12 December 2024
EMA/4794/2025
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Jemperli

International non-proprietary name: Dostarlimab

Procedure No. EMEA/H/C/005204/II/0032

Note

Variation assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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List of abbreviations

2L	Second-line
ADA	Antidrug antibody
ADR	Adverse drug reaction
AE	Adverse event
ASIR	Age-standardized incidence rate
BICR	Blinded independent central review
BMI	Body Mass Index
Carbo/pac	Carboplatin and paclitaxel
CBC	Complete blood count
CI	Confidence interval
CL	Clearance
CMA	Conditional marketing authorisation
Cmax	Maximum observed concentration
Cmax,ss	Maximum observed concentration at steady state
Cmin	Minimum observed concentration
Cmin,ss	Minimum observed concentration at steady state
CO	Clinical overview
CSR	clinical study report
DCO	data cutoff
DCR	disease control rate
dMMR	mismatch repair-deficient
DOR	duration of response
EC	endometrial cancer
ECOG	Eastern Cooperative Oncology Group
EMA	European Medicines Agency
EORTC	European Organization for Research and Treatment of Cancer
EQ-5D-5L	European Quality of Life scale, 5-Dimensions, 5-Levels
ESMO	European Society for Medical Oncology
EU	European Union
FDA	Food and Drug Administration
GSK	GlaxoSmithKline
HR	Hazard ratio

ICI	Immune checkpoint inhibitor
IgG4	Immunoglobulin G4
IHC	Immunohistochemistry
irAE	Immune-related adverse event
ITT	Intention-to-treat
KM	Kaplan-Meier
MMR	Mismatch repair
MMRp	Mismatch repair-proficient
MSI	Microsatellite instability
MSI-H	Microsatellite instability-high
MSS	Microsatellite stable
NAb	Neutralizing antibody
NCA	Non-compartmental analysis
NCCN	National Comprehensive Cancer Network
NGS	Next generation sequencing
NSCLC	Non-small cell lung cancer
ORR	Objective response rate
OS	Overall survival
PBRER	Periodic benefit-risk evaluation report
PCR	Polymerase chain reaction
PD	Progressive disease
PD-1	Programmed cell death protein-1
PD-L1	Programmed cell death ligand 1
PD-L2	Programmed cell death ligand 2
PFS	Progression-free survival
PFS2	Progression-free survival 2
PIP	Pediatric investigation plan
PK	Pharmacokinetic(s)
POLE-mut	Polymerase epsilon-mutated
PRO	Patient-Reported Outcomes
Q3W	Every 3 weeks
Q6W	Every 6 weeks
QLQ-C30	Quality of Life Questionnaire C30 (Core)

QLQ-EN24	Endometrial Cancer Module
QoL	Quality of life
RDI	Relative dose intensity
RECIST v1.1	Response Evaluation Criteria in Solid Tumors version 1.1
RTD	Recommended therapeutic dose
SAE	Serious adverse event
SmPC	Summary of Product Characteristics
SOC	Standard of care
TEAE	Treatment-emergent adverse event
TIL	Tumor-infiltrating lymphocyte
US	United States
USPI	United States Prescribing Information

1. Background information on the procedure

1.1. Type II variation

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, GlaxoSmithKline (Ireland) Limited submitted to the European Medicines Agency on 22 May 2024 an application for a variation.

The following variation was requested:

Variation requested		**Type**	**Annexes affected**
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I and IIIB

Extension of indication for JEMPERLI to include, in combination with carboplatin and paclitaxel, the treatment of adult patients with primary advanced or recurrent endometrial cancer (EC) and who are candidates for systemic therapy based on Interim Analysis 1 and 2 from study RUBY Part 1 (213361). This is a phase 3, randomized, double-blind, controlled study evaluating the efficacy and safety of dostarlimab plus carboplatin and paclitaxel in primary advanced or recurrent EC versus placebo plus carboplatin and paclitaxel.
As a consequence, sections 4.1, 4.2, 4.4, 4.8, and 5.1 of the SmPC are updated. The Package Leaflet is updated in accordance. Version 4.0 of the RMP has also been submitted. In addition, the Marketing authorisation holder (MAH) took the opportunity to implement editorial changes to the SmPC and to align the PI with the latest QRD template version 10.4.

The requested variation proposed amendments to the Summary of Product Characteristics and Package Leaflet and to the Risk Management Plan (RMP).

Information on paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included (an) EMA Decision(s) P/0211/2021 on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP P/0211/2021 was not yet completed as some measures were deferred.

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the MAH did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

Scientific advice

The MAH received Scientific advice from the CHMP on 28 February 2019 (EMEA/H/SA/3585/2/2018/II). The Scientific advice pertained clinical aspects of the dossier.

1.2. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Antonio Gomez-Outes Co-Rapporteur: Boje Kvorning Pires Ehmsen

Timetable	Actual dates
Submission date	22 May 2024
Start of procedure:	22 June 2024
CHMP Rapporteur Assessment Report	16 August 2024
PRAC Rapporteur Assessment Report	20 August 2024
PRAC Outcome	5 September 2024
CHMP members comments	9 September 2024
Updated CHMP Rapporteur(s) (Joint) Assessment Report	12 September 2024
Request for supplementary information (RSI)	19 September 2024
CHMP Rapporteur Assessment Report	12 November 2024
PRAC Rapporteur Assessment Report	14 November 2024
PRAC members comments	20 November 2024
Updated PRAC Rapporteur Assessment Report	21 November 2024
PRAC Outcome	28 November 2024
CHMP members comments	2 December 2024
Updated CHMP Rapporteur Assessment Report	5 December 2024
Opinion	12 December 2024

2. Scientific discussion

2.1. Introduction

2.1.1. Problem statement

Disease or condition

Advanced or recurrent endometrial cancer.

State the claimed therapeutic indication

The new claimed indication is as follows:

JEMPERLI is indicated in combination with carboplatin and paclitaxel for the treatment of adult patients with ~~mismatch repair deficient (dMMR)/ microsatellite instability high (MSI-H)~~ primary advanced or recurrent endometrial cancer (EC) and who are candidates for systemic therapy.

Epidemiology and risk factors

Endometrial cancer (EC) accounted for 4.3% of all new cancer cases in women diagnosed in 2022, being the second most common gynaecological cancer after cervical cancer and the sixth most common type of malignancy diagnosed in women worldwide[1]. In Europe, there were a total of 124,936 new cases of EC and 30,272 deaths due to EC in 2022.

EC is predominantly a disease of post-menopausal women and most common in women over 50 years of age. The incidence of EC increases with age such that in Europe in 2020 the age-standardized incidence rate (ASIR) of EC was 0.26 per 100,000 among women aged between 15 and 19 years and 84.3 per 100,000 among women aged at least 60 years. EC is more prevalent in high/intermediate developed countries.

Risk factors include age, obesity, diabetes mellitus, nulliparity, late menopause, unopposed oestrogen intake or oestrogen-producing tumours, a history of breast cancer and the use of tamoxifen.

Biologic features, aetiology and pathogenesis

Among EC, there are two histologic categories: type I tumours, which include tumours of endometrioid histology that are grade 1 or 2, comprise approximately 80% of EC and have a favourable prognosis, and type II tumours, that account for 10-20% of EC and include grade 3 endometrioid tumours as well as tumours of non-endometrioid histology (serous, clear cell, mucinous, squamous, transitional cell, mesonephric, and undifferentiated).

The Cancer Genome Atlas has identified 4 molecular subgroups that more accurately reflect the underlying tumour. These include POLE-mut/ultramutated, MSI-H, copy number low, and copy number high. These subgroups have been replicated by using surrogate markers to allow increased reproducibility between laboratories, and include p53-abn, POLE-mut, dMMR and no specific molecular profile. Approximately 25% to 30% of ECs are dMMR/MSI-H and have biological features that result in increased antitumour activity with an anti- PD-1 antibody therapy[2].

Clinical presentation, diagnosis and stage/prognosis

The majority of patients with EC are diagnosed in early stages (Stage I or II) and receive surgery with curative intent; however, approximately 20% of patients are diagnosed with high-risk primary advanced or metastatic disease (Stage III or IV) for which a surgical cure is not possible. The prognosis for patients with advanced or recurrent EC depends upon site and extent of the recurrence, tumour size, whether the patient had received prior radiotherapy, the relapse-free interval, and histology. Approximately 40% of ECs are diagnosed as locally advanced tumours, and most recurrences occur within 3 years of primary treatment.

Survival rates vary across cancer stage and histologic subtype. Patients with early-stage disease have excellent outcomes with 5-year OS >95% for patients with stage I tumours. However, outcomes in women with primary advanced (Stage III or IV) or recurrent EC remain poor with 5-year OS rates of 20% to 25%[3].

[1] Ferlay J, Ervik M, Lam F, Laversanne M, Colombet M, Mery L, Piñeros M, Znaor A, Soerjomataram I, Bray F (2024). Global Cancer Observatory: Cancer Today. Lyon, France: International Agency for Research on Cancer. Available from: https://gco.iarc.who.int/today, accessed [01 August 2024].
[2] Kandoth C, Schultz N, Cherniack AD, et al. Integrated genomic characterization of endometrial carcinoma. Nature. 2013;497(7447):67-73.
[3] Koskas M, Amant F, Mirza MR, et al. Cancer of the corpus uteri: 2021 update. Int J Gynaecol Obstet. 2021;155(suppl 1):45-60

Management

For patients with advanced or recurrent disease of any histological subtype, surgery is recommended only when optimal cytoreduction can be achieved. Radiotherapy can be used as a primary treatment in patients with unresectable disease, or where there are medical contraindications to surgery. Patients with primary advanced Stage III or IV EC with extrauterine disease are at increased risk of recurrence and there is a need for adjuvant therapy. The recommended treatment options include systemic chemotherapy and/or external beam radiotherapy with or without brachytherapy. For patients with recurrent tumours, treatment options include surgery, radiotherapy and systemic therapy. For relapsed disease not amenable to surgery and/or RT, the standard approach is chemotherapy or hormonal therapy.[4]

Carboplatin and paclitaxel is considered as the standard of care (SOC) in first line setting to treat the advanced or metastatic EC based on its similar efficacy and less toxicity compared to cisplatin, doxorubicin and paclitaxel. Hormone therapy is indicated for patients with advanced or recurrent EC and endometrioid histology and has demonstrated a favourable toxicity profile. Patients with Grade 1 to 2 endometrioid tumours and those with hormone receptor-positive disease are most likely to experience clinical benefit from hormone therapy[5].

On 7th December 2023 (date of EC Decision), dostarlimab in combination with carboplatin and paclitaxel was approved in the EU for the treatment of adult patients with dMMR/MSI-H primary advanced or recurrent EC and who are candidates for systemic therapy (EMEA/H/C/005204/II/0023) based on the results of the RUBY Part 1 study. Recently, on 27 June 2024, the CHMP adopted a positive opinion for Imfinzi in combination with carboplatin and paclitaxel for the first-line treatment of adult patients with primary advanced or recurrent EC who are candidates for systemic therapy, followed by maintenance treatment with Imfinzi as monotherapy in EC that is dMMR or in combination with olaparib in EC that is pMMR, based on the results of the DUO-E study (EMEA/H/C/WS2463, date of EC Decision 26/07/2024).

In the second-line setting, dostarlimab and pembrolizumab have been approved in the EU as monotherapy for adult patients with dMMR or dMMR/MSI-H EC. Pembrolizumab is also approved in combination with lenvatinib for the treatment of patients who have failed a previous platinum-based chemotherapy, and who are not candidates for curative surgery or radiotherapy (RT) (SmPC Keytruda).

2.1.2. About the product

Dostarlimab is an anti-PD-1 immunoglobulin (Ig) G4 humanised monoclonal antibody that binds to programmed cell death protein 1 (PD-1), resulting in inhibition of binding to programmed cell death 1 ligand 1 (PD-L1) and programmed cell death 1 ligand 2 (PD-L2).

On 21 April 2021, dostarlimab (Jemperli®) was granted a conditional marketing authorisation (CMA) by the European Commission for the following indication:

JEMPERLI is indicated as monotherapy for the treatment of adult patients with mismatch repair deficient (dMMR)/microsatellite instability-high (MSI-H) recurrent or advanced endometrial cancer (EC) that has progressed on or following prior treatment with a platinum-containing regimen.

In December 2023 an extension of indication was granted for the following indication and the CMA was converted to a full marketing authorisation (not subject to specific obligations), since the specific obligations of the CMA were fulfilled:

[4] Oaknin A, Bosse TJ, Creutzberg CL et al; ESMO Guidelines Committee. Endometrial cancer: ESMO Clinical Practice Guideline for diagnosis, treatment and follow-up. Ann Oncol. 2022 Sep;33(9):860-877.
[5] Miller et al. 2020, Oaknin et al. 2022, NCCN 2023

JEMPERLI is indicated in combination with carboplatin and paclitaxel for the treatment of adult patients with mismatch repair deficient (dMMR)/microsatellite instability high (MSI-H) primary advanced or recurrent endometrial cancer (EC) and who are candidates for systemic therapy.

2.1.3. The development programme/compliance with CHMP guidance/scientific advice

The MAH received Scientific advice from the CHMP on 28 February 2019 (EMEA/H/SA/3585/2/2018/II). The Scientific advice pertained to clinical aspects of the dossier. Scientific advice was received on the key elements of the proposed pivotal Phase 3 study (RUBY) design to support registration of dostarlimab in combination with carboplatin and paclitaxel in 1L EC and the use of the study to support the conversion from a CMA to a full marketing authorisation.

2.1.4. General comments on compliance with GCP

According to the MAH all studies were conducted with the approval of Ethics Committees or Institutional Review Boards. Informed consent was obtained for all participants, and the studies were performed in accordance with the version of the Declaration of Helsinki that applied at the time the studies were conducted. Where required, regulatory approval was obtained from the relevant health authority.

2.2. Non-clinical aspects

No new non-clinical data have been submitted in this application, which is considered acceptable by the CHMP.

Ecotoxicity/environmental risk assessment

The provided ERA consists of a justification for not performing any ERA studies due to the nature of the product being a monoclonal antibody unlikely to result in a significant risk to the environment. Monoclonal antibodies are broken down by proteolysis and the use of which will not alter the concentration or distribution of the substance in the environment. Therefore, dostarlimab is not expected to pose a risk to the environment (see discussion on non-clinical aspects).

2.2.1. Discussion and conclusion on the non-clinical aspects

A full non-clinical package was included in the original MAA, no additional non-clinical data have been generated. This is considered acceptable.

Dostarlimab, is a protein and therefore no environmental risk assessment studies have been submitted, in line with the ERA guideline (EMEA/CHMP/SWP/4447/00 corr 2). Dostarlimab is not expected to pose a significant risk to the environment.

2.3. Clinical aspects

2.3.1. Introduction

GCP

The Clinical trials were performed in accordance with GCP as claimed by the MAH.

The MAH has provided a statement to the effect that clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

- Tabular overview of clinical studies

Table 1. Overview of clinical studies.

Study ID	Study Countries	Study Design, Objective(s)	Healthy Participants or Diagnosis of Patients	Treatment Details (Test Product(s); Dosage Regimen; Route; Duration)	Total No. of Participants by Group Enrolled / Completed	Study Reporting Status (Type of Report)	Location
Efficacy and Safety Studies: Controlled Clinical Studies Pertinent to the Claimed Indication							
213361, RUBY (Formerly known as 4010-03-001)	Belarus, Belgium, Canada, Czechia, Denmark, Finland, Germany, Greece, Hungary, Israel, Italy, Netherlands, Norway, Poland, Sweden, Turkey, Ukraine, United Kingdom, and United States,	Phase 3, Global, multicenter, randomized, double-blind, controlled study. Part 1: Primary Objectives: • To compare the PFS of participants treated with dostarlimab plus carboplatin-paclitaxel followed by dostarlimab to participants treated with placebo plus carboplatin-paclitaxel followed by placebo, as assessed by the investigator per RECIST v.1.1, in the following: • All participants with recurrent or primary advanced endometrial cancer	Females ≥18 years old participants with recurrent or primary advanced endometrial cancer	Part 1 Arm 1: Dostarlimab: 500 mg IV Q3W (Cycles 1 to 6) and 1000 mg IV Q6W (Cycle 7 and thereafter) Carboplatin: AUC 5 mg•mL/min IV Q3W (Cycles 1 to 6 only) Paclitaxel: 175 mg/m² IV Q3W (Cycles 1 to 6 only) Arm 2: Placebo: IV Q3W (Cycles 1 to 6) and IV Q6W (Cycle 7 and thereafter) Carboplatin: AUC 5 mg•mL/min IV Q3W (Cycles 1 to 6 only)	Part 1 Arm 1: 245 enrolled/ 130 completed [a] Arm 2: 249 enrolled/ 160 completed [a]	Ongoing Part 1 IA1 CSR (DCO: 28 September 2022) Part 1 IA1 CSR Errata Part 1 Admin OS Supplemental CSR (DCO: 01 March 2023) Part 1 IA2 CSR (DCO: 28 September 2023)	M5.3.5.1 M5.3.5.1 M5.3.5.1
		• Participants with dMMR/MSI-H recurrent or primary advanced endometrial cancer • To compare the OS of participants treated with dostarlimab plus carboplatin-paclitaxel followed by dostarlimab to participants treated with placebo plus carboplatin-paclitaxel followed by placebo, in participants with recurrent or primary advanced endometrial cancer.		Paclitaxel: 175 mg/m² IV Q3W (Cycles 1 to 6 only)			

Abbreviations: CSR = Clinical Study Report; DCO = Data Cut-off; dMMR = deficient mismatch repair; IA = interim analysis; IV = intravenous; MSI-H = microsatellite instability-high; OS = overall survival; PFS = progression-free survival; QxW = every x weeks; RECIST = Response Evaluation Criteria in Solid Tumors.
NOTE: Part 2 of RUBY will be submitted separately.
a. Participants who had their last study visit by the DCO for analysis reported in the Part 1 IA2 CSR.

2.3.2. Pharmacokinetics

To date, clinical pharmacology data are available from the first clinical study conducted with dostarlimab, GARNET Parts 1, 2A, and 2B, and the ongoing Phase 3 study, RUBY Part 1 (Table 2). Both studies are interventional trials. Dostarlimab PK has not been evaluated in healthy volunteers.

Data from participants enrolled in Part 1 of the RUBY study are included in this current IA2 submission, using a data cut-off (DCO) date of 08 August 2022 for PK and immunogenicity data. No new PK or immunogenicity data has been provided since IA1 submission. PK data included in IA1 has been assessed during previous procedure EMEA/H/C/005204/II/0023.

Less than 150 PK and less than 150 ADA samples have accrued between IA1 and IA2 data cuts and constitute less than 2% of the total number of PK/ADA samples used for popPK modelling at IA1. Moreover, the majority of samples collected between the two interim analyses came from later cycles (post Cycle 20) and end of treatment, with only a few samples from Cycle 15 and safety follow-ups. With

such a low proportion of additional PK and ADA data collected late in the study, no new information is anticipated to be gained and minimal changes in population PK parameter estimates and conclusions are expected. Accordingly, there were no updates made to the corresponding analysis datasets at the time of IA2.

Data from Part 2 of the RUBY study are out of scope for this submission.

Table 2. Studies included to support the clinical pharmacology evaluation of dostarlimab

Study	Type of Study	Study Design	Treatment
213346 (GARNET)[a]	Phase 1	Open-label, multicenter, first-in-human, 2-part study (including dose escalation and expansion)	*Dostarlimab monotherapy* Part 1 (dose escalation): Q2W DL1 (1 mg/kg); DL2 (3 mg/kg); DL3 (10 mg/kg) Part 2A (flat-dose safety run-in): Cohort 1 - 1000 mg Q6W; Cohort 2 - 500 mg Q3W Part 2B (expansion) - 500 mg Q3W for first 4 cycles, 1000 mg Q6W for all subsequent cycles
213361 (RUBY)[b]	Phase 3	Double-blind, multicenter, randomized, controlled, 2-part study	*Dostarlimab in combination with carboplatin and paclitaxel* Part 1[c]: Dostarlimab 500 mg Q3W for first 6 cycles, and then 1000 mg Q6W for all subsequent cycles or placebo Q3W for first 6 cycles, and then Q6W for all subsequent cycles + carboplatin AUC of 5 mg/mL/min and paclitaxel 175 mg/m^2 Q3W for 6 cycles Part 2[c, d]: 500 mg Q3W for 6 cycles in combination with carboplatin-paclitaxel and followed by 1000 mg Q6W dostarlimab + niraparib (at an individualized dose)

Abbreviations: AUC: area under the concentration-time curve; DL: dose level; GSK: GlaxoSmithKline; IV: intravenous; PO: by mouth; Q2W: every 2 weeks; Q3W: every 3 weeks; Q6W: every 6 weeks

NOTES:

a. Study number shown is the GSK study number. This study has been referred to as Study 4010-01-001 in former/other documents.

b. Study number shown is the GSK study number. This study has been referred to as Study 4010-03-001 in former/other documents.

c. Order of infusion: Dostarlimab or placebo (first), paclitaxel (second), and carboplatin (third). Carboplatin could be administered before paclitaxel if this was the current local institutional practice.

d. Dostarlimab or placebo IV is to be administered before the participant takes niraparib or placebo PO on days when both drugs are received.

Absorption

Bioavailability of dostarlimab is complete since it is administered by IV infusion. Maximum dostarlimab serum concentrations were generally observed at, or shortly after, the end of the infusion.

Based on population PK model predictions, the Cycle 1 geometric mean (CV%) Cmax and AUC(0-tau) of dostarlimab are 144 µg/mL (18.1%) and 31 800 µg•h/mL (18.9%), respectively, after the first dose of 500 mg, and 248 µg/mL (24.2%) and 73 100 µg•h/mL (31.1%), respectively, after multiple dosing of 500 mg Q3W at steady state.

Distribution

Based on the population PK analysis, dostarlimab had a small volume of distribution at steady state (geometric mean [CV%] 6.13 L [14.5%]), consistent with distribution largely in the systemic circulation and interstitial spaces.

Elimination

Metabolism

Dostarlimab is a therapeutic mAb IgG4, which is expected to be catabolized into small peptides, amino acids, and small carbohydrates by lysosomes through fluid-phase or receptor-mediated endocytosis. Therefore, the metabolic pathways are well understood, and conventional metabolism and elimination studies are not required for dostarlimab.

Excretion

Molecules of the size of dostarlimab are essentially excluded from glomerular filtration, and there is no evidence for renal tubular secretion of an IgG antibody [Bohle, 1988; Norden, 2001]. Based on the population PK analysis, the maximum decrease in CL over time was estimated to be 10.7% based on the pooled analysis.

The dostarlimab CL at the start of treatment was estimated to be 0.00732 L/h and based on individual post hoc PK parameters from the participants in the GARNET study (Part 2B) and the RUBY study (Part 1), dostarlimab geometric mean (CV%) CL at steady state and volume of Vss were estimated to be 0.00681 L/h (30.2%) and 5.81 L (14.9%), respectively. The geometric mean t½ (CV%) was estimated to be 23.2 days (20.8%).

Dose proportionality and time dependencies

Dose proportionality was assessed via Non-compartmental analysis (NCA) using data from Part 1 and Part 2A of the GARNET study, and exposure appeared to be dose proportional (previously submitted data).

Using pooled data from the GARNET and RUBY studies, AUC(0-tau) values from the population PK model simulations indicated an approximately dose-proportional increase in exposure at steady state for the clinically relevant 500- and 1000-mg flat doses (Table 3). Overall, dostarlimab PK is approximately dose proportional over the dose range evaluated. Additionally, dostarlimab showed an approximately 2-fold accumulation when comparing exposure (AUC[0-tau] and Cmax) after the first 500-mg dose Q3W with steady-state exposure following both 500-mg Q3W and 1000-mg Q6W doses.

Table 3. Summary of predicted dostarlimab exposure after first dose and steady state

Dose	AUC(0-tau) (µg•h/mL) (CV%)	Cmax (µg/mL) (CV%)
GARNET Study		
First dose (500 mg)	32500 (17.6%)	157 (19.6%)
Steady state (500 mg)	71200 (29%)	256 (22.8%)
Steady state (1000 mg)	144000 (29.6%)	388 (21.1%)
RUBY Study		
First dose (500 mg)	31800 (18.9%)	144 (18.1%)
Steady state (500 mg)	73100 (31.1%)	248 (24.2%)
Steady state (1000 mg)	148000 (32%)	369 (21.5%)
All		
First dose (500 mg)	32300 (18%)	154 (19.5%)
Steady state (500 mg)	71800 (29.6%)	253 (23.2%)
Steady state (1000 mg)	145000 (30.3%)	382 (21.3%)

Abbreviations: AUC(0-tau): area under the concentration-time curve for a dosing interval; Cmax: maximum observed concentration; CV=coefficient of variation
NOTE: Data in this table are based on Part 2b participants for the GARNET study and all participants included in the final population PK model for the RUBY study.

Special populations

No dedicated studies have been performed to evaluate dostarlimab PK in special patient populations. However, the effects of hepatic and renal impairment on dostarlimab exposure have been evaluated as covariates in the population PK analyses.

No dose adjustment is recommended based on these intrinsic factors.

Pharmacokinetic interaction studies

No drug-drug interaction studies have been conducted. Dostarlimab and other mAbs are not substrates for CYPs or drug transporters. It is not a cytokine and is unlikely to be a cytokine modulator. In a non-clinical study, dostarlimab did not cause an extensive release of cytokines. Therefore, it is unlikely that dostarlimab impacts the expression of CYPs and drug transporters or indirectly alters the clearance of small molecules. Additionally, PK-drug interactions of dostarlimab with small molecule drugs are not expected [Seitz, 2007; Wang, 2014; Silva, 2015; Varga 2015]. Also, the nonspecific clearance of mAbs through lysosome degradation [Seitz, 2007; Silva, 2015] disqualifies dostarlimab as either a perpetrator or victim drug in combination with carboplatin (mainly renal clearance) or paclitaxel (metabolized by CYP2C8 and CYP3A4).

During the population PK analysis, the effect of concomitant use of chemotherapy was evaluated as a covariate. Participants treated with dostarlimab in combination with carboplatin-paclitaxel were estimated to have 7.79% lower CL as compared to when treated with dostarlimab monotherapy. There was no meaningful impact of concomitant carboplatin-paclitaxel on dostarlimab exposure.

2.3.3. Pharmacodynamics

Primary and secondary pharmacology

Immunogenicity

No additional updates to immunogenicity analysis are reported for IA2 as there was a limited number of additional samples collected since the IA1 analysis DCO (08 August 2022). With no treatment emergent ADA reported in the IA1 analysis, and limited sample accrual post IA1, little or no impact of immunogenicity is anticipated on OS or safety endpoints at IA2.

2.3.4. PK/PD modelling

Exposure-response analysis

During IA1, an exposure-efficacy analysis was performed using population PK model-predicted dostarlimab exposures. The primary efficacy variable of PFS (as assessed by the investigator per RECIST v1.1) in the RUBY study and the key secondary efficacy endpoint, DOR, were modelled using time-to-event model structures (see EMEA/H/C/005204/II/0023).

No additional updates for exposure-PFS and exposure-DOR analyses were made based on IA2.

During IA1, an exposure-efficacy analysis was performed using population PK model-predicted dostarlimab exposures and the primary efficacy variable of OS in the RUBY study. As of the DCO (28 September 2022), the OS data had 33% maturity and the median OS had not been reached for either treatment arm. Thus, a formal analysis of exposure-response relationships with respect to OS was not included at that time. However, an exploratory graphical analysis of OS versus exposure showed a high degree of overlap of survival probabilities across exposure quartiles (see EMEA/H/C/005204/II/0023), suggesting no effect of dostarlimab exposure on OS.

An IA2 exposure-OS analysis was conducted using DCO 22 September 2023 data that included more mature overall survival (51.2% OS data maturity) data than in IA1. The IA2 exposure-OS analysis was conducted for the overall population with 232 OS observations from 232 subjects with at least 2 quantified dostarlimab concentrations in the dostarlimab arm of study 4010-03-001.

An exposure-safety analysis was performed to evaluate possible relationships between dostarlimab exposure and the occurrence of selected relevant drug-related TEAEs (those TEAEs with the 5 highest incidences seen in the RUBY study related to dostarlimab alone or in any combination with carboplatin-paclitaxel) in the target population. The 5 most prevalent TEAEs related to dostarlimab alone or in any combination with carboplatin-paclitaxel in the IA2 analysis as assessed by the investigator in the dostarlimab plus carboplatin-paclitaxel arm were fatigue, nausea, diarrhoea, rash and arthralgia.

Dataset

In total 241 patients were present in the SOC and dostarlimab treatment arm. A summary of the demographics of the patients included in the efficacy and safety analysis by treatment group is provided in the table below.

Table 4. Summary of Demographics by Treatment Group

	SoC+dotarlimab (N = 232)	SoC+placebo (N = 246)	All (N = 478)
Anti drug antibody status			
Missing	3 (1.29%)	246 (100%)	249 (52.1%)
Negaitve	229 (98.7%)		229 (47.9%)
Combined positive score category at baseline			
Negative	37 (15.9%)	36 (14.6%)	73 (15.3%)
Positive	94 (40.5%)	91 (37%)	185 (38.7%)
Unknown	101 (43.5%)	119 (48.4%)	220 (46%)
Diagnosis (Source verified)			
dMMR/MSI-H	49 (21.1%)	65 (26.4%)	114 (23.8%)
MMRp/MSS	183 (78.9%)	181 (73.6%)	364 (76.2%)
Disease Status			
Primary Stage III	44 (19%)	44 (17.9%)	88 (18.4%)
Primary Stage IV	73 (31.5%)	83 (33.7%)	156 (32.6%)
Recurrent	115 (49.6%)	119 (48.4%)	234 (49%)
dMMR only status			
No	183 (78.9%)	183 (74.4%)	366 (76.6%)
Yes	49 (21.1%)	63 (25.6%)	112 (23.4%)
ECOG			
0 (Fully active)	142 (61.2%)	159 (64.6%)	301 (63%)
1 (Ambulatory)	90 (38.8%)	86 (35%)	176 (36.8%)
2 (Capable of all selfcare)		1 (0.407%)	1 (0.209%)
Geographic location			
Eastern Europe	13 (5.6%)	14 (5.69%)	27 (5.65%)
North America	164 (70.7%)	186 (75.6%)	350 (73.2%)
Western Europe	55 (23.7%)	46 (18.7%)	101 (21.1%)
Histology			
Endometrioid Carcinoma	110 (47.4%)	111 (45.1%)	221 (46.2%)
Other	122 (52.6%)	135 (54.9%)	257 (53.8%)
Neutralizing antibody status			
Missing	196 (84.5%)	246 (100%)	442 (92.5%)
Negative	18 (7.76%)		18 (3.77%)
Positive	18 (7.76%)		18 (3.77%)
Prior external pelvic radiotherapy			
No	192 (82.8%)	201 (81.7%)	393 (82.2%)
Yes	40 (17.2%)	45 (18.3%)	85 (17.8%)

Efficacy variables

The main focus of this ER analysis of efficacy was the primary endpoint OS, defined as the time from randomization to the date of death by any cause. Only IA2 data is in scope of this analysis.

Two hundred twenty-nine patients had negative anti-drug antibody (ADA) status, the remaining 3 patients were missing ADA information hence ADA was not included as a covariate in the analysis. The majority of patients were missing information on neutralizing antibody status (ADNAS) status (84% missing) and PD-L1 expression (44% missing) hence these covariates were not included in the analysis. All dostarlimab treated patients in the tumour diagnosis category dMMR/MSI-H were source-verified data and were dMMR. Hence dMMR was not included as a separate covariate in the analysis.

Safety variables

Safety variables were analysed for all patients participating in study 4010-03-001. The analysis included safety variables that were the top five occurring dostarlimab-related TEAEs as assessed by investigators: fatigue, nausea, rash, diarrhoea, and arthralgia. Only IA2 data is in scope of this analysis. A summary of the occurrence of these events is shown in Table 5. Only two of the placebo patients in the tumour diagnosis category dMMR/MSI-H were not dMMR. Hence dMMR was not included as a separate covariate in the analysis.

Table 5. Summary of dostarlimab-related TEAEs

TEAE	Period	Total Number of Patients	Number of Patients With a TEAE	Percentage of Patients With an TEAE
Arthralgia	All cycles	478	89	18.6 %
Arthralgia	Cycle 1-6	478	64	13.4 %
Arthralgia	Cycle 7 and beyond	478	37	7.7 %
Diarrhoea	All cycles	478	80	16.7 %
Diarrhoea	Cycle 1-6	478	73	15.3 %
Diarrhoea	Cycle 7 and beyond	478	20	4.2 %
Fatigue	All cycles	478	164	34.3 %
Fatigue	Cycle 1-6	478	153	32 %
Fatigue	Cycle 7 and beyond	478	34	7.1 %
Nausea	All cycles	478	116	24.3 %
Nausea	Cycle 1-6	478	100	20.9 %
Nausea	Cycle 7 and beyond	478	26	5.4 %
Rash	All cycles	478	65	13.6 %
Rash	Cycle 1-6	478	53	11.1 %
Rash	Cycle 7 and beyond	478	18	3.8 %

TEAE: Treatment-emergent adverse event, dostarlimab-related.

Efficacy analysis

Time-to-event Modelling Approach

The primary efficacy parameter OS was assessed using Cox proportional hazard models with exposure as the independent predictor. The analysis included subjects in the SOC + dostarlimab arm.

Covariates

The following covariates were considered for inclusion in the ER modelling of efficacy:

- Tumour diagnosis (dMMR/MSI-H or MMRp/MSS per source verified data)
- Disease status in EC (recurrent, primary Stage III, or primary Stage IV)
- Prior external pelvic radiotherapy (yes or no)
- Baseline ECOG performance (0 means Fully active or 1 means Ambulatory)
- Geographic location (Western Europe, Eastern Europe, or North America)
- Histology (endometrioid carcinoma or non-endometrial, categorized as "Other")

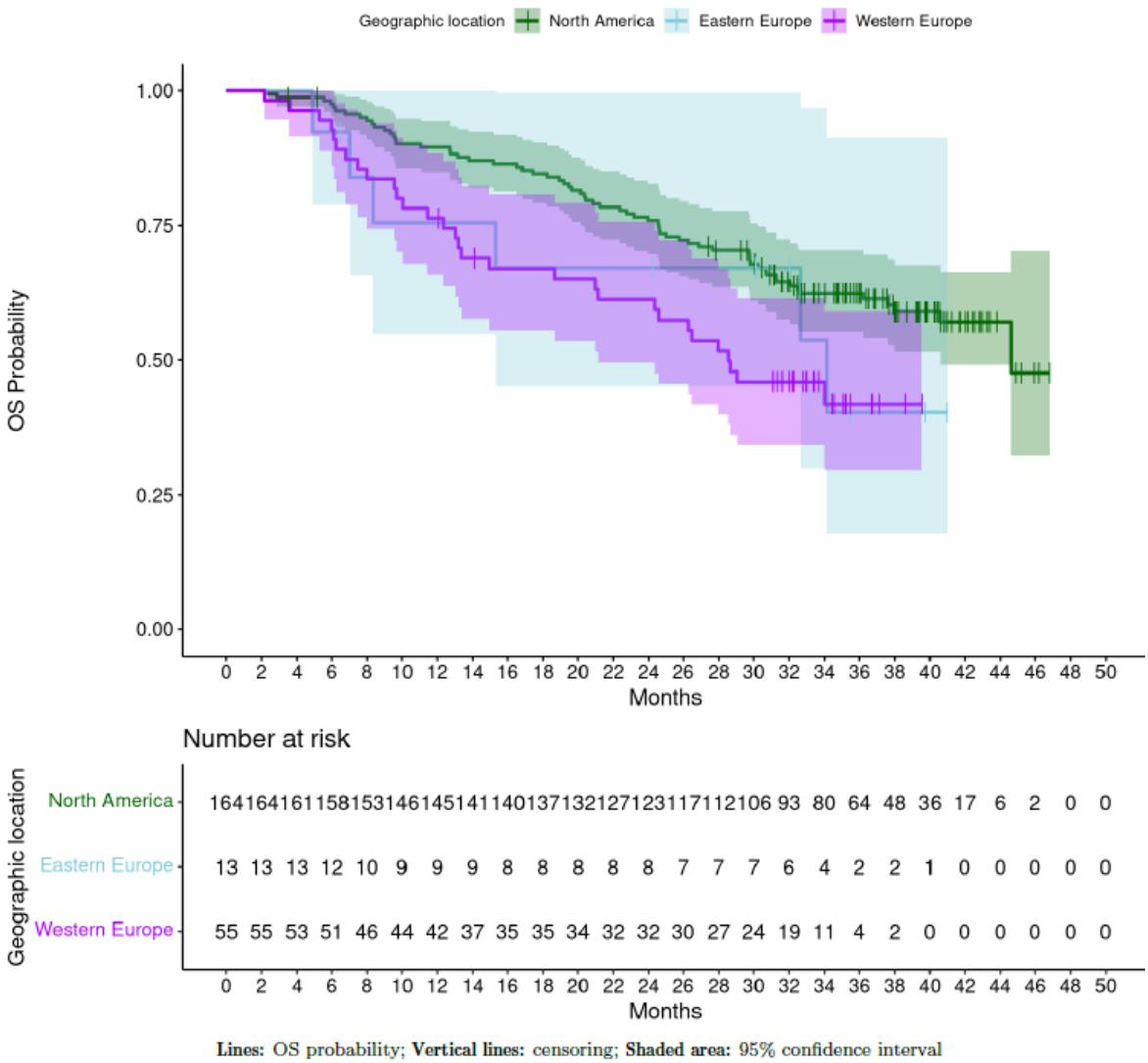
Results

A total of 232 OS observations from 232 subjects with at least 2 quantified dostarlimab concentration in the dostarlimab arm of study 4010-03-001 were used for OS evaluation.

OS probability over time for the three exposure metrics of interest area under the concentration versus time curve (AUC), Cmax and Cmin during the first 3 weeks after the first dose (i.e. 500 mg during the first 21 days) and showed high degree of overlap between exposure categories. OS appeared to be independent of any of the three exposure metrics.

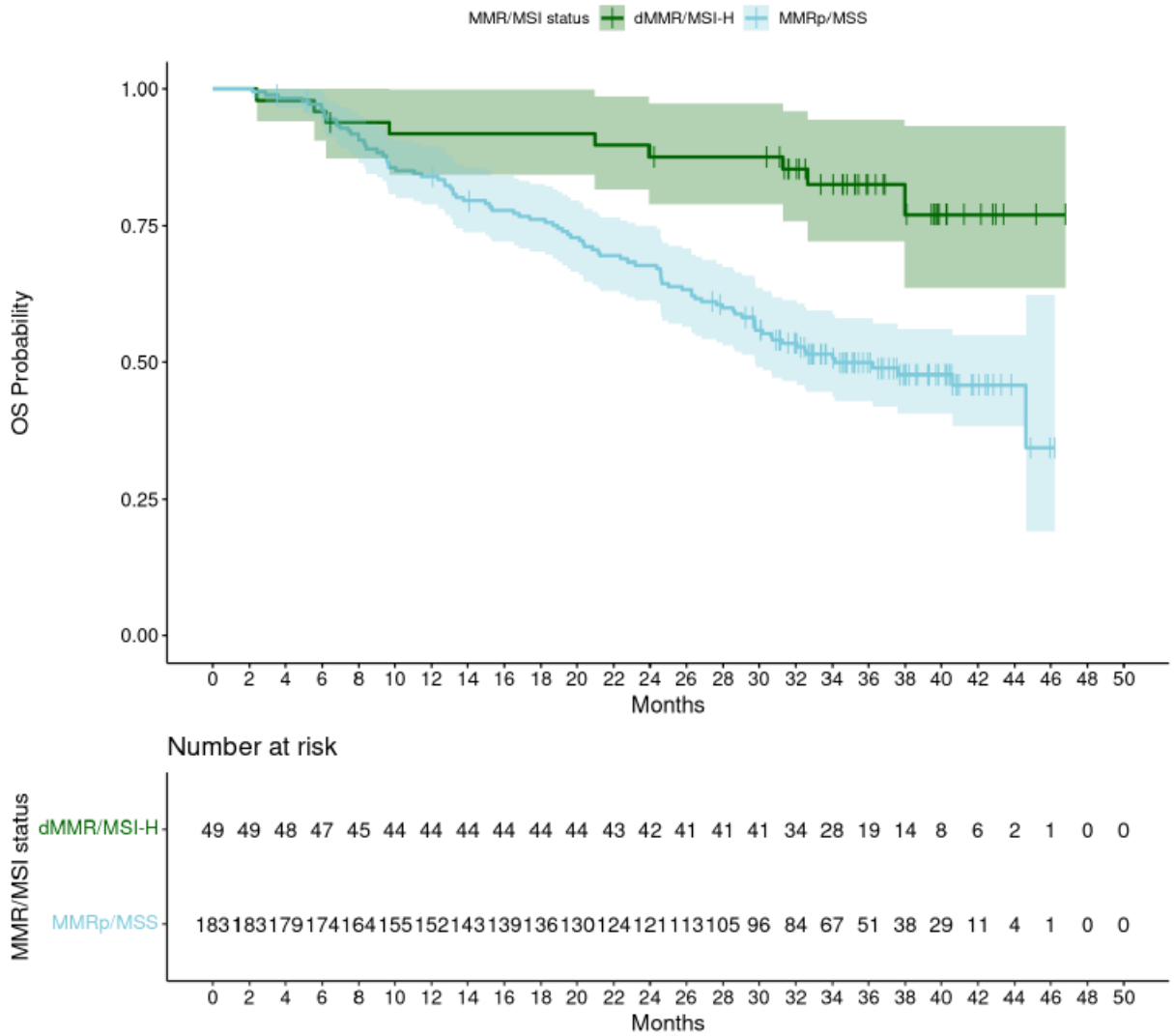
Disease status in EC, prior external pelvic radiotherapy, baseline ECOG performance showed no apparent relationship with OS probability. Patients in Eastern and Western Europe appear to have lower probability of OS compared to North American patients (Figure 1). A large difference in OS was observed between dMMR/MSI-H and MMRp/MSS patients (Figure 2). Patients with histology endometrioid carcinoma appear to have lower probability of OS compared to other (Figure 3). OS probability stratified by tumour diagnosis appeared to be independent of AUC, Cmax and Cmin in these patient groups with high overlap across exposure categories.

Figure 1. OS vs. Time Stratified by Geographic Location



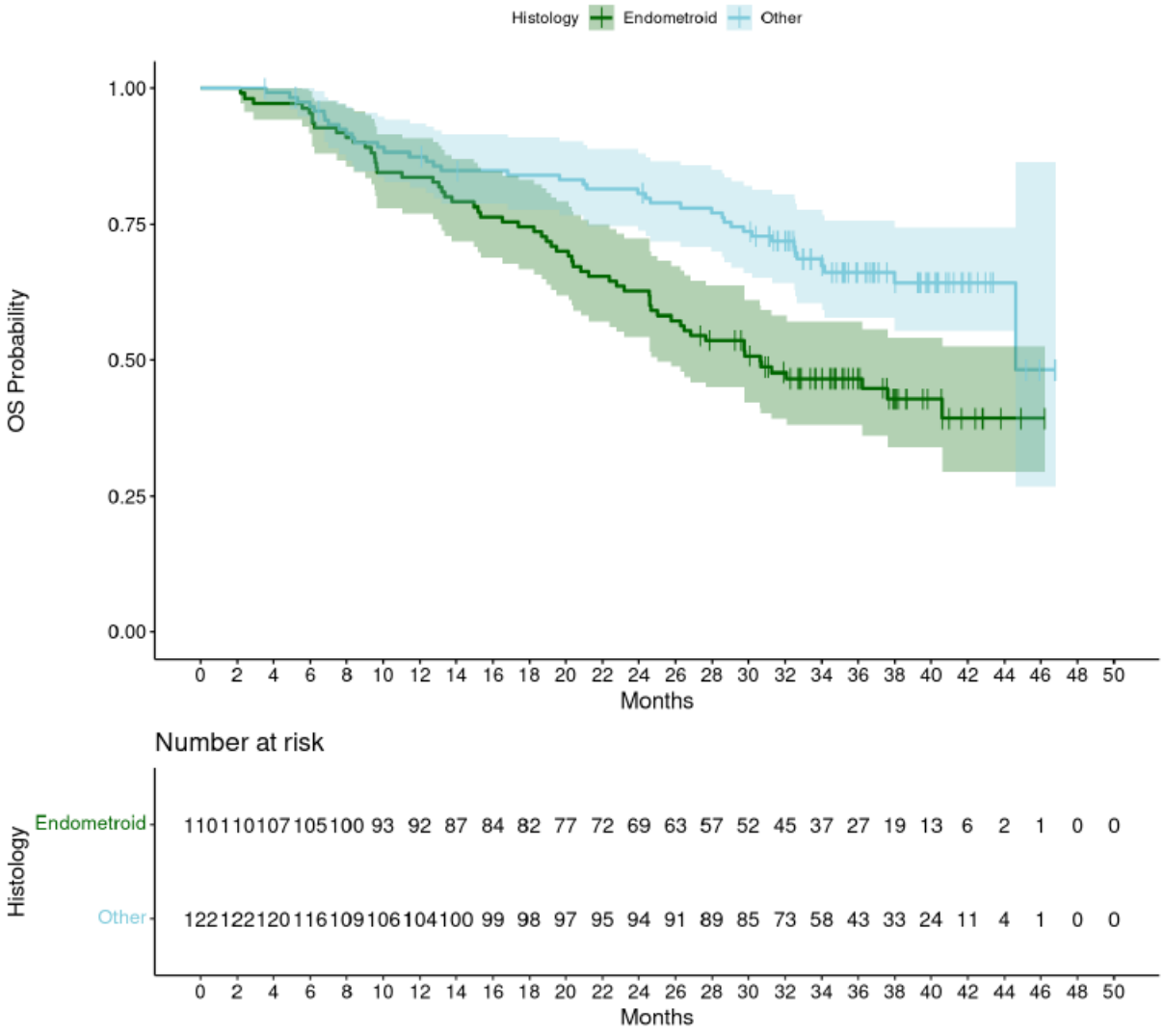
Lines: OS probability; **Vertical lines:** censoring; **Shaded area:** 95% confidence interval

Figure 2: OS vs. Time Stratified by Tumour Diagnosis



Lines: OS probability; **Vertical lines:** censoring; **Shaded area:** 95% confidence interval; **dMMR:** deficient mismatch repair; **MSI-H:** microsatellite instability high; **MMRp:** mismatch repair proficient; **MSS:** microsatellite stable

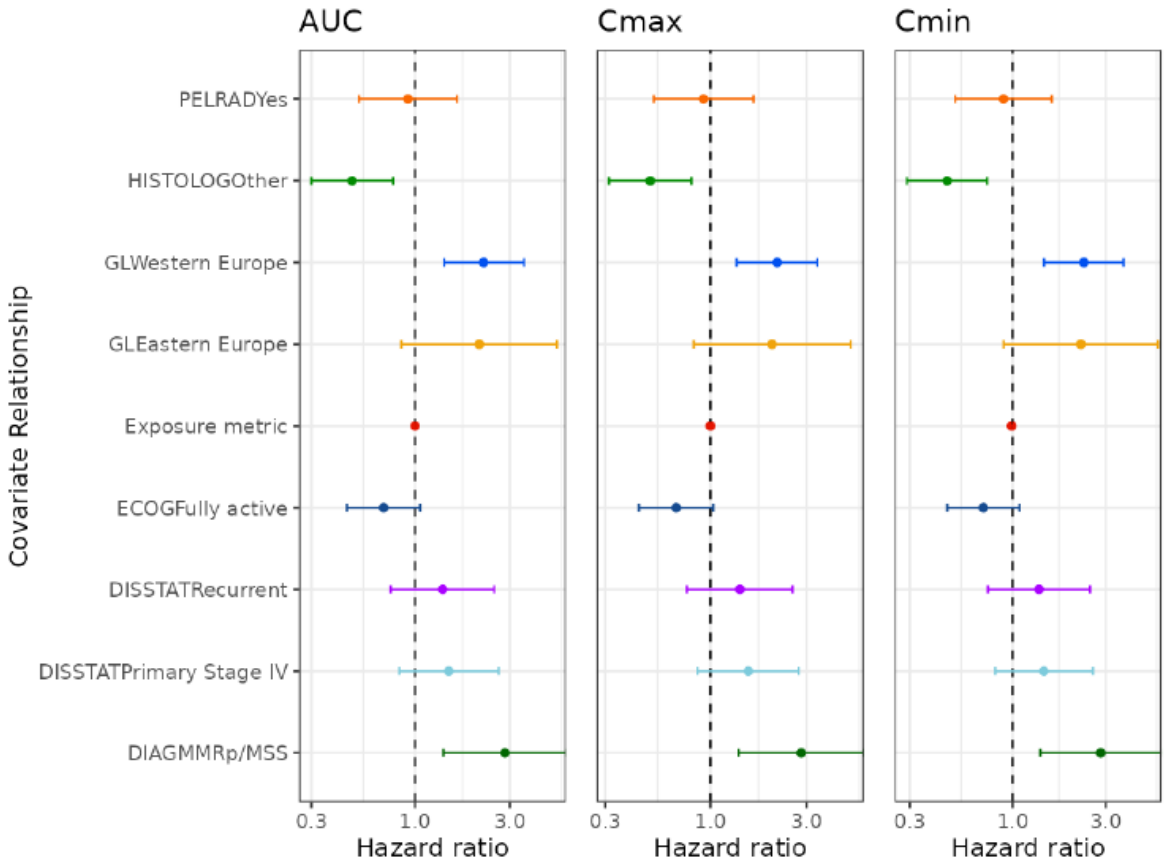
Figure 3: OS vs. Time Stratified by Histology



Lines: OS probability; **Vertical lines:** censoring; **Shaded area:** 95% confidence interval;

The hazards for OS for the different covariates were proportional in the overall population. Hence Cox (proportional hazards) regression was performed without stratification for the three exposure metrics (AUC, Cmax and Cmin) with the additional tumour diagnosis, covariates disease status in EC, prior external pelvic radiotherapy, baseline ECOG performance, histology and geographic location. None of the tested exposure metrics had a statistically significant relationship with OS ($\alpha = 0.05$) with p-values of 0.90, 0.45 and 0.43 for AUC, Cmax and Cmin, respectively. Thus, the IA2 exposure-OS analysis demonstrated that the exposure-OS relationship achieved a plateau over the range of exposures achieved with the therapeutic dose and regimen in RUBY Part 1. The hazard ratios of the tested covariates can be seen below.

Figure 4: Hazard Ratio Multivariate Analysis, OS



Circle: Hazard ratio; **Lines:** 95% confidence interval; PELRAD - Prior external pelvic radiotherapy (reference No); HISTOLOG - Histology (reference endometrioid carcinoma); GL - Geographic location (reference North America); ECOG - Baseline ECOG performance (reference Ambulatory (ECOG=1)); DISSTAT - Disease status in EC (reference Primary Stage III); DIAG - Tumor diagnosis (reference dMMR/MSI-H); **AUC**: Area under the curve during the first 21 days; **Cmax**: Maximum concentration during the first 21 days; **Cmin**: Minimum concentration at Day 21.

Table 6: Hazard Ratio Multivariate OS Analysis, AUC

Covariate	Hazard Ratio	95% CI of Hazard Ratio	p-value
Exposure metric	1.00	1-1	0.90
DIAGMMRp/MSS	2.84	1.39-5.78	0.00
DISSTATPrimary Stage IV	1.48	0.835-2.64	0.18
DISSTATRecurrent	1.38	0.754-2.51	0.30
PELRADYes	0.92	0.522-1.63	0.78
ECOGFully active	0.69	0.455-1.06	0.09
GLEastern Europe	2.11	0.852-5.21	0.11
GLWestern Europe	2.22	1.4-3.55	0.00
HISTOLOGOther	0.48	0.3-0.773	0.00

PELRAD - Prior external pelvic radiotherapy (reference No); HISTOLOG - Histology (reference endometrioid carcinoma); GL - Geographic location (reference North America); ECOG - Baseline ECOG performance (reference Ambulatory); DISSTAT - Disease status in EC (reference Primary Stage III); AUC - Area under the concentration versus time curve during first 21 days.

Table 7: Hazard Ratio Multivariate OS Analysis, Cmax

Covariate	Hazard Ratio	95% CI of Hazard Ratio	p-value
Exposure metric	1.00	0.995-1.01	0.45
DIAGMMRp/MSS	2.82	1.38-5.76	0.00
DISSTATPrimary Stage IV	1.54	0.863-2.74	0.14
DISSTATRecurrent	1.40	0.764-2.55	0.28
PELRADYes	0.92	0.523-1.63	0.78
ECOGFully active	0.68	0.442-1.03	0.07
GLEastern Europe	2.02	0.824-4.96	0.12
GLWestern Europe	2.14	1.35-3.39	0.00
HISTOLOGOther	0.50	0.314-0.805	0.00

PELRAD - Prior external pelvic radiotherapy (reference No); HISTOLOG - Histology (reference endometrioid carcinoma); GL - Geographic location (reference North America); ECOG - Baseline ECOG performance (reference Ambulatory); DISSTAT - Disease status in EC (reference Primary Stage III); Cmax - maximum concentration during first 21 days.

Table 8: Hazard Ratio Multivariate OS Analysis, Cmin

Covariate	Hazard Ratio	95% CI of Hazard Ratio	p-value
Exposure metric	0.99	0.972-1.01	0.43
DIAGMMRp/MSS	2.83	1.39-5.77	0.00
DISSTATPrimary Stage IV	1.45	0.817-2.58	0.20
DISSTATRecurrent	1.37	0.751-2.5	0.30
PELRADYes	0.90	0.51-1.59	0.72
ECOGFully active	0.71	0.466-1.09	0.12
GLEastern Europe	2.24	0.902-5.56	0.08
GLWestern Europe	2.32	1.45-3.7	0.00
HISTOLOGOther	0.46	0.289-0.744	0.00

PELRAD - Prior external pelvic radiotherapy (reference No); HISTOLOG - Histology (reference endometrioid carcinoma); GL - Geographic location (reference North America); ECOG - Baseline ECOG performance (reference Ambulatory); DISSTAT - Disease status in EC (reference Primary Stage III); Cmin - Minimum concentration after first dose, day 21.

Safety analysis

3 different periods were considered:

i) Cycle 1 through 6 which gives a comparison of dostarlimab vs. SOC,

ii) Cycle 7 and beyond which gives comparison of dostarlimab vs. placebo,

iii) All cycles which takes all above components into account.

Covariates

The following covariates were included in the ER modelling of safety:

• Tumour diagnosis (dMMR/MSI-H or MMRp/MSS)

• Disease status in EC (recurrent, primary Stage III, or primary Stage IV)

• Prior external pelvic radiotherapy (yes or no)

• Baseline ECOG performance (0 means Fully active or 1 means Ambulatory)

• Geographic location (Western Europe, Eastern Europe, or North America).

Likelihood Models

Logistic regression was used to describe the relationships between the occurrence of each dostarlimab-related TEAE type and the available exposure metrics. The probability of AE of interest was modelled as a function of exposure.

A univariate analysis with exposure as the independent predictor was performed in a first step.

Subsequently, covariates were explored via a full covariate model approach, i.e. a multivariate analysis with all covariates included in the model at once.

