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Original Article

Exposure–Response Relationship of Dostarlimab in Primary Advanced/Recurrent Endometrial Cancer: Results From Interim Analysis 2 of Part 1 of the RUBY Trial

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Abstract

Dostarlimab in combination with carboplatin–paclitaxel was approved for primary advanced or recurrent endometrial cancer (pA/rEC). The first interim analysis (IA1) of RUBY Part 1 (NCT03981796) showed no significant exposure–response (ER) relationship for progression-free survival or for the five most common dostarlimab-related adverse events (AEs), except rash. Herein, we report the ER relationship between dostarlimab exposure and overall survival (OS) and between dostarlimab exposure and dostarlimab-related AEs. Population pharmacokinetic model was based on IA1, and the predicted exposure metrics from Cycle 1 were used to perform ER analysis at the second interim analysis (IA2). AE analysis was completed for three periods: Cycles 1-6 (chemotherapy phase), Cycle 7 and beyond (monotherapy phase),

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and all cycles. Included in the OS analysis were 232 patients treated with dostarlimab + carboplatin–paclitaxel. Cox regression of OS showed no significant ER relationship based on dostarlimab Cycle 1 exposure, except for rash and arthralgia. The increase in predicted probabilities for rash and arthralgia for patients with high versus low exposure was limited, ranging from 5.6% to 10.4% for rash and 4.3% to 17.7% for arthralgia (deemed not clinically relevant). These data support the risk/benefit profile at the selected dose of dostarlimab + carboplatin–paclitaxel as standard of care in patients with pA/rEC.

Keywords

anticancer drugs, clinical pharmacology, drug safety, pharmacokinetics, therapeutics

Endometrial cancer (EC) is the sixth most commonly diagnosed cancer among women globally and the second most common type of gynecologic cancer.[1,2] As cancer incidence and mortality rates increase, there is an urgent need for new treatment strategies to delay cancer recurrence or progression and prolong patient survival.[3] Recent advances have led to a new standard of care for frontline treatment of primary advanced or recurrent EC using a combination of immunotherapy plus carboplatin–paclitaxel.[3–5]

The immune checkpoint inhibitor dostarlimab is a humanized monoclonal antibody of the immunoglobulin G4 isotype that binds with high affinity and specificity to programmed cell death protein-1 (PD-1) and blocks the interaction with its ligands, PD-L1 and PD-L2.[6] At the first interim analysis (IA1) of Part 1 of the Phase 3 RUBY trial (NCT03981796), there was a statistically significant improvement in progression-free survival (PFS) in both the intent-to-treat population and in patients with mismatch repair deficient/microsatellite instability-high (dMMR/MSI-H) primary advanced or recurrent EC who were treated with dostarlimab in combination with carboplatin–paclitaxel followed by dostarlimab monotherapy. This result led to the approval of the treatment regimen as a frontline therapy, first in the United States and then in multiple countries for patients with dMMR/MSI-H primary advanced or recurrent EC.[4,7–10] At the second interim analysis (IA2), dostarlimab in combination with carboplatin–paclitaxel followed by dostarlimab monotherapy led to statistically significant improvements in overall survival (OS) in the intent-to-treat population, leading to label expansion for frontline use in multiple countries including the United States and EU for all adult patients with primary advanced or recurrent EC.[3,7,10]

Pharmacokinetic (PK) and exposure–response (ER) relationships of new agents provide important information for selection of dosing regimens to optimize the risk–benefit profile of new agents.[11] A population PK (PopPK) model and ER analysis for dostarlimab was previously established using data from the GARNET trial (NCT02715284).[12] This model was then validated using data collected at IA1 (August 8, 2022) of Part 1 of the RUBY trial.[13] The PK model was also used to obtain exposure metrics.[13] At IA1, an ER analysis explored the relationship between dostarlimab exposure and PFS and no clinically significant exposure–PFS relationship was found.[13] However, the ER relationship to the critical endpoint of OS was not examined at IA1 because OS data were not sufficiently mature. Hence, the OS analysis is being reported in this article, which can be considered a confirmatory analysis from a regulatory standpoint. Additionally, exposure–safety responses were also examined at IA1 for the five most common adverse events (AEs; arthralgia, diarrhea, fatigue, nausea, and rash). No statistically significant effects were found among safety endpoints with the exception of rash in all patients; however, this was deemed not clinically relevant.[13] In this updated analysis of exposure–safety responses, a longer follow-up time with an additional 13 months than the previous analysis is reported.

The aim of this analysis was to characterize the ER relationship for dostarlimab at IA2 of Part 1 of the RUBY trial. Herein, we report the ER relationship between dostarlimab exposure and OS and an updated analysis of the ER relationship for the five most common dostarlimab-related AEs (fatigue, nausea, rash, diarrhea, and arthralgia).

Methods

Study Design

The protocol for the RUBY study was approved by the Advarra Institutional Review Board (ref No Pro00033913) and had institutional review board approval at each institution participating in the trial. All patients provided informed consent for participation. RUBY Part 1 trial sites can be found in the Supplemental Appendix. RUBY Part 1 is a Phase 3, randomized, double-blind, multicenter study of dostarlimab plus carboplatin–paclitaxel versus placebo plus carboplatin–paclitaxel in patients with primary advanced or recurrent EC. Details of the study design have been previously published.[3,4] Patients were randomized 1:1 to receive dostarlimab plus carboplatin–paclitaxel or placebo plus carboplatin–paclitaxel fol-

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lowed by dostarlimab or placebo monotherapy. Patients received 500 mg intravenous (IV) dostarlimab or placebo in combination with standard-of-care carboplatin (area under the curve [AUC], 5 mg·mg/mL) and paclitaxel (175 mg/m^2) every 3 weeks for 6 cycles followed by 1000 mg IV dostarlimab or placebo every 6 weeks for up to 3 years, progressive disease, toxicity, withdrawal of consent, investigator's decision, or death (whichever occurred first). Six cycles of dostarlimab plus carboplatin–paclitaxel was chosen to align with the regular treatment cycles for carboplatin–paclitaxel.

