Dostarlimab (endometrial cancer)

Addendum to Project A23-143 (dossier assessment)[1]

ADDENDUM

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List of abbreviations

Abbreviation	Meaning
ACT	appropriate comparator therapy
AE	adverse event
CTCAE	Common Terminology Criteria for Adverse Events
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
dMMR	mismatch repair deficiency
EORTC	European Organization for Research and Treatment of Cancer
EORTC QLQ-C30	European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire – Core 30
EORTC QLQ-EN24	EORTC Quality of Life Questionnaire – Endometrial Cancer Module 24
FIGO	Fédération Internationale de Gynécologie et d'Obstétrique (International Federation of Gynecology and Obstetrics)
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
MedDRA	Medical Dictionary for Regulatory Activities
MMRM	mixed-effects model with repeated measures
MSI-H	high microsatellite instability
PT	Preferred Term
RCT	randomized controlled trial
SAE	serious adverse event
SGB	Sozialgesetzbuch (Social Code Book)
SOC	System Organ Class
VAS	visual analogue scale

1 Background

On 7 May 2024, the Federal Joint Committee (G-BA) commissioned the Institute for Quality and Efficiency in Health Care (IQWiG) to conduct supplementary assessments for Project A23-143 (Dostarlimab – Benefit assessment according to § 35a Social Code Book V) [1].

The commission comprises the assessment of the analyses for a new RUBY study data cut-off from 22 September 2023 presented by the pharmaceutical company (hereinafter referred to as the “company”) in the commenting procedure [2], taking into account the information provided in the dossier [3].

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

2 Assessment

For the benefit assessment A23-143 [1] of dostarlimab in adult patients with primary advanced or recurrent endometrial cancer with mismatch repair deficiency (dMMR)/high microsatellite instability (MSI-H) who are eligible for systemic therapy, the RUBY study was included. The RUBY study is an ongoing 2-part randomized, double-blind study, with Part 1 and Part 2 of the study being conducted independently of each other. Part 1 compares dostarlimab in combination with carboplatin and paclitaxel (hereinafter referred to as dostarlimab + carboplatin + paclitaxel) with placebo in combination with carboplatin and paclitaxel (hereinafter referred to as placebo + carboplatin + paclitaxel). This part of the study was used for the benefit assessment.

The benefit assessment A23-143 was based on the results of the 1st data cut-off of the RUBY study from 28 September 2022. As part of the commenting procedure, the company presented analyses of a prespecified 2nd data cut-off (22 September 2023) for the RUBY study [4-6], which are assessed in the following.

2.1 Study characteristics

A detailed description of the RUBY study can be found in benefit assessment A23-143 [1]. The following text describes only those characteristics for which changes resulted from the 2nd data cut-off.

2nd data cut-off from 22 September 2023

In the commenting procedure, the company submitted analyses of a 2nd data cut-off dated 22 September 2023. This is the second interim analysis, which was to take place after 221 deaths in the total study population and was conducted after 253 events.

Treatment duration and observation period

Table 1 shows the patients' mean and median treatment duration and the mean and median observation period for individual outcomes.

Table 1: Information on the course of the study – RCT, direct comparison: dostarlimab + carboplatin + paclitaxel vs. placebo + carboplatin + paclitaxel (multipage table)

Study **Duration of the study phase** **Outcome category**	**Dostarlimab + carboplatin + paclitaxel** **N = 53**	**Placebo + carboplatin + paclitaxel** **N = 65**
RUBY		
Treatment duration [months]		
For dostarlimab/placebo		
Median [Q1; Q3]	17.6 [5.7; 35.4][a]	7.3 [4.8; 11.5][a]
Mean (SD)	20.5 (14.8)[a]	11.6 (11.1)[a]
For carboplatin		
Median [Q1; Q3]	4.1 [4.1; 4.4][a]	4.1 [4.1; 4.4][a]
Mean (SD)	4.0 (0.9)[a]	4.1 (0.9)[a]
For paclitaxel		
Median [Q1; Q3]	4.1 [4.1; 4.4][a]	4.1 [4.1; 4.3][a]
Mean (SD)	3.9 (1.0)[a]	3.9 (1.0)[a]
Observation period [months]		
Overall survival[b]		
Median [Q1; Q3]	34.0 [30.4; 38.0]	24.1 [11.8; 34.2]
Mean (SD)	29.5 (13.4)	23.8 (12.8)
Morbidity		
Symptoms (EORTC QLQ-C30, EORTC QLQ-EN24)		
Median [Q1; Q3]	34.0 [30.4; 38.0]	24.1 [11.8; 34.2]
Mean (SD)	29.5 (13.4)	23.8 (12.8)
Health status (EQ-5D VAS)		
Median [Q1; Q3]	34.0 [30.4; 38.0]	24.1 [11.8; 34.2]
Mean (SD)	29.5 (13.4)	23.8 (12.8)
Health-related quality of life (EORTC QLQ-C30, EORTC QLQ-EN24)		
Median [Q1; Q3]	34.0 [30.4; 38.0]	24.1 [11.8; 34.2]
Mean (SD)	29.5 (13.4)	23.8 (12.8)
Side effects		
AEs, severe AEs[c], specific AEs		
Median [Q1; Q3]	18.2 [ND; ND]	6.0 [ND; ND]
Mean (SD)	ND	ND
SAEs		
Median [Q1; Q3]	19.8 [ND; ND]	8.5 [ND; ND]
Mean (SD)	ND	ND

a. Institute's calculation (conversion from weeks to months).
b. The observation period was calculated based on the observed time to event/censoring/end of study of all patients (deceased and non-deceased).
c. Operationalized as CTCAE grade ≥ 3.

Table 1: Information on the course of the study – RCT, direct comparison: dostarlimab + carboplatin + paclitaxel vs. placebo + carboplatin + paclitaxel (multipage table)

Study **Duration of the study phase** **Outcome category**	**Dostarlimab + carboplatin + paclitaxel** **N = 53**	**Placebo + carboplatin + paclitaxel** **N = 65**
AE: adverse event; CTCAE: Common Terminology Criteria for Adverse Events; EORTC: European Organization for Research and Treatment of Cancer; EQ-5D: European Quality of Life – 5 Dimensions; N: number of patients; ND: no data; Q1: 1st quartile; Q3: 3rd quartile; QLQ-C30: Quality of Life Questionnaire – Core 30; QLQ-EN24: Quality of Life Questionnaire – Endometrial Cancer Module 24; RCT: randomized controlled trial; SD: standard deviation; SAE: serious adverse event; VAS: visual analogue scale		

The median treatment duration has not changed compared to the 1st data cut-off. The treatment duration in the intervention arm was 17.6 months, about 2.5 times as long as in the comparator arm (7.3 months). The treatment duration for carboplatin and paclitaxel, which was to be administered for a maximum of 6 cycles at 21 days each, is comparable in the 2 treatment arms. The median observation periods for overall survival and for the outcomes in the category of morbidity and health-related quality of life were about 34 months in the intervention arm and 24 months in the comparator arm.

For the outcomes in the adverse event categories whose observation period is linked to the end of treatment (plus 90 days for serious adverse events [SAEs] and 30 or 42 days for all other adverse events [AEs] in the side effect category, see also A23-143 [1]), the observation periods are significantly shorter compared to the outcomes that were observed until death, especially in the comparator arm.

In benefit assessment A23-143, no data on the observation period for the outcomes in the adverse events category were available for the 1st data cut-off. It is noticeable in the data presented for the 2nd data cut-off that the median observation periods for these outcomes are shorter than the planned duration of each follow-up observation. In the control arm in particular, the median observation period for AEs is 1 month shorter than the median treatment duration. Overall, these data are implausible. This is taken into account when assessing the risk of bias.

Subsequent therapies

Table 2 shows the subsequent therapies patients received after discontinuing the study medication.

Table 2: Information on subsequent antineoplastic therapies – RCT, direct comparison: dostarlimab + carboplatin + paclitaxel vs. placebo + carboplatin + paclitaxel (multipage table)

Study **Drug class** **Drug**	**Patients with subsequent therapy[a] n (%)**	
	Dostarlimab + carboplatin + paclitaxel **N = 53**	**Placebo + carboplatin + paclitaxel** **N = 65**
RUBY		
Total	15 (28)	39 (60)
Immunotherapy	8 (53[b])	27 (69[b])
Pembrolizumab	4 (27[b])	21 (54[b])
Pembrolizumab/lenvatinib	3 (20[b])	2 (5[b])
Dostarlimab	0	3 (8[b])
MK7694A	0	1 (3[b])
Pembrolizumab/tamoxifen	1 (7[b])	0
Retifanlimab/epacadostat	1 (7[b])	0
Chemotherapy	7 (47[b])	11 (28[b])
Doxorubicin	3 (20[b])	3 (8[b])
Paclitaxel/carboplatin	3 (20[b])	2 (5[b])
Carboplatin	2 (13[b])	0
Cisplatin	0	2 (5[b])
Doxorubicin, PEG liposomal	1 (7[b])	1 (3[b])
Carboplatin/vinorelbine	0	1 (3[b])
Epirubicin	1 (7[b])	0
Gemcitabine	0	1 (3[b])
Paclitaxel	1 (7[b])	0
Topotecan	0	1 (3[b])
Hormonal therapy	4 (27[b])	10 (26[b])
Letrozole	1 (7[b])	6 (15[b])
Megestrol acetate	1 (7[b])	2 (5[b])
Megestrol acetate/tamoxifen	1 (7[b])	1 (3[b])
Abemaciclib/letrozole	1 (7[b])	0
Everolimus	1 (7[b])	0
Everolimus/letrozole	1 (7[b])	0
Medroxyprogesterone acetate	0	1 (3[b])
Tamoxifen	1 (7[b])	0
Radiotherapy	2 (13[b])	8 (21[b])
Radiation treatment	1 (7[b])	8 (21[b])
palliative radiotherapy	1 (7[b])	0
Stereotactic radiosurgery	1 (7[b])	0
Other	1 (7[b])	0
Pemigatinib	1 (7[b])	0

Table 2: Information on subsequent antineoplastic therapies – RCT, direct comparison: dostarlimab + carboplatin + paclitaxel vs. placebo + carboplatin + paclitaxel (multipage table)

Study Drug class Drug	Patients with subsequent therapy[a] n (%)	
	Dostarlimab + carboplatin + paclitaxel N = 53	Placebo + carboplatin + paclitaxel N = 65
a. Patients may be counted in more than one subsequent therapy. b. Institute's calculation; based on the proportion of patients with subsequent antineoplastic therapy. n: number of patients with subsequent therapy; N: number of analysed patients; PEG: polyethylene glycol; RCT: randomized controlled trial		

The study documents do not describe any limitations regarding the types of subsequent therapies. A total of 28% of patients in the intervention arm and 60% of patients in the comparator arm received subsequent therapy. As in the 1st data cut-off, the proportions of the drugs or drug classes used differed between the treatment arms. After discontinuation of study medication, 53% and 69% of patients received immunotherapy, with pembrolizumab (27% versus 54%) and the combination of pembrolizumab + lenvatinib (20% versus 5%) being the most commonly used. At 47%, more patients in the intervention arm received chemotherapy as subsequent therapy than in the comparator arm (28%). Doxorubicin (20% versus 8%) and the combination of paclitaxel + carboplatin (20% versus 5%) were administered. In both study arms, hormonal therapy was used in comparable proportions after discontinuation of the study medication (27% versus 26%). Radiotherapy was administered to 13% and 21% of the patients.

Overall, the subsequent therapies used are comparable to the 1st data cut-off and the drugs used largely reflect the recommendations of the guidelines for the treatment of endometrial cancer [7-9].

2.2 Results on added benefit

2.2.1 Risk of bias

The risk of bias across outcomes for the RUBY study is rated as low (see A23-143 [1]).

Table 3 describes the risk of bias for the results of the relevant outcomes.

Table 3: Risk of bias across outcomes and outcome-specific risk of bias – RCT, direct comparison: dostarlimab + carboplatin + paclitaxel vs. placebo + carboplatin + paclitaxel

Study	Study level	Outcomes										
		Overall survival	Symptoms (EORTC QLQ-C30, EORTC QLQ-EN24)	Health status (EQ-5D VAS)	Health-related quality of life (EORTC QLQ-C30, EORTC QLQ-EN24)	SAEs	Severe AEs[a]	Discontinuation due to AEs	Immune-mediated SAEs[c]	Immune-mediated severe AEs[a, c]	Infusion-related reactions	Urinary tract infections (PT, AEs)
RUBY	L	L	H[d]	H[d]	H[d]	H[e]	H[e]	L[f]	H[e]	H[e]	-[g]	H[e]

a. Severe AEs are operationalized as CTCAE ≥ 3.
b. Discontinuation of at least one drug component.
c. The operationalization was based on an a priori defined list of Preferred Terms (PTs); only immune-mediated AEs with CTCAE grade ≥ 2 could be considered immune-mediated, however.
d. Marked decrease in questionnaire return rates in the course of the study, which differed between treatment arms.
e. Incomplete observations for potentially informative reasons and additionally implausible information on the observation periods.
f. Despite the low risk of bias, the certainty of results is presumably limited for the outcome of discontinuation due to AE.
g. No suitable data available (for the reasoning, see A23-143 [1]).

AE: adverse event; CTCAE: Common Terminology Criteria for Adverse Events; EORTC: European Organisation for Research and Treatment of Cancer; H: high; L: low; PT: Preferred Term; QLQ-C30: Quality of Life Questionnaire-Core 30; QLQ-EN24: Quality of Life Questionnaire-Endometrial Cancer Module 24; RCT: randomized controlled trial; SAE: serious adverse event; VAS: visual analogue scale

For the present 2nd data cut-off, the outcome-specific risk of bias is high for the results of all outcomes except overall survival and discontinuation due to AEs, as was already the case for the 1st data cut-off. The risk of bias of the results for the patient-reported outcomes (EORTC QLQ-C30, EORTC QLQ-EN24, EQ-5D VAS) is to be rated as high due to the marked decrease in the response rates of the questionnaires, which differed between treatment arms. Due to incomplete observation for potentially informative reasons with different follow-up observation periods between treatment groups, the outcomes of the side effects category have a high risk of bias. (see also A23-143 [1]). In addition, there are implausible data on the observation periods (see Section 2.1). Overall, there is no change in the assessment of the risk of bias due to the data subsequently submitted by the company.

2.2.2 Results

Table 4 summarizes the results of the supplementary data comparing dostarlimab + carboplatin + paclitaxel with placebo + carboplatin + paclitaxel in adult patients with dMMR/MSI-H primary advanced or recurrent endometrial cancer and who are candidates for systemic therapy, taking into account the 2nd data cut-off of the RUBY study. Where necessary, IQWiG calculations are provided to supplement the data from the company's dossier.

The Kaplan-Meier curves on the time-to-event analyses are presented in Appendix A, and the tables on common AEs, SAEs, severe AEs, and discontinuations due to AEs can be found in Appendix B of the present addendum. Appendix C of the present addendum presents the results on the occurred immune-mediated AEs, SAEs and severe AEs summarized in categories defined by the company. The analyses additionally presented by the company on the patient-reported outcomes (symptoms, health status and health-related quality of life) based on a mixed-effects model with repeated measures (MMRM) over the entire observation period are presented in Appendix D of the present addendum.

Table 4: Results (mortality, morbidity, health-related quality of life, side effects) – RCT, direct comparison: dostarlimab + carboplatin + paclitaxel vs. placebo + carboplatin + paclitaxel (multipage table)

Study **Outcome category** **Outcome**	**Dostarlimab + carboplatin + paclitaxel**		**Placebo + carboplatin + paclitaxel**		**Dostarlimab + carboplatin + paclitaxel vs. placebo + carboplatin + paclitaxel**
	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]**
RUBY					
Mortality					
Overall survival	53	NA 12 (22.6)	65	31.4 [20.3; NC] 35 (53.8)	0.32 [0.17; 0.63]; < 0.001
Morbidity					
Symptoms (EORTC QLQ-C30 – time to first deterioration[b])					
Fatigue	53	2.3 [1.6; 4.0] 41 (77.4)	65	1.4 [1.0; 2.8] 52 (80.0)	0.84 [0.55; 1.28]; 0.410
Nausea and vomiting	53	5.8 [2.8; 14.9] 36 (67.9)	65	4.5 [2.6; 11.3] 41 (63.1)	0.87 [0.54; 1.38]; 0.539
Pain	53	11.5 [2.8; 27.1] 31 (58.5)	65	3.3 [2.2; 4.9] 47 (72.3)	0.64 [0.40; 1.03]; 0.058
Dyspnoea	53	4.4 [2.6; 17.7] 35 (66.0)	65	3.7 [2.1; 10.6] 42 (64.6)	0.90 [0.56; 1.45]; 0.661

Table 4: Results (mortality, morbidity, health-related quality of life, side effects) – RCT, direct comparison: dostarlimab + carboplatin + paclitaxel vs. placebo + carboplatin + paclitaxel (multipage table)

Study **Outcome category** **Outcome**	**Dostarlimab + carboplatin + paclitaxel**		**Placebo + carboplatin + paclitaxel**		**Dostarlimab + carboplatin + paclitaxel vs. placebo + carboplatin + paclitaxel**
	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]**
Insomnia	53	7.5 [2.1; NC] 29 (54.7)	65	4.2 [2.8; NC] 36 (55.4)	0.96 [0.59; 1.57]; 0.862
Appetite loss	53	19.8 [5.6; NC] 25 (47.2)	65	8.5 [2.8; 27.6] 39 (60.0)	0.68 [0.41; 1.14]; 0.144
Constipation	53	2.8 [1.0; 33.8] 32 (60.4)	65	3.9 [2.1; 5.8] 44 (67.7)	0.87 [0.54; 1.40]; 0.518
Diarrhoea	53	4.6 [2.4; 14.9] 36 (67.9)	65	5.7 [3.7; 28.5] 37 (56.9)	1.18 [0.73; 1.89]; 0.503
Symptoms (EORTC QLQ-EN24 – time to first deterioration[b])					
Lymphoedema	53	2.8 [2.1; 4.4] 39 (73.6)	65	2.8 [1.7; 3.5] 50 (76.9)	0.87 [0.56; 1.33]; 0.518
Urological symptoms	53	NA [7.2; NC] 22 (41.5)	65	3.8 [2.1; NC] 36 (55.4)	0.60 [0.35; 1.04]; 0.068
Gastrointestinal symptoms	53	26.7 [4.4; NC] 24 (45.3)	65	11.7 [6.5; NC] 33 (50.8)	0.91 [0.53; 1.56]; 0.736
Sexual/vaginal problems			No usable data available[c]		
Pain in back and pelvis	53	21.6 [8.8; NC] 23 (43.4)	65	24.0 [4.6; NC] 32 (49.2)	0.82 [0.48; 1.41]; 0.473
Tingling/numbness	53	1.5 [1.0; 2.1] 45 (84.9)	65	1.4 [0.9; 2.1] 56 (86.2)	0.88 [0.58; 1.32]; 0.509
Muscular pain	53	1.4 [0.9; 3.5] 43 (81.1)	65	2.1 [1.4; 2.9] 50 (76.9)	1.15 [0.76; 1.75]; 0.556
Hair loss	53	0.8 [0.7; 0.8] 47 (88.7)	65	0.8 [0.7; 0.8] 61 (93.8)	1.15 [0.77; 1.71]; 0.574
Taste change	53	2.2 [0.9; 3.5] 37 (69.8)	65	2.2 [1.4; 3.0] 48 (73.8)	0.90 [0.58; 1.40]; 0.609
Health status (EQ-5D VAS – time to first deterioration[d])	53	NA 15 (28.3)	65	16.3 [4.2; NC] 29 (44.6)	0.54 [0.28; 1.02]; 0.055

Table 4: Results (mortality, morbidity, health-related quality of life, side effects) – RCT, direct comparison: dostarlimab + carboplatin + paclitaxel vs. placebo + carboplatin + paclitaxel (multipage table)

Study Outcome category Outcome	Dostarlimab + carboplatin + paclitaxel		Placebo + carboplatin + paclitaxel		Dostarlimab + carboplatin + paclitaxel vs. placebo + carboplatin + paclitaxel
	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]
Health-related quality of life					
EORTC QLQ-C30 – time to first deterioration[e]					
Global health status	53	12.9 [4.0; NC] 29 (54.7)	65	4.2 [2.0; 9.0] 48 (73.8)	0.63 [0.39; 1.02]; 0.055
Physical functioning	53	4.0 [2.1; 23.5] 32 (60.4)	65	3.7 [2.1; 10.8] 42 (64.6)	0.93 [0.58; 1.49]; 0.759
Role functioning	53	4.4 [2.3; 30.4] 31 (58.5)	65	2.5 [1.4; 4.4] 48 (73.8)	0.61 [0.38; 0.98]; 0.040
Emotional functioning	53	20.5 [3.5; NC] 27 (50.9)	65	13.9 [4.2; 27.7] 35 (53.8)	0.83 [0.50; 1.40]; 0.478
Cognitive functioning	53	4.0 [2.3; 8.8] 34 (64.2)	65	2.9 [2.1; 4.1] 48 (73.8)	0.70 [0.44; 1.11]; 0.119
Social functioning	53	4.2 [2.5; NC] 28 (52.8)	65	2.8 [1.5; 8.8] 48 (73.8)	0.57 [0.35; 0.92]; 0.020
EORTC QLQ-EN24 – time to first deterioration[e]					
Sexual interest	53	NA 10 (18.9)	65	NA 17 (26.2)	0.63 [0.29; 1.38]; 0.242
Sexual activity	53	NA 6 (11.3)	65	NA 5 (7.7)	1.22 [0.37; 4.01]; 0.738
Sexual enjoyment			No usable data available[f]		
Poor body image[g]	53	1.4 [0.8; 4.0] 32 (60.4)	65	1.4 [0.9; 1.4] 52 (80.0)	0.70 [0.45; 1.10]; 0.126
Side effects[h]					
AEs (supplementary information)	52	0.1 [0.0; 0.1] 52 (100)	65	0.1 [0.0; 0.1] 65 (100)	–
SAEs	52	NA [23.8; NC] 17 (32.7)	65	26.4 [13.5; NC] 21 (32.3)	0.86 [0.44; 1.66]; 0.633
Severe AEs[i]	52	3.2 [1.4; 5.2] 39 (75.0)	65	3.4 [1.9; 9.9] 43 (66.2)	1.22 [0.77; 1.91]; 0.402
Discontinuation due to AEs[j]	52	NA 10 (19.2)	65	NA 11 (16.9)	0.86 [0.34; 2.17]; 0.751
Immune-mediated AEs (supplementary information)[k]	52	2.8 [0.7; 4.6] 39 (75.0)	65	25.8 [2.1; NC] 26 (40.0)	–

Table 4: Results (mortality, morbidity, health-related quality of life, side effects) – RCT, direct comparison: dostarlimab + carboplatin + paclitaxel vs. placebo + carboplatin + paclitaxel (multipage table)

Study Outcome category Outcome	Dostarlimab + carboplatin + paclitaxel		Placebo + carboplatin + paclitaxel		Dostarlimab + carboplatin + paclitaxel vs. placebo + carboplatin + paclitaxel
	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]
Immune-mediated SAEs[k]	52	NR 3 (5.8)	65	NR 2 (3.1)	1.53 [0.24; 9.81]; 0.652
Immune-mediated severe AEs[i, k]	52	NA [31.8; NC] 12 (23.1)	65	NR 0	ND[l]
Infusion-related reactions	No usable data available[m]				
Urinary tract infections (PT, AEs)	52	NR 4 (7.7)	65	NA [13.3; NC] 16 (24.6)	0.25 [0.08; 0.78]; 0.010

a. Effect and CI: Cox proportional hazards model; p-value: log-rank test. In each case stratified according to prior pelvic radiotherapy (yes vs. no) and disease status at baseline (primary FIGO stage III vs. primary FIGO stage IV vs. recurrent).
b. A score increase by ≥ 10 points from baseline is defined as a clinically relevant deterioration (scale range 0 to 100).
c. 81% of the patients had no value at baseline and were therefore not included in the analysis.
d. A score decrease by ≥ 15 points from baseline is defined as a clinically relevant deterioration (scale range 0 to 100).
e. A score decrease by ≥ 10 points from baseline is defined as a clinically relevant deterioration (scale range 0 to 100).
f. 82% of the patients had no value at baseline and were therefore not included in the analysis.
g. In departure from the company's approach, this scale was assigned to health-related quality of life, rather than to symptoms.
h. According to the study protocol, events which were attributable to progression of the underlying disease were not to be reported as AEs. However, 2 (3.1%) patients with event for the PT "cancer pain" from the System Organ Class (SOC) "neoplasms benign, malignant and unspecified (incl. cysts and polyps)" were documented under AEs in the control arm.
i. Operationalized as CTCAE grade ≥ 3.
j. Discontinuation of one or more drug components.
k. The operationalization was based on an a priori defined list of PTs; only immune-mediated AEs with CTCAE grade ≥ 2 could be considered immune-mediated, however.
l. The company did not present any information on HR (including 95% CI) and p-value. In the present data constellation, with an event rate of 23% (n = 12) in the intervention arm versus 0% (n = 0) in the comparator arm, and with Kaplan-Meier curves clearly separating early in the course of the study (see Figure 32), a statistically significant difference to the disadvantage of dostarlimab + carboplatin + paclitaxel can be assumed.
m. For the reasoning, see A23-143 [1].