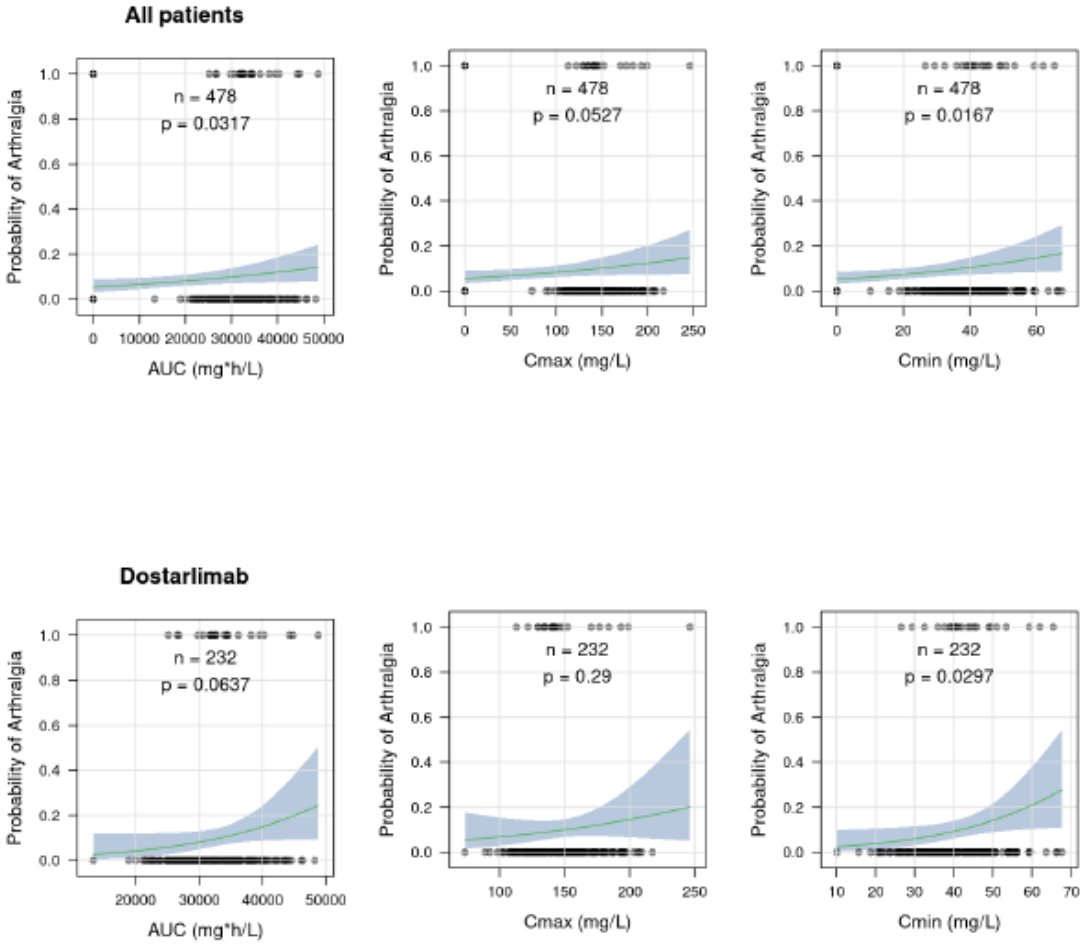
Results

Univariate analysis

Binary data for the five most prevalent dostarlimab-related TEAEs as assessed by investigators (fatigue, nausea, rash, diarrhoea, and arthralgia) from 478 patients (232 subjects with at least 2 quantified dostarlimab concentration in the dostarlimab arm, 246 in the placebo arm) of study 4010-03-001 were analysed using univariate logistic regression.

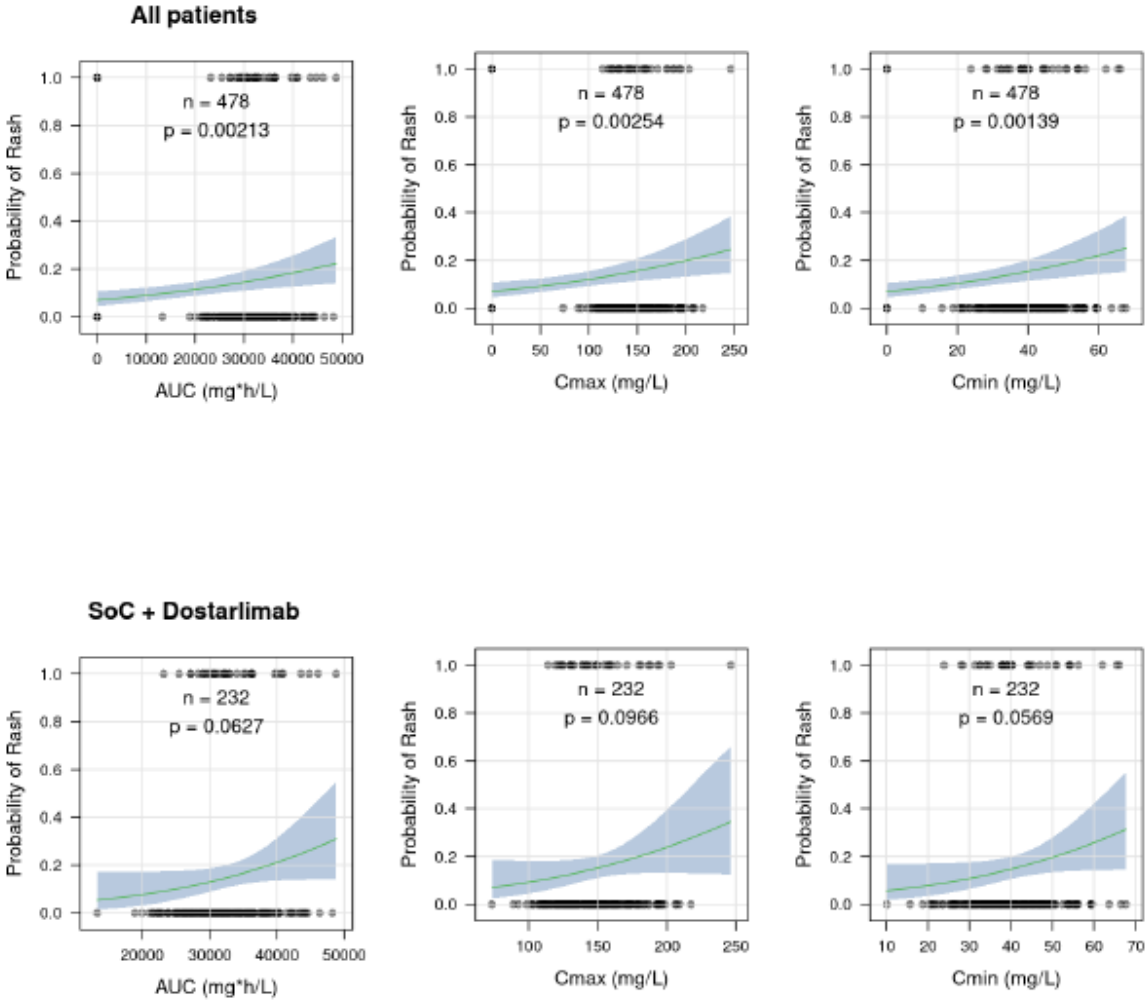
When all patients were included, significant ER relationships for rash was seen for all exposure metrics (AUC, Cmax and Cmin) in all periods. However, when placebo subjects were excluded, the ER relationships were no longer significant ($p<0.05$). For arthralgia AUC and Cmin were significant in the period cycle 7 and beyond when all patients were included. However, when excluding the placebo arm, AUC is no longer significant ($p<0.05$). No other significant relationships were seen for any of the other dostarlimab-related TEAEs in any of the tested time periods.

Figure 5: Arthralgia vs Exposure Metrics Cycle 7 and Beyond



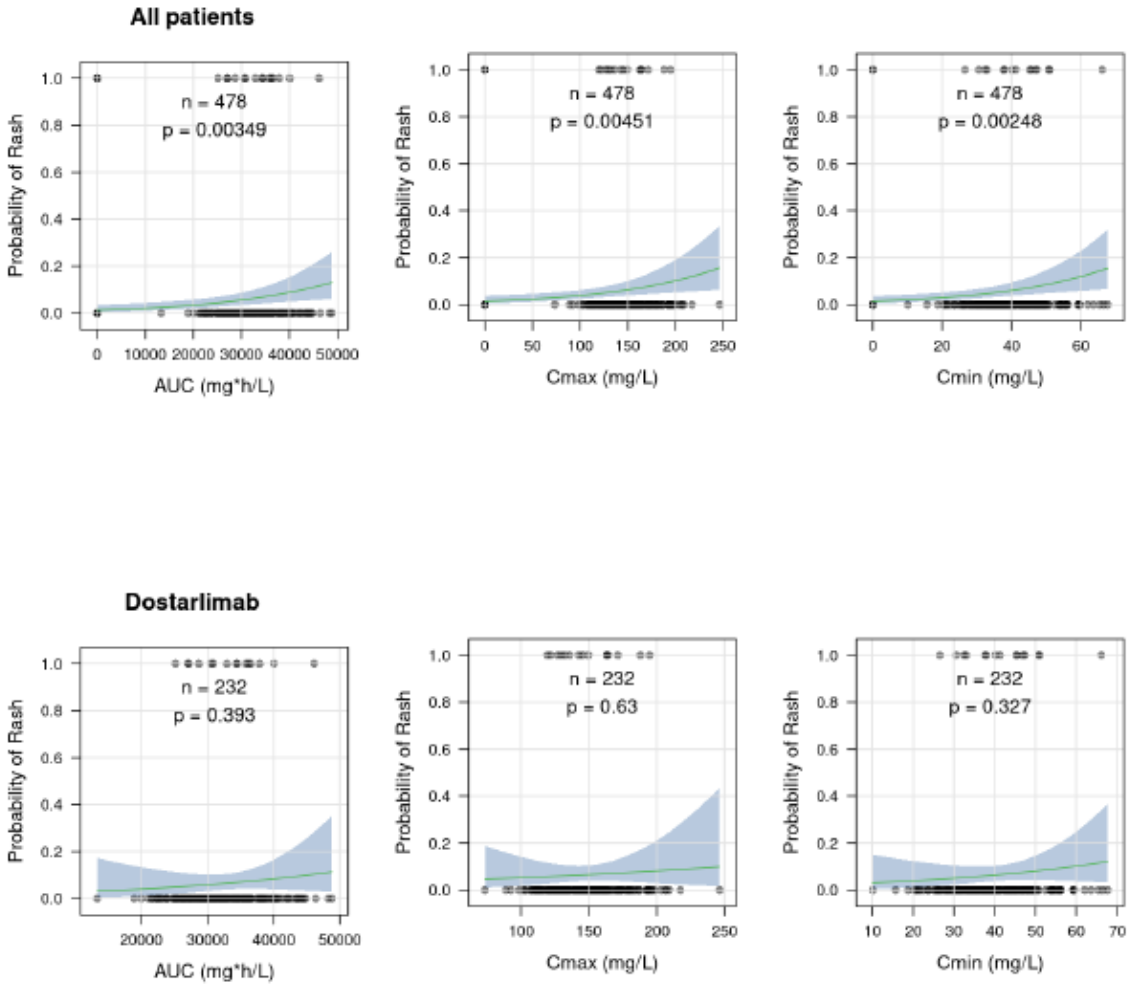
Line: Predicted probability; **Shaded area**: 95% confidence interval; **Circles**: Data; **AUC**: Area under the curve during the first 21 days; **Cmax**: Maximum concentration during the first 21 days; **Cmin**: Minimum concentration at Day 21.

Figure 6: Rash vs Exposure Metrics Cycle 1-6



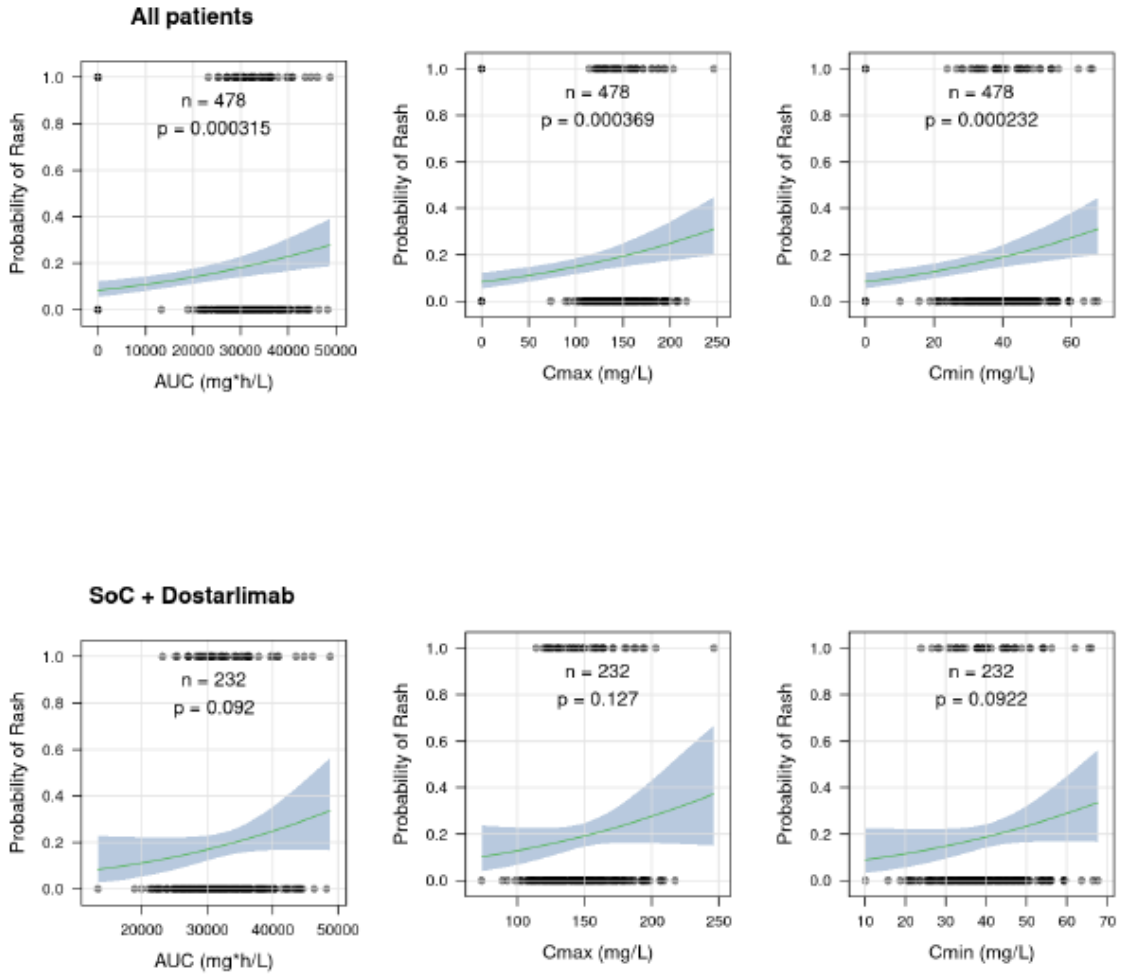
Line: Predicted probability; **Shaded area**: 95% confidence interval; **Circles**: Data; **AUC**: Area under the curve during the first 21 days; **Cmax**: Maximum concentration during the first 21 days; **Cmin**: Minimum concentration at Day 21; **SoC**: Standard of care.

Figure 7: Rash vs Exposure Metrics Cycle 7 and Beyond



Line: Predicted probability; **Shaded area**: 95% confidence interval; **Circles**: Data; **AUC**: Area under the curve during the first 21 days; **Cmax**: Maximum concentration during the first 21 days; **Cmin**: Minimum concentration at Day 21.

Figure 8: Rash vs Exposure Metrics All Cycles



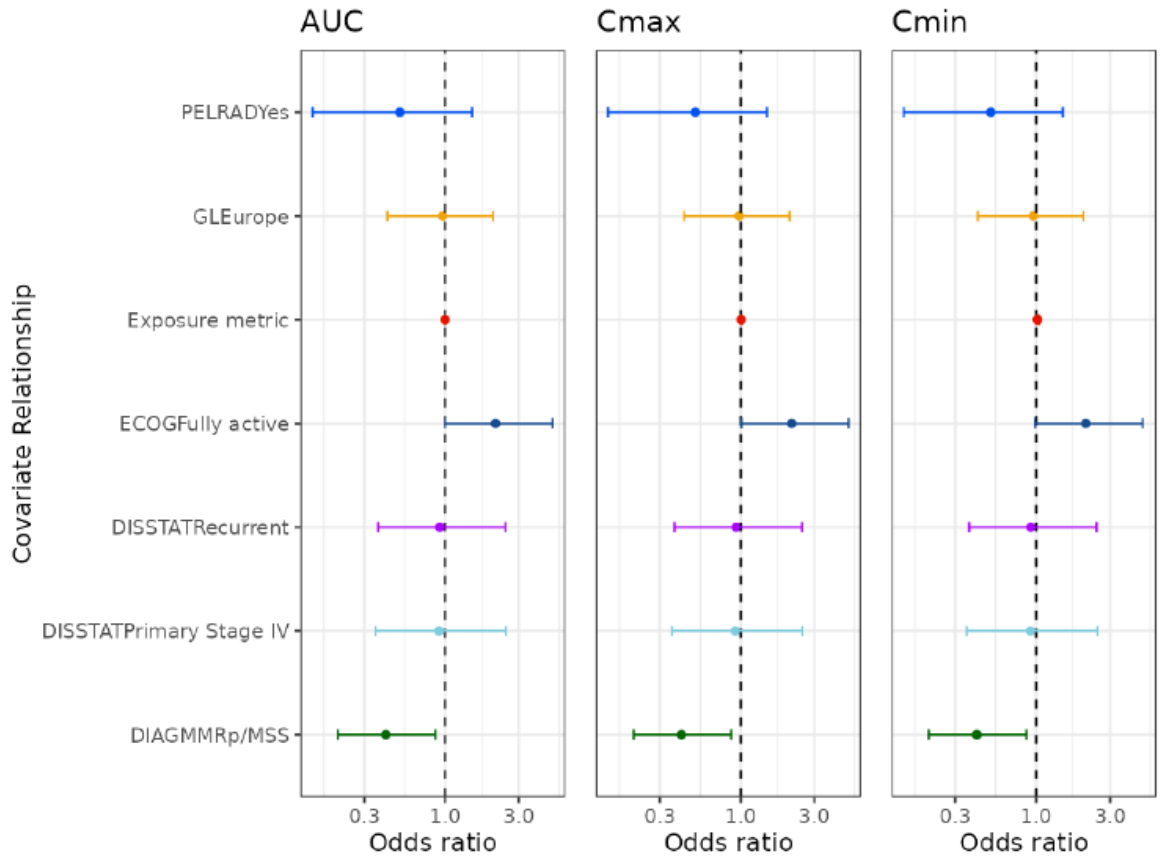
Line: Predicted probability; **Shaded area**: 95% confidence interval; **Circles**: Data; **AUC**: Area under the curve during the first 21 days; **Cmax**: Maximum concentration during the first 21 days; **Cmin**: Minimum concentration at Day 21; **SoC**: Standard of care.

Multivariate analysis

For some dostarlimab-related TEAEs in some time periods there were no events in the category Eastern Europe. For these, Eastern Europe and Western Europe were lumped together in the category Europe. Multivariate logistic regression was performed for the dostarlimab-related TEAEs and time periods that showed significant univariate ER relationships.

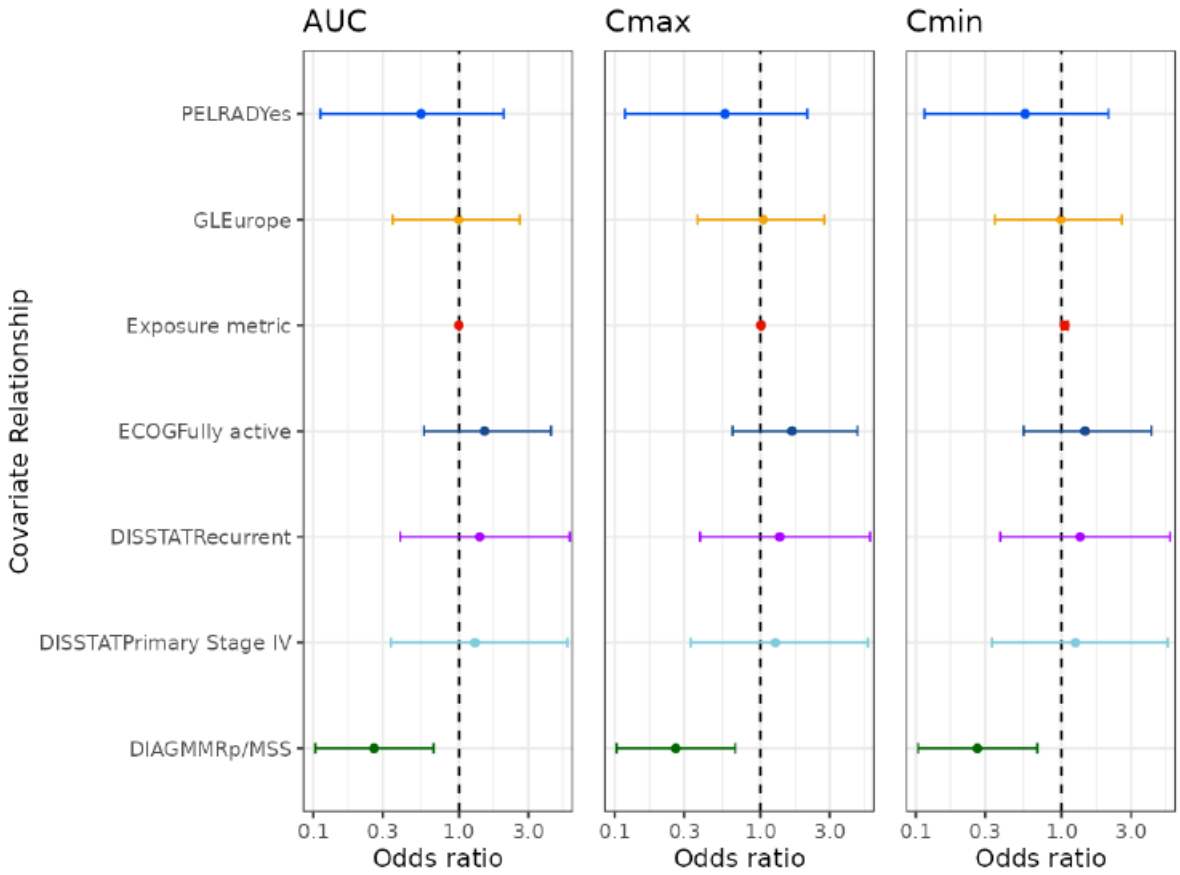
In addition to the exposure metrics AUC, Cmax and Cmin, the covariates disease status in EC, prior external pelvic radiotherapy, baseline ECOG performance, tumour diagnosis and geographic location were investigated. The odds ratios of the tested covariates for arthralgia in the period cycle 7 and beyond for all patients and dostarlimab treated patients can be seen in the figures and tables below.

Figure 9: Odds Ratio Multivariate Analysis, Arthralgia, Cycle 7 and Beyond, all patients



Circles: Odds ratio; **Lines:** 95% confidence interval; PELRAD - Prior external pelvic radiotherapy (reference No); GL - Geographic location (reference North America); ECOG - Baseline ECOG performance (reference Ambulatory (ECOG=1)); DISSTAT - Disease status in EC (reference Primary Stage III); DIAG - Tumor diagnosis (reference dMMR/MSI-H); **AUC**: Area under the curve during the first 21 days; **Cmax**: Maximum concentration during the first 21 days; **Cmin**: Minimum concentration at Day 21.

Figure 10: Odds Ratio Multivariate Analysis, Arthralgia, Cycle 7 and Beyond, Dostarlimab Treated



Circles: Odds ratio; **Lines:** 95% confidence interval; PELRAD - Prior external pelvic radiotherapy (reference No); GL - Geographic location (reference North America); ECOG - Baseline ECOG performance (reference Ambulatory (ECOG=1)); DISSTAT - Disease status in EC (reference Primary Stage III); DIAG - Tumor diagnosis (reference dMMR/MSI-H); **AUC**: Area under the curve during the first 21 days; **Cmax**: Maximum concentration during the first 21 days; **Cmin**: Minimum concentration at Day 21.

Table 9: Odds Ratio Multivariate Analysis, Arthralgia, Cycle 7 and Beyond, all patients, Cmin

Covariate	Odds Ratio	95% CI of Odds Ratio	p-value
Exposure metric	1.02	1-1.04	0.011
DIAGMMRp/MSS	0.413	0.202-0.866	0.0163
DISSTATPrimary Stage IV	0.919	0.356-2.49	0.863
DISSTATRecurrent	0.923	0.368-2.46	0.867
PELRADYes	0.509	0.139-1.49	0.253
ECOGFully active	2.09	0.984-4.88	0.0673
GLEurope	0.955	0.419-2.02	0.907

DIAG - Tumor diagnosis (reference dMMR/MSI-H); DISSTAT - Disease status in EC (reference Primary Stage III); PELRAD - Prior external pelvic radiotherapy (reference No); ECOG - Baseline ECOG performance (reference 1=Ambulatory); GL - Geographic location (reference North America); Cmin - Minimum concentration after first dose, day 21.

Table 10: Odds Ratio Multivariate Analysis, Arthralgia, Cycle 7 and Beyond, all patients, AUC

Covariate	Odds Ratio	95% CI of Odds Ratio	p-value
Exposure metric	1	1-1	0.0196
DIAGMMRp/MSS	0.414	0.203-0.868	0.0167
DISSTATPrimary Stage IV	0.917	0.356-2.48	0.859
DISSTATRecurrent	0.926	0.37-2.46	0.873
PELRADYes	0.509	0.139-1.49	0.253
ECOGFully active	2.12	1-4.95	0.0618
GLEurope	0.965	0.424-2.04	0.929

DIAG - Tumor diagnosis (reference dMMR/MSI-H); DISSTAT - Disease status in EC (reference Primary Stage III); PELRAD - Prior external pelvic radiotherapy (reference No); ECOG - Baseline ECOG performance (reference 1=Ambulatory); GL - Geographic location (reference North America); Cmin - Minimum concentration after first dose, day 21.

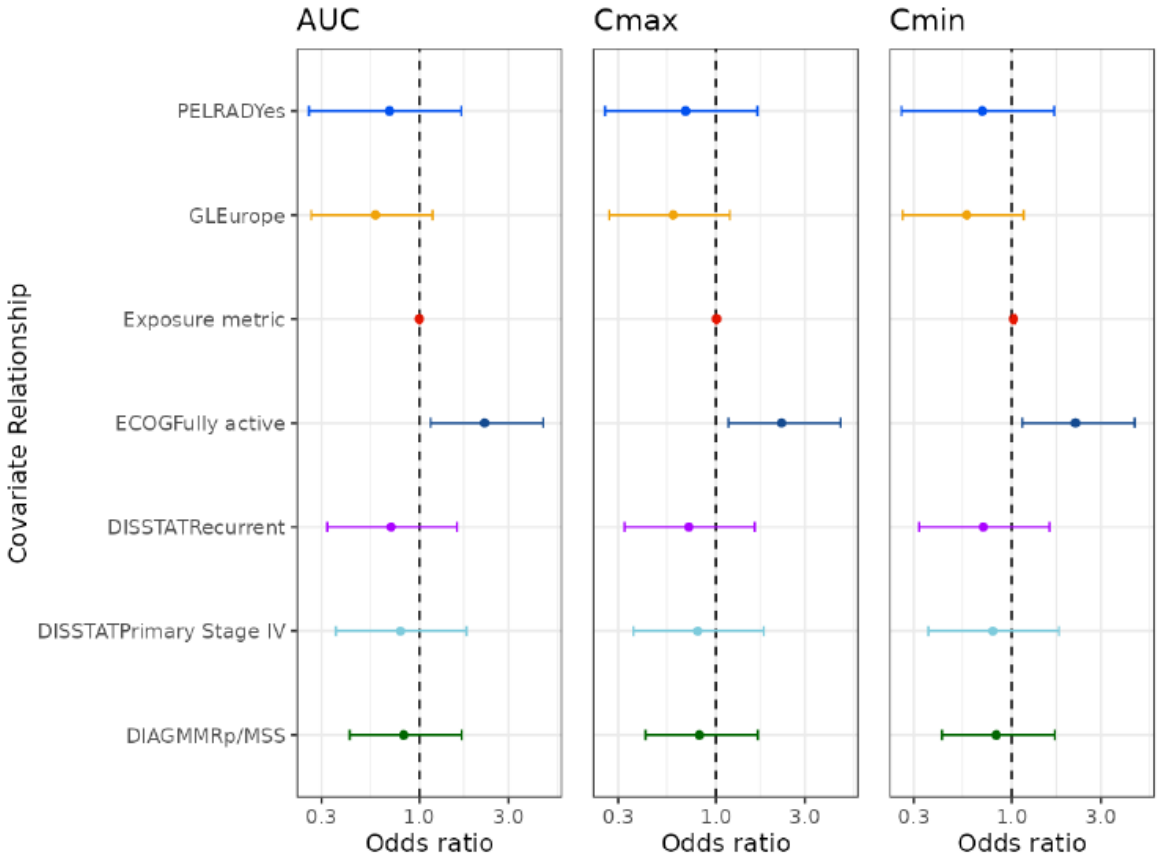
Table 11: Odds Ratio Multivariate Analysis, Arthralgia, Cycle 7 and Beyond, Dostarlimab Treated, Cmin

Covariate	Odds Ratio	95% CI of Odds Ratio	p-value
Exposure metric	1.05	1.01-1.1	0.0294
DIAGMMRp/MSS	0.265	0.104-0.68	0.005
DISSTATPrimary Stage IV	1.25	0.333-5.35	0.745
DISSTATRecurrent	1.34	0.381-5.55	0.658
PELRADYes	0.564	0.115-2.1	0.426
ECOGFully active	1.45	0.551-4.14	0.468
GLEurope	0.988	0.348-2.59	0.982

DIAG - Tumor diagnosis (reference dMMR/MSI-H); DISSTAT - Disease status in EC (reference Primary Stage III); PELRAD - Prior external pelvic radiotherapy (reference No); ECOG - Baseline ECOG performance (reference 1=Ambulatory); GL - Geographic location (reference North America); Cmin - Minimum concentration after first dose, day 21.

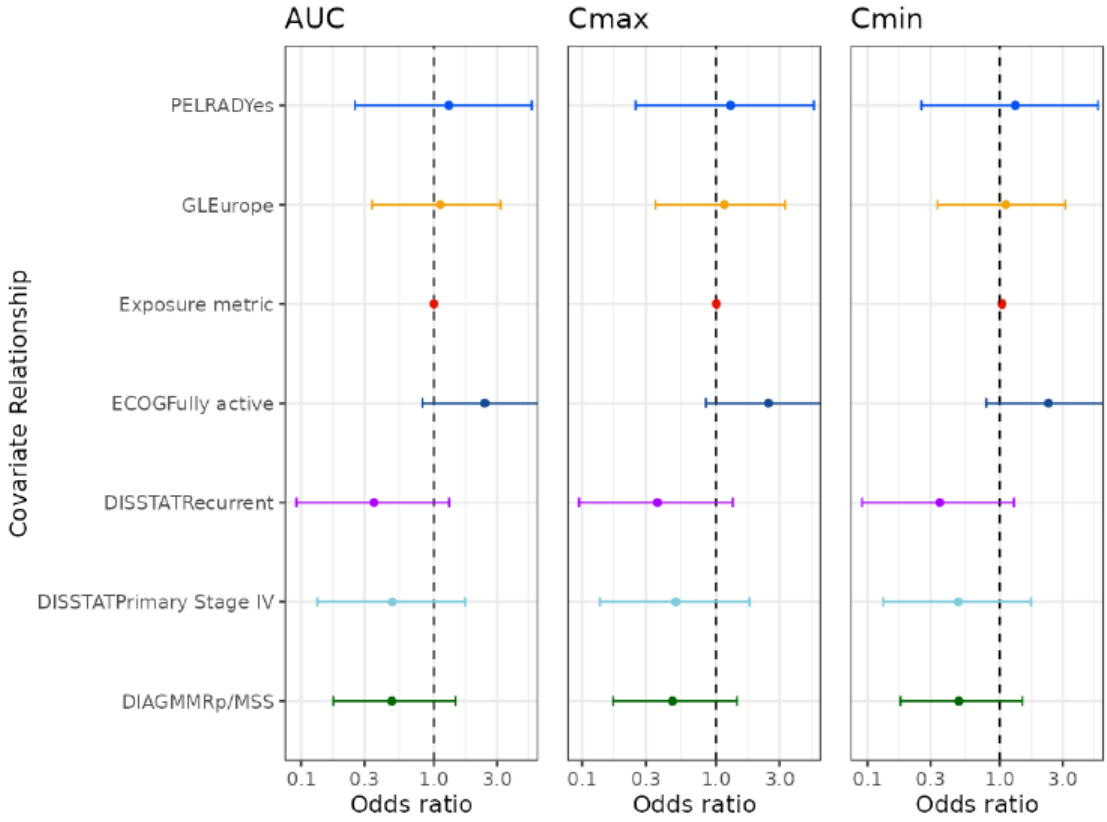
The odds ratios of the tested covariates for rash for all patients in period cycle 1-6, cycle 7 and beyond and all cycles can be seen in the figures and tables included below.

Figure 11: Odds Ratio Multivariate Analysis, Rash, Cycle 1-6, All Patients



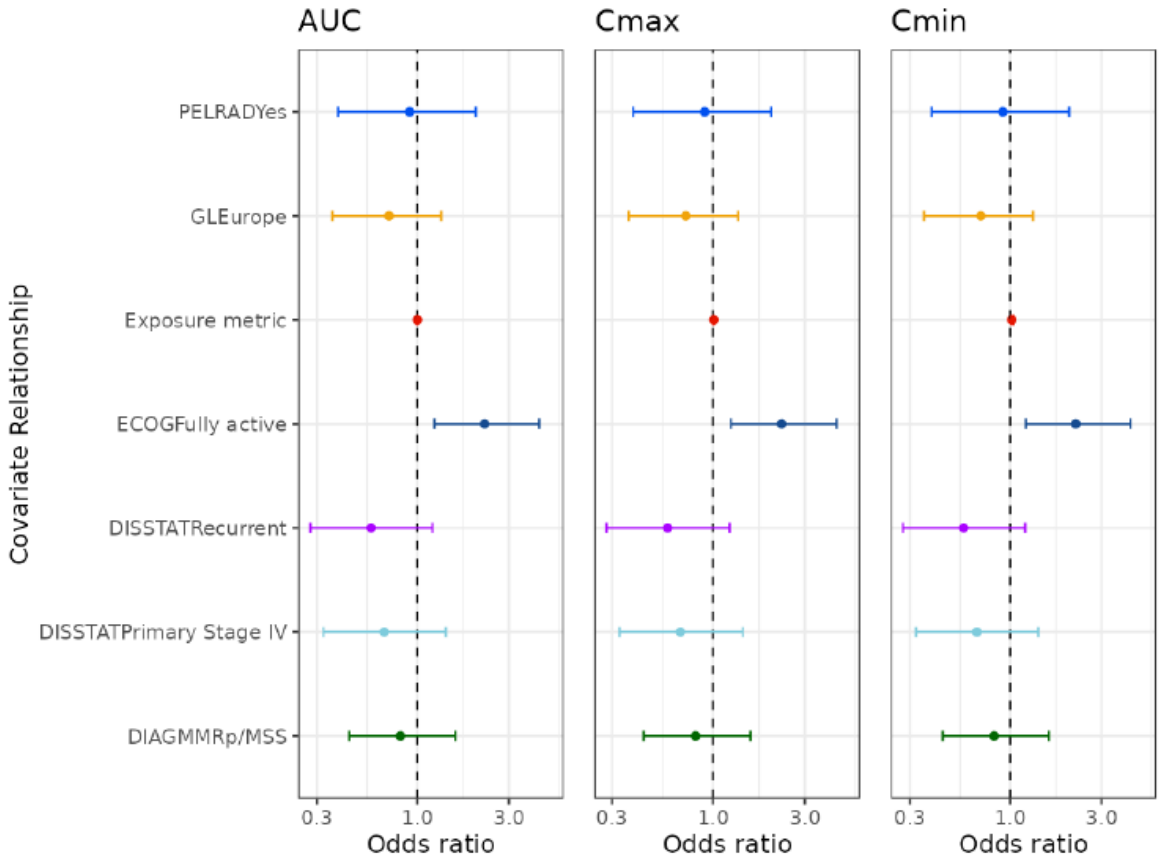
Circles: Odds ratio; **Lines:** 95% confidence interval; PELRAD - Prior external pelvic radiotherapy (reference No); GL - Geographic location (reference North America); ECOG - Baseline ECOG performance (reference Ambulatory (ECOG=1)); DISSTAT - Disease status in EC (reference Primary Stage III); DIAG - Tumor diagnosis (reference dMMR/MSI-H); **AUC**: Area under the curve during the first 21 days; **Cmax**: Maximum concentration during the first 21 days; **Cmin**: Minimum concentration at Day 21.

Figure 12: Odds Ratio Multivariate Analysis, Rash, Cycle 7 and Beyond, All Patients



Circles: Odds ratio; **Lines:** 95% confidence interval; PELRAD - Prior external pelvic radiotherapy (reference No); GL - Geographic location (reference North America); ECOG - Baseline ECOG performance (reference Ambulatory (ECOG=1)); DISSTAT - Disease status in EC (reference Primary Stage III); DIAG - Tumor diagnosis (reference dMMR/MSI-H); **AUC**: Area under the curve during the first 21 days; **Cmax**: Maximum concentration during the first 21 days; **Cmin**: Minimum concentration at Day 21.

Figure 13: Odds Ratio Multivariate Analysis, Rash, All Cycles, All Patients



Circles: Odds ratio; **Lines:** 95% confidence interval; PELRAD - Prior external pelvic radiotherapy (reference No); GL - Geographic location (reference North America); ECOG - Baseline ECOG performance (reference Ambulatory (ECOG=1)); DISSTAT - Disease status in EC (reference Primary Stage III); DIAG - Tumor diagnosis (reference dMMR/MSI-H); **AUC**: Area under the curve during the first 21 days; **Cmax**: Maximum concentration during the first 21 days; **Cmin**: Minimum concentration at Day 21.

Table 12: Odds Ratio Multivariate Analysis, Rash, Cycle 1-6, All Patients, AUC

Covariate	Odds Ratio	95% CI of Odds Ratio	p-value
Exposure metric	1	1-1	0.0002
DIAGMMRp/MSS	0.818	0.442-1.58	0.533
DISSTATPrimary Stage IV	0.672	0.324-1.41	0.287
DISSTATRecurrent	0.575	0.277-1.2	0.138
PELRADYes	0.912	0.387-2.02	0.824
ECOGFully active	2.24	1.23-4.32	0.0114
GLEurope	0.712	0.36-1.33	0.306

DIAG - Tumor diagnosis (reference dMMR/MSI-H); DISSTAT - Disease status in EC (reference Primary Stage III); PELRAD - Prior external pelvic radiotherapy (reference No); ECOG - Baseline ECOG performance (reference 1=Ambulatory); GL - Geographic location (reference North America); AUC - Area under the concentration versus time curve during first 21 days.

Table 13: Odds Ratio Multivariate Analysis, Rash, Cycle 1-6, All Patients, Cmax

Covariate	Odds Ratio	95% CI of Odds Ratio	p-value
Exposure metric	1.01	1-1.01	0.0002
DIAGMMRp/MSS	0.811	0.438-1.56	0.515
DISSTATPrimary Stage IV	0.679	0.327-1.43	0.301
DISSTATRecurrent	0.582	0.281-1.22	0.147
PELRADYes	0.906	0.385-2	0.813
ECOGFully active	2.27	1.24-4.37	0.0103
GLEurope	0.723	0.366-1.35	0.328

DIAG - Tumor diagnosis (reference dMMR/MSI-H); DISSTAT - Disease status in EC (reference Primary Stage III); PELRAD - Prior external pelvic radiotherapy (reference No); ECOG - Baseline ECOG performance (reference 1=Ambulatory); GL - Geographic location (reference North America); Cmax - maximum concentration during first 21 days.

Table 14: Odds Ratio Multivariate Analysis, Rash, Cycle 1-6, All Patients, Cmin

Covariate	Odds Ratio	95% CI of Odds Ratio	p-value
Exposure metric	1.02	1.01-1.04	0.0002
DIAGMMRp/MSS	0.824	0.446-1.59	0.549
DISSTATPrimary Stage IV	0.671	0.323-1.4	0.284
DISSTATRecurrent	0.572	0.276-1.2	0.135
PELRADYes	0.916	0.389-2.03	0.833
ECOGFully active	2.2	1.21-4.24	0.0133
GLEurope	0.704	0.356-1.32	0.291

DIAG - Tumor diagnosis (reference dMMR/MSI-H); DISSTAT - Disease status in EC (reference Primary Stage III); PELRAD - Prior external pelvic radiotherapy (reference No); ECOG - Baseline ECOG performance (reference 1=Ambulatory); GL - Geographic location (reference North America); Cmin - Minimum concentration after first dose, day 21.

Table 15: Odds Ratio Multivariate Analysis, Rash, Cycle 7 and Beyond, All Patients, AUC

Covariate	Odds Ratio	95% CI of Odds Ratio	p-value
Exposure metric	1	1-1	0.0002
DIAGMMRp/MSS	0.818	0.442-1.58	0.533
DISSTATPrimary Stage IV	0.672	0.324-1.41	0.287
DISSTATRecurrent	0.575	0.277-1.2	0.138
PELRADYes	0.912	0.387-2.02	0.824
ECOGFully active	2.24	1.23-4.32	0.0114
GLEurope	0.712	0.36-1.33	0.306

DIAG - Tumor diagnosis (reference dMMR/MSI-H); DISSTAT - Disease status in EC (reference Primary Stage III); PELRAD - Prior external pelvic radiotherapy (reference No); ECOG - Baseline ECOG performance (reference 1=Ambulatory); GL - Geographic location (reference North America); AUC - Area under the concentration versus time curve during first 21 days.

Table 16: Odds Ratio Multivariate Analysis, Rash, Cycle 7 and Beyond, All Patients, Cmax

Covariate	Odds Ratio	95% CI of Odds Ratio	p-value
Exposure metric	1.01	1-1.01	0.0002
DIAGMMRp/MSS	0.811	0.438-1.56	0.515
DISSTATPrimary Stage IV	0.679	0.327-1.43	0.301
DISSTATRecurrent	0.582	0.281-1.22	0.147
PELRADYes	0.906	0.385-2	0.813
ECOGFully active	2.27	1.24-4.37	0.0103
GLEurope	0.723	0.366-1.35	0.328

DIAG - Tumor diagnosis (reference dMMR/MSI-H); DISSTAT - Disease status in EC (reference Primary Stage III); PELRAD - Prior external pelvic radiotherapy (reference No); ECOG - Baseline ECOG performance (reference 1=Ambulatory); GL - Geographic location (reference North America); Cmax - maximum concentration during first 21 days.

Table 17: Odds Ratio Multivariate Analysis, Rash, Cycle 7 and Beyond, All Patients, Cmin

Covariate	Odds Ratio	95% CI of Odds Ratio	p-value
Exposure metric	1.02	1.01-1.04	0.0002
DIAGMMRp/MSS	0.824	0.446-1.59	0.549
DISSTATPrimary Stage IV	0.671	0.323-1.4	0.284
DISSTATRecurrent	0.572	0.276-1.2	0.135
PELRADYes	0.916	0.389-2.03	0.833
ECOGFully active	2.2	1.21-4.24	0.0133
GLEurope	0.704	0.356-1.32	0.291

DIAG - Tumor diagnosis (reference dMMR/MSI-H); DISSTAT - Disease status in EC (reference Primary Stage III); PELRAD - Prior external pelvic radiotherapy (reference No); ECOG - Baseline ECOG performance (reference 1=Ambulatory); GL - Geographic location (reference North America); Cmin - Minimum concentration after first dose, day 21.

Table 18: Odds Ratio Multivariate Analysis, Rash, all Cycles, All Patients, AUC

Covariate	Odds Ratio	95% CI of Odds Ratio	p-value
Exposure metric	1	1-1	0.0002
DIAGMMRp/MSS	0.818	0.442-1.58	0.533
DISSTATPrimary Stage IV	0.672	0.324-1.41	0.287
DISSTATRecurrent	0.575	0.277-1.2	0.138
PELRADYes	0.912	0.387-2.02	0.824
ECOGFully active	2.24	1.23-4.32	0.0114
GLEurope	0.712	0.36-1.33	0.306

DIAG - Tumor diagnosis (reference dMMR/MSI-H); DISSTAT - Disease status in EC (reference Primary Stage III); PELRAD - Prior external pelvic radiotherapy (reference No); ECOG - Baseline ECOG performance (reference 1=Ambulatory); GL - Geographic location (reference North America); AUC - Area under the concentration versus time curve during first 21 days.

Table 19: Odds Ratio Multivariate Analysis, Rash, all Cycles, All Patients, Cmax

Covariate	Odds Ratio	95% CI of Odds Ratio	p-value
Exposure metric	1.01	1-1.01	0.0002
DIAGMMRp/MSS	0.811	0.438-1.56	0.515
DISSTATPrimary Stage IV	0.679	0.327-1.43	0.301
DISSTATRecurrent	0.582	0.281-1.22	0.147
PELRADYes	0.906	0.385-2	0.813
ECOGFully active	2.27	1.24-4.37	0.0103
GLEurope	0.723	0.366-1.35	0.328

DIAG - Tumor diagnosis (reference dMMR/MSI-H); DISSTAT - Disease status in EC (reference Primary Stage III); PELRAD - Prior external pelvic radiotherapy (reference No); ECOG - Baseline ECOG performance (reference 1=Ambulatory); GL - Geographic location (reference North America); Cmax - maximum concentration during first 21 days.

Table 20: Odds Ratio Multivariate Analysis, Rash, all Cycles, All Patients, Cmin

Covariate	Odds Ratio	95% CI of Odds Ratio	p-value
Exposure metric	1.02	1.01-1.04	0.0002
DIAGMMRp/MSS	0.824	0.446-1.59	0.549
DISSTATPrimary Stage IV	0.671	0.323-1.4	0.284
DISSTATRecurrent	0.572	0.276-1.2	0.135
PELRADYes	0.916	0.389-2.03	0.833
ECOGFully active	2.2	1.21-4.24	0.0133
GLEurope	0.704	0.356-1.32	0.291

DIAG - Tumor diagnosis (reference dMMR/MSI-H); DISSTAT - Disease status in EC (reference Primary Stage III); PELRAD - Prior external pelvic radiotherapy (reference No); ECOG - Baseline ECOG performance (reference 1=Ambulatory); GL - Geographic location (reference North America); Cmin - Minimum concentration after first dose, day 21.

Table 21 compares the increase in probability for the 10th percentile vs the 90th percentile of the predicted cycle 1 exposures. Going from the 10th percentile to the 90th percentile gives an increase in

the probability of arthralgia by 4.3 and 6.5 % for AUC and Cmin respectively for all patients and 17.7 % for Cmin for only dostarlimab treated patients. The probability increase for rash for all patients was between 5.6 and 10.4 % depending on exposure metric and time period.

Table 21: Probability Increase for Exposure Metrics 90th vs 10th Percentile

TEAE	Period	Subset	Exposure	P 10th perc (%)	P 90th perc (%)	Increase P (%)
Arthralgia	Cycle 7 and beyond	All patients	AUC	11.5	15.8	4.3
Arthralgia	Cycle 7 and beyond	All patients	Cmin	11	17.5	6.5
Arthralgia	Cycle 7 and beyond	Dostarlimab treated	Cmin	8.6	26.3	17.7
Rash	Cycle 1-6	All patients	AUC	13.2	18.9	5.7
Rash	Cycle 7 and beyond	All patients	AUC	7.1	14.1	7
Rash	All cycles	All patients	AUC	17.3	24.9	7.6
Rash	Cycle 1-6	All patients	Cmax	13.1	18.7	5.6
Rash	Cycle 7 and beyond	All patients	Cmax	7	13.6	6.6
Rash	All cycles	All patients	Cmax	17.2	24.7	7.5
Rash	Cycle 1-6	All patients	Cmin	12.4	20.5	8.1
Rash	Cycle 7 and beyond	All patients	Cmin	6.3	15.5	9.2
Rash	All cycles	All patients	Cmin	16.2	26.6	10.4

AUC: Area under the curve during the first 21 days; **Cmax**: Maximum concentration during the first 21 days; **Cmin**: Minimum concentration at Day 21; **Perc**: Percentile; **P**: Probability; **TEAE**: Treatment-emergent adverse event, dostarlimab-related.

2.3.1. Discussion on clinical pharmacology

The proposed posology of 500 mg of dostarlimab Q3W in combination with carboplatin and paclitaxel Q3W for 6 cycles followed by 1000 mg of dostarlimab as monotherapy Q6W is the already approved posology for patients with dMMR/ MSI H primary advanced or recurrent EC and who are candidates for systemic therapy (EMEA/H/C/005204/II/0023).

Based on results from the RUBY IA2, an update of the exposure-response analysis has been provided.

The exposure-efficacy analysis was performed with data from 232 subjects in the dostarlimab plus SOC arm from the RUBY study. The primary endpoint OS was used as the efficacy outcome and as exposure metric the predicted cycle 1 Cmin, Cmax and AUC using the current Population PK model.

The results from the Kaplan-Meier stratified by exposure quartiles indicate that OS seems to be independent of exposure (high degree of overlapping). Cox regression was performed with the additional tumour diagnosis, covariates disease status in EC, prior external pelvic radiotherapy, baseline ECOG performance, histology and geographic location. None of the texted exposure metrics had a statistically significant relationship with OS. However, as previously suggested (EMEA/H/C/005204/II/0023) the range of exposure evaluated is too limited to be able to identify differences on the efficacy endpoints, since the accumulated dose in the study arm is equivalent throughout the study (500 mg Q3W vs 1000 mg Q6W). In the absence of an informative exposure-efficacy study, with dose levels or regimens that allow for a greater range of exposure, it can only be concluded that the exposure-efficacy relationship in the present analysis is flat at the proposed dosing regimen. However, these results cannot be extrapolated to other dosage regimens or dose levels other than those evaluated, for which it will be necessary to have additional experimental information. Tumour diagnosis (MMRp/MSS) was identified as a statistically significant covariate for OS, suggesting a 2.8 times probability of death in the dMMRp/MSS vs dMMR/MSI-H population. Despite the large impact observed in OS for each sub-population of tumour diagnosis, a 0.79 HR was predicted in the dMMRp/MSS population when receiving dostarlimab +SoC (n=183) vs placebo + SoC (n=181).

The exposure-safety analysis was conducted with the five most prevalent drug-related adverse events (arthralgia, diarrhoea, fatigue, nausea and rash) from 478 patients (232 from the dostarlimab arm and

246 from the placebo arm). The analysis was performed based on the following 3 periods, cycles 1 thorough 6, cycle 7 and beyond and all cycles. Cycle 1 exposure (AUC, Cmax and Cmin) was used as the exposure metric valid for the 3 periods studied.

Univariate analysis revealed a significant relationship for rash for all exposure metrics in all periods when all patients were included and for arthralgia for Cmin and AUC in period cycle 7 and beyond when all patients were included in the analysis and when excluding the placebo arm, the significant relationship was not observed for AUC. No other significant relationships were observed. Subsequently, a multivariate analysis was carried out with these dostarlimab-related TEAEs and time periods. The exposure metrics were still significant. However, the increase in probability for the 10th percentile vs the 90th percentile of the predicted exposures indicates a rather flat exposure response relationship. The five most prevalent dostarlimab-related TEAEs as assessed by investigators (fatigue, nausea, rash, diarrhoea, and arthralgia) at IA2 were the same as the five most prevalent dostarlimab related TEAE at IA1 with similar prevalence. Overall, a slightly higher probability of rash and arthralgia is observed in patients receiving dostarlimab vs only SoC, although the probabilities are in general lower than 25% at the highest exposure range.

No changes to the SmPC based on clinical pharmacology data, have been introduced which is endorsed.

2.3.2. Conclusions on clinical pharmacology

The clinical pharmacology properties of dostarlimab in combination with platinum-containing chemotherapy for the treatment of adult patients with primary advanced or recurrent EC and who are candidates for systemic therapy, based on results from study 213361 (RUBY) Part 1 have been adequately characterized with a previously developed population PK model, with the identification of significant covariates as predictors of PK properties, evaluation of exposure-response relationships with efficacy and safety endpoints in participants, and concentration-QTc analysis. The immunogenicity risk and incidence of ADAs and NAbs was also previously assessed and reported. Results from the RUBY IA2 analysis included an updated exposure-OS and exposure-safety data for the overall population.

2.4. Clinical efficacy

2.4.1. Dose response studies

No dose-response studies were submitted as part of this application.

2.4.2. Main study

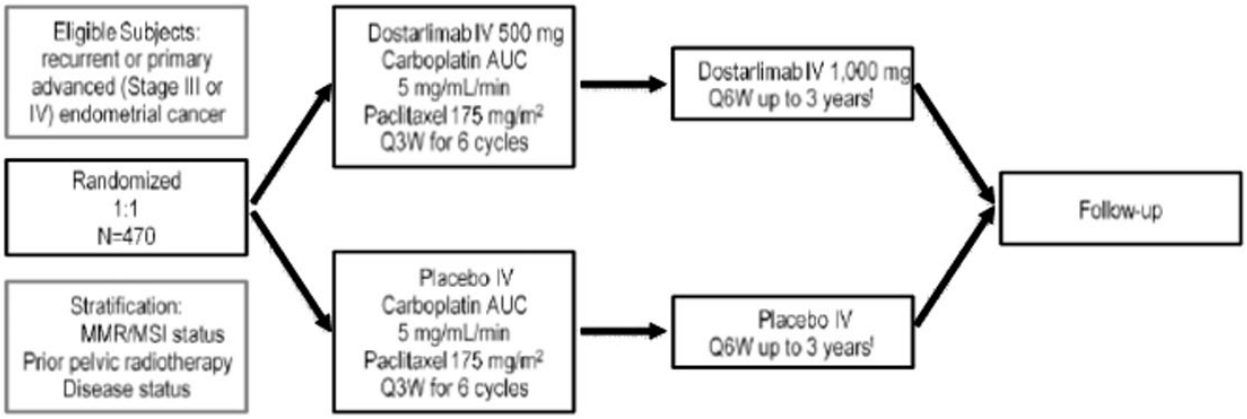
Study RUBY: A Phase 3, Randomized, Double-blind, Multicenter Study of Dostarlimab (TSR-042) plus Carboplatin-paclitaxel versus Placebo plus Carboplatin-paclitaxel in Patients with Recurrent or Primary Advanced Endometrial Cancer

Methods

RUBY is a Phase 3, randomized, double-blind, multicenter study consisting of 2 parts. Part 1 of the study is to evaluate the efficacy and safety of treatment with dostarlimab (500 mg IV every 3 weeks – 6 cycles) plus carboplatin-paclitaxel followed by dostarlimab (1000 mg IV every 6 weeks; up to 3 years) versus treatment with placebo plus carboplatin-paclitaxel followed by placebo in participants with primary advanced (Stage III or IV) or recurrent endometrial cancer (EC). Part 2 is to evaluate the efficacy and safety of treatment with dostarlimab plus carboplatin-paclitaxel followed by dostarlimab plus niraparib versus treatment with placebo plus carboplatin-paclitaxel followed by placebo in patients with primary advanced (Stage III or IV) or recurrent endometrial cancer (EC).

Only Part 1 of this study is assessed in this procedure. It should also be noted that RUBY Part 1 (results of IA1) was already assessed as part of procedure EMEA/H/C/005204/II/0023 and supported the authorisation of dostarlimab in the dMMR/MSI-h population (7 Dec 2023).

Figure 14. Study 213361 (RUBY) Part 1 design



Abbreviations: AUC=area under the plasma or serum concentration-time curve; IV=intravenous; MMR=mismatch repair of DNA; MSI=microsatellite instability; QxW=every x weeks.
[1] Treatment ends after 3 years, progression of disease, toxicity, withdrawal of consent, Investigator's decision, or death, whichever occurs first. Continued treatment with dostarlimab or placebo IV beyond 3 years may be considered following discussion between the sponsor and the Investigator.

Study participants

Inclusion criteria

Participants were eligible to be included in Part 1 of the study, only if all criteria applied.

