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Pembrolizumab plus chemotherapy in advanced or recurrent endometrial cancer: overall survival and exploratory analyses of the NRG GY018 phase 3 randomized trial

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Abstract

Historically, the treatment of patients with advanced stage/recurrent endometrial cancer included paclitaxel plus carboplatin. Immunotherapy in combination with chemotherapy resulted in improved clinical outcomes in several solid tumors. In the phase 3 NRG GY018 study, pembrolizumab plus chemotherapy significantly improved investigator-assessed progression-free survival (PFS; primary endpoint) versus placebo plus chemotherapy in patients with advanced/metastatic/recurrent endometrial cancer (EC) regardless of mismatch repair (MMR) status. Here,

we report on key secondary endpoints/exploratory analyses. Patients were women ≥18 years with newly diagnosed stage III or IVA EC with measurable disease or stage IVB or recurrent EC with or without measurable disease. Patients (N=810) were randomized (1:1) to pembrolizumab or placebo plus paclitaxel-carboplatin followed by maintenance pembrolizumab or placebo for up to 24 months. Overall survival (OS) was a secondary endpoint and PFS per RECISTv1.1 by blinded independent central review (BICR) was an exploratory endpoint. OS data were immature; HRs favored pembrolizumab (mismatch repair-proficient: 0.79 [0.53−1.17]; 1-sided nominal *P*=0.1157; mismatch repair-deficient: 0.55 [0.25−1.19]; 1-sided nominal *P*=0.0617). HRs (95% CIs) for PFS per BICR favored pembrolizumab (mismatch repair-proficient: 0.64 [0.49−0.85]; *P*=0.0008; mismatch repair-deficient: 0.45 [0.27−0.73]; *P*=0.0005). These findings further support the use of pembrolizumab plus chemotherapy as first-line treatment for patients with advanced stage or recurrent EC regardless of MMR status (NRG-GY018 ClinicalTrials.gov identifier: NCT03914612).

INTRODUCTION

Numerous studies have investigated the efficacy and safety of immune checkpoint inhibitors, alone and in combination with other agents, for treatment of patients with advanced or recurrent endometrial cancer.[1,2] In the phase 2 KEYNOTE-158 study, monotherapy with the anti−PD-1 monoclonal antibody pembrolizumab resulted in objective responses in 48% (95% CI, 37%−60%) of patients with previously treated advanced, microsatellite instability-high/mismatch repair-deficient (dMMR) endometrial cancer.[3] In the phase 3 KEYNOTE-775 study, combination therapy with pembrolizumab and the multitargeted tyrosine kinase inhibitor lenvatinib led to statistically significant and clinically meaningful improvements in progression-free survival (PFS) and overall survival (OS) versus chemotherapy of the treating physician's choice (doxorubicin or paclitaxel) in patients with previously treated advanced, recurrent, or metastatic endometrial cancer.[4,5] Benefits were seen in patients with mismatch repair-proficient (pMMR) tumors and all-comers. Results from the KEYNOTE-158 and KEYNOTE-775 studies led to regulatory approval of pembrolizumab alone (dMMR or tumor mutational burden-high) or with lenvatinib (pMMR or all-comers, depending on country) in patients with endometrial cancer following prior systemic (platinum) based therapy.[6,7]

The phase 3 NRG GY018 study evaluated the addition of pembrolizumab to first-line paclitaxel plus carboplatin in patients with advanced, metastatic, or recurrent endometrial cancer.[8] Pembrolizumab plus paclitaxel and carboplatin resulted in statistically significant and clinically meaningful improvement in investigator-assessed PFS (primary endpoint) versus placebo plus chemotherapy in both the pMMR and dMMR populations at interim analysis (IA). Pembrolizumab did not increase the frequency of adverse events (AEs) commonly associated with paclitaxel plus carboplatin.[8] Based on these results, the pembrolizumab plus chemotherapy regimen was approved, irrespective of MMR status, in the United States (June 17, 2024) and Europe (October 24, 2024) and is now included as a recommended option in several treatment guidelines.[9,10] We present secondary and exploratory analyses from the NRG GY018 study.

RESULTS

Interim Analyses

Patients: At IA (DCO, December 6, 2022 for pMMR; December 16, 2022 for dMMR), 810 patients were randomized across 4 countries (United States, Canada, Japan, and Republic of Korea). In the pMMR population (n=588), 294 patients were randomized to pembrolizumab plus chemotherapy and 294 were randomized to placebo plus chemotherapy (Fig 1). In the dMMR population (n=222), 110 patients were randomized to pembrolizumab plus chemotherapy and 112 were randomized to placebo plus chemotherapy. Demographics and baseline clinical characteristics were generally balanced between treatment groups in both the pMMR and dMMR populations (Table 1). Most patients in both populations had PD-L1 combined positive score (CPS) ≥1 tumors (71.7%, pMMR; 83.6%, dMMR). Median (range) follow-up for IA was 10.0 (0.0−37.8) months in the pMMR population and 14.4 (4.0−39.4) months in the dMMR population.

Primary Endpoint

PFS by Investigator Assessment. Using the intention-to-treat principle, in the pMMR population, 95 events (32.3%) occurred in the pembrolizumab plus chemotherapy group and 138 (46.9%) occurred in the placebo plus chemotherapy group (Fig 2A). Median PFS was 13.1 (95% CI, 10.6−19.5) and 8.7 (95% CI, 8.4−11.0) months, respectively. The hazard ratio (HR) for PFS significantly favored pembrolizumab plus chemotherapy (0.57 [95% CI, 0.44−0.74]; $P<0.0001$ [prespecified boundary for statistical significance, 0.001162]). In the dMMR population, 29 events (26.4%) occurred in the pembrolizumab plus chemotherapy group and 60 (53.6%) occurred in the placebo plus chemotherapy group (Fig 2B). Median PFS was not reached and 8.3 (95% CI, 6.5−12.3) months, respectively. The HR for PFS significantly favored pembrolizumab plus chemotherapy (0.34 [95% CI, 0.22−0.53]; $P<0.0001$ [prespecified boundary for statistical significance, 0.002074]).

Secondary Endpoints

Local and Central MMR Immunohistochemistry (IHC). There was a high level of concordance between local and central MMR IHC assessments (Data Supplement, Table 1). Among 749 patients with both local and central results, 721 (96.3%) had concordant MMR status; Cohen kappa coefficient was 0.9068.

OS. Survival data were immature at IA. The pMMR population had an information fraction of 27.2%; 45 deaths (15.3%) occurred in the pembrolizumab plus chemotherapy group and 54 (18.4%) occurred in the placebo plus chemotherapy group (Fig 3A). The HR for OS was 0.79 (95% CI, 0.53−1.17; 1-sided nominal $P=0.1157$). The dMMR population had an information fraction of 18.0%; 10 deaths (9.1%) occurred in the pembrolizumab plus chemotherapy group and 17 (15.2%) occurred in the placebo plus chemotherapy group (Fig 3B). The HR for OS was 0.55 (95% CI, 0.25−1.19; 1-sided nominal $P=0.0617$).

Among those who discontinued treatment, more patients in the placebo versus pembrolizumab group received subsequent PD-1/PD-L1 inhibitors in the pMMR (45.0%

[76/169] vs 19.3% [28/145]) and dMMR (54.5% [42/77] vs 19.1% [9/47]) populations (Data Supplement, Table 2).

Exploratory Endpoints

PFS by Demographics and Baseline Characteristics. HRs for PFS by investigator assessment favored pembrolizumab plus chemotherapy across all subgroups defined by demographics and baseline clinical characteristics, including histology, in both the pMMR (Fig 4A) and dMMR (Fig 4B) populations.

PFS by Tumor PD-L1 Expression. In the pMMR population, the HR (95% CI) for PFS by investigator assessment was 0.59 (0.43−0.80) in patients with PD-L1 CPS ≥1 tumors (Fig 4C) and 0.44 (0.26−0.75) in patients with PD-L1 CPS <1 tumors (Fig 4D). In the dMMR population, the corresponding HRs (95% CIs) for PFS were 0.27 (0.16−0.47; Fig 4E) and 0.30 (0.11−0.83; Fig 4F), respectively, although there were few patients and events in the PD-L1 CPS <1 subgroup.

PFS by Methylation Status in dMMR Population. The HR (95% CI) for PFS by investigator assessment was 0.30 (0.18−0.50) in patients with methylation and 0.17 (0.04−0.79) in patients without methylation, suggestive of MMR gene mutation (Extended Data Fig 1).

PFS by Blinded Independent Central Review (BICR). In the pMMR population, median PFS was 19.5 (95% CI, 13.1−28.0) and 11.0 (95% CI, 9.0−11.5) months with pembrolizumab plus chemotherapy versus placebo plus chemotherapy, respectively (HR, 0.64 [95% CI, 0.49−0.85]; 1-sided nominal P=0.0008; Extended Data Fig 2A). In the dMMR population, median PFS was not reached with pembrolizumab plus chemotherapy and 14.1 months (95% CI, 8.5 months−not reached) with placebo plus chemotherapy (HR, 0.45 [95% CI, 0.27−0.73]; 1-sided nominal P=0.0005; Extended Data Fig 2B).

Ad Hoc Analyses (DCO, August 18, 2023): The secondary endpoints of OS, ORR, and safety were assessed at the time of the ad hoc analyses.

Patients: At the time of the ad hoc analysis, 819 patients were randomized (see Extended Data Fig 3 and Extended Data Table 1 for disposition and demographics and baseline clinical characteristics, respectively). Median (range) follow-up for ad hoc analyses was 20.8 (7.9−46.2) months in the pMMR population and 22.5 (12.0−47.4) months in the dMMR population.

Secondary Endpoints

OS. The pMMR population had an information fraction of 46.4%; 77 deaths (25.8%) occurred in the pembrolizumab plus chemotherapy group and 92 (30.8%) occurred in the placebo plus chemotherapy group (Extended Data Fig 4A). Thus, 32 and 38 more OS events, respectively, had occurred at the time of the ad hoc analyses compared with the IA. The HR for OS was 0.80 (95% CI, 0.59−1.08; 1-sided nominal P=0.0683). The dMMR population had an information fraction of 29.3%; 17 deaths (15.5%) occurred in the pembrolizumab

plus chemotherapy group and 27 (24.1%) occurred in the placebo plus chemotherapy group (Extended Data Fig 4B). Thus, 7 and 10 more OS event, respectively, had occurred at the time of the ad hoc analyses compared with the IA. The HR for OS was 0.57 (95% CI, 0.31−1.04; 1-sided nominal P=0.0323).

Among those who discontinued treatment, more patients in the placebo versus pembrolizumab group received subsequent PD-1/PD-L1 inhibitors in the pMMR (42.9% [118/275] vs 21.9% [47/215]) and dMMR (51.0% [53/104] vs 17.9% [10/56]) populations (Data Supplement, Table 3). Results of the sensitivity analysis demonstrated a lower HR for OS in the pMMR population (HR, 0.70; 95% CI, 0.50−0.98) when accounting for poststudy immunotherapy use (Extended Data Fig 4C). Due to sparse OS events in the dMMR population with/without subsequent anti−PD-1/PD-L1 therapies with or without lenvatinib, the model and bootstrap samples were not stable for the dMMR population during the first stage parametric survival model. Consequently, the 2-stage model result for the dMMR population is not presented.