PopPK Model

The previously published PopPK model for dostarlimab was initially created based on the GARNET trial (data cutoff date: March 1, 2020),[12] and was updated using a combined dataset from GARNET (data cutoff date, November 1, 2021) and RUBY Part 1 (data cutoff date, August 8, 2022).[13] Details of the model development, model evaluation, model validation, and methods have been previously published.[12,13]

To avoid bias and minimize the confounding effects of baseline factors (baseline-driven ER) and time-varying clearance (response-driven ER), exposure based on Cycle 1 was selected for evaluating the ER relationship. The predicted exposure metrics from Cycle 1 were used to perform ER analysis at IA2 due to the time-dependent clearance (CL), which decreases over time, and because all modeled AEs had an early onset in Cycle 1. The analysis was conducted across three distinct time periods: Cycles 1-6 (chemotherapy phase [dostarlimab plus carboplatin–paclitaxel or placebo plus carboplatin–paclitaxel]); Cycle 7 and beyond (monotherapy phase [dostarlimab or placebo alone]); and all cycles. This approach enabled comparison of dostarlimab with chemotherapy and placebo. Because of the limited number of PK samples collected after IA1, no further PK analyses were performed at IA2.[13] The clinical relevance of statistically significant covariates was determined by evaluating their effects on steady-state pharmacokinetic parameters, including the area under the concentration–time curve (AUC), maximum concentration (C_{max}), and minimum concentration (C_{min}), using forest plots. AUC, C_{max}, and C_{min} were chosen for these analyses based on prior experience from dostarlimab[12] and other checkpoint inhibitors[14–16] to identify overall drug exposure and efficacy, acute safety, and sustained efficacy.

Bioanalytical Analysis

The bioanalytical assay used in this study was an enzyme-linked immunosorbent assay (ELISA). Briefly, the ELISA plate was coated with human PD-1 extracellular domain-mIgG2aFc, then the samples and a biotinylated anti-human IgG4 antibody were added. Thereafter, streptavidin-horseradish peroxidase followed by 3,3′,5,5′-tetramethylbenzidine were added. The ELISA plate was analyzed using a plate reader at 450 nm and the validated assay range was 32.0 to 814 ng/mL.

ER Analyses

ER Analyses: Efficacy and Safety. The ER analysis of efficacy was the primary endpoint of OS, which was defined as the time from randomization to the date of death by any cause. The ER analysis of safety included the five most common dostarlimab-related AEs (fatigue, nausea, rash, diarrhea, and arthralgia) of any grade occurring at any time as assessed by investigators. Only data from the IA2 data cutoff date (September 22, 2023) were used in this analysis.

Statistical Analyses. ER analyses were performed in R version 4.0.5 (Comprehensive R Network, http://cran.r-project.org/). For the analysis, the placebo plus carboplatin–paclitaxel group was assigned as conc = 0. Cox regression of OS was used to assess the ER relationship with drug exposure as the independent predictor. Logistic regression was used to describe the relationship between dostarlimab exposure and the occurrence of dostarlimab-related AEs. Covariates included mismatch repair/microsatellite instability status (dMMR/MSI-H or mismatch repair proficient/microsatellite stable [MMRp/MSS]), disease status in EC (recurrent, primary Stage III, or primary Stage IV), prior external pelvic radiotherapy (yes or no), baseline Eastern Cooperative Oncology Group performance status (ECOG PS; 0 [fully active] or 1 [ambulatory]), geographic location (Western Europe, Eastern Europe, or North America), and histology (endometrioid carcinoma or nonendometrial [categorized as other]). Analysis of OS included patients in both the dostarlimab and placebo arms. Formulas for time-to-event modeling can be found in the Supplemental Appendix.

Analysis of safety included patients from both the dostarlimab plus carboplatin–paclitaxel arm and the placebo plus carboplatin–paclitaxel arm or from only the dostarlimab plus carboplatin–paclitaxel arm. Binary data for the five most common dostarlimab-related AEs (fatigue, nausea, rash, diarrhea, and arthralgia) as assessed by investigators were analyzed using univariate logistic regression. The analysis was conducted using exposure metrics across three distinct time frames. A multivariate logistic regression was used for the dostarlimab-related AEs and time periods that showed significant univariate ER relationships. Covariates included those discussed previously for OS with the exception of histology, which was not included in the safety analysis.

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Table 1. Patient Demographics

Characteristic, n (%)	Dostarlimab + CP (n = 232)	Placebo + CP (n = 246)	All Patients (N = 478)
MMR/MSI status			
dMMR/MSI-H	49 (21.1)	65 (26.4)	114 (23.8)
MMRp/MSS	183 (78.9)	181 (73.6)	364 (76.2)
Disease status			
Primary Stage III	44 (19.0)	44 (17.9)	88 (18.4)
Primary Stage IV	73 (31.5)	83 (33.7)	156 (32.6)
Recurrent	115 (49.6)	119 (48.4)	234 (49.0)
ECOG PS			
0 (fully active)	142 (61.2)	159 (64.6)	301 (63.0)
1 (ambulatory)[a]	90 (38.8)	87 (35.4)	177 (37.0)
Geographic location			
Eastern Europe	13 (5.6)	14 (5.7)	27 (5.6)
Western Europe	55 (23.7)	46 (18.7)	101 (21.1)
North America	164 (70.7)	186 (75.6)	350 (73.2)
Histology			
Endometrioid carcinoma	110 (47.4)	111 (45.1)	221 (46.2)
Other	122 (52.6)	135 (54.9)	257 (53.8)
Prior external pelvic radiotherapy			
No	192 (82.8)	201 (81.7)	393 (82.2)
Yes	40 (17.2)	45 (18.3)	85 (17.8)

CP, carboplatin–paclitaxel; dMMR, mismatch repair deficient; ECOG PS, Eastern Cooperative Oncology Group performance status; MSI-H, microsatellite instability-high; MMRp, mismatch repair proficient; MSS, microsatellite stable.
[a] One patient in the placebo + CP arm had ECOG PS 2 and was included in the ECOG PS 1 group in this analysis.

Results

Data Selection

In Part 1 of the RUBY trial, 494 patients were randomized: 245 to dostarlimab plus carboplatin–paclitaxel and 249 to placebo plus carboplatin–paclitaxel. The PK analysis population included 232 patients treated with dostarlimab plus carboplatin–paclitaxel with ≥2 quantified dostarlimab concentrations and 246 patients treated with placebo plus carboplatin–paclitaxel. Patient characteristics were well balanced across trial arms in the overall population (Table 1). Most patients (n = 229, 98.7%) treated with dostarlimab plus carboplatin–paclitaxel had a negative antidrug antibody (ADA) status; the remaining 3 patients (1.3%) were missing ADA information. The majority of patients (84.5%) were missing information on neutralizing antibody status; hence, ADA and neutralizing antibody status were not included in the analysis. Overall, 114 patients (23.8%) had dMMR/MSI-H EC and 364 (76.2%) had MMRp/MSS EC (Table 1). At baseline, 88 (18.4%), 156 (32.6%), and 234 patients (49.0%) had primary Stage III, primary Stage IV, and recurrent EC, respectively (Table 1).

ER Analysis

Overall Survival. A total of 232 OS observations from 232 patients from the dostarlimab plus carboplatin–paclitaxel arm were used for the OS evaluation. A summary of exposure metrics for patients included in the ER analysis of OS is shown in Table S1. Patients were predicted to have a mean (standard deviation) AUC of 32 300.00 (5850.00) mg·h/L, C_{max} of 147.00 (26.40) mg/L, and C_{min} of 39.70 (9.94) mg/L.