Key inclusion criteria are listed below:

1. Female participant is at least 18 years of age, able to understand the study procedures, and agrees to participate in the study by providing written informed consent.
2. Participant has histologically or cytologically proven EC with advanced or recurrent disease.
3. Participant must provide adequate tumour tissue sample at screening for MMR/MSI status testing. Note: The quality of the tumour tissue sample must be confirmed by the central laboratory during screening. Participants should not be randomized without central laboratory confirmation.
4. Participant must have primary Stage III or Stage IV disease or first recurrent EC, with a low potential for cure by radiation therapy or surgery alone or in combination, and meet at least 1 of the following criteria:
    a. Participant has primary Stage IIIA to IIIC1 disease with presence of evaluable or measurable disease per RECIST v.1.1 based on Investigator's assessment. Lesions that are equivocal or can be representative of post-operative change should be biopsied and confirmed for the presence of tumour.
    b. Participant has primary Stage IIIC1 disease with carcinosarcoma, clear cell, serous, or mixed histology (containing ≥10% carcinosarcoma, clear cell, or serous histology), regardless of presence of evaluable or measurable disease on imaging.

c. Participant has primary Stage IIIC2 or Stage IV disease, regardless of presence of evaluable or measurable disease.

d. Participant has first recurrent disease and is naïve to systemic anticancer therapy.

e. Participant has received prior neoadjuvant/adjuvant systemic anticancer therapy and had a recurrence or PD ≥6 months after completing treatment (first recurrence only).

Note: Participants with uterine sarcoma are not allowed.

5. Participant has an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1.
6. Participant has adequate organ function, as defined in Protocol Section 8.1.

Exclusion criteria

Participants satisfying any of these criteria were not eligible for enrolment in Part 1 of the study. Key exclusion criteria are listed below:

1. Participant has received neoadjuvant/adjuvant systemic anticancer therapy for primary Stage III or IV disease and 1 of the following:

   a. Has not had a recurrence or progressive disease (PD) prior to first dose on the study

OR

   b. Has had a recurrence or PD within 6 months of completing systemic anticancer therapy treatment prior to first dose on the study

   Note: Low-dose cisplatin given as a radiation sensitizer or hormonal therapies do not exclude participants from study participation.

2. Participant has had >1 recurrence of EC.
3. Participant has received prior therapy with an anti-PD-1, anti-PD-L1, or anti-PD-L2 agent.
4. Participant has received prior anticancer therapy (chemotherapy, targeted therapies, hormonal therapy, radiotherapy, or immunotherapy) within 21 days or <5 times the half-life of the most recent therapy prior to Study Day 1, whichever is shorter.

   Note: Palliative radiation therapy to a small field of ≥1 week prior to Day 1 of study intervention may be allowed.

5. Participant has a concomitant malignancy, had a prior non-endometrial invasive malignancy but has been disease free for <3 years, or received any active treatment in the last 3 years for that malignancy. Non-melanoma skin cancer is allowed.
6. Participant has known uncontrolled central nervous system metastases, carcinomatosis meningitis, or both. Note: Participants with previously treated brain metastases may participate provided they are stable (without evidence of PD by imaging [using the identical imaging modality for each assessment, either magnetic resonance imaging {MRI} or computed tomography {CT} scan] for at least 4 weeks prior to the first dose of study intervention and any neurologic symptoms have returned to baseline), have no evidence of new or enlarging brain metastases, and have not been using steroids for at least 7 days prior to study intervention. Carcinomatous meningitis precludes a participant from study participation regardless of clinical stability.
7. Patient has known history of HIV or active hepatitis B or hepatitis C;
8. Patient has immunodeficiency or receiving immunosuppressive therapy within 7 days;

9. Patient is considered a poor medical risk due to a serious, uncontrolled medical disorder, non-malignant systemic disease, or active infection requiring systemic therapy; or receiving a live vaccine within 30 days before first dose of study treatment, during study treatment, and for up to 180 days after receiving the last dose of study treatment.

Treatments

The study interventions used in Part 1 are presented in the following table:

Table 22. Part 1 study intervention

Product name	Dostarlimab	Placebo IV	Carboplatin	Paclitaxel
Dosage form	Infusion	Infusion	Infusion	Infusion
Unit dose	500 mg Q3W (Cycles 1 to 6) and 1000 mg Q6W (Cycle 7 and thereafter)	Q3W (Cycles 1 to 6) and Q6W (Cycle 7 and thereafter)	AUC 5 mg•mL/min Q3W (Cycles 1 to 6 only)	175 mg/m^2 Q3W (Cycles 1 to 6 only)
Route of administration	IV	IV	IV	IV
Physical description	Solution for IV infusion in single-use vial	Solution for IV infusion	Solution for IV infusion	Solution for IV infusion
Source	Sponsor/designee	Locally supplied	Locally supplied or sponsor/designee	Locally supplied or sponsor/designee

Abbreviations: AUC=area under the plasma or serum concentration-time curve; IV=intravenous; Q3W=every three weeks; Q6W=every six weeks.

Objectives

Primary Objective

The dual primary objectives of Part 1 of the RUBY study were:

- To compare the progression-free survival (PFS) of participants treated with dostarlimab plus carboplatin-paclitaxel followed by dostarlimab to participants administered placebo plus carboplatin-paclitaxel followed by placebo, as assessed by the Investigator per Response Evaluation Criteria in Solid Tumours version 1.1 (RECIST v.1.1) in the following:
  - Participants with dMMR/MSI-H primary advanced or recurrent EC
  - All participants with primary advanced or recurrent EC
- To compare the overall survival (OS) of participants treated with dostarlimab plus carboplatin-paclitaxel followed by dostarlimab to participants administered placebo plus carboplatin-paclitaxel followed by placebo.
  - All participants with primary advanced or recurrent EC.

Secondary Objectives

The secondary objectives of Part 1 of the RUBY study were:

- To evaluate the following measures of clinical benefit of treatment with dostarlimab plus carboplatin-paclitaxel followed by dostarlimab to treatment with placebo plus carboplatin-paclitaxel followed by placebo in dMMR/MSI-H and all participants with primary advanced or recurrent EC:
  - PFS based on blinded independent central review (BICR) assessment

- ORR based on BICR and Investigator assessment
- DOR based on BICR and Investigator assessment
- DCR based on BICR and Investigator assessment
- Patient-reported outcomes (PROs): European Quality of Life scale, 5-Dimensions, 5-Levels (EQ5D-5L) and European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaires (C30 [Core; QLQ-C30] and Endometrial Cancer Module [QLQ-EN24])
- Progression-free survival 2 (PFS2). PFS2 was defined as the time from treatment randomization to the date of assessment of progression on the first subsequent anticancer therapy following study intervention or death by any cause, whichever is earlier.

- To evaluate the safety and tolerability of dostarlimab plus carboplatin-paclitaxel followed by dostarlimab compared to placebo plus carboplatin-paclitaxel followed by placebo (all comers).
- To assess the pharmacokinetics (PK) and immunogenicity of dostarlimab when given in combination with carboplatin and paclitaxel (all comers).

Outcomes/endpoints

The dual primary efficacy endpoints were PFS by investigator assessment per RECIST v1.1 and OS.

The primary efficacy endpoint of PFS is based on investigator assessment using RECIST v1.1, defined as the time from the date of randomization to the earliest date of radiographic assessment of PD or death by any cause in the absence of PD, whichever occurs first. PFS was assessed in both in the dMMR/MSI-H and overall populations of participants with primary advanced or recurrent EC.

The primary efficacy endpoint of OS is defined as the time from randomization to the date of death by any cause. This primary endpoint was assessed only in the overall population.

Secondary efficacy endpoints included the following:

- PFS based on BICR, defined as the time from randomization to the earliest date of assessment of PD per RECIST v1.1 or death by any cause in the absence of PD per RECIST v1.1, whichever occurs first
- ORR based on BICR and Investigator assessment, defined as the proportion of subjects with a best overall response (BOR) of complete response (CR) or partial response (PR)
- DOR based on BICR and investigator assessment, defined as the time from the first documentation of CR or PR until the time of the first documentation of subsequent PD per RECIST v1.1 or death by any cause in the absence of PD per RECIST v1.1, whichever occurs first
- DCR based on BICR and investigator assessment, defined as the proportion of participants who have achieved a BOR of CR, PR, SD, non-CR/non-PD, or no disease per RECIST v1.1
- PFS2, defined as the time from treatment randomization to the date of assessment of progression on the first subsequent anticancer therapy following study intervention or death by any cause, whichever is earlier
- PRO assessment of treatment using EQ-5D-5L, EORTC QLQ-C30, and EORTC QLQ-EN24
- PK and immunogenicity of dostarlimab All secondary endpoints were evaluated in the overall and dMMR/MSI-H populations of participants with primary advanced or recurrent EC.

All secondary endpoints were evaluated in the overall and dMMR/MSI-H populations of participants with primary advanced or recurrent EC.

Table 23. Overview of planned analyses for secondary efficacy endpoints

Endpoint	Analysis	Analysis Set/Subset/Cohorts for the Planned Analyses
PFS based on BICR assessment	Stratified log-rank test/ stratified Cox model/KM estimate, Analyzed using the same censoring rule for primary analysis of PFS	Summarized for dMMR/MSI-H subset of ITT, ITT
ORR based on investigator assessment	Summarize number and percentage (95% CI)	Summarized for: (1) participants who had target or non-target lesions at baseline and (2) participants who had target lesions at baseline in the dMMR/MSI-H subset of ITT, MMRp/MSS subset of ITT, ITT
ORR based on BICR assessment	Summarize number and percentage (95% CI)	Summarized for: (1) participants who had target or non-target lesions at baseline and (2) participants who had target lesions at baseline in the dMMR/MSI-H subset of ITT, ITT
DCR based on investigator assessment	Summarize number and percentage (95% CI)	Summarized for: (1) participants who had target or non-target lesions at baseline (2) participants who had target lesions at baseline and (3) all participants in the dMMR/MSI-H subset of ITT, ITT; Summarized for: (1) participants who had target or non-target lesions at baseline and (2) participants who had target lesions at baseline in the MMRp/MSS subset of ITT
DCR based on BICR assessment	Summarize number and percentage (95% CI)	Summarized for (1) participants who had target or non-target lesions at baseline (2) participants who had target lesions at baseline and (3) all participants in the dMMR/MSI-H subset of ITT, ITT
DoR based on both BICR and investigator assessment	KM estimate Using the same censoring rule for primary analysis of PFS	Summarized for dMMR/MSI-H subset of ITT, ITT
PFS2	KM estimate	Summarized for dMMR/MSI-H subset of ITT, ITT

Abbreviations: BICR=blinded independent central review; DCR=disease control rate; dMMR=mismatch repair deficient; DoR=duration of response; KM=Kaplan-Meier; MSI-H=microsatellite instability-high; ORR=objective response rate; PFS=progression-free survival; PFS2=progression-free survival 2.

Sample size

The sample size calculation was driven by the primary efficacy endpoint of PFS, as assessed by the Investigator using RECIST v.1.1. The following assumptions were made for the sample size calculation:

- dMMR/MSI Status Independent Participant Population (all-comers): HR of 0.67, corresponding to an increase in median PFS from 10 months in the placebo plus carboplatin-paclitaxel arm to 15 months in the dostarlimab plus carboplatin-paclitaxel arm
- dMMR/MSI-H Participant Population: HR of 0.50, corresponding to an increase in median PFS from 10 months in the placebo plus carboplatin-paclitaxel arm to 20 months in the dostarlimab plus carboplatin-paclitaxel arm
- Participant distribution by tumour MMR/MSI status: 25% with dMMR/MSI-H and 75% with MMRp/MSS
- 1:1 randomization
- Alpha=0.02 (1-sided)
- Power=approximately 89% for testing of H1
- Accrual over a period of 22 months
- Assuming an annual dropout rate of 5%

- Exponential distribution of PFS.

With the assumptions above, and a group sequential log-rank test design with 2 analyses planned: 1 IA at approximately 84.6% information and 1 FA, based on a Lan-DeMets (O'Brien-Fleming) alpha spending function [Lan, 1983], a total sample size of 470 participants was planned, and approximately 118 participants were expected to be dMMR/MSI-H. To maintain the natural distribution of dMMR/MSI-H (25%) and MMRp/MSS (75%) participants in the overall EC population in this study, the number of participants enrolled with dMMR/MSI-H or MMRp/MSS EC would be capped at approximately 120 or 350, respectively. In addition, the total number of participants with carcinosarcoma was capped at 50 (approximately 10%) to prevent overrepresentation of this patient population.

Randomisation

Subjects who met the inclusion and exclusion criteria were randomized in a 1:1 ratio to receive either dostarlimab plus chemotherapy (carboplatin-paclitaxel) or placebo plus chemotherapy (carboplatin-paclitaxel).

Randomization was completed in a blinded manner using an interactive web response system. Randomization was stratified by 3 stratification factors:

- MMR/MSI status: Determined by local IHC, PCR, or next-generation sequencing test, or by central IHC testing when local testing was not available. The MMR/MSI status for randomization was derived from the data entered at the time of randomization.
- Prior external pelvic radiotherapy (yes or no): Determined from radiation therapy history provided by investigators at the time of randomization.
- Disease status (recurrent, primary Stage III, or primary Stage IV): Derived from the cancer history and disease stage provided by investigators at the time of randomization. Data provided for the most recent FIGO stage and recurrence status were used to assign the participant to the appropriate stratum. If recurrence was selected, participants were assigned to recurrent strata. If no recurrence was selected, then participants were assigned to primary Stage III or primary Stage IV based on most recent FIGO stage.

Blinding (masking)

The participant, investigator, study staff, the sponsor study team, and its representatives were blinded to the assigned treatment from the time of randomization until database lock as described in the protocol.

Treatment assignment could be unblinded by the investigator for urgent or non-urgent clinical reasons as described in the protocol.

Study intervention assignment was available to the investigator upon request for post-study intervention planning.

Statistical methods

The original statistical analysis plan (SAP) was issued on 29 October 2019. The SAP was amended once, and SAP Amendment 1 was issued on 06 October 2022 prior to the unblinding of RUBY Part 1 on 23 November 2022.

Statistical Hypothesis

- Hypothesis 1 (H1): Dostarlimab plus carboplatin-paclitaxel followed by dostarlimab (Arm 1) prolongs PFS per RECIST v.1.1, as assessed by the Investigator, in participants with dMMR/MSI-H primary

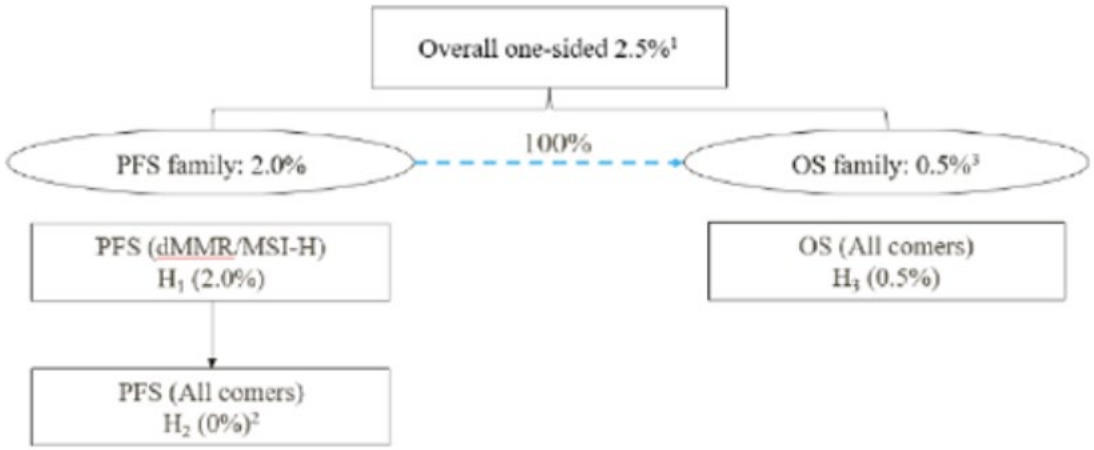
advanced or recurrent EC compared to placebo plus carboplatin-paclitaxel followed by placebo (Arm 2), with null hypothesis H01: $\theta 1 \geq 1$ and alternative hypothesis HA1: $\theta 1 < 1$, where $\theta 1$ is the PFS Hazard Ratio in dMMR/MSI-H population (Arm 1 vs Arm 2).

- Hypothesis 2 (H2): Dostarlimab plus carboplatin-paclitaxel followed by dostarlimab (Arm 1) prolongs PFS per RECIST v.1.1, as assessed by the Investigator, in participants with primary advanced or recurrent EC compared to placebo plus carboplatin-paclitaxel followed by placebo (Arm 2), with null hypothesis H02: $\theta 2 \geq 1$ and alternative hypothesis HA2: $\theta 2 < 1$, where $\theta 2$ is the PFS Hazard Ratio in all-comers (Arm 1 vs Arm 2).
- Hypothesis 3 (H3): Dostarlimab plus carboplatin-paclitaxel followed by dostarlimab (Arm 1) prolongs OS, in participants with primary advanced or recurrent EC compared to placebo plus carboplatin-paclitaxel followed by placebo (Arm 2), with null hypothesis H03: $\theta 3 \geq 1$ and alternative hypothesis HA3: $\theta 3 < 1$, where $\theta 3$ is the OS Hazard Ratio in all-comers (Arm 1 vs Arm 2).

Multiplicity adjustment

Part 1 of the study used the graphical method [Maurer, 2013] to provide strong multiplicity control for multiple hypotheses as well as interim analyses. The family-wise type I error for this study is strongly controlled at 2.5% (one-sided). The initial one-sided alpha-allocation for PFS and OS is presented graphically in Figure 15. Hypotheses presented as nodes in squares are divided into 2 subfamilies presented in ellipsoids. The weights for re-allocation from each subfamily/hypothesis to the others are represented on the lines connecting hypotheses.

Figure 15. Multiplicity Control Strategy for Comparisons Between Dostarlimab plus Carboplatin - Paclitaxel Followed by Dostarlimab and Placebo plus Carboplatin-Paclitaxel Followed by Placebo



1. The alpha level assigned to a subfamily will be rolled over only if the hypotheses within the subfamily are all significant based on the weight for re-allocation presented on the dashed lines connecting subfamilies. Within each subfamily, the weights for re-allocation from each hypothesis to the others are represented on the solid lines connecting hypotheses.

2. Hypothesis testing for PFS in all-comers will only be performed if null hypothesis of PFS has been rejected in dMMR/MSI-H.

3. Hypothesis testing for OS will start at the time when the hypothesis testing for PFS has completed (i.e. no further hypothesis testing could be performed for PFS), at re-allocated alpha level (2.5%) if both null hypotheses have been rejected for H1 and H2; otherwise, OS will be tested at initial alpha level (0.5%).

Interim analyses

To test hypothesis 1 (H1) (PFS in dMMR/MSI-H), a stratified group sequential log-rank test with one IA and one FA was planned. The IA was planned at approximately 77 events, and the FA was planned at 91 events. The boundary for declaring superiority of Arm 1 over Arm 2 is based on a Lan-DeMets (O'BrienFleming) alpha spending function [Lan, 1983] with overall alpha=0.02, 1-tailed. The IA of PFS in dMMR/MSI-H was based on the data cut-off date of 28 September 2022, when 66 PFS events were observed in the dMMR/MSI-H population. The stopping boundary was adjusted based on the actual observed number of PFS events with a p-value stopping boundary=0.00630.

To test hypothesis 3 (H3) (OS in all-comers), a stratified group sequential log-rank test based on a LanDeMets (O'Brien-Fleming) alpha spending function [Lan, 1983] was planned. Based on the positive testing results of PFS in both the dMMR/MSI-H (H1) and all-comers (H2) populations at the IA of PFS in dMMR/MSI-H population, the alpha level and number of planned analyses for OS followed scenario 1 (i.e. OS was tested at one-sided alpha level of 0.025 with 3 planned IAs and 1 FA at 321 OS events). The first IA of OS was conducted at the same time as the IA of PFS in the dMMR/MSI-H population, when 165 deaths were observed.

The stopping boundary for this first IA of OS was adjusted based on the actual observed number of deaths with a p-value stopping boundary of 0.00177.

The IA to assess superiority was performed by an IDMC.

Table 24. Summary of Timing, Number of Events and Stopping Boundaries at the Planned OS Analyses in All Comers (Part 1)

Endpoint/ Hypothesis/ Scenarios	Population	Analysis	Expected number of events (Information Fraction)/ Expected Time of Analysis (months)[2]	Efficacy Stopping boundary[1]		Cumulative alpha spent	Cumulative power
				p-value	Hazard Ratio		
OS (H_3) S1	All comers	IA1	~170 (~53%) /~ 36	0.00207	0.644	0.00207	0.301
		IA2	221 (~69%) / ~48	0.00627	0.715	0.00691	0.578
		IA3	273 (~85%) / ~64	0.01288	0.763	0.01508	0.781
		FA	321 / 88	0.02009	0.795	0.025	0.889
OS (H_3) S2	All comers	IA1	170 (~53%) / ~36	0.00011	0.568	0.00011	0.091
		IA2	221 (~69%) / ~48	0.00068	0.65	0.00072	0.302
		IA3	273 (~85%) / ~64	0.00211	0.707	0.00234	0.551
		FA	321 / ~88	0.00425	0.745	0.005	0.733
OS (H_3) S3	All comers	IA1	221 (~69%) / ~48	0.00691	0.718	0.00691	0.585
		IA2	273 (~85%) / ~64	0.01304	0.764	0.01508	0.782
		FA	321 / ~88	0.02018	0.795	0.025	0.889
OS (H_3) S4	All comers	IA1	221 (~69%) / ~48	0.00072	0.651	0.00072	0.304
		IA2	273 (~85%) / ~64	0.00211	0.707	0.00234	0.552
		FA	321 / ~88	0.00425	0.745	0.005	0.733

1. Stopping boundaries will be adjusted based on the actual number of events/information fraction observed at the time of analysis
2. Estimate of timing is based on the assumptions in Section 13.2 and the actual timing may vary if the assumptions do not hold

The planned interim analyses were performed after the completion of the following sequential steps:

1. All required database cleaning activities were completed, database release and database freeze were declared by Data Management.

2. All criteria for unblinding the randomization codes/kit numbers were met.

3. Randomization codes/kit Numbers were distributed according to RUBY Study Unblinding Plan for Planned Analyses.

Analyses populations

The analysis sets evaluated in Part 1 of this study are presented in the following table:

Table 25. Analysis Sets

Analysis set	Definition/criteria	Analyses evaluated
Screened	• All participants who were screened for eligibility.	Study population
Enrolled	• All participants who entered the study. • Participants who were randomized by error are included in the Enrolled analysis set. • Note: Screening failures (who never passed screening even if rescreened) and participants screened but never enrolled into the study (met eligibility but not needed) are excluded from the Enrolled analysis set as they did not enter the study.	Study population
ITT	• All participants who were randomized. Participants will be analyzed according to the treatment assigned at randomization even if no study intervention was received. • Participants who were incorrectly stratified at randomization will be analyzed and presented according to the stratum assigned at randomization.	Study population Efficacy PRO
Safety	• All participants who received any amount of study intervention. • Participants will be analyzed according to the treatment received 1.	Safety
PP	• All participants in the ITT analysis set excluding those who did not meet the critical eligibility criteria or discontinued from the study before receiving any dose of assigned treatment. • Critical eligibility criteria: Inclusion criteria 2, 3 and 4; exclusion criteria 1, 2, and 3.	Efficacy The PP analysis set will not be used for analyses if this analysis set comprises more than 90% or less than 60% of the ITT analysis set.
ADA	• All participants who received at least 1 dose of dostarlimab and have provided a pretreatment sample and at least 1 predose blood sample after first treatment. The ADA analysis set is defined as all participants who received at least 1 dose of dostarlimab and who have at least 1 sample with ADA result.	Immunogenicity
PK	• All participants who received at least 1 dose of dostarlimab and provided at least 1 posttreatment PK sample with a measurable concentration.	PK
Biomarker	• All participants in the Safety analysis set who had at least 1 postbaseline tumor assessment and provided sufficient tumor or blood sample for analysis.	Biomarker

Abbreviations: ADA=antidrug antibody; ITT=intent-to-treat; PK=pharmacokinetic; PP=per-protocol; PRO=patient reported outcome.

1. For the Safety analysis set, participants who received any amount of dostarlimab were to be assigned to the active treatment arm (actual); participants who received any amount of any study intervention but did not receive any amount of dostarlimab were to be assigned to the placebo treatment arm (actual)

dMMR/MSI-H and MMRp/MSS Subset of Analysis Set

The dMMR/MSI-H and MMRp/MSS populations were defined as the subset of the analysis set defined above based on the actual MMR/MSI status collected in eCRF (i.e. source verified classifications of dMMR/MSI-H or MMRp/MSS). Unless otherwise specified, all analyses in each of the analysis sets above were performed in the corresponding dMMR/MSI-H subset. Selected analyses were performed in the corresponding MMRp/MSS subset as specified in the statistical analysis plan.

For any analysis of efficacy endpoints (PFS, OS, ORR, DCR, DOR, PFS2) performed on dMMR/MSI-H and MMRp/MSS subset of the ITT analysis set based on source verified MMR/MSI classification collected in eCRF, a paired sensitivity analysis was also performed on dMMR/MSI-H and MMRp/MSS cohorts within the ITT analysis set based on MMR/MSI classification entered for randomization.

Subgroup analyses

The following exploratory subgroup analyses of PFS per Investigator assessment and primary censoring rule and OS (primary endpoints) were performed based on the ITT analysis set and dMMR/MSI-H subset of the ITT analysis set to explore the homogeneity of the treatment effect across relevant participant subsets:

- Age (< 65 years or ≥65 years)
- Race (White or Other)
- Region (North America or Europe or Western Europe or Eastern Europe)
- Histology (Endometrioid carcinoma or Other)
- Disease status at baseline (recurrent, primary Stage III, or primary Stage IV), according to the eCRF (source verified classification)
- MMR/MSI status at baseline (dMMR/MSI-H or MMRp/MSS or dMMR), according to the eCRF (source verified classification)
- Prior external pelvic radiotherapy (yes or no), according to the eCRF (source verified classification)
- Subjects with "No disease" at baseline.

Additional subgroup analyses of PFS per Investigator assessment and primary censoring rule were conducted for participants with target lesions or non-target lesions at baseline and participants who had target lesions at baseline, respectively.

Post-hoc subgroup analyses were also performed in the MMRp/MSS subset, if not prespecified in the SAP Amendment 1.

Sensitivity analyses

Sensitivity analyses for primary endpoint of PFS per Investigator assessment

The following sensitivity analyses for PFS per Investigator assessment were performed (Sensitivity Analysis- to Sensitivity Analysis were planned and performed based on the ITT analysis set, and dMMR/MSI-H subsets of ITT).

- Sensitivity Analysis 1: The potential attrition bias was assessed by using sensitivity analysis censoring rule 1. The stratification factors used in the primary analysis (i.e. stratification factors entered at randomization) were applied in the stratified log-rank test and stratified Cox model. The sensitivity censoring rule 1 was the same as the primary analysis censoring rule except that for subjects who have PD or death, the date of PD was the date of the first assessment at which PD was objectively documented per RECIST v.1.1 or death date, whichever occurred earlier, regardless of whether PD or death was documented after ≥2 missed disease assessments.
- Sensitivity Analysis 2: The potential attrition bias was assessed by using sensitivity analysis censoring rule 2. The stratification factors used in the primary analysis (i.e. stratification factors entered at randomization) were applied in the stratified log-rank test and stratified Cox model. The sensitivity censoring rule 2 was the same as the sensitivity analysis censoring rule 1 except that it considered discontinuation of treatment or initiation of new anticancer therapy, whichever occurred later, to be a PD event for subjects without documented PD or death.
- Sensitivity Analysis 3: The potential impact of ascertainment bias was assessed by sensitivity analysis using the BICR-assessed PFS. The stratification factors (i.e. stratification factors entered at randomization) and censoring rules used in the primary analysis were applied in the stratified logrank test and stratified Cox model. In addition, the distribution of discrepancy in progression assessment between BICR and Investigator was summarized by treatment group.

- Sensitivity Analysis 4: The potential impact of misclassification of randomization stratification factors was assessed by using the source verified values from eCRF as the stratification factors in the stratified log-rank test and stratified cox model in this sensitivity analysis. The censoring rules used in the primary analysis was applied. In addition, the distribution of discrepancy in each stratification factor between the values of stratification factors entered at randomization and the source verified values of stratification factors from eCRF was summarized by treatment group.
- Sensitivity Analysis 5: The Investigator assessment data was planned to be assessed using the per protocol analysis set in this sensitivity analysis. The stratification factors would have been based on the source verified values from eCRF. The censoring rules used in the primary analysis would have been applied. The sensitivity analysis based on per-protocol analysis set was not conducted because the per-protocol analysis set comprised >90% of the ITT analysis set.

Additional sensitivity analyses to the efficacy endpoints

For any analysis of PFS, OS, ORR, DCR, DOR, or PFS2 performed on the dMMR/MSI-H and MMRp/MSS subsets based on the source verified MMR/MSI classification collected in eCRF, a paired sensitivity analysis (post-hoc) was performed on the dMMR/MSI-H and MMRp/MSS subsets based on the MMR/MSI classification entered at randomization.

Results

Participant flow

Figure 16. Participant flow

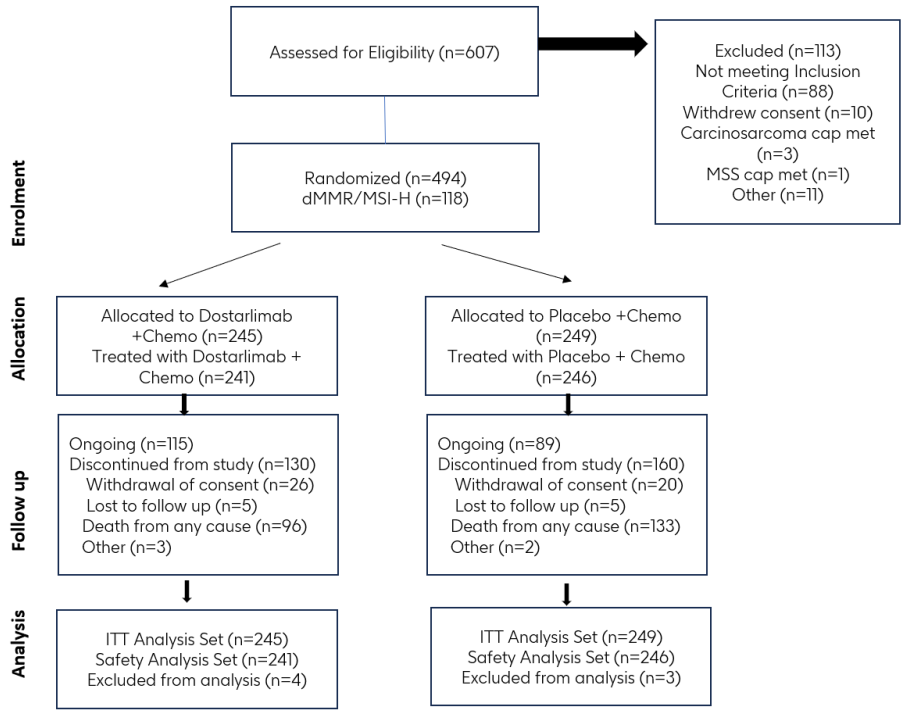


Table 26. Summary of Subject Disposition

	Overall Population		dMMR/MSI-H Population		MMRp/MSS Population	
	Dostar + carbo/pac (N=245)	Placebo + carbo/pac (N=249)	Dostar + carbo/pac (N=53)	Placebo + carbo/pac (N=65)	Dostar + carbo/pac (N=192)	Placebo + carbo/pac (N=184)
Participants' status, n (%)						
Discontinued from study	130 (53.1%)	160 (64.3%)	16 (30.2%)	40 (61.5%)	114 (59.4%)	120 (65.2%)
Ongoing	115 (46.9%)	89 (35.7%)	37 (69.8%)	25 (38.5%)	78 (40.6%)	64 (34.8%)
On study treatment	27 (11.0%)	22 (8.8%)	12 (22.6%)	5 (7.7%)	15 (7.8%)	17 (9.2%)
In follow-up	88 (35.9%)	67 (26.9%)	25 (47.2%)	20 (30.8%)	63 (32.8%)	47 (25.5%)
Reason for discontinuation from study, n (%)						
Withdrawal of consent	26 (10.6%)	20 (8.0%)	3 (5.7%)	6 (9.2%)	23 (12.0%)	14 (7.6%)
Lost to follow-up	5 (2.0%)	5 (2.0%)	2 (3.8%)	3 (4.6%)	3 (1.6%)	2 (1.1%)
Death from any cause	96 (39.2%)	133 (53.4%)	10 (18.9%)	30 (46.2%)	86 (44.8%)	103 (56.0%)
Sponsors decision to terminate study	0	0	0	0	0	0
Other [a]	3 (1.2%)	2 (0.8%)	1 (1.9%)	1 (1.5%)	2 (1.0%)	1 (0.5%)
Primary cause of death, n (%)						
Disease progression	81 (33.1%)	114 (45.8%)	7 (13.2%)	24 (36.9%)	74 (38.5%)	90 (48.9%)
Adverse event [b]	5 (2.0%)	1 (0.4%)	2 (3.8%)	0	3 (1.6%)	1 (0.5%)
Unknown	9 (3.7%)	16 (6.4%)	1 (1.9%)	5 (7.7%)	8 (4.2%)	11 (6.0%)
Other [c]	1 (0.4%)	2 (0.8%)	0	1 (1.5%)	1 (0.5%)	1 (0.5%)

Abbreviations: carbo=carboplatin; Dostar=dostarlimab; f/u=follow-up; ITT=intent-to-treat; pac=paclitaxel.

a. Reasons for discontinuation 'Other' from the study included investigator decision to not administer study treatment or placebo due to participant's health poor condition-renal function (N=1), randomization error (N=1), reaction to carboplatin (N=1), disease progression (N=2), and lost to f/u (N=1).

b. Adverse event as primary cause of death while on study, i.e., death occurring after informed consent and before end of study.

c. "Other" reasons for death in dMMR/MSI-H population was stroke (N=1), in MMRp/MSS population there were 2 deaths; hemorrhagic stroke (N=1) and COVID-19 (N=1). All 3 events were considered unrelated to the investigational medicinal product by the Investigator.

Note: Results presented were performed on analysis set based on source verified data.

Table 27. Summary of treatment status and reasons for discontinuation of study treatment

	Dostar + carbo/pac (N=241)	Placebo + carbo/pac (N=246)	Total (N=487)
Treatment status, n (%)			
Ongoing on any component of study treatment	27 (11.2%)	22 (8.9%)	49 (10.1%)
Ongoing on dostarlimab or placebo	27 (11.2%)	22 (8.9%)	49 (10.1%)
Ongoing on paclitaxel	3 (1.2%)[a]	0	3 (0.6%)[a]
Ongoing on carboplatin	3 (1.2%)[a]	0	3 (0.6%)[a]
Discontinued any component of study treatment	238 (98.8%)	246 (100%)	484 (99.4%)
Discontinued dostarlimab or placebo	214 (88.8%)	224 (91.1%)	438 (89.9%)
Discontinued paclitaxel	238 (98.8%)	246 (100%)	484 (99.4%)
Discontinued carboplatin	238 (98.8%)	246 (100%)	484 (99.4%)
Discontinued all components of study treatment	214 (88.8%)	224 (91.1%)	438 (89.9%)
Reason for treatment discontinuation – dostarlimab or placebo, n (%)			
Adverse event [b]	53 (22.0%)	25 (10.2%)	78 (16.0%)
Clinical progression	7 (2.9%)	8 (3.3%)	15 (3.1%)
PD according to RECIST v.1.1 criteria per IA	111 (46.1%)	165 (67.1%)	276 (56.7%)
Risk to participant, as judged by the Investigator, Sponsor, or both	3 (1.2%)	2 (0.8%)	5 (1.0%)
Severe noncompliance with the protocol, as judged by the Investigator, Sponsor, or both	1 (0.4%)	1 (0.4%)	2 (0.4%)
Participant became pregnant	0	0	0
Withdrawal by participant	21 (8.7%)	8 (3.3%)	29 (6.0%)
Lost to follow-up	1 (0.4%)	1 (0.4%)	2 (0.4%)
Death from any cause	0	1 (0.4%)	1 (0.2%)
Confirmed complete response, treated for at least 3 years with study treatment	7 (2.9%)	3 (1.2%)	10 (2.1%)
Other [c]	10 (4.1%)	10 (4.1%)	20 (4.1%)
Reason for treatment discontinuation – paclitaxel, n (%)			
Adverse event [b]	33 (13.7%)	27 (11.0%)	60 (12.3%)
Clinical progression	1 (0.4%)	2 (0.8%)	3 (0.6%)
PD according to RECIST v.1.1 criteria per IA	8 (3.3%)	14 (5.7%)	22 (4.5%)
Risk to participant, as judged by the Investigator, Sponsor, or both	2 (0.8%)	0	2 (0.4%)
Severe noncompliance with the protocol, as judged by the Investigator, Sponsor, or both	1 (0.4%)	0	1 (0.2%)
Participant became pregnant	0	0	0
Withdrawal of consent	5 (2.1%)	4 (1.6%)	9 (1.8%)
Lost to follow-up	1 (0.4%)	0	1 (0.2%)
Death from any cause	1 (0.4%)	0	1 (0.2%)
Completed planned course [d]	183 (75.9%)	194 (78.9%)	377 (77.4%)
Other [e]	3 (1.2%)	5 (2.0%)	8 (1.6%)
Reason for treatment discontinuation – carboplatin, n (%)			
Adverse event [b]	26 (10.8%)	19 (7.7%)	45 (9.2%)
Clinical progression	1 (0.4%)	2 (0.8%)	3 (0.6%)
PD according to RECIST v.1.1 criteria per Investigator assessment	8 (3.3%)	14 (5.7%)	22 (4.5%)
Risk to participant, as judged by the Investigator, Sponsor, or both	2 (0.8%)	1 (0.4%)	3 (0.6%)
Severe noncompliance with the protocol, as judged by the Investigator, Sponsor, or both	1 (0.4%)	0	1 (0.2%)
Participant became pregnant	0	0	0

	Dostar + carbo/pac (N=241)	Placebo + carbo/pac (N=246)	Total (N=487)
Withdrawal of consent	5 (2.1%)	4 (1.6%)	9 (1.8%)
Lost to follow-up	1 (0.4%)	0	1 (0.2%)
Death from any cause	1 (0.4%)	0	1 (0.2%)
Participant has completed planned course	4 (1.7%)	1 (0.4%)	5 (1.0%)
Completed planned course	187 (77.6%)	203 (82.5%)	390 (80.1%)
Other [f]	2 (0.8%)	2 (0.8%)	4 (0.8%)

Abbreviations: carbo=carboplatin; Dostar=dostarlimab; IA=Investigator assessment; ITT=intent-to-treat; pac=paclitaxel.

a. Three participants have discontinued paclitaxel/carboplatin prior to the data cut-off as of 28-Sep-2023. They were still counted under 'Ongoing on Paclitaxel'/'ongoing on Carboplatin' category as it was not applicable to map the end of treatment data for paclitaxel/carboplatin to SDTM for these 3 participants at this analysis
b. Adverse event as primary reason for treatment discontinuation while on study, i.e., discontinuation occurring after informed consent and before end of study
c. "Other" reasons for discontinuation from placebo/dostarlimab treatment included participants who completed 3 years treatment course (N=4), withdrawal of consent (N=6), underwent total hysterectomy (N=1), persistent disease (N=1), requires other treatment (N=3), hospice care (N=2), secondary malignancy (N=1), inclusion/exclusion criteria not met (N=1), and AE's (N=1).
d. The values in this row are a sum of "participant has completed planned course" and "completed planned course" which are equivalent categories, but captured separately in the CRF.
e. "Other" reasons for discontinuation from paclitaxel treatment included toxicity (N=1), withdrawal of consent (N=2), risk to participant (N=1), inclusion/exclusion criteria not met (N=1), poor performance (N=2), and change of therapy (N=1).
f. "Other" reasons for discontinuation from carboplatin treatment included toxicity (N=1), withdrawal of consent (N=1), inclusion/exclusion criteria not met (N=1), and hospice care (N=1).

Recruitment

The first participant was enrolled on 07 August 2019. The study was conducted in 158 centres in 19 countries. As of the DCO on 22 September 2023 (IA2), there were 49 participants remaining on treatment. Part 1 had closed enrolment in January 2021.

Conduct of the study

Protocol amendments

There were five amendments to the original protocol, dated 13 March 2019; although Amendment 4 (version 5.0 of the protocol; dated 25 January 2023) was finally withdrawn based on regulatory feedback.

Protocol amendments 1 to 3 were already described as part of procedure EMEA/H/C/005204/II/0023. For further details on those protocol amendments, see the assessment report of that procedure.

Document	Date
Amendment 05 (Version 6.0)	31 March 2023
Amendment 04 (Version 5.0)*	25 January 2023
Amendment 03 (Version 4.0)	31 March 2022
Amendment 02 (Version 3.0)	23 September 2021
Amendment 01 (Version 2.0)	11 November 2020
Original protocol (Version 1.1)	13 March 2019

*amendment withdrawn based on regulatory feedback

Protocol Amendment 4 (Version 5.0, dated 25 January 2023)

The primary reasons for this amendment were to revise the hypothesis testing strategy for OS and to update the timing of future OS analyses.

However, this amendment was not implemented. Following discussion with the US FDA on 21 February 2023, the Sponsor decided to withdraw this amendment globally and reverted to Protocol Amendment 3 (Version 4.0 dated 31 March 2022) in some countries. Subsequently, Protocol Amendment 5 (Version 6.0 dated 03 April 2023) was issued to unify study conduct and analysis globally.

Protocol Amendment 5 (Version 6.0; dated 31 March 2023)

The primary reasons for this amendment were:

- Addition of an administrative OS interim analysis to Part 1. A nominal alpha spend was incorporated for the administrative OS interim analysis and stopping boundaries of planned interim OS analyses for hypothesis testing were adjusted accordingly.
- Specified that all future analyses were to be performed for the overall population, and the corresponding dMMR/MSI-H and MMRp/MSS subpopulations, unless otherwise specified.

Protocol deviations

In May 2020, the clinical study transitioned from TESARO protocol deviation definitions and methodologies to those of GSK. Discussion of protocol deviations focused on significant protocol deviations (according to the TESARO definition) and important protocol deviations (according to the TESARO and GSK definitions) as these align with protocol deviation categories with potential impact on study integrity or participant safety. It was noted that the SAP definition did not include significant proocol deviations (TESARO definition), therefore a post-hoc analysis was performed to include these in the summary of the protocol deviation data. According to the MAH, the relatively high frequency of resulting protocol deviations is likely due to the variation in the definitions in the two methodologies, since the TESARO definitions included categories with a broader scope.

Table 28. Summary of important protocol deviations (>1 reported incident in total) (Overall population, ITT analysis set)

Protocol deviation category	Deviation n (%), number of events		
	Dostar + carbo/pac (N=245)	Placebo + carbo/pac (N=249)	Total (N=494)
Any important protocol deviations	106 (43.3%),223	93 (37.3%),216	199 (40.3%),439
Assessment or time point completion	58 (23.7%), 74	47 (18.9%), 60	105 (21.3%),134
Out of window – efficacy assessment	37 (15.1%), 47	26 (10.4%), 32	63 (12.8%), 79
Missed assessment	15 (6.1%), 17	23 (9.2%), 26	38 (7.7%), 43
Assessment not properly performed	3 (1.2%), 3	1 (0.4%), 1	4 (0.8%), 4
Other assessment or time point window	4 (1.6%), 4	0	4 (0.8%), 4
Out of window – safety assessment	2 (0.8%), 2	1 (0.4%), 1	3 (0.6%), 3
Wrong study treatment/ administration/ dose	22 (9.0%), 34	15 (6.0%), 17	37 (7.5%), 51
Failure to report safety events per protocol	12 (4.9%), 13	11 (4.4%), 13	23 (4.7%), 26
Study visit/procedures blood sample for dostarlimab ADA and PK	14 (5.7%), 24	9 (3.6%), 15	23 (4.7%), 39
Study visit/procedures chemistry	9 (3.7%), 11	10 (4.0%), 26	19 (3.8%), 37
Informed consent	11 (4.5%), 13	4 (1.6%), 4	15 (3.0%), 17
Study procedures	7 (2.9%), 7	7 (2.8%), 10	14 (2.8%), 17
Study visit/procedures urinalysis	4 (1.6%), 5	4 (1.6%), 8	8 (1.6%), 13
Study visit/procedures vital signs	2 (0.8%), 3	6 (2.4%), 7	8 (1.6%), 10
Study visit/procedures dostarlimab or placebo study treatment	2 (0.8%), 2	4 (1.6%), 4	6 (1.2%), 6
Eligibility criteria not met	3 (1.2%), 3	1 (0.4%), 1	4 (0.8%), 4
IP admin/study treatment dostarlimab or placebo study treatment	3 (1.2%), 4	1 (0.4%), 1	4 (0.8%), 5

Study visit/procedures patient-reported outcomes (PRO) summary	2 (0.8%), 10	2 (0.8%), 6	4 (0.8%), 16
Excluded medication, vaccine or device	2 (0.8%), 2	1 (0.4%), 1	3 (0.6%), 3
IP admin/study treatment carboplatin study treatment	2 (0.8%), 6	1 (0.4%), 2	3 (0.6%), 8
Study visit/procedures carboplatin study treatment	0	3 (1.2%), 3	3 (0.6%), 3
Study visit/procedures coagulation	2 (0.8%), 2	1 (0.4%), 1	3 (0.6%), 3
Study visit/procedures EORTC QLQ-EN24	1 (0.4%), 2	2 (0.8%), 4	3 (0.6%), 6
Study visit/procedures hematology	1 (0.4%), 3	2 (0.8%), 5	3 (0.6%), 8
Study visit/procedures local laboratory sample collection summary v2	0	3 (1.2%), 3	3 (0.6%), 3
Study visit/procedures paclitaxel study treatment	0	3 (1.2%), 3	3 (0.6%), 3
Disallowed medication blood sample for dostarlimab ADA and PK	1 (0.4%), 1	1 (0.4%), 1	2 (0.4%), 2
IP admin/study treatment paclitaxel study treatment	2 (0.8%), 2	0	2 (0.4%), 2
Randomization MMR/MSI test	1 (0.4%), 1	1 (0.4%), 1	2 (0.4%), 2
Study visit/procedures EORTC QLQ-C30	1 (0.4%), 1	1 (0.4%), 1	2 (0.4%), 2
Study visit/procedures local laboratory sample collection summary	0	2 (0.8%), 2	2 (0.4%), 2
Study visit/procedures vital signs summary	0	2 (0.8%), 2	2 (0.4%), 2

Abbreviations: ADA=antidrug antibody; carbo=carboplatin; Dostar=dostarlimab; EORTC=European Organization for Research and Treatment of Cancer; ITT=intent-to-treat; pac=paclitaxel; QLQ=Quality of Life Questionnaire.
Note: Significant protocol deviations are also included in the display as "significant" protocol deviations are also considered as "important".
Note: Results presented were performed on analysis set based on source verified data.

Baseline data

Baseline demographic characteristics

Table 29. Summary of demographic characteristics (overall population, ITT analysis set)

Characteristic	Dostar + carbo/pac (N=245)	Placebo + carbo/pac (N=249)	Total (N=494)
Age (years)			
Median	64.0	65.0	65.0
Min, max	41, 81	28, 85	28, 85
Age group, n (%)			
19-64	127 (51.8%)	114 (45.8%)	241 (48.8%)
≥65	118 (48.2%)	135 (54.2%)	253 (51.2%)
BMI (kg/m²)			
n	240	246	486
Mean (std)	31.99 (8.295)	32.99 (8.888)	32.50 (8.606)
Min, max	17.6, 60.6	17.7, 68.0	17.6, 68.0
BSA (m²)			
n	241	246	487
Mean (std)	1.896 (0.2592)	1.939 (0.2906)	1.918 (0.2761)
Min, max	1.35, 3.03	1.33, 3.03	1.33, 3.03
ECOG performance status, n (%)			
n	241	246	487
0	145 (60.2%)	160 (65.0%)	305 (62.6%)
1	96 (39.8%)	86 (35.0%)	182 (37.4%)
Childbearing status, n (%)			
Childbearing potential	1 (0.4%)	2 (0.8%)	3 (0.6%)
Nonchildbearing potential	244 (99.6%)	247 (99.2%)	491 (99.4%)
Race, n (%)			
White	189 (77.1%)	191 (76.7%)	380 (76.9%)
Black or African American	28 (11.4%)	31 (12.4%)	59 (11.9%)
Asian	7 (2.9%)	8 (3.2%)	15 (3.0%)
American Indian or Alaska Native	1 (0.4%)	1 (0.4%)	2 (0.4%)
Native Hawaiian or other Pacific Islander	1 (0.4%)	0	1 (0.2%)
Unknown	13 (5.3%)	8 (3.2%)	21 (4.3%)
Not reported	6 (2.4%)	10 (4.0%)	16 (3.2%)
Ethnicity, n (%)			
Hispanic or Latino	7 (2.9%)	9 (3.6%)	16 (3.2%)
Not Hispanic or Latino	224 (91.4%)	227 (91.2%)	451 (91.3%)
Unknown	9 (3.7%)	6 (2.4%)	15 (3.0%)
Not reported	5 (2.0%)	7 (2.8%)	12 (2.4%)

Abbreviations: BMI=body-mass index; BSA=body surface area; carbo=carboplatin; Dostar=dostarlimab; ECOG=Eastern Cooperative Oncology Group; ITT=intent-to-treat; pac=paclitaxel.

Baseline disease characteristics

Table 30. Summary of disease history (overall population, ITT analysis set)

Category, n (%)	Dostar + carbo/pac (N=245)	Placebo + carbo/pac (N=249)	Total (N=494)
FIGO stage at initial diagnosis			
Stage I	65 (26.5%)	71 (28.5%)	136 (27.5%)
Stage II	13 (5.3%)	13 (5.2%)	26 (5.3%)
Stage III	75 (30.6%)	65 (26.1%)	140 (28.3%)
Stage IV	72 (29.4%)	84 (33.7%)	156 (31.6%)
Unknown	20 (8.2%)	16 (6.4%)	36 (7.3%)
Histology at diagnosis			
Carcinosarcoma	25 (10.2%)	19 (7.6%)	44 (8.9%)
Clear cell adenocarcinoma	8 (3.3%)	9 (3.6%)	17 (3.4%)
Endometrioid carcinoma (adenocarcinoma or adenocarcinoma variants)	134 (54.7%)	136 (54.6%)	270 (54.7%)
Mixed carcinoma with ≥10% of carcinosarcoma, clear cell or serous histology	10 (4.1%)	9 (3.6%)	19 (3.8%)
Mucinous adenocarcinoma	0	1 (0.4%)	1 (0.2%)
Other	17 (6.9%)	21 (8.4%)	38 (7.7%)
Serous adenocarcinoma	50 (20.4%)	52 (20.9%)	102 (20.6%)
Undifferentiated carcinoma	1 (0.4%)	2 (0.8%)	3 (0.6%)
Grade at diagnosis			
Grade 1	49 (20.0%)	42 (16.9%)	91 (18.4%)
Grade 2	52 (21.2%)	56 (22.5%)	108 (21.9%)
Grade 3	124 (50.6%)	123 (49.4%)	247 (50.0%)
Not assessable	20 (8.2%)	28 (11.2%)	48 (9.7%)

Abbreviations: carbo=carboplatin; Dostar=dostarlimab; FIGO=International Federation of Gynecology and Obstetrics; pac=paclitaxel.

Medical history

Nearly all participants (97.0%) had prior reported medical conditions, and these were generally similar between treatment arms (<5% difference). The most frequently reported (>50% of total participants) medical history conditions by system organ class were vascular disorders (62.8%), gastrointestinal disorders (59.5%), and metabolism and nutrition disorders (56.3%). The most frequently reported (>50% of total participants) medical history condition by preferred term was hypertension (55.3%).

Prior medications and other treatments

Table 31. Summary of prior anticancer radiotherapy, surgery, and treatment (Overall population, ITT analysis set)

Agent	Dostar + carbo/pac (N=245)	Placebo + carbo/pac (N=249)	Total (N=494)
Received previous radiotherapy for EC	71 (29.0%)	69 (27.7%)	140 (28.3%)
External pelvic	41 (16.7%)	45 (18.1%)	86 (17.4%)
Internal pelvic	32 (13.1%)	31 (12.4%)	63 (12.8%)
Other	22 (9.0%)	19 (7.6%)	41 (8.3%)
Received prior anticancer surgery for EC	224 (91.4%)	224 (90.0%)	448 (90.7%)
Received prior anticancer treatment for EC	48 (19.6%)	52 (20.9%)	100 (20.2%)

Abbreviations: carbo=carboplatin; Dostar=dostarlimab; EC=endometrial cancer; pac=paclitaxel.

a. Participants may have been included in more than one category for previous radiotherapy for endometrial cancer.
b. Diagnostic procedure only are not included as anticancer surgery.

Numbers analysed

Table 32. Summary of analysis sets (screened analysis set)

Analysis set, n (%)	Dostar + carbo/pac	Placebo + carbo/pac	Total (N=607)
Screened Analysis Set, n			607
Screen failures [a]			113 (18.6%)
Enrolled Analysis Set, n	245	249	494 [b]
ITT Analysis Set [c]	245 (100%)	249 (100%)	494 (100%)
Safety Analysis Set [c]	241 (98.4%)	246 (98.8%)	487 (98.6%)
Per-Protocol Analysis Set [c]	241 (98.4%)	246 (98.8%)	487 (98.6%)

Abbreviations: carbo=carboplatin; Dostar=dostarlimab; ITT=intent-to-treat; pac=paclitaxel.

a. Percentage is based on all screened participants. Screen failures included all participants who were screened but not enrolled.

b. 8 participants who did not meet all eligibility criteria were included in the Enrolled Analysis Set, 0 participants were enrolled but not randomized.

c. Percentage is based on number of participants in the Enrolled analysis set.

Outcomes and estimation

Primary efficacy endpoints

- **Progression-free survival (PFS) by Investigator assessment**

Since PFS met statistical significance at IA1 (DCO: 28 Sep 2022), it was not further evaluated at IA2. For further information on IA1 assessment, see the assessment report of the procedure which led to the authorisation of Jemperli in the dMMR/MSI-h population (EMEA/H/C/005204/II/0023).

Overall population

At IA1, the RUBY Part 1 study met the dual-primary endpoint for PFS by investigator in the overall population with a median follow-up of 25.38 months and 312 PFS events observed (63% maturity).

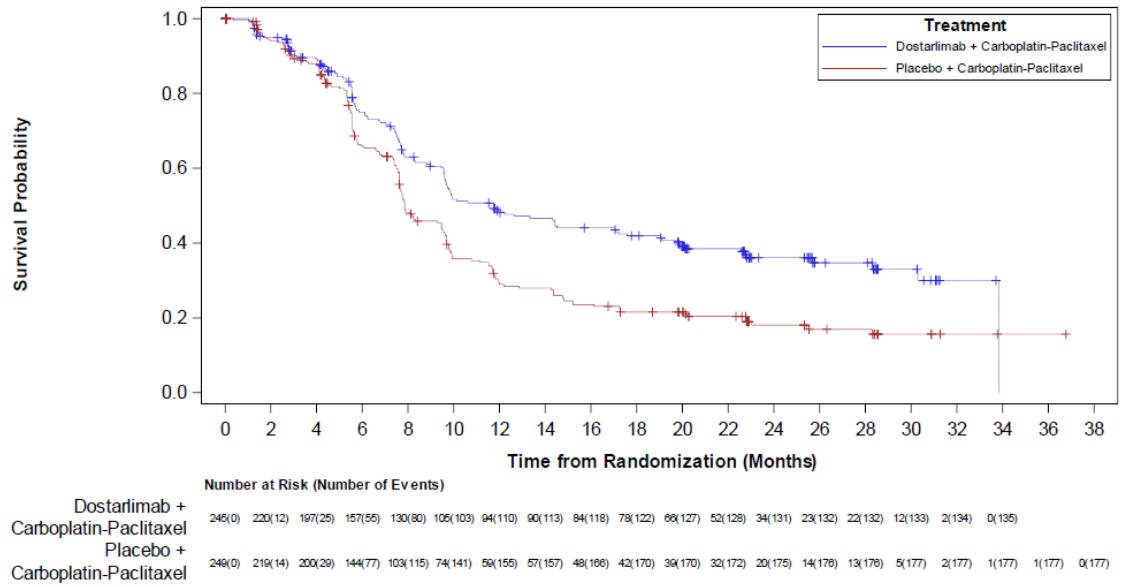
Table 33. Kaplan-Meier analysis of progression-free survival - RECIST v1.1 by investigator assessment (IA1) (Overall Population, ITT Analysis Set)

Category subcategory	Dostar + carbo/pac (N=245)	Placebo + carbo/pac (N=249)
PFS status, n (%)		
Events observed	135 (55.1%)	177 (71.1%)
Disease progression	125 (51.0%)	169 (67.9%)
Death	10 (4.1%)	8 (3.2%)
Censored	110 (44.9%)	72 (28.9%)
PFS (months) Quartile (95% CI) [a]		
25%	6.1 (5.6, 7.5)	5.5 (5.3, 5.7)
50%	11.8 (9.6, 17.1)	7.9 (7.6, 9.5)
75%	33.8 (30.3, NR)	14.8 (11.8, 22.8)
PFS distribution function (95% CI)		
Month 6	75.0% (68.7%, 80.2%)	65.9% (59.3%, 71.7%)
Month 12	48.2% (41.3%, 54.8%)	29.0% (23.0%, 35.2%)
Month 18	41.9% (35.1%, 48.6%)	21.6% (16.3%, 27.4%)
Month 24	36.1% (29.3%, 42.9%)	18.1% (13.0%, 23.9%)
Hazard ratio (95% CI) [b]	0.64 (0.507, 0.800)	
p-value of 1-sided stratified log-rank test	<0.0001	

carbo=carboplatin; Dostar=dostarlimab; ITT=intent-to-treat; NR=not reached; pac=paclitaxel; PFS=progression-free survival.

a. 95% CIs generated using the method of Brookmeyer and Crowley (1982).
b. Based on stratified Cox regression.

