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Dostarlimab for primary advanced or recurrent endometrial cancer

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ORIGINAL ARTICLE

Dostarlimab for Primary Advanced or Recurrent Endometrial Cancer

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ABSTRACT

BACKGROUND

Dostarlimab is an immune-checkpoint inhibitor that targets the programmed cell death 1 receptor. The combination of chemotherapy and immunotherapy may have synergistic effects in the treatment of endometrial cancer.

METHODS

We conducted a phase 3, global, double-blind, randomized, placebo-controlled trial. Eligible patients with primary advanced stage III or IV or first recurrent endometrial cancer were randomly assigned in a 1:1 ratio to receive either dostarlimab (500 mg) or placebo, plus carboplatin (area under the concentration–time curve, 5 mg per milliliter per minute) and paclitaxel (175 mg per square meter of body-surface area), every 3 weeks (six cycles), followed by dostarlimab (1000 mg) or placebo every 6 weeks for up to 3 years. The primary end points were progression-free survival as assessed by the investigator according to Response Evaluation Criteria in Solid Tumors (RECIST), version 1.1, and overall survival. Safety was also assessed.

RESULTS

Of the 494 patients who underwent randomization, 118 (23.9%) had mismatch repair–deficient (dMMR), microsatellite instability–high (MSI-H) tumors. In the dMMR–MSI-H population, estimated progression-free survival at 24 months was 61.4% (95% confidence interval [CI], 46.3 to 73.4) in the dostarlimab group and 15.7% (95% CI, 7.2 to 27.0) in the placebo group (hazard ratio for progression or death, 0.28; 95% CI, 0.16 to 0.50; P<0.001). In the overall population, progression-free survival at 24 months was 36.1% (95% CI, 29.3 to 42.9) in the dostarlimab group and 18.1% (95% CI, 13.0 to 23.9) in the placebo group (hazard ratio, 0.64; 95% CI, 0.51 to 0.80; P<0.001). Overall survival at 24 months was 71.3% (95% CI, 64.5 to 77.1) with dostarlimab and 56.0% (95% CI, 48.9 to 62.5) with placebo (hazard ratio for death, 0.64; 95% CI, 0.46 to 0.87). The most common adverse events that occurred or worsened during treatment were nausea (53.9% of the patients in the dostarlimab group and 45.9% of those in the placebo group), alopecia (53.5% and 50.0%), and fatigue (51.9% and 54.5%). Severe and serious adverse events were more frequent in the dostarlimab group than in the placebo group.

CONCLUSIONS

Dostarlimab plus carboplatin–paclitaxel significantly increased progression-free survival among patients with primary advanced or recurrent endometrial cancer, with a substantial benefit in the dMMR–MSI-H population. (Funded by GSK; RUBY ClinicalTrials.gov number, NCT03981796.)

The authors' full names, academic degrees, and affiliations are listed in the Appendix. Dr. Mirza can be contacted at mansoor@rh.regionh.dk or at the Department of Oncology, Rigshospitalet, Copenhagen University Hospital, Department of Cancer Treatment–5073, Blegdamsvej 9, 2100 Copenhagen, Denmark.

*A list of the RUBY investigators is provided in the Supplementary Appendix, available at NEJM.org.

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Endometrial cancer is the sixth most common cancer among women worldwide and the second most common type of gynecologic cancer.[1-5] Carboplatin plus paclitaxel is standard chemotherapy for first-line treatment of primary advanced or recurrent endometrial cancer; however, long-term outcomes remain poor, with median overall survival of less than 3 years.[6-9]

Mismatch repair–deficient (dMMR), microsatellite instability–high (MSI-H) tumors account for 25 to 30% of endometrial cancers.[10-12] Increased expression of programmed cell death 1 (PD-1) receptor and its ligands (PD-L1 and PD-L2) and the high tumor mutational burden associated with dMMR–MSI-H tumors make them potentially susceptible to anti–PD-1 and anti–PD-L1 therapies.[10,13,14]

Dostarlimab is an active immune-checkpoint inhibitor targeting the PD-1 receptor.[15] On the basis of the results of the GARNET trial,[16,17] dostarlimab was approved in the European Union for dMMR–MSI-H advanced or recurrent endometrial cancer[18] and in the United States for dMMR advanced solid tumors.[19] Data from the GARNET trial also support durable antitumor activity in patients with mismatch repair–proficient (pMMR), microsatellite-stable (MSS) tumors, although responses were less common than among patients with dMMR–MSI-H tumors.[17]

Cytotoxic chemotherapy can produce immunomodulatory effects, such as disruption of immunosuppressive pathways and enhanced cytotoxic T-cell response.[20] Thus, the combination of chemotherapy and immunotherapy may have synergistic effects in the tumor microenvironment.[21-25] Clinical benefits, including improved survival, have been reported with this combination in several cancer types.[26-32]

In the ENGOT-EN-6-NSGO/GOG-3031/RUBY trial, we evaluated the efficacy and safety of dostarlimab in combination with carboplatin and paclitaxel as compared with placebo plus carboplatin and paclitaxel in patients with primary advanced or recurrent endometrial cancer.

Methods

Patients

We enrolled patients who were at least 18 years of age and had histologically or cytologically confirmed primary advanced or recurrent (International Federation of Gynecology and Obstetrics [FIGO] stage III or IV) endometrial cancer that was not amenable to curative therapy. Patients were required to have met 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; or disease that either was in its first recurrence and had not been treated with systemic therapy or had been treated with neoadjuvant or adjuvant systemic therapy and had recurred or progressed at least 6 months after completion of treatment (first recurrence). Tumor samples that were sufficient for the assessment of MMR and microsatellite status were required. The full list of eligibility and exclusion criteria is provided in the protocol, available with the full text of this article at NEJM.org.