The OS probability over time for the three exposure metrics, AUC, C_{max}, and C_{min}, during the first 21 days after the first dose is shown in Figure 1. The two lowest C_{max} ranges [73.4-127.75 mg/L] and (127.75-145 mg/L] demonstrated a numerically higher OS probability; however, the confidence intervals overlap with the other evaluated ranges (Figure 1B). OS was independent of the three exposure metrics.

Cox regression was performed without stratification for the three exposure metrics after adjusting for the covariates. Cox regression of OS showed no statistically significant ER relationship ($P > .05$) based on dostarlimab Cycle 1 exposure (Table 2). All evaluated exposure metrics showed consistent outcomes for OS. Hazard ratios of the tested covariates can be found in Figure 2. Most tested covariates had 95% confidence intervals that included 1, indicating no significance. However, with all of the subgroups, the treatment difference was exploratory and should be interpreted with caution, as the analysis was not powered to detect differences in any of the subgroups.

Given the mechanism of action of dostarlimab, a greater OS benefit was expected in the dMMR/MSH-

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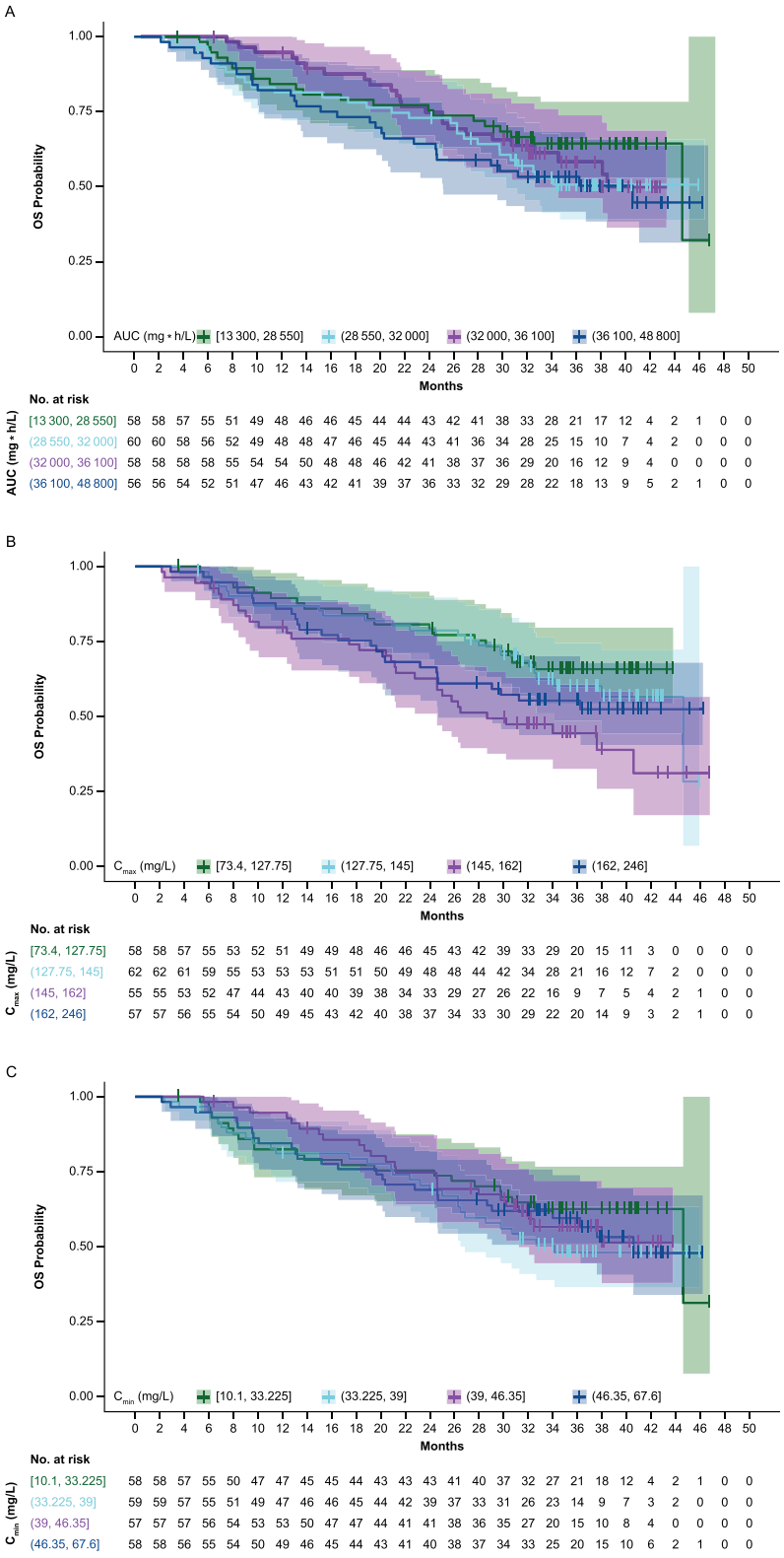

Figure 1. OS versus time stratified by AUC (A), C_{max} (B), and C_{min} (C) exposure quartiles. AUC and C_{max} during the first 21 days; C_{min} at day 21. Lines indicate OS probability; vertical lines indicate censoring; shaded area indicates 95% confidence interval; parentheses indicate excluded endpoint; brackets indicate included endpoint. AUC, area under the curve; C_{max}, maximum concentration; C_{min}, minimum concentration; OS, overall survival.

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Table 2. HR Multivariate OS Analysis with C_{min}, C_{max}, and AUC as Covariates

Exposure Metric	HR (95% CI)	*P* Value
C_{min}	0.99 (0.972-1.01)	0.43
C_{max}	1.00 (0.995-1.01)	0.45
AUC	1.00 (1.00-1.00)	0.90

AUC, area under the curve; CI, confidence interval; C_{max}, maximum concentration; C_{min}, minimum concentration; ECOG PS, Eastern Cooperative Oncology Group performance status; HR, hazard ratio.
HR was obtained after adjusting for prior external pelvic radiotherapy (yes/no), histology (endometrioid carcinoma/other), geographic location (North America/Eastern Europe/Western Europe), baseline ECOG PS (0/1), and disease status in endometrial cancer (III/IV). AUC and C_{max} were during the first 21 days of treatment, whereas C_{min} was at day 21.

H group compared with the MMRp/MSS group. Compared with placebo plus carboplatin–paclitaxel, dostarlimab plus carboplatin–paclitaxel reduced deaths by 21% with a hazard ratio of 0.79 (95% confidence interval, 0.60-1.04; nominal stratified log-rank test, $P = .0493$) in the MMRp/MSS population,[3] indicating an OS benefit in this population as well.