Figure 17. Kaplan-Meier curves of progression-free survival - RECIST v1.1 by investigator assessment (IA1) (Overall population, ITT Analysis Set)



dMMR/MSI-h population

At IA1, the RUBY Part 1 study met the dual-primary endpoint for PFS in the dMMR/MSI-h population, with a median follow-up of 24.79 months and 66 PFS events observed (56% maturity).

Table 34. Kaplan-Meier analysis of progression-free survival - RECIST v1.1 by investigator assessment (IA1) (dMMR/MSI-H Population, ITT Analysis set, MMR/MSI Status per source verified data)

Category subcategory	Dostar + carbo/pac (N=53)	Placebo + carbo/pac (N=65)
PFS status, n (%)		
Events observed	19 (35.8%)	47 (72.3%)
Disease progression	16 (30.2%)	44 (67.7%)
Death	3 (5.7%)	3 (4.6%)
Censored	34 (64.2%)	18 (27.7%)
PFS (months) Quartile (95% CI) [a]		
25%	6.7 (4.1, 12.2)	5.6 (4.1, 5.6)
50%	NR (11.8, NR)	7.7 (5.6, 9.7)
75%	NR (NR, NR)	11.8 (9.7, NR)
PFS distribution function (95% CI)		
Month 6	80.2% (66.3%, 88.8%)	59.7% (46.2%, 70.9%)
Month 12	63.5% (48.5%, 75.3%)	24.4% (13.9%, 36.4%)
Month 18	61.4% (46.3%, 73.4%)	17.9% (8.9%, 29.5%)
Month 24	61.4% (46.3%, 73.4%)	15.7% (7.2%, 27.0%)
Hazard ratio (95% CI) [b]	0.28 (0.162, 0.495)	
p-value of 1-sided stratified log-rank test	<0.0001	

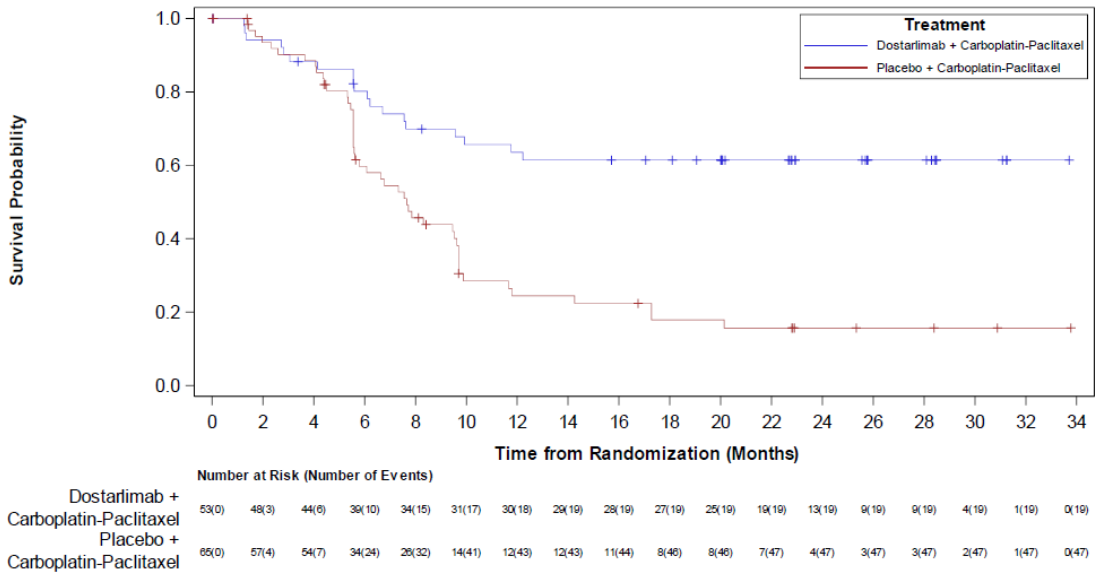
carbo=carboplatin; Dostar=dostarlimab; ITT=intent-to-treat; NR=not reached; pac=paclitaxel; PFS=progression-free survival.

NOTE: Results for dMMR/MSI-H population was performed on analysis set based on source verified MMR status.

a. 95% Confidence intervals generated using the method of Brookmeyer and Crowley (1982).

b. Stratified Cox regression

Figure 18. Kaplan-Meier curves of progression-free survival - RECIST v1.1 by investigator assessment (IA1) (dMMR/MSI-H Population, ITT Analysis Set, MMR/MSI Status per source verified data)



NOTE: Results for dMMR/MSI-H population was performed on analysis set based on source verified MMR status.

MMRp/MSS population

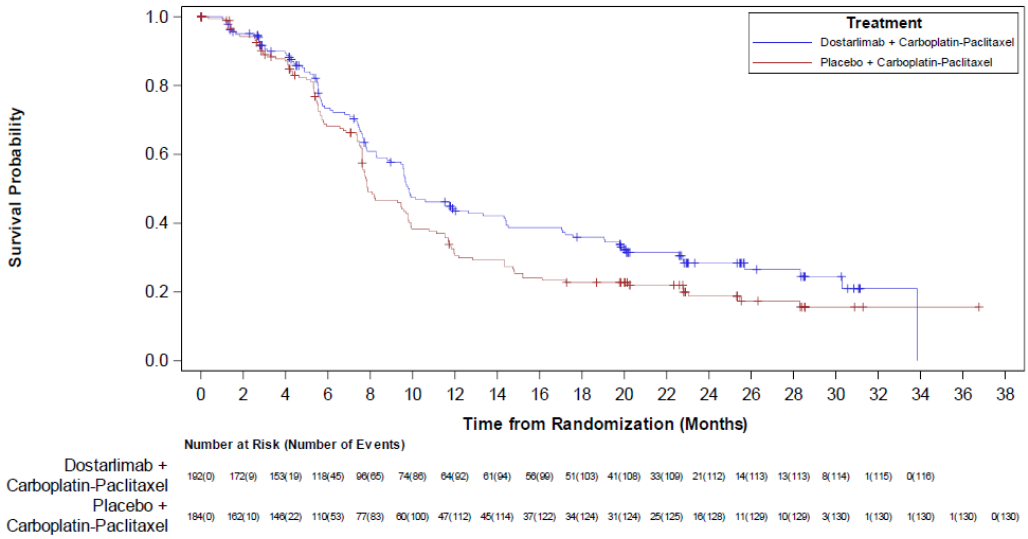
The PFS maturity in the MMRp/MSS population was 65%.

Table 35. Kaplan-Meier analysis of progression-free survival - RECIST v1.1 by investigator assessment (IA1) (MMRp/MSS Population, ITT Analysis Set, MMR/MSI Status per source verified data)

Category subcategory	Dostar + carbo/pac (N=192)	Placebo + carbo/pac (N=184)
PFS status, n (%)		
Events observed	116 (60.4%)	130 (70.7%)
Disease progression	109 (56.8%)	125 (67.9%)
Death	7 (3.6%)	5 (2.7%)
Censored	76 (39.6%)	54 (29.3%)
PFS (months) Quartile (95% CI) [a]		
25%	5.7 (5.5, 7.4)	5.5 (5.2, 5.9)
50%	9.9 (9.0, 13.3)	7.9 (7.6, 9.8)
75%	28.3 (20.1, NR)	15.2 (12.0, 25.4)
PFS distribution function (95% CI)		
Month 6	73.4% (66.1%, 79.5%)	68.1% (60.4%, 74.6%)
Month 12	43.5% (35.7%, 51.0%)	30.6% (23.6%, 37.8%)
Month 18	35.9% (28.4%, 43.4%)	22.8% (16.6%, 29.6%)
Month 24	28.4% (21.2%, 36.0%)	18.8% (12.8%, 25.7%)
Hazard ratio (95% CI) [b]	0.76 (0.592, 0.981)	
Nominal p-value of 1-sided stratified log-rank test	0.0177	

carbo=carboplatin; CI=confidence interval; Dostar=dostarlimab; ITT=intent-to-treat; pac=paclitaxel; NR=not reached; DOR=duration of response.
NOTE: Results for MMRp/MSS population was performed on analysis set based on source verified MMR status.
a. 95% Confidence intervals generated using the method of Brookmeyer and Crowley (1982).
b. Stratified Cox regression.

Figure 19. Kaplan-Meier curves of progression-free survival - RECIST v1.1 by investigator assessment (IA1) (MMRp/MSS Population, ITT Analysis Set, MMR/MSI Status per source verified data)



NOTE: Results for MMRp/MSS population was performed on analysis set based on source verified MMR status.

- **Overall survival (OS)**

The dual-primary endpoint of OS in the overall population was not met at the IA1 (see procedure EMEA/H/C/005204/II/0023).

Overall population

At IA2, the RUBY Part 1 study met the dual-primary endpoint for OS in the overall population with a median follow-up of 37 months from randomisation to DCO and 253 OS events observed (51.2% maturity).

Table 36. Kaplan-Meier analysis of overall survival (overall population, ITT analysis set)

Category subcategory	Dostar + carbo/pac (N=245)	Placebo + carbo/pac (N=249)
OS status, n (%)		
Events observed	109 (44.5%)	144 (57.8%)
Censored	136 (55.5%)	105 (42.2%)
Estimates for OS (months) Quartile (95% CI) [a]		
25%	19.6 (13.4, 24.5)	13.6 (12.2, 16.1)
50%	44.6 (32.6, NR)	28.2 (22.1, 35.6)
75%	NR (NR, NR)	NR (41.9, NR)
OS probability (95% CI)		
Month 12	83.3% (77.9%, 87.4%)	80.9% (75.4%, 85.3%)
Month 18	77.3% (71.4%, 82.1%)	65.6% (59.3%, 71.2%)
Month 24	70.1% (63.8%, 75.5%)	54.3% (47.8%, 60.3%)
Month 30	60.5% (54.0%, 66.5%)	49.1% (42.6%, 55.3%)
Hazard ratio (95% CI) [b]	0.69 (0.539, 0.890)	
p-value of 1-sided stratified log-rank test	0.0020	

Abbreviations: carbo=carboplatin; Dostar=dostarlimab; ITT=intent-to-treat; NR=not reached; pac=paclitaxel; PFS=progression-free survival.

a. 95% Confidence intervals generated using the method of Brookmeyer and Crowley (1982).

b. Stratified Cox regression model

Figure 20. Kaplan-Meier analysis overall survival (overall population, ITT analysis set)

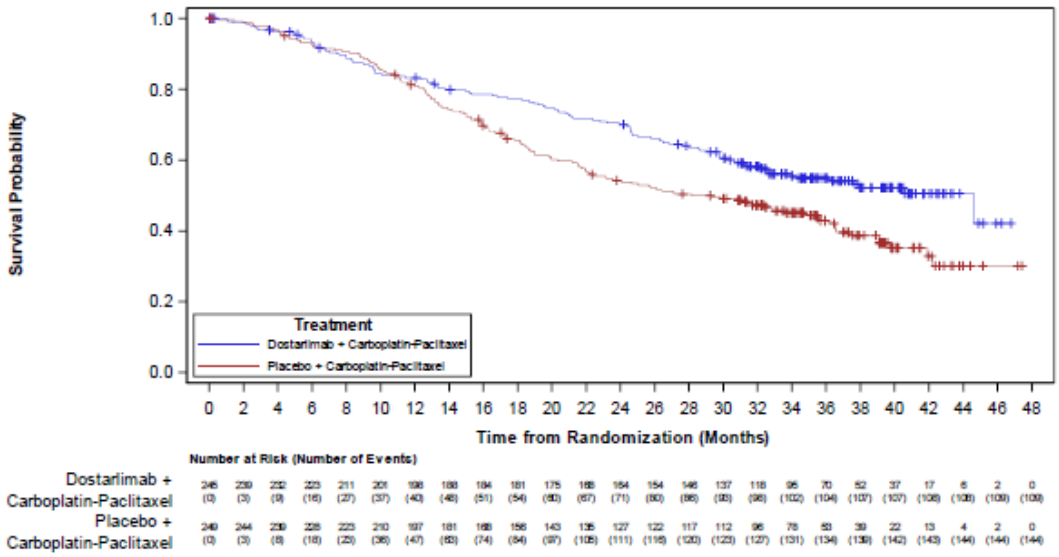


Table 37. Summary of censoring status and reasons for OS (ITT Analysis Set)

MMR/MSI status: All subjects

Parameter Censoring Status Censoring Reason	Dostarlimab + Carboplatin/Paclitaxel (N=245)	Placebo + Carboplatin/Paclitaxel (N=249)
Overall Survival		
Censored [1]	136 (55.5%)	105 (42.2%)
Censored, follow-up ended	7 (2.9%)	9 (3.6%)
Censor: Last contact date	7 (2.9%)	9 (3.6%)
Reasons for follow-up ended [2]		
Discontinued from study	6 (2.4%)	8 (3.2%)
Lost-to-follow-up in the survival follow-up	1 (0.4%)	1 (0.4%)
Patient no longer willing to participate in the survival follow-up	0	0
Censor: Date of randomization	0	0
Reasons for follow-up ended [2]		
Discontinued from study	0	0
Lost-to-follow-up in the survival follow-up	0	0
Patient no longer willing to participate in the survival follow-up	0	0
Censored, follow-up ongoing	129 (52.7%)	96 (38.6%)
Censor: Last contact date	128 (52.2%)	96 (38.6%)
Censor: Date of randomization	1 (0.4%)	0

1. If a participant did not die prior to the data cut off, the participant was censored.
2. If a participant fell into multiple categories below, the following hierarchy was applied to determine under which category, the participant should be counted: "Discontinued from study" > "Lost-to-follow-up in the survival follow-up" > "Patient no longer willing to participate in the survival follow-up"

Program: t-14-2-1-50b.sas, Output: t_14_2_1_50b.rtf, Generated on: 07NOV2023 08:14, Data Cutoff Date: 22SEP2023

dMMR/MSI-H population

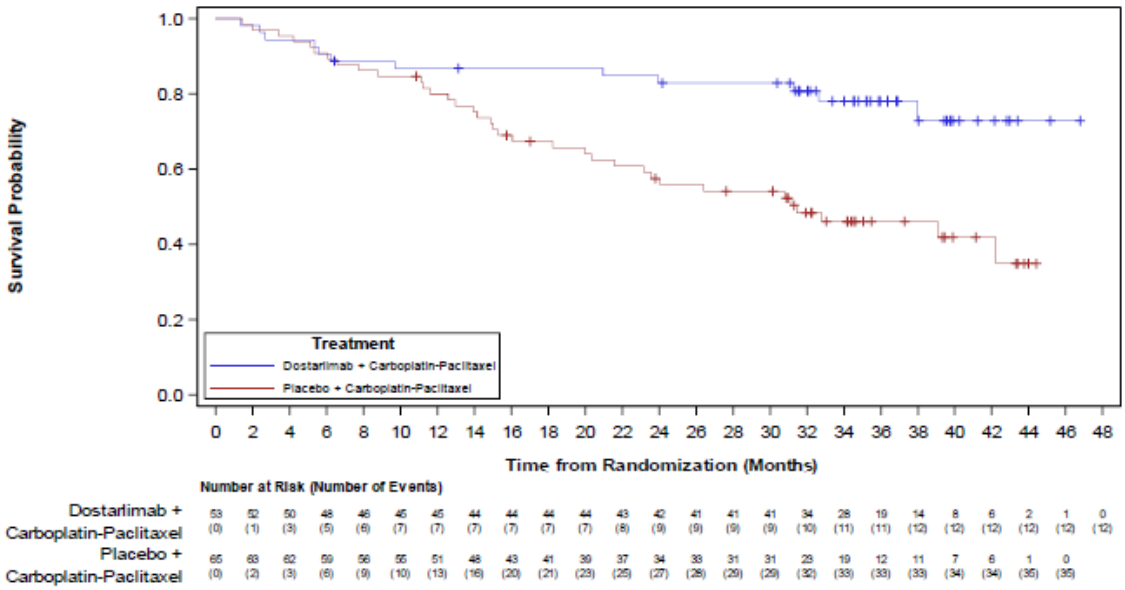
At IA2, the OS maturity in de dMMR/MSI-H population was 40.2%.

Table 38. Kaplan-Meier analysis of overall survival (dMMR/MSI-H population, ITT analysis set, MMR/MSI Status per source verified data)

Category subcategory	Dostar + carbo/pac (N=53)	Placebo + carbo/pac (N=65)
OS status, n (%)		
Events observed	12 (22.6%)	35 (53.8%)
Censored	41 (77.4%)	30 (46.2%)
Estimates for OS (months) Quartile (95% CI) [a]		
25%	38.0 (9.7, NR)	14.2 (8.8, 20.0)
50%	NR (NR, NR)	31.4 (20.3, NR)
75%	NR (NR, NR)	NR (42.2, NR)
OS probability (95% CI)		
Month 12	86.8% (74.2%, 93.5%)	79.9% (67.9%, 87.8%)
Month 18	86.8% (74.2%, 93.5%)	67.3% (54.4%, 77.3%)
Month 24	82.8% (69.5%, 90.7%)	57.5% (44.4%, 68.6%)
Month 30	82.8% (69.5%, 90.7%)	54.1% (41.0%, 65.5%)
Hazard ratio (95% CI) [b]	0.32 (0.166, 0.629)	
Nominal p-value of 1-sided stratified log-rank test	0.0002	

Abbreviations: carbo=carboplatin; dMMR=mismatch repair deficient; Dostar=dostarlimab; ITT=intent-to-treat; MSI-H=microsatellite instability-high; NR=not reached; OS=overall survival; pac=paclitaxel.
NOTE: Results presented were performed on analysis set based on source verified MMR status.
a. 95% Confidence intervals generated using the method of Brookmeyer and Crowley (1982).
b. Stratified Cox regression model

Figure 21. Kaplan-Meier analysis overall survival (dMMR/MSI-H population, ITT analysis set, MMR/MSI Status per source verified data)



MMRp/MSS population

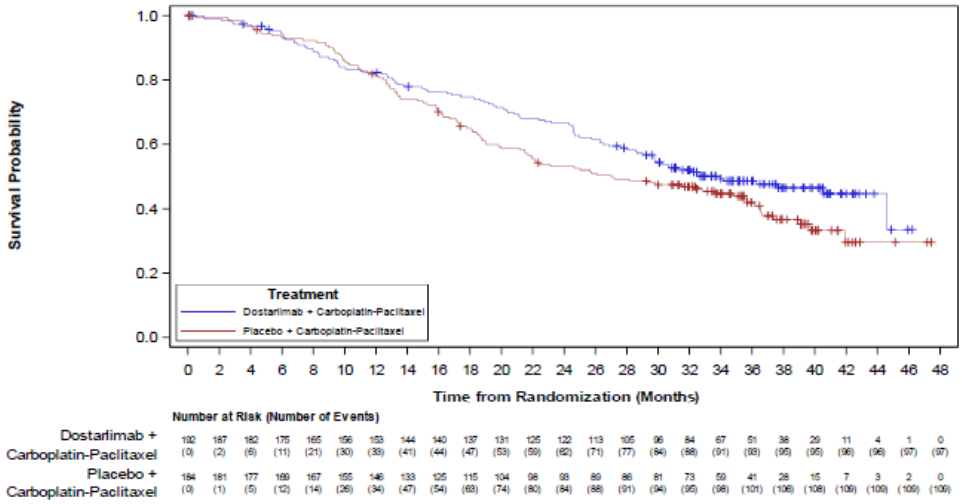
At IA2, the OS maturity in the MMRp/MSS population was 54.8%.

Table 39. Kaplan-Meier analysis of overall survival (MMRp/MSS population, ITT analysis set, MMR/MSI Status per source verified data)

Category subcategory	Dostar + carbo/pac (N=192)	Placebo + carbo/pac (N=184)
OS status, n (%)		
Events observed	97 (50.5%)	109 (59.2%)
Censored	95 (49.5%)	75 (40.8%)
OS (months) Quartile (95% CI) [a]		
25%	17.4 (12.7, 21.1)	13.5 (12.0, 16.3)
50%	34.0 (28.6, NR)	27.0 (21.5, 35.6)
75%	NR (44.6, NR)	NR (39.7, NR)
OS probability (95% CI)		
Month 12	82.3% (76.0%, 87.1%)	81.2% (74.7%, 86.2%)
Month 18	74.7% (67.8%, 80.3%)	65.1% (57.6%, 71.5%)
Month 24	66.5% (59.2%, 72.8%)	53.2% (45.6%, 60.2%)
Month 30	54.4% (46.9%, 61.3%)	47.4% (39.9%, 54.5%)
Hazard ratio (95% CI) [b]	0.79 (0.602, 1.044)	
Nominal p-value of 1-sided stratified log-rank test	0.0493	

Abbreviations: carbo=carboplatin; Dostar=dostarlimab; ITT=intent-to-treat; MMRp=mismatch repair proficient; MSS=microsatellite stable; NR=not reached; OS=overall survival; pac=paclitaxel.
NOTE: Results presented were performed on analysis set based on source verified MMR status.
a. 95% Confidence intervals generated using the method of Brookmeyer and Crowley (1982).
b. Stratified Cox regression model

Figure 22. Kaplan-Meier analysis overall survival (MMRp/MSS population, ITT analysis set, MMR/MSI Status per source verified data)



- Follow-up anticancer therapies

Table 40. Summary of subsequent therapies in the overall population and by MRR status

	Overall Population		dMMR/MSI-H		MMRp/MSS	
Subsequent Therapy (n [%])	**Dostar+ carbo/pac (n=245)**	**Placebo + carbo/pac (n=249)**	**Dostar+ carbo/pac (n=53)**	**Placebo + carbo/pac (n=65)**	**Dostar+ carbo/pac (n=192)**	**Placebo + carbo/pac (n=184)**
Any FUACT	120 (49%)	173 (69.5%)	15 (28.3%)	39 (60%)	105 (54.7%)	134 (72.8%)
Immunotherapy	42 (17.1%)	95 (38.2%)	8 (15.1%)	27 (41.5%)	34 (17.7%)	68 (37.0%)
Pem	13 (5.3%)	41 (16.5%)	4 (7.5%)	21 (32.3%)	9 (4.7%)	20 (10.9%)
Pem/Len	25 (10.2%)	45 (18.1%)	3 (5.7%)	2 (3.1%)	22 (11.5%)	43 (23.4%)
Dostar	0 (0%)	3 (1.2%)	0 (0%)	3 (4.6%)	0 (0%)	0 (0%)
MK769A	0 (0%)	1 (0.4%)	0 (0%)	1 (1.5%)	0 (0%)	0 (0%)
Other IO[a]	5 (2.0%)	11 (4.4%)	2 (3.8%)	0 (0%)	3 (1.6%)	11 (6.0%)
Chemotherapy	70 (28.6%)	72 (28.9%)	7 (13.2%)	11 (16.9%)	63 (32.8%)	61 (33.2%)
Hormonal Therapy	22 (9.0%)	30 (12.0%)	4 (7.5%)	10 (15.4%)	18 (9.4%)	20 (10.9%)
Radiation Therapy	28 (11.4%)	29 (11.6%)	2 (3.8%)	8 (12.3%)	26 (13.5%)	21 (11.4%)
Other[b]	9 (3.7%)	20 (8.0%)	1 (1.9%)	0 (0%)	8 (4.2%)	20 (10.9%)

Abbreviations: carbo=carboplatin; Dostar=dostarlimab; FUACT=follow up anti-cancer therapy; IO=immunotherapy; Len=lenvatinib; pac= paclitaxel; Pem=pembrolizumab.

a. Other subsequent immunotherapy received by study participants. Therapies included either retifanlimab/epacadostat, durvalumab/cediranib, durvalumab/olaparib, atezolizumab/ipatasertib, avelumab/axitinib, bevacizumab/atezolizumab, investigational product, nivolumab/bms-986207/com701, nivolumab/lucitanib, pembrolizumab/tamoxifen or SGN-ALPV.

b. Other: bevacizumab, trastuzumab, investigational product, sacituzumab govetecan, cediranib, CPI-0209, niraparib, pemigatinib, surgery, temsirolimus, trametinib, ZN-C3, trastuzumab/tucatinib, zoledronic acid.

Secondary efficacy endpoints

Results of PFS by BICR, ORR, DoR, DCR, PFS2 and PROs in the dMMR/MSI-h population at IA1 were assessed in the procedure which led to the authorisation of Jemperli in the dMMR/MSI-h population (EMEA/H/C/005204/II/0023). For further information on the IA1 assessment, see the assessment report of the referred procedure.

Updated PFS2 data at IA2 are assessed within this procedure; together with the results of ORR, DoR, DCR and PROs in the overall population (together with the dMMR/MSI-h and MMRp/MSS populations) at IA1.

- **PFS by blinded independent central review (BICR)**

Overall population

Table 41. Summary of Kaplan-Meier Analysis of progression-free survival – per RECIST v1.1 based on BICR assessment (IA1) (ITT Analysis Set, MMR/MSI Status per source verified data)

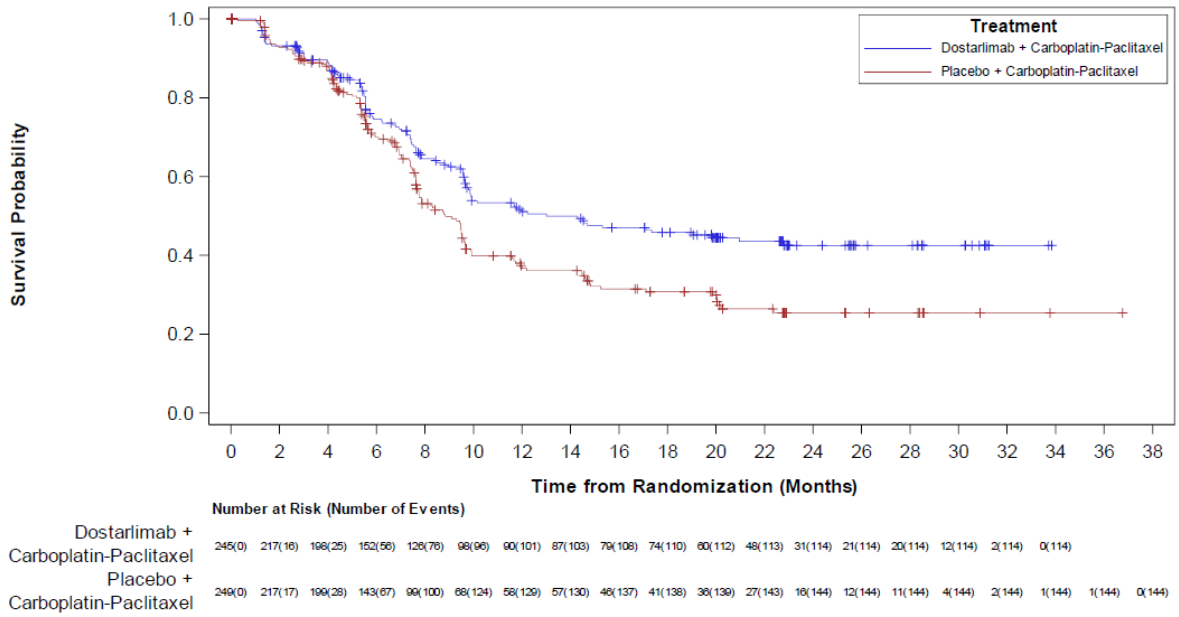
	Overall Population	
	Dostar + carbo/pac (N=245)	Placebo + carbo/pac (N=249)
Hazard ratio (95% CI) [a]	0.66 (0.517, 0.853)	
Nominal p-value of 1 sided stratified log-rank test	0.0006	
Median PFS, months (95% CI) [b]	13.0 (9.8, 22.8)	8.8 (7.7, 9.7)
PFS Probability at 24 Months (95% CI)	42.5% (35.2%, 49.6%)	25.4% (18.9%, 32.4%)

carbo=carboplatin; Dostar=dostarlimab; ITT=intent-to-treat; NR=not reached; pac=paclitaxel; PFS=progression-free survival.

a. Stratified Cox regression

b. 95% Confidence intervals generated using the method of Brookmeyer and Crowley (1982).

Figure 23. Kaplan-Meier curves of progression-free survival - RECIST v1.1 by BICR assessment (IA1) (Overall Population, ITT Analysis Set, MMR/MSI Status per source verified data)



- **Objective response (ORR), duration of response (DoR) and disease control rate (DCR)**

Overall population and dMMR/MSI-h population

Table 42. Summary of tumour response – RECIST v.1.1 by Investigator assessment (ITT analysis set)

	Overall Population		dMMR/MSI-H Population	
	Dostar + carbo/pac (N=245)	Placebo + carbo/pac (N=249)	Dostar + carbo/pac (N=53)	Placebo + carbo/pac (N=65)
Best response by RECIST v.1.1, n (%)				
CR	53 (21.6%)	43 (17.3%)	15 (28.3%)	12 (18.5%)
PR	96 (39.2%)	99 (39.8%)	23 (43.4%)	28 (43.1%)
SD	42 (17.1%)	49 (19.7%)	6 (11.3%)	10 (15.4%)
Non-CR/Non-PD	0	0	0	0
No disease	31 (12.7%)	30 (12.0%)	4 (7.5%)	8 (12.3%)
PD	9 (3.7%)	16 (6.4%)	2 (3.8%)	4 (6.2%)
Not evaluable	14 (5.7%)	12 (4.8%)	3 (5.7%)	3 (4.6%)
Disease control rate				
n (%)	222 (90.6%)	221 (88.8%)	48 (90.6%)	58 (89.2%)
95% CI [a]	(86.2%, 94.0%)	(84.2%, 92.4%)	(79.3%, 96.9%)	(79.1%, 95.6%)
Objective response rate [b]				
n/N (%)	149/212 (70.3%)	142/219 (64.8%)	38/49 (77.6%)	40/58 (69.0%)
95% CI [a]	(63.6%, 76.3%)	(58.1%, 71.2%)	(63.4%, 88.2%)	(55.5%, 80.5%)

Abbreviations: carbo=carboplatin; CR=complete response; dMMR=mismatch repair deficient; DCR=disease control rate; Dostar=dostarlimab; ITT=intent-to-treat; MSI-H=microsatellite instability-high; pac=paclitaxel; PD=progressive disease; PR=partial response; RECIST=Response Evaluation Criteria in Solid Tumors.
Note: DCR is defined as the percentage of participants with a RECIST v.1.1 CR, PR, SD, Non-CR/Non-PD, No disease.

a. Exact 2-sided 95% confidence interval for the binomial proportion.
b. Denominator is the number of participants with target or non-target lesions at baseline.

Table 43. Summary of Kaplan Meier Analysis of Duration of Response - RECIST v1.1 based on Investigator Assessment and Primary Censoring Rule (ITT Analysis Set)

	Overall Population		dMMR/MSI-H Population	
Variable [n (%)]	Dostar + carbo/pac (N=245)	Placebo + carbo/pac (N=249)	Dostar + carbo/pac (N=53)	Placebo + carbo/pac (N=65)
Number of responders				
n	149	142	38	40
Status [n (%)]				
Events observed	82 (55.0)	115 (81.0)	14 (36.8%)	33 (82.5%)
Disease progression	79 (53.0)	112 (78.9)	13 (34.2%)	33 (82.5%)
Death	3 (2.0)	3 (2.1)	1 (2.6%)	0
Censored	67 (45.0)	27 (19.0)	24 (63.2%)	7 (17.5%)
Estimates for DOR (months) Quartile (95% CI) [a]				
25%	4.9 (4.1, 6.3)	3.3 (2.8, 4.1)	6.2 (1.4, NR)	3.0 (2.8, 4.2)
50%	10.6 (8.2, 17.6)	6.2 (4.4, 6.7)	NR (10.1, NR)	5.4 (3.9, 8.1)
75%	NR (26.9, NR)	10.2 (8.3, 13.6)	NR (NR, NR)	8.3 (6.9, NR)
Duration ≥6 months	94 (63.1)	69 (48.6)	28 (73.7%)	18 (45.0%)
Duration ≥12 months	60 (40.3)	29 (20.4)	22 (57.9%)	7 (17.5%)
Probability of DOR (95% CI)				
Month 6	69.4%	50.8%	76.1%	46.2%
	(60.9%, 76.4%)	(42.2%, 58.8%)	(59.0%, 86.8%)	(30.2%, 60.7%)
Month 12	47.3%	22.6%	62.1%	19.2%
	(38.6%, 55.5%)	(15.9%, 30.0%)	(44.4%, 75.5%)	(8.6%, 33.1%)
Month 18	41.4%	16.0%	62.1%	13.2%
	(32.9%, 49.7%)	(10.3%, 22.9%)	(44.4%, 75.5%)	(4.6%, 26.3%)
Month 24	38.0%	13.0%	62.1%	13.2%
	(29.4%, 46.5%)	(7.5%, 20.2%)	(44.4%, 75.5%)	(4.6%, 26.3%)

Abbreviations: carbo=carboplatin; dMMR=mismatch repair deficient; DOR=duration of response; Dostar=dostarlimab; ITT=intent-to-treat; MSI-H=microsatellite instability-high; NR=not reached; pac=paclitaxel; PFS2=progression-free survival 2.

[a] 95% Cis generated using the method of Brookmeyer and Crowley (1982).

- **Progression-free survival 2 (PFS2)**

At IA2, the median follow-up was 32.3 months.

Table 44. Summary of Kaplan-Meier analysis of progression-free survival 2 (IA2) (ITT Analysis Set, MMR/MSI Status per source verified data)

	Overall Population		dMMR/MSI-H Population		MMRp/MSS Population	
	Dostar + carbo/pac (N=245)	Placebo + carbo/pac (N=249)	Dostar + carbo/pac (N=53)	Placebo + carbo/pac (N=65)	Dostar + carbo/pac (N=192)	Placebo + carbo/pac (N=184)
Hazard ratio (95% CI) [a]	0.66 (0.520, 0.842)		0.33 (0.175, 0.627)		0.74 (0.571, 0.970)	
Median PFS2, months (95% CI) [b]	32.3 (24.6, NR)	18.4 (14.9, 22.0)	NR (NR, NR)	21.6 (13.4, 39.1)	24.6 (20.1, 32.6)	15.9 (13.6, 22.0)
PFS2 Probability at 12 Months (95% CI)	76.4% (70.4%, 81.4%)	67.2% (60.9%, 72.7%)	83.9% (70.4%, 91.6%)	70.3% (57.5%, 79.9%)	74.4% (67.3%, 80.1%)	66.1% (58.6%, 72.5%)
PFS2 Probability at 24 Months (95% CI)	56.8% (50.0%, 63.1%)	40.8% (34.4%, 47.0%)	77.6% (63.1%, 86.9%)	46.8% (33.9%, 58.6%)	51.0% (43.3%, 58.2%)	38.7% (31.4%, 45.8%)

carbo=carboplatin; dMMR=mismatch repair deficient; Dostar=dostarlimab; ITT=intent-to-treat; MSI-H=microsatellite instability-high; NR=not reached; pac=paclitaxel; PFS2=progression-free survival 2.

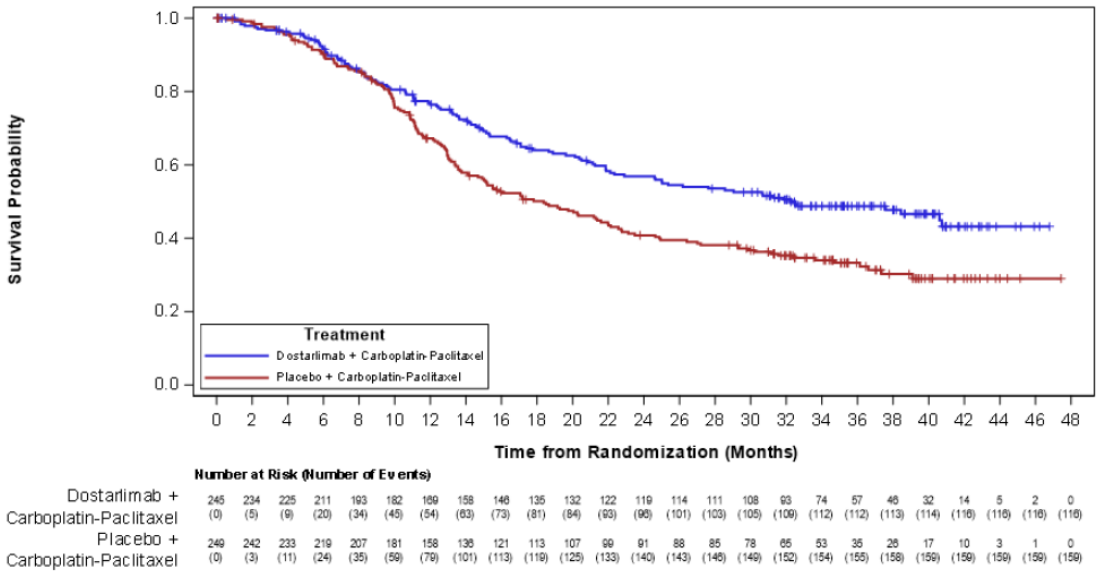
NOTE: Results for dMMR/MSI-H and MMRp/MSS populations were performed on analysis set based on source verified MMR status.

a. Stratified Cox regression.

b. 95% CIs generated using the method of Brookmeyer and Crowley (1982).

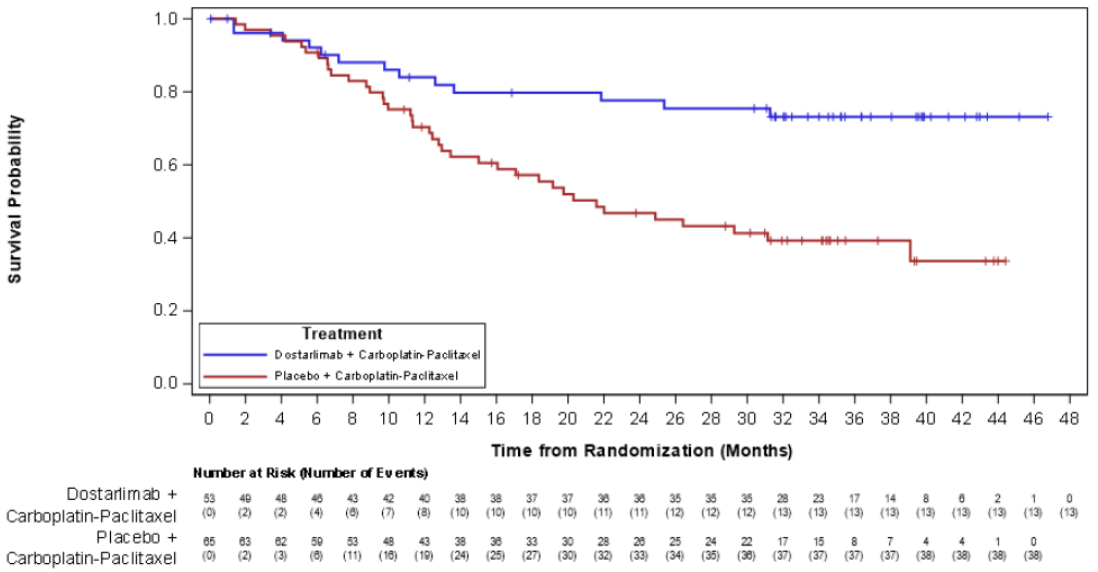
Overall population

Figure 24. Kaplan-Meier curves of progression-free survival 2 (IA2) (Overall population, ITT analysis set, MMR/MSI Status per source verified data)



dMMR/MSI-h population

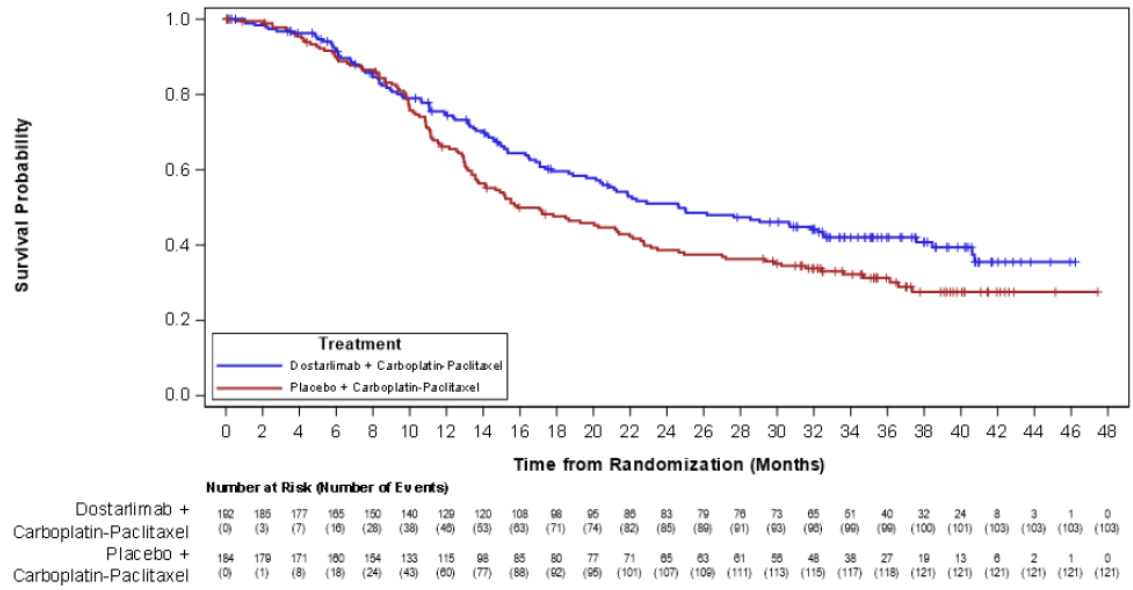
Figure 25. Kaplan-Meier curves of progression-free survival 2 (IA2) (dMMR/MSI-H Population, ITT Analysis Set, MMR/MSI Status per source verified data)



NOTE: Results for dMMR/MSI-H population was performed on analysis set based on source verified MMR status.

MMRp/MSS population

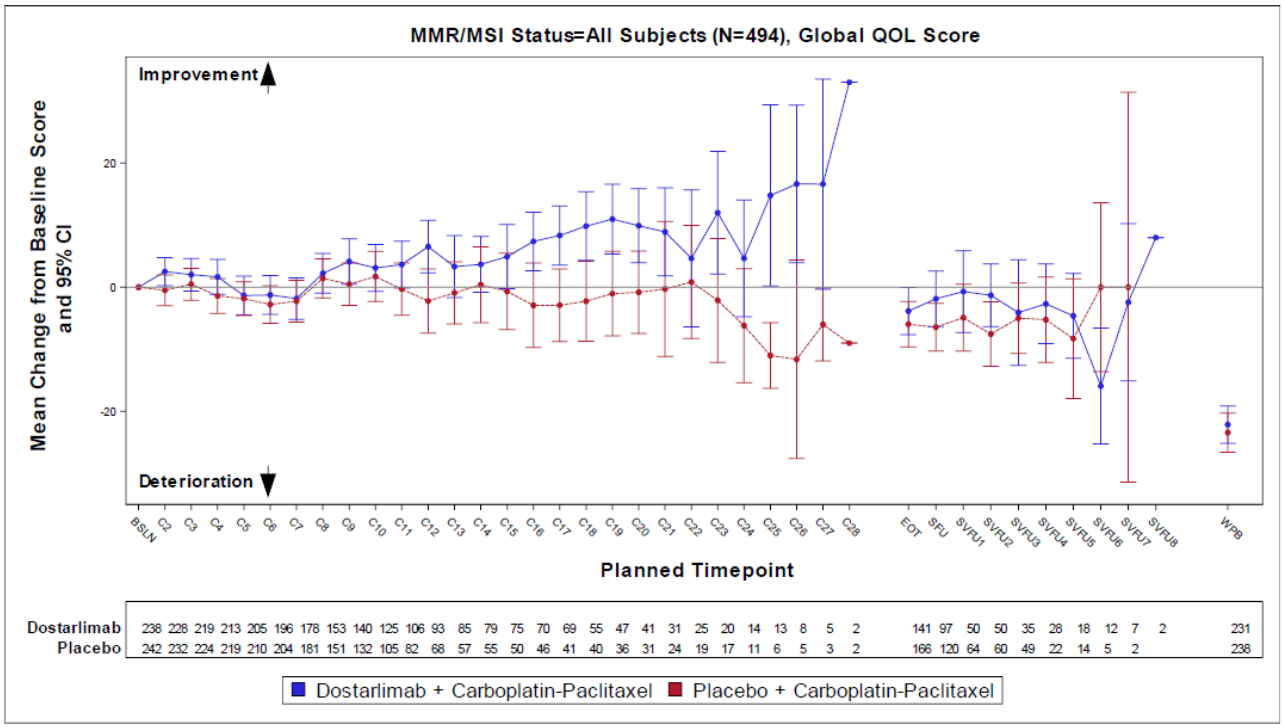
Figure 26. Kaplan-Meier curves of progression-free survival 2 (IA2) (MMRp/MSS Population, ITT Analysis Set, MMR/MSI Status per source verified data)



NOTE: Results for MMRp/MSS population was performed on analysis set based on source verified MMR status.

- **PROs**

Figure 27. Changes from baseline and confidence intervals in EORTC QLQ-C30 global QoL score (ITT analysis set)



Overall population and dMMR/MSI-h population

Table 45. Summary of changes from baseline in EORTC QLQ-C30 global QoL score (ITT analysis set)

	Overall Population		dMMR/MSI-H Population	
	Dostar + carbo/pac (N=245)	Placebo + carbo/pac (N=249)	Dostar + carbo/pac (N=53)	Placebo + carbo/pac (N=65)
All participants (n)	238	242	51	64
Mean (SD) baseline score	67.7 (21.63)	69.7 (21.15)	66.7 (25.91)	67.3 (23.93)
Status at Cycle 7 (n) [a]	178	181	39	48
Mean (SD) change from baseline to Cycle 7	-1.8 (22.79)	-2.3 (23.10)	1.4 (23.33)	-6.0 (26.12)
Improved	41 (23.0%)	47 (26.0%)	14 (35.9%)	12 (25.0%)
Stable	80 (44.9%)	76 (42.0%)	15 (38.5%)	16 (33.3%)
Worsened	57 (32.0%)	58 (32.0%)	10 (25.6%)	20 (41.7%)
Status at Cycle 13 (n)	85	57	27	14
Mean (SD) change from baseline to Cycle 13	3.3 (23.51)	-0.9 (19.25)	7.7 (14.01)	-5.2 (10.26)
Improved	31 (36.5%)	12 (21.1%)	12 (44.4%)	2 (14.3%)
Stable	36 (42.4%)	29 (50.9%)	12 (44.4%)	7 (50.0%)
Worsened	18 (21.2%)	16 (28.1%)	3 (11.1%)	5 (35.7%)

Abbreviations: carbo=carboplatin; dMMR=mismatch repair deficient; Dostar=dostarlimab; EORTC QLQ=European Organization for Research and Treatment of cancer quality of life questionnaire; ITT=intent-to-treat; MSI-H=microsatellite instability-high; pac=paclitaxel; QoL=quality of life.

a. Number of participants with non-missing value at both baseline and the corresponding postbaseline visit

MMRp/MSS population

Table 46. Summary of change from baseline in EORTC-QLQ-C30 global QoL score (MMRp/MSS population, ITT analysis set)

	Dostar + carbo/pac (N=192)	Placebo + carbo/pac (N=184)
All participants (n)	187	178
Mean (SD) baseline score	68.0 (20.38)	70.6 (20.06)
Mean (SD) change from baseline to Cycle 7	-2.7 (22.63)	-0.9 (21.87)
Status at Cycle 7	139	133
Improved	27 (19.4%)	35 (26.3%)
Stable	65 (46.8%)	60 (45.1%)
Worsened	47 (33.8%)	38 (28.6%)
Mean (SD) change from baseline to Cycle 13	0.6 (25.57)	1.6 (19.77)
Status at Cycle 13	58	43
Improved	19 (32.8%)	10 (23.3%)
Stable	24 (41.4%)	22 (51.2%)
Worsened	15 (25.9%)	11 (25.6%)

Abbreviations: carbo=carboplatin; EORTC QLQ=European Organization for Research and Treatment of cancer quality of life questionnaire; Dostar=dostarlimab; ITT=intent-to-treat; MMRp=mismatch repair proficient; MSS=microsatellite stable; pac=paclitaxel; SD=standard deviation.

Ancillary analyses

Subgroup analyses

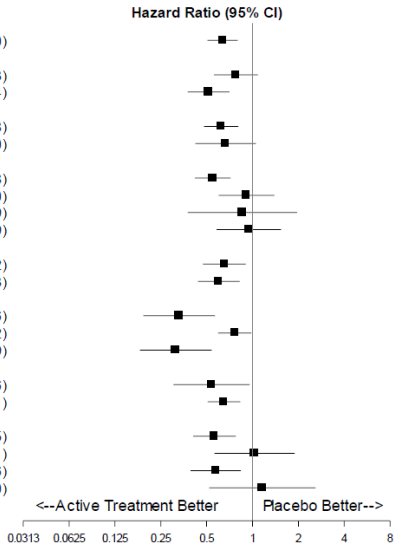
Prespecified subgroup analyses

- PFS

Overall population

Figure 28. Forest plot of progression-free survival and 95% confidence intervals by subgroup – RECIST v.1.1 by Investigator assessment (IA1) (Overall population, ITT analysis set)

Categories	Dostarlimab (No. of Subjects / No. of Events)	Placebo (No. of Subjects / No. of Events)	Dostarlimab (Median PFS - Months)	Placebo (Median PFS - Months)	HR(95% CI)
All Patients	245/135	249/177	11.8	7.9	0.64 (0.507, 0.800)
Age					
<65 yr	127/69	114/72	11.9	9.6	0.78 (0.559, 1.083)
>=65 yr	118/66	135/105	10.6	7.7	0.51 (0.376, 0.704)
Race					
White	189/101	191/135	12.0	7.9	0.62 (0.481, 0.808)
Other	56/34	58/42	9.7	7.8	0.67 (0.422, 1.050)
Region					
North America	171/91	187/133	14.4	7.9	0.55 (0.419, 0.718)
Europe	74/44	62/44	7.8	7.9	0.91 (0.602, 1.390)
Eastern Europe	16/11	14/12	8.3	8.7	0.86 (0.377, 1.959)
Western Europe	58/33	48/32	7.7	7.9	0.95 (0.581, 1.539)
Histology category					
Endometrioid carcinoma	130/64	136/89	12.0	9.5	0.65 (0.473, 0.902)
Other	115/71	113/88	10.6	7.6	0.60 (0.439, 0.823)
MMR/MSI Status*					
dMMR/MSI-H	53/19	65/47	NE	7.7	0.33 (0.192, 0.566)
MMRp/MSS	192/116	184/130	9.9	7.9	0.76 (0.595, 0.982)
dMMR Status (Derived)	53/19	63/47	NE	7.6	0.31 (0.182, 0.539)
Prior External Pelvic Radiotherapy*					
Yes	41/21	45/31	11.8	8.2	0.54 (0.303, 0.956)
No	204/114	204/146	10.6	7.8	0.65 (0.508, 0.831)
Disease Status*					
Recurrent	117/68	119/89	9.9	7.9	0.56 (0.408, 0.775)
Primary Stage III	45/21	47/21	14.5	22.8	1.03 (0.563, 1.891)
Primary Stage IV	83/46	83/67	12.6	7.5	0.57 (0.392, 0.836)
No Disease at Baseline	33/12	30/12	30.3	28.3	1.16 (0.520, 2.590)



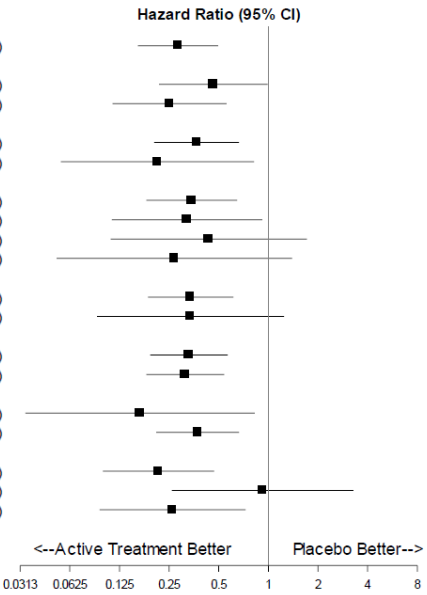
Note: HRs presented are from unstratified Cox regression model.
NOTE: Results for dMMR/MSI-H and MMRp/MSS populations were performed on analysis set based on source verified MMR status.

dMMR/MSI-h population

Figure 29. Forest plot of progression-free survival and 95% confidence intervals by subgroup – RECIST v.1.1 by Investigator assessment (Primary Analysis) (dMMR/MSI-H population, ITT analysis set)

MMR/MSI Status=dMMR/MSI-H

Categories	Dostarlimab (No. of Subjects / No. of Events)	Placebo (No. of Subjects / No. of Events)	Dostarlimab (Median PFS - Months)	Placebo (Median PFS - Months)	HR(95% CI)
All Patients	53/19	65/47	NE	7.7	0.28 (0.162, 0.495)
Age					
<65 yr	30/11	30/18	NE	9.5	0.46 (0.217, 0.990)
>=65 yr	23/8	35/29	NE	7.6	0.25 (0.113, 0.558)
Race					
White	44/16	56/38	NE	8.3	0.37 (0.203, 0.663)
Other	9/3	9/9	NE	5.6	0.21 (0.055, 0.818)
Region					
North America	36/14	50/35	NE	7.6	0.34 (0.182, 0.646)
Europe	17/5	15/12	NE	7.7	0.32 (0.112, 0.916)
Eastern Europe	7/3	7/7	9.9	7.7	0.43 (0.111, 1.710)
Western Europe	10/2	8/5	NE	7.7	0.27 (0.052, 1.392)
Histology category					
Endometrioid carcinoma	45/16	54/37	NE	7.7	0.34 (0.186, 0.612)
Other	8/3	11/10	NE	6.1	0.34 (0.092, 1.247)
MMR/MSI Status*					
dMMR/MSI-H	53/19	65/47	NE	7.7	0.33 (0.192, 0.566)
dMMR Status (Derived)	53/19	63/47	NE	7.6	0.31 (0.182, 0.539)
Prior External Pelvic Radiotherapy*					
Yes	8/2	13/8	NE	6.6	0.17 (0.034, 0.825)
No	45/17	52/39	NE	7.7	0.37 (0.209, 0.663)
Disease Status*					
Recurrent	27/10	32/25	NE	7.7	0.22 (0.099, 0.468)
Primary Stage III	10/4	14/6	NE	NE	0.92 (0.260, 3.279)
Primary Stage IV	16/5	19/16	NE	5.6	0.26 (0.095, 0.728)
No Disease at Baseline	4/0	7/4	NE	20.1	Not Applicable



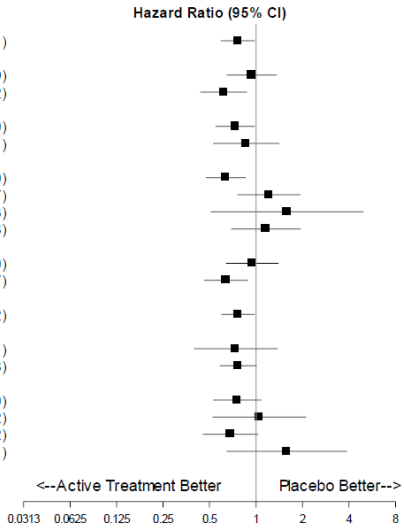
Note: HRs presented are from unstratified Cox regression model.
NOTE: Results for dMMR/MSI-H and MMRp/MSS populations were performed on analysis set based on source verified MMR status.