Table 4: Results (mortality, morbidity, health-related quality of life, side effects) – RCT, direct comparison: dostarlimab + carboplatin + paclitaxel vs. placebo + carboplatin + paclitaxel (multipage table)

Study Outcome category Outcome	Dostarlimab + carboplatin + paclitaxel		Placebo + carboplatin + paclitaxel		Dostarlimab + carboplatin + paclitaxel vs. placebo + carboplatin + paclitaxel
	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]
AE: adverse event; CI: confidence interval; CTCAE: Common Terminology Criteria for Adverse Events; EORTC: European Organisation for Research and Treatment of Cancer; FIGO: Fédération Internationale de Gynécologie et d'Obstétrique (International Federation of Gynecology and Obstetrics); HR: hazard ratio; n: number of patients with (at least one) event; N: number of analysed patients; NA: not achieved; NC: not calculable; ND: no data; PT: Preferred Term; QLQ-C30: Quality of Life Questionnaire-Core 30; QLQ-EN24: Quality of Life Questionnaire-Endometrial Cancer Module 24; RCT: randomized controlled trial; SAE: serious adverse event; SOC: System Organ Class; VAS: visual analogue scale					

On the basis of the available information, at most an indication, e.g. of added benefit, can be derived for the outcome of overall survival, and due to the high risk of bias or limited certainty of results (discontinuation due to AEs), at most hints can be derived for the outcomes in the categories of morbidity, health-related quality of life, and side effects.

Mortality

Overall survival

For the outcome of overall survival, a statistically significant difference was found in favour of dostarlimab + carboplatin + paclitaxel. There is an effect modification by the characteristic of disease status at baseline for this outcome (see Section 2.2.3). For patients with recurrent disease at baseline, there is an indication of added benefit of dostarlimab + carboplatin + paclitaxel compared with placebo + carboplatin + paclitaxel. For patients with primary advanced FIGO stage III or FIGO stage IV disease at baseline, there is no hint of an added benefit of dostarlimab + carboplatin + paclitaxel compared with placebo + carboplatin + paclitaxel; an added benefit is therefore not proven for these patients.

Morbidity

Symptoms (EORTC QLQ-C30 and EORTC QLQ-EN24)

The symptoms outcomes were recorded with the instruments EORTC QLQ-C30 and EORTC QLQ-EN24. Time to first deterioration by ≥ 10 points (scale range 0 to 100) was considered.

Tingling and numbness (EORTC QLQ-EN24)

No statistically significant difference between treatment groups was found for the outcome of tingling and numbness. There is an effect modification by the characteristic of disease status at baseline, however (see Section 2.2.3). For patients with primary advanced FIGO stage IV disease at baseline, there is a hint of an added benefit of dostarlimab + carboplatin + paclitaxel compared with placebo + carboplatin + paclitaxel. For patients with primary advanced FIGO stage III disease or recurrent disease at baseline, there is no hint of an added benefit of dostarlimab + carboplatin + paclitaxel compared with placebo + carboplatin + paclitaxel; an added benefit is therefore not proven for these patients.

Fatigue, nausea and vomiting, pain, dyspnoea, insomnia, appetite loss, constipation, diarrhoea (EORTC QLQ-C30), lymphoedema, urological symptoms, gastrointestinal symptoms, pain in back and pelvis, muscular pain, hair loss, taste change (EORTC QLQ-EN24)

No statistically significant difference between treatment groups was found for the scales of fatigue, nausea and vomiting, pain, dyspnoea, insomnia, appetite loss, constipation, and diarrhoea of the EORTC QLQ-C30, and for the scales of lymphoedema, urological symptoms, gastrointestinal symptoms, pain in back and pelvis, muscular pain, hair loss, and taste change of the EORTC QLQ-EN24. In each case, there is no hint of an added benefit of dostarlimab + carboplatin + paclitaxel in comparison with placebo + carboplatin + paclitaxel; an added benefit is therefore not proven for any of them.

Sexual/vaginal problems (EORTC QLQ-EN24)

No usable data are available for the EORTC QLQ-EN24 scale of sexual/vaginal problems because only 19% of patients were included in the analysis. There is no hint of an added benefit of dostarlimab + carboplatin + paclitaxel in comparison with placebo + carboplatin + paclitaxel; an added benefit is therefore not proven.

Health status (EQ-5D VAS)

No statistically significant difference between treatment groups was shown for the outcome of health status recorded with the EQ-5D VAS. There is no hint of an added benefit of dostarlimab + carboplatin + paclitaxel in comparison with placebo + carboplatin + paclitaxel; an added benefit is therefore not proven.

Health-related quality of life

EORTC QLQ-C30 and EORTC QLQ-EN24

The health-related quality of life outcomes were recorded with the instruments EORTC QLQ-C30 and EORTC QLQ-EN24. Time to first deterioration by ≥ 10 points (scale range 0 to 100) was considered.

Role functioning, social functioning (EORTC QLQ-C30)

For each of the outcomes of role functioning and social functioning, a statistically significant difference was found in favour of dostarlimab + carboplatin + paclitaxel. In each case, there is a hint of an added benefit of dostarlimab + carboplatin + paclitaxel in comparison with placebo + carboplatin + paclitaxel.

Global health status, physical functioning, emotional functioning, cognitive functioning (EORTC QLQ-C30), sexual interest, sexual activity, poor body image (EORTC QLQ-EN24)

No statistically significant difference between treatment groups was found for the scales of global health status, physical functioning, emotional functioning, and cognitive functioning of the EORTC QLQ-C30, and for the scales of sexual interest, sexual activity, and poor body image of the EORTC QLQ-EN24. In each case, there is no hint of an added benefit of dostarlimab + carboplatin + paclitaxel in comparison with placebo + carboplatin + paclitaxel; an added benefit is therefore not proven for any of them.

Sexual enjoyment (EORTC QLQ-EN24)

No usable data are available for the EORTC QLQ-EN24 scale of sexual enjoyment because only 18% of patients were included in the analysis. There is no hint of an added benefit of dostarlimab + carboplatin + paclitaxel in comparison with placebo + carboplatin + paclitaxel; an added benefit is therefore not proven.

Side effects

Severe AEs

No significant difference between treatment groups was found for the outcome of severe AEs. There is an effect modification by the characteristic of disease status at baseline, however (see Section 2.2.3). For patients with primary advanced FIGO stage III disease at baseline, there is a hint of greater harm of dostarlimab + carboplatin + paclitaxel compared with placebo + carboplatin + paclitaxel. In the pooled subgroup of patients with primary advanced FIGO stage IV disease or recurrent disease at baseline, there is no hint of greater or lesser harm of dostarlimab + carboplatin + paclitaxel compared with placebo + carboplatin + paclitaxel; greater or lesser harm is therefore not proven.

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. In each case, there is no hint of greater or lesser harm from dostarlimab + carboplatin + paclitaxel in comparison with placebo + carboplatin + paclitaxel; greater or lesser harm is therefore not proven for any of them.

Specific AEs

Immune-mediated severe AEs

The company provided no information on the hazard ratio (including 95% confidence interval) and p-value for the outcome of immune-mediated severe AEs, as was also the case for benefit assessment A23-143. In the present data constellation, with an event rate of 23% (n = 12) in the intervention arm versus 0% (n = 0) in the comparator arm, and with Kaplan-Meier curves clearly separating early in the course of the study (see Figure 32), a statistically significant difference to the disadvantage of dostarlimab + carboplatin + paclitaxel can be assumed. There is a hint of greater harm of dostarlimab + carboplatin + paclitaxel in comparison with placebo + carboplatin + paclitaxel.

Immune-mediated SAEs

No statistically significant difference between treatment groups was shown for the outcome of immune-mediated SAEs. There is no hint of greater or lesser harm from dostarlimab + carboplatin + paclitaxel in comparison with placebo + carboplatin + paclitaxel; greater or lesser harm is therefore not proven.

Infusion-related reactions

No usable data are available for infusion-related reactions (for the reasoning, see benefit assessment A23-143 [1]). There is no hint of greater or lesser harm from dostarlimab + carboplatin + paclitaxel in comparison with placebo + carboplatin + paclitaxel; greater or lesser harm is therefore not proven.

Urinary tract infections (AEs)

For the outcome of urinary tract infections (AEs), a statistically significant difference was found in favour of dostarlimab + carboplatin + paclitaxel. There is a hint of lesser harm of dostarlimab + carboplatin + paclitaxel in comparison with placebo + carboplatin + paclitaxel.

2.2.3 Subgroups and other effect modifiers

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

- age (< 65 years versus ≥ 65 years)
- disease status at baseline (primary FIGO stage III versus primary FIGO stage IV versus recurrent)

All mentioned subgroup characteristics and cut-off values had been prespecified for the primary outcomes of overall survival and progression-free survival.

Interaction tests are performed when at least 10 patients per subgroup are included in the analysis. Moreover, for binary data, there have to 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. Subgroup results where the extent does not differ between subgroups are not presented.

The results are presented in Table 5. The Kaplan-Meier curves on the subgroup results are presented in Appendix A.5 of the present addendum.

Table 5: Subgroups (mortality, morbidity, side effects) – RCT, direct comparison: dostarlimab + carboplatin + paclitaxel vs. placebo + carboplatin + paclitaxel (multipage table)

Study Outcome Characteristic Subgroup	Dostarlimab + carboplatin + paclitaxel N	Median time to event in months [95 % CI] Patients with event n (%)	Placebo + carboplatin + paclitaxel N	Median time to event in months [95 % CI] Patients with event n (%)	Dostarlimab + carboplatin + paclitaxel vs. placebo + carboplatin + paclitaxel HR [95% CI][a]	p-value[b]
RUBY						
Mortality						
Overall survival						
Disease status at baseline						
Primary FIGO stage III	9[c]	NA [2.4; NC] 3 (33.3)	14	NA [20.0; NC] 3 (21.4)	1.85 [0.37; 9.18]	0.445
Primary FIGO stage IV	17[c]	NA [21.0; NC] 6 (35.3)	19	18.2 [11.6; NC] 11 (57.9)	0.53 [0.19; 1.43]	0.201
Recurrent	27	NA 3 (11.1)	32	24.0 [13.0; 42.2] 21 (65.6)	0.12 [0.04; 0.42]	< 0.001
					Interaction[d]:	0.032
Morbidity						
Symptoms (EORTC QLQ-EN24 – time to first deterioration[e])						
Tingling/numbness						
Disease status at baseline						
Primary FIGO stage III	9[c]	1.4 [0.7; 2.1] 9 (100)	14	1.2 [0.8; 2.1] 12 (85.7)	1.03 [0.43; 2.45]	0.950
Primary FIGO stage IV	17[c]	3.5 [2.1; 7.2] 11 (64.7)	19	0.8 [0.7; 2.1] 18 (94.7)	0.34 [0.16; 0.75]	0.005
Recurrent	27	1.0 [0.8; 2.1] 25 (92.6)	32	1.8 [1.4; 2.3] 26 (81.3)	1.35 [0.77; 2.36]	0.317
					Interaction[d]:	0.016
Severe AEs[f]						
Disease status at baseline						
Primary FIGO stage III	9[c]	4.1 [0.0; 4.6] 8 (88.9)	14	16.5 [2.6; NC] 7 (50.0)	5.40 [1.57; 18.53]	0.003
Primary FIGO stage IV	16[c]	4.1 [0.3; 11.3] 12 (75.0)	19	2.4 [0.7; 4.5] 15 (78.9)	0.82 [0.37; 1.79]	0.605
Recurrent	27	2.7 [1.0; 25.6] 19 (70.4)	32	2.3 [1.4; 9.9] 21 (65.6)	0.91 [0.48; 1.74]	0.763
					Interaction[d]:	0.031

Table 5: Subgroups (mortality, morbidity, side effects) – RCT, direct comparison: dostarlimab + carboplatin + paclitaxel vs. placebo + carboplatin + paclitaxel (multipage table)

Study Outcome Characteristic Subgroup	Dostarlimab + carboplatin + paclitaxel N	Median time to event in months [95 % CI] Patients with event n (%)	Placebo + carboplatin + paclitaxel N	Median time to event in months [95 % CI] Patients with event n (%)	Dostarlimab + carboplatin + paclitaxel vs. placebo + carboplatin + paclitaxel HR [95% CI][a]	p-value[b]
Primary FIGO stage III	9[c]	4.1 [0.0; 4.6] 8 (88.9)	14	16.5 [2.6; NC] 7 (50.0)	5.40 [1.57; 18.53]	0.003
Primary FIGO stage IV and recurrent[g]	43[c, h]	ND 31 (72.1)[h]	51[g]	ND 36 (70.6)[h]	0.87 [0.53; 1.44][i]	0.593[i]
					Interaction[j]:	0.007

a. Effect and CI: Cox proportional hazards model stratified according to prior pelvic radiotherapy (yes vs. no) and disease status at baseline (primary FIGO stage III vs. primary FIGO stage IV vs. recurrent).
b. p-value: log-rank test stratified according to prior pelvic radiotherapy (yes vs. no) and disease status at baseline (primary FIGO stage III vs. primary FIGO stage IV vs. recurrent).
c. As part of the commenting procedure, the company stated that after a correction of the assignment of the FIGO stages in the 2nd data cut-off, one patient was regrouped from the primary FIGO stage III subgroup to the primary FIGO stage IV subgroup. It did not provide any further details.
d. p-value of the interaction term of the stratified Cox proportional hazards model.
e. A score increase by ≥ 10 points from baseline is defined as a clinically relevant deterioration (scale range 0 to 100).
f. Operationalized as CTCAE grade ≥ 3.
g. Summary of the subgroups of primary FIGO stage IV and recurrent.
h. Institute's calculation.
i: Institute's calculation: meta-analytical summary of the subgroup results for primary FIGO stage IV and recurrent (fixed-effect model).
j. Institute's calculation: p-value from Q test for heterogeneity, related to the 2 subgroups of primary FIGO stage III vs. primary FIGO stage IV and recurrent.

AE: adverse event; CI: confidence interval; CTCAE: Common Terminology Criteria for Adverse Events; EORTC: European Organisation for Research and Treatment of Cancer; FIGO: Fédération Internationale de Gynécologie et d'Obstétrique (International Federation of Gynecology and Obstetrics); HR: hazard ratio; n: number of patients with (at least one) event; N: number of analysed patients; NA: not achieved; NC: not calculable; ND: no data; QLQ-EN24: Quality of Life Questionnaire-Endometrial Cancer Module 24; RCT: randomized controlled trial

Mortality

Overall survival

There is an effect modification for the characteristic of disease status at baseline for the outcome of overall survival. First, it was examined whether subgroups could be meaningfully summarized. In contrast to the data cut-off of the dossier assessment, this is not meaningfully

possible for this outcome in the present data constellation because it does not result in a sufficiently homogeneous data situation.

In patients with primary advanced FIGO stage III or FIGO stage IV disease at baseline, there was no statistically significant difference between treatment groups. For patients with primary advanced FIGO stage III or FIGO stage IV disease at baseline, there is no hint of an added benefit of dostarlimab + carboplatin + paclitaxel compared with placebo + carboplatin + paclitaxel; an added benefit is therefore not proven for these patients.

For patients with recurrent disease at baseline, there was a statistically significant difference in favour of dostarlimab + carboplatin + paclitaxel. For patients with recurrent disease at baseline, there is a hint of an indication of added benefit of dostarlimab + carboplatin + paclitaxel compared with placebo + carboplatin + paclitaxel.

Morbidity

Symptoms (EORTC QLQ-C30)

Tingling and numbness (EORTC QLQ-EN24)

There is an effect modification for the characteristic of disease status at baseline for the outcome of tingling and numbness. First, it was examined whether subgroups could be meaningfully summarized. In the present data constellation, this was not meaningful for this outcome.

In patients with primary advanced FIGO stage III disease or recurrent disease at baseline, there was no statistically significant difference between treatment groups. For patients with primary advanced FIGO stage III disease or recurrent disease at baseline, there is no hint of an added benefit of dostarlimab + carboplatin + paclitaxel compared with placebo + carboplatin + paclitaxel; an added benefit is not proven for these patients.

For patients with primary advanced FIGO stage IV disease at baseline, there was a statistically significant difference in favour of dostarlimab + carboplatin + paclitaxel. For patients with primary advanced FIG stage IV disease at baseline, there is a hint of an added benefit of dostarlimab + carboplatin + paclitaxel compared with placebo + carboplatin + paclitaxel.

Side effects

Severe AEs

There is an effect modification for the characteristic of disease status at baseline for the outcome of severe AEs. First, it was examined whether subgroups could be meaningfully summarized. Calculations conducted by the Institute show that a pooled consideration of the subgroups of primary FIGO stage IV and recurrent result in a homogeneous data situation for

the outcome of severe AEs (see Appendix E). Below, the derivation of added benefit for the outcome of severe AEs is based on the results of calculations conducted by the Institute.

In patients with primary advanced FIGO stage III disease at baseline, there was a statistically significant difference to the disadvantage of dostarlimab + carboplatin + paclitaxel. For patients with primary advanced FIGO stage III disease at baseline, there is a hint of greater harm of dostarlimab + carboplatin + paclitaxel compared with placebo + carboplatin + paclitaxel.

For patients with primary advanced FIGO stage IV disease or recurrent disease at baseline, there was no statistically significant difference between treatment groups. For patients with primary advanced FIGO stage IV disease or recurrent disease at baseline, there is no hint of greater or lesser harm of dostarlimab + carboplatin + paclitaxel compared with placebo + carboplatin + paclitaxel; greater or lesser harm is therefore not proven for these patients.

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 [10].

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.

Assessment of added benefit at outcome level

The extent of the respective added benefit at outcome level is estimated from the results presented in Section 2.2.2 (see Table 6).

Determination of the outcome category for the outcomes on side effects

It cannot be inferred from the dossier whether the following outcomes were serious/severe or non-serious/non-severe. Reasoning is provided for the classification of these outcomes.

Symptoms

Tingling/numbness (EORTC QLQ-EN24)

For the outcome of tingling/numbness, insufficient severity data are available which would allow classifying them as serious/severe. The outcome of tingling/numbness was therefore assigned to the outcome category of non-serious/non-severe symptoms/late complications.

Urinary tract infections (AEs)

The clinical study report (CSR) contains information on the CTCAE severity grade of the specific side effect of urinary tract infections (PT, AEs), which show that the majority of events were non-serious or non-severe (CTCAE grade < 3). Therefore, the specific AE was assigned to the outcome category of non-serious/non-severe side effects.

Table 6: Extent of added benefit at outcome level: dostarlimab + carboplatin + paclitaxel vs. placebo + carboplatin + paclitaxel (multipage table)

Outcome category **Outcome** **Effect modifier** **Subgroup**	**Dostarlimab + carboplatin + paclitaxel vs. placebo + carboplatin + paclitaxel** **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		
Disease status at baseline		
Primary FIGO stage III	NA vs. NA HR: 1.85 [0.37; 9.18]; p = 0.445	Lesser/added benefit not proven
Primary FIGO stage IV	NA vs. 18.2 HR: 0.53 [0.19; 1.43]; p = 0.201	Lesser/added benefit not proven
Recurrent	NA vs. 24.0 HR: 0.12 [0.04; 0.42]; p < 0.001 Probability: “indication”	Outcome category: mortality CI_u < 0.85 Added benefit, extent: “major”

Table 6: Extent of added benefit at outcome level: dostarlimab + carboplatin + paclitaxel vs. placebo + carboplatin + paclitaxel (multipage table)

Outcome category **Outcome** **Effect modifier** **Subgroup**	**Dostarlimab + carboplatin + paclitaxel vs. placebo + carboplatin + paclitaxel** **Median time to event (months)** **Effect estimation [95% CI];** **p-value** **Probability**[a]	**Derivation of extent**[b]
Morbidity		
Symptoms (EORTC QLQ-C30 – time to first deterioration by ≥ 10 points)		
Fatigue	2.3 vs. 1.4 HR: 0.84 [0.55; 1.28]; p = 0.410	Lesser/added benefit not proven
Nausea and vomiting	5.8 vs. 4.5 HR: 0.87 [0.54; 1.38]; p = 0.539	Lesser/added benefit not proven
Pain	11.5 vs. 3.3 HR: 0.64 [0.40; 1.03]; p = 0.058	Lesser/added benefit not proven
Dyspnoea	4.4 vs. 3.7 HR: 0.90 [0.56; 1.45]; p = 0.661	Lesser/added benefit not proven
Insomnia	7.5 vs. 4.2 HR: 0.96 [0.59; 1.57]; p = 0.862	Lesser/added benefit not proven
Appetite loss	19.8 vs. 8.5 HR: 0.68 [0.41; 1.14]; p = 0.144	Lesser/added benefit not proven
Constipation	2.8 vs. 3.9 HR: 0.87 [0.54; 1.40]; p = 0.518	Lesser/added benefit not proven
Diarrhoea	4.6 vs. 5.7 HR: 1.18 [0.73; 1.89]; p = 0.503	Lesser/added benefit not proven
Symptoms (EORTC QLQ-EN24 – time to first deterioration by ≥ 10 points)		
Lymphoedema	2.8 vs. 2.8 HR: 0.87 [0.56; 1.33]; p = 0.518	Lesser/added benefit not proven
Urological symptoms	NA vs. 3.8 HR: 0.60 [0.35; 1.04]; p = 0.068	Lesser/added benefit not proven
Gastrointestinal symptoms	26.7 vs. 11.7 HR: 0.91 [0.53; 1.56]; p = 0.736	Lesser/added benefit not proven

Table 6: Extent of added benefit at outcome level: dostarlimab + carboplatin + paclitaxel vs. placebo + carboplatin + paclitaxel (multipage table)

Outcome category **Outcome** **Effect modifier** **Subgroup**	**Dostarlimab + carboplatin + paclitaxel vs. placebo + carboplatin + paclitaxel** **Median time to event (months)** **Effect estimation [95% CI];** **p-value** **Probability[a]**	**Derivation of extent[b]**
Sexual/vaginal problems	No usable data available	Lesser/added benefit not proven
Pain in back and pelvis	21.6 vs. 24.0 HR: 0.82 [0.48; 1.41]; p = 0.473	Lesser/added benefit not proven
Tingling/numbness		
Disease status at baseline		
Primary FIGO stage III	1.4 vs. 1.2 HR: 1.03 [0.43; 2.45]; p = 0.950	Lesser/added benefit not proven
Primary FIGO stage IV	3.5 vs. 0.8 HR: 0.34 [0.16; 0.75]; p = 0.005 Probability: “hint”	Outcome category: non-serious/non-severe symptoms/late complications $CI_u < 0.80$ Added benefit; extent: “considerable”
Recurrent	1.0 vs. 1.8 HR: 1.35 [0.77; 2.36]; p = 0.317	Lesser/added benefit not proven
Muscular pain	1.4 vs. 2.1 HR: 1.15 [0.76; 1.75]; p = 0.556	Lesser/added benefit not proven
Hair loss	0.8 vs. 0.8 HR: 1.15 [0.77; 1.71]; p = 0.574	Lesser/added benefit not proven
Taste change	2.2 vs. 2.2 HR: 0.90 [0.58; 1.40]; p = 0.609	Lesser/added benefit not proven
Health status		
EQ-5D VAS – time to first deterioration by ≥ 15 points	NA vs. 16.3 HR: 0.54 [0.28; 1.02]; p = 0.055	Lesser/added benefit not proven

