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

Addendum to Project A24-99 (dossier assessment)[1]

ADDENDUM

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List of abbreviations

Abbreviation	Meaning
ACT	appropriate comparator therapy
AE	adverse event
BPI-SF	Brief Pain Inventory-Short Form
CTCAE	Common Terminology Criteria for Adverse Events
ECOG PS	Eastern Cooperative Oncology Group Performance Status
EORTC QLQ-C30	European Organisation for Research and Treatment of Cancer – Quality of Life Questionnaire-Core 30
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
IPTW	inverse probability of treatment weighting
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care
MedDRA	Medical Dictionary for Regulatory Activities
PD-1	Programmed Cell Death 1
PD-L1	Programmed Cell Death-Ligand 1
RCT	randomized controlled trial
SAE	serious adverse event
SGB	Sozialgesetzbuch (Social Code Book)
SMQ	standardized MedDRA query
SOC	System Organ Class
SPC	Summary of Product Characteristics
VAS	visuelle Analogskala

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 for Project A24-99 (Pembrolizumab – Benefit assessment according to §35a Social Code Book V) [1].

The commission comprises the assessment of the analyses [2] presented by the pharmaceutical company (hereinafter referred to as the "company") in the commenting procedure, taking into account the information in the dossier [3], including the assessment of the results of the 1st and 2nd data cut-off, including additional analyses such as sensitivity and matching analyses, as well as the sensitivity analyses on side effects presented by the company in the commenting procedure, information on proportions of patients with or without avelumab maintenance therapy and information on the time between the last dose of platinum-based chemotherapy and the start of avelumab maintenance therapy.

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 research questions of the benefit assessment of pembrolizumab in dossier assessment A24-99 [1] comprised the 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) or for whom cisplatin and carboplatin-based therapy are not suitable (research question 3).

In its dossier [3], the company presented results of the randomized controlled trial (RCT) EV-302/KN-A39 for research questions 1 and 2 , which investigated the comparison of pembrolizumab in combination with enfortumab vedotin (pembrolizumab + enfortumab vedotin) versus platinum-based chemotherapy (cisplatin/carboplatin + gemcitabine) in the first-line treatment of adult patients with unresectable or metastatic urothelial carcinoma for whom platinum-based chemotherapy is an option. No data were available for research question 3.

In Module 4 A of its dossier, the company presented the results of the 1st data cut-off of the RCT EV-302/KN-A39 of 8 August 2023 and used them for its assessment. A second data cut-off, which had originally been pre-specified, was requested by the FDA [4] and conducted [1]. According to the company, the results of the 2nd data cut-off were not yet available at the time of dossier submission.

Irrespective of this, the presented data of the 1st data cut-off of the RCT EV-302/KN-A39 were not used for the benefit assessment in dossier assessment A24-99, as it remained unclear on the basis of the information in the company's dossier whether the treatment used in the study represents an adequate implementation of the appropriate comparator therapy (ACT) (including maintenance therapy with avelumab) for the patients in the comparator arm of the subpopulations of study EV-302/KN-A39 relevant for research question 1 and research question 2. Rather, it can be derived from the information available in the dossier that a relevant proportion of patients did not receive maintenance treatment with avelumab, although this would have been indicated.

As part of the commenting procedure, the company presented information on the proportion of patients in RCT EV-302/KN-A39 for whom it considered maintenance treatment with avelumab to be an option and in whom it was either implemented or not implemented. Based on this information, the implementation of maintenance therapy with avelumab and thus the ACT for the present addendum can be assessed. In addition, the company presented further analyses of the RCT EV-302/KN-A39 both on the 1st data cut-off of 08 August 2023 and on the 2nd data cut-off, which was conducted on 08 August 2024 (i.e. 1 year after the 1st data cut-off). These are described in more detail in the following sections.

Results for the 2nd data cut-off incomplete in terms of content

Within the framework of the commenting procedure, the company presented analyses of the RCT EV-302/KN-A39 for the 2nd data cut-off of 08 August 2024 [2]. Among others, these comprise results on overall survival, on morbidity and health-related quality of life outcomes, and on the outcomes on side effects. The company presented analyses on the course of the study for the outcomes of morbidity and health-related quality of life. Further operationalizations of these outcomes are not available for the 2nd data cut-off. Moreover, the company presented additional sensitivity analyses:

- For overall survival, sensitivity analyses analogous to sensitivity analyses 1 and 3 described in dossier assessment A24-98 [5] were presented, but not analogous to sensitivity analysis 2 (maximum assumption) for the second data cut-off. In addition, further sensitivity analyses were presented using inverse probability of treatment weighting (IPTW) estimate and multiple imputation.
- Sensitivity analyses on the overall rates of adverse events (AEs), serious adverse events (SAEs) and severe adverse events were presented for the side effects, in the context of which patients for whom avelumab therapy was suitable according to the company and in whom no corresponding event had yet occurred were censored at the time of the data cut-off and thus imputed as event-free up to the data cut-off.

The analyses presented by the company on the 2nd data cut-off are incomplete in terms of content, as responder analyses on the patient-reported outcomes and subgroup analyses are missing. Furthermore, the analyses were not prepared in a structured manner. Furthermore, there is a lack of necessary information on the methods, for example on the sensitivity analyses using IPTW and multiple imputation. Therefore, the analyses on the 2nd data cut-off were not used for the benefit assessment.

Results of the 1st data cut-off were used for the assessment

On the basis of the information subsequently submitted by the company in the commenting procedure on the proportion of patients in RCT EV-302/KN-A39 for whom maintenance treatment with avelumab had been an option and in whom it was either implemented or not implemented, the implementation of maintenance treatment with avelumab and thus the ACT can be assessed for the present addendum. This information allows an interpretation of the study results for research questions 1 and 2 of the dossier assessment (see 2.1.2 for an explanation). Since the results on the 2nd data cut-off are incomplete as described above, the results on the 1st data cut-off are used for the benefit assessment.

As described in dossier assessment A24-99, the RCT EV-302/KN-A39 is not relevant for research question 3 of the dossier assessment (patients with unresectable or metastatic urothelial carcinoma for whom cisplatin- and carboplatin-based therapy is not suitable), and

the company presented no further data for this research question within the comments. Therefore, this research question is not subject of the present addendum.

2.1 Study characteristics (aspects across research questions)

A detailed characterisation of study EV-302/KN-A39 including data on study design, intervention and study population can be found in dossier assessment A24-99. The following therefore only describes aspects for which the present addendum yields relevant changes compared with dossier assessment A24-99. 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 in a superordinate manner. Research question-specific aspects for research question 1 are described in Section 2.2, and those for research question 2 are described in Section 2.3.

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

Treatment with cisplatin/carboplatin + gemcitabine

As described in dossier assessment A24-99, the use of carboplatin + gemcitabine essentially complied with the specifications of Annex VI to Section K of the Pharmaceutical Directive. For the treatment with cisplatin + gemcitabine, however, there are deviations from the Summary of Product Characteristics (SPC), which are described below.

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

In the present therapeutic indication, the SPC for gemcitabine - when combined with cisplatin - specifies a cycle length of 28 days with administration of 1000 mg/m² body surface area of gemcitabine on days 1, 8 and 15 of a cycle [6]. In accordance with the SPC, cisplatin is administered at a dose of 70 mg/m² body surface area on Day 1 after gemcitabine or on Day 2 of each 28-day treatment cycle [6].

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

In its comments, the company stated that the dosing regimen of cisplatin + gemcitabine used in the EV-302/KN-A39 study corresponded to the treatment standards in clinical practice both in terms of cycle length and number of cycles. Among other things, it refers to the hearing on the benefit assessment of nivolumab in the therapeutic indication of urothelial carcinoma [7].

In the overall view of the available information from publicly available sources [8] and the discussion in the oral hearings on the benefit assessment of nivolumab (A24-70) [7] and on

the present benefit assessment of enfortumab vedotin + pembrolizumab (A24-98 and A24-99) [9], it is assumed that no additional uncertainty arises from this deviation in the present situation.

It is overall assumed 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.

Maximum number of treatment cycles with cisplatin + gemcitabine

In the comparator arm of the EV-302/KN-A39 study, treatment with cisplatin + gemcitabine was limited to a maximum treatment duration of 6 cycles, in deviation from the specifications in the SPC. However, the SPC does not specify any fixed upper limit for the number of treatment cycles [6,10]. In the total population of the EV-302/KN-A39 study, patients in the comparator arm received a median [Q1; Q3] of 6 [4; 6] cycles of cisplatin / carboplatin + gemcitabine. The current national S3 guideline does not include a recommendation regarding the duration of treatment with cisplatin + gemcitabine [11]; the guideline of the European Society for Medical Oncology (ESMO) recommends 4 to 6 cycles of platinum-based chemotherapy in this therapeutic indication [12]. Therefore, it is assumed for the present benefit assessment that the limitation of treatment with cisplatin + gemcitabine to a maximum of 6 cycles does not represent a relevant restriction of study EV-302/KN-A39.

Possibility of a single treatment switch between cisplatin and carboplatin

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

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

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

The G-BA specified treatment with cisplatin + gemcitabine (research question 1) or carboplatin + gemcitabine (research question 2) as ACT for adult patients with unresectable or metastatic

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

According to the company's information in the context of the commenting procedure, only 34.7% (research question 1) or 25.2% (research question 2) of patients in the comparator arm of the respective relevant subpopulation received maintenance treatment with avelumab in the EV-302/KN-A39 study (see Table 1). Overall, this does initially not represent an adequate implementation of the G-BA's ACT.

However, analogous to dossier assessment A24-98 [5] the company provided further information on the use of avelumab in the EV-302/KN-A39 study. Based on the data provided by the company, a distinction can be made 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

The company's information on the proportion of these 3 groups of patients in the comparator arm of the respective subpopulation is shown in Table 1 and was supplemented by the Institute's calculations.

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 (1st data cut-off 08 August 2023)		
Maintenance therapy with avelumab possible according to company and avelumab received[c], n (%)	84 (34.7[d])	51 (25.2[d])
Maintenance therapy with avelumab not possible according to the company, n (%)	83 (34.3[d])	98 (48.5[d])
Maintenance therapy with avelumab possible according to company, but nevertheless avelumab not received, n (%)	69 (28.5)[d]	48 (23.8)[d]
Avelumab not received and alive[e]	48 (19.8[d])	29 (14.4[d])
Avelumab not received and deceased	21 (8.7[d])	19 (9.4[d])

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.
f. Chemotherapy completed and alive at the time of the data cut-off.

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

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

In its comments, the company argued that the data of the EV-302/KN-A39 study presented in the dossier were nevertheless suitable for deriving the added benefit of pembrolizumab + enfortumab vedotin. Among other things, the company argues that the use of avelumab as a subsequent therapy was permitted from the time of approval and that the study protocol was additionally adapted on 11 November 2021 with Amendment 4 and defined the use of avelumab as maintenance therapy in the comparator arm at the investigator's discretion and subject to local availability.

The company's argumentation and its approach of presenting information 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 is basically suitable for assessing the interpretability of the results of the RCT EV-302/KN-A39 for the benefit assessment. However, there are several points regarding the subdivision that require comment.

Lack of information on the use of avelumab

Avelumab was not part of the study medication of the RCT EV-302/KN-A39, but, as per the study design, could be used after completion or discontinuation of platinum-containing chemotherapy according to the investigator's assessment and depending on local availability. Following the start of the study on 30 March 2020 and the approval of avelumab in the European Union on 21 January 2021 [13], Amendment 4 to the study protocol on 11 November 2021 explicitly described the possibility of maintenance therapy with avelumab (at the investigator's discretion and subject to local availability); Amendment 7 of 30 November 2022 specified that avelumab should be used in accordance with the local SPC. However, there is a lack of specific information on the use of avelumab, especially before the amendment of 30 November 2022.

In its comments, the company stated that only the dose regimen used in the approval study was established for avelumab in the present therapeutic indication, on which also the specifications of the German SPC are based. It was therefore not to be expected that there would be any relevant deviations from the SPC regarding the dosage of avelumab for the period before 30 November 2022 [2].

However, the initial approval of avelumab was for a different indication and for a dosing regimen of 10 mg/kg every 2 weeks [14]. This regimen deviates from the specification of the SPC applicable in Germany, which provides for a dose of 800 mg every 2 weeks across all indications [15], but corresponds to the cross-indication specifications of the local SPCs of several countries in which the RCT EV-302/KN-A39 was conducted, including Switzerland and Canada [16,17].

Overall, it remains unclear to what extent the specifications of the SPC for avelumab applicable in Germany were complied with, as the company still does not provide any corresponding specific data, for example on the dosage used.

Duration of time between platinum-based chemotherapy and maintenance therapy

The SPC does not specify a time window or point in time after completion of chemotherapy at which maintenance therapy with avelumab is to be started. According to the SPC, it is therefore also possible to start maintenance treatment with avelumab immediately after completion of platinum-based chemotherapy if there is no progression [15]. The time window in the avelumab approval study JAVELIN Bladder 100 [18] was defined as 4 to 10 weeks after receipt of the last dose of chemotherapy.

In the company's dossier, there was also no information available on the time point at which maintenance therapy with avelumab had been started after completion of chemotherapy. It has therefore also remained unclear for patients who had received avelumab whether earlier use of maintenance therapy with avelumab would have been possible, from which they would potentially have benefited.

In its comments, the company presented information on the duration of the time between the end of platinum-based chemotherapy and the start of maintenance therapy with avelumab in all relevant patients. These are presented in Table 2.

Table 2: Information on the duration of time between the end of platinum-based chemotherapy and the start of maintenance therapy with avelumab in the EV-302/KN-A39 study

Study (data cut-off) **duration of the study phase** **category**	**Cisplatin + gemcitabine** **N = 242**	**Carboplatin + gemcitabine** **N = 202**
EV-302/KN-A39 (1st data cut-off 08 August 2023)		
Maintenance therapy with avelumab possible according to company and avelumab received, n (%)	84 (34.7[a])	51 (25.2[a])
Time between chemotherapy and avelumab maintenance therapy[b] [weeks]		
Median [Q1; Q3]	6.1 [4.9; 8.0]	5.1 [4.6; 8.0]
Range [min; max]	[2.0; 38.1]	[2.0; 22.0]
Mean (SD)	7.2 (4.6)	6.4 (3.6)

a. Institute's calculation.
b. The time between chemotherapy and maintenance therapy is defined as the time between the last dose of chemotherapy and the start of maintenance therapy with avelumab.

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

The median duration of the time between the end of platinum-based chemotherapy and the start of maintenance therapy with avelumab was within the time window of the RCT JAVELIN Bladder 100 in both subpopulations relevant to the research questions of the dossier assessment. Overall, it is therefore assumed that the duration of the time between the end of platinum-based chemotherapy and the start of maintenance therapy with avelumab was appropriate for the majority of patients, so that no additional uncertainty arises from this.

Patients who did not receive avelumab and died

With regard to patients for whom maintenance treatment 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 the 1st data cut-off with its commenting procedure in order to address the consequences of the lack of implementation of the ACT for the outcome

of overall survival in these patients. These analyses were conducted analogously to the 3 sensitivity analyses described in dossier assessment A24-98 [5]. They are described in Section 2.2.2.1 and are overall considered appropriate to address this point in respect of the outcome of overall survival, so that no additional uncertainty arises.

Conclusion and consequences for the benefit assessment

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

The results of study EV-302/KN-A39 can be interpreted on the basis of the information presented by the company on the implementation of maintenance therapy with avelumab and the associated sensitivity analyses on the outcome of overall survival despite the uncertainties described within the framework of the present addendum for research questions 1 and 2 of the benefit assessment. The consequences resulting from the incomplete implementation of the ACT were examined at outcome level and described in Section 2.2.2.1.

However, the informative value of the study is limited, particularly due to the incomplete implementation of maintenance therapy with avelumab. 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 benefit assessment for all outcomes.

2.1.3 Relevance of the Chinese cohort

The documents of the EV-302/KN-A39 study presented in the company's records comprise the data of 886 globally recruited patients. These patients were recruited in accordance with the study design and were considered in the presented first data cut-off. In addition, Protocol Amendment 6 of 12 April 2022 provided for the recruitment of further patients in China, which was to be continued after completion of the recruitment phase for the global cohort. This Chinese cohort was to include a total of 130 patients, 2 of whom were already included in the 886 globally recruited patients. Only the data of these 2 patients were considered in the present benefit assessment. The company did not provide any data on the 128 other patients in the Chinese cohort. The Chinese cohort is to be analysed separately from the global cohort in accordance with the study planning. There is no indication in the company's documents as to whether the Chinese cohort has already been analysed.

The patients in the Chinese cohort represent a relevant subpopulation for the present benefit assessment. However, the proportion of the additional 128 patients of the Chinese cohort in the total number of both cohorts (1014 patients in total) is only 13%. In addition, in accordance with the study protocol, the recruitment of additional patients into the Chinese cohort should only begin after the end of recruitment into the global cohort. As recruitment to the global cohort was not completed before 5 October 2022 [19], it is assumed that analyses of the Chinese cohort were still pending at the time the dossier was submitted. Therefore, the non-consideration of the Chinese cohort has no consequences for the present benefit assessment.

2.1.4 Planned duration of follow-up observation

Table 3 shows the planned duration of patient follow-up observation for the individual outcomes.

Table 3: Planned duration of follow-up observation – RCT, direct comparison: pembrolizumab + enfortumab vedotin + 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[b]	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 design, the study was to end at the latest 5 years after the last patient had been included or when no patient remained in the follow-up observation. The sponsor may terminate the study at any time.
b. Presented is the planned duration of follow-up observation according to the study design; according to the information in Module 4 A, patients who had not experienced a first deterioration since the start of the study before the initiation of subsequent antineoplastic therapy were censored on the date of the last available recording of the outcome. 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. The company presented no information on this.
c. Operationalized as CTCAE grade ≥ 3.

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

It is generally positive to note that, in accordance with the study design, the outcomes on symptoms, health status and health-related quality of life in the EV-302/KN-A39 study, as well as overall survival, were to be observed beyond disease progression until the end of the study.
b. However, according to the information in Module 4 A, patients who had not experienced a first deterioration since the start of the study before the initiation of subsequent antineoplastic therapy were censored on the date of the last available recording of the outcome. 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. Regardless of the planned observation period, the actual observation periods for these outcomes were shortened (see information on the course of the study in Section 2.2.1.2).

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

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

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 characteristics across research questions of the EV-302/KN-A39 study, including information on the study design, treatment in the comparator arm, comments on the implementation of the ACT, relevance of the Chinese cohort, data cut-offs and on the planned duration of follow-up observation, see Section 2.1 and dossier assessment A24-99.

2.2.1.1 Patient characteristics

The table on the presentation of the characteristics of the patients in the subpopulation relevant for research question 1 can be found in dossier assessment A24-99.

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

The company neither provides data on the primary origin of the disease for the respective subpopulations nor does it provide more detailed information on the metastasis of the disease. For the total population of the study, the origin of the disease was in the urinary bladder in 67% vs. 74% of patients. In the total population, visceral metastases were present in 72% of patients in both arms at baseline, including liver metastases in around 23%.

The most common reasons for treatment discontinuation in the relevant subpopulation were disease progression (36% versus 13%) or an adverse event (21% versus 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. Study discontinuation for reasons other than death (in all cases due to withdrawal of consent) occurred only sporadically in both treatment arms, in around 3% vs. 4% of patients.

2.2.1.2 Information on the course of the study

Table 4 shows the median treatment durations of the patients and the 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: pembrolizumab + enfortumab vedotin vs. cisplatin + gemcitabine (subpopulation: cisplatin suitable)

Study **duration of the study phase** **outcome category/outcome**	**Pembrolizumab + enfortumab vedotin** **N = 240**	**Cisplatin + gemcitabine** **N = 242**
EV-302/KN-A39 (1st data cut-off 08 August 2023)		
Treatment duration [months]		
Median [Q1; Q3]	9.6 [ND]	4.1 [ND]
Observation period [months]		
Overall survival		
Median [Q1; Q3]	14.4 [ND]	12.2 [ND]
Symptoms (BPI-SF; EORTC QLQ-C30), health status (EQ-5D VAS), health-related quality of life (EORTC QLQ-C30)		
Median [Q1; Q3]	10.7 [ND]	6.6 [ND]
Side effects		
AEs/severe AEs		
Median [Q1; Q3]	9.5 [ND]	4.7 [ND]
SAEs		
Median [Q1; Q3]	10.7 [ND]	4.7 [ND]

a. No information on the methods used to calculate treatment duration and observation times.

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

Within the relevant subpopulation, the patients' median treatment duration was higher in the intervention arm, at 9.6 months, than in the comparator arm, at 4.1 months. This is due to the fact that in the intervention arm treatment was planned to be administered until disease progression or the occurrence of unacceptable toxicity (pembrolizumab for a maximum of 35 cycles), while treatment in the comparator arm was limited to a maximum of 6 cycles. The stated treatment duration for the comparator arm does not take into account the duration of a possible maintenance therapy with avelumab.

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

Observation beyond disease progression up to the end of the study was planned for the outcomes on symptoms, health status and health-related quality of life. Nevertheless, the observation period of these outcomes is shorter compared to the outcome of overall survival (in the intervention arm by approx. 4 months, in the control arm by approx. 6 months). Furthermore, the observation period in the intervention arm is approx. 4 months longer than in the comparator arm. As described in Section 2.1.4, according to the information in Module 4 A, patients who had not experienced a first deterioration since the start of the study before the initiation of subsequent antineoplastic therapy were censored on the date of the last available recording of the outcome. In the present data situation, it is not assumed that this influences the results to a relevant extent; for an explanation, see Section 2.2.2.1 of the present addendum.

For the side effects outcomes, the observation period in the intervention arm is up to 6 months longer than in the comparator arm. In addition, the fixed treatment duration in the comparator arm and the linking of the observation time for side effects to the treatment duration means that the effect estimate only reflects approximately the first 6 months after randomization and thus only the period of chemotherapy in the comparator arm, but not a possible maintenance therapy with avelumab, and only the first 6 months of a possibly longer-lasting therapy in the intervention arm. This has been taken into account in the derivation of the certainty of conclusions for the outcomes on side effects (see Section 2.2.2.1).

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 the first subsequent antineoplastic therapy (≥ 1% of patients in ≥ 1 treatment arm) – RCT, direct comparison: pembrolizumab + enfortumab vedotin versus cisplatin + gemcitabine (subpopulation: cisplatin suitable)

Study **drug class** **drug**	**Patients with subsequent therapy, n (%)**	
	pembrolizumab + enfortumab vedotin **N = 240**	**cisplatin + gemcitabine** **N = 242**
Study EV-302/KN-A39 (1st data cut-off 08 August 2023)		
Any subsequent therapy[a]	81 (33.8)	110 (45.5)
Subsequent systemic therapy[a]	79 (32.9)	106 (43.8)
Non-palliative radiotherapy	1 (0.4)	4 (1.7)
No subsequent therapy[a] received, deceased	32 (13.3)	51 (21.1)
No subsequent therapy[a] received, alive at the data cut-off	127 (52.9)	81 (33.5)
First subsequent systemic therapy[a]	79 (32.9)	106 (43.8)
Platinum-based therapy	70 (29.2)	10 (4.1)
PD-1/PD-L1-based therapy	2 (0.8)	66 (27.3)
Avelumab	0 (0)	3 (1.2)
Atezolizumab	0 (0)	19 (7.9)
Pembrolizumab	2 (0.8)	42 (17.4)
Other drugs	7 (2.9)	30 (12.4)
Enfortumab vedotin	2 (0.8)	15 (6.2)
Paclitaxel	0 (0)	7 (2.9)

a. According to the company, maintenance therapy with avelumab received after treatment discontinuation or termination of chemotherapy in the comparator arm or any local therapy according to physician's choice does not count as subsequent systemic therapy.

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

In the EV-302/KN-A39 study, subsequent therapies were permitted without restrictions in both study arms. In the subpopulation relevant to research question 1, a total of 79 (32.9%) patients in the intervention arm and 106 (43.8%) patients in the comparator arm received at least 1 subsequent antineoplastic systemic therapy for the treatment of progressive disease. However, the company's documents do not provide any information on the proportion of patients in the relevant subpopulation who experienced disease progression. Therefore, it is not possible to assess what proportion of patients with disease progression received subsequent therapy, and thus whether subsequent therapies were used appropriately in a sufficient proportion of patients in the subpopulation of study EV-302/KN-A39 relevant to research question 1.

According to current guideline recommendations, platinum-based chemotherapy or, in certain patients, erdafitinib is recommended as a subsequent therapy after disease

progression under pembrolizumab + enfortumab vedotin [12]; platinum-based chemotherapy was the predominant first subsequent therapy in the intervention arm, which 29% of patients received.

Atezolizumab or pembrolizumab is recommended as first-line therapy in case of disease progression under platinum-based chemotherapy [11,12]. In the comparator arm, 8% and 17% of patients in the respective relevant subpopulation received these agents as their first Programmed Cell Death 1 (PD-1)/ Programmed Cell Death-Ligand 1 (PD-L1)-based subsequent systemic therapy, which was not maintenance therapy; this corresponds to 18% and 40% of patients who received subsequent systemic therapy, respectively.

In cases of disease progression under maintenance treatment with avelumab following platinum-based chemotherapy as first-line treatment, erdafitinib (in certain patients) and enfortumab vedotin are primarily recommended, and sacituzumab govitecan, vinflunine or taxanes [12] are recommended with a lower recommendation grade. In the comparator arm, 6% of patients received enfortumab vedotin as first subsequent systemic therapy; this corresponds to 14% of patients who received subsequent systemic therapy.

Information on subsequent therapies in later treatment lines is not available in the company's documents.

Based on the available data, it is not possible to assess whether subsequent therapies were used appropriately in a sufficient proportion of patients in the subpopulation of study EV-302/KN-A39 relevant to research question 1. This results in a high risk of bias of the results on overall survival (see Section 2.2.2.2).

2.2.1.4 Risk of bias across outcomes (study level)

Table 6 shows the risk of bias across outcomes (risk of bias at study level).

Table 6: Risk of bias across outcomes (study level) – RCT, direct comparison: pembrolizumab + enfortumab vedotin vs. cisplatin/carboplatin + gemcitabine

Study	Adequate random sequence generation	Allocation concealment	Blinding		Reporting independent of the results	No additional aspects	Risk of bias at study level
			Patients	Treating staff			
EV-302/KN-A39	Yes	Yes	No	No	Yes	Yes	Low
RCT: randomized controlled trial							

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

Limitations resulting from the open-label study design are described in Section 2.2.2.2 with the outcome-specific risk of bias.

2.2.1.5 Transferability of the study results to the German health care context

The company stated that the results of study EV-302-KN-A39 can be transferred to the German health care context due to the characteristics of the investigated patient population, the study design and the approval-compliant use of pembrolizumab in combination with enfortumab vedotin.

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

2.2.2 Results on added benefit

2.2.2.1 Outcomes included

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

- Mortality
  - overall survival
- Morbidity
  - worst pain (BPI-SF item 3)
  - pain interference (BPI-SF items 9a–g)
  - symptoms, recorded with the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30 (EORTC QLQ-C30)
  - health status, recorded using the EQ-5D visual analogue scale (VAS)
- Health-related quality of life
  - recorded with the EORTC QLQ-C30
- Side effects
  - SAEs
  - severe AEs (Common Terminology Criteria for Adverse Events [CTCAE] grade ≥ 3)
  - discontinuation due to AEs
  - immune-related SAEs
  - immune-related severe AEs (CTCAE grade ≥ 3)

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

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

Table 7 shows the outcomes for which data for research question 1 are available in the included study.

Table 7: Matrix of outcomes – RCT, direct comparison: pembrolizumab + enfortumab vedotin 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[ae]
EV-302/KN-A39	Yes	Yes	No[f]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No[f]	Yes	Yes	Yes	Yes

a. Severe AEs are operationalized as CTCAE grade ≥ 3.
b. In each case, the operationalization of a specific, predefined MedDRA PT collection from the outcome of AEOSI (Version 25.0) presented by the company is used (PT collection Version 25.0, MedDRA-Version 26.0).
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), diarrhoea (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), and general disorders and administration site conditions (SOC, severe AEs).
f. No suitable data available; see Section 2.2.2.1 of the present addendum for reasoning.

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

Notes on outcomes

As described in Section 2.1.2, the ACT was only incompletely implemented in study EV-302/KN-A39, as maintenance therapy with avelumab was not part of the study treatment and not all patients who were eligible for maintenance treatment with avelumab also received it. The consequences for the benefit assessment resulting from this at outcome level are described below together with other aspects.

Overall survival: sensitivity analyses of the company

In order to address the uncertainty for the results on overall survival resulting from the incomplete implementation of the maintenance therapy with avelumab, the company presented 3 sensitivity analyses as well as a so-called matching analysis on sensitivity analysis 2 with its comments. In the sensitivity analyses, patients who had not received avelumab despite suitability according to the company's criteria and who died are considered in different ways.

- In sensitivity analysis 1, patients who had been eligible for maintenance therapy with avelumab and who had not received avelumab and died were censored at the time of death. This means that the observation period of these patients until death is included in the analysis without taking the event itself into account.
- In sensitivity analysis 2, patients who had been eligible for maintenance therapy with avelumab and who had not received avelumab and died were censored at the time of the data cut-off and thus imputed as event-free (i.e. survived) up to the data cut-off.
- In sensitivity analysis 3, patients for whom maintenance treatment with avelumab had been an option and who had not received avelumab and died were imputed with a modified time of death or censored at the time of the data cut-off, depending on which event occurred earlier. In this analysis, a simplified assumption was made that the patients would have benefited from treatment with avelumab to an extent that, according to the company's assessment, can be learned from the JAVELIN Bladder 100 study [20]. The imputed median benefit in terms of overall survival was 8.8 months for patients who had received cisplatin + gemcitabine and 7.0 months for patients who had received carboplatin + gemcitabine. This median benefit was added to the actually observed time of death and a hypothetical modified date of death was determined and included in the analysis.

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

According to the company, the so-called matching analysis compares those patients for whom, according to the company, maintenance treatment with avelumab was an option and

who did not receive avelumab and died, with patients who received avelumab based on baseline characteristics. However, the company's comments lack basic information on the methods of this analysis, so that they cannot be interpreted for the present addendum and are not used for it.

The sensitivity analyses 1 to 3 presented by the company are suitable to adequately address the uncertainty due to the incomplete implementation of maintenance therapy with avelumab with regard to those patients who did not receive avelumab despite suitability according to the company's criteria and died. Taking into account the sensitivity analyses, it is therefore possible to interpret the results of the outcome of overall survival in the present data constellation.

Morbidity and health-related quality of life

The median time to event for all patient-reported outcomes on morbidity and health-related quality of life, for which there are generally usable data, was a maximum of 4.5 months in both arms (see Table 9 for research question 1 and Table 17 for research question 2) and is thus only sporadically and insignificantly longer than the median duration of treatment with chemotherapy of 4.1 months (see Table 4 for research question 1 and Table 13 for research question 2). However, the Kaplan-Meier curves show that the majority of events for the outcomes of morbidity and health-related quality of life occurred early in the course of the study during the chemotherapy period in the comparator arm (see Appendix A). In the present data situation, it is therefore assumed that the incomplete implementation of the subsequent maintenance therapy does not have a relevant impact on the results. For this reason, the patient-reported outcomes on morbidity and health-related quality of life were used to derive the added benefit. However, it should be noted that the available results chiefly refer to the first months of observation under treatment and are therefore of limited informative value for the present research question. At the same time, analyses covering a longer period would not be interpretable without corresponding sensitivity analyses due to the incomplete implementation of maintenance therapy.

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

Outcomes on pain (BPI-SF)

In the EV-302/KN-A39 study, the BPI-SF questionnaire is used to record pain. In Module 4 A, the company presented analyses of worst pain (BPI-SF item 3) and pain interference (BPI-SF items 9a-g). It also presents analyses of progression accompanied by pain.

The outcomes of worst pain (BPI-SF item 3) and pain interference (BPI-SF items 9a-9g) were used for the benefit assessment.

However, the outcome of progression accompanied by pain is not used for the benefit assessment. This is explained below.

Pain or symptomatic disease progression is always relevant to the patient. For several reasons, however, the chosen operationalization of the outcome of progression accompanied by pain is not suitable for adequately capturing this outcome. It is a post hoc defined outcome; however, the threshold value of an increase in BPI-SF item 3 by 1 unit assumed in the present operationalization is not justified by the company on the basis of pre-specified criteria. According to the IQWiG General Methods [21], a response threshold of ≥ 15% of the scale range should therefore be used. However, the threshold value applied by the company does not correspond to a change of ≥ 15% of the scale range. Moreover, the methods used to select this criterion are insufficiently described. Furthermore, temporal proximity to an event does not sufficiently prove a causal relationship. For these reasons, the outcome of progression accompanied by pain is not used for the assessment. Irrespective of this, pain is relevant regardless of disease progression and is already comprehensively mapped via other outcomes.

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

The response threshold of ≥ 2 points was predefined only for item 3 of the BPI-SF and, in accordance with the IQWiG *General Methods* [21], is therefore used for the outcome of worst pain. No response threshold was predefined for the outcome of pain interference (BPI-SF items 9a-g); therefore, the response threshold of ≥ 15% of the scale range is used for the assessment in accordance with the IQWiG *General Methods*.

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

Side effects

Only analyses that do not cover the entire observation period of study EV-302/A-39 are available for the side effects outcomes. The fixed treatment duration and the associated discontinuation of observation after the end of study medication in the comparator arm mean that the effect estimate only reflects approximately the first 6 months after randomization. This essentially corresponds to the treatment duration with cisplatin/carboplatin +

gemcitabine plus 30 days (see Table 3 and Table 4 for research question 1 and Table 13 for research question 2); the period of possible maintenance treatment with avelumab is not shown. For the period of a possible maintenance therapy with avelumab in progression-free patients, the side effects outcomes were not followed up and events that occur under such therapy are therefore not included in the analyses on side effects presented by the company. Therefore, statements on the full duration of therapy in the sense of the ACT are not possible for the side effects outcomes. Even in the intervention arm, only the first 6 months of a possibly longer-lasting therapy are taken into account. This shortened observation in the comparator arm or consideration of data collected in the intervention arm limits the certainty of conclusions on the results on AEs. The results can nevertheless be used for assessment in the present data situation, as a high proportion of the events already occur in this period. The particular data constellation presented here is taken into account accordingly when weighing up the added benefit.

With its comments, the company presented sensitivity analyses on the overall rates of AEs, SAEs and severe AEs, in the context of which patients for whom avelumab therapy was suitable according to the company and in whom no corresponding event had yet occurred were censored at the time of the data cut-off and thus imputed as event-free up to the data cut-off. However, these sensitivity analyses only relate to the 2nd data cut-off and are therefore not considered for the assessment of the 1st data cut-off in the context of this addendum.

Immune-related SAEs and immune-related severe AEs

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

Peripheral neuropathy (SMQ, AEs)

The recording of the outcome of peripheral neuropathy (SMQ, AEs) was pre-specified according to the study design of RCT EV-302/KN-A39 and corresponding results are available in the study documents for the total population of the study. However, no results on this outcome were presented in the company's documents for the relevant subpopulations of research questions 1 and 2 of the benefit assessment. Therefore, no suitable data are available for the outcome of peripheral neuropathy (SMQ, AEs).

Discontinuation due to AEs

In Module 4 A of the dossier, no information is available on whether the outcome is 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 8 describes the risk of bias for the results of the relevant outcomes for research question 1.

Table 8: Risk of bias across outcomes and outcome-specific risk of bias – RCT, direct comparison: pembrolizumab + enfortumab vedotin vs. cisplatin + gemcitabine (subpopulation: cisplatin suitable)

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	H[f]	H[g, h]	–[i]	H[g, h]	H[g, h]	H[g, h]	H[j]	H[j]	H[k]	H[j]	H[j]	–[i]	H[g, j]	H[j]	H[j]	H[g, j]

a. Severe AEs are operationalized as CTCAE grade ≥ 3.
b. In each case, the operationalization of a specific, predefined MedDRA PT collection from the outcome of AEOSI (Version 25.0) presented by the company is used (PT collection Version 25.0, MedDRA-Version 26.0).
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), diarrhoea (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), and general disorders and administration site conditions (SOC, severe AEs).
f. Due to uncertainties in the use of subsequent therapies.
g. Lack of blinding in subjective recording of outcomes, unless serious or severe AEs are involved.
h. Declining response rate of questionnaires over the course of the study; high proportion of patients not included in the analysis (> 10 %) or large difference between the treatment groups (> 5 percentage points).
i. No suitable data available; see Section 2.2.2.1 of the present addendum for reasoning.
j. Incomplete observations for potentially informative reasons.
k. Lack of blinding in the presence of subjective decision on 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 is rated as high for all patient-relevant outcomes.

For the results of the outcome "overall survival", the outcome-specific risk of bias is rated as high, as no information on the proportion of patients with disease progression is available in the company's documents and it is therefore not possible to adequately assess on the basis of these documents whether subsequent therapies were used appropriately (for explanation see Section 2.2.1.3).

The outcome-specific risk of bias for the results of the outcomes of worst pain (BPI-SF item 3), symptoms (EORTC QLQ-C30), health status (EQ-5D VAS) and health-related quality of life (EORTC QLQ-C30) is rated as high. The reason therefore is the decreasing response to the respective questionnaire in the course of the study, the large proportion of patients not considered in the analysis (> 10%) and the large difference between the treatment groups (> 5 percentage points). This is accompanied by the lack of blinding in subjective recording of outcomes.

No suitable data are available for the outcomes of pain interference (BPI-SF items 9a-9g) and peripheral neuropathy (SMQ, AEs) (see Section 2.2.2.1 for an explanation), so the assessment of the risk of bias is not applicable.

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

Summary assessment of the certainty of conclusions

In addition to the described bias aspects, there are uncertainties for the EV-302/KN-A39 study, as described in Section 2.1.1 and Section 2.1.2, particularly in the implementation of the ACT. In the present specific data constellation, the results of the study can nevertheless be interpreted for the research questions of the present benefit assessment, but the certainty of the study results for the present assessment is reduced. Based on the EV-302/KN-A39 study, at most hints, e.g. of an added benefit, can be derived for both research questions.

Moreover, for the outcomes in the side effects category, analyses are only available for a significantly shortened period, which in the comparator arm only reflects the treatment with chemotherapy, but not the period of a possible maintenance therapy with avelumab, and in the intervention arm only takes into account the first 6 months of a possibly longer-lasting treatment (see Section 2.2.2.1). This shortened observation in the comparator arm or

consideration of recorded data in the intervention arm contributes to a limited certainty of conclusions and additionally justifies the fact that at most hints can be derived.

2.2.2.3 Results

Table 9 summarizes the results of the comparison of pembrolizumab + enfortumab vedotin with cisplatin + gemcitabine for first-line treatment in adult patients with unresectable or metastatic urothelial carcinoma for whom cisplatin-based therapy is suitable. Where necessary, IQWiG calculations are provided to supplement the data from the company's dossier.

Kaplan-Meier curves on the presented time-to-event analyses can be found in Appendix A.1. Results on common AEs, SAEs, severe AEs, and discontinuation due to AEs are presented in Appendix B.1. Kaplan-Meier curves for outcomes of the outcome categories "health-related quality of life" and "side effects" with non-significant results are not available in the company's dossier. Likewise, the company's dossier does not provide a list of the categories of immune-related AEs, immune-related SAEs and immune-related severe AEs.

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

Study outcome category outcome	Pembrolizumab + enfortumab vedotin		Cisplatin + gemcitabine		Pembrolizumab + enfortumab vedotin vs. cisplatin + gemcitabine
	N	median time to event in months [95% CI] patients with event n (%)	N	median time to event in months [95% CI] patients with event n (%)	HR [95% CI]; p-value
EV-302/KN-A39 (1st data cut-off 08 August 2023)					
Mortality					
Overall survival	240	31.5 [25.4; NC] 69 (28.8)	242	18.4 [15.6; 27.5] 110 (45.5)	0.54 [0.40; 0.73]; < 0.001[a]
Overall survival (sensitivity analysis 1[b])	240	31.5 [25.4; NC] 69 (28.8)	242	27.5 [18.4; NC] 89 (36.8)	0.66 [0.48; 0.90]; 0.009[a]
Overall survival (sensitivity analysis 2[c])	240	31.5 [25.4; NC] 69 (28.8)	242	NA [18.4; NC] 89 (36.8)	0.70 [0.51; 0.97]; 0.030[a]
Overall survival (sensitivity analysis 3[d])	240	31.5 [25.4; NC] 69 (28.8)	242	20.4 [17.9; 30.9] 101 (41.7)	0.61 [0.45; 0.82]; 0.001[a]
Morbidity[e]					
Worst Pain (BPI-SF Item 3 – time to 1st deterioration) [f]	210	2.0 [1.3; 4.5] 130 (61.9)	189	1.8 [1.1; 3.2] 113 (59.8)	0.93 [0.72; 1.21]; 0.601[a]
Pain interference (BPI-SF items 9a-g – time to first deterioration)[g]	No suitable data available[h]				
Symptoms (EORTC QLQ-C30 – time to first deterioration)[if]					
Fatigue	210	0.4 [0.4; 0.6] 169 (80.5)	189	0.4 [0.4; 0.6] 157 (83.1)	0.80 [0.64; 1.00]; 0.052[a]
Nausea and vomiting	210	2.0 [1.1; 4.6] 131 (62.4)	189	0.4 [0.4; 0.8] 142 (75.1)	0.54 [0.42; 0.69]; < 0.001[a]
Pain	210	0.7 [0.5; 1.3] 147 (70.0)	189	1.1 [0.6; 1.4] 130 (68.8)	0.97 [0.76; 1.23]; 0.801[a]
Dyspnoea	210	2.4 [1.6; 4.6] 134 (63.8)	189	2.0 [1.7; 3.9] 107 (56.6)	1.00 [0.77; 1.29]; 0.973[a]
Insomnia	210	2.3 [0.9; 4.5] 125 (59.5)	189	2.0 [0.9; 3.8] 113 (59.8)	0.85 [0.65; 1.09]; 0.203[a]
Appetite loss	210	0.9 [0.6; 1.7] 141 (67.1)	189	0.6 [0.4; 0.9] 130 (68.8)	0.77 [0.61; 0.98]; 0.037[a]
Constipation	210	2.2 [1.5; 4.5] 125 (59.5)	189	0.7 [0.4; 1.3] 133 (70.4)	0.58 [0.45; 0.74]; < 0.001[a]
Diarrhoea	210	2.0 [1.3; 3.8] 132 (62.9)	189	3.1 [2.0; 10.1] 96 (50.8)	1.15 [0.88; 1.51]; 0.290[a]

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

Study **outcome category** **outcome**	**Pembrolizumab + enfortumab vedotin**		**Cisplatin + gemcitabine**		**Pembrolizumab + enfortumab vedotin vs. cisplatin + gemcitabine**
	N	**median time to event in months [95% CI]** **patients with event n (%)**	**N**	**median time to event in months [95% CI]** **patients with event n (%)**	**HR [95% CI]; p-value**
Health status (EQ-5D VAS - time to first deterioration)[j]	210	2.5 [1.3; 5.2] 138 (65.7)	189	2.2 [1.6; 3.2] 110 (58.2)	0.99 [0.77; 1.28]; 0.948[a]
health-related quality of life[e]					
EORTC-QLQ C30 – time to first deterioration[k]					
Global health status	210	0.7 [0.6; 1.3] 158 (75.2)	189	0.9 [0.6; 1.1] 132 (69.8)	0.93 [0.73; 1.17]; 0.519[a]
Physical functioning	210	1.1 [0.6; 1.6] 165 (78.6)	189	0.9 [0.6; 1.1] 136 (72.0)	0.91 [0.72; 1.14]; 0.407[a]
Role functioning	210	0.6 [0.4; 0.8] 164 (78.1)	189	0.4 [0.4; 0.9] 140 (74.1)	0.90 [0.71; 1.13]; 0.343[a]
Emotional functioning	210	3.2 [2.0; 10.1] 120 (57.1)	189	3.8 [2.0; NC] 93 (49.2)	1.05 [0.80; 1.37]; 0.751[a]
Cognitive functioning	210	1.8 [1.1; 2.3] 143 (68.1)	189	0.9 [0.6; 1.5] 130 (68.8)	0.82 [0.64; 1.04]; 0.098[a]
Social functioning	210	0.7 [0.5; 1.1] 161 (76.7)	189	0.9 [0.6; 1.1] 129 (68.3)	1.08 [0.85; 1.36]; 0.526[a]
Side effects[l, m]					
AEs (supplementary information)	239	0.9 [0.2; 0.2] 239 (100.0)	236	0.6 [0.1; 0.2] 234 (99.2)	–
SAEs	239	NA [9.6; NC] 107 (44.8)	236	NA 83 (35.2)	0.93 [0.69; 1.26]; 0.639[n]
Severe AEs[o]	239	4.2 [3.0; 6.1] 164 (68.6)	236	1.4 [1.0; 1.8] 175 (74.2)	0,51 [0,41; 0,65]; < 0.001[n]
Discontinuation due to AEs[p]	239	19.3 [12.0; NC] 92 (38.5)	236	NA 58 (24.6)	0,94 [0,65; 1,34]; 0,725[n]
Immune-related AEs[q] (supplementary information)			*No suitable data available[h]*		
Immune-related SAEs[q]	239	NA 34 (14.2)	236	NA 2 (0.8)	11.64 [2.76; 49.11]; < 0.001[n]
Immune-related severe AEs[o, q]	239	NA 49 (20.5)	236	NA 3 (1.3)	11,06 [3,39; 36,07]; < 0.001[n]
Peripheral neuropathy (SMQ, AEs)			No suitable data availableh		

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

Study outcome category outcome	Pembrolizumab + enfortumab vedotin		Cisplatin + gemcitabine		Pembrolizumab + enfortumab vedotin vs. cisplatin + gemcitabine
	N	median time to event in months [95% CI] patients with event n (%)	N	median time to event in months [95% CI] patients with event n (%)	HR [95% CI]; p-value
Skin reactions, operationalized as skin and subcutaneous tissue disorders (SOC, AEs)[r]	239	0.5 [0.4; 0.6] 204 (85.4)	236	NA 61 (25.8)	5,88 [4,39; 7,87]; < 0.001[n]
Severe hyperglycaemia (PT, severe AEs)[o]	239	NA 20 (8.4)	236	NA 2 (0.8)	7,68 [1,76; 33,49]; 0,007[n]
Severe nephrotoxicity, operationalized as renal and urinary disorders (SOC, severe AEs)[o]	239	NA 16 (6.7)	236	NA 16 (6.8)	0.69 [0.33; 1.46]; 0.331[n]
Other specific AEs					
Nausea (PT, AEs)	239	NA 61 (25.5)	236	3.1 [2.1; NC] 120 (50.8)	0,35 [0,26; 0,49]; < 0.001[n]
Diarrhoea (PT, AEs)	239	NA [16.4; NC] 89 (37.2)	236	NA 40 (16.9)	1.90 [1.29; 2.79]; 0.001[n]
Vomiting (PT, AEs)	239	NA 24 (10.0)	236	NA 42 (17.8)	0.44 [0.26; 0.75]; 0.003[n]
Eye disorders (SOC, AEs)	239	19.7 [12.7; NC] 88 (36.8)	236	NA 14 (5.9)	5,30 [2,98; 9,41]; < 0.001[n]
Ear and labyrinth disorders (SOC, AEs)	239	NA 17 (7.1)	236	NA 33 (14.0)	0,17 [0,07; 0,40]; < 0.001[n]
Endocrine disorders (SOC, AEs)	239	NA 34 (14.2)	236	NA 2 (0.8)	12,38 [2,94; 52,19]; < 0.001[n]
Gastrointestinal disorders (SOC, SAEs)	239	NA 24 (10.0)	236	NA 6 (2.5)	3.21 [1.29; 7.97]; 0.012[n]
Respiratory, thoracic and mediastinal disorders (SOC, SAEs)	239	NA 25 (10.5)	236	NA 4 (1.7)	4.26 [1.45; 12.53]; 0.009[n]
Blood and lymphatic system disorders (SOC, severe AEs)[o]	239	NA 17 (7.1)	236	4.9 [3.0; NC] 110 (46.6)	0,08 [0,05; 0,15]; < 0.001[n]
Urinary tract infection (PT, severe AEs)[o]	239	NA 8 (3.3)	236	6.1 [6.1; NC] 19 (8.1)	0.32 [0.13; 0.76]; 0.010[n]
General disorders and administration site conditions (SOC, severe AEs)[o]	239	NA 13 (5.4)	236	NA 24 (10.2)	0.30 [0.14; 0.67]; 0.003[n]

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

Study outcome category outcome	Pembrolizumab + enfortumab vedotin		Cisplatin + gemcitabine		Pembrolizumab + enfortumab vedotin vs. cisplatin + gemcitabine
	N	median time to event in months [95% CI] patients with event n (%)	N	median time to event in months [95% CI] patients with event n (%)	HR [95% CI]; p-value

a. HR and CI: Cox proportional hazards model, stratified by PD-L1 expression (high vs. low) and liver metastases (present vs. not present); p-value: Wald test.
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.
e. Patients for whom no further data were available other than at baseline were excluded from the analysis (FAS population).
f. A score increase by ≥ 2 points from baseline was considered a clinically relevant deterioration (scale range: 0 to 10); for explanation, see Section 2.2.2.1.
g. A score increase by ≥ 1.5 points from baseline was considered a clinically relevant deterioration (scale range: 0 to 10); for explanation, see Section 2.2.2.1.
h. See Section 2.2.2.1 for reasons.
i. An EORTC QLQ-C30 score increase by ≥ 10 points from baseline was considered a clinically relevant deterioration (scale range: 0 to 100).
j. An EQ-5D VAS score decrease by ≥ 15 points from baseline was considered a clinically relevant deterioration (scale range: 0 to 100).
k. An EORTC QLQ-C30 score decrease by ≥ 10 points from baseline was considered a clinically relevant deterioration (scale range: 0 to 100).
l. 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.
m. Conversion of median times-to-event from weeks into months. HR and CI: unstratified Cox proportional hazards model, p-value: Wald test, score test in case of 0 events in one of the study arms.
n. HR and CI: unstratified Cox proportional hazards model; p-value: Wald test.
o. Operationalized as CTCAE grade ≥ 3.
p. There are relevant deviations from dossier assessment A24-98 [5] for the outcome "discontinuation due to AEs".
q. In each case, the operationalization of a specific, predefined MedDRA PT collection from the outcome of AESI presented by the company is used (PT- collection Version 25.0, MedDRA-Version 26.0).
r. The following result is shown for the severe AEs of the SOC “skin and subcutaneous tissue disorders” included in the results on AEs: 39 (16.3) vs. 0 (0); HR: NC; p < 0.001; Kaplan-Meier curve see Figure 25.

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 Sections 2.1.1 and 2.1.2 for the reasoning).

When interpreting the results on side effects, it should be noted that due to the fixed treatment duration and the associated discontinuation of observation in the comparator arm, the effect estimate only covers approximately the first 6 months after randomization (see Section 2.2.1.2).

Mortality

Overall survival

For the outcome of overall survival, a statistically significant difference was found in favour of pembrolizumab + enfortumab vedotin in comparison with cisplatin + gemcitabine. The 3 sensitivity analyses presented by the company, in which patients in the comparator arm for whom maintenance treatment with avelumab would potentially have been indicated and who died without maintenance treatment were accounted for differently (see Section 2.2.2.1), also showed a statistically significant difference in favour of pembrolizumab + enfortumab vedotin compared with cisplatin + gemcitabine in each case. This effect remains even in case of the maximum assumption that all these patients in the comparator arm would have survived to the present data cut-off (sensitivity analysis 2). In this data constellation, there is a hint of added benefit of pembrolizumab + enfortumab vedotin in comparison with the ACT. However, the results of the main analysis and the 3 sensitivity analyses on overall survival presented by the company differ in terms of their extent (from minor in sensitivity analysis 2 to major in the main analysis and sensitivity analysis 3; see Section 2.2.3.1). Therefore, the extent of the added benefit for the outcome of overall survival cannot be quantified.

Morbidity

Worst pain (BPI-SF item 3)

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

Pain interference (BPI-SF items 9a–g)

No suitable data are available for the outcome of pain interference (recorded using BPI-SF items 9a-9g) (for reasons, see Section 2.2.2.1). There is no hint of an added benefit of pembrolizumab + enfortumab vedotin in comparison with the ACT; an added benefit is therefore not proven.

Symptoms

EORTC QLQ-C30

Fatigue, pain, dyspnoea, constipation, 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 pembrolizumab + enfortumab vedotin in comparison with the ACT; an added benefit is therefore not proven.