MMRp/MSS population

Figure 30. Forest plot of progression-free survival and 95% confidence intervals by subgroup – RECIST v.1.1 by Investigator assessment (Primary Analysis) (MMRp/MSS population, ITT analysis set)

MMR/MSI Status=MMRp/MSS

Categories	Dostarlimab (No. of Subjects / No. of Events)	Placebo (No. of Subjects / No. of Events)	Dostarlimab (Median PFS - Months)	Placebo (Median PFS - Months)	HR(95% CI)
All Patients	192/116	184/130	9.9	7.9	0.76 (0.592, 0.981)
Age					
<65 yr	97/58	84/54	9.8	9.8	0.94 (0.647, 1.359)
>=65 yr	95/58	100/76	9.9	7.8	0.62 (0.436, 0.872)
Race					
White	145/85	135/97	9.9	7.9	0.73 (0.547, 0.980)
Other	47/31	49/33	9.7	7.9	0.86 (0.527, 1.411)
Region					
North America	135/77	137/98	11.9	7.9	0.64 (0.472, 0.860)
Europe	57/39	47/32	7.5	9.5	1.21 (0.759, 1.937)
Eastern Europe	9/8	7/5	7.9	11.5	1.59 (0.508, 4.963)
Western Europe	48/31	40/27	7.5	9.5	1.16 (0.691, 1.943)
Histology category					
Endometrioid carcinoma	85/48	82/52	9.6	9.8	0.94 (0.637, 1.400)
Other	107/68	102/78	10.2	7.7	0.64 (0.461, 0.887)
MMR/MSI Status*					
MMRp/MSS	192/116	184/130	9.9	7.9	0.76 (0.595, 0.982)
Prior External Pelvic Radiotherapy*					
Yes	33/19	32/23	11.8	9.8	0.74 (0.395, 1.381)
No	159/97	152/107	9.7	7.8	0.77 (0.582, 1.008)
Disease Status*					
Recurrent	90/58	87/64	9.6	7.9	0.75 (0.528, 1.080)
Primary Stage III	35/17	33/15	14.4	22.8	1.05 (0.524, 2.112)
Primary Stage IV	67/41	64/51	9.9	7.7	0.68 (0.451, 1.032)
No Disease at Baseline	29/12	23/8	20.1	28.3	1.58 (0.645, 3.881)



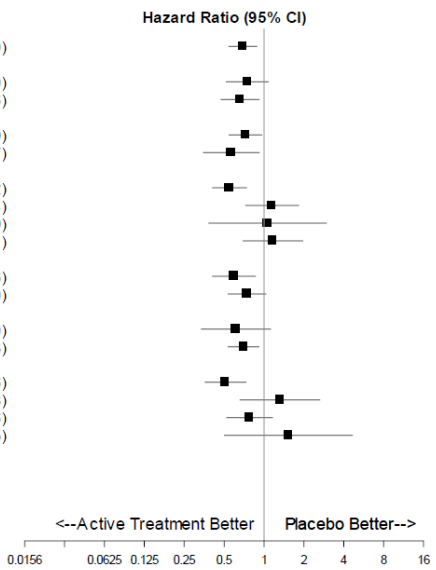
Note: HRs presented are from unstratified Cox regression model.
NOTE: Results for dMMR/MSI-H and MMRp/MSS populations were performed on analysis set based on source verified MMR status.

- OS

Figure 31. Forest plot of overall survival and 95% confidence intervals by subgroup (Overall population, ITT analysis set)

MMR/MSI Status=All Subjects

Categories	Dostarlimab (No. of Subjects / No. of Events)	Placebo (No. of Subjects / No. of Events)	Dostarlimab (Median OS - Months)	Placebo (Median OS - Months)	HR(95% CI)
All Patients	245/109	249/144	44.6	28.2	0.69 (0.539, 0.890)
Age					
<65 yr	127/54	114/57	44.6	35.5	0.75 (0.517, 1.090)
>=65 yr	118/55	135/87	37.6	26.1	0.66 (0.471, 0.926)
Race					
White	189/82	191/104	44.6	32.4	0.72 (0.542, 0.969)
Other	56/27	58/40	32.1	22.0	0.57 (0.348, 0.927)
Region					
North America	171/69	187/112	44.6	26.4	0.55 (0.407, 0.742)
Europe	74/40	62/32	28.6	32.4	1.15 (0.723, 1.834)
Eastern Europe	16/8	14/7	32.7	22.4	1.06 (0.382, 2.969)
Western Europe	58/32	48/25	28.0	32.4	1.17 (0.691, 1.971)
Histology category					
Endometrioid carcinoma	129/44	136/70	44.6	36.5	0.59 (0.407, 0.866)
Other	116/65	113/74	29.8	22.2	0.74 (0.533, 1.040)
Prior External Pelvic Radiotherapy*					
Yes	41/17	45/27	NE	26.1	0.62 (0.335, 1.130)
No	204/92	204/117	40.6	31.1	0.70 (0.534, 0.923)
Disease Status*					
Recurrent	117/48	119/77	44.6	23.1	0.51 (0.357, 0.736)
Primary Stage III	44/18	47/14	NE	NE	1.32 (0.657, 2.658)
Primary Stage IV	84/43	83/53	31.3	22.1	0.78 (0.520, 1.166)
No Disease at Baseline	33/8	30/5	NE	NE	1.53 (0.500, 4.685)



Note: HRs presented are from unstratified Cox regression model.

Subgroup analyses of OS by Region

Figure 32. Kaplan-Meier analysis OS for RUBY Part I Participants in <u>Europe</u> (Overall population, ITT analysis set)

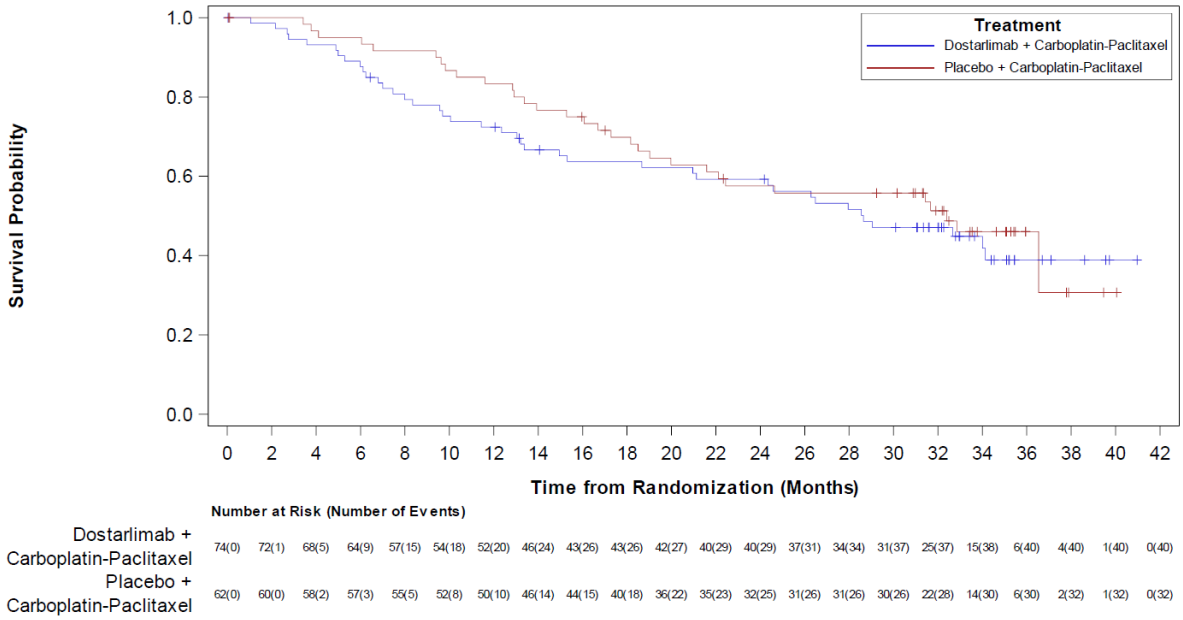


Figure 33. Kaplan-Meier analysis OS for RUBY Part I Participants in <u>North America</u> (Overall population, ITT analysis set)

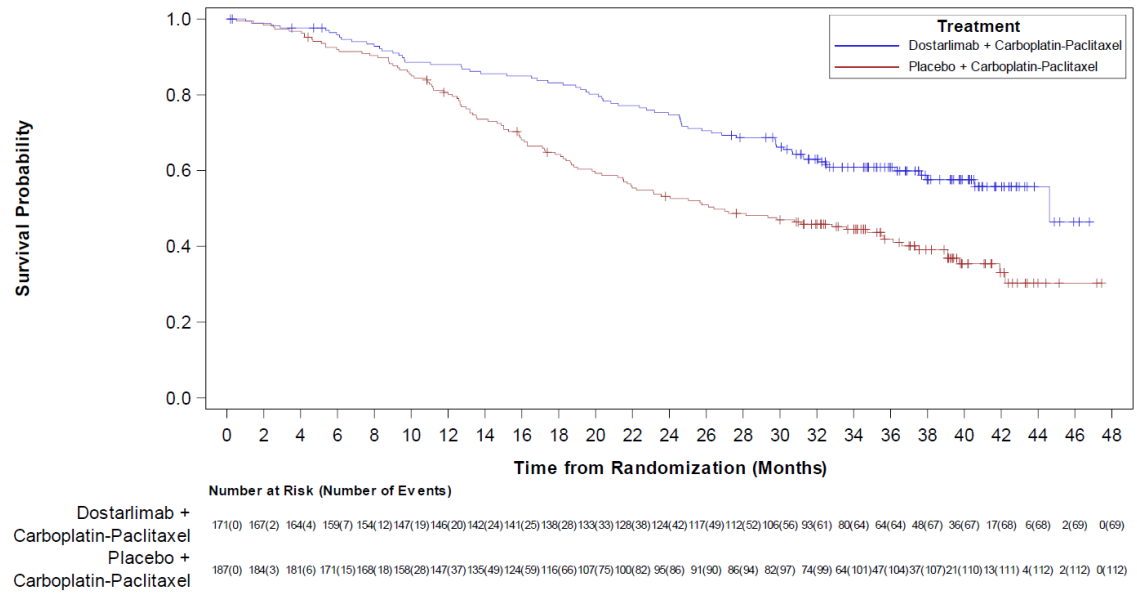


Table 47. Baseline Characteristics for Participants by Region (ITT analysis set)

Characteristic	North America		Europe		Eastern Europe [a]		Western Europe [a]	
	Dostar + carbo/pac (N=171)	Placebo + carbo/pac (N=187)	Dostar + carbo/pac (N=74)	Placebo + carbo/pac (N=62)	Dostar + carbo/pac (N=16)	Placebo + carbo/pac (N=14)	Dostar + carbo/pac (N=58)	Placebo + carbo/pac (N=48)
Age (years)								
Median	64.0	65.0	64.5	66.0	64.0	62.5	66.5	67.0
BMI (kg/m²)								
Median	31.95	34.00	27.80	29.05	28.30	35.15	27.40	26.40
ECOG performance status, n (%)								
N	169	186	72	60	15	14	57	46
0	110 (65.1%)	118 (63.4%)	35 (48.6%)	41 (68.3%)	4 (26.7%)	9 (64.3%)	31 (54.4%)	32 (69.6%)
1	59 (34.9%)	67 (36.0%)	37 (51.4%)	19 (31.7%)	11 (73.3%)	5 (35.7%)	26 (45.6%)	14 (30.4%)
Race, n (%)								
White	124 (72.5%)	136 (72.7%)	65 (87.8%)	55 (88.7%)	16 (100%)	14 (100%)	49 (84.5%)	41 (85.4%)
Black or African American	27 (15.8%)	31 (16.6%)	1 (1.4%)	0	0	0	1 (1.7%)	0
Histology, n (%)								
Endometrioid carcinoma	77 (45.0%)	102 (54.5%)	52 (70.3%)	34 (54.8%)	14 (87.5%)	11 (78.6%)	38 (65.5%)	23 (47.9%)
Serous adenocarcinoma	45 (26.3%)	35 (18.7%)	10 (13.5%)	13 (21.0%)	0	1 (7.1%)	10 (17.2%)	12 (25.0%)
Carcinosarcoma	21 (12.3%)	20 (10.7%)	3 (4.1%)	2 (3.2%)	0	0	3 (5.2%)	2 (4.2%)
Clear Cell adenocarcinoma	5 (2.9%)	3 (1.6%)	3 (4.1%)	5 (8.1%)	1 (6.3%)	0	2 (3.4%)	5 (10.4%
Prior EBT								
Yes	31 (18.1%)	36 (19.3%)	10 (13.5%)	9 (14.5%)	3 (18.8%)	2 (14.3%)	7 (12.1%)	7 (14.6%)
No	140 (81.9%)	151 (80.7%)	64 (86.5%)	53 (85.5%)	13 (81.3%)	12 (85.7%)	51 (87.9%)	41 (85.4%)
MMR Status								
dMMR/MSI-H	36 (21.1%)	50 (26.7%)	17 (23.0%)	15 (24.2%)	7 (43.8%)	7 (50.0%)	10 (17.2%)	8 (16.7%)
MMRp/MSS	135 (78.9%)	137 (73.3%)	57 (77.0%)	47 (75.8%)	9 (56.3%)	7 (50.0%)	48 (82.8%)	40 (83.3%)
Disease Status								
Recurrent	81 (47.4%)	91 (48.7%)	36 (48.6%)	28 (45.2%)	7 (43.8%)	8 (57.1%)	29 (50.0%)	20 (41.7%)
Primary Stage III	36 (21.1%)	35 (18.7%)	8 (10.8%)	12 (19.4%)	1 (6.3%)	4 (28.6%)	7 (12.1%)	8 (16.7%)
Primary Stage IV	54 (31.6%)	61 (32.6%)	30 (40.5%)	22 (35.5%)	8 (50.0%)	2 (14.3%)	22 (37.9%)	20 (41.7%)
Evaluable Disease at Baseline, n (%)								
Yes	144 (84.2%)	169 (90.4%)	68 (91.9%)	50 (80.6%)	16 (100%)	13 (92.9%)	52 (89.7%)	37 (77.1%)
No	27 (15.8%)	18 (9.6%)	6 (8.1%)	12 (19.4%)	0	1 (7.1%)	6 (10.3%)	11 (22.9%)

Abbreviations: BMI=body-mass index; carbo=carboplatin; dMMR=mismatch repair deficient; Dostar=dostarlimab; EBT=external beam therapy; MMR=mismatch repair; ECOG=Eastern Cooperative Oncology Group; MMRp=mismatch repair proficient; MSI-H=microsatellite instability-high; MSS=microsatellite stable; pac=paclitaxel.

a. Eastern Europe and Western Europe data are subsets of the Europe group.

Note: Evaluable disease at baseline is defined as Target or non-target lesions per RECIST v1.1.

Note: Results for MMR status was performed on analysis set based on source verified MMR status.

Table 48. Summary of Subsequent Anti-Cancer Therapy by Region (ITT Analysis Set)

Subsequent Therapy (n[%])	North America		Europe	
	Dostar + carbo/pac (N=171)	Placebo + carbo/pac (N=187)	Dostar + carbo/pac (N=74)	Placebo + carbo/pac (N=62)
Any FUACT	91 (53.2%)	132 (70.6%)	29 (39.2%)	41 (66.1%)
Immunotherapy	41 (24.0%)	88 (47.1%)	1 (1.4%)	7 (11.3%)
Pem/Len	24 (14.0%)	44 (23.5%)	1 (1.4%)	1 (1.6%)
Pem	13 (7.6%)	40 (21.4%)	0	1 (1.6%)
Dostar	0	0	0	3 (4.8%)
MK769A	0	0	0	1 (1.6%)
Other IO [a]	5 (2.9%)	10 (5.3%)	0	1 (1.6%)
Chemotherapy	47 (27.5%)	41 (21.9%)	23 (31.1%)	31 (50.0%)
Hormonal Therapy	15 (8.8%)	19 (10.2%)	7 (9.5%)	11 (17.7%)
Radiation Therapy	22 (12.9%)	25 (13.4%)	6 (8.1%)	4 (6.5%)
Other	8 (4.7%)	17 (9.1%)	1 (1.4%)	3 (4.8%)

Abbreviations: carbo=carboplatin; Dostar=dostarlimab; FUACT=follow up anti-cancer therapy; IO=immunotherapy; Len=lenvatinib; pac=paclitaxel; Pem=pembrolizumab.

a. Other subsequent immunotherapy received by study participants. Therapies included either retifanlimab/epacadostat, durvalumab/cediranib, durvalumab/olaparib, atezolizumab/ipatasertib, avelumab/axitinib, bevacizumab/atezolizumab, investigational product, nivolumab/bms-986207/com701, nivolumab/lucitanib, pembrolizumab/tamoxifen or SGN-ALPV.

Subgroup Analyses of OS by Disease Status

Figure 34. Kaplan-Meier analysis overall survival for Participants with <u>Stage III</u> EC (Overall population, ITT analysis set)

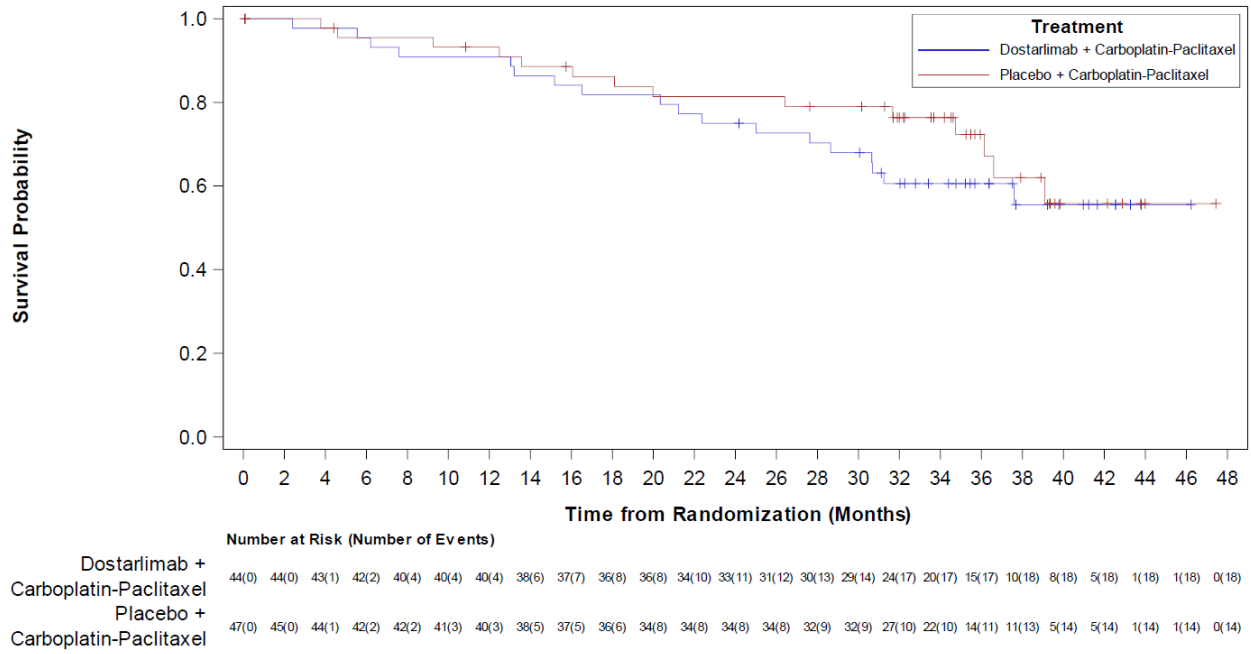


Figure 35. Kaplan-Meier analysis overall survival for Participants with <u>Stage IV</u> EC (Overall population, ITT analysis set)

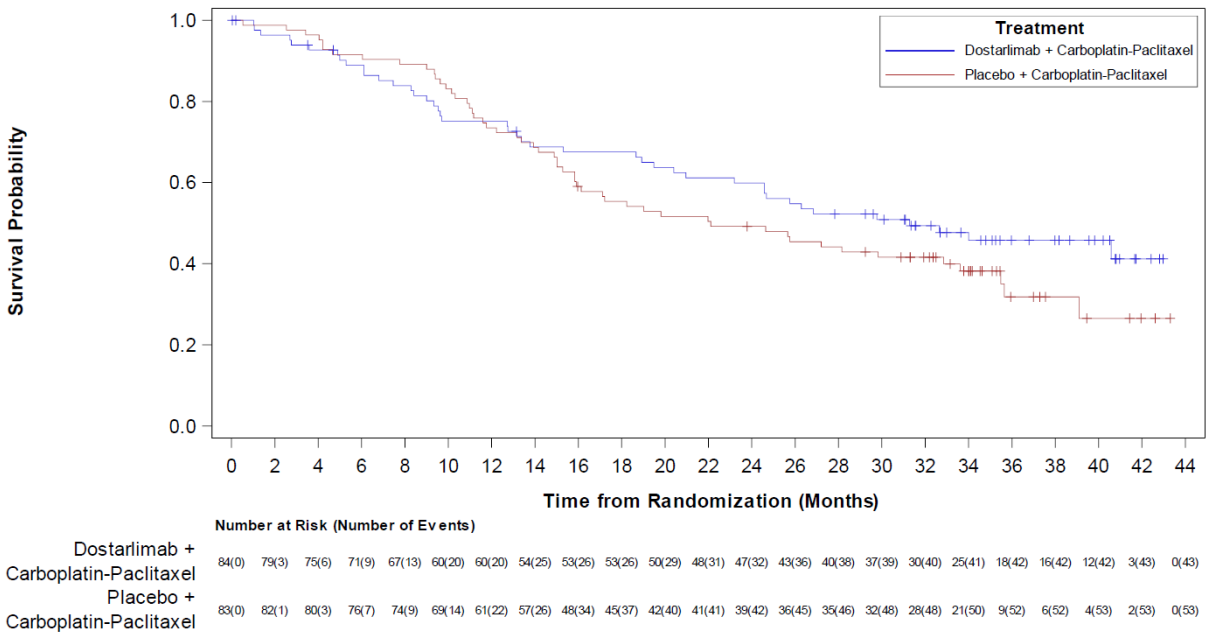


Figure 36. Kaplan-Meier analysis overall survival for Participants with <u>Recurrent</u> EC (Overall population, ITT analysis set)

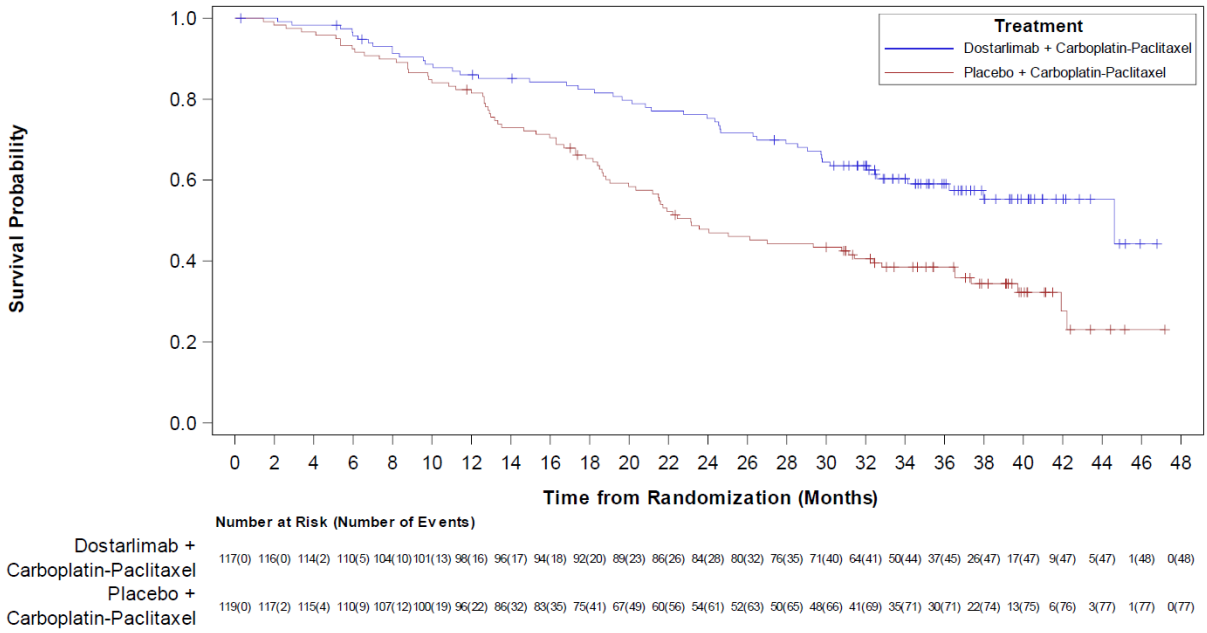


Table 49. Baseline Characteristics for Participants with Stage III and Stage IV/Recurrent EC

Characteristic	Stage III		Stage IV		Recurrent	
	Dostar + carbo/pac (N=44)	Placebo + carbo/pac (N=47)	Dostar + carbo/pac (N=84)	Placebo + carbo/pac (N=83)	Dostar + carbo/pac (N=117)	Placebo + carbo/pac (N=119)
Age (years)						
Median	67.0	63.0	63.5	64.0	64.0	66.0
BMI (kg/m²)						
Median	31.80	32.30	30.50	31.00	30.55	33.90
ECOG performance status, n (%)						
n	44	44	81	83	116	119
0	25 (56.8%)	30 (68.2%)	42 (51.9%)	55 (66.3%)	78 (67.2%)	74 (62.2%)
1	19 (43.2%)	14 (31.8%)	39 (48.1%)	28 (33.7%)	38 (32.8%)	44 (37.0%)
Race, n (%)						
White	35 (79.5%)	36 (76.6%)	67 (79.8%)	62 (74.7%)	87 (74.4%)	93 (78.2%)
Black or African American	5 (11.4%)	5 (10.6%)	10 (11.9%)	12 (14.5%)	13 (11.1%)	14 (11.8%)
Histology, n (%)						
Endometrioid carcinoma	16 (36.4%)	19 (40.4%)	40 (47.6%)	40 (48.2%)	73 (62.4%)	77 (64.7%)
Serous adenocarcinoma	11 (25.0%)	11 (23.4%)	26 (31.0%)	16 (19.3%)	18 (15.4%)	21 (17.6%)
Carcinosarcoma	9 (20.5%)	8 (17.0%)	4 (4.8%)	10 (12.0%)	11 (9.4%)	4 (3.4%)
Clear Cell adenocarcinoma	4 (9.1%)	1 (2.1%)	3 (3.6%)	4 (4.8%)	1 (0.9%)	3 (2.5%)
Prior EBT						
Yes	0	2 (4.3%)	2 (2.4%)	1 (1.2%)	39 (33.3%)	42 (35.3%)
No	44 (100%)	45 (95.7%)	82 (97.6%)	82 (98.8%)	78 (66.7%)	77 (64.7%)
MMR Status						
dMMR/MSI-H	9 (20.5%)	14 (29.8%)	17 (20.2%)	19 (22.9%)	27 (23.1%)	32 (26.9%)
MMRp/MSS	35 (79.5%)	33 (70.2%)	67 (79.8%)	64 (77.1%)	90 (76.9%)	87 (73.1%)
Evaluable Disease at Baseline, n (%)						
Yes	27 (61.4%)	32 (68.1%)	71 (84.5%)	73 (88.0%)	114 (97.4%)	114 (95.8%)
No	17 (38.6%)	15 (31.9%)	13 (15.5%)	10 (12.0%)	3 (2.6%)	5 (4.2%)

Abbreviations: BMI=body-mass index; carbo=carboplatin; dMMR=mismatch repair deficient; Dostar=dostarlimab; EBT=external beam therapy; ECOG=Eastern Cooperative Oncology Group; MMR=mismatch repair; MMRp=mismatch repair proficient; MSI-H=microsatellite instability-high; MSS=microsatellite stable; pac=paclitaxel.
Note: Evaluable disease at baseline is defined as Target or non-target lesions per RECIST v1.1.
NOTE: Results for MMR status was performed on analysis set based on source verified MMR status.

Table 50. Summary of Follow-up Anti-Cancer Therapy by Disease Status (ITT Analysis Set)

Subsequent Therapy (n[%])	Primary Stage III		Primary Stage IV		Recurrent	
	Dostar + carbo/pac (N=44)	Placebo + carbo/pac (N=47)	Dostar + carbo/pac (N=84)	Placebo + carbo/pac (N=83)	Dostar + carbo/pac (N=117)	Placebo + carbo/pac (N=119)
Any FUACT	24 (54.5%)	20 (42.6%)	33 (39.3%)	66 (79.5%)	63 (53.8%)	87 (73.1%)
Chemotherapy	14 (31.8%)	9 (19.1%)	21 (25.0%)	32 (38.6%)	35 (29.9%)	31 (26.1%)
Immunotherapy	6 (13.6%)	11 (23.4%)	16 (19.0%)	37 (44.6%)	20 (17.1%)	47 (39.5%)
Pem/Len	4 (9.1%)	6 (12.8%)	7 (8.3%)	19 (22.9%)	14 (12.0%)	20 (16.8%)
Pem	1 (2.3%)	4 (8.5%)	7 (8.3%)	16 (19.3%)	5 (4.3%)	21 (17.6%)
Durvalumab/olaparib	1 (2.3%)	0	1 (1.2%)	0	0	0
MK7694A	0	1 (2.1%)	0	0	0	0
Radiation Therapy	7 (15.9%)	6 (12.8%)	6 (7.1%)	13 (15.7%)	15 (12.8%)	10 (8.4%)
Hormonal Therapy	3 (6.8%)	3 (6.4%)	5 (6.0%)	11 (13.3%)	14 (12.0%)	16 (13.4%)
Other	1 (2.3%)	5 (10.6%)	2 (2.4%)	4 (4.8%)	6 (5.1%)	11 (9.2%)

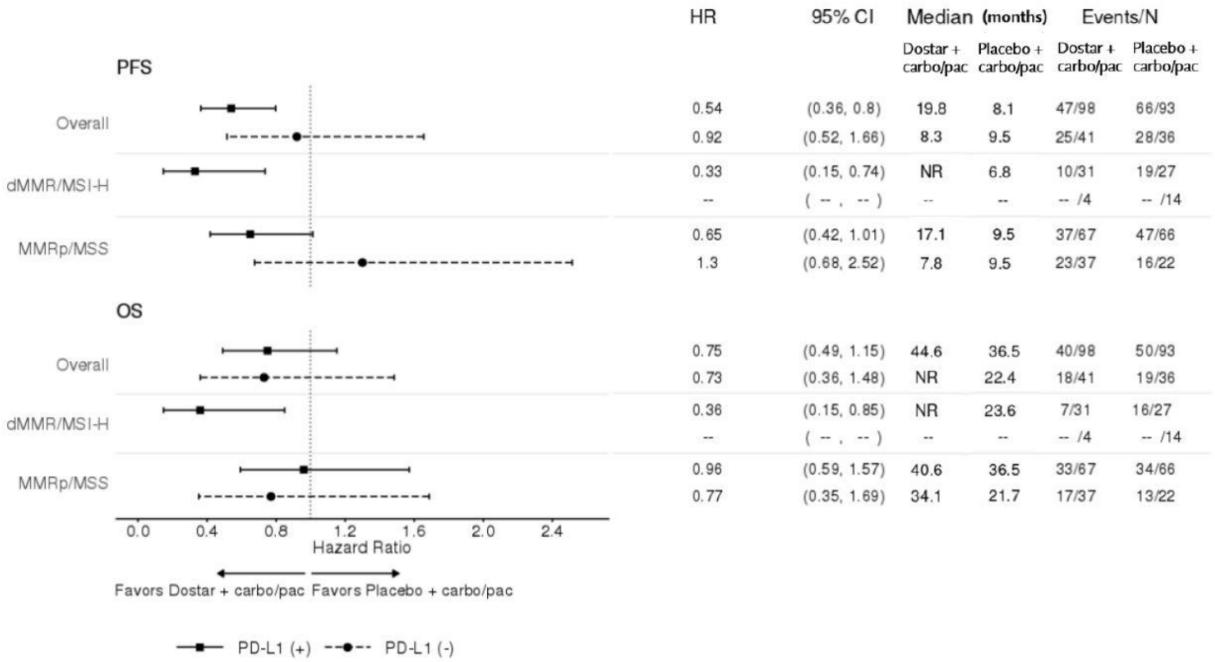
Post-hoc subgroup analyses

- PD-L1 expression

PD-L1 status was evaluated by retrospective central testing in a post-hoc exploratory analysis for biopsy samples collected from RUBY Part 1 participants. PD-L1 status was determined using the anti PD-L1 22C3 antibody (DAKO) to calculate a combined positive score (CPS) on available archival tumour specimens following central testing for MMR status. A CPS cut-off of ≥1 was selected based on receiver operating characteristic (ROC) curve analysis and was used to define PD-L1 positive (PD-L1+) status in an exploratory setting. Participants were neither stratified nor selected according to PD-L1 status, and the study was not powered to detect a difference in PFS or OS according to PD-L1 status.

PD-L1 test results were available for a total of 268/494 participants (54% overall), including 76/118 (64%) participants with dMMR/MSI-H EC and 192/376 (51%) participants with MMRp/MSS EC. Among those with PD-L1 status available, PD-L1+ status (CPS ≥1) was similar but slightly more frequent in dMMR/MSI-H (58 out of 76 [76%]) compared with MMRp/MSS participants (133 out of 192 [69%].

Figure 37. Forest Plot of PFS (IA1) and OS (IA2) by PD-L1 expression (ITT analysis set)



- PFS Excluding Carcinosarcomas from the Primary Analyses

A post-hoc exploratory subgroup analysis was performed for PFS excluding participants with carcinosarcoma: PFS HR=0.64 (95% CI 0.503, 0.815; median PFS 12.0 months vs 7.9 months) in the overall population; PFS HR=0.24 (95% CI 0.133, 0.439; median PFS not reached vs 7.7 months) in the dMMR/MSI-H population, and PFS HR=0.80 (95% CI 0.613, 1.047; median PFS 9.9 months vs 8.2 months) in the MMRp/MSS population.

- PFS based on disease at baseline

A subgroup analysis of participants with no evaluable disease at baseline demonstrated an HR=1.16 (95% CI: 0.520, 2.590). A post-hoc exploratory subgroup analyses assessing PFS was performed as part of IA1 in participants with evaluable disease at baseline (target or non-target lesions) and in participants with measurable disease (target lesions) at baseline.

Table 51. Subgroup Analysis: Summary of Kaplan Meier Analysis of Progression Free Survival in Participants with Evaluable disease (ITT Analysis Set)

Subgroup Analysis	Overall Population		dMMR/MSI-H Population		MMRp/MSS Population	
	Dostar + carbo/pac	Placebo + carbo/pac	Dostar + carbo/pac	Placebo + carbo/pac	Dostar + carbo/pac	Placebo + carbo/pac
PFS by IA for Participants with Target or Non-target Lesions at Baseline Subgroup Analysis						
N	212	219	49	58	163	161
Hazard ratio (95% CI) [a]	0.59 (0.469, 0.754)		0.30 (0.173, 0.536)		0.70 (0.538, 0.911)	
PFS by IA for Participants with Target Lesions at Baseline Subgroup Analysis						
N	172	185	39	46	133	139
Hazard ratio (95% CI) [a]	0.61 (0.471, 0.787)		0.34 (0.187, 0.616)		0.70 (0.530, 0.937)	

carbo=carboplatin; Dostar=dostarlimab; ITT=intent-to-treat; pac=paclitaxel.
Stratified Cox regression model

Sensitivity analyses

Prespecified sensitivity analyses

Several sensitivity analyses were performed to interrogate the data and evaluate for potential biases.

Table 52. Hazard Ratios of Progression-Free Survival from Sensitivity Analyses (ITT Analysis Set)

Sensitivity Analysis	Hazard ratio (95% CI) [a]					
	Overall Population		dMMR/MSI-H Population		MMRp/MSS Population	
	Dostar + carbo/pac (N=245)	Placebo + carbo/pac (N=249)	Dostar + carbo/pac (N=53)	Placebo + carbo/pac (N=65)	Dostar + carbo/pac (N=192)	Placebo + carbo/pac (N=184)
PFS Sensitivity Analysis 1	0.64 (0.510, 0.798)		0.27 (0.156, 0.472)		0.77 (0.602, 0.991)	
PFS Sensitivity Analysis 2	0.81 (0.663, 0.985)		0.38 (0.239, 0.619)		0.94 (0.755, 1.177)	
PFS Sensitivity Analysis 3	0.66 (0.517, 0.853)		0.29 (0.158, 0.543)		0.79 (0.597, 1.038)	
PFS Sensitivity Analysis 4	0.63 (0.504, 0.795)		0.30 (0.169, 0.514)		0.76 (0.588, 0.976)	

Abbreviations: carbo=carboplatin; dMMR=mismatch repair deficient; Dostar=dostarlimab; MMRp=mismatch repair proficient; MSS=microsatellite stable; MSI-H=microsatellite instability-high; pac=paclitaxel; PFS=progression-free survival.

a. Stratified Cox regression model

A paired sensitivity analysis was also performed by defining the dMMR/MSI-H and MMRp/MSS populations based on MMR/MSI classification entered at the time of randomization, in addition to the analysis based on the source verified data at the time of the data cut-off.

Table 53. Hazard Ratios of Progression-Free Survival and Overall Survival from Paired Sensitivity Analyses in the dMMR/MSI-H Population

Paired Sensitivity Analysis	Hazard ratio (95% CI) [a]			
	dMMR/MSI-H Population classification based on value entered at randomization		dMMR/MSI-H Population classification based on source verified value	
	Dostar + carbo/pac (N=60)	Placebo + carbo/pac (N=62)	Dostar + carbo/pac (N=53)	Placebo + carbo/pac (N=65)
PFS Primary Censoring Rule	0.29 (0.172, 0.497)		0.28 (0.162, 0.495)	
PFS Sensitivity Analysis 1	0.28 (0.167, 0.476)		0.27 (0.156, 0.472)	
PFS Sensitivity Analysis 2	0.44 (0.280, 0.678)		0.38 (0.239, 0.619)	
PFS Sensitivity Analysis 3	0.33 (0.181, 0.587)		0.29 (0.158, 0.543)	
PFS Sensitivity Analysis 4	0.30 (0.177, 0.510)		0.30 (0.169, 0.514)	
OS	0.29 (0.129, 0.644)		0.30 (0.127, 0.699)	

Abbreviations: carbo=carboplatin; dMMR=mismatch repair deficient; Dostar=dostarlimab; MSI-H=microsatellite instability-high; pac=paclitaxel; PFS=progression-free survival.

a. Stratified Cox regression model

Table 54. Hazard Ratios of Progression-Free Survival and Overall Survival from Paired Sensitivity Analyses in the MMRp/MSS Population

Paired Sensitivity Analysis	Hazard ratio (95% CI) [a]			
	MMRp/MSS Population classification based on value entered at randomization		MMRp/MSS Population classification based on source verified value	
	Dostar + carbo/pac (N=185)	Placebo + carbo/pac (N=187)	Dostar + carbo/pac (N=192)	Placebo + carbo/pac (N=184)
PFS Primary Censoring Rule	0.78 (0.602, 1.002)		0.76 (0.592, 0.981)	
PFS Sensitivity Analysis 1	0.79 (0.613, 1.012)		0.77 (0.602, 0.991)	
PFS Sensitivity Analysis 2	0.95 (0.763, 1.193)		0.94 (0.755, 1.177)	
PFS Sensitivity Analysis 3	0.79 (0.597, 1.041)		0.79 (0.597, 1.038)	
PFS Sensitivity Analysis 4	0.77 (0.598, 0.996)		0.76 (0.588, 0.976)	
OS	0.76 (0.535, 1.069)		0.73 (0.515, 1.024)	

Abbreviations: carbo=carboplatin; Dostar=dostarlimab; MMRp=mismatch repair proficient; MSS=microsatellite stable; pac=paclitaxel; PFS=progression-free survival.

a. Stratified Cox regression model

Post-hoc sensitivity analyses

- PFS Censored at last Tumour Assessment Regardless of if Still on Therapy

A further post-hoc sensitivity analysis was performed based on censoring rule 3 "censored at last TA regardless of if still on therapy or not", showing the following results: PFS HR=0.63 (95% CI 0.506, 0.785; median PFS 11.8 months vs 7.9 months) in the overall population; PFS HR=0.27 (95% CI 0.154, 0.462; median PFS not reached vs 7.6 months) in the dMMR/MSI-H population, and PFS HR=0.76 (95% CI 0.596, 0.971; median PFS 9.9 months vs 8.1 months) in the MMRp/MSS population.

- Tipping Point and Imputational Analyses

Post-hoc tipping point and imputation analyses were performed to investigate the robustness of the clinical benefit observed with PFS by investigator assessment and OS in RUBY Part 1. These analyses assess the impact of participants who were categorized to be censored early.

For purposes of these analyses, early censored (early dropout) participants were participants who met any of the following criteria:

- Early Censoring Category 1: Any participant who withdrew consent from study and was censored with follow-up ended,
- Early Censoring Category 2: Any participant who was lost to follow-up and was censored with follow-up ended,
- Early Censoring Category 3: Any participant who was censored at randomization with follow-up ended,
- Early Censoring Category 4: Any participant who was censored within 90 days post-randomization despite being listed as follow-up ongoing in the clinical database.

The tipping point and imputation analyses of PFS and OS were performed for both the overall population and the MMRp/MSS population. Consistent with the primary analyses of the primary endpoints, PFS analyses were performed using data from IA1 (DCO 28 Sept 2022) and OS analyses were performed based on IA2 (DCO 22 September 2023). Consistent with the primary analysis model, data were analyzed using a Cox regression model, stratified by MMR/MSI status, prior external pelvic radiotherapy and disease status in the overall population, and by the latter two stratification factors in the MMRp/MSS population. Results from the MMRp/MSS population are presented based on source-verified MMR/MSI status unless otherwise noted. Paired sensitivity analyses were also conducted based on the randomized MMR/MSI status to further assess consistency of the results.

The baseline characteristics of participants censored early for PFS were similar to those in the overall trial population. The characteristics of participants by MMR/MSI status, histology and race were similar to those seen overall. There was a higher proportion of primary advanced Stage III participants among those censored early for PFS in the placebo arm (39%) compared to the overall population (19%) and conversely a lower proportion of Primary Stage IV participants (11% in early censored on the control arm vs. 33% overall). No such differences by disease status were observed comparing the participants censored early for PFS in the dostarlimab arm to the overall population.

The baseline characteristics of participants censored early for OS were also similar to those in the overall population. Within the placebo arm the participants censored early for OS had similar baseline characteristics to those in the overall population except in terms of disease status where they had a higher proportion of Primary Stage III participants (55%) compared to the overall population (19%). It must be noted however that there were only 9 participants censored early for OS on the placebo arm so a difference in proportions of baseline characteristics is not unexpected given the size of the subset. No such differences by disease status were observed comparing the participants censored early for OS in the dostarlimab arm to the overall population.

Table 55. Summary of Early Dropouts From the Study for Participants by Reason (Overall Population)

		Dostar + carbo/pac (N=245)	Placebo + carbo/pac (N=249)
Early Censoring Category	**PFS by Investigator Assessment**		
NA	Total Early Withdrawal participants [a]	23 (9.4%)	18 (7.2%)
1	Withdrew Consent from the study	15 (6.1%)	11 (4.4%)
2	Lost to Follow-up	3 (1.2%)	1 (0.4%)
3	Randomized and Censored with follow-up ended on Day 1 [b]	10 (4.0%)	11 (4.4%)
4	Following up ongoing and censored before 90 days	0	0
Early Censoring Category	**Overall Survival**		
NA	Total Early Withdrawal participants [a]	8 (3.3%)	9 (3.6%)
1	Withdrew Consent from the study	6 (2.4%)	8 (3.2%)
2	Lost to Follow-up	0	0
3	Randomized and Censored with follow-up ended on Day 1	0	0
4	Following up ongoing and censored before 90 days	2 (0.8%)	1 (0.4%)

carbo=carboplatin; Dostar=dostarlimab; pac=paclitaxel; CI=confidence interval; HR=hazard ratio; NA=not applicable; PFS=progression-free survival.

a. Due to the small number of participants who met the early censored criteria, participants were considered as an early dropout participant without regard to time of censoring.

b. Five participants in each arm were censored due to consent withdrawal or lost to follow-up.

- Tipping Point Analyses

In order to evaluate the impact of the early censored participants on the primary efficacy results, tipping point analyses were performed for PFS and OS in the overall population and in the MMRp/MSS population. In the tipping point analyses, the early censored participants in the placebo plus carboplatin-paclitaxel arm were assumed to have a reduced risk of progression or death compared to completers (those participants that did not fall into any of the four early censoring categories). A grid search algorithm was used to find the minimal percentage reduction needed (in increments of 5%, from 5% to 95%) such that the confidence interval for the hazard ratio comparing the dostarlimab and carboplatin-paclitaxel arm to the placebo and carboplatin-paclitaxel arm will include 1. If a participant's imputed PFS/OS time was greater than their maximum follow-up time for PFS/OS (either due to death or the maximum time from randomization to data cut-off) then the maximum follow-up time was used. If this maximum follow-up time was a death, then the imputed time was considered an event for PFS/OS, otherwise it was considered a censoring.

For each tipping point analysis, confidence intervals for the hazard ratio were constructed based on the efficacy boundary (2-sided) in accordance with the RUBY study statistical testing framework.

Table 56. Tipping Point Statistical Testing Framework

	Overall Population		MMRp/MSS Population [a]	
Endpoint	**PFS**	**OS**	**PFS**	**OS**
p-value stopping boundary	0.04	0.02202	NA	NA
Confidence Interval (%)	96	97.8	95	95

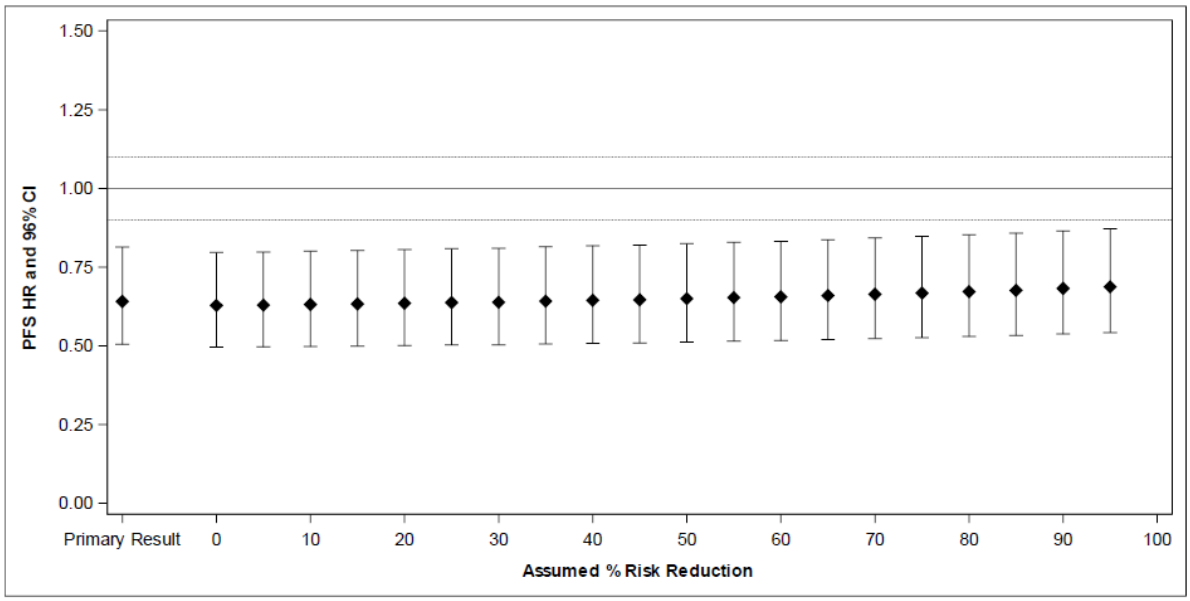
MMRp=mismatch repair proficient; MSS=microsatellite stable; NA = not applicable; PFS=progression-free survival; OS=overall survival.

a. Analysis of the MMRp/MSS population was pre-specified exploratory.

NOTE: This table is based on the GSK statistical testing framework.

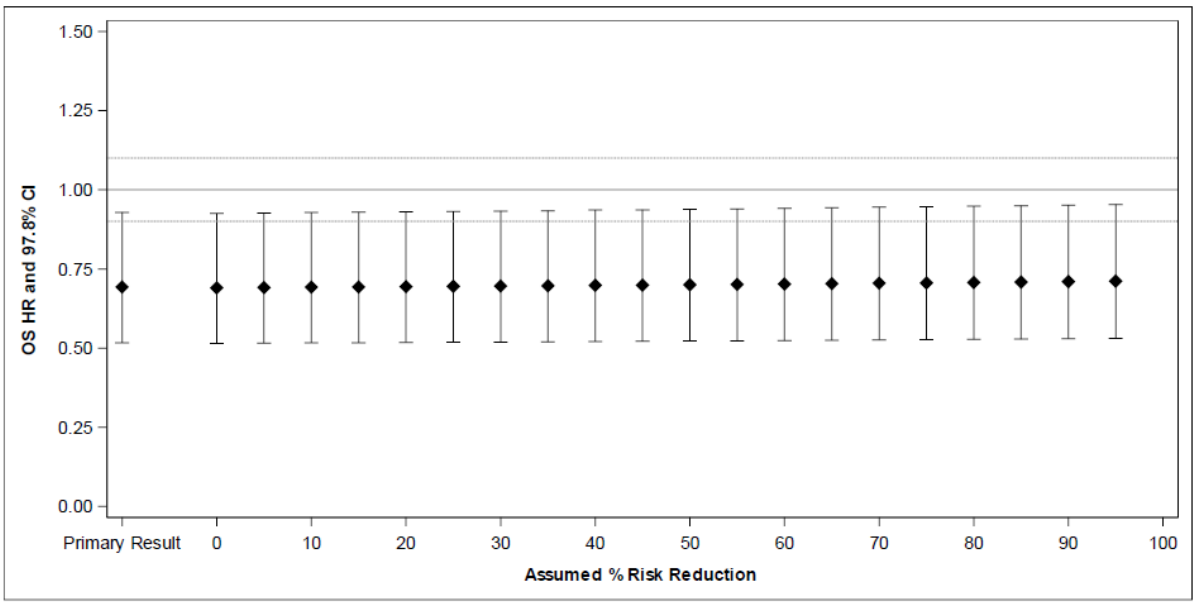
Overall population

Figure 38. Tipping Point Analysis for PFS: Change in Estimated Hazard Ratios for Varying Assumptions for Participants who were Early Censored in RUBY Part I (Overall Population) Imputation in Control Arm Only



PFS=progression-free survival.

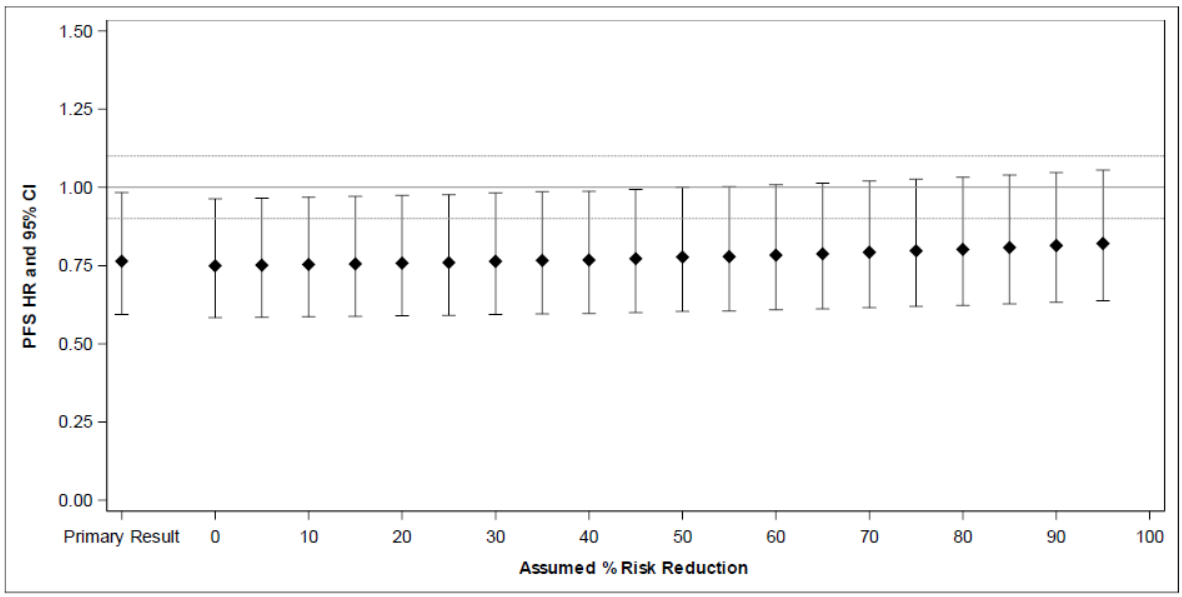
Figure 39. Tipping Point Analysis for OS: Change in Estimated Hazard Ratios for Varying Assumptions for Participants who were Early Censored from RUBY Part I (Overall Population) Imputation in Control Arm Only



OS=overall survival

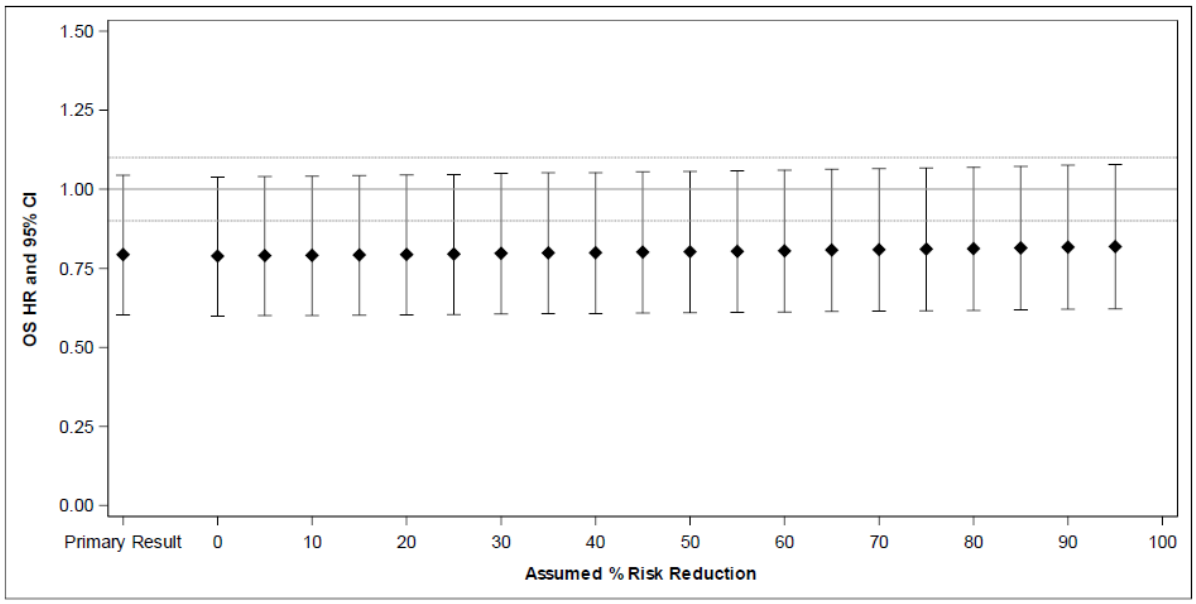
MMRp/MSS population

Figure 40. Tipping Point Analysis for PFS: Change in Estimated Hazard Ratios for Varying Assumptions for Participants who were Early Censored from RUBY Part I (MMRp/MSS Population) Imputation in Control Arm Only



MMRp=mismatch repair proficient; MSS=microsatellite stable; PFS=progression-free survival.
NOTE: Results for MMRp/MSS population was performed on analysis set based on source verified MMR status.

