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ORIGINAL ARTICLE

Population pharmacokinetics and exposure–response relationships of dostarlimab in primary advanced or recurrent endometrial cancer in part 1 of RUBY

Mita Kuchimanchi[1] | Trine Lembrecht Jørgensen[2] | Eva Hanze[3] | Thierry André[4] | Angela Jain[5] | Dominique Berton[6] | Oskar Alskär[3] | Oleksandr Zub[7] | Ana Oaknin[8] | Mark S. Shahin[9] | Anthoula Koliadi[10] | Bhavana Pothuri[11] | Tom Krivak[12] | Mikalai Pishchyk[13] | Yakir Segev[14] | Floor J. Backes[15] | Christine Gennigens[16,17] | Sara Bouberhan[18] | Stefan Zajic[19] | Murad Melhem[1] | Joseph Buscema[20]

Correspondence
Mita Kuchimanchi, Clinical Pharmacology Modeling and Simulation, GSK, 1000 Winter St, Waltham, MA 02451, USA.
Email: mita.x.kuchimanchi@gsk.com

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Aims: Dostarlimab-gxly is a humanized monoclonal antibody of the IgG4 isotype that binds to the programmed cell death protein-1 (PD-1) receptor and blocks its ligands. RUBY (NCT03981796) is a two-part multicentre study in patients with recurrent or primary advanced endometrial cancer. The overall aims were to characterise the population pharmacokinetics (PopPK) from Part 1 of this study, identify relevant covariates of interest, and assess exposure–efficacy/safety (ER) relationships.

Methods: A PopPK model developed using GARNET (NCT02715284) study data for dostarlimab monotherapy was externally validated with RUBY Part 1 study data. Subsequently, the model was updated with data across the two studies. Exposure–safety analyses for adverse events related to dostarlimab alone or in combination with standard of care (SOC) were modelled using logistic regression. Exposure–efficacy analysis included Cox proportional hazards analysis of the primary efficacy endpoint of progression-free survival (PFS).

Results: For the model update, 7957 pharmacokinetics observations from 868 patients pooled from both RUBY and GARNET studies were available. The model was consistent with the previous model. Dostarlimab clearance was estimated to be 7.79% lower when dostarlimab was given as SOC combination therapy. However, no significant covariates were clinically relevant. Hepatic or renal impairment did not affect pharmacokinetics. Among the safety endpoints, only rash showed a small yet statistically significant effect ($P < .05$) in all subjects; however, this was not not deemed clinically relevant. There were no other clinically significant exposure–safety or exposure–PFS relationships.

For affiliations refer to page 853

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Conclusions: The addition of chemotherapy to dostarlimab had limited effect on dostarlimab PopPK, with no clinically significant covariates or clinically relevant exposure–safety or exposure–PFS relationships.

KEYWORDS
clinical pharmacology, oncology, pharmacokinetics, therapeutics

1 | INTRODUCTION

Dostarlimab is a humanized monoclonal antibody (mAb) of the immunoglobulin G4 (IgG4) isotype that binds with high affinity and specificity to programmed cell death protein-1 (PD-1) and blocks its interaction with both of its ligands, PD-L1 and PD-L2, thereby releasing PD-1 pathway-mediated inhibition of the immune response, including the antitumour response.[1]

Based on data from the ongoing GARNET trial[2] (NCT02715284), dostarlimab monotherapy is approved in the US for patients with mismatch repair deficient (dMMR) recurrent or advanced solid tumours who have progressed on or following prior treatment and who have no satisfactory alternative treatment options.[3–6] Dostarlimab monotherapy is also approved for patients with dMMR (US) or dMMR/microsatellite instability-high (MSI-H; EU) recurrent or advanced endometrial cancer (EC) that has progressed on or following treatment with a platinum-containing regimen.[3–6] Based on the statistically significant improvements in progression-free survival (PFS) observed in Part 1 of the RUBY trial[7] (NCT03981796), dostarlimab, in combination with carboplatin-paclitaxel (CP), followed by dostarlimab monotherapy is approved as first-line therapy in multiple countries for patients with dMMR/MSI-H primary advanced or recurrent EC.[3,5,8,9] Recently, dostarlimab plus carboplatin-paclitaxel followed by dostarlimab monotherapy was approved in the US for all adult patients with primary advanced or recurrent EC.[3]

A population pharmacokinetic (PopPK) model and exposure–response (ER) analysis for dostarlimab was previously published on the basis of interim data from GARNET.[10] Dostarlimab PK, similar to other anti–PD(L)-1 mAbs, was well described by a two-compartment model; no relationship between dostarlimab exposure and adverse events (AEs) were seen across solid tumours, including EC.[10,11]

In this analysis, the previously developed PopPK model for dostarlimab was externally validated using PK data collected in RUBY Part 1 from patients with primary advanced or recurrent EC. First external validation was performed using the PK data collected from RUBY Part 1 as an independent dataset to determine the accuracy and bias of the model that was previously developed using GARNET PK data. A covariate search using combined data from RUBY Part 1 and GARNET was then performed, and the model was updated. An ER analysis explored potential relationships between dostarlimab exposure and efficacy using the endpoints of PFS and duration of response (DOR) at the first interim analysis of RUBY Part 1. The relationship between dostarlimab exposure and the probability of relevant AEs was also explored.

What is already known about this subject

- Dostarlimab pharmacokinetics were well described in a two-compartment model with time-dependent linear elimination based on the GARNET study.
- In the phase 3 RUBY trial, dostarlimab plus carboplatin-paclitaxel demonstrated significant progression-free survival benefits in patients with primary advanced or recurrent endometrial cancer.

What this study adds

- Dostarlimab pharmacokinetics from the RUBY trial were well described by the previously developed PopPK model.
- Dose recommendations for dostarlimab were supported by the PopPK and exposure–response data; dose adjustment based on any covariate was not warranted, supported by the lack of clinically meaningful exposure–response relationships between exposure and efficacy/exposure and safety.

2 | METHODS

2.1 | Dose regimens

Details related to study design and patients are available in the supporting information and have been published previously.[2,7] Patients from GARNET were assigned to dostarlimab dose regimens of 1, 3 or 10 mg/kg intravenously (IV) every 2 weeks in a dose-escalation manner in Part 1; 500 mg IV every 3 weeks (Q3W) or 1000 mg IV every 6 weeks (Q6W) in Part 2A; or 500 mg IV Q3W for 4 cycles followed by 1000 mg IV Q6W thereafter in Part 2B. Patients enrolled in RUBY Part 1 were randomized 1:1 to receive 500 mg IV dostarlimab or placebo in combination with carboplatin (area under the curve [AUC] 5 mg/mL/min) and paclitaxel (175 mg/m^2) Q3W for six cycles followed by 1000 mg IV dostarlimab or placebo Q6W for up to 3 years or until disease progression. The six cycles of dostarlimab in RUBY Part 1 were chosen to align with the treatment cycles for carboplatin and paclitaxel.

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2.2 | PopPK model development

Initially, the previously published PopPK model for dostarlimab (based on the March 1, 2020, GARNET data cut) was externally validated.[10] Prior to the PK covariate analysis and the ER analyses, the dostarlimab PopPK model was updated using a combined dataset from GARNET (November 1, 2021, data cut) and RUBY Part 1 (August 8, 2022, data cut).

Structural model development for PopPK was not performed for RUBY because the GARNET model was available. Separate residual error for RUBY was estimated and observations were excluded based on conditional weighted residual and visual inspection. Details of software used, model development, model evaluation, model validation, and updated methods (including covariate modelling) can be found in the supporting information.

