26 February 2026
EMADOC-1700519818-2758954
Medicinal Products for Human Use (CHMP)

Assessment report

Keytruda

International non-proprietary name: Pembrolizumab

Procedure No. EMA/VR/0000293815

Note

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

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List of abbreviations

Abbreviation	Full Text
1L	first-line
2L	second-line
ADA	anti-drug antibodies
ADC	antibody drug conjugate
AE	adverse event
AEOSI	adverse event of special interest
ALT	alanine aminotransferase
APaT	all participants as treated
BICR	blinded independent central review
BRCA	breast cancer gene
CI	confidence interval
CL	clearance
COVID-19	Coronavirus disease 2019
CPS	combined positive score
CR	complete response
DCO	data cutoff
DOR	duration of response
ECOG ^{PS}	Eastern Cooperative Oncology Group Performance Status
EMA	European Medicines Agency
EU	European Union
FA	final analysis
FDA	US Food and Drug Administration
FRα	folate receptor-alpha
GLOBOCAN	The Global Cancer Observatory
H	hypothesis
HER2	human epidermal growth factor receptor 2
HGSC	high-grade serous carcinoma
HR	hazard ratio
HRQoL	health-related quality of life
HRT	hormone replacement therapy
IA	interim analysis
IC	Investigator's choice chemotherapy
ICI	immune checkpoint inhibitor
IND	Investigational New Drug
ITT	intention-to-treat
KM	Kaplan Meier (Michaelis-Menten constant)
mOS	median overall survival
mPFS	median progression free survival
MSI	microsatellite instability
OC	ovarian cancer

Abbreviation	Full Text
ORR	objective response rate
OS	overall survival
PARP(i)	poly ADP ribose polymerase (inhibitor)
PD	pharmacodynamics
PD-1	programmed cell death protein 1
PD-L1	programmed cell death ligand 1
PD-L2	programmed cell death ligand 2
PFI	platinum-free interval
PFS	progression-free survival
PK	pharmacokinetics
PLD	pegylated liposomal doxorubicin
PR	partial response
PRO	patient-reported outcome
PROC	platinum-resistant ovarian cancer
PRROC	platinum-resistant recurrent ovarian cancer
PT	preferred term
RECIST1.1	Response Evaluation Criteria in Solid Tumors version 1.1
ROW	rest of world
RSD	reference safety dataset
SAE	serious adverse event
SD	stable disease
SDTM	Study Data Tabulation Model
SOC	standard of care
TIL	tumor infiltrating lymphocytes
ULN	upper limit of normal
US	United States
vs	versus

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 27 August 2025 an application for a variation.

The following changes were proposed:

Variation(s) requested		**Type**
C.I.6.a	C.I.6.a Addition of a new therapeutic indication or modification of an approved one	Variation type II

Extension of indication to include in combination with paclitaxel, with or without bevacizumab, the treatment of platinum-resistant epithelial ovarian, fallopian tube, or primary peritoneal carcinoma in adults whose tumours express PD-L1 with a CPS ≥ 1 and who have received one or two prior systemic treatment regimens for KEYTRUDA, based on interim results from study PB96V01MK3475 (KEYNOTE-B96); this is a Phase 3, randomized, double-blind study of pembrolizumab in combination with paclitaxel with or without bevacizumab for the treatment of platinum-resistant recurrent ovarian cancer. As a consequence, sections 4.1 and 5.1 of the SmPC are updated. The Package Leaflet is updated in accordance. Version 50.1 of the RMP has also been submitted. In addition, the MAH took the opportunity to introduce minor editorial changes to the PI.

The requested variation(s) proposed 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.

The PDCO issued an opinion on compliance for the PIP P/0043/2018.

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 application included a critical report addressing the possible similarity with authorised orphan medicinal products.

Scientific advice

The MAH did not seek Scientific Advice at the CHMP.

1.2. Steps taken for the assessment of the product

The Rapporteurs appointed by the CHMP were:

CHMP Rapporteur: Paolo Gasparini

Timetable	Actual dates
Submission date	27 August 2025
Start of procedure:	13 September 2025
CHMP Rapporteur's preliminary assessment report circulated on:	14 November 2025
PRAC Rapporteur's preliminary assessment report circulated on:	17 November 2025
PRAC members' comments:	19 November 2025
PRAC Rapporteur's updated assessment report circulated on:	20 November 2025
PRAC RMP advice and assessment overview adopted by PRAC:	27 November 2025
CHMP members' comments:	1 December 2025
CHMP Rapporteur's updated assessment report circulated on:	4 December 2025
Request for supplementary information and extension of timetable adopted by the CHMP on:	11 December 2025
MAH's responses submitted to the CHMP on:	19 December 2025
CHMP Rapporteur's preliminary assessment report on the MAH's responses circulated on:	3 February 2026
CHMP members' comments:	16 February 2026
CHMP Rapporteur's updated assessment report on the MAH's responses circulated on:	20 February 2026
CHMP opinion:	26 February 2026
The CHMP adopted a report for Keytruda on similarity product with Zejula and Elahere on:	26 February 2026

2. Scientific discussion

2.1.1. Problem statement

The scope of this variation is to add a new therapeutic indication for Keytruda for the treatment of platinum resistant epithelial ovarian, fallopian tube, or primary peritoneal carcinoma in adults based on the results of the KEYNOTE-B96 study.

Disease or condition

The MAH initially applied for the following indication:

"KEYTRUDA, in combination with paclitaxel, with or without bevacizumab, is indicated for the treatment of platinum-resistant epithelial ovarian, fallopian tube, or primary peritoneal carcinoma in adults whose tumours express PDL1 with a CPS ≥ 1 and who have received one or two prior systemic treatment regimens."

Epidemiology and risk factors

Ovarian cancer (OC) is the most lethal gynaecological cancer. Worldwide, as per GLOBOCAN 2022 estimates, there were 324,398 new cases of OC and 206,839 deaths due to OC, accounting for about 3.4% of cancer incidence and 4.8% of cancer mortality among women[1]. In 2022, 40,714[2] new cases were reported in the EU. An estimated 26,900 deaths will have occurred in 2025[3] in the EU.

Mortality due to OC has been declining in most of Europe since 1990s, largely due to the widespread use of combined oral contraceptives in the post-1950 generations in Europe. Advances in surgery and novel chemotherapeutic regimens, as well as diagnosis and management may have had some additional impact[4]. In the US, the overall 5-year relative survival rate for OC is ~51%, and ~31% for those with distant metastases. Lower 5-year relative survival rates are reported for elderly vs younger patients, and in Black patients[5] [6]. In the EU, the overall 5-year survival rate is less than 40%[7].

Infertility or nulliparity, oestrogen hormone treatment (such as HRT) and obesity have been reported as risk factors for epithelial OC (EOC)[8], while oral contraceptive use, especially over longer periods, and breastfeeding can reduce incidence[9]. Deleterious germline BRCA1/2 mutations are associated with a 16-65% increased risk of EOC, predominantly of high-grade serous histology[10]. Additionally, women with mutations in mismatch repair genes (Lynch syndrome) have a 10-12% lifetime risk of developing EOC[11].

Biologic features, aetiology and pathogenesis

The most common type of OC is epithelial OC (EOC), which represents a heterogeneous spectrum of disease entities at a clinical, pathological and molecular level. EOC is further subdivided into serous (high- and low-grade), endometrioid, clear cell, mucinous, carcinosarcoma, malignant Brenner tumour and others, based on histopathological, immunophenotypic features and molecular genetic findings. High-grade serous carcinoma (HGSC) is the most common type of epithelial OC (70%)[12].

[1] Bray F, Laversanne M, Sung H, Ferlay J, Siegel RL, Soerjomataram I, et al. Global cancer statistics 2022: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin. 2024;74:229-63.
[2] ECIS - European Cancer Information System. Available at https://ecis.jrc.ec.europa.eu. Accessed October 6, 2025.
[3] Wojtyla C, Bertuccio P, Giermaziak W, Santucci C, Odone A, Ciebiera M, et al. European trends in ovarian cancer mortality, 1990-2020 and predictions to 2025. Eur J Cancer. 2023;194:113350.
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[12] Matulonis UA. Management of newly diagnosed or recurrent ovarian cancer. Clin Adv Hematol Oncol. 2018 Jun;16(6):426-39.

Clinical presentation, diagnosis and stage/prognosis

Most patients with OC (70-80%) are still diagnosed at advanced stages due to lack of effective screening methods for early detection and absence of tumour-specific symptoms[13]. Irrespective of stage, patients with low grade serous and endometrioid tumours show better survival rates than HGSC. Carcinosarcoma has generally worse prognosis compared to HGSC[14].

Management

The standard systemic treatment for OC is platinum-based chemotherapy. Most (~85%) patients initially sensitive to platinum therapy ultimately develop recurrence and acquire progressive resistance over time[15]. Patients with platinum resistant disease have worse survival outcomes compared with patients with platinum-sensitive disease. Data from several retrospective studies showed mOS ranging from 16.7 to 22 months for patients with platinum-resistant recurrent ovarian cancer (PRROC) vs 54 to 95 months for platinum-sensitive (PSOC) patients. Median PFS was also shorter, at 4 to 7.9 months for PRROC vs 13.6 to 19.6 months for PSOC[16] [17].

First line treatment options for newly diagnosed OC include either cytoreductive surgery in patients who are fit for surgery, followed by platinum- and taxane-based, adjuvant/neoadjuvant chemotherapy, typically 6 cycles, with the addition of bevacizumab to SOC as an option in eligible patients. Patients with germline or somatic BRCA1/2 mutations (6-15% of all EOC, 22% of HGSC) can benefit from maintenance PARPi +/- bevacizumab. For patients without BRCA1/2 mutations who achieve either a CR or PR, maintenance therapy with a PARPi +/- bevacizumab, is recommended for patients with HRD-positive tumours, whereas bevacizumab alone remains an option for patients with no HRD positivity[18] [19].

Although ~80% of patients achieve response after 1L treatment, most patients (70-80%) relapse. Second line treatment consists of chemotherapy, depending on the platinum-sensitivity. Based on the platinum-free interval (PFI) i.e. the time between the last platinum dose and the date of relapse, OC is classified as platinum-resistant (progression within 6 months) or platinum-sensitive (progression ≥6 months). Platinum-refractory OC is defined as disease that has progressed within the first month of the last dose of last platinum-based therapy for OC[20]. Patients with platinum-sensitive disease may benefit

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[14] Lan A, Yang G. Clinicopathological parameters and survival of invasive epithelial ovarian cancer by histotype and disease stage. Future Oncol. 2019;15(17):2029-39.
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[18] National Comprehensive Cancer Network. NCCN clinical practice guidelines in oncology: ovarian cancer including fallopian tube cancer and primary peritoneal cancer; version 3.2024. Plymouth Meeting (PA): National Comprehensive Cancer Network (NCCN); 2024. 241 p.
[19] González-Martín A, Harter P, Leary A, Lorusso D, Miller RE, Pothuri B, Ray-Coquard I, Tan DSP, Bellet E, Oaknin A, Ledermann JA; ESMO Guidelines Committee. Newly diagnosed and relapsed epithelial ovarian cancer: ESMO Clinical Practice Guideline for diagnosis, treatment and follow-up. Ann Oncol. 2023 Oct;34(10):833-848.
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from 2L combination chemotherapy of platinum with paclitaxel, gemcitabine or PLD, followed by treatment with bevacizumab or PARP inhibitors (in patients with BRCA mutations)[21] [22].

Most patients with recurrent disease eventually develop platinum resistance. For patients with platinum-refractory/resistant OC, common treatment options are monotherapy with non-platinum compounds including weekly paclitaxel, topotecan, gemcitabine, PLD and oral metronomic cyclophosphamide, which have shown generally modest (<20%) response rates[23] [24]. There are no robust randomised data to support one agent over another, the choice is guided by patient preference and toxicity profile[25].

The addition of bevacizumab to single-agent chemotherapy (weekly paclitaxel, PLD, or topotecan) in the AURELIA study statistically improved PFS (median 6.7 vs 3.4 months) and ORR (27.3% vs 11.8%), but not OS (median 16.6 vs 13.3 months), compared with chemotherapy alone, with the largest effect seen when bevacizumab was combined with weekly paclitaxel in an exploratory analysis[26]. According to ESMO guidelines, bevacizumab should be recommended in combination with weekly paclitaxel, PLD or topotecan in patients without contraindications to bevacizumab and not previously exposed to bevacizumab[27].

More recently, mirvetuximab soravtansine, a folate receptor alpha (FRα)-directed ADC, showed in the phase 3 MIRASOL study statistically significant longer mPFS (5.62 vs 3.98 months) and mOS (16.46 vs 12.75 months) compared with chemotherapy alone[28], leading to FDA and EMA approval in FR-α positive OC[29]. Treatments with the HER2-directed antibody and topoisomerase inhibitor conjugate trastuzumab deruxtecan was approved in the US in HER2-expressing tumours, including resistant OC, based on the phase 2 DESTINY-PanTumor-02 which showed an ORR of 45% in the ovarian HER2 expressing cohort[30].

