12 October 2023
EMA/483641/2023
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

JEMPERLI

International non-proprietary name: dostarlimab

Procedure No. EMEA/H/C/005204/II/0023

Note

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

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Table of contents

List of abbreviations

1L	First-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
CBC	Complete blood count
CI	Confidence interval
CL	Clearance
C_{max}	Maximum observed concentration
$C_{max,ss}$	Maximum observed concentration at steady state
C_{min}	minimum observed concentration
$C_{min,ss}$	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
IND	Investigational New Drug
irAE	Immune-related adverse event
ITT	Intention-to-treat
KM	Kaplan-Meier
mAb	Monoclonal antibody
MMR	Mismatch repair
MMRp	Mismatch repair-proficient
MSI	Microsatellite instability
MSI-H	Microsatellite instability-high
MSS	Microsatellite stable
NAb	Neutralizing antibody
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
PK	Pharmacokinetic(s)
PMR	Post-marketing requirement
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 Tumours version 1.1
RTD	Recommended therapeutic dose
SAE	Serious adverse event
SmPC	Summary of Product Characteristics
TEAE	Treatment-emergent adverse event
TIL	Tumour-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 28 March 2023 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, II and IIIB

Extension of indication to include in combination with platinum-containing chemotherapy 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, based on results from study 213361 (RUBY) Part 1, listed as a Specific Obligation in the Annex II; this is 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. As a consequence, sections 4.1, 4.2, 4.8, 5.1 and 5.2 of the SmPC are updated. The Annex II and Package Leaflet are updated in accordance. Version 3.0 of the RMP has also been submitted. In addition, the marketing authorisation holder (MAH) took the opportunity to introduce minor editorial changes to the PI. As part of the application, the MAH is requesting a 1-year extension of the market protection.

The variation requested amendments to the Summary of Product Characteristics, Annex II 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.

MAH request for additional market protection

The MAH requested consideration of its application in accordance with Article 14(11) of Regulation (EC) 726/2004 - one year of market protection for a new 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 to clinical aspects of the dossier.

1.2. Steps taken for the assessment of the product

The Rapporteur appointed by the CHMP was:

Rapporteur: Carolina Prieto Fernandez

Timetable	Actual dates
Submission date	28 March 2023
Start of procedure:	22 April 2023
CHMP Rapporteur Assessment Report	5 July 2023
PRAC Rapporteur Assessment Report	27 June 2023
Updated PRAC Rapporteur Assessment Report	29 June 2023
PRAC Outcome	6 July 2023
CHMP members comments	10 July 2023
Updated CHMP Rapporteur(s) (Joint) Assessment Report	15 July 2023
Request for supplementary information (RSI)	20 July 2023
CHMP Rapporteur Assessment Report	20 September 2023
PRAC Rapporteur Assessment Report	18 September 2023
PRAC members comments	20 September 2023
Updated PRAC Rapporteur Assessment Report	21 September 2023
PRAC Outcome	28 September 2023
CHMP members comments	2 October 2023
Updated CHMP Rapporteur Assessment Report	5 October 2023
Opinion	12 October 2023

2. Scientific discussion

2.1. Introduction

2.1.1. Problem statement

Disease or condition

The marketing authorisation holder (MAH) proposes to add the following new indication:

JEMPERLI is indicated in combination with platinum-containing chemotherapy 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 4.5% of all new cancer cases in women diagnosed in 2020, being the second most common gynecological cancer after cervical cancer and the sixth most common type of malignancy diagnosed in women worldwide[1]. In Europe, there were a total of 130,051 new cases of EC and 29,963 deaths due to EC in 2020.

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 favorable prognosis, and type II tumours, that account for 10-20% of EC and include grade 3 endometrioid tumours as well as tumours of nonendometrioid 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

[1] Sung H, Ferlay J, Siegel RL et al. Global Cancer Statistics 2020: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries. CA Cancer J Clin. 2021 May;71(3):209-249. doi: 10.3322/caac.21660. Epub 2021 Feb 4. PMID: 33538338.
[2] Kandoth C, Schultz N, Cherniack AD, et al. Integrated genomic characterization of endometrial carcinoma. Nature. 2013;497(7447):67-73.

women with primary advanced (Stage III or IV) or recurrent EC remain poor with 5-year OS rates of 20% to 25%.[3]

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.[5] 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.[6]

At the present time, standard of care for all patients with primary advanced or recurrent EC is the same, and patients who are candidates for systemic therapy are recommended to receive carboplatin-paclitaxel regardless of MMR/MSI status. Immune checkpoint inhibitor (ICIs) have been investigated as potential options in EC. Thus far, dostarlimab and pembrolizumab have been approved in the EU as monotherapy in second-line 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 RT.[7]

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 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.

[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.
[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 DS, Filiaci VL, Mannel RS, et al. Carboplatin and Paclitaxel for Advanced Endometrial Cancer: Final Overall Survival and Adverse Event Analysis of a Phase III Trial (NRG Oncology/GOG0209). J Clin Oncol. 2020;38(33):3841-3850.
[6] Colombo, N et al. ESMO-ESGO-ESTRO Consensus Conference on Endometrial Cancer: Diagnosis, Treatment and Follow-up. Int J Gynecol Cancer. 2016;26(1), 2-30.
[7] Galon J, Bruni D. Approaches to treat immune hot, altered and cold tumours with combination immunotherapies. Nat Rev Drug Discov. 2019 Mar;18(3):197-218. doi: 10.1038/s41573-018-0007-y. PMID: 30610226.

The approved treatment regimen (also referred to as RTD) is dostarlimab at 500 mg Q3W for the first 4 cycles, followed by dostarlimab at 1000 mg Q6W for all subsequent cycles.

In the context of the present application, the final agreed indication is:

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.

The recommended dose is 500 mg dostarlimab every 3 weeks in combination with carboplatin and paclitaxel every 3 weeks for 6 cycles followed by 1000 mg dostarlimab as monotherapy every 6 weeks for all cycles thereafter.

The dosage regimen in combination with carboplatin and paclitaxel is presented below:

	500 mg once every 3 weeks in combination with carboplatin and paclitaxel[a] (1 Cycle = 3 weeks)							**1000 mg once every 6 weeks as monotherapy until disease progression or unacceptable toxicity (1 Cycle = 6 weeks)**			
Cycle	Cycle 1	Cycle 2	Cycle 3	Cycle 4	Cycle 5	Cycle 6		Cycle 7	Cycle 8	Cycle 9	Continue dosing Q6W
Week	1	4	7	10	13	16		19	25	31	

3 weeks between Cycle 6 and Cycle 7

[a] dostarlimab should be administered prior to carboplatin and paclitaxel on the same day.

Administration of dostarlimab should continue according to the recommended schedule until disease progression or unacceptable toxicity, or for a duration of up to 3 years (see section 5.1 of the SmPC).

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

The initial approval was based on interim data from the Study 213346 (GARNET), a Phase 1 dose escalation and cohort expansion study of dostarlimab in patients with advanced solid tumours.

The CMA contained two Specific Obligations (SOBs) for the conversion to full approval.

Number	Description	Status
SOB-clin-001	In order to confirm the efficacy and safety of dostarlimab in 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, the MAH should submit updated results of the GARNET study, Cohort A1, including at least 131 patients with measurable disease followed for at least 12 months from the onset of response.	Variation II/13: positive opinion issued on December 2022.
SOB-clin-002	In order to confirm the efficacy and safety of dostarlimab in adult patients with mismatch repair deficient (dMMR)/microsatellite instability-	Due Date: 31 August 2023-

	high (MSI-H) recurrent or advanced endometrial cancer (EC) that has progressed on or following prior treatment with a platinum-containing regimen, the MAH should submit the results of the phase III, randomised, double-blind study RUBY, comparing the efficacy and safety of dostarlimab in combination with chemotherapy to chemotherapy alone in patients with recurrent or advanced endometrial cancer who have not received prior systemic anticancer therapy for recurrent or advanced disease.	ongoing procedure: Jemperli II/23.

The current application concerns a Type II variation to enable the fulfilment of the remaining SOB of the Jemperli CMA (SOB-clin-002).

Dostarlimab is being investigated as a single agent or as combination therapy in 15 ongoing global clinical studies in various tumour types including EC, ovarian cancer, non-small cell lung cancer (NSCLC), and other solid tumours.

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 conversion to full marketing authorization of the planned initial CMA application.

2.1.4. General comments on compliance with GCP

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 was considered acceptable by the CHMP.

2.2.1. 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).

2.2.2. Conclusion on the non-clinical aspects

The active substances, 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)

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: Tabular Listing of All Clinical Studies

Study Identifier (Identifier of Study Report	Study Objective(s)	Study Design	Healthy Subjects or Diagnosis of Patients	Treatment Details (Test Product(s); Dosage Regimen; Route; Duration)	Total No. of Subjects by Group Entered/ Completed	Study Reporting Status (Type of Report)
Efficacy and Safety Studies: Controlled Clinical Studies Pertinent to the Claimed Indication						
213361, RUBY (formerly known as 4010-03-001)	**Part 1**: Efficacy and safety of dostarlimab plus carboplatin-paclitaxel followed by dostarlimab versus placebo plus carboplatin-paclitaxel followed by placebo in participants with recurrent or primary advanced (Stage III or IV) endometrial cancer.	Global, multicenter, randomized, double-blind, controlled study	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) Paclitaxel: 175 mg/m² IV Q3W (Cycles 1 to 6 only)	Planned enrollment: Up to 470 across cohorts Actual: Part 1: 494	Ongoing Part 1 CSR (28 Sep 2022 cut-off)

CSR = Clinical Study Report IV = intravenous QxW = every x weeks

NOTE: Part 2 of RUBY will be submitted separately.

2.3.1. Analytical Methods

The bioanalytical and validation reports submitted for dostarlimab are summarised in Table 2:

Table 2: Bioanalytical and validation reports for determination of dostarlimab, anti-dostarlimab antibodies, and neutralising anti-dcorstalimab antibodies in human serum.

Study number	Study title	Analytical laboratory	Bioanalytical report number	Analyte	Validation report number
213346, GARNET (formerly 4010-01-001)	A Phase 1 dose escalation and cohort expansion study of TSR-042, an anti-PD-1 monoclonal antibody, in patients with advanced solid tumors	Charles River Laboratories, Inc.	KB-0068-RI-AS-RPT-02	Dostarlimab	KB-0067-RI-AV-RPT-01
					KB-0239-RI-AV-RPT-01
			KB-0084-RI-AS-RPT-02	Antidrug antibodies	KB-0083-RI-AV-RPT-02
					KB-0240-RI-AV-RPT-04
		Frontage Labs	TES-R7740A1	Neutralizing antibodies	TES-R6445
213361, RUBY (formerly 4010-03-001)	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)	Charles River Laboratories, Inc.	KB-0253-RI-AS-RPT-01	Dostarlimab	KB-0067-RI-AV-RPT-01
					KB-0239-RI-AV-RPT-01
			KB-0253-RI-AS-RPT-02	Antidrug antibodies	KB-0083-RI-AV-RPT-02
					KB-0240-RI-AV-RPT-04
		Frontage Labs	964-R11538	Neutralizing antibodies	TES-R6445

PD-1=Programmed cell death protein 1

The validation reports submitted for RUBY study were already submitted for GARNET study. These bioanalytical validation reports were found acceptable in previous procedures (see Jemperli EPAR).

The bioanalytical reports that were newly submitted for this extension of indication (based on RUBY study) were:

- Report KB-0253-RI-AS-RPT-01: Determination of dostarlimab in human serum
- Report KB-0253-RI-AS-RPT-02: Analysis of Anti-dostarlimab antibodies in human serum
- Report 964-R11538: Detection of neutralizing Anti-dostarlimab antibodies in human serum

Report KB-0253-RI-AS-RPT-01: Determination of dostarlimab in human serum

The bioanalytical evaluation of dostarlimab (TSR-042) in human serum samples was carried out using a validated enzyme-linked immunosorbent assay (ELISA) method by Charles River Laboratories, Inc. (334 South Street Shrewsbury, MA 01545 United States) from 06 April 2021 to 13 October 2022.

A total of 9379 samples from RUBY study were received in 68 shipments between February 2021 and September 2022 including both PK and ADA samples. There were 4702 PK samples of which 2326 were to be analysed. 2376 Placebo and duplicate samples were not analysed. Two samples collected in error were discarded per sponsors' request on 20 Sep 2022. All Samples were received in good condition per study protocol specified. All samples were received frozen, packaged on dry ice, and were stored in a -80°C freezer upon receipt.

Calibration standards were prepared at 8 different concentrations: 32.0, 71.3, 107, 161, 241, 362, 651 and 814 ng/mL. Two accessory standards were included (21.3 and 1020 ng/mL). For every run, one calibration standard per concentration level was used.

Each run included 3 QCs (81.3, 254 and 611 ng/mL) per duplicate. The LQC, MQC and HQC were distributed throughout the calibration range (approximately 3 times the LLOQ, 30% and 75% of the calibration range, respectively).

180 study samples (incurred samples) were selected for reanalysis to evaluate the overall performance of the bioanalytical assay. 73.6 % of re-assayed samples met the acceptance criteria (±30% of the original

value).

Report KB-0253-RI-AS-RPT-02: Analysis of Anti-Dostarlimab Antibodies in Human Serum

The bioanalytical evaluation of anti-dostarlimab antibodies in human serum samples was carried out by Charles River Laboratories, Inc. using a validated qualitative indirect electrochemiluminescent (ELC) method. The bioanalytical phase started on 14 April 2021 and the completion date was 12 October 2022.

The ECL method was utilized to detect and confirm anti-dostarlimab antibodies in human serum and determine their titer. Samples mixed with biotinylated drug and sulfo-tagged drug were added to a streptavidin plate. After washing, the plate was stopped with read buffer, and the ECL response was read. Analysis was conducted in 3 stages: a positive initial screening analysis, followed by a confirmatory analysis, and then a titer analysis.

A total of 9379 samples from RUBY study were received in 68 shipments between February 2021 and September 2022. There were 4677 ADA samples and 4702 PK samples. Two samples (one PK and one ADA) were discarded per sponsor's request. All samples were received frozen in good condition, were packaged on dry ice, and were stored in a -80°C freezer upon receipt.

Of the 4677 ADA samples received, 1273 samples were reported and 3404 samples were not tested and reported for the following reasons: placebo samples (2349), duplicate samples (5), samples with timepoints not requiring analysis (1042), affected by ambient temperature (6), discarded per sponsors request (1), insufficient volume (1).

Positive control (PC) samples were prepared by spiking blank human serum with appropriate amounts of polyclonal antibody (Low PC of 3.45 ng/mL and 40.0 ng/mL, Medium PC of 500 ng/mL and High PC of 20,000 ng/mL). Negative Control (NC) samples were prepared using pooled human serum diluted to the MRD in assay buffer.

Five replicates of the NC sample (10 wells) were included in each microtiter plate. The mean ECL value of the NC replicate samples was used to calculate the plate specific cutpoint (PSCP). Two replicates of each PC sample were run, each in duplicate wells. For a run to be considered acceptable, the positive and negative controls must meet the pre-defined acceptance criteria.

Samples were analysed in duplicate in the screening assay and the ECL value was compared to the PSCP. Samples with values above the relevant cut point were reported as screen positive. Any sample with an ECL value greater than the PSCP in the screening assay were analysed in the confirmatory assay with TSR-042 to confirm the sample status as positive or negative for anti TSR-042 antibodies. Any sample confirmed positive with TSR-042 were analysed in the titer assay based on procedures and acceptance criteria detailed in the Laboratory Method (Appendix 2). The SCF [screening cut point factor (1.09)], TCF [titer cut point factor (1.26)], and CCP [confirmatory cut point (21.0%)] previously determined in study KB-0240-RI-AV were utilized for this study (Table 3).

Table 3: Cut points for the determination of anti-dostarlimab antibodies in human serum

Screening assay	Confirmatory assay	Titer assay

Cut point factor=1.09, based on a robust parametric 90% LCL estimate and representing a 5.0% false positive error rate	Cut point=21.0% inhibition, based on a robust parametric 80% LCL estimate and representing a 1.0% false positive rate	Cut point factor=1.26, based on a parametric estimate and representing a 0.1% false positive error rate

Report 964-R11538: Detection of Neutralizing Anti-Dostarlimab Antibodies in Human Serum

The neutralizing activity of anti-dostarlimab antibodies in human serum samples was evaluated by Frontage Laboratories, Inc. using a validated Electrochemiluminescent Immunoassay on the Meso Scale Discovery (MSD®) platform. The analysis conducted from 23 February 2022 to 01 November 2022.

A total of 4584 samples were received at Frontage Laboratories frozen on dry ice between 19 March 2021 and 13 September 2022. Frontage laboratories was informed by the Sponsor that a total of 39 samples, which were shown to be ADA-positive for dostarlimab by Charles River laboratories using its confirmatory assay, were up for further analysis to determine the presence of neutralizing antibodies.

The mean ECL values must have a %CV ≤ 20%. Samples with mean ECL values greater than or equal to the plate specific cut point were classified as positive while samples with mean ECL values less than the plate specific cut point were classified as negative. 39 samples had been analysed, and per sponsor's request, only 37 samples were reported. One sample was not reported due to the sample being received at central lab at ambient condition, another sample was not reported due to pending ADA titer results. Of the 37 samples screened, 19 samples resulted in positive results. The screening cut point factor of 1.18 had been determined during the validation.

2.3.2. Pharmacokinetics

The data provided in the current submission aims to support the dose recommendation for dostarlimab (500 mg Q3W for the first 6 cycles followed by 1000 mg Q6W for all subsequent cycles) in combination with carboplatin and paclitaxel in patients with dMMR/MSI-H primary advanced or recurrent EC and who are candidates for systemic therapy.

To date, clinical pharmacology data are available from the first clinical study with dostarlimab, GARNET Parts 1, 2A, and 2B, and the ongoing Phase 3 study, RUBY Part 1 (Table 4). Both studies are interventional trials. Dostarlimab PK has not been evaluated in healthy volunteers.

Table 4: 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/m² 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)

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

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.

Pharmacokinetics in the target population

Population PK modelling

A structural population PK model for dostarlimab based on data from the GARNET study as of the 01 March 2020 data cutoff date was described in the previous submission (see Jemperli EPAR).

Since then, PK data were collected from an additional 92 participants in this study (an approximately 18% increase in the number of participants with at least 1 PK sample) between 01 March 2020 and 01 November 2021. These additional data, as well as data available from the RUBY study as of 08 August 2022 (233 participants), are included in the updated population PK analysis described below.

Objectives

The overall aims were to characterize the PK and to explore the exposure-response relationships for dostarlimab.

This was achieved through the following objectives:

• To do an external validation of current structural PopPK model and refine if necessary. Identify the covariates of clinical interest;

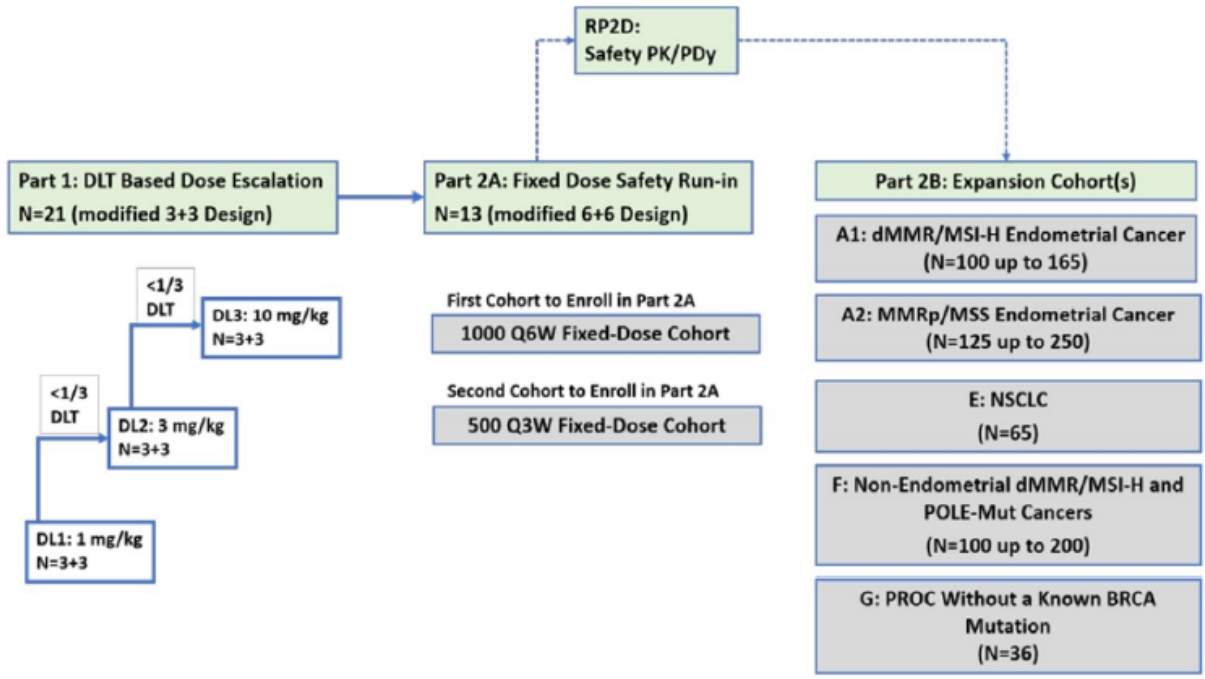
• To evaluate the exposure-response relationship between dostarlimab, PFS and DOR (as data permits);

• To evaluate the exposure-response relationship between dostarlimab and occurrence of relevant AEs.

Summary of PK Data Included in the Analysis

Study 4010-01-001 (GARNET)

Figure 1: Study Design, 4010-01-001



Note: DL=dose level; DLT=dose-limiting toxicity; dMMR=mismatch repair deficient; MSI-H=microsatellite instability high; MMRp=mismatch repair proficient; MSS=microsatellite stable; NSCLC=non-small cell lung cancer; N or n=number (of patients); POLE-mut=polymerase ϵ mutated; Q3W=every 3 week; Q6W=every 6 week; RP2D=recommended Phase 2 dose

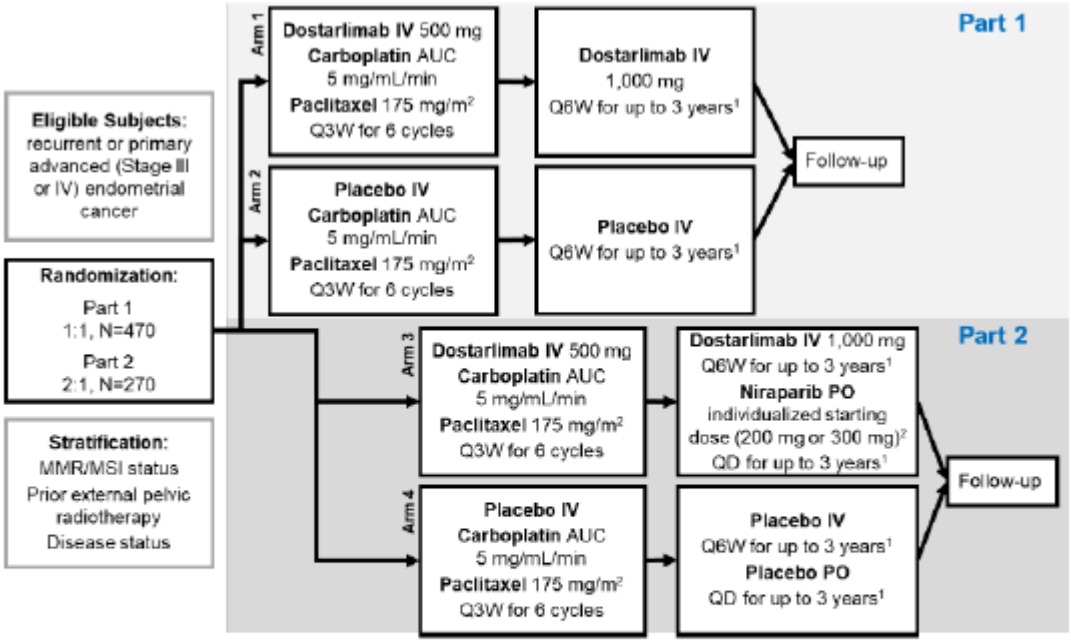
Table 5: Overview of Study Data Included in the Analyses, 4010-01-001

Study Part	Dose Level	N Patients Available (November 01 2021 Data Cut)
Part 1	1 mg/kg, 3 mg/kg and 10 mg/kg	N=21
Part 2A	500 mg Q3W or 1000 mg Q6W	N=13
Part 2B	500 mg Q3W 4 cycles followed by 1000 mg Q6W	N=602

Q3W: Once every third week; Q6W: Once every sixth week

Study 4010-03-001 (RUBY)

Figure 2: Study Design 4010-03-001



Abbreviations: AUC=area under the plasma or serum concentration-time curve; IV=intravenous; MMR=mismatch repair of DNA; MSI=microsatellite instability; PO=oral; Q3W=every 3 weeks; Q6W=every 6 weeks; QD=daily.

[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/placebo IV or niraparib/placebo PO beyond 3 years may be considered following discussion between the Sponsor and the Investigator.

[2] Niraparib starting dose: 300 mg in subjects with an actual body weight ≥77 kg and platelet count ≥150,000/μL; 200 mg in subjects with an actual body weight <77 kg or platelet count <150,000/μL or both.

Table 6: Overview of Study Data Included in the Analyses, 4010-03-001

Arm	Dostarlimab Dose Level	N Subjects available in this data cut
dostarlimab + carboplatin-paclitaxel	500 mg Q3W 6 cycles followed by 1000 mg Q6W	N≈235
placebo + carboplatin-paclitaxel	placebo	N≈235

Q3W: Once every third week; Q6W: Once every sixth week

Summary of Demographics and Analysis Data

Table 7: Summary of Demographics by Study

Treatment	4010-01-001	4010-03-001	All
	(N = 636)	(N = 233)	(N = 869)
Age (yr)			
Mean (SD)	62.3 (11)	63.8 (9.2)	62.7 (11)
Median (range)	64.0 (24.0 - 86.0)	64.0 (41.0 - 81.0)	64.0 (24.0 - 86.0)
Elderly patients			
75 years and older	74 (11.6%)	25 (10.7%)	99 (11.4%)
Younger than 75 years	562 (88.4%)	208 (89.3%)	770 (88.6%)
Sex			
Female	480 (75.5%)	233 (100.0%)	713 (82.0%)
Male	156 (24.5%)		156 (18.0%)
Race			
American Indian or Alaska native	4 (0.6%)	1 (0.4%)	5 (0.6%)
Asian	13 (2.0%)	7 (3.0%)	20 (2.3%)
Black or African American	21 (3.3%)	26 (11.2%)	47 (5.4%)
Native Hawaiian or other Pacific Islander		1 (0.4%)	1 (0.1%)
Not reported	121 (19.0%)	5 (2.1%)	126 (14.5%)
Other	6 (0.9%)		6 (0.7%)
Unknown	4 (0.6%)	12 (5.2%)	16 (1.8%)
White	467 (73.4%)	181 (77.7%)	648 (74.6%)
Ethnicity			
Hispanic or Latino	23 (3.6%)	7 (3.0%)	30 (3.5%)
Non-Hispanic or Latino	479 (75.3%)	213 (91.4%)	692 (79.6%)
Not reported	126 (19.8%)	5 (2.1%)	131 (15.1%)
Unknown	8 (1.3%)	8 (3.4%)	16 (1.8%)
Geographic Location			
Europe	388 (61.0%)	68 (29.2%)	456 (52.5%)
North America	248 (39.0%)	165 (70.8%)	413 (47.5%)
Weight (kg)			
Mean (SD)	73.7 (20)	84.1 (23)	76.5 (21)
Median (range)	71.0 (34.0 - 182)	80.9 (42.8 - 181)	73.0 (34.0 - 182)
Hepatic Impairment			
Mild	74 (11.6%)	18 (7.7%)	92 (10.6%)
Moderate	5 (0.8%)		5 (0.6%)
Normal	557 (87.6%)	215 (92.3%)	772 (88.8%)
Renal Impairment			
Mild	270 (42.5%)	127 (54.5%)	397 (45.7%)
Moderate	114 (17.9%)	50 (21.5%)	164 (18.9%)
Normal	250 (39.3%)	55 (23.6%)	305 (35.1%)
Severe	2 (0.3%)	1 (0.4%)	3 (0.3%)

n=1 patients with missing WT were imputed to sex median.

Table 8: Summary of Demographics by Study, Continued

Treatment	4010-01-001	4010-03-001	All
	(N = 636)	(N = 233)	(N = 869)
Immuno Modulators			
No	634 (99.7%)	231 (99.1%)	865 (99.5%)
Yes	2 (0.3%)	2 (0.9%)	4 (0.5%)
Immuno Stimulants			
No	631 (99.2%)	198 (85.0%)	829 (95.4%)
Yes	5 (0.8%)	35 (15.0%)	40 (4.6%)
Corticosteroids			
No	379 (59.6%)	214 (91.8%)	593 (68.2%)
Yes	257 (40.4%)	19 (8.2%)	276 (31.8%)
ADAs if ever positive			
ADA ever positive	101 (15.9%)		101 (11.6%)
ADA never positive	445 (70.0%)	230 (98.7%)	675 (77.7%)
Missing	90 (14.2%)	3 (1.3%)	93 (10.7%)
ECOG			
Ambulatory	373 (58.6%)	90 (38.6%)	463 (53.3%)
Fully active	262 (41.2%)	143 (61.4%)	405 (46.6%)
Missing	1 (0.2%)		1 (0.1%)
Diagnosis			
EC MSI-H/dMMR	153 (24.1%)	50 (21.5%)	203 (23.4%)
EC MSS/MMRp	160 (25.2%)	183 (78.5%)	343 (39.5%)
Missing	47 (7.4%)		47 (5.4%)
Non-EC MSI-H and POLE-mutated	209 (32.9%)		209 (24.1%)
NSCLC	67 (10.5%)		67 (7.7%)
Disease Status			
Primary Stage III		45 (19.3%)	45 (5.2%)
Primary Stage IV		72 (30.9%)	72 (8.3%)
Recurrent	636 (100.0%)	116 (49.8%)	752 (86.5%)

Patients had Eastern Cooperative Oncology Group Performance Status (ECOG) grade 0 or 1; these grades will be referred to as "fully active" and "ambulatory" in this report. See note about ADA definition in 3.8. **ADA:** anti-drug antibody; **ECOG:** Eastern cooperative oncology group performance status; **EC:** endometrial cancer; **dMMR:** deficient mismatch repair; **MSI-H:** microsatellite instability high; **MSS:** microsatellite stable; **MMRp:** mismatch repair proficient; **NSCLC:** non-small cell lung cancer.

Table 9: Summary of Baseline Lab Values in Analysis Dataset by Study

Treatment	4010-01-001	4010-03-001	All
	(N = 636)	(N = 233)	(N = 869)
eGFR (mL/min/m2)			
Mean (SD)	85.8 (31)	76.5 (23)	83.3 (29)
Median (range)	83.7 (19.5 - 336)	75.5 (28.7 - 196)	81.4 (19.5 - 336)
Creatinine Clearance (mL/min)*			
Mean (SD)	90.3 (30)	92.8 (29)	90.9 (30)
Median (range)	86.8 (19.3 - 150)	89.8 (27.0 - 150)	87.8 (19.3 - 150)
Alanine Aminotransferase (U/L)			
Mean (SD)	21.5 (17)	19.3 (11)	20.9 (16)
Median (range)	17.0 (2.90 - 243)	17.0 (6.00 - 92.0)	17.0 (2.90 - 243)
Aspartate Aminotransferase (U/L)			
Mean (SD)	25.3 (17)	22.7 (12)	24.6 (16)
Median (range)	21.0 (5.00 - 166)	20.0 (9.00 - 105)	21.0 (5.00 - 166)
Alkaline Phosphate (U/L)			
Mean (SD)	123 (94)	94.6 (45)	115 (85)
Median (range)	97.0 (33.0 - 855)	84.0 (42.0 - 448)	93.0 (33.0 - 855)
Albumin (g/L)			
Mean (SD)	38.1 (5.1)	39.4 (5.1)	38.5 (5.2)
Median (range)	39.0 (19.0 - 51.0)	40.0 (21.0 - 51.0)	39.0 (19.0 - 51.0)
Bilirubin (umol/L)			
Mean (SD)	7.81 (3.9)	7.01 (3.3)	7.60 (3.8)
Median (range)	6.84 (1.71 - 31.0)	6.84 (0.0110 - 20.5)	6.84 (0.0110 - 31.0)
Lymphocyte Count(109 Cell/L)			
Mean (SD)	1.36 (0.63)	1.41 (0.62)	1.37 (0.63)
Median (range)	1.27 (0.200 - 5.19)	1.38 (0.270 - 3.30)	1.30 (0.200 - 5.19)

*n=1 with missing creatinine clearance were imputed to median. eGFR: estimated glomerular filtration rate;

Table 10: Number of Patients (%) and PK Samples in Analysis Dataset by Study

Treatment	401001001	401003001	All
	(N = 636)	(N = 233)	(N = 869)
Combination Therapy		233 (100.0%)	233 (26.8%)
Monotherapy	636 (100.0%)	183 (78.5%)	636 (73.2%)
Number of Serum Obs	5975	2057	8032

Obs: Observations. **Combination therapy:** dostarlimab in combination with SOC chemotherapy. **Monotherapy:** dostarlimab alone. Concentration below the lower limit of quantification and observations excluded based on other predefined exclusion criteria are not included in the table. 75 observations with conditional weighted residual (CWRES) >5 or observations identified based on visual inspection were excluded from the analysis, resulting in 7957 observations and 868 patients (of which 232 from 4010-03-001) in the final model.

Prior Knowledge

Dostarlimab exhibits typical PK behavior as other mAb's in the PD-1 class. A PopPK model for dostarlimab has been developed based on 4010-01-001 data (GARNET, data cut March 1 2020). This PopPK model was a 2-compartment model with linear, time-dependent elimination, with WT as a covariate on CL, volume of distribution of the central compartment (Vc) and volume of distribution of peripheral compartment (Vp) (WT on intercompartment clearance to peripheral compartment (Q) was not supported and resulted in a model with a worse fit) with a proportional residual error model.

The parameter estimates of the 4010-01-001 (GARNET) model are given in Table 11.

Table 11: Parameter Estimates of the 4010-01-001 (GARNET) PopPK Model

Parameter	Alias	Estimate	Relative SE (%)	95% CI
θ_1	Clearance (CL ($L \cdot h^{-1}$))	0.00745	1.57	(0.00722 - 0.00768)
θ_2	Central volume of distribution (Vc (L))	2.98	0.871	(2.93 - 3.03)
θ_3	Proportional Error	0.133	2.45	(0.126 - 0.139)
θ_4	Additive Error (mg/L)	2.79	14.7	(1.98 - 3.59)
θ_5	Intercompartmental clearance (Q ($L \cdot h^{-1}$))	0.0228	9.18	(0.0192 - 0.0271)
θ_6	Peripheral volume of distribution (Vp (L))	2.10	2.00	(2.02 - 2.18)
θ_7	Imax	-0.161	8.53	(-0.187 - -0.134)
θ_8	T50 (days)	108	7.47	(92.6 - 124)
θ_9	Hill	5.29	9.12	(4.34 - 6.23)
θ_{10}	Effect of WT on CL	0.470	6.12	(0.414 - 0.527)
θ_{11}	Effect of WT on Vc and Vp	0.419	5.29	(0.376 - 0.463)
θ_{12}	Effect of age on CL	-0.227	29.7	(-0.360 - -0.0951)
θ_{13}	Effect of ALB on CL	-1.01	8.64	(-1.18 - -0.835)
θ_{14}	Effect of ALT on CL	-0.0585	32.4	(-0.0956 - -0.0213)
θ_{15}	Effect of male on CL	0.165	18.4	(0.106 - 0.225)
θ_{16}	Effect of ALB on Vc	-0.153	35.8	(-0.261 - -0.0461)
θ_{17}	Effect of male on Vc	0.162	12.6	(0.122 - 0.202)
$\omega_{1.1}$	ω^2_{CL}	0.0551	7.51	(0.0470 - 0.0632)
$\omega_{2.1}$	$\omega^2_{CL,Vc}$	0.0210	11.1	(0.0164 - 0.0255)
$\omega_{2.2}$	ω^2_{Vc}	0.0258	7.48	(0.0220 - 0.0296)
$\omega_{5.5}$	ω^2_{Imax}	0.537	16.4	(0.365 - 0.710)

Parameter values for the final PopPK model. **CL:** apparent systemic clearance; **Vc:** apparent central volume of distribution; **Q:** apparent intercompartment clearance; **Vp:** apparent peripheral volume of distribution; **WT:** body weight; **ALB:** albumin; **ALT:** alanine aminotransferase; **Imax:** maximal decrease in clearance relative to baseline; **T50:** time at which 50% of Imax is reached; **RSE:** relative standard error; **CI:** confidence interval; ω^2_X: variance of the inter-individual variability (IIV) of parameter X, IIV is derived from variance according to $\sqrt{\omega^2_X} \cdot 100$.

Modelling Assumptions

The study 4010-03-001 (RUBY) data will be used for external validation of the developed PopPK model. Initially, the predictive performance of the model will be evaluated graphically. Predicted observations will be obtained by fixing the parameters in the structural and variance models to the parameter estimates in the final models using posthoc Bayesian forecasting with NONMEM 7.4. The $ESTIMATION command will be set as MAXEVAL=0. The population prediction (PRED) and individual prediction (IPRED) will be compared with the corresponding observed concentrations, and conditional weighted residual (CWRES) vs time and PRED will be evaluated. Parameter (ETA) distribution will also be compared. In addition, simulation based evaluation (VPC) will be performed where the median and 95% prediction interval of the observed data is compared to model based simulations.

Prior to the covariate search estimation of the model will be performed with the combined 4010-01-001 (GARNET) and 4010-03-001 (RUBY) data.

Results

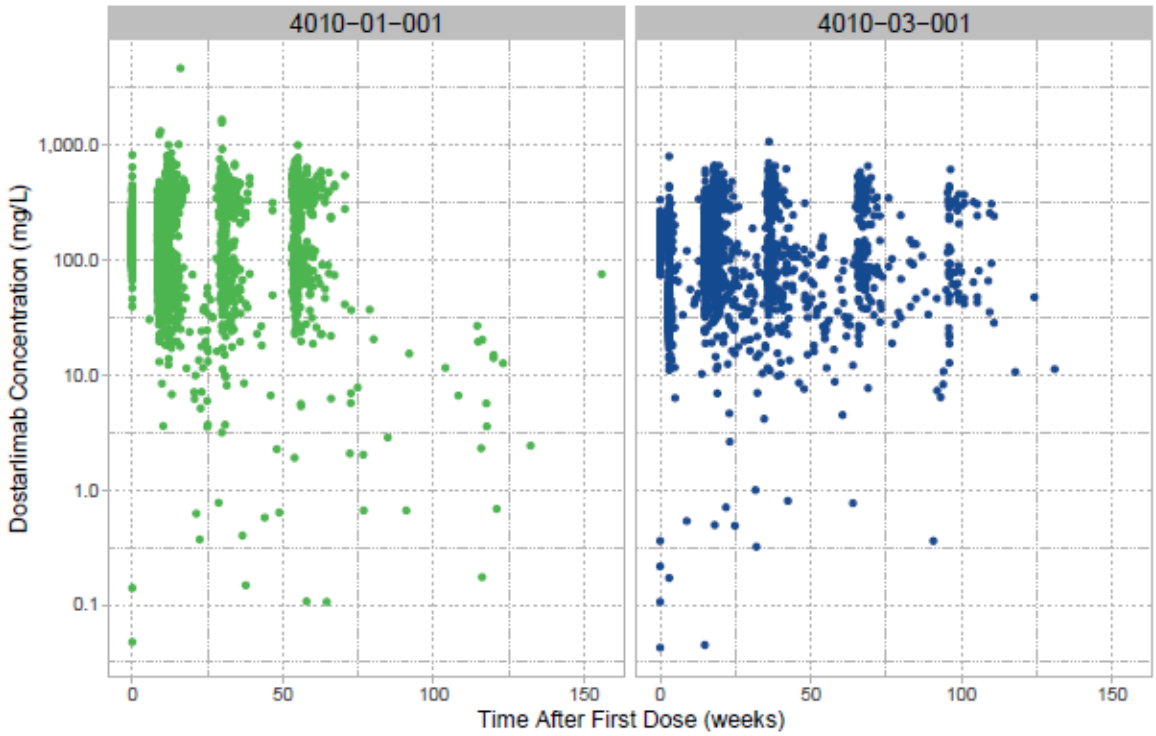
Patients with at least 2 dostarlimab PK observations were included in the analysis. In total, 2057 PK observations from 233 patients were included in the external validation of the RUBY data. From these data, 44 observations were removed due to high CWRES (>5) or based on visual inspection, during the model development.

A total of 8032 PK observations from 869 patients from both study 4010-01-001 (GARNET) and study 4010-03-001 (RUBY) studies were included in the model development after excluding 1060 (13.2%)

observations, of which 842 observations were BQL observations collected prior to first dose. Additionally, 75 observations were removed due to high CWRES (>5) or based on visual inspection throughout the modelling, resulting in a total of 7957 PK observations from 868 patients (n=232 from study 4010-03-001) in the final model.

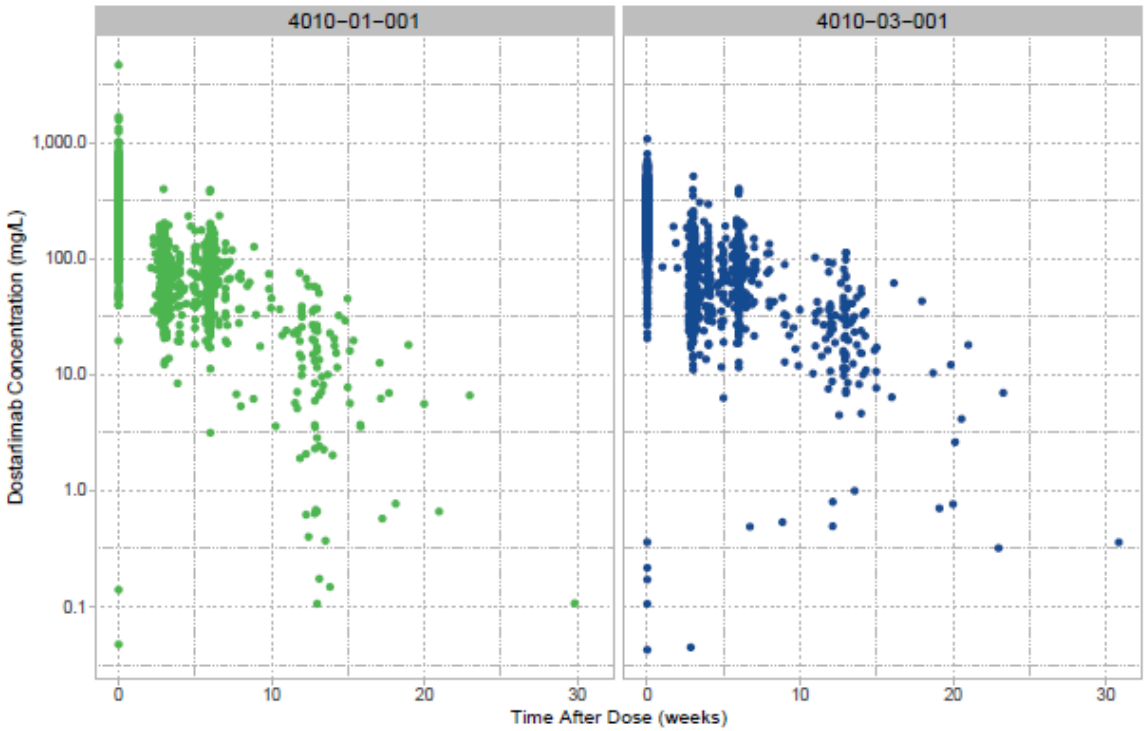
Dostarlimab serum concentrations are shown in Figure 3 for time after first dose and for time after dose in Figure 4.

Figure 3: Dostarlimab Serum Concentrations vs Time After First Dose, By Study



Circles: Individual dostarlimab serum concentration.

Figure 4: Dostarlimab Serum Concentrations vs Time After Dose, By Study



Circles: Individual dostarlimab serum concentration.

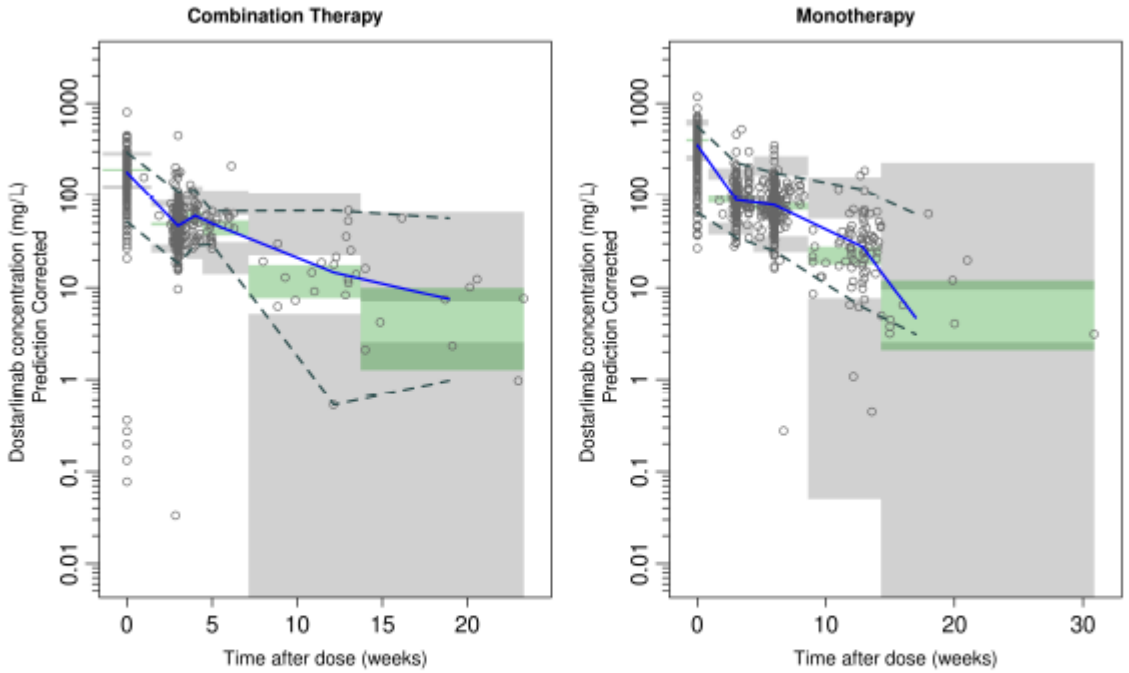
External Validation

Initially, the current dostarlimab PopPK model (GARNET, data cut March 1 2020) was externally validated against the study 4010-03-001 (RUBY) PK data.

There were no major trends identified in the VPC (Figure 5) or GOF (Figure 6, Figure 7 and Figure 8) plots.

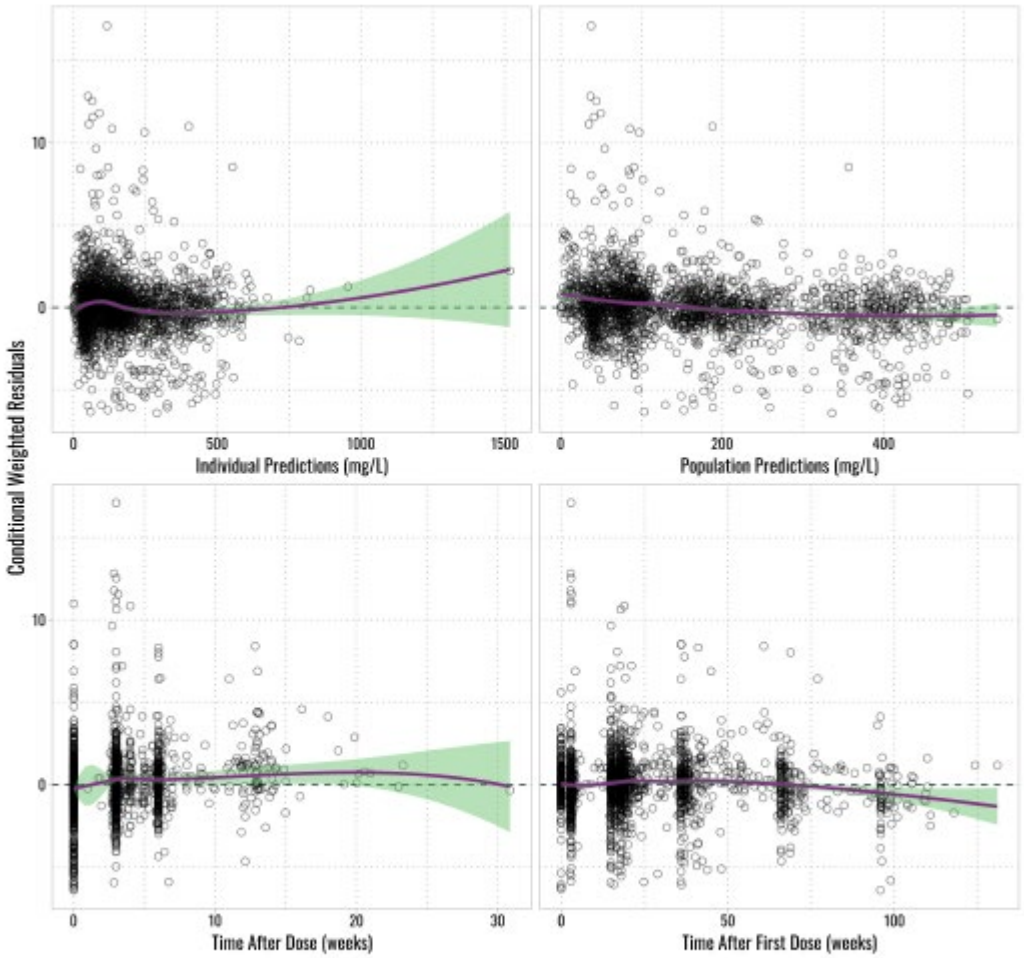
Some observations were associated with large CWRES and were considered for omission during structural model update.

Figure 5: Prediction Corrected Visual Predictive Check, 4010-03-001 External Validation



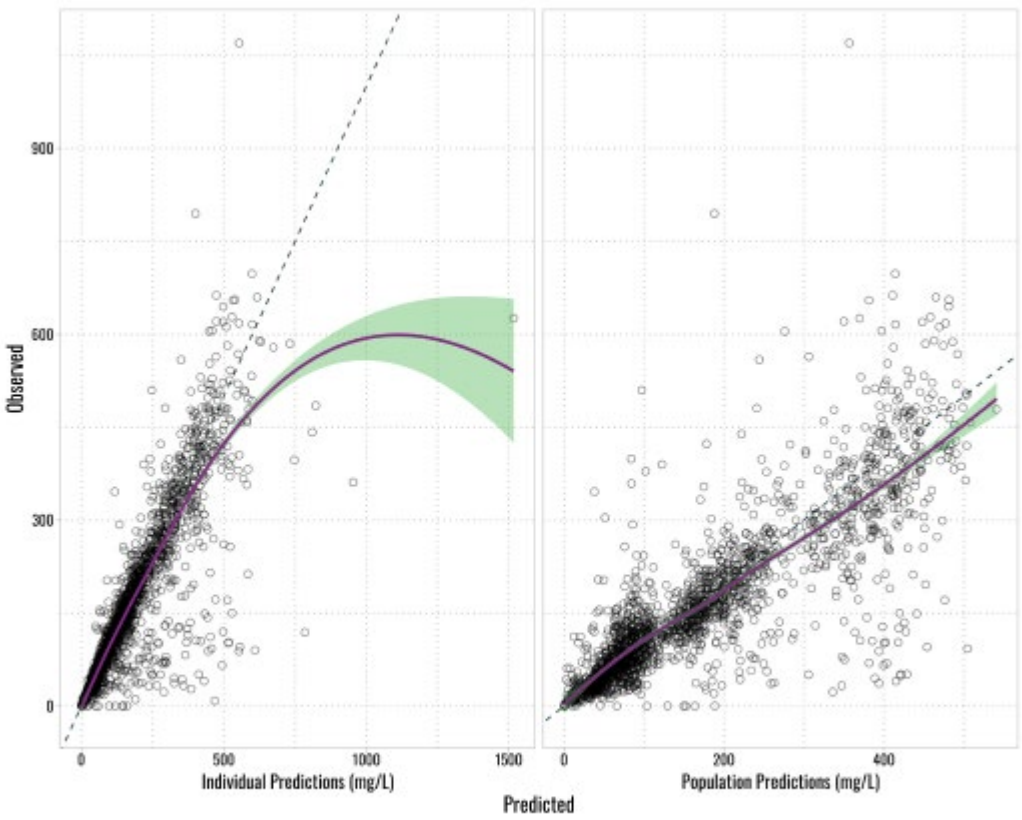
Solid Blue Line: Median of the observed dostarlimab concentrations; **Dashed Lines**: 2.5^{th} and 97.5^{th} percentiles of the observed dostarlimab concentrations; **Shaded Area**: The shaded areas indicate the 95% CI around the prediction-corrected median (green area), and 2.5^{th} and 97.5^{th} percentiles of the simulated concentrations (grey areas); **Grey Circles**: Observations. All observations and predictions are adjusted using prediction correction as described in Bergstrand et al. Bergstrand et al. (2011). 4010-03-001 (RUBY) data only.