Table 6: Extent of added benefit at outcome level: dostarlimab + carboplatin + paclitaxel vs. placebo + carboplatin + paclitaxel (multipage table)

Outcome category **Outcome** **Effect modifier** **Subgroup**	**Dostarlimab + carboplatin + paclitaxel vs. placebo + carboplatin + paclitaxel** **Median time to event (months)** **Effect estimation [95% CI];** **p-value** **Probability**[a]	**Derivation of extent**[b]
Health-related quality of life		
EORTC QLQ-C30 (time to first deterioration by ≥ 10 points)		
Global health status	12.9 vs. 4.2 HR: 0.63 [0.39; 1.02]; p = 0.055	Lesser/added benefit not proven
Physical functioning	4.0 vs. 3.7 HR: 0.93 [0.58; 1.49]; p = 0.759	Lesser/added benefit not proven
Role functioning	4.4 vs. 2.5 HR: 0.61 [0.38; 0.98]; p = 0.040 Probability: “hint”	Outcome category: health-related quality of life $0.90 \leq CI_u < 1.00$ Added benefit, extent: “minor”
Emotional functioning	20.5 vs. 13.9 HR: 0.83 [0.50; 1.40]; p = 0.478	Lesser/added benefit not proven
Cognitive functioning	4.0 vs. 2.9 HR: 0.70 [0.44; 1.11]; p = 0.119	Lesser/added benefit not proven
Social functioning	4.2 vs. 2.8 HR: 0.57 [0.35; 0.92]; p = 0.020 Probability: “hint”	Outcome category: health-related quality of life $0.90 \leq CI_u < 1.00$ Added benefit, extent: “minor”
EORTC QLQ-EN24 (time to first deterioration by ≥ 10 points)		
Sexual interest	NA vs. NA HR: 0.63 [0.29; 1.38]; p = 0.242	Lesser/added benefit not proven
Sexual activity	NA vs. NA HR: 1.22 [0.37; 4.01]; p = 0.738	Lesser/added benefit not proven
Sexual enjoyment	No usable data available	Lesser/added benefit not proven
Poor body image	1.4 vs. 1.4 HR: 0.70 [0.45; 1.10]; p = 0.126	Lesser/added benefit not proven

Table 6: Extent of added benefit at outcome level: dostarlimab + carboplatin + paclitaxel vs. placebo + carboplatin + paclitaxel (multipage table)

Outcome category **Outcome** **Effect modifier** **Subgroup**	**Dostarlimab + carboplatin + paclitaxel vs. placebo + carboplatin + paclitaxel** **Median time to event (months)** **Effect estimation [95% CI];** **p-value** **Probability**[a]	**Derivation of extent**[b]
Outcomes with shortened observation period		
Side effects		
SAEs	NA vs. 26.4 HR: 0.86 [0.44; 1.66]; p = 0.633	Greater/lesser harm not proven
Severe AEs Disease status at baseline		
Primary FIGO stage III	4.1 vs. 16.5 HR: 5.40 [1.57; 18.53] HR: 0.19 [0.05; 0.64][c]; p = 0.003 Probability: "hint"	Outcome category: serious/severe side effects CI_u < 0.75; risk ≥ 5% Greater harm, extent: "major"
Primary FIGO stage IV and recurrent	N D HR: 0.87 [0.53; 1.44]; p = 0.593	Greater/lesser harm not proven
Discontinuation due to AEs	NA vs. NA HR: 0.86 [0.34; 2.17]; p = 0.751	Greater/lesser harm not proven
Immune-mediated SAEs	NA vs. NA HR: 1.53 [0.24; 9.81]; p = 0.652	Greater/lesser harm not proven
Immune-mediated severe AEs	NA vs. NA (patients with event: 23% vs. 0%) HR: ND p: ND Probability: "hint"	Outcome category: serious/severe side effects Greater harm, extent: "non-quantifiable", at least "considerable"[d]
Infusion-related reactions	No usable data available	Greater/lesser harm not proven
Urinary tract infections (PT, AEs)	NA vs. NA HR: 0.25 [0.08; 0.78]; p = 0.010 Probability: "hint"	Outcome category: non-serious/non-severe side effects CI_u < 0.80 Lesser harm, extent: "considerable"

Table 6: Extent of added benefit at outcome level: dostarlimab + carboplatin + paclitaxel vs. placebo + carboplatin + paclitaxel (multipage table)

Outcome category **Outcome** **Effect modifier** **Subgroup**	**Dostarlimab + carboplatin + paclitaxel vs. placebo + carboplatin + paclitaxel** **Median time to event (months)** **Effect estimation [95% CI];** **p-value** **Probability**[a]	**Derivation of extent**[b]

a. Probability provided if there is a statistically significant and relevant effect.
b. Depending on the outcome category, the effect size is estimated using different limits based on the upper limit of the confidence interval (CI_u).
c. Institute's calculation; inverse direction of effect to enable use of limits to derive the extent of the added benefit.
d. The company did not present any information on HR (including 95% CI) and p-value. In the present data constellation, with an event rate of 23% (n = 12) in the intervention arm versus 0% (n = 0) in the comparator arm, and with Kaplan-Meier curves clearly separating early in the course of the study (see Figure 32), a statistically significant difference to the disadvantage of dostarlimab + carboplatin + paclitaxel can be assumed. The extent is estimated to be "non-quantifiable", but be at least "considerable".

AE: adverse event; CI: confidence interval; CI_u: upper limit of the confidence interval; EORTC: European Organisation for Research and Treatment of Cancer; FIGO: International Federation of Gynecology and Obstetrics; HR: hazard ratio; NA: not achieved; NC: not calculable; ND: no data; PT: Preferred Term; QLQ-C30: Quality of Life Questionnaire-Core 30; QLQ-EN24: Quality of Life Questionnaire-Endometrial Cancer Module 24; SAE: serious adverse event; VAS: visual analogue scale

2.2.4 Overall conclusion on added benefit

Table 7 summarizes the results taken into account in the overall conclusion on the extent of added benefit.

Table 7: Positive and negative effects from the assessment of dostarlimab + carboplatin + paclitaxel in comparison with carboplatin + paclitaxel

Positive effects	**Negative effects**
Outcomes with observation over the entire study duration	
Mortality Overall survival Disease status at baseline (recurrent): indication of an added benefit – extent: “major”	–
Non-serious/non-severe symptoms/late complications Symptoms (EORTC QLQ-EN24): Tingling/numbness Disease status at baseline (primary FIGO stage IV): hint of an added benefit – extent: “considerable”	–
Health-related quality of life EORTC QLQ-C30: Role functioning: hint of an added benefit – extent: “minor” Social functioning: hint of an added benefit – extent: “minor”	–
Outcomes with shortened observation period	
–	Serious/severe side effects Severe AEs: Disease status at baseline (primary FIGO stage III): hint of greater harm – extent: “major” Immune-mediated severe AEs: hint of greater harm – extent: “non-quantifiable”, at least “considerable”
Non-serious/non-severe side effects Urinary tract infection (AE): hint of lesser harm – extent: “considerable”	–
No usable data are available for the outcome of infusion-related reactions from the side effects category.	
AE: adverse event; EORTC: European Organisation for Research and Treatment of Cancer; FIGO: International Federation of Gynecology and Obstetrics; QLQ-C30: Quality of Life Questionnaire-Core 30; QLQ-EN24: Quality of Life Questionnaire-Endometrial Cancer Module 24	

Overall, in the 2nd data cut-off, both positive and negative effects of dostarlimab + carboplatin + paclitaxel were found in comparison with the appropriate comparator therapy (ACT). For overall survival and the outcomes in the categories of morbidity and health-related quality of life, the observed effects relate to the entire observation period. For the side effects, however, they refer exclusively to the shortened period (planned until the end of treatment [plus a maximum of 90 days]). The characteristic of disease status at baseline is an effect modifier for various outcomes. Due to the effect modifications, the results on the added benefit of dostarlimab + carboplatin + paclitaxel compared with the ACT are derived separately by disease status at baseline:

Patients with primary advanced FIGO stage III disease

On the side of positive effects, there is a hint of a minor added benefit in both role functioning and social functioning in the category of health-related quality of life for patients with primary advanced FIGO stage III disease at baseline. In addition, there is a hint of lesser harm of considerable extent in the outcome of urinary tract infections (AEs). In view of the therapy regimens investigated, however, it is questionable whether the positive effect regarding this outcome is to be allocated to the outcome category of side effects or whether it rather reflects improved symptoms of the disease. A clear distinction is not possible on the basis of the available information.

In contrast, there are negative effects in the category of serious/severe side effects with major or non-quantifiable, but at least considerable extent in the overall rate of severe AEs and in immune-mediated severe AEs. It should be noted that the immune-mediated severe AEs are also included in the analyses of the severe AEs. Overall, the positive effects on health-related quality of life outcomes, which, like all patient-reported outcomes, are recorded until the end of the study, have become clearer with the present data cut-off and are also supported by the additional analyses of the continuous data (MMRM analyses). In summary, weighing up the positive and negative effects for patients with primary advanced FIGO stage III disease at baseline, the added benefit is not proven.

Patients with primary advanced FIGO stage IV disease

In addition, for patients with primary advanced FIGO stage III disease at baseline, there are multiple positive effects with minor or considerable extent in the categories of non-serious/non-severe symptoms/late complications, role functioning and social functioning of health-related quality of life, and non-serious/non-severe side effects. In view of the therapy regimens investigated, however, it is questionable whether the positive effect regarding the outcome of urinary tract infections (AEs) is to be allocated to the outcome category of side effects or whether it rather reflects improved symptoms of the disease. A clear distinction is not possible on the basis of the available information. In contrast, in the category of serious/severe side effects, there is a negative effect with non-quantifiable, but at least considerable extent in immune-mediated severe AEs. This does not call the positive effects into question. As described above, the positive effects on health-related quality of life outcomes, which, like all patient-reported outcomes, are recorded until the end of the study, have become clearer with the present data cut-off and are also supported by the additional analyses of the continuous data (MMRM analyses). Overall, a hint of a minor added benefit is derived for patients with primary advanced FIGO stage IV disease at baseline.

Patients with recurrent disease

For patients with recurrent disease at baseline, there is an indication of major added benefit for the outcome of overall survival. In addition, there are further positive effects with minor

or considerable extent in the categories of role functioning and social functioning of health-related quality of life, and non-serious/non-severe side effects. In view of the therapy regimens investigated, however, it is questionable whether the positive effect regarding the outcome of urinary tract infections (AEs) is to be allocated to the outcome category of side effects or whether it rather reflects improved symptoms of the disease. A clear distinction is not possible on the basis of the available information. In contrast, in the category of serious/severe side effects, there is a negative effect with non-quantifiable, but at least considerable extent in immune-mediated severe AEs. This does not call into question the positive effects, especially the major added benefit in overall survival. Overall, an indication of major added benefit is derived for patients with recurrent disease at baseline.

Summary

In summary, there is no hint of added benefit of dostarlimab + carboplatin + paclitaxel in comparison with the ACT carboplatin + paclitaxel for patients with dMMR/MSI-H primary advanced FIGO stage III endometrial cancer and who are candidates for systemic therapy; an added benefit is therefore not proven for these patients. There is a hint of a minor added benefit of dostarlimab + carboplatin + paclitaxel in comparison with the ACT carboplatin + paclitaxel for patients with dMMR/MSI-H primary advanced FIGO stage IV endometrial cancer and who are candidates for systemic therapy. There is an indication of major added benefit of dostarlimab + carboplatin + paclitaxel in comparison with the ACT carboplatin + paclitaxel for patients with dMMR/MSI-H recurrent endometrial cancer and who are candidates for systemic therapy.

2.3 Summary

The data subsequently submitted by the company in the commenting procedure changed the conclusion on the added benefit of dostarlimab + carboplatin + paclitaxel from dossier assessment A23-143: For the subgroup of patients with dMMR/MSI-H primary advanced endometrial carcinoma in FIGO stage III and who are candidates for systemic therapy, there was no evidence of added benefit on the basis of the 2nd data cut-off compared with the appropriate comparator therapy carboplatin + paclitaxel. Based on the 2nd data cut-off, there is no hint of an added benefit of dostarlimab + carboplatin + paclitaxel in comparison with the ACT carboplatin + paclitaxel; an added benefit is therefore not proven for these patients. There is a hint of a minor added benefit of dostarlimab + carboplatin + paclitaxel in comparison with the ACT carboplatin + paclitaxel for the subgroup of patients with dMMR/MSI-H primary advanced FIGO stage IV endometrial cancer and who are candidates for systemic therapy. For the subgroup of patients with dMMR/MSI-H recurrent endometrial cancer and who are candidates for systemic therapy, there is no change compared to dossier assessment A23-143.

The following Table 8 shows the result of the benefit assessment of dostarlimab + carboplatin + paclitaxel, taking into account dossier assessment A23-143 and the present addendum.

Table 8: Dostarlimab + carboplatin + paclitaxel – probability and extent of added benefit

Therapeutic indication	**ACT[a]**	**Probability and extent of added benefit**
Adult patients with dMMR/MSI-H primary advanced or recurrent[b] endometrial cancer and who are candidates for systemic therapy[c]	Carboplatin + paclitaxel[d]	Patients with primary FIGO stage III: added benefit not proven Patients with primary FIGO stage IV: hint of a minor added benefit[e] Patients with recurrent disease: indication of major added benefit[e]

a. Presented is the respective ACT specified by the G-BA.
b. In the recurrent setting, it is assumed that local therapy options for treating the recurrence (resection, radiotherapy) are not an option.
c. In this therapeutic indication, the G-BA assumes that the patients have not yet received systemic therapy as postoperative or adjuvant therapy to treat the primary advanced disease and have not yet received chemotherapy to treat the recurrence.
d. For patients in this therapeutic indication, the evidence-based guideline recommendation and the written statement of the scientific-medical societies recommend treatment with carboplatin in combination with paclitaxel. Treatment with carboplatin in combination with paclitaxel is not approved for this therapeutic indication. Accordingly, the use of carboplatin in combination with paclitaxel represents an off-label use. For patients in the present therapeutic indication, the off-label use is generally preferable to the drugs currently approved in the therapeutic indication, according to the generally recognized state of medical knowledge.
e. The RUBY study included only patients with an ECOG PS of 0 or 1. It remains unclear whether the observed effects can be transferred to patients with an ECOG PS of ≥ 2.

ACT: appropriate comparator therapy; dMMR: mismatch repair deficient; ECOG PS: Eastern Cooperative Oncology Group Performance Status; FIGO: International Federation of Gynecology and Obstetrics; G-BA: Federal Joint Committee; MSI-H: microsatellite instability-high

The G-BA decides on the added benefit.

3 References

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

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Appendix A Kaplan-Meier curves

A.1 Mortality

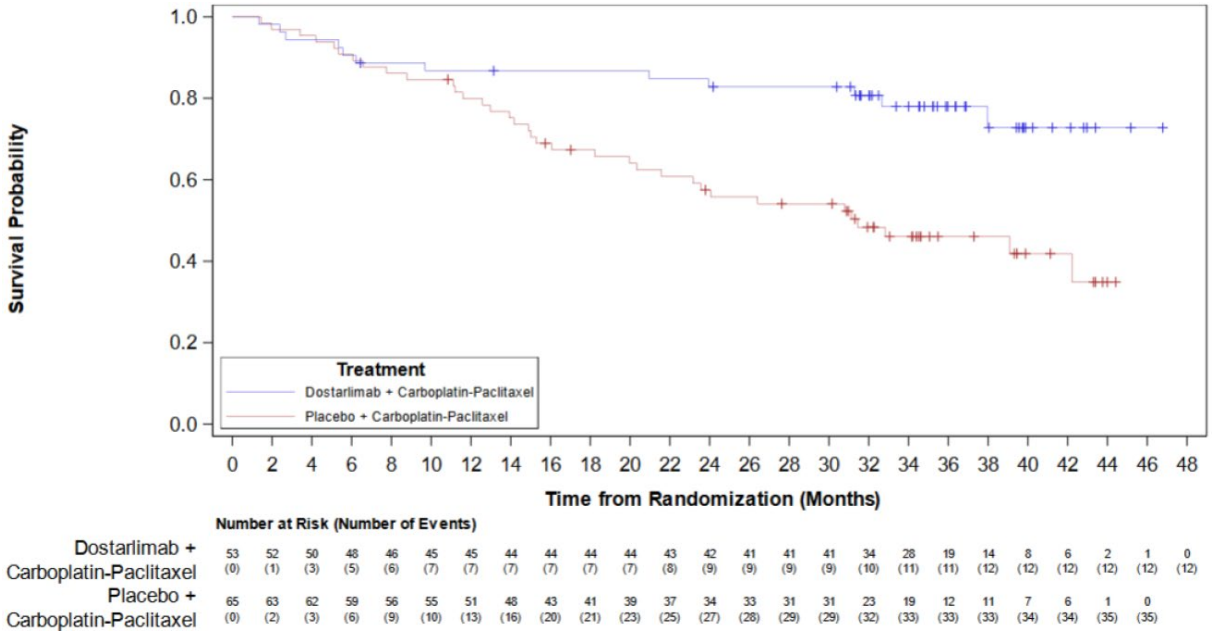

Figure 1: Kaplan-Meier curves on the outcome “overall survival” (data cut-off: 22 September 2023)

A.2 Morbidity

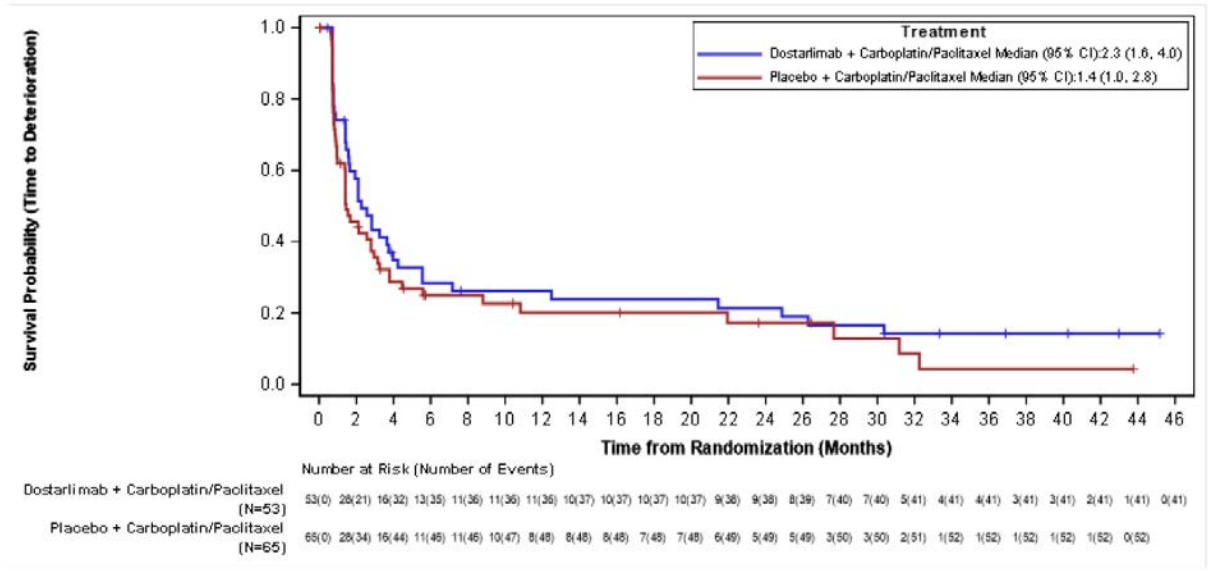

Figure 2: Kaplan-Meier curves on the outcome “fatigue” (EORTC QLQ C30, first deterioration by ≥ 10 points; data cut-off: 22 September 2023)

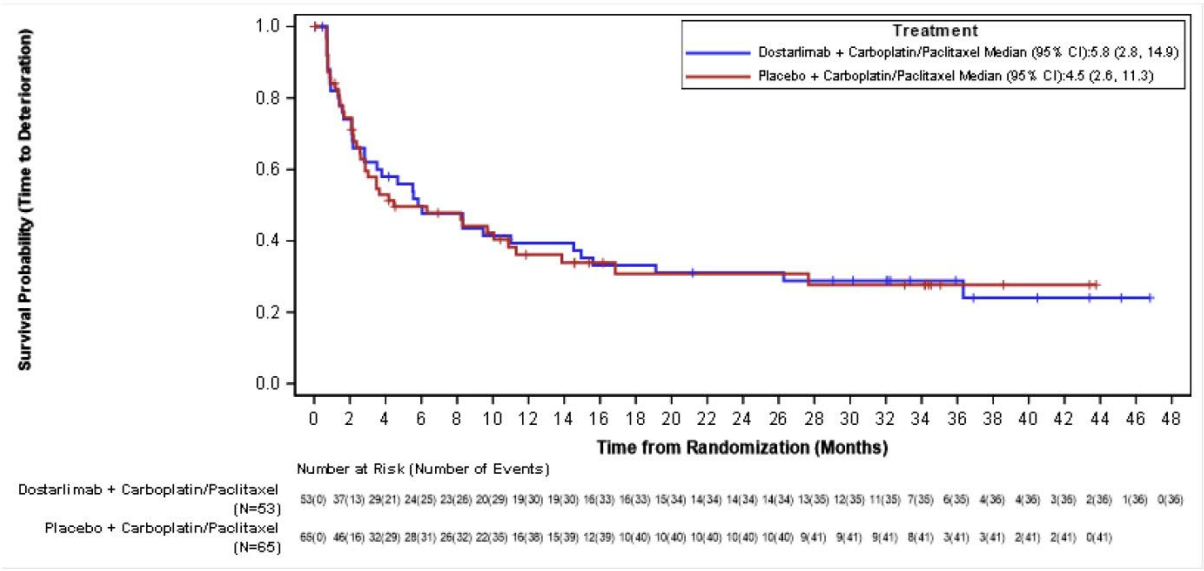

Figure 3: Kaplan-Meier curves on the outcome “nausea and vomiting” (EORTC QLQ C30, first deterioration by ≥ 10 points; data cut-off: 22 September 2023)

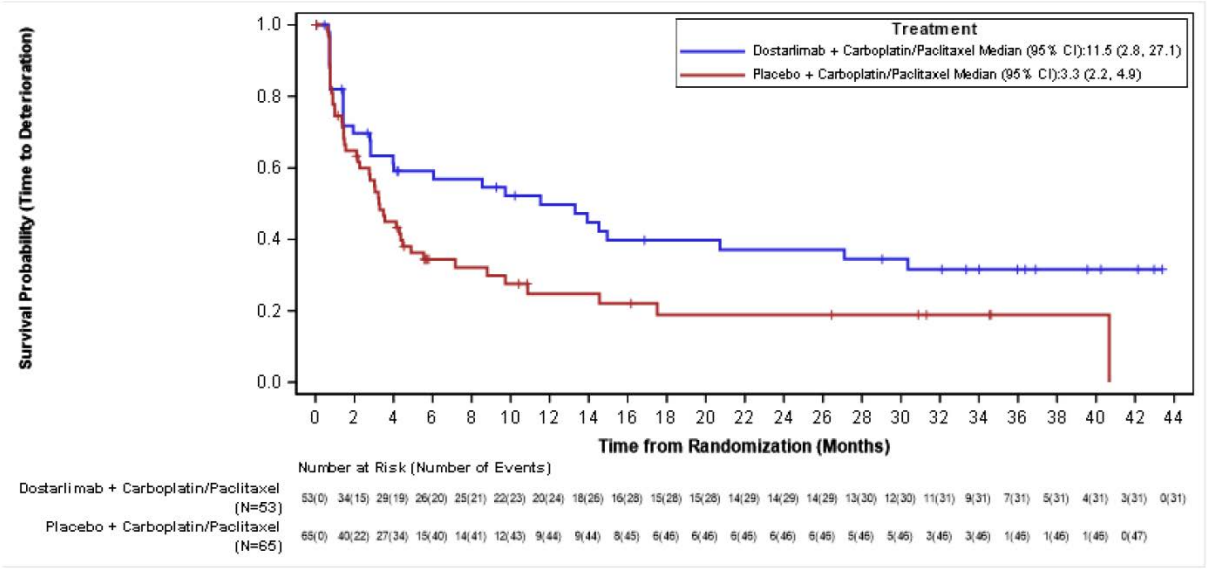

Figure 4: Kaplan-Meier curves on the outcome “pain” (EORTC QLQ C30, first deterioration by ≥ 10 points; data cut-off: 22 September 2023)