Novel and effective therapies are still necessary in this advanced setting.

The efficacy of immune-checkpoint inhibitors (ICIs) in EOC is less clear compared to other gynaecological malignancies. Despite evidence that immune-checkpoint molecules such as PD-1 and PD-L1 can be expressed in ovarian cancer cells, and that a positive correlation between the presence of tumour-infiltrating lymphocytes and favourable survival outcomes, the results of trials with ICIs in OC

[21] National Comprehensive Cancer Network. NCCN clinical practice guidelines in oncology: ovarian cancer including fallopian tube cancer and primary peritoneal cancer; version 3.2024. Plymouth Meeting (PA): National Comprehensive Cancer Network (NCCN); 2024. 241 p.
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[26] Pujade-Lauraine E, Hilpert F, Weber B, Reuss A, Poveda A, Kristensen G, et al. Bevacizumab combined with chemotherapy for platinum-resistant recurrent ovarian cancer: The AURELIA open-label randomized phase III trial. J Clin Oncol. 2014 May 1;32(13):1302-8. Erratum in: J Clin Oncol. 2014 Dec 10;32(35):4025.
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[28] Moore KN, Angelergues A, Konecny GE, Garcia Y, Banerjee S, Lorusso D, et al. Mirvetuximab soravtansine in FR alpha-Positive, platinum-resistant ovarian cancer. N Engl J Med. 2023 Dec 7;389(23):2162-74.
[29] EMA/473768/2024 - Elahere CHMP EPAR EMEA/H/C/005036/0000, https://www.ema.europa.eu/en/documents/assessment-report/elahere-epar-public-assessment-report_en.pdf
[30] Meric-Bernstam F, Makker V, Oaknin A, Oh DY, Banerjee S, Gonzalez-Martin A, et al. Efficacy and safety of trastuzumab deruxtecan in patients with HER2-expressing solid tumors: primary results from the DESTINY-PanTumor02 phase II trial. J Clin Oncol. 2023 Oct 23;42(1):47-58.

have been disappointing so far, and no ICIs has received regulatory approval to date for this tumour type[31] [32].

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. The PD-1 receptor is a negative regulator of T cell activity that has been shown to be involved in the control of T cell immune responses. KEYTRUDA potentiates T cell responses, including anti-tumour responses, through blockade of PD-1 binding to PD-L1 and PD-L2, which are expressed in antigen presenting cells and may be expressed by tumours or other cells in the tumour microenvironment.

In the EU, KEYTRUDA was granted first approval by the European Commission on 17 July 2015 for patients with advanced melanoma, and is currently approved for several indications in solid tumours.

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

Table 1 Overview of Pembrolizumab Clinical Development Program in Ovarian Cancer

Study Number/ Status	Design	Population	Dosage, Regimen	Primary Efficacy Endpoint(s)
Phase 1				
KEYNOTE-028 NCT02054806 (ovarian cohort completed)	Phase 1b, open-label, non-randomized multi-cohort study of pembrolizumab monotherapy	Participants with recurrent OC and positive PD-L1 expression who were not responsive to prior chemotherapies	Pembrolizumab 10 mg Q2W	ORR

[31] Ghisoni E, Morotti M, Sarivalasis A, Grimm AJ, Kandalaft L, Laniti DD, Coukos G. Immunotherapy for ovarian cancer: towards a tailored immunophenotype-based approach. Nat Rev Clin Oncol. 2024 Nov;21(11):801-817.
[32] Yanaihara N, Tse KY, Lee SJ, Yoo JG, Wilailak S. Immune checkpoint inhibitors in gynecologic oncology: Current status and perspectives. Int J Gynaecol Obstet. 2025 Sep;171 Suppl 1(Suppl 1):166-188.

Study Number/ Status	Design	Population	Dosage, Regimen	Primary Efficacy Endpoint(s)
KEYNOTE-PN409 NCT02606305 Completed	Phase 1b/2 open-label, non-randomized to evaluate safety, tolerability and PK of mirvetuximab soravtansine in combination with bevacizumab, carboplatin, PLD, pembrolizumab, or bevacizumab + carboplatin	Participants with folate receptor alpha positive advanced epithelial ovarian cancer, primary peritoneal cancer, or fallopian tube cancer	Regimen A: mirvetuximab soravtansine + bevacizumab Dose Escalation and Dose Expansion phase. Regimen B: mirvetuximab soravtansine + carboplatin in Dose Escalation phase. Regimen C: mirvetuximab soravtansine + PLD in Dose Escalation Phase. Regimen D: mirvetuximab soravtansine + pembrolizumab in Dose Escalation and Dose Expansion phase. Regimen E: mirvetuximab soravtansine + bevacizumab + carboplatin in Dose Expansion phase.	AEs and safety profile, ORR
KEYNOTE-C70 NCT05271318 Ongoing	Phase 1, open-label, dose-escalation of oncolytic adenovirus TILT-123 in combination with pembrolizumab	Participants with PRROC (including fallopian tube and primary peritoneal cancer)	Multiple administrations of TILT-123 and pembrolizumab. Escalation to the next dose of TILT-123 level will occur when the safety data has been evaluated for all participants in the preceding dose level	AEs and safety profile

Study Number/ Status	Design	Population	Dosage, Regimen	Primary Efficacy Endpoint(s)
Phase 2				
KEYNOTE-100 NCT02674061 Completed	Phase 2, open-label study of pembrolizumab monotherapy	Cohort A: Recurrent OC, 1 to 3 prior lines of therapy and PFI or TFI of 3 to 12 months. Cohort B: Participants with recurrent OC, 4 to 6 prior lines of therapy and PFI or TFI of ≥3 months (Cohort B).	Pembrolizumab 200 mg Q3W	ORR
KEYNOTE-162 NCT02657889 Completed	Phase 1/2 multicenter, open-label, single-arm study of niraparib in combination with pembrolizumab	Advanced/metastatic TNBC: Phase 1: up to 4 lines of therapy Phase 2: up to 2 lines of therapy Recurrent OC Phase 1: up to 5 lines of therapy Phase 2: up to 4 lines of therapy	Pembrolizumab 200 mg Q3W Niraparib: 100 mg to 300 mg qd in Phase 1 200 mg qd in Phase 2 (RP2D)	Phase 1: Evaluate DLTs, establish RP2D Phase 2: ORR
KEYNOTE-191 NCT02537444 Completed	Phase 2, multicenter, open-label, randomized study of ACP-196 monotherapy and the combination of ACP-196 and pembrolizumab	Participants with platinum-sensitive recurrent OC after anticancer treatment with at least 1 taxane	Monotherapy Arm: ACP-A96 100 mg bid Combination Arm: ACP-A96 100 mg bid	Characterize the safety profile of ACP-196 and pembrolizumab

Study Number/ Status	Design	Population	Dosage, Regimen	Primary Efficacy Endpoint(s)
MK-4830-002 NCT05446870 Completed	Phase 2 multicenter, open-label study of pembrolizumab and chemotherapy with or without MK-4830	Participants with advanced HGSOC who are candidates for interval debulking surgery	Arm 1: Neoadjuvant phase: 3 cycles of carboplatin/paclitaxel + pembrolizumab + MK-4830 before surgery. Adjuvant phase: 3 cycles of carboplatin/paclitaxel + pembrolizumab + MK-4830 ± bevacizumab after surgery Arm 2: Neoadjuvant phase: 3 cycles of carboplatin/paclitaxel + pembrolizumab prior to surgery. Adjuvant phase: 3 cycles of carboplatin/paclitaxel + pembrolizumab ± bevacizumab after surgery	ctDNA: change from baseline
KEYNOTE-409/KEYNOTE-E24/GOG-3081 NCT05446298 Ongoing	Phase 2 Randomized Open-label Multicenter Study of Combination of ONC-392 and Pembrolizumab for the Treatment of Patients With Platinum Resistant Ovarian Cancer (PROC)	Participants with ovarian cancer who are resistant to platinum-based chemotherapy and have disease progression on line of therapy containing bevacizumab.	Arm A: Pembrolizumab, followed by ONC-392 at 1.0 mg/kg, q3w. Arm B: Pembrolizumab, followed by ONC-392 at 2.0 mg/kg, q3w.	ORR

Study Number/ Status	Design	Population	Dosage, Regimen	Primary Efficacy Endpoint(s)
Phase 3				
KEYNOTE-B96 NCT05116189 Ongoing	Phase 3, randomized, placebo-controlled, multi-site, double-blind study of pembrolizumab in combination with paclitaxel/docetaxel ± bevacizumab	Participants with PRROC (all comers and those whose tumors have PD-L1 expression) and have received ≤ 2 prior lines of therapy.	Arm 1 (pembrolizumab + paclitaxel ± bevacizumab) Arm 2 (placebo + paclitaxel ± bevacizumab)	PFS per RECIST 1.1 by inv in CPS ≥1 PFS per RECIST 1.1 by inv in all participants
KEYNOTE-C71 Completed NCT05092360	Phase 3, multicenter, open-label, randomized study of nemvaleukin in combination with pembrolizumab versus protocol-specific investigator's choice chemotherapy	Participants with PRROC who have received ≥1 and ≤5 prior lines of therapy and ≥1 line of therapy containing bevacizumab	Arm 1: Nemvaleukin and pembrolizumab combination therapy Arm 2: Pembrolizumab (enrollment completed) Arm 3: Nemvaleukin (enrollment completed) Arm 4: Investigator's choice chemotherapy (PLD, paclitaxel, topotecan, or gemcitabine)	OS

Study Number/ Status	Design	Population	Dosage, Regimen	Primary Efficacy Endpoint(s)
KEYLYNK-001 / ENGOT-ov43 / GOG-3036) Ongoing NCT03740165	Phase 3, randomized, double-blind, 3-arm, parallel study of chemotherapy with or without pembrolizumab followed by maintenance with olaparib or placebo	Participants with previously untreated BRCA1/2 non-mutated advanced EOC	Arm 1: Treatment: carboplatin/ paclitaxel for 5 cycles + pembrolizumab 200 mg Q3W for up to 35 infusions Maintenance: olaparib 300 mg bid Arm 2: Treatment: carboplatin/ paclitaxel for 5 cycles + pembrolizumab 200 mg Q3W for up to 35 infusions Maintenance: olaparib placebo (bid) Arm 3: Treatment: carboplatin/ paclitaxel for 5 cycles + pembrolizumab placebo Q3W for up to 35 infusions Maintenance: olaparib placebo (bid)	PFS

No Scientific Advice was requested to the CHMP by the MAH on the KEYNOTE-B96 study.

2.1.4. General comments on compliance with GCP

The assessment of the data has not raised concerns regarding GCP compliance of the pivotal KEYNOTE-B96 study.

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 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 community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

- **Tabular overview of clinical studies**

Table 2 Conducted clinical studies

KEYNOTE-B96 NCT05116189 Ongoing	Phase 3, randomized, placebo-controlled, multi-site, double-blind study of pembrolizumab in combination with paclitaxel/docetaxel ± bevacizumab	Participants with PRROC (all comers and those whose tumors have PD-L1 expression) and have received ≤ 2 prior lines of therapy.	Arm 1 (pembrolizumab + paclitaxel ± bevacizumab) Arm 2 (placebo + paclitaxel ± bevacizumab)	PFS per RECIST 1.1 by inv in CPS ≥1 PFS per RECIST 1.1 by inv in all participants

2.3.2. Pharmacokinetics

The recommended dose of KEYTRUDA in adults is either 200 mg every 3 weeks or 400 mg every 6 weeks administered as an intravenous infusion over 30 minutes.

Pharmacokinetic (PK) data from study KEYNOTE-B96 were used in support of 400 mg Q6W (as well as 200 mg Q3W) as the recommended dose of pembrolizumab in combination with paclitaxel, with or without bevacizumab, in participants with PRROC who have received up to 2 prior lines of therapy.

Substantial characterization of the PK and immunogenicity of pembrolizumab 200 mg Q3W have been provided in previous submissions. In particular, pembrolizumab PK disposition has been characterized via pooled population PK analyses using serum concentration-time data contributed from subjects across various clinical studies using a time-dependent PK (TDPK) model. The PK reference dataset for monotherapy includes all available PK data from subjects enrolled in studies KEYNOTE-001, KEYNOTE-002, KEYNOTE-006, KEYNOTE-010, and KEYNOTE-024, with an overall sample size of 2993. This serves as the PK reference analysis to support descriptions of pembrolizumab pharmacokinetics in the USPI and in the EU SmPC.

In addition to initially licensed dosing regimens of 200 mg Q3W or 2 mg/kg Q3W, an additional dosing regimen of 400 mg Q6W was subsequently approved in the EU for all adult monotherapy indications (procedure number EMEA/H/C/003820/II/0062) and for all adult indications in combination with other anticancer agents (procedure number EMEA/H/C/003820/II/0102) regardless of the combination treatment type.

