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Enfortumab vedotin (urothelial carcinoma1) –

Addendum to Commission A22-61 (dossier assessment)[1]

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List of abbreviations

Abbreviation	Meaning
AE	adverse event
CTCAE	Common Terminology Criteria for Adverse Events
EORTC QLQ-C30	European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
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 protein 1
PD-L1	programmed cell death protein 1
PT	Preferred Term
RCT	Randomized controlled Trial
SAE	serious adverse event
SGB	Sozialgesetzbuch (Social Code Book)
SMQ	Standardized MedDRA Query
SOC	System Organ Class
VAS	visual analogue scale

1 Background

On 11 October 2022, the Federal Joint Committee (G-BA) commissioned the Institute for Quality and Efficiency in Health Care (IQWiG) to conduct supplementary assessments on Commission A22-61 (enfortumab vedotin – benefit assessment according to §35a Social Code Book V) [1].

The commission comprised the assessment of the total population of the EV-301 study on the basis of the analyses submitted by the company, taking into account the information from the dossier [2].

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 randomized controlled trial (RCT) EV-301 was included for the assessment of enfortumab vedotin in adult patients with locally advanced or metastatic urothelial carcinoma who have received a prior platinum-containing chemotherapy and a programmed cell death protein 1 (PD-1) or programmed cell death ligand 1 (PD-L1) inhibitor. The EV-301 study is an ongoing open-label RCT on the comparison of enfortumab vedotin with chemotherapy of physician's choice choosing from vinflunine, paclitaxel and docetaxel, each as monotherapy.

In its dossier, the company presented results for both the total population and a subpopulation that included only those patients from the intervention or the control arm who were to receive vinflunine if assigned to the comparator arm (vinflunine subpopulation). The benefit assessment was based on the results of the vinflunine subpopulation, as of the 3 chemotherapies used, only vinflunine represented an option of the G-BA's ACT.

In compliance with the commission, the total population of the EV-301 study is assessed in the following sections. All data in the following sections refer to the total population (N = 608).

2.1 Study characteristics

Dossier assessment A22-61 provides a detailed characterization of the EV-301 study. Table 1 presents the characteristics of the EV-301 study.

Table 1: Characteristics of the intervention – RCT, direct comparison: enfortumab vedotin vs. treatment of physician's choice[a]

Study	Intervention	Comparison[a]
EV-301	Enfortumab vedotin 1.25 mg/kg BW[b] IV, on days 1, 8 and 15 of a 28-day cycle	Vinflunine 320 mg/m² BSA IV[c], on day 1 of a 21-day cycle or docetaxel[d] 75 mg/m² BSA, IV, on day 1 of a 21-day cycle or paclitaxel[e] 175 mg/m² BSA, IV, on day 1 of a 21-day cycle
	Treatment adjustment dose adjustment or interruption of treatment is possible as needed[f]	
	Pretreatment <u>required</u> ▪ platinum-based chemotherapy (cisplatin or carboplatin) and 1 PD-1 or PD-L1 inhibitor <u>not allowed</u> ▪ enfortumab vedotin or other MMAE-based antibody-drug conjugates (ADCs) ▪ pretreatment with all chemotherapies possible in the comparator arm (docetaxel, vinflunine and paclitaxel) ▪ > 1 chemotherapy in the locally advanced or metastatic stage, including adjuvant or neoadjuvant chemotherapy with recurrence within 12 months after end of treatment ▪ not completed treatment with chemotherapy, biologics, immunotherapies or other investigational drugs ≤ 2 weeks before the first dose of the study medication ▪ radiation or major surgical intervention ≤ 4 weeks before the first dose of the study medication **Concomitant treatment** <u>not allowed</u> ▪ other chemotherapy or anticancer therapy (except endocrine therapy for the adjuvant treatment of breast cancer or drugs for the treatment of bone metastases) ▪ radiation (exception in case of symptomatic singular lesions or at the bones, after consultation with the sponsor)	

Table 1: Characteristics of the intervention – RCT, direct comparison: enfortumab vedotin vs. treatment of physician's choice[a]

Study	Intervention	Comparison[a]

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

d. In accordance with the requirements of the SPC, all patients were to be pretreated with corticosteroids (e.g. dexamethasone 16 mg/day) for 3 days before every administration of docetaxel to reduce the probability and severity of a fluid retention and a hypersensitivity reaction.
e. In accordance with the requirements of the SPC, all patients were to be pretreated with the following drugs prior to each administration of paclitaxel according to a therapy regimen specified by the treating physician in order to avoid a severe hypersensitivity reaction:
- dexamethasone 20 mg orally (12 and 6 hours before the administration of paclitaxel)
- diphenhydramine (or equivalent) 50 mg IV (30 to 60 minutes before the administration of paclitaxel)
- cimetidine 300 mg or ranitidine 50 mg, IV (30 to 60 minutes before the administration of paclitaxel).

f. Toxicity-related dose adjustments up to treatment discontinuation were made in patients receiving vinflunine or enfortumab vedotin without relevant deviation from the requirements in the respective SPC. The respective SPC provides no information on dose adjustments for the taxanes docetaxel and paclitaxel in this therapeutic indication.

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

Treatment with enfortumab vedotin and vinflunine was largely in compliance with the requirements of the respective SPC [3,4]. Deviations from the specifications of the SPC are described in dossier assessment A22-61. The SPC provides no information on the dosage and type of use of the taxanes paclitaxel and docetaxel in the therapeutic indication of urothelial carcinoma, as there is no approval for these in the therapeutic indication. However, the dosage of docetaxel and paclitaxel corresponds to the respective recommended dosages of docetaxel and paclitaxel monotherapies of other approved therapeutic indications [5,6].

Characteristics of the study population

Table 2 shows the characteristics of the patients in the total population of the EV-301 study.

Table 2: Characteristics of the study population as well as study/treatment discontinuation – RCT, direct comparison: enfortumab vedotin vs. treatment of physician's choice[a] (multipage table)

Study characteristic category	Enfortumab vedotin N[b] = 301	Treatment of physician's choice[a] N[b] = 307
EV-301		
Age [years], mean (SD)	67 (9)	67 (10)
Sex [F/M], %	21/79	24/76
Family origin, n (%)		
White	159 (53)	155 (51)
Asian	97 (32)	103 (34)
Other/unknown	45 (15)[c]	49 (16)[c]
Region, n (%)		
Western Europe	126 (42)	129 (42)
United States	43 (14)	44 (14)
Rest of the world	132 (44)	134 (44)
ECOG-PS, n (%)		
0	120 (40)	124 (40)
1	181 (60)	183 (60)
Liver metastases, n (%)		
Yes	93 (31)	95 (31)
No	208 (69)	212 (69)
Visceral metastases, n (%)		
Yes	234 (78)	250 (82)
No	67 (22)	56 (18)
Primary origin of the disease		
Upper tract	98 (33)	107 (35)
Bladder/other	203 (67)	200 (65)
Present extent of disease, n (%)		
Metastatic	290 (96)	289 (94)
Locally advanced	11 (4)	18 (6)
Number of prior lines of treatment, n (%)		
1	39 (13)[d]	32 (10)[d]
2	223 (74)	238 (78)
≥ 3	39 (13)	37 (12)
Treatment discontinuation first data cut-off 15 July 2020, n (%)[e]	245 (81)	285 (93)
Study discontinuation first data cut-off 15 July 2020, n (%)[f]	147 (49)	183 (60)
Treatment discontinuation second data cut-off 30 July 2021, n (%)[g]	285 (95)	301 (98)
Study discontinuation second data cut-off 30 July 2021, n (%)[h]	224 (74)	254 (83)

Table 2: Characteristics of the study population as well as study/treatment discontinuation – RCT, direct comparison: enfortumab vedotin vs. treatment of physician's choice[a] (multipage table)

Study characteristic category	Enfortumab vedotin N[b] = 301	Treatment of physician's choice[a] N[b] = 307

a. In the EV-301 study, therapy could be chosen from the chemotherapies vinflunine, paclitaxel and docetaxel.
b. Number of randomized patients.
c. Institute's calculation.
d. Within the framework of a clinical study, patients with only one prior line of treatment received a combination therapy of a platinum-containing chemotherapy and a PD-(L)1 inhibitor.
e. Common reasons for treatment discontinuation in the intervention versus the control arm were: disease progression (59% vs. 59%), AEs (14% vs. 15%), withdrawal of consent (5% vs. 9%).
c. Common reasons for study discontinuation in the intervention versus the control arm were: death (45% vs. 54%), withdrawal of consent (4% vs. 5 %).
g. Common reasons for treatment discontinuation in the intervention versus the control arm were: disease progression (67% vs. 62%), AEs (17% vs. 16%), withdrawal of consent (5% vs. 9 %).
h. Common reasons for study discontinuation in the intervention versus the control arm were: death (69% vs. 77%), withdrawal of consent (5% vs. 5%).

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

Both study arms were comparable in terms of patients' demographic and clinical characteristics.

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

Information on the course of the study

Table 3 shows the mean/median treatment duration of the total population and the mean/median observation period for individual outcomes.

Table 3: Information on the course of the study – RCT, direct comparison: enfortumab vedotin vs. treatment of physician's choice[a]

Study **duration of the study phase** **outcome category**	**Enfortumab vedotin** **N[b] = 301**	**Treatment of physician's choice[a]** **N[b] = 307**
EV-301		
Treatment duration, first data cut-off 15 July 2020 [months]	n = 296	n = 291
Median [min; max]	5.0 [0.5; 19.4]	3.5 [0.2; 15.0]
Mean (SD)	5.4 (3.7)	4.0 (3.0)
Treatment duration, second data cut-off 30 July 2021 [months][c]		
Median [min; max]	5.0 [0.5; 29.9]	3.4 [0.2; 26.4]
Mean (SD)	6.5 (5.8)	4.5 (4.4)
Observation period [months][c]	n = 301	n = 307
Overall survival, second data cut-off 30 July 2021		
Median [min; max][d]	11.7 [0.3; 35.8]	8.5 [0.0; 32.1]
Mean (SD)[d]	13.2 (8.6)	11.1 (8.3)
Morbidity (EORTC QLQ-C30 and EQ-5D VAS) and health-related quality of life (EORTC QLQ-C30), first data cut-off 15 July 2020	n = 301	n = 307
Median [min; max]	5.4 [0.0; 19.1]	3.5 [0.0; 15.0]
Mean (SD)	5.6 (3.8)	4.1 (3.1)
Side effects, second data cut-off 30 July 2021	n = 296	n = 291
Median [min; max]	5.6 [1.0; 30.7]	3.8 [1.0; 31.1]
Mean (SD)	7.2 (6.0)	5.3 (5.3)

a. In the EV-301 study, therapy could be chosen from the chemotherapies vinflunine, paclitaxel and docetaxel.
b. Number of randomized patients.
c. Institute's calculation from data in days.
d. Information on how the observation period was calculated is not available.

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

At both data cut-offs, the median duration of treatment with the study medication was longer in the intervention than in the control arm.

The median observation period for overall survival was 11.7 months in the intervention arm and 8.5 months in the control arm. For the outcomes of morbidity, health-related quality of life and side effects, whose observation period was linked to treatment end (see A22-61), the observation periods were markedly shorter in comparison. For these outcomes, conclusions can therefore be drawn only regarding the time under treatment with the study medication (plus 30 days); the median treatment time in both treatment arms was approximately half of the median observation time for overall survival (Table 3). Data for the entire observation period are missing for these outcomes.

Information on subsequent therapies

Table 4 shows the subsequent therapies patients received after discontinuing the study mediation.

Table 4: Information on subsequent antineoplastic therapies[a] - RCT, direct comparison: enfortumab vedotin vs. treatment of physician's choice[b], second data cut-off: 30 July 2021

Study drug	Patients with subsequent therapy n (%)	
	enfortumab vedotin N = 301	treatment of physician's choice[b] N = 307
EV-301		
Total[c]	132 (43.9)	145 (47.2)
Radiotherapy	24 (8.0)	31 (10.1)
Paclitaxel	18 (6.0)	12 (3.9)
Pembrolizumab	14 (4.7)	15 (4.9)
Enfortumab vedotin	3 (1.0)	16 (5.2)[d]
Carboplatin + gemcitabine	8 (2.7)	4 (1.3)
Vinflunine	9 (3.0)	0 (0)
Sacituzumab govitecan	1 (0.3)	7 (2.3)
Cisplatin + gemcitabine	3 (1.0)	4 (1.3)
Erdafitinib	3 (1.0)	4 (1.3)
Pemetrexed	3 (1.0)	3 (1.0)
Cisplatin + doxorubicin + methotrexate + vinblastine	2 (0.7)	3 (1.0)
Cisplatin + gemcitabine + paclitaxel	1 (0.3)	4 (1.3)
Docetaxel	3 (1.0)	2 (0.7)
Carboplatin + paclitaxel	2 (0.7)	2 (0.7)
Gemcitabine + paclitaxel	3 (1.0)	1 (0.3)
Combinations of antineoplastic drugs	12 (4.0)	10 (3.3)
Any other therapeutic products	3 (1.0)	6 (2.0)

a. Subsequent therapies taken in at least 1% in a study arm.
b. In the EV-301 study, therapy could be chosen from the chemotherapies vinflunine, paclitaxel and docetaxel.
a. Patients with at least one subsequent antineoplastic therapy; subsequent data on the specific therapies only refer to the first subsequent therapy.
d. According to Amendment 3 of the study protocol of 14 September 2020 after the first data cut-off (15 July 2020), a switch from the comparator arm to treatment of the intervention arm with enfortumab vedotin was possible. By the 2nd data cut-off, this option had been taken by 13 patients (4.2%). 3 other patients received enfortumab vedotin outside the framework of the described treatment switch.
n: number of patients with subsequent therapy; N: number of analysed patients; RCT: randomized controlled trial

After discontinuation of the study medication, 44% (enfortumab vedotin arm) and 47% (chemotherapy arm) of the patients received subsequent therapy. The most common subsequent therapy in both study arms was radiotherapy.

2.2 Results

2.2.1 Outcomes included

The following patient-relevant outcomes are presented:

- Mortality
  - overall survival
- Morbidity
  - symptoms measured with the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30 (EORTC QLQ-C30) symptom scales
  - health status measured using the EQ-5D visual analogue scale (VAS)
- Health-related quality of life
  - measured with the EORTC QLQ-C30 functional scales
- Side effects
  - serious adverse events (SAEs)
  - severe adverse events (AEs) (Common Terminology Criteria for Adverse Events [CTCAE] grade ≥ 3)
  - discontinuation due to adverse events (AEs)
  - constipation
  - peripheral neuropathy (Standardized Medical Dictionary for Regulatory Activities (MedDRA) Query [SMQ], AE)
  - febrile neutropenia (preferred term [PT], SAEs)
  - hyperglycaemia (PT, severe AEs)
  - further specific AEs, if any

Table 5 shows the outcomes for which data were available in the included study.

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

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

a. In the EV-301 study, therapy could be chosen from the chemotherapies vinflunine, paclitaxel and docetaxel.
b. Operationalized as CTCAE grade ≥ 3.
c. The following events (MedDRA coding) were considered: eye disorders (SOC, AEs), gait disorder (PT, AEs), myalgia (PT, AEs), dysgeusia (PT, AEs), acute kidney injury (PT, SAEs), blood and lymphatic system disorders (SOC, severe AEs), nervous system disorders (SOC, severe AEs), skin and subcutaneous tissue disorders (SOC, SAEs), infections and infestations (SOC, severe AEs) and investigations (SOC, severe AEs).
d. Does not apply to the symptom scale "constipation", for which no usable data are available; for justification see dossier assessment A22-61.
e. No usable data available; for justification see dossier assessment A22-61.

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

Comments on the response criteria for the scales of the EORTC QLQ-C30 and the EQ-5D VAS as well as on the outcomes of the category of side effects (overall rates of SAEs and severe AEs, as well as constipation) can be found in dossier assessment A22-61.

2.2.2 Results

Table 6 summarizes the results on the comparison of enfortumab vedotin with chemotherapy of physician's choice in patients with locally advanced or metastatic urothelial carcinoma, who had received prior platinum-containing chemotherapy and a PD-1 or PD-L1 inhibitor and for whom chemotherapy is suitable. Where necessary, calculations conducted by the Institute are provided in addition to the data from the company's dossier. The results on common AEs, SAEs, severe AEs and discontinuation due to AEs are presented in Appendix A of the full dossier assessment and the Kaplan-Meier curves on the included outcomes are presented in Appendix B of the full dossier assessment.

Table 6: Results (mortality, morbidity, health-related quality of life, side effects) – RCT, direct comparison: enfortumab vedotin vs. treatment of physician's choice[a] (multipage table)

Study outcome category outcome	Enfortumab vedotin		Treatment of physician's choice[a]		Enfortumab vedotin vs. treatment of physician's choice[a]
	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][b]; p-value[c]
EV-301					
Mortality					
Overall survival (second data cut-off 30 July 2021)	301	12.91 [11.01; 14.92] 207 (68.8)	307	8.94 [8.25; 10.25] 237 (77.2)	0.70 [0.58; 0.85]; < 0.001
Morbidity					
EORTC QLQ-C30 (first data cut-off 15 July 2020)[d]					
Fatigue	301	0.76 [0.59; 0.89] 197 (65.4)	307	0.72 [0.49; 0.82] 180 (58.6)	0.88 [0.71; 1.09]; 0.226
Nausea and vomiting	301	1.71 [1.41; 2.37] 140 (46.5)	307	1.28 [0.99; 1.87] 141 (45.9)	0.83 [0.65; 1.05]; 0.121
Pain	301	1.08 [0.95; 1.54] 165 (54.8)	307	1.08 [0.95; 1.38] 159 (51.8)	0.87 [0.69; 1.09]; 0.220
Dyspnoea	301	4.44 [1.71; NC] 118 (39.2)	307	1.94 [1.51; 2.60] 130 (42.3)	0.78 [0.61; 1.01]; 0.055
Insomnia	301	1.81 [1.05; 2.60] 139 (46.2)	307	1.48 [1.08; 2.33] 134 (43.6)	0.85 [0.67; 1.09]; 0.194
Appetite loss	301	1.08 [0.82; 1.51] 164 (54.5)	307	1.15 [0.99; 1.71] 142 (46.3)	1.00 [0.80; 1.26]; 0.969
Constipation	No usable data[e]				
Diarrhoea	301	2.14 [1.45; 7.49] 129 (42.9)	307	2.79 [1.58; 7.69] 114 (37.1)	1.01 [0.78; 1.30]; 0.938
Health status (EQ-5D VAS, first data cut-off)[f]	301	2.53 [1.68; 5.52] 132 (43.9)	307	2.10 [1.51; 2.53] 136 (44.3)	0.79 [0.62; 1.01]; 0.069
Health-related quality of life					
EORTC QLQ-C30 (first data cut-off 15 July 2020)[g]					
Global health status	301	1.41 [1.02; 1.91] 162 (53.8)	307	0.99 [0.79; 1.18] 156 (50.8)	0.79 [0.63; 0.99]; 0.046
Physical functioning	301	1.87 [1.25; 2.66] 153 (50.8)	307	1.45 [1.12; 1.68] 151 (49.2)	0.78 [0.62; 0.99]; 0.041
Role functioning	301	0.99 [0.79; 1.38] 174 (57.8)	307	0.79 [0.72; 0.99] 175 (57.0)	0.76 [0.62; 0.95]; 0.015
Emotional functioning	301	5.45 [2.46; 6.54] 116 (38.5)	307	2.43 [1.48; 4.17] 124 (40.4)	0.73 [0.56; 0.95]; 0.019
Cognitive functioning	301	1.71 [1.28; 2.20] 155 (51.5)	307	1.45 [1.02; 1.64] 143 (46.6)	0.91 [0.72; 1.14]; 0.401
Social functioning	301	1.02 [0.79; 1.41] 167 (55.5)	307	0.89 [0.76; 1.08] 156 (50.8)	0.87 [0.69; 1.09]; 0.203

Table 6: Results (mortality, morbidity, health-related quality of life, side effects) – RCT, direct comparison: enfortumab vedotin vs. treatment of physician's choice[a] (multipage table)

