting procedure do not change the conclusion on the added benefit of enfortumab vedotin + pembrolizumab drawn in dossier assessment A23-98 [1].

Table 21 below shows the result of the benefit assessment of enfortumab vedotin + pembrolizumab, taking into account dossier assessment A24-98 and the present addendum.

Table 21: Enfortumab vedotin + pembrolizumab – probability and extent of added benefit

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

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

G-BA: Joint Federal Committee; ECOG-PS: Eastern Cooperative Oncology Group - Performance Status

The G-BA decides on the added benefit.

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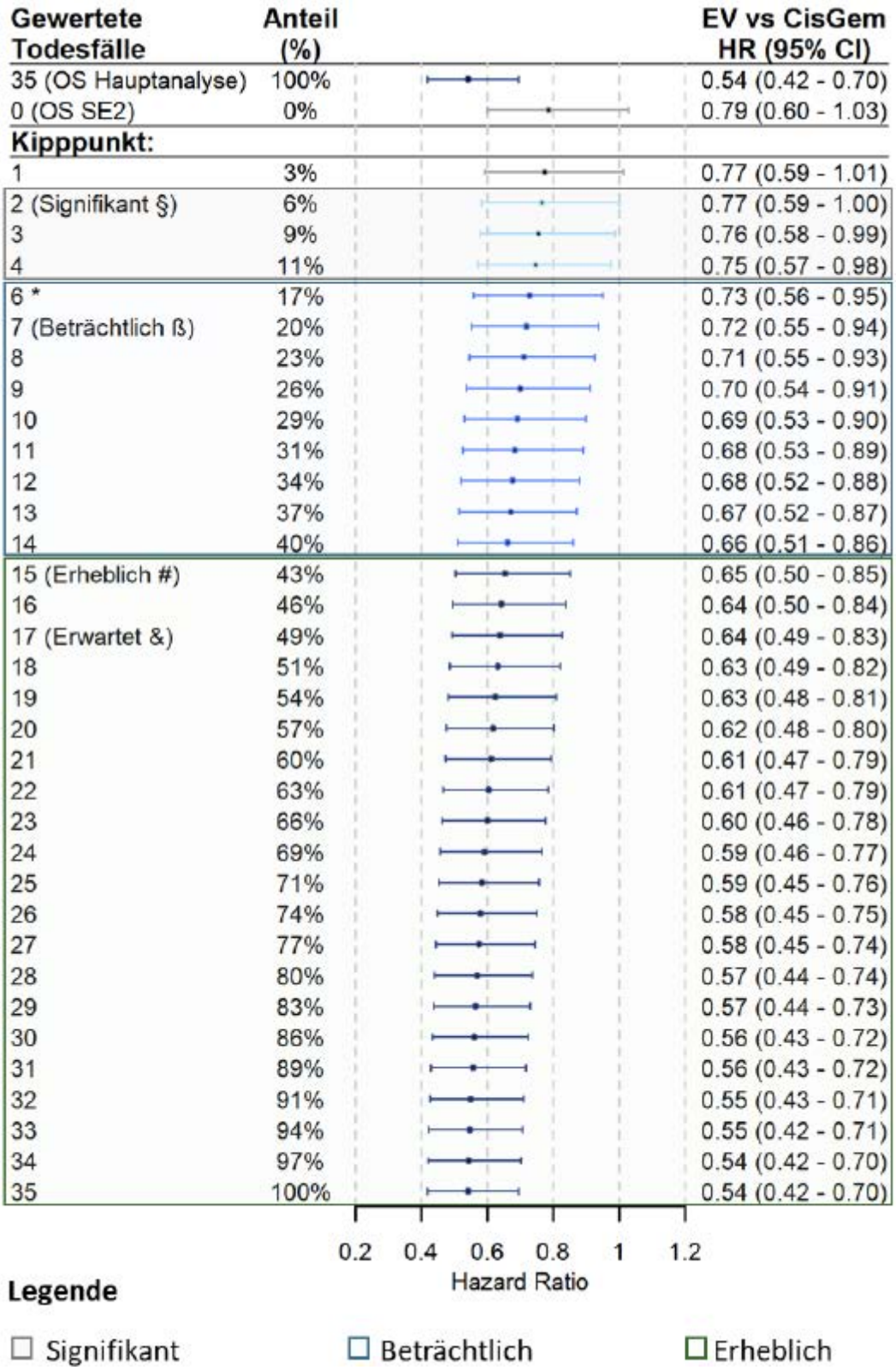
Appendix A Tipping point analyses (supplementary presentation)



Gewertete Todesfälle: deaths included in the analysis
Anteil: proportion
Hauptanalyse: main analysis

Kipppunkt:	tipping point
Signifikant:	significant
Erheblich:	major
Beträchtlich:	considerable
Erwartet:	expected
Legende:	caption

Patients in subpopulation 1 (cisplatin suitable) for whom avelumab was an option according to the company and who did not receive it and died during the observation period (N = 35) were not rated as deceased in sensitivity analysis 2, but censored at the data cut-off, which corresponds to an imputation as "survived". In the tipping point analysis for sensitivity analysis 2, death results are successively rated as such again, in ascending order (i.e. patients with the shortest survival time are the first to be rated as deceased again). HR and 95% CI each based on stratified Cox proportional hazards regression. No adjustment was made for multiple testing.

§: tipping point for statistical significance (upper limit of the 95% CI of 1.00 undercut)

ß: tipping point for considerable added benefit

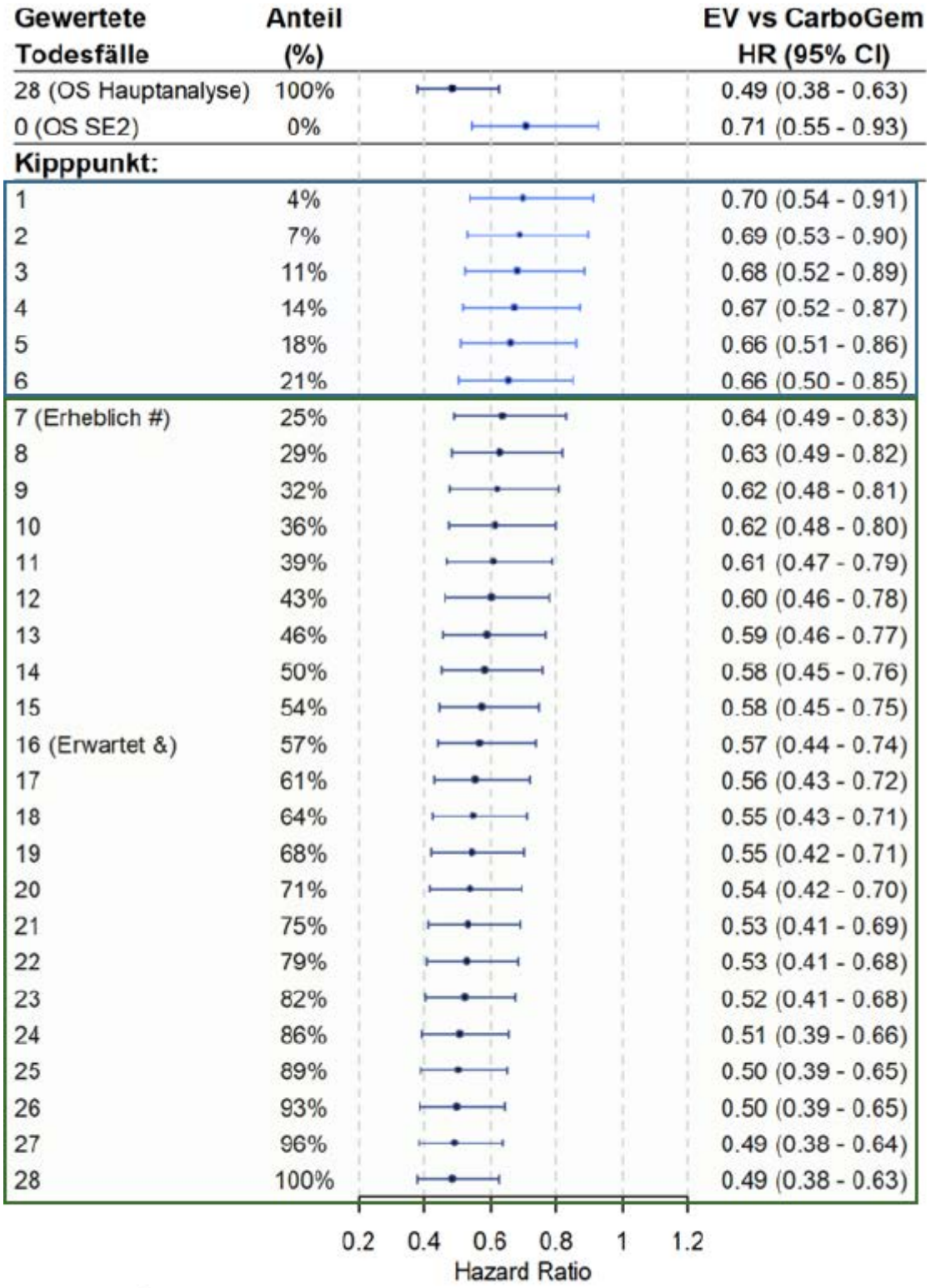
#: tipping point for major added benefit (upper limit of the 95% CI of 0.85 undercut)

&: expected proportion of deaths according to the company, based on the proportion of deaths among patients in the relevant subpopulation who had received maintenance treatment with avelumab (41/84).

*: In relation to the randomization date, two patients died on the same day.

CI: confidence interval; HR: hazard ratio

Figure 1: Tipping point analysis for the outcome of overall survival of RCT EV-302/KN-A39, 2nd data cut-off (08 August 2024), subpopulation 1 (cisplatin suitable) - supplementary presentation



Gewertete Todesfälle: deaths included in the analysis
Anteil: proportion

Hauptanalyse:	main analysis
Kipppunkt:	tipping point
Signifikant:	significant
Erheblich:	major
Beträchtlich:	considerable
Erwartet:	expected
Legende:	caption

Patients in subpopulation 2 (cisplatin unsuitable) for whom avelumab was an option according to the company and who did not receive it and died during the observation period (N = 28) were not rated as deceased in sensitivity analysis 2, but censored at the data cut-off, which corresponds to an imputation as "survived". In the tipping point analysis for sensitivity analysis 2, death results are successively rated as such again, in ascending order (i.e. patients with the shortest survival time are the first to be rated as deceased again). HR and 95% CI each based on stratified Cox proportional hazards regression. No adjustment was made for multiple testing.

#: tipping point for major added benefit (upper limit of the 95% CI of 0.85 undercut)

&: expected proportion of deaths according to the company, based on the proportion of deaths among patients in the relevant subpopulation who had received maintenance treatment with avelumab (28/49).

CI: confidence interval; HR: hazard ratio

Figure 2: Tipping point analysis for the outcome of overall survival of RCT EV-302/KN-A39, 2nd data cut-off (08 August 2024), subpopulation 2 (cisplatin unsuitable) - supplementary presentation

Appendix B Kaplan-Meier curves

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

B.1.1 Mortality

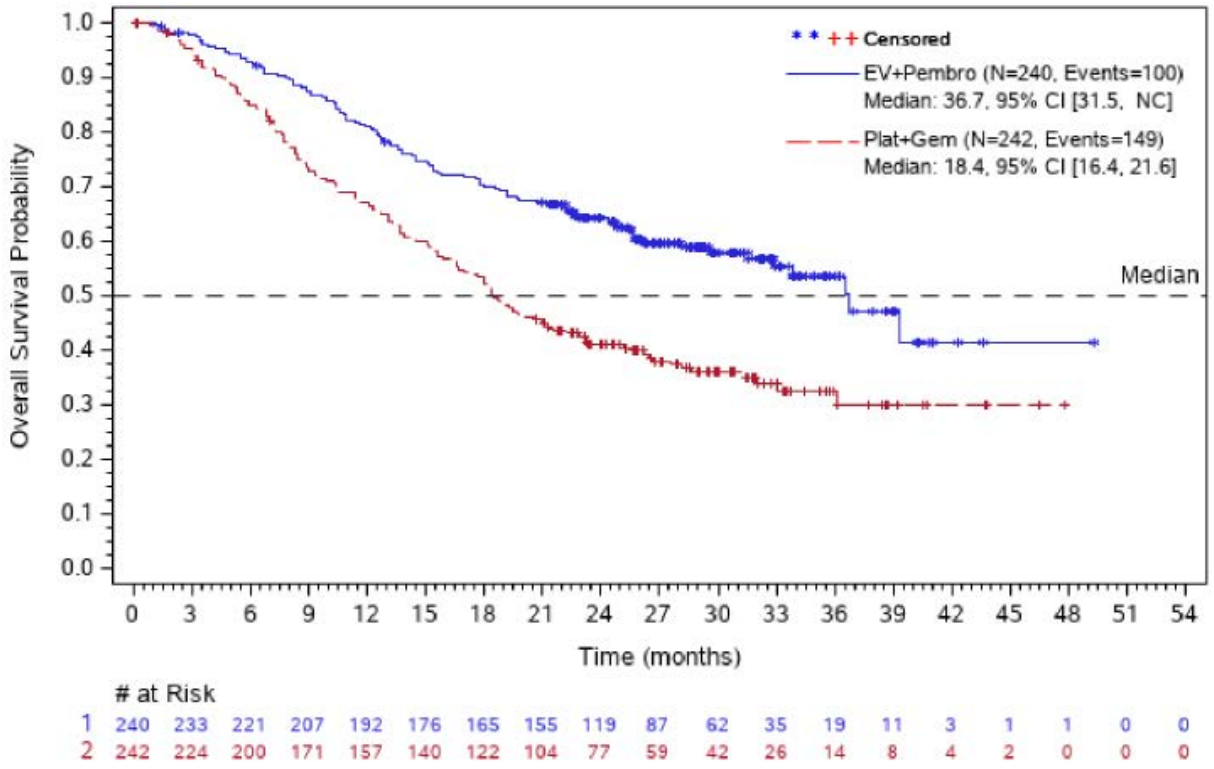


Figure 3: Kaplan-Meier curves for the outcome of overall survival of the RCT EV-302/KN-A39, 2nd data cut-off (08 August 2024), subpopulation 1 (cisplatin suitable)

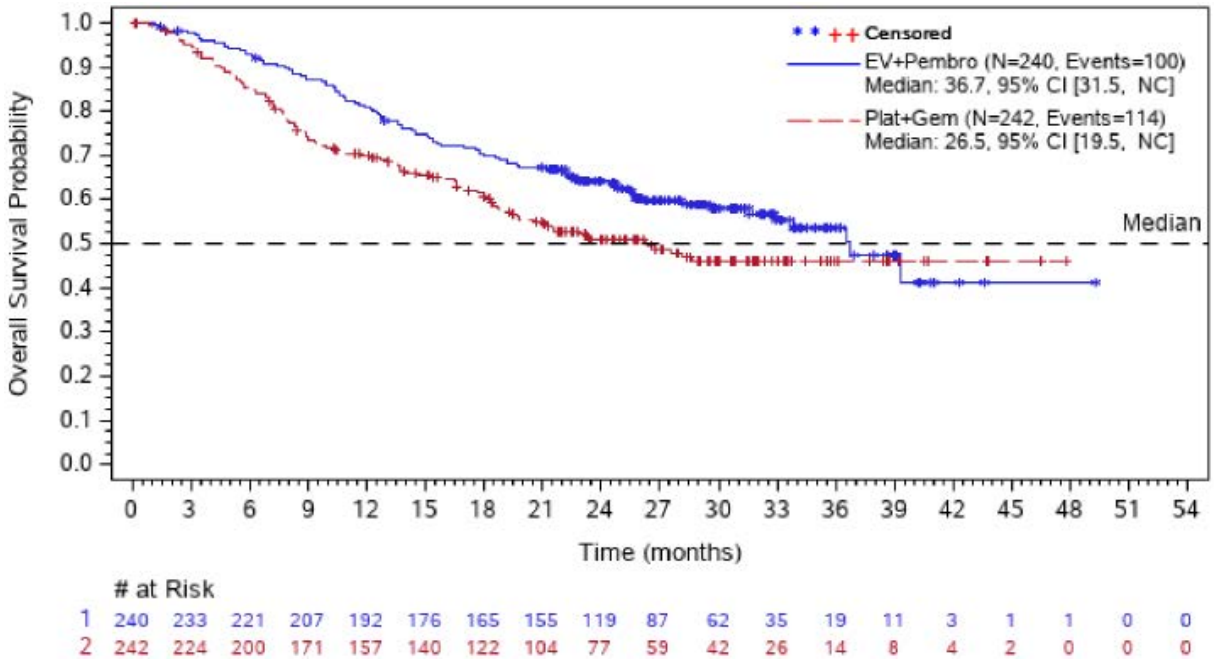


Figure 4: Kaplan-Meier curves for sensitivity analysis 1 of the company for the outcome of overall survival of the RCT EV-302/KN-A39, 2nd data cut-off (8 August 2024), subpopulation 1 (cisplatin suitable)

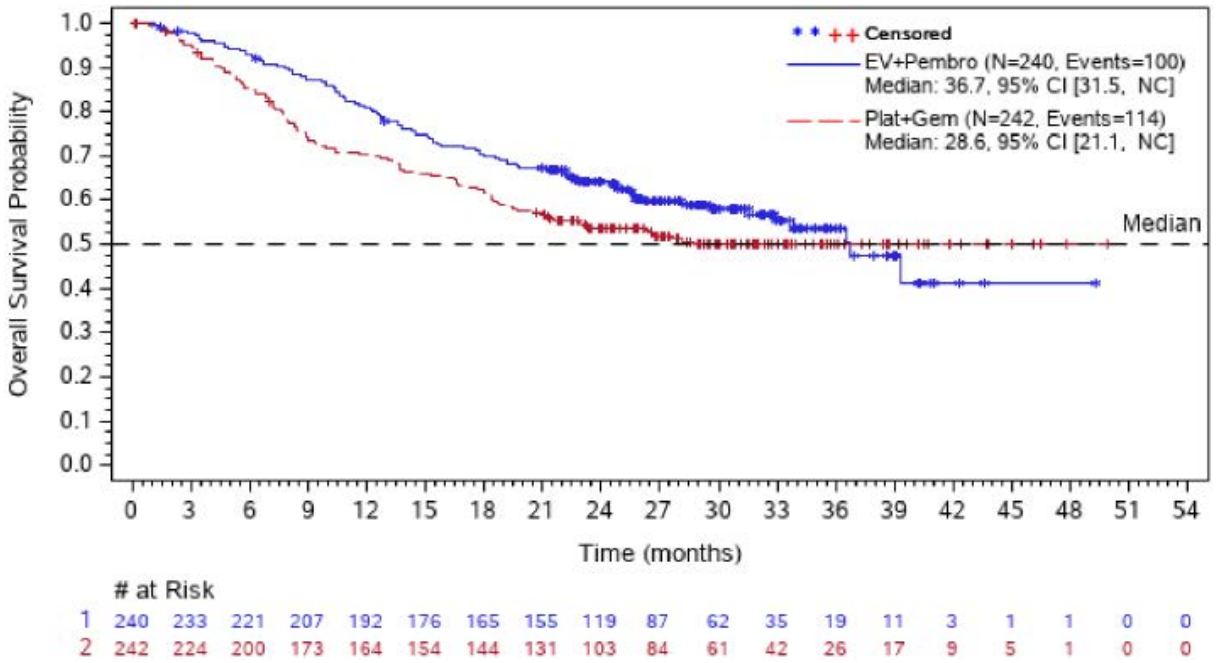


Figure 5: Kaplan-Meier curves for sensitivity analysis 2 of the company for the outcome of overall survival of RCT EV-302/KN-A39, 2nd data cut-off (8 August 2024), subpopulation 1 (cisplatin suitable)

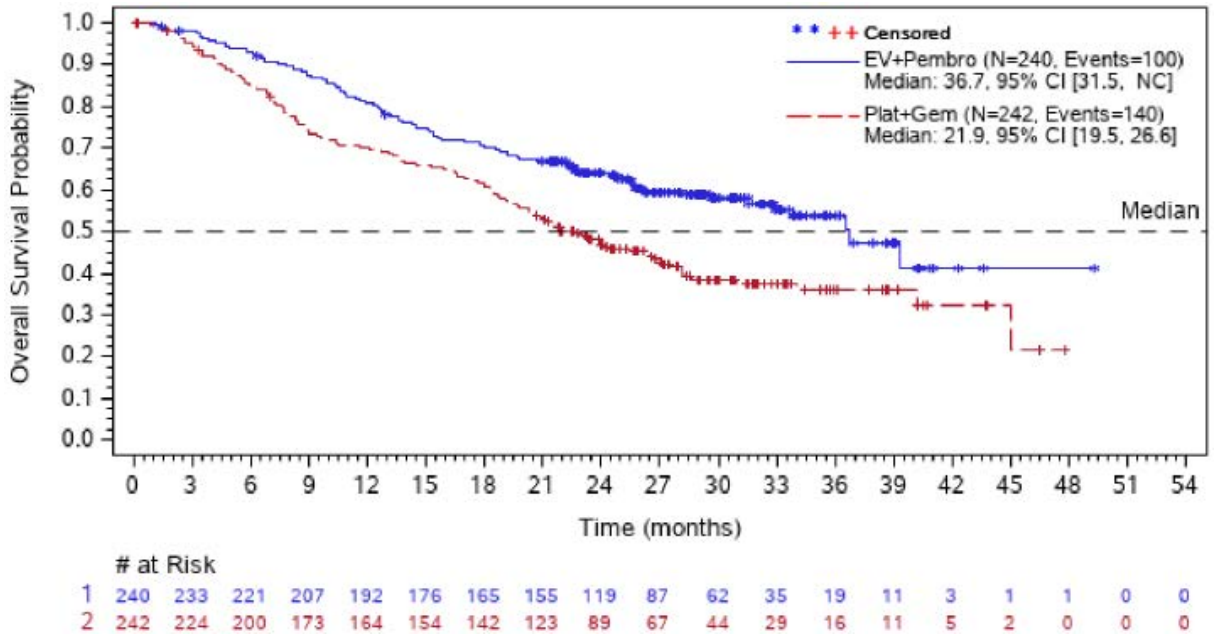


Figure 6: Kaplan-Meier curves for sensitivity analysis 3 of the company for the outcome of overall survival of the RCT EV-302/KN-A39, 2nd data cut-off (8 August 2024), subpopulation 1 (cisplatin suitable)

B.1.2 Morbidity

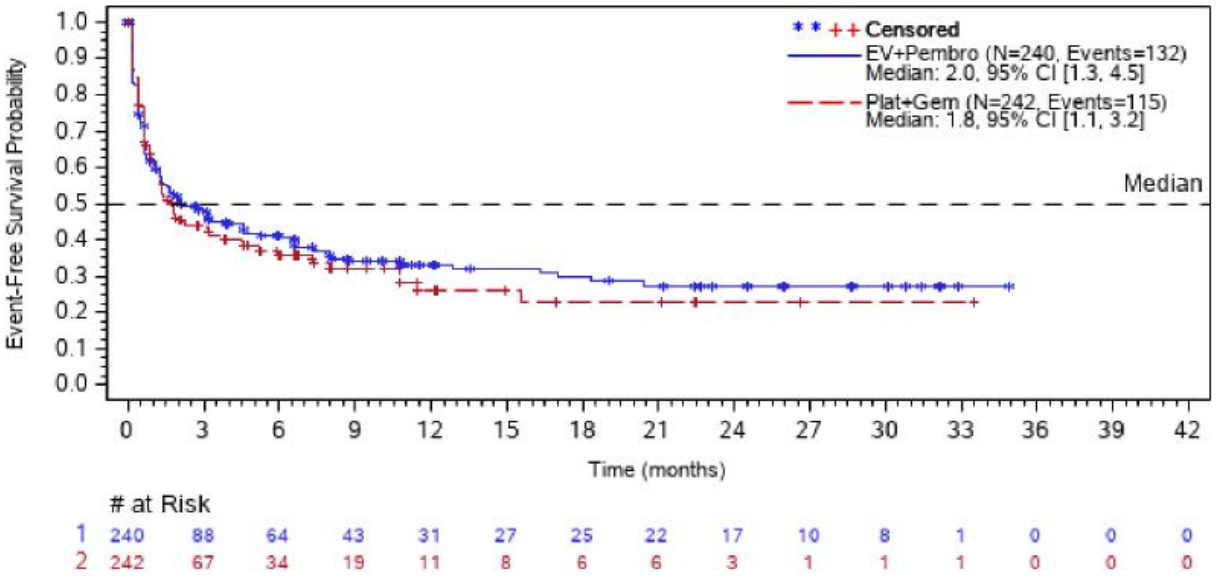


Figure 7: Kaplan-Meier curves for the outcome of worst pain (BPI-SF item 3 - time to 1st deterioration) of RCT EV-302/KN-A39, 2nd data cut-off (08 August 2024), subpopulation 1 (cisplatin suitable)

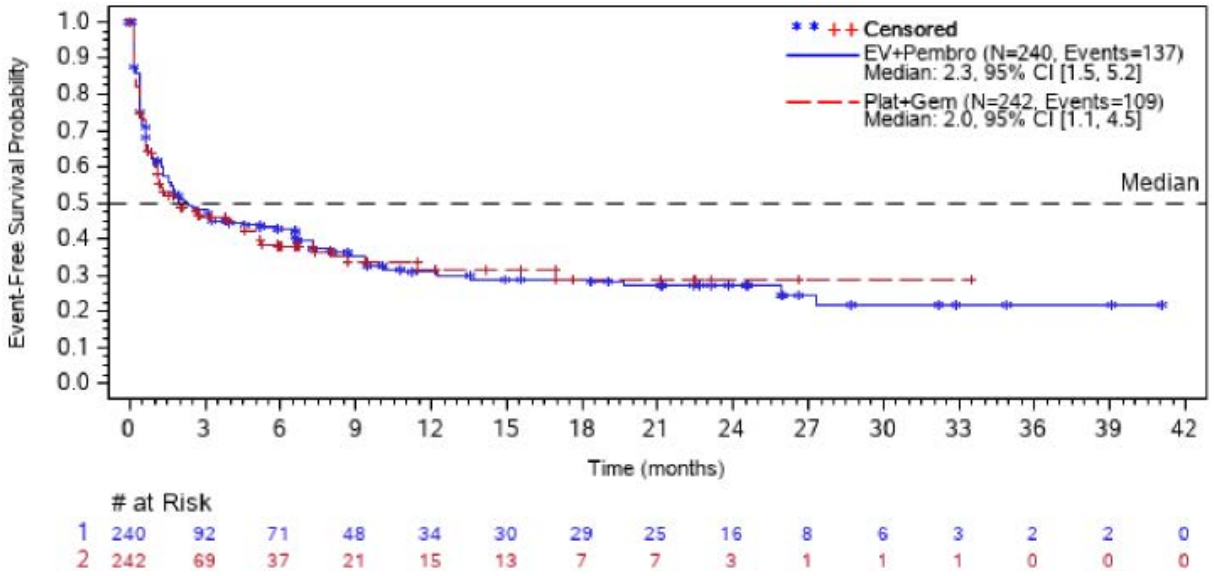


Figure 8: Kaplan-Meier curves for the outcome of pain interference (BPI-SF items 9a-9g - time to 1st deterioration) of the RCT EV-302/KN-A39, 2nd data cut-off (08 August 2024), subpopulation 1 (cisplatin suitable)

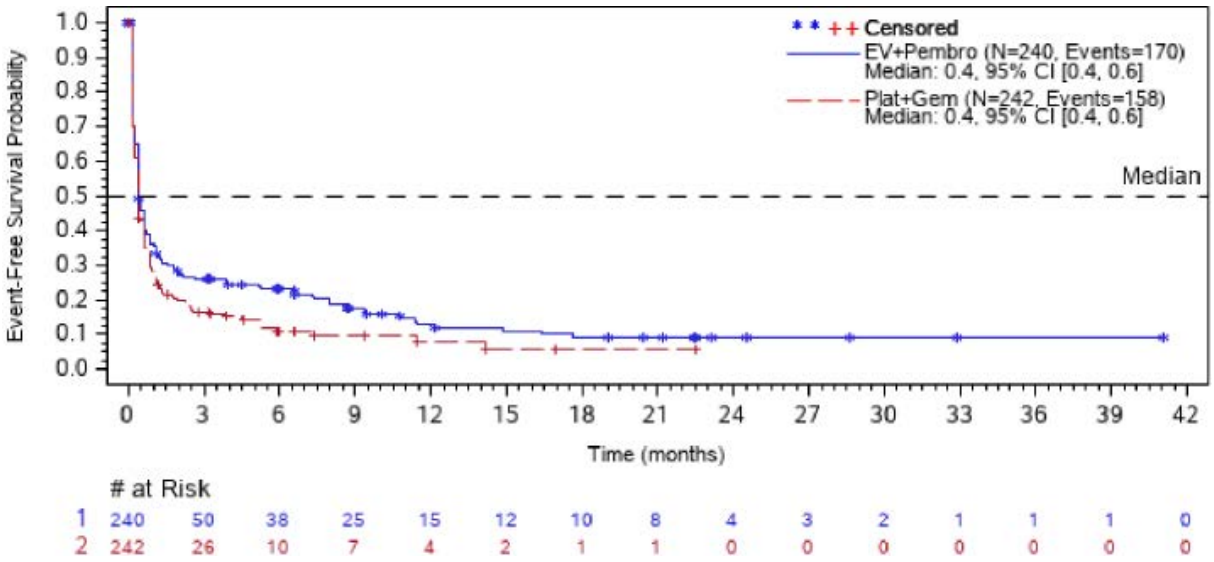


Figure 9: Kaplan-Meier curves for the outcome of fatigue (EORTC-QLQ-C30 - time to 1st deterioration) of the RCT EV-302/KN-A39, 2nd data cut-off (08 August 2024), subpopulation 1 (cisplatin suitable)

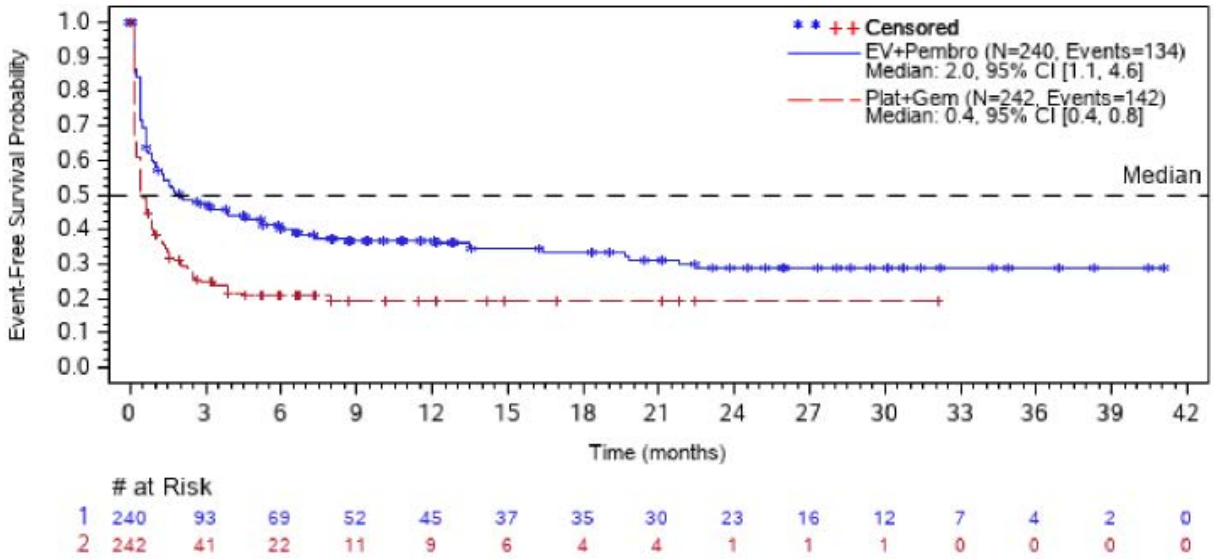


Figure 10: Kaplan-Meier curves for the outcome of nausea and vomiting (EORTC QLQ-C30 - time to 1st deterioration) of the RCT EV-302/KN-A39, 2nd data cut-off (08 August 2024), subpopulation 1 (cisplatin suitable)

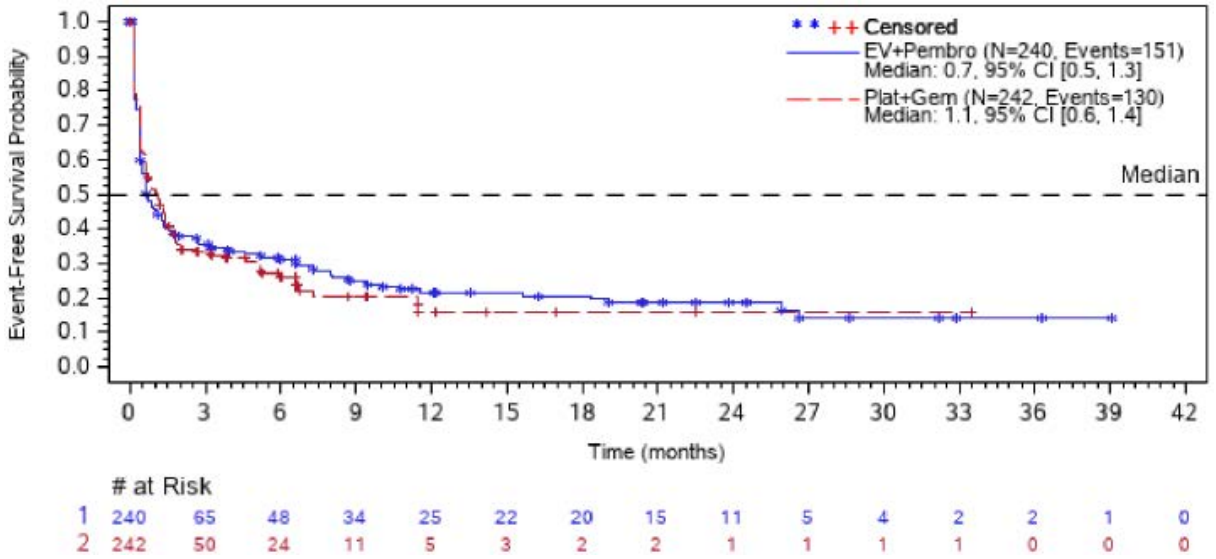


Figure 11: Kaplan-Meier curves for the outcome of pain (EORTC QLQ-C30 - time to 1st deterioration) of the RCT EV-302/KN-A39, 2nd data cut-off (08 August 2024), subpopulation 1 (cisplatin suitable)

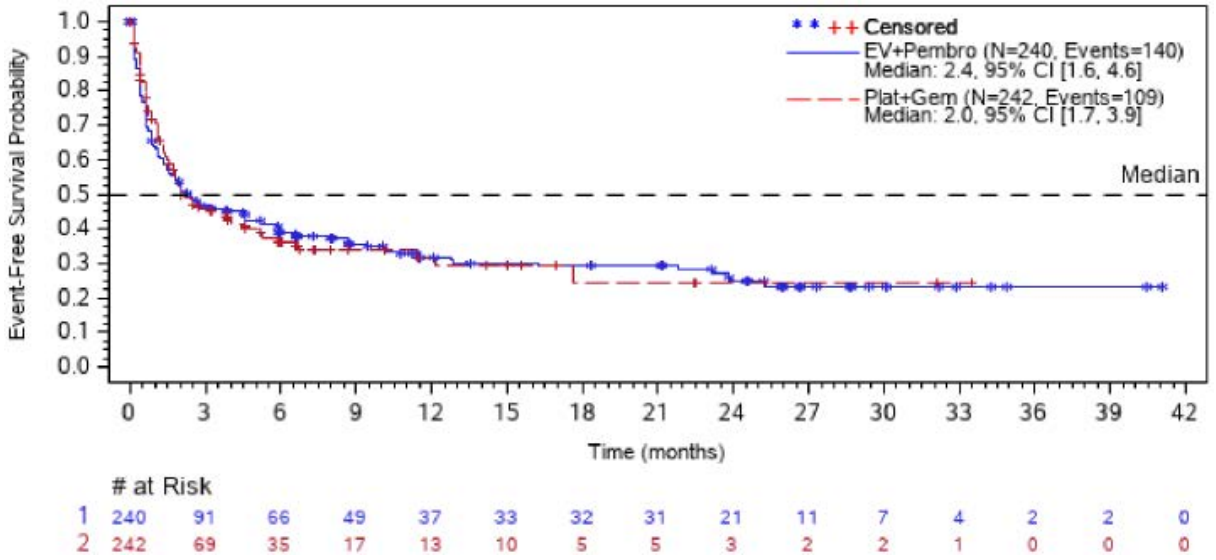


Figure 12: Kaplan-Meier curves for the outcome of dyspnoea (EORTC-QLQ-C30 - time to 1st deterioration) of the RCT EV-302/KN-A39, 2nd data cut-off (08 August 2024), subpopulation 1 (cisplatin suitable)

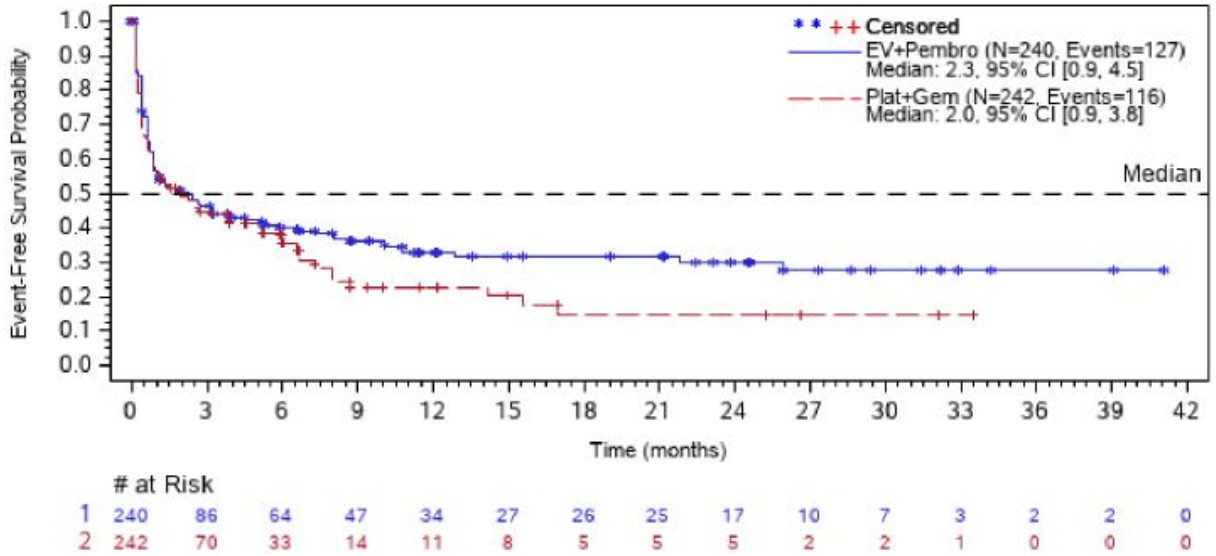


Figure 13: Kaplan-Meier curves for the outcome of insomnia (EORTC-QLQ-C30 - time to 1st deterioration) of the RCT EV-302/KN-A39, 2nd data cut-off (08 August 2024), subpopulation 1 (cisplatin suitable)