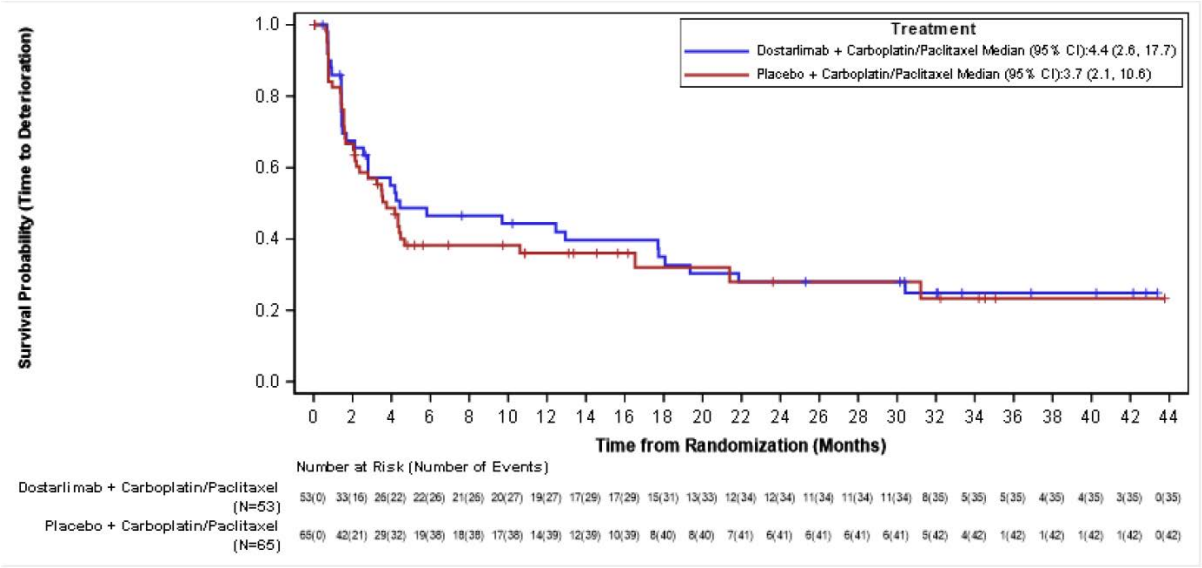

Figure 5: Kaplan-Meier curves on the outcome “dyspnoea” (EORTC QLQ C30, first deterioration by ≥ 10 points; data cut-off: 22 September 2023)

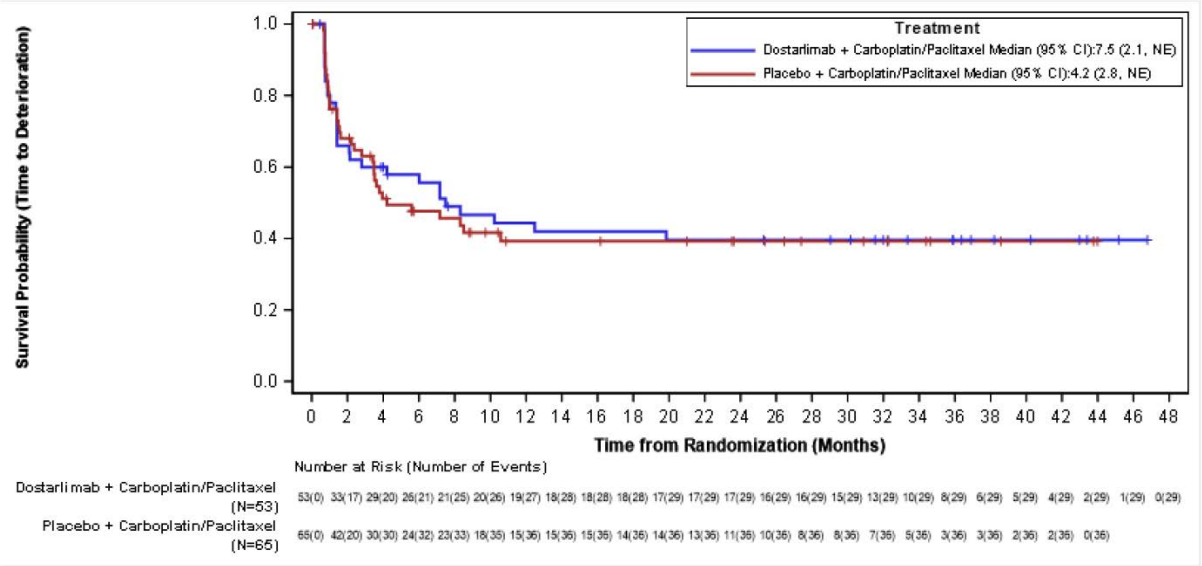

Figure 6: Kaplan-Meier curves on the outcome “insomnia” (EORTC QLQ C30, first deterioration by ≥ 10 points; data cut-off: 22 September 2023)

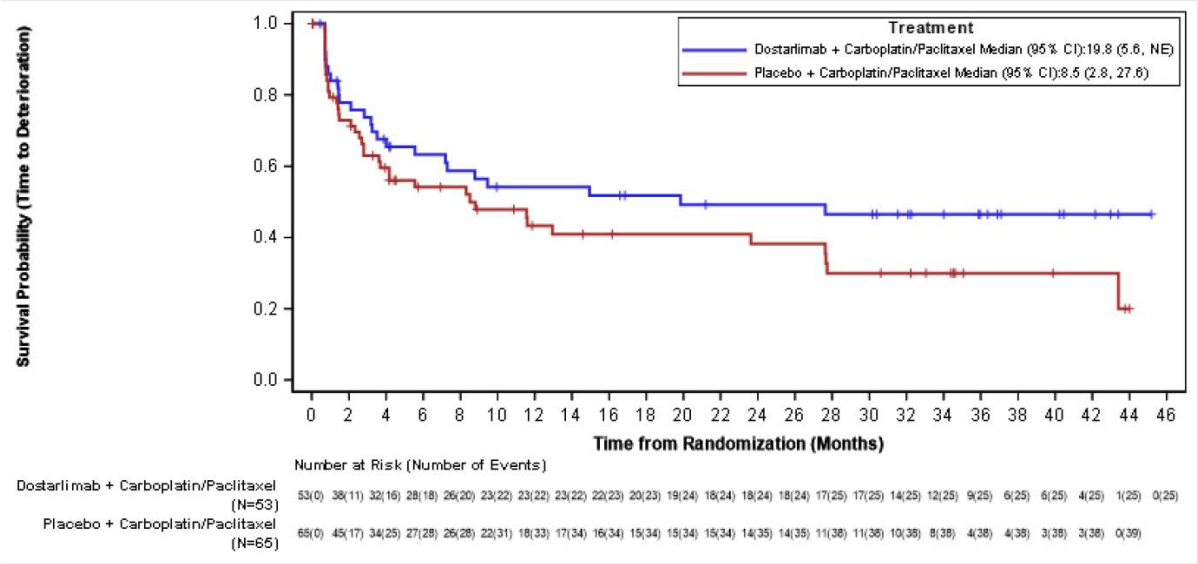

Figure 7: Kaplan-Meier curves on the outcome “appetite loss” (EORTC QLQ C30, first deterioration by ≥ 10 points; data cut-off: 22 September 2023)

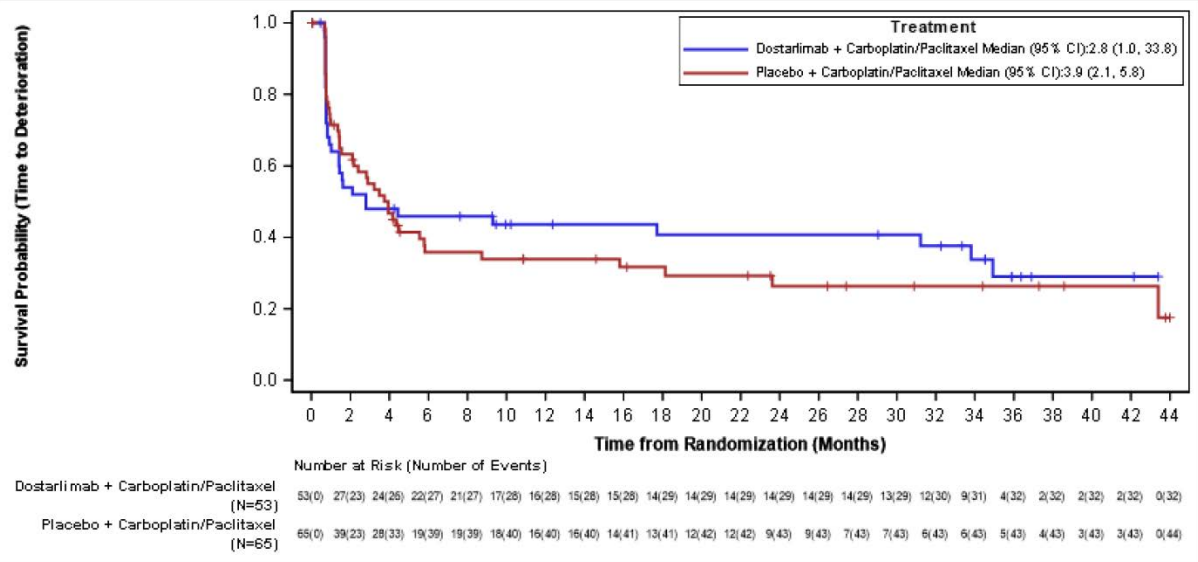

Figure 8: Kaplan-Meier curves on the outcome “constipation” (EORTC QLQ C30, first deterioration by ≥ 10 points; data cut-off: 22 September 2023)

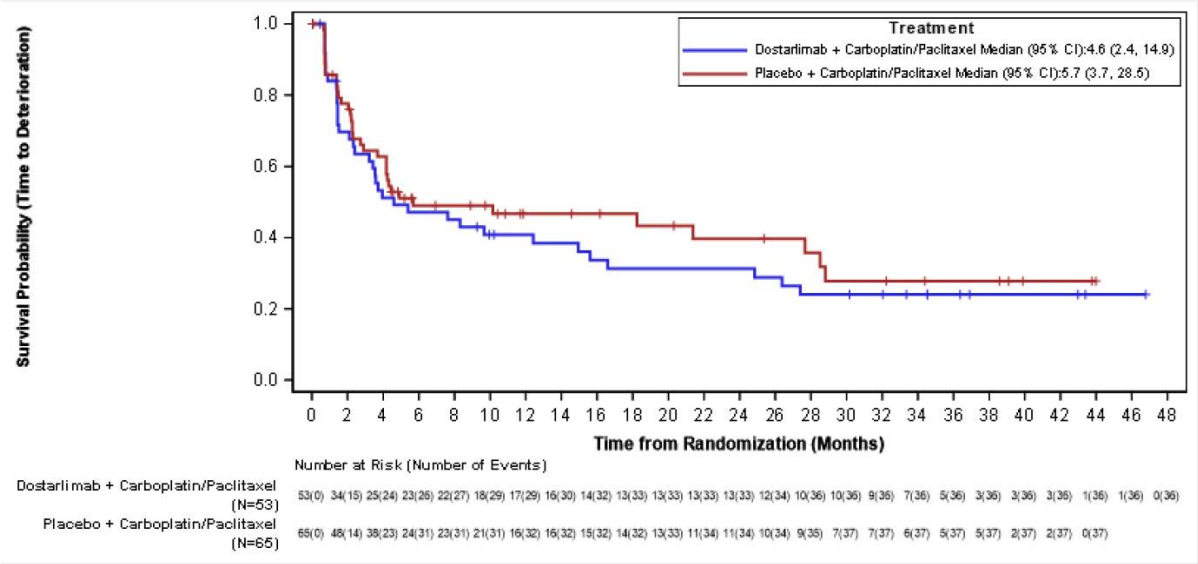

Figure 9: Kaplan-Meier curves on the outcome “diarrhoea” (EORTC QLQ C30, first deterioration by ≥ 10 points; data cut-off: 22 September 2023)

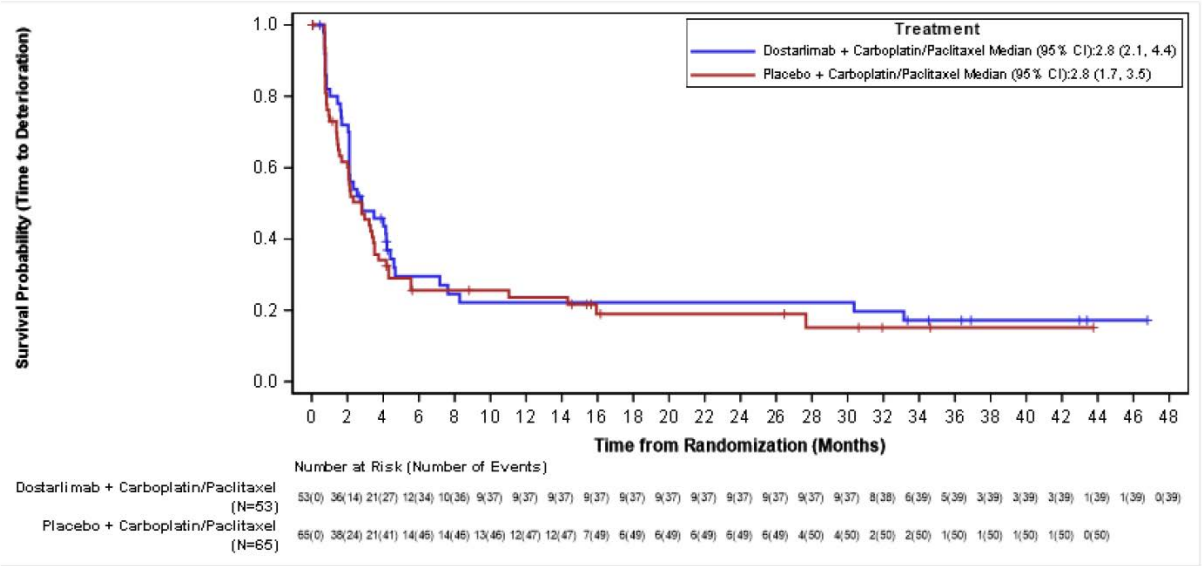

Figure 10: Kaplan-Meier curves on the outcome “lymphoedema” (EORTC QLQ EN24, first deterioration by ≥ 10 points; data cut-off: 22 September 2023)

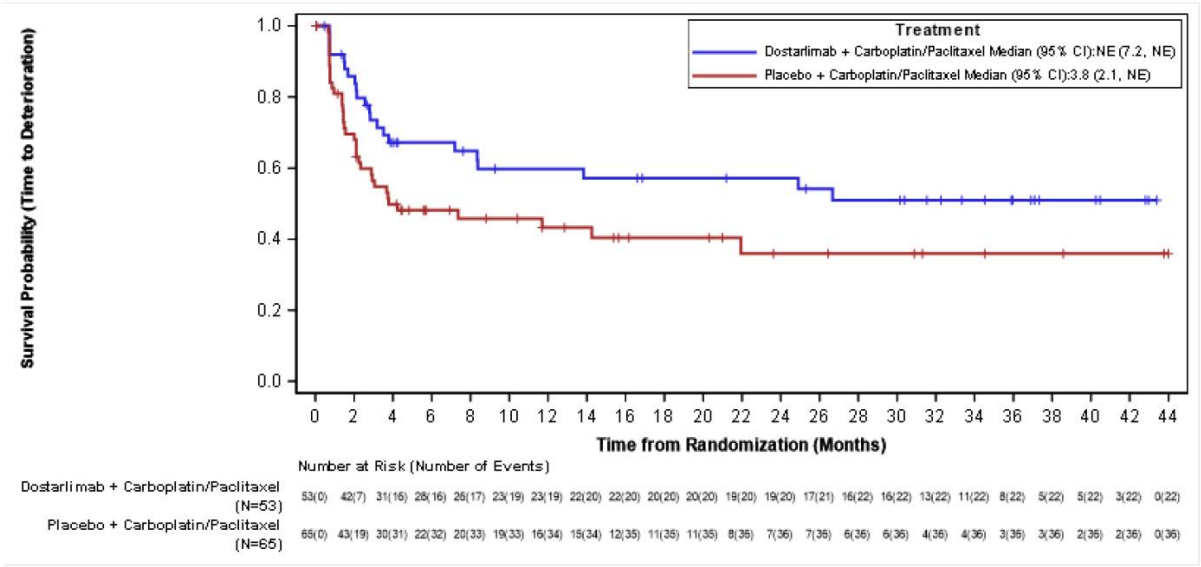

Figure 11: Kaplan-Meier curves on the outcome “urological symptoms” (EORTC QLQ EN24, first deterioration by ≥ 10 points; data cut-off: 22 September 2023)

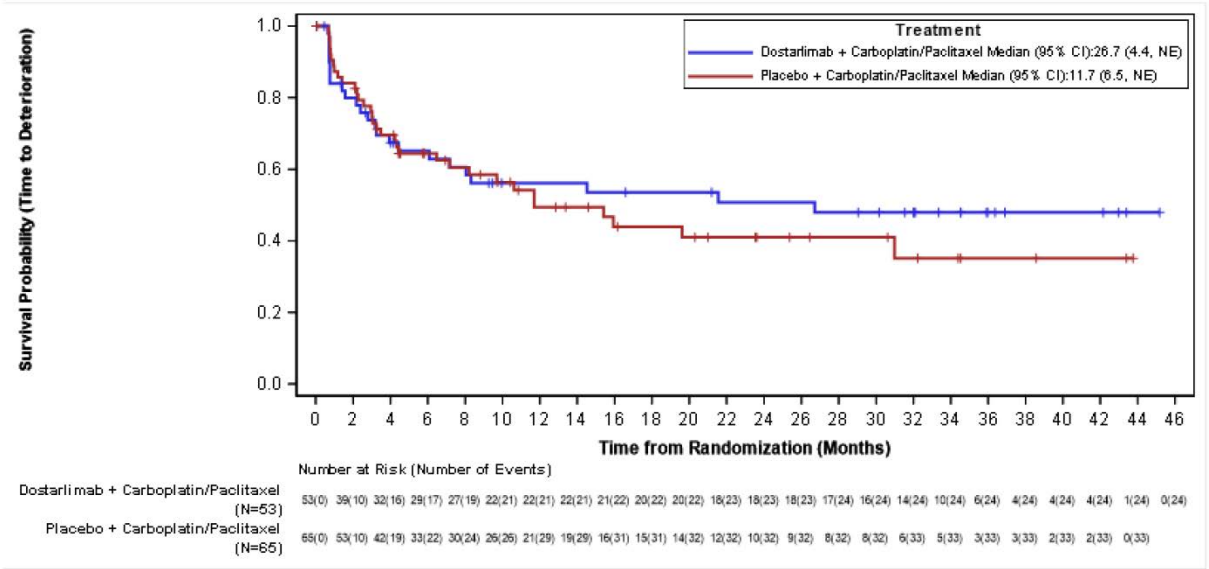

Figure 12: Kaplan-Meier curves on the outcome “gastrointestinal symptoms” (EORTC QLQ EN24, first deterioration by ≥ 10 points; data cut-off: 22 September 2023)

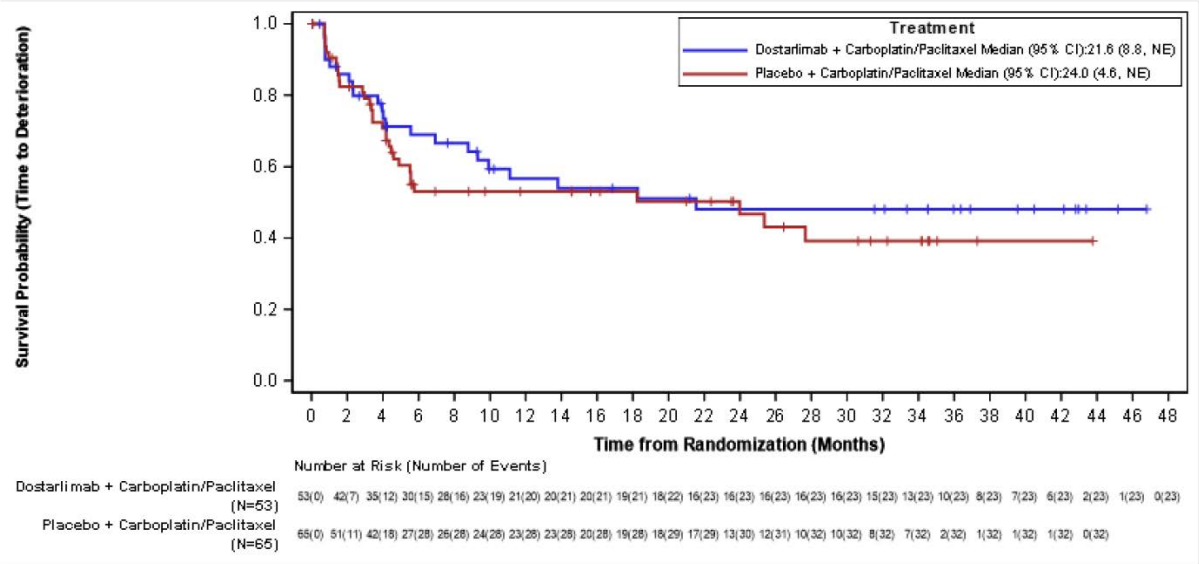

Figure 13: Kaplan-Meier curves on the outcome “pain in back and pelvis” (EORTC QLQ EN24, first deterioration by ≥ 10 points; data cut-off: 22 September 2023)

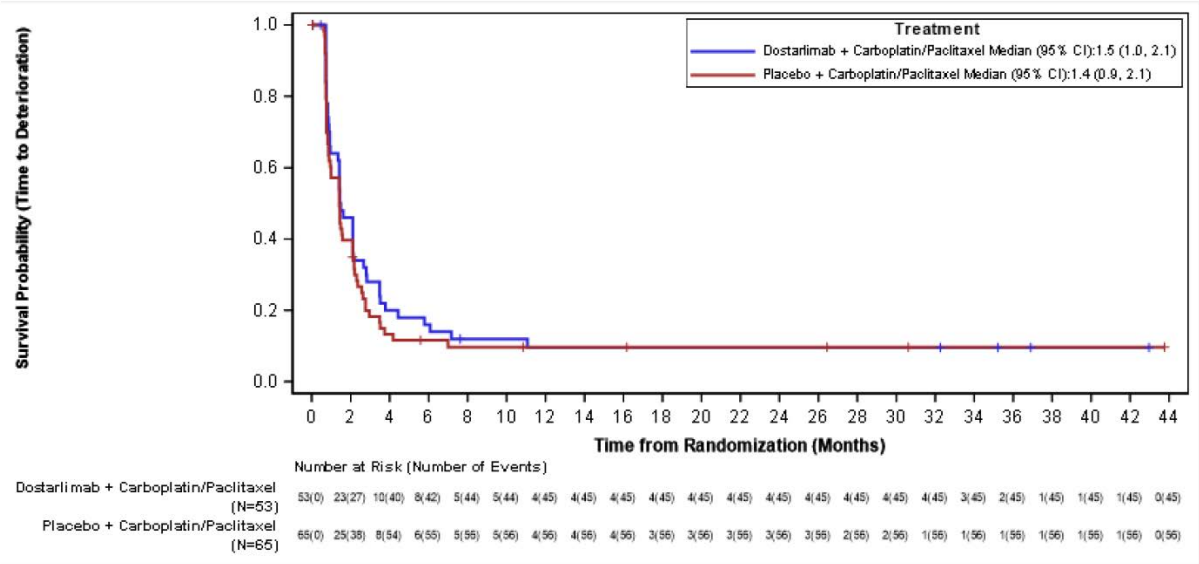

Figure 14: Kaplan-Meier curves on the outcome “tingling/numbness” (EORTC QLQ EN24, first deterioration by ≥ 10 points; data cut-off: 22 September 2023)