Study outcome category outcome	Enfortumab vedotin		Treatment of physician's choice[a]		Enfortumab vedotin vs. treatment of physician's choice[a]
	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][b]; p-value[c]
Side effects (second data cut-off 30 July 2021)[h]					
AEs (supplementary information)	296	0.20 [0.16; 0.23] 290 (98.0)	291	0.13 [0.10; 0.16] 288 (99.0)	–
SAEs	296	14.36 [5.45; NC] 143 (48.3)	291	NA [5.26; NC] 135 (46.4)	0.94 [0.75; 1.20]; 0.643
Severe AEs[i]	296	1.77 [1.28; 2.27] 216 (73.0)	291	1.41 [0.95; 2.14] 200 (68.7)	0.96 [0.79; 1.17]; 0.734
Discontinuation due to AEs	296	NA 62 (20.9)	291	NA 61 (21.0)	0.93 [0.65; 1.33]; 0.697
Constipation	No usable data[e]				
Peripheral neuropathy (SMQ, AEs)	296	5.68 [4.63; 8.34] 153 (51.7)	291	NA 104 (35.7)	1.40 [1.09; 1.81] 0.008
Febrile neutropenia (PT, SAEs)	296	NA 4 (1.4)	291	NA 16 (5.5)	0.23 [0.08; 0.70] 0.005
Hyperglycaemia (PT, severe AEs[i])	296	NA 21 (7.1)	291	NA 3 (1.0)	6.93 [2.07; 23.25] < 0.001
Eye disorders (SOC, AEs)	296	NA 86 (29.1)	291	NA 26 (8.9)	3.67 [2.36; 5.70]; < 0.001
Gait disorder (PT, AEs)	296	NA 10 (3.4)	291	NA 0 (0)	NC; 0.004
Myalgia (PT, AEs)	296	NA 15 (5.1)	291	NA 35 (12.0)	0.40 [0.22; 0.73] 0.002
Dysgeusia (PT, AEs)	296	NA 75 (25.3)	291	NA 24 (8.2)	3.28 [2.07; 5.21] < 0.001
Acute kidney injury (PT, SAEs)	296	NA 20 (6.8)	291	NA 9 (3.1)	2.17 [0.99; 4.77] 0.048
Blood and lymphatic system disorders (SOC, severe AEs)j	296	NA 32 (10.8)	291	NA 71 (24.4)	0.38 [0.25; 0.58]; < 0.001
Nervous system disorders (SOC, severe AEsi)k	296	NA 32 (10.8)	291	NA 14 (4.8)	2.03 [1.08; 3.82] 0.026
Skin and subcutaneous tissue disorders (SOC, AEs)	296	NA 14 (4.7)	291	NA 1 (0.3)	14.23 [1.87; 108.27] < 0.001
Infections and infestations (SOC, severe AEs[i])[l]	296	NA 58 (19.6)	291	NA 35 (12.0)	1.62 [1.07; 2.47] 0.022
Investigations (SOC, severe AEsi)m	296	NA 46 (15.5)	291	NA 64 (22.0)	0.61 [0.42; 0.90] 0.012

Table 6: Results (mortality, morbidity, health-related quality of life, side effects) – RCT, direct comparison: enfortumab vedotin vs. treatment of physician's choice[a] (multipage table)

Study outcome category outcome	Enfortumab vedotin		Treatment of physician's choice[a]		Enfortumab vedotin vs. treatment of physician's choice[a]
	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][b]; p-value[c]
a. In the EV-301 study, therapy could be chosen from the chemotherapies vinflunine, paclitaxel and docetaxel. b. Effect and CI: Cox proportional hazards model, stratified by ECOG PS (0 vs. 1), region (United States vs. Western Europe vs. other) and liver metastases (yes versus no). c. p-value: 2-sided log-rank test. d. Time to first deterioration; a score increase by ≥ 10 points from baseline is defined as a clinically relevant deterioration (scale range 0 to 100). e. See dossier assessment A22-61 for reasons. f. Time to first deterioration; a score decrease by ≥ 15 points from baseline is defined as a clinically relevant deterioration (scale range 0 to 100). g. Time to first deterioration; a score decrease by ≥ 10 points from baseline is defined as a clinically relevant deterioration (scale range 0 to 100). h. Including events caused by progression of the underlying disease. i. Operationalized as CTCAE grade ≥ 3. j. Including the PTs "anaemia", "febrile neutropenia" and "neutropenia" as most common manifestations. k. Including the PT "peripheral sensory neuropathy" as most common manifestation. l. Including the PTs "pneumonia" and "bacterial urinary tract infection" as most common manifestations. m. Including the PTs "neutrophil count decreased" and "white blood cell count decreased" as most common manifestations. AE: adverse event; CI: confidence interval; 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; HR: hazard ratio; n: number of patients with (at least 1) event; N: number of analysed patients; NA: not achieved; NC: not calculable; PT: Preferred Term; RCT: randomized controlled trial; SAE: serious adverse event; SMQ: Standardized MedDRA Query; SOC: System Organ Class; VAS: visual analogue scale					

Overall, for the outcome of overall survival, for the functional scales global health status, physical functioning, role functioning and emotional functioning, as well as for the outcomes of febrile neutropenia (SAEs), myalgia (AEs), blood and lymphatic system disorders (severe AEs) and investigations (severe AEs), there was a statistically significant difference in favour of enfortumab vedotin compared to chemotherapy of physician's choice. In this context, there is an effect modification by the characteristic "sex" for each of the outcomes of overall survival and febrile neutropenia (SAEs), by the characteristic "age" for the functional scale "global health status" and the outcome "blood and lymphatic system disorders" (severe AEs), and by the characteristic "liver metastases" for the outcome "investigations" (severe AEs) (see Section 2.2.3). No statistically significant difference between the treatment arms was shown for the "appetite loss" symptom scale, but there was an effect modification by the characteristic "sex".

Statistically significant differences to the disadvantage of enfortumab vedotin versus chemotherapy according to physician's choice was shown for the outcomes "peripheral

neuropathy (AEs)", "hyperglycaemia (severe AEs)", "eye disorders (AEs)", "gait disorders (AEs)", "dysgeusia (AEs)", "acute kidney injury (SAE)", "nervous system disorders (severe AEs)", "skin and subcutaneous tissue disorders (SAEs)" and "infections and infestations (severe AEs)".

No statistically significant differences between the treatment arms were shown for the remaining outcomes recorded.

2.2.3 Subgroups and other effect modifiers

The following potential effect modifiers were taken into account for the present addendum:

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

The characteristics mentioned were prespecified.

Interaction tests are performed if 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 1 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.

The results are presented in Table 7. The Kaplan-Meier curves on the subgroup results are presented in Appendix B of the full dossier assessment.

Table 7: Subgroups (mortality, morbidity, health-related quality of life) – RCT, direct comparison: enfortumab vedotin vs. treatment of physician's choice[a] (multipage table)

Study outcome characteristic subgroup	Enfortumab vedotin		Treatment of physician's choice[a]		Enfortumab vedotin vs. treatment of physician's choice[a]	
	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[b]
EV-301						
Mortality (second data cut-off 30 July 2021)						
Overall survival						
Sex						
Male	238	13.47 [11.01; 17.02] 159 (66.8)	232	8.87 [8.05; 10.02] 187 (80.6)	0.64 [0.52; 0.79]	< 0.001
Female	63	11.40 [8.28; 14.92] 48 (76.2)	75	10.68 [7.62; 17.25] 50 (66.7)	1.19 [0.80; 1.78]	0.368
Total					Interaction:	0.006[c]
Morbidity						
EORTC QLQ-C30 (first data cut-off 15 July 2020)[d]						
Appetite loss						
Sex						
Male	238	0.99 [0.76; 1.28] 136 (57.1)	232	1.51 [0.99; 1.97] 102 (44.0)	1.13 [0.87; 1.46]	0.347
Female	63	1.68 [0.82; NC] 28 (44.4)	75	0.99 [0.62; 1.15] 40 (53.3)	0.60 [0.37; 0.97]	0.024
Total					Interaction:	0.022[c]
Health-related quality of life						
EORTC QLQ-C30 (first data cut-off 15 July 2020)[e]						
Global health status						
Age						
< 65 years	108	1.45 [0.82; 2.17] 58 (53.7)	111	2.17 [0.99; 5.36] 43 (38.7)	1.16 [0.78; 1.73]	0.466
≥ 65 years	193	1.41 [1.02; 1.94] 104 (53.9)	196	0.95 [0.62; 1.12] 113 (57.7)	0.66 [0.51; 0.87]	0.003
Total					Interaction:	0.021[c]
Side effects (second data cut-off 30 July 2021)						
Febrile neutropenia (PT, SAEs)						
Sex						
Male	234	NA [NC; NC] 2 (0.9)	219	NA [NC; NC] 15 (6.8)	0.12 [0.03; 0.52]	< 0.001
Female	62	NA [NC; NC] 2 (3.2)	72	NA [NC; NC] 1 (1.4)	2.36 [0.21; 26.05]	0.447
Total					Interaction:	0.037[c]

Table 7: Subgroups (mortality, morbidity, health-related quality of life) – RCT, direct comparison: enfortumab vedotin vs. treatment of physician's choice[a] (multipage table)

Study outcome characteristic subgroup	Enfortumab vedotin		Treatment of physician's choice[a]		Enfortumab vedotin vs. treatment of physician's choice[a]	
	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[b]
Blood and lymphatic system disorders (SOC, severe AEs)f						
Age						
< 65 years	106	NA [NC; NC] 15 (14.2)	103	NA [NC; NC] 19 (18.4)	0.69 [0.35; 1.36]	0.300
≥ 65 years	190	NA [NC; NC] 17 (8.9)	188	NA [NC; NC] 52 (27.7)	0.28 [0.16; 0.49]	< 0.001
Total					Interaction:	0.042[c]
Investigations (SOC, severe AEs)f						
Liver metastases						
Yes	92	NA [NC; NC] 16 (17.4)	87	NA [NC; NC] 12 (13.8)	1.22 [0.58; 2.57]	0.618
No	204	NA [NC; NC] 30 (14.7)	204	NA [NC; NC] 52 (25.5)	0.51 [0.32; 0.80]	0.003
Total					Interaction:	0.049[c]

a. In the EV-301 study, therapy could be chosen from the chemotherapies vinflunine, paclitaxel and docetaxel.
b. p-value from 2-sided log rank test, unstratified.
c. p-value: Cox proportional hazards model, unstratified, adjusted for subgroup effect and interaction of treatment and subgroup effect.
d. Time to first deterioration; a score increase by ≥ 10 points from baseline is defined as a clinically relevant deterioration (scale range 0 to 100).
e. Time to first deterioration; a score decrease by ≥ 10 points from baseline is defined as a clinically relevant deterioration (scale range 0 to 100).
f. Operationalized as CTCAE ≥ 3.

AE: adverse event; CI: confidence interval; CTCAE: Common Terminology Criteria for Adverse Events; EORTC QLQ-C30: European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30; HR: hazard ratio; n: number of patients with event; N: number of analysed patients; NA: not achieved; NC: not calculable; RCT: randomized controlled trial; SAE: serious adverse event; SOC: System Organ Class

For the outcomes "overall survival" and "febrile neutropenia" (SAEs), a statistically significant difference was found in favour of enfortumab vedotin in comparison with treatment of physician's choice. For women, there was no statistically significant difference between treatment arms.

For the outcome of appetite loss, a statistically significant difference in favour of enfortumab vedotin in comparison with treatment of physician's choice was found for women. For men, there was no statistically significant difference between the treatment arms.

For the outcomes “global health status” and “blood and lymphatic system disorders” (severe AEs), a statistically significant difference was found in favour of enfortumab vedotin in comparison with treatment of physician’s choice for patients ≥ 65 years. In each case, there was no statistically significant difference between the treatment arms for patients < 65 years.

For the outcome of investigations (severe AEs), a statistically significant difference in favour of enfortumab vedotin in comparison with treatment of physician’s choice was shown for patients without liver metastases. No statistically significant difference between the treatment arms was found for patients with liver metastases.

2.3 Summary

For the total population, the EV-301 study overall showed the following results for enfortumab vedotin versus chemotherapy of physician’s choice choosing from vinflunine, paclitaxel and docetaxel:

- Statistically significant difference in favour of enfortumab vedotin:
  - overall survival (sex [male])
  - EORTC QLQ-C30 symptom scale: appetite loss (sex [female])
  - EORTC QLQ-C30 functional scales: global health status (age [≥ 65 years]), physical functioning, role functioning, and emotional functioning
  - febrile neutropenia (SAEs; sex [male])
  - myalgia (AEs), blood and lymphatic system disorders (severe AEs; age [≥ 65 years]) and investigations (severe AEs; liver metastases [no])
- Statistically significant difference in favour of enfortumab vedotin:
  - peripheral neuropathy (SMQ, AE)
  - hyperglycaemia (severe AEs)
  - eye disorders (AEs), gait disorders (AEs), dysgeusia (AEs), acute kidney injury (SAEs), nervous system disorders (severe AEs), skin and subcutaneous tissue disorders (SAEs) and infections and infestations (severe AEs)

3 References

1. Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen. Enfortumab Vedotin (Urothelkarzinom) – Nutzenbewertung gemäß § 35a SGB V; Dossierbewertung [online]. 2022 [Accessed: 02.09.2022]. URL: https://www.iqwig.de/download/a22-61_enfortumab-vedotin_nutzenbewertung-35a-sgb-v_v1-0.pdf.

2. Astellas Pharma. Enfortumab Vedotin (PADCEV); Dossier zur Nutzenbewertung gemäß § 35a SGB V [online]. 2022 [Accessed: 09.09.2022]. URL: https://www.g-ba.de/bewertungsverfahren/nutzenbewertung/836/#dossier.

3. Astellas Pharma Europe. Padcev 20 mg/30 mg Pulver für ein Konzentrat zur Herstellung einer Infusionslösung: Fachinformation [online]. 2022 [Accessed: 19.04.2022]. URL: https://www.fachinfo.de.

4. Pierre Fabre Medicament. Javlor 25 mg/ml Konzentrat zur Herstellung einer Infusionslösung: Fachinformation [online]. 2022 [Accessed: 01.04.2022]. URL: https://www.fachinfo.de.

5. Bristol-Myers Squibb. Abraxane 5 mg/ml Pulver zur Herstellung einer Infusionsdispersion [online]. 2021 [Accessed: 11.08.2022]. URL: https://fachinfo.de.

6. Hikma Farmacêutica. Docetaxel Hikma: Fachinformation [online]. 2021 [Accessed: 01.04.2022]. URL: https://www.lauer-fischer.de.

Appendix A Results on side effects

For the overall rates of AEs, SAEs and severe AEs (e. g. CTCAE grade ≥ 3) the following tables present events for System Organ Class (SOC) and PTs according to the MedDRA, each based on the following criteria:

- overall rate of AEs (irrespective of severity grade): events which occurred in at least 10% of patients of 1 study arm
- overall rates of severe AEs (e. g. CTCAE grade ≥ 3) and SAEs: events which occurred in at least 5% of patients in 1 study arm
- in addition, for all events irrespective of severity grade: events which occurred in at least 10 patients and in at least 1% of patients in 1 study arm

For the outcome "discontinuation due to AEs", a complete presentation of all events (SOCs/PTs) that resulted in discontinuation is provided.

Table 8: Common AEs[a] - RCT, direct comparison: enfortumab vedotin vs. treatment of physician's choice[b], second data cut-off: 30 July 2021 (multipage table)

Study	**Patients with event n (%)**	
SOC[c] **PT[c]**	**Enfortumab vedotin** **N = 296**	**Treatment of physician's choice[b]** **N = 291**
EV-301		
Overall AE rate[d]	290 (98.0)	288 (99.0)
Blood and lymphatic system disorders	87 (29.4)	128 (44.0)
Anaemia	62 (20.9)	91 (31.3)
Febrile neutropenia	4 (1.4)	16 (5.5)
Neutropenia	20 (6.8)	29 (10.0)
Thrombocytopenia	11 (3.7)	7 (2.4)
Cardiac disorders	25 (8.4)	16 (5.5)
Ear and labyrinth disorders	11 (3.7)	5 (1.7)
Eye disorders	86 (29.1)	26 (8.9)
Cataract	10 (3.4)	2 (0.7)
Dry eye	20 (6.8)	3 (1.0)
Lacrimation increased	34 (11.5)	12 (4.1)
Vision blurred	17 (5.7)	5 (1.7)
Gastrointestinal disorders	211 (71.3)	188 (64.6)
Abdominal pain	42 (14.2)	29 (10.0)
Abdominal pain upper	13 (4.4)	8 (2.7)
Constipation	85 (28.7)	80 (27.5)
Diarrhoea	106 (35.8)	70 (24.1)
Dry mouth	24 (8.1)	7 (2.4)
Dyspepsia	20 (6.8)	10 (3.4)
Nausea	95 (32.1)	78 (26.8)
Stomatitis	27 (9.1)	21 (7.2)
Vomiting	44 (14.9)	47 (16.2)
General disorders and administration site conditions	217 (73.3)	191 (65.6)
Asthenia	49 (16.6)	42 (14.4)
Chills	20 (6.8)	6 (2.1)
Fatigue	110 (37.2)	81 (27.8)
Gait disorder	10 (3.4)	0 (0)
General physical health deterioration	8 (2.7)	11 (3.8)
Malaise	13 (4.4)	23 (7.9)
Mucosal inflammation	15 (5.1)	14 (4.8)
Oedema peripheral	33 (11.1)	43 (14.8)
Pain	5 (1.7)	11 (3.8)
Pyrexia	68 (23.0)	45 (15.5)

Table 8: Common AEs[a] - RCT, direct comparison: enfortumab vedotin vs. treatment of physician's choice[b], second data cut-off: 30 July 2021 (multipage table)

Study	**Patients with event n (%)**	
SOC[c] **PT[c]**	**Enfortumab vedotin** **N = 296**	**Treatment of physician's choice[b]** **N = 291**
Hepatobiliary disorders	14 (4.7)	9 (3.1)
Infections and infestations	157 (53.0)	111 (38.1)
Conjunctivitis	19 (6.4)	3 (1.0)
Nasopharyngitis	15 (5.1)	10 (3.4)
Oral candidiasis	10 (3.4)	3 (1.0)
Pneumonia	22 (7.4)	12 (4.1)
Urinary tract infection	28 (9.5)	21 (7.2)
Bacterial urinary tract infection	24 (8.1)	13 (4.5)
Injury, poisoning, and procedural complications	45 (15.2)	34 (11.7)
Fall	20 (6.8)	9 (3.1)
Infusion related reaction	7 (2.4)	11 (3.8)
Investigations	141 (47.6)	124 (42.6)
Alanine aminotransferase increased	27 (9.1)	7 (2.4)
Amylase increased	12 (4.1)	4 (1.4)
Aspartate aminotransferase increased	36 (12.2)	6 (2.1)
Blood alkaline phosphatase increased	9 (3.0)	11 (3.8)
Blood creatinine increased	28 (9.5)	8 (2.7)
Lipase increased	12 (4.1)	11 (3.8)
Lymphocyte count decreased	15 (5.1)	18 (6.2)
Neutrophil count decreased	34 (11.5)	56 (19.2)
Weight loss (weight decreased)	48 (16.2)	21 (7.2)
White blood cell count decreased	16 (5.4)	34 (11.7)
Metabolism and nutrition disorders	176 (59.5)	131 (45.0)
Decreased appetite	123 (41.6)	82 (28.2)
Dehydration	11 (3.7)	8 (2.7)
Hyperglycaemia	31 (10.5)	6 (2.1)
Hyperkalaemia	9 (3.0)	12 (4.1)
Hypoalbuminaemia	14 (4.7)	11 (3.8)
Hypocalcaemia	10 (3.4)	11 (3.8)
Hypokalaemia	19 (6.4)	10 (3.4)
Hypomagnesaemia	18 (6.1)	10 (3.4)
Hyponatraemia	19 (6.4)	14 (4.8)
Hypophosphataemia	12 (4.1)	11 (3.8)

Table 8: Common AEs[a] - RCT, direct comparison: enfortumab vedotin vs. treatment of physician's choice[b], second data cut-off: 30 July 2021 (multipage table)

Study	**Patients with event n (%)**	
SOC[c] **PT[c]**	**Enfortumab vedotin** **N = 296**	**Treatment of physician's choice[b]** **N = 291**
Musculoskeletal and connective tissue disorders	106 (35.8)	123 (42.3)
Arthralgia	29 (9.8)	41 (14.1)
Back pain	31 (10.5)	27 (9.3)
Muscle spasms	11 (3.7)	8 (2.7)
Muscular weakness	16 (5.4)	7 (2.4)
Myalgia	15 (5.1)	35 (12.0)
Pain in extremity	20 (6.8)	16 (5.5)
Neoplasms benign, malignant and unspecified (incl. cysts and polyps)	24 (8.1)	26 (8.9)
Malignant neoplasm progression	12 (4.1)	10 (3.4)
Nervous system disorders	192 (64.9)	139 (47.8)
Dizziness	27 (9.1)	16 (5.5)
Dysgeusia	75 (25.3)	24 (8.2)
Headache	13 (4.4)	17 (5.8)
Peripheral neuropathy	21 (7.1)	17 (5.8)
Paraesthesia	16 (5.4)	10 (3.4)
Peripheral motor neuropathy	13 (4.4)	0 (0)
Peripheral sensory neuropathy	105 (35.5)	68 (23.4)
Dysgeusia	11 (3.7)	0 (0)
Psychiatric disorders	57 (19.3)	49 (16.8)
Depression	11 (3.7)	2 (0.7)
Insomnia	35 (11.8)	25 (8.6)
Renal and urinary disorders	84 (28.4)	57 (19.6)
Acute kidney injury	20 (6.8)	9 (3.1)
Dysuria	11 (3.7)	5 (1.7)
Haematuria	41 (13.9)	26 (8.9)
Reproductive system and breast disorders	11 (3.7)	12 (4.1)
Respiratory, thoracic, and mediastinal disorders	102 (34.5)	74 (25.4)
Cough	25 (8.4)	19 (6.5)
Dyspnoea	29 (9.8)	30 (10.3)
Epistaxis	11 (3.7)	4 (1.4)
Rhinorrhoea	15 (5.1)	9 (3.1)

Table 8: Common AEs[a] - RCT, direct comparison: enfortumab vedotin vs. treatment of physician's choice[b], second data cut-off: 30 July 2021 (multipage table)

Study	**Patients with event n (%)**	
SOC[c] **PT[c]**	**Enfortumab vedotin** **N = 296**	**Treatment of physician's choice[b]** **N = 291**
Skin and subcutaneous tissue disorders	238 (80.4)	155 (53.3)
Alopecia	141 (47.6)	113 (38.8)
Drug rash	26 (8.8)	6 (2.1)
Dry skin	53 (17.9)	13 (4.5)
Erythema	13 (4.4)	5 (1.7)
itching	103 (34.8)	22 (7.6)
Rash	52 (17.6)	21 (7.2)
Rash erythematous	10 (3.4)	1 (0.3)
Rash maculo-papular	52 (17.6)	8 (2.7)
Hyperpigmentation of the skin	20 (6.8)	2 (0.7)
Vascular disorders	48 (16.2)	44 (15.1)
Hypertension	13 (4.4)	14 (4.8)
Hypotension	13 (4.4)	8 (2.7)

a. Events that occurred in ≥ 10 patients in at least one study arm.
b. In the EV-301 study, therapy could be chosen from the chemotherapies vinflunine, paclitaxel and docetaxel.
c. MedDRA version 24.0; SOCs and PTs taken from Module 4 without adaptation.
d. Including events caused by progression of the underlying disease.

