19 September 2024
EMA/480998/2024
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Keytruda

International non-proprietary name: Pembrolizumab

Procedure No. EMEA/H/C/003820/II/0153

Note

Variation assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

Official address Domenico Scarlattilaan 6 ● 1083 HS Amsterdam ● The Netherlands
Address for visits and deliveries Refer to www.ema.europa.eu/how-to-find-us
Send us a question Go to www.ema.europa.eu/contact **Telephone** +31 (0)88 781 6000 An agency of the European Union

Table of contents

List of abbreviations

1L	First-line
ADR	Adverse drug reaction
AE	Adverse event(s)
AESI	Adverse events of special interest
AERS	Adverse event reporting system
APaT	All participants as treated
BICR	Blinded Independent Central Review
CDICS	Clinical Data Interchange Standards Consortium
CDHR	Center for Devices and Radiological Health
CI	Confidence interval
CPS	Combined Positive Score
CR	Complete response
CRADA	Cooperative Research and Development Agreement
CRC	Colorectal cancer
CRF	Case report form
CSR	Clinical study report
CTCAE	Common Terminology Criteria for Adverse Events
CTEP	Cancer Therapy Evaluation Program
DCO	Data cutoff date
DMC	Data Monitoring Committee
dMMR	Mismatch repair deficient
DOR	Duration of response
Dx	Diagnosis
EC	Endometrial carcinoma
EC_{50}	Half maximal effective concentration
ECOG PS	Eastern Cooperative Oncology Group performance status
EOP	End-of-Phase
ESMO	European Society for Medical Oncology
EU	European Union
FACT-En TOI	Functional Assessment of Cancer Therapy-Endometrial Trial Outcome Index
FACT/GOG-Ntx	Functional Assessment of Cancer Therapy/Gynecologic Oncology Group-Neurotoxicity
FACT-GP5	Functional Assessment of Cancer Therapy - Item GP5
FDA	Food and Drug Administration
HNSCC	Head and neck squamous cell carcinoma
HR	Hazard ratio
IA	Interim analysis
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IFN	Interferon
Ig	Immunoglobulin
IHC	Immunohistochemistry
IL-2	Interleukin-2
IND	Investigational New Drug
IO	Immunotherapy
iPSP	Initial pediatric study plan
ITT	Intent-to-treat population
IV	Intravenously
KM	Kaplan-Meier
mAb	Monoclonal antibody
MedDRA	Medical Dictionary for Regulatory Activities
MMR	Mismatch repair status
MSI	Microsatellite instability
MSI-H	Microsatellite instability - high
MTD	Maximum tolerated dose
NCCN	National Comprehensive Cancer Network
NCI	National Cancer Institute
NCTN	National Clinical Trials Network
NR	Not reached
NSCLC	Non-small cell lung cancer
ORR	Objective response rate

OS	Overall survival
PD	Progressive disease
PD-1	Programmed death 1 receptor
PD-L1	Programmed death, ligand 1
PD-L2	Programmed death, ligand 2
PFS	Progression-free survival
PFS2	Progression-free Survival on Next-line Therapy
PI	Product insert
PK	Pharmacokinetic(s)
pMMR	Mismatch repair proficient
PR	Partial response
PREA	Pediatric Research Equity Act
PRO	Patient-reported outcome
PROMIS	Patient Reported Outcomes Measurement Information System
q3w	Every 3 weeks
QoL	Quality of life
RAVE	NRG clinical database
RCC	Renal cell carcinoma
RECIST	Response Evaluation Criteria in Solid Tumors
RSD	Reference safety data
SAP	Statistical analysis plan
SAE	Serious adverse event
sBLA	Supplemental biologic license application
SD	Safety dataset
SOC	Standard of care
sPMA	Supplemental Premarket Application
sSAP	Supplemental statistical analysis plan
TAP	Paclitaxel, doxorubicin, cisplatin
TC	Carboplatin and paclitaxel
TNBC	Triple negative breast cancer
TNFα	Tumor necrosis factor-α
TPC	Treatment of physician’s choice
US	United States

1. Background information on the procedure

1.1. Type II variation

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, Merck Sharp & Dohme B.V. submitted to the European Medicines Agency on 13 March 2024 an application for a variation.

The following variation was requested:

Variation requested		**Type**	**Annexes affected**
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I and IIIB

Extension of indication for KEYTRUDA in combination with carboplatin and paclitaxel to include first-line treatment of primary advanced or recurrent endometrial carcinoma in adults, based on final results from study KEYNOTE-868. This is a randomized Phase 3, placebo-controlled, double-blind study of pembrolizumab vs placebo in combination with chemotherapy (paclitaxel plus carboplatin) for newly diagnosed Stage III/Stage IVA, Stage IVB, or recurrent endometrial cancer.
As a consequence, sections 4.1 and 5.1 of the SmPC are updated. Version 46.1 of the RMP has also been submitted.

The variation requested amendments to the Summary of Product Characteristics and Package Leaflet and to the Risk Management Plan (RMP).

Information on paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included an EMA Decision P/0043/2018 on the agreement of a paediatric investigation plan (PIP).
At the time of submission of the application, the PIP P/0043/2018 was completed.

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the MAH did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication

Scientific advice

The MAH did not seek Scientific Advice at the CHMP.

1.2. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Paolo Gasparini

Timetable	Actual dates
Submission date	13 March 2024
Start of procedure:	30 March 2024
CHMP Rapporteur Assessment Report	28 May 2024
PRAC Rapporteur Assessment Report	30 May 2024
PRAC Outcome	13 June 2024
CHMP members comments	17 June 2024
Updated CHMP Rapporteurs (Joint) Assessment Report	20 June 2024
Request for supplementary information (RSI)	27 June 2024
CHMP Rapporteur Assessment Report	28 August 2024
CHMP members comments	9 September 2024
Updated CHMP Rapporteur Assessment Report	12 September 2024
Opinion	19 September 2024

2. Scientific discussion

2.1. Introduction

2.1.1. Problem statement

Disease or condition

The initially proposed indication is:

KEYTRUDA, in combination with carboplatin and paclitaxel, is indicated for the first-line treatment of primary advanced or recurrent endometrial carcinoma in adults.

The indication as adopted by the CHMP is:

KEYTRUDA, in combination with carboplatin and paclitaxel, is indicated for the first-line treatment of primary advanced or recurrent endometrial carcinoma in adults who are candidates for systemic therapy.

Epidemiology and risk factors, biologic features, aetiology and pathogenesis

Endometrial carcinoma (or carcinoma of the uterine corpus) is the second most common gynaecological malignancy worldwide. In Europe, there were an estimated 124,874 new cases and 30,272 deaths in 2022, with the highest incidence rates in Eastern Europe and the lowest in Western Europe[1]. Incidence, prevalence, and mortality for EC are rising, likely related to increases in exposure to endogenous and exogenous estrogens associated with risk factors including obesity, diabetes, and increased life

[1] Ferlay J, Ervik M, Lam F, Laversanne M, Colombet M, Mery L, et al. Global Cancer Observatory (GCO): Cancer Today [Internet]. Lyon (France): International Agency for Research on Cancer (IARC); c2024. Global incidence and mortality data for endometrial cancer (cancer of the corpus uteri) in 2022. Available from: https://gco.iarc.who.int/today.

expectancy[2]. Approximately 5-10% of EC are hereditary, usually as a part of the hereditary non-polyposis colorectal cancer syndrome (HNPCC) or Lynch syndrome[3].

Adenocarcinoma is the most common histologic type, which has been classically classified into Type 1 or Type 2 histologic categories. Type 1 tumors are more common (70-80%) and less aggressive, with endometrioid histology being the most common. Type 2 tumors typically have a poorer prognosis, often have non-endometrioid histology (e.g. clear cell and serous cell types) and are not clearly associated with estrogen stimulation[4]. A more recent molecular classification categorizes EC into four molecular subtypes with distinct prognosis: (1) polymerase epsilon (POLE)-ultramutated (POLEmut), (2) MSI-hypermutated, (3) Copy-number high, (4) Copy-number low[5]. To increase clinical utility of this classification, a categorization based on immunohistochemistry (IHC) has been developed including four TCGA-correlated subtypes: (1) deoxyribonucleic acid (DNA) polymerase epsilon mutant (POLE-mut); (2) mismatch repair protein deficiency (dMMR); (3) protein 53 abnormal expression (p53abn); and (4) no specific molecular profile (NSMP)[6]. ESMO Guidelines recommend molecular classification through well-established IHC staining for p53 and MMR proteins (MLH1, PMS2, MSH2, MSH6) in combination with targeted tumour sequencing (POLE hotspot analysis) for all EC pathology specimens regardless of histological type [IV, A][7].

Clinical presentation, diagnosis and stage/prognosis

The prognosis for EC is significantly influenced by disease stage. At diagnosis, 67% have localized disease, while 21% have regional disease, and approximately 9% have distant metastases. While patients with localized disease have a 5-year survival rate of 95%, in those with regional and distant metastatic disease this is 69% and 17%, respectively[8]. Approximately 20% of early detected EC cases recur, mostly within 3 years of primary treatment, with poorer prognosis[9]. The population of patients with recurrent EC represents a heterogeneous mix of different histological subtypes and grades, stages at initial diagnosis, prior therapy, duration of recurrence-free intervals, and site(s) of recurrence (distant or local)[10]. Outcomes of advanced/recurrent disease remain poor, with 5-year OS rates of 20-25%[9].

There is no definitive evidence of a significant association between MMR status and detrimental survival[11].

Management

In early-stage EC, the aim of surgery is to remove macroscopic tumour, examine for microscopic metastases and stage the tumour to assess the need for adjuvant therapy[9].

The treatment of patients with recurrent/metastatic EC should always require a multidisciplinary approach in specialised centres and should be guided by the patient's condition, extent of the disease, prior therapies and molecular profile. For recurrent/metastatic disease not amenable to surgery and/or RT, the

[2] Morice P, Leary A, Creutzberg C, Abu-Rustum N, Darai E. Endometrial cancer. Lancet. 2016 Mar 12;387(10023):1094-108.
[3] Domchek SM, Robson ME. Update on genetic testing in gynecologic cancer. J Clin Oncol. 2019;37(27):2501-2509.
[4] Tran AQ, Gehrig P. Recent Advances in Endometrial Cancer. F1000Res. 2017 Jan 27;6:81.
[5] The Cancer Genome Atlas (TCGA) Research Network; Kandoth C, Schultz N, Cherniack AD, et al. Integrated genomic characterization of endometrial carcinoma. Nature 2013;497:67-73.
[6] McAlpine J, Leon-Castillo A, Bosse T. The rise of a novel classification system for endometrial carcinoma; integration of molecular subclasses. J Pathol. 2018;244(5):538-549.
[7] Oaknin A, Bosse TJ, Creutzberg CL, Giornelli G, Harter P, Joly F, Lorusso D, Marth C, Makker V, Mirza MR, Ledermann JA, Colombo N; ESMO Guidelines Committee. Endometrial cancer: ESMO Clinical Practice Guideline for diagnosis, treatment and follow-up. Ann Oncol. 2022 Sep;33(9):860-877.
[8] National Cancer Institute. Bethesda (MD): National Cancer Institute. 2019. SEER cancer stat facts: uterine cancer. Available from: https://seer.cancer.gov/statfacts/html/corp.html.
[9] Suhaimi SS, Ab Mutalib NS, Jamal R. Understanding molecular landscape of endometrial cancer through next generation sequencing: what we have learned so far? Front Pharmacol. 2016 Nov 1;7:409.
[10] Obel JC, Friberg G, Fleming GF. Chemotherapy in endometrial cancer. Clin Adv Hematol Oncol. 2006 Jun;4(6):459-68.
[11] Prendergast EN, Holman LL, Liu AY, Lai TS, Campos MP, Fahey JN, et al. Comprehensive genomic profiling of recurrent endometrial cancer: implications for selection of systemic therapy. Gynecol Oncol. 2019;154:461-6.

standard approach remains chemotherapy or hormonal therapy. Carboplatin AUC 5-6 plus paclitaxel 175 mg/m2 every 21 days for six cycles should be considered the first-line therapy for advanced or recurrent EC following the results of GOG-209. Chemotherapy options beyond first-line therapy are limited, with agents such as taxanes and doxorubicin displaying moderate activity (ORR 20%). Rechallenge with platinum can be considered if relapse occurred >6 months after prior platinum-based treatment[9]. Hormonal therapy is an accepted first-line therapy option for advanced EC in a selected group of patients (low-grade endometrioid histology, low volume/indolent disease).

Immunotherapy with anti-PD(L)1 agents in EC:

Immunotherapy (IO) is emerging as a potential strategy to enhance traditional EC treatments including chemotherapy.

First line: in the EU, **dostarlimab in combination with carboplatin and paclitaxel** was approved in December 2023 for the treatment of adult patients with **dMMR/MSI-H** primary advanced or recurrent EC and who are candidates for systemic therapy, based on the results of RUBY phase 3 study where this was compared to placebo + carboplatin-paclitaxel. Dostarlimab/placebo were administered in association with 6 cycles of chemotherapy then continued for up to 3 years. An all-comer population was enrolled, stratified based on MMR-MSI status. Among participants with MSI-H/dMMR tumours (median duration of follow-up of 24.8 months at interim analysis), PFS by investigator was HR 0.28 (95% CI: 0.16, 0.50; p<0.0001), with median PFS not reached in the dostarlimab arm was (95% CI: 11.8, NR), vs 7.7 months (95% CI: 5.6, 9.7) in the placebo arm. Almost all patents with MSI-H disease were PD-L1 positive. Statistical significance was also reached in the overall population (PFS HR=0.64, 95% CI: 0.51, 0.80; p<0.0001). In the ITT population, although a positive trend was observed, statistical significance was not reached for OS in the ITT population at first interim analysis. In the MSI-H population, OS was not statistically tested, although the most recent analysis showed a trend in favour of dostarlimab (OS HR=0.33, 95% CI: 0.155, 0.722), with medians not reached in either arm. According to subgroup analyses, in the pMMR/MSS subset (>75% of the ITT population) PFS was HR=0.76 (95%CI 0.59, 0.98) and OS was HR=0.73 (95% 0.52, 1.025)[12] [13].

Similar results were reported by the AtTEnd/ENGOT-EN7 study. Of the 549 patents included in the ITT population, 125 (22.8%) had dMMR tumours in whom the addition of atezolizumab to carboplatin/paclitaxel followed by atezolizumab until PD showed a statistically significant improvement of PFS (HR 0.36 95% CI:0.23-0.57; p<0.0005; median PFS NR vs. 6.9 months). Superiority in PFS was shown also in all comers (HR 0.74 95%CI:0.61-0.91; p<0.0219; median PFS: 10.1 vs 8.9 months)[14].

Another recent phase III study DUO-E tested first-line platinum-based chemotherapy in combination with durvalumab, followed by maintenance durvalumab with or without olaparib in patients with newly diagnosed advanced or recurrent endometrial cancer. In the ITT population, approximately 20% of patients were MSI-H (MMR status was a stratification factor). The study met its primary objective reporting a statistically significant improvement in PFS by investigator for both comparisons. These results are currently under regulatory assessment worldwide including in the EU and US[15] [16].

[12] Mirza MR, Chase DM, Slomovitz BM, et al; RUBY Investigators. Dostarlimab for Primary Advanced or Recurrent Endometrial Cancer. N Engl J Med. 2023 Jun 8;388(23):2145-2158.
[13] EMA/483641/2023, Jemperli-H-C-005204-II-0023: EPAR - Assessment Report - Variation https://www.ema.europa.eu/en/documents/variation-report/jemperli-h-c-005204-ii-0023-epar-assessment-report-variation_en.pdf
[14] Colombo N, Harano K, Hudson E, et al. LBA40 Phase III double-blind randomized placebo-controlled trial of atezolizumab in combination with carboplatin and paclitaxel in women with advanced/recurrent endometrial carcinoma. Ann Oncol. 2023;34(S2):S1281-2.
[15] Westin SN, Moore K, Chon HS, et al; DUO-E Investigators. 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. 2024 Jan 20;42(3):283-299.
[16] AZ News Release 18 March 2024 https://www.astrazeneca-us.com/media/press-releases/2024/lynparza-olaparib-and-imfinzi-durvalumab-demonstrated-strong-clinical-benefit-and-more-than-doubled-median-duration-of-response-vs-chemotherapy-in-patients-with-mismatch-repair-proficient-advanced-or-recurrent-endometrial-cancer.html

Interest in exploring de-intensified strategies, including chemotherapy-free options, is also rising. GINECO-EN105b/ENGOT-en13, DOMENICA (NCT05201547), and KEYNOTE-C93/MK-3475-C93/GOG-3064/ENGOT-en15 (NCT05173987) trials, comparing immunotherapy versus chemotherapy in dMMR/MSI-H endometrial cancer for first-line advanced/metastatic settings, are currently ongoing[17].

Second line and above: in the EU, **pembrolizumab in combination with lenvatinib** was approved in November 2021 for the treatment of advanced or recurrent endometrial carcinoma in adults who have disease progression on or **following prior treatment with a platinum-containing therapy** in any setting and who are not candidates for curative surgery or radiation. Of note, while in the EU the indication is **regardless MSI status**, in the US this indication is limited to patients whose EC is not microsatellite instability-high or mismatch repair deficient. The indication was approved based on the pivotal phase 3 Study 309/KEYNOTE-775 where participants were randomised to lenvatinib in combination with pembrolizumab vs treatment of physician's choice (paclitaxel or doxorubicin). Statistically significant PFS and OS results were observed in the ITT as well as in the pMMR subgroup (representing about 85% of the all-comers). Subgroup analysis confirmed PFS and OS benefit also in the dMMR/MSI population (not statistically tested), efficacy of the combination appears higher compared to what observed in the pMMR population[18] [19]. Later in April 2022, **pembrolizumab** as monotherapy was also approved in the EU in advanced or recurrent endometrial carcinoma who are **dMMR/MSI-H**, who have disease progression on or **following prior treatment with a platinum-containing therapy** in any setting and who are not candidates for curative surgery or radiation, based on the results of the single arm study KEYNOTE-158[20] [21]. Similarly, **dostarlimab** is approved as monotherapy in the EU for the treatment of adult patients with **dMMR/MSI-H** recurrent or advanced EC that has progressed on or **following prior treatment with a platinum-containing regimen**, based on the single arm GARNET study[22] [23].

2.1.2. About the product

KEYTRUDA is a humanised monoclonal antibody which binds to the programmed cell death-1 (PD-1) receptor and blocks its interaction with ligands PD-L1 and PD-L2.

Pharmacological classification: Antineoplastic agents, PD-1/PDL-1 (Programmed cell death protein 1/death ligand 1) inhibitors. ATC code: L01FF02

Pembrolizumab already holds an indication as monotherapy (in MSI-H/dMMR only) and in combination with lenvatinib (regardless MSI status) for the treatment of advanced or recurrent EC in adults who have disease progression on or following prior treatment with a platinum-containing therapy in any setting and who are not candidates for curative surgery or radiation.

[17] Bogani G, Monk BJ, Powell MA, et al. Adding immunotherapy to first-line treatment of advanced and metastatic endometrial cancer. Ann Oncol. 2024 May;35(5):414-428.
[18] Makker V, Colombo N, Casado Herraez A, Santin AD, Colomba E, Miller DS, et al. Lenvatinib plus pembrolizumab for advanced endometrial cancer. N Engl J Med. 2022 Feb 3;386(5):437-48.
[19] EMA/617606/2021, Keytruda-H-C-003820-II-0105: EPAR - Assessment Report - Variation https://www.ema.europa.eu/en/documents/variation-report/keytruda-h-c-003820-ii-0105-epar-assessment-report-variation_en.pdf
[20] O'Malley DM, Bariani GM, Cassier PA, Marabelle A, Hansen AR, De Jesus Acosta A, et al. Pembrolizumab in patients with microsatellite instability-high advanced endometrial cancer: results from the KEYNOTE-158 study. J Clin Oncol. 2022;40(7):752-61. Additional material; 1 p.
[21] EMA/224161/2022, Keytruda-H-C-003820-II-0109: EPAR - Assessment report – Variation https://www.ema.europa.eu/en/documents/variation-report/keytruda-h-c-003820-ii-0109-epar-assessment-report-variation_en.pdf
[22] Oaknin A, Pothuri B, Gilbert L, et al. Safety, Efficacy, and Biomarker Analyses of Dostarlimab in Patients with Endometrial Cancer: Interim Results of the Phase I GARNET Study. Clin Cancer Res. 2023 Nov 14;29(22):4564-4574.
[23] EMA/176464/2021, Jemperli: EPAR - Public assessment report https://www.ema.europa.eu/en/documents/assessment-report/jemperli-epar-public-assessment-report_en.pdf

2.1.3. The development programme/compliance with CHMP guidance/scientific advice

Table 1: Summary of the Clinical Development of Pembrolizumab in Advanced or Recurrent Endometrial Cancer

Study	Design	Participant Population	Primary Endpoint(s)	Status
KN146	A Multicenter, Open-Label Phase 1b/2 Trial of Lenvatinib (E7080) Plus Pembrolizumab in Subjects With Selected Solid Tumors *(KEYNOTE-146)*	*124 participants with EC were enrolled. The EC cohort has completed enrollment.* *Participants must have had histologically and/or cytologically confirmed metastatic selected solid tumors that had progressed after treatment (if previously treated). Phase 1b: no limit to number of prior treatments; Phase 2 expansion: 0 to 2 prior treatments.*	Phase 1b: Determination of the MTD for lenvatinib plus pembrolizumab 200 mg IV q3w. Phase 2-Expansion: ORR (Week 24)	Completed
KN158	A Clinical Trial of Pembrolizumab (MK-3475) Evaluating Predictive Biomarkers in Subjects with Advanced Solid Tumors (KEYNOTE-158) (Endometrial Carcinoma: Cohort D and K)	Participants with advanced EC that had progressed after standard of care therapy Cohort D: N=107 pMMR: n=90 dMMR: n=11 Unknown: n=6 Cohort K: N=79 dMMR	ORR based on IIR by RECIST 1.1	Ongoing
KN775	A Multicenter, Open label, Randomised, Phase 3 Trial to Compare the Efficacy and Safety of Lenvatinib in Combination with Pembrolizumab Versus Treatment of Physician's Choice in Participants with Advanced Endometrial Carcinoma (KEYNOTE-775)	827 participants were randomised (697 pMMR and 130 dMMR participants). Participants must have had radiographic evidence of disease progression after 1 prior systemic, platinum-based chemotherapy regimen for EC. Participants may have received up to 1 additional line of platinum-based chemotherapy if given in the neoadjuvant or adjuvant treatment setting.	PFS OS	Ongoing; Final OS results available.
KN868/NRG-GY018	A Phase 3, Randomised, Placebo-Controlled Study of Pembrolizumab in Addition to Paclitaxel and Carboplatin for Measurable Stage III or IVA, Stage IVB or Recurrent Endometrial Carcinoma	810 total participants were enrolled (588 pMMR and 222 dMMR participants) Adult female participants with measurable Stage III, IVA, Stage IVB or recurrent EC	PFS	Ongoing
KNB21	A Phase 3, Randomised, Double-Blind Study of Pembrolizumab versus Placebo in Combination With Adjuvant Chemotherapy With or Without Radiotherapy for the Treatment of Newly Diagnosed High-Risk Endometrial Carcinoma After Surgery With Curative Intent (KEYNOTE-B21 / ENGOT-en11 / GOB-3053)	1095 enrolled participants with newly diagnosed EC at high risk of recurrence following curative intent surgery	DFS OS	Ongoing

Study	Design	Participant Population	Primary Endpoint(s)	Status
KNC93	A Phase 3 Randomised, Open-label, Active-comparator Controlled Clinical Study of Pembrolizumab vs. Platinum Doublet Chemotherapy in Participants With Mismatch Repair Deficient (dMMR) Advanced or Recurrent Endometrial Carcinoma in the First-line Setting (KEYNOTE-C93)	280 (planned) participants with dMMR advanced or recurrent EC in the First-line Setting	PFS OS	Ongoing
7902-001	A Phase 3 Randomised, Open-Label, Study of Pembrolizumab (MK-3475) Plus Lenvatinib (E7080/MK-7902) Versus Chemotherapy for First-line Treatment of Advanced or Recurrent Endometrial Carcinoma (LEAP-001)	842 total participants were enrolled (642 pMMR and 200 dMMR participants). Participants without prior chemotherapy or with disease progression following neoadjuvant/adjuvant chemotherapy, and who are not candidates for curative surgery or radiation for EC were included.	PFS OS	Ongoing*

Abbreviations: DFS=disease-free survival, dMMR=mismatch repair deficient, EC=endometrial carcinoma, IV=intravenous, MTD=maximum tolerated dose, ORR=objective response rate, OS=overall survival, PFS=progression-free survival, pMMR= mismatch repair proficient, q3w=every 3 weeks, RECIST=Response Evaluation Criteria in Solid Tumors

*MSD publicly announced study update on 8-DEC-2023 that KEYTRUDA plus LENVIMA did not improve OS or PFS sufficiently to meet the study's prespecified statistical criteria in the 1L treatment of certain patients with advanced or recurrent EC versus a standard of care, platinum-based chemotherapy doublet (carboplatin plus paclitaxel).[24]

No Scientific Advice was requested to the CHMP, while the study design was discussed with FDA.

A pre-submission meeting was held on 9 February 2024 with Rapporteur and CoRapporteur's teams.

2.1.4. General comments on compliance with GCP

The MAH stated that the clinical studies were conducted in accordance with current standard research approaches and following appropriate Good Clinical Practice standards and considerations for the ethical treatment of human participants that were in place at the time the studies were performed.

During the assessment, no issues have been identified leading to consider triggering a GCP inspection.

2.2. Non-clinical aspects

No new non-clinical data have been submitted in this application, which was considered acceptable by the CHMP.

2.2.1. Ecotoxicity/environmental risk assessment

Pembrolizumab is a protein, which is expected to biodegrade in the environment and not be a significant risk to the environment. Thus, according to the "Guideline on the Environmental Risk Assessment of Medicinal Products for Human Use" (EMEA/CHMP/SWP/4447/00), pembrolizumab is exempt from

[24] https://www.merck.com/news/merck-and-eisai-provide-update-on-phase-3-leap-001-trial-evaluating-pembrolizumab-plus-lenvima-lenvatinib-as-first-line-treatment-for-patients-with-advanced-or-recurrent-endometrial-carcinom/ MSD News Release 8 December 2023

preparation of an Environmental Risk Assessment as the product and excipients do not pose a significant risk to the environment.

2.3. Clinical aspects

2.3.1. Introduction

GCP

The clinical trials were performed in accordance with GCP as claimed by the MAH.

The MAH has provided a statement to the effect that clinical trials conducted outside the EU were carried out in accordance with the ethical standards of Directive 2001/20/EC.

- Tabular overview of clinical studies

Study ID	Phase	Country/ Region	Study Title	Study Design	Dosing Regimen	Study Population	Participant Exposure
3475-868 [Ref. 5.3.5.1: P868V01MK3475]	3	Canada Japan South Korea USA	A Phase III Randomized, Placebo-controlled Study of Pembrolizumab (MK-3475, NSC #776864) in Addition to Paclitaxel and Carboplatin for Measurable Stage III or IVA, Stage IVB or Recurrent Endometrial Cancer	Multicenter, randomized, double-blind, parallel-group, active-control with placebo intervention study	Arm 1: Placebo plus chemotherapy Placebo IV q3w for 6 cycles then q6w for up to 14 cycles* + Paclitaxel 175 mg/m^2 IV q3w for 6 cycles + Carboplatin AUC 5 IV q3w for 6 cycles Arm 2: Pembrolizumab plus chemotherapy Pembrolizumab 200 mg IV q3w for 6 cycles then 400 mg IV q6w for up to 14 cycles* + Paclitaxel 175 mg/m^2 IV q3w for 6 cycles + Carboplatin AUC 5 IV q3w for 6 cycles *Before implementation of protocol amendment 05 (14-OCT-2020), pembrolizumab 200 mg/placebo was administered q3w throughout the study for up to a total of 35 cycles.	Females Age: ≥18 years Primary, advanced, metastatic, or recurrent endometrial cancer	pMMR population As of 06-DEC-2022: Pembrolizumab plus chemotherapy: 275 Placebo plus chemotherapy: 272 dMMR population As of 16-DEC-2022: Pembrolizumab plus chemotherapy: 107 Placebo plus chemotherapy: 105

2.3.2. Clinical pharmacology

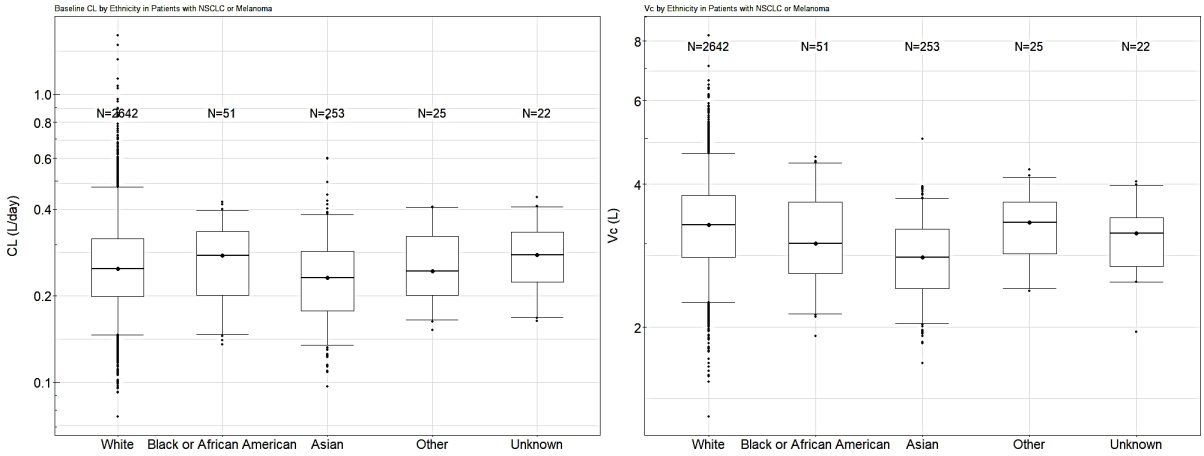
No new clinical pharmacology analyses beyond those conducted in previous submissions have been generated for this procedure. A rationale for the applicability of foreign data to the EU population was provided.

Applicability of foreign data to the EU population

An assessment of the impact of ethnicity on the PK parameters systemic clearance (CL) and central volume of distribution (Vc) was conducted with a reference PK dataset consisting of pembrolizumab concentrations from 2993 participants with melanoma or NSCLC treated with pembrolizumab monotherapy on KEYNOTE-001, -002, -006, -010, and -024 and population PK model which support the EU SmPC and other global labeling documents.

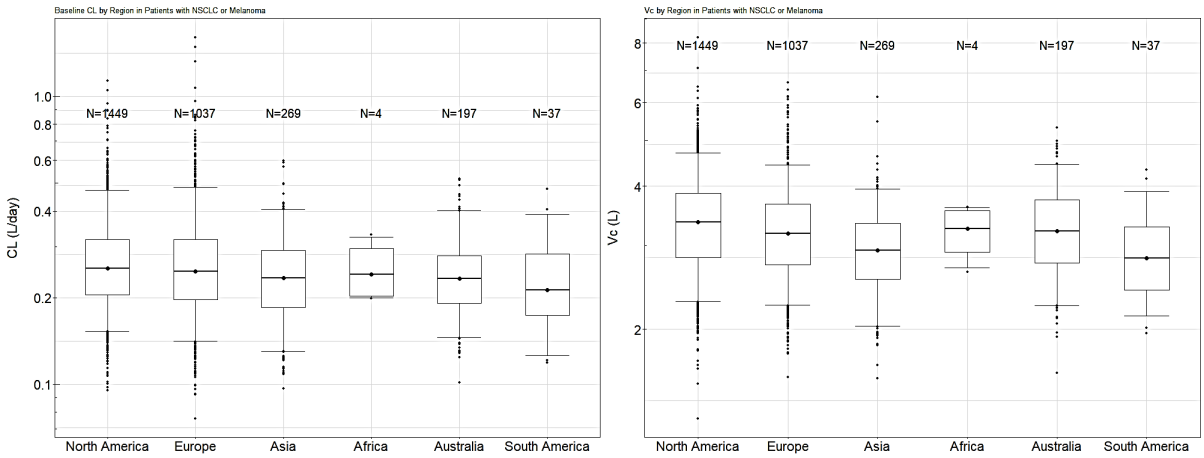
Ethnicity was not found to be a statistically significant covariate on either CL or Vc in these participants (see Figure 1 below).

Figure 1: Estimated CL (left) and Vc (right) by Ethnicity of Participants in PK Reference Dataset (KEYNOTE-001, -002, -006, -010, and -024)



Further analysis of participants in the pembrolizumab PK reference dataset demonstrates that the estimated CL and Vc of pembrolizumab are also consistent across geographic regions (see Figure 2 below).

Figure 2: Estimated CL (left) and Vc (right) by Geographic Region of Participants in PK Reference Dataset (KEYNOTE-001, -002, -006, -010, and -024)



2.3.1. Discussion on clinical pharmacology

In Study KEYNOTE-868 (NRG-GY018), participants with primary advanced, metastatic, or recurrent EC received pembrolizumab at 200 mg q3w for 6 cycles plus paclitaxel and carboplatin, followed by 400 mg q6w pembrolizumab monotherapy for 14 cycles in the maintenance phase of treatment. Prior to Amendment 05 of the protocol, 200 mg q3w was administered for up to 29 cycles in the treatment maintenance phase.

Study KEYNOTE-868 (NRG-GY018) is presented in detail in section 2.4 below. The clinical data in participants with primary advanced, metastatic, or recurrent EC demonstrate efficacy with the aforementioned regimen and support the recommendation of 200 mg q3w pembrolizumab for 6 cycles in combination with chemotherapies, followed by 400 mg q6w or 200 mg q3w pembrolizumab monotherapy as the appropriate regimen for patients with primary advanced, metastatic, or recurrent EC.

Currently, the 200 mg q3w and 400 mg q6w dosing regimens are being evaluated in multiple clinical studies. Pembrolizumab is approved at 200 mg q3w dosing regimen for multiple indications in monotherapy and combination therapy settings across the globe. An additional dosing regimen of 400 mg q6w has been approved in the US, EU, and other markets in adults for all approved pembrolizumab monotherapy as well as combination indications. Approvals for the 400 mg q6w regimen were mainly supported by a modelling and simulation-based approach, bridging PK and E-R data between the 200 mg q3w and 400 mg q6w dosing regimens for approved adult indications. Additionally, the applications were also supported by interim KEYNOTE-555 (Cohort B) clinical efficacy, safety, and PK data at 400 mg q6w dosing.

Overall, based on the robust understanding of pembrolizumab clinical pharmacology and its well-established flat E-R profiles over a 5-fold dose range, the safety and efficacy of the 400 mg q6w dosing regimen in combination with chemotherapies would have a similar benefit/risk profile as the 200 mg q3w dosing regimen in the same combination setting in adults with primary advanced, metastatic, or recurrent EC.

Based on the robust understanding of pembrolizumab clinical pharmacology and its well-established flat E-R profiles over a 5-fold dose range, the safety and efficacy of the 400 mg q6w dosing regimen in combination with chemotherapies would have a similar benefit-risk profile as the 200 mg q3w dosing regimen in the same combination setting in adults with primary advanced, metastatic, or recurrent EC. Pembrolizumab already holds an indication as monotherapy (in MSI-H/dMMR only) and in combination with lenvatinib (regardless MSI status) for the treatment of advanced or recurrent EC in adults who have disease progression on or following prior treatment with a platinum-containing therapy in any setting and who are not candidates for curative surgery or radiation.

The study was conducted primarily in North America (US mostly). As no EU participants were included, a justification for applicability of study data to the EU patient population was provided. It is agreed that, based on the data provided, the PK of pembrolizumab were shown to be consistent across ethnicity and region.

2.3.2. Conclusions on clinical pharmacology

No new clinical pharmacology analyses beyond those conducted previously have been generated, and no labeling revisions for the Clinical Pharmacology section of the PI are proposed which is acceptable. A substantial characterisation of the PK and immunogenicity of pembrolizumab has been provided in previous applications. It is acknowledged that ethnicity and region do not impact the PK profile of pembrolizumab.

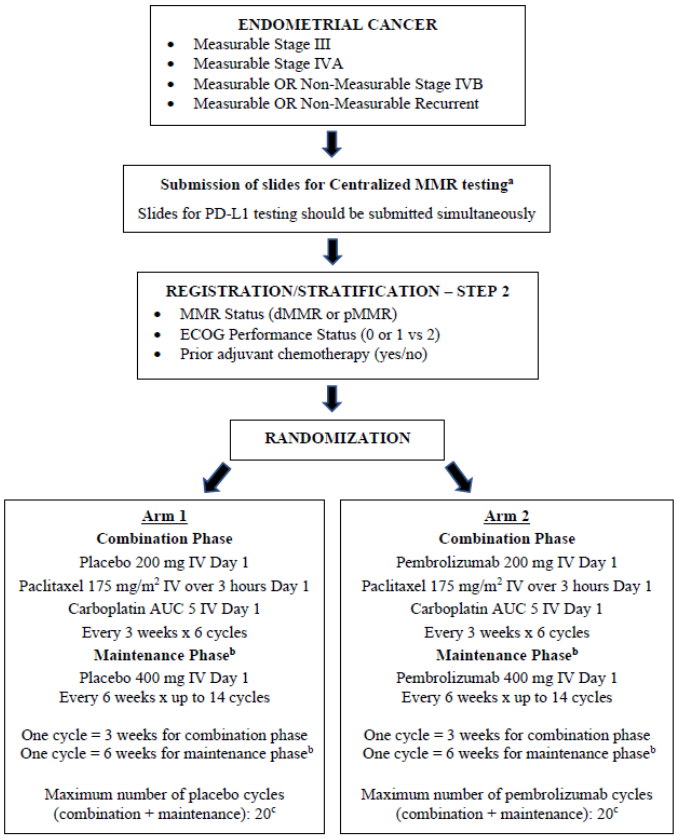
2.4. Clinical efficacy

2.4.1. Main study

NRG-GY018/KEYNOTE-868

A Phase III, Randomised, Multicentre, Double-blind, Placebo-controlled Study of Pembrolizumab in Addition to Paclitaxel and Carboplatin for Measurable Stage III or IVA, Stage IVB or Recurrent Endometrial Cancer

Figure 3: Study Design for NRG-GY018/KEYNOTE-868



Abbreviations: AUC=area under the curve; dMMR=mismatch repair deficient; ECOG PS=Eastern Cooperative Oncology Group Performance Status; IHC=immunohistochemistry; IV=intravenous; MMR=mismatch repair proteins (MLH1, MSH2, MSH6, PMS2); MSI=microsatellite instability; MSI-H=microsatellite instability-high; MSS=microsatellite stable; PCR=polymerase chain reaction; PD-1=programmed cell death protein 1; PD-L1=programmed cell death ligand 1; pMMR=mismatch repair proficient.

a. Before implementation of protocol amendment 09, sites were required to wait for the return of centralised MMR IHC test results before randomising a participant. After implementation of protocol amendment 09, randomisation based on institutional (local) MMR IHC test results was permitted. However, central laboratory confirmation of a randomised participant's MMR status was still required.
b. Before implementation of protocol amendment 05 (14 October 2020) study interventions were administered q3w for up to 29 maintenance cycles (1 cycle = 3 weeks).
c. Before implementation of protocol amendment 5, the maximum number of placebo or pembrolizumab cycles (combination phase + maintenance phase) was 35.

Methods

Study participants

Inclusion criteria

- Female ≥18 years of age.
- Adequate organ function as defined in the study protocol.
- ECOG PS of 0, 1, or 2.
- Measurable Stage III, measurable Stage IVA, Stage IVB (with or without measurable disease), or recurrent (with or without measurable disease) endometrial cancer. In participants with measurable disease, lesions were defined and monitored by RECIST 1.1.

- Pathology report showing results of institutional MMR IHC testing (submission of tumour specimens for centralized MMR IHC testing was required before Step 2 registration/stratification/randomisation).
- One of the following confirmed histologic subtypes of EC: endometrioid adenocarcinoma, serous adenocarcinoma, dedifferentiated/undifferentiated carcinoma, clear cell adenocarcinoma, mixed epithelial carcinoma, adenocarcinoma not otherwise specified.
- As prior therapy, participants may have received:
    - NO prior chemotherapy for treatment of EC.
    - Prior adjuvant chemotherapy (e.g., paclitaxel/carboplatin alone or as a component of concurrent chemotherapy and radiation therapy [with or without cisplatin]) provided adjuvant chemotherapy was completed ≥12 months before.
    - Prior radiation therapy completed at least 4 weeks before.
    - Prior hormonal therapy discontinued at least 3 weeks before.
    - Interval or cytoreductive surgery, after start of treatment on this study, and before documentation of disease progression, was NOT permitted.
- For participants of childbearing potential: negative urine or serum pregnancy test. Women of childbearing potential had to agree to use adequate contraception (hormonal or barrier method of birth control; abstinence) from at least 14 days before randomisation (for oral contraceptives), during treatment, and for 120 days after the last dose of study medication.
- Informed consent before study entry.
- Participants with prior or concurrent malignancy whose natural history or treatment did not have the potential to interfere with safety or efficacy assessment of the investigational regimen were eligible.
- Participants with treated brain metastases were eligible if follow-up brain imaging after CNS-directed therapy showed no evidence of progression, and they had been off steroids for at least 4 weeks and remained clinically stable.

<u>Exclusion Criteria</u>

- History of a severe hypersensitivity reaction to monoclonal antibody or pembrolizumab and/or its excipients; and/or a severe hypersensitivity reaction to paclitaxel and/or carboplatin.
- Active autoimmune disease or history of autoimmune disease that might recur, which may affect vital organ function or require immune suppressive treatment including systemic corticosteroids. Participants with vitiligo, endocrine deficiencies including type I diabetes mellitus, thyroiditis managed with replacement hormones including physiologic corticosteroids were eligible.
- Patients with endometrial sarcoma, including carcinosarcoma
- History of (non-infectious) pneumonitis that required steroids, or current pneumonitis.
- Uncontrolled intercurrent illness that would limit compliance with study requirements.
- Known clinically significant liver disease, including active viral, alcoholic, or other hepatitis; and cirrhosis.
- For participants with chronic HBV infection, HBV viral load must have been undetectable on suppressive therapy, if indicated. Participants with a history of HCV infection must have been treated and cured, or with undetectable HCV viral load if under treatment.
- Prior treatment with anti-PD-1, anti-PD-L1 or anti-CTLA-4 therapeutic antibody or similar agents.

- Diagnosis of immunodeficiency or were receiving systemic steroid therapy or any other form of immunosuppressive therapy within 7 days randomisation.
- Participation and received investigational cancer-directed study therapy within 4 weeks.
- Pregnant or lactating

Treatments

Patients were randomised (1:1) to one of the following treatment arms:

- Pembrolizumab 200 mg every 3 weeks, paclitaxel 175 mg/m^2 and carboplatin AUC 5 mg/mL/min for 6 cycles, followed by pembrolizumab 400 mg every 6 weeks for up to 14 cycles.
- Placebo every 3 weeks, paclitaxel 175 mg/m^2 and carboplatin AUC 5 mg/mL/min for 6 cycles, followed by placebo every 6 weeks for up to 14 cycles.

Table 2: Treatments characteristics by arm and phase in Keynote-868

Arm Name	Intervention Name	Unit Dose Strength(s)	Dosage Level(s)	Route of Administration	Regimen/ Treatment Period/ Vaccination Regimen	Use
Arm 1 Combination Phase	Placebo	N/A	N/A	IV Infusion	q3w for 6 cycles	Placebo
Arm 1 Combination Phase	Paclitaxel	Variable	175 mg/m^2	IV Infusion	q3w for 6 cycles	Background Treatment
Arm 1 Combination Phase	Carboplatin	Variable	AUC 5	IV Infusion	q3w for 6 cycles	Background Treatment
Arm 1 Maintenance Phase	Placebo	N/A	N/A	IV Infusion	q6w for up to 14 cycles	Placebo
Arm 2 Combination Phase	Pembrolizumab	25 mg/mL	200 mg	IV Infusion	q3w for 6 cycles	Test Product
Arm 2 Combination Phase	Paclitaxel	Variable	175 mg/m^2	IV Infusion	q3w for 6 cycles	Background Treatment
Arm 2 Combination Phase	Carboplatin	Variable	AUC 5	IV Infusion	q3w for 6 cycles	Background Treatment
Arm 2 Maintenance Phase	Pembrolizumab	25 mg/mL	400 mg	IV Infusion	q6w for up to 14 cycles	Test Product

AUC=area under the curve; IV=intravenous; N/A=not applicable; PR=partial response; q3w=every 3 weeks; q6w=every 6 weeks; SD=stable disease.

Participants with stable disease (SD) or partial response (PR) who still had measurable disease at the completion of Cycle 6 may have continued to receive paclitaxel and carboplatin (with pembrolizumab or normal saline) up to a total of 10 cycles (if deemed necessary by the treating investigator). Participants who continued with Cycles 7-10 were to continue with all study assessments as described for Cycles 1-6.

Per the study protocol, it was acceptable to substitute docetaxel or nab-paclitaxel in participants who had a reaction to paclitaxel with a failed re-challenge (or were not amenable to re-challenge).

Initially, study intervention pembrolizumab/placebo during the maintenance phase was administered q3w. After implementation of protocol Amendment 05 (implemented due to COVID-19 pandemic) where maintenance pembrolizumab/placebo was administered q6w.

All study medications were administered as an intravenous infusion on Day 1 of each treatment cycle. Treatment continued until disease progression, unacceptable toxicity or a maximum of 20 cycles (up to approximately 24 months). Patients with measurable disease who had RECIST-defined stable disease or partial response at the completion of cycle 6 were permitted to continue receiving paclitaxel and carboplatin with pembrolizumab or placebo for up to 10 cycles as determined by the investigator.

Assessment of tumour status was performed every 9 weeks for the first 9 months and then every 12 weeks thereafter.

Objectives / endpoints

Table 3: Objectives and endpoints in Keynote-868

Primary Objective	Primary Endpoint
To evaluate the efficacy of pembrolizumab (MK-3475) in combination with paclitaxel and carboplatin in participants with advanced stage (measurable Stage III or IVA), Stage IVB and recurrent endometrial cancer. Efficacy will be determined via investigator assessed PFS as assessed by RECIST 1.1 in two distinct populations referred to as proficient and deficient mismatch repair (pMMR and dMMR).	PFS

Secondary Objectives	Secondary Endpoints
To determine the nature, frequency and degree of toxicity as assessed by CTCAE for each treatment arm	AEs as assessed by CTCAE
To evaluate BICR assessed or investigator assessed ORR as assessed by RECIST 1.1 by treatment arm and by MMR IHC status in participants who enter the study with measurable disease	Objective tumor response as assessed by RECIST 1.1
To evaluate BICR assessed or investigator assessed DOR by treatment arm and by MMR IHC status in participants who enter the study with measurable disease	Duration of objective response (the time difference between the dates of first response and first progression; participants who do not progress are considered censored)*
To evaluate the effect of pembrolizumab (MK-3475) on OS in participants with pMMR or dMMR	OS
To determine whether the addition of pembrolizumab (MK-3475) to standard combination chemotherapy is associated with improved patient-reported physical function as measured with the PROMIS-physical function scale (short form), quality of life as measured with the FACT-En TOI and worsened fatigue as measured with the PROMIS-Fatigue scale (short form) in the pMMR participants	QoL and PROs, measured by the FACT-En-TOI, PROMIS-Fatigue (short form), and the PROMIS-physical function (short form)
To determine concordance between institutional MMR IHC testing and centralized MMR IHC	Concordance between institutional MMR IHC testing and centralized MMR IHC

Tertiary/Exploratory Objectives	Tertiary/Exploratory Endpoints
To explore whether the addition of pembrolizumab (MK-3475) to standard combination chemotherapy is associated with self-reported neurotoxicity as measured with the FACT/GOG-Ntx subscale (short) and the extent to which participants differ on their self-reported bother from side effects of cancer therapy in the pMMR participants	Pembrolizumab (MK-3475) treatment and self-reported neurotoxicity as measured by the FACT/GOG-Ntx subscale (short), and a single-item GP5 of the FACT-G measuring bother from side effects of cancer therapy

PFS2, defined as the time from randomization to disease progression by investigator assessment or death (whichever occurs first) on subsequent anticancer therapy, was an additional exploratory endpoint.

Sample size

This is a study of two populations (pMMR and dMMR). KEYNOTE-868 was powered for primary endpoint PFS in both populations and was planned to randomise between 2 treatment arms approximately 590 patients in pMMR group and 220 patients in dMMR group. The accrual should have been completed in 29.5 months and 44 months for the pMMR and dMMR patients, respectively. The null hypothesis of equal hazard rates (i.e. H0: HR = 1.0) was tested with a one-sided log-rank test and starting with a total alpha for each population of 0.0125. It was expected that approximately 70% or more of the information would have been available at the time of the IA1 for both populations. In this case the study should have 58% and 50% power to detect the alternative hypotheses for the respective populations (Ha: HR=0.70 for pMMR and Ha: HR=0.60 for dMMR). Patients were to be monitored for a final efficacy analysis until 394 and 168 PFS events occur in pMMR and dMMR group, respectively. At final analysis the study would have 90% and 85% power of detecting a true HR=0.7 and HR=0.6 for pMMR and dMMR group, respectively. These data were expected after 36-41 months for pMMR group and 55-68 months in dMMR group.

Randomisation

Patients were randomised in a 1:1 fashion to 2 treatment arms. Randomisation was stratified based on the following criteria:

1. Mismatch repair deficient (dMMR) (yes/no)
2. ECOG Performance Status (0 or 1 vs 2)
3. Prior chemotherapy (yes/no)

Patient registration and randomisation occurred using the Oncology Patient Enrollment Network (OPEN). OPEN is a web-based registration system available on a 24/7 basis. Block randomisation was used.

Blinding (masking)

This is a placebo-controlled, double-blind study.

The sponsor, investigator, study participant and MSD were blinded to group assignments. Each study site had an unblinded pharmacist with access to subject's study identification number, and drug assignment and accordingly prepared the solutions for infusion. Chemotherapy agents were open label.

Only one participant was reported to have been prematurely unblinded (in the pMMR population).

Statistical methods

Statistical Methods for Efficacy Analyses

Analyses of the primary efficacy endpoint were based on the ITT population, consisting of all randomised participants, which were included in the treatment group to which they are randomised.

Within the pMMR and dMMR populations, primary efficacy analyses were based on the ITT population, which included all participants who were randomized on or before the data cutoff dates for the 2 study populations. Participants were included in the treatment group to which they were randomized using institutional (local) or centralized MMR IHC test results. This population is referred to as the ITT MMR. Two additional analysis populations were defined for sensitivity efficacy analyses including:

- Central MMR: the MMR population based on central laboratory assessment only

DMC MMR: the MMR population used for DMC

Participants who enter the study without measurable disease were excluded from the ORR and DOR analysis.