Trial Design and Treatment

This trial is a phase 3, 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 per milliliter per minute and paclitaxel at a dose of 175 mg per square meter of body-surface area intravenously every 3 weeks for the first six 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 decision to withdraw the patient, or death. Given this dosing regimen, cycle 7 day 1 would be considered the end of the chemotherapy period.

Patients underwent randomization on the basis of local or central MMR and MSI testing. Central testing was used when local results were not available (additional details are provided in the Supplementary Appendix, available at NEJM.org). The primary analysis of progression-free survival in the dMMR–MSI-H population was performed in the population with source verification of MMR–MSI status. A post hoc sensitivity analysis

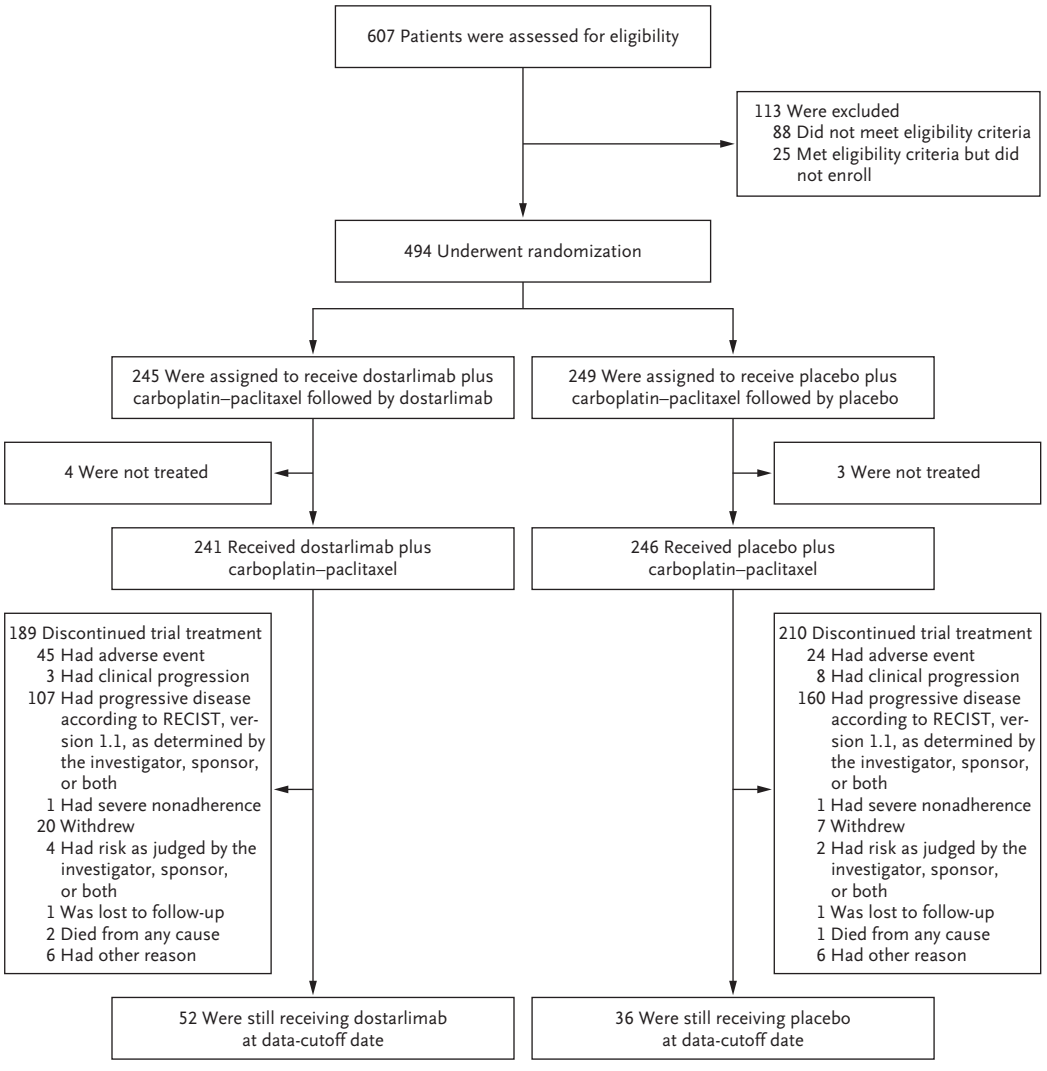


Figure 1. Enrollment and Randomization.

RECIST denotes Response Evaluation Criteria in Solid Tumors.

was performed in the dMMR–MSI-H population that was based on MMR–MSI status at randomization.

Randomization was performed in a blinded manner with an interactive Web response system and stratified according to MMR–MSI status (dMMR–MSI-H or pMMR–MSS), previous external pelvic radiotherapy (yes or no), and disease status (recurrent, primary stage III, or primary stage IV). Guidelines for dose modification, interruption, and discontinuation are provided in the protocol.