Absorption

Pembrolizumab is dosed via the intravenous route and therefore is immediately and completely bioavailable.

Distribution

Consistent with a limited extravascular distribution, the volume of distribution of pembrolizumab at steady state is small (6.0 L; coefficient of variation [CV]: 20%). As expected for an antibody, pembrolizumab does not bind to plasma proteins in a specific manner.

Elimination

Pembrolizumab clearance (CL) is approximately 23% lower (geometric mean, 195 mL/day [CV%: 40%]) after achieving maximal change at steady state compared with the first dose (252 mL/day [CV%: 37%]); this decrease in CL with time is not considered clinically meaningful. The geometric mean value (CV%) for the terminal half-life is 22 days (32%) at steady-state.

Pharmacokinetic in target population

Considering that an extensive characterization of the PK and immunogenicity profile of pembrolizumab have been provided in previous submissions, in this procedure the focus is on the data related to the characterization of the pharmacology for the combination of pembrolizumab with paclitaxel, with or without bevacizumab, in the context of its intended use for the treatment of patients with PRROC.

PK data from KEYNOTE-B96

KEYNOTE-B96 is an ongoing, randomized, phase 3, placebo-controlled, multisite, double-blind study of pembrolizumab in combination with paclitaxel, with or without bevacizumab, in participants with PRROC who have received up to 2 prior lines of therapy (for study design, see figure 3 in section 2.4.1).

Participants enrolled into the KEYNOTE-B96 study who were randomized to the pembrolizumab in combination with paclitaxel, with or without bevacizumab arm for the treatment of platinum-resistant recurrent ovarian cancer were dosed with pembrolizumab 400 mg Q6W.

PK analysis of pembrolizumab

The objectives of the PK analysis were:

- To evaluate pembrolizumab (MK-3475) concentrations obtained from participants receiving pembrolizumab in combination with paclitaxel and bevacizumab, in study KEYNOTE-B96
- To compare observed pembrolizumab PK data in KEYNOTE-B96 for participants receiving pembrolizumab in combination with paclitaxel and bevacizumab with reference model (TDPK model based) predicted pembrolizumab PK.

Table 3 Overview of participants included in KEYNOTE-B96 Pembrolizumab PK Analysis

Study/Cohort	Cancer Type	Treatment	Number of Participants Providing PK[a]
KEYNOTE-B96	platinum-resistant recurrent ovarian cancer	400 mg pembrolizumab Q6W + paclitaxel with bevacizumab	132

a Unique participants providing an evaluable PK sample;
Q6W = Every 6 weeks.

Data source: 08W5JH - adpc

Pharmacokinetic samples collected with a cut-off date of 05 March 2025 were measured for 132 participants. Samples from 10 patients were excluded from the final PK analysis, due to different reasons such as PK samples with unreliable values, Cycle 1 predose samples with a concentration above BLQ, PK samples with incorrect visit information, PK samples which are drawn out of the time window, and outliers.

The PK analysis dataset was constructed from the final locked Study Data Tabulation Model (SDTM) datasets using SAS version 9.4 and contains the observed pembrolizumab serum concentrations and actual elapsed blood sampling times relative to the corresponding time of dose. Summary statistics were calculated based on nominal time after administered dose.

The PK sampling schedule in the KEYNOTE-B96 study included pre-infusion pembrolizumab serum concentrations (Ctrough) obtained within 72 hours prior to dose administration in Cycle 1, 2 and Cycle 5.

Phoenix™ WinNonlin® (Version 8.6.0) software was used for pharmacokinetic analysis.

Summary descriptive statistics of the pre-dose and post-dose concentrations by cycle are presented in the below table.

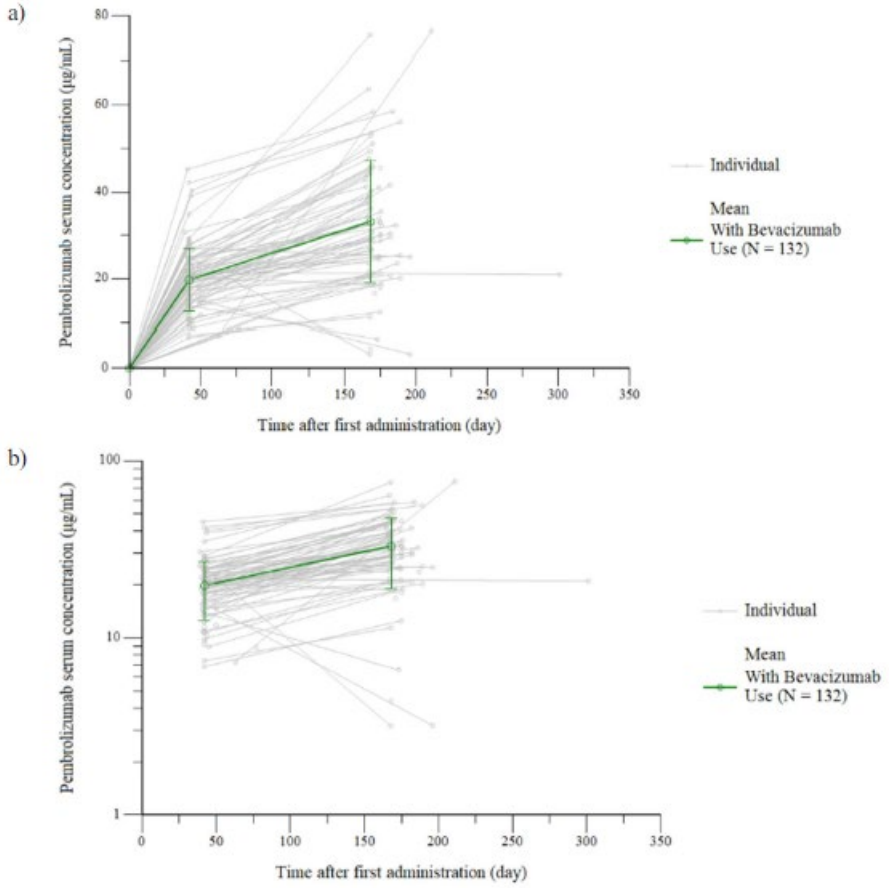
Table 4 Summary Statistics of pembrolizumab predose (C_{trough}) serum concentration values after pembrolizumab (400 mg Q6W) with paclitaxel and bevacizumab administration, in participants with platinum-resistant recurrent ovarian cancer (KEYNOTE-B96)

Bevacizumab	Cycle	N	GM (%GCV)	AM (SD)	Min (µg/mL)	Median (µg/mL)	Max (µg/mL)
With Bevacizumab Use	1	91	-	0.00 (0.00)	0.00	0.00	0.00
	2	108	18.5 (38.4)	19.8 (7.17)	6.91	19.3	45.3
	5	87	29.4 (61.7)	33.1 (14.1)	3.17	32.1	76.5
AM = Arithmetic mean; GM = Geometric mean; %GCV = Geometric coefficient of variation; SD = Standard deviation; - = not applicable.							

Data source: 08W5JH - adpc

Individual pre-dose serum pembrolizumab concentration-time profiles with mean ± SD profile overlaid are shown in the figure below.

Figure 1 Individual and arithmetic mean (SD) pembrolizumab predose concentration – time profiles after pembrolizumab (400 mg Q6W) with paclitaxel and bevacizumab administration, in participants with platinum-resistant recurrent ovarian cancer (KEYNOTE-B96), (a) Linear scale, (b) Log scale

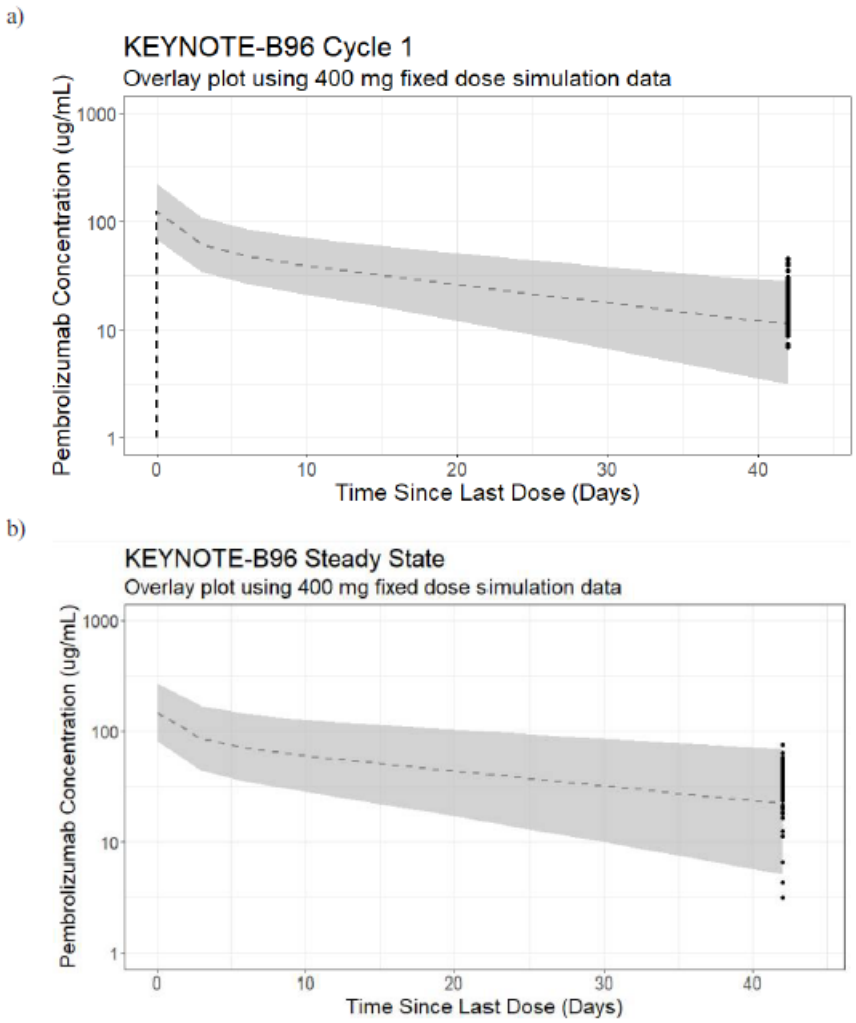


Note: Note: Grey lines represent individual concentration observations. Green lines represent arithmetic mean concentrations and error bars are associated +/- SD (Standard deviation).

Data source: 08W5JH – adpc

Observed pembrolizumab concentration data in the KEYNOTE-B96 study for pembrolizumab are overlaid on the simulated profile using the reference PK model (both at cycle 1 and steady-state) as shown in the below figure.

Figure 2 Observed pembrolizumab concentration data after pembrolizumab (400 mg Q6W) with paclitaxel and bevacizumab administration, with reference model-predicted pharmacokinetic profile for 400 mg Q6W dose regimen at Cycle 1 to Steady State (KEYNOTE-B96)



Note: Pembrolizumab model predictions and observed concentration data from KEYNOTE-B96 participants of the global Study a) after 1st dose and b) at Cycle 5 (24 weeks), with a 84 day time since last dose sample cut off ; Symbols are individual observed data (nominal time); black dashed line is median predicted concentrations from the model for a regimen of 400 mg Q6W and the grey shaded area represents the 90% prediction interval; plots are displayed on log scale.

Data source: 08W5JH - adpc

2.3.3. Pharmacodynamics

Mechanism of action

KEYTRUDA is an antibody that binds to the programmed death-1 (PD-1) receptor and blocks its interaction with ligands PD-L1 and PD-L2. The PD-1 receptor is a negative regulator of T-cell activity that has been shown to be involved in the control of T-cell immune responses. KEYTRUDA potentiates T-cell responses, including anti-tumour responses, through blockade of PD-1 binding to PD-L1 and PD-L2, which are expressed in antigen presenting cells and may be expressed by tumours or other cells in the tumour microenvironment.

Primary and secondary pharmacology

Immunogenicity

The existing immunogenicity assessment for pembrolizumab for the monotherapy setting is based on a sufficiently large dataset of patients across several indications, with very low observed rates of total treatment ADA across different pembrolizumab regimens (1.4 – 3.8%) as well as of neutralizing antibodies (0.4 – 1.6%). This analysis has not demonstrated an impact on the efficacy or safety, as currently summarized in the EU SmPC and USPI. This low rate of immunogenicity has been shown to be consistent across tumour type and no clinically meaningful consequences have been observed in the subjects with a positive immunogenicity reading. Additionally, incidence of ADA has not been impacted by the presence of other drugs (small molecule or chemotherapy) in combination with pembrolizumab.

An immunogenicity evaluation after treatment with pembrolizumab in combination with bevacizumab and paclitaxel has been performed in the context of this extension of indication, using data from the KEYNOTE-B96 study in participants with platinum-resistant recurrent ovarian cancer. Only the participants treated with pembrolizumab combined with bevacizumab and paclitaxel are included in this analysis.