Progression-free survival: PFS hypotheses were tested with a stratified log-rank statistic. In addition, the non-parametric Kaplan-Meier method to estimate the PFS curves and a stratified Cox proportional hazard model were implemented. The stratification factor prior chemotherapy (yes/no) were applied to both the stratified log-rank test and the stratified Cox model. PFS was assessed as per RECIST 1.1 by investigator. A sensitivity analysis of PFS based on the BICR's assessment was also performed.

Duration of Response: For participants with measurable at baseline who demonstrate CR or PR, DOR was defined as the time from first documented evidence of CR or PR until disease progression or death due to any cause, whichever occurs first. The censoring rule for DOR followed the PFS Primary (Preferred) Censoring Rule.

A sensitivity analysis considering intercurrent events (including death) was provided. If a participant met multiple criteria for censoring, the censoring criterion that occurs earliest was applied.

No subgroup analyses and effect of baseline factors were planned in the study protocol, with exception of prespecified stratification factors.

Interim Analyses

Each population (dMMR and pMMR) had one futility interim, one efficacy interim and one final analysis for PFS. An interim efficacy analysis occurred after the population (both pMMR and dMMR) completed accrual and a sufficient number of PFS events (50% information fraction) were observed, whichever was later. In each group, at the time of the final PFS analysis (significant interim or final analysis), an interim OS futility analysis was performed and the OS interim analysis results released along with the PFS results, at that time.

The analyses planned, endpoints evaluated, and drivers of timing are summarised in the table below.

Table 4: Analyses, endpoints evaluated and drivers of timing

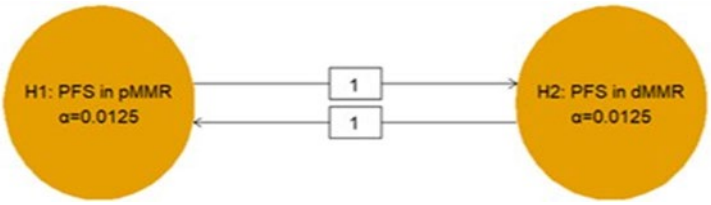
Analyses	Endpoints	Populations	Planned Timing (estimated time after first patients randomised if available)
Futility interim	PFS	pMMR	Triggered when ~196 PFS events, 50% information fraction (IF)
		dMMR	Triggered when ~84 PFS events, 50% IF
IA	PFS OS (descriptive)	pMMR and dMMR	Triggered when accrual to both populations completed & at least 50% IF in both MMR populations
FA	PFS	pMMR	Triggered when ~ 394 PFS events are observed (~ 60 months)
		dMMR	Triggered when ~ 168 PFS events are observed (~ 82 months)
	OS (descriptive)	pMMR	Triggered when ~ 364 OS events are observed (~ 60 months)
		dMMR	Triggered when ~ 150 OS events are observed (~ 86 months)

Error probabilities, adjustment for multiplicity

The overall Type I error rate was strongly controlled at a 0.025 (one-sided) alpha level. The trial used the graphical method of Maurer and Bretz to control multiplicity for multiple hypotheses, as well as interim analyses. A Lan-DeMets spending function approximate O'Brien-Fleming type of stopping boundary was

used for the efficacy interim analysis in each MMR population. Figure below shows the initial 1-sided α allocation for each hypothesis and the weights for reallocation from each hypothesis to the others.

Figure 4: initial 1-sided α allocation for each hypothesis



Protocol Amendments involving statistical methods

The protocol was subject to 12 general amendments, of which Amendment No. 1 (03 July 2019), Amendment No. 2 (24 September 2019), Amendment No. 10 (19 May 2022) and Amendment No. 11 (30 September 2022) modified the SAP language as shown below:

Amendment 1:

- The total alpha for each population will start at 0.0125 one-sided.
- The interim analysis will be for efficacy.

Amendment 2:

- An interim efficacy analysis will occur after the population (both pMMR and dMMR) completes accrual even if a sufficient number (defined at 50% information time of PFS events) are observed beforehand.

Amendment 10:

- Statistical analyses of pMMR and dMMR groups are based on central laboratory results; patients without central MMR status will be excluded from these analyses. If the null hypothesis for one group is rejected before the other group is tested, then all of the alpha (a total of 0.0125) will be forwarded to the other group.

Amendment 11:

- Statistical analyses of pMMR and dMMR groups are based on central laboratory results; patients without central MMR status will be excluded from these analyses. If the null hypothesis for one group is rejected before the other group is tested, then all of the alpha (a total of 0.0125) will be forwarded to the other group. If accrual to both populations (dMMR and pMMR) completes before 50% of the information time (IT) is acquired in either population, then the study will wait until at least 50% IT is obtained in that population before the efficacy interim analysis is conducted. Each population will be evaluated separately and independently.

The Statistical Analysis Plan (SAP) was amended once. The supplementary SAP (sSAP), dated 26 January 2023 and published before the DMC meeting, provided additional details, including PFS censoring rules.

Table 5: Censoring rules for primary analysis

Situation	Primary Analysis
PD or death documented after ⩽1 missed disease assessment, and before new anticancer therapy, if any	Progressed at date of documented PD or death
PD or death documented immediately after ⩾2 consecutive missed disease assessments or after new anticancer therapy, if any	Progressed at date of documented PD or death
No PD and no death; new anticancer treatment is not initiated	Censored at last contact date
No PD and no death; new anticancer treatment is initiated	Censored at last contact date

In addition, MSD made updates to the planned analyses, including different censoring rules for sensitivity analyses (see tables below). Additionaly, PFS2 (defined as the time from randomisation to disease progression by investigator assessment or death on subsequent anticancer therapy), was also assessed as exploratory efficacy endpoint. These changes were made after study unblinding.

Table 6: Censoring rules for sensitivity analyses of PFS

	MSD Primary (Preferred) Censoring Rule	MSD Sensitivity Censoring Rule 1	MSD Sensitivity Censoring Rule 2
Documented in sSAP? [16.1.9] (Sec. 3.6.1.1, Table 1)	Yes: called "Sensitivity Analysis 1" in sSAP	Yes: called "Sensitivity Analysis 2" in sSAP	No
Population	ITT MMR	ITT MMR	ITT MMR
Stratification factor(s)	Prior adjuvant chemotherapy (yes/no)	Prior adjuvant chemotherapy (yes/no)	Prior adjuvant chemotherapy (yes/no)
Situation: PD or death documented after ≤1 missed disease assessment, and before new anticancer therapy, if any	Progressed at date of documented PD or death	Progressed at date of documented PD or death	Progressed at date of documented PD or death
Situation: PD or death documented immediately after ≥2 consecutive missed disease assessments or after new anticancer therapy, if any	Censored at last disease assessment prior to the earlier date of ≥2 consecutive missed disease assessments and new anticancer therapy, if any	Progressed at date of documented PD or death	Progressed at date of documented PD or death
Situation: No PD and no death; new anticancer treatment is not initiated	Censored at last disease assessment	Censored at last disease assessment	Progressed at treatment discontinuation; otherwise censored at last disease assessment.
Situation: No PD and no death; new anticancer treatment is initiated	Censored at last disease assessment before new anticancer treatment	Censored at last disease assessment	Progressed at date of initiation of new anticancer treatment or discontinuation of treatment, whichever occurs later

Abbreviations: ITT=intent to treat; MMR=mismatch repair; MSD=Merck Sharp & Dohme LLC; PD=progressive disease; sSAP=supplemental statistical analysis plan.

	Protocol Censoring Rule by Central MMR Determination	Protocol Censoring Rule With Both Stratification Factors by ITT MMR	DMC Censoring Rule by DMC MMR (Used by NRG for the IA DMC Meeting)
Documented in sSAP? [16.1.9] (Sec. 3.6.1.1, Table 1)	No	No	No
Population	Central MMR	ITT MMR[a]	DMC MMR
Stratification factor(s)	Prior adjuvant chemotherapy (yes/no)	Prior adjuvant chemotherapy (yes/no) and ECOG PS (0 and 1/2)	Prior adjuvant chemotherapy (yes/no) and ECOG PS (0 and 1/2)
Additional information	Censoring rules were identical to the primary PFS analysis [Sec. 11.1.1], with the exception that only the central MMR data source was used	Censoring rules were identical to the primary PFS analysis [Sec. 11.1.1], with the exception that both stratification factors (prior adjuvant chemotherapy and ECOG PS) were used in the analysis instead of only prior adjuvant chemotherapy (Cox model and log-rank test)	Censoring rules were identical to the primary PFS analysis [Sec. 11.1.1]. The MMR population source is as follows: If a participant had central MMR results at the time of the DMC, those results were used. Otherwise, institutional (local) MMR results were used. Three participants with "indeterminate" central MMR results were excluded. Data sources to determine PFS events were different from primary PFS analysis and reflect the analysis prepared for the DMC. Death and PD information were obtained from NRG Oncology's "Follow-up" CRF.

Abbreviations: CRF=case report form; DMC=Data Monitoring Committee; ECOG PS=Eastern Cooperative Oncology Group performance status; IA=interim analysis; IHC=immunohistochemistry; ITT=intent to treat; MMR=mismatch repair; PD=progressive disease; PFS=progression-free survival; RECIST 1.1=Response Evaluation Criteria in Solid Tumors version 1.1; sSAP=supplemental statistical analysis plan.
Note: For the DMC censoring rule, not all follow-up PD dates recorded on the CRF were based on RECIST 1.1. Last contact date also utilized less CRF data points compared to MSD's preferred method.
[a] The ITT MMR included all participants who were randomized on or before the data cutoff dates for the 2 study populations, included in the treatment group to which they were randomized using institutional (local) or centralized MMR IHC test results.

Table 7: Censoring rules for Overall survival and PFS2 for Completely Missing Death Date

	Primary Censoring Rule for OS and PFS2	Sensitivity Censoring Rule 1	Sensitivity Censoring Rule 2
Population	ITT MMR[a]	ITT MMR[a]	ITT MMR[a]
Stratification factor(s)	Prior adjuvant chemotherapy (yes/no)	Prior adjuvant chemotherapy (yes/no)	Prior adjuvant chemotherapy (yes/no)
Censoring Rule Description	Event on the day after last known alive date (Day-A+1)	Censored on the last known alive date (Day-A)	Event on the mid-point of last known alive date, and death confirmation date (Day-A+Day-B)/2.

Abbreviations: Day-A=last known alive date; Day-B=death confirmation date; ITT=intent to treat; MMR=mismatch repair; OS=overall survival; PFS2= the time from randomization to disease progression by investigator assessment or death (whichever occurs first) on subsequent anticancer therapy.
[a] The ITT MMR included all participants who were randomized on or before the data cutoff dates for the 2 study populations, included in the treatment group to which they were randomized using institutional (local) or centralized MMR IHC test results.
Rules applied for participants with completely missing death date (no death date/month/year). Denote the participant's last known alive date as Day-A, date obtaining death confirmation as Day-B.
One participant in pMMR cohort was impacted, the participant experienced investigator-assessed progression prior to last known alive date (Day-A), therefore PFS was not affected.

Statistical Methods for Safety Analyses

Safety analyses were based on the All Participants as Treated (APaT) population, defined as all randomised participants who received at least 1 dose of study intervention in the pMMR and dMMR populations. Participants were analysed according to the study intervention they received.

Statistical Methods for PRO analyses

Analyses of PRO endpoints were conducted using the pMMR FAS population, defined as pMMR participants who provided a valid baseline PRO assessment and at least 1 follow-up PRO assessment.

Results

Participant flow

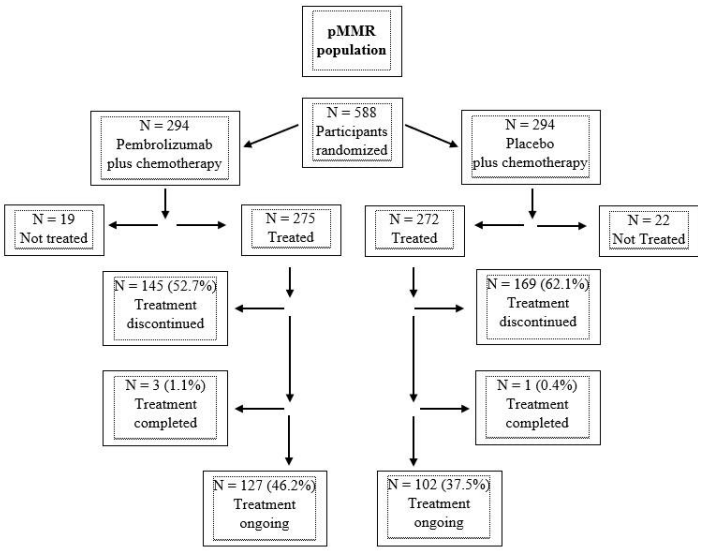
A total of 1064 participants were screened and 810 were randomised.

No information is available for the 254 patients who were screened but not randomised.

Of patients randomised, 588 (73%) had pMMR tumours and 222 (27%) had dMMR tumours at baseline.

Figure 5: Disposition of Participants – Study Intervention (ITT Population) (IA)

pMMR



dMMR

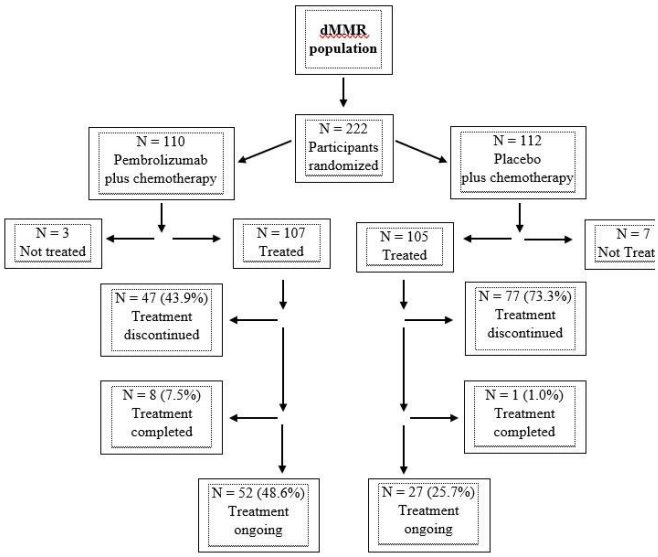


Table 8: Disposition of Participants (ITT Population)

pMMR

	Paclitaxel + Carboplatin + Pembrolizumab		Paclitaxel + Carboplatin + Placebo		Total	
	n	(%)	n	(%)	n	(%)
Participants in population	294		294		588	
Status for Trial						
Discontinued	63	(21.4)	68	(23.1)	131	(22.3)
Death	45	(15.3)	54	(18.4)	99	(16.8)
Lost To Follow-Up	1	(0.3)	0	(0.0)	1	(0.2)
Subject Decision To Withdraw From Study	16	(5.4)	14	(4.8)	30	(5.1)
Other	1	(0.3)	0	(0.0)	1	(0.2)
Ongoing	231	(78.6)	226	(76.9)	457	(77.7)
Status for Study Medication in Trial						
Started	275		272		547	
Completed	3	(1.1)	1	(0.4)	4	(0.7)
Discontinued	145	(52.7)	169	(62.1)	314	(57.4)
Adverse Event/Side Effects/Complications	36	(13.1)	17	(6.3)	53	(9.7)
Alternative Therapy (In Absence Of Progression)	2	(0.7)	3	(1.1)	5	(0.9)
Death On Study	6	(2.2)	2	(0.7)	8	(1.5)
Disease Progression, Relapse During Active Treatment	80	(29.1)	99	(36.4)	179	(32.7)
Patient Off-Treatment For Other Complicating Disease	4	(1.5)	1	(0.4)	5	(0.9)
Patient Withdrawal/Refusal After Beginning Protocol Therapy	11	(4.0)	11	(4.0)	22	(4.0)
Symptomatic Deterioration	2	(0.7)	2	(0.7)	4	(0.7)
Other	4	(1.5)	34	(12.5)	38	(6.9)
Ongoing	127	(46.2)	102	(37.5)	229	(41.9)

If the overall count of participants is calculated and displayed within a section in the first row, then it is used as the denominator for the percentage calculation. Otherwise, participants in population is used as the denominator for the percentage calculation.
Database Cutoff Date: 16DEC2022 for dMMR participants and 06DEC2022 for pMMR participants.

dMMR

	Paclitaxel + Carboplatin + Pembrolizumab		Paclitaxel + Carboplatin + Placebo		Total	
	n	(%)	n	(%)	n	(%)
Participants in population	110		112		222	
Status for Trial						
Discontinued	13	(11.8)	24	(21.4)	37	(16.7)
Death	10	(9.1)	17	(15.2)	27	(12.2)
Subject Decision To Withdraw From Study	3	(2.7)	7	(6.3)	10	(4.5)
Ongoing	97	(88.2)	88	(78.6)	185	(83.3)
Status for Study Medication in Trial						
Started	107		105		212	
Completed	8	(7.5)	1	(1.0)	9	(4.2)
Discontinued	47	(43.9)	77	(73.3)	124	(58.5)
Adverse Event/Side Effects/Complications	17	(15.9)	6	(5.7)	23	(10.8)
Death On Study	1	(0.9)	2	(1.9)	3	(1.4)
Disease Progression, Relapse During Active Treatment	18	(16.8)	48	(45.7)	66	(31.1)
Patient Off-Treatment For Other Complicating Disease	1	(0.9)	1	(1.0)	2	(0.9)
Patient Withdrawal/Refusal After Beginning Protocol Therapy	6	(5.6)	4	(3.8)	10	(4.7)
Symptomatic Deterioration	0	(0.0)	3	(2.9)	3	(1.4)
Other	4	(3.7)	13	(12.4)	17	(8.0)
Ongoing	52	(48.6)	27	(25.7)	79	(37.3)

If the overall count of participants is calculated and displayed within a section in the first row, then it is used as the denominator for the percentage calculation. Otherwise, participants in population is used as the denominator for the percentage calculation.
Database Cutoff Date: 16DEC2022 for dMMR participants and 06DEC2022 for pMMR participants.

Recruitment

First participant first visit: 12 August 2019

Last participant in: 20 December 2022 for pMMR; 17 August 2022 for dMMR.

Data cut-off for Interim Analysis: 06 December 2022 for pMMR population; 16 December 2022 for dMMR population.

The study is currently ongoing.

This study was conducted at 217 centres in 4 countries, primarily in the US (750 out of 810 patients randomised, 94%), with a subset of participants randomised from Canada (51), Japan (7), and South Korea (2).

Conduct of the study

This study was performed in collaboration with NCI-CTEP. CTEP was the IND-holder/Sponsor while the NCTN group "NRG" operationalized the study. MSD collaborated on study design, execution, and analysis as well as clinical supplies origination. The primary efficacy results at the IA underwent initial review by the NRG DMC on 26 January 2023, followed by discussions with NCI-CTEP and subsequent communication with MSD's Executive Oversight Committee.

The statistical analyses of the data obtained from this study were initially the responsibility of NCI-CTEP. However, the statistical analyses are being conducted by MSD for the purpose of the CSR submitted for regulatory assessment.

Table 9: Protocol Amendments

Document	Date of Issue	Summary of Major Changes
Amendment 12	24-FEB-2023	Sec 6.2: Dose modification and supportive care guidelines for pembrolizumab were updated. CAEPR and risks were updated.
Amendment 11	30-SEP-2022	• Secs 14.1 and 14.4: If accrual to both populations (dMMR and pMMR) completes before 50% of the information time (IT) is acquired in either population, then the study will wait until at least 50% IT is obtained in that population before the efficacy interim analysis is conducted. Each population will be evaluated separately and independently. • Sec 14.4: In the case(s) where both null hypotheses are being tested at the same time, the null hypothesis associated with the dMMR population will be tested first, then followed by the pMMR population.
Amendment 10	19-MAY-2022	• Secs 14.1, 14.3.3, 14.4: Statistical analyses of pMMR and dMMR groups are based on central laboratory results; patients without central MMR status will be excluded from these analyses. If the null hypothesis for one group is rejected before the other group is tested, then all of the alpha (a total of 0.0125) will be forwarded to the other group.
Amendment 9	09-MAR-2022	• Sec 5.7: Slide for centralized MMR and PD-L1 IHC testing must be submitted prior to Step 2 randomization, but results do not need to be returned before Step 2 randomization. • Sec 3.2.9: If TSH is not within normal range despite no symptoms of thyroid dysfunction, normal Free T4 level is required. • Sec 6.1: If substitution of paclitaxel is required for reasons other than hypersensitivity reaction, study team review and approval must be obtained. • Secs 8 and 9: CTEP PMB will no longer supply saline vials. Placebo infusions will be prepared using supplies provided by the site. • Appendix XIV: Country-specific appendix for Japan added.
Amendment 8	06-OCT-2021	No major changes were implemented; CAEPR and risks were updated.
Amendment 7	21-MAY-2021	• Sec 3.3.2: Severe hypersensitivity reaction to paclitaxel and/or carboplatin is an ineligibility criterion. • Sec 6.1: Chemotherapy (paclitaxel and carboplatin) dose modifications and supportive care can be per investigator discretion and/or institutional, NCCN, and/or ASCO guidelines. It is acceptable to substitute docetaxel or paclitaxel protein-bound particles for injectable suspension in patients who had a reaction to paclitaxel with a failed re-challenge (or not amenable to re-challenge).
Amendment 6	08-DEC-2020	No major changes were implemented.

Document	Date of Issue	Summary of Major Changes
Amendment 5	14-OCT-2020	• Sec 5.1: Maintenance will be given every 6 weeks (was 3 weeks), with a 400 mg pembrolizumab dose (was 200 mg). Treatment will be given up to 20 total cycles (combination and maintenance). • Sec 5.2: Unblinding procedures were expanded to include 1) unblinding for subsequent treatment planning upon progression of disease due to pembrolizumab being available for second-line therapy), 2) unblinding related to COVID-19 safety concerns. • Sec 5.9: Dosing interruptions of greater than 9 weeks (was 8 weeks) may require treatment discontinuation. • Added Appendix XIII "Treatment Considerations in the Context of the COVID-19 Pandemic and Placebo Design".
Amendment 4	27-FEB-2020	No major changes were implemented; CAEPR and risks were updated.
Amendment 3	07-FEB-2020	Sec 3.23: Palliative radiation therapy prior to step 2 registration is allowed.
Amendment 2	24-SEP-2019	• Sec 3.3.8: Uncomplicated urinary tract infection does not render a patient ineligible. • Sec 6.2.3: Dose modification and toxicity management guidelines for immune-related AEs associated with pembrolizumab were updated. • Sec 14.1: An interim efficacy analysis will occur after the population (both pMMR and dMMR) completes accrual even if a sufficient number (defined as 50% information time) of PFS events are observed beforehand.
Amendment 1	03-JUL-2019	• Sec 1.1.1: PFS will be assessed by RECIST 1.1. • Sec 1.2.2: Evaluation of ORR by RECIST 1.1 will be BICR assessed or investigator assessed by treatment arm and by MMR status in patients who enter the study with measurable disease. • Sec 1.2.3: Evaluation of DOR will be BICR assessed or investigator assessed by treatment arm and by MMR status in patients who enter the study with measurable disease. • Sec 3.2.1: Dedifferentiated carcinoma was added as an eligible histology. • Sec 3.2.7: Renal function will be measured as creatinine $\leq$ 1.5 x institutional/laboratory ULN. • Sec 3.2.1.3: Patients with a prior or concurrent malignancy whose natural history or treatment does not have the potential to interfere with the safety or efficacy assessment of the investigational regimen are eligible. • Sec 3.3.2: Patients who have a history of a severe hypersensitivity reaction to monoclonal antibody or pembrolizumab and/or its excipients are not eligible. • Sec. 14.1: The total alpha for each population will start at 0.0125 one-sided. • Sec. 14.3.3: The interim analysis will be for efficacy.
Initial	14-JUN-2019	

Table 10: Measures Implemented by the Sponsor to Manage Study Conduct During the COVID-19 Pandemic

Process	Measure
Study enrollment	• Study enrollment was paused temporarily (06-APR-2020 to 30-NOV-2020) in order to implement strategies that mitigated risk to participants.
Protocol deviations	• COVID-19 was noted for study procedures not performed; RAVE form was added to capture start and stop dates of deviations in the clinical database.
Clinical supplies (including study intervention)	• PPD clinical supply shipment delays to sites
Informed consent	• Amended to allow unblinding requests for safety concerns and change in treatment times to reduce clinic visits (treatment every 6 weeks in maintenance phase to reduce the number of visits)

Protocol Deviations

In the **pMMR** population, important protocol deviations were reported for 7 vs 10 participants in the pembrolizumab vs placebo group, respectively. Of these, in 6 patients in each treatment group were considered to be clinically important. Protocol deviations associated with the pandemic were reported for 12 vs 9 participants in the pembrolizumab vs placebo group respectively, all considered not important.

In the **dMMR** population, important protocol deviations were reported for 12 vs 7 participants in the pembrolizumab vs placebo group, respectively. Of these, 5 vs 3 had important protocol deviations that were considered to be clinically important. Protocol deviations associated with the pandemic were reported for 5 vs 4 participants in the pembrolizumab vs placebo group respectively. These were all not important deviations in study procedures, except for 1 participant in the pembrolizumab plus chemotherapy group who received incorrect study medication (Cycle 2 study intervention was restarted before steroid treatment was completed).

No protocol deviations were classified as a serious GCP compliance issue, and no participant's data were excluded due to protocol deviations.

Baseline data

In both the pMMR and dMMR populations, all participants were female, with a median age of 66.1 years, and most participants were white, not Hispanic or Latino, and had an ECOG PS of 0 or 1.

The most common histologic subtypes were serous and endometrioid adenocarcinoma (Grades 1-3) in the pMMR population and endometrioid adenocarcinoma (Grades 1-3) in the dMMR population. One participant in the pMMR population was randomised as endometrioid adenocarcinoma Grade 2, but actually had carcinosarcoma; this was recorded as a protocol deviation.

Prior adjuvant chemotherapy for treatment of EC was more common in the pMMR population (~25%) than the dMMR population (~5%), while just over 40% of participants in both the pMMR and dMMR populations had received prior radiotherapy for treatment of EC.

Table 11: Participant Characteristics in pMMR Participants (ITT Population)

	Paclitaxel + Carboplatin + Pembrolizumab		Paclitaxel + Carboplatin + Placebo		Total	
	n	(%)	n	(%)	n	(%)
Participants in population	294		294		588	
Sex						
Female	294	(100.0)	294	(100.0)	588	(100.0)
Age (Years)						
< 65	135	(45.9)	135	(45.9)	270	(45.9)
>= 65	159	(54.1)	159	(54.1)	318	(54.1)
Mean	65.5		65.3		65.4	
SD	9.5		9.8		9.6	
Median	66.0		66.1		66.1	
Range	31 to 94		29 to 91		29 to 94	
Race						
American Indian Or Alaska Native	2	(0.7)	2	(0.7)	4	(0.7)
Asian	17	(5.8)	14	(4.8)	31	(5.3)
Black Or African American	46	(15.6)	50	(17.0)	96	(16.3)
Multiple	1	(0.3)	1	(0.3)	2	(0.3)
Native Hawaiian Or Other Pacific Islander	1	(0.3)	3	(1.0)	4	(0.7)
White	212	(72.1)	212	(72.1)	424	(72.1)
Missing	15	(5.1)	12	(4.1)	27	(4.6)
Ethnicity						
Hispanic Or Latino	21	(7.1)	14	(4.8)	35	(6.0)
Not Hispanic Or Latino	265	(90.1)	274	(93.2)	539	(91.7)
Not Reported	4	(1.4)	3	(1.0)	7	(1.2)
Unknown	4	(1.4)	3	(1.0)	7	(1.2)
Age (Years)						
< 65	135	(45.9)	135	(45.9)	270	(45.9)
>= 65 to < 75	113	(38.4)	121	(41.2)	234	(39.8)
>= 75	46	(15.6)	38	(12.9)	84	(14.3)
Age (Years) at Initial Diagnosis						

< 65	157	(53.4)	167	(56.8)	324	(55.1)
>= 65	137	(46.6)	127	(43.2)	264	(44.9)
Age (Years) at Initial Diagnosis						
Participants with data	294		294		588	
Mean	63.5		63.5		63.5	
SD	9.8		9.8		9.8	
Median	64.1		64.0		64.1	
Range	30.0 to 92.6		27.5 to 90.6		27.5 to 92.6	
Region						
North America	287	(97.6)	287	(97.6)	574	(97.6)
Rest of the World	7	(2.4)	7	(2.4)	14	(2.4)
Central MMR Status						
dMMR	3	(1.0)	2	(0.7)	5	(0.9)
pMMR	287	(97.6)	289	(98.3)	576	(98.0)
INDETERMINATE	2	(0.7)	1	(0.3)	3	(0.5)
Missing	2	(0.7)	2	(0.7)	4	(0.7)
ECOG (Randomization)						
0	198	(67.3)	197	(67.0)	395	(67.2)
1	87	(29.6)	88	(29.9)	175	(29.8)
2	9	(3.1)	9	(3.1)	18	(3.1)
ECOG (CRF)						
0	190	(64.6)	194	(66.0)	384	(65.3)
1	94	(32.0)	88	(29.9)	182	(31.0)
2	10	(3.4)	12	(4.1)	22	(3.7)
Measurable Disease at Baseline						
Y	220	(74.8)	235	(79.9)	455	(77.4)
N	74	(25.2)	59	(20.1)	133	(22.6)
Prior Chemotherapy (Randomization)						
Y	74	(25.2)	76	(25.9)	150	(25.5)
N	220	(74.8)	218	(74.1)	438	(74.5)
Prior Chemotherapy (CRF)						
Y	76	(25.9)	75	(25.5)	151	(25.7)
N	218	(74.1)	219	(74.5)	437	(74.3)
Prior Radiation Therapy						
Y	118	(40.1)	124	(42.2)	242	(41.2)
N	176	(59.9)	170	(57.8)	346	(58.8)
Elapsed Time (Years) from Initial Diagnosis						
Participants with data	294		294		588	
Mean	1.9		1.8		1.9	
SD	2.6		2.4		2.5	
Median	1.2		0.7		1.0	
Range	0.0 to 18.3		0.0 to 14.4		0.0 to 18.3	
Histology						
Endometrioid, grade 1	55	(18.7)	45	(15.3)	100	(17.0)
Endometrioid, grade 2	51	(17.3)	59	(20.1)	110	(18.7)
Endometrioid, grade 3	53	(18.0)	42	(14.3)	95	(16.2)
Serous	79	(26.9)	76	(25.9)	155	(26.4)
Clear cell	19	(6.5)	20	(6.8)	39	(6.6)
Dedifferentiated/undifferentiated	7	(2.4)	6	(2.0)	13	(2.2)
Mixed epithelial	6	(2.0)	10	(3.4)	16	(2.7)
Adenocarcinoma, NOS	24	(8.2)	35	(11.9)	59	(10.0)
Missing	0	(0.0)	1	(0.3)	1	(0.2)
FIGO Stage at Initial Diagnosis						
IA	69	(23.5)	67	(22.8)	136	(23.1)
IB	33	(11.2)	36	(12.2)	69	(11.7)
II	25	(8.5)	25	(8.5)	50	(8.5)
IIIA	11	(3.7)	14	(4.8)	25	(4.3)
IIIB	8	(2.7)	7	(2.4)	15	(2.6)
IIIC1	21	(7.1)	17	(5.8)	38	(6.5)
IIIC2	16	(5.4)	8	(2.7)	24	(4.1)

IVA	11	(3.7)	5	(1.7)	16	(2.7)
IVB	100	(34.0)	115	(39.1)	215	(36.6)
Status of Disease						
Recurrent	172	(58.5)	159	(54.1)	331	(56.3)
Persistant	2	(0.7)	1	(0.3)	3	(0.5)
Primary	120	(40.8)	134	(45.6)	254	(43.2)
Prior Brachytherapy						
Y	69	(23.5)	86	(29.3)	155	(26.4)
N	225	(76.5)	208	(70.7)	433	(73.6)
Prior Hormonal Therapy						
Y	14	(4.8)	12	(4.1)	26	(4.4)
N	280	(95.2)	282	(95.9)	562	(95.6)

SD=Standard deviation.
Database Cutoff Date: 16DEC2022 for dMMR participants and 06DEC2022 for pMMR participants.

Table 12: Participant Characteristics in dMMR Participants (ITT Population)

	Paclitaxel + Carboplatin + Pembrolizumab		Paclitaxel + Carboplatin + Placebo		Total	
	n	(%)	n	(%)	n	(%)
Participants in population	110		112		222	
Sex						
Female	110	(100.0)	112	(100.0)	222	(100.0)
Age (Years)						
< 65	47	(42.7)	52	(46.4)	99	(44.6)
>= 65	63	(57.3)	60	(53.6)	123	(55.4)
Mean	65.8		65.5		65.7	
SD	8.4		9.1		8.8	
Median	67.2		66.0		66.1	
Range	39 to 82		37 to 86		37 to 86	
Race						
American Indian Or Alaska Native	0	(0.0)	2	(1.8)	2	(0.9)
Asian	3	(2.7)	4	(3.6)	7	(3.2)
Black Or African American	10	(9.1)	9	(8.0)	19	(8.6)
White	91	(82.7)	85	(75.9)	176	(79.3)
Missing	6	(5.5)	12	(10.7)	18	(8.1)
Ethnicity						
Hispanic Or Latino	4	(3.6)	7	(6.3)	11	(5.0)
Not Hispanic Or Latino	104	(94.5)	97	(86.6)	201	(90.5)
Not Reported	1	(0.9)	4	(3.6)	5	(2.3)
Unknown	1	(0.9)	4	(3.6)	5	(2.3)
Age (Years)						
< 65	47	(42.7)	52	(46.4)	99	(44.6)
>= 65 to < 75	49	(44.5)	43	(38.4)	92	(41.4)
>= 75	14	(12.7)	17	(15.2)	31	(14.0)
Age (Years) at Initial Diagnosis						
< 65	57	(51.8)	61	(54.5)	118	(53.2)
>= 65	53	(48.2)	51	(45.5)	104	(46.8)

Age (Years) at Initial Diagnosis						
Participants with data	110		112		222	
Mean	64.2		63.8		64.0	
SD	8.2		9.1		8.6	
Median	64.9		63.6		64.4	
Range	38.5 to 81.0		37.3 to 85.5		37.3 to 85.5	
Region						
North America	110	(100.0)	111	(99.1)	221	(99.5)
Rest of the World	0	(0.0)	1	(0.9)	1	(0.5)
Central MMR Status						
dMMR	108	(98.2)	110	(98.2)	218	(98.2)
pMMR	1	(0.9)	1	(0.9)	2	(0.9)
Missing	1	(0.9)	1	(0.9)	2	(0.9)
ECOG (Randomization)						
0	70	(63.6)	72	(64.3)	142	(64.0)
1	39	(35.5)	35	(31.3)	74	(33.3)
2	1	(0.9)	5	(4.5)	6	(2.7)
ECOG (CRF)						
0	72	(65.5)	70	(62.5)	142	(64.0)
1	37	(33.6)	36	(32.1)	73	(32.9)
2	1	(0.9)	6	(5.4)	7	(3.2)
Measurable Disease at Baseline						
Y	95	(86.4)	95	(84.8)	190	(85.6)
N	15	(13.6)	17	(15.2)	32	(14.4)
Prior Chemotherapy (Randomization)						
Y	4	(3.6)	8	(7.1)	12	(5.4)
N	106	(96.4)	104	(92.9)	210	(94.6)
Prior Chemotherapy (CRF)						
Y	4	(3.6)	6	(5.4)	10	(4.5)
N	106	(96.4)	106	(94.6)	212	(95.5)
Prior Radiation Therapy						
Y	42	(38.2)	54	(48.2)	96	(43.2)
N	68	(61.8)	58	(51.8)	126	(56.8)
Elapsed Time (Years) from Initial Diagnosis						
Participants with data	110		112		222	
Mean	1.6		1.8		1.7	
SD	2.2		2.1		2.1	
Median	0.7		1.2		0.9	
Range	0.0 to 13.0		0.0 to 11.7		0.0 to 13.0	
Histology						
Endometrioid, grade 1	20	(18.2)	34	(30.4)	54	(24.3)
Endometrioid, grade 2	52	(47.3)	43	(38.4)	95	(42.8)
Endometrioid, grade 3	15	(13.6)	16	(14.3)	31	(14.0)
Serous	4	(3.6)	1	(0.9)	5	(2.3)
Dedifferentiated/undifferentiated	4	(3.6)	4	(3.6)	8	(3.6)
Mixed epithelial	3	(2.7)	2	(1.8)	5	(2.3)
Adenocarcinoma, NOS	12	(10.9)	12	(10.7)	24	(10.8)
FIGO Stage at Initial Diagnosis						
IA	26	(23.6)	34	(30.4)	60	(27.0)
IB	18	(16.4)	23	(20.5)	41	(18.5)
II	14	(12.7)	13	(11.6)	27	(12.2)
IIIA	5	(4.5)	2	(1.8)	7	(3.2)
IIIB	1	(0.9)	0	(0.0)	1	(0.5)
IIIC1	6	(5.5)	4	(3.6)	10	(4.5)
IIIC2	6	(5.5)	5	(4.5)	11	(5.0)
IVA	2	(1.8)	4	(3.6)	6	(2.7)
IVB	32	(29.1)	27	(24.1)	59	(26.6)
Status of Disease						
Recurrent	64	(58.2)	71	(63.4)	135	(60.8)

Persistant	2	(1.8)	2	(1.8)	4	(1.8)
Primary	44	(40.0)	39	(34.8)	83	(37.4)
Prior Brachytherapy						
Y	29	(26.4)	35	(31.3)	64	(28.8)
N	81	(73.6)	77	(68.8)	158	(71.2)
Prior Hormonal Therapy						
Y	9	(8.2)	8	(7.1)	17	(7.7)
N	101	(91.8)	104	(92.9)	205	(92.3)
SD=Standard deviation. Database Cutoff Date: 16DEC2022 for dMMR participants and 06DEC2022 for pMMR participants.						

In vitro biomarker testing

Central MMR status was determined using the IHC Ventana MMR RxDx panel, which is FDA approved as a companion diagnostic to determine dMMR tumor status for pembrolizumab.

Table 13: Concordance of Central and Institutional MMR IHC Testing Results (ITT Population)

Central MMR IHC Results	Institutional MMR IHC Results			Kappa Coefficient (95% CI)
	dMMR	pMMR	Total	
dMMR	194	16	210	0.9068 (0.8730, 0.9406)
pMMR	12	527	539	
Total	206	543	749	
Database Cutoff Date: 16DEC2022 for dMMR participants and 06DEC2022 for pMMR participants.				

Medical History and Concurrent Illnesses

The most frequently reported medical history conditions (incidence ≥20% in one or both treatment groups) were anaemia, anxiety, constipation, fatigue, hyperlipidaemia, hypertension, and neoplasm in the pMMR population, and abdominal pain, anaemia, anxiety, constipation, fatigue, gastroesophageal reflux disease, hyperlipidaemia, hypertension, hypothyroidism, and neoplasm in the dMMR population.

Concomitant medication

In the **pMMR** population, the reported concomitant medications were generally balanced between participants in the 2 treatment groups, except for a ≥10% higher incidence of use of antidiarrheals, intestinal anti-inflammatory/anti-infective agents, and thyroid therapy in the pembrolizumab plus chemotherapy group compared with the placebo plus chemotherapy group.

In the **dMMR** population, use of several categories of concomitant medications had a ≥10% higher incidence of use in the pembrolizumab plus chemotherapy group compared with the placebo plus chemotherapy group, including antidiarrheals, intestinal anti-inflammatory/ anti-infective agents, drugs used in diabetes, mineral supplements, other alimental tract and metabolism products, antibacterials for systemic use, antithrombotic agents, agents acting on the renin-angiotensin system, lipid modifying agents, and other dermatological preparations.

Subsequent anticancer treatments

In both the **pMMR** and **dMMR** populations, among patients who discontinued study treatment, a higher proportion in the placebo plus chemotherapy group initiated subsequent systemic anticancer therapy after discontinuing study intervention compared with the pembrolizumab plus chemotherapy group, similarly in both subsets (pMMR: 68% vs 46.2%; dMMR: 66.2% vs 42.6%). In both populations, more participants received subsequent PD-1/PD-L1 inhibitors in the comparator arm. In addition, in the pMMR population more patients received anti-angiogenic drugs.

Table 14: Summary of Subsequent Systemic Anti-Cancer Treatment in Participants Who Discontinued Study Treatment (ITT Population)

pMMR

	Paclitaxel + Carboplatin + Pembrolizumab (N=145)	Paclitaxel + Carboplatin + Placebo (N=169)	Total (N=314)
Started Study Treatment	145 (100.0)	169 (100.0)	314 (100.0)
Discontinued Study Treatment	145 (100.0)	169 (100.0)	314 (100.0)
Received Any Subsequent Systemic Anti-cancer Therapy	67 (46.2)	115 (68.0)	182 (58.0)
Subsequent systemic therapy by type			
Any Anti-PD-1/PD-L1	28 (19.3)	76 (45.0)	104 (33.1)
atezolizumab	0 (0.0)	1 (0.6)	1 (0.3)
durvalumab	1 (0.7)	2 (1.2)	3 (1.0)
nivolumab	0 (0.0)	2 (1.2)	2 (0.6)
pembrolizumab	27 (18.6)	72 (42.6)	99 (31.5)
Any Anti-angiogenic	32 (22.1)	70 (41.4)	102 (32.5)
bevacizumab	12 (8.3)	7 (4.1)	19 (6.1)
bevacizumab awwb	2 (1.4)	1 (0.6)	3 (1.0)
bevacizumab bvzr	0 (0.0)	1 (0.6)	1 (0.3)
cediranib	1 (0.7)	2 (1.2)	3 (1.0)
lenvatinib	19 (13.1)	61 (36.1)	80 (25.5)
Any Chemotherapy	34 (23.4)	35 (20.7)	69 (22.0)
carboplatin	8 (5.5)	18 (10.7)	26 (8.3)
cisplatin	3 (2.1)	3 (1.8)	6 (1.9)
docetaxel	0 (0.0)	3 (1.8)	3 (1.0)
doxorubicin	9 (6.2)	6 (3.6)	15 (4.8)
gemcitabine	2 (1.4)	1 (0.6)	3 (1.0)
liposomal doxorubicin	8 (5.5)	3 (1.8)	11 (3.5)
liposomal doxorubicin hydrochloride	3 (2.1)	0 (0.0)	3 (1.0)
other therapeutic products	0 (0.0)	1 (0.6)	1 (0.3)
paclitaxel	7 (4.8)	19 (11.2)	26 (8.3)
pegylated liposomal doxorubicin	0 (0.0)	1 (0.6)	1 (0.3)
pegylated liposomal doxorubicin hydrochloride	6 (4.1)	2 (1.2)	8 (2.5)
topotecan	3 (2.1)	0 (0.0)	3 (1.0)
Any Other Investigational or Approved Agents	8 (5.5)	15 (8.9)	23 (7.3)
abemaciclib	1 (0.7)	0 (0.0)	1 (0.3)
afatinib	1 (0.7)	0 (0.0)	1 (0.3)
alpelisib	0 (0.0)	1 (0.6)	1 (0.3)
capivasertib	0 (0.0)	3 (1.8)	3 (1.0)
etigilimab	0 (0.0)	2 (1.2)	2 (0.6)
everolimus	1 (0.7)	4 (2.4)	5 (1.6)
margetuximab	0 (0.0)	1 (0.6)	1 (0.3)
methotrexate	0 (0.0)	1 (0.6)	1 (0.3)
olaparib	1 (0.7)	4 (2.4)	5 (1.6)
onapristone	1 (0.7)	0 (0.0)	1 (0.3)
rebastinib	0 (0.0)	1 (0.6)	1 (0.3)
tebotelimab	0 (0.0)	1 (0.6)	1 (0.3)
trastuzumab	3 (2.1)	2 (1.2)	5 (1.6)
trastuzumab deruxtecan nxki	1 (0.7)	0 (0.0)	1 (0.3)

Every participant is counted a single time for each applicable specific anti-cancer treatment.
A participant with multiple anti-cancer treatments within a therapy category is counted a single time for that category.
Database Cutoff Date: 16DEC2022 for dMMR participants and 06DEC2022 for pMMR participants.

dMMR

	Paclitaxel + Carboplatin + Pembrolizumab (N=47)	Paclitaxel + Carboplatin + Placebo (N=77)	Total (N=124)
Started Study Treatment	47 (100.0)	77 (100.0)	124 (100.0)
Discontinued Study Treatment	47 (100.0)	77 (100.0)	124 (100.0)
Received Any Subsequent Systemic Anti-cancer Therapy	20 (42.6)	51 (66.2)	71 (57.3)
Subsequent systemic therapy by type			
Any Anti-PD-1/PD-L1	9 (19.1)	42 (54.5)	51 (41.1)
durvalumab	1 (2.1)	1 (1.3)	2 (1.6)
pembrolizumab	8 (17.0)	40 (51.9)	48 (38.7)
retifanlimab	0 (0.0)	1 (1.3)	1 (0.8)
Any Anti-angiogenic	4 (8.5)	9 (11.7)	13 (10.5)
bevacizumab	0 (0.0)	3 (3.9)	3 (2.4)
cediranib	1 (2.1)	0 (0.0)	1 (0.8)
lenvatinib	3 (6.4)	6 (7.8)	9 (7.3)
Any Chemotherapy	5 (10.6)	9 (11.7)	14 (11.3)
carboplatin	3 (6.4)	2 (2.6)	5 (4.0)
doxorubicin	1 (2.1)	3 (3.9)	4 (3.2)
liposomal doxorubicin	1 (2.1)	3 (3.9)	4 (3.2)
paclitaxel	3 (6.4)	1 (1.3)	4 (3.2)
pegylated liposomal doxorubicin	0 (0.0)	1 (1.3)	1 (0.8)
pegylated liposomal doxorubicin hydrochloride	0 (0.0)	1 (1.3)	1 (0.8)
Any Other Investigational or Approved Agents	2 (4.3)	7 (9.1)	9 (7.3)
everolimus	2 (4.3)	3 (3.9)	5 (4.0)
olaparib	0 (0.0)	1 (1.3)	1 (0.8)
onapristone	0 (0.0)	1 (1.3)	1 (0.8)
vibostolimab	0 (0.0)	2 (2.6)	2 (1.6)

Every participant is counted a single time for each applicable specific anti-cancer treatment.
A participant with multiple anti-cancer treatments within a therapy category is counted a single time for that category.
Database Cutoff Date: 16DEC2022 for dMMR participants and 06DEC2022 for pMMR participants.

Extent of Exposure to Study Interventions

At the time of data cutoff for the IA (06 December 2022 for pMMR and 16 December 2022 for dMMR), the median duration of exposure to study intervention was longer for the pembrolizumab plus chemotherapy arm compared with the placebo plus chemotherapy arm in both pMMR and dMMR populations. Median duration of therapy was longer in the dMMR than in the pMMR groups. The median duration of exposure to all assigned medication was 106 days in both treatment arms of each population, equivalent to the protocol-specified 6 × q3w cycles.

Table 15: Summary of Drug Exposure (APaT Population)

pMMR

	Paclitaxel + Carboplatin + Pembrolizumab (N=275)	Paclitaxel + Carboplatin + Placebo (N=272)
Duration on Therapy[a] (days)		
n	275	272
Mean (SD)	183.1 (146.3)	157.4 (126.5)
Median	165	126.5
Range	1 to 729	1 to 651
Duration on All Drugs[b] (days)		
n	275	270
Mean (SD)	93.7 (47.6)	95 (49.7)
Median	106	106
Range	1 to 224	1 to 303
Dur on Pac/Doce/Pac prot-bound[c] (days)		
n	275	272
Mean (SD)	96.2 (46.8)	96.5 (50.6)
Median	106	106
Range	1 to 224	1 to 303
Duration on Carboplatin[d] (days)		
n	275	271
Mean (SD)	99.1 (48)	98.1 (49.9)
Median	106	106
Range	1 to 224	1 to 303
Duration on Pembrolizumab/Placebo[e] (days)		
n	275	271
Mean (SD)	181 (147.7)	157.4 (126.6)
Median	165	126
Range	1 to 729	1 to 651
Number of Pembrolizumab/Placebo Doses Received		
n	275	271
Mean (SD)	7.7 (4.6)	7 (3.8)
Median	7	7
Range	1 to 25	1 to 19

[a] Duration on Therapy is calculated as the days between first dose date and last dose date of any study medication.
[b] For all drug duration, defined as the duration from the first date when all drugs were taken until the date when one of the drugs was first discontinued.
[c] For Paclitaxel/Docetaxel/Paclitaxel protein-bound particles, defined as the duration from the first date when Paclitaxel/Docetaxel/Paclitaxel protein-bound particles was taken until the date when Paclitaxel/Docetaxel/Paclitaxel protein-bound particles was last discontinued. Docetaxel or paclitaxel protein-bound particles for injectable suspension are acceptable substitutes in patients who had a reaction to paclitaxel with a failed re-challenge (or not amendable to re-challenge).
[d] For Carboplatin, defined as the duration from the first date when Carboplatin was taken until the date when Carboplatin was discontinued.
[e] For Pembrolizumab/placebo, defined as the duration from the first date when Pembrolizumab/placebo was taken until the date when Pembrolizumab/placebo was discontinued.
Database Cutoff Date: 16DEC2022 for dMMR participants and 06DEC2022 for pMMR participants.

dMMR

	Paclitaxel + Carboplatin + Pembrolizumab (N=107)	Paclitaxel + Carboplatin + Placebo (N=105)
Duration on Therapy[a] (days)		
n	107	105
Mean (SD)	287.4 (194.8)	186.7 (136.6)
Median	234	162
Range	1 to 702	1 to 636
Duration on All Drugs[b] (days)		
n	107	105
Mean (SD)	105.5 (42.9)	106.2 (37.1)
Median	106	106
Range	1 to 204	1 to 223
Dur on Pac/Doce/Pac prot-bound[c] (days)		
n	107	105
Mean (SD)	107.8 (41.4)	106.4 (36.8)
Median	107	106
Range	1 to 212	1 to 223
Duration on Carboplatin[d] (days)		
n	107	105
Mean (SD)	111.5 (43.3)	109.5 (36.4)
Median	108	106
Range	1 to 212	1 to 223
Duration on Pembrolizumab/Placebo[e] (days)		
n	107	105
Mean (SD)	285.5 (196.3)	186.4 (136.8)
Median	234	162
Range	1 to 702	1 to 636
Number of Pembrolizumab/Placebo Doses Received		
n	107	105
Mean (SD)	10.7 (5.9)	7.9 (3.7)
Median	9	7
Range	1 to 29	1 to 19

[a] Duration on Therapy is calculated as the days between first dose date and last dose date of any study medication.
[b] For all drug duration, defined as the duration from the first date when all drugs were taken until the date when one of the drugs was first discontinued.
[c] For Paclitaxel/Docetaxel/Paclitaxel protein-bound particles, defined as the duration from the first date when Paclitaxel/Docetaxel/Paclitaxel protein-bound particles was taken until the date when Paclitaxel/Docetaxel/Paclitaxel protein-bound particles was last discontinued. Docetaxel or paclitaxel protein-bound particles for injectable suspension are acceptable substitutes in patients who had a reaction to paclitaxel with a failed re-challenge (or not amendable to re-challenge).
[d] For Carboplatin, defined as the duration from the first date when Carboplatin was taken until the date when Carboplatin was discontinued.
[e] For Pembrolizumab/placebo, defined as the duration from the first date when Pembrolizumab/placebo was taken until the date when Pembrolizumab/placebo was discontinued.
Database Cutoff Date: 16DEC2022 for dMMR participants and 06DEC2022 for pMMR participants.