Objective Response (Investigator Assessment). The objective response rate (ORR) in the pMMR population was 72.3% (95% CI, 66.0%−78.1%) in the pembrolizumab plus chemotherapy group and 59.0% (95% CI, 52.5%−65.3%) in the placebo plus chemotherapy group (Extended Data Fig 5A and Extended Data Table 2). Median duration of response (DOR) was 8.1 (range, 0.0+ to 40.9+; + indicates no progressive disease at last disease assessment) and 6.4 (range, 0.0+ to 28.3+) months, respectively (Extended Data Fig 6A). In the dMMR population, the ORR was 82.1% (95% CI, 72.9%−89.2%) in the pembrolizumab plus chemotherapy group and 71.6% (95% CI, 61.4%−80.4%) in the placebo plus chemotherapy group (Extended Data Fig 5B). Median DOR was not reached (range, 0.0+ to 41.8+) and 4.8 (range, 0.0+ to 42.2+) months, respectively (Extended Data Fig 6B). Waterfall plots are shown in Extended Data Fig 7. Response rates at IA, when some patients had no postbaseline assessment available for response evaluation, are summarized in Extended Data Table 3. Notably, the ORR and DOR still favored the pembrolizumab plus chemotherapy group.

Safety. In the combined pMMR and dMMR populations, AEs were reported in 99.2% of patients in the pembrolizumab plus chemotherapy group and 99.7% in the placebo plus chemotherapy group (Table 2). Grade ≥3 AEs occurred in 65.7% and 49.2% of patients, respectively. The most common AEs (≥20% of patients in either group) are shown in Table 2. Treatment-related AEs occurred in 96.9% of patients in the pembrolizumab plus chemotherapy group and 96.1% in the placebo plus chemotherapy group and were grade ≥3 in 49.9% and 34.0%, respectively. Study treatment was discontinued because of AEs in 18.2% and 7.2% of patients, respectively (Extended Data Fig 3). Immune-mediated AEs and infusion reactions were experienced by 39.6% of patients in the pembrolizumab plus chemotherapy group and 26.3% in the placebo plus chemotherapy group and were grade ≥3 in 9.7% and 4.1%, respectively (Table 2).

DISCUSSION

At the IA, the NRG GY018 study met its primary endpoint, with the addition of pembrolizumab (vs placebo) to chemotherapy significantly prolonging investigator-assessed PFS regardless of MMR status.[8] As noted, patients were categorized as pMMR or dMMR somewhat differently in the current analysis (intention to treat [ITT] using value assigned at stratification whether central or local result) compared with the previous analysis.[8] It is not surprising, however, that outcomes showed limited differences given the high level of concordance between central and local MMR testing. Investigator-assessed PFS HRs were 0.57 in the current analysis and 0.54 in the previous analysis for the pMMR population and 0.34 and 0.30, respectively, for the dMMR population.[8]

Notably, investigator-assessed PFS favored pembrolizumab plus chemotherapy in all subgroups, including those based on PD-L1 CPS (both populations), methylation (assessed in dMMR population), and histology (both populations). Importantly, in both the pMMR and dMMR populations, results for PFS were consistent in showing clinically meaningful improvement regardless of assessment by investigators or BICR with risk reductions of 43% and 36%, respectively, in the pMMR population and 66% and 55%, respectively, in the dMMR population. Differences between BICR and investigator assessment are expected. Generally, BICR has a more limited and conservative approach to declaring progressive disease by RECIST v1.1. This phenomenon where progressive disease is declared at a later time point by BICR versus investigator is often observed in clinical studies whether blinded or open-label as investigators, unlike BICR, have knowledge of corollary data (including but not limited to signs, symptoms, laboratory abnormalities, and procedures such as biopsy with pathological assessment or supplemental imaging). Consistent findings between investigator- and BICR-assessed PFS were also reported in the GOG-3031/RUBY[11] and GOG-3041/DUO-E studies.[12]

Most patients had PD-L1 CPS ≥1 tumors in both the pMMR and dMMR populations. In the pMMR population, addition of pembrolizumab to chemotherapy reduced the risk of investigator-assessed disease progression or death by 41% and 56% in patients with PD-L1 CPS ≥1 and <1 tumors, respectively. Respective risk reductions in the dMMR population were 73% and 70%. In the GOG-3041/DUO-E study, most patients (67.3% overall) had PD-L1−positive tumors (Ventana SP263 IHC assay).[12] For the overall population, an exploratory analysis was performed showing that the addition of durvalumab to chemotherapy reduced the risk of investigator-assessed disease progression or death by a greater magnitude in patients with PD-L1−positive tumors (HR, 0.63; 95% CI, 0.48−0.83) compared with PD-L1−negative tumors (HR, 0.89; 95% CI, 0.59−1.34).[12] The discrepancy between NRG-GY018 and GOG-3041/DUO-E could be related to the assay used (eg, different antibodies and PD-L1 scoring methods) or the therapy (anti−PD-1 with pembrolizumab vs anti−PD-L1 with durvalumab).

Analysis of OS at IA suggested a directionally favorable benefit with the addition of pembrolizumab versus placebo to chemotherapy in both the pMMR and dMMR populations. This benefit was maintained at 9 months additional follow-up, despite substantial poststudy

immunotherapy, and improved with sensitivity analysis accounting for the poststudy immunotherapy.

As the DCO was in close proximity to the last patient enrolled and not all patients were yet randomized, some patients in our study did not have a postbaseline assessment available for response evaluation at the DCOs used for IA. An ad hoc analysis was therefore conducted with approximately 9 additional months of follow-up demonstrating higher response rates, depth of response (including complete response rate), and durability with the addition of pembrolizumab to chemotherapy.

Despite the biostatistical parameters of IA where the power to detect a difference was modest, especially in the pMMR population, the study met its primary endpoint secondary to robust improvement in PFS when adding pembrolizumab to carboplatin and paclitaxel. This led to the Data Monitoring Committee recommending discontinuation of study with sponsor unblinding to investigators and patients to their treatment arm so that the vast majority of participants would discontinue placebo. Due to conduct of the study in regions where there is widespread access to immunotherapy, as expected a substantial portion of patients received post study immunotherapy especially in the control arm. Sensitivity analysis accounting for this discrepancy still suggested a favorable OS benefit with the addition of pembrolizumab. Patients continue to be followed in the study; updated OS results, which were immature at the time of both the IA and ad hoc analyses, will be reported in the future. The study was a collaborative effort led by CTEP and NRG Oncology and a registrational trial for the manufacturer of pembrolizumab. Variations in statistical methodology used in this manuscript compared with the previous publication[8] (eg, categorization approach for patients into pMMR and dMMR populations, and statistical methodology details) were driven by increased harmonization with analytical approaches for other registrational KEYNOTE studies evaluating pembrolizumab that employed ITT principles and did not result in any meaningful differences in numerical values or study conclusions.

No safety concerns were identified with longer follow-up. Results continued to show that rates of chemotherapy-related AEs were not increased with the addition of pembrolizumab. In both treatment groups, rates of immune-mediated AEs and infusion reactions were slightly higher in this ad hoc analysis (39.6% with pembrolizumab plus chemotherapy, 26.3% with placebo plus chemotherapy) than in the primary publication (34.8% and 21.6%, respectively).[8] Rates of immune-mediated AEs in the pembrolizumab arm were consistent with those previously described for pembrolizumab monotherapy in patients with endometrial cancer.[3]

In conclusion, addition of pembrolizumab to first-line chemotherapy and continued as maintenance significantly prolonged investigator-assessed PFS, with secondary analysis showing HRs for OS favoring the pembrolizumab arm, despite substantial rates of poststudy immunotherapy, in patients with advanced, metastatic, or recurrent endometrial cancer regardless of MMR status. Combining pembrolizumab with chemotherapy improved investigator-assessed PFS regardless of PD-L1 expression, mechanism of MMR loss, or histology and led to more responses and better durability in both the pMMR and

dMMR endometrial cancer populations. PFS results were consistent when assessed by investigators versus BICR. These findings are supportive of the addition of pembrolizumab to chemotherapy as a first-line treatment for patients with advanced, metastatic, or recurrent endometrial cancer regardless of MMR status.

ONLINE METHODS

Patients.

Eligible patients in the NRG GY018 study (ClinicalTrials.gov, NCT03914612) were women ≥18 years with confirmed advanced (locoregional advanced stage III and IVA), metastatic (stage IVB), or recurrent endometrial cancer. Key inclusion criteria included newly diagnosed stage III or IVA endometrial cancer with measurable disease per RECIST v1.1 or stage IVB or recurrent endometrial cancer, with or without measurable disease; Eastern Cooperative Oncology Group (ECOG) performance status ≤ 2; and adequate hematologic, renal, and hepatic function. Patients with carcinosarcoma were not eligible for enrollment. Patients who received previous radiation or hormonal therapy were eligible. Prohibited previous treatments included immunotherapy (agents targeting PD-1, PD-L1, or cytotoxic T-lymphocyte antigen 4) and chemotherapy except for adjuvant chemotherapy if the treatment-free interval was ≥12 months. Central MMR IHC testing was required; local testing with central confirmation was also allowed (except for sites in Japan). Further details can be found in the study protocol (https://www.nejm.org/doi/suppl/10.1056/NEJMoa2302312/suppl_file/nejmoa2302312_protocol.pdf).

The study was conducted in accordance with the International Council for Harmonisation Good Clinical Practice guidelines and ethical principles that have their origin in the Declaration of Helsinki. The protocol was approved by an ethics body at each study site (see Data Supplement for a list of study sites). Patients provided written informed consent. Patients were not compensated for their participation in the study.

Study Design and Treatment.

In this phase 3, international, double-blind study, patients were randomized (1:1) to receive either pembrolizumab plus paclitaxel and carboplatin or placebo plus paclitaxel and carboplatin (6 cycles) followed by pembrolizumab or placebo maintenance (up to 14 cycles). Randomization was stratified according to MMR status (dMMR vs pMMR), ECOG performance status (0/1 vs 2), and receipt of previous adjuvant chemotherapy (yes vs no). All treatments were administered intravenously. Pembrolizumab 200 mg (or placebo), paclitaxel 175 mg/m^2, and carboplatin area under the curve 5 mg/mL/min were administered on day 1 of each 3-week cycle during the first 6 cycles. Pembrolizumab 400 mg or placebo was administered once every 6 weeks during maintenance.

The study was unblinded after meeting its primary endpoint of investigator-assessed PFS at IA (DCOs of December 6, 2022 and December 16, 2022 for pMMR and dMMR populations, respectively). Investigators were informed of patients' assigned treatment, and patients were made aware of the study outcome and their treatment assignment. Consequently, nearly all patients (>99%) in the placebo plus chemotherapy group

discontinued study treatment by the time of the ad hoc analysis reported herein (DCO, August 18, 2023), with some participants subsequently receiving immunotherapy outside the study. There were no clinically important protocol deviations; the approved protocol amendments are reflected in this manuscript and detailed in the study protocol.

Endpoints.