The clinical importance of the statistically significant covariates was evaluated by assessing the impact on exposure metrics (area under the concentration *vs.* time curve at steady state [AUC_{ss}], maximum concentration at steady state [$C_{max,ss}$] and minimum concentration at steady state [$C_{min,ss}$]) using forest plots. The reference patient was designed using the medians for all virtual patients and was a female with a body weight of 70 kg, aged 64.0 years, albumin of 39 g/L and alanine aminotransferase (ALT) of 18 U/L.

2.3 | ER analysis

2.3.1 | Efficacy

The dual-primary efficacy endpoints from RUBY Part 1 were PFS by investigator assessment per Response Evaluation Criteria in Solid Tumours version 1.1 (RECIST v1.1) in the dMMR/MSI-H and overall populations and overall survival (OS) in the overall population. DOR was a secondary efficacy endpoint in RUBY Part 1 and was defined as the time from the first documentation of complete or partial response to the time of first documentation of progressive disease by investigators (evaluated using RECIST v1.1) or death due to any cause. For the ER analysis, PFS and DOR data were analysed using a Cox regression with drug exposure as the independent predictor. PFS was additionally stratified by tumour biomarker status (dMMR/MSI-H *vs.* mismatch repair proficient/microsatellite stable [MMRp/MSS]). Covariates included tumour diagnosis, disease status in EC (recurrent, primary stage III or primary stage IV), prior external pelvic radiotherapy, baseline Eastern Cooperative Oncology Group performance status (ECOG PS), geographic location and histology. Drug exposure was represented by AUC, C_{max} and C_{min} from cycle 1 for efficacy assessment due to time-dependent clearance (CL), which decreases over time.[12–14] Additionally, potential confounding effects, such as baseline patient characteristics and effect of disease status (e.g., cancer-associated cachexia) on PK, in particular time-dependent CL, can lead to biased estimates of ER relationships. To mitigate the confounding effects of baseline factors (baseline-driven ER) and time-varying CL (response-driven ER) and to avoid potential bias, exposure based on cycle 1 was used for the assessment of the relationship between exposure and response.[12]

2.3.2 | Safety

Patients from both the dostarlimab plus CP and placebo plus CP arms of RUBY Part 1 were included in the AE analysis. Logistic regression was used to describe the relationship between the occurrence of drug-related AEs and dostarlimab exposure. The probability of AEs of interest was modelled as a function of exposure. The safety analysis was based on any-grade AEs at any time for arthralgia, diarrhoea, fatigue, nausea and rash. These AEs were chosen before the ER analysis as they were the five highest incidences seen in RUBY Part 1 with dostarlimab alone or in combination with chemotherapy. Drug exposure parameters from cycle 1 were used to assess ER because all modelled AEs had an early onset in cycle 1. The analysis was completed for three different periods: cycles 1–6 (chemotherapy phase), cycles 7 and later (monotherapy phase) and all cycles enabling comparison of dostarlimab with chemotherapy, placebo and overall.

3 | RESULTS

3.1 | Data selection

Patients with at least two dostarlimab PK observations were included in the analysis (Table S1). The analysis included 5975 observations from GARNET, from a total of 636 patients across Parts 1, 2A and 2B (including 1118 PK observations from the November 1, 2021, GARNET data cut) and 2057 PK observations from 232 patients from RUBY Part 1.

Baseline demographics and clinical characteristics are summarized in Table 1. The median age of patients was 64.0 years (range: 24–86 years), of whom 82% (713) were women, and the median weight was 73.0 kg (range: 34–182 kg). Overall, 23.4% (203) of patients had dMMR/MSI-H EC and 39.5% (343) had MMRp/MSS EC. At baseline, 11.2% (97) of patients had mild-to-moderate hepatic impairment and 64.6% (561) had mild-to-moderate renal impairment.

3.2 | External validation of the GARNET PopPK model

The dostarlimab PopPK model is a two-compartment model with a time-dependent linear elimination (Figure S1). From the available dataset, 2056 PK observations from 233 patients from RUBY Part 1 were included in the external validation of the model. From these data, 44 additional observations were removed due to high conditional weighted residuals (>5) or based on visual inspection during the base model development. The overall dostarlimab PK profile for patients in RUBY Part 1 was well described by the updated GARNET-based model with no major trends identified in the visual predictive checks stratified by dostarlimab plus CP or dostarlimab monotherapy (Figure S2).

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TABLE 1 Patient demographics of the overall analysis set.

Treatment	GARNET $N = 636$	RUBY Part 1 $N = 233$	All $N = 869$
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)
Female, *n* (%)	480 (75.5)	233 (100.0)	713 (82.0)
Race, *n* (%)			
White	467 (73.4)	181 (77.7)	648 (74.6)
Black or African American	21 (3.3)	26 (11.2)	47 (5.4)
Asian	13 (2.0)	7 (3.0)	20 (2.3)
American Indian or Alaska native	4 (0.6)	1 (0.4)	5 (0.6)
Native Hawaiian or other Pacific Islander	0	1 (0.4)	1 (0.1)
Other	6 (0.9)	–	6 (0.7)
Unknown	4 (0.6)	12 (5.2)	16 (1.8)
Not reported	121 (19.0)	5 (2.1)	126 (14.5)
Geographic location, *n* (%)			
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)
Diagnosis, *n* (%)			
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, *n* (%)			
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)
Hepatic impairment,[a] *n* (%)			
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,[a] *n* (%)			
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)
Concomitant medications, *n* (%)			
Use of immunomodulators			
No	634 (99.7)	231 (99.1)	865 (99.5)
Yes	2 (0.3)	2 (0.9)	4 (0.5)
Use of immunostimulants			
No	631 (99.2)	198 (85.0)	829 (95.4)
Yes	5 (0.8)	35 (15.0)	40 (4.6)

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TABLE 1 (Continued)

Treatment	GARNET $N = 636$	RUBY Part 1 $N = 233$	All $N = 869$
Corticosteroids			
No	379 (59.6)	214 (91.8)	593 (68.2)
Yes	257 (40.4)	19 (8.2)	276 (31.8)
ADAs, *n* (%)			
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)
eGFR (mL/min/m^2)			
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)[b]			
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 (19.0–1.0)	40.0 (21.0–51.0)	39.0 (19.0–51.0)
Bilirubin (μmol/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 (10^9 cells/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)
ECOG PS, *n* (%)			
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)

[a]Hepatic and renal impairment were classified as a categorical covariate based on the baseline GFR (mL/min/1.73 m^2); categories were coded as normal (eGFR ≥90), mild impairment (eGFR 60–89), moderate impairment (eGFR 30–59), and severe impairment (eGFR 15–29).
[b]$n = 1$ with missing creatinine clearance was imputed to median. Abbreviations: ADA, anti-drug antibody; dMMR, mismatch repair deficient; EC, endometrial cancer; ECOG PS, Eastern Cooperative Oncology Group performance status; eGFR, estimated glomerular filtration rate; MMRp, mismatch repair proficient; MSI-H, microsatellite instability-high; MSS, microsatellite stable; NSCLC, non-small cell lung cancer; *POLE*, polymerase epsilon.

3.3 | Combined trial data model update

The final model remained composed of a two-compartment model, with time-dependent linear elimination (Figure S1). The model incorporated interindividual variability on CL, V_c and I_{max} as independent random effects with estimations of 28% coefficient of variation (CV), 17.8% CV and 95.0% CV, respectively. Shrinkage in CL, V_c and I_{max} were 14.1%, 12.7% and 46.3%, respectively.