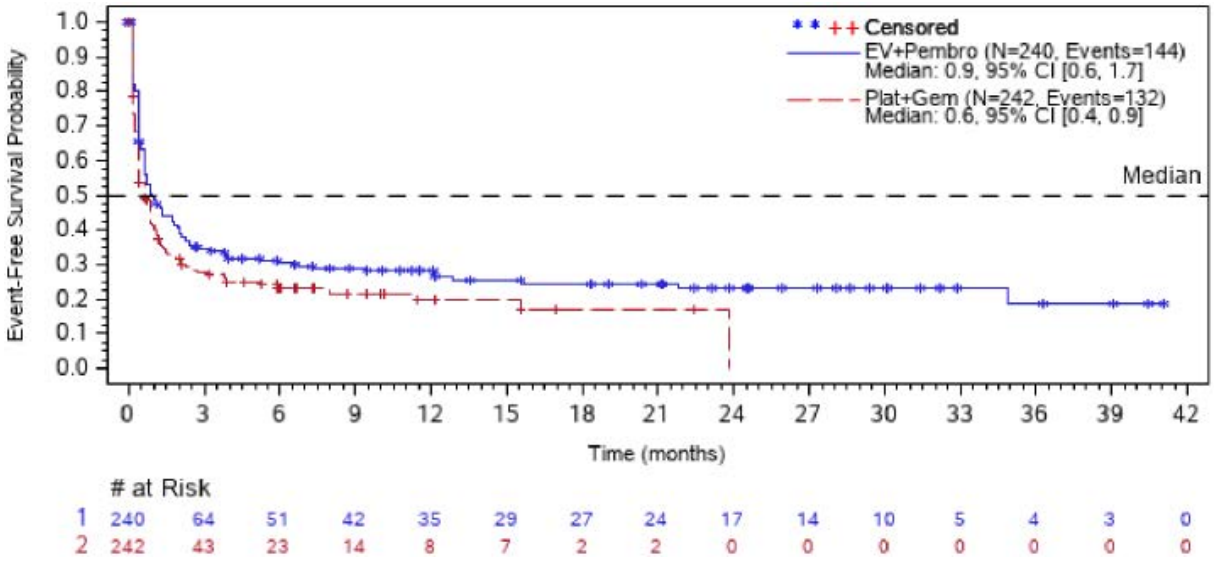


Figure 14: Kaplan-Meier curves for the outcome of appetite loss (EORTC QLQ-C30 - time to 1st deterioration) of the RCT EV-302/KN-A39, 2nd data cut-off (08 August 2024), subpopulation 1 (cisplatin suitable)

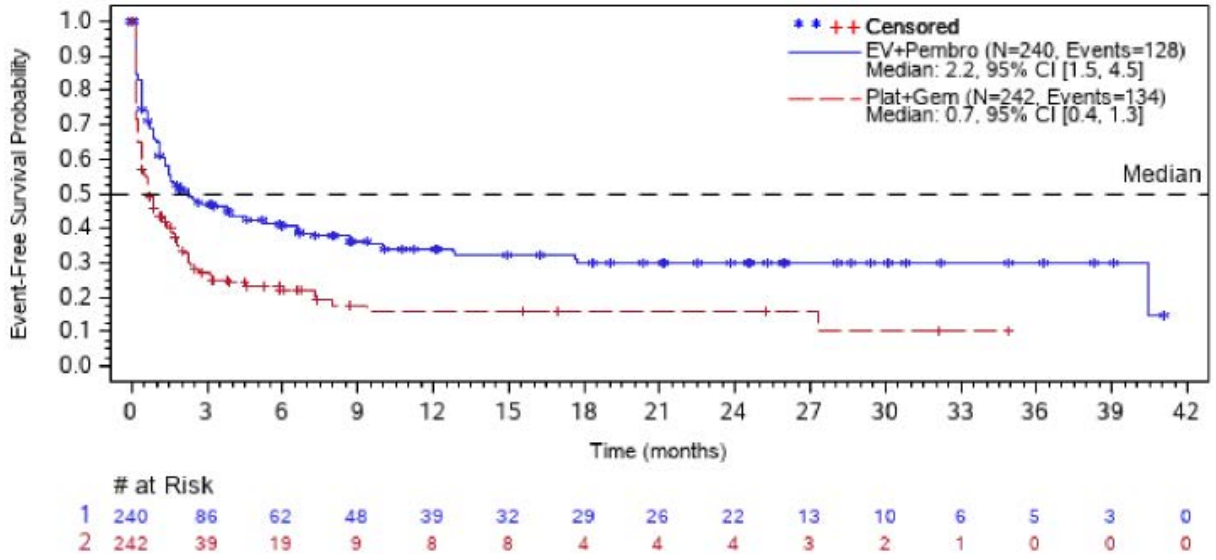


Figure 15: Kaplan-Meier curves for the outcome of constipation (EORTC-QLQ-C30 - time to 1st deterioration) of the RCT EV-302/KN-A39, 2nd data cut-off (08 August 2024), subpopulation 1 (cisplatin suitable)

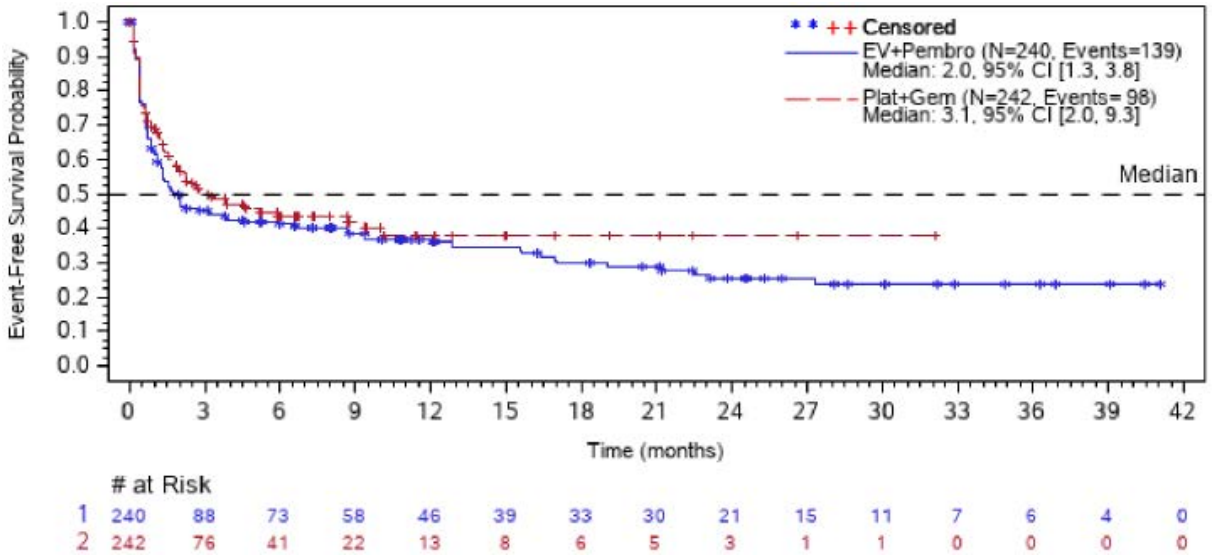


Figure 16: Kaplan-Meier curves for the outcome of diarrhoea (EORTC-QLQ-C30 - time to 1st deterioration) of the RCT EV-302/KN-A39, 2nd data cut-off (08 August 2024), subpopulation 1 (cisplatin suitable)

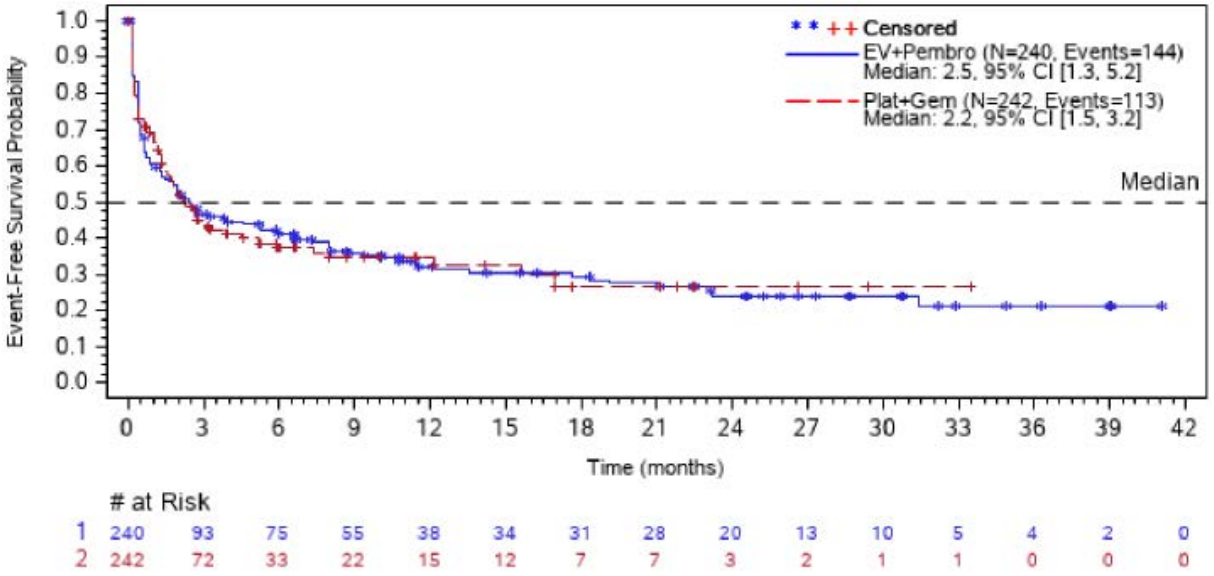


Figure 17: Kaplan-Meier curves for the outcome of health status (EQ-5D VAS - time to 1st deterioration) of the RCT EV-302/KN-A39, 2nd data cut-off (08 August 2024), subpopulation 1 (cisplatin suitable)

B.1.3 Health-related quality of life

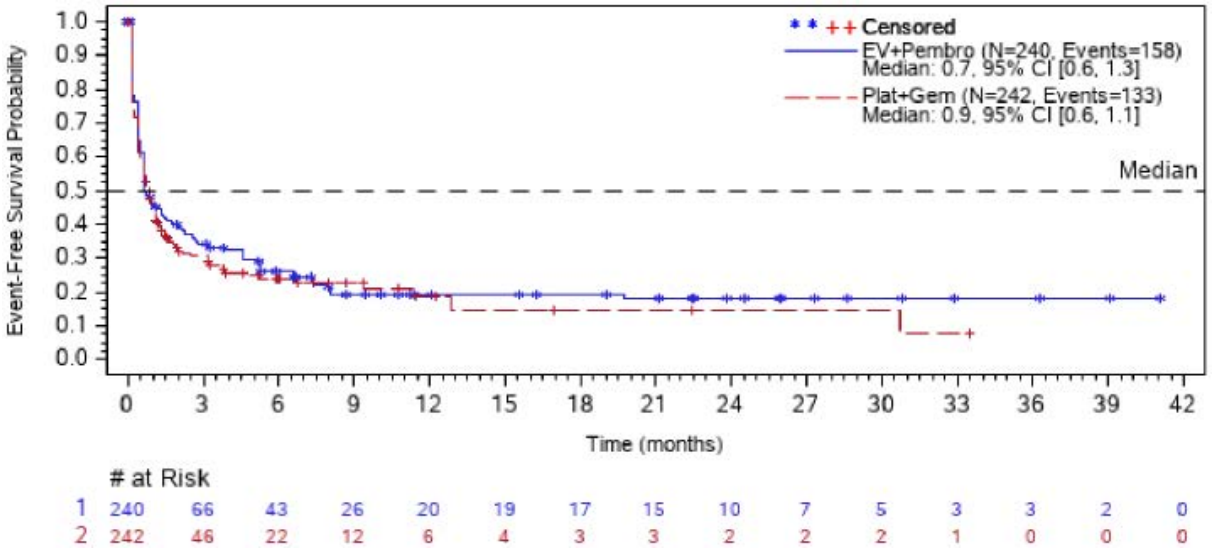


Figure 18: Kaplan-Meier curves for the outcome of global health status (EORTC-QLQ-C30 - time to 1st deterioration) of the RCT EV-302/KN-A39, 2nd data cut-off (08 August 2024), subpopulation 1 (cisplatin suitable)

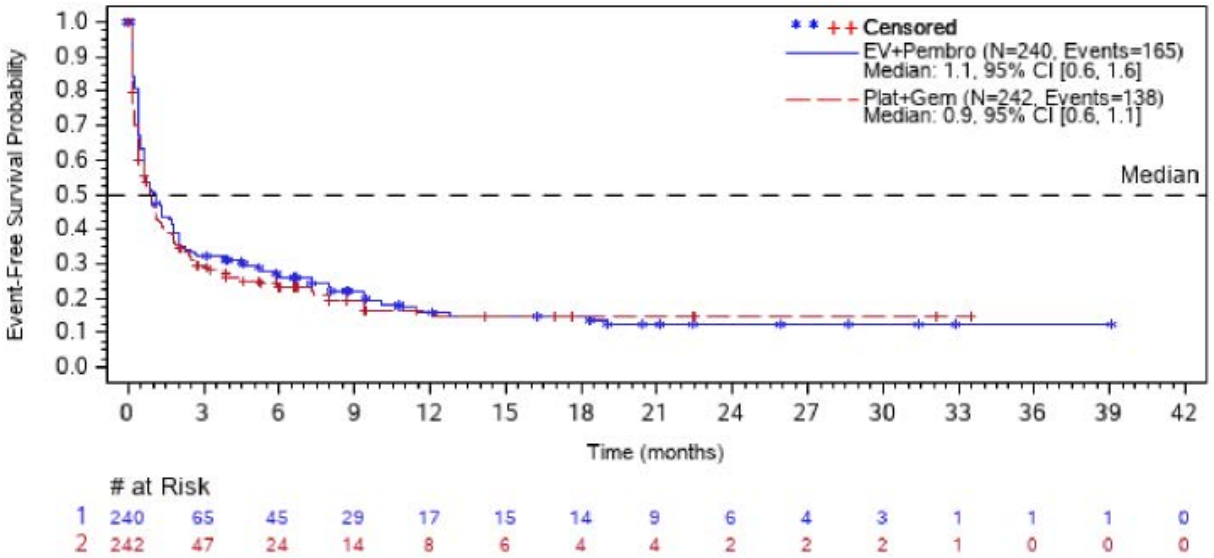


Figure 19: Kaplan-Meier curves for the outcome of physical functioning (EORTC QLQ-C30 - time to 1st deterioration) of the RCT EV-302/KN-A39, 2nd data cut-off (08 August 2024), subpopulation 1 (cisplatin suitable)

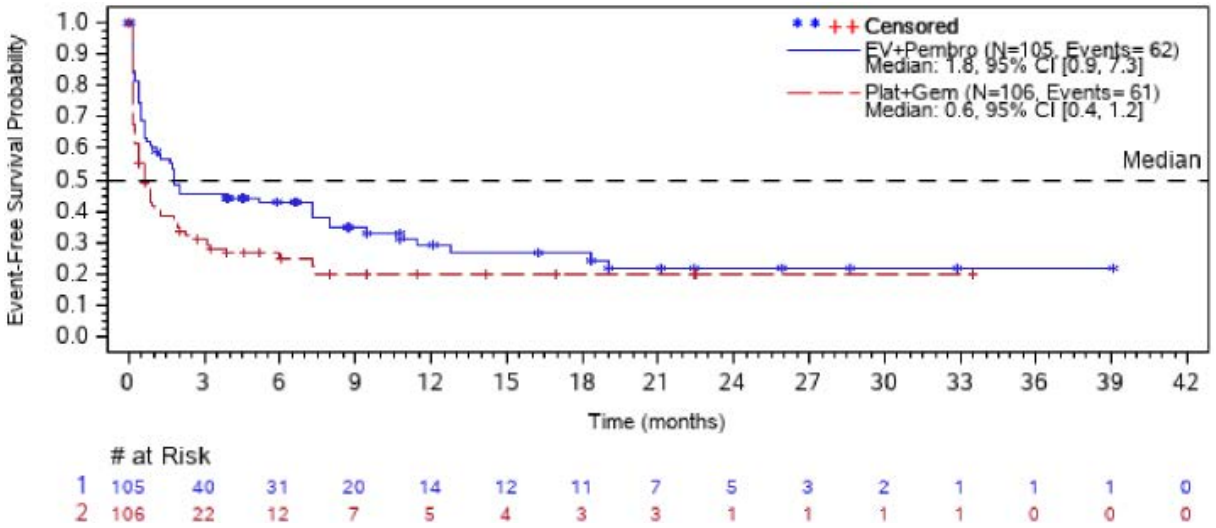


Figure 20: Kaplan-Meier curves for the outcome of physical functioning (EORTC-QLQ-C30 - time to 1st deterioration) of the RCT EV-302/KN-A39, 2nd data cut-off (08 August 2024), subpopulation 1 (cisplatin suitable), subgroup: < 65 years

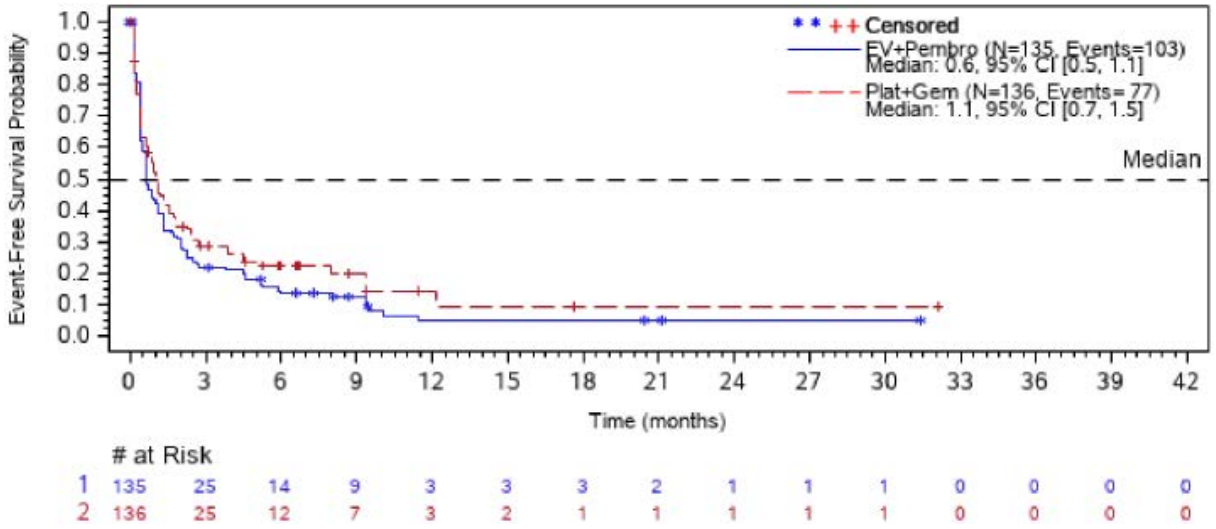


Figure 21: Kaplan-Meier curves for the outcome of physical functioning (EORTC-QLQ-C30 - time to 1st deterioration) of the RCT EV-302/KN-A39, 2nd data cut-off (08 August 2024), subpopulation 1 (cisplatin suitable), subgroup: ≥ 65 years

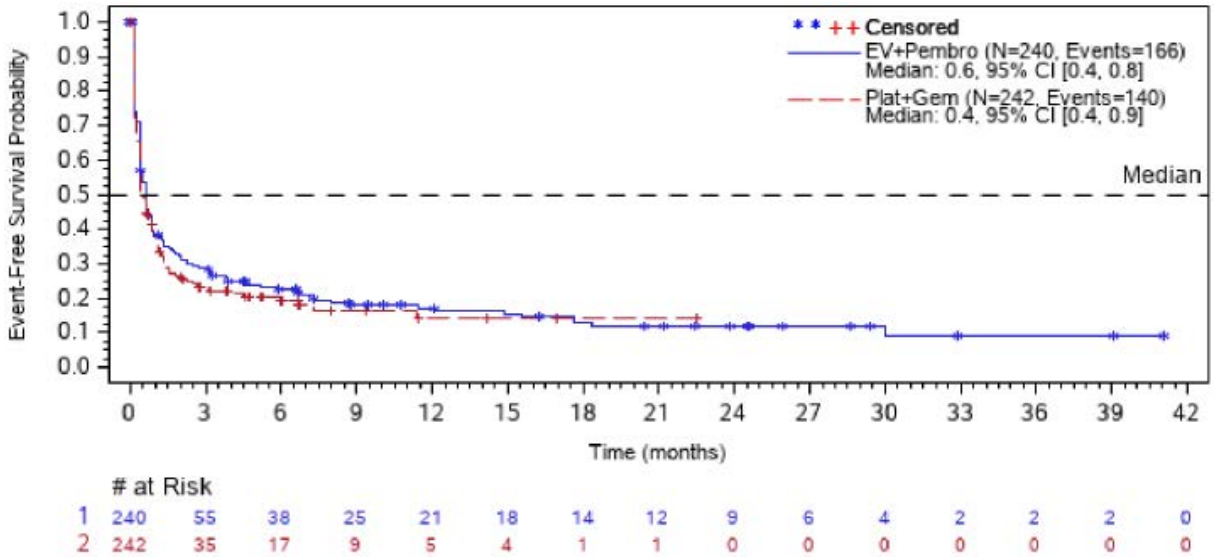


Figure 22: Kaplan-Meier curves for the outcome of role functioning (EORTC-QLQ-C30 - time to 1st deterioration) of the RCT EV-302/KN-A39, 2nd data cut-off (08 August 2024), subpopulation 1 (cisplatin suitable)

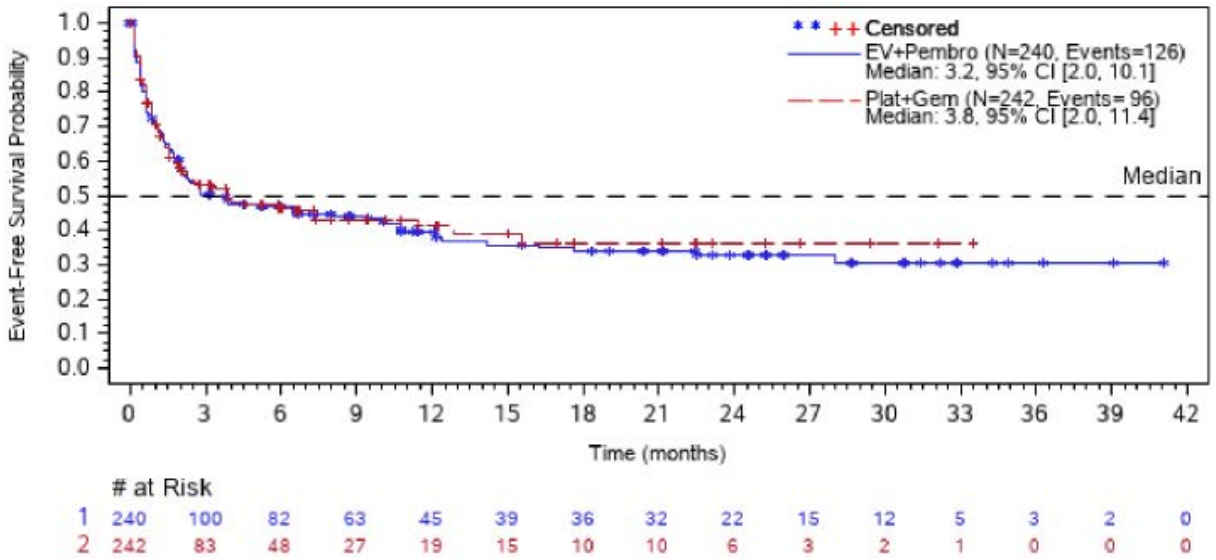


Figure 23: Kaplan-Meier curves for the outcome of emotional functioning (EORTC QLQ-C30 - time to 1st deterioration) of the RCT EV-302/KN-A39, 2nd data cut-off (08 August 2024), subpopulation 1 (cisplatin suitable)

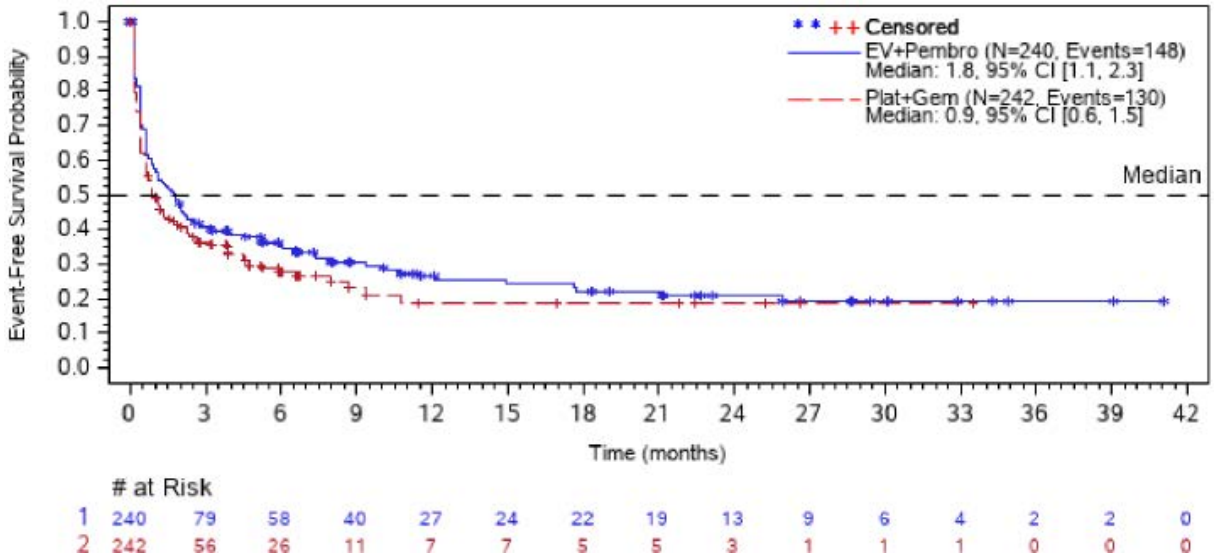


Figure 24: Kaplan-Meier curves for the outcome of cognitive functioning (EORTC QLQ-C30 - time to 1st deterioration) of the RCT EV-302/KN-A39, 2nd data cut-off (08 August 2024), subpopulation 1 (cisplatin suitable)

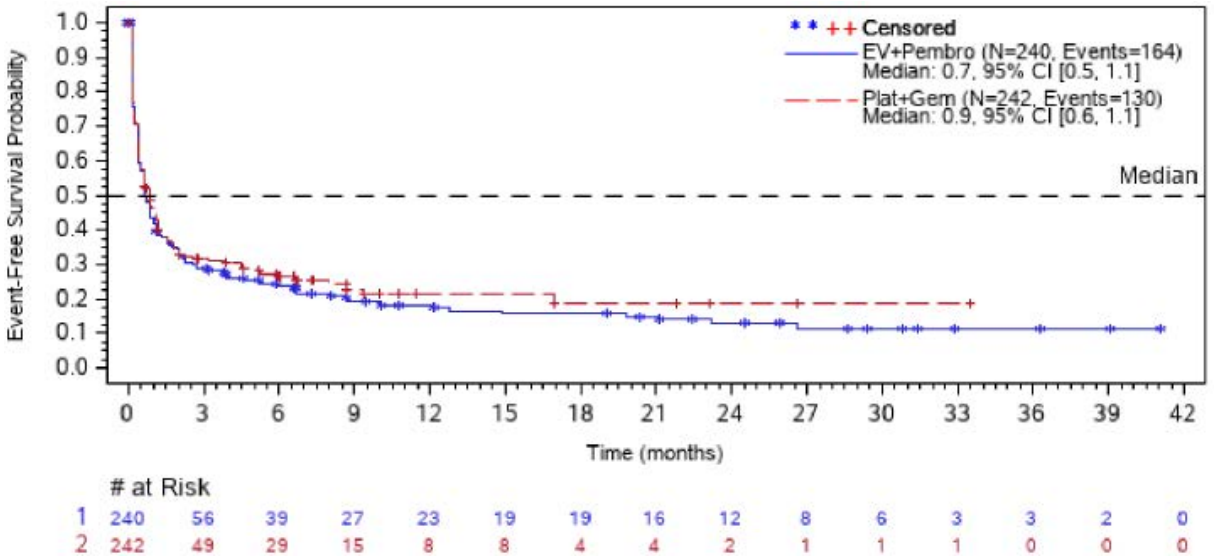


Figure 25: Kaplan-Meier curves for the outcome of social functioning (EORTC QLQ-C30 - time to 1st deterioration) of the RCT EV-302/KN-A39, 2nd data cut-off (08 August 2024), subpopulation 1 (cisplatin suitable)

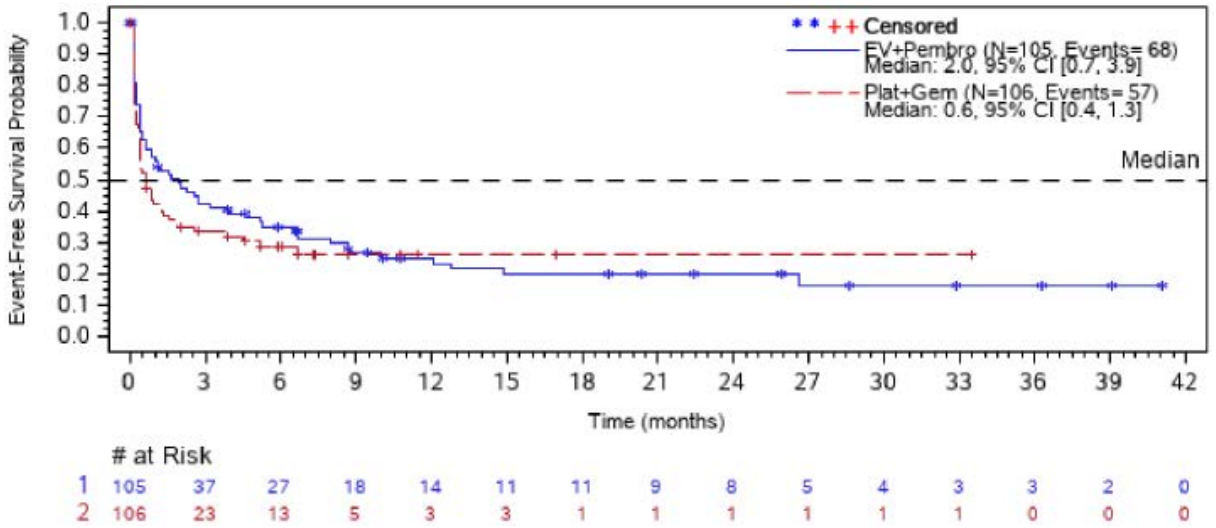


Figure 26: Kaplan-Meier curves for the outcome of social functioning (EORTC-QLQ-C30 - time to 1st deterioration) of the RCT EV-302/KN-A39, 2nd data cut-off (08 August 2024), subpopulation 1 (cisplatin suitable), subgroup: < 65 years

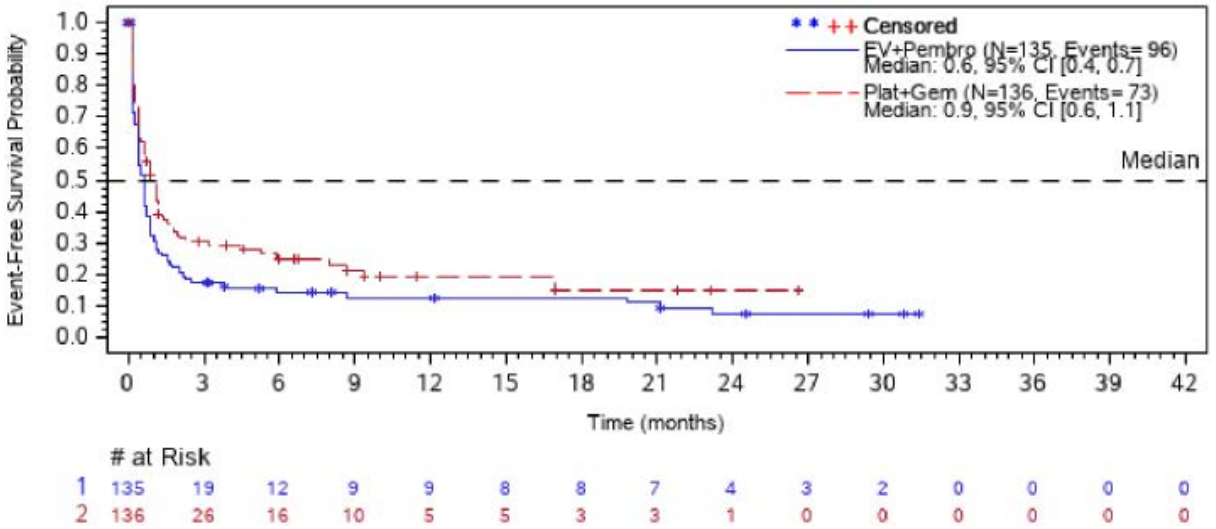


Figure 27: Kaplan-Meier curves for the outcome of social functioning (EORTC-QLQ-C30 - time to 1st deterioration) of the RCT EV-302/KN-A39, 2nd data cut-off (08 August 2024), subpopulation 1 (cisplatin suitable), subgroup: ≥ 65 years

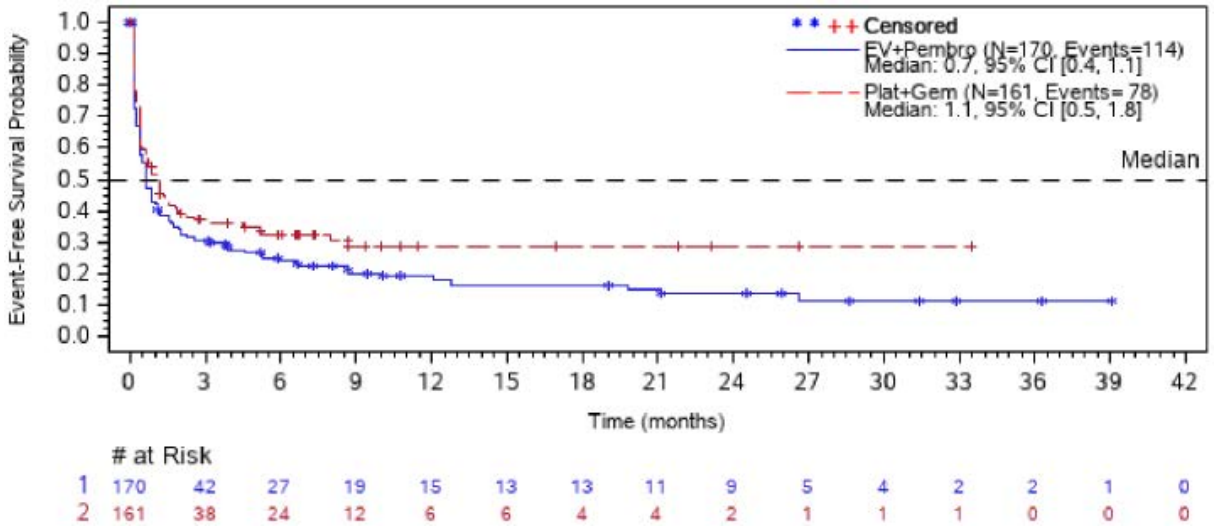


Figure 28: : Kaplan-Meier curves for the outcome of social functioning (EORTC-QLQ-C30 - time to 1st deterioration) of the RCT EV-302/KN-A39, 2nd data cut-off (08 August 2024), subpopulation 1 (cisplatin suitable), subgroup: visceral metastases

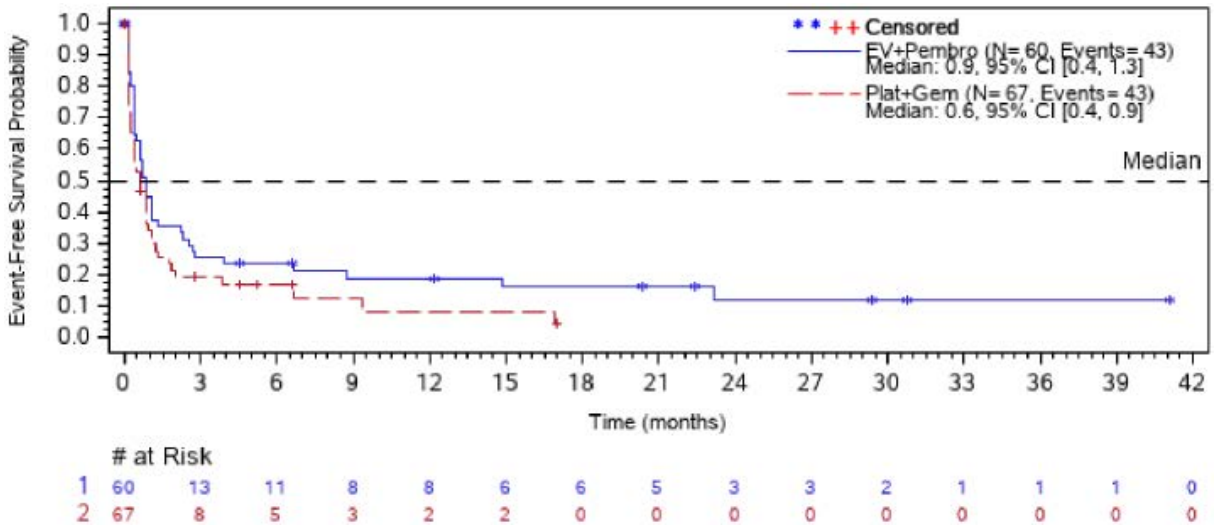


Figure 29: Kaplan-Meier curves for the outcome of social functioning (EORTC-QLQ-C30 - time to 1st deterioration) of the RCT EV-302/KN-A39, 2nd data cut-off (08 August 2024), subpopulation 1 (cisplatin suitable), subgroup: exclusively lymph node metastases