Figure 6: Conditional Weighted Residuals vs Predictions and Time, 4010-03-001 External Validation



Purple line and green area: Loess smooth with 95% CI; **Circles:** Observed values. 4010-03-001 (RUBY) data only.

Figure 7: Observations (DV) vs Population and Individual Predictions, 4010-03-001 External Validation



Purple line and green area: Loess smooth with 95% CI; **Black dashed line:** Line of identity; **Circles:** Observed values. 4010-03-001 (RUBY) data only.

Structural Model

Table 12: Summary of Modelling Steps

Run	Ref	OFV	dOFV	Minimization	CovStep	Description
1	1040	49357.3	–	-	-	GARNET Data, MAXEVAL=0
2	1	48627.9	-729.3	Successful	Successful	Estimation GARNET data
3	2	47833.2	-794.8	Successful	Successful	Exclude high CWRES
4	3	70217.7	22384.5	-	-	Include RUBY data, MAXEVAL=0
5	4	66839.4	-3378.3	Successful	Successful	Estimation
6	5	65727.1	-1112.2	Successful	Successful	Different residual error
7	5	65727.4	-1112	Successful	Successful	Different proportional residual error, same additive
8	7	65101.1	-626.3	Successful	Successful	Exclude high CWRES
9	8	64414.8	-686.3	Successful	Successful	Exclude outlying observations based on visual inspection
10	9	64790.0	375.3	Successful	Successful	Remove covariates (not WT)
11	10	64923.7	133.7	Successful	Successful	Remove OMEGA BLOCK
12	11	64803.9	-119.8	Successful	Successful	IIV on Vp

Ref: Reference model; **OFV:** Objective Function Value; **dOFV:** Change in OFV; **CovStep:** Covariance step; **IIV:** Interindividual variability; **Vp:** Peripheral volume of distribution; **CWRES:** Conditional weighted residual; **WT:** Body weight;

The initial model (Run 1) was the previously reported 4010-01-001 model (GARNET, data cut March 1 2020), using the updated data cut for 4010-01-001 (GARNET, November 01 2021).

The model for the external validation of the 4010-03-001 (RUBY, August 08 2022 data cut) data was Run 4.

Run 11 was chosen as the structural model for the evaluation of the impact of patient covariates on dostarlimab PK.

Table 13: Parameter Estimates of the Structural PopPK Model

Parameter	Alias	Estimate	Relative SE (%)	95% CI
θ_1	Clearance (CL ($L \cdot h^{-1}$))	0.00764	1.51	(0.00741 - 0.00786)
θ_2	Central volume of distribution (Vc (L))	3.18	0.724	(3.14 - 3.23)
θ_3	Proportional Error, GARNET	0.160	3.04	(0.151 - 0.170)
θ_4	Additive Error (mg/L)	4.50	18.9	(2.83 - 6.16)
θ_5	Intercompartmental clearance (Q ($L \cdot h^{-1}$))	0.0208	8.54	(0.0177 - 0.0244)
θ_6	Peripheral volume of distribution (Vp (L))	2.40	5.47	(2.16 - 2.66)
θ_7	Imax	-0.118	14.3	(-0.151 - -0.0852)
θ_8	T50 (days)	142	11.4	(110 - 174)
θ_9	Hill	6.86	18.0	(4.44 - 9.29)
θ_{10}	WT on CL	0.485	2.97	(0.457 - 0.513)
θ_{11}	WT on Vc and Vp	0.481	5.23	(0.431 - 0.530)
θ_{12}	Proportional Error, RUBY	0.248	3.94	(0.229 - 0.267)
$\omega_{1.1}$	ω^2_{CL}	0.0787	7.32	(0.0674 - 0.0900)
$\omega_{2.2}$	$\omega^2_{V_c}$	0.0317	7.59	(0.0270 - 0.0364)
$\omega_{5.5}$	$\omega^2_{I_{max}}$	1.00	21.9	(0.572 - 1.43)

Parameter values for the structural PopPK model. **CL:** systemic clearance; **Vc:** central volume of distribution; **Q:** intercompartment clearance; **Vp:** peripheral volume of distribution; **Imax:** maximal change in clearance relative to baseline; **T50:** time at which 50% of Imax is reached; **WT:** body weight; **Relative SE:** relative standard error; **CI:** confidence interval; ω^2_X: variance of the IIV of parameter X, IIV is derived from variance according to $\sqrt{\omega^2_X} \cdot 100$.

Stepwise covariate Model Building

WT was included as a covariate in the structural model. The effect of WT was modeled based on the principles of allometry, and included as a covariate for CL, Vc and Vp, (standardized to a 70-kg person, arbitrary number).

Additional covariates, listed in Table 14, were tested using the SCM procedure.

Table 14: Covariates

CL	Age, sex, tumor diagnosis, ADA, corticosteroids, liver function, renal function, ALB, ALT, BILI, CL_{cr}, geographic location, monotherapy, ECOG, lymphocyte count, disease state
V_c	Age, sex, tumor diagnosis, ADA, corticosteroids, ALB
V_p	Age, sex, tumor diagnosis, ADA, corticosteroids, ALB
Imax	Overall response

ADA: anti-drug antibody; **ALB:** albumin; **ALT:** alanine aminotransferase; **BILI:** bilirubin; **CL_{cr}:** creatinine clearance; **CL:** Clearance; **V_c:** Central volume of distribution; **V_p:** Peripheral volume of distribution; eGFR, AST and ALP were not included in the covariate search due to highly correlated with CLCR (eGFR) and ALT (AST and ALP). Race and ethnicity had very few non-whites. Baseline and time varying SLDR had many missing (approximately 30%) and was not evaluated in the SCM. Concomitant use of immune simulators (yes/no) or immune suppressors (yes/no) were not evaluated due to very few patients receiving these types of medicines. ALB, ALT, BILI and CL_{cr} were evaluated as both baseline and time-varying covariates. Lymphocyte count was evaluated as a time-varying covariate. ADA status were tested in 3 different ways: as time-invariant (never positive vs if ever positive), time-variant as 1. positive or negative as observed at each measurement 2. negative until first positive, then carried forward as positive for the rest of the study.

A summary of the results of the SCM is provided in Table 15.

Table 15: SCM Results Summary

Relations included after final forward step:						
CL	AGE-5	ALB-5	ALT-5	SEX-2	CLCR-5	MONOTR-2
V_c	ALB-5	DIAG-2	SEX-2			
V_p	AGE-5	CORT-2				
Relations included after final backward step:						
CL	AGE-5	ALB-5	ALT-5	SEX-2	MONOTR-2	
V_c	ALB-5	SEX-2				

-2: Indicates fractional covariate relationship for categorical variables; **-5:** Indicates power relationship for continuous covariates. **ALB:** albumin; **ALT:** alanine aminotransferase; **CL:** Clearance; **CLCR:** creatinine clearance; **CORT:** corticosteroids; **DIAG:** tumor diagnosis; **MONOTR:** monotherapy vs combination therapy with standard of care treatment, **V_c:** Central volume of distribution; **V_p:** Peripheral volume of distribution;

Run 100 was the final model from the SCM (Table 15).

The correlation between CL and Vc was re-added (Run 101, ΔOFV of -109 compared to Run 100).

Table 16: Additional Modelling Steps

Run	Ref	OFV	dOFV	Minimization	CovStep	Description
100	11	64496.4	-294	Successful	Successful	Final from SCM
101	100	64387.7	-108.7	Successful	Successful	Add OMEGA block V_c/V_p - Final Model

OFV: Objective Function Value; **dOFV:** Change in OFV; **CovStep:** Covariance step; **IIV:** Interindividual variability; **CL:** Clearance; **V_c:** Central volume of distribution; **V_p:** Peripheral volume of distribution;

Final Population PK Model

A schematic depiction of the model structure is shown in Figure 8 and is mathematically described by:

$$\frac{dA_{central}}{dt} = -k_{10} \cdot A_{central} - k_{12} \cdot A_{central} + k_{21} \cdot A_{peripheral}$$
$$\frac{dA_{peripheral}}{dt} = k_{12} \cdot A_{central} - k_{21} \cdot A_{peripheral}$$

with time-dependent elimination

$$CL_{\text{time-base}} = CL_{\text{base}} \cdot exp\left(\frac{Imax \cdot Day^{Hill}}{T50^{Hill} + Day^{Hill}}\right)$$

where the micro-constants of the mass transfer are defined as

$$k_0 = \frac{CL}{Vc} \quad k_{12} = \frac{Q}{Vc} \quad k_{21} = \frac{Q}{Vp}.$$

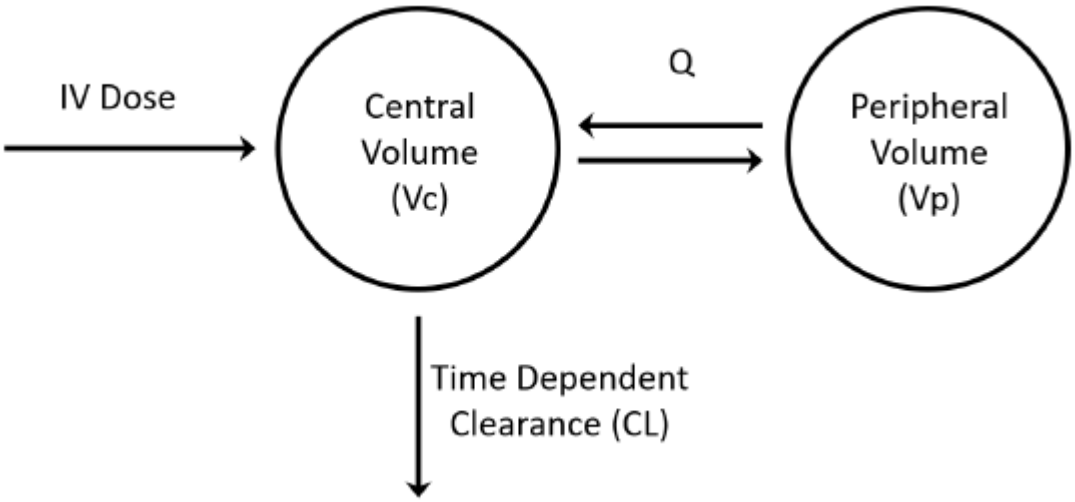
The age, ALB, ALT, and sex effects are given by

$$CL = CL_{\text{time-base}} \cdot \left(\frac{WT}{70}\right)^{\theta_{CL,WT}} \cdot \left(\frac{AGE}{64}\right)^{\theta_{CL,AGE}} \cdot \left(\frac{ALB}{39}\right)^{\theta_{CL,ALB}} \cdot \left(\frac{ALT}{18}\right)^{\theta_{CL,ALT}} \cdot \left(1 - \theta_{CL-MONOTR}\right) \cdot \left(1 + \theta_{CL-SEX}\right),$$

$$Vc = Vc_{\text{base}} \cdot \left(\frac{WT}{70}\right)^{\theta_{Vcp,WT}} \cdot \left(\frac{ALB}{39}\right)^{\theta_{Vc,ALB}} \cdot \left(1 + \theta_{Vc-SEX}\right),$$

$$Vp = Vp_{\text{base}} \cdot \left(\frac{WT}{70}\right)^{\theta_{Vcp,WT}}$$

Figure 8: Schematic Representation of the Final Population PK Model Structure



The parameter estimates of the final model are given in Table 17.

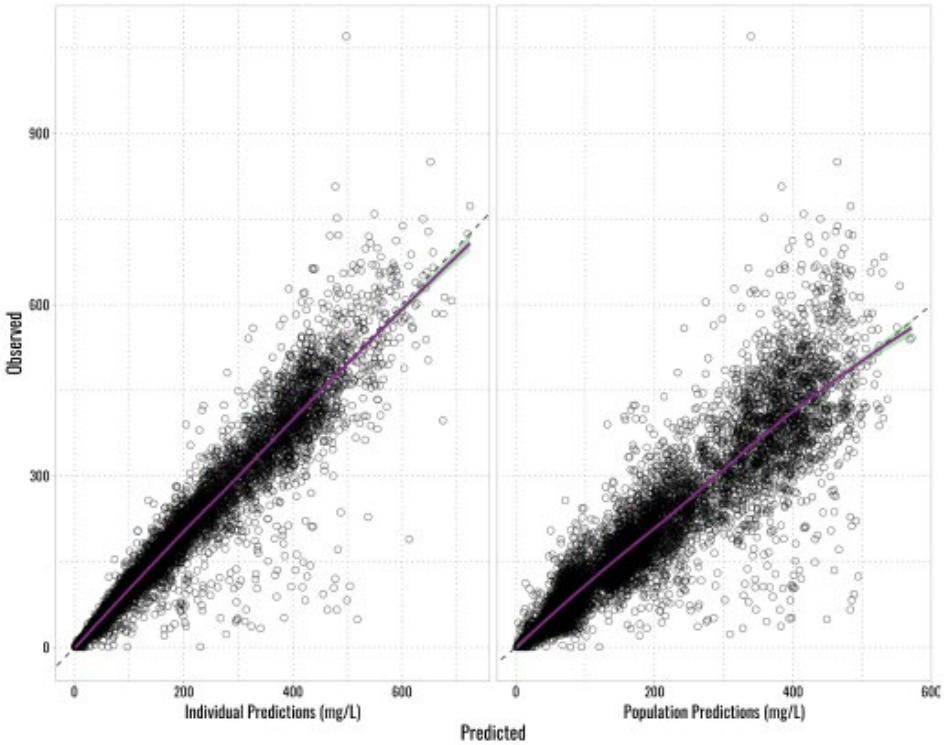
Table 17: Parameter Estimates of the Final PopPK Model

Parameter	Alias	Estimate	Relative SE (%)	95% CI
θ_1	Clearance (CL ($L \cdot h^{-1}$))	0.00732	2.03	(0.00704 - 0.00761)
θ_2	Central volume of distribution (Vc (L))	3.09	0.754	(3.04 - 3.13)
θ_3	Proportional Error, GARNET	0.16	3.09	(0.151 - 0.170)
θ_4	Additive Error (mg/L)	4.22	19.7	(2.60 - 5.85)
θ_5	Intercompartmental clearance (Q ($L \cdot h^{-1}$))	0.0191	12.0	(0.0153 - 0.0239)
θ_6	Peripheral volume of distribution (Vp (L))	2.48	5.18	(2.25 - 2.74)
θ_7	Imax	-0.113	19.4	(-0.157 - -0.0704)
θ_8	T50 (days)	145	12.9	(109 - 182)
θ_9	Hill	7.05	29.1	(3.03 - 11.1)
θ_{10}	Effect of WT on CL	0.523	7.78	(0.443 - 0.602)
θ_{11}	Effect of WT on Vc and Vp	0.48	4.75	(0.435 - 0.525)
θ_{12}	Proportional Error, RUBY	0.246	3.79	(0.228 - 0.264)
θ_{13}	Effect of age on CL	-0.238	26.2	(-0.360 - -0.116)
θ_{14}	Effect of ALB on CL	-0.922	7.93	(-1.06 - -0.778)
θ_{15}	Effect of ALT on CL	-0.0623	26.5	(-0.0947 - -0.0300)
θ_{16}	Effect of Combination Therapy on CL	-0.0779	25.9	(-0.118 - -0.0384)
θ_{17}	Effect of male on CL	0.15	18.8	(0.0948 - 0.205)
θ_{18}	Effect of ALB on Vc	-0.132	35.0	(-0.222 - -0.0409)
θ_{19}	Effect of male on Vc	0.137	14.1	(0.0992 - 0.175)
$\omega_{1.1}$	ω^2_{CL}	0.0563 (23.7% CV)	6.97	(0.0486 - 0.0639)
$\omega_{2.1}$	$\text{Covariance}_{CL,Vc}$	0.0193	11.4	(0.0150 - 0.0236)
$\omega_{2.2}$	ω^2_{Vc}	0.0278 (16.7% CV)	8.30	(0.0232 - 0.0323)
$\omega_{5.5}$	ω^2_{Imax}	0.903 (95.0% CV)	27.5	(0.417 - 1.39)

Parameter values for the final PopPK model. **CL:** systemic clearance; **Vc:** central volume of distribution; **Q:** intercompartment clearance; **Vp:** peripheral volume of distribution; **WT:** body weight; **ALB:** albumin; **ALT:** alanine aminotransferase; **Imax:** maximal decrease in clearance relative to baseline; **T50:** time at which 50% of Imax is reached; **Relative SE:** relative standard error; **CI:** confidence interval; ω^2_X: variance of the IIV of parameter X, IIV is derived from variance according to $\sqrt{\omega^2_X} \cdot 100$.

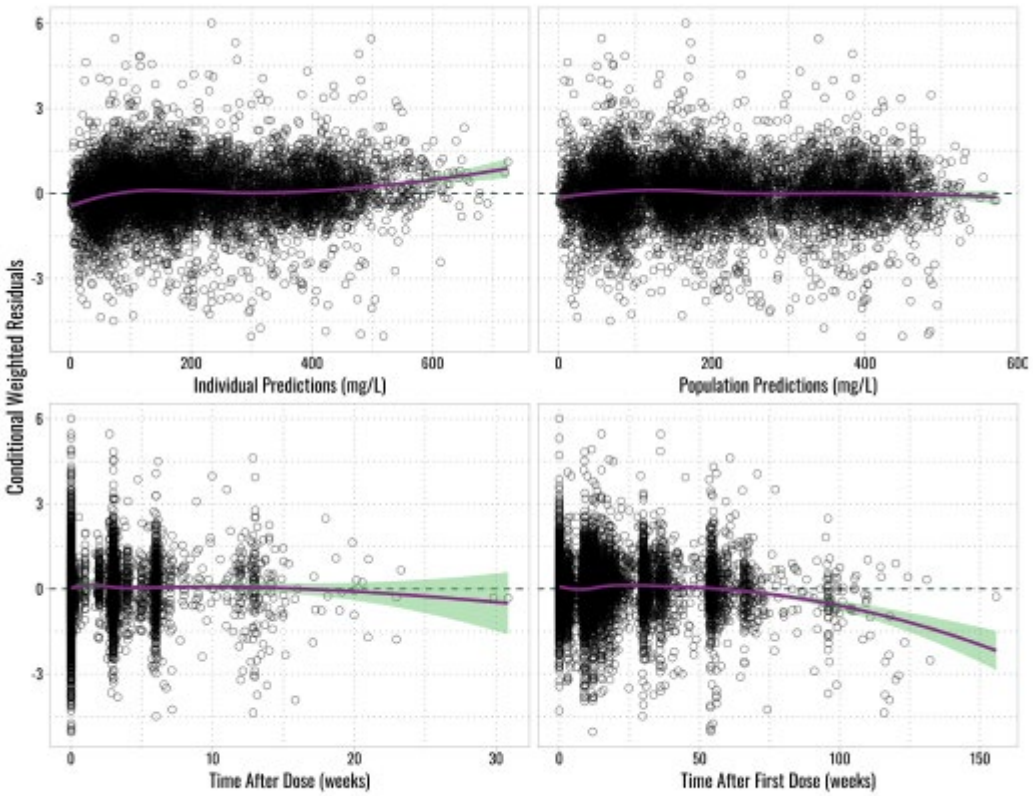
Figure 9: Observations (DV) vs Population and Individual Predictions, Final Model

Figure 14: Observations (DV) vs Population and Individual Predictions, Final Model



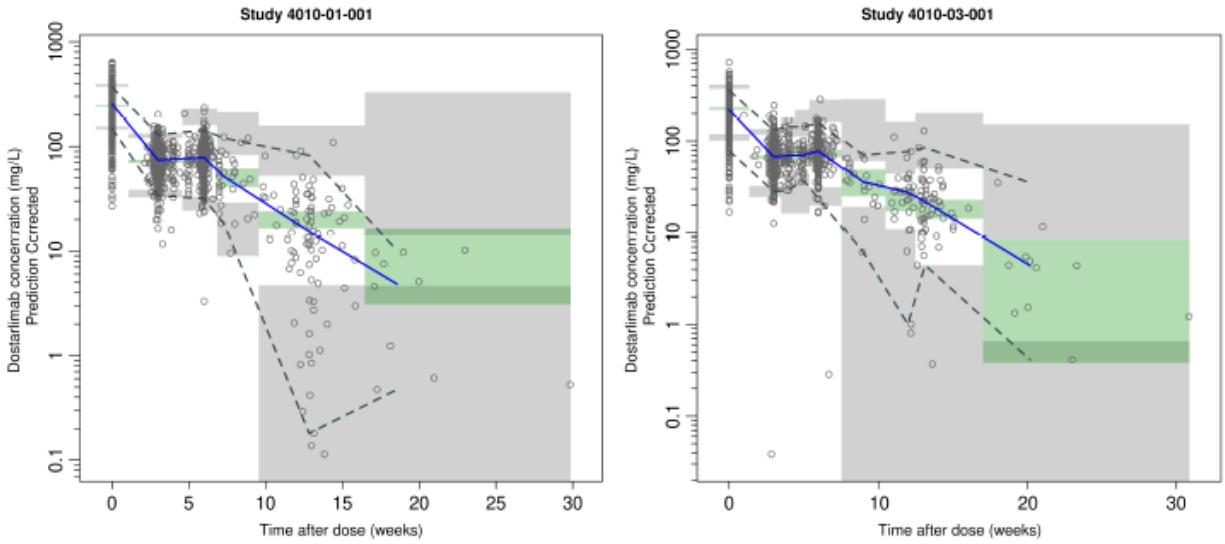
Purple line and green area: Loess smooth with 95% CI; **Black dashed line:** Line of identity; **Circles:** Observed values.

Figure 10: Conditional Weighted Residuals vs Time and Predictions, Final Model



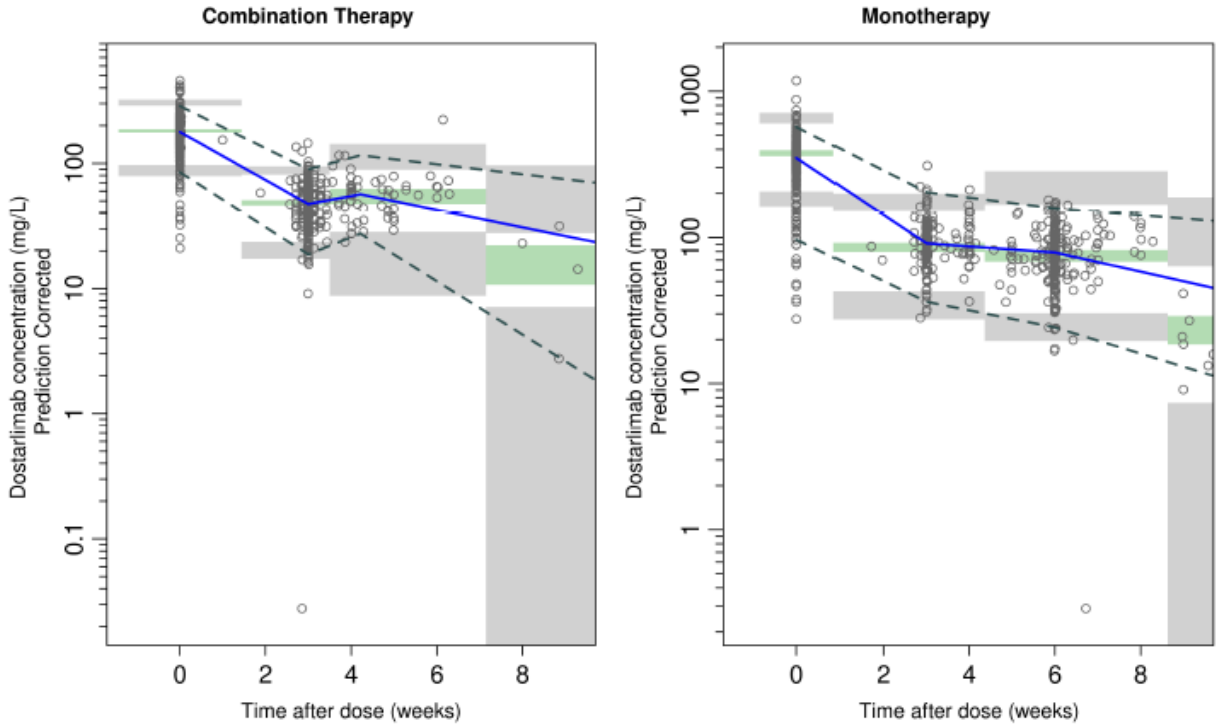
Purple line and green area: Loess smooth with 95% CI; **Circles:** Observed values.

Figure 11: Prediction Corrected Visual Predictive Check by Study, Final Model



Solid Blue Line: Median of the observed dostarlimab concentrations; **Dashed Lines:** 2.5^{th} and 97.5^{th} percentiles of the observed dostarlimab concentrations; **Shaded Area:** The shaded areas indicate the 95% CI around the prediction-corrected median (green area), and 2.5^{th} and 97.5^{th} percentiles of the simulated concentrations (grey areas). **Grey Circles:** Observations. All observations and predictions are adjusted using prediction correction as described in Bergstrand et al. Bergstrand et al. (2011). VPC is based on data for the RTD (500 mg dostarlimab Q3W for the first 4 cycles followed by 1000 mg dostarlimab Q6W for 4010-01-001 and 500 mg dostarlimab Q3W for the first 6 cycles followed by 1000 mg dostarlimab Q6W for 4010-03-001).

Figure 12: Prediction Corrected Visual Predictive Check by Monotherapy, Final Model



Solid Blue Line: Median of the observed dostarlimab concentrations; **Dashed Lines:** 2.5^{th} and 97.5^{th} percentiles of the observed dostarlimab concentrations; **Shaded Area:** The shaded areas indicate the 95% CI around the prediction-corrected median (green area), and 2.5^{th} and 97.5^{th} percentiles of the simulated concentrations (grey areas). **Grey Circles:** Observations.All observations and predictions are adjusted using prediction correction as described in Bergstrand et al. Bergstrand et al. (2011). VPC is based on data from study 4010-03-001. x-axis cut at 10 weeks to increase visibility.

Summary of Individual Predicted Exposure Estimates

Individual dostarlimab concentration versus time proles for the patients included in the PK analysis were simulated using individual posthoc PK parameter estimates from the final model. In Table 18, a summary

of the individual model predicted exposure following Cycle 1 and steady state are shown (planned dosing).

Table 18: Summary of Individual Predicted Exposure Following Cycle 1 and at Steady State, By Study

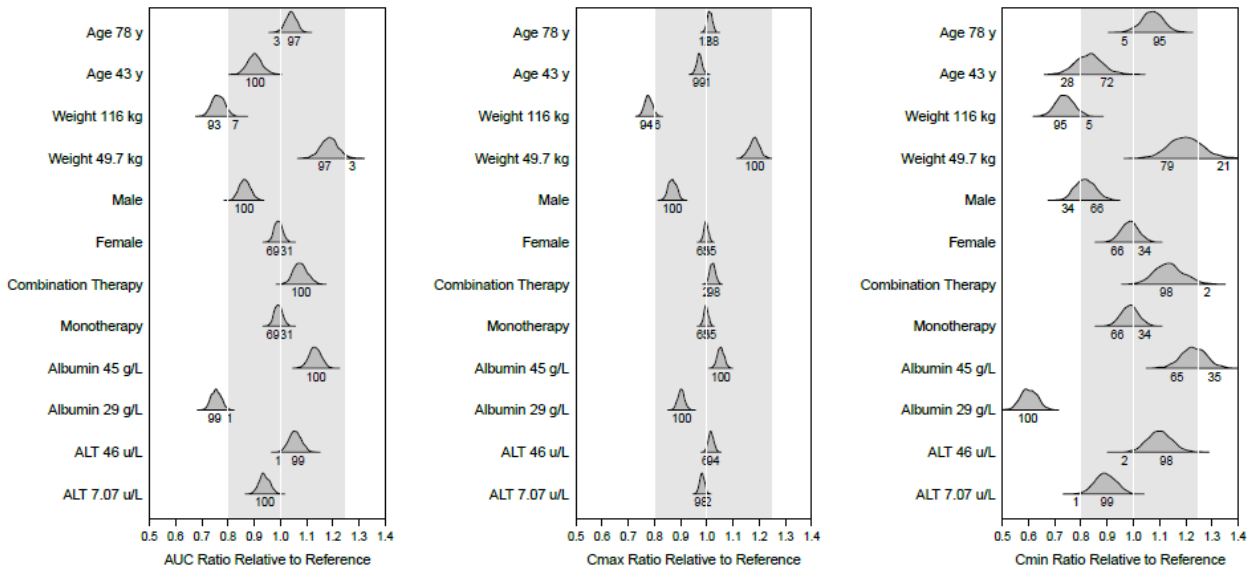
Study	Dose	$AUC_{0\text{-}tau}$ (mg*h)/L), (CV%)	C_{max} (mg/L), (CV%)	C_{min} (mg/L), (CV%)	n
4010-01-001	First dose (500 mg)	32500 (17.6)	157 (19.6)	37.6 (25.4)	602
4010-01-001	Steady state (500 mg)	71200 (29)	256 (22.8)	95.5 (37.9)	602
4010-01-001	Steady state (1000 mg)	144000 (29.6)	388 (21.1)	68.8 (47.3)	602
4010-03-001	First dose (500 mg)	31800 (18.9)	144 (18.1)	38.4 (27.4)	232
4010-03-001	Steady state (500 mg)	73100 (31.1)	248 (24.2)	101 (39.7)	232
4010-03-001	Steady state (1000 mg)	148000 (32)	369 (21.5)	76.1 (48)	232
All	First dose (500 mg)	32300 (18)	154 (19.5)	37.8 (25.9)	834
All	Steady state (500 mg)	71800 (29.6)	253 (23.2)	97.1 (38.5)	834
All	Steady state (1000 mg)	145000 (30.3)	382 (21.3)	70.8 (47.7)	834

$AUC_{0\text{-}tau}$ area under the concentration versus time curve for a dosing interval; C_{max}: maximum concentration; C_{min}: minimum concentration (trough). Geometric mean and CV%. Including Part 2b patients for 4010-01-001 (GARNET) and all patients included in the final PopPK model for 4010-03-001 (RUBY).

Covariate Effects on Predicted Exposure, Final Model

The impact of the covariates on exposure at steady state is shown in Figure 13.

Figure 13: Forest Plots Illustrating the Covariate Effects on Exposure At Steady State



Forest plot of AUC_{ss} $C_{max,ss}$ and $C_{min,ss}$ ratios as compared to median reference patient (female, 70 kg, age 64 years, ALB 39 g/L and ALT 17 U/L). The distributions represent the ratios based on 1,000 set of parameter estimates re-sampled from the variance covariance matrix. Plotted numbers indicate actual percent of each distribution in a bounded region (here the central reference line). The grey area represent the 0.8 and 1.25 boundaries.

Table 19: Covariate Impact on Exposure, Summary of AUC, Cmax and Cmin Ratios

Covariate	Value	AUC ratio	C_{max} ratio	C_{min} ratio
WT, 5th percentile	49.7	1.19	1.18	1.2
WT, 95th percentile	116	0.763	0.777	0.738
ALB, 5th percentile	29	0.7549	0.902	0.6012
ALB, 95th percentile	45	1.132	1.053	1.229
ALT, 5th percentile	7.07	0.938	0.981	0.893
ALT, 95th percentile	46	1.06	1.02	1.1
Sex	Male	0.864	0.869	0.816
Age, 5th percentile	43	0.902	0.971	0.832
Age, 95th percentile	78	1.04	1.01	1.07
Combination Therapy	Combination Therapy	1.08	1.02	1.13

AUC: area under the concentration versus time curve (steady state); **Cmax:** maximum concentration (steady state); **Cmin:** minimum concentration (steady state); **WT:** body weight; **ALB:** albumin; **ALT:** alanine aminotransferase. Median ratio based on 1,000 sets of parameter estimates re-sampled from the variance covariance matrix.

Model Predicted Dostarlimab Cmin;ss

The PopPK model predicted Cmin;ss for the 500 mg Q3W and 1000 mg Q6W regimens were 106 mg/L and 79.5 mg/L, respectively, with 90% PI of 50.4 - 223 mg/L and 34.1 - 186 mg/L, respectively.

The lower bounds of the 90% PI of the Cmin;ss for the 500 mg Q3W and 1000 mg Q6W regimens were approximately 2.80-fold and 1.89-fold higher respectively, as compared to 18 mg/L, the estimated concentration for maintenance of 90% of maximal peripheral PD-1 suppression (Austin et al., 2023).

Table 20: Summary of Predicted Dostarlimab Cmin;ss (mg/L), by Dose Regimen

Dose regimen	Median	Geometric Mean (CV%)	90% PI	total n
1000 mg Q6W	79.5	79.3 (59.4)	34.1 - 186	1000
500 mg Q3W	106	105 (48.3)	50.4 - 223	1000

$C_{min,ss}$: lowest predicted concentration during a dose interval at steady state. **Q3W:** once every third week; **Q6W:** once every sixth week; **CV:** coefficient of variation; **PI:** prediction interval.

Albumin and Weight Effects on Dostarlimab Cmin at Cycle 1 and Steady State

Based on simulated profiles for the recommended therapeutic dose, the Cmin were calculated and were used to derive the percentage of subjects with Cmin at Cycle 1 and at steady-state greater than 18 mg/L for subjects with low ALB (<29 g/L) or high WT (≥116kg)

Table 21: Summary of Subjects with Predicted Dostarlimab Cmin Concentration Higher than 18 mg/L at Cycle 1 and Steady State, by WT Category

Cycle	Body Weight Category	total n	Percent of Subjects with $C_{min} > 18$ mg/L
Cycle 1	< 116	1000	99.6 %
Cycle 1	>= 116	1000	97.9 %
Steady State	< 116	1000	99.8 %
Steady State	>= 116	1000	99.2 %

The cycle length is defined as a dosing interval, 3 weeks for Q3W and Cycle 1 RTD, 6 weeks for Q6W at steady state. C_{min}: lowest predicted concentration during a dose interval. **RTD:** recommended therapeutic dose (500 mg Q3W for 6 cycles followed by 1000 mg Q6W thereafter); **Q3W:** once every third week; **Q6W:** once every sixth week.

Table 22: Summary of Subjects with Predicted Dostarlimab Cmin Concentration Higher than 18 mg/L at Cycle 1 and Steady State, by ALB Category

Cycle	Albumin Category	total n	Percent of Subjects with $C_{min} > 18$ mg/L
Cycle 1	< 29 g/L	1000	94.3 %
Cycle 1	>= 29 g/L	1000	99.8 %
Steady State	< 29 g/L	1000	92.7 %
Steady State	>= 29 g/L	1000	99.7 %

The cycle length is defined as a dosing interval, 3 weeks for Q3W and Cycle 1 RTD, 6 weeks for Q6W at steady state. C_{min}: lowest predicted concentration during a dose interval. **RTD:** recommended therapeutic dose (500 mg Q3W for 6 cycles followed by 1000 mg Q6W thereafter); **Q3W:** once every third week; **Q6W:** once every sixth week; **ALB:** albumin.

Absorption

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 73100 µg • h/mL (31.1%), respectively, after multiple dosing of 500 mg Q3W at steady state.

Distribution

The mean volume of distribution of dostarlimab at steady state is approximately 5.8 L (CV % of 14.9 %).

Elimination

The mean clearance is 0.007 L/h (CV % of 30.2 %) at steady state. The $t_{1/2}$ at steady state is 23.2 days (CV % of 20.8 %).

Dostarlimab clearance was estimated to be 7.8% lower when dostarlimab was given in combination with carboplatin and paclitaxel.

Special populations

Dostarlimab PK was similar between participants with normal renal function and those with mild or moderate renal impairment (Table 23). Similarly, mild hepatic impairment did not appear to cause a

significant change in the PK of dostarlimab when compared to participants with normal hepatic function (Table 24).

Table 23 Summary of predicted exposure at first dose and steady state by renal impairment (geometric means)

Renal Function	n	Cmax (µg/mL)		AUC(0-21 days) (µg•h/mL)	AUC(0-42 days) (µg•h/mL)
		First Dose (500 mg)	Steady State (1000 mg)	First Dose (500 mg)	Steady State (1000 mg)
Normal	292	151.80	375.90	32020.00	141400.00
Mild	385	156.60	391.50	32940.00	149300.00
Moderate [a]	157	149.10	372.40	31440.00	142100.00

Source: m5.3.5.3, Population PK and Exposure-Response Analysis Report, Table A.10.1

AUC(0-21 days)=area under the concentration-time curve to 21 days postdose; AUC(0-42 days)=area under the concentration-time curve to 42 days postdose; Cmax=maximum observed concentration; PK=pharmacokinetic

a. Due to a limited number of participants (n=3) with severe renal impairment, these participants were pooled with participants in the moderate category.

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.

Table 24 Summary of predicted exposure at first dose and steady state by hepatic impairment (geometric means)

Hepatic Function	n	Cmax (µg/mL)		AUC(0-21 days) (µg•h/mL)	AUC(0-42 days) (µg•h/mL)
		First Dose (500 mg)	Steady State (1000 mg)	First Dose (500 mg)	Steady State (1000 mg)
Normal	742	153.50	381.80	32330.00	144600.00
Mild [a]	92	153.80	386.50	32380.00	149600.00

Source: m5.3.5.3, Population PK and Exposure-Response Analysis Report, Table A.10.2

AUC(0-21 days)=area under the concentration-time curve to 21 days postdose; AUC(0-42 days)=area under the concentration-time curve to 42 days postdose; Cmax=maximum observed concentration; PK=pharmacokinetic

a. Due to a limited number of participants (n=5) with moderate hepatic impairment, these participants were pooled with participants in the mild category.

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.

The tables with summary of predicted exposures are based on patients receiving the dose of 500 mg Q3W for 4 cycles (Garnet, part 2 B subjects only) or 500 mg Q3W 6 cycles (Ruby), followed by 1000 mg Q6W.

The number of all patients in RUBY and Garnet study who were treated with dostarlimab alone or in combination with paclitaxel and carboplatin with PK data available at time of analysis, and were included in the PopPK analysis by study, were as follows:

- Based on the estimated creatinine clearance, normal: n= 305; mild: n = 397; moderate: n = 164.

- Based on hepatic dysfunction by total bilirubin and AST, normal: n = 772; mild: n = 92.

Pharmacokinetic interaction studies

No interaction studies have been performed.

During the population PK analysis, concomitant chemotherapy, immune suppressors, immune stimulators, and the systemic use of corticosteroids were planned to be evaluated as covariates.

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 (see section 2.3.3).

2.3.3. PK/PD modelling

Exposure-efficacy analysis

The analysis included subjects in the dostarlimab plus SOC arm.

Efficacy Variables

The main focus for the ER of efficacy was the primary efficacy endpoint PFS, as assessed by the investigator per RECIST v.1.1.

DOR was evaluated as the key secondary efficacy endpoint and was defined as the time from first documentation of complete response (CR) or partial response (PR) until the time of first documentation of progressive disease evaluated (using RECIST v1.1), or death due to any cause for the patients with objective response. OS was only explored using exploratory plots, and no formal analysis was performed as data was deemed immature (33% maturity in ITT population).

A summary of covariates in the ER dataset is shown in Table 25.

Table 23: Summary of Covariates for Dostarlimab Treated Patients

Covariate	Level	Count
ADBAS	Missing	3
	Negaitve	229
ANBAS	Missing	196
	Negative	18
	Positive	18
DIAG	dMMR/MSI-H	49
	MMRp/MSS	183
DISSTAT	Primary Stage III	45
	Primary Stage IV	72
	Recurrent	115
DMMR	No	183
	Yes	49
ECOG	Ambulatory	90
	Fully active	142
GL	Eastern Europe	13
	North America	164
	Western Europe	55
HISTOLOG	EC	109
	Other	123
PDL1CAT	Negative	37
	Positive	94
	Unknown	101
PELRAD	No	192
	Yes	40

ADBAS: Anti drug antibody status; **ANBAS:** Neutralizing antibody status; **DIAG:** Tumor Diagnosis; **DISSTAT:** Disease status in EC; **dMMR:** deficient mismatch repair; **MSI-H:** microsatellite instability high; **MSS:** microsatellite stable; **MMRp:** mismatch repair proficient; **ECOG:** Baseline ECOG performance; **GL:** Geographic location; **HISTOLOG:** Histology; **PDL1CAT:** Combined positive score category at baseline; **PELRAD:** Prior external pelvic radiotherapy. All dostarlimab treated patients in the tumor diagnosis category dMMR/MSI-H were dMMR.

Two hundred twenty-nine patients had negative 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 dMMR. Hence dMMR was not included as a separate covariate in the analysis.

Time-to-event Modelling Approach

For time to event (TTE) data (PFS and DOR), Kaplan-Meier plots stratified by quartiles of exposure were constructed to guide model development. Kaplan-Meier plots stratified by quartiles of exposure were constructed for visual exploration of exposure-OS relationship (no formal model analysis was performed as data was deemed immature with 33% maturity in ITT population).

The primary efficacy parameter PFS and key secondary efficacy parameter DOR, were assessed using Cox proportional hazard models with exposure as the independent predictor.

As a first step, a univariate analysis with exposure as the independent predictor was performed. Subsequently, covariates were explored via a full covariate model approach, i.e. a multivariate analysis with all covariates included in the model at once.

- ***Progression Free Survival***

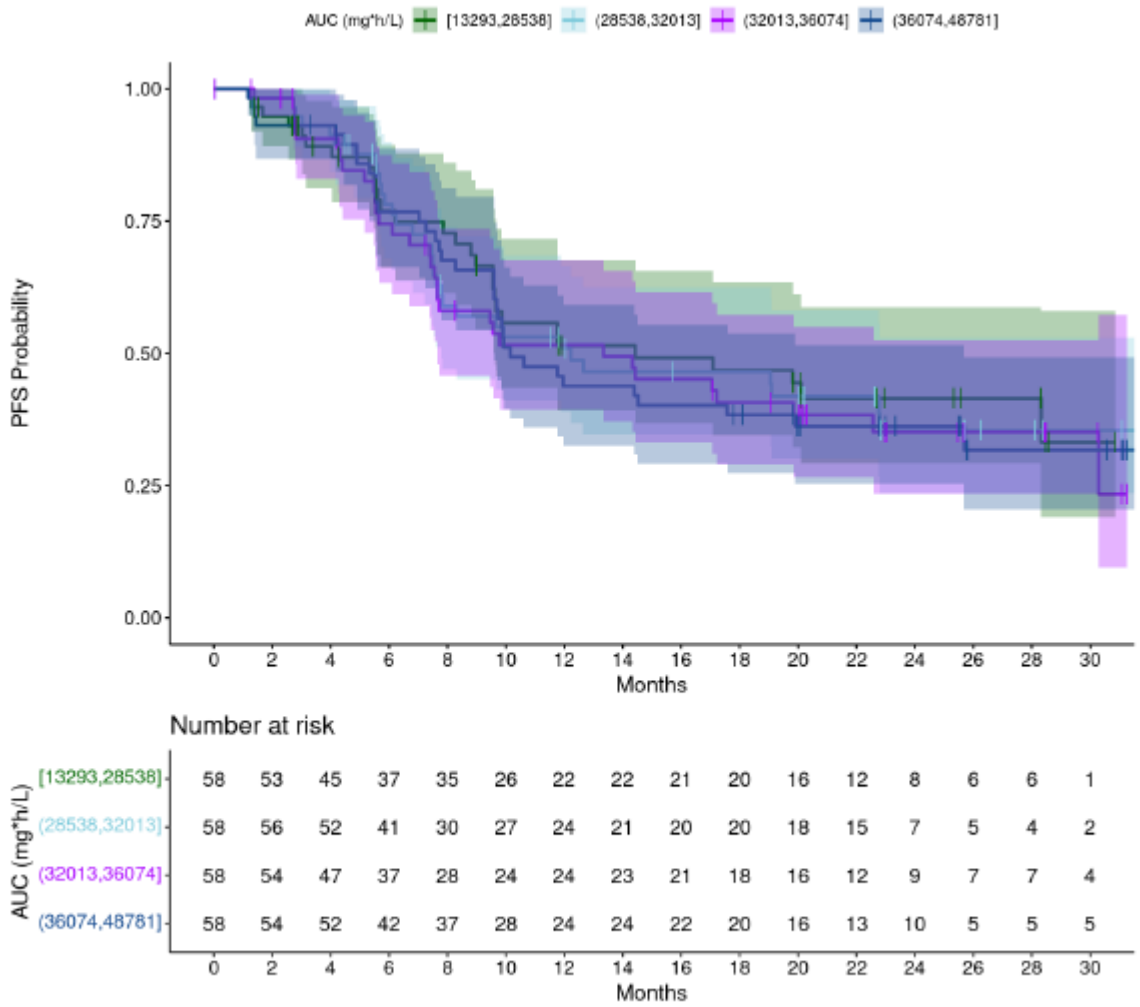
A total of 232 PFS observations from 232 subjects with quantified dostarlimab concentrations in the dostarlimab arm of study 4010-03-001 were used for PFS evaluation. A summary of the exposure metrics for the patients included in the exposure-response analysis of PFS are shown in Table 26.

Table 24: Summary of Predicted Cycle 1 Cmin, Cmax, and AUC for Patients in the Analysis of Progression Free Survival

Metric	Minimum	Maximum	Mean	SD
C_{min} (mg/L)	10.10	67.60	39.70	9.94
C_{max} (mg/L)	73.40	246.00	147.00	26.40
AUC (mg*h/L)	13300.00	48800.00	32300.00	5850.00

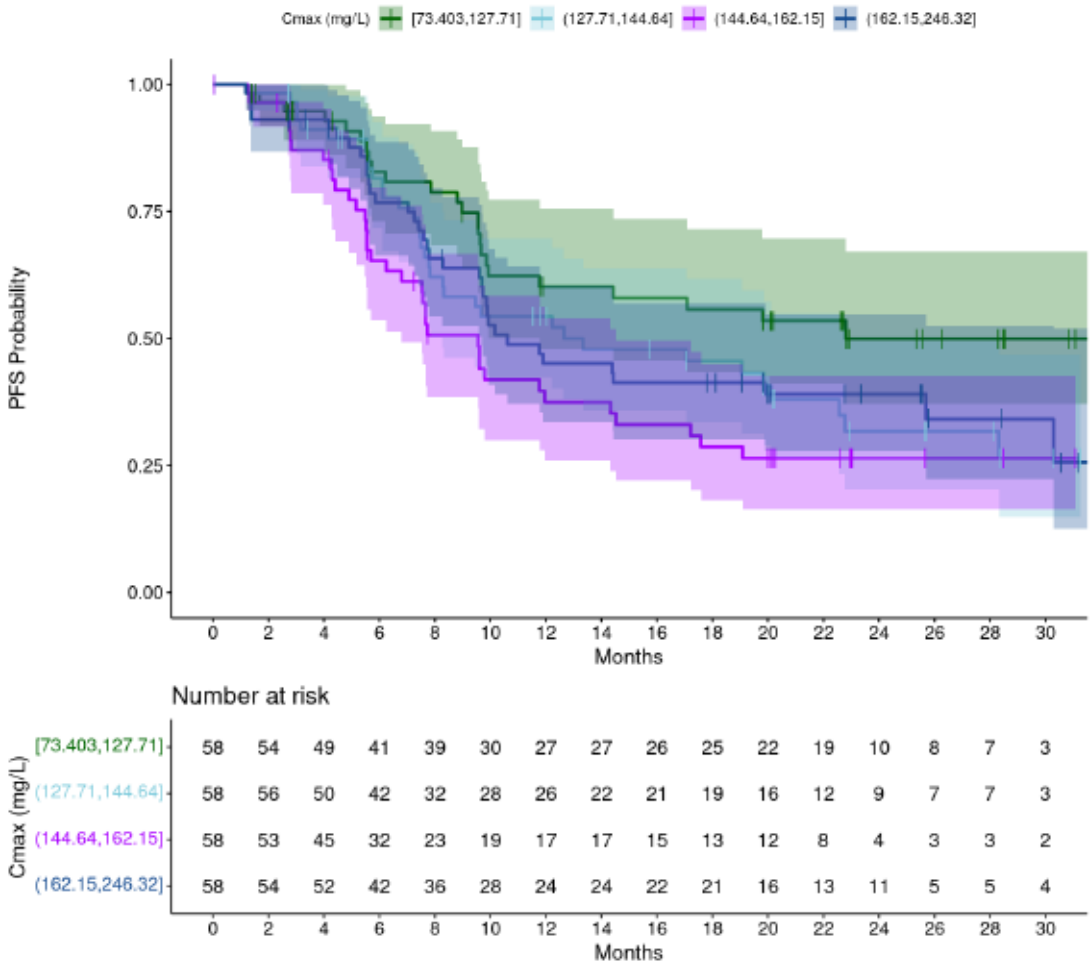
SD: standard deviation. **AUC**: Area under the curve during the first 21 days; C_{max}: Maximum concentration during the first 21 days; C_{min}: Minimum concentration at Day 21.

Figure 14: PFS vs. Time Stratified by AUC Exposure Quartiles



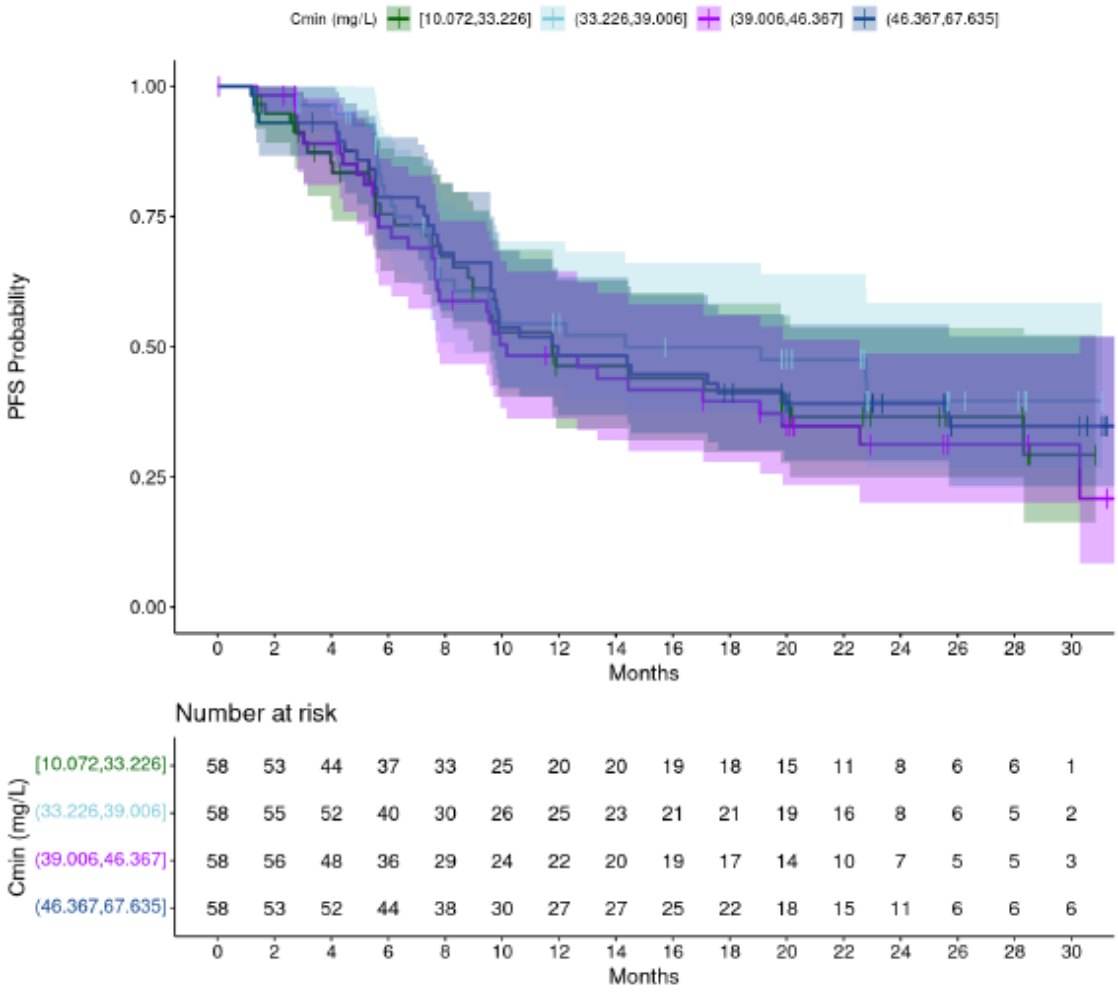
Lines: progression-free survival probability; **Vertical lines:** censoring; **Shaded area:** 95% confidence interval; **AUC**: area under the curve during the first 21 days.

