Pembrolizumab or Placebo Plus Adjuvant Chemotherapy With or Without Radiotherapy for Newly Diagnosed, High-Risk Endometrial Cancer: Results in Mismatch Repair-Deficient Tumors

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ABSTRACT

Mismatch repair-deficient (dMMR) endometrial cancer (EC) is an inflamed phenotype with poor outcomes when meeting high-risk criteria and limited treatment options in the adjuvant setting. We report protocol-prespecified subgroup analysis of patients with dMMR tumors from the phase III ENGOT-en11/GOG-3053/KEYNOTE-B21 study (ClinicalTrials.gov identifier: NCT04634877) in newly diagnosed, high-risk EC after surgery with curative intent. Patients were randomly assigned to pembrolizumab 200 mg or placebo (six cycles) plus carboplatin-paclitaxel (four to six cycles) once every 3 weeks, then pembrolizumab 400 mg or placebo once every 6 weeks (six cycles), respectively. MMR status was a stratification factor. Patients received radiotherapy at investigator discretion. Investigator-assessed disease-free survival (DFS) was a primary end point. No formal hypothesis testing was performed for subgroup analysis. In the intention-to-treat population, 141 patients in the pembrolizumab arm and 140 in the placebo arm had dMMR tumors. At this interim analysis, hazard ratio for DFS favored pembrolizumab (0.31 [95% CI, 0.14 to 0.69]); median DFS was not reached in either group. Two-year DFS rates were 92.4% (95% CI, 84.4 to 96.4) and 80.2% (95% CI, 70.8 to 86.9), respectively. No new safety signals occurred. Longer-term follow-up of outcomes will be evaluated at final analysis. Preplanned subgroup analysis on the basis of the study's stratification factors suggests that pembrolizumab plus chemotherapy improves DFS and is clinically relevant for patients with dMMR tumors in the curative-intent setting.

ACCOMPANYING CONTENT

- Listen to the podcast by Dr Westin and Dr Slomovitz at https://ascopubs.org/do/adjuvant-pembrolizumab-high-risk-dmmr-endometrial-cancer
- Appendix
- Data Sharing Statement
- Protocol

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INTRODUCTION

Approximately 25%-30% of patients with endometrial cancer (EC) have mismatch repair-deficient (dMMR) tumors,[1,2] which are characterized by an inflamed phenotype with increased neoantigen load, tumor-infiltrating lymphocytes (TILs), tumor mutational burden (TMB), and PD-L1 expression versus mismatch repair-proficient (pMMR) tumors.[3,4] Retrospective analyses suggest poorer outcomes in patients with newly diagnosed, endometrioid dMMR EC versus pMMR p53 wild-type tumors,[5-7] despite similar standard-of-care adjuvant treatment[7] (typically systemic chemotherapy ± radiotherapy).[8-11]

In phase III studies for advanced/recurrent disease, addition of a PD-(L)1 inhibitor to first-line carboplatin-paclitaxel provided numerically greater benefit in dMMR versus pMMR EC.[12-14] In the phase III ENGOT-en11/GOG-3053/KEYNOTE-B21 study (ClinicalTrials.gov identifier: NCT04634877), adjuvant pembrolizumab (*v* placebo) plus