Nausea and vomiting, constipation

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

Appetite loss

For the outcome of appetite loss, a statistically significant difference was shown in favour of pembrolizumab + enfortumab vedotin 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 pembrolizumab + enfortumab vedotin 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 (recorded using the EQ-5D VAS). There is no hint of an added benefit of pembrolizumab + enfortumab vedotin in comparison with the ACT; an added benefit is therefore not proven.

Health-related quality of life

EORTC QLQ-C30

Global health status, 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. There is no hint of an added benefit of pembrolizumab + enfortumab vedotin in comparison with the ACT; an added benefit is therefore not proven in each 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 pembrolizumab + enfortumab vedotin versus the ACT for patients < 65 years of age. For patients ≥ 65 years, there was no hint of an added benefit of pembrolizumab + enfortumab vedotin 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 characteristic of age (see Section 2.2.2.4). For patients < 65 years, there was no hint of an added benefit of pembrolizumab + enfortumab vedotin versus the ACT; an added benefit is therefore not proven for patients < 65 years of age. There was a hint of lesser benefit of pembrolizumab + enfortumab vedotin versus the ACT for patients ≥ 65 years of age.

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 pembrolizumab + enfortumab vedotin 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 shown in favour of pembrolizumab + enfortumab vedotin in comparison with cisplatin + gemcitabine. There is a hint of lesser harm from pembrolizumab + enfortumab vedotin in comparison with the ACT.

Immune-related SAEs, immune-related severe 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), there was a statistically significant difference to the disadvantage of pembrolizumab + enfortumab vedotin compared to cisplatin + gemcitabine. For each of them, there was a hint of greater harm from pembrolizumab + enfortumab vedotin in comparison with the ACT.

Peripheral neuropathy (AEs)

No suitable data are available for the outcome of peripheral neuropathy (AEs) (see Section 2.2.2.1 for reasons). There is no hint of greater or lesser harm from pembrolizumab + enfortumab vedotin in comparison with the ACT; greater or lesser harm is therefore not proven.

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 pembrolizumab + enfortumab vedotin in comparison with the ACT; greater or lesser harm is therefore not proven.

Other specific AEs

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

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

Diarrhoea (AEs), eye disorders (AEs), endocrine disorders (AEs), gastrointestinal disorders (SAEs), respiratory, thoracic and mediastinal disorders (SAEs)

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

Ear and labyrinth disorders (AE)

For the outcome of ear and labyrinth disorders (AEs), there was a statistically significant difference in favour of pembrolizumab + enfortumab vedotin 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 was a hint of lesser harm from pembrolizumab + enfortumab vedotin 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 10. The Kaplan-Meier curves on the subgroup results are presented in Appendix A.1.

Table 10: Subgroups (morbidity, health-related quality of life, side effects) – RCT, direct comparison: pembrolizumab + enfortumab vedotin vs. cisplatin + gemcitabine (subpopulation: cisplatin suitable)

Study outcome characteristic subgroup	Pembrolizumab + enfortumab vedotin		Cisplatin + gemcitabine		Pembrolizumab + enfortumab vedotin 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						
Health-related quality of life (EORTC QLQ-C30, physical functioning - time to first deterioration[b, c]						
Age						
< 65 years	94	1.8 [0.9; 7.3] 62 (66.0)	84	0.6 [0.4; 1.2] 61 (72.6)	0.66 [0.46; 0.94]	0.022
≥ 65 years	116	0.6 [0.5; 1.1] 103 (88.8)	105	1.1 [0.7; 1.5] 75 (71.4)	1.19 [0.88; 1.61]	0.253
					Interaction:	0.007[d]
Health-related quality of life (EORTC QLQ-C30, social functioning - time to first deterioration[b, c]						
Age						
< 65 years	94	2.0 [0.7; 3.9] 66 (70.2)	84	0.6 [0.4; 1.3] 57 (67.9)	0.80 [0.56; 1.15]	0.223
≥ 65 years	116	0.6 [0.4; 0.7] 95 (81.9)	105	0.9 [0.6; 1.1] 72 (68.6)	1.39 [1.02; 1.91]	0.037
					Interaction:	0.026[d]
Ear and labyrinth disorders (SOC, AEs)						
Age						
< 65 years	105	NA 5 (4.8)	102	NA 20 (19.6)	0.09 [0.02; 0.37]	< 0.001
≥ 65 years	134	NA 12 (9.0)	134	NA 13 (9.7)	0.30 [0.10; 0.89]	0.030
					Interaction:	0.014[d]

a. HR and CI: Cox proportional hazards model, stratified by PD-L1 expression and liver metastases; p-value: Wald test.
b. Patients for whom no further data were available other than at baseline were excluded from the analysis (FAS population).
c. An EORTC QLQ-C30 score decrease by ≥ 10 points from baseline was considered a clinically relevant deterioration (scale range: 0 to 100).
d. p-value from likelihood ratio test based on Cox proportional hazards model with the variables PD-L1 expression and liver metastases as well as the interaction term subgroup and treatment.

AE: adverse event; CI: confidence interval; EORTC QLQ-C30: European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30; FAS: full analysis set; HR: hazard ratio; n: number of patients with (at least 1) event; N: number of analysed patients; NA: not achieved; PD-L1: programmed cell death ligand 1; 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 of physical functioning. A statistically significant difference in favour of pembrolizumab + enfortumab vedotin in comparison with cisplatin + gemcitabine was shown for patients < 65 years. There was a hint of added benefit of pembrolizumab + enfortumab vedotin 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 pembrolizumab + enfortumab vedotin 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 characteristic of age for the outcome of social functioning. There was no statistically significant difference between the treatment groups for patients < 65 years. There is no hint of an added benefit of pembrolizumab + enfortumab vedotin in comparison with the ACT for this patient group; an added benefit is therefore not proven.

However, a statistically significant difference to the disadvantage of pembrolizumab + enfortumab vedotin in comparison with cisplatin + gemcitabine was shown for patients ≥ 65 years. For this patient group, there was a hint of lesser benefit of pembrolizumab + enfortumab vedotin in comparison with the ACT.

Side effects

Specific AEs

Ear and labyrinth disorders (AE)

For the outcome of ear and labyrinth disorders (AEs), there is an effect modification by the characteristic of age. A statistically significant difference in favour of pembrolizumab + enfortumab vedotin in comparison with cisplatin + gemcitabine was shown for both patients < 65 years and patients ≥ 65 years. In each case, there was a hint of added benefit of pembrolizumab + enfortumab vedotin 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 [21].

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 (see Table 11).

Determination of the outcome category for symptom outcomes

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

Symptoms (EORTC QLQ-C30)

Nausea and vomiting, loss of appetite, and constipation

For the outcomes of nausea and vomiting, appetite loss as well as constipation, 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 11: Extent of added benefit at outcome level: pembrolizumab + enfortumab vedotin vs. cisplatin + gemcitabine (subpopulation: cisplatin suitable) (multipage table)

Outcome category **outcome** **effect modifier** **subgroup**	**Pembrolizumab + enfortumab vedotin vs. cisplatin + gemcitabine** **median time to event (months)** **effect estimation [95% CI];** **p-value** **probability[a]**	**Derivation of extent[b]**
Outcomes with observation over the entire study duration		
Mortality		
Overall survival		Outcome category: mortality added benefit, extent: "non-quantifiable"
Main analysis	31.5 vs. 18.4 months HR: 0.54 [0.40; 0.73]; p < 0.001 probability: "hint"	
Sensitivity analysis 1[c]	31.5 vs. 27.5 months HR: 0.66 [0.48; 0.90]; p = 0.009	
Sensitivity analysis 2[d]	31.5 vs. NA months HR: 0.70 [0.51; 0.97]; p = 0.030	
Sensitivity analysis 3[e]	31.5 vs. 20.4 months HR: 0.61 [0.45; 0.82]; 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: 0.93 [0.72; 1.21]; p = 0.601	Lesser/added benefit not proven
Pain interference (BPI-SF items 9a–g)	No suitable data[f]	Lesser/added benefit not proven
Symptoms (EORTC QLQ-C30 – time to first deterioration)		
Fatigue	0.4 vs. 0.4 months HR: 0.80 [0.64; 1.00]; p = 0.052 probability: "hint"	Lesser/added benefit not proven
Nausea and vomiting	2.0 vs. 0.4 months HR: 0.54 [0.42; 0.69]; p < 0.001 probability: "hint"	Outcome category: non-serious/non-severe symptoms/late complications CI_u < 0.80 added benefit; extent: "considerable"
Pain	0.7 vs. 1.1 months HR: 0.97 [0.76; 1.23]; p = 0.801	Lesser/added benefit not proven

Table 11: Extent of added benefit at outcome level: pembrolizumab + enfortumab vedotin vs. cisplatin + gemcitabine (subpopulation: cisplatin suitable) (multipage table)

Outcome category **outcome** **effect modifier** **subgroup**	**Pembrolizumab + enfortumab vedotin vs. cisplatin + gemcitabine** **median time to event (months)** **effect estimation [95% CI];** **p-value** **probability**[a]	**Derivation of extent**[b]
Dyspnoea	2.4 vs. 2.0 months HR: 1.00 [0.77; 1.29]; p = 0.973	Lesser/added benefit not proven
Insomnia	2.3 vs. 2.0 months HR: 0.85 [0.65; 1.09]; p = 0.203	Lesser/added benefit not proven
Appetite loss	0.9 vs. 0.6 months HR: 0.77 [0.61; 0.98]; p = 0.037	Outcome category: non-serious/non-severe symptoms/late complications $0.90 \leq CI_u < 1.00$ lesser benefit/added benefit not proven[g]
Constipation	2.2 vs. 0.7 months HR: 0.58 [0.45; 0.74]; 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: 1.15 [0.88; 1.51]; p = 0.290	Lesser/added benefit not proven
Health status (EQ-5D VAS, time to first deterioration)	2.5 vs. 2.2 months HR: 0.99 [0.77; 1.28]; p = 0.948	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: 0.93 [0.73; 1.17]; p = 0.519	Lesser/added benefit not proven
Physical functioning Age		
< 65 years	1.8 vs. 0.6 months HR: 0.66 [0.46; 0.94]; p = 0.022 Probability: “hint”	Outcome category: health-related quality of life $0.90 \leq CI_u < 1.00$ added benefit, extent: “minor”
≥ 65 years	0.6 vs. 1.1 months HR: 1.19 [0.88; 1.61]; p = 0.253	Lesser/added benefit not proven

Table 11: Extent of added benefit at outcome level: pembrolizumab + enfortumab vedotin vs. cisplatin + gemcitabine (subpopulation: cisplatin suitable) (multipage table)

Outcome category **outcome** **effect modifier** **subgroup**	**Pembrolizumab + enfortumab vedotin vs. cisplatin + gemcitabine** **median time to event (months)** **effect estimation [95% CI];** **p-value** **probability[a]**	**Derivation of extent[b]**
Role functioning	0.6 vs. 0.4 months HR: 0.90 [0.71; 1.13]; p = 0.343	Lesser/added benefit not proven
Emotional functioning	3.2 vs. 3.8 months HR: 1.05 [0.80; 1.37]; p = 0.751	Lesser/added benefit not proven
Cognitive functioning	1.8 vs. 0.9 months HR: 0.82 [0.64; 1.04]; p = 0.098	Lesser/added benefit not proven
Social functioning Age		
< 65 years	2.0 vs. 0.6 months HR: 0.80 [0.56; 1.15]; p = 0.223 probability: “hint”	Lesser/added benefit not proven
≥ 65 years	0.6 vs. 0.9 months HR: 1.39 [1.02; 1.91] HR: 0.72 [0.52; 0.98][h]; p = 0.037 probability: “hint”	Outcome category: health-related quality of life $0.90 \leq CI_u < 1.00$ lesser benefit, extent: “minor”
Side effects[i]		
SAEs	NA vs. NA months HR: 0.93 [0.69; 1.26]; p = 0.639	Greater/lesser harm not proven
Severe AEs	4.2 vs. 1.4 months HR: 0.51 [0.41; 0.65]; p < 0.001 probability: “hint”	Outcome category: serious/severe side effects $CI_u < 0.75$; risk ≥ 5% lesser harm, extent: “major”
Discontinuation due to AEs[j]	19.3 vs. NR months HR: 0.94 [0.65; 1.34]; p = 0.725	Greater/lesser harm not proven
Immune-related SAEs	NA vs. NA months HR: 11.64 [2.76; 49.11] HR: 0.09 [0.02; 0.36][h]; p < 0.001 probability: “hint”	Outcome category: serious/severe side effects $CI_u < 0.75$; risk ≥ 5% greater harm, extent: “major”

Table 11: Extent of added benefit at outcome level: pembrolizumab + enfortumab vedotin vs. cisplatin + gemcitabine (subpopulation: cisplatin suitable) (multipage table)

Outcome category **outcome** **effect modifier** **subgroup**	**Pembrolizumab + enfortumab vedotin vs. cisplatin + gemcitabine** **median time to event (months)** **effect estimation [95% CI];** **p-value** **probability**[a]	**Derivation of extent**[b]
Immune-related severe AEs	NA vs. NA months HR: 11.06 [3.39; 36.07] HR: 0.09 [0.03; 0.29][h]; p < 0.001 probability: “hint”	Outcome category: serious/severe side effects CI_u < 0.75; risk ≥ 5% greater harm, extent: “major”
peripheral neuropathy (AEs)	No suitable data[f]	Lesser/added benefit not proven
Skin reactions (AEs)	0.5 vs. NA months HR: 5.88 [4.39; 7.87] HR: 0.17 [0.13; 0.23][h]; p < 0.001 probability: “hint”	Outcome category: non-serious/non-severe side effects CI_u < 0.80 greater harm, extent: “considerable”
Severe hyperglycaemia (severe AEs)	NA vs. NA months HR: 7.68 [1.76; 33.49] HR: 0.13 [0.03; 0.57][h]; p = 0.007 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 = 0.331	Greater/lesser harm not proven
Other specific AEs		
Nausea (AEs)	NA vs. 3.1 months HR: 0.35 [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”
Diarrhoea (AEs)	NA vs. NA months HR: 1.90 [1.29; 2.79] HR: 0.53 [0.36; 0.78][h]; p = 0.001 probability: “hint”	Outcome category: non-serious/non-severe side effects CI_u < 0.80 greater harm, extent: “considerable”
Vomiting (AEs)	NA vs. NA months HR: 0.44 [0.26; 0.75]; p = 0.003 probability: “hint”	Outcome category: non-serious/non-severe side effects CI_u < 0.80 lesser harm, extent: “considerable”

Table 11: Extent of added benefit at outcome level: pembrolizumab + enfortumab vedotin vs. cisplatin + gemcitabine (subpopulation: cisplatin suitable) (multipage table)

Outcome category **outcome** **effect modifier** **subgroup**	**Pembrolizumab + enfortumab vedotin vs. cisplatin + gemcitabine** **median time to event (months)** **effect estimation [95% CI];** **p-value** **probability[a]**	**Derivation of extent[b]**
Eye disorders (AEs)	19.7 vs. NA months HR: 5.30 [2.98; 9.41] HR: 0.19 [0.11; 0.34][h]; p < 0.001 probability: "hint"	Outcome category: non-serious/non-severe side effects CI_u < 0.80 greater harm, extent: "considerable"
Ear and labyrinth disorders (AE) Age		
< 65 years	NA vs. NA months HR: 0.09 [0.02; 0.37]; p < 0.001 probability: "hint"	Outcome category: non-serious/non-severe side effects CI_u < 0.80 lesser harm, extent: "considerable"
≥ 65 years	NA vs. NA months HR: 0.30 [0.10; 0.89]; p = 0.030 probability: "hint"	Outcome category: non-serious/non-severe side effects 0.80 ≤ CI_u < 0.90 lesser harm, extent: "minor"
Endocrine disorders (AEs)	NA vs. NA months HR: 12.38 [2.94; 52.19] HR: 0.08 [0.02; 0.34][h]; p < 0.001 probability: "hint"	Outcome category: non-serious/non-severe side effects CI_u < 0.80 G greater harm, extent: "considerable"
Gastrointestinal disorders (SAEs)	NA vs. NA months HR: 3.21 [1.29; 7.97] HR: 0.31 [0.13; 0.78][h]; p = 0.012 probability: "hint"	Outcome category: serious/severe side effects 0.75 ≤ CI_u < 0.90 greater harm, extent: "considerable"
Respiratory, thoracic and mediastinal disorders (SAEs)	NA vs. NA months HR: 4.26 [1.45; 12.53] HR: 0.23 [0.08; 0.69][h]; p = 0.009 probability: "hint"	Outcome category: serious/severe side effects CI_u < 0.75; risk ≥ 5% greater harm, extent: "major"
Blood and lymphatic system disorders (severe AEs)	NA vs. 4.9 months HR: 0.08 [0.05; 0.15]; p < 0.001 probability: "hint"	Outcome category: serious/severe side effects CI_u < 0.75; risk ≥ 5% lesser harm, extent: "major"

Table 11: Extent of added benefit at outcome level: pembrolizumab + enfortumab vedotin vs. cisplatin + gemcitabine (subpopulation: cisplatin suitable) (multipage table)

Outcome category **outcome** **effect modifier** **subgroup**	**Pembrolizumab + enfortumab vedotin vs. cisplatin + gemcitabine** **median time to event (months)** **effect estimation [95% CI];** **p-value** **probability[a]**	**Derivation of extent[b]**
Urinary tract infection (severe AEs)	NA vs. 6.1 months HR: 0.32 [0.13; 0.76]; p = 0.010 probability: "hint"	Outcome category: serious/severe side effects $0.75 \leq CI_u < 0.90$ lesser harm, extent: "considerable"
General disorders and administration site conditions (severe AEs)	NA vs. NA months HR: 0.30 [0.14; 0.67]; p = 0.003 probability: "hint"	Outcome category: serious/severe side effects $CI_u < 0.75$; risk ≥ 5% lesser harm, extent: "major"

a. Probability provided if there is a statistically significant and relevant effect.
b. Depending on the outcome category, the effect size is estimated using different limits based on the upper limit of the confidence interval (CI_u).
c. Censoring at the time of death: avelumab-eligible patients who had not received avelumab and died were censored at the time of death.
d. Censoring at data cut-off: avelumab-eligible patients who had not received avelumab and died were censored at the time of data cut-off.
e. Modified time of death: avelumab-eligible patients who had not received avelumab and died were censored with a modified time of death. A simplified assumption was made that the patients would have benefited from treatment with avelumab to the extent shown in the approval study of avelumab (JAVELIN Bladder 100); see Section 2.2.2.1 for explanation.
f. See Section 2.2.2.1 of the present addendum for reasons.
g. The extent of the effect in this non-serious/non-severe outcome was no more than marginal.
h. Institute's calculation; reversed direction of effect to enable use of limits to derive the extent of the added benefit.
i. The fixed treatment duration and the associated discontinuation of observation after the end of study medication in the comparator arm mean that the effect estimate only reflects approximately the first 6 months after randomization.
j. There are relevant deviations from dossier assessment A24-98 [5] for the outcome of discontinuation due to AEs.

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

Table 12: Positive and negative effects from the assessment of pembrolizumab + enfortumab vedotin in comparison with the ACT (subpopulation: cisplatin suitable)

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 functioning (each EORTC-QLQ-C30) ▫ age (< 65 years): hint of added benefit – extent: minor	Health-related quality of life ▪ social functioning (EORTC QLQ-C30) ▫ age (≥ 65 years): hint of lesser 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”
Non-serious/non-severe side effects ▪ nausea (AEs), vomiting (AEs): hint of lesser harm each – extent: “considerable” ▪ ear and labyrinth disorders (AE) ▫ age (< 65 years): hint of lesser harm – extent: "considerable" ▫ age (≥ 65 years): hint of lesser harm – extent: "minor"	Non-serious/non-severe side effects ▪ skin reactions (AEs), diarrhoea (AEs), eye disorders (AEs), endocrine disorders (AEs): hint of greater harm each - extent: “considerable”
No suitable data are available for the outcomes "pain interference" (BPI-SF items 9a-9g) and “peripheral neuropathy” (AEs). There are relevant deviations from dossier assessment A24-98 [5] for the outcome "discontinuation due to AEs".	
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 pembrolizumab + enfortumab vedotin compared with the ACT. For mortality, the observed effects refer to the entire observation period. In particular for the outcomes of side effects, however, the observed effects relate to a shortened period and only represent the roughly

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

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

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

There are relevant deviations from dossier assessment A24-98 [5] for the outcome "discontinuation due to AEs".

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 pembrolizumab + enfortumab vedotin over 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)

For characteristics across research questions of the EV-302/KN-A39 study, including information on the study design, treatment in the comparator arm, comments on the implementation of the ACT, relevance of the Chinese cohort, data cut-offs and on the planned duration of follow-up observation, see Section 2.1 and dossier assessment A24-99.

2.3.1.1 Patient characteristics

The table on the presentation of the characteristics of the patients in the subpopulation relevant for research question 2 can be found in dossier assessment A24-99.

The patient characteristics for the relevant subpopulation in the EV-302/KN-A39 study are sufficiently comparable between the two treatment arms. The mean age of the patients was 71 vs. 72 years. With 37%, fewer patients in the intervention arm came from the European region than in the comparator arm (47%). With 5%, only very few patients in both arms had

an ECOG PS of 2, so it is unclear whether the observed effects can be transferred to patients with an ECOG PS ≥ 2.

The company neither provides data on the primary origin of the disease for the respective subpopulations nor does it provide more detailed information on the metastasis of the disease. For the total population of the study, the origin of the disease was in the urinary bladder in 67% vs. 74% of patients. In the total population, visceral metastases were present in 72% of patients in both arms at baseline, including liver metastases in around 23%.

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

The most common reasons for treatment discontinuation in the relevant subpopulation were disease progression (34% versus 21%) or an adverse event (23% versus 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 3% vs. 4% of patients.

2.3.1.2 Information on the course of the study

Table 13 shows the median treatment durations of the patients and the 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: pembrolizumab + enfortumab vedotin vs. carboplatin + gemcitabine (subpopulation: cisplatin unsuitable)

Study **duration of the study phase** **outcome category/outcome**	**Pembrolizumab + enfortumab vedotin** **N = 240**	**Cisplatin + gemcitabine** **N = 242**
EV-302/KN-A39 (1st data cut-off 08 August 2023)		
Treatment duration [months]		
Median [Q1; Q3]	9.2 [ND]	4.1 [ND]
Observation period [months]		
Overall survival		
Median [Q1; Q3]	13.7 [ND]	10.7 [ND]
Symptoms (BPI-SF; EORTC QLQ-C30), health status (EQ-5D VAS), health-related quality of life (EORTC QLQ-C30)		
Median [Q1; Q3]	10.1 [ND]	5.2 [ND]
Side effects		
AEs/severe AEs		
Median [Q1; Q3]	9.5 [ND]	4.6 [ND]
SAEs		
Median [Q1; Q3]	10.8 [ND]	4.6 [ND]

a. No information on the methods used to calculate treatment duration and observation times.

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

Within the relevant subpopulation, the patients' median treatment duration was 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 (pembrolizumab for a maximum of 35 cycles), while treatment in the comparator arm was limited to a maximum of 6 cycles. The stated treatment duration for the comparator arm does not take into account the duration of a possible maintenance therapy with avelumab.

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

Observation beyond disease progression up to the end of the study was planned for the outcomes on symptoms, health status and health-related quality of life. Nevertheless, the observation period of these outcomes is shorter compared to the outcome of overall survival (in the intervention arm by approx. 4 months, in the control arm by approx. 6 months). Furthermore, the observation period in the intervention arm is approx. 5 months longer than in the comparator arm. As described in Section 2.1.4, according to the information in Module

4 A, patients who had not experienced a first deterioration since the start of the study before the initiation of subsequent antineoplastic therapy were censored on the date of the last recording of the outcome. It is unclear to what extent this censoring scheme affects the stated observation durations.

For the side effects outcomes, the observation period in the intervention arm is up to 6 months longer than in the comparator arm. In addition, the fixed treatment duration in the comparator arm and the linking of the observation time for side effects to the treatment duration means that the effect estimate only reflects approximately the first 6 months after randomization and thus only the period of chemotherapy in the comparator arm, but not a possible maintenance therapy with avelumab and only the first 6 months of a possibly longer-lasting therapy in the intervention arm. This has been taken into account in the derivation of the certainty of conclusions for the outcomes on side effects (see Section 2.2.2.1).

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 the first subsequent antineoplastic therapy (≥ 1% of patients in ≥ 1 treatment arm) – RCT, direct comparison: pembrolizumab + enfortumab vedotin versus carboplatin + gemcitabine (subpopulation: cisplatin unsuitable)

Study **drug class** **drug**	**Patients with subsequent therapy, n (%)**	
	Pembrolizumab + enfortumab vedotin **N = 202**	**Carboplatin + gemcitabine** **N = 202**
Study EV-302/KN-A39 (1st data cut-off 08 August 2023)		
Any subsequent therapy[a]	47 (23.3)	96 (47.5)
Subsequent systemic therapy[a]	46 (22.8)	96 (47.5)
No subsequent therapy[a] received, deceased	44 (21.8)	56 (27.7)
No subsequent therapy[a] received, alive at the data cut-off	111 (55.0)	50 (24.8)
First subsequent systemic therapy[a]	46 (22.8)	96 (47.5)
Platinum-based therapy	38 (18.8)	9 (4.5)
PD-1/PD-L1-based therapy	4 (2.0)	57 (28.2)
Atezolizumab	0 (0)	23 (11.4)
Pembrolizumab	4 (2.0)	33 (16.3)
Other drugs	4 (2.0)	30 (14.9)
Enfortumab vedotin	1 (0.5)	12 (5.9)
Paclitaxel	0 (0)	9 (4.5)
Gemcitabine	1 (0.5)	2 (1.0)
Erdafitinib	0 (0)	2 (1.0)

a. According to the company, maintenance therapy with avelumab received after treatment discontinuation or termination of chemotherapy in the comparator arm or any local therapy according to physician's choice does not count as subsequent systemic therapy.

n: number of patients with subsequent therapy; N: number of analysed patients; ND: no data; PD-1: programmed cell death 1; PD-L1: programmed cell death ligand 1; RCT: randomized controlled trial

In the EV-302/KN-A39 study, subsequent therapies were permitted without restrictions in both study arms. In the subpopulation relevant to research question 2, a total of 46 (22.8%) patients in the intervention arm and 96 (47.5%) patients in the comparator arm received at least 1 subsequent antineoplastic systemic therapy for the treatment of progressive disease. However, the company's documents do not provide any information on the proportion of patients in the relevant subpopulation who experienced disease progression. Therefore, it is not possible to assess what proportion of patients with disease progression received subsequent therapy, and thus whether subsequent therapies were used appropriately in a sufficient proportion of patients in the subpopulation of study EV-302/KN-A39 relevant to research question 2.

According to current guideline recommendations, platinum-based chemotherapy or, in certain patients, erdafitinib is recommended as a subsequent therapy after disease progression under pembrolizumab + enfortumab vedotin [12]; platinum-based chemotherapy was the predominant first subsequent therapy in the intervention arm, which 19% of patients received.

Atezolizumab or pembrolizumab is recommended as first-line therapy in case of disease progression under platinum-based chemotherapy [11,12]. In the comparator arm, 11% and 16% of patients in the respective relevant subpopulation received these agents as their first PD-1/PD-L1-based subsequent systemic therapy, which was not maintenance therapy; this corresponds to 24% and 34% of patients who received subsequent systemic therapy, respectively.

In cases of disease progression under maintenance treatment with avelumab following platinum-based chemotherapy as first-line treatment, erdafitinib (in certain patients) and enfortumab vedotin are primarily recommended, and sacituzumab govitecan, vinflunine or taxanes [12] are recommended with a lower recommendation grade. Among the patients in the comparator arm, 6% received enfortumab vedotin, 5% received paclitaxel and 1% received erdafitinib as first subsequent systemic therapy; this corresponds to 13%, 9% and 2% of patients who received subsequent systemic therapy, respectively.

Information on subsequent therapies in later treatment lines is not available in the company's documents.

Based on the available data, it is not possible to assess whether subsequent therapies were used appropriately for the most part in a sufficient proportion of patients in the subpopulation of study EV-302/KN-A39 relevant to research question 2. This results in a high risk of bias of the results on overall survival (see Section 2.3.2.2).

2.3.1.4 Risk of bias across outcomes (study level)

The risk of bias across outcomes (risk of bias at study level) is described in Table 6 in Section 2.2.1.4 and was rated as low.

Limitations resulting from the open-label study design are described in Section 2.2.2.2 under the outcome-specific risk of bias and apply equally to research questions 1 and 2.

2.3.1.5 Transferability of the study results to the German health care context

The company's assessment regarding the transferability of the study results to the German health care context is described in Section 2.2.1.5.

2.3.2 Results on added benefit

2.3.2.1 Outcomes included

The patient-relevant outcomes that were to be included in the assessment are identical for research questions 1 and 2 can be found in Section 2.2.2.1.

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: pembrolizumab + enfortumab vedotin 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	No[f]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No[f]	Yes	Yes	Yes	Yes

a. Severe AEs are operationalized as CTCAE grade ≥ 3.
b. In each case, the operationalization of a specific, predefined MedDRA PT collection from the outcome of AEOSI (Version 25.0) presented by the company is used (PT collection Version 25.0, MedDRA-Version 26.0).
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) and blood and lymphatic system disorders (SOC, severe AEs).
f. No suitable data available; see Section 2.2.2.1 of the present addendum for reasoning.

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

Notes on outcomes

As described in Section 2.1.2, the ACT was only incompletely implemented in study EV-302/KN-A39, as maintenance therapy with avelumab was not part of the study treatment and not all patients who were eligible for maintenance treatment with avelumab also received it. The consequences for the benefit assessment resulting from this at outcome level can be found in Section 2.2.2.1, together with further aspects on the outcomes, such as in particular the company's sensitivity analyses on the outcome of overall survival.

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: pembrolizumab + enfortumab vedotin 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	H[f]	H[g, h]	–[i]	H[g, h]	H[g, h]	H[g, h]	H[j]	H[j]	H[k]	H[j]	H[j]	–[i]	H[g, j]	H[j]	H[j]	H[g, j]

a. Severe AEs are operationalized as CTCAE grade ≥ 3.
b. In each case, the operationalization of a specific, predefined MedDRA PT collection from the outcome of AEOSI (Version 25.0) presented by the company is used (PT collection Version 25.0, MedDRA-Version 26.0).
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) and blood and lymphatic system disorders (SOC, severe AEs).
f. Due to uncertainties in the use of subsequent therapies.
g. Lack of blinding in subjective recording of outcomes, unless serious or severe AEs are involved.
h. Declining response rate of questionnaires over the course of the study; high proportion of patients not included in the analysis (> 10 %) or large difference between the treatment groups (> 5 percentage points).
i. No suitable data available; see Section 2.2.2.1 of the present addendum for reasoning.
j. Incomplete observations for potentially informative reasons.
k. Lack of blinding in the presence of subjective decision on 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 and can therefore be found in Section 2.2.2.2.

Summary assessment of the certainty of conclusions

In addition to the described aspects of bias, there are uncertainties for study EV-302/KN-A39, as described in Sections 2.1.1 and 2.1.2, particularly in the implementation of the ACT. In the present specific data constellation, the results of the study can nevertheless be interpreted for the research questions of the present benefit assessment, but the certainty of the study results for the present assessment is reduced. Based on the EV-302/KN-A39 study, at most hints, e.g. of an added benefit, can be derived for both research questions.

Moreover, for the outcomes in the side effects category, analyses are only available for a significantly shortened period, which in the comparator arm only reflects the treatment with chemotherapy, but not the period of a possible maintenance therapy with avelumab, and in the intervention arm only takes into account the first 6 months of a possibly longer-lasting treatment (see Section 2.2.2.1). This shortened observation in the comparator arm or consideration of recorded data in the intervention arm contributes to a limited certainty of conclusions and additionally justifies the fact that at most hints can be derived.

2.3.2.3 Results

Table 17 summarizes the results of the comparison of pembrolizumab + enfortumab vedotin with carboplatin + gemcitabine for first-line treatment in adult patients with unresectable or metastatic urothelial carcinoma for whom cisplatin-based therapy is unsuitable. Where necessary, IQWiG calculations are provided to supplement the data from the company's dossier.

Kaplan-Meier curves on the presented time-to-event analyses can be found in Appendix A.2. Results on common AEs, SAEs, severe AEs, and discontinuation due to AEs are presented in Appendix B.2. Kaplan-Meier curves for outcomes of the outcome categories "health-related quality of life" and "side effects" with non-significant results are not available in the company's dossier. Likewise, the company's dossier does not provide a list of the categories of immune-related AEs, immune-related SAEs and immune-related severe AEs.

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

Study outcome category outcome	Pembrolizumab + enfortumab vedotin		Carboplatin + gemcitabine		Pembrolizumab + enfortumab vedotin vs. carboplatin + gemcitabine
	N	median time to event in months [95% CI] patients with event n (%)	N	median time to event in months [95% CI] patients with event n (%)	HR [95% CI]; p-value
EV-302/KN-A39					
Mortality					
Overall survival	202	NA [22,9; NC] 64 (31,7)	202	12.9 [11.4; 15.9] 116 (57.4)	0.41 [0.30; 0.56]; < 0.001[a]
Overall survival (sensitivity analysis 1[b])	202	NA [22.9; NC] 64 (31.7)	202	15.1 [12.5; 20.6] 97 (48.0)	0.49 [0.36; 0.68]; < 0.001[a]
Overall survival (sensitivity analysis 2[c])	202	NA [22.9; NC] 64 (31.7)	202	16.3 [12.9; NC] 97 (48.0)	0.55 [0.40; 0.76]; < 0.001[a]
Overall survival (sensitivity analysis 3[d])	202	NA [22.9; NC] 64 (31.7)	202	15.1 [12.9; 17.7] 110 (54.5)	0.45 [0.33; 0.62]; < 0.001[a]
Morbidity[e]					
Worst Pain (BPI-SF Item 3 – time to deterioration) [f]	166	3.2 [1.6; 10.7] 85 (51.2)	166	1.3 [0.7; 2.2] 104 (62.7)	0.67 [0.50; 0.89]; 0.006[a]
Pain interference (BPI-SF items 9a-g – time to first deterioration)[g]	No suitable data availableh				
Symptoms (EORTC QLQ-C30 – time to first deterioration)					
Fatigue	166	0.6 [0.4; 0.8] 130 (78.3)	166	0.4 [0.4; 0.6] 131 (78.9)	0.84 [0.65; 1.07]; 0.152[a]
Nausea and vomiting	166	1.8 [1.1; 2.7] 103 (62.0)	166	0.9 [0.4; 1.5] 117 (70.5)	0.71 [0.54; 0.92]; 0.011[a]
Pain	166	1.1 [0.7; 1.8] 106 (63.9)	166	0.9 [0.5; 1.3] 117 (70.5)	0.78 [0.60; 1.02]; 0.069[a]
Dyspnoea	166	2.0 [1.3; 2.7] 101 (60.8)	166	1.5 [1.1; 2.2] 103 (62.0)	0.87 [0.66; 1.15]; 0.336[a]
Insomnia	166	1.5 [1.1; 2.2] 101 (60.8)	166	1.3 [0.9; 2.2] 92 (55.4)	0.96 [0.72; 1.28]; 0.793[a]
Appetite loss	166	0.9 [0.7; 1.3] 116 (69.9)	166	1.1 [0.6; 1.5] 110 (66.3)	0.94 [0.72; 1.23]; 0.664[a]
Constipation	166	2.2 [1.5; 3.1] 93 (56.0)	166	0.4 [0.4; 0.9] 112 (67.5)	0.51 [0.39; 0.68]; < 0.001[a]
Diarrhoea	166	2.0 [1.3; 3.2] 101 (60.8)	166	4.5 [2.0; NC] 77 (46.4)	1.37 [1.02; 1.85]; 0.037[a]

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

Study **outcome category** **outcome**	**Pembrolizumab + enfortumab vedotin**		**Carboplatin + gemcitabine**		**Pembrolizumab + enfortumab vedotin 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**
Health status (EQ-5D VAS - time to first deterioration[j])	166	1.5 [1.0; 3.2] 105 (63.3)	166	1.3 [0.9; 2.0] 110 (66.3)	0.84 [0.64; 1.10]; 0.202[a]
health-related quality of lifee					
EORTC-QLQ C30 – time to first deterioration[e]					
Global health status	166	1.1 [0.6; 1.6] 117 (70.5)	166	0.9 [0.6; 1.3] 113 (68.1)	0.97 [0.74; 1.26]; 0.803[a]
Physical functioning	166	1.1 [0.7; 1.6] 121 (72.9)	166	0.7 [0.4; 1.1] 124 (74.7)	0.78 [0.61; 1.01]; 0.062[a]
Role functioning	166	0.7 [0.5; 1.1] 125 (75.3)	166	0.4 [0.4; 0.6] 136 (81.9)	0.69 [0.54; 0.89]; 0.004[a]
Emotional functioning	166	4.5 [2.1; 9.4] 90 (54.2)	166	2.0 [1.1; 3.2] 94 (56.6)	0.77 [0.58; 1.04]; 0.088[a]
Cognitive functioning	166	1.5 [1.1; 1.8] 112 (67.5)	166	0.9 [0.6; 1.5] 114 (68.7)	0.83 [0.64; 1.08]; 0.173[a]
Social functioning	166	0.9 [0.6; 1.3] 118 (71.1)	166	0.9 [0.4; 1.1] 111 (66.9)	0.98 [0.75; 1.28]; 0.877[a]
Side effects[l, m]					
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	7.6 [4.8; 13.1] 113 (56.2)	197	5.4 [4.2; NC] 86 (43.7)	0.91 [0.67; 1.22]; 0.525[n]
Severe AEs[o]	201	2.6 [2.0; 4.0] 157 (78.1)	197	0.7 [0.5; 0.9] 166 (84.3)	0.46 [0.36; 0.58]; < 0.001[n]
Discontinuation due to AEs[p]	201	20.3 [9.9; NC] 83 (41.3)	197	NA 35 (17.8)	1.77 [1.17; 2.66]; 0.007[n]
Immune-related AEs[q] (supplementary information)			*No suitable data available[h]*		
Immune-related SAEs[q]	201	NA 20 (10.0)	197	NA 2 (1.0)	7.16 [1.64; 31.21]; 0.009[n]
Immune-related severe AEs[o, q]	201	NA 42 (20.9)	197	NA 2 (1.0)	15.91 [3.82; 66.35]; < 0.001[n]
Peripheral neuropathy (SMQ, AEs)[o]			No suitable data available[h]		

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

Study **outcome category** **outcome**	**Pembrolizumab + enfortumab vedotin**		**Carboplatin + gemcitabine**		**Pembrolizumab + enfortumab vedotin 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**
Skin reactions, operationalized as skin and subcutaneous tissue disorders (SOC, AEs)f	201	0.6 [0.5; 0.7] 162 (80.6)	197	NA 51 (25.9)	4.95 [3.60; 6.81]; < 0.001[n]
Severe hyperglycaemia (PT, severe AEs)[o]	201	NA 12 (6.0)	197	NA 1 (0.5)	10.71 [1.38; 82.93]; 0.023[n]
Severe nephrotoxicity, operationalized as renal and urinary disorders (SOC, severe AEs)[o]	201	NA 25 (12.4)	197	NA 15 (7.6)	1.12 [0.57; 2.23]; 0.736[n]
Other specific AEs					
Constipation (PT, AEs)	201	NA 49 (24.4)	197	NA 71 (36.0)	0.45 [0.30; 0.66]; < 0.001[n]
Diarrhoea (PT, AEs)	201	NA [11.1; NC] 77 (38.3)	197	NA 29 (14.7)	2.30 [1.48; 3.56]; < 0.001[n]
Dysgeusia (PT, AEs)	201	NA 46 (22.9)	197	NA 9 (4.6)	4.83 [2.35; 9.92]; < 0.001[n]
Eye disorders (SOC, AEs)	201	NA [16.6; NC] 64 (31.8)	197	NA 12 (6.1)	3.85 [2.04; 7.26]; < 0.001[n]
Endocrine disorders (SOC, AEs)	201	NA 36 (17.9)	197	NA 4 (2.0)	5.47 [1.90; 15.79]; 0.002[n]
Blood and lymphatic system disorders (SOC, severe AEs)[o]	201	NA 43 (21.4)	197	1.3 [1.0; 1.6] 135 (68.5)	0.14 [0.09; 0.20]; < 0.001[n]

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

Study outcome category outcome	Pembrolizumab + enfortumab vedotin		Carboplatin + gemcitabine		Pembrolizumab + enfortumab vedotin 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, stratified by PD-L1 expression (high vs. low) and liver metastases (present vs. not present); p-value: Wald test.
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.
e. Patients for whom no further data were available other than at baseline were excluded from the analysis (FAS population).
f. A score increase by ≥ 2 points from baseline was considered a clinically relevant deterioration (scale range: 0 to 10); for explanation, see Section 2.2.2.1.
g. A score increase by ≥ 1.5 points from baseline was considered a clinically relevant deterioration (scale range: 0 to 10); for explanation, see Section 2.2.2.1.
h. For reasons, see Section 2.2.2.1 of this dossier assessment.
i. An EORTC QLQ-C30 score increase by ≥ 10 points from baseline was considered a clinically relevant deterioration (scale range: 0 to 100).
j. An EQ-5D VAS score decrease by ≥ 15 points from baseline was considered a clinically relevant deterioration (scale range: 0 to 100).
k. An EORTC QLQ-C30 score decrease by ≥ 10 points from baseline was considered a clinically relevant deterioration (scale range: 0 to 100).
l. 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.
m. Conversion of median times-to-event from weeks into months.
n. HR and CI: unstratified Cox proportional hazards model; p-value: Wald test.
o. Operationalized as CTCAE grade ≥ 3.
p. There are relevant deviations from dossier assessment A24-98 [5] for the outcome "discontinuation due to AEs".
q. In each case, the operationalization of a specific, predefined MedDRA PT collection from the outcome of AESI presented by the company is used (PT- collection Version 25.0, MedDRA-Version 26.0).
r. The following result is shown for the severe AEs of the SOC “skin and subcutaneous tissue disorders” included in the results on AEs: 39 (19.4) vs. 2 (1.0); HR: 15.28. [3.65; 63.88]; p < 0.001; Kaplan-Meier curve see Figure 73.

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 Sections 2.1 and 2.2.2.2 for the reasoning).

When interpreting the results on side effects, it should be noted that due to the fixed treatment duration and the associated discontinuation of observation in the comparator arm, the effect estimate only covers approximately the first 6 months after randomization (see Section 2.3.1.2).

Mortality

Overall survival

For the outcome of overall survival, a statistically significant difference was found in favour of pembrolizumab + enfortumab vedotin in comparison with carboplatin + gemcitabine. The 3 sensitivity analyses presented by the company, in which patients in the comparator arm for whom maintenance treatment with avelumab would potentially have been indicated and who died without maintenance treatment were accounted for differently (see Section 2.2.2.1), also showed a statistically significant difference in favour of pembrolizumab + enfortumab vedotin compared with carboplatin + gemcitabine in each case. This effect therefore remains even if the maximum situation is assumed that all these patients in the comparator arm have survived to the present data cut-off. In this data constellation, there is a hint of added benefit of pembrolizumab + enfortumab vedotin in comparison with the ACT. The extent of the added benefit is major both in the main analysis and in all sensitivity analyses (see Section 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 pembrolizumab + enfortumab vedotin 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 pembrolizumab + enfortumab vedotin versus the ACT; an added benefit is therefore not proven for this patient group. There was a hint of an added benefit of pembrolizumab + enfortumab vedotin versus the ACT for patients with exclusively lymph node metastases.

Pain interference (BPI-SF items 9a–g)

No suitable data are available for the outcome of pain interference (recorded using BPI-SF items 9a-9g) (for reasons, see Section 2.2.2.1). There is no hint of an added benefit of pembrolizumab + enfortumab vedotin 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 was a hint of added benefit of pembrolizumab + enfortumab vedotin in comparison with the ACT. For men, there was no hint of an added benefit of pembrolizumab + enfortumab vedotin 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 pembrolizumab + enfortumab vedotin 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 pembrolizumab + enfortumab vedotin in comparison with the ACT; an added benefit is therefore not proven.

Diarrhoea

For the outcome of diarrhoea, a statistically significant difference was found to the disadvantage of pembrolizumab + enfortumab vedotin 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 pembrolizumab + enfortumab vedotin in comparison with the ACT; an added benefit is therefore not proven.

Pain, dyspnoea, insomnia and appetite loss

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

Constipation

For the outcome of constipation, a statistically significant difference was found in favour of pembrolizumab + enfortumab vedotin 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 was a hint of added benefit of pembrolizumab + enfortumab vedotin 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 (recorded using the EQ-5D VAS). There is no hint of an added benefit of pembrolizumab + enfortumab vedotin in comparison with the ACT; an added benefit is therefore not proven.

Health-related quality of life

EORTC QLQ-C30

Global health status, physical functioning, and cognitive functioning

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

Role functioning, emotional functioning, and social functioning

For the outcome of role functioning, there was a statistically significant difference in favour of pembrolizumab + enfortumab vedotin compared to carboplatin + gemcitabine, while there was no statistically significant difference between the treatment groups for the outcomes of emotional functioning and social functioning. However, there is an effect modification by the characteristic of sex for all of these outcomes (see Section 2.3.2.4). In each case, there was a hint of added benefit of pembrolizumab + enfortumab vedotin in comparison with the ACT for women. For men, there was no hint of an added benefit of pembrolizumab + enfortumab vedotin in comparison with the ACT in each case; an added benefit is therefore not proven for men.

Side effects

SAEs

No statistically significant difference between treatment groups was found for the outcome of SAEs. There is no hint of greater or lesser harm from pembrolizumab + enfortumab vedotin 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 shown in favour of pembrolizumab + enfortumab vedotin in comparison with carboplatin + gemcitabine. There is a hint of lesser harm from pembrolizumab + enfortumab vedotin in comparison with the ACT.

Discontinuation due to AEs

For the outcome of discontinuation due to AEs, a statistically significant difference was shown to the disadvantage of pembrolizumab + enfortumab vedotin in comparison with

carboplatin + gemcitabine. There is a hint of greater harm from pembrolizumab + enfortumab vedotin in comparison with the ACT.

Immune-related SAEs, immune-related severe 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), there was a statistically significant difference to the disadvantage of pembrolizumab + enfortumab vedotin compared to carboplatin + gemcitabine. For each of them, there was a hint of greater harm from pembrolizumab + enfortumab vedotin in comparison with the ACT.

Peripheral neuropathy (AEs)

No suitable data are available for the outcome of peripheral neuropathy (AEs) (see Section 2.2.2.1 for reasons). There is no hint of greater or lesser harm from pembrolizumab + enfortumab vedotin in comparison with the ACT; greater or lesser harm is therefore not proven.

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 pembrolizumab + enfortumab vedotin in comparison with the ACT; greater or lesser harm is therefore not proven.

Other specific AEs

Constipation (AEs)

For the outcome of constipation (AEs), a statistically significant difference was shown in favour of pembrolizumab + enfortumab vedotin in comparison with cisplatin + gemcitabine. However, there is an effect modification by the characteristic of sex (see Section 2.2.2.4). For both women and men, there was a hint of lesser harm from pembrolizumab + enfortumab vedotin compared with the ACT; however, the extent of differs (see Section 2.3.3.1).

Diarrhoea (AEs), dysgeusia (AEs), eye disorders (AEs) and endocrine disorders (AEs)

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

Blood and lymphatic system disorders (severe AEs)

For the outcome of blood and lymphatic system disorders (severe AEs), there was a statistically significant difference in favour of pembrolizumab + enfortumab vedotin in comparison with carboplatin + gemcitabine. There is a hint of lesser harm from pembrolizumab + enfortumab vedotin 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 A.2.

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

Study outcome characteristic subgroup	Pembrolizumab + enfortumab vedotin		Carboplatin + gemcitabine		Pembrolizumab + enfortumab vedotin vs. carboplatin + gemcitabine	
	N	median time to event in months [95% CI] patients with event n (%)	N	median time to event in months [95 % CI] patients with event n (%)	HR [95% CI][a]	p-value[a]
EV-302/KN-A39						
Worst pain (BPI-SF item 3 - time to first deterioration[b, c])						
Metastases						
Visceral metastases	121	2.7 [1.1; 4.5] 67 (55.4)	128	1.7 [0.8; 2.5] 79 (61.7)	0.79 [0.57; 1.10]	0.164
Lymph nodes only	36	NA [1.5; NC] 16 (44.4)	30	0.5 [0.2; 2.4] 21 (70.0)	0.37 [0.19; 0.72]	0.004
					Interaction:	0.032[d]
Symptoms (EORTC QLQ-C30, fatigue – time to first deterioration[b, e])						
Sex						
Female	43	0.7 [0.4; 2.2] 30 (69.8)	40	0.4 [0.2; 0.6] 35 (87.5)	0.41 [0.23; 0.73]	0.002
Male	123	0.5 [0.4; 0.7] 100 (81.3)	126	0.4 [0.4; 0.6] 96 (76.2)	0.97 [0.73; 1.29]	0.855
					Interaction:	0.023[d]
Symptoms (EORTC QLQ-C30, constipation – time to first deterioration[b, e])						
Metastases						
Visceral metastases	121	2.0 [0.9; 3.1] 71 (58.7)	128	0.6 [0.4; 1.7] 79 (61.7)	0.63 [0.45; 0.87]	0.006
Lymph nodes only	36	2.1 [0.6; NC] 19 (52.8)	30	0.3 [0.2; 0.5] 25 (83.3)	0.29 [0.15; 0.55]	< 0.001
					Interaction:	0.007[d]
Health-related quality of life (EORTC QLQ-C30, role functioning – time to first deterioration[b, f])						
Sex						
Female	43	0.7 [0.4; 1.1] 34 (79.1)	40	0.2 [0.2; 0.4] 37 (92.5)	0.39 [0.22; 0.68]	< 0.001
Male	123	0.7 [0.4; 1.1] 91 (74.0)	126	0.5 [0.4; 0.9] 99 (78.6)	0.78 [0.58; 1.05]	0.106
					Interaction:	0.017[d]

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

Study outcome characteristic subgroup	Pembrolizumab + enfortumab vedotin		Carboplatin + gemcitabine		Pembrolizumab + enfortumab vedotin 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]
Health-related quality of life (EORTC QLQ-C30, emotional functioning - time to first deterioration[b, f]						
Sex						
Female	43	10.7 [1.8; NC] 20 (46.5)	40	0.9 [0.4; 1.1] 27 (67.5)	0.42 [0.22; 0.79]	0.007
Male	123	3.2 [1.7; 9.4] 70 (56.9)	126	2.7 [1.3; 5.9] 67 (53.2)	0.92 [0.65; 1.29]	0.621
					Interaction:	0.012[d]
Health-related quality of life (EORTC QLQ-C30, social functioning - time to first deterioration[b, f]						
Sex						
Female	43	0.7 [0.4; 1.3] 30 (69.8)	40	0.4 [0.2; 0.6] 34 (85.0)	0.55 [0.32; 0.93]	0.025
Male	123	0.9 [0.5; 1.7] 88 (71.5)	126	1.3 [0.6; 2.3] 77 (61.1)	1.16 [0.85; 1.59]	0.351
					Interaction:	0.015[d]
Constipation (PT, AEs)[g]						
Sex						
Female	56	NA [16.4; NC] 9 (16.1)	49	NA [1.5; NC] 20 (40.8)	0.22 [0.09; 0.52]	< 0.001
Male	145	24.5 [19.1; NC] 40 (27.6)	148	NA 51 (34.5)	0.56 [0.36; 0.87]	0.010
					Interaction:	0.046[d]

a. HR and CI: Cox proportional hazards model, stratified by PD-L1 expression and liver metastases; p-value: Wald test.
b. Patients for whom no further data were available other than at baseline were excluded from the analysis (FAS population).
c. A score increase by ≥ 2 points from baseline is considered a clinically relevant deterioration (scale range 0 to 10).
d. p-value from likelihood ratio test based on Cox proportional hazards model with the variables PD-L1 expression and liver metastases as well as the interaction term subgroup and treatment.
e. An EORTC QLQ-C30 score increase by ≥ 10 points from baseline was considered a clinically relevant deterioration (scale range: 0 to 100).
f. An EORTC QLQ-C30 score decrease by ≥ 10 points from baseline was considered a clinically relevant deterioration (scale range: 0 to 100).
g. Conversion of median times-to-event from weeks into months. HR and CI: unstratified Cox proportional hazards model, p-value: Wald test, score test in case of 0 events in one of the study arms.