AE: adverse event; 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; SOC: System Organ Class

Table 9: Common SAEs[a] - RCT, direct comparison: enfortumab vedotin vs. treatment of physician's choice[b], second data cut-off: 30 July 2021

Study	**Patients with event n (%)**	
SOC[c] **PT[c]**	**Enfortumab vedotin** **N = 296**	**Treatment of physician's choice[b]** **N = 291**
EV-301		
Total SAE rate[d]	143 (48.3)	135 (46.4)
Blood and lymphatic system disorders	12 (4.1)	32 (11.0)
Febrile neutropenia	4 (1.4)	16 (5.5)
Gastrointestinal disorders	23 (7.8)	27 (9.3)
General disorders and administration site conditions	24 (8.1)	25 (8.6)
Infections and infestations	57 (19.3)	38 (13.1)
Pneumonia	12 (4.1)	9 (3.1)
Bacterial urinary tract infection	13 (4.4)	3 (1.0)
Metabolism and nutrition disorders	19 (6.4)	17 (5.8)
Neoplasms benign, malignant and unspecified (incl. cysts and polyps)	17 (5.7)	14 (4.8)
Malignant neoplasm progression	12 (4.1)	10 (3.4)
Nervous system disorders	13 (4.4)	4 (1.4)
Renal and urinary disorders	29 (9.8)	18 (6.2)
Acute kidney injury	20 (6.8)	9 (3.1)
Respiratory, thoracic, and mediastinal disorders	11 (3.7)	10 (3.4)
Skin and subcutaneous tissue disorders	14 (4.7)	1 (0.3)

a. Events that occurred in ≥ 10 patients in at least one study arm.
b. In the EV-301 study, therapy could be chosen from the chemotherapies vinflunine, paclitaxel and docetaxel.
c. MedDRA version 24.0; SOCs and PTs taken from Module 4 without adaptation.
d. Including events caused by progression of the underlying disease.

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 event; SOC: System Organ Class

Table 10: Common severe AEs (CTCAE grade ≥ 3)[a] - RCT, direct comparison: enfortumab vedotin vs. treatment of physician's choice[b], second data cut-off: 30 July 2021 (multipage table)

Study	**Patients with event n (%)**	
SOC[c] **PT[c]**	**Enfortumab vedotin N = 296**	**Treatment of physician's choice[b] N = 291**
EV-301		
Overall rate of severe AEs[d]	216 (73.0)	200 (68.7)
Blood and lymphatic system disorders	32 (10.8)	71 (24.4)
Anaemia	19 (6.4)	36 (12.4)
Febrile neutropenia	4 (1.4)	16 (5.5)
Neutropenia	14 (4.7)	22 (7.6)
Gastrointestinal disorders	30 (10.1)	35 (12.0)
Diarrhoea	13 (4.4)	5 (1.7)
General disorders and administration site conditions	43 (14.5)	32 (11.0)
Fatigue	21 (7.1)	14 (4.8)
Infections and infestations	58 (19.6)	35 (12.0)
Pneumonia	13 (4.4)	7 (2.4)
Bacterial urinary tract infection	13 (4.4)	4 (1.4)
Investigations	46 (15.5)	64 (22.0)
Lymphocyte count decreased	9 (3.0)	13 (4.5)
Neutrophil count decreased	21 (7.1)	45 (15.5)
White blood cell count decreased	4 (1.4)	22 (7.6)
Metabolism and nutrition disorders	67 (22.6)	35 (12.0)
Decreased appetite	16 (5.4)	8 (2.7)
Hyperglycaemia	21 (7.1)	3 (1.0)
Hyponatraemia	13 (4.4)	7 (2.4)
Musculoskeletal and connective tissue disorders	10 (3.4)	16 (5.5)
Neoplasms benign, malignant and unspecified (incl. cysts and polyps)	20 (6.8)	18 (6.2)
Malignant neoplasm progression	12 (4.1)	10 (3.4)
Nervous system disorders	32 (10.8)	14 (4.8)
Peripheral sensory neuropathy	16 (5.4)	7 (2.4)
Renal and urinary disorders	20 (6.8)	15 (5.2)
Respiratory, thoracic, and mediastinal disorders	17 (5.7)	11 (3.8)
Skin and subcutaneous tissue disorders	51 (17.2)	6 (2.1)
Rash maculo-papular	22 (7.4)	1 (0.3)
Vascular disorders	10 (3.4)	10 (3.4)

Table 10: Common severe AEs (CTCAE grade ≥ 3)[a] - RCT, direct comparison: enfortumab vedotin vs. treatment of physician's choice[b], second data cut-off: 30 July 2021 (multipage table)

Study	**Patients with event n (%)**	
SOC[c] **PT[c]**	**Enfortumab vedotin** **N = 296**	**Treatment of physician's choice[b]** **N = 291**

a. Events that occurred in ≥ 10 patients in at least one study arm.
b. In the EV-301 study, therapy could be chosen from the chemotherapies vinflunine, paclitaxel and docetaxel.
c. MedDRA version 24.0; SOCs and PTs taken from Module 4 without adaptation.
d. Including events caused by progression of the underlying disease.

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 11: Discontinuations due to AEs - RCT, direct comparison: enfortumab vedotin vs. treatment of physician's choice[a], second data cut-off: 30 July 2021 (multipage table)

Study	**Patients with event n (%)**	
SOC[b] **PT[b]**	**Enfortumab vedotin N = 296**	**Treatment of physician's choice[a] N = 291**
EV-301		
Total rate of discontinuations due to AEs[c]	62 (20.9)	61 (21.0)
Blood and lymphatic system disorders	2 (0.7)	9 (3.1)
Anaemia	0 (0)	3 (1.0)
Febrile neutropenia	0 (0)	3 (1.0)
Neutropenia	1 (0.3)	2 (0.7)
Pancytopenia	0 (0)	1 (0.3)
Thrombocytopenia	1 (0.3)	0 (0)
Cardiac disorders	0 (0)	2 (0.7)
Cardiac arrest	0 (0)	1 (0.3)
Cardiogenic shock	0 (0)	1 (0.3)
Eye disorders	0 (0)	1 (0.3)
Retinal detachment	0 (0)	1 (0.3)
Gastrointestinal disorders	0 (0)	5 (1.7)
Colitis	0 (0)	1 (0.3)
Constipation	0 (0)	3 (1.0)
Intestinal obstruction	0 (0)	1 (0.3)
Nausea	0 (0)	1 (0.3)
Small bowel obstruction	0 (0)	1 (0.3)
Vomiting	0 (0)	1 (0.3)
General disorders and administration site conditions	2 (0.7)	7 (2.4)
Asthenia	0 (0)	1 (0.3)
Condition worsened	0 (0)	1 (0.3)
Death	0 (0)	1 (0.3)
Fatigue	1 (0.3)	0 (0)
General physical health deterioration	0 (0)	3 (1.0)
Multiple organ dysfunction syndrome	1 (0.3)	0 (0)
Pyrexia	0 (0)	1 (0.3)
Hepatobiliary disorders	2 (0.7)	1 (0.3)
Abnormal liver function	2 (0.7)	1 (0.3)
Immune system disorders	1 (0.3)	0 (0)
Hypersensitivity	1 (0.3)	0 (0)

Table 11: Discontinuations due to AEs - RCT, direct comparison: enfortumab vedotin vs. treatment of physician's choice[a], second data cut-off: 30 July 2021 (multipage table)

Study	**Patients with event n (%)**	
SOC[b] **PT[b]**	**Enfortumab vedotin N = 296**	**Treatment of physician's choice[a] N = 291**
Infections and infestations	6 (2.0)	7 (2.4)
Conjunctivitis	1 (0.3)	0 (0)
Infected skin ulceration	0 (0)	1 (0.3)
Pelvic abscess	1 (0.3)	0 (0)
Pneumocystis jirovecii pneumonia	0 (0)	1 (0.3)
Pneumonia	2 (0.7)	2 (0.7)
Sepsis	0 (0)	3 (1.0)
Septic shock	1 (0.3)	0 (0)
Bacterial urinary tract infection	1 (0.3)	1 (0.3)
Injury, poisoning, and procedural complications	1 (0.3)	1 (0.3)
Fall	1 (0.3)	0 (0)
Infusion related reaction	0 (0)	1 (0.3)
Investigations	1 (0.3)	4 (1.4)
Hepatic enzyme increased	1 (0.3)	0 (0)
Lipase increased	0 (0)	1 (0.3)
Neutrophil count decreased	0 (0)	2 (0.7)
Platelet count decreased	0 (0)	2 (0.7)
White blood cell count decreased	0 (0)	1 (0.3)
Metabolic and nutritional disorders	7 (2.4)	4 (1.4)
Cell death	0 (0)	1 (0.3)
Decreased appetite	1 (0.3)	2 (0.7)
Hypercalcaemia	1 (0.3)	0 (0)
Hyperglycaemia	2 (0.7)	0 (0)
Hypoglycaemia	0 (0)	1 (0.3)
Hyponatraemia	2 (0.7)	0 (0)
Metabolic acidosis	1 (0.3)	0 (0)
Musculoskeletal and connective tissue disorders	1 (0.3)	2 (0.7)
Arthropathy	0 (0)	1 (0.3)
Back pain	0 (0)	1 (0.3)
Muscular weakness	1 (0.3)	0 (0)
Neoplasms benign, malignant and unspecified (incl. cysts and polyps)	5 (1.7)	9 (3.1)
Malignant ascites	0 (0)	1 (0.3)
Malignant neoplasm progression	5 (1.7)	6 (2.1)
Metastases to central nervous system	0 (0)	1 (0.3)
Bladder cancer with metastases	0 (0)	1 (0.3)

Table 11: Discontinuations due to AEs - RCT, direct comparison: enfortumab vedotin vs. treatment of physician's choice[a], second data cut-off: 30 July 2021 (multipage table)

Study	**Patients with event n (%)**	
SOC[b] **PT[b]**	**Enfortumab vedotin N = 296**	**Treatment of physician's choice[a] N = 291**
Nervous system disorders	27 (9.1)	11 (3.8)
Cerebral haematoma	1 (0.3)	0 (0)
Dizziness	1 (0.3)	0 (0)
Peripheral neuropathy	3 (1.0)	1 (0.3)
Paraesthesia	1 (0.3)	0 (0)
Peripheral motor neuropathy	5 (1.7)	0 (0)
Peripheral sensorimotor neuropathy	2 (0.7)	1 (0.3)
Peripheral sensory neuropathy	14 (4.7)	8 (2.7)
Polyneuropathy	1 (0.3)	1 (0.3)
Syncope	1 (0.3)	0 (0)
Renal and urinary disorders	4 (1.4)	0 (0)
Acute kidney injury	3 (1.0)	0 (0)
Renal insufficiency	1 (0.3)	0 (0)
Respiratory, thoracic, and mediastinal disorders	0 (0)	3 (1.0)
Interstitial lung disease	0 (0)	1 (0.3)
Pneumonitis	0 (0)	1 (0.3)
Shortage of breath	0 (0)	1 (0.3)
Skin and subcutaneous tissue disorders	13 (4.4)	3 (1.0)
Dermatitis bulloes	2 (0.7)	0 (0)
Drug rash	2 (0.7)	1 (0.3)
Pruritus	1 (0.3)	0 (0)
Rash	1 (0.3)	2 (0.7)
Rash erythematous	1 (0.3)	0 (0)
Rash maculo-papular	5 (1.7)	0 (0)
Skin hyperpigmentation	1 (0.3)	0 (0)
Toxic skin eruption	1 (0.3)	0 (0)

a. In the EV-301 study, therapy could be chosen from the chemotherapies vinflunine, paclitaxel and docetaxel.
b. MedDRA version 24.0; SOCs and PTs taken from Module 4.
c. Including events caused by progression of the underlying disease.

AE: adverse event; 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; SOC: System Organ Class

Appendix B Kaplan-Meier curves on the included outcomes

B.1 Mortality

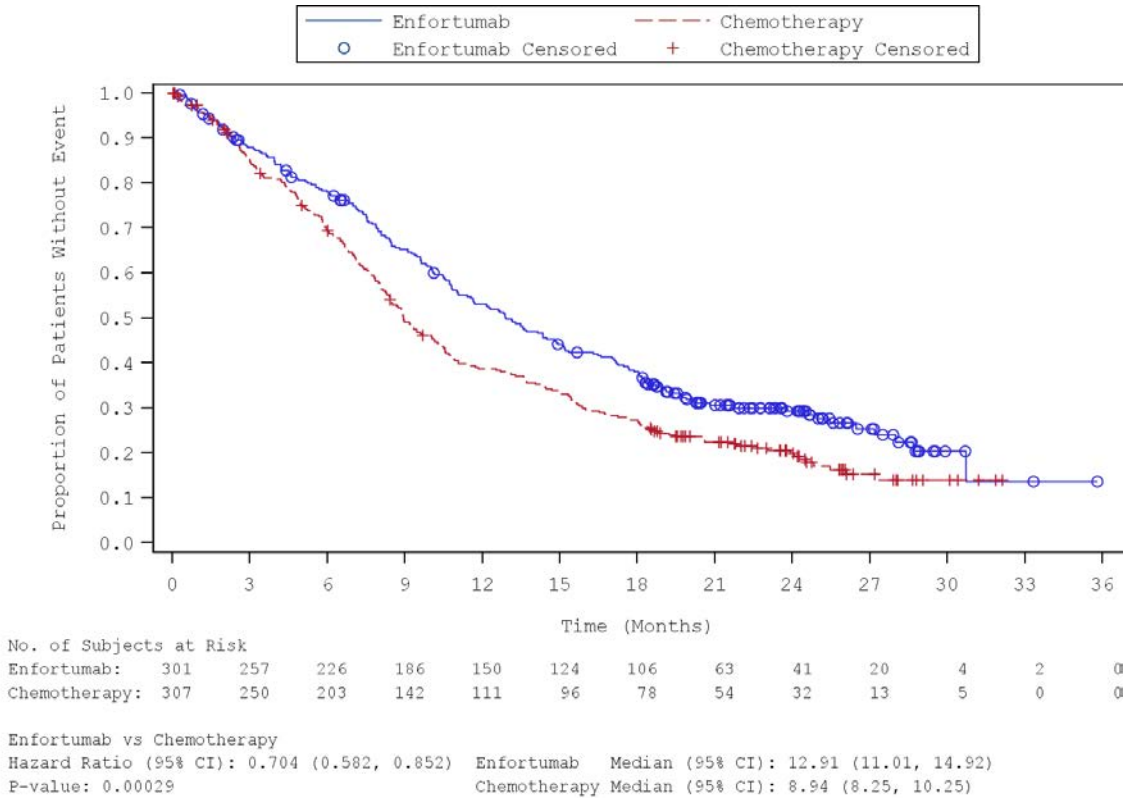

Figure 1: Kaplan-Meier curves on the outcome of overall survival - second data cut-off: 30 July 2021

B.2 Morbidity

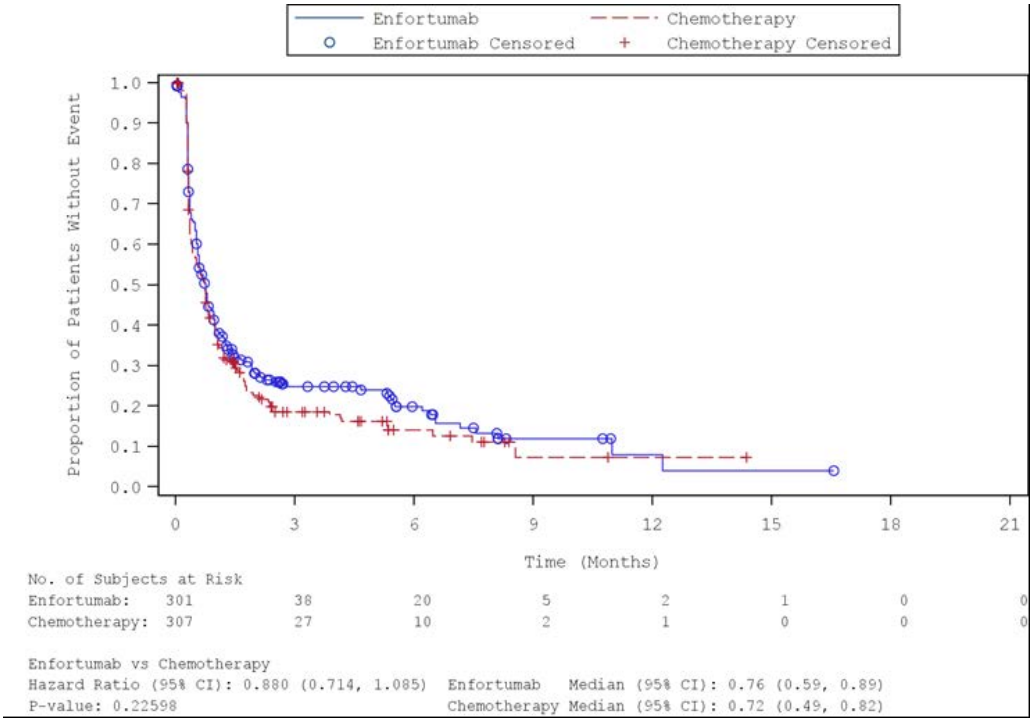

Figure 2: Kaplan-Meier curves on the outcome "fatigue" (EORTC QLQ-C30, first deterioration by ≥ 10 points), first data cut-off: 15 July 2020

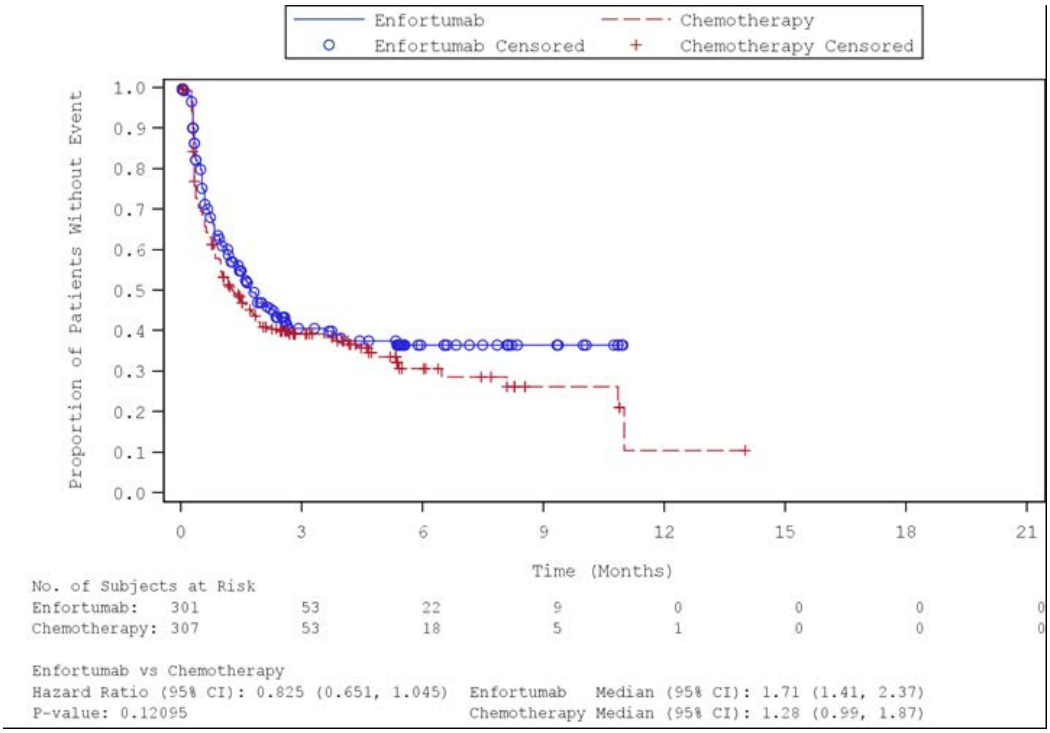

Figure 3: Kaplan-Meier curves on the outcome "nausea and vomiting" (EORTC QLQ-C30, first deterioration by ≥ 10 points) - first data cut-off: 15 July 2020