Results for the primary endpoint, PFS per RECIST v1.1 as assessed by the investigator in the pMMR and dMMR populations, were previously reported.[8] Secondary endpoints reported herein include concordance between local and central MMR IHC testing; OS; ORR, best overall response (BOR), and DOR per RECIST v1.1 as assessed by the investigator; and safety. Exploratory endpoints presented include the association between PD-L1 CPS with MMR status, subgroup analyses of investigator-assessed PFS per RECIST v1.1, and PFS per RECIST v1.1 as assessed by BICR. Secondary and exploratory endpoints were assessed separately in the pMMR and dMMR populations except for safety (combined population) and subgroup analyses of investigator-assessed PFS based on methylation status (dMMR population only).

Assessments.

Radiographic tumor measurements were performed within 28 days before treatment (baseline), every 9 weeks for the first 9 months, and every 12 weeks thereafter until disease progression or initiation of subsequent anticancer therapy (see Assessments in Data Supplement for more details). Formalin-fixed, paraffin-embedded unstained sections were provided for central MMR IHC testing; local MMR IHC testing was performed per institutional practice. PD-L1 expression in tumor samples was determined centrally using PD-L1 IHC 22C3 pharmDx (Agilent Technologies, Carpinteria, CA). Tumors with PD-L1 CPS ≥1 were considered PD-L1 positive. AEs that occurred from randomization through 30 days after the last dose of study drug were graded per National Cancer Institute Common Terminology Criteria for Adverse Events version 5.0.

Statistical Analyses.

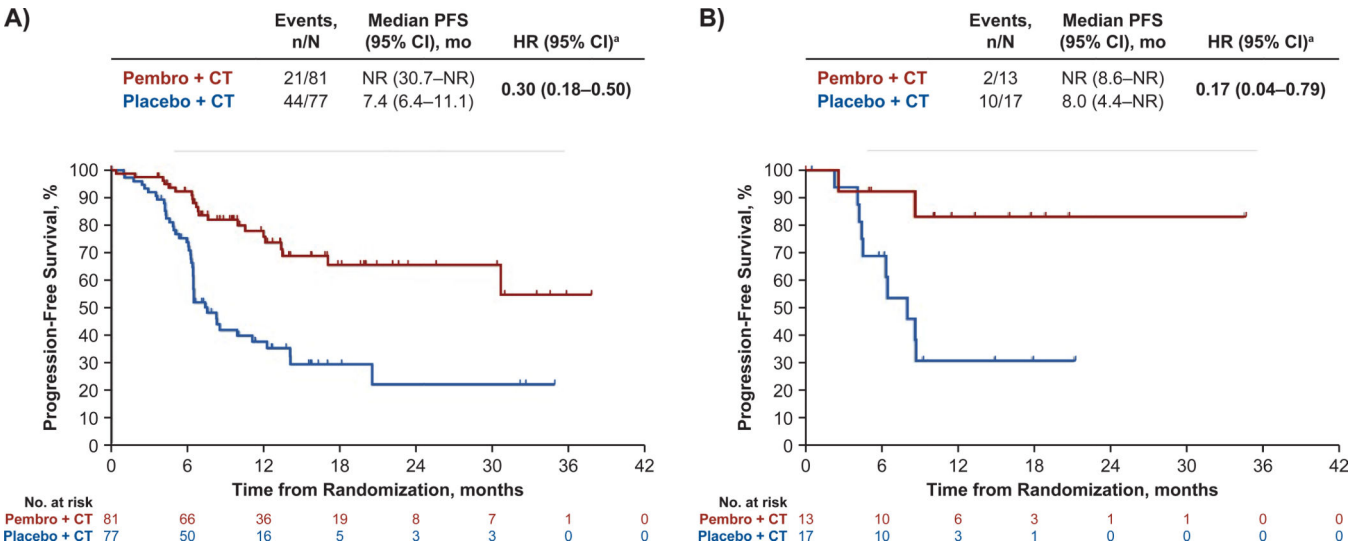
The expected number of PFS events for the final analysis was 394 (~196 at IA) in the pMMR population and 168 (~84 at IA) in the dMMR population. The initial alpha level for PFS hypothesis testing was set at 0.0125 1-sided and could be transferred to the other population upon achieving statistical significance. The expected number of deaths for the final analysis was 364 in the pMMR population and 150 in the dMMR population. Statistical analyses for secondary and exploratory endpoints are descriptive in nature; *P* values are nominal. Concordance between local and central MMR IHC testing was characterized using a Cohen kappa coefficient. PFS, OS, and DOR were analyzed using the Kaplan-Meier method for censored data. For both PFS and OS, data were censored at the last contact date if the event had not occurred. HRs and 95% CIs for PFS and OS were based on a Cox regression model with the Efron method of tie handling with treatment as a covariate stratified by prior chemotherapy. One-sided *P*-values were based on the log-rank test stratified by prior chemotherapy. Subgroup analyses of PFS were based on an unstratified Cox regression model. Gender analyses were not carried out as eligible patients were women. The 95% CIs for objective responses were based on the binomial exact method;

between-group differences and 95% CIs were based on the Miettinen and Nurminen method stratified by prior chemotherapy.

The primary DCO for the IA were December 6, 2022, for the pMMR population and December 16, 2022, for the dMMR population. Efficacy analyses at IA (PFS per investigator assessment including in subgroups, PFS by BICR, and OS) were conducted in the intention-to-treat population. Because some patients had no postbaseline assessment available for response evaluation at the December 2022 DCOs, an ad hoc analysis of ORR, BOR, and DOR was performed using a later DCO of August 18, 2023. Patients had to have measurable disease at baseline to be included in the analyses of objective responses. OS in the intention-to-treat population, along with sensitivity analysis for poststudy subsequent anticancer therapy, and safety in all randomized and treated patients were also assessed as part of the ad hoc analysis. Statistical methods for the confounding effect of subsequent anticancer therapy on OS are described in the Data Supplement.

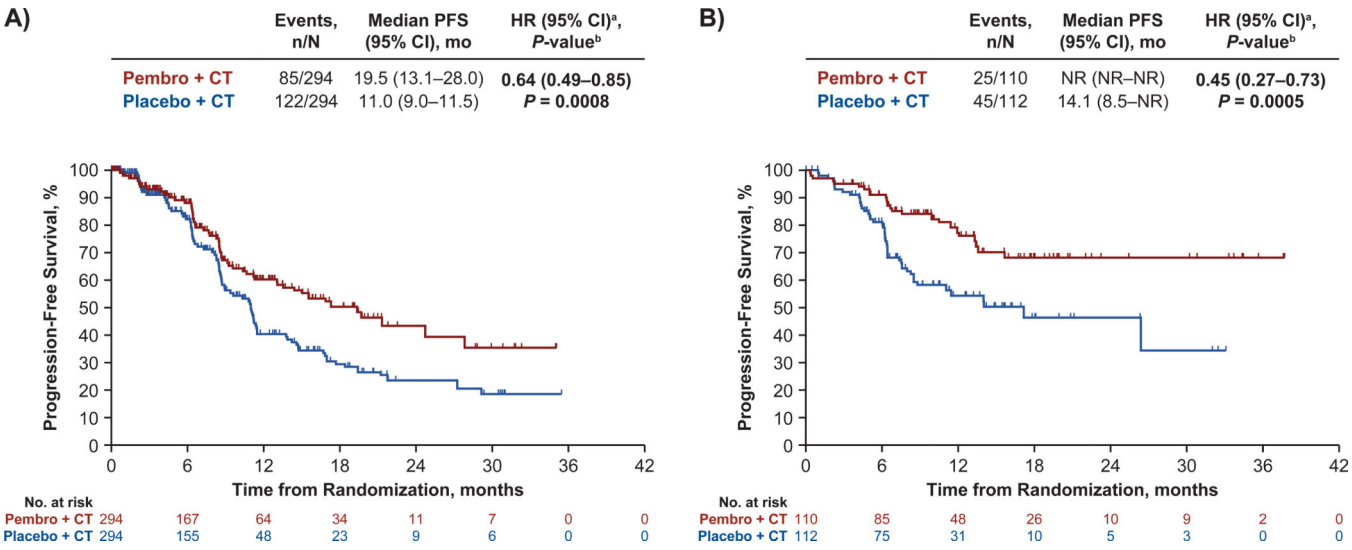
The current analyses and those described previously[1] used different methods of categorizing patients into either the pMMR or dMMR population. In the previous analyses, central MMR status was used, if available, with local MMR status being used in the absence of central results. Patients with indeterminate central MMR status were excluded as per protocol. For all of the current analyses presented here, patients were categorized based on the MMR stratification status used for randomization, which could have been based on either central or local MMR results. At the end of randomization, 819 patients had been randomized in the study. Nine patients in the pMMR population were randomized after the December 6, 2022 DCO and therefore were not included in both the current and previous PFS and OS analyses using the IA DCOs, but are included in the ad hoc analyses (August 18, 2023 DCO).

Extended Data



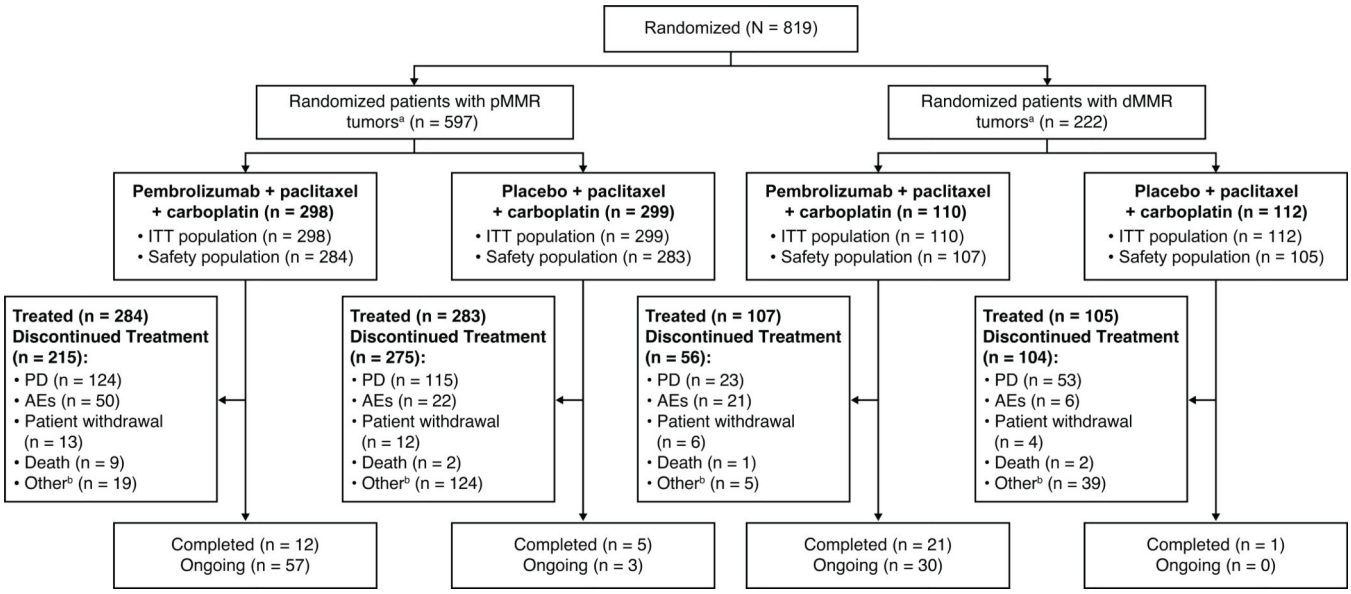
Extended Data Fig 1.
Kaplan-Meier–estimated PFS per RECIST v1.1 as assessed by the investigators in the dMMR population (A) with methylation and (B) with no methylation at interim analysis.

