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Patient-reported outcomes in the subpopulation of patients with mismatch repair-deficient/microsatellite instability-high primary advanced or recurrent endometrial cancer treated with dostarlimab plus chemotherapy compared with chemotherapy alone in the ENGOT-EN6-NSGO/GOG3031/RUBY trial

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ABSTRACT

Objective In the ENGOT-EN6-NSGO/GOG3031/RUBY trial, dostarlimab+carboplatin–paclitaxel demonstrated significant improvement in progression free survival and a positive trend in overall survival compared with placebo+carboplatin–paclitaxel, with manageable toxicity, in patients with primary advanced or recurrent endometrial cancer. Here we report on patient-reported outcomes in the mismatch repair-deficient/microsatellite instability-high population, a secondary endpoint in the trial.

Methods Patients were randomized 1:1 to dostarlimab+carboplatin–paclitaxel or placebo+carboplatin–paclitaxel every 3 weeks for 6 cycles followed by dostarlimab or placebo monotherapy every 6 weeks for ≤3 years or until disease progression. Patient-reported outcomes, assessed with the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 and Endometrial Cancer Module, were prespecified secondary endpoints. A mixed model for repeated measures analysis, a prespecified exploratory analysis, was conducted to generate least-squares means to compare between-treatment differences while adjusting for correlations across multiple time points within a patient and controlling for the baseline value. Results are provided with 2-sided, nominal p values.

Results Of 494 patients enrolled, 118 were mismatch repair-deficient/microsatellite instability-high. In this population, mean change from baseline to end of treatment showed visual improvements in global quality of life (QoL), emotional and social function, pain, and back/pelvis pain for dostarlimab+carboplatin–paclitaxel. Meaningful differences (least-squares mean [standard

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Endometrial cancer incidence and mortality rates are increasing, and new treatment options are needed, especially for patients with primary advanced or recurrent endometrial cancer.

⇒ The effects on quality of life with long-term immunotherapy use in patients with primary advanced or recurrent endometrial cancer are not well described at present.

WHAT THIS STUDY ADDS

⇒ This study adds important information on the quality of life that patients experience while receiving dostarlimab+chemotherapy followed by dostarlimab monotherapy, for primary advanced or recurrent endometrial cancer.

⇒ This analysis showed that patients with mismatch repair-deficient/microsatellite instability-high endometrial cancer received notable benefits in patient-reported quality of life outcomes when treated with dostarlimab+chemotherapy.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ This study further supports the use of dostarlimab+chemotherapy as a standard of care in patients with mismatch repair-deficient/microsatellite instability-high primary advanced or recurrent endometrial cancer and provides additional evidence that quality of life data should be an integral part of cancer clinical trials.

error]) favoring the dostarlimab arm were reported for change from baseline to end of treatment for QoL (14.7 [5.45]; p=0.01), role function (12.7 [5.92]); p=0.03), emotional function (14.3 [4.92]; p<0.01), social function (13.5 [5.43]; p=0.01), and fatigue (−13.3 [5.84]; p=0.03).

Conclusions Patients with mismatch repair-deficient/microsatellite instability-high primary advanced or recurrent endometrial cancer receiving dostarlimab+carboplatin–paclitaxel demonstrated improvements in several QoL domains over patients receiving placebo+carboplatin–paclitaxel. The observed improvements in progression free survival and overall survival while improving or maintaining QoL further supports dostarlimab+carboplatin–paclitaxel as a standard of care in this setting.

Trial registration ClinicalTrials.gov NCT03981796

INTRODUCTION

Globally, endometrial cancer is the sixth most common female cancer, and the second most commonly diagnosed gynecologic cancer.[1] The highest incidence rates of endometrial cancer are currently found in North America, Europe, and Australasia,[1] and they have increased worldwide over the past two decades.[2] By 2040, it is estimated that global endometrial cancer rates will have increased by approximately 50%.[3]

A molecular description of endometrial cancer subtypes, including mismatch repair-deficient/microsatellite instability-high disease, has led to fundamental changes in treatment and a new understanding of prognosis.[4] The landscape of endometrial cancer treatment is evolving to include molecular classifications, such as Cancer Genome Atlas or Proactive Molecular Risk Classifier for Endometrial Cancer classification and updated International Federation of Gynecology Obstetrics staging to help inform on prognosis and, in some instances, predict the likelihood of benefit with specific treatments.[4–7] For example, immune checkpoint inhibitors targeting programmed cell death protein 1 (PD-1) have been shown to be effective therapies in patients with recurrent or advanced mismatch repair-deficient/microsatellite instability-high endometrial cancer that has progressed on or after treatment with platinum-containing chemotherapy.[8–10]

In the phase 3 RUBY trial (NCT03981796) of patients with primary advanced or recurrent endometrial cancer, dostarlimab, an anti–PD-1 antibody, plus carboplatin–paclitaxel, significantly improved progression free survival compared with carboplatin–paclitaxel alone in the mismatch repair-deficient/microsatellite instability-high and overall populations and showed a positive trend in overall survival in the overall population at the first interim analysis.[11] Based on the substantial magnitude of benefit observed in the mismatch repair-deficient/microsatellite instability-high population and the need for additional overall survival follow-up for the overall population, dostarlimab+carboplatin–paclitaxel was prioritized for obtaining regulatory approval in the mismatch repair-deficient/microsatellite instability-high population for primary advanced or recurrent endometrial cancer.[12–15]

Gynecologic cancers, including endometrial cancer, have significant negative impacts on the health-related quality of life (QoL) of affected women. Physical and emotional functioning decrease because of the disease itself and the effects of treatments,[16 17] with worsened health-related QoL most apparent in patients with advanced disease.[17] As the use of immunotherapy in endometrial cancer increases, it is necessary to understand the health-related QoL impact to comprehensively compare the overall benefit/risk profile of immunotherapy with that of traditional chemotherapy and/or radiation and other emerging therapies.[18 19] This dynamic is particularly relevant for long-term administration of therapies.[19 20]

The use of patient-reported outcomes, measured through patient questionnaires, during both investigational and routine clinical cancer treatment, is encouraged by regulatory agencies to measure patient experiences related to an intervention, such as treatment with a new therapy.[21–24] However, few immunotherapies for endometrial cancer have reported health-related QoL outcomes, with no data reported for the primary systemic treatment setting.[25–27] In the phase 1 GARNET study evaluating the efficacy of dostarlimab monotherapy in patients with recurrent or advanced mismatch repair-deficient/microsatellite instability-high endometrial cancer that had progressed on or after platinum-based chemotherapy, patient-reported outcome assessments demonstrated stable or improved QoL with dostarlimab monotherapy.[27]

To our knowledge, the phase 3 RUBY trial of dostarlimab+chemotherapy is the first clinical trial to report patient-reported outcome assessments for an immunotherapy plus chemotherapy combination in primary advanced or recurrent endometrial cancer. Herein, we report patient-reported outcome assessment data in the mismatch repair-deficient/microsatellite instability-high subpopulation of the RUBY trial (NCT03981796) that received regulatory approval by several major health authorities.

METHODS

Study Design and Patients

RUBY is a phase 3, randomized, double blind, multicenter study of dostarlimab+carboplatin–paclitaxel versus placebo+carboplatin–paclitaxel in patients with primary advanced or recurrent endometrial cancer. The trial was conducted in accordance with the principles of the Declaration of Helsinki, Good Clinical Practice guidelines, and all applicable local laws; all patients provided written informed consent for participation.

Full details of the study design have been reported[11]; in brief, patients were randomized 1:1 to receive dostarlimab+chemotherapy or placebo+chemotherapy and stratified according to mismatch repair/microsatellite instability status, previous external pelvic radiotherapy, and disease status (primary advanced or recurrent). Patients received either intravenous dostarlimab (500 mg) or placebo in combination with carboplatin–paclitaxel every 3 weeks for 6 cycles, followed by 1000 mg of dostarlimab or placebo every 6 weeks. Monotherapy treatment with dostarlimab or placebo continued for ≤3 years or until disease progression, unacceptable toxicity, withdrawal of consent, investigator's decision, or death, whichever occurred first.

Eligible patients were aged ≥18 years, with histologically or cytologically confirmed primary advanced or recurrent endometrial cancer that was not amenable to cure by radiation therapy, surgery alone, or a combination of both. Full eligibility requirements have been previously published.[11] Tumor samples were required for assessment of mismatch repair and microsatellite status.