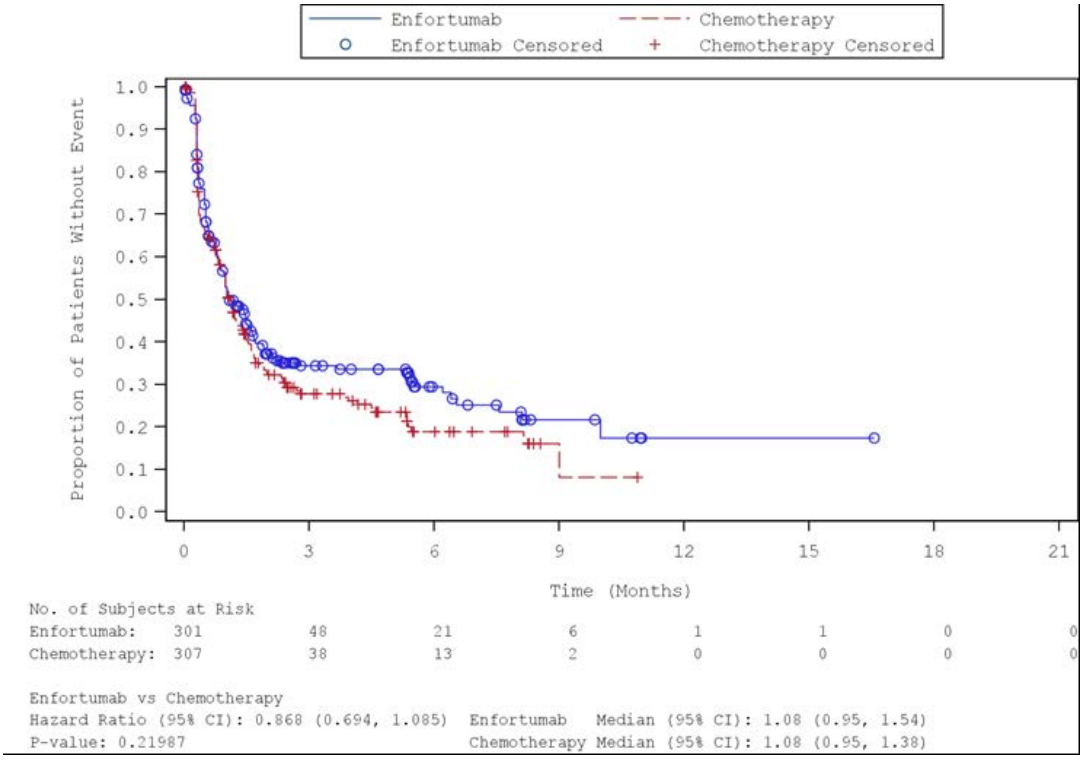

Figure 4: Kaplan-Meier curves on the outcome “pain” (EORTC QLQ-C30, first deterioration by ≥ 10 points) - first data cut-off: 15 July 2020

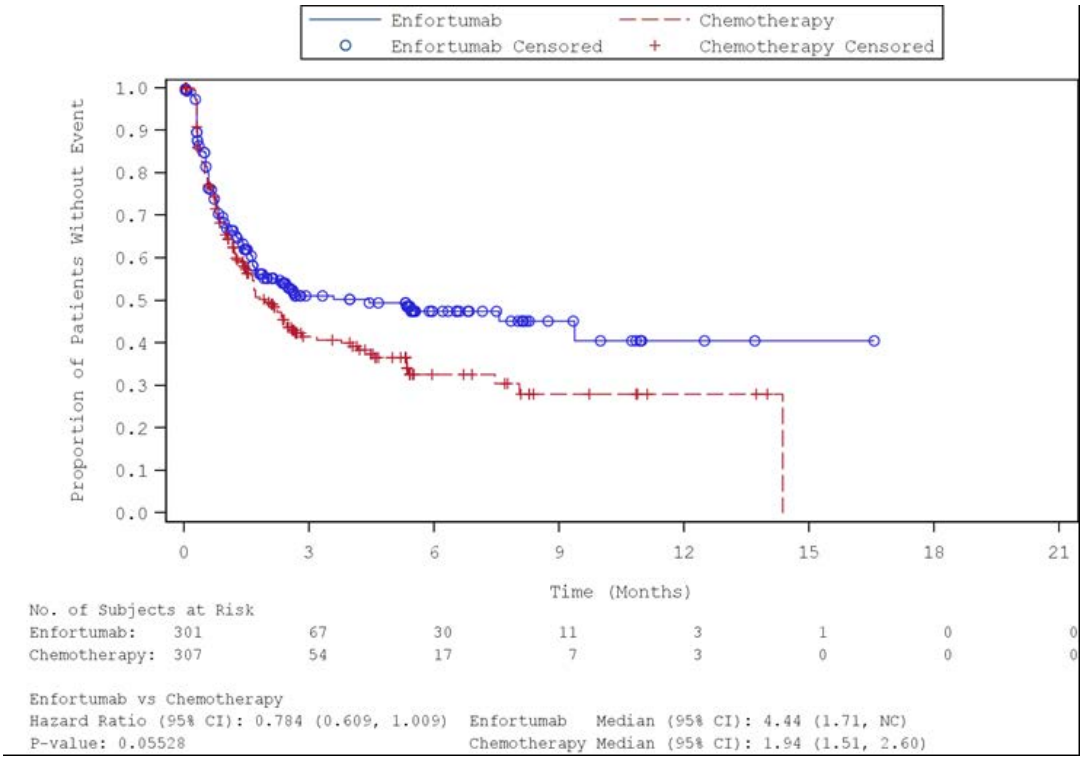

Figure 5: Kaplan-Meier curves on the outcome “dyspnoea” (EORTC QLQ-C30, first deterioration by ≥ 10 points) - first data cut-off: 15 July 2020

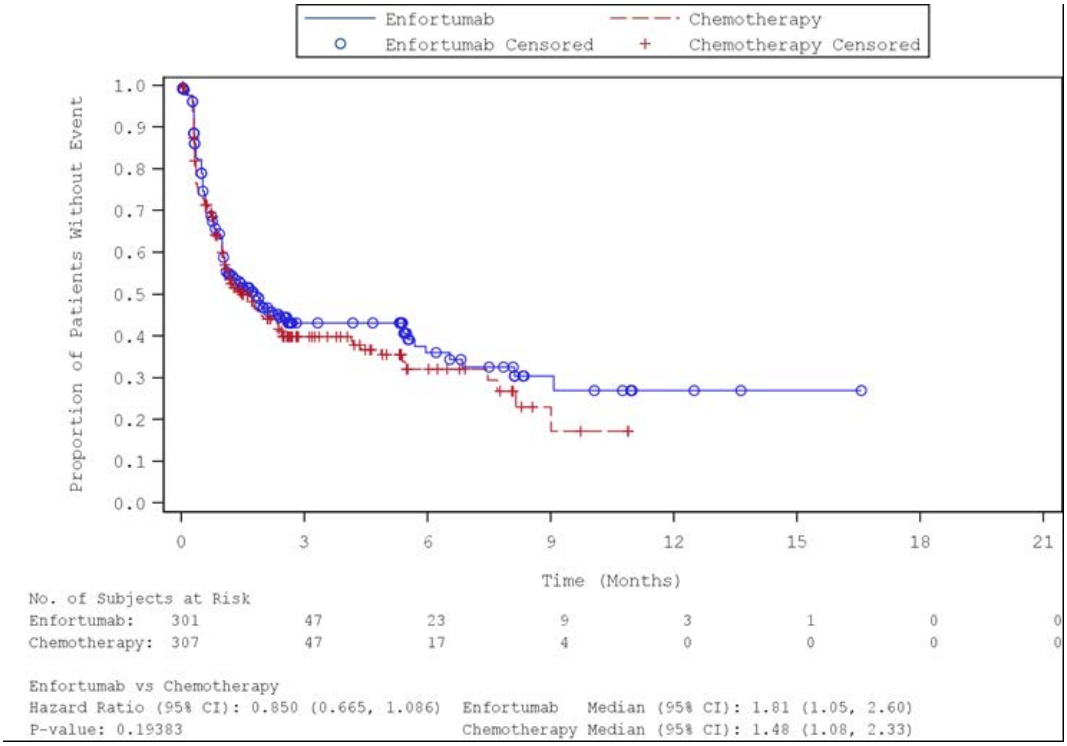

Figure 6: Kaplan-Meier curves on the outcome "insomnia" (EORTC QLQ-C30, first deterioration by ≥ 10 points) - first data cut-off: 15 July 2020

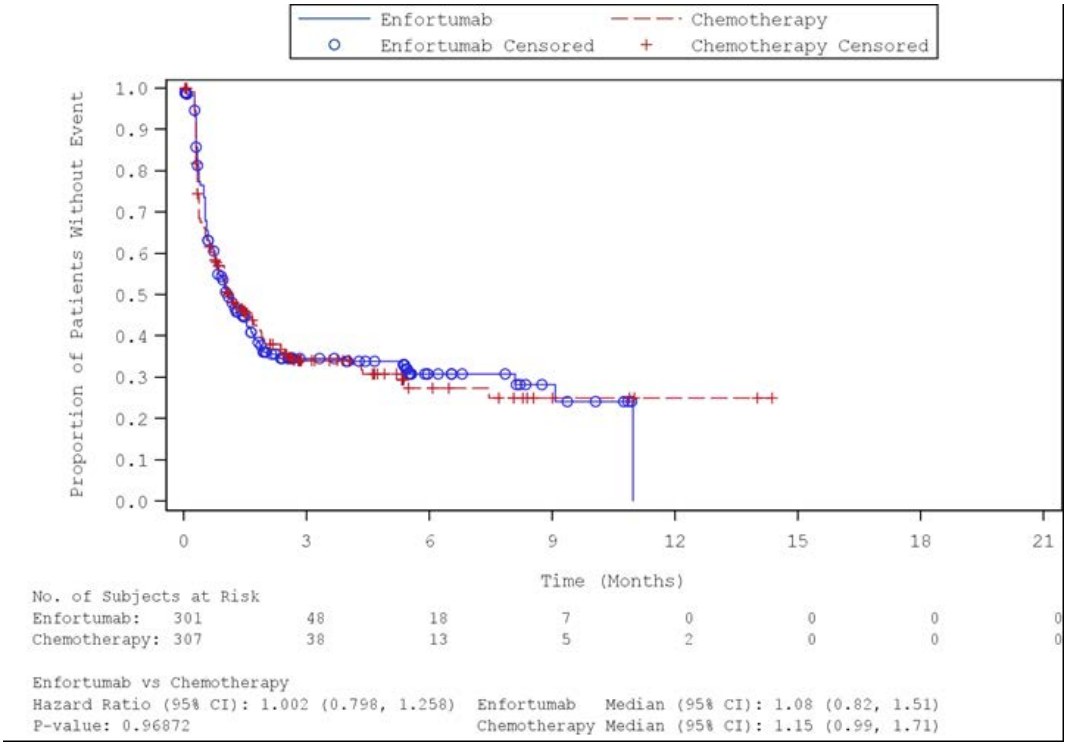

Figure 7: Kaplan-Meier curves on the outcome "appetite loss" (EORTC QLQ-C30, first deterioration by ≥ 10 points) - first data cut-off: 15 July 2020

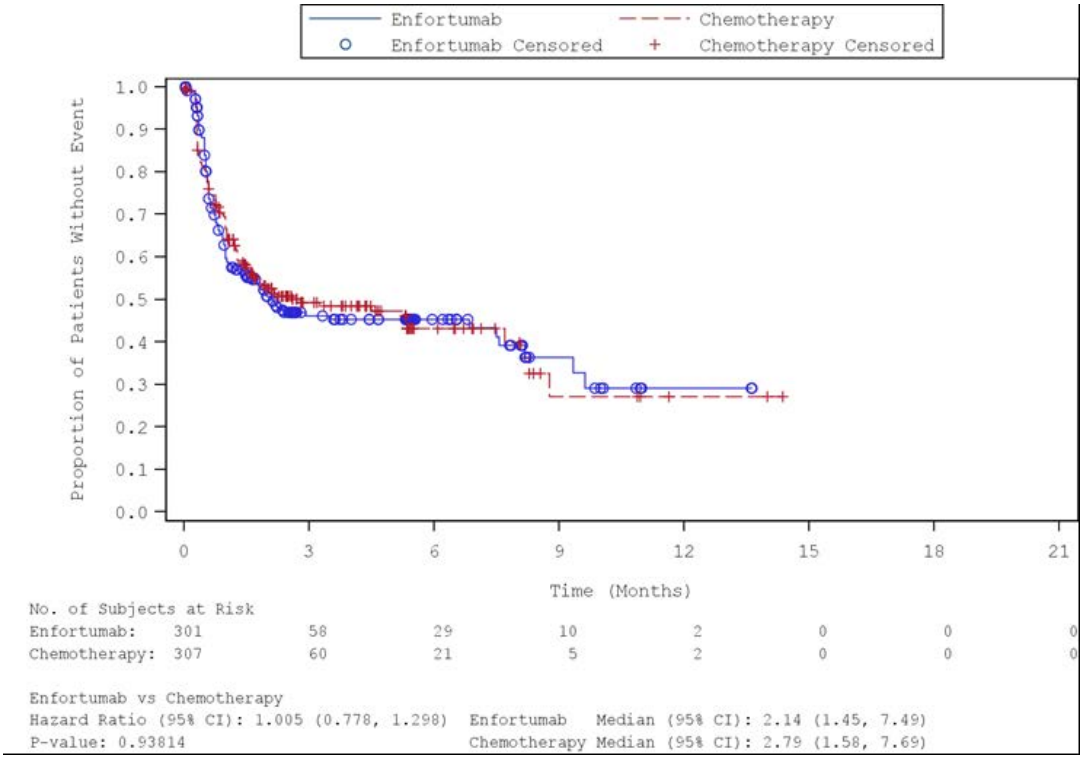

Figure 8: Kaplan-Meier curves on the outcome "diarrhoea" (EORTC QLQ-C30, first deterioration by ≥ 10 points) - first data cut-off: 15 July 2020

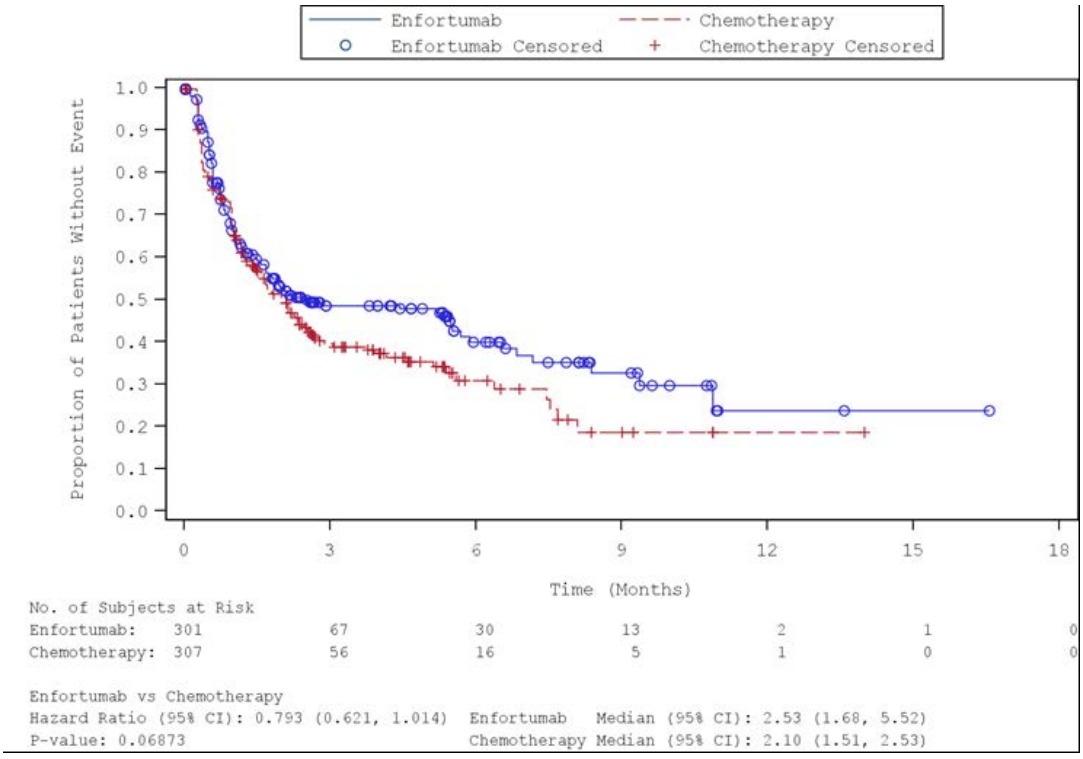

Figure 9: Kaplan-Meier curves on the outcome "health status" (EQ-5D VAS, first deterioration by ≥ 15 points) - first data cut-off: 15 July 2020

B.3 Health-related quality of life

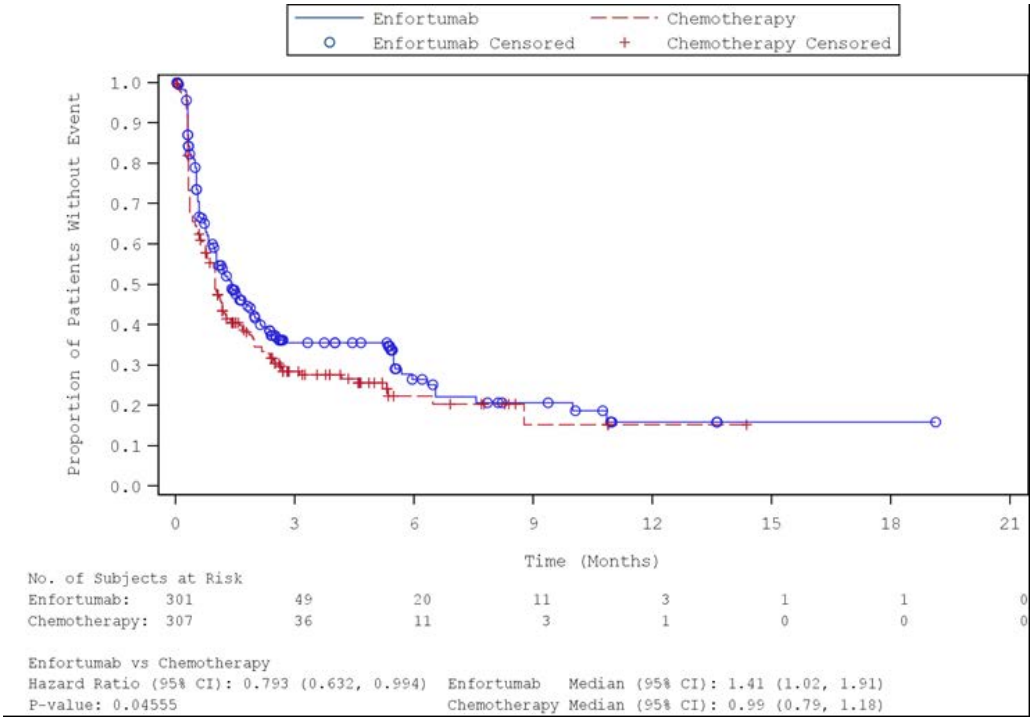

Figure 10: Kaplan-Meier curves on the outcome “global health status” (EORTC QLQ-C30, first deterioration by ≥ 10 points) - first data cut-off: 15 July 2020