Data cutoff date: December 16, 2022. [a]Based on a Cox regression model with the Efron method of tie handling with treatment as a covariate. CT, chemotherapy; dMMR, mismatch repair-deficient; HR, hazard ratio; NR, not reached; pembro, pembrolizumab; PFS, progression-free survival; pMMR, mismatch repair-proficient; RECIST, Response Evaluation Criteria in Solid Tumors.



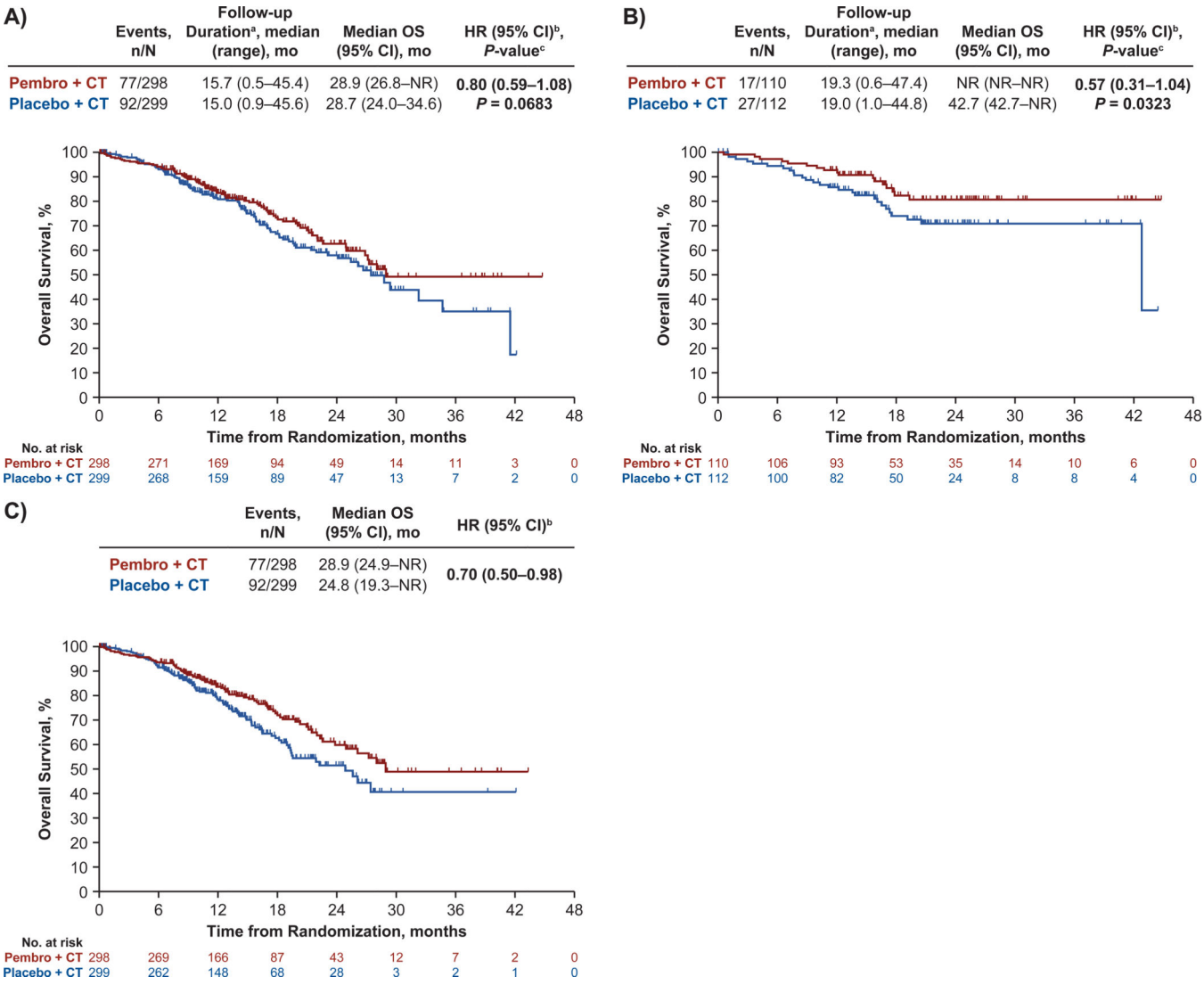
Extended Data Fig 2.

Kaplan-Meier–estimated PFS per RECIST v1.1 as assessed by BICR in the (A) pMMR and (B) dMMR populations at interim analysis. Data cutoff dates: December 6, 2022 (pMMR); December 16, 2022 (dMMR). [a]Based on a Cox regression model with the Efron method of tie handling with treatment as a covariate stratified by prior chemotherapy. [b]One-sided *P* value based on log-rank test stratified by prior chemotherapy. CT, chemotherapy; dMMR, mismatch repair-deficient; HR, hazard ratio; NR, not reached; pembro, pembrolizumab; PFS, progression-free survival; pMMR, mismatch repair-proficient; RECIST, Response Evaluation Criteria in Solid Tumors.



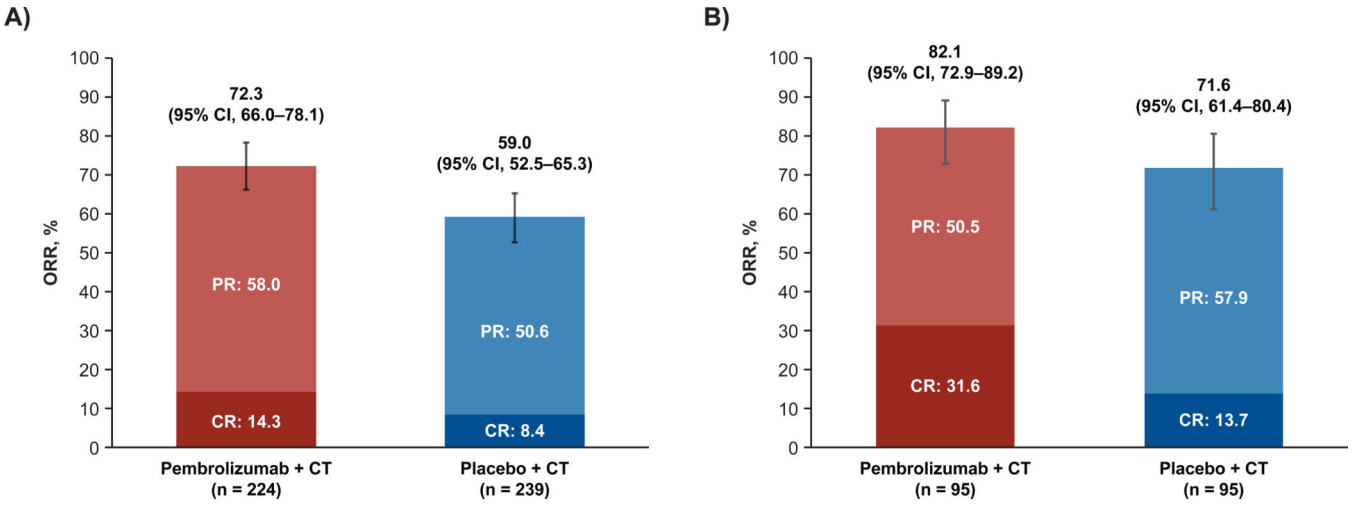
Extended Data Fig 3.

Patient disposition in the pMMR and dMMR populations at ad hoc analysis. Data cutoff date: August 18, 2023. [a]By central or local immunohistochemistry. [b]Includes alternative therapy (in absence of progression), off treatment due to other complicating disease, symptomatic deterioration, and other (not otherwise specified). AE, adverse event; dMMR, mismatch repair-deficient; ITT, intention to treat; PD, progressive disease; pMMR, mismatch repair-proficient.



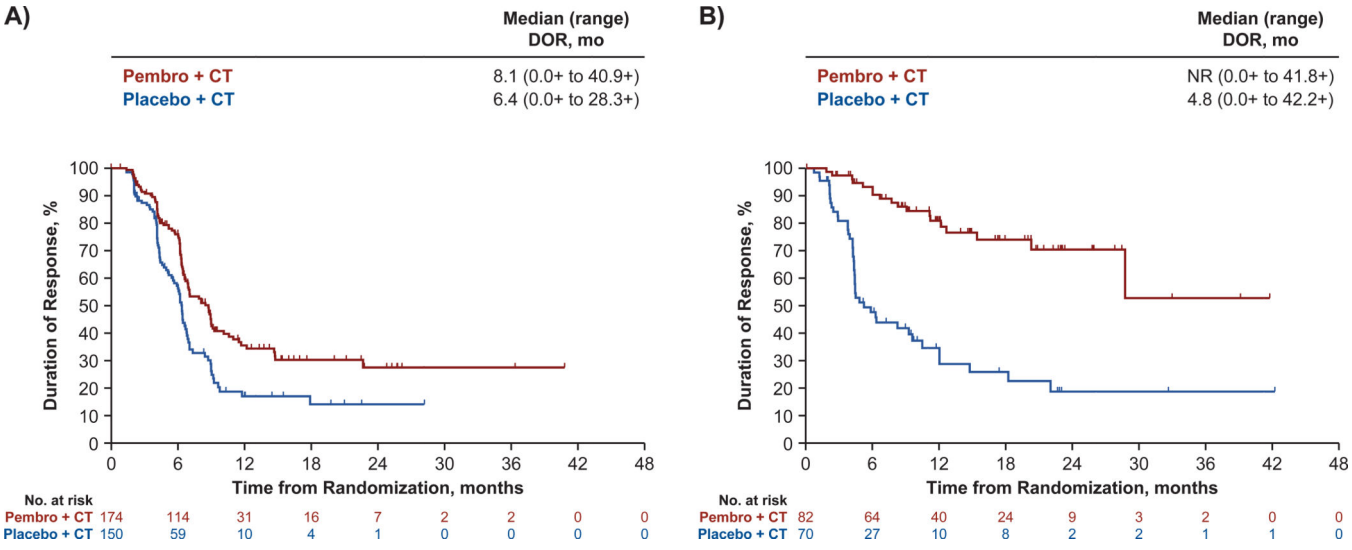
Extended Data Fig 4.

Kaplan-Meier–estimated OS in the (A) pMMR and (B) dMMR populations and (C) sensitivity analysis in the pMMR population at ad hoc analysis. OS data were immature (46.4% information fraction for pMMR population [169/364 events needed for final analysis had occurred] and 29.3% information fraction for dMMR population [44/150 events needed for final analysis had occurred]). Data cutoff date: August 18, 2023. [a]Follow-up duration is the time from randomization to the date of death or the database cutoff date if the participant is still alive; follow-up duration was not calculated for the sensitivity analysis (panel C) owing to the nature of the bootstrap analysis. [b]Based on a Cox regression model with the Efron method of tie handling with treatment as a covariate stratified by prior chemotherapy. [c]One-sided *P* value based on log-rank test stratified by prior chemotherapy. CT, chemotherapy; dMMR, mismatch repair-deficient; HR, hazard ratio; NR, not reached; OS, overall survival; pembro, pembrolizumab; pMMR, mismatch repair-proficient.