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

Study outcome characteristic subgroup	Pembrolizumab + enfortumab vedotin		Carboplatin + gemcitabine		Pembrolizumab + enfortumab vedotin 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]
AE: adverse event; CI: confidence interval; EORTC QLQ-C30: European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30; FAS: full analysis set; HR: hazard ratio; n: number of patients with (at least 1) 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						

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

A statistically significant difference in favour of pembrolizumab + enfortumab vedotin in comparison with carboplatin + gemcitabine was shown for patients with exclusively lymph node metastases. There was a hint of added benefit of pembrolizumab + enfortumab vedotin 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 found in favour of pembrolizumab + enfortumab vedotin in comparison with carboplatin + gemcitabine. There was a hint of added benefit of pembrolizumab + enfortumab vedotin 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 pembrolizumab + enfortumab vedotin 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 pembrolizumab + enfortumab vedotin in comparison with carboplatin + gemcitabine was shown both for patients with visceral metastases and patients with exclusively lymph node metastases. In each case, there was a hint of added benefit of pembrolizumab + enfortumab vedotin 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, emotional functioning, and social functioning

There was an effect modification by the characteristic of sex for each of the outcomes "role functioning", "emotional functioning" and "social functioning". In each case, a statistically significant difference was found in favour of pembrolizumab + enfortumab vedotin in comparison with carboplatin + gemcitabine for women. In each case, there was a hint of added benefit of pembrolizumab + enfortumab vedotin 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 pembrolizumab + enfortumab vedotin in comparison with the ACT for this patient group; an added benefit is therefore not proven.

Side effects

Specific AEs

Constipation (AEs)

There was an effect modification by the characteristic of sex for the outcome of constipation (AEs). For both men and women, a statistically significant difference was found in favour of pembrolizumab + enfortumab vedotin in comparison with carboplatin + gemcitabine. In each case, there was a hint of lesser harm from pembrolizumab + enfortumab vedotin in comparison with the ACT the extents of which , however, differ.

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 [21].

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 (see Table 19).

Determination of the outcome category for the outcomes "symptoms" and "side effects"

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

Worst pain (BPI-SF item 3)

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

Symptoms (EORTC QLQ-C30)

Fatigue, nausea and vomiting, constipation, and diarrhoea

For the outcomes of fatigue, nausea and vomiting, constipation as well as diarrhoea, 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.

Discontinuation due to AEs

The outcome of discontinuation due to AEs was allocated to the outcome category of non-serious/non-severe side effects because no information was available on the severity of the AEs which led to discontinuation of therapy.

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

Outcome category **outcome** **effect modifier** **subgroup**	**Pembrolizumab + enfortumab vedotin vs. carboplatin + gemcitabine** **median time to event (months)** **effect estimation [95% CI];** **p-value** **probability**[a]	**Derivation of extent**[b]
Outcomes with observation over the entire study duration		
Mortality		
Overall survival Main analysis	NA vs. 12.9 months HR: 0.41 [0.30; 0.56]; p < 0.001 probability: “hint”	Outcome category: mortality CI_u < 0.85 added benefit, extent: “major”
Sensitivity analysis 1[c]	NA vs. 15.1 months HR: 0.49 [0.36; 0.68]; p < 0.001	
Sensitivity analysis 2[d]	NA vs. 16.3 months HR: 0.55 [0.40; 0.76]; p < 0.001	
Sensitivity analysis 3[e]	NA vs. 15.1 months HR: 0.45 [0.33; 0.62]; p < 0.001	
Outcomes with shortened observation period		
Morbidity		
Worst pain (BPI-SF item 3 - time to first deterioration) Metastases		
Visceral metastases	2.7 vs. 1.7 months HR: 0.79 [0.57; 1.10]; p = 0.164	Lesser/added benefit not proven
Lymph nodes only	NA vs. 0.5 months HR: 0.37 [0.19; 0.72]; p = 0.004 probability: “hint”	Outcome category "non-serious/non-severe symptoms/late complications" CI_u < 0.80 added benefit; extent: “considerable”
Pain interference (BPI-SF items 9a–g)	No suitable data[f]	Lesser/added benefit not proven
Symptoms (EORTC QLQ-C30 – time to first deterioration)		
Fatigue Sex		

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

Outcome category **outcome** **effect modifier** **subgroup**	**Pembrolizumab + enfortumab vedotin vs. carboplatin + gemcitabine** **median time to event (months)** **effect estimation [95% CI];** **p-value** **probability**[a]	**Derivation of extent**[b]
Female	0.7 vs. 0.4 months HR: 0.41 [0.23; 0.73]; p = 0.002 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 [0.73; 1.29]; p = 0.855	Lesser/added benefit not proven
Nausea and vomiting	1.8 vs. 0.9 months HR: 0.71 [0.54; 0.92]; p = 0.011	Outcome category: non-serious/non-severe symptoms/late complications $0.90 \leq CI_u < 1.00$ lesser benefit/added benefit not proven[g]
Pain	1.1 vs. 0.9 months HR: 0.78 [0.60; 1.02]; p = 0.069	Lesser/added benefit not proven
Dyspnoea	2.0 vs. 1.5 months HR: 0.87 [0.66; 1.15]; p = 0.336	Lesser/added benefit not proven
Insomnia	1.5 vs. 1.3 months HR: 0.96 [0.72; 1.28]; p = 0.793	Lesser/added benefit not proven
Appetite loss	0.9 vs. 1.1 months HR: 0.94 [0.72; 1.23]; p = 0.664	Lesser/added benefit not proven
Constipation Metastases		
Visceral metastases	2.0 vs. 0.6 months HR: 0.63 [0.45; 0.87]; p = 0.006 probability: “hint”	Outcome category: non-serious/non-severe symptoms/late complications $0.80 \leq CI_u < 0.90$ added benefit, extent: “minor”
Lymph nodes only	2.1 vs. 0.3 months HR: 0.29 [0.15; 0.55]; 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. 4.5 months HR: 1.37 [1.02; 1.85] HR: 0.73 [0.54; 0.98][i]; p = 0.037	Outcome category: non-serious/non-severe symptoms/late complications $0.90 \leq CI_u < 1.00$ lesser benefit/added benefit not proven[g]

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

Outcome category **outcome** **effect modifier** **subgroup**	**Pembrolizumab + enfortumab vedotin vs. carboplatin + gemcitabine** **median time to event (months)** **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: 0.84 [0.64; 1.10]; p = 0.202	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: 0.97 [0.74; 1.26]; p = 0.803	Lesser/added benefit not proven
Physical functioning	1.1 vs. 0.7 months HR: 0.78 [0.61; 1.01]; p = 0.062	Lesser/added benefit not proven
Role functioning Sex		
Female	0.7 vs. 0.2 months HR: 0.39 [0.22; 0.68]; p < 0.001 probability: “hint”	Outcome category: health-related quality of life CI_u < 0.75, risk ≥ 5% added benefit, extent: “major”
Male	0.7 vs. 0.5 months HR: 0.78 [0.58; 1.05]; p = 0.106	Lesser/added benefit not proven
Emotional functioning Sex		
Female	10.7 vs. 0.9 months HR: 0.42 [0.22; 0.79]; p = 0.007 probability: “hint”	Outcome category: health-related quality of life 0.75 ≤ CI_u < 0.90 added benefit; extent: “considerable”
Male	3.2 vs. 2.7 months HR: 0.92 [0.65; 1.29]; p = 0.621	Lesser/added benefit not proven
Cognitive functioning	1.5 vs. 0.9 months HR: 0.83 [0.64; 1.08]; p = 0.173	Lesser/added benefit not proven
Social functioning Sex		

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

Outcome category **outcome** **effect modifier** **subgroup**	**Pembrolizumab + enfortumab vedotin vs. carboplatin + gemcitabine** **median time to event (months)** **effect estimation [95% CI];** **p-value** **probability**[a]	**Derivation of extent**[b]
Female	0.7 vs. 0.4 months HR: 0.55 [0.32; 0.93]; p = 0.025 probability: "hint"	Outcome category: health-related quality of life $0.90 \leq CI_u < 1.00$ added benefit, extent: "minor"
Male	0.9 vs. 1.3 months HR: 1.16 [0.85; 1.59]; p = 0.351	Lesser/added benefit not proven
Side effects[h]		
SAEs	7.6 vs. 5.4 months HR: 0.91 [0.67; 1.22]; p = 0.525	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[j]	20.3 vs. NR months HR: 1.77 [1.17; 2.66] HR: 0.56 [0.38; 0.85][i]; p = 0.007	Outcome category: non-serious/non-severe side effects $0.80 \leq CI_u < 0.90$ greater harm, extent: "minor"
Immune-related SAEs	NA vs. NA months HR: 7.16 [1.64; 31.21] HR: 0.14 [0.03; 0.61][i]; p = 0.009 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: 15.91 [3.82; 66.35] 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)	No suitable data[f]	Lesser/added benefit not proven
Skin reactions (AEs)	0.6 vs. NA months HR: 4.95 [3.60; 6.81] HR: 0.20 [0.15; 0.28][i]; p < 0.001 probability: "hint"	Outcome category: non-serious/non-severe side effects $CI_u < 0.80$ greater harm, extent: "considerable"

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

Outcome category **outcome** **effect modifier** **subgroup**	**Pembrolizumab + enfortumab vedotin vs. carboplatin + gemcitabine** **median time to event (months)** **effect estimation [95% CI];** **p-value** **probability**[a]	**Derivation of extent**[b]
Severe hyperglycaemia (severe AEs)	NA vs. NA months HR: 10.71 [1.38; 82.93] HR: 0.09 [0.01; 0.72][i]; p = 0.023 probability: “hint”	Outcome category: serious/severe side effects CI_u < 0.75; risk ≥ 5% greater harm, extent: “major”
Severe nephrotoxicity, (severe AEs)	NA vs. NA months HR: 1.12 [0.57; 2.23]; p = 0.736	Greater/lesser harm not proven
Other specific AEs		
Constipation (AEs) Sex		
Female	NA vs. NA months HR: 0.22 [0.09; 0.52]; p < 0.001 probability: “hint”	Outcome category: non-serious/non-severe side effects CI_u < 0.80 lesser harm, extent: “considerable”
Male	24.5 vs. NR months HR: 0.56 [0.36; 0.87]; p = 0.010 probability: “hint”	Outcome category: non-serious/non-severe side effects 0.80 ≤ CI_u < 0.90 lesser harm, extent: “minor”
Diarrhoea (AEs)	NA vs. NA months HR: 2.30 [1.48; 3.56] HR: 0.43 [0.28; 0.68][i]; p < 0.001 probability: “hint”	Outcome category: non-serious/non-severe side effects CI_u < 0.80 greater harm, extent: “considerable”
Dysgeusia (AEs)	NA vs. NA months HR: 4.83 [2.35; 9.92] HR: 0.21 [0.10; 0.43][i]; p < 0.001 probability: “hint”	Outcome category: non-serious/non-severe side effects CI_u < 0.80 greater harm, extent: “considerable”
Eye disorders (AEs)	NA vs. NA months HR: 3.85 [2.04; 7.26] HR: 0.26 [0.14; 0.49][i]; p < 0.001 probability: “hint”	Outcome category: non-serious/non-severe side effects CI_u < 0.80 greater harm, extent: “considerable”

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

Outcome category **outcome** **effect modifier** **subgroup**	**Pembrolizumab + enfortumab vedotin vs. carboplatin + gemcitabine** **median time to event (months)** **effect estimation [95% CI];** **p-value** **probability**[a]	**Derivation of extent**[b]
Endocrine disorders (AEs)	NA vs. NA months HR: 5.47 [1.90; 15.79] HR: 0.18 [0.06; 0.53][i]; p = 0.002 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”

a. Probability provided if there is a statistically significant and relevant effect.
b. Depending on the outcome category, the effect size is estimated using different limits based on the upper limit of the confidence interval (CI_u).
c. Censoring at the time of death: avelumab-eligible patients who had not received avelumab and died were censored at the time of death.
d. Censoring at data cut-off: avelumab-eligible patients who had not received avelumab and died were censored at the time of data cut-off.
e. Modified time of death: avelumab-eligible patients who had not received avelumab and died were censored with a modified time of death. A simplified assumption was made that the patients would have benefited from treatment with avelumab to the extent shown in the approval study of avelumab (JAVELIN Bladder 100); see Section 2.2.2.1 for explanation.
f. See Section 2.2.2.1 for reasons.
g. The extent of the effect in this non-serious/non-severe outcome was no more than marginal.
h. The fixed treatment duration and the associated discontinuation of observation after the end of study medication in the comparator arm mean that the effect estimate only reflects approximately the first 6 months after randomization.
i. Institute's calculation; reversed direction of effect to enable use of limits to derive the extent of the added benefit.
j. There are relevant deviations from dossier assessment A24-98 [5] for the outcome of discontinuation due to AEs.

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 pembrolizumab + enfortumab vedotin in comparison with the ACT (subpopulation: cisplatin unsuitable) (multipage table)

Positive effects	**Negative effects**
Outcomes with observation over the entire study duration	
Mortality ▪ overall survival: hint of an added benefit – extent: “major”	–
Outcomes with shortened observation period[a]	
Health-related quality of life ▪ role functioning (EORTC-QLQ-C30) ▫ sex (female): hint of added benefit - extent: “considerable” ▪ emotional functioning (EORTC QLQ-C30) ▫ sex (female): hint of an added benefit extent: “considerable” ▪ social 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”
Non-serious/non-severe side effects ▪ constipation (AEs) ▫ sex (female) hint of lesser harm – extent "considerable" ▫ sex (male): hint of lesser harm – extent “minor”	Non-serious/non-severe side effects ▪ discontinuation due to AEs: hint of greater harm – extent: “minor” ▪ specific AEs: skin reactions (AEs), diarrhoea (AEs), dysgeusia (AEs), eye disorders (AEs), endocrine disorders (AEs): hint of greater harm in each case - extent: “considerable”
No suitable data are available for the outcomes "pain interference" (BPI-SF items 9a-9g) and “peripheral neuropathy” (AEs). There are relevant deviations from dossier assessment A24-98 [5] for the outcome "discontinuation due to AEs".	

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

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

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

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

There are relevant deviations from dossier assessment A24-98 [5] for the outcome "discontinuation due to AEs".

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 pembrolizumab + enfortumab vedotin over the ACT.

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

2.4 Summary

Table 21 below shows the result of the benefit assessment of pembrolizumab, taking into account dossier assessment A24-99 and the present addendum.

Table 21: Pembrolizumab + enfortumab vedotin – probability and extent of added benefit

Research question	Therapeutic indication	ACT[a]	Probability and extent of added benefit
First-line treatment of adult patients with unresectable or metastatic urothelial carcinoma			
1	For whom cisplatin-based therapy is an option	Cisplatin in combination with gemcitabine followed by avelumab as maintenance therapy (maintenance therapy with avelumab only for progression-free patients[b])	Hint of non-quantifiable added benefit[c]
2	For whom cisplatin-based therapy is not an option[d]	Carboplatin in combination with gemcitabine in accordance with Annex VI to Section K of the Pharmaceutical Directive[e], followed by avelumab as maintenance therapy (maintenance therapy with avelumab only for progression-free patients[b])	Hint of major added benefit[c]
3	For whom cisplatin-based therapy and carboplatin-based therapy are unsuitable	individualized treatment[f] selected from ▪ atezolizumab as monotherapy ▪ pembrolizumab as monotherapy ▪ best supportive care[g] taking into account the PD-L1 status and the general condition	Added benefit not proven

a. Presented is the respective ACT specified by the G-BA.
b. According to the G-BA, it is assumed that patients who are not progression-free following platinum-based chemotherapy will not be treated further as part of first-line treatment.
c. The EV-302/KN-A39 study almost exclusively included patients with an ECOG PS of 0 or 1 (ECOG PS ≥ 2 in the respectively relevant subpopulation: research question 1: 4 [2%] vs. 2 [1%]; research question 2: 11 [5%] vs. 9 [5%]). It remains unclear whether the observed effects are transferable to patients with an ECOG PS ≥ 2.
d. According to the G-BA, it is assumed that the patients in question have an increased risk of cisplatin-induced side effects in the context of a combination therapy (e.g. pre-existing neuropathy or relevant hearing impairment, renal failure, heart failure).
e. With regard to the present indication, this is a use in an unapproved therapeutic indication (off-label use). For the present indication, carboplatin in combination with gemcitabine can be prescribed in off-label use, see Appendix VI to Section K of the Pharmaceutical Directive.
f. For the implementation of individualized therapy in a direct comparative study, the investigator is expected as per G-BA to have a selection of several treatment options at disposal to permit an individualized treatment decision taking into account the listed criteria (multicomparator study). A rationale must be provided for the choice and any limitation of treatment options.
g. Best supportive care refers to the therapy which provides the patient with the best possible, individually optimized, supportive treatment to alleviate symptoms and improve the quality of life.

G-BA: Joint Federal Committee; PD-L1: Programmed Cell Death Ligand 1; ECOG PS: Eastern Cooperative Oncology Group - Performance Status

The G-BA decides on the added benefit.

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Appendix A Kaplan-Meier curves

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

A.1.1 Mortality

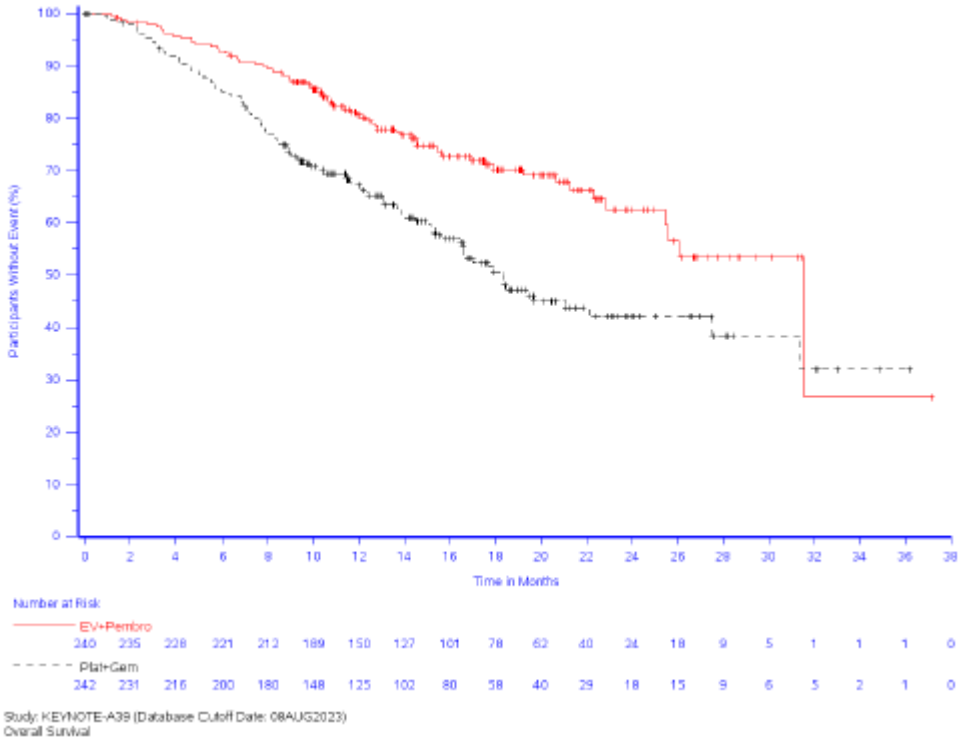

Figure 1: Kaplan-Meier curves for the outcome of overall survival of the RCT EV-302/KN-A39, 2nd data cut-off (08 August 2023), subpopulation 1 (cisplatin suitable)

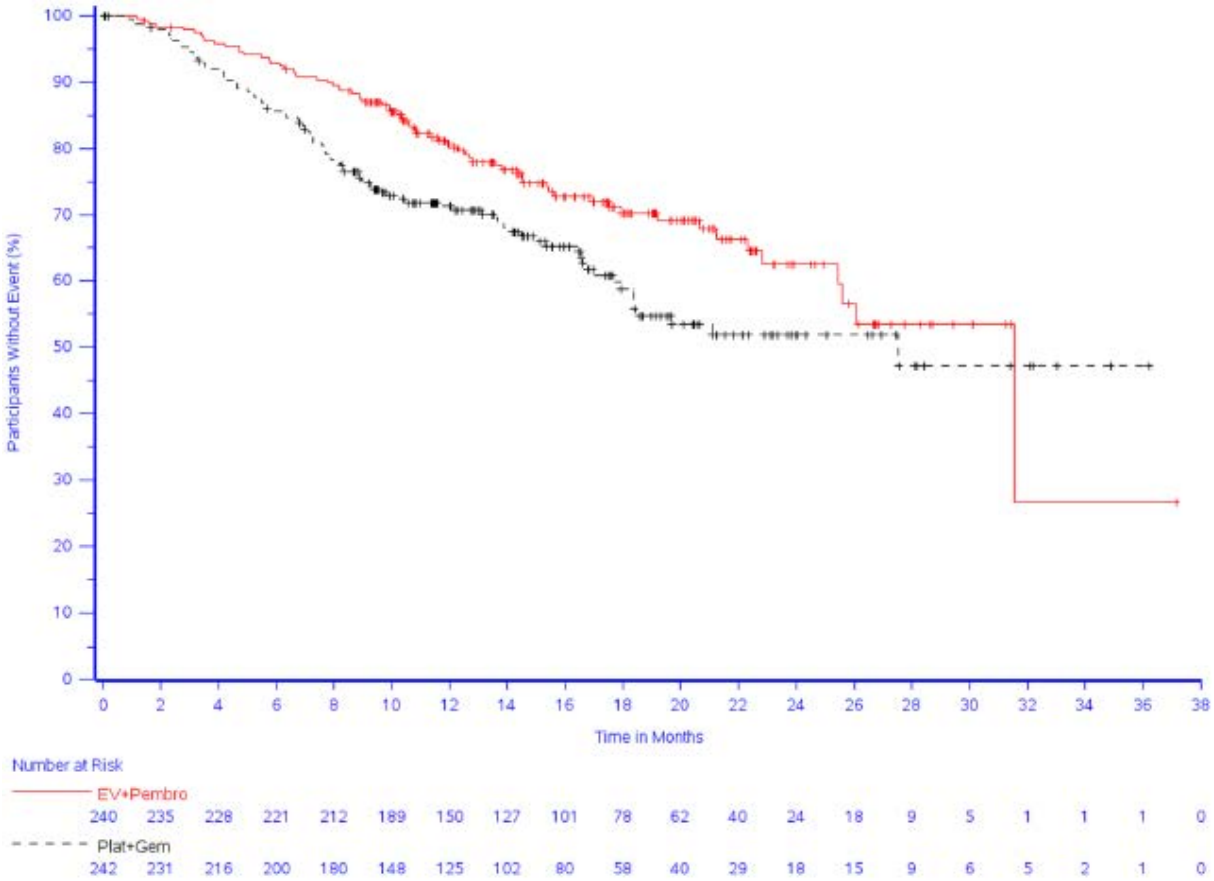

Figure 2: Kaplan-Meier curves for sensitivity analysis 1 of the company for the outcome of overall survival of the RCT EV-302/KN-A39, 1st data cut-off (8 August 2023), subpopulation 1 (cisplatin suitable)

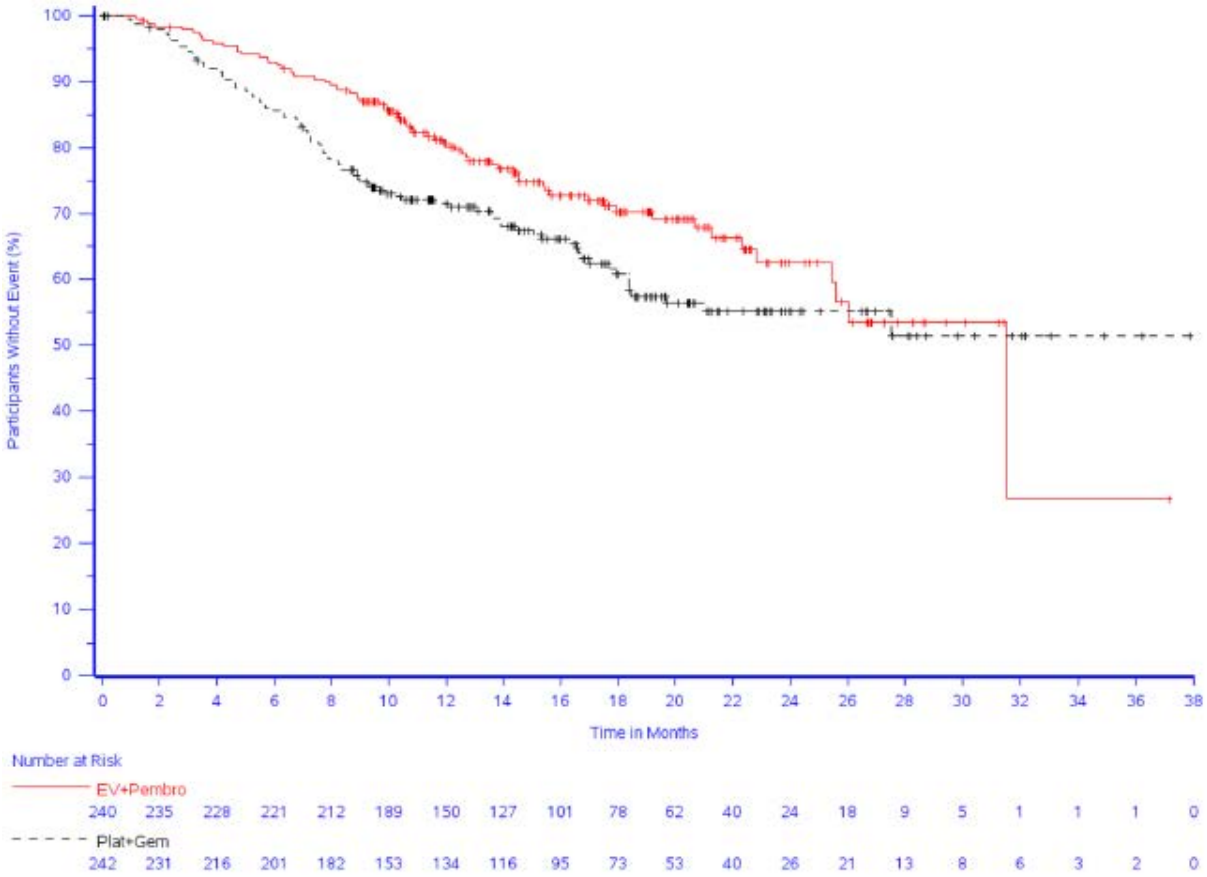

Figure 3: Kaplan-Meier curves for sensitivity analysis 2 of the company for the outcome of overall survival of the RCT EV-302/KN-A39, 1st data cut-off (8 August 2023), subpopulation 1 (cisplatin suitable)

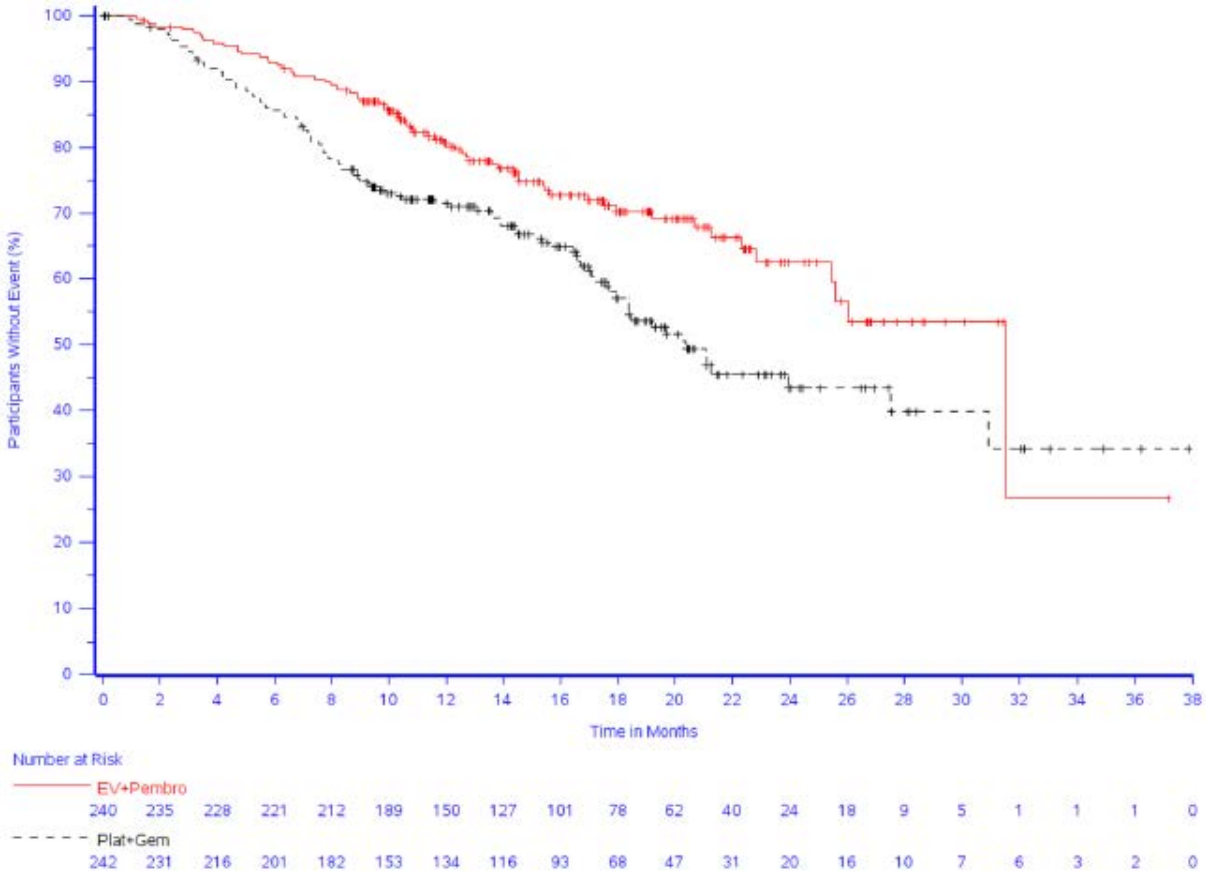

Figure 4: Kaplan-Meier curves for sensitivity analysis 3 of the company for the outcome of overall survival of the RCT EV-302/KN-A39, 1st data cut-off (8 August 2023), subpopulation 1 (cisplatin suitable)

Morbidity

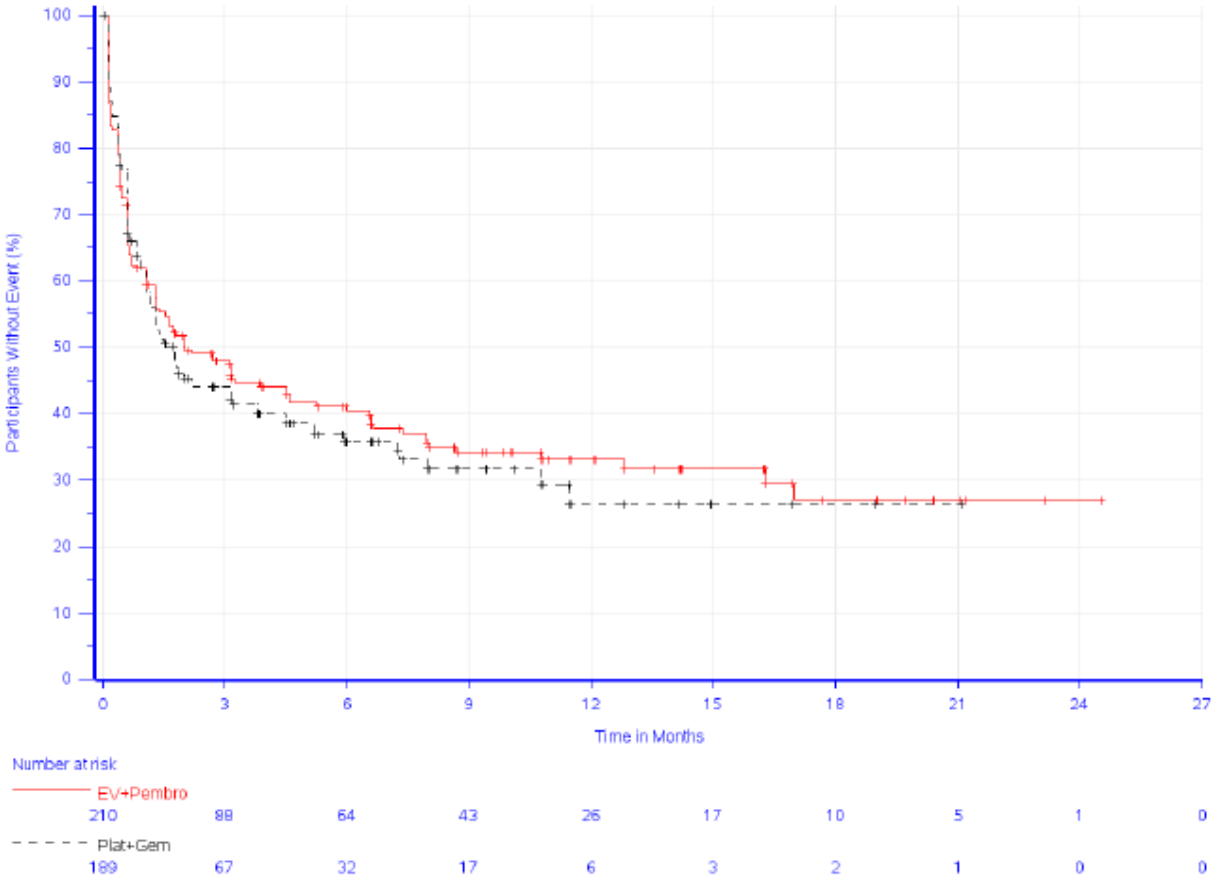

Figure 5: Kaplan-Meier curves for the outcome of worst pain (BPI-SF item 3 - time to 1st deterioration) of RCT EV-302/KN-A39, 1st data cut-off (08 August 2023), subpopulation 1 (cisplatin suitable)

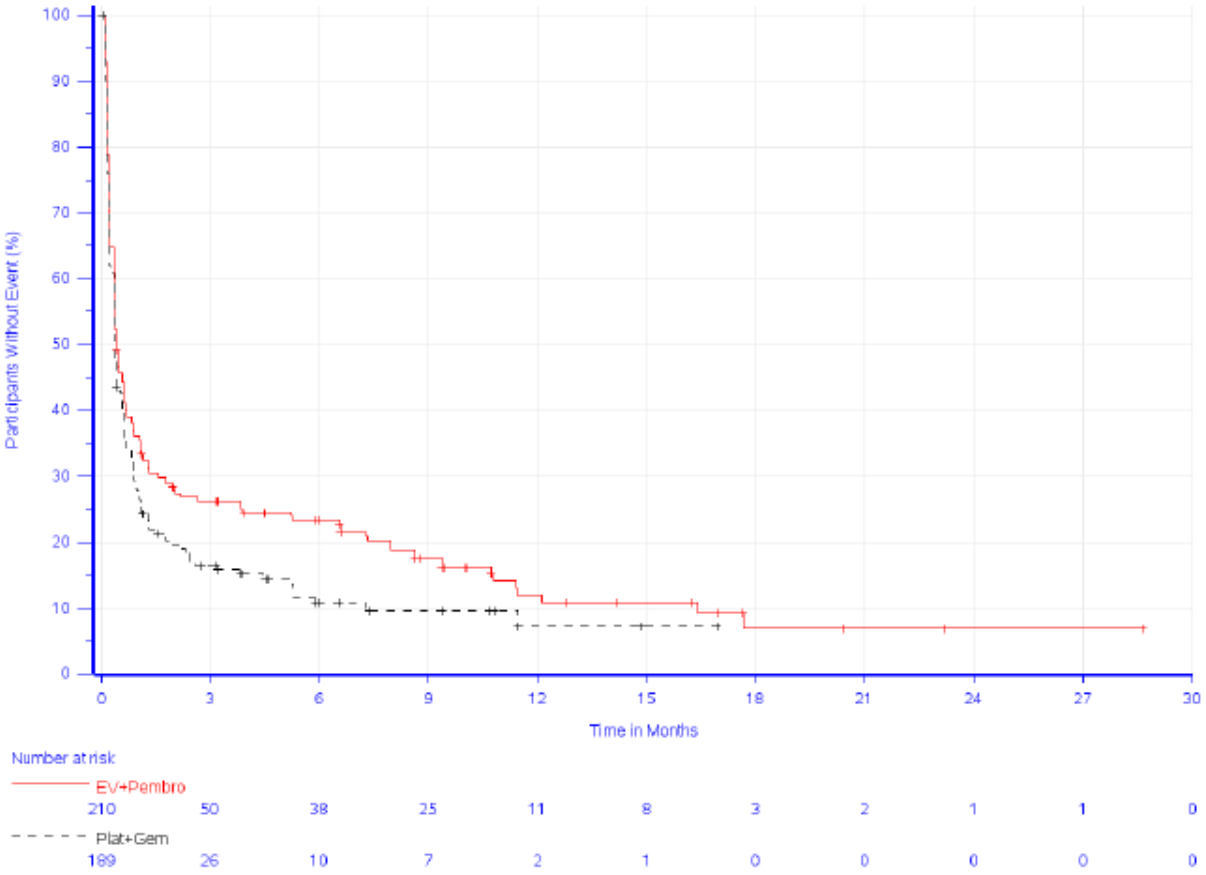

Figure 6: Kaplan-Meier curves for the outcome of fatigue (EORTC-QLQ-C30 - time to 1st deterioration) of the RCT EV-302/KN-A39, 1st data cut-off (08 August 2023), subpopulation 1 (cisplatin suitable)

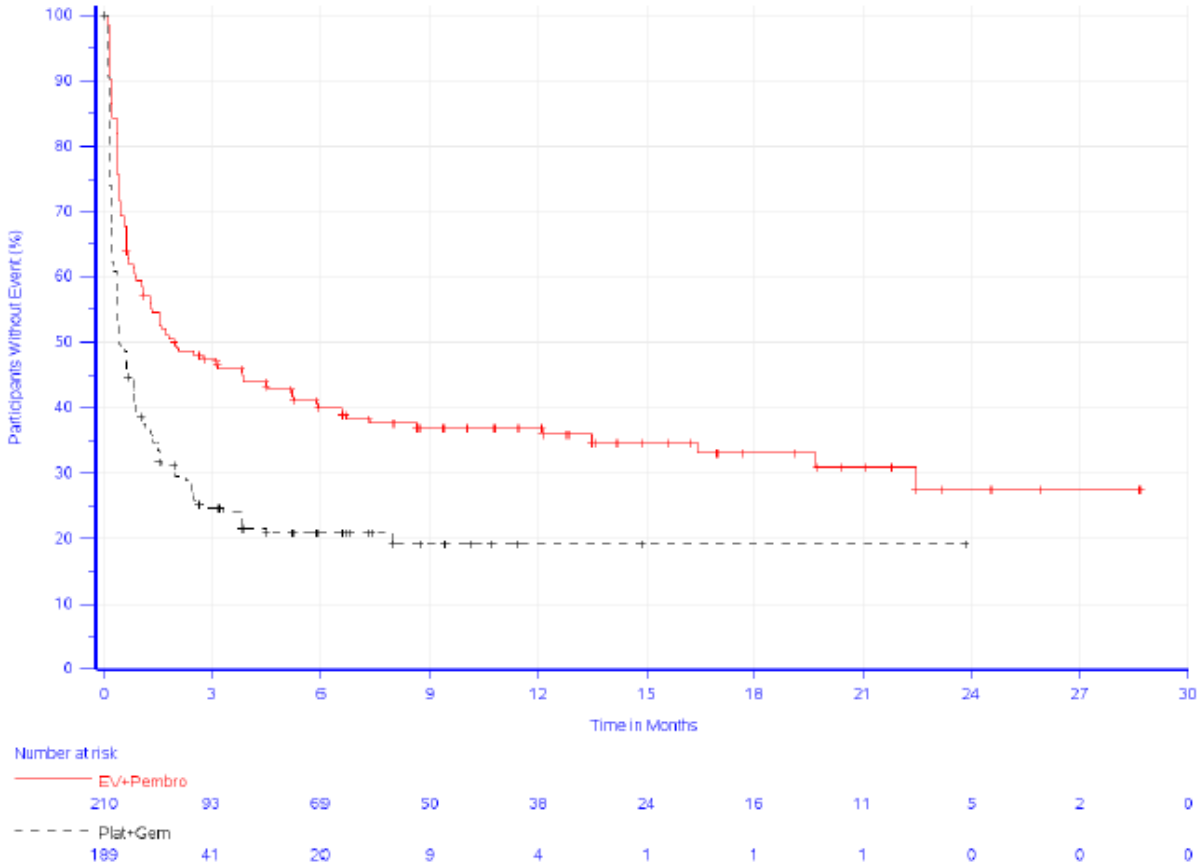

Figure 7: Kaplan-Meier curves for the outcome of nausea and vomiting (EORTC QLQ-C30 - time to 1st deterioration) of the RCT EV-302/KN-A39, 1st data cut-off (08 August 2023), subpopulation 1 (cisplatin suitable)

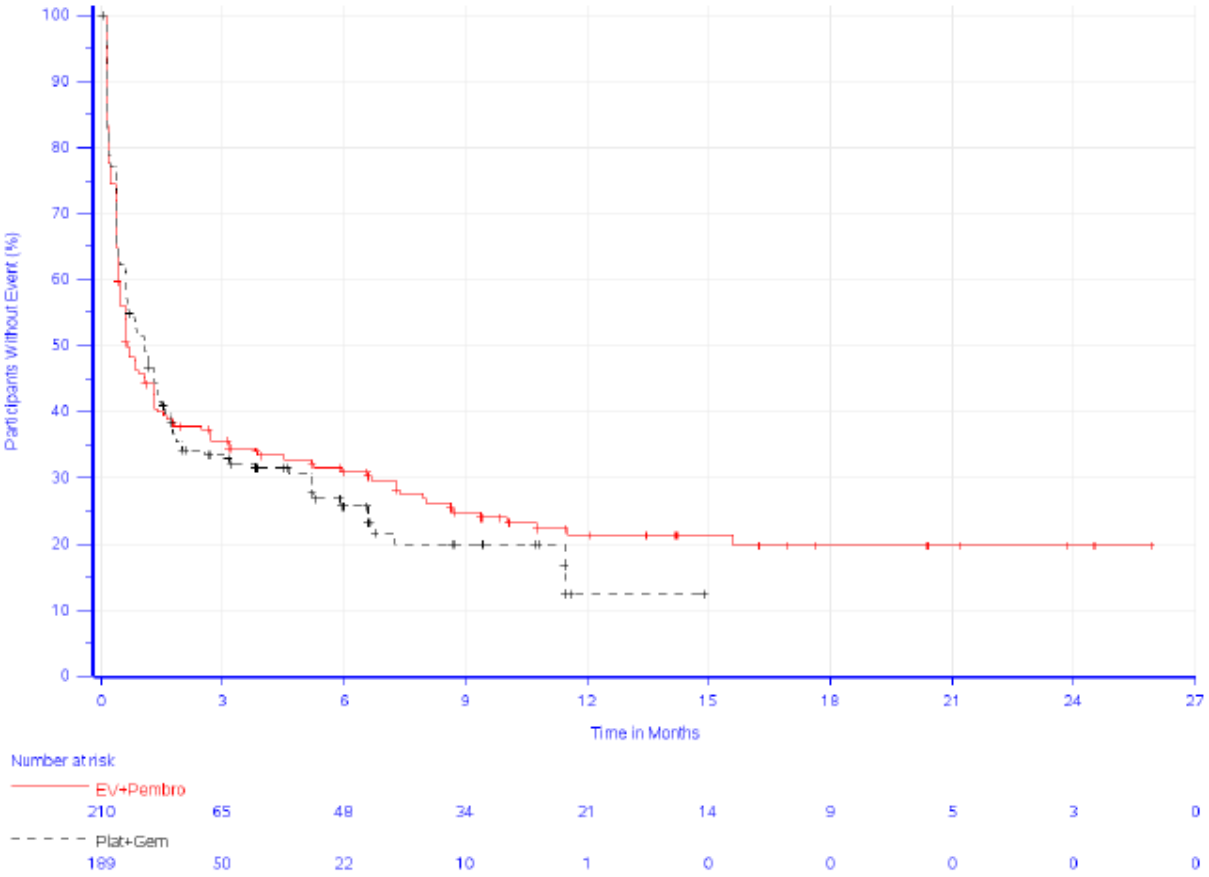

Figure 8: Kaplan-Meier curves for the outcome of pain (EORTC QLQ-C30 - time to 1st deterioration) of the RCT EV-302/KN-A39, 1st data cut-off (08 August 2023), subpopulation 1 (cisplatin suitable)

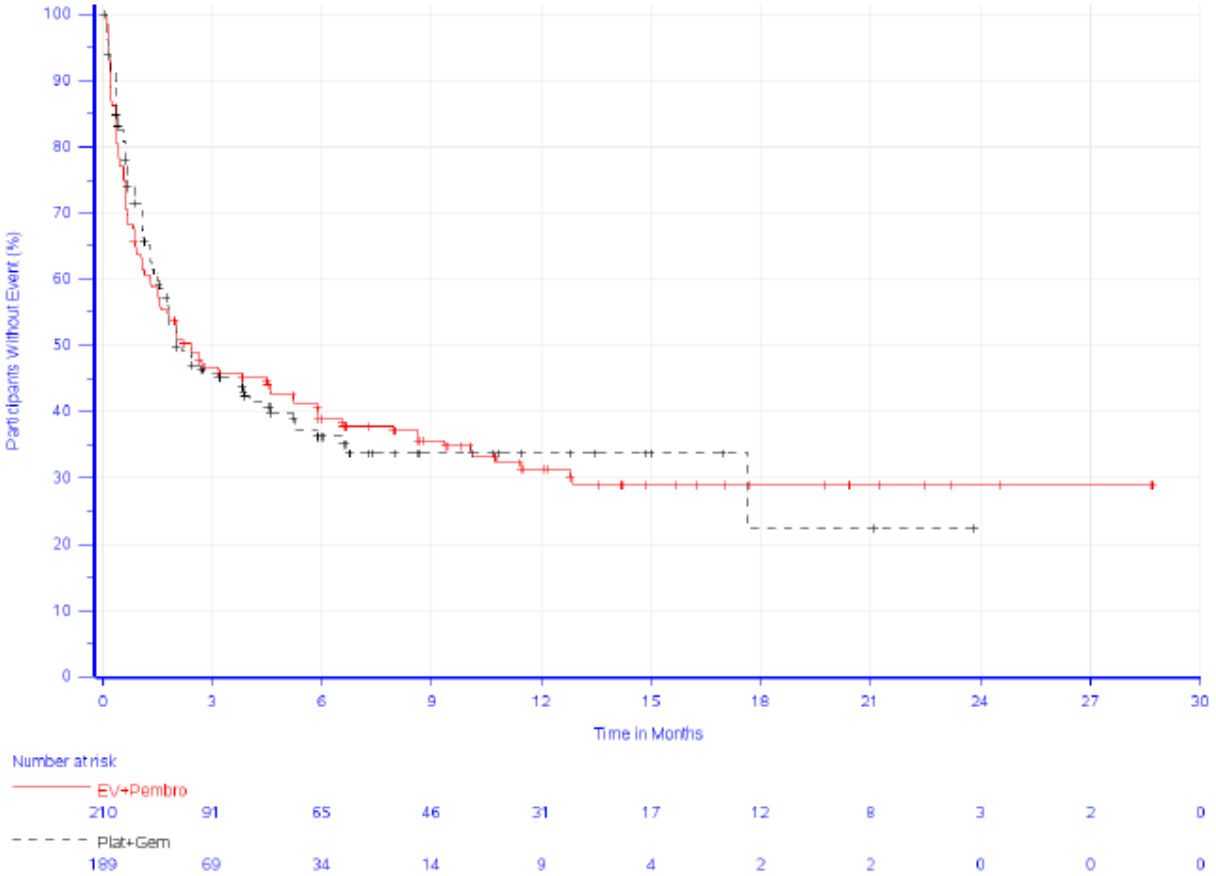

Figure 9: Kaplan-Meier curves for the outcome of dyspnoea (EORTC-QLQ-C30 - time to 1st deterioration) of the RCT EV-302/KN-A39, 1st data cut-off (08 August 2023), subpopulation 1 (cisplatin suitable)

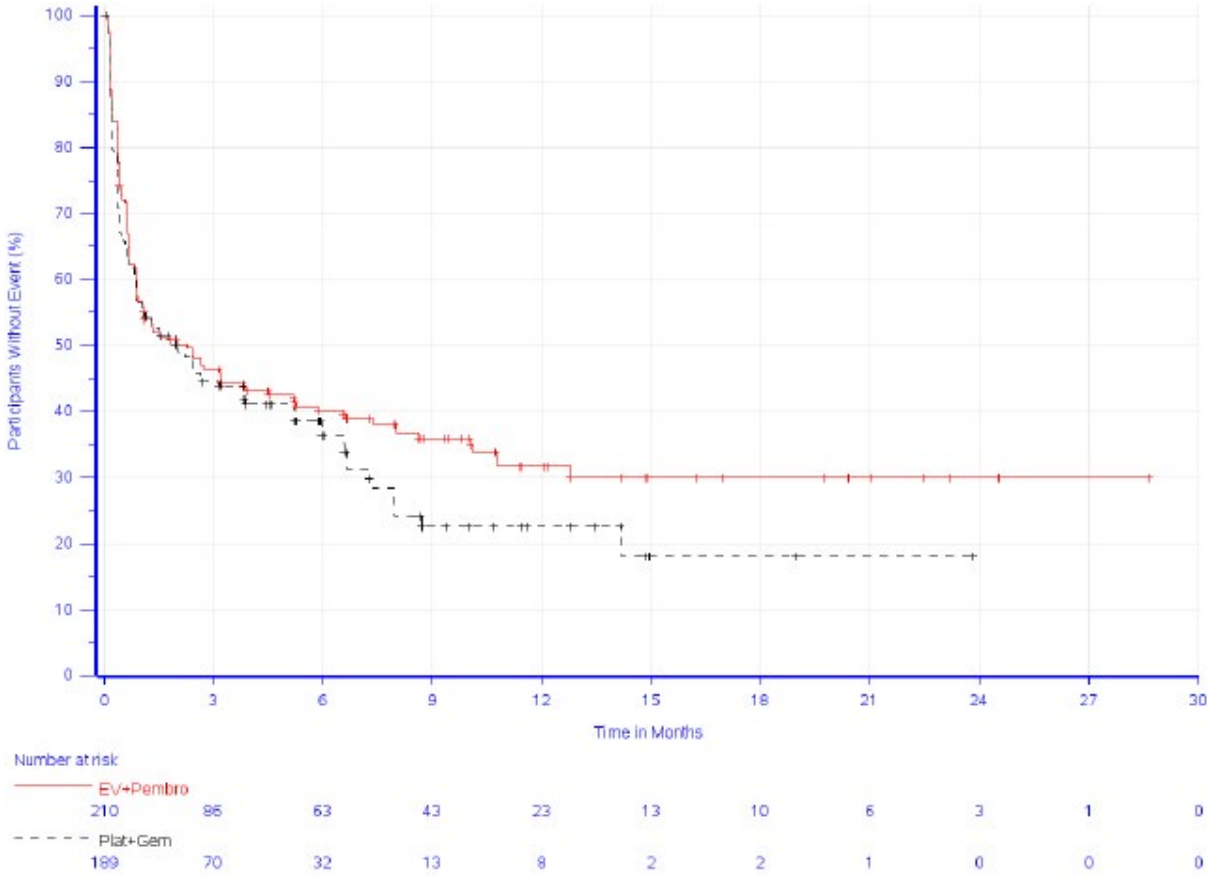

Figure 10: Kaplan-Meier curves for the outcome of insomnia (EORTC-QLQ-C30 - time to 1st deterioration) of the RCT EV-302/KN-A39, 1st data cut-off (08 August 2023), subpopulation 1 (cisplatin suitable)