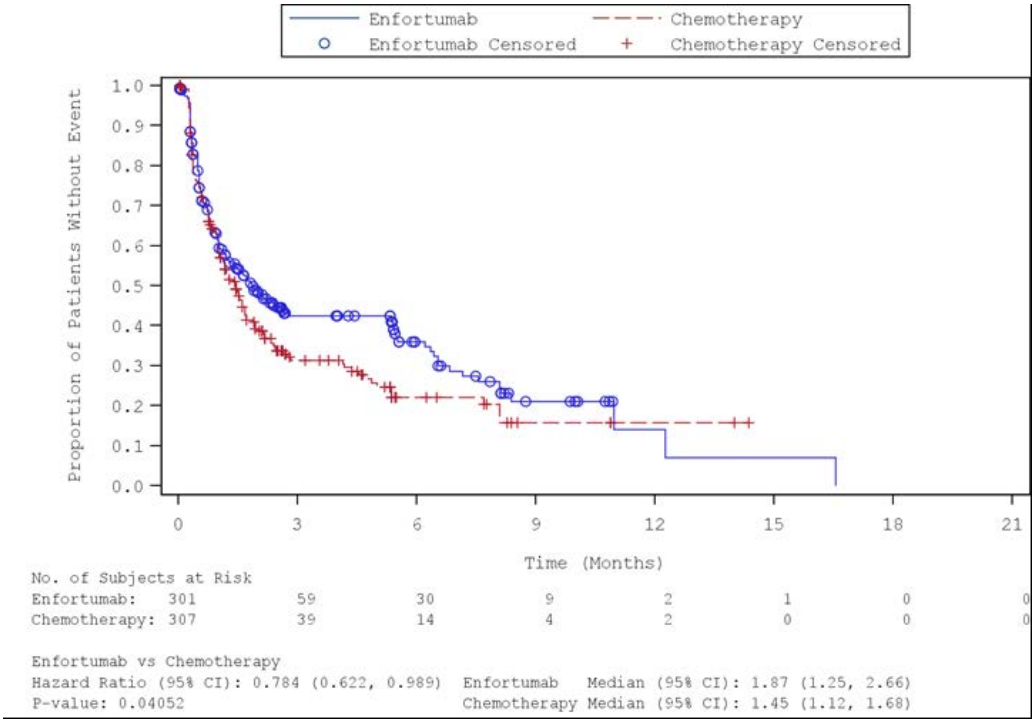

Figure 11: Kaplan-Meier curves on the outcome "physical functioning" (EORTC QLQ-C30, first deterioration by ≥ 10 points) - first data cut-off: 15 July 2020

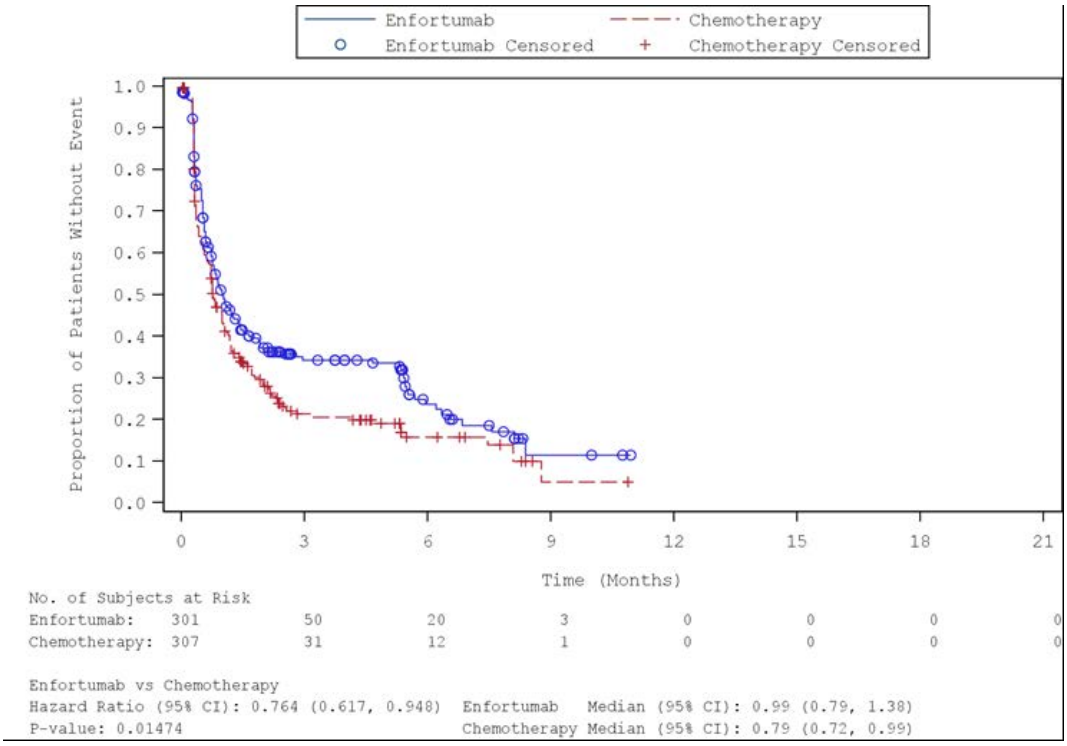

Figure 12: Kaplan-Meier curves on the outcome "role functioning" (EORTC QLQ-C30, first deterioration by ≥ 10 points) - first data cut-off: 15 July 2020

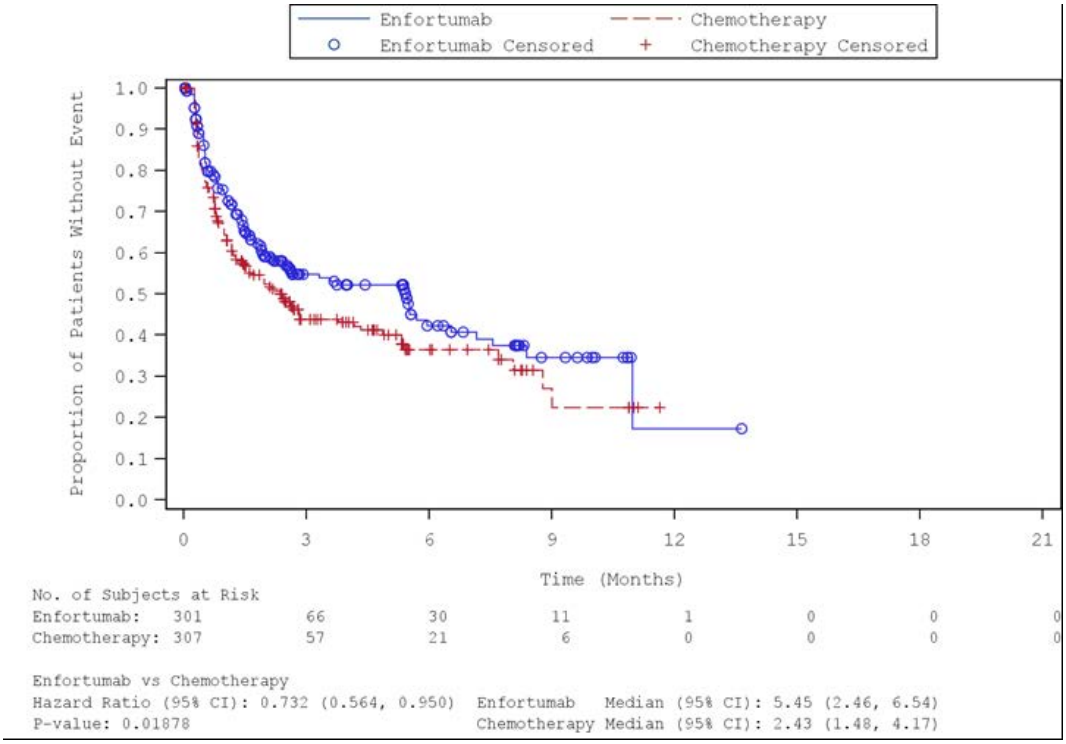

Figure 13: Kaplan-Meier curves on the outcome "emotional functioning" (EORTC QLQ-C30, first deterioration by ≥ 10 points) - first data cut-off: 15 July 2020

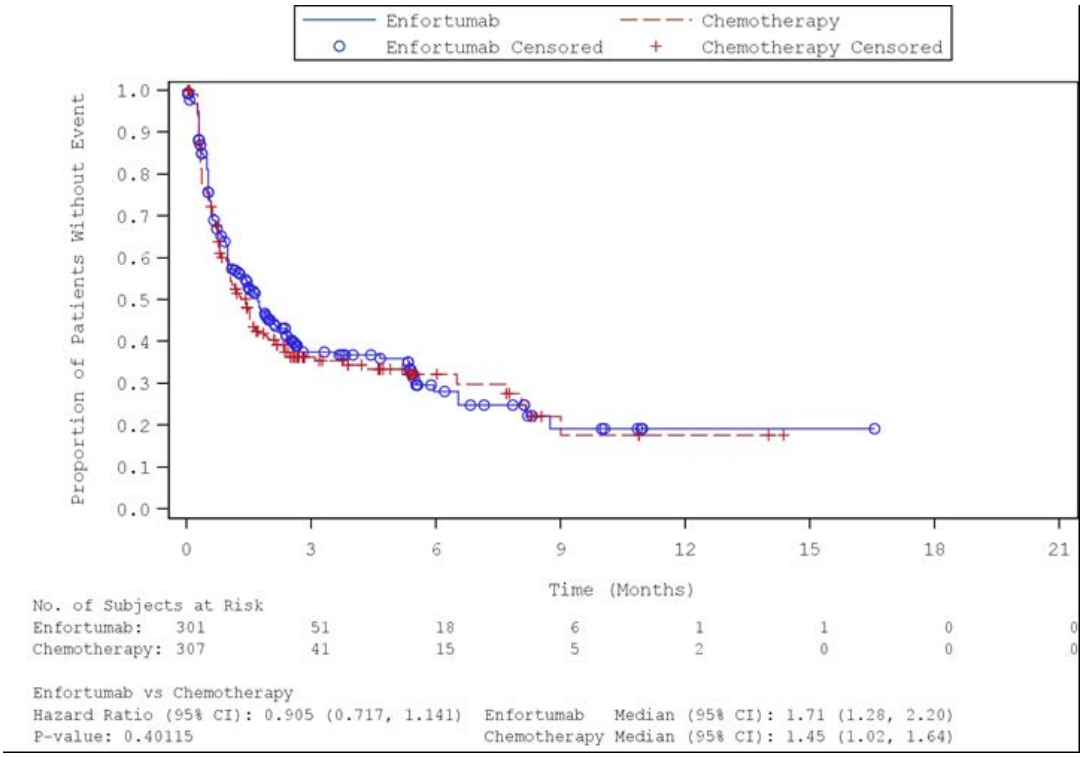

Figure 14: Kaplan-Meier curves on the outcome "cognitive functioning" (EORTC QLQ-C30, first deterioration by ≥ 10 points) - first data cut-off: 15 July 2020

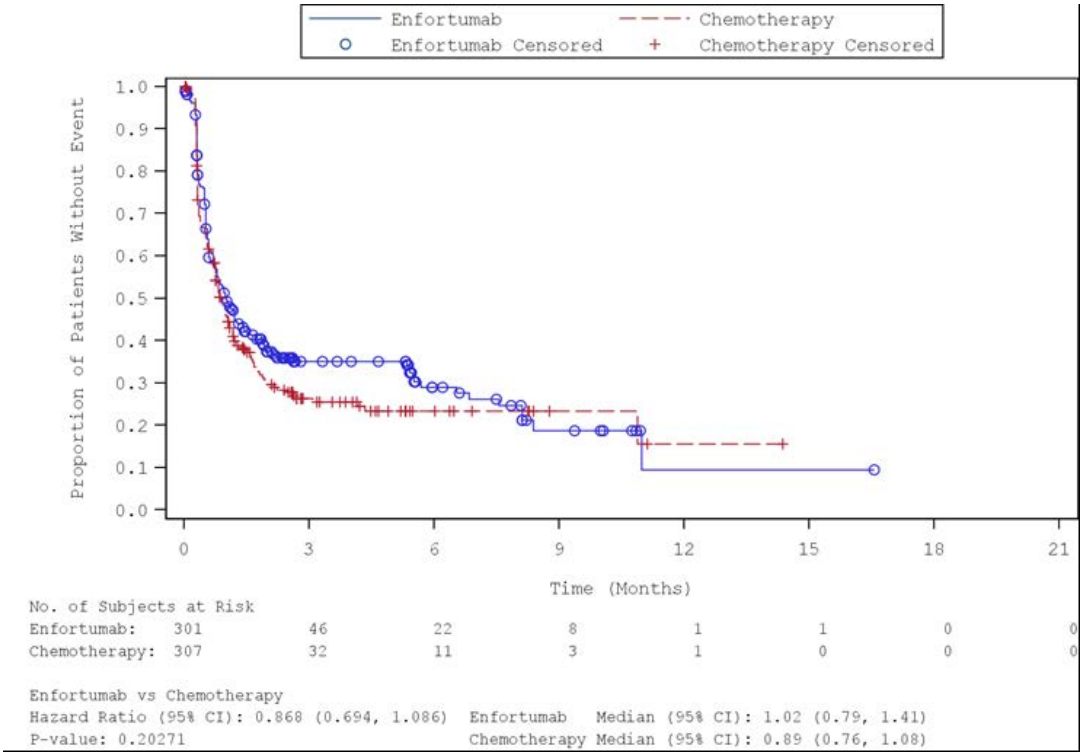

Figure 15: Kaplan-Meier curves on the outcome "social functioning" (EORTC QLQ-C30, first deterioration by ≥ 10 points) - first data cut-off: 15 July 2020

B.4 Side effects

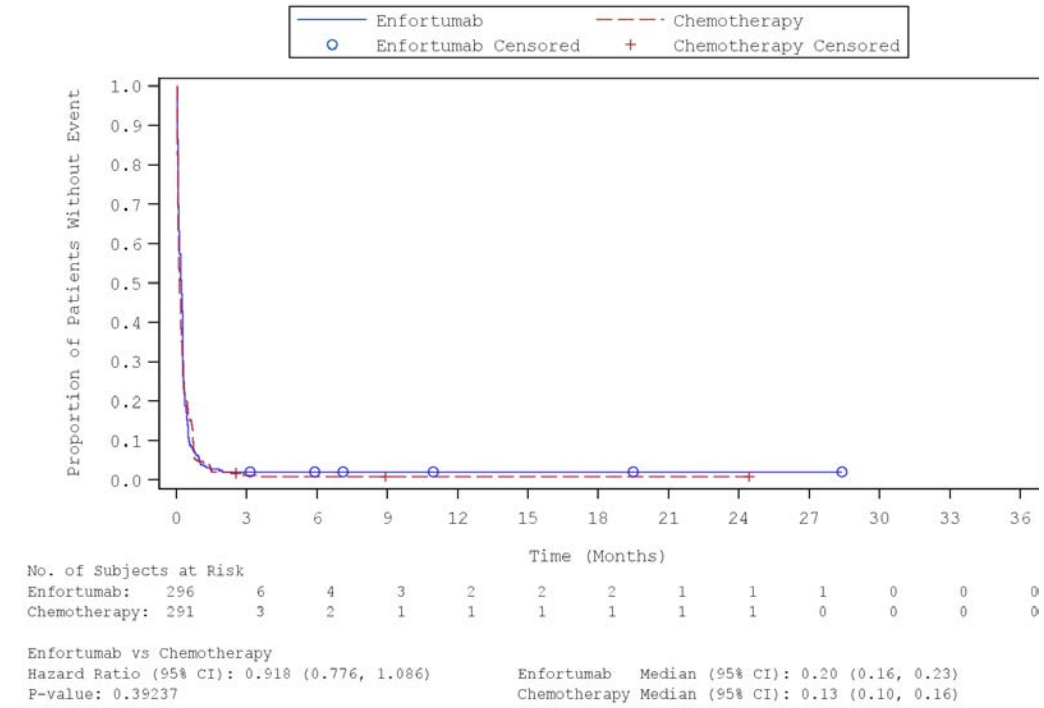

Figure 16: Kaplan-Meier curves on the outcome "AEs" (presented as supplementary information) - second data cut-off: 30 July 2021

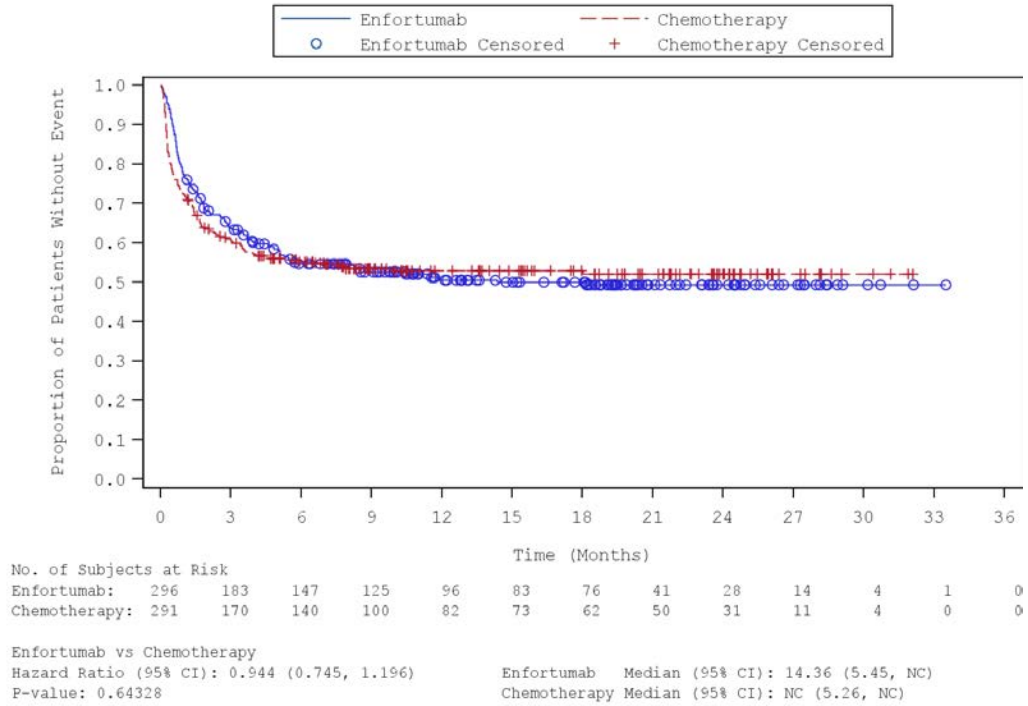

Figure 17: Kaplan-Meier curves on the outcome "SAEs" - second data cut-off: 30 July 2021

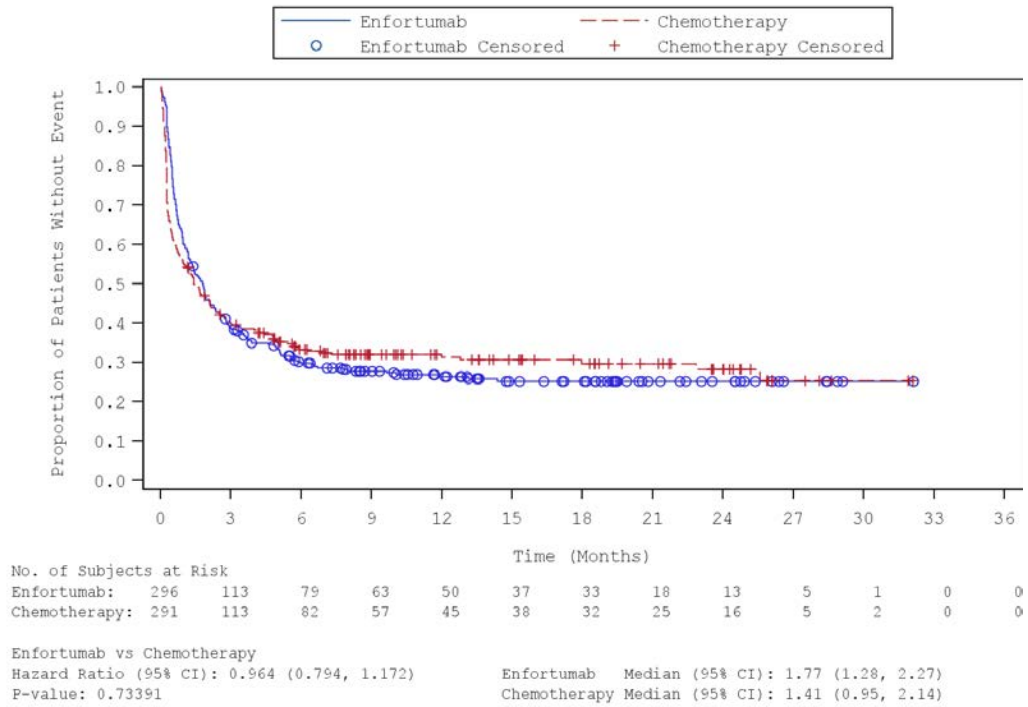

Figure 18: Kaplan-Meier curves on the outcome "severe AEs" (CTCAE grade ≥ 3) - second data cut-off 30 July 2021