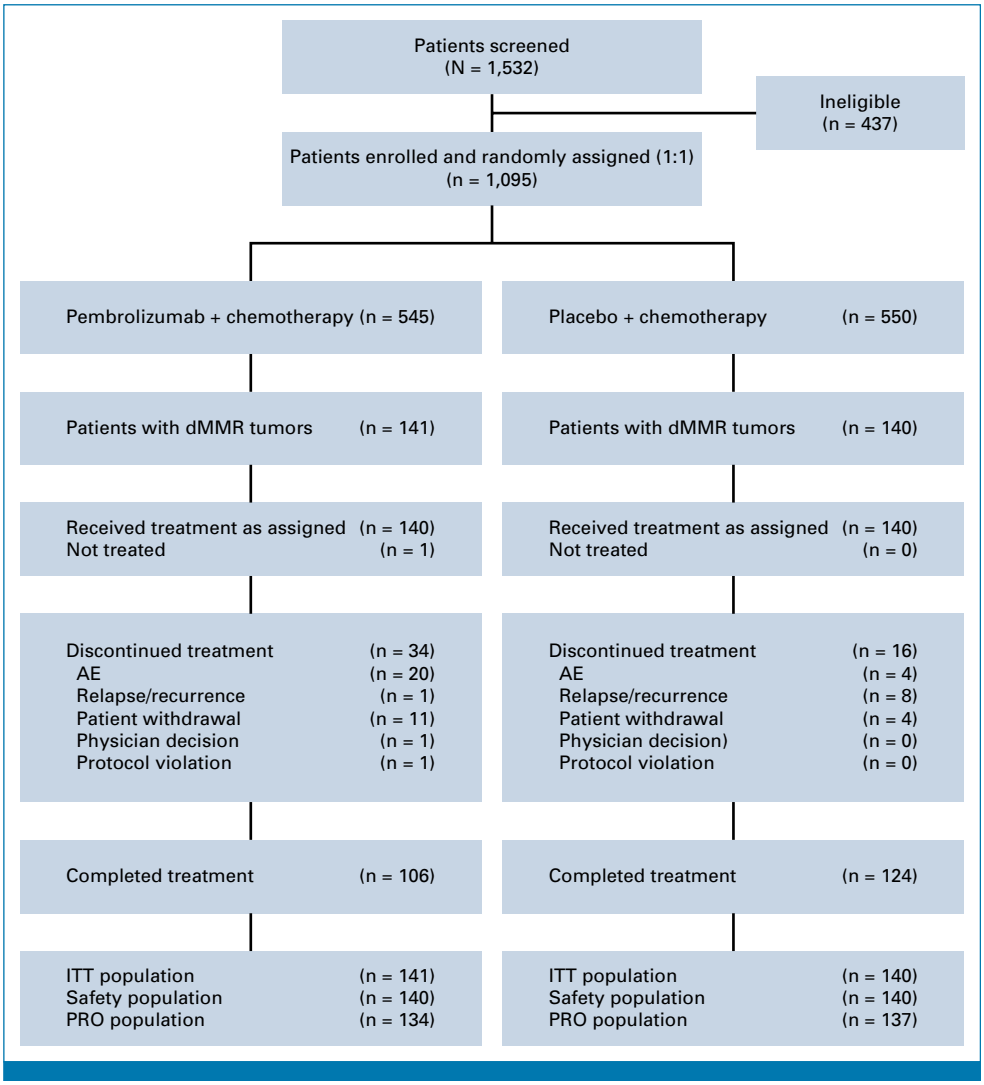

FIG 1. CONSORT diagram: patient disposition for the ITT population. AE, adverse event; dMMR, mismatch repair-deficient; ITT, intention-to-treat; PRO, patient-reported outcome.

carboplatin-paclitaxel (±radiotherapy) did not improve disease-free survival (DFS) in all-comers with newly diagnosed, high-risk EC after curative-intent surgery.[15] We report results from protocol-prespecified subgroup analyses of patients with dMMR tumors (MMR status was initial stratification factor).

METHODS

Methods were previously published.[15] Patients were randomly assigned to six once-every-3-week cycles of pembrolizumab 200 mg or placebo plus adjuvant carboplatin-paclitaxel (four to six cycles) followed by pembrolizumab 400 mg or placebo once every 6 weeks for six cycles, respectively, which is approximately 1 year of total treatment unless earlier recurrence or discontinuation criteria were met. Radiotherapy (external-beam radiation therapy ± cisplatin and/or vaginal brachytherapy) was determined before random assignment at investigator discretion. Primary end points were DFS assessed radiographically per investigator or by histopathologic confirmation and overall survival (OS) in the intention-to-treat (ITT) population.

Tumor imaging was performed at baseline, once every 12 weeks after random assignment through week 96, at weeks 120 and 144, annually thereafter, and at the end of treatment.

The Kaplan-Meier method was used to evaluate DFS and OS. A stratified Cox proportional hazards model was used to assess the magnitude of treatment difference (hazard ratios [HRs] and 95% CIs). A constrained longitudinal data analysis model was used to evaluate patient-reported outcomes (PROs). Efficacy was assessed in all randomly assigned patients, safety in all treated patients, and PROs in all treated patients with data available. No formal hypothesis testing was performed and no alpha was assigned for these analyses.

TABLE 1. Demographics and Baseline Disease Characteristics in the Mismatch Repair-Deficient Subgroup Within the Intention-to-Treat Population

Characteristic	Pembrolizumab + Chemotherapy (n = 141)	Placebo + Chemotherapy (n = 140)
Age, years, median (range)	59.0 (37.0-82.0)	58.0 (36.0-84.0)
<65	102 (72.3)	101 (72.1)
≥65	39 (27.7)	39 (27.9)
Race		
White	90 (63.8)	90 (64.3)
Asian	38 (27.0)	44 (31.4)
Black or African American	3 (2.1)	2 (1.4)
American Indian or Alaska Native	1 (0.7)	2 (1.4)
Multiple	7 (5.0)	1 (0.7)
Missing	2 (1.4)	1 (0.7)
Region		
Western Europe	40 (28.4)	36 (25.7)
North America	25 (17.7)	32 (22.9)
Rest of the world	76 (53.9)	72 (51.4)
ECOG performance status		
0	106 (75.2)	115 (82.1)
1	35 (24.8)	25 (17.9)
Lymph node dissection		
Yes	132 (93.6)	129 (92.1)
No	9 (6.4)	11 (7.9)
FIGO (2009) stage		
IA/B	27 (19.1)	22 (15.7)
II	8 (5.7)	8 (5.7)
IIIA/B	31 (22.0)	25 (17.9)
IIIC	70 (49.6)	84 (60.0)
IVA	5 (3.5)	1 (0.7)
Histology		
Endometrioid	108 (76.6)	104 (74.3)
Grade 1	20 (14.2)	18 (12.9)
Grade 2	52 (36.9)	60 (42.9)
Grade 3	36 (25.5)	26 (18.6)
Nonendometrioid	33 (23.4)	36 (25.7)
Undifferentiated/dedifferentiated carcinoma	13 (9.2)	13 (9.3)
Carcinosarcoma	9 (6.4)	5 (3.6)
Clear cell carcinoma	5 (3.5)	8 (5.7)
Mixed cell	3 (2.1)	8 (5.7)
Serous carcinoma	3 (2.1)	2 (1.4)
p53 by IHC		
Abnormal expression	49 (34.8)	41 (29.3)
Normal expression	50 (35.5)	51 (36.4)
Not done	42 (29.8)	48 (34.3)
PD-L1 status		
CPS <1	6 (4.3)	12 (8.6)
CPS ≥1	133 (94.3)	124 (88.6)
Missing	2 (1.4)	4 (2.9)
TMB status		
TMB-high (≥10 mut/Mb)	124 (87.9)	123 (87.9)
TMB-low (<10 mut/Mb)	8 (5.7)	9 (6.4)
Missing	9 (6.4)	8 (5.7)

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TABLE 1. Demographics and Baseline Disease Characteristics in the Mismatch Repair-Deficient Subgroup Within the Intention-to-Treat Population (continued)

Characteristic	Pembrolizumab + Chemotherapy (n = 141)	Placebo + Chemotherapy (n = 140)
Planned radiotherapy		
EBRT with cisplatin	24 (17.0)	26 (18.6)
EBRT without cisplatin	81 (57.4)	65 (46.4)
Brachytherapy only	9 (6.4)	9 (6.4)
No EBRT or brachytherapy	27 (19.1)	40 (28.6)
Lymph node involvement		
No	70 (49.6)	52 (37.1)
Yes	71 (50.4)	83 (59.3)
Not evaluable	0	5 (3.6)
Myometrial invasion		
Yes	133 (94.3)	132 (94.3)
No	8 (5.7)	8 (5.7)
Lymphovascular invasion		
Yes	75 (53.2)	84 (60.0)
No	61 (43.3)	52 (37.1)
Unknown	5 (3.5)	4 (2.9)

NOTE. All data are No. (%) unless stated otherwise.
Abbreviations: CPS, combined positive score; EBRT, external-beam radiation therapy; ECOG, Eastern Cooperative Oncology Group; FIGO, International Federation of Gynecology and Obstetrics; IHC, immunohistochemistry; TMB, tumor mutational burden.