Numbers analysed

Efficacy analyses were based on the **ITT population**, which included all participants who were randomised for the pMMR population (N=588) and the dMMR population (N=222).

In the pMMR population, 9 pMMR participants were enrolled before or at enrolment closing date of 06 December 2022 (IA data cutoff date) but were randomised and began study treatment after the IA data cutoff. Four of them were randomised in the pembrolizumab plus chemotherapy group and 5 in the placebo plus chemotherapy group. Those subjects were thus not included in the IA, but were included in the updated analysis.

Participants without measurable disease at baseline per RECIST 1.1 were excluded from the ORR and DOR analysis.

The PRO analyses were based on the pMMR FAS population, defined as pMMR participants who provided a valid baseline PRO assessment and at least 1 follow-up PRO assessment.

Safety analyses were based on the **APaT population**, which included all randomised participants who received at least 1 dose of study intervention in the pMMR and dMMR populations (N=547 and N=212, respectively).

Outcomes and estimation

Results of the Interim Analysis (IA) for PFS were submitted. For the pMMR population, data cut-off is 06 December 2022, with median duration of follow-up 8.7 months (range 0.1, 37.2). For the dMMR population, data cut-off is 16 December 2022, with median duration of follow-up 13.6 months (range 0.6, 39.4).

During the procedure, following a request from CHMP, unplanned descriptive updated analyses based on a DCO of 18 August 2023 with 9 months of additional follow-up since IA were also provided [median duration of FU: pMMR 15.3 months (range 0.5, 45.6); dMMR 19.2 months (range 0.6, 47.4)].

pMMR population

Primary endpoint – PFS assessed by Investigator per RECIST 1.1

Statistically significant improvement in PFS for pembrolizumab plus chemotherapy vs placebo plus chemotherapy was shown. The observed p-value of <0.0001 (1-sided) was less than the prespecified boundary of 0.001162 (1-sided) for pMMR at IA.

Table 16: Analysis of Progression-Free Survival Based on Investigator Assessment per RECIST 1.1 (Protocol Censoring Rule) in pMMR Participants (ITT Population)

	Paclitaxel + Carboplatin + Pembrolizumab (N=294)	Paclitaxel + Carboplatin + Placebo (N=294)
Number of Events (%)	95 (32.3)	138 (46.9)
Death	12 (4.1)	15 (5.1)
Documented progression	83 (28.2)	123 (41.8)
Kaplan-Meier Estimates (months)[a]		
Median (95% CI)	13.1 (10.6, 19.5)	8.7 (8.4, 11.0)
[Q1, Q3]	[7.3,]	[6.2, 14.3]
Person-months	2310.8	2009.7
Event Rate / 100 Person-months	4.1	6.9
vs Paclitaxel + Carboplatin + Placebo		
Hazard Ratio (95% CI)[b]	0.57 (0.44, 0.74)	
p-value[c]	<0.0001	
PFS Rate at month 6 (%) (95% CI)	85.8 (80.6, 89.8)	77.1 (70.9, 82.1)
PFS Rate at month 12 (%) (95% CI)	52.0 (43.8, 59.5)	29.5 (22.4, 37.0)
PFS Rate at month 18 (%) (95% CI)	43.8 (35.0, 52.2)	20.8 (14.1, 28.3)
PFS Rate at month 24 (%) (95% CI)	38.3 (28.8, 47.7)	13.5 (6.9, 22.2)
PFS Rate at month 30 (%) (95% CI)	38.3 (28.8, 47.7)	10.1 (3.8, 19.9)
PFS Rate at month 36 (%) (95% CI)	NR (NR, NR)	NR (NR, NR)

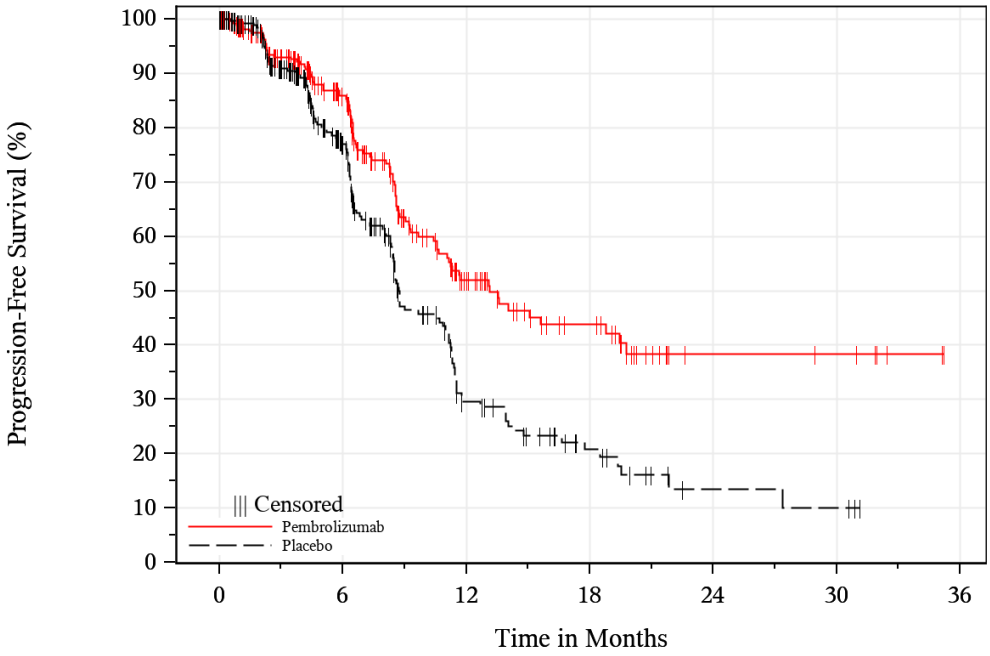
[a] From product-limit (Kaplan-Meier) method for censored data.

[b] Based on Cox regression model with Efron's 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.

NR = Not reached.
Database Cutoff Date: 06 December 2022.

Figure 6: Kaplan-Meier Plot of Progression-Free Survival Based on Investigator Assessment per RECIST 1.1 (Protocol Censoring Rule) in pMMR Participants (ITT Population)



Number of Participants at Risk

Pembrolizumab	294	162	57	29	7	6	0
Placebo	294	144	36	15	4	3	0

Database Cutoff Date: 06 December 2022.

A retrospective **BICR** assessment per RECIST 1.1 was also performed.

Table 17: Summary of Primary Efficacy Results in pMMR Participants for NRG-GY018 (ITT Population)

	By Investigator Assessment		By BICR	
	Pembrolizumab + Chemotherapy (N=294)	Placebo + Chemotherapy (N=294)	Pembrolizumab + Chemotherapy (N=294)	Placebo + Chemotherapy (N=294)
PFS per RECIST 1.1				
Median PFS[a], months (95% CI)	13.1 (10.6, 19.5)	8.7 (8.4, 11.0)	19.5 (13.1, 28.0)	11.0 (9.0, 11.5)
HR (95% CI)[b] *p*-value[c]	0.57 (0.44, 0.74) <0.0001		0.64 (0.49, 0.85) 0.0008[d]	
PFS Rate per RECIST 1.1				
12 months (%) (95% CI)	52.0 (43.8, 59.5)	29.5 (22.4, 37.0)	60.1 (52.1, 67.2)	39.7 (31.8, 47.4)
18 months (%) (95% CI)	43.8 (35.0, 52.2)	20.8 (14.1, 28.3)	50.4 (41.1, 58.9)	29.1 (21.3, 37.4)

BICR=blinded independent central review, CI=confidence interval, HR=hazard ratio, ITT=intent-to-treat population, PFS=progression-free survival, pMMR=mismatch repair proficient, RECIST 1.1=Response Evaluation Criteria in Solid Tumors version 1.1

[a] From product-limit (Kaplan-Meier) method for censored data.

[b] Based on Cox regression model with Efron's 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.

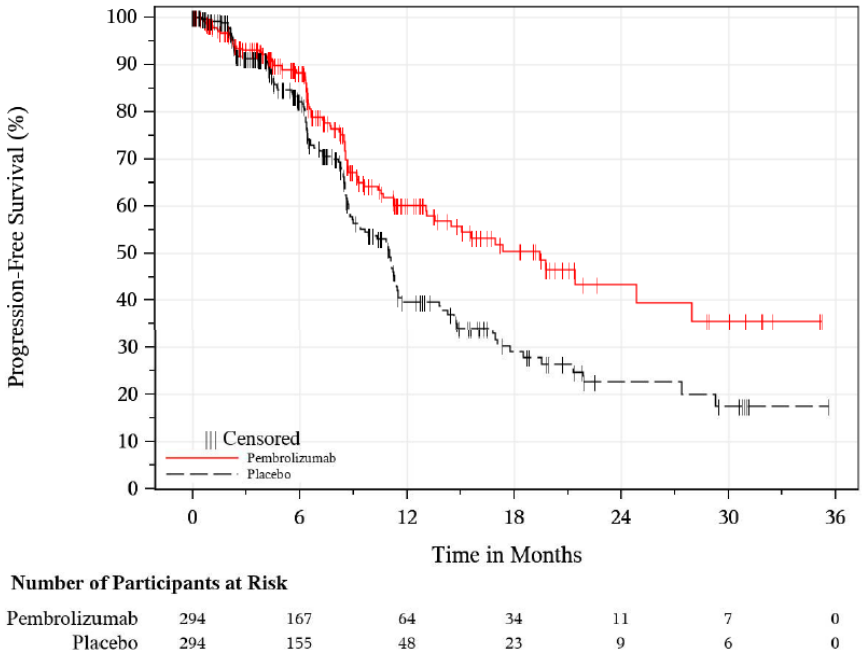
	By Investigator Assessment		By BICR	
	Pembrolizumab + Chemotherapy (N=294)	Placebo + Chemotherapy (N=294)	Pembrolizumab + Chemotherapy (N=294)	Placebo + Chemotherapy (N=294)
[d] Nominal *p* value Database Cutoff Date: 06 December 2022.				

Table 18: Analysis of Progression-Free Survival Based on BICR Assessment per RECIST 1.1 (Protocol Censoring Rule) in pMMR Participants (ITT Population)

	Paclitaxel + Carboplatin + Pembrolizumab (N=294)	Paclitaxel + Carboplatin + Placebo (N=294)
Number of Events (%)	85 (28.9)	122 (41.5)
Death	19 (6.5)	28 (9.5)
Documented progression	66 (22.4)	94 (32.0)
Kaplan-Meier Estimates (months)[a]		
Median (95% CI)	19.5 (13.1, 28.0)	11.0 (9.0, 11.5)
[Q1, Q3]	[8.5, NR]	[6.5, 21.3]
Person-months	2439.5	2264.3
Event Rate / 100 Person-months	3.5	5.4
vs Paclitaxel + Carboplatin + Placebo		
Hazard Ratio (95% CI)[b]	0.64 (0.49, 0.85)	
p-value[c]	0.0008	
PFS Rate at month 6 (%) (95% CI)	88.3 (83.5, 91.8)	82.2 (76.5, 86.6)
PFS Rate at month 12 (%) (95% CI)	60.1 (52.1, 67.2)	39.7 (31.8, 47.4)
PFS Rate at month 18 (%) (95% CI)	50.4 (41.1, 58.9)	29.1 (21.3, 37.4)
PFS Rate at month 24 (%) (95% CI)	43.4 (32.4, 53.8)	22.6 (14.7, 31.6)
PFS Rate at month 30 (%) (95% CI)	35.5 (22.6, 48.6)	17.6 (9.7, 27.5)
PFS Rate at month 36 (%) (95% CI)	NR (NR, NR)	NR (NR, NR)

[a] From product-limit (Kaplan-Meier) method for censored data.
[b] Based on Cox regression model with Efron's 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.
NR = Not reached.
Database Cutoff Date: 16DEC2022 for dMMR participants and 06DEC2022 for pMMR participants.

Figure 7: Kaplan-Meier Plot of Progression-Free Survival Based on BICR Assessment per RECIST 1.1 (Protocol Censoring Rule) in pMMR Participants (ITT Population)



Database Cutoff Date: 16DEC2022 for dMMR participants and 06DEC2022 for pMMR participants.

Secondary endpoints

- **OS**

As of the 06 December 2022 DCO date, 27.2% (99 of the 364) events needed for the final analysis had occurred. P-values are nominal.

Table 19: Analysis of Overall Survival in pMMR Participants (ITT Population)

	Paclitaxel + Carboplatin + Pembrolizumab (N=294)	Paclitaxel + Carboplatin + Placebo (N=294)
Number of Events (%)	45 (15.3)	54 (18.4)
Kaplan-Meier Estimates (months)[a]		
Median (95% CI)	27.96 (21.42, NR)	27.37 (19.52, NR)
[Q1, Q3]	[17.05,]	[14.82, 32.17]
Person-months	2891.0	2783.9
Event Rate / 100 Person-months	1.6	1.9
vs Paclitaxel + Carboplatin + Placebo		
Hazard Ratio (95% CI)[b]	0.79 (0.53, 1.17)	
p-value[c]	0.1157	
OS Rate at month 6 (%) (95% CI)	94.0 (90.03, 96.43)	92.8 (88.43, 95.53)
OS Rate at month 12 (%) (95% CI)	85.9 (79.71, 90.34)	83.3 (76.67, 88.17)
OS Rate at month 18 (%) (95% CI)	72.1 (62.29, 79.85)	66.3 (56.37, 74.40)
OS Rate at month 24 (%) (95% CI)	60.7 (47.52, 71.46)	52.0 (38.42, 63.97)
OS Rate at month 30 (%) (95% CI)	49.3 (33.50, 63.26)	42.6 (26.64, 57.59)

OS Rate at month 36 (%) (95% CI)	49.3 (33.50, 63.26)	NR (NR, NR)

[a] From product-limit (Kaplan-Meier) method for censored data.

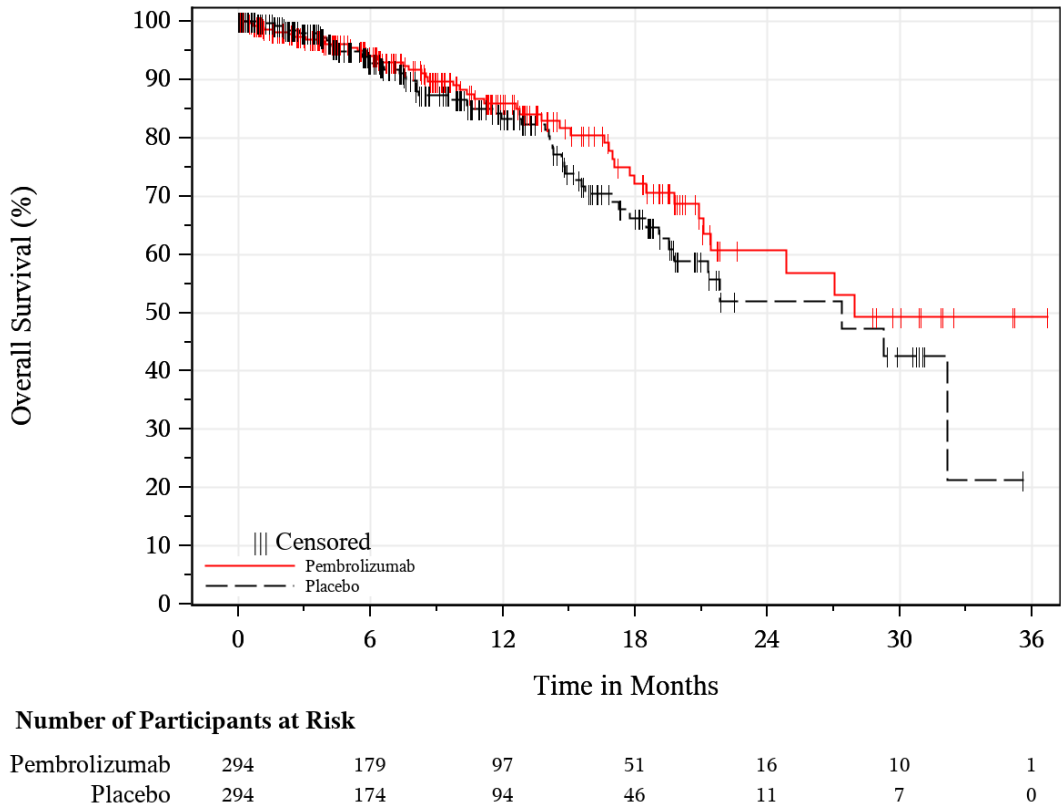
[b] Based on Cox regression model with Efron's method of tie handling with treatment as a covariate stratified by prior chemotherapy.

[c] One-sided p-value based on log-rank test stratified by prior chemotherapy.

NR = Not reached.

Database Cutoff Date: 06 December 2022.

Figure 8: Kaplan-Meier Plot of Overall Survival in pMMR Participants (ITT Population)



Database Cutoff Date: 06 December 2022.

- **ORR**

ORR was evaluated by Investigator per RECIST 1.1 only in patients with measurable disease at baseline, which were 220/294 (75%) in the pembrolizumab arm vs 235/294 (80%) in the placebo arm of the ITT population. ORR was 61.4% (54.6, 67.8) vs 51.5% (44.9, 58.0).

Table 20: Summary of Best Overall Response Based on Investigator Assessment per RECIST 1.1 in pMMR Participants (ITT Population with Measurable Disease at Baseline)

Response Evaluation	Paclitaxel + Carboplatin + Pembrolizumab			Paclitaxel + Carboplatin + Placebo		
	n	%	95% CI[a]	n	%	95% CI[a]
Participants in population	220			235		
Complete Response (CR)	24	10.9	(7.1, 15.8)	16	6.8	(3.9, 10.8)
Partial Response (PR)	111	50.5	(43.7, 57.2)	105	44.7	(38.2, 51.3)
Overall Response (CR+PR)	**135**	**61.4**	**(54.6, 67.8)**	**121**	**51.5**	**(44.9, 58.0)**
Stable Disease (SD)	29	13.2	(9.0, 18.4)	52	22.1	(17.0, 28.0)
Disease Control (CR+PR+SD≥8Weeks)	**152**	**69.1**	**(62.5, 75.1)**	**160**	**68.1**	**(61.7, 74.0)**
Clinical Benefit (CR+PR+ SD≥23Weeks)	**141**	**64.1**	**(57.4, 70.4)**	**131**	**55.7**	**(49.1, 62.2)**
Progressive Disease (PD)	12	5.5	(2.8, 9.3)	19	8.1	(4.9, 12.3)
NE	2	0.9	(0.1, 3.2)	2	0.9	(0.1, 3.0)
No Assessment	42	19.1	(14.1, 24.9)	41	17.4	(12.8, 22.9)

[a] Based on binomial exact confidence interval method.
Non-evaluable: Post-baseline assessment(s) available, but not evaluable.
No Assessment: No post-baseline assessment available for response evaluation.
Patients who enter the study with no measurable disease are excluded from the calculation.
Database Cutoff Date: 16DEC2022 for dMMR participants and 06DEC2022 for pMMR participants.

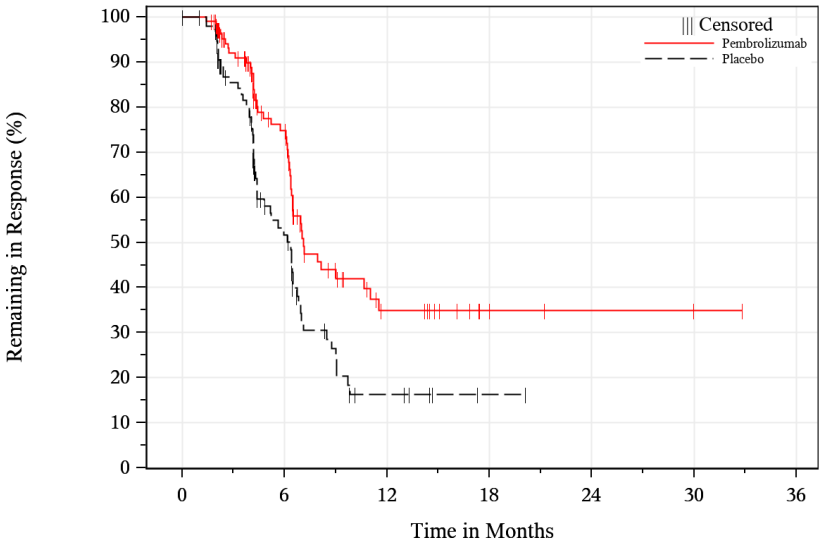
- **DOR**

Table 21: Summary of Time to Response and Duration of Response Based on Investigator Assessment per RECIST 1.1 in Participants with Response (ITT Population with pMMR with Measurable Disease at Baseline)

	Paclitaxel + Carboplatin + Pembrolizumab (N=220)	Paclitaxel + Carboplatin + Placebo (N=235)
Number of participants with response[a]	135	121
Time to Response (months)		
Mean (SD)	2.9 (1.9)	2.8 (1.2)
Median (Range)	2.3 (1.9-19.6)	2.3 (1.0-7.1)
Response Duration[b] (months)		
Median (Range)	7.1 (0.0+ - 32.8+)	6.4 (0.0+ - 20.1+)
Number (%[b]) of Participants with Extended Response Duration:		
≥6 months	55 (74.8)	32 (51.6)
≥12 months	13 (35.0)	6 (16.2)
≥18 months	4 (35.0)	1 (16.2)
≥24 months	2 (35.0)	0 (NR)

[a] Includes participants with complete response or partial response
[b] From product-limit (Kaplan-Meier) method for censored data.
"+" indicates there is no progressive disease by the time of last disease assessment.
NR = Not Reached.
Database Cutoff Date: 06 December 2022.

Figure 9: Kaplan-Meier Estimates of Duration of Response in Participants with Response Based on Investigator Assessment per RECIST 1.1 in pMMR Participants (ITT Population with Measurable Disease at Baseline)



Database Cutoff Date: 06 December 2022.

Median DOR based on BICR assessment per RECIST 1.1 (in patients with measurable disease at baseline by BICR) was 15.2 (range 0.0+ - 32.8+) vs 6.6 (range 0.0+ - 28.4+) months.

- **PRO**

PROs were assessed in the pMMR population only. Changes from baseline at prespecified time points in PROs for QoL, physical function, and fatigue were assessed by the FACT-En TOI, PROMIS-Physical Function Scale (short form) score, and PROMIS-Fatigue Scale (short form) score, respectively. Both treatment groups had slight worsening in the FACT-En TOI, PROMIS-Physical Function Scale (short form) score, and PROMIS-Fatigue Scale (short form) score.

Figure 10: Line Plot of Empirical Mean Change from Baseline and 95% CI for the FACT-EN TOI Over Time by Treatment Group (PRO pMMR Population)

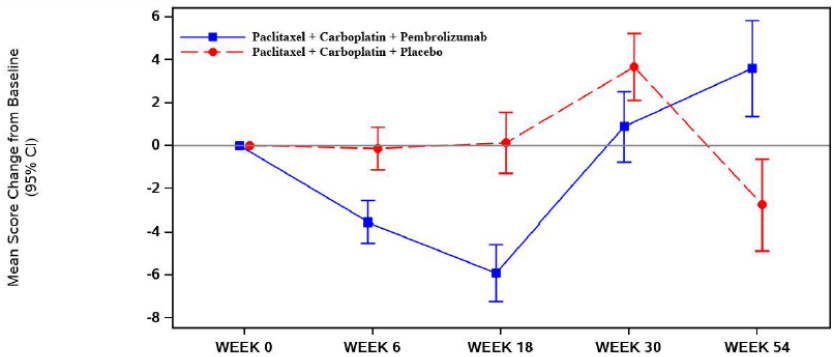
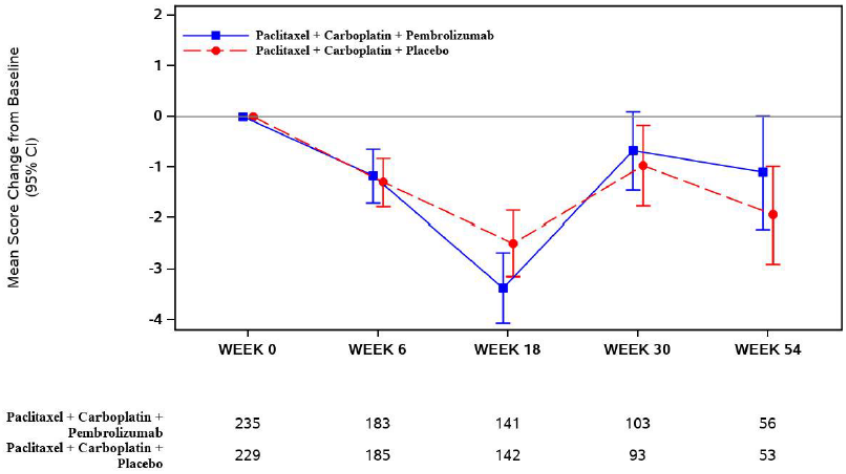
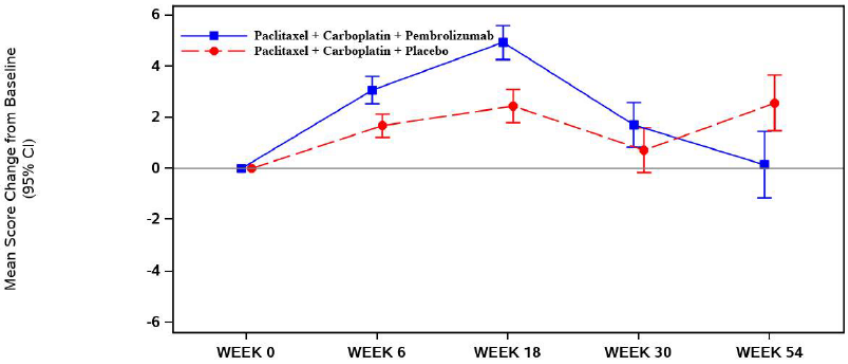


Figure 11: Line Plot of Empirical Mean Change from Baseline and 95% CI for the PROMIS Physical Function (8C) Over Time by Treatment Group (PRO pMMR Population)



Paclitaxel + Carboplatin + Pembrolizumab	235	183	141	103	56
Paclitaxel + Carboplatin + Placebo	229	185	142	93	53

Figure 12: Line Plot of Empirical Mean Change from Baseline and 95% CI for the PROMIS Fatigue (7A) Over Time by Treatment Group (PRO pMMR Population)



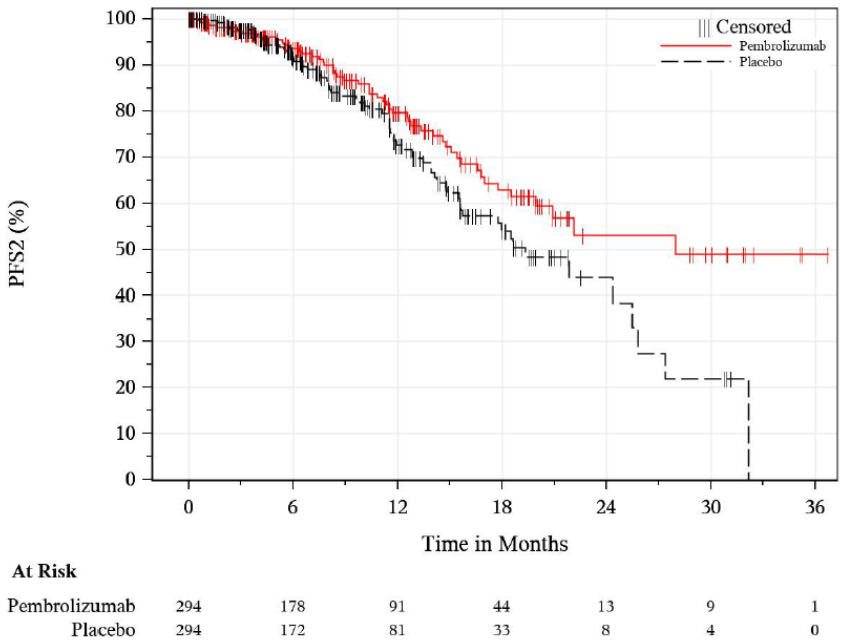
Paclitaxel + Carboplatin + Pembrolizumab	241	189	143	105	54
Paclitaxel + Carboplatin + Placebo	236	191	142	95	52

Exploratory endpoints

- **PFS2**

In the pMMR population, PFS2 HR was 0.68 (95% CI: 0.48, 0.97). The median PFS2 was 27.96 months (95% CI: 19.94, NR) for pembrolizumab plus chemotherapy, and 19.32 months (95% CI: 15.61, 25.46) for placebo plus chemotherapy.

Figure 13: Kaplan-Meier Estimates of Progression-Free Survival On Next Line Therapy (PFS2) Based on Investigator Assessment in pMMR Participants (ITT Population)



- **PRO**

Both treatment groups had slight worsening in the FACT/GOG-Ntx subscale evaluating Neurotoxicity/peripheral neuropathy, and "bothering by side effect" assessed by FACT GP5 scores. Scores were generally similar between the 2 treatment groups (data not shown).

- **Exploratory PD-L1 analyses**

Overall, 98% of the pMMR population had known PD-L1 status. PD-L1 status was positive (CPS≥1) in about 70% of patients in each treatment arm.

Table 22: baseline PD-L1 status in pMMR population (table made by assessor)

pMMR	**Pembrolizumab arm**	**Placebo arm**
Total	294	294
CPS≥1	208 (71%)	205 (70%)
CPS<1	80 (27%)	83 (28%)
Unknown	6 (2%)	6 (2%)

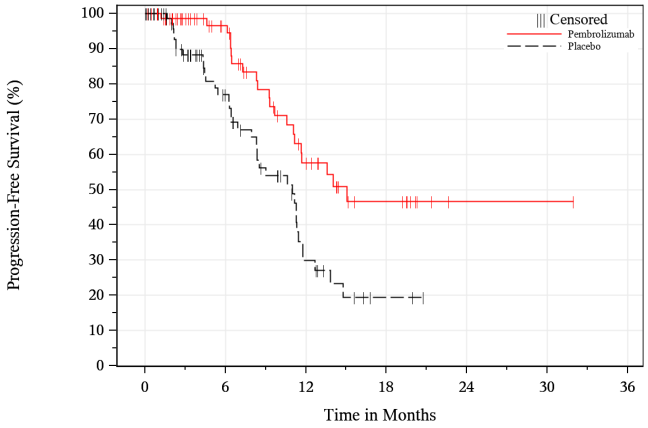
Table 23: efficacy results in pMMR population by PD-L1 status (table made by assessor)

pMMR	**PFS**	**OS**
ITT	*0.57 (0.44, 0.74)*	*0.79 (0.53, 1.17)*
CPS<1	0.44 (0.26, 0.75)	0.69 (0.29, 1.63)
CPS≥1	0.59 (0.43, 0.80)	0.82 (0.52, 1.29)

Figure 14: Kaplan-Meier Plot of PFS Based on Investigator Assessment per RECIST 1.1 (Protocol Censoring Rule) and of OS in pMMR Participants by PD-L1 (ITT Population)

CPS<1

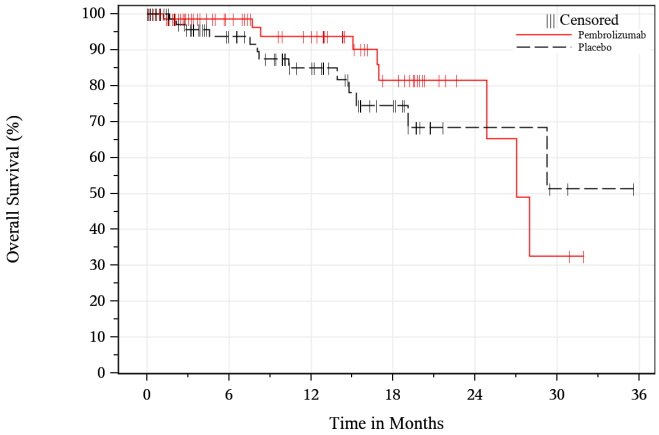
PFS



Number of Participants at Risk

Pembrolizumab	80	45	21	9	1	1	0
Placebo	83	39	11	2	0	0	0

OS

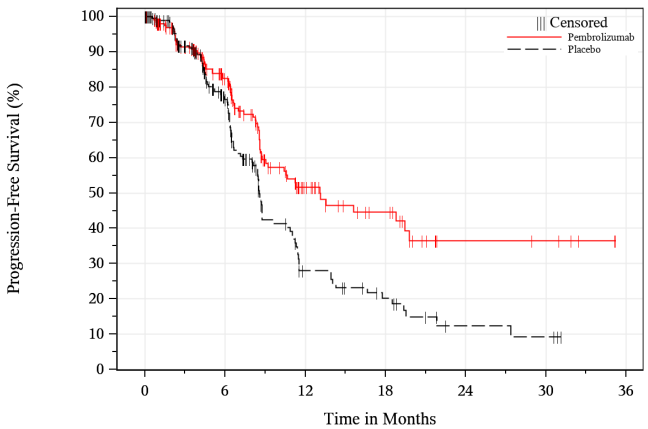


Number of Participants at Risk

Pembrolizumab	80	46	36	18	5	2	0
Placebo	83	48	32	16	4	2	0

CPS≥1

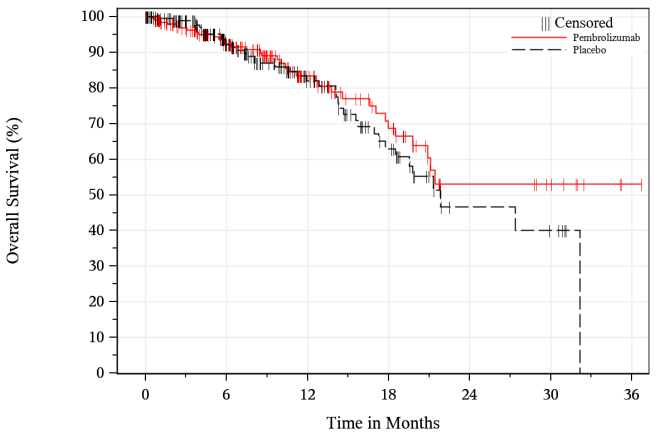
PFS



Number of Participants at Risk

Pembrolizumab	208	115	36	20	6	5	0
Placebo	205	101	23	13	4	3	0

OS



Number of Participants at Risk

Pembrolizumab	208	130	61	33	11	8	1
Placebo	205	122	59	30	7	5	0

Updated descriptive analysis- pMMR (DCO 18 August 2023)

Table 24: Disposition of pMMR Participants (ITT Population)

	Paclitaxel + Carboplatin + Pembrolizumab		Paclitaxel + Carboplatin + Placebo		Total	
	n	(%)	n	(%)	n	(%)
Participants in population	298		299		597	
Status for Trial						
Discontinued	100	(33.6)	113	(37.8)	213	(35.7)
Death	77	(25.8)	92	(30.8)	169	(28.3)
Lost To Follow-Up	1	(0.3)	1	(0.3)	2	(0.3)
Subject Decision To Withdraw From Study	19	(6.4)	17	(5.7)	36	(6.0)
Other	3	(1.0)	3	(1.0)	6	(1.0)
Ongoing	198	(66.4)	186	(62.2)	384	(64.3)
Status for Study Medication in Trial						
Started	284		283		567	
Completed	12	(4.2)	5	(1.8)	17	(3.0)
Discontinued	215	(75.7)	275	(97.2)	490	(86.4)
Adverse Event/Side Effects/Complications	50	(17.6)	22	(7.8)	72	(12.7)
Agent Not Given, No Sensitivity To Paclitaxel	0	(0.0)	1	(0.4)	1	(0.2)
Alternative Therapy (In Absence Of Progression)	5	(1.8)	5	(1.8)	10	(1.8)
Death On Study	9	(3.2)	2	(0.7)	11	(1.9)
Disease Progression, Relapse During Active Treatment	124	(43.7)	115	(40.6)	239	(42.2)
Patient Off-Treatment For Other Complicating Disease	5	(1.8)	1	(0.4)	6	(1.1)
Patient Withdrawal/Refusal After Beginning Protocol Therapy	13	(4.6)	12	(4.2)	25	(4.4)
Symptomatic Deterioration	2	(0.7)	2	(0.7)	4	(0.7)
Other	7	(2.5)	115	(40.6)	122	(21.5)
Ongoing	57	(20.1)	3	(1.1)	60	(10.6)

If the overall count of participants is calculated and displayed within a section in the first row, then it is used as the denominator for the percentage calculation. Otherwise, participants in population is used as the denominator for the percentage calculation.
Database Cutoff Date: 18AUG2023.

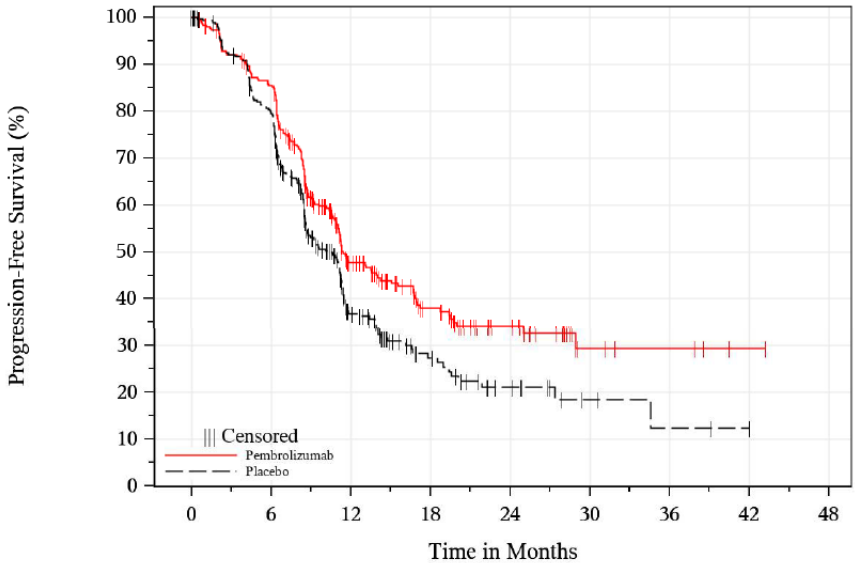
PFS by investigator per RECIST 1.1

Table 25: Analysis of Progression-Free Survival Based on Investigator Assessment per RECIST 1.1 (Protocol Censoring Rule) in pMMR Participants (ITT Population)

	Paclitaxel + Carboplatin + Pembrolizumab (N=298)	Paclitaxel + Carboplatin + Placebo (N=299)
Number of Events (%)	163 (54.7)	187 (62.5)
Death	23 (7.7)	23 (7.7)
Documented progression	140 (47.0)	164 (54.8)
Kaplan-Meier Estimates (months)[a]		
Median (95% CI)	11.4 (10.9, 15.1)	10.6 (8.7, 11.3)
[Q1, Q3]	[7.1, NR]	[6.3, 19.4]
Person-months	3451.5	2920.4
Event Rate / 100 Person-months	4.7	6.4
vs Paclitaxel + Carboplatin + Placebo		
Hazard Ratio (95% CI)[b]	0.74 (0.60, 0.91)	
p-value[c]	0.0022	
PFS Rate at month 6 (%) (95% CI)	85.5 (80.9, 89.1)	79.9 (74.8, 84.1)
PFS Rate at month 12 (%) (95% CI)	47.7 (41.4, 53.7)	36.8 (30.8, 42.9)
PFS Rate at month 18 (%) (95% CI)	38.0 (31.5, 44.4)	27.4 (21.2, 33.9)
PFS Rate at month 24 (%) (95% CI)	34.1 (27.5, 40.8)	21.2 (15.0, 28.1)
PFS Rate at month 30 (%) (95% CI)	29.4 (21.0, 38.3)	18.5 (11.7, 26.7)
PFS Rate at month 36 (%) (95% CI)	29.4 (21.0, 38.3)	12.4 (4.0, 25.7)

[a] From product-limit (Kaplan-Meier) method for censored data.
[b] Based on Cox regression model with Efron's 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.
NR = Not reached.
Database Cutoff Date: 18AUG2023.

Figure 15: Kaplan-Meier Plot of Progression-Free Survival Based on Investigator Assessment per RECIST 1.1 (Protocol Censoring Rule) in pMMR Participants (ITT Population)



Number of Participants at Risk

Pembrolizumab	298	245	98	53	27	7	5	1	0
Placebo	299	229	66	29	14	4	2	1	0

Database Cutoff Date: 18AUG2023.

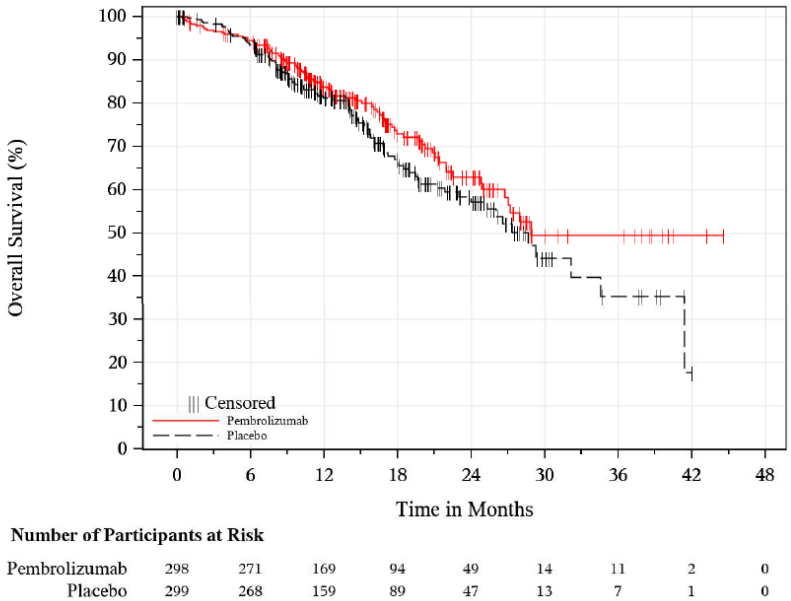
OS

Table 26: Analysis of Overall Survival in pMMR Participants (ITT Population)

	Paclitaxel + Carboplatin + Pembrolizumab (N=298)	Paclitaxel + Carboplatin + Placebo (N=299)
Number of Events (%)	77 (25.8)	92 (30.8)
Kaplan-Meier Estimates (months)[a]		
Median (95% CI)	28.9 (26.8, NR)	28.7 (24.0, 34.6)
[Q1, Q3]	[17.5, NR]	[15.3, 41.4]
Person-months	4556.4	4385.7
Event Rate / 100 Person-months	1.7	2.1
vs Paclitaxel + Carboplatin + Placebo		
Hazard Ratio (95% CI)[b]	0.80 (0.59, 1.08)	
p-value[c]	0.0683	
OS Rate at month 6 (%) (95% CI)	94.5 (91.2, 96.6)	93.4 (89.9, 95.7)
OS Rate at month 12 (%) (95% CI)	83.8 (78.7, 87.7)	81.2 (75.9, 85.4)
OS Rate at month 18 (%) (95% CI)	72.9 (66.1, 78.6)	67.1 (59.9, 73.2)
OS Rate at month 24 (%) (95% CI)	63.0 (54.5, 70.3)	58.3 (50.1, 65.6)
OS Rate at month 30 (%) (95% CI)	49.5 (37.9, 60.1)	44.2 (32.6, 55.1)
OS Rate at month 36 (%) (95% CI)	49.5 (37.9, 60.1)	35.3 (21.6, 49.4)
OS Rate at month 42 (%) (95% CI)	49.5 (37.9, 60.1)	17.7 (1.9, 47.1)
OS Rate at month 48 (%) (95% CI)	NR (NR, NR)	NR (NR, NR)

[a] From product-limit (Kaplan-Meier) method for censored data.
[b] Based on Cox regression model with Efron's 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.
NR = Not reached.
Database Cutoff Date: 18AUG2023.

Figure 16: Kaplan-Meier Plot of Overall Survival in pMMR Participants (ITT Population)



Database Cutoff Date: 18AUG2023.

ORR

Table 27: Summary of Best Overall Response Based on Investigator Assessment per RECIST 1.1 in pMMR Participants (ITT Population with Measurable Disease at Baseline)

Response Evaluation	Paclitaxel + Carboplatin + Pembrolizumab			Paclitaxel + Carboplatin + Placebo		
	n	%	95% CI[a]	n	%	95% CI[a]
Participants in population	224			239		
Complete Response (CR)	32	14.3	(10.0, 19.6)	20	8.4	(5.2, 12.6)
Partial Response (PR)	130	58.0	(51.3, 64.6)	121	50.6	(44.1, 57.1)
Overall Response (CR+PR)	**162**	**72.3**	**(66.0, 78.1)**	**141**	**59.0**	**(52.5, 65.3)**
Stable Disease (SD)	26	11.6	(7.7, 16.5)	55	23.0	(17.8, 28.9)
Disease Control (CR+PR+SD≥8Weeks)	**183**	**81.7**	**(76.0, 86.5)**	**191**	**79.9**	**(74.3, 84.8)**
Clinical Benefit (CR+PR+ SD≥23Weeks)	**173**	**77.2**	**(71.2, 82.6)**	**159**	**66.5**	**(60.2, 72.5)**
Progressive Disease (PD)	16	7.1	(4.1, 11.3)	19	7.9	(4.9, 12.1)
NE	2	0.9	(0.1, 3.2)	3	1.3	(0.3, 3.6)
No Assessment	18	8.0	(4.8, 12.4)	21	8.8	(5.5, 13.1)

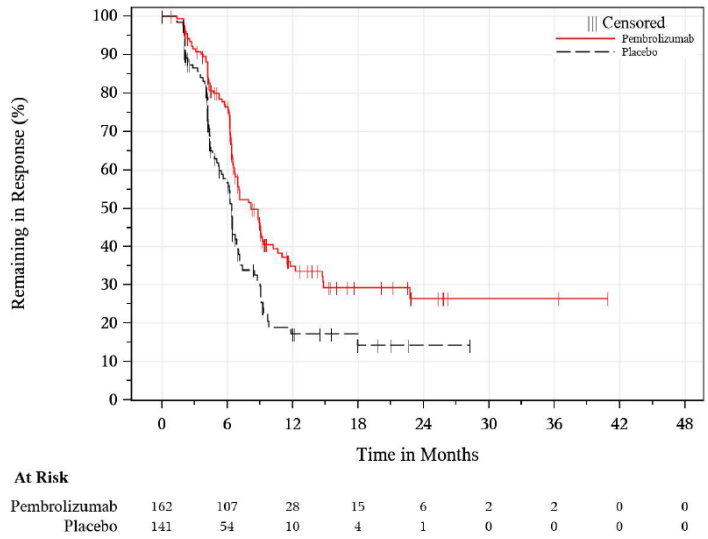
[a] Based on binomial exact confidence interval method.
Non-evaluable: Post-baseline assessment(s) available, but not evaluable.
No Assessment: No post-baseline assessment available for response evaluation.
Patients who enter the study with no measurable disease are excluded from the calculation.
Database Cutoff Date: 18AUG2023.

Table 28: Summary of Time to Response and Duration of Response Based on Investigator Assessment per RECIST 1.1 in Participants with Response (ITT Population with pMMR with Measurable Disease at Baseline)

	Paclitaxel + Carboplatin + Pembrolizumab (N=224)	Paclitaxel + Carboplatin + Placebo (N=239)
Number of participants with response[a]	162	141
Time to Response (months)		
Mean (SD)	3.0 (1.9)	2.9 (1.3)
Median (Range)	2.3 (1.9-19.6)	2.3 (1.0-7.1)
Response Duration[b] (months)		
Median (Range)	8.1 (0.0+ - 40.9+)	6.4 (0.0+ - 28.3+)
Number (%[b]) of Participants with Extended Response Duration:		
≥6 months	107 (76.3)	54 (56.7)
≥12 months	28 (35.0)	10 (17.2)
≥18 months	15 (29.3)	4 (14.3)
≥24 months	6 (26.4)	1 (14.3)

[a] Includes participants with complete response or partial response
[b] From product-limit (Kaplan-Meier) method for censored data.
"+" indicates there is no progressive disease by the time of last disease assessment.
Database Cutoff Date: 18AUG2023.

Figure 17: Kaplan-Meier Estimates of Duration of Response in Participants with Response Based on Investigator Assessment per RECIST 1.1 in pMMR Participants (ITT Population with Measurable Disease at Baseline)



Database Cutoff Date: 18AUG2023.