Figure 15: PFS vs. Time Stratified by Cmax Exposure Quartiles



Lines: progression-free survival probability; **Vertical lines:** censoring; **Shaded area:** 95% confidence interval; C_{max}: Maximum concentration during the first 21 days.

Figure 16: PFS vs. Time Stratified by Cmin Exposure Quartiles

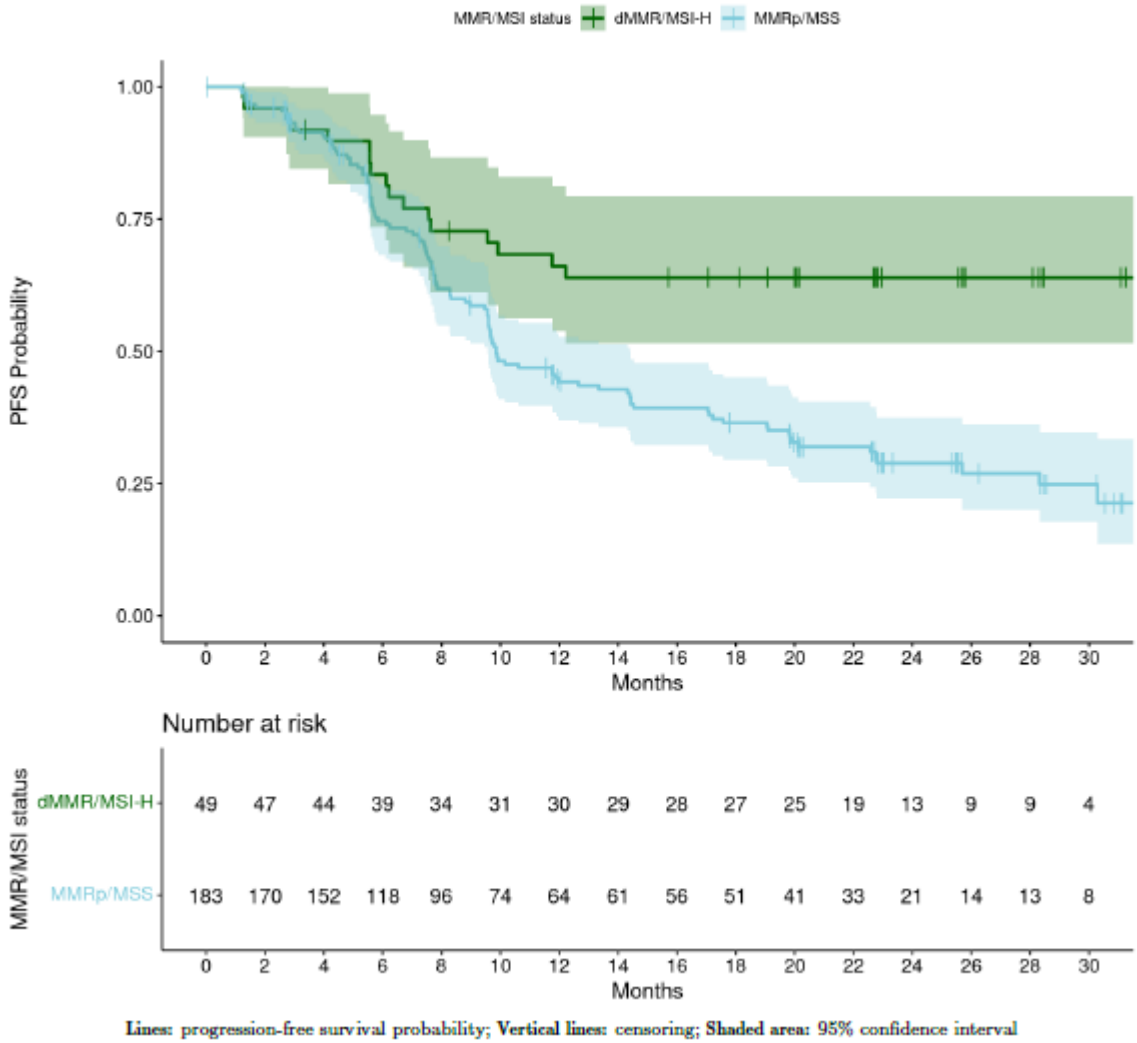


Lines: progression-free survival probability; **Vertical lines:** censoring; **Shaded area:** 95% confidence interval; C_{min}: Minimum concentration at Day 21.

Disease status in EC, prior external pelvic radiotherapy, baseline ECOG performance and histology showed no apparent relationship with PFS probability (Figure 17 - Figure 18). Patients in North America appear to have a significantly longer PFS compared to European patients (Figure 18). However, the samples size in Europe (n=68) is smaller than North America.

A large difference in PFS was observed between dMMR/MSI-H and MMRp/MSS patients (Figure 17).

Figure 17: PFS vs. Time Stratified by Tumour Diagnosis

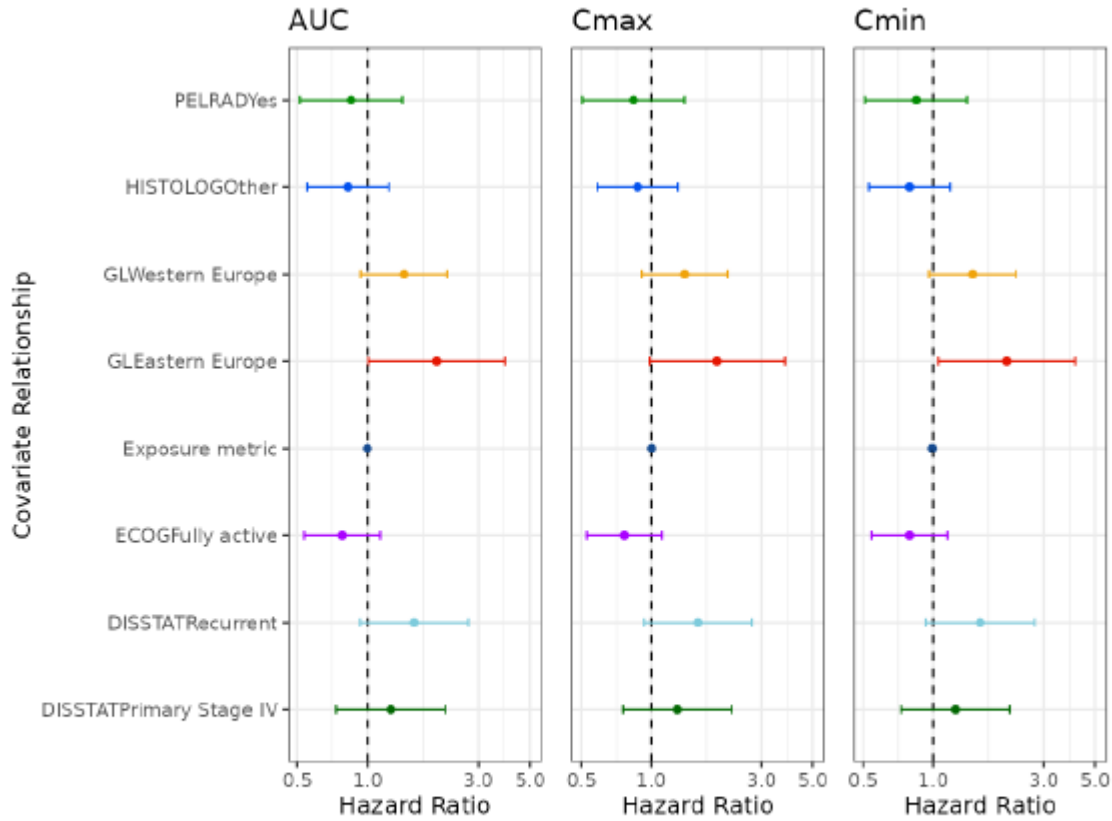


Lines: progression-free survival probability; **Vertical lines:** censoring; **Shaded area:** 95% confidence interval

PFS appeared to be independent of AUC and Cmin. An apparent relationship where higher exposures result in lower efficacy was seen for Cmax in MMRp/MSS patients. However, the 95%CI overlap to great extent.

Since the hazards for tumour diagnosis were non-proportional, Cox (proportional hazards) regression stratified by tumour diagnosis was performed for the three exposure metrics (AUC, Cmax and Cmin) with the additional 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 PFS (α = 0,05) with p-values of 0.90, 0.28 and 0.40 for AUC, Cmax and Cmin, respectively. The hazard ratios of the tested covariates can be seen in Figure 18 and Table 27. The 95% CI of geographic location Eastern Europe does not include 1 when tested with the exposure metrics AUC and Cmin while the other tested covariates include 1. The 95% CI for geographic location, Eastern Europe, were 1.008-3.91, 1.052-4.105 for AUC and Cmin, respectively.

Figure 18: Hazard Ratio Multivariate Analysis, PFS



Circle: Hazard ratio; **Lines:** 95% confidence interval; PELRAD - Prior external pelvic radiotherapy (reference No); HISTOLOG - Histology (reference EC); 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 curve during the first 21 days; C_{max}: Maximum concentration during the first 21 days; C_{min}: Minimum concentration at Day 21.

Table 25: Hazard Ratios PFS Analysis (AUC, Cmax, Cmin)

Table A.13.1: Hazard Ratio Multivariate PFS Analysis, AUC

Covariate	Hazard Ratio	95% CI of Hazard Ratio	p-value
Exposure metric	1.00	1-1	0.90
DISSTATPrimary Stage IV	1.26	0.7356-2.161	0.40
DISSTATRecurrent	1.59	0.9295-2.725	0.09
PELRADYes	0.85	0.5133-1.411	0.53
ECOGFully active	0.78	0.5348-1.135	0.19
GLEastern Europe	1.99	1.008-3.91	0.05
GLWestern Europe	1.44	0.9349-2.209	0.10
HISTOLOGOther	0.82	0.5503-1.234	0.35

PELRAD - Prior external pelvic radiotherapy (reference No); HISTOLOG - Histology (reference EC); 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 A.13.2: Hazard Ratio Multivariate PFS Analysis, C_{max}

Covariate	Hazard Ratio	95% CI of Hazard Ratio	p-value
Exposure metric	1.00	0.9971-1.01	0.28
DISSTATPrimary Stage IV	1.30	0.7577-2.231	0.34
DISSTATRecurrent	1.60	0.9332-2.738	0.09
PELRADYes	0.84	0.5055-1.394	0.50
ECOGFully active	0.77	0.5273-1.115	0.16
GLEastern Europe	1.93	0.9846-3.784	0.06
GLWestern Europe	1.40	0.9126-2.136	0.12
HISTOLOGOther	0.87	0.5845-1.308	0.51

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

Table A.13.3: Hazard Ratio Multivariate PFS Analysis, C_{min}

Covariate	Hazard Ratio	95% CI of Hazard Ratio	p-value
Exposure metric	0.99	0.9745-1.01	0.40
DISSTATPrimary Stage IV	1.25	0.7279-2.138	0.42
DISSTATRecurrent	1.60	0.9331-2.733	0.09
PELRADYes	0.85	0.5107-1.402	0.52
ECOGFully active	0.79	0.5445-1.156	0.23
GLEastern Europe	2.08	1.052-4.105	0.04
GLWestern Europe	1.48	0.9615-2.278	0.07
HISTOLOGOther	0.79	0.5308-1.185	0.26

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

- ***Duration of response***

A total of 147 DOR observations from 147 subjects with quantified dostarlimab concentrations in the dostarlimab arm of study 4010-03-001 were used for DOR evaluation. A summary of the exposure metrics for the patients included in the exposure-response analysis of DOR are shown in Table 28.

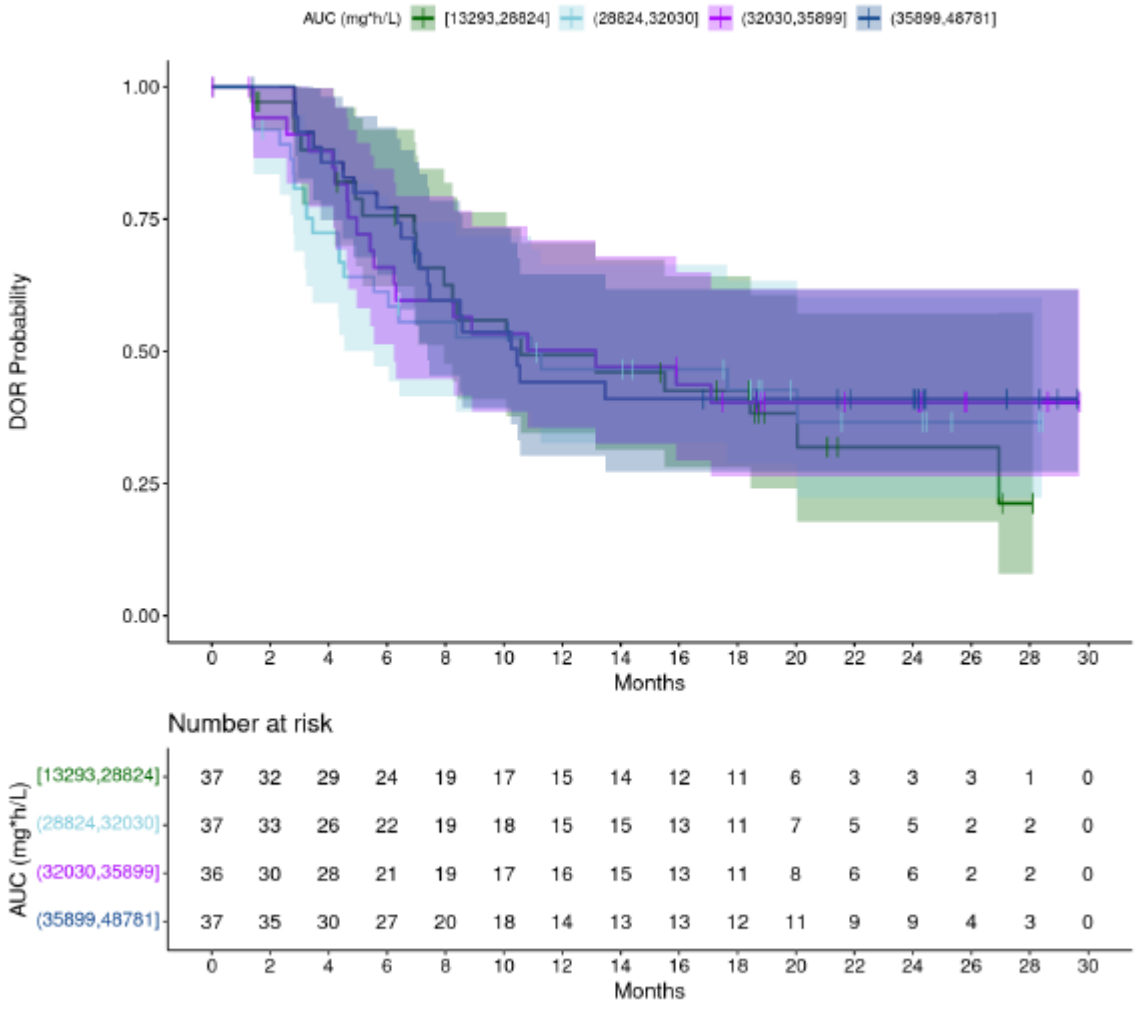
Table 26: Summary of Predicted Cycle 1 Cmin, Cmax, and AUC for Patients in the Analysis of Duration of Response

Metric	Minimum	Maximum	Mean	SD
C_{min} (mg/L)	10.10	67.60	39.50	9.61
C_{max} (mg/L)	73.40	246.00	145.00	25.20
AUC (mg*h/L)	13300.00	48800.00	32100.00	5640.00

SD: Standard deviation; **AUC**: Area under the curve during the first 21 days; C_{max}: Maximum concentration during the first 21 days; C_{min}: Minimum concentration at Day 21.

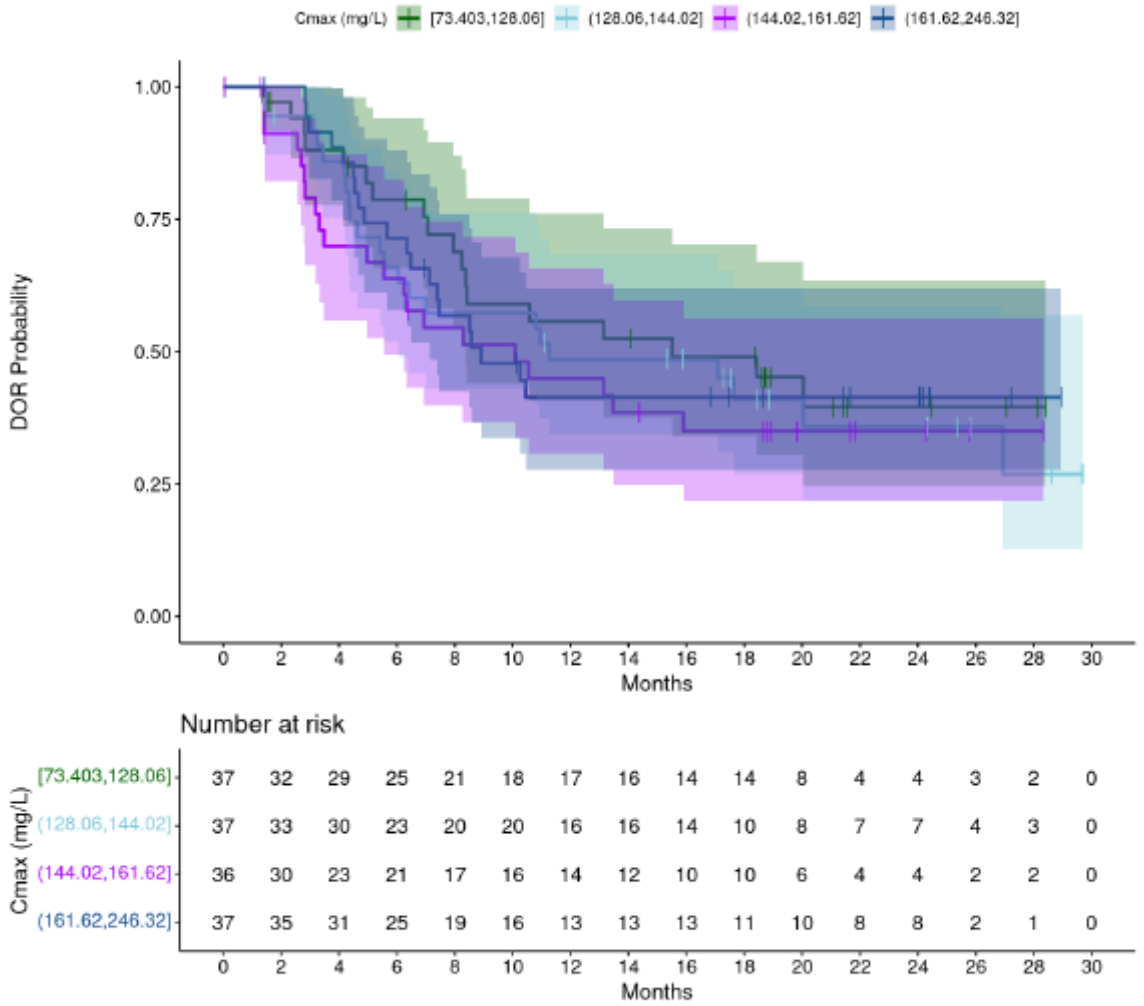
Figure 19, Figure 20 and Figure 21 shows the DOR probability over time for the three exposure metrics of interest AUC, Cmax and Cmin.

Figure 19: DOR vs. Time Stratified by AUC Exposure Quartiles



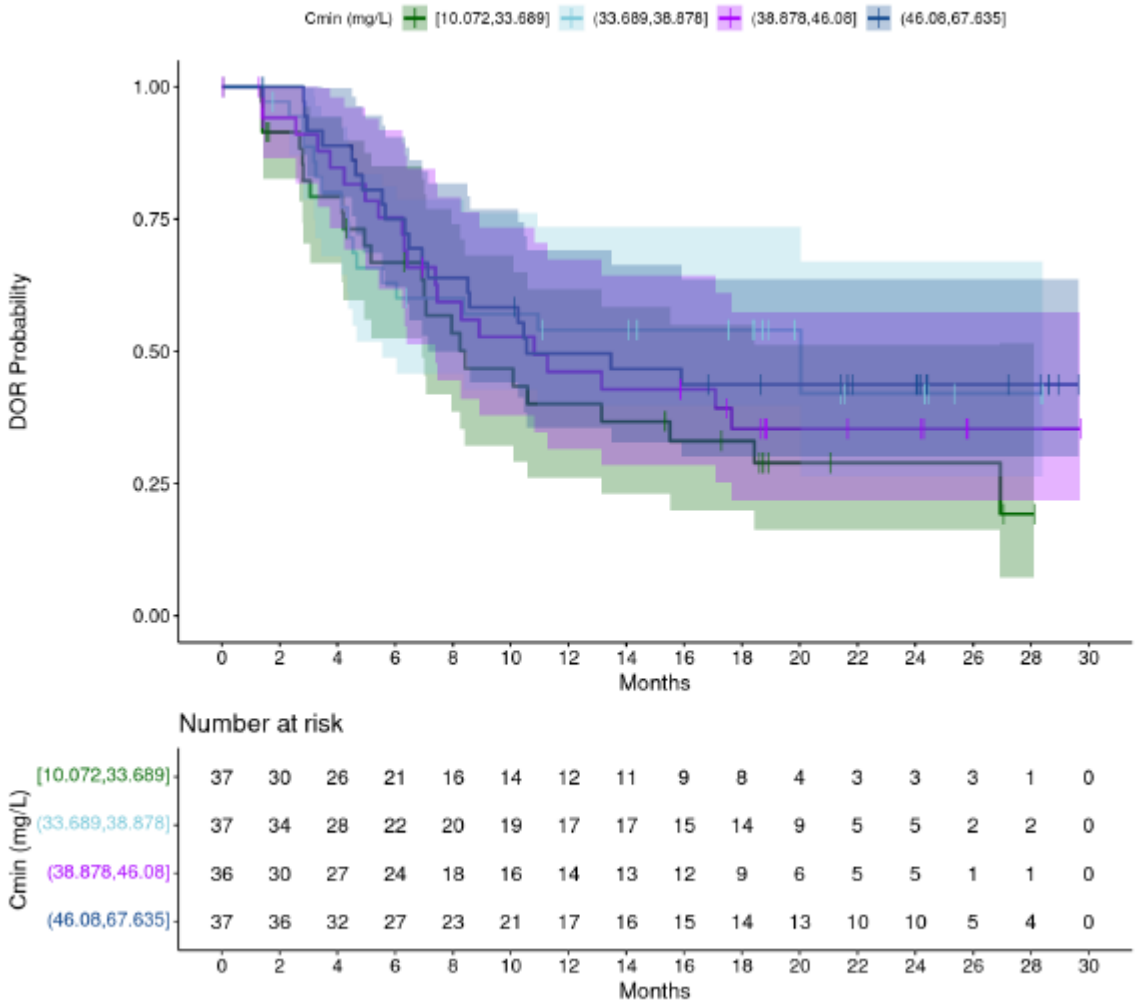
Lines: Duration of response probability; **Vertical lines:** censoring; **Shaded area:** 95% confidence interval; **AUC:** Area under the curve during the first 21 days.

Figure 20: DOR vs. Time Stratified by Cmax Exposure Quartiles



Lines: Duration of response probability; **Vertical lines:** censoring; **Shaded area:** 95% confidence interval; C_{max}: Maximum concentration during the first 21 days.

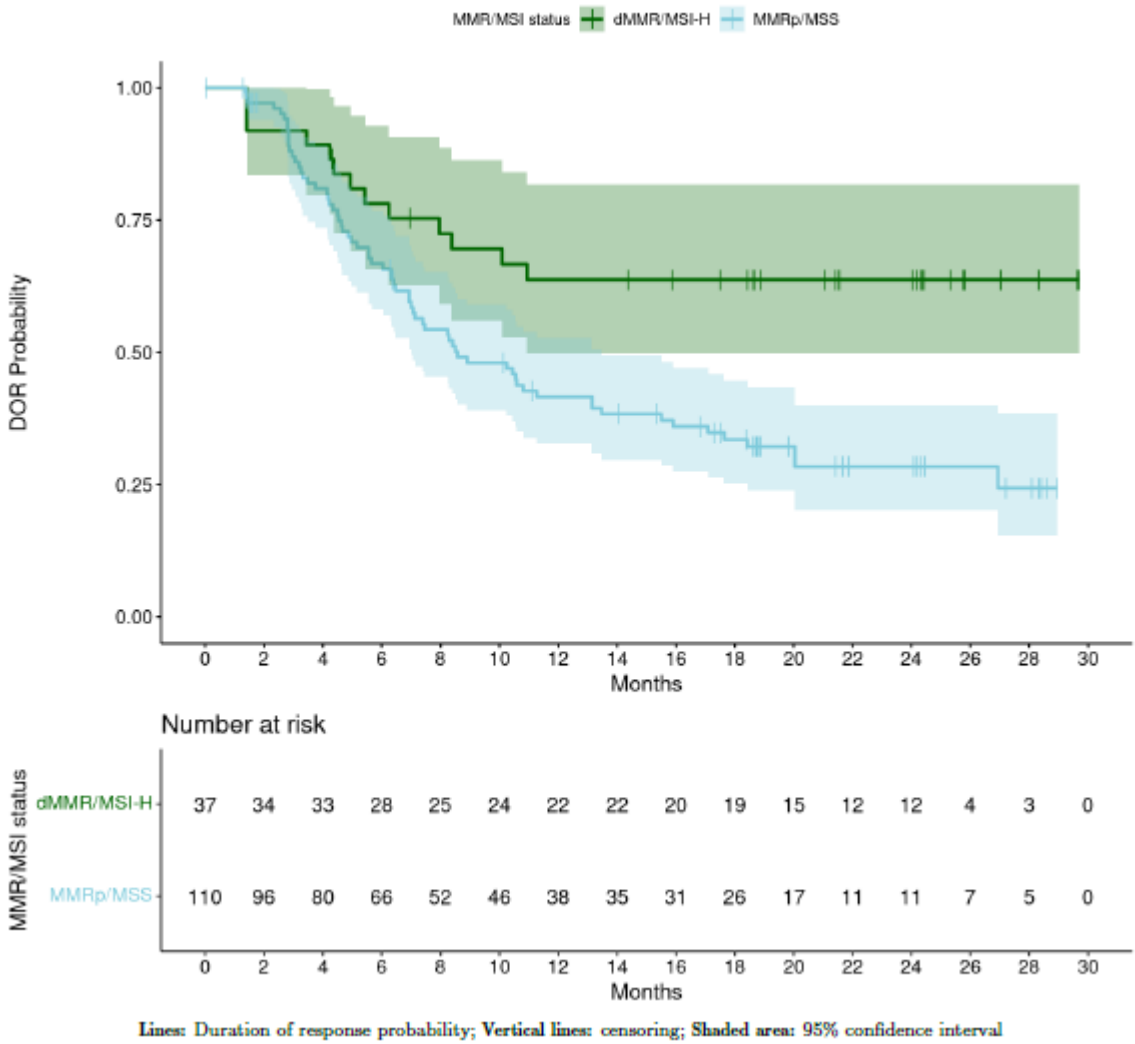
Figure 21: DOR vs. Time Stratified by Cmin Exposure Quartiles



Lines: Duration of response probability; **Vertical lines:** censoring; **Shaded area:** 95% confidence interval; C_{min}: Minimum concentration at Day 21.

Disease status in EC, prior external pelvic radiotherapy, baseline ECOG performance and histology showed no apparent relationship with DOR probability (Figure 23 - Figure 24). Patients in North America and Western Europe appear to have higher probability of DOR compared to Eastern European patients. A large difference in DOR was observed between dMMR/MSI-H and MMRp/MSS patients (Figure 22). DOR appeared to be independent of AUC, Cmax and Cmin in these patient groups**.**

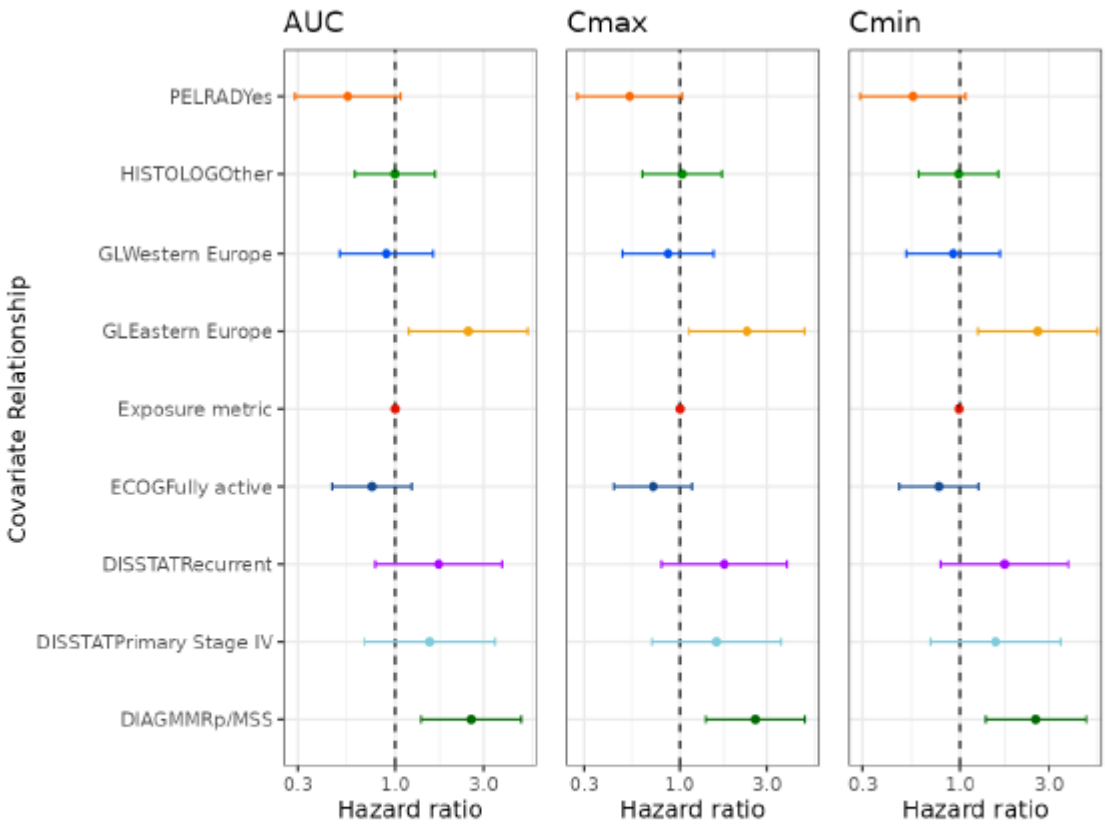
Figure 22: DOR vs. Time Stratified by Tumour Diagnosis



Lines: Duration of response probability; **Vertical lines:** censoring; **Shaded area:** 95% confidence interval

The hazards for DOR for the different covariates were proportional. Hence Cox (proportional hazards) regression was performed without stratification for the three exposure metrics (AUC, Cmax and Cmin) with the additional 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 DOR ($\alpha = 0.05$) with p-values of 0.69, 0.45 and 0.32 for AUC, Cmax and Cmin, respectively. The hazard ratios of the tested covariates can be seen in Figure 23 and Table 29. The 95% CI of geographic location, Eastern Europe, does not include 1 when tested with the exposure metrics AUC, Cmax and Cmin. The 95% CI for geographic location, Eastern Europe, were 1.187-5.162, 1.125-4.822, 1.251-5.466 for AUC, Cmax and Cmin, respectively. The 95% CI of tumour diagnosis does not include 1 when tested with the exposure metrics AUC, Cmax and Cmin. The 95% CI for tumour diagnosis, DIAGMMRp/MSS, were 1.375-4.784, 1.383-4.844, 1.37-4.748 for AUC, Cmax and Cmin, respectively. While the 95% CI for the other tested covariates include 1.

Figure 23: Hazard Ratio Multivariate Analysis, DOR



Circle: Hazard ratio; **Lines:** 95% confidence interval; PELRAD - Prior external pelvic radiotherapy (reference No); HISTOLOG - Histology (reference EC); GL - Geographic location (reference North America); ECOG - Baseline ECOG performance (reference Ambulatory); 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; C_{max}: Maximum concentration during the first 21 days; C_{min}: Minimum concentration at Day 21.

Table 27: Hazard Ratios DOR Analysis (AUC, Cmax, Cmin)

Table A.14.1: Hazard Ratio Multivariate DOR Analysis, AUC

Covariate	Hazard Ratio	95% CI of Hazard Ratio	p-value
Exposure metric	1.00	1-1	0.69
DIAGMMRp/MSS	2.56	1.375-4.784	0.00
DISSTATPrimary Stage IV	1.53	0.6866-3.432	0.30
DISSTATRecurrent	1.72	0.7813-3.775	0.18
PELRADYes	0.56	0.2894-1.066	0.08
ECOGFully active	0.75	0.46-1.229	0.26
GLEastern Europe	2.48	1.187-5.162	0.02
GLWestern Europe	0.90	0.5024-1.598	0.71
HISTOLOGOther	1.00	0.6071-1.635	0.99

PELRAD - Prior external pelvic radiotherapy (reference No); HISTOLOG - Histology (reference EC); 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 A.14.2: Hazard Ratio Multivariate DOR Analysis, C_{max}

Covariate	Hazard Ratio	95% CI of Hazard Ratio	p-value
Exposure metric	1.00	0.9946-1.012	0.45
DIAGMMRp/MSS	2.59	1.383-4.844	0.00
DISSTATPrimary Stage IV	1.59	0.7057-3.566	0.26
DISSTATRecurrent	1.75	0.7926-3.864	0.17
PELRADYes	0.53	0.2762-1.027	0.06
ECOGFully active	0.72	0.4372-1.17	0.18
GLEastern Europe	2.33	1.125-4.822	0.02
GLWestern Europe	0.86	0.4856-1.533	0.61
HISTOLOGOther	1.03	0.6236-1.694	0.91

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

Table A.14.3: Hazard Ratio Multivariate DOR Analysis, C_{min}

Covariate	Hazard Ratio	95% CI of Hazard Ratio	p-value
Exposure metric	0.99	0.965-1.012	0.32
DIAGMMRp/MSS	2.55	1.37-4.748	0.00
DISSTATPrimary Stage IV	1.55	0.6923-3.465	0.29
DISSTATRecurrent	1.73	0.788-3.801	0.17
PELRADYes	0.56	0.2909-1.068	0.08
ECOGFully active	0.77	0.4727-1.259	0.30
GLEastern Europe	2.62	1.251-5.466	0.01
GLWestern Europe	0.92	0.5147-1.64	0.77
HISTOLOGOther	0.98	0.6007-1.608	0.95

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

- ***Overall survival***

OS was only explored using exploratory plots, and no formal analysis was performed as data was deemed immature (33% maturity in ITT population). Kaplan-Meier plots stratified by quartiles of exposure show a high degree of overlap.

Exposure-safety analysis

Patients from both arm 1 (SoC + dostarlimab) and arm 2 (SoC + Placebo) were included in the AE analysis.

Safety Variables

Safety variables were analyzed for all patients participating in Study 4010-03-001. The analysis included safety variables that were the top five occurring drug related AEs as assessed by investigators: arthralgia, diarrhoea, fatigue, nausea, and rash. A summary of the occurrence of these events is shown in Table 30. A summary of covariates for the placebo arm is shown in Table 31. 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 28: Summary of AEs

Adverse Event	Period	Total Number of Patients	Number of Patients With an AE	Percentage of Patients With an AE
Arthralgia	All cycles	478	87	18.2 %
Arthralgia	Cycle 1-6	478	64	13.4 %
Arthralgia	Cycle 7 and beyond	478	33	6.9 %
Diarrhoea	All cycles	478	80	16.7 %
Diarrhoea	Cycle 1-6	478	73	15.3 %
Diarrhoea	Cycle 7 and beyond	478	17	3.6 %
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	64	13.4 %
Rash	Cycle 1-6	478	53	11.1 %
Rash	Cycle 7 and beyond	478	16	3.3 %

AE: adverse event.

Table 29: Summary of Covariates for Placebo Patients

Covariate	Level	Count
ADBAS	Missing	246
ANBAS	Missing	246
DIAG	dMMR/MSI-H	65
	MMRp/MSS	181
DISSTAT	Primary Stage III	44
	Primary Stage IV	83
	Recurrent	119
DMMR	No	183
	Yes	63
ECOG	Ambulatory	86
	Fully active	160
GL	Eastern Europe	14
	North America	186
	Western Europe	46
HISTOLOG	EC	111
	Other	135
PDL1CAT	Negative	36
	Positive	91
	Unknown	119
PELRAD	No	201
	Yes	45

ADBAS: Anti drug antibody status; **ANBAS:** Neutralizing antibody status; **DIAG:** Tumor Diagnosis; **DISSTAT:** Disease status in EC; **dMMR:** deficient mismatch repair; **MSI-H:** microsatellite instability high; **MSS:** microsatellite stable; **MMRp:** mismatch repair proficient; **ECOG:** Baseline ECOG performance; **GL:** Geographic location; **HISTOLOG:** Histology; **PDL1CAT:** Combined positive score category at baseline; **PELRAD:** Prior external pelvic radiotherapy. Only two of the placebo patients in the tumor diagnosis category dMMR/MSI-H were not dMMR.

The exposure-safety analysis was performed based on the following 3 periods:

- Cycles 1 through 6, which gives a comparison of dostarlimab plus chemotherapy versus standard-of-care chemotherapy;
- Cycle 7 and beyond, which gives a comparison of dostarlimab versus placebo; and
- All cycles, which takes all above components into account.

Model Development

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

As for efficacy, 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.

Cycle 1 exposure (AUC, Cmax and Cmin) were used to represent an early exposure given it is expected that the first AE occur early rather than late following dostarlimab administration. This was valid for the 3 different periods that were analyzed.

Results

A summary of the exposure metrics for the patients included in the exposure-response analysis of safety are shown in Table 32.

Table 30: Summary of Predicted Cycle 1 Cmin, Cmax, and AUC for Dostarlimab Treated Patients in the Safety Analysis

Metric	Minimum	p10	p90	Maximum	Mean	SD
C_{min} (mg/L)	10.10	27.80	53.70	67.60	39.70	9.94
C_{max} (mg/L)	73.40	116.00	183.00	246.00	147.00	26.40
AUC (mg*h/L)	13300.00	25200.00	40100.00	48800.00	32300.00	5850.00

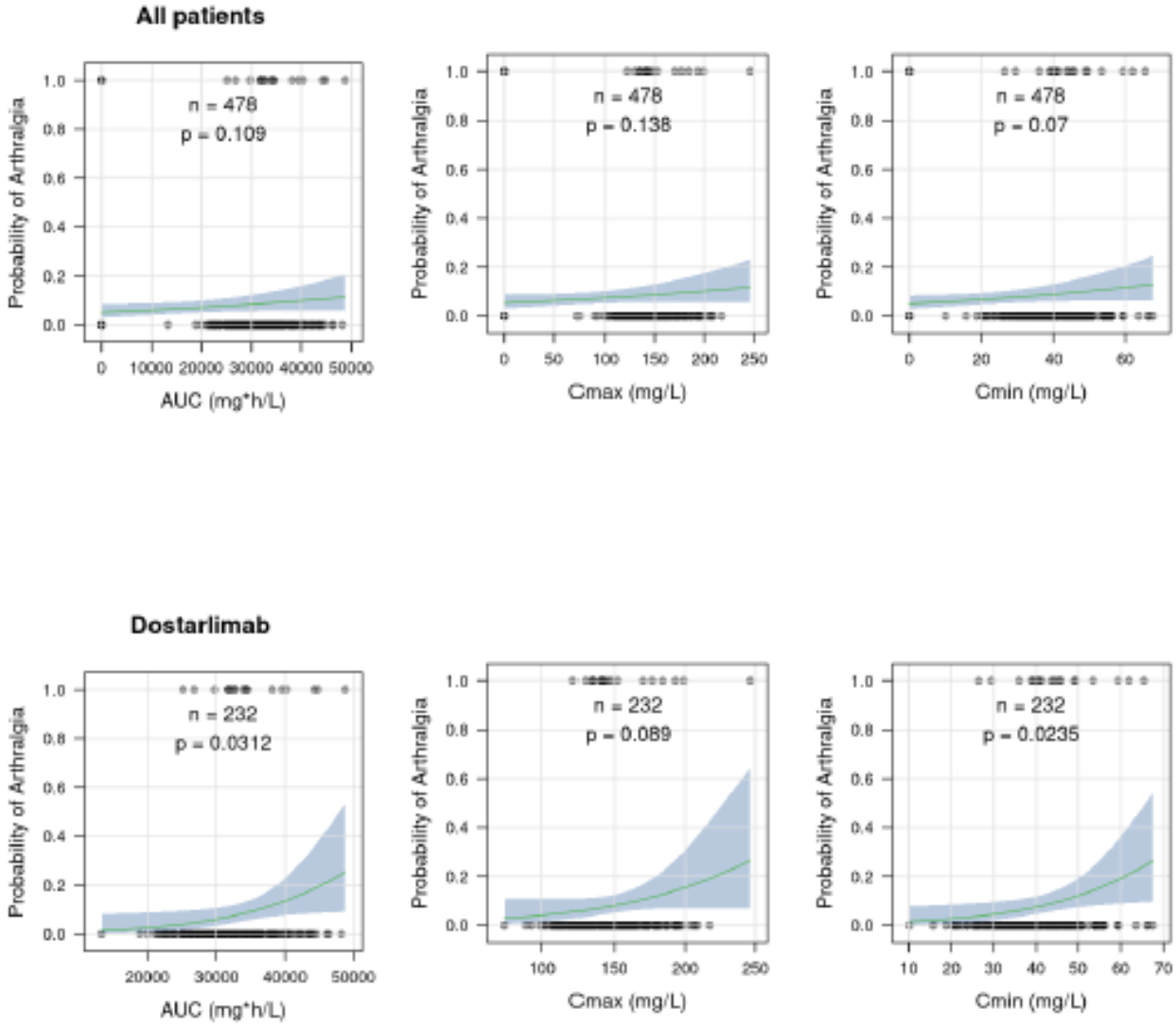
AUC: Area under the curve during the first 21 days; C_{max}: Maximum concentration during the first 21 days; C_{min}: Minimum concentration at Day 21; **P10**: 10^{th} percentile; **P90**: 90^{th} percentile.

Univariate Analysis

Binary data for the five most prevalent drug related AEs as assessed by investigators (arthralgia, diarrhoea, fatigue, nausea and rash) from 478 patients (232 in the dostarlimab arm, 246 in the placebo arm) of study 4010-03-001 were analyzed using univariate logistic regression. The explanatory variables were AUC, Cmax and Cmin during the first 3 weeks after the first dose (i.e 21 days). The analysis was divided into three different time periods, cycle 1-6, cycle 7 and beyond and all cycles. The analysis was also performed for the dostarlimab treated subjects alone.

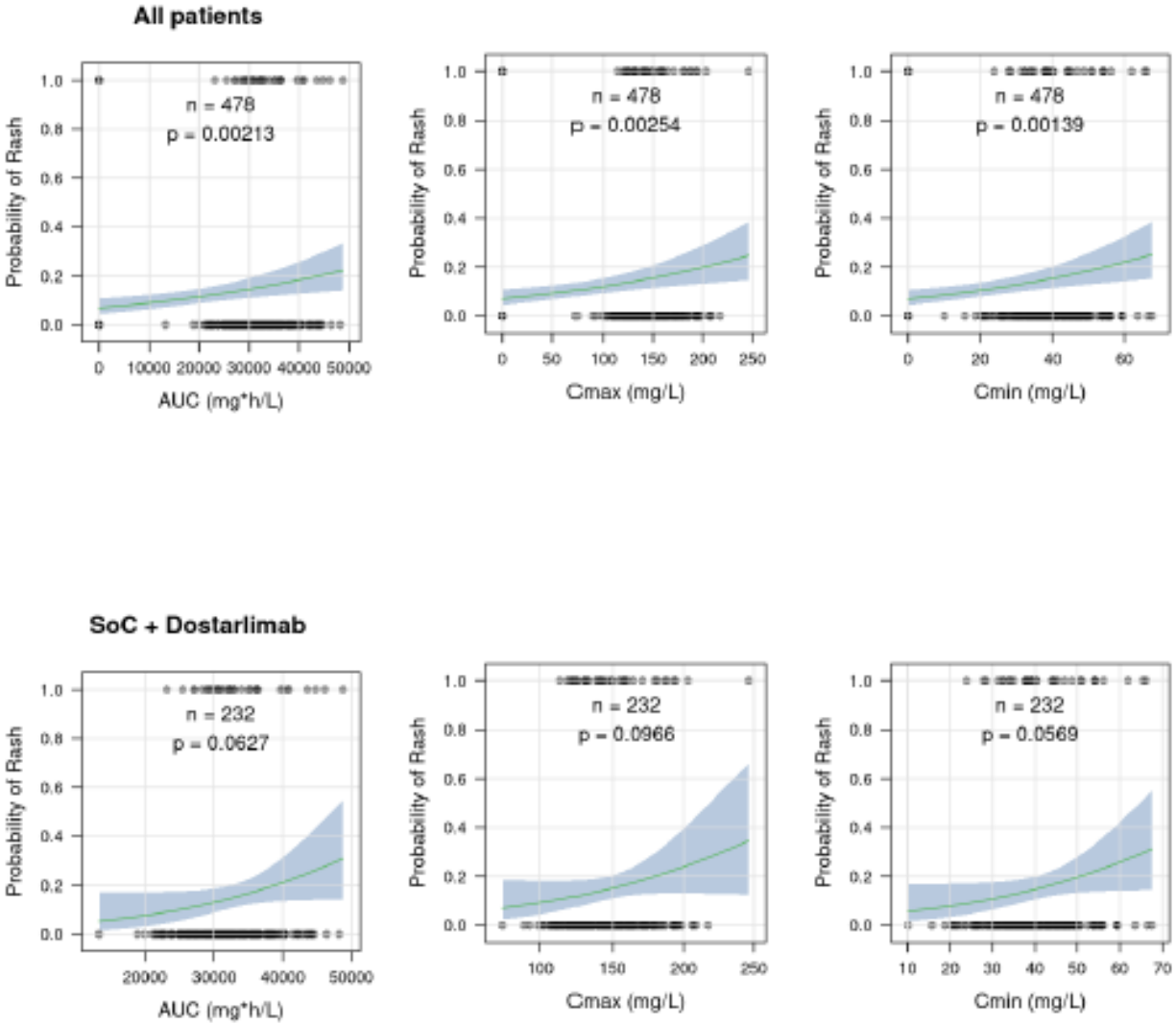
When all patients were included, significant ER relationships for rash was seen for all exposure metrics (AUC, Cmax and Cmin) in all periods. However, when placebo subjects were excluded the ER relationships were no longer significant. No exposure response relationships were detected for arthralgia when all patients were included. However, excluding the placebo arm gives significant exposure response relationships for AUC and Cmin in the period cycle 7 and beyond. No other significant relationships were seen for any of the other AEs in any of the tested time periods.

Figure 24: Arthralgia vs Exposure Metrics Cycle 7 and Beyond



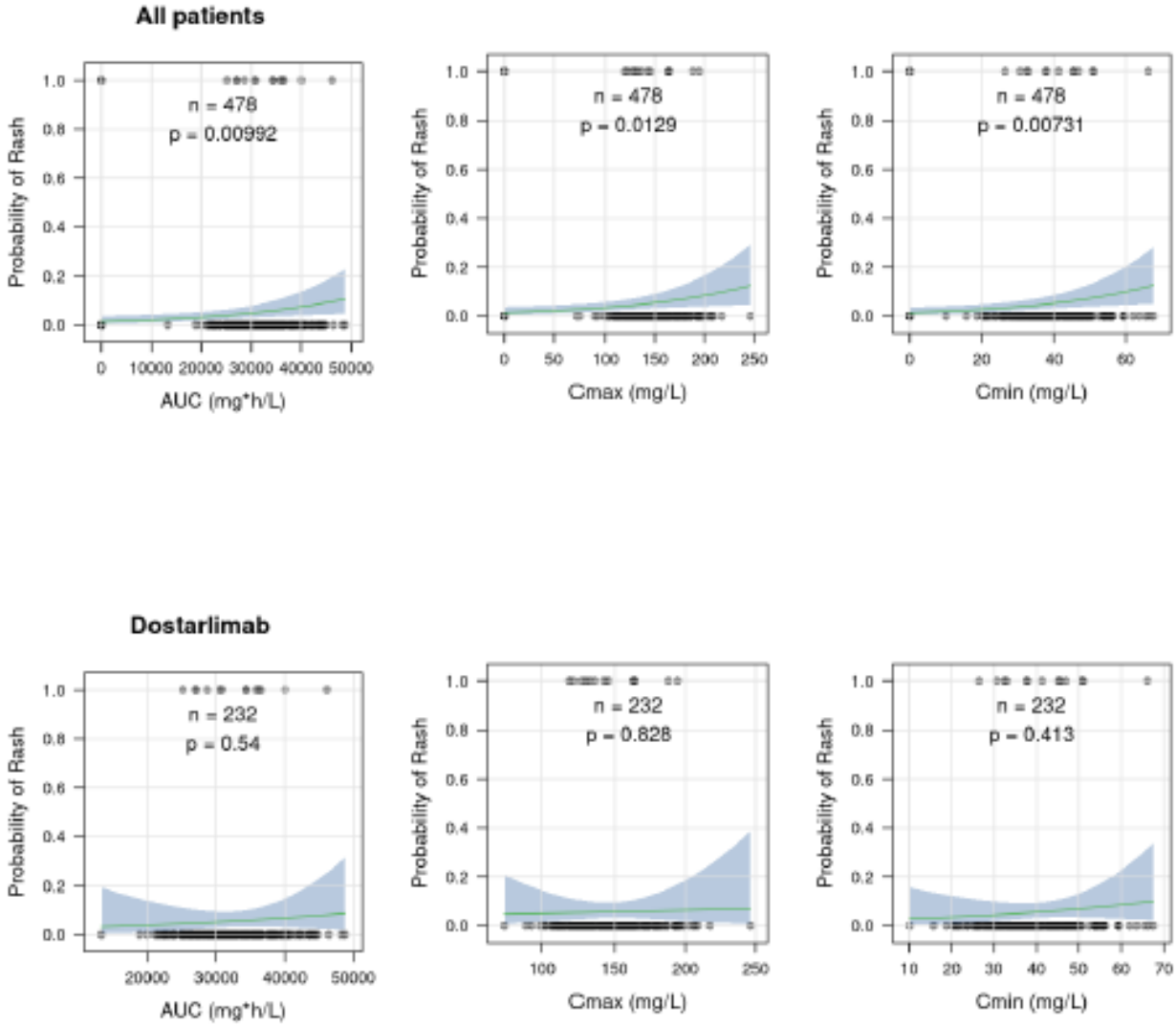
Line: Predicted probability; **Shaded area**: 95% confidence interval; **Circles**: Data; **AUC**: Area under the curve during the first 21 days; C_{max}: Maximum concentration during the first 21 days; C_{min}: Minimum concentration at Day 21.