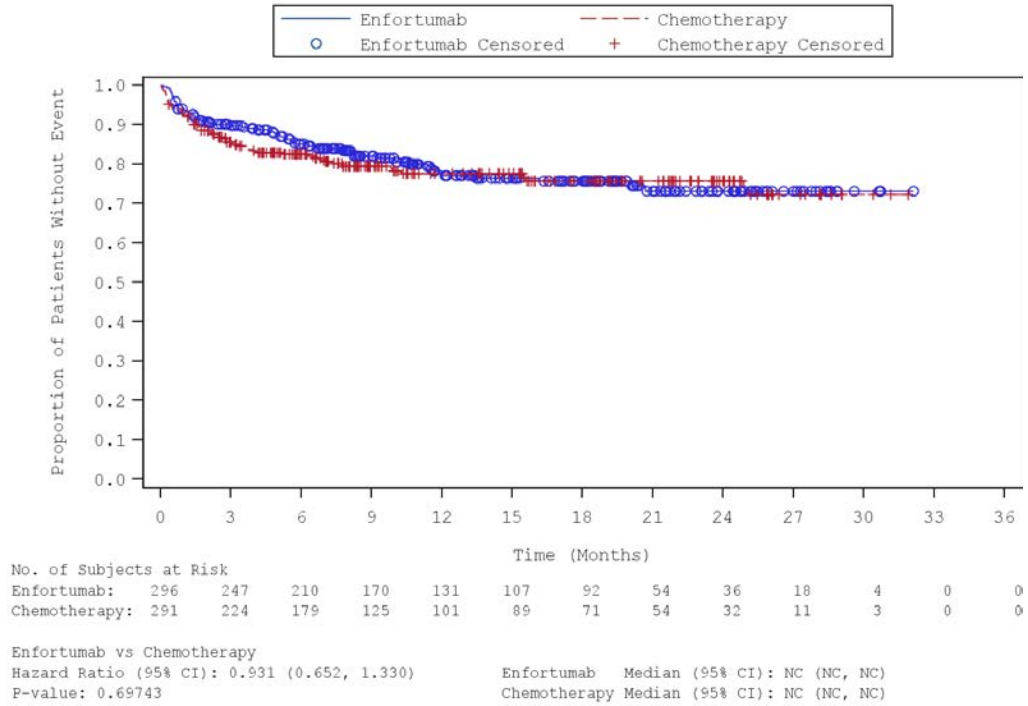

Figure 19: Kaplan-Meier curves on the outcome "discontinuation due to AEs" - second data cut-off: 30 July 2021

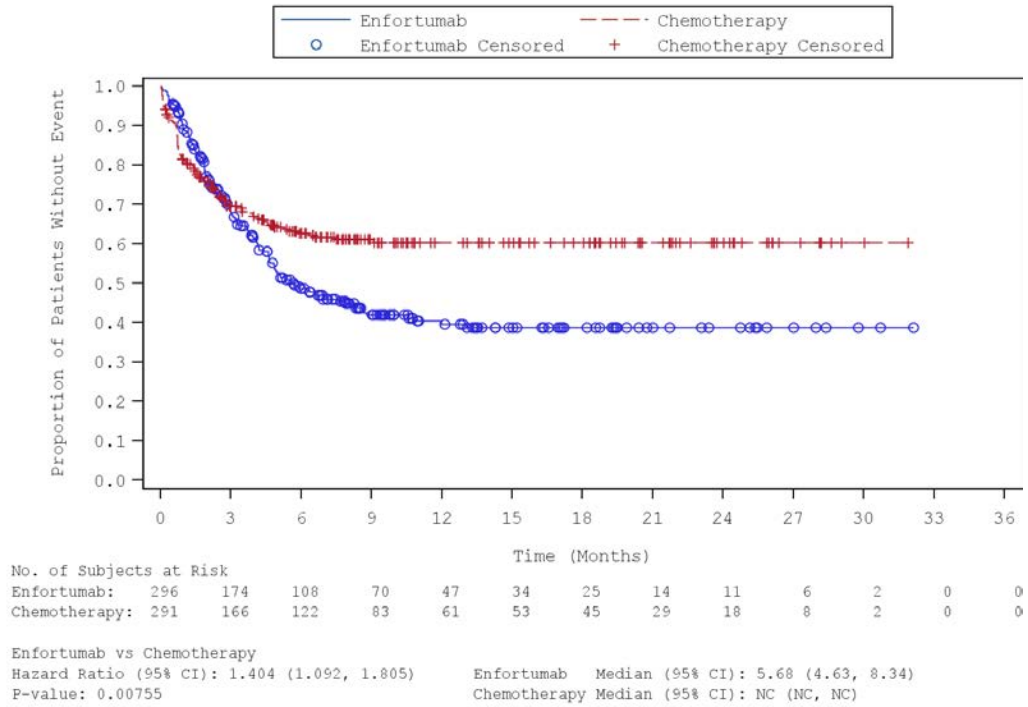

Figure 20: Kaplan-Meier curves on the outcome “peripheral neuropathy” (SMQ, AEs) - second data cut-off: 30 July 2021

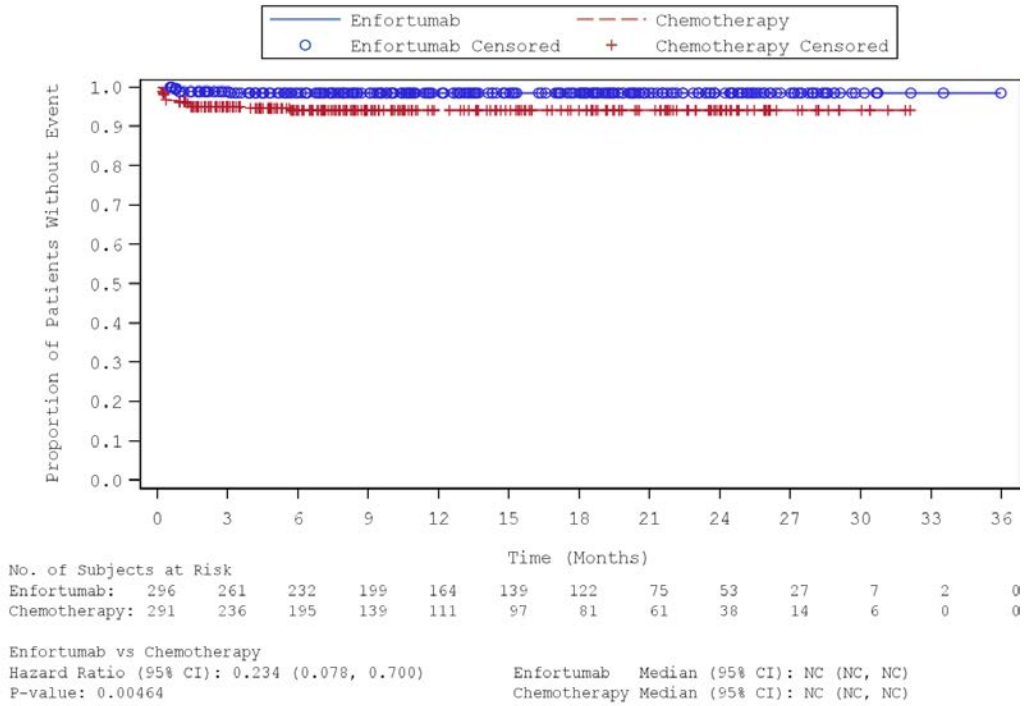

Figure 21: Kaplan-Meier curves on the outcome "febrile neutropenia" (PT, SAEs) - second data cut-off: 30 July 2021

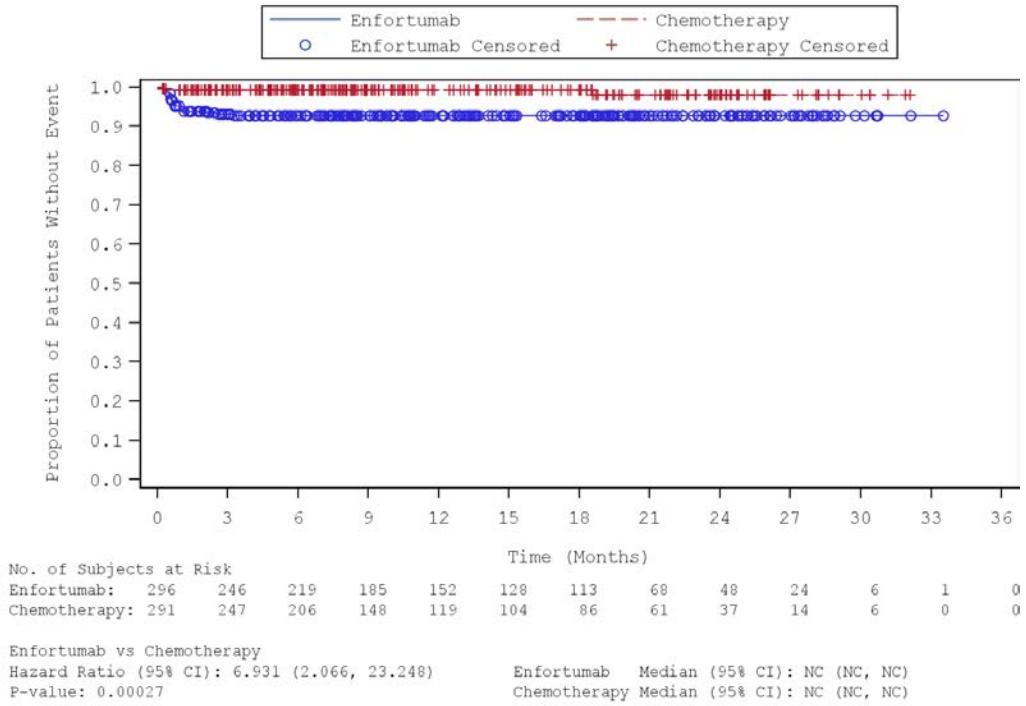

Figure 22: Kaplan-Meier curves on the outcome "hyperglycaemia" (PT, severe AEs) - second data cut-off: 30 July 2021

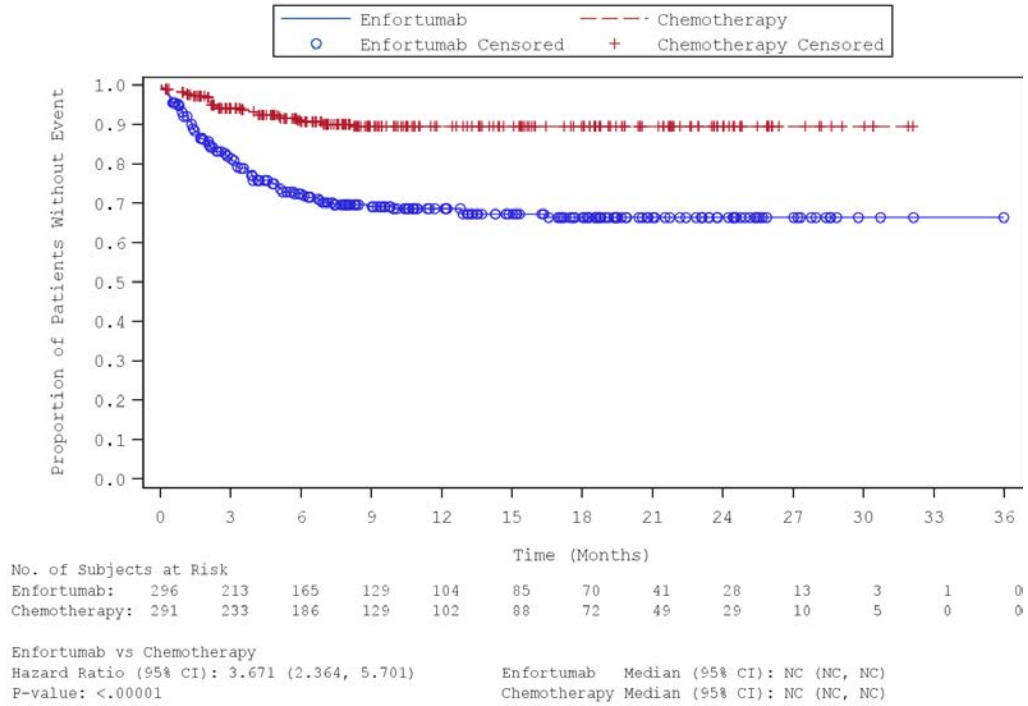

Figure 23: Kaplan-Meier curves on the outcome “eye disorders” (SOC, AEs) - second data cut-off: 30 July 2021

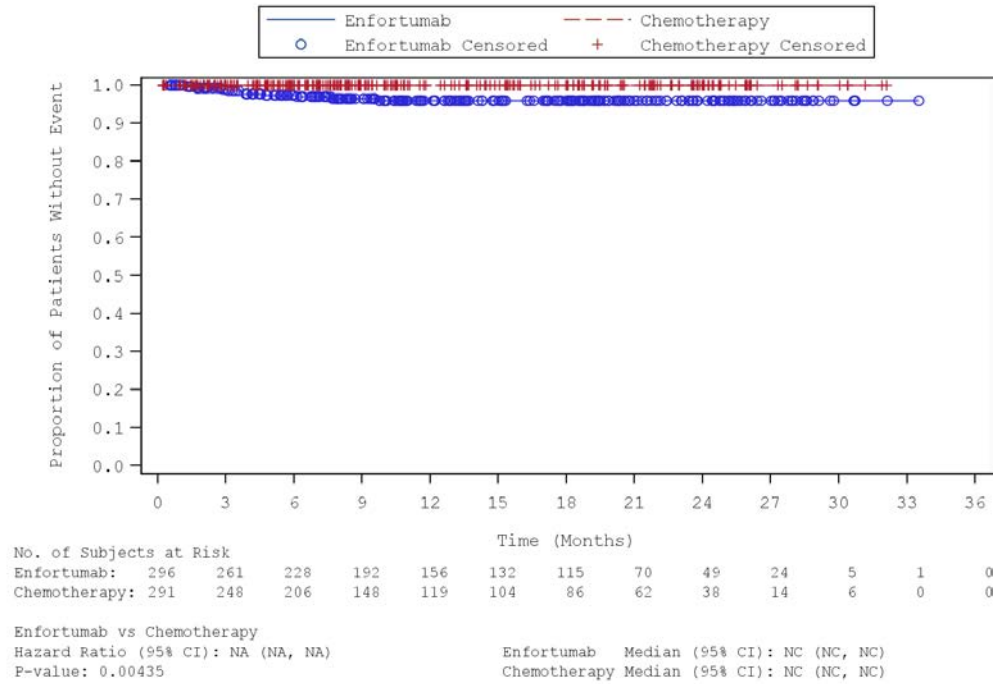

Figure 24: Kaplan-Meier curves on the outcome “gait disorder” (PT, AEs) - second data cut-off: 30 July 2021

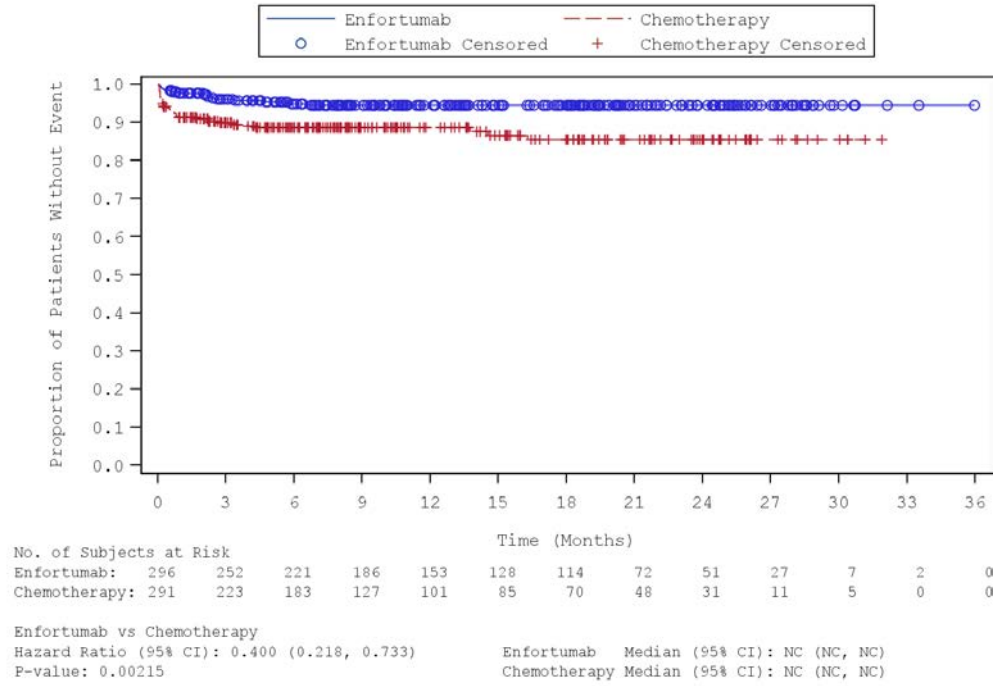

Figure 25: Kaplan-Meier curves on the outcome “myalgia” (PT, AEs) - second data cut-off: 30 July 2021

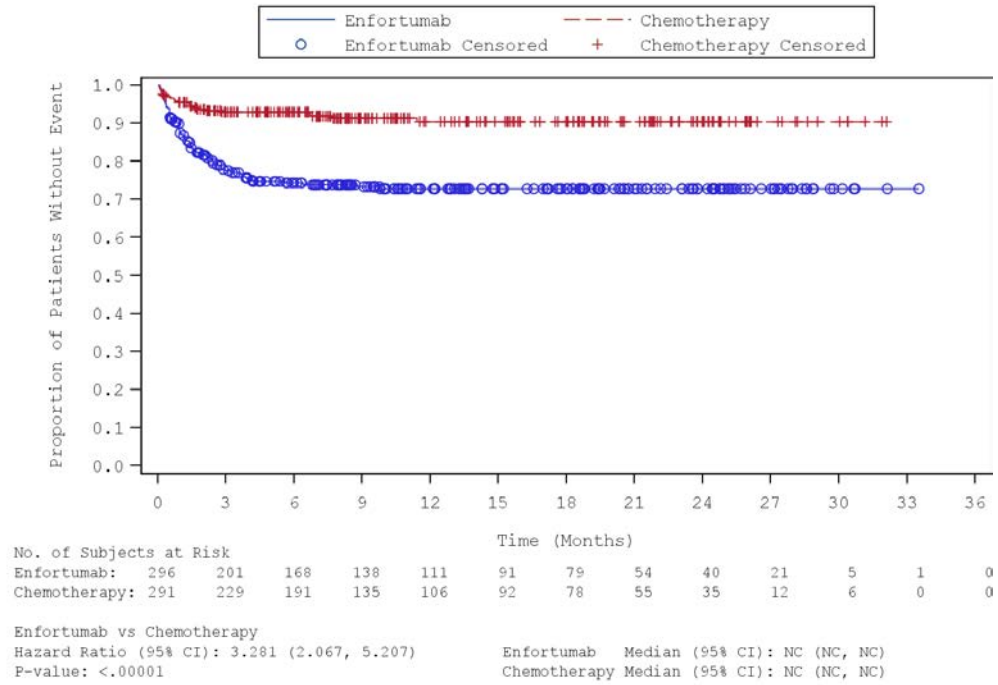

Figure 26: Kaplan-Meier curves on the outcome “dysgeusia” (PT, AEs) - second data cut-off: 30 July 2021

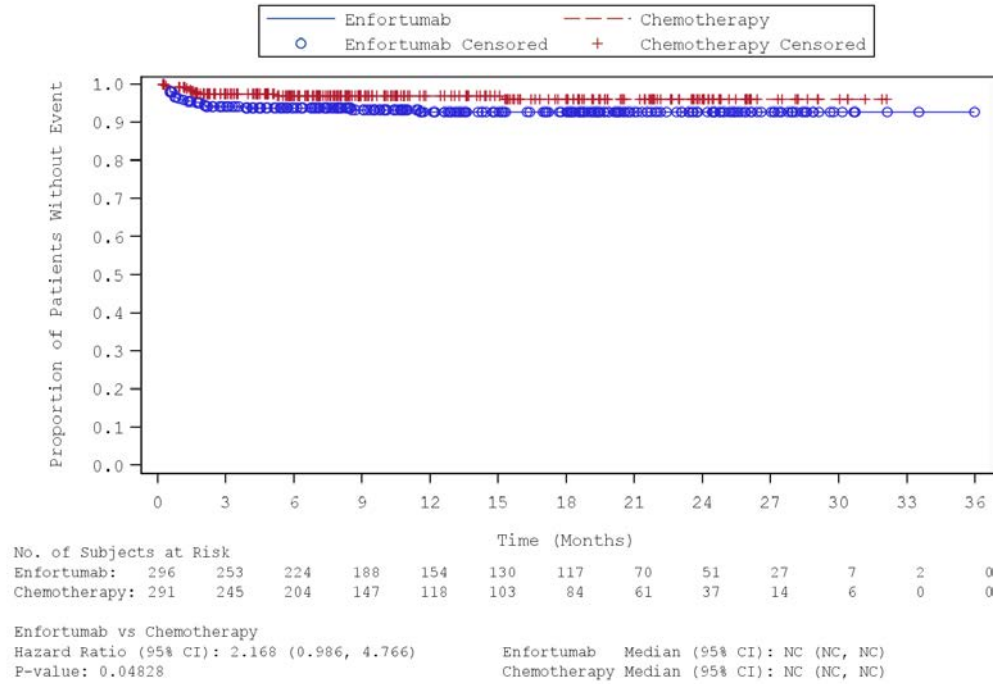

Figure 27: Kaplan-Meier curves on the outcome “acute kidney injury” (PT, SAEs) - second data cut-off: 30 July 2021