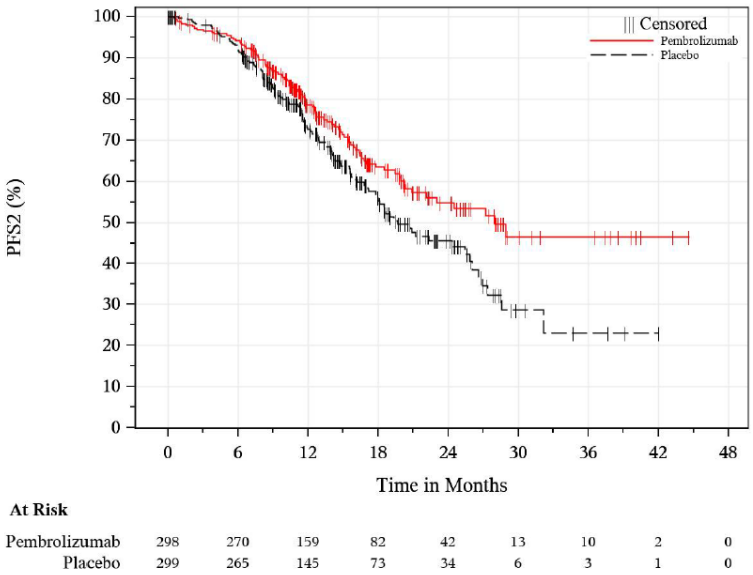
PFS2

Table 29: Analysis of Progression-Free Survival On Next Line Therapy (PFS2) Based on Investigator Assessment in pMMR Participants (ITT Population)

	Paclitaxel + Carboplatin + Pembrolizumab (N=298)	Paclitaxel + Carboplatin + Placebo (N=299)
Number of Events (%)	94 (31.5)	119 (39.8)
Death	55 (18.5)	60 (20.1)
Progression after next-line therapy	39 (13.1)	59 (19.7)
Kaplan-Meier Estimates (months)[a]		
Median (95% CI)	28.0 (20.9, NR)	19.6 (17.8, 25.8)
[Q1, Q3]	[13.3, NR]	[11.6, 32.2]
Person-months	4349.6	4029.3
Event Rate / 100 Person-months	2.2	3.0
vs Paclitaxel + Carboplatin + Placebo		
Hazard Ratio (95% CI)[b]	0.72 (0.55, 0.94)	
p-value[c]	0.0076	
PFS2 Rate at month 6 (%) (95% CI)	94.1 (90.7, 96.3)	92.4 (88.6, 94.9)
PFS2 Rate at month 12 (%) (95% CI)	78.6 (73.1, 83.2)	72.6 (66.6, 77.7)
PFS2 Rate at month 18 (%) (95% CI)	63.5 (56.3, 69.8)	56.0 (48.7, 62.7)
PFS2 Rate at month 24 (%) (95% CI)	54.8 (46.5, 62.3)	45.5 (37.5, 53.2)
PFS2 Rate at month 30 (%) (95% CI)	46.5 (35.9, 56.5)	28.7 (18.2, 40.1)
PFS2 Rate at month 36 (%) (95% CI)	46.5 (35.9, 56.5)	23.0 (11.2, 37.2)
PFS2 Rate at month 42 (%) (95% CI)	46.5 (35.9, 56.5)	23.0 (11.2, 37.2)
PFS2 Rate at month 48 (%) (95% CI)	NR (NR, NR)	NR (NR, NR)

[a] From product-limit (Kaplan-Meier) method for censored data.
[b] Based on Cox regression model with Efron's 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.
NR = Not reached.
Database Cutoff Date: 18AUG2023.

Figure 18: Kaplan-Meier Estimates of Progression-Free Survival On Next Line Therapy (PFS2) Based on Investigator Assessment in pMMR Participants (ITT Population)



Database Cutoff Date: 18AUG2023.

Table 30: Efficacy results in pMMR population by PD-L1 status – updated analysis (table made by assessor)

pMMR	PFS	OS	ORR
ITT	*0.74 (0.60, 0.91)*	*0.80 (0.59, 1.08)*	*72.3% vs 59%*
CPS<1	0.75 (0.49, 1.14)	0.55 (0.29. 1.04)	77.8% vs 49.3%
CPS≥1	0.73 (0.57. 0.93)	0.87 (0.61. 1.23)	69.9% vs 62.2%

dMMR population

Primary endpoint – PFS assessed by Investigator per RECIST 1.1

Statistically significant improvement in PFS for pembrolizumab plus chemotherapy vs placebo plus chemotherapy was shown. The observed p-value of <0.0001 (1-sided) was less than the prespecified boundary of 0.002074 (1-sided) for dMMR population at IA.

Table 31: Analysis of Progression-Free Survival Based on Investigator Assessment per RECIST 1.1 (Protocol Censoring Rule) in dMMR Participants (ITT Population)

	Paclitaxel + Carboplatin + Pembrolizumab (N=110)	Paclitaxel + Carboplatin + Placebo (N=112)
Number of Events (%) Death Documented progression	29 (26.4) 6 (5.5) 23 (20.9)	60 (53.6) 5 (4.5) 55 (49.1)
Kaplan-Meier Estimates (months)[a] Median (95% CI) [Q1, Q3]	 NR (30.7, NR) [11.5,]	 8.3 (6.5, 12.3) [5.4, 24.3]

Person-months	1355.5	939.9
Event Rate / 100 Person-months	2.1	6.4
vs Paclitaxel + Carboplatin + Placebo		
Hazard Ratio (95% CI)[b]	0.34 (0.22, 0.53)	
p-value[c]	<0.0001	
PFS Rate at month 6 (%) (95% CI)	90.6 (83.3, 94.8)	73.8 (64.1, 81.3)
PFS Rate at month 12 (%) (95% CI)	73.0 (62.0, 81.3)	40.0 (29.3, 50.4)
PFS Rate at month 18 (%) (95% CI)	65.2 (52.7, 75.2)	32.9 (22.5, 43.8)
PFS Rate at month 24 (%) (95% CI)	65.2 (52.7, 75.2)	27.4 (15.2, 41.1)
PFS Rate at month 30 (%) (95% CI)	65.2 (52.7, 75.2)	20.6 (7.9, 37.3)
PFS Rate at month 36 (%) (95% CI)	57.1 (37.5, 72.6)	NR (NR, NR)

[a] From product-limit (Kaplan-Meier) method for censored data.

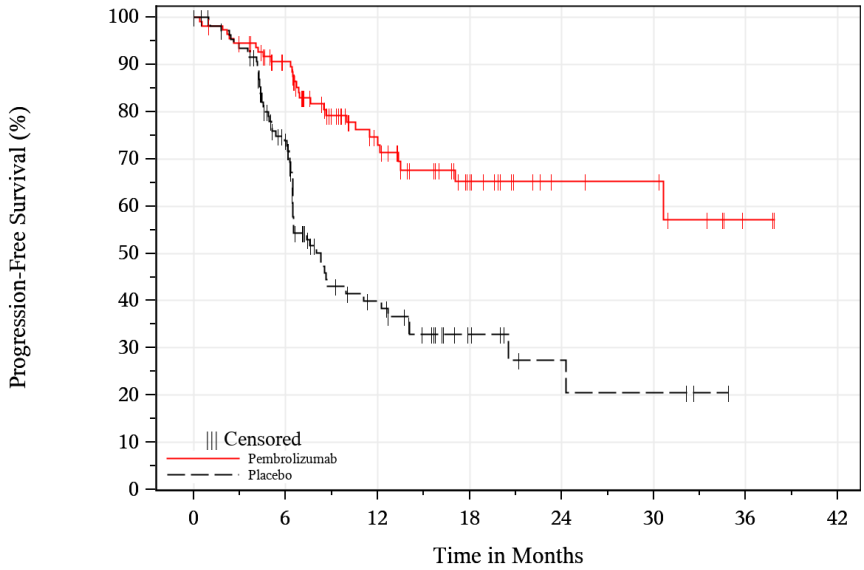
[b] Based on Cox regression model with Efron's method of tie handling with treatment as a covariate stratified by prior chemotherapy.

[c] One-sided p-value based on log-rank test stratified by prior chemotherapy.

NR = Not reached.

Database Cutoff Date: 16 December 2022.

Figure 19: Kaplan-Meier Plot of Progression-Free Survival Based on Investigator Assessment per RECIST 1.1 (Protocol Censoring Rule) in dMMR Participants (ITT Population)



Number of Participants at Risk

Pembrolizumab	110	85	45	24	10	9	2	0
Placebo	112	69	25	9	4	3	0	0

Database Cutoff Date: 16 December 2022.

A retrospective **BICR** assessment per RECIST 1.1 was also performed.

Table 32: Summary of Primary Efficacy Results in dMMR Participants for NRG-GY018 (ITT Population)

	By Investigator Assessment		By BICR	
	Pembrolizumab + Chemotherapy (N=110)	Placebo + Chemotherapy (N=112)	Pembrolizumab + Chemotherapy (N=110)	Placebo + Chemotherapy (N=112)
PFS per RECIST 1.1				
Median PFS[a], months (95% CI)	NR (30.7, NR)	8.3 (6.5, 12.3)	NR (NR, NR)	14.1 (8.5, NR)
HR (95% CI)[b] *p*-value[c]	0.34 (0.22, 0.53) <0.0001		0.45 (0.27, 0.73) 0.0005[d]	
PFS Rate per RECIST 1.1				
12 months (%) (95% CI)	73.0 (62.0, 81.3)	40.0 (29.3, 50.4)	77.5 (66.9, 85.1)	54.3 (42.9, 64.3)
18 months (%) (95% CI)	65.2 (52.7, 75.2)	32.9 (22.5, 43.8)	68.2 (55.8, 77.8)	45.7 (32.3, 58.1)

Abbreviations: BICR=blinded independent central review; CI=confidence interval; dMMR=mismatch repair deficient, HR=hazard ratio; ITT=intent-to-treat population, NR=not reached, PFS=progression-free survival; RECIST 1.1=Response Evaluation Criteria in Solid Tumors version 1.1

a From product-limit (Kaplan-Meier) method for censored data.

b Based on Cox regression model with Efron's 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.

d Nominal *p* value

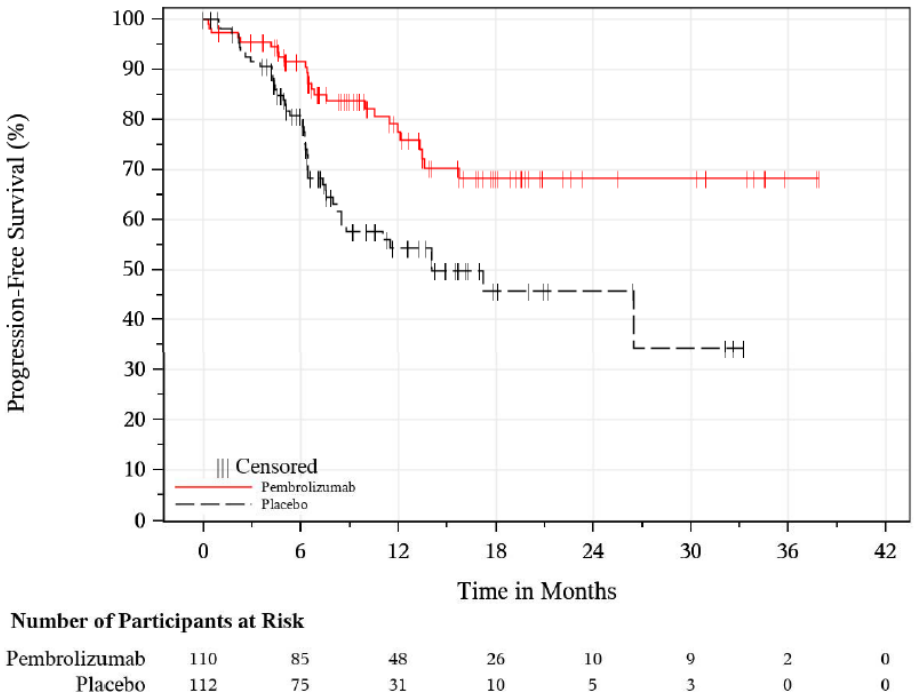
Database Cutoff Date: 16 December 2022.

Table 33: Analysis of Progression-Free Survival Based on BICR Assessment per RECIST 1.1 (Protocol Censoring Rule) in dMMR Participants (ITT Population)

	Paclitaxel + Carboplatin + Pembrolizumab (N=110)	Paclitaxel + Carboplatin + Placebo (N=112)
Number of Events (%)	25 (22.7)	45 (40.2)
Death	7 (6.4)	8 (7.1)
Documented progression	18 (16.4)	37 (33.0)
Kaplan-Meier Estimates (months)[a]		
Median (95% CI)	NR (NR, NR)	14.1 (8.5, NR)
[Q1, Q3]	[13.4, NR]	[6.3, NR]
Person-months	1388.3	1037.8
Event Rate / 100 Person-months	1.8	4.3
vs Paclitaxel + Carboplatin + Placebo		
Hazard Ratio (95% CI)[b]	0.45 (0.27, 0.73)	
p-valuec	0.0005	
PFS Rate at month 6 (%) (95% CI)	91.5 (84.3, 95.5)	80.7 (71.7, 87.1)
PFS Rate at month 12 (%) (95% CI)	77.5 (66.9, 85.1)	54.3 (42.9, 64.3)
PFS Rate at month 18 (%) (95% CI)	68.2 (55.8, 77.8)	45.7 (32.3, 58.1)
PFS Rate at month 24 (%) (95% CI)	68.2 (55.8, 77.8)	45.7 (32.3, 58.1)
PFS Rate at month 30 (%) (95% CI)	68.2 (55.8, 77.8)	34.3 (14.4, 55.3)
PFS Rate at month 36 (%) (95% CI)	68.2 (55.8, 77.8)	NR (NR, NR)

[a] From product-limit (Kaplan-Meier) method for censored data.
[b] Based on Cox regression model with Efron's 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.
NR = Not reached.
Database Cutoff Date: 16DEC2022 for dMMR participants and 06DEC2022 for pMMR participants.

Figure 20: Kaplan-Meier Plot of Progression-Free Survival Based on BICR Assessment per RECIST 1.1 (Protocol Censoring Rule) in dMMR Participants (ITT Population)



Database Cutoff Date: 16DEC2022 for dMMR participants and 06DEC2022 for pMMR participants.

Secondary endpoints

- **OS**

As of the 16 December 2022 DCO date, 18% (27 of the 150) events needed for the final analysis had occurred. P-values are nominal.

Table 34: Analysis of Overall Survival in dMMR Participants (ITT Population)

	Paclitaxel + Carboplatin + Pembrolizumab (N=110)	Paclitaxel + Carboplatin + Placebo (N=112)
Number of Events (%)	10 (9.1)	17 (15.2)
Kaplan-Meier Estimates (months)[a]		
Median (95% CI)	NR (NR, NR)	NR (NR, NR)
[Q1, Q3]	[,]	[19.09,]
Person-months	1502.3	1336.2
Event Rate / 100 Person-months	0.7	1.3
vs Paclitaxel + Carboplatin + Placebo		
Hazard Ratio (95% CI)[b]	0.55 (0.25, 1.19)	
p-value[c]	0.0617	
OS Rate at month 6 (%) (95% CI)	97.2 (91.52, 99.08)	94.3 (87.80, 97.41)
OS Rate at month 12 (%) (95% CI)	91.3 (82.27, 95.88)	85.0 (75.38, 91.13)
OS Rate at month 18 (%) (95% CI)	85.1 (73.22, 92.03)	77.9 (64.64, 86.66)
OS Rate at month 24 (%) (95% CI)	85.1 (73.22, 92.03)	73.0 (56.44, 84.12)
OS Rate at month 30 (%) (95% CI)	85.1 (73.22, 92.03)	73.0 (56.44, 84.12)

OS Rate at month 36 (%) (95% CI)	85.1 (73.22, 92.03)	73.0 (56.44, 84.12)

[a] From product-limit (Kaplan-Meier) method for censored data.

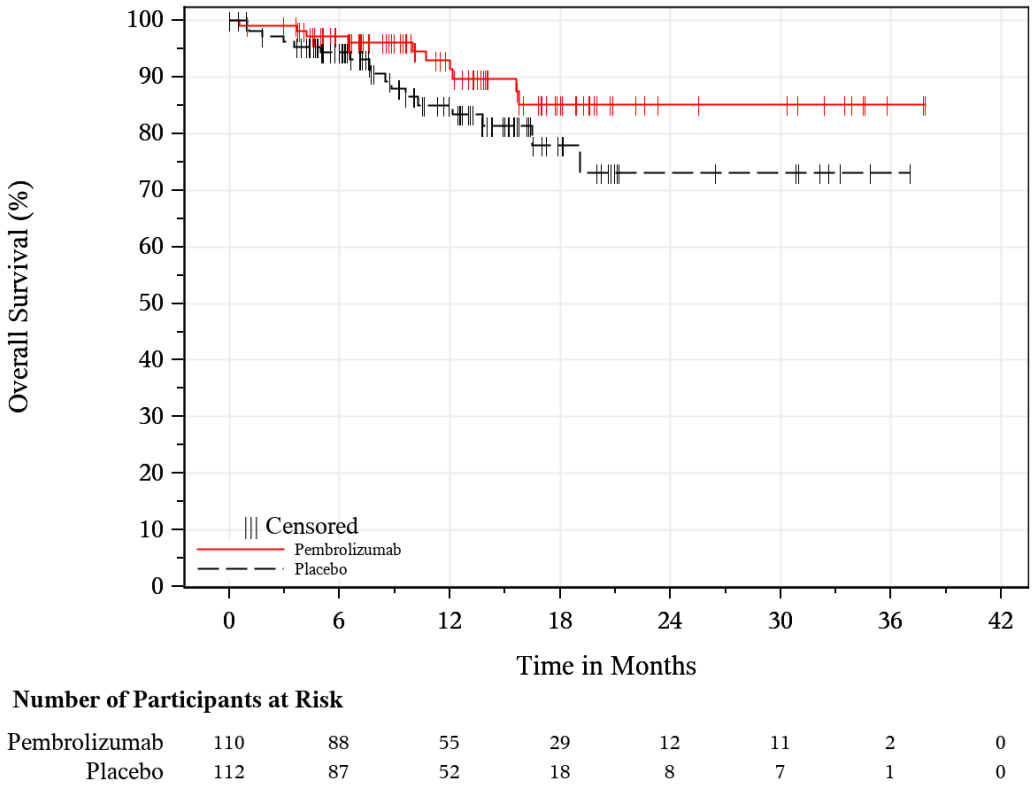
[b] Based on Cox regression model with Efron's method of tie handling with treatment as a covariate stratified by prior chemotherapy.

[c] One-sided p-value based on log-rank test stratified by prior chemotherapy.

NR = Not reached.

Database Cutoff Date: 16 December 2022.

Figure 21: Kaplan-Meier Plot of Overall Survival in dMMR Participants (ITT Population)



Number of Participants at Risk

Pembrolizumab	110	88	55	29	12	11	2	0
Placebo	112	87	52	18	8	7	1	0

Database Cutoff Date: 16 December 2022.

- **ORR**

ORR was evaluated by Investigator per RECIST 1.1 only in patients with measurable disease at baseline, which were 95/110 (86%) in the pembrolizumab arm vs 95/112 (85%) in the placebo arm of the ITT population.

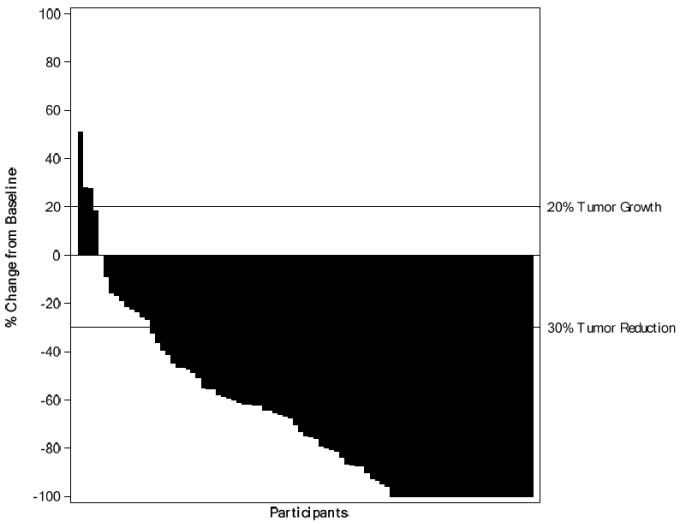
Table 35: Summary of Best Overall Response Based on Investigator Assessment per RECIST 1.1 in dMMR Participants (ITT Population with Measurable Disease at Baseline)

Response Evaluation	Paclitaxel + Carboplatin + Pembrolizumab			Paclitaxel + Carboplatin + Placebo		
	n	%	95% CI[a]	n	%	95% CI[a]
Participants in population	95			95		
Complete Response (CR)	27	28.4	(19.6, 38.6)	11	11.6	(5.9, 19.8)
Partial Response (PR)	47	49.5	(39.1, 59.9)	55	57.9	(47.3, 68.0)
Overall Response (CR+PR)	**74**	**77.9**	**(68.2, 85.8)**	**66**	**69.5**	**(59.2, 78.5)**
Stable Disease (SD)	10	10.5	(5.2, 18.5)	17	17.9	(10.8, 27.1)
Disease Control (CR+PR+SD≥8Weeks)	**83**	**87.4**	**(79.0, 93.3)**	**78**	**82.1**	**(72.9, 89.2)**
Clinical Benefit (CR+PR+ SD≥23Weeks)	**76**	**80.0**	**(70.5, 87.5)**	**68**	**71.6**	**(61.4, 80.4)**
Progressive Disease (PD)	5	5.3	(1.7, 11.9)	3	3.2	(0.7, 9.0)
NE	0	0.0	(0.0, 3.8)	1	1.1	(0.0, 5.7)
No Assessment	6	6.3	(2.4, 13.2)	8	8.4	(3.7, 15.9)

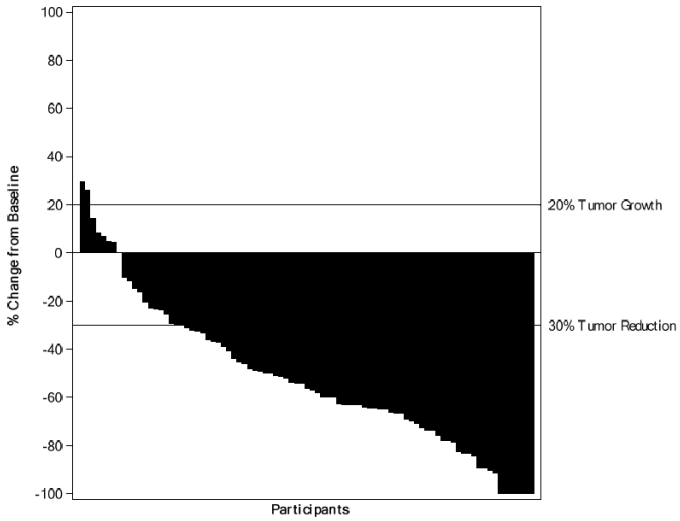
[a] Based on binomial exact confidence interval method.
Non-evaluable: Post-baseline assessment(s) available, but not evaluable.
No Assessment: No post-baseline assessment available for response evaluation.
Patients who enter the study with no measurable disease are excluded from the calculation.
Database Cutoff Date: 16DEC2022 for dMMR participants and 06DEC2022 for pMMR participants.

Figure 22: Waterfall Plot of Best Percentage Change From Baseline for Target Lesions Based on Investigator Assessment per RECIST 1.1 in pMMR Participants with Measurable Disease (Paclitaxel + Carboplatin + Pembrolizumab/Placebo)

Pembrolizumab arm



Placebo arm



- **DOR**

Table 36: Summary of Time to Response and Duration of Response Based on Investigator Assessment per RECIST 1.1 in Participants with Response (ITT Population with dMMR with Measurable Disease at Baseline)

	Paclitaxel + Carboplatin + Pembrolizumab (N=95)	Paclitaxel + Carboplatin + Placebo (N=95)
Number of participants with response[a]	74	66
Time to Response (months)		
Mean (SD)	2.7 (1.5)	2.6 (0.9)
Median (Range)	2.3 (1.3-11.5)	2.2 (2.0-6.2)

Response Duration[b] (months)		
Median (Range)	NR (0.0+ - 33.0+)	4.4 (0.0+ - 32.8+)
Number (%[b]) of Participants with Extended Response Duration:		
≥6 months	42 (88.5)	17 (43.0)
≥12 months	21 (79.3)	6 (21.4)
≥18 months	9 (75.1)	3 (21.4)
≥24 months	4 (75.1)	1 (7.1)

[a] Includes participants with complete response or partial response

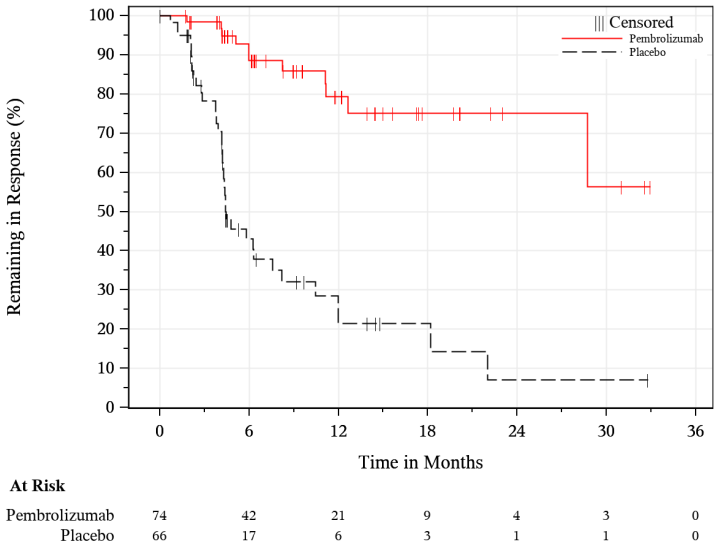
[b] From product-limit (Kaplan-Meier) method for censored data.

"+" indicates there is no progressive disease by the time of last disease assessment.

NR = Not Reached.

Database Cutoff Date: 16 December 2022.

Figure 23: Kaplan-Meier Estimates of Duration of Response in Participants with Response Based on Investigator Assessment per RECIST 1.1 in dMMR Participants (ITT Population with Measurable Disease at Baseline)



Database Cutoff Date: 16 December 2022.

- **PRO**

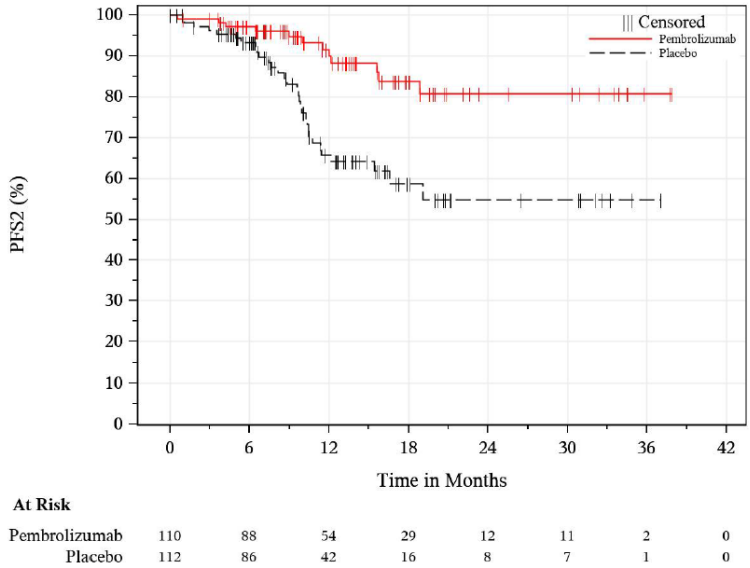
PRO were not evaluated in dMMR population.

Exploratory endpoints

- **PFS2**

In the dMMR population, PFS2 HR was 0.31 (95% CI: 0.16, 0.62). The median PFS2 was NR (NR, NR) for pembrolizumab plus chemotherapy, and NR (15.41, NR) for placebo plus chemotherapy.

Figure 24: Kaplan-Meier Estimates of Progression-Free Survival On Next Line Therapy (PFS2) Based on Investigator Assessment in dMMR Participants (ITT Population)



- **Exploratory PD-L1 analyses**

Almost all patients in the dMMR population had known PD-L1 status. PD-L1 status was positive (CPS≥1) in more than 80% of patients overall.

Participants with dMMR had lower odds of having CPS <1 (indicating lower PD-L1 expression) compared with pMMR participants (see table below).

Table 37: Association of MMR IHC status and PD-L1 CPS (ITT Population)

MMR IHC Results	PD-L1 CPS			Odds Ratio[a](95% CI) [P-Value][b]
	CPS<1	CPS>=1	Total	
dMMR	36	183	219	0.4984 (0.3241, 0.7530)
pMMR	163	413	576	[0.0005]
Total	199	596	795	

[a]Odds ratio presented is the odds of CPS<1 comparing dMMR to pMMR participants.
[b]Two-sided p-value from Fishers exact test.
Database Cutoff Date: 16 December 2022 for dMMR participants and 06 December 2022 for pMMR participants.

Table 38: Baseline PD-L1 status in dMMR population (table made by assessor)

dMMR	**Pembro arm**	**Placebo arm**
Total	110	112
CPS<1	22 (20%)	14 (12%)
CPS≥1	86 (78%)	97 (87%)
Unknown	2 (2%)	1 (1%)

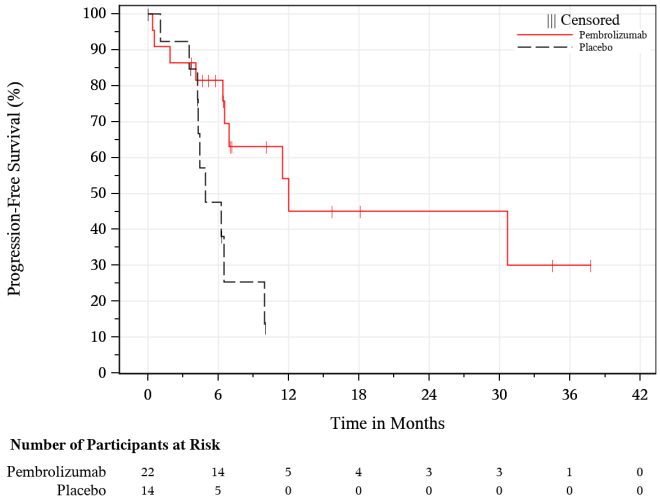
Table 39: Efficacy results in dMMR population by PD-L1 status (table made by assessor)

dMMR	PFS	OS
ITT	*0.34 (0.22, 0.53)*	*0.55 (0.25, 1.19)*
CPS<1	0.30 (0.11, 0.83)	0.42 (0.09, 1.90)
CPS≥1	0.27 (0.16, 0.47)	0.55 (0.22, 1.37)

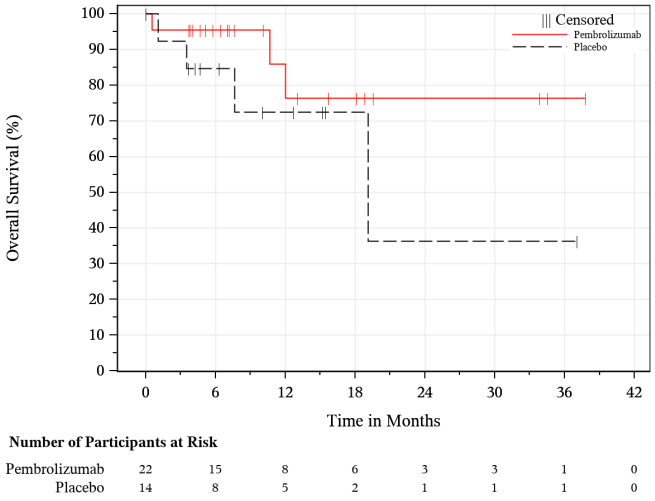
Figure 25: Kaplan-Meier Plot of PFS Based on Investigator Assessment per RECIST 1.1 (Protocol Censoring Rule) and of OS in dMMR Participants by PD-L1 (ITT Population)

CPS<1

PFS

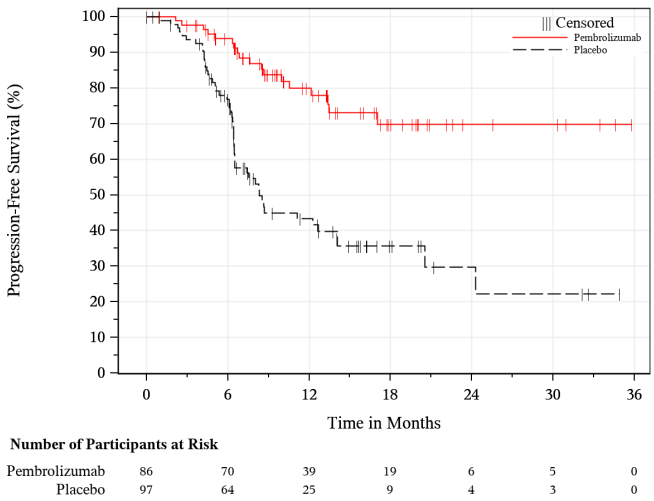


OS

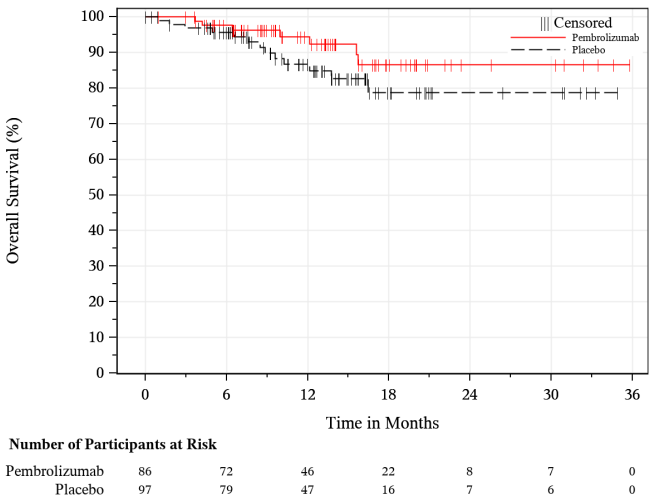


CPS≥1

PFS



OS



Updated descriptive analysis - dMMR (DCO 18 August 2023)

Descriptive analyses for PFS, OS, ORR/BOR/DOR were conducted with data based on a DCO of 18-AUG-2023. As the pre-specified primary hypotheses testing for PFS in dMMR and pMMR populations achieved statistical significance at the interim analyses (IA) (DCO 06-DEC-2022 for the pMMR population and 16-DEC-2022 for the dMMR population), all subsequent analyses after the IA, including the EUR, are only descriptive in nature with nominal p-values.

Table 40: Disposition of dMMR Participants (ITT Population)

	Paclitaxel + Carboplatin + Pembrolizumab		Paclitaxel + Carboplatin + Placebo		Total	
	n	(%)	n	(%)	n	(%)
Participants in population	110		112		222	
Status for Trial						
Discontinued	21	(19.1)	34	(30.4)	55	(24.8)
Death	17	(15.5)	27	(24.1)	44	(19.8)
Subject Decision To Withdraw From Study	4	(3.6)	7	(6.3)	11	(5.0)
Ongoing	89	(80.9)	78	(69.6)	167	(75.2)
Status for Study Medication in Trial						
Started	107		105		212	
Completed	21	(19.6)	1	(1.0)	22	(10.4)
Discontinued	56	(52.3)	104	(99.0)	160	(75.5)
Adverse Event/Side Effects/Complications	21	(19.6)	6	(5.7)	27	(12.7)
Death On Study	1	(0.9)	2	(1.9)	3	(1.4)
Disease Progression, Relapse During Active Treatment	23	(21.5)	53	(50.5)	76	(35.8)
Patient Off-Treatment For Other Complicating Disease	1	(0.9)	1	(1.0)	2	(0.9)
Patient Withdrawal/Refusal After Beginning Protocol Therapy	6	(5.6)	4	(3.8)	10	(4.7)
Symptomatic Deterioration	0	(0.0)	3	(2.9)	3	(1.4)
Other	4	(3.7)	35	(33.3)	39	(18.4)
Ongoing	30	(28.0)	0	(0.0)	30	(14.2)

If the overall count of participants is calculated and displayed within a section in the first row, then it is used as the denominator for the percentage calculation. Otherwise, participants in population is used as the denominator for the percentage calculation.
Database Cutoff Date: 18AUG2023.

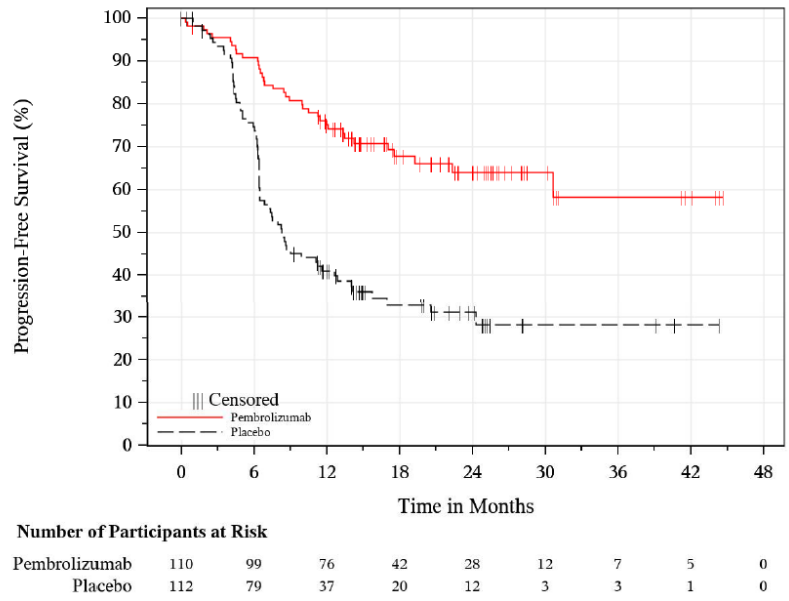
PFS by investigator per RECIST 1.1

Table 41: Analysis of Progression-Free Survival Based on Investigator Assessment per RECIST 1.1 (Protocol Censoring Rule) in dMMR Participants (ITT Population)

	Paclitaxel + Carboplatin + Pembrolizumab (N=110)	Paclitaxel + Carboplatin + Placebo (N=112)
Number of Events (%)	36 (32.7)	70 (62.5)
Death	8 (7.3)	7 (6.3)
Documented progression	28 (25.5)	63 (56.3)
Kaplan-Meier Estimates (months)[a]		
Median (95% CI)	NR (30.7, NR)	8.3 (6.5, 12.7)
[Q1, Q3]	[12.1, NR]	[5.9, NR]
Person-months	1922.8	1214.7
Event Rate / 100 Person-months	1.9	5.8
vs Paclitaxel + Carboplatin + Placebo		
Hazard Ratio (95% CI)[b]	0.35 (0.23, 0.52)	
p-value[c]	<0.0001	
PFS Rate at month 6 (%) (95% CI)	90.8 (83.6, 95.0)	74.7 (65.3, 81.9)
PFS Rate at month 12 (%) (95% CI)	75.2 (65.9, 82.2)	41.0 (31.6, 50.3)
PFS Rate at month 18 (%) (95% CI)	67.8 (57.5, 76.1)	32.9 (23.5, 42.6)
PFS Rate at month 24 (%) (95% CI)	64.0 (53.0, 73.2)	31.1 (21.7, 40.9)
PFS Rate at month 30 (%) (95% CI)	64.0 (53.0, 73.2)	28.3 (18.5, 38.8)
PFS Rate at month 36 (%) (95% CI)	58.2 (42.7, 70.9)	28.3 (18.5, 38.8)

[a] From product-limit (Kaplan-Meier) method for censored data.
[b] Based on Cox regression model with Efron's 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.
NR = Not reached.
Database Cutoff Date: 18AUG2023.

Figure 26: Kaplan-Meier Plot of Progression-Free Survival Based on Investigator Assessment per RECIST 1.1 (Protocol Censoring Rule) in dMMR Participants (ITT Population)



Database Cutoff Date: 18AUG2023.

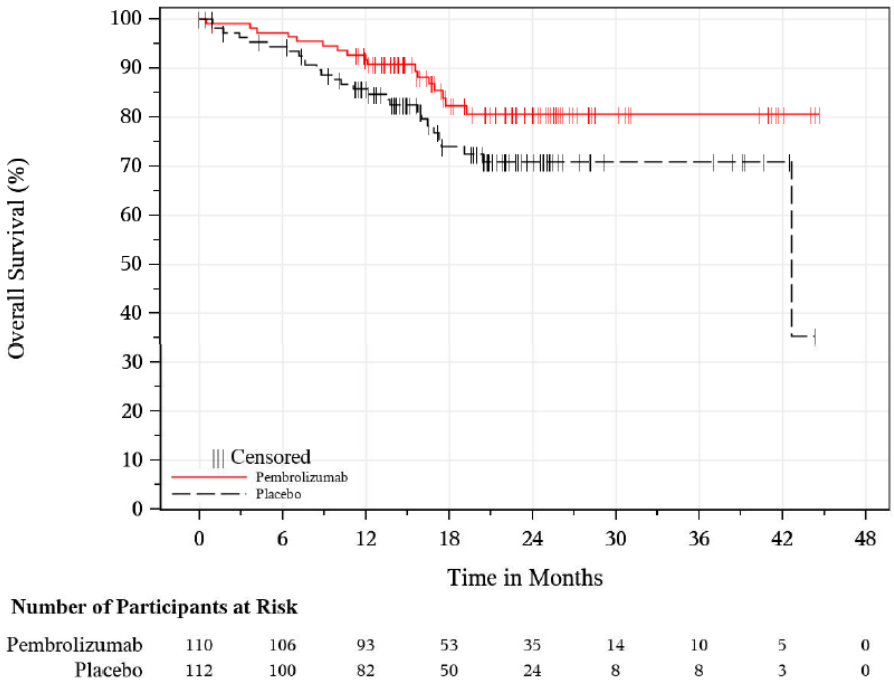
OS

Table 42: Analysis of Overall Survival in dMMR Participants (ITT Population)

	Paclitaxel + Carboplatin + Pembrolizumab (N=110)	Paclitaxel + Carboplatin + Placebo (N=112)
Number of Events (%)	17 (15.5)	27 (24.1)
Kaplan-Meier Estimates (months)[a]		
Median (95% CI)	NR (NR, NR)	42.7 (42.7, NR)
[Q1, Q3]	[NR, NR]	[17.4, NR]
Person-months	2222.0	1959.5
Event Rate / 100 Person-months	0.8	1.4
vs Paclitaxel + Carboplatin + Placebo		
Hazard Ratio (95% CI)[b]	0.57 (0.31, 1.04)	
p-value[c]	0.0323	
OS Rate at month 6 (%) (95% CI)	97.3 (91.7, 99.1)	94.4 (88.0, 97.4)
OS Rate at month 12 (%) (95% CI)	91.7 (84.6, 95.6)	85.7 (77.4, 91.1)
OS Rate at month 18 (%) (95% CI)	82.3 (72.4, 88.9)	73.9 (63.3, 81.9)
OS Rate at month 24 (%) (95% CI)	80.7 (70.3, 87.7)	70.9 (59.8, 79.4)
OS Rate at month 30 (%) (95% CI)	80.7 (70.3, 87.7)	70.9 (59.8, 79.4)
OS Rate at month 36 (%) (95% CI)	80.7 (70.3, 87.7)	70.9 (59.8, 79.4)
OS Rate at month 42 (%) (95% CI)	80.7 (70.3, 87.7)	70.9 (59.8, 79.4)
OS Rate at month 48 (%) (95% CI)	NR (NR, NR)	NR (NR, NR)

[a] From product-limit (Kaplan-Meier) method for censored data.
[b] Based on Cox regression model with Efron's 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.
NR = Not reached.
Database Cutoff Date: 18AUG2023.

Figure 27: Kaplan-Meier Plot of Overall Survival in dMMR Participants (ITT Population)



Database Cutoff Date: 18AUG2023.

ORR

Table 43: Summary of Best Overall Response Based on Investigator Assessment per RECIST 1.1 in dMMR Participants (ITT Population with Measurable Disease at Baseline)

Response Evaluation	Paclitaxel + Carboplatin + Pembrolizumab			Paclitaxel + Carboplatin + Placebo		
	n	%	95% CI[a]	n	%	95% CI[a]
Participants in population	95			95		
Complete Response (CR)	30	31.6	(22.4, 41.9)	13	13.7	(7.5, 22.3)
Partial Response (PR)	48	50.5	(40.1, 60.9)	55	57.9	(47.3, 68.0)
Overall Response (CR+PR)	**78**	**82.1**	**(72.9, 89.2)**	**68**	**71.6**	**(61.4, 80.4)**
Stable Disease (SD)	7	7.4	(3.0, 14.6)	16	16.8	(9.9, 25.9)
Disease Control (CR+PR+SD≥8Weeks)	**85**	**89.5**	**(81.5, 94.8)**	**82**	**86.3**	**(77.7, 92.5)**
Clinical Benefit (CR+PR+ SD≥23Weeks)	**80**	**84.2**	**(75.3, 90.9)**	**72**	**75.8**	**(65.9, 84.0)**
Progressive Disease (PD)	4	4.2	(1.2, 10.4)	3	3.2	(0.7, 9.0)
No Assessment	6	6.3	(2.4, 13.2)	8	8.4	(3.7, 15.9)

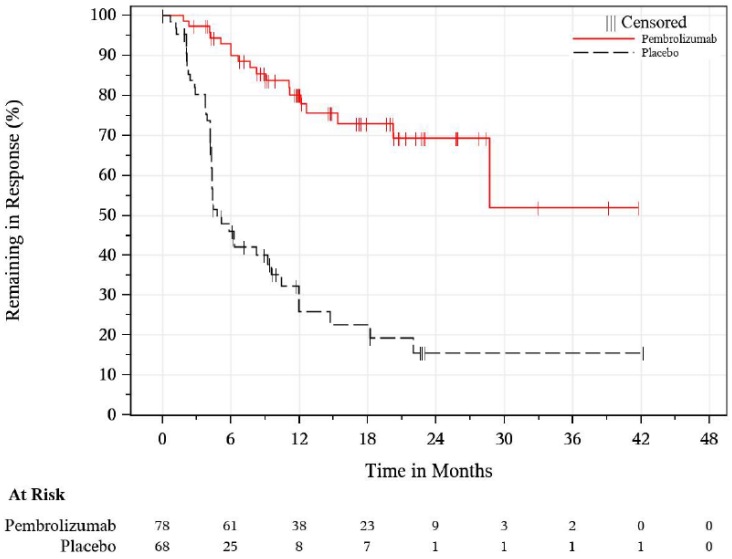
[a] Based on binomial exact confidence interval method.
Non-evaluable: Post-baseline assessment(s) available, but not evaluable.
No Assessment: No post-baseline assessment available for response evaluation.
Patients who enter the study with no measurable disease are excluded from the calculation.
Database Cutoff Date: 18AUG2023.

Table 44: Summary of Time to Response and Duration of Response Based on Investigator Assessment per RECIST 1.1 in Participants with Response (ITT Population with dMMR with Measurable Disease at Baseline)

	Paclitaxel + Carboplatin + Pembrolizumab (N=95)	Paclitaxel + Carboplatin + Placebo (N=95)
Number of participants with response[a]	78	68
Time to Response (months)		
Mean (SD)	3.0 (2.1)	2.8 (1.7)
Median (Range)	2.3 (1.6-11.6)	2.3 (2.0-14.5)
Response Duration[b] (months)		
Median (Range)	NR (0.0+ - 41.8+)	4.8 (0.0+ - 42.2+)
Number (%[b]) of Participants with Extended Response Duration:		
≥6 months	61 (90.0)	25 (46.0)
≥12 months	38 (80.1)	8 (25.8)
≥18 months	23 (73.0)	7 (22.6)
≥24 months	9 (69.4)	1 (15.5)

[a] Includes participants with complete response or partial response
[b] From product-limit (Kaplan-Meier) method for censored data.
"+" indicates there is no progressive disease by the time of last disease assessment.
NR = Not Reached.
Database Cutoff Date: 18AUG2023.

Figure 28: Kaplan-Meier Estimates of Duration of Response in Participants with Response Based on Investigator Assessment per RECIST 1.1 in dMMR Participants (ITT Population with Measurable Disease at Baseline)



Database Cutoff Date: 18AUG2023.

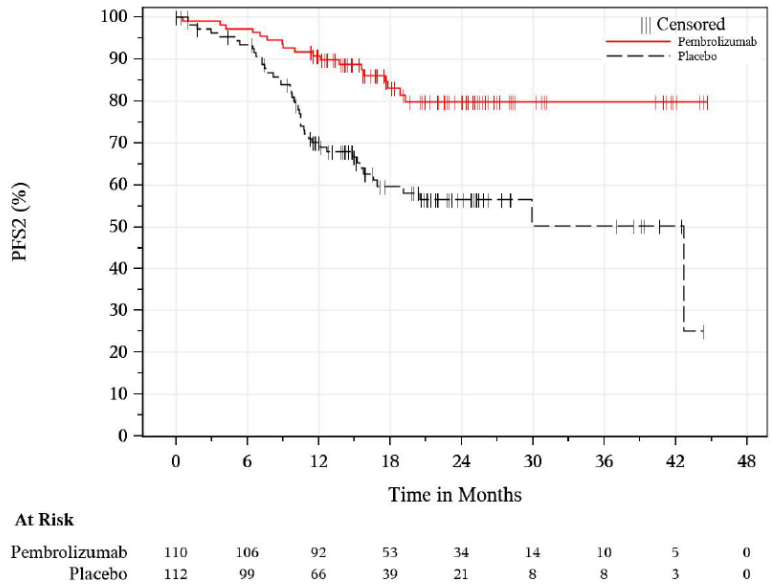
PFS2

Table 45: Analysis of Progression-Free Survival On Next Line Therapy (PFS2) Based on Investigator Assessment in dMMR Participants (ITT Population)

	Paclitaxel + Carboplatin + Pembrolizumab (N=110)	Paclitaxel + Carboplatin + Placebo (N=112)
Number of Events (%)	18 (16.4)	43 (38.4)
Death	13 (11.8)	19 (17.0)
Progression after next-line therapy	5 (4.5)	24 (21.4)
Kaplan-Meier Estimates (months)[a]		
Median (95% CI)	NR (NR, NR)	42.7 (16.9, NR)
[Q1, Q3]	[NR, NR]	[10.5, NR]
Person-months	2200.6	1786.6
Event Rate / 100 Person-months	0.8	2.4
vs Paclitaxel + Carboplatin + Placebo		
Hazard Ratio (95% CI)[b]	0.34 (0.19, 0.59)	
p-value[c]	<0.0001	
PFS2 Rate at month 6 (%) (95% CI)	97.3 (91.7, 99.1)	93.5 (86.8, 96.8)
PFS2 Rate at month 12 (%) (95% CI)	90.8 (83.6, 94.9)	70.1 (60.2, 77.9)
PFS2 Rate at month 18 (%) (95% CI)	83.1 (73.5, 89.4)	59.7 (48.8, 68.9)
PFS2 Rate at month 24 (%) (95% CI)	79.8 (69.3, 87.0)	56.5 (45.4, 66.2)
PFS2 Rate at month 30 (%) (95% CI)	79.8 (69.3, 87.0)	50.2 (34.7, 63.9)
PFS2 Rate at month 36 (%) (95% CI)	79.8 (69.3, 87.0)	50.2 (34.7, 63.9)
PFS2 Rate at month 42 (%) (95% CI)	79.8 (69.3, 87.0)	50.2 (34.7, 63.9)
PFS2 Rate at month 48 (%) (95% CI)	NR (NR, NR)	NR (NR, NR)

[a] From product-limit (Kaplan-Meier) method for censored data.
[b] Based on Cox regression model with Efron's 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.
NR = Not reached.
Database Cutoff Date: 18AUG2023.

Figure 29: Kaplan-Meier Estimates of Progression-Free Survival On Next Line Therapy (PFS2) Based on Investigator Assessment in dMMR Participants (ITT Population)



Database Cutoff Date: 18AUG2023.