Figure 25: Rash vs Exposure Metrics Cycle 1-6



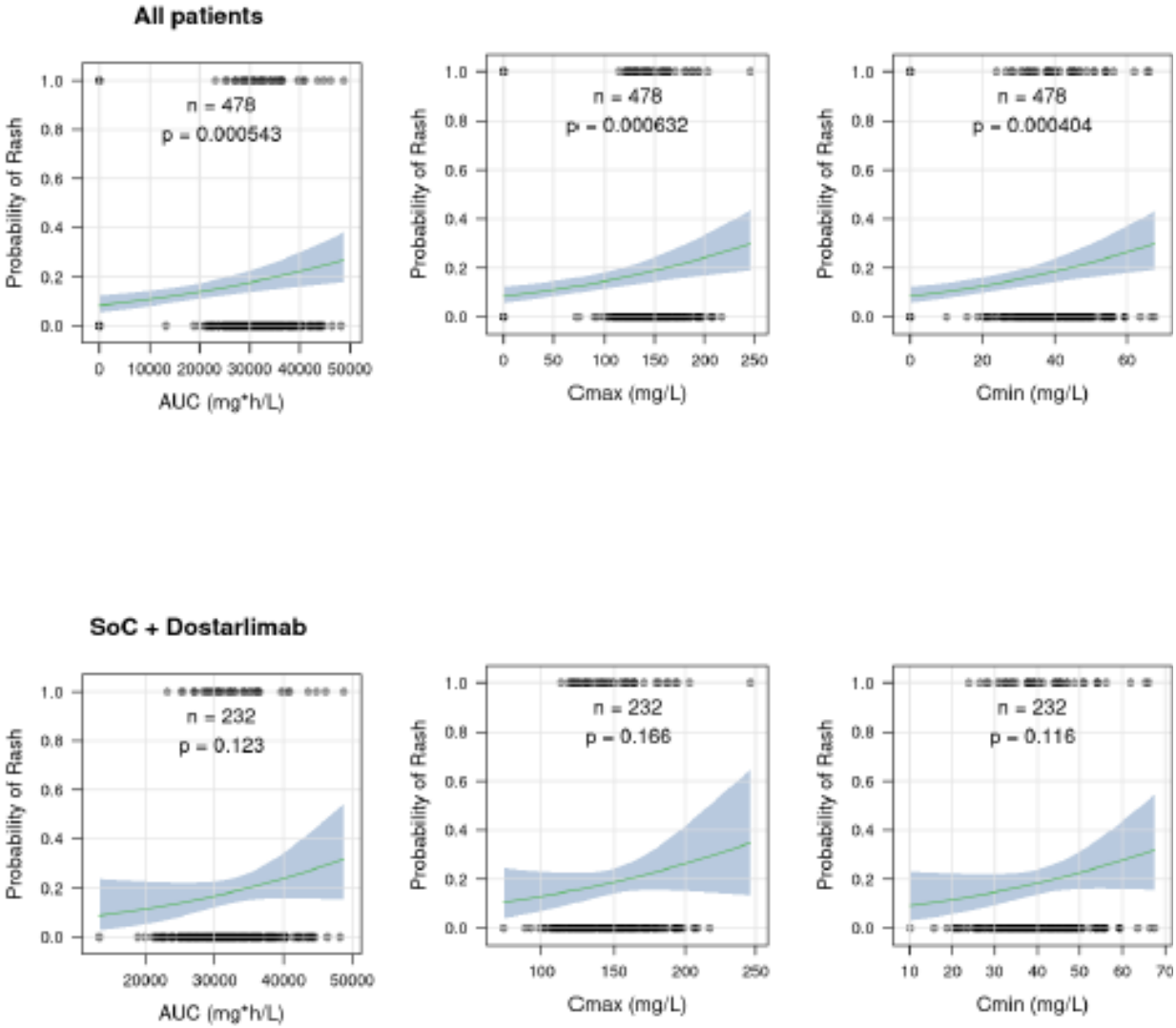
Line: Predicted probability; **Shaded area**: 95% confidence interval; **Circles**: Data; **AUC**: Area under the curve during the first 21 days; C_{max}: Maximum concentration during the first 21 days; C_{min}: Minimum concentration at Day 21.

Figure 26: 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; C_{max}: Maximum concentration during the first 21 days; C_{min}: Minimum concentration at Day 21.

Figure 27: Rash vs Exposure Metrics All Cycles

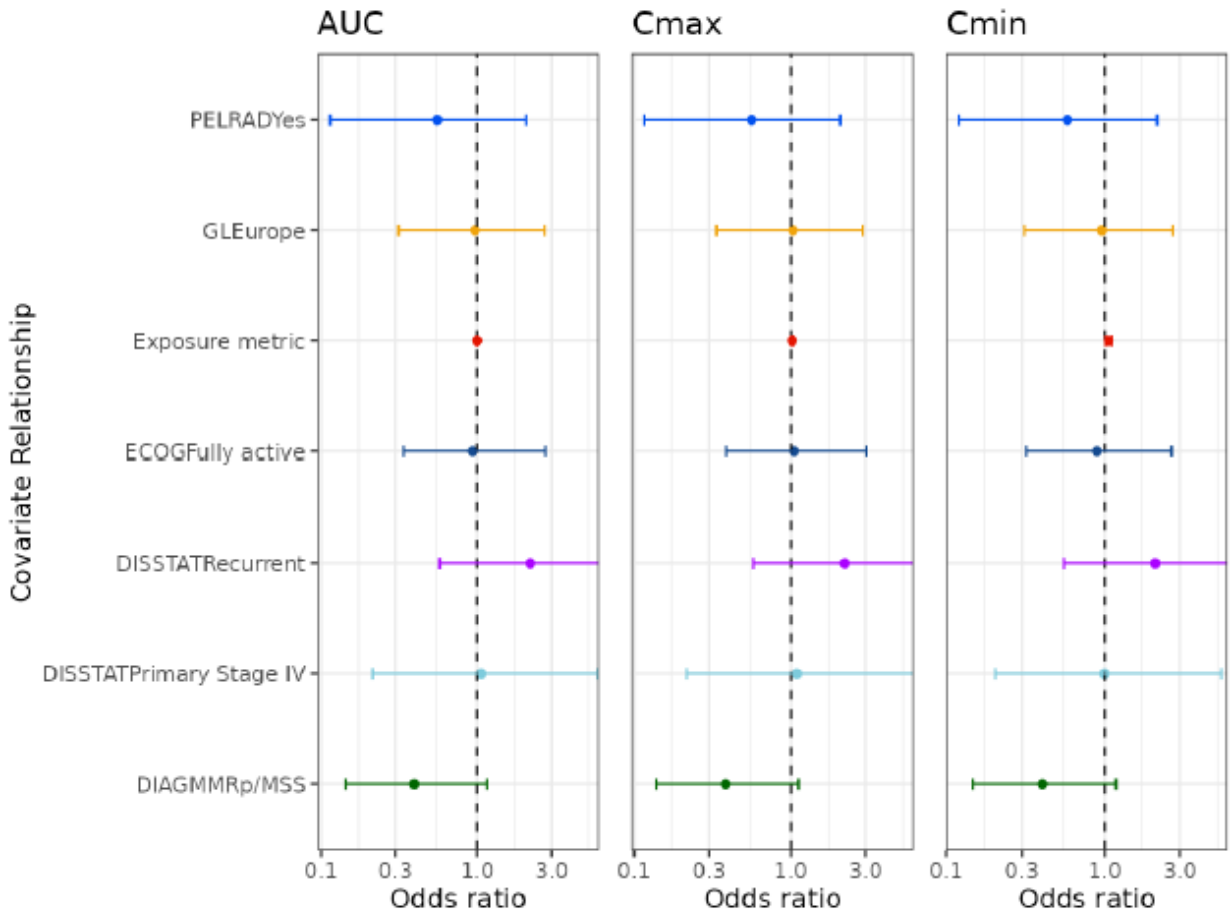


Line: Predicted probability; **Shaded area**: 95% confidence interval; **Circles**: Data; **AUC**: Area under the curve during the first 21 days; C_{max}: Maximum concentration during the first 21 days; C_{min}: Minimum concentration at Day 21.

Multivariate Analysis

Multivariate logistic regression was performed for the AEs 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, histology and geographic location were investigated. The odds ratios of the tested covariates for arthralgia in the period cycle 7 and beyond for dostarlimab treated patients can be seen in Figure 28. No significant relationships other than AUC and Cmin were found.

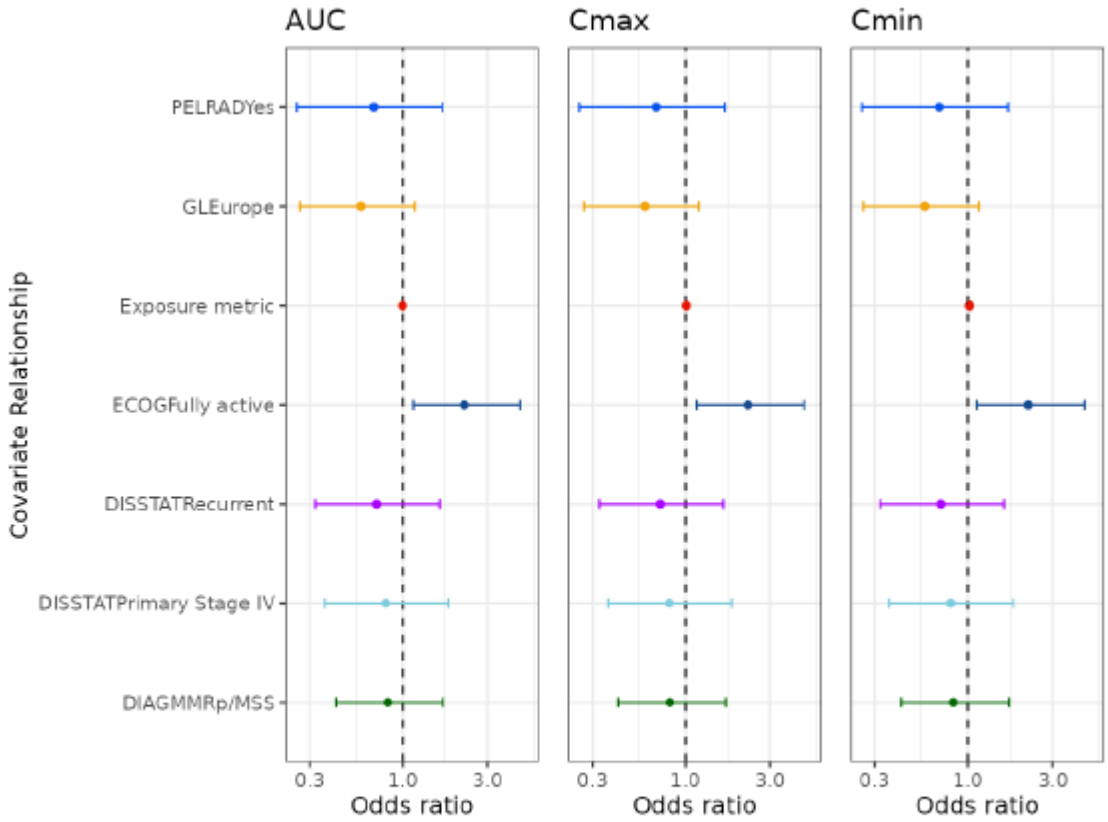
Figure 28: Odds Ratio Multivariate Analysis, Arthralgia, Cycle 7 and Beyond, Dostarlimab Treated



Circles: Odds ratio; **Lines:** 95% confidence interval; PELRAD - Prior external pelvic radiotherapy (reference No); GL - Geographic ocation (reference North America); ECOG - Baseline ECOG performance (reference Ambulatory); 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; C_{max}: Maximum concentration during the first 21 days; C_{min}: Minimum concentration at Day 21.

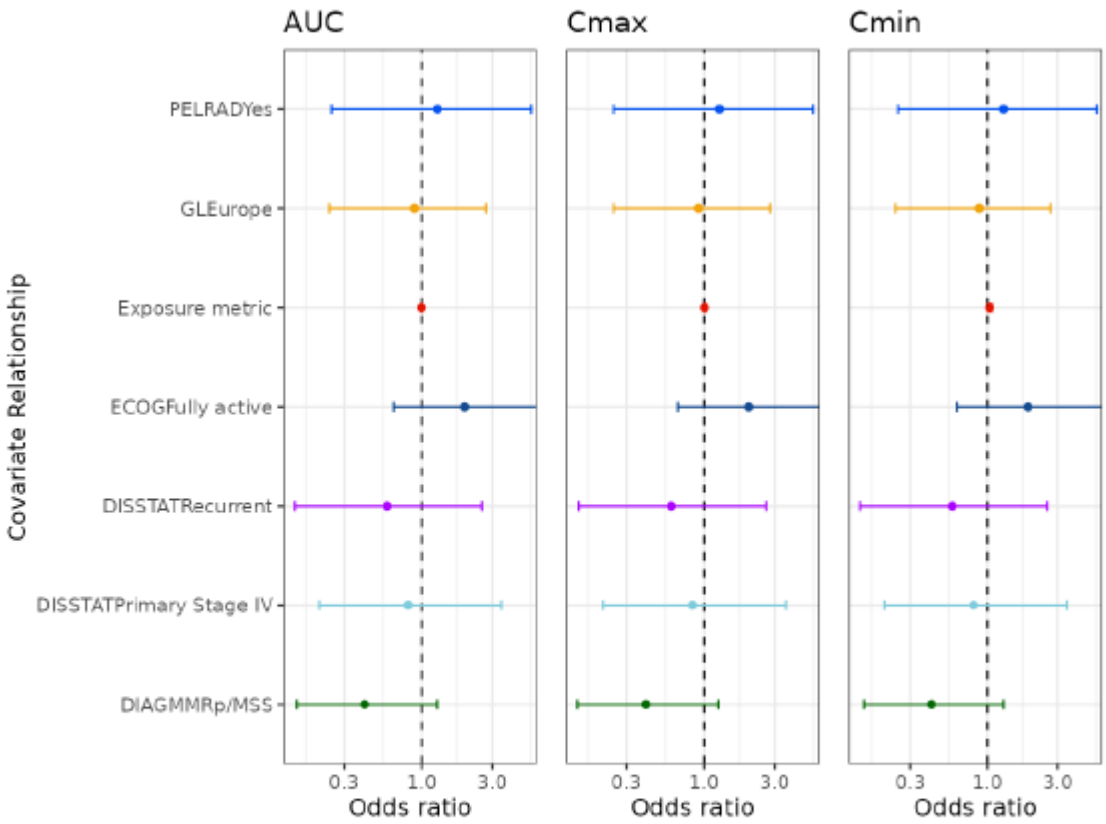
The odds ratios of the tested covariates for Rash for all patients in period cycle 1-6, cycle 7 and beyond and all cycles can be seen in Figure 29 - Figure 31. All three exposure metrics were significant in all periods. In addition, ECOG status, Fully active, have higher risk of Rash compared to, Ambulatory, in the time periods cycle 1-6 and all cycles under all exposure metrics.

Figure 29: Odds Ratio Multivariate Analysis, Rash, Cycle 1-6, All Patients



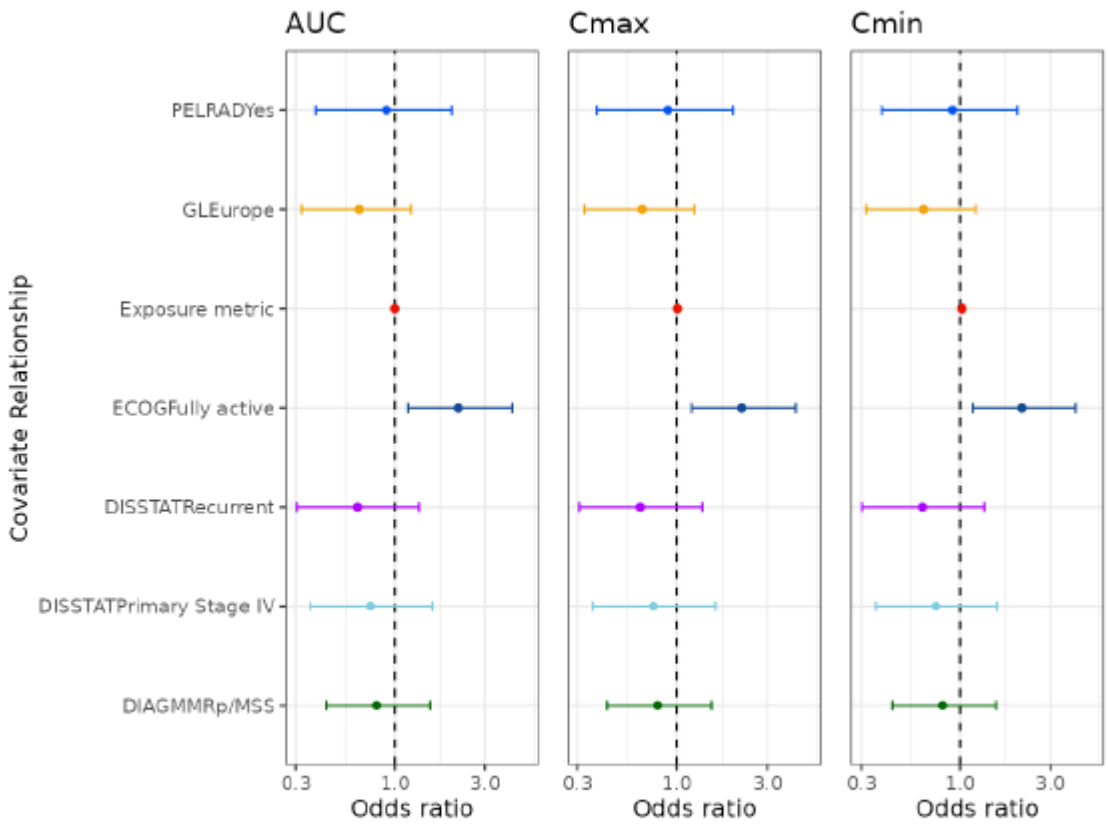
Circles: Odds ratio; **Lines:** 95% confidence interval; PELRAD - Prior external pelvic radiotherapy (reference No); GL - Geographic location (reference North America); ECOG - Baseline ECOG performance (reference Ambulatory); DISSTAT - Disease status in EC (reference Primary Stage III); DIAG - Tumor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

Figure 30: 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); 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; C_{max}: Maximum concentration during the first 21 days; C_{min}: Minimum concentration at Day 21.

Figure 31: 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); 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; C_{max}: Maximum concentration during the first 21 days; C_{min}: Minimum concentration at Day 21.

Table 33 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 in gives an increase in the probability of arthralgia by 14.2 and 15.5 % for AUC and Cmin respectively. The probability increase for Rash was between 5.2 and 10 % depending on exposure metric and time period.

Table 31: Probability Increase for Exposure Metrics 90th vs 10th Percentile

AE	Period	Subset	Exposure	P 10th perc (%)	P 90th perc (%)	Increase P (%)
Arthralgia	Cycle 7 and beyond	Dostarlimab treated	AUC	5.3	19.5	14.2
Arthralgia	Cycle 7 and beyond	Dostarlimab treated	C_{min}	5.5	21	15.5
Rash	Cycle 1-6	All patients	AUC	13.1	18.9	5.8
Rash	Cycle 7 and beyond	All patients	AUC	6.1	11.6	5.5
Rash	All cycles	All patients	AUC	16.8	24	7.2
Rash	Cycle 1-6	All patients	C_{max}	13.1	18.7	5.6
Rash	Cycle 7 and beyond	All patients	C_{max}	6	11.2	5.2
Rash	All cycles	All patients	C_{max}	16.7	23.8	7.1
Rash	Cycle 1-6	All patients	C_{min}	12.4	20.4	8
Rash	Cycle 7 and beyond	All patients	C_{min}	5.5	12.9	7.4
Rash	All cycles	All patients	C_{min}	15.7	25.7	10

AE: Adverse Event; **AUC**: Area under the curve during the first 21 days; C_{max}: Maximum concentration during the first 21 days; C_{min}: Minimum concentration at Day 21; **Perc**: Percentile; **P**: Probability.

Immunogenicity

Dostarlimab immunogenicity was studied in participants with primary advanced or recurrent EC enrolled in the GARNET and RUBY studies. The immunogenicity results presented here are from the 01 March 2020 data cutoff for the GARNET study and the 08 August 2022 data cutoff for the RUBY study.

Study 213346 (GARNET)

In the GARNET study data, 418 of 549 overall enrolled participants were evaluable for treatment-emergent ADAs. Of these, 384 participants were dosed in Part 2B with dostarlimab monotherapy at the recommended therapeutic dose regimen, contributed at least 1 evaluable predose immunogenicity pair, and were included in the PK immunogenicity analysis. The incidence of treatment-emergent positive ADA samples was low and comparable to that of other anti-PD-1 antibodies. The overall incidence of treatment-emergent ADAs was 2.1%, with 1.0% being NAb positive. The development of ADAs was not found to have a significant effect on dostarlimab PK, and ADA/Nab status did not affect clinical efficacy or safety. The overall immunogenicity risk for dostarlimab was determined to be low (see Jemperli EPAR).

Study 213361 (RUBY)

Overall, none of the 225 participants in the ADA Analysis Set had treatment-induced or treatment-boosted ADAs, for an overall incidence of treatment-emergent ADAs of 0.0%.

Thirty-four participants (15.1%) had treatment-unaffected ADAs (i.e., pre-existing reactive antibodies to dostarlimab at baseline with no meaningful increase in titer postdose). One hundred eighty-five participants (82.2%) were classified as ADA-negative, and 6 participants (2.7%) were classified as inconclusive with respect to treatment-emergent ADAs.

Seventeen of the 34 participants (50.0%) who were categorized as having treatment-unaffected ADAs, were positive for NAb at any time during the study; these participants were all NAb-positive at baseline, with 1 participant also NAb-positive at Cycle 2. None of the participants who were classified as inconclusive had positive Nab results during the study.

Observed serum dostarlimab concentrations were similar in participants with ADA-positive-samples at baseline (treatment-unaffected ADA) and those who were negative for ADAs at all time points indicating no impact of pre-existing ADAs on the PK of dostarlimab. Based on updated population PK analysis, the development of ADAs was also not found to have a significant effect on dostarlimab CL.

The efficacy and safety results were similar between participants with treatment-unaffected ADA and participants who tested negative at all time points. Furthermore, at this point in time, there is no evidence of a clinically meaningful impact of pre-existing ADAs or NAbs on any safety or efficacy measures.

Table 32: Incidence of subjects with and without treatment-emergent ADAs postbaseline (ADA population)

		Participants with Treatment-Emergent ADA [a]		Participants with Treatment-Unaffected ADA [b]		Participants Negative for ADA [b]		Participants with Inconclusive ADA Status [b]	
Population	N	n	%	n	%	n	%	n	%
Overall Population	225	0	0.0	34	15.1	185	82.2	6	2.7
dMMR/MSI-H	50	0	0.0	8	16.0	41	82.0	1	2.0
MMRp/MSS	175	0	0.0	26	14.9	144	82.3	5	2.9

Abbreviations: ADA=antidrug antibody; MMR=mismatch repair.

[a] Treatment-induced or -boosted

[b] Using drug tolerance limit of 250 µg/mL

Table 33: Subjects with positive neutralising antibodies results by ADA response (ADA population)

	Participants with Treatment-Emergent ADA [a] (N=0)		Participants with Treatment-Unaffected ADA [b] (N= 34)		Participants with Inconclusive ADA Status [b] (N=6) [c]	
	n	%	n	%	n	%
Positive for NAb	0	0.0	17	50.0	-	-
Negative for NAb	0	0.0	17	50.0	1	16.7

Abbreviations: ADA=antidrug antibody; NAb=neutralizing antibody.

[a] Treatment-induced and treatment-boosted;

[b] Using drug tolerance limit of 250 µg/mL;

[c] Subjects with inconclusive ADA status may not have had any positive ADA results and, therefore, may not have been tested for NAb.

2.3.4. Discussion on clinical pharmacology

The clinical pharmacology update includes previously submitted pharmacokinetic data from the GARNET study (cutoff date 1st of November 2021) and new data from the RUBY study (cutoff date 8th of August 2022), an update of the previous population PK analysis, an exposure-response analysis and an immunogenicity evaluation update.

Dostarlimab in combination with carboplatin and paclitaxel for the treatment of adult patients with dMMR/MSI-H primary advanced or recurrent EC and who are candidates for systemic therapy is being evaluated in the ongoing pivotal phase 3 study 213361 (RUBY).

During the procedure, the MAH confirmed that the percentage of QCs with respect to the total number of samples analysed was sufficient.

Reasons for sample reassay and reported concentrations were listed in the report but were initially not described. This information was provided later on during the procedure. In addition, a previously validated dilution factor was used for samples above the limit of quantitation.

During the procedure, the MAH confirmed that all study samples were analysed within the proven stability period. Currently, long term stability has been established up to 1780 days. Freeze-thaw stability has been established up to 10 cycles.

The bioanalytical methods used for RUBY study were the same as the ones used for the GARNET study, which were found acceptable in previous regulatory procedures. Overall, the determination of dostarlimab in human serum for RUBY study samples was satisfactorily carried out in accordance with the principles of ICH M10 Guideline.

Immunogenicity studies for the determination of ADAs and Nabs were conducted according to the state of the art.

After excluding 1060 (13.2%) BLQ observation (842 collected prior to first dose), the final dataset for the current Population PK model included data from both GARNET and RUBY studies, 8032 observation records from 869 patients, 233 patients treated with the combination treatment and 636 patients receiving the monotherapy. Additionally 75 observations were removed due to high CWRES or visual inspection.

A population PK analysis was previously performed based on data from the GARNET study (cutoff date 1st of March 2020). Dostarlimab PK was described using a 2-compartment model with linear and time

dependency in clearance and estimated allometric exponents for body weight on Cl and volume parameters (Vc and Vp).

The modelling strategy encompasses, firstly, the external evaluation of a previously developed population PK model with data from RUBY study. Subsequently, the population PK model was refined through a re-analysis of covariate effects with all data available. Overall, the strategy is endorsed because it first evaluates the adequacy of a previously developed population PK model, suggesting similar PK behaviour of dostarlimab in RUBY study. Similarly, as more experimental evidence has been collected, further refinement in the identification and estimation of covariate effects would enrich model predictions.

The current population PK model development of dostarlimab includes the re-use of the previously developed model to characterize the PK of dostarlimab in subjects with dMMR/MSI-H primary advanced or recurrent EC treated with the combination therapy. Based on pcVPC and GOF plots, no major deviations at the structural and individual level were observed when the previous population PK model was applied to RUBY data. Then, the previous model was used as the new base model. Subsequently, additional changes were introduced and covariate search using SCM method was carried out.

The final PK model contains 9 covariates effects including WT on CL and Vp and Vc, included in the base model using the principles of allometry and age, time-varying ALB, ALT, combination therapy, sex on CL and time varying ALB and sex on Vc, included using the SCM method. The final parameter estimates of the final model are adequate based on the RSE, which is <40%. Shrinkage values were 14.1%, 12.7% and 46.3 % for CL, Vc and Imax respectively. Low-to-moderate inter-individual variability has been characterized on CL (23.7%) and VC (16.7%), as a consequence of the 9 covariate effects included in the final population PK model. However, high inter-individual variability on Imax (95%) was obtained. Different patient related time-varying covariates (albumin (ALB), creatinine clearance, alanine aminotransferase (ALT), bilirubin, and lymphocyte count) and previously responder versus non-responder status have been investigated on Imax during the SCM step. However, only time-varying albumin was found to be statistically significant. The clinical relevance of including time-varying albumin is negligible in terms of parameter estimate (2%) and inter-individual variability reduction (3%). In terms of model parsimony, the submitted final covariate model is adequate.

Standard GOF and pcVPC plots suggest no relevant model deviations either for the combination therapy of the monotherapy, showing the adequacy of the final population PK model to describe the observed data.

A forest plot has been provided to assess the clinical relevance of the covariates selected based on the change on the PK exposure parameters (AUC, Cmax and Cmin) at steady state. Forest plot has also been provided to evaluate the predicted changes in exposure at cycle 1.

The clinical relevance analysis at steady-state did not identify changes in exposure greater than 20%, except for low levels of albumin (below 29 g/L) and high body weight (>116 kg). To support the appropriateness of the current dose regimen, simulations have been performed to predict dostarlimab Cmin concentration at cycle 1 and at steady state by WT and Albumin category. The results showed that most of the patients achieved values greater than 18 mg/L (concentration estimated for maintenance of 90% of maximal peripheral PD-1 suppression).

No differences in exposure are expected in patients with mild and moderate renal impairment vs patients with normal renal function, based on the predicted exposure (Cmax and AUC) levels with the proposed dosing regimen. Similarly, no differences in exposure are expected in patients with mild hepatic impairment vs patients with normal hepatic function with the proposed dosing regimen. These results were expected since no statistically significant covariates related to renal or hepatic function were associated to any PK parameter.

No interaction studies have been performed. Monoclonal antibodies (mAb) such as dostarlimab are not substrates for cytochrome P450 or active substance transporters. Dostarlimab is not a cytokine and is unlikely to be a cytokine modulator. Additionally, pharmacokinetic (PK) interaction of dostarlimab with small molecule active substances is not expected. There is no evidence of interaction mediated by non-specific clearance of lysosome degradation for antibodies. The impact of concomitant carboplatin and paclitaxel on exposure was limited and not of clinical relevance. There were not enough individuals in each category of immune suppressors or immune stimulators for evaluation as covariates. No impact of systemic use of corticosteroids on dostarlimab PK was found.

Immunogenicity was assessed in Studies GARNET and RUBY. In the GARNET study, the overall incidence was low, 2.1% of the patients (N=418, 384 received the monotherapy) tested positive for ADA, and 1% had Nab. In the RUBY study, the incidence of treatment induced ADA was 0% (N=225), 34 participants (15.1%) had treatment unaffected ADA and 6 participants (2.7%) had inconclusive results. 50% of patients with treatment unaffected ADA had positive Nab. Similar immunogenicity was observed between the dMMR/MSI-H and the MMRp/MSS populations. There were no treatment-emergent ADAs in Part 1 of the RUBY study and no observed impact of dostarlimab immunogenicity on safety, efficacy, or PK endpoints. These data are consistent with the immunogenicity results from the GARNET study and confirm the overall immunogenicity risk for dostarlimab is low. The low immunogenicity risk of dostarlimab is consistent with other anti-PD-1 antibodies [Keytruda SmPC 2022; Opdivo USPI 2022; Opdivo SmPC 2022].

The exposure-efficacy analysis was performed with data from subjects in the dostarlimab plus SOC arm from the RUBY study, where patients received 500 mg Q3W for 6 cycles plus 1000 mg Q6W afterwards. PFS and DOR were used as the efficacy outcome and as exposure metric predicted cycle 1 Cmin, Cmax and AUC. (232 subjects with PFS data and 147 DOR observations were included in the dataset).

Kaplan-Meier plots stratified by quartiles of exposures were constructed for both efficacy endpoints. The results from the Kaplan-Meier suggest PFS and DOR seem to be independent of exposure (high degree of overlapping), which was then confirmed with the Cox regression models for PFS and DOR. However, what actually happens is that 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.

The exposure-safety analysis was conducted with the five most prevalent drug-related adverse events (arthralgia, diarrhoea, fatigue, nausea and rash). 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 over placebo with all three exposure metrics. The predicted probability in the dostarlimab arm is less than 30% with the proposed dosing regimen, suggesting a minor clinical impact. In the case of arthralgia, no relationship was detected when all patients were included, however, when the placebo patients were excluded a significant relationship was observed. However, the predicted probability of arthralgia is less than 20% at the higher range of dostarlimab exposure at steady-state with the proposed regimen, which is not clinically relevant.

2.3.5. Conclusions on clinical pharmacology

The clinical pharmacology properties of dostarlimab 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,

based on results from study 213361 (RUBY) Part 1 have been adequately characterized using a previously developed population PK model, which has been updated with the available experimental evidence. Overall, the modelling strategy and analyses conducted are endorsed.

2.4. Clinical efficacy

2.4.1. Dose response study

No dose-response studies were submitted as part of this application (see section 2.3.3).

2.4.2. Main study

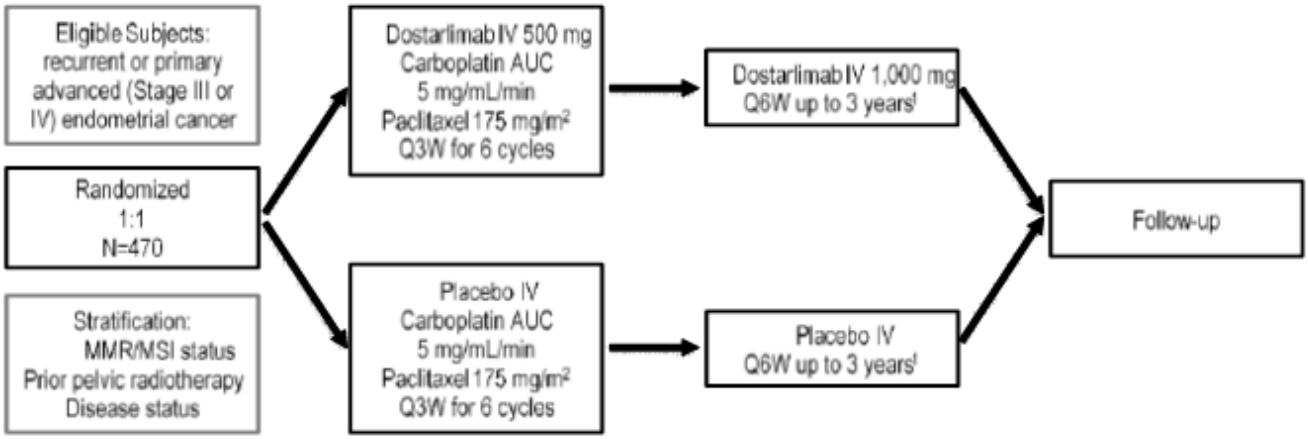
Study RUBY: A Phase 3, Randomized, Double-blind, Multicenter Study of Dostarlimab (TSR-042) plus Carboplatin-paclitaxel versus Placebo plus Carboplatin-paclitaxel in Patients with Recurrent or Primary Advanced Endometrial Cancer

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.

Figure 32. 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 tumor tissue sample at Screening for MMR/MSI status testing. Note: The quality of the tumor 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 tumor.
    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 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.

Treatments

The study interventions used in Part 1 are presented in Table 36.

Table 36. 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 Tumors 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 (EQ-5D-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.

Table 37. 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 tumor 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.

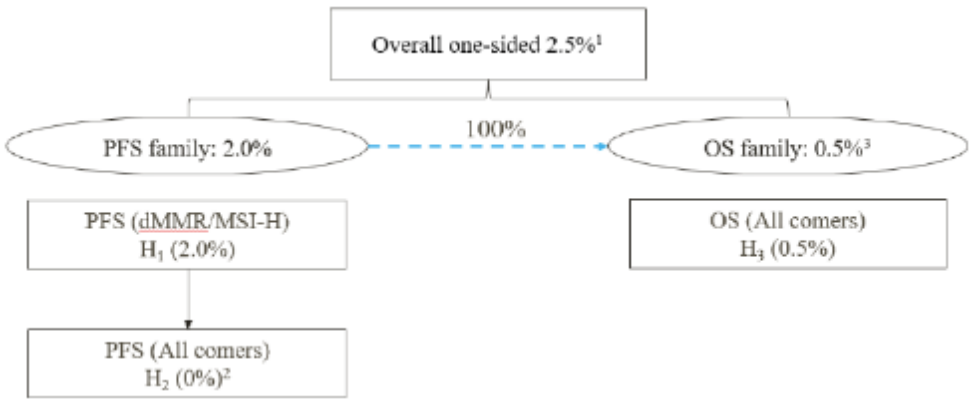
Statistical Hypothesis

- Hypothesis 1 (H_1): 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 (H_2): 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 (H_3): 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 2. 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 33. 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'Brien-Fleming) 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 cutoff 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 Lan-DeMets (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 38. 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 39. 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 log-rank 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.

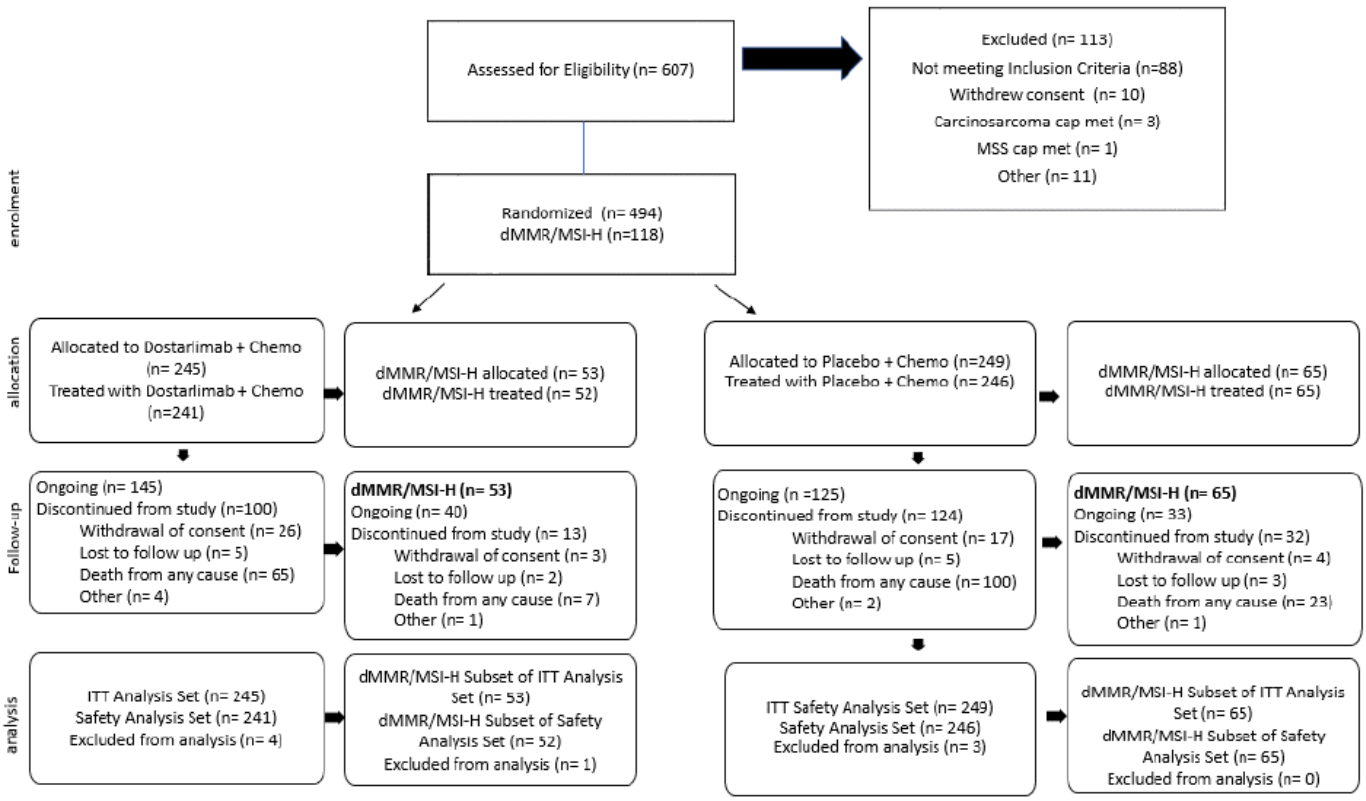
Additional sensitivity analyses to the efficacy endpoints

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 34. Participant flow



dMMR/MSI-H population

As of the data cut-off date of 28 September 2022, there were 607 participants with primary advanced or recurrent EC who were screened for eligibility, and of these, 494 participants were enrolled and randomized in RUBY Part 1 (results from an additional DCO of 1 March 2023 were provided only for OS).

In the **dMMR/MSI-H population** as of the data cut-off date, 75.5% of participants in the dostarlimab plus carboplatin-paclitaxel arm and 50.8% of participants in the placebo plus carboplatin-paclitaxel arm remained ongoing in the study. Death due to disease progression was the most frequently reported reason for discontinuation from the study.

The median duration of follow-up was 24.79 months and was consistent between treatment arms.

In both treatment arms, the most common reason for dostarlimab or placebo discontinuation was PD according to RECIST v.1.1 criteria per Investigator assessment (25.0% dostarlimab plus carboplatin-paclitaxel, 61.5% placebo plus carboplatin-paclitaxel). The most common reason for discontinuation for carboplatin or paclitaxel was AE.

The prespecified dMMR/MSI-H population was determined by the source verified value of MMR/MSI status. Although MMR/MSI status was a stratification factor, there was an imbalance noted between the 2 treatment arms in the dMMR/MSI-H subset of the ITT analysis set (n=53 in the dostarlimab plus carboplatin-paclitaxel arm and n=65 in the placebo plus carboplatin-paclitaxel arm). This was because the prespecified classification for the primary analysis was based on the'true'source verified value entered by

the site for dMMR/MSI-H classification at the time of database lock, and not the site data entry for randomization purpose at the time of randomization. The reason for the observed imbalance between the arms based on source verified value for dMMR/MSI-H characterization was due to mis-stratification of MMR/MSI data entered for randomization purpose at the time of randomization (n=22), which was then sourced verified in the MMR/MSI eCRF page. The number of participants in each arm determined by the dMMR/MSI-H value entered at randomization was 60 (dostarlimab plus carboplatin-paclitaxel arm) vs 62 (placebo plus carboplatin-paclitaxel arm).

For each efficacy analysis performed based on the dMMR/MSI-H subset of the ITT analysis set determined by the source verified value, a paired sensitivity analysis based on the subset determined by the value entered at randomization was also performed showing consistent results using both values for dMMR/MSI-H characterization.

Table 40. Summary of Subject Disposition (dMMR/MSI-H population, ITT analysis set)

Variable Reason [n (%)]	Dostarlimab + Carboplatin/Paclitaxel (N=53)	Placebo + Carboplatin/Paclitaxel (N=65)	Total (N=118)
Subject Status			
Discontinued from Study	13 (24.5)	32 (49.2)	45 (38.1)
Ongoing	40 (75.5)	33 (50.8)	73 (61.9)
On Study Treatment	23 (43.4)	8 (12.3)	31 (26.3)
In Follow-up	17 (32.1)	25 (38.5)	42 (35.6)
Reasons for Discontinuation from Study			
Withdrawal of consent	3 (5.7)	4 (6.2)	7 (5.9)
Lost to follow up	2 (3.8)	3 (4.6)	5 (4.2)
Death from any cause	7 (13.2)	24 (36.9)	31 (26.3)
Sponsors decision to terminate study	0	0	0
Other	1 (1.9)	1 (1.5)	2 (1.7)
Main Cause of Death			
Disease Progression	5 (9.4)	19 (29.2)	24 (20.3)
Adverse Event	2 (3.8)	0	2 (1.7)
Unknown	0	5 (7.7)	5 (4.2)
Other	0	0	0

Data Cutoff Date: 28SEP2022

Table 41. Summary of treatment status and reasons for discontinuation of study treatment (dMMR/MSI-H population, Safety analysis set)

Variable Reason [n (%)]	Dostarlimab + Carboplatin/Paclitaxel (N=52)	Placebo + Carboplatin/Paclitaxel (N=65)	Total (N=117)
Study Treatment Status			
Ongoing on any component of study treatment	23 (44.2)	9 (13.8)	32 (27.4)
Ongoing on Dostarlimab/Placebo	23 (44.2)	8 (12.3)	31 (26.5)
Ongoing on Paclitaxel	0	1 (1.5)	1 (0.9)
Ongoing on Carboplatin	0	0	0
Discontinued any component of study treatment	52 (100)	65 (100)	117 (100)
Discontinued Dostarlimab/Placebo	29 (55.8)	57 (87.7)	86 (73.5)
Discontinued Paclitaxel	52 (100)	64 (98.5)	116 (99.1)
Discontinued Carboplatin	52 (100)	65 (100)	117 (100)
Discontinued all components of study treatment	29 (55.8)	56 (86.2)	85 (72.6)
Reasons for discontinuation of treatment - Dostarlimab/Placebo			
AE	9 (17.3)	7 (10.8)	16 (13.7)
Clinical progression	1 (1.9)	0	1 (0.9)
PD according to RECIST v1.1 criteria per investigator assessment	13 (25.0)	40 (61.5)	53 (45.3)

Variable Reason [n (%)]	Dostarlimab + Carboplatin/Paclitaxel (N=52)	Placebo + Carboplatin/Paclitaxel (N=65)	Total (N=117)
Risk to subject, as judged by the investigator, sponsor, or both	1 (1.9)	2 (3.1)	3 (2.6)
Severe noncompliance with the protocol, as judged by the investigator, sponsor, or both	0	1 (1.5)	1 (0.9)
Subject becomes pregnant	0	0	0
Withdrawal by subject	1 (1.9)	3 (4.6)	4 (3.4)
Lost to follow-up	1 (1.9)	1 (1.5)	2 (1.7)
Death from any cause	1 (1.9)	0	1 (0.9)
Sponsor decision to terminate study	0	0	0
Confirmed complete response, treated for at least 3 years with study treatment	0	0	0
Other	2 (3.8)	3 (4.6)	5 (4.3)
Reasons for discontinuation of treatment - Paclitaxel			
AE	4 (7.7)	10 (15.4)	14 (12.0)
Clinical progression	1 (1.9)	0	1 (0.9)
PD according to RECIST v1.1 criteria per investigator assessment	1 (1.9)	2 (3.1)	3 (2.6)
Risk to subject, as judged by the investigator, sponsor, or both	1 (1.9)	0	1 (0.9)
Severe noncompliance with the protocol, as judged by the investigator, sponsor, or both	0	0	0
Subject becomes pregnant	0	0	0
Withdrawal by subject	0	1 (1.5)	1 (0.9)
Lost to follow-up	1 (1.9)	0	1 (0.9)
Death from any cause	0	0	0
Sponsor decision to terminate study	0	0	0
Subject has completed planned course	2 (3.8)	1 (1.5)	3 (2.6)
Completed planned course	42 (80.8)	49 (75.4)	91 (77.8)
Other	0	1 (1.5)	1 (0.9)
Reasons for discontinuation of treatment - Carboplatin			
AE	5 (9.6)	5 (7.7)	10 (8.5)
Clinical progression	1 (1.9)	0	1 (0.9)
PD according to RECIST v1.1 criteria per investigator assessment	1 (1.9)	2 (3.1)	3 (2.6)
Risk to subject, as judged by the investigator, sponsor, or both	1 (1.9)	0	1 (0.9)
Severe noncompliance with the protocol, as judged by the investigator, sponsor, or both	0	0	0
Subject becomes pregnant	0	0	0
Withdrawal by subject	0	1 (1.5)	1 (0.9)
Lost to follow-up	1 (1.9)	0	1 (0.9)
Death from any cause	0	0	0
Sponsor decision to terminate study	0	0	0
Subject has completed planned course	2 (3.8)	1 (1.5)	3 (2.6)
Completed planned course	41 (78.8)	55 (84.6)	96 (82.1)
Other	0	1 (1.5)	1 (0.9)

1 subject (USUBJID=4010-03-001-840383-0383) who died and discontinued from study, is still being counted under 'Ongoing on Paclitaxel' category due to unavailability of end of treatment data for Paclitaxel in database.
Data Cutoff Date: 28SEP2022

In the **overall population**, as of the data cut-off date 28-Sept-2022, 59.2% of participants in the dostarlimab plus carboplatin-paclitaxel arm and 50.2% of participants in the placebo plus carboplatin-paclitaxel arm remained ongoing in the study. Death due to disease progression was the most frequently reported reason for discontinuation from the study.

The median duration of follow-up was 25.38 months and was consistent between treatment arms.

Table 42. Summary of Participant Disposition (Overall population, ITT Analysis Set)

	Dostar + carbo/pac (N=245)	Placebo + carbo/pac (N=249)	Total (N=494)
Participants' status, n (%)			
Discontinued from study	100 (40.8%)	124 (49.8%)	224 (45.3%)
Ongoing	145 (59.2%)	125 (50.2%)	270 (54.7%)
On study treatment	52 (21.2%)	36 (14.5%)	88 (17.8%)
In follow-up	93 (38.0%)	89 (35.7%)	182 (36.8%)
Reason for discontinuation from study, n (%)			
Withdrawal of consent	26 (10.6%)	17 (6.8%)	43 (8.7%)
Lost to follow-up	5 (2.0%)	5 (2.0%)	10 (2.0%)
Death from any cause	65 (26.5%)	100 (40.2%)	165 (33.4%)
Sponsors decision to terminate study	0	0	0
Other [a]	4 (1.6%)	2 (0.8%)	6 (1.2%)
Primary cause of death, n (%)			
Disease progression	57 (23.3%)	87 (34.9%)	144 (29.1%)
Adverse event [b]	6 (2.4%)	2 (0.8%)	8 (1.6%)
Unknown	2 (0.8%)	11 (4.4%)	13 (2.6%)
Other	0	0	0

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

a. "Other" reasons for discontinuation from the study included investigator decision due to participant poor condition (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.

Source: Listing 16.1.1 and Table 14.1.1.5

Recruitment

The first participant was enrolled on 07 August 2019. The study was conducted in 158 centres in 19 countries. As of the data cut-off on 28 September 2022, there were 88 participants remaining on treatment. Part 1 had closed enrolment in January 2021.

Conduct of the study

Protocol amendments

The original protocol was issued on 13 March 2019. Three global amendments to the study protocol were implemented prior to the time of the data cut-off:

DOCUMENT HISTORY	
Document	**Date**
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

Protocol Amendment 1 (Version 2.0, Dated 11 November 2020)

The primary reasons for this amendment were:

- The addition of Part 2 to the RUBY study to evaluate the efficacy and safety of treatment with dostarlimab plus carboplatin-paclitaxel followed by dostarlimab plus niraparib (Arm 3) versus

treatment with placebo plus carboplatin-paclitaxel followed by placebo (Arm 4) in subjects with recurrent or primary advanced (Stage III or IV) endometrial cancer.

- The primary endpoint was changed from PFS per Investigator Assessment to PFS per BICR. This was to mitigate the potential risk of bias associated with some investigators requesting to unblind treatment allocation when participants entered the treatment maintenance phase, to keep those that were assigned to the placebo arm from visiting the study site during the COVID-19 pandemic.

Protocol Amendment 2 (Version 3.0, Dated 23 September 2021)

The primary reasons for this amendment were:

- To revise the RUBY Part 1 statistical design to include both PFS and OS as dual primary endpoints with alpha splitting (one-sided 0.02 for PFS and one-sided 0.005 for OS), which also allows alpha recycling from PFS to OS.

- Within PFS, the original Hochberg procedure for multiplicity control of hypothesis testing was revised to a hierarchical testing strategy for PFS in the dMMR/MSI-H followed by the overall population.

Protocol Amendment 3 (Version 4.0, Dated 31 March 2022)

The primary reasons for this amendment were:

- The primary endpoint was reverted to PFS assessed by the investigator, as was initially proposed with the original protocol. Accordingly, PFS assessed by BICR was changed to a secondary endpoint.

  - The RUBY study was initially designed with PFS per Investigator assessment as the primary objective, which was amended to PFS per BICR with the release of Protocol amendment 1 (Version 2.0 dated 11 November 2020) to mitigate the risk of bias associated with potential unblinding during the COVID-19 pandemic.

  - The potential risk of bias that drove the initial change in the primary objective did not materialize as only 4 participants were eventually unblinded in one site in the United States. Therefore, the primary endpoint was reverted to the original design of PFS per Investigator assessment (RECIST v1.1).

- The statistical design for RUBY Part 2 was updated. Per regulator feedback, the interim PFS analysis was removed. Additionally, the nominal power of PFS was increased to mitigate the impact of potential non-proportional hazards. Hypothesis testing for key secondary endpoint OS was added.

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 protocol deviations (TESARO definition), therefore a post-hoc analysis was performed to include these in the summary of the protocol deviation data. 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.