Assessments

Primary study endpoints were investigator assessed progression free survival in the mismatch repair-deficient/microsatellite

instability-high and overall populations, and overall survival in the overall population. Results of these endpoints have been previously published.[11] Health-related QoL and patient-reported outcome assessments were prespecified secondary endpoints of the trial in the overall and mismatch repair-deficient/microsatellite instability-high populations, and an exploratory analysis in the mismatch repair-proficient/microsatellite-stable population.

The European Organisation for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire Core 30, version 3.0 (QLQ-C30),[28] and Endometrial Cancer Module (QLQ-EN24)[29] were used to collect patient-reported outcome data in the trial. Specific information on these assessments can be found in Online Supplemental Table 1. Of note in the QLQ-EN24, the items constituting the sexual function scales are accompanied by the further specific instructions of "answer these questions only if you have been sexually active during the past 4 weeks."

Patients completed each instrument before receiving treatment on the first day of each treatment cycle, at the end of treatment, and at safety and survival follow-ups. Data from cycle 1, day 1, provided baseline QoL scores. Cycle 7, day 1 was the start of the monotherapy phase of the trial (patients would no longer receive carboplatin–paclitaxel). Cycle 13, day 1 was the start of the first cycle in the second year of treatment. Patients completed assessments on paper forms, and the information was then entered into an electronic database by the clinical research team at each study site.

Statistical Analyses

An estimated study sample size of 470 patients was determined based on the primary endpoint of investigator assessed progression free survival.[11] For this prespecified analysis, EORTC QLQ-C30 and EORTC QLQ-EN24 were evaluated in the mismatch repair-deficient/microsatellite instability-high subgroup, the population for which treatment approval has been given.

The completion rate was calculated for each of the QLQ-C30 and QLQ-EN24 domains. For multi-item scales, the number and percentage of patients who completed all questions and completed the minimum requirement for scoring the instrument were tabulated by visit. For single item scales, the number and percentage of patients who completed each question were tabulated by visit. Percentages were calculated based on the number of potentially evaluable patients at each visit.

Scoring was conducted according to published user guides for each instrument, and changes from baseline were calculated.[29 30] Scores were calculated by averaging items within scales and linearly transforming mean scores. Formulas used for linear transformation can be found in Online Supplemental Figure 1. For both scales, a change of 10 points in scale and summary scores was considered to be a minimum clinically important difference.[31] Changes from baseline were calculated for all patients, with corresponding scores for each scale at baseline and at each visit. If data for single items (those requiring input from single questions) were missing, the score was set to missing. For those scales requiring the combination of multiple items (those requiring input from multiple questions), if data for at least half of the items were available, the score was calculated based on available items; if data for more than half of the items were missing, the score was set to missing.[32]

A mixed model for repeated measures analysis was conducted to generate least-squares means to compare between-treatment differences while adjusting for correlations across multiple time points within a patient and controlling for the baseline value. The mixed model for repeated measures included patient, treatment, analysis visit, and treatment-by-visit interaction as explanatory variables and the baseline value as a covariate, along with the baseline-by-visit interaction. Treatment, visit, and treatment-by-visit interactions were fixed effects, and patients were treated as a random effect. An unstructured covariance matrix was used to model the within-patient variance, and the Kenward–Roger approximation was used to estimate the degrees of freedom. If the fit of the unstructured covariance structure failed to converge, the following covariance structures were used in order until convergence was reached: Toeplitz with heterogeneity, autoregressive with heterogeneity, Toeplitz, and autoregressive. If there were still issues with model convergence, visits with too few patients having data available were excluded, and the model searching algorithm described above was implemented again on the subset of the data after the exclusion of visits. Adjusted mean difference and 95% confidence intervals were calculated. Mixed model for repeated measures analyses were not adjusted for multiple testing/multiplicity; therefore, all p values are nominal.

RESULTS

Patients

In the RUBY trial, 494 patients were randomly assigned to treatment; 118 were categorized as mismatch repair-deficient/microsatellite instability-high (53 to dostarlimab+carboplatin–paclitaxel and 65 to placebo+carboplatin–paclitaxel). Full baseline demographic and clinical details have been published previously[11]; a summary of the mismatch repair-deficient/microsatellite instability-high population is provided in Online Supplemental Table 2. No notable differences were observed in the characteristics of patients in the two arms in the mismatch repair-deficient/microsatellite instability-high population. Overall, patients were considered to be representative of the clinical population with primary advanced or recurrent endometrial cancer.

Completion Rates

Completion rates for the QLQ-C30 and QLQ-EN24 in the mismatch repair-deficient/microsatellite instability-high population were consistent between the two treatment arms at baseline, cycle 7, cycle 13, and end of treatment (Online Supplemental Table 3). Completion rates ranged from 94% to 100% in both arms at baseline, cycle 7, and cycle 13, and from 75% to 79% at the end of treatment. Completion rates were high for all QLQ-EN24 domains, with the exception of sexual function scales and symptoms, likely because of additional completion instructions, as mentioned previously.

Patient-reported Outcome Changes from Baseline

In the mismatch repair-deficient/microsatellite instability-high population, mean changes over time in the two arms for global QoL and functioning scales are shown in Figure 1 (symptom scales are shown in Online Supplemental Figure 2). Significant differences over the 3-year period were seen with the least-squares mean