Table 46: efficacy results in dMMR population by PD-L1 status – updated analysis (table made by assessor)

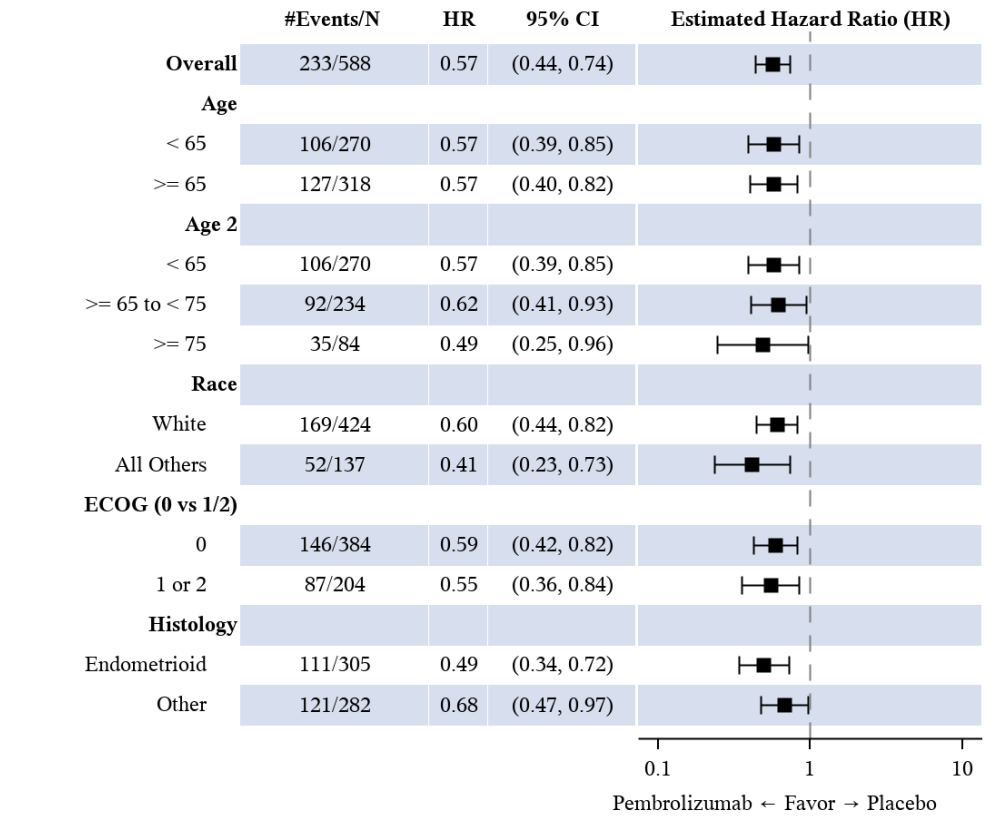
dMMR	PFS	OS	ORR
ITT	*0.35 (0.23, 0.52)*	*0.57 (0.31, 1.04)*	*82.1% vs 71.6%*
CPS<1	0.34 (0.14, 0.88)	0.31 (0.09. 1.05)	66.7% vs 61.5%
CPS≥1	0.31 (0.19. 0.49)	0.68 (0.34. 1.39)	86.3% vs 74.1%

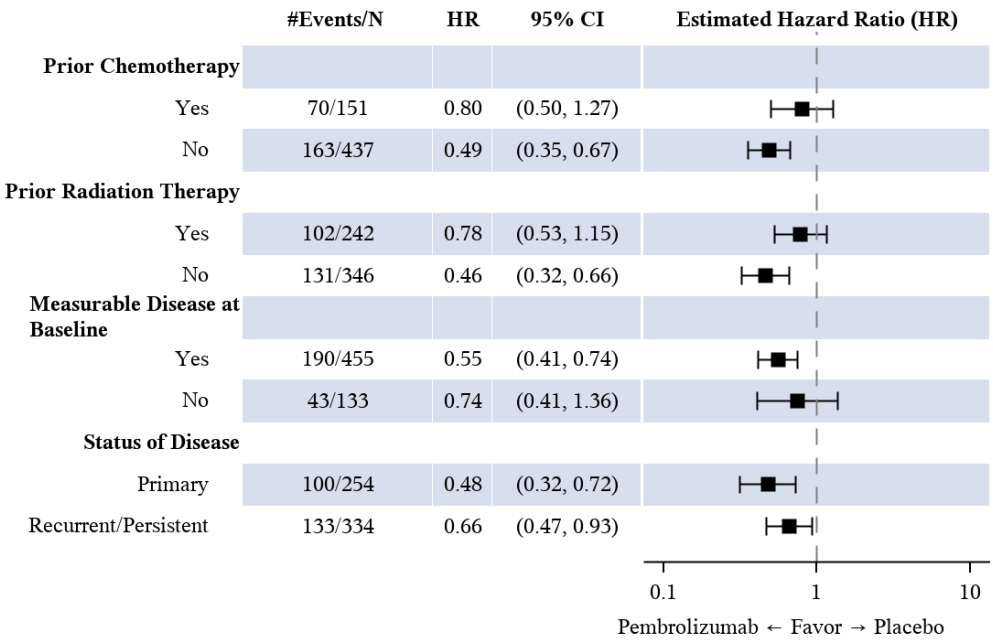
Ancillary analyses

pMMR population

PFS

Figure 30: Forest Plot of Progression-Free Survival by Subgroup Factors Based on Investigator Assessment per RECIST 1.1 (Protocol Censoring Rule) in pMMR Participants (ITT Population)





Subgroup analyses are based on unstratified Cox regression model with Efron's method of tie handling with treatment as a covariate.
If the number of participants in a category of a subgroup variable is less than 5% of the ITT population, or if there is no event in a category of a subgroup variable, the subgroup analysis will not be performed.
"Other" histology includes serous, clear cell, dedifferentiated/undifferentiated, mixed epithelial, adenocarcinoma NOS.
Database Cutoff Date: 06 December 2022 for pMMR participants.

Sensitivity analyses were performed to evaluate the robustness of the PFS endpoint per RECIST 1.1.

- Primary analysis (protocol censoring rule): HR 0.57 (95%CI 0.44, 0.74)
- MSD Primary (Preferred) Censoring Rule by ITT MMR: HR 0.60 (0.46, 0.78)
- MSD Sensitivity Censoring Rule 1 by ITT MMR: HR 0.61 (0.47, 0.79)
- MSD Sensitivity Censoring Rule 2 by ITT MMR: HR 0.81 (0.65, 1.01)
- Protocol Censoring Rule by Central MMR Determination: HR 0.56 (0.43, 0.73)
- Protocol Censoring Rule With Both Stratification Factors by ITT MMR: HR 0.57 (0.44, 0.74)
- DMC Censoring Rule by DMC MMR: HR 0.57 (0.44, 0.74)

A retrospective **BICR** assessment per RECIST 1.1 was also performed.

OS

Sensitivity analyses were performed to account for 1 participant for whom the date of death was not provided by the family, and also using MMR population based on central laboratory assessment, and using both stratified factors.

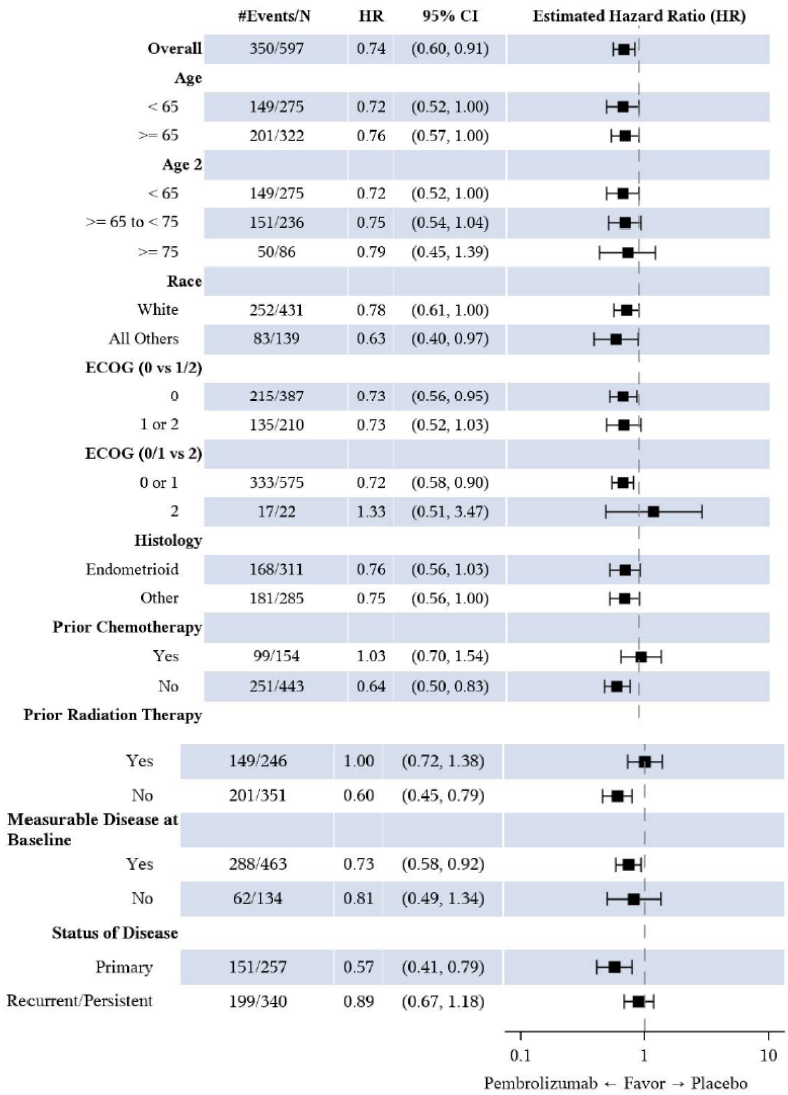
- Primary analysis (protocol censoring rule): HR 0.79 (95%CI (0.53, 1.17)
- Sensitivity Censoring Rule 1 (handling completely missing death date): HR 0.77 (0.51, 1.14)
- Sensitivity Censoring Rule 2 (handling completely missing death date): HR 0.78 (0.53, 1.17)
- Primary Censoring Rule by Central MMR Determination: HR 0.80 (0.54, 1.19)
- Primary Censoring Rule with Both Stratification Factors by ITT MMR: HR 0.83 (0.56, 1.24)

Updated descriptive analysis pMMR population (DCO 18 August 2023)

Sensitivity analyses for PFS HR:

- MSD Primary (Preferred) Censoring Rule by ITT MMR: 0.70 (95% CI: 0.56, 0.87)
- MSD Sensitivity Censoring Rule 1 by ITT MMR: 0.72 (95% CI: 0.58, 0.89)
- MSD Sensitivity Censoring Rule 2 by ITT MMR: 0.58 (95% CI: 0.49, 0.69)
- Protocol Censoring Rule by Central MMR Determination: 0.73 (95% CI: 0.59, 0.90)
- Protocol Censoring Rule With Both Stratification Factors by ITT MMR: 0.74 (95% CI: 0.60, 0.91)
- DMC Censoring Rule by DMC MMR: 0.67 (95% CI: 0.55, 0.83)

Figure 31: Forest Plot of Progression-Free Survival by Subgroup Factors Based on Investigator Assessment per RECIST 1.1 (Protocol Censoring Rule) in pMMR Participants (ITT Population)



Subgroup analyses are based on unstratified Cox regression model with Efron's method of tie handling with treatment as a covariate.

"Other" histology includes serous, clear cell, dedifferentiated/undifferentiated, mixed epithelial, adenocarcinoma NOS.

Database Cutoff Date: 18 August 2023.

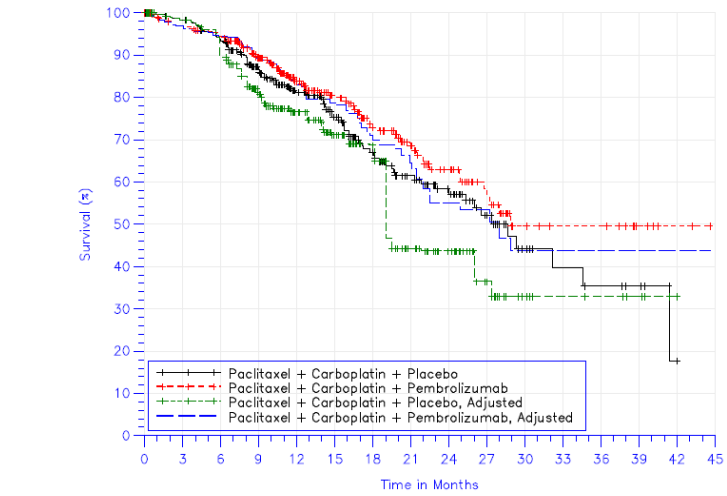
Sensitivity analyses for OS adjusting for subsequent anti-PD(L)1 therapies with or without lenvatinib in the pMMR population are provided below:

- IPCW method: 0.68 (95% CI: 0.39, 1.26; 2-sided *p*-value based on IPCW log-rank test nominal *p*=0.1231)
- 2-Stage model: 0.70 (95% CI: 0.50, 0.98)

Table 47: Summary of Subsequent Systemic Anti-Cancer Treatment in pMMR Participants Who Discontinued Study Treatment (ITT Population) – CCOD 18 August 2023

	Paclitaxel + Carboplatin + Pembrolizumab (N=215)	Paclitaxel + Carboplatin + Placebo (N=275)	Total (N=490)
Started Study Treatment	215 (100.0)	275 (100.0)	490 (100.0)
Discontinued Study Treatment	215 (100.0)	275 (100.0)	490 (100.0)
Received Any Subsequent Systemic Anti-cancer Therapy	115 (53.5)	175 (63.6)	290 (59.2)
Subsequent systemic therapy by type			
Any Anti-PD-1/PD-L1	47 (21.9)	118 (42.9)	165 (33.7)
atezolizumab	0 (0.0)	3 (1.1)	3 (0.6)
durvalumab	2 (0.9)	4 (1.5)	6 (1.2)
nivolumab	0 (0.0)	2 (0.7)	2 (0.4)
pembrolizumab	45 (20.9)	110 (40.0)	155 (31.6)

Figure 32: Kaplan-Meier Curves of Overall Survival Adjusting for Treatment Switch to Subsequent anti-PD-1/PD-L1 Therapies with or without Lenvatinib in Both Arms Using IPCW Model in pMMR Participants (ITT Population)



Numbers at Risk

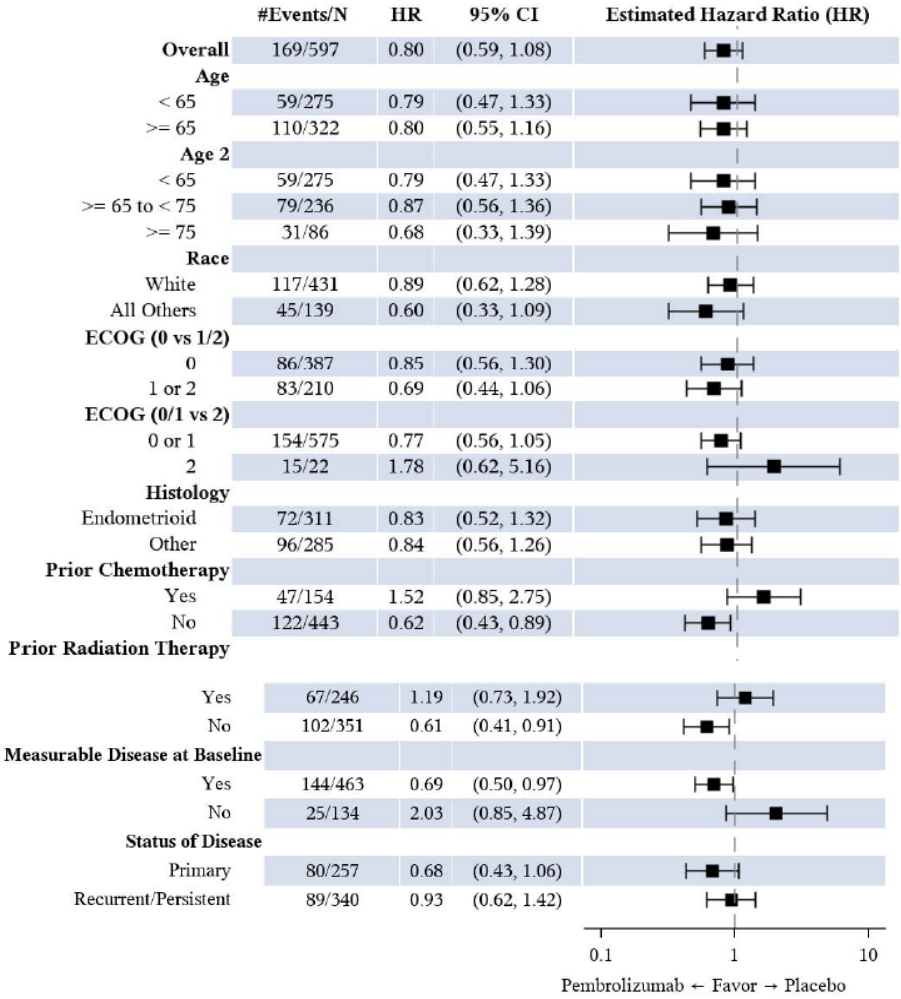
Paclitaxel + Carboplatin + Placebo
299 285 268 217 159 119 89 64 47 26 13 9 7 5 1 0

Paclitaxel + Carboplatin + Pembrolizumab
298 281 271 232 169 127 94 69 49 32 14 11 11 5 2 0

Paclitaxel + Carboplatin + Placebo, Adjusted
299 285 268 217 159 119 90 64 47 28 13 9 7 5 1 0

Paclitaxel + Carboplatin + Pembrolizumab, Adjusted
298 281 271 232 170 127 96 69 49 32 14 11 11 5 2 0

Figure 33: Forest Plot of Overall Survival by Subgroup Factors in pMMR Participants (ITT Population)



Subgroup analyses are based on unstratified Cox regression model with Efron's method of tie handling with treatment as a covariate.

"Other" histology includes serous, clear cell, dedifferentiated/undifferentiated, mixed epithelial, adenocarcinoma NOS.

Database Cutoff Date: 18 August 2023.

ORR

Sensitivity analyses performed with both stratification factors and by central MMR determination gave same results as the primary analysis.

A retrospective **BICR assessment** per RECIST 1.1 was also performed:

Table 48: Summary of Key Secondary Efficacy Results in pMMR Participants for NRG-GY018 (ITT Population with Measurable Disease at Baseline)

	By Investigator Assessment		By BICR	
	Pembrolizumab + Chemotherapy (N=220)	Placebo + Chemotherapy (N=235)	Pembrolizumab + Chemotherapy (N=263)	Placebo + Chemotherapy (N=271)
ORR per RECIST 1.1				
% (95% CI)	61.4 (54.6, 67.8)	51.5 (44.9, 58.0)	57.8 (51.6, 63.8)	53.1 (47.0, 59.2)
Difference % (95% CI) Nominal *p*-value[a]	9.9 (0.7, 18.8) 0.01718		4.7 (-3.8, 13.0) 0.13954	
DOR (months)				
Median (range)	7.1 (0.0+ - 32.8+)	6.4 (0.0+ - 20.1+)	15.2 (0.0+ - 32.8+)	6.6 (0.0+ - 28.4+)

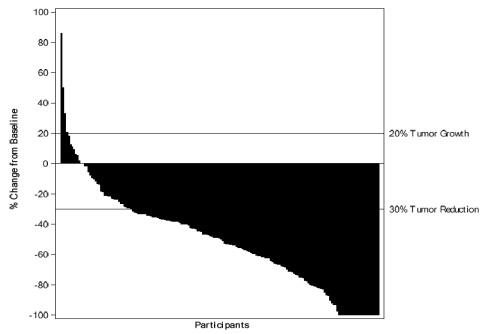
BICR=blinded independent central review, CI=confidence interval, DOR=duration of response, ITT=intent-to-treat population, ORR=objective response rate, pMMR=mismatch repair proficient, RECIST 1.1=Response Evaluation Criteria in Solid Tumors version 1.1

[a] One-sided *p*-value for testing. H0: difference in % = 0 versus H1: difference in % > 0.

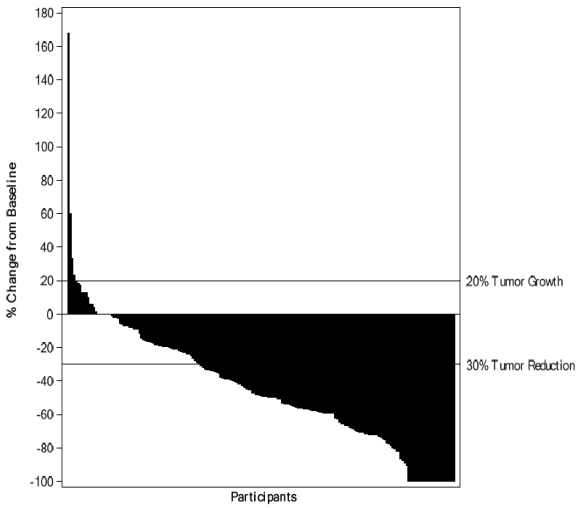
Database Cutoff Date: 06-DEC-2022

Figure 34: Waterfall Plot of Best Percentage Change From Baseline for Target Lesions Based on Investigator Assessment per RECIST 1.1 in pMMR Participants with Measurable Disease (Paclitaxel + Carboplatin + Pembrolizumab/Placebo)

Pembrolizumab arm



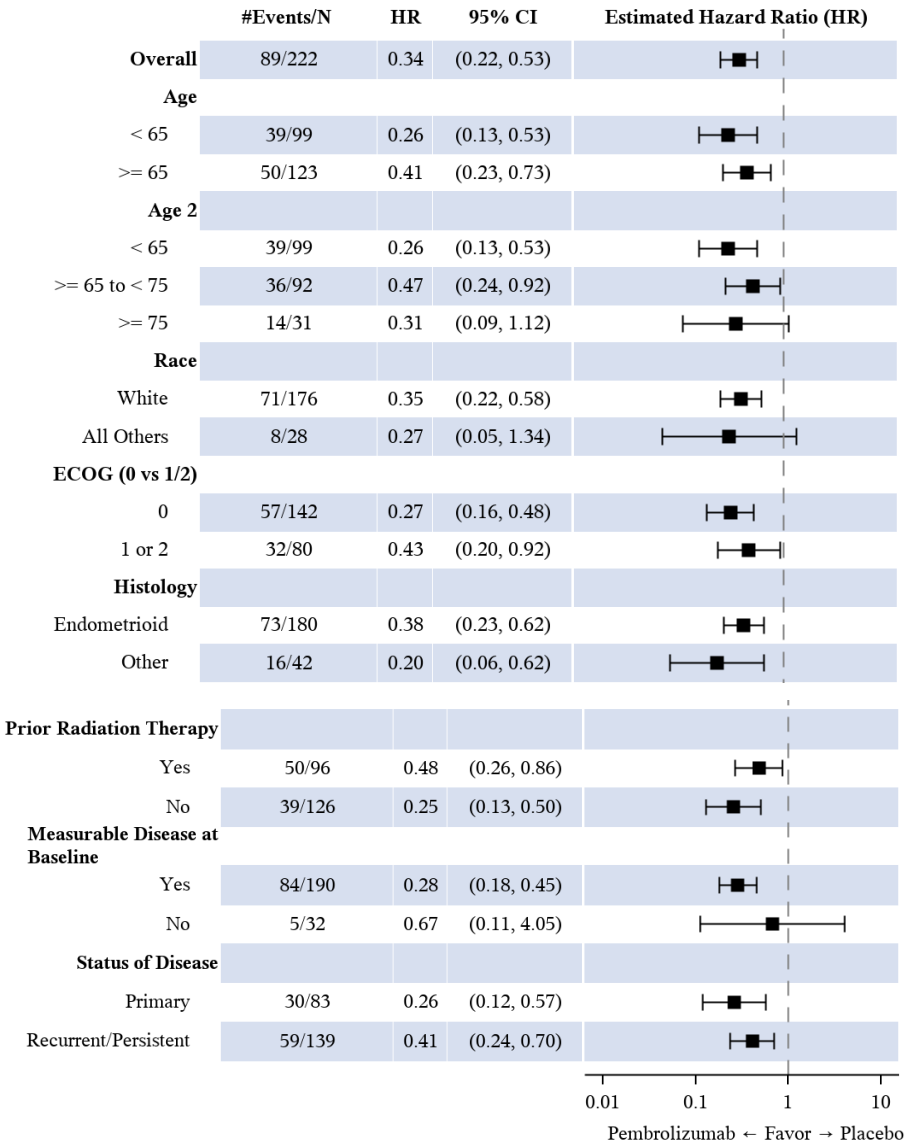
Placebo arm



dMMR population

PFS

Figure 35: Forest Plot of Progression-Free Survival by Subgroup Factors Based on Investigator Assessment per RECIST 1.1 (Protocol Censoring Rule) in dMMR Participants (ITT Population)



Subgroup analyses are based on unstratified Cox regression model with Efron's method of tie handling with treatment as a covariate.
If the number of participants in a category of a subgroup variable is less than 5% of the ITT population, or if there is no event in a category of a subgroup variable, the subgroup analysis will not be performed.
"Other" histology includes serous, clear cell, dedifferentiated/undifferentiated, mixed epithelial, adenocarcinoma NOS.
Database Cutoff Date: 16 December 2022.

Sensitivity analyses were performed to evaluate the robustness of the PFS endpoint per RECIST 1.1.

- Primary analysis (protocol censoring rule): HR 0.34 (95%CI 0.22, 0.53)
- MSD Primary (Preferred) Censoring Rule by ITT MMR: HR 0.30 (0.19, 0.48)
- MSD Sensitivity Censoring Rule 1 by ITT MMR: HR 0.31 (0.20, 0.49)
- MSD Sensitivity Censoring Rule 2 by ITT MMR: HR 0.39 (0.27, 0.57)
- Protocol Censoring Rule by Central MMR Determination: HR 0.32 (0.20, 0.50)
- Protocol Censoring Rule With Both Stratification Factors by ITT MMR: HR 0.33 (0.21, 0.52)

- DMC Censoring Rule by DMC MMR: HR 0.32 (0.21, 0.50)

OS

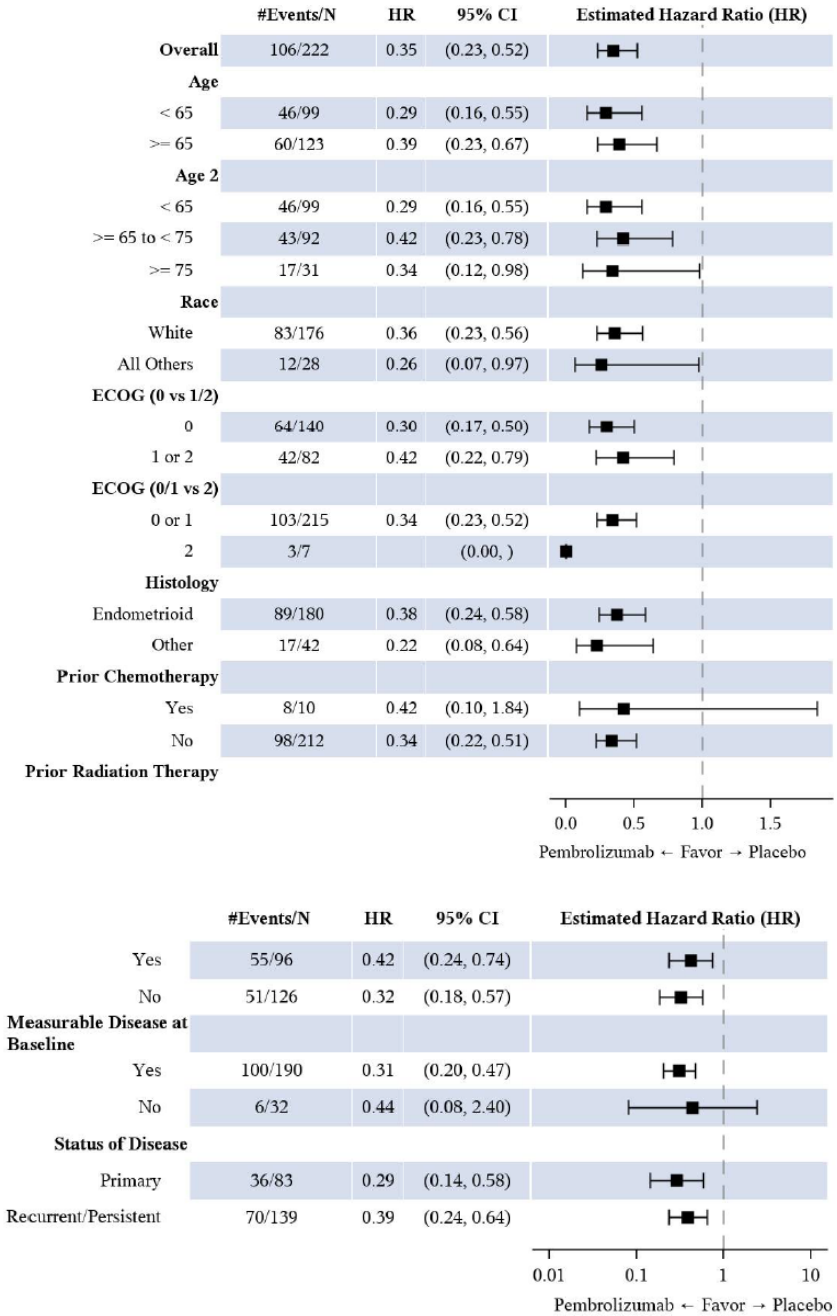
Sensitivity analyses were performed using MMR population based on central laboratory assessment (HR 0.51 [0.24, 1.11]), and using both stratified factors (HR 0.55 [0.25, 1.21]).

Sensitivity analyses performed with both stratification factors and by central MMR determination showed similar results as the primary analysis.

Updated descriptive analysis dMMR (DCO 18 August 20243)

Sensitivity analyses for PFS confirmed the primary analysis (HR estimates from 0.27 to 0.35).

Figure 36: Forest Plot of Progression-Free Survival by Subgroup Factors Based on Investigator Assessment per RECIST 1.1 (Protocol Censoring Rule) in dMMR Participants (ITT Population)



Subgroup analyses are based on unstratified Cox regression model with Efron's method of tie handling with treatment as a covariate.

"Other" histology includes serous, clear cell, dedifferentiated/undifferentiated, mixed epithelial, adenocarcinoma NOS.

Database Cutoff Date: 18 August 2023.

OS

Sensitivity analysis for OS based on IPCW method to adjusting for subsequent anti-PD(L)1 therapies with or without lenvatinib in the dMMR population resulted HR 0.54 (95% CI: 0.22, 1.69; 2-sided *p*-value based on IPCW log-rank test nominal *p*=0.1602).

Table 49: Summary of Subsequent Systemic Anti-Cancer Treatment in dMMR Participants Who Discontinued Study Treatment (ITT Population)

	Paclitaxel + Carboplatin + Pembrolizumab (N=56)	Paclitaxel + Carboplatin + Placebo (N=104)	Total (N=160)
Started Study Treatment	56 (100.0)	104 (100.0)	160 (100.0)
Discontinued Study Treatment	56 (100.0)	104 (100.0)	160 (100.0)
Received Any Subsequent Systemic Anti-cancer Therapy	26 (46.4)	64 (61.5)	90 (56.3)
Subsequent systemic therapy by type			
Any Anti-PD-1/PD-L1	10 (17.9)	53 (51.0)	63 (39.4)
durvalumab	1 (1.8)	3 (2.9)	4 (2.5)
nivolumab	0 (0.0)	1 (1.0)	1 (0.6)
pembrolizumab	9 (16.1)	50 (48.1)	59 (36.9)
retifanlimab	0 (0.0)	1 (1.0)	1 (0.6)

Figure 37: Kaplan-Meier Curves of Overall Survival Adjusting for Treatment Switch to Subsequent anti-PD-1/PD-L1 Therapies with or without Lenvatinib in Both Arms Using IPCW Model in dMMR Participants (ITT Population)

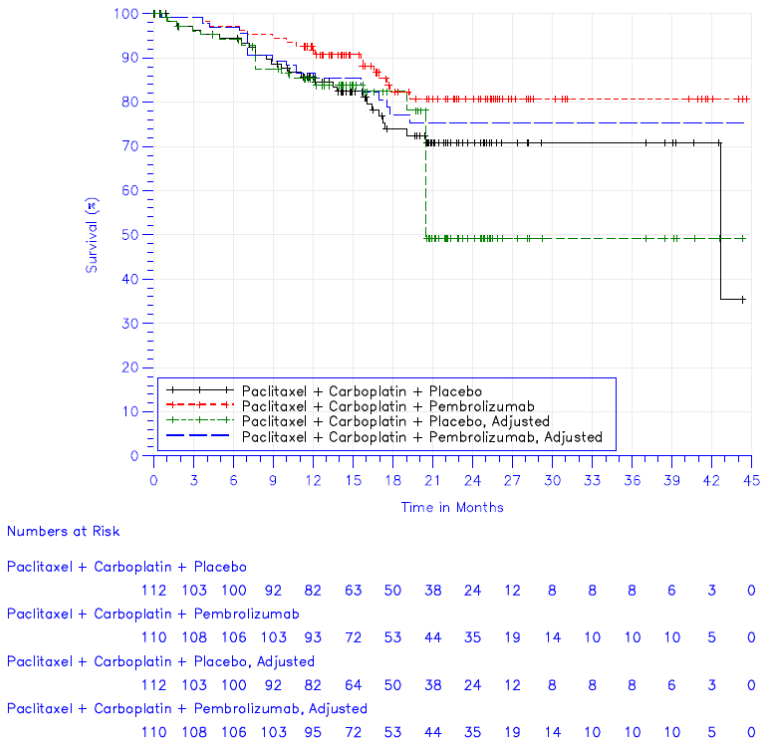
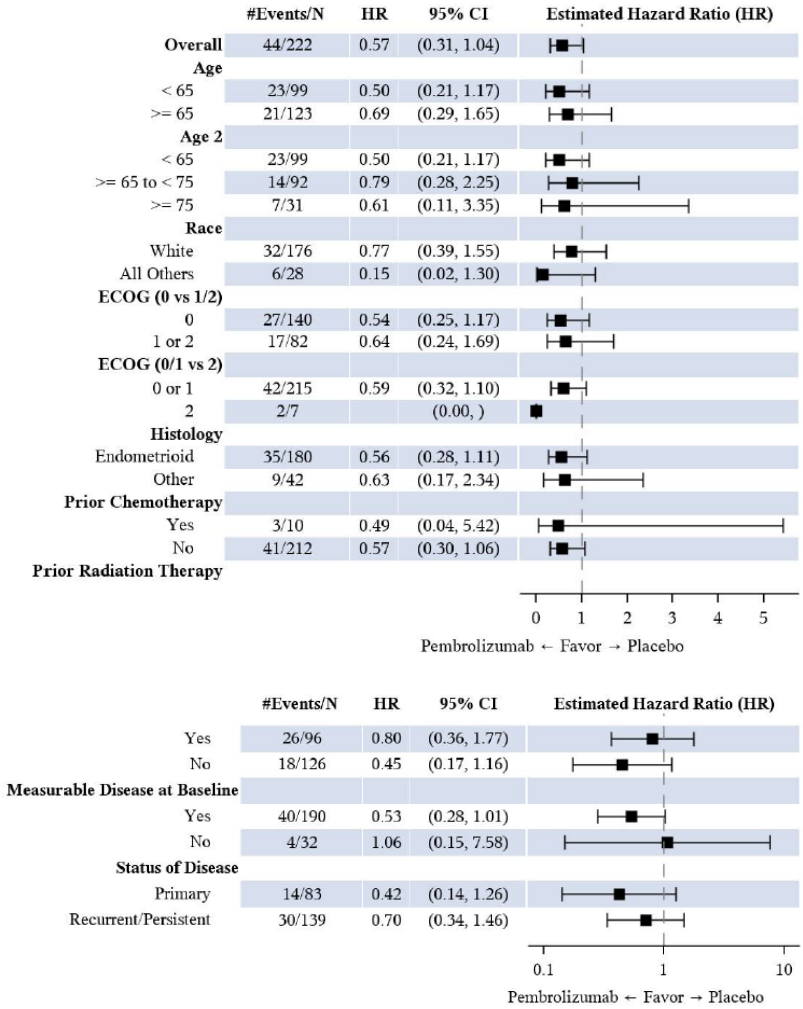


Figure 38: Forest Plot of Overall Survival by Subgroup Factors in dMMR Participants (ITT Population)



Subgroup analyses are based on unstratified Cox regression model with Efron's method of tie handling with treatment as a covariate.
"Other" histology includes serous, clear cell, dedifferentiated/undifferentiated, mixed epithelial, adenocarcinoma NOS.
Database Cutoff Date: 18 August 2023.

Summary of main study(ies)

The following tables summarise the efficacy results from the main studies supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see Section 3).

Table 50: Summary of Efficacy for trial NRG-GY018/KEYNOTE-868

Title: A Phase III Randomised, Placebo-controlled Study of Pembrolizumab (MK-3475, NSC #776864) in Addition to Paclitaxel and Carboplatin for Measurable Stage III or IVA, Stage IVB or Recurrent Endometrial Cancer		
Study identifier	IND: 140014; EudraCT: NA; EU CT: NA; NCT: NCT03914612	
Design	Phase 3, randomised, multicenter, parallel assignment, double blind, placebo-controlled, interventional study	
	Duration of main phase:	Study Initiation (FPFV: 12 August 2019) Primary Completion: Ongoing

			Data cutoff date: pMMR population: 06 December 2022 dMMR population: 16 December 2022
	Duration of Run-in phase		not applicable
	Duration of Extension phase		not applicable
Hypothesis	Superiority		
Treatments groups	Pembrolizumab plus chemotherapy group		Chemotherapy in combination with pembrolizumab (200 mg q3w for 6 cycles) followed by pembrolizumab monotherapy (400 mg q6w for up to 14 cycles). pMMR population: Randomised N = 294 dMMR population: Randomised N = 110
	Placebo plus chemotherapy group		Chemotherapy in combination with placebo (q3w for 6 cycles) followed by placebo alone (q6w for up to 14 cycles) pMMR population: Randomised N = 294 dMMR population: Randomised N = 112
Endpoints and definitions	Primary endpoint	PFS (investigator assessed per RECIST 1.1)	Defined as the time from randomisation to disease progression or death, whichever occurred first, or date of last contact if neither progression nor death had occurred
	Secondary endpoint	OS	Defined as the duration of time from study entry to time of death or the date of last contact
	Secondary endpoint	ORR	ORR, defined as the proportion of participants with CR or PR per RECIST 1.1, was evaluated by treatment arm and MMR IHC status in patients with measurable disease as assessed by investigator
	Secondary endpoint	DOR	DOR, defined as the time from the first response to the first progression, was assessed by investigator. Patients who did not experience progression were treated as censored in the analysis
	Secondary endpoint	QoL and PROs, measured by the FACT-En-TOI, the PROMIS-Fatigue (short form), and the PROMIS-physical function (short form)	PRO analyses were based on the pMMR FAS population, defined as pMMR participants who provided valid baseline and at least 1 follow-up QoL/PRO assessments.

	Exploratory endpoint	PFS2	Defined as the time from randomisation to disease progression by investigator assessment or death (whichever occurs first) on subsequent anticancer therapy
Database lock	06 December 2022 for pMMR population and 16 December 2022 for dMMR population		

Results and Analysis

Analysis description	**Primary Analysis – pMMR population**		
Analysis population and time point description	Intent to treat population (IA; data cutoff date: 06 December 2022)		
Descriptive statistics and estimate variability	**Treatment group**	**Pembrolizumab + Chemotherapy**	**Placebo + Chemotherapy**
	Number of subjects (N)	294	294
	PFS median in months (95% CI)	13.1 (10.6, 19.5)	8.7 (8.4, 11.0)
	OS median in months (95% CI)	27.96 (21.42, NR)	27.37 (19.52, NR)
	Number of subjects (N)	220	235
	ORR % (95% CI)	61.4 (54.6, 67.8)	51.5 (44.9, 58.0)
	Number of subjects (N)	135	121
	Median DOR, months (range)	7.1 (0.0+ - 32.8+)	6.4 (0.0+ - 20.1+)

Effect estimate per comparison	Primary endpoint PFS	Comparison groups	Pembrolizumab +chemo vs placebo + chemo
		HR	0.57
		95%CI	0.44, 0.74
		P-value	<0.0001
	Secondary endpoint OS	Comparison groups	Pembrolizumab +chemo vs placebo + chemo
		HR	0.79
		95%CI	0.53, 1.17
		P-value	0.1157
Notes	pMMR and dMMR populations were tested separately. PFS only is statistically tested. OS p-value is nominal.		

Analysis description	**Primary Analysis – dMMR population**		
Analysis population and time point description	Intent to treat population (IA; data cutoff date: 16 December 2022)		
Descriptive statistics and estimate variability	**Treatment group**	**Pembrolizumab + Chemotherapy**	**Placebo + Chemotherapy**
	Number of subjects (N)	110	112
	PFS median in months (95% CI)	NR (30.7, NR)	8.3 (6.5, 12.3)
	OS median in months (95% CI)	NR (NR, NR)	NR (NR, NR)
	Number of subjects (N)	95	95

	ORR % (95% CI)	77.9 (68.2, 85.8)	69.5 (59.2, 78.5)
	Number of subjects (N)	74	66
	Median DOR, months (range)	NR (0.0+ - 33.0+)	4.4 (0.0+ - 32.8+)
Effect estimate per comparison	Primary endpoint PFS	Comparison groups	Pembrolizumab +chemo vs placebo + chemo
		HR	0.34
		95%CI	0.22, 0.53
		P-value	<0.0001
	Secondary endpoint OS	Comparison groups	Pembrolizumab +chemo vs placebo + chemo
		HR	0.55
		95%CI	0.25, 1.19
		P-value	0.0617
Notes	pMMR and dMMR populations were tested separately. PFS only is statistically tested. OS p-value is nominal.		

Analysis performed across trials (pooled analyses and meta-analysis)

None.

Clinical studies in special populations

There were no specific studies in the paediatric population. The patients in the age categories above 65 included in the study that are part of the controlled study KN-868/NRG-GY018 are included in Table 52.

Table 51: Clinical studies in special populations

KN-868		**pMMR (n=514)**		**dMMR (n=204)**	
APaT Population with post-baseline Labs **Total n= 718**		N= 257 (Paclitaxel + Carboplatin + Pembrolizumab)	N=257 (Paclitaxel + Carboplatin + Placebo)	N= 101 (Paclitaxel + Carboplatin + Pembrolizumab)	N=103 (Paclitaxel + Carboplatin + Placebo)
Renal impairment* patients (Subjects number /total number)	All ages combined	13/257 (5.1%)	2/257 (0.8%)	4/101 (4.0%)	3/103 (2.9%)
	<65 years old	3/257 (1.2%)	0/257 (0.0%)	2/101 (2.0%)	1/103 (1.0%)
	≥65 to <75 years old	5/257 (1.9%)	2/257 (0.8%)	2/101 (2.0%)	2/103 (1.9%)
	75+ years old	5/257 (1.9%)	0/257 (0.0%)	0/101 (0%)	0/103 (0.0%)
Hepatic impairment patients (Subjects number /total number)**		0/257 (0.0%)	0/257 (0.0%)	0/101 (0.0%)	0/103 (0.0%)
APaT Population with post-baseline Labs (Subjects	<65 years old	118/257 (45.9%)	119/257 (46.3%)	43/101 (42.6%)	48/103 (46.6%)
	≥65 to <75 years old	100/257 (38.9%)	105/257 (40.9%)	45/101 (44.6%)	38/103 (36.9%)

number /total number)	75+ years old	39/257 (15.2%)	33/257 (12.8%)	13/101 (12.9%)	17/103 (16.5%)

* : Renal impairment is defined has having serum creatinine ≥1.5 x ULN
**: Hepatic impairment is defined as having total bilirubin ≥1.5 x ULN and ASTA/ALT ≥ 3 x ULN

Supportive study(ies)

None.

2.4.2. Discussion on clinical efficacy

The MAH has applied for an extension of indication for Keytruda in first line treatment of primary advanced or recurrent endometrial cancer (EC) in combination with carboplatin and paclitaxel in adults, based on the interim results of the pivotal phase III study KEYNOTE-868/NRG-GY018.

Pembrolizumab is already approved in the EU for the treatment of advanced endometrial cancer after prior platinum-based chemotherapy, both as monotherapy in dMMR/MSI-H population and in combination with lenvatinib regardless of MSI status.

Design and conduct of clinical studies

KEYNOTE-868 is an ongoing, Phase 3, randomised, placebo-controlled, double-blind study performed in collaboration with NCI-CTEP. Adult patients with newly diagnosed, Stage III or IVA EC, or Stage IVB or recurrent adenocarcinoma of the endometrium, who have not received prior chemotherapy (except in the adjuvant setting/concurrently with RT completed more than 12 months earlier), were eligible.

Subjects received 6 cycles of carboplatin/paclitaxel, which is agreed being the standard first-line treatment in EC (NCCN and ESMO guidelines). Pembrolizumab/placebo were administered Q3W concomitantly to chemotherapy, then continued as maintenance treatment as monotherapy, until disease progression (up to max 2 years of total treatment). Paclitaxel could have been replaced by docetaxel/nab-paclitaxel due to AE/IRR: this occurred in both populations only in a minority of patients (about 5%) balanced between treatment arms, thus no impact on the efficacy result is expected. In addition, if deemed necessary by treating physician, up to a total of 10 cycles of chemotherapy + pembrolizumab/placebo were allowed. The number of patients who received more than 6 cycles of carboplatin/paclitaxel were only a minority (approximately 12-13%) and balanced between treatment arms in both dMMR and pMMR populations, thus it is unlikely that this might have impacted on the study results. In the maintenance phase, pembrolizumab was administered every 3 weeks (200 mg) initially, then every 6 weeks (400 mg). This change can be followed as implemented for practical reason in the context of COVID-19 pandemic. Further, both dosing regimens of pembrolizumab are already approved. Therefore, this approach is considered acceptable.

The study assessed separately two populations, dMMR and pMMR, making it essentially two clinical trials. This is appreciated and endorsed, given the known predictive value of dMMR/MSI-H status for activity of anti-PD(L)1 agents, as already shown in previous clinical trials of pembrolizumab and other anti-PD(L)1 drugs in EC. MMR status was assessed centrally initially by IHC, then locally (but with central confirmation). Robust concordance between central and institutional determination of MMR IHC status was shown, raising no concern. Further, sensitivity analyses based on central MMR determination have been conducted, which were consistent with primary analyses. Data on POLE mutation have not been collected. However, the MAH stated that the number of patients expected in the first line metastatic setting with POLE mutation, given the favourable prognosis (i.e., very low rate of recurrence/distant

metastasis) is anticipated to be very low on NRG-GY018. For reference, a clinical study in the same setting, the RUBY study evaluating dostarlimab in first line endometrial cancer, presented at ESMO 2023 Congress (Abstract #740MO), showed 5 out of 400 subjects (1.3%) with POLE mutations precluding any meaningful analysis. This is acknowledged.

KEYNOTE-868 was powered for the primary endpoint PFS in both pMMR and dMMR populations. The sample size calculation is comprehensible and reproducible, and amendments did not affect the sample size and power calculation. MMR status was one of the stratification factors, together with ECOG and prior chemotherapy, which are considered appropriate. The combination of these categories resulted in 2x2x2=8 strata. The procedure used to generate the random allocation sequence was web-based and a block randomisation was used. The pharmacist providing the infusion was the only one unblinded. Patient treatment assignment was unblinded after IA, and while placebo administration was stopped, all other study related treatment and evaluation proceeded as per protocol. Some updates to the planned analyses following study unblinding were made by the MAH, however, no concerns emerged due to these analyses.

Statistical methods were well reported in the protocol and in the SAP and can be considered overall appropriate. The graphical approach of Maurer and Bretz was applied to re-allocate alpha among the hypotheses for PFS in pMMR and dMMR population, while the Lan-DeMets O'Brien-Fleming methods was used to allocate alpha among the interim and final analyses in each MMR population; these approaches are both endorsed. There were twelve protocol amendments over the study course, four of these partially modified the SAP language. The rationale for these changes was described and, overall, all changes introduced seem not to affect the consistency of study results.

Primary endpoint was PFS, assessed by investigator per RECIST 1.1. The investigator's assessment can be accepted in the context of a double-blind study. A sensitivity analysis of PFS by BICR was planned and provided. The MAH clarified that BICR was performed in its entirety as a retrospective analysis, and that BICR verification of investigator's declared progression was not required before a participant was discontinued. Overall, the post-hoc analyses by BICR supported the primary results by INV. However, the interpretation of the results by BICR is hampered by the retrospective nature of the BICR review and the fact that no BICR verification of investigator's declared progression before treatment discontinuation was requested during the study. Several sensitivity analyses were added by the MAH after protocol unblinding and were performed to evaluate the robustness of the PFS endpoint based on different sets of censoring rules. Those can be considered overall adequate.

OS was a secondary endpoint for this study, but it was not included in the multiplicity strategy. In this context, the significance of this endpoint cannot be correctly evaluated, and OS analysis is only descriptive. Subgroups analyses were not pre-specified. PFS2 was added as exploratory endpoint to support the assessment for other efficacy endpoint, particularly OS, which is endorsed.

Efficacy data and additional analyses

The MAH submitted the results of the PFS interim analysis, with data cut-off (DCO) 06 December 2022 for pMMR population and 16 December 2022 for dMMR population. While randomisation was closed on 17 August 2022 in the dMMR thus allowing a minimum follow-up of approximately 4 months between the completion of enrolment and the IA (i.e. the time of unblinding), randomisation in the pMMR population closed on 20 December 2022 after the IA DCO. Indeed, a total of 9 additional pMMR participants were enrolled before or at IA data cutoff date, but randomised afterwards (4 in the experimental and 5 in the control arm), thus not included in the IA analysis.

The median duration of follow up for the ITT population was similar between the 2 treatment groups within each population of pMMR (median: 8.7 months, range: 0.1-37.2) and dMMR (median: 13.6 months, range: 0.6-39.4). At time of DCO for the interim analysis, 233 PFS events occurred in pMMR

group (95 (32%) in the pembrolizumab arm and 138 (47%) in the placebo arm), that means a 59.1% of information fraction, a 39.1% of data maturity and a maximum power expected of 58%. In pMMR population, 89 PFS events occurred in dMMR group (29 (26%) in the pembrolizumab arm and 60 (54%) in the placebo arm), that means a 53% of information fraction, a 40% of data maturity and a maximum power expected of 50%. Further, almost 40% of patients were still under treatment at the IA DCO. Overall, results at the time of the IA were considered still immature especially in terms of follow-up time. Therefore, following a request from the CHMP, the MAH submitted the results of an updated descriptive analysis of KEYNOTE-868.

Importantly, the study was unblinded after the pre-planned IA (when statistical significance was reached in both populations). Indeed, the CTEP/NRG notified investigators on 03 February 2023 of the participant's assigned treatment, requesting the investigators make participants aware of the study outcome and their treatment assignment. Consequently, the majority of patients in the control arm discontinued soon after unblinding, including prior to investigator assessed progressive disease.