Safety Analysis. In total, 478 patients (232 receiving dostarlimab plus carboplatin–paclitaxel; 246 receiving placebo plus carboplatin–paclitaxel) were included in the ER analysis of safety with approximately 13 additional months of follow-up at IA2 compared with IA1.[13] The mean (standard deviation) predicted AUC, C_{max}, and C_{min} for the safety population were the same as for the OS population. Consistent with the previous IA1 results, there were no statistically significant ER relationships for diarrhea, fatigue, or nausea.[13]

A significant ER relationship ($P < .05$) was observed for rash with all three exposure metrics at all time periods when all patients were included in the analysis (Figure 3), consistent with IA1.[13] When placebo plus carboplatin–paclitaxel-treated patients were excluded,

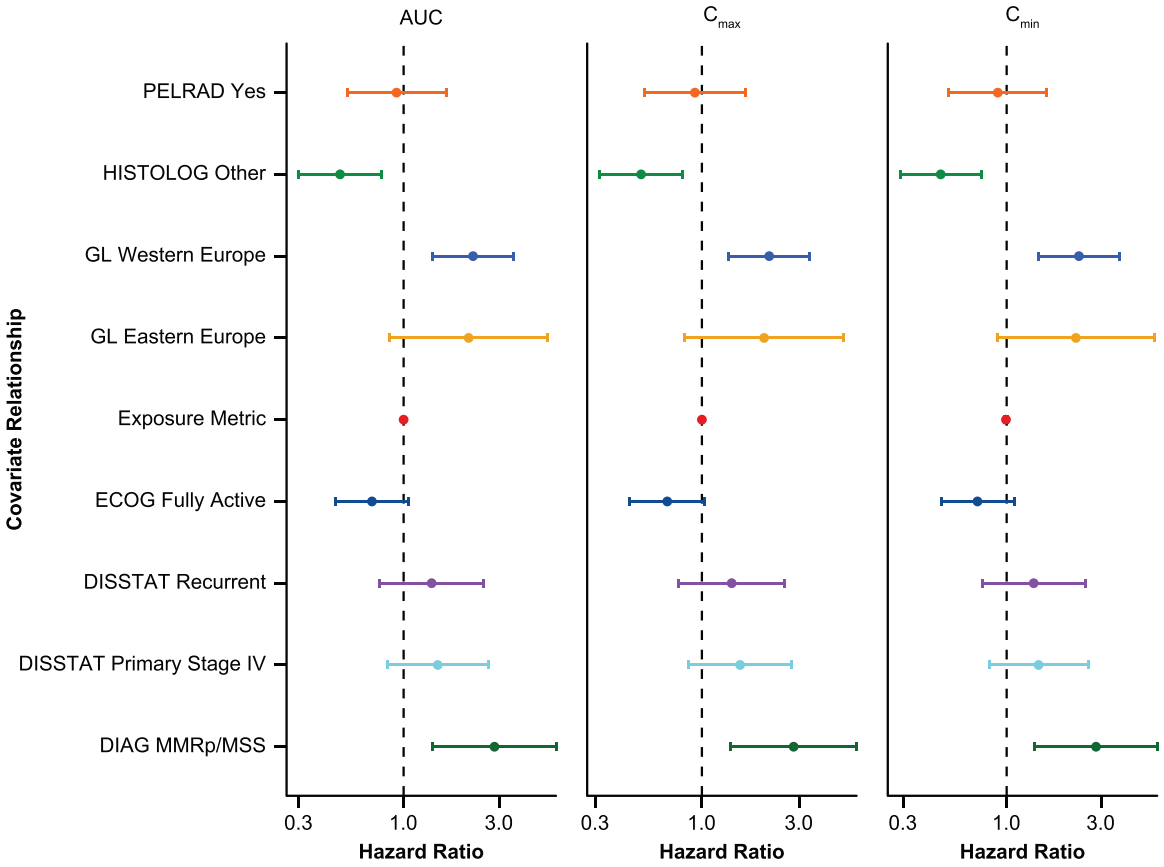

Figure 2. Hazard ratio multivariate analysis overall survival. AUC and C_{max} during the first 21 days; C_{min} at day 21. Circles indicate hazard ratios; lines indicate 95% confidence interval. AUC, area under the curve; C_{max}, maximum concentration; C_{min}, minimum concentration; DIAG, tumor diagnosis (reference, mismatch repair deficient/microsatellite instability-high); DISSTAT, disease status in endometrial cancer (reference, primary Stage III); ECOG, baseline Eastern Cooperative Oncology Group fully active (ECOG = 0) performance status (reference, ambulatory [ECOG = 1]); GL, geographic location (reference, North America); HISTOLOG, histology (reference, endometrioid carcinoma); MMRp, mismatch repair proficient; MSS, microsatellite stable; PELRAD, prior external pelvic radiotherapy (reference, no).

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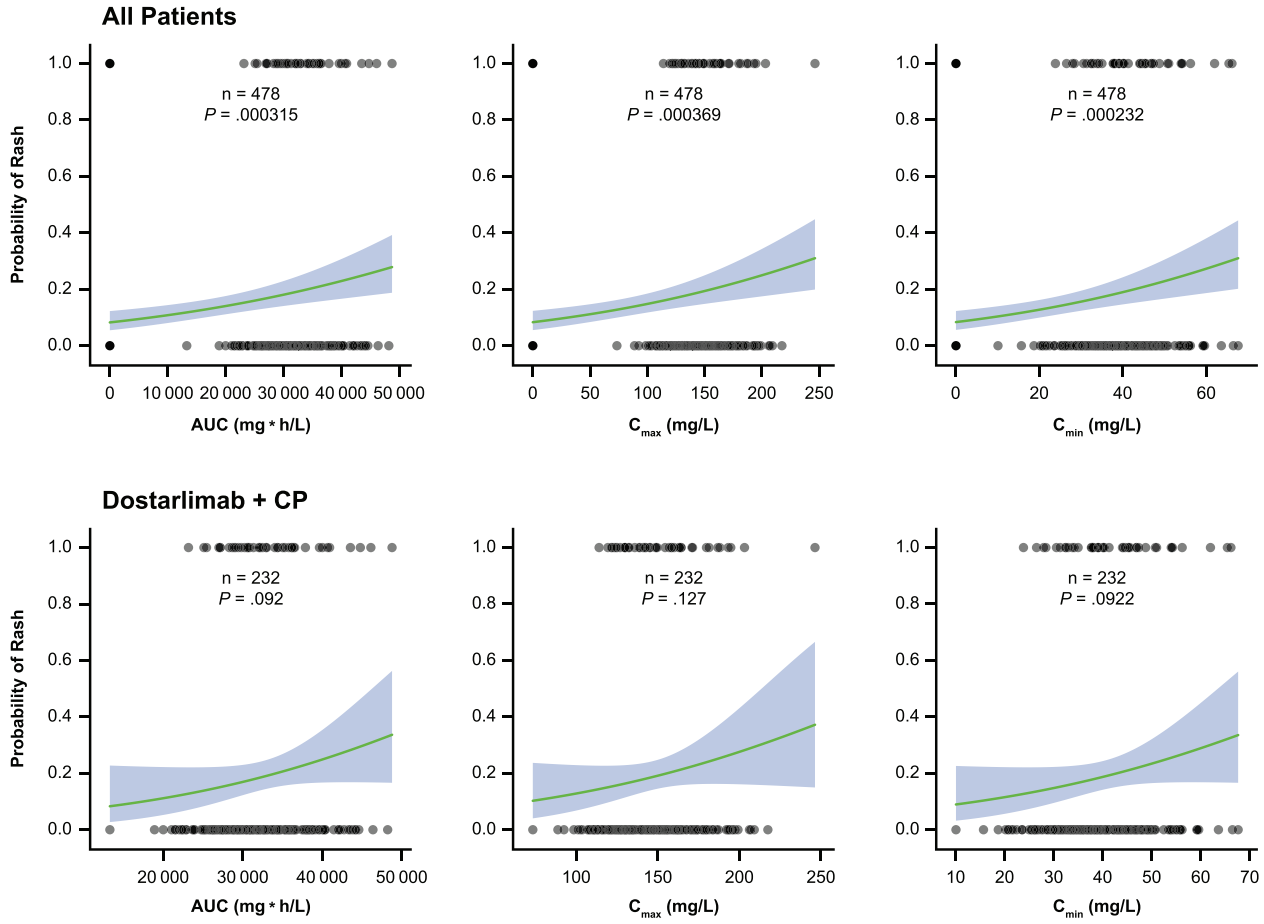