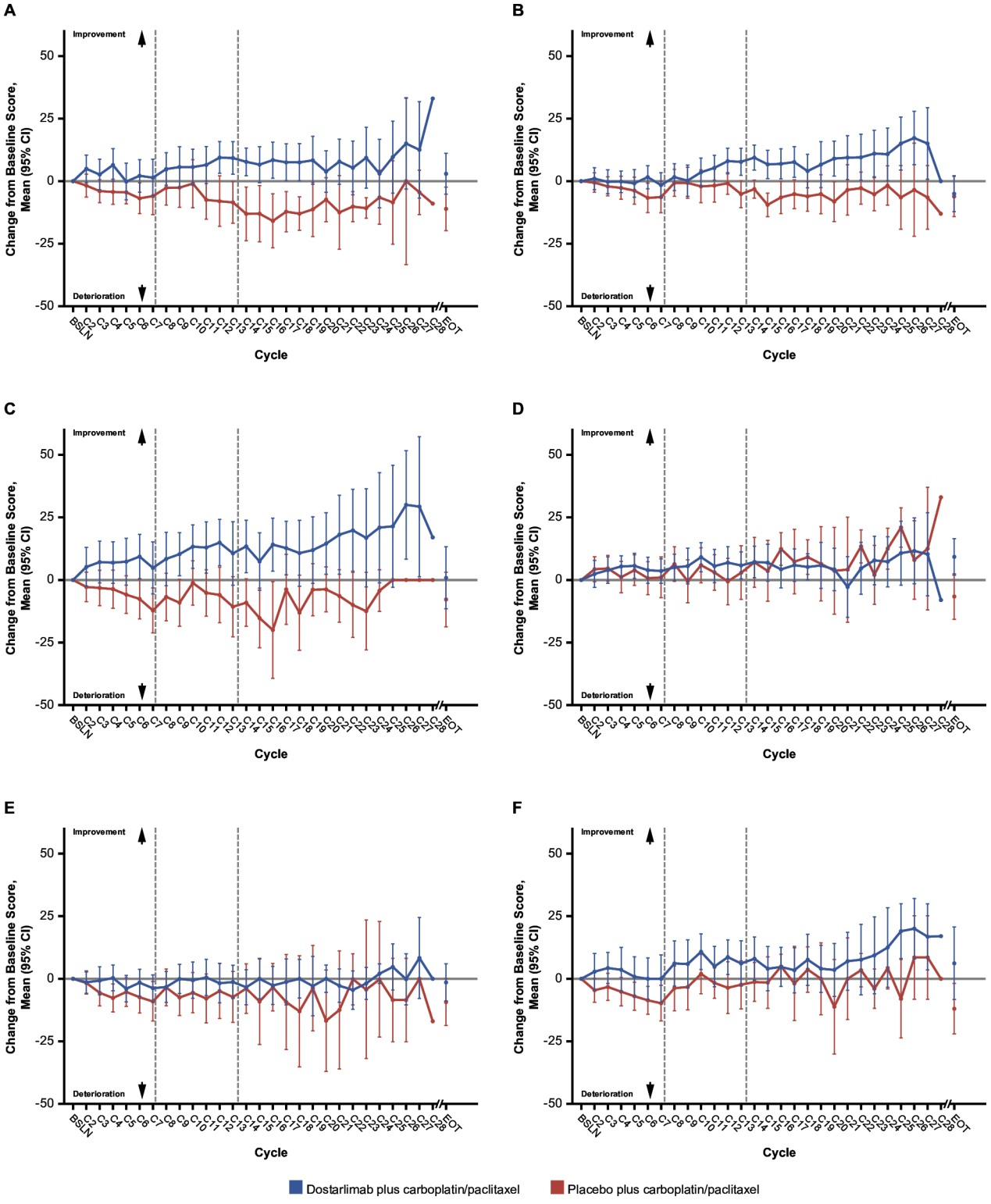

Figure 1 Mean changes from baseline in patient-reported outcome scores for global QoL and functional scales in the mismatch repair-deficient/microsatellite instability-high population. (A) QLQ-C30 global QoL; (B) QLQ-C30 physical functioning; (C) QLQ-C30 role functioning; (D) QLQ-C30 emotional functioning; (E) QLQ-C30 cognitive functioning; and (F) QLQ-C30 social functioning. Error bars indicate 95% confidence intervals. BSLN, baseline; EOT, end of treatment; QLQ-C30, Quality of Life Questionnaire Core 30; QoL, quality of life.

change (standard error [SE]) from baseline between arms for the QLQ-C30 scales of global QoL (8.8 [2.96]; p<0.01), social functioning (8.2 [2.84]; p=0.04), and pain (−7.6 [3.77]; p=0.04) and for the QLQ-EN24 scales of lymphedema (−9.1 [3.68]; p=0.01), urological symptoms (−5.4 [2.66]; p=0.04), and pain in the back and pelvis (−8.4 [4.15]; p=0.05).

Least-squares mean change (SE) from baseline at cycle 7 (end of chemotherapy) indicated a notable improvement in global QoL

(9.4 [3.72]; p=0.01), physical functioning (7.5 [3.61]; p=0.04), role functioning (11.7 [5.23]; p=0.03), and the symptom scales of pain (−16.8 [4.78]; p<0.01), dyspnea (−11.1 [4.99]; p=0.03), and back and pelvis pain (−12.1 [5.55]; p=0.03) for patients treated with dostarlimab compared with patients treated with placebo (Figure 2). While numerical differences persisted, the least-squares mean changes (least-squares mean [SE]) between arms were not different at cycle 13 (Figure 3), except for urological symptoms (−9.5 [3.56]; p=0.01). At the end of treatment, the least-squares mean change from baseline demonstrated clinically important differences in QoL (least-squares mean [SE]; 14.7 [5.45]; p=0.01), role functioning (12.7 [5.92]; p=0.03), emotional functioning (14.3 [4.92]; p<0.01), social functioning (13.5 [5.43]; p=0.01), and in the symptom scales of fatigue (−13.3 [5.84]; p=0.03), nausea and vomiting (−12.0 [3.52]; p<0.01), appetite loss (−20.1 [5.49]; p<0.01), and financial difficulties (−13.9 [5.10]; p=0.01) for patients treated with dostarlimab compared with those treated with placebo (Figure 4).

The QLQ-C30 global QoL scores were translated into summary scores of improved, remained stable, and worsened (Table 1). A higher percentage of patients in the dostarlimab+carboplatin–paclitaxel arm reported improved scores than patients in the placebo+carboplatin–paclitaxel arm at cycle 7 (35.9% vs 25.0%) and cycle 13 (44.4% vs 14.3%). At the end of treatment, a higher percentage of patients in the dostarlimab+carboplatin–paclitaxel arm reported improved or stable scores than patients in the placebo+carboplatin–paclitaxel arm (81.8% vs 51.2%).

Patient-reported Outcome Assessments in the Overall and Mismatch Repair-proficient/Microsatellite-stable Populations

Global QoL was similar between arms for patients in the overall population and in the mismatch repair-proficient/microsatellite-stable population. Least-squares mean change over time for the overall population and the mismatch repair-proficient/microsatellite-stable population for the EORTC QLQ-C30 and QLQ-EN24 are provided in Online Supplemental Table 4. Few differences were seen across the 3 year period between the arms in either population.

DISCUSSION

Summary of Main Results

To our knowledge, RUBY is the first trial to report data from a prospective evaluation of patient-reported outcome assessments in primary advanced or recurrent endometrial cancer patients receiving standard of care chemotherapy with or without immunotherapy. In this report, we showed that substantial progression-free survival benefits and a positive trend in overall survival reported with the use of dostarlimab+carboplatin–paclitaxel in the mismatch repair-deficient/microsatellite instability-high patient population were accompanied by improvement or maintenance in health-related QoL.[11] Although efficacy outcomes in the mismatch repair-proficient/microsatellite-stable population were exploratory, consistent numerical benefits across survival outcomes were seen, and patient reported outcomes in this population were consistent with patient-reported outcomes in the overall population. Together, these outcomes support improved survival outcomes while maintaining or improving QoL relative to placebo+carboplatin–paclitaxel across all populations.

In the mismatch repair-deficient/microsatellite instability-high population, dostarlimab+carboplatin–paclitaxel was associated with numerical improvements in global QoL, role and emotional functioning, pain, and back and pelvis pain at cycle 7 compared with baseline. With the exception of emotional functioning, these improvements showed a difference when compared with the placebo arm. In addition, numerical improvements from baseline with notable differences from the placebo arm at end of treatment were observed for role, emotional, and social functioning, QoL, pain, nausea/vomiting, appetite loss, financial difficulties, and fatigue in the dostarlimab arm. While our analysis did not demonstrate a notable difference at the 1-year landmark, numerical benefits persisted. Given the relatively small number of patients and the reduction in those contributing to the analysis at later time points, this lack of difference is most likely a reflection of insufficient power rather than a reduction of QoL benefits at later time points.

Results in the Context of Published Literature

These data are broadly aligned with those from the phase 1 GARNET study of dostarlimab monotherapy in advanced or recurrent endometrial cancer, in which sustained improvements relative to baseline in overall QoL, emotional and social functioning, and pain were observed from cycles 2 through 7, and improvements in fatigue were observed from cycles 4 through 7.[27]

Although endometrial cancer affects many women worldwide, detailed patient-reported outcome data reporting patient experience during and after therapy are lacking.[33–35] To our knowledge, this is the first report of clinically important differences in key QoL domains during immunotherapy treatment in patients with primary advanced or recurrent endometrial cancer. The greater number of patients treated with dostarlimab who had meaningfully improved global QoL (based on a minimum clinically important difference of 10 points) compared with patients treated with placebo at cycle 7 and cycle 13 is particularly notable, because this implies that patients achieved substantial benefit in the overall quality of their daily lives. While the impact of cancer on daily life is multifactorial, QoL can be negatively affected by treatment related factors, such as frequency of hospital visits[36] and occurrence of adverse events.[37] These data suggest that these types of impacts were minimal with dostarlimab treatment. Further, these results provide additional information supporting the overall efficacy of dostarlimab, as the anticancer effect was sufficient to also have benefits in addressing symptoms and burdens associated with advanced or recurrent endometrial cancer. For patients who achieved a durable benefit from dostarlimab, health-related QoL improvements reflect the corresponding alleviation of disease symptoms and complications.