A more mature unplanned descriptive analysis was performed based on a DCO of 18 August 2023, i.e. 9 months of additional follow-up since IA. By the time of the data cutoff of the updated analysis, almost all participants (99.2%) except 3 (0.8%) in the placebo plus chemotherapy arm discontinued from the study treatment, with some participants subsequently receiving immunotherapy (IO) incorporated into their treatment regimen. As this updated analysis was conducted after the unblinding and subsequent initiation of post study IO after discontinuation in the control arm, this has likely introduced bias in estimation of HR favoring the placebo plus chemotherapy group, especially as participants discontinued prior to investigator assessed disease progression and/or the protocol specified schedule of assessments was not adhered too. This limits the interpretability of the updated analysis overall.

After this updated analysis, the pre-planned final PFS and OS analyses will not be conducted by the MAH. It is acknowledged that final analysis would be difficult to interpret and not really informative due to study unblinding occurring after IA.

Applicability to the EU population: The study was conducted primarily in North America (US mostly). As no EU participants were included, a justification for applicability of study data to the EU patient population and medical practice was provided by the MAH. Although a slightly higher incidence and mortality for EC (especially among African/American population) is reported in North America as compared to EU[25], in both regions EC is rising, likely partly related to increases in exposure to shared risk factors including obesity, diabetes, increased life expectancy and environmental risk factors. The prevalence of dMMR alteration among EC appears consistent between the two regions[26] [27]. It is acknowledged that NCCN and ESMO guidelines both recommend carboplatin-paclitaxel in 1L and are also aligned with respect to second line treatments, with the exception of pembrolizumab+lenvatinib (approved in the pMMR only population in the US and in all comers in the EU)[28] [29]. This is indeed reflected in the post-study treatments, but it is considered that it had no meaningful impact on the results in the dMMR population. It is also agreed that, based on the data provided, the PK of pembrolizumab were shown to be consistent across ethnicity and region (see clinical pharmacology section 2.3.2). Main baseline characteristics of the enrolled population

[25] Ferlay J, Ervik M, Lam F, Laversanne M, Colombet M, Mery L, et al. Global Cancer Observatory (GCO): Cancer Today [Internet]. Lyon (France): International Agency for Research on Cancer (IARC); c2024. Global incidence and mortality data for endometrial cancer (cancer of the corpus uteri) in 2022; [cited 2024 Feb 14]. Available from: https://gco.iarc.who.int/today.
[26] Kelkar SS, Prabhu VS, Zhang J, Ogando YM, Roney K, Verma RP, Miles N, Marth C. Real-world prevalence of microsatellite instability testing and related status in women with advanced endometrial cancer in Europe. Arch Gynecol Obstet. 2024 Apr 18
[27] Lorenzi M, Amonkar M, Zhang J, Mehta S, Liaw KL. Epidemiology of microsatellite instability high (MSI-H) and deficient mismatch repair (dMMR) in solid tumors: a structured literature review. J Oncol. 2020 Mar 9;2020:1807929.
[28] Oaknin A, Bosse TJ, Creutzberg CL, Giornelli G, Harter P, Joly F, Lorusso D, Marth C, Makker V, Mirza MR, Ledermann JA, Colombo N; ESMO Guidelines Committee. Endometrial cancer: ESMO Clinical Practice Guideline for diagnosis, treatment and follow-up. Ann Oncol. 2022 Sep;33(9):860-877.
[29] NCCN guidelines Uterine Neoplasms Version 2.2024

are broadly comparable with recent worldwide studies in the same setting[30] [31] [32]. From an efficacy perspective, PFS subgroup analyses by race (White vs All Others) showed overall consistent results. In conclusion, data from the overall study population of NRG-GY018 generated in regions outside the EU are expected to be applicable to the EU population.

pMMR population

Overall, 588 patients were randomised in the pMMR population (294 in each treatment group). Quite a few patients were randomised but not treated in both study arms (19 vs 22). Slightly more patients have already discontinued treatment in the control arm, mostly for disease progression (29.1% vs 36.4%). Discontinuation due to side effect was more common in the experimental arm (13.1% vs 6.3%), as expected in the add-on treatment. Still 46.2% vs 37.5% of the patients were under treatment at the DCO of the IA. It is also noted the higher treatment discontinuation rate due to "other" reasons seen in both dMMR and pMMR subsets in the control arm (3.7% versus 12.4% and 1.5% versus 12.5%). Thus, some uncertainty remains regarding the complete effectiveness of blinding. However, additional analyses/data would not change the results and the overall conclusion, as, if any, such differences would have likely favoured the comparator arm.

In both the **pMMR and dMMR** populations, the most frequently reported medical history conditions were generally as expected for participants with advanced or recurrent EC and were generally well balanced between the 2 treatment groups.

With 32.3% vs 46.9% of patients experiencing PFS event at IA, PFS reached statistical significance [HR 0.57 (0.44, 0.74), p<0.0001)], with a gain in median PFS of 4.4 months (13.1 vs 8.7). The PFS KM curves divided after month 3-4. A quite high censoring is observed in both arms in the first 6 months, because enrolment was just completed at the DCO, confirming the immaturity of IA. It was reassuring that the early censoring was balanced between treatment arms. Among sensitivity analyses, it was noted the discrepancy between MSD Sensitivity Censoring Rule 2 (HR 0.81) with respect to other sensitivity analyses performed. It can be agreed that the observed treatment benefit in the MSD Sensitivity Censoring Rule 2 is much diluted due to equivalent number of participants who discontinued study medication or initiated new anti-cancer therapy. PFS results in the subgroups analysed seem consistent with ITT analysis, although CI crossed 1 in patients who have received prior chemotherapy, prior RT and without measurable disease at baseline.

OS was immature (15.3% vs 18.4% of events). HR was 0.79 (0.53, 1.17), with same median OS in both arms (28.0 vs 27.4 months) and curves overlapping at least up to month 15. Data is descriptive and not yet interpretable. PFS2 HR was 0.68 (95% CI: 0.48, 0.97): while positive trend is suggested, curves diverge quite late.

Data according to PD-L1 status were provided. The study was not stratified by PD-L1 status, but PD-L1 was determined centrally in almost all patents (2% unknown status). Most patients (about 70%) were PD-L1 positive (CPS≥1), and this was balanced in both groups. Results suggest that PFS and OS benefit is maintained also in the PD-L1 negative population (PFS 0.44, OS 0.69). Although considering the limit of small sample size of the negative subgroup and the exploratory nature of the analysis, PD-L1 does not appear to be a relevant biomarker to select patients who do or do not achieve benefit from the addition of pembrolizumab in the target pMMR EC population. Little information has been found to assess the biological plausibility of this finding. Indeed, in the RCT KEYNOTE-755 (pembrolizumab + lenvatinib in EC after prior treatment) PD-L1 status was not collected. Limited data by PD-L1 status is available from the

[30] Mirza MR, Chase DM, Slomovitz BM, et al; RUBY Investigators. Dostarlimab for Primary Advanced or Recurrent Endometrial Cancer. N Engl J Med. 2023 Jun 8;388(23):2145-2158.
[31] EMA/483641/2023, Jemperli-H-C-005204-II-0023: EPAR - Assessment Report - Variation
[32] Westin SN, Moore K, Chon HS, et al; DUO-E Investigators. 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. 2024 Jan 20;42(3):283-299.

single arm study KEYNOTE-148: in a pretreated population with pMMR EC, pembrolizumab + lenvatinib did show similar ORR regardless PD-L1 status, although based on a limited number of patents[33].

There was no relevant increase in ORR (61.4% vs 51.5%) and median DOR was quite similar (7.1 vs 6.4 months), contrary to what observed in the dMMR population.

PROs were evaluated only in the pMMR population. Worsening QOL and increase in fatigue appeared more pronounced in the pembrolizumab group at week 18 as compared to the placebo group (i.e. corresponding to the 6 cycles of chemotherapy), while returning to baseline afterwards. This seems in line with some increase in toxicity with the combination treatment.

Updated descriptive analysis results were provided for the pMMR population. Updated PFS results by INV per RECIST 1.1 worsened as compared to the IA: with 54.7% vs 62.5% of events, HR increased from 0.57 at IA to HR 0.74 (95% CI: 0.60, 0.91), corresponding to a median PFS gain of less than 1 month (11.4 vs 10.6), and late separation of KM curve. However, as discussed above, this finding might be explained by the fact that the updated analysis was conducted after the unblinding and subsequent initiation of post study IO after discontinuation in the control arm, which might have likely introduced bias in estimation of HR favouring the placebo plus chemotherapy group, thus limiting the interpretability of the updated analysis overall. Reassuringly, PFS was still in favour of the pembrolizumab combo arm. The results of the other endpoints in the pMMR population overall confirmed the findings at the IA, in particular no detriment in OS was suggested with longer follow-up, which is reassuring. Updated analysis confirmed also the conclusion at IA that PD-L1 does not appear a useful biomarker to select pMMR patients in this study benefitting more from the addition of pembrolizumab.

dMMR population

A total of 222 patients were included in the dMMR population (110 in the pembrolizumab arm and 112 in the placebo arm), showing balanced baseline patients and disease characteristics between the two treatment groups. There were more endometrioid tumours as compared to the pMMR population, which is consistent with literature data. A total of 10 patients did not receive any treatment. Among treated subjects, more discontinued therapy in the control group mainly for progressive disease (45.7%), with 25.7% still under treatment. In the experimental arm almost half of the patients had treatment ongoing at the DCO of the IA, with 16.8% of subjects stopping for disease progression. As expected, more patients in the pembrolizumab containing arm had to stop treatment due to side effect (15.9% vs 5.7%).

The addition of pembrolizumab lead to a statistically significant and clinically relevant improvement in PFS at the IA [HR 0.34 (0.22, 0.53), p<0.0001], with large separation of KM curves (median NR vs 8.3 months, PFS rate at 1 year 73% vs 40%), confirmed by several sensitivity analyses. The benefit appears overall consistent across main subgroups.

Still immature descriptive OS data (9.1% vs 15.2% of subjects with OS events) suggested positive OS trend [HR 0.55 (0.25, 1.19)], supported by positive PFS2 HR 0.31 (95% CI: 0.16, 0.62).

While the ORR gain is modest on top of an already high ORR with chemotherapy alone (77.9% vs 69.5%), responses are deeper (CR 28.4% vs 11.6%) and more durable (mDOR NR vs 4.4 months) by adding pembrolizumab.

Most (82%) patients with dMMR EC have PD-L1 positive status, and indeed patients with dMMR had lower odds of having CPS <1 expression compared with pMMR participants. This is consistent with literature data and information from other studies. No conclusion can be drawn in the PD-L1 CPS <1 negative population as there are too few patients.

[33] Makker V, Taylor MH, Aghajanian C, et al. Lenvatinib Plus Pembrolizumab in Patients With Advanced Endometrial Cancer. J Clin Oncol. 2020 Sep 10;38(26):2981-2992.

In the dMMR population, the results of the descriptive updated analysis were overall consistent with IA data [PFS HR 0.35 (95% CI: 0.23, 0.52); OS HR 0.57 (95%CI 0.31, 1.04)], confirming the clinically relevant effect of the addition of pembrolizumab to standard chemotherapy in this subset.

Additional expert consultation

None requested.

Assessment of paediatric data on clinical efficacy

Not applicable.

2.4.3. Conclusions on the clinical efficacy

Pembrolizumab has been investigated in KEYNOTE-868 as an add-on treatment to standard first line carboplatin and paclitaxel chemotherapy and continued as maintenance in adults with recurrent/advanced endometrial cancer who were candidates for systemic therapy. In line with previous procedures, the finally agreed indication was reworded to reflect that the studied population were candidates for systemic therapy.

In the **pMMR** population, statistical significance was reached in PFS at the interim analysis, however the analysis was considered immature especially in view of the high number of patients still under treatment at the data cut-off and the short minimum follow-up. Updated results at a following descriptive analysis showed reduced PFS improvement as compared to the IA. However, due to the unblinding of the study after IA and consequent treatment discontinuation in the control arm including prior to investigator assessed progressive disease, the overall interpretation of the updated analysis is hampered, due to possible bias favouring the placebo plus chemotherapy group. Reassuringly, PFS was still in favour of the pembrolizumab combo arm, and no OS detriment is suggested after longer follow-up. PD-L1 does not appear to be useful to discriminate patients who can gain benefit from the addition of pembrolizumab among pMMR EC.

In the **dMMR** population, the results at the IA showed statistically significant and clinically relevant PFS improvement with durable responses and higher rate of complete response, supported by positive OS and PFS2 trends. Data were confirmed by the updated analysis. Higher benefit in the dMMR population as compared to pMMR is biologically expected and consistent with external data from pembrolizumab and other anti-PD(L)1 agents in dMMR/MSI-H endometrial cancer.

2.5. Clinical safety

Introduction

The safety profile of pembrolizumab in combination with carboplatin and paclitaxel, in the context of its intended use for the first-line treatment of primary advanced or recurrent endometrial carcinoma in adults who are candidates for systemic therapy, is based on an interim analysis of the Phase 3 study KEYNOTE-868/NRG GY018, with a data cutoff date of 06 December 2022 for participants with pMMR tumours and 16 December 2022 for participants with dMMR tumours and complemented with updated descriptive safety data based on a DCO of 18 August 2023 with approximately 9 months of additional data since interim analysis, upon CHMP request. Safety data from the interim analysis are reported below, unless otherwise noted.

Safety data are provided from participants treated with pembrolizumab plus chemotherapy versus participants treated with placebo plus chemotherapy in KN868/NRG-GY018. In addition, pooled safety data from studies of pembrolizumab in combination with chemotherapy (hereafter, the pooled pembrolizumab plus chemotherapy SD) are also included to provide information on the safety profile of pembrolizumab in combination with chemotherapy from multiple approved indications. Participants in the pooled pembrolizumab plus chemotherapy SD received pembrolizumab in combination with single agent or combination chemotherapies, including platinum-based chemotherapy, 5 fluorouracil, paclitaxel/nab-paclitaxel, and pemetrexed. The pembrolizumab monotherapy reference safety database (RSD) is also included to enable a comparison of the safety profile of pembrolizumab plus chemotherapy observed in NRG-GY018 with the established safety profile of pembrolizumab.

Patient exposure

In the pMMR population, as of the data cutoff (06 December 2022), 275 participants received at least 1 dose of pembrolizumab plus chemotherapy, and 272 participants received at least 1 dose of placebo plus chemotherapy in NRG-GY018. A total of 127 (46.2%) and 102 (37.5%) participants were still receiving treatment in the pembrolizumab plus chemotherapy group and the placebo plus chemotherapy group, respectively.

In the dMMR population, as of the data cutoff (16 December 2022), 107 participants received at least 1 dose of pembrolizumab plus chemotherapy, and 105 participants received at least 1 dose of placebo plus chemotherapy in NRG-GY018. A total of 52 (48.6%) and 27 (25.7%) participants were still receiving treatment in the pembrolizumab plus chemotherapy group and the placebo plus chemotherapy group, respectively.

A total of 29 participants in the pMMR population (5.3%) and 14 participants in the dMMR population (6.6%) received a chemotherapy agent other than paclitaxel (docetaxel or nab-paclitaxel), as permitted in the protocol in case of AE/IRR.

> dMMR population: A total of 8 participants (7.5%) in the pembrolizumab plus chemotherapy group and 6 participants (5.7%) in the placebo plus chemotherapy group were treated with alternative chemotherapy agents (docetaxel or nab-paclitaxel) due to AE/IRR
>
> pMMR population: A total of 14 participants (5.1%) in the pembrolizumab plus chemotherapy group and 15 participants (5.5%) in the placebo plus chemotherapy group were treated with alternative chemotherapy agents (docetaxel or nab-paclitaxel) due to AE/IRR

The median duration of exposure is provided below:

Table 52: Summary of Drug Exposure (APaT Population)

	Pembrolizumab + Chemotherapy (N=382)	Placebo + Chemotherapy (N=377)	Pooled Safety Dataset for Pembrolizumab + Chemotherapy (N=3473)	Pembrolizumab Monotherapy Reference Safety Dataset (N=7631)
Duration on therapy (days)				
Mean	212.3	165.6	305.1	239.1
Median	170.0	127.0	249.5	176.0
SD	167.75	129.86	226.40	210.22
Range	1.00 to 729.00	1.00 to 651.00	1.00 to 1,461.00	1.00 to 1,157.00

Duration of exposure is the time from the first dose date to the last dose date, and is calculated as last dose date - first dose date + 1.

Database cutoff date for KEYNOTE-868: 16 December 2022 for dMMR participants and 06 December

2022 for pMMR participants.

Table 53: Drug Exposure by Duration (APaT Population)

	KN868 Pembrolizumab + Chemotherapy (N=382)			KN868 Placebo + Chemotherapy (N=377)			Pooled Safety Dataset for Pembrolizumab + Chemotherapy (N=3473)			Pembrolizumab Monotherapy Reference Safety Dataset (N=7631)		
	n	(%)	Person-years	n	(%)	Person-years	n	(%)	Person-years	n	(%)	Person-years
Duration of Exposure (month)												
> 0	382	(100.0)	222.0	377	(100.0)	170.9	3,468	(99.9)	2,896.9	7,631	(100.0)	4,995.0
≥ 1	341	(89.3)	221.0	340	(90.2)	169.7	3,223	(92.8)	2,888.6	6,637	(87.0)	4,962.4
≥ 3	288	(75.4)	211.9	281	(74.5)	160.3	2,834	(81.6)	2,820.2	5,023	(65.8)	4,693.1
≥ 6	176	(46.1)	169.5	118	(31.3)	101.2	2,088	(60.1)	2,535.8	3,781	(49.5)	4,240.0
≥ 12	66	(17.3)	92.3	34	(9.0)	45.1	1,333	(38.4)	1,996.8	1,673	(21.9)	2,558.8

Each participant is counted once on each applicable duration category row.
Duration of exposure is the time from the first dose date to the last dose date.
Database cutoff date for KN868: 16DEC2022 for dMMR participants and 06DEC2022 for pMMR participants.
The list of studies and database cutoff dates for the aggregate safety datasets within this table are provided in the appendix of Module 2.7.4.

Source: [ISS: adam-adsl; adexsum]

At the time of data cut-off, in pMMR population, a total of 127 (46.2%) and 102 (37.5%) participants were still receiving treatment in the pembrolizumab plus chemotherapy group and the placebo plus chemotherapy group, respectively. In dMMR population, a total of 52 (48.6%) and 27 (25.7%) participants were still receiving treatment in the pembrolizumab plus chemotherapy group and the placebo plus chemotherapy group, respectively. Considering that almost half of patients in pembrolizumab plus chemotherapy group were still receiving treatment as of the data cutoff, updated safety data based on a DCO of 18 August 2023 with approximately 9 months of additional data since interim analysis (IA), have been provided upon request from CHMP.

Demographic and baseline characteristics

Table 54: Participant Characteristics (APaT Population)

	Pembrolizumab + Chemotherapy		Placebo + Chemotherapy		Pooled Safety Dataset for Pembrolizumab + Chemotherapy		Pembrolizumab Monotherapy Reference Safety Dataset	
	n	(%)	n	(%)	n	(%)	n	(%)
Participants in population	382		377		3,473		7,631	
Sex								
Male	0	(0.0)	0	(0.0)	1,326	(38.2)	4,889	(64.1)
Female	382	(100.0)	377	(100.0)	2,147	(61.8)	2,742	(35.9)
Age (Years)								
<65	172	(45.0)	174	(46.2)	2,381	(68.6)	4,524	(59.3)
>=65	210	(55.0)	203	(53.8)	1,092	(31.4)	3,107	(40.7)
Mean	65.5		65.4		57.0		59.9	
SD	9.2		9.7		12.5		13.4	
Median	66.3		66.1		58.0		62.0	
Range	31 to 94		29 to 91		19 to 94		15 to 94	
Race								
American Indian Or Alaska Native	2	(0.5)	3	(0.8)	60	(1.7)	59	(0.8)
Asian	17	(4.5)	15	(4.0)	805	(23.2)	826	(10.8)
Black Or African American	53	(13.9)	53	(14.1)	110	(3.2)	146	(1.9)
Multiracial	1	(0.3)	1	(0.3)	70	(2.0)	86	(1.1)
Native Hawaiian Or Other Pacific Islander	1	(0.3)	3	(0.8)	2	(0.1)	5	(0.1)
White	288	(75.4)	280	(74.3)	2,305	(66.4)	5,838	(76.5)

Missing	20	(5.2)	22	(5.8)	121	(3.5)	671	(8.8)
Ethnicity								
Hispanic Or Latino	23	(6.0)	21	(5.6)	467	(13.4)	604	(7.9)
Not Hispanic Or Latino	349	(91.4)	344	(91.2)	2,811	(80.9)	6,064	(79.5)
Not Reported	5	(1.3)	6	(1.6)	106	(3.1)	808	(10.6)
Unknown	5	(1.3)	6	(1.6)	68	(2.0)	145	(1.9)
Missing	0	(0.0)	0	(0.0)	21	(0.6)	10	(0.1)
Age Category (year)								
<65	172	(45.0)	174	(46.2)	2,381	(68.6)	4,524	(59.3)
65-74	153	(40.1)	149	(39.5)	884	(25.5)	2,173	(28.5)
>=75	57	(14.9)	54	(14.3)	208	(6.0)	934	(12.2)
ECOG Performance Status								
[0] Normal Activity	258	(67.5)	252	(66.8)	1,914	(55.1)	4,016	(52.6)
[1] Symptoms, but ambulatory	116	(30.4)	113	(30.0)	1,553	(44.7)	3,440	(45.1)
Other/Missing	8	(2.1)	12	(3.2)	6	(0.2)	175	(2.3)
	n	(%)	n	(%)	n	(%)	n	(%)
Geographic Region								
US	352	(92.1)	350	(92.8)	487	(14.0)	2,296	(30.1)
Ex-US	30	(7.9)	27	(7.2)	2,986	(86.0)	5,335	(69.9)
North America	376	(98.4)	371	(98.4)	665	(19.1)	2,669	(35.0)
Western Europe	0	(0.0)	0	(0.0)	1,161	(33.4)	2,856	(37.4)
Rest of the World	6	(1.6)	6	(1.6)	1,647	(47.4)	2,106	(27.6)

SD=Standard deviation.

Database cutoff date for KEYNOTE-868: 16 December 2022 for dMMR participants and 06 December 2022 for pMMR participants.

Adverse events

Table 55: Adverse Event Summary (APaT Population)

	KN868 Pembrolizumab + Chemotherapy		KN868 Placebo + Chemotherapy		Pooled Safety Dataset for Pembrolizumab + Chemotherapy		Pembrolizumab Monotherapy Reference Safety Dataset	
	n	(%)	n	(%)	n	(%)	n	(%)
Participants in population	382		377		3,473		7,631	
with one or more adverse events	376	(98.4)	375	(99.5)	3,444	(99.2)	7,375	(96.6)
with no adverse event	6	(1.6)	2	(0.5)	29	(0.8)	256	(3.4)
with drug-related[a] adverse events	365	(95.5)	358	(95.0)	3,361	(96.8)	5,462	(71.6)
with toxicity grade 3-5 adverse events	225	(58.9)	174	(46.2)	2,727	(78.5)	3,514	(46.0)
with toxicity grade 3-5 drug-related adverse events	172	(45.0)	120	(31.8)	2,303	(66.3)	1,208	(15.8)
with serious adverse events	132	(34.6)	73	(19.4)	1,613	(46.4)	2,742	(35.9)
with serious drug-related adverse events	82	(21.5)	43	(11.4)	998	(28.7)	840	(11.0)
who died	6	(1.6)	4	(1.1)	182	(5.2)	346	(4.5)
who died due to a drug-related adverse event	1	(0.3)	2	(0.5)	53	(1.5)	42	(0.6)

[a] Determined by the investigator to be related to the drug.

Non-serious adverse events up to 30 days of last dose and serious adverse events up to 90 days of last dose are included.

MedDRA preferred terms "Neoplasm Progression", "Malignant Neoplasm Progression" and "Disease Progression" not related to the drug are excluded.

For KN868, reporting of unrelated serious adverse events between 30 and 90 days of last dose are not required.

For KN868, grades are based on NCI CTCAE version 5.0.

Database cutoff date for KN868: 16DEC2022 for dMMR participants and 06DEC2022 for pMMR participants.

The list of studies and database cutoff dates for the aggregate safety datasets within this table are provided in the appendix of Module 2.7.4.

Table 56: Exposure-Adjusted Adverse Event Summary (Including Multiple Occurrences of Events) (APaT Population)

	Event Count and Rate (Events/100 person-months)[a]							
	KN868 Pembrolizumab + Chemotherapy		KN868 Placebo + Chemotherapy		Pooled Safety Dataset for Pembrolizumab + Chemotherapy		Pembrolizumab Monotherapy Reference Safety Dataset	
Number of participants exposed	382		377		3,473		7,631	
Total exposure[b] in person-months	2942.53		2352.59		38439.25		66840.89	
Total events (rate)								
adverse events	7,685	(261.17)	5,951	(252.96)	72,863	(189.55)	76,878	(115.02)
drug-related[c] adverse events	4,452	(151.30)	3,440	(146.22)	44,254	(115.13)	24,542	(36.72)
toxicity grade 3-5 adverse events	744	(25.28)	452	(19.21)	10,285	(26.76)	7,463	(11.17)
toxicity grade 3-5 drug-related adverse events	442	(15.02)	268	(11.39)	7,311	(19.02)	1,770	(2.65)
serious adverse events	314	(10.67)	167	(7.10)	3,215	(8.36)	4,801	(7.18)
serious drug-related adverse events	159	(5.40)	88	(3.74)	1,622	(4.22)	1,093	(1.64)
adverse events leading to death	6	(0.20)	4	(0.17)	188	(0.49)	353	(0.53)
drug-related adverse events leading to death	1	(0.03)	2	(0.09)	54	(0.14)	42	(0.06)
adverse events resulting in drug discontinuation	0	(0.00)	0	(0.00)	1,285	(3.34)	1,165	(1.74)
drug-related adverse events resulting in drug discontinuation	0	(0.00)	0	(0.00)	1,067	(2.78)	703	(1.05)
serious adverse events resulting in drug discontinuation	0	(0.00)	0	(0.00)	584	(1.52)	753	(1.13)
serious drug-related adverse events resulting in drug discontinuation	0	(0.00)	0	(0.00)	420	(1.09)	363	(0.54)

[a] Event rate per 100 person-months of exposure = event count *100/person-months of exposure.
[b] Drug exposure is defined as the interval between the first dose date + 1 day and the earlier of the last dose date +30 or the cutoff date.
[c] Determined by the investigator to be related to the drug.
For KN868, grades are based on NCI CTCAE version 5.0.
Non-serious adverse events up to 30 days of last dose and serious adverse events up to 90 days of last dose are included.
MedDRA preferred terms "Neoplasm Progression", "Malignant Neoplasm Progression" and "Disease Progression" not related to the drug are excluded.
For KN001 and KN054, a new AE episode was recorded when there was any AE change in grade, relationship, or seriousness. If the episode date ranges were continuous, then these records were counted as one AE episode.
Database cutoff date for KN868: 16DEC2022 for dMMR participants and 06DEC2022 for pMMR participants.
The list of studies and database cutoff dates for the aggregate safety datasets within this table are provided in the appendix of Module 2.7.4.

Most Frequently Reported Adverse Events

Table 57: Participants With Adverse Events by Decreasing Frequency of Preferred Term (Incidence ≥ 10% in One or More Treatment Groups) (APaT Population)

	Pembrolizumab + Chemotherapy		Placebo + Chemotherapy		Pooled Safety Dataset for Pembrolizumab + Chemotherapy		Pembrolizumab Monotherapy Reference Safety Dataset	
	n	(%)	n	(%)	n	(%)	n	(%)
Participants in population	382		377		3,473		7,631	
with one or more adverse events	376	(98.4)	375	(99.5)	3,444	(99.2)	7,375	(96.6)
with no adverse events	6	(1.6)	2	(0.5)	29	(0.8)	256	(3.4)
Fatigue	257	(67.3)	226	(59.9)	1,278	(36.8)	2,368	(31.0)
Anaemia	212	(55.5)	205	(54.4)	1,861	(53.6)	982	(12.9)
Alopecia	207	(54.2)	213	(56.5)	1,107	(31.9)	118	(1.5)
Nausea	183	(47.9)	165	(43.8)	1,863	(53.6)	1,534	(20.1)
Constipation	175	(45.8)	154	(40.8)	1,166	(33.6)	1,179	(15.5)
Diarrhoea	148	(38.7)	129	(34.2)	1,254	(36.1)	1,678	(22.0)
Peripheral sensory neuropathy	138	(36.1)	145	(38.5)	478	(13.8)	83	(1.1)
Neuropathy peripheral	122	(31.9)	108	(28.6)	530	(15.3)	146	(1.9)
White blood cell count decreased	119	(31.2)	126	(33.4)	519	(14.9)	70	(0.9)
Arthralgia	114	(29.8)	133	(35.3)	683	(19.7)	1,436	(18.8)
Platelet count decreased	113	(29.6)	89	(23.6)	472	(13.6)	95	(1.2)
Neutrophil count decreased	99	(25.9)	100	(26.5)	717	(20.6)	53	(0.7)
Dyspnoea	87	(22.8)	65	(17.2)	440	(12.7)	1,130	(14.8)
Decreased appetite	82	(21.5)	81	(21.5)	960	(27.6)	1,312	(17.2)
Hyperglycaemia	82	(21.5)	67	(17.8)	192	(5.5)	360	(4.7)
Lymphocyte count decreased	80	(20.9)	71	(18.8)	148	(4.3)	130	(1.7)
Vomiting	76	(19.9)	48	(12.7)	998	(28.7)	945	(12.4)
Myalgia	74	(19.4)	64	(17.0)	373	(10.7)	575	(7.5)
Hypomagnesaemia	71	(18.6)	60	(15.9)	260	(7.5)	184	(2.4)
Blood creatinine increased	68	(17.8)	30	(8.0)	330	(9.5)	358	(4.7)

Headache	66	(17.3)	48	(12.7)	591	(17.0)	946	(12.4)
Dizziness	63	(16.5)	57	(15.1)	382	(11.0)	564	(7.4)
Pruritus	62	(16.2)	42	(11.1)	496	(14.3)	1,435	(18.8)
Abdominal pain	58	(15.2)	52	(13.8)	361	(10.4)	671	(8.8)
Alanine aminotransferase increased	58	(15.2)	39	(10.3)	627	(18.1)	572	(7.5)
Pain in extremity	58	(15.2)	44	(11.7)	296	(8.5)	506	(6.6)
Cough	56	(14.7)	50	(13.3)	688	(19.8)	1,392	(18.2)
Rash	56	(14.7)	36	(9.5)	672	(19.3)	1,175	(15.4)
Infusion related reaction	54	(14.1)	51	(13.5)	163	(4.7)	75	(1.0)
Hypertension	53	(13.9)	59	(15.6)	237	(6.8)	416	(5.5)
Urinary tract infection	53	(13.9)	41	(10.9)	355	(10.2)	511	(6.7)
Hyponatraemia	52	(13.6)	33	(8.8)	245	(7.1)	387	(5.1)
Rash maculo-papular	50	(13.1)	19	(5.0)	170	(4.9)	295	(3.9)
Aspartate aminotransferase increased	49	(12.8)	26	(6.9)	575	(16.6)	538	(7.1)
Blood alkaline phosphatase increased	49	(12.8)	46	(12.2)	194	(5.6)	322	(4.2)
Hypokalaemia	49	(12.8)	69	(18.3)	389	(11.2)	324	(4.2)
Hypothyroidism	47	(12.3)	14	(3.7)	471	(13.6)	937	(12.3)
Insomnia	47	(12.3)	39	(10.3)	421	(12.1)	528	(6.9)
	n	(%)	n	(%)	n	(%)	n	(%)
Hypoalbuminaemia	46	(12.0)	33	(8.8)	206	(5.9)	209	(2.7)
Oedema peripheral	46	(12.0)	38	(10.1)	375	(10.8)	630	(8.3)
Back pain	41	(10.7)	44	(11.7)	386	(11.1)	847	(11.1)
Anxiety	40	(10.5)	31	(8.2)	171	(4.9)	296	(3.9)
Paraesthesia	39	(10.2)	37	(9.8)	215	(6.2)	217	(2.8)
Dysgeusia	36	(9.4)	42	(11.1)	345	(9.9)	150	(2.0)
Weight decreased	36	(9.4)	31	(8.2)	438	(12.6)	628	(8.2)
Stomatitis	34	(8.9)	19	(5.0)	489	(14.1)	201	(2.6)
Pyrexia	30	(7.9)	10	(2.7)	683	(19.7)	934	(12.2)
Neutropenia	22	(5.8)	22	(5.8)	1,170	(33.7)	82	(1.1)
Asthenia	16	(4.2)	16	(4.2)	708	(20.4)	880	(11.5)
Thrombocytopenia	15	(3.9)	13	(3.4)	615	(17.7)	117	(1.5)
Mucosal inflammation	11	(2.9)	7	(1.9)	390	(11.2)	111	(1.5)
Leukopenia	3	(0.8)	3	(0.8)	379	(10.9)	52	(0.7)

Every participant is counted a single time for each applicable row and column.

A specific adverse event appears on this report only if its incidence in one or more of the columns meets the incidence criterion in the report title, after rounding.

Non-serious adverse events up to 30 days of last dose and serious adverse events up to 90 days of last dose are included.

For KEYNOTE-868, reporting of unrelated serious adverse events between 30 and 90 days of last dose are not required.

MedDRA preferred terms "Neoplasm Progression", "Malignant Neoplasm Progression" and "Disease Progression" not related to the drug are excluded.

Database cutoff date for KEYNOTE-868: 16 December 2022 for dMMR participants and 06 December 2022 for pMMR participants.

Drug-related Adverse Events

Table 58: Participants With Drug-Related Adverse Events by Decreasing Frequency of Preferred Term (Incidence ≥ 5% in One or More Treatment Groups) (APaT Population)

	Pembrolizumab + Chemotherapy		Placebo + Chemotherapy		Pooled Safety Dataset for Pembrolizumab + Chemotherapy		Pembrolizumab Monotherapy Reference Safety Dataset	
	n	(%)	n	(%)	n	(%)	n	(%)
Participants in population	382		377		3,473		7,631	
with one or more adverse events	365	(95.5)	358	(95.0)	3,361	(96.8)	5,462	(71.6)

with no adverse events	17	(4.5)	19	(5.0)	112	(3.2)	2,169	(28.4)
Fatigue	225	(58.9)	197	(52.3)	1,108	(31.9)	1,476	(19.3)
Anaemia	178	(46.6)	162	(43.0)	1,574	(45.3)	234	(3.1)
Alopecia	163	(42.7)	167	(44.3)	1,078	(31.0)	57	(0.7)
Nausea	146	(38.2)	129	(34.2)	1,667	(48.0)	675	(8.8)
Peripheral sensory neuropathy	117	(30.6)	113	(30.0)	455	(13.1)	35	(0.5)
Constipation	112	(29.3)	90	(23.9)	532	(15.3)	184	(2.4)
Diarrhoea	110	(28.8)	103	(27.3)	910	(26.2)	904	(11.8)
Neuropathy peripheral	98	(25.7)	86	(22.8)	469	(13.5)	54	(0.7)
White blood cell count decreased	97	(25.4)	107	(28.4)	495	(14.3)	34	(0.4)
Platelet count decreased	93	(24.3)	77	(20.4)	452	(13.0)	43	(0.6)
Neutrophil count decreased	87	(22.8)	81	(21.5)	695	(20.0)	34	(0.4)
Arthralgia	80	(20.9)	97	(25.7)	322	(9.3)	661	(8.7)
Decreased appetite	66	(17.3)	65	(17.2)	752	(21.7)	525	(6.9)
Lymphocyte count decreased	62	(16.2)	60	(15.9)	123	(3.5)	64	(0.8)
Myalgia	61	(16.0)	52	(13.8)	277	(8.0)	312	(4.1)
Vomiting	48	(12.6)	37	(9.8)	781	(22.5)	248	(3.2)
Pruritus	47	(12.3)	34	(9.0)	372	(10.7)	1,143	(15.0)
Rash	44	(11.5)	25	(6.6)	516	(14.9)	884	(11.6)
Rash maculo-papular	43	(11.3)	17	(4.5)	148	(4.3)	237	(3.1)
Alanine aminotransferase increased	42	(11.0)	31	(8.2)	505	(14.5)	336	(4.4)
Infusion related reaction	42	(11.0)	43	(11.4)	154	(4.4)	73	(1.0)
Hypomagnesaemia	41	(10.7)	34	(9.0)	154	(4.4)	37	(0.5)
Hypothyroidism	41	(10.7)	11	(2.9)	406	(11.7)	810	(10.6)
Aspartate aminotransferase increased	40	(10.5)	18	(4.8)	452	(13.0)	312	(4.1)
Blood creatinine increased	39	(10.2)	12	(3.2)	232	(6.7)	105	(1.4)
Pain in extremity	37	(9.7)	26	(6.9)	100	(2.9)	90	(1.2)
Blood alkaline phosphatase increased	35	(9.2)	33	(8.8)	114	(3.3)	118	(1.5)
Dyspnoea	34	(8.9)	28	(7.4)	119	(3.4)	232	(3.0)
Headache	32	(8.4)	22	(5.8)	195	(5.6)	250	(3.3)
Hyponatraemia	32	(8.4)	14	(3.7)	117	(3.4)	63	(0.8)
Hypokalaemia	31	(8.1)	39	(10.3)	150	(4.3)	43	(0.6)
Stomatitis	31	(8.1)	15	(4.0)	444	(12.8)	103	(1.3)
Dizziness	30	(7.9)	28	(7.4)	137	(3.9)	120	(1.6)
Paraesthesia	27	(7.1)	27	(7.2)	165	(4.8)	63	(0.8)
Dysgeusia	26	(6.8)	29	(7.7)	309	(8.9)	79	(1.0)
Bone pain	25	(6.5)	26	(6.9)	55	(1.6)	28	(0.4)
Muscular weakness	25	(6.5)	20	(5.3)	38	(1.1)	55	(0.7)

Grade 3 to 5 Adverse Events

Table 59: Participants With Grade 3-5 Adverse Events by Decreasing Frequency of Preferred Term (Incidence ≥ 5% in One or More Treatment Groups) (APaT Population)

	Pembrolizumab + Chemotherapy		Placebo + Chemotherapy		Pooled Safety Dataset for Pembrolizumab + Chemotherapy		Pembrolizumab Monotherapy Reference Safety Dataset	
	n	(%)	n	(%)	n	(%)	n	(%)
Participants in population	382		377		3,473		7,631	
with one or more adverse events	225	(58.9)	174	(46.2)	2,727	(78.5)	3,514	(46.0)
with no adverse events	157	(41.1)	203	(53.8)	746	(21.5)	4,117	(54.0)
Anaemia	59	(15.4)	38	(10.1)	664	(19.1)	275	(3.6)
Neutrophil count decreased	51	(13.4)	49	(13.0)	472	(13.6)	10	(0.1)

White blood cell count decreased	33	(8.6)	29	(7.7)	223	(6.4)	5	(0.1)
Lymphocyte count decreased	23	(6.0)	17	(4.5)	64	(1.8)	33	(0.4)
Hypertension	18	(4.7)	20	(5.3)	98	(2.8)	148	(1.9)
Neutropenia	15	(3.9)	10	(2.7)	750	(21.6)	21	(0.3)
Febrile neutropenia	13	(3.4)	4	(1.1)	261	(7.5)	11	(0.1)
Fatigue	5	(1.3)	10	(2.7)	174	(5.0)	166	(2.2)
Thrombocytopenia	2	(0.5)	2	(0.5)	214	(6.2)	23	(0.3)

Every participant is counted a single time for each applicable row and column.

A specific adverse event appears on this report only if its incidence in one or more of the columns meets the incidence criterion in the report title, after rounding.

For KEYNOTE-868, grades are based on NCI CTCAE version 5.0.

Non-serious adverse events up to 30 days of last dose and serious adverse events up to 90 days of last dose are included.

For KEYNOTE-868, reporting of unrelated serious adverse events between 30 and 90 days of last dose are not required.

Database cutoff date for KEYNOTE-868: 16 December 2022 for dMMR participants and 06 December 2022 for pMMR participants.

Table 60: Exposure-Adjusted Grade 3-5 Adverse Events by System Organ Class and Preferred Term (Including Multiple Occurrences of Events) (Incidence ≥ 5% in One or More Treatment Groups) (APaT Population)

	Event Count and Rate (Events/100 person-months)[a]			
	KN868 Pembrolizumab + Chemotherapy	KN868 Placebo + Chemotherapy	Pooled Safety Dataset for Pembrolizumab + Chemotherapy	Pembrolizumab Monotherapy Reference Safety Dataset
Participants in population	382	377	3,473	7,631
Total exposure[b] in person-months	2945.9	2354.9	38439.3	66840.9
Total events (rate)	744 (25.3)	452 (19.2)	10,285 (26.8)	7,463 (11.2)
AE category				
Blood and lymphatic system disorders	**135 (4.6)**	**68 (2.9)**	**3,220 (8.4)**	**445 (0.7)**
Anaemia	78 (2.6)	48 (2.0)	785 (2.0)	303 (0.5)
Febrile neutropenia	15 (0.5)	4 (0.2)	294 (0.8)	11 (0.0)
Neutropenia	31 (1.1)	12 (0.5)	1,476 (3.8)	24 (0.0)
Thrombocytopenia	2 (0.1)	3 (0.1)	306 (0.8)	25 (0.0)
Gastrointestinal disorders	**46 (1.6)**	**31 (1.3)**	**848 (2.2)**	**771 (1.2)**
General disorders and administration site conditions	**17 (0.6)**	**14 (0.6)**	**551 (1.4)**	**534 (0.8)**
Fatigue	5 (0.2)	10 (0.4)	208 (0.5)	168 (0.3)
Infections and infestations	**60 (2.0)**	**29 (1.2)**	**733 (1.9)**	**1,032 (1.5)**
Investigations	**226 (7.7)**	**150 (6.4)**	**2,291 (6.0)**	**700 (1.0)**
Lymphocyte count decreased	36 (1.2)	21 (0.9)	94 (0.2)	38 (0.1)
Neutrophil count decreased	83 (2.8)	75 (3.2)	1,052 (2.7)	16 (0.0)
White blood cell count decreased	47 (1.6)	34 (1.4)	426 (1.1)	5 (0.0)
Metabolism and nutrition disorders	**52 (1.8)**	**39 (1.7)**	**723 (1.9)**	**912 (1.4)**
Nervous system disorders	**42 (1.4)**	**23 (1.0)**	**297 (0.8)**	**274 (0.4)**
Respiratory, thoracic and mediastinal disorders	**30 (1.0)**	**15 (0.6)**	**312 (0.8)**	**731 (1.1)**
Vascular disorders	**36 (1.2)**	**26 (1.1)**	**230 (0.6)**	**310 (0.5)**
Vascular disorders	**36 (1.2)**	**26 (1.1)**	**230 (0.6)**	**310 (0.5)**
Hypertension	23 (0.8)	20 (0.8)	120 (0.3)	168 (0.3)

Table 61: Participants With Grade 3-5 Drug-Related Adverse Events by Decreasing Frequency of Preferred Term (Incidence ≥ 1% in One or More Treatment Groups) (APaT Population)

	Pembrolizumab	Placebo +	Pooled Safety	Pembrolizumab

	+ Chemotherapy		Chemotherapy		Dataset for Pembrolizumab + Chemotherapy		Monotherapy Reference Safety Dataset	
	n	(%)	n	(%)	n	(%)	n	(%)
Participants in population	382		377		3,473		7,631	
with one or more adverse events	172	(45.0)	120	(31.8)	2,303	(66.3)	1,208	(15.8)
with no adverse events	210	(55.0)	257	(68.2)	1,170	(33.7)	6,423	(84.2)
Anaemia	53	(13.9)	29	(7.7)	545	(15.7)	33	(0.4)
Neutrophil count decreased	42	(11.0)	39	(10.3)	456	(13.1)	6	(0.1)
White blood cell count decreased	26	(6.8)	23	(6.1)	214	(6.2)	2	(0.0)
Lymphocyte count decreased	15	(3.9)	13	(3.4)	53	(1.5)	9	(0.1)
Platelet count decreased	14	(3.7)	7	(1.9)	132	(3.8)	2	(0.0)
Neutropenia	12	(3.1)	8	(2.1)	732	(21.1)	13	(0.2)
Hyperglycaemia	7	(1.8)	0	(0.0)	12	(0.3)	20	(0.3)
Urinary tract infection	7	(1.8)	0	(0.0)	9	(0.3)	0	(0.0)
Aspartate aminotransferase increased	6	(1.6)	0	(0.0)	69	(2.0)	47	(0.6)
Febrile neutropenia	6	(1.6)	3	(0.8)	246	(7.1)	0	(0.0)
Rash maculo-papular	6	(1.6)	2	(0.5)	32	(0.9)	21	(0.3)
Diarrhoea	5	(1.3)	4	(1.1)	105	(3.0)	75	(1.0)
Fatigue	5	(1.3)	7	(1.9)	145	(4.2)	75	(1.0)
Acute kidney injury	4	(1.0)	2	(0.5)	40	(1.2)	16	(0.2)
Hypertension	4	(1.0)	6	(1.6)	34	(1.0)	15	(0.2)
Hyponatraemia	4	(1.0)	1	(0.3)	56	(1.6)	32	(0.4)
Nausea	4	(1.0)	4	(1.1)	110	(3.2)	13	(0.2)
Peripheral sensory neuropathy	4	(1.0)	2	(0.5)	39	(1.1)	2	(0.0)
Alanine aminotransferase increased	3	(0.8)	2	(0.5)	99	(2.9)	56	(0.7)
Hypokalaemia	3	(0.8)	11	(2.9)	52	(1.5)	12	(0.2)
Infusion related reaction	3	(0.8)	5	(1.3)	21	(0.6)	1	(0.0)
Neuropathy peripheral	3	(0.8)	0	(0.0)	41	(1.2)	2	(0.0)
Asthenia	2	(0.5)	1	(0.3)	89	(2.6)	26	(0.3)
Leukopenia	2	(0.5)	0	(0.0)	144	(4.1)	3	(0.0)
Myalgia	2	(0.5)	4	(1.1)	9	(0.3)	10	(0.1)
Pneumonia	2	(0.5)	0	(0.0)	42	(1.2)	17	(0.2)
Pneumonitis	2	(0.5)	0	(0.0)	47	(1.4)	91	(1.2)
Stomatitis	2	(0.5)	0	(0.0)	64	(1.8)	5	(0.1)
Syncope	2	(0.5)	5	(1.3)	12	(0.3)	2	(0.0)
Thrombocytopenia	2	(0.5)	1	(0.3)	196	(5.6)	11	(0.1)
Vomiting	2	(0.5)	4	(1.1)	91	(2.6)	12	(0.2)
Decreased appetite	1	(0.3)	2	(0.5)	60	(1.7)	23	(0.3)
Dehydration	1	(0.3)	4	(1.1)	21	(0.6)	9	(0.1)
Mucosal inflammation	1	(0.3)	0	(0.0)	56	(1.6)	6	(0.1)
Pulmonary embolism	1	(0.3)	4	(1.1)	24	(0.7)	10	(0.1)

Every participant is counted a single time for each applicable row and column.

A specific adverse event appears on this report only if its incidence in one or more of the columns meets the incidence criterion in the report title, after rounding.

For KEYNOTE-868, grades are based on NCI CTCAE version 5.0.

Non-serious adverse events up to 30 days of last dose and serious adverse events up to 90 days of last dose are included.

For KEYNOTE-868, reporting of unrelated serious adverse events between 30 and 90 days of last dose are not required.

Database cutoff date for KEYNOTE-868: 16 December 2022 for dMMR participants and 06 December 2022 for pMMR participants.

Serious adverse event/deaths/other significant events

Death

Of the **6 participants** in the pembrolizumab plus chemotherapy group with a fatal AE, **1 AE was related** to study treatment as assessed by the investigator (cardiac arrest).

Table 62: Participants With Adverse Events Resulting in Death Up to 90 Days of Last Dose by Decreasing Frequency of Preferred Term (at least one case in KEYNOTE-868 Treatment Groups) (APaT Population)

	KN868 Pembrolizumab + Chemotherapy		KN868 Placebo + Chemotherapy		Pooled Safety Dataset for Pembrolizumab + Chemotherapy		Pembrolizumab Monotherapy Reference Safety Dataset	
	n	(%)	n	(%)	n	(%)	n	(%)
Participants in population	382		377		3,473		7,631	
with one or more adverse events	6	(1.6)	4	(1.1)	182	(5.2)	346	(4.5)
with no adverse events	376	(98.4)	373	(98.9)	3,291	(94.8)	7,285	(95.5)
COVID-19	2	(0.5)	0	(0.0)	3	(0.1)	0	(0.0)
Death	2	(0.5)	0	(0.0)	20	(0.6)	49	(0.6)
Cardiac arrest	1	(0.3)	0	(0.0)	10	(0.3)	9	(0.1)
Small intestinal obstruction	1	(0.3)	0	(0.0)	0	(0.0)	0	(0.0)
Lower gastrointestinal haemorrhage	0	(0.0)	1	(0.3)	0	(0.0)	0	(0.0)
Sepsis	0	(0.0)	2	(0.5)	10	(0.3)	11	(0.1)
Septic shock	0	(0.0)	1	(0.3)	8	(0.2)	11	(0.1)

Every participant is counted a single time for each applicable row and column.
A specific adverse event appears on this report only if its incidence in one or more of th columns meets the incidence criterion in the report title, after rounding.
Non-serious adverse events up to 30 days of last dose and serious adverse events up to 90 days of last dose are included.
For KN868, reporting of unrelated serious adverse events between 30 and 90 days of last dose are not required.
MedDRA preferred terms "Neoplasm Progression", "Malignant Neoplasm Progression" and "Disease Progression" not related to the drug are excluded.
Database cutoff date for KN868: 16DEC2022 for dMMR participants and 06DEC2022 for pMMR participants.
The list of studies and database cutoff dates for the aggregate safety datasets within this table are provided in the appendix of Module 2.7.4.