B.1.4 Side effects

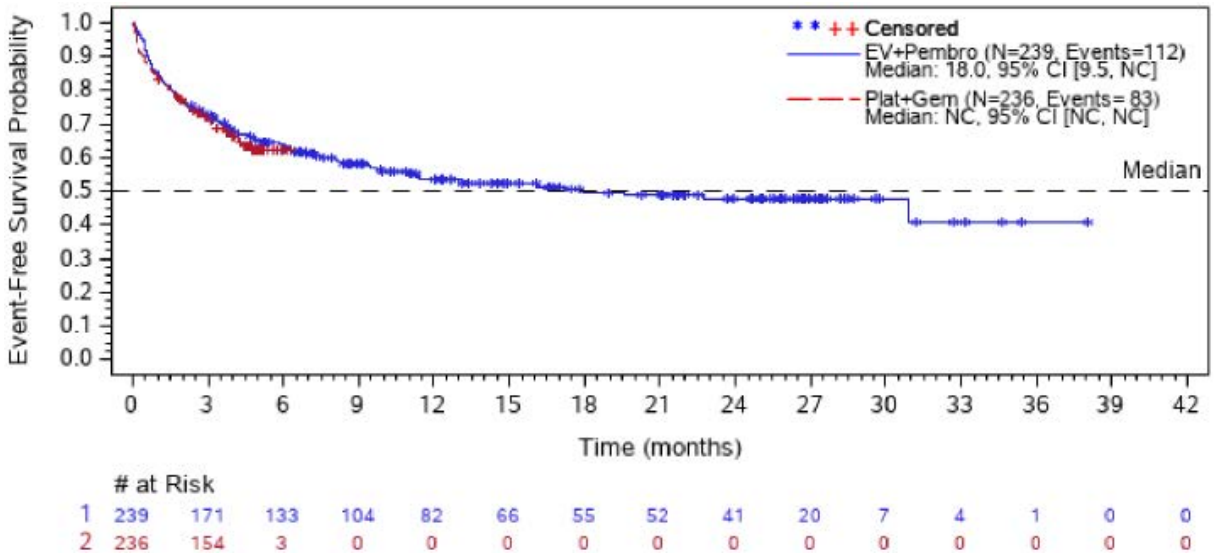


Figure 30: Kaplan-Meier curves for the outcome of SAEs of the RCT EV-302/KN-A39, 2nd data cut-off (08 August 2024), subpopulation 1 (cisplatin suitable)

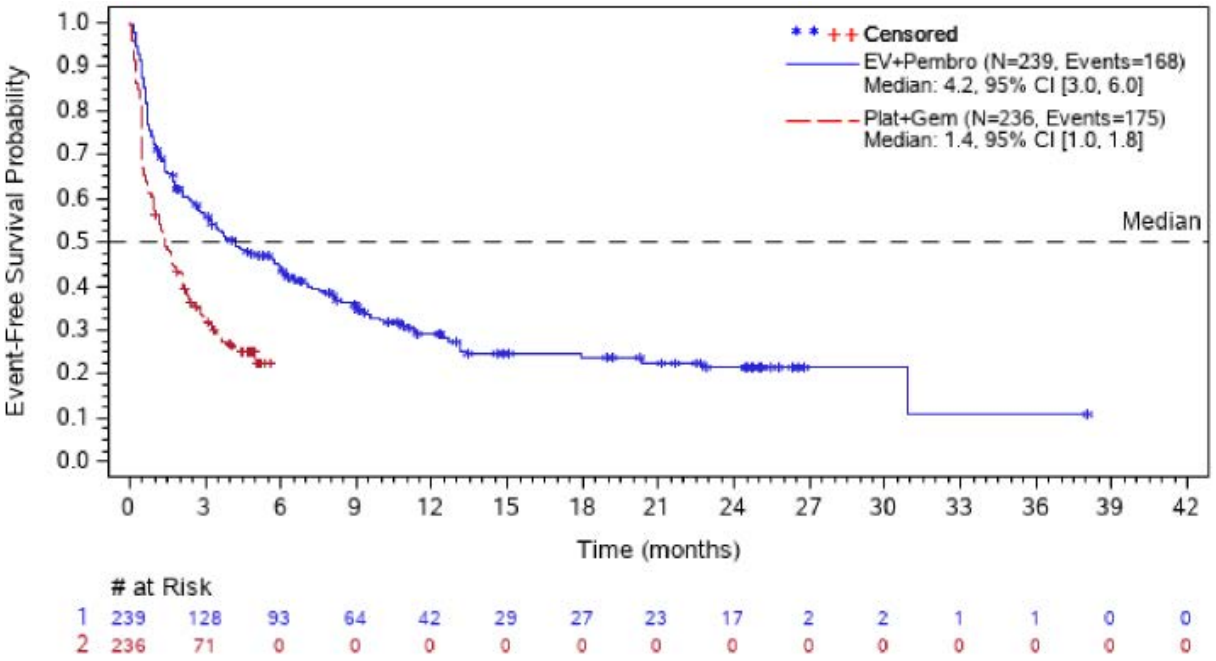


Figure 31: Kaplan-Meier curves for the outcome of severe AEs of the RCT EV-302/KN-A39, 2nd data cut-off (08 August 2024), subpopulation 1 (cisplatin suitable)

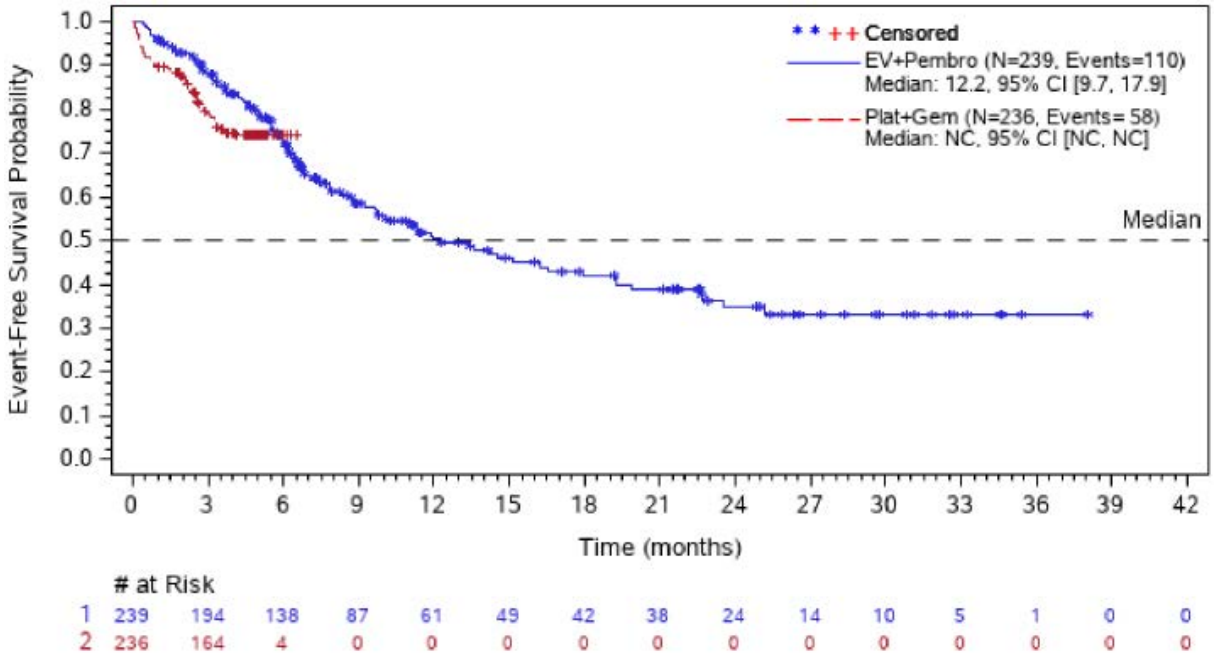


Figure 32: Kaplan-Meier curves for the outcome of discontinuation due to AEs of the RCT EV-302/KN-A39, 2nd data cut-off (08 August 2024), subpopulation 1 (cisplatin suitable)

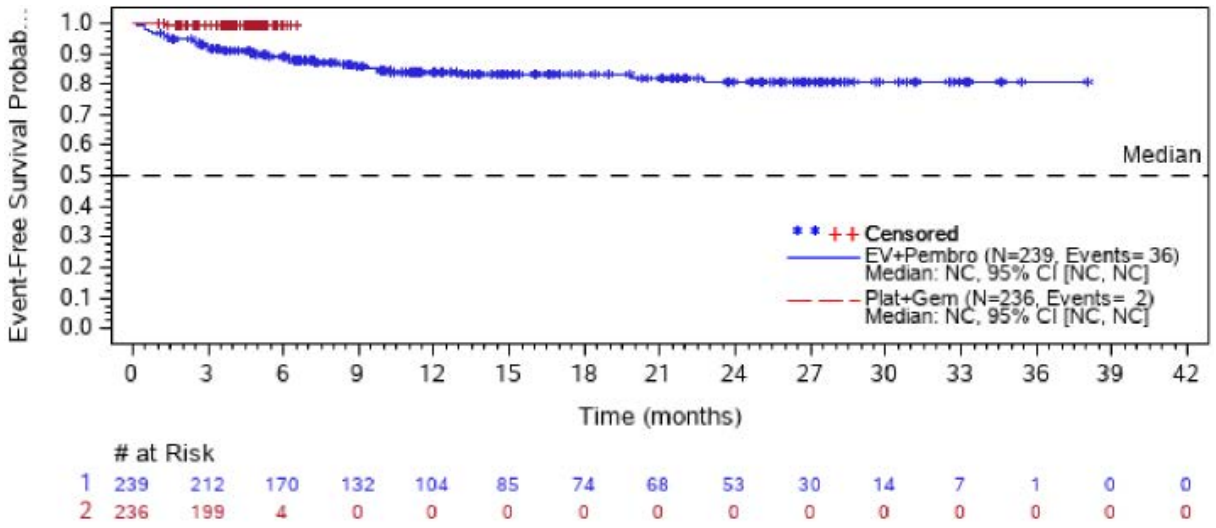


Figure 33: Kaplan-Meier curves for the outcome of immune-related SAEs of the RCT EV-302/KN-A39, 2nd data cut-off (08 August 2024), subpopulation 1 (cisplatin suitable)

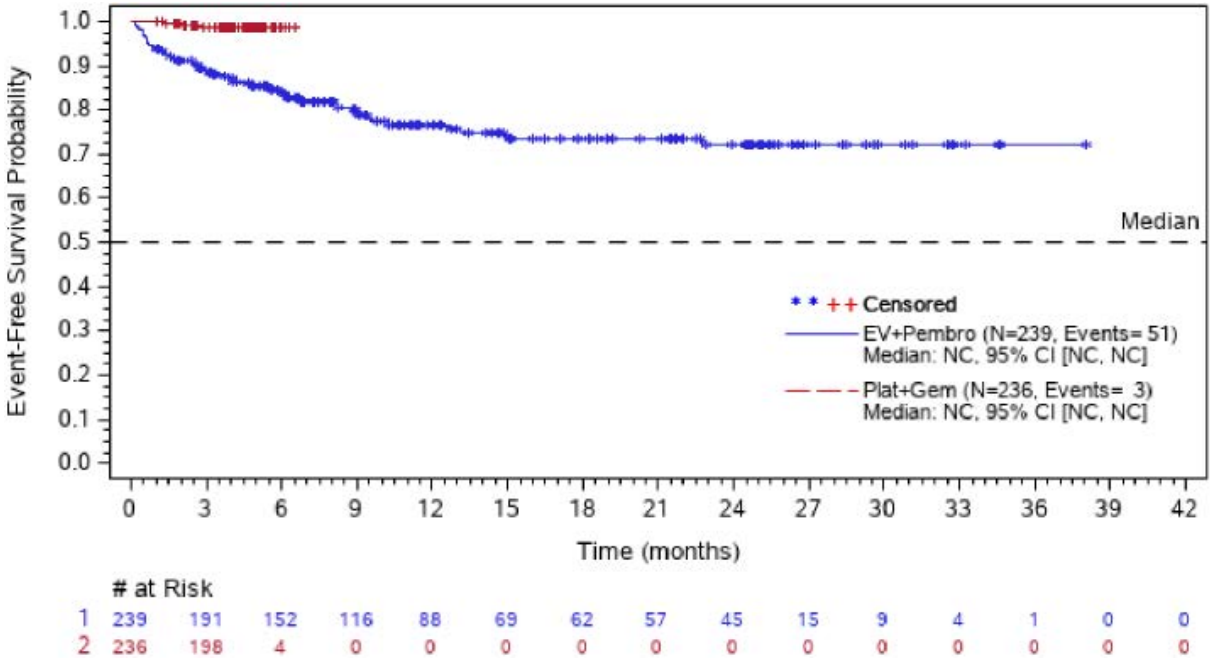


Figure 34: Kaplan-Meier curves for the outcome of immune-related severe AEs of the RCT EV-302/KN-A39, 2nd data cut-off (08 August 2024), subpopulation 1 (cisplatin suitable)

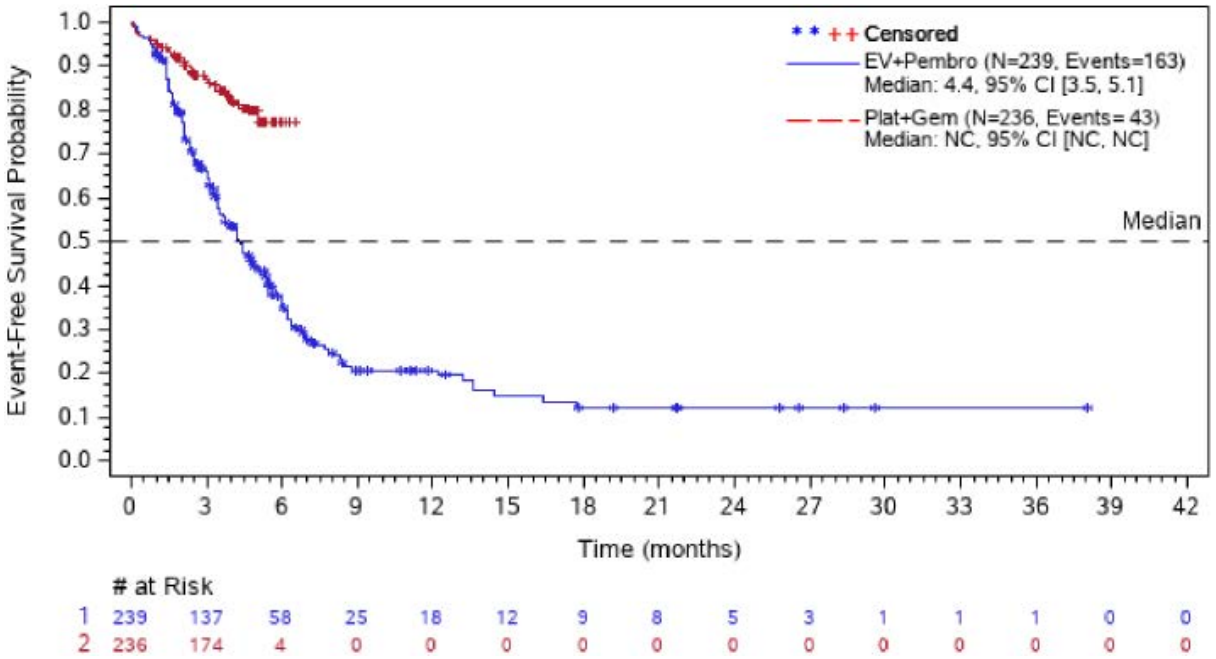


Figure 35: Kaplan-Meier curves for the outcome of peripheral neuropathy (AEs) of the RCT EV-302/KN-A39, 2nd data cut-off (08 August 2024), subpopulation 1 (cisplatin suitable)

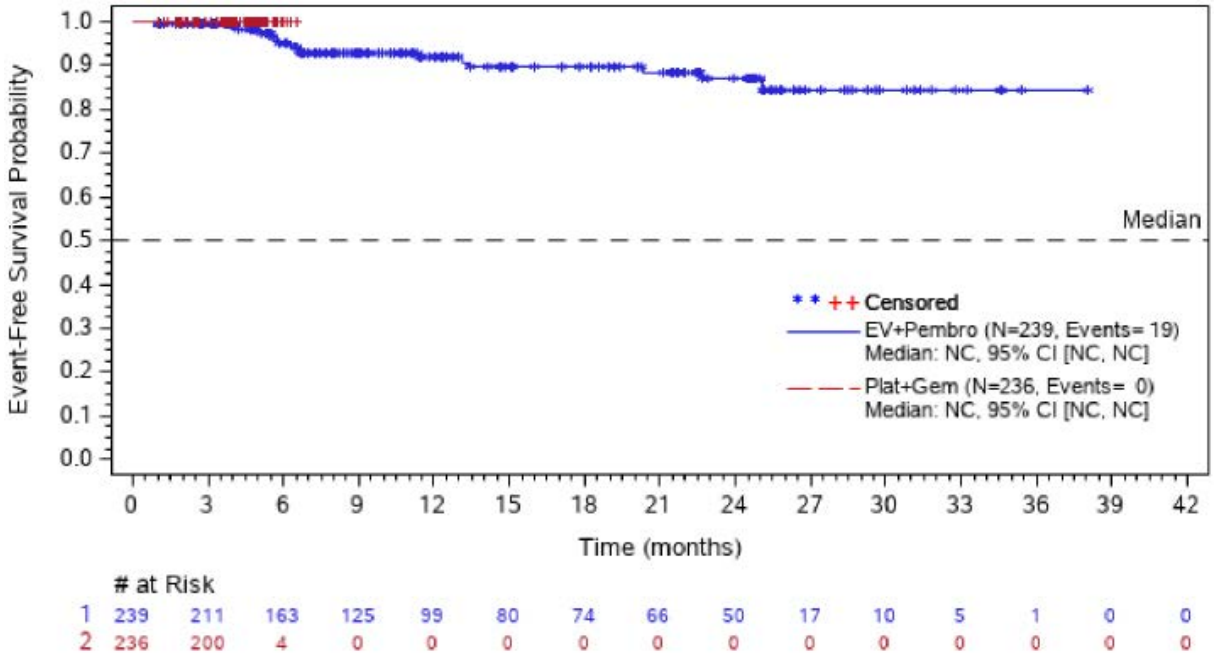


Figure 36: Kaplan-Meier curves for the outcome of severe peripheral neuropathy (severe AEs) of the RCT EV-302/KN-A39, 2nd data cut-off (08 August 2024), subpopulation 1 (cisplatin suitable) - supplementary presentation

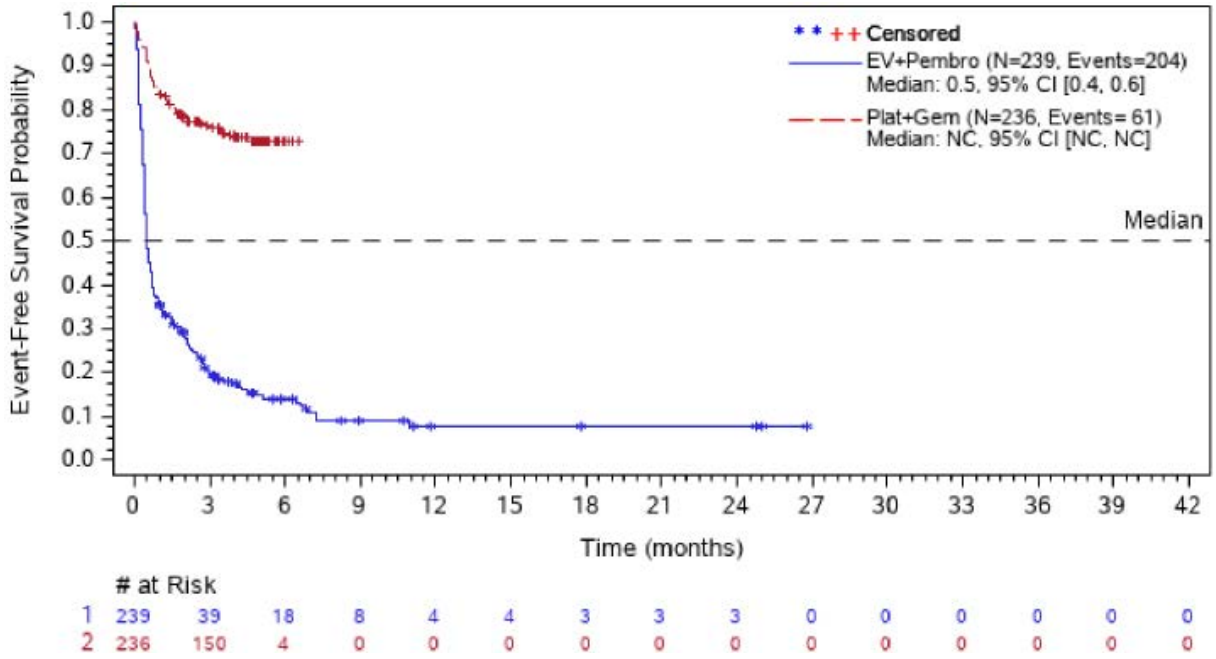


Figure 37: Kaplan-Meier curves for the outcome of skin reactions (AEs) of the RCT EV-302/KN-A39, 2nd data cut-off (08 August 2024), subpopulation 1 (cisplatin suitable)

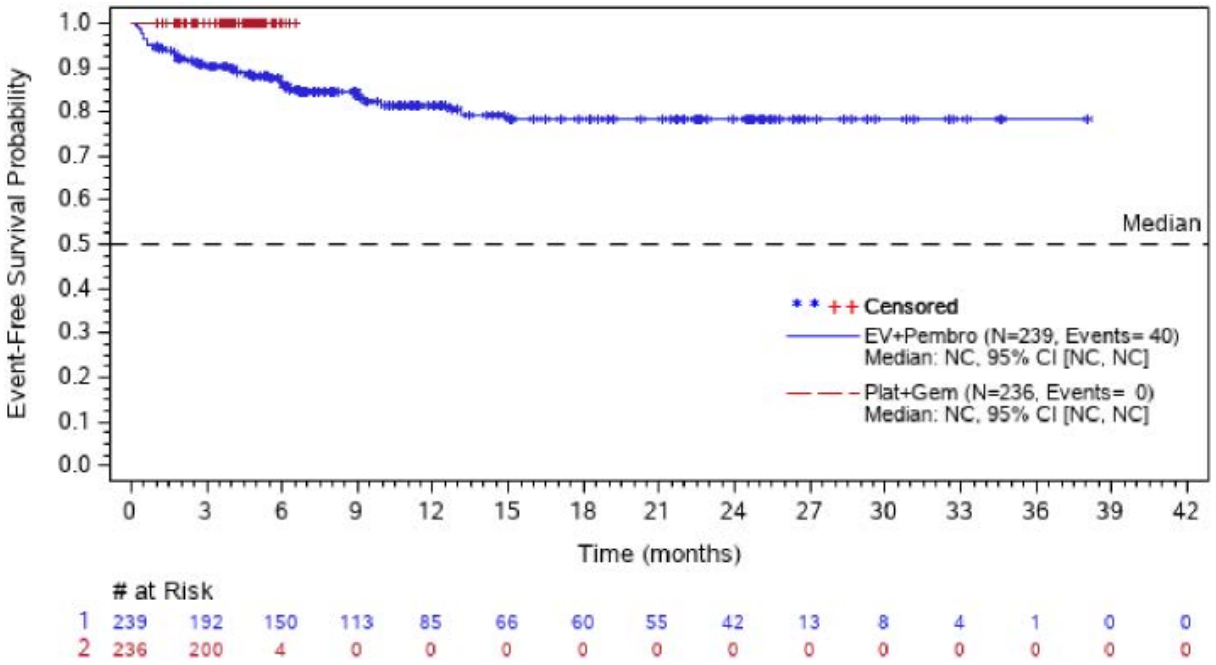


Figure 38: Kaplan-Meier curves for the outcome of severe skin reactions (severe AEs) of the RCT EV-302/KN-A39, 2nd data cut-off (08 August 2024), subpopulation 1 (cisplatin suitable) - supplementary presentation

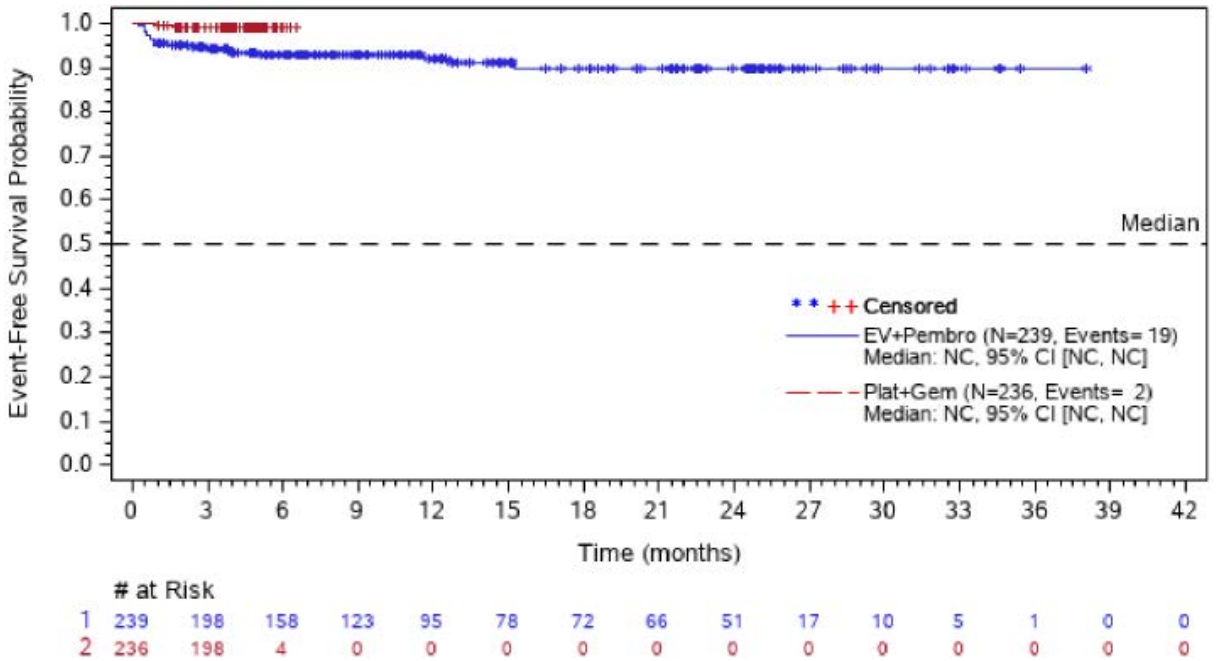


Figure 39: Kaplan-Meier curves for the outcome of severe hyperglycaemia (severe AEs) of the RCT EV-302/KN-A39, 2nd data cut-off (08 August 2024), subpopulation 1 (cisplatin suitable)

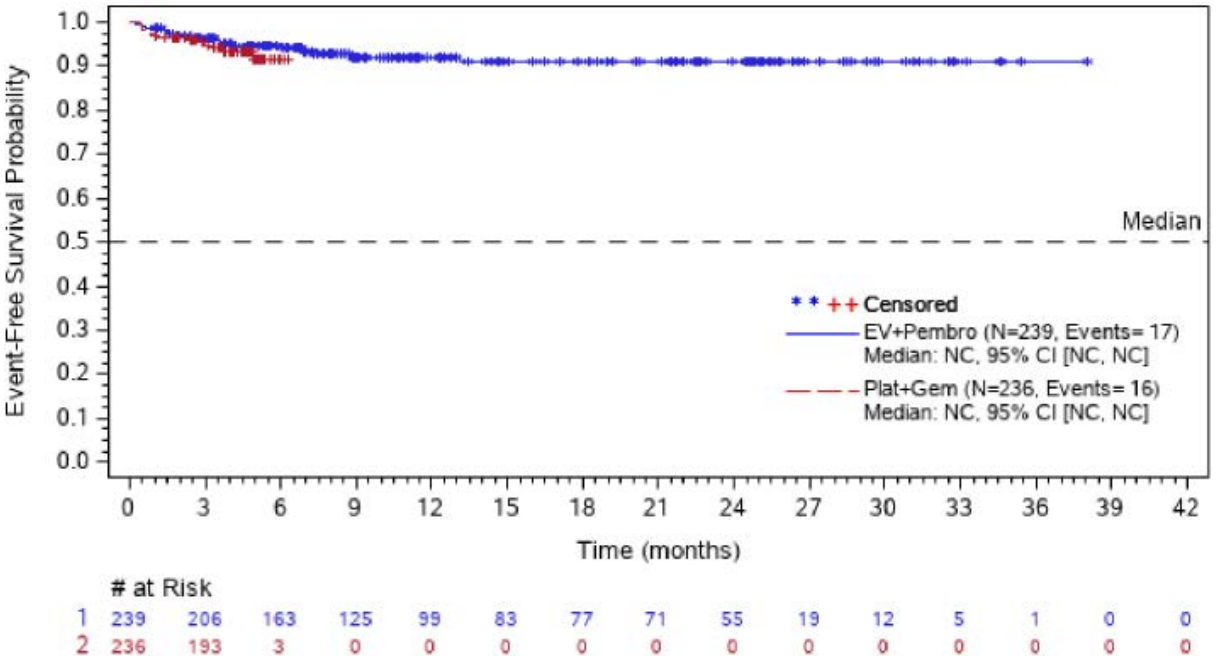


Figure 40: Kaplan-Meier curves for the outcome of severe nephrotoxicity (severe AEs) of the RCT EV-302/KN-A39, 2nd data cut-off (08 August 2024), subpopulation 1 (cisplatin suitable)

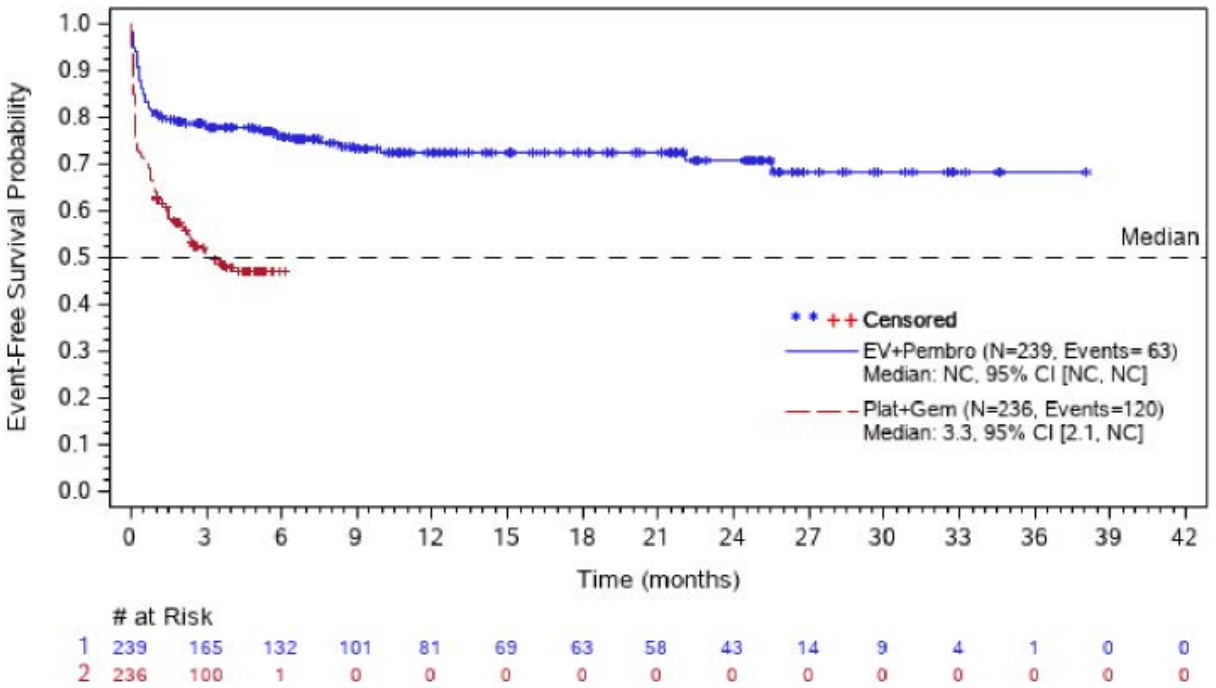


Figure 41: Kaplan-Meier curves for the outcome of nausea (AEs) of the RCT EV-302/KN-A39, 2nd data cut-off (08 August 2024), subpopulation 1 (cisplatin suitable)

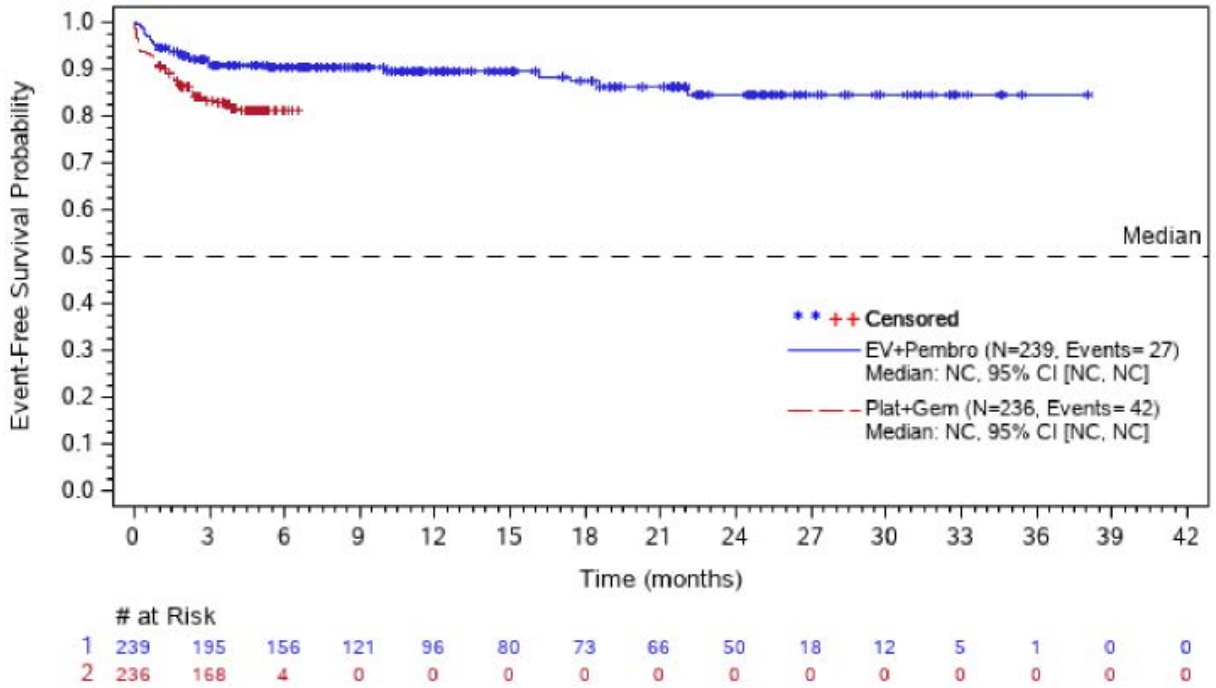


Figure 42: Kaplan-Meier curves for the outcome of vomiting (AEs) of the RCT EV-302/KN-A39, 2nd data cut-off (08 August 2024), subpopulation 1 (cisplatin suitable)

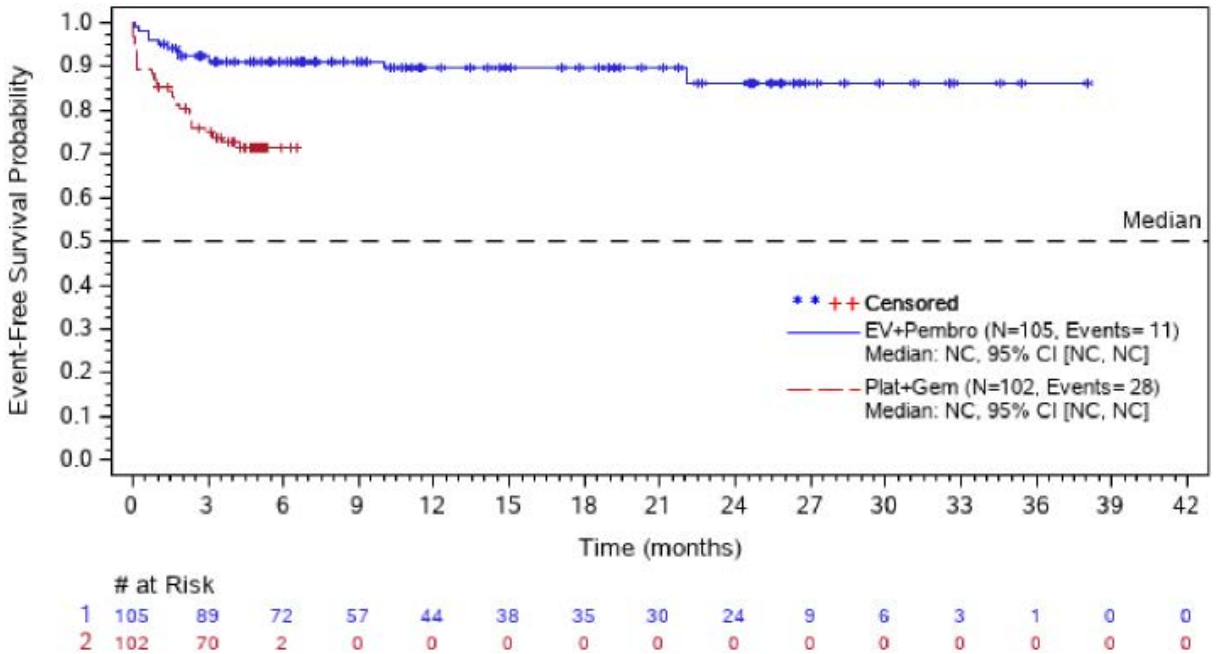


Figure 43: Kaplan-Meier curves for the outcome of vomiting (AEs) of the RCT EV-302/KN-A39, 2nd data cut-off (08 August 2024), subpopulation 1 (cisplatin suitable), subgroup: < 65 years

