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ORIGINAL ARTICLE

Overall survival in patients with endometrial cancer treated with dostarlimab plus carboplatin—paclitaxel in the randomized ENGOT-EN6/GOG-3031/RUBY trial

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Background: Part 1 of the RUBY trial (NCT03981796) evaluated dostarlimab plus carboplatin—paclitaxel compared with placebo plus carboplatin—paclitaxel in patients with primary advanced or recurrent endometrial cancer (EC). At the first interim analysis, the trial met one of its dual primary endpoints with statistically significant progression-free survival benefits in the mismatch repair-deficient/microsatellite instability-high (dMMR/MSI-H) and overall populations. Overall survival (OS) results are reported from the second interim analysis.

Patients and methods: RUBY is a phase III, global, double-blind, randomized, placebo-controlled trial. Part 1 of RUBY enrolled eligible patients with primary advanced stage III or IV or first recurrent EC who were randomly assigned (1 : 1) to receive either dostarlimab (500 mg) or placebo, plus carboplatin—paclitaxel every 3 weeks for 6 cycles followed by dostarlimab (1000 mg) or placebo every 6 weeks for up to 3 years. OS was a dual primary endpoint.

Results: A total of 494 patients were randomized (245 in the dostarlimab arm; 249 in the placebo arm). In the overall population, with 51% maturity, RUBY met the dual primary endpoint for OS at this second interim analysis, with a statistically significant reduction in the risk of death [hazard ratio (HR) = 0.69, 95% confidence interval (CI) 0.54-0.89, $P = 0.0020$] in patients treated with dostarlimab plus carboplatin—paclitaxel versus carboplatin—paclitaxel alone. The risk of death was lower in the dMMR/MSI-H population (HR = 0.32, 95% CI 0.17-0.63, nominal $P = 0.0002$) and a trend in favor of dostarlimab was seen in the mismatch repair-proficient/microsatellite stable population (HR = 0.79, 95% CI 0.60-1.04, nominal $P = 0.0493$). The safety profile for dostarlimab plus carboplatin—paclitaxel was consistent with the first interim analysis.

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Conclusions: Dostarlimab in combination with carboplatin—paclitaxel demonstrated a statistically significant and clinically meaningful OS benefit in the overall population of patients with primary advanced or recurrent EC while demonstrating an acceptable safety profile.

Key words: endometrial cancer, dostarlimab, anti-PD-1, mismatch repair status, overall survival, chemotherapy

INTRODUCTION

Endometrial cancer (EC) is the second most common gynecologic cancer in the world with both increasing incidence and mortality rates.[1-5] First-line treatment for primary advanced or recurrent EC has traditionally been carboplatin—paclitaxel; however, outcomes remained poor with a median overall survival (OS) of <3 years.[6-8] Improved treatment strategies are urgently needed to help prevent or delay recurrence and prolong survival. Immune checkpoint inhibitors have demonstrated durable responses after failure of platinum-based chemotherapy in recurrent EC, particularly in patients with mismatch repair-deficient/microsatellite instability-high (dMMR/MSI-H) EC.[9-12] Recently, advances have been made in the treatment of primary advanced or recurrent EC using combination treatment approaches of immunotherapy with chemotherapy.[13,14]

At the first interim analysis of RUBY Part 1, data cut-off 28 September 2022, the dual primary endpoint of progression-free survival (PFS) was reached with statistically significant improvements in PFS observed in both the dMMR/MSI-H [hazard ratio (HR) = 0.28, 95% confidence interval (CI) 0.16-0.50, $P < 0.0001$] and overall populations (HR = 0.64, 95% CI 0.51-0.80, $P < 0.0001$).[13] With 33% OS maturity in the overall population, treatment with dostarlimab demonstrated a trend for improved OS compared with the placebo regimen (HR for death = 0.64, 95% CI 0.46-0.87, $P = 0.0021$). However, the stopping boundary for statistical significance (P value of 0.00177) was not crossed at that time.[13]

Based on the PFS results at interim analysis 1, dostarlimab plus carboplatin—paclitaxel was approved in multiple countries as the first immunotherapy plus chemotherapy combination for adult patients with primary advanced or recurrent dMMR/MSI-H EC.[15-18]

Here we present updated OS, PFS2, and safety results from the second interim analysis for OS of Part 1 of the RUBY trial of dostarlimab plus carboplatin—paclitaxel compared with carboplatin—paclitaxel alone in patients with primary advanced or recurrent EC.

PATIENTS AND METHODS

Patients

Eligible patients were ≥18 years of age with histologically or cytologically confirmed primary advanced (International Federation of Gynecology and Obstetrics stage III/IV) or recurrent EC not amenable to cure by radiation therapy, surgery, or both. Patients were required to have one of the following inclusion criteria: primary advanced stage IIIA, IIIB, or IIIC1 disease that could be evaluated or measured with the use of Response Evaluation Criteria in Solid Tumors (RECIST), version 1.1, as determined by the investigator; primary advanced stage IIIC1 disease with carcinosarcoma, clear cell, serous, or mixed histologic characteristics, regardless of the presence of disease that could be evaluated or measured; primary advanced stage IIIC2 or stage IV disease, regardless of the presence of disease that could be evaluated or measured; initial recurrent disease without previous systemic therapy; or recurrent disease previously treated with neoadjuvant or adjuvant systemic therapy with recurrence or progression at least 6 months after completion of treatment (first recurrence). Sufficient tumor samples for assessment of mismatch repair (MMR) and microsatellite status were also required. Full eligibility and exclusion criteria are provided in the protocol which has been previously published with the first interim analysis of RUBY Part 1.[13]

Trial design and treatment

RUBY is a phase III, randomized, double-blind, multicenter trial. Patients were randomly assigned in a 1 : 1 ratio to receive dostarlimab (500 mg) or placebo intravenously in combination with carboplatin at an area under the curve of 5 mg/ml/min and paclitaxel at a dose of 175 mg/m^2 of body surface area intravenously every 3 weeks for the first 6 cycles, followed by dostarlimab (1000 mg) or placebo intravenously every 6 weeks for up to 3 years or until disease progression, treatment discontinuation due to toxic effects, patient withdrawal, investigator's decision to withdraw the patient, or death.