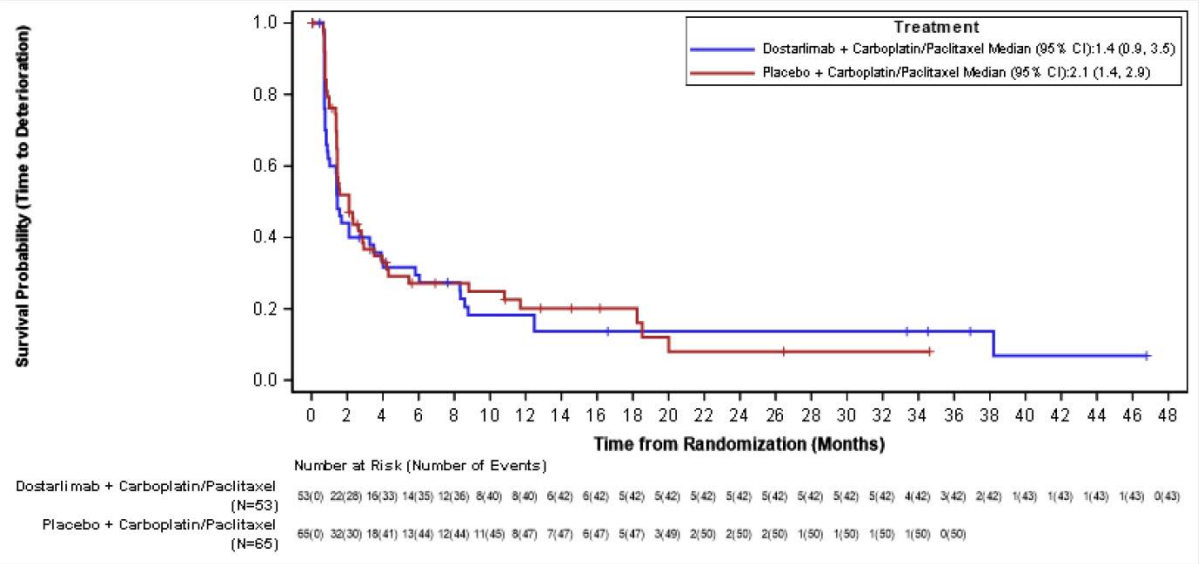

Figure 15: Kaplan-Meier curves on the outcome “muscular pain” (EORTC QLQ EN24, first deterioration by ≥ 10 points; data cut-off: 22 September 2023)

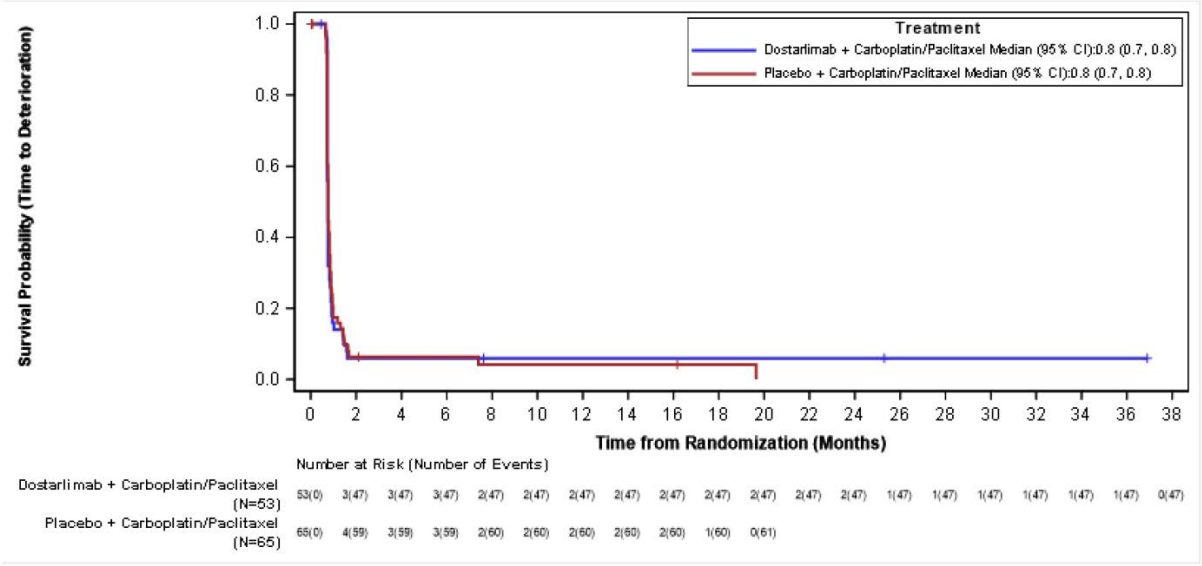

Figure 16: Kaplan-Meier curves on the outcome “hair loss” (EORTC QLQ EN24, first deterioration by ≥ 10 points; data cut-off: 22 September 2023)

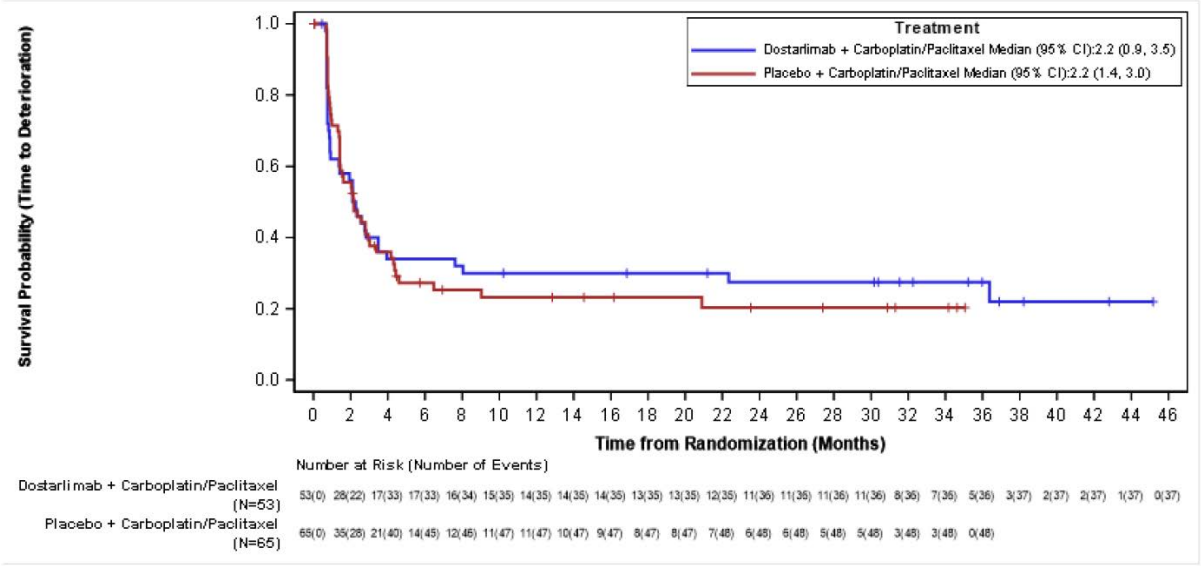

Figure 17: Kaplan-Meier curves on the outcome “taste change” (EORTC QLQ EN24, first deterioration by ≥ 10 points; data cut-off: 22 September 2023)

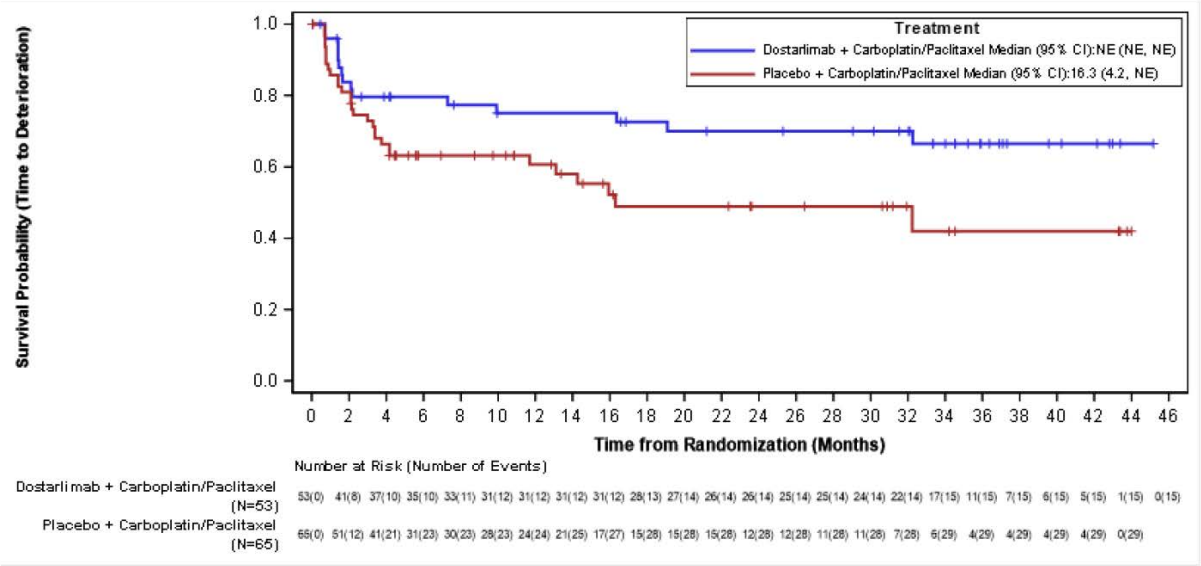

Figure 18: Kaplan-Meier curves on the outcome “health status” (EORTC VAS EN24, first deterioration by ≥ 15 points; data cut-off: 22 September 2023)

A.3 Health-related quality of life

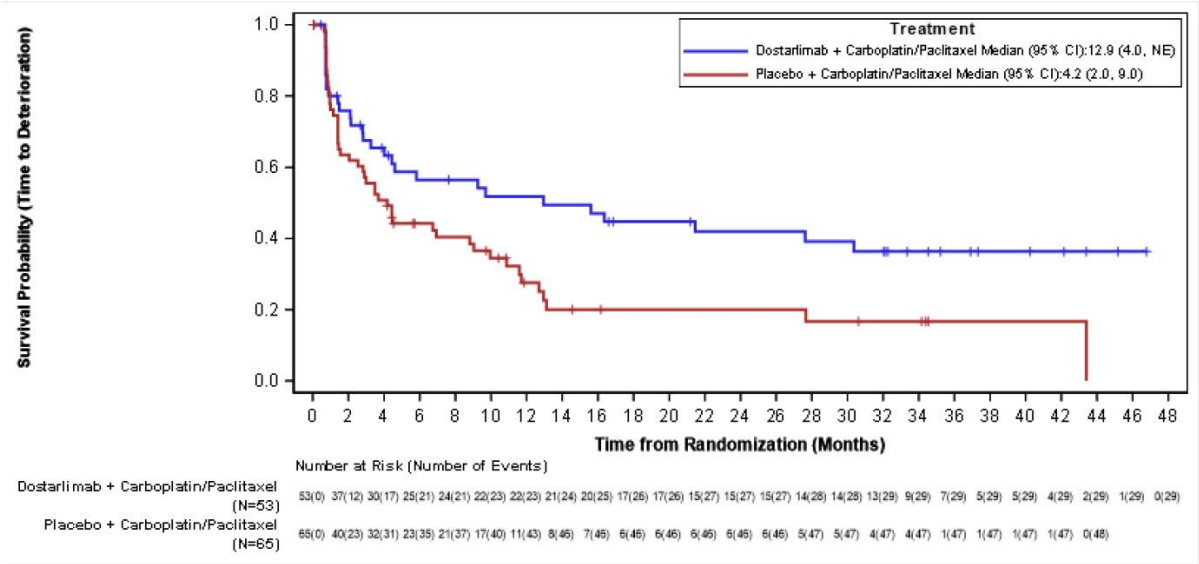

Figure 19: Kaplan-Meier curves on the outcome "global health status" (EORTC QLQ C30, first deterioration by ≥ 10 points; data cut-off: 22 September 2023)

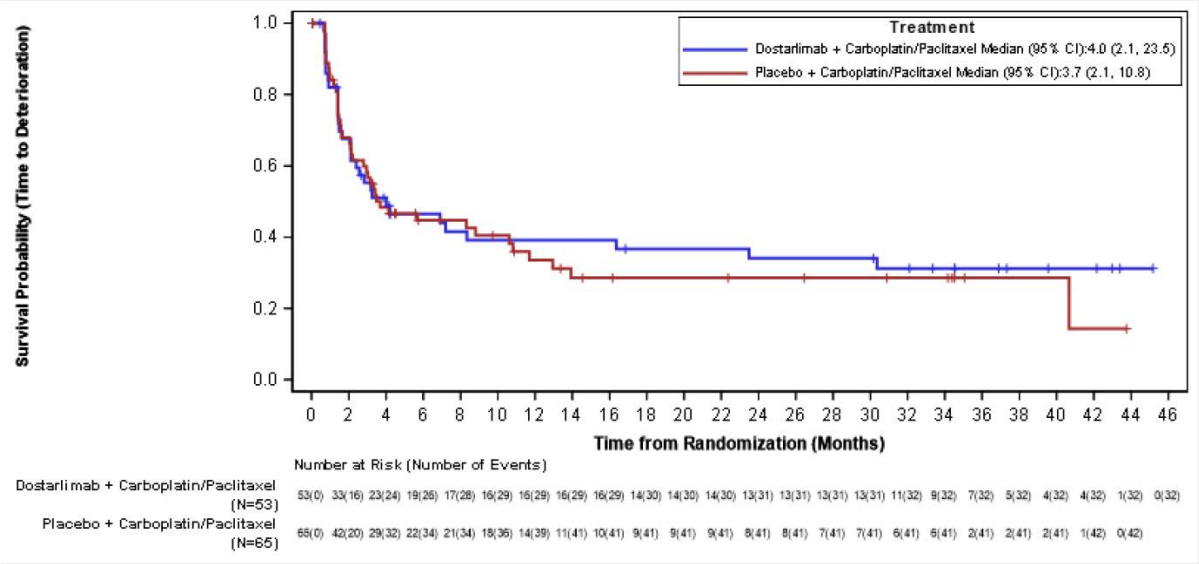

Figure 20: Kaplan-Meier curves on the outcome "physical functioning" (EORTC QLQ C30, first deterioration by ≥ 10 points; data cut-off: 22 September 2023)

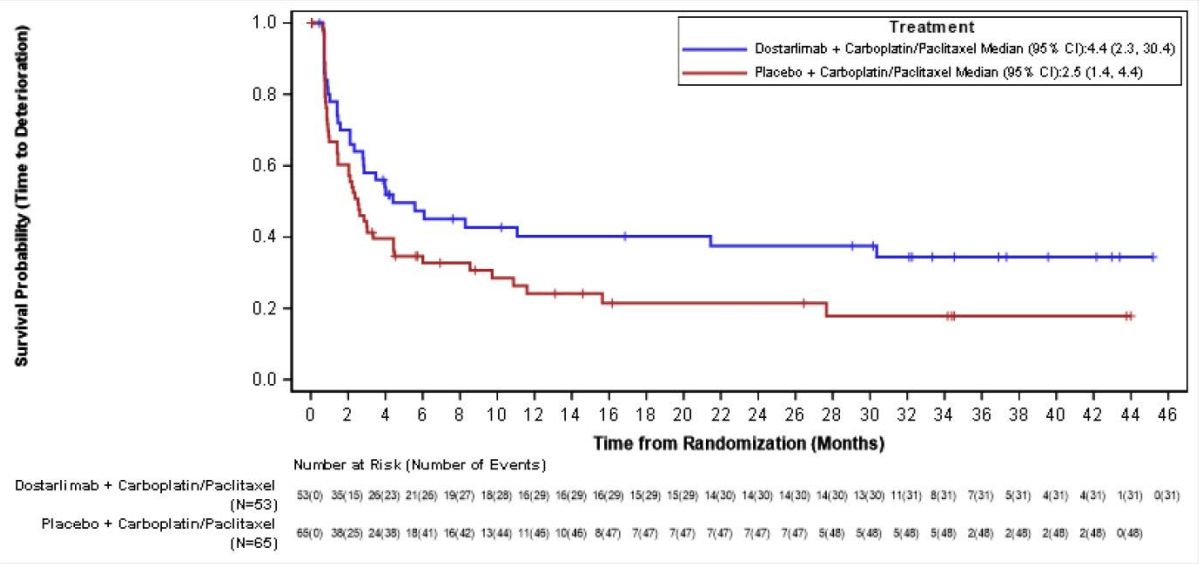

Figure 21: Kaplan-Meier curves on the outcome “role functioning” (EORTC QLQ C30, first deterioration by ≥ 10 points; data cut-off: 22 September 2023)

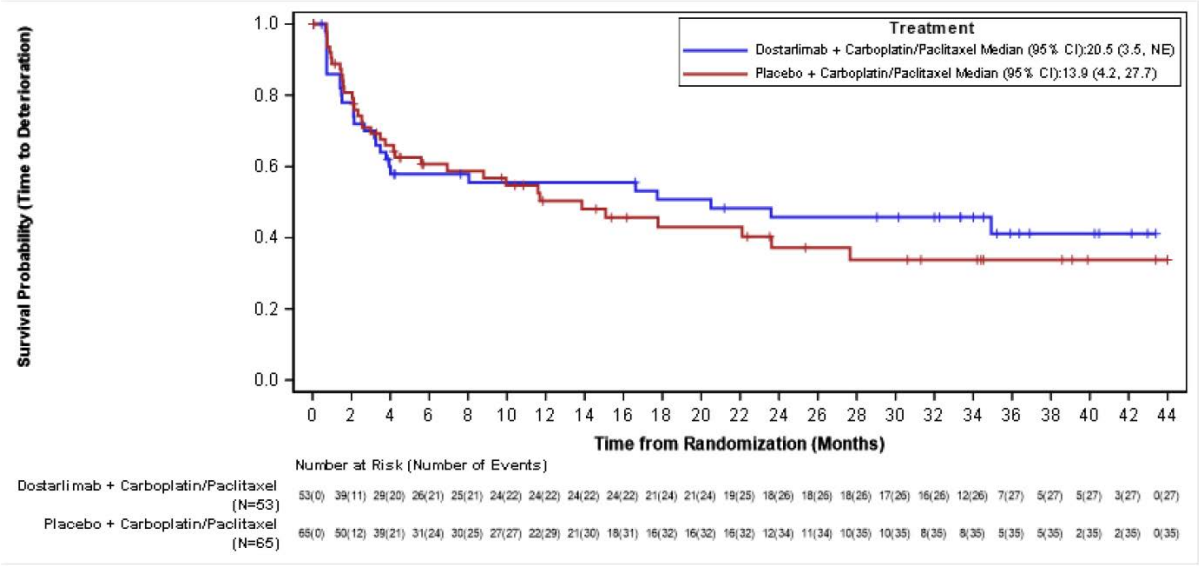

Figure 22: Kaplan-Meier curves on the outcome “emotional functioning” (EORTC QLQ C30, first deterioration by ≥ 10 points; data cut-off: 22 September 2023)

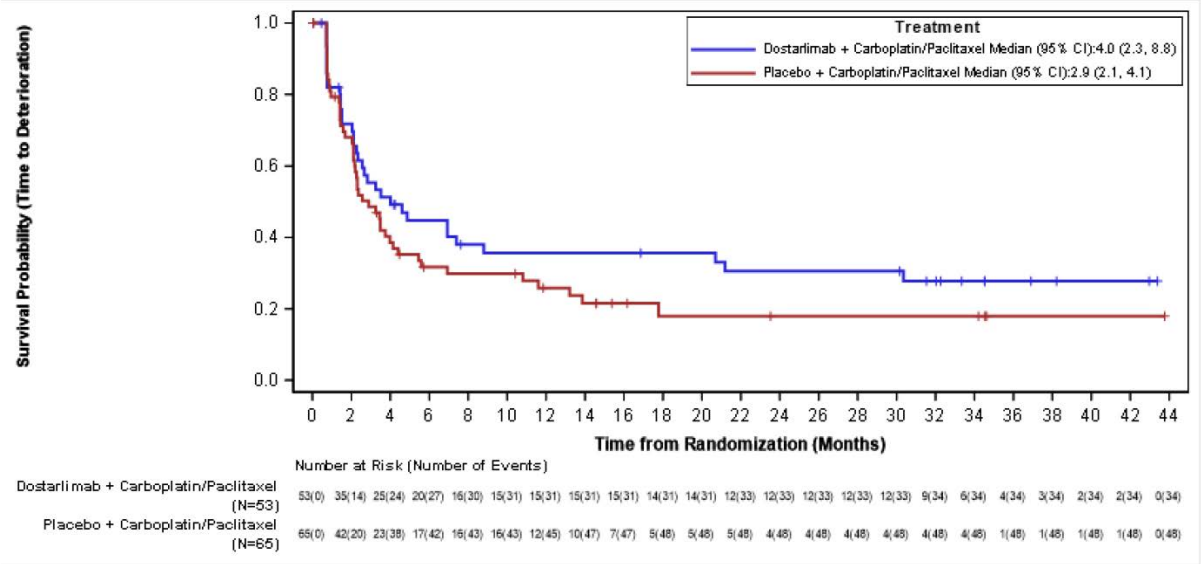

Figure 23: Kaplan-Meier curves on the outcome “cognitive functioning” (EORTC QLQ C30, first deterioration by ≥ 10 points; data cut-off: 22 September 2023)

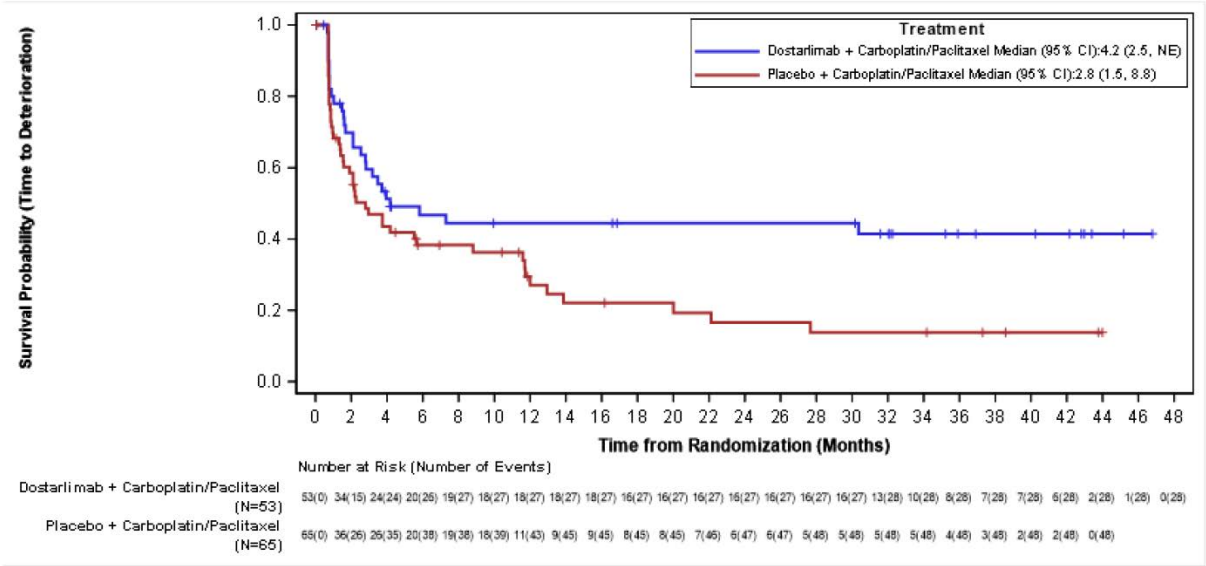

Figure 24: Kaplan-Meier curves on the outcome “social functioning” (EORTC QLQ C30, first deterioration by ≥ 10 points; data cut-off: 22 September 2023)