Study procedures received ethical approval. Patients provided informed consent.

RESULTS

Patients and Treatments

One thousand ninety-five patients were randomly assigned between January 2021 and October 2022 (dMMR subgroup: pembrolizumab, n = 141; placebo, n = 140; Fig 1). Demographics and notable baseline disease characteristics for the dMMR subgroup were generally well balanced (Table 1). Most randomly assigned patients had stage III disease (74.7%), endometrioid histology (75.4%), were TMB-high (87.9%), and were PD-L1–positive (91.5%). Overlap of histology and biomarkers is shown in Appendix Figure A1 (online only). At this interim analysis (data cutoff, March 4, 2024), median follow-up was 24.6 (range, 3.6-35.3) months. Exposure to study treatment and subsequent anticancer therapies are summarized in Appendix Tables A1-A3. Most patients with recurrence in the placebo group (13/23 [56.5%]) received poststudy immunotherapy (Appendix Table A4).

Efficacy

In the dMMR subgroup, DFS events occurred in eight patients (5.7%) in the pembrolizumab group and 25 (17.9%) in the placebo group (Fig 2). There were three recurrences (one locoregional/two distant) and five deaths in the pembrolizumab group and 23 recurrences (12 locoregional/11 distant) and two deaths in the placebo group. No patient died because of treatment-related AEs. Baseline characteristics and details regarding recurrence or death for patients with DFS events by investigator are summarized in Appendix Table A4.

Recurrences were assessed per investigator (pembrolizumab, n = 3; placebo, n = 23). HR for DFS was 0.31 (95% CI, 0.14 to 0.69); median DFS was not reached in either group (see Appendix Fig A2 for results in subgroups of interest within the dMMR subgroup). Kaplan-Meier estimates of 2-year DFS rates were 92.4% (95% CI, 84.4 to 96.4) and 80.2% (95% CI, 70.8 to 86.9) in the pembrolizumab and placebo groups. HR for DFS by blinded independent central review (BICR) was 0.60 (95% CI, 0.31 to 1.16; Appendix Table A5). There was discordance in BICR versus investigator assessment in both treatment groups (Appendix Table A6). In the pembrolizumab group, there were nine BICR events versus three investigator events. This was due to seven BICR recurrences that were not investigator recurrences and one investigator recurrence that was not a BICR recurrence. Notably, for patients with recurrence by BICR in the pembrolizumab group, one was confirmed as recurrence by investigator after data cutoff, one withdrew consent, one was revised by BICR to not have recurrence after data cutoff, and four had ≥1 year of follow-up from the time of BICR-assessed recurrence with no clinical signs/symptoms, new anticancer therapy, death, or investigator assessment of recurrence contrary to actual recurrence. In the placebo group, there were 21 BICR events versus 23 investigator events. This was due to three BICR recurrences that were not investigator recurrences and five investigator recurrences