Overall population

Table 43. 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	105 (42.9%), 219	87 (34.9%), 211	192 (38.9%), 430
Assessment or time point completion	60 (24.5%), 75	44 (17.7%), 56	104 (21.1%),131
Out of window – efficacy assessment	41 (16.7%), 50	25 (10.0%), 31	66 (13.4%), 81
Missed assessment	14 (5.7%), 16	19 (7.6%), 23	33 (6.7%), 39
Assessment not properly performed	3 (1.2%), 3	1 (0.4%), 1	4 (0.8%), 4
Other assessment or time point window	3 (1.2%), 3	0	3 (0.6%), 3
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
Study procedures	7 (2.9%), 7	7 (2.8%), 10	14 (2.8%), 17
Informed consent	6 (2.4%), 7	2 (0.8%), 2	8 (1.6%), 9
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
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
Excluded medication, vaccine or device	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".
Source: Table 14.1.1.7

dMMR/MSI-H population

Table 44. Summary of Important Protocol Deviations (dMMR/MSI-H population, ITT Analysis Set)

Category Deviation [n (%), number of events]	Dostarlimab + Carboplatin/Paclitaxel (N=53)	Placebo + Carboplatin/Paclitaxel (N=65)	Total (N=118)
Any important protocol deviations	24 (45.3), 50	23 (35.4), 73	47 (39.8),123
Assessment or time point completion	9 (17.0), 11	8 (12.3), 10	17 (14.4), 21
Out of window - efficacy assessment	8 (15.1), 10	4 (6.2), 6	12 (10.2), 16
Missed assessment	1 (1.9), 1	4 (6.2), 4	5 (4.2), 5
Wrong study treatment/ administration/ dose	7 (13.2), 12	6 (9.2), 8	13 (11.0), 20
Study treatment not administered per protocol	3 (5.7), 4	4 (6.2), 4	7 (5.9), 8
Wrong study treatment or assignment administered	3 (5.7), 6	2 (3.1), 3	5 (4.2), 9
Study treatment not prepared as per protocol (e.g. Reconstitution)	1 (1.9), 2	0	1 (0.8), 2
Study Treatment Administered While Contraindication	0	1 (1.5), 1	1 (0.8), 1
Study visit/procedures chemistry	3 (5.7), 4	4 (6.2), 11	7 (5.9), 15
Test not attempted	3 (5.7), 4	4 (6.2), 11	7 (5.9), 15
Study visit/procedures blood sample for dostarlimab ADA and PK	3 (5.7), 5	3 (4.6), 5	6 (5.1), 10
Specimen collected out of window	2 (3.8), 4	2 (3.1), 2	4 (3.4), 6
Assessment not done	1 (1.9), 1	2 (3.1), 3	3 (2.5), 4
Failure to report safety events per protocol	3 (5.7), 3	2 (3.1), 2	5 (4.2), 5
SAE not reported within the expected time frame	3 (5.7), 3	2 (3.1), 2	5 (4.2), 5
Study procedures	1 (1.9), 1	4 (6.2), 4	5 (4.2), 5
Randomisation procedure (subj assigned to wrong stratum, subj rand out of order)	1 (1.9), 1	4 (6.2), 4	5 (4.2), 5
Study visit/procedures dostarlimab or placebo study treatment	1 (1.9), 1	2 (3.1), 2	3 (2.5), 3
Study drug administered out of window	1 (1.9), 1	1 (1.5), 1	2 (1.7), 2
Study drug administered after window	0	1 (1.5), 1	1 (0.8), 1
Informed consent	2 (3.8), 2	0	2 (1.7), 2
Informed consent/assent not signed and/or dated by appropriate site staff	1 (1.9), 1	0	1 (0.8), 1
Other informed consent/assent deviations	1 (1.9), 1	0	1 (0.8), 1
Study visit/procedures EORTC-QLQ-EN24	1 (1.9), 2	1 (1.5), 2	2 (1.7), 4
Subject did not make pro entry	1 (1.9), 2	1 (1.5), 2	2 (1.7), 4
Study visit/procedures hematology	1 (1.9), 3	1 (1.5), 3	2 (1.7), 6
Test not attempted	1 (1.9), 3	1 (1.5), 3	2 (1.7), 6
Study visit/procedures urinalysis	1 (1.9), 2	1 (1.5), 5	2 (1.7), 7
Test not attempted	1 (1.9), 2	1 (1.5), 5	2 (1.7), 7
Inclusion/exclusion criteria chemistry	0	1 (1.5), 1	1 (0.8), 1
Direct bilirubin was not collected at screening.	0	1 (1.5), 1	1 (0.8), 1
IP admin/study treatment carboplatin study treatment	0	1 (1.5), 2	1 (0.8), 2
Study drug dosage incorrect	0	1 (1.5), 2	1 (0.8), 2
IP admin/study treatment paclitaxel study treatment	1 (1.9), 1	0	1 (0.8), 1
Subject received wrong study dose	1 (1.9), 1	0	1 (0.8), 1
Randomization MMR/MSI test	0	1 (1.5), 1	1 (0.8), 1
Error in stratification	0	1 (1.5), 1	1 (0.8), 1
Study visit/procedures blood sample for dostarlimab ADA and PK - end of treatment	0	1 (1.5), 1	1 (0.8), 1
Assessment not done	0	1 (1.5), 1	1 (0.8), 1
Study visit/procedures carboplatin study treatment	0	1 (1.5), 1	1 (0.8), 1
Study drug administered out of window	0	1 (1.5), 1	1 (0.8), 1
Study visit/procedures ECG summary	0	1 (1.5), 1	1 (0.8), 1
Assessment not done	0	1 (1.5), 1	1 (0.8), 1

Category Deviation [n (%), number of events]	Dostarlimab + Carboplatin/Paclitaxel (N=53)	Placebo + Carboplatin/Paclitaxel (N=65)	Total (N=118)
Study visit/procedures ECOG performance status summary	0	1 (1.5), 1	1 (0.8), 1
Assessment not done	0	1 (1.5), 1	1 (0.8), 1
Study visit/procedures EORTC-QLQ-C30	1 (1.9), 1	0	1 (0.8), 1
Subject did not make pro entry.	1 (1.9), 1	0	1 (0.8), 1
study visit/procedures exploratory biomarker and CTDNA blood sample	0	1 (1.5), 1	1 (0.8), 1
Specimen collection not done	0	1 (1.5), 1	1 (0.8), 1
Study visit/procedures local laboratory sample collection summary	0	1 (1.5), 1	1 (0.8), 1
Assessment not done	0	1 (1.5), 1	1 (0.8), 1
Study visit/procedures local laboratory sample collection summary V2	0	1 (1.5), 1	1 (0.8), 1
Assessment not done	0	1 (1.5), 1	1 (0.8), 1
Study visit/procedures local laboratory sample collection summary V3	0	1 (1.5), 3	1 (0.8), 3
Assessment not done	0	1 (1.5), 3	1 (0.8), 3
Study visit/procedures paclitaxel study treatment	0	1 (1.5), 1	1 (0.8), 1
Study drug administered out of window	0	1 (1.5), 1	1 (0.8), 1
Study visit/procedures patient-reported outcomes (PRO) summary	0	1 (1.5), 3	1 (0.8), 3
Assessment not done	0	1 (1.5), 3	1 (0.8), 3
Study visit/procedures thyroid panel	0	1 (1.5), 2	1 (0.8), 2
Test not attempted	0	1 (1.5), 1	1 (0.8), 1
Test not attempted.	0	1 (1.5), 1	1 (0.8), 1
Study visit/procedures vital signs	1 (1.9), 1	0	1 (0.8), 1
Assessment not done	1 (1.9), 1	0	1 (0.8), 1
Study visit/procedures vital signs summary	0	1 (1.5), 1	1 (0.8), 1
Assessment not done	0	1 (1.5), 1	1 (0.8), 1
Visit completion	1 (1.9), 1	0	1 (0.8), 1
Out of window visit/phone contact	1 (1.9), 1	0	1 (0.8), 1

Note: Significant protocol deviations are also included in the display as "significant" protocol deviations are also considered as "important".
Data Cutoff Date: 28SEP2022

Baseline data

Demographics

Overall population

Table 45. Summary of demographic characteristics (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.
Source: Table 14.1.1.15

dMMR/MSI-H population

Table 46. Summary of demographic characteristics (dMMR/MSI-H population, ITT Analysis set)

Characteristic	Dostarlimab + Carboplatin/Paclitaxel (N=53)	Placebo + Carboplatin/Paclitaxel (N=65)	Total (N=118)
Child-bearing status [n (%)]			
n	53	65	118
Child-bearing potential	0	2 (3.1)	2 (1.7)
Non-child-bearing potential	53 (100.0)	63 (96.9)	116 (98.3)

Characteristic	Dostarlimab + Carboplatin/Paclitaxel (N=53)	Placebo + Carboplatin/Paclitaxel (N=65)	Total (N=118)
Race [n (%)]			
n	53	65	118
White	44 (83.0)	56 (86.2)	100 (84.7)
Black or African American	4 (7.5)	6 (9.2)	10 (8.5)
Asian	2 (3.8)	0	2 (1.7)
American Indian or Alaska Native	0	1 (1.5)	1 (0.8)
Native Hawaiian or other Pacific Islander	1 (1.9)	0	1 (0.8)
Mixed Race	0	0	0
Unknown	1 (1.9)	1 (1.5)	2 (1.7)
Not Reported	1 (1.9)	1 (1.5)	2 (1.7)
Ethnicity [n (%)]			
n	53	65	118
Hispanic or Latino	0	0	0
Not Hispanic or Latino	50 (94.3)	63 (96.9)	113 (95.8)
Unknown	2 (3.8)	0	2 (1.7)
Not Reported	1 (1.9)	2 (3.1)	3 (2.5)
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	23 (43.4)	35 (53.8)	58 (49.2)
Weight (kg)			
n	52	65	117
Mean (std)	83.00 (25.391)	94.10 (27.212)	89.17 (26.884)
Median	75.85	92.00	84.00
Q1, Q3	65.15, 90.00	71.00, 113.00	69.90, 106.10
Min, Max	46.7, 180.6	50.5, 185.9	46.7, 185.9
Height (cm)			
n	52	65	117
Mean (std)	162.52 (7.580)	162.38 (7.906)	162.45 (7.730)
Median	162.60	162.00	162.50
Q1, Q3	155.60, 167.30	157.00, 165.10	157.00, 167.00
Min, Max	150.0, 186.0	149.2, 185.4	149.2, 186.0
BMI (kg/m^2)[a]			
n	52	65	117
Mean (std)	31.28 (8.221)	35.44 (8.925)	33.59 (8.831)
Median	30.55	35.50	32.60
Q1, Q3	25.00, 36.45	29.30, 41.60	26.30, 39.20
Min, Max	20.1, 54.4	17.9, 58.1	17.9, 58.1
BSA (m^2)[b]			
n	52	65	117
Mean (std)	1.899 (0.2968)	2.012 (0.3154)	1.962 (0.3111)
Median	1.835	1.990	1.930
Q1, Q3	1.710, 2.000	1.750, 2.220	1.740, 2.140
Min, Max	1.41, 3.03	1.53, 3.03	1.41, 3.03
ECOG Performance Status [n (%)]			
n	52	65	117
0	28 (53.8)	39 (60.0)	67 (57.3)
1	24 (46.2)	26 (40.0)	50 (42.7)

Characteristic	Dostarlimab + Carboplatin/Paclitaxel (N=53)	Placebo + Carboplatin/Paclitaxel (N=65)	Total (N=118)
2	0	0	0
3	0	0	0
4	0	0	0
5	0	0	0
>=2	0	0	0

[a] BMI = Body Mass Index
[b] BSA = Body Surface Area
Data Cutoff Date: 28SEP2022

Baseline disease characteristics

Overall population

Table 47. 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.
Source: Table 14.1.1.17

dMMR/MSI-H population

The frequency of endometrioid tumours was higher in the dMMR/MSI-H population with >80% having endometrioid histology. This distribution was expected based on the known association of MMR status with histology.

Table 48. Summary of disease history (dMMR/MSI-H population, ITT analysis set)

Category [n (%)]	Dostarlimab + Carboplatin/Paclitaxel (N=53)	Placebo + Carboplatin/Paclitaxel (N=65)	Total (N=118)
FIGO Stage at Initial diagnosis			

Category [n (%)]	Dostarlimab + Carboplatin/Paclitaxel (N=53)	Placebo + Carboplatin/Paclitaxel (N=65)	Total (N=118)
Stage I	18 (34.0)	22 (33.8)	40 (33.9)
Stage II	3 (5.7)	5 (7.7)	8 (6.8)
Stage III	14 (26.4)	20 (30.8)	34 (28.8)
Stage IV	14 (26.4)	15 (23.1)	29 (24.6)
Unknown	4 (7.5)	3 (4.6)	7 (5.9)
Histology at diagnosis			
Carcinosarcoma	4 (7.5)	1 (1.5)	5 (4.2)
Endometrioid carcinoma (adenocarcinoma or adenocarcinoma-variants)	44 (83.0)	56 (86.2)	100 (84.7)
Mixed carcinoma with >=10% of carcinosarcoma, clear cell or serous histology	2 (3.8)	4 (6.2)	6 (5.1)
Other	2 (3.8)	3 (4.6)	5 (4.2)
Serous adenocarcinoma	1 (1.9)	1 (1.5)	2 (1.7)
Grade at diagnosis			
Grade 1	16 (30.2)	19 (29.2)	35 (29.7)
Grade 2	21 (39.6)	22 (33.8)	43 (36.4)
Grade 3	15 (28.3)	21 (32.3)	36 (30.5)
Not assessable	1 (1.9)	3 (4.6)	4 (3.4)
Most recent histology			
Carcinosarcoma	4 (7.5)	2 (3.1)	6 (5.1)
Endometrioid carcinoma (adenocarcinoma or adenocarcinoma-variants)	45 (84.9)	54 (83.1)	99 (83.9)
Mixed carcinoma with >=10% of carcinosarcoma, clear cell or serous histology	1 (1.9)	4 (6.2)	5 (4.2)
Other	3 (5.7)	3 (4.6)	6 (5.1)
Serous adenocarcinoma	0	1 (1.5)	1 (0.8)
Undifferentiated carcinoma	0	1 (1.5)	1 (0.8)
Most recent Grade of Disease			
Grade 1	10 (18.9)	16 (24.6)	26 (22.0)
Grade 2	15 (28.3)	21 (32.3)	36 (30.5)
Grade 3	21 (39.6)	20 (30.8)	41 (34.7)
Not accessible	0	1 (1.5)	1 (0.8)
Not assessable	7 (13.2)	7 (10.8)	14 (11.9)
Recurrence of Endometrial Cancer			
Yes	27 (50.9)	32 (49.2)	59 (50.0)
No	26 (49.1)	33 (50.8)	59 (50.0)

Data Cutoff Date: 28SEP2022

Medical history

Overall population

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%).

dMMR/MSI-H population

Medical history for the dMMR/MSI-H population was generally similar to the overall population. In the dMMR/MSI-H population there was a bit more variation between treatment arms, however differences between treatment arms remained <10%.

Prior and concomitant medications and other treatments

Overall population

Table 49. 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.

Source: Table 14.1.1.22

dMMR/MSI-H population

Approximately 14% of participants in the dMMR/MSI-H population received prior anticancer therapy: 13.2% in the dostarlimab arm vs. 15.4% in the placebo arm.

Prior non-anticancer medications in the dMMR/MSI population were similar to the overall population. No noteworthy differences were observed in prior non-anticancer treatment use between treatment arms.

In the dMMR/MSI-H population, 92.4% of participants had received prior anticancer surgical interventions for EC and 34.7% of participants received previous radiotherapy.

Fewer participants in the dostarlimab plus carboplatin-paclitaxel had received external pelvic radiotherapy than the placebo plus carboplatin-paclitaxel arm (15.1% versus 20.0%).

Table 50. Summary of Prior Anti-Cancer Radiotherapy, Surgery and Treatment (dMMR/MSI-H population, ITT Analysis Set)

Variable [n (%)]	Dostarlimab + Carboplatin/Paclitaxel (N=53)	Placebo + Carboplatin/Paclitaxel (N=65)	Total (N=118)
Received Previous Radiotherapy for Endometrial Cancer [a]	19 (35.8)	22 (33.8)	41 (34.7)
External pelvic	8 (15.1)	13 (20.0)	21 (17.8)
Internal pelvic	8 (15.1)	11 (16.9)	19 (16.1)
Other	6 (11.3)	8 (12.3)	14 (11.9)
Received Prior Anti-cancer Surgery for Endometrial Cancer [b]	49 (92.5)	60 (92.3)	109 (92.4)
Received Prior Anticancer Treatment for Endometrial Cancer	7(13.2)	10(15.4)	17(14.4)

[a]Subjects may be included in more than one category for Previous Radiotherapy for Endometrial Cancer.

[b]Diagnostic procedure only are not included as anti-cancer surgery.

Data Cutoff Date: 28SEP2022

Table 51. Summary of prior anticancer treatment (dMMR/MSI-H population, ITT analysis set)

Agent [n (%)]	Dostarlimab + Carboplatin/Paclitaxel (N=53)	Placebo + Carboplatin/Paclitaxel (N=65)	Total (N=118)
Any Prior Anticancer Treatment	7 (13.2)	10 (15.4)	17 (14.4)
Paclitaxel w/carboplatin	4 (7.5)	6 (9.2)	10 (8.5)
Carboplatin	2 (3.8)	1 (1.5)	3 (2.5)
Cisplatin	1 (1.9)	2 (3.1)	3 (2.5)
Paclitaxel	2 (3.8)	0	2 (1.7)

Agent [n (%)]	Dostarlimab + Carboplatin/Paclitaxel (N=53)	Placebo + Carboplatin/Paclitaxel (N=65)	Total (N=118)
Docetaxel	1 (1.9)	0	1 (0.8)
Letrozole	0	1 (1.5)	1 (0.8)

Patients treated with the same agent more than once will only be counted once.
Patients treated with more than one agent will be counted in each agent.
Data Cutoff Date: 28SEP2022

Concomitant medications

Overall population

The most frequent (>50% of total participants) concomitant medications in the overall population were dexamethasone, paracetamol, ondansetron, and famotidine, which was generally similar for the dMMR/MSI-H population.

In the overall population there were no noteworthy differences in concomitant medications (>10%) between the dostarlimab plus carboplatin-paclitaxel arm compared to the placebo plus carboplatin-paclitaxel arm with the exception of prednisone (18.7% dostarlimab plus carboplatin-paclitaxel, 6.9% placebo plus carboplatin-paclitaxel). Increased use of glucocorticoids as a concomitant medication was expected in the dostarlimab plus carboplatin-paclitaxel arm based on the known side effect profile of immune checkpoint inhibitors.

dMMR/MSI-H population

In the dMMR/MSI-H population the reported use of ondansetron, prednisone, ascorbic acid, and levoglutamide was >10% higher in the dostarlimab plus carboplatin-paclitaxel arm compared with the placebo plus carboplatin-paclitaxel arm, whereas reported use of lisinopril, palonosetron, aprepitant, metformin, and potassium was higher (>10% difference) in the placebo plus carboplatin-paclitaxel arm compared with the dostarlimab plus carboplatin-paclitaxel arm.

Numbers analysed

The ITT analysis set (n=494) comprised participants who were randomized (regardless of treatment received). Enrolled participants were randomized 1:1 to receive either dostarlimab plus carboplatin - paclitaxel (245 participants) or placebo plus carboplatin-paclitaxel (249 participants). The overall population included all 494 participants in the ITT analysis set, which included the dMMR/MSI-H population (118 participants) or the MMRp/MSS population (376 participants).

The prespecified dMMR/MSI-H population for efficacy analysis was determined by the source verified value of MMR/MSI status. The number of participants in each arm of the dMMR/MSI-H subset of ITT analysis set determined by the source verified value of MMR/MSI status was 53 (dostarlimab plus carboplatin-paclitaxel arm) vs 65 (placebo plus carboplatin-paclitaxel arm).

The per-protocol population included 487 participants. Given that it comprised >90% of the ITT analysis set, efficacy analyses were not carried out for the per-protocol population.

Table 52. 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]
Intention-to-treat (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. In total, 7 participants were excluded from the ITT analysis set based on the Per-Protocol analysis set definition.

Source: Table 14.1.1.1

Outcomes and estimation

Primary efficacy endpoints

- **Progression-free survival by Investigator assessment**

dMMR/MSI-H population

At the time of data cutoff (56% PFS maturity), dostarlimab plus carboplatin-paclitaxel reduced the risk of progression or death by 72%, with a HR for progression or death of 0.28 (95% CI 0.162, 0.495, stratified log-rank test p-value <0.0001; median PFS not reached versus 7.7 months, respectively). The stopping boundary (p=0.00630) for claiming superiority of dostarlimab plus carboplatin-paclitaxel over placebo plus carboplatin-paclitaxel in prolonging PFS in the dMMR/MSI-H population at the interim analysis was crossed. The estimated Kaplan-Meier probability of progression-free survival at 24 months were 61.4% and 15.7% in the dostarlimab plus carboplatin-paclitaxel and placebo plus carboplatin-paclitaxel arms, respectively.

Figure 35. Kaplan-Meier curves of progression-free survival – RECIST v.1.1 by Investigator assessment (Primary Analysis) (dMMR/MSI-H population, ITT analysis set)

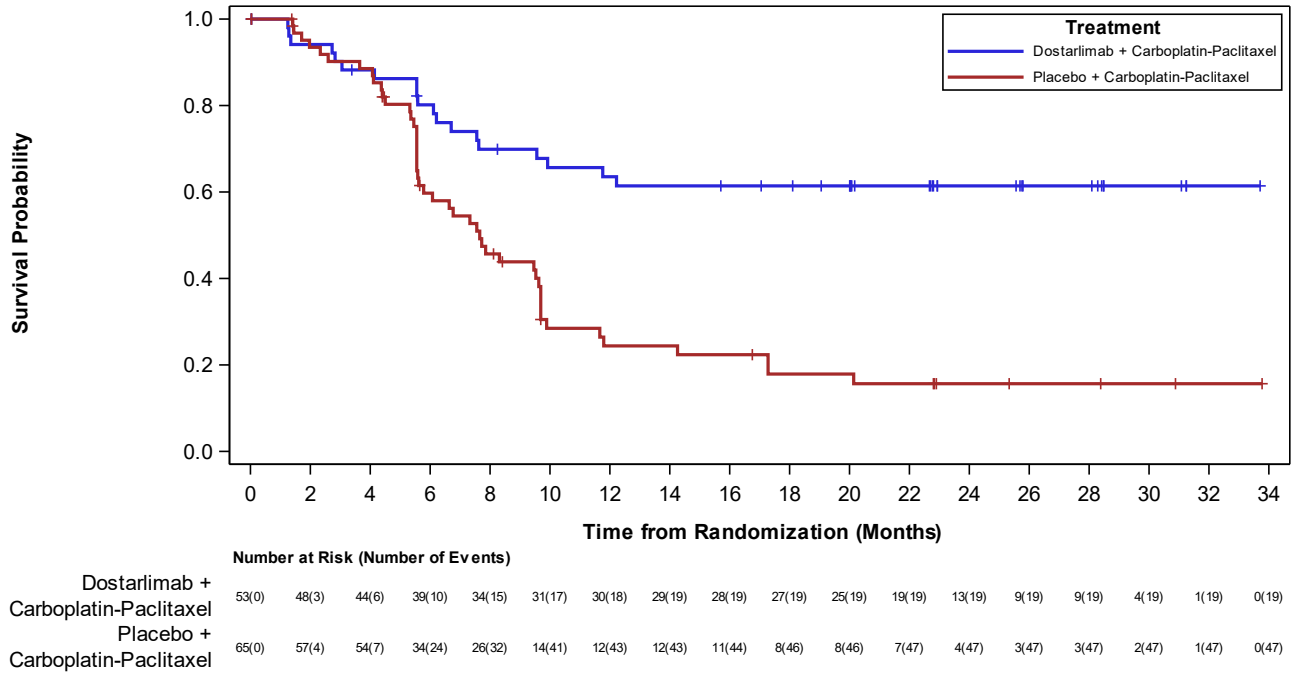


Table 53. Kaplan-Meier analysis of progression-free survival – RECIST v.1.1 by Investigator assessment (Primary analysis) (dMMR/MSI-H population, ITT analysis set)

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; dMMR=mismatch repair deficient; Dostar=dostarlimab; ITT=intent-to-treat; MSI-H=microsatellite instability-high; NR=not reached; pac=paclitaxel; PFS=progression-free survival.
a. 95% CIs generated using the method of Brookmeyer and Crowley (1982).
Based on stratified Cox regression.

Overall population

At the time of data cutoff (63% PFS maturity), dostarlimab plus carboplatin-paclitaxel reduced the risk of progression or death by 36% with a HR of 0.64 (95% CI 0.507, 0.800, stratified log-rank test p-

value<0.0001; median PFS 11.8 months versus 7.9 months) in participants with primary advanced or recurrent EC. The stopping boundary (p=0.02) for claiming superiority of dostarlimab plus carboplatin-paclitaxel over placebo plus carboplatin-paclitaxel in prolonging PFS in the overall population was crossed. The estimated Kaplan-Meier probability of progression-free survival at 24 months were 36.1% and 18.1% in the dostarlimab plus carboplatin-paclitaxel and placebo plus carboplatin-paclitaxel arms, respectively.

Figure 36. Kaplan-Meier curves of progression-free survival – RECIST v.1.1 by Investigator assessment (Primary Analysis) (Overall population, ITT analysis set)

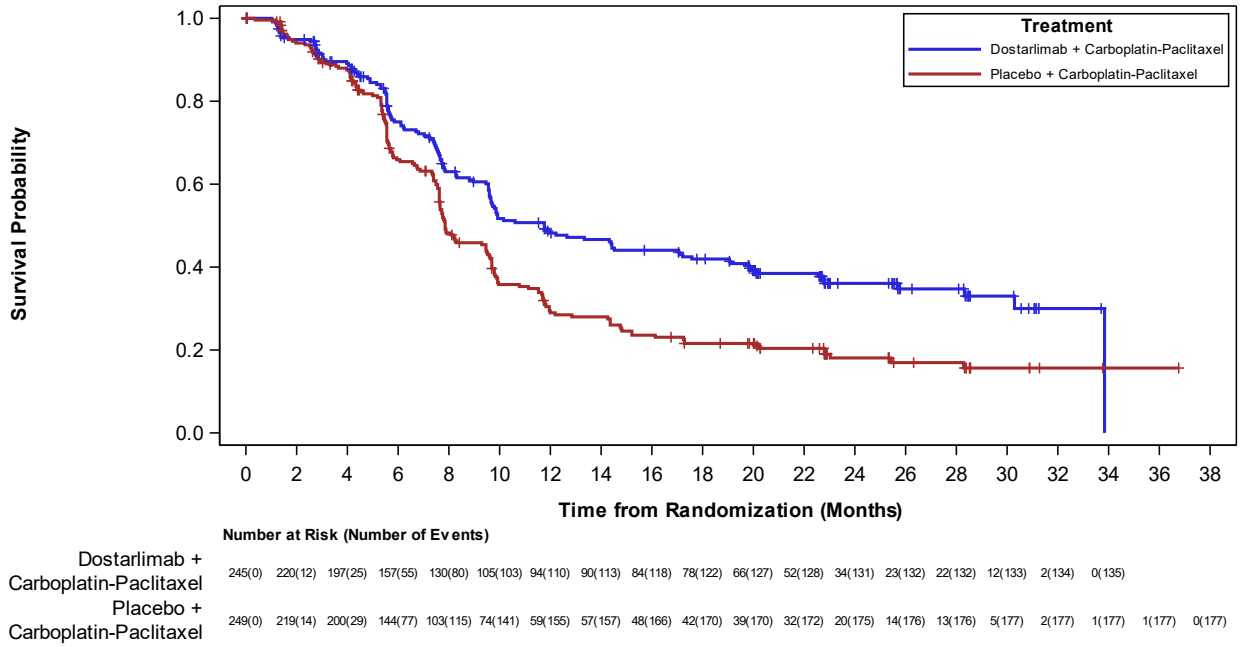


Table 54. Kaplan-Meier analysis of progression-free survival - RECIST v1.1 by investigator assessment (primary analysis) (Overall Population, ITT Analysis Set)

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

- **Overall survival**

dMMR/MSI-H population

Although OS in the dMMR/MSI-H population is not a primary endpoint, a prespecified subgroup analysis of OS in this population was also performed. At 26% OS maturity, there was a trend in favor of the dostarlimab plus carboplatin-paclitaxel arm with a 70% reduction in deaths and a HR of 0.30 (95% CI 0.127,0.699; nominal stratified log-rank test p-value=0.0016; median OS not reached for either arm). The Kaplan-Meier probability of survival at 24 months was 83.3% and 58.7% in the dostarlimab plus carboplatin-paclitaxel and placebo plus carboplatin-paclitaxel arms, respectively.

Figure 37. Kaplan-Meier analysis overall survival (dMMR/MSI-H population, ITT analysis set)

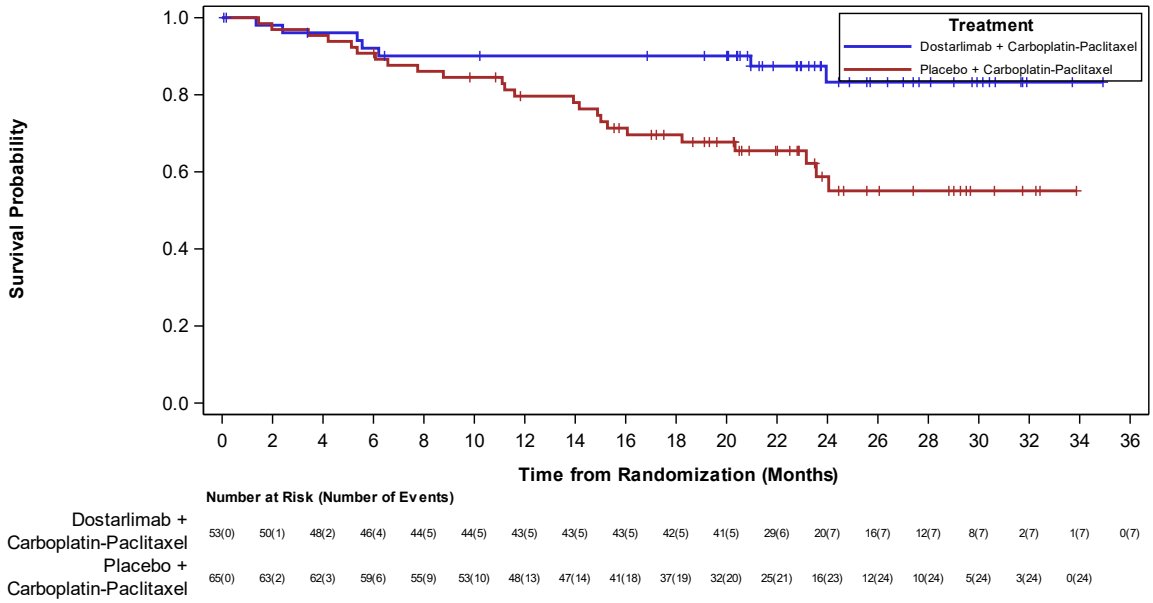


Table 55. Kaplan-Meier analysis of overall survival (dMMR/MSI-H Population, ITT Analysis Set)

Category subcategory	Dostar + carbo/pac (N=53)	Placebo + carbo/pac (N=65)
OS status, n (%)		
Events observed	7 (13.2%)	24 (36.9%)
Censored	46 (86.8%)	41 (63.1%)
OS (months) Quartile (95% CI) [a]		
25%	NR (21.0, NR)	14.9 (7.8, 23.2)
50%	NR (NR, NR)	NR (23.2, NR)
75%	NR (NR, NR)	NR (NR, NR)
OS probability (95% CI)		
Month 12	90.1% (77.8%, 95.7%)	79.6% (67.5%, 87.6%)
Month 18	90.1% (77.8%, 95.7%)	69.6% (56.5%, 79.4%)
Month 24	83.3% (66.8%, 92.0%)	58.7% (43.4%, 71.2%)
Month 30	83.3% (66.8%, 92.0%)	55.1% (39.1%, 68.4%)
Hazard ratio (95% CI) [b]	0.30 (0.127, 0.699)	
Nominal p-value of 1-sided stratified log-rank test	0.0016	

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

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

Based on stratified Cox regression.

1-sided p-value based on Stratified log-rank test.

Overall population

At this OS interim analysis with 33% OS maturity, there was a trend in favor of the dostarlimab plus carboplatin-paclitaxel arm with a 36% reduction in deaths and a HR of 0.64 (95% CI 0.464, 0.870; p=0.0021; [P-value stopping boundary for significance was 0.00177]). Median OS was not reached for either arm.

Figure 38. Kaplan-Meier analysis overall survival (Overall Population, ITT Analysis Set)

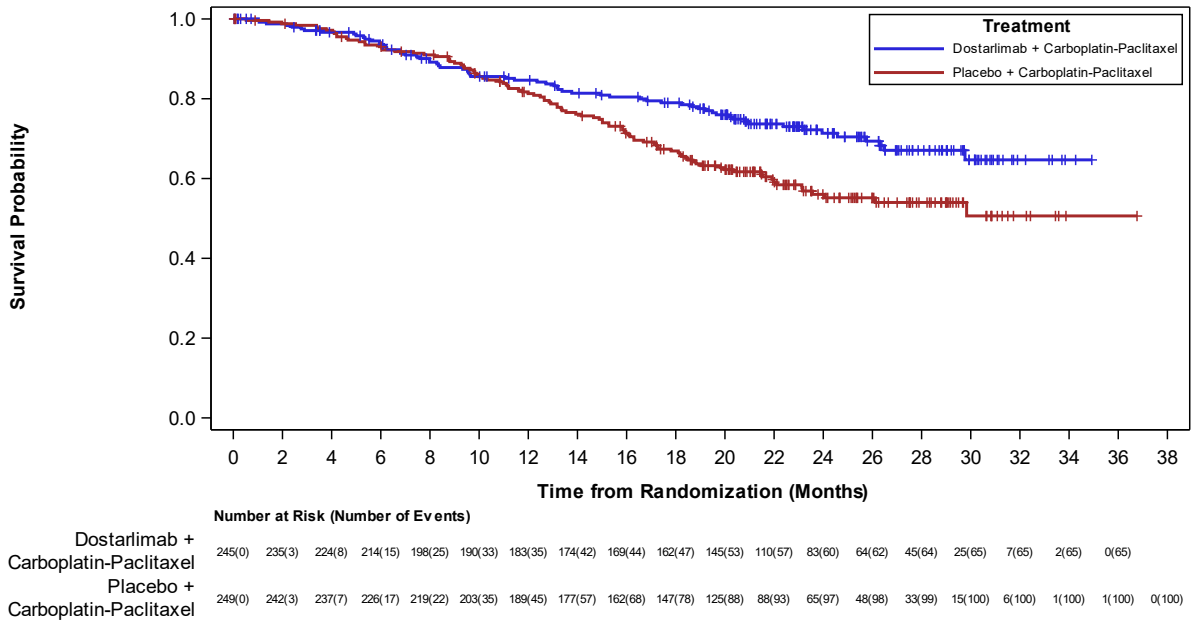


Table 56. Kaplan-Meier analysis of overall survival (Overall Population, ITT Analysis Set)

Category subcategory	Dostar + carbo/pac (N=245)	Placebo + carbo/pac (N=249)
OS status, n (%)		
Events observed	65 (26.5%)	100 (40.2%)
Censored	180 (73.5%)	149 (59.8%)
OS (months) Quartile (95% CI) [a]		
25%	20.3 (15.3, 26.3)	14.9 (12.5, 16.7)
50%	NR (NR, NR)	NR (23.2, NR)
75%	NR (NR, NR)	NR (NR, NR)
OS probability (95% CI)		
Month 12	84.6% (79.2%, 88.7%)	81.3% (75.7%, 85.7%)
Month 18	79.0% (73.0%, 83.8%)	66.9% (60.4%, 72.5%)
Month 24	71.3% (64.5%, 77.1%)	56.0% (48.9%, 62.5%)
Month 30	64.7% (55.6%, 72.3%)	50.6% (41.0%, 59.4%)
Hazard ratio (95% CI) [b]	0.64 (0.464, 0.870)	
p-value of 1-sided stratified log-rank test	0.0021	

carbo=carboplatin; Dostar=dostarlimab; ITT=intent-to-treat; NR=not reached; pac=paclitaxel; OS=overall survival.
a. 95% Confidence intervals generated using the method of Brookmeyer and Crowley (1982).
b. Stratified Cox regression
c. 1-sided p-value based on Stratified log-rank test.
Source: m5.3.5.1, RUBY Part 1 CSR, Table 14.2.1.8

- *Updated OS data (DCO: 01 Mar 2023)*

Updated OS data for the dMMR/MSI-H and overall population were available from an administrative IA for OS performed with 193 OS events (39% maturity) (DCO: 01 Mar 2023).

A summary of the results from this administrative IA for OS are presented in the table below.

Table 34. Administrative interim analysis of overall survival

	Overall population		dMMR/MSI-H population[c]	
Category subcategory	**Dostar + carbo/pac (N = 245)**	**Placebo + carbo/pac (N = 249)**	**Dostar + carbo/pac (N = 53)**	**Placebo + carbo/pac (N = 65)**
Events observed	81 (33.1%)	112 (45.0%)	9 (17.0%)	26 (40.0%)
Censored	164 (66.9%)	137 (55.0%)	44 (83.0%)	39 (60.0%)
Median OS, months (95% CI) [a]	NR (32.7, NR)	35.6 (23.6, NR)	NR (NR, NR)	NR (23.2, NR)
Hazard ratio (95% CI) [b, d] **P-value**	0.68 (0.513, 0.911); p = 0.0046		0.33 (0.155, 0.722); p = 0.0018	
OS Maturity	39%		30%	

Abbreviations: Carbo = carboplatin; Dostar = dostarlimab; ITT = intent-to-treat; NR = not reached; Pac = paclitaxel.

a. 95% Confidence intervals generated using the method of Brookmeyer and Crowley (1982).
b. Stratified Cox regression model
c. Prespecified exploratory analysis
d. Nominal P-value was not part of multiple testing procedure and not used for hypothesis testing

Source: Available upon request

Secondary endpoints

- **Progression-free Survival (Blinded Independent Central Review)**

In the dMMR/MSI-H population, dostarlimab plus carboplatin-paclitaxel reduced the risk of progression or death by 71% with a HR of 0.29 (95% CI 0.158, 0.543, nominal stratified log-rank test p-value<0.0001; median PFS not reached versus 9.5 months).

Figure 39. Kaplan-Meier curves of progression-free survival – RECIST v.1.1 by BICR assessment (dMMR/MSI-H population, ITT analysis set)

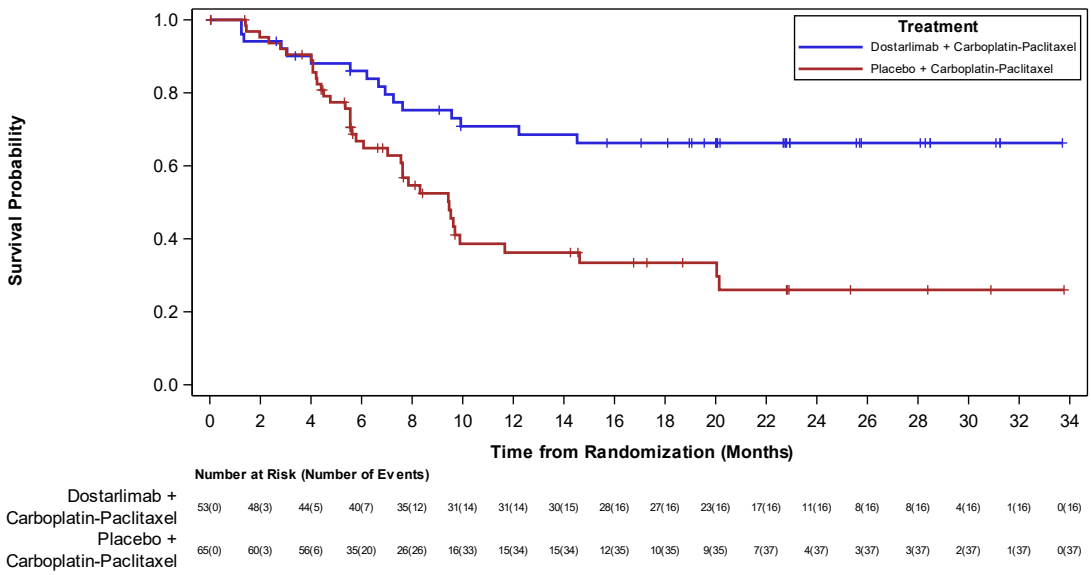


Table 57. Summary of Kaplan-Meier analysis of progression free survival – per RECIST v1.1 based on BICR assessment (ITT Analysis Set)

	dMMR/MSI-H Population	
	Dostar + carbo/pac (N=53)	Placebo + carbo/pac (N=65)
Hazard ratio (95% CI) [a]	0.29 (0.158, 0.543)	
Nominal p-value of 1-sided stratified log-rank test	<0.0001	
Median PFS, months (95% CI) [b]	NR (NR, NR)	9.5 (7.0, 11.7)
PFS Probability at 24 Months (95% CI)	66.3% (50.8%, 77.9%)	26.0% (13.5%, 40.5%)

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 [Brookmeyer, 1982].

- **Progression-free Survival 2**

At the time of data cutoff, dostarlimab plus carboplatin-paclitaxel reduced the risk of progression following first subsequent anticancer therapy or death in the dMMR/MSI-H population, by demonstrating a HR of 0.37 (95% CI: 0.189, 0.727).

Figure 40. Kaplan-Meier curves of progression-free survival 2 (dMMR/MSI-H population, ITT analysis set)

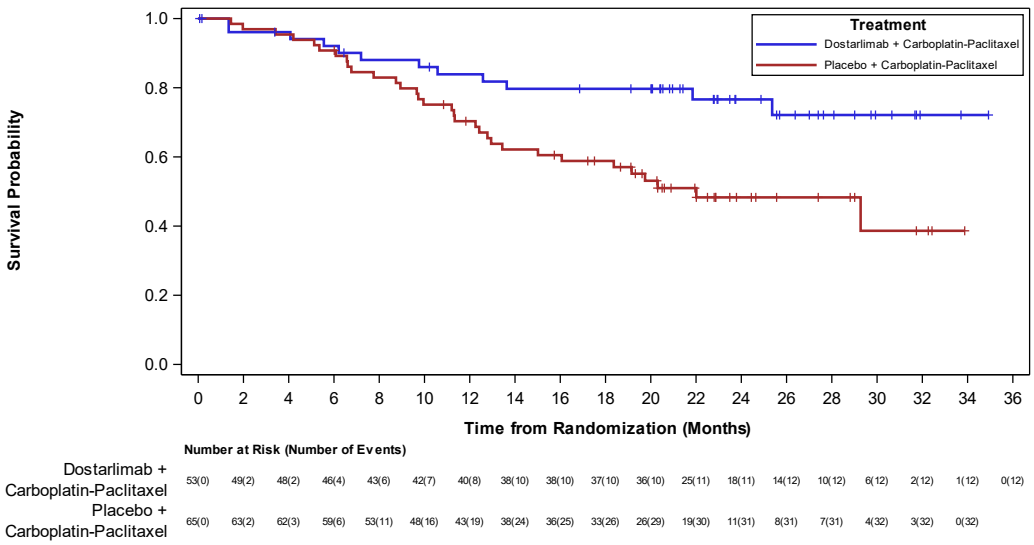


Table 58. Summary of Kaplan-Meier analysis of progression-free survival 2 (ITT Analysis Set)

	dMMR/MSI-H Population	
	Dostar + carbo/pac (N=53)	Placebo + carbo/pac (N=65)
Hazard ratio (95% CI) [a]	0.37 (0.189, 0.727)	
Median PFS2, months (95% CI) [b]	NR	22.0 (13.4, NR)
PFS2 Probability at 24 Months (95% CI)	76.6% (61.4%, 86.5%)	48.3% (34.7%, 60.6%)

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.

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

- **Objective Response and Disease Control Rate**

Table 59. Summary of tumour response – RECIST v.1.1 by Investigator assessment (dMMR/MSI-H population, ITT analysis set)

	dMMR/MSI-H Population	
	Dostar + carbo/pac (N=53)	**Placebo + carbo/pac (N=65)**
Best response by RECIST v1.1, n (%)		
CR	15 (28.3%)	12 (18.5%)
PR	23 (43.4%)	28 (43.1%)
SD	6 (11.3%)	10 (15.4%)
Non-CR/Non-PD	0	0
No disease	4 (7.5%)	8 (12.3%)
PD	2 (3.8%)	4 (6.2%)
Not evaluable	3 (5.7%)	3 (4.6%)
Disease control rate		
n (%)	48 (90.6%)	58 (89.2%)
95% CI [a]	(79.3%, 96.9%)	(79.1%, 95.6%)
Objective response rate [b]		
n (%)	38/49 (77.6%)	40/58 (69.0%)
95% CI [a]	(63.4%, 88.2%)	(55.5%, 80.5%)

carbo=carboplatin; CI=confidence interval; Dostar=dostarlimab, pac= paclitaxel
Note: DCR is defined as the percentage of participants with a RECIST v1.1 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 lesion at baseline.

Table 60. Summary of Tumour Response – RECIST v1.1 based on BICR Assessment (dMMR/MSI-H population, ITT Analysis Set)

Variable	Dostarlimab + Carboplatin/Paclitaxel (N=53)	Placebo + Carboplatin/Paclitaxel (N=65)
Best Overall Response by RECIST v1.1 [n(%)][a]		
CR	11 (20.8)	8 (12.3)
PR	26 (49.1)	30 (46.2)
SD	3 (5.7)	13 (20.0)
Non-CR/Non-PD	4 (7.5)	4 (6.2)
No disease	4 (7.5)	5 (7.7)
PD	2 (3.8)	2 (3.1)
Not Evaluable	3 (5.7)	3 (4.6)
Disease Control Rate (DCR)		
n(%)	48 (90.6)	60 (92.3)
95% CIb	(79.3, 96.9)	(83.0, 97.5)

Note: DCR is defined as the percentage of patients with a RECIST v1.1 CR, PR, SD, Non-CR/Non-PD, No disease.
[a]CR=Complete Response, PR=Partial Response, SD=Stable Disease, PD= Progressive Disease.
[b]Exact 2 sided 95% confidence interval for the binomial proportion.
NE = Not Estimable.
Data Cutoff Date: 28SEP2022

- **Duration of Response**

dMMR/MSI-H population

Within the dMMR/MSI-H population, median DOR was not reached in the dostarlimab plus carboplatin - paclitaxel arm compared to 5.4 months (95% CI: 3.9, 8.1) in the placebo plus carboplatin-paclitaxel arm.

Figure 41. Kaplan-Meier curves of duration of response – RECIST v.1.1 based on Investigator assessment (dMMR/MSI-H population, ITT analysis set)

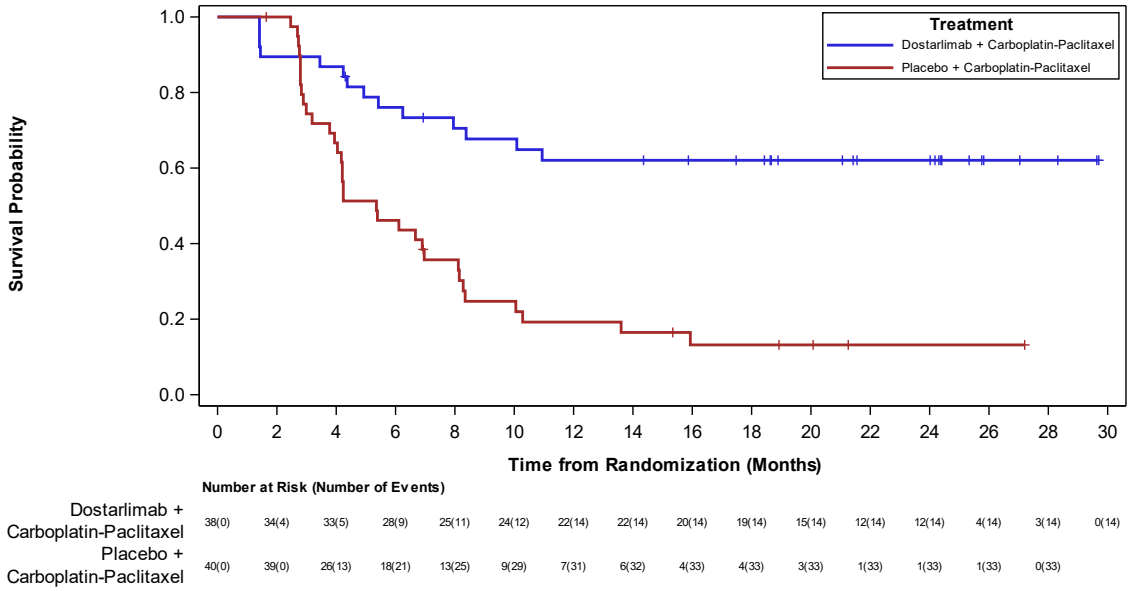


Table 61. Kaplan-Meier analysis of duration of response - RECIST v1.1 based on investigator assessment and primary censoring rule (ITT Analysis Set)

	dMMR/MSI-H Population	
Variable [n (%)]	**Dostar + carbo/pac (N=53)**	**Placebo + carbo/pac (N=65)**
Number of responders		
n	38	40
Status [n (%)]		
Events observed	14 (36.8%)	33 (82.5%)
Disease progression	13 (34.2%)	33 (82.5%)
Death	1 (2.6%)	0
Censored	24 (63.2%)	7 (17.5%)
Estimates for DOR (months) Quartile (95% CI) [a]		
25%	6.2 (1.4, NR)	3.0 (2.8, 4.2)
50%	NR (10.1, NR)	5.4 (3.9, 8.1)
75%	NR (NR, NR)	8.3 (6.9, NR)
Duration ≥6 months	28 (73.7%)	18 (45.0%)
Duration ≥12 months	22 (57.9%)	7 (17.5%)
Probability of DOR (95% CI)		
Month 6	76.1%	46.2%
	(59.0%, 86.8%)	(30.2%, 60.7%)
Month 12	62.1%	19.2%
	(44.4%, 75.5%)	(8.6%, 33.1%)
Month 18	62.1%	13.2%
	(44.4%, 75.5%)	(4.6%, 26.3%)
Month 24	62.1%	13.2%
	(44.4%, 75.5%)	(4.6%, 26.3%)

carbo=carboplatin; Dostar=dostarlimab; ITT=intent-to-treat; pac=paclitaxel; NR=not reached; DOR=duration of response.

a. 95% CIs generated using the method of Brookmeyer and Crowley [Brookmeyer, 1982].