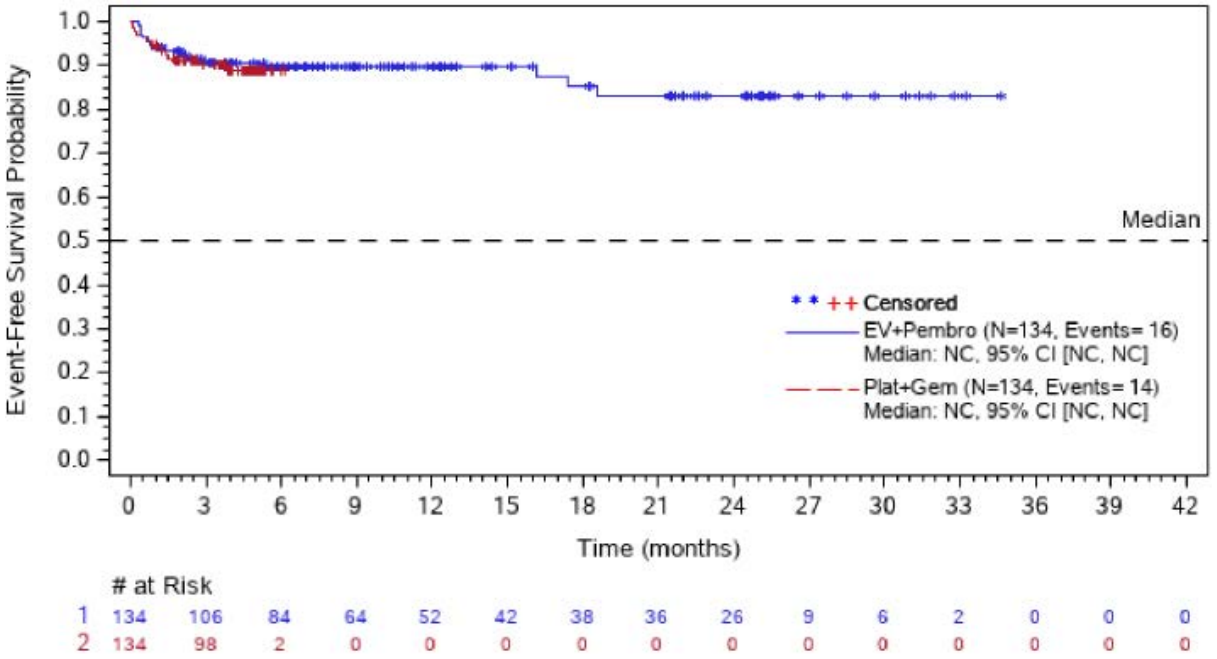


Figure 44: Kaplan-Meier curves for the outcome of vomiting (AEs) of the RCT EV-302/KN-A39, 2nd data cut-off (08 August 2024), subpopulation 1 (cisplatin suitable), subgroup: ≥ 65 years

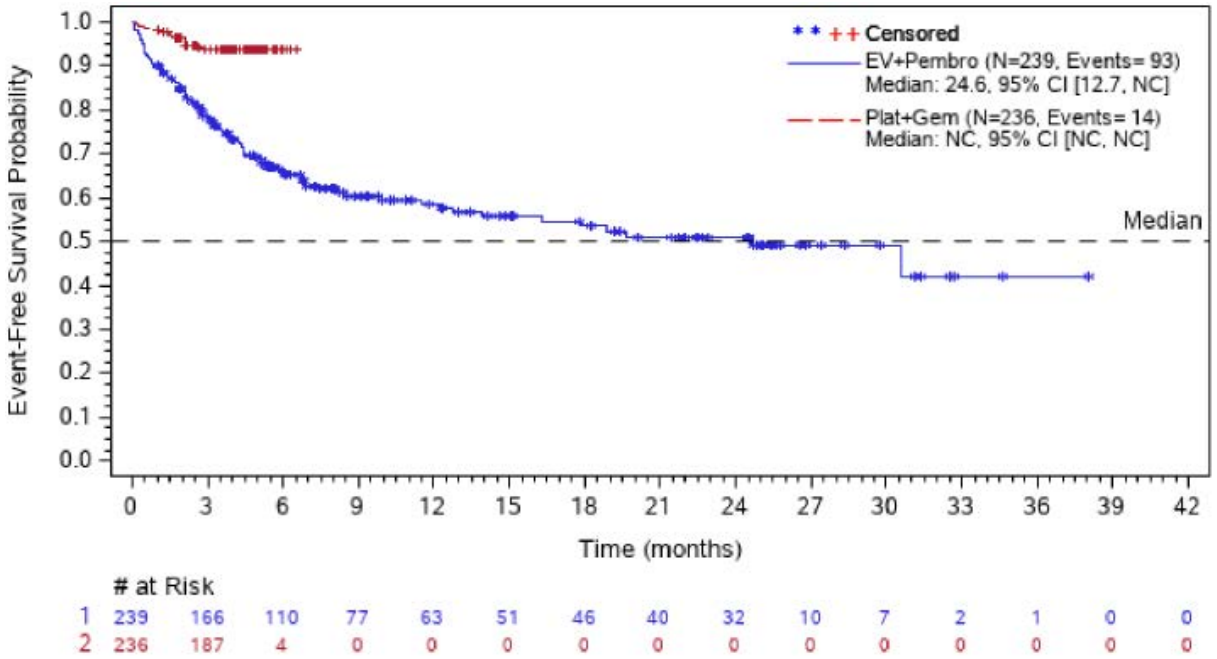


Figure 45: Kaplan-Meier curves for the outcome of eye disorders (AEs) of the RCT EV-302/KN-A39, 2nd data cut-off (08 August 2024), subpopulation 1 (cisplatin suitable)

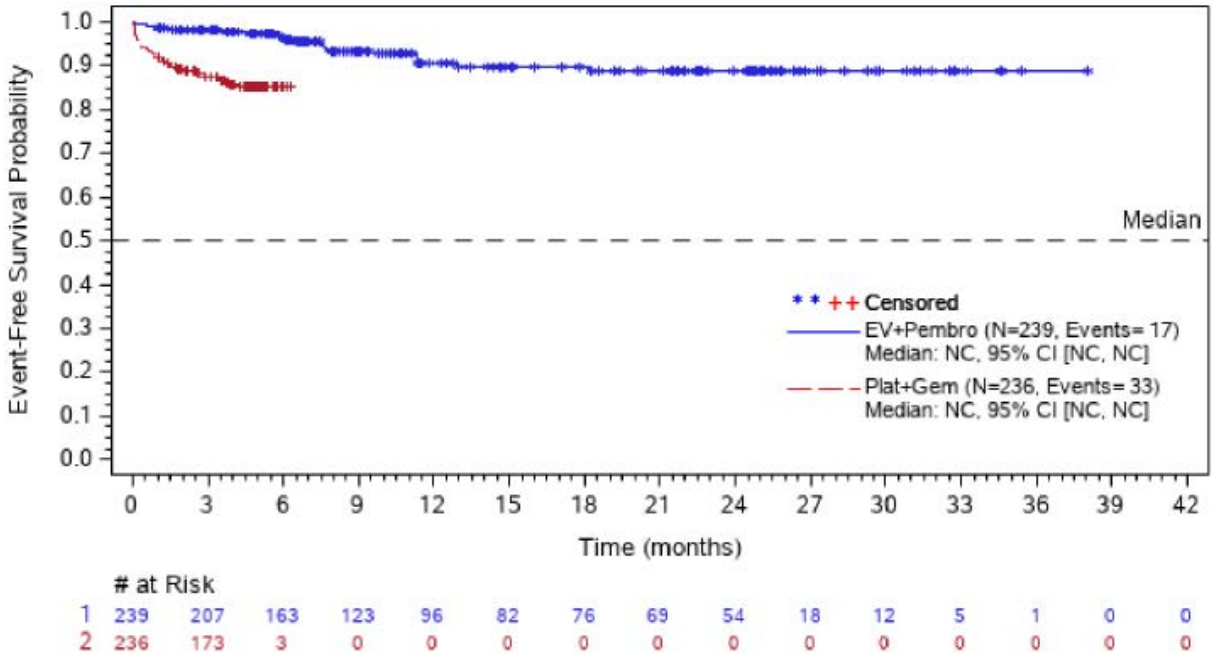


Figure 46: Kaplan-Meier curves for the outcome of ear and labyrinth disorders (AEs) of the RCT EV-302/KN-A39, 2nd data cut-off (08 August 2024), subpopulation 1 (cisplatin suitable)

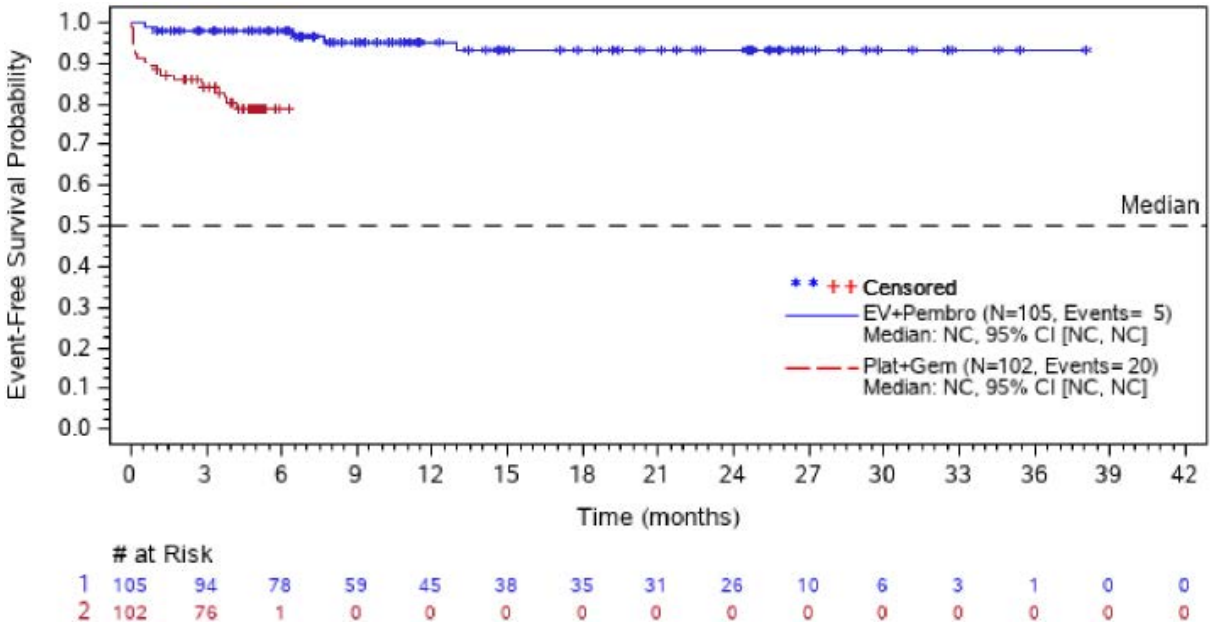


Figure 47: Kaplan-Meier curves for the outcome of ear and labyrinth disorders (AEs) of the RCT EV-302/KN-A39, 2nd data cut-off (08 August 2024), subpopulation 1 (cisplatin suitable), subgroup: < 65 years

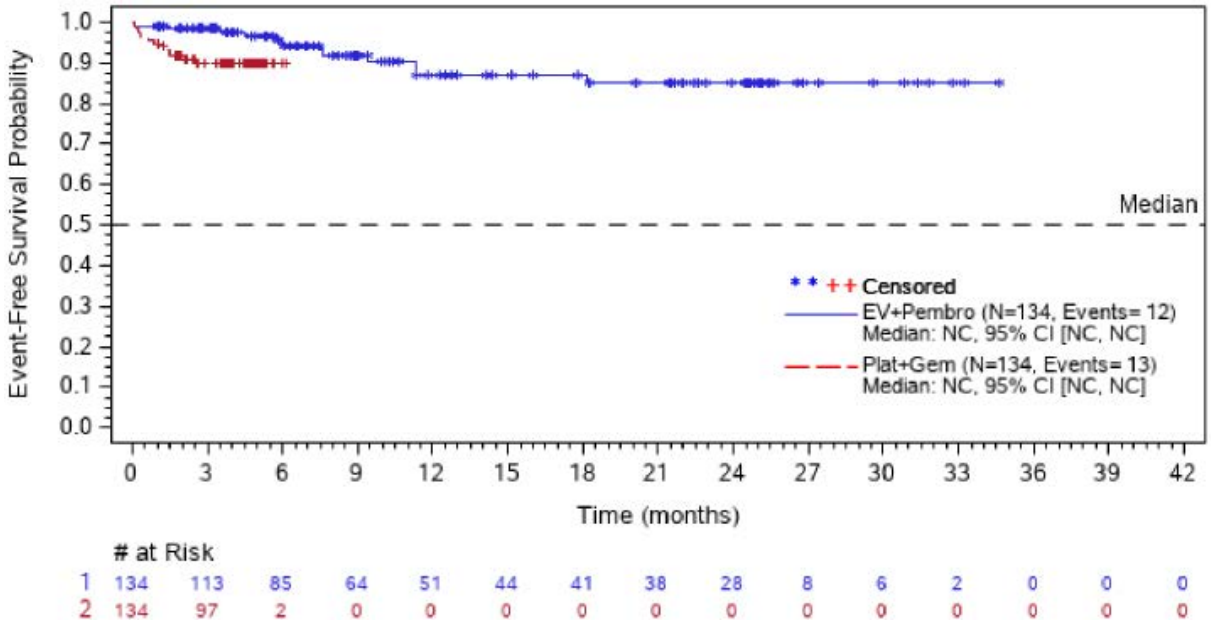


Figure 48: Kaplan-Meier curves for the outcome of ear and labyrinth disorders (AEs) of the RCT EV-302/KN-A39, 2nd data cut-off (08 August 2024), subpopulation 1 (cisplatin suitable), subgroup: ≥ 65 years

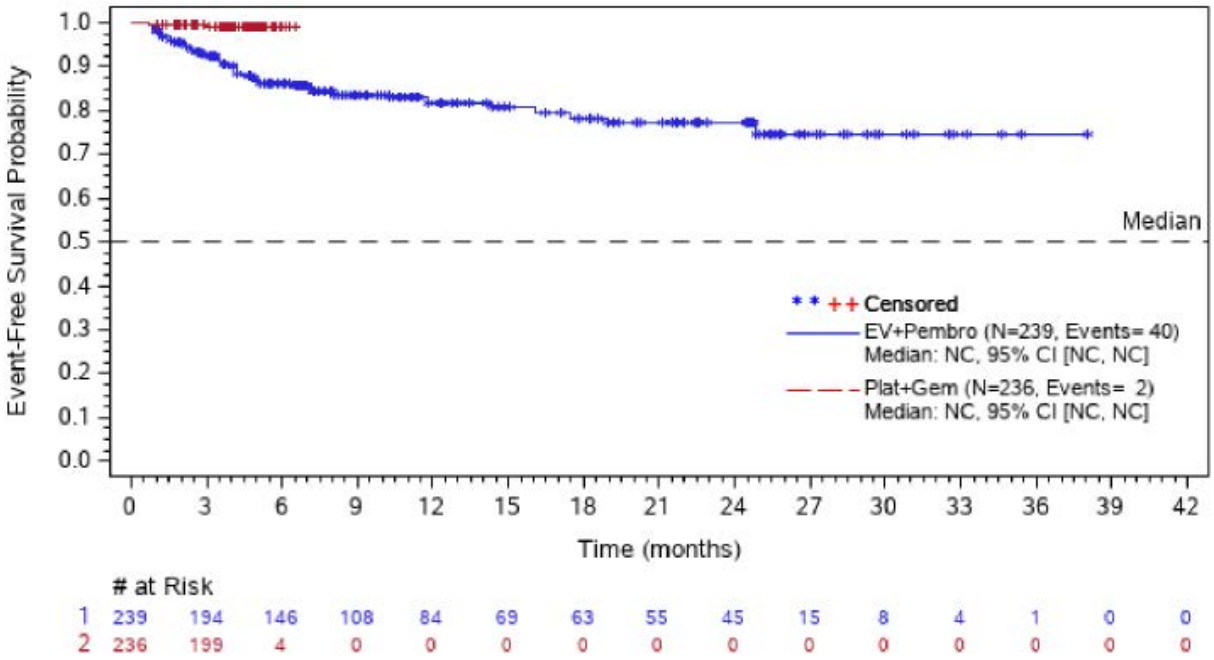


Figure 49: Kaplan-Meier curves for the outcome of endocrine disorders (AEs) of the RCT EV-302/KN-A39, 2nd data cut-off (08 August 2024), subpopulation 1 (cisplatin suitable)

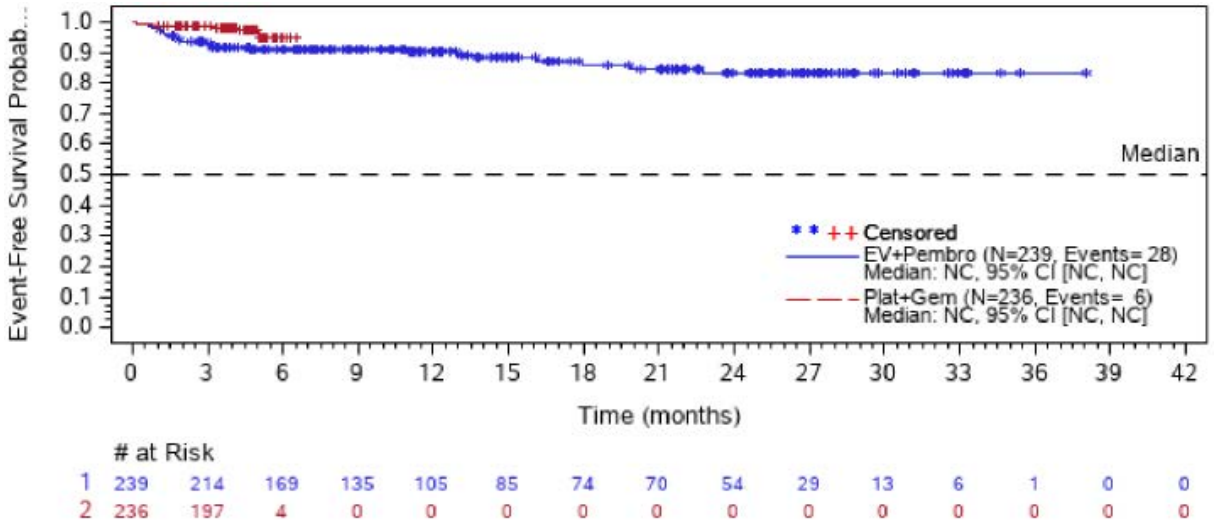


Figure 50: Kaplan-Meier curves for the outcome of gastrointestinal disorders (SAEs) of the RCT EV-302/KN-A39, 2nd data cut-off (08 August 2024), subpopulation 1 (cisplatin suitable)

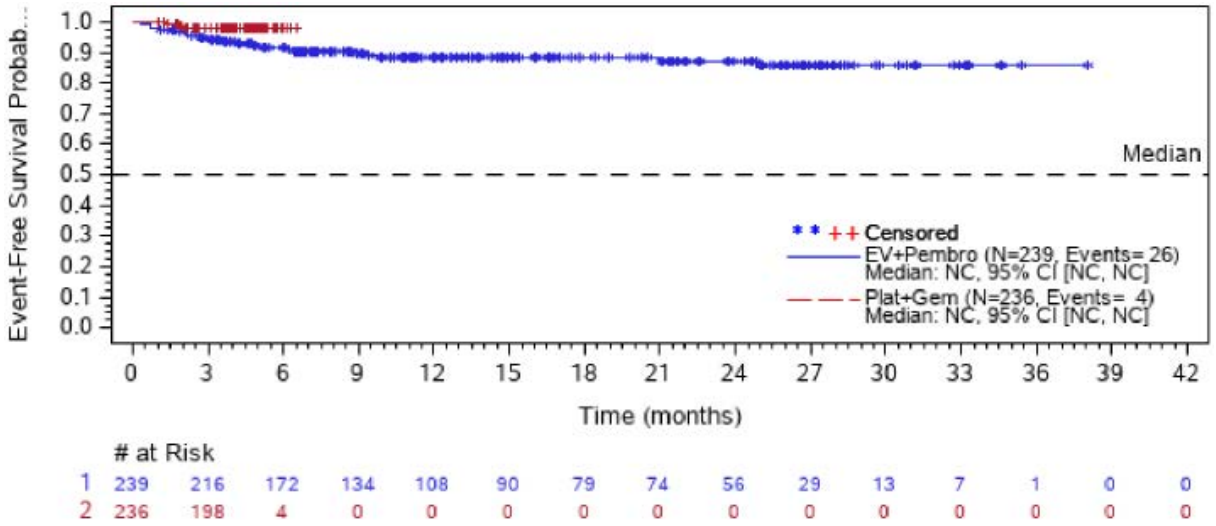


Figure 51: Kaplan-Meier curves for the outcome of respiratory, thoracic and mediastinal disorders (SAEs) of the RCT EV-302/KN-A39, 2nd data cut-off (08 August 2024), subpopulation 1 (cisplatin suitable)

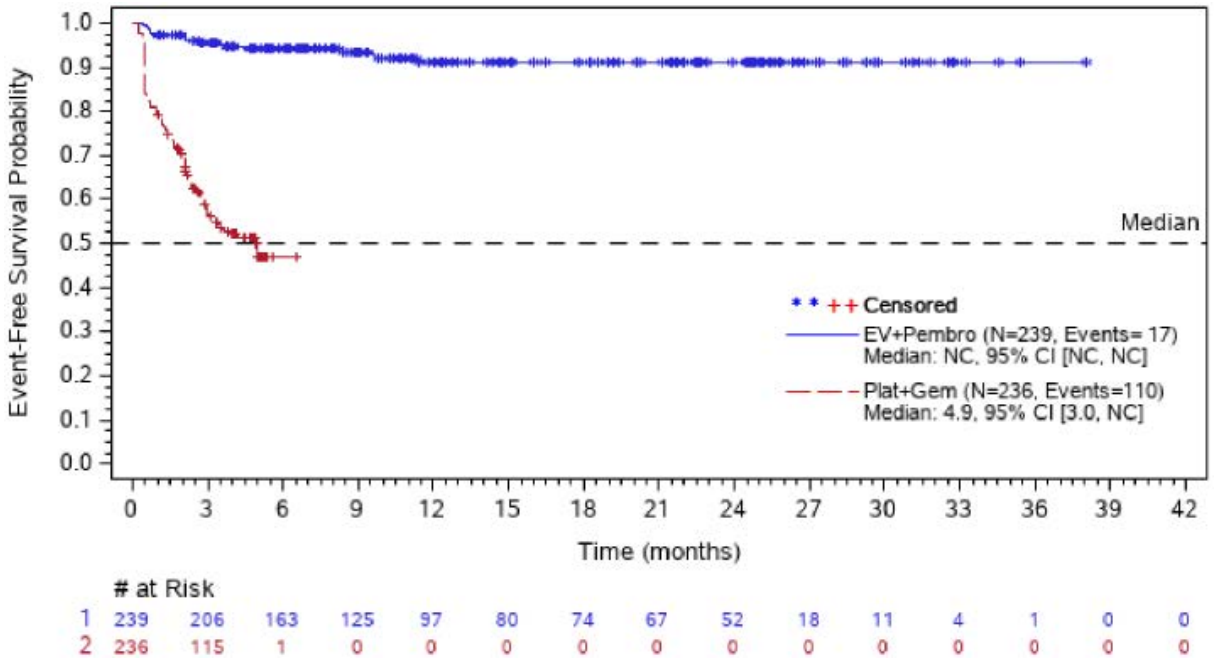


Figure 52: Kaplan-Meier curves for the outcome of blood and lymphatic system disorders (severe AEs) of the RCT EV-302/KN-A39, 2nd data cut-off (08 August 2024), subpopulation 1 (cisplatin suitable)

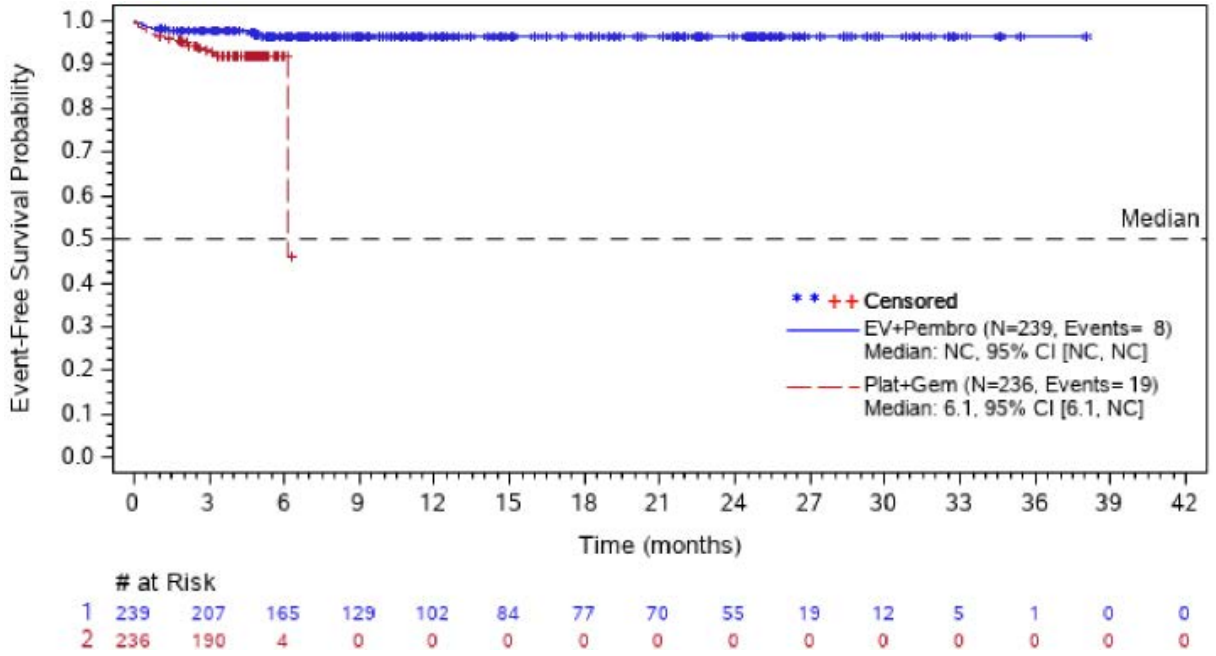


Figure 53: Kaplan-Meier curves for the outcome of urinary tract infection (severe AEs) of the RCT EV-302/KN-A39, 2nd data cut-off (08 August 2024), subpopulation 1 (cisplatin suitable)

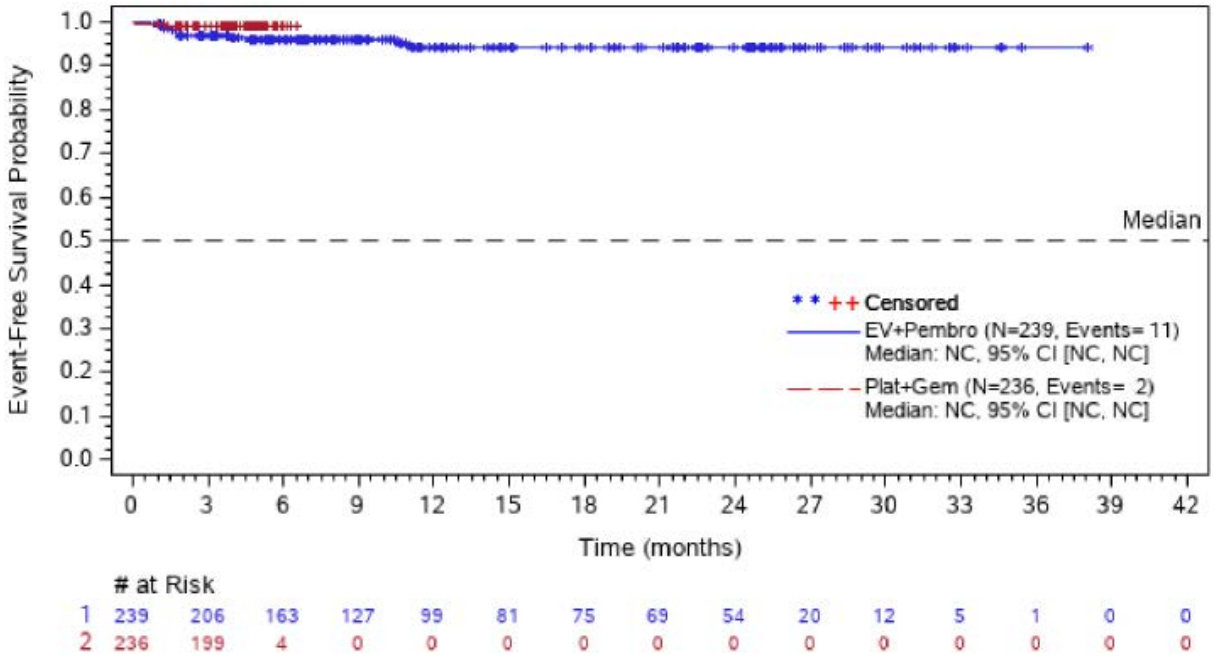


Figure 54: Kaplan-Meier curves for the outcome of diarrhoea (severe AEs) of the RCT EV-302/KN-A39, 2nd data cut-off (08 August 2024), subpopulation 1 (cisplatin suitable)

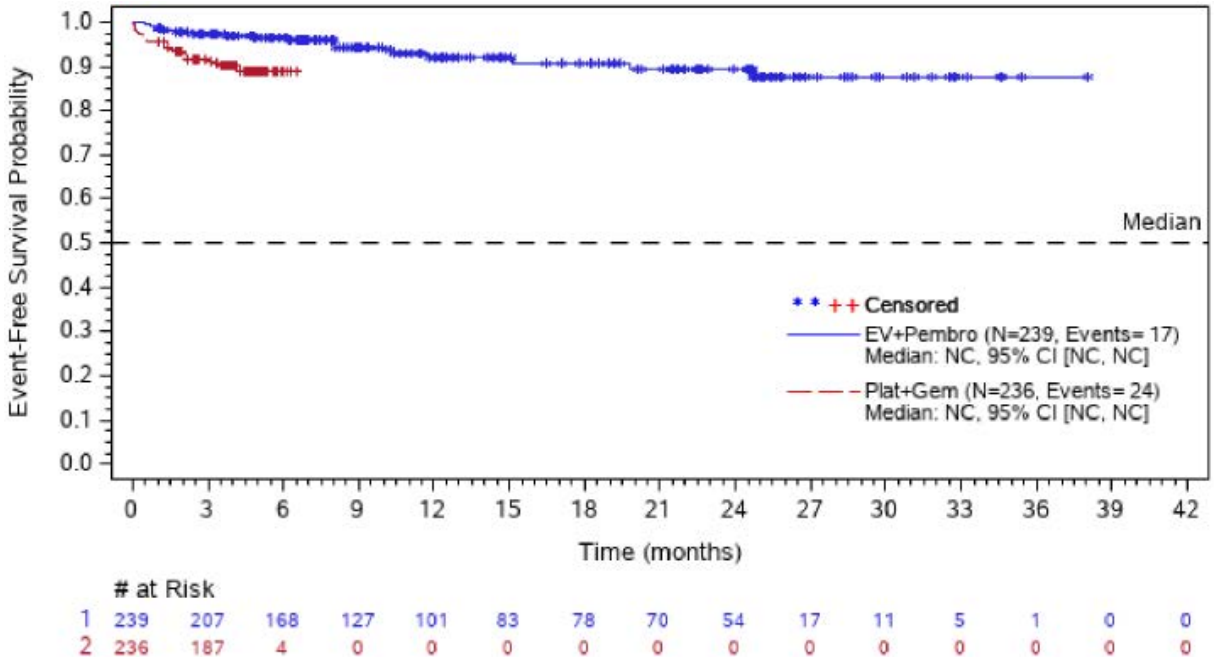


Figure 55: Kaplan-Meier curves for the outcome of general disorders and administration site conditions (severe AEs) of the RCT EV-302/KN-A39, 2nd data cut-off (08 August 2024), subpopulation 1 (cisplatin suitable)

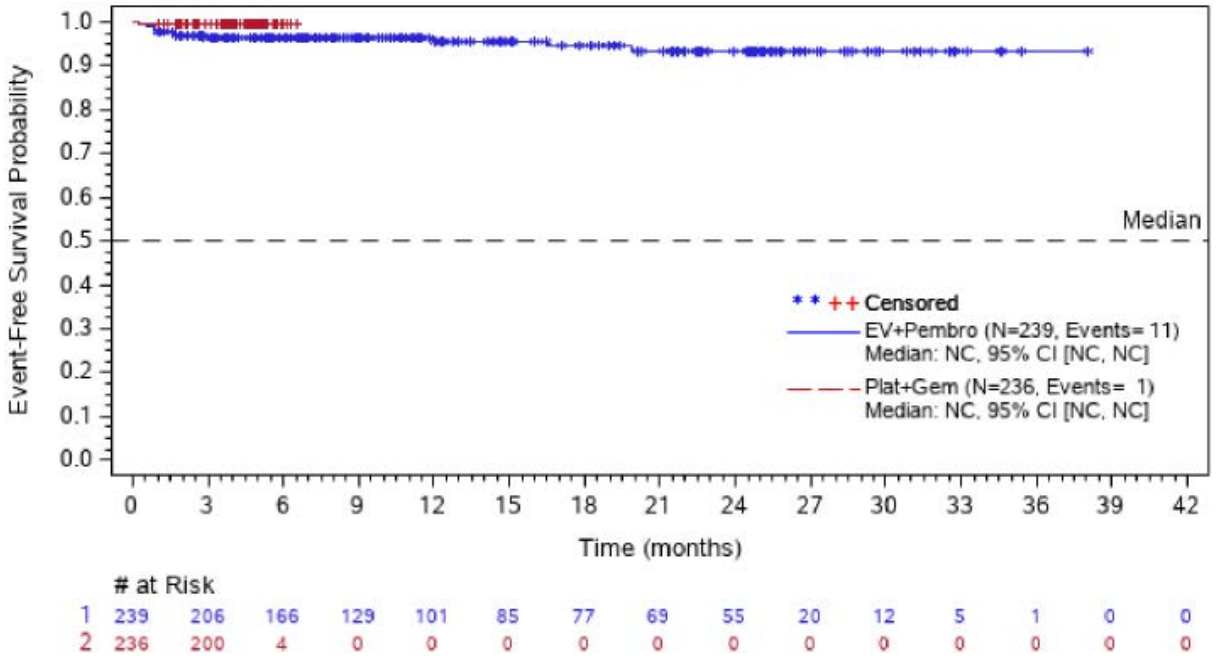


Figure 56: Kaplan-Meier curves for the outcome of hepatobiliary disorders (severe AEs) of the RCT EV-302/KN-A39, 2nd data cut-off (08 August 2024), subpopulation 1 (cisplatin suitable)

B.2 Research question 2: Patients for whom cisplatin-based therapy is unsuitable

B.2.1 Mortality

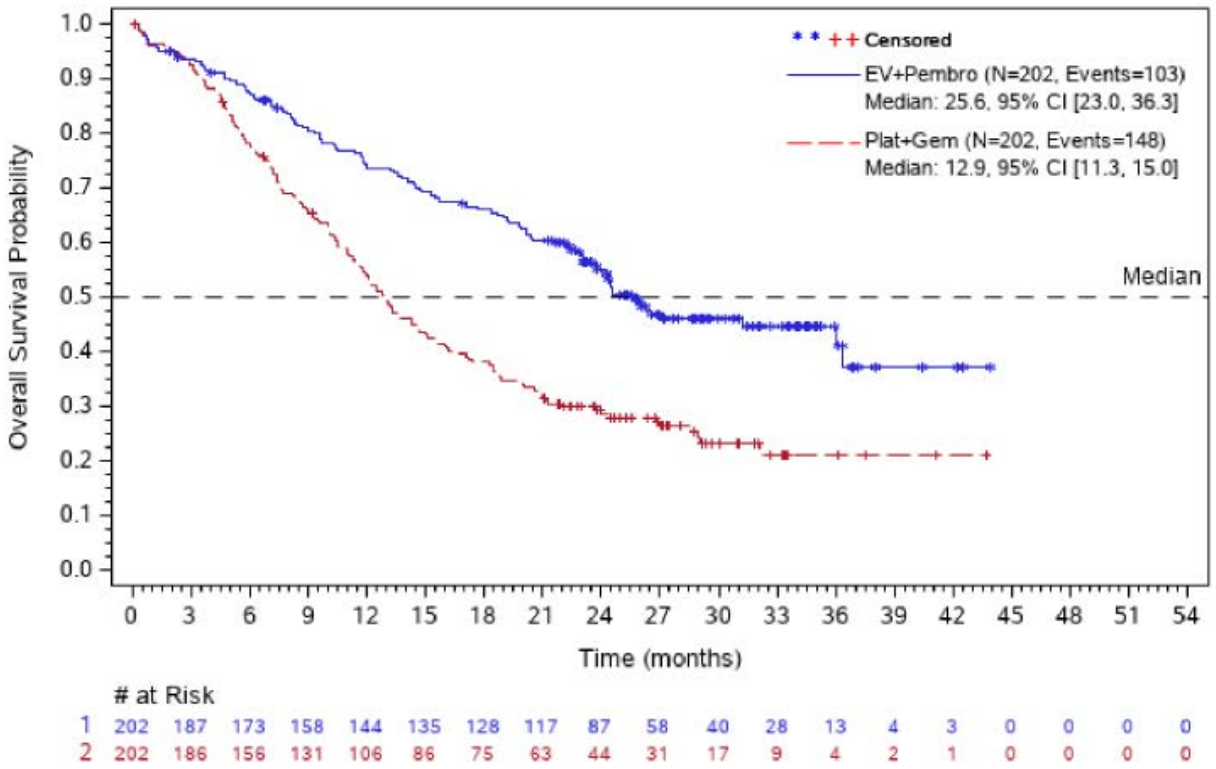


Figure 57: Kaplan-Meier curves for the outcome of overall survival of the RCT EV-302/KN-A39, 2nd data cut-off (08 August 2024), subpopulation 2 (cisplatin unsuitable)