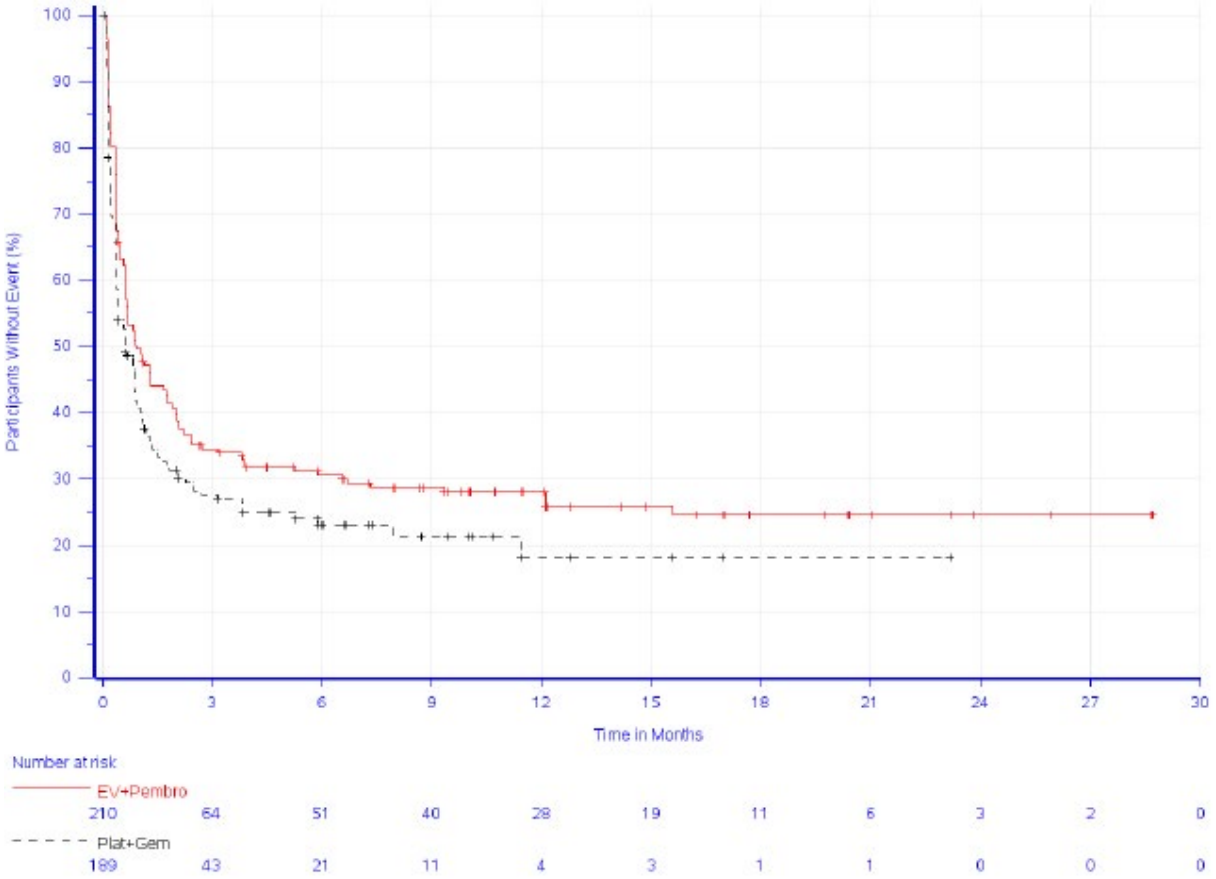

Figure 11: Kaplan-Meier curves for the outcome of appetite loss (EORTC QLQ-C30 - time to 1st deterioration) of the RCT EV-302/KN-A39, 1st data cut-off (08 August 2023), subpopulation 1 (cisplatin suitable) *

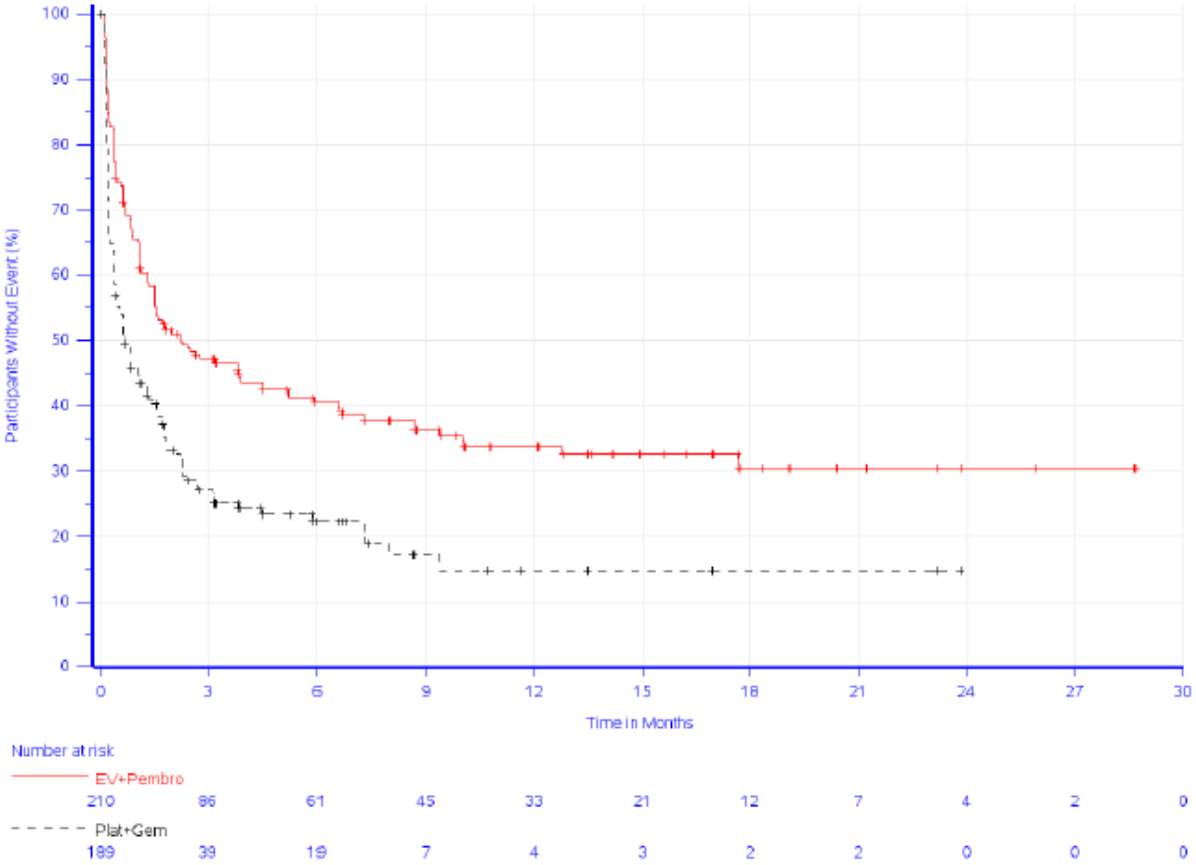

Figure 12: Kaplan-Meier curves for the outcome of constipation (EORTC-QLQ-C30 - time to 1st deterioration) of the RCT EV-302/KN-A39, 1st data cut-off (08 August 2023), subpopulation 1 (cisplatin suitable)

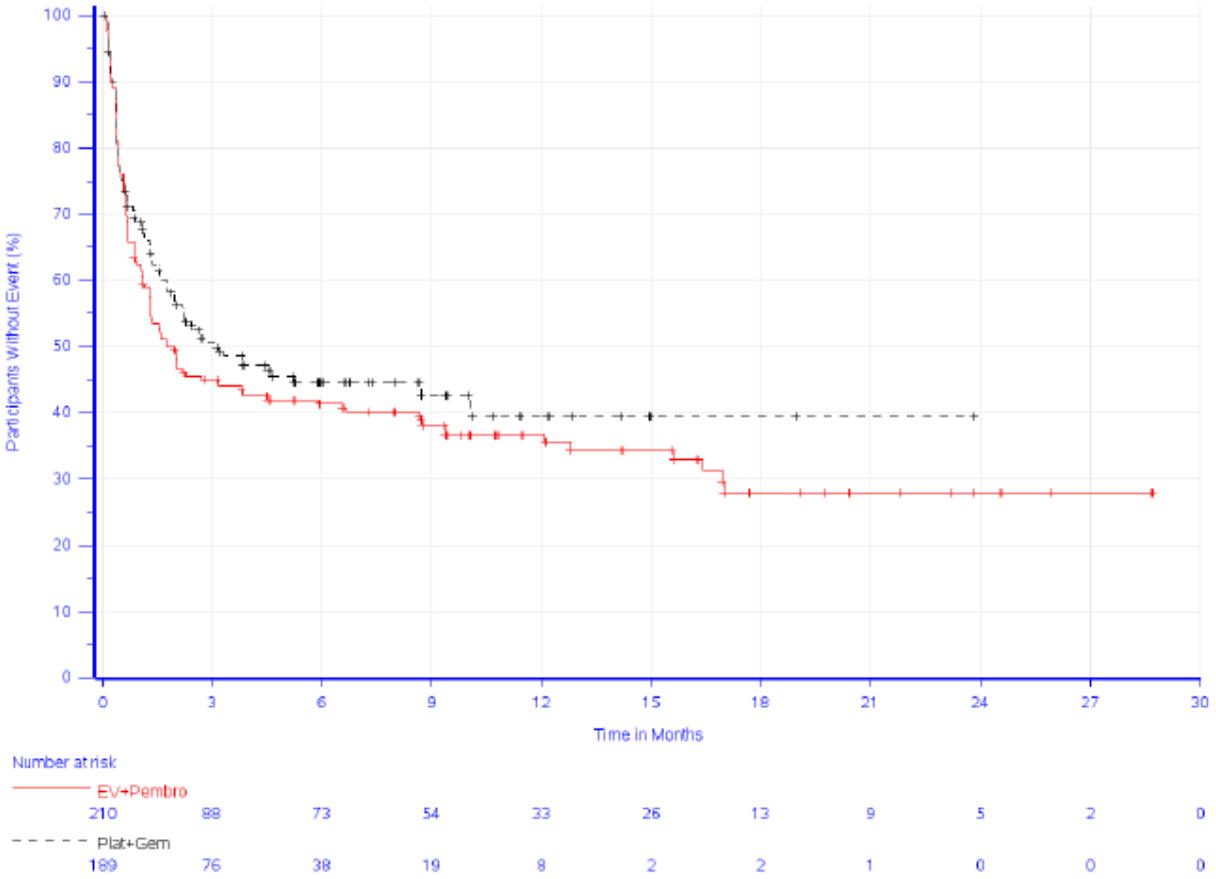

Figure 13: Kaplan-Meier curves for the outcome of diarrhoea (EORTC-QLQ-C30 - time to 1st deterioration) of the RCT EV-302/KN-A39, 1st data cut-off (08 August 2023), subpopulation 1 (cisplatin suitable)

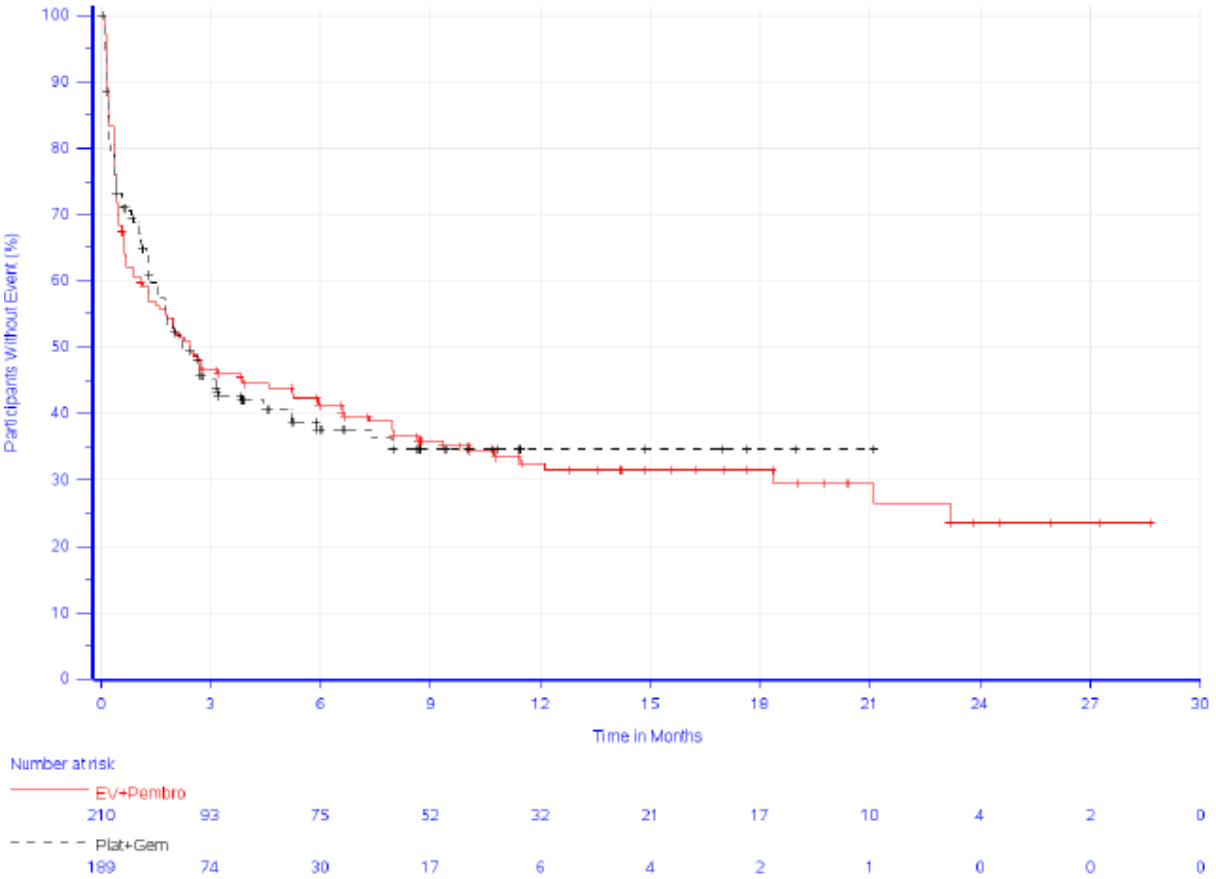

Figure 14: Kaplan-Meier curves for the outcome of health status (EQ-5D VAS - time to 1st deterioration) of the RCT EV-302/KN-A39, 1st data cut-off (08 August 2023), subpopulation 1 (cisplatin suitable)

A.1.2 Health-related quality of life

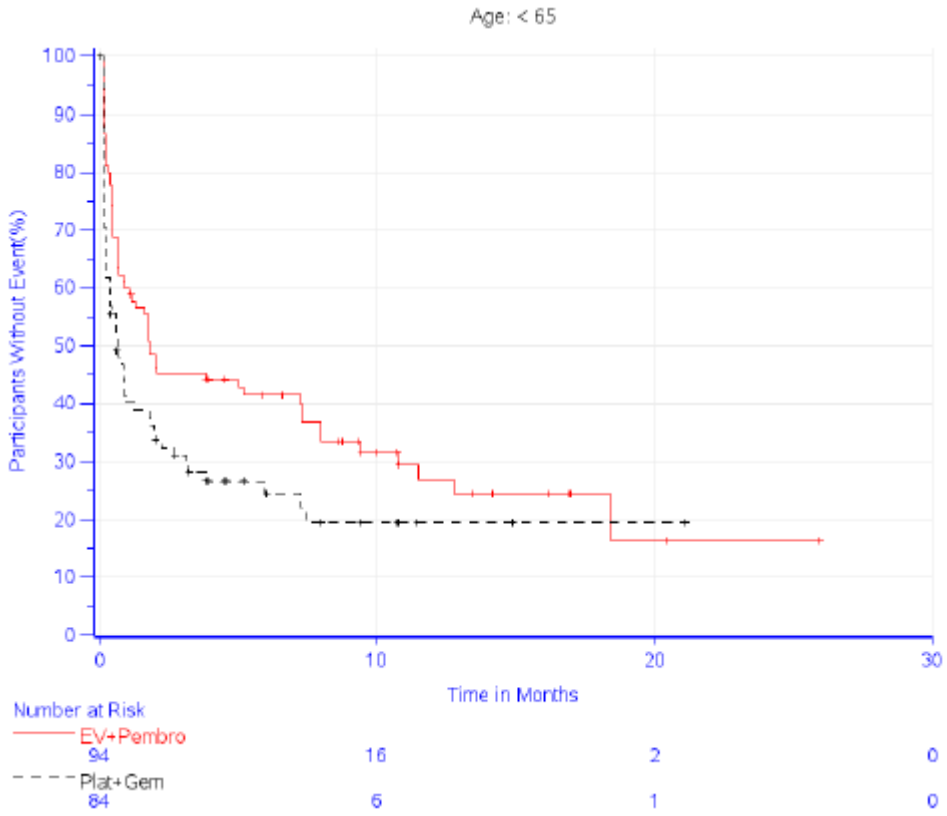

Figure 15: Kaplan-Meier curves for the outcome of physical functioning (EORTC-QLQ-C30 - time to 1st deterioration) of the RCT EV-302/KN-A39, 1st data cut-off (08 August 2023), subpopulation 1 (cisplatin suitable), subgroup: < 65 years

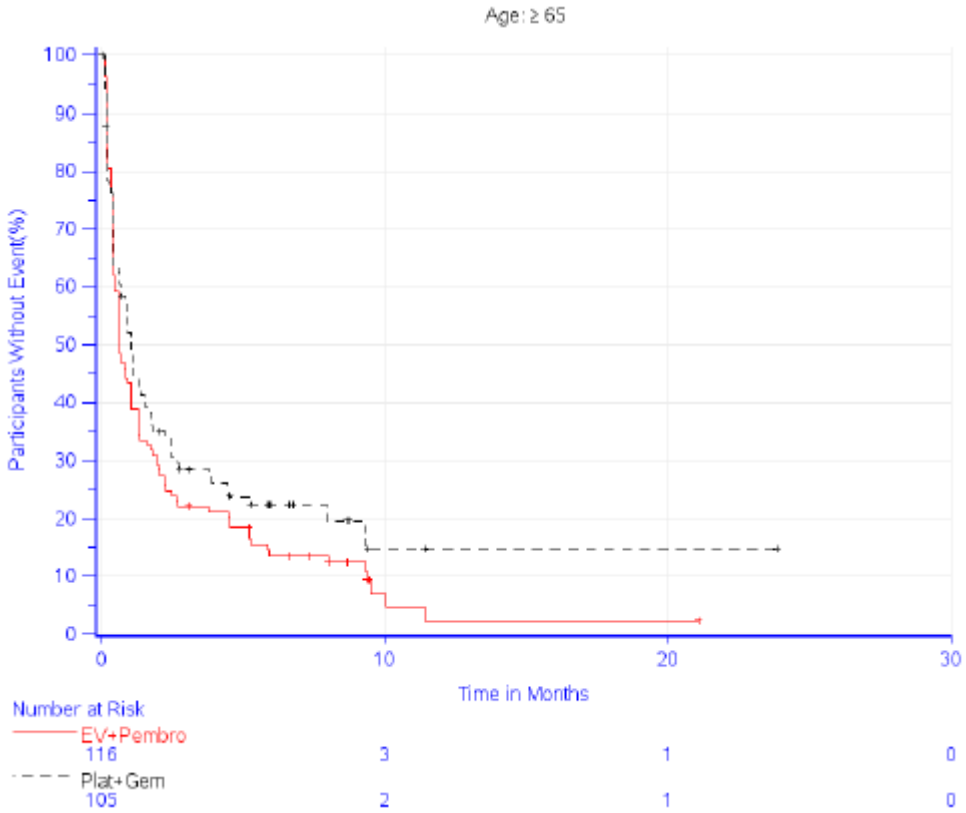

Figure 16: Kaplan-Meier curves for the outcome of physical functioning (EORTC-QLQ-C30 - time to 1st deterioration) of the RCT EV-302/KN-A39, 1st data cut-off (08 August 2023), subpopulation 1 (cisplatin suitable), subgroup: ≥ 65 years

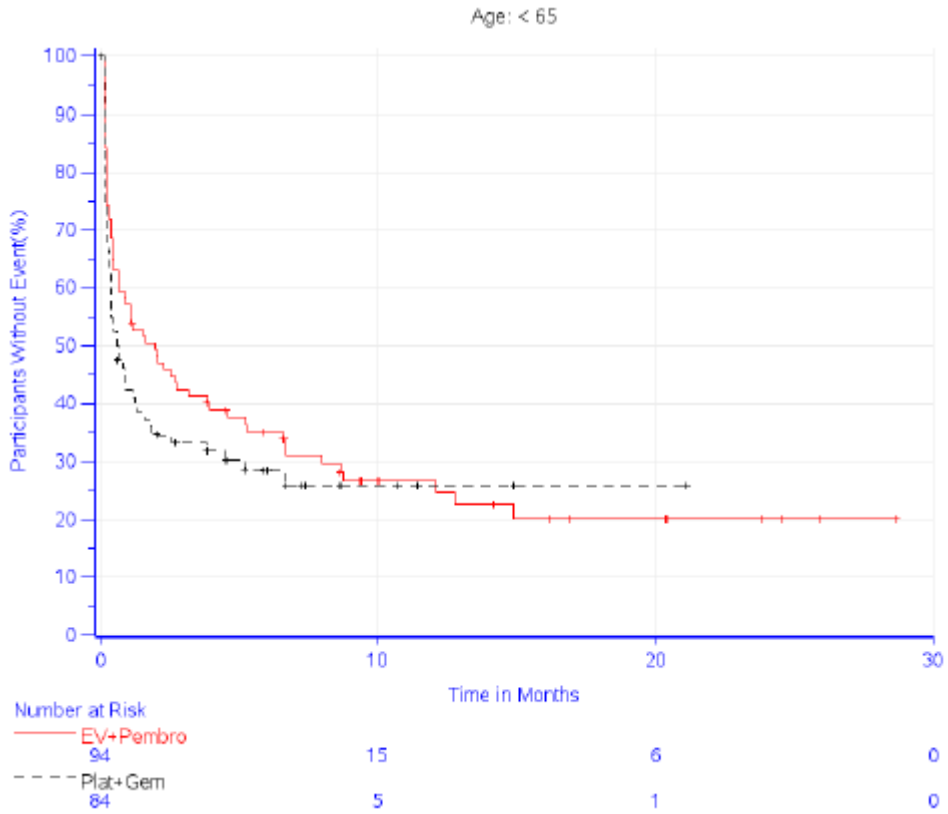

Figure 17: Kaplan-Meier curves for the outcome of social functioning (EORTC-QLQ-C30 - time to 1st deterioration) of the RCT EV-302/KN-A39, 1st data cut-off (08 August 2023), subpopulation 1 (cisplatin suitable), subgroup: < 65 years

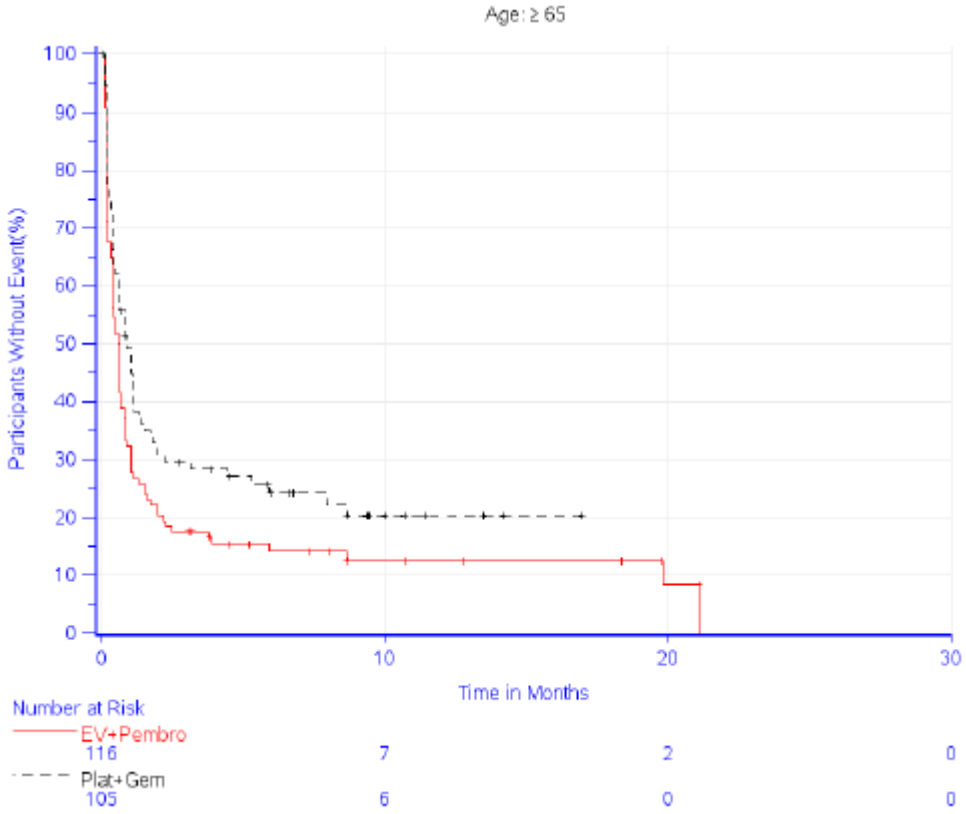

Figure 18: Kaplan-Meier curves for the outcome of social functioning (EORTC-QLQ-C30 - time to 1st deterioration) of the RCT EV-302/KN-A39, 1st data cut-off (08 August 2023), subpopulation 1 (cisplatin suitable), subgroup: ≥ 65 years

A.1.3 Side effects

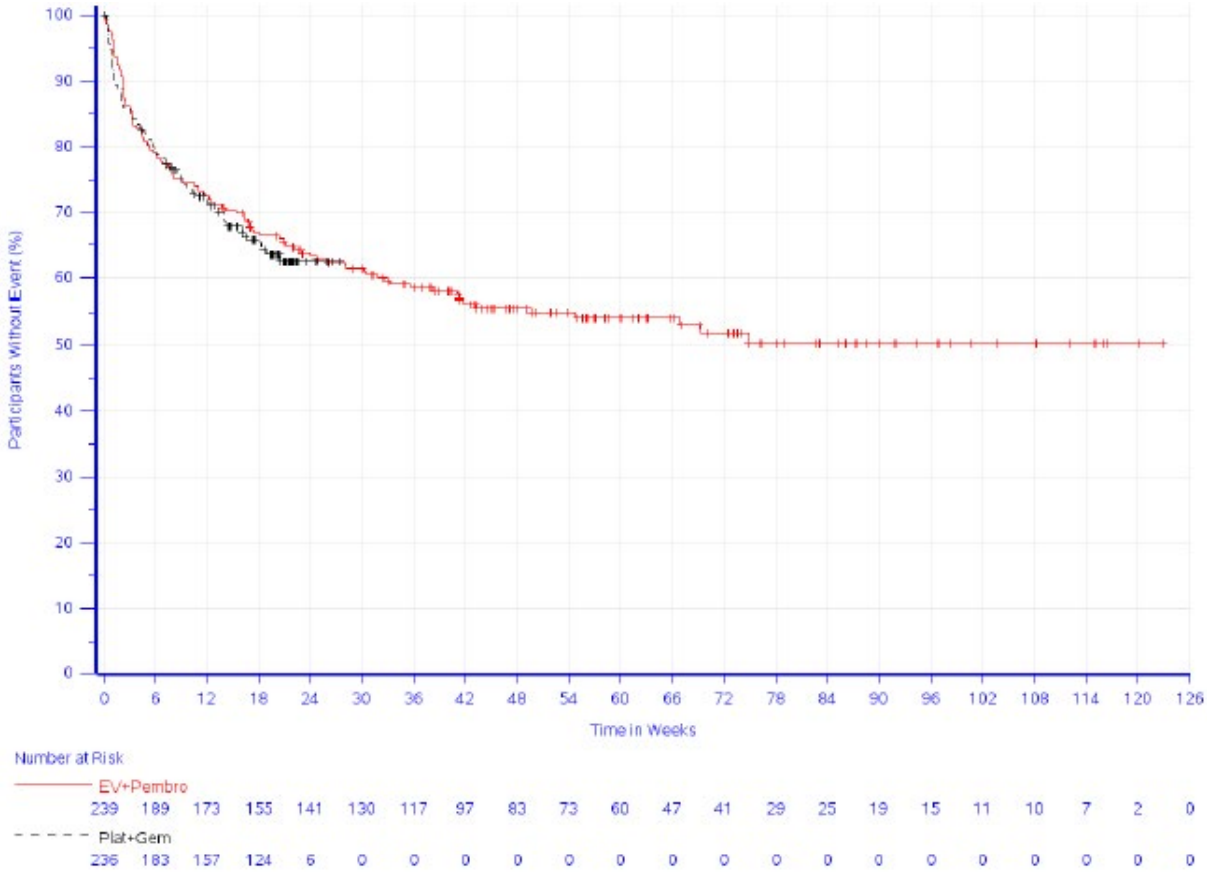

Figure 19: Kaplan-Meier curves for the outcome of SAEs of the RCT EV-302/KN-A39, 1st data cut-off (08 August 2023), subpopulation 1 (cisplatin suitable)

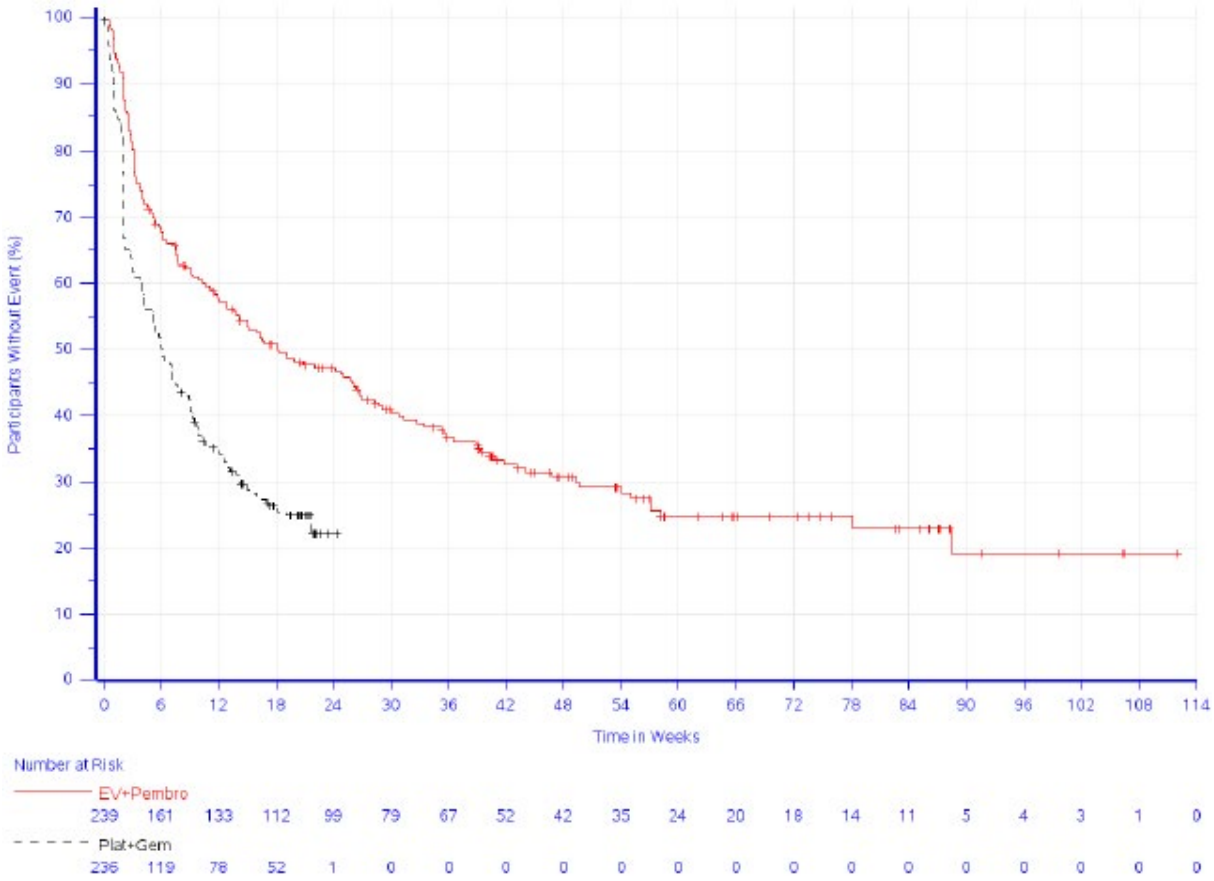

Figure 20: Kaplan-Meier curves for the outcome of severe AEs of the RCT EV-302/KN-A39, 1st data cut-off (08 August 2023), subpopulation 1 (cisplatin suitable)

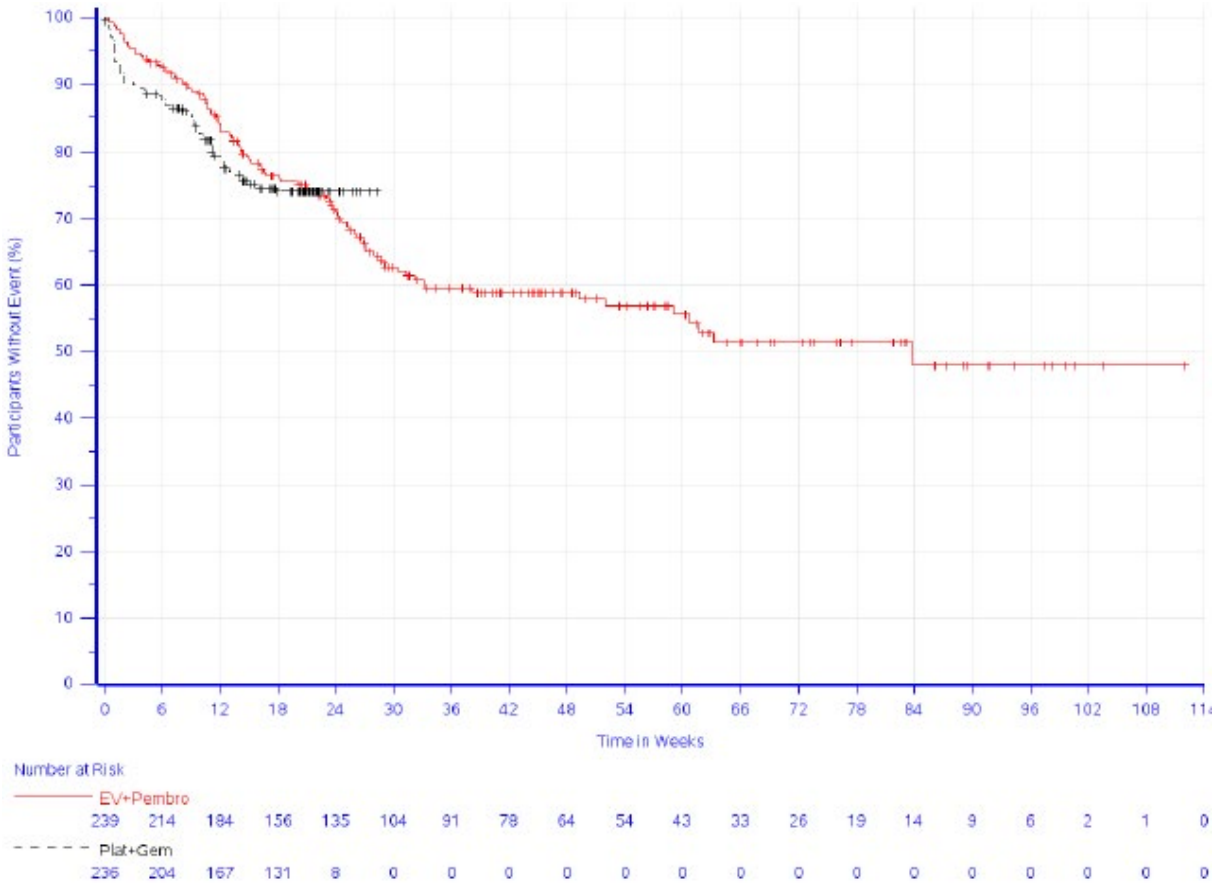

Figure 21: Kaplan-Meier curves for the outcome of discontinuation due to AEs of the RCT EV-302/KN-A39, 1st data cut-off (08 August 2023), subpopulation 1 (cisplatin suitable)

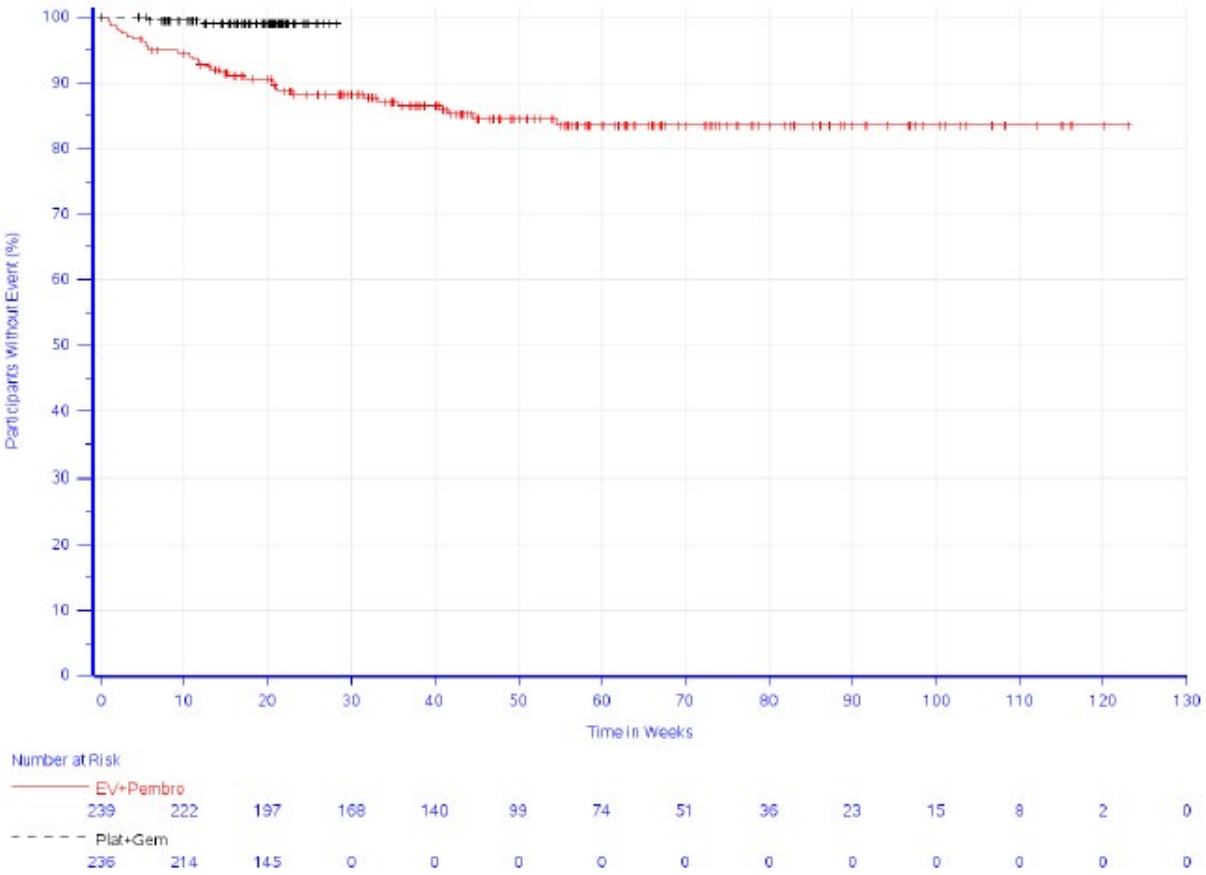

Figure 22: Kaplan-Meier curves for the outcome of immune-related SAEs of the RCT EV-302/KN-A39, 1st data cut-off (08 August 2023), subpopulation 1 (cisplatin suitable)

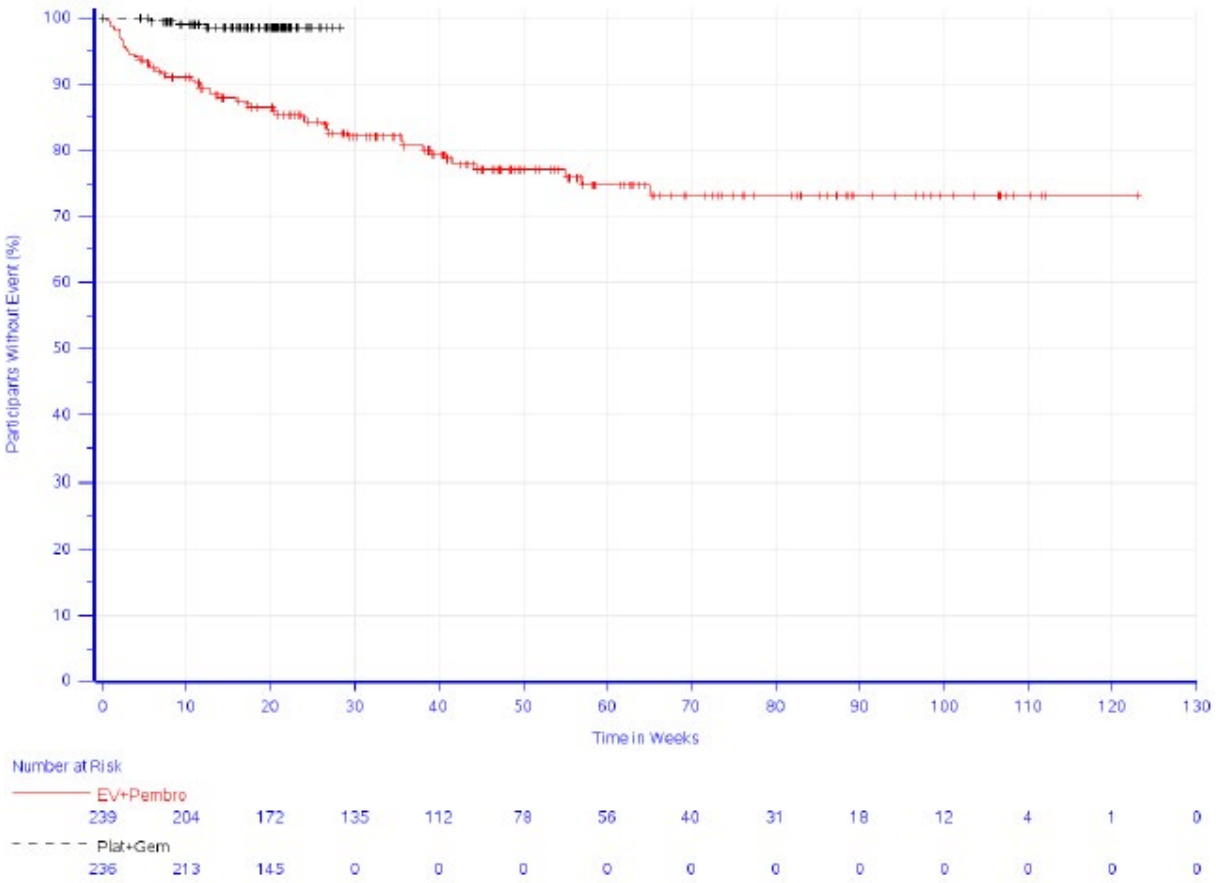

Figure 23: Kaplan-Meier curves for the outcome of immune-related severe AEs of the RCT EV-302/KN-A39, 1st data cut-off (08 August 2023), subpopulation 1 (cisplatin suitable)

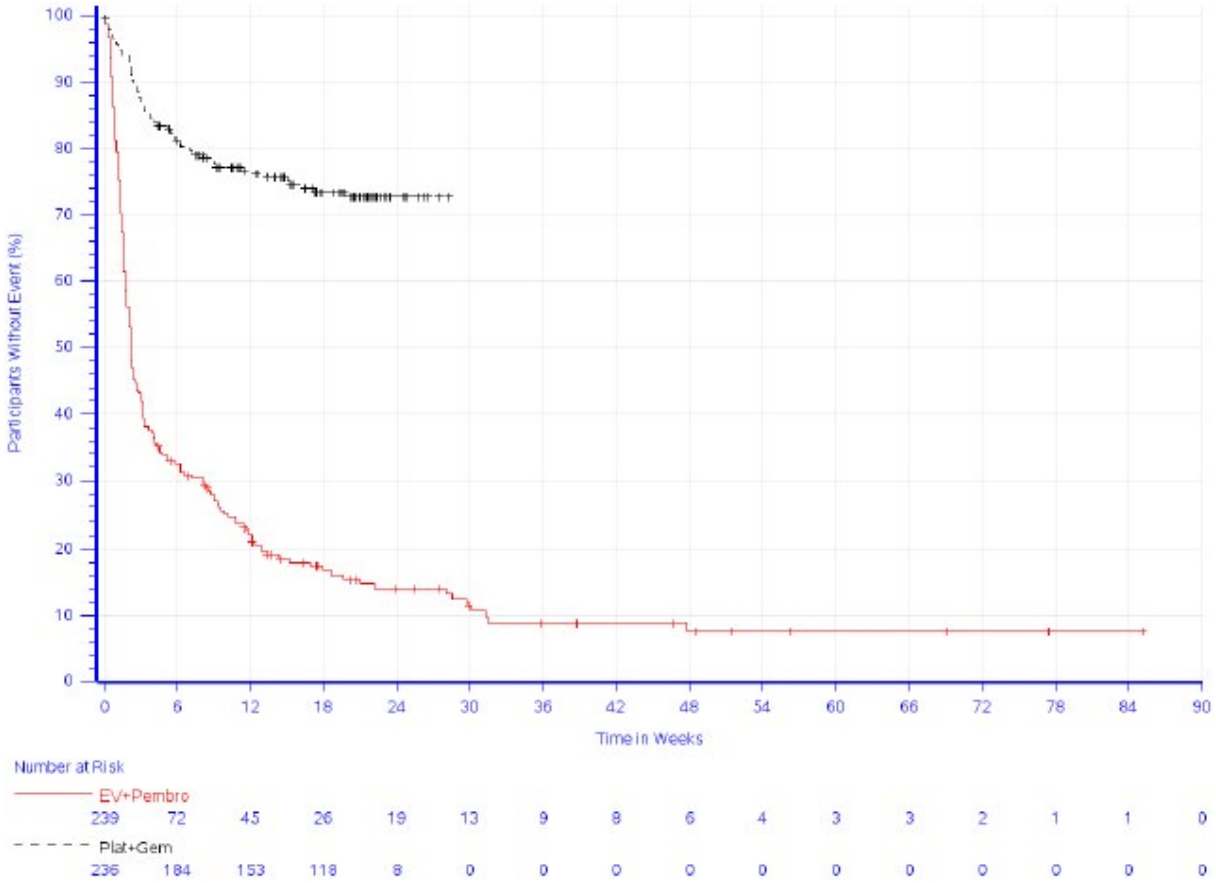

Figure 24: Kaplan-Meier curves for the outcome of skin reactions (AEs) of the RCT EV-302/KN-A39, 1st data cut-off (08 August 2023), subpopulation 1 (cisplatin suitable)

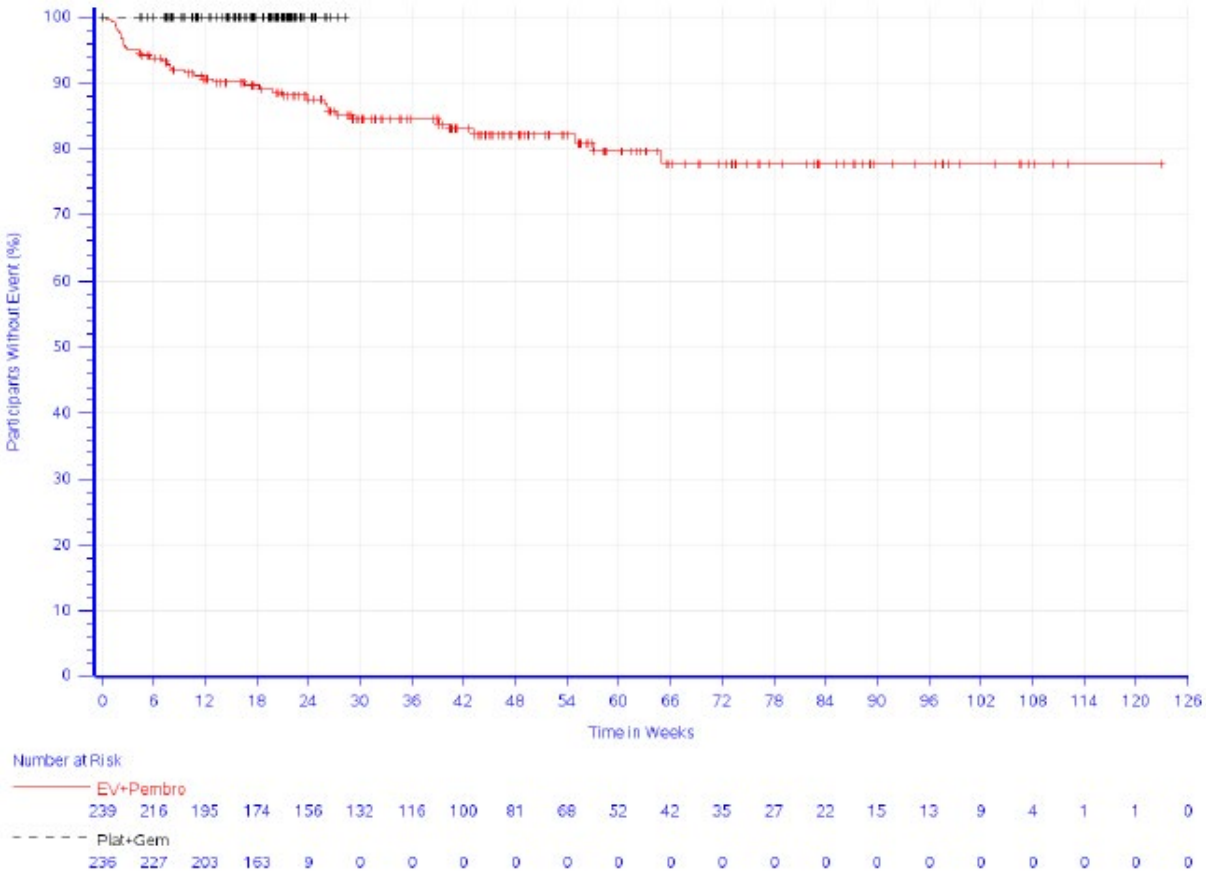

Figure 25: Kaplan-Meier curves for the outcome of severe skin reactions (severe AEs) of the RCT EV-302/KN-A39, 1st data cut-off (08 August 2023), subpopulation 1 (cisplatin suitable) - supplementary presentation

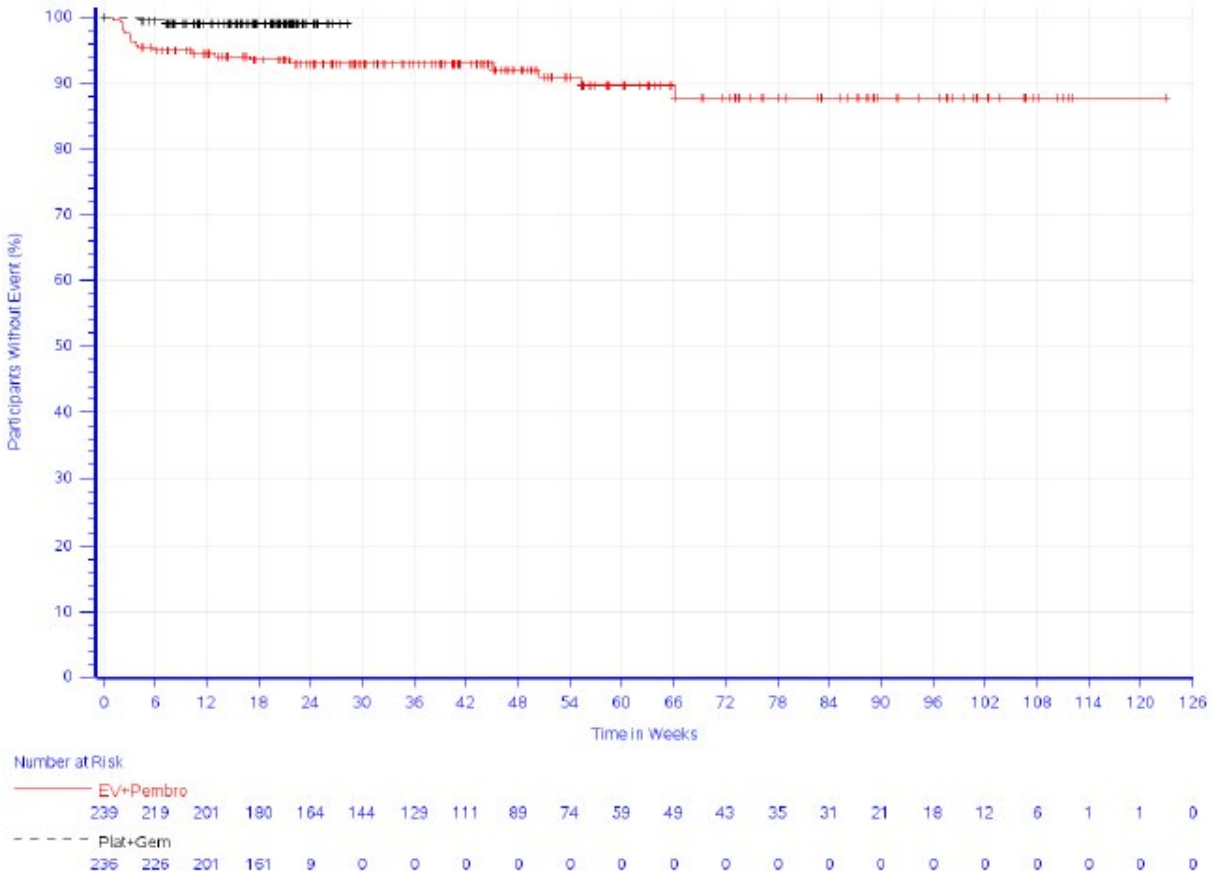

Figure 26: Kaplan-Meier curves for the outcome of severe hyperglycaemia (severe AEs) of the RCT EV-302/KN-A39, 1st data cut-off (08 August 2023), subpopulation 1 (cisplatin suitable)