ASSESSMENTS

Imaging assessments during the treatment period (computed tomography or magnetic resonance imaging) were performed every 6 weeks (±7 days) from randomization until week 25 (cycle 8), followed by every 9 weeks (±7 days) until week 52. Subsequent imaging was performed every 12 weeks (±7 days) until radiographic progressive disease was documented by investigator assessment in accordance with RECIST, version 1.1, followed by one additional imaging assessment 4 to 6 weeks later, or until subsequent anti-

Table 1. Demographic and Clinical Characteristics of the Patients at Baseline.*

Characteristic	dMMR–MSI-H Population		Overall Population	
	Dostarlimab (N=53)	Placebo (N=65)	Dostarlimab (N=245)	Placebo (N=249)
Age				
Median (range) — yr	61 (45–81)	66 (39–85)	64 (41–81)	65 (28–85)
≥65 Yr — no. (%)	23 (43)	35 (54)	118 (48.2)	135 (54.2)
Race or ethnic group — no. (%)†				
White	44 (83)	56 (86)	189 (77.1)	191 (76.7)
Black	4 (8)	6 (9)	28 (11.4)	31 (12.4)
Asian	2 (4)	0	7 (2.9)	8 (3.2)
American Indian or Alaska Native	0	1 (2)	1 (0.4)	1 (0.4)
Native Hawaiian or other Pacific Islander	1 (2)	0	1 (0.4)	0
Unknown or not reported	2 (4)	2 (3)	19 (7.8)	18 (7.2)
ECOG performance category — no./total no. (%)‡				
0	28/52 (54)	39/65 (60)	145/241 (60.2)	160/246 (65.0)
1	24/52 (46)	26/65 (40)	96/241 (39.8)	86/246 (35.0)
FIGO stage at diagnosis — no. (%)§				
I	18 (34)	22 (34)	65 (26.5)	71 (28.5)
II	3 (6)	5 (8)	13 (5.3)	13 (5.2)
III	14 (26)	20 (31)	75 (30.6)	65 (26.1)
IV	14 (26)	15 (23)	72 (29.4)	84 (33.7)
Unknown	4 (8)	3 (5)	20 (8.2)	16 (6.4)
Disease status — no. (%)				
Primary stage III	10 (19)	14 (22)	45 (18.4)	47 (18.9)
Primary stage IV	16 (30)	19 (29)	83 (33.9)	83 (33.3)
Recurrent	27 (51)	32 (49)	117 (47.8)	119 (47.8)
Median BMI (range)¶	30.6 (20.1–54.4)	35.5 (17.9–58.1)	30.8 (17.6–60.6)	32.8 (17.7–68.0)
Histologic type — no. (%)				
Carcinosarcoma	4 (8)	1 (2)	25 (10.2)	19 (7.6)
Endometrioid	44 (83)	56 (86)	134 (54.7)	136 (54.6)
Mixed carcinoma ≥10% of carcinosarcoma, clear-cell, or serous histologic type	2 (4)	4 (6)	10 (4.1)	9 (3.6)
Serous adenocarcinoma	1 (2)	1 (2)	50 (20.4)	52 (20.9)
Clear-cell adenocarcinoma	0	0	8 (3.3)	9 (3.6)
Mucinous adenocarcinoma	0	0	0	1 (0.4)
Undifferentiated carcinoma	0	0	1 (0.4)	2 (0.8)
Other	2 (4)	3 (5)	17 (6.9)	21 (8.4)
MMR–MSI status — no. (%)				
dMMR–MSI-H	53 (100)	65 (100)	53 (21.6)	65 (26.1)
pMMR–MSS	0	0	192 (78.4)	184 (73.9)

Table 1. (Continued.)

Characteristic	dMMR–MSI-H Population		Overall Population	
	Dostarlimab (N=53)	Placebo (N=65)	Dostarlimab (N=245)	Placebo (N=249)
Previous external pelvic radiotherapy — no./total no. (%)				
Yes	8 (15)	13 (20)	41 (16.7)	45 (18.1)
No	45 (85)	52 (80)	204 (83.3)	204 (81.9)

* Percentages may not total 100 because of rounding. The abbreviation dMMR denotes mismatch repair–deficient, MMR mismatch repair, MSI microsatellite instability, MSI-H microsatellite instability–high, MSS microsatellite stable, and pMMR mismatch repair–proficient.
† Race and ethnic group were reported by the patients.
‡ Eastern Cooperative Oncology Group (ECOG) performance-status scores range from 0 to 5, with higher scores indicating greater disability.
§ International Federation of Gynecology and Obstetrics (FIGO) stages indicate whether and the extent to which the cancer has spread outside the uterus, with higher stage numbers indicating more extensive spread.
¶ The body-mass index (BMI) is the weight in kilograms divided by the square of the height in meters. Data were missing for 1 patient in the dostarlimab group in the dMMR–MSI-H population, 5 patients in the dostarlimab group in the overall population, and 3 patients in the placebo group in the overall population.

cancer therapy was started, whichever occurred first.

END POINTS

The primary end points were progression-free survival as assessed by the investigator according to RECIST, version 1.1, among patients who had dMMR–MSI-H primary advanced or recurrent endometrial cancer and in the overall population and overall survival in the overall population. Both primary end points were evaluated in time-to-event analyses. Progression-free survival was defined as the time from randomization to the earliest date of radiographic assessment of progressive disease (according to RECIST, version 1.1) or death from any cause in the absence of progressive disease, whichever occurred first. Tumor response was evaluated with the use of RECIST, version 1.1. Overall survival was defined as the time from randomization to the date of death from any cause.

Secondary end points included progression-free survival as determined by blinded independent central review, objective response, disease control, response duration, time to second progressive disease, patient-reported outcomes (scores on the European Organization for Research and Treatment of Cancer [EORTC] Core Quality of Life Questionnaire [QLQ-C30], the EORTC Quality of Life Questionnaire Endometrial Cancer [QLQ-EN24], and the EuroQoL 5-Dimensions 5-Level [EQ-5D-5L] instruments), and pharmacokinetic and immunogenicity analyses. Safety was assessed through monitoring of adverse events, laboratory testing, measurement of vital signs, and physical examination.