In the KEYNOTE-B96 study, ADA samples were available from 150 participants, of which 135 were treated with pembrolizumab combined with bevacizumab and paclitaxel. A subset of the 135 participants was not assessable for drug-induced immunogenicity because the participants were not treated with pembrolizumab or only a pre-treatment ADA sample was available (N=7). The remaining 128 participants (including 22 Chinese and 6 Japanese participants) were assessable for drug-induced immunogenicity analysis.

Table 5 Overview of participants included in the immunogenicity analysis after pembrolizumab (400 mg Q6W) combination therapy with paclitaxel and bevacizumab, in participants with platinum-resistant recurrent ovarian cancer (KEYNOTE-B96)

Study	Number of Participants		
	Participants Providing ADA Samples	Participants treated with Pembrolizumab and Bevacizumab and Paclitaxel	Assessable Participants Dosed with Pembrolizumab and Post Treatment Samples
Pembrolizumab Combination Therapy			
KEYNOTE-B96	150	135	128

Data source: 08X0CR - adada

An overview of the immunogenicity status of all assessable participants is reported in the below table.

Table 6 Summary of participant pembrolizumab immunogenicity results after pembrolizumab (400 mg Q6W) combination therapy with bevacizumab and paclitaxel, in participants with platinum-resistant recurrent ovarian cancer (KEYNOTE-B96)

Pembrolizumab Therapy			
Immunogenicity status	**All participants**	**Chinese participants**	**Japanese participants**
Total participants[a]	135	24	6
Not Evaluable participants[b]	7	2	0
Evaluable participants[c]	**128**	**22**	**6**
Negative[d]	125 (97.7%)	22 (100%)	6 (100%)
Inconclusive[e]	3 (2.3%)	0 (0%)	0 (0%)
Non-Treatment emergent positive[d]	0 (0%)	0 (0%)	0 (0%)
Treatment emergent positive[d]	0 (0%)	0 (0%)	0 (0%)
Treatment induced	0 (0%)	0 (0%)	0 (0%)
Treatment boosted	0 (0%)	0 (0%)	0 (0%)

a: All participants with at least one ADA sample available.
b: Not evaluable participants are the number of participants who do not have a ADA sample available after treatment with pembrolizumab.
c: Evaluable participants are the total number of negative and positive participants (non-treatment emergent and treatment emergent).
d: Denominator was total number of evaluable participants.
e: Inconclusive participants are the number of participants with no positive ADA samples present and the drug concentration in the last sample above the drug tolerance level.

Data source: 08X0CR - adada

The observed incidence of treatment emergent ADA in the evaluable participants in the KEYNOTE-B96 study is 0% (0 out of 128), based on no (0) participants with confirmed treatment emergent positive status, 3 inconclusive subjects and 125 with a negative immunogenicity status.

2.3.4. PK/PD modelling

No new information regarding PK/PD modelling for pembrolizumab is available within this extension of indication.

2.3.5. Discussion on clinical pharmacology

This variation application to extend the use of pembrolizumab (Keytruda; 400 mg Q6W and 200 mg Q3W) in combination with paclitaxel with or without bevacizumab for the treatment of platinum-resistant epithelial ovarian, fallopian tube, or primary peritoneal carcinoma is supported by the pivotal clinical study KEYNOTE-B96. In this procedure, the focus is on PK data from study KEYNOTE-B96. Characterizations of pembrolizumab's PK and ADA in the same combination treatment was assessed by CHMP during the KEYNOTE-826 review procedure (EMEA/H/C/003820/II/0117 extension of indication : Keytruda, in combination with chemotherapy with or without bevacizumab, is indicated for the treatment of persistent, recurrent, or metastatic cervical cancer in adults whose tumours express PD-L1 with a CPS ≥ 1).

PK data from the KEYNOTE-B96 study showed that the observed pembrolizumab serum concentration values in subjects with PRROC are contained within the 90% CI of the reference PK model, which indicates consistency with the historical data, after first dose (pre-dose cycle 2) and at steady state (cycle 5).

Making references to data submitted in other extension of indications, the concentrations reached at steady-state in patients with PROC from study KEYNOTE-B96 seems similar to that reached in other studies where pembrolizumab was administered as a single agent.

In the KEYNOTE-B96 study, ADA samples were available from 150 participants, of which 135 were treated with pembrolizumab combined with bevacizumab and paclitaxel and 128 participants were assessable for the drug-induced immunogenicity analysis.

The observed incidence of treatment emergent ADA in the evaluable participants in the KEYNOTE-B96 study is 0% (0 out of 128), based on no (0) participants with confirmed treatment emergent positive status, 3 inconclusive subjects and 125 with a negative immunogenicity status.

In conclusion, the PK and ADA results from participants in the KEYNOTE-B96 study were consistent with the previously reported data, confirming that pembrolizumab PK's disposition is not affected by co-administration of paclitaxel and bevacizumab.

2.3.6. Conclusions on clinical pharmacology

Pembrolizumab's PK disposition is not affected by the co-administration with paclitaxel and bevacizumab in patients with PROC. Observed concentrations from the KEYNOTE-B96 study overlaid on the reference model predicted median concentrations both at Cycle 1 and at steady state and are consistent with other globally approved studies for pembrolizumab in different cancer indications. In the same way, the known immunogenicity profile of pembrolizumab is not affected by the co-administration of bevacizumab.

2.4. Clinical efficacy

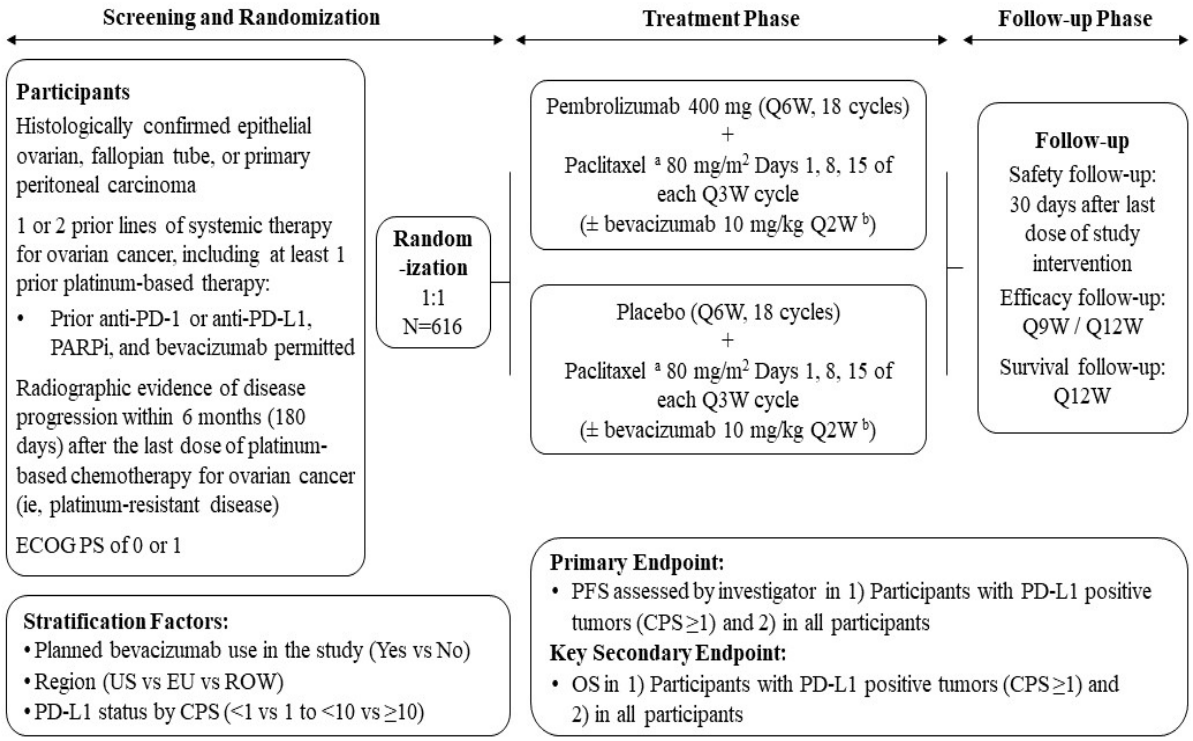
2.4.1. Dose response study

No dose-response studies specific for the indication in ovarian cancer have been performed.

2.4.2. Main study

KEYNOTE-B96 / ENGOT-ov65: A Phase 3, Randomized, Double-Blind Study of Pembrolizumab versus Placebo in Combination With Paclitaxel With or Without Bevacizumab for the Treatment of Platinum-resistant Recurrent Ovarian Cancer

Figure 3 KEYNOTE-B96 Study Diagram



Abbreviations: CPS=combined positive score; ECOG PS =Eastern Cooperative Oncology Group Performance Status; EU=European Union; OS=overall survival; PARPi=poly(adenosine-ribose) polymerase inhibitor; PD-1=programmed cell death 1; PD-L1=programmed cell death 1 ligand 1; PFS=progression-free survival; q2/3/6/9/12w=every 2/3/6/9/12 weeks; ROW=Rest of World; US=United States.

Pembrolizumab/placebo may only be administered for 18 q6w cycles. Paclitaxel and/or bevacizumab may continue until disease progression, prohibitive toxicity, other protocol-defined reason for discontinuation, or the participant has received the maximum duration (if applicable) per the respective approved label or local practice.

[a] Paclitaxel-related toxicities were to be managed according to local practice and institutional guidelines with supportive care measures, dose interruptions, and reductions before consideration of discontinuation, if clinically appropriate. Docetaxel (75 mg/m^2 q3w) could be considered for participants who experienced either a severe hypersensitivity reaction to paclitaxel or an AE requiring discontinuation of paclitaxel only after consultation with the Sponsor. Refer to Appendix 7 of the protocol [Ref. 5.3.5.1: PB96V01MK3475: 16.1.1] for country-specific requirements.

[b] The use of bevacizumab was optional and could be administered to eligible participants at the investigator's discretion. Use of bevacizumab had to be decided before randomization as it was a stratification factor.

Methods

Study participants

Main inclusion criteria

Female participants at least 18 years of age were eligible if they met all of the following key inclusion criteria:

- Had histologically confirmed epithelial (including high-grade serous or predominantly serous, low-grade serous, any-grade endometrioid, malignant mixed Müllerian tumours [carcinosarcoma], or clear cell) ovarian, fallopian tube, or primary peritoneal carcinoma.
- Had received 1 or 2 prior lines of systemic therapy for OC, including at least 1 prior platinum-based therapy.

    - Participants must have received at least 4 cycles but not more than 9 cycles of platinum-based therapy in 1L.
    - Participants may have received a prior PARPi, anti-PD-1/anti-PD-L1 or bevacizumab.
- Had radiographic evidence of disease progression within 6 months (180 days) after the last dose of platinum-based chemotherapy for OC (i.e. platinum-resistant disease).
    - Note: Participants with secondary platinum-refractory disease who were either platinum-resistant or platinum-sensitive in the 1L were eligible.
- Was a candidate for paclitaxel chemotherapy (and bevacizumab, if using).
- Had an ECOG performance status of 0 to 1 assessed within 3 days before randomization.
- Provided tumour tissue sample for prospective determination of PD-L1 status.

Main exclusion criteria

Participants were excluded from the study if they met any of the following key exclusion criteria:

- Had nonepithelial cancers (germ cell tumours and sex cord-stromal tumours), borderline tumours (low malignant potential), mucinous, seromucinous that was predominantly mucinous, malignant Brenner's tumour and undifferentiated carcinoma.
- Had primary platinum-refractory disease, defined as disease that had progressed per radiographic imaging while receiving or within 28 days of the last dose of first-line platinum-based therapy.
- Had prior disease progression on weekly paclitaxel alone.
- Had received >2 prior lines of systemic therapy for OC.
- For participants who were to receive bevacizumab:
    - Had uncontrolled hypertension.
    - Had current, clinically relevant bowel obstruction (including subocclusive disease) including related to underlying epithelial OC, abdominal fistula or gastrointestinal perforation, intra-abdominal abscess, or evidence of rectosigmoid involvement by pelvic exam.
    - Had a history of thrombotic disorders, hemorrhage, hemoptysis, or active GI bleeding within 6 months before randomization.
- Has an active autoimmune disease that has required systemic treatment in the past 2 years (i.e. with use of disease modifying agents, corticosteroids, or immunosuppressive drugs). Replacement therapy (e.g. thyroxine, insulin, or physiologic corticosteroid replacement therapy for adrenal or pituitary insufficiency) is not considered a form of systemic treatment and is allowed.

Treatments

Pembrolizumab IV 400 mg Q6W for 18 cycles or placebo IV Q6W for 18 cycles were given in combination with paclitaxel IV 80 mg/m2 on days 1, 8, 15 of each Q3W cycle until disease progression or prohibitive toxicity (docetaxel IV 75 mg/m2 Q3W until disease progression or prohibitive toxicity was used in place of paclitaxel in participants who discontinued or had a severe hypersensitivity reaction to paclitaxel, only after sponsor consultation), and bevacizumab (if using) IV 10 mg/kg Q2W

until disease progression or prohibitive toxicity. The option to use bevacizumab was by investigator choice prior to randomisation.