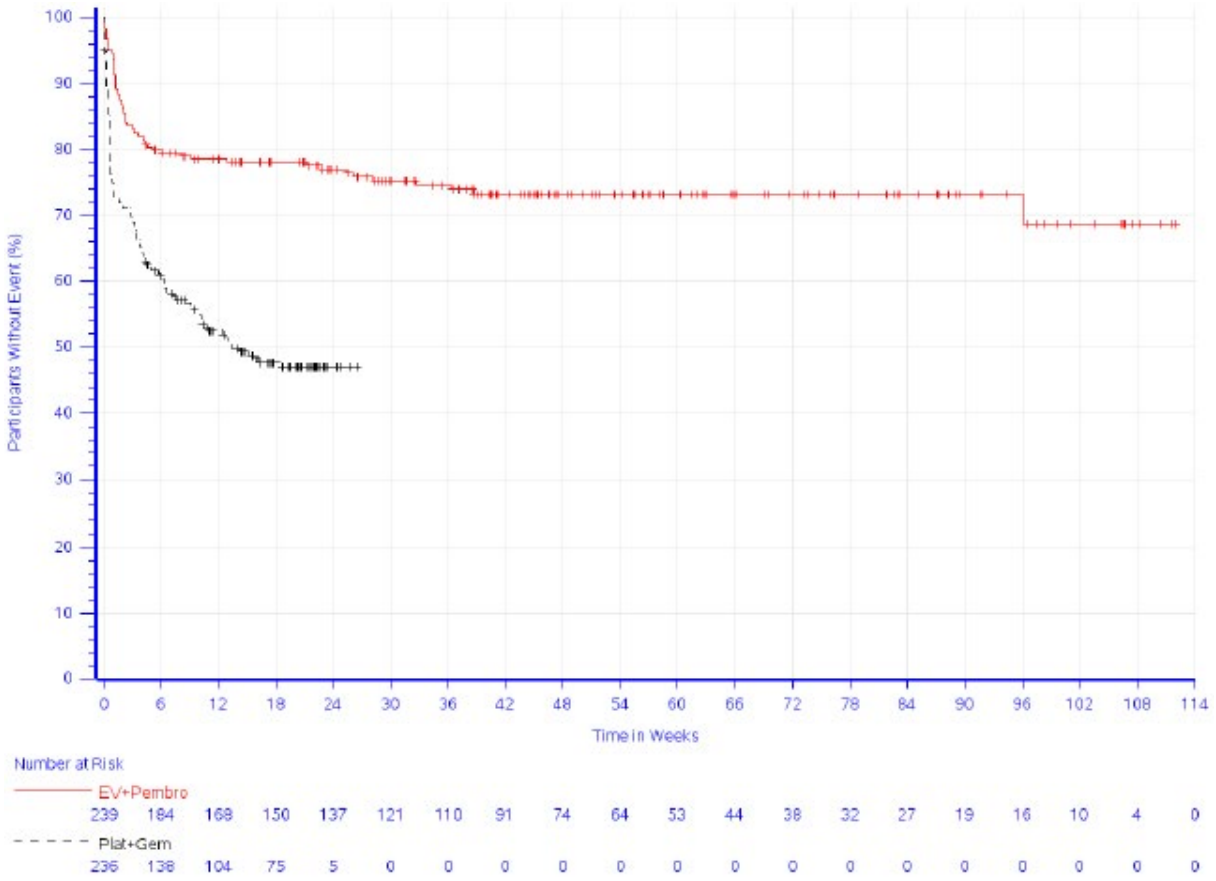

Figure 27: Kaplan-Meier curves for the outcome of nausea (AEs) of the RCT EV-302/KN-A39, 1st data cut-off (08 August 2023), subpopulation 1 (cisplatin suitable)

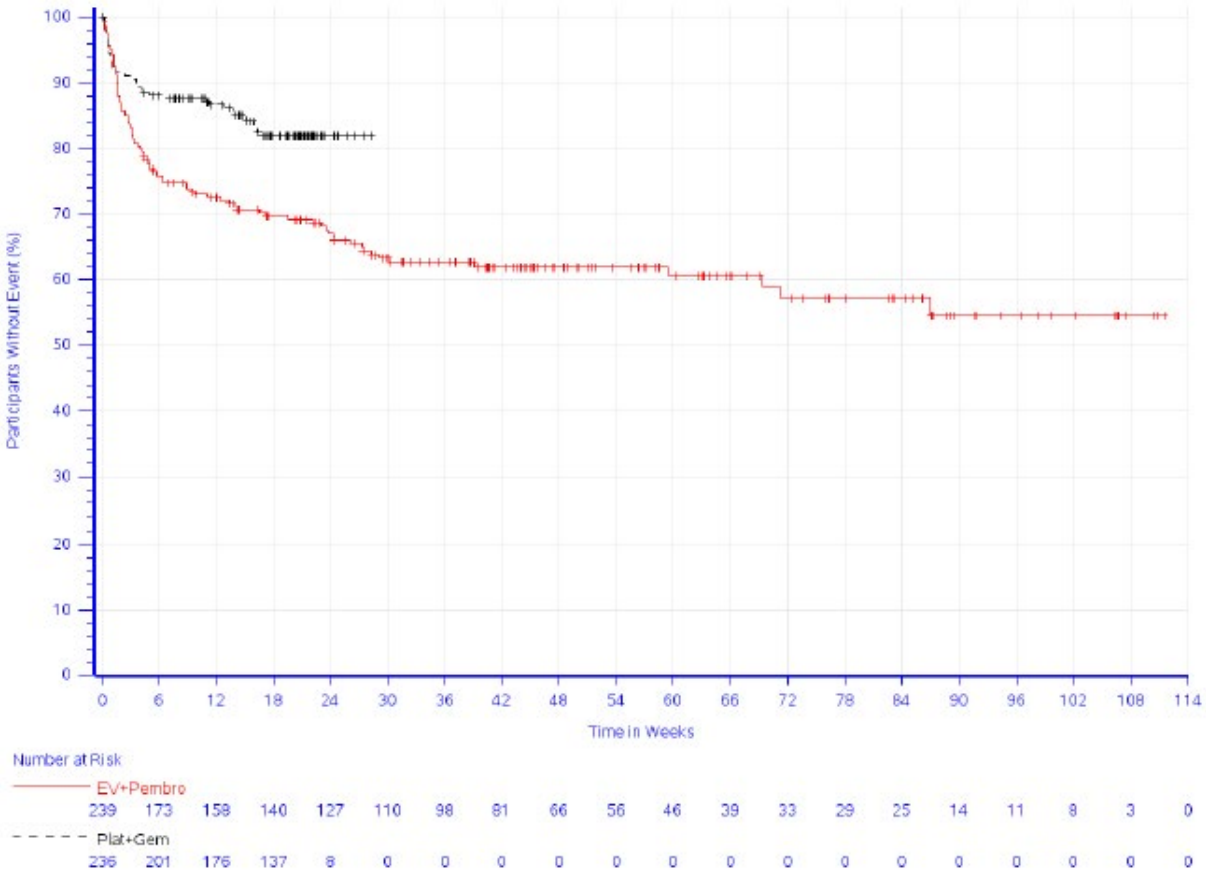

Figure 28: Kaplan-Meier curves for the outcome of diarrhoea (AEs) of the RCT EV-302/KN-A39, 1st data cut-off (08 August 2023), subpopulation 1 (cisplatin suitable)

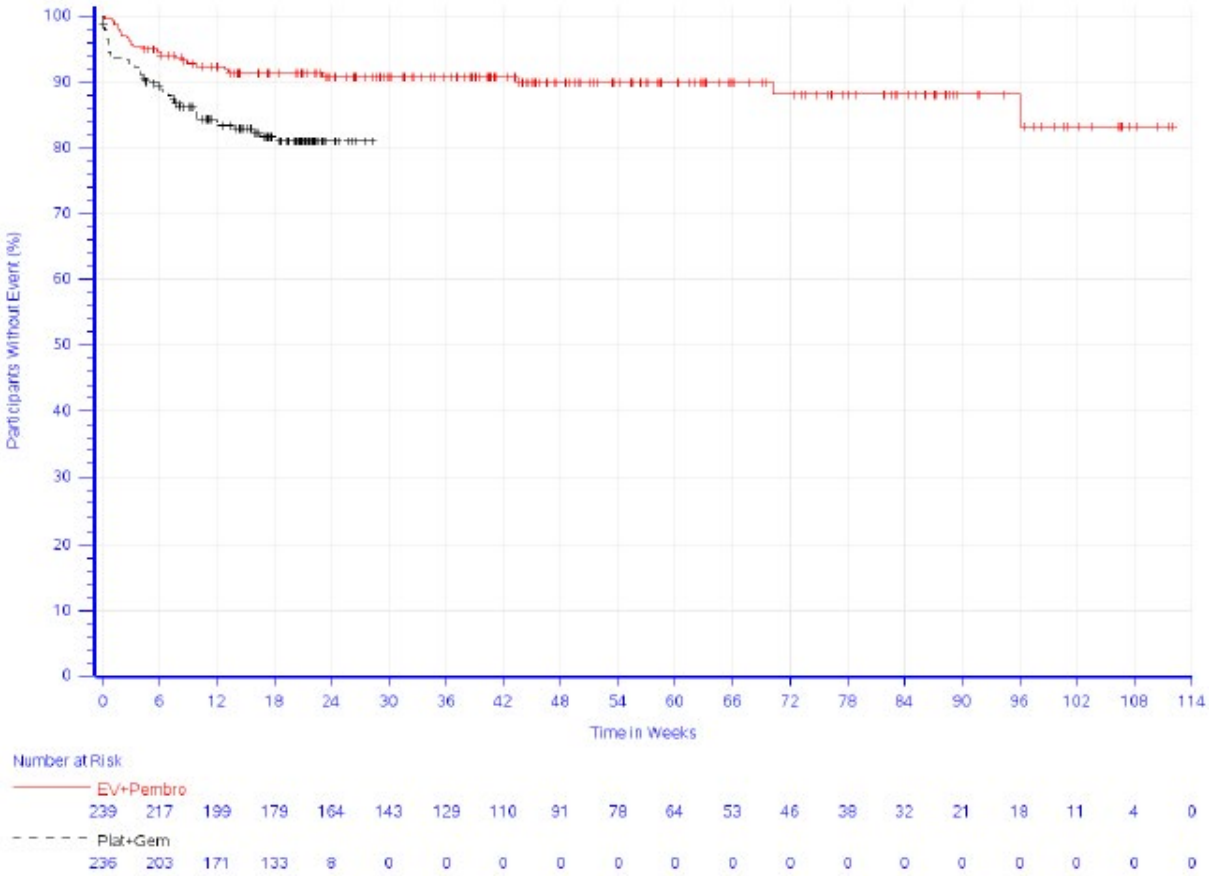

Figure 29: Kaplan-Meier curves for the outcome of vomiting (AEs) of the RCT EV-302/KN-A39, 1st data cut-off (08 August 2023), subpopulation 1 (cisplatin suitable)

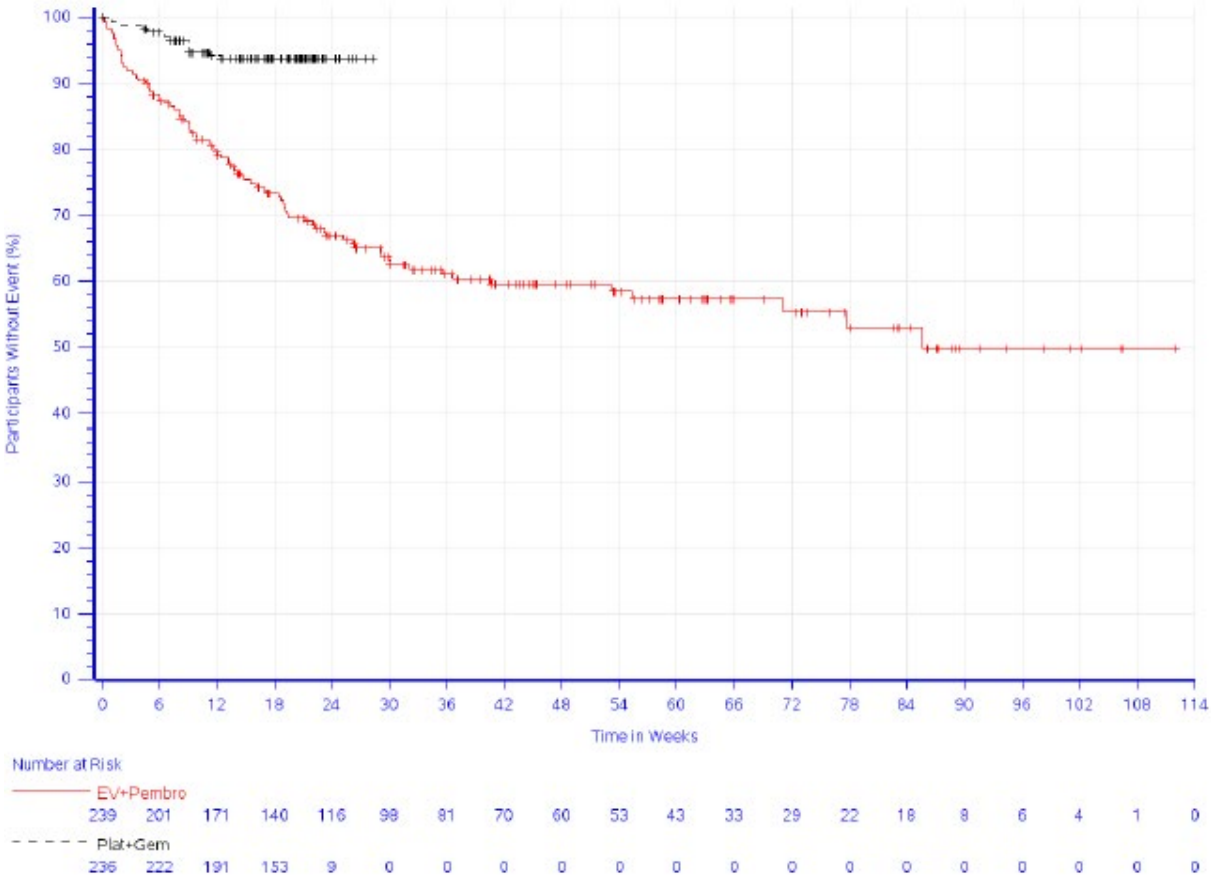

Figure 30: Kaplan-Meier curves for the outcome of eye disorders (AEs) of the RCT EV-302/KN-A39, 1st data cut-off (08 August 2023), subpopulation 1 (cisplatin suitable)

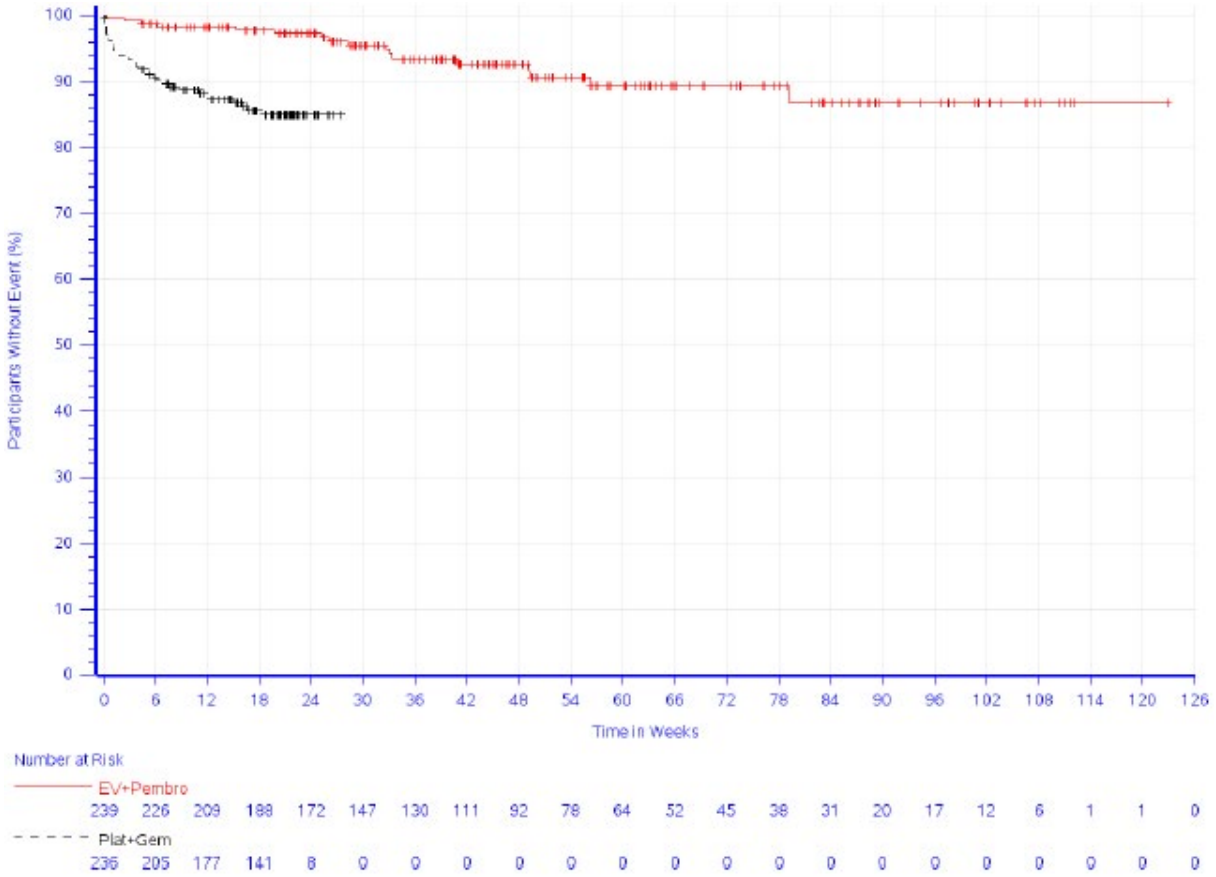

Figure 31: Kaplan-Meier curves for the outcome of ear and labyrinth disorders (AEs) of the RCT EV-302/KN-A39, 1st data cut-off (08 August 2023), subpopulation 1 (cisplatin suitable)

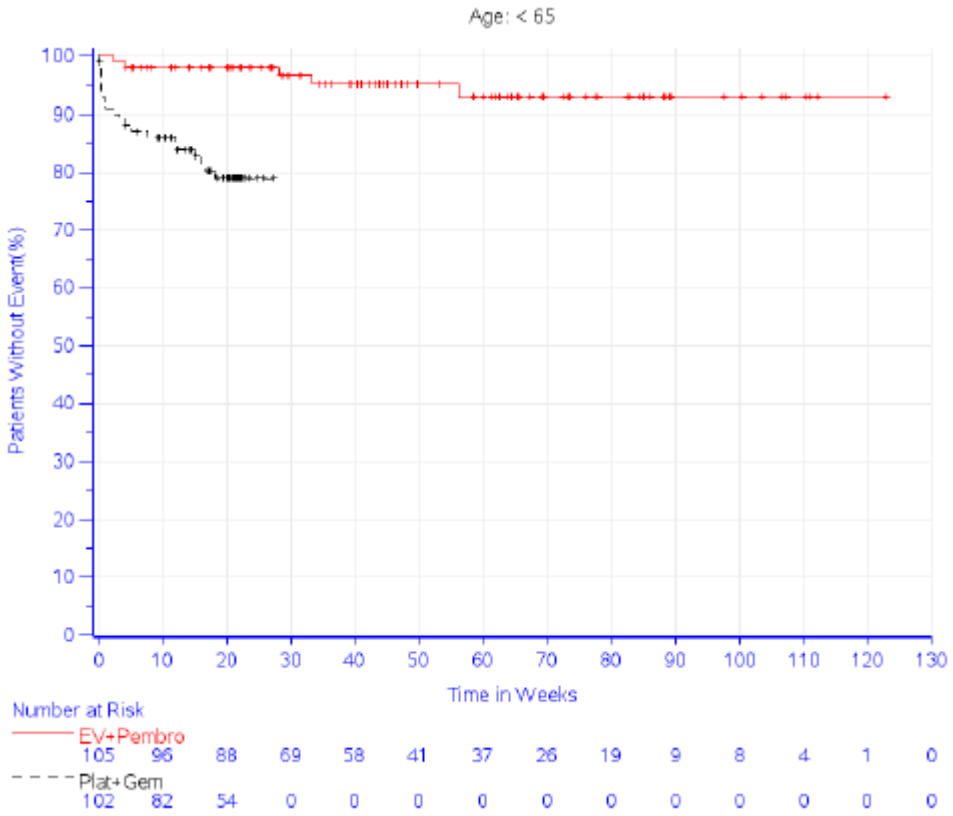

Figure 32: Kaplan-Meier curves for the outcome of ear and labyrinth disorders (AEs) of the RCT EV-302/KN-A39, 1st data cut-off (08 August 2023), subpopulation 1 (cisplatin suitable), subgroup: < 65 years

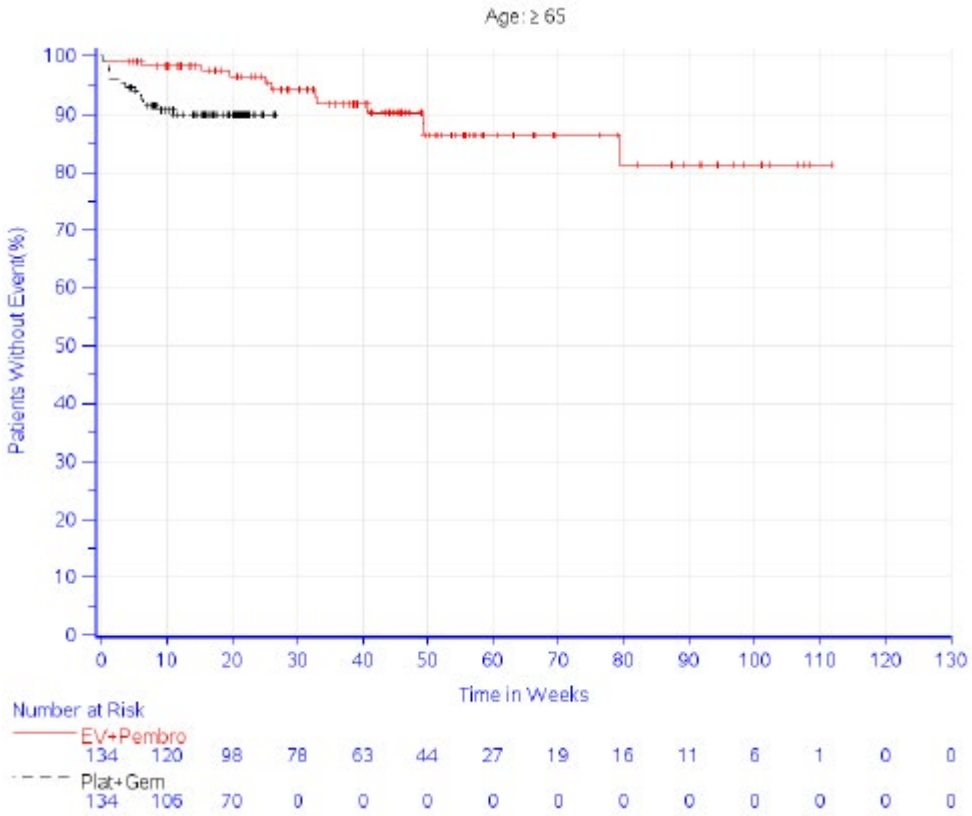

Figure 33: Kaplan-Meier curves for the outcome of ear and labyrinth disorders (AEs) of the RCT EV-302/KN-A39, 1st data cut-off (08 August 2023), subpopulation 1 (cisplatin suitable), subgroup: ≥ 65 years

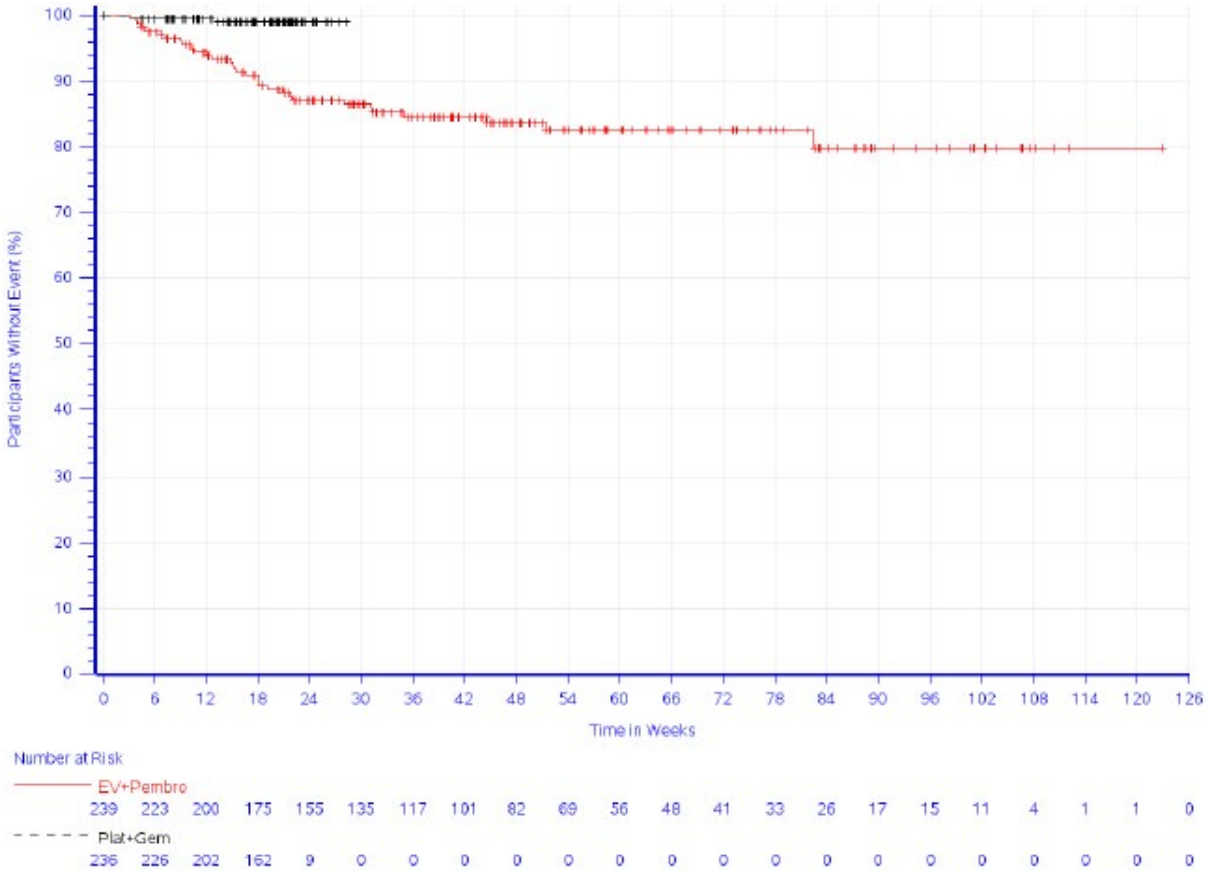

Figure 34: Kaplan-Meier curves for the outcome of endocrine disorders (AEs) of the RCT EV-302/KN-A39, 1st data cut-off (08 August 2023), subpopulation 1 (cisplatin suitable)

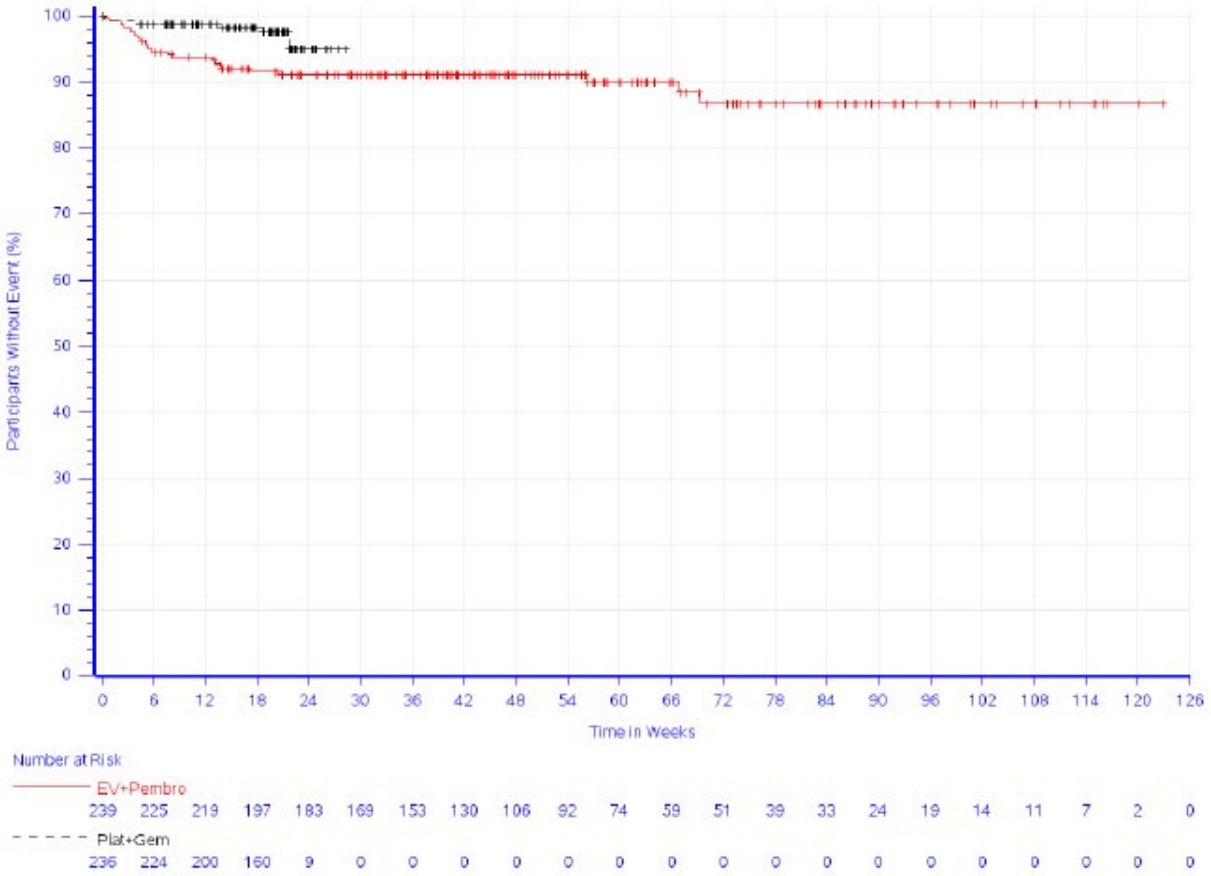

Figure 35: Kaplan-Meier curves for the outcome of gastrointestinal disorders (SAEs) of the RCT EV-302/KN-A39, 1st data cut-off (08 August 2023), subpopulation 1 (cisplatin suitable)

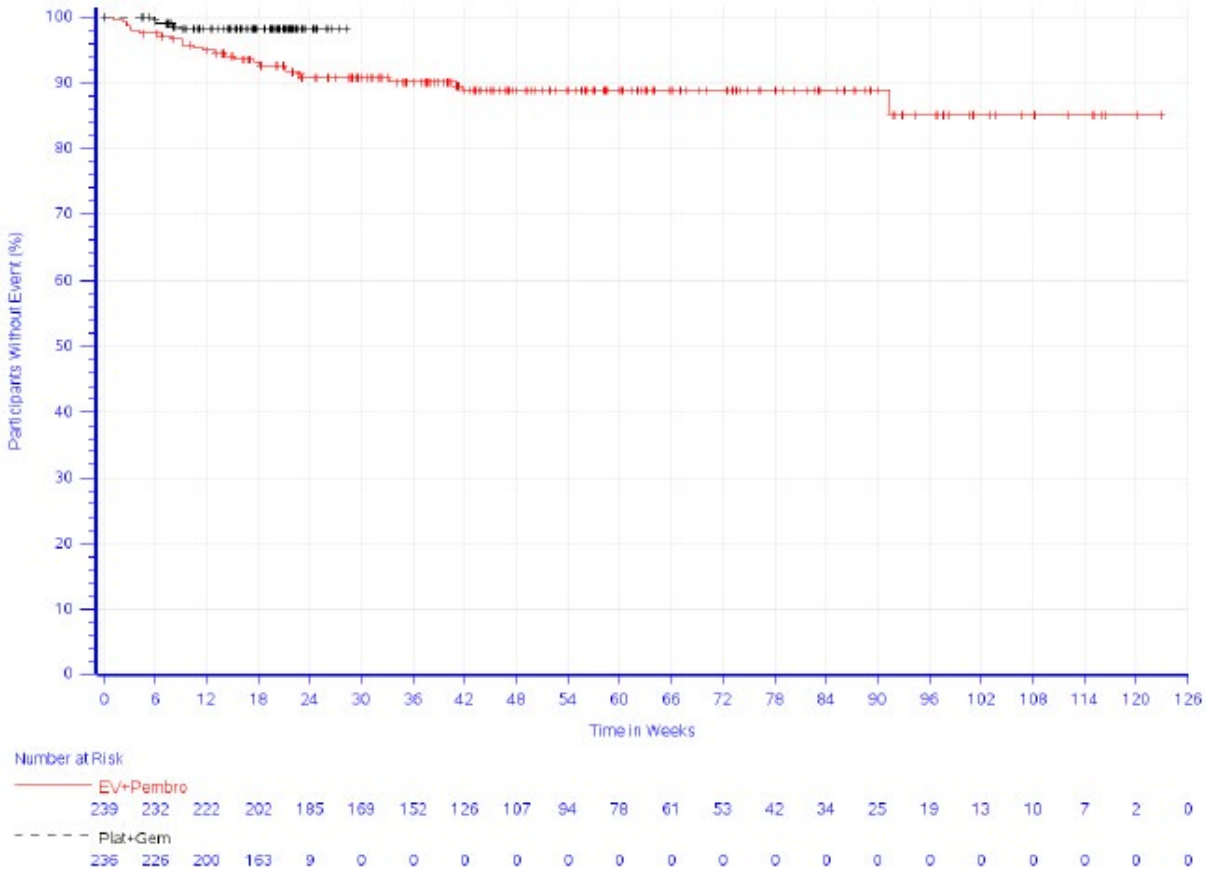

Figure 36: Kaplan-Meier curves for the outcome of respiratory, thoracic and mediastinal disorders (SAEs) of the RCT EV-302/KN-A39, 1st data cut-off (08 August 2023), subpopulation 1 (cisplatin suitable)

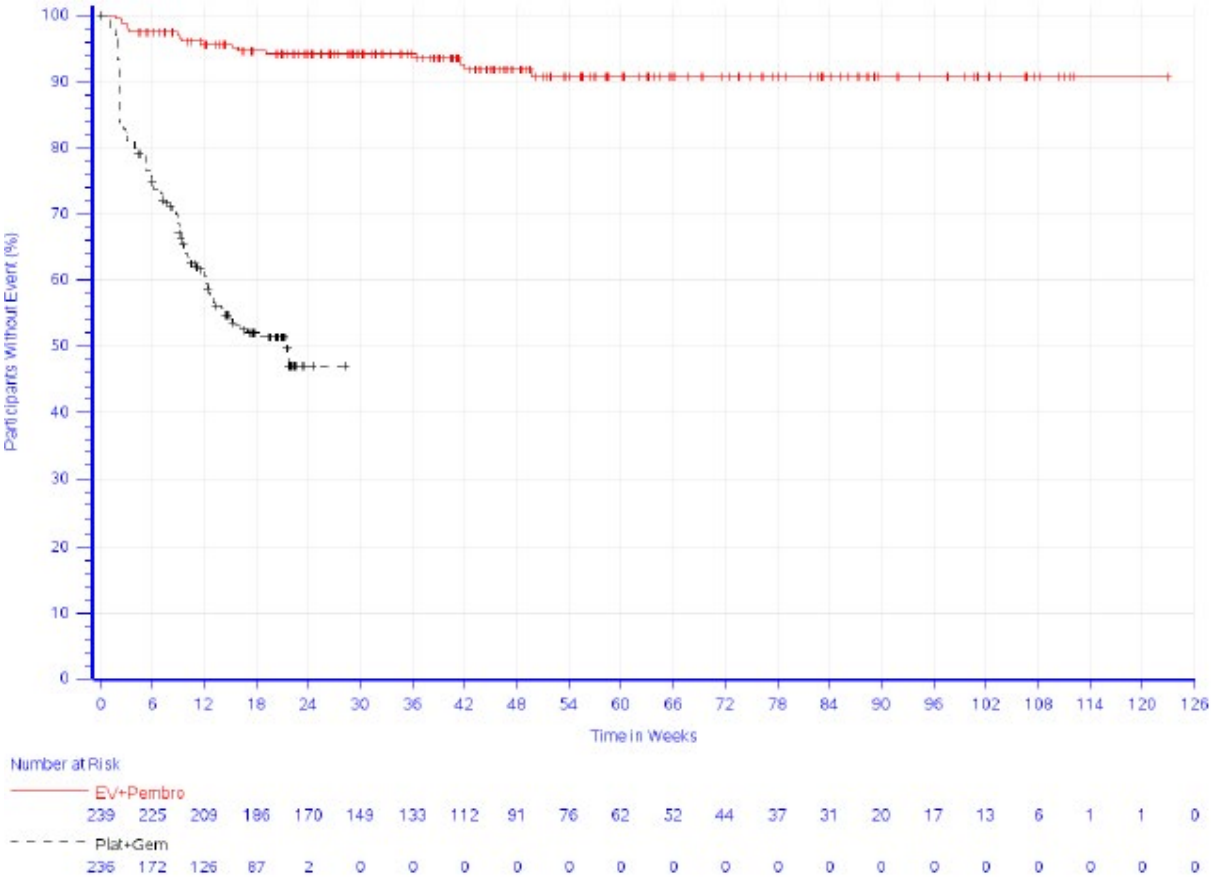

Figure 37: Kaplan-Meier curves for the outcome of blood and lymphatic system disorders (severe AEs) of the RCT EV-302/KN-A39, 1st data cut-off (08 August 2023), subpopulation 1 (cisplatin suitable)

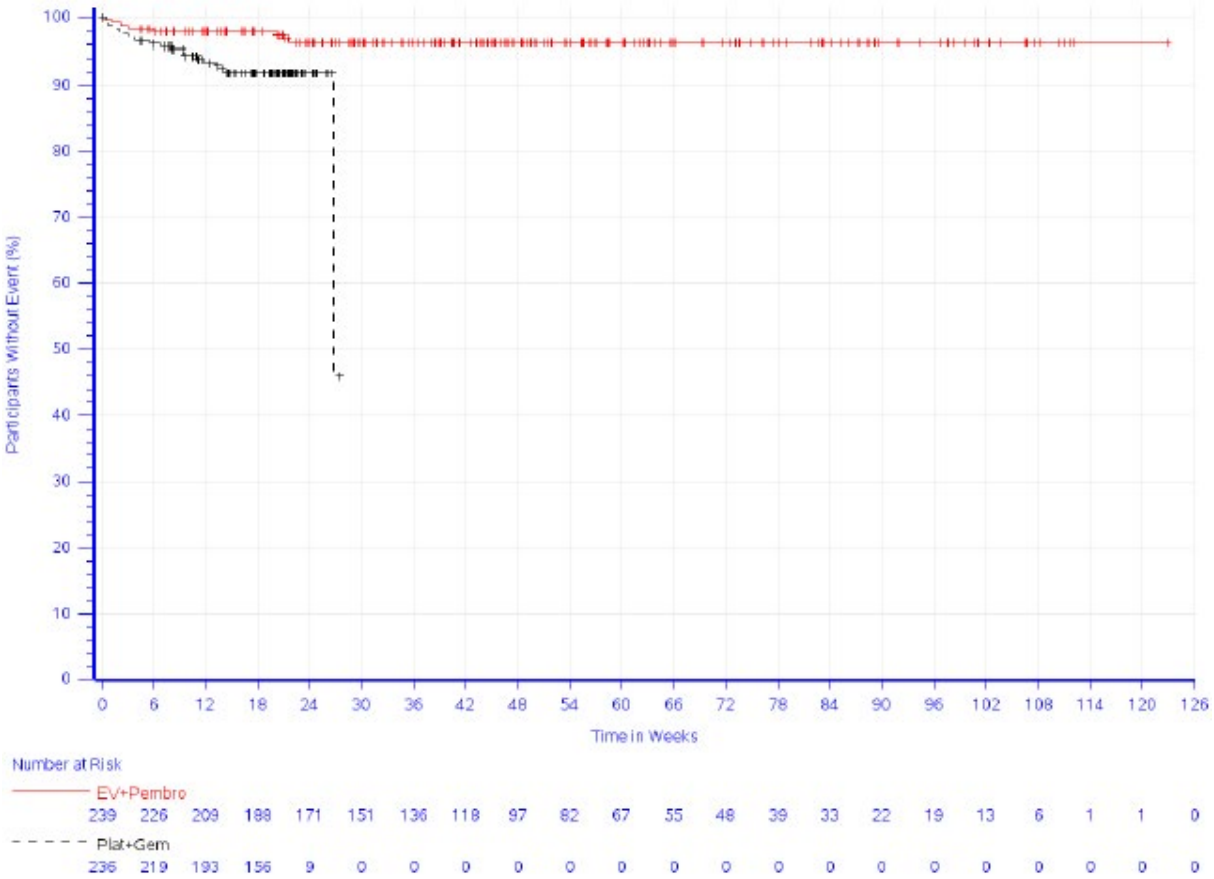

Figure 38: Kaplan-Meier curves for the outcome of urinary tract infection (severe AEs) of the RCT EV-302/KN-A39, 1st data cut-off (08 August 2023), subpopulation 1 (cisplatin suitable)

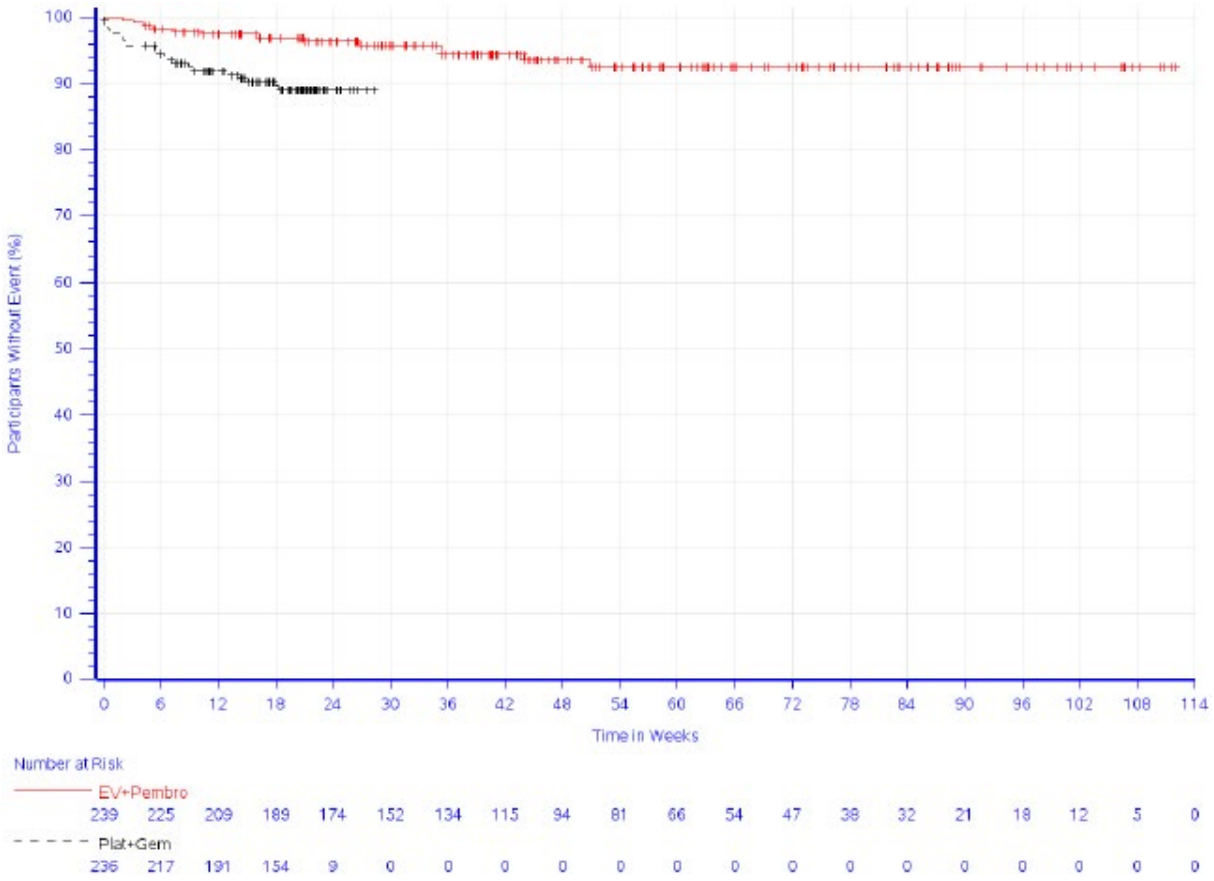

Figure 39: Kaplan-Meier curves for the outcome of general disorders and administration site conditions (severe AEs) of the RCT EV-302/KN-A39, 1st data cut-off (08 August 2023), subpopulation 1 (cisplatin suitable)

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

A.2.1 Mortality

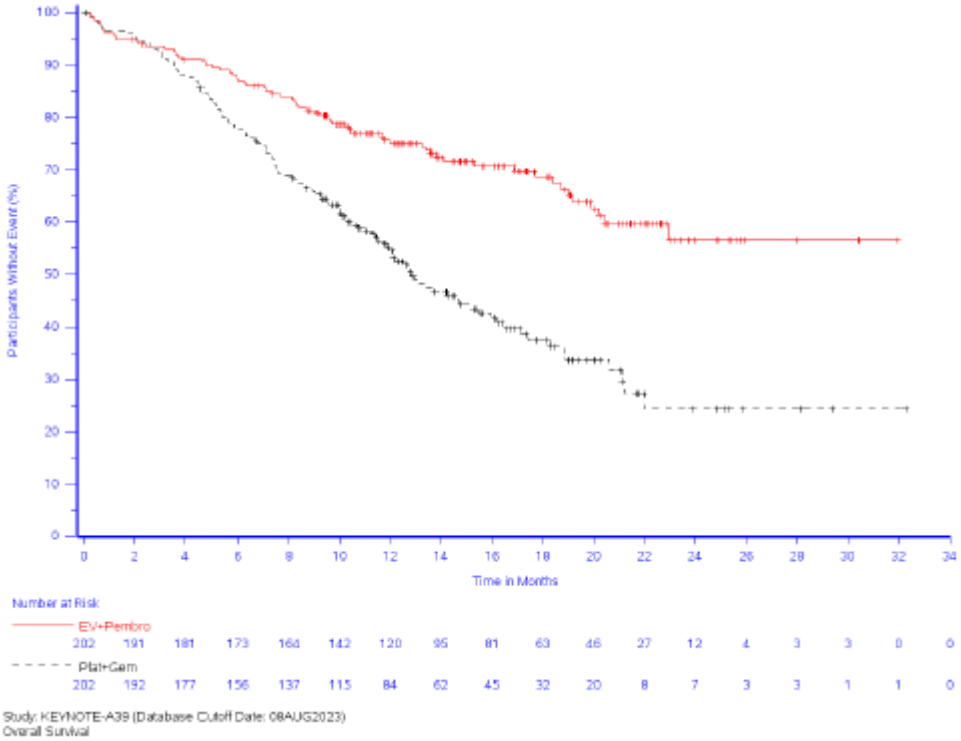

Figure 40: Kaplan-Meier curves for the outcome of overall survival of the RCT EV-302/KN-A39, 1st data cut-off (08 August 2023), subpopulation 2 (cisplatin unsuitable)

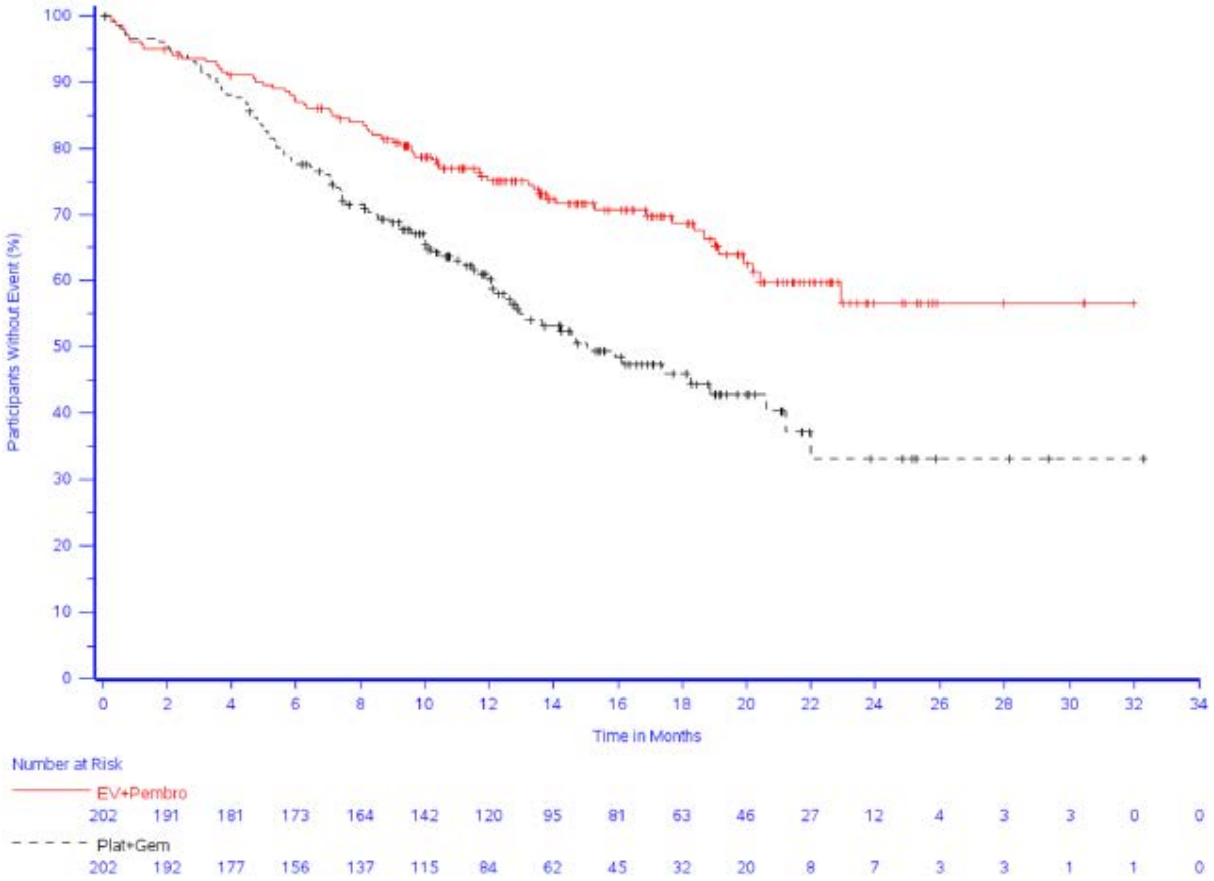

Figure 41: Kaplan-Meier curves for sensitivity analysis 1 of the company for the outcome of overall survival of the RCT EV-302/KN-A39, 1st data cut-off (8 August 2023), subpopulation 2 (cisplatin unsuitable)