Randomization was carried out in a blinded manner with the use of an interactive web response system stratified by locally determined MMR/MSI status, prior external pelvic radiotherapy, and disease status. Guidelines for dose modification, interruption, or discontinuation are detailed in the protocol.

Endpoints

Primary endpoints were PFS as assessed by the investigator according to RECIST version 1.1 in the dMMR/MSI-H and overall populations and OS in the overall population.[13] OS in the dMMR/MSI-H and mismatch repair-proficient/microsatellite stable (MMRp/MSS) populations was a prespecified exploratory endpoint. Both primary endpoints were evaluated in time-to-event analyses. OS was defined as the time from randomization to the date of death from any cause. The threshold for the primary endpoint of PFS was crossed at the first interim analysis; therefore, PFS was not evaluated at this second interim analysis.[13] PFS2, defined as the time from treatment randomization to the date of assessment of progression on the first subsequent

anticancer therapy following study treatment or death by any cause, whichever is earlier, was a secondary endpoint that was re-evaluated at the second interim analysis. Safety was assessed through monitoring of adverse events (AEs), laboratory testing, measurement of vital signs, and physical examination. AEs were assessed by the investigator for intensity according to Common Terminology Criteria for Adverse Events version 4.03 (CTCAE v4.03). Additional information on safety assessments can be found in the protocol.

Trial oversight

The trial adhered to the principles of the Declaration of Helsinki, Good Clinical Practice guidelines, and all local laws under the auspices of an independent data and safety monitoring committee. The trial was approved by the institutional review board at each study site and conducted in accordance with the Declaration of Helsinki and Good Clinical Practice Guidelines of the International Council for Harmonisation. All patients provided written informed consent. The trial was designed and sponsored by GSK in collaboration with the authors and academic groups under the European Network of Gynaecological Oncological Trial (ENGOT) groups and the GOG Foundation. The sponsor was responsible for overseeing the collection, analysis, and interpretation of data. Trial outcomes and all significant outcomes reported were verified independently by the Nordic Society of Gynaecological Oncology Clinical Trial Unit (ENGOT lead group) statistician. The authors had full access to trial data, wrote the manuscript, attested to the accuracy and completeness of data, confirmed adherence of the trial to the protocol, and made the final decision to submit the manuscript for publication. GSK funded medical writing assistance with the submitted manuscript.

Statistical analysis

The statistical analysis was previously published with the first interim analysis of RUBY Part 1.[13] At the first interim analysis, the null hypotheses for PFS in the dMMR/MSI-H population and overall population were rejected. However, the *P* value stopping boundary for OS in the overall population (0.00177) was not crossed.

At the second interim analysis, 221 events were targeted. Between data cut-off date and database lock date, additional survival status information was obtained from public records on patients who had discontinued the trial for reasons other than death when possible. Thus, 253 events were observed (information fraction on 78.8%), surpassing the planned number of events. To account for this, the *P* value stopping boundary for 253 events was adjusted to 0.01101, with a cumulative alpha spend of 0.0115793. All analyses were conducted on the source-verified data as previously described.[13] The 95% CIs of the HR reported were based on the stratified Cox regression model and were not used for hypothesis testing. All *P* values reported were based on the stratified log-rank test.

RESULTS

Patients

From 18 July 2019 through 23 February 2021, a total of 607 patients from 113 sites in 19 countries were screened and 494 underwent randomization; 245 were assigned to receive dostarlimab plus carboplatin—paclitaxel (dostarlimab group), and 249 were assigned to receive placebo plus carboplatin—paclitaxel (placebo group; Figure 1). At the data cut-off date of 22 September 2023, 27 patients (11.0%) were still receiving dostarlimab and 22 patients (8.8%) were still receiving placebo. Treatment discontinuations in both groups are presented in Supplementary