Figure 41. Tipping Point Analysis for OS: Change in Estimated Hazard Ratios for Varying Assumptions for Participants who were Early Censored from RUBY Part I (MMRp/MSS Population) Imputation in Control Arm Only



MMRp=mismatch repair proficient; MSS=microsatellite stable; OS=overall survival.
NOTE: Results for MMRp/MSS population was performed on analysis set based on source verified MMR status.

- Imputational Analysis

Sensitivity analyses were performed in which PFS and OS times for the early dropout participants who met the censoring criteria were imputed. Analyses were performed separately for PFS and for OS. In the

multiple imputations, the early dropout participants were sampled from the top 20% best event times observed (based on Kaplan-Meier estimation to account for censoring).

The following multiple imputation sensitivity analyses were performed:

- Multiple Imputation 1: Imputing control arm early dropouts using all participants.
- Multiple Imputation 2: Imputing control arm early dropouts using only control participants.
- Multiple Imputation 3: Imputing all early dropouts using all participants.
- Multiple Imputation 4: Imputing all early dropouts using all participants within their own treatment arm.

Hazard ratios and confidence intervals for PFS and OS are presented using the same confidence interval boundaries as presented for the tipping point analyses.

Table 57. Sensitivity Analyses of PFS to Investigate Impact of Early Censoring

Sensitivity Analysis of PFS	Key Assumption/ Description	Overall Population HR (96% CI)	MMRp/MSS Population HR (95% CI)
Primary Analysis per protocol	NA	0.64 (0.50, 0.81)	0.76 (0.59, 0.98)
PFS Multiple Imputation 1	Control arm PFS times sampled from 20% best PFS times in both arms	0.69 (0.54, 0.86)	0.82 (0.64, 1.05)
PFS Multiple Imputation 2	Control arm PFS times sampled from 20% best PFS times in control arm	0.68 (0.54, 0.86)	0.82 (0.64, 1.05)
PFS Multiple Imputation 3	Both treatment arms PFS times sampled from 20% best PFS times in both arms	0.62 (0.49, 0.78)	0.73 (0.57, 0.94)
PFS Multiple Imputation 4	Both treatment arms PFS times sampled from 20% best PFS times within each treatment arm	0.61 (0.48, 0.77)	0.73 (0.57, 0.94)
PFS Tipping Point Analysis	Overall population: No tipping point. MMRp/MSS population: 55% lower risk of event than other control arm participants.	NA	0.78 (0.61, 1.00)

CI=confidence interval; HR=hazard ratio; MMRp=mismatch repair proficient; MSS=microsatellite stable; NA=not applicable; PFS=progression-free survival.
NOTE: Results for MMRp/MSS population was performed on analysis set based on source verified MMR status.

Table 58. Sensitivity Analyses of OS to Investigate Impact of Early Censoring

Sensitivity Analysis of OS	Key Assumption/ Description	Overall Population HR (97.8% CI)	MMRp/MSS Population HR (95% CI)
Primary Analysis per protocol	NA	0.69 (0.52, 0.93)	0.79 (0.60, 1.04)
OS Multiple Imputation 1	Control arm OS times sampled from 20% best OS times in both arms	0.71 (0.53, 0.96)	0.82 (0.62, 1.08)
OS Multiple Imputation 2	Control arm OS times sampled from 20% best OS times in control arm	0.71 (0.53, 0.96)	0.82 (0.62, 1.08)
OS Multiple Imputation 3	Both treatment arms OS times sampled from 20% best OS times in both arms	0.68 (0.51, 0.91)	0.78 (0.59, 1.03)
OS Multiple Imputation 4	Both treatment arms OS times sampled from 20% best OS times within each treatment arm	0.68 (0.51, 0.91)	0.78 (0.59, 1.03)
OS Tipping Point Analysis	Overall population: No tipping point. MMRp/MSS population: CI from primary analysis included 1.	NA	NA

CI=confidence interval; HR=hazard ratio; MMRp=mismatch repair proficient; MSS=microsatellite stable; NA=not applicable; OS=overall survival.
NOTE: Results for MMRp/MSS population was performed on analysis set based on source verified MMR status.

- Additional sensitivity analyses: restricted mean survival time (RSMT) and weighted log-rank using the Fleming-Harrington family of test statistics

Table 59. Summary of Sensitivity Analyses for Overall Survival in Overall and MMRp/MSS Populations

	Overall	MMRp/MSS
	Difference in RMST estimate (95% CI), months	
12 months	0.0 (-0.4, 0.4)	-0.1 (-0.5, 0.4)
24 months	1.3 (0.1, 2.5)	0.9 (-0.4, 2.3)
36 months	2.7 (0.6, 4.8)	1.8 (-0.5, 4.2)
46 months	4.3 (1.5, 7.1)	2.9 (-0.3, 6.1)
	One-sided p-value from WLR test	
Early difference (FH[1,0])	0.0025	0.0511
Middle difference (FH[1,1])	0.0008	0.0324
Late difference (FH[0,1])	0.0018	0.0540

Source: Appendix 1, Tables 14.2.2.2 and 14.2.2.4.
Note: p-values for the stratified log-rank test conducted as the primary analyses were p=0.0020 for the overall population and p=0.0493 for the MMRp/MSS population (m5.3.5.1, RUBY Part 1 IA2 CSR, Section 6.1).

Table 60. Summary of Sensitivity Analyses for Progression Free Survival per Investigator Assessment in Overall and MMRp/MSS Populations

	Difference in RMST estimate (95% CI), months	
	Overall	MMRp/MSS
12 months	0.9 (0.3, 1.6)	0.6 (-0.1, 1.4)
24 months	3.2 (1.7, 4.8)	2.1 (0.3, 3.8)
33 months	4.7 (2.5, 6.9)	2.8 (0.4, 5.2)
	One-sided p-value from WLR test	
Early difference [FH(1,0)]	0.0002	0.0236
Middle difference [FH(1,1)]	<0.0001	0.0144
Late difference [FH(0,1)]	<0.0001	0.0380

Source: Appendix 1, Tables 14.2.2.1 and 14.2.2.3.
Note: p-values for the stratified log-rank test conducted as the primary analyses were p<0.0001 for the overall population and p=0.0177 for the MMRp/MSS population (m5.3.5.1, RUBY Part 1 IA1 CSR, Section 6.1.1.1 and 6.3.1).

Summary of main study

The following table summarises the efficacy results from the main studies supporting the present application. This summary should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Table 61. Summary of Efficacy for trial RUBY Part 1

Title: A Phase 3, Randomized, Double-blind, Multicenter Study of Dostarlimab (TSR-042) plus Carboplatin-paclitaxel versus Placebo plus Carboplatin-paclitaxel in Patients with Recurrent or Primary Advanced Endometrial Cancer (RUBY)	
Study identifier	Study number: 213361 Sponsor Protocol No.: 4010-03-001 EudraCT No.: 2019-001576-11 Additional Study Identifiers: ENGOT EN-6/GOG-3031

Design	RUBY is a Phase 3, randomized, double-blind, multicenter study. Part 1 of the study is to evaluate the efficacy and safety of treatment with dostarlimab plus carboplatin-paclitaxel followed by dostarlimab versus treatment with placebo plus carboplatin-paclitaxel followed by placebo in participants with primary advanced (Stage III or IV) or recurrent endothelial cancer (EC)		
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:		From 07-Aug-2019. Ongoing. Not applicable. Not applicable.
Hypothesis	Superiority		
Treatment groups	Dostarlimab plus carboplatin-paclitaxel		Dostarlimab (500 mg IV every 3 weeks – 6 cycles) plus carboplatin-paclitaxel, followed by dostarlimab (1000 mg IV every 6 weeks; up to 3 years). N=245
	Placebo plus carboplatin-paclitaxel		Placebo plus carboplatin-paclitaxel (every 3 weeks – 6 cycles) followed by placebo (every 6 weeks; up to 3 years). N=249
Endpoints and definitions	Dual-primary endpoints	PFS by investigator	Time from the date of randomization to the earliest date of radiographic assessment of PD or death by any cause in the absence of PD, whichever occurs first. Tumor response will be evaluated using RECIST v.1.1
		OS	Time from randomization to the date of death by any cause
	Secondary efficacy endpoints	PFS by BICR	Time from randomization to the earliest date of assessment of PD per RECIST v.1.1 or death by any cause in the absence of PD per RECIST v.1.1, whichever occurs first
		PFS2	Time from treatment randomization to the date of assessment of progression on the first subsequent anticancer therapy following study intervention or death by any cause, whichever was earlier
		ORR by investigator and BICR	Proportion of participants with a best overall response (BOR) of complete response (CR) or partial response (PR) per RECIST v.1.1
		DCR by investigator and BICR	Proportion of participants who have achieved a BOR of CR, PR, or stable disease per RECIST v.1.1
		DoR by investigator and BICR	Time from first documentation of CR or PR until the time of first documentation of subsequent PD per RECIST v.1.1 or death by any cause in the absence of PD per RECIST v.1.1, whichever occurred first
Database lock	Interim Analysis 1 (IA1): DCO 28-Sept-2022 (data unblinding: 23-Nov-2022) Interim Analysis 2 (IA2): DCO 22-Sept-2023 (data unblinding: 20-Oct-2023)		

Results and Analysis

Analysis description	**Primary Analysis**				
Analysis population and time point description	**PFS by investigator in overall, and dMMR/MSI-H populations (IA1)**				
		Overall population		dMMR/MSI-H Population	
Descriptive statistics and	Treatment group	Dostar + carbo/pac	Placebo + carbo/pac	Dostar + carbo/pac	Placebo + carbo/pac

estimate variability	Number of participants	245	249	53	65
	PFS by investigator (median, months)	11.8	7.9	NR	7.7
	95% CI	(9.6, 17.1)	(7.6, 9.5)	(11.8, NR)	(5.6, 9.7)
Effect estimate per comparison	Comparison groups	Dostarlimab vs Placebo		Dostarlimab vs Placebo	
	Hazard ratio (95% CI)	0.64 (0.507, 0.800)		0.28 (0.162, 0.495)	
	p-value of 1-sided stratified log-rank test	<0.0001		<0.0001	
Analysis population and time point description	**OS in overall population (IA2)**				
Descriptive statistics and estimate variability	Treatment group	Dostar + carbo/pac		Placebo + carbo/pac	
	Number of participants	245		249	
	OS (median, months)	44.6		28.2	
	95% CI	(32.6, NR)		(22.1, 35.6)	
Effect estimate per comparison	Comparison groups	Dostarlimab vs Placebo			
	Hazard ratio (95% CI)	0.69 (0.539, 0.890)			
	p-value of 1-sided stratified log-rank test	0.0020			
Analysis description	**Secondary analysis**				
Analysis population and time point description	**PFS by BICR in overall, dMMR/MSI-H and MMRp/MSS populations (IA1)**				
		Overall population		dMMR/MSI-H Population	MMRp/MSS population
Descriptive statistics and estimate variability	Treatment group	Dostar + carbo/pac	Placebo + carbo/pac	Dostar + carbo/pac / Placebo + carbo/pac	Dostar + carbo/pac / Placebo + carbo/pac
	Number of participants	245	249	53 / 65	192 / 184
	Median PFS, months (95% CI)	13.0 (9.8, 22.8)	8.8 (7.7, 9.7)	NR (NR, NR) / 9.5 (7.0, 11.7)	9.9 (9.5, 14.7) / 8.8 (7.7, 9.7)
Effect estimate per comparison	Comparison groups	Dostarlimab vs Placebo		Dostarlimab vs Placebo	Dostarlimab vs Placebo
	Hazard ratio (95% CI)	0.66 (0.517, 0.853)		0.29 (0.158, 0.543)	0.79 (0.597, 1.038)

2.4.3. Special populations

The summary of the number of patients by age groups who received dostarlimab + carboplatin/paclitaxel and placebo + carboplatin/paclitaxel per subgroup (dMMR/MSI-H and pMMR/MSS) is shown in the tables below.

Table 62. Special populations by age group in all patients

MMR/MSI status: All subjects

Characteristic	Dostarlimab + Carboplatin/Paclitaxel (N=245)	Placebo + Carboplatin/Paclitaxel (N=249)	Total (N=494)
Age (years)			
n	245	249	494
Mean (std)	64.0 (9.20)	63.9 (10.14)	63.9 (9.68)
Median	64.0	65.0	65.0
Q1, Q3	58.0, 71.0	59.0, 70.0	58.0, 71.0
Min, Max	41, 81	28, 85	28, 85
Age Group [n (%)]			
n	245	249	494
<=18	0	0	0
19-64	127 (51.8%)	114 (45.8%)	241 (48.8%)
65-74	90 (36.7%)	98 (39.4%)	188 (38.1%)
>=75	28 (11.4%)	37 (14.9%)	65 (13.2%)

Table 63. Special populations by age group in the dMMR/MSI-H population

MMR/MSI status: dMMR/MSI-H

Characteristic	Dostarlimab + Carboplatin/Paclitaxel (N=53)	Placebo + Carboplatin/Paclitaxel (N=65)	Total (N=118)
Age (years)			
n	53	65	118
Mean (std)	63.5 (10.05)	63.1 (10.57)	63.3 (10.29)
Median	61.0	66.0	64.0
Q1, Q3	58.0, 71.0	56.0, 70.0	57.0, 70.0
Min, Max	45, 81	39, 85	39, 85
Age Group [n (%)]			
n	53	65	118
<=18	0	0	0
19-64	30 (56.6%)	30 (46.2%)	60 (50.8%)
65-74	13 (24.5%)	27 (41.5%)	40 (33.9%)
>=75	10 (18.9%)	8 (12.3%)	18 (15.3%)

Table 64. Special populations by age group in the pMMR/MSS population

MMR/MSI status: MMRp/MSS

Characteristic	Dostarlimab + Carboplatin/Paclitaxel (N=192)	Placebo + Carboplatin/Paclitaxel (N=184)	Total (N=376)
Age (years)			
n	192	184	376
Mean (std)	64.1 (8.98)	64.2 (10.00)	64.1 (9.48)
Median	64.0	65.0	65.0
Q1, Q3	58.0, 71.0	59.0, 71.0	58.5, 71.0
Min, Max	41, 81	28, 83	28, 83
Age Group [n (%)]			
n	192	184	376
<=18	0	0	0
19-64	97 (50.5%)	84 (45.7%)	181 (48.1%)
65-74	77 (40.1%)	71 (38.6%)	148 (39.4%)
>=75	18 (9.4%)	29 (15.8%)	47 (12.5%)

2.4.4. Discussion on clinical efficacy

The scope of this variation concerns an extension of the indication for Jemperli, in combination with carboplatin and paclitaxel for the treatment of adult patients with primary advanced or recurrent EC and who are candidates for systemic therapy. To support this application, IA2 results from study RUBY Part 1 have been submitted.

Of note, in October 2023 the CHMP recommended the authorisation of Jemperli in combination with carboplatin and paclitaxel for the treatment of adult patients with mismatch repair deficient (dMMR)/ microsatellite instability high (MSI-H) [thereinafter referred as "dMMR/MSI-h"] primary advanced or

recurrent EC and who are candidates for systemic therapy (EMEA/H/C/005204/II/0023). At the DCO for that submission (28 September 2022), the MAH presented the results of IA1, in which one of the dual-primary endpoints was met (PFS by investigator), while the other dual-primary endpoint (OS) had not met statistical significance yet. The indication sought by the MAH at that moment was solely for the subset of dMMR/MSI-h patients and, therefore, the granted indication referred only to this subset of the overall population included in the RUBY Part 1 study.

With the current variation the MAH seeks to obtain the indication for the overall population, presenting the IA2 results in which OS met statistical significance. This IA2 submission includes only the results of OS (dual-primary endpoint) and PFS2 (secondary endpoint), with no (new) additional results for the other endpoints. Therefore, the data assessed in this submission is compounded by the newly submitted results of IA2 (OS and PFS2), together with the previously submitted results of the IA1 (PFS, ORR, DoR, DCR and PROs), but for the overall population.

Additionally, with this submission the MAH also intends to fulfil the post-authorisation measure (PAM) imposed during the assessment of the IA1 of the RUBY study in which the MAH was requested to submit the results of the final OS analysis of RUBY Part 1 as a PAES (Annex II.D).

Design and conduct of clinical studies

The study RUBY is a phase 3, randomized, double-blind, multicentre study comparing dostarlimab plus carboplatin-paclitaxel versus placebo plus carboplatin-paclitaxel in patients with recurrent or primary advanced EC. This study has two parts, with Part 1 being the object of this variation.

Part 1 of the study is to evaluate the efficacy and safety of treatment with dostarlimab (500 mg IV every 3 weeks – 6 cycles) plus carboplatin-paclitaxel, followed by dostarlimab (1000 mg IV every 6 weeks; up to 3 years) versus treatment with placebo plus carboplatin-paclitaxel followed by placebo in participants with primary advanced (Stage III or IV) or recurrent EC.

The dual primary endpoints of RUBY Part 1 were PFS by investigator (in both the overall population and the dMMR/MSI-H population) and OS (in the overall population). Randomization was stratified by MMR/MSI status (dMMR/MSI-H or MMRp/MSS), prior external pelvic radiotherapy (yes or no) and disease status (recurrent, primary Stage III, or primary Stage IV).

At IA1, uncertainties remained regarding the long-term treatment effects of dostarlimab since only 6 dMMR/MSI-h patients had received dostarlimab for 3 years, which was the proposed - and finally recommended - duration of treatment. It should be noted that at IA2, 58 (24.1%) patients in the overall population had received dostarlimab for > 2 years (102 weeks), and 27 (11.2%) patients had received dostarlimab for > 3 years (156 weeks).

The design of the RUBY Part 1 study was already discussed and considered acceptable in the procedure that led to the authorisation of Jemperli in the dMMR/MSI-h population (EMEA/H/C/005204/II/0023). For additional details on the discussion on the design of the study, study participants, endpoints, sample size and statistical methods; see the assessment report of the referred procedure.

Conduct of the study

Protocol amendments

The protocol was amended five times since its initial version, dated 13 March 2019. Protocol amendments 1 to 3 were discussed in the procedure EMEA/H/C/005204/II/0023. For further details on those protocol amendments, see the discussion on clinical efficacy of the referred procedure.

Protocol amendment 4 (version 5 of the protocol; dated 25th of January 2023) was withdrawn and never implemented.

Protocol amendment 5 (version 6 of the protocol) was implemented, on 31 March 2023, to add one administrative interim analysis of OS; which was submitted upon request to support the filing of the procedure EMEA/H/C/005204/II/0023 (DCO 01 March 2023). Other changes were to specify that all analyses will be performed for both the entire population and the corresponding dMMR/MSI-h and MMRp/MSS subsets; and to add additional analyses for PFS2. Overall, these changes are unlikely to negatively affect the interpretation of the results; and, therefore, no concerns are raised in this regard.

Protocol deviations

A relatively high number of important protocol deviations is noted in both arms, with a slight imbalance towards a higher percentage in the dostarlimab arm (43.3% vs. 37.3% in the placebo arm). The most frequently reported protocol deviation category was "assessment or time point completion" (23.7% vs. 18.9%), being "out of window – efficacy assessment" the subcategory most frequently reported (15.1% vs. 10.4%). Apart from that slight difference, no particular trend in terms of the frequency of protocol deviations by event category is observed, which is reassuring.

Efficacy data and additional analyses

Up to IA2 DCO date (22 September 2023), 607 patients were screened for eligibility and of these, 494 participants were randomized 1:1 to receive either dostarlimab plus carboplatin - paclitaxel (N=245) or placebo plus carboplatin-paclitaxel (N=249).

At IA2 DCO, 115 (46.9%) patients in the dostarlimab arm were ongoing in the study, vs. 89 (35.7%) in the placebo arm. Of those patients, 27 (11%) were still on study treatment in the dostarlimab arm, vs. 22 (8.8%) in the placebo arm.

Demographic and baseline disease characteristics

Overall, demographic characteristics were similar between both arms. The only remarkable difference between both arms was a slight imbalance in terms of patients with an ECOG performance status of 0: 60.2% in the dostarlimab arm vs. 65% in the placebo arm. No relevant differences between arms in terms of disease characteristics were observed either. Patients with FIGO stage I (27.5%), stage III (28.3%) and stage IV (31.6%) were equally represented. Stage II was by a large margin the stage less represented, with only 5.3% of patients. Regarding histology at diagnosis, most patients had an endometrioid carcinoma (54.7%), followed by serous adenocarcinoma (20.6%). Of note, 8.9% of patients had a carcinosarcoma; which is a more aggressive histology type. For further discussion on the inclusion of subjects with rare histology subtypes associated with a possible different response, see the clinical efficacy discussion of procedure EMEA/H/C/005204/II/0023.

Prior treatments

Prior treatments were also well-balanced between both arms. Most of patients had received prior anticancer surgery for EC (90.7%); and 20.2% of patients had received prior anticancer treatment for EC. Additionally, 28.3% of patients had received previous radiotherapy for EC; either external (17.4%), internal (12.8%) or other (8.3%).

Primary endpoints

The primary endpoints of the RUBY Part 1 study were PFS by investigator (in both the overall population and the dMMR/MSI-h population) and OS in the overall population. The PFS data presented for this submission are based on the IA1 (DCO 28 September 2022), while the OS data are based on the IA2 (DCO 22 September 2023). No updated PFS data have been presented with this submission.

At IA1, RUBY Part 1 met the dual-primary endpoint of **PFS by investigator** in the overall population, as well as in the dMMR/MSI-h population. In the overall population, with 63% maturity and a median follow-

up of 25.38 months, the HR point estimate was 0.64 (95% CI: 0.507, 0.800; p<0.0001); with a mPFS of 11.8 months in dostarlimab vs. 7.9 in placebo. The KM curves start to separate at around month 3, but the separation becomes more evident from month 5 onwards. There were 135 (55.1%) events in dostarlimab, vs. 177 (71.1%) events in placebo; being most of them disease progression in both arms (51% in dostarlimab vs. 67.9% in placebo).

PFS by investigator in the *dMMR/MSI-h population* was prespecified and included in the hierarchical multiplicity testing procedure. At IA1, PFS by investigator in the dMMR/MSI-h also met statistical significance, with a HR point estimate of 0.28 (95% CI: 0.162, 0.495; p<0.0001) and a mPFS of 7.7 months in the placebo arm and a mPFS not reached in the dostarlimab arm.

PFS by investigator also resulted in an improvement in the *MMRp/MSS population*; with a HR point estimate of 0.76 (95% CI: 0.592, 0.981) and mPFS of 9.9 months for dostarlimab vs. 7.9 months for placebo. Data maturity was 65%, and the median follow-up was 25.66 months (see section 5.1 of the SmPC). KM curves show separation at around month 4; although the separation is subtler than the one observed in the dMMR/MSI-h population. Although the clinical benefit seems to be lower than in the dMMR/MSI-h population, MMRp/MSS patients also seem to obtain a clinical benefit from the treatment with dostarlimab; reflected by the lower percentage of events in the dostarlimab arm than in the placebo arm (60.4% in dostarlimab vs. 70.7% in placebo), the differences in the mPFS (9.9 months vs. 7.9 months), as well as by the differences in the PFS rate at month 24 (28.4% in dostarlimab vs. 18.8% in placebo).

At IA2 (with 51.2% maturity and a median follow-up of 37 months) **OS** in the overall population reached statistical significance, with a HR point estimate of 0.69 (95% CI: 0.539, 0.890; p=0.0020) and a mOS of 44.6 months in the dostarlimab arm vs. 28.2 months in the placebo arm, crossing the stopping boundary (p=0.01101) for claiming superiority of dostarlimab over placebo. KM curves show a clear separation at around month 11. There were 109 events observed (44.5%) in the dostarlimab arm, compared with 144 events (57.8%) in the placebo arm (see section 5.1 of the SmPC). The number of censored patients is higher in the dostarlimab arm compared with the placebo arm [136 (55.5%) vs. 105 (42.2%) patients], however most of the censoring occurred because patients were still participating in the study; otherwise the reasons for censoring are balanced between the treatment arms.

To evaluate the robustness of PFS and OS for the overall population, HRs for PFS and OS were calculated from paired sensitivity analyses for both populations. Additionally, post-hoc tipping point and imputation analyses were conducted to assess the impact of patients who were censored early. Due to the low number of patients in the early censoring category, the results align with the main analysis, and no issues are found with these patients, even in a conservative scenario. Additionally, to assess the robustness of the OS results in the overall population, four types of multiple imputation analyses have been conducted, providing certain assurance that early dropouts do not affect the final estimation of overall survival. The MAH has also provided the results of a sensitivity analysis using restricted mean survival time (RMST) at different time points, and a weighted log-rank test using the Fleming-Harrington family; obtaining similar results as the ones obtained at the primary analysis, and therefore confirming their robustness.

Regarding the *dMMR/MSI-h population,* with 12 events (22.6%) in the dostarlimab arm vs. 35 events (53.8%) in the placebo arm (data maturity: 39.8%), a clear benefit was observed in OS with dostarlimab (HR 0.32; 95% CI: 0.166, 0.629; median OS not reached in the dostarlimab arm vs. 31.4 months in the placebo arm) consistent with the results of the 1IA.

In terms of the *MMRp/MSS population,* OS resulted in a HR point estimate of 0.79 (95% CI: 0.602, 1.044) and a median OS of 34 months in the dostarlimab arm vs. 27 months in the placebo arm. KM curves separate at around month 12; although the separation is also subtler than in the dMMR/MSI-h population. Due to this delayed separation of the KM curves, the MAH provided additional sensitivity analyses using RMST, which does not rely on the proportional hazards assumption. Similar to the trend

observed in PFS, a benefit in the MMRp/MSS population is of a lower magnitude than the one observed in the dMMR/MSI-h population. This benefit is reflected by the number of events [97 events (50.5%) in dostarlimab vs. 109 events (59.2%) in placebo], in the mPFS (34 months in dostarlimab vs. 27 months in placebo), and in the OS rate at month 30 (54.4% in dostarlimab vs. 47.4% in placebo).

Regarding follow-up anticancer therapies, a higher percentage of patients received subsequent anticancer therapies in the placebo arm than in the dostarlimab arm (69.5% in placebo vs. 49% in dostarlimab). In terms of the type of subsequent anticancer therapy, a higher percentage of patients in the placebo arm than in the dostarlimab arm received immunotherapy (38.2% in placebo vs. 17.1% in dostarlimab), which could be expected. No relevant differences were observed between the dMMR/MSI-h and MMRp/MSS population, except for the higher percentage of patients in the MMRp/MSS population than in the dMMR/MSI-h receiving chemotherapy as subsequent therapy (33% vs. 15.3%).

Overall, although the benefit observed in the overall population for both PFS and OS is unarguably driven by the subset of dMMR/MSI-h patients, the MMRp/MSS patients also obtain benefit from the treatment with dostarlimab.

Secondary endpoints

Secondary endpoints in RUBY Part 1 included PFS by BICR, PFS2, ORR, DoR, DCR and PROs. The results of PFS by BICR, ORR, DoR, DCR and PROs are based on IA1, while the results of PFS2 are based on IA2.

PFS by BICR in the overall population was consistent with PFS by investigator, with a HR point estimate of 0.66 (95% CI: 0.517, 0.853). PFS by BICR in the dMMR/MSI-h and MMRp/MSS populations were also consistent [*dMMR/MSI-h population*: HR=0.29 (95% CI: 0.158, 0.543); *MMRp/MSS population*: HR=0.79 (95% CI: 0.597, 1.038)]. Of note, consistence of this endpoint was of great importance, considering that the MAH initially designed the study with PFS by investigator as primary endpoint, then it was changed to PFS by BICR; and it was finally reverted to PFS by investigator.

PFS2 in the overall population also favoured treatment with dostarlimab, with a HR point estimate of 0.66 (95% CI: 0.520, 0.842), a mPFS of 32.3 months for dostarlimab vs. 18.4 months for placebo, and KM curves separating at around month 10. In the *dMMR/MSI-h population* the HR point estimate was 0.33 (95% CI: 0.175, 0.627), with a mPFS of 21.6 months for placebo and not reached for dostarlimab, and KM curves separating at around month 6; and in the *MMRp/MSS population* the HR point estimate was 0.74 (95% CI: 0.571, 0.970), with a mPFS of 24.6 months for dostarlimab vs. 15.9 months for placebo, and KM curves separating at around month 10.

ORR by investigator in the overall population was 70.3% (95% CI: 63.6%, 76.3%) in the dostarlimab arm (149/212) vs. 64.8% (95% CI: 58.1%, 71.2%) in the placebo arm (142/219). **Median DoR** was 10.6 months (95% CI: 8.2, 17.6) in the dostarlimab arm vs. 6.2 months (95% CI: 4.4, 6.7) in the placebo arm.

Patient Reported Outcomes (PRO) measured by means of the EORTC QLQ-C30 did not show a quality of life's worsening of patients in dostarlimab over patients in placebo.

Subgroup analyses

The MAH presented subgroup analyses of PFS (IA1) and of OS (IA2). Overall, PFS and OS results were similar among subgroups; with the exception of the results observed for European patients, for stage III patients, and for patients with no disease at baseline, although the latter was a small subgroup and therefore the CIs are wide, thus hampering any conclusion.

The MAH provided further justification regarding the results observed in patients with Stage III (n= 91; 18.4%) and European patients (n=136; 27.5%). It should be noted that no PFS differences are observed by region or for patients with no disease at baseline in the dMMR/MSI-h population. Therefore, in the

procedure which led to the marketing authorisation of dostarlimab in this population (EMEA/H/C/005204/II/0023), the only subgroup results which were discussed were the ones obtained for primary stage III patients. Similarly, it should be noted that when the OS IA1 results were assessed, OS data were too immature and no differences could be observed in the dMMR/MSI-h population, which was the targeted population with that submission.

In terms of patients with **primary stage III EC**, several factors could have contributed to the results observed in PFS [HR=1.03 (95% CI: 0.563, 1.891)] and in OS [HR=1.32 (95% CI: 0.657, 2.658)]; which are thought to be those also contributing to the differences observed for patients with no disease at baseline [PFS HR=1.16 (95% CI: 0.520, 2.590); OS HR=1.53 (95% CI: 0.5, 4.685]. These factors are described as follows:

Firstly, the lower number of stage III patients (n=91) compared with the recurrent patients (N=236) and with the stage IV patients (n=167). Secondly, the lower data maturity in the stage III patients (PFS maturity: 46%; OS maturity: 35.1%) compared with the recurrent patients (PFS maturity: 66.5%; OS maturity: 52.9%) and with the stage IV patients (PFS maturity: 68%; OS maturity: 57.4%). Due to the (more) favourable prognosis of these patients, it may take longer to observe events. In this regard, it is noted that at OS IA2 the results of stage III patients seem to be more favourable when compared with the results at OS IA1 [IA1: HR=1.52 (95% CI: 0.540, 4.280)].

Thirdly, a significantly longer mPFS was observed in the placebo arm of the stage III patients (22.8 months), compared with the recurrent patients (7.9 months) and with the stage IV patients (7.5 months). Besides, mOS was not reached in the stage III patients, while it was 23.1 months in the recurrent patients and 22.1 months in the stage IV patients. This longer mPFS in stage III patients might be due to differences in baseline characteristics between the dostarlimab arm and the placebo arm. However, no relevant and clear differences were identified between both arms; hence this hypothesis, although understood, could not be corroborated. It is also noted that in patients treated with dostarlimab, a longer mPFS was observed in the stage III patients (14.5 months) compared to the stage IV patients (12.6 months), and the recurrent patients (9.9 months); suggesting that the benefit of dostarlimab in stage III patients is not lower; and that the observed HR point estimate in the stage III patients may be due to the unexpected longer mPFS in the placebo arm.

The MAH also considered the existence of differences in baseline characteristics of stage III patients compared to Stage IV or recurrent patients as a potential contributing factor to the observed differences. However, no major/clear differences have been identified. Besides, the MAH considered the differences in treatment with subsequent therapies as a potential contributing factor. While it is acknowledged that some differences in terms of the number of patients receiving follow-up anti-cancer therapy seem to exist, particularly in the placebo arms (42.6% in stage III vs. 79.5% in stage IV vs. 73.1% in recurrent) or in terms of the type of subsequent therapy received (stage III: 13.6% in dostarlimab received immunotherapy vs. 23.4% in placebo; stage IV: 19% in dostarlimab received immunotherapy vs. 44.6% in placebo; recurrent: 17.1% in dostarlimab received immunotherapy vs. 39.4% in placebo), no clear conclusions can be drawn from these results.

Therefore, it seems that patients with stage III and patients with no disease at baseline, rather than responding differently to treatment with dostarlimab compared with recurrent or stage IV patients; they might need longer follow-up and greater data maturity to allow detecting a treatment difference. Besides, the relatively small number of patients with stage III could have also impacted the results. Considering the limited number of stage III patients (as opposed to stage IV) and the lower number of reported events, indicating the better prognosis of this subgroup of patients, it is highly unlikely that this uncertainty could be alleviated based on the study results. Unfortunately, no updates in PFS are expected from this study.

Regarding **European patients**, the MAH argues that several factors could have contributed to the results observed in PFS [HR=0.91 (95% CI: 0.602, 1.390)] and in OS [HR=1.15 (95% CI: 0.723, 1.834)] in this subgroup of patients compared to patients from North America. Of note, the effect in this subgroup appears to be driven by the subgroup of MMRp/MMS patients (HR 1.40; 95% CI: 0.84, 2.33). These factors are described as follows:

Firstly, the lower number of European patients (N=136, 27.5%) included in the study compared with the number of North-American patients (N=358, 72.5%) explained by the limitations to remote clinical trial monitoring during the COVID-19 pandemic impacting sites in Europe leading to low trial recruitment. Secondly, the longer-than-expected mPFS and mOS in the placebo arm in the European patients compared to North-American patients and the overall population. In terms of PFS, this longer mPFS is only observed for the MMRp/MSS (median PFS 7.5 vs 9.5 months in European patients, 11.9 months vs 7.9 months in North-American patients and 9.9 vs 7.9 months in the overall population; in the dostarlimab vs placebo arms, respectively). In terms of OS, in the overall population mOS was remarkably longer in the placebo arm (28.6 months vs 32.4 months in the European patients; 44.6 months vs. 26.4 months in the North-American patients and 44.6 months vs 28.6 months in the overall population). Therefore, it seems that in the subgroup of European patients, the response to placebo was higher than expected (and higher than in their North-American counterparts) while the response to dostarlimab was somehow lower, which translates into the HR point estimates observed for the European patients. The MAH pointed out some differences in baseline characteristics between the dostarlimab arm and the placebo arm among European patients as an additional factor to explain these differences; although it is difficult to conclude whether these differences observed in baseline characteristics are the reason for the different OS results.

Thirdly, the existing differences in the treatment with subsequent therapies between both regions. Overall, fewer European patients received subsequent anti-cancer therapy (39.2% in dostarlimab vs. 66.1% in placebo) than North-American patients (53.2% in dostarlimab vs. 70.6% in placebo). Of note, the percentage of patients who received subsequent immunotherapy is relevantly lower in the European patients, both in the dostarlimab arm and in the placebo arm (1.4% in dostarlimab vs. 11.3% in placebo), than in the North-American patients (24% in dostarlimab vs. 47.1% in placebo). These marked differences in the type of subsequent therapy administered are not fully understood, since NCCN and ESMO guidelines are aligned in their recommendations for both the first-line and the second-line treatment; only with the exception of pembrolizumab+lenvatinib, which is only approved for the pMMR/MSS population in the US, whereas it is approved for the overall population in the EU. Those differences in the type of subsequent therapy administered are likely to have contributed to the OS results; although it should be noted that the differences between European/North-American patients are not only observed for OS, but, as previously mentioned, also for PFS; which is not affected by the type of subsequent therapy administered. Therefore, although the MAH's justification is followed and it is agreed that this could partially explain the differences observed in terms of OS, this would not explain the differences in PFS; suggesting that there are other underlying reasons behind the observed differences.

Lastly, the AEs leading to treatment discontinuation (including dostarlimab, carboplatin and paclitaxel) were higher in the European subgroup. The percentages of any AE leading to treatment discontinuation were higher in the European subgroup (30.6% in dostarlimab vs. 20% in placebo) than in the North-American subgroup (22.5% in dostarlimab vs. 15.1% in placebo). The percentage of AEs leading to treatment discontinuation is not only higher in the European patients for the dostarlimab/placebo discontinuations, but also for the carboplatin/paclitaxel discontinuations. These differences in discontinuation rates, translating into drug exposure imbalances, are considered to be of relevance for the observed efficacy differences between North-American and European patients.

All things considered, it is agreed that *a priori* there is no biological plausibility as to why patients in Europe would respond differently to dostarlimab when compared with participants in North-America and that the observed results may be impacted by several confounding factors.

Additionally, the MAH also submitted post-hoc exploratory subgroup analyses by **PD-L1 status** for both PFS and OS. It is noted that PD-L1 status was only available for a total of 268/494 (54%) participants, which impairs drawing any firm conclusion. Out of those patients, 76/118 (64%) were dMMR/MSI-h patients and 192/376 (51%) were MMRp/MSS patients. The PFS and OS results did not show any relevant difference between PD-L1 positive and PD-L1 negative patients, although it is noted that due to the small number of patients in the dMMR/MSI-h population PD-L1 negative subgroup, PFS and OS results are not provided. Therefore, although it is not possible to draw any conclusion on any potential impact of the PD-L1 status of patients on their PFS/OS outcomes, *a priori* no relevant differences are observed.

Wording of the indication

The indication sought by the MAH is as follows:

"*JEMPERLI is indicated in combination with carboplatin and paclitaxel for the first-line treatment of adult patients with primary advanced or recurrent endometrial cancer (EC) and who are candidates for systemic therapy*".

The wording of the indication is considered acceptable.

Fulfilment of PAM (PAES)

With this variation, the MAH also intends to fulfil the post-authorisation measure imposed during the assessment of the IA1 of the RUBY study (EMEA/H/C/005204/II/0023) in which the MAH committed to submit the results of the final OS analysis of RUBY Part 1:

"*Post-authorisation efficacy study (PAES): in order to further characterise the efficacy of dostarlimab in combination with carboplatin and paclitaxel for the treatment of adult patients with mismatch repair deficient / microsatellite instability-high primary advanced or recurrent endometrial cancer and who are candidates for systemic therapy, the MAH should submit the results of the final OS analysis of RUBY part 1 – Final Study Report Submission*. Due date: 30 June 2029."

Instead of submitting the results of the final OS analysis, the MAH has submitted the results of the OS IA2, which were statistically significant in the intended target population with this submission (the overall population). Since OS met statistical significance in this second interim analysis, the uncertainties which led to imposing this PAM have been alleviated; and, therefore, the descriptive final OS analysis is not considered key for the B/R of dostarlimab in the current indication. Thus, this PAES is considered to be fulfilled.

Nevertheless, since the final OS results are of potential interest to prescribers, the MAH will submit the final OS results, including the final OS results by subgroups (dMMR/pMMR), when available (**REC**).

2.4.5. Conclusions on the clinical efficacy

The study RUBY Part 1 showed statistically significant results in its two dual-primary endpoints (PFS and OS) for dostarlimab in combination with carboplatin-paclitaxel, for the treatment of adult patients with primary advanced or recurrent EC and who are candidates for systemic therapy.

While the benefit observed in the overall population for both PFS and OS appears driven by the subset of dMMR/MSI-h patients (indication already authorised), the MMRp/MSS patients also obtain benefit from the treatment with dostarlimab, although this benefit is more modest than the benefit in the dMMR/MSI-h patients.

With this submission the annex II.D PAES imposed during the assessment of the IA1 of the RUBY study, in which the MAH was requested to commit to submit the results of the final OS analysis of RUBY Part 1 is considered fulfilled. Nevertheless, since the final OS results are also informative for prescribers, the MAH will submit the final OS results, including subgroup analyses (**REC**).

2.5. Clinical safety

Introduction

Safety data for this evaluation is primarily based on data from a second interim analysis (IA2) of Part 1 of the dostarlimab study 213361, referred to as RUBY with a DCO of 22 September 2023. Additionally, some data from IA1 (DCO of 28 September 2022) which has been previously reported are included (such as demographics and baseline characteristics).

The Safety Analysis Set includes all participants who received any amount of study treatment regardless of randomization. All safety analyses were performed on the as treated principle, where participants were allocated to the treatment that they actually received. Participants who received any amount of dostarlimab were assigned to the dostarlimab treatment arm, and participants who did not receive any amount of dostarlimab were assigned to the placebo treatment arm.

The safety analyses were based on the Safety Analysis Set (overall population, all comers) and the dMMR/MSI-H (N= 117) and MMRp/MSS (N=370) subpopulations of the Safety Analysis Set (N=487).

Patient exposure

As of the IA2 DCO (22 September 2023), 241 participants had received treatment with dostarlimab in combination with carboplatin-paclitaxel and 246 participants had received treatment with placebo in combination with carboplatin-paclitaxel and were included in the Safety Analysis Set. The Safety Analysis Set included participants who were stratified as dMMR/MSI-H (117 participants) or MMRp/MSS (370 participants). There were no changes in demographic information between IA1 and IA2.

The overall median treatment duration was 43.00 weeks (range: 3.0 to 192.6 weeks) for participants in the dostarlimab plus carboplatin-paclitaxel arm and 36.00 weeks (range: 2.1 to 193.1 weeks) for participants in the placebo plus carboplatin-paclitaxel arm. The median treatment duration of both carboplatin and paclitaxel was 18.00 weeks (range: 3.0 to 27.1 weeks) for participants in the dostarlimab plus carboplatin-paclitaxel arm and 18.00 weeks for participants in the placebo plus carboplatin-paclitaxel arm (range: 2.1 to 28.1 weeks).

The median number of actual dosing cycles was 6.0 for carboplatin and for paclitaxel in both treatment arms.

- **dMMR/MSI-H population**

The overall median treatment duration was 76.50 weeks (range: 3.0 to 192.6 weeks) for participants in the dostarlimab plus carboplatin-paclitaxel arm and 31.86 weeks (range: 3.0 to 193.1 weeks) for participants in the placebo plus carboplatin-paclitaxel arm.

The median number of actual dosing cycles was 15.5 in the dostarlimab plus carboplatin paclitaxel arm and 8.0 in the placebo plus carboplatin paclitaxel arm.

- **MMRp/MSS population**

The overall median treatment duration was 39.00 weeks (range: 3.0 to 190.7 weeks) for participants in the dostarlimab plus carboplatin-paclitaxel arm and 36.00 weeks (range: 2.1 to 187.0 weeks) for participants in the placebo plus carboplatin-paclitaxel arm.

The median number of actual dosing cycles was 9.0 in both treatment arms, the dostarlimab plus carboplatin paclitaxel arm and the placebo plus carboplatin paclitaxel arm.

Table 65. Treatment exposure (Safety Analysis Set)

	Overall Population		dMMR/MSI-H Population		MMRp/MSS Population	
	Dostar + carbo/pac (N=241)	**Placebo + carbo/pac (N=246)**	**Dostar + carbo/pac (N=52)**	**Placebo + carbo/pac (N=65)**	**Dostar + carbo/pac (N=189)**	**Placebo + carbo/pac (N=181)**
Duration of treatment interval, n (%) [a,b]						
> Week 54	93 (38.6%)	65 (26.4%)	29 (55.8%)	14 (21.5%)	64 (33.9%)	51 (28.2%)
> Week 102	58 24.1%)	41 (16.7%)	23 (44.2%)	9 (13.8%)	35 (18.5%)	32 (17.7%)
> Week 156	27 (11.2%)	21 (8.5%)	11 (21.2%)	6 (9.2%)	16 (8.5%)	15 (8.3%)
Overall duration of treatment (weeks) [c]						
n	241	246	52	65	189	181
Median	43.00	36.00	76.50	31.86	39.00	36.00
Min, max	3.0,192.6	2.1, 193.1	3.0, 192.6	3.0, 193.1	3.0, 190.7	2.1, 187.0
Number of cycles of study treatment						
n	241	246	52	65	189	181
Median	10.0	9.0	15.5	8.0	9.0	9.0
Min, max	1, 35	1, 35	1, 35	1, 35	1, 32	1, 34
Relative dose intensity <7 treatment cycles – (dostarlimab or placebo), %						
n	241	246	52	65	189	181
Median	99.21	99.21	96.95	97.67	99.21	99.21
Min, max	57.5, 105.0	33.3, 102.4	63.2, 105.0	57.7, 102.4	57.5, 105.0	33.3, 102.4
Relative dose intensity ≥7 treatment cycles – (dostarlimab or placebo), %						
n	184	184	40	48	144	136
Median	100.00	100.00	99.39	100.00	100.0	100.0
Min, max	63.2, 104.1	85.4, 123.5	78.4, 101.2	85.4, 103.7	63.2, 104.1	87.2, 123.5
Relative dose intensity – (carboplatin), % [d]						
n	240	246	52	65	188	181
Median	87.09	85.24	88.07	83.37	86.31	87.01
Min, max	37.8, 131.9	32.0, 132.0	58.4, 104.6	32.0, 102.5	37.8, 131.9	38.5, 132.0
Relative dose intensity – (paclitaxel), % [d]						
n	241	246	52	65	189	181
Median	95.74	96.95	95.25	95.69	95.79	97.40
Min, max	4.5, 120.4	2.2, 119.4	30.8, 104.7	2.2, 113.5	4.5, 120.4	50.0, 119.4

Abbreviations: carbo=carboplatin; dMMR=mismatch repair-deficient; Dostar=dostarlimab; max=maximum; min=minimum; MMRp=mismatch repair-proficient; MSI-H=microsatellite instability-high; MSS=microsatellite stable; pac=paclitaxel.

[a.] Intervals were inclusive of the upper week number, e.g., Week 1 to ≤Week 3 was equivalent to Day 1 to Day 21 (inclusive).

[b.] Note that the duration of exposure for 1 year and 2 years were defined as 54 weeks (3-weeks * 6 cycles + 6 weeks * 6 cycles; the expected duration of exposure closest to 1-year [52 weeks]) and 102 weeks (3-weeks * 6 cycles + 6-weeks * 14 cycles; the expected duration of exposure closest to 2-years [104 weeks]).

[c.] Overall duration of treatment was calculated as follows: If no ≥Cycle 7 non-zero dose was infused: minimum of (Last dose date – Start dose date + 21) and (Death date – Start dose date + 1). If at least 1 ≥Cycle 7 nonzero dose was infused: minimum of (Last dose date – Start dose date + 42) and (Death date – Start dose date + 1).

[d.] Carboplatin and paclitaxel were only administered in the first 6 cycles of study treatment.

Adverse events

Table 66. Overall summary of treatment-emergent adverse events (Safety Analysis Set)

	RUBY Part 1 IA1		RUBY Part 1 IA2					
	Overall population		Overall population		dMMR/MSI-H population		MMRp/MSS population	
Adverse event category, n (%)	**Dostarlimab + carbo/pac (N=241)**	**Placebo + carbo/pac (N=246)**	**Dostarlimab + carbo/pac (N=241)**	**Placebo + carbo/pac (N=246)**	**Dostarlimab + carbo/pac (N=52)**	**Placebo + carbo/pac (N=65)**	**Dostarlimab + carbo/pac (N=189)**	**Placebo + carbo/pac (N=181)**
Any TEAEs	241 (100%)	246 (100%)	241 (100%)	246 (100%)	52 (100%)	65 (100%)	189 (100%)	181 (100%)
Any treatment-related TEAEs	236 (97.9%)	243 (98.8%)	236 (97.9%)	243 (98.8%)	52 (100%)	65 (100%)	184 (97.4%)	178 (98.3%)
Related to dostarlimab/placebo	203 (84.2%)	183 (74.4%)	203 (84.2%)	183 (74.4%)	47 (90.4%)	46 (70.8%)	156 (82.5%)	137 (75.7%)
Related to dostarlimab/placebo only[a]	146 (60.6%)	103 (41.9%)	148 (61.4%)	103 (41.9%)	38 (73.1%)	23 (35.4%)	110 (58.2%)	80 (44.2%)
Related to carboplatin/paclitaxel	233 (96.7%)	235 (95.5%)	233 (96.7%)	236 (95.9%)	52 (100%)	62 (95.4%)	181 (95.8%)	174 (96.1%)
Related to carboplatin/paclitaxel only[b]	215 (89.2%)	218 (88.6%)	217 (90.0%)	220 (89.4%)	48 (92.3%)	58 (89.2%)	169 (89.4%)	162 (89.5%)
Any Grade ≥3 TEAEs	170 (70.5%)	147 (59.8%)	174 (72.2%)	148 (60.2%)	39 (75.0%)	43 (66.2%)	135 (71.4%)	105 (58.0%)
Any Grade ≥3 treatment-related TEAEs	122 (50.6%)	114 (46.3%)	128 (53.1%)	115 (46.7%)	32 (61.5%)	32 (49.2%)	96 (50.8%)	83 (45.9%)
Related to dostarlimab/placebo	80 (33.2%)	48 (19.5%)	87 (36.1%)	49 (19.9%)	25 (48.1%)	11 (16.9%)	62 (32.8%)	38 (21.0%)
Related to dostarlimab/placebo only[a]	45 (18.7%)	23 (9.3%)	53 (22.0%)	24 (9.8%)	16 (30.8%)	4 (6.2%)	37 (19.6%)	20 (11.0%)
Related to carboplatin/paclitaxel	94 (39.0%)	101 (41.1%)	94 (39.0%)	101 (41.1%)	21 (40.4%)	32 (49.2%)	73 (38.6%)	69 (38.1%)
Related to carboplatin/paclitaxel only[b]	72 (29.9%)	87 (35.4%)	72 (29.9%)	87 (35.4%)	15 (28.8%)	30 (46.2%)	57 (30.2%)	57 (31.5%)
Any serious TEAEs	91 (37.8%)	68 (27.6%)	96 (39.8%)	69 (28.0%)	17 (32.7%)	21 (32.3%)	79 (41.8%)	48 (26.5%)
Any treatment-related serious TEAEs	44 (18.3%)	30 (12.2%)	47 (19.5%)	30 (12.2%)	11 (21.2%)	9 (13.8%)	36 (19.0%)	21 (11.6%)

	RUBY Part 1 IA1		RUBY Part 1 IA2					
	Overall population		Overall population		dMMR/MSI-H population		MMRp/MSS population	
Adverse event category, n (%)	**Dostar + carbo/ pac (N=241)**	**Placebo + carbo/ pac (N=246)**	**Dostar + carbo/ pac (N=241)**	**Placebo + carbo/ pac (N=246)**	**Dostar + carbo/ pac (N=52)**	**Placebo + carbo/ pac (N=65)**	**Dostar + carbo/ pac (N=189)**	**Placebo + carbo/ pac (N=181)**
Related to dostarlimab/placebo	30 (12.4%)	17 (6.9%)	33 (13.7%)	17 (6.9%)	8 (15.4%)	5 (7.7%)	25 (13.2%)	12 (6.6%)
Related to dostarlimab/placebo only[a]	12 (5.0%)	8 (3.3%)	16 (6.6%)	8 (3.3%)	5 (9.6%)	2 (3.1%)	11 (5.8%)	6 (3.3%)
Related to carboplatin/paclitaxel	33 (13.7%)	24 (9.8%)	33 (13.7%)	24 (9.8%)	6 (11.5%)	8 (12.3%)	27 (14.3%)	16 (8.8%)
Related to carboplatin/paclitaxel only[b]	17 (7.1%)	15 (6.1%)	17 (7.1%)	15 (6.1%)	3 (5.8%)	5 (7.7%)	14 (7.4%)	10 (5.5%)
Any TEAE leading to infusion interruption	49 (20.3%)	49 (19.9%)	50 (20.7%)	49 (19.9%)	17 (32.7%)	14 (21.5%)	33 (17.5%)	35 (19.3%)
Dostarlimab/placebo infusion interruption	5 (2.1%)	1 (0.4%)	6 (2.5%)	1 (0.4%)	3 (5.8%)	0	3 (1.6%)	1 (0.6%)
Carboplatin infusion interruption	15 (6.2%)	13 (5.3%)	15 (6.2%)	13 (5.3%)	5 (9.6%)	1 (1.5%)	10 (5.3%)	12 (6.6%)
Paclitaxel infusion interruption	32 (13.3%)	37 (15.0%)	32 (13.3%)	37 (15.0%)	10 (19.2%)	13 (20.0%)	22 (11.6%)	24 (13.3%)
Any TEAE leading to infusion delay	109 (45.2%)	97 (39.4%)	114 (47.3%)	99 (40.2%)	26 (50.0%)	30 (46.2%)	88 (46.6%)	69 (38.1%)
Dostarlimab/placebo infusion delayed	103 (42.7%)	91 (37.0%)	108 (44.8%)	93 (37.8%)	25 (48.1%)	29 (44.6%)	83 (43.9%)	64 (35.4%)
Carboplatin infusion delayed	69 (28.6%)	74 (30.1%)	69 (28.6%)	74 (30.1%)	16 (30.8%)	27 (41.5%)	53 (28.0%)	47 (26.0%)
Paclitaxel infusion delayed	66 (27.4%)	67 (27.2%)	66 (27.4%)	67 (27.2%)	13 (25.0%)	23 (35.4%)	53 (28.0%)	44 (24.3%)
Any TEAE leading to dose reduction	68 (28.2%)	68 (27.6%)	68 (28.2%)	68 (27.6%)	11 (21.2%)	18 (27.7%)	57 (30.2%)	50 (27.6%)
Carboplatin dose reduced	18 (7.5%)	25 (10.2%)	18 (7.5%)	25 (10.2%)	1 (1.9%)	6 (9.2%)	17 (9.0%)	19 (10.5%)
Paclitaxel dose reduced	61 (25.3%)	57 (23.2%)	61 (25.3%)	57 (23.2%)	11 (21.2%)	13 (20.0%)	50 (26.5%)	44 (24.3%)
Any TEAE leading to treatment discontinuation	57 (23.7%)	41 (16.7%)	60 (24.9%)	40 (16.3%)	10 (19.2%)	11 (16.9%)	50 (26.5%)	29 (16.0%)
Dostarlimab/placebo discontinuation	42 (17.4%)	23 (9.3%)	46 (19.1%)	20 (8.1%)	9 (17.3%)	5 (7.7%)	37 (19.6%)	15 (8.3%)

	RUBY Part 1 IA1		RUBY Part 1 IA2					
	Overall population		Overall population		dMMR/MSI-H population		MMRp/MSS population	
Adverse event category, n (%)	**Dostar + carbo/pac (N=241)**	**Placebo + carbo/pac (N=246)**	**Dostar + carbo/pac (N=241)**	**Placebo + carbo/pac (N=246)**	**Dostar + carbo/pac (N=52)**	**Placebo + carbo/pac (N=65)**	**Dostar + carbo/pac (N=189)**	**Placebo + carbo/pac (N=181)**
Carboplatin discontinuation	24 (10.0%)	19 (7.7%)	20 (8.3%)	15 (6.1%)	3 (5.8%)	5 (7.7%)	17 (9.0%)	10 (5.5%)
Paclitaxel discontinuation	24 (10.0%)	23 (9.3%)	26 (10.8%)	25 (10.2%)	2 (3.8%)	10 (15.4%)	24 (12.7%)	15 (8.3%)
Any TEAE with the outcome of death	5 (2.1%)	0	5 (2.1%)	0	2 (3.8%)	0	3 (1.6%)	0
Any treatment-related TEAE leading to death	2 (0.8%)	0	2 (0.8%)	0	2 (3.8%)	0	0	0
Related to dostarlimab/placebo	2 (0.8%)	0	2 (0.8%)	0	2 (3.8%)	0	0	0
Related to dostarlimab/placebo only[a]	1 (0.4%)	0	1 (0.4%)	0	1 (1.9%)	0	0	0
Related to carboplatin/paclitaxel	1 (0.4%)	0	1 (0.4%)	0	1 (1.9%)	0	0	0
Related to carboplatin/paclitaxel only[b]	0	0	0	0	0	0	0	0
Any immune-related TEAE	137 (56.8%)	88 (35.8%)	141 (58.5%)	91 (37.0%)	39 (75.0%)	26 (40.0%)	102 (54.0%)	65 (35.9%)
Any dostarlimab/placebo-related immune-related TEAE	92 (38.2%)	38 (15.4%)	98 (40.7%)	40 (16.3%)	29 (55.8%)	10 (15.4%)	69 (36.5%)	30 (16.6%)
Any infusion-related reactions	44 (18.3%)	49 (19.9%)	44 (18.3%)	49 (19.9%)	12 (23.1%)	13 (20.0%)	32 (16.9%)	36 (19.9%)
Any dostarlimab/placebo-related infusion-related reactions	5 (2.1%)	2 (0.8%)	5 (2.1%)	2 (0.8%)	0	0	5 (2.6%)	2 (1.1%)
Any carboplatin-related infusion-related reactions	14 (5.8%)	15 (6.1%)	14 (5.8%)	15 (6.1%)	4 (7.7%)	1 (1.5%)	10 (5.3%)	14 (7.7%)
Any paclitaxel-related infusion-related reactions	31 (12.9%)	38 (15.4%)	31 (12.9%)	38 (15.4%)	8 (15.4%)	12 (18.5%)	23 (12.2%)	26 (14.4%)

Abbreviations: carbo=carboplatin; dMMR=mismatch repair-deficient; Dostar=dostarlimab; IA1=first interim analysis (DCO: 28 September 2022); IA2=second interim analysis (DCO:22 September 2023); MMRp=mismatch repair proficient; MSI-H=microsatellite instability-high; MSS=microsatellite stable; pac=paclitaxel; TEAE=treatment emergent adverse event.

a. TEAEs included in this row were assessed by the investigator to be not related to carboplatin or paclitaxel and only related to dostarlimab or placebo.

b. TEAEs included in this row were assessed by the investigator to be not related to dostarlimab or placebo and only related to carboplatin or paclitaxel.