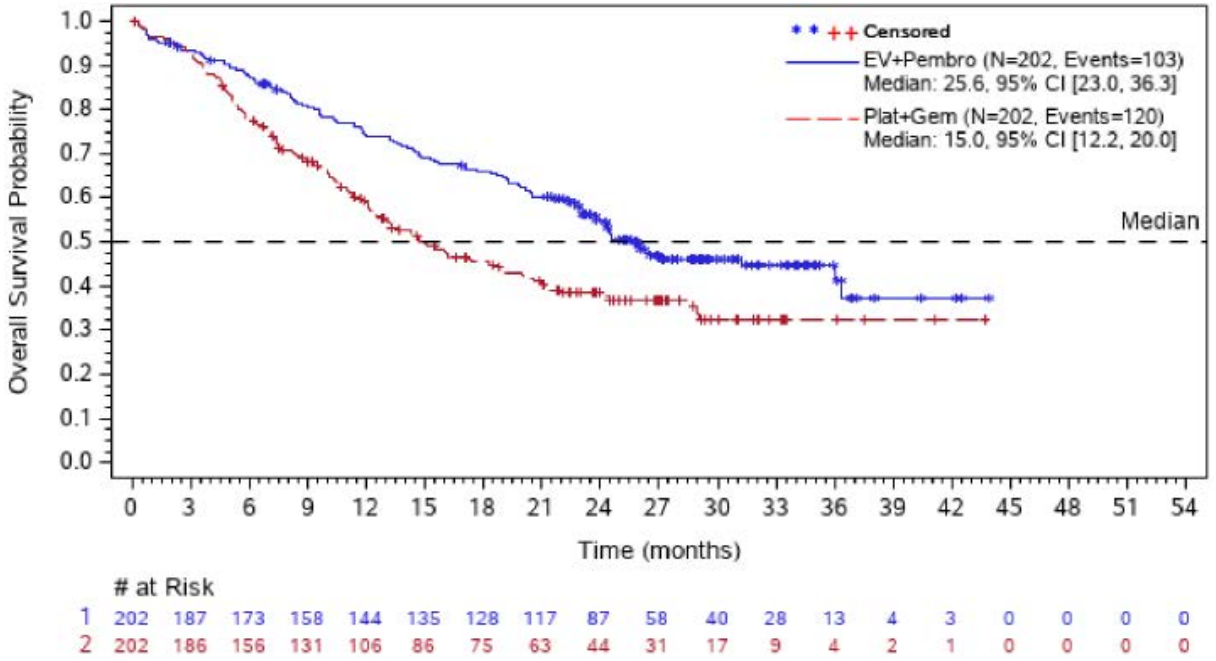


Figure 58: Kaplan-Meier curves for sensitivity analysis 1 of the company for the outcome of overall survival of the RCT EV-302/KN-A39, 2nd data cut-off (8 August 2024), subpopulation 2 (cisplatin unsuitable)

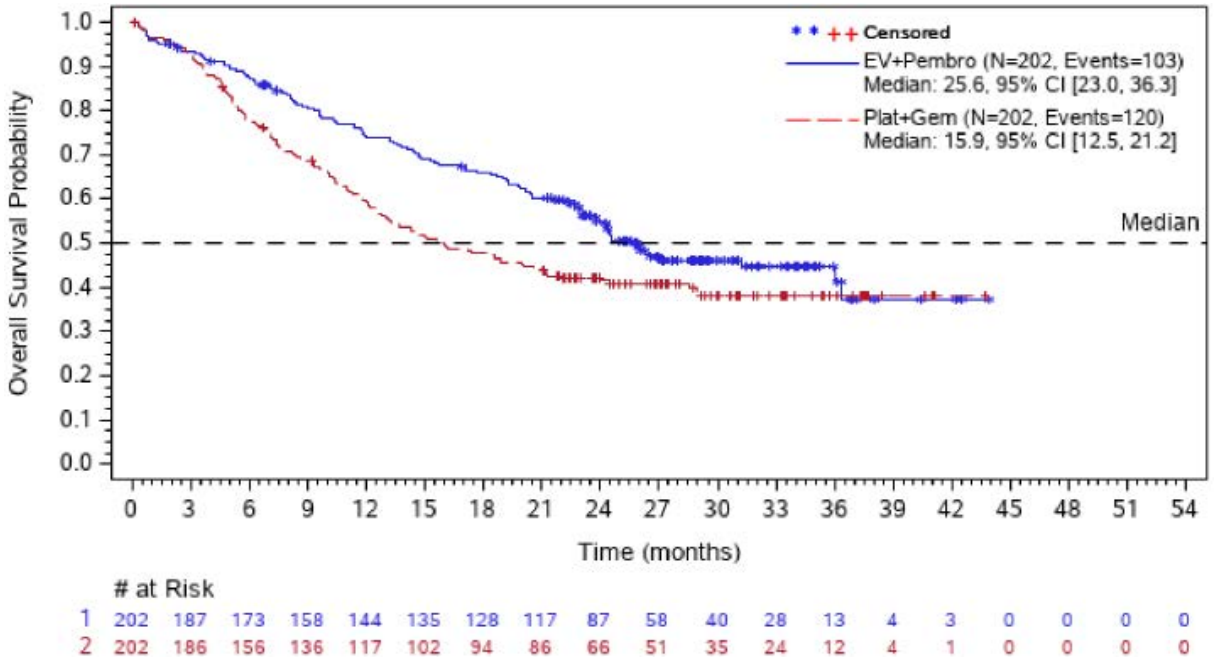


Figure 59: Kaplan-Meier curves for sensitivity analysis 2 of the company for the outcome of overall survival of the RCT EV-302/KN-A39, 2nd data cut-off (8 August 2024), subpopulation 2 (cisplatin unsuitable)

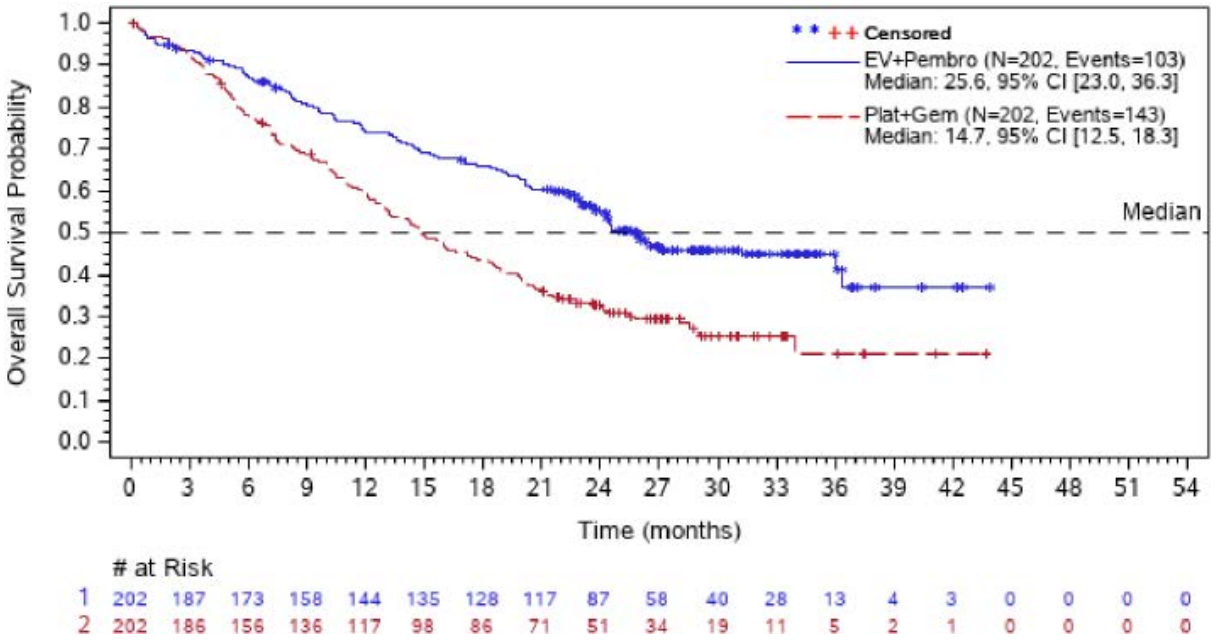


Figure 60: Kaplan-Meier curves for sensitivity analysis 2 of the company for the outcome of overall survival of the RCT EV-302/KN-A39, 2nd data cut-off (8 August 2024), subpopulation 2 (cisplatin unsuitable)

B.2.2 Morbidity

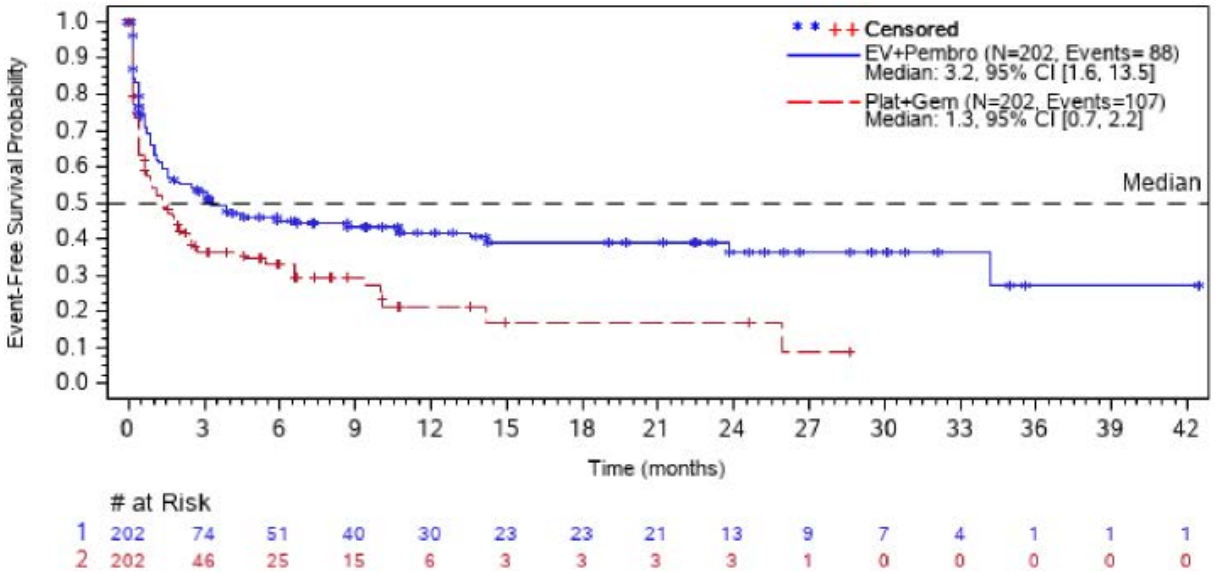


Figure 61: Kaplan-Meier curves for the outcome of worst pain (BPI-SF item 3 - time to 1st deterioration) of the RCT EV-302/KN-A39, 2nd data cut-off (08 August 2024), subpopulation 2 (cisplatin unsuitable)

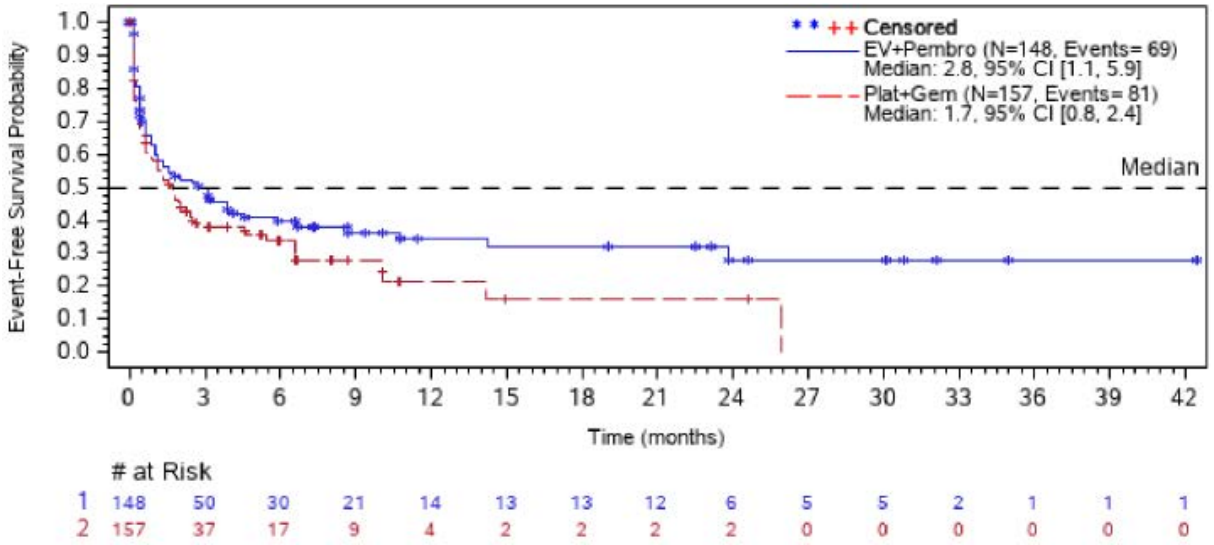


Figure 62: Kaplan-Meier curves for the outcome of worst pain (BPI-SF item 3 - time to 1st deterioration) of the RCT EV-302/KN-A39, 2nd data cut-off (08 August 2024), subpopulation 2 (cisplatin unsuitable), subgroup: visceral metastases

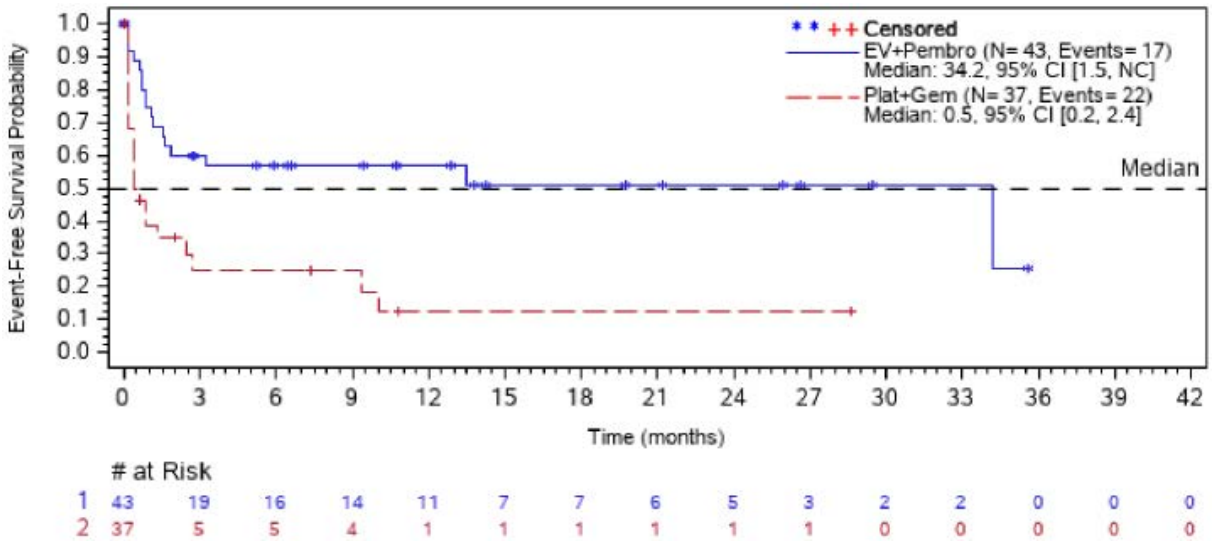


Figure 63: Kaplan-Meier curves for the outcome of worst pain (BPI-SF item 3 - time to 1st deterioration) of the RCT EV-302/KN-A39, 2nd data cut-off (08 August 2024), subpopulation 2 (cisplatin unsuitable), subgroup: exclusively lymph node metastases

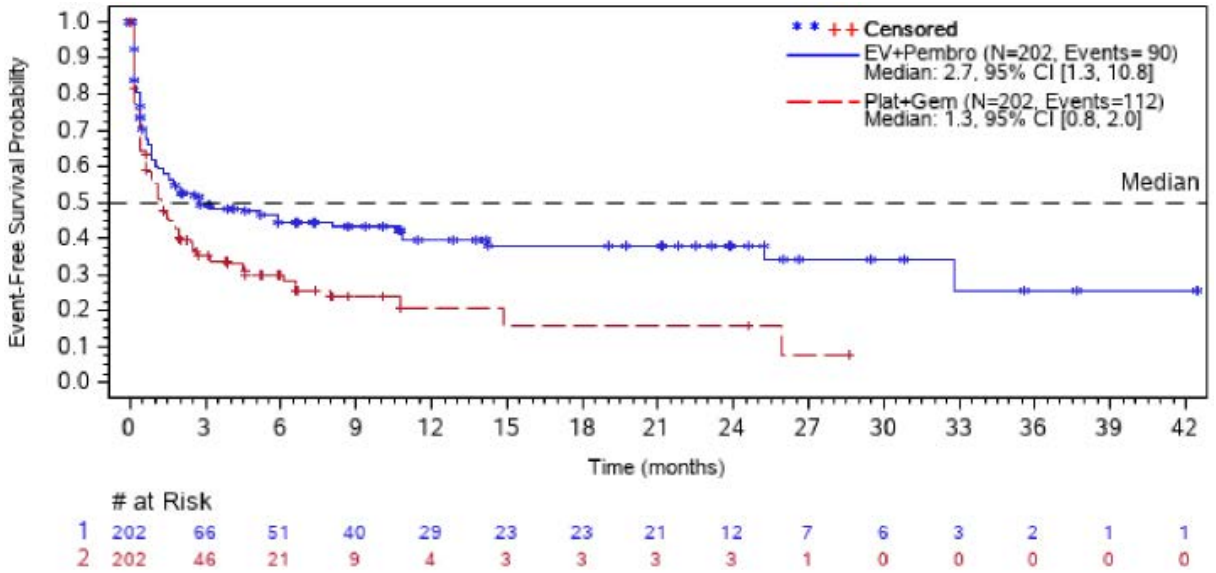


Figure 64: Kaplan-Meier curves for the outcome of pain interference (BPI-SF items 9a-9g - time to 1st deterioration) of the RCT EV-302/KN-A39, 2nd data cut-off (08 August 2024), subpopulation 2 (cisplatin unsuitable)

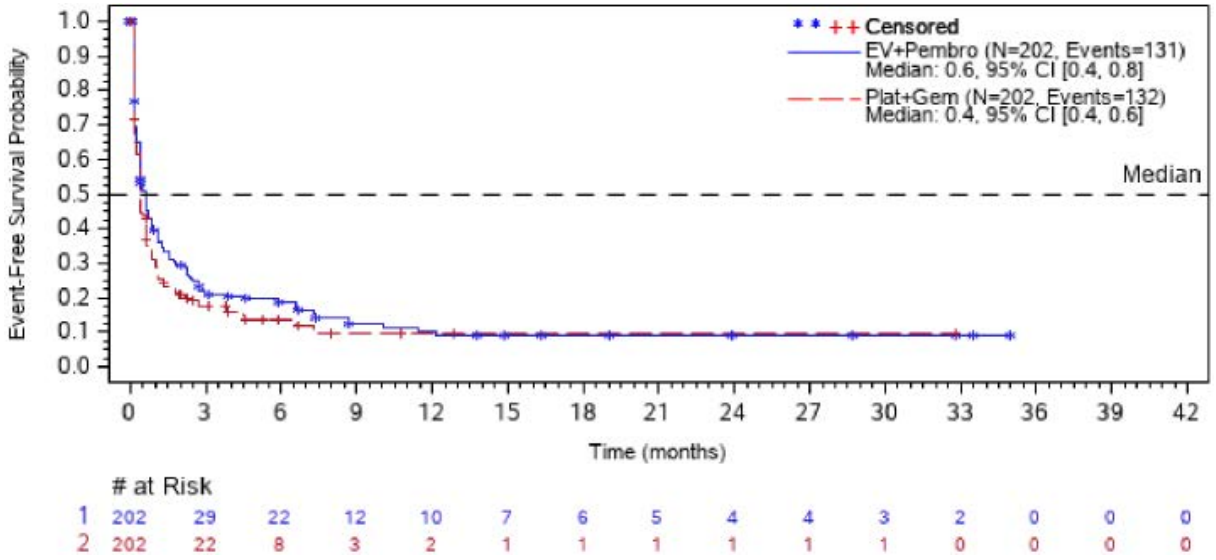


Figure 65: Kaplan-Meier curves for the outcome of fatigue (EORTC-QLQ-C30 - time to 1st deterioration) of the RCT EV-302/KN-A39, 2nd data cut-off (08 August 2024), subpopulation 2 (cisplatin unsuitable)

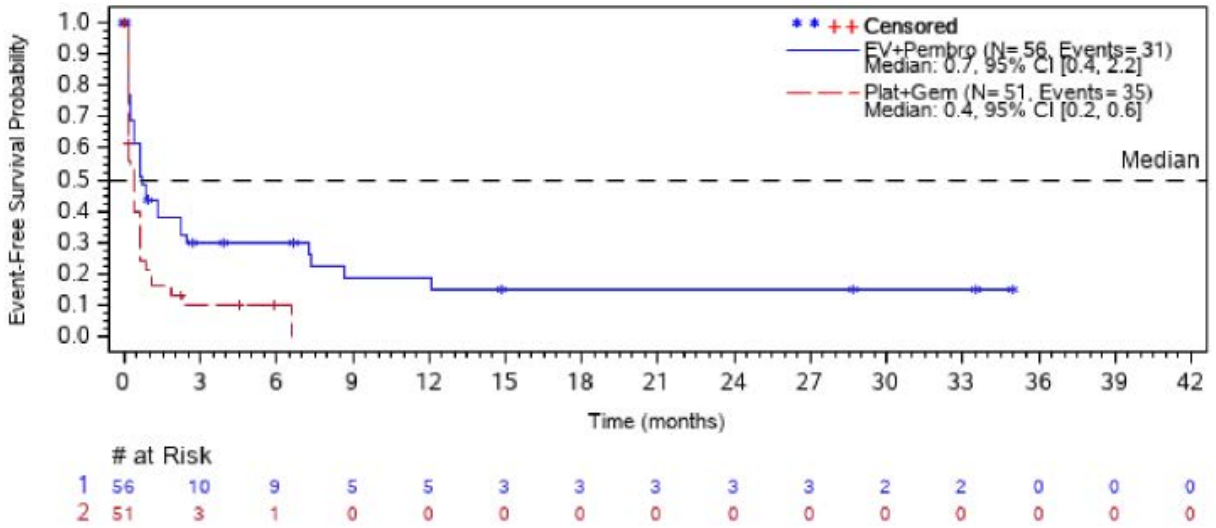


Figure 66: Kaplan-Meier curves for the outcome of fatigue (EORTC-QLQ-C30 - time to 1st deterioration) of the RCT EV-302/KN-A39, 2nd data cut-off (08 August 2024), subpopulation 2 (cisplatin unsuitable), subgroup: women

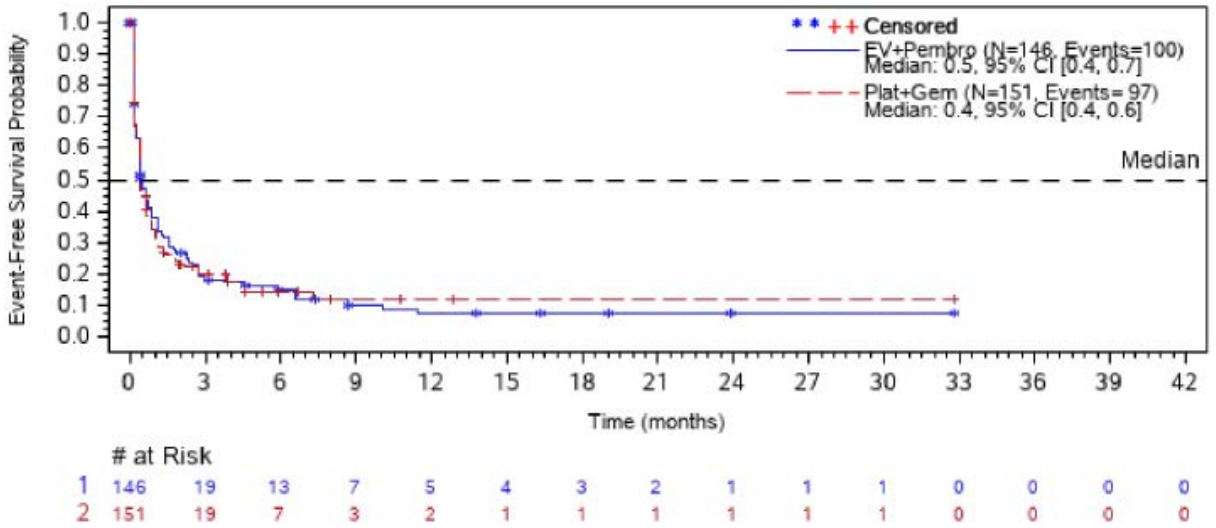


Figure 67: Kaplan-Meier curves for the outcome of fatigue (EORTC-QLQ-C30 - time to 1st deterioration) of the RCT EV-302/KN-A39, 2nd data cut-off (08 August 2024), subpopulation 2 (cisplatin unsuitable), subgroup: men

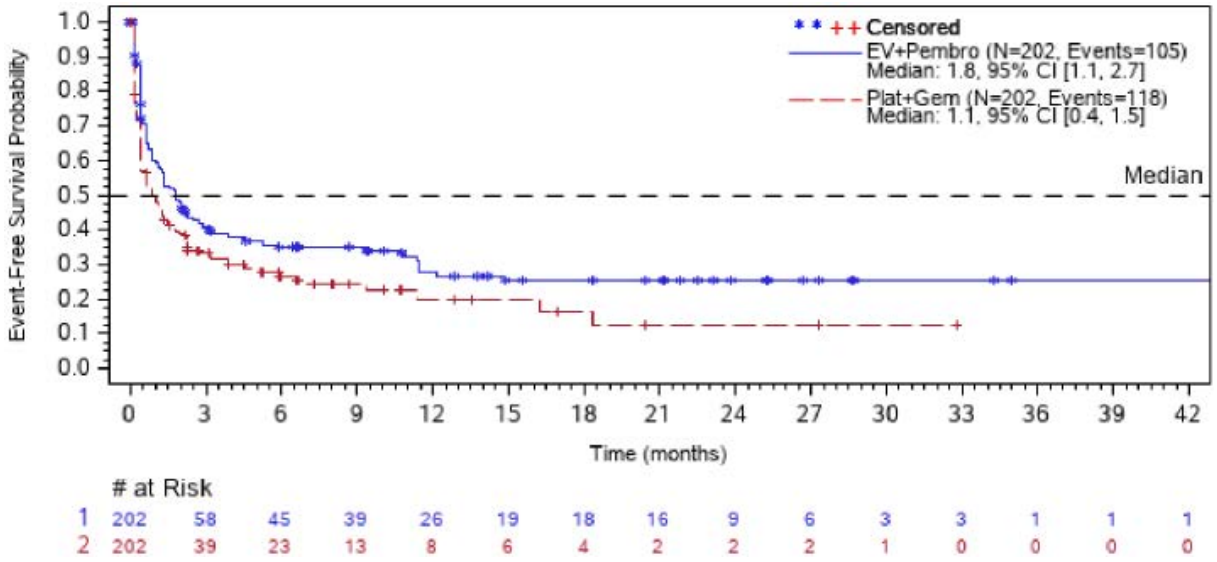


Figure 68: Kaplan-Meier curves for the outcome of nausea and vomiting (EORTC QLQ-C30 - time to 1st deterioration) of the RCT EV-302/KN-A39, 2nd data cut-off (08 August 2024), subpopulation 2 (cisplatin unsuitable)

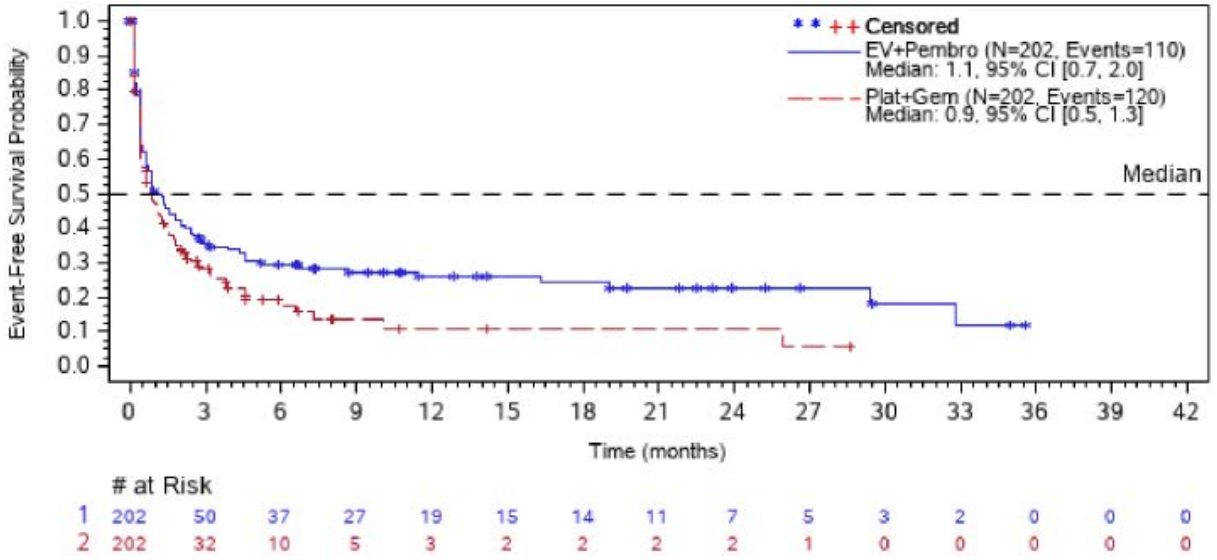


Figure 69: Kaplan-Meier curves for the outcome of pain (EORTC-QLQ-C30 - time to 1st deterioration) of the RCT EV-302/KN-A39, 2nd data cut-off (08 August 2024), subpopulation 2 (cisplatin unsuitable)

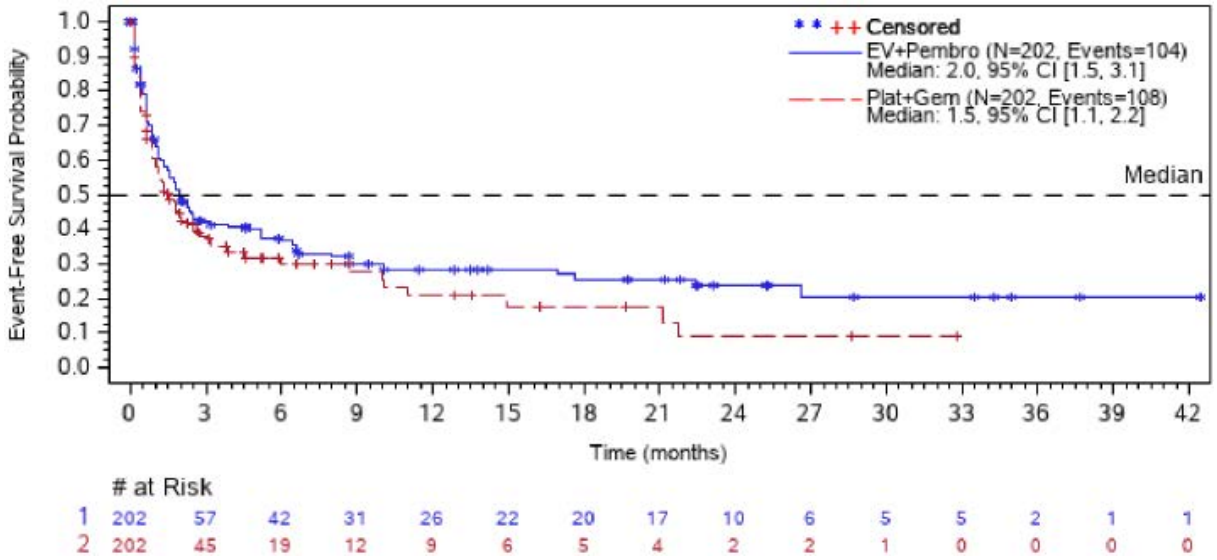


Figure 70: Kaplan-Meier curves for the outcome of dyspnoea (EORTC-QLQ-C30 - time to 1st deterioration) of the RCT EV-302/KN-A39, 2nd data cut-off (08 August 2024), subpopulation 2 (cisplatin unsuitable)

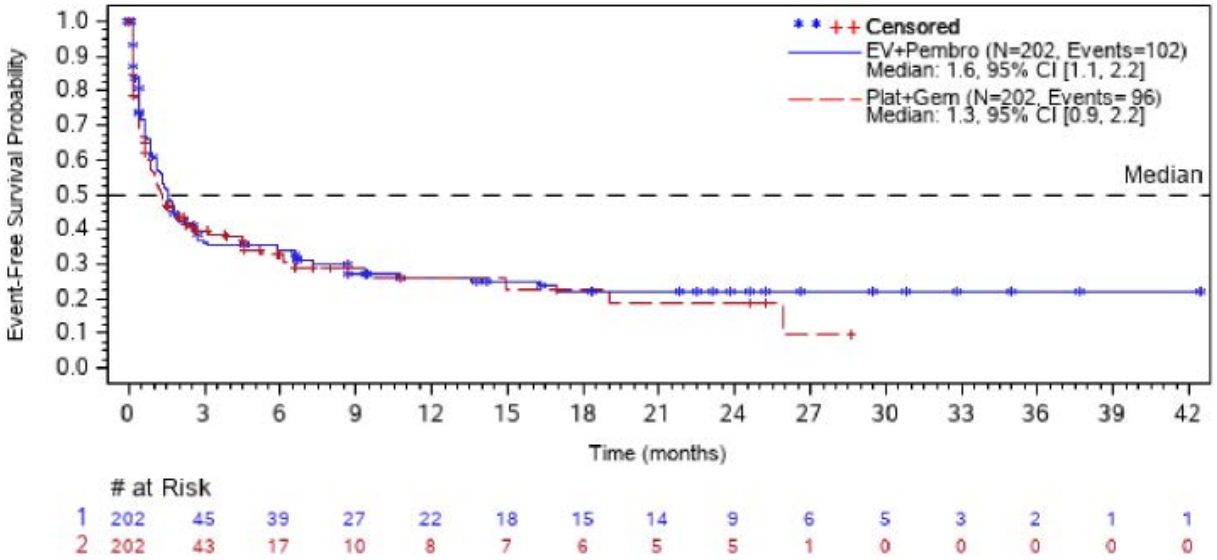


Figure 71: Kaplan-Meier curves for the outcome of insomnia (EORTC-QLQ-C30 - time to 1st deterioration) of the RCT EV-302/KN-A39, 2nd data cut-off (08 August 2024), subpopulation 2 (cisplatin unsuitable)

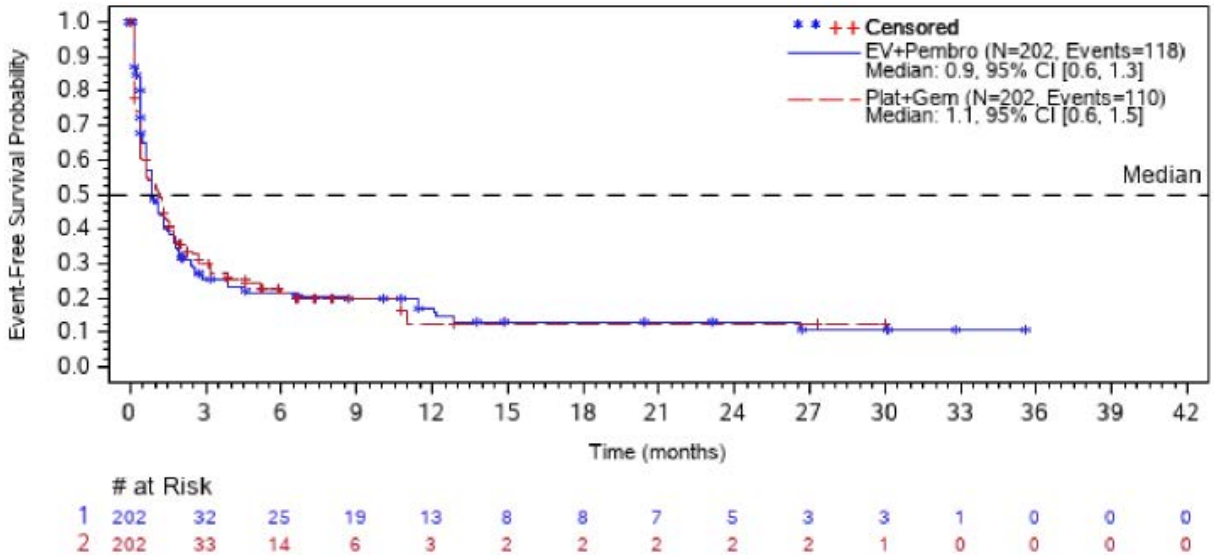


Figure 72: Kaplan-Meier curves for the outcome of appetite loss (EORTC-QLQ-C30 - time to 1st deterioration) of the RCT EV-302/KN-A39, 2nd data cut-off (08 August 2024), subpopulation 2 (cisplatin unsuitable)

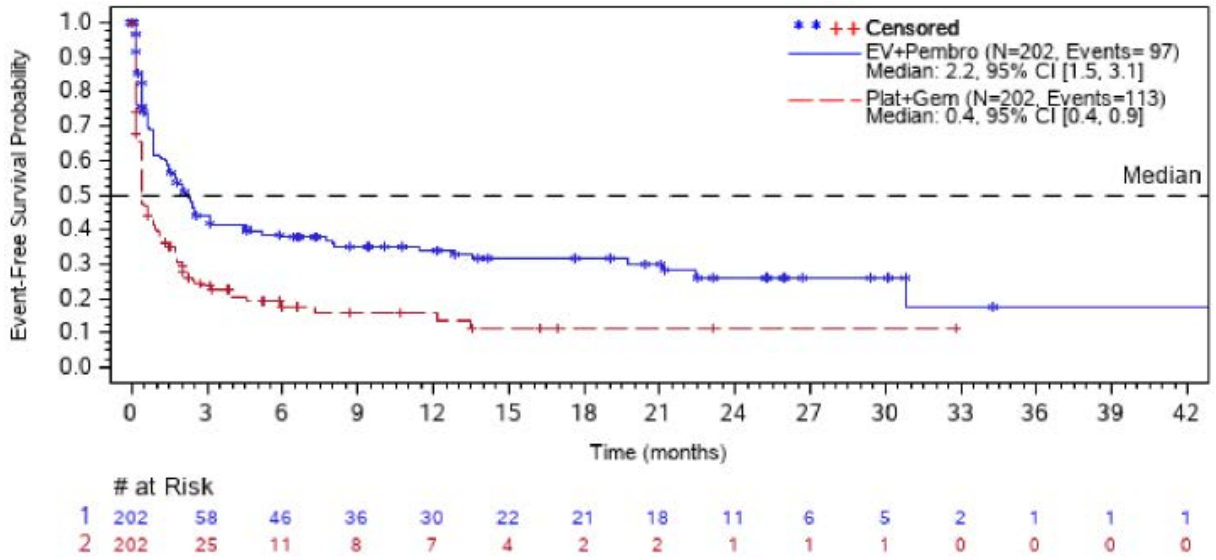


Figure 73: Kaplan-Meier curves for the outcome of constipation (EORTC-QLQ-C30 - time to 1st deterioration) of the RCT EV-302/KN-A39, 2nd data cut-off (08 August 2024), subpopulation 2 (cisplatin unsuitable)