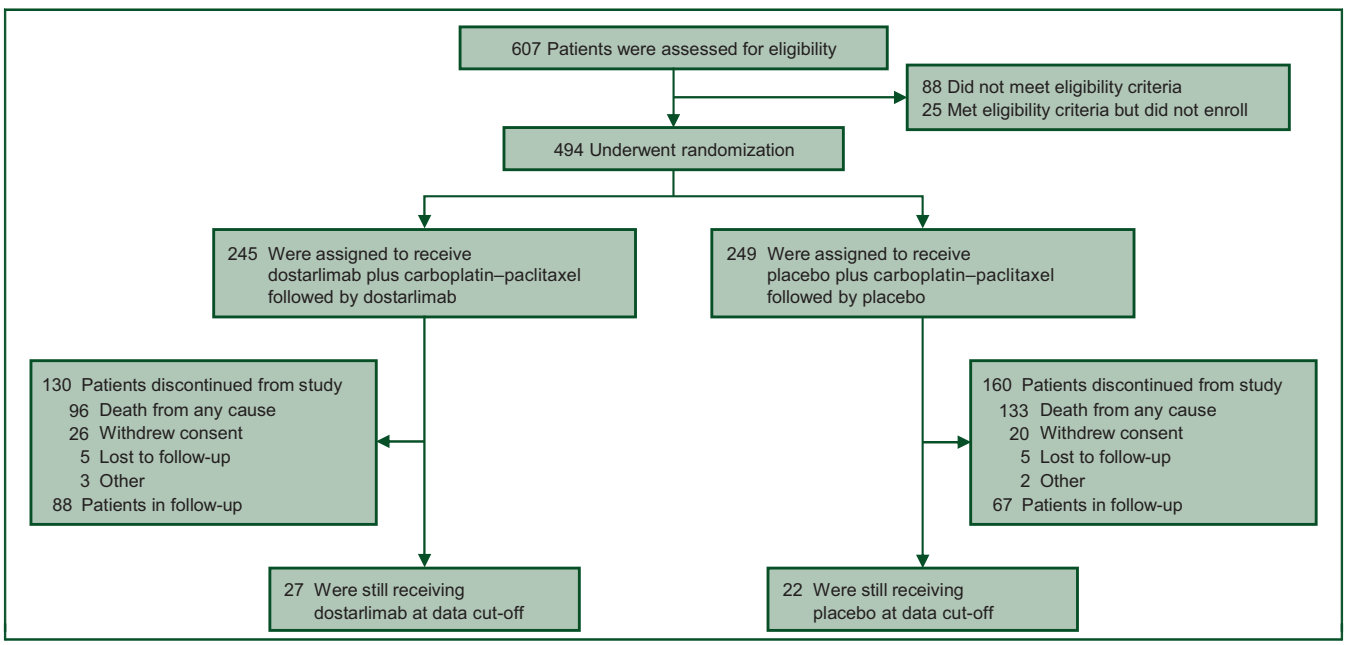

Figure 1. Enrollment and randomization of patients.

Table S1, available at https://doi.org/10.1016/j.annonc.2024.05.546. The expected median duration of follow-up was 37.2 months (range 31.0-49.5 months) in the overall population, 36.6 months (range 31.0-48.7 months) in the dMMR/MSI-H population, and 37.5 months (range 31.2-49.5 months) in the MMRp/MSS population.

Demographic and clinical characteristics at baseline were previously published (Table 1); characteristics were well balanced across trial arms in the overall population.[13] The study population of Part 1 of the RUBY trial reflected the target primary advanced or recurrent EC population.

Table 1. Patient demographics and clinical characteristics at baseline

Characteristic	Dostarlimab plus carboplatin—paclitaxel (n = 245)	Placebo plus carboplatin—paclitaxel (n = 249)
Age		
Age, median (range), years	64 (41-81)	65 (28-85)
<65 years, n (%)	127 (51.8)	114 (45.8)
≥65 years, n (%)	118 (48.2)	135 (54.2)
Race, n (%)		
White	189 (77.1)	191 (76.7)
Black or African American	28 (11.4)	31 (12.4)
Asian	7 (2.9)	8 (3.2)
American Indian or Alaska Native	1 (0.4)	1 (0.4)
Native Hawaiian or other Pacific Islander	1 (0.4)	0
Unknown or not reported	19 (7.8)	18 (7.2)
ECOG PS, n (%)[a]		
0	145 (60.2)	160 (65.0)
1	96 (39.8)	86 (35.0)
FIGO stage at diagnosis, n (%)		
I	65 (26.5)	71 (28.5)
II	13 (5.3)	13 (5.2)
III	75 (30.6)	65 (26.1)
IV	72 (29.4)	84 (33.7)
Unknown	20 (8.2)	16 (6.4)
Disease status, n (%)		
Primary stage III	45 (18.4)	47 (18.9)
Primary stage IV	83 (33.9)	83 (33.3)
Recurrent	117 (47.8)	119 (47.8)
BMI[b]		
BMI, median (range), kg/m^2	30.80 (17.6-60.6)	32.75 (17.7-68.0)
Histology type, n (%)		
Carcinosarcoma	25 (10.2)	19 (7.6)
Endometrioid	134 (54.7)	136 (54.6)
Mixed carcinoma ≥10% of carcinosarcoma, clear cell, or serous histology	10 (4.1)	9 (3.6)
Serous adenocarcinoma	50 (20.4)	52 (20.9)
Clear-cell adenocarcinoma	8 (3.3)	9 (3.6)
Mucinous adenocarcinoma	0	1 (0.4)
Undifferentiated carcinoma	1 (0.4)	2 (0.8)
Other	17 (6.9)	21 (8.4)
MMR/MSI status, n (%)		
dMMR/MSI-H	53 (21.6)	65 (26.1)
MMRp/MSS	192 (78.4)	184 (73.9)
Prior external pelvic radiotherapy, n (%)		
Yes	41 (16.7)	45 (18.1)
No	204 (83.3)	204 (81.9)

BMI, body mass index; dMMR, mismatch repair deficient; ECOG PS, Eastern Cooperative Oncology Group performance status; FIGO, International Federation of Gynecology and Obstetrics; MMR, mismatch repair; MMRp, mismatch repair proficient; MSI, microsatellite instability; MSI-H, microsatellite instability-high; MSS, microsatellite stable.

[a]ECOG PS was available for 241 patients in the dostarlimab plus carboplatin—paclitaxel arm and 246 patients in the placebo plus carboplatin—paclitaxel arm.

[b]BMI was available for 240 patients in the dostarlimab plus carboplatin—paclitaxel arm and 246 patients in the placebo plus carboplatin—paclitaxel arm.