Weight was included as a covariate in the structural model (Table S2). The effect of weight was modelled on the basis of principles of allometry and included as a covariate for CL, V_c and V_p (standardis-ed to the 70-kg reference patient). Additional covariates were

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tested using the stepwise covariate modelling procedure. In the forward inclusion steps, age, sex, time-varying albumin, time-varying ALT and monotherapy *vs.* combination therapy were found to affect dostarlimab CL and remained statistically significant after the backward elimination step. Similarly, both time-varying albumin and sex were found to affect V_c in the forward inclusion steps and remained statistically significant. Anti-drug antibodies did not have a statistically significant effect on dostarlimab CL. Dostarlimab CL was estimated to be 7.9% lower when dostarlimab was given as part of a combination therapy with chemotherapy than when given as monotherapy. No covariates were found to be significant for V_p or I_{max} following the backward step.

The final PopPK model is mathematically described by the following equations (details are provided in the supplemental methods):

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

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

With time-dependent elimination,

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

where the microconstants of the mass transfer are defined as

$$k_0 = \frac{CL}{V_c}$$

$$k_{12} = \frac{Q}{V_c}$$

$$k_{21} = \frac{Q}{V_p}$$

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

$$CL = CL_{time-base} \cdot \left(\frac{WT}{70}\right)^{\Theta CL,WT} \cdot \left(\frac{AGE}{64}\right)^{\Theta CL,AGE} \cdot \left(\frac{ALB}{39}\right)^{\Theta CL,ALB} \cdot \left(\frac{ALT}{18}\right)^{\Theta CL,ALT} \cdot (1 - \Theta_{CL\_MONOTR}) \cdot (1 + \Theta_{CL\_SEX})$$

$$V_c = V_{cbase} \cdot \left(\frac{WT}{70}\right)^{\Theta Vcp,WT} \cdot \left(\frac{ALB}{39}\right)^{\Theta Vc,ALB} \cdot (1 + \Theta_{Vc\_SEX})$$

$$V_p = V_{pbase} \cdot \left(\frac{WT}{70}\right)^{\Theta Vcp,WT}$$

where $\theta_{CL\text{-}SEX}$ and $\theta_{Vc\text{-}SEX}$ are equal to 0 for females (most common) and estimated for males.

3.4 | PopPK model performance

The final model demonstrated appropriate agreement between observed and model predicted values with no obvious bias. Further details can be found in Supplemental Figures S3, S4 and S5.

The prediction-corrected visual predictive checks of the final PopPK model stratified by study (for the 500 mg Q3W and 1000 mg Q6W treatment for GARNET) or by combination or monotherapy are shown in Figure S6 and Figure 1. The parameter estimates for the final model are provided in Table 2. All parameters were estimated with sufficient precision (relative standard error <50%). Time dependency in CL was described by a sigmoid-I_{max} function, with decreasing CL over time. The Hill parameter of the sigmoid function describing I_{max} was 7.05, while the maximum decrease in CL over time was estimated to be 10.7%. The estimated steady state dostarlimab geometric mean CL was 0.00681 L/h (30.2% CV) with a volume of distribution of 5.81 L (14.9% CV). The geometric mean terminal elimination half-life at steady state was estimated to be 23.2 days (20.8% CV).

3.5 | Predicted exposure and clinical relevance of covariates

Predicted dostarlimab concentration *vs.* time profiles for patients included in the PK analysis were simulated using individual post hoc PK parameter estimates from the final model. Geometric mean AUC_{ss} and $C_{max,ss}$ were estimated at 145000 mg*h/L (30.3% CV) and 382 mg/L (21.3% CV) in the 1000 mg Q6W dosing phase. Dostarlimab showed approximately a 2-fold accumulation (2.3-fold and 1.72-fold for AUC *vs.* time curve for a dosing interval [$AUC_{0\text{-}tau}$] and C_{max}, respectively) when comparing individual predicted exposure after the first 500-mg dose with steady state exposure following 500 mg Q3W in RUBY Part 1. The PopPK model predicted median $C_{min;ss}$ (90% prediction interval [PI]) for the 500 mg Q3W and 1000 mg Q6W regimens were 106 (50.4–223) mg/L and 79.5 (34.1–186) mg/L, respectively. The lower bounds of these 90% PIs were approximately 2.80-fold and 1.89-fold higher, respectively, compared with the estimated concentration for maintenance of 90% of maximal peripheral PD-1 suppression (18 mg/L).[13] Exposure was similar regardless of renal or hepatic status for the available impairment categories.

The impact of statistically significant covariates on exposure at steady state (dostarlimab 1000 mg Q6W) is shown in Figure 2. The impact of weight on exposure at steady state was 0.8–1.25-fold at the 5th and 95th percentiles of the covariate distribution compared with the reference patient. AUC_{ss} in a reference patient with the 5th (49.7 kg) and 95th (116 kg) percentiles of the covariate value was estimated to be 19.0% higher and 23.7% lower, respectively. The impact on $C_{min;ss}$ and $C_{max;ss}$ was of similar magnitude. Albumin impact on AUC_{ss} was 0.8–1.25-fold with 24.5% lower and 13.2% higher AUC_{ss} in a reference patient with the 5th and 95th percentiles of the

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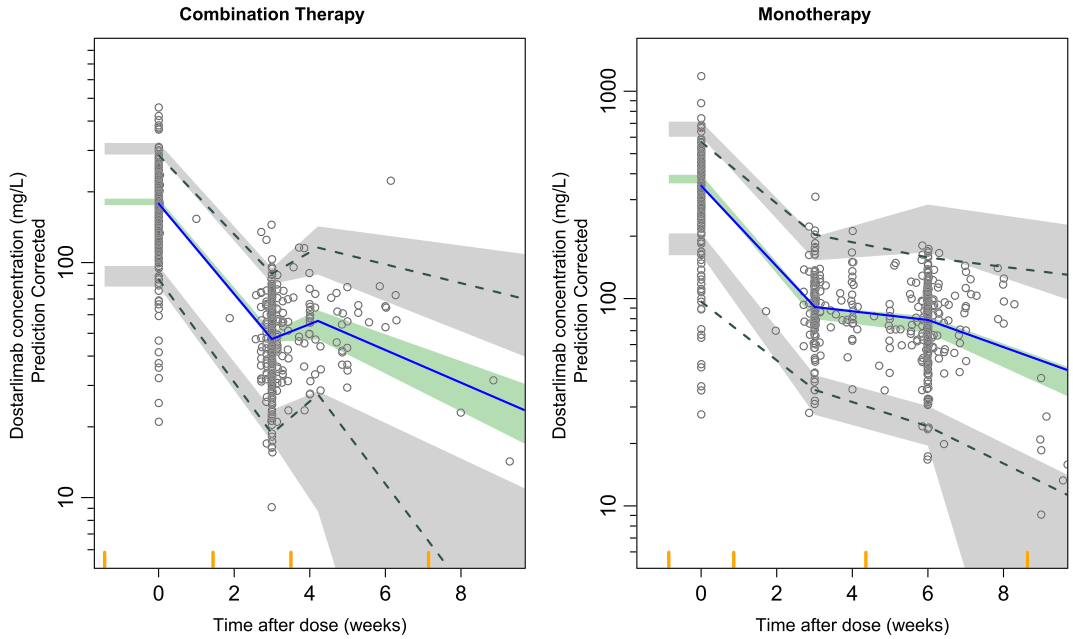

FIGURE 1 Prediction-corrected visual predicative check by therapy. Solid blue line: median of the observed dostarlimab concentrations. Dashed lines: 2.5th and 97.5th percentiles of the observed dostarlimab concentrations. Shaded areas: 95% confidence intervals around the prediction-corrected median (green area) and 2.5th and 97.5th percentiles of the simulated concentrations (grey areas). Grey circles: observations. Orange lines: binning intervals for the visual predictive check. All observations and predictions are adjusted using prediction correction as described in Bergstrand et al.[15] Visual predictive checks are based on data from RUBY Part 1. To increase visibility, the *x*-axis was cut at 10 weeks.

covariate value, respectively (independent of any time-varying CL, based on the typical value of the covariate effect). The largest impact of albumin was noted for $C_{min;ss}$, with 39.9% lower $C_{min;ss}$ in a patient at the 5th percentile of albumin (29 g/L).