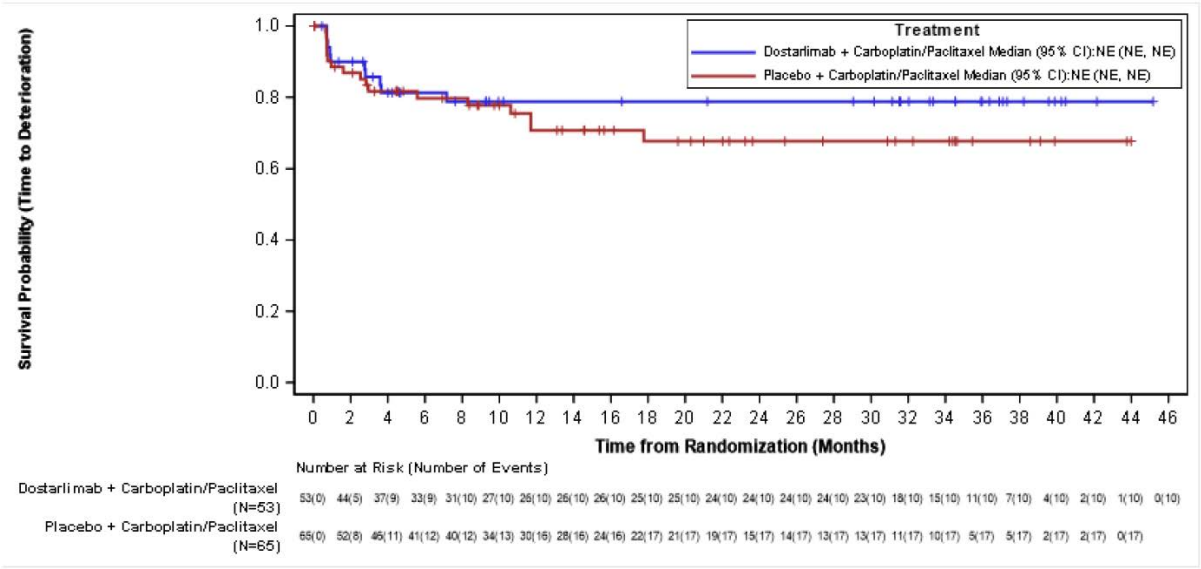

Figure 25: Kaplan-Meier curves on the outcome “sexual interest” (EORTC QLQ EN24, first deterioration by ≥ 10 points; data cut-off: 22 September 2023)

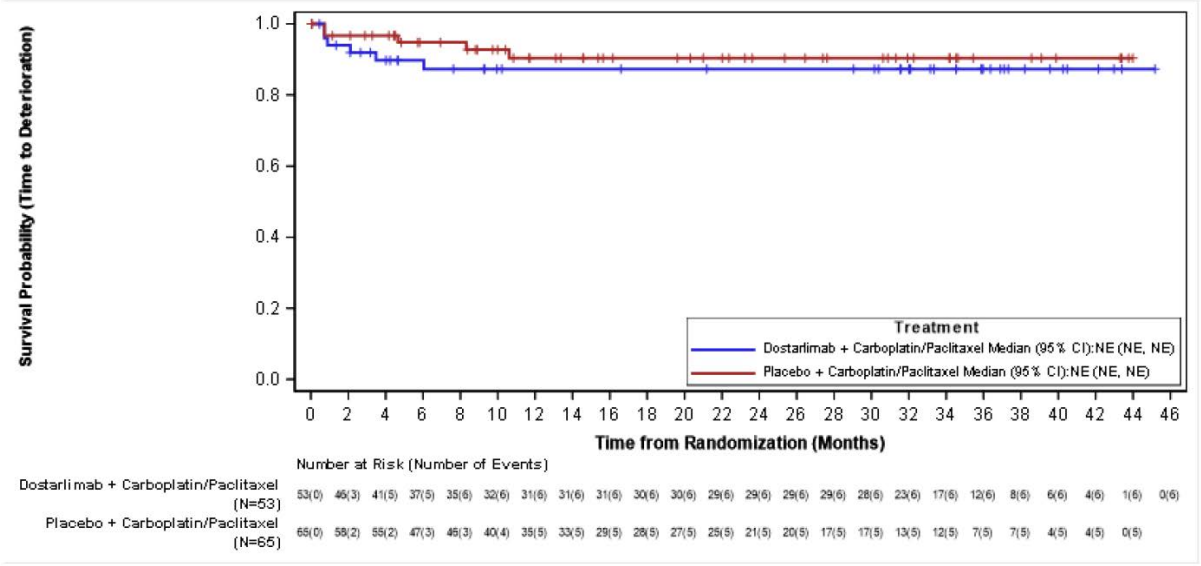

Figure 26: Kaplan-Meier curves on the outcome “sexual activity” (EORTC QLQ EN24, first deterioration by ≥ 10 points; data cut-off: 22 September 2023)

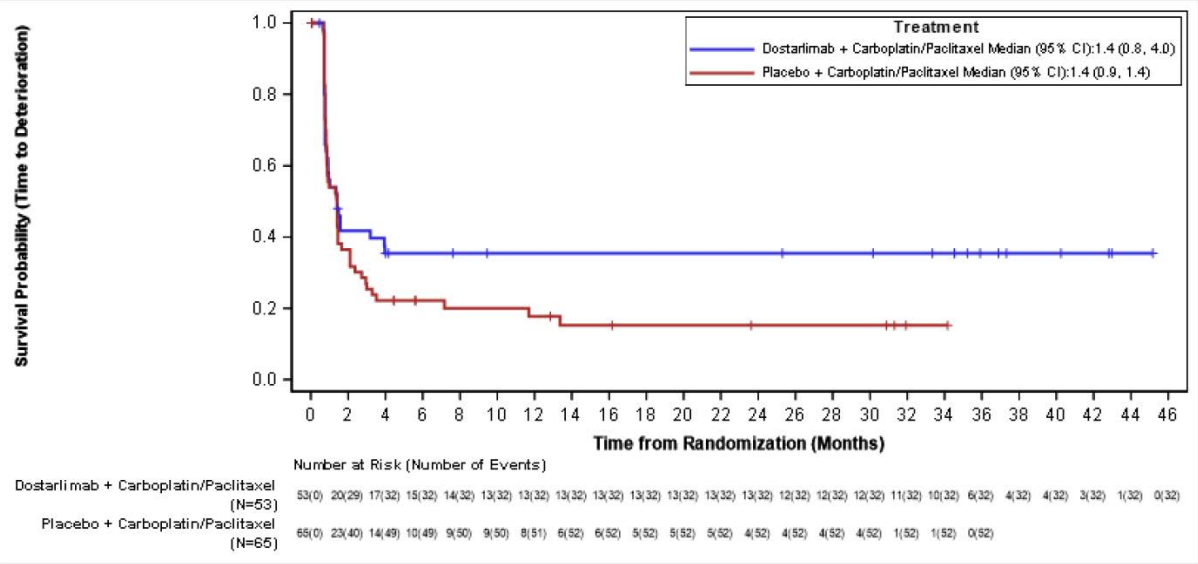

Figure 27: Kaplan-Meier curves on the outcome “poor body image” (EORTC QLQ EN24, first deterioration by ≥ 10 points; data cut-off: 22 September 2023)

A.4 Side effects

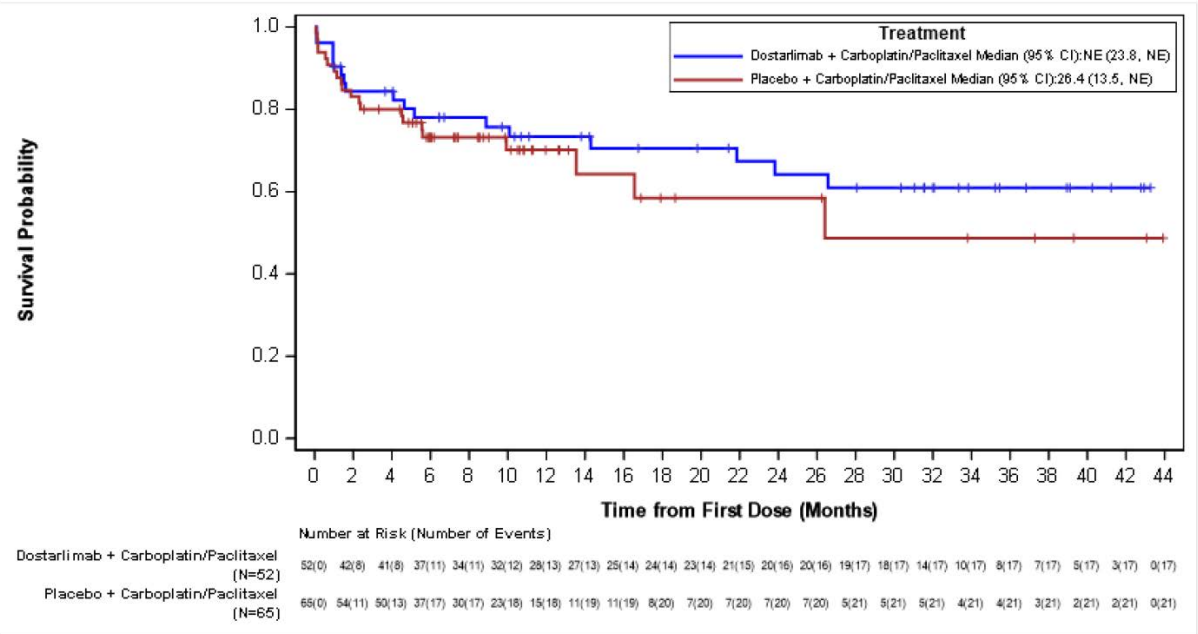

Figure 28: Kaplan-Meier curves on the outcome “SAEs” (data cut-off: 22 September 2023)

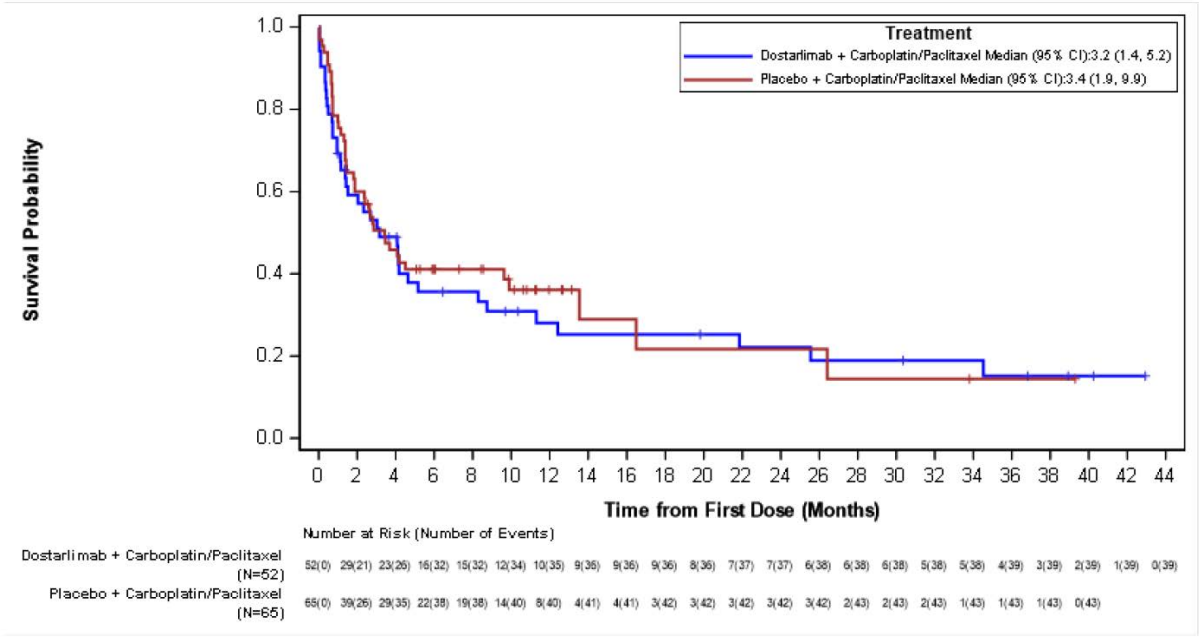

Figure 29: Kaplan-Meier curves on the outcome “severe AEs” (CTCAE grade ≥ 3; data cut-off: 22 September 2023)

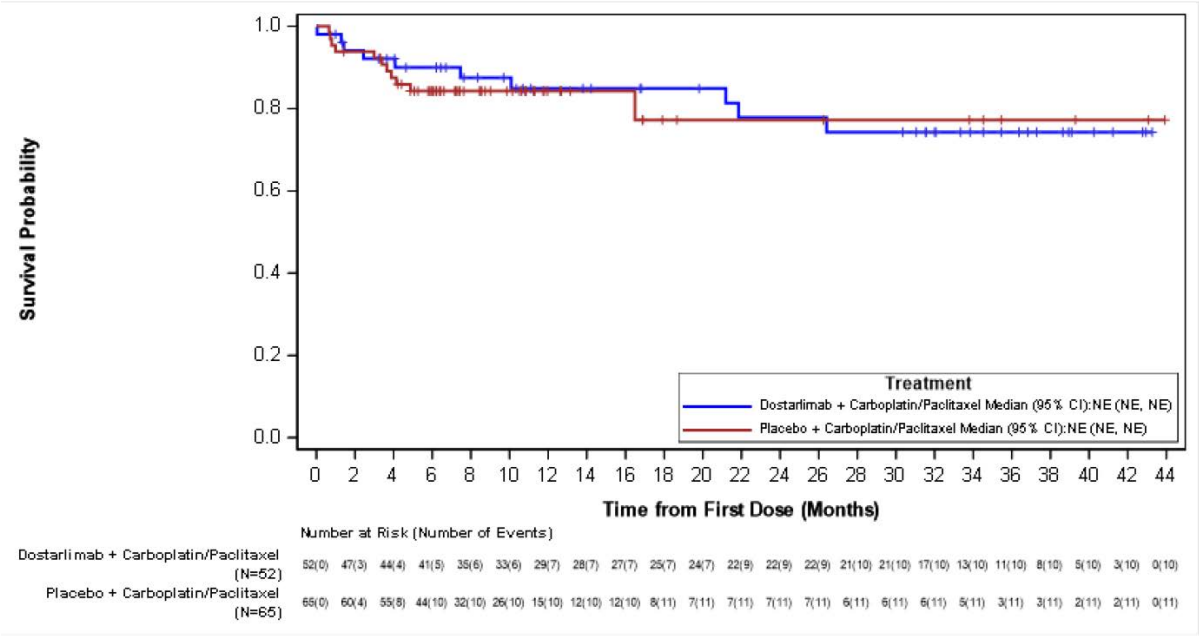

Figure 30: Kaplan-Meier curves on the outcome "discontinuation due to AEs” (data cut-off: 22 September 2023)

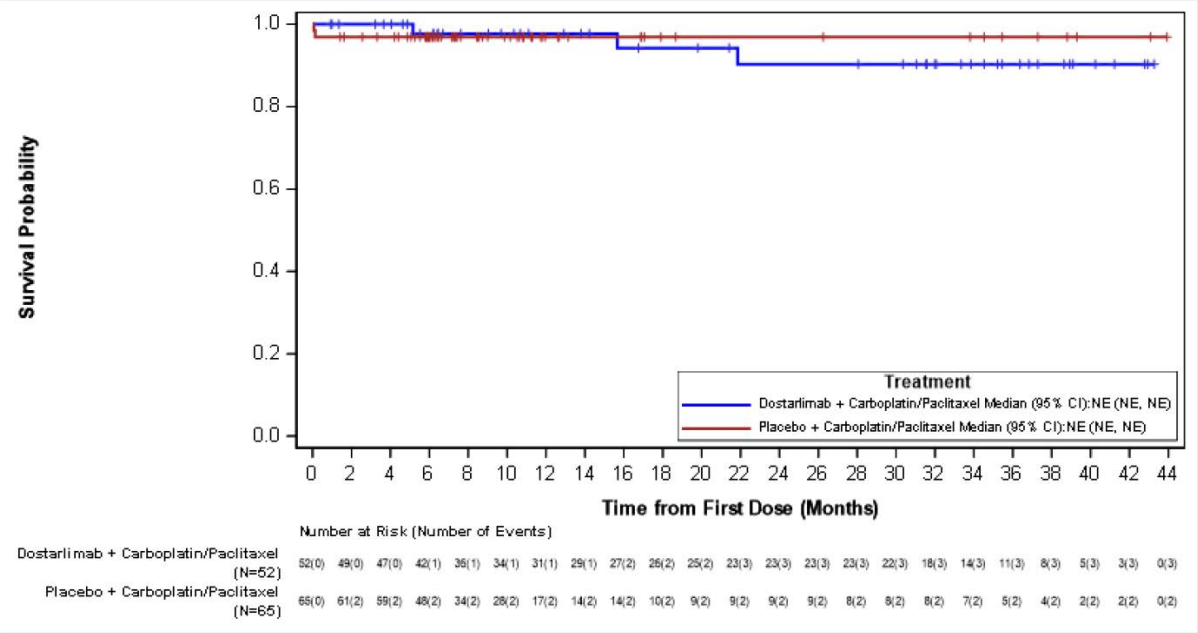

Figure 31: Kaplan-Meier curves on the outcome “immune-mediated SAEs” (data cut-off: 22 September 2023)

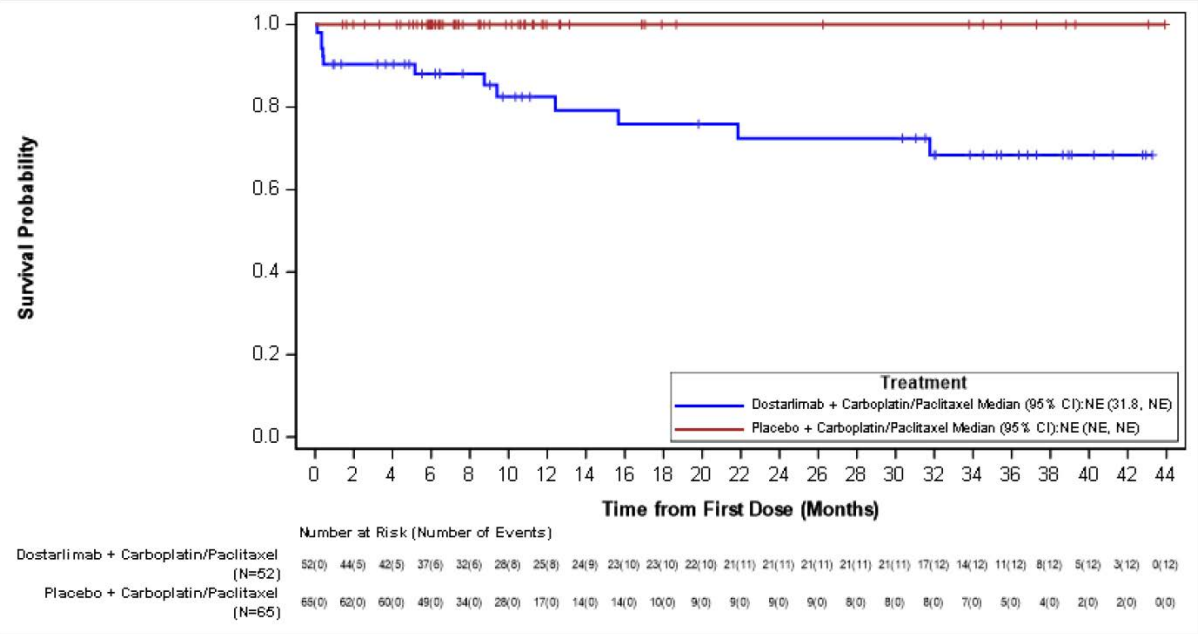

Figure 32: Kaplan-Meier curve on the outcome “immune-mediated severe AEs” (CTCAE grade ≥ 3) (data cut-off: 22 September 2023)

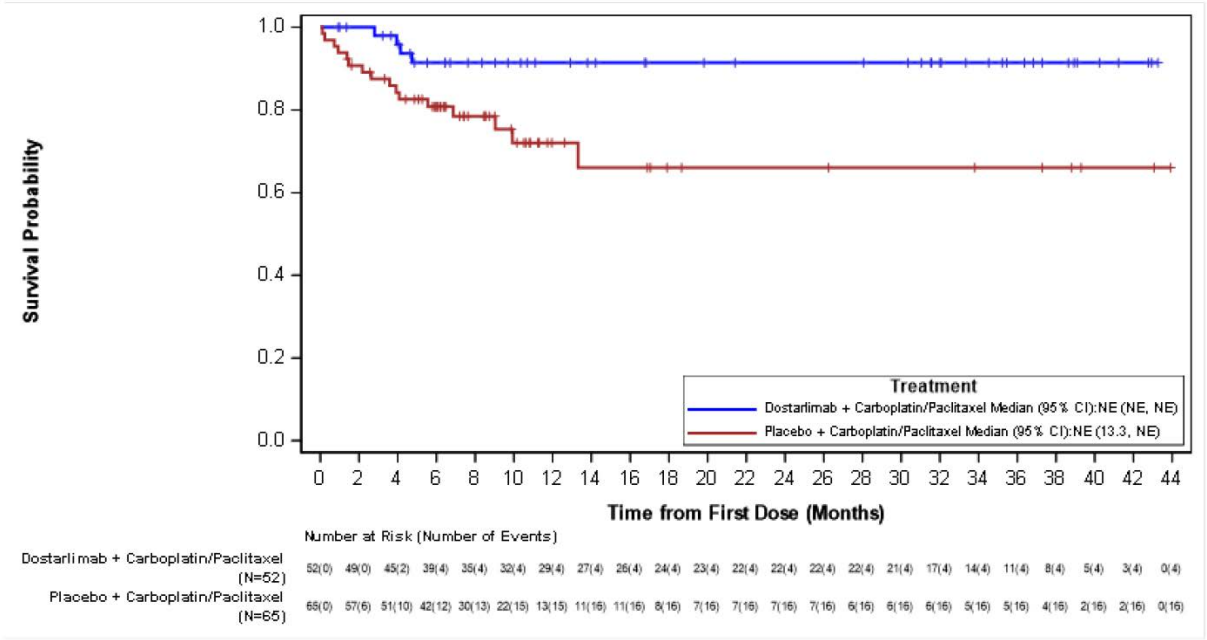

Figure 33: Kaplan-Meier curves on the outcome “urinary tract infections” (PT, AEs; data cut-off: 22 September 2023)

A.5 Kaplan-Meier curves by subgroups

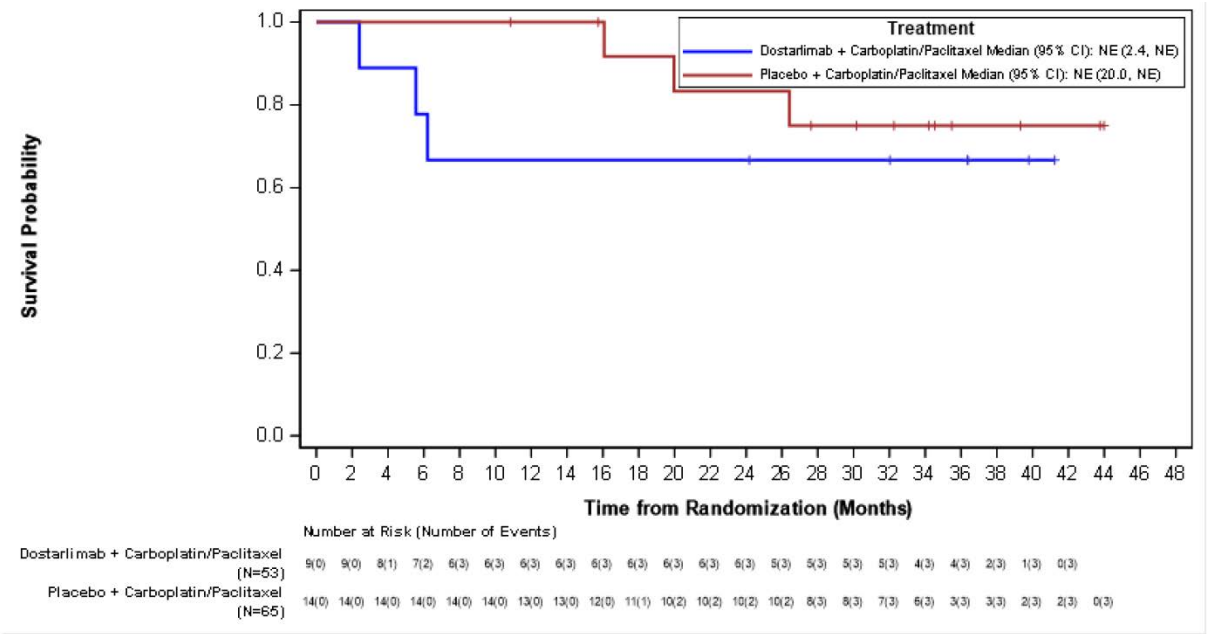

Figure 34: Kaplan-Meier curves on the outcome “overall survival” for patients with primary advanced FIGO stage III disease at baseline (data cut-off: 22 September 2023)