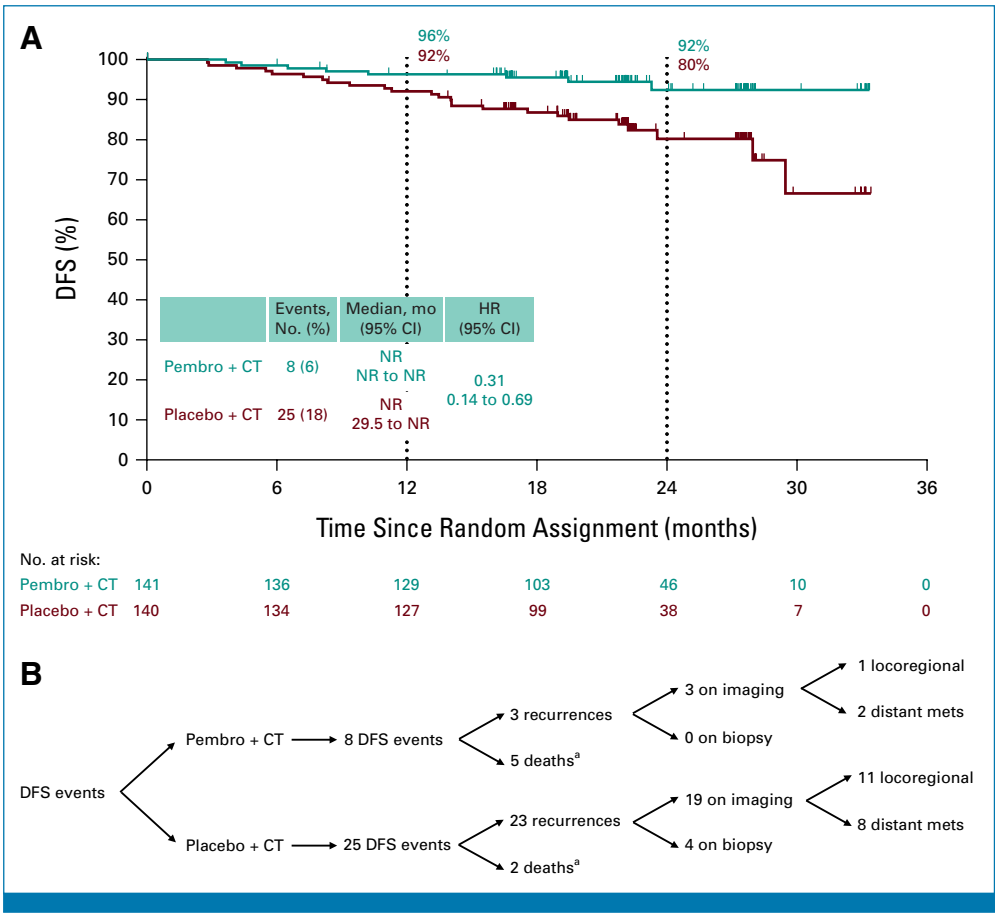

FIG 2. (A) Kaplan-Meier–estimated DFS and (B) flowchart of recurrences in the dMMR subgroup within the ITT population. The interaction *P* value for MMR status was .002. DFS was defined as the time from random assignment to local or distant recurrence of endometrial cancer (assessed radiographically by the investigator or by histopathologic confirmation) or death from any cause. The HR (95% CI) for DFS was previously reported for the ITT population (1.02 [0.79 to 1.32]; $P = .570$) and the pMMR subgroup (1.20 [0.91 to 1.57]).[15] In the ITT population, 2-year DFS rates were 75% in the pembrolizumab group and 76% in the placebo group.[15] [a]No deaths were determined to be treatment-related (pembro arm: four deaths due to non-TRAEs and one due to endometrial cancer; placebo arm: two deaths due to non-TRAEs). CT, chemotherapy; DFS, disease-free survival; dMMR, mismatch repair-deficient; HR, hazard ratio; ITT, intention-to-treat; mets, metastasis; NR, not reached; pembro, pembrolizumab; pMMR, mismatch repair-proficient; TRAE, treatment-related adverse event. Figure 2A is reproduced with permission from *Annals of Oncology*.[15]

that were not a BICR recurrence. For the coprimary end point of OS, data were only 3.6% mature. Longer follow-up is ongoing.

Patient-Reported Outcomes

Results are presented in Appendix 1.

Safety

Grade ≥3 AEs occurred in 110 patients (78.6%) and 93 patients (66.4%) in the pembrolizumab and placebo groups, respectively (Table 2). AEs led to death in three patients (2.1%) and one patient (0.7%), respectively; none of the AEs resulting in death were considered treatment-related. AEs resulted in discontinuation of any study drug (ie, either chemotherapy or placebo/pembrolizumab) in 33 patients (23.6%) and 19 patients (13.6%), respectively. Results for immune-mediated AEs and infusion reactions are shown in Table 2.

DISCUSSION

No difference in DFS was seen between the treatment groups in the ITT population.[15] However, in this protocol-prespecified nonanalytical (no alpha assigned) subgroup analysis (MMR status was the initial stratification factor), addition of pembrolizumab to adjuvant carboplatin-paclitaxel (±radiotherapy) suggested improvement for DFS that was clinically relevant, especially considering the study population was at high risk for recurrence.[5-7]

Biologic features of dMMR tumors (eg, high neoantigen load, TILs, TMB, and PD-L1 expression[3,4]) make them

TABLE 2. AEs in the Mismatch Repair-Deficient Subgroup Within the Safety Population

AE	Pembrolizumab + Chemotherapy (n = 140)	Placebo + Chemotherapy (n = 140)
Any AE	140 (100)	140 (100)
Grade 3-5	110 (78.6)	93 (66.4)
Led to discontinuation of any treatment	33 (23.6)	19 (13.6)
Pembrolizumab or placebo	18 (12.9)	3 (2.1)
Paclitaxel	15 (10.7)	13 (9.3)
Carboplatin	8 (5.7)	3 (2.1)
Cisplatin	7 (5.0)	2 (1.4)
Radiotherapy	3 (2.1)	2 (1.4)
Docetaxel	0	0
Led to death	3 (2.1)[a]	1 (0.7)[a]
Treatment-related AEs leading to death	0	0

AE Occurring in ≥20% of Patients in Either Treatment Group	Any Grade	Grade 3-5	Any Grade	Grade 3-5
Alopecia	92 (65.7)	0	92 (65.7)	0
Anemia	76 (54.3)	14 (10.0)	70 (50.0)	13 (9.3)
Nausea	58 (41.4)	5 (3.6)	67 (47.9)	2 (1.4)
Diarrhea	67 (47.9)	4 (2.9)	51 (36.4)	5 (3.6)
Arthralgia	45 (32.1)	0	43 (30.7)	1 (0.7)
Constipation	41 (29.3)	2 (1.4)	46 (32.9)	0
Decreased neutrophil count	44 (31.4)	25 (17.9)	42 (30.0)	33 (23.6)
Decreased WBC count	42 (30.0)	20 (14.3)	40 (28.6)	15 (10.7)
Peripheral neuropathy	38 (27.1)	2 (1.4)	43 (30.7)	0
Fatigue	33 (23.6)	1 (0.7)	39 (27.9)	2 (1.4)
Neutropenia	33 (23.6)	24 (17.1)	33 (23.6)	20 (14.3)
Asthenia	33 (23.6)	4 (2.9)	25 (17.9)	1 (0.7)
Decreased platelet count	34 (24.3)	7 (5.0)	24 (17.1)	7 (5.0)
Increased ALT	29 (20.7)	3 (2.1)	27 (19.3)	0
Decreased appetite	24 (17.1)	1 (0.7)	31 (22.1)	0
Thrombocytopenia	29 (20.7)	4 (2.9)	24 (17.1)	3 (2.1)
Rash	30 (21.4)	3 (2.1)	20 (14.3)	1 (0.7)
Hypothyroidism	31 (22.1)	1 (0.7)	5 (3.6)	0

AE	Pembrolizumab + Chemotherapy (n = 140)	Placebo + Chemotherapy (n = 140)
Immune-mediated AEs	57 (40.7)	34 (24.3)
Grade 3-5	12 (8.6)	5 (3.6)
Led to discontinuation of any drug	7 (5.0)	6 (4.3)
Led to death	0	0