Strengths and Weaknesses

The strengths of this study include the inclusion of patient-reported outcome analyses as prespecified secondary endpoints for the RUBY trial, high completion rates in both arms throughout, and the administration of validated questionnaires specific to oncology and endometrial cancer. Limitations of the analysis include the relatively small mismatch

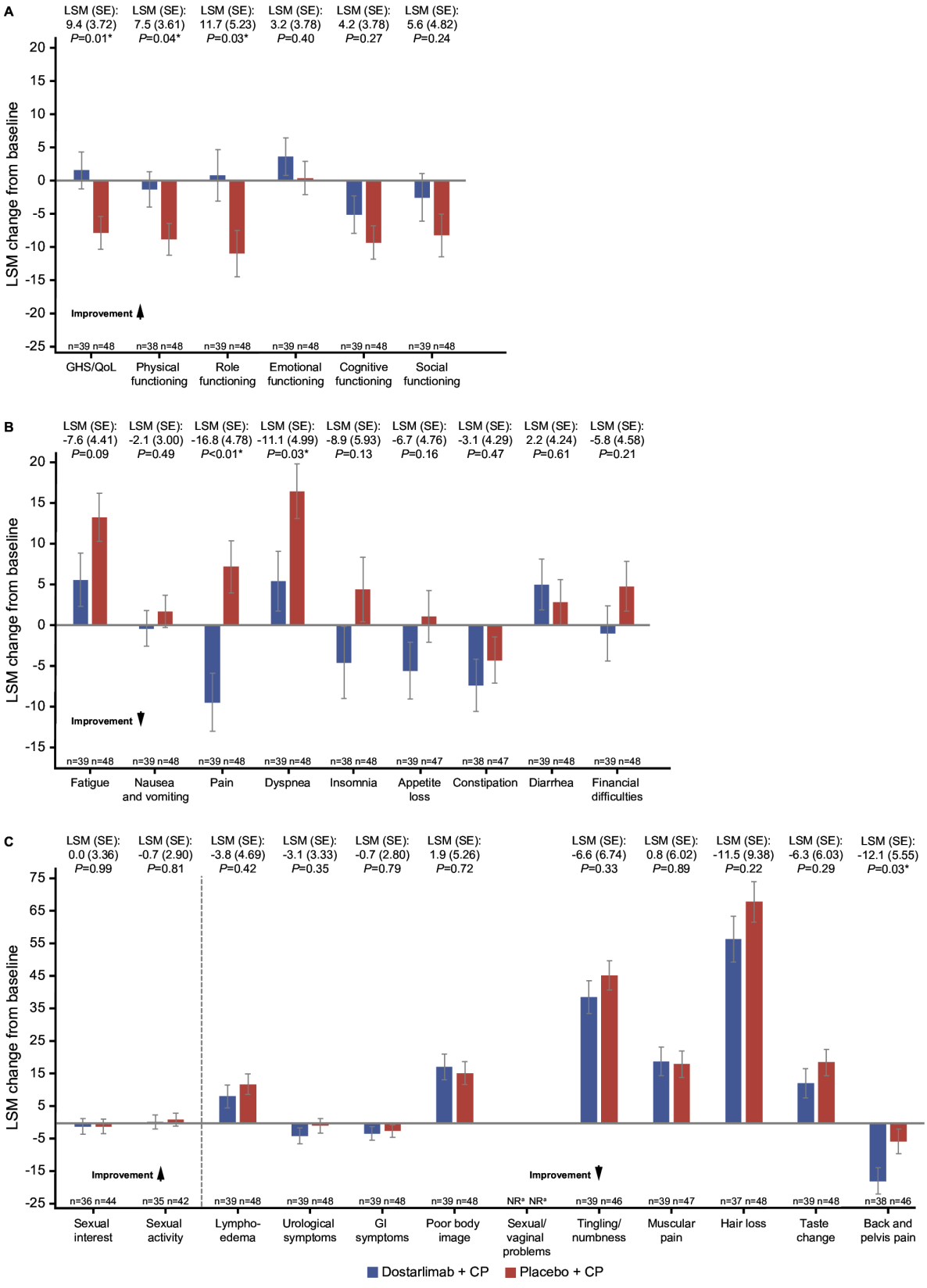

Figure 2 Least-squares mean change from baseline at cycle 7 for the (A) EORTC QLQ-C30 functional scales, (B) EORTC QLQ-C30 symptom scales, and (C) EORTC QLQ-EN24 scores. Error bars indicate standard error of the mean (SE). n indicates number of patients in each arm with completed item data at cycle 7. *Nominal between-arm significance. [a]Visits with fewer than three patients in either of the treatment arms were excluded from the analysis. CP, carboplatin–paclitaxel; EORTC, European Organisation for Research and Treatment of Cancer; GHS, global health scale; GI, gastrointestinal; LSM, least-squares mean; NR, not reported; QLQ-C30, Quality of Life Questionnaire Core 30; QLQ-EN24, Quality of Life Questionnaire-Endometrial Cancer Module; QoL, quality of life.

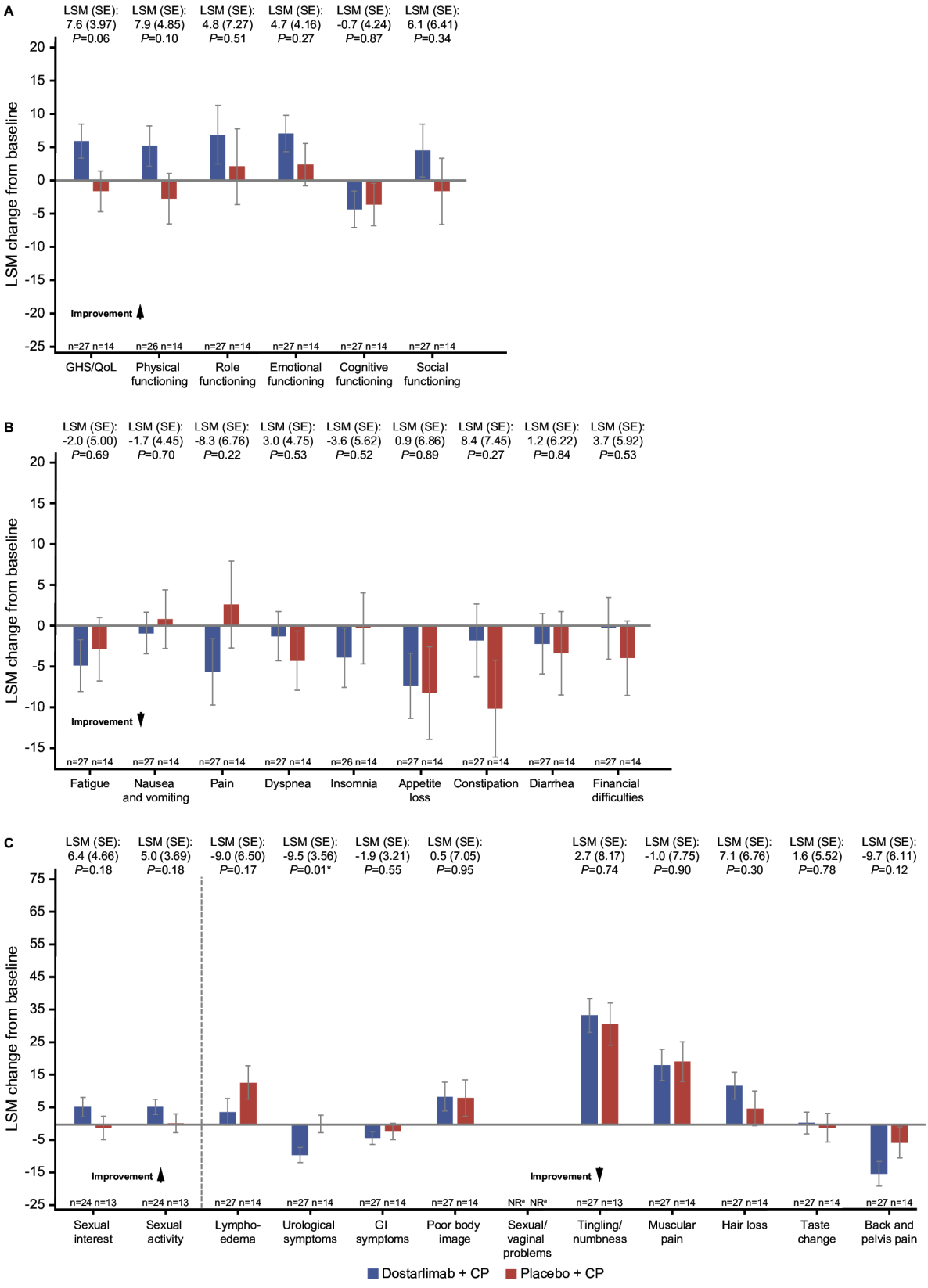

Figure 3 Least-squares mean change from baseline at cycle 13 for the (A) EORTC QLQ-C30 functional scales, (B) EORTC QLQ-C30 symptom scales, and (C) EORTC QLQ-EN24 scores, Error bars indicate standard error of the mean (SE). n indicates number of patients in each arm with completed item data at cycle 13. *Nominal between-arm significance. [a]Visits with fewer than three patients in either of the treatment arms were excluded from the analysis. CP, carboplatin–paclitaxel; EORTC, European Organisation for Research and Treatment of Cancer; GHS, global health scale; GI, gastrointestinal; LSM, least-squares mean; NR, not reported; QLQ-C30, Quality of Life Questionnaire Core 30; QLQ-EN24, Quality of Life Questionnaire Endometrial Cancer Module; QoL, quality of life.