Tumour assessment

Tumour assessment was performed at screening. The first on-study scan was performed at 9 weeks from the date of randomization. Subsequent tumour scans were performed every 9 weeks or more frequently if clinically indicated, and every 12 weeks after 54 weeks. Scans were performed until disease progression identified by the investigator, or until the start of new anticancer treatment, withdrawal of consent, pregnancy, death, or the end of the study, whichever occurs first. Participants who were clinically stable may be treated beyond RECIST 1.1 radiographic progression after consultation with the Sponsor.

Objective responses were confirmed by a repeat scan performed at least 4 weeks after the first indication of a response was observed.

Participant eligibility and the primary PFS endpoint were determined using local assessment (investigator assessment) based on RECIST 1.1. All scheduled scans were submitted for assessment of the secondary PFS endpoint by BICR.

Objectives and endpoints

Table 7 Objectives and endpoints

Primary Objective	**Primary Endpoint**
To compare pembrolizumab plus paclitaxel with or without bevacizumab to placebo plus paclitaxel with or without bevacizumab, with respect to PFS per RECIST 1.1 as assessed by the investigator Hypothesis (H1): pembrolizumab plus paclitaxel with or without bevacizumab is superior to placebo plus paclitaxel with or without bevacizumab, with respect to PFS per RECIST 1.1 as assessed by the investigator for participants with PD-L1 positive tumors (CPS ⩾1) Hypothesis (H2): pembrolizumab plus paclitaxel with or without bevacizumab is superior to placebo plus paclitaxel with or without bevacizumab, with respect to PFS per RECIST 1.1 as assessed by the investigator for all participants	PFS: The time from randomization to the first documented disease progression or death due to any cause, whichever occurs first
Secondary Objectives	**Secondary Endpoints**
To compare pembrolizumab plus paclitaxel with or without bevacizumab to placebo plus paclitaxel with or without bevacizumab, with respect to OS Hypothesis (H3): Pembrolizumab plus paclitaxel with or without bevacizumab is superior to placebo plus paclitaxel with or without bevacizumab, with respect to OS for participants with PD-L1 positive tumors (CPS ≥1)	OS: The time from randomization to death due to any cause

Hypothesis (H4): Pembrolizumab plus paclitaxel with or without bevacizumab is superior to placebo plus paclitaxel with or without bevacizumab, with respect to OS for all participants	
To compare pembrolizumab plus paclitaxel with or without bevacizumab to placebo plus paclitaxel with or without bevacizumab, with respect to PFS per RECIST 1.1 by BICR for participants with PD-L1 positive tumors (CPS ≥1) and all participants	PFS
To evaluate the safety and tolerability of pembrolizumab in combination with paclitaxel with or without bevacizumab	- AEs - Study treatment discontinuation due to AEs
To compare pembrolizumab plus paclitaxel with or without bevacizumab to placebo plus paclitaxel with or without bevacizumab, with respect to GHS/QoL score using the EORTC QLQ-C30 and abdominal and GI symptoms using the EORTC QLQ-OV28 abdominal/GI symptom scale for participants with PD-L1 positive tumors (CPS ≥1) and all participants	Change from baseline and TTD of the QoL and symptom scores from the GHS/QoL scale (items 29 and 30) of the EORTC QLQ-C30 and the abdominal/GI symptom scale (items 31 to 36) of the EORTC QLQ-OV28 respectively.
Tertiary/Exploratory Objectives	**Tertiary/Exploratory Endpoints**
To evaluate the ORR per RECIST 1.1 as assessed by the investigator, in participants with measurable disease per RECIST 1.1 at baseline, for participants with PD-L1 positive tumors (CPS ≥1) and all participants	Objective response: confirmed CR or PR
To evaluate the TFST, the TSST, and the TDT for participants with PD-L1 positive tumors (CPS ≥1) and all participants	-TFST: The time from the date of randomization until initiation of first subsequent anticancer treatment or death due to any cause, whichever occurs first -TSST: The time from the date of randomization until initiation of second subsequent anticancer treatment or death due to any cause, whichever occurs first -TDT: The time from the date of randomization to discontinuation of study treatment or death due to any cause, whichever occurs first
To evaluate the TWiST for participants with PD-L1 positive tumors (CPS ≥1) and all participants	TWiST, the time from the date of randomization until disease progression or treatment-related toxicity, whichever occurs first
To evaluate other health-related QoL scale scores of the EORTC QLQ-C30 and the EORTC QLQ-OV28 for participants with PD-L1 positive tumors (CPS ≥1) and all participants	Health-related QoL using scales/items of the EORTC QLQ-C30 and the EORTC QLQ-OV28 other than the GHS/QoL scale (items 29 and 30) of the EORTC QLQ-C30 and the abdominal/GI symptom scale (items 31 to 36) of the EORTC QLQ-OV28

To characterize health utilities using the EQ-5D-5L for participants with PD-L1 positive tumors (CPS ≥1) and all participants	Health utilities using the EQ-5D-5L
To evaluate the PFS2 after discontinuation of study intervention as determined by the investigator according to the local standard of practice for participants with PD-L1 positive tumors (CPS ≥1) and all participants	PFS2: The time from randomization to subsequent disease progression after initiation of new anticancer treatment as assessed by the investigator according to the local standard of practice, or death due to any cause, whichever occurs first

Sample size

In the initial protocol, the study planned to randomize ~616 participants in a 1:1 ratio into the pembrolizumab plus paclitaxel with or without bevacizumab arm and in the placebo plus paclitaxel with or without bevacizumab arm, assuming a 50% prevalence of PD-L1 CPS ≥1 in the study population. By using the same assumptions and methodologies of the original protocol, the target number of events, as well as the sample size and power calculations, were updated on 31 January 2024 in the final protocol (version 04) to reflect the actual PD-L1 CPS prevalence. In the final protocol, it was reported that the study randomized 643 participants, based on blinded review of study data showing that the observed prevalence of PD-L1 CPS ≥1 in this study was about 72%.

For PFS in participants with CPS ≥1, based on a target number of ~ 389 events at the final PFS analysis (IA2) and 1 interim analysis at approximately 85% of the target number of events, the study has ~ 98% power to detect a HR of 0.66 at the initially allocated α=0.02 (1-sided). For PFS in all participants, based on a target number of ~ 541 events at the final PFS analysis (IA2) and 1 interim analysis at approximately 85% of the target number of events, the study has ~ 94% power to detect a HR of 0.70 at the initially allocated α=0.005 (1-sided).

OS in participants with CPS ≥1 was only to be tested if the null hypotheses of PFS in all participants and in participants with CPS ≥1 are rejected. For OS in participants with CPS ≥1, based on a target number of ~ 369 events at the final analysis and 2 interim analyses at approximately 53%, and 74% of the target number of events, the study has ~ 96% power to detect a HR of 0.68 at the α=0.025 (1-sided). OS in all participants is to be tested if the null hypothesis of OS in participants with CPS ≥1 is rejected. For OS in all participants, based on a target number of ~ 512 events at the final analysis and 2 interim analyses at approximately 53%, and 74% of the target number of events, the study has ~ 98% power to detect a HR of 0.70 at the α=0.025 (1-sided). The power calculations are based on a constant HR assumption, and assume the following:

a. PFS follows an exponential distribution with a median of 7 months for the control group.

b. OS follows an exponential distribution with a median of 18 months for the control group.

c. Enrollment period of 18 months.

d. An annual dropout rate of 8% and 2% for PFS and OS, respectively.

e. A follow-up period of ~ 20 and ~ 46 months for PFS and OS, respectively, after the last participant is randomized.

Randomisation

Participants were assigned randomly in a 1:1 ratio, stratified according to the following factors:

1. Planned bevacizumab use in the study (yes vs no)

2. Region (US vs EU vs ROW)

3. PD-L1 status (CPS <1 vs CPS 1 to <10 vs CPS≥10)

Intervention randomization occurred centrally using an interactive response technology (IRT) system; a permuted block design with block size of 4 for each stratum was used.

Blinding (masking)

KEYNOTE-B96 is a double-blind study. Pembrolizumab and pembrolizumab placebo were prepared and/or dispensed in a blinded fashion by an unblinded pharmacist or qualified study-site personnel. The participant, the investigator, and Sponsor personnel or delegate(s) involved in the study intervention administration or clinical evaluation of the participants were unaware of the intervention assignments. Study intervention identification information was to be unmasked only if necessary for the welfare of the participant.

The Sponsor ensured that unblinded aggregated efficacy endpoint events and safety data were monitored to safeguard the participants in the study. Treatment-level results from the interim analyses were provided to the data monitoring committee (DMC) by the unblinded statistician. The official, final database was not to be unblinded until medical/scientific review has been performed, protocol deviations have been identified, and data has been declared final and complete. Overall, unblinding occurred similarly in both treatment arms (pembrolizumab= 31/322=9.6% vs placebo= 43/321=13.4%; median time (days) to unblinding: Pembrolizumab=324 vs Placebo=351). Additional analyses exclude biases in PFS assessments after unblinding.

Statistical methods

Statistical methods for key efficacy analyses and sensitivity analyses

The stratification factors used for randomization, eventually combined as specified in the SAP, were planned to be used for all stratified analyses.

The nonparametric Kaplan-Meier method was used to estimate PFS and OS in each treatment group. The treatment difference in PFS was assessed by the stratified log-rank test. A stratified Cox proportional hazard model with Efron’s method of tie handling was used to assess the magnitude of the treatment difference (i.e. HR) between the treatment arms. The HR and its 95% CI from the stratified Cox model with a single treatment covariate were reported.

The censoring rules for the primary and sensitivity analyses of PFS are summarized below:

Table 8 Censoring rules for primary and sensitivity analyses of PFS

Situation	Primary Analysis	Sensitivity Analysis 1	Sensitivity Analysis 2
PD or death documented after ≤1 missed disease assessment, and before new anticancer treatment, 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
Death or progression immediately after ≥2 consecutive missed disease assessments, or after new anticancer treatment	Censored at last disease assessment prior to the earlier date of ≥2 consecutive missed disease assessment and new anticancer treatment, if any	Progressed at date of documented PD or death	Progressed at date of documented PD or death
No PD and no death; and new anticancer treatment is not initiated	Censored at last disease assessment	Censored at last disease assessment	Progressed at treatment discontinuation due to reasons other than complete response; otherwise censored at last disease assessment if still on study treatment or completed study treatment.
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 new anticancer treatment

Abbreviation: PD=progressive disease

Only the primary censoring rule were applied for the analysis of PFS by BICR assessment.

For OS, participants without documented death at the time of analysis were censored at the date the participant was last known to be alive.

For PFS2, participants alive and for whom a disease progression following initiation of new anticancer treatment was not observed were censored at the last time the participant was known to be alive and without disease progression. The same stratified Cox proportional hazard model was used to estimate the HR and its 95% CI.

The stratified Miettinen and Nurminen method was used for the comparison of ORR between the two treatment arms. The difference in ORR and its 95% CI from the stratified Miettinen and Nurminen method with strata weighting by sample size were reported.

Strata

According to factors used in the randomization procedure, a total of 18 strata were used for randomization. For the purpose of analysis, small strata were planned to be combined to ensure sufficient data in each stratum; details regarding the pooling strategy were planned to be pre-specified in the sSAP prior to the database lock for the first efficacy analysis.

Subgroup analyses

The between-group treatment effect for PFS and OS (with a nominal 95% CI) was estimated and plotted by treatment group within each category of the subgroup variables listed below, to assess the consistency of treatment effect, using descriptive statistics. The subgroup analyses for PFS and OS were conducted using an unstratified Cox model. The subgroup analyses were performed in participants with CPS ≥1 and in all participants, with the exception of the analysis by tumour PD-L1 expression level, which was only performed in all participants. If the number of participants in a category of a subgroup variable was less than 10% of the ITT population, the subgroup analysis may have not be performed for this category. Enclosed below is a list of planned subgroup analyses:

- Actual bevacizumab use in the study (yes vs no)
- Region (US vs EU vs ROW)
- Actual PD-L1 status (CPS<1 vs CPS 1 to <10 vs CPS>=10)

- Age (<65 years versus >=65 years)
- Race (white vs non-white)
- ECOG performance status (0 vs 1)
- Prior PARPi use (yes vs no)
- Platinum free interval (<3 months vs 3-6 months from last platinum therapy to subsequent progression).

Interim analyses

Two efficacy interim analyses were planned in addition to the final analysis, see table below.