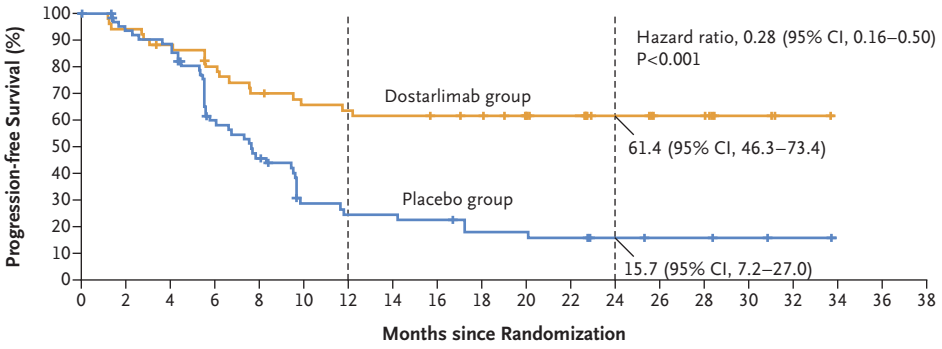
TRIAL OVERSIGHT

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. 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. Authors had full access to trial data, wrote the manuscript, attest to the accuracy and completeness of data, confirm adherence of the trial to the protocol, and made the final decision to submit the manuscript for publication. Medical writing assistance with the submitted manuscript was funded by GSK.

STATISTICAL ANALYSIS

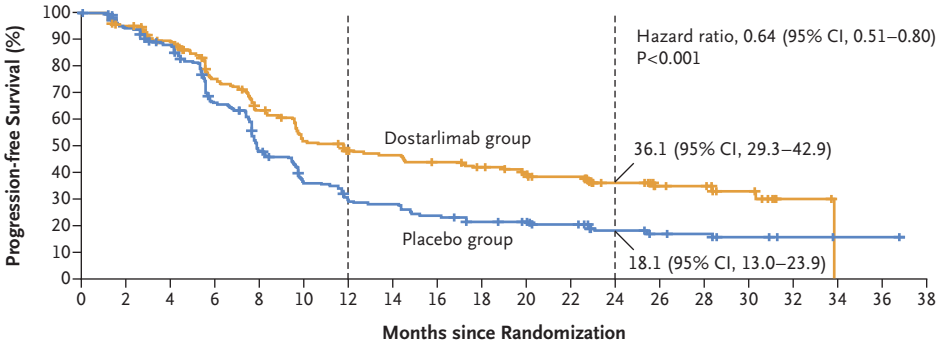
The graphical method was used for multiplicity control of multiple hypotheses of primary end

A dMMR–MSI-H Population



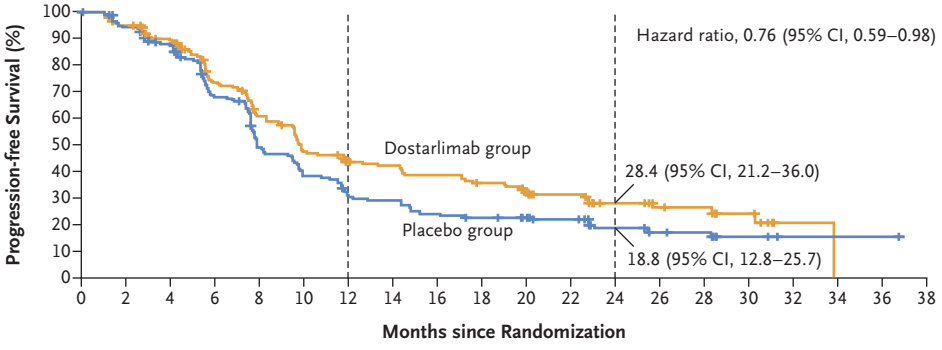
No. at Risk																		
Dostarlimab group	53	48	44	39	34	31	30	29	28	27	25	19	13	9	9	4	1	0
Placebo group	65	57	54	34	26	14	12	12	11	8	8	7	4	3	3	2	1	0
No. of Events																		
Dostarlimab group	0	3	6	10	15	17	18	19	19	19	19	19	19	19	19	19	19	19
Placebo group	0	4	7	24	32	41	43	43	44	46	46	47	47	47	47	47	47	47

B Overall Population



No. at Risk																			
Dostarlimab group	245	220	197	157	130	105	94	90	84	78	66	52	34	23	22	12	2	0	
Placebo group	249	219	200	144	103	74	59	57	48	42	39	32	20	14	13	5	2	1	1	0
No. of Events																			
Dostarlimab group	0	12	25	55	80	103	110	113	118	122	127	128	131	132	132	133	134	135	
Placebo group	0	14	29	77	115	141	155	157	166	170	170	172	175	176	176	177	177	177	177	177

C pMMR–MSS Population



No. at Risk																		
Dostarlimab group	192	172	153	118	96	74	64	61	56	51	41	33	21	14	13	8	1	0
Placebo group	184	162	146	110	77	60	47	45	37	34	31	25	16	11	10	3	1	1	1	0
No. of Events																		
Dostarlimab group	0	9	19	45	65	86	92	94	99	103	108	109	112	113	113	114	115	116	
Placebo group	0	10	22	53	83	100	112	114	122	124	124	125	128	129	129	130	130	130	130	130

Figure 2 (facing page). Progression-free Survival as Assessed by the Investigator According to RECIST, Version 1.1.