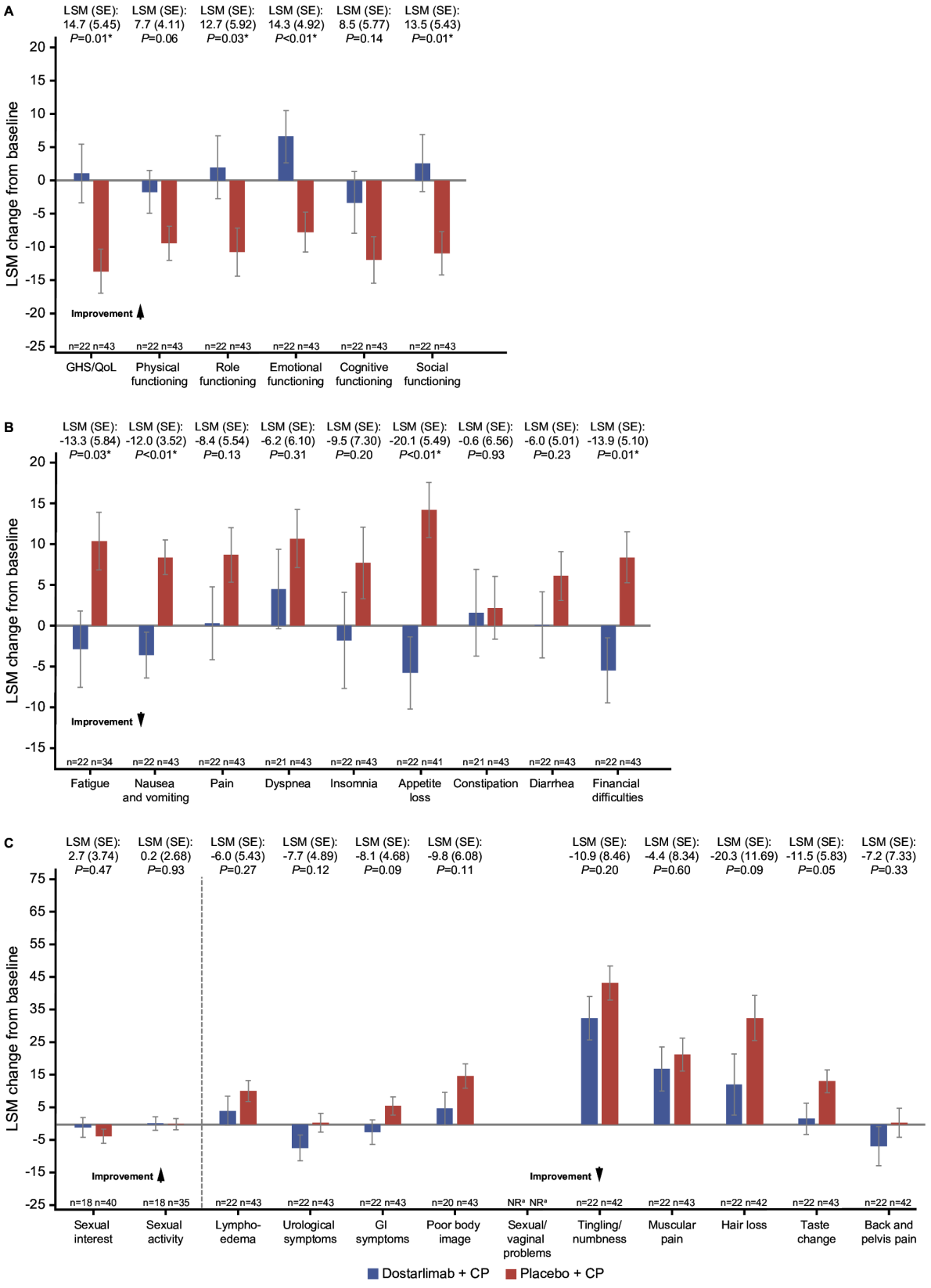

Figure 4 Least-squares mean change from baseline at end of treatment for the (A) EORTC QLQ-C30 functional scales, (B) EORTC QLQ-C30 symptom scales, and (C) EORTC QLQ-EN24 scores. Error bars indicate standard error of the mean (SE). n indicates number of patients in each arm with completed item data at end of treatment visit. *Nominal between-arm significance. [a]Visits with fewer than three patients in either of the treatment arms were excluded from the analysis. CP, carboplatin–paclitaxel; EORTC, European Organisation for Research and Treatment of Cancer; GHS, global health scale; GI, gastrointestinal; LSM, least-squares mean; QLQ-C30, Quality of Life Questionnaire Core 30; QLQ-EN24, Quality of Life Questionnaire-Endometrial Cancer Module; QoL, quality of life.

Table 1 Summary of changes from baseline in EORTC QLQ-C30 global QoL

	dMMR/MSI-H population	
	Dostarlimab (n=53)	Placebo (n=65)
Evaluable patients, n	51	64
Baseline score, mean (SD)	66.7 (25.91)	67.3 (23.93)
No. of patients at cycle 7	39	48
Change from baseline, mean (SD)	1.4 (23.33)	–6.0 (26.12)
Improved, n (%)	14 (35.9)	12 (25.0)
Stable, n (%)	15 (38.5)	16 (33.3)
Worsened, n (%)	10 (25.6)	20 (41.7)
No. of patients at cycle 13	27	14
Change from baseline, mean (SD)	9.2 (17.30)	–8.5 (15.86)
Improved, n (%)	12 (44.4)	2 (14.3)
Stable, n (%)	12 (44.4)	7 (50.0)
Worsened, n (%)	3 (11.1)	5 (35.7)
No. of patients at EOT	22	43
Change from baseline, mean (SD)	3.0 (19.42)	–11.1 (29.10)
Improved, n (%)	4 (18.2)	9 (20.9)
Stable, n (%)	14 (63.6)	13 (30.2)
Worsened, n (%)	4 (18.2)	21 (48.8)

dMMR, mismatch repair-deficient; EORTC, European Organisation for Research and Treatment of Cancer; EOT, end of treatment; MSI-H, microsatellite instability-high; QLQ-C30, Quality of Life Questionnaire Core 30; QoL, quality of life.

repair-deficient/microsatellite instability-high population and the risk of bias introduced over time based on patients who remained in the study, specifically that those patients with improved QoL may potentially remain on study longer than those with worsened QoL, which could skew later results, although it would be expected that this would affect both arms of the study. In addition, neither the EORTC QLQ-C30 nor the QLQ-EN24 are specifically designed for immunotherapy and may not adequately describe the specific QoL measurements impacted by long-term immunotherapy use.

Implications for Practice and Future Research

The RUBY trial previously reported progression-free survival and overall survival benefits with the addition of dostarlimab to carboplatin–paclitaxel, and a safety profile consistent with the known profiles of the individual drugs. Additionally, this report on patient-reported outcome assessments in the RUBY trial provides evidence that QoL data should be an integral part of cancer clinical trials because the assessments further characterize the patient experience.

CONCLUSIONS

The addition of dostarlimab to chemotherapy improved patient-reported outcomes in the mismatch repair-deficient/microsatellite instability-high population and maintained QoL in both the overall and mismatch repair-proficient/microsatellite-stable populations compared with the placebo+chemotherapy group. These data further support the use of dostarlimab+carboplatin–paclitaxel as a standard of care in patients with primary advanced or recurrent endometrial cancer.

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Patient-Reported Outcomes in the Subpopulation of Patients With Mismatch Repair Deficient/Microsatellite Instability–High Primary Advanced or Recurrent Endometrial Cancer Treated With Dostarlimab Plus Chemotherapy Compared With Chemotherapy Alone in the ENGOT-EN6-NSGO/GOG3031/RUBY trial

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Supplementary Material

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Supplementary Table 1. Patient-reported outcome assessments: domains and scoring.