Efficacy

Overall survival. At the second interim analysis, RUBY met the dual primary endpoint for OS in the overall population with 253 observed OS events (51% OS maturity). In patients treated with dostarlimab plus carboplatin—paclitaxel, there was a statistically significant reduction in the risk of death by 31% (HR = 0.69, 95% CI 0.54-0.89, stratified log-rank P = 0.0020) when compared to patients receiving placebo plus carboplatin—paclitaxel, and the prespecified P value stopping boundary for the log-rank test was crossed (P = 0.01101). A clinically meaningful improvement of 16.4 months in median OS was reported for patients receiving dostarlimab plus carboplatin—paclitaxel compared with carboplatin—paclitaxel alone (median OS of 44.6 months versus 28.2 months), with the Kaplan—Meier probability of survival at 24 months of 70.1% (95% CI 63.8% to 75.5%) in the dostarlimab arm and 54.3% (95% CI 47.8% to 60.3%) in the placebo arm (Figure 2A).

In the prespecified exploratory analysis of OS in the dMMR/MSI-H population, 12 of 53 patients (22.6%) in the dostarlimab group and 35 of 65 patients (53.8%) in the placebo group had died. With 40% OS maturity, the risk of death was lower in the dostarlimab arm than in the placebo arm (HR = 0.32, 95% CI 0.17-0.63, nominal P = 0.0002). Median OS was not reached for the dostarlimab arm and was 31.4 months for the placebo arm, with the Kaplan—Meier probability of survival at 24 months of 82.8% (95% CI 69.5% to 90.7%) in the dostarlimab arm and 57.5% (95% CI 44.4% to 68.6%) in the placebo arm (Figure 2B).

In the prespecified exploratory analysis of OS in the MMRp/MSS population, 97 of 192 patients (50.5%) in the dostarlimab group and 109 of 184 patients (59.2%) in the placebo group had died. With 55% OS maturity, there was a clear trend in favor of dostarlimab suggesting a 21% reduction in the risk of death (HR = 0.79, 95% CI 0.60-1.04, nominal P = 0.0493). Median OS in the dostarlimab arm was 34.0 months and in the placebo arm it was 27.0 months with the Kaplan—Meier probability of survival at 24 months of 66.5% (95% CI 59.2% to 72.8%) and 53.2% (95% CI 45.6% to 60.2%), respectively (Figure 2C).

Results from the prespecified subgroup analysis of OS are shown in Supplementary Figure S1, available at https://doi.org/10.1016/j.annonc.2024.05.546. OS benefit with dostarlimab plus carboplatin—paclitaxel was consistent across most protocol-specified subgroups.

Subsequent anticancer therapy. In the overall population, a higher proportion of patients (173/249 patients, 69.5%) in the placebo arm received subsequent anticancer therapy than patients in the dostarlimab arm (120/245 patients, 49.0%; Table 2).