Shown are Kaplan–Meier estimates of progression-free survival in the population with mismatch repair–deficient (dMMR), microsatellite instability–high (MSI-H) disease (Panel A), the overall population (Panel B), and the population with mismatch repair–proficient (pMMR), microsatellite-stable (MSS) disease (Panel C). In all three panels, tick marks indicate censored data.

points (Fig. S1 in the Supplementary Appendix),[33] and family-wise one-sided type I error (alpha) was controlled at 0.025. On the basis of the graphical method, an alpha level of 0.02 was initially allocated to hypotheses regarding progression-free survival by investigator assessment and an alpha level of 0.005 was initially allocated to hypotheses regarding overall survival. For progression-free survival, hypotheses were hierarchically tested in the dMMR–MSI-H population and then in the overall population; overall survival was tested in the overall population. If the null hypotheses for progression-free survival were all rejected, the 0.02 alpha level would be recycled to the hypothesis of overall survival, which would be tested at a one-sided alpha level of 0.025; otherwise, overall survival would be tested only at the initially allocated one-sided alpha level of 0.005.

The sample size was driven by the analysis of the primary end point of progression-free survival as determined by investigator assessment. A planned enrollment of approximately 470 patients in the overall population would include approximately 118 patients with dMMR–MSI-H tumors and would provide a power of approximately 89% to detect a significant difference in progression-free survival between the treatment groups at a one-sided alpha level of 0.02 among patients with dMMR–MSI-H tumors. The sample size and power calculation corresponded to an assumed hazard ratio for disease progression or death of 0.50, with one interim analysis planned for when approximately 77 events had occurred and the final analysis planned for when 91 events had occurred in the dMMR–MSI-H population.

The 95% confidence intervals of the hazard ratios reported were based on the Cox regression model and were not used for hypothesis testing. All P values reported were based on the stratified log-rank test. Additional details regarding the multiplicity-control strategy, sample-size determination, and statistical analysis are provided in the Supplementary Appendix, protocol, and statistical analysis plan (available with the protocol).

RESULTS

PATIENTS

From July 18, 2019, through February 23, 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 and paclitaxel (dostarlimab group) and 249 were assigned to receive placebo plus carboplatin and paclitaxel (placebo group). Seven patients (4 in dostarlimab group and 3 in the placebo group) did not receive treatment and were excluded from the safety analysis. Of the 494 patients who underwent randomization, 118 had dMMR–MSI-H tumors confirmed by source-verified classification (53 in the dostarlimab group and 65 in the placebo group). As of the data-cutoff date of September 28, 2022, a total of 88 patients in the overall population were receiving treatment in one of the two groups (Fig. 1).

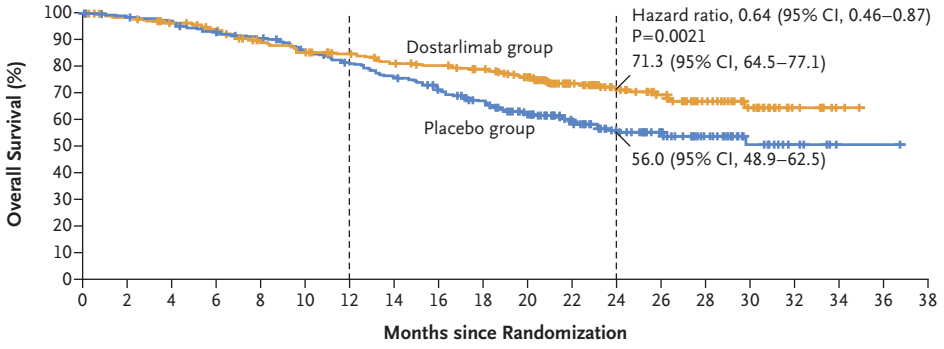
No substantial between-group differences were noted in the demographic and clinical characteristics of patients in the dMMR–MSI-H population or in the overall population (Table 1). The demographic characteristics of the patients were generally representative of patients with primary advanced or recurrent endometrial cancer (Table S1). In the overall population, 18.6% of the patients had primary stage III, 33.6% had primary stage IV, and 47.8% had recurrent disease. In total, 54.7%, 20.6%, and 8.9% of the patients had a diagnosis of endometrioid carcinoma, serous adenocarcinoma, and carcinosarcoma, respectively. Most patients (82.6%) had not previously received external pelvic radiation.

No differences were seen between the treatment groups with respect to carboplatin or paclitaxel infusion interruptions, infusion delays, missed infusions, or dose reductions (Table S2). Details of the duration of overall treatment (Table S3) and subsequent therapies (Table S4) are provided in the Supplementary Appendix.

EFFICACY

As of the data cutoff date, in the dMMR–MSI-H population, 19 patients (36%) in the dostarlimab group and 47 patients (72%) in the placebo group

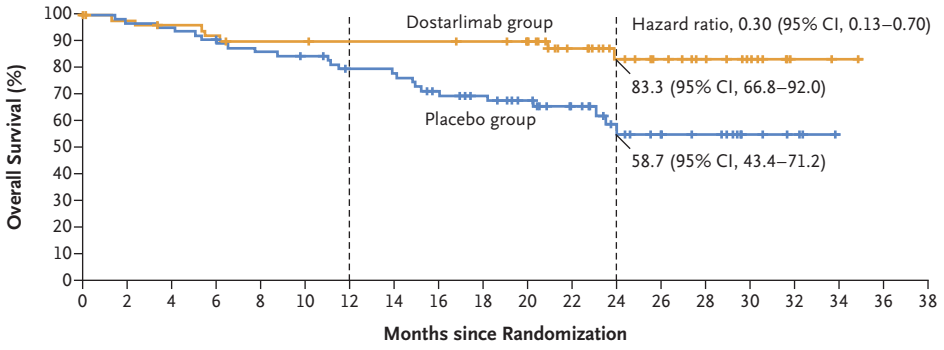
A Overall Population



No. at Risk																			
Dostarlimab group	245	235	224	214	198	190	183	174	169	162	145	110	83	64	45	25	7	2	0
Placebo group	249	242	237	226	219	203	189	177	162	147	125	88	65	48	33	15	6	1	1	0