Instrument	Domains assessed	Score	Higher score indicates
EORTC QLQ-C30[a]	**Global health status/QoL**	0–100	Better HRQoL
	Functional scales: physical, role, emotional, cognitive, social	0–100	Better functioning
	Symptoms: fatigue, nausea & vomiting, pain, dyspnea, insomnia, appetite loss, constipation, diarrhea, financial difficulties	0–100	Worse symptoms
EORTC QLQ-EN24[b]	**Functional scales**: sexual interest, sexual activity, sexual enjoyment	0–100	Better functioning
	Symptoms: lymphedema, urological, gastrointestinal, poor body image, vaginal, pain in back and pelvis, tingling/numbness, muscular pain, hair loss, taste change	0–100	Worse symptoms

[a]Aaronson NK, Ahmedzai S, Bergman B, et al. The European Organization for Research and Treatment of Cancer QLQ-C30: A quality-of-life instrument for use in international clinical trials in oncology. J Natl Cancer Inst. 1993;85(5):365-76.

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EORTC, European Organisation for Research and Treatment of Cancer; HRQoL, health-related quality of life; QLQ-C30, Quality of Life Questionnaire Core 30; QLQ-EN24, Quality of Life Questionnaire Endometrial Cancer Module; QoL, quality of life.

Supplementary Table 2. Summary of patient demographics and baseline characteristics.

	dMMR/MSI-H population	
Variable	**Dostarlimab + CP N=53**	**Placebo + CP N=65**
Age, median, (range) years	61 (45–81)	66 (39–85)
Race, n (%)		
White	44 (83.0)	56 (86.2)
Black	4 (7.5)	6 (9.2)
Asian	2 (3.8)	0
Other[a]	3 (5.7)	3 (4.6)
ECOG performance status, n (%)[b]		
0	28 (53.8)	39 (60.0)
1	24 (46.2)	26 (40.0)
BMI, median (range), kg/m^2	30.6 (20.1–54.4)	35.5 (17.9–58.1)
Disease status, n (%)		
Primary stage III	10 (18.9)	14 (21.5)
Primary stage IV	16 (30.2)	19 (29.2)
Recurrent	27 (50.9)	32 (49.2)
Prior treatment,n (%)		
Anticancer therapy	7 (13.2)	10 (15.4)
Anticancer surgery	49 (92.5)	60 (92.3)
External pelvic radiation	8 (15.1)	13 (20.0)
Histology, n (%)		
Endometrioid	44 (83.0)	56 (86.2)
Non-endometrioid[c]	9 (17.0)	9 (13.8)

[a]Includes patients identifying as American Indian or Alaska native, native Hawaiian or other Pacific Islander, unknown, or not reported. [b]Calculated based on patients with ECOG score available. [c]Includes carcinosarcoma, clear cell adenocarcinoma, mucinous adenocarcinoma, serous adenocarcinoma, undifferentiated carcinoma, mixed carcinoma (≥10% of carcinosarcoma, clear cell, or serous histology), and other.

BMI, body mass index; CP, carboplatin-paclitaxel; dMMR, mismatch repair deficient; ECOG, Eastern Cooperative Oncology Group; MSI-H, microsatellite instability-high.

Supplementary Table 3. Completion rates for each instrument.

Completion rate, n(%)	Baseline		Cycle 7		Cycle 13		End of treatment	
EORTC QLQ-C30	Dostarlimab +CP n=53	Placebo +CP n=65	Dostarlimab +CP n=40	Placebo +CP n=48	Dostarlimab +CP n=28	Placebo +CP n=14	Dostarlimab +CP n=28	Placebo +CP n=56
Global QoL	51 (96.2)	64 (98.5)	39 (97.5)	48 (100)	27 (96.4)	14 (100)	22 (78.6)	44 (78.6)
Functional Scales								
Physical	50 (94.3)	64 (98.5)	39 (97.5)	48 (100)	27 (96.4)	14 (100)	22 (78.6)	44 (78.6)
Role	51 (96.2)	64 (98.5)	39 (97.5)	48 (100)	27 (96.4)	14 (100)	22 (78.6)	44 (78.6)
Emotional	51 (96.2)	63 (96.9)	39 (97.5)	48 (100)	27 (96.4)	14 (100)	22 (78.6)	44 (78.6)
Cognitive	51 (96.2)	64 (98.5)	39 (97.5)	48 (100)	27 (96.4)	14 (100)	22 (78.6)	44 (78.6)
Social	51 (96.2)	63 (96.9)	39 (97.5)	48 (100)	27 (96.4)	14 (100)	22 (78.6)	44 (78.6)
Symptom Scales								
Fatigue	51 (96.2)	63 (96.9)	39 (97.5)	48 (100)	27 (96.4)	14 (100)	22 (78.6)	44 (78.6)
Pain	51 (96.2)	64 (98.5)	39 (97.5)	48 (100)	27 (96.4)	14 (100)	22 (78.6)	44 (78.6)
Nausea and vomiting	51 (96.2)	63 (96.9)	39 (97.5)	48 (100)	27 (96.4)	14 (100)	22 (78.6)	44 (78.6)
Dyspnea	51 (96.2)	63 (96.9)	39 (97.5)	48 (100)	27 (96.4)	14 (100)	21 (77.8)[b]	44 (78.6)
Appetite loss	51 (96.2)	62 (95.4)	39 (97.5)	48 (100)	27 (96.4)	14 (100)	22 (78.6)	43 (78.2)[c]
Insomnia	50 (94.3)	64 (98.5)	39 (97.5)	48 (100)	27 (96.4)	14 (100)	22 (78.6)	44 (78.6)
Constipation	50 (94.3)	63 (96.9)	39 (97.5)	47 (100)[d]	27 (96.4)	14 (100)	22 (78.6)	44 (78.6)
Diarrhea	51 (96.2)	64 (98.5)	39 (97.5)	48 (100)	27 (96.4)	14 (100)	22 (78.6)	44 (78.6)
Financial difficulty	51 (96.2)	63 (96.9)	39 (97.5)	48 (100)	27 (96.4)	14 (100)	22 (78.6)	44 (78.6)
EORTC QLQ-EN24	Dostarlimab +CP n=53	Placebo +CP n=65	Dostarlimab +CP n=40	Placebo +CP n=48	Dostarlimab +CP n=28	Placebo +CP n=14	Dostarlimab +CP n=28	Placebo +CP n=56
Functional Scales								
Sexual interest	51 (96.2)	61 (93.8)	36 (97.3)[e]	44 (100)[f]	24 (96.0)[g]	13 (100)[h]	18 (75.0)[i]	41 (77.4)[j]
Sexual activity	51 (96.2)	58 (89.2)	35 (97.2)[k]	44 (100)[f]	24 (96.0)[g]	13 (100)[h]	18 (75.0)[i]	38 (76.0)[l]
Sexual enjoyment	9 (17.0)	12 (18.5)	9 (90.0)[m]	11 (100)[n]	8 (88.9)[o]	2 (100)[p]	3 (33.3)[o]	9 (42.9)[q]
Symptom scales								
Lymphedema	51 (96.2)	64 (98.5)	39 (97.5)	48 (100)	27 (96.4)	14 (100)	22 (78.6)	44 (78.6)
Urological	51 (96.2)	63 (96.9)	39 (97.5)	48 (100)	27 (96.4)	14 (100)	22 (78.6)	44 (78.6)
Gastrointestinal	51 (96.2)	63 (96.9)	39 (97.5)	48 (100)	27 (96.4)	14 (100)	22 (78.6)	44 (78.6)
Poor body image	51 (96.2)	64 (98.5)	39 (97.5)	48 (100)	27 (96.4)	14 (100)	20 (76.9)[r]	44 (78.6)
Sexual/vaginal	10 (18.9)	12 (18.5)	9 (90.0)[m]	11 (100)[n]	8 (88.9)[o]	2 (100)[p]	3 (33.3)[o]	10 (45.5)[s]

Back and pelvis pain	51 (96.2)	61 (93.8)	38 (97.4)[t]	48 (100)	27 (96.4)	14 (100)	22 (78.6)	44 (78.6)
Tingling/numbness	51 (96.2)	61 (93.8)	39 (97.5)	48 (100)	27 (96.4)	13 (100)[h]	22 (78.6)	44 (78.6)
Muscular pain	51 (96.2)	63 (96.9)	39 (97.5)	47 (100)[d]	27 (96.4)	14 (100)	22 (78.6)	44 (78.6)
Hair loss	51 (96.2)	63 (96.9)	37 (97.4)[u]	48 (100)	27 (96.4)	14 (100)	22 (78.6)	43 (78.2)[c]
Taste change	51 (96.2)	63 (96.9)	39 (97.5)	48 (100)	27 (96.4)	14 (100)	22 (78.6)	44 (78.6)

[a]Percentages were calculated based on the number of questionnaires completed that met the minimum for scoring of the instruments per the number of patients expected to complete the questionnaire at that specific visit. Percent calculations based on a denominator (patients expected to complete) of [b]n=27, [c]n=55, [d]n=47, [e]n=37, [f]n=44, [g]n=25, [h]n=13, [i]n=24, [j]n=53, [k]n=36, [l]n=50, [m]n=10, [n]n=11, [o]n=9, [p]n=2, [q]n=21, [r]n=26, [s]n=22, [t]n=39; [u]n=38.