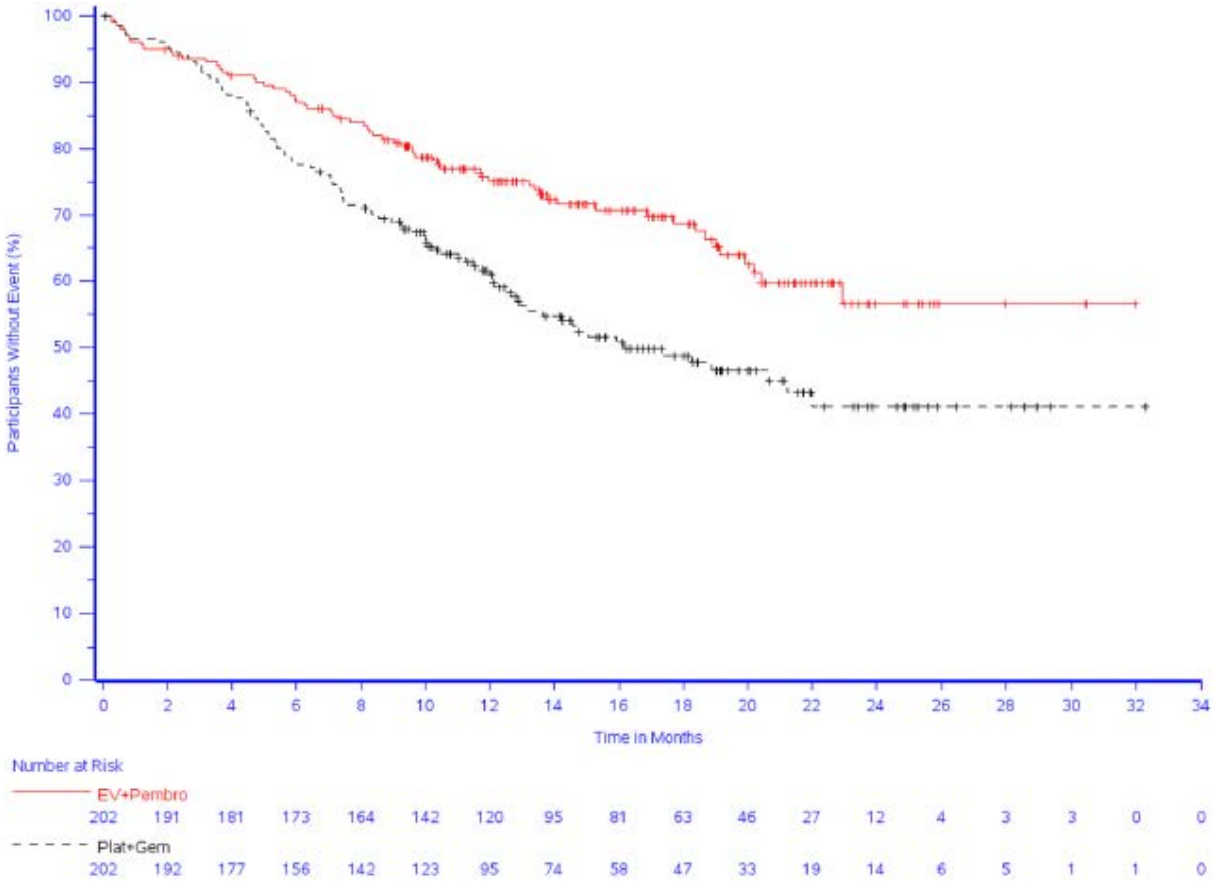

Figure 42: Kaplan-Meier curves for sensitivity analysis 2 of the company for the outcome of overall survival of the RCT EV-302/KN-A39, 1st data cut-off (8 August 2023), subpopulation 2 (cisplatin unsuitable)

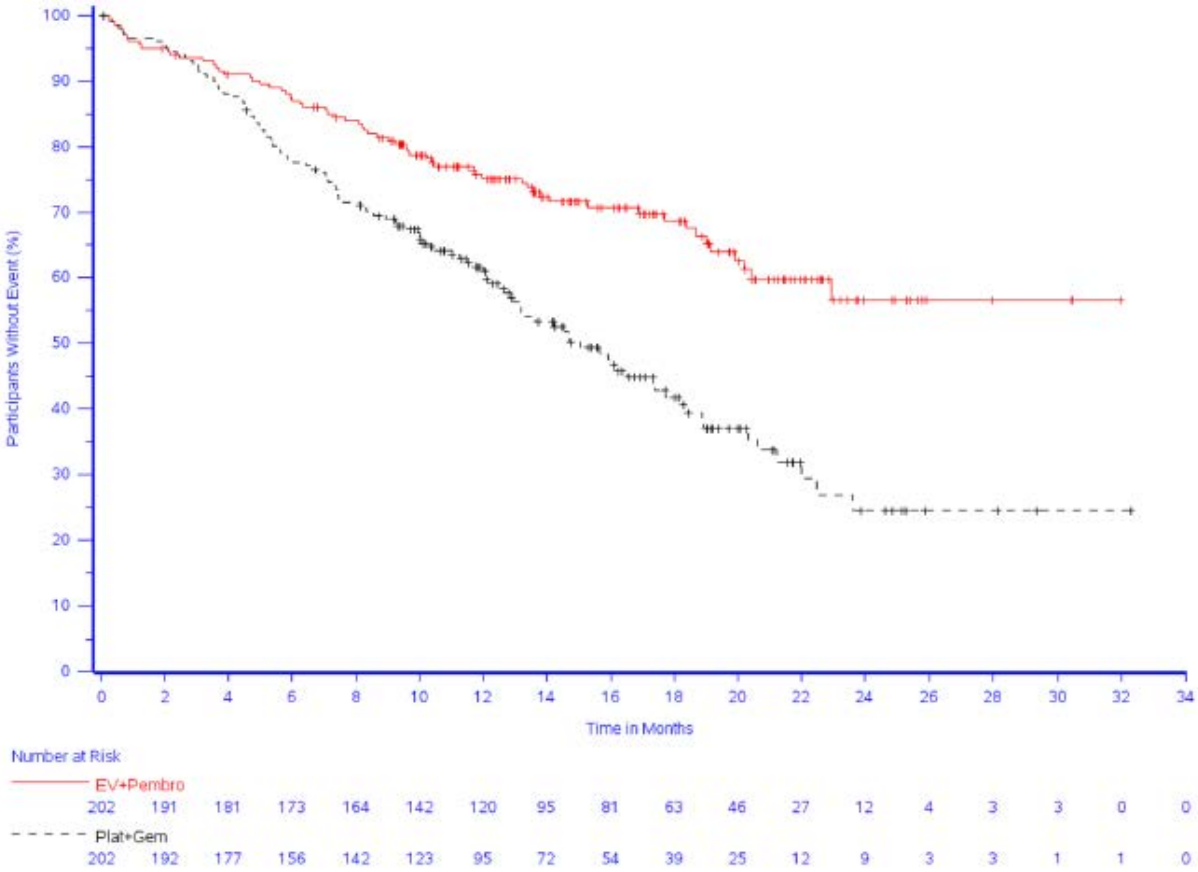

Figure 43: Kaplan-Meier curves for sensitivity analysis 3 of the company for the outcome of overall survival of the RCT EV-302/KN-A39, 1st data cut-off (8 August 2023), subpopulation 2 (cisplatin unsuitable)

A.2.2 Morbidity

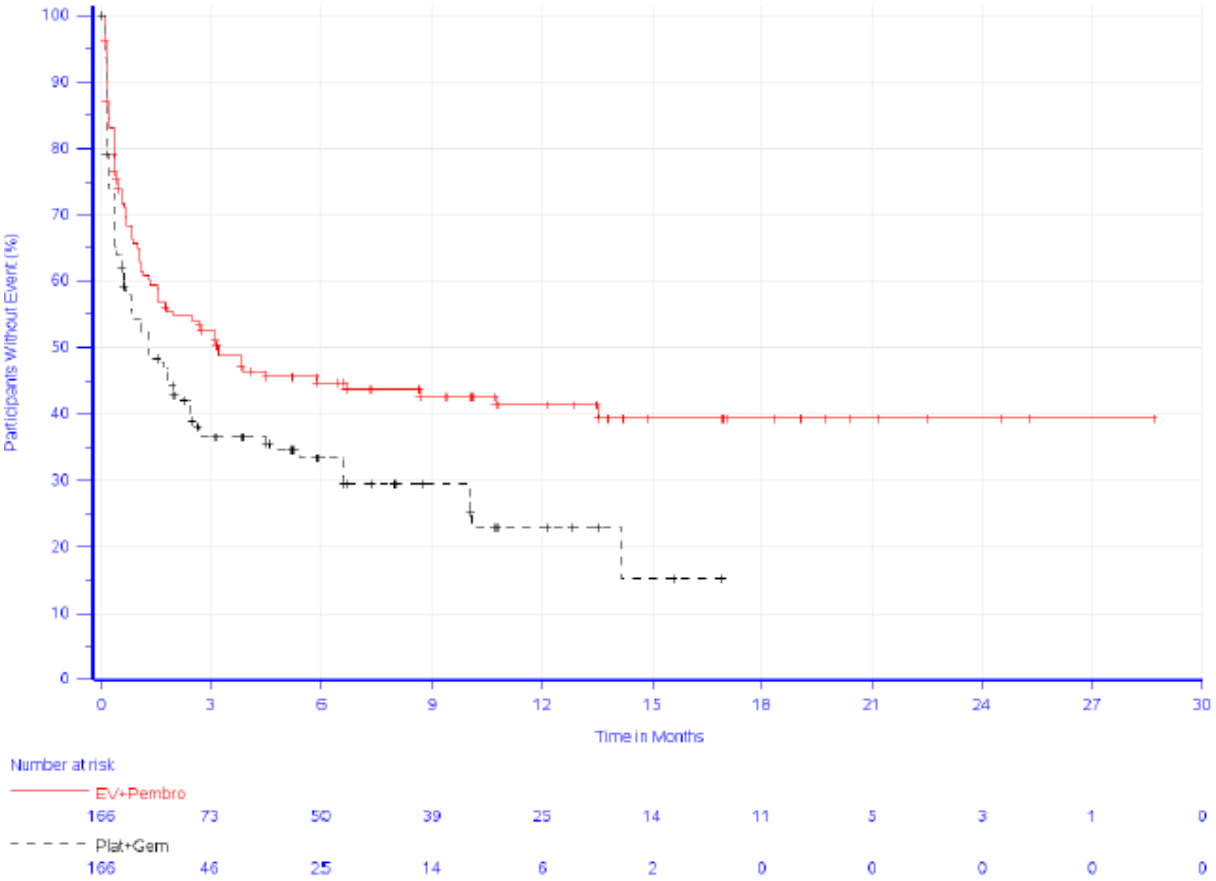

Figure 44: Kaplan-Meier curves for the outcome of worst pain (BPI-SF item 3 - time to 1st deterioration) of the RCT EV-302/KN-A39, 1st data cut-off (08 August 2023), subpopulation 2 (cisplatin unsuitable)

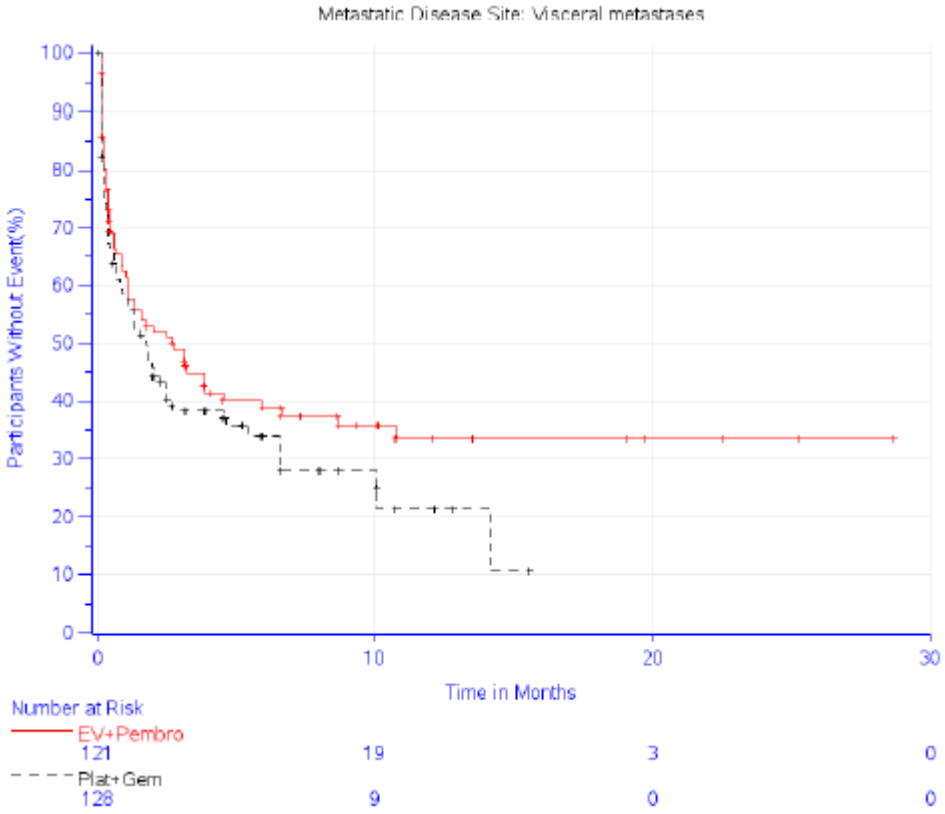

Figure 45: Kaplan-Meier curves for the outcome of worst pain (BPI-SF item 3 - time to 1st deterioration) of the RCT EV-302/KN-A39, 1st data cut-off (08 August 2023), subpopulation 2 (cisplatin unsuitable), subgroup: visceral metastases

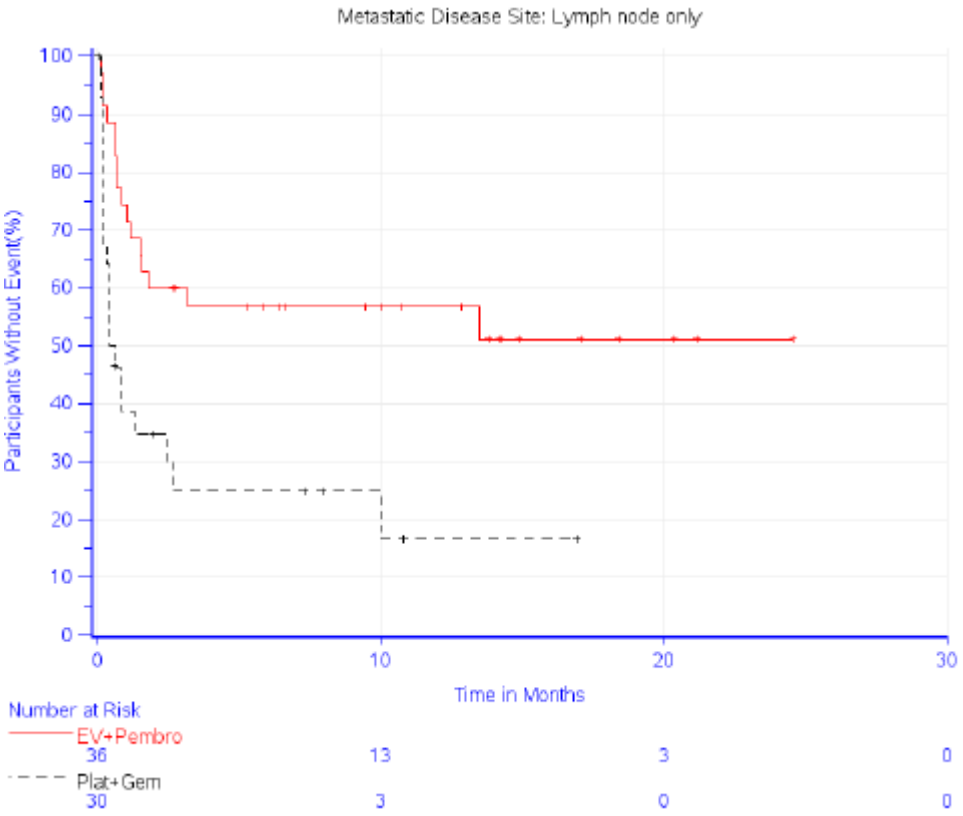

Figure 46: Kaplan-Meier curves for the outcome of worst pain (BPI-SF item 3 - time to 1st deterioration) of the RCT EV-302/KN-A39, 1st data cut-off (08 August 2023), subpopulation 2 (cisplatin unsuitable), subgroup: exclusively lymph node metastases

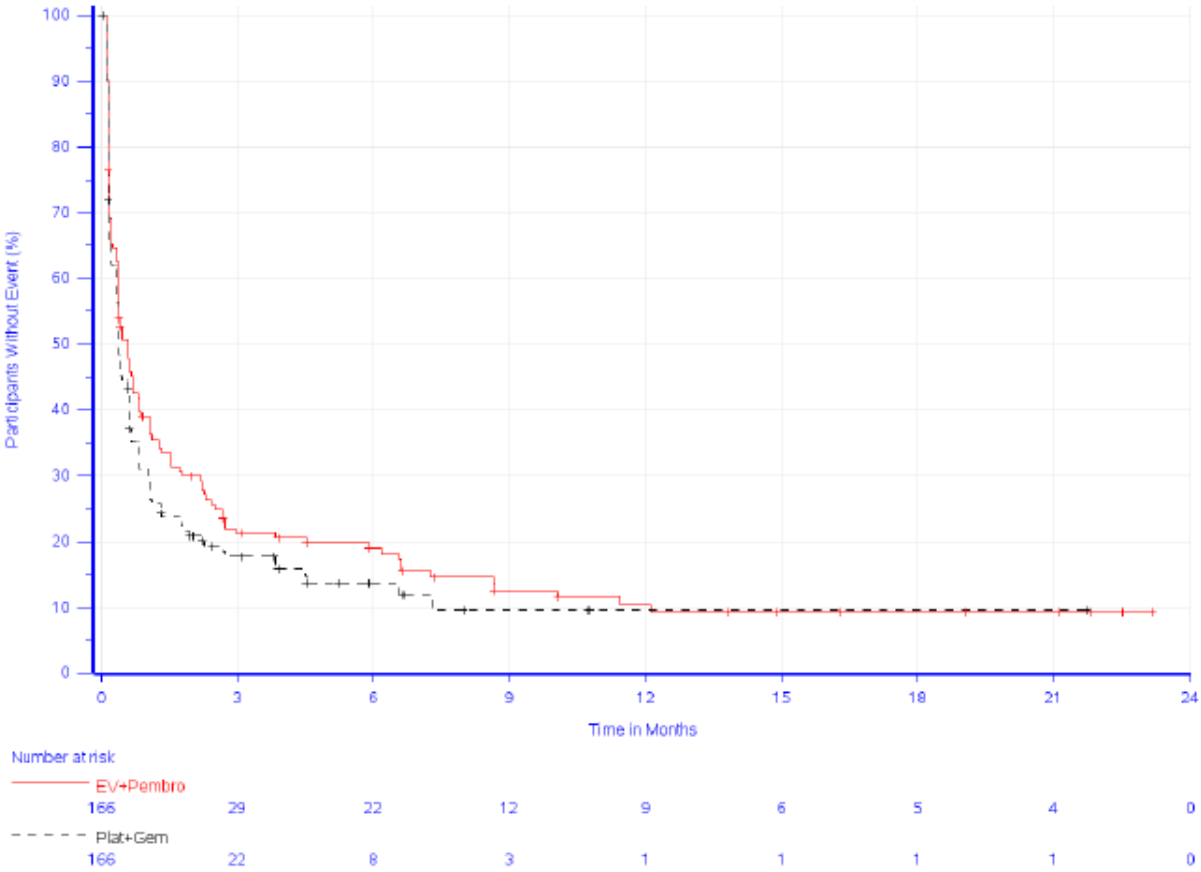

Figure 47: Kaplan-Meier curves for the outcome of fatigue (EORTC-QLQ-C30 - time to 1st deterioration) of the RCT EV-302/KN-A39, 1st data cut-off (08 August 2023), subpopulation 2 (cisplatin unsuitable)

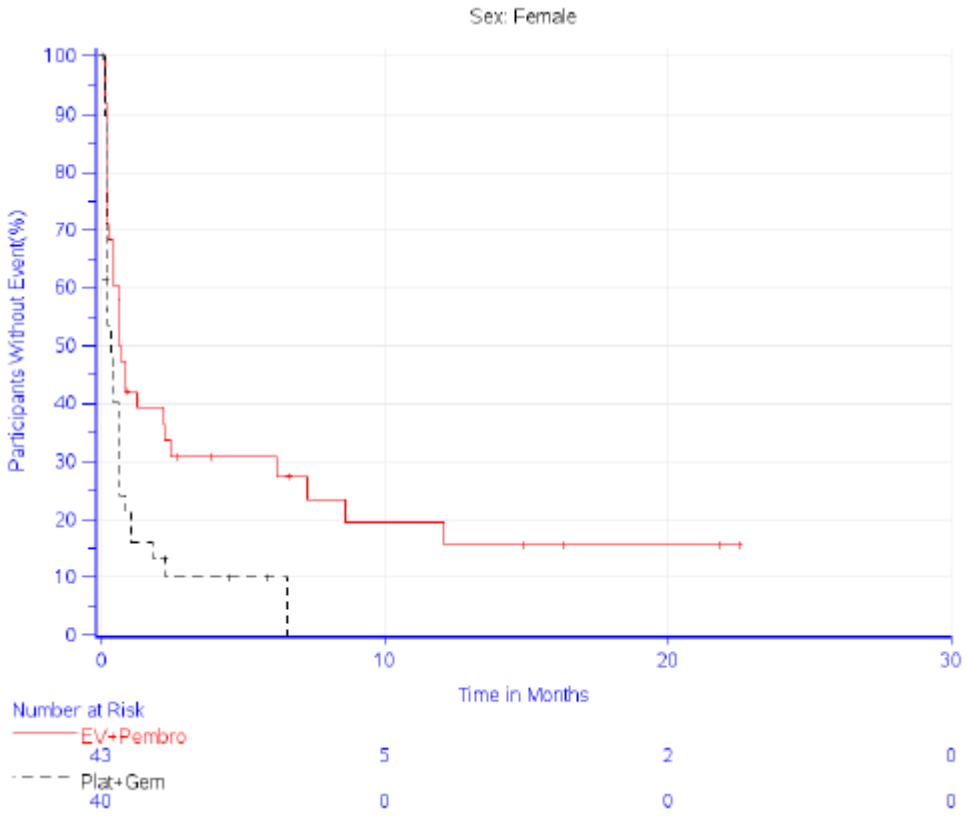

Figure 48: Kaplan-Meier curves for the outcome of fatigue (EORTC-QLQ-C30 - time to 1st deterioration) of the RCT EV-302/KN-A39, 1st data cut-off (08 August 2023), subpopulation 2 (cisplatin unsuitable), subgroup: women

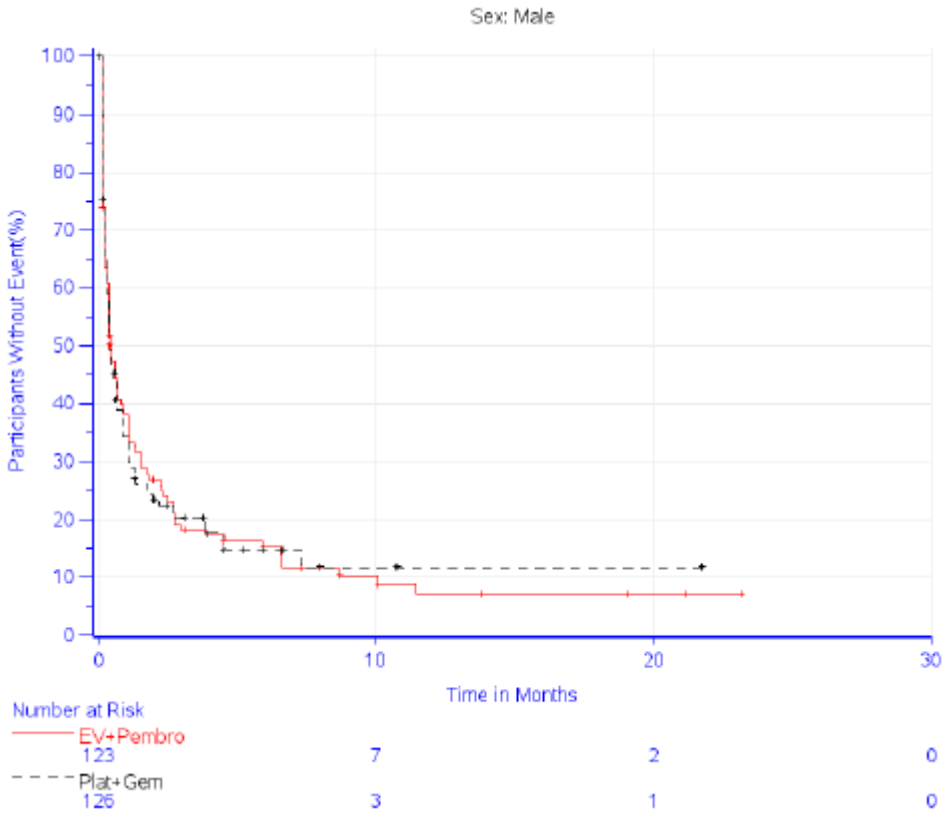

Figure 49: Kaplan-Meier curves for the outcome of fatigue (EORTC-QLQ-C30 - time to 1st deterioration) of the RCT EV-302/KN-A39, 1st data cut-off (08 August 2023), subpopulation 2 (cisplatin unsuitable), subgroup: men

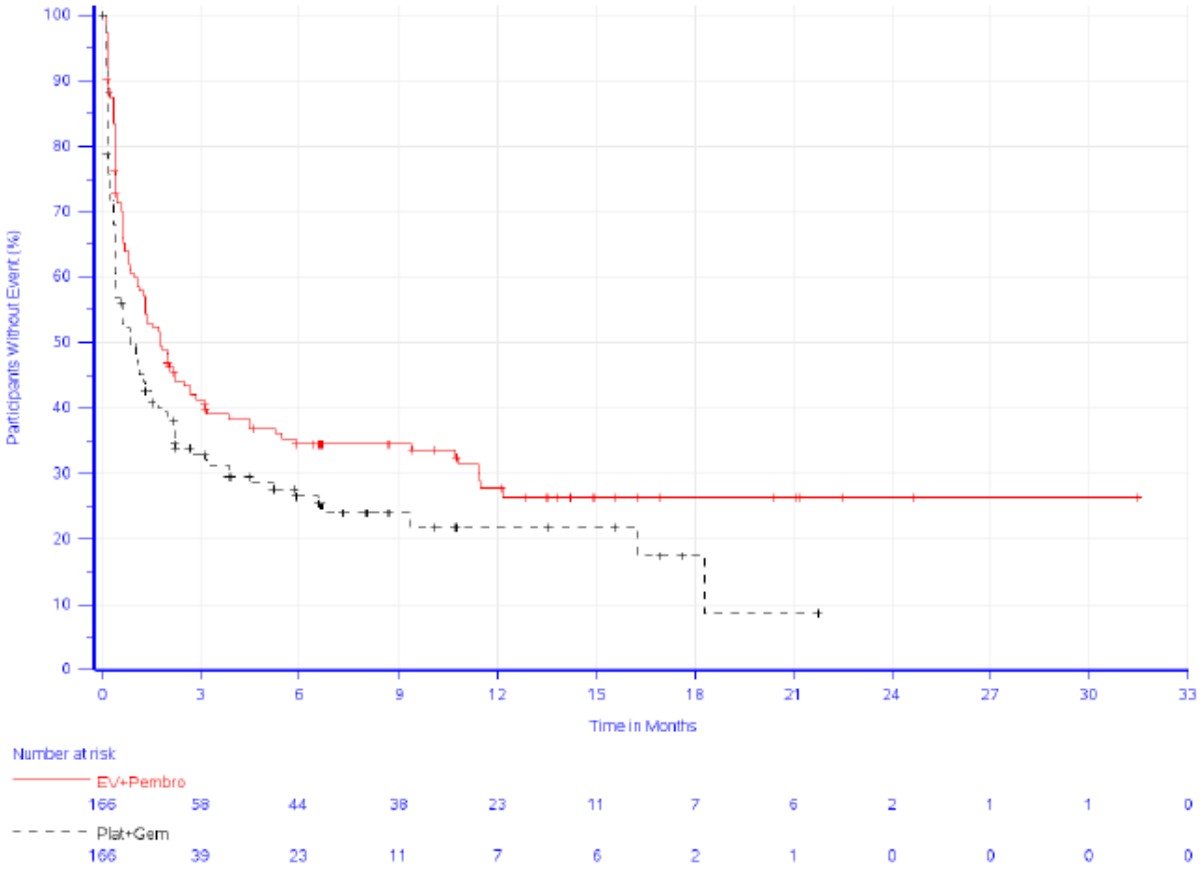

Figure 50: Kaplan-Meier curves for the outcome of nausea and vomiting (EORTC QLQ-C30 - time to 1st deterioration) of the RCT EV-302/KN-A39, 1st data cut-off (08 August 2023), subpopulation 2 (cisplatin unsuitable)

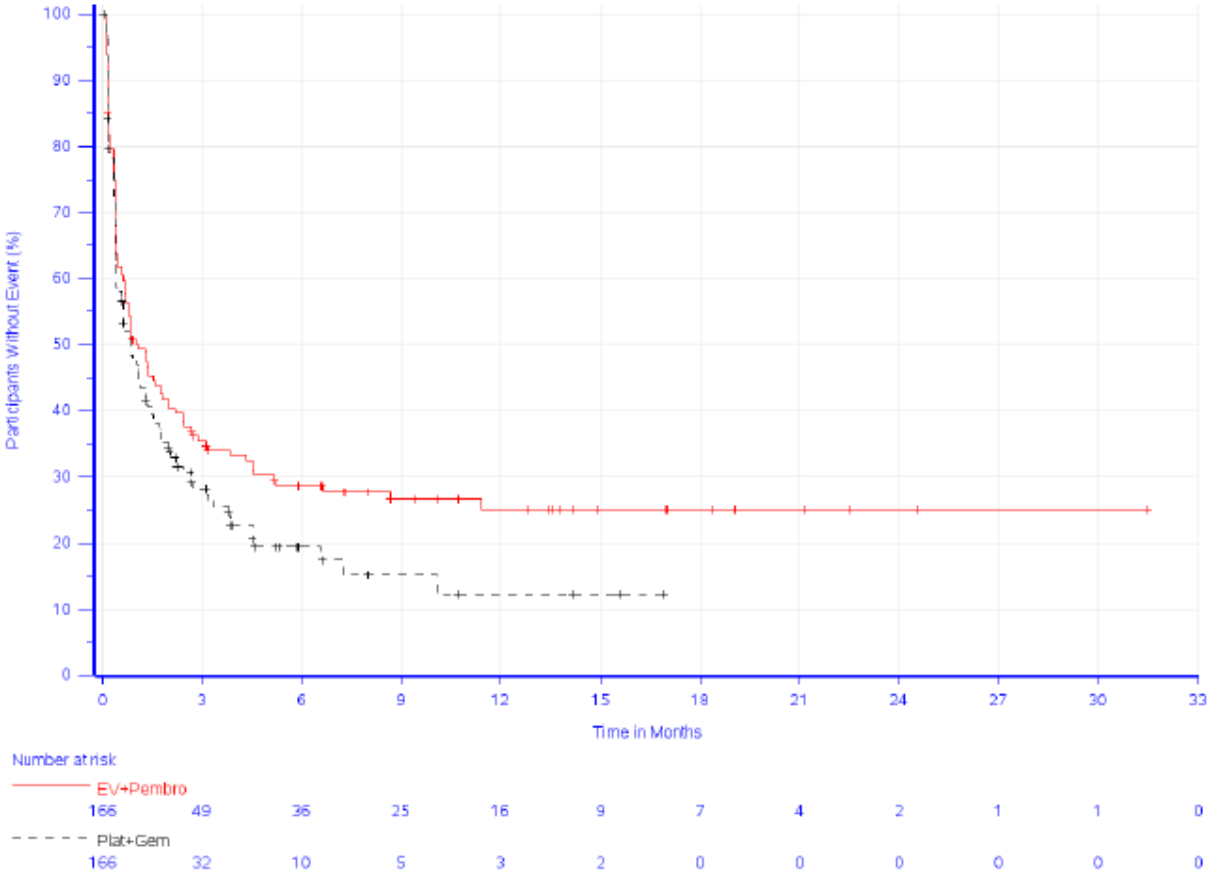

Figure 51: Kaplan-Meier curves for the outcome of pain (EORTC-QLQ-C30 - time to 1st deterioration) of the RCT EV-302/KN-A39, 1st data cut-off (08 August 2023), subpopulation 2 (cisplatin unsuitable)

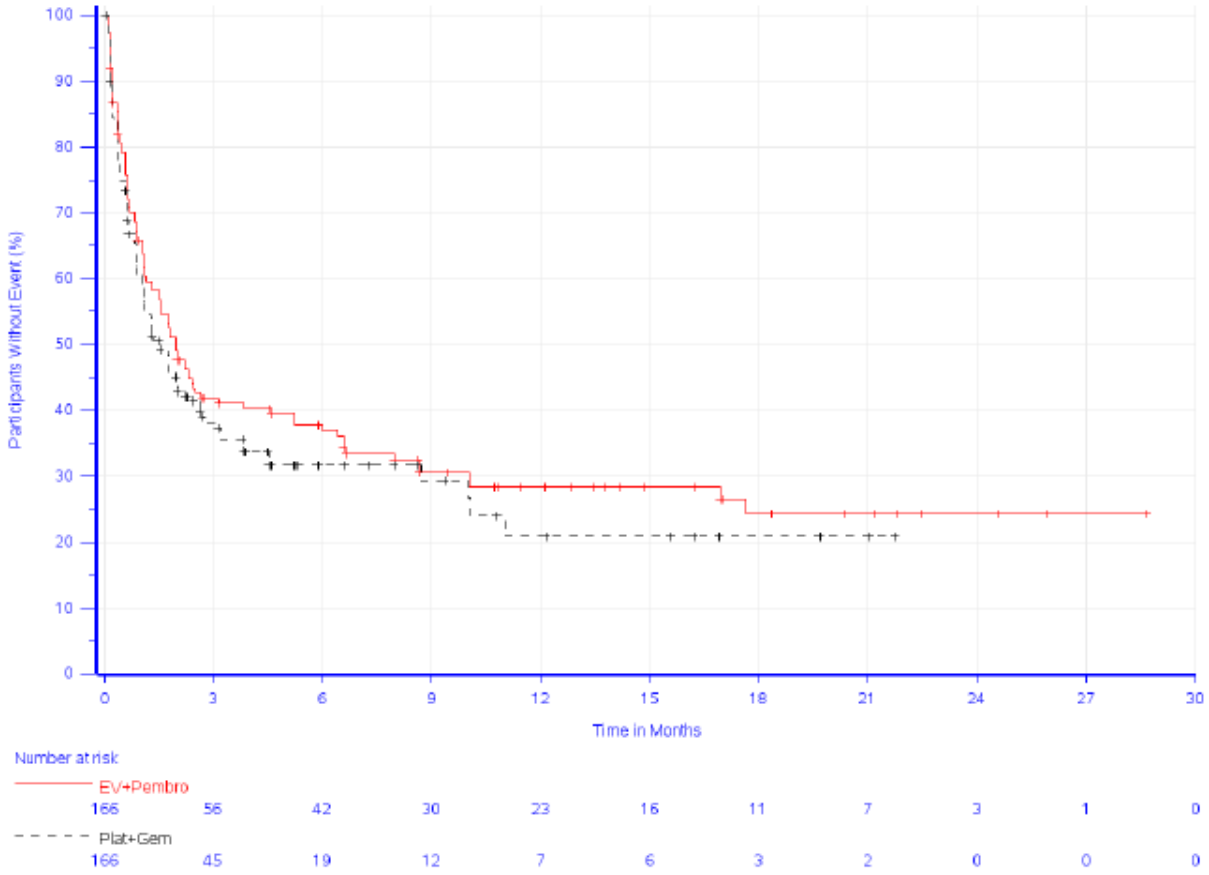

Figure 52: Kaplan-Meier curves for the outcome of dyspnoea (EORTC-QLQ-C30 - time to 1st deterioration) of the RCT EV-302/KN-A39, 1st data cut-off (08 August 2023), subpopulation 2 (cisplatin unsuitable)

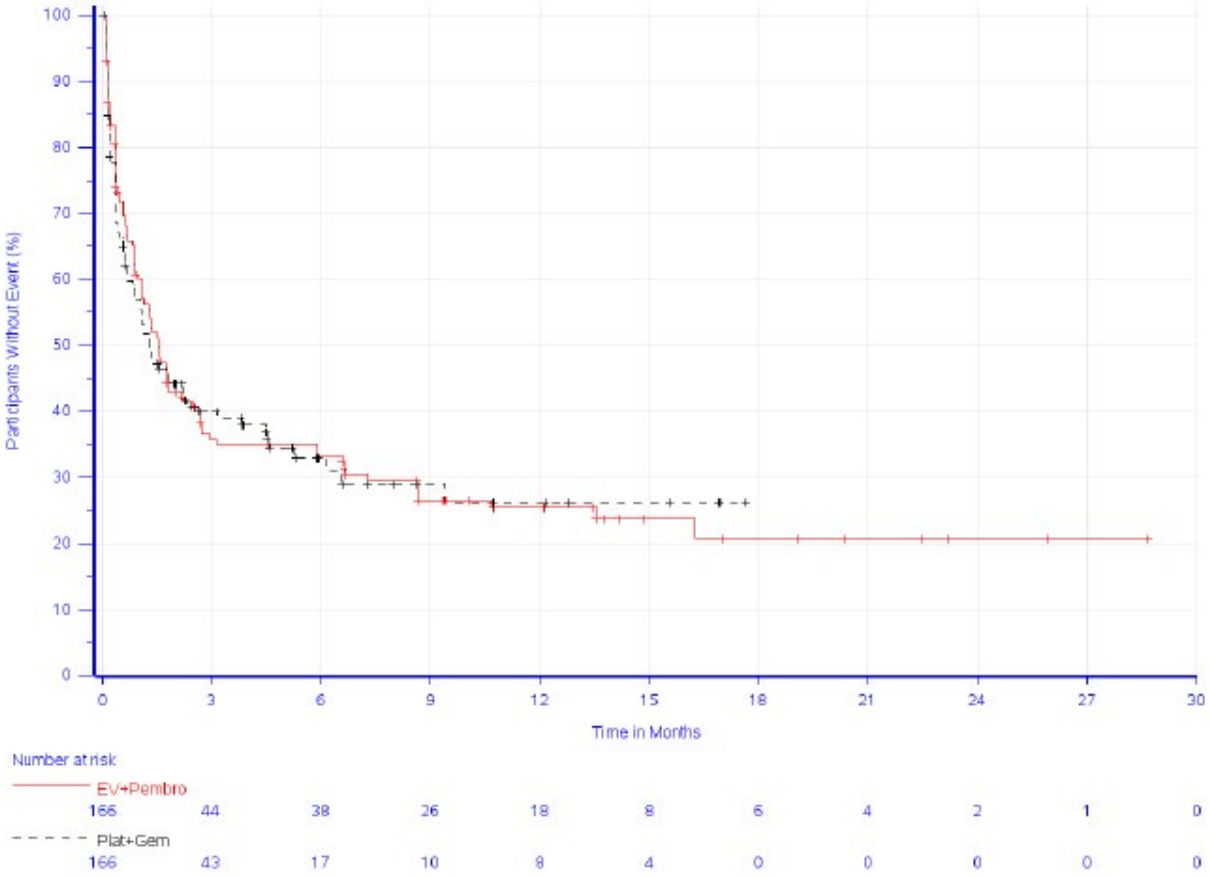

Figure 53: Kaplan-Meier curves for the outcome of insomnia (EORTC-QLQ-C30 - time to 1st deterioration) of the RCT EV-302/KN-A39, 1st data cut-off (08 August 2023), subpopulation 2 (cisplatin unsuitable)

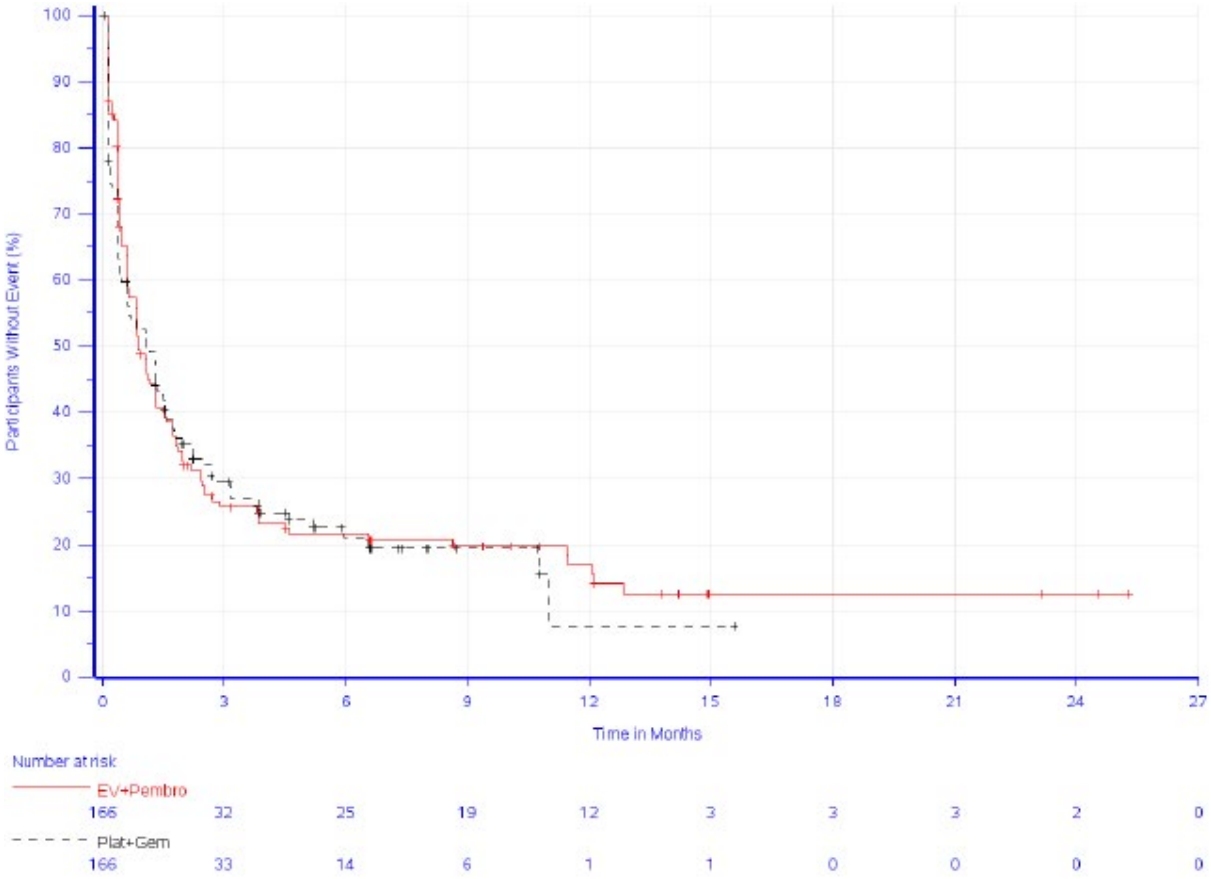

Figure 54: Kaplan-Meier curves for the outcome of appetite loss (EORTC-QLQ-C30 - time to 1st deterioration) of the RCT EV-302/KN-A39, 1st data cut-off (08 August 2023), subpopulation 2 (cisplatin unsuitable)

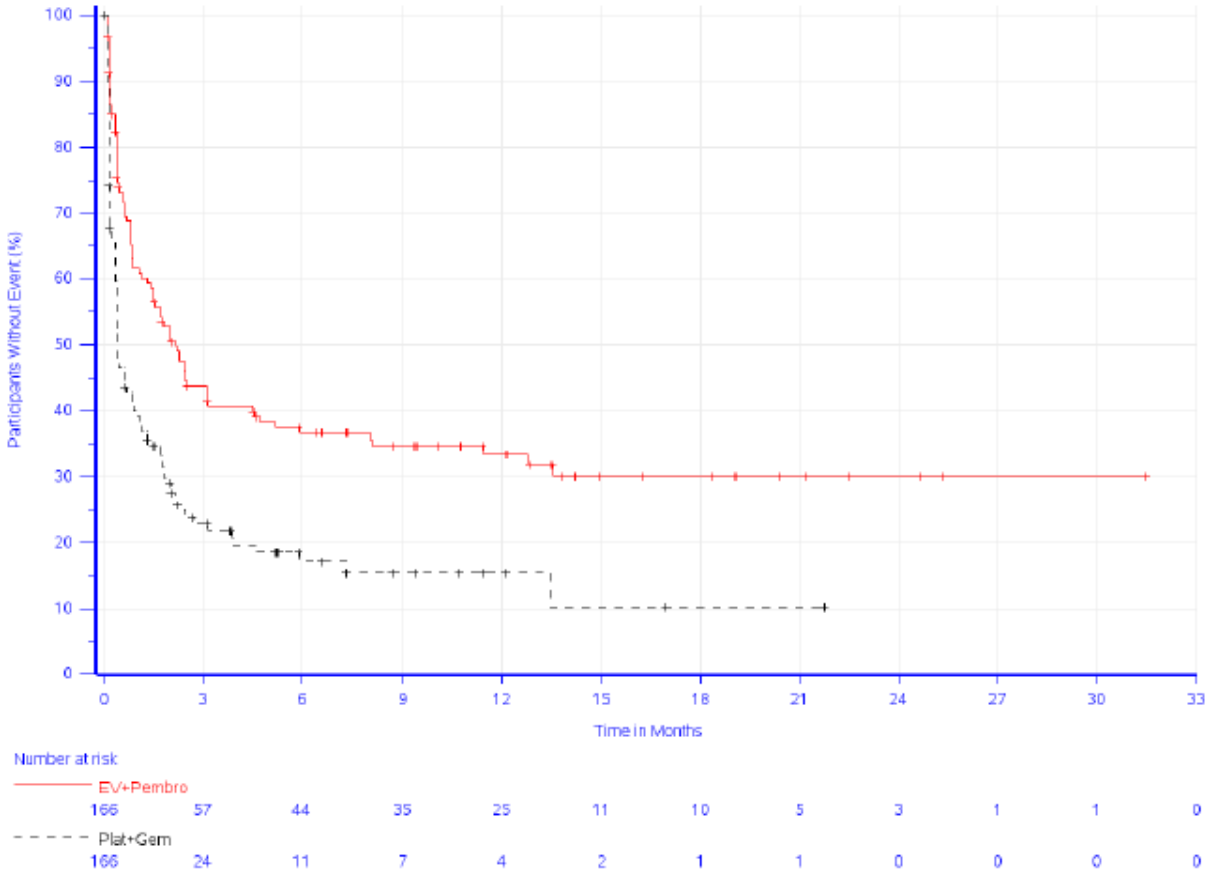

Figure 55: Kaplan-Meier curves for the outcome of constipation (EORTC-QLQ-C30 - time to 1st deterioration) of the RCT EV-302/KN-A39, 1st data cut-off (08 August 2023), subpopulation 2 (cisplatin unsuitable)

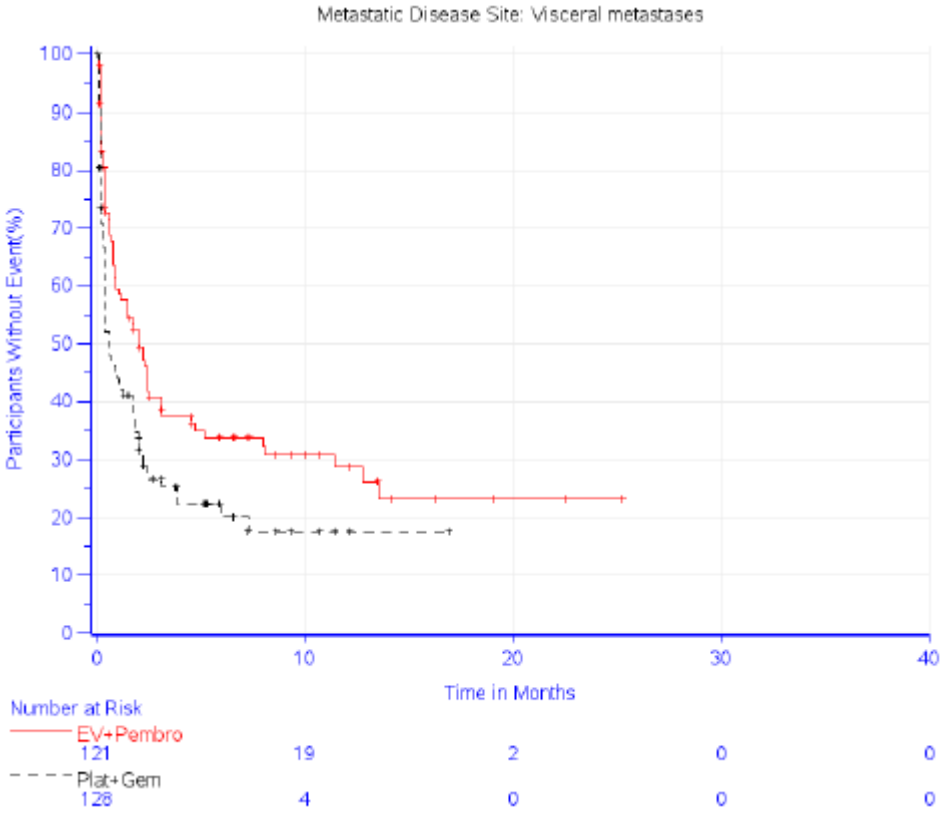

Figure 56: Kaplan-Meier curves for the outcome of constipation (EORTC-QLQ-C30 - time to 1st deterioration) of the RCT EV-302/KN-A39, 1st data cut-off (08 August 2023), subpopulation 2 (cisplatin unsuitable), subgroup: visceral metastases

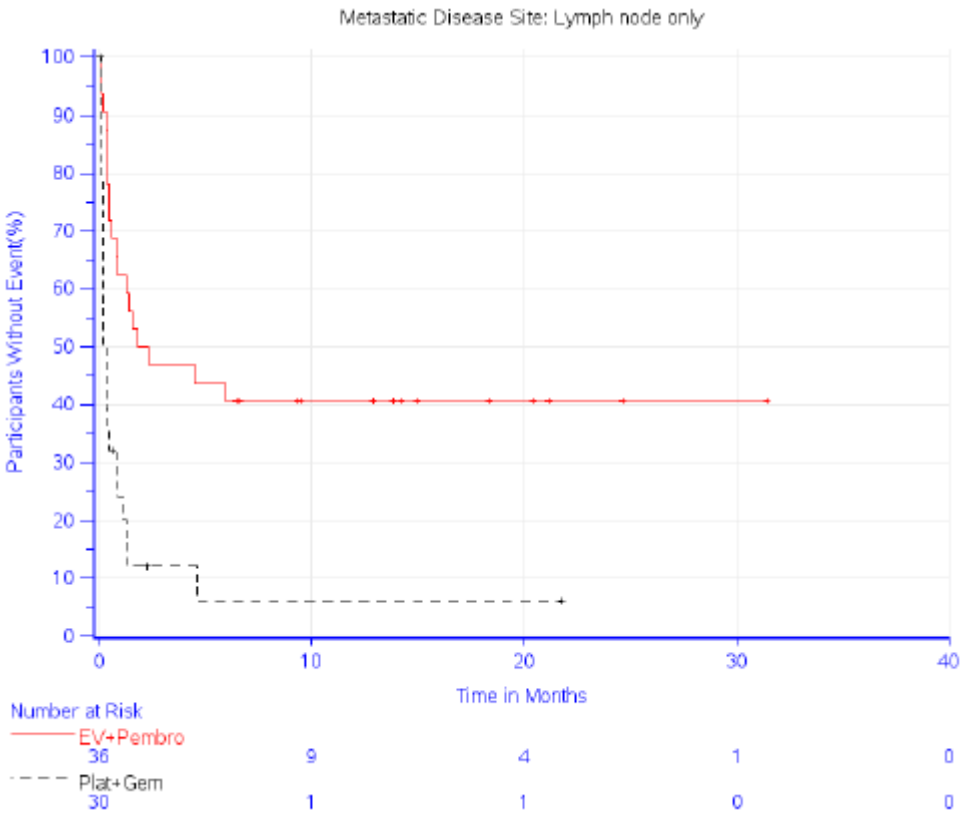

Figure 57: Kaplan-Meier curves for the outcome of constipation (EORTC-QLQ-C30 - time to 1st deterioration) of the RCT EV-302/KN-A39, 1st data cut-off (08 August 2023), subpopulation 2 (cisplatin unsuitable), subgroup: exclusively lymph node metastases