Death events occurred in each of the population pMMR and dMMR of study KEYNOTE-868 are reported separately in the tables below:

Table 63: Participants With Adverse Events Resulting in Death (Incidence > 0% in One or More Treatment Groups) in pMMR Participants (APaT Population)

	Paclitaxel + Carboplatin + Pembrolizumab		Paclitaxel + Carboplatin + Placebo	
	n	(%)	n	(%)
Participants in population	275		272	
with one or more adverse events	5	(1.8)	2	(0.7)
with no adverse events	270	(98.2)	270	(99.3)
Cardiac disorders	**1**	**(0.4)**	**0**	**(0.0)**
Cardiac arrest	1	(0.4)	0	(0.0)
Gastrointestinal disorders	**1**	**(0.4)**	**0**	**(0.0)**
Small intestinal obstruction	1	(0.4)	0	(0.0)
General disorders and administration site conditions	**1**	**(0.4)**	**0**	**(0.0)**
Death	1	(0.4)	0	(0.0)
Infections and infestations	**2**	**(0.7)**	**2**	**(0.7)**
COVID-19	2	(0.7)	0	(0.0)
Sepsis	0	(0.0)	2	(0.7)

Every participant is counted a single time for each applicable row and column.
Serious adverse events up to 90 days of last treatment are included.
MedDRA V26.0 preferred terms "Neoplasm progression", "Malignant neoplasm progression" and "Disease progression" not related to the drug are excluded.
Reporting of unrelated serious adverse events between 30 and 90 days of last dose are not required.
Database Cutoff Date: 16DEC2022 for dMMR participants and 06DEC2022 for pMMR participants.

Table 64: Participants With Drug-related Adverse Events Resulting in Death (Incidence > 0% in One or More Treatment Groups) in pMMR Participants (APaT Population)

	Paclitaxel + Carboplatin + Pembrolizumab		Paclitaxel + Carboplatin + Placebo	
	n	(%)	n	(%)
Participants in population	275		272	
with one or more adverse events	1	(0.4)	1	(0.4)
with no adverse events	274	(99.6)	271	(99.6)
Cardiac disorders	**1**	**(0.4)**	**0**	**(0.0)**
Cardiac arrest	1	(0.4)	0	(0.0)
Infections and infestations	**0**	**(0.0)**	**1**	**(0.4)**
Sepsis	0	(0.0)	1	(0.4)

Every participant is counted a single time for each applicable row and column.
Serious adverse events up to 90 days of last treatment are included.
Database Cutoff Date: 16DEC2022 for dMMR participants and 06DEC2022 for pMMR participants.

Table 65: Participants With Adverse Events Resulting in Death (Incidence > 0% in One or More Treatment Groups) in dMMR Participants (APaT Population)

	Paclitaxel + Carboplatin + Pembrolizumab		Paclitaxel + Carboplatin + Placebo	
	n	(%)	n	(%)
Participants in population	107		105	
with one or more adverse events	1	(0.9)	2	(1.9)
with no adverse events	106	(99.1)	103	(98.1)
Gastrointestinal disorders	**0**	**(0.0)**	**1**	**(1.0)**
Lower gastrointestinal haemorrhage	0	(0.0)	1	(1.0)
General disorders and administration site conditions	**1**	**(0.9)**	**0**	**(0.0)**
Death	1	(0.9)	0	(0.0)
Infections and infestations	**0**	**(0.0)**	**1**	**(1.0)**
Septic shock	0	(0.0)	1	(1.0)

Every participant is counted a single time for each applicable row and column.
Serious adverse events up to 90 days of last treatment are included.
MedDRA V26.0 preferred terms "Neoplasm progression", "Malignant neoplasm progression" and "Disease progression" not related to the drug are excluded.
Reporting of unrelated serious adverse events between 30 and 90 days of last dose are not required.
Database Cutoff Date: 16DEC2022 for dMMR participants and 06DEC2022 for pMMR participants.

Table 66: Participants With Drug-related Adverse Events Resulting in Death (Incidence > 0% in One or More Treatment Groups) in dMMR Participants (APaT Population)

	Paclitaxel + Carboplatin + Pembrolizumab		Paclitaxel + Carboplatin + Placebo	
	n	(%)	n	(%)
Participants in population	107		105	
with one or more adverse events	0	(0.0)	1	(1.0)
with no adverse events	107	(100.0)	104	(99.0)
Infections and infestations	**0**	**(0.0)**	**1**	**(1.0)**
Septic shock	0	(0.0)	1	(1.0)

Every participant is counted a single time for each applicable row and column.
Serious adverse events up to 90 days of last treatment are included.
Database Cutoff Date: 16DEC2022 for dMMR participants and 06DEC2022 for pMMR participants.

Overall, 6 participants in the pembrolizumab plus chemotherapy group had a **fatal AE** (5 in pMMR group and 1 in dMMR group) of which 1 AE occurred in pMMR group was considered related to study treatment as assessed by the investigator (cardiac arrest). The other fatal events were due to COVID-19 in two

cases, small intestine obstruction in 1 case and due to not specified reasons in 2 cases. No new safety concerns were identified.

Updated safety data (DCO of 18 August 2023) showed that a total of 10 participants with a fatal AE in the pembrolizumab plus chemotherapy group (4 additional deaths from previous IA) have been reported, of which 3 are considered related (2 due to cardiac arrest and 1 due to sepsis) (see tables below).

Table 67: Participants With Adverse Events Resulting in Death (Incidence > 0% in One or More Treatment Groups) in Combined dMMR and pMMR Participants (APaT Population)

	Paclitaxel + Carboplatin + Pembrolizumab		Paclitaxel + Carboplatin + Placebo	
	n	(%)	n	(%)
Participants in population	391		388	
with one or more adverse events	10	(2.6)	4	(1.0)
with no adverse events	381	(97.4)	384	(99.0)
Cardiac disorders	**3**	**(0.8)**	**0**	**(0.0)**
Cardiac arrest	3	(0.8)	0	(0.0)
Gastrointestinal disorders	**2**	**(0.5)**	**1**	**(0.3)**
Lower gastrointestinal haemorrhage	0	(0.0)	1	(0.3)
Malignant gastrointestinal obstruction	1	(0.3)	0	(0.0)
Small intestinal obstruction	1	(0.3)	0	(0.0)
General disorders and administration site conditions	**2**	**(0.5)**	**0**	**(0.0)**
Death	2	(0.5)	0	(0.0)
Infections and infestations	**3**	**(0.8)**	**3**	**(0.8)**
COVID-19	2	(0.5)	0	(0.0)
Sepsis	1	(0.3)	2	(0.5)
Septic shock	0	(0.0)	1	(0.3)

Every participant is counted a single time for each applicable row and column.
Serious adverse events up to 90 days of last treatment are included.
MedDRA V26.1 preferred terms "Neoplasm progression", "Malignant neoplasm progression" and "Disease progression" not related to the drug are excluded.
Reporting of unrelated serious adverse events between 30 and 90 days of last dose are not required.
Database Cutoff Date: 18AUG2023.

Table 68: Participants With Drug-Related Adverse Events Resulting in Death (Incidence > 0% in One or More Treatment Groups) in Combined dMMR and pMMR Participants (APaT Population)

	Paclitaxel + Carboplatin + Pembrolizumab		Paclitaxel + Carboplatin + Placebo	
	n	(%)	n	(%)
Participants in population	391		388	
with one or more adverse events	3	(0.8)	2	(0.5)
with no adverse events	388	(99.2)	386	(99.5)
Cardiac disorders	**2**	**(0.5)**	**0**	**(0.0)**
Cardiac arrest	2	(0.5)	0	(0.0)
Infections and infestations	**1**	**(0.3)**	**2**	**(0.5)**
Sepsis	1	(0.3)	1	(0.3)
Septic shock	0	(0.0)	1	(0.3)

Every participant is counted a single time for each applicable row and column.
Serious adverse events up to 90 days of last treatment are included.
Database Cutoff Date: 18AUG2023.

Serious adverse events

Table 69: Participants With Serious Adverse Events Up to 90 Days of Last Dose by Decreasing Frequency of Preferred Term (Incidence ≥ 1% in One or More Treatment Groups) (APaT Population)

	Pembrolizumab + Chemotherapy		Placebo + Chemotherapy		Pooled Safety Dataset for Pembrolizumab + Chemotherapy		Pembrolizumab Monotherapy Reference Safety Dataset	
	n	(%)	n	(%)	n	(%)	n	(%)
Participants in population	382		377		3,473		7,631	
with one or more adverse events	132	(34.6)	73	(19.4)	1,613	(46.4)	2,742	(35.9)
with no adverse events	250	(65.4)	304	(80.6)	1,860	(53.6)	4,889	(64.1)
Anaemia	16	(4.2)	13	(3.4)	90	(2.6)	65	(0.9)
Febrile neutropenia	11	(2.9)	5	(1.3)	218	(6.3)	8	(0.1)
Urinary tract infection	8	(2.1)	6	(1.6)	33	(1.0)	67	(0.9)
White blood cell count decreased	8	(2.1)	4	(1.1)	2	(0.1)	0	(0.0)
Dyspnoea	7	(1.8)	0	(0.0)	18	(0.5)	91	(1.2)
Hyperglycaemia	7	(1.8)	0	(0.0)	4	(0.1)	12	(0.2)
Neutrophil count decreased	7	(1.8)	7	(1.9)	12	(0.3)	1	(0.0)
Pulmonary embolism	7	(1.8)	8	(2.1)	53	(1.5)	78	(1.0)
Sepsis	7	(1.8)	5	(1.3)	46	(1.3)	56	(0.7)
COVID-19	6	(1.6)	0	(0.0)	7	(0.2)	0	(0.0)
Diarrhoea	6	(1.6)	3	(0.8)	64	(1.8)	70	(0.9)
Embolism	6	(1.6)	1	(0.3)	8	(0.2)	13	(0.2)
Hypokalaemia	6	(1.6)	2	(0.5)	21	(0.6)	9	(0.1)
Acute kidney injury	5	(1.3)	3	(0.8)	61	(1.8)	65	(0.9)
Nausea	5	(1.3)	2	(0.5)	32	(0.9)	30	(0.4)
Platelet count decreased	5	(1.3)	0	(0.0)	21	(0.6)	0	(0.0)
Pleural effusion	5	(1.3)	0	(0.0)	31	(0.9)	88	(1.2)
Pneumonia	5	(1.3)	2	(0.5)	163	(4.7)	272	(3.6)
Pyrexia	5	(1.3)	0	(0.0)	77	(2.2)	79	(1.0)
Seizure	5	(1.3)	1	(0.3)	10	(0.3)	15	(0.2)
Atrial fibrillation	4	(1.0)	3	(0.8)	15	(0.4)	28	(0.4)
Hyponatraemia	4	(1.0)	3	(0.8)	21	(0.6)	43	(0.6)
Hypotension	4	(1.0)	2	(0.5)	12	(0.3)	13	(0.2)
Neutropenia	4	(1.0)	3	(0.8)	50	(1.4)	3	(0.0)
Syncope	4	(1.0)	3	(0.8)	13	(0.4)	22	(0.3)
Dehydration	3	(0.8)	5	(1.3)	23	(0.7)	44	(0.6)
Vomiting	3	(0.8)	4	(1.1)	48	(1.4)	32	(0.4)
Abdominal pain	2	(0.5)	6	(1.6)	9	(0.3)	43	(0.6)
Infusion related reaction	1	(0.3)	4	(1.1)	18	(0.5)	5	(0.1)
Pneumonitis	1	(0.3)	0	(0.0)	61	(1.8)	136	(1.8)
Thrombocytopenia	0	(0.0)	0	(0.0)	44	(1.3)	10	(0.1)

Every participant is counted a single time for each applicable row and column.

A specific adverse event appears on this report only if its incidence in one or more of the columns meets the incidence criterion in the report title, after rounding.

Serious adverse events up to 90 days of last treatment are included.

For KEYNOTE-868, reporting of unrelated serious adverse events between 30 and 90 days of last dose are not required.

MedDRA preferred terms "Neoplasm Progression", "Malignant Neoplasm Progression" and "Disease Progression" not related to the drug are excluded.

Database cutoff date for KEYNOTE-868: 16 December 2022 for dMMR participants and 06 December 2022 for pMMR participants.

Table 70: Exposure-Adjusted Serious Adverse Events by System Organ Class and Preferred Term (Including Multiple Occurrences of Events) (Incidence ≥ 1% in One or More Treatment Groups) (APaT Population)

	Event Count and Rate (Events/100 person-months)[a]			
	KN868 Pembrolizumab + Chemotherapy	KN868 Placebo + Chemotherapy	Pooled Safety Dataset for Pembrolizumab + Chemotherapy	Pembrolizumab Monotherapy Reference Safety Dataset
Participants in population	382	377	3,473	7,631
Total exposure[b] in person-months	2945.9	2354.9	38439.3	66840.9
Total events (rate)	314 (10.7)	167 (7.1)	3,215 (8.4)	4,801 (7.2)
AE category				
Blood and lymphatic system disorders	**38 (1.3)**	**22 (0.9)**	**505 (1.3)**	**116 (0.2)**
Anaemia	17 (0.6)	14 (0.6)	97 (0.3)	68 (0.1)
Febrile neutropenia	13 (0.4)	5 (0.2)	238 (0.6)	8 (0.0)
Neutropenia	6 (0.2)	3 (0.1)	55 (0.1)	3 (0.0)
Thrombocytopenia	0 (0.0)	0 (0.0)	49 (0.1)	11 (0.0)
Cardiac disorders	**14 (0.5)**	**5 (0.2)**	**124 (0.3)**	**228 (0.3)**
Atrial fibrillation	4 (0.1)	3 (0.1)	16 (0.0)	30 (0.0)
Endocrine disorders	**2 (0.1)**	**0 (0.0)**	**56 (0.1)**	**98 (0.1)**
Gastrointestinal disorders	**39 (1.3)**	**26 (1.1)**	**439 (1.1)**	**584 (0.9)**
Abdominal pain	2 (0.1)	6 (0.3)	9 (0.0)	46 (0.1)
Diarrhoea	7 (0.2)	3 (0.1)	72 (0.2)	76 (0.1)
Nausea	5 (0.2)	2 (0.1)	33 (0.1)	32 (0.0)
Vomiting	4 (0.1)	4 (0.2)	59 (0.2)	32 (0.0)
General disorders and administration site conditions	**11 (0.4)**	**6 (0.3)**	**206 (0.5)**	**303 (0.5)**
Pyrexia	5 (0.2)	0 (0.0)	84 (0.2)	85 (0.1)
Hepatobiliary disorders	**1 (0.0)**	**0 (0.0)**	**69 (0.2)**	**96 (0.1)**
Immune system disorders	**4 (0.1)**	**1 (0.0)**	**24 (0.1)**	**30 (0.0)**
Infections and infestations	**39 (1.3)**	**21 (0.9)**	**648 (1.7)**	**950 (1.4)**
COVID-19	6 (0.2)	0 (0.0)	7 (0.0)	0 (0.0)
Pneumonia	5 (0.2)	2 (0.1)	174 (0.5)	296 (0.4)
Sepsis	7 (0.2)	5 (0.2)	49 (0.1)	60 (0.1)
Urinary tract infection	9 (0.3)	6 (0.3)	36 (0.1)	76 (0.1)
Injury, poisoning and procedural complications	**4 (0.1)**	**6 (0.3)**	**101 (0.3)**	**131 (0.2)**
Infusion related reaction	2 (0.1)	4 (0.2)	19 (0.0)	5 (0.0)
Investigations	**36 (1.2)**	**18 (0.8)**	**102 (0.3)**	**83 (0.1)**
Neutrophil count decreased	7 (0.2)	8 (0.3)	12 (0.0)	1 (0.0)
Platelet count decreased	5 (0.2)	0 (0.0)	22 (0.1)	0 (0.0)
White blood cell count decreased	8 (0.3)	5 (0.2)	2 (0.0)	0 (0.0)
Metabolism and nutrition disorders	**30 (1.0)**	**19 (0.8)**	**157 (0.4)**	**285 (0.4)**
Dehydration	4 (0.1)	6 (0.3)	25 (0.1)	46 (0.1)
Hyperglycaemia	7 (0.2)	0 (0.0)	4 (0.0)	12 (0.0)

Drug-related Serious Adverse Events

Table 71: Participants With Drug-Related Serious Adverse Events Up to 90 Days of Last Dose by Decreasing Frequency of Preferred Term (Incidence ≥ 1% in One or More Treatment Groups) (APaT Population)

	Pembrolizumab + Chemotherapy		Placebo + Chemotherapy		Pooled Safety Dataset for Pembrolizumab + Chemotherapy		Pembrolizumab Monotherapy Reference Safety Dataset	
	n	(%)	n	(%)	n	(%)	n	(%)
Participants in population	382		377		3,473		7,631	
with one or more adverse events	82	(21.5)	43	(11.4)	998	(28.7)	840	(11.0)
with no adverse events	300	(78.5)	334	(88.6)	2,475	(71.3)	6,791	(89.0)
Anaemia	13	(3.4)	9	(2.4)	69	(2.0)	6	(0.1)
Febrile neutropenia	6	(1.6)	4	(1.1)	209	(6.0)	0	(0.0)
Hyperglycaemia	6	(1.6)	0	(0.0)	2	(0.1)	4	(0.1)
Neutrophil count decreased	6	(1.6)	4	(1.1)	11	(0.3)	0	(0.0)

White blood cell count decreased	5	(1.3)	3	(0.8)	2	(0.1)	0	(0.0)
Diarrhoea	4	(1.0)	3	(0.8)	50	(1.4)	44	(0.6)
Hypokalaemia	4	(1.0)	2	(0.5)	12	(0.3)	3	(0.0)
Nausea	4	(1.0)	2	(0.5)	30	(0.9)	7	(0.1)
Neutropenia	4	(1.0)	3	(0.8)	46	(1.3)	1	(0.0)
Platelet count decreased	4	(1.0)	0	(0.0)	20	(0.6)	0	(0.0)
Acute kidney injury	3	(0.8)	1	(0.3)	40	(1.2)	19	(0.2)
Pyrexia	3	(0.8)	0	(0.0)	41	(1.2)	22	(0.3)
Dehydration	2	(0.5)	4	(1.1)	10	(0.3)	5	(0.1)
Vomiting	2	(0.5)	4	(1.1)	36	(1.0)	9	(0.1)
Pneumonia	1	(0.3)	0	(0.0)	45	(1.3)	19	(0.2)
Pneumonitis	1	(0.3)	0	(0.0)	55	(1.6)	129	(1.7)
Infusion related reaction	0	(0.0)	4	(1.1)	17	(0.5)	5	(0.1)
Thrombocytopenia	0	(0.0)	0	(0.0)	42	(1.2)	6	(0.1)

Every participant is counted a single time for each applicable row and column.

A specific adverse event appears on this report only if its incidence in one or more of the columns meets the incidence criterion in the report title, after rounding.

Serious adverse events up to 90 days of last treatment are included.

For KEYNOTE-868, reporting of unrelated serious adverse events between 30 and 90 days of last dose are not required.

Database cutoff date for KEYNOTE-868: 16 December 2022 for dMMR participants and 06 December 2022 for pMMR participants.

Adverse Event of Special Interest (AESI) for Pembrolizumab

Table 72: Adverse Event Summary for AESI (APaT Population)

	KN868 Pembrolizumab + Chemotherapy		KN868 Placebo + Chemotherapy		Pooled Safety Dataset for Pembrolizumab + Chemotherapy		Pembrolizumab Monotherapy Reference Safety Dataset	
	n	(%)	n	(%)	n	(%)	n	(%)
Participants in population	382		377		3,473		7,631	
with one or more adverse events	137	(35.9)	96	(25.5)	1,223	(35.2)	2,082	(27.3)
with no adverse event	245	(64.1)	281	(74.5)	2,250	(64.8)	5,549	(72.7)
with drug-related[a] adverse events	118	(30.9)	79	(21.0)	1,085	(31.2)	1,808	(23.7)
with toxicity grade 3-5 adverse events	33	(8.6)	16	(4.2)	367	(10.6)	534	(7.0)
with toxicity grade 3-5 drug-related adverse events	27	(7.1)	12	(3.2)	335	(9.6)	467	(6.1)
with serious adverse events	15	(3.9)	8	(2.1)	289	(8.3)	517	(6.8)
with serious drug-related adverse events	12	(3.1)	6	(1.6)	264	(7.6)	455	(6.0)
who died	0	(0.0)	0	(0.0)	12	(0.3)	13	(0.2)
who died due to a drug-related adverse event	0	(0.0)	0	(0.0)	11	(0.3)	13	(0.2)

[a] Determined by the investigator to be related to the drug.
Non-serious adverse events up to 30 days of last dose and serious adverse events up to 90 days of last dose are included.
For KN868, grades are based on NCI CTCAE version 5.0.
Database cutoff date for KN868: 16DEC2022 for dMMR participants and 06DEC2022 for pMMR participants.
The list of studies and database cutoff dates for the aggregate safety datasets within this table are provided in the appendix of Module 2.7.4.

Table 73: Participants With Adverse Events of Special Interest by AESI Category and Preferred Term (Incidence > 0% in One or More Treatment Groups) (APaT Population)

	Pembrolizumab + Chemotherapy		Placebo + Chemotherapy		Pooled Safety Dataset for Pembrolizumab + Chemotherapy		Pembrolizumab Monotherapy Reference Safety Dataset	
	n	(%)	n	(%)	n	(%)	n	(%)
Participants in population	382		377		3,473		7,631	
with one or more adverse events	137	(35.9)	96	(25.5)	1,223	(35.2)	2,082	(27.3)
with no adverse events	245	(64.1)	281	(74.5)	2,250	(64.8)	5,549	(72.7)
Adrenal Insufficiency	**4**	**(1.0)**	**1**	**(0.3)**	**44**	**(1.3)**	**74**	**(1.0)**
Addison's disease	0	(0.0)	0	(0.0)	1	(0.0)	2	(0.0)
Adrenal insufficiency	4	(1.0)	1	(0.3)	43	(1.2)	69	(0.9)
Adrenocortical insufficiency acute	0	(0.0)	0	(0.0)	0	(0.0)	2	(0.0)

Secondary adrenocortical insufficiency	0	(0.0)	0	(0.0)	0	(0.0)	2	(0.0)
Arthritis	**0**	**(0.0)**	**0**	**(0.0)**	**1**	**(0.0)**	**5**	**(0.1)**
Autoimmune arthritis	0	(0.0)	0	(0.0)	0	(0.0)	4	(0.1)
Immune-mediated arthritis	0	(0.0)	0	(0.0)	1	(0.0)	1	(0.0)
Cholangitis Sclerosing	**0**	**(0.0)**	**0**	**(0.0)**	**2**	**(0.1)**	**0**	**(0.0)**
Cholangitis sclerosing	0	(0.0)	0	(0.0)	1	(0.0)	0	(0.0)
Immune-mediated cholangitis	0	(0.0)	0	(0.0)	1	(0.0)	0	(0.0)
Colitis	**7**	**(1.8)**	**3**	**(0.8)**	**101**	**(2.9)**	**159**	**(2.1)**
Autoimmune colitis	0	(0.0)	0	(0.0)	4	(0.1)	6	(0.1)
Colitis	6	(1.6)	3	(0.8)	77	(2.2)	134	(1.8)
Colitis microscopic	0	(0.0)	0	(0.0)	1	(0.0)	4	(0.1)
Enterocolitis	0	(0.0)	0	(0.0)	16	(0.5)	11	(0.1)
Immune-mediated enterocolitis	1	(0.3)	0	(0.0)	4	(0.1)	6	(0.1)
Encephalitis	**1**	**(0.3)**	**0**	**(0.0)**	**5**	**(0.1)**	**5**	**(0.1)**
Encephalitis	1	(0.3)	0	(0.0)	2	(0.1)	4	(0.1)
Encephalitis autoimmune	0	(0.0)	0	(0.0)	3	(0.1)	1	(0.0)
Gastritis	**1**	**(0.3)**	**0**	**(0.0)**	**80**	**(2.3)**	**57**	**(0.7)**
Gastritis	1	(0.3)	0	(0.0)	79	(2.3)	52	(0.7)
Gastritis erosive	0	(0.0)	0	(0.0)	2	(0.1)	7	(0.1)
Guillain-Barre Syndrome	**1**	**(0.3)**	**0**	**(0.0)**	**2**	**(0.1)**	**6**	**(0.1)**
Axonal neuropathy	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)
Demyelinating polyneuropathy	0	(0.0)	0	(0.0)	1	(0.0)	1	(0.0)
Guillain-Barre syndrome	1	(0.3)	0	(0.0)	1	(0.0)	4	(0.1)
Hepatitis	**0**	**(0.0)**	**0**	**(0.0)**	**42**	**(1.2)**	**80**	**(1.0)**
Autoimmune hepatitis	0	(0.0)	0	(0.0)	16	(0.5)	35	(0.5)
Hepatitis	**0**	**(0.0)**	**0**	**(0.0)**	**42**	**(1.2)**	**80**	**(1.0)**
Drug-induced liver injury	0	(0.0)	0	(0.0)	0	(0.0)	8	(0.1)
Hepatitis	0	(0.0)	0	(0.0)	16	(0.5)	34	(0.4)
Hepatitis acute	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)
Immune-mediated hepatitis	0	(0.0)	0	(0.0)	11	(0.3)	3	(0.0)
Hyperthyroidism	**25**	**(6.5)**	**10**	**(2.7)**	**187**	**(5.4)**	**398**	**(5.2)**
Graves' disease	0	(0.0)	0	(0.0)	2	(0.1)	0	(0.0)
Hyperthyroidism	25	(6.5)	10	(2.7)	185	(5.3)	398	(5.2)
Hypoparathyroidism	**0**	**(0.0)**	**0**	**(0.0)**	**1**	**(0.0)**	**1**	**(0.0)**
Hypoparathyroidism	0	(0.0)	0	(0.0)	1	(0.0)	1	(0.0)
Hypophysitis	**2**	**(0.5)**	**0**	**(0.0)**	**32**	**(0.9)**	**52**	**(0.7)**
Hypophysitis	2	(0.5)	0	(0.0)	21	(0.6)	32	(0.4)
Hypopituitarism	0	(0.0)	0	(0.0)	11	(0.3)	19	(0.2)
Lymphocytic hypophysitis	0	(0.0)	0	(0.0)	0	(0.0)	2	(0.0)
Hypothyroidism	**47**	**(12.3)**	**14**	**(3.7)**	**471**	**(13.6)**	**939**	**(12.3)**
Autoimmune hypothyroidism	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)
Hypothyroidism	47	(12.3)	14	(3.7)	471	(13.6)	937	(12.3)
Immune-mediated hypothyroidism	0	(0.0)	0	(0.0)	1	(0.0)	0	(0.0)
Myxoedema	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)
Primary hypothyroidism	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)
Infusion Reactions	**67**	**(17.5)**	**66**	**(17.5)**	**302**	**(8.7)**	**165**	**(2.2)**
Anaphylactic reaction	3	(0.8)	0	(0.0)	11	(0.3)	10	(0.1)
Anaphylactoid reaction	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)
Cytokine release syndrome	0	(0.0)	0	(0.0)	5	(0.1)	8	(0.1)
Drug hypersensitivity	8	(2.1)	7	(1.9)	46	(1.3)	24	(0.3)
Hypersensitivity	6	(1.6)	10	(2.7)	86	(2.5)	49	(0.6)
Infusion related reaction	54	(14.1)	51	(13.5)	163	(4.7)	75	(1.0)
Serum sickness	0	(0.0)	0	(0.0)	1	(0.0)	0	(0.0)
Myasthenic Syndrome	**1**	**(0.3)**	**0**	**(0.0)**	**1**	**(0.0)**	**8**	**(0.1)**
Myasthenia gravis	1	(0.3)	0	(0.0)	1	(0.0)	5	(0.1)

Myasthenic syndrome	0	(0.0)	0	(0.0)	0	(0.0)	3	(0.0)
Myelitis	**0**	**(0.0)**	**0**	**(0.0)**	**0**	**(0.0)**	**3**	**(0.0)**
Myelitis	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)
Myelitis	**0**	**(0.0)**	**0**	**(0.0)**	**0**	**(0.0)**	**3**	**(0.0)**
Myelitis transverse	0	(0.0)	0	(0.0)	0	(0.0)	2	(0.0)
Myocarditis	**1**	**(0.3)**	**0**	**(0.0)**	**8**	**(0.2)**	**9**	**(0.1)**
Autoimmune myocarditis	0	(0.0)	0	(0.0)	1	(0.0)	0	(0.0)
Myocarditis	1	(0.3)	0	(0.0)	7	(0.2)	9	(0.1)
Myositis	**2**	**(0.5)**	**1**	**(0.3)**	**14**	**(0.4)**	**34**	**(0.4)**
Autoimmune myositis	0	(0.0)	0	(0.0)	1	(0.0)	0	(0.0)
Dermatomyositis	0	(0.0)	0	(0.0)	1	(0.0)	0	(0.0)
Myopathy	0	(0.0)	0	(0.0)	5	(0.1)	8	(0.1)
Myositis	2	(0.5)	1	(0.3)	6	(0.2)	22	(0.3)
Necrotising myositis	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)
Rhabdomyolysis	1	(0.3)	0	(0.0)	1	(0.0)	3	(0.0)
Nephritis	**2**	**(0.5)**	**0**	**(0.0)**	**29**	**(0.8)**	**37**	**(0.5)**
Acute kidney injury	0	(0.0)	0	(0.0)	0	(0.0)	2	(0.0)
Autoimmune nephritis	0	(0.0)	0	(0.0)	2	(0.1)	5	(0.1)
Glomerulonephritis	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)
Glomerulonephritis acute	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)
Glomerulonephritis membranous	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)
Nephritis	2	(0.5)	0	(0.0)	17	(0.5)	10	(0.1)
Nephrotic syndrome	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)
Renal failure	0	(0.0)	0	(0.0)	0	(0.0)	2	(0.0)
Tubulointerstitial nephritis	0	(0.0)	0	(0.0)	11	(0.3)	14	(0.2)
Optic Neuritis	**0**	**(0.0)**	**0**	**(0.0)**	**0**	**(0.0)**	**2**	**(0.0)**
Optic neuritis	0	(0.0)	0	(0.0)	0	(0.0)	2	(0.0)
Pancreatitis	**1**	**(0.3)**	**0**	**(0.0)**	**15**	**(0.4)**	**28**	**(0.4)**
Autoimmune pancreatitis	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)
Pancreatitis	1	(0.3)	0	(0.0)	11	(0.3)	24	(0.3)
Pancreatitis acute	0	(0.0)	0	(0.0)	5	(0.1)	4	(0.1)
Pneumonitis	**4**	**(1.0)**	**2**	**(0.5)**	**145**	**(4.2)**	**324**	**(4.2)**
Autoimmune lung disease	0	(0.0)	0	(0.0)	1	(0.0)	0	(0.0)
Immune-mediated lung disease	0	(0.0)	0	(0.0)	1	(0.0)	4	(0.1)
Interstitial lung disease	0	(0.0)	0	(0.0)	12	(0.3)	29	(0.4)
Organising pneumonia	0	(0.0)	0	(0.0)	1	(0.0)	3	(0.0)
Pneumonitis	4	(1.0)	2	(0.5)	131	(3.8)	291	(3.8)
Sarcoidosis	**0**	**(0.0)**	**0**	**(0.0)**	**1**	**(0.0)**	**20**	**(0.3)**
Cutaneous sarcoidosis	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)
Pulmonary sarcoidosis	0	(0.0)	0	(0.0)	0	(0.0)	2	(0.0)
Sarcoidosis	0	(0.0)	0	(0.0)	1	(0.0)	18	(0.2)
Severe Skin Reactions	**13**	**(3.4)**	**6**	**(1.6)**	**99**	**(2.9)**	**130**	**(1.7)**
Dermatitis bullous	2	(0.5)	0	(0.0)	8	(0.2)	9	(0.1)
Dermatitis exfoliative	0	(0.0)	0	(0.0)	0	(0.0)	5	(0.1)
Dermatitis exfoliative generalised	0	(0.0)	0	(0.0)	5	(0.1)	2	(0.0)
Erythema multiforme	0	(0.0)	1	(0.3)	6	(0.2)	8	(0.1)
Exfoliative rash	0	(0.0)	0	(0.0)	0	(0.0)	2	(0.0)
Lichen planus	0	(0.0)	0	(0.0)	0	(0.0)	6	(0.1)
Oral lichen planus	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)
Pemphigoid	0	(0.0)	0	(0.0)	1	(0.0)	3	(0.0)
Pemphigus	0	(0.0)	0	(0.0)	0	(0.0)	2	(0.0)
Pruritus	2	(0.5)	2	(0.5)	7	(0.2)	16	(0.2)
Pruritus genital	0	(0.0)	0	(0.0)	0	(0.0)	2	(0.0)
Rash	3	(0.8)	3	(0.8)	37	(1.1)	44	(0.6)
Rash erythematous	0	(0.0)	0	(0.0)	1	(0.0)	1	(0.0)
Rash maculo-papular	6	(1.6)	2	(0.5)	38	(1.1)	23	(0.3)

Rash pruritic	0	(0.0)	0	(0.0)	1	(0.0)	4	(0.1)
Rash pustular	0	(0.0)	0	(0.0)	1	(0.0)	2	(0.0)
Skin necrosis	0	(0.0)	0	(0.0)	0	(0.0)	2	(0.0)
Stevens-Johnson syndrome	0	(0.0)	0	(0.0)	1	(0.0)	4	(0.1)
Toxic skin eruption	0	(0.0)	0	(0.0)	2	(0.1)	4	(0.1)
Thyroiditis	**0**	**(0.0)**	**0**	**(0.0)**	**45**	**(1.3)**	**74**	**(1.0)**
Autoimmune thyroiditis	0	(0.0)	0	(0.0)	13	(0.4)	22	(0.3)
Immune-mediated thyroiditis	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)
Thyroid disorder	0	(0.0)	0	(0.0)	2	(0.1)	3	(0.0)
Thyroiditis	0	(0.0)	0	(0.0)	29	(0.8)	50	(0.7)
Thyroiditis acute	0	(0.0)	0	(0.0)	1	(0.0)	0	(0.0)
Type 1 Diabetes Mellitus	**2**	**(0.5)**	**0**	**(0.0)**	**12**	**(0.3)**	**34**	**(0.4)**
Diabetic ketoacidosis	2	(0.5)	0	(0.0)	3	(0.1)	15	(0.2)
Type 1 diabetes mellitus	0	(0.0)	0	(0.0)	10	(0.3)	25	(0.3)
Uveitis	**3**	**(0.8)**	**1**	**(0.3)**	**4**	**(0.1)**	**25**	**(0.3)**
Chorioretinitis	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)
Iridocyclitis	0	(0.0)	0	(0.0)	1	(0.0)	5	(0.1)
Iritis	1	(0.3)	0	(0.0)	0	(0.0)	4	(0.1)
Uveitis	2	(0.5)	1	(0.3)	3	(0.1)	16	(0.2)
Vasculitis	**1**	**(0.3)**	**1**	**(0.3)**	**27**	**(0.8)**	**5**	**(0.1)**
Central nervous system vasculitis	0	(0.0)	0	(0.0)	1	(0.0)	0	(0.0)
Giant cell arteritis	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)
Vasculitis	1	(0.3)	1	(0.3)	26	(0.7)	4	(0.1)

Every participant is counted a single time for each applicable row and column.

A bolded term or specific adverse event appears on this report only if its incidence in one or more of the columns meets the incidence criterion in the report title, after rounding.

Non-serious adverse events up to 30 days of last dose and serious adverse events up to 90 days of last dose are included.

For KEYNOTE-868, reporting of unrelated serious adverse events between 30 and 90 days of last dose are not required.

Database cutoff date for KEYNOTE-868: 16 December 2022 for dMMR participants and 06 December 2022 for pMMR participants.

Adverse drug reactions

The MAH has updated section 4.8 of the SmPC to include the population of primary advanced or recurrent endometrial carcinoma patients (study KEYNOTE-868/NRG-GY018), into the "Pembrolizumab in combination with chemotherapy or chemoradiotherapy" pooled dataset (RSD) which includes all chemotherapy or chemoradiotherapy combination indications approved in the EU or expected to be approved concurrently with the KEYNOTE-868 procedure, i.e. the population of primary advanced or recurrent endometrial cancer patients from KEYNOTE-A18 (EMEA/H/C/003820/II/0145). Therefore, the changes included in section 4.8 of the current procedure EMEA/H/C/003820/II/0153 represent the most updated safety pool and a consolidated version that includes also the changes from EMEA/H/C/003820/II/0145.

In addition, the MAH proposed revisions to align the adverse reactions by decreased frequency within each System Organ Class in Table 2 of section 4.8 of the SmPC, for pembrolizumab in combination with chemotherapy or chemoradiotherapy, including KEYNOTE-A18 and KEYNOTE-868 safety data.

As a result of the updated safety pool, several ADRs frequencies were updated as follows:

- Haemolytic anaemia: from rare to uncommon
- Dizziness: from common to very common
- Uveitis: from rare to uncommon

- Lichenoid keratosis: from rare to uncommon
- Oedema: from common to very common
- Blood creatinine increased: from common to very common

Meningitis (aseptic), which was already reflected in the monotherapy column, was added to the combination with chemotherapy column with frequency rare.

The paragraph for laboratory abnormalities for the combination with chemotherapy was updated to include the data from KEYNOTE-A18 and KEYNOTE-868.

Tables supporting the updates made in section 4.8 of the SmPC are presented below.

Table 74: Adverse Reactions in Patients Treated With Pembrolizumab in Combination With Chemotherapy (APaT Population)

		Combination Therapy (N=6093)	
		All AEs % (n)	Gr 3-5 AEs n
Infections and infestations			
Common	Pneumonia	6.6% (405)	223
Blood and lymphatic system disorders			
Very common	Anaemia	53.3% (3248)	1129
Very common	Neutropenia	24.0% (1462)	885
Very common	Thrombocytopenia	13.2% (804)	241
	Febrile Neutropenia	5.1% (310)	299
Common			
Common	Leukopenia	9.6% (584)	234
Common	Lymphopenia	3.3% (200)	91
Uncommon	Haemolytic Anaemia[a]	0.1% (8)	7
Uncommon	Eosinophilia	0.7% (45)	4
Rare	Immune Thrombocytopenia	0.05% (3)	2
Immune system disorders			
Common	Infusion Reactions[b]	7.1% (435)	77
Rare	Sarcoidosis	0.03% (2)	0
Endocrine disorders			
Very common	Hypothyroidism[c]	13.7% (834)	18
Common	Adrenal Insufficiency[d]	1.1% (66)	26
	Hyperthyroidism[e]	5.8% (355)	8
Common			
Common	Thyroiditis[f]	1.2% (72)	7
Uncommon	Hypophysitis[g]	0.7% (42)	23
Rare	Hypoparathyroidism	0.03% (2)	0
Metabolism and nutrition disorders			
Very common	Hypokalaemia	12.3% (747)	222
Very common	Decreased Appetite	26.7% (1629)	119
Common	Hyponatraemia	8.5% (520)	188
Common	Hypocalcaemia	4.7% (289)	43
	Type 1 Diabetes Mellitus[h]	0.3% (20)	19
Uncommon			
Psychiatric disorders			
Very common	Insomnia	10.7% (654)	9

Nervous system disorders			
Very common	Neuropathy Peripheral	14.1% (861)	57
Very common	Headache	14.0% (852)	19
Very common	Dizziness	10.0% (612)	15
Common	Dysgeusia	8.5% (516)	3
Common	Lethargy	1.0% (61)	2
Uncommon	Encephalitis[i]	0.1% (9)	9
Uncommon	Epilepsy	0.1% (7)	3
Rare	Myasthenic Syndrome[j]	0.08% (5)	5
Rare	Guillain-Barre Syndrome[k]	0.07% (4)	4
Rare	Optic Neuritis	0.02% (1)	1
Rare	Meningitis (Aseptic)	0.02% (1)	1
Eye disorders			
Common	Dry Eye	3.0% (180)	1
Uncommon	Uveitis[l]	0.2% (10)	0
Cardiac disorders			
Common	Cardiac Arrhythmia (Including Atrial Fibrillation)[m]	3.9% (236)	56
Uncommon	Myocarditis[n]	0.2% (11)	9
Uncommon	Pericardial Effusion	0.4% (24)	8
Uncommon	Pericarditis	0.1% (7)	2
Vascular disorders			
Common	Hypertension	6.9% (419)	175
Uncommon	Vasculitis[o]	0.5% (33)	5
Respiratory, thoracic and mediastinal disorders			
Very common	Dyspnoea	11.7% (710)	77
Very common	Cough	15.0% (916)	5
Common	Pneumonitis[p]	3.8% (232)	86
Gastrointestinal disorders			
Very common	Diarrhoea	35.6% (2168)	240
Very common	Nausea	52.4% (3190)	184
Very common	Vomiting	27.9% (1699)	184
Very common	Abdominal Pain[q]	19.1% (1161)	76
Very common	Constipation	32.2% (1964)	22
Common	Colitis[r]	2.7% (162)	76
Common	Gastritis[s]	2.1% (126)	9
Common	Dry Mouth	4.4% (267)	1
Uncommon	Pancreatitis[t]	0.4% (25)	19
Uncommon	Gastrointestinal Ulceration[u]	0.4% (24)	4
Rare	Pancreatic Exocrine Insufficiency	(0)	0
Rare	Small Intestinal Perforation	0.03% (2)	2
Rare	Coeliac Disease	(0)	0
Hepatobiliary disorders			
Common	Hepatitis[v]	1.1% (65)	47
Rare	Cholangitis Sclerosing[w]	0.03% (2)	2
Skin and subcutaneous tissue disorders			
Very common	Alopecia	23.6% (1438)	6
Very common	Pruritus[x]	14.0% (851)	6
Very common	Rash[y]	20.4% (1245)	4
Common	Severe Skin Reactions[z]	2.5% (153)	129
Common	Dermatitis	1.5% (93)	4
Common	Erythema	3.3% (199)	3
Common	Dry Skin	5.2% (314)	2
Common	Dermatitis Acneiform	2.0% (119)	2
Common	Eczema	1.2% (74)	1
Uncommon	Psoriasis	0.6% (37)	5
Uncommon	Lichenoid Keratosis[aa]	0.1% (8)	1
Uncommon	Vitiligo[bb]	0.5% (33)	0
Uncommon	Papule	0.2% (10)	0
Rare	Stevens-Johnson Syndrome	0.03% (2)	2
Rare	Erythema Nodosum	0.07% (4)	0

Rare	Hair Colour Changes	0.02% (1)	0
Musculoskeletal and connective tissue disorders			
Very common	Musculoskeletal Pain[cc]	13.2% (807)	41
Very common	Arthralgia	16.0% (973)	38
Common	Myositis[dd]	9.1% (556)	23
Common	Pain In Extremity	7.2% (441)	12
Common	Arthritis[ee]	1.6% (95)	9
Uncommon	Tenosynovitis[ff]	0.3% (20)	1
Rare	Sjogren's Syndrome	0.02% (1)	0
Renal and urinary disorders			
Common	Acute Kidney Injury	3.2% (194)	100
Uncommon	Nephritis[gg]	0.7% (40)	22
Uncommon	Cystitis Noninfective	0.2% (14)	0
General disorders and administration site conditions			
Very common	Fatigue	35.1% (2141)	256
Very common	Asthenia	17.7% (1077)	164
Very common	Pyrexia	17.6% (1074)	48
Very common	Oedema[hh]	13.2% (804)	24
Common	Influenza Like Illness	2.5% (155)	2
Common	Chills	3.0% (181)	0
Investigations			
Very common	Alanine Aminotransferase Increased	17.4% (1063)	177
Very common	Aspartate Aminotransferase Increased	17.0% (1038)	149
Very common	Blood Creatinine Increased	10.2% (623)	32
Common	Blood Bilirubin Increased	4.9% (296)	50
Common	Blood Alkaline Phosphatase Increased	6.8% (417)	44
Common	Hypercalcaemia	1.7% (106)	21
Uncommon	Amylase Increased	0.7% (40)	10

Laboratory findings

The most frequently reported laboratory abnormalities in the pembrolizumab plus chemotherapy group reflected events associated with the combination of pembrolizumab with chemotherapy. Most laboratory abnormalities were Grade 1 or 2 and were generally consistent with the pooled pembrolizumab plus chemotherapy SD. The most frequently observed (incidence ≥10%) Grade 3 or 4 laboratory abnormalities in the pembrolizumab plus chemotherapy group were **haemoglobin decreased** (13.7%), **lymphocytes decreased** (12.4%), and **neutrophils decreased** (11.8%); the incidence of Grade 3 to 4 lab abnormalities was consistent with the pooled pembrolizumab plus chemotherapy SD.

Laboratory abnormalities of all grades that were higher in the pembrolizumab plus chemotherapy group versus the pembrolizumab monotherapy RSD (≥20% point difference) were haemoglobin decreased, leukocytes decreased, neutrophils decreased, and platelets decreased; these differences were consistent with the chemotherapy administered in the Study KEYNOTE-868/NRG-GY018.

Safety in special populations

Age

Safety data have been provided for patients below and over 65 years, and for classes of age < 65, 65-74, ≥ 75 Years. Data by age separately by pMMR and dMMR populations from study KEYNOTE-868/NRG-GY018 is also reported below.

Table 75: Adverse Event Summary by Age Category (< 65, >= 65 Years) (APaT Population)

	KN868 Pembrolizumab + Chemotherapy				KN868 Placebo + Chemotherapy				Pooled Safety Dataset for Pembrolizumab + Chemotherapy				Pembrolizumab Monotherapy Reference Safety Dataset			
	<65		>=65		<65		>=65		<65		>=65		<65		>=65	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Participants in population	172		210		174		203		2,381		1,092		4,524		3,107	
with one or more adverse events	169	(98.3)	207	(98.6)	173	(99.4)	202	(99.5)	2,361	(99.2)	1,083	(99.2)	4,364	(96.5)	3,011	(96.9)
with no adverse event	3	(1.7)	3	(1.4)	1	(0.6)	1	(0.5)	20	(0.8)	9	(0.8)	160	(3.5)	96	(3.1)
with drug-related[a] adverse events	162	(94.2)	203	(96.7)	165	(94.8)	193	(95.1)	2,308	(96.9)	1,053	(96.4)	3,231	(71.4)	2,231	(71.8)
with toxicity grade 3-5 adverse events	97	(56.4)	128	(61.0)	82	(47.1)	92	(45.3)	1,872	(78.6)	855	(78.3)	1,917	(42.4)	1,597	(51.4)
with toxicity grade 3-5 drug-related adverse events	74	(43.0)	98	(46.7)	56	(32.2)	64	(31.5)	1,586	(66.6)	717	(65.7)	629	(13.9)	579	(18.6)
with non-serious adverse events	168	(97.7)	205	(97.6)	170	(97.7)	201	(99.0)	2,348	(98.6)	1,075	(98.4)	4,282	(94.7)	2,940	(94.6)
with serious adverse events	54	(31.4)	78	(37.1)	33	(19.0)	40	(19.7)	1,031	(43.3)	582	(53.3)	1,457	(32.2)	1,285	(41.4)
with serious drug-related adverse events	33	(19.2)	49	(23.3)	20	(11.5)	23	(11.3)	644	(27.0)	354	(32.4)	451	(10.0)	389	(12.5)
who died	3	(1.7)	3	(1.4)	1	(0.6)	3	(1.5)	80	(3.4)	102	(9.3)	158	(3.5)	188	(6.1)
who died due to a drug-related adverse event	1	(0.6)	0	(0.0)	1	(0.6)	1	(0.5)	22	(0.9)	31	(2.8)	21	(0.5)	21	(0.7)

[a] Determined by the investigator to be related to the drug.
For KN868, grades are based on NCI CTCAE version 5.0.
Non-serious adverse events up to 30 days of last dose and serious adverse events up to 90 days of last dose are included.
For KN868, reporting of unrelated serious adverse events between 30 and 90 days of last dose are not required.
MedDRA preferred terms "Neoplasm Progression", "Malignant Neoplasm Progression" and "Disease Progression" not related to the drug are excluded.
Database cutoff date for KN868: 16DEC2022 for dMMR participants and 06DEC2022 for pMMR participants.
The list of studies and database cutoff dates for the aggregate safety datasets within this table are provided in the appendix of Module 2.7.4.

Table 76: Adverse Event Summary by Age Category (< 65, 65-74, >= 75 Years) (APaT Population) in KEYNOTE-868

	KN868 Pembrolizumab + Chemotherapy						KN868 Placebo + Chemotherapy					
	<65		65-74		>=75		<65		65-74		>=75	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Participants in population	172		153		57		174		149		54	
with one or more adverse events	169	(98.3)	150	(98.0)	57	(100.0)	173	(99.4)	149	(100.0)	53	(98.1)
with no adverse event	3	(1.7)	3	(2.0)	0	(0.0)	1	(0.6)	0	(0.0)	1	(1.9)
with drug-related[a] adverse events	162	(94.2)	150	(98.0)	53	(93.0)	165	(94.8)	142	(95.3)	51	(94.4)
with toxicity grade 3-5 adverse events	97	(56.4)	86	(56.2)	42	(73.7)	82	(47.1)	66	(44.3)	26	(48.1)
with toxicity grade 3-5 drug-related adverse events	74	(43.0)	65	(42.5)	33	(57.9)	56	(32.2)	48	(32.2)	16	(29.6)
with non-serious adverse events	168	(97.7)	149	(97.4)	56	(98.2)	170	(97.7)	149	(100.0)	52	(96.3)
with serious adverse events	54	(31.4)	47	(30.7)	31	(54.4)	33	(19.0)	28	(18.8)	12	(22.2)
with serious drug-related adverse events	33	(19.2)	29	(19.0)	20	(35.1)	20	(11.5)	17	(11.4)	6	(11.1)
who died	3	(1.7)	0	(0.0)	3	(5.3)	1	(0.6)	1	(0.7)	2	(3.7)
who died due to a drug-related adverse event	1	(0.6)	0	(0.0)	0	(0.0)	1	(0.6)	0	(0.0)	1	(1.9)

Table 77: Adverse Event Summary by Age Category (< 65, 65-74, >= 75 Years) (APaT Population) in pooled safety dataset for pembrolizumab + chemotherapy and pembrolizumab monotherapy RSD

	Pooled Safety Dataset for Pembrolizumab + Chemotherapy						Pembrolizumab Monotherapy Reference Safety Dataset					
	<65		65-74		>=75		<65		65-74		>=75	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Participants in population	2,381		884		208		4,524		2,173		934	
with one or more adverse events	2,361	(99.2)	876	(99.1)	207	(99.5)	4,364	(96.5)	2,097	(96.5)	914	(97.9)
with no adverse event	20	(0.8)	8	(0.9)	1	(0.5)	160	(3.5)	76	(3.5)	20	(2.1)
with drug-related[a] adverse events	2,308	(96.9)	856	(96.8)	197	(94.7)	3,231	(71.4)	1,552	(71.4)	679	(72.7)
with toxicity grade 3-5 adverse events	1,872	(78.6)	687	(77.7)	168	(80.8)	1,917	(42.4)	1,071	(49.3)	526	(56.3)
with toxicity grade 3-5 drug-related adverse events	1,586	(66.6)	587	(66.4)	130	(62.5)	629	(13.9)	391	(18.0)	188	(20.1)
with non-serious adverse events	2,348	(98.6)	870	(98.4)	205	(98.6)	4,282	(94.7)	2,051	(94.4)	889	(95.2)
with serious adverse events	1,031	(43.3)	460	(52.0)	122	(58.7)	1,457	(32.2)	839	(38.6)	446	(47.8)
with serious drug-related adverse events	644	(27.0)	280	(31.7)	74	(35.6)	451	(10.0)	265	(12.2)	124	(13.3)
who died	80	(3.4)	62	(7.0)	40	(19.2)	158	(3.5)	113	(5.2)	75	(8.0)
who died due to a drug-related adverse event	22	(0.9)	20	(2.3)	11	(5.3)	21	(0.5)	13	(0.6)	8	(0.9)

[a] Determined by the investigator to be related to the drug.
For KN868, grades are based on NCI CTCAE version 5.0.
Non-serious adverse events up to 30 days of last dose and serious adverse events up to 90 days of last dose are included.
For KN868, reporting of unrelated serious adverse events between 30 and 90 days of last dose are not required.
MedDRA preferred terms "Neoplasm Progression", "Malignant Neoplasm Progression" and "Disease Progression" not related to the drug are excluded.
Database cutoff date for KN868: 16DEC2022 for dMMR participants and 06DEC2022 for pMMR participants.
The list of studies and database cutoff dates for the aggregate safety datasets within this table are provided in the appendix of Module 2.7.4.