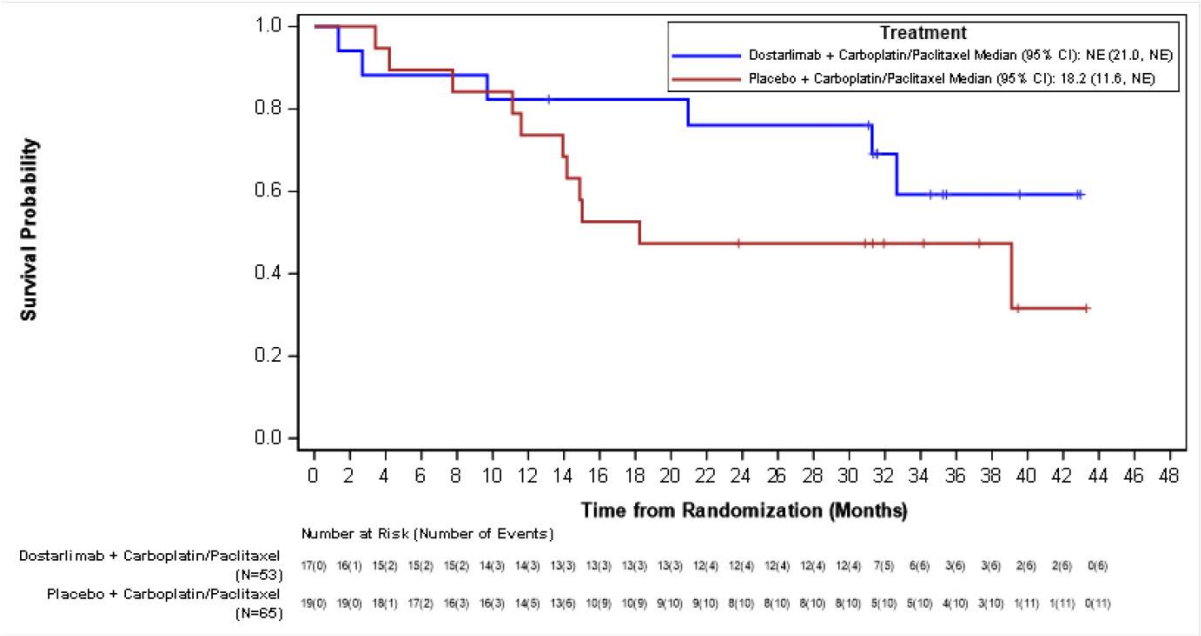

Figure 35: Kaplan-Meier curves on the outcome “overall survival” for patients with primary advanced FIGO stage IV disease at baseline (data cut-off: 22 September 2023)

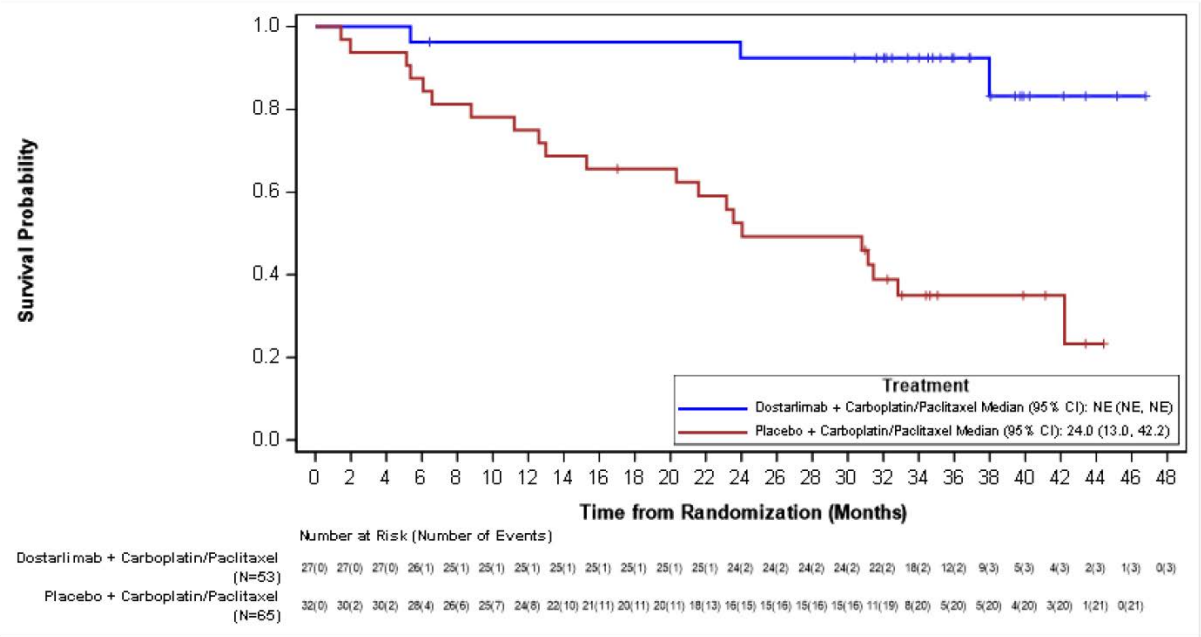

Figure 36: Kaplan-Meier curves on the outcome “overall survival” for patients with recurrent disease at baseline (data cut-off: 22 September 2023)

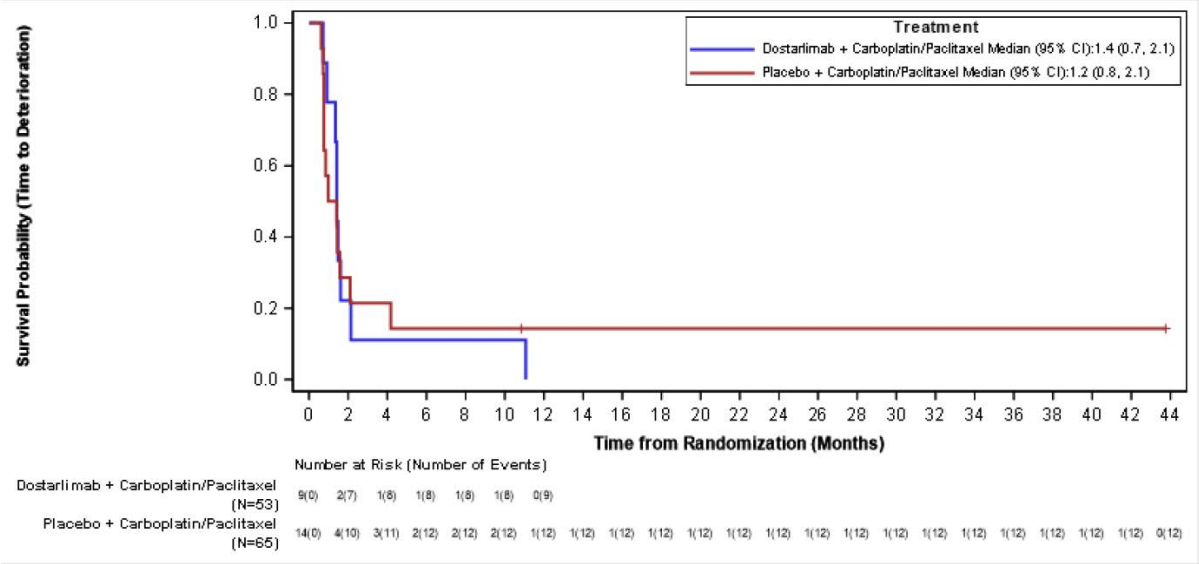

Figure 37: Kaplan-Meier curves on the outcome “tingling/numbness” (EORTC QLQ-EN24, first deterioration by ≥ 10 points) for patients with primary advanced FIGO stage III disease at baseline (data cut-off: 22 September 2023)

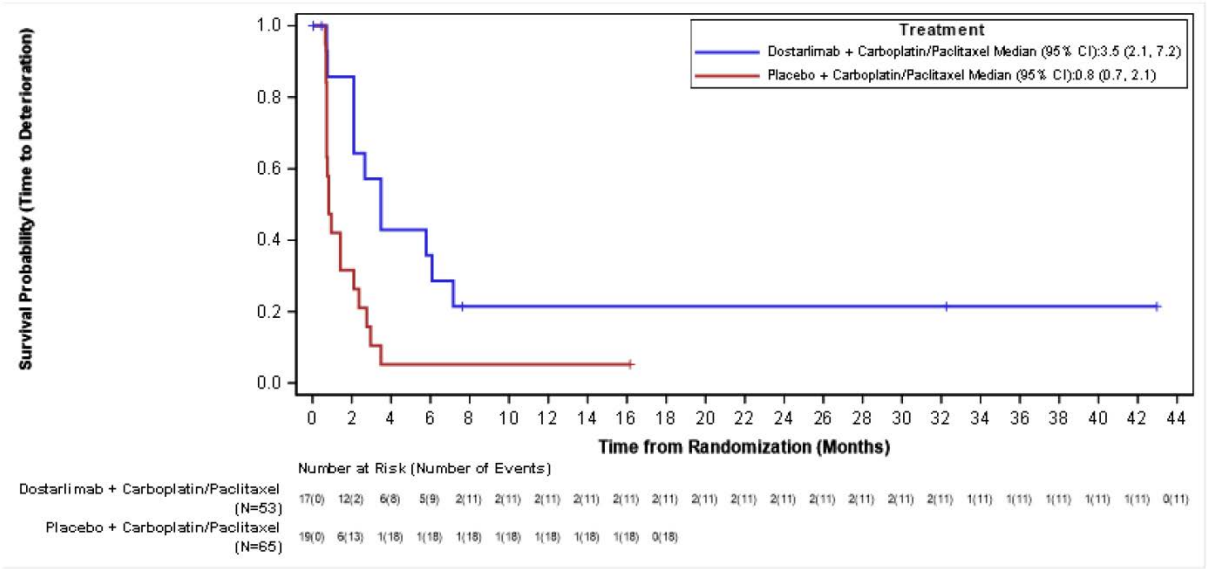

Figure 38: Kaplan-Meier curves on the outcome “tingling/numbness” (EORTC QLQ-EN24, first deterioration by ≥ 10 points) for patients with primary advanced FIGO stage IV disease at baseline (data cut-off: 22 September 2023)

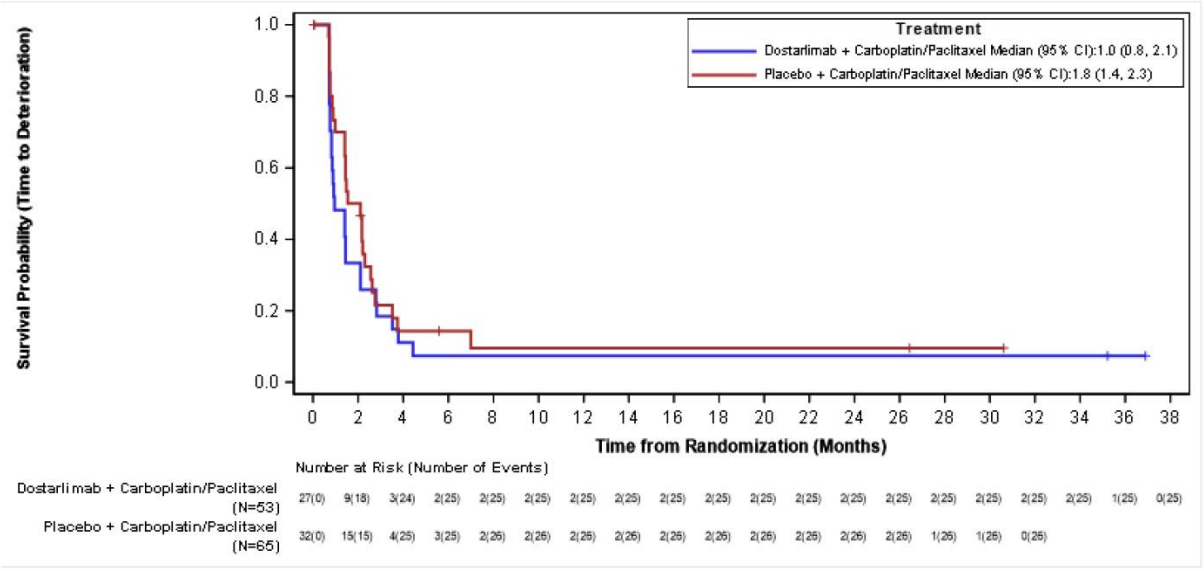

Figure 39: Kaplan-Meier curves on the outcome “tingling/numbness” (EORTC QLQ-EN24, first deterioration by ≥ 10 points) for patients with recurrent disease at baseline (data cut-off: 22 September 2023)

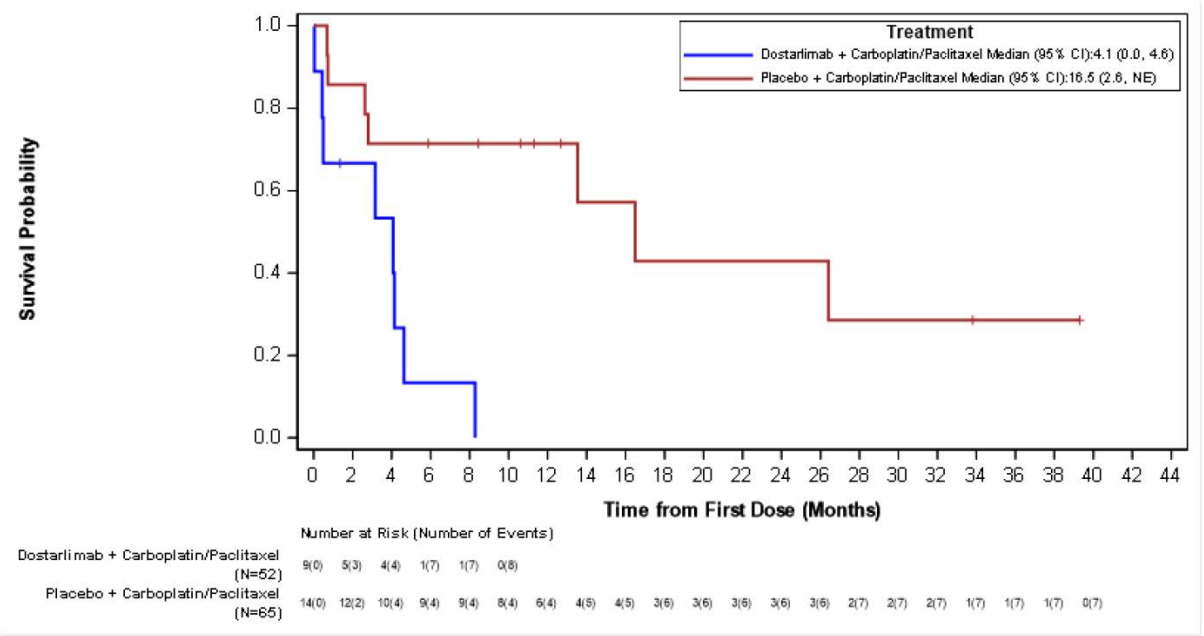

Figure 40: Kaplan-Meier curves on the outcome “severe AEs” (CTCAE grade ≥ 3) for patients with primary advanced FIGO stage III disease at baseline (data cut-off: 22 September 2023)

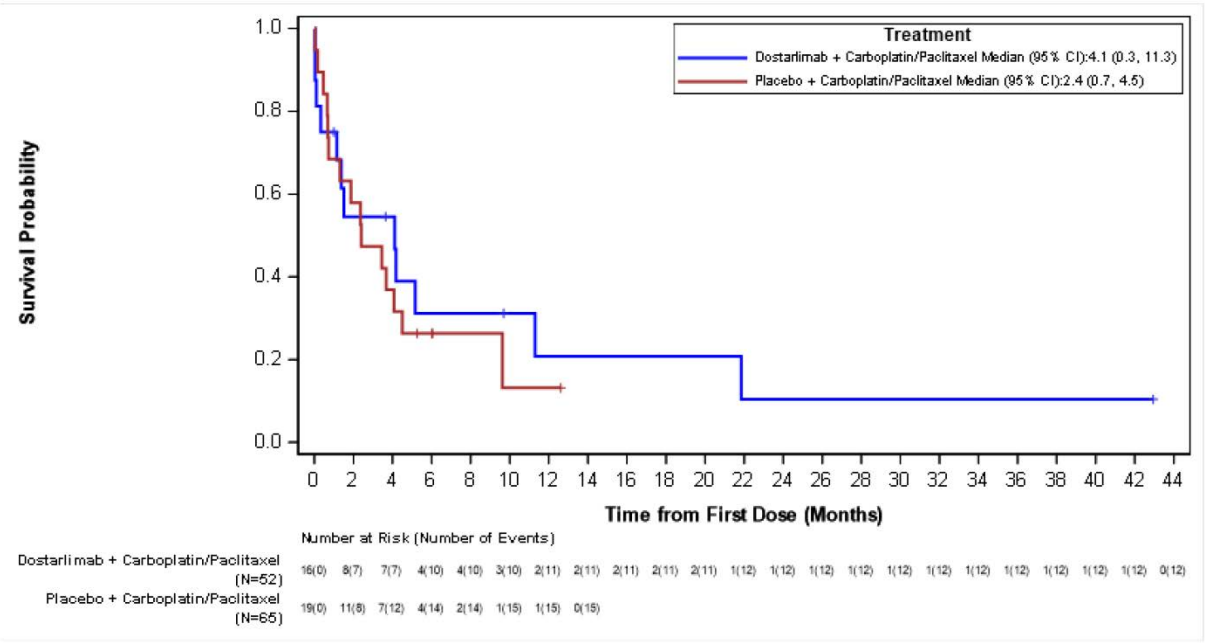

Figure 41: Kaplan-Meier curves on the outcome “severe AEs” (CTCAE grade ≥ 3) for patients with primary advanced FIGO stage IV disease at baseline (data cut-off: 22 September 2023)

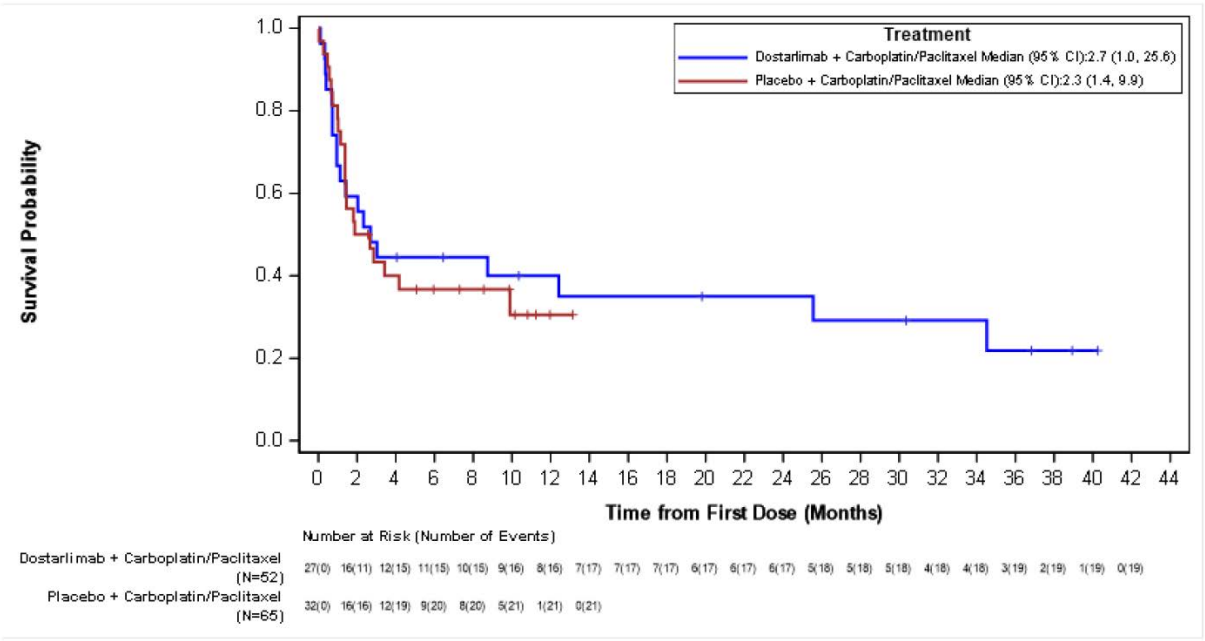

Figure 42: Kaplan-Meier curves on the outcome “severe AEs” (CTCAE grade ≥ 3) for patients with recurrent disease at baseline (data cut-off: 22 September 2023)

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): events which 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 patients in one study arm
- additionally, for all events irrespective of severity: events which 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, a complete presentation of all results (SOCs/PTs) that resulted in discontinuation is provided.

Table 9: Common AEsa – RCT, direct comparison: dostarlimab + carboplatin + paclitaxel vs. placebo + carboplatin + paclitaxel (multipage table)

Study	**Patients with event n (%)**	
SOC[b] PT[b]	**Dostarlimab + carboplatin + paclitaxel N = 52**	**Placebo + carboplatin + paclitaxel N = 65**
RUBY		
Overall AE rate	52 (100)	65 (100)
Gastrointestinal disorders	46 (88.5)	55 (84.6)
Nausea	30 (57.7)	30 (46.2)
Diarrhoea	21 (40.4)	21 (32.3)
Constipation	15 (28.8)	23 (35.4)
Vomiting	14 (26.9)	14 (21.5)
Abdominal pain	8 (15.4)	14 (21.5)
Abdominal pain upper	5 (9.6)	5 (7.7)
Dyspepsia	5 (9.6)	5 (7.7)
Skin and subcutaneous tissue disorders	46 (88.5)	44 (67.7)
Alopecia	30 (57.7)	39 (60.0)
Rash	15 (28.8)	11 (16.9)
Itching	9 (17.3)	6 (9.2)
Dry skin	5 (9.6)	5 (7.7)
Maculo-papular rash	8 (15.4)	2 (3.1)

Table 9: Common AEsa – RCT, direct comparison: dostarlimab + carboplatin + paclitaxel vs. placebo + carboplatin + paclitaxel (multipage table)

Study	**Patients with event n (%)**	
SOC[b] **PT[b]**	**Dostarlimab + carboplatin + paclitaxel** **N = 52**	**Placebo + carboplatin + paclitaxel** **N = 65**
General disorders and administration site conditions	37 (71.2)	49 (75.4)
Fatigue	26 (50.0)	37 (56.9)
Asthenia	7 (13.5)	12 (18.5)
Peripheral oedema	6 (11.5)	10 (15.4)
Fever	7 (13.5)	1 (1.5)
Nervous system disorders	41 (78.8)	51 (78.5)
Peripheral neuropathy	22 (42.3)	29 (44.6)
Peripheral sensory neuropathy	12 (23.1)	12 (18.5)
Headache	8 (15.4)	12 (18.5)
Dizziness	4 (7.7)	12 (18.5)
Taste change	3 (5.8)	7 (10.8)
Musculoskeletal and connective tissue disorders	36 (69.2)	44 (67.7)
Arthralgia	24 (46.2)	26 (40.0)
Myalgia	13 (25.0)	17 (26.2)
Pain in extremity	7 (13.5)	11 (16.9)
Back pain	6 (11.5)	9 (13.8)
Bone pain	6 (11.5)	6 (9.2)
Blood and lymphatic system disorders	25 (48.1)	44 (67.7)
Anaemia	18 (34.6)	34 (52.3)
Neutropenia	11 (21.2)	11 (16.9)
Thrombocytopenia	5 (9.6)	11 (16.9)
Metabolism and nutrition disorders	29 (55.8)	41 (63.1)
Hypomagnesaemia	11 (21.2)	19 (29.2)
Decreased appetite	9 (17.3)	13 (20.0)
Hypokalaemia	8 (15.4)	11 (16.9)
Hyperglycaemia	4 (7.7)	8 (12.3)
Respiratory, thoracic, and mediastinal disorders	22 (42.3)	31 (47.7)
Dyspnoea	7 (13.5)	19 (29.2)
Cough	8 (15.4)	5 (7.7)
Pulmonary embolism	4 (7.7)	7 (10.8)

Table 9: Common AEsa – RCT, direct comparison: dostarlimab + carboplatin + paclitaxel vs. placebo + carboplatin + paclitaxel (multipage table)

Study	**Patients with event n (%)**	
SOC[b] **PT[b]**	**Dostarlimab + carboplatin + paclitaxel** **N = 52**	**Placebo + carboplatin + paclitaxel** **N = 65**
Investigations	30 (57.7)	33 (50.8)
Neutrophil count decreased	5 (9.6)	15 (23.1)
White blood cell count decreased	4 (7.7)	13 (20.0)
Platelet count decreased	6 (11.5)	7 (10.8)
Alanine aminotransferase increased	6 (11.5)	4 (6.2)
Blood creatinine increased	5 (9.6)	5 (7.7)
Infections and infestations	30 (57.7)	31 (47.7)
Urinary tract infection	4 (7.7)	16 (24.6)
COVID-19	7 (13.5)	6 (9.2)
Injury, poisoning and procedural complications	17 (32.7)	18 (27.7)
Infusion related reaction	8 (15.4)	10 (15.4)
Vascular disorders	15 (28.8)	23 (35.4)
Hypertension	11 (21.2)	7 (10.8)
Psychiatric disorders	17 (32.7)	16 (24.6)
Insomnia	9 (17.3)	8 (12.3)
Depression	5 (9.6)	6 (9.2)
Endocrine disorders	12 (23.1)	5 (7.7)
Hypothyroidism	11 (21.2)	4 (6.2)
Eye disorders	9 (17.3)	13 (20.0)
Blurred vision	5 (9.6)	5 (7.7)
Reproductive system and breast disorders	11 (21.2)	13 (20.0)
Vaginal bleeding	2 (3.8)	7 (10.8)
Renal and urinary disorders	11 (21.2)	14 (21.5)
Cardiac disorders	6 (11.5)	6 (9.2)
Immune system disorders	8 (15.4)	5 (7.7)

a. Events that occurred in ≥ 10% of patients in at least one study arm.
b. MedDRA version 25.0; SOC and PT notation taken from Module 4.