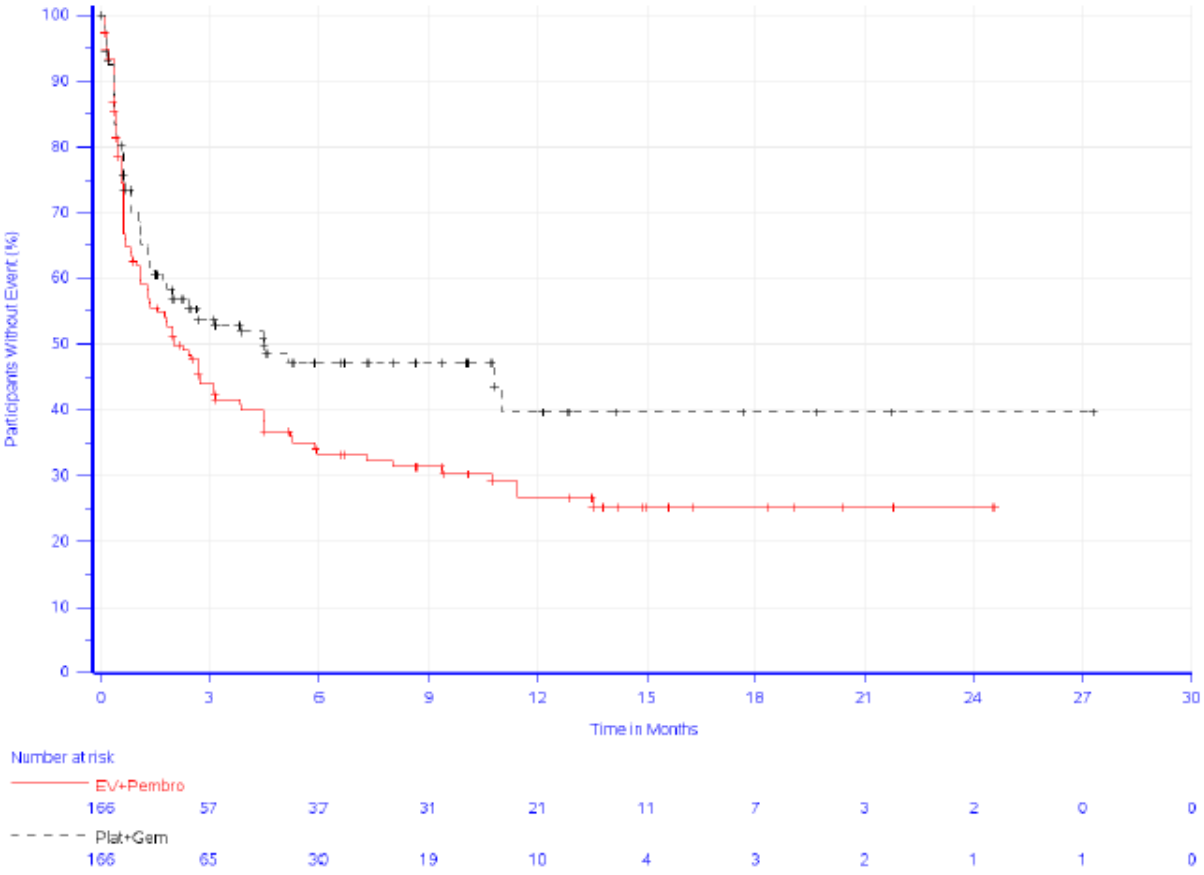

Figure 58: Kaplan-Meier curves for the outcome of diarrhoea (EORTC-QLQ-C30 - time to 1st deterioration) of the RCT EV-302/KN-A39, 1st data cut-off (08 August 2023), subpopulation 2 (cisplatin unsuitable)

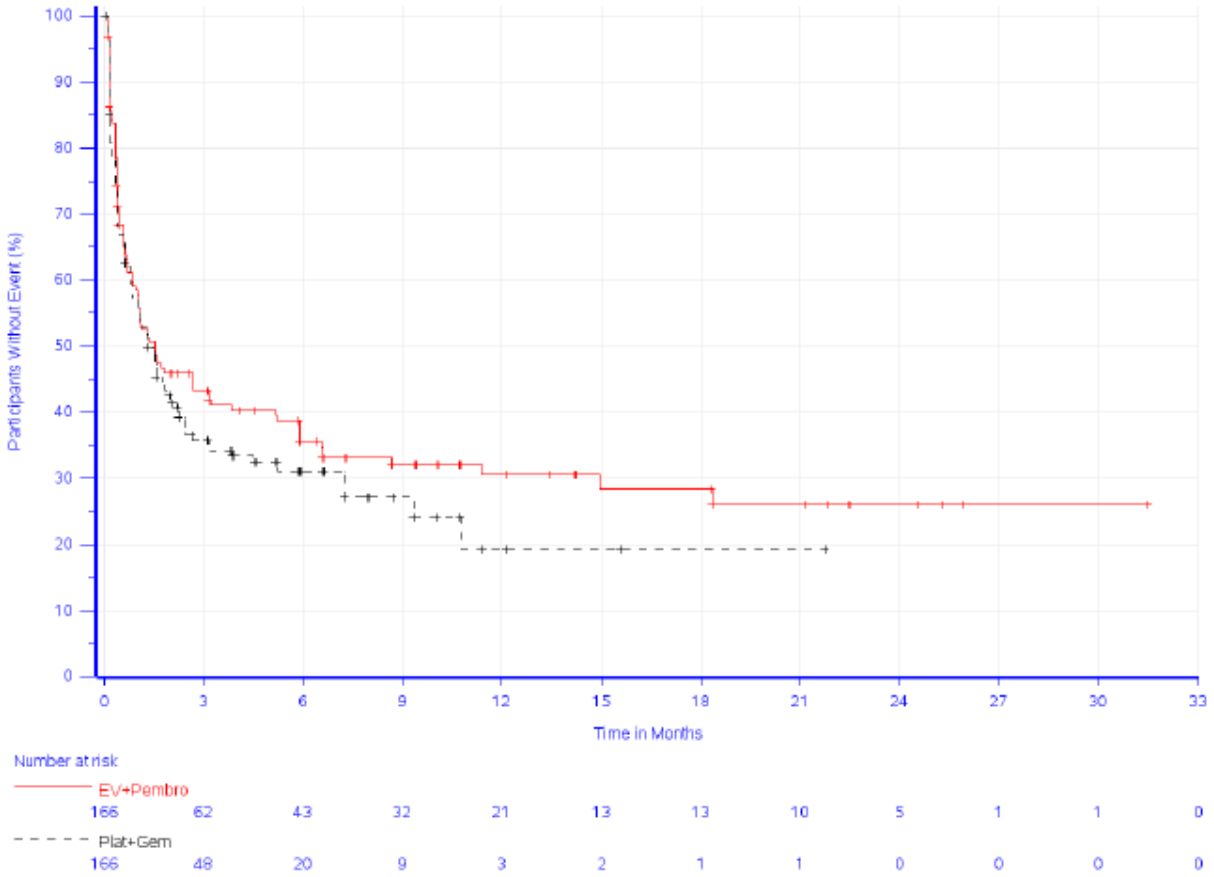

Figure 59: Kaplan-Meier curves for the outcome of health status (EQ-5D VAS - time to 1st deterioration) of the RCT EV-302/KN-A39, 1st data cut-off (08 August 2023), subpopulation 2 (cisplatin unsuitable)

A.2.3 Health-related quality of life

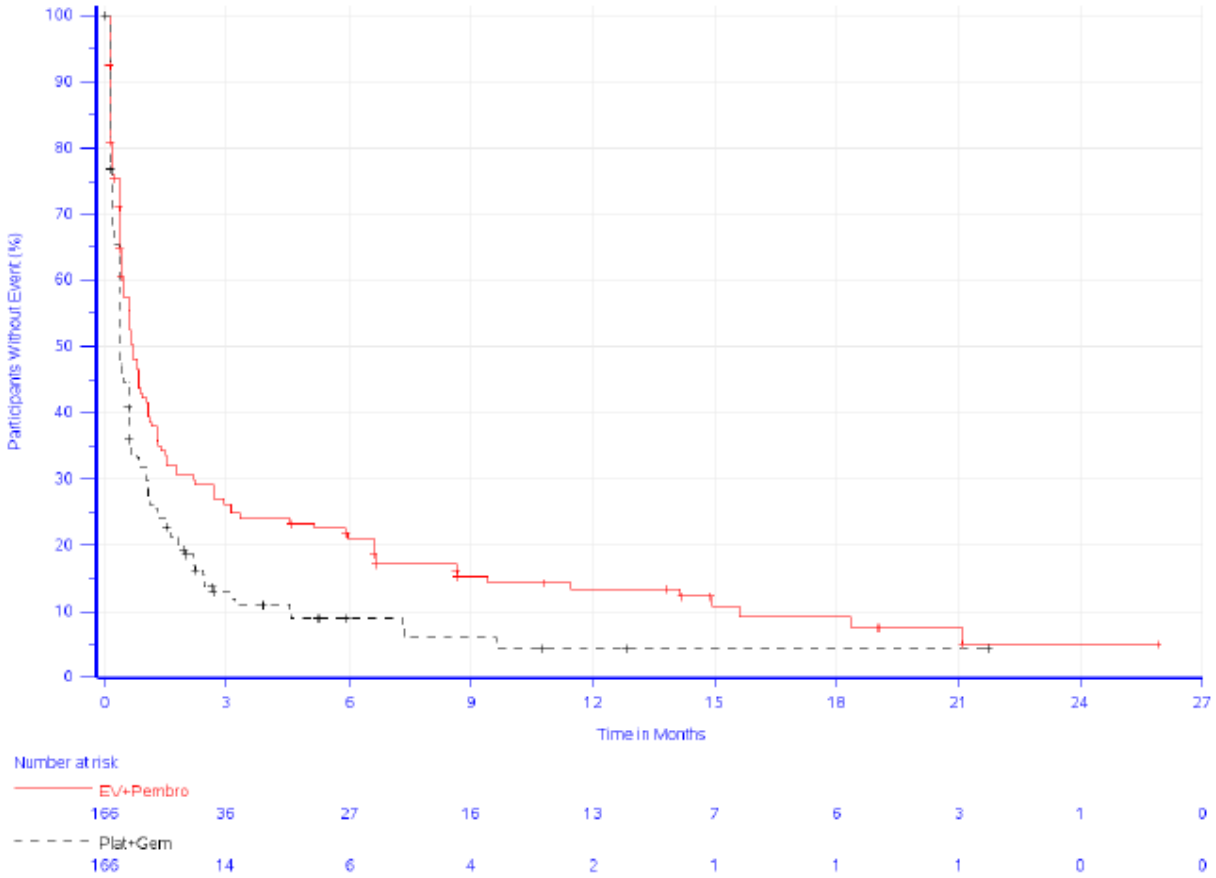

Figure 60: Kaplan-Meier curves for the outcome of role functioning (EORTC-QLQ-C30 - time to 1st deterioration) of the RCT EV-302/KN-A39, 1st data cut-off (08 August 2023), subpopulation 2 (cisplatin unsuitable)

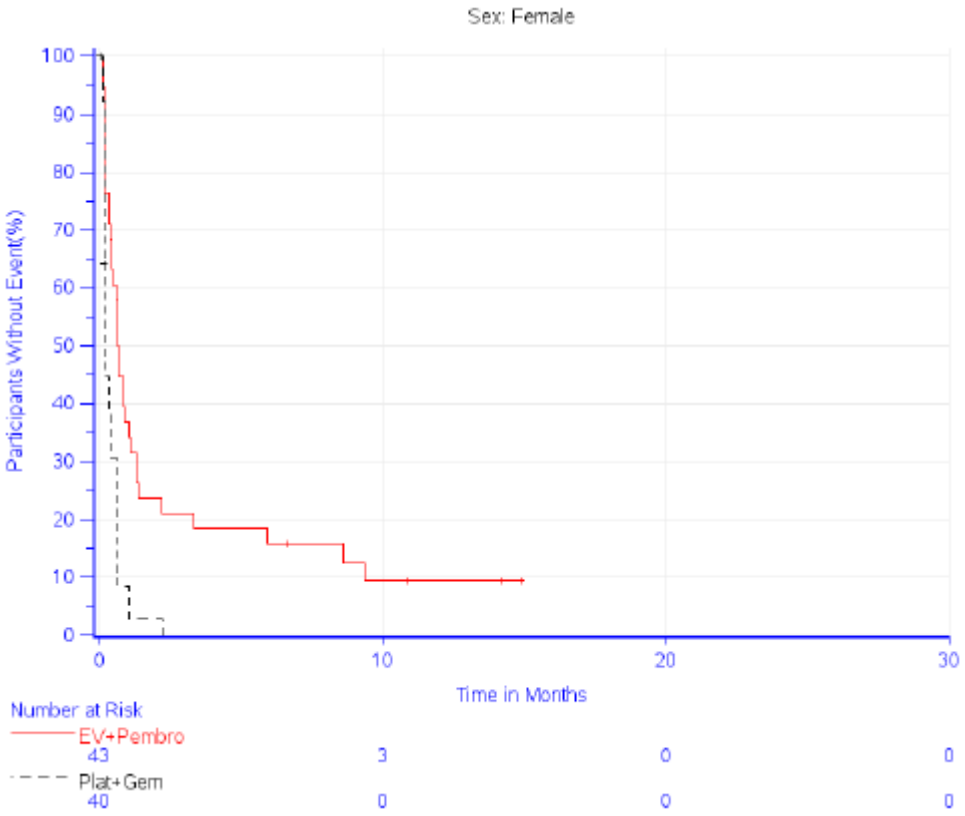

Figure 61: Kaplan-Meier curves for the outcome of role functioning (EORTC-QLQ-C30 - time to 1st deterioration) of the RCT EV-302/KN-A39, 1st data cut-off (08 August 2023), subpopulation 2 (cisplatin unsuitable), subgroup: women

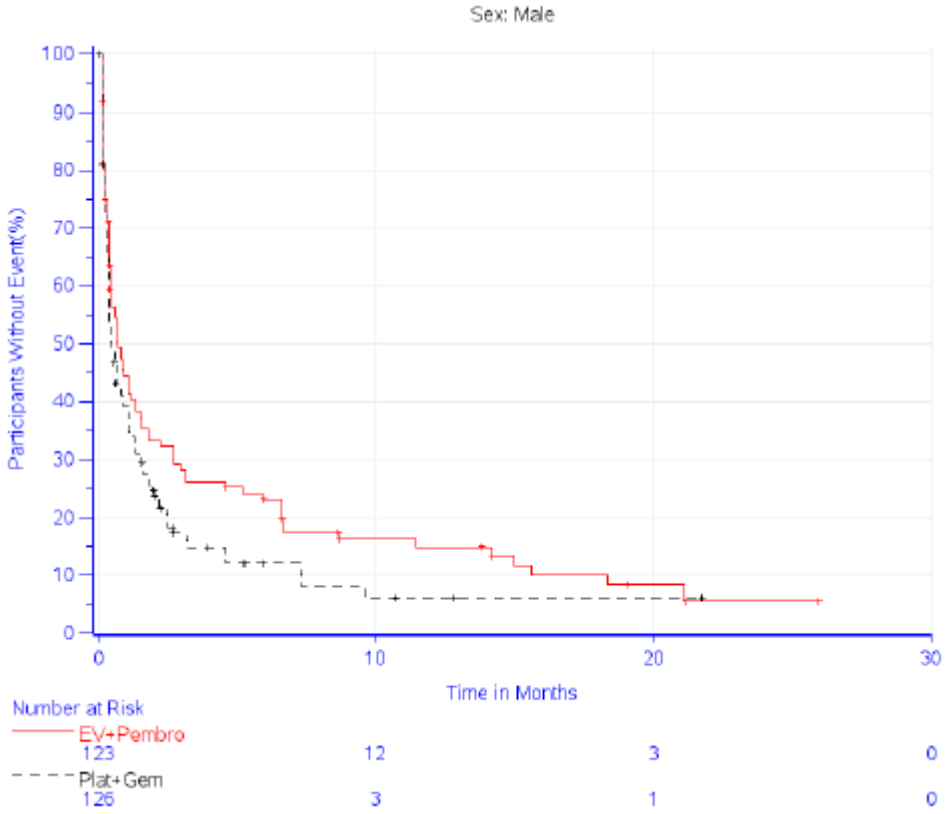

Figure 62: Kaplan-Meier curves for the outcome of role functioning (EORTC-QLQ-C30 - time to 1st deterioration) of the RCT EV-302/KN-A39, 1st data cut-off (08 August 2023), subpopulation 2 (cisplatin unsuitable), subgroup: men

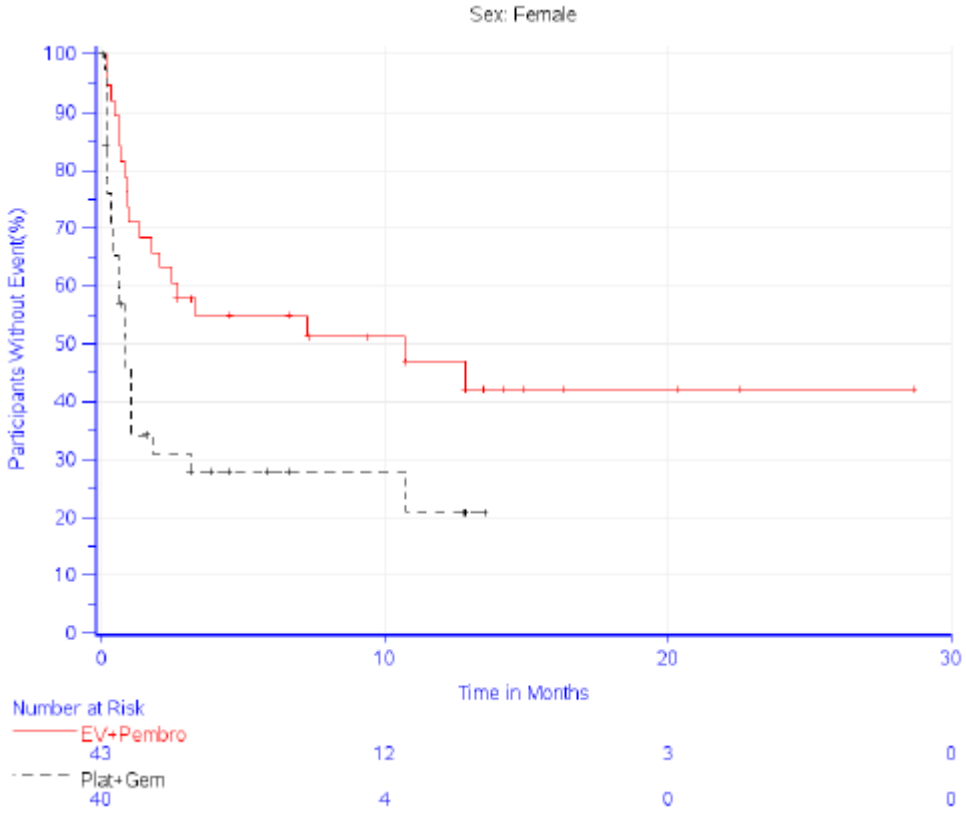

Figure 63: Kaplan-Meier curves for the outcome of emotional functioning (EORTC-QLQ-C30 - time to 1st deterioration) of the RCT EV-302/KN-A39, 1st data cut-off (08 August 2023), subpopulation 2 (cisplatin unsuitable), subgroup: women

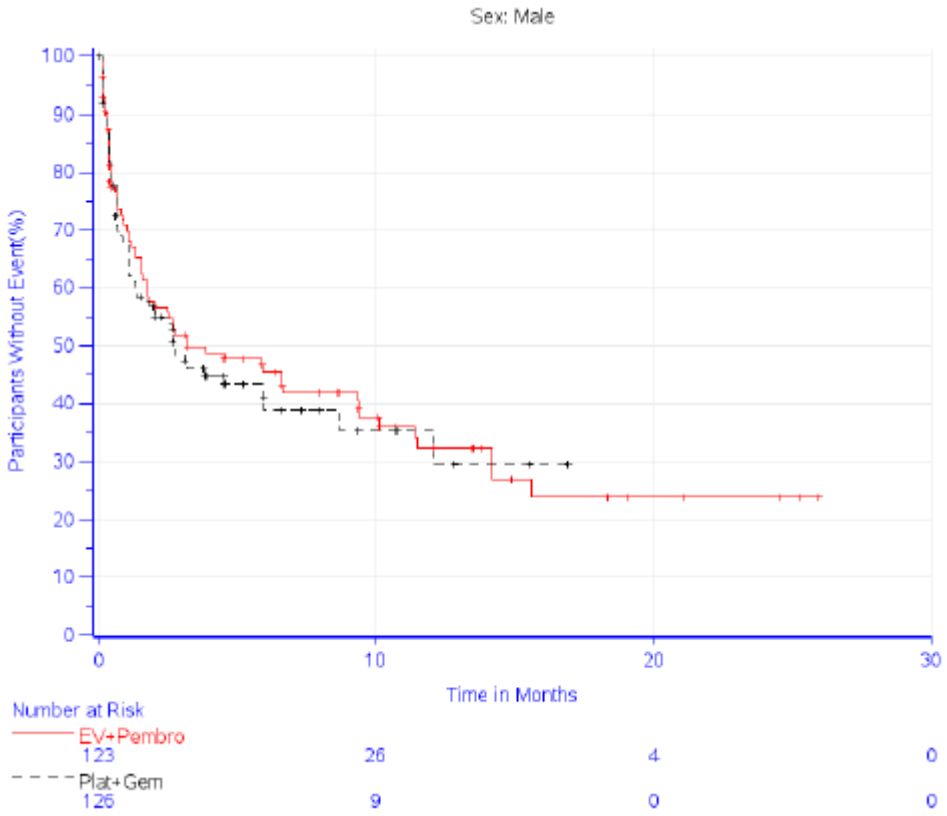

Figure 64: Kaplan-Meier curves for the outcome of emotional functioning (EORTC-QLQ-C30 - time to 1st deterioration) of the RCT EV-302/KN-A39, 1st data cut-off (08 August 2023), subpopulation 2 (cisplatin unsuitable), subgroup: men

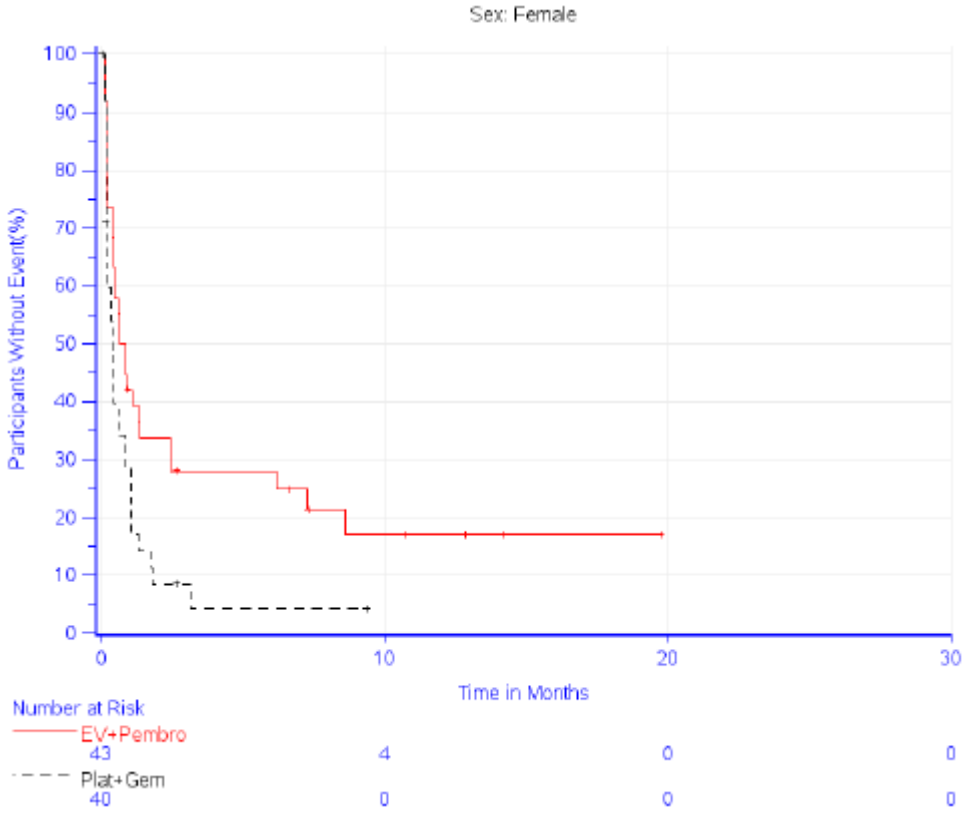

Figure 65: Kaplan-Meier curves for the outcome of social functioning (EORTC-QLQ-C30 - time to 1st deterioration) of the RCT EV-302/KN-A39, 1st data cut-off (08 August 2023), subpopulation 2 (cisplatin unsuitable), subgroup: women

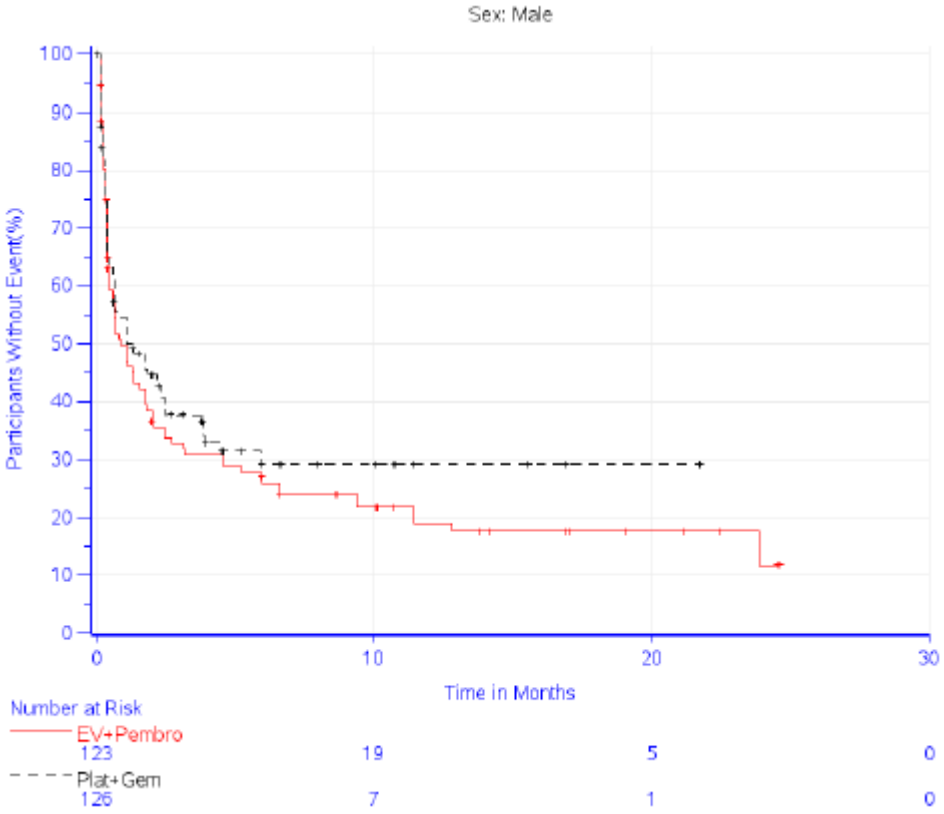

Figure 66: Kaplan-Meier curves for the outcome of social functioning (EORTC-QLQ-C30 - time to 1st deterioration) of the RCT EV-302/KN-A39, 1st data cut-off (08 August 2023), subpopulation 2 (cisplatin unsuitable), subgroup: men

A.2.4 Side effects

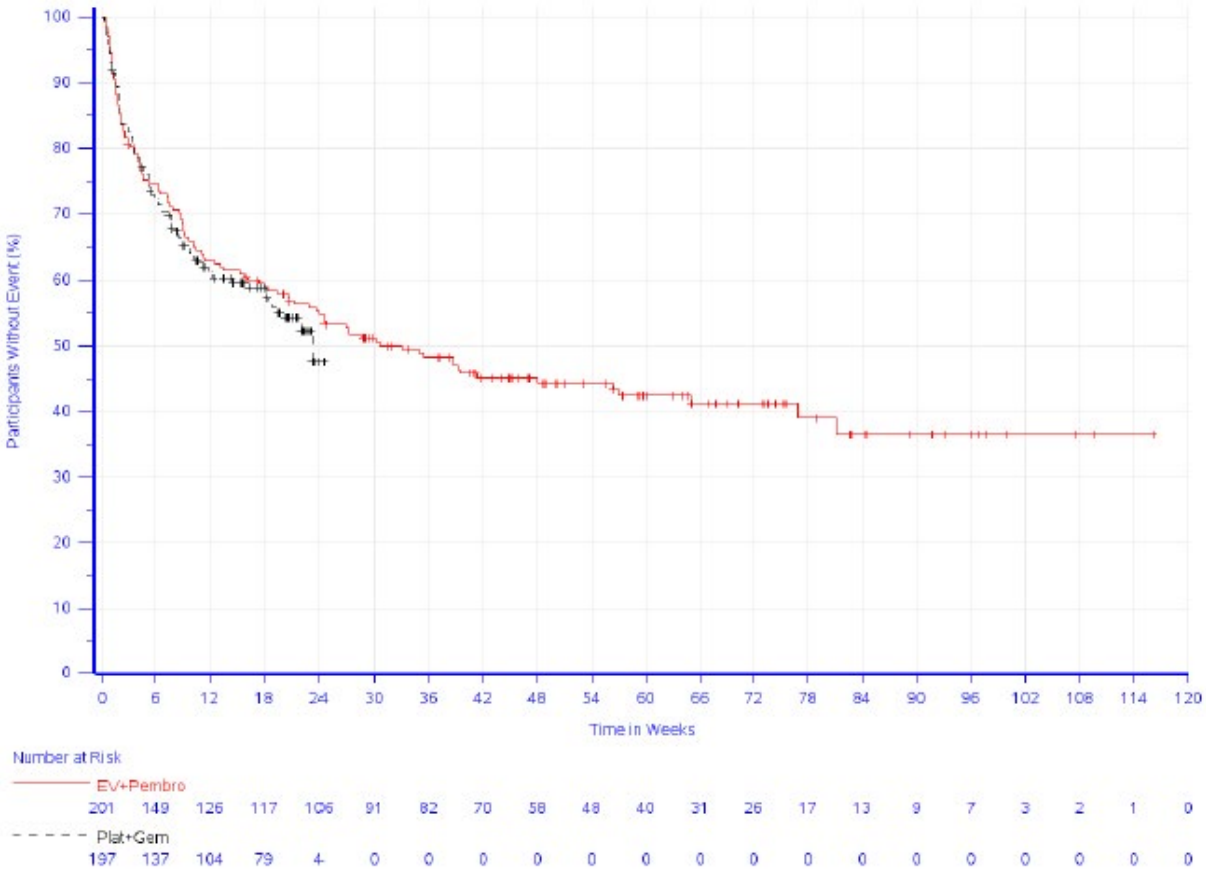

Figure 67: Kaplan-Meier curves for the outcome of SAEs of the RCT EV-302/KN-A39, 1st data cut-off (08 August 2023), subpopulation 2 (cisplatin unsuitable)

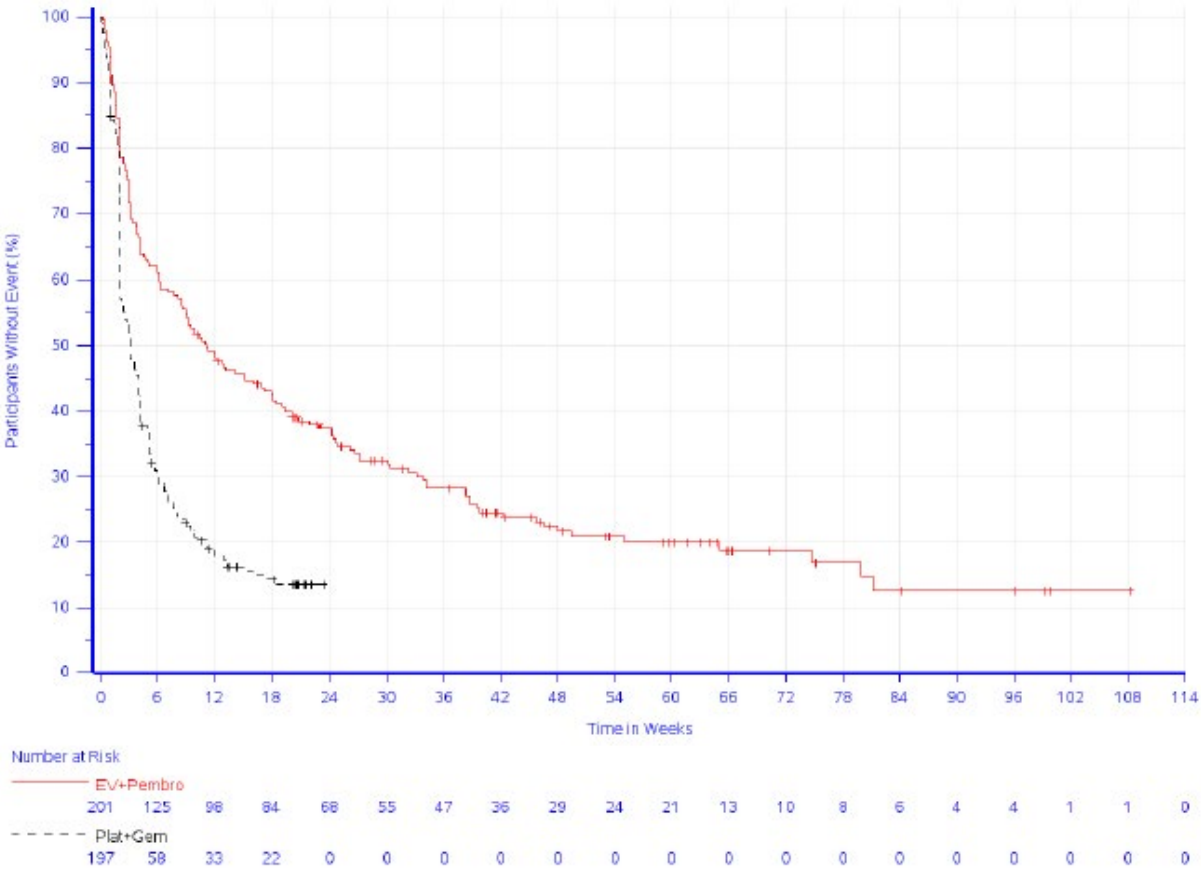

Figure 68: Kaplan-Meier curves for the outcome severe AEs (CTCAE grade ≥ 3) of RCT EV-302/KN-A39, 1st data cut-off (08 August 2023), subpopulation 2 (cisplatin unsuitable)

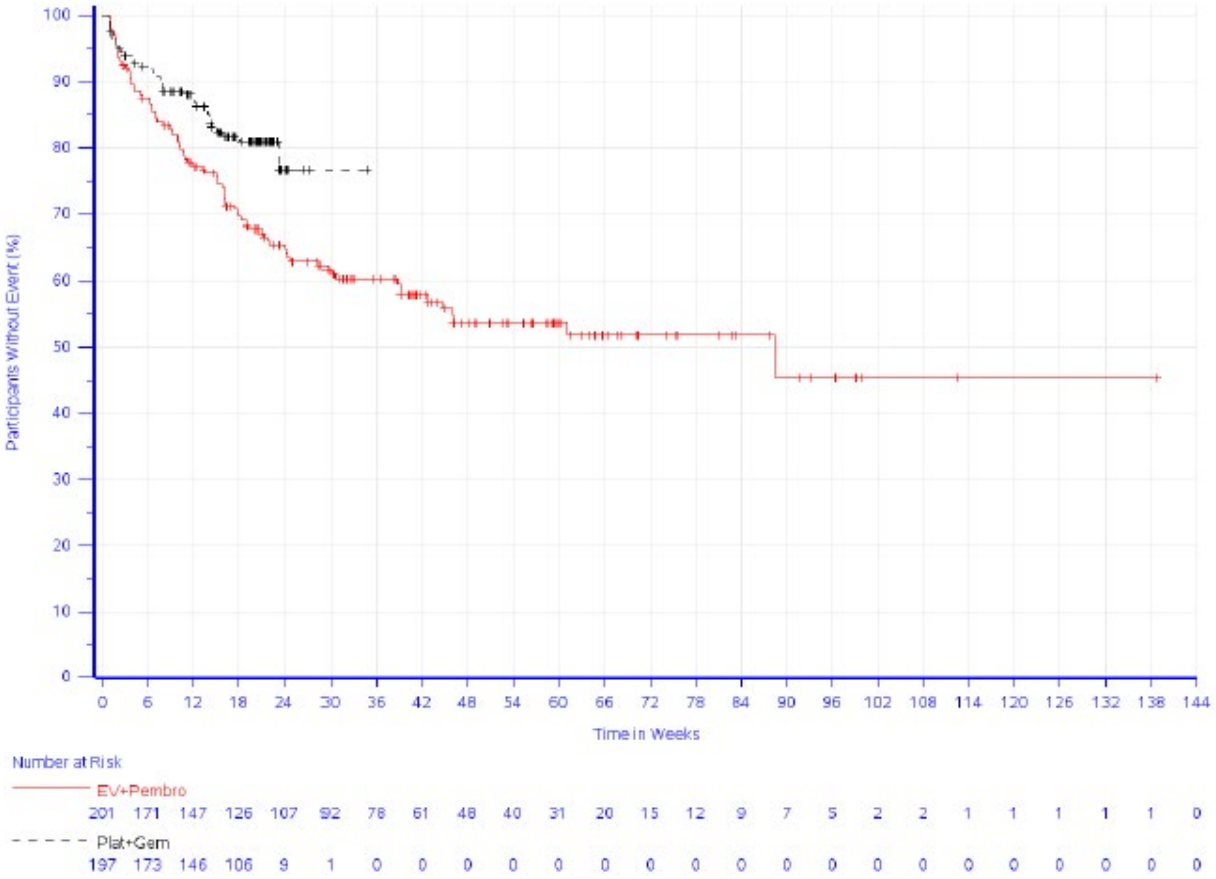

Figure 69: Kaplan-Meier curves for the outcome of discontinuation due to AEs of the RCT EV-302/KN-A39, 1st data cut-off (08 August 2023), subpopulation 2 (cisplatin unsuitable)

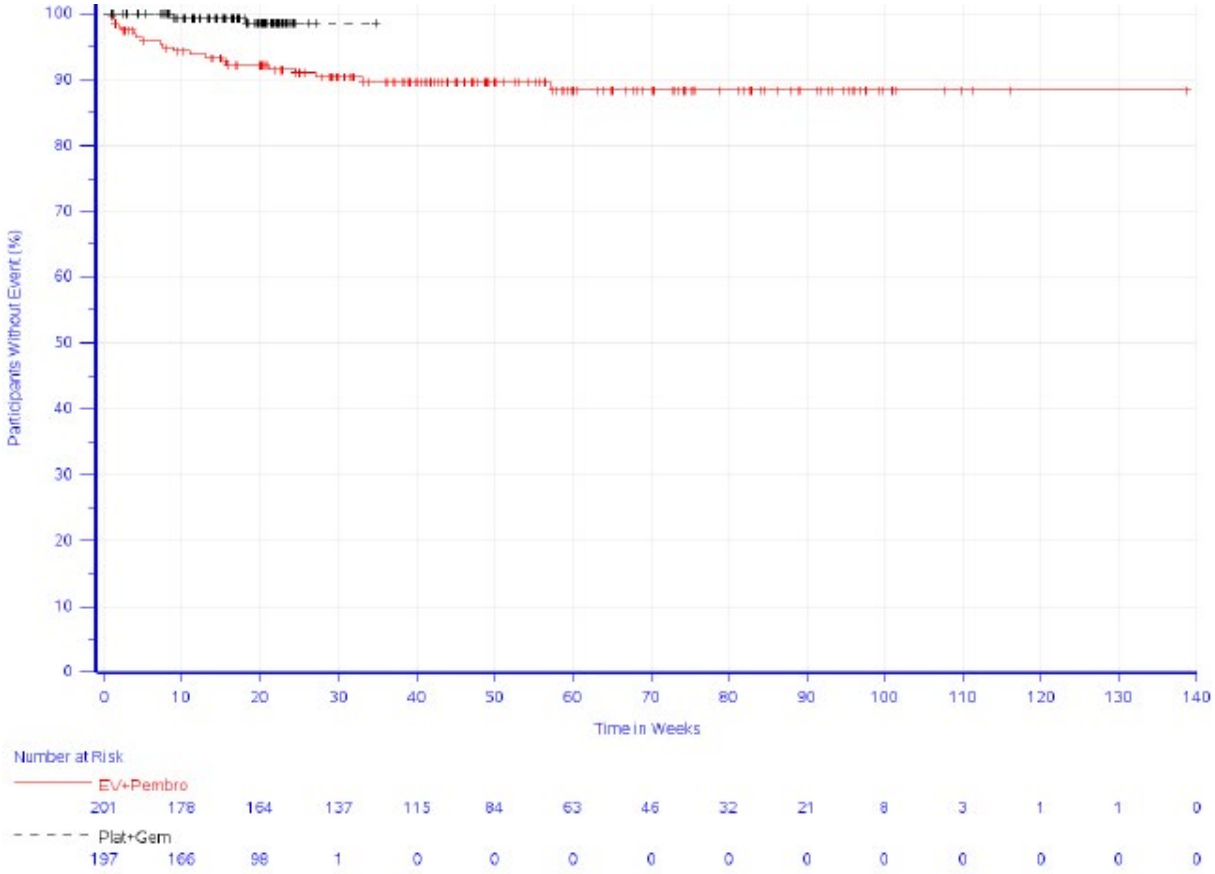

Figure 70: Kaplan-Meier curves for the outcome of immune-related SAEs of the RCT EV-302/KN-A39, 1st data cut-off (08 August 2023), subpopulation 2 (cisplatin unsuitable)

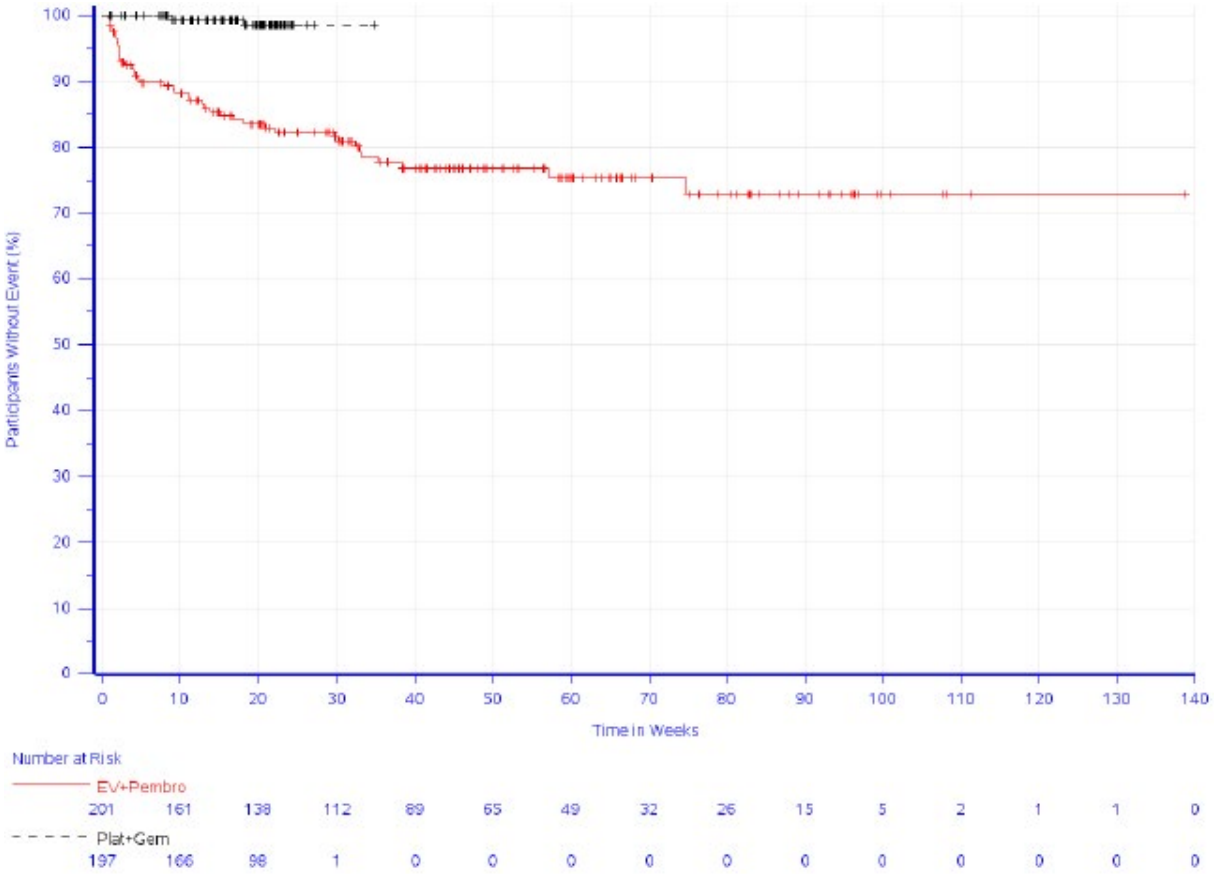

Figure 71: Kaplan-Meier curves for the outcome of immune-related severe AEs of the RCT EV-302/KN-A39, 1st data cut-off (08 August 2023), subpopulation 2 (cisplatin unsuitable)

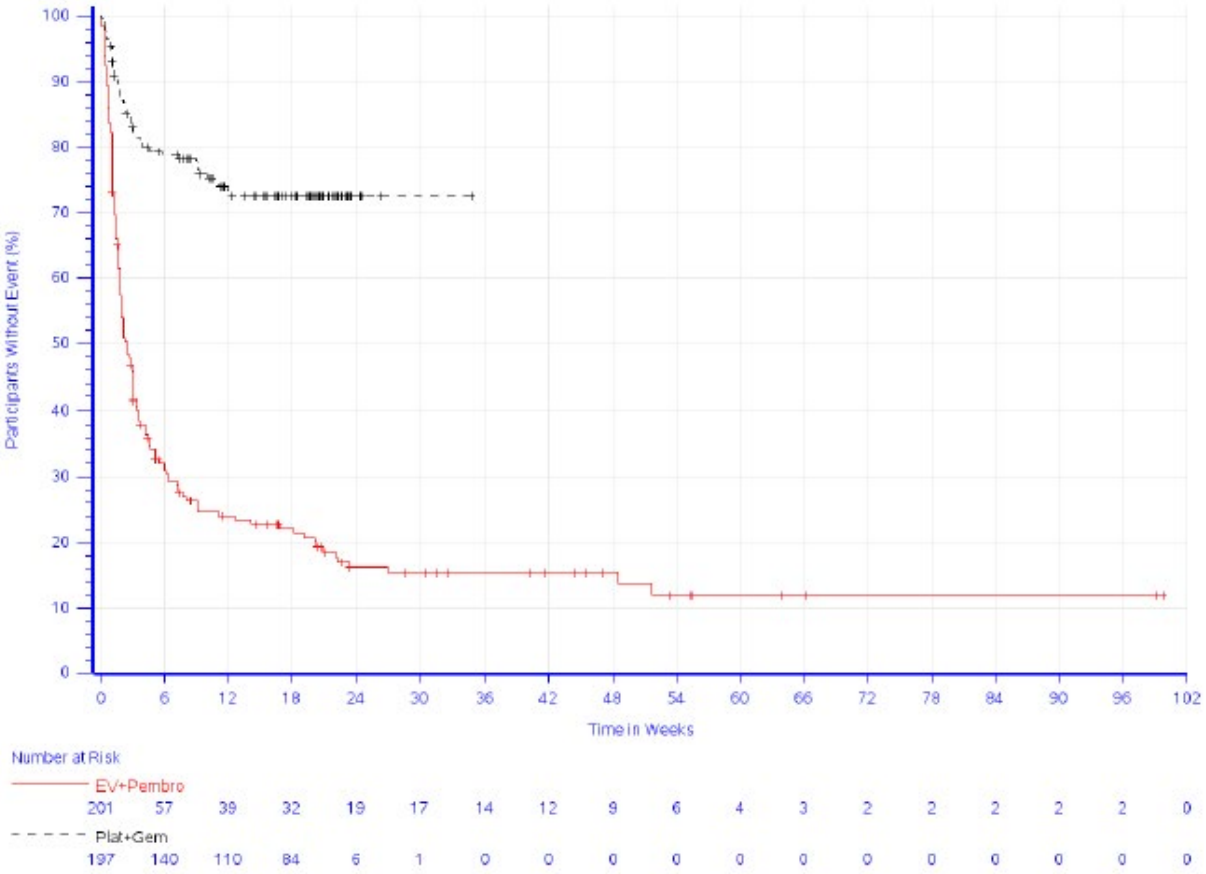

Figure 72: Kaplan-Meier curves for the outcome of skin reactions (AEs) of the RCT EV-302/KN-A39, 1st data cut-off (08 August 2023), subpopulation 2 (cisplatin unsuitable)

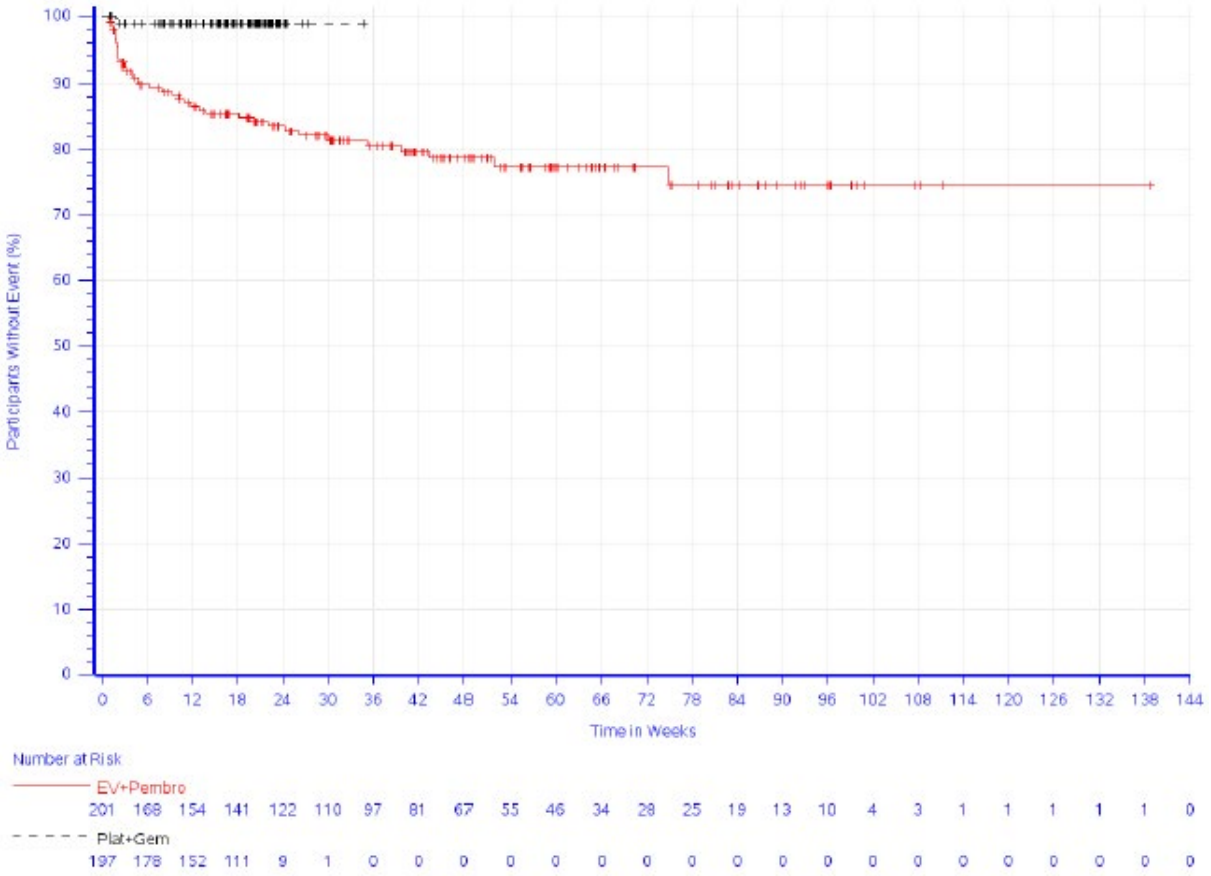

Figure 73: Kaplan-Meier curves for the outcome of severe skin reactions (severe AEs) of the RCT EV-302/KN-A39, 1st data cut-off (08 August 2023), subpopulation 2 (cisplatin unsuitable) - supplementary presentation