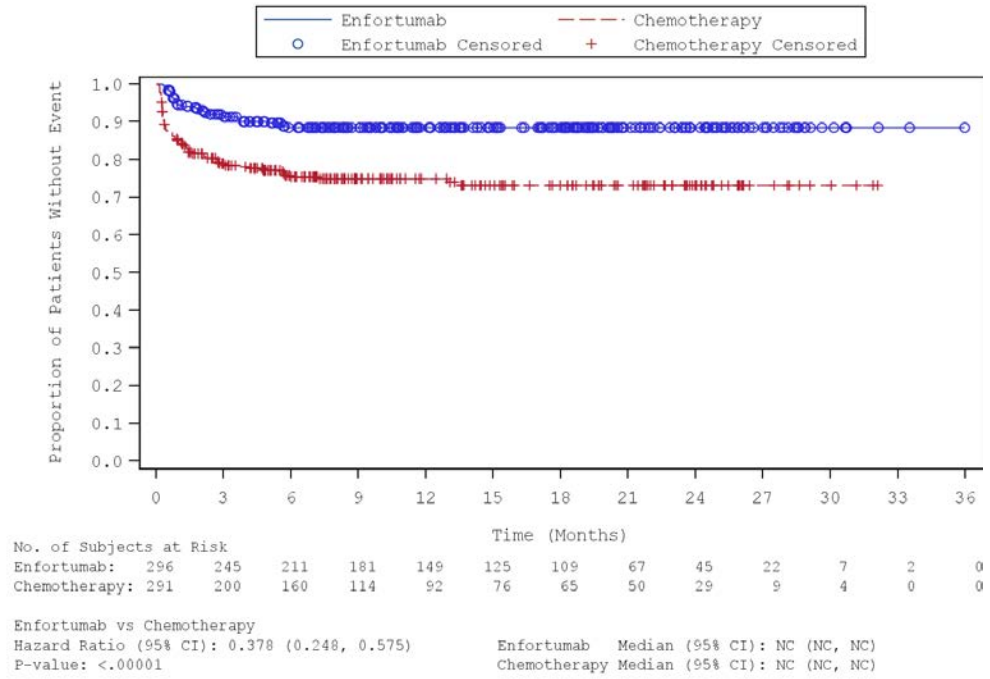

Figure 28: Kaplan-Meier curves on the outcome “blood and lymphatic system disorders” (SOC, severe AEs) - second data cut-off: 30 July 2021

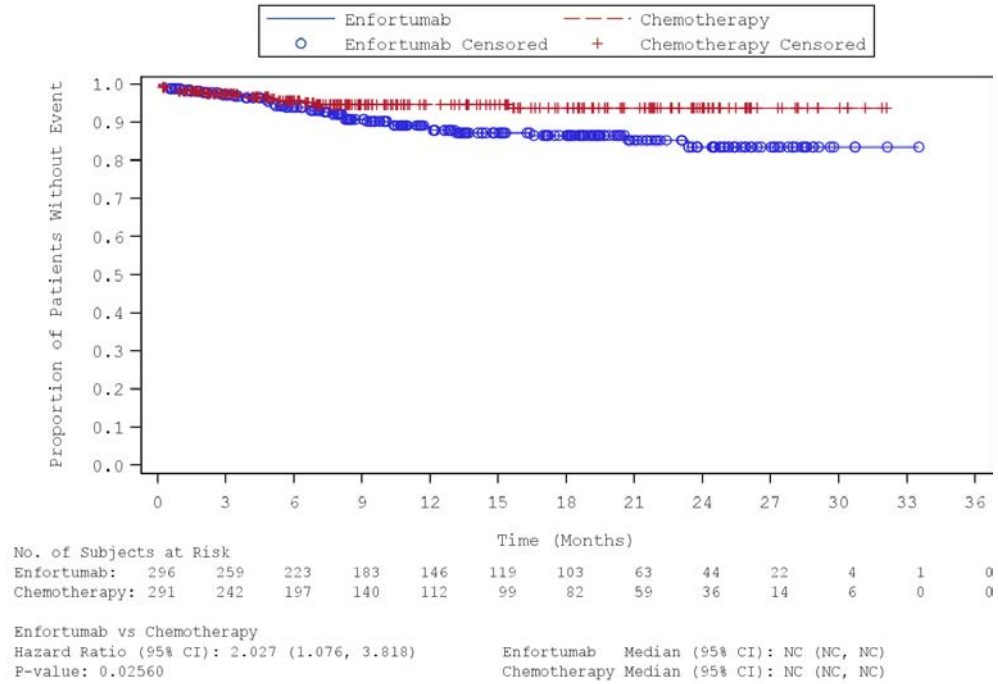

Figure 29: Kaplan-Meier curves on the outcome “nervous system disorders” (SOC, AEs) - second data cut-off: 30 July 2021

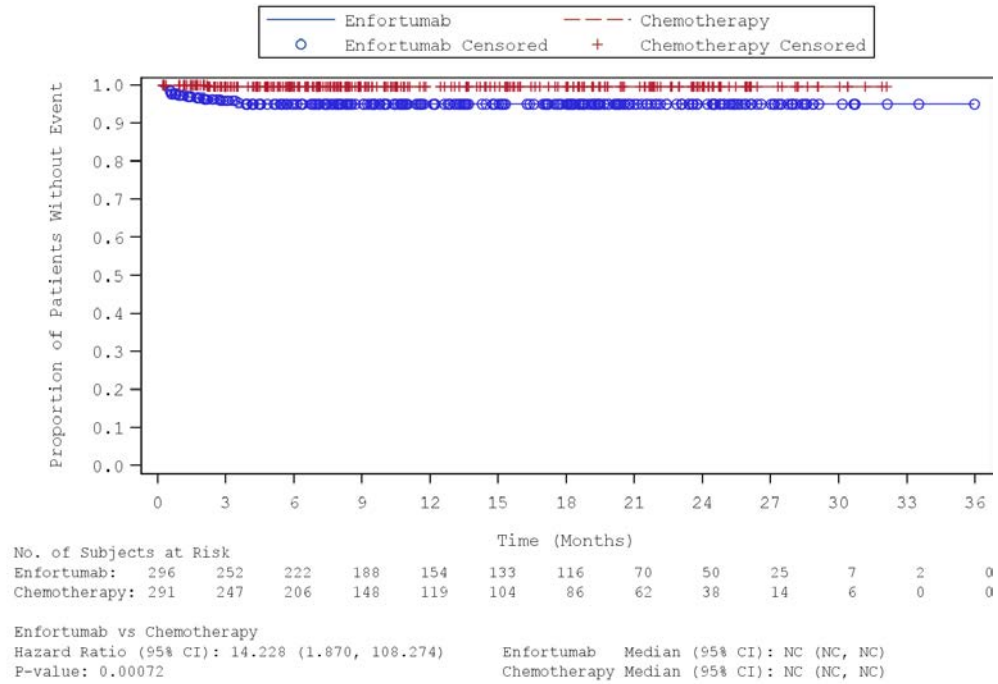

Figure 30: Kaplan-Meier curves on the outcome “skin and subcutaneous tissue disorders” (SOC, SAEs) - second data cut-off: 30 July 2021

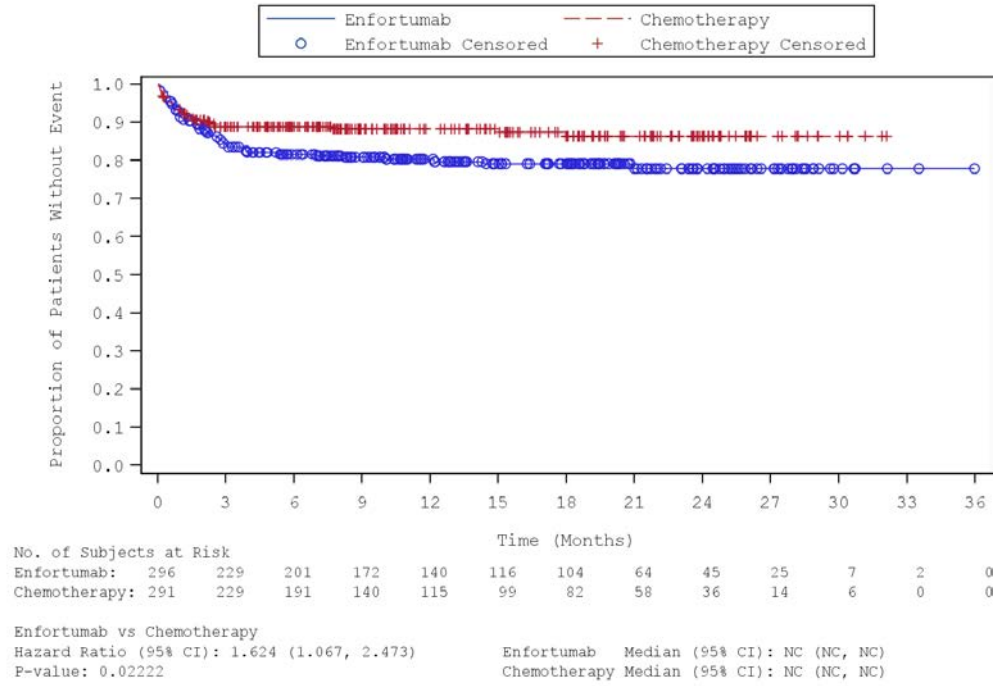

Figure 31: Kaplan-Meier curves on the outcome “infections and infestations” (SOC, severe AEs) - second data cut-off: 30 July 2021

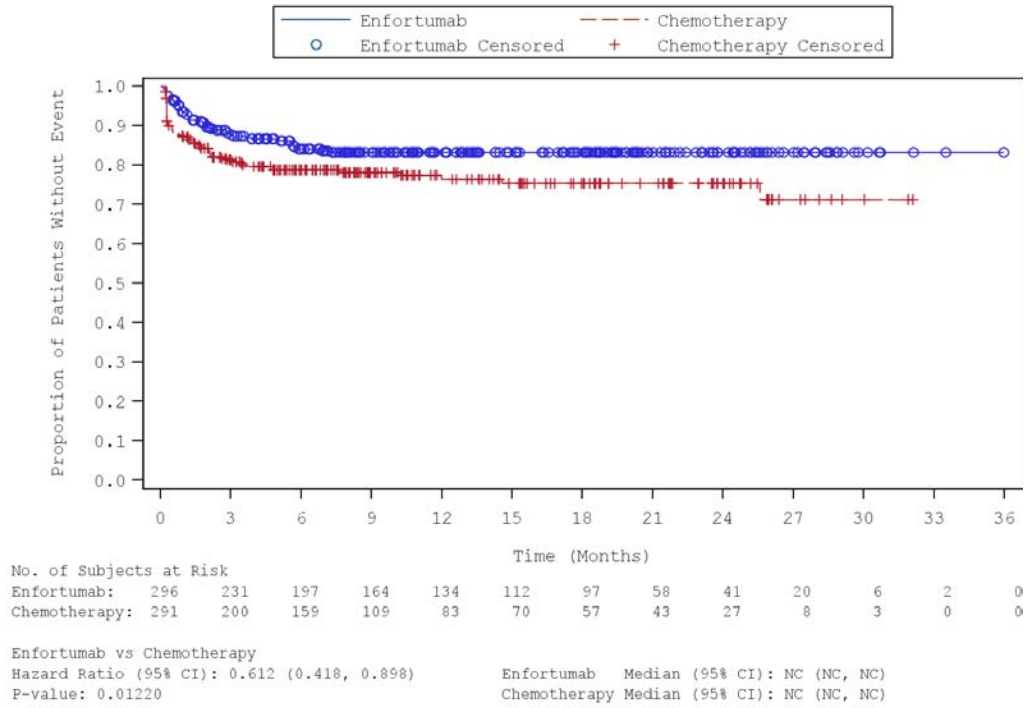

Figure 32: Kaplan-Meier curves on the outcome “investigations” (SOC, severe AEs) - second data cut-off: 30 July 2021

B.5 Subgroup analyses

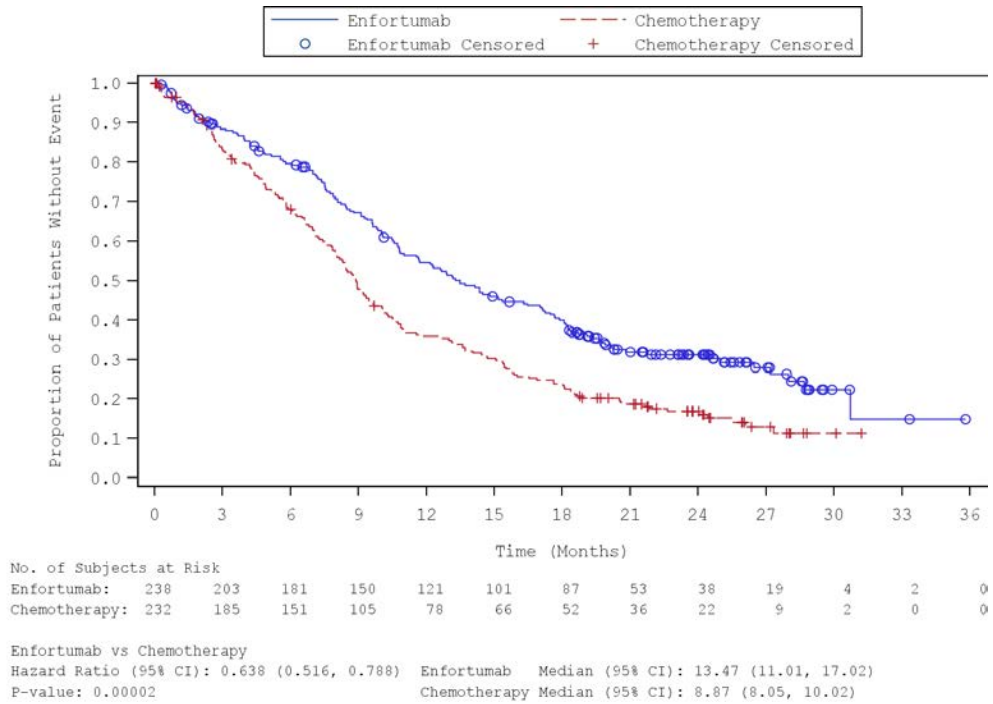

Figure 33: Kaplan-Meier curves on the outcome "overall survival", sex: male - second data cut-off: 30 July 2021

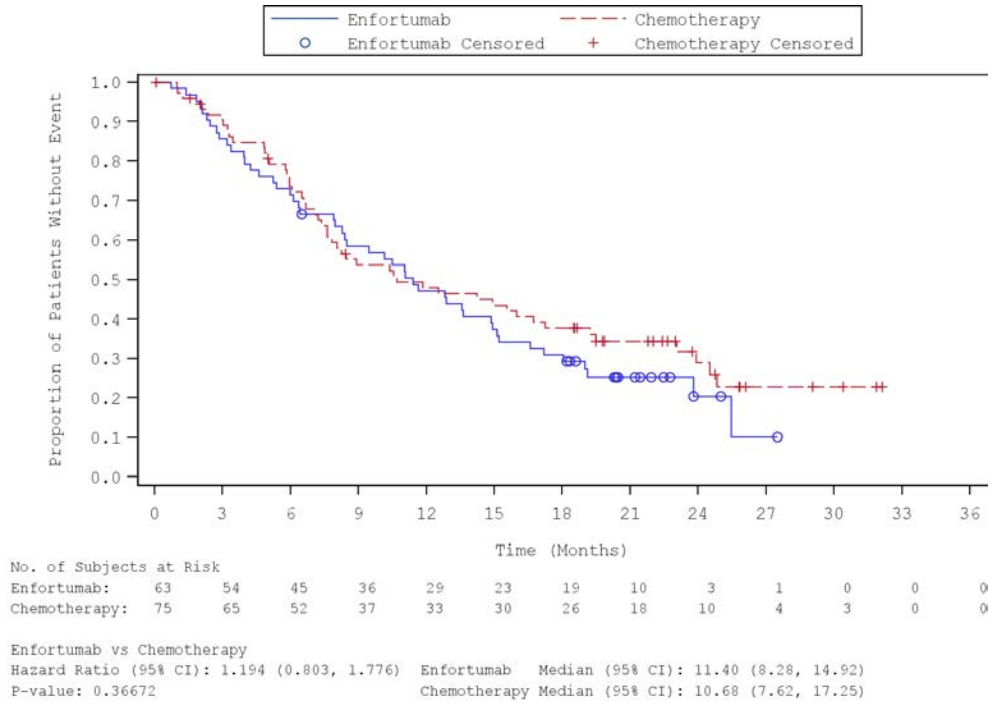

Figure 34: Kaplan-Meier curves on the outcome "overall survival", sex: female - second data cut-off: 30 July 2021

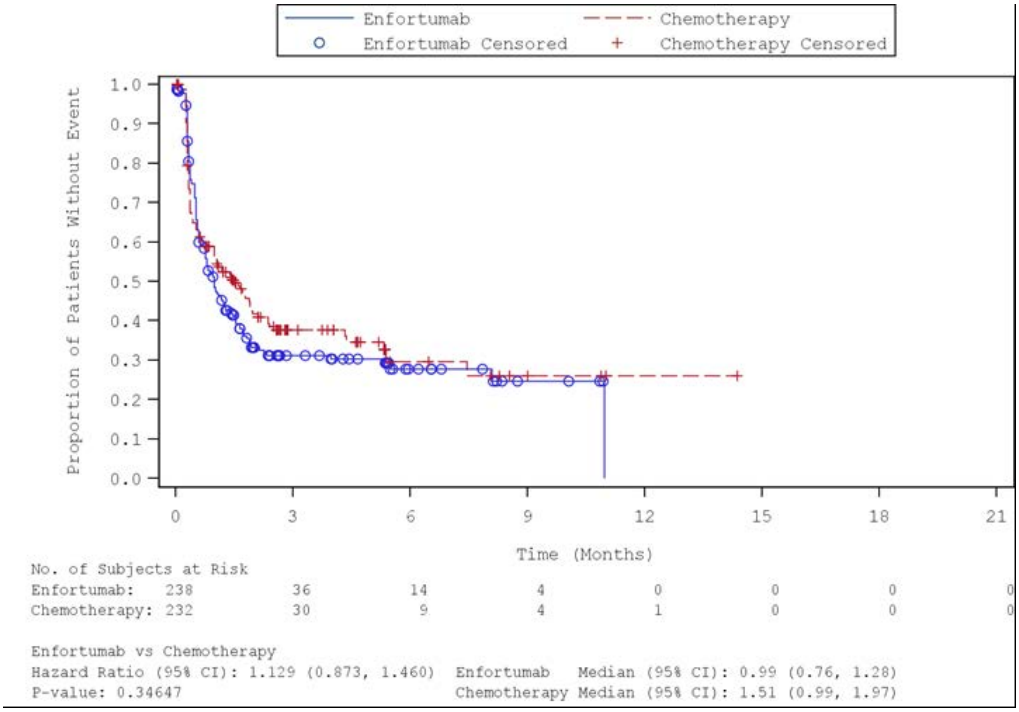

Figure 35: Kaplan-Meier curves on the outcome "appetite loss" (EORTC QLQ-C30, first deterioration by ≥ 10 points), sex: male - first data cut-off: 15 July 2020

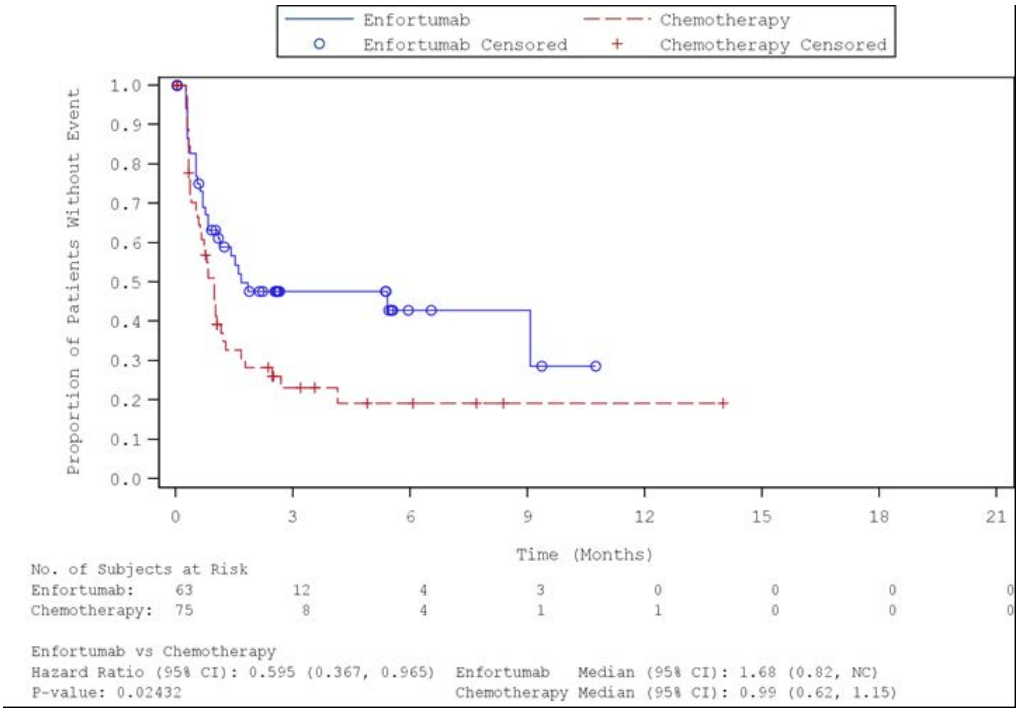

Figure 36: Kaplan-Meier curves on the outcome "appetite loss" (EORTC QLQ-C30, first deterioration by ≥ 10 points), sex: female - first data cut-off: 15 July 2020