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 10: Common SAEsa – RCT, direct comparison: dostarlimab + carboplatin + paclitaxel vs. placebo + carboplatin + paclitaxel

Study	**Patients with event n (%)**	
SOC[b] PT[b]	**Dostarlimab + carboplatin + paclitaxel N = 52**	**Placebo + carboplatin + paclitaxel N = 65**
RUBY		
Overall SAE rate	17 (32.7)	21 (32.3)
Infections and infestations	5 (9.6)	7 (10.8)
Urinary tract infection	0 (0)	4 (6.2)
Gastrointestinal disorders	4 (7.7)	5 (7.7)
Blood and lymphatic system disorders	3 (5.8)	4 (6.2)
Nervous system disorders	3 (5.8)	3 (4.6)
General disorders and administration site conditions	1 (1.9)	4 (6.2)
Musculoskeletal and connective tissue disorders	3 (5.8)	1 (1.5)
Metabolism and nutrition disorders	3 (5.8)	0 (0)

a. Events that occurred in ≥ 5% of patients in at least one study arm.
b. MedDRA version 25.0; SOC and PT notation taken from Module 4.

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 11: Common severe AEsa – RCT, direct comparison: dostarlimab + carboplatin + paclitaxel vs. placebo + carboplatin + paclitaxel

Study	Patients with event n (%)	
SOC[b] PT[b]	Dostarlimab + carboplatin + paclitaxel N = 52	Placebo + carboplatin + paclitaxel N = 65
RUBY		
Overall rate of severe AEs (CTCAE grade ≥ 3)	39 (75.0)	43 (66.2)
Blood and lymphatic system disorders	17 (32.7)	25 (38.5)
Anaemia	8 (15.4)	14 (21.5)
Neutropenia	9 (17.3)	8 (12.3)
Thrombocytopenia	1 (1.9)	4 (6.2)
Investigations	12 (23.1)	19 (29.2)
Neutrophil count decreased	4 (7.7)	12 (18.5)
White blood cell count decreased	2 (3.8)	8 (12.3)
Lymphocyte count decreased	3 (5.8)	6 (9.2)
Lipase increased	3 (5.8)	0 (0)
Vascular disorders	6 (11.5)	5 (7.7)
Hypertension	5 (9.6)	4 (6.2)
Metabolism and nutrition disorders	6 (11.5)	10 (15.4)
Hypokalaemia	3 (5.8)	4 (6.2)
Hyponatraemia	3 (5.8)	2 (3.1)
General disorders and administration site conditions	3 (5.8)	7 (10.8)
Asthenia	2 (3.8)	4 (6.2)
Gastrointestinal disorders	7 (13.5)	9 (13.8)
Abdominal pain	1 (1.9)	4 (6.2)
Respiratory, thoracic, and mediastinal disorders	3 (5.8)	4 (6.2)
Pulmonary embolism	2 (3.8)	4 (6.2)
Infections and infestations	5 (9.6)	9 (13.8)
Urinary tract infection	0 (0)	4 (6.2)
Skin and subcutaneous tissue disorders	5 (9.6)	1 (1.5)
Rash	3 (5.8)	0 (0)
Nervous system disorders	4 (7.7)	6 (9.2)
Musculoskeletal and connective tissue disorders	3 (5.8)	1 (1.5)

a. Events that occurred in ≥ 5% of patients in at least one study arm.
b. MedDRA version 25.0; SOC and PT notation taken from Module 4.

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 12: Discontinuation due to AEsa – RCT, direct comparison: dostarlimab + carboplatin + paclitaxel vs. placebo + carboplatin + paclitaxel (multipage table)

Study	**Patients with event n (%)**	
SOC[b] PT[b]	**Dostarlimab + carboplatin + paclitaxel N = 52**	**Placebo + carboplatin + paclitaxel N = 65**
RUBY		
Total rate of discontinuations due to AEs	10 (19.2)	11 (16.9)
Nervous system disorders	0 (0)	5 (7.7)
Peripheral neuropathy	0 (0)	4 (6.2)
Cerebrovascular accident	0 (0)	1 (1.5)
Blood and lymphatic system disorders	1 (1.9)	2 (3.1)
Thrombocytopenia	0 (0)	2 (3.1)
Myelosuppression	1 (1.9)	0 (0)
General disorders and administration site conditions	1 (1.9)	0 (0)
Fatigue	1 (1.9)	0 (0)
Injury, poisoning and procedural complications	1 (1.9)	1 (1.5)
Infusion related reaction	1 (1.9)	1 (1.5)
Investigations	0 (0)	1 (1.5)
Platelet count decreased	0 (0)	1 (1.5)
Eye disorders	1 (1.9)	0 (0)
Keratitis	1 (1.9)	0 (0)
Gastrointestinal disorders	1 (1.9)	0 (0)
Pancreatitis	1 (1.9)	0 (0)
Immune system disorders	1 (1.9)	0 (0)
Drug hypersensitivity	1 (1.9)	0 (0)
Infections and infestations	0 (0)	1 (1.5)
Peritonitis	0 (0)	1 (1.5)
Musculoskeletal and connective tissue disorders	2 (3.8)	0 (0)
Arthralgia	1 (1.9)	0 (0)
Muscular weakness	1 (1.9)	0 (0)
Polmyalgia rheumatica	1 (1.9)	0 (0)
Neoplasms benign, malignant, and unspecified (incl. cysts and polyps)	0 (0)	1 (1.5)
Myelodysplastic syndrome	0 (0)	1 (1.5)
Renal and urinary disorders	1 (1.9)	0 (0)
Chronic kidney disease	1 (1.9)	0 (0)
Reproductive system and breast disorders	0 (0)	1 (1.5)
Vaginal bleeding	0 (0)	1 (1.5)

Table 12: Discontinuation due to AEsa – RCT, direct comparison: dostarlimab + carboplatin + paclitaxel vs. placebo + carboplatin + paclitaxel (multipage table)

Study	**Patients with event n (%)**	
SOC[b] PT[b]	**Dostarlimab + carboplatin + paclitaxel N = 52**	**Placebo + carboplatin + paclitaxel N = 65**
Skin and subcutaneous tissue disorders	1 (1.9)	0 (0)
Rash maculo-papular	1 (1.9)	0 (0)

a. MedDRA version 25.0; SOC and PT notation taken from Module 4.

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 C Supplementary presentation of results on categories of serious adverse event (SAEs), immune-mediated adverse events (AEs), immune-mediated SAEs and immune-mediated severe AEs (Common Terminology Criteria for Adverse Events [CTCAE] grade ≥ 3)

Table 13: Categories of immune-mediated AEsa – RCT, direct comparison: dostarlimab + carboplatin + paclitaxel vs. placebo + carboplatin + paclitaxel

Study	Patients with event n (%)	
Category[b] Subcategory[b]	Dostarlimab + carboplatin + paclitaxel N = 52	Placebo + carboplatin + paclitaxel N = 65
RUBY		
Overall rate of immune-mediated AEs	39 (75.0)	26 (40.0)
Hypersensitivity	13 (25.0)	12 (18.5)
Non-hypersensitivity	36 (69.2)	18 (27.7)
Musculoskeletal disorders	10 (19.2)	10 (15.4)
Endocrinopathy	12 (23.1)	3 (4.6)
Adverse skin reactions	14 (26.9)	2 (3.1)
Liver disorders	6 (11.5)	1 (1.5)
Gastrointestinal area	1 (1.9)	4 (6.2)
Pancreatitis	2 (3.8)	0 (0)

a. In each case, the operationalization of a specific, predefined PT list of AEs with a CTCAE-grade ≥ 2 from the outcome of further AEs submitted by the company is used.
b. Category notation taken unmodified from Module 4.

AE: adverse event; CTCAE: Common Terminology Criteria for Adverse Events; n: number of patients with at least one event; N: number of analysed patients; PT: Preferred Term; RCT: randomized controlled trial

Table 14: Categories of immune-mediated SAEsa – RCT, direct comparison: dostarlimab + carboplatin + paclitaxel vs. placebo + carboplatin + paclitaxel

Study	**Patients with event n (%)**	
Category[b] **Subcategory[b]**	**Dostarlimab + carboplatin + paclitaxel** **N = 52**	**Placebo + carboplatin + paclitaxel** **N = 65**
RUBY		
Overall rate of immune-mediated SAEs	3 (5.8)	2 (3.1)
Hypersensitivity	0 (0)	0 (0)
Non-hypersensitivity	3 (5.8)	2 (3.1)
Endocrinopathy	1 (1.9)	0 (0)
Gastrointestinal area	0 (0)	2 (3.1)
Pancreatitis	1 (1.9)	0 (0)
Musculoskeletal disorders	1 (1.9)	0 (0)

a. In each case, the operationalization of a specific, predefined PT list of AEs with a CTCAE-grade ≥ 2 from the outcome of further AEs submitted by the company is used.
b. Category notation taken unmodified from Module 4.

AE: adverse event; CTCAE: Common Terminology Criteria for Adverse Events; 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

Table 15: Categories of immune-mediated severe AEsa – RCT, direct comparison: dostarlimab + carboplatin + paclitaxel vs. placebo + carboplatin + paclitaxel

Study	**Patients with event n (%)**	
Category[b] **Subcategory[b]**	**Dostarlimab + carboplatin + paclitaxel** **N = 52**	**Placebo + carboplatin + paclitaxel** **N = 65**
RUBY		
Overall rate of immune-mediated severe AEs (CTCAE grade ≥ 3)	12 (23.1)	0 (0)
Hypersensitivity	0 (0)	0 (0)
Non-hypersensitivity	12 (23.1)	0 (0)
Adverse skin reactions	5 (9.6)	0 (0)
Endocrinopathy	2 (3.8)	0 (0)
Gastrointestinal area	1 (1.9)	0 (0)
Liver disorders	1 (1.9)	0 (0)
Musculoskeletal disorders	2 (3.8)	0 (0)
Pancreatitis	1 (1.9)	0 (0)

a. In each case, the operationalization of a specific, predefined PT list of AEs with a CTCAE-grade ≥ 2 from the outcome of further AEs submitted by the company is used.
b. Category notation taken unmodified from Module 4.

AE: adverse event; CTCAE: Common Terminology Criteria for Adverse Events; n: number of patients with at least one event; N: number of analysed patients; PT: Preferred Term; RCT: randomized controlled trial

Appendix D Supplementary presentation of results on morbidity and health-related quality of life

Table 16: Results (morbidity, health-related quality of life, continuous) – RCT, direct comparison: dostarlimab + carboplatin + paclitaxel vs. placebo + carboplatin + paclitaxel (multipage table)

Study Outcome category Outcome	Dostarlimab + carboplatin + paclitaxel			Placebo + carboplatin + paclitaxel			Dostarlimab + carboplatin + paclitaxel vs. placebo + carboplatin + paclitaxel
	N[a]	Values at baseline mean (SD)	Mean change in the course of the study LS mean[b] (SE)	N[a]	Values at baseline mean (SD)	Mean change in the course of the study LS mean[b] (SE)	MD [95% CI]; p-value[b]
RUBY							
Morbidity							
Symptoms (EORTC QLQ-C30)[c]							
Fatigue	49	33.9 (25.2)	-1.4 (2.4)	61	35.1 (27.7)	7.3 (2.3)	-8.8 [-15.3; -2.3]; 0.009 SMD: −0.50 [−0.88; -0.12]
Nausea and vomiting	49	7.9 (18.1)	-0.4 (1.3)	61	9.0 (20.3)	3.0 (1.3)	-3.4 [-7.2; 0.3]; 0.072
Pain	49	32.3 (27.3)	-4.1 (2.7)	62	32.3 (32.1)	5.7 (2.6)	-9.7 [-17.1; -2.4]; 0.010 SMD: −0.49 [−0.87; -0.11]
Dyspnoea	49	10.4 (19.4)	0.7 (2.3)	61	15.8 (24.6)	9.4 (2.2)	-8.8 [-15.2; -2.4]; 0.007 SMD: −0.52 [−0.90; -0.13]
Insomnia	48	30.6 (28.5)	-6.6 (2.9)	62	37.4 (35.4)	2.1 (2.7)	-8.6 [-16.4; -0.8]; 0.030 SMD: −0.41 [−0.79; -0.03]
Appetite loss	49	19.6 (30.0)	-4.8 (2.5)	60	20.9 (29.7)	2.0 (2.4)	-6.8 [-13.6; -0.0]; 0.049 SMD: −0.37 [−0.76; 0.01]
Constipation	48	17.2 (22.5)	-6.6 (2.1)	61	19.0 (26.6)	-0.8 (2.1)	-5.8 [-11.6; -0.0]; 0.048 SMD: −0.38 [−0.76; 0.01]

Table 16: Results (morbidity, health-related quality of life, continuous) – RCT, direct comparison: dostarlimab + carboplatin + paclitaxel vs. placebo + carboplatin + paclitaxel (multipage table)

Study Outcome category Outcome	Dostarlimab + carboplatin + paclitaxel			Placebo + carboplatin + paclitaxel			Dostarlimab + carboplatin + paclitaxel vs. placebo + carboplatin + paclitaxel
	N[a]	Values at baseline mean (SD)	Mean change in the course of the study LS mean[b] (SE)	N[a]	Values at baseline mean (SD)	Mean change in the course of the study LS mean[b] (SE)	MD [95% CI]; p-value[b]
Diarrhoea	49	8.4 (16.0)	2.6 (1.9)	62	10.9 (21.4)	3.6 (1.9)	-1.0 [-6.3; 4.3]; 0.701
Symptoms (EORTC QLQ-EN24)[c]							
Lymphoedema	49	15.4 (25.7)	2.5 (2.4)	62	16.5 (25.6)	12.2 (2.3)	-9.7 [-16.3; -3.1]; 0.004 SMD: −0.55 [−0.93; -0.17]
Urological symptoms	49	22.2 (20.0)	-5.7 (1.9)	61	20.3 (20.2)	-0.5 (1.7)	-5.1 [-10.0; -0.3]; 0.039 SMD: −0.38 [−0.76; 0.0]
Gastrointestinal symptoms	49	14.5 (12.0)	-2.8 (1.7)	61	14.8 (16.1)	0.6 (1.6)	-3.3 [-7.9; 1.2]; 0.151
Sexual/vaginal problems	No usable data available[d]						
Pain in back and pelvis	49	35.3 (31.0)	-10.0 (2.9)	59	36.5 (32.7)	-2.0 (2.9)	-7.9 [-16.0; 0.2]; 0.055
Tingling/numbness	49	9.1 (18.9)	29.1 (3.6)	59	14.2 (25.4)	34.2 (3.5)	-5.1 [-15.1; 4.9]; 0.316
Muscular pain	49	15.0 (23.4)	17.5 (3.0)	61	21.1 (28.3)	17.5 (2.9)	0.0 [-8.2; 8.2]; 0.998
Hair loss	49	2.6 (14.7)	23.3 (2.7)	61	4.7 (15.6)	23.5 (2.7)	-0.2 [-7.7; 7.3]; 0.957
Taste change	49	8.5 (21.0)	4.5 (2.4)	61	7.9 (19.6)	9.3 (2.3)	-4.8 [-11.4; 1.8]; 0.151
Health status (EQ-5D VAS)[e]	48	74.4 (22.6)	5.1 (2.1)	61	78.0 (20.0)	-2.6 (1.9)	7.7 [2.1; 13.4]; 0.008 SMD: 0.51 [0.13; 0.90]

Table 16: Results (morbidity, health-related quality of life, continuous) – RCT, direct comparison: dostarlimab + carboplatin + paclitaxel vs. placebo + carboplatin + paclitaxel (multipage table)

Study Outcome category Outcome	Dostarlimab + carboplatin + paclitaxel			Placebo + carboplatin + paclitaxel			Dostarlimab + carboplatin + paclitaxel vs. placebo + carboplatin + paclitaxel
	N[a]	Values at baseline mean (SD)	Mean change in the course of the study LS mean[b] (SE)	N[a]	Values at baseline mean (SD)	Mean change in the course of the study LS mean[b] (SE)	MD [95% CI]; p-value[b]
Health-related quality of life							
EORTC QLQ-C30[e]							
Global health status	49	66.7 (25.9)	3.7 (2.1)	62	67.3 (23.9)	-6.9 (1.9)	10.6 [5.0; 16.2]; < 0.001 SMD: 0.71 [0.32; 1.09]
Physical functioning	48	74.9 (21.8)	0.3 (2.2)	62	69.1 (23.3)	-6.5 (2.1)	6.8 [0.9; 12.8]; 0.025 SMD: 0.42 [0.04; 0.81]
Role functioning	49	66.6 (32.2)	4.5 (3.0)	62	72.9 (32.2)	-5.9 (2.9)	10.5 [2.2; 18.8]; 0.014 SMD: 0.47 [0.09; 0.85]
Emotional functioning	49	75.9 (18.1)	4.9 (2.3)	61	75.9 (20.1)	0.3 (2.2)	4.6 [-1.7; 11.0]; 0.149
Cognitive functioning	49	86.3 (20.7)	-3.3 (2.3)	62	88.0 (19.3)	-7.9 (2.2)	4.6 [-1.7; 10.8]; 0.148
Social functioning	49	74.5 (30.3)	3.3 (2.8)	61	80.2 (27.2)	-5.9 (2.6)	9.2 [1.6; 16.9]; 0.018 SMD: 0.46 [0.08; 0.84]
EORTC QLQ-EN24							
Sexual interest[e]	49	7.1 (15.3)	2.1 (1.8)	59	11.4 (18.1)	-1.3 (1.7)	3.4 [-1.4; 8.2]; 0.163
Sexual activity[e]	49	4.5 (11.5)	2.9 (1.4)	56	2.8 (9.3)	2.0 (1.4)	0.9 [-2.9; 4.8]; 0.629
Sexual enjoyment	No usable data available[f]						
Body image problems[c,g]	49	11.4 (17.8)	6.3 (2.9)	62	12.8 (22.4)	5.6 (2.7)	0.7 [-7.2; 8.6]; 0.863

Table 16: Results (morbidity, health-related quality of life, continuous) – RCT, direct comparison: dostarlimab + carboplatin + paclitaxel vs. placebo + carboplatin + paclitaxel (multipage table)

Study Outcome category Outcome	Dostarlimab + carboplatin + paclitaxel			Placebo + carboplatin + paclitaxel			Dostarlimab + carboplatin + paclitaxel vs. placebo + carboplatin + paclitaxel
	N[a]	Values at baseline mean (SD)	Mean change in the course of the study LS mean[b] (SE)	N[a]	Values at baseline mean (SD)	Mean change in the course of the study LS mean[b] (SE)	MD [95% CI]; p-value[b]

a. Number of patients taken into account in the analysis for calculating the effect estimation; baseline values may be based on other patient numbers.
b. MMRM with treatment, time point and the interaction of treatment and time point as fixed effects, the value at baseline and the interaction of value at baseline and time point as covariates.
c. Lower (decreasing) values indicate improved symptoms; negative effects (intervention minus comparator) indicate an advantage for the intervention (scale range of 0 to 100).
d. 86% of the patients were not included in the analysis.
e. Higher (increasing) values indicate better health status or better health-related quality of life; positive effects (intervention minus comparator) indicate an advantage for the intervention (scale range 0 to 100).
f. 87% of the patients were not included in the analysis.
g. In departure from the company's approach, this scale was assigned to health-related quality of life, rather than to symptoms.

CI: confidence interval; EORTC: European Organisation for Research and Treatment of Cancer; LS: Least Squares; MD: mean difference; MMRM: mixed-effects model repeated measures; N: number of analysed patients; QLQ-C30: Quality of Life Questionnaire – Core 30; QLQ-EN24: Quality of Life Questionnaire – Endometrial Cancer Module 24; RCT: randomized controlled trial; SD: standard deviation; SE: standard error; SMD: standardized mean difference; VAS: visual analogue scale

Appendix E Forest plots for the Institute's calculations

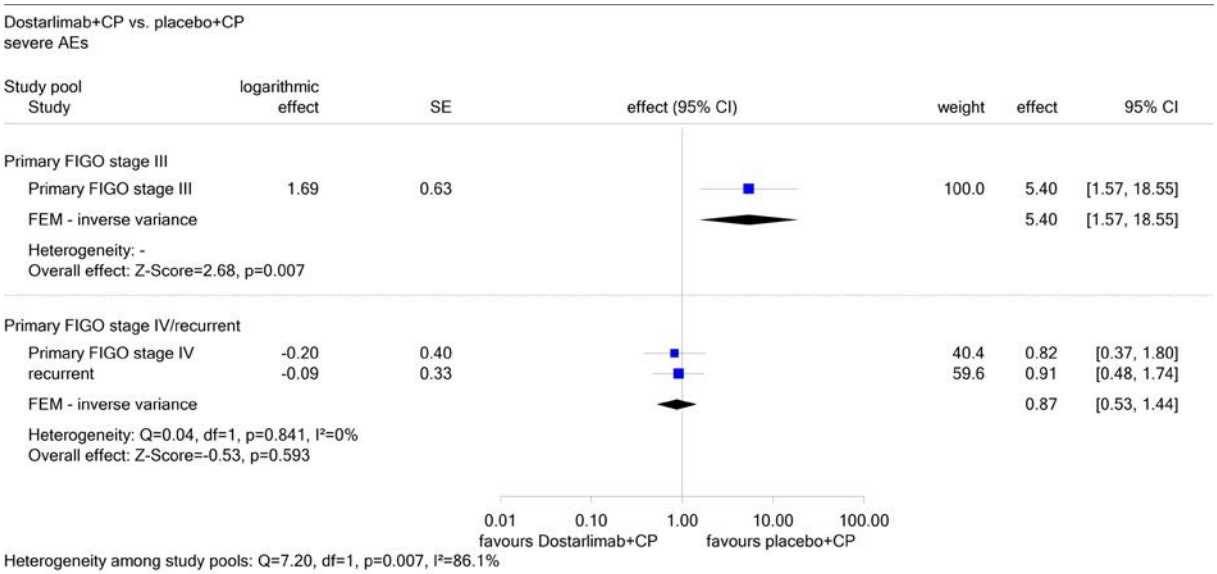

Figure 43: Subgroup analysis for the outcome "severe AEs" (CTCAE grade ≥ 3) for the subgroup combinations primary FIGO stage III vs. primary FIGO stage IV and recurrent