Figure 3. Rash versus exposure metrics: all cycles. AUC and C_{max} during the first 21 days; C_{min} at day 21. Lines indicate predicted probability; shaded area indicates 95% confidence interval; circles indicate data. AUC, area under the curve; C_{max}, maximum concentration; C_{min}, minimum concentration; CP, carboplatin–paclitaxel.

the ER relationships for rash were no longer significant. The increase in predicted probability for rash in all patients was limited (between 5.6% and 10.4% for patients with high exposure [90th percentile] versus low exposure [10th percentile], depending on the exposure metric and time period assessed), and the relationship was deemed not clinically relevant (Table S2). The multivariate analysis for rash for all patients in Cycles 1-6, Cycle 7 and beyond, and all cycles showed significant exposure metrics (Figure 4). ECOG PS status of fully active (ECOG PS = 0) had a higher risk of rash than ambulatory (ECOG PS = 1) in Cycles 1-6 and all cycles under all exposure metrics.

Arthralgia exhibited a significant ER relationship ($P < .05$) in Cycle 7 and beyond for C_{min} for both analysis populations (all patients and dostarlimab plus carboplatin–paclitaxel treatment arms only; Figure 5). A significant ER for AUC was identified when all patients were included in the analysis, but this relationship was not significant when only the dostarlimab plus carboplatin–paclitaxel treatment arm was included, indicating that the prevalence of arthralgia in the placebo arm was low enough to render this relationship significant (prevalence of 9.9% and 5.7% for patients treated with dostarlimab and placebo, respectively, in Cycle 7 and beyond). There was an increase in predicted probabilities of arthralgia by 4.3% and 6.5% with increasing exposure (10th vs 90th percentile) for AUC and C_{min}, respectively, for all patients, whereas there was an increase in the predicted probability of arthralgia with increasing exposure (10th vs 90th percentile) by 17.7% for C_{min} for only those patients treated with dostarlimab (Table S2).

Multivariate logistic regression was performed for the dostarlimab-related AEs and time periods that showed significant univariate ER relationships. The exposure metrics were still found to be significant. In addition, patients with MMRp/MSS status were found to have a lower risk of arthralgia than patients with dMMR/MSI-H status in the time period Cycle 7 and

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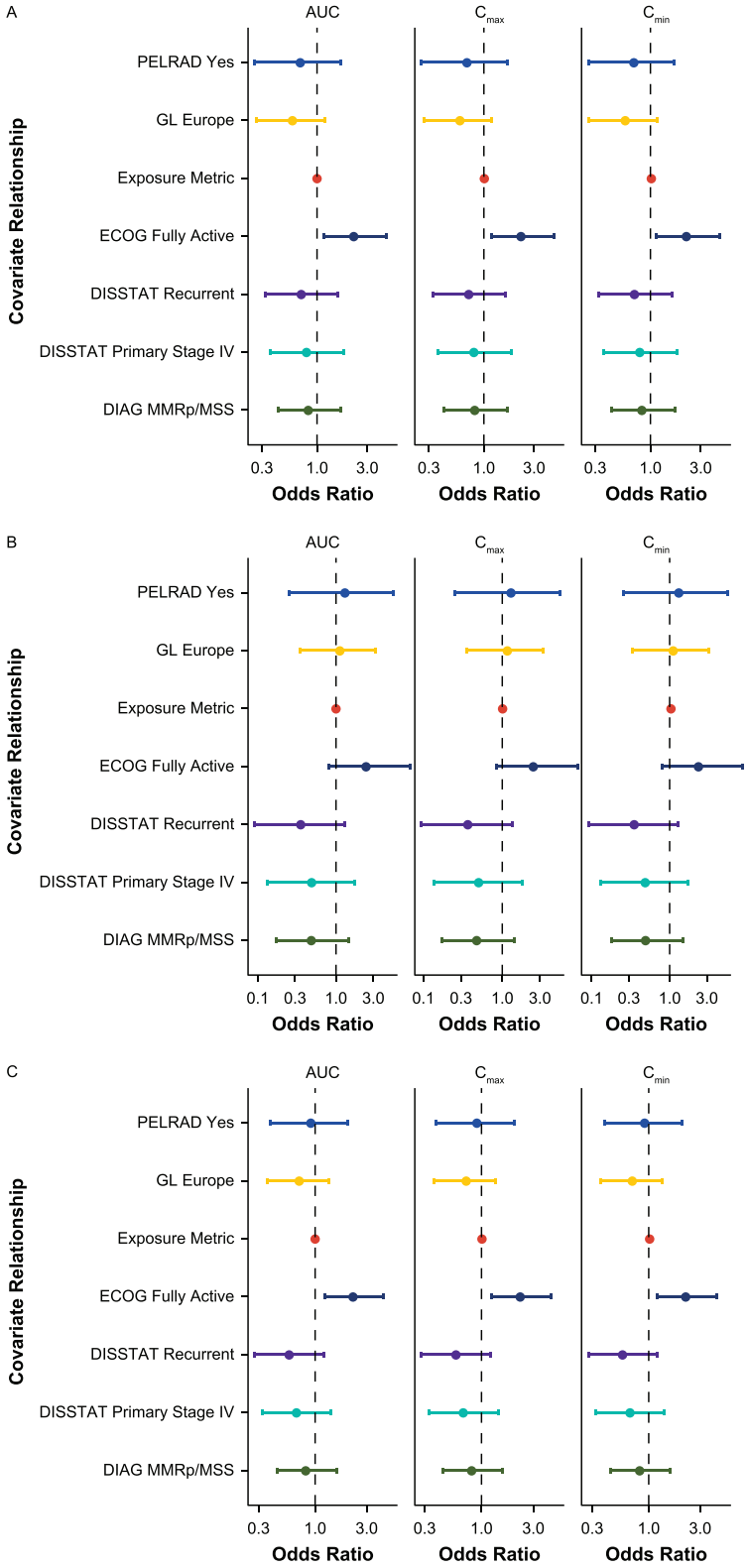