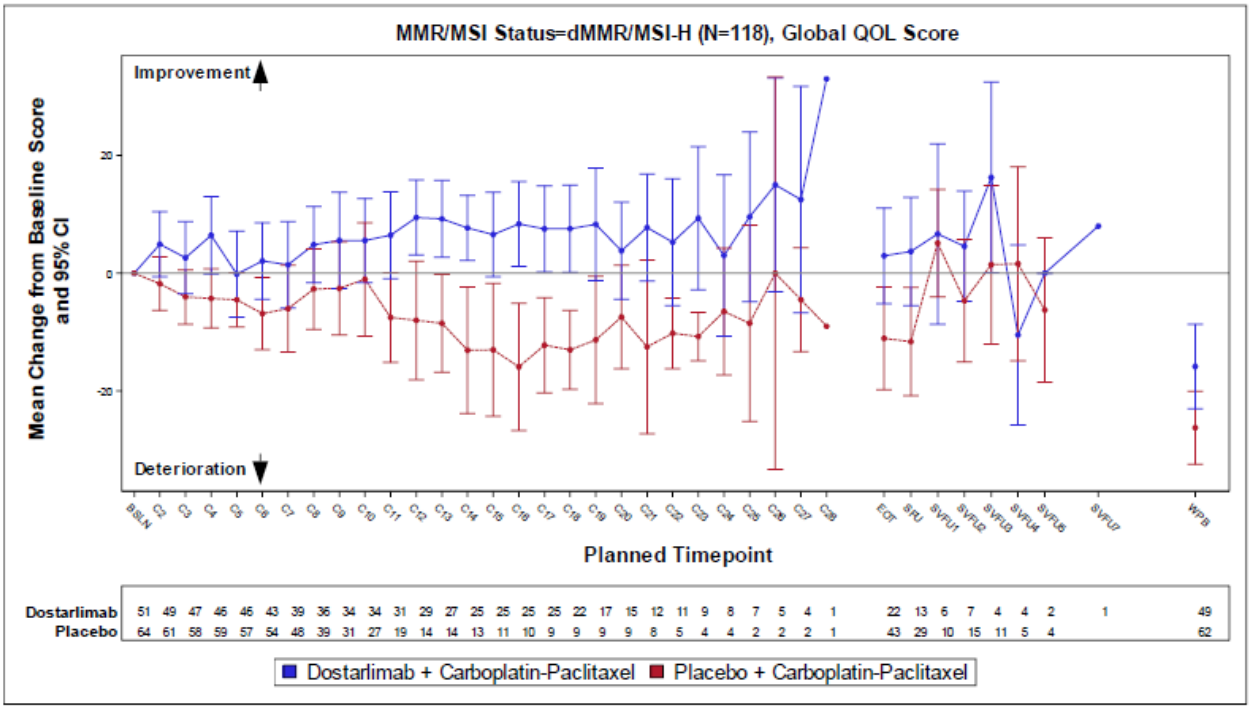
Table 35. Summary of Tumor Response – RECIST v1.1 for Subjects with Target Lesion or Non-target Lesion at Baseline based on BICR Assessment (dMMR/MSI-H population, ITT Analysis Set)

Variable	Dostarlimab + Carboplatin/Paclitaxel (N=53)	Placebo + Carboplatin/Paclitaxel (N=65)
Number of Subjects with Target Lesion or Non-Target Lesion at Baseline		
n	48	60
Best Overall Response by RECIST v1.1 [n(%)][a,c]		
CR	11 (22.9)	8 (13.3)
PR	26 (54.2)	30 (50.0)
SD	3 (6.3)	13 (21.7)
Non-CR/Non-PD	4 (8.3)	4 (6.7)
No disease	0	0
PD	2 (4.2)	2 (3.3)
Not Evaluable	2 (4.2)	3 (5.0)
Objective Response Rate (ORR)[c]		
n(%)	37 (77.1)	38 (63.3)
95% CIb	(62.7, 88.0)	(49.9, 75.4)
Disease Control Rate (DCR)[c]		
n(%)	44 (91.7)	55 (91.7)
95% CIb	(80.0, 97.7)	(81.6, 97.2)

Note: DCR is defined as the percentage of patients with a RECIST v1.1 CR, PR, SD, Non-CR/Non-PD, No disease.
[a]CR=Complete Response, PR=Partial Response, SD=Stable Disease, PD= Progressive Disease.
[b]Exact 2 sided 95% confidence interval for the binomial proportion.
[c]Denominator is number of subjects with target lesion at baseline.
NE = Not Estimable.
Data Cutoff Date: 28SEP2022

- **Patient-reported Outcomes**

Figure 42. Changes from baseline and confidence intervals in EORTC QLQ-C30 global QoL score (dMMR/MSI-H population, ITT analysis set)



Source: Figure 15.4.2

Table 36. Summary of changes from baseline in EORTC QLQ-C30 global QoL score (dMMR/MSI-H population, ITT analysis set)

	Dostarlimab + Carboplatin/Paclitaxel (N=53)	Placebo + Carboplatin/Paclitaxel (N=65)
All participants (n)	51	64
Mean (SD) baseline score	66.7 (25.91)	67.3 (23.93)
Status at Cycle 7 (n)[a]	39	48
Mean (SD) change from baseline to Cycle 7	1.4 (23.33)	-6.0 (26.12)
Improved [n (%)]	14 (35.9)	12 (25.0)
Stable [n (%)]	15 (38.5)	16 (33.3)
Worsened [n (%)]	10 (25.6)	20 (41.7)
Status at Cycle 13 (n)	27	14
Mean (SD) change from baseline to Cycle 13	7.7 (14.01)	-5.2 (10.26)
Improved [n (%)]	12 (44.4)	2 (14.3)
Stable [n (%)]	12 (44.4)	7 (50.0)
Worsened [n (%)]	3 (11.1)	5 (35.7)

Abbreviations: dMMR=mismatch repair deficient; EORTC QLQ=European Organization for Research and Treatment of cancer quality of life questionnaire; ITT=intent-to-treat; MSI-H=microsatellite instability-high; QoL=quality of life.
[a]Number of participants with non-missing value at both baseline and the corresponding postbaseline visit.
Source: Table 14.4.1.1 and Table 14.4.1.2

Ancillary analyses

Subgroup analyses

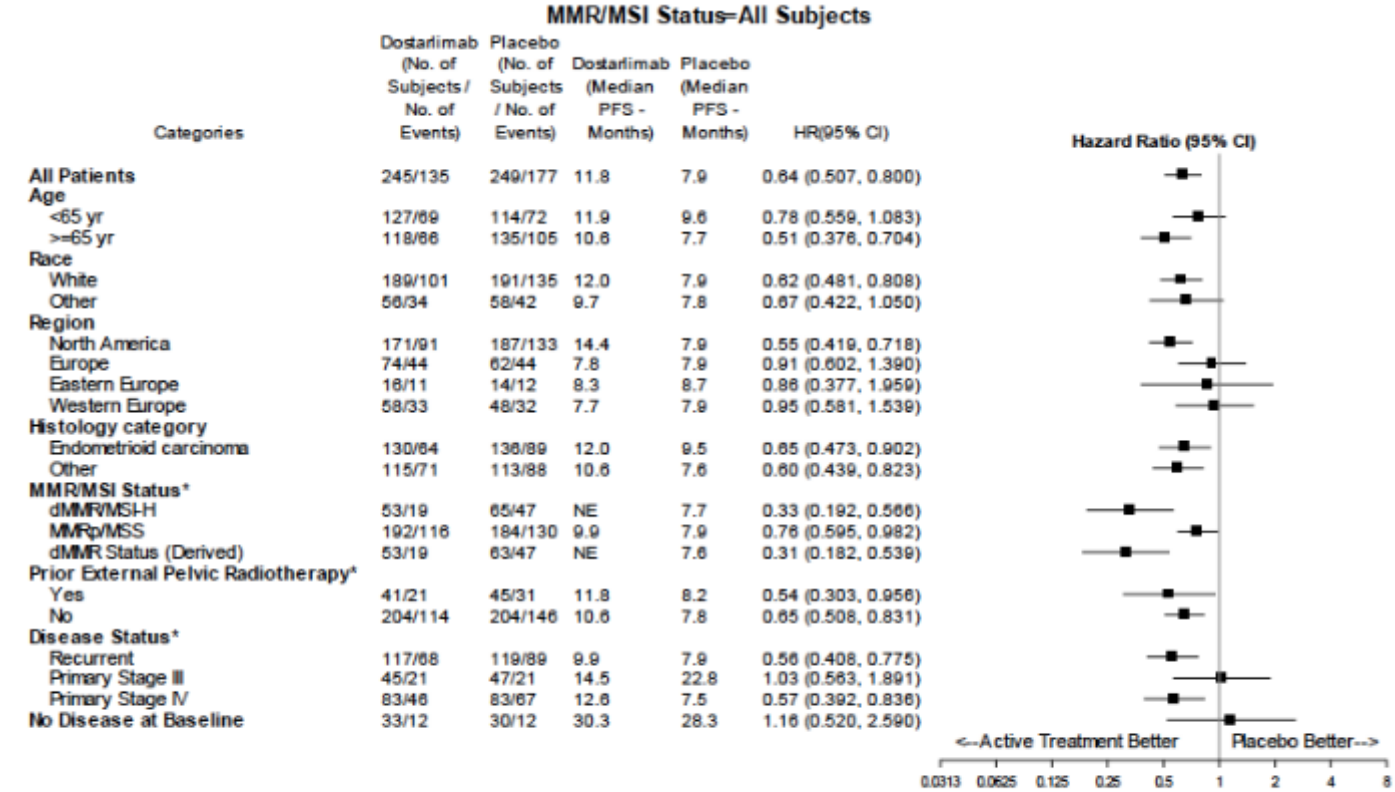
Progression-free Survival

A forest plot of PFS in the **overall population** showed HRs <1 for all subgroups, with the only exceptions being the categories of Stage III primary disease status (HR of 1.03 [95% CI 0.563, 1.891]) and no

baseline disease (HR of 1.16 [95% CI 0.520, 2.590]). In addition, higher HRs were observed in Europe versus North America. The inability to detect a treatment difference in PFS in certain subgroups should be interpreted with caution and may be attributed to the smaller participant numbers, the low data maturity in some subgroups, and the fact that the analysis was not powered to detect treatment differences in any subgroup.

A forest plot of PFS in the **dMMR/MSI-H population** showed HRs <1 for all subgroups with generally similar trends as in the overall population, although individual subgroups in this population have small numbers of participants.

Figure 43. Forest plot of progression free survival and 95% confidence intervals by subgroup - RECIST v1.1 by investigator assessment (Primary Analysis) (Overall population, ITT analysis set)

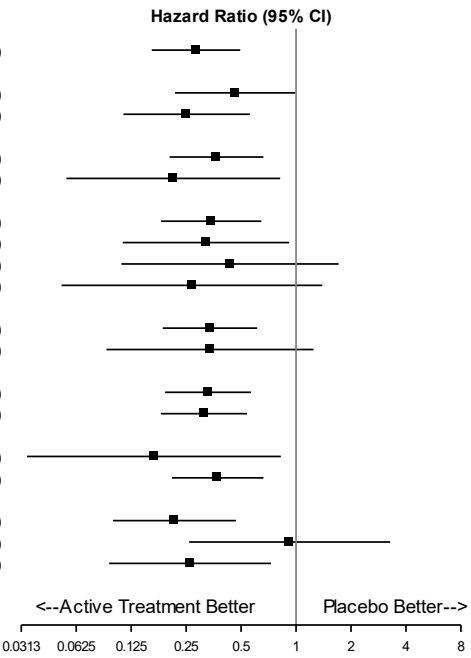


Note: HRs presented are from unstratified Cox regression model.
Source: Figure 15.2.1

Figure 44. Forest plot of progression free survival and 95% confidence intervals by subgroup - RECIST v1.1 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



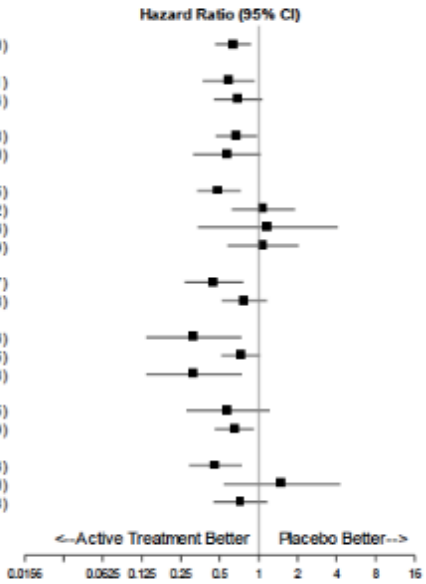
Note: HRs presented are from unstratified Cox regression model.

Overall Survival

Figure 45. Forest plot of overall survival and 95% confidence intervals by subgroup (Overall population, ITT analysis set)

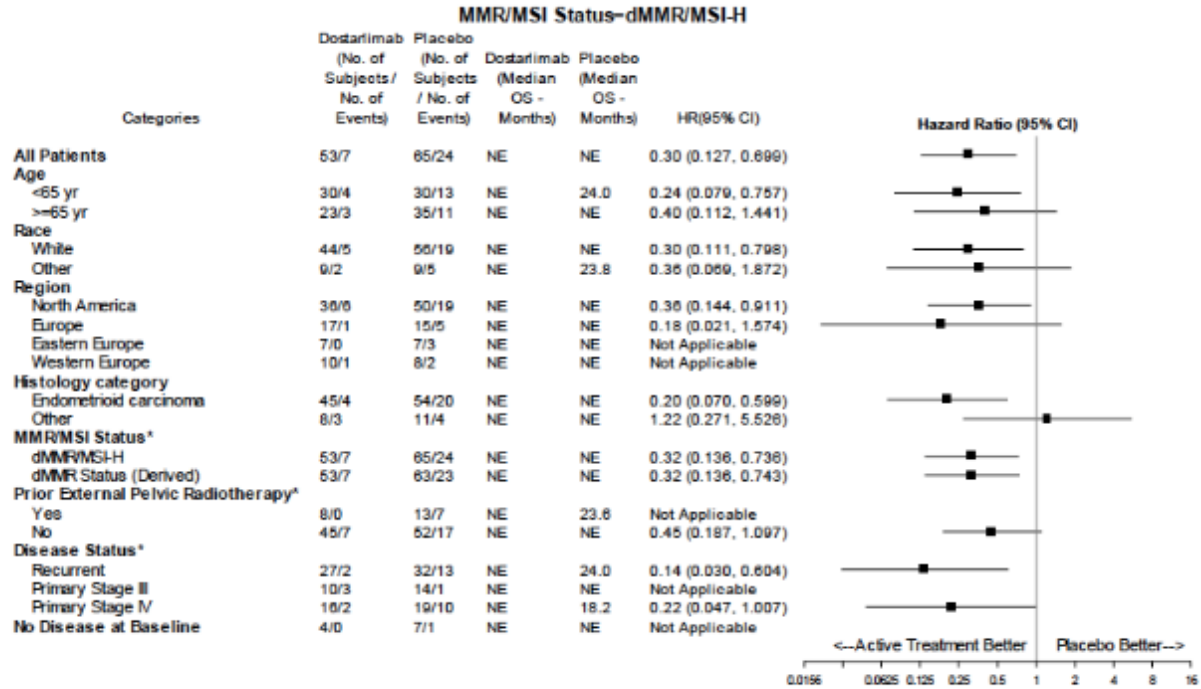
MMR/MSI Status=All Subjects

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	245/65	249/100	NE	NE	0.64 (0.464, 0.870)
Age					
<65 yr	127/31	114/44	NE	29.8	0.59 (0.370, 0.931)
>=65 yr	118/34	135/56	NE	NE	0.69 (0.453, 1.064)
Race					
White	189/48	191/71	NE	NE	0.67 (0.465, 0.968)
Other	56/17	58/29	29.8	22.0	0.57 (0.313, 1.040)
Region					
North America	171/39	187/77	NE	NE	0.49 (0.335, 0.725)
Europe	74/26	62/23	NE	NE	1.09 (0.620, 1.912)
Eastern Europe	16/5	14/5	NE	NE	1.18 (0.341, 4.096)
Western Europe	58/21	48/18	26.5	NE	1.08 (0.575, 2.029)
Histology category					
Endometrioid carcinoma	130/21	136/47	NE	NE	0.45 (0.270, 0.757)
Other	115/44	113/53	29.8	23.1	0.78 (0.520, 1.156)
MMR/MSI Status*					
dMMR/MSI-H	53/7	65/24	NE	NE	0.32 (0.136, 0.736)
MMRp/MSS	192/58	184/76	NE	29.8	0.73 (0.517, 1.025)
dMMR Status (Derived)	53/7	63/23	NE	NE	0.32 (0.136, 0.743)
Prior External Pelvic Radiotherapy*					
Yes	41/11	45/20	NE	26.1	0.58 (0.278, 1.215)
No	204/54	204/80	NE	NE	0.65 (0.460, 0.919)
Disease Status*					
Recurrent	117/26	119/52	NE	26.1	0.46 (0.289, 0.743)
Primary Stage III	45/9	47/8	NE	NE	1.52 (0.540, 4.260)
Primary Stage IV	83/30	83/42	29.8	22.1	0.72 (0.462, 1.163)
No Disease at Baseline	33/3	30/1	NE	NE	Not Applicable



Note: HRs presented are from unstratified Cox regression model.
Source: Figure 15.2.2

Figure 46. Forest plot of overall survival and 95% confidence intervals by subgroup (dMMR/MSI-H population, ITT analysis set)



Note: HRs presented are from unstratified Cox regression model.
Source: Figure 15.2.2

Progression-Free Survival Based on Evaluable Disease Status at Baseline

- Participants with Target or non-Target Lesions at Baseline

The PFS results in the subgroup analysis of participants with evaluable disease (those who have target or non-target lesions) at baseline were consistent with the PFS results by Investigator assessment (primary analysis).

- Participants with Target Lesions at Baseline

The PFS results in the subgroup analysis of participants with measurable disease (those who have target lesions) at baseline were consistent with the PFS results by Investigator assessment (primary analysis).

Table 37. 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 (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 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)	

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

a. Stratified Cox regression model

Source: Table 14.2.1.18 and Table 14.2.1.19

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 cutoff 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 participants (54% overall), including 76 participants with dMMR/MSI-H EC and 192 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%]. Due to the small number of participants in the dMMR/MSI-H subgroup with PDL1- (CPS <1), efficacy results of only ORR and DOR are provided.

Table 38. Summary of PD-L1 Status at Baseline (ITT Analysis Set)

MMR/MSI status: dMMR/MSI-H

Category [n (%)]	Dostarlimab + Carboplatin/Paclitaxel (N=53)	Placebo + Carboplatin/Paclitaxel (N=65)	Total (N=118)
PD-L1 status*			
PD-L1+	31 (58.5%)	27 (41.5%)	58 (49.2%)
PD-L1-	4 (7.5%)	14 (21.5%)	18 (15.3%)
Not Evaluable	18 (34.0%)	24 (36.9%)	42 (35.6%)

MMR/MSI status: MMRp/MSS

Category [n (%)]	Dostarlimab + Carboplatin/Paclitaxel (N=192)	Placebo + Carboplatin/Paclitaxel (N=184)	Total (N=376)
PD-L1 status*			
PD-L1+	67 (34.9%)	66 (35.9%)	133 (35.4%)
PD-L1-	37 (19.3%)	22 (12.0%)	59 (15.7%)
Not Evaluable	88 (45.8%)	96 (52.2%)	184 (48.9%)

Table 39. Efficacy data by PD-L1 expression

	dMMR/MSI-H			
	PDL1 negative		PDL1 positive	
	Dostarlimab + Carboplatin/Paclitaxel	**Placebo + Carboplatin/Paclitaxel**	**Dostarlimab + Carboplatin/Paclitaxel**	**Placebo + Carboplatin/Paclitaxel**
	n=4	n=14	n=31	n=27
ORR (n/N, %)	4/4 (100%)	8/14 (57.1%)	21/31 (67.8%)	16/27 (59.2%)
ORR, target or NT at baseline[a] (n/N, %)	4/4 (100%)	8/13 (61.5%)	21/29 (72.4%)	16/21 (76.2%)
DOR (months, 95%CI)	NR (1.4, NR)	6.4 (3.8, 10.1)	NR (8.4, NR)	4.2 (2.8, 7.0)
PFS (HR, 95%CI)	--		0.33 (0.147, 0.736), p = 0.0029	
OS (HR, 95%CI)	--		0.32 (0.115, 0.901), p=0.0118	

dMMR=mismatch repair deficient; PD-L1=programmed cell death-ligand 1; NR=not reached

[a]The population with Target or Non-target lesions at baseline includes 4 and 13 PDL1 negative participants and 29 and 21 PDL1+ participants in dostarlimab and chemo arms, respectively

Source: Appendix 4, Table 14.1.1.35, Table 14.2.1.45a, Table 14.2.1.46a, Table 14.2.1.52, Table 14.2.1.53

Sensitivity analyses

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

Sensitivity analyses 1 and 2 used alternate censoring rules for PFS, sensitivity analysis 3 used BICR assessment instead of investigator assessment (and was performed as a secondary endpoint), and sensitivity analysis 4 was performed to address the potential misclassification of randomization stratification factors (using stratification factors based on the source verified values from eCRF in the stratified log-rank test and stratified cox model). Sensitivity analysis 5 based on the per protocol analysis set was not conducted because the per-protocol analysis set comprised >90% of the ITT analysis set.

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 dMMR/MSI-H and MMRp/MSS populations prespecified based on the source verified data at the time of the data cutoff. This paired sensitivity analysis was performed for PFS, to the primary analysis and sensitivity analyses 1-4.

The paired sensitivity analysis was also conducted on other efficacy endpoints as assessed by the Investigator including OS, ORR, DOR, PFS2, and for PFS in those with measurable disease (target lesions) at baseline; or evaluable disease (target or non-target lesions) at baseline.

Table 40. Hazard Ratios of Progression-Free Survival from Sensitivity Analyses

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

Source: Table 14.2.1.2, Table 14.2.1.3, Table 14.2.1.4, Table 14.2.1.5

Table 41. 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=60)	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

Source: Table 14.2.1.1, Table 14.2.1.2, Table 14.2.1.3, Table 14.2.1.4, Table 14.2.1.5, Table 14.2.1.8, Table 14.2.1.20, Table 14.2.1.21, Table 14.2.1.22, Table 14.2.1.23, Table 14.2.1.24, Table 14.2.1.27

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", which showed a PFS HR of 0.63 (95% CI 0.506, 0.785; median

PFS 11.8 months vs 7.9 months) in the overall population, as well as HR 0.27 (95% CI 0.154, 0.462; median PFS not reached vs 7.6 months) in the dMMR/MSI-H population.

Table 42. Summary of Kaplan Meier Analysis of Progression Free Survival - per RECIST v1.1 based on Investigator Assessment and Sensitivity Censoring Rule 3 using Stratification Factors from Randomization List (dMMR/MSI-H population, ITT Analysis Set)

Variable	Dostarlimab + Carboplatin/Paclitaxel (N=53)	Placebo + Carboplatin/Paclitaxel (N=65)
PFS		
Status [n (%)]		
Events observed	19 (35.8)	52 (80.0)
Disease progression	16 (30.2)	45 (69.2)
Death	3 (5.7)	7 (10.8)
Censored	34 (64.2)	13 (20.0)
Estimates for PFS (months)		
Quartile (95% CI)[a]		
25%	6.7 (4.1, 12.2)	5.4 (4.1, 5.6)
50%	NE (11.8, NE)	7.6 (5.6, 9.5)
75%	NE (NE, NE)	11.7 (9.6, 20.1)
PFS probability (95% CI) at		
Month 6	80.2% (66.3, 88.8)	57.6% (44.5, 68.6)
Month 12	63.5% (48.5, 75.3)	22.0% (12.5, 33.2)
Month 18	61.4% (46.3, 73.4)	16.1% (7.9, 26.9)
Month 24	61.4% (46.3, 73.4)	14.1% (6.5, 24.6)
Hazard ratio[b] (95% CI)	0.27 (0.154, 0.462)	
Hazard ratio[b] (96% CI)	0.27 (0.150, 0.475)	
p-value of 1-sided stratified log-rank test	<.0001	

[a]95% Confidence intervals generated using the method of Brookmeyer and Crowley (1982).
[b]Stratified Cox regression.
NE = Not Estimable.
Data Cutoff Date: 28SEP2022

Summary of main study(ies)

The following tables summarise the efficacy results from the main studies supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Table 70. 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) – Part 1		
Study identifier	Study 213361 (formerly referred to as 4010-03-001; ENGOT EN-6; GOG-3031) EudraCT: 2019-001576-11	
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 (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 sought indication is a subset of the overall population: the dMMR/MSI-H population.	
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:	From 07-AUG-2019. Ongoing. Not applicable Not applicable
Hypothesis	Superiority	

Treatments 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	Primary endpoint (dual)	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. PFS was assessed in both in the dMMR/MSI-H and overall populations of participants with primary advanced or recurrent EC.
	Primary endpoint (dual)	OS	Time from randomization to the date of death by any cause. OS was formally assessed only in the overall population.
	Secondary endpoint	PFS by BICR	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.
	Secondary endpoint	ORR by BICR and investigator	Proportion of subjects with a best overall response (BOR) of complete response (CR) or partial response (PR).
	Secondary endpoint	DOR by BICR and investigator	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.
	Secondary endpoint	DCR by BICR and investigator	Proportion of participants who have achieved a BOR of CR, PR, SD, non-CR/non-PD, or no disease per RECIST v1.1.
	Secondary endpoint	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 is earlier.
Database lock	23 Nov 2022 (data unblinding); 28 Sep 2022 (data cut-off)		

Results and Analysis

Analysis description	**Primary Analysis (dMMR/MSI-H population)**		
Analysis population and time point description	118 subjects (dostarlimab plus carboplatin-paclitaxel: 53, and placebo plus carboplatin-paclitaxel: 65)		
Descriptive statistics and estimate variability	Treatment group	Dostarlimab+carboplatin-paclitaxel	Placebo+carboplatin-paclitaxel
	Number of subjects	53	65
	PFS by investigator (median, months)	NR	7.7
	95 % CI	(11.8, NR)	(5.6, 9.7)
	OS (median, months)	NR	NR
	95 % CI		(23.2, NR)
	PFS by BICR (median, months) 95 % CI	NR NR	9.5 (7.0, 11.7)
	ORR by investigator (%) 95 % CI	77.6 (63.4, 88.2)	69.0 (55.5, 80.5)
	DOR by investigator (median, months) 95 % CI	NR (10.1, NR)	5.4 (3.9, 8.1)

	DCR by investigator (%) 95 % CI	90.6 (79.3, 96.9)	89.2 (79.1, 95.6)
	PFS2 (median, months) 95 % CI	NR	22.0 (13.4, NR)
Effect estimate per comparison	Primary endpoint: PFS by investigator	Comparison groups	Dostarlimab plus carboplatin-paclitaxel vs. Placebo plus carboplatin-paclitaxel
		Hazard ratio (HR)	0.28
		95% CI	0.162, 0.495
		P-value	<0.0001
	Secondary endpoint: PFS by BICR	Comparison groups	Dostarlimab plus carboplatin-paclitaxel vs. Placebo plus carboplatin-paclitaxel
		Hazard ratio (HR)	0.29
		95% CI	0.158, 0.543
		P-value	p<0.0001
	Secondary endpoint: PFS2	Comparison groups	Dostarlimab plus carboplatin-paclitaxel vs. Placebo plus carboplatin-paclitaxel
		Hazard ratio (HR)	0.37
		95% CI	0.189, 0.727
		P-value	0.0013 (1-sided)
	Prespecified Additional Analysis: OS	Comparison groups	Dostarlimab plus carboplatin-paclitaxel vs. Placebo plus carboplatin-paclitaxel
		Hazard ratio (HR)	0.30
		95% CI	0.127, 0.699
		P-value	0.0016 (nominal)

2.4.3. Discussion on clinical efficacy

With the current application, the MAH is applying for an extension of the indication for Jemperli, in combination with carboplatin and paclitaxel, to be used for the treatment of adult patients with primary advanced or recurrent dMMR/MSI-H endometrial cancer (EC) and who are candidates for systemic therapy. To support this application, results from study RUBY Part 1 have been submitted.

Additionally, with the submission of this type II variation the MAH also intends to fulfil SOB-clin-002 and convert the conditional marketing authorisation (CMA) into full approval.

Design and conduct of clinical studies

Design

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 recurrent or primary advanced EC. This study has two parts, with Part 1 being the object of this submission. Additionally, the intended target population is not the overall population included in Part 1 of the study, but the dMMR/MSI-H population, which was a subset of the overall population. Thus, this discussion is focused on the dMMR/MSI-H population; although results in the overall population have been considered as supportive data in some instances, and, therefore, references to the overall population are made all along the discussion.

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. It is noted that the number of cycles of dostarlimab 500 mg in the applied indication, in which it is administered in combination with chemotherapy, is higher than the number of doses already approved for the indication of dostarlimab as monotherapy (i.e. 6 and 4, respectively). The MAH states that this switch was done to align the cycles of dostarlimab 500 mg with the chemotherapy treatment cycles, which is considered acceptable and endorsed.

Randomization was stratified by MMR/MSI status (dMMR/MSI-H or MMR-proficient [MMRp]/MSS), prior external pelvic radiotherapy (yes or no) and disease status (recurrent, primary Stage III, or primary Stage IV). Those randomization factors are considered adequate.

The comparator and its posology are also deemed acceptable and in line with the international guidelines (i.e., ESMO guideline) and clinical practice in EU.

Overall, the design of the study is considered adequate to establish the efficacy and safety of dostarlimab in the sought indication.

Study participants

Participants were eligible to be included in Part 1 of this study if they had primary Stage III or Stage IV disease (FIGO staging) or first recurrent EC with a low potential for cure by radiation therapy or surgery alone or in combination. Additionally, participants had to meet at least 1 of the following criteria: Stage IIIA to IIIC1 with measurable disease; Stage IIIC1 disease with carcinosarcoma, clear cell, serous, or mixed histology, regardless of presence of measurable disease; Stage IIIC2 or Stage IV disease, regardless of presence of measurable disease; first recurrent disease and naïve to systemic anticancer therapy; prior neoadjuvant/adjuvant systemic anticancer therapy with recurrence or PD ≥6 months after completing treatment. Patients with uterine sarcoma were not allowed.

Patients were excluded if they had 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. Of note, radiotherapy was not allowed during the study.

Endpoints

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). In this context, although OS would have been the preferred option, a dual (PFS and OS) primary endpoint was also considered acceptable, provided relatively mature and positive/supportive OS data would be available at the time of a benefit-risk assessment, as pointed out in the scientific advice (EMEA/H/SA/3585/2/2018/II). In this regard, it should be noted that the advice provided referred to the overall population instead of to the dMMR/MSI-H population. Since the object of this submission is the dMMR/MSI-H population, and for this population the OS data was not formally assessed, OS data from the overall population has been considered as supportive data.

Secondary endpoints included PFS by a blinded independent central review (BICR), ORR by BICR and investigator, DOR by BICR and investigator, DCR by BICR and investigator, PFS2 and PROs. All secondary endpoints are overall endorsed. Additional comments on the adequacy of primary and secondary endpoints, and its changes over the conduct of the clinical trial, are further discussed in the section "Protocol amendments".

Sample size and statistical methods

The assumptions and operating characteristics presented justify the total sample size of 470 patients that was planned considering that the study would have been powered at a level of 89% at the end of the

study using a one-sided 2% alpha. In addition, one interim analysis was planned when 84.6% of the information is accrued and, in case that both tests would have not been significant, then the dual primary endpoint would have been tested at the time of the final analysis. The overall plan is acceptable.

A graphical approach has been used to control the type I error for the dual endpoints. This approach also allows recycling the alpha from PFS to OS in case the first endpoint is significant. This method controls the type I error appropriately and is endorsed.

It is important to note that the duration of treatment that the MAH proposes is for up to 3 years (or until disease progression or unacceptable toxicity): in section 4.2 of the SmPC it is stated that "*Administration of dostarlimab should continue according to the recommended schedule until disease progression or unacceptable toxicity, or for a duration of up to 3 years (see section 5.1).*" At the time of the DCO 16 (30.8%) patients in the dostarlimab arm and 8 (12.3%) in the placebo arm have received >2 years of treatment. According to the MAH, a 3-year treatment duration was chosen because most recurrences in EC are diagnosed within 3 years of primary treatment. In the updated data provided after approximately 5 additional months of follow-up (DCO: 1-Mar-2023), 8 participants with dMMR/MSI-H have received 3 years of dostarlimab or placebo, out of 117. 6 out of the 8 participants were in the dostarlimab plus chemo arm. Although uncertainties still remain regarding the long-term treatment effects (due to the fact that only 6 patients received dostarlimab for 3 years), the proposed treatment duration is considered acceptable. Section 5.1 of the SmPC includes a sentence specifying the number of patients who received treatment for 3 years.

Conduct of the study

Protocol amendments

The protocol has been amended three times since its initial version, dated 13 March 2019. These amendments included relevant changes regarding the definition of the primary endpoint: with amendment 1 (11 November 2020) it was first changed from "PFS per investigator assessment" to "PFS per BICR"; with amendment 2 (23 September 2021) it was changed to a dual primary endpoint including both PFS and OS; and finally, with amendment 3 (31 March 2022) it was reverted to "PFS assessed by the investigator". According to the MAH the initial change of the primary endpoint was made to mitigate the potential risk of bias associated with some investigators requesting to unblind treatment allocation when participants entered the treatment maintenance phase, with the aim of keeping those that were assigned to the placebo arm from visiting the study site during the COVID-19 pandemic. The rationale of this amendment is not fully clear, since it is understood that patients were supposed to visit the study site regardless of their allocation. Additionally, with amendment 1 the MAH also included Part 2 of the RUBY study. With amendment 2, OS was included as dual primary endpoint (as suggested in the scientific advice EMEA/H/SA/3585/2/2018/II) splitting the alpha (2% for PFS and 0.5% for OS) allowing alpha recycling from PFS to OS. Also, the MAH changed the Hochberg procedure to hierarchical testing strategy for PFS (also recommended in the scientific advice). Finally, with amendment 3, apart from the reversion of the primary endpoint from "PFS by BICR" to "PFS by investigator", the PFS analysis in Part 2 was removed per regulator's feedback. No further comments are made regarding Part 2 of the RUBY study, since that part of the study is not part of this submission.

No clear justification of the (last) change from "PFS by BICR" to "PFS by investigator". Additionally, even if the inclusion of OS as a (dual) primary endpoint is welcome, it is unclear why OS was added as a dual primary endpoint in Protocol amendment 2 (dated September 2021), instead of considering it as a primary endpoint since the very beginning of the clinical trial, as it was advised by the CHMP during the SA in February 2019 (EMEA/H/SA/3585/2/2018/II). Even if changes in the endpoints during the conduct of a study should be avoided, the inclusion of OS as primary endpoint is endorsed. Besides, regarding PFS, the fact that the study was double blind and results between BICR and investigator appear consistent is reassuring.

Protocol deviations

A relatively high number of important protocol deviations is noted in both arms of the dMMR/MSI-H population, with a slight imbalance towards a higher percentage in the dostarlimab arm (45.3% vs. 35.4% in the placebo arm). Although the number of events in the dostarlimab arm is lower than in the placebo arm (50 in the dostarlimab arm vs. 73 in the placebo arm). The most frequently reported protocol deviation category was "assessment or time point completion" (17.0% vs. 12.3%), being "out of window – efficacy assessment" the subcategory most frequently reported (15.1% vs. 6.2%). Apart from that slight difference, no particular trend in terms of the frequency of protocol deviations by event category is observed, which is reassuring.

Baseline data

As of the data cut-off date 607 patients were screened for eligibility and of these, 494 participants (overall population) were randomized 1:1 to receive either dostarlimab plus carboplatin - paclitaxel (N=245) or placebo plus carboplatin-paclitaxel (N=249). The most frequently reported reason for not meeting eligibility was not meeting inclusion criterion 1 (*Female subject at least 18 years of age, who is able to understand the study procedures and agrees to participate in the study by providing written informed consent)*
: 21 subjects (3.5%). All the other reasons for not meeting eligibility were reported with a similar frequency, with no particular trend observed.

Among the overall population, **118 patients** (53 in the dostarlimab plus carboplatin-paclitaxel arm and 65 in the placebo plus carboplatin-paclitaxel arm) were **dMMR/MSI-H**. The prespecified dMMR/MSI-H population for efficacy analysis was determined by the source verified value of MMR/MSI status.

At DCO, in the dostarlimab arm of the dMMR/MSI-H population 75.5% of patients were ongoing in the study (43.4% were on study treatment and 32.1% were in follow-up), vs. 50.8% in the placebo arm (12.3% were on study treatment and 38.5% in follow-up). In both arms most patients discontinued from the study due to death from any cause, but the incidence in the dostarlimab arm was notably lower than in the placebo arm: 13.2% vs. 36.9%. The most frequent reason of death was disease progression in both arms, but, similarly, this percentage was lower in the dostarlimab arm than in the placebo arm: 9.4% vs. 29.2%. AEs were the primary cause of death in 3.8% patients in the dostarlimab arm, while in the placebo arm no patient died with AE as the primary cause of death.

As previously outlined, at DCO, 44.2% patients in the dostarlimab arm were ongoing on dostarlimab, and 12.3% were ongoing on placebo; that is, the percentage of patients on study treatment was more than three times higher in the dostarlimab arm than in the placebo arm. Primary reason for discontinuation of study treatment was progression disease in both arms: 25.0% in the dostarlimab arm vs. 61.5% in the placebo arm; which is also considered as a relevant difference. AEs were the primary reason for treatment discontinuation of dostarlimab or placebo in 17.3% of patients in the dostarlimab arm vs. 10.8% in the placebo arm, which remains within acceptable limits.

Demographic characteristics

In the *dMMR/MSI-H population* the demographic characteristics were overall similar between arms, although some differences have been observed. Median age was 61.0 years (range: 45, 81) in the dostarlimab arm, vs. 66.0 years (range: 39, 85) in the placebo arm. In line with this observation, the percentage of patients ≥65 years was higher in the placebo arm in comparison with the dostarlimab arm: 53.8% vs. 43.4%, respectively. Median weight was also higher in the placebo arm than in the dostarlimab arm: 92.00 kg in the placebo arm vs. 75.85 kg in the dostarlimab arm. In line with this, median BMI was also higher in the placebo arm than in the dostarlimab arm: 35.50 in the placebo arm vs. 30.55 in the dostarlimab arm. A slight difference was also noted in the ECOG performance status: 60.0% of patients in the placebo arm had a score of 0, vs. 53.8% of patients in the dostarlimab arm.

Disease characteristics

Most patients were Stage III or IV at initial diagnosis: 26.4% were Stage III in the dostarlimab arm vs. 30.8% in the placebo arm; and 26.4% were Stage IV in the dostarlimab arm vs. 23.1% in the placebo arm. The percentages of Stage I and II patients were similar between both arms: 34.0% vs. 33.8% were Stage I; and 5.7% vs. 7.7% were Stage II. The proportion of patients with recurrent endometrial cancer was of 50.9% in the dostarlimab arm vs. 49.2% in the placebo arm.

Endometrioid carcinoma was the most frequent histology type at diagnosis, accounting for 83.9%. Four (7.5%) patients in the dostarlimab arm had carcinosarcoma, vs. 2 (3.5%) patients in the placebo arm. Of note, in the scientific advice (EMEA/H/SA/3585/2/2018/II) the CHMP expressed their concerns regarding the possible heterogeneity in response in the rare histology types, like carcinosarcoma (which is a more aggressive histological subtype). The CHMP suggested that an option to mitigate the risk of including rare histology subtypes with a possible different response could be to allow the enrolment in the study but to exclude these subjects from the primary efficacy analysis. Of note, this approach has not been followed, although, again, it is acknowledged that the SA received was based on the overall population submission, instead of on the dMMR/MSI-H population. Considering the low number of patients in each arm, the MAH's approach of not excluding those patients from the primary analysis is considered acceptable. Of note, subgroup analyses by histology (i.e. endometrial carcinoma vs other), showed consistent results.

Prior treatments

In the *dMMR/MSI-H population* 13.2% of patients in the dostarlimab arm vs. 15.4% in the placebo arm had received any prior anticancer treatment. It is understood that those patients received treatment in the (neo)adjuvant setting and had a recurrence setting, since the ones in the primary setting are supposed to be newly diagnosed; and, therefore, are not supposed to have received any prior anticancer treatment. Most of those patients had received paclitaxel with carboplatin: 7.5% in the dostarlimab arm vs. 9.2% in the placebo arm. No relevant differences between treatment arms are observed in terms of prior anticancer treatments received; although it is noted that the total number of patients who received prior anticancer treatment in each arm is very small (N=7 in the dostarlimab arm and N=10 in the placebo arm). The majority of patients had not received prior external pelvic radiotherapy (84.7%) and had received prior EC surgery (92.4%).

Regarding surgery, around 92% of patients had received prior anticancer surgery for the endometrial cancer.

All this considered, it can be concluded that there were no relevant differences between arms in terms of prior medications and prior surgery in the dMMR/MSI-H population.

Efficacy data and additional analyses

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). Since the object of this submission is the dMMR/MSI-H population, the efficacy discussion is focused on this population rather than on the overall population. Nevertheless, OS and PFS by investigator in the overall population are considered as supportive data, and, as such, are also briefly discussed. It should be noted that since the only formal OS analysis was conducted in the overall population, for the assessment of the OS data the analysis in this population is of greater importance. Median follow-up in the dMMR/MSI-H population was of 24.79 months (2 years, DCO 28-Sep-2022).

Primary endpoints

The primary endpoint in the *dMMR/MSI-H population* (**PFS by investigator**) was met: dostarlimab in combination with carboplatin-paclitaxel reduced the risk of progression of death by 72% in the dMMR/MSI-H primary advanced or recurrent endometrial cancer patients (HR: 0.28; 95% CI 0.162, 0.495; p-value <0.0001). The stopping boundary (p=0.00630) for claiming superiority of dostarlimab over placebo at the interim analysis was crossed. Additionally, the KM curve shows a clear benefit of dostarlimab over placebo, with curves separating at around the fourth month. In the dostarlimab arm there were 19 events observed (35.8%), vs. 47 events (72.3%) in the placebo arm. Of the events observed, there were 16 disease progressions (30.2%) in the dostarlimab and 44 (67.7%) in the placebo arm; together with 3 deaths in each arm, which accounted for the 5.7% in the dostarlimab arm and for the 4.6% in the placebo arm. Regarding the number of patients censored, it is noted that in the dostarlimab arm the number of censored patients is relevantly higher compared with the placebo arm: 34 (64.2%) vs. 18 (27.7%) patients, respectively. Median PFS in the dostarlimab arm was not reached (95% CI: 11.8, NR), vs. a median PFS of approximately 7.7 (95% CI: 5.6, 9.7) months in the placebo arm.

Several sensitivity analyses were conducted by the MAH using alternate censoring rules for PFS (sensitivity analysis 1 and 2), using BICR assessment instead of investigator assessment (sensitivity analysis 3, which was also performed as a secondary endpoint) and using stratification factors based on the source verified values from eCRF in the stratified log-rank test and stratified cox model to address the potential misclassification of randomization stratification factors (sensitivity analysis 4). Additionally, a post-hoc sensitivity analysis was performed based on censoring rule 3 "censored at last tumour assessment regardless if still on therapy or not", as requested in the scientific advice (EMEA/H/SA/3585/2/2018/II). All those sensitivity analyses showed a highly consistent effect in the dMMR/MSI-H population.

PFS by investigator in the *overall population* (at 63% PFS maturity) was also met, with a HR of 0.64 (95% CI 0.507, 0.800). Median PFS was 11.8 months in the dostarlimab arm, vs. 7.9 months in the placebo arm. The stopping boundary (p=0.02) for claiming superiority of dostarlimab over placebo was crossed (p<0.0001) at this interim analysis.

Of note, updated efficacy data of PFS and the other secondary endpoints were requested, but the MAH stated that no additional analysis for PFS or other secondary endpoints were planned in the protocol, and, as such, no further data are available.

OS in the *dMMR/MSI-H population* was not a primary endpoint, but a prespecified analysis was performed. At 26% maturity (31 events) there was a trend in favour of dostarlimab, with an HR of 0.30 (95% CI: 0.127, 0.699; nominal p=0.0016). The KM curve shows a separation between arms at approximately month 7, with no arm reaching median OS. It should be noted that although the number of events is low (N=7 [13.2%] in the dostarlimab arm and N=24 [36.9%] in the placebo arm), and, therefore, no clear conclusion can be drawn from these data, it seems evident that at least at this point in time there is a difference between arms, discarding a potential detrimental effect of dostarlimab. Updated OS data with a longer follow-up (DCO: 1st March 2023) were provided during the procedure. At 30% maturity (35 events) a trend in favour of dostarlimab continues to be observed, with a HR of 0.33 (95% CI: 0.155, 0.722). These results are quite consistent with the results initially submitted, which is not surprising considering that only 4 additional events were included with this update. However, considering the low number of events, the MAH will submit the final OS analysis of study RUBY part 1 as a post authorisation efficacy study (PAES) by 30 June 2029.

Regarding censored patients, for both PFS and OS analyses, no concerning data was identified when analysing reasons for censoring. In the same way, further assessment of intercurrent events and handling strategy did not reveal any concerning trend.

OS in the *overall population* was one of the dual primary endpoints. At this OS (first) interim analysis at 33% maturity (165 events) there was a trend in favour of dostarlimab, although statistical significance

was not reached. HR was 0.64 (95% CI 0.464, 0.870; p=0.0021; p-value stopping boundary for significance = 0.00177).

Secondary endpoints

PFS by BICR in the dMMR/MSI-H population was consistent with PFS by investigator, with a HR of 0.29 (95% CI 0.158, 0.543; nominal p<0.0001). Median PFS was not reached in the dostarlimab arm, vs. 9.5 months in the placebo arm. Similarly, to the PFS by investigator's KM curve, in this KM curve a separation between arms is evident, also at approximately month 4. 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 results also favoured the dostarlimab arm over the placebo arm; with an HR of 0.37 (95% CI 0.189, 0.727). Although the confidence interval is wide due to the small number of events observed (12 in the dostarlimab arm and 32 in the placebo arm), these results are consistent with the PFS and the OS results, reassuring about the apparent lack of a detrimental long-term effect.

ORR by investigator was 77.6% (95% CI: 63.4%, 88.2%) in the dostarlimab arm (38/49), vs. 69.0% (95% CI: 55.5%, 80.5%) in the placebo arm (40/58). In the dostarlimab arm there were 15 CRs (28.3%) and 23 PRs (43.4%), whereas in the placebo arm there were 12 CRs (18.5%) and 28 PRs (43.1%). Disease control rate (DCR) was 90.6% in the dostarlimab arm, vs. 89.2% in the placebo arm; which are high and pretty similar percentages. No relevant differences were observed in the analysis of tumour response by BICR. Median duration of response was not reached in the dostarlimab arm and was of 5.4 (95% CI: 3.9, 8.1) months in the placebo arm.

Patient Reported Outcomes (PRO) showed that patients on dostarlimab had similar quality of life than patients on placebo in the dMMR/MSI-H population. Although no statistical analyses were performed, it seems that overall results in the dostarlimab arm were similar to results in the placebo arm. This seems to discard a potential quality of life worsening of patients in the dostarlimab arm compared with patients in the placebo arm.

Subgroup analyses

Overall, subgroup analysis for PFS by Investigator in the dMMR/MSI-H population were generally consistent with the primary analysis except for the subgroup of "primary stage III" with a HR of 0.92 (95% CI 0.260, 3.279). A similar pattern was observed in the overall population (HR 1.03; 95% CI 0.563, 1.891), with a median PFS that was particularly higher in the placebo arm (22.8 months). The MAH justifies these observations by stating that patients with primary stage III would require longer follow-up to detect a treatment difference, since they are expected to have a longer median PFS. Nevertheless, the number of events in this subgroup was very low and CI is wide and, therefore, no conclusions can be drawn. Results in subjects with evaluable disease (i.e., subjects with target or non-target lesions) and in subjects with measurable disease (i.e., subjects with target lesions) were consistent with the results of the primary analysis, both in the overall population and in the dMMR/MSI-H population.

Subgroup analysis for OS have also been provided but in the dMMR/MSI-H population the number of events was so low that it is not possible to draw any conclusion.

PDL-1 positive status (CPS ≥ 1) was slightly more frequent in dMMR/MSI-H patients than in MMRp/MSS patients: 76% of patients were PDL-1 positive in the dMMR/MSI-H subgroup vs. 69% in the MMRp/MSS subgroup. Among dMMR/MSI-H subjects PD-L1 test results were available for a total of 76 (64%) subjects: 35 in the dostarlimab arm and 41 in the placebo arm. Of note, most dMMR/MSI-H subjects for which PD-L1 results were available were PD-L1 positive: 58 patients were PD-L1 positive, vs. 18 PD-L1 negative.

The MAH has provided ORR and DOR data for both the PDL-1 positive and PDL-1 negative subgroups; but, due to the small datasize, PFS and OS data have only been provided for the PDL-1 positive subgroup. Notably, in the PDL-1 negative subgroup there were only 18 subjects in total: 4 in the dostarlimab arm and 14 in the placebo arm. Such low number of subjects impairs drawing any conclusion on potential differences between subgroups. PFS and OS data in the PDL-1 subgroup were similar to the results obtained in the dMMR/MSI-H population regardless of PDL-1 status: the HR for PFS was 0.33 (95% CI: 0.147, 0.736; p=0.0029) and the HR for OS was 0.32 (95% CI: 0.115, 0.901; p=0.0118). It should be noted that ORR between the dostarlimab arm and the placebo arm were not markedly different. The reasons for this finding remain unclear, although no conclusions can be drawn considering the low number of patients. In summary, the low number of PD-L1 negative patients impairs drawing any conclusion on potential efficacy differences between PD-L1 positive patients and PD-L1 negative patients.

Fulfilment of SOB-clin-002

The MAH, with this submission, also intends to fulfil SOB-clin-002 and convert the CMA into full approval. SOB-clin-002:

"In order to confirm the efficacy and safety of dostarlimab in 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, the MAH should submit the results of the phase III, randomised, double-blind study RUBY, comparing the efficacy and safety of dostarlimab in combination with chemotherapy to chemotherapy alone in patients with recurrent or advanced endometrial cancer who have not received prior systemic anticancer therapy for recurrent or advanced disease. The CSR should be submitted by 31 August 2023."

The MAH has presented the results of the RUBY study, in due time. The results of this study have confirmed the efficacy and safety of dostarlimab in adult patients with dMMR/MSI-H recurrent or advanced endometrial cancer. Thus, the SOB-clin-002 can be considered fulfilled and the CMA can be converted into full approval.

2.4.4. Conclusions on the clinical efficacy

The results from the pre-planned interim analysis of the RUBY study have shown a statistically significant improvement in PFS by investigator for dostarlimab in combination with carboplatin-paclitaxel compared to chemotherapy alone in the treatment of patients with primary advanced or recurrent dMMR/MSI-H endometrial cancer and who are candidates for systemic therapy. The OS data at the time of the IA were immature (33% maturity) and, although updated OS data were provided during the procedure, data were still considered immature. Although there is a trend towards an OS improvement and a detrimental effect seems unlikely, uncertainty remains due to the immaturity of the data. Thus, to further characterise the efficacy of dostarlimab in combination with carboplatin and paclitaxel, results from the final OS analysis will be provided by 30 June 2029 (see Annex II condition, PAES).

As the combination treatment phrase in the initially proposed therapeutic indication (i.e. carboplatin and paclitaxel) does not match the treatment allowed by protocol, since only carboplatin and paclitaxel were used as backbone in the pivotal trial, the final indication wording was revised to accurately reflect that (see section 2.1.1).

Additionally, with this submission the MAH intended to fulfil SOB-clin-002, which refers to the submission of the results of Ruby study. The SOB is considered fulfilled, and, as such, the CMA conversion to a full approval is endorsed.

The following measures are considered necessary to address issues related to efficacy:

Post-authorisation efficacy study (PAES): In order to further characterise the efficacy of dostarlimab in combination with carboplatin and paclitaxel chemotherapy 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 final results of the RUBY study part 1.

2.5. Clinical safety

Introduction

This report describes safety data from an interim analysis of Part 1 of the dostarlimab Study 213361, referred to as RUBY (also known as Study 4010-03-001; ENGOT EN-6; GOG-3031) with a data cut-off date of 28 September 2022.

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 subset of the Safety Analysis Set.

Patient exposure

As of the 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 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). Within the dMMR/MSI-H safety population, there were 52 participants in the dostarlimab plus carboplatin-paclitaxel arm and 65 participants in the placebo plus carboplatin-paclitaxel arm.

The overall median treatment duration was 43.00 weeks (range: 3.0 to 150.9 weeks) for participants in the dostarlimab plus carboplatin-paclitaxel arm and 36.00 weeks (range: 2.1 to 165.1 weeks) for participants in the placebo plus carboplatin-paclitaxel arm (Table 71). 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.

Table 43. Treatment exposure (overall population, Safety Analysis Set)

	Dostar + carbo/pac (N=241)	Placebo + carbo/pac (N=246)	Total (N=487)
Duration of treatment interval, n (%)[a]			
>Week 54	93 (38.6%)	65 (26.4%)	158 (32.4%)
> Week 102	43 (17.8%)	31 (12.6%)	74 (15.2%)
> Week 156	0	1 (0.4%)	1 (0.2%)
Overall duration of treatment (weeks)[b]			

	Dostar + carbo/pac (N=241)	Placebo + carbo/pac (N=246)	Total (N=487)
Median	43.00	36.00	38.00
Min, max	3.0, 150.9	2.1, 165.1	2.1, 165.1
Number of cycles of study treatment			
n	241	246	487
Median	10.0	9.0	9.0
Min, max	1, 28	1, 28	1, 28
Relative dose intensity <7 treatment cycles - (dostarlimab or placebo) (%)			
n	241	246	487
Median	99.21	99.21	99.21
Min, Max	57.5, 105.0	33.3, 102.4	33.3, 105.0
Relative dose intensity ≥7 treatment cycles - (dostarlimab or placebo) (%)			
n	184	184	368
Median	100.00	100.00	100.00
Min, Max	63.2, 104.1	81.6, 123.5	63.2, 123.5
Relative dose intensity - (carboplatin) (%)[c]			
n	240	246	486
Median	87.09	85.24	86.10
Min, max	37.8, 131.9	32.0, 132.0	32.0, 132.0
Relative dose intensity - (paclitaxel) (%)[c]			
n	241	246	487
Median	95.74	96.95	96.23
Min, max	4.5, 120.4	2.2, 119.4	2.2, 120.4

Abbreviations: carbo=carboplatin; Dostar=dostarlimab; max=maximum; min=minimum; pac=paclitaxel.
Intervals were inclusive of the upper week number, e.g., Week 1 to ≤Week 3 was equivalent to Day 1 to Day 21 (inclusive).
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 non-zero dose was infused: minimum of (Last dose date – Start dose date + 42) and (Death date – Start dose date + 1).
Carboplatin and paclitaxel were only administered in the first 6 cycles of study treatment.

dMMR/MSI-H population

The overall median treatment duration was 76.50 weeks (range: 3.0 to 150.3 weeks) for participants in the dostarlimab plus carboplatin-paclitaxel arm and 31.86 weeks (range: 3.0 to 153.0 weeks) for participants in the placebo plus carboplatin-paclitaxel arm (Table 72).