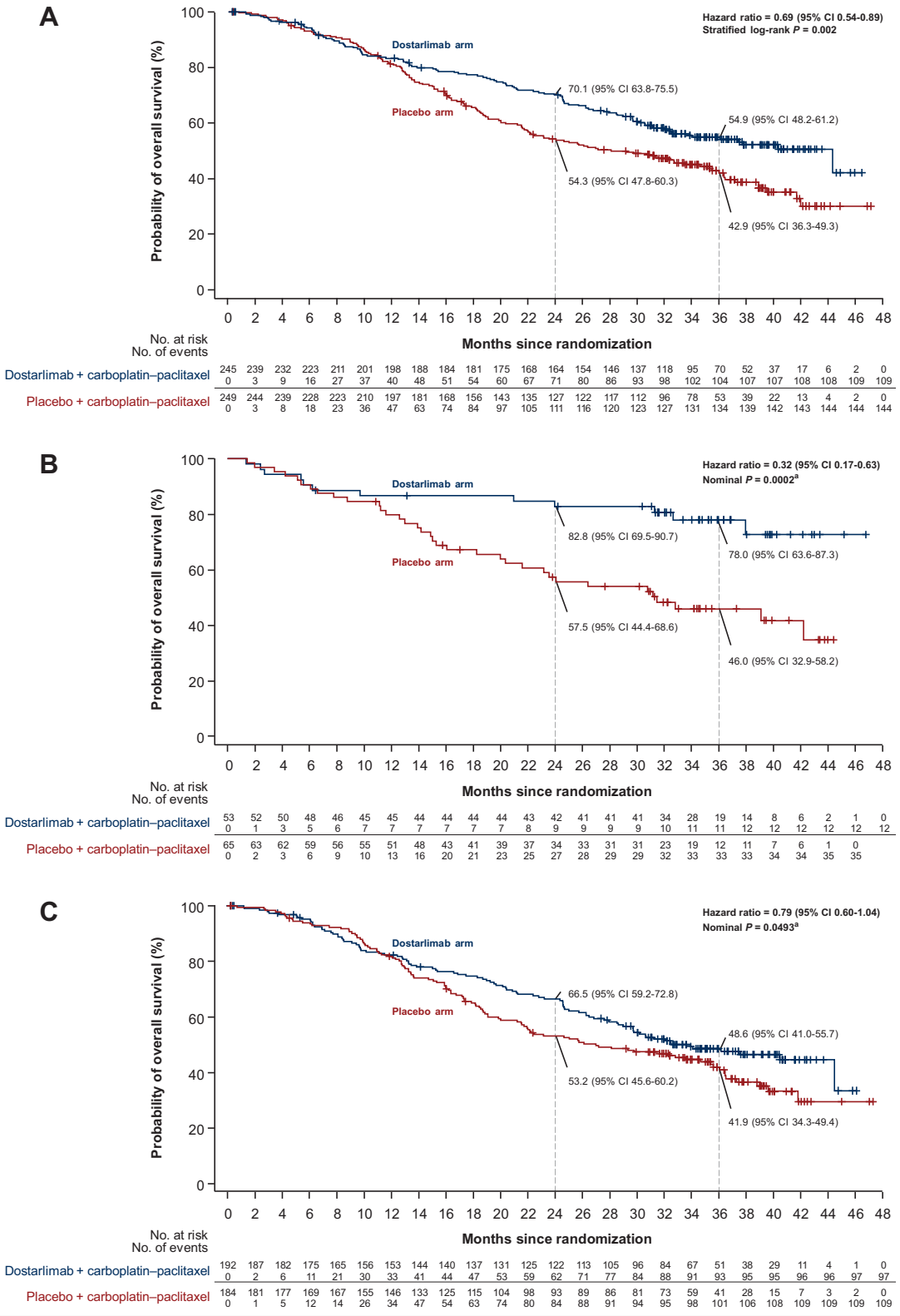

Figure 2. Kaplan–Meier estimate of OS. (A) Overall population, (B) dMMR/MSI-H population, and (C) MMRp/MSS population.
dMMR, mismatch repair-deficient; HR, hazard ratio; MMRp, mismatch repair-proficient; MSI-H, microsatellite instability-high; MSS, microsatellite stable; OS, overall survival. [a]OS analyses in the dMMR/MSI-H and MMRp/MSS populations were prespecified exploratory endpoints.

Of the 173 patients in the placebo arm and 120 patients in the dostarlimab arm who received subsequent anticancer therapy, 54.9% of patients (95/173) in the placebo arm received subsequent immunotherapy compared to 35.0% of patients (42/120) in the dostarlimab arm. The most common subsequent immunotherapy in both arms was the

Table 2. Subsequent immunotherapy use

	dMMR/MSI-H		MMRp/MSS		Overall	
	Dostarlimab plus carboplatin—paclitaxel (n = 53)	Placebo plus carboplatin—paclitaxel (n = 65)	Dostarlimab plus carboplatin—paclitaxel (n = 192)	Placebo plus carboplatin—paclitaxel (n = 184)	Dostarlimab plus carboplatin—paclitaxel (n = 245)	Placebo plus carboplatin—paclitaxel (n = 249)
Any follow-up anticancer therapy, *n* (%)	15 (28.3)	39 (60.0)	105 (54.7)	134 (72.8)	120 (49.0)	173 (69.5)
Immunotherapy	8 (15.1)	27 (41.5)	34 (17.7)	68 (37.0)	42 (17.1)	95 (38.2)
Pembrolizumab	4 (7.5)	21 (32.3)	9 (4.7)	20 (10.9)	13 (5.3)	41 (16.5)
Pembrolizumab—lenvatinib	3 (5.7)	2 (3.1)	22 (11.5)	43 (23.4)	25 (10.2)	45 (18.1)
Dostarlimab	0	3 (4.6)	0	0	0	3 (1.2)
MK7694A	0	1 (1.5)	0	0	0	1 (0.4)
Pembrolizumab—tamoxifen	1 (1.9)	0	0	0	1 (0.4)	0
Retifanlimab—epacadostat	1 (1.9)	0	0	2 (1.1)	1 (0.4)	2 (0.8)
Investigational product	0	0	1 (0.5)	1 (0.5)	1 (0.4)	1 (0.4)
Atezolizumab—ipatasertib	0	0	0	1 (0.5)	0	1 (0.4)
Avelumab—axitinib	0	0	0	1 (0.5)	0	1 (0.4)
Bevacizumab—atezolizumab	0	0	0	1 (0.5)	0	1 (0.4)
Durvalumab—cediranib	0	0	0	2 (1.1)	0	2 (0.8)
Durvalumab—olaparib	0	0	2 (1.0)	0	2 (0.8)	0
Nivolumab—BMS986207—COM701	0	0	0	1 (0.5)	0	1 (0.4)
Nivolumab—lucitanib	0	0	0	1 (0.5)	0	1 (0.4)
SGN-ALPV	0	0	0	1 (0.5)	0	1 (0.4)

dMMR, mismatch repair deficient; MMRp, mismatch repair proficient; MSI-H, microsatellite instability-high; MSS, microsatellite stable.

combination of pembrolizumab plus lenvatinib that was received in 10.2% of patients in the dostarlimab arm [59.5% of those who received follow-up immunotherapy (25/42)] and 18.1% of patients in the placebo arm [47.4% of those who received follow-up immunotherapy (45/95)].

In the dMMR/MSI-H population, 60% of patients (39/65) in the placebo arm and 28.3% of patients (15/53) in the dostarlimab arm received follow-up anticancer therapy. Of the 39 patients in the placebo arm who received follow-up anticancer therapy, 69.2% (27/39) received subsequent immunotherapy; of the 15 patients in the dostarlimab arm who received follow-up anticancer therapy, 53.3% (8/15) received subsequent immunotherapy. Of the 27 patients in the placebo arm who received subsequent immunotherapy in the dMMR/MSI-H population, 21 (77.8%) received pembrolizumab and 2 (7.4%) received pembrolizumab plus lenvatinib.

In the MMRp/MSS population, 72.8% of patients (134/184) in the placebo arm and 54.7% of patients (105/192) in the dostarlimab arm received follow-up anticancer therapy. Of the 134 patients in the placebo arm who received follow-up anticancer therapy, 50.7% (68/134) received subsequent immunotherapy; of the 105 patients in the dostarlimab arm who received follow-up anticancer therapy, 32.4% (34/105) received subsequent immunotherapy. Of the 68 patients in the placebo arm who received subsequent immunotherapy in the MMRp/MSS population, 20 (29.4%) received pembrolizumab and 43 (63.2%) received pembrolizumab plus lenvatinib.