Figure 4. Odds ratio multivariate analysis, rash, for Cycles 1-6 (A), Cycle 7 and beyond (B), and all cycles (C) for all patients. AUC and C_{max} during the first 21 days; C_{min} at day 21. Circles indicate odds ratios; lines indicate 95% confidence intervals. AUC, area under the curve; C_{max}, maximum concentration; C_{min}, minimum concentration; DIAG, tumor diagnosis (reference, mismatch repair deficient/microsatellite instability-high); DISSTAT, disease status in endometrial cancer (reference, primary Stage III); ECOG, baseline Eastern Cooperative Oncology Group fully active (ECOG = 0) performance status (reference, ambulatory [ECOG = 1]); GL, geographic location (reference, North America); MMRp, mismatch repair proficient; MSS, microsatellite stable; PELRAD, prior external pelvic radiotherapy (reference, no).

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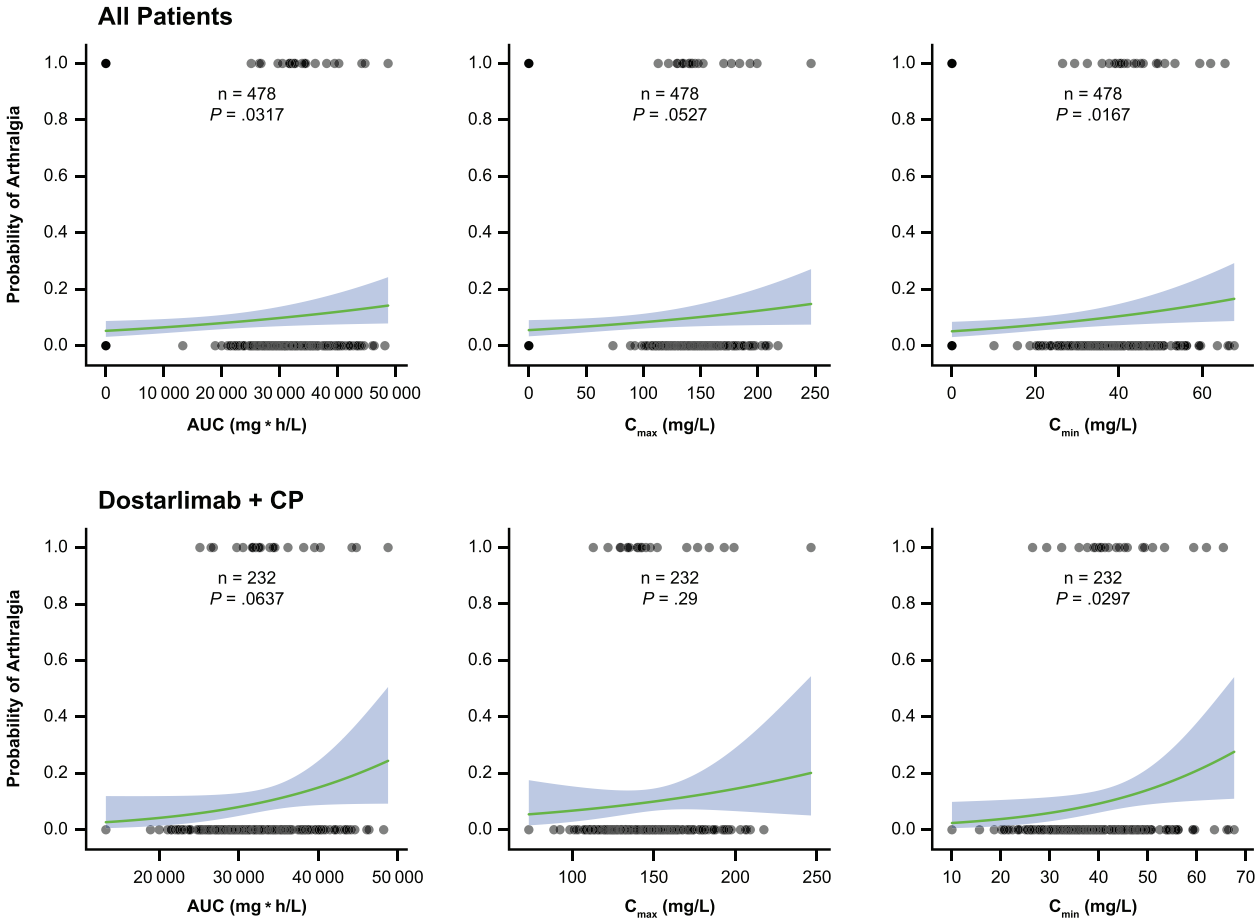

Figure 5. Arthralgia versus exposure metrics: Cycle 7 and beyond. AUC and C_{max} during the first 21 days; C_{min} at day 21. Lines indicate predicted probability; shaded area indicates 95% confidence interval; circles indicate data. AUC, area under the curve; C_{max}, maximum concentration; C_{min}, minimum concentration; CP, carboplatin–paclitaxel.

beyond for all patients and for only dostarlimab-treated patients for all three exposure metrics (Figure 6).

Discussion

In this study, we characterized the ER relationship between dostarlimab exposure and OS, and between dostarlimab exposure and the five most common dostarlimab-related AEs (fatigue, nausea, rash, diarrhea, and arthralgia) in IA2 of RUBY Part 1 at the data cutoff date of September 22, 2023. OS is a gold standard in oncology efficacy endpoints and is often considered a confirmatory analysis across regulators. Cox regression of OS showed no ER relationship for the three exposure metrics, demonstrating that the exposure–efficacy relationship achieved a plateau over the range of exposures achieved with the dosing regimen used in Part 1 of the RUBY study. Exposure to the immune checkpoint inhibitor dostarlimab is associated with immune-mediated adverse events, including pneumonitis, colitis, hepatitis, and dermatologic reactions, among others.[7] In this study, the safety analysis focused on the five most common dostarlimab-related AEs as assessed by investigators. No statistically significant ER relationships were observed for diarrhea, fatigue, and nausea. Only rash and arthralgia exhibited significant ER relationships.