The median RDI for carboplatin was 88.07% in the dostarlimab plus carboplatin-paclitaxel arm, and 83.37% in the placebo plus carboplatin-paclitaxel arm (Table 72). The median RDI for paclitaxel was 95.25% in the dostarlimab plus carboplatin-paclitaxel arm and 95.69% in the placebo plus carboplatin-paclitaxel arm (Table 72). The median number of actual dosing cycles was 6.0 for carboplatin and for paclitaxel in both treatment arms.

Table 44: Treatment exposure (dMMR/MSI H population, Safety Analysis Set)

	Dostar + carbo/pac (N=52)	Placebo + carbo/pac (N=65)	Total (N=117)
Duration of treatment interval, n (%)[a]			
>Week 54	29 (55.8%)	14 (21.5%)	43 (36.8%)
> Week 102	16 (30.8%)	8 (12.3%)	24 (20.5%)
> Week 156	0	0	0
Overall duration of treatment (weeks)[b]			

	Dostar + carbo/pac (N=52)	Placebo + carbo/pac (N=65)	Total (N=117)
Median	76.50	31.86	43.00
Min, max	3.0, 150.3	3.0, 153.0	3.0, 153.0
Number of cycles of study treatment			
n	52	65	117
Median	15.5	8.0	10.0
Min, max	1, 28	1, 28	1, 28
Relative dose intensity <7 treatment cycles - (dostarlimab or placebo) (%)			
n	52	65	117
Median	96.95	97.67	97.67
Min, Max	63.2, 105.0	57.7, 102.4	57.7, 105.0
Relative dose intensity ≥7 treatment cycles - (dostarlimab or placebo) (%)			
n	40	48	88
Median	100.00	100.00	100.00
Min, Max	78.9, 101.2	85.4, 103.7	78.9, 103.7
Relative dose intensity - (carboplatin) (%) [c]			
n	52	65	117
Median	88.07	83.37	85.27
Min, max	58.4, 104.6	32.0, 102.5	32.0, 104.6
Relative dose intensity - (paclitaxel) (%) [c]			
n	52	65	117
Median	95.25	95.69	95.66
Min, max	30.8, 104.7	2.2, 113.5	2.2, 113.5

Abbreviations: carbo=carboplatin; dMMR=mismatch repair-deficient; Dostar=dostarlimab; max=maximum; min=minimum; MSI-H=microsatellite instability-high; 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. 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 non-zero dose was infused: minimum of (Last dose date – Start dose date + 42) and (Death date – Start dose date + 1).
c. Carboplatin and paclitaxel were only administered in the first 6 cycles of study treatment.

Adverse events

Overall population

Table 45: Overall summary of treatment-emergent adverse events (overall population, Safety Analysis Set)

Adverse event category, n (%)	Dostar + carbo/pac (N=241)	Placebo + carbo/pac (N=246)	Total (N=487)
Any TEAEs	241 (100%)	246 (100%)	487 (100%)
Any treatment-related TEAEs	236 (97.9%)	243 (98.8%)	479 (98.4%)
Related to dostarlimab/placebo	203 (84.2%)	183 (74.4%)	386 (79.3%)
Related to dostarlimab/placebo only[a]	146 (60.6%)	103 (41.9%)	249 (51.1%)
Related to carboplatin/paclitaxel	233 (96.7%)	235 (95.5%)	468 (96.1%)
Related to carboplatin/paclitaxel only[b]	215 (89.2%)	218 (88.6%)	433 (88.9%)
Any Grade ≥3 TEAEs	170 (70.5%)	147 (59.8%)	317 (65.1%)
Any Grade ≥3 treatment-related TEAEs	122 (50.6%)	114 (46.3%)	236 (48.5%)
Related to dostarlimab/placebo	80 (33.2%)	48 (19.5%)	128 (26.3%)
Related to dostarlimab/placebo only[a]	45 (18.7%)	23 (9.3%)	68 (14.0%)
Related to carboplatin/paclitaxel	94 (39.0%)	101 (41.1%)	195 (40.0%)
Related to carboplatin/paclitaxel only[b]	72 (29.9%)	87 (35.4%)	159 (32.6%)
Any serious TEAEs	91 (37.8%)	68 (27.6%)	159 (32.6%)
Any treatment-related serious TEAEs	44 (18.3%)	30 (12.2%)	74 (15.2%)
Related to dostarlimab/placebo	30 (12.4%)	17 (6.9%)	47 (9.7%)
Related to dostarlimab/placebo only[a]	12 (5.0%)	8 (3.3%)	20 (4.1%)
Related to carboplatin/paclitaxel	33 (13.7%)	24 (9.8%)	57 (11.7%)
Related to carboplatin/paclitaxel only[b]	17 (7.1%)	15 (6.1%)	32 (6.6%)
Any TEAE leading to infusion interruption	49 (20.3%)	49 (19.9%)	98 (20.1%)
Dostarlimab/placebo infusion interruption	5 (2.1%)	1 (0.4%)	6 (1.2%)
Carboplatin infusion interruption	15 (6.2%)	13 (5.3%)	28 (5.7%)
Paclitaxel infusion interruption	32 (13.3%)	37 (15.0%)	69 (14.2%)
Any TEAE leading to infusion delay	109 (45.2%)	97 (39.4%)	206 (42.3%)
Dostarlimab/placebo infusion delayed	103 (42.7%)	91 (37.0%)	194 (39.8%)
Carboplatin infusion delayed	69 (28.6%)	74 (30.1%)	143 (29.4%)
Paclitaxel infusion delayed	66 (27.4%)	67 (27.2%)	133 (27.3%)
Any TEAE leading to dose reduction	68 (28.2%)	68 (27.6%)	136 (27.9%)
Carboplatin dose reduced	18 (7.5%)	25 (10.2%)	43 (8.8%)
Paclitaxel dose reduced	61 (25.3%)	57 (23.2%)	118 (24.2%)
Any TEAE leading to treatment discontinuation	57 (23.7%)	41 (16.7%)	98 (20.1%)
Dostarlimab/placebo discontinuation	42 (17.4%)	23 (9.3%)	65 (13.3%)
Carboplatin discontinuation	24 (10.0%)	19 (7.7%)	43 (8.8%)
Paclitaxel discontinuation	24 (10.0%)	23 (9.3%)	47 (9.7%)
Any TEAE with the outcome of death	5 (2.1%)	0	5 (1.0%)
Any treatment-related TEAE leading to death	2 (0.8%)	0	2 (0.4%)
Related to dostarlimab/placebo	2 (0.8%)	0	2 (0.4%)
Related to dostarlimab/placebo only[a]	1 (0.4%)	0	1 (0.2%)
Related to carboplatin/paclitaxel	1 (0.4%)	0	1 (0.2%)
Related to carboplatin/paclitaxel only[b]	0	0	0
Any immune-related TEAE	137 (56.8%)	88 (35.8%)	225 (46.2%)
Any dostarlimab/placebo-related immune-related TEAE	92 (38.2%)	38 (15.4%)	130 (26.7%)
Any infusion-related reactions	44 (18.3%)	49 (19.9%)	93 (19.1%)
Any dostarlimab/placebo-related infusion-related reactions	5 (2.1%)	2 (0.8%)	7 (1.4%)
Any carboplatin-related infusion-related reactions	14 (5.8%)	15 (6.1%)	29 (6.0%)
Any paclitaxel-related infusion-related reactions	31 (12.9%)	38 (15.4%)	69 (14.2%)

Abbreviations: carbo=carboplatin; Dostar=dostarlimab; 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.

dMMR/MSI-H population

Table 46: Overall summary of treatment-emergent adverse events (dMMR/MSI H population, Safety Analysis Set)

Adverse event category, n (%)	Dostar + carbo/pac (N=52)	Placebo + carbo/pac (N=65)	Total (N=117)
Any TEAEs	52 (100%)	65 (100%)	117 (100%)
Any treatment-related TEAEs	52 (100%)	65 (100%)	117 (100%)
Related to dostarlimab/placebo	47 (90.4%)	46 (70.8%)	93 (79.5%)
Related to dostarlimab/placebo only[a]	36 (69.2%)	23 (35.4%)	59 (50.4%)
Related to carboplatin/paclitaxel	52 (100%)	61 (93.8%)	113 (96.6%)
Related to carboplatin/paclitaxel only[b]	47 (90.4%)	57 (87.7%)	104 (88.9%)
Any Grade ≥3 TEAEs	37 (71.2%)	42 (64.6%)	79 (67.5%)
Any Grade ≥3 treatment-related TEAEs	30 (57.7%)	32 (49.2%)	62 (53.0%)
Related to dostarlimab/placebo	22 (42.3%)	11 (16.9%)	33 (28.2%)
Related to dostarlimab/placebo only[a]	13 (25.0%)	4 (6.2%)	17 (14.5%)
Related to carboplatin/paclitaxel	21 (40.4%)	32 (49.2%)	53 (45.3%)
Related to carboplatin/paclitaxel only[b]	15 (28.8%)	30 (46.2%)	45 (38.5%)
Any serious TEAEs	14 (26.9%)	20 (30.8%)	34 (29.1%)
Any treatment-related serious TEAEs	9 (17.3%)	9 (13.8%)	18 (15.4%)
Related to dostarlimab/placebo	6 (11.5%)	5 (7.7%)	11 (9.4%)
Related to dostarlimab/placebo only[a]	3 (5.8%)	2 (3.1%)	5 (4.3%)
Related to carboplatin/paclitaxel	6 (11.5%)	8 (12.3%)	14 (12.0%)
Related to carboplatin/paclitaxel only[b]	3 (5.8%)	5 (7.7%)	8 (6.8%)
Any TEAE leading to infusion interruption	16 (30.8%)	14 (21.5%)	30 (25.6%)
Dostarlimab/placebo infusion interruption	2 (3.8%)	0	2 (1.7%)
Carboplatin infusion interruption	5 (9.6%)	1 (1.5%)	6 (5.1%)
Paclitaxel infusion interruption	10 (19.2%)	13 (20.0%)	23 (19.7%)
Any TEAE leading to infusion delay	24 (46.2%)	28 (43.1%)	52 (44.4%)
Dostarlimab/placebo infusion delayed	23 (44.2%)	27 (41.5%)	50 (42.7%)
Carboplatin infusion delayed	16 (30.8%)	27 (41.5%)	43 (36.8%)
Paclitaxel infusion delayed	13 (25.0%)	23 (35.4%)	36 (30.8%)
Any TEAE leading to dose reduction	11 (21.2%)	18 (27.7%)	29 (24.8%)
Carboplatin dose reduced	1 (1.9%)	6 (9.2%)	7 (6.0%)
Paclitaxel dose reduced	11 (21.2%)	13 (20.0%)	24 (20.5%)
Any TEAE leading to treatment discontinuation	9 (17.3%)	11 (16.9%)	20 (17.1%)
Dostarlimab/placebo discontinuation	8 (15.4%)	7 (10.8%)	15 (12.8%)
Carboplatin discontinuation	5 (9.6%)	5 (7.7%)	10 (8.5%)
Paclitaxel discontinuation	2 (3.8%)	8 (12.3%)	10 (8.5%)
Any TEAE with the outcome of death	2 (3.8%)	0	2 (1.7%)
Any treatment-related TEAE leading to death	2 (3.8%)	0	2 (1.7%)
Related to dostarlimab/placebo	2 (3.8%)	0	2 (1.7%)
Related to dostarlimab/placebo only[a]	1 (1.9%)	0	1 (0.9%)
Related to carboplatin/paclitaxel	1 (1.9%)	0	1 (0.9%)
Related to carboplatin/paclitaxel only[b]	0	0	0
Any immune-related TEAE	38 (73.1%)	24 (36.9%)	62 (53.0%)
Any dostarlimab/placebo-related immune-related TEAE	25 (48.1%)	8 (12.3%)	33 (28.2%)

Adverse event category, n (%)	Dostar + carbo/pac (N=52)	Placebo + carbo/pac (N=65)	Total (N=117)
Any infusion-related reactions	12 (23.1%)	13 (20.0%)	25 (21.4%)
Any dostarlimab/placebo-related infusion-related reactions	0	0	0
Any carboplatin-related infusion-related reactions	4 (7.7%)	1 (1.5%)	5 (4.3%)
Any paclitaxel-related infusion-related reactions	8 (15.4%)	12 (18.5%)	20 (17.1%)

Abbreviations: carbo=carboplatin; dMMR=mismatch repair-deficient; Dostar=dostarlimab; MSI-H=microsatellite instability-high; 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

Overall population

The most frequently reported TEAEs (>40%) in the dostarlimab plus carboplatin-paclitaxel arm were nausea, alopecia, fatigue, and neuropathy peripheral, while those in the placebo plus carboplatin-paclitaxel arm included fatigue, alopecia, nausea, anemia, and neuropathy peripheral. These common TEAEs were maximal Grade 1 or 2 in severity in most participants for whom the TEAEs were reported, with the exception of anemia, which was Grade 2 or 3 in most participants with anemia.

Table 75. Summary of treatment-emergent adverse events in ≥20% of participants (any arm) by preferred term (overall population, Safety Analysis Set)

Preferred term, n (%)	Dostar + carbo/pac (N=241)	Placebo + carbo/pac (N=246)	Total (N=487)
Any TEAE	241 (100%)	246 (100%)	487 (100%)
Gastrointestinal disorders	202 (83.8%)	193 (78.5%)	395 (81.1%)
Nausea	130 (53.9%)	113 (45.9%)	243 (49.9%)
Constipation	83 (34.4%)	88 (35.8%)	171 (35.1%)
Diarrhoea	75 (31.1%)	71 (28.9%)	146 (30.0%)
Nervous system disorders	192 (79.7%)	191 (77.6%)	383 (78.6%)
Neuropathy peripheral	106 (44.0%)	101 (41.1%)	207 (42.5%)
Peripheral sensory neuropathy	51 (21.2%)	47 (19.1%)	98 (20.1%)
General disorders and administration site conditions	166 (68.9%)	179 (72.8%)	345 (70.8%)
Fatigue	125 (51.9%)	134 (54.5%)	259 (53.2%)
Skin and subcutaneous tissue disorders	179 (74.3%)	163 (66.3%)	342 (70.2%)
Alopecia	129 (53.5%)	123 (50.0%)	252 (51.7%)
Rash	55 (22.8%)	34 (13.8%)	89 (18.3%)
Musculoskeletal and connective tissue disorders	152 (63.1%)	162 (65.9%)	314 (64.5%)
Arthralgia	86 (35.7%)	86 (35.0%)	172 (35.3%)
Myalgia	63 (26.1%)	68 (27.6%)	131 (26.9%)
Metabolism and nutrition disorders	135 (56.0%)	135 (54.9%)	270 (55.4%)
Hypomagnesaemia	52 (21.6%)	70 (28.5%)	122 (25.1%)
Decreased appetite	52 (21.6%)	43 (17.5%)	95 (19.5%)
Blood and lymphatic system disorders	115 (47.7%)	128 (52.0%)	243 (49.9%)
Anaemia	91 (37.8%)	104 (42.3%)	195 (40.0%)
Respiratory, thoracic and mediastinal disorders	106 (44.0%)	95 (38.6%)	201 (41.3%)
Dyspnoea	44 (18.3%)	50 (20.3%)	94 (19.3%)

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

dMMR/MSI-H population

Table 76. Summary of treatment-emergent adverse events in ≥20% of participants (any arm) by preferred term (dMMR/MSI H population, Safety Analysis Set)

Preferred term, n (%)	Dostar + carbo/pac (N=52)	Placebo + carbo/pac (N=65)	Total (N=117)
Any TEAE	52 (100%)	65 (100%)	117 (100%)
Gastrointestinal disorders	44 (84.6%)	54 (83.1%)	98 (83.8%)
Nausea	29 (55.8%)	30 (46.2%)	59 (50.4%)
Diarrhoea	21 (40.4%)	20 (30.8%)	41 (35.0%)
Constipation	15 (28.8%)	22 (33.8%)	37 (31.6%)
Vomiting	14 (26.9%)	14 (21.5%)	28 (23.9%)
Abdominal pain	8 (15.4%)	14 (21.5%)	22 (18.8%)
Nervous system disorders	40 (76.9%)	51 (78.5%)	91 (77.8%)
Neuropathy peripheral	22 (42.3%)	28 (43.1%)	50 (42.7%)
Peripheral sensory neuropathy	12 (23.1%)	12 (18.5%)	24 (20.5%)
Skin and subcutaneous tissue disorders	46 (88.5%)	43 (66.2%)	89 (76.1%)
Alopecia	29 (55.8%)	39 (60.0%)	68 (58.1%)
Rash	15 (28.8%)	10 (15.4%)	25 (21.4%)
General disorders and administration site conditions	37 (71.2%)	48 (73.8%)	85 (72.6%)
Fatigue	26 (50.0%)	36 (55.4%)	62 (53.0%)
Musculoskeletal and connective tissue disorders	34 (65.4%)	44 (67.7%)	78 (66.7%)
Arthralgia	22 (42.3%)	26 (40.0%)	48 (41.0%)
Myalgia	12 (23.1%)	17 (26.2%)	29 (24.8%)
Blood and lymphatic system disorders	25 (48.1%)	44 (67.7%)	69 (59.0%)
Anaemia	18 (34.6%)	34 (52.3%)	52 (44.4%)
Neutropenia	11 (21.2%)	11 (16.9%)	22 (18.8%)
Metabolism and nutrition disorders	28 (53.8%)	41 (63.1%)	69 (59.0%)
Hypomagnesaemia	10 (19.2%)	19 (29.2%)	29 (24.8%)
Decreased appetite	9 (17.3%)	13 (20.0%)	22 (18.8%)
Investigations	28 (53.8%)	32 (49.2%)	60 (51.3%)
Neutrophil count decreased	5 (9.6%)	15 (23.1%)	20 (17.1%)
White blood cell count decreased	4 (7.7%)	13 (20.0%)	17 (14.5%)
Infections and infestations	27 (51.9%)	31 (47.7%)	58 (49.6%)
Urinary tract infection	4 (7.7%)	16 (24.6%)	20 (17.1%)
Respiratory, thoracic and mediastinal disorders	21 (40.4%)	30 (46.2%)	51 (43.6%)
Dyspnoea	7 (13.5%)	18 (27.7%)	25 (21.4%)
Vascular disorders	15 (28.8%)	23 (35.4%)	38 (32.5%)
Hypertension	11 (21.2%)	7 (10.8%)	18 (15.4%)
Endocrine disorders	12 (23.1%)	5 (7.7%)	17 (14.5%)
Hypothyroidism	11 (21.2%)	4 (6.2%)	15 (12.8%)

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

Grade ≥3 Adverse Events

Overall Population

Table 77: Summary of treatment-emergent adverse events of maximum Grade 3 or higher in ⩾ 2% participants 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 Grade ≥3 TEAE	170 (70.5%)	147 (59.8%)	317 (65.1%)
Blood and lymphatic system disorders	59 (24.5%)	67 (27.2%)	126 (25.9%)
Anaemia	36 (14.9%)	40 (16.3%)	76 (15.6%)
Neutropenia	23 (9.5%)	23 (9.3%)	46 (9.4%)
Thrombocytopenia	7 (2.9%)	10 (4.1%)	17 (3.5%)
Investigations	63 (26.1%)	61 (24.8%)	124 (25.5%)
Neutrophil count decreased	20 (8.3%)	34 (13.8%)	54 (11.1%)
Lymphocyte count decreased	13 (5.4%)	18 (7.3%)	31 (6.4%)
White blood cell count decreased	16 (6.6%)	13 (5.3%)	29 (6.0%)
Platelet count decreased	5 (2.1%)	10 (4.1%)	15 (3.1%)
Lipase increased	9 (3.7%)	3 (1.2%)	12 (2.5%)
Amylase increased	7 (2.9%)	4 (1.6%)	11 (2.3%)
Metabolism and nutrition disorders	37 (15.4%)	29 (11.8%)	66 (13.6%)
Hypokalaemia	12 (5.0%)	9 (3.7%)	21 (4.3%)
Hyponatraemia	9 (3.7%)	8 (3.3%)	17 (3.5%)
Hyperglycaemia	8 (3.3%)	4 (1.6%)	12 (2.5%)
Gastrointestinal disorders	23 (9.5%)	25 (10.2%)	48 (9.9%)
Nausea	7 (2.9%)	4 (1.6%)	11 (2.3%)
Infections and infestations	28 (11.6%)	15 (6.1%)	43 (8.8%)
Urinary tract infection	6 (2.5%)	4 (1.6%)	10 (2.1%)
Nervous system disorders	19 (7.9%)	21 (8.5%)	40 (8.2%)
Neuropathy peripheral	5 (2.1%)	5 (2.0%)	10 (2.1%)
Vascular disorders	24 (10.0%)	11 (4.5%)	35 (7.2%)
Hypertension	17 (7.1%)	8 (3.3%)	25 (5.1%)
General disorders and administration site conditions	14 (5.8%)	17 (6.9%)	31 (6.4%)
Asthenia	5 (2.1%)	9 (3.7%)	14 (2.9%)
Respiratory, thoracic and mediastinal disorders	16 (6.6%)	13 (5.3%)	29 (6.0%)
Pulmonary embolism	12 (5.0%)	12 (4.9%)	24 (4.9%)
Skin and subcutaneous tissue disorders	15 (6.2%)	7 (2.8%)	22 (4.5%)
Rash	10 (4.1%)	3 (1.2%)	13 (2.7%)

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

Table 47: Summary of treatment-related treatment-emergent adverse events of maximum Grade 3 or higher in ≥2% participants 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 Grade ≥3 treatment-related TEAE	122 (50.6%)	114 (46.3%)	236 (48.5%)
Blood and lymphatic system disorders	54 (22.4%)	59 (24.0%)	113 (23.2%)
Anaemia	31 (12.9%)	33 (13.4%)	64 (13.1%)
Neutropenia	23 (9.5%)	22 (8.9%)	45 (9.2%)
Thrombocytopenia	7 (2.9%)	9 (3.7%)	16 (3.3%)
Investigations	48 (19.9%)	53 (21.5%)	101 (20.7%)
Neutrophil count decreased	18 (7.5%)	34 (13.8%)	52 (10.7%)
White blood cell count decreased	14 (5.8%)	12 (4.9%)	26 (5.3%)
Lymphocyte count decreased	10 (4.1%)	12 (4.9%)	22 (4.5%)
Platelet count decreased	4 (1.7%)	9 (3.7%)	13 (2.7%)
Nervous system disorders	14 (5.8%)	10 (4.1%)	24 (4.9%)
Neuropathy peripheral	5 (2.1%)	5 (2.0%)	10 (2.1%)
Skin and subcutaneous tissue disorders	14 (5.8%)	6 (2.4%)	20 (4.1%)
Rash	9 (3.7%)	3 (1.2%)	12 (2.5%)

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

dMMR/MSI-H population

Table 79. Summary of treatment-emergent adverse events of maximum Grade 3 or higher in ≥2% participants by system organ class and preferred term (dMMR/MSI H population, Safety Analysis Set)

System organ class, n (%) Preferred term, n (%)	Dostar + carbo/pac (N=52)	Placebo + carbo/pac (N=65)	Total (N=117)
Any Grade ≥3 TEAE	37 (71.2%)	42 (64.6%)	79 (67.5%)
Blood and lymphatic system disorders	17 (32.7%)	25 (38.5%)	42 (35.9%)
Anaemia	8 (15.4%)	14 (21.5%)	22 (18.8%)
Neutropenia	9 (17.3%)	8 (12.3%)	17 (14.5%)
Thrombocytopenia	1 (1.9%)	4 (6.2%)	5 (4.3%)
Leukopenia	2 (3.8%)	1 (1.5%)	3 (2.6%)
Investigations	12 (23.1%)	19 (29.2%)	31 (26.5%)
Neutrophil count decreased	4 (7.7%)	12 (18.5%)	16 (13.7%)
White blood cell count decreased	2 (3.8%)	8 (12.3%)	10 (8.5%)
Lymphocyte count decreased	3 (5.8%)	6 (9.2%)	9 (7.7%)
Amylase increased	0	3 (4.6%)	3 (2.6%)
Lipase increased	3 (5.8%)	0	3 (2.6%)
Platelet count decreased	1 (1.9%)	2 (3.1%)	3 (2.6%)
Metabolism and nutrition disorders	6 (11.5%)	10 (15.4%)	16 (13.7%)
Hypokalaemia	3 (5.8%)	4 (6.2%)	7 (6.0%)
Hyponatraemia	2 (3.8%)	2 (3.1%)	4 (3.4%)
Gastrointestinal disorders	6 (11.5%)	9 (13.8%)	15 (12.8%)
Abdominal pain	1 (1.9%)	4 (6.2%)	5 (4.3%)
Infections and infestations	5 (9.6%)	9 (13.8%)	14 (12.0%)
Urinary tract infection	0	4 (6.2%)	4 (3.4%)
Vascular disorders	6 (11.5%)	5 (7.7%)	11 (9.4%)
Hypertension	5 (9.6%)	4 (6.2%)	9 (7.7%)

System organ class, n (%) Preferred term, n (%)	Dostar + carbo/pac (N=52)	Placebo + carbo/pac (N=65)	Total (N=117)
Nervous system disorders	4 (7.7%)	6 (9.2%)	10 (8.5%)
Neuropathy peripheral	1 (1.9%)	3 (4.6%)	4 (3.4%)
General disorders and administration site conditions	3 (5.8%)	6 (9.2%)	9 (7.7%)
Asthenia	2 (3.8%)	4 (6.2%)	6 (5.1%)
Respiratory, thoracic and mediastinal disorders	1 (1.9%)	4 (6.2%)	5 (4.3%)
Pulmonary embolism	1 (1.9%)	4 (6.2%)	5 (4.3%)
Skin and subcutaneous tissue disorders	4 (7.7%)	(1.5%)	5 (4.3%)
Rash	3 (5.8%)	0	3 (2.6%)

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

Table 80. Summary of treatment-related treatment-emergent adverse events of maximum Grade 3 or higher in ≥2% participants by system organ class and preferred term (dMMR/MSI H population, Safety Analysis Set)

System organ class, n (%) Preferred term, n (%)	Dostar + carbo/pac (N=52)	Placebo + carbo/pac (N=65)	Total (N=117)
Any Grade ≥3 treatment-related TEAE	30 (57.7%)	32 (49.2%)	62 (53.0%)
Blood and lymphatic system disorders	16 (30.8%)	22 (33.8%)	38 (32.5%)
Anaemia	7 (13.5%)	12 (18.5%)	19 (16.2%)
Neutropenia	9 (17.3%)	8 (12.3%)	17 (14.5%)
Thrombocytopenia	1 (1.9%)	3 (4.6%)	4 (3.4%)
Leukopenia	2 (3.8%)	1 (1.5%)	3 (2.6%)
Investigations	7 (13.5%)	16 (24.6%)	23 (19.7%)
Neutrophil count decreased	3 (5.8%)	12 (18.5%)	15 (12.8%)
White blood cell count decreased	2 (3.8%)	7 (10.8%)	9 (7.7%)
Lymphocyte count decreased	3 (5.8%)	5 (7.7%)	8 (6.8%)
Platelet count decreased	1 (1.9%)	2 (3.1%)	3 (2.6%)
Nervous system disorders	4 (7.7%)	4 (6.2%)	8 (6.8%)
Neuropathy peripheral	1 (1.9%)	3 (4.6%)	4 (3.4%)
Metabolism and nutrition disorders	1 (1.9%)	6 (9.2%)	7 (6.0%)
Hypokalaemia	0	3 (4.6%)	3 (2.6%)
Skin and subcutaneous tissue disorders	4 (7.7%)	1 (1.5%)	5 (4.3%)
Rash	3 (5.8%)	0	3 (2.6%)
General disorders and administration site conditions	3 (5.8%)	1 (1.5%)	4 (3.4%)
Asthenia	2 (3.8%)	1 (1.5%)	3 (2.6%)
Vascular disorders	4 (7.7%)	0	4 (3.4%)
Hypertension	3 (5.8%)	0	3 (2.6%)

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

Serious adverse event/deaths/other significant events

Deaths

Overall population

A total of 5 participants overall (1.0%) had a TEAE leading to death. All of these deaths were in the dostarlimab plus carboplatin-paclitaxel arm (Table 81 and Table 82). Two participants died from treatment-related TEAEs: the death due to myelosuppression was assessed by the investigator as related to dostarlimab, carboplatin, and paclitaxel, and the death due to hypovolemic shock was assessed by the investigator as related to dostarlimab.

Three participants who received dostarlimab plus carboplatin-paclitaxel died due to an overdose of opiates, COVID-19, and general physical health deterioration each; none were considered treatment related.

dMMR/MSI-H population

A total of 2 participants (1.7%) in the dMMR/MSI-H EC population, both in the dostarlimab plus carboplatin-paclitaxel arm, had a TEAE leading to death: myelosuppression was considered related to dostarlimab, carboplatin, and paclitaxel, and hypovolemic shock was considered related to dostarlimab.

Table 81: Summary of deaths (overall population, Safety Analysis Set)

Occurrence of death [n (%)]	Dostar + carbo/pac (N=241)	Placebo + carbo/pac (N=246)	Total (N=487)
Overall			
Death [n (%)]	65 (27.0%)	100 (40.7%)	165 (33.9%)
Primary reason of death [n (%)]			
Disease progression	57 (23.7%)	87 (35.4%)	144 (29.6%)
Adverse event	6 (2.5%)	2 (0.8%)	8 (1.6%)
Unknown	2 (0.8%)	11 (4.5%)	13 (2.7%)
Within 90 days after last dose			
Death [n (%)]	22 (9.1%)	17 (6.9%)	39 (8.0%)
Primary reason of death [n (%)]			
Disease progression	17 (7.1%)	16 (6.5%)	33 (6.8%)
Adverse event	5 (2.1%)	0	5 (1.0%)
Unknown	0	1 (0.4%)	1 (0.2%)
After 90 days after last dose			
Death [n (%)]	43 (17.8%)	83 (33.7%)	126 (25.9%)
Primary reason of death [n (%)]			
Disease progression	40 (16.6%)	71 (28.9%)	111 (22.8%)
Adverse event	1 (0.4%)	2 (0.8%)	3 (0.6%)
Unknown	2 (0.8%)	10 (4.1%)	12 (2.5%)

Abbreviations: carbo=carboplatin; Dostar=dostarlimab; pac=paclitaxel.

Table 82: Summary of treatment-emergent adverse events leading to death 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 AE leading to death	5 (2.1%)	0	5 (1.0%)
Blood and lymphatic system disorders	1 (0.4%)	0	1 (0.2%)
Myelosuppression	1 (0.4%)	0	1 (0.2%)
General disorders and administration site conditions	1 (0.4%)	0	1 (0.2%)
General physical health deterioration	1 (0.4%)	0	1 (0.2%)
Infections and infestations	1 (0.4%)	0	1 (0.2%)
COVID-19	1 (0.4%)	0	1 (0.2%)
Injury, poisoning and procedural complications	1 (0.4%)	0	1 (0.2%)
Overdose[a]	1 (0.4%)	0	1 (0.2%)
Vascular disorders	1 (0.4%)	0	1 (0.2%)
Hypovolaemic shock	1 (0.4%)	0	1 (0.2%)

Abbreviations: AE=adverse event; carbo=carboplatin; COVID-19=coronavirus disease 2019; Dostar=dostarlimab; pac=paclitaxel; SAE=serious adverse event.

a. One participant died due to an overdose of opiates. This death was reported as an SAE and was not considered treatment related.

Serious Adverse Events

Overall Population

Table 83. Summary of treatment-emergent serious adverse events in ≥1% of participants (total) 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 SAE	91 (37.8%)	68 (27.6%)	159 (32.6%)
Respiratory, thoracic and mediastinal disorders	12 (5.0%)	7 (2.8%)	19 (3.9%)
Pulmonary embolism	6 (2.5%)	5 (2.0%)	11 (2.3%)
Dyspnoea	5 (2.1%)	1 (0.4%)	6 (1.2%)
Blood and lymphatic system disorders	12 (5.0%)	14 (5.7%)	26 (5.3%)
Anaemia	3 (1.2%)	6 (2.4%)	9 (1.8%)
Febrile neutropenia	4 (1.7%)	4 (1.6%)	8 (1.6%)
Infections and infestations	27 (11.2%)	14 (5.7%)	41 (8.4%)
Sepsis	8 (3.3%)	1 (0.4%)	9 (1.8%)
Urinary tract infection	3 (1.2%)	5 (2.0%)	8 (1.6%)
General disorders and administration site conditions	14 (5.8%)	14 (5.7%)	28 (5.7%)
Asthenia	2 (0.8%)	6 (2.4%)	8 (1.6%)
Pyrexia	6 (2.5%)	2 (0.8%)	8 (1.6%)
General physical health deterioration	3 (1.2%)	2 (0.8%)	5 (1.0%)
Gastrointestinal disorders	18 (7.5%)	19 (7.7%)	37 (7.6%)
Vomiting	4 (1.7%)	3 (1.2%)	7 (1.4%)
Nausea	4 (1.7%)	2 (0.8%)	6 (1.2%)
Diarrhoea	2 (0.8%)	3 (1.2%)	5 (1.0%)
Small intestinal obstruction	1 (0.4%)	4 (1.6%)	5 (1.0%)
Musculoskeletal and connective tissue disorders	6 (2.5%)	1 (0.4%)	7 (1.4%)
Muscular weakness	5 (2.1%)	1 (0.4%)	6 (1.2%)
Vascular disorders	5 (2.1%)	4 (1.6%)	9 (1.8%)
Hypertension	3 (1.2%)	2 (0.8%)	5 (1.0%)

Abbreviations: carbo=carboplatin; Dostar=dostarlimab; pac=paclitaxel; SAE=serious adverse event.

Table 84. Summary of treatment-emergent serious adverse events related to dostarlimab or placebo (>1 participant in any 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)	
	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	30 (12.4%)	12 (5.0%)	17 (6.9%)	8 (3.3%)
Gastrointestinal disorders	5 (2.1%)	3 (1.2%)	6 (2.4%)	2 (0.8%)
Diarrhoea	1 (0.4%)	1 (0.4%)	3 (1.2%)	0
Blood and lymphatic system disorders	5 (2.1%)	0	4 (1.6%)	1 (0.4%)
Anaemia	2 (0.8%)	0	1 (0.4%)	0
Pancytopenia	0	0	2 (0.8%)	1 (0.4%)
General disorders and administration site conditions	3 (1.2%)	0	6 (2.4%)	1 (0.4%)
Asthenia	0	0	4 (1.6%)	0
General physical health deterioration	1 (0.4%)	0	2 (0.8%)	1 (0.4%)
Pyrexia	2 (0.8%)	0	0	0
Respiratory, thoracic and mediastinal disorders	3 (1.2%)	1 (0.4%)	2 (0.8%)	0
Pulmonary embolism	2 (0.8%)	1 (0.4%)	2 (0.8%)	0

Abbreviations: carbo=carboplatin; Dostar=dostarlimab; 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 85. Summary of treatment-emergent serious adverse events related to chemotherapy (>1 participant in any 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)	
	Related to carboplatin or paclitaxel	Related to carboplatin or paclitaxel only[a]	Related to carboplatin or paclitaxel	Related to carboplatin or paclitaxel only[a]
Any SAE related to chemotherapy	33 (13.7%)	17 (7.1%)	24 (9.8%)	15 (6.1%)
Blood and lymphatic system disorders	11 (4.6%)	6 (2.5%)	13 (5.3%)	11 (4.5%)
Febrile neutropenia	4 (1.7%)	3 (1.2%)	4 (1.6%)	4 (1.6%)
Anaemia	2 (0.8%)	0	5 (2.0%)	4 (1.6%)
Neutropenia	2 (0.8%)	2 (0.8%)	2 (0.8%)	1 (0.4%)
General disorders and administration site conditions	4 (1.7%)	1 (0.4%)	7 (2.8%)	2 (0.8%)
Asthenia	0	0	4 (1.6%)	0
Pyrexia	3 (1.2%)	1 (0.4%)	1 (0.4%)	1 (0.4%)
Metabolism and nutrition disorders	4 (1.7%)	2 (0.8%)	4 (1.6%)	2 (0.8%)
Dehydration	2 (0.8%)	1 (0.4%)	1 (0.4%)	0

System organ class, n (%) Preferred term, n (%)	Dostar + carbo/pac (N=241)		Placebo + carbo/pac (N=246)	
	Related to carboplatin or paclitaxel	Related to carboplatin or paclitaxel only[a]	Related to carboplatin or paclitaxel	Related to carboplatin or paclitaxel only[a]
Gastrointestinal disorders	3 (1.2%)	1 (0.4%)	4 (1.6%)	0
Diarrhoea	0	0	3 (1.2%)	0
Vomiting	2 (0.8%)	1 (0.4%)	0	0
Infections and infestations	5 (2.1%)	3 (1.2%)	2 (0.8%)	2 (0.8%)
Sepsis	2 (0.8%)	2 (0.8%)	0	0
Respiratory, thoracic and mediastinal disorders	2 (0.8%)	0	2 (0.8%)	0
Pulmonary embolism	1 (0.4%)	0	2 (0.8%)	0
Musculoskeletal and connective tissue disorders	3 (1.2%)	2 (0.8%)	0	0
Muscular weakness	3 (1.2%)	2 (0.8%)	0	0
Injury, poisoning and procedural complications	2 (0.8%)	2 (0.8%)	0	0
Infusion-related reaction	2 (0.8%)	2 (0.8%)	0	0

Abbreviations: carbo=carboplatin; Dostar=dostarlimab; 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

dMMR/MSI-H population

Table 86. Summary of treatment-emergent serious adverse events in ≥1% of participants (total) by system organ class and preferred term (dMMR/MSI H population, Safety Analysis Set)

System organ class, n (%) Preferred term, n (%)	Dostar + carbo/pac (N=52)	Placebo + carbo/pac (N=65)	Total (N=117)
Any SAE	14 (26.9%)	20 (30.8%)	34 (29.1%)
Infections and infestations	5 (9.6%)	7 (10.8%)	12 (10.3%)
Urinary tract infection	0	4 (6.2%)	4 (3.4%)
Sepsis	2 (3.8%)	0	2 (1.7%)
Blood and lymphatic system disorders	3 (5.8%)	4 (6.2%)	7 (6.0%)
Anaemia	0	3 (4.6%)	3 (2.6%)
Febrile neutropenia	1 (1.9%)	1 (1.5%)	2 (1.7%)
General disorders and administration site conditions	1 (1.9%)	4 (6.2%)	5 (4.3%)
Asthenia	0	3 (4.6%)	3 (2.6%)
Musculoskeletal and connective tissue disorders	2 (3.8%)	1 (1.5%)	3 (2.6%)
Muscular weakness	1 (1.9%)	1 (1.5%)	2 (1.7%)
Respiratory, thoracic and mediastinal disorders	0	2 (3.1%)	2 (1.7%)
Pulmonary embolism	0	2 (3.1%)	2 (1.7%)

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

Treatment-related SAEs were experienced by 15.4% of the participants in the dMMR/MSI-H EC population. The frequency of treatment-related SAEs was approximately 4% higher in the dostarlimab plus carboplatin-paclitaxel arm compared with the placebo plus carboplatin-paclitaxel arm (Table 4). None of the treatment-related SAEs was experienced by >1 participant in either treatment arm with the exception of anemia, experienced by 2 participants in the placebo plus carboplatin-paclitaxel arm.

SAEs considered not related to carboplatin/paclitaxel but related to dostarlimab/placebo only were experienced by 5.8% of participants in the dostarlimab plus carboplatin-paclitaxel arm and 3.1% in the placebo plus carboplatin-paclitaxel arm, and each TEAE preferred term was experienced by 1 participant. SAEs considered related to carboplatin/paclitaxel only were experienced by 5.8% of participants in the dostarlimab plus carboplatin-paclitaxel arm and 7.7% in the placebo plus carboplatin-paclitaxel arm. The only treatment-emergent SAE related to carboplatin/paclitaxel only experienced by >1 participant was anemia (0% dostarlimab, 3.1% placebo).

Immune-related adverse events

Overall population

Table 87. Most frequently occurring immune-related TEAEs (reported in ≥3% of participants in either arm) (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	**137 (56.8%)**	**92 (38.2%)**	**88 (35.8%)**	**38 (15.4%)**
Arthralgia	32 (13.3%)	14 (5.8%)	31 (12.6%)	16 (6.5%)
Infusion-related reaction	31 (12.9%)	4 (1.7%)	30 (12.2%)	0
Hypothyroidism	27 (11.2%)	27 (11.2%)	8 (3.3%)	7 (2.8%)
Hypersensitivity/ Drug hypersensitivity	6 (2.5%)/ 7 (2.9%)	0/ 0	4 (1.6%)/ 11 (4.5%)	1 (0.4%)/ 1 (0.4%)
Rash	21 (8.7%)	16 (6.6%)	6 (2.4%)	5 (2.0%)
Rash maculo-papular	16 (6.6%)	11 (4.6%)	0	0
Pruritus	15 (6.2%)	8 (3.3%)	4 (1.6%)	3 (1.2%)
ALT increased	15 (6.2%)	14 (5.8%)	2 (0.8%)	2 (0.8%)
AST increased	12 (5.0%)	10 (4.1%)	1 (0.4%)	1 (0.4%)
Hyperthyroidism	8 (3.3%)	8 (3.3%)	1 (0.4%)	1 (0.4%)

Abbreviations: AE=adverse event; ALT=alanine aminotransferase; AST=aspartate aminotransferase; carbo=carboplatin; Dostar=dostarlimab; pac=paclitaxel; TEAE=treatment-emergent adverse event.

Grade ≥3 irAEs were observed in 16.6% 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 12.4% 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 Grade ≥3 irAEs in the dostarlimab plus carboplatin-paclitaxel arm were rash (3.7%), rash maculo-papular, alanine aminotransferase increased, and aspartate aminotransferase increased (2.1% each); all other dostarlimab-related Grade ≥3 irAEs occurred in ≤2 participants each.

Serious irAEs were observed in 5.8% of participants in the dostarlimab plus carboplatin-paclitaxel arm, and in 2.0% of participants in the placebo plus carboplatin-paclitaxel arm; none were reported in ≥1% of participants.

IrAEs leading to dostarlimab/placebo treatment discontinuation were observed in 7.9% of participants in the dostarlimab plus carboplatin-paclitaxel arm, and in 3.7% of participants in the placebo plus carboplatin-paclitaxel arm. Discontinuations due to irAEs in the dostarlimab plus carboplatin-paclitaxel arm occurred with similar frequency during the dostarlimab plus carboplatin-paclitaxel phase (10 participants) and the dostarlimab phase (9 participants). All were reported in 1 participant each with the exception of rash maculo-papular and infusion-related reaction in 3 participants each, and alanine aminotransferase increased, aspartate aminotransferase increased, and pneumonitis in 2 participants

each, in the dostarlimab plus carboplatin-paclitaxel arm and colitis in 2 participants in the placebo plus carboplatin-paclitaxel arm.

In the post-treatment-emergent period (>90 days post last dose through end of study), a total of 4 irAEs were reported in the overall population: colitis (0.4% dostarlimab, 0.2% placebo), alanine aminotransferase increased (0.4% versus 0.2%), aspartate aminotransferase increased (0.4% versus 0.2%), and arthralgia (0.4% versus 0.2%).

dMMR/MSI-H population

Table 88. Most frequently occurring immune-related TEAEs (reported in ≥3% of participants in either arm) (dMMR/MSI H population, Safety Analysis Set)

Category, n (%) Preferred term, n (%)	Dostar + carbo/pac (N=52)		Placebo + carbo/pac (N=65)	
	All events	Dostarlimab-related	All events	Placebo-related
Any immune-related AE	**38 (73.1%)**	**25 (48.1%)**	**24 (36.9%)**	**8 (12.3%)**
Infusion-related reaction	8 (15.4%)	0	8 (12.3%)	0
Hypothyroidism	8 (15.4%)	8 (15.4%)	3 (4.6%)	3 (4.6%)
Arthralgia	7 (13.5%)	4 (7.7%)	10 (15.4%)	3 (4.6%)
Rash	6 (11.5%)	4 (7.7%)	1 (1.5%)	0
Pruritus	5 (9.6%)	1 (1.9%)	1 (1.5%)	0
ALT increased	4 (7.7%)	3 (5.8%)	0	0
AST increased	4 (7.7%)	2 (3.8%)	0	0
Hypersensitivity/ Drug hypersensitivity	1 (1.9%)/ 3 (5.8%)	0/ 0	1 (1.5%)/ 3 (4.6%)	0/ 0
Hyperthyroidism	3 (5.8%)	3 (5.8%)	1 (1.5%)	1 (1.5%)
Rash maculo-papular	3 (5.8%)	3 (5.8%)	0	0

Abbreviations: AE=adverse event; ALT=alanine aminotransferase; AST=aspartate aminotransferase; carbo=carboplatin; dMMR=mismatch repair-deficient; Dostar=dostarlimab; MSI-H=microsatellite instability-high; pac=paclitaxel; TEAE=treatment-emergent adverse event.

Grade ≥3 irAEs were observed in 19.2% of participants in the dostarlimab plus carboplatin-paclitaxel arm and in 0% of participants in the placebo plus carboplatin-paclitaxel arm, while dostarlimab/placebo-related Grade ≥3 irAEs were observed in 17.3% of participants in the dostarlimab plus carboplatin-paclitaxel arm. The most frequently observed dostarlimab-related Grade ≥3 irAE was rash (5.8% dostarlimab versus 0% placebo), all other dostarlimab-related Grade ≥3 irAEs occurred in 1 participant each.

Serious irAEs were observed in 2 participants (3.8%; type 1 diabetes mellitus, pancreatitis) in the dostarlimab plus carboplatin-paclitaxel arm, and in 1 participant (1.5%, colitis) in the placebo plus carboplatin-paclitaxel arm.

IrAEs leading to dostarlimab treatment discontinuation were observed in 2 participants (3.8%; rash maculo-papular, infusion-related reaction) in the dostarlimab plus carboplatin-paclitaxel arm; none were reported in the placebo plus carboplatin-paclitaxel arm.

In the post-treatment-emergent period (>90 days post last dose through end of study) 1 participant (1.9%) in the dMMR/MSI-H population, in the dostarlimab plus carboplatin-paclitaxel arm, reported 2 irAEs including colitis and arthralgia; both were related to dostarlimab.

Infusion-related Reactions

Overall population

In the overall population, IRRs were comparable between treatment arms and were reported in 18.3% of participants in the dostarlimab plus carboplatin-paclitaxel arm and in 19.9% of participants in the placebo plus carboplatin-paclitaxel arm (Table 73). The incidence of IRRs related to dostarlimab or placebo was low and comparable between the dostarlimab plus carboplatin-paclitaxel arm (5 participants [2.1%]) and the placebo plus carboplatin-paclitaxel arm (2 participants [0.8%]). Serious IRRs, IRRs of Grade ≥3 severity, or IRRs leading to infusion delay or discontinuation related to any study treatment occurred in <3% of participants in either treatment arm. No IRRs led to death in any arm.

The incidence of IRRs related to carboplatin was comparable between the dostarlimab plus carboplatin-paclitaxel arm (14 participants [5.8%]) and the placebo plus carboplatin-paclitaxel arm (15 participants [6.1%]).The incidence of IRRs related to paclitaxel was comparable between the dostarlimab plus carboplatin-paclitaxel arm (31 participants [12.9%]) and the placebo plus carboplatin-paclitaxel arm (38 participants [15.4%]).

dMMR/MSI-H population

In the dMMR/MSI-H population IRRs were comparable between treatment arms, reported in 23.1% of participants in the dostarlimab plus carboplatin-paclitaxel arm and in 20.0% of participants in the placebo plus carboplatin-paclitaxel arm (Table 74). No IRRs related to dostarlimab or placebo were reported in the dMMR/MSI-H EC population. IRRs related to carboplatin were higher in the dostarlimab plus carboplatin-paclitaxel arm (4 participants [7.7%]) compared to the placebo plus carboplatin-paclitaxel arm (1 participant [1.5%]). IRRs related to paclitaxel were comparable in the dostarlimab plus carboplatin-paclitaxel arm (8 participants [15.4%]) and the placebo plus carboplatin-paclitaxel arm (12 participants [18.5%]).

Covid-19-related adverse events

Overall population

In the overall population, COVID-19 adverse events were comparable between treatment arms (<10% difference) (Table 89). While all COVID-19 SAEs, COVID-19 AEs leading to treatment discontinuation, COVID-19 Grade ≥3 AEs, and COVID-19 AEs leading to death occurred in the dostarlimab plus carboplatin-paclitaxel arm, these incidences remain small (approximately 1% of participants) and are considered to have been incidental and unlikely driven by the treatment received.

Table 89. Summary of COVID-19 adverse events (overall population, Safety Analysis Set)

Adverse event category, n (%)	Dostar + carbo/pac (N=241)	Placebo + carbo/pac (N=246)	Total (N=487)
Any COVID-19 AEs	21 (8.7%)	18 (7.3%)	39 (8.0%)
Any COVID-19 SAEs	3 (1.2%)	0	3 (0.6%)
Any COVID-19 AE leading to treatment discontinuation	1 (0.4%)	0	1 (0.2%)
Any Grade ≥3 COVID-19 AEs	3 (1.2%)	0	3 (0.6%)
Any COVID-19 AEs leading to death	1 (0.4%)	0	1 (0.2%)

Abbreviations: AE=adverse event; carbo=carboplatin; COVID-19=coronavirus disease 2019; Dostar=dostarlimab; pac=paclitaxel; SAE=serious adverse event.

dMMR/MSI-H population

COVID-19 adverse events were comparable between treatment arms in the dMMR/MSI H population (9.6% and 6.2% in the dostarlimab plus carboplatin-paclitaxel arm and the placebo plus carboplatin-paclitaxel arm, respectively). No COVID-19 SAEs, COVID-19 AEs leading to treatment discontinuation, COVID-19 Grade ≥3 AEs, or COVID-19 AEs leading to death were observed in either treatment arm.

Laboratory findings

Hematology

Overall population

In the overall population, baseline hematology results were generally Grade 0 (>95% of participants) in both treatment arms, with the exception of hemoglobin decreased (Grade 0: 56.4% in dostarlimab plus carboplatin paclitaxel arm, 63.4% in placebo plus carboplatin-paclitaxel arm) and lymphocyte count decreased (Grade 0: 71.8% in dostarlimab plus carboplatin paclitaxel arm, 71.1% in placebo plus carboplatin paclitaxel arm). 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 postbaseline value.

Shifts to Grade 3 or 4 hematology parameters of >2 grades from baseline to maximum postbaseline value in the overall population 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 (17.9%).

dMMR/MSI-H population

In the dMMR/MSI-H EC population, baseline hematology results were generally Grade 0 (>95% of participants) in both treatment arms, with the exception of hemoglobin decreased (Grade 0: 48.1% in dostarlimab plus carboplatin paclitaxel arm, 56.9% in placebo plus carboplatin paclitaxel arm) and lymphocyte count decreased (Grade 0: 75.0% in dostarlimab plus carboplatin paclitaxel arm, 72.3% in placebo plus carboplatin paclitaxel arm).

Shifts to Grade 3 or 4 hematology parameters of >2 grades from baseline to maximum postbaseline value in the dMMR/MSI-H population 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 (12.4%), platelet count decreased (12.3%), and lymphocyte count decreased (10.8%).

Clinical Chemistry

Overall population

In the overall population, baseline chemistry results were generally Grade 0 (>80% of participants) in either treatment arm. For hyperglycemia, the Grade 0 incidence was 50.2% in the dostarlimab plus carboplatin paclitaxel arm and 47.6% in the placebo plus carboplatin paclitaxel arm. Baseline Grade 4 chemistry results were only reported for hypoglycemia (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 generally infrequent. No shifts to Grade 4 chemistry parameters occurred in >2% of the participants.

dMMR/MSI-H population

In the dMMR/MSI-H population, baseline chemistry results were generally Grade 0 (>80% of participants) in either treatment arm, with the exception of hyperglycemia, where the incidence was similar in both arms (hyperglycemia: dostarlimab plus carboplatin-paclitaxel arm 51.9%, placebo plus carboplatin-paclitaxel arm 46.2%). Results for shifts from baseline for chemistry parameters were generally similar in

the dMMR/MSI-H EC population. In the dMMR/MSI-H EC population, no participants had Grade 4 chemistry results at baseline.