CP, carboplatin-paclitaxel; dMMR, mismatch repair deficient; EORTC, European Organisation for Research and Treatment of Cancer; MSI-H, microsatellite instability–high; QLQ-C30, Quality of Life Questionnaire Core 30; QLQ-EN24, Quality of Life Questionnaire Endometrial Cancer Module; QoL, quality of life.

Supplementary Table 4. Overall least square mean change from baseline in the overall and MMRp/MSS populations

	Overall		MMRp/MSS	
LSM change from baseline (SE)	Dostarlimab +CP N=231	Placebo + CP N=238	Dostarlimab +CP N=182	Placebo +CP N=176
EORTC QLQ-C30				
Global QoL	−0.1 (0.94)	−0.6 (1.05)	−1.1 (1.05)	0.7 (1.14)
	0.5 (1.42) *P*=0.724		−1.8 (1.56) *P*=0.242	
Physical functioning	−3.7 (0.96)	−3.0 (1.01)	−5.3 (1.21)	−3.3 (1.40)
	−0.7 (1.39) *P*=0.628		−1.9 (1.74) *P*=0.271	
Role functioning	−3.2 (1.56)	−1.5 (1.85)	−6.1 (1.58)	−1.6 (1.81)
	−1.7 (2.26) *P*=0.450		−4.5 (2.44) *P*=0.068	
Emotional functioning	2.3 (0.97)	4.0 (1.05)	1.8 (1.04)	3.9 (1.11)
	−1.7 (1.44) *P*=0.232		−2.1 (1.54) *P*=0.175	
Cognitive functioning	−5.4 (1.06)	−4.2 (1.21)	−6.2 (1.16)	−4.1 (1.29)
	−1.3 (1.59) *P*=0.425		−2.0 (1.73) *P*=0.237	
Social functioning	−1.8 (1.39)	−0.9 (1.62)	−3.3 (1.46)	−0.1 (1.56)
	−0.9 (2.05) *P*=0.655		−3.2 (2.15) *P*=0.139	
Fatigue	2.9 (1.18)	2.7 (1.32)	4.1 (1.36)	2.4 (1.52)
	0.2 (1.75) *P*=0.912		1.8 (2.02) *P*=0.383	
Nausea and vomiting	0.5 (0.71)	−0.5 (0.80)	0.5 (0.82)	−1.4 (0.90)
	1.1 (1.06) *P*=0.318		1.9 (1.21) *P*=0.113	
Pain	−0.9 (1.45)	0.1 (1.77)	1.4 (1.40)	0.4 (1.57)
	−1.0 (1.99) *P*=0.622		1.1 (2.11) *P*=0.617	
Dyspnea	3.8 (1.11)	4.7 (1.21)	4.8 (1.27)	3.9 (1.33)
	−0.9 (1.62) *P*=0.580		0.9 (1.84) *P*=0.623	
Insomnia	−6.4 (1.65)	−8.4 (1.66)	−7.6 (1.45)	−10.0 (1.57)

	2.0 (2.47) *P*=0.248		2.4 (2.13) *P*=0.257	
Appetite loss	−2.9 (1.21)	−3.6 (1.41)	−2.9 (1.20)	−2.8 (1.32)
	0.7 (1.91) *P*=0.716		−0.1 (1.84) *P*=0.969	
Constipation	−0.7 (1.18)	−2.3 (1.40)	1.7 (1.34)	−2.0 (1.51)
	1.6 (1.84) *P*=0.374		3.7 (2.02) *P*=0.066	
Diarrhea	3.3 (0.83)	1.4 (0.90)	2.4 (0.86)	1.1 (0.91)
	1.8 (1.23) *P*=0.134		1.3 (1.25) *P*=0.300	
Financial difficulties	−0.4 (1.22)	−1.9 (1.35)	0.5 (1.31)	−2.7 (1.38)
	1.5 (1.83) *P*=0.405		3.2 (1.92) *P*=0.099	
EORTC QLQ-EN24				
Sexual interest	0.3 (0.98)	3.4 (1.06)	−0.5 (1.11)	3.6 (1.18)
	−3.0 (1.45) *P*=0.038*		−4.1 (1.63) *P*=0.012*	
Sexual activity	1.7 (0.86)	2.1 (0.90)	0.1 (0.95)	1.8 (0.99)
	−0.4 (1.26) *P*=0.761		−1.6 (1.38) *P*=0.245	
Sexual enjoyment	−0.7 (3.88)	−1.2 (4.42)	−1.8 (4.26)	−2.9 (4.16)
	0.5 (5.89) *P*=0.939		1.2 (5.99) *P*=0.847	
Lymphedema	5.9 (1.15)	6.5 (1.23)	6.8 (1.30)	5.4 (1.41)
	−0.6 (1.70) *P*=0.724		1.4 (1.94) *P*=0.475	
Urological symptoms	−2.7 (0.84)	−1.3 (0.88)	−1.7 (0.94)	−0.8 (1.01)
	−1.5 (1.21) *P*=0.223		−0.9 (1.39) *P*=0.512	
Gastrointestinal symptoms	−1.2 (0.64)	−1.1 (0.71)	−1.0 (0.76)	−1.5 (0.86)
	−0.1 (0.95) *P*=0.881		0.5 (1.07) *P*=0.645	
Poor body image	9.0 (1.46)	5.7 (1.47)	9.2 (1.68)	5.0 (1.74)
	3.3 (2.07) *P*=0.111		4.2 (2.42) *P*=0.082	
Sexual/vaginal problems	6.3 (2.71)	2.0 (3.52)	6.2 (3.09)	2.2 (3.24)
	4.3 (4.43) *P*=0.328		4.0 (4.49) *P*=0.381	

Back and pelvis pain	−4.1 (1.34)	−2.6 (1.50)	−1.7 (1.49)	−1.1 (1.63)
	−1.5 (2.06) *P*=0.462		−0.6 (2.21) *P*=0.777	
Tingling/numbness	31.3 (1.74)	26.0 (1.83)	31.5 (2.10)	23.8 (2.24)
	5.3 (2.53) *P*=0.036*		7.7 (3.13) *P*=0.014*	
Muscular pain	14.9 (1.37)	12.8 (1.47)	14.5 (1.54)	11.8 (1.70)
	2.1 (1.98) *P*=0.289		2.7 (2.30) *P*=0.236	
Hair loss	22.5 (1.39)	21.3 (1.48)	21.8 (2.16)	20.6 (2.29)
	1.2 (2.03) *P*=0.569		1.2 (3.17) *P*=0.694	
Taste change	9.6 (1.63)	7.6 (1.60)	10.7 (1.73)	8.2 (1.85)
	2.0 (2.33) *P*=0.418		2.5 (2.57) *P*=0.336	

*Denotes nominally significant difference between arms.

CP, carboplatin-paclitaxel; LSM, least squares mean; MMRp, mismatch repair proficient; MSS, microsatellite stable; QoL, quality of life; SE, standard error.

Supplementary Figure 1. Formulas for linear transformation of (A) EORTC QLQ-C30 and (B) QLQ-EN24 scores[a,b]

A.

Raw score

$$RS = \frac{(I_1 + I_2 + \cdots + I_n)}{n}$$

Linear transformation: functional scales[c]

$$S = \left\{1 - \frac{(RS-1)}{range}\right\} * 100$$

Linear transformation: symptom scales / items[c]

$$S = \left\{\frac{(RS-1)}{range}\right\} * 100$$

Linear transformation: global health status / HRQoL[c]

$$S = \left\{\frac{(RS-1)}{range}\right\} * 100$$

B.