At IA1 of RUBY Part 1, there was no significant ER relationship for PFS.[13] The only covariate that showed a significant ER relationship was geographic location, wherein patients in Eastern Europe had a reduced likelihood of PFS when treated with dostarlimab plus carboplatin–paclitaxel. However, there were a limited number of patients within this location therefore the analysis should be interpreted with caution because of the small sample size. Also found at IA1 of RUBY Part 1, Cox regression of the duration of response showed no ER relationship for AUC, C_{max}, and C_{min}. At IA2 of RUBY Part 1, dostarlimab plus carboplatin–paclitaxel showed a statistically significant and clinically meaningful OS benefit in patients with primary advanced or recurrent EC.[3] In this study, consistent OS benefits were

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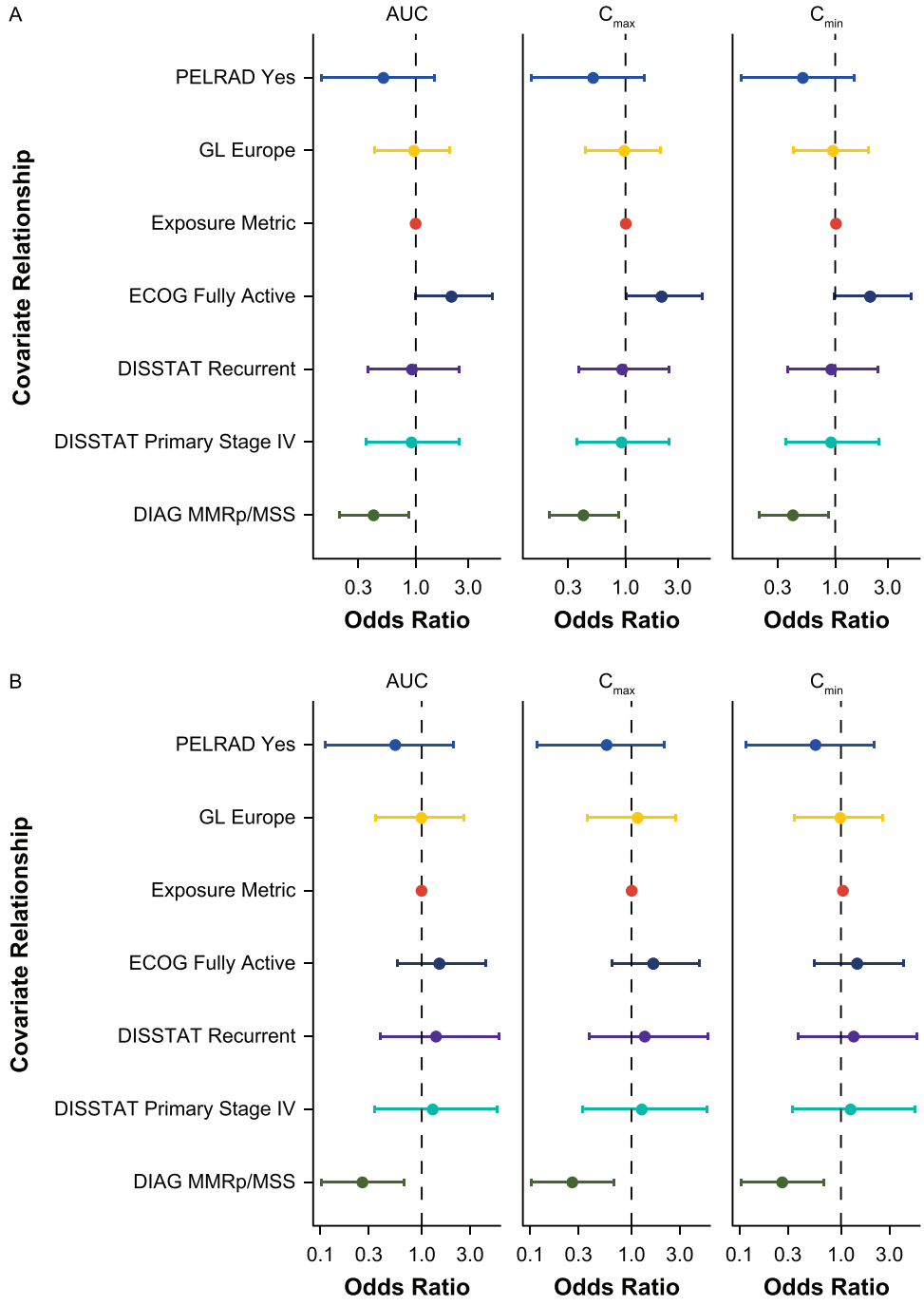

Figure 6. Odds ratio multivariate analysis, arthralgia, Cycle 7 and beyond for (A) all patients and (B) dostarlimab-treated patients. AUC and C_{max} during the first 21 days; C_{min} at day 21. Circles indicate odds ratios; lines indicate 95% confidence intervals. No events were seen in the category Eastern Europe, so Eastern Europe and Western Europe were placed together in the category Europe. AUC, area under the curve; C_{max}, maximum concentration; C_{min}, minimum concentration; DIAG, tumor diagnosis (reference, mismatch repair deficient/microsatellite instability-high); DISSTAT, disease status in endometrial cancer (reference, primary Stage III); ECOG, baseline Eastern Cooperative Oncology Group fully active (ECOG = 0) performance status (reference, ambulatory [ECOG = 1]); GL, geographic location (reference, North America); MMRp, mismatch repair proficient; MSS, microsatellite stable; PELRAD, prior external pelvic radiotherapy (reference, no).

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observed across the range of exposures (AUC, C_{max}, and C_{min}).

The safety data observed at IA2 differ from IA1 in follow-up time, with IA2 having an additional 13 months of follow-up.[13] The five most common dostarlimab-related AEs (fatigue, nausea, rash, diarrhea, and arthralgia) at IA2 (data cutoff date, September 22, 2023) were the same as the five most common dostarlimab-related AEs at IA1 (data cutoff date, August 08, 2022), with similar prevalence. At IA1 of RUBY Part 1, there was no significant ER relationship for the five most common dostarlimab-related AEs, except for rash.[13] Similarly, at IA2, no clinically meaningful ER relationships between dostarlimab exposure and safety were seen because the range of observed exposure from the regimen in the RUBY study did not affect the incidence of AEs.[13] There was no statistically significant ER relationship for diarrhea, fatigue, and nausea in either analysis.[13] However, both analyses revealed a significant ER relationship for rash and all three exposure metrics at all time periods when all patients were included in the analysis, with increased probability between 5.6% and 10.4% at IA2 depending on the exposure metric and time period, which was comparable to the 5.2%-10.0% probability identified at IA1.[13] Skin-related AEs are commonly associated with chemotherapy and immune checkpoint inhibitor treatment but are managed with supportive measures and treatments.[17,18] However, when only dostarlimab plus carboplatin–paclitaxel-treated patients were included the analysis, the ER relationship was no longer significant since the relationships were less supported in the narrower range of exposures. The increase in predicted probability for rash in all patients was limited, depending on exposure metric and time period; therefore, the relationship was deemed not clinically relevant.