Based on simulated profiles for the recommended therapeutic dose, the C_{min} were calculated and used to derive the percentage of patients with C_{min} at cycle 1 and at steady state greater than 18 mg/L for patients with low albumin (<29 g/L) or high weight (≥116 kg). Simulations demonstrated that the majority of patients were expected to reach $C_{min;ss}$ concentration above 18 mg/L, with 99.2% of the high-weight (≥116 kg) patients and 92.7% of the low-albumin (<29 g/L) patients reaching $C_{min;ss}$ > 18 mg/L. All other identified statistically significant covariates had limited impact on exposure (effect size within 0.8–1.25-fold for AUC_{ss}, $C_{max;ss}$ and $C_{min;ss}$). Race/ethnicity, tumour type and renal impairment also had no clinically significant impact on exposure.

3.6 | ER analyses

3.6.1 | PFS

A summary of the exposure ranges for the patients included in the ER analysis of PFS from RUBY Part 1 ($n = 232$) are shown in Table S3. Patients were predicted to have a mean (standard deviation [SD]) C_{min} of 39.70 (9.94) mg/L (during the first 21 days), C_{max} of 147 (26.40) mg/L (at Day 21) and AUC of 32300.00 (5850.00) mg*h/L (during the first 21 days). Plots of PFS probability over time for the exposure metrics show a large degree of overlap across quartiles (Figure 3). An apparent relationship where higher exposures result in lower efficacy was seen for C_{max}; however, the 95% CIs greatly overlapped.

When PFS probability *vs.* time was stratified by MMR/MSI status, a large difference in PFS was observed between patients with dMMR/MSI-H and MMRp/MSS tumours (Figure 4). The hazards for tumour diagnosis were non-proportional, so a Cox regression stratified by tumour diagnosis was performed for the three exposure metrics, AUC, C_{max} and C_{min}, with the additional covariates of disease status in EC, prior external pelvic radiotherapy, baseline ECOG PS, histology and geographic location. None of the tested exposure metrics had a statistically significant relationship with PFS with *P*-values of .90, .28 and .40 for AUC, C_{max} and C_{min}, respectively.

Additional covariates were subsequently included in a multivariate analysis, and the hazard ratios (HRs) of the tested covariates are shown in Figure S7. Patients with the geographic location of Eastern Europe ($n = 13$ in the dostarlimab plus CP arm) had an increased risk of tumour progression or death (in terms of PFS) compared with reference patients in North America ($n = 164$ in the dostarlimab plus CP arm; HR ≈ 2 for PFS); however, interpretability of these results was limited because of the small number of patients from Eastern Europe. None of the covariates included in these analyses correlated with each other to any appreciable extent.

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TABLE 2 Parameter estimates of the final structural PopPK model.

Parameter	Estimate	Relative SE, %	95% CI
Clearance (CL [L·h^{-1}])	0.00732	2.03	(0.00704–0.00761)
Central volume of distribution (V_c (L))	3.09	0.754	(3.04–3.13)
Proportional error, GARNET	0.16	3.09	(0.151–0.170)
Additive error (mg/L)	4.22	19.7	(2.60–5.85)
Intercompartmental clearance (Q [L·h^{-1}])	0.0191	12.0	(0.0153–0.0239)
Peripheral volume of distribution (V_p (L))	2.48	5.18	(2.25–2.74)
I_{max}	−0.113	19.4	(−0.157 to −0.0704)
T50 (days)	145	12.9	(109–182)
Hill	7.05	29.1	(3.03–11.1)
Effect of WT on CL	0.523	7.78	(0.443–0.602)
Effect of WT on V_c and V_p	0.48	4.75	(0.435–0.525)
Proportional error, RUBY	0.246	3.79	(0.228–0.264)
Effect of age on CL	−0.238	26.2	(−0.360 to −0.116)
Effect of ALB on CL	−0.922	7.93	(−1.06 to −0.778)
Effect of ALT on CL	−0.0623	26.5	(−0.0947 to −0.0300)
Effect of combination therapy on CL	−0.0779	25.9	(−0.118 to −0.0384)
Effect of male on CL	0.15	18.8	(0.0948–0.205)
Effect of ALB on V_c	−0.132	35.0	(−0.222 to −0.0409)
Effect of male on V_c	0.137	14.1	(0.0992–0.175)
ω^2_{CL}	0.0563 (23.7% CV)	6.97	(0.0486–0.0639)
Covariance$_{CL, VC}$	0.0193	11.4	(0.0150–0.0236)
ω^2_{VC}	0.0278 (16.7% CV)	8.30	(0.0232–0.0323)
ω^2_{Imax}	0.903 (95.0% CV)	27.5	(0.417–1.39)

Abbreviations: ALB, albumin; ALT, alanine aminotransferase; CI, confidence interval; CL, systemic clearance; I_{max}, maximal decrease in clearance relative to baseline; V_c, central volume of distribution; PopPK, population pharmacokinetic; Q, intercompartment clearance; SE, standard error; T50, time at which 50% of I_{max} is reached; V_c, central volume of distribution; V_p, peripheral volume of distribution; WT, body weight; ω^2_x, variance of the IIV of parameter X, IIV is derived from variance according to $\sqrt{\omega^2_x} \cdot 100$.

3.6.2 | DOR

A total of 147 DOR observations from 147 patients in the dostarlimab arm of RUBY Part 1 with quantified dostarlimab concentrations were used for DOR evaluation. Exposure metrics were similar to those in the PFS analysis (Table S4). Patients were predicted to have a mean (SD) C_{min} of 39.50 (9.61) mg/L (at Day 21), C_{max} of 145 (25.20) mg/L (during the first 21 days) and AUC of 32100.00 (5640.00) mg*h/L (during the first 21 days). DOR appeared to be independent of all three exposure metrics (Figure S8). The hazards for DOR for the covariates were proportional; therefore, a Cox regression was performed without stratification for AUC, C_{max} and C_{min}. None of the covariates of disease status in EC, prior external pelvic radiotherapy, baseline ECOG PS, histology or geographic location (Figure S9) had a statistically significant relationship with DOR, with *P*-values of .69, .45 and .32 for AUC, C_{max} and C_{min}, respectively.

MMRp/MSS tumour status was identified as a statistically significant covariate, with an HR of ≈2.6 ($P < .01$). Similar to PFS, the small number of patients in Eastern Europe had an increased risk in tumour progression or death compared with patients in North America (HR ≈ 2.5). Again, the interpretability was limited because of the small sample size of this population.

3.6.3 | Safety

A total of 478 patients from RUBY Part 1 (232 receiving dostarlimab, 246 receiving placebo) were included in the AE analysis. The mean (SD) predicted dostarlimab exposure metrics were the same as for the PFS analysis (Table S5). Binary data for the five most prevalent drug-related AEs as assessed by investigators were analysed using univariate logistic regression.