Table 78: Adverse Event Summary for Elderly Participants by Age in pMMR Participants (APaT Population)

	Age (Years)											
	Paclitaxel + Carboplatin + Pembrolizumab						Paclitaxel + Carboplatin + Placebo					
	< 65		>= 65 to < 75		>= 75		< 65		>= 65 to < 75		>= 75	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Participants in Population	126		106		43		126		109		37	
with one or more adverse events	123	(97.6)	104	(98.1)	43	(100.0)	125	(99.2)	109	(100.0)	36	(97.3)
who died	3	(2.4)	0	(0.0)	2	(4.7)	0	(0.0)	0	(0.0)	2	(5.4)
with serious adverse events	38	(30.2)	33	(31.1)	22	(51.2)	21	(16.7)	23	(21.1)	7	(18.9)
CNS (confusion/extrapyramidal)	16	(12.7)	15	(14.2)	9	(20.9)	14	(11.1)	10	(9.2)	3	(8.1)
AE related to falling	11	(8.7)	23	(21.7)	6	(14.0)	10	(7.9)	8	(7.3)	5	(13.5)
CV events	43	(34.1)	42	(39.6)	13	(30.2)	39	(31.0)	39	(35.8)	13	(35.1)
Cerebrovascular events	1	(0.8)	1	(0.9)	1	(2.3)	0	(0.0)	1	(0.9)	0	(0.0)
Infections	43	(34.1)	35	(33.0)	22	(51.2)	38	(30.2)	33	(30.3)	13	(35.1)

AEs were followed 30 days after last dose of study treatment; SAEs were followed 90 days after last dose of study treatment.
MedDRA V26.0 preferred terms "Neoplasm progression", "Malignant neoplasm progression" and "Disease progression" not related to the drug are excluded.
Reporting of unrelated serious adverse events between 30 and 90 days of last dose are not required.
Database Cutoff Date: 16DEC2022 for dMMR participants and 06DEC2022 for pMMR participants.

Table 79: Adverse Event Summary for Elderly Participants by Age in dMMR Participants (APaT Population)

	Age (Years)											
	Paclitaxel + Carboplatin + Pembrolizumab						Paclitaxel + Carboplatin + Placebo					
	< 65		>= 65 to < 75		>= 75		< 65		>= 65 to < 75		>= 75	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Participants in Population	46		47		14		48		40		17	
with one or more adverse events	46	(100.0)	46	(97.9)	14	(100.0)	48	(100.0)	40	(100.0)	17	(100.0)
who died	0	(0.0)	0	(0.0)	1	(7.1)	1	(2.1)	1	(2.5)	0	(0.0)
with serious adverse events	16	(34.8)	14	(29.8)	9	(64.3)	12	(25.0)	5	(12.5)	5	(29.4)
CNS (confusion/extrapyramidal)	8	(17.4)	10	(21.3)	4	(28.6)	5	(10.4)	5	(12.5)	3	(17.6)
AE related to falling	10	(21.7)	5	(10.6)	4	(28.6)	6	(12.5)	6	(15.0)	2	(11.8)
CV events	20	(43.5)	21	(44.7)	6	(42.9)	13	(27.1)	13	(32.5)	7	(41.2)
Cerebrovascular events	1	(2.2)	1	(2.1)	1	(7.1)	0	(0.0)	0	(0.0)	1	(5.9)
Infections	29	(63.0)	20	(42.6)	5	(35.7)	19	(39.6)	11	(27.5)	5	(29.4)

AEs were followed 30 days after last dose of study treatment; SAEs were followed 90 days after last dose of study treatment.
MedDRA V26.0 preferred terms "Neoplasm progression", "Malignant neoplasm progression" and "Disease progression" not related to the drug are excluded.
Reporting of unrelated serious adverse events between 30 and 90 days of last dose are not required.
Database Cutoff Date: 16DEC2022 for dMMR participants and 06DEC2022 for pMMR participants.

Sex

All participants in the Study KEYNOTE-868/NRG-GY018 were female.

Geographic Region

The small sample size of the pembrolizumab plus chemotherapy group in the Western Europe (n=0) and Rest of World (n=6) regions versus the North American region (n=376) precludes a meaningful comparison of the AE summary profile by geographic region.

Race

Table 80: Adverse Event Summary by Race (White, All-others) in pMMR Participants (APaT Population)

	Paclitaxel + Carboplatin + Pembrolizumab				Paclitaxel + Carboplatin + Placebo			
	White		All Others		White		All Others	
	n	(%)	n	(%)	n	(%)	n	(%)
Participants in population	199		61		200		61	
with one or more adverse events	197	(99.0)	59	(96.7)	198	(99.0)	61	(100.0)
with no adverse event	2	(1.0)	2	(3.3)	2	(1.0)	0	(0.0)
with drug-related[a] adverse events	193	(97.0)	54	(88.5)	190	(95.0)	58	(95.1)
with toxicity grade 3-5 adverse events	113	(56.8)	38	(62.3)	94	(47.0)	25	(41.0)
with toxicity grade 3-5 drug-related adverse events	85	(42.7)	31	(50.8)	65	(32.5)	18	(29.5)
with serious adverse events	68	(34.2)	22	(36.1)	35	(17.5)	14	(23.0)
with serious drug-related adverse events	36	(18.1)	17	(27.9)	19	(9.5)	8	(13.1)
who died	4	(2.0)	1	(1.6)	2	(1.0)	0	(0.0)
who died due to a drug-related adverse event	0	(0.0)	1	(1.6)	1	(0.5)	0	(0.0)

[a] Determined by the investigator to have definite, probable or possible attribution to the drug.
Non-serious adverse events up to 30 days of last treatment and serious adverse events up to 90 days of last treatment are included.
Reporting of unrelated serious adverse events between 30 and 90 days of last dose are not required.
MedDRA V26.0 preferred terms "Neoplasm progression", "Malignant neoplasm progression" and "Disease progression" not related to the drug are excluded.
Grades are based on NCI CTCAE version 5
Database Cutoff Date: 16DEC2022 for dMMR participants and 06DEC2022 for pMMR participants.

Table 81: Adverse Event Summary by Race (White, All-others) in dMMR Participants (APaT Population)

	Paclitaxel + Carboplatin + Pembrolizumab				Paclitaxel + Carboplatin + Placebo			
	White		All Others		White		All Others	
	n	(%)	n	(%)	n	(%)	n	(%)
Participants in population	89		13		80		14	
with one or more adverse events	88	(98.9)	13	(100.0)	80	(100.0)	14	(100.0)
with no adverse event	1	(1.1)	0	(0.0)	0	(0.0)	0	(0.0)
with drug-related[a] adverse events	88	(98.9)	12	(92.3)	75	(93.8)	13	(92.9)
with toxicity grade 3-5 adverse events	52	(58.4)	11	(84.6)	42	(52.5)	5	(35.7)
with toxicity grade 3-5 drug-related adverse events	39	(43.8)	9	(69.2)	30	(37.5)	1	(7.1)
with serious adverse events	32	(36.0)	5	(38.5)	19	(23.8)	1	(7.1)
with serious drug-related adverse events	21	(23.6)	4	(30.8)	13	(16.3)	0	(0.0)
who died	1	(1.1)	0	(0.0)	1	(1.3)	0	(0.0)
who died due to a drug-related adverse event	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)

[a] Determined by the investigator to have definite, probable or possible attribution to the drug.
Non-serious adverse events up to 30 days of last treatment and serious adverse events up to 90 days of last treatment are included.
Reporting of unrelated serious adverse events between 30 and 90 days of last dose are not required.
MedDRA V26.0 preferred terms "Neoplasm progression", "Malignant neoplasm progression" and "Disease progression" not related to the drug are excluded.
Grades are based on NCI CTCAE version 5
Database Cutoff Date: 16DEC2022 for dMMR participants and 06DEC2022 for pMMR participants.

ECOG

Table 82: Adverse Event Summary by ECOG Performance Status Category (0, 1) (APaT Population)

	KN868 Pembrolizumab + Chemotherapy				KN868 Placebo + Chemotherapy				Pooled Safety Dataset for Pembrolizumab + Chemotherapy				Pembrolizumab Monotherapy Reference Safety Dataset			
	[0] Normal Activity		[1] Symptoms, but ambulatory		[0] Normal Activity		[1] Symptoms, but ambulatory		[0] Normal Activity		[1] Symptoms, but ambulatory		[0] Normal Activity		[1] Symptoms, but ambulatory	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Participants in population	258		116		252		113		1,914		1,553		4,016		3,440	
with one or more adverse events	253	(98.1)	115	(99.1)	251	(99.6)	112	(99.1)	1,899	(99.2)	1,539	(99.1)	3,883	(96.7)	3,324	(96.6)
with no adverse event	5	(1.9)	1	(0.9)	1	(0.4)	1	(0.9)	15	(0.8)	14	(0.9)	133	(3.3)	116	(3.4)
with drug-related[a] adverse events	245	(95.0)	112	(96.6)	237	(94.0)	109	(96.5)	1,867	(97.5)	1,488	(95.8)	3,072	(76.5)	2,295	(66.7)
with toxicity grade 3-5 adverse events	147	(57.0)	71	(61.2)	102	(40.5)	66	(58.4)	1,485	(77.6)	1,236	(79.6)	1,540	(38.3)	1,866	(54.2)
with toxicity grade 3-5 drug-related adverse events	115	(44.6)	52	(44.8)	67	(26.6)	48	(42.5)	1,303	(68.1)	996	(64.1)	623	(15.5)	555	(16.1)
with non-serious adverse events	251	(97.3)	114	(98.3)	247	(98.0)	112	(99.1)	1,891	(98.8)	1,526	(98.3)	3,845	(95.7)	3,214	(93.4)
with serious adverse events	84	(32.6)	42	(36.2)	45	(17.9)	25	(22.1)	812	(42.4)	795	(51.2)	1,157	(28.8)	1,491	(43.3)
with serious drug-related adverse events	55	(21.3)	22	(19.0)	24	(9.5)	17	(15.0)	525	(27.4)	470	(30.3)	442	(11.0)	381	(11.1)
who died	3	(1.2)	2	(1.7)	3	(1.2)	1	(0.9)	54	(2.8)	127	(8.2)	93	(2.3)	237	(6.9)
who died due to a drug-related adverse event	0	(0.0)	1	(0.9)	1	(0.4)	1	(0.9)	24	(1.3)	29	(1.9)	13	(0.3)	29	(0.8)

[a] Determined by the investigator to be related to the drug.
For KN868, grades are based on NCI CTCAE version 5.0.
Non-serious adverse events up to 30 days of last dose and serious adverse events up to 90 days of last dose are included.
For KN868, reporting of unrelated serious adverse events between 30 and 90 days of last dose are not required.
MedDRA preferred terms "Neoplasm Progression", "Malignant Neoplasm Progression" and "Disease Progression" not related to the drug are excluded.
Database cutoff date for KN868: 16DEC2022 for dMMR participants and 06DEC2022 for pMMR participants.
The list of studies and database cutoff dates for the aggregate safety datasets within this table are provided in the appendix of Module 2.7.4.

Safety related to drug-drug interactions and other interactions

No dedicated DDI studies have been performed.

Studies evaluating pharmacodynamic drug interactions with pembrolizumab have not been conducted. As systemic corticosteroids may be used in combination with pembrolizumab to ameliorate potential side effects, the potential for a pharmacokinetic DDI with pembrolizumab as a victim was assessed as part of the population pharmacokinetic analysis.

Discontinuation due to adverse events

The KEYNOTE-868/NRG-GY018 protocol did not require study investigators to attribute which specific AE led to treatment discontinuation. However, the AEs noted around the date of study treatment discontinuation due to AEs are described in the participant narratives.

pMMR Population

In the pMMR population, the incidence of participants who discontinued study intervention due to AEs/side effects/complications was 13.1% in the pembrolizumab plus chemotherapy group and 6.3% in the placebo plus chemotherapy group.

The proportion of participants discontinuing each chemotherapy drug was similar in both treatment groups:

• Paclitaxel: 12.9% in the pembrolizumab plus chemotherapy group and 13.7% in the placebo plus chemotherapy group.

• Carboplatin: 8.7% in the pembrolizumab plus chemotherapy group and 6.6% in the placebo plus chemotherapy group.

dMMR Population

In the dMMR population, the incidence of participants who discontinued study intervention due to AEs/side effects/complications was 15.9% in the pembrolizumab plus chemotherapy group and 5.7% in the placebo plus chemotherapy group.

There was a higher incidence of discontinuations of each individual study intervention in the pembrolizumab plus chemotherapy group compared with the placebo plus chemotherapy group:

• Pembrolizumab/placebo: 15.0% in the pembrolizumab plus chemotherapy group and 5.7% in the placebo plus chemotherapy group.

• Paclitaxel: 16.0% in the pembrolizumab plus chemotherapy group and 11.4% in the placebo plus chemotherapy group.

• Carboplatin: 11.2% in the pembrolizumab plus chemotherapy group and 5.7% in the placebo plus chemotherapy group

Post marketing experience

There are no records of any pembrolizumab registration being revoked or withdrawn for safety reasons in any country.

2.5.1. Discussion on clinical safety

The safety profile of pembrolizumab in combination with carboplatin and paclitaxel, in the context of its intended use for the first-line treatment of primary advanced or recurrent endometrial carcinoma in adults who are candidates for systemic therapy, is based on an interim analysis of the Phase 3 study NRG GY018/KEYNOTE-868 with a data cutoff date of 06 December 2022 for participants with pMMR tumours and 16 December 2022 for participants with dMMR tumours. Reference safety datasets for pembrolizumab in combination with chemotherapy and for pembrolizumab monotherapy were provided for comparison.

An updated safety data based on a DCO of 18 August 2023 with approximately 9 months of additional data since IA, was provided during the procedure. No important differences in safety profile of pembrolizumab with chemotherapy for primary advanced or recurrent endometrial carcinoma were highlighted by the MAH in the updated safety analysis compared to previous IA. No new safety signals or new AESI were observed.

Demographic and baseline characteristic are well balanced between treatment and placebo groups in NRG-GY018. In both arms of NRG-GY018, a higher proportion of participants were ≥65 years of age, Black or African American, and had an ECOG PS of 0 compared with the pooled pembrolizumab plus chemotherapy SD and the pembrolizumab monotherapy RSD.

Almost all participants experienced AEs and about 95% in both arms experienced drug-related AEs. The following AEs occurred in a higher proportion of participants in the pembrolizumab plus chemotherapy group: Grade 3 to 5 AEs, Grade 3 to 5 drug-related AEs, SAEs, and drug-related SAEs. This difference was mainly driven by serious AEs, which showed a higher incidence in pembrolizumab plus chemotherapy group (10.67 events/100 pers-months vs 8.36). Moreover, the proportion of participants with drug-related AEs, Grade 3 to 5 AEs, Grade 3 to 5 drug-related AEs, and drug-related SAEs was higher in the pembrolizumab plus chemotherapy group compared with the pembrolizumab monotherapy RSD, although it should be considered that these differences could be due to the addition of chemotherapy to pembrolizumab.

The incidence and type of common (incidence ≥10%) AEs in the pembrolizumab plus chemotherapy group was quite similar compared to the placebo plus chemotherapy group. Among these, no AEs were reported with a higher incidence (≥10% point difference) in the pembrolizumab plus chemotherapy group compared with placebo plus chemotherapy group. The most commonly reported AEs (>30%) were: fatigue, anaemia, alopecia, nausea, constipation, diarrhoea, peripheral sensory neuropathy, peripheral neuropathy, white blood cell count decreased.

Moreover, as expected, the incidence of chemotherapy-related AEs was higher in the pembrolizumab plus chemotherapy group compared with the RSD.

However, when considering drug-related AEs, the incidences are similar between the two study arms, but slightly higher for some AEs in the pembrolizumab plus chemotherapy group compared to the pooled pembrolizumab plus chemotherapy SD. Also in this case, different type of chemotherapy regimen may have contributed to different safety profile.

The overall incidence of Grade 3-5 AEs and drug-related Grade 3-5 AEs were slightly higher in the pembrolizumab plus chemotherapy group (58.9% and 45%, respectively) compared with the placebo plus chemotherapy group (46.2% and 31.8%, respectively), but lower than the incidence in pooled pembrolizumab plus chemotherapy SD (78.5% and 66.3%, respectively). Also, when adjusted for exposure, event rates of frequently reported Grade 3 to 5 AEs (incidence ≥5%) were generally lower than in the pooled pembrolizumab plus chemotherapy SD group (25.3 events/100 pers-months 26.8). However, some Grade 3-5 AEs such as white blood cell count decreased and lymphocyte count decreased

were higher in pembrolizumab plus chemotherapy group (8.6% and 6%, respectively) compared to pooled pembrolizumab plus chemotherapy SD (6.4% and 1.8%, respectively).

The overall incidence of SAEs in the pembrolizumab plus chemotherapy group (34.6%) was higher than in the placebo plus chemotherapy group (19.4%) with a proportion not ≥2% point difference in individual SAEs. The only SAE occurring with a higher proportion (≥2% point difference) in pembrolizumab plus chemotherapy group compared with the pooled pembrolizumab plus chemotherapy SD was white blood cell count decreased (2.1% vs 0.1%). The overall incidence of SAEs in the pembrolizumab plus chemotherapy group was similar compared to the pembrolizumab monotherapy RSD (35.9%), but higher after exposure adjustment (10.7 events/100 person-months), which is expected due to the addition of chemotherapy. Regarding drug-related SAEs the incidence was overall higher in the pembrolizumab plus chemotherapy group (21.5%) compared to both placebo plus chemotherapy group (11.4%) and pembrolizumab monotherapy RSD (11%), but similar or slightly lower to pooled pembrolizumab plus chemotherapy SD (28.7%). The most common drug-related SAE by PT was anaemia.

The MAH updated Section 4.8 of the SmPC to include the population of primary advanced or recurrent endometrial cancer patients receiving pembrolizumab in combination with chemotherapy (study KEYNOTE-868) based on IA safety data (DCO of 06 December 2022 for participants with pMMR tumours and 16 December 2022 for participants with dMMR tumours) into the current chemotherapy combination Reference Safety Dataset which includes all chemotherapy combination indications approved in the EU or expected to be approved concurrently with the KEYNOTE-868 procedure, i.e., the population of cervical cancer from KEYNOTE-A18 (EMEA/H/C/003820/II/0145). Therefore, the changes included in section 4.8 of the current procedure EMEA/H/C/003820/II/0153 represent the most updated safety pool and a consolidated version that includes also the changes from EMEA/H/C/003820/II/0145.

In addition, the MAH proposed revisions to align the adverse reactions by decreased frequency within each System Organ Class in Table 2 of section 4.8 of the SmPC, for pembrolizumab in combination with chemotherapy, including KEYNOTE-868 safety data.

As a result of the updated safety pool, several ADRs frequencies were updated as follows:

- Haemolytic anaemia: from rare to uncommon
- Dizziness: from common to very common
- Uveitis: from rare to uncommon
- Lichenoid keratosis: from rare to uncommon
- Oedema: from common to very common
- Blood creatinine increased: from common to very common

Meningitis (aseptic), which was already reflected in the monotherapy column, was added to the combination with chemotherapy column with frequency rare.

The paragraph for laboratory abnormalities for the combination with chemotherapy was updated to include the data from KEYNOTE-868.

With regard to death due to AE, the incidence of fatal AEs in the pembrolizumab plus chemotherapy group was consistent with the placebo plus chemotherapy group, and lower than the pooled pembrolizumab plus chemotherapy SD and pembrolizumab monotherapy RSD. Overall, 6 participants in the pembrolizumab plus chemotherapy group had a fatal AE (5 in pMMR group and 1 in dMMR group) of which 1 AE occurred in pMMR group was related to study treatment as assessed by the investigator (cardiac arrest). The MAH provided, upon request, more details of the participant's history and clinical course leading to the fatal cardiac event and suggests that there were potentially confounding factors in

the participant's clinical course, such as a prior medical history of thrombosis (concurrently requiring anticoagulation), dyspnea, diabetes, and extensive thoracic and intraabdominal metastatic endometrial carcinoma with the presence of ascites and pleural effusion. Moreover, an autopsy was not performed, and the cause of death was not identified. However, the causality with pembrolizumab was assessed as possible by the investigator and the applicant preferred to keep a conservative approach, which is acceptable. Therefore, considering the presence of confounding factors and the uncertain cause of death, an update of the SmPC was not deemed necessary. In addition, based on a DCO of 18 August 2023, a total of 10 participants with a fatal AE in the pembrolizumab plus chemotherapy group (4 additional deaths from previous IA) occurred, of which 3 are considered related (2 due to cardiac arrest and 1 due to sepsis). Nevertheless, it was noticed that also in placebo plus chemotherapy group, 2 participants experienced drug-related adverse events resulting in death, both in the SOC of infections and infestations, one due to sepsis and one due to septic shock. Therefore, for the time being, no imbalance in deaths due to infections are observed between the two arms.

The other fatal events were due to COVID-19 in two cases, small intestine obstruction in 1 case and due to not specified reasons in 2 cases. From the narrative of patient died due to small intestine obstruction was reported that on Day 183 a diagnostic laparoscopy showed a nonresectable malignant obstruction; therefore small intestinal obstruction was considered related to the endometrial cancer which is plausible.

AESI are generally consistent with those known with pembrolizumab treatment and already reported in the SmPC. No new indication-specific, immune-mediated AEs causally associated with pembrolizumab were identified in NRG-GY018. The overall incidence of AESI in the pembrolizumab plus chemotherapy group (35.9%) is higher compared to placebo plus chemotherapy group (25.5%) and to the pembrolizumab monotherapy RSD (27.3%), but generally consistent with the pooled pembrolizumab plus chemotherapy SD (35.2%). AESIs are especially driven by infusion reactions in both pembrolizumab plus chemotherapy group and placebo plus chemotherapy group (17.5% each) with a higher incidence compared to all other groups, i.e., in the Pooled Safety Dataset for Pembrolizumab + Chemotherapy and in the Pembrolizumab Monotherapy Reference Safety Dataset (8.7% and 2.2%). Most infusion reactions were Grade 1 or 2 and manageable with standard clinical practice, such as administration of systemic corticosteroids and/or treatment interruption/discontinuation. This difference could be attributed to the taxol and platinum chemotherapy combination used in NRG-GY018, as the same incidence in both treatment arms of the study is reported. Moreover, in support of this hypothesis, it is also noted that 29 participants in the pMMR population (5.3%) and 14 participants in the dMMR population (6.6%) received a chemotherapy agent other than paclitaxel (docetaxel or nab-paclitaxel) due to AE/IRR.

Hyperthyroidism is also more common in pembrolizumab plus chemotherapy group (6.5%) than in placebo plus chemotherapy group (2.7%) and similar or slightly higher than in pembrolizumab monotherapy RSD (5.2%). Hyperthyroidism is a known AESI of pembrolizumab already reported in the SmPC.

The NRG-GY018 protocol did not require study investigators to attribute which specific AE led to treatment discontinuation. However, in the pMMR population, the incidence of participants who discontinued study intervention due to AEs/side effects/complications was higher in the pembrolizumab plus chemotherapy group (13.1%) than in the placebo plus chemotherapy group (6.3%). The same was for the dMMR population (15.9% in the pembrolizumab plus chemotherapy group vs 5.7% in the placebo plus chemotherapy group). The higher incidence of discontinuation of study intervention due to AEs/side effects/complications in the pembrolizumab plus chemotherapy group was likely due to a higher rate of participants discontinuing pembrolizumab in the pembrolizumab plus chemotherapy group (13.8%) compared with participants discontinuing placebo in the placebo plus chemotherapy group (6.3%).

The most frequently reported laboratory abnormalities in the pembrolizumab plus chemotherapy group reflected events associated with the combination of pembrolizumab with chemotherapy. Most laboratory

abnormalities were Grade 1 or 2 and were generally consistent with the pooled pembrolizumab plus chemotherapy SD. Incidence of Grade 3 to 4 lab abnormalities was consistent with the pooled pembrolizumab plus chemotherapy SD and no new safety concerns based on laboratory abnormalities were identified.

A higher rate of participants with Grade 3-5 AEs, Grade 3-5 drug-related AEs, SAEs, and drug-related SAEs was observed in participants ≥75 years old compared to those <75 years old in pembrolizumab plus chemotherapy group. These differences would be in principle expected for the older patients. A similar pattern was observed in the pooled pembrolizumab plus chemotherapy SD and pembrolizumab monotherapy RSD, although with a smaller difference between groups, while it was not observed in the placebo plus chemotherapy group. This trend suggests that pembrolizumab could be less tolerated in patients ≥75 years old. However, when analyzing different type of AEs, no firm conclusion on a specific trend can be drawn. In section 4.4 of the SmPC, a general warning is already reported stating that "Pembrolizumab in combination with chemotherapy should be used with caution in patients ≥ 75 years after careful consideration of the potential benefit/risk on an individual basis". Thus, there is no need for additional wording. In both pMMR and dMMR populations, a higher rate of patients with Grade 3-5 AEs, Grade 3-5 drug-related AEs and drug-related SAEs was observed in all others group compared to white group when stratified by race. The available data are considered representative of European patients. In addition, in the dMMR population, the number of patients in other race groups is too low to make any conclusion.

No important differences were noted when subjects are stratified by ECOG Performance Status Category (0, 1). Patients with ECOG 2 were also eligible in study NRG-GY018. Approximately 3% of patients with ECOG 2 were included in each population (18 in the pMMR population and 7 in the dMMR population), balanced between treatment arms. However, due to the small numbers it is not possible to make any conclusion with regard to toxicity specifically in this subset, thus it is acceptable that safety data separately in ECOG 2 have not been provided by the MAH.

2.5.2. Conclusions on clinical safety

The overall safety profile of pembrolizumab plus chemotherapy in the first-line treatment of primary advanced or recurrent endometrial carcinoma seems to be in line with that already known of pembrolizumab associated to chemotherapy regimens from other authorised indications. No new safety signals have been observed. A higher incidence of AEs is seen compared to the placebo plus chemotherapy arm, as expected from the add-on treatment. A higher incidence of infusion reactions was reported among AESI, likely attributable to the use of paclitaxel as same incidence in both treatment arms of study NRG-GY018 is reported. A worst safety profile was observed in participants ≥75 years old, however, this is already reflected with a general warning in section 4.4 of the Keytruda SmPC.

2.5.3. PSUR cycle

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

2.6. Risk management plan

The MAH submitted an updated RMP version 46.1, DLP 03 September 2023, dated 27 February 2024 with this application. The main proposed RMP changes were the following:

- Addition of a new indication for pembrolizumab; in combination with carboplatin and paclitaxel for the first-line treatment of primary advanced or recurrent endometrial carcinoma in adults.
- Addition of study KEYNOTE-868 in modules SIII, SVII and SVIII; no changes to the risk profile in Modules SIII, SVII and SVIII are proposed.

The CHMP received the following PRAC Advice on the submitted RMP:

The PRAC considered that the RMP version 46.1 is acceptable.

The CHMP endorsed the consolidated Risk Management Plan version 44.0 with the following content:

Safety concerns

Table SVIII.1: Summary of Safety Concerns

Summary of safety concerns	
Important identified risks	Immune-mediated adverse reactions
Important potential risks	For hematologic malignancies: increased risk of severe complications of allogeneic stem cell transplantation (SCT) in patients who have previously received pembrolizumab Graft versus host disease (GVHD) after pembrolizumab administration in patients with a history of allogeneic stem cell transplant (SCT)
Missing information	None

Pharmacovigilance plan

There are no ongoing or planned additional pharmacovigilance studies that are required for pembrolizumab.

Risk minimisation measures

Table V.3.1: Summary Table of Pharmacovigilance Activities and Risk Minimisation Activities by Safety Concern

Safety Concern	**Risk minimisation Measures**	**Pharmacovigilance Activities**
Important Identified Risks: Immune-Mediated Adverse Reactions		
Immune-mediated adverse reactions	Routine risk minimisation measures: ▪ The risk of the immune-mediated adverse reactions associated with the use of pembrolizumab is described in the SmPC, Section 4.2, 4.4, 4.8 and appropriate advice is provided to the prescriber to minimize the risk.	Routine pharmacovigilance activities
	Additional risk minimisation measures: ▪ Patient card	Additional pharmacovigilance including: • Safety monitoring in all ongoing MAH-sponsored clinical trials for pembrolizumab in various tumor types
Important Potential Risks		

Table V.3.1: Summary Table of Pharmacovigilance Activities and Risk Minimisation Activities by Safety Concern

Safety Concern	Risk minimisation Measures	Pharmacovigilance Activities
For hematologic malignancies: increased risk of severe complications of allogeneic SCT in patients who have previously received pembrolizumab	Routine risk minimisation measures: ▪ For Hematologic malignancies: the increased risk of severe complications of allogeneic SCT in patients who have previously received pembrolizumab is described in the SmPC, Section 4.4, 4.8 and appropriate advice is provided to the prescriber to minimize the risk. No additional risk minimisation measures warranted	Routine pharmacovigilance activities Additional pharmacovigilance including: ▪ Safety monitoring in the ongoing HL trial (KN204).
GVHD after pembrolizumab administration in patients with a history of allogeneic SCT	Routine risk minimisation measures: ▪ GVHD after pembrolizumab administration in patients with a history of allogeneic SCT is described in the SmPC, Section 4.4 and appropriate advice is provided to the prescriber to minimize the risk. No additional risk minimisation measures warranted	Routine pharmacovigilance activities Additional pharmacovigilance including: • Safety monitoring in all ongoing MAH-sponsored clinical trials for pembrolizumab in various tumor types

2.7. Update of the Product information

As a consequence of this new indication, sections 4.1, 4.8 and 5.1 of the SmPC have been updated. The Package Leaflet has been updated accordingly.

2.7.1. User consultation

A justification for not performing a full user consultation with target patient groups on the package leaflet has been submitted by the MAH and has been found acceptable for the following reasons: the changes to the patient leaflet are minimal; in particular the key messages for the safe use of the medicinal product are not impacted. Furthermore, the design, layout and format of the package leaflet will not be affected by the proposed revisions.

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

The final wording of the indication is the following: "*KEYTRUDA, in combination with carboplatin and paclitaxel, is indicated for the first-line treatment of primary advanced or recurrent endometrial carcinoma in adults who are candidates for systemic therapy*."

3.1.2. Available therapies and unmet medical need

Endometrial carcinoma (EC) is the second most common gynaecological malignancy worldwide. Incidence, prevalence, and mortality for EC are rising, likely related to increases risk factors including obesity, diabetes, and increased life expectancy[34]. Approximately 20-30% of patients with advanced or recurrent EC have dMMR/MSI-H disease[35] [36], in which immune-checkpoint inhibitors have demonstrated relevant activity, so that molecular classification through IHC staining for MMR proteins is currently recommended[37].

For recurrent/metastatic EC not amenable to surgery and/or RT, carboplatin plus paclitaxel should be considered the first-line therapy[39]. In combination with standard chemotherapy, dostarlimab has been approved as first-line treatment in the dMMR/MSI-H disease in the EU (based on RUBY trial)[38]. Results of similar studies of IO in combination with chemotherapy have been recently reported (AtTEnd, DUO-E), although anti-PD(L)1 agents are under investigation also as monotherapy in dMMR/MSI-H population, tested against chemotherapy (GINECO-EN105b/ENGOT-en13, DOMENICA, KEYNOTE-C93)[39]

Outcomes of advanced/recurrent disease remain poor, with 5-year OS rates of 20-25%. There is a need to improve outcomes in this population.

Pembrolizumab is already approved in the EU following prior platinum-containing therapy, as monotherapy in dMMR/MSI-H disease (EMEA/H/C/003820/II/0109, EC decision 25 April 2022) and in combination with lenvatinib regardless of MRR status (EMEA/H/C/003820/II/0105, EC decision 15 November 2021).

3.1.3. Main clinical studies

This extension of indication for Keytruda is based on the interim PFS analysis from the pivotal Phase III randomised, placebo-controlled NRG-GY018/KEYNOTE-868 study of pembrolizumab in addition to paclitaxel and carboplatin followed by pembrolizumab monotherapy for patients with stage III or IVA, stage IVB or recurrent EC. This is a study of two populations (pMMR and dMMR), powered for the primary endpoint PFS separately in each group. OS is descriptive secondary endpoint only. The results of the

[34] Morice P, Leary A, Creutzberg C, Abu-Rustum N, Darai E. Endometrial cancer. Lancet. 2016 Mar 12;387(10023):1094-108.
[35] Lorenzi M, Amonkar M, Zhang J, Mehta S, Liaw KL. Epidemiology of microsatellite instability high (MSI-H) and deficient mismatch repair (dMMR) in solid tumors: a structured literature review. J Oncol. 2020 Mar 9;2020:1807929.
[36] Kelkar SS, Prabhu VS, Zhang J, Ogando YM, Roney K, Verma RP, Miles N, Marth C. Real-world prevalence of microsatellite instability testing and related status in women with advanced endometrial cancer in Europe. Arch Gynecol Obstet. 2024 Apr 18.
[37] Oaknin A, Bosse TJ, Creutzberg CL, Giornelli G, Harter P, Joly F, Lorusso D, Marth C, Makker V, Mirza MR, Ledermann JA, Colombo N; ESMO Guidelines Committee. Endometrial cancer: ESMO Clinical Practice Guideline for diagnosis, treatment and follow-up. Ann Oncol. 2022 Sep;33(9):860-877.
[38] EMA/483641/2023, Jemperli-H-C-005204-II-0023: EPAR - Assessment Report - Variation
[39] Bogani G, Monk BJ, Powell MA, et al. Adding immunotherapy to first-line treatment of advanced and metastatic endometrial cancer. Ann Oncol. 2024 May;35(5):414-428.

Interim Analysis (IA), where the primary endpoint reached statistical significance in both populations, were submitted, followed by a descriptive updated analysis with 9 additional months of follow-up. The study was unblinded after IA. No final PFS analysis will be performed.

3.2. Favourable effects

- **pMMR**: a statistically significant PFS improvement (by investigator per RECIST 1.1) of the pembrolizumab +chemo vs placebo + chemo arm [HR 0.57 (95%CI 0.44, 0.74), p<0.0001), corresponding to a gain of 4.4 months in median PFS (13.1 vs 8.7)], was reached at IA. Minimal numerical increase in ORR (61.4% vs 51.5%) and DOR (7.1 vs 6.4 months). OS curves were overlapping and immature [HR 0.79 (95%CI 0.53, 1.17), but median OS was similar between both arms (28.0 vs 27.4 months)]. Updated descriptive analysis confirmed the PFS improvement with the addition of pembrolizumab, although reduced in magnitude [HR 0.74 (95%CI: 0.60, 0.91)]. The results of the other endpoints confirmed overall the findings at the IA, in particular no detriment in OS is suggested with longer follow-up [HR 0.80 (95% CI: 0.59, 1.08)].
- **dMMR**: a statistically significant PFS improvement with the addition of pembrolizumab vs placebo-containing arm [HR 0.34 (0.22, 0.53), p<0.0001, median NR vs 8.3 months, PFS rate at 1 y 73% vs 40%], with clear separation of KM curves was shown. More durable (mDOR NR vs 4.4 months) and deeper responses with increased CR rate (28.4% vs 11.6%). Positive (though still immature) OS trend [HR 0.55 (95%C: 0.25, 1.19)], supported by PFS2 [HR 0.31 (95% CI: 0.16, 0.62)]. The results of the updated descriptive analysis overall confirmed prior data [PFS HR 0.35 (95% CI: 0.23, 0.52); OS HR 0.57 (95%CI 0.31, 1.04)]. Biological plausibility of the observed more pronounced benefit from the addition of anti-PD1 in dMMR as compared to pMMR EC.

3.3. Uncertainties and limitations about favourable effects

- Post-hoc analyses by BICR are overall supportive of results by Investigator, although the retrospective nature of the BICR review and the fact that no BICR verification of investigator's declared progression before treatment discontinuation during the study was required limit the interpretation of analysis based on BICR assessment.
- tPD-L1 does not appear to be used as a biomarker to further select pMMR subjects for the treatment with pembrolizumab, although PD-L1 expression was not a stratification factor and there was a limited number of patients with negative PD-L1 tumors.

3.4. Unfavourable effects

- Almost all participants experienced **AEs** in all groups and about 95% in both arms experienced drug-related AEs. The following AEs occurred in a higher proportion of participants in the pembrolizumab plus chemotherapy group: Grade 3 to 5 AEs, Grade 3 to 5 drug-related AEs, SAEs, and drug-related SAEs.
- The incidence of the following AEs was higher (≥10% point difference) in the pembrolizumab plus chemotherapy group compared with the pooled pembrolizumab plus chemotherapy SD: fatigue, alopecia, constipation, peripheral sensory neuropathy, peripheral neuropathy, white blood cell count decreased, arthralgia, platelet count decreased, dyspnea, hyperglycemia, lymphocyte count decreased, and hypomagnesemia. The MAH argues that differences between the two groups may be due to variation in the chemotherapy regimens used and this could be reasonable.

- The overall incidence of **grade 3-5** Adverse Events and **related grade 3-5** Adverse Events were slightly higher in the pembrolizumab plus chemotherapy group (58.9% and 45%, respectively) compared with the placebo plus chemotherapy group (46.2% and 31.8%, respectively), but lower than the incidence in pooled pembrolizumab plus chemotherapy SD (78.5% and 66.3%, respectively). However, some grade 3-5 AEs such as white blood cell count decreased and lymphocyte count decreased were higher in pembrolizumab plus chemotherapy group (8.6% and 6%, respectively) compared to pooled pembrolizumab plus chemotherapy SD (6.4% and 1.8%, respectively).
- The overall incidence of **SAEs** in the pembrolizumab plus chemotherapy group (34.6%) was higher than the placebo plus chemotherapy group (19.4%), with a proportion not ≥2% point difference in individual SAEs.
- The most common **drug-related SAE** by PT was anaemia (3.4% vs 2.4% and 2%, respectively in pembrolizumab plus chemotherapy group, placebo plus chemotherapy group and pooled pembrolizumab plus chemotherapy SD).
- Overall, 6 participants in the pembrolizumab plus chemotherapy group had a **fatal AE** (5 in pMMR group and 1 in dMMR group) of which 1 AE occurring in the pMMR group was related to study treatment as assessed by the investigator (cardiac arrest).
- The overall incidence of **AESI** in the pembrolizumab plus chemotherapy group (35.9%) is higher compared to placebo plus chemotherapy group (25.5%) and to the pembrolizumab monotherapy RSD (27.3%), but generally consistent with the pooled pembrolizumab plus chemotherapy SD (35.2%). AESIs are especially driven by **infusion reactions** in both pembrolizumab plus chemotherapy group and placebo plus chemotherapy group (17.5% each) with a higher incidence compared to all other groups (8.7% and 2.2%).
- A higher rate of participants with Grade 3-5 AEs, Grade 3-5 drug-related AEs, SAEs, and drug-related SAEs was observed in **participants ≥75 years** old compared to those <75 years old in pembrolizumab plus chemotherapy group.
- With regards to the only fatal AE considered related to treatment, a causal relationship with pembrolizumab could not be established due to potentially confounding factors in the participant's clinical course, such as a prior medical history of thrombosis (concurrently requiring anticoagulation), dyspnea, diabetes, and extensive thoracic and intraabdominal metastatic endometrial carcinoma with the presence of ascites and pleural effusion. The causality with pembrolizumab was assessed as possible by the investigator and the Applicant preferred to keep a conservative approach, which is acceptable. However, from the updated safety analysis with DCO of 18 August 2023, a total of 10 participants with a fatal AE in the pembrolizumab plus chemotherapy group (4 additional deaths from previous IA) have been reported, of which 3 are considered related (2 due to cardiac arrest and 1 due to sepsis). Nevertheless, it was noticed that also in the placebo plus chemotherapy group, 2 participants experienced drug-related adverse events resulting in death, both in the SOC of infections and infestations, one due to sepsis and one due to septic shock. Therefore, for the time being, no imbalance in deaths due to infections are observed between the two arms, suggesting a possible causal contribution of chemotherapy.

3.5. Uncertainties and limitations about unfavourable effects

- Regarding the higher incidence of some AEs observed in **participants ≥75 years**, a similar pattern was observed in the pooled pembrolizumab plus chemotherapy SD and pembrolizumab monotherapy RSD, although with a smaller difference between groups, while it was not observed in the placebo plus chemotherapy group. However, when analyzing different type of AEs, no firm conclusion on a

specific trend can be drawn. In section 4.4 of the SmPC, a general warning for elderly patients over 75 years is already reflected.

3.6. Effects Table

Table 83: Effects Table for KEYTRUDA in combination with carboplatin and paclitaxel for the first-line treatment of primary advanced or recurrent endometrial carcinoma in adults who are candidates for systemic therapy [study KEYNOTE-868] (data cut-off: 16 December 2022 for dMMR participants and 06 December 2022 for pMMR participants)

Effect	Short description	Unit	Treatment	Control	Uncertainties / Strength of evidence	References
Favourable Effects						
PFS	By INV per RECIST 1.1, from randomisation to time of progression or death, whichever occurred first, or date of last contact if neither progression nor death had occurred.	Median (95%CI) HR (95%CI)	*pMMR* 13.1 (10.6, 19.5) *dMMR* NR (30.7, NR) *pMMR* 0.57 (0.44, 0.74) p<0.0001 *dMMR* 0.34 (0.22, 0.53) p<0.0001	*pMMR* 8.7 (8.4, 11) *dMMR* 8.3 (6.5, 12.3)	Updated PFS analysis confirmed the benefit of pembrolizumab, although interpretation is hampered by unblinding. BICR assessment supportive but BICR review limited.	CSR
OS	From randomisation to death or the date of last contact.	Median (95%CI) HR (95%CI)	*pMMR* 27.96 (21.4, NR) *dMMR* NR (NR, NR) *pMMR* 0.79 (0.53, 1.17) *dMMR* 0.55 (0.25, 1.19)	*pMMR* 27.37 (19.52, NR) *dMMR* NR (NR, NR)	Descriptive, immature; No detriment suggested with longer FU in pMMR	
ORR	Proportion of participants with CR or PR per RECIST 1.1 by INV in pts with measurable disease	ORR (95%CI)	*pMMR* 61.4% (54.6, 67.8) *dMMR* 77.9% (68.2, 85.8)	*pMMR* 51.5% (44.9, 58) *dMMR* 69.5%(59.2, 78.5)	BICR assessment supportive but BICR review limited.	
DOR	Time from the first response to the first progression	Median (range)	*pMMR* 7.1 (0+ - 32.8+) *dMMR* NR (0.0+ - 33.0+)	*pMMR* 6.4 (0+ - 20.1+) *dMMR* 4.4 (0.0+ - 32.8+)		
Unfavourable Effects						
		%	Pembro+chemo	Plb+chemo		
	Grade 3-5 AEs		58.9	46.2		
	SAEs		34.6	19.4		
	Serious drug-related		21.5	11.4		
	Deaths		6 (1.6%)	4 (1.1%)		

Abbreviations: PFS: progression-free survival; OS: overall survival; ORR: objective response rate; CR: complete response; PR: partial response; DOR: duration of response; PFS2: progression-free survival on next-line therapy; pMMR: mismatch repair proficient; dMMR: mismatch repair deficient; HR: hazard ratio

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

The pivotal phase 3 study KEYNOTE-868/NRG-GY018 investigated the use of pembrolizumab vs placebo added to standard 6 cycles of carboplatin/paclitaxel chemotherapy and then continued as maintenance as monotherapy in the first line advanced/recurrent endometrial cancer. PFS was used as primary endpoint, OS was a secondary endpoint however not statistically tested and thus descriptive only. It is endorsed that the study was designed to test separately the pMMR and dMMR populations, given the known higher activity of anti-PD(L)1 agents in dMMR EC, as already shown by pembrolizumab in 2L+ studies. Indeed, at the interim analysis, in the **dMMR** population the addition of pembrolizumab showed clinically relevant and statistically significant improvement in PFS together with durable responses and higher rate of CR. OS showed a positive numerical trend, but was highly immature and not statistically tested as per study design. Updated descriptive analysis overall confirmed the interim analysis findings.

As expected, the benefit of the addition of pembrolizumab in the **pMMR** population appeared more modest, although the PFS gain was statistically significant. Updated PFS analysis were provided and confirmed the benefit of adding pembrolizumab to chemotherapy, although more limited in magnitude as compared to IA. However, the study was unblinded after IA and patients in the control group were started on immunotherapy (IO) even before investigator's declared progression, hampering the interpretation of the updated analysis results. OS KM curves were mostly overlapping, but still immature at the IA and descriptive. Updated OS analysis suggest no detrimental trend with longer follow-up. Exploratory data according to PD-L1 status did not suggest that PD-L1 can be used as a biomarker to further select pMMR subjects for the treatment with pembrolizumab, acknowledging the fact that PD-L1 expression was not a stratification factor and the limited number of patients with negative PD-L1 expression.

The add-on treatment including a maintenance monotherapy phase led to increased toxicity compared to standard therapy, as expected, however, no new safety signal was identified in the pivotal study.

3.7.2. Balance of benefits and risks

The data showed a statistically significant PFS improvement and clinically relevant benefit of pembrolizumab in combination with carboplatin and paclitaxel for the first line treatment of the dMMR population of endometrial cancer, and of lower magnitude in the pMMR population. Benefits are considered outweighing the risks of the add-on pembrolizumab to standard chemotherapy.

3.7.3. Additional considerations on the benefit-risk balance

None.

3.8. Conclusions

The overall B/R of Keytruda is positive.

4. Recommendations

Outcome

Based on the review of the submitted data, the CHMP considers the following variation acceptable and therefore recommends by a majority the variation to the terms of the Marketing Authorisation, concerning the following change:

Variation accepted		**Type**	**Annexes affected**
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I and IIIB

Extension of indication for KEYTRUDA in combination with carboplatin and paclitaxel to include first-line treatment of primary advanced or recurrent endometrial carcinoma in adults who are candidates for systemic therapy, based on final results from study KEYNOTE-868. This is a randomised Phase 3, placebo-controlled, double-blind study of pembrolizumab vs placebo in combination with chemotherapy (paclitaxel plus carboplatin) for newly diagnosed Stage III/Stage IVA, Stage IVB, or recurrent endometrial cancer.
As a consequence, sections 4.1, 4.8 and 5.1 of the SmPC are updated. The package leaflet is updated accordingly. Version 46.1 of the RMP has also been agreed.

The variation leads to amendments to the Summary of Product Characteristics and Package Leaflet and to the Risk Management Plan (RMP).

Amendments to the marketing authorisation

In view of the data submitted with the variation, amendments to Annexes I and IIIB and to the Risk Management Plan are recommended.

5. EPAR changes

The EPAR will be updated following Commission Decision for this variation. In particular the EPAR module 8 "*steps after the authorisation*" will be updated as follows:

Scope

Please refer to the Recommendations section above.

Summary

Please refer to Scientific Discussion: Keytruda-H-C-3820-II-153.

Attachments

1. Product Information (changes highlighted) as adopted by the CHMP on 19 September 2024.

Reminders to the MAH

1. In accordance with Article 13(3) of Regulation (EC) No 726/2004 the Agency makes available a European Public Assessment Report (EPAR) on the medicinal product assessed by the Committee for Medicinal Products for Human Use. The EPAR is first published after the granting of the initial marketing authorisation (MA) and is continuously updated during the lifecycle of the medicinal product. In particular, following a major change to the MA, the Agency further publishes the assessment report of the CHMP and the reasons for its opinion in favour of granting the change to the authorisation, after deletion of any information of a commercially confidential nature.

   Should you consider that the CHMP assessment report contains commercially confidential information, **please provide the EMA Procedure Assistant your proposal for deletion of commercially confidential information** (CCI) in "track changes" and with detailed justification by 04 October 2024. The principles to be applied for the deletion of CCI are published on the EMA website at https://www.ema.europa.eu/en/documents/other/heads-medicines-agencies/european-medicines-agency-guidance-document-identification-commercially-confidential-information_en.pdf

   In addition, should you consider that the CHMP assessment report contains personal data, please provide the EMA Procedure Assistant your proposal for deletion of these data in "track changes" and with detailed justification by 04 October 2024. We would like to remind you that, according to Article 4(1) of Regulation (EU) 2016/679 (General Data Protection Regulation, "GDPR") 'personal data' means any information, relating to an identified or identifiable natural person (the 'data subject'). An identifiable natural person is one who can be identified, directly or indirectly, in particular by reference to an identifier such as a name, an identification number, location data, an online identifier or to one or more factors specific to the physical, physiological, genetic, mental, economic, cultural or social identity of that natural person.

   It is important to clarify that pseudonymised data are also considered personal data. According to Article 4(5) of GDPR pseudonymisation means that personal data is processed in a manner that the personal data can no longer be attributed to a specific data subject without the use of additional information (e.g. key-coded data).

   Accordingly, the name and the patient identification number are two examples of personal data which may relate to an identified or identifiable natural person. The definitions also encompass for instance: office e-mail address or phone number of a company, data concerning health, e.g. information in medical records, clinical reports or case narratives which relates to an identifiable individual."

2. The MAH is reminded to submit an eCTD closing sequence with the final documents provided by Eudralink during the procedure (including final PI translations, if applicable) within 15 days after the Commission Decision, if there will be one within 2 months from adoption of the CHMP Opinion, or prior to the next regulatory activity, whichever is first. If the Commission Decision will be adopted within 12 months from CHMP Opinion, the closing sequence should be submitted within 30 days after the Opinion. For additional guidance see chapter 4.1 of the Harmonised Technical Guidance for eCTD Submissions in the EU.

3. If a revised RMP is being approved as part of this procedure, **please send to the EMA Procedure Assistant** one redacted PDF document containing the RMP body, Annex 4 and Annex 6, as applicable, together with a redacted RMP file that can show the content that is proposed for redaction, and the signed RMP Publication Declaration, **by** 04 October 2024.