Conversely, in this updated analysis, arthralgia exhibited a statistically significant ER relationship in Cycle 7 and beyond for C_{min} for all patients and for the dostarlimab plus carboplatin–paclitaxel treatment arm only. The ER relationship for AUC was statistically significant when all patients were included in the analysis. The prevalence of arthralgia in the placebo arm was low enough to render this relationship significant. From Cycle 7 and beyond, arthralgia of any grade was experienced by 14.1% of patients in the dostarlimab arm and 0.5% of patients in the placebo arm; grade $\geq$3 arthralgia was experienced by 7.6% of patients in the dostarlimab arm and 0.5% of patients in the placebo arm.[19] The updated analyses from IA2 indicate that treatment with dostarlimab plus carboplatin–paclitaxel may result in increased risk of arthralgia for all patients. This observation is not surprising, as newly induced musculoskeletal and rheumatic diseases are common AEs associated with immune checkpoint inhibitor therapy but can be managed with treatment.[20]

The PopPK model used to describe dostarlimab PK previously demonstrated similar PK properties to other anti-PD-1 monoclonal antibodies.[12] In this study, because of the time-varying clearance, Cycle 1 exposure was used in the ER analysis for the three different periods to avoid potential bias as described by Dai et al.[21] In addition, Cycle 1 exposure was used to represent exposure early in treatment, given it was expected that the first dostarlimab-related AE occurred earlier rather than later after dostarlimab administration. While logistic regression was used to describe the relationship between dostarlimab exposure and dostarlimab-related AEs, this approach is limited because it does not account for the timing of AE onset, for which a time-to-event analysis could provide additional insight. In Cycle 1, all dostarlimab-treated patients received a dose of 500 mg. For the ER analyses, only the 500-mg dose regimen was used to establish exposure. This was a limitation because the ER analysis used only the 500-mg dose regimen from the Phase 3 RUBY trial and did not involve a wide range of doses. However, the exposure range varied 3-6-fold depending on the exposure metrics (Table S1). The increased risk of rash and arthralgia with dostarlimab exposure was limited within this studied dose regimen and was generally consistent with the association of these potential AEs that has been described for any exposure to immunotherapy.[5,22]

Conclusion

These data support the benefit/risk profile of dostarlimab at the selected dose in combination with carboplatin–paclitaxel as a new standard of care in patients with primary advanced or recurrent EC and further investigation of the combination in other tumor types.

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Conflicts of Interest

Eva Hanze and Oskar Alskär report institutional consulting fees from GSK. Mark S. Shahin reports consulting fees from AstraZeneca, GSK, and MSD; honoraria for lectures,

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presentations, speakers' bureaus, or educational events from AstraZeneca, Caris Life Sciences, Eisai, Genmab, GSK, ImmunoGen/AbbVie, MSD, and Myriad Genetics; and board membership for Unite for Her. Anthoula Koliadi reports consulting fees from Eisai and GSK. Bhavana Pothuri reports institutional research support from Acrivon Therapeutics, Agenus, Alkermes, AstraZeneca, Celgene/Bristol Myers Squibb, Clovis Oncology, Daiichi Sankyo, DualityBio, Eisai, I-Mab Biopharma, ImmunoGen/AbbVie, Imunon, Incyte, Karyopharm Therapeutics, LOXO Oncology/Lilly, Mersana Therapeutics, MSD, NRG Oncology, Onconova Therapeutics/Traws Pharma, Pfizer, Roche/Genentech, Seagen/Pfizer, Sutro Biopharma, Takeda, Tesaro/GSK, Toray Industries, VBL Therapeutics, and Xencor; and consulting/advisory board fees from AstraZeneca, BeiGene, BioNTech, DualityBio, Eisai, GOG Foundation, I-Mab Biopharma, ImmunoGen/AbbVie, Imunon, Imvax, Incyte, InxMed, Karyopharm Therapeutics, LOXO Oncology/Lilly, Mersana Therapeutics, Natera, Nuvation Bio, Onconova Therapeutics/Traws Pharma, OnCusp Therapeutics, R Pharm, Regeneron, Seagen/Pfizer, Sutro Biopharma, and Tesaro/GSK. Thomas Krivak reports consulting and speakers' bureau fees from AbbVie, AstraZeneca, Genmab, GSK, and Pfizer; speaking fees from MSD and Myriad Genetics; and research support from AstraZeneca, MSD, and Myriad Genetics. Floor J. Backes reports institutional research grants from AstraZeneca, Clovis Oncology, Eisai, ImmunoGen/AbbVie, MSD, Natera, and Tempus; royalty fees from UpToDate; advisory board fees from AstraZeneca, BioNTech, Clovis Oncology, Daiichi Sankyo, Eisai, EMD Serono, GSK, ImmunoGen/AbbVie, MSD, and Myriad Genetics; CME lecture fees from Clinical Care Options, Clinical Educational Concepts, CMR institute, Global Learning Initiative/Prova, GOG Foundation, i3Health, Medscape/WebMD, Med Learning, OncLive, Research To Practice, and Targeted Oncology; travel support from BioNTech and GSK; and leadership roles in IGCS Education360 (co-chair), NRG Oncology developmental therapeutics committee (co-chair), and SGO (board member). Christine Gennigens reports grants/contracts from AstraZeneca, Deciphera, and GSK; consulting fees from GSK, Ipsen, and MSD; honoraria from AstraZeneca, Bristol Myers Squibb, Ipsen, MSD, Pfizer, and PharmaMar; support for attending meetings from AstraZeneca, GSK, Ipsen, MSD, Pfizer, and PharmaMar; and participation on a data safety monitoring or advisory board from AstraZeneca, Bristol Myers Squibb, Eisai, Genmab, GSK, Ipsen, MSD, and pharma& GmbH. Sara Bouberhan reports consulting fees from ImmunoGen, speaking fees from OncLive, and participation on an advisory board from AbbVie. Joseph Buscema reports payment for participation on an advisory board from GSK. Angela Jain, Trine Lembrecht Jørgensen, Mikalai Pishchyk, Yakir Segev, and Oleksandr Zub have nothing to disclose.

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Prior presentation

Portions of the data reported in this manuscript were previously reported at the 15th Annual American Conference on Pharmacometrics Meeting (November 10-13, 2024; Phoenix, AZ).

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/

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