Among the safety endpoints included in the analysis, only rash showed a small yet statistically significant effect ($P < .05$) when all patients were included in the analysis (Figure 5). The increase in predicted probability of rash with high exposure (90th percentile) *vs*. low exposure (10th percentile) was limited; the increased probability was 5.2–10% with high exposure, depending upon the exposure metric and time period. However, when only patients treated with

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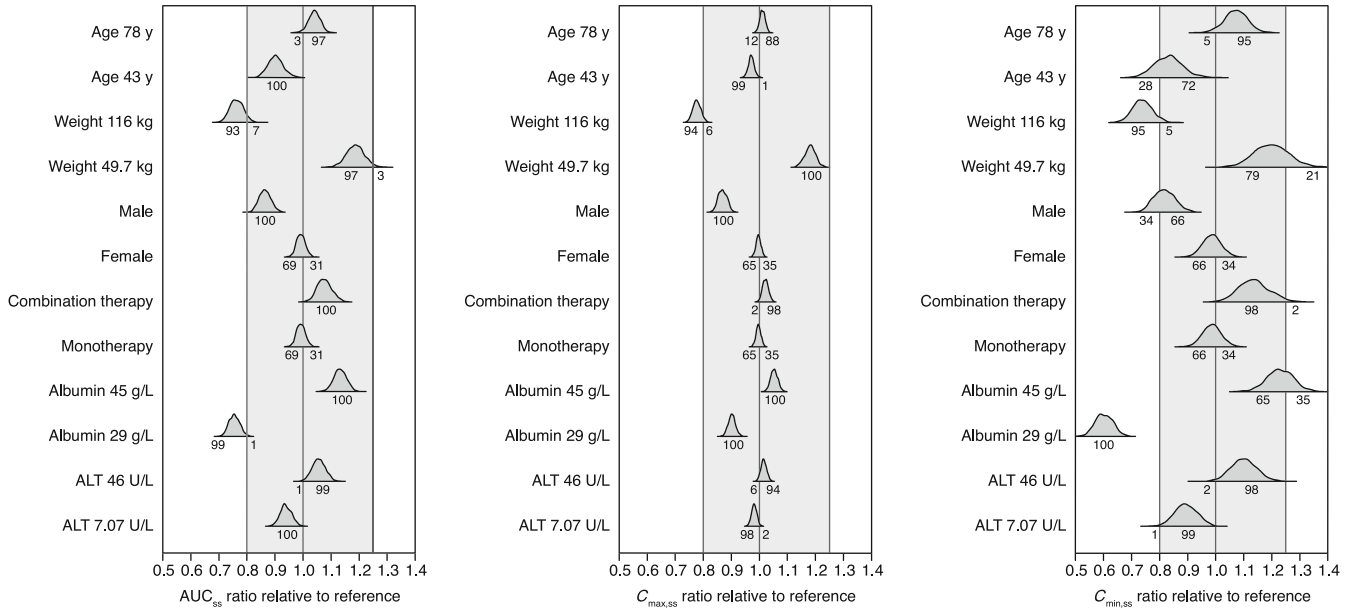

FIGURE 2 Forest plots illustrating the covariate effects on exposure at steady state (dostarlimab 1000 mg Q6W). Forest plots of AUC_{ss}, $C_{max,ss}$ and $C_{min,ss}$ ratios as compared to median reference patient (female, 70 kg, age, 64 years, albumin, 39 g/L and ALT, 17 U/L). The distributions represent the ratios based on 1000 sets of parameter estimates resampled from the variance covariance matrix. Plotted numbers: actual percentage of each distribution in a bounded region (here, the central reference line). Grey area: represents the 0.8 and 1.25 boundaries. ALT, alanine aminotransferase; AUC_{ss}, area under the concentration–time curve at steady state; $C_{max,ss}$, maximum concentration at steady state; $C_{min,ss}$, minimum concentration at steady state.

dostarlimab plus CP were included in the analysis, the ER relationships were no longer significant because the relationships were less supported in the lower range of exposures.

Significant relationships for AUC and C_{min} were found for arthralgia in the cycle 7+ period for dostarlimab-treated patients on the basis of predicted cycle 1 exposure (Figure 6). Going from low exposure (10th percentile) to high exposure (90th percentile), there was an increase in the probability of arthralgia by 14.2% for AUC and 15.5% for C_{min}. When all patients were included in the analysis for this period, the prevalence of arthralgia in the placebo arm (1.2% *vs.* 5.6% in the dostarlimab plus CP arm) rendered the ER relationships non-significant. No significant relationships were observed at any of the tested periods for the other three AEs included in this analysis (diarrhoea, fatigue, nausea).

4 | DISCUSSION

This analysis evaluated PK data collected from the ongoing phase 1 GARNET and Part 1 of the phase 3 RUBY trial. We found that data from RUBY Part 1 were well described by the updated GARNET-based PopPK model, and the parameters of the final model were generally similar to PK parameters reported for other anti–PD-1 mAbs[11] and consistent with the previous analysis of dostarlimab.[10]

In the final dostarlimab PopPK model, the maximum change in CL over time was estimated to be 10.7%, which is lower in magnitude than other anti–PD-1 mAbs (20–30%).[16] Furthermore, the estimated Hill parameter was high in comparison with other anti–PD-1 mAbs,[16] suggesting that the time-CL relationship is relatively steep. This may be due to sparse PK sampling in the RUBY study, especially at time intervals when most change in CL is expected. However, the effect on CL is limited; therefore, the clinical impact is expected to be low. A lower maximum change in CL and relatively steep Hill coefficient was also a characteristic of the previous dostarlimab PopPK model, which was based on only GARNET data.[10]

With the addition of data from RUBY Part 1 to the dostarlimab PopPK model, monotherapy *vs.* combination therapy was newly identified as a statistically significant covariate on CL. Dostarlimab CL was estimated to be 7.79% lower when dostarlimab was given in combination with chemotherapy than when administered as a monotherapy, translating into 1.08-fold higher AUC *vs.* monotherapy. The impact of combination therapy on exposure was limited and not of clinical relevance. The exact mechanism for this CL reduction is unknown because the combination therapy is confounded with the study and could possibly be a study effect rather than an actual effect of chemotherapy on dostarlimab CL. It could also be due to other confounding covariates such as differences in chemotherapy cycles between the two studies and certain baseline characteristics, including tumour types (not a statistically significant covariate in this analysis), which were highly correlated; therefore, their respective effects could not be differentiated.

Albumin demonstrated the most significant impact on exposure, with the largest impact noted for $C_{min;ss}$. However, although this significant impact was noted, albumin was determined to be not clinically