Common adverse events

The most frequently reported TEAEs (>40%) in both treatment arms were nausea (54.4% vs 46.3%), alopecia (53.9% vs 50.0%), fatigue (52.3% vs 54.9%), and neuropathy peripheral (44.0% vs 41.9%), while those in the placebo plus carboplatin-paclitaxel arm included anaemia (37.8% vs 42.7%).

Table 67. Summary of treatment-emergent adverse events in ≥20% of participants (any arm) by preferred term (Safety Analysis Set)

	Overall population		dMMR/MSI-H population		MMRp/MSS population	
Preferred term, n (%)	**Dostar + carbo/pac (N=241)**	**Placebo + carbo/pac (N=246)**	**Dostar + carbo/pac (N=52)**	**Placebo + carbo/pac (N=65)**	**Dostar + carbo/pac (N=189)**	**Placebo + carbo/pac (N=181)**
Any TEAE	241 (100%)	246 (100%)	52 (100%)	65 (100%)	189 (100%)	181 (100%)
Gastrointestinal disorders	204 (84.6%)	194 (78.9%)	46 (88.5%)	55 (84.6%)	158 (83.6%)	139 (76.8%)
Nausea	131 (54.4%)	114 (46.3%)	30 (57.7%)	30 (46.2%)	101 (53.4%)	84 (46.4%)
Constipation	84 (34.9%)	89 (36.2%)	15 (28.8%)	23 (35.4%)	69 (36.5%)	66 (36.5%)
Diarrhoea	76 (31.5%)	72 (29.3%)	21 (40.4%)	21 (32.3%)	55 (29.1%)	51 (28.2%)
Vomiting	49 (20.3%)	48 (19.5%)	14 (26.9%)	14 (21.5%)	35 (18.5%)	34 (18.8%)
Abdominal pain	38 (15.8%)	47 (19.1%)	8 (15.4%)	14 (21.5%)	30 (15.9%)	33 (18.2%)
Nervous system disorders	193 (80.1%)	192 (78.0%)	41 (78.8%)	51 (78.5%)	152 (80.4%)	141 (77.9%)
Neuropathy peripheral	106 (44.0%)	103 (41.9%)	22 (42.3%)	29 (44.6%)	84 (44.4%)	74 (40.9%)
Peripheral sensory neuropathy	51 (21.2%)	47 (19.1%)	12 (23.1%)	12 (18.5%)	39 (20.6%)	35 (19.3%)
General disorders and administration site conditions	168 (69.7%)	180 (73.2%)	37 (71.2%)	49 (75.4%)	131 (69.3%)	131 (72.4%)
Fatigue	126 (52.3%)	135 (54.9%)	26 (50.0%)	37 (56.9%)	100 (52.9%)	98 (54.1%)
Skin and subcutaneous tissue disorders	179 (74.3%)	164 (66.7%)	46 (88.5%)	44 (67.7%)	133 (70.4%)	120 (66.3%)
Alopecia	130 (53.9%)	123 (50.0%)	30 (57.7%)	39 (60.0%)	100 (52.9%)	84 (46.4%)
Rash	56 (23.2%)	35 (14.2%)	15 (28.8%)	11 (16.9%)	41 (21.7%)	24 (13.3%)
Pruritus	47 (19.5%)	35 (14.2%)	9 (17.3%)	6 (9.2%)	38 (20.1%)	29 (16.0%)
Musculoskeletal and connective tissue disorders	155 (64.3%)	162 (65.9%)	36 (69.2%)	44 (67.7%)	119 (63.0%)	118 (65.2%)
Arthralgia	90 (37.3%)	87 (35.4%)	24 (46.2%)	26 (40.0%)	66 (34.9%)	61 (33.7%)
Myalgia	64 (26.6%)	68 (27.6%)	13 (25.0%)	17 (26.2%)	51 (27.0%)	51 (28.2%)
Metabolism and nutrition disorders	136 (56.4%)	138 (56.1%)	29 (55.8%)	41 (63.1%)	107 (56.6%)	97 (53.6%)
Hypomagnesaemia	53 (22.0%)	71 (28.9%)	11 (21.2%)	19 (29.2%)	42 (22.2%)	52 (28.7%)
Decreased appetite	52 (21.6%)	44 (17.9%)	9 (17.3%)	13 (20.0%)	43 (22.8%)	31 (17.1%)

	Overall population		dMMR/MSI-H population		MMRp/MSS population	
Preferred term, n (%)	**Dostar + carbo/pac (N=241)**	**Placebo + carbo/pac (N=246)**	**Dostar + carbo/pac (N=52)**	**Placebo + carbo/pac (N=65)**	**Dostar + carbo/pac (N=189)**	**Placebo + carbo/pac (N=181)**
Hypokalaemia	47 (19.5%)	35 (14.2%)	8 (15.4%)	11 (16.9%)	39 (20.6%)	24 (13.3%)
Blood and lymphatic system disorders	116 (48.1%)	128 (52.0%)	25 (48.1%)	44 (67.7%)	91 (48.1%)	84 (46.4%)
Anaemia	91 (37.8%)	105 (42.7%)	18 (34.6%)	34 (52.3%)	73 (38.6%)	71 (39.2%)
Neutropenia	33 (13.7%)	34 (13.8%)	11 (21.2%)	11 (16.9%)	22 (11.6%)	23 (12.7%)
Investigations	144 (59.8%)	127 (51.6%)	30 (57.7%)	33 (50.8%)	114 (60.3%)	94 (51.9%)
Neutrophil count decreased	33 (13.7%)	45 (18.3%)	5 (9.6%)	15 (23.1%)	28 (14.8%)	30 (16.6%)
White blood cell count decreased	32 (13.3%)	30 (12.2%)	4 (7.7%)	13 (20.0%)	28 (14.8%)	17 (9.4%)
Infections and infestations	124 (51.5%)	105 (42.7%)	30 (57.7%)	31 (47.7%)	94 (49.7%)	74 (40.9%)
Urinary tract infection	43 (17.8%)	43 (17.5%)	4 (7.7%)	16 (24.6%)	39 (20.6%)	27 (14.9%)
Respiratory, thoracic and mediastinal disorders	108 (44.8%)	95 (38.6%)	22 (42.3%)	31 (47.7%)	86 (45.5%)	64 (35.4%)
Dyspnoea	46 (19.1%)	51 (20.7%)	7 (13.5%)	19 (29.2%)	39 (20.6%)	32 (17.7%)
Vascular disorders	68 (28.2%)	67 (27.2%)	15 (28.8%)	23 (35.4%)	53 (28.0%)	44 (24.3%)
Hypertension	32 (13.3%)	20 (8.1%)	11 (21.2%)	7 (10.8%)	21 (11.1%)	13 (7.2%)
Endocrine disorders	46 (19.1%)	19 (7.7%)	12 (23.1%)	5 (7.7%)	34 (18.0%)	14 (7.7%)
Hypothyroidism	35 (14.5%)	14 (5.7%)	11 (21.2%)	4 (6.2%)	24 (12.7%)	10 (5.5%)

Abbreviations: carbo=carboplatin; dMMR=mismatch repair-deficient; Dostar=dostarlimab; MMRp=mismatch repair proficient; MSI-H=microsatellite instability-high; MSS=microsatellite stable; pac=paclitaxel; TEAE=treatment emergent adverse event.

Adverse events by severity

Table 68. Summary of treatment-emergent adverse events of maximum Grade ≥3 in ≥2% participants (any arm) by system organ class and preferred term (Safety Analysis Set)

	Overall population		dMMR/MSI-H population		MMRp/MSS population	
System organ class, n (%) **Preferred term, n (%)**	**Dostar + carbo/pac (N=241)**	**Placebo + carbo/pac (N=246)**	**Dostar + carbo/pac (N=52)**	**Placebo + carbo/pac (N=65)**	**Dostar + carbo/pac (N=189)**	**Placebo + carbo/pac (N=181)**
Any Grade ≥3 TEAE	174 (72.2%)	148 (60.2%)	39 (75.0%)	43 (66.2%)	135 (71.4%)	105 (58.0%)
Blood and lymphatic system disorders	60 (24.9%)	67 (27.2%)	17 (32.7%)	25 (38.5%)	43 (22.8%)	42 (23.2%)

	Overall population		dMMR/MSI-H population		MMRp/MSS population	
System organ class, n (%) **Preferred term, n (%)**	**Dostar + carbo/pac (N=241)**	**Placebo + carbo/pac (N=246)**	**Dostar + carbo/pac (N=52)**	**Placebo + carbo/pac (N=65)**	**Dostar + carbo/pac (N=189)**	**Placebo + carbo/pac (N=181)**
Anaemia	36 (14.9%)	41 (16.7%)	8 (15.4%)	14 (21.5%)	28 (14.8%)	27 (14.9%)
Neutropenia	23 (9.5%)	23 (9.3%)	9 (17.3%)	8 (12.3%)	14 (7.4%)	15 (8.3%)
Thrombocytopenia	8 (3.3%)	10 (4.1%)	1 (1.9%)	4 (6.2%)	7 (3.7%)	6 (3.3%)
Febrile neutropenia	5 (2.1%)	4 (1.6%)	1 (1.9%)	1 (1.5%)	4 (2.1%)	3 (1.7%)
Leukopenia	5 (2.1%)	3 (1.2%)	2 (3.8%)	1 (1.5%)	3 (1.6%)	2 (1.1%)
Lymphopenia	3 (1.2%)	2 (0.8%)	0	2 (3.1%)	3 (1.6%)	0
Investigations	66 (27.4%)	61 (24.8%)	12 (23.1%)	19 (29.2%)	54 (28.6%)	42 (23.2%)
Neutrophil count decreased	20 (8.3%)	34 (13.8%)	4 (7.7%)	12 (18.5%)	16 (8.5%)	22 (12.2%)
Lymphocyte count decreased	13 (5.4%)	18 (7.3%)	3 (5.8%)	6 (9.2%)	10 (5.3%)	12 (6.6%)
White blood cell count decreased	16 (6.6%)	13 (5.3%)	2 (3.8%)	8 (12.3%)	14 (7.4%)	5 (2.8%)
Platelet count decreased	5 (2.1%)	10 (4.1%)	1 (1.9%)	2 (3.1%)	4 (2.1%)	8 (4.4%)
Lipase increased	11 (4.6%)	3 (1.2%)	3 (5.8%)	0	8 (4.2%)	3 (1.7%)
Amylase increased	9 (3.7%)	4 (1.6%)	0	3 (4.6%)	9 (4.8%)	1 (0.6%)
Aspartate aminotransferase increased	5 (2.1%)	2 (0.8%)	1 (1.9%)	0	4 (2.1%)	2 (1.1%)
Alanine aminotransferase increased	5 (2.1%)	1 (0.4%)	0	0	5 (2.6%)	1 (0.6%)
Metabolism and nutrition disorders	39 (16.2%)	29 (11.8%)	6 (11.5%)	10 (15.4%)	33 (17.5%)	19 (10.5%)
Hypokalaemia	12 (5.0%)	9 (3.7%)	3 (5.8%)	4 (6.2%)	9 (4.8%)	5 (2.8%)
Hyponatraemia	11 (4.6%)	8 (3.3%)	3 (5.8%)	2 (3.1%)	8 (4.2%)	6 (3.3%)
Hyperglycaemia	8 (3.3%)	4 (1.6%)	2 (3.8%)	0	6 (3.2%)	4 (2.2%)
Dehydration	7 (2.9%)	1 (0.4%)	0	0	7 (3.7%)	1 (0.6%)
Decreased appetite	5 (2.1%)	1 (0.4%)	0	0	5 (2.6%)	1 (0.6%)
Gastrointestinal disorders	24 (10.0%)	25 (10.2%)	7 (13.5%)	9 (13.8%)	17 (9.0%)	16 (8.8%)
Abdominal pain	4 (1.7%)	5 (2.0%)	1 (1.9%)	4 (6.2%)	3 (1.6%)	1 (0.6%)
Nausea	7 (2.9%)	4 (1.6%)	0	2 (3.1%)	7 (3.7%)	2 (1.1%)
Vomiting	4 (1.7%)	4 (1.6%)	0	1 (1.5%)	4 (2.1%)	3 (1.7%)
Infections and infestations	30 (12.4%)	15 (6.1%)	5 (9.6%)	9 (13.8%)	25 (13.2%)	6 (3.3%)
Urinary tract infection	7 (2.9%)	4 (1.6%)	0	4 (6.2%)	7 (3.7%)	0
Sepsis	7 (2.9%)	1 (0.4%)	2 (3.8%)	0	5 (2.6%)	1 (0.6%)
Nervous system disorders	19 (7.9%)	21 (8.5%)	4 (7.7%)	6 (9.2%)	15 (7.9%)	15 (8.3%)
Neuropathy peripheral	5 (2.1%)	5 (2.0%)	1 (1.9%)	3 (4.6%)	4 (2.1%)	2 (1.1%)
Peripheral sensory neuropathy	6 (2.5%)	0	1 (1.9%)	0	5 (2.6%)	0

	Overall population		dMMR/MSI-H population		MMRp/MSS population	
System organ class, n (%) **Preferred term, n (%)**	**Dostar + carbo/pac (N=241)**	**Placebo + carbo/pac (N=246)**	**Dostar + carbo/pac (N=52)**	**Placebo + carbo/pac (N=65)**	**Dostar + carbo/pac (N=189)**	**Placebo + carbo/pac (N=181)**
Vascular disorders	24 (10.0%)	11 (4.5%)	6 (11.5%)	5 (7.7%)	18 (9.5%)	6 (3.3%)
Hypertension	17 (7.1%)	8 (3.3%)	5 (9.6%)	4 (6.2%)	12 (6.3%)	4 (2.2%)
General disorders and administration site conditions	14 (5.8%)	18 (7.3%)	3 (5.8%)	7 (10.8%)	11 (5.8%)	11 (6.1%)
Asthenia	5 (2.1%)	9 (3.7%)	2 (3.8%)	4 (6.2%)	3 (1.6%)	5 (2.8%)
Fatigue	4 (1.7%)	5 (2.0%)	0	3 (4.6%)	4 (2.1%)	2 (1.1%)
Respiratory, thoracic and mediastinal disorders	19 (7.9%)	13 (5.3%)	3 (5.8%)	4 (6.2%)	16 (8.5%)	9 (5.0%)
Pulmonary embolism	14 (5.8%)	12 (4.9%)	2 (3.8%)	4 (6.2%)	12 (6.3%)	8 (4.4%)
Skin and subcutaneous tissue disorders	17 (7.1%)	7 (2.8%)	5 (9.6%)	1 (1.5%)	12 (6.3%)	6 (3.3%)
Rash	11 (4.6%)	3 (1.2%)	3 (5.8%)	0	8 (4.2%)	3 (1.7%)
Rash maculo-papular	6 (2.5%)	0	2 (3.8%)	0	4 (2.1%)	0
Musculoskeletal and connective tissue disorders	10 (4.1%)	7 (2.8%)	3 (5.8%)	1 (1.5%)	7 (3.7%)	6 (3.3%)
Arthralgia	3 (1.2%)	1 (0.4%)	2 (3.8%)	0	1 (0.5%)	1 (0.6%)
Renal and urinary disorders	6 (2.5%)	6 (2.4%)	2 (3.8%)	2 (3.1%)	4 (2.1%)	4 (2.2%)
Acute kidney injury	5 (2.1%)	1 (0.4%)	1 (1.9%)	1 (1.5%)	4 (2.1%)	0

Abbreviations: carbo=carboplatin; dMMR=mismatch repair-deficient; Dostar=dostarlimab; MMRp=mismatch repair proficient; MSI-H=microsatellite instability-high; MSS=microsatellite stable; pac=paclitaxel; TEAE=treatment emergent adverse event.

Table 69. Summary of treatment-related treatment-emergent adverse events of maximum Grade ≥3 in ≥2% participants (any arm) by system organ class and preferred term (Safety Analysis Set)

	Overall population		dMMR/MSI-H population		MMRp/MSS population	
System organ class, n (%) **Preferred term, n (%)**	**Dostar + carbo/pac (N=241)**	**Placebo + carbo/pac (N=246)**	**Dostar + carbo/pac (N=52)**	**Placebo + carbo/pac (N=65)**	**Dostar + carbo/pac (N=189)**	**Placebo + carbo/pac (N=181)**
Any Grade ≥3 treatment-related TEAE	128 (53.1%)	115 (46.7%)	32 (61.5%)	32 (49.2%)	96 (50.8%)	83 (45.9%)
Blood and lymphatic system disorders	54 (22.4%)	59 (24.0%)	16 (30.8%)	22 (33.8%)	38 (20.1%)	37 (20.4%)
Anaemia	31 (12.9%)	33 (13.4%)	7 (13.5%)	12 (18.5%)	24 (12.7%)	21 (11.6%)
Neutropenia	23 (9.5%)	22 (8.9%)	9 (17.3%)	8 (12.3%)	14 (7.4%)	14 (7.7%)
Febrile neutropenia	5 (2.1%)	4 (1.6%)	1 (1.9%)	1 (1.5%)	4 (2.1%)	3 (1.7%)
Leukopenia	5 (2.1%)	3 (1.2%)	2 (3.8%)	1 (1.5%)	3 (1.6%)	2 (1.1%)
Thrombocytopenia	7 (2.9%)	9 (3.7%)	1 (1.9%)	3 (4.6%)	6 (3.2%)	6 (3.3%)
Investigations	51 (21.2%)	54 (22.0%)	7 (13.5%)	16 (24.6%)	44 (23.3%)	38 (21.0%)

System organ class, n (%) Preferred term, n (%)	Overall population		dMMR/MSI-H population		MMRp/MSS population	
	Dostar + carbo/pac (N=241)	Placebo + carbo/pac (N=246)	Dostar + carbo/pac (N=52)	Placebo + carbo/pac (N=65)	Dostar + carbo/pac (N=189)	Placebo + carbo/pac (N=181)
Neutrophil count decreased	18 (7.5%)	34 (13.8%)	3 (5.8%)	12 (18.5%)	15 (7.9%)	22 (12.2%)
Lipase increased	9 (3.7%)	3 (1.2%)	1 (1.9%)	0	8 (4.2%)	3 (1.7%)
Lymphocyte count decreased	10 (4.1%)	12 (4.9%)	3 (5.8%)	5 (7.7%)	7 (3.7%)	7 (3.9%)
Platelet count decreased	4 (1.7%)	9 (3.7%)	1 (1.9%)	2 (3.1%)	3 (1.6%)	7 (3.9%)
White blood cell count decreased	14 (5.8%)	12 (4.9%)	2 (3.8%)	7 (10.8%)	12 (6.3%)	5 (2.8%)
Alanine aminotransferase increased	5 (2.1%)	0	0	0	5 (2.6%)	0
Amylase increased	9 (3.7%)	2 (0.8%)	0	1 (1.5%)	9 (4.8%)	1 (0.6%)
Aspartate aminotransferase increased	5 (2.1%)	1 (0.4%)	1 (1.9%)	0	4 (2.1%)	1 (0.6%)
Metabolism and nutrition disorders	16 (6.6%)	15 (6.1%)	2 (3.8%)	6 (9.2%)	14 (7.4%)	9 (5.0%)
Dehydration	5 (2.1%)	1 (0.4%)	0	0	5 (2.6%)	1 (0.6%)
Hypokalaemia	2 (0.8%)	6 (2.4%)	0	3 (4.6%)	2 (1.1%)	3 (1.7%)
Nervous system disorders	14 (5.8%)	10 (4.1%)	4 (7.7%)	4 (6.2%)	10 (5.3%)	6 (3.3%)
Neuropathy peripheral	5 (2.1%)	5 (2.0%)	1 (1.9%)	3 (4.6%)	4 (2.1%)	2 (1.1%)
Peripheral sensory neuropathy	6 (2.5%)	0	1 (1.9%)	0	5 (2.6%)	0
Skin and subcutaneous tissue disorders	16 (6.6%)	6 (2.4%)	5 (9.6%)	1 (1.5%)	11 (5.8%)	5 (2.8%)
Rash	10 (4.1%)	3 (1.2%)	3 (5.8%)	0	7 (3.7%)	3 (1.7%)
Rash maculo-papular	6 (2.5%)	0	2 (3.8%)	0	4 (2.1%)	0
General disorders and administration site conditions	7 (2.9%)	9 (3.7%)	3 (5.8%)	1 (1.5%)	4 (2.1%)	8 (4.4%)
Asthenia	3 (1.2%)	5 (2.0%)	2 (3.8%)	1 (1.5%)	1 (0.5%)	4 (2.2%)
Vascular disorders	7 (2.9%)	0	4 (7.7%)	0	3 (1.6%)	0
Hypertension	5 (2.1%)	0	3 (5.8%)	0	2 (1.1%)	0
Musculoskeletal and connective tissue disorders	5 (2.1%)	3 (1.2%)	2 (3.8%)	0	3 (1.6%)	3 (1.7%)
Arthralgia	2 (0.8%)	1 (0.4%)	2 (3.8%)	0	0	1 (0.6%)
Respiratory, thoracic and mediastinal disorders	5 (2.1%)	4 (1.6%)	0	1 (1.5%)	5 (2.6%)	3 (1.7%)
Pulmonary embolism	4 (1.7%)	4 (1.6%)	0	1 (1.5%)	4 (2.1%)	3 (1.7%)

Abbreviations: carbo=carboplatin; dMMR=mismatch repair-deficient; Dostar=dostarlimab; MMRp=mismatch repair proficient; MSI-H=microsatellite instability-high; MSS=microsatellite stable; pac=paclitaxel; TEAE=treatment emergent adverse event.

Serious adverse event/deaths/other significant events

Deaths

There were no new TEAEs leading to deaths at IA2. Adverse events leading to deaths were reported in 5 patients (2.1%) in the dostarlimab plus carboplatin-paclitaxel and one patient (0.4%) in the placebo plus carboplatin paclitaxel arm.

Table 70. Summary of deaths (Safety Analysis Set)

	Overall population		**dMMR/MSI-H population**		**MMRp/MSS population**	
Occurrence of death [n (%)]	**Dostar + carbo/pac (N=241)**	**Placebo + carbo/pac (N=246)**	**Dostar + carbo/pac (N=52)**	**Placebo + carbo/pac (N=65)**	**Dostar + carbo/pac (N=189)**	**Placebo + carbo/pac (N=181)**
Overall						
Death [n (%)]	95 (39.4%)	133 (54.1%)	10 (19.2%)	30 (46.2%)	85 (45.0%)	103 (56.9%)
Primary reason of death [n (%)]						
Disease progression	80 (33.2%)	114 (46.3%)	7 (13.5%)	24 (36.9%)	73 (38.6%)	90 (49.7%)
Adverse event	5 (2.1%)	1 (0.4%)	2 (3.8%)	0	3 (1.6%)	1 (0.6%)
Unknown	9 (3.7%)	16 (6.5%)	1 (1.9%)	5 (7.7%)	8 (4.2%)	11 (6.1%)
Other	1 (0.4%)	2 (0.8%)	0	1 (1.5%)	1 (0.5%)	1 (0.6%)
Within 90 days after last dose						
Death [n (%)]	22 (9.1%)	17 (6.9%)	5 (9.6%)	6 (9.2%)	17 (9.0%)	11 (6.1%)
Primary reason of death [n (%)]						
Disease progression	17 (7.1%)	16 (6.5%)	3 (5.8%)	6 (9.2%)	14 (7.4%)	10 (5.5%)
Adverse event	5 (2.1%)	0	2 (3.8%)	0	3 (1.6%)	0
Unknown	0	1 (0.4%)	0	0	0	1 (0.6%)
After 90 days after last dose						
Death [n (%)]	73 (30.3%)	116 (47.2%)	5 (9.6%)	24 (36.9%)	68 (36.0%)	92 (50.8%)
Primary reason of death [n (%)]						
Disease progression	63 (26.1%)	16 (6.5%)	4 (7.7%)	18 (27.7%)	59 (31.2%)	80 (44.2%)
Adverse event	0	1 (0.4%)	0	0	0	1 (0.6%)
Unknown	9 (3.7%)	15 (6.1%)	1 (1.9%)	5 (7.7%)	8 (4.2%)	10 (5.5%)
Other	1 (0.4%)	2 (0.8%)	0	1 (1.5%)	1 (0.5%)	1 (0.6%)

Abbreviations: carbo=carboplatin; dMMR=mismatch repair-deficient; Dostar=dostarlimab; MMRp=mismatch repair proficient; MSI-H=microsatellite instability-high; MSS=microsatellite stable; pac=paclitaxel.

Table 71. Summary of treatment-emergent adverse events leading to death by system organ class and preferred term (Safety Analysis Set)

	Overall population		dMMR/MSI-H population		MMRp/MSS population	
System organ class, n (%) **Preferred term, n (%)**	**Dostar + carbo/pac (N=241)**	**Placebo + carbo/pac (N=246)**	**Dostar + carbo/pac (N=52)**	**Placebo + carbo/pac (N=65)**	**Dostar + carbo/pac (N=189)**	**Placebo + carbo/pac (N=181)**
Any AE leading to death	5 (2.1%)	0	2 (3.8%)	0	3 (1.6%)	0
Blood and lymphatic system disorders	1 (0.4%)	0	1 (1.9%)	0	0	0
Myelosuppression	1 (0.4%)	0	1 (1.9%)	0	0	0
General disorders and administration site conditions	1 (0.4%)	0	0	0	1 (0.5%)	0
General physical health deterioration	1 (0.4%)	0	0	0	1 (0.5%)	0
Infections and infestations	1 (0.4%)	0	0	0	1 (0.5%)	0
COVID-19	1 (0.4%)	0	0	0	1 (0.5%)	0
Injury, poisoning and procedural complications	1 (0.4%)	0	0	0	1 (0.5%)	0
Overdose[a]	1 (0.4%)	0	0	0	1 (0.5%)	0
Vascular disorders	1 (0.4%)	0	1 (1.9%)	0	0	0
Hypovolaemic shock	1 (0.4%)	0	1 (1.9%)	0	0	0

Abbreviations: AE=adverse event; COVID-19=coronavirus disease 2019; carbo=carboplatin; dMMR=mismatch repair deficient; Dostar=dostarlimab; MMRp=mismatch repair proficient; MSI-H=microsatellite instability-high; MSS=microsatellite stable; pac=paclitaxel; SAE=serious adverse event.

a. One participant died due to an overdose of opiates.

Serious Adverse Events

Table 69. Summary of treatment-emergent serious adverse events in ≥2% of participants (any arm) by system organ class and preferred term (Safety Analysis Set)

System organ class, n (%) **Preferred term, n (%)**	**Overall population**		**dMMR/MSI-H population**		**MMRp/MSS population**	
	Dostar + carbo/pac (N=241)	**Placebo + carbo/pac (N=246)**	**Dostar + carbo/pac (N=52)**	**Placebo + carbo/pac (N=65)**	**Dostar + carbo/pac (N=189)**	**Placebo + carbo/pac (N=181)**
Any SAE	96 (39.8%)	69 (28.0%)	17 (32.7%)	21 (32.3%)	79 (41.8%)	48 (26.5%)
Respiratory, thoracic and mediastinal disorders	15 (6.2%)	7 (2.8%)	2 (3.8%)	2 (3.1%)	13 (6.9%)	5 (2.8%)
Pulmonary embolism	8 (3.3%)	5 (2.0%)	1 (1.9%)	2 (3.1%)	7 (3.7%)	3 (1.7%)
Dyspnoea	5 (2.1%)	1 (0.4%)	0	0	5 (2.6%)	1 (0.6%)
Blood and lymphatic system disorders	12 (5.0%)	14 (5.7%)	0	2 (3.1%)	9 (4.8%)	10 (5.5%)
Anaemia	3 (1.2%)	6 (2.4%)	0	3 (4.6%)	3 (1.6%)	3 (1.7%)

System organ class, n (%) Preferred term, n (%)	Overall population		dMMR/MSI-H population		MMRp/MSS population	
	Dostar + carbo/pac (N=241)	Placebo + carbo/pac (N=246)	Dostar + carbo/pac (N=52)	Placebo + carbo/pac (N=65)	Dostar + carbo/pac (N=189)	Placebo + carbo/pac (N=181)
Infections and infestations	27 (11.2%)	14 (5.7%)	5 (9.6%)	7 (10.8%)	22 (11.6%)	7 (3.9%)
Sepsis	8 (3.3%)	1 (0.4%)	2 (3.8%)	0	6 (3.2%)	1 (0.6%)
Urinary tract infection	3 (1.2%)	5 (2.0%)	0	4 (6.2%)	3 (1.6%)	1 (0.6%)
General disorders and administration site conditions	15 (6.2%)	14 (5.7%)	1 (1.9%)	4 (6.2%)	14 (7.4%)	10 (5.5%)
Asthenia	2 (0.8%)	6 (2.4%)	0	3 (4.6%)	2 (1.1%)	3 (1.7%)
Pyrexia	7 (2.9%)	2 (0.8%)	0	0	7 (3.7%)	2 (1.1%)
Gastrointestinal disorders	19 (7.9%)	19 (7.7%)	4 (7.7%)	5 (7.7%)	15 (7.9%)	14 (7.7%)
Colitis	2 (0.8%)	2 (0.8%)	0	2 (3.1%)	2 (1.1%)	0
Vomiting	5 (2.1%)	3 (1.2%)	0	1 (1.5%)	5 (2.6%)	2 (1.1%)
Musculoskeletal and connective tissue disorders	7 (2.9%)	1 (0.4%)	3 (5.8%)	1 (1.5%)	4 (2.1%)	0
Muscular weakness	5 (2.1%)	1 (0.4%)	1 (1.9%)	1 (1.5%)	4 (2.1%)	0

Abbreviations: carbo=carboplatin; dMMR=mismatch repair deficient; Dostar=dostarlimab; MMRp=mismatch repair proficient; MSI H=microsatellite instability-high; MSS=microsatellite stable; pac=paclitaxel; SAE=serious adverse event.

Table 72. Summary of treatment-emergent serious adverse events related to dostarlimab or placebo (>1 participant in any column) by system organ class and preferred term (Safety Analysis Set)

	Overall population				dMMR/MSI-H population				MMRp/MSS population			
System organ class, n (%) Preferred term, n (%)	Dostar + carbo/pac (N=241)		Placebo + carbo/pac (N=246)		Dostar + carbo/pac (N=52)		Placebo + carbo/pac (N=65)		Dostar + carbo/pac (N=189)		Placebo + carbo/pac (N=181)	
	Related to dostar or placebo	Related to dostar or placebo only[a]	Related to dostar or placebo	Related to dostar or placebo only[a]	Related to dostar or placebo	Related to dostar or placebo only[a]	Related to dostar or placebo	Related to dostar or placebo only[a]	Related to dostar or placebo	Related to dostar or placebo only[a]	Related to dostar or placebo	Related to dostar or placebo only[a]
Any SAE related to dostarlimab or placebo	33 (13.7 %)	16 (6.6 %)	17 (6.9 %)	8 (3.3 %)	8 (15.4 %)	5 (9.6 %)	5 (7.7 %)	2 (3.1 %)	25 (13.2 %)	11 (5.8 %)	12 (6.6 %)	6 (3.3 %)
Gastrointestinal disorders	6 (2.5 %)	4 (1.7 %)	6 (2.4 %)	2 (0.8 %)	2 (3.8 %)	2 (3.8 %)	3 (4.6 %)	2 (3.1 %)	4 (2.1 %)	2 (1.1 %)	3 (1.7 %)	0
Colitis	1 (0.4 %)	1 (0.4 %)	2 (0.8 %)	1 (0.4 %)	0	0	2 (3.1 %)	1 (1.5 %)	1 (0.5 %)	1 (0.5 %)	0	0

	Overall population				dMMR/MSI-H population				MMRp/MSS population			
System organ class, n (%) **Preferred term, n (%)**	**Dostar + carbo/pac (N=241)**		**Placebo + carbo/pac (N=246)**		**Dostar + carbo/pac (N=52)**		**Placebo + carbo/pac (N=65)**		**Dostar + carbo/pac (N=189)**		**Placebo + carbo/pac (N=181)**	
	Related to dostar or placebo	**Related to dostar or placebo only[a]**	**Related to dostar or placebo**	**Related to dostar or placebo only[a]**	**Related to dostar or placebo**	**Related to dostar or placebo only[a]**	**Related to dostar or placebo**	**Related to dostar or placebo only[a]**	**Related to dostar or placebo**	**Related to dostar or placebo only[a]**	**Related to dostar or placebo**	**Related to dostar or placebo only[a]**
Diarrhoea	1 (0.4 %)	1 (0.4 %)	2 (0.8 %)	0	0	0	0	0	1 (0.5 %)	1 (0.5 %)	2 (1.1 %)	0
Blood and lymphatic system disorders	5 (2.1 %)	0	4 (1.6 %)	1 (0.4 %)	1 (1.9 %)	0	0	0	4 (2.1 %)	0	4 (2.2 %)	1 (0.6 %)
Anaemia	2 (0.8 %)	0	1 (0.4 %)	0	0	0	0	0	2 (1.1 %)	0	1 (0.6 %)	0
Pancytopenia	0	0	2 (0.8 %)	1 (0.4 %)	0	0	0	0	0	0	2 (1.1 %)	1 (0.6 %)
General disorders and administration site conditions	4 (1.7 %)	1 (0.4 %)	6 (2.4 %)	1 (0.4 %)	1 (1.9 %)	0	1 (1.5 %)	0	3 (1.6 %)	1 (0.5 %)	5 (2.8 %)	1 (0.6 %)
Asthenia	0	0	4 (1.6 %)	0	0	0	1 (1.5 %)	0	0	0	3 (1.7 %)	0
General physical health deterioration	1 (0.4 %)	0	2 (0.8 %)	1 (0.4 %)	1 (1.9 %)	0	0	0	0	0	2 (1.1 %)	1 (0.6 %)
Pyrexia	3 (1.2 %)	1 (0.4 %)	0	0	0	0	0	0	3 (1.6 %)	1 (0.5 %)	0	0
Respiratory, thoracic and mediastinal disorders	4 (1.7 %)	2 (0.8 %)	2 (0.8 %)	0	0	0	1 (1.5 %)	0	4 (2.1 %)	2 (1.1 %)	1 (0.6 %)	0
Pulmonary embolism	3 (1.2 %)	2 (0.8 %)	2 (0.8 %)	0	0	0	1 (1.5 %)	0	3 (1.6 %)	2 (1.1 %)	1 (0.6 %)	0
Skin and subcutaneous tissue disorders	2 (0.8 %)	2 (0.8 %)	0	0	0	0	0	0	2 (1.1 %)	2 (1.1 %)	0	0
Rash	2 (0.8 %)	2 (0.8 %)	0	0	0	0	0	0	2 (1.1 %)	2 (1.1 %)	0	0
Metabolism and	4 (1.7 %)	2 (0.8 %)	2 (0.8 %)	0	2 (3.8 %)	2 (3.8 %)	0	0	2 (1.1 %)	0	2 (1.1 %)	0

	Overall population				dMMR/MSI-H population				MMRp/MSS population			
System organ class, n (%) **Preferred term, n (%)**	**Dostar + carbo/pac (N=241)**		**Placebo + carbo/pac (N=246)**		**Dostar + carbo/pac (N=52)**		**Placebo + carbo/pac (N=65)**		**Dostar + carbo/pac (N=189)**		**Placebo + carbo/pac (N=181)**	
	Related to dostar or placebo	**Related to dostar or placebo only[a]**	**Related to dostar or placebo**	**Related to dostar or placebo only[a]**	**Related to dostar or placebo**	**Related to dostar or placebo only[a]**	**Related to dostar or placebo**	**Related to dostar or placebo only[a]**	**Related to dostar or placebo**	**Related to dostar or placebo only[a]**	**Related to dostar or placebo**	**Related to dostar or placebo only[a]**
nutrition disorders												
Hyponatraemia	2 (0.8 %)	1 (0.4 %)	0	0	1 (1.9 %)	1 (1.9 %)	0	0	1 (0.5 %)	0	0	0

Abbreviations: carbo=carboplatin; dMMR=mismatch repair-deficient; Dostar=dostarlimab; MMRp=mismatch repair-proficient; MSI-H=microsatellite instability-high; MSS=microsatellite stable; pac=paclitaxel; SAE=serious adverse event.

a. Assessed by the investigator to be not related to carboplatin or paclitaxel and only related to dostarlimab or placebo

Table 73. Summary of treatment-emergent serious adverse events related to chemotherapy (>1 participant in any column) by system organ class and preferred term (Safety Analysis Set)

	Overall population				dMMR/MSI-H population				MMRp/MSS population			
System organ class, n (%) **Preferred term, n (%)**	**Dostar + carbo/pac (N=241)**		**Placebo + carbo/pac (N=246)**		**Dostar + carbo/pac (N=52)**		**Placebo + carbo/pac (N=65)**		**Dostar + carbo/pac (N=189)**		**Placebo + carbo/pac (N=181)**	
	Related to carbo/pac	**Related to carbo/pac only[a]**	**Related to carbo/pac**	**Related to carbo/pac only[a]**	**Related to carbo/pac**	**Related to carbo/pac only[a]**	**Related to carbo/pac**	**Related to carbo/pac only[a]**	**Related to carbo/pac**	**Related to carbo/pac only[a]**	**Related to carbo/pac**	**Related to carbo/pac only[a]**
Any SAE related to chemotherapy	33 (13.7 %)	17 (7.1%)	24 (9.8%)	15 (6.1%)	6 (11.5 %)	3 (5.8%)	8 (12.3 %)	5 (7.7%)	27 (14.3 %)	14 (7.4%)	16 (8.8%)	10 (5.5%)
Blood and lymphatic system disorders	11 (4.6%)	6 (2.5%)	13 (5.3%)	11 (4.5%)	3 (5.8%)	2 (3.8%)	4 (6.2%)	4 (6.2%)	8 (4.2%)	4 (2.1%)	9 (5.0%)	7 (3.9%)
Febrile neutropenia	4 (1.7%)	3 (1.2%)	4 (1.6%)	4 (1.6%)	1 (1.9%)	1 (1.9%)	1 (1.5%)	1 (1.5%)	3 (1.6%)	2 (1.1%)	3 (1.7%)	3 (1.7%)
Anaemia	2 (0.8%)	0	5 (2.0%)	4 (1.6%)	0	0	2 (3.1%)	2 (3.1%)	2 (1.1%)	0	3 (1.7%)	2 (1.1%)

	Overall population				dMMR/MSI-H population				MMRp/MSS population			
System organ class, n (%) **Preferred term, n (%)**	**Dostar + carbo/pac (N=241)**		**Placebo + carbo/pac (N=246)**		**Dostar + carbo/pac (N=52)**		**Placebo + carbo/pac (N=65)**		**Dostar + carbo/pac (N=189)**		**Placebo + carbo/pac (N=181)**	
	Related to carbo/pac	**Related to carbo/pac only[a]**	**Related to carbo/pac**	**Related to carbo/pac only[a]**	**Related to carbo/pac**	**Related to carbo/pac only[a]**	**Related to carbo/pac**	**Related to carbo/pac only[a]**	**Related to carbo/pac**	**Related to carbo/pac only[a]**	**Related to carbo/pac**	**Related to carbo/pac only[a]**
Neutropenia	2 (0.8%)	2 (0.8%)	2 (0.8%)	1 (0.4%)	1 (1.9%)	1 (1.9%)	0	0	1 (0.5%)	1 (0.5%)	2 (1.1%)	1 (0.6%)
General disorders and administration site conditions	4 (1.7%)	1 (0.4%)	7 (2.8%)	2 (0.8%)	1 (1.9%)	0	1 (1.5%)	0	3 (1.6%)	1 (0.5%)	6 (3.3%)	2 (1.1%)
Asthenia	0	0	4 (1.6%)	0	0	0	1 (1.5%)	0	3 (1.6%)	0	1 (0.6%)	0
Pyrexia	3 (1.2%)	1 (0.4%)	1 (0.4%)	1 (0.4%)	0	0	0	0	0	1 (0.5%)	3 (1.7%)	1 (0.6%)
Metabolism and nutrition disorders	4 (1.7%)	2 (0.8%)	4 (1.6%)	2 (0.8%)	0	0	0	0	4 (2.1%)	2 (1.1%)	4 (2.2%)	2 (1.1%)
Dehydration	2 (0.8%)	1 (0.4%)	1 (0.4%)	0	0	0	0	0	2 (1.1%)	1 (0.5%)	1 (0.6%)	0
Gastrointestinal disorders	3 (1.2%)	1 (0.4%)	4 (1.6%)	0	0	0	1 (1.5%)	0	3 (1.6%)	1 (0.5%)	3 (1.7%)	0
Diarrhoea	0	0	2 (0.8%)	0	0	0	0	0	0	0	2 (1.1%)	0

	Overall population				dMMR/MSI-H population				MMRp/MSS population			
System organ class, n (%) **Preferred term, n (%)**	**Dostar + carbo/pac (N=241)**		**Placebo + carbo/pac (N=246)**		**Dostar + carbo/pac (N=52)**		**Placebo + carbo/pac (N=65)**		**Dostar + carbo/pac (N=189)**		**Placebo + carbo/pac (N=181)**	
	Related to carbo/pac	**Related to carbo/pac only[a]**	**Related to carbo/pac**	**Related to carbo/pac only[a]**	**Related to carbo/pac**	**Related to carbo/pac only[a]**	**Related to carbo/pac**	**Related to carbo/pac only[a]**	**Related to carbo/pac**	**Related to carbo/pac only[a]**	**Related to carbo/pac**	**Related to carbo/pac only[a]**
Vomiting	2 (0.8%)	1 (0.4%)	0	0	0	0	0	0	2 (1.1%)	1 (0.5%)	0	0
Infections and infestations	5 (2.1%)	3 (1.2%)	2 (0.8%)	2 (0.8%)	1 (1.9%)	0	1 (1.5%)	1 (1.5%)	4 (2.1%)	3 (1.6%)	1 (0.6%)	1 (0.6%)
Sepsis	2 (0.8%)	2 (0.8%)	0	0	0	0	0	0	2 (1.1%)	2 (1.1%)	0	0
Respiratory, thoracic and mediastinal disorders	2 (0.8%)	0	2 (0.8%)	0	0	0	1 (1.5%)	0	2 (1.1%)	0	1 (0.6%)	0
Pulmonary embolism	1 (0.4%)	0	2 (0.8%)	0	0	0	1 (1.5%)	0	1 (0.5%)	0	1 (0.6%)	0
Musculoskeletal and connective tissue disorders	3 (1.2%)	2 (0.8%)	0	0	1 (1.9%)	1 (1.9%)	0	0	2 (1.1%)	1 (0.5%)	0	0
Muscular weakness	3 (1.2%)	2 (0.8%)	0	0	1 (1.9%)	1 (1.9%)	0	0	2 (1.1%)	1 (0.5%)	0	0

	Overall population				dMMR/MSI-H population				MMRp/MSS population			
System organ class, n (%) **Preferred term, n (%)**	**Dostar + carbo/pac (N=241)**		**Placebo + carbo/pac (N=246)**		**Dostar + carbo/pac (N=52)**		**Placebo + carbo/pac (N=65)**		**Dostar + carbo/pac (N=189)**		**Placebo + carbo/pac (N=181)**	
	Related to carbo/pac	**Related to carbo/pac only[a]**	**Related to carbo/pac**	**Related to carbo/pac only[a]**	**Related to carbo/pac**	**Related to carbo/pac only[a]**	**Related to carbo/pac**	**Related to carbo/pac only[a]**	**Related to carbo/pac**	**Related to carbo/pac only[a]**	**Related to carbo/pac**	**Related to carbo/pac only[a]**
Injury, poisoning and procedural complications	2 (0.8%)	2 (0.8%)	0	0	0	0	0	0	2 (1.1%)	2 (1.1%)	0	0
Infusion-related reaction	2 (0.8%)	2 (0.8%)	0	0	0	0	0	0	2 (1.1%)	2 (1.1%)	0	0

Abbreviations: carbo=carboplatin; dMMR=mismatch repair-deficient; Dostar=dostarlimab; MMRp=mismatch repair-proficient; MSI-H=microsatellite instability-high; MSS=microsatellite stable; pac=paclitaxel; SAE=serious adverse event.

a. Assessed by the investigator to be not related to dostarlimab or placebo and only related to carboplatin or paclitaxel

Infusion-related Reactions

Infusion-related reactions (IRRs) were defined as any drug component-related AEs which occurred on or within 1 day after drug component infusion and were identified based on a pre-specified search list of preferred terms and MedDRA Version 26.0.

Overall population

The incidence of IRRs related to dostarlimab or placebo was low and similar between the dostarlimab plus carboplatin-paclitaxel arm (5 participants [2.1%]) and the placebo plus carboplatin-paclitaxel arm (2 participants [0.8%]). IRRs related to paclitaxel occurred in 12.9% of participants in the dostarlimab plus carboplatin-paclitaxel arm, and in 15.4% of participants in the placebo plus carboplatin-paclitaxel arm. No IRRs led to death in any arm.

Immune-related Adverse Events

Overall population

Table 74. Summary of treatment-emergent immune-related adverse events in >2% of participants (in any column) by immune-related adverse event category and preferred term (Overall population, Safety analysis set)

Category, n (%) Preferred term, n (%)	Dostar + carbo/pac (N=241)		Placebo + carbo/pac (N=246)	
	All events	Dostarlimab-related	All events	Placebo-related
Any immune-related AE	141 (58.5%)	98 (40.7%)	91 (37.0%)	40 (16.3%)
Arthralgia	36 (14.9%)	16 (6.6%)	32 (13.0%)	16 (6.5%)
Infusion-related reaction	31 (12.9%)	4 (1.7%)	30 (12.2%)	0
Hypothyroidism	29 (12.0%)	29 (12.0%)	8 (3.3%)	7 (2.8%)
Hypersensitivity/ Drug hypersensitivity	7 (2.9%)/ 7 (2.9%)	0/ 0	4 (1.6%)/ 11 (4.5%)	1 (0.4%)/ 1 (0.4%)
Rash	22 (9.1%)	17 (7.1%)	6 (2.4%)	5 (2.0%)
Rash maculo-papular	17 (7.1%)	12 (5.0%)	0	0
Pruritus	16 (6.6%)	8 (3.3%)	4 (1.6%)	3 (1.2%)
ALT increased	15 (6.2%)	15 (6.2%)	4 (1.6%)	3 (1.2%)
AST increased	12 (5.0%)	10 (4.1%)	3 (1.2%)	2 (0.8%)
Hyperthyroidism	8 (3.3%)	8 (3.3%)	1 (0.4%)	1 (0.4%)

Abbreviations: AE=adverse event; carbo=carboplatin; Dostar=dostarlimab; pac=paclitaxel.
Note: AEs were coded using MedDRA Version 26.0. AE severity coded using NCI CTCAE v4.03.
Immune-related AEs are identified as any ≥Grade 2 AEs based on a pre-specified preferred terms list.

Grade ≥3 irAEs were observed in 17.4% of participants in the dostarlimab plus carboplatin-paclitaxel arm and in 6.1% of participants in the placebo plus carboplatin paclitaxel arm, while dostarlimab/placebo-related Grade ≥3 irAEs were observed in 13.3% of participants in the dostarlimab plus carboplatin-paclitaxel arm and in 3.3% of participants in the placebo plus carboplatin-paclitaxel arm. In the dostarlimab plus carboplatin-paclitaxel arm, irAEs which were Grade ≥3, SAEs, or leading to discontinuation were reported in 1 or 2 participants each with the exception of irAEs Grade ≥3 of rash (4.6%), rash maculo-papular (2.5%), alanine aminotransferase increased and aspartate aminotransferase increased (2.1% each) and arthralgia (1.2%), and irAEs leading to discontinuation of rash maculo-papular and IRRs (1.2% each).

There were no reported irAEs leading to death.

During post-treatment-emergent period (>90 days post last dose through end of study) five irAEs including colitis, alanine aminotransferase increased, aspartate aminotransferase increased, arthralgia, and rash maculo-papular were reported in 3 participants (1.2%) in the dostarlimab plus carboplatin-paclitaxel arm, all were related to dostarlimab.

Laboratory findings

Haematology

Overall population

Three participants (2 in the dostarlimab plus carboplatin paclitaxel arm, 1 in the placebo plus carboplatin paclitaxel arm) had Grade 4 white blood cell decreased at baseline and as maximum post-baseline value.

Shifts to Grade 3 or 4 haematology parameters of >2 grades from baseline to maximum post-baseline value were most frequently (>10%) reported in participants in the dostarlimab plus carboplatin-paclitaxel arm for neutrophil count decreased (13.7%) and white blood cell count decreased (10.7%), and in the placebo plus carboplatin-paclitaxel arm for neutrophil count decreased (17.5%).

dMMR/MSI-H population

Shifts to Grade 3 or 4 haematology parameters of >2 grades from baseline to maximum postbaseline value were most frequently (>10%) reported in participants in the dostarlimab plus carboplatin-paclitaxel arm for neutrophil count decreased (15.4%), and in the placebo plus carboplatin-paclitaxel arm for neutrophil count decreased (23.1%), white blood cell count decreased (12.3%), platelet count decreased (12.3%), and lymphocyte count decreased (10.8%).

MMRp/MSS population

Shifts to Grade 3 or 4 haematology parameters of >2 grades from baseline to maximum postbaseline value were most frequently (>10%) reported in participants in the dostarlimab plus carboplatin-paclitaxel arm for neutrophil count decreased (13.2%) and white blood cell count decreased (11.1%), and in the placebo plus carboplatin-paclitaxel arm for neutrophil count decreased (15.5%).

Clinical chemistry

Overall population

Baseline Grade 4 chemistry results were only reported for hypoglycaemia (1 participant in the dostarlimab plus carboplatin-paclitaxel arm and 2 participants in placebo plus carboplatin-paclitaxel arm); Grade 4 results were also reported as maximum postbaseline values for these participants.

Shifts to Grade 3 or 4 chemistry parameters of >2 grades from baseline to maximum postbaseline value were most frequently (>3%) reported in participants in the dostarlimab plus carboplatin-paclitaxel arm for hyponatremia (4.6%), serum amylase increased (4.1%), hyperglycaemia (3.7%), and hypokalaemia (3.3%). No shifts to Grade 3 or 4 chemistry parameters of >2 grades from baseline to maximum postbaseline value were reported in the placebo plus carboplatin-paclitaxel arm.

dMMR/MSI-H population

Shifts to Grade 3 or 4 chemistry parameters of >2 grades from baseline to maximum postbaseline value were most frequently (>3%) reported in the dostarlimab plus carboplatin-paclitaxel arm for hyponatremia (9.6%) and hypokalaemia (3.8%), and in the placebo plus carboplatin-paclitaxel arm for hypokalaemia (6.2%) and hypophosphatemia (4.6%).

MMRp/MSS population

Shifts to Grade 3 or 4 chemistry parameters of >2 grades from baseline to maximum postbaseline value were most frequently (>3%) reported in the dostarlimab plus carboplatin-paclitaxel arm for hyperglycaemia (4.8%), serum amylase increased (4.8%), hyponatremia (3.2%), ALT increased (3.2%), and hypokalaemia (3.2%) and in the placebo plus carboplatin-paclitaxel arm for hyponatremia (3.3%).

Liver-related assessments

No participant met the criteria for potential Hy's law (concurrent AST or ALT ≥3×ULN, in combination with bilirubin ≥2×ULN and ALP <2×ULN). The incidence of potential liver toxicity events was generally higher in the dostarlimab plus carboplatin-paclitaxel arm than in the placebo plus carboplatin paclitaxel arm; however, the difference between arms for each parameter was <5%. One participant in the placebo plus carboplatin-paclitaxel arm reported ALT ≥20×ULN and AST ≥20×ULN; no participants in the dostarlimab plus carboplatin-paclitaxel arm reported ALT or AST ≥20×ULN. The toxicity criterion with the highest overall frequency (6.8%) and greatest difference in frequency between treatment arms was (ALT or AST) ≥3×ULN; 10.8% and 2.8% in the dostarlimab plus carboplatin-paclitaxel arm and the placebo plus carboplatin-paclitaxel arm, respectively.

Table 75. Incidence of potential liver toxicity events (Safety Analysis Set)

	Overall population		dMMR/MSI-H population		MMRp/MSS population	
Toxicity criterion	**Dostar + carbo/pac (N=241)**	**Placebo + carbo/pac (N=246)**	**Dostar + carbo/pac (N=52)**	**Placebo + carbo/pac (N=65)**	**Dostar + carbo/pac (N=189)**	**Placebo + carbo/pac (N=181)**
ALT ≥3×ULN	17 (7.1%)	6 (2.4%)	6 (11.5%)	1 (1.5%)	11 (5.8%)	5 (2.8%)
ALT ≥5×ULN	6 (2.5%)	2 (0.8%)	0	0	6 (3.2%)	2 (1.1%)
ALT ≥10×ULN	3 (1.2%)	1 (0.4%)	0	0	3 (1.6%)	1 (0.6%)
ALT ≥20×ULN	0	1 (0.4%)	0	0	0	1 (0.6%)
AST ≥3×ULN	20 (8.3%)	5 (2.0%)	7 (13.5%)	1 (1.5%)	13 (6.9%)	4 (2.2%)
AST ≥5×ULN	8 (3.3%)	4 (1.6%)	2 (3.8%)	0	6 (3.2%)	4 (2.2%)
AST ≥10×ULN	2 (0.8%)	1 (0.4%)	0	0	2 (1.1%)	1 (0.6%)
AST ≥20×ULN	0	1 (0.4%)	0	0	0	1 (0.6%)
(ALT or AST) ≥3×ULN	26 (10.8%)	7 (2.8%)	10 (19.2%)	1 (1.5%)	16 (8.5%)	6 (3.3%)
(ALT or AST) ≥5×ULN	9 (3.7%)	4 (1.6%)	2 (3.8%)	0	7 (3.7%)	4 (2.2%)
(ALT or AST) ≥10×ULN	4 (1.7%)	1 (0.4%)	0	0	4 (2.1%)	1 (0.6%)
(ALT or AST) ≥20×ULN	0	1 (0.4%)	0	0	0	1 (0.6%)
Total bilirubin ≥2×ULN	4 (1.7%)	1 (0.4%)	2 (3.8%)	1 (1.5%)	2 (1.1%)	0
Concurrent ALT ≥3×ULN and total bilirubin ≥2×ULN	2 (0.8%)	0	1 (1.9%)	0	1 (0.5%)	0
Concurrent AST ≥3×ULN and total bilirubin ≥2×ULN	3 (1.2%)	0	2 (3.8%)	0	1 (0.5%)	0
Concurrent (ALT or AST) ≥3×ULN and total bilirubin ≥2×ULN	3 (1.2%)	0	2 (3.8%)	0	1 (0.5%)	0
Concurrent (ALT or AST) ≥3×ULN and total bilirubin ≥2×ULN and ALP >2×ULN	3 (1.2%)	0	2 (3.8%)	0	1 (0.5%)	0

	Overall population		dMMR/MSI-H population		MMRp/MSS population	
Toxicity criterion	**Dostar + carbo/pac (N=241)**	**Placebo + carbo/pac (N=246)**	**Dostar + carbo/pac (N=52)**	**Placebo + carbo/pac (N=65)**	**Dostar + carbo/pac (N=189)**	**Placebo + carbo/pac (N=181)**
Potential Hy's law: Concurrent (ALT or AST) ≥3×ULN and total bilirubin ≥2×ULN and ALP <2×ULN	0	0	0	0	0	0

Abbreviations: ALP=alkaline phosphatase; ALT=alanine aminotransferase; AST=aspartate aminotransferase; carbo=carboplatin; dMMR=mismatch repair-deficient; Dostar=dostarlimab; MMRp=mismatch repair proficient; MSI H=microsatellite instability-high; MSS=microsatellite stable; pac=paclitaxel; ULN=upper limit of normal.