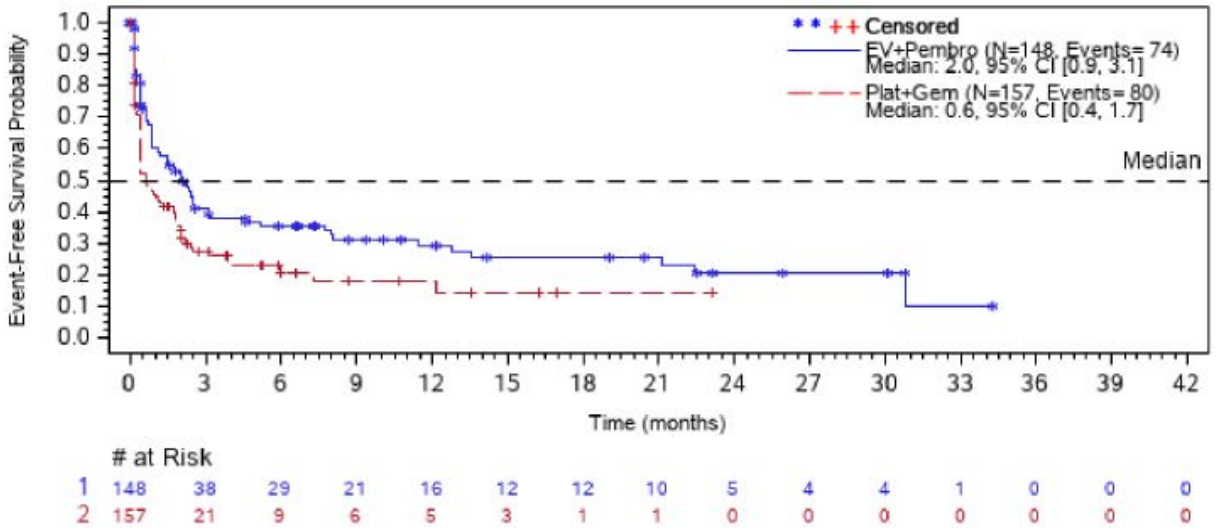


Figure 74: Kaplan-Meier curves for the outcome of constipation (EORTC-QLQ-C30 - time to 1st deterioration) of the RCT EV-302/KN-A39, 2nd data cut-off (08 August 2024), subpopulation 2 (cisplatin unsuitable), subgroup: visceral metastases

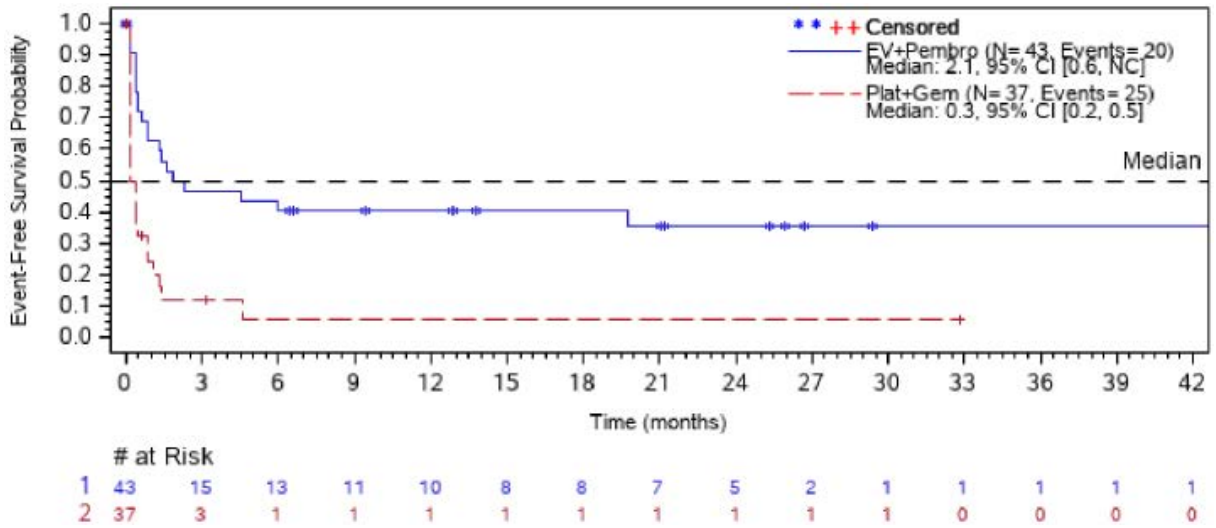


Figure 75: Kaplan-Meier curves for the outcome of constipation (EORTC-QLQ-C30 - time to 1st deterioration) of the RCT EV-302/KN-A39, 2nd data cut-off (08 August 2024), subpopulation 2 (cisplatin unsuitable), subgroup: exclusively lymph node metastases

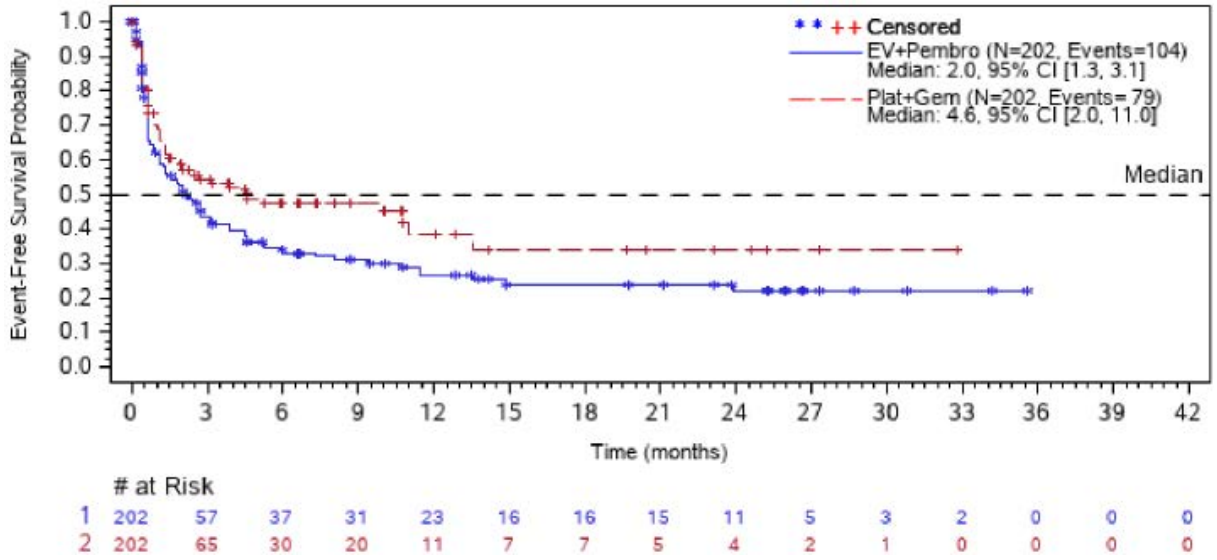


Figure 76: Kaplan-Meier curves for the outcome of diarrhoea (EORTC-QLQ-C30 - time to 1st deterioration) of the RCT EV-302/KN-A39, 2nd data cut-off (08 August 2024), subpopulation 2 (cisplatin unsuitable)

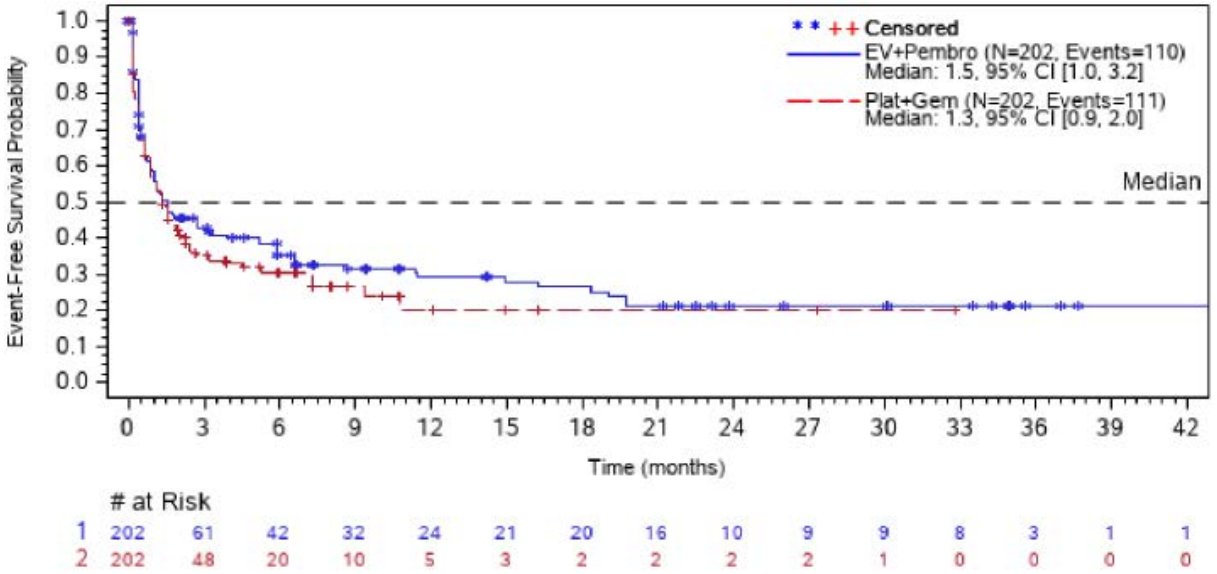


Figure 77: Kaplan-Meier curves for the outcome of health status (EQ-5D - time to 1st deterioration) of the RCT EV-302/KN-A39, 2nd data cut-off (08 August 2024), subpopulation 2 (cisplatin unsuitable)

B.2.3 Health-related quality of life

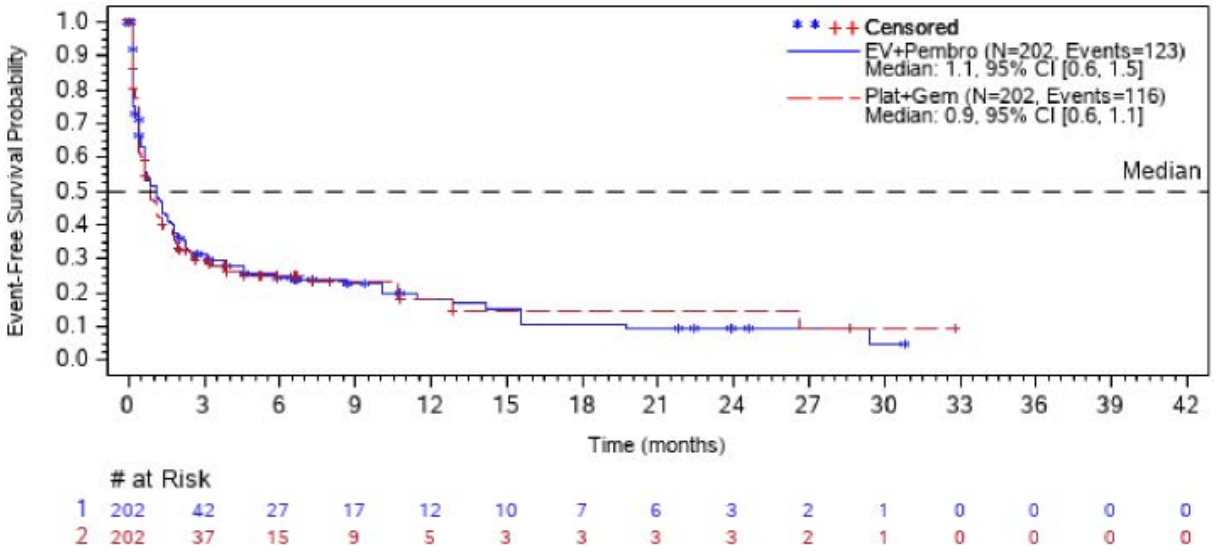


Figure 78: Kaplan-Meier curves for the outcome of global health status (EORTC-QLQ-C30 - time to 1st deterioration) of the RCT EV-302/KN-A39, 2nd data cut-off (08 August 2024), subpopulation 2 (cisplatin unsuitable)

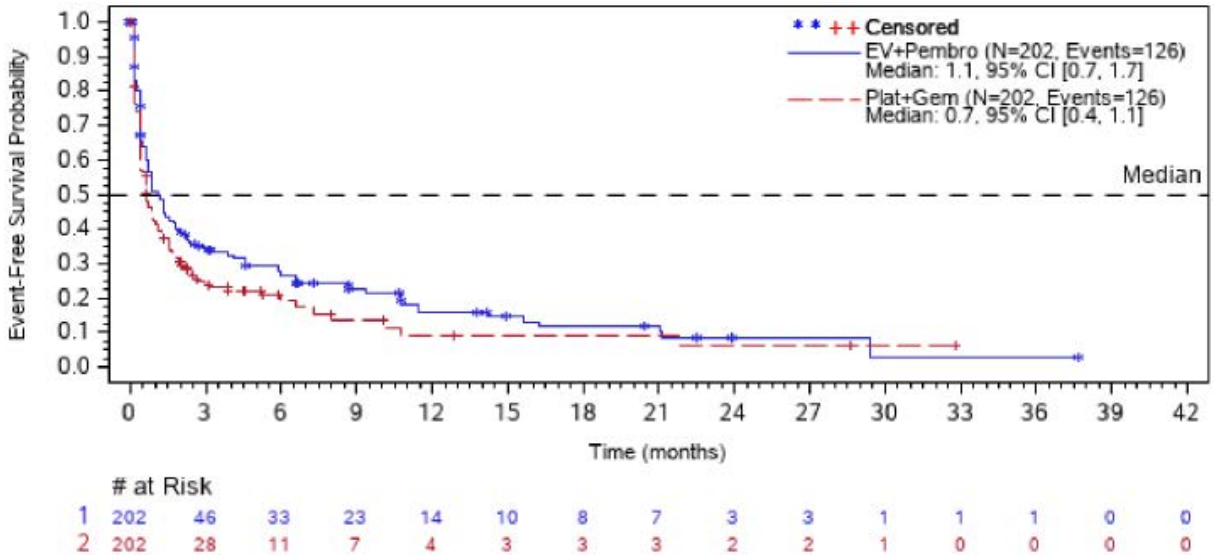


Figure 79: Kaplan-Meier curves for the outcome of physical functioning (EORTC QLQ-C30 - time to 1st deterioration) of the RCT EV-302/KN-A39, 2nd data cut-off (08 August 2024), subpopulation 2 (cisplatin unsuitable)

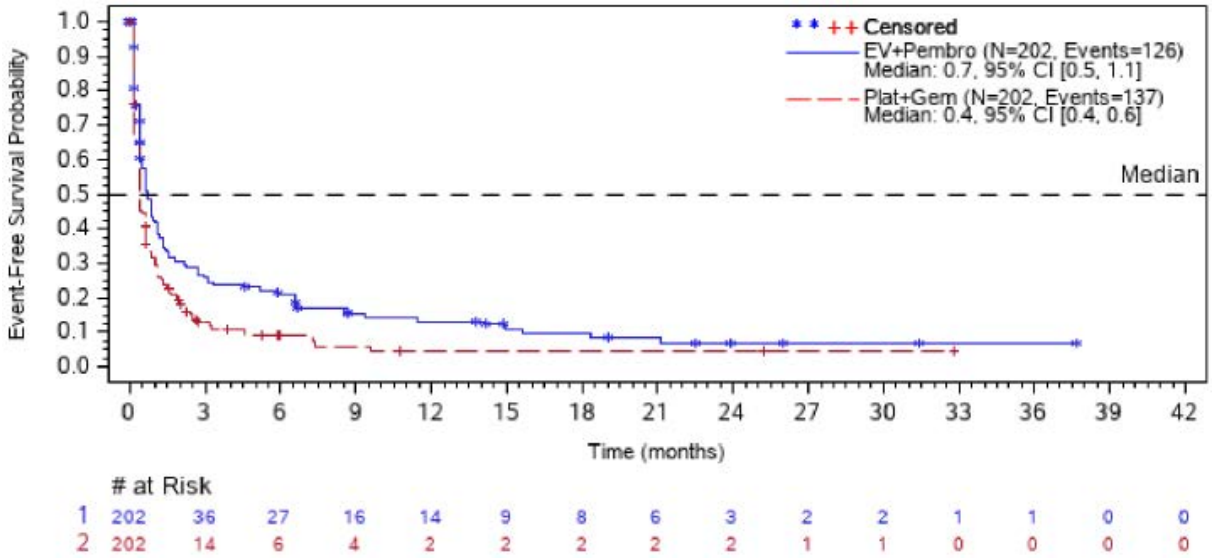


Figure 80: Kaplan-Meier curves for the outcome of role functioning (EORTC-QLQ-C30 - time to 1st deterioration) of the RCT EV-302/KN-A39, 2nd data cut-off (08 August 2024), subpopulation 2 (cisplatin unsuitable)

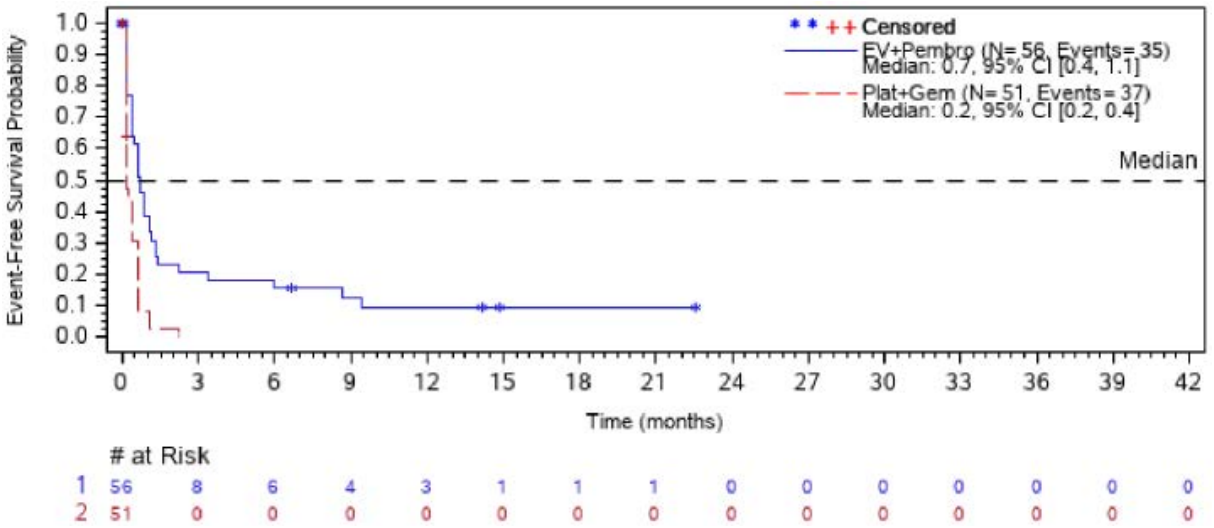


Figure 81: Kaplan-Meier curves for the outcome of role functioning (EORTC-QLQ-C30 - time to 1st deterioration) of the RCT EV-302/KN-A39, 2nd data cut-off (08 August 2024), subpopulation 2 (cisplatin unsuitable), subgroup: women

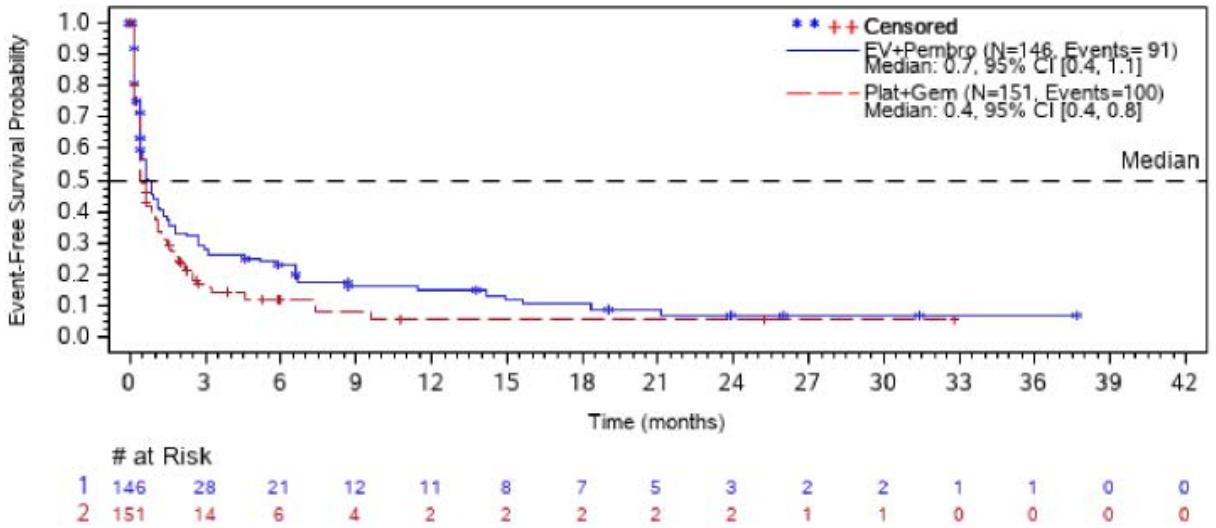


Figure 82: Kaplan-Meier curves for the outcome of role functioning (EORTC-QLQ-C30 - time to 1st deterioration) of the RCT EV-302/KN-A39, 2nd data cut-off (08 August 2024), subpopulation 2 (cisplatin unsuitable), subgroup: men

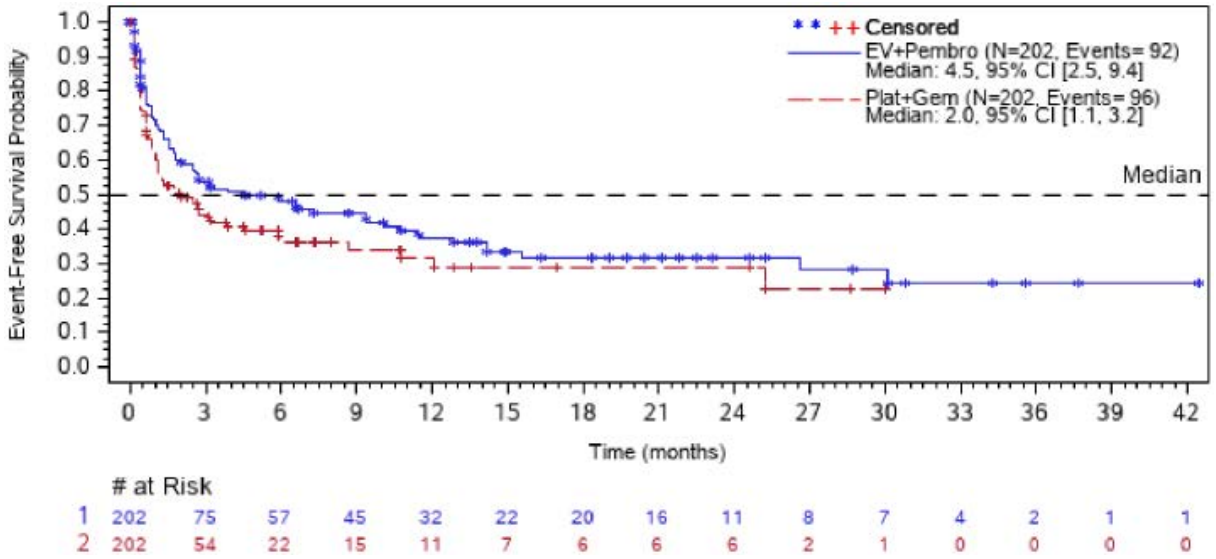


Figure 83: Kaplan-Meier curves for the outcome of emotional functioning (EORTC QLQ-C30 - time to 1st deterioration) of the RCT EV-302/KN-A39, 2nd data cut-off (08 August 2024), subpopulation 2 (cisplatin unsuitable)

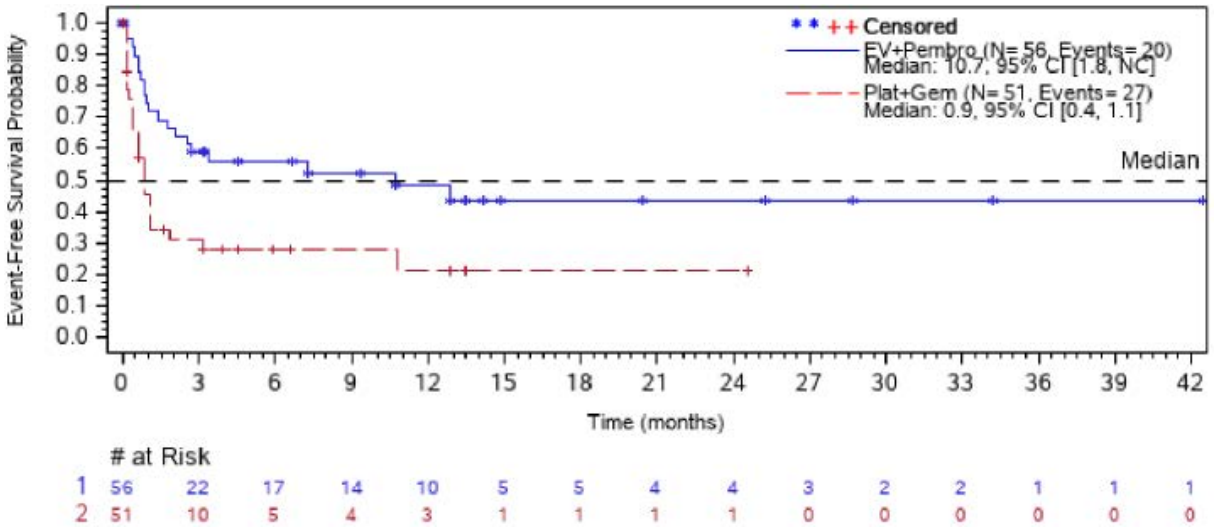


Figure 84: Kaplan-Meier curves for the outcome of emotional functioning (EORTC-QLQ-C30 - time to 1st deterioration) of the RCT EV-302/KN-A39, 2nd data cut-off (08 August 2024), subpopulation 2 (cisplatin unsuitable), subgroup: women

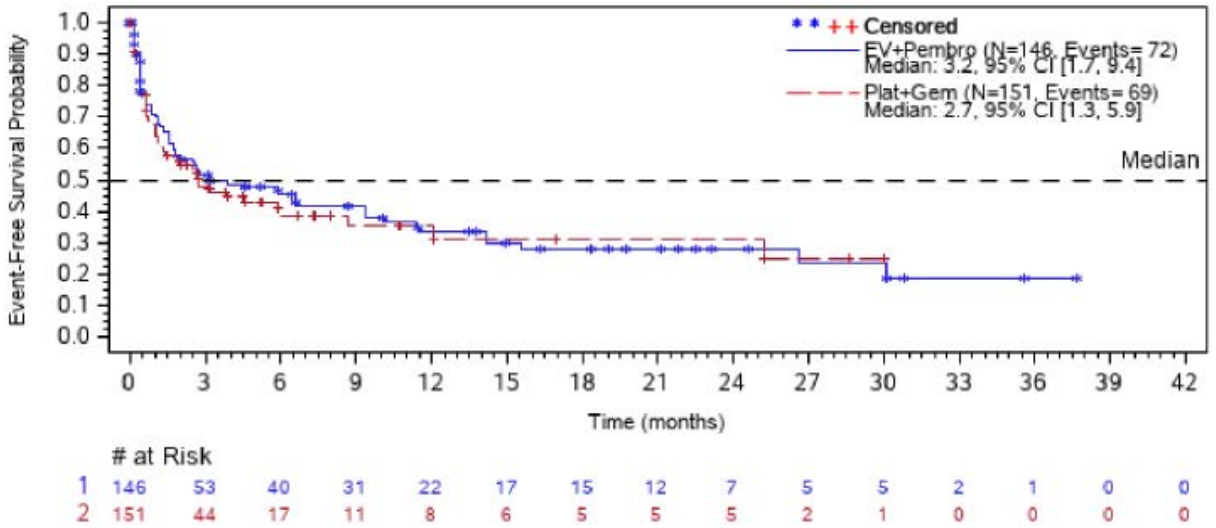


Figure 85: Kaplan-Meier curves for the outcome of emotional functioning (EORTC-QLQ-C30 - time to 1st deterioration) of the RCT EV-302/KN-A39, 2nd data cut-off (08 August 2024), subpopulation 2 (cisplatin unsuitable), subgroup: men

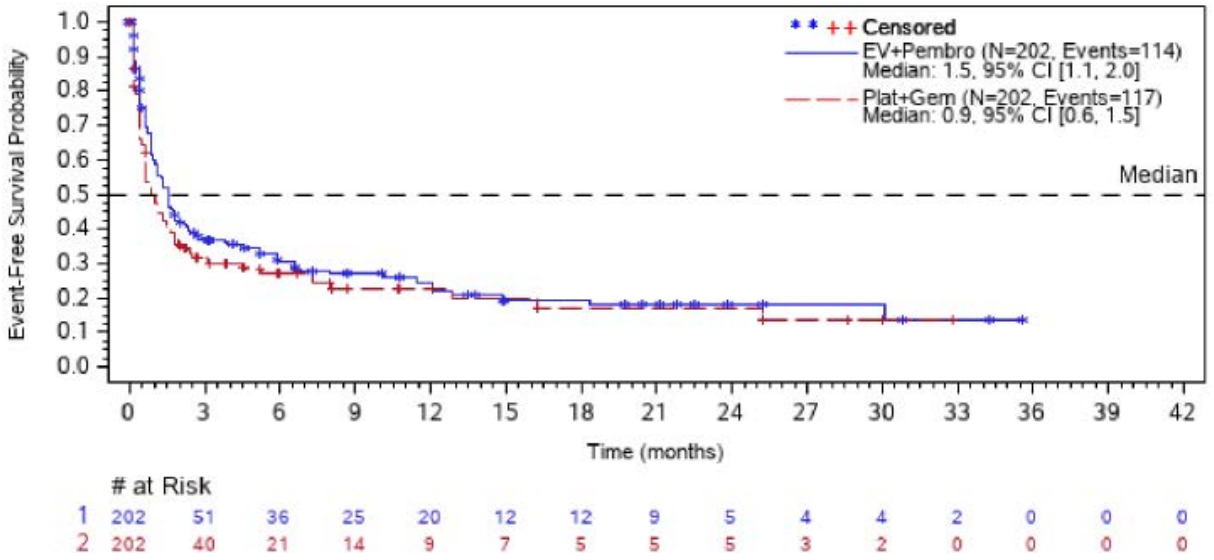


Figure 86: Kaplan-Meier curves for the outcome of cognitive functioning (EORTC QLQ-C30 - time to 1st deterioration) of the RCT EV-302/KN-A39, 2nd data cut-off (08 August 2024), subpopulation 2 (cisplatin unsuitable)

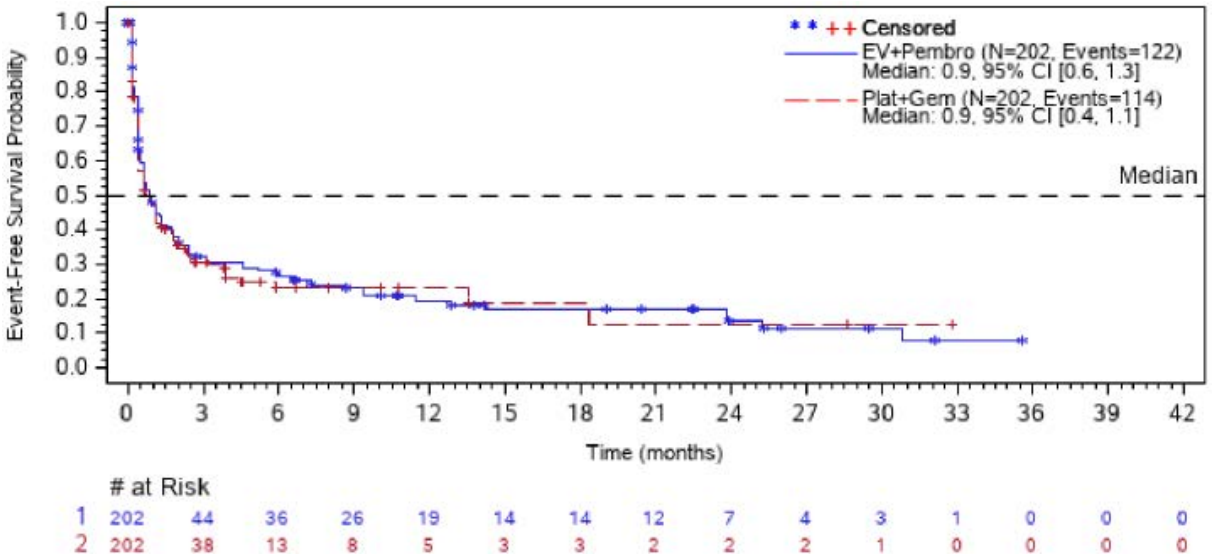


Figure 87: Kaplan-Meier curves for the outcome of social functioning (EORTC QLQ-C30 - time to 1st deterioration) of the RCT EV-302/KN-A39, 2nd data cut-off (08 August 2024), subpopulation 2 (cisplatin unsuitable)

B.2.4 Side effects

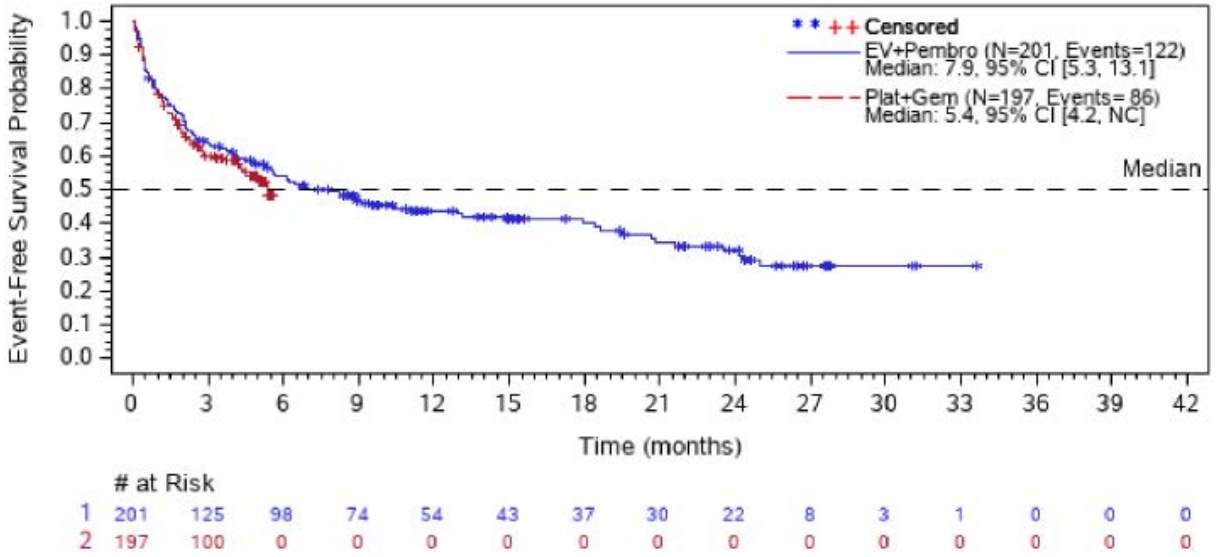


Figure 88: Kaplan-Meier curves for the outcome of SAEs of the RCT EV-302/KN-A39, 2nd data cut-off (08 August 2024), subpopulation 2 (cisplatin unsuitable)

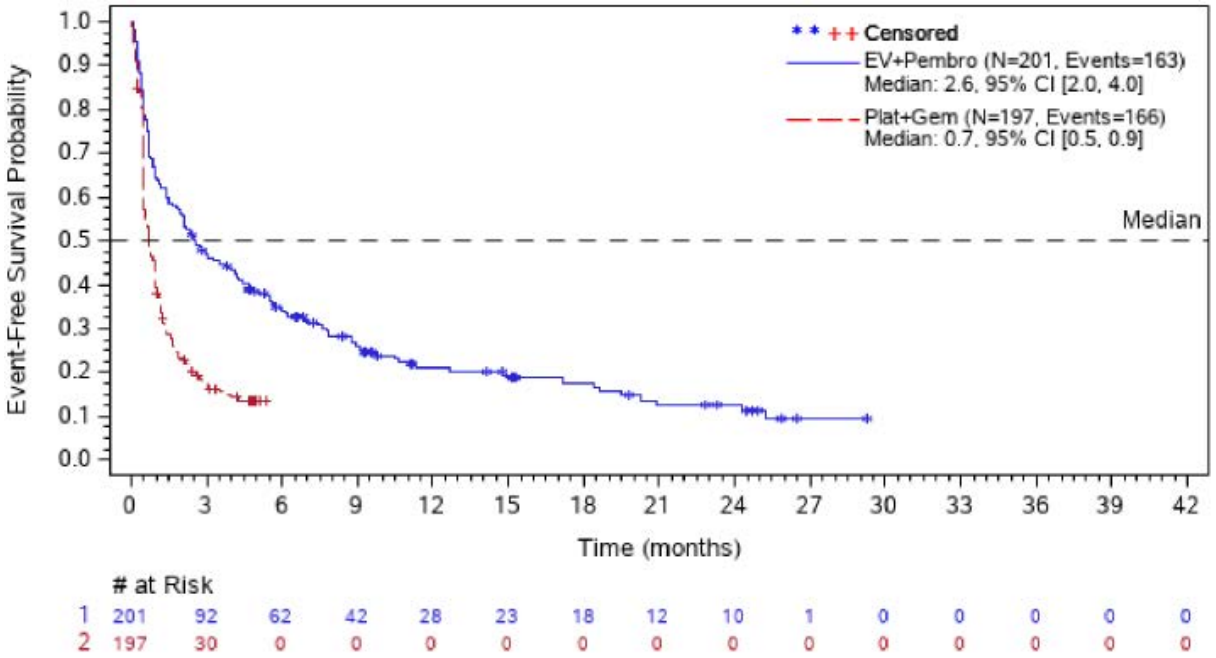


Figure 89: Kaplan-Meier curves for the outcome of severe AEs of the RCT EV-302/KN-A39, 2nd data cut-off (08 August 2024), subpopulation 2 (cisplatin unsuitable)