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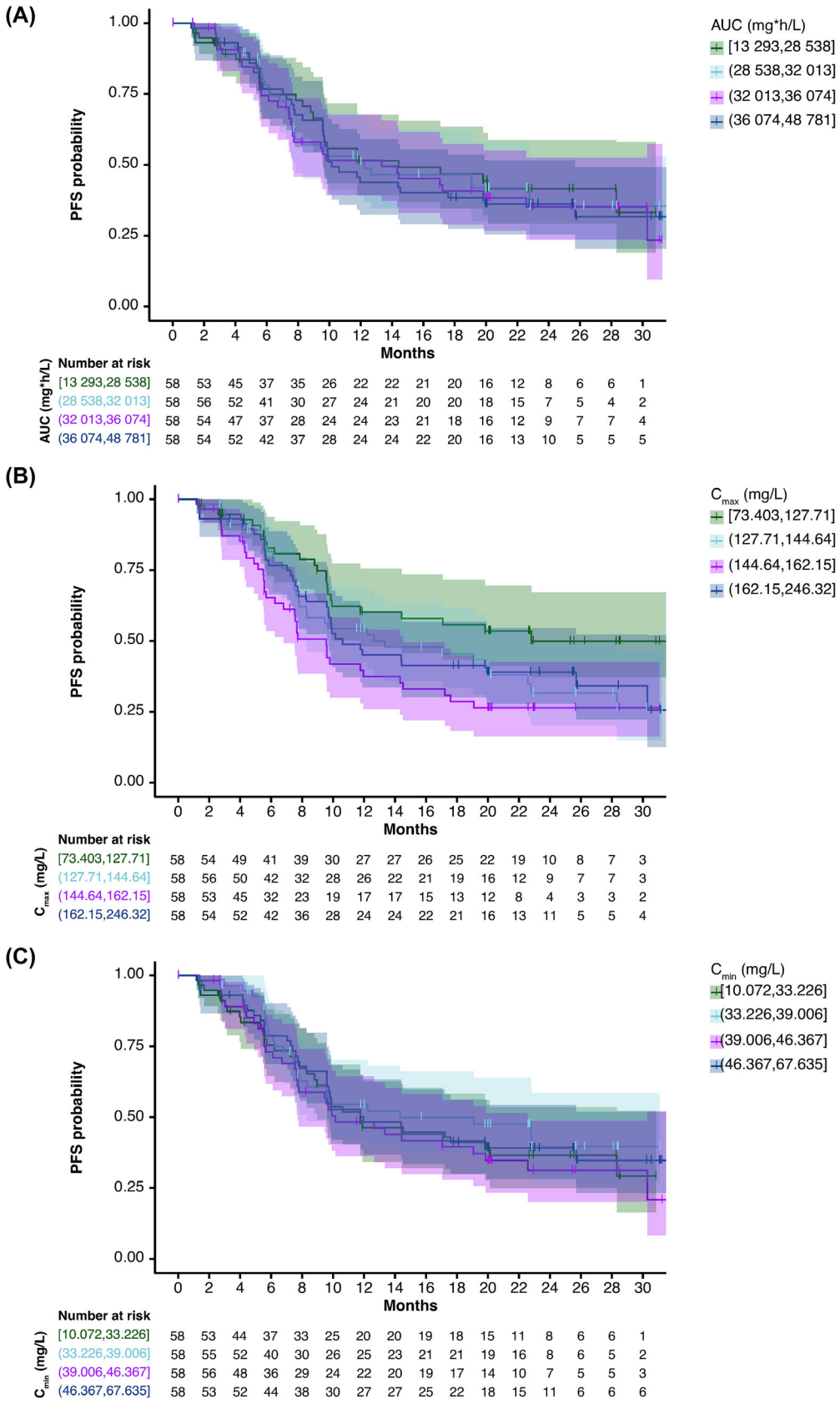

FIGURE 3 PFS *vs.* time, stratified by (A) AUC, (B) C_{max}, and (C) C_{min} exposure quartiles. AUC and C_{max} during the first 21 days; C_{min} at day 21. Lines: PFS probability. Vertical lines: censoring. Shaded areas: 95% confidence intervals. Parentheses: excluded endpoints. Brackets: included endpoints. AUC, area under the curve; C_{max}, maximum concentration; C_{min}, minimum concentration; PFS, progression-free survival; Q, quartile.

relevant. While a patient at the 5th percentile of albumin (29 g/L) is expected to have a 39.9% lower $C_{min;ss}$ than the reference median (39 g/L), simulations demonstrated that 92.7% of patients with low albumin (<29 g/L) were predicted to reach dostarlimab $C_{min;ss}$ levels >18 mg/L (the estimated dostarlimab trough concentration for maintenance of 90% of maximal peripheral PD-1 suppression).[12–14] Low

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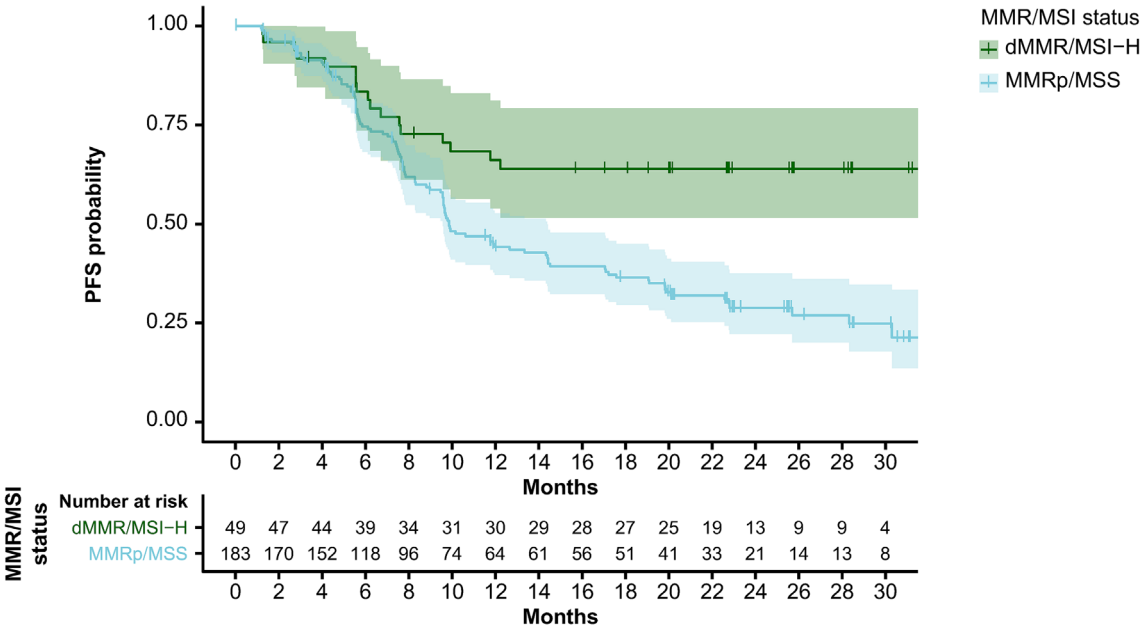

FIGURE 4 PFS *vs.* time, stratified by tumour MMR/MSI status. Lines: PFS probability. Vertical lines: censoring. Shaded areas: 95% CI. dMMR, mismatch repair deficient; MMR, mismatch repair; MMRp, mismatch repair proficient; MSI, microsatellite instability; MSI-H, microsatellite instability–high; MSS, microsatellite stable; PFS, progression-free survival.