Liver-related Assessments

Overall population

The incidence of potential liver toxicity events is summarized in Table 90. No participant with primary advanced or recurrent EC met the criteria for potential Hy's law (concurrent AST or ALT ≥3×ULN, in combination with bilirubin ≥2×ULN and ALP <2×ULN or missing). The toxicity criterion with the greatest difference in frequency between treatment arms was (ALT or AST) ≥3×ULN; 10.4% and 2.8% in the dostarlimab plus carboplatin-paclitaxel arm and the placebo plus carboplatin-paclitaxel arm, respectively (Table 90).

Table 90. Incidence of potential liver toxicity events (overall population, Safety Analysis Set)

Toxicity criterion	Dostar + carbo/pac (N=241)	Placebo + carbo/pac (N=246)	Total (N=487)
ALT ≥3×ULN	17 (7.1%)	6 (2.4%)	23 (4.7%)
ALT ≥5×ULN	6 (2.5%)	2 (0.8%)	8 (1.6%)
ALT ≥10×ULN	3 (1.2%)	1 (0.4%)	4 (0.8%)
ALT ≥20×ULN	0	1 (0.4%)	1 (0.2%)
AST ≥3×ULN	19 (7.9%)	5 (2.0%)	24 (4.9%)
AST ≥5×ULN	8 (3.3%)	4 (1.6%)	12 (2.5%)
AST ≥10×ULN	2 (0.8%)	1 (0.4%)	3 (0.6%)
AST ≥20×ULN	0	1 (0.4%)	1 (0.2%)
(ALT or AST) ≥3×ULN	25 (10.4%)	7 (2.8%)	32 (6.6%)
(ALT or AST) ≥5×ULN	9 (3.7%)	4 (1.6%)	13 (2.7%)
(ALT or AST) ≥10×ULN	4 (1.7%)	1 (0.4%)	5 (1.0%)
(ALT or AST) ≥20×ULN	0	1 (0.4%)	1 (0.2%)
Total bilirubin ≥2×ULN	4 (1.7%)	1 (0.4%)	5 (1.0%)
Concurrent ALT ≥3×ULN and total bilirubin ≥2×ULN	2 (0.8%)	0	2 (0.4%)
Concurrent AST ≥3×ULN and total bilirubin ≥2×ULN	3 (1.2%)	0	3 (0.6%)
Concurrent (ALT or AST) ≥3×ULN and total bilirubin ≥2×ULN	3 (1.2%)	0	3 (0.6%)
Concurrent (ALT or AST) ≥3×ULN and total bilirubin ≥2×ULN and ALP >2×ULN	3 (1.2%)	0	3 (0.6%)
Potential Hy's law: Concurrent (ALT or AST) ≥3×ULN and total bilirubin ≥2×ULN and ALP <2×ULN	0	0	0

Abbreviations: ALP=alkaline phosphatase; ALT=alanine aminotransferase; AST=aspartate aminotransferase; carbo=carboplatin; Dostar=dostarlimab; pac=paclitaxel; ULN=upper limit of normal.

dMMR/MSI-H population

In the dMMR/MSI-H EC population, ALT or AST ≥3×ULN was higher in the dostarlimab plus carboplatin-paclitaxel arm (19.2%) as compared to the placebo plus carboplatin-paclitaxel arm (1.5%). There were no incidences of ≥10×ULN or ≥20×ULN ALT or AST in either treatment arm (Table 91).

Table 91. Incidence of potential liver toxicity events (dMMR/MSI H EC population, Safety Analysis Set)

Toxicity criterion	Dostar + carbo/pac (N=52)	Placebo + carbo/pac (N=65)	Total (N=117)
ALT ≥3×ULN	6 (11.5%)	1 (1.5%)	7 (6.0%)
ALT ≥5×ULN	0	0	0
ALT ≥10×ULN	0	0	0
ALT ≥20×ULN	0	0	0
AST ≥3×ULN	7 (13.5%)	1 (1.5%)	8 (6.8%)
AST ≥5×ULN	2 (3.8%)	0	2 (1.7%)
AST ≥10×ULN	0	0	0
AST ≥20×ULN	0	0	0
(ALT or AST) ≥3×ULN	10 (19.2%)	1 (1.5%)	11 (9.4%)
(ALT or AST) ≥5×ULN	2 (3.8%)	0	2 (1.7%)
(ALT or AST) ≥10×ULN	0	0	0
(ALT or AST) ≥20×ULN	0	0	0
Total bilirubin ≥2×ULN	2 (3.8%)	1 (1.5%)	3 (2.6%)
Concurrent ALT ≥3×ULN and total bilirubin ≥2×ULN	1 (1.9%)	0	1 (0.9%)
Concurrent AST ≥3×ULN and total bilirubin ≥2×ULN	2 (3.8%)	0	2 (1.7%)
Concurrent (ALT or AST) ≥3×ULN and total bilirubin ≥2×ULN	2 (3.8%)	0	2 (1.7%)
Concurrent (ALT or AST) ≥3×ULN and total bilirubin ≥2×ULN and ALP >2×ULN	2 (3.8%)	0	2 (1.7%)
Potential Hy's law: Concurrent (ALT or AST) ≥3×ULN and total bilirubin ≥2×ULN and ALP <2×ULN	0	0	0

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

Safety in special populations

Intrinsic factors

Age

In the overall population, in the dostarlimab plus carboplatin-paclitaxel arm, 126 (52.3%) participants were <65 years, 88 (36.5%) were 65 to <75 years, and 27 (11.2%) were 75 years or older; in the placebo plus carboplatin-paclitaxel arm, 112 (45.5%) of participants were <65 years, 97 (39.4%) were 65 to <75 years, and 37 (15.0%) were 75 years or older including 1 participant who was 85 years of age. Overall, key safety risks were not observed to be significantly increased in older participants compared to younger participants in participants in the dostarlimab plus carboplatin-paclitaxel arm, and in comparison to participants receiving only chemotherapy in the placebo plus carboplatin-paclitaxel arm.

The incidences of TEAEs and any treatment-related TEAEs were similar (>95%) between all age groups in each arm. The incidence of Grade ≥3 TEAEs was similar between participants aged <65 years and 65 to <75 years in the dostarlimab plus carboplatin-paclitaxel arm (~70%), and between participants aged <65 years and 65 to <75 years in the placebo plus carboplatin-paclitaxel arm (~57% each group), with Grade ≥3 TEAEs higher in the dostarlimab plus carboplatin-paclitaxel arm compared to the placebo plus carboplatin-paclitaxel arm. Grade ≥3 TEAEs were higher in participants aged ≥75 years in both arms (78% dostarlimab and 75% placebo, respectively). A similar pattern was observed with treatment-related Grade ≥3 TEAEs, with approximately 5% higher incidence in each age group in participants in the dostarlimab plus carboplatin-paclitaxel arm compared to the placebo plus carboplatin-paclitaxel arm.

The incidence of SAEs and any treatment-related SAEs was similar between all age groups in the dostarlimab plus carboplatin-paclitaxel arm (~40% SAEs, ~23% 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), and which were higher in the dostarlimab plus carboplatin-paclitaxel arm compared to the placebo plus carboplatin-paclitaxel arm. SAEs (51%) and any treatment-related SAEs (43%) 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 in each arm, ranging from 34% to 48%. The incidence of TEAEs leading to dose reduction of carboplatin and/or paclitaxel was similar between all age groups in each arm, ranging from 22% to 33%, with the exception of dose reductions for participants aged ≥75 years in the placebo plus carboplatin-paclitaxel arm (49%).

The incidence of TEAEs leading to treatment discontinuation was lower in participants aged <65 years in the dostarlimab plus carboplatin-paclitaxel arm (19%), and those aged <65 years (15%) and 65 to <75 years (12%) in the placebo plus carboplatin-paclitaxel arm, compared to those aged 65 to <75 years <65 (28%) and ≥75 years (30%) in the dostarlimab plus carboplatin-paclitaxel arm and aged ≥75 years in the placebo plus carboplatin-paclitaxel arm (33%).

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 (33% to 39%), and between participants aged <65 years and 65 to <75 years (13% to 14%) in the placebo plus carboplatin-paclitaxel arm, with dostarlimab/placebo-related irAEs higher in the dostarlimab plus carboplatin-paclitaxel arm compared to the placebo plus carboplatin-paclitaxel arm for these age groups. Dostarlimab/placebo-related irAEs were higher in participants aged ≥75 years in both arms (52% dostarlimab and 25% placebo, respectively).

Ethnicity

There were 15 participants in total of the 487 participants in the Safety Analysis Set who were Hispanic or Latino; 7 were in the dostarlimab plus carboplatin-paclitaxel arm and 8 were in the placebo plus carboplatin-paclitaxel arm. Due to the small number of participants who were Hispanic or Latino, a meaningful comparison based on ethnicity could not be made.

Race

In the overall population, in the dostarlimab plus carboplatin-paclitaxel arm, 7 (2.9%) participants were Asian, 27 (11.2%) were Black or African American, and 187 (77.6%) were White with the remainder Other; in the placebo plus carboplatin-paclitaxel arm, 8 (3.3%) participants were Asian, 31 (12.6%) were Black or African American, and 190 (77.2%) were White with the remainder Other. Overall, based on limited data, safety risks were not observed to be significantly increased in Black or African American participants compared to White participants in the dostarlimab plus carboplatin-paclitaxel arm. Due to the small number of participants who were Asian a meaningful comparison to safety in Black/African American and White participants could not be made.

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 70%, respectively) and treatment-related Grade ≥3 TEAEs (44% and 52%, respectively) in the dostarlimab plus carboplatin-paclitaxel arm; in the placebo plus carboplatin-paclitaxel arm incidences were higher in White participants compared to Black/African American participants for Grade ≥3 TEAEs (62% and 52%, respectively) and treatment-related Grade ≥3 TEAEs (49% and 29%, respectively). The incidences of other parameters were too low for meaningful comparison.

BMI

In the overall population, in the dostarlimab plus carboplatin-paclitaxel arm, 2 (0.8%) participants were underweight, 47 (19.5%) were of normal weight, 62 (25.7%) were overweight and 129 (53.5%) were obese; in the placebo plus carboplatin-paclitaxel arm, 5 (0.2%) participants were underweight, 44 (17.9%) were of normal weight, 51 (20.7%) were overweight and 146 (59.3%) were obese. Due to the small number of participants with an underweight BMI, a meaningful comparison could not be made with other BMI categories. Overall, safety risks were not observed to be significantly increased between participants with normal, overweight or obese BMIs in the dostarlimab plus carboplatin-paclitaxel arm.

The incidence of TEAEs and treatment-related TEAEs by BMI were similar (>90%) in participants with normal BMI (≥18.5 to <25 kg/m2), overweight BMI (≥25 to 30 kg/m2), and obese BMI (≥30 kg/m2) in each arm. The incidences of Grade ≥3 TEAEs in participants with normal, overweight or obese BMIs were similar within the dostarlimab plus carboplatin-paclitaxel arm (range 66% 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 compared to the placebo plus carboplatin-paclitaxel arm. Treatment-related Grade ≥3 TEAEs were similar within the dostarlimab plus carboplatin-paclitaxel arm (range 43% to 55%) 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 34% to 42%) and within the placebo plus carboplatin-paclitaxel arm (range 25% to 31%); these ranges were higher in participants in the dostarlimab plus carboplatin-paclitaxel arm compared with 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 42% to 55%; placebo plus carboplatin-paclitaxel range 38% to 41%). Dose reductions of chemotherapy were lower in participants with normal BMI in both treatment arms (~15%) 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 (14% to 23%) with the exception of normal BMI participants in the dostarlimab plus carboplatin-paclitaxel arm (32%). The incidence of dostarlimab/placebo-related irAEs in participants with normal or overweight BMIs within the dostarlimab plus carboplatin-paclitaxel arm (43% and 50%, respectively) were higher than in obese participants (30%). The incidences of other parameters were too low for meaningful comparison.

Baseline kidney function

Kidney function was defined as normal for CrCl ≥90 mL/min, mildly impaired for CrCl <90 to ≥60 mL/min, moderately impaired for CrCl <60 to ≥30 mL/min, and as severely impaired for CrCl <30 mL/min.

In the overall population, in the dostarlimab plus carboplatin-paclitaxel arm, 118 (49.0%) participants had normal baseline kidney function, 94 (39.0%) participants had mildly impaired baseline kidney function, 28 (11.6%) participants had moderately impaired baseline kidney function and 1 (0.4%) participant had severely impaired baseline kidney function; in the placebo plus carboplatin-paclitaxel arm, 126 (51.2%) participants had normal baseline kidney function, 91 (37.8%) participants had mildly impaired baseline kidney function, 29 (11.8%) participants had moderately impaired baseline kidney function and none had severely impaired baseline kidney function. Due to the small number of participants with severely impaired baseline kidney function, a meaningful comparison could not be made with other categories. Overall safety risks were not observed to be significantly increased between participants with normal, mildly impaired or moderately impaired baseline kidney function in the dostarlimab plus carboplatin-paclitaxel arm.

The incidences of TEAEs and any treatment-related TEAEs were similar (>95%) between participants with normal, mildly impaired and moderately impaired baseline kidney function in each arm. The incidences were similar between participants with normal, mildly impaired, and moderately impaired baseline kidney function for Grade ≥3 TEAEs (range 65% to 75%) and treatment-related Grade ≥3 TEAEs (range 50% 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%) compared to those with normal (56%) or mildly impaired (60%) baseline kidney function, with similar treatment-related Grade ≥3 TEAEs (range 44% 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. The incidences of other parameters were too low for participants with moderately impaired baseline kidney function for meaningful comparison.

Baseline hepatic function

Hepatic function was defined based on the maximum CTCAE grade for ALT or AST at baseline (normal = Grade 0 to 1, mildly impaired = Grade 2, moderately impaired = Grade 3, severely impaired = Grade 4).

There were only 3 participants in each treatment arm with a mildly impaired baseline hepatic function, with no participants in either treatment arm with moderately or severely impaired baseline hepatic function. Due to the small number of participants with an impaired baseline hepatic function, a meaningful comparison based on baseline hepatic function could not be made.

Extrinsic factors

Geographic region

In the overall population, in the dostarlimab plus carboplatin-paclitaxel arm, 169 (70.1%) participants were from North America and 57 (23.7%) were from Western Europe; in the placebo plus carboplatin-paclitaxel arm, 186 (75.6%) participants were from North America and 46 (18.7%) were from Western Europe. There were only 29 participants in total from Eastern Europe, therefore, a meaningful comparison based on geographic region could not be made with the other region categories. Overall safety risks were not observed to be significantly increased between participants from North America and Western Europe in the dostarlimab plus carboplatin-paclitaxel arm.

The incidences of participants with TEAEs, any treatment-related TEAEs, Grade ⩾3 TEAEs, treatment-related Grade ⩾3 TEAEs, TEAEs leading to chemotherapy dose reduction, TEAEs leading to treatment discontinuation and dostarlimab-related irAEs were generally similar in the dostarlimab plus carboplatin-paclitaxel arm between North America and Western Europe. SAEs were higher in participants from Western Europe (49%) as compared to North America (34%) in the dostarlimab plus carboplatin-paclitaxel arm; Grade ⩾3 TEAEs were higher in participants from Western Europe (74%) as compared to North America (56%) in the placebo plus carboplatin-paclitaxel arm. The incidences of other parameters were too low 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

Overall population

In the overall population, TEAEs leading to discontinuation of any study treatment were experienced by 23.7% of participants in the dostarlimab plus carboplatin-paclitaxel arm compared with 16.7% in the placebo plus carboplatin-paclitaxel arm. The incidence in individual system organ class and TEAEs by preferred term were similar (<3% difference) between treatment arms. The most frequently reported TEAEs leading to discontinuation (≥2.0% of participants in either arm) were peripheral sensory neuropathy (2.9% dostarlimab versus 0.4% placebo) and infusion-related reaction (2.1% versus 3.3%) in the dostarlimab plus carboplatin-paclitaxel arm, and infusion-related reaction, neuropathy peripheral (1.2% versus 2.4%), and thrombocytopenia (0.4% versus 2.0%) in the placebo plus carboplatin-paclitaxel arm.

TEAEs leading to discontinuation of dostarlimab or placebo were higher in participants in the dostarlimab plus carboplatin-paclitaxel arm (17.4%) compared with the placebo plus carboplatin-paclitaxel arm (9.3%). The majority of discontinuations in both treatment arms occurred during the dostarlimab plus carboplatin-paclitaxel phase (25 of 42 participants) or placebo plus carboplatin-paclitaxel phase (17 of 23 participants) rather than the dostarlimab/placebo maintenance phase. Individual system organ classes and TEAE by preferred term incidences were comparable (<3% difference) between treatment arms (Table 92. TEAEs leading to discontinuation of dostarlimab or placebo in both treatment arms occurred in ≤2 participants each, with the exception of rash maculo-papular (1.2% in dostarlimab plus carboplatin-paclitaxel arm, 0% in placebo plus carboplatin-paclitaxel arm), infusion-related reaction (1.2% versus 0.4%), and thrombocytopenia (0.4% versus 1.2%).

Table 92. Summary of treatment-emergent adverse events leading to discontinuation of dostarlimab or placebo in >1 participant 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 dostarlimab or placebo	42 (17.4%)	23 (9.3%)	65 (13.3%)
Blood and lymphatic system disorders	3 (1.2%)	6 (2.4%)	9 (1.8%)
Thrombocytopenia	1 (0.4%)	3 (1.2%)	4 (0.8%)
Anaemia	1 (0.4%)	1 (0.4%)	2 (0.4%)
Investigations	5 (2.1%)	3 (1.2%)	8 (1.6%)
Alanine aminotransferase increased	2 (0.8%)	1 (0.4%)	3 (0.6%)
Aspartate aminotransferase increased	2 (0.8%)	0	2 (0.4%)
General disorders and administration site conditions	6 (2.5%)	3 (1.2%)	6 (1.2%)
Asthenia	1 (0.4%)	1 (0.4%)	3 (0.6%)
Fatigue	2 (0.8%)	2 (0.8%)	2 (0.4%)
General physical health deterioration	2 (0.8%)	0	2 (0.4%)
Gastrointestinal disorders	3 (1.2%)	3 (1.2%)	6 (1.2%)
Diarrhoea	2 (0.8%)	1 (0.4%)	3 (0.6%)
Colitis	0	2 (0.8%)	2 (0.4%)
Skin and subcutaneous tissue disorders	3 (1.2%)	3 (1.2%)	6 (1.2%)
Rash maculo-papular	3 (1.2%)	0	3 (0.6%)
Rash	0	2 (0.8%)	2 (0.4%)
Immune system disorders	2 (0.8%)	2 (0.8%)	4 (0.8%)
Hypersensitivity	1 (0.4%)	1 (0.4%)	2 (0.4%)
Injury, poisoning and procedural complications	3 (1.2%)	1 (0.4%)	4 (0.8%)

System organ class, n (%) Preferred term, n (%)	Dostar + carbo/pac (N=241)	Placebo + carbo/pac (N=246)	Total (N=487)
Infusion-related reaction	3 (1.2%)	1 (0.4%)	4 (0.8%)
Musculoskeletal and connective tissue disorders	3 (1.2%)	1 (0.4%)	4 (0.8%)
Muscular weakness	2 (0.8%)	0	2 (0.4%)
Hepatobiliary disorders	1 (0.4%)	2 (0.8%)	3 (0.6%)
Autoimmune hepatitis	1 (0.4%)	1 (0.4%)	2 (0.4%)
Respiratory, thoracic and mediastinal disorders	3 (1.2%)	0	3 (0.6%)
Pneumonitis	2 (0.8%)	0	2 (0.4%)
Reproductive system and breast disorders	0	2 (0.8%)	2 (0.4%)
Vaginal hemorrhage	0	2 (0.8%)	2 (0.4%)

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

TEAEs leading to discontinuation of carboplatin, as well as individual system organ classes and TEAEs, were comparable in participants between the dostarlimab plus carboplatin-paclitaxel and the placebo plus carboplatin-paclitaxel arms (<3% difference). The most frequently reported TEAEs leading to discontinuation of carboplatin (≥1.0% of participants) were infusion-related reaction (1.7% dostarlimab versus 1.6% placebo) and thrombocytopenia (0% versus 1.6%).

TEAEs leading to discontinuation of paclitaxel, as well as individual system organ classes and TEAEs were comparable between the dostarlimab plus carboplatin-paclitaxel and the placebo plus carboplatin-paclitaxel arms (<3% difference). The most frequently reported TEAEs leading to discontinuation of paclitaxel (≥1.0% of participants) were peripheral sensory neuropathy (2.9% dostarlimab versus 0.4% placebo), neuropathy peripheral (1.2% versus 2.4%), infusion-related reaction (1.2% versus 2.0%), and thrombocytopenia (0.4% versus 1.2%).

dMMR/MSI-H population

TEAEs leading to discontinuation of any study treatment were comparable between the dostarlimab plus carboplatin-paclitaxel arm (17.3%) and the placebo plus carboplatin-paclitaxel arm (16.9%). The most frequently reported TEAE leading to discontinuation (≥2% of participants) was neuropathy peripheral (0% dostarlimab and 4.6% placebo); all TEAEs leading to discontinuation in the dostarlimab plus carboplatin-paclitaxel arm occurred in 1 participant each.

TEAEs leading to discontinuation of dostarlimab or placebo occurred in 15.4% of participants in the dostarlimab plus carboplatin-paclitaxel arm compared with 10.8% of participants in the placebo plus carboplatin-paclitaxel arm. The majority of discontinuations in both treatment arms occurred during the dostarlimab plus carboplatin-paclitaxel phase (5 of 8 participants) or placebo plus carboplatin-paclitaxel phase (5 of 7 participants) rather than the dostarlimab/placebo maintenance phase. The only TEAE leading to discontinuation of dostarlimab or placebo in ≥2% of participants was thrombocytopenia (0% dostarlimab and 3.1% placebo); all TEAEs leading to discontinuation in the dostarlimab plus carboplatin-paclitaxel arm occurred in 1 participant each.

TEAEs leading to discontinuation of carboplatin, as well as individual system organ class and TEAE incidences, were comparable between the dostarlimab plus carboplatin-paclitaxel and the placebo plus carboplatin-paclitaxel arms (<2% difference). All TEAEs leading to discontinuation of carboplatin in both treatment arms occurred in 1 participant each.

TEAEs leading to discontinuation of paclitaxel occurred in 3.8% of participants in the dostarlimab plus carboplatin-paclitaxel arm compared with 12.3% of participants in the placebo plus carboplatin-paclitaxel arm. The only TEAE leading to discontinuation of paclitaxel in ≥2% of participants was neuropathy peripheral (0% dostarlimab and 4.6% placebo); all TEAEs leading to discontinuation in the dostarlimab plus carboplatin-paclitaxel arm occurred in 1 participant each.

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 45.2% in participants in the dostarlimab plus carboplatin-paclitaxel arm compared with 39.4% in participants in the placebo plus carboplatin-paclitaxel arm. The most frequently reported TEAEs (>5%) leading to delays of infusion were thrombocytopenia (7.5% dostarlimab versus 5.7% placebo), neuropathy peripheral (5.8% versus 2.0%), and anemia (5.4% versus 6.1%) in the dostarlimab plus carboplatin-paclitaxel arm, and platelet count decreased (5.0% versus 7.3%), neutrophil count decreased (1.2% versus 6.5%), anemia, thrombocytopenia, and neutropenia (3.3% versus 5.3%) in the placebo plus carboplatin-paclitaxel arm.

The incidence of TEAEs leading to delays of dostarlimab/placebo infusion was 42.7% in participants in the dostarlimab plus carboplatin-paclitaxel arm compared with 37.0% in participants in the placebo plus carboplatin-paclitaxel arm. However, no notable differences were observed in system organ classes or preferred terms between treatment arms. The most frequently reported TEAEs (>5%) leading to delays of dostarlimab/placebo infusion in the dostarlimab plus carboplatin-paclitaxel arm were thrombocytopenia (7.1% versus 5.3%) and anemia (5.4% versus 6.1%), and in the placebo plus carboplatin-paclitaxel arm were platelet count decreased (4.1% versus 7.3%), neutrophil count decreased (1.2% versus 6.1%), anemia, thrombocytopenia, and neutropenia (3.3% versus 5.3%).

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

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

dMMR/MSI-H population

In the dMMR/MSI-H EC population, the incidence of TEAEs leading to delays of any drug component of any study treatment was comparable between the dostarlimab plus carboplatin-paclitaxel arm (46.2%) and the placebo plus carboplatin-paclitaxel arm (43.1%). No notable differences (>10%) were observed in the incidence of TEAEs between treatment arms. The most frequently reported TEAEs (>5%) leading to delays of infusion were anemia (7.7% versus 9.2%), thrombocytopenia (7.7% versus 9.2%), and platelet count decreased (7.7% each) in both treatment arms, as well as neuropathy peripheral (5.8% versus 4.6%) in the dostarlimab plus carboplatin-paclitaxel arm and neutropenia (1.9% versus 6.2%) in the placebo plus carboplatin-paclitaxel arm.

The incidence of TEAEs leading to delays of dostarlimab or placebo infusion was 44.2% for participants in the dostarlimab plus carboplatin-paclitaxel arm and 41.5% for participants in the placebo plus carboplatin-paclitaxel arm. With the exception of neuropathy peripheral, the most frequently reported TEAEs (>5%) leading to delays of dostarlimab or placebo infusion were the same as those observed for the delay of any study treatment described above.

The incidence of TEAEs leading to delays of carboplatin infusion was lower in the dostarlimab plus carboplatin-paclitaxel arm (30.8%) compared with the placebo plus carboplatin-paclitaxel arm (41.5%). With the exception of neuropathy peripheral, the most frequently reported TEAEs (>5%) leading to delays of carboplatin infusion were the same as those observed for the delay of any study treatment described above.

The incidence of TEAEs leading to delays of paclitaxel infusion was lower in the dostarlimab plus carboplatin-paclitaxel arm compared with the placebo plus carboplatin-paclitaxel arm (25.0% and 35.4%, respectively). The most frequently reported TEAEs (>4%) leading to delays of paclitaxel infusion were thrombocytopenia (5.8% versus 9.2%) and platelet count decreased (5.8% versus 7.7%) in both treatment arms, and neutropenia (1.9% versus 4.6%), anemia (5.8% versus 4.6%), and neuropathy peripheral (0% versus 4.6%) in the placebo plus carboplatin-paclitaxel arm.

Adverse Drug Reactions

A 2-step, holistic approach was utilized to review TEAEs from all participants in RUBY Part 1 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

ADRs for the CCDS 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 28 September 2022. Final identification of ADRs (Table 93) is based on the overall quantitative analysis and the qualitative assessment.

The majority of the ADRs for dostarlimab plus carboplatin-paclitaxel (Table 93 were previously identified as ADRs for dostarlimab monotherapy as 2L+ in participants with advanced or recurrent solid tumors. New terms included as ADRs for dostarlimab plus carboplatin-paclitaxel based on data from RUBY Part 1 are:

- Immune-mediated hypothyroidism: immune-mediated hypothyroidism was identified in 1 participant in the dostarlimab plus carboplatin-paclitaxel arm, considered related to dostarlimab by the investigator, with laboratory data and treatment consistent with hypothyroidism. Hypothyroidism was also identified as an ADR for dostarlimab plus carboplatin-paclitaxel based on quantitative analysis of RUBY Part 1 data.
- Dry skin met the quantitative screening criteria. Approximately one-half of the TEAEs of dry skin occurring in the dostarlimab plus carboplatin-paclitaxel arm were considered related to dostarlimab, as well as carboplatin or paclitaxel, by the investigator.

The most frequently reported ADRs (≥10% of participants) in participants receiving dostarlimab plus carboplatin-paclitaxel are rash (22.8%), rash maculo-papular (14.1%), hypothyroidism (14.1%), alanine aminotransferase increased (12.9%), aspartate aminotransferase increased (12.0%), pyrexia (12.0%), and dry skin (10.4%) (Table 93.

Based on the dostarlimab mechanism of action, following medical review, immune-mediated AEs with incidence <10% were identified as ADRs including hyperthyroidism (4.1%), pneumonitis (2.1%), colitis (1.2%), adrenal insufficiency (1.2%), pancreatitis (0.8%), 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%) (Table 93).

AEs that met the quantitative criteria and which were not considered to be causally attributable to dostarlimab in the CCDS include hypertension, blood creatinine increased, hypoesthesia,

hypoalbuminemia, toothache, hypocalcemia, and sepsis. These events 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 (hypertension, blood creatinine increased, hypoalbuminemia, and hypocalcemia), 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 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).

Table 93. Adverse drug reactions in patients with recurrent or primary advanced endometrial cancer (overall population, Safety Analysis Set)

Preferred term, n (%)/ Sub preferred term, n (%)	Overall (N=241)	SAE	Leading to dostar/plac interruption	Leading to dostar/plac discontin
Any adverse drug reactions	146 (60.6%)	14 (5.8%)	1 (0.4%)	12 (5.0%)
Rash	84 (34.9%)	1 (0.4%)	0	3 (1.2%)
Rash	55 (22.8%)	1 (0.4%)	0	0
Rash maculo-papular	34 (14.1%)	0	0	3 (1.2%)
Hypothyroidism	35 (14.5%)	0	0	1 (0.4%)
Hypothyroidism	34 (14.1%)	0	0	1 (0.4%)
Immune-mediated hypothyroidism	1 (0.4%)	0	0	0
Alanine aminotransferase increased	31 (12.9%)	0	1 (0.4%)	2 (0.8%)
Aspartate aminotransferase increased	29 (12.0%)	0	0	2 (0.8%)
Pyrexia	29 (12.0%)	6 (2.5%)	0	1 (0.4%)
Dry skin	25 (10.4%)	0	0	0
Hyperthyroidism	10 (4.1%)	0	0	0
Pneumonitis	5 (2.1%)	0	0	2 (0.8%)
Adrenal insufficiency	3 (1.2%)	2 (0.8%)	0	1 (0.4%)
Colitis	3 (1.2%)	2 (0.8%)	0	0
Pancreatitis	2 (0.8%)	1 (0.4%)	0	1 (0.4%)
Immune-mediated arthritis	1 (0.4%)	0	0	0
Myocarditis	1 (0.4%)	1 (0.4%)	0	0
Thyroiditis	1 (0.4%)	0	0	0
Type 1 diabetes mellitus	1 (0.4%)	1 (0.4%)	0	0
Uveitis	1 (0.4%)	0	0	1 (0.4%)

Abbreviations: discont=discontinuation; dostar=dostarlimab; plac=placebo; SAE=serious adverse event.

Post marketing experience

There are no data from post marketing experience in this new indication.

2.5.1. Discussion on clinical safety

The current safety assessment for dostarlimab, in combination with carboplatin-paclitaxel is based on the results from an interim analysis from Part 1 of the dostarlimab Study 213361, referred to as RUBY, with a data cut-off date of 28 September 2022. RUBY Part 1 enrolled participants with primary advanced (Stage III or IV) or recurrent EC who were randomized 1:1 to receive dostarlimab in combination with carboplatin-paclitaxel followed by dostarlimab or placebo in combination with carboplatin-paclitaxel followed by placebo. Treatment ended after 3 years, progression of disease, unacceptable toxicity, withdrawal of consent, investigator's decision, or death, whichever occurred first. The Safety Analysis Set

(n=487) includes all participants who received any amount of study treatment regardless of randomization.

As of the 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. Within the dMMR/MSI-H safety population (n=117), there were 52 participants in the dostarlimab plus carboplatin-paclitaxel arm and 65 participants in the placebo plus carboplatin-paclitaxel arm.

The median number of actual dosing cycles was 10.0 in the dostarlimab plus carboplatin-paclitaxel arm and 9.0 in the placebo plus carboplatin-paclitaxel arm. The overall median treatment duration was 43.00 weeks (range: 3.0 to 150.9 weeks) for participants in the dostarlimab plus carboplatin-paclitaxel arm and 36.00 weeks (range: 2.1 to 165.1 weeks) for participants in the placebo plus carboplatin-paclitaxel arm. The median treatment duration of both carboplatin and paclitaxel was 18.00 weeks in both arms. For the dMMR/MSI-H population, the overall median treatment duration was 76.50 weeks (range: 3.0 to 150.3 weeks) for participants in the dostarlimab plus carboplatin-paclitaxel arm and 31.86 weeks (range: 3.0 to 153.0 weeks) for participants in the placebo plus carboplatin-paclitaxel arm.

Overall, baseline characteristics were well balanced between the 2 treatment arms, with no clinically meaningful differences for the safety assessment.

All participants in both treatment arms experienced at least 1 TEAE (100%). Incidences of participants experiencing Grade ≥3 TEAEs and SAEs were higher in the dostarlimab plus carboplatin-paclitaxel arm compared with the placebo plus carboplatin-paclitaxel arm (70.5% versus 59.8%, respectively and 37.8% versus 27.6%, respectively). For the dMMR/MSI-H population, all parameters were comparable (≤10% difference between the treatment arms) with the exception of participants experiencing immune-related TEAEs (73.1% dostarlimab versus 36.9% placebo).

The most frequently reported TEAEs (>40%) in the dostarlimab plus carboplatin-paclitaxel arm were nausea, alopecia, fatigue, and neuropathy peripheral, while those in the placebo plus carboplatin-paclitaxel arm included fatigue, alopecia, nausea, anemia, and neuropathy peripheral. Overall, incidences of TEAEs were comparable between participants in the 2 treatment arms (≤10% difference), with the exception of rash maculo-papular (14.1% in the dostarlimab plus carboplatin-paclitaxel arm compared with 3.7% in the placebo plus carboplatin-paclitaxel arm). The frequency of treatment-related TEAEs was comparable between the treatment arms (97.9% in the dostarlimab plus carboplatin-paclitaxel and 98.8% in the placebo plus carboplatin-paclitaxel arms). The most frequently reported TEAEs related to any study treatment (>40%) in the dostarlimab plus carboplatin-paclitaxel arm were alopecia, fatigue, nausea, and neuropathy peripheral, while those in the placebo plus carboplatin-paclitaxel arm included alopecia, fatigue, and nausea. The incidences of TEAEs were comparable between the treatment arms with frequency differences of <10%. 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 (27.4% and 11.8%, respectively) primarily driven by TEAEs of rash and rash maculo-papular, and Endocrine disorders (16.6% and 5.7%, respectively) mainly driven by hypothyroidism. For the dMMR/MSI-H EC population, at least 50% of subjects in both treatment arms had alopecia and fatigue, while the incidence of nausea was 55.8% in the dostarlimab plus carboplatin-paclitaxel arm, and anemia was 52.3% in the placebo plus carboplatin-paclitaxel arm. The most frequently reported TEAEs (>40%) in the dostarlimab plus carboplatin-paclitaxel arm were nausea (55.8%), alopecia (55.8%), fatigue (50.0%), neuropathy peripheral (42.3%), arthralgia (42.3%), and diarrhea (40.4%), while those in the placebo plus carboplatin-paclitaxel arm included alopecia (60.0%), fatigue (55.4%), anemia (52.3%), nausea (46.2%), and neuropathy peripheral (43.1%). The following TEAEs were higher in the dostarlimab plus carboplatin-paclitaxel arm compared with the placebo plus carboplatin-paclitaxel arm: rash (28.8% dostarlimab versus 15.4% placebo),

hypertension (21.2% versus 10.8%), hypothyroidism (21.2% versus 6.2%), rash maculo-papular (13.5% versus 3.1%), and pyrexia (13.5% versus 1.5%).

A total of 65.1% of all participants experienced a Grade ≥3 TEAE. The most frequently reported treatment-related Grade ≥3 TEAEs in both treatment arms were anemia, neutropenia, and neutrophil count decreased. In the dMMR/MSI H EC population, the most frequently reported Grade ≥3 TEAEs were neutropenia (17.3% dostarlimab versus 12.3% placebo), anemia (15.4% versus 21.5%), neutrophil count decreased (7.7% versus 18.5%), and white blood cell decreased (3.8% versus 12.3%).

Regarding deaths, in the overall population, 165 participants died while on study: 65 participants (27.0%) in the dostarlimab plus carboplatin-paclitaxel arm and 100 participants (40.7%) in the placebo plus carboplatin-paclitaxel arm, disease progression being the most common cause of death (23.7% dostarlimab, 35.4% placebo). A total of 5 participants overall (1.0%) had a TEAE leading to death; 2 were in the dMMR/MSI H EC population. All of these deaths were reported in patients from the dostarlimab plus carboplatin-paclitaxel arm. Two participants died from treatment-related TEAEs: these deaths were due to myelosuppression and hypovolemic shock (both in the dMMR/MSI-H population). Three participants who received dostarlimab plus carboplatin-paclitaxel died due to an overdose of opiates, COVID-19, and general physical health deterioration each (considered as not related to treatment).

In the overall population, 32.6% of the participants presented SAEs. The most frequently reported SAEs in the dostarlimab plus carboplatin-paclitaxel arm were sepsis, pulmonary embolism, and pyrexia, while those in the placebo plus carboplatin-paclitaxel arm were anemia and asthenia. Treatment-related SAEs were experienced by 15.2% of the participants. The most frequently reported treatment-related SAEs (>1%) in the dostarlimab plus carboplatin-paclitaxel arm were febrile neutropenia (1.7%), and pyrexia, sepsis, and muscular weakness (1.2% each), and in the placebo plus carboplatin-paclitaxel arm were anemia (2.0%), febrile neutropenia (1.6%), asthenia (1.6%), and diarrhea (1.2%). In the dMMR/MSI-H EC population, the overall incidence of SAEs was 26.9% in the dostarlimab plus carboplatin-paclitaxel arm and 30.8% in the placebo plus carboplatin-paclitaxel arm.

Focusing on treatment modifications, dostarlimab or placebo dose reductions were not permitted but dostarlimab or placebo treatment could be interrupted or discontinued due to toxicity. In the overall population, TEAEs leading to discontinuation of any study treatment were experienced by 23.7% of participants in the dostarlimab plus carboplatin-paclitaxel arm compared with 16.7% in the placebo plus carboplatin-paclitaxel arm. The most frequently reported TEAEs leading to discontinuation were peripheral sensory neuropathy (2.9% dostarlimab versus 0.4% placebo) and infusion-related reaction (2.1% versus 3.3%) in the dostarlimab plus carboplatin-paclitaxel arm, and infusion-related reaction, neuropathy peripheral (1.2% versus 2.4%), and thrombocytopenia (0.4% versus 2.0%) in the placebo plus carboplatin-paclitaxel arm. In the dMMR/MSI H EC population, TEAEs leading to discontinuation of any study treatment were comparable between the dostarlimab plus carboplatin-paclitaxel arm (17.3%) and the placebo plus carboplatin-paclitaxel arm (16.9%).

Considering dostarlimab mechanism of action, immune-related AEs were reported by 56.8% of patients in the dostarlimab plus carboplatin-paclitaxel arm and 35.8% in the placebo plus carboplatin-paclitaxel. A total of 38.2% of participants in the dostarlimab plus carboplatin-paclitaxel arm, and 15.4% 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 (≥5% of participants) were hypothyroidism, rash, arthralgia, and alanine aminotransferase increased; all but arthralgia were higher in incidence in the dostarlimab plus carboplatin-paclitaxel arm. Grade ≥3 irAEs were observed in 16.6% 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 12.4% 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 Grade ≥3 irAEs in the dostarlimab plus carboplatin-paclitaxel arm were rash (3.7%), rash maculo-papular, alanine aminotransferase increased, and aspartate aminotransferase increased (2.1% each). In the dMMR/MSI-H EC population, 73.1% of participants in the dostarlimab plus carboplatin-paclitaxel arm and 36.9% in the placebo plus carboplatin-paclitaxel arm reported an irAE and a total of 48.1% of patients in the dostarlimab plus carboplatin-paclitaxel arm, and 12.3% of participants in the placebo plus carboplatin-paclitaxel arm, had irAEs assessed by the investigator as related to dostarlimab / placebo, being endocrinopathies (23.1% versus 4.6%) and immune-mediated skin adverse reactions (15.4% dostarlimab versus 0% placebo) the most common categories among them. Two cases of serious irAEs were reported in the dostarlimab plus paclitaxel-carboplatin group (type 1 diabetes mellitus and pancreatitis) and one in the placebo plus paclitaxel-carboplatin treatment arm (colitis).

Infusion-related reactions were reported with similar incidences in both treatment arms, suggesting that they may be related to chemotherapy infusion rather than dostarlimab, as expected.

ADR identification was done primarily based on a frequentist approach and then a qualitative assessment by medical review including causality analyses. Most of the indentified ADRs had been previously included in the PI based on data from patients treated in 2L EC and other solid tumours but two ADRs have been identified in this RUBY Part 1 study: immune-mediated hypothyroidism and dry skin. According to the MAH, additional potentially immune-related AEs were not identified as ADRs following medical review 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). Some clarifications were provided regarding these events but, considering the low incidence and the general recommendation in place to monitor suspected immune-mediated adverse events for this kind of products, no further measures were considered needed at this stage.

Regarding laboratory assessments, potential liver toxicity events were significantly higher in the dostarlimab plus carboplatin-paclitaxel treatment arm. However, none of these events were considered clinically relevant.

Safety in special populations was also assessed. In the dostarlimab + chemo arm, 88 (36.5%) patients were 65 to <75 years, and 27 (11.2%) were 75 years or older while in the chemo arm, these figures were 97 (39.4%) participants of 65 to <75 years, and 37 (15.0%) of 75 years or older. A trend towards higher incidences of Grade ≥3 TEAEs and SAEs in elderly patients was observed in both arms. Between arms, as expected, slightly higher incidences of events were reported in the dostarlimab plus carboplatin-paclitaxel treatment arm but the differences regarding the age ranges are not considered clinically relevant. For TEAEs leading to treatment discontinuation, again, higher incidences were observed in patients ≥75 but the difference between age ranges were similar in both treatment arms. For other intrinsic and extrinsic factors, no relevant differences were observed.

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 RUBY study, which provides comparative safety data, based on a larger dataset, for dostarlimab. Overall, no new risks have been identified, confirming the toxicity profile that was observed for the initial authorization. As expected, higher incidences of TEAEs have been reported for the combination and typical chemotherapy-related events have been observed. Identified ADRs for dostarlimab in combination treatment have been added to the PI. Once again, considering the

dostarlimab mechanism of action, fast identification and management of irAEs continues to be crucial in this setting. No change in the summary of safety concerns is required as part of this procedure.

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 with this application.

No changes in the summary of safety concerns, PhV plan or risk minimisation measures are required as part of this procedure.

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

The PRAC considered that the risk management plan version 3.2 is acceptable.

The CHMP endorsed this advice without changes.

The CHMP endorsed the Risk Management Plan version 3.2 with the following content:

Safety concerns

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

Pharmacovigilance plan

There are no on-going or planned additional pharmacovigilance activities.

Risk minimisation measures

Summary of pharmacovigilance activities and risk minimisation activities by safety concern

Safety concern	**Routine risk minimisation activities**
Immune-related adverse reactions (including pneumonitis, colitis, hepatitis,	**Routine risk communication**: SmPC Sections 4.2: Posology and method of administration 4.4: Special warnings and precautions for use

endocrinopathies, immune-related skin adverse reactions, nephritis and other IrARs)	4.8: Undesirable effects Patient leaflet (PL) Sections 2. What you need to know before you take Dostarlimab 4. Possible side effects **Routine risk minimisation activities recommending specific clinical measures to address the risk**: Recommended treatment modifications are provided in SmPC section 4.2. Instruction regarding symptom evaluation, treatment modifications and interventions are provided in SmPC section 4.4. **Other routine risk minimisation measures beyond the Product Information**: - Prescription only medicine - Use restricted to physicians experienced in the use of anticancer medicinal products
Long-term safety	**Routine risk communication**: None proposed. **Other routine risk minimisation measures beyond the Product Information**: - Prescription only medicine - Use restricted to physicians experienced in the use of anticancer medicinal products

2.7. Update of the Product information

As a result of this variation, sections 4.1, 4.2, 4.8, 5.1 and 5.2 of the SmPC are being updated. The Package Leaflet (PL) is updated accordingly.

Changes are made to the Annex II conditions as detailed in the recommendations section.

Please refer to Attachment 1 which includes all changes to the Product Information.

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 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

There is no approved treatment in the first-line setting for primary advanced or recurrent EC, but carboplatin-paclitaxel is considered as standard of care 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 (see 2.1.1).

3.1.3. Main clinical studies

The current application is based on the results from the first interim analysis 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). OS data were not formally tested in the dMMR/MSI-H population.

3.2. Favourable effects

The combination of dostarlimab plus carboplatin-paclitaxel for the treatment of patients with primary advanced or recurrent dMMR/MSI-H endometrial cancer and who are candidates for systemic therapy showed an improved PFS by investigator compared with placebo plus chemotherapy in a prespecified interim analysis [HR: 0.28 (95% CI 0.162, 0.495); p-value <0.0001; median PFS not reached vs. 7.7 months]. Results from the PFS subgroup analyses were generally consistent with the main analysis and also favoured the dostarlimab plus carboplatin-paclitaxel arm. Several sensitivity analyses for PFS have also confirmed the reported main results.

A first interim analysis of OS was performed (33% maturity) in the overall population, the only population in which OS was formally assessed. Although data are still immature and no statistical significance was reached, a positive trend in OS has been observed [HR: 0.64 (95% CI 0.464, 0.870); p=0.0021; p-value stopping boundary for significance = 0.00177]. Additionally, although OS was not formally assessed in the dMMR/MSI-H population and the data are still immature (26% maturity), the descriptive OS results in the dMMR/MSI-H population seemed to confirm the observed trend in the overall population [HR: 0.30 (95% CI: 0.127, 0.699); nominal p=0.0016]. Updated OS data were in line with the previously reported results, both for the overall population [HR= 0.68 (95% CI: 0.513, 0.911); 39% maturity] and for the dMMR/MSI-H population [HR= 0.33 (95% CI: 0.155, 0.722); 30% maturity].

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 OS data at the time of the IA were immature (33% maturity) and, although updated OS data were provided within the procedure, data were still considered immature. Although there is a trend towards an OS improvement and a detrimental effect seems unlikely, uncertainty remains due to the immaturity of the data. Thus, to further characterise the efficacy of dostarlimab in combination with carboplatin and paclitaxel, results from the final OS analysis will be provided once available (see Annex II condition, PAES).

3.4. Unfavourable effects

Based on a safety analysis set of 487 patients included in RUBY study, 100% of the patients reported any TEAEs. Observed treatment-related AEs were reported by 98.4% of patients. Grade ≥3 TEAEs were reported by 70.5% and 59.8% of patients in the dostarlimab + carbo/pac arm and carbo/pac treatment arm, respectively. SAEs have been observed in the 37.8% of participants in the dostarlimab-chemo arm and 27.6% in the chemo treatment arm. TEAEs leading to treatment discontinuation were reported by 23.7% of patients in the dostarlimab + carbo/pac arm and 16.7% 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 were observed in the 56.8% of participants from the dostarlimab + carbo/pac arm and 35.8% in the carbo/pac treatment arm.

3.5. Uncertainties and limitations about unfavourable effects

Chemotherapy-related AEs may confound the identification of irAEs for dostarlimab. Considering the fact that immune-mediated events are known effects of dostarlimab and close monitoring is advised, no further measures are considered needed at this moment.

3.6. Effects Table

Table 94. Effects Table for dostarlimab, 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) (data cut-off: 28-Sep-2022)

Effect	Short description	Unit	Treatment	Control	Uncertainties / Strength of evidence	References
Favourable Effects						
Primary endpoints (dMMR/MSI-H)						
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)	NR (11.8, NR)	7.7 (5.6, 9.7)		CSR (DCO: 28-SEP-2022)
			0.28 (0.162, 0.495)		p<0.0001	

Effect	Short description	Unit	Treatment	Control	Uncertainties / Strength of evidence	References
OS (not formally tested in the dMMR/MSI-H population)	Overall survival: Time from randomization to the date of death by any cause.	Median, months (95% CI)	NR	NR (23.2, NR)	Immature data	
		HR	0.3 (0.127, 0.699)			
Secondary endpoints (dMMR/MSI-H)						
PFS (BICR)	Progression-free-survival: 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.	Median, months (95% CI)	NR	9.5 (7.0, 11.7)		CSR (DCO: 28-SEP-2022)
		HR	0.29 (0.158, 0.543)			
PFS2	Progression-free-survival 2: 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.	Median, months (95% CI)	NR	22.0 (13.4, NR)		
		HR	0.37 (0.189, 0.727)			
Unfavourable Effects						
Grade ⩾3 TEAEs		N (%)	170 (70.5%)	147 (59.8%)		CSR (DCO: 28-SEP-2022)
Grade ⩾3 treatment-related TEAEs			122 (50.6%)	114 (46.3%)		
Any serious TEAEs			91 (37.8%)	68 (27.6%)		
Any TEAE leading to treatment discontinuation			57 (23.7%)	41 (16.7%)		
Any TEAE with the outcome of death			5 (2.1%)	0		

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

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

The Part 1 of the RUBY study targeted patients with primary advanced or recurrent endometrial cancer and who are candidates for systemic therapy. Nevertheless, the MAH is applying for the indication in a subset of patients of this overall population i.e., dMMR/MSI-H population, instead of applying for the broad indication.

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

At the time of the DCO, OS data were still immature. The MAH will provide the final OS analysis once available (Annex II PAES).

With regard to safety, overall, the results from RUBY Part 1 seem to confirm the observed safety profile for dostarlimab in the initial assessment. However, the addition of chemotherapy 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 relevant risk minimisation activities are in place.

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 in the treatment of patients with primary advanced or recurrent dMMR/MSI-H 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, except for the added toxicity of chemotherapy. It can be concluded that the benefits of dostarlimab in this new indication outweigh the risks.

3.7.3. Additional considerations on the benefit-risk balance

With this submission the MAH also intends to fulfil SOB-clin-002 and convert the CMA into full approval. SOB-clin-002 is as follows:

"In order to confirm the efficacy and safety of dostarlimab in 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, the MAH should submit the results of the phase III, randomised, double-blind study RUBY, comparing the efficacy and safety of dostarlimab in combination with chemotherapy to chemotherapy alone in patients with recurrent or advanced endometrial cancer who have not received prior systemic anticancer therapy for recurrent or advanced disease. The CSR should be submitted by 31 August 2023."

The MAH has presented the results of the RUBY study, in due time. The results of this study have confirmed the efficacy and safety of dostarlimab in adult patients with dMMR/MSI-H recurrent or advanced endometrial cancer. Thus, the SOB-clin-002 can be considered fulfilled and the CMA can be converted into full approval.

3.8. Conclusions

The overall B/R of Jemperli is positive.

The following measures are considered necessary to address issues related to efficacy in accordance with the Commission Delegated Regulation (EC) No 357/2014, (a) an initial efficacy assessment that is based on surrogate endpoints, which requires verification of the impact of the intervention on clinical outcome or disease progression or confirmation of previous efficacy assumptions:

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 final results of the RUBY study part 1.

4. Recommendations

Outcome

Based on the review of the submitted data, the CHMP considers the following variation acceptable and therefore recommends 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 to include in combination with carboplatin and paclitaxel 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, based on results from study 213361 (RUBY) Part 1, listed as a Specific Obligation in the Annex II; this is 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. As a consequence, sections 4.1, 4.2, 4.8, 5.1 and 5.2 of the SmPC are updated. The Annex II and Package Leaflet are updated in accordance. Version 3.2 of the RMP has also been submitted. This submission fulfils SOB-clin-002 thus supporting the switch from CMA to full MA. In addition, the marketing authorisation holder (MAH) took the opportunity to introduce minor editorial changes to the PI. As part of the application, the MAH is requesting a 1-year extension of the market protection.

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 Annex(es) I, II and IIIB and to the Risk Management Plan are recommended.

The following specific obligation (SOB) has been fulfilled, and therefore it is recommended that is be deleted from the Annex II E:

In order to confirm the efficacy and safety of dostarlimab in 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, the MAH should submit the results of the phase III, randomised, double-blind study RUBY, comparing the efficacy and safety of dostarlimab in combination with chemotherapy to chemotherapy alone in patients with recurrent or advanced endometrial cancer who have not received prior systemic anticancer therapy for recurrent or advanced disease.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

Risk management plan (RMP)

The Marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

In addition, an updated RMP should be submitted:

At the request of the European Medicines Agency;

Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

Obligation to conduct post-authorisation measures

The MAH shall complete, within the stated timeframe, the below measures:

Description	Due date
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 final results of the RUBY study part 1.	30 June 2029

Additional market protection

Furthermore, the CHMP reviewed the data submitted by the MAH, taking into account the provisions of Article 14(11) of Regulation (EC) No 726/2004, and considers that the new therapeutic indication brings significant clinical benefit in comparison with existing therapies.