No. of Events																			
Dostarlimab group	0	3	8	15	25	33	35	42	44	47	53	57	60	62	64	65	65	65	65	
Placebo group	0	3	7	17	22	35	45	57	68	78	88	93	97	98	99	100	100	100	100	100

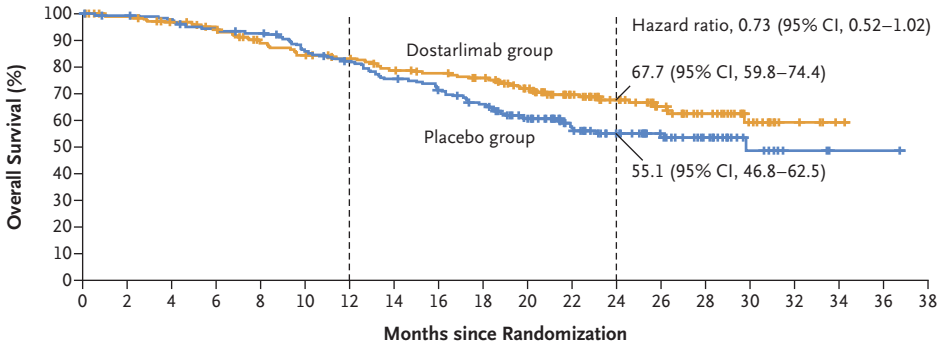
B dMMR–MSI-H Population



No. at Risk																			
Dostarlimab group	53	50	48	46	44	44	43	43	43	42	41	29	20	16	12	8	2	1	0
Placebo group	65	63	62	59	55	53	48	47	41	37	32	25	16	12	10	5	3	0	

No. of Events																			
Dostarlimab group	0	1	2	4	5	5	5	5	5	5	5	6	7	7	7	7	7	7	7
Placebo group	0	2	3	6	9	10	13	14	18	19	20	21	23	24	24	24	24	24	

C pMMR–MSS Population



No. at Risk																			
Dostarlimab group	192	185	176	168	154	146	140	131	126	120	104	81	63	48	33	17	5	1	0
Placebo group	184	179	175	167	164	150	141	130	121	110	93	63	49	36	23	10	3	1	1	0

No. of Events																			
Dostarlimab group	0	2	6	11	20	28	30	37	39	42	48	51	53	55	57	58	58	58	58	
Placebo group	0	1	4	11	13	25	32	43	50	59	68	72	74	74	75	76	76	76	76	76

Figure 3 (facing page). Overall Survival.
Shown are Kaplan–Meier estimates of overall survival in the overall population (Panel A), the dMMR–MSI-H population (Panel B), and the pMMR–MSS population (Panel C). The results in the overall population did not reach the level of significance that was established as the stopping rule (P value stopping boundary of 0.00177). In all three panels, tick marks indicate censored data.

had died or had disease progression as assessed by the investigator according to RECIST, version 1.1. In the overall population, 135 patients (55.1%) in the dostarlimab group and 177 patients (71.1%) in the placebo group had died or had disease progression. The median duration of follow-up was 24.8 months (range, 19.2 to 36.9) in the dMMR–MSI-H population and 25.4 months (range, 19.2 to 37.8) in the overall population.

PROGRESSION-FREE AND OVERALL SURVIVAL

Among the patients with dMMR–MSI-H tumors, the estimated Kaplan–Meier probability of progression-free survival at 24 months was 61.4% (95% confidence interval [CI], 46.3 to 73.4) in the dostarlimab group and 15.7% (95% CI, 7.2 to 27.0) in the placebo group (Fig. 2A). The dostarlimab regimen was associated with a 72% lower risk of progression or death than the placebo regimen (hazard ratio, 0.28; 95% CI, 0.16 to 0.50; P<0.001) among patients with dMMR–MSI-H tumors.

In the overall population, progression-free survival at 24 months was 36.1% (95% CI, 29.3 to 42.9) in the dostarlimab group and 18.1% (95% CI, 13.0 to 23.9) in the placebo group (hazard ratio for progression or death, 0.64; 95% CI, 0.51 to 0.80; P<0.001) (Fig. 2B). Progression-free survival in prespecified subgroups in both the dMMR–MSI-H population and the overall population is shown in Figure S2. The results of the analyses appeared to favor the dostarlimab regimen across most evaluated subgroups; however, the results in the subgroups of patients with stage III disease and the patients with no disease at baseline were not consistent with those in other subgroups. Results in subgroups of the overall population were more heterogeneous than those in the dMMR–MSI-H population.

At the time of this first interim analysis of overall survival in the overall population, 65 of 245 patients (26.5%) in the dostarlimab group and 100 of 249 patients (40.2%) in the placebo group had died. With 25.4 months of follow-up in the overall population, overall survival was longer with the dostarlimab regimen than with the placebo regimen (hazard ratio for death, 0.64; 95% CI, 0.46 to 0.87; P=0.0021), but the results did not reach the level of significance that was established as the stopping rule (P value stopping boundary of 0.00177). The Kaplan–Meier probability of survival at 24 months was 71.3% (95% CI, 64.5 to 77.1) with the dostarlimab regimen and 56.0% (95% CI, 48.9 to 62.5) with the placebo regimen (Fig. 3A).