Progression-free survival 2. At this second interim analysis, dostarlimab plus carboplatin—paclitaxel reduced the risk of progression following initiation of first subsequent anticancer therapy or death in the overall, dMMR/MSI-H, and MMRp/MSS populations. In the overall population, 116 of 245 patients (47.3%) in the dostarlimab group and 159 of 249 patients (63.9%) in the placebo group had experienced either progression on the first subsequent anticancer therapy or death; HR for PFS2 was 0.66 (95% CI 0.52-0.84). An improvement of 13.9 months in median PFS2 was observed in patients receiving dostarlimab plus carboplatin—paclitaxel (median PFS2 of 32.3 months for dostarlimab and 18.4 months for placebo; Figure 3A).

In the dMMR/MSI-H population, 13 of 53 patients (24.5%) in the dostarlimab group and 38 of 65 patients (58.5%) in the placebo group had experienced either progression on the first subsequent anticancer therapy or death. HR for PFS2 was 0.33 (95% CI 0.18-0.63). The numerical improvement in PFS2 could not yet be calculated in this population as median PFS2 was not yet reached in the dostarlimab arm versus 21.6 months in the placebo arm (Figure 3B).

Furthermore, in the MMRp/MSS population, 103 of 192 patients (53.6%) in the dostarlimab group and 121 of 184 patients (65.8%) in the placebo group had experienced either progression on the first subsequent anticancer therapy or death. HR for PFS2 was 0.74 (95% CI 0.57-0.97). A difference of 8.7 months in median PFS2 was observed with dostarlimab plus carboplatin—paclitaxel (median PFS2 of 24.6 months for dostarlimab and 15.9 months for placebo; Figure 3C).

Safety

The median duration of treatment at this second interim analysis in the overall population was 43.0 weeks in the dostarlimab arm (range 3.0-192.6 weeks) and 36.0 weeks in the placebo arm (range 2.1-193.1 weeks).

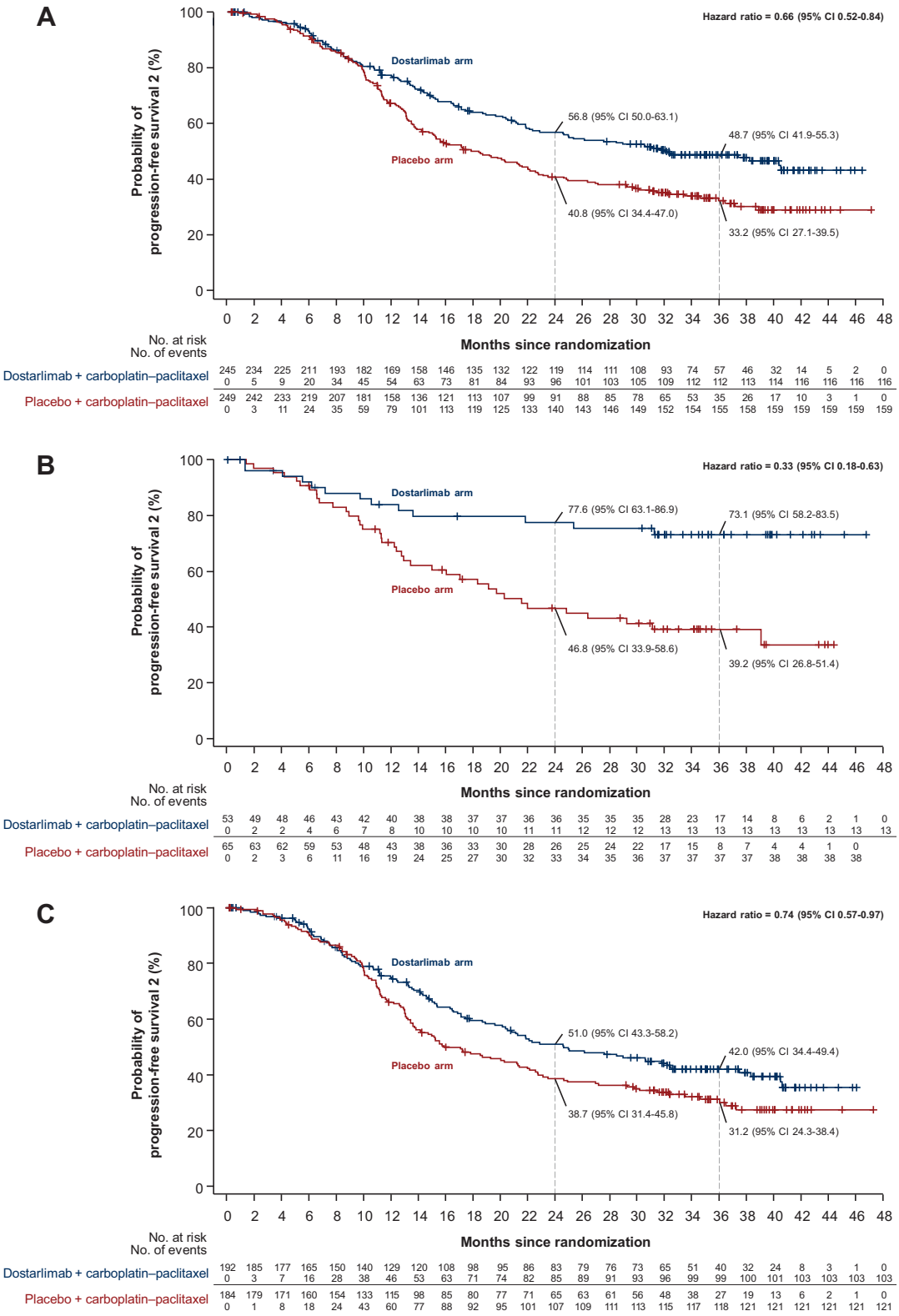

Figure 3. Kaplan–Meier estimate of PFS2. (A) Overall population, (B) dMMR/MSI-H population, and (C) MMRp/MSS population. PFS2 was defined as time from treatment randomization to the date of assessment of progression on the first subsequent anticancer therapy after study treatment or death by any cause, whichever is earlier.

dMMR, mismatch repair-deficient; HR, hazard ratio; MMRp, mismatch repair-proficient; MSI-H, microsatellite instability-high; MSS, microsatellite stable; PFS2, progression-free survival 2.