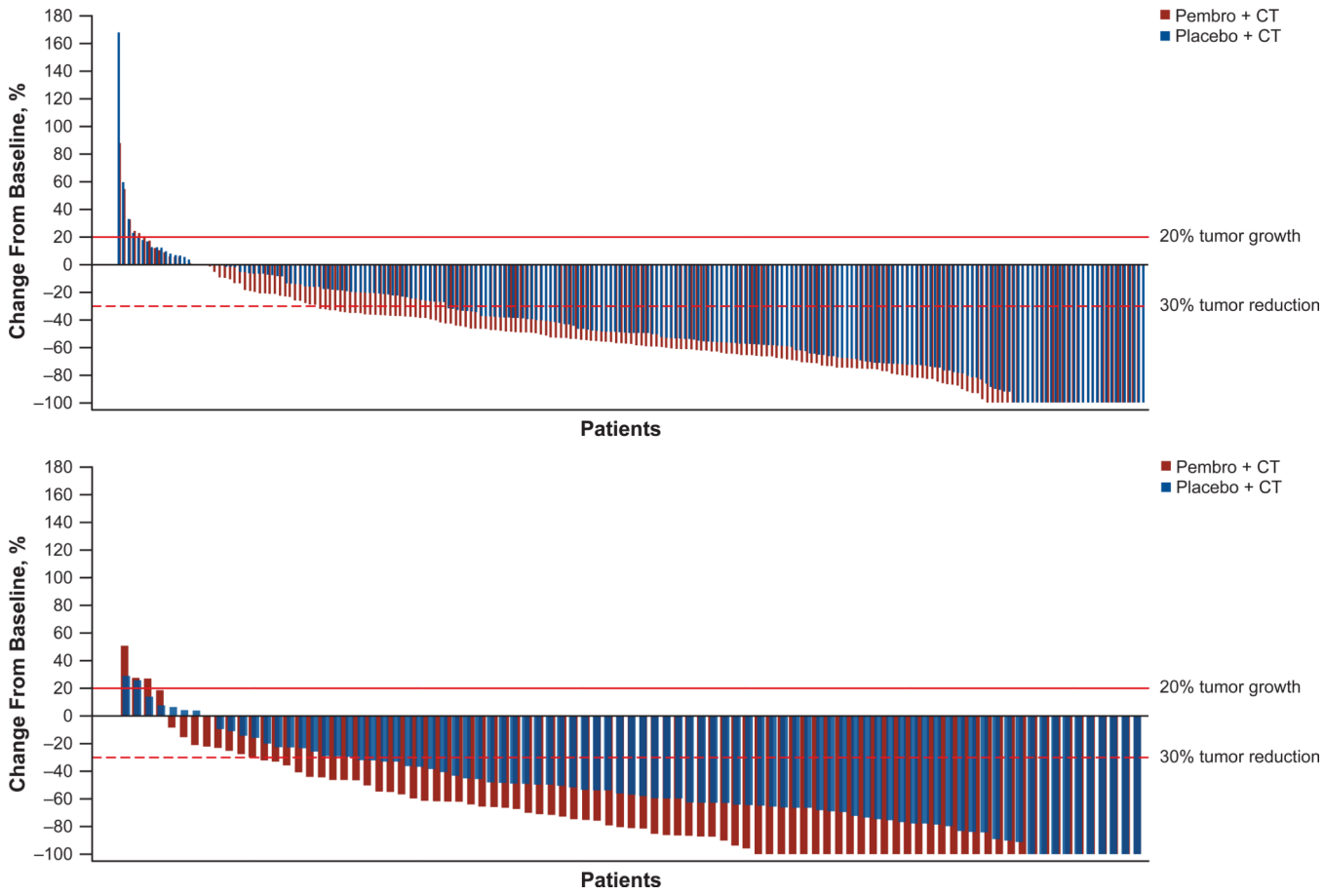
Extended Data Fig 5.

Investigator-assessed response rates per RECIST v1.1 at ad hoc analysis in the (A) pMMR and (B) dMMR populations. Analysis included patients in the intention-to-treat population with measurable disease at baseline. Data cutoff date: August 18, 2023. Data shown are the mean ORR and 95% CIs based on the binomial exact method. CR, complete response; CT, chemotherapy; dMMR, mismatch repair-deficient; ORR, objective response rate; pMMR, mismatch repair-proficient; PR, partial response; RECIST, Response Evaluation Criteria in Solid Tumors.



Extended Data Fig 6.

Kaplan-Meier–estimated DOR per RECIST v1.1 as assessed by the investigators in the (A) pMMR and (B) dMMR populations at ad hoc analysis. Data cutoff date: August 18, 2023. +, no progressive disease at last disease assessment; CT, chemotherapy; dMMR, mismatch repair-deficient; DOR, duration of response; NR, not reached; pembro, pembrolizumab; pMMR, mismatch repair-proficient; RECIST, Response Evaluation Criteria in Solid Tumors.



Extended Data Fig 7.

Investigator-assessed best percentage change from baseline in target lesions per RECIST v1.1 in the (A) pMMR and (B) dMMR populations at ad hoc analysis. Data cutoff date: August 18, 2023. CT, chemotherapy; dMMR, mismatch repair-deficient; pembro, pembrolizumab; pMMR, mismatch repair-proficient; RECIST, Response Evaluation Criteria in Solid Tumors.

Extended Data Table 1.

Demographics and Baseline Clinical Characteristics at Ad Hoc Analysis (ITT Population)

	pMMR Population			dMMR Population		
	Pembrolizumab + Chemotherapy (n = 298)	**Placebo + Chemotherapy (n = 299)**	**All Patients (n = 597)**	**Pembrolizumab + Chemotherapy(n = 110)**	**Placebo + Chemotherapy (n = 112)**	**All Patients (n = 222)**
Age, median (range), y	66.2 (31.0−94.0)	66.0 (29.0−91.0)	66.1 (29.0−94.0)	67.2 (39.0−82.0)	66.0 (37.0−86.0)	66.1 (37.0−86.0)
Race, n (%)						
White	216 (72.5)	215 (71.9)	431 (72.2)	91 (82.7)	85 (75.9)	176 (79.3)
Black or African American	46 (15.4)	51 (17.1)	97 (16.2)	10 (9.1)	9 (8.0)	19 (8.6)

	pMMR Population			dMMR Population		
	Pembrolizumab + Chemotherapy (n = 298)	**Placebo + Chemotherapy (n = 299)**	**All Patients (n = 597)**	**Pembrolizumab + Chemotherapy(n = 110)**	**Placebo + Chemotherapy (n = 112)**	**All Patients (n = 222)**
Asian	17 (5.7)	15 (5.0)	32 (5.4)	3 (2.7)	4 (3.6)	7 (3.2)
American Indian or Alaska Native	2 (0.7)	2 (0.7)	4 (0.7)	0 (0)	2 (1.8)	2 (0.9)
Native Hawaiian or other Pacific Islander	1 (0.3)	3 (1.0)	4 (0.7)	0 (0)	0 (0)	0 (0)
Multiracial	1 (0.3)	1 (0.3)	2 (0.3)	0 (0)	0 (0)	0 (0)
Missing data	15 (5.0)	12 (4.0)	27 (4.5)	6 (5.5)	12 (10.7)	18 (8.1)
Hispanic ethnic group, n (%)						
No	267 (89.6)	278 (93.0)	545 (91.3)	104 (94.5)	97 (86.6)	201 (90.5)
Yes	23 (7.7)	15 (5.0)	38 (6.4)	4 (3.6)	7 (6.3)	11 (5.0)
Unknown	4 (1.3)	3 (1.0)	7 (1.2)	1 (0.9)	4 (3.6)	5 (2.3)
Not reported	4 (1.3)	3 (1.0)	7 (1.2)	1 (0.9)	4 (3.6)	5 (2.3)
ECOG PS, n (%)						
0	200 (67.1)	201 (67.2)	401 (67.2)	70 (63.6)	72 (64.3)	142 (64.0)
1	89 (29.9)	89 (29.8)	178 (29.8)	39 (35.5)	35 (31.3)	74 (33.3)
2	9 (3.0)	9 (3.0)	18 (3.0)	1 (0.9)	5 (4.5)	6 (2.7)
PD-L1 CPS,[a] n	291	294	585	109	111	220
≥1, n (%)	209 (71.8)	209 (71.1)	418 (71.5)	87 (79.8)	97 (87.4)	184 (83.6)
<1, n (%)	82 (28.2)	85 (28.9)	167 (28.5)	22 (20.2)	14 (12.6)	36 (16.4)
Methylation, n	–	–	–	94	94	188
Yes, n (%)	–	–	–	81 (86.2)	77 (81.9)	158 (84.0)
No, n (%)	–	–	–	13 (13.8)	17 (18.1)	30 (16.0)
Histology, n (%)						
Adenocarcinoma NOS	24 (8.1)	35 (11.7)	59 (9.9)	12 (10.9)	12 (10.7)	24 (10.8)
Clear cell	19 (6.4)	20 (6.7)	39 (6.5)	0 (0)	0 (0)	0 (0)
Dedifferentiated or undifferentiated	7 (2.3)	6 (2.0)	13 (2.2)	4 (3.6)	4 (3.6)	8 (3.6)
Endometrioid						
Grade 1	56 (18.8)	46 (15.4)	102 (17.1)	20 (18.2)	34 (30.4)	54 (24.3)
Grade 2	52 (17.4)	59 (19.7)	111 (18.6)	52 (47.3)	43 (38.4)	95 (42.8)
Grade 3	53 (17.8)	45 (15.1)	98 (16.4)	15 (13.6)	16 (14.3)	31 (14.0)
Mixed epithelial	6 (2.0)	10 (3.3)	16 (2.7)	3 (2.7)	2 (1.8)	5 (2.3)
Serous	81 (27.2)	77 (25.8)	158 (26.5)	4 (3.6)	1 (0.9)	5 (2.3)
Missing	0 (0)	1 (0.3)	1 (0.2)	0 (0)	0 (0)	0 (0)

	pMMR Population			dMMR Population		
	Pembrolizumab + Chemotherapy (n = 298)	Placebo + Chemotherapy (n = 299)	All Patients (n = 597)	Pembrolizumab + Chemotherapy(n = 110)	Placebo + Chemotherapy (n = 112)	All Patients (n = 222)
FIGO stage at initial diagnosis						
I	105 (35.2)	104 (34.8)	209 (35.0)	45 (40.9)	57 (50.9)	102 (45.9)
II	25 (8.4)	25 (8.4)	50 (8.4)	13 (11.8)	13 (11.6)	26 (11.7)
III	57 (19.1)	47 (15.7)	104 (17.4)	18 (16.4)	11 (9.8)	29 (13.1)
IVA	11 (3.7)	5 (1.7)	16 (2.7)	2 (1.8)	4 (3.6)	6 (2.7)
IVB	99 (33.2)	118 (39.5)	217 (36.3)	32 (29.1)	27 (24.1)	59 (26.6)
Missing	1 (0.3)	0	1 (0.2)	0	0	0
Previous therapy, n (%)						
Chemotherapy	75 (25.2)	77 (25.8)	152 (25.5)	4 (3.6)	8 (7.1)	12 (5.4)
Radiotherapy	120 (40.3)	126 (42.1)	246 (41.2)	42 (38.2)	54 (48.2)	96 (43.2)
Surgery	269 (90.3)	253 (84.6)	522 (87.4)	97 (88.2)	104 (92.9)	201 (90.5)

Data cutoff date: August 18, 2023.