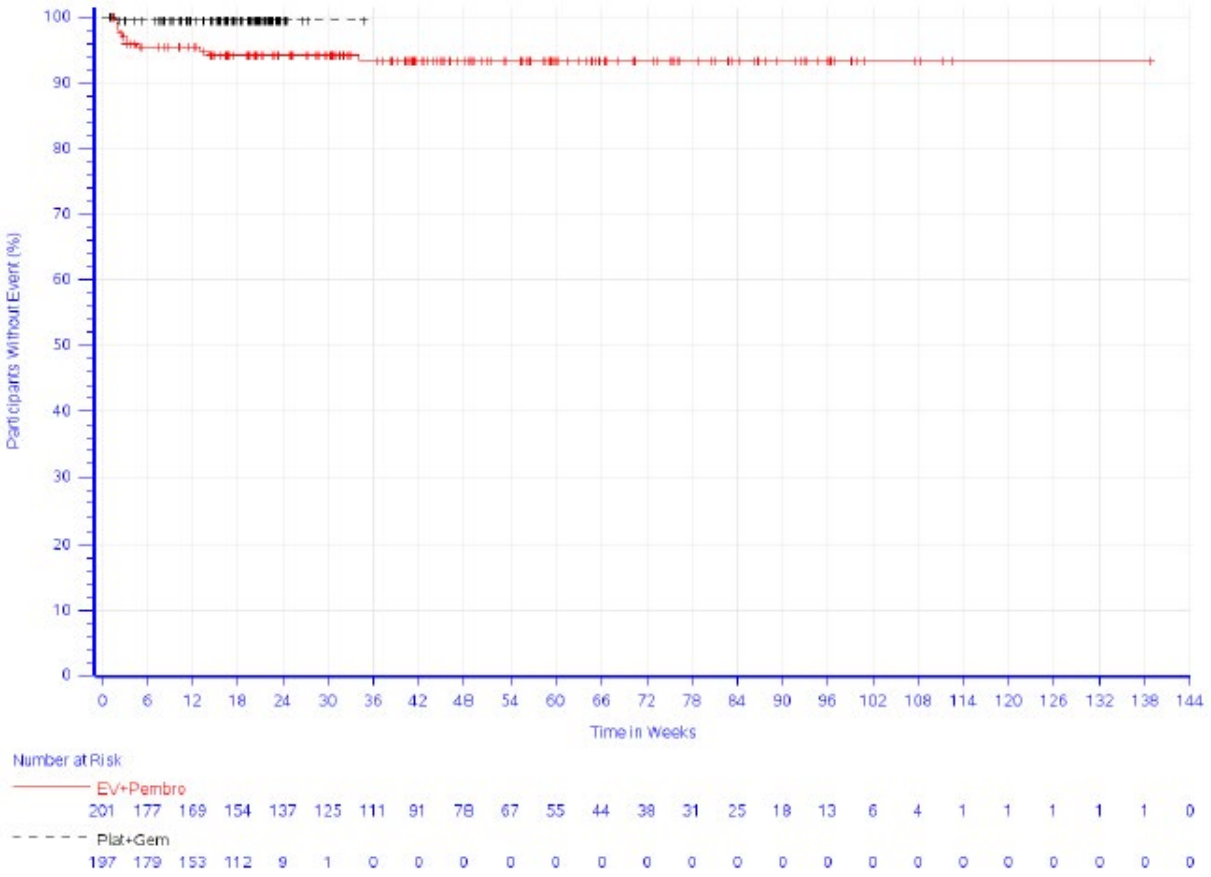

Figure 74: Kaplan-Meier curves for the outcome of severe hyperglycaemia (severe AEs) of the RCT EV-302/KN-A39, 1st data cut-off (08 August 2023), subpopulation 2 (cisplatin unsuitable)

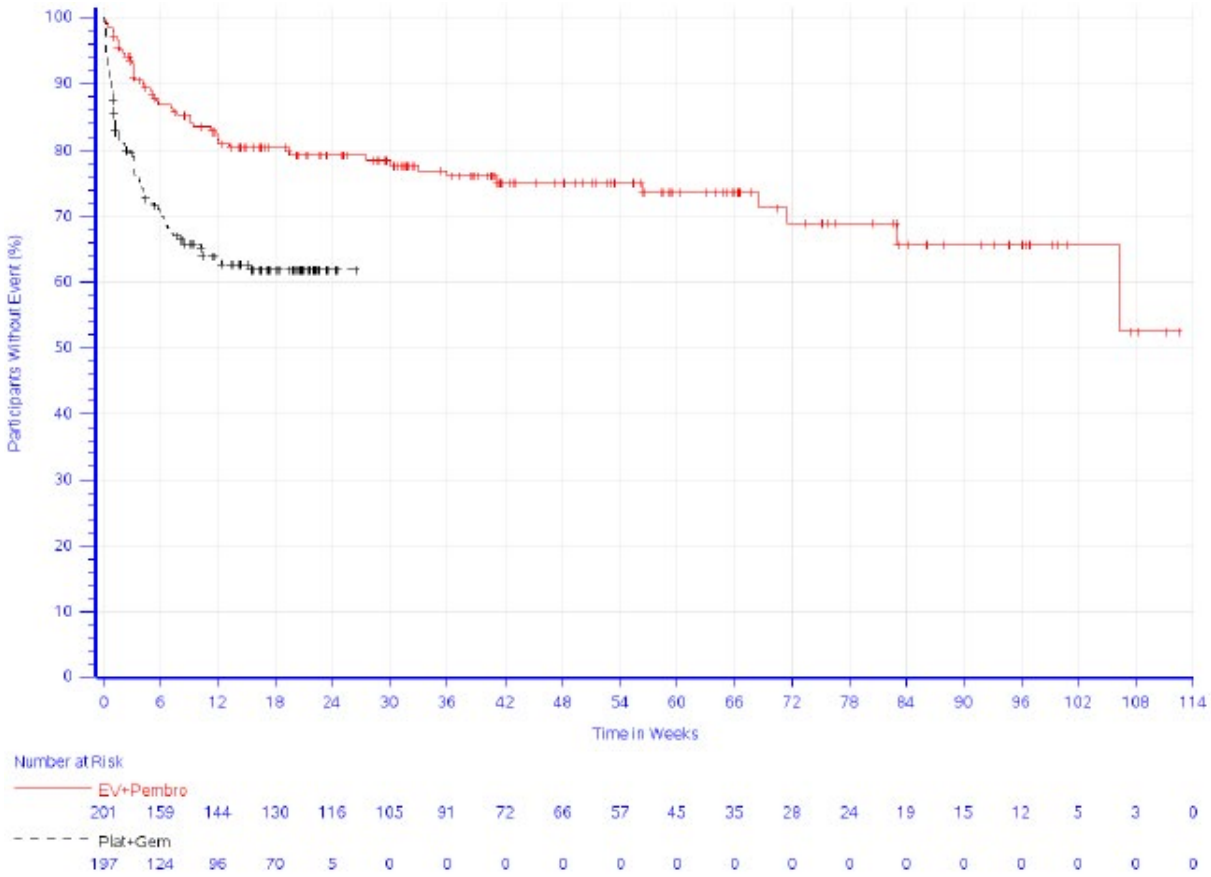

Figure 75: Kaplan-Meier curves for the outcome of constipation (AEs) of the RCT EV-302/KN-A39, 1st data cut-off (08 August 2023), subpopulation 2 (cisplatin unsuitable)

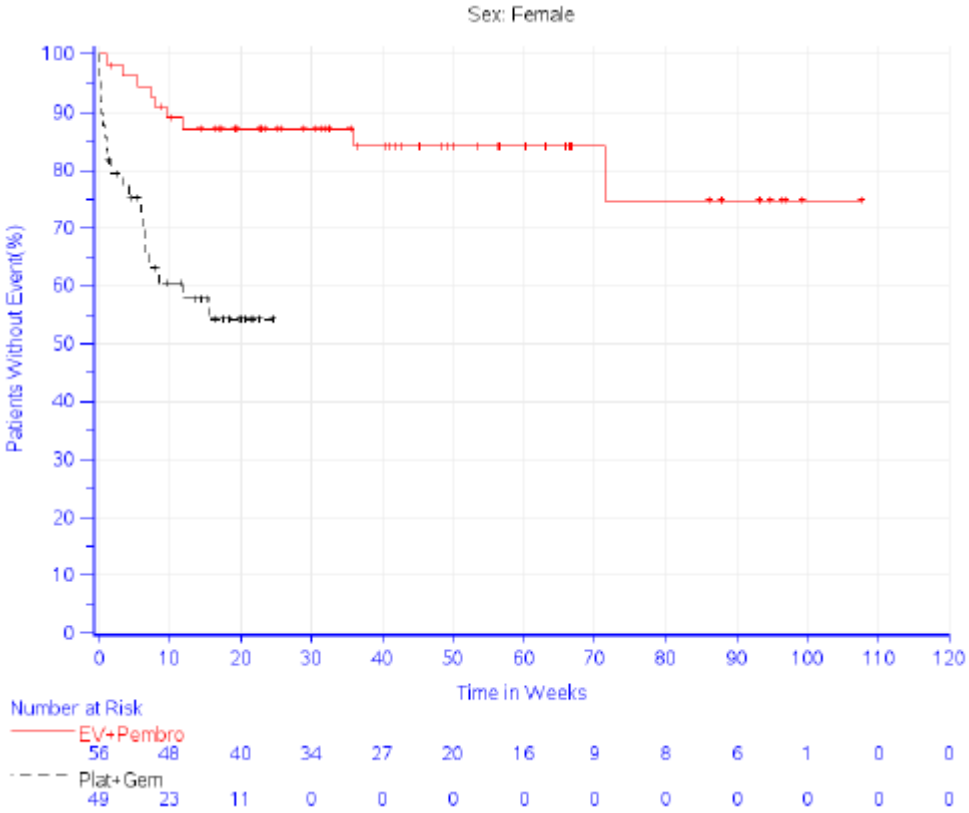

Figure 76: Kaplan-Meier curves for the outcome of constipation (AEs) of the RCT EV-302/KN-A39, 1st data cut-off (08 August 2023), subpopulation 2 (cisplatin unsuitable), subgroup: women

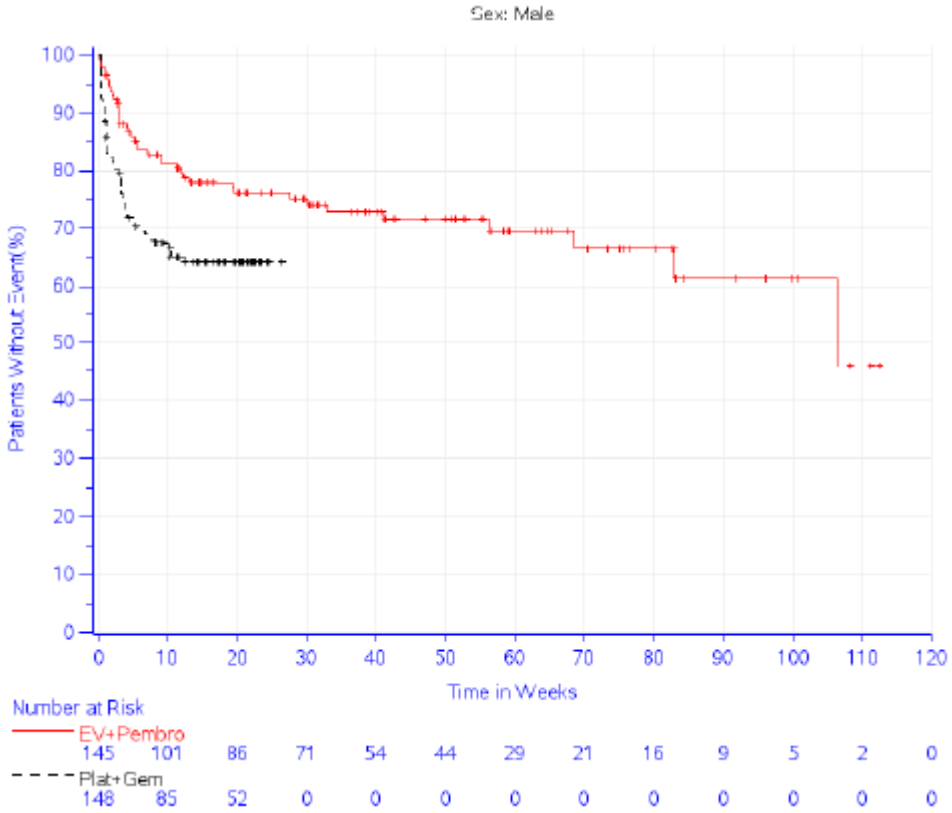

Figure 77: Kaplan-Meier curves for the outcome of constipation (AEs) of the RCT EV-302/KN-A39, 1st data cut-off (08 August 2023), subpopulation 2 (cisplatin unsuitable), subgroup: men

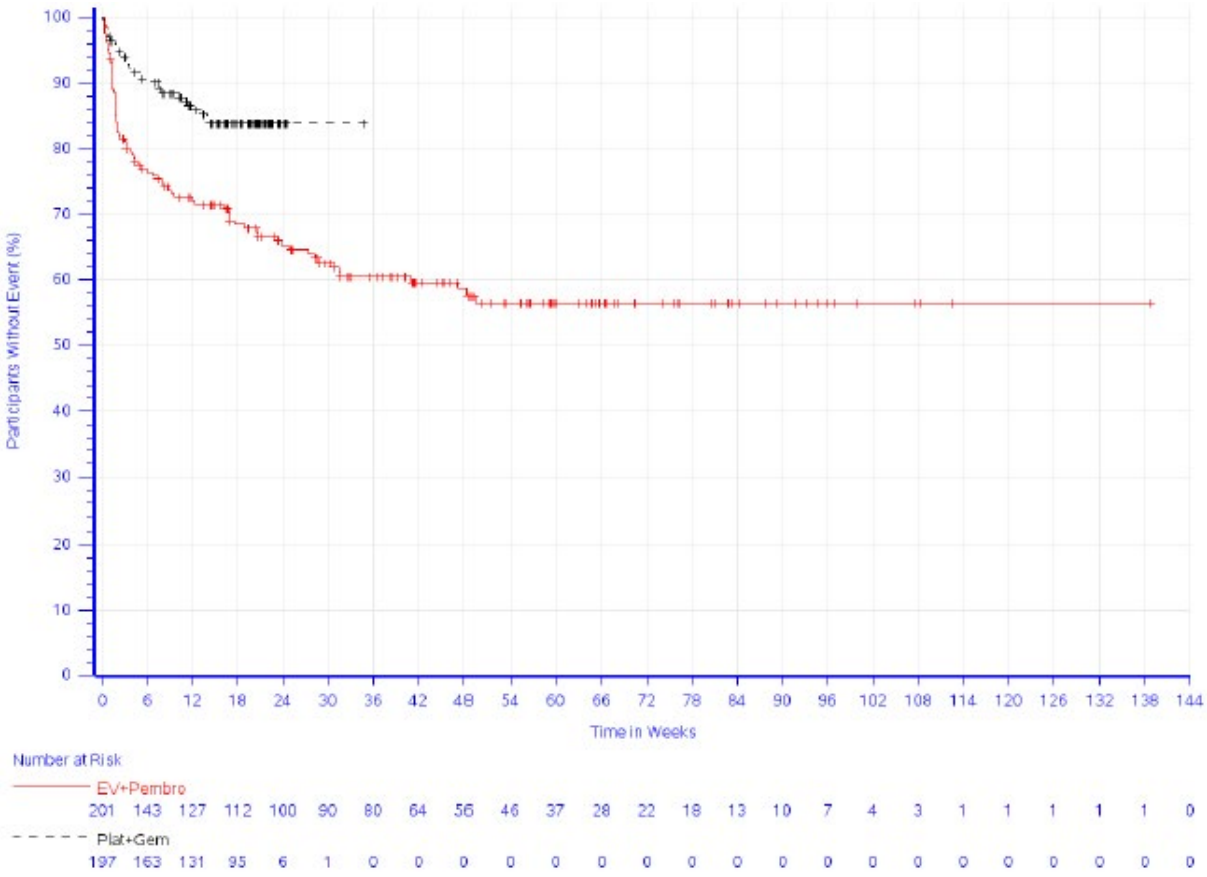

Figure 78: Kaplan-Meier curves for the outcome of diarrhoea (AEs) of the RCT EV-302/KN-A39, 1st data cut-off (08 August 2023), subpopulation 2 (cisplatin unsuitable)

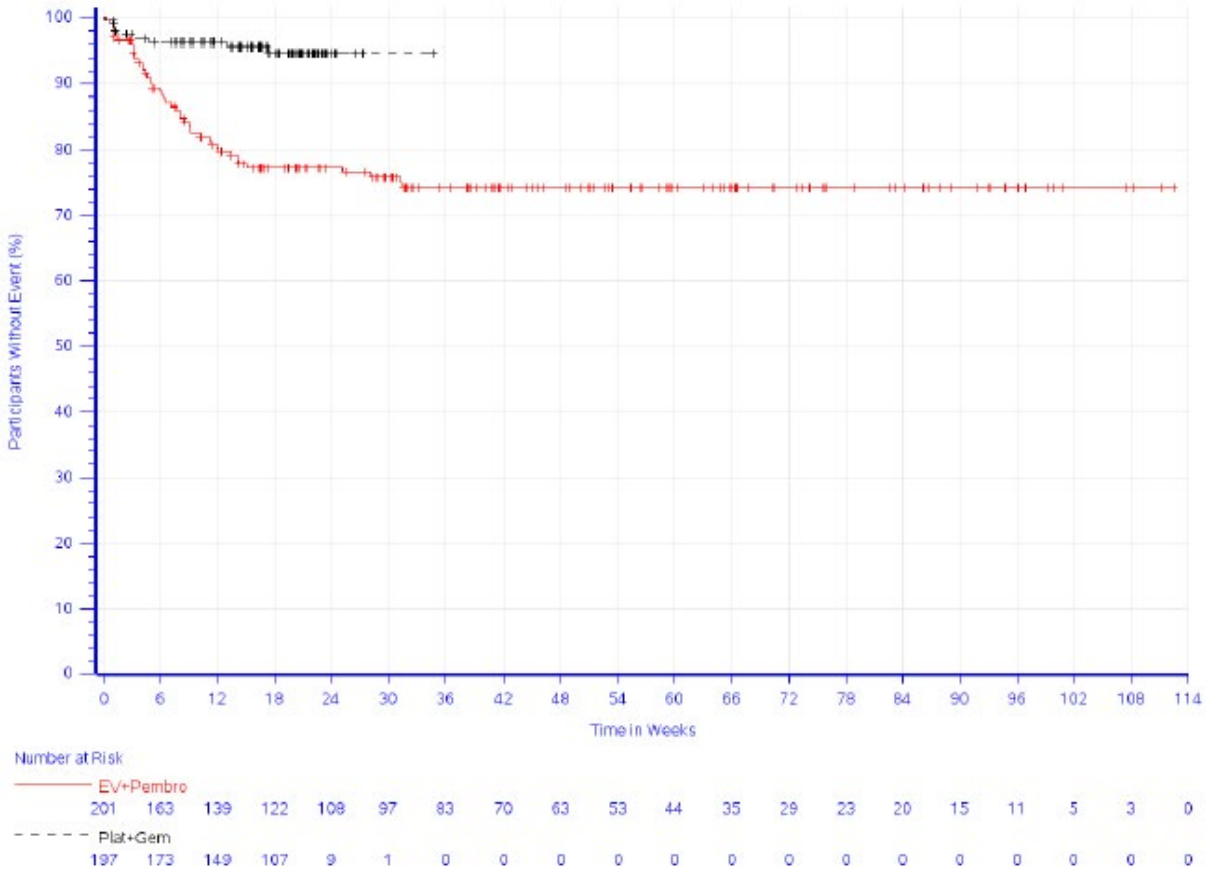

Figure 79: Kaplan-Meier curves for the outcome of dysgeusia (AEs) of the RCT EV-302/KN-A39, 1st data cut-off (08 August 2023), subpopulation 2 (cisplatin unsuitable)

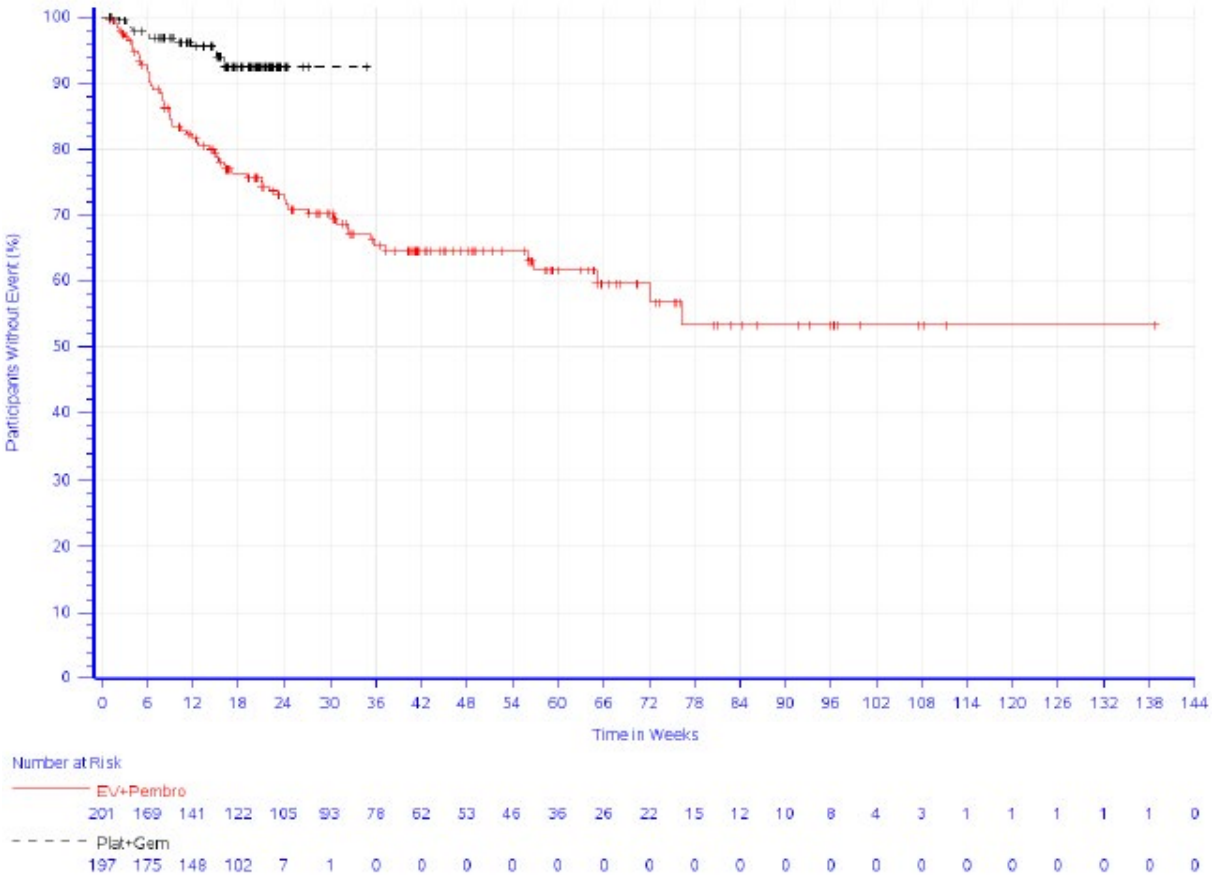

Figure 80: Kaplan-Meier curves for the outcome of eye disorders (AEs) of the RCT EV-302/KN-A39, 1st data cut-off (08 August 2023), subpopulation 2 (cisplatin unsuitable)

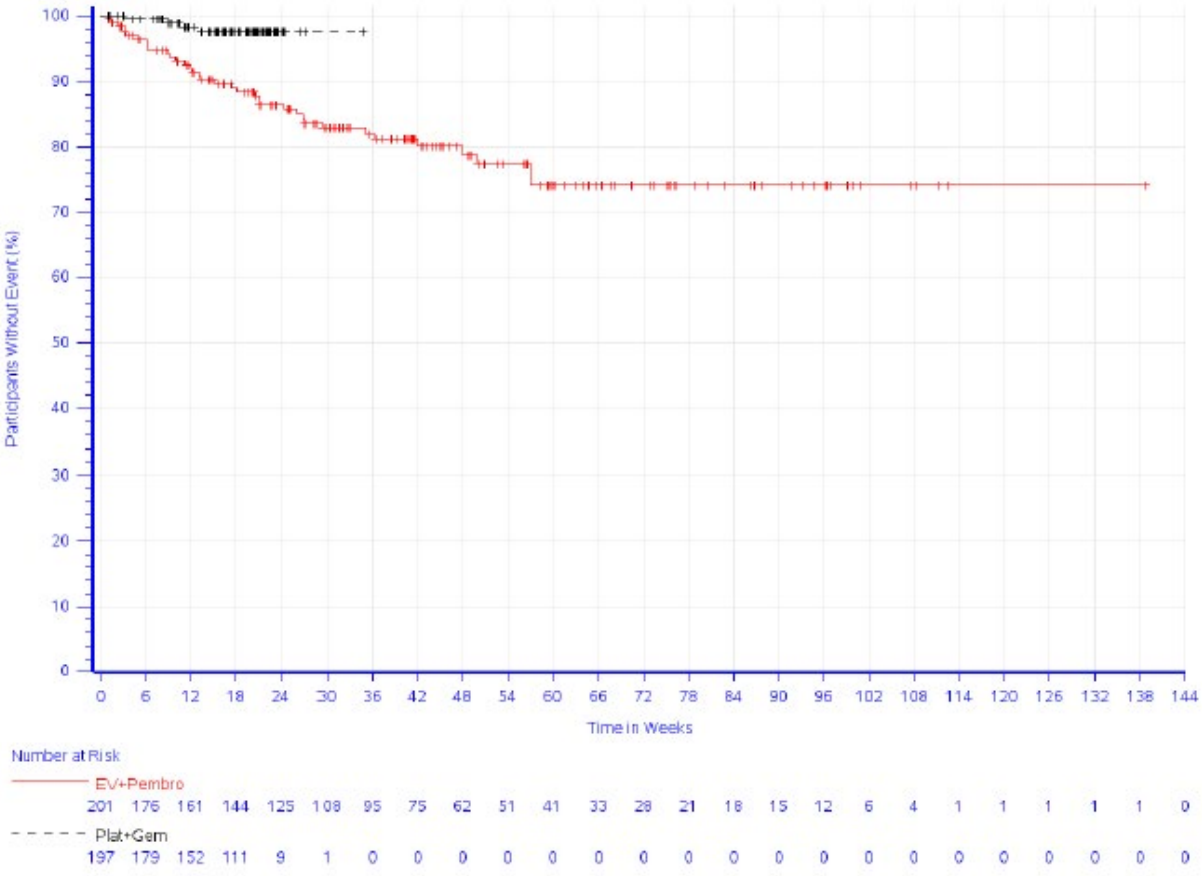

Figure 81: Kaplan-Meier curves for the outcome of endocrine disorders (AEs) of the RCT EV-302/KN-A39, 1st data cut-off (08 August 2023), subpopulation 2 (cisplatin unsuitable)

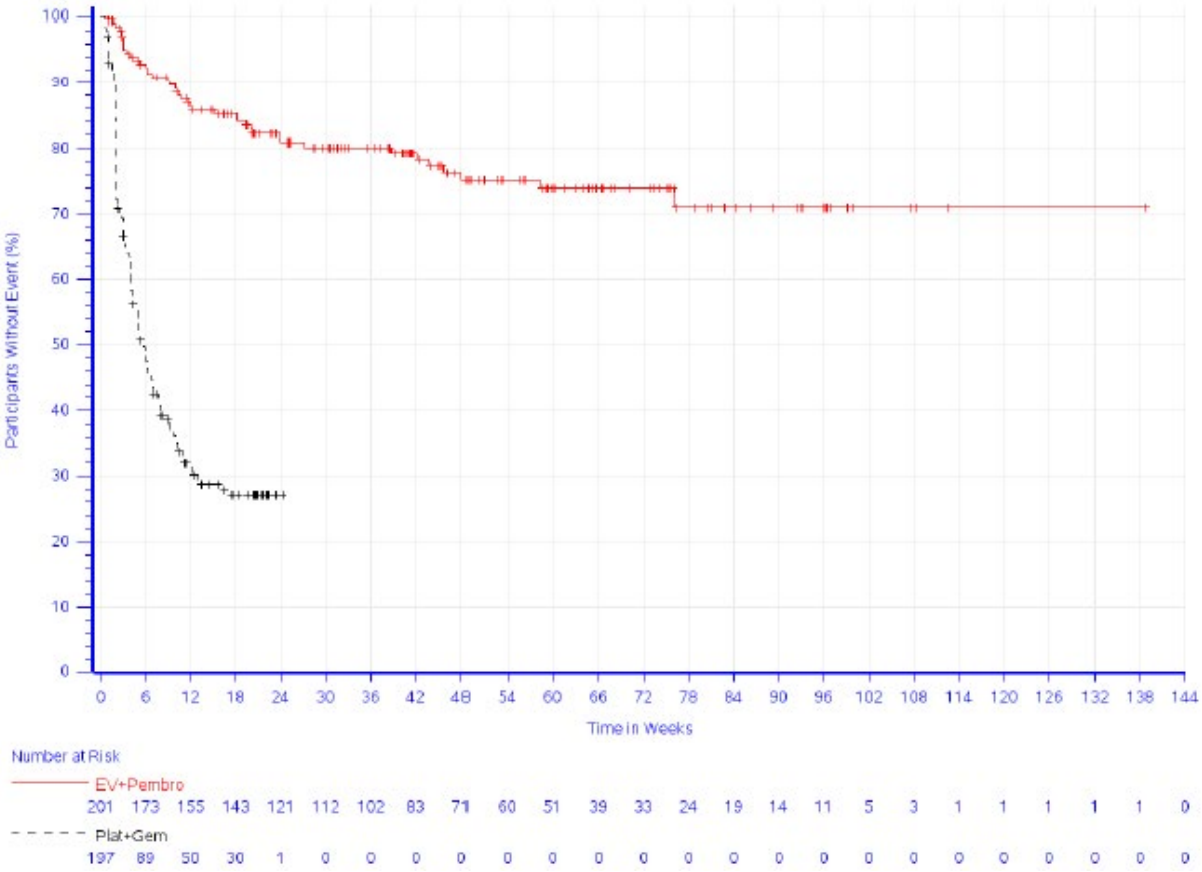

Figure 82: Kaplan-Meier curves for the outcome of blood and lymphatic system disorders (severe AEs) of the RCT EV-302/KN-A39, 1st data cut-off (08 August 2023), subpopulation 2 (cisplatin unsuitable)

Appendix B 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 which occurred in at least 5% of the patients in 1 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.

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

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

Study	Patients with event n (%)	
SOC[b] PT[b]	**pembrolizumab + enfortumab vedotin N = 239**	**cisplatin + gemcitabine N = 236**
EV-302/KN-A39 (1st data cut-off 08 August 2023)		
Overall rate of AEs[c]	239 (100.0)	234 (99.2)
Gastrointestinal disorders	179 (74.9)	184 (78.0)
Nausea	61 (25.5)	120 (50.8)
Constipation	67 (28.0)	76 (32.2)
Diarrhoea	89 (37.2)	40 (16.9)
Vomiting	24 (10.0)	42 (17.8)
Abdominal pain	27 (11.3)	21 (8.9)
Stomatitis	27 (11.3)	16 (6.8)
Dry mouth	24 (10.0)	6 (2.5)
Dyspepsia	13 (5.4)	11 (4.7)
Gastrooesophageal reflux disease	12 (5.0)	9 (3.8)
Abdominal pain upper	12 (5.0)	7 (3.0)
Haemorrhoids	10 (4.2)	2 (0.8)

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

Study	**Patients with event n (%)**	
SOC[b] **PT[b]**	**pembrolizumab + enfortumab vedotin** **N = 239**	**cisplatin + gemcitabine** **N = 236**
General disorders and administration site conditions	159 (66.5)	167 (70.8)
Fatigue	79 (33.1)	101 (42.8)
Asthenia	43 (18.0)	45 (19.1)
Fever	41 (17.2)	32 (13.6)
Peripheral oedema	29 (12.1)	22 (9.3)
Nervous system disorders	186 (77.8)	96 (40.7)
Peripheral sensory neuropathy	126 (52.7)	34 (14.4)
Dysgeusia	47 (19.7)	28 (11.9)
Dizziness	24 (10.0)	26 (11.0)
Headache	19 (7.9)	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	10 (4.2)	1 (0.4)
Skin and subcutaneous tissue disorders	204 (85.4)	61 (25.8)
Pruritus	105 (43.9)	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	12 (5.0)	2 (0.8)
Erythematous rash	12 (5.0)	2 (0.8)
Dermatitis	13 (5.4)	0 (0)
Bladder	10 (4.2)	0 (0)
Investigations	134 (56.1)	107 (45.3)
Weight loss	73 (30.5)	23 (9.7)
Alanine aminotransferase increased	49 (20.5)	13 (5.5)
Aspartate aminotransferase increased	47 (19.7)	10 (4.2)
Blood creatinine increased	12 (5.0)	27 (11.4)
Neutrophil count decreased	7 (2.9)	32 (13.6)

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

Study	**Patients with event n (%)**	
SOC[b] **PT[b]**	**pembrolizumab + enfortumab vedotin** **N = 239**	**cisplatin + gemcitabine** **N = 236**
Platelet count decreased	1 (0.4)	30 (12.7)
Blood alkaline phosphatase increased	12 (5.0)	8 (3.4)
Lipase increased	17 (7.1)	0 (0)
White blood cell count decreased	1 (0.4)	14 (5.9)
Metabolism and nutrition disorders	132 (55.2)	109 (46.2)
Decreased appetite	72 (30.1)	59 (25.0)
Hyperglycaemia	44 (18.4)	6 (2.5)
Hypokalaemia	16 (6.7)	16 (6.8)
Hyponatraemia	12 (5.0)	19 (8.1)
Hypomagnesaemia	9 (3.8)	20 (8.5)
Blood and lymphatic system disorders	69 (28.9)	170 (72.0)
Anaemia	41 (17.2)	132 (55.9)
Neutropenia	21 (8.8)	86 (36.4)
Thrombocytopenia	9 (3.8)	57 (24.2)
Leukopenia	9 (3.8)	26 (11.0)
Infections and infestations	145 (60.7)	85 (36.0)
Urinary tract infection	43 (18.0)	44 (18.6)
COVID-19	43 (18.0)	12 (5.1)
Conjunctivitis	18 (7.5)	0 (0)
Pneumonia	12 (5.0)	4 (1.7)
Upper respiratory tract infection	11 (4.6)	1 (0.4)
Respiratory, thoracic and mediastinal disorders	100 (41.8)	83 (35.2)
Dyspnoea	29 (12.1)	24 (10.2)
Cough	26 (10.9)	13 (5.5)
Hiccups	7 (2.9)	22 (9.3)
Epistaxis	6 (2.5)	19 (8.1)
Pulmonary embolism	8 (3.3)	15 (6.4)
Pneumonitis	17 (7.1)	1 (0.4)
Dysphonia	13 (5.4)	4 (1.7)
Musculoskeletal and connective tissue disorders	108 (45.2)	68 (28.8)
Back pain	37 (15.5)	21 (8.9)
Arthralgia	36 (15.1)	11 (4.7)
Pain in the extremities	21 (8.8)	15 (6.4)
Myalgia	17 (7.1)	7 (3.0)
Muscular weakness	13 (5.4)	4 (1.7)

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

Study	**Patients with event n (%)**	
SOC[b] **PT[b]**	**pembrolizumab + enfortumab vedotin** **N = 239**	**cisplatin + gemcitabine** **N = 236**
Renal and urinary disorders	74 (31.0)	76 (32.2)
Haematuria	31 (13.0)	20 (8.5)
Acute kidney injury	11 (4.6)	25 (10.6)
Dysuria	13 (5.4)	8 (3.4)
Eye disorders	88 (36.8)	14 (5.9)
Dry eye	29 (12.1)	3 (1.3)
Lacrimation increased	25 (10.5)	1 (0.4)
Blurred vision	16 (6.7)	4 (1.7)
Cataract	10 (4.2)	1 (0.4)
Vascular disorders	38 (15.9)	46 (19.5)
Hypertension	13 (5.4)	17 (7.2)
Psychiatric disorders	39 (16.3)	24 (10.2)
Insomnia	22 (9.2)	14 (5.9)
Anxiety	10 (4.2)	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	34 (14.2)	16 (6.8)
Fall	11 (4.6)	3 (1.3)
Cardiac disorders	22 (9.2)	20 (8.5)
Hepatobiliary disorders	32 (13.4)	8 (3.4)
Hypertransaminasaemia	10 (4.2)	5 (2.1)
Endocrine disorders	34 (14.2)	2 (0.8)
Hypothyroidism	23 (9.6)	1 (0.4)
Reproductive system and breast disorders	19 (7.9)	6 (2.5)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	13 (5.4)	7 (3.0)

a. Events that occurred in ≥ 10 patients in at least one study arm.
b. MedDRA version 26.0; SOC and PT notation taken from Module 4 without adaptation.
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 SAEsa – RCT, direct comparison: pembrolizumab + enfortumab vedotin vs. cisplatin + gemcitabine (subpopulation: cisplatin suitable)

Study	**Patients with event n (%)**	
SOC[b] PT[b]	**pembrolizumab + enfortumab vedotin N = 239**	**cisplatin + gemcitabine N = 236**
EV-302/KN-A39 (1st data cut-off 08 August 2023)		
Overall rate of SAEs[c]	107 (44.8)	83 (35.2)
Infections and infestations	24 (10.0)	39 (16.5)
Urinary tract infection	4 (1.7)	17 (7.2)
Renal and urinary disorders	18 (7.5)	17 (7.2)
Gastrointestinal disorders	24 (10.0)	6 (2.5)
Respiratory, thoracic and mediastinal disorders	25 (10.5)	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)
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 26.0; SOC and PT notation taken from Module 4 without adaptation.
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: pembrolizumab + enfortumab vedotin vs. cisplatin+ gemcitabine (subpopulation: cisplatin suitable)

Study	**Patients with event n (%)**	
SOC[b] **PT[b]**	**pembrolizumab + enfortumab vedotin** **N = 239**	**cisplatin + gemcitabine** **N = 236**
EV-302/KN-A39 (1st data cut-off 08 August 2023)		
Overall rate of severe AEs (CTCAE grade ≥ 3)[c]	164 (68.6)	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	28 (11.7)	39 (16.5)
Urinary tract infection	8 (3.3)	19 (8.1)
Investigations	33 (13.8)	34 (14.4)
Neutrophil count decreased	4 (1.7)	21 (8.9)
Platelet count decreased	0 (0)	12 (5.1)
Metabolism and nutrition disorders	41 (17.2)	25 (10.6)
Hyperglycaemia	20 (8.4)	2 (0.8)
Gastrointestinal disorders	29 (12.1)	17 (7.2)
Diarrhoea	10 (4.2)	2 (0.8)
Skin and subcutaneous tissue disorders	39 (16.3)	0 (0)
Maculopapular rash	16 (6.7)	0 (0)
General disorders and administration site conditions	13 (5.4)	24 (10.2)
Fatigue	6 (2.5)	12 (5.1)
Respiratory, thoracic and mediastinal disorders	24 (10.0)	13 (5.5)
Pulmonary embolism	5 (2.1)	10 (4.2)
Renal and urinary disorders	16 (6.7)	16 (6.8)
Nervous system disorders	23 (9.6)	5 (2.1)
Musculoskeletal and connective tissue disorders	10 (4.2)	8 (3.4)

a. Events that occurred in ≥ 10 patients in at least one study arm.
b. MedDRA version 26.0; SOC and PT notation taken from Module 4 without adaptation.
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 AEsa – RCT, direct comparison: pembrolizumab + enfortumab vedotin vs. cisplatin + gemcitabine (subpopulation: cisplatin suitable) (multipage table)

Study	Patients with event n (%)	
SOC[b] PT[b]	pembrolizumab + enfortumab vedotin N = 239	cisplatin + gemcitabine N = 236
EV-302/KN-A39 (1st data cut-off 08 August 2023)		
Overall rate of discontinuations due to AEs[c]	92 (38.5)	58 (24.6)
Nervous system disorders	44 (18.4)	1 (0.4)
Peripheral sensory neuropathy	29 (12.1)	1 (0.4)
Paraesthesia	4 (1.7)	0 (0)
Peripheral motor neuropathy	3 (1.3)	0 (0)
Peripheral sensorimotor neuropathy	3 (1.3)	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	17 (7.1)	0 (0)
Maculopapular rash	4 (1.7)	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	13 (5.4)	0 (0)
Pneumonitis	5 (2.1)	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)
Neutropenia	0 (0)	2 (0.8)
Gastrointestinal disorders	5 (2.1)	4 (1.7)
Diarrhoea	3 (1.3)	1 (0.4)
Nausea	0 (0)	3 (1.3)
General disorders and administration site conditions	2 (0.8)	5 (2.1)
Fatigue	1 (0.4)	5 (2.1)
Hepatobiliary disorders	7 (2.9)	0 (0)
Immune-mediated hepatitis	2 (0.8)	0 (0)

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

Study	**Patients with event n (%)**	
SOC[b] PT[b]	**pembrolizumab + enfortumab vedotin N = 239**	**cisplatin + gemcitabine N = 236**
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	2 (0.8)	0 (0)

a. Events that occurred in ≥ 2 patients in at least one study arm.
b. MedDRA version 26.0; SOC and PT notation taken from Module 4 without adaptation.
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

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

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

Study SOC[b] PT[b]	Patients with event n (%) pembrolizumab + enfortumab vedotin N = 201	 carboplatin + gemcitabine N = 197
EV-302/KN-A39 (1st data cut-off 08 August 2023)		
Overall rate of AEs[c]	200 (99.5)	193 (98.0)
Gastrointestinal disorders	151 (75.1)	129 (65.5)
Constipation	49 (24.4)	71 (36.0)
Nausea	55 (27.4)	58 (29.4)
Diarrhoea	77 (38.3)	29 (14.7)
Vomiting	27 (13.4)	27 (13.7)
Abdominal pain	24 (11.9)	6 (3.0)
Stomatitis	12 (6.0)	11 (5.6)
Dyspepsia	13 (6.5)	7 (3.6)
Dry mouth	17 (8.5)	1 (0.5)
Abdominal distension	10 (5.0)	2 (1.0)
General disorders and administration site conditions	136 (67.7)	136 (69.0)
Fatigue	76 (37.8)	69 (35.0)
Asthenia	34 (16.9)	43 (21.8)
Fever	36 (17.9)	35 (17.8)
Peripheral oedema	31 (15.4)	26 (13.2)
Blood and lymphatic system disorders	88 (43.8)	170 (86.3)
Anaemia	67 (33.3)	135 (68.5)
Neutropenia	22 (10.9)	95 (48.2)
Thrombocytopenia	10 (5.0)	96 (48.7)
Leukopenia	8 (4.0)	21 (10.7)
Febrile neutropenia	1 (0.5)	10 (5.1)
Skin and subcutaneous tissue disorders	162 (80.6)	51 (25.9)
Pruritus	77 (38.3)	16 (8.1)
Maculopapular rash	70 (34.8)	6 (3.0)
Alopecia	61 (30.3)	12 (6.1)
Dry skin	37 (18.4)	2 (1.0)
Macular rash	17 (8.5)	4 (2.0)
Eczema	17 (8.5)	2 (1.0)
Papular rash	13 (6.5)	2 (1.0)
Dermatitis	10 (5.0)	1 (0.5)

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

Study	**Patients with event n (%)**	
SOC[b] **PT[b]**	**pembrolizumab + enfortumab vedotin** **N = 201**	**carboplatin + gemcitabine** **N = 197**
Metabolism and nutrition disorders	122 (60.7)	86 (43.7)
Decreased appetite	73 (36.3)	53 (26.9)
Hyponatraemia	28 (13.9)	11 (5.6)
Hyperglycaemia	28 (13.9)	5 (2.5)
Hyperphosphataemia	22 (10.9)	10 (5.1)
Hypokalaemia	20 (10.0)	9 (4.6)
Hyperkalaemia	8 (4.0)	14 (7.1)
Hypocalcaemia	9 (4.5)	11 (5.6)
Hypoalbuminaemia	11 (5.5)	6 (3.0)
Hypomagnesaemia	10 (5.0)	7 (3.6)
Dehydration	12 (6.0)	4 (2.0)
Investigations	111 (55.2)	87 (44.2)
Weight loss	72 (35.8)	15 (7.6)
Blood creatinine increased	27 (13.4)	23 (11.7)
Alanine aminotransferase increased	27 (13.4)	20 (10.2)
Aspartate aminotransferase increased	22 (10.9)	17 (8.6)
Platelet count decreased	3 (1.5)	34 (17.3)
Neutrophil count decreased	9 (4.5)	24 (12.2)
Blood alkaline phosphatase increased	10 (5.0)	8 (4.1)
White blood cell count decreased	4 (2.0)	11 (5.6)
Infections and infestations	120 (59.7)	75 (38.1)
Urinary tract infection	48 (23.9)	39 (19.8)
COVID-19	20 (10.0)	9 (4.6)
Pneumonia	15 (7.5)	3 (1.5)
Nervous system disorders	143 (71.1)	48 (24.4)
Peripheral sensory neuropathy	103 (51.2)	10 (5.1)
Dysgeusia	46 (22.9)	9 (4.6)
Dizziness	12 (6.0)	17 (8.6)
Headache	14 (7.0)	10 (5.1)
Paraesthesia	12 (6.0)	2 (1.0)
Peripheral motor neuropathy	10 (5.0)	0 (0)
Respiratory, thoracic and mediastinal disorders	82 (40.8)	61 (31.0)
Dyspnoea	29 (14.4)	27 (13.7)
Cough	28 (13.9)	10 (5.1)
Pneumonitis	12 (6.0)	0 (0.0)

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

Study	**Patients with event n (%)**	
SOC[b] PT[b]	**pembrolizumab + enfortumab vedotin N = 201**	**carboplatin + gemcitabine N = 197**
Musculoskeletal and connective tissue disorders	78 (38.8)	53 (26.9)
Arthralgia	22 (10.9)	10 (5.1)
Back pain	16 (8.0)	13 (6.6)
Pain in the extremities	11 (5.5)	9 (4.6)
Muscular weakness	16 (8.0)	3 (1.5)
Renal and urinary disorders	69 (34.3)	49 (24.9)
Haematuria	27 (13.4)	19 (9.6)
Acute kidney injury	16 (8.0)	8 (4.1)
Eye disorders	64 (31.8)	12 (6.1)
Dry eye	21 (10.4)	2 (1.0)
Cataract	12 (6.0)	0 (0)
Lacrimation increased	11 (5.5)	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	30 (14.9)	27 (13.7)
Injury, poisoning and procedural complications	27 (13.4)	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	36 (17.9)	4 (2.0)
Hypothyroidism	23 (11.4)	2 (1.0)
Hyperthyroidism	11 (5.5)	1 (0.5)
Cardiac disorders	17 (8.5)	13 (6.6)

a. Events that occurred in ≥ 10 patients in at least one study arm.
b. MedDRA version 26.0; SOC and PT notation taken from Module 4 without adaptation.
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 SAEsa – RCT, direct comparison: pembrolizumab + enfortumab vedotin vs. carboplatin + gemcitabine (subpopulation: cisplatin unsuitable)

Study	**Patients with event n (%)**	
SOC[b] PT[b]	**pembrolizumab + enfortumab vedotin N = 201**	**carboplatin + gemcitabine N = 197**
EV-302/KN-A39 (1st data cut-off 08 August 2023)		
Overall SAE rate[c]	113 (56.2)	86 (43.7)
Infections and infestations	46 (22.9)	34 (17.3)
Urinary tract infection	12 (6.0)	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	21 (10.4)	11 (5.6)
Acute kidney injury	14 (7.0)	4 (2.0)
General disorders and administration site conditions	13 (6.5)	18 (9.1)
Respiratory, thoracic and mediastinal disorders	13 (6.5)	11 (5.6)
Metabolism and nutrition disorders	13 (6.5)	5 (2.5)
Skin and subcutaneous tissue disorders	11 (5.5)	1 (197)

a. Events that occurred in ≥ 10 patients in the intervention arm, or in ≥ 5 % of patients in the control arm.
b. MedDRA version 26.0; SOC and PT notation taken from Module 4 without adaptation.
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: pembrolizumab + enfortumab vedotin vs. carboplatin + gemcitabine (subpopulation: cisplatin unsuitable)

Study	**Patients with event n (%)**	
SOC[b] PT[b]	**pembrolizumab + enfortumab vedotin N = 201**	**carboplatin + gemcitabine N = 197**
EV-302/KN-A39 (1st data cut-off 08 August 2023)		
Overall rate of severe AEs (CTCAE grade ≥ 3)[c]	157 (78.1)	166 (84.3)
Blood and lymphatic system disorders	43 (21.4)	135 (68.5)
Anaemia	26 (12.9)	80 (4.6)
Neutropenia	14 (7.0)	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	49 (24.4)	36 (18.3)
Urinary tract infection	14 (7.0)	16 (8.1)
Metabolism and nutrition disorders	45 (22.4)	21 (10.7)
Hyponatraemia	15 (7.5)	7 (3.6)
Hyperglycaemia	12 (6.0)	1 (0.5)
Investigations	29 (14.4)	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	24 (11.9)	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	39 (19.4)	2 (1.0)
Maculopapular rash	20 (10.0)	0 (0)
Renal and urinary disorders	25 (12.4)	15 (7.6)
Acute kidney injury	14 (7.0)	4 (2.0)
Respiratory, thoracic and mediastinal disorders	16 (8.0)	16 (8.1)
Nervous system disorders	20 (10.0)	4 (2.0)
Peripheral sensory neuropathy	11 (5.5)	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 26.0; SOC and PT notation taken from Module 4 without adaptation.
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 AEsa – RCT, direct comparison: pembrolizumab + enfortumab vedotin vs. carboplatin + gemcitabine (subpopulation: cisplatin unsuitable) (multipage table)

Study	Patients with event n (%)	
SOC[b] PT[b]	pembrolizumab + enfortumab vedotin (N = 201)	carboplatin + gemcitabine N = 197
EV-302/KN-A39 (1st data cut-off 08 August 2023)		
Overall rate of discontinuations due to AEs[c]	83 (41.3)	35 (17.8)
Nervous system disorders	27 (13.4)	1 (0.5)
Peripheral sensory neuropathy	20 (10.0)	0 (0)
Paraesthesia	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	13 (6.5)	1 (0.5)
Maculopapular rash	3 (1.5)	0 (0)
Toxic epidermal necrolysis	2 (1.0)	0 (0)
Respiratory, thoracic and mediastinal disorders	9 (4.5)	2 (1.0)
Pneumonitis	4 (2.0)	0 (0)
Immune-related lung disease	2 (1.0)	0 (0)
General disorders and administration site conditions	7 (3.5)	3 (1.5)
Asthenia	3 (1.5)	0 (0)
General deterioration in physical health	0 (0)	2 (1.0)
Renal and urinary disorders	9 (4.5)	0 (0)
Acute glomerulonephritis	4 (2.0)	0 (0)
Renal failure	2 (1.0)	0 (0)
Infections and infestations	5 (2.5)	3 (1.5)
Cardiac disorders	4 (2.0)	1 (0.5)
Gastrointestinal disorders	5 (2.5)	0 (0)
Diarrhoea	2 (1.0)	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	2 (1.0)	0 (0)

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

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

a. Events that occurred in ≥ 2 patients in at least one study arm.
b. MedDRA version 26.0; SOC and PT notation taken from Module 4 without adaptation.
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