The safety profile for dostarlimab plus carboplatin—paclitaxel was consistent with that seen in the first interim analysis. The most frequently reported treatment-emergent adverse events (TEAEs; ≥40%) in both treatment arms were primarily related to chemotherapy (Table 3). Anemia was also seen at ≥40% in the placebo plus carboplatin—paclitaxel arm. These common TEAEs were grade 1 or 2 in most patients except for anemia, which was grade 2 or 3 in most patients. Serious treatment-related AEs were experienced by 19.5% of patients in the dostarlimab arm and 12.2% of patients in the placebo arm. Discontinuation of dostarlimab or placebo due to AEs occurred in 19.1% of patients in the dostarlimab arm and 8.1% of patients in the placebo arm. The most common AEs leading to discontinuation of dostarlimab or placebo were infusion-related reaction (1.2%) and maculopapular rash (1.2%) in patients in the dostarlimab group and thrombocytopenia (1.2%) and rash (0.8%) in patients in the placebo group. The most common treatment-related treatment-emergent immune-related AEs were hypothyroidism (dostarlimab 12.0% versus placebo 2.8%), rash (dostarlimab 7.1% versus placebo 2.0%), arthralgia (dostarlimab 6.6% versus placebo 6.5%), and increased alanine aminotransferase (dostarlimab 6.2% versus placebo 1.2%). No new deaths due to AEs occurred at this second interim analysis.

Table 3. Summary of adverse events in the overall population

	Dostarlimab plus carboplatin—paclitaxel (n = 241)	Placebo plus carboplatin—paclitaxel (n = 246)
Summary, *n* (%)		
Any TEAE	241 (100)	246 (100)
Any TRAE	236 (97.9)	243 (98.8)
Related to dostarlimab/placebo	203 (84.2)	183 (74.4)
Related to carboplatin/paclitaxel	233 (96.7)	236 (95.9)
Any grade ≥3 TEAE	174 (72.2)	148 (60.2)
Any grade ≥3 TRAE	128 (53.1)	115 (46.7)
Related to dostarlimab/placebo	87 (36.1)	49 (19.9)
Related to carboplatin/paclitaxel	94 (39.0)	101 (41.1)
Serious TEAE	96 (39.8)	69 (28.0)
Any serious TRAE	47 (19.5)	30 (12.2)
Serious TEAE related to dostarlimab/placebo	33 (13.7)	17 (6.9)
Serious TEAE related to carboplatin/paclitaxel	33 (13.7)	24 (9.8)
Any treatment-related irAE	98 (40.7)	40 (16.3)
Any TEAE leading to discontinuation of dostarlimab or placebo	46 (19.1)	20 (8.1)
Any TEAE leading to dose reduction	68 (28.2)	68 (27.6)
Any TEAE leading to death	5 (2.1)	0
TEAEs in >30% of patients in either arm, *n* (%)		
Fatigue	126 (52.3)	135 (54.9)
Alopecia	130 (53.9)	123 (50.0)
Nausea	131 (54.4)	114 (46.3)
Neuropathy, peripheral	106 (44.0)	103 (41.9)
Anemia	91 (37.8)	105 (42.7)
Arthralgia	90 (37.3)	87 (35.4)
Constipation	84 (34.9)	89 (36.2)
Diarrhea	76 (31.5)	72 (29.3)
Grade ≥3 TEAEs in >5% of patients in either arm, *n* (%)		
Anemia	36 (14.9)	41 (16.7)
Neutropenia	23 (9.5)	23 (9.3)
Neutrophil count decreased	20 (8.3)	34 (13.8)
Lymphocyte count decreased	13 (5.4)	18 (7.3)
White blood cell count decreased	16 (6.6)	13 (5.3)
Hypertension	17 (7.1)	8 (3.3)
Pulmonary embolism	14 (5.8)	12 (4.9)
Serious AEs in >2% of patients in either arm, *n* (%)		
Sepsis	8 (3.3)	1 (0.4)
Pulmonary embolism	8 (3.3)	5 (2.0)
Pyrexia	7 (2.9)	2 (0.8)
Dyspnea	5 (2.1)	1 (0.4)
Muscular weakness	5 (2.1)	1 (0.4)
Vomiting	5 (2.1)	3 (1.2)
Anemia	3 (1.2)	6 (2.4)
Asthenia	2 (0.8)	6 (2.4)

AE, adverse event; irAE, immune-related adverse event; TEAE, treatment-emergent adverse event; TRAE, treatment-related adverse event.