CPS, combined positive score; dMMR, mismatch repair-deficient; ECOG PS, Eastern Cooperative Oncology Group performance status; FIGO, International Federation of Gynecology and Obstetrics; ITT, intention to treat; NOS, not otherwise specified; PD-L1, programmed cell death ligand 1; pMMR mismatch repair-proficient.

[a]CPS was defined as the number of PD-L1−positive cells (tumor cells, lymphocytes, and macrophages) divided by the total number of tumor cells, multiplied by 100.

Extended Data Table 2.

Investigator-Assessed Best Overall Response per RECIST v1.1 at Ad Hoc Analysis (ITT Population With Measurable Disease at Baseline)

	pMMR Population		dMMR Population	
	Pembrolizumab + Chemotherapy (n = 224)	Placebo + Chemotherapy (n = 239)	Pembrolizumab + Chemotherapy (n = 95)	Placebo + Chemotherapy (n = 95)
ORR, n (%) [95% CI]	162 (72.3) [66.0−78.1]	141 (59.0) [52.5−65.3]	78 (82.1) [72.9−89.2]	68 (71.6) [61.4−80.4]
Best overall response, n (%)				
CR	32 (14.3)	20 (8.4)	30 (31.6)	13 (13.7)
PR	130 (58.0)	121 (50.6)	48 (50.5)	55 (57.9)
SD	26 (11.6)	55 (23.0)	7 (7.4)	16 (16.8)
PD	16 (7.1)	19 (7.9)	4 (4.2)	3 (3.2)
Not evaluable[a]	2 (0.9)	3 (1.3)	0	0
No assessment[b]	18 (8.0)	21 (8.8)	6 (6.3)	8 (8.4)
TTR, median (range), mo	2.3 (1.9–19.6)	2.3 (1.0–7.1)	2.3 (1.6–11.6)	2.3 (2.0–14.5)
DOR, median (range), mo	8.1 (0.0+ to 40.9+)	6.4 (0.0+ to 28.3+)	NR (0.0+ to 41.8+)	4.8 (0.0+ to 42.2+)

Data cutoff date: August 18, 2023.

"+" indicates no PD by the time of last disease assessment.

CR, complete response; dMMR, mismatch repair-deficient; DOR, duration of response; ITT, intention to treat; NR, not reached; ORR, objective response rate; PD, progressive disease; pMMR mismatch repair-proficient; PR, partial response; RECIST, Response Evaluation Criteria in Solid Tumors; SD, stable disease; TTR, time to response.

[a] Postbaseline assessment available but not evaluable.

[b] No postbaseline assessment available for response evaluation.

Extended Data Table 3.

Investigator-Assessed Best Overall Response Per RECIST v1.1 at Interim Analysis (ITT Population With Measurable Disease at Baseline)

	pMMR Population		dMMR Population	
	Pembrolizumab + Chemotherapy (n = 220)	**Placebo + Chemotherapy (n = 235)**	**Pembrolizumab + Chemotherapy (n = 95)**	**Placebo + Chemotherapy (n = 95)**
ORR, n (%) [95% CI]	135 (61.4) [54.6−67.8]	121 (51.5) [44.9−58.0]	74 (77.9) [68.2−85.8]	66 (69.5) [59.2−78.5]
Best overall response, n (%)				
CR	24 (10.9)	16 (6.8)	27 (28.4)	11 (11.6)
PR	111 (50.5)	105 (44.7)	47 (49.5)	55 (57.9)
SD	29 (13.2)	52 (22.1)	10 (10.5)	17 (17.9)
PD	12 (5.5)	19 (8.1)	5 (5.3)	3 (3.2)
Not evaluable[a]	2 (0.9)	2 (0.9)	0	1 (1.1)
No assessment[b]	42 (19.1)	41 (17.4)	6 (6.3)	8 (8.4)
TTR, median (range), mo	2.3 (1.9−19.6)	2.3 (1.0−7.1)	2.3 (1.3−11.5)	2.2 (2.0−6.2)
DOR, median (range), mo	7.1 (0.0+ to 32.8+)	6.4 (0.0+ to 20.1+)	NR (0.0+ to 33.0+)	4.4 (0.0+ to 32.8+)

Data cutoff dates: December 6, 2022 (pMMR); December 16, 2022 (dMMR).

"+" indicates no PD by the time of last disease assessment.

CR, complete response; dMMR, mismatch repair-deficient; DOR, duration of response; ITT, intention to treat; NR, not reached; ORR, objective response rate; PD, progressive disease; pMMR mismatch repair-proficient; PR, partial response; RECIST, Response Evaluation Criteria in Solid Tumors; SD, stable disease; TTR, time to response.

[a] Postbaseline assessment available but not evaluable.

[b] No postbaseline assessment available for response evaluation.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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DATA AVAILABILITY

Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, NJ, USA (MSD) is committed to providing qualified scientific researchers access to anonymized data and clinical study reports from the company's clinical trials for the purpose of conducting legitimate scientific research. MSD is also obligated to protect the rights and privacy of trial participants and, as such, has a procedure in place for evaluating and fulfilling requests for sharing company clinical trial data with qualified external scientific researchers. The MSD data sharing website (available at: https://externaldatasharing-msd.com/) outlines the process and requirements for submitting a data request. Applications will be promptly assessed for completeness and policy compliance. Feasible requests will be reviewed by a committee of MSD subject matter experts to assess the scientific validity of the request and the qualifications of the requestors. In line with data privacy legislation, submitters of approved requests must enter into a standard data-sharing agreement with MSD before data

access is granted. Data will be made available for request after product approval in the US and EU or after product development is discontinued. There are circumstances that may prevent MSD from sharing requested data, including country- or region-specific regulations. If the request is declined, it will be communicated to the investigator. Access to genetic or exploratory biomarker data requires a detailed, hypothesis-driven statistical analysis plan that is collaboratively developed by the requestor and MSD subject matter experts; after approval of the statistical analysis plan and execution of a data-sharing agreement, MSD will either perform the proposed analyses and share the results with the requestor or will construct biomarker covariates and add them to a file with clinical data that is uploaded to an analysis portal so that the requestor can perform the proposed analyses.

REFERENCES

1. Mamat Yusof MN et al. Efficacy and safety of PD-1/PD-L1 inhibitor as single-agent immunotherapy in endometrial cancer: a systematic review and meta-analysis. Cancers 15, 4032 (2023). [PubMed: 37627060]
2. Bartoletti M et al. Incorporation of anti-PD1 or anti PD-L1 agents to platinum-based chemotherapy for the primary treatment of advanced or recurrent endometrial cancer. A meta-analysis. Cancer Treat Rev 125, 102701 (2024).
3. O'Malley DM et al. Pembrolizumab in patients with microsatellite instability-high advanced endometrial cancer: results from the KEYNOTE-158 study. J Clin Oncol 40, 752–761 (2022). [PubMed: 34990208]
4. Makker V et al. Lenvatinib plus pembrolizumab for advanced endometrial cancer. N Engl J Med 386, 437–448 (2022). [PubMed: 35045221]
5. Makker V et al. Lenvatinib plus pembrolizumab in previously treated advanced endometrial cancer: updated efficacy and safety from the randomized phase III study 309/KEYNOTE-775. J Clin Oncol 41, 2904–2910 (2023). [PubMed: 37058687]
6. U.S. Food and Drug Administration. Keytruda (pembrolizumab). Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, NJ, USA (2024).
7. European Medicines Agency. Summary of Product Characteristics. Keytruda (pembrolizumab). Haarlem, The Netherlands, Merck Sharp & Dohme B.V. (2024).
8. Eskander RN et al. Pembrolizumab plus chemotherapy in advanced endometrial cancer. N Engl J Med 388, 2159–2170 (2023). [PubMed: 36972022]
9. National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines). Uterine Neoplasms. Version 2. September 23, 2024.
10. Tempfer C et al. Statement of the Uterus Commission of the Gynecological Oncology Working Group (AGO) on the use of primary chemoimmunotherapy to treat patients with locally advanced or recurrent endometrial cancer. Geburtshilfe und Frauenheilkunde 83, 1095–1101 (2023). [PubMed: 38230409]
11. Powell MA et al. Dostarlimab for primary advanced or recurrent (A/R) endometrial cancer (EC): outcomes by blinded independent central review (BICR) of the RUBY trial (ENGOT-EN6-NSGO/GOG-3031/RUBY). J Clin Oncol 41, Abstract 5503 (2023).
12. Westin SN et al. Durvalumab plus carboplatin/paclitaxel followed by maintenance durvalumab with or without olaparib as first-line treatment for advanced endometrial cancer: the phase III DUO-E trial. J Clin Oncol 42, 283–299 (2024). [PubMed: 37864337]

METHODS-ONLY REFERENCES

1. Eskander RN et al. Pembrolizumab plus chemotherapy in advanced endometrial cancer. N Engl J Med 388, 2159–2170 (2023). [PubMed: 36972022]

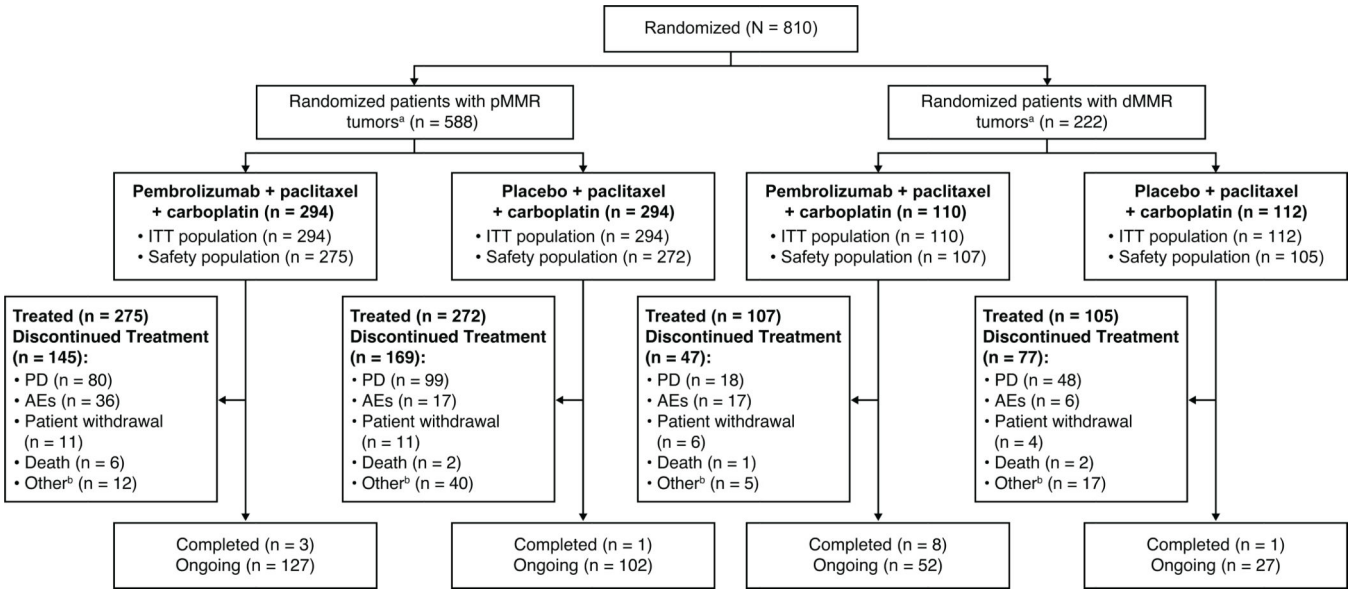

Fig 1.