Raw Score[d]

$$RS = \frac{(I_1 + I_2 + \cdots + I_n)}{n}$$

Linear transformation: symptom and functional scales/items[c]

$$S = \left\{\frac{(RS-1)}{range}\right\} * 100$$

[a]Fayers PM, Aaronson NK, Bjordal K, et al, on behalf of the EORTC Quality of Life Group. The EORTC QLQ-C30 Scoring Manual (3rd Edition). Published by: European Organisation for Research and Treatment of Cancer, Brussels 2001.

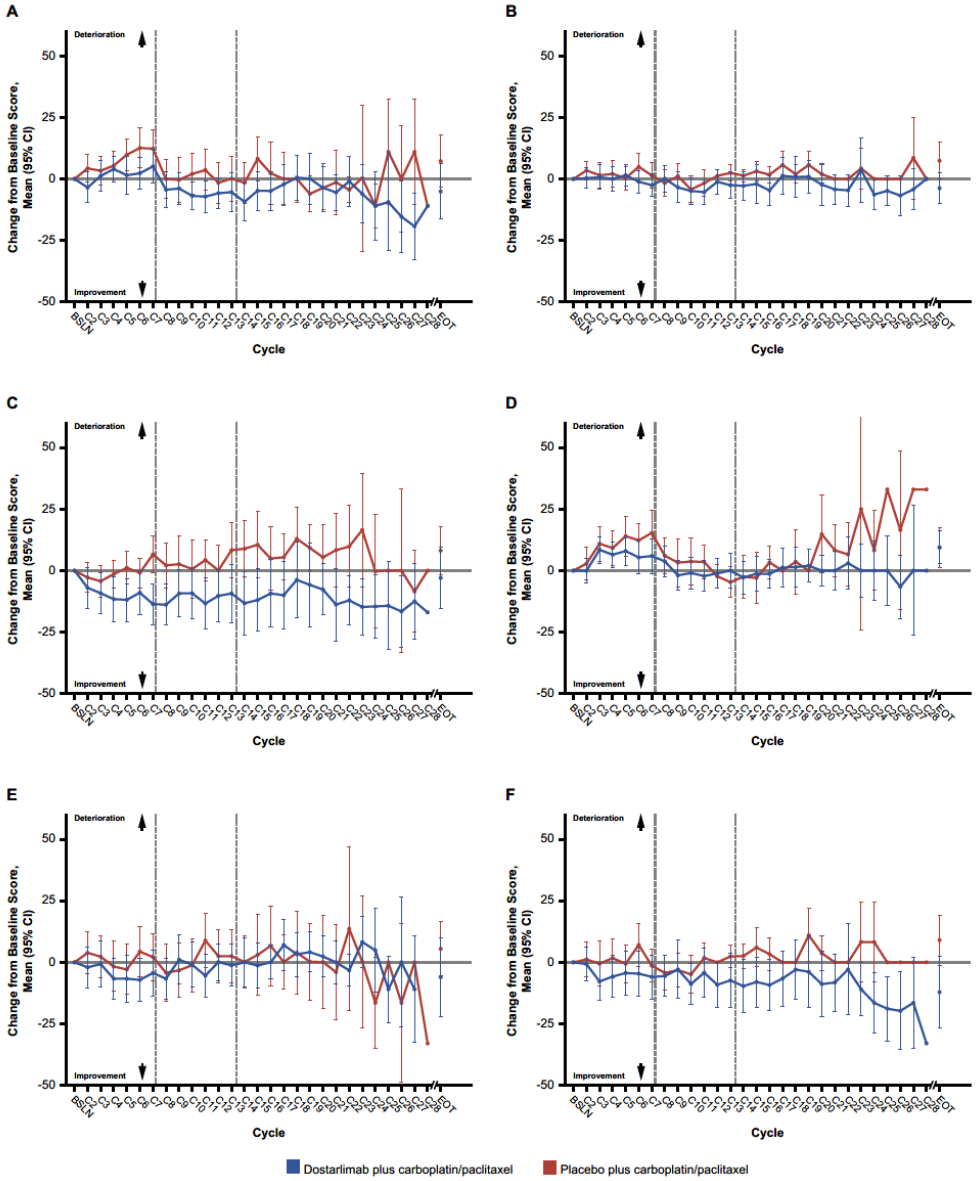
[b]Greimel E, Nordin A, Lanceley A, et al. Psychometric validation of the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Endometrial Cancer Module (EORTC QLQ-EN24). European Journal of Cancer. 2011;47(2):183-190.

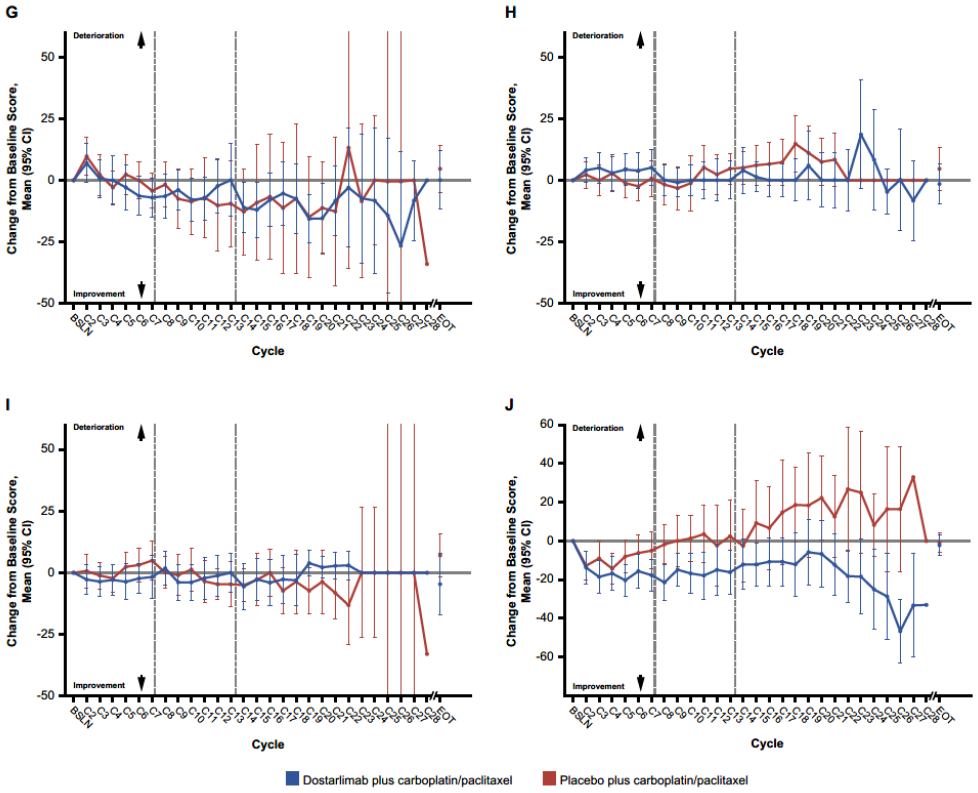
[c]Range is the difference between the maximum possible value of RS and the minimum possible value.

[d]For the EORTC QLQ-EN24, for each single-item measure, the score of the item corresponds to the raw score.

EORTC, European Organisation for Research and Treatment of Cancer; I, item; QLQ-C30, Quality of Life Questionnaire Core 30; QLQ-EN24, Quality of Life Questionnaire Endometrial Cancer Module. RS, raw score; S, score.

Supplementary Figure 2. Mean change from baseline in PRO scores for symptom scales in the dMMR/MSI-H population. (A) QLQ-C30 fatigue; (B) QLQ-C30 nausea and vomiting; (C) QLQ-C30 pain; (D) QLQ-C30 dyspnea; (E) QLQ-C30 insomnia; (F) QLQ-C30 appetite loss; (G) QLQ-C30 constipation; (H) QLQ-C30 diarrhea; (I) QLQ-C30 financial difficulties; (J) QLQ-EN24 pain in back and pelvis





Error bars indicate 95% CIs.

BSLN, baseline; CP, carboplatin-paclitaxel; dMMR, mismatch repair deficient; EORTC, European Organisation for Research and Treatment of Cancer; EOT, end of treatment; MSI-H, microsatellite instability–high; PRO, patient-reported outcome; QLQ-C30, Quality of Life Questionnaire Core 30; QLQ-EN24, Quality of Life Questionnaire Endometrial Cancer Module.