Among patients with dMMR–MSI-H tumors, 7 (13%) in the dostarlimab group and 24 (37%) in the placebo group died. Overall survival at 24 months was 83.3% (95% CI, 66.8 to 92.0) in the dostarlimab group and 58.7% (95% CI, 43.4 to 71.2) in the placebo group (hazard ratio, 0.30; 95% CI, 0.13 to 0.70) (Fig. 3B). The sensitivity analysis of progression-free survival in the dMMR–MSI-H population based on the MMR and MSI status at randomization is shown in Table S5 and Figure S3.

Results of assessments of tumor response, including complete response as assessed by the investigator according to RECIST, version 1.1; data on response duration; and other secondary end points are shown in Table S6 and Figures S4 and S5.

PMMR–MSS POPULATION

Among patients with pMMR–MSS tumors, a progression-free survival benefit was observed with the dostarlimab regimen as compared with the placebo regimen: progression-free survival at 24 months was 28.4% (95% CI, 21.2 to 36.0) in the dostarlimab group and 18.8% (95% CI, 12.8 to 25.7) in the placebo group (hazard ratio for disease progression or death, 0.76; 95% CI, 0.59 to 0.98) (Fig. 2C). Overall survival at 24 months was 67.7% (95% CI, 59.8 to 74.4) in the dostarlimab group and 55.1% (95% CI, 46.8 to 62.5) in the placebo group (hazard ratio for death, 0.73; 95% CI, 0.52 to 1.02) (Fig. 3C).

SAFETY

Common adverse events are listed in Table 2. In the overall population, the most common adverse events that occurred or worsened during treatment were nausea (53.9% of the patients in the dostarlimab group and 45.9% of those in the placebo group), alopecia (53.5% and 50.0%), and

Table 2. Adverse Events That Occurred or Worsened during Treatment in the Overall Population.

Event	Dostarlimab (N=241)	Placebo (N=246)
	no. of patients (%)	
Any event	241 (100.0)	246 (100.0)
Event related to a trial drug or placebo	236 (97.9)	243 (98.8)
Event related to dostarlimab or placebo	203 (84.2)	183 (74.4)
Event related to carboplatin or paclitaxel	233 (96.7)	235 (95.5)
Any grade ≥3 event	170 (70.5)	147 (59.8)
Grade ≥3 event related to a trial drug or placebo	122 (50.6)	114 (46.3)
Grade ≥3 event related to dostarlimab or placebo	80 (33.2)	48 (19.5)
Grade ≥3 event related to carboplatin or paclitaxel	94 (39.0)	101 (41.1)
Any serious event	91 (37.8)	68 (27.6)
Serious event related to a trial drug or placebo	44 (18.3)	30 (12.2)
Serious event related to dostarlimab or placebo	30 (12.4)	17 (6.9)
Serious event related to carboplatin or paclitaxel	33 (13.7)	24 (9.8)
Immune-related event related to a trial drug or placebo	92 (38.2)	38 (15.4)
Event leading to discontinuation of dostarlimab or placebo	42 (17.4)	23 (9.3)
Event leading to discontinuation of carboplatin	24 (10.0)	19 (7.7)
Event leading to discontinuation of paclitaxel	24 (10.0)	23 (9.3)
Event leading to death	5 (2.1)	0
Events of any grade occurring in >20% of patients in either group		
Fatigue	125 (51.9)	134 (54.5)
Alopecia	129 (53.5)	123 (50.0)
Nausea	130 (53.9)	113 (45.9)
Peripheral neuropathy	106 (44.0)	101 (41.1)
Anemia	91 (37.8)	104 (42.3)
Arthralgia	86 (35.7)	86 (35.0)
Constipation	83 (34.4)	88 (35.8)
Diarrhea	75 (31.1)	71 (28.9)
Myalgia	63 (26.1)	68 (27.6)
Hypomagnesemia	52 (21.6)	70 (28.5)
Peripheral sensory neuropathy	51 (21.2)	47 (19.1)
Decreased appetite	52 (21.6)	43 (17.5)
Dyspnea	44 (18.3)	50 (20.3)
Rash	55 (22.8)	34 (13.8)
Grade ≥3 events occurring in >5% of patients in either group		
Anemia	36 (14.9)	40 (16.3)
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-cell count decreased	16 (6.6)	13 (5.3)
Hypertension	17 (7.1)	8 (3.3)
Pulmonary embolism	12 (5.0)	12 (4.9)
Hypokalemia	12 (5.0)	9 (3.7)

Table 2. (Continued.)

Event	Dostarlimab (N=241)	Placebo (N=246)
	no. of patients (%)	
Serious events occurring in >2% of patients in either group		
Sepsis	8 (3.3)	1 (0.4)
Pulmonary embolism	6 (2.5)	5 (2.0)
Pyrexia	6 (2.5)	2 (0.8)
Dyspnea	5 (2.1)	1 (0.4)
Muscular weakness	5 (2.1)	1 (0.4)
Anemia	3 (1.2)	6 (2.4)
Asthenia	2 (0.8)	6 (2.4)
Urinary tract infection	3 (1.2)	5 (2.0)