Table 9 Summary of Interim and Final analysis strategy

Analyses	Key Endpoints	Timing	Estimated Time After First Participant Randomized	Primary Purpose of Analysis
IA1	PFS OS	• ~ 9 months after last participant randomized, and • ~ 331 PFS events have been observed in participants with CPS ≥1, and • ~ 460 PFS events have been observed in all participants. [a]	~ 27 months	• Interim PFS analysis • Interim OS analysis
IA2	PFS OS	• ~ 20 months after last participant randomized, and • ~ 389 PFS events have been observed in participants with CPS ≥1, and • ~ 541 PFS events have been observed in all participants. a	~ 38 months	• Final PFS analysis • Interim OS analysis
FA	OS	• ~ 369 OS events have been observed in participants with CPS ≥1, and • ~ 512 OS events have been observed in all participants. [b]	~ 64 months	• Final OS analysis

Abbreviations: CPS=combined positive score; FA=final analysis; IA1=interim analysis 1; IA2=interim analysis 2; OS=overall survival; PFS=progression-free survival.

Note that IA1, IA2, and the FA are triggered by the specified number of events in both populations (CPS ≥1 and all participants).

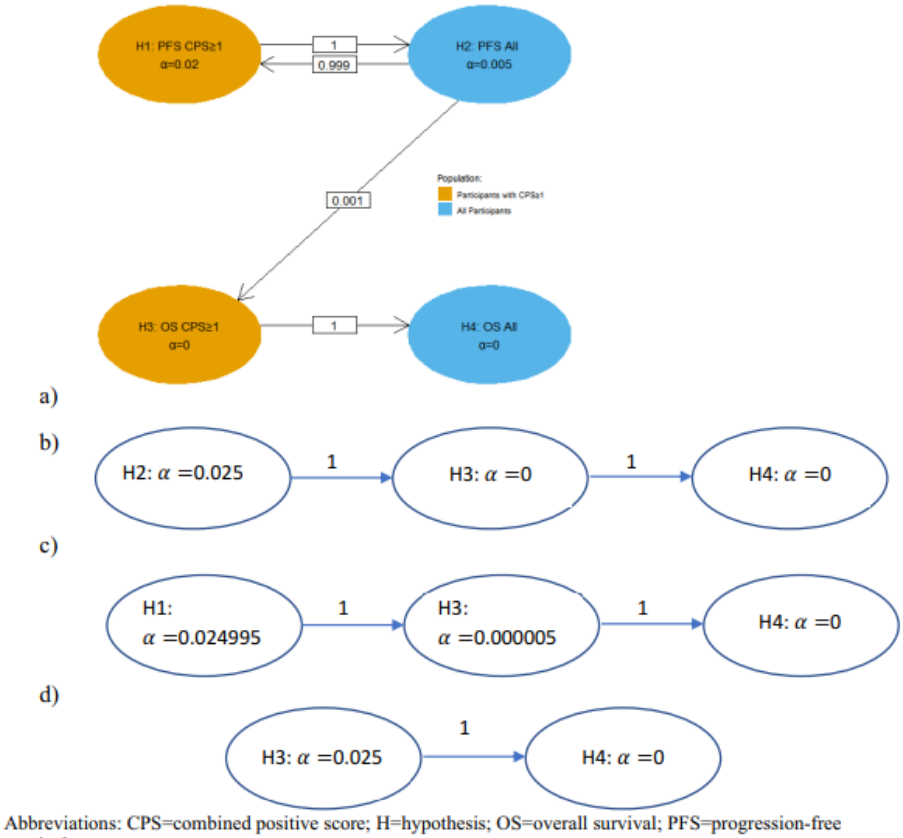
[a] IA1 and IA2 may be delayed for up to 2 months if one of the planned numbers of PFS events in participants with CPS ≥1 or PFS events in all participants has been reached, but the other has not yet been reached.

[b] FA may be delayed for up to 6 months if one of the planned numbers of OS events in participants with CPS ≥1 or OS events in all participants has been reached, but the other has not yet been reached.

Multiplicity control

The study used the graphical method of Maurer and Bretz (Maurer, W. and Bretz, F.et al. 2013) to provide strong multiplicity control for multiple hypotheses as well as interim analyses. The family-wise Type I error rate for this study was strongly controlled at 0.025 (one-sided) across the 2 primary hypotheses on PFS and the 2 secondary hypotheses on OS. The initial α assigned to PFS endpoints was 0.02 to PFS in participants with CPS ≥1 and 0.005 to PFS in all participants, respectively. No initial α was assigned to OS endpoints. If the null hypothesis of PFS in participants with CPS ≥1 (H1) is rejected, the corresponding alpha can be reallocated to PFS in all participants (H2). If the null hypothesis of PFS in all participants (H2) is rejected, the corresponding alpha can be reallocated to PFS in participants with CPS ≥1 (H1). If both H1 and H2 are rejected, the corresponding alpha can be reallocated to OS in participants with CPS ≥1 (H3). If the null hypothesis of OS in participants with CPS ≥1 is rejected (H3), the corresponding alpha can be reallocated to OS in all participants (H4). A detailed graphical illustration of multiplicity strategy with illustration of the fallback procedure is provided below.

Figure 4 Multiplicity diagram for Type I error control



Abbreviations: CPS=combined positive score; H=hypothesis; OS=overall survival; PFS=progression-free survival.

Bounds and boundary properties

Updated efficacy boundaries and properties derived using a Lan-DeMets spending function approximating O'Brien-Fleming bounds – according to the parameters specified in sample size calculations - are reported in the below tables.

Table 10 Efficacy Boundaries and Properties for Progression-free Survival Analysis

Endpoint: PFS in Participants With CPS ≥1			
Analysis	**Value**	**α=0.02**	**α=0.025[e]**
IA1: 85%* N = 466 Events: 331 Month: 27	Z	2.2692	2.1688
	p (1-sided)[a]	0.0116	0.0150
	~HR at bound[b]	0.7791	0.7877
	P(Cross) if HR=1[c]	0.0116	0.0150
	P(Cross) if HR=0.66[d]	0.9352	0.9470
IA2 (Final PFS Analysis) N = 466 Events: 389 Month: 38	Z	2.1279	2.0392
	p (1-sided)[a]	0.0167	0.0207
	~HR at bound[b]	0.8059	0.8131
	P(Cross) if HR=1[c]	0.0200	0.0250
	P(Cross) if HR=0.66[d]	0.9780	0.9824
Endpoint: PFS in All Participants			
Analysis	**Value**	**α=0.005**	**α=0.025**
IA1: 85%* N = 643 Events: 460 Month: 27	Z	2.8297	2.1687
	p (1-sided)[a]	0.0023	0.0151
	~HR at bound[b]	0.7680	0.8169
	P(Cross) if HR=1[c]	0.0023	0.0151
	P(Cross) if HR=0.7[d]	0.8421	0.9519
IA2 (Final PFS Analysis) N = 643 Events: 541 Month: 38	Z	2.6269	2.0391
	p (1-sided)[a]	0.0043	0.0207
	~HR at bound[b]	0.7978	0.8392
	P(Cross) if HR=1[c]	0.0050	0.0250
	P(Cross) if HR=0.7[d]	0.9400	0.9845

Abbreviations: CPS=combined positive score; HR=hazard ratio; IA1=interim analysis 1; IA2=interim analysis 2; PFS=progression-free survival.

The number of events and timing are estimated.

*Percentage of total planned events at the interim analysis.

[a] *p* (1-sided) is the nominal α for testing.

[b] HR at bound is the approximate HR required to reach an efficacy bound.

[c] P (Cross if HR=1) is the probability of crossing a bound under the null hypothesis.

[d] P(Cross if HR=0.66) or P(Cross if HR=0.7) is the probability of crossing a bound under the alternative hypothesis (power) for each PFS endpoint, respectively.

[e] The numbers in this column are calculated at α level of 0.024995 (0.02+0.005*0.999) for PFS in participants with CPS≥1.

Table 11 Efficacy Boundaries and Properties for Overall Survival Analysis

Endpoint: OS in Participants With CPS ≥1		
Analysis	**Value**	**α=0.025**
IA1: 53%* N = 466 Events: 196 Month: 27	Z	2.8660
	p (1-sided)[a]	0.0021
	~HR at bound[b]	0.6635
	P(Cross) if HR=1[c]	0.0021
	P(Cross) if HR=0.68[d]	0.4337
IA2: 74%* N = 466 Events: 273 Month: 38	Z	2.3858
	p (1-sided)[a]	0.0085
	~HR at bound[b]	0.7490
	P(Cross) if HR=1[c]	0.0092
	P(Cross) if HR=0.68[d]	0.7927
Final N = 466 Events: 369 Month: 64	Z	2.0121
	p (1-sided)[a]	0.0221
	~HR at bound[b]	0.8109
	P(Cross) if HR=1[c]	0.0250
	P(Cross) if HR=0.68[d]	0.9570

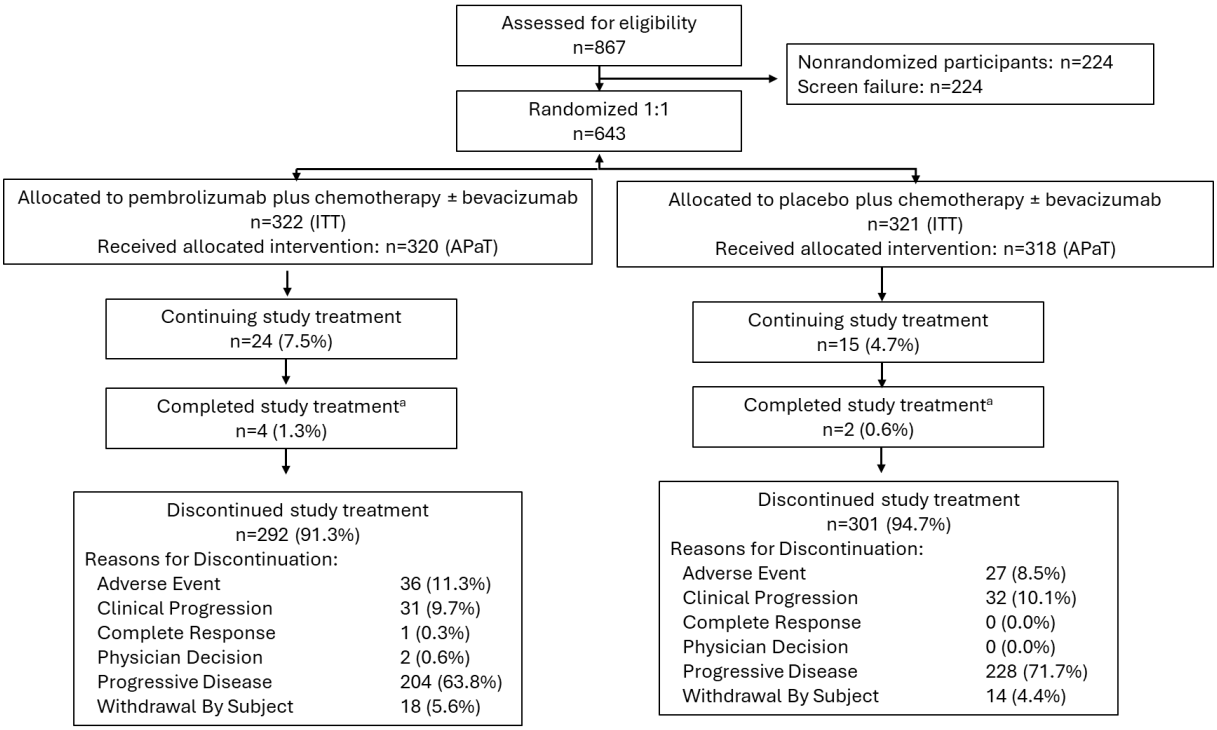
Endpoint: OS in All Participants		
Analysis	**Value**	**α=0.025**
IA1: 53%* N: 643 Events: 271 Month: 27	Z	2.8660
	p (1-sided)[a]	0.0021
	~HR at bound[b]	0.7060
	P(Cross) if HR=1[c]	0.0021
	P(Cross) if HR=0.70[d]	0.5292
IA2: 74%* N: 643 Events: 369 Month: 38	Z	2.3858
	p (1-sided)[a]	0.0085
	~HR at bound[b]	0.7825
	P(Cross) if HR=1[c]	0.0092
	P(Cross) if HR=0.70[d]	0.8641
Final N: 643 Events: 512 Month: 64	Z	2.0121
	p (1-sided)[a]	0.0221
	~HR at bound[b]	0.8370
	P(Cross) if HR=1[c]	0.0250
	P(Cross) if HR=0.70[d]	0.9796

Abbreviations: CPS=combined positive score; HR=hazard ratio; IA1=interim analysis 1; IA2=interim analysis 2; OS=overall survival.
The number of events and timing are estimated.
The scenario of α=0.000005 is not included in the table due to very small numbers.
*Percentage of total planned events at the interim analysis.
[a] *p* (1-sided) is the nominal α for testing.
[b] HR at bound is the approximate HR required to reach an efficacy bound.
[c] P (Cross if HR=1) is the probability of crossing a bound under the null hypothesis.
[d] P(Cross if HR=0.68) or P(Cross if HR=0.70) is the probability of crossing a bound under the alternative hypothesis (power) for each OS endpoint, respectively.