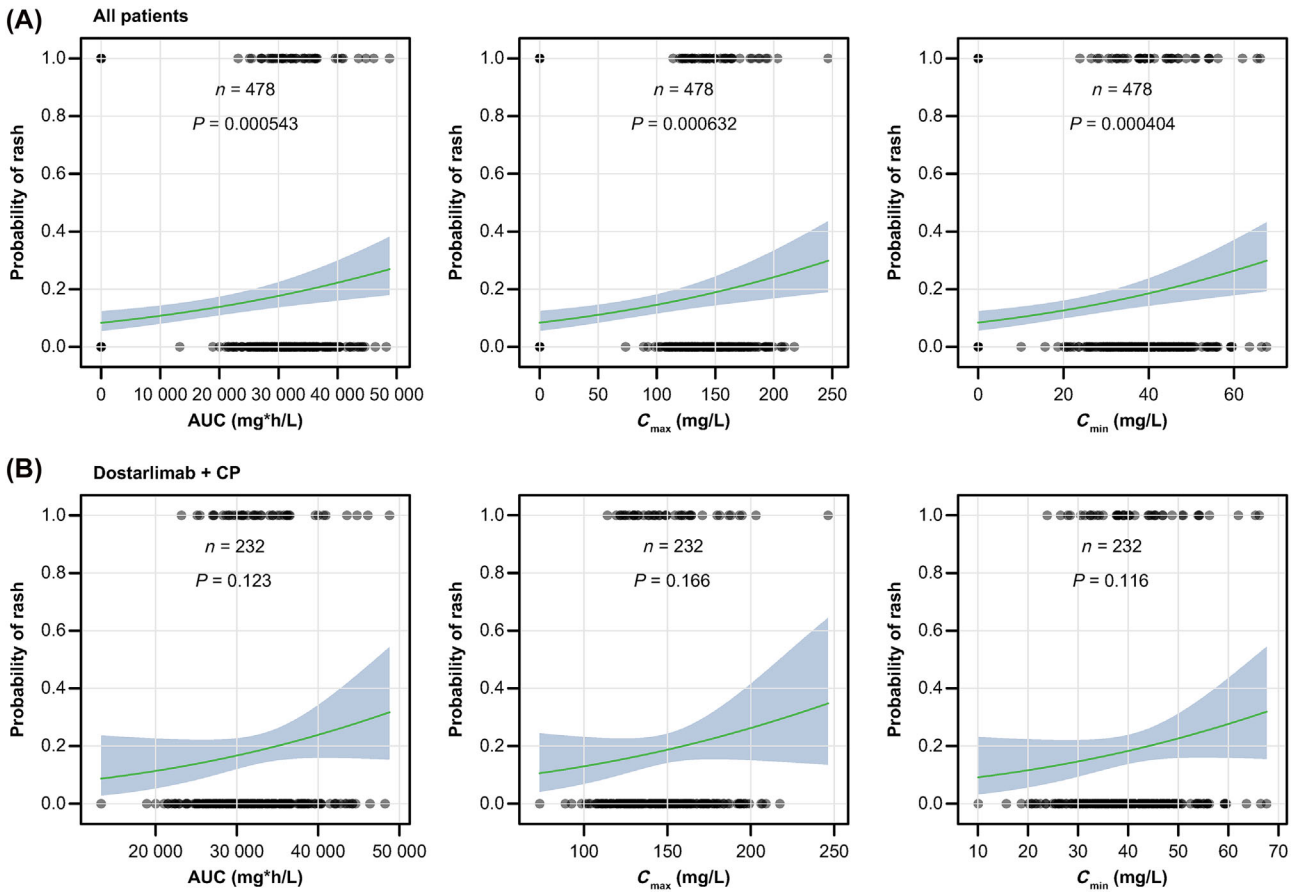

FIGURE 5 Rash *vs.* exposure metrics: all cycles. AUC and C_{max} during the first 21 days; C_{min} at day 21. Lines: predicted probability. Shaded areas: 95% confidence intervals. Circles: data. AUC, area under the curve; C_{max}, maximum concentration; C_{min}, minimum concentration; CP, carboplatin-paclitaxel.

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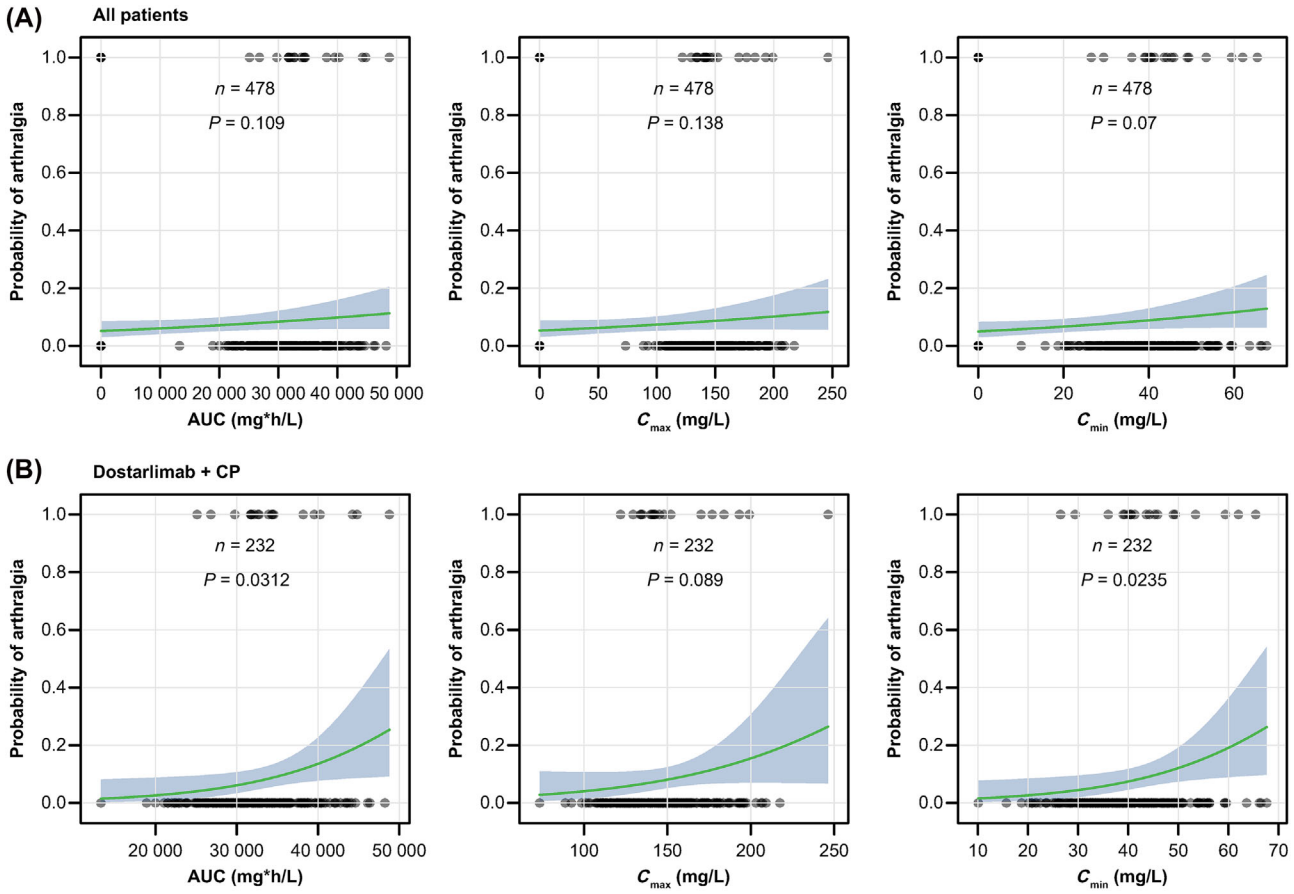

FIGURE 6 Arthralgia *vs.* exposure metrics: cycle 7 and beyond. AUC and C_{max} during the first 21 days; C_{min} at day 21. Lines: indicate predicted probability. Shaded areas: 95% confidence intervals. Circles: data. AUC, area under the curve; C_{max}, maximum concentration; C_{min}, minimum concentration; CP, carboplatin-paclitaxel.

albumin levels are associated with progressive disease and have frequently been reported to be inversely correlated with CL for mAbs,[14] including anti-PD-(L)1 mAbs such as durvalumab.[17]

Cox regression of PFS stratified by MMR/MSI status showed no ER relationships for AUC, C_{max} and C_{min}. The only covariate included in the subsequent multivariate analysis with a significant relationship was geographic location, wherein patients in Eastern Europe had an increased risk of PFS. However, results should be interpreted with caution because of the low number of patients ($n = 13$) located in Eastern Europe, with high interpatient variability as reflected by the wide 95% CIs with a lower bound close to 1.