All Immune-Mediated AEs and Infusion Reactions[b]	Any Grade	Grade 3-5	Any Grade	Grade 3-5
Hypothyroidism	31 (22.1)	1 (0.7)	5 (3.6)	0
Infusion reactions	11 (7.9)	0	15 (10.7)	3 (2.1)
Hyperthyroidism	16 (11.4)	0	5 (3.6)	0
Severe skin reactions	7 (5.0)	6 (4.3)	2 (1.4)	1 (0.7)
Colitis	3 (2.1)	1 (0.7)	3 (2.1)	1 (0.7)
Gastritis	3 (2.1)	0	3 (2.1)	0
Thyroiditis	5 (3.6)	0	1 (0.7)	0
Pneumonitis	3 (2.1)	0	2 (1.4)	1 (0.7)
Adrenal insufficiency	3 (2.1)	2 (1.4)	1 (0.7)	0

(continued on following page)

TABLE 2. AEs in the Mismatch Repair-Deficient Subgroup Within the Safety Population (continued)

All Immune-Mediated AEs and Infusion Reactions[b]	Any Grade	Grade 3-5	Any Grade	Grade 3-5
Type 1 diabetes mellitus	2 (1.4)	2 (1.4)	0	0
Arthritis	1 (0.7)	0	0	0
Nephritis	1 (0.7)	0	0	0
Sarcoidosis	1 (0.7)	0	0	0
Vasculitis	0	0	1 (0.7)	0

NOTE. All data are No. (%).
Abbreviation: AE, adverse event.
[a]The three deaths in the pembrolizumab group were because of dementia Alzheimer's type (n = 1), death (not otherwise specified; n = 1), and multiple organ dysfunction syndrome (n = 1), and the death in the placebo group was because of cardiac arrest.
[b]Immune-mediated AEs and infusion reactions were based on a list of preferred terms intended to capture known risks of pembrolizumab and were considered regardless of attribution to study treatment by the investigator.

more immunogenic, potentially even when microscopic levels of residual disease and less tumor antigen are present, explaining the greater benefit seen in the dMMR versus pMMR subgroup for EC in our study.[15] The magnitude of treatment benefit (HR, approximately 0.3) was consistent with studies of anti–PD-(L)1 agents combined with the same chemotherapy combination (carboplatin-paclitaxel) in the first-line advanced/recurrent setting.[12-14]

Differences in the number of recurrences per investigator (3 with pembrolizumab *v* 23 with placebo) compared with BICR (9 *v* 21) assessment suggest substantial limitations of BICR in determining recurrence after surgery. In the context of prolonged follow-up of the majority of the patients cited as having a recurrence by BICR, no clinical or radiologic evidence of disease was demonstrated on follow-up or sequential imaging per investigator. These limitations could be due to the absence of other pertinent clinical information (eg, clinical symptoms, physical examination findings, laboratory values [tumor markers/circulating tumor DNA], intermittent medical diagnoses, AEs that appear as recurrence, biopsies for confirmation, etc) available to the investigator but not to BICR during assessment after a curative-intent surgery. Therefore, investigator assessment in this specific setting when a study is double-blinded and placebo-controlled is expected to be a more reliable assessment of disease status. The safety profile of combination therapy was manageable in the dMMR subgroup with no new safety concerns, and no clinically meaningful between-group differences were observed in QLQ-C30 GHS/QoL scores. Safety and PRO findings were consistent with those in all-comers,[15] and the types of AEs were as expected on the basis of the safety profiles of the individual agents.[10,11,16] The study remains ongoing to collect additional data. Longer-term follow-up of outcomes in the dMMR subgroup are planned for further evaluation at protocol-prespecified final analysis (OS).

Limited studies in patients with dMMR EC in the adjuvant setting are anticipated to yield data in the near future; one phase III study evaluating pembrolizumab with radiation in high-intermediate risk, dMMR, endometrioid EC is fully enrolled and awaiting data maturity.[17] RUBY enrolled too few patients (dostarlimab, n = 4; placebo, n = 7) without radiologically apparent disease to make any inferences regarding the utilization of dostarlimab for dMMR EC in the curative-intent setting.[13] An ongoing study (KEYNOTE-C93/GOG-3064/ENGOT-en15) is evaluating first-line pembrolizumab versus carboplatin-paclitaxel in dMMR advanced/recurrent EC including patients with stage IVB with no evidence of disease after surgery.[18]

Our data suggest a clinically relevant improvement in DFS when pembrolizumab is added to standard of care for the dMMR subgroup, a well-established biomarker on the basis of biology and a population in which anti–PD-(L)1 agents have demonstrated potent antitumor activity across treatment settings.

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CLINICAL TRIAL INFORMATION

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Pembrolizumab or Placebo Plus Adjuvant Chemotherapy With or Without Radiotherapy for Newly Diagnosed, High-Risk Endometrial Cancer: Results in Mismatch Repair-Deficient Tumors

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APPENDIX 1. SUPPLEMENTAL MATERIAL

Ethics Statement

The study was conducted in compliance with the ethical principles originating from the Declaration of Helsinki and with the International Council on Harmonisation Good Clinical Practice guidelines and all applicable regulations. An institutional review board at each study site approved the protocol, amendments, and informed consent forms before the study began at that site. All patients provided written informed consent to participate.

Patient-Reported Outcomes

Analysis of European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire–Core 30 global health status/quality of life (QLQ-C30 GHS/QoL) scores demonstrated least-squares mean changes from baseline to week 45 of −0.86 (95% CI, −3.94 to 2.21) in the pembrolizumab group and 0.95 (95% CI, −2.05 to 3.94) in the placebo group (difference, −1.81 [95% CI, −5.75 to 2.12]).