fatigue (51.9% and 54.5%). The differences in the incidence of the most common adverse events before and after cycle 7 are shown in Table S7. Rash and maculopapular rash were the adverse events with the largest differences between the treatment groups and were reported more frequently in the dostarlimab group than in the placebo group (22.8% vs. 13.8% for rash and 14.1% vs. 3.7% for maculopapular rash). The incidences of grade 3 or higher adverse events and serious adverse events that occurred or worsened during treatment were each approximately 10 percentage points higher in the dostarlimab group than in the placebo group (adverse events, 70.5% vs. 59.8%; serious adverse events, 37.8% vs. 27.6%). Discontinuation of dostarlimab or placebo because of adverse events occurred in 17.4% of patients in the dostarlimab group and in 9.3% of patients in the placebo group. The most common adverse events leading to discontinuation of dostarlimab or placebo were maculopapular rash and infusion-related reaction (1.2% each) in the dostarlimab group and thrombocytopenia (1.2%) in the placebo group. The most common immune-related adverse events were hypothyroidism (11.2% of the patients in the dostarlimab group and 2.8% of those in the placebo group), rash (6.6% and 2.0%), arthralgia (5.8% and 6.5%), and an increase in alanine aminotransferase levels (5.8% and 0.8%) (Table S8).

Five deaths due to adverse events that occurred or worsened during treatment occurred in the dostarlimab group. No deaths occurred in the placebo group. One death that was reported by the investigator as related to the dostarlimab regimen occurred during the first six cycles (myelosuppression), one death was related to dostarlimab and occurred during the 90-day safety follow-up (hypovolemic shock), and three were judged not to be related to the dostarlimab regimen (opiate overdose, coronavirus disease 2019, and general deterioration of physical health).

PATIENT-REPORTED OUTCOMES

During the chemotherapy period, the mean change from baseline in EORTC-QLQ-C30 global health status and quality-of-life scores indicated no differences between groups. Results were similar in both the overall population and the dMMR–MSI-H population (Fig. S6).

DISCUSSION

The regimen containing dostarlimab, carboplatin, and paclitaxel was associated with a significantly lower risk of progression or death than the regimen containing placebo, carboplatin, and paclitaxel among patients with primary advanced or recurrent endometrial cancer, with a 72% lower risk of progression or death in the dMMR–MSI-H population and a 36% lower risk in the overall population. Additional survival analyses are planned as follow-up time increases.

Dostarlimab showed durable benefit as second-line monotherapy treatment in patients with advanced or recurrent dMMR–MSI-H endometrial cancer who had disease progression during or after platinum chemotherapy.[16-19] The presence

of dMMR is a well-established biomarker for immune-checkpoint inhibition in several tumor types. Testing for MMR and MSI status is important, because it is considered both prognostic and predictive for the potential use of immune-checkpoint inhibitor treatments in endometrial cancer.[34-36] In the dMMR–MSI-H population, the dostarlimab regimen provided a significant progression-free survival benefit, with a 61.4% probability of progression-free survival at 24 months.

Although dMMR–MSI-H tumors are predominantly endometrioid, pMMR–MSS tumors are more heterogeneous and include high-risk histologic subtypes, including carcinosarcomas, and patients with carcinosarcomas were eligible for the trial.[37,38] Tumors that are pMMR–MSS generally have a reduced tumor mutational burden, but PD-1 expression is prevalent in pMMR–MSS endometrial cancer. In line with this, durable responses in previously treated patients with pMMR–MSS disease have been observed with dostarlimab monotherapy.[17] Approximately three quarters of the population in our trial had pMMR–MSS disease, which is consistent with the known prevalence.

We also observed a benefit with the dostarlimab regimen in the pMMR–MSS population, although it was smaller in magnitude than that in the dMMR–MSI-H population. The benefit of the dostarlimab regimen was observed consistently with respect to progression-free survival and overall survival based on the prespecified analyses of the two end points in the pMMR–MSS population. Overall survival curves in the pMMR–MSS population diverged at 1 year and remained separated, with 69.8% and 58.7% of the patients remaining alive at the time of data cutoff in the dostarlimab group and the placebo group, respectively.

The progression-free survival benefit in the dostarlimab group did not appear to be consistent across all prespecified subgroups; extended follow-up may be necessary in order to observe a treatment effect in the subgroup of patients with stage III disease and the subgroup of patients with no disease at baseline because of the limited sample size and the relatively short follow-up period.

Progression-free survival in the placebo group in our trial was lower than that in the GOG-0209 trial (studying carboplatin–paclitaxel as a noninferior alternative to paclitaxel–doxorubicin–cisplatin in advanced and recurrent endometrial cancer); however, this was expected on the basis of differences between the patient populations. The GOG-0209 trial included a higher percentage of patients with stage III disease (41.7%) or nonmeasurable stage III or IV disease (43.9%) and a lower percentage of patients with recurrent disease (27.3%) than in our trial (18.6% with stage III and 47.8% with recurrent disease).[7] Similar median progression-free survival has been reported in trials with similar patient populations that received the same treatment in the control group, although cross-trial comparisons are difficult.[39,40]

The safety profile of dostarlimab–carboplatin–paclitaxel was consistent with that of the individual components of the regimen. The frequencies of severe and serious adverse events were approximately 10 percentage points higher with the dostarlimab regimen than with the placebo regimen. The frequency of discontinuations of chemotherapy was similar in the two groups. Quality of life was also similar in the two groups during the chemotherapy period.

The combination of dostarlimab, carboplatin, and paclitaxel significantly improved outcomes for patients with newly diagnosed primary advanced or recurrent endometrial cancer, with substantial benefit seen in dMMR–MSI-H tumors. More severe and serious adverse events occurred in the dostarlimab group than in the placebo group; the safety profile of the combination was generally consistent with the known profiles of the individual drugs in the regimen.

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APPENDIX

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