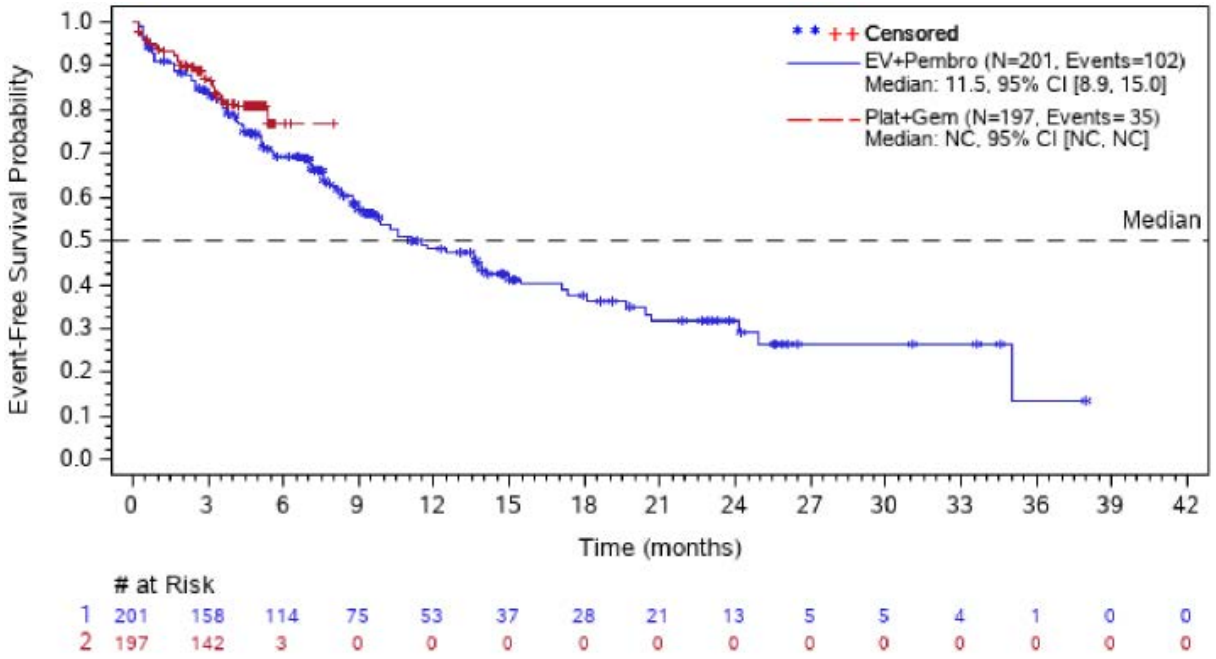


Figure 90: Kaplan-Meier curves for the outcome of discontinuation due to AEs of the RCT EV-302/KN-A39, 2nd data cut-off (08 August 2024), subpopulation 2 (cisplatin suitable)

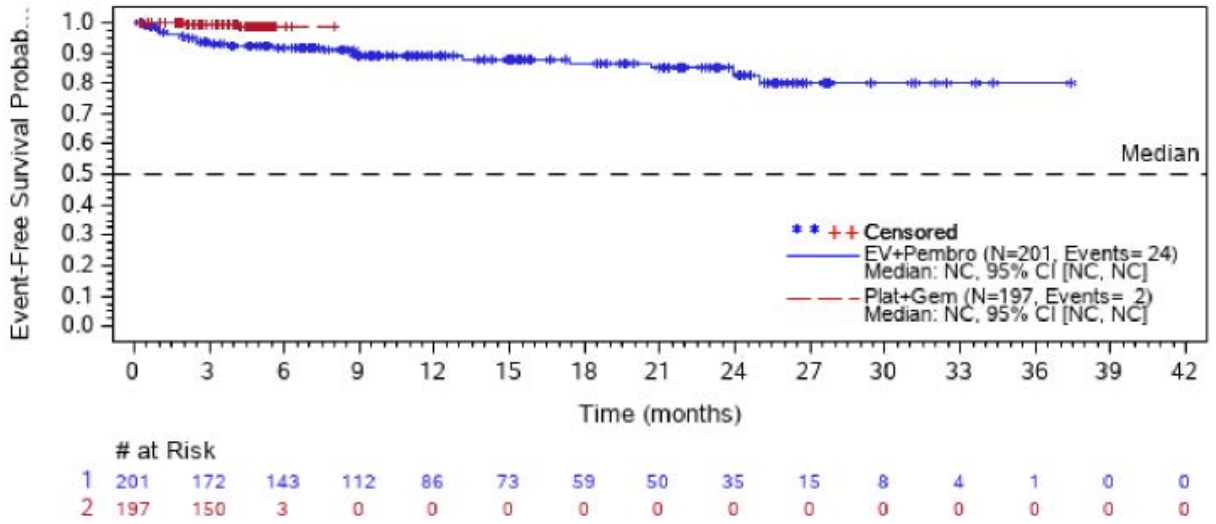


Figure 91: Kaplan-Meier curves for the outcome of immune-related SAEs of the RCT EV-302/KN-A39, 2nd data cut-off (08 August 2024), subpopulation 2 (cisplatin unsuitable)

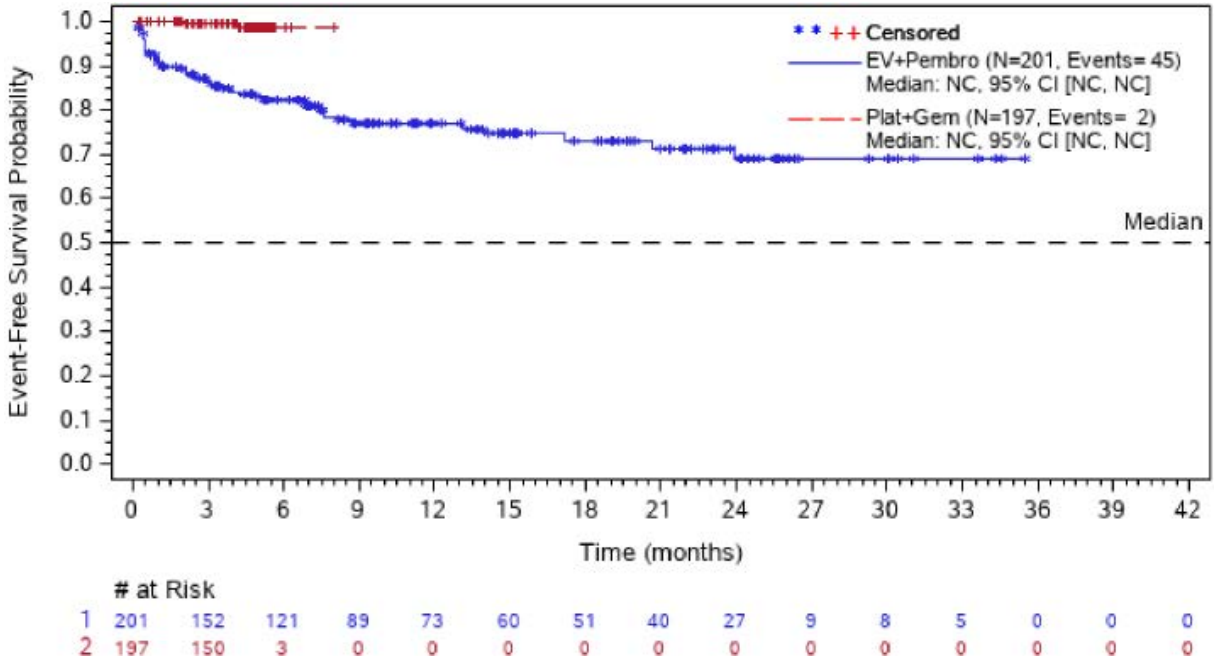


Figure 92: Kaplan-Meier curves for the outcome of immune-related severe AEs of the RCT EV-302/KN-A39, 2nd data cut-off (08 August 2024), subpopulation 2 (cisplatin unsuitable)

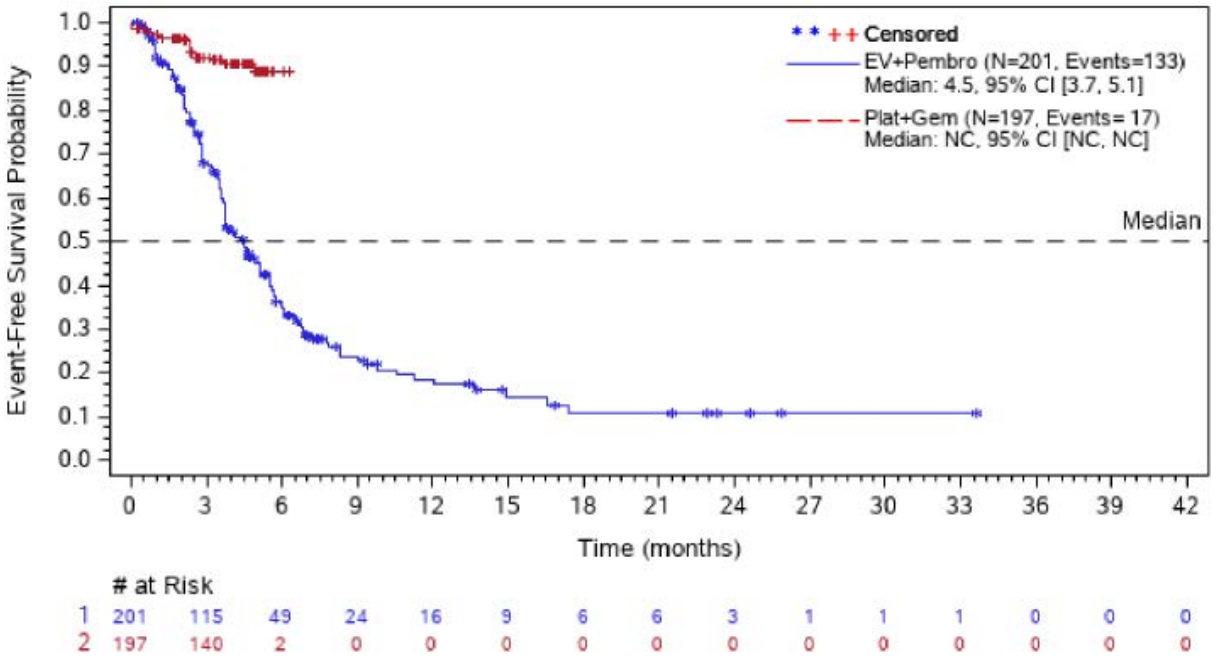


Figure 93: Kaplan-Meier curves for the outcome of peripheral neuropathy (AEs) of the RCT EV-302/KN-A39, 2nd data cut-off (08 August 2024), subpopulation 2 (cisplatin unsuitable)

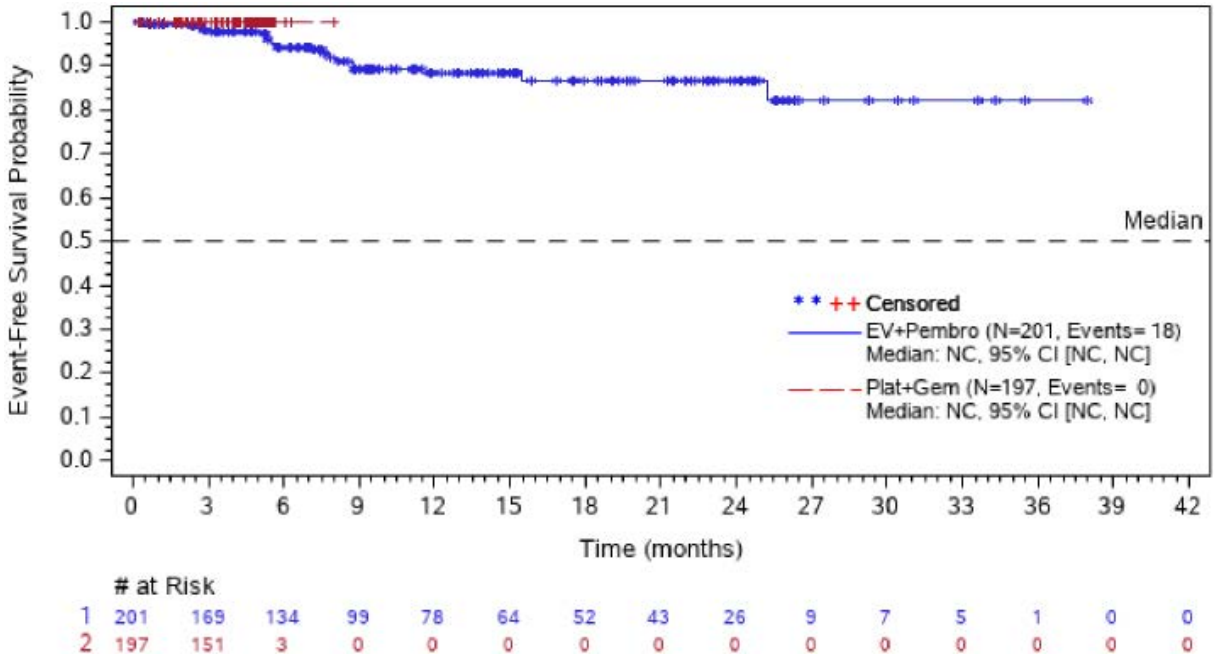


Figure 94: Kaplan-Meier curves for the outcome of severe peripheral neuropathy (severe AEs) of the RCT EV-302/KN-A39, 2nd data cut-off (08 August 2024), subpopulation 2 (cisplatin unsuitable) - supplementary presentation

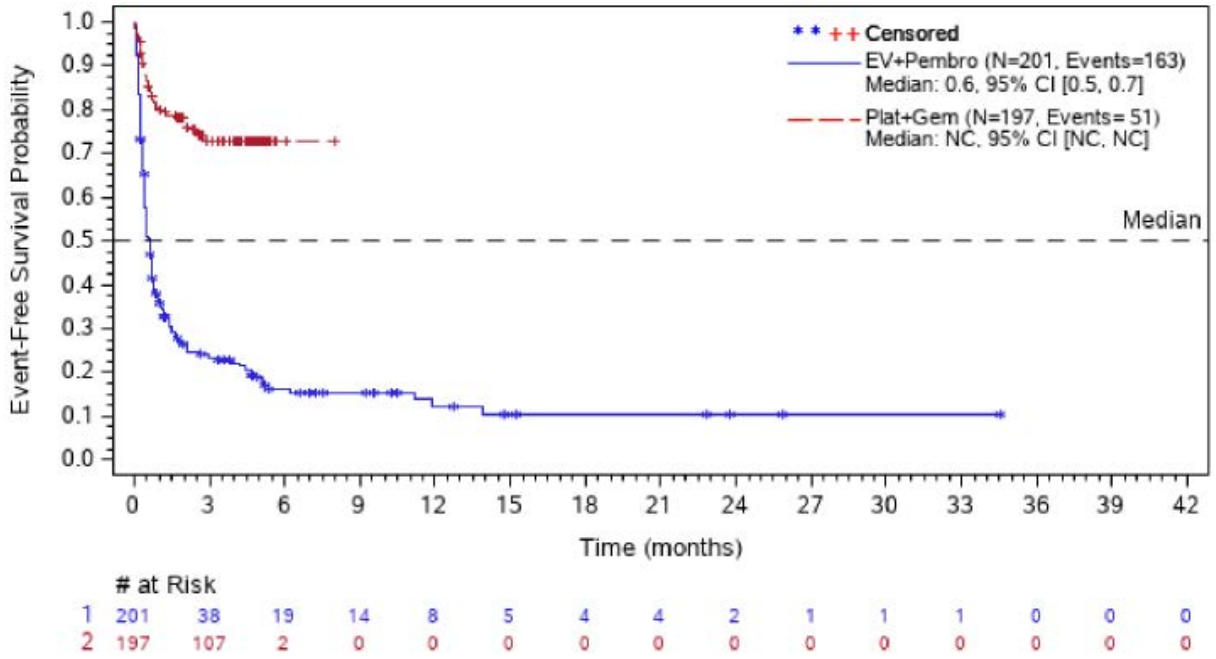


Figure 95: Kaplan-Meier curves for the outcome of skin reactions (AEs) of the RCT EV-302/KN-A39, 2nd data cut-off (08 August 2024), subpopulation 2 (cisplatin unsuitable)

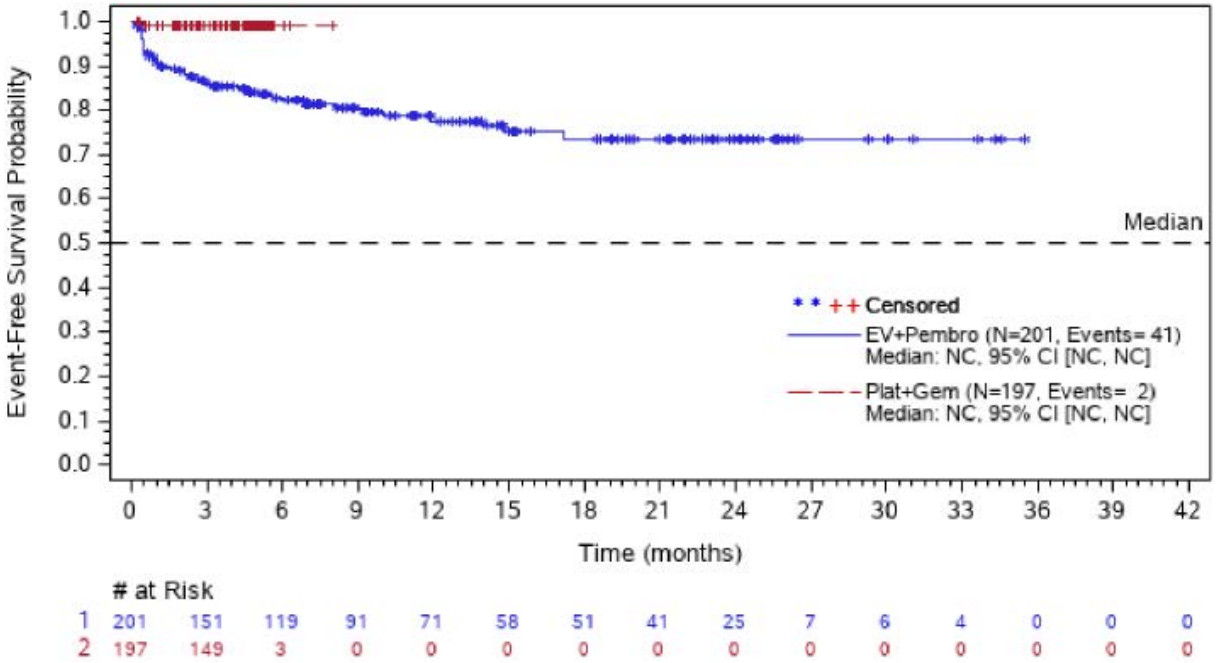


Figure 96: Kaplan-Meier curves for the outcome of severe skin reactions (severe AEs) of the RCT EV-302/KN-A39, 2nd data cut-off (08 August 2024), subpopulation 2 (cisplatin unsuitable) - supplementary presentation

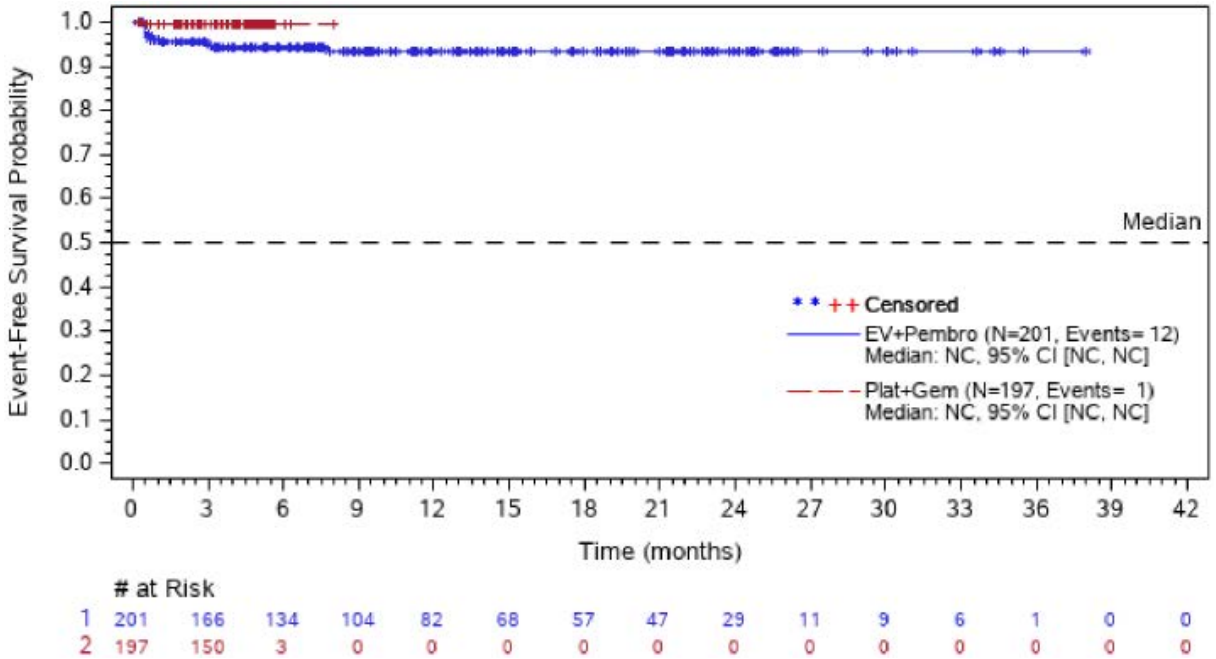


Figure 97: Kaplan-Meier curves for the outcome of severe hyperglycaemia (severe AEs) of the RCT EV-302/KN-A39, 2nd data cut-off (08 August 2024), subpopulation 2 (cisplatin unsuitable)

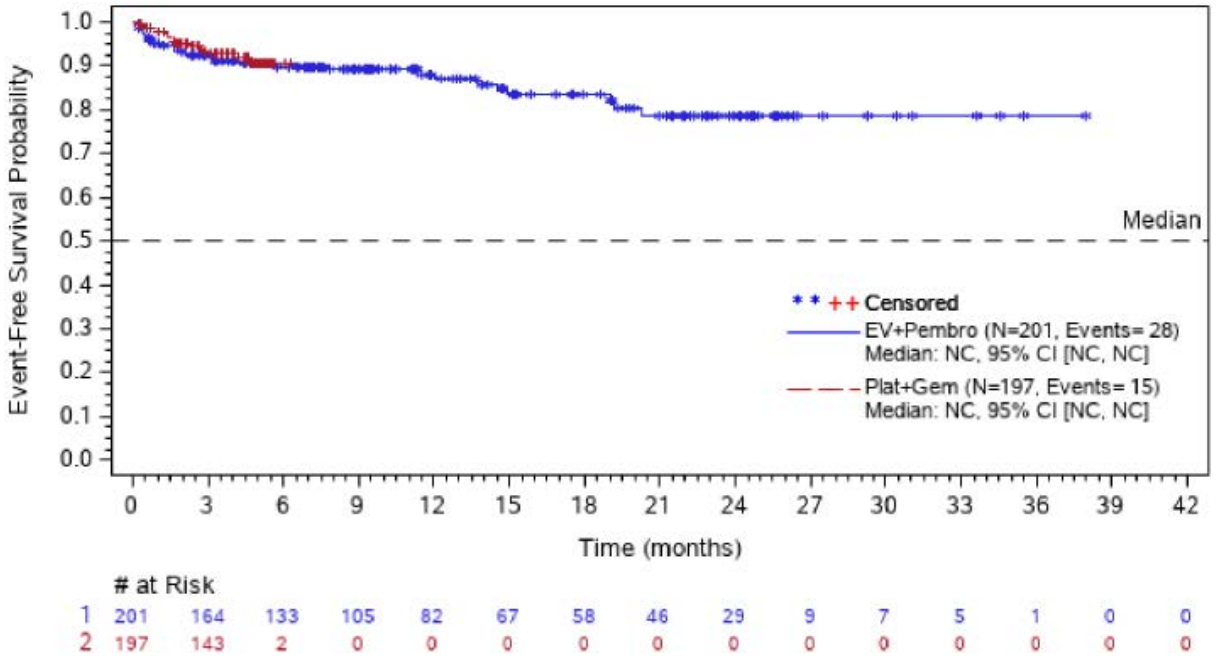


Figure 98: Kaplan-Meier curves for the outcome of severe nephrotoxicity (severe AEs) of the RCT EV-302/KN-A39, 2nd data cut-off (08 August 2024), subpopulation 2 (cisplatin unsuitable)

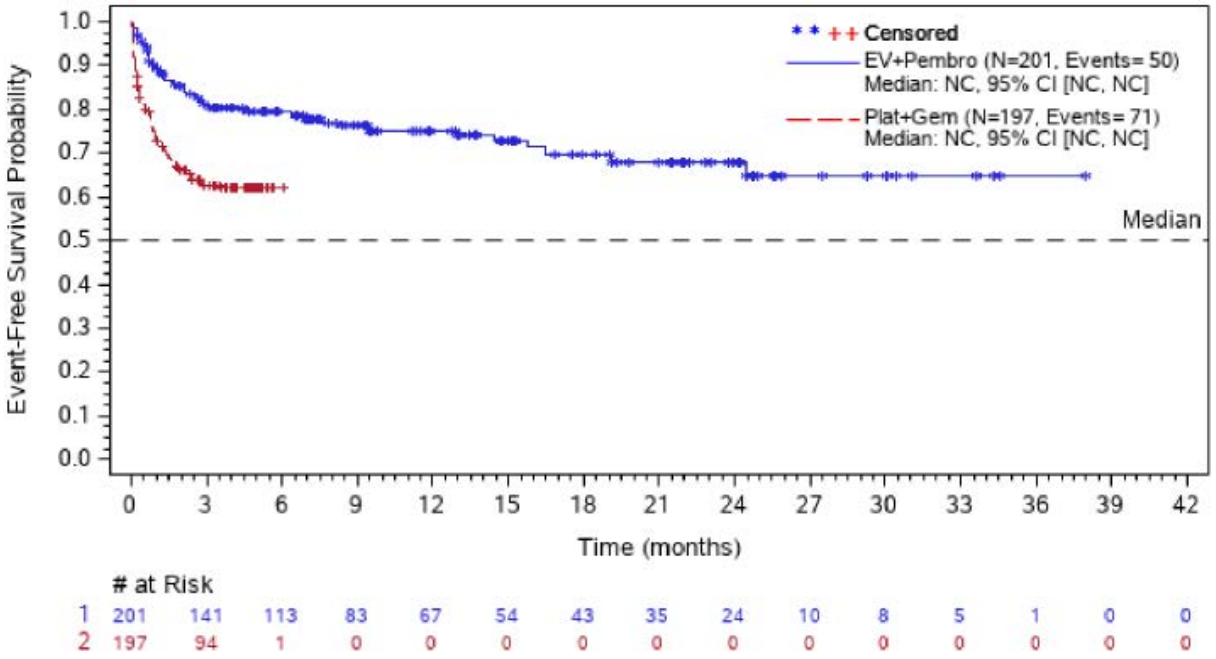


Figure 99: Kaplan-Meier curves for the outcome of constipation (AEs) of the RCT EV-302/KN-A39, 2nd data cut-off (08 August 2024), subpopulation 2 (cisplatin unsuitable)

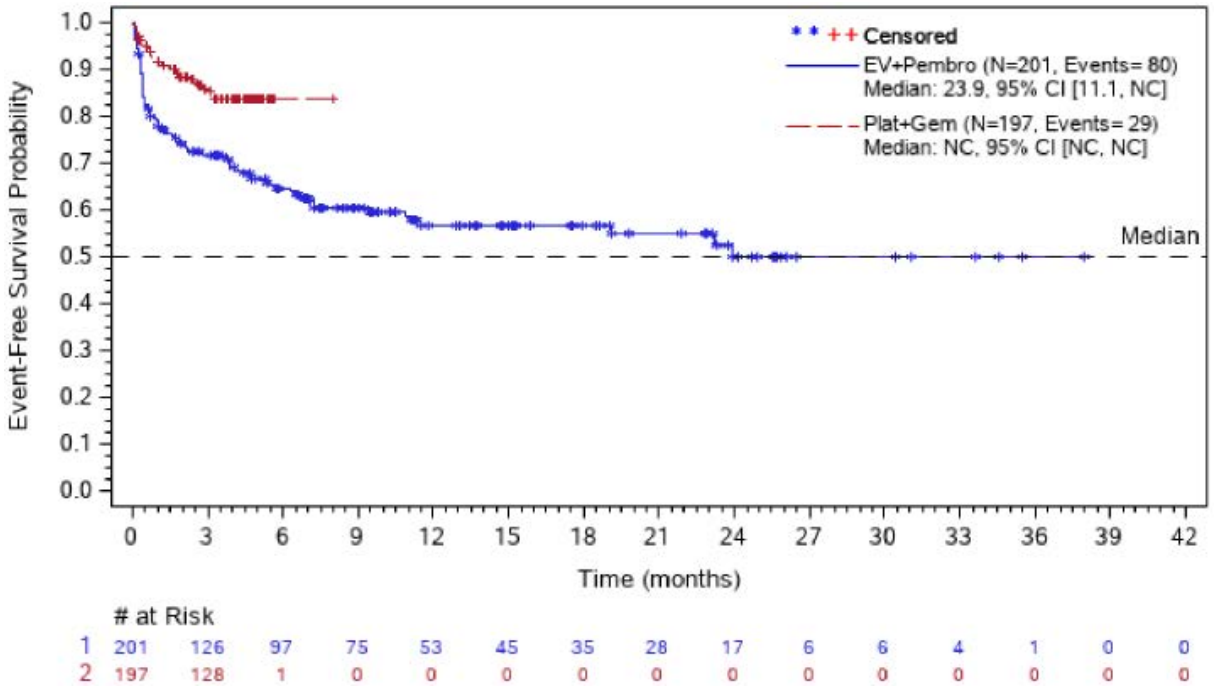


Figure 100: Kaplan-Meier curves for the outcome of diarrhoea (AEs) of the RCT EV-302/KN-A39, 2nd data cut-off (08 August 2024), subpopulation 2 (cisplatin unsuitable)

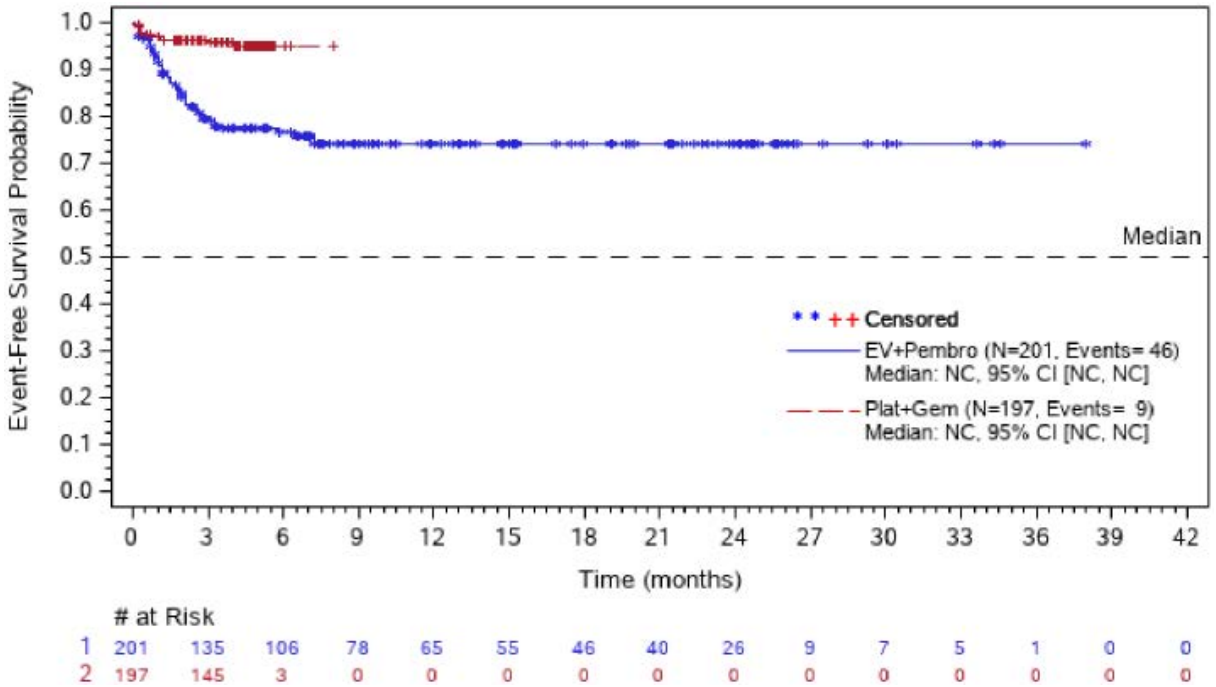


Figure 101: Kaplan-Meier curves for the outcome of dysgeusia (AEs) of the RCT EV-302/KN-A39, 2nd data cut-off (08 August 2024), subpopulation 2 (cisplatin unsuitable)

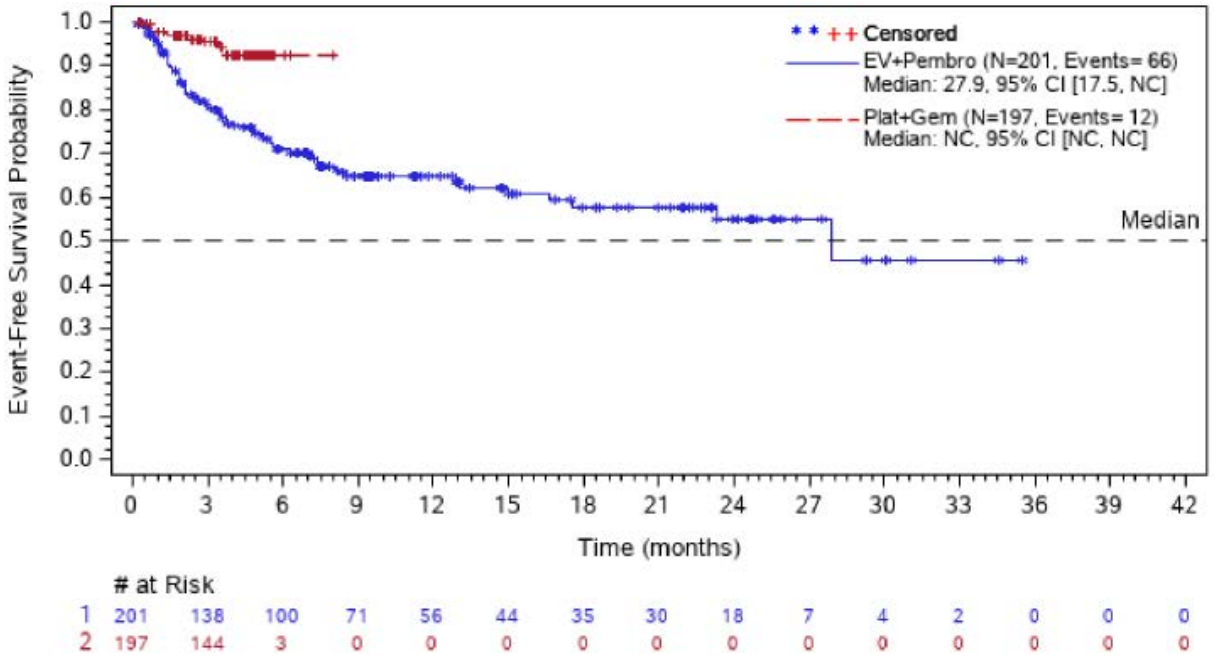


Figure 102: Kaplan-Meier curves for the outcome of eye disorders (AEs) of the RCT EV-302/KN-A39, 2nd data cut-off (08 August 2024), subpopulation 2 (cisplatin unsuitable)

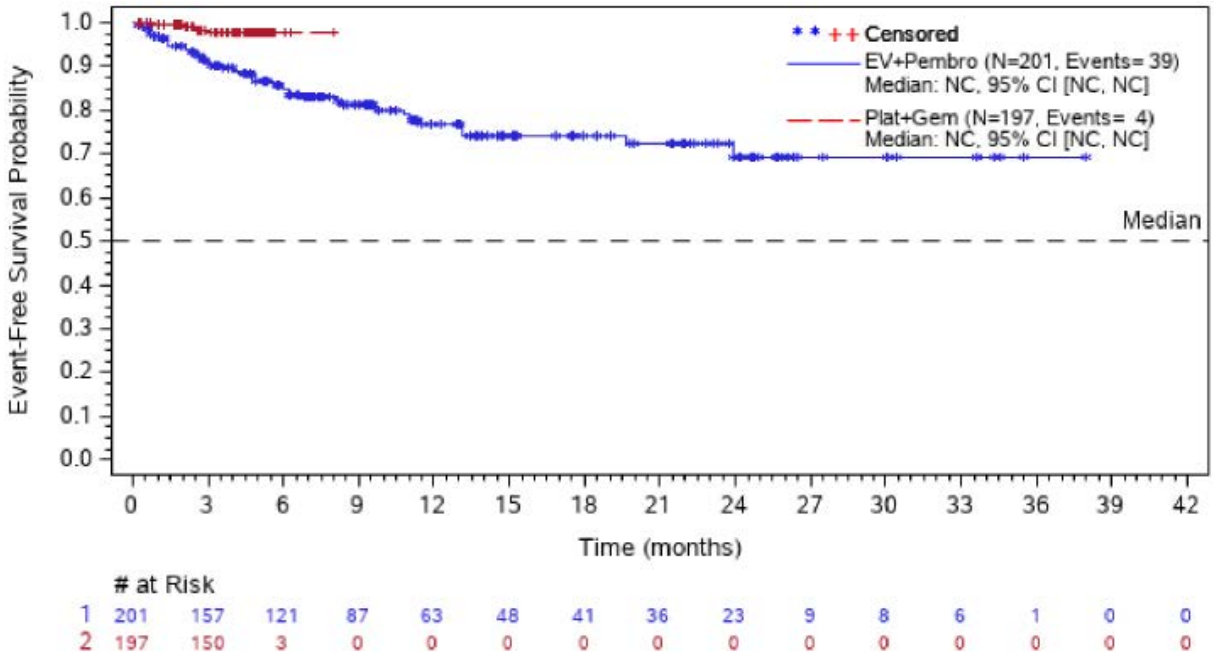


Figure 103: Kaplan-Meier curves for the outcome of endocrine disorders (AEs) of the RCT EV-302/KN-A39, 2nd data cut-off (08 August 2024), subpopulation 2 (cisplatin unsuitable)