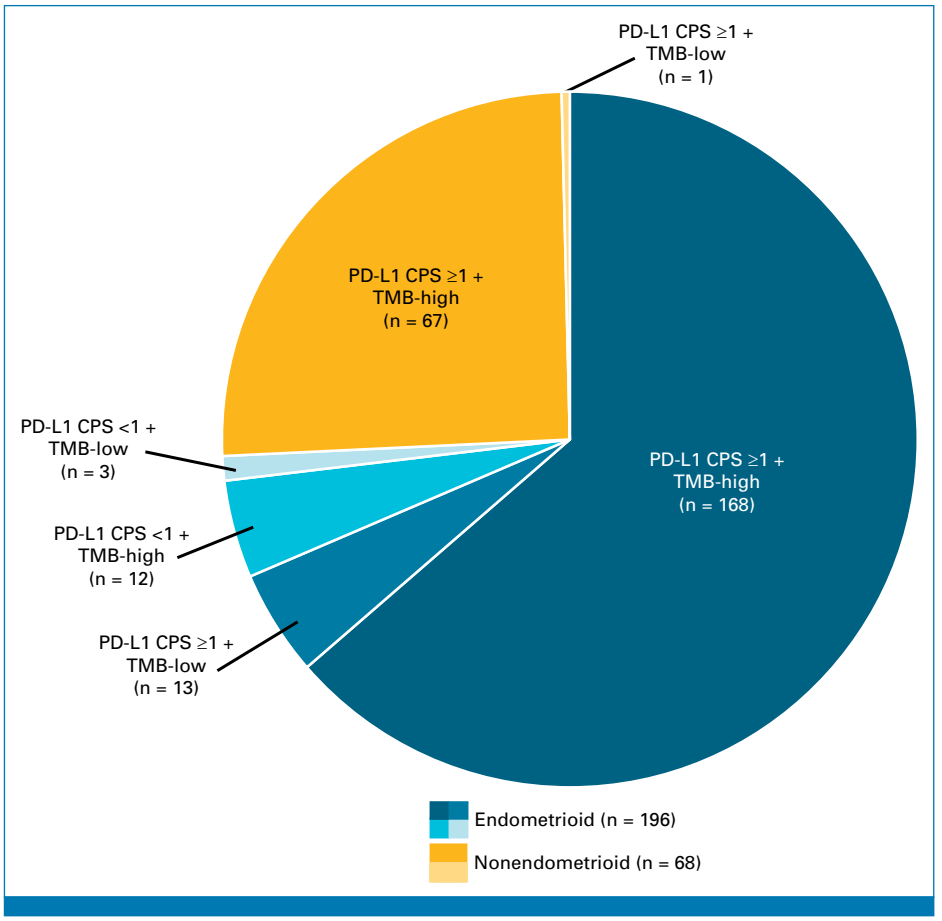

FIG A1. Pie chart diagram of histology and biomarkers in the dMMR subgroup within the ITT population. Patients with missing PD-L1 and/or TMB assessments (n = 17) are not included. CPS, combined positive score; dMMR, mismatch repair-deficient; ITT, intention-to-treat; TMB-high, tumor mutational burden-high (≥10 mut/Mb); TMB-low, tumor mutational burden-low (<10 mut/Mb).

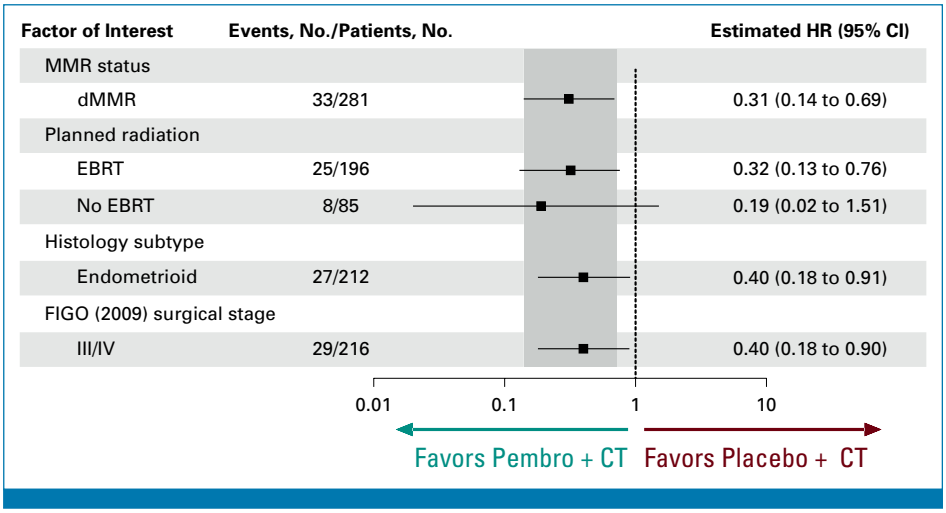

FIG A2. Forest plot of HR for DFS by specific factors of interest in the dMMR subgroup within the ITT population. DFS was defined as the time from random assignment to local or distant recurrence of endometrial cancer (assessed radiographically by the investigator or by histopathologic confirmation) or death from any cause. The subgroup of patients with FIGO (2009) surgical stage I/II (n = 65) experienced 4 events (pembrolizumab group, 0/35; placebo group, 4/30) and the nonendometrioid subgroup (n = 69) experienced 6 events (pembrolizumab group, 0/33; placebo group, 6/36); these subgroups are not included in the figure because their 95% CIs were not estimable. CT, chemotherapy; DFS, disease-free survival; dMMR, mismatch repair-deficient; EBRT, external-beam radiation therapy; FIGO, International Federation of Gynecology and Obstetrics; HR, hazard ratio; ITT, intention-to-treat; MMR, mismatch repair.

TABLE A1. Systemic Treatment in the Mismatch Repair-Deficient Subgroup Within the Safety Population

Systemic Treatment	Pembrolizumab + Chemotherapy (n = 140)	Placebo + Chemotherapy (n = 140)
Duration of pembrolizumab or placebo + chemotherapy during cycles 1-6, months	3.6 (0.7-6.2)	3.6 (0-5.6)
Duration on pembrolizumab or placebo during the study, months	11.2 (0-15.5)	11.3 (0-14.3)
Cycles of pembrolizumab or placebo during the study, No.	12.0 (1.0-12.0)	12.0 (1.0-12.0)
Cycles of chemotherapy during cycles 1-6, No.	6.0 (1.0-6.0)	6.0 (1.0-7.0[a])

NOTE. Data are median (range).