Patient disposition in the pMMR and dMMR populations at interim analysis. Data cutoff dates: December 6, 2022 (pMMR); December 16, 2022 (dMMR). [a]By central or local immunohistochemistry. [b]Includes alternative therapy (in absence of progression), off treatment due to other complicating disease, symptomatic deterioration, and other (not otherwise specified). AE, adverse event; dMMR, mismatch repair-deficient; ITT, intention to treat; PD, progressive disease; pMMR, mismatch repair-proficient.

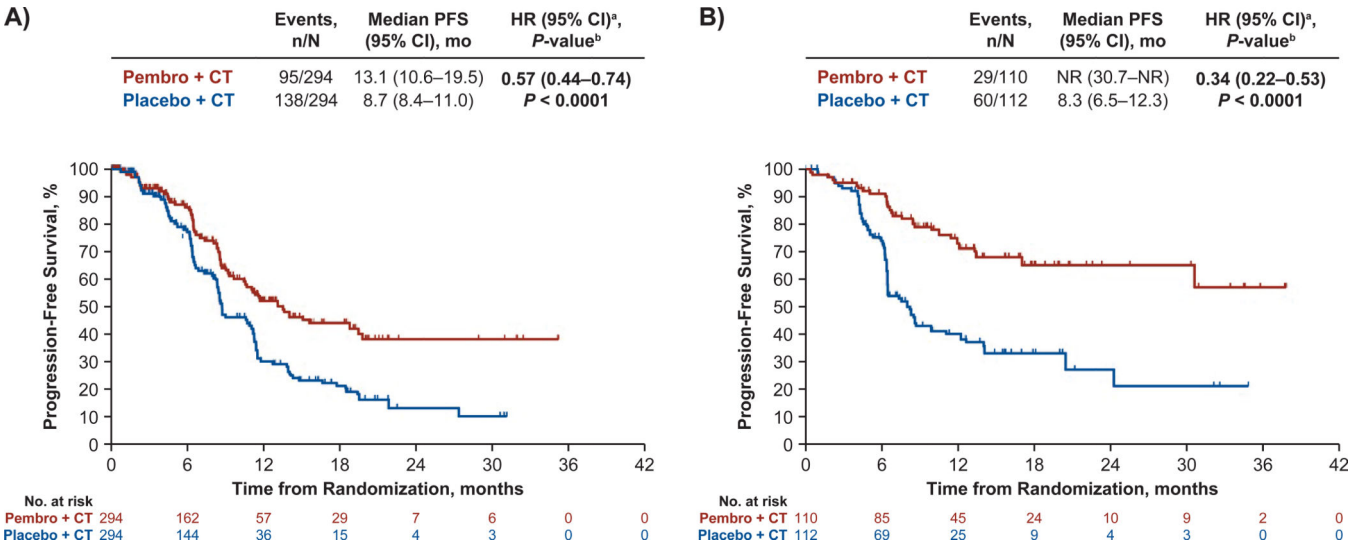

Fig 2.

Kaplan-Meier–estimated PFS per RECIST v1.1 as assessed by the investigators in the (A) pMMR and (B) dMMR populations at interim analysis. Tick marks indicate censored data. Data cutoff dates: December 6, 2022 (pMMR); December 16, 2022 (dMMR). [a]Based on a Cox regression model with the Efron method of tie handling with treatment as a covariate stratified by prior chemotherapy. [b]One-sided *P* value based on log-rank test stratified by prior chemotherapy. CT, chemotherapy; dMMR, mismatch repair-deficient; HR, hazard ratio; NR, not reached; pembro, pembrolizumab; PFS, progression-free survival; pMMR, mismatch repair-proficient; RECIST, Response Evaluation Criteria in Solid Tumors.

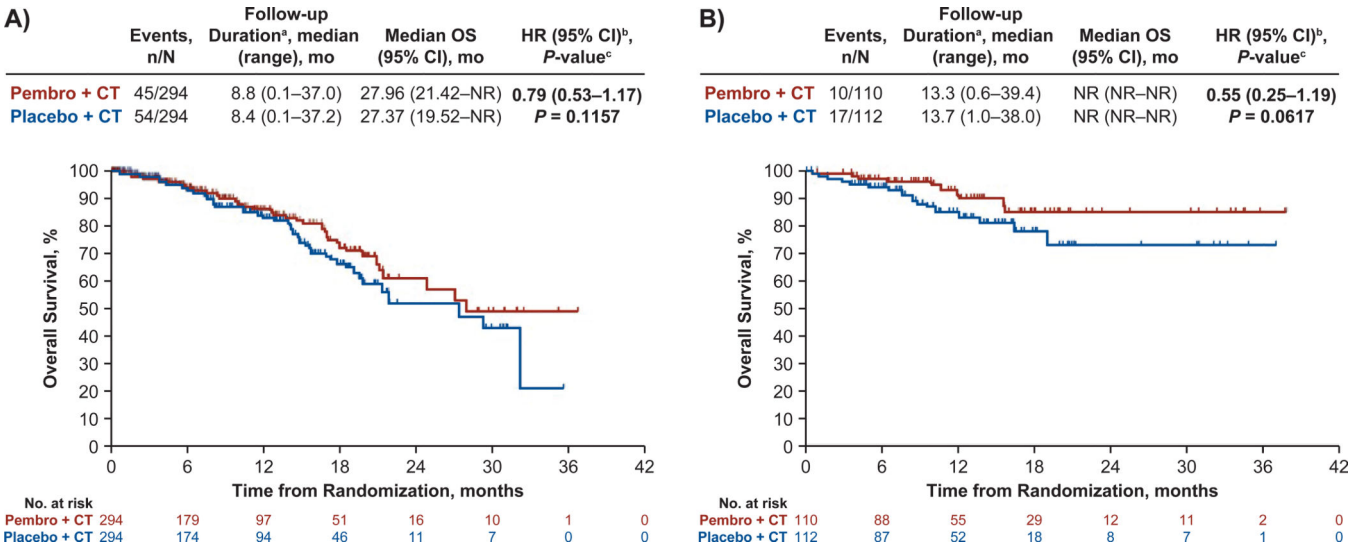

Fig 3.

Kaplan-Meier–estimated OS in the (A) pMMR and (B) dMMR populations at interim analysis. OS data were immature (27.2% information fraction for pMMR population [99/364 events needed for final analysis had occurred] and 18.0% information fraction for dMMR population [27/150 events needed for final analysis had occurred]). Tick marks indicated censored data. Data cutoff dates: December 6, 2022 (pMMR); December 16, 2022 (dMMR). [a]Follow-up duration is the time from randomization to the date of death or the database cutoff date if the participant is still alive. [b]Based on a Cox regression model with the Efron method of tie handling with treatment as a covariate stratified by prior chemotherapy. [c]One-sided *P* value based on log-rank test stratified by prior chemotherapy. CT, chemotherapy; dMMR, mismatch repair-deficient; HR, hazard ratio; OS, overall survival; NR, not reached; pembro, pembrolizumab; pMMR, mismatch repair-proficient.

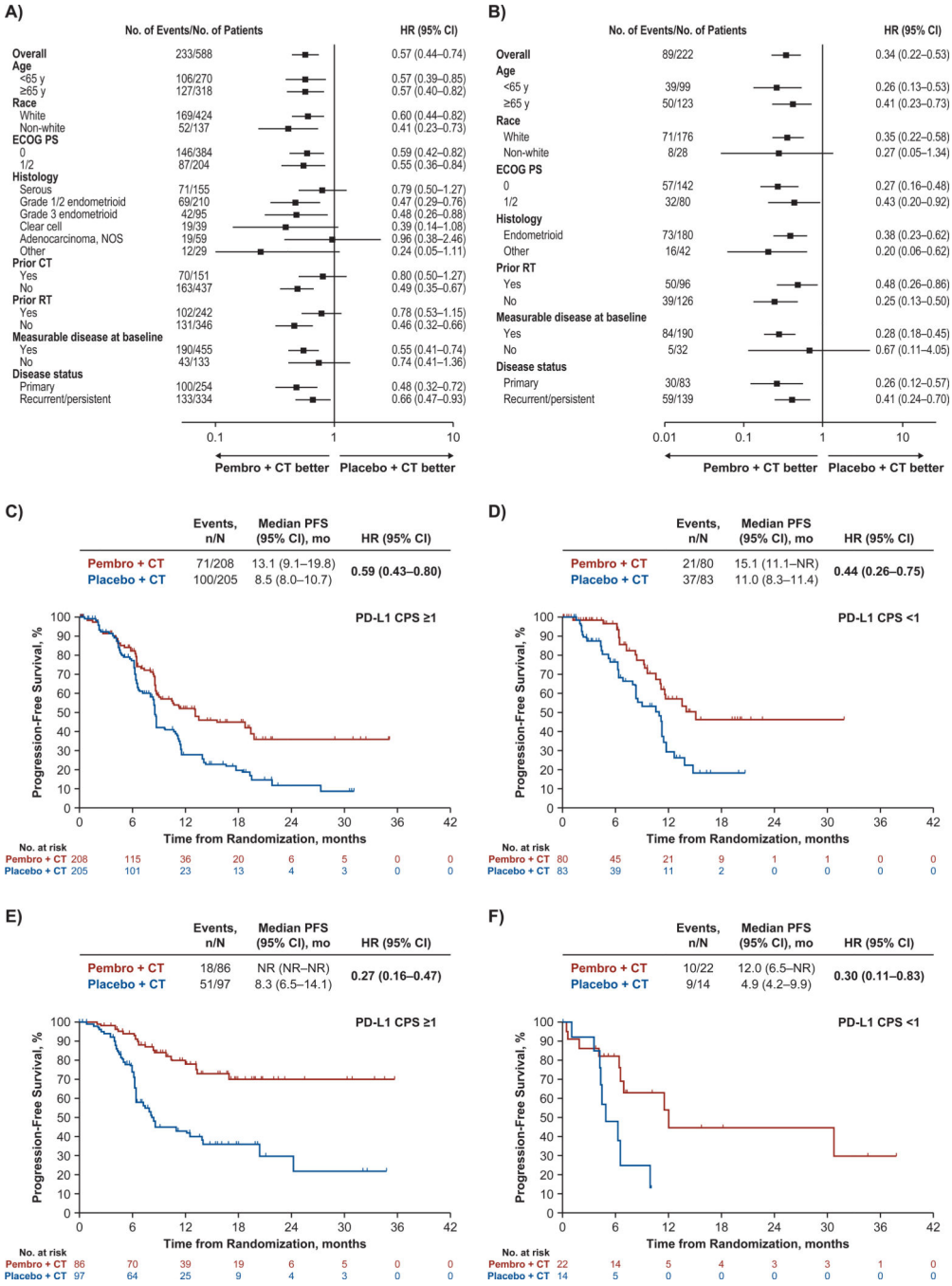

Fig 4.