Safety in special populations

Intrinsic factors

Age

The incidence of SAEs and any treatment-related SAEs was similar between all age groups in the dostarlimab plus carboplatin-paclitaxel arm (~40% SAEs, ~20% treatment related SAEs), and between participants aged <65 years and 65 to <75 years in the placebo plus carboplatin-paclitaxel arm (~23% SAEs, ~8% treatment-related SAEs), which were higher in the dostarlimab plus carboplatin-paclitaxel arm than in the placebo plus carboplatin-paclitaxel arm. SAEs (50%) and any treatment-related SAEs (36%) were higher in participants aged ≥75 years in the placebo plus carboplatin-paclitaxel arm. TEAEs with outcome of death were 3.2% (n=4) in the <65-year group, including 2 deaths related to study treatment, and 1.1% in the 65 to <75-year group in the dostarlimab plus carboplatin-paclitaxel arm; no other deaths due to TEAEs were reported in the study.

The incidence of TEAEs leading to infusion delay was similar between all age groups (excluding ≥85 years age group with single participant) in each arm, ranging from 35% to 50%. The incidence of TEAEs leading to dose reduction of carboplatin and/or paclitaxel was similar between all age groups (excluding ≥85 years age group with single participant) in each arm, ranging from 22% to 33%, except for dose reductions for participants aged ≥75 years in the placebo plus carboplatin-paclitaxel arm (47%).

The incidence of TEAEs leading to treatment discontinuation was lower in participants aged <65 years in the dostarlimab plus carboplatin-paclitaxel arm (20%), and those aged <65 years (17%) and 65 to <75 years (10%) in the placebo plus carboplatin-paclitaxel arm, than those aged 65 to <75 years (31%) and ≥75 years (30%) in the dostarlimab plus carboplatin-paclitaxel arm and aged ≥75 years in the placebo plus carboplatin-paclitaxel arm (31%).

The incidence of dostarlimab/placebo-related irAEs was similar between participants aged <65 years and 65 to <75 years in the dostarlimab plus carboplatin-paclitaxel arm (34% to 42%), and between participants aged <65 years and 65 to <75 years (13% to 16%) in the placebo plus carboplatin-paclitaxel arm, with dostarlimab/placebo-related irAEs higher in the dostarlimab plus carboplatin-paclitaxel arm than in the placebo plus carboplatin-paclitaxel arm for these age groups. Dostarlimab/placebo-related irAEs were higher in participants aged ≥75 years in both arms (56% in the dostarlimab plus carboplatin-paclitaxel arm and 25% in the placebo plus carboplatin-paclitaxel arm).

Race

The incidences of TEAEs and any treatment-related TEAEs were similar (>95%) between Black/African American and White participants in each arm. The incidences were similar between Black/African

American and White participants for Grade ≥3 TEAEs (67% and 72%, respectively) and treatment-related Grade ≥3 TEAEs (44% and 55%, respectively) in the dostarlimab plus carboplatin-paclitaxel arm, and Grade ≥3 TEAEs (52% and 62%, respectively) and treatment-related Grade ≥3 TEAEs (29% and 50%, respectively) in the placebo plus carboplatin-paclitaxel arm, were higher (≥10%) in Black/African American participants than in White participants.

The incidence of SAEs in Black/African American and White participants were similar within the dostarlimab plus carboplatin-paclitaxel arm (range 33% to 40%) and within the placebo plus carboplatin-paclitaxel arm (range 29% to 32%); the incidence of SAEs was higher in White participants in the dostarlimab plus carboplatin-paclitaxel arm than in the placebo plus carboplatin-paclitaxel arm.

The incidence of infusion delays was higher in White participants than in Black/African American participants in the dostarlimab plus carboplatin-paclitaxel arm (51% versus 22%, respectively) as well as in the placebo plus carboplatin paclitaxel arm (42% versus 32%, respectively).

The incidences of TEAEs leading dose reduction were similar between Black/African American and White participants within each treatment arm (26% to 29%).

The incidences of TEAEs leading to treatment discontinuations were similar within and between treatment arms (16% to 19%) except for White participants in the dostarlimab plus carboplatin-paclitaxel arm (27%).

The incidence of dostarlimab/placebo-related irAEs in White participants within the dostarlimab plus carboplatin paclitaxel arm (44%) was higher than in Black/African American participants (30%). The incidences of other parameters were too low for meaningful comparison.

BMI

The incidences of Grade≥3 TEAEs in participants with normal, overweight, or obese BMIs were similar within the dostarlimab plus carboplatin-paclitaxel arm (range 70% to 73%) and within the placebo plus carboplatin-paclitaxel arm (range 57% to 64%); these ranges were higher in participants in the dostarlimab plus carboplatin-paclitaxel arm than in the placebo plus carboplatin paclitaxel arm. Treatment-related Grade ≥3 TEAEs were similar within the dostarlimab plus carboplatin-paclitaxel arm (range 45% to 57%) and within the placebo plus carboplatin-paclitaxel arm (range 43% to 57%) and were similar between arms.

The incidence of SAEs in participants with normal, overweight, or obese BMIs were similar within the dostarlimab plus carboplatin-paclitaxel arm (range 36% to 45%) and within the placebo plus carboplatin-paclitaxel arm (range 26% to 31%); these ranges were higher in the dostarlimab plus carboplatin-paclitaxel arm than in the placebo plus carboplatin-paclitaxel arm.

The incidences of infusion delays were similar between normal, overweight, and obese BMIs within each treatment arm (dostarlimab plus carboplatin-paclitaxel range 44% to 55%; placebo plus carboplatin paclitaxel range 39% to 41%). Dose reductions of chemotherapy were lower in participants with normal BMI in both treatment arms (~14%) compared to participants with overweight or obese BMIs (28% to 32%). The incidences of participants with TEAEs leading to treatment discontinuations were similar within and between treatment arms (11% to 24%), except for normal BMI participants in the dostarlimab plus carboplatin-paclitaxel arm (34%). The incidence of dostarlimab/placebo-related irAEs in participants with normal or overweight BMIs within the dostarlimab plus carboplatin paclitaxel arm (43% and 53%, respectively) were higher than in obese participants (33%). The incidences of other parameters were too low for meaningful comparison.

Baseline kidney function

The incidences were similar between participants with normal, mildly impaired, and moderately impaired baseline kidney function for Grade ≥3 TEAEs (range 67% to 75%) and treatment-related Grade ≥3 TEAEs (range 52% to 61%) in the dostarlimab plus carboplatin-paclitaxel arm; in the placebo plus carboplatin paclitaxel arm, incidences were higher in participants with moderately impaired baseline kidney function for Grade ≥3 TEAEs (76%) than in those with normal (56%) or mildly impaired (60%) baseline kidney function, with similar treatment related Grade ≥3 TEAEs (range 45% to 55%). Other parameters (SAEs, treatment-related SAEs, TEAEs leading to infusion interruption/delay, TEAEs leading to chemotherapy dose reduction, TEAEs leading to treatment discontinuation) were similar with <10% differences between participants with normal or mildly impaired baseline kidney function within each arm, except for normal participants in the dostarlimab plus carboplatin-paclitaxel arm who had a higher incidence than participants with mildly impaired baseline kidney function (52% versus 40%, respectively). The incidences of other parameters were too low for participants with moderately impaired baseline kidney function for meaningful comparison.

Safety related to drug-drug interactions and other interactions

No dedicated drug interaction studies have been conducted. mAbs such as dostarlimab are not substrates for CYP or drug transporters. Dostarlimab is not a cytokine and is unlikely to be a cytokine modulator. Additionally, PK drug interaction of dostarlimab with small molecule drugs is not expected. There is no evidence of drug interaction mediated by nonspecific clearance of lysosome degradation for antibodies.

Discontinuation due to adverse events

In the overall population, TEAEs leading to discontinuation of any study treatment were higher in participants in the dostarlimab plus carboplatin-paclitaxel arm (24.9%) than in the placebo plus carboplatin-paclitaxel arm (16.3%).

Table 76. Summary of treatment-emergent adverse events leading to discontinuation of dostarlimab or placebo in >1 participant (any arm) by system organ class and preferred term (Safety Analysis Set)

	Overall population		**dMMR/MSI-H population**		**MMRp/MSS population**	
System organ class, n (%) **Preferred term, n (%)**	**Dostar + carbo/pac (N=241)**	**Placebo + carbo/pac (N=246)**	**Dostar + carbo/pac (N=52)**	**Placebo + carbo/pac (N=65)**	**Dostar + carbo/pac (N=189)**	**Placebo + carbo/pac (N=181)**
Any TEAE leading to discontinuation of dostarlimab or placebo	46 (19.1%)	20 (8.1%)	9 (17.3%)	5 (7.7%)	37 (19.6%)	15 (8.3%)
Blood and lymphatic system disorders	3 (1.2%)	5 (2.0%)	1 (1.9%)	2 (3.1%)	2 (1.1%)	3 (1.7%)
Thrombocytopenia	1 (0.4%)	3 (1.2%)	0	2 (3.1%)	1 (0.5%)	1 (0.6%)
Investigations	6 (2.5%)	2 (0.8%)	0	0	6 (3.2%)	2 (1.1%)
Alanine aminotransferase increased	2 (0.8%)	1 (0.4%)	0	0	2 (1.1%)	1 (0.6%)
Aspartate aminotransferase increased	2 (0.8%)	0	0	0	2 (1.1%)	0

	Overall population		dMMR/MSI-H population		MMRp/MSS population	
System organ class, n (%) **Preferred term, n (%)**	**Dostar + carbo/pac (N=241)**	**Placebo + carbo/pac (N=246)**	**Dostar + carbo/pac (N=52)**	**Placebo + carbo/pac (N=65)**	**Dostar + carbo/pac (N=189)**	**Placebo + carbo/pac (N=181)**
General disorders and administration site conditions	5 (2.1%)	1 (0.4%)	1 (1.9%)	0	4 (2.1%)	1 (0.6%)
Fatigue	2 (0.8%)	0	1 (1.9%)	0	1 (0.5%)	0
Gastrointestinal disorders	4 (1.7%)	2 (0.8%)	1 (1.9%)	0	3 (1.6%)	2 (1.1%)
Diarrhoea	2 (0.8%)	1 (0.4%)	0	0	2 (1.1%)	1 (0.6%)
Pancreatitis	2 (0.8%)	0	1 (1.9%)	0	1 (0.5%)	0
Skin and subcutaneous tissue disorders	4 (1.7%)	3 (1.2%)	1 (1.9%)	0	3 (1.6%)	3 (1.7%)
Rash	1 (0.4%)	2 (0.8%)	0	0	1 (0.5%)	2 (1.1%)
Rash maculo-papular	3 (1.2%)	0	1 (1.9%)	0	2 (1.1%)	0
Immune system disorders	3 (1.2%)	2 (0.8%)	0	0	3 (1.6%)	2 (1.1%)
Anaphylactic reaction	2 (0.8%)	0	0	0	2 (1.1%)	0
Injury, poisoning and procedural complications	3 (1.2%)	1 (0.4%)	1 (1.9%)	0	2 (1.1%)	1 (0.6%)
Infusion-related reaction	3 (1.2%)	1 (0.4%)	1 (1.9%)	0	2 (1.1%)	1 (0.6%)
Musculoskeletal and connective tissue disorders	4 (1.7%)	1 (0.4%)	2 (3.8%)	0	2 (1.1%)	1 (0.6%)
Arthralgia	2 (0.8%)	0	1 (1.9%)	0	1 (0.5%)	0
Respiratory, thoracic and mediastinal disorders	4 (1.7%)	0	0	0	4 (2.1%)	0
Pneumonitis	2 (0.8%)	0	0	0	2 (1.1%)	0

Abbreviations: carbo=carboplatin; dMMR=mismatch repair-deficient; Dostar=dostarlimab; MMRp=mismatch repair-proficient; MSI-H=microsatellite instability-high; MSS=microsatellite stable; pac=paclitaxel; TEAE=treatment-emergent adverse event.

Table 77. Summary of treatment-emergent adverse events leading to discontinuation of carboplatin in >1 participant (total column) by system organ class and preferred term (Overall population, Safety analysis set)

System organ class, n (%) Preferred term, n (%)	Dostar + carbo/pac (N=241)	Placebo + carbo/pac (N=246)	Total (N=487)
Any TEAE leading to discontinuation of carboplatin	20 (8.3%)	15 (6.1%)	35 (7.2%)
Immune system disorders	6 (2.5%)	3 (1.2%)	9 (1.8%)
Drug hypersensitivity	2 (0.8%)	1 (0.4%)	3 (0.6%)
Hypersensitivity	2 (0.8%)	1 (0.4%)	3 (0.6%)
Anaphylactic reaction	1 (0.4%)	1 (0.4%)	2 (0.4%)
Injury, poisoning and procedural complications	4 (1.7%)	4 (1.6%)	8 (1.6%)
Infusion-related reaction	4 (1.7%)	4 (1.6%)	8 (1.6%)
Blood and lymphatic system disorders	2 (0.8%)	4 (1.6%)	6 (1.2%)
Thrombocytopenia	0	3 (1.2%)	3 (0.6%)

Abbreviations: carbo=carboplatin; Dostar=dostarlimab; pac=paclitaxel; SAE=serious adverse event; TEAE=treatment-emergent adverse event

Table 78. Summary of treatment-emergent adverse events leading to discontinuation of paclitaxel in >1 participant (total column) by system organ class and preferred term (Overall population, Safety analysis set)

System organ class, n (%) Preferred term, n (%)	Dostar + carbo/pac (N=241)	Placebo + carbo/pac (N=246)	Total (N=487)
Any TEAE leading to discontinuation of paclitaxel	26 (10.8%)	25 (10.2%)	51 (10.5%)
Nervous system disorders	11 (4.6%)	10 (4.1%)	21 (4.3%)
Neuropathy peripheral	4 (1.7%)	7 (2.8%)	11 (2.3%)
Peripheral sensory neuropathy	7 (2.9%)	1 (0.4%)	8 (1.6%)
Injury, poisoning and procedural complications	3 (1.2%)	5 (2.0%)	8 (1.6%)
Infusion-related reaction	3 (1.2%)	5 (2.0%)	8 (1.6%)
Blood and lymphatic system disorders	2 (0.8%)	3 (1.2%)	5 (1.0%)
Thrombocytopenia	1 (0.4%)	3 (1.2%)	4 (0.8%)
Immune system disorders	3 (1.2%)	2 (0.8%)	5 (1.0%)
Drug hypersensitivity	1 (0.4%)	1 (0.4%)	2 (0.4%)
Hypersensitivity	1 (0.4%)	1 (0.4%)	2 (0.4%)
General disorders and administration site conditions	1 (0.4%)	1 (0.4%)	2 (0.4%)
Asthenia	1 (0.4%)	1 (0.4%)	2 (0.4%)

Abbreviations: carbo=carboplatin; Dostar=dostarlimab; pac=paclitaxel; SAE=serious adverse event; TEAE=treatment-emergent adverse event.

Table 79. Summary of adverse events leading to discontinuation in the overall population and by region

	North America		Europe	
Adverse Events (n[%])	Dostar+ carbo/pac (n=169)	Placebo + carbo/pac (n=186)	Dostar+ carbo/pac (n=72)	Placebo + carbo/pac (n=60)
Any AE leading to treatment discontinuation	38 (22.5%)	28 (15.1%)	22 (30.6%)	12 (20.0%)
Dostarlimab/placebo discontinuation	30 (17.8%)	15 (8.1%)	16 (22.2%)	5 (8.3%)
Carboplatin discontinuation	9 (5.3%)	12 (6.5%)	11 (15.3%)	3 (5.0%)
Paclitaxel discontinuation	15 (8.9%)	18 (9.7%)	11 (15.3%)	7 11.6%)

TEAEs leading to study drug infusion interruption

Overall population

In the overall population, TEAEs leading to infusion interruption of any drug component of study treatment were similar (≤5% difference) between the dostarlimab plus carboplatin paclitaxel arm and placebo plus carboplatin-paclitaxel arm (20.7% versus 19.9%, respectively) and were mostly due to infusion interruptions of carboplatin and/or paclitaxel. The most frequent TEAE leading to interruption of study treatment infusion was IRR in both treatment arms (10.8% in the dostarlimab plus carboplatin-paclitaxel arm and 11.8% in the placebo plus carboplatin-paclitaxel arm).

The incidence of TEAEs leading to infusion interruption of dostarlimab/placebo was 1.4%, with TEAEs occurring in 1 participant each, except for ALT increased, which occurred in 2 participants. The incidence of TEAEs leading to infusion interruption of carboplatin was similar between the dostarlimab plus carboplatin-paclitaxel arm (6.2%) and the placebo plus carboplatin paclitaxel arm (5.3%). In addition, the incidence of TEAEs leading to infusion interruption of paclitaxel was similar between the dostarlimab plus carboplatin-paclitaxel arm (13.3%) and the placebo plus carboplatin-paclitaxel arm (15.0%).

TEAEs leading to study drug infusion delay

Overall population

The incidence of TEAEs leading to delays of infusion of any drug component of study treatment was 47.3% in participants in the dostarlimab plus carboplatin-paclitaxel arm and 40.2% in participants in the placebo plus carboplatin-paclitaxel arm. The most frequently reported TEAEs (>5% in any arm) leading to delays of infusion were platelet count decreased (5.0% versus 7.3%), neutrophil count decreased (1.2% versus 6.5%), thrombocytopenia (7.9% versus 5.7%), anaemia (5.4% versus 6.1%), neutropenia (3.3% versus 5.3%), and neuropathy peripheral (5.8% versus 2.0%) in the dostarlimab plus carboplatin-paclitaxel versus the placebo plus carboplatin-paclitaxel arms, respectively.

The incidence of TEAEs leading to delays of dostarlimab/placebo infusion was higher in participants in the dostarlimab plus carboplatin-paclitaxel arm (44.8%) than in the placebo plus carboplatin-paclitaxel arm (37.8%). However, no notable differences (>10%) in the incidence of TEAEs were observed between the treatment arms. The most frequently reported TEAEs (>5% in any arm) leading to delays of dostarlimab/placebo infusion were thrombocytopenia (7.5% versus 5.3%), anaemia (5.4% versus 6.1%), neutropenia (3.3% versus 5.3%), platelet count decreased (4.1% versus 7.3%), and neutrophil count

decreased (1.2% versus 6.1%) in the dostarlimab plus carboplatin paclitaxel arm versus placebo plus carboplatin paclitaxel arm, respectively.

The incidence of TEAEs leading to delays of carboplatin infusion was similar between the dostarlimab plus carboplatin-paclitaxel arm (28.6%) and the placebo plus carboplatin paclitaxel arm (30.1%). The most frequently reported TEAEs (>4% in any arm) leading to delays of carboplatin infusion were thrombocytopenia (4.6% versus 4.5%), anaemia (3.7% versus 4.9%), neutropenia (2.9% versus 4.5%), platelet count decreased (3.7% versus 5.7%), neutrophil count decreased (1.2% versus 5.3%), and neuropathy peripheral (4.6% versus 1.6%) in the dostarlimab plus carboplatin-paclitaxel arm versus placebo plus carboplatin-paclitaxel arm, respectively.

The incidence of TEAEs leading to delays of paclitaxel infusion was similar between the dostarlimab plus carboplatin-paclitaxel arm (27.4%) and the placebo plus carboplatin paclitaxel arm (27.2%). The most frequently reported TEAEs (>4% in any arm) leading to delays of paclitaxel infusion were thrombocytopenia (4.6% versus 4.9%), anaemia (3.3% versus 4.5%), platelet count decreased (4.1% versus 6.5%), and neutrophil count decreased (1.2% versus 4.5%) in the dostarlimab plus carboplatin paclitaxel arm versus placebo plus carboplatin-paclitaxel arm, respectively.

Differences between IA2 and IA1 in the dostarlimab plus carboplatin-paclitaxel arm were 2.1% for TEAEs leading to infusion delays and for dostarlimab-related TEAEs leading to infusion delays.

Differences were based on additional TEAEs occurring in single participants with the exception of pyrexia, reported in 2 additional participants at IA2 as compared to IA1.

Adverse Drug Reactions

A 2-step, holistic approach was used to review TEAEs from all participants in RUBY Part 1 IA2 for the identification of dostarlimab ADRs. TEAEs leading to treatment discontinuation and TEAEs leading to death were also evaluated, but these occurred in relatively few participants and were of limited value in the assessment of ADRs.

Adverse drug reactions for dostarlimab in combination with carboplatin-paclitaxel for IA2

ADRs for the SmPC have been identified based on data from all participants who received dostarlimab plus carboplatin-paclitaxel (N=241) in comparison with participants receiving placebo plus carboplatin-paclitaxel (N=246) using a data cutoff date of 22 September 2023. Final identification of ADRs is based on the overall quantitative analysis and the qualitative assessment.

The majority of the ADRs identified for IA2 for dostarlimab plus carboplatin-paclitaxel were previously identified as ADRs for dostarlimab monotherapy as second-line in participants with advanced or recurrent solid tumours and were consistent with those identified from RUBY Part 1 IA1. No new terms were identified as ADRs for dostarlimab plus carboplatin-paclitaxel based on review of data from RUBY Part 1 IA2 compared to those identified in IA1.

The most frequently reported ADRs (≥10% of participants) in participants receiving dostarlimab plus carboplatin-paclitaxel were identical between IA1 and IA2: rash (23.2%), rash maculo-papular (14.5%), hypothyroidism (14.5%), ALT increased (12.9%), AST increased (12.0%), pyrexia (12.9%), and dry skin (10.0%), with frequencies comparable (<1% differences) to those reported based on IA1.

Based on the dostarlimab mechanism of action, following medical review, immune-mediated AEs with incidence <10% were identical between IA1 and IA2 and including hyperthyroidism (4.1%), pneumonitis (2.1%), colitis (1.2%), adrenal insufficiency (0.8%), pancreatitis (1.2%), immune-mediated hypothyroidism (0.4%), thyroiditis (0.4%), immune-mediated arthritis (0.4%), myocarditis (0.4%), Type 1 diabetes mellitus (0.4%), and uveitis (0.4%), with frequencies comparable (<0.5% differences) to those reported based on IA1.

AEs that met the quantitative criteria based on IA2 and which were not considered to be causally attributable to dostarlimab in the SmPC include blood creatinine increased, hypoesthesia, hypoalbuminemia, toothache, hypocalcaemia, sepsis, peripheral swelling, nasopharyngitis, and seasonal allergy. Blood creatinine increased, hypoesthesia, hypoalbuminemia, toothache, hypocalcaemia, and sepsis had previously been described as meeting the quantitative criteria and were not considered to be causally attributable to dostarlimab based on IA1. These events, as well as peripheral swelling, nasopharyngitis, and seasonal allergy, were excluded as ADRs based on the relatively low frequency considered related to dostarlimab by the investigator, lack of biological plausibility, and/or for AEs with vital signs/laboratory analyses (blood creatinine increased, hypoalbuminemia, and hypocalcaemia), the comparable data between the dostarlimab plus carboplatin-paclitaxel and placebo plus carboplatin-paclitaxel arms. Additional potentially immune-related AEs were not identified as ADRs following medical review based on IA1 and IA2 as they were not considered to be causally attributable to dostarlimab by the investigator or sponsor (infusion-related hypersensitivity reaction; Raynaud's phenomenon; iritis), laboratory data for diagnosis was not provided (immune-mediated adrenal insufficiency; immune-mediated hypophysitis), or was confounded by long-term ibuprofen use (colitis microscopic). Additionally, polymyalgia rheumatica was reported in a single participant at IA2 but was not considered to be causally attributable to dostarlimab by the sponsor as diagnostic laboratory data was not provided.

Post marketing experience

Information relating to the benefit-risk profile of dostarlimab from the reporting period (21 April 2023 to 20 October 2023) and cumulatively (21 April 2021 to 20 October 2023) was included in the most recent dostarlimab PSUR. Exposure to dostarlimab from post-marketing experience in the reporting period was estimated to be 185.1 patient-years, and cumulatively was estimated to be 528.9 patient-years.

2.5.1. Discussion on clinical safety

The current safety assessment for dostarlimab, in combination with carboplatin-paclitaxel is based on the results from a second interim analysis (IA2) from Part 1 of the RUBY study, with a DCO of 22 September 2023 and with a median follow-up of 47.2 months. Results of the first IA (DCO: 28 September 2022) were assessed as part of variation application EMEA/H/C/5204/II/0023.

As of the IA2 data cut-off date, 241 participants had received treatment with dostarlimab in combination with carboplatin-paclitaxel and 246 participants had received treatment with placebo in combination with carboplatin-paclitaxel.

Patient exposure

The overall median duration of treatment was 43.00 weeks (range: 3.0 to 192.6 weeks) in the dostarlimab plus carboplatin-paclitaxel arm and 36.00 weeks (range: 2.1 to 193.1 weeks) in the placebo plus carboplatin-paclitaxel arm. The median treatment duration of both carboplatin and paclitaxel was 18.0 weeks in both arms for the overall population.

For the dMMR/MSI-H population, the median number of actual dosing cycles was much longer for the dostarlimab plus carboplatin-paclitaxel arm (15.5) compared to the placebo plus carboplatin-paclitaxel arm (8.0). In the MMRp/MSS population, there is no difference between treatment arms in the median number of cycles (9.0) being lower compared to the dMMR/MSI-H population in the dostarlimab plus carboplatin-paclitaxel arm.

The mean duration of exposure in the dostarlimab plus carboplatin-paclitaxel arm was longer for the dMMR/MSI-H population (76.50 weeks; range: 3.0 to 192.6 weeks) compared to the placebo plus carboplatin-paclitaxel arm (31.86 weeks; range: 3.0 to 193.1 weeks). While in the MMRp/MSS population, the overall median treatment duration was 39.00 weeks (range: 3.0 to 190.7 weeks) for

participants in the dostarlimab plus carboplatin-paclitaxel arm and 36.00 weeks (range: 2.1 to 187.0 weeks) for participants in the placebo plus carboplatin-paclitaxel arm.

There were no changes in the baseline characteristics between IA1 and IA2.

Adverse events (AEs)

The **most frequently reported TEAEs** (>40%) in both treatment arms for the overall population were nausea (54.4% vs 46.3%), alopecia (53.9% vs 50.0%), fatigue (52.3% vs 54.9%) neuropathy peripheral (44.0% vs 41.9%), and anaemia (37.8% vs 42.7%) in the placebo plus carboplatin-paclitaxel arm. The highest (>10%) difference between treatment arms was observed for rash maculo-papular (14.5% in the dostarlimab plus carboplatin-paclitaxel arm compared with 3.7% in the placebo plus carboplatin-paclitaxel arm).

In the dMMR/MSI-H population, more than 50% of subjects in both treatment arms had alopecia and fatigue, and nausea in the dostarlimab arm was higher than the placebo arm (57.7% vs 46.2%, respectively) in this subpopulation. The most frequently reported TEAEs (>40%) were nausea (57.7%), alopecia (57.7%), fatigue (50.0%), arthralgia (46.2%), neuropathy peripheral (42.3%) and diarrhoea (40.4% vs 32.3%) in the dostarlimab plus carboplatin-paclitaxel arm; while those in the placebo plus carboplatin paclitaxel arm included alopecia (60.0%), fatigue (56.9%), anaemia (52.3%), nausea (46.2%), and neuropathy peripheral (44.6%). The highest (>10%) difference between treatment arms was observed for hypothyroidism (21.2% in the dostarlimab plus carboplatin-paclitaxel arm compared with 6.2% in the placebo plus carboplatin-paclitaxel arm), rash (28.8% vs 16.9%), hypertension (21.2% vs 10.8%), rash maculo papular (15.4% versus 3.1%), and pyrexia (13.5% versus 1.5%).

While for the MMRp/MSS population, more than 50% of subjects in both treatment arms had fatigue, and nausea and alopecia were higher in the dostarlimab arm. The most frequently reported TEAEs (>40%) in both treatment arms were nausea (53.4% vs 46.4%), alopecia (52.9% vs 46.4%), fatigue (52.9% vs 54.1%) and neuropathy peripheral (44.4% vs 40.9%). The highest (>10%) difference between treatment arms was observed for rash maculo-papular (14.3% vs 3.9% in the dostarlimab plus carboplatin-paclitaxel arm compared with the placebo plus carboplatin-paclitaxel arm, respectively).

The frequency of **treatment-related TEAEs** was comparable between the treatment arms for the overall population (97.9% in the dostarlimab plus carboplatin-paclitaxel and 98.8% in the placebo plus carboplatin-paclitaxel arms) as well as for the two subpopulations, dMMR/MSI-H population (100% vs 100%) and MMRp/MSS population (97.4% vs 98.3%). The most frequently reported TEAEs related to any study treatment (>40%) in both treatment arms were alopecia, fatigue, nausea, and neuropathy peripheral. In the dMMR/MSI-H population, a ≤10% difference in the incidence of treatment related TEAEs between treatment arms was observed with the exception of diarrhoea (32.7% versus 20.0%), rash (21.2% versus 10.8%), and hypothyroidism (21.2% versus 6.2%), which were >10% higher in the dostarlimab plus carboplatin-paclitaxel arm than in the placebo plus carboplatin-paclitaxel arm and anaemia (26.9% versus 46.2%), neutrophil count decreased (7.7% versus 23.1%), and white blood cell decreased (7.7% versus 18.5%), which were >10% higher in the placebo plus carboplatin-paclitaxel arm than in the dostarlimab plus carboplatin-paclitaxel arm. While in the MMRp/MSS population, a ≤10% difference between treatment arms in the incidence of treatment related TEAEs in participants was observed.

The incidence of treatment-related TEAEs was higher in the dostarlimab plus carboplatin-paclitaxel arm versus the placebo plus carboplatin-paclitaxel arm in the system organ classes of skin and subcutaneous tissue disorders (28.2% and 13.0%, respectively) primarily driven by TEAEs of rash and rash maculo-papular, and endocrine disorders (17.4% and 5.7%, respectively) mainly driven by hypothyroidism for the overall population. This difference was primarily driven by rash (19.2% versus 3.1%) and hypothyroidism (21.2% versus 6.2%) in the dostarlimab plus carboplatin-paclitaxel and placebo plus

carboplatin-paclitaxel arms, respectively, in the dMMR/MSI-H population. In the MMRp/MSS population, this difference was also driven by hypothyroidism (12.2% versus 4.4%) and rash (11.6% versus 6.6%), but also by rash maculo-papular (5.8% versus 0.6%) in the dostarlimab plus carboplatin-paclitaxel and placebo plus carboplatin-paclitaxel arms, respectively.

TEAEs considered related to carboplatin/paclitaxel only were similar between arms: 90.0% in the dostarlimab plus carboplatin-paclitaxel arm and 89.4% in the placebo plus carboplatin-paclitaxel arm for the overall population, 92.3% vs 89.2% in the dMMR/MSI-H population, and 89.4% vs 89.5% for MMRp/MSS population.

The most frequently reported treatment-related TEAEs considered by the investigator as related to carboplatin or paclitaxel only (>30%) in the dostarlimab plus carboplatin-paclitaxel and placebo plus carboplatin-paclitaxel arms were alopecia (44.8% and 41.9%, respectively) and neuropathy peripheral (38.2% and 36.6%, respectively) for the overall population.

Adverse events by severity, SAE and Adverse events leading to death

A higher proportion of participants experienced Grade ≥3 TEAEs and SAEs in the dostarlimab plus carboplatin-paclitaxel arm compared with the placebo plus carboplatin-paclitaxel arm (72.2% versus 60.2%, respectively and 39.8% versus 28.0%, respectively) for the overall population. Between the two populations according to MMR status, the incidence of participants experiencing Grade ≥3 TEAEs are similar, 75.0% vs 66.2% for the dMMR/MSI-H population, and 71.4% vs 58.0% for the MMRp/MSS population. However, these incidences between populations are slightly different for the SAEs. A higher proportion of MMRp/MSS participants experienced SAEs (41.8%) compared with dMMR/MSI-H population (32.7%) in the dostarlimab plus carboplatin-paclitaxel arm. The incidences of SAEs in the dMMR/MSI-H population are similar between arms, 32.7% in the dostarlimab plus carboplatin-paclitaxel arm and 32.3% in the placebo plus carboplatin-paclitaxel arm.

Regarding the Grade ≥3 TEAEs, the most frequently reported in both treatment arms were anaemia (14.9% vs 16.7%), neutropenia (9.5% vs 9.3%) and neutrophil count decreased (8.3% vs 13.8%) in the overall population. In the dMMR/MSI population, were neutropenia (17.3% vs 12.3%), anaemia (15.4% vs 21.5%), neutrophil count decreased (7.7% vs 18.5%), lymphocyte count decreased (5.8% vs 9.2%), white blood cell decreased (3.8% versus 12.3%), and hypertension (9.6% vs 6.2%). While in the MMRp/MSS population, were anaemia (14.8% and 14.9%, respectively), neutrophil count decreased (8.5% and 12.2%, respectively) and neutropenia (7.4% vs 8.3%). It is noted that the incidence of neutropenia was higher in the dMMR/MSI population (17.3% vs 12.3%) than in the MMRp/MSS population (7.4% vs 8.3%) in the dostarlimab plus carboplatin-paclitaxel arm.

In the overall population, 39.8% of the participants in the dostarlimab plus carboplatin-paclitaxel arm and 28.0% in the placebo plus carboplatin-paclitaxel arm presented **SAEs**. The most frequently reported SAEs (≥2%) in the dostarlimab plus carboplatin-paclitaxel arm were sepsis and pulmonary embolism (3.3% each), pyrexia (2.9%), dyspnoea, vomiting and muscular weakness (2.1% each); while those in the placebo plus carboplatin-paclitaxel arm were asthenia and anaemia (2.4% each), urinary tract infection and pulmonary embolism (2.0% each). Treatment-related SAEs were experienced by 15.8% of participants (19.5% vs 12.2%). The most frequently reported **treatment-related SAEs** (>1%) in the dostarlimab plus carboplatin-paclitaxel arm were febrile neutropenia and pyrexia (1.7%), and sepsis, pulmonary embolism and muscular weakness (1.2% each); while in the placebo plus carboplatin-paclitaxel arm were anaemia (2.0%), febrile neutropenia and asthenia (1.6% each).

There were no new **TEAEs leading to death** at IA2.In the dostarlimab plus carboplatin-paclitaxel arm, TEAEs leading to death were reported in 5 patients overall (2.1%), 2 (3.8%) patients in the dMMR/MSI population (myelosuppression was considered related to dostarlimab, carboplatin, and paclitaxel, and hypovolemic shock was considered related to dostarlimab), and 3 patients (1.6%) in the MMRp/MSS

population (COVID-19, general physical health deterioration, and opiate overdose; which were considered not related to dostarlimab, carboplatin, or paclitaxel). No additional deaths due to TEAEs were reported compared with IA1.

Infusion-related Reactions (IRRs)

IRRs were reported with similar incidences in both treatment arms, 5 participants (2.1%) in the dostarlimab plus carboplatin-paclitaxel arm and 2 participants (0.8%) in the placebo plus carboplatin-paclitaxel arm; suggesting that they may be related to chemotherapy infusion rather than dostarlimab, as expected. All IRRs were reported in the MMRp/MSS population. No IRRs led to death in any arm.

Immune-related AEs (irAEs)

The incidence of irAEs was higher in the dostarlimab plus carboplatin-paclitaxel arm (58.5 %) compared to the placebo plus carboplatin-paclitaxel (37.0%), which considering dostarlimab mechanism of action was expected. A total of 40.7% of participants in the dostarlimab plus carboplatin-paclitaxel arm, and 16.3% of participants in the placebo plus carboplatin-paclitaxel arm had irAEs assessed by the investigator as related to dostarlimab or placebo. The most frequently observed dostarlimab-related irAEs (>2% of participants) were hypothyroidism (12.0%), rash (7.1%), arthralgia (6.6%), and ALT increased (6.2%); all with a higher incidence in the dostarlimab plus carboplatin-paclitaxel arm except for arthralgia with a similar incidence in the placebo arm (6.5%).

Grade ≥3 irAEs were observed in 17.4% of participants in the dostarlimab plus carboplatin-paclitaxel arm and in 6.1% of participants in the placebo plus carboplatin paclitaxel arm, while dostarlimab/placebo-related Grade ≥3 irAEs were observed in 13.3% of participants in the dostarlimab plus carboplatin-paclitaxel arm and in 3.3% of participants in the placebo plus carboplatin-paclitaxel arm. The most frequently observed dostarlimab-related irAEs which were Grade ≥3, SAEs, or AEs leading to discontinuation in the dostarlimab plus carboplatin-paclitaxel arm were reported in 1 or 2 participants each with the exception of irAEs Grade ≥3 of rash (4.6%), rash maculo-papular (2.5%), ALT increased and AST increased (2.1% each) and arthralgia (1.2%), and irAEs leading to discontinuation of rash maculo-papular and IRRs (1.2% each).

No irAEs leading to death were reported.

Adverse drug reactions (ADRs)

The majority of the identified ADRs for IA2 had been previously included in the PI based on data from patients treated in 2L in participants with advanced or recurrent solid tumours and were consistent with those identified from RUBY Part 1 IA1: rash (23.2%), rash maculo-papular (14.5%), hypothyroidism (14.5%), ALT increased (12.9%), AST increased (12.0%), pyrexia (12.9%), and dry skin (10.0%), with frequencies comparable (<1% differences) to those reported based on IA1.

Additional potential immune-related AEs were not identified as ADRs following medical review based on IA1 and IA2 as they were not considered to be causally associated with dostarlimab (infusion-related hypersensitivity reaction; Raynaud's phenomenon; iritis), laboratory data for diagnosis was not provided (immune mediated adrenal insufficiency; immune-mediated hypophysitis), or was confounded by long-term ibuprofen use (colitis microscopic). Additionally, polymyalgia rheumatica was reported in a single participant at IA2 but was not considered to be causally associated with dostarlimab as diagnostic laboratory data was not provided.

Laboratory assessments

Regarding laboratory assessments, Grade 3 or 4 laboratory abnormalities with incidence >10% reported were neutrophil count decreased (13.7%) and white blood cell count decreased (10.7%) in the

dostarlimab plus carboplatin-paclitaxel treatment arm, and in the placebo plus carboplatin-paclitaxel arm for neutrophil count decreased (17.5%).

The incidence of potential liver toxicity events were significantly higher in the dostarlimab plus carboplatin-paclitaxel treatment arm for the dMMR/MSI-H EC population, with 19.2% ALT or AST ≥3× ULN compared to the MMRp/MSS EC population (8.5%). However, no participants in the dostarlimab plus carboplatin-paclitaxel arm reported ALT or AST ≥20×ULN.

Special populations

Safety assessment in special populations had not changed with those identified from IA1, with the exception of the updated incidences of Grade ≥3 TEAEs between Black/African American and White participants.

Dose modifications and discontinuations due to adverse events

For TEAEs leading to treatment discontinuation, again, higher incidences were observed in participants in the dostarlimab plus carboplatin-paclitaxel arm (24.9%) than in the placebo plus carboplatin-paclitaxel arm (16.3%) in the overall population, being the most frequently reported AEs neuropathy peripheral (2.1% versus 2.8%), IRRs (2.1% versus 3.3%), and peripheral sensory neuropathy (2.9% versus 0.4%) in the dostarlimab plus carboplatin paclitaxel arm and placebo plus carboplatin-paclitaxel arm, respectively. In addition, in the MMRp/MSS population the incidence of TEAEs leading to treatment discontinuation was even higher in the dostarlimab arm (26.5% vs 16.0%) compared to those in the dMMR/MSI-H population (19.2% vs 16.9%).

Regarding dose interruptions, AEs leading to dose interruptions of any study treatment were similar (≤5% difference) between the dostarlimab plus carboplatin paclitaxel arm and placebo plus carboplatin-paclitaxel arm (20.7% vs 19.9%, respectively) and were mostly due to infusion interruptions of carboplatin and/or paclitaxel, being IRR the most frequent in both treatment arms (10.8% in the dostarlimab plus carboplatin-paclitaxel arm and 11.8% in the placebo plus carboplatin-paclitaxel arm). In MMRp/MSS population the incidences of TEAEs leading to treatment interruption were lower (17.5% vs 19.3) than in the dMMR/MSI-H population (32.7% vs 21.5%).

With respect to the dose delays, differences between IA2 and IA1 in the dostarlimab plus carboplatin-paclitaxel arm were 2.1% for TEAEs leading to infusion delays and for dostarlimab-related TEAEs leading to infusion delays. Differences were based on additional TEAEs occurring in single participants with the exception of pyrexia, reported in 2 additional participants at IA2 as compared to IA1.

2.5.2. Conclusions on clinical safety

The safety profile of dostarlimab, in combination with carboplatin-paclitaxel, in the target indication has been assessed based on the results from a second interim analysis (IA2) from Part 1 of the RUBY study, which provides comparative safety data with a follow-up of 47.2 months. Overall, the safety profile at IA2 (DCO: 22 September 2023) was generally consistent with that observed for IA1 (DCO: 28 September 2022). No new safety concerns nor any new ADRs for dostarlimab in combination treatment have been identified, confirming the toxicity profile that was observed for the initial authorisation and with respect to risks found in the IA1 (28 September 2022).

Of note, some differences have been observed in the MMRp/MSS EC population (N=370) with respect to the dMMR/MSI-H population (N=117) in terms of SAEs, TEAEs, AEs leading to discontinuation, and AEs leading to dose modifications. However, considering that there were differences between the two EC populations in terms of number of participants and the median number of dosing cycles in the dostarlimab plus carboplatin-paclitaxel arm (15.5 cycles in dMMR/MSI-H population and 9.0 cycles in the

MMRp/MSS population), firm conclusions on differences in the safety profile between the two populations cannot be reached.

Once again, considering the dostarlimab mechanism of action, fast identification and management of irAEs continues to be crucial in this setting.

2.5.3. PSUR cycle

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal

2.6. Risk management plan

The MAH submitted an updated RMP version (version 4.2) with this application.

There are no changes to the summary of safety concerns:

Table 80: **SVIII.1: Summary of the Safety Concerns**

Summary of safety concerns	
Important identified risks	▪ Immune-related adverse reactions (including pneumonitis, colitis, hepatitis, endocrinopathies, immune-related skin adverse reactions, nephritis and other IrARs)
Important potential risks	None
Missing information	▪ Long-term safety

Table 81: **Part IV.1: Planned and ongoing post-authorisation efficacy studies that are conditions of the marketing authorisation or that are specific obligations**

Study (type and study number)	**Objectives**	**Efficacy concerns addressed**	**Status** (Planned, started, completed, results submitted)	**Date for submission of interim or final reports** (planned or actual)
Efficacy studies which are conditions of the marketing authorisation				
None				

~~RUBY Part 1 (Study 213361)~~ ~~Phase 3 Randomized, Double-Blind Study of Dostarlimab plus Carboplatin - paclitaxel vs Carboplatin - paclitaxel in patients with Recurrent or Primary Advanced Endometrial Cancer~~ ~~Ongoing~~	~~To compare the overall survival of subjects treated with dostarlimab plus carboplatin-paclitaxel followed by dostarlimab to subjects treated with placebo plus carboplatin- paclitaxel followed by placebo in subjects with dMMR/MSI-H recurrent or primary advanced endometrial cancer and who are candidates for systemic therapy.~~	~~Clinical benefit as determined by overall survival~~	~~Final Ruby Study Report Submission~~	~~30 June 2029~~
Efficacy studies which are Specific Obligations in the context of a conditional marketing authorisation or a marketing authorisation under exceptional circumstances				
None				

There were no changes to the risk minimisation measures. Routine risk minimisation measures are sufficient to minimise the risks of the product in the proposed indication.

The CHMP received the following PRAC Advice on the submitted Risk Management Plan:

The PRAC considered that the risk management plan version 4.2 is acceptable.

The CHMP endorsed this advice without changes.

2.7. Update of the Product information

As a consequence of this new indication, sections 4.1, 4.2, 4.4, 4.8 and 5.1 of the SmPC have been updated. Annex II.D and the Package Leaflet has been updated accordingly.

2.7.1. User consultation

A justification for not performing a full user consultation with target patient groups on the package leaflet has been submitted by the MAH and has been found acceptable for the following reasons:

The proposed changes in the package leaflet do not have a relevant impact that would require the need for user consultation.

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

JEMPERLI is indicated in combination with carboplatin and paclitaxel for the first-line treatment of adult patients with ~~mismatch repair deficient (dMMR)/ microsatellite instability high (MSI-H)~~ primary advanced or recurrent endometrial cancer (EC) and who are candidates for systemic therapy.

3.1.2. Available therapies and unmet medical need

According to ESMO guidelines, carboplatin-paclitaxel is considered as standard of care for recurrent/metastatic EC not amenable to surgery and/or RT regardless of MMR/MSI status. Although cisplatin-paclitaxel in combination with doxorubicin has a similar efficacy to carboplatin-paclitaxel, it is not commonly used due to the higher toxicity observed with this regimen. Based on the results of the landmark GOG 209 study, carboplatin-paclitaxel is the preferred regimen for systemic therapy in the first-line setting for patients with primary advanced or recurrent EC. Hormone therapy may be an option for patients with advanced or recurrent EC and endometrioid histology and has demonstrated a favourable toxicity profile. Patients with Grade 1 to 2 endometrioid tumours and those with hormone receptor-positive disease are most likely to experience clinical benefit from hormone therapy.

Based on the results from the RUBY Part 1 (IA1) study, dostarlimab in combination with carboplatin and paclitaxel was authorized in the EU for the treatment of adult patients with dMMR/MSI-H primary advanced or recurrent EC who are candidates for systemic therapy (EMEA/H/C/005204/II/0023, Date of EC Decision 07/12/2023). In June 2024 the CHMP adopted a positive opinion recommending durvalumab in combination with carboplatin and paclitaxel for the first-line treatment of adults with primary advanced or recurrent EC who are candidates for systemic therapy, followed by maintenance treatment with durvalumab as monotherapy in EC that is dMMR or by durvalumab in combination with olaparib in EC that is pMMR (EMEA/H/C/004771/WS2463/0063, EMEA/H/C/003726/WS2463/0066, 26/07/2024). In September 2024 the CHMP adopted a positive opinion recommending pembrolizumab in combination with carboplatin and paclitaxel for the first-line treatment of primary advanced or recurrent endometrial carcinoma in adults who are candidates for systemic therapy (EMEA/H/C/003820/II/0153, 19/09/2024).

3.1.3. Main clinical studies

The current application is based on the results from the second interim analysis (IA2) of the Part 1 of Study RUBY. The study RUBY is a phase 3, randomized, double-blind, multicenter study comparing dostarlimab plus carboplatin-paclitaxel versus placebo plus carboplatin-paclitaxel in patients with primary advanced or recurrent endometrial cancer and who are candidates for systemic therapy. Part 1 of the study is to evaluate the efficacy and safety of treatment with dostarlimab (500 mg IV every 3 weeks – 6 cycles) plus carboplatin-paclitaxel, followed by dostarlimab (1000 mg IV every 6 weeks; up to 3 years) versus treatment with placebo plus carboplatin-paclitaxel followed by placebo in participants with primary advanced (Stage III or IV) or recurrent EC. The dual primary endpoints were PFS by investigator (in both the overall population and the dMMR/MSI-H population) and OS (in the overall population).

3.2. Favourable effects

The combination of dostarlimab plus carboplatin-paclitaxel showed a statistically significant improvement in PFS by investigator compared with placebo plus chemotherapy in the first prespecified interim analysis

[HR: 0.64 (95% CI: 0.507, 0.800; p<0.0001); median PFS 11.8 months vs. 7.9 months]. Several sensitivity analyses for PFS have also confirmed the reported main results.

OS, which was the other dual-primary endpoint, was met in the second prespecified interim analysis [HR: 0.69 (95% CI: 0.539, 0.8900; p=0.0020); median OS 44.6 months vs. 28.2 months].

Secondary endpoints (PFS by BICR, PFS2, ORR by investigator and PROs) also favoured the combination of dostarlimab plus carboplatin-paclitaxel with pretty consistent and robust results.

3.3. Uncertainties and limitations about favourable effects

The number of patients who completed the treatment duration proposed in the PI (3 years) is still limited (n=48). Uncertainties remain regarding the long-term effects of dostarlimab.

Uncertainties remain regarding long-term OS outcomes. Final OS results will be submitted post authorisation (REC).

3.4. Unfavourable effects

The safety assessment is based on a safety analysis set of 487 patients (370 patients for the MMRp/MSS EC population, and 117 patients for the dMMR/MSI-H EC population) included in Part 1 of the RUBY study, of whom 241 received treatment with dostarlimab in combination with carboplatin and paclitaxel.

Grade ≥3 TEAEs were reported by 72.2% and 60.2% of patients in the dostarlimab + carbo/pac arm and carbo/pac treatment arm, respectively. The most frequently reported Grade ≥3 TEAEs were anaemia (14.9% dostarlimab + carbo/pac vs 16.7% carbo/pac), neutropenia (9.5% vs 9.3%) and neutrophil count decreased (8.3% vs 13.8%).

SAEs have been observed in 39.8% of participants in the dostarlimab + carbo/pac arm and 28.0% in the carbo/pac treatment arm.

TEAEs leading to treatment discontinuation were reported by 24.9% of patients in the dostarlimab + carbo/pac arm and 16.3% in the carbo/pac arm.

Five cases of TEAEs leading to death were reported in the study, all of them in the dostarlimab + chemo arm.

Immune-related AEs (irAEs) were observed in the 58.5% of participants from the dostarlimab + carbo/pac arm and 37.0% in the carbo/pac treatment arm. The most frequently reported dostarlimab-related irAEs (>2% of participants) were hypothyroidism (12.0%), rash (7.1%), arthralgia (6.6%), and ALT increased (6.2%).

3.5. Uncertainties and limitations about unfavourable effects

Overall the safety profile of dostarlimab in combination with carboplatin and paclitaxel is well characterised.

3.6. Effects Table

Table 82: **Effects Table for dostarlimab, in combination with carboplatin and paclitaxel for the treatment of adult patients with primary advanced or recurrent EC (DCO: 28-Sep-2022 and 22-Sep-2023)**

Effect	Short description	Unit	Treatment	Control	Uncertainties / Strength of evidence	References
Favourable Effects						
PFS (investigator)	Progression-free-survival: Time from the date of randomization to the earliest date of radiographic assessment of PD or death by any cause in the absence of PD, whichever occurs first.	Median, months (95% CI)	11.8 (9.6, 17.1)	7.9 (7.6, 9.5)	HR: 0.64 (0.507, 0.800); p<0.0001	CSR (DCO: 28-SEP-2022)
OS	Overall survival: Time from randomization to the date of death by any cause.	Median, months (95% CI)	44.6 (32.6, NR)	28.2 (22.1, 35.6)	HR: 0.69 (0.539, 0.890); p=0.0020	CSR (DCO: 22-SEP-2023)
Unfavourable Effects						
Grade ≥3 TEAEs	Treatment emergent adverse events of CTCAE grade ⩾3	N (%)	174 (72.2)	148 (60.2)		CSR (DCO: 22-SEP-2023)
Grade ≥3 treatment-related TEAEs	Treatment emergent adverse events of CTCAE grade ≥3 causality related to treatment	N (%)	128 (53.1)	115 (46.7)		
Serious TEAEs	Treatment emergent serious AEs regardless causality	N (%)	96 (39.8)	69 (28.0)		
TEAEs leading to treatment discontinuation	Any treatment emergent adverse event leading to treatment discontinuation	N (%)	60 (24.9)	40 (16.3)		
TEAEs with the outcome of death	Any treatment emergent adverse event with the outcome of death	N (%)	5 (2.1)	0		

Abbreviations: Abbreviations: CI: confidence interval; CSR: clinical study report; NR: not reached.

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

The combination of dostarlimab with carboplatin-paclitaxel demonstrated a statistically significant and clinically relevant improvement in PFS by investigator and OS in the overall population. Results of PFS by BICR were consistent with the results of the main analysis. Secondary endpoints and sensitivity analyses were also in line and supported these results.

The effect observed in the overall population for both PFS and OS appears to be (mostly) driven by the subset of dMMR/MSI-h patients, in which the combination is currently approved, although the MMRp/MSS patients also obtain benefit from the treatment with dostarlimab, albeit this benefit is more modest than the benefit in the dMMR/MSI-h patients.

With regards to safety, overall, the results from RUBY Part 1 confirm the already known safety profile of dostarlimab. No new safety signals have been identified. However, the addition of chemotherapy increases toxicity and carries a different type of adverse events that may complicate early identification and management of immune-related AEs. Immune-related ARs were identified as a safety concern at the time of initial MA (and are reflected as an important identified risk in the RMP) and relevant risk minimisation activities are in place (information reflected in sections 4.2, 4.4 and 4.8 of the SmPC).

3.7.2. Balance of benefits and risks

Dostarlimab in combination with carboplatin-paclitaxel has demonstrated a statistically significant and clinically relevant improvement in PFS by investigator and OS in patients with primary advanced or recurrent endometrial cancer and who are candidates for systemic therapy. This improvement has been supported by secondary endpoints. The safety profile appears in line with what is known for dostarlimab, and chemotherapy.

3.8. Conclusions

The overall B/R of Jemperli in combination with carboplatin and paclitaxel for the first-line treatment of adult patients with primary advanced or recurrent EC and who are candidates for systemic therapy positive is positive.

4. Recommendations

Outcome

Based on the review of the submitted data, the CHMP considers the following variation acceptable and therefore recommends by consensus the variation to the terms of the Marketing Authorisation, concerning the following change:

Variation accepted		**Type**	**Annexes affected**
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I, II and IIIB

Extension of indication for JEMPERLI to include, in combination with carboplatin and paclitaxel, the first-line treatment of adult patients with primary advanced or recurrent endometrial cancer (EC) and who are candidates for systemic therapy based on Interim Analysis 1 and 2 from study RUBY Part 1 (213361).

This is a phase 3, randomized, double-blind, controlled study evaluating the efficacy and safety of dostarlimab plus carboplatin and paclitaxel in primary advanced or recurrent EC versus placebo plus carboplatin and paclitaxel. As a consequence, sections 4.1, 4.2, 4.4, 4.8, and 5.1 of the SmPC are updated. The Annex II.D and Package Leaflet are updated in accordance. Version 4.2 of the RMP has also been submitted. In addition, the Marketing authorisation holder (MAH) took the opportunity to implement editorial changes to the SmPC and to align the PI with the latest QRD template version 10.4.

The variation leads to amendments to the Summary of Product Characteristics, Annex II and Package Leaflet and to the Risk Management Plan (RMP).

Amendments to the marketing authorisation

In view of the data submitted with the variation, amendments to Annexes I, II and III.B and to the Risk Management Plan are recommended.