[a]There was one patient who received a small volume of paclitaxel at cycle 1 before it was interrupted for an infusion reaction; the site then decided to give the remaining volume of paclitaxel as a later cycle, which was recorded as seven cycles in the electronic case report form.

TABLE A2. Radiation Treatment in the Mismatch Repair-Deficient Subgroup Among Patients Who Received Radiation Treatment

Radiation Treatment	Pembrolizumab + Chemotherapy (n = 109)	Placebo + Chemotherapy (n = 95)
EBRT with or without cisplatin		
No.	99	88
Duration, days	36.0 (11.0-82.0)	37.0 (30.0-61.0)
Total dose, Gy	45.0 (14.4-60.0)	45.0 (45.0-60.0)
Fractions, No.	25.0 (8.0-30.0)	25.0 (23.0-30.0)
Brachytherapy		
Duration of brachytherapy		
No.	57	58
Duration, days	8.0 (1.0-36.0)	7.0 (1.0-15.0)
HDR		
No.	57	57
Total HDR dose, Gy	12.0 (6.0-31.5)	12.0 (6.0-30.0)
HDR fractions, No.	2.0 (1.0-6.0)	2.0 (1.0-5.0)
LDR		
No.	NA	1
Total LDR dose, Gy	NA	30.0 (30.0-30.0)
LDR fractions, No.	NA	1.0 (1.0-1.0)
Radiosensitizing cisplatin[a]		
No.	22	24
Doses, No.	2.0 (1.0-2.0)	2.0 (1.0-3.0)

NOTE. Data are median (range) unless stated otherwise.
Abbreviations: EBRT, external-beam radiation therapy; HDR, high-dose rate; LDR, low-dose rate; NA, not applicable.
[a]Only for patients selected to receive chemotherapy plus EBRT.

TABLE A3. Subsequent Systemic Anticancer Therapies in the Mismatch Repair-Deficient Subgroup Within the Intention-to-Treat Population

Subsequent Anticancer Therapy	Pembrolizumab + Chemotherapy (n = 141)	Placebo + Chemotherapy (n = 140)
Any subsequent anticancer therapy	2 (1.4)	16 (11.4)
Adjuvant therapy[a]	1 (0.7)	0
Platinum compounds	1 (0.7)	0
Taxanes	1 (0.7)	0
VEGF/VEGFR inhibitors	1 (0.7)	0
Disease recurrence or progression	1 (0.7)	16 (11.4)
Anthracyclines	1 (0.7)	1 (0.7)
Protein kinase inhibitors	0	2 (1.4)
PD-1/PD-L1 inhibitors	0	13 (9.3)
Pembrolizumab	0	8 (5.7)
Dostarlimab	0	4 (2.9)
Retifanlimab	0	1 (0.7)
Platinum compounds	0	5 (3.6)
Progestogens	0	1 (0.7)
Taxanes	0	5 (3.6)

NOTE. Data are No. (%).
Abbreviations: VEGF, vascular endothelial growth factor; VEGFR, vascular endothelial growth factor receptor.
[a]Includes patients who discontinued study treatment during their adjuvant chemotherapy (for toxicity or patient choice) but the investigator decided to complete adjuvant chemotherapy off study.

TABLE A4. Listing of Patients With a Confirmed DFS Event per Investigator in the Mismatch Repair-Deficient Subgroup Within the Intention-to-Treat Population

Patient	Country	FIGO Stage	Histology	PD-L1 CPS	TMB, mut/Mb	Cycles of CT/Pembrolizumab or Placebo, No.	RT	Event of Confirmed DFS per Inv	Location of Recurrence if Confirmed by Image per Inv	Event of Confirmed DFS per BICR	Time to DFS per Inv/BICR From Random Assignment, days	Survival	New Anticancer Treatment	Oncologic Treatments Received After Study
Pembrolizumab + chemotherapy														
1	France	IIIB	EC	1	29.0	5/12	Yes	RC	Distant	RC	709/709	Alive	Yes	Radiation
2	Germany	IIIC1	EC	6	26.6	4/5	No	Death		Death	133/133	Death	No	
3	Turkey	IIIC2	EC	1	3.9	4/5	Yes	Death		Death	111/111	Death	No	
4	Turkey	IIIC1	EC	5	11.0	6/12	Yes	RC	Locoregional	RC	505/505	Alive	Yes	Bevacizumab/carboplatin/paclitaxel, cytoreductive surgery
5	Russian Federation	IIIA	EC	0.5	2.4	6/7	Yes	RC	Distant	No event	198/censored	Alive	Yes	Doxorubicin
6	United States	IIIC2	EC	6	38.4	6/9	Yes	Death		Death	252/252	Death	No	
7	United States	IVA	EC	5	43.0	6/8	No	Death		Death	592/592	Death	No	
8	China	IIIC2	EC	65	—	2/2	No	Death		Death	311/311	Death	No	
Placebo + chemotherapy														
1	Chile	II	CCC	30	58.8	4/6	Yes	RC	Locoregional	RC	85/85	Death	Yes	Doxorubicin
2	Italy	IIIC1	U/D C	10	23.5	6/12	Yes	HC		RC	717/603	Alive	Yes	Dostarlimab, radiation, cancer surgery
3	Italy	IIIC1	EC	20	27.4	6/12	Yes	RC	Locoregional	No event	676/censored	Alive	Yes	Dostarlimab
4	Italy	IB	MC	40	52.4	6/12	Yes	RC	Distant	RC	472/349	Alive	Yes	Lymphadenectomy
5	Italy	IIIC2	EC	5	19.6	6/12	No	HC		RC	410/260	Alive	Yes	Retifanlimab
6	Italy	IIIC1	EC	5	26.6	6/9	No	HC		HC	220/220	Alive	Yes	Dostarlimab/doxorubicin HCl
7	Norway	IIIB	EC	30	24.3	6/12	No	RC	Locoregional	HC	334/355	Death	Yes	Dostarlimab/megestrol acetate
8	Spain	IA	CS	1	1.6	4/10	Yes	RC	Distant	RC	247/247	Death	Yes	Paclitaxel
9	Turkey	IIIC1	EC	10	20.4	6/12	Yes	Death		Death	897/897	Death	No	
10	Turkey	IIIC2	EC	10	23.5	6/12	Yes	RC	Locoregional	RC	593/593	Alive	Yes	Carboplatin/paclitaxel, cytoreductive surgery
11	Turkey	IIIC2	EC	0.5	73.5	6/10	Yes	RC	Locoregional	RC	254/254	Alive	Yes	Carboplatin/paclitaxel/pembrolizumab
12	Ukraine	IIIC1	EC	15	0.8	6/7	Yes	RC	Distant	RC	167/167	Alive	No	