Results

Participant flow

Figure 5 Participant flow diagram



APaT=all participants as treated; ITT=intent-to-treat
[a] Completed study treatment refers to completion of 18 cycles of pembrolizumab or placebo

A total of 867 participants were screened, and 224 nonrandomized participants were screen failure. Not randomised participants who did not meet inclusion criteria/did meet exclusion criteria (n=221) were mostly due to not having adequate organ function as per protocol (n=39, 17.6%) or not providing informed consent (n=20, 9%).

Table 12 Disposition of Participants - All Participants (ITT population)

	Pembrolizumab + Chemotherapy		Placebo + Chemotherapy		Total	
	n	(%)	n	(%)	n	(%)
Participants in population	322		321		643	
Status for Study Medication in Trial						
Started	320		318		638	
Completed	4	(1.3)	2	(0.6)	6	(0.9)
Discontinued	292	(91.3)	301	(94.7)	593	(92.9)
Adverse Event	36	(11.3)	27	(8.5)	63	(9.9)
Clinical Progression	31	(9.7)	32	(10.1)	63	(9.9)
Complete Response	1	(0.3)	0	(0.0)	1	(0.2)
Physician Decision	2	(0.6)	0	(0.0)	2	(0.3)
Progressive Disease	204	(63.8)	228	(71.7)	432	(67.7)
Withdrawal By Subject	18	(5.6)	14	(4.4)	32	(5.0)
Ongoing	24	(7.5)	15	(4.7)	39	(6.1)
Status for Trial						
Discontinued	227	(70.5)	248	(77.3)	475	(73.9)
Death	221	(68.6)	240	(74.8)	461	(71.7)
Withdrawal By Subject	6	(1.9)	8	(2.5)	14	(2.2)
Ongoing	95	(29.5)	73	(22.7)	168	(26.1)

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: 05MAR2025

Table 13 Disposition of Participants All Participants With PD-L1 CPS⩾1 (ITT Population)

	Pembrolizumab + Chemotherapy		Placebo + Chemotherapy		Total	
	n	(%)	n	(%)	n	(%)
Participants in population	234		232		466	
Status for Study Medication in Trial						
Started	233		230		463	
Completed	4	(1.7)	1	(0.4)	5	(1.1)
Discontinued	210	(90.1)	216	(93.9)	426	(92.0)
Adverse Event	28	(12.0)	20	(8.7)	48	(10.4)
Clinical Progression	14	(6.0)	18	(7.8)	32	(6.9)
Complete Response	1	(0.4)	0	(0.0)	1	(0.2)
Physician Decision	1	(0.4)	0	(0.0)	1	(0.2)
Progressive Disease	152	(65.2)	166	(72.2)	318	(68.7)
Withdrawal By Subject	14	(6.0)	12	(5.2)	26	(5.6)
Ongoing	19	(8.2)	13	(5.7)	32	(6.9)
Status for Trial						
Discontinued	158	(67.5)	177	(76.3)	335	(71.9)
Death	154	(65.8)	172	(74.1)	326	(70.0)
Withdrawal By Subject	4	(1.7)	5	(2.2)	9	(1.9)
Ongoing	76	(32.5)	55	(23.7)	131	(28.1)

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: 05MAR2025

Recruitment

First participant first visit: 13 December 2021

Last participant randomized: 03 July 2023

Interim analysis 1 (IA1): Data cut-off date 03 April 2024; median survival follow-up duration for all participants 11.8 months (range 0.1, 27).

Interim analysis 2 (IA2): Data cut-off date 05 March 2025; median survival follow-up duration for all participants 15.6 months (range 0.1, 38).

Final analysis (FA): Data cut-off date 5 September 2025; median follow-up duration for all participants 15.6 months (range 0.1, 44.1).

The study was conducted at 156 centres in 24 countries (Australia, Belgium, Brazil, Canada, Chile, China, Columbia, Denmark, Finland, France, Germany, Ireland, Israel, Italy, Japan, Republic of Korea, Mexico, Netherlands, New Zealand, Norway, Poland, Turkey, UK, and US).

Table 14 Summary of Follow-up Duration IA1 Population With PD-L1 CPS>=1 (ITT Population)

Follow-up duration (months)[a]	Pembrolizumab + Chemotherapy (N=234)	Placebo + Chemotherapy (N=232)	Total (N=466)
Median (Range)	12.3 (0.7, 26.7)	11.5 (0.5, 27.0)	12.0 (0.5, 27.0)
Mean (SD)	12.5 (5.1)	11.8 (5.1)	12.2 (5.1)
[a] Follow-up duration is defined as the time from randomization to the date of death or the database cutoff date if the participant is still alive. Database Cutoff Date: 03APR2024			

Table 15 Summary of Follow-up Duration IA2 Population With PD-L1 CPS>=1 (ITT Population)

Follow-up duration (months)[a]	Pembrolizumab + Chemotherapy (N=234)	Placebo + Chemotherapy (N=232)	Total (N=466)
Median (Range)	18.2 (0.7, 37.5)	14.0 (0.5, 38.0)	15.8 (0.5, 38.0)
Mean (SD)	17.5 (8.6)	15.5 (8.4)	16.5 (8.6)
[a] Follow-up duration is defined as the time from randomization to the date of death or the database cutoff date if the participant is still alive. Database Cutoff Date: 05MAR2025			

Table 16 Summary of Follow-up Duration FA population With PD-L1 CPS>=1 (ITT Population)

Follow-up duration (months)[a]	Pembrolizumab + Chemotherapy (N=234)	Placebo + Chemotherapy (N=232)	Total (N=466)
Median (Range)	18.2 (0.7, 43.5)	14.0 (0.5, 44.1)	15.8 (0.5, 44.1)
Mean (SD)	19.1 (10.5)	16.7 (10.0)	17.9 (10.3)
[a] Follow-up duration is defined as the time from randomization to the date of death or the database cutoff date if the participant is still alive. Database Cutoff Date: 05SEP2025			

Conduct of the study

Table 17 Protocol amendments

Document	Date of Issue	Overall Rationale
Amendment 04/ Global Amendment	31-JAN-2024	To update the target number of events for the interim/final analyses and sample size and power calculations to reflect the actual PD-L1 CPS prevalence within the study based on blinded data review.
Amendment 03/ Global Amendment	22-JUN-2022	To add collection of blood samples for pembrolizumab PK and ADA/NAb analysis for participants receiving bevacizumab due to Health Authority request, to provide additional clarifications for inclusion/exclusion criteria, and to change the Sponsor entity name and address.
Amendment 02/ Germany-specific Amendment	22-DEC-2021	To clarify in the Schedule of Assessments that pregnancy testing is to continue in posttreatment for 120 days after the last dose of pembrolizumab/placebo or 180 days after the last dose of paclitaxel, docetaxel (if applicable), or bevacizumab (if using) and to remove the contraceptive language from the Germany country-specific appendix that was incorrectly included.
Amendment 01/ Japan-specific Amendment	13-OCT-2021	To indicate docetaxel as IMP in Japan, and permit a starting dose for docetaxel (if using) of 70 mg/m^2 for Japanese participants.
Original Protocol	27-JUL-2021	Not applicable

Table 18 Summary of Important Protocol Deviations Considered to be Clinically Important All Participants (ITT Population)

	Pembrolizumab + Chemotherapy		Placebo + Chemotherapy		Total	
	n	(%)	n	(%)	n	(%)
Participants in population	322		321		643	
with one or more clinically important protocol deviations	12	(3.7)	8	(2.5)	20	(3.1)
with no clinically important protocol deviations	310	(96.3)	313	(97.5)	623	(96.9)
Discontinuation Criteria	**1**	**(0.3)**	**1**	**(0.3)**	**2**	**(0.3)**
Participant developed study intervention discontinuation criteria, but was not discontinued from study intervention.	1	(0.3)	1	(0.3)	2	(0.3)
Study Intervention	**11**	**(3.4)**	**7**	**(2.2)**	**18**	**(2.8)**
Participant was administered improperly stored study intervention that was deemed unacceptable for use.	8	(2.5)	6	(1.9)	14	(2.2)
Participant was dispensed study intervention other than what was assigned in the allocation schedule, i.e. incorrect medication or potential cross-treatment.	3	(0.9)	1	(0.3)	4	(0.6)

Every participant is counted a single time for each applicable row and column.
Database Cutoff Date: 05MAR2025.

No protocol deviations were classified as a serious GCP compliance issue.

Participants with one or more not clinically important protocol deviations were 38 (11.8%) vs 31 (9.7%).

Baseline data

Table 19 Participant Characteristics All Participants With PD-L1 CPS>=1 (ITT Population)

	Pembrolizumab + Chemotherapy		Placebo + Chemotherapy		Total	
	n	(%)	n	(%)	n	(%)
Participants in population	234		232		466	
Sex						
Female	234	(100.0)	232	(100.0)	466	(100.0)
Age (Years)						
< 65	145	(62.0)	144	(62.1)	289	(62.0)
>= 65	89	(38.0)	88	(37.9)	177	(38.0)
Mean	61.5		61.3		61.4	
SD	10.2		9.8		10.0	
Median	62.0		61.5		62.0	
Range	37 to 85		37 to 82		37 to 85	
Race						
Asian	51	(21.8)	40	(17.2)	91	(19.5)
Black Or African American	5	(2.1)	4	(1.7)	9	(1.9)
Multiple	5	(2.1)	11	(4.7)	16	(3.4)
American Indian Or Alaska Native, White	3	(1.3)	7	(3.0)	10	(2.1)
Black Or African American, White	1	(0.4)	3	(1.3)	4	(0.9)
White, Asian	1	(0.4)	1	(0.4)	2	(0.4)
Native Hawaiian Or Other Pacific Islander	1	(0.4)	1	(0.4)	2	(0.4)
White	155	(66.2)	158	(68.1)	313	(67.2)
Missing	17	(7.3)	18	(7.8)	35	(7.5)
Ethnicity						
Hispanic Or Latino	27	(11.5)	35	(15.1)	62	(13.3)
Not Hispanic Or Latino	195	(83.3)	186	(80.2)	381	(81.8)
Not Reported	8	(3.4)	7	(3.0)	15	(3.2)
Unknown	4	(1.7)	4	(1.7)	8	(1.7)

Geographic Region 1						
US	26	(11.1)	24	(10.3)	50	(10.7)
EU	109	(46.6)	109	(47.0)	218	(46.8)
ROW	99	(42.3)	99	(42.7)	198	(42.5)
Geographic Region 2						
North America	44	(18.8)	53	(22.8)	97	(20.8)
Western Europe	87	(37.2)	90	(38.8)	177	(38.0)
ROW	103	(44.0)	89	(38.4)	192	(41.2)
ECOG Performance Scale at Baseline						
0	133	(56.8)	125	(53.9)	258	(55.4)
1	101	(43.2)	105	(45.3)	206	(44.2)
Missing	0	(0.0)	2	(0.9)	2	(0.4)
Bevacizumab Use						
Yes	169	(72.2)	169	(72.8)	338	(72.5)
No	65	(27.8)	63	(27.2)	128	(27.5)
PD-L1 Status						
CPS 1 to <10	133	(56.8)	132	(56.9)	265	(56.9)
CPS >=10	101	(43.2)	100	(43.1)	201	(43.1)
FIGO 2014 Stage at Initial Diagnosis						
IA	5	(2.1)	1	(0.4)	6	(1.3)
IB	1	(0.4)	0	(0.0)	1	(0.2)
IC	7	(3.0)	5	(2.2)	12	(2.6)
II	1	(0.4)	1	(0.4)	2	(0.4)
IIA	0	(0.0)	2	(0.9)	2	(0.4)
IIB	3	(1.3)	4	(1.7)	7	(1.5)
III	4	(1.7)	4	(1.7)	8	(1.7)
IIIA	0	(0.0)	2	(0.9)	2	(0.4)
IIIA1	7	(3.0)	5	(2.2)	12	(2.6)
IIIA2	5	(2.1)	7	(3.0)	12	(2.6)
IIIB	16	(6.8)	14	(6.0)	30	(6.4)
IIIC	96	(41.0)	98	(42.2)	194	(41.6)
IVA	28	(12.0)	19	(8.2)	47	(10.1)
IVB	61	(26.1)	70	(30.2)	131	(28.1)
Histology Subtype						
High Grade Serous	206	(88.0)	208	(89.7)	414	(88.8)
Low Grade Serous	4	(1.7)	6	(2.6)	10	(2.1)
Carcinosarcoma	3	(1.3)	3	(1.3)	6	(1.3)
Clear Cell	14	(6.0)	13	(5.6)	27	(5.8)
Endometrioid	5	(2.1)	2	(0.9)	7	(1.5)
Others (Carcinoma)	2	(0.9)	0	(0.0)	2	(0.4)
Prior Lines of Therapy						
One line	88	(37.6)	81	(34.9)	169	(36.3)
Two lines	145	(62.0)	151	(65.1)	296	(63.5)
Three lines	1	(0.4)	0	(0.0)	1	(0.2)
Prior Anti-PD-1 or Anti-PD-L1						
Yes	5	(2.1)	7	(3.0)	12	(2.6)
No	229	(97.9)	225	(97.0)	454	(97.4)
Prior Bevacizumab/bev-biosimilar						
Yes and bevacizumab treated in study	68	(29.1)	66	(28.4)	134	(28.8)
Yes and bevacizumab not treated in study	40	(17.1)	42	(18.1)	82	(17.6)
No	126	(53.8)	124	(53.4)	250	(53.6)
Prior PARPi						
Yes	85	(36.3)	96	(41.4)	181	(38.8)

No	149	(63.7)	136	(58.6)	285	(61.2)
Prior Anti-VEGF Therapy						
Yes, both bevacizumab/bev-biosimilar and other VEGF inhibitors	0	(0.0)	2	(0.9)	2	(0.4)
Yes, bevacizumab/bev-biosimilar only	108	(46.2)	106	(45.7)	214	(45.9)
Yes, other VEGF inhibitors only	1	(0.4)	0	(0.0)	1	(0.2)
No	125	(53.4)	124	(53.4)	249	(53.4)
Platinum Free Interval						
<3 months from last platinum therapy to subsequent progression	103	(44.0)	115	(49.6)	218	(46.8)
3-6 months from last platinum therapy to subsequent progression	130	(55.6)	115	(49.6)	245	(52.6)
>6 months from last platinum therapy to subsequent progression	1	(0.4)	2	(0.9)	3	(0.6)

SD=Standard deviation.
Missing values in race are mainly because this information is not permitted to report in France and Netherlands.
Western Europe includes countries in the European Economic Area, United Kingdom, and Switzerland.
Database Cutoff Date: 05MAR2025.