Cox regression of DOR also showed no ER relationship for AUC, C_{max} and C_{min}. In addition to geographic location, MMRp/MSS status was identified as a statistically significant covariate for DOR with an HR of 2.6. It should be noted that the power to detect a relationship between exposure and DOR was limited owing to the overall low number of patients with available DOR data ($n = 147$). Additionally, DOR data from RUBY Part 1 may be confounded by responses to chemotherapy, as opposed to a dostarlimab-specific response. While the median DOR for patients receiving dostarlimab monotherapy in GARNET has not yet been reached for patients with either dMMR/MSI-H or MMRp/MSS EC, 63.6% of responders with MMRp/MSS EC in GARNET had an ongoing response with an 11.5-month median follow-up, whereas the response to chemotherapy in advanced/recurrent EC is known to be non-durable.[18,19]

Safety analysis of the five most prevalent drug-related AEs showed no significant relationships for diarrhoea, fatigue or nausea as the range of observed exposure from the regimen in the RUBY study did not affect their incidence. Arthralgia showed significant relationships with AUC and C_{min} in the time period of cycle 7+ when only dostarlimab-treated patients were included in the analysis. Newly induced musculoskeletal and rheumatic diseases are known AEs associated with immune checkpoint inhibitors.[16] However, the inclusion of the placebo arm in this ER analysis resulted in the absence of significance, indicating that the prevalence of arthralgia was similar in both arms. Dostarlimab did not increase the risk of arthralgia significantly, rendering this as clinically non-significant. Skin-related AEs are also known to be associated with treatment with immune checkpoint inhibitors,[20] and in this analysis, rash showed significant ER relationships for all three exposure metrics in all three time periods when all patients were included in the analysis. However, when only dostarlimab-treated patients were included in the analysis, the ER relationships were no longer significant because the relationships were less supported in the lower range of exposures. The increase in

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predicted probability for rash was limited: between 5.2% and 10% for patients with high exposure in comparison with low exposure, depending on exposure metric and time period, rendering this relationship as clinically nonsignificant.

The robustness of the dostarlimab PopPK model presented herein is strengthened by the inclusion of a large number of patients with similar dosing schedules, but with multiple tumour types, and patients being treated with both dostarlimab monotherapy and in combination with chemotherapy. However, certain aspects of this study may be limited by the relatively sparse data (both pre- and post-dose), which could introduce shrinkage towards the population estimates. In the RUBY study, there were limited PK data available beyond Week 8 (given dosing was every 6 weeks post cycle 6, and PK sampling was sparse), resulting in some overprediction for the later time points. In the PopPK analysis, estimating the time-dependent elimination may be limited due to the sampling scheme timing of the acquisition of third trough samples, which provided limited sampling near the timing of CL impact. For the ER analyses, only the 500 mg dose regimen was used to establish exposure. Hence the ER analysis is limited to the concentration range observed with this regimen. Additionally, the DOR analysis was limited by the relatively few patients who had complete DOR information at the time of the data cut. In addition, in randomised clinical trials, such as Part 1 of the RUBY trial, patients are balanced across treatment arms, but not necessarily across the exposure-based groups, which we have tried to mitigate here by using multivariate analyses, including stratification factors in this study.

In conclusion, these results indicate that dose adjustment based on any covariate tested was not warranted. Flat dosing was supported by the lack of any clinically meaningful relationships between dostarlimab exposure and efficacy or safety. Collectively, these analyses support the recommended dose of 500 mg Q3W followed by 1000 mg Q6W for dostarlimab monotherapy and in combination with chemotherapy. These results further support evaluation of dostarlimab in combination with CP given the limited impact of chemotherapy on dostarlimab PopPK.

AUTHOR CONTRIBUTIONS

M.K., S.Z. and M.M. contributed to study conception/design. M.K., T.L.J., E.H., T.A., A.J., D.B., O.A., O.Z., A.O., M.S.S., A.K., B.P., T.K., M.P., Y.S., F.B., C.G., S.B., S.Z., M.M. and J.B. contributed to data analysis and interpretation. T.L.J., T.A., A.J., D.B., O.Z., A.O., M.S.S., A.K., B.P., T.K., M.P., Y.S., F.B., C.G., S.B. and J.B. contributed to investigation.

AFFILIATIONS

[1]GSK, Waltham, MA, USA
[2]Odense University Hospital, Odense, Denmark
[3]qPharmetra, Uppsala, Sweden
[4]Saint-Antoine Hospital, INSERM, Unité Mixte de Recherche Scientifique 938, and SIRIC CURAMUS, Sorbonne University, Paris, France
[5]Fox Chase Cancer Center, Philadelphia, PA, USA
[6]GINECO & Institut de Cancerologie de l'Ouest, Centre René Gauducheau, Saint-Herblain, France
[7]Chernihiv Medical Center of Modern Oncology, Chernihiv Regional Council, Chernihiv, Ukraine
[8]Vall d'Hebron University Hospital, Vall d'Hebron Institute of Oncology (VHIO), Barcelona, Spain
[9]Hanjani Institute for Gynecologic Oncology Abington Hospital–Jefferson Health, Asplundh Cancer Pavilion, Sidney Kimmel Medical College of Thomas Jefferson University, Willow Grove, PA, USA
[10]Uppsala University Hospital, Uppsala, Sweden
[11]GOG Foundation and Departments of Obstetrics/Gynecology and Medicine, Division of Gynecologic Oncology, Laura & Isaac Perlmutter Cancer Center, NYU Langone Health, New York, NY, USA
[12]Division of Gynecologic Oncology, The Western Pennsylvania Hospital, Pittsburgh, PA, USA
[13]Grodno Regional Clinical Hospital, Grodno, Belarus
[14]Carmel Medical Center, Technion-Israel Institute of Technology, Haifa, Israel
[15]The Ohio State University College of Medicine, The James Cancer Hospital and Solove Research Institute, Columbus, OH, USA
[16]Department of Medical Oncology, CHU of Liège, Liège, Belgium
[17]Belgium and Luxembourg Gynaecological Oncology Group (BGOG), Leuven, Belgium
[18]Massachusetts General Hospital, Boston, MA, USA
[19]GSK, Collegeville, PA, USA
[20]Arizona Oncology, Tucson, AZ, USA

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M. Kuchimanchi is an employee of GSK and may have stock or stock options in GSK.
T.L. Jørgensen has nothing to disclose.
E. Hanze reports institutional consulting fees from GSK.
T. André reports attending advisory board meetings and receiving consulting fees from AbbVie, Aptitude Health, Bristol Myers Squibb, Gritstone Bio, GamaMabs Pharma, Gilead, Nordic, GSK, Merck & Co., Seagen, Servier and Takeda; honoraria for lectures, presentations, speakers' bureaus, manuscript writing or educational events from Bristol Myers Squibb, Gritstone Bio, GSK, Merck & Co., Merck Serono, Roche/Ventana, Seagen and Servier; support for attending meetings from Bristol Myers Squibb and Merck & Co.; data safety monitoring board for NSPIRNA: Phase 2 randomized controlled trial of ompenaclid in 2nd line RAS mutant metastatic colorectal cancer; and leadership or fiduciary role in ARCAD foundation (Aide à la recherché en cancérologie digestive).
A. Jain has nothing to disclose.
D. Berton has nothing to disclose.
O. Alskär reports institutional consulting fees from GSK.
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S. Zajic is an employee of GSK and reports stock at GSK.

M. Melham is a full-time employee of GSK and owns stocks/shares.

J. Buscema has nothing to disclose.

DATA AVAILABILITY STATEMENT

GSK is committed to sharing anonymized subject-level data from interventional trials as per GSK policies and as applicable. Requests for subject-level data should be done via the GSK link: https://www.gsk-studyregister.com/en/.

ORCID

Mita Kuchimanchi https://orcid.org/0000-0003-0349-7756

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Additional supporting information can be found online in the Supporting Information section at the end of this article.

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