(continued on following page)

TABLE A4. Listing of Patients With a Confirmed DFS Event per Investigator in the Mismatch Repair-Deficient Subgroup Within the Intention-to-Treat Population (continued)

Patient	Country	FIGO Stage	Histology	PD-L1 CPS	TMB, mut/Mb	Cycles of CT/Pembrolizumab or Placebo, No.	RT	Event of Confirmed DFS per Inv	Location of Recurrence if Confirmed by Image per Inv	Event of Confirmed DFS per BICR	Time to DFS per Inv/BICR From Random Assignment, days	Survival	New Anticancer Treatment	Oncologic Treatments Received After Study
13	Czech Republic	IIIC1	EC	1	14.1	6/12	Yes	RC	Locoregional	HC	427/443	Alive	Yes	Pembrolizumab
14	Canada	IIIC1	EC	25	35.2	6/12	Yes	HC		HC	577/577	Alive	Yes	Breast-conserving surgery
15	United States	IIIC1	EC	0	44.6	6/7	No	RC	Distant	RC	176/176	Alive	Yes	Pembrolizumab
16	United States	II	U/D C	20	55.6	6/12	Yes	RC	Distant	No event	663/censored	Alive	Yes	Radiation, craniotomy
17	United States	IIIC1	EC	10	35.2	6/6	No	Death		Death	126/126	Death	No	
18	United States	IIIC1	EC	1	22.7	6/12	Yes	RC	Locoregional	RC	400/327	Alive	Yes	Carboplatin/paclitaxel/pembrolizumab
19	China	IIIC1	SC	8	—	4/8	Yes	RC	Locoregional	RC	285/285	Alive	Yes	Pembrolizumab
20	China	IIIC2	EC	17	47.9	4/7	Yes	RC	Distant	No event	535/censored	Alive	No	
21	China	IIIC2	EC	6	18.1	6/12	Yes	RC	Locoregional	No event	851/censored	Alive	No	
22	Taiwan	IIIC1	EC	0.5	27.4	4/4	No	RC	Distant	RC	87/87	Alive	Yes	Cisplatin, laparotomy
23	Taiwan	IIIC1	EC	5	25.0	6/12	No	RC	Locoregional	RC	344/344	Alive	Yes	Cisplatin/paclitaxel/pembrolizumab
24	Japan	IIIC1	EC	11	7.8	6/12	No	RC	Locoregional	No event	428/censored	Alive	Yes	Lenvatinib/pembrolizumab, radiation
25	Japan	IIIC2	EC	1	44.6	6/12	No	RC	Distant	RC	428/262	Alive	Yes	Lenvatinib/pembrolizumab

Abbreviations: BICR, blinded independent central review; CCC, clear cell carcinoma; CPS, combined positive score; CS, carcinosarcoma; CT, chemotherapy; DFS, disease-free survival; EC, endometrioid carcinoma; FIGO, International Federation of Gynecology and Obstetrics; HC, histopathologic confirmation; Inv, investigator; MC, mixed cell; RC, radiographic confirmation; RT, radiation therapy; SC, serous carcinoma; TMB, tumor mutational burden (high, ≥10 mut/Mb; low, <10 mut/Mb); U/D C, undifferentiated/dedifferentiated carcinoma.

TABLE A5. Results for DFS in the Mismatch Repair-Deficient Subgroup on the Basis of Investigator and BICR Assessment

Result	Investigator Assessment		BICR Assessment	
	Pembrolizumab + Chemotherapy (n = 141)	Placebo + Chemotherapy (n = 140)	Pembrolizumab + Chemotherapy (n = 141)	Placebo + Chemotherapy (n = 140)
DFS events, No. (%)	8 (5.7)	25 (17.9)	14 (9.9)	23 (16.4)
Recurrences	3 (2.1)	23 (16.4)	9 (6.4)	21 (15.0)
Radiographic confirmation	3 (2.1)	19 (13.6)	9 (6.4)	17 (12.1)
Histopathologic confirmation	0	4 (2.9)	0	4 (2.9)
Death	5 (3.5)	2 (1.4)	5 (3.5)	2 (1.4)
DFS, median (95% CI)	NR (NR to NR)	NR (29.5 to NR)	NR (NR to NR)	NR (29.5 to NR)
TTR, days, median (range)	505 (198-709)	410 (85-851)	479 (85-709)	285 (85-603)
HR for DFS (95% CI)	0.31 (0.14 to 0.69)		0.60 (0.31 to 1.16)	

Abbreviations: BICR, blinded independent central review; DFS, disease-free survival; HR, hazard ratio; NR, not reached; TTR, time from random assignment to recurrence.

TABLE A6. Summary of Concordance for Disease-Free Survival on the Basis of Radiographic and Histopathologic Assessment for the Mismatch Repair-Deficient Subgroup

Assessment	Pembrolizumab + Chemotherapy		Placebo + Chemotherapy	
	BICR	Investigator	BICR	Investigator
Radiographic confirmation	9	3	17	19
Histopathologic confirmation	0	0	4	4
Concordance				
BICR and investigator	2		18	
BICR only	7		3	
Investigator only	1		5	

Abbreviation: BICR, blinded independent central review.