Kaplan-Meier–estimated PFS per RECIST v1.1 as assessed by the investigators in subgroups defined by demographics and baseline clinical characteristics in the (A) pMMR population and (B) dMMR population at interim analysis. Results are also shown for the (C) pMMR population with PD-L1 CPS ≥1 tumors, (D) pMMR population with PD-L1 CPS <1 tumors, (E) dMMR population with PD-L1 CPS ≥1 tumors, and (F) dMMR population with PD-L1 CPS <1 tumors at interim analysis. Data shown in panels A and B are the HRs (pembrolizumab plus chemotherapy vs placebo plus chemotherapy) and the

corresponding 95% CIs. Data cutoff dates: December 6, 2022 (pMMR); December 16, 2022 (dMMR). Subgroup analyses of PFS were based on an unstratified Cox regression model. CPS was defined as the number of PD-L1−positive cells (tumor cells, lymphocytes, and macrophages) divided by the total number of tumor cells, multiplied by 100. CPS, combined positive score; CT, chemotherapy; dMMR, mismatch repair-deficient; ECOG PS, Eastern Cooperative Oncology Group performance status; HR, hazard ratio; NOS, not otherwise specified; NR, not reached; pembro, pembrolizumab; PD-L1, programmed cell death ligand 1; PFS, progression-free survival; pMMR, mismatch repair-proficient; RECIST, Response Evaluation Criteria in Solid Tumors; RT, radiotherapy

Table 1.

Demographics and Baseline Clinical Characteristics at Interim Analysis (ITT Population)

	pMMR Population			dMMR Population		
	Pembrolizumab + Chemotherapy (n = 294)	**Placebo + Chemotherapy (n = 294)**	**All Patients (n = 588)**	**Pembrolizumab + Chemotherapy (n = 110)**	**Placebo + Chemotherapy (n = 112)**	**All Patients (n = 222)**
Age, median (range), y	66.0 (31.0–94.0)	66.1 (29.0–91.0)	66.1 (29.0–94.0)	67.2 (39.0–82.0)	66.0 (37.0–86.0)	66.1 (37.0–86.0)
Race, n (%)						
White	212 (72.1)	212 (72.1)	424 (72.1)	91 (82.7)	85 (75.9)	176 (79.3)
Black or African American	46 (15.6)	50 (17.0)	96 (16.3)	10 (9.1)	9 (8.0)	19 (8.6)
Asian	17 (5.8)	14 (4.8)	31 (5.3)	3 (2.7)	4 (3.6)	7 (3.2)
American Indian or Alaska Native	2 (0.7)	2 (0.7)	4 (0.7)	0 (0)	2 (1.8)	2 (0.9)
Native Hawaiian or other Pacific Islander	1 (0.3)	3 (1.0)	4 (0.7)	0 (0)	0 (0)	0 (0)
Multiracial	1 (0.3)	1 (0.3)	2 (0.3)	0 (0)	0 (0)	0 (0)
Missing data	15 (5.1)	12 (4.1)	27 (4.6)	6 (5.5)	12 (10.7)	18 (8.1)
Hispanic ethnic group, n (%)						
No	265 (90.1)	274 (93.2)	539 (91.7)	104 (94.5)	97 (86.6)	201 (90.5)
Yes	21 (7.1)	14 (4.8)	35 (6.0)	4 (3.6)	7 (6.3)	11 (5.0)
Unknown	4 (1.4)	3 (1.0)	7 (1.2)	1 (0.9)	4 (3.6)	5 (2.3)
Not reported	4 (1.4)	3 (1.0)	7 (1.2)	1 (0.9)	4 (3.6)	5 (2.3)
ECOG PS, n (%)						
0	198 (67.3)	197 (67.0)	395 (67.2)	70 (63.6)	72 (64.3)	142 (64.0)
1	87 (29.6)	88 (29.9)	175 (29.8)	39 (35.5)	35 (31.3)	74 (33.3)
2	9 (3.1)	9 (3.1)	18 (3.1)	1 (0.9)	5 (4.5)	6 (2.7)
PD-L1 CPS,[a] n	288	288	576	108	111	219
≥1, n (%)	208 (72.2)	205 (71.2)	413 (71.7)	86 (79.6)	97 (87.4)	183 (83.6)
<1, n (%)	80 (27.8)	83 (28.8)	163 (28.3)	22 (20.4)	14 (12.6)	36 (16.4)
Methylation, n	–	–	–	94	94	188
Yes, n (%)	–	–	–	81 (86.2)	77 (81.9)	158 (84.0)
No, n (%)	–	–	–	13 (13.8)	17 (18.1)	30 (16.0)
Histology, n (%)						
Adenocarcinoma NOS	24 (8.2)	35 (11.9)	59 (10.0)	12 (10.9)	12 (10.7)	24 (10.8)
Clear cell	19 (6.5)	20 (6.8)	39 (6.6)	0 (0)	0 (0)	0 (0)
Dedifferentiated or undifferentiated	7 (2.4)	6 (2.0)	13 (2.2)	4 (3.6)	4 (3.6)	8 (3.6)
Endometrioid						
Grade 1	55 (18.7)	45 (15.3)	100 (17.0)	20 (18.2)	34 (30.4)	54 (24.3)
Grade 2	51 (17.3)	59 (20.1)	110 (18.7)	52 (47.3)	43 (38.4)	95 (42.8)
Grade 3	53 (18.0)	42 (14.3)	95 (16.2)	15 (13.6)	16 (14.3)	31 (14.0)
Mixed epithelial	6 (2.0)	10 (3.4)	16 (2.7)	3 (2.7)	2 (1.8)	5 (2.3)

	pMMR Population			dMMR Population		
	Pembrolizumab + Chemotherapy (n = 294)	**Placebo + Chemotherapy (n = 294)**	**All Patients (n = 588)**	**Pembrolizumab + Chemotherapy (n = 110)**	**Placebo + Chemotherapy (n = 112)**	**All Patients (n = 222)**
Serous	79 (26.9)	76 (25.9)	155 (26.4)	4 (3.6)	1 (0.9)	5 (2.3)
Missing	0 (0)	1 (0.3)	1 (0.2)	0 (0)	0 (0)	0 (0)
FIGO stage at initial diagnosis						
I	102 (34.7)	103 (35.0)	205 (34.9)	44 (40.0)	57 (50.9)	101 (45.5)
II	25 (8.5)	25 (8.5)	50 (8.5)	14 (12.7)	13 (11.6)	27 (12.2)
III	56 (19.0)	46 (15.6)	102 (17.3)	18 (16.4)	11 (9.8)	29 (13.1)
IVA	11 (3.7)	5 (1.7)	16 (2.7)	2 (1.8)	4 (3.6)	6 (2.7)
IVB	100 (34.0)	115 (39.1)	215 (36.6)	32 (29.1)	27 (24.1)	59 (26.6)
Previous therapy, n (%)						
Chemotherapy	74 (25.2)	76 (25.9)	150 (25.5)	4 (3.6)	8 (7.1)	12 (5.4)
Radiotherapy	118 (40.1)	124 (42.2)	242 (41.2)	42 (38.2)	54 (48.2)	96 (43.2)
Surgery	265 (90.1)	248 (84.4)	513 (87.2)	97 (88.2)	104 (92.9)	201 (90.5)

Data cutoff dates: December 6, 2022 (pMMR); December 16, 2022 (dMMR).

CPS, combined positive score; dMMR, mismatch repair-deficient; ECOG PS, Eastern Cooperative Oncology Group performance status; FIGO, International Federation of Gynecology and Obstetrics; ITT, intention to treat; NOS, not otherwise specified; PD-L1, programmed cell death ligand 1; pMMR mismatch repair-proficient.

[a]CPS was defined as the number of PD-L1−positive cells (tumor cells, lymphocytes, and macrophages) divided by the total number of tumor cells, multiplied by 100.

Table 2.

Safety at Ad Hoc Analysis (Safety Population)

AE	Pembrolizumab + Chemotherapy (n = 391)	Placebo + Chemotherapy (n = 388)
Any AE	388 (99.2)	387 (99.7)
Treatment-related AEs	379 (96.9)	373 (96.1)
Most common AEs (≥20% of patients in either treatment group)		
Fatigue	275 (70.3)	248 (63.9)
Anemia	234 (59.8)	220 (56.7)
Alopecia	215 (55.0)	223 (57.5)
Nausea	200 (51.2)	178 (45.9)
Constipation	184 (47.1)	162 (41.8)
Diarrhea	165 (42.2)	138 (35.6)
Peripheral sensory neuropathy	146 (37.3)	158 (40.7)
Decreased white blood cell count	137 (35.0)	134 (34.5)
Peripheral neuropathy	135 (34.5)	116 (29.9)
Decreased platelet count	131 (33.5)	102 (26.3)
Arthralgia	128 (32.7)	140 (36.1)
Decreased neutrophil count	111 (28.4)	114 (29.4)
Dyspnea	97 (24.8)	72 (18.6)
Decreased lymphocyte count	94 (24.0)	75 (19.3)
Hyperglycemia	93 (23.8)	71 (18.3)
Decreased appetite	88 (22.5)	89 (22.9)
Vomiting	83 (21.2)	50 (12.9)
Hypomagnesemia	82 (21.0)	67 (17.3)
Myalgia	79 (20.2)	70 (18.0)
Immune-mediated AEs and infusion reactions	155 (39.6)	102 (26.3)
Infusion reactions	74 (18.9)	72 (18.6)
Hypothyroidism	54 (13.8)	15 (3.9)
Hyperthyroidism	32 (8.2)	10 (2.6)
Severe skin reactions	15 (3.8)	6 (1.5)
Colitis	8 (2.0)	3 (0.8)
Adrenal insufficiency	5 (1.3)	1 (0.3)
Pneumonitis	5 (1.3)	2 (0.5)
Myositis	3 (0.8)	1 (0.3)
Uveitis	3 (0.8)	1 (0.3)
Gastritis	2 (0.5)	0
Hypophysitis	2 (0.5)	0
Myasthenic syndrome	2 (0.5)	0
Nephritis	2 (0.5)	0
Type 1 diabetes mellitus	2 (0.5)	0
Thyroiditis	2 (0.5)	0
Vasculitis	2 (0.5)	1 (0.3)

AE	Pembrolizumab + Chemotherapy (n = 391)	Placebo + Chemotherapy (n = 388)
Encephalitis	1 (0.3)	0
Guillain-Barre syndrome	1 (0.3)	0
Myocarditis	1 (0.3)	0
Pancreatitis	1 (0.3)	0
Sarcoidosis	1 (0.3)	0

All data are n (%).

Data cutoff date: August 18, 2023.

AE, adverse event.