DISCUSSION

At this protocol-specified second interim analysis, with an expected median duration of follow-up of 37.2 months, RUBY Part 1 met the dual primary endpoint for OS in the overall population, demonstrating a statistically significant improvement in patients treated with dostarlimab plus carboplatin—paclitaxel, with a 31% lower risk of death compared to patients treated with carboplatin—paclitaxel alone. This is the only phase III trial to demonstrate statistically significant OS improvement in primary advanced or recurrent EC in two decades, showing survival beyond what has been achieved with carboplatin—paclitaxel alone.[19] Moreover, the median OS of 44.6 months for patients treated with dostarlimab plus carboplatin—paclitaxel is considerably improved relative to carboplatin—paclitaxel alone (28.2 months) comparing favorably to the historical expected survival outcomes of this population.[7,8,20] The statistically significant PFS benefit that was reported in both the overall and dMMR/MSI-H populations at the first interim analysis is now affirmed with the statistically significant OS benefit in the overall population reported here. These results are practice-changing for primary advanced or recurrent EC.

Exploratory analyses of OS in the dMMR/MSI-H and MMRp/MSS populations were prespecified and indicated a potential lower risk of death with dostarlimab plus carboplatin—paclitaxel. There was an unprecedented reduction in the risk of death of 68% (HR = 0.32, 95% CI 0.17-0.63) in the dMMR/MSI-H population, supporting the use of dostarlimab to achieve long-term remission and to improve survival. In the MMRp/MSS population, there was a trend in favor of dostarlimab, with the HR suggesting a 21% reduction in the risk of death (HR = 0.79, 95% CI 0.60-1.04) and a clinically meaningful difference in median OS of 7 months. These findings were observed despite 41.5% and 37.0% of patients being treated with immunotherapy as the first subsequent anticancer therapy in the carboplatin—paclitaxel control arm of the dMMR/MSI-H and MMRp/MSS subpopulations, respectively, and despite the 23.4% of patients who received subsequent immunotherapy in the

carboplatin—paclitaxel control arm in the MMRp/MSS subgroup receiving pembrolizumab—lenvatinib.

The observed OS benefit was further supported by the improvements in PFS2, which depict a clinical benefit beyond the first progression in patients receiving dostarlimab plus carboplatin—paclitaxel in this population. PFS2 was consistent with the primary efficacy analyses of PFS and OS, demonstrating that benefits were sustained on the first subsequent anticancer therapy with delayed time to next progression or death.

At this second interim analysis, subgroup analyses for OS generally favored dostarlimab with exceptions for patients with stage III disease, patients with no disease at baseline, and patients in Europe. These results should be interpreted with caution because of the low number of patients in these subgroups and potential confounding factors when evaluating populations in which stratification may be impacted. Of note, RUBY Part 1 recruited patients during the coronavirus disease 2019 pandemic. Consequently, a smaller number of patients from Europe ($n = 136$) enrolled in the trial compared with North America ($n = 358$) because of limitations in remote clinical trial monitoring impacting sites in Europe. Importantly, it would not be expected for patients in Europe to respond to treatment differently than those in North America, and this cannot be attributed to variances in treatment practice outlined by national guidelines.[21,22]

While the HR for stage III at interim analysis 2 was higher than that for other subgroups, it is known that patients with stage III EC are at high risk of both local and systemic recurrence and benefit from adjuvant therapy. In EC, the prognosis for patients with stage III disease or with no evaluable disease at baseline following surgery is better relative to patients with stage IV or recurrent disease. With treatment in both arms and low data maturity in this population, it would not yet be expected to see a difference in these patients without additional data maturity. Aligned with this, at interim analysis 2, with more follow-up time and more events relative to interim analysis 1, the HR point estimate for stage III disease directionally shifted toward dostarlimab (1.32 at second interim analysis versus 1.52 at first interim analysis). Furthermore, there is no biological rationale for patients with stage III EC to respond differently to treatment than patients with stage IV or recurrent EC, which is supported by the literature.[7,23-26] Finally, although the benefits are not confirmed in this subgroup, it is also important to consider that interpretation is confounded by the small number of patients and subsequent variability in the population for this exploratory analysis.

At the second interim analysis of Part 1 of the RUBY trial, safety risks associated with the addition of dostarlimab to standard-of-care carboplatin—paclitaxel chemotherapy showed no unexpected toxicities and the safety profile remained manageable. No new safety signals were observed with extended follow-up; the safety profile was similar to that reported in the first interim analysis.

Although the RUBY trial has provided substantial, statistically significant evidence for the use of combination dostarlimab with chemotherapy followed by dostarlimab maintenance in EC, as of now it is unknown how single-agent dostarlimab compares directly to chemotherapy. Two ongoing trials are attempting to bridge this gap: DOMENICA [GINECO-EN1-5b/ENGOT-en13 (NCT05201547)] and KEYNOTE-C93 [GOG-3064/ENGOT-en15 (NCT05173987)] are two open-label, phase III, randomized trials exploring first-line dostarlimab or pembrolizumab, respectively, compared with carboplatin—paclitaxel in patients with advanced or recurrent dMMR EC.[27,28]

The significant OS results from RUBY touch upon the ongoing question of the optimal duration of immunotherapy. As observed in other immunotherapy trials, a plateau of the PFS curve is seen in the RUBY trial in the dMMR/MSI-H population, and future research into the significance of this plateau as it relates to treatment duration could help to address this question. When the RUBY trial was designed, the rationale for a maximum of up to 3-year immunotherapy treatment duration stemmed from the median OS of patients with primary advanced or recurrent EC on standard-of-care chemotherapy being <3 years, which was confirmed in the RUBY trial control arm.[7] Future trials are needed to examine optimal duration of long-term use and benefit from immunotherapies.

In the high unmet need patient population of primary advanced or recurrent EC, where conventional chemotherapy results in short-lived, modest benefit, dostarlimab in combination with carboplatin—paclitaxel demonstrated a statistically significant and clinically meaningful OS benefit in the overall population of patients with primary advanced or recurrent EC while demonstrating an acceptable safety profile, representing a new standard of care.

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DATA SHARING

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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