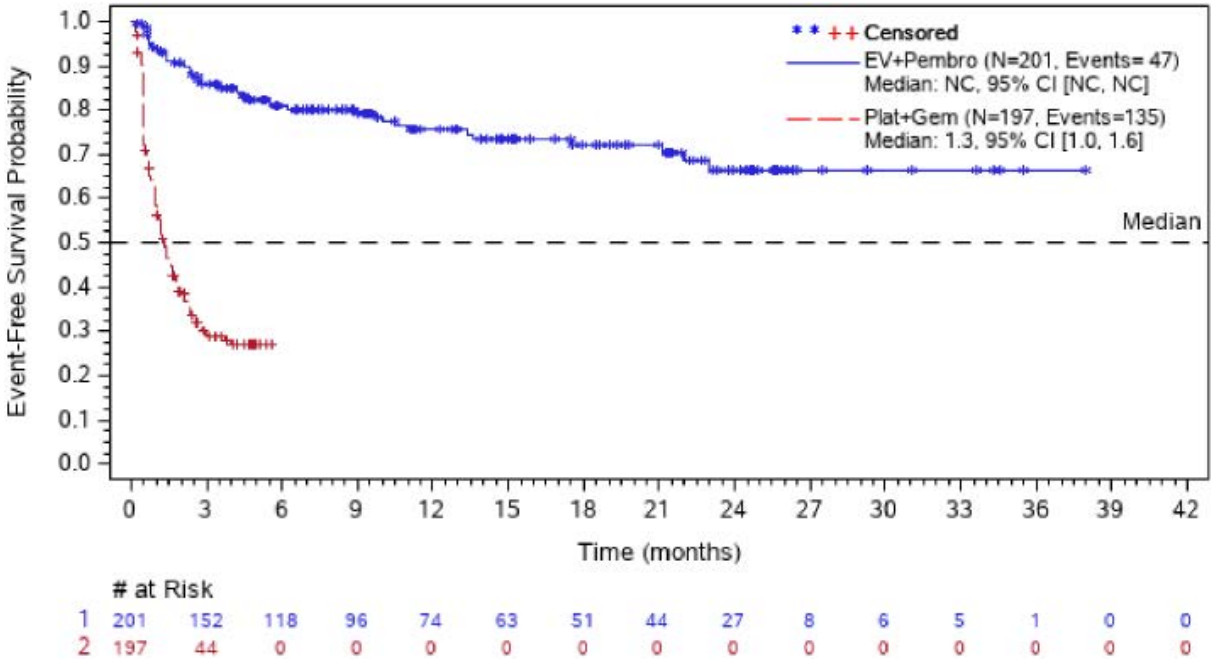


Figure 104: Kaplan-Meier curves for the outcome of blood and lymphatic system disorders (severe AEs) of the RCT EV-302/KN-A39, 2nd data cut-off (08 August 2024), subpopulation 2 (cisplatin unsuitable)

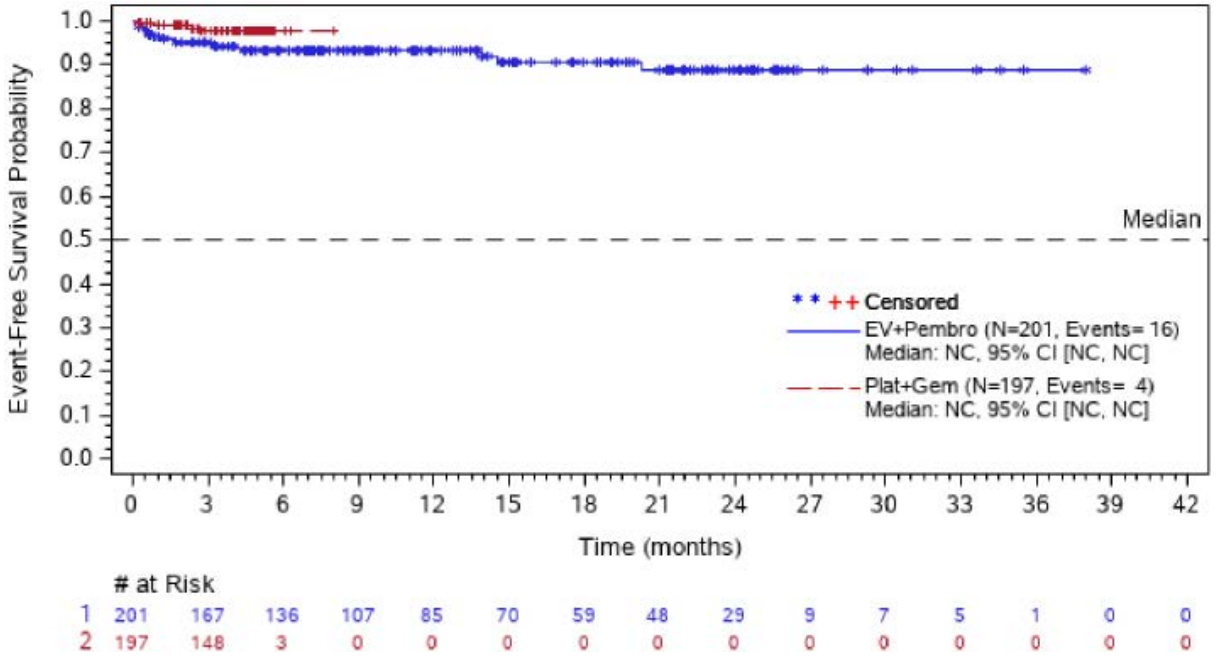


Figure 105: Kaplan-Meier curves for the outcome of acute kidney injury (severe AEs) of the RCT EV-302/KN-A39, 2nd data cut-off (08 August 2024), subpopulation 2 (cisplatin unsuitable)

Appendix C Results on side effects

For the overall rates of AEs, SAEs, and severe AEs (CTCAE grade ≥ 3), the following tables present events for SOCs and PTs according to the Medical Dictionary for Regulatory Activities (MedDRA), each on the basis of the following criteria:

- Overall rate of AEs (irrespective of severity grade): events that occurred in at least 10% of patients in one study arm
- Overall rates of severe AEs (CTCAE grade ≥ 3) and SAEs: events that occurred in at least 5% of patients in one study arm
- In addition, for all events irrespective of severity grade: events that occurred in at least 10 patients and in at least 1% of patients in one study arm

For the outcome of discontinuation due to AEs, all events that occurred in at least 2 patients in at least one study arm are presented.

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

Table 22: Common AEs[a] – RCT, direct comparison: enfortumab vedotin + pembrolizumab vs. cisplatin + gemcitabine (subpopulation: cisplatin suitable) (multipage table)

Study (data cut-off)	Patients with event n (%)	
SOC[b] PT[b]	enfortumab vedotin + pembrolizumab N = 239	cisplatin + gemcitabine N = 236
EV-302/KN-A39 (2nd data cut-off 08 August 2024)		
Overall rate of AEs[c]	239 (100.0)	234 (99.2)
Gastrointestinal disorders	182 (76.2)	184 (78.0)
Nausea	63 (26.4)	120 (50.8)
Constipation	72 (30.1)	76 (32.2)
Diarrhoea	91 (38.1)	40 (16.9)
Vomiting	27 (11.3)	42 (17.8)
Abdominal pain	29 (12.1)	21 (8.9)
Stomatitis	28 (11.7)	16 (6.8)
Dry mouth	24 (10.0)	6 (2.5)
Dyspepsia	13 (5.4)	11 (4.7)
Gastrooesophageal reflux disease	12 (5.0)	11 (4.7)
Abdominal pain upper	12 (5.0)	7 (3.0)
Haemorrhoids	10 (4.2)	2 (0.8)
General disorders and administration site conditions	161 (67.4)	167 (70.8)
Fatigue	81 (33.9)	101 (42.8)
Asthenia	45 (18.8)	45 (19.1)
Fever	44 (18.4)	32 (13.6)
Peripheral oedema	31 (13.0)	22 (9.3)
Nervous system disorders	186 (77.8)	96 (40.7)
Peripheral sensory neuropathy	129 (54.0)	34 (14.4)
Dysgeusia	48 (20.1)	28 (11.9)
Dizziness	24 (10.0)	26 (11.0)
Headache	22 (9.2)	16 (6.8)
Paraesthesia	24 (10.0)	6 (2.5)
Hypoaesthesia	12 (5.0)	1 (0.4)
Peripheral motor neuropathy	11 (4.6)	1 (0.4)
Dysgeusia	10 (4.2)	2 (0.8)
Peripheral sensorimotor neuropathy	11 (4.6)	1 (0.4)

Table 22: Common AEs[a] – RCT, direct comparison: enfortumab vedotin + pembrolizumab vs. cisplatin + gemcitabine (subpopulation: cisplatin suitable) (multipage table)

Study (data cut-off)	**Patients with event n (%)**	
SOC[b] **PT[b]**	**enfortumab vedotin + pembrolizumab** **N = 239**	**cisplatin + gemcitabine** **N = 236**
Skin and subcutaneous tissue disorders	204 (85.4)	61 (25.8)
Pruritus	107 (44.8)	13 (5.5)
Alopecia	91 (38.1)	22 (9.3)
Maculopapular rash	76 (31.8)	9 (3.8)
Dry skin	39 (16.3)	4 (1.7)
Macular rash	27 (11.3)	2 (0.8)
Papular rash	21 (8.8)	1 (0.4)
Skin hyperpigmentation	17 (7.1)	0 (0)
Erythema	12 (5.0)	3 (1.3)
Bullous dermatitis	14 (5.9)	0 (0)
Eczema	13 (5.4)	2 (0.8)
Erythematous rash	12 (5.0)	2 (0.8)
Dermatitis	13 (5.4)	0 (0)
Bladder	10 (4.2)	0 (0)
Rash	10 (4.2)	1 (0.4)
Investigations	142 (59.4)	108 (45.8)
Weight loss	76 (31.8)	23 (9.7)
Alanine aminotransferase increased	49 (20.5)	13 (5.5)
Aspartate aminotransferase increased	48 (20.1)	11 (4.7)
Blood creatinine increased	15 (6.3)	28 (11.9)
Neutrophil count decreased	8 (3.3)	32 (13.6)
Platelet count decreased	2 (0.8)	30 (12.7)
Blood alkaline phosphatase increased	15 (6.3)	8 (3.4)
Lipase increased	17 (7.1)	0 (0)
White blood cell count decreased	2 (0.8)	14 (5.9)
Metabolism and nutrition disorders	135 (56.5)	109 (46.2)
Decreased appetite	75 (31.4)	59 (25.0)
Hyperglycaemia	44 (18.4)	6 (2.5)
Hypokalaemia	18 (7.5)	16 (6.8)
Hyponatraemia	14 (5.9)	19 (8.1)
Hypomagnesaemia	9 (3.8)	20 (8.5)
Hypophosphataemia	10 (4.2)	7 (3.0)

Table 22: Common AEs[a] – RCT, direct comparison: enfortumab vedotin + pembrolizumab vs. cisplatin + gemcitabine (subpopulation: cisplatin suitable) (multipage table)

Study (data cut-off)	**Patients with event n (%)**	
SOC[b] **PT[b]**	**enfortumab vedotin + pembrolizumab** **N = 239**	**cisplatin + gemcitabine** **N = 236**
Blood and lymphatic system disorders	70 (29.3)	170 (72.0)
Anaemia	42 (17.6)	132 (55.9)
Neutropenia	22 (9.2)	86 (36.4)
Thrombocytopenia	11 (4.6)	57 (24.2)
Leukopenia	9 (3.8)	26 (11.0)
Infections and infestations	150 (62.8)	85 (36.0)
Urinary tract infection	43 (18.0)	44 (18.6)
COVID-19	45 (18.8)	12 (5.1)
Conjunctivitis	21 (8.8)	0 (0)
Pneumonia	12 (5.0)	4 (1.7)
Upper respiratory tract infection	12 (5.0)	1 (0.4)
Cellulitis	10 (4.2)	1 (0.4)
Respiratory, thoracic and mediastinal disorders	103 (43.1)	83 (35.2)
Dyspnoea	30 (12.6)	24 (10.2)
Cough	27 (11.3)	13 (5.5)
Hiccups	7 (2.9)	22 (9.3)
Epistaxis	6 (2.5)	19 (8.1)
Pulmonary embolism	10 (4.2)	15 (6.4)
Pneumonitis	17 (7.1)	1 (0.4)
Dysphonia	13 (5.4)	4 (1.7)
Nasal congestion	10 (4.2)	1 (0.4)
Musculoskeletal and connective tissue disorders	115 (48.1)	68 (28.8)
Back pain	38 (15.9)	21 (8.9)
Arthralgia	40 (16.7)	11 (4.7)
Pain in the extremities	24 (10.0)	15 (6.4)
Myalgia	17 (7.1)	7 (3.0)
Muscular weakness	15 (6.3)	4 (1.7)
Muscle spasms	10 (4.2)	1 (0.4)
Renal and urinary disorders	77 (32.2)	76 (32.2)
Haematuria	33 (13.8)	20 (8.5)
Acute kidney injury	12 (5.0)	25 (10.6)
Dysuria	13 (5.4)	8 (3.4)
Pollakiuria	10 (4.2)	6 (2.5)

Table 22: Common AEs[a] – RCT, direct comparison: enfortumab vedotin + pembrolizumab vs. cisplatin + gemcitabine (subpopulation: cisplatin suitable) (multipage table)

Study (data cut-off)	**Patients with event n (%)**	
SOC[b] **PT[b]**	**enfortumab vedotin + pembrolizumab** **N = 239**	**cisplatin + gemcitabine** **N = 236**
Eye disorders	93 (38.9)	14 (5.9)
Dry eye	29 (12.1)	3 (1.3)
Lacrimation increased	26 (10.9)	1 (0.4)
Blurred vision	16 (6.7)	4 (1.7)
Cataract	18 (7.5)	1 (0.4)
Vascular disorders	42 (17.6)	46 (19.5)
Hypertension	16 (6.7)	17 (7.2)
Psychiatric disorders	42 (17.6)	24 (10.2)
Insomnia	24 (10.0)	14 (5.9)
Anxiety	11 (4.6)	3 (1.3)
Ear and labyrinth disorders	17 (7.1)	33 (14.0)
Tinnitus	5 (2.1)	27 (11.4)
Injury, poisoning and procedural complications	44 (18.4)	16 (6.8)
Fall	13 (5.4)	3 (1.3)
Cardiac disorders	23 (9.6)	20 (8.5)
Hepatobiliary disorders	35 (14.6)	8 (3.4)
Hypertransaminasaemia	11 (4.6)	5 (2.1)
Endocrine disorders	40 (16.7)	2 (0.8)
Hypothyroidism	26 (10.9)	1 (0.4)
Hyperthyroidism	10 (4.2)	1 (0.4)
Reproductive system and breast disorders	20 (8.4)	6 (2.5)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	16 (6.7)	7 (3.0)

a. Events that occurred in ≥ 10 patients in at least one study arm.
b. MedDRA version 27.0; SOC and PT notation taken without adaptation from the documents provided by the company.
c. The terms of disease progression, progression of a disease and progression of a malignant disease as well as similar terms were not taken into account in the assessment of AEs.

AE: adverse event; MedDRA: Medical Dictionary for Regulatory Activities; n: number of patients with at least one event; N: number of analysed patients; PT: Preferred Term; RCT: randomized controlled trial; SOC: System Organ Class

Table 23: Common SAEs[a] – RCT, direct comparison: enfortumab vedotin + pembrolizumab vs. cisplatin + gemcitabine (subpopulation: cisplatin suitable)

Study (data cut-off)	**Patients with event n (%)**	
SOC[b] PT[b]	**enfortumab vedotin + pembrolizumab N = 239**	**cisplatin + gemcitabine N = 236**
EV-302/KN-A39 (2nd data cut-off 08 August 2024)		
Overall SAE rate[c]	112 (46.9)	83 (35.2)
Infections and infestations	27 (11.3)	39 (16.5)
Urinary tract infection	4 (1.7)	17 (7.2)
Renal and urinary disorders	19 (7.9)	17 (7.2)
Gastrointestinal disorders	28 (11.7)	6 (2.5)
Respiratory, thoracic and mediastinal disorders	26 (10.9)	4 (1.7)
Metabolism and nutrition disorders	14 (5.9)	10 (4.2)
Blood and lymphatic system disorders	5 (2.1)	16 (6.8)
Anaemia	0 (0)	10 (4.2)
Cardiac disorders	7 (2.9)	10 (4.2)
General disorders and administration site conditions	10 (4.2)	8 (3.4)
Skin and subcutaneous tissue disorders	15 (6.3)	0 (0)
Nervous system disorders	11 (4.6)	3 (1.3)

a. Events that occurred in ≥ 10 patients in at least one study arm.
b. MedDRA version 27.0; SOC and PT notation taken without adaptation from the documents provided by the company.
c. The terms of disease progression, progression of a disease and progression of a malignant disease as well as similar terms were not taken into account in the assessment of AEs.

MedDRA: Medical Dictionary for Regulatory Activities; n: number of patients with at least 1 event; N: number of analysed patients; PT: Preferred Term; RCT: randomized controlled trial; SAE: serious adverse events; SOC: System Organ Class

Table 24; Common severe AEs (CTCAE grade ≥ 3)[a] – RCT, direct comparison: enfortumab vedotin + pembrolizumab vs. cisplatin + gemcitabine (subpopulation: cisplatin suitable)

Study (data cut-off)	**Patients with event n (%)**	
SOC[b] PT[b]	**enfortumab vedotin + pembrolizumab N = 239**	**cisplatin + gemcitabine N = 236**
EV-302/KN-A39 (2nd data cut-off 08 August 2024)		
Overall rate of severe AEs (CTCAE grade ≥ 3)[c]	168 (70.3)	175 (74.2)
Blood and lymphatic system disorders	17 (7.1)	110 (46.6)
Anaemia	5 (2.1)	68 (28.8)
Neutropenia	8 (3.3)	52 (22.0)
Thrombocytopenia	2 (0.8)	28 (11.9)
Infections and infestations	31 (13.0)	39 (16.5)
Urinary tract infection	8 (3.3)	19 (8.1)
Investigations	35 (14.6)	34 (14.4)
Neutrophil count decreased	5 (2.1)	21 (8.9)
Platelet count decreased	0 (0)	12 (5.1)
Metabolism and nutrition disorders	42 (17.6)	25 (10.6)
Hyperglycaemia	19 (7.9)	2 (0.8)
Gastrointestinal disorders	33 (13.8)	17 (7.2)
Diarrhoea	11 (4.6)	2 (0.8)
Skin and subcutaneous tissue disorders	40 (16.7)	0 (0)
Maculopapular rash	16 (6.7)	0 (0)
General disorders and administration site conditions	17 (7.1)	24 (10.2)
Fatigue	8 (3.3)	12 (5.1)
Respiratory, thoracic and mediastinal disorders	26 (10.9)	13 (5.5)
Pulmonary embolism	7 (2.9)	10 (4.2)
Renal and urinary disorders	17 (7.1)	16 (6.8)
Nervous system disorders	25 (10.5)	5 (2.1)
Musculoskeletal and connective tissue disorders	11 (4.6)	8 (3.4)
Vascular disorders	10 (4.2)	8 (3.4)
Hepatobiliary disorders	11 (4.6)	1 (0.4)

a. Events that occurred in ≥ 10 patients in at least one study arm.
b. MedDRA version 27.0; SOC and PT notation taken without adaptation from the documents provided by the company.
c. The terms of disease progression, progression of a disease and progression of a malignant disease as well as similar terms were not taken into account in the assessment of AEs.

AE: adverse event; CTCAE: Common Terminology Criteria for Adverse Events; MedDRA: Medical Dictionary for Regulatory Activities; n: number of patients with at least one event; N: number of analysed patients; PT: Preferred Term; RCT: randomized controlled trial; SOC: System Organ Class

Table 25: Discontinuations due to AEs[a] – RCT, direct comparison: enfortumab vedotin + pembrolizumab vs. cisplatin + gemcitabine (subpopulation: cisplatin suitable) (multipage table)

Study	**Patients with event n (%)**	
SOC[b] PT[b]	**enfortumab vedotin + pembrolizumab N = 239**	**cisplatin + gemcitabine N = 236**
EV-302/KN-A39 (2nd data cut-off 08 August 2024)		
Total rate of discontinuations due to AEs[c]	110 (46.0)	58 (24.6)
Nervous system disorders	57 (23.8)	1 (0.4)
Peripheral sensory neuropathy	38 (15.9)	1 (0.4)
Paraesthesia	4 (1.7)	0 (0)
Peripheral motor neuropathy	5 (2.1)	0 (0)
Peripheral sensorimotor neuropathy	4 (1.7)	0 (0)
Neurotoxicity	2 (0.8)	0 (0)
Renal and urinary disorders	2 (0.8)	19 (8.1)
Acute kidney injury	1 (0.4)	10 (4.2)
Chronic kidney disease	0 (0)	3 (1.3)
Renal failure	0 (0)	2 (0.8)
Renal insufficiency	0 (0)	2 (0.8)
Skin and subcutaneous tissue disorders	19 (7.9)	0 (0)
Maculopapular rash	5 (2.1)	0 (0)
Macular rash	3 (1.3)	0 (0)
Generalized exfoliative dermatitis	2 (0.8)	0 (0)
Investigations	3 (1.3)	11 (4.7)
Blood creatinine increased	0 (0)	8 (3.4)
Aspartate aminotransferase increased	2 (0.8)	0 (0)
Platelet count decreased	0 (0)	2 (0.8)
Respiratory, thoracic and mediastinal disorders	14 (5.9)	0 (0)
Pneumonitis	6 (2.5)	0 (0)
Immune-related lung disease	4 (1.7)	0 (0)
Interstitial lung disease	2 (0.8)	0 (0)
Blood and lymphatic system disorders	1 (0.4)	11 (4.7)
Anaemia	1 (0.4)	7 (3.0)
Neutropenia	0 (0)	2 (0.8)
Gastrointestinal disorders	8 (3.3)	4 (1.7)
Diarrhoea	4 (1.7)	1 (0.4)
Nausea	0 (0)	3 (1.3)
Colitis	2 (0.8)	0 (0)
General disorders and administration site conditions	3 (1.3)	5 (2.1)
Fatigue	1 (0.4)	5 (2.1)

Table 25: Discontinuations due to AEs[a] – RCT, direct comparison: enfortumab vedotin + pembrolizumab vs. cisplatin + gemcitabine (subpopulation: cisplatin suitable) (multipage table)

Study	**Patients with event n (%)**	
SOC[b] PT[b]	**enfortumab vedotin + pembrolizumab N = 239**	**cisplatin + gemcitabine N = 236**
Hepatobiliary disorders	8 (3.3)	0 (0)
Immune-mediated hepatitis	3 (1.3)	0 (0)
Cardiac disorders	1 (0.4)	3 (1.3)
Infections and infestations	2 (0.8)	2 (0.8)
Ear and labyrinth disorders	0 (0)	3 (1.3)
Metabolism and nutrition disorders	0 (0)	2 (0.8)
Musculoskeletal and connective tissue disorders	3 (1.3)	0 (0)

a. Events that occurred in ≥ 2 patients in at least one study arm.
b. MedDRA version 27.0; SOC and PT notation taken without adaptation from the documents provided by the company.
c. The terms of disease progression, progression of a disease and progression of a malignant disease as well as similar terms were not taken into account in the assessment of AEs.

AE: adverse event; MedDRA: Medical Dictionary for Regulatory Activities; n: number of patients with at least one event; N: number of analysed patients; PT: Preferred Term; RCT: randomized controlled trial; SOC: System Organ Class

C.2 Research question 2: Patients for whom cisplatin-based therapy is not suitable (cisplatin unsuitable)

Table 26: Common AEs[a] – RCT, direct comparison: enfortumab vedotin + pembrolizumab vs. carboplatin + gemcitabine (subpopulation: cisplatin unsuitable) (multipage table)

Study (data cut-off)	Patients with event n (%)	
SOC[b] PT[b]	enfortumab vedotin + pembrolizumab N = 201	carboplatin + gemcitabine N = 197
EV-302/KN-A39 (2nd data cut-off 08 August 2024)		
Overall rate of AEs[c]	200 (99.5)	193 (98.0)
Gastrointestinal disorders	156 (77.6)	129 (65.5)
Constipation	50 (24.9)	71 (36.0)
Nausea	59 (29.4)	58 (29.4)
Diarrhoea	80 (39.8)	29 (14.7)
Vomiting	30 (14.9)	27 (13.7)
Abdominal pain	24 (11.9)	6 (3.0)
Stomatitis	13 (6.5)	11 (5.6)
Dyspepsia	13 (6.5)	7 (3.6)
Dry mouth	18 (9.0)	1 (0.5)
Abdominal distension	11 (5.5)	2 (1.0)
General disorders and administration site conditions	142 (70.6)	136 (69.0)
Fatigue	78 (38.8)	69 (35.0)
Asthenia	37 (18.4)	43 (21.8)
Fever	37 (18.4)	35 (17.8)
Peripheral oedema	34 (16.9)	26 (13.2)
Blood and lymphatic system disorders	93 (46.3)	170 (86.3)
Anaemia	74 (36.8)	135 (68.5)
Neutropenia	25 (12.4)	95 (48.2)
Thrombocytopenia	11 (5.5)	96 (48.7)
Leukopenia	8 (4.0)	21 (10.7)
Febrile neutropenia	1 (0.5)	10 (5.1)
Skin and subcutaneous tissue disorders	163 (81.1)	51 (25.9)
Pruritus	79 (39.3)	16 (8.1)
Maculopapular rash	71 (35.3)	6 (3.0)
Alopecia	61 (30.3)	12 (6.1)
Dry skin	38 (18.9)	2 (1.0)
Macular rash	17 (8.5)	4 (2.0)
Eczema	18 (9.0)	2 (1.0)
Papular rash	13 (6.5)	2 (1.0)
Dermatitis	11 (5.5)	1 (0.5)

Table 26: Common AEs[a] – RCT, direct comparison: enfortumab vedotin + pembrolizumab vs. carboplatin + gemcitabine (subpopulation: cisplatin unsuitable) (multipage table)

Study (data cut-off)	**Patients with event n (%)**	
SOC[b] **PT[b]**	**enfortumab vedotin + pembrolizumab** **N = 201**	**carboplatin + gemcitabine** **N = 197**
Metabolism and nutrition disorders	126 (62.7)	86 (43.7)
Decreased appetite	74 (36.8)	53 (26.9)
Hyponatraemia	29 (14.4)	11 (5.6)
Hyperglycaemia	29 (14.4)	5 (2.5)
Hyperphosphataemia	23 (11.4)	10 (5.1)
Hypokalaemia	22 (10.9)	9 (4.6)
Hyperkalaemia	9 (4.5)	14 (7.1)
Hypocalcaemia	10 (5.0)	11 (5.6)
Hypoalbuminaemia	12 (6.0)	6 (3.0)
Hypomagnesaemia	11 (5.5)	7 (3.6)
Dehydration	12 (6.0)	4 (2.0)
Investigations	116 (57.7)	87 (44.2)
Weight loss	76 (37.8)	15 (7.6)
Blood creatinine increased	30 (14.9)	23 (11.7)
Alanine aminotransferase increased	30 (14.9)	20 (10.2)
Aspartate aminotransferase increased	25 (12.4)	17 (8.6)
Platelet count decreased	4 (2.0)	34 (17.3)
Neutrophil count decreased	9 (4.5)	24 (12.2)
Blood alkaline phosphatase increased	14 (7.0)	8 (4.1)
White blood cell count decreased	4 (2.0)	11 (5.6)
Infections and infestations	127 (63.2)	75 (38.1)
Urinary tract infection	51 (25.4)	39 (19.8)
COVID-19	22 (10.9)	9 (4.6)
Pneumonia	18 (9.0)	3 (1.5)
Nervous system disorders	145 (72.1)	48 (24.4)
Peripheral sensory neuropathy	106 (52.7)	10 (5.1)
Dysgeusia	46 (22.9)	9 (4.6)
Dizziness	13 (6.5)	17 (8.6)
Headache	14 (7.0)	10 (5.1)
Paraesthesia	12 (6.0)	2 (1.0)
Respiratory, thoracic and mediastinal disorders	89 (44.3)	61 (31.0)
Dyspnoea	30 (14.9)	27 (13.7)
Cough	31 (15.4)	10 (5.1)
Pneumonitis	13 (6.5)	0 (0.0)

Table 26: Common AEs[a] – RCT, direct comparison: enfortumab vedotin + pembrolizumab vs. carboplatin + gemcitabine (subpopulation: cisplatin unsuitable) (multipage table)

Study (data cut-off)	**Patients with event n (%)**	
SOC[b] PT[b]	**enfortumab vedotin + pembrolizumab N = 201**	**carboplatin + gemcitabine N = 197**
Musculoskeletal and connective tissue disorders	83 (41.3)	53 (26.9)
Arthralgia	27 (13.4)	10 (5.1)
Back pain	17 (8.5)	13 (6.6)
Pain in the extremities	12 (6.0)	9 (4.6)
Muscular weakness	16 (8.0)	3 (1.5)
Myalgia	10 (5.0)	4 (2.0)
Renal and urinary disorders	72 (35.8)	49 (24.9)
Haematuria	28 (13.9)	19 (9.6)
Acute kidney injury	20 (10.0)	8 (4.1)
Eye disorders	66 (32.8)	12 (6.1)
Dry eye	22 (10.9)	2 (1.0)
Cataract	14 (7.0)	0 (0)
Lacrimation increased	12 (6.0)	1 (0.5)
Blurred vision	10 (5.0)	1 (0.5)
Psychiatric disorders	37 (18.4)	20 (10.2)
Insomnia	23 (11.4)	10 (5.1)
Vascular disorders	34 (16.9)	27 (13.7)
Hypotension	11 (5.5)	1 (0.5)
Injury, poisoning and procedural complications	31 (15.4)	22 (11.2)
Fall	10 (5.0)	5 (2.5)
Hepatobiliary disorders	32 (15.9)	13 (6.6)
Hypertransaminasaemia	10 (5.0)	8 (4.1)
Endocrine disorders	39 (19.4)	4 (2.0)
Hypothyroidism	26 (12.9)	2 (1.0)
Hyperthyroidism	11 (5.5)	1 (0.5)
Cardiac disorders	19 (9.5)	13 (6.6)
Reproductive system and breast disorders	11 (5.5)	7 (3.6)

a. Events that occurred in ≥ 10 patients in at least one study arm.
b. MedDRA version 27.0; SOC and PT notation taken without adaptation from the documents provided by the company.
c. The terms of disease progression, progression of a disease and progression of a malignant disease as well as similar terms were not taken into account in the assessment of AEs.

AE: adverse event; MedDRA: Medical Dictionary for Regulatory Activities; n: number of patients with at least one event; N: number of analysed patients; PT: Preferred Term; RCT: randomized controlled trial; SOC: System Organ Class

Table 27: Common SAEs[a] – RCT, direct comparison: enfortumab vedotin + pembrolizumab vs. carboplatin + gemcitabine (subpopulation: cisplatin unsuitable)

Study (data cut-off)	**Patients with event n (%)**	
SOC[b] PT[b]	**enfortumab vedotin + pembrolizumab N = 201**	**carboplatin + gemcitabine N = 197**
EV-302/KN-A39 (2nd data cut-off 08 August 2024)		
Overall SAE rate[c]	122 (60.7)	86 (43.7)
Infections and infestations	51 (25.4)	34 (17.3)
Urinary tract infection	13 (6.5)	14 (7.1)
Gastrointestinal disorders	23 (11.4)	11 (5.6)
Blood and lymphatic system disorders	6 (3.0)	26 (13.2)
Renal and urinary disorders	22 (10.9)	11 (5.6)
Acute kidney injury	16 (8.0)	4 (2.0)
General disorders and administration site conditions	14 (7.0)	18 (9.1)
Respiratory, thoracic and mediastinal disorders	16 (8.0)	11 (5.6)
Metabolism and nutrition disorders	14 (7.0)	5 (2.5)
Skin and subcutaneous tissue disorders	11 (5.5)	1 (0.5)

a. Events that occurred in ≥ 10 patients in the intervention arm, or in ≥ 5 % of patients in the control arm.
b. MedDRA version 27.0; SOC and PT notation taken without adaptation from the documents provided by the company.
c. The terms of disease progression, progression of a disease and progression of a malignant disease as well as similar terms were not taken into account in the assessment of AEs.

MedDRA: Medical Dictionary for Regulatory Activities; n: number of patients with at least one event; N: number of analysed patients; PT: Preferred Term; RCT: randomized controlled trial; SAE: serious adverse event; SOC: System Organ Class

Table 28: Common severe AEs (CTCAE grade ≥ 3)[a] – RCT, direct comparison: enfortumab vedotin + pembrolizumab vs. cisplatin + gemcitabine (subpopulation: cisplatin unsuitable)

Study	Patients with event n (%)	
SOC[b] PT[b]	enfortumab vedotin + pembrolizumab N = 201	carboplatin + gemcitabine N = 197
EV-302/KN-A39 (2nd data cut-off 08 August 2024)		
Overall rate of severe AEs (CTCAE grade ≥ 3)[c]	163 (81.1)	166 (84.3)
Blood and lymphatic system disorders	47 (23.4)	135 (68.5)
Anaemia	29 (14.4)	80 (40.6)
Neutropenia	17 (8.5)	78 (39.6)
Thrombocytopenia	2 (1.0)	59 (29.9)
Leukopenia	2 (1.0)	13 (6.6)
Febrile neutropenia	1 (0.5)	10 (5.1)
Infections and infestations	54 (26.9)	36 (18.3)
Urinary tract infection	15 (7.5)	16 (8.1)
Metabolism and nutrition disorders	47 (23.4)	21 (10.7)
Hyponatraemia	15 (7.5)	7 (3.6)
Hyperglycaemia	12 (6.0)	1 (0.5)
Investigations	30 (14.9)	36 (18.3)
Neutrophil count decreased	7 (3.5)	19 (9.6)
Platelet count decreased	0 (0)	17 (8.6)
General disorders and administration site conditions	25 (12.4)	23 (11.7)
Fatigue	11 (5.5)	8 (4.1)
Gastrointestinal disorders	27 (13.4)	16 (8.1)
Diarrhoea	11 (5.5)	4 (2.0)
Skin and subcutaneous tissue disorders	41 (20.4)	2 (1.0)
Maculopapular rash	20 (10.0)	0 (0)
Renal and urinary disorders	28 (13.9)	15 (7.6)
Acute kidney injury	16 (8.0)	4 (2.0)
Respiratory, thoracic and mediastinal disorders	17 (8.5)	16 (8.1)
Nervous system disorders	21 (10.4)	4 (2.0)
Peripheral sensory neuropathy	12 (6.0)	0 (0)

a. Events that occurred in ≥ 10 patients in the intervention arm, or in ≥ 5 % of patients in the control arm.
b. MedDRA version 27.0; SOC and PT notation taken without adaptation from the documents provided by the company.
c. The terms of disease progression, progression of a disease and progression of a malignant disease as well as similar terms were not taken into account in the assessment of AEs.

AE: adverse event; CTCAE: Common Terminology Criteria for Adverse Events; MedDRA: Medical Dictionary for Regulatory Activities; n: number of patients with at least one event; N: number of analysed patients; PT: Preferred Term; RCT: randomized controlled trial; SOC: System Organ Class

Table 29: Discontinuations due to AEs[a] – RCT, direct comparison: enfortumab vedotin + pembrolizumab vs. carboplatin + gemcitabine (subpopulation: cisplatin unsuitable) (multipage table)

Study	**Patients with event n (%)**	
SOC[b] **PT[b]**	**enfortumab vedotin + pembrolizumab** **N = 201**	**carboplatin + gemcitabine** **N = 197**
EV-302/KN-A39 (2nd data cut-off 08 August 2024)		
Total rate of discontinuations due to AEs[c]	102 (50.7)	35 (17.8)
Nervous system disorders	39 (19.4)	1 (0.5)
Peripheral sensory neuropathy	30 (14.9)	0 (0)
Paraesthesia	2 (1.0)	0 (0)
Peripheral sensorimotor neuropathy	2 (1.0)	0 (0)
Blood and lymphatic system disorders	3 (1.5)	18 (9.1)
Anaemia	1 (0.5)	5 (2.5)
Thrombocytopenia	1 (0.5)	5 (2.5)
Neutropenia	0 (0)	5 (2.5)
Febrile neutropenia	0 (0)	2 (1.0)
Skin and subcutaneous tissue disorders	14 (7.0)	1 (0.5)
Maculopapular rash	3 (1.5)	0 (0)
Toxic epidermal necrolysis	2 (1.0)	0 (0)
Respiratory, thoracic and mediastinal disorders	10 (5.0)	2 (1.0)
Pneumonitis	5 (2.5)	0 (0)
Immune-related lung disease	2 (1.0)	0 (0)
General disorders and administration site conditions	10 (5.0)	3 (1.5)
Asthenia	3 (1.5)	0 (0)
Fatigue	2 (1.0)	1 (0.5)
General deterioration in physical health	0 (0)	2 (1.0)
Renal and urinary disorders	10 (5.0)	0 (0)
Acute glomerulonephritis	5 (2.5)	0 (0)
Renal failure	2 (1.0)	0 (0)
Infections and infestations	6 (3.0)	3 (1.5)
Sepsis	2 (1.0)	1 (0.5)
Cardiac disorders	4 (2.0)	1 (0.5)
Gastrointestinal disorders	6 (3.0)	0 (0)
Diarrhoea	3 (1.5)	0 (0)
Investigations	3 (1.5)	2 (1.0)
Alanine aminotransferase increased	2 (1.0)	0 (0)
Hepatobiliary disorders	2 (1.0)	1 (0.5)
Vascular disorders	2 (1.0)	1 (0.5)
Musculoskeletal and connective tissue disorders	3 (1.5)	0 (0)

Table 29: Discontinuations due to AEs[a] – RCT, direct comparison: enfortumab vedotin + pembrolizumab vs. carboplatin + gemcitabine (subpopulation: cisplatin unsuitable) (multipage table)

Study	**Patients with event n (%)**	
SOC[b] PT[b]	**enfortumab vedotin + pembrolizumab N = 201**	**carboplatin + gemcitabine N = 197**
Arthralgia	2 (1.0)	0 (0)

a. Events that occurred in ≥ 2 patients in at least one study arm.
b. MedDRA version 27.0; SOC and PT notation taken without adaptation from the documents provided by the company.
c. The terms of disease progression, progression of a disease and progression of a malignant disease as well as similar terms were not taken into account in the assessment of AEs.

AE: adverse event; MedDRA: Medical Dictionary for Regulatory Activities; n: number of patients with at least one event; N: number of analysed patients; PT: Preferred Term; RCT: randomized controlled trial; SOC: System Organ Class