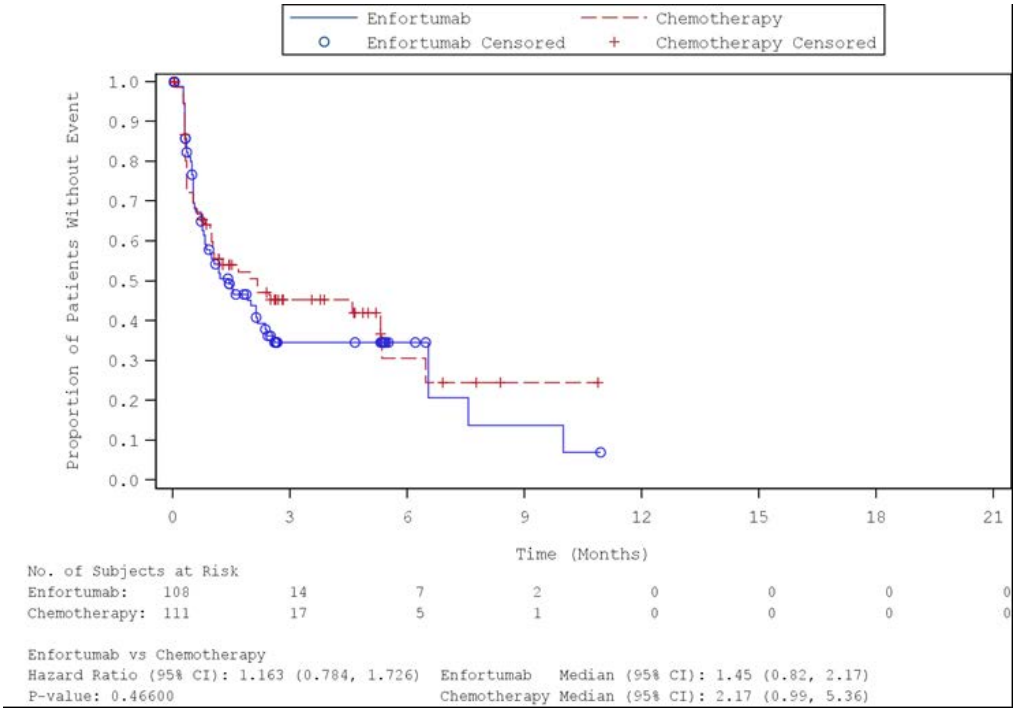

Figure 37: Kaplan-Meier curves on the outcome "global health status" (EORTC QLQ-C30, first deterioration by ≥ 10 points), age: < 65 years - first data cut-off: 15 July 2020

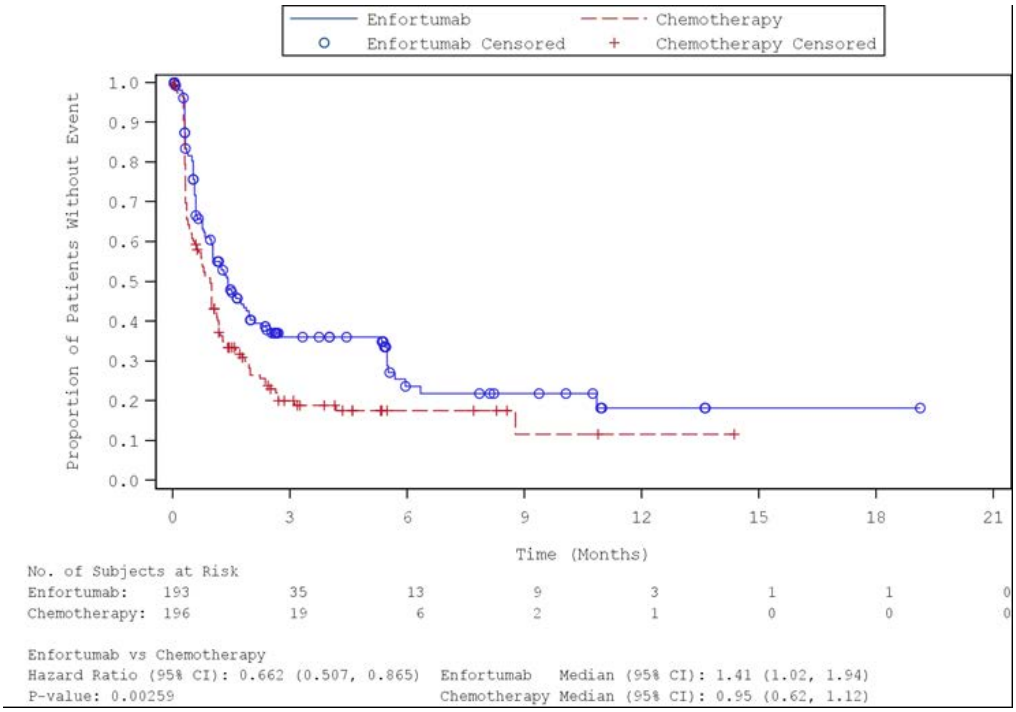

Figure 38: Kaplan-Meier curves on the outcome "global health status" (EORTC QLQ-C30, first deterioration by ≥ 10 points), age ≥ 65 years - first data cut-off: 15 July 2020

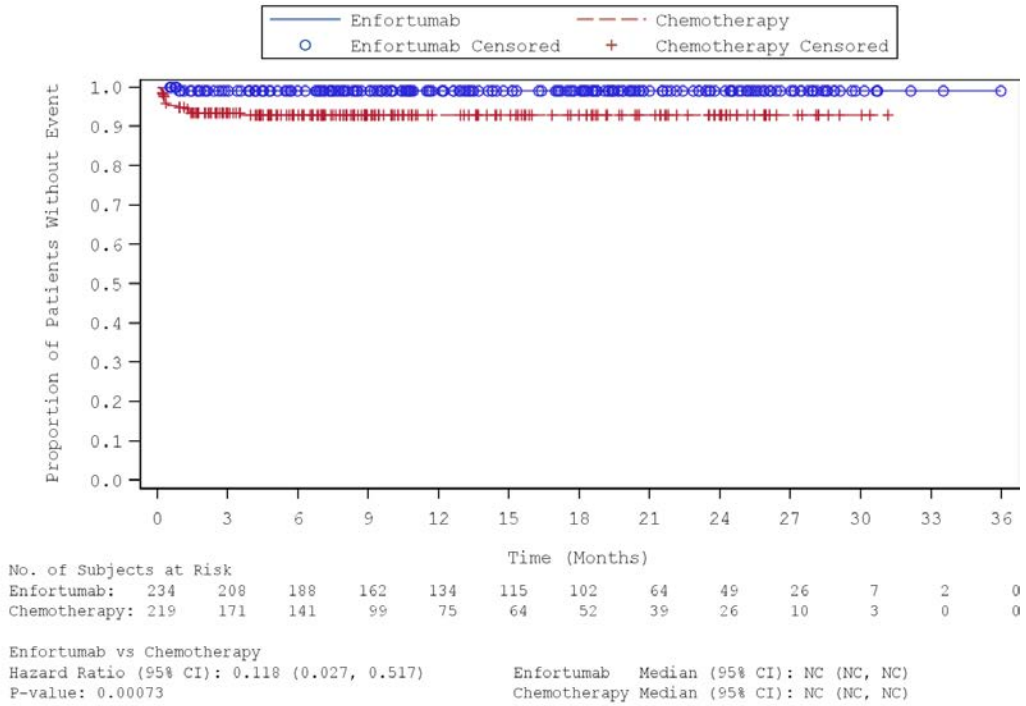

Figure 39: Kaplan-Meier curves on the outcome "febrile neutropenia" (PT, SAEs), sex: male - second data cut-off: 30 July 2021

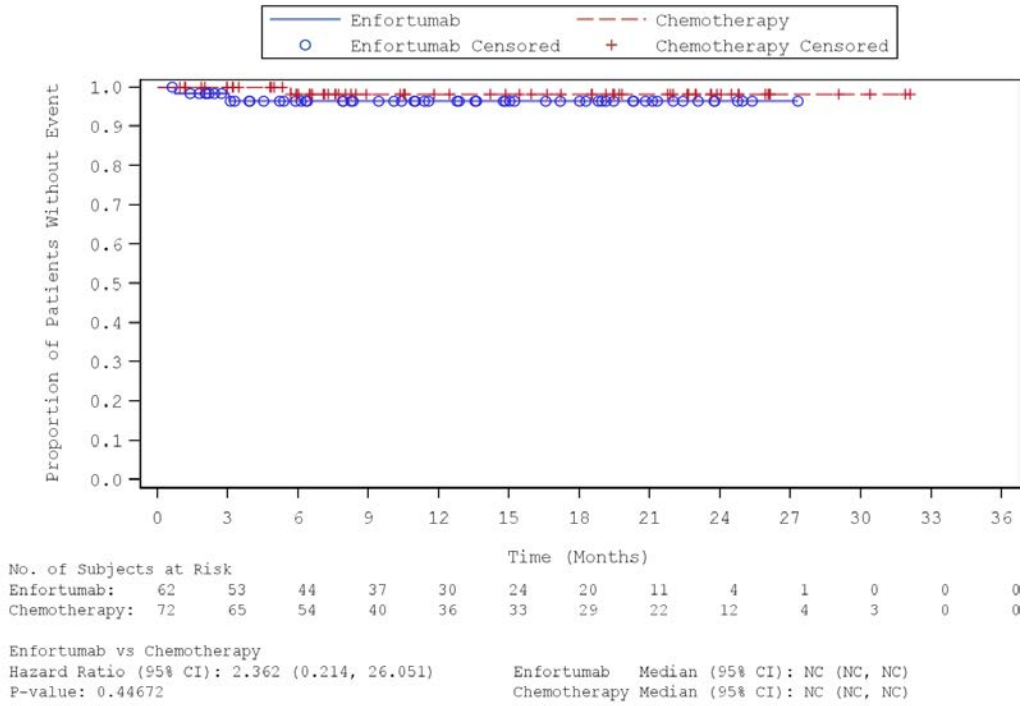

Figure 40: Kaplan-Meier curves on the outcome "febrile neutropenia" (PT, SAEs), sex: female - second data cut-off: 30 July 2021

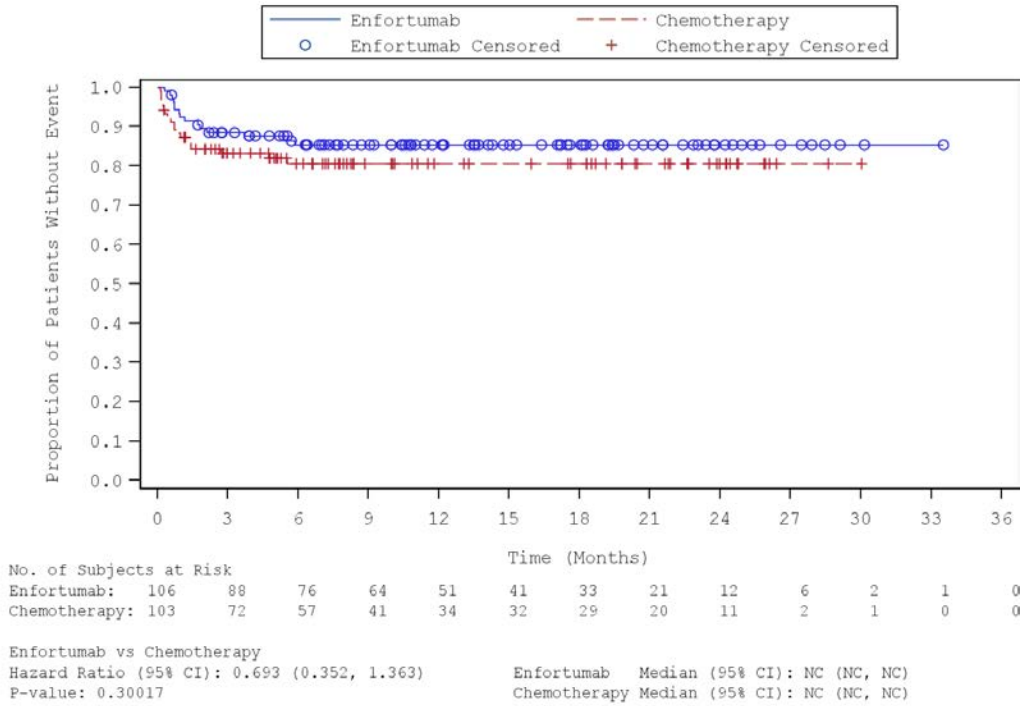

Figure 41: Kaplan-Meier curves on the outcome "blood and lymphatic system disorders" (SOC, severe AEs), age < 65 years - second data cut-off: 30 July 2021

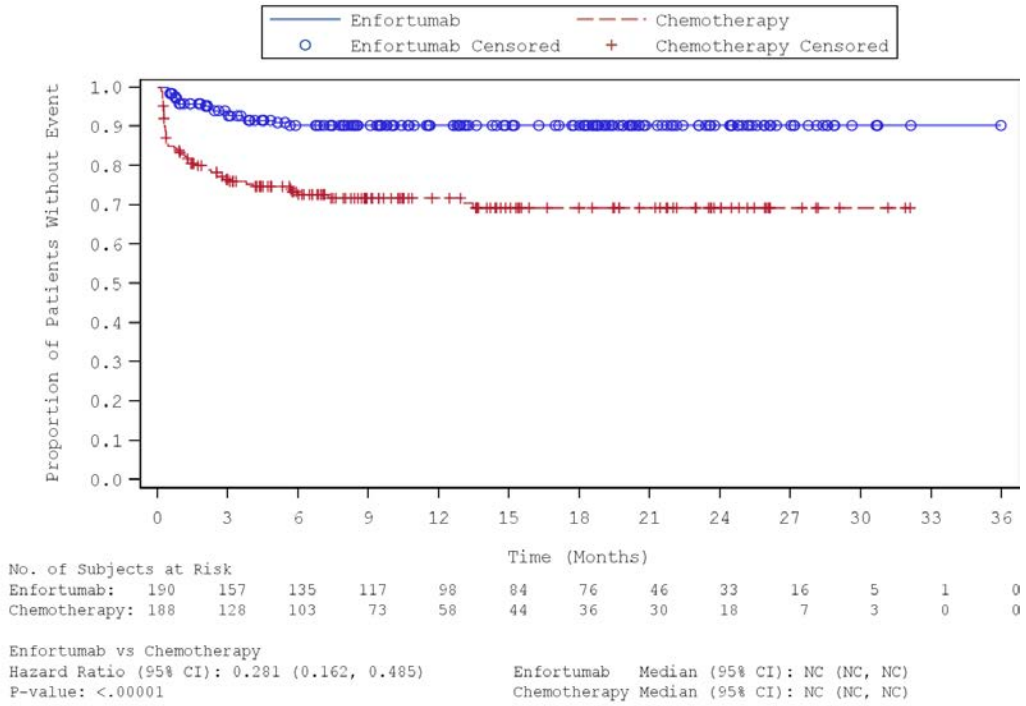

Figure 42: Kaplan-Meier curves on the outcome "blood and lymphatic system disorders" (SOC, severe AEs), age ≥ 65 years - second data cut-off: 30 July 2021

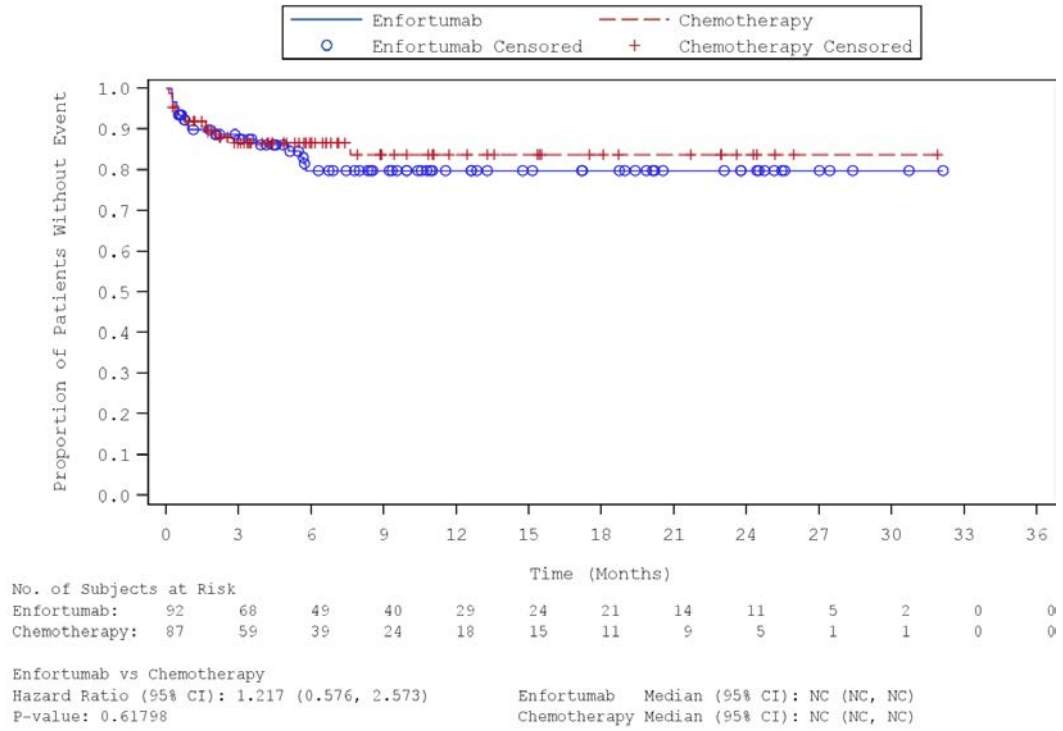

Figure 43: Kaplan-Meier curves on the outcome "investigations" (SOC, severe AEs), liver metastases: yes - second data cut-off: 30 July 2021

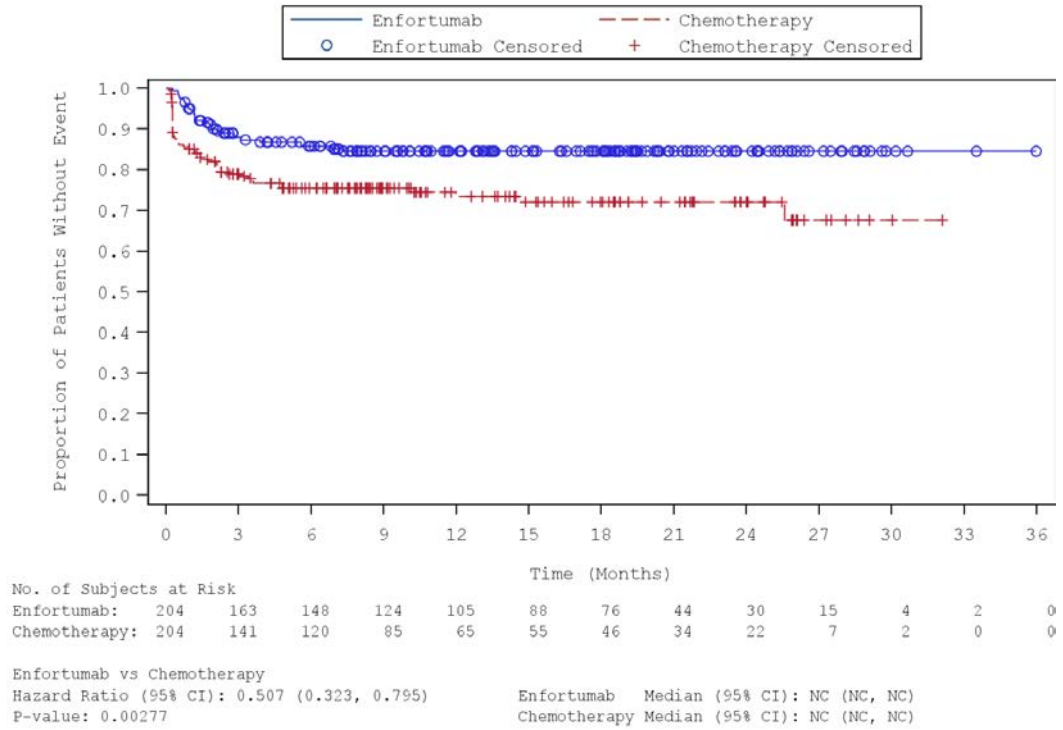

Figure 44: Kaplan-Meier curves on the outcome "investigations" (SOC, severe AEs), liver metastases: no - second data cut-off: 30 July 2021