Table 20 Summary of Platinum Free Interval All Participants With PD-L1 CPS>=1 (ITT Population)

	Pembrolizumab + Chemotherapy	Placebo + Chemotherapy
Participants in population	234	232
Platinum Free Interval (Months)		
Participants with data	234	232
Mean	3.0	2.9
SD	1.79	1.85
Median	3.30	3.07
Q1 to Q3	1.3 to 4.4	1.0 to 4.4
Range	0.0 to 6.1	0.0 to 10.4

SD=Standard deviation; Q1=First quartile, Q3=Third quartile.
Database Cutoff Date: 05MAR2025.

Table 21 Participant Characteristics All Participants (ITT Population)

	Pembrolizumab + Chemotherapy		Placebo + Chemotherapy		Total	
	n	(%)	n	(%)	n	(%)
Participants in population	322		321		643	
Sex						
Female	322	(100.0)	321	(100.0)	643	(100.0)
Age (Years)						
< 65	200	(62.1)	207	(64.5)	407	(63.3)
>= 65	122	(37.9)	114	(35.5)	236	(36.7)
Mean	61.1		60.6		60.8	
SD	10.7		9.9		10.3	
Median	62.0		61.0		61.0	
Range	37 to 85		37 to 82		37 to 85	
Race						
Asian	72	(22.4)	58	(18.1)	130	(20.2)
Black Or African American	8	(2.5)	6	(1.9)	14	(2.2)
Multiple	12	(3.7)	17	(5.3)	29	(4.5)
American Indian Or Alaska Native, White	9	(2.8)	12	(3.7)	21	(3.3)
Black Or African American, White	2	(0.6)	4	(1.2)	6	(0.9)
White, Asian	1	(0.3)	1	(0.3)	2	(0.3)
Native Hawaiian Or Other Pacific Islander	1	(0.3)	1	(0.3)	2	(0.3)
White	207	(64.3)	217	(67.6)	424	(65.9)
Missing	22	(6.8)	22	(6.9)	44	(6.8)
Ethnicity						
Hispanic Or Latino	46	(14.3)	52	(16.2)	98	(15.2)
Not Hispanic Or Latino	261	(81.1)	255	(79.4)	516	(80.2)
Not Reported	10	(3.1)	8	(2.5)	18	(2.8)
Unknown	5	(1.6)	6	(1.9)	11	(1.7)
Geographic Region 1						
US	30	(9.3)	29	(9.0)	59	(9.2)
EU	149	(46.3)	151	(47.0)	300	(46.7)
ROW	143	(44.4)	141	(43.9)	284	(44.2)
Geographic Region 2						
North America	58	(18.0)	70	(21.8)	128	(19.9)
Western Europe	118	(36.6)	126	(39.3)	244	(37.9)
ROW	146	(45.3)	125	(38.9)	271	(42.1)
ECOG Performance Scale at Baseline						
0	179	(55.6)	175	(54.5)	354	(55.1)
1	142	(44.1)	144	(44.9)	286	(44.5)
Missing	1	(0.3)	2	(0.6)	3	(0.5)
Bevacizumab Use						
Yes	235	(73.0)	236	(73.5)	471	(73.3)
No	87	(27.0)	85	(26.5)	172	(26.7)
PD-L1 Status						
CPS < 1	88	(27.3)	89	(27.7)	177	(27.5)
CPS 1 to <10	133	(41.3)	132	(41.1)	265	(41.2)
CPS >=10	101	(31.4)	100	(31.2)	201	(31.3)
FIGO 2014 Stage at Initial Diagnosis						
IA	6	(1.9)	4	(1.2)	10	(1.6)
IB	1	(0.3)	1	(0.3)	2	(0.3)
IC	11	(3.4)	9	(2.8)	20	(3.1)
II	1	(0.3)	1	(0.3)	2	(0.3)
IIA	2	(0.6)	3	(0.9)	5	(0.8)
IIB	4	(1.2)	8	(2.5)	12	(1.9)
III	4	(1.2)	6	(1.9)	10	(1.6)

IIIA	0	(0.0)	2	(0.6)	2	(0.3)
IIIA1	9	(2.8)	6	(1.9)	15	(2.3)
IIIA2	5	(1.6)	10	(3.1)	15	(2.3)
IIIB	24	(7.5)	20	(6.2)	44	(6.8)
IIIC	141	(43.8)	145	(45.2)	286	(44.5)
IVA	31	(9.6)	26	(8.1)	57	(8.9)
IVB	83	(25.8)	80	(24.9)	163	(25.3)
Histology Subtype						
High Grade Serous	278	(86.3)	275	(85.7)	553	(86.0)
Low Grade Serous	6	(1.9)	10	(3.1)	16	(2.5)
Carcinosarcoma	3	(0.9)	5	(1.6)	8	(1.2)
Clear Cell	24	(7.5)	26	(8.1)	50	(7.8)
Endometrioid	9	(2.8)	4	(1.2)	13	(2.0)
Others (Carcinoma)	2	(0.6)	1	(0.3)	3	(0.5)
Prior Lines of Therapy						
One line	121	(37.6)	113	(35.2)	234	(36.4)
Two lines	200	(62.1)	207	(64.5)	407	(63.3)
Three lines	1	(0.3)	1	(0.3)	2	(0.3)
Prior Anti-PD-1 or Anti-PD-L1						
Yes	7	(2.2)	7	(2.2)	14	(2.2)
No	315	(97.8)	314	(97.8)	629	(97.8)
Prior Bevacizumab/bev-biosimilar						
Yes and bevacizumab treated in study	98	(30.4)	91	(28.3)	189	(29.4)
Yes and bevacizumab not treated in study	51	(15.8)	55	(17.1)	106	(16.5)
No	173	(53.7)	175	(54.5)	348	(54.1)
Prior PARPi						
Yes	112	(34.8)	123	(38.3)	235	(36.5)
No	210	(65.2)	198	(61.7)	408	(63.5)
Prior Anti-VEGF Therapy						
Yes, both bevacizumab/bev-biosimilar and other VEGF inhibitors	0	(0.0)	3	(0.9)	3	(0.5)
Yes, bevacizumab/bev-biosimilar only	149	(46.3)	143	(44.5)	292	(45.4)
Yes, other VEGF inhibitors only	1	(0.3)	0	(0.0)	1	(0.2)
No	172	(53.4)	175	(54.5)	347	(54.0)
Platinum Free Interval						
<3 months from last platinum therapy to subsequent progression	137	(42.5)	162	(50.5)	299	(46.5)
3-6 months from last platinum therapy to subsequent progression	183	(56.8)	154	(48.0)	337	(52.4)
>6 months from last platinum therapy to subsequent progression	2	(0.6)	4	(1.2)	6	(0.9)
Missing	0	(0.0)	1	(0.3)	1	(0.2)
SD=Standard deviation.						
Missing values in race are mainly because this information is not permitted to report in France and Netherlands.						
Western Europe includes countries in the European Economic Area, United Kingdom, and Switzerland.						
Database Cutoff Date: 05MAR2025.						

Prior Lines of Platinum Therapy						
One line	160	(49.7)	150	(46.7)	310	(48.2)
Two lines	162	(50.3)	171	(53.3)	333	(51.8)
Database Cutoff Date: 05MAR2025.						

Table 22 Summary for HRD and BRCA Mutation Status All Participants (ITT Population)

	Pembrolizumab + Chemotherapy		Placebo + Chemotherapy		Total	
	n	(%)	n	(%)	n	(%)
Participants in population	322		321		643	

HRD status						
Positive	29	(9.0)	24	(7.5)	53	(8.2)
Negative	79	(24.5)	69	(21.5)	148	(23.0)
Undetermined	4	(1.2)	7	(2.2)	11	(1.7)
Missing	210	(65.2)	221	(68.8)	431	(67.0)
BRCA mutation status						
Yes	28	(8.7)	25	(7.8)	53	(8.2)
No	145	(45.0)	161	(50.2)	306	(47.6)
Undetermined	3	(0.9)	6	(1.9)	9	(1.4)
Missing	146	(45.3)	129	(40.2)	275	(42.8)
Database Cutoff Date: 05MAR2025. HRD and BRCA testing results were collected if testing was performed prior to enrollment to KEYNOTE-B96 study.						

Numbers analysed

Table 23 Study populations

	Pembrolizumab + Chemotherapy	Placebo + Chemotherapy	Total
Number of Participants Screened			867
Number of Participants Randomized (ITT)	322	321	643
Number of Participants Received Post-randomization Treatment (Actual Treatment) (APaT)	320	318	638
Number of Participants Randomized and Did not Receive Post-randomization Treatment	2	3	5
Database Cutoff Date: 05MAR2025.			

PD-L1 CPS ≥1 participants were 466 in total, corresponding to the 72.5% of the ITT population; those were 234 vs 232 in the pembrolizumab + chemotherapy vs placebo + chemotherapy arm, respectively.

The primary efficacy analyses were based on the ITT population, except for the ORR analysis that was based on the population with measurable disease per RECIST 1.1 at baseline, and the DOR analysis that was based on the population of the responders with measurable disease per RECIST 1.1 at baseline.

Outcomes and estimation

Primary endpoint: PFS per RECIST 1.1 by Investigator

At IA1, statistically significant PFS improvement was demonstrated for pembrolizumab + chemotherapy vs placebo + chemotherapy for both PD-L1 CPS ≥1 (observed p-value of 0.0014 crossed the prespecified p-value boundary of 0.0116) and all participants. Since the PFS hypotheses were successful at IA1, all alpha was allocated to OS, therefore PFS was not statistically tested at IA2 and at FA, thus PFS analyses are descriptive and p-values provided at IA2 and FA are nominal.

PFS results from IA1, IA2 and FA for CPS≥1 and all-comers are reported below.

PFS in the CPS≥1 population

Table 24 Analysis of Progression-Free Survival (Primary Censoring Rule) Based on Investigator Assessment per RECIST 1.1 Population With PD-L1 CPS≥1 (ITT Population) IA1

	Pembrolizumab + Chemotherapy (N=234)	Placebo + Chemotherapy (N=232)
Number of Events (%)	162 (69.2)	180 (77.6)
Death	18 (7.7)	18 (7.8)
Documented progression	144 (61.5)	162 (69.8)
Number of Censored (%)	72 (30.8)	52 (22.4)
Last assessment prior to missing >=2 consecutive assessments immediately before event	5 (2.1)	3 (1.3)
Last assessment prior to new anti-cancer therapy showing no progression	9 (3.8)	9 (3.9)
Last assessment showing no progression	57 (24.4)	38 (16.4)
Randomization	1 (0.4)	2 (0.9)
Kaplan-Meier Estimates (months)[a]		
Median (95% CI)	8.3 (7.0, 9.4)	7.2 (6.2, 8.1)
[Q1, Q3]	[5.2, 14.7]	[4.1, 11.1]
Person-months	1922.5	1688.8
Event Rate / 100 Person-months	8.4	10.7
vs Placebo + Chemotherapy		
Hazard Ratio (95% CI)[b]	0.72 (0.58, 0.89)	
p-value[c]	0.0014	
PFS Rate at month 6 (%) (95% CI)	71.1 (64.7, 76.5)	62.3 (55.6, 68.3)
PFS Rate at month 12 (%) (95% CI)	35.2 (28.8, 41.7)	22.6 (17.0, 28.7)
PFS Rate at month 18 (%) (95% CI)	17.3 (10.8, 25.0)	9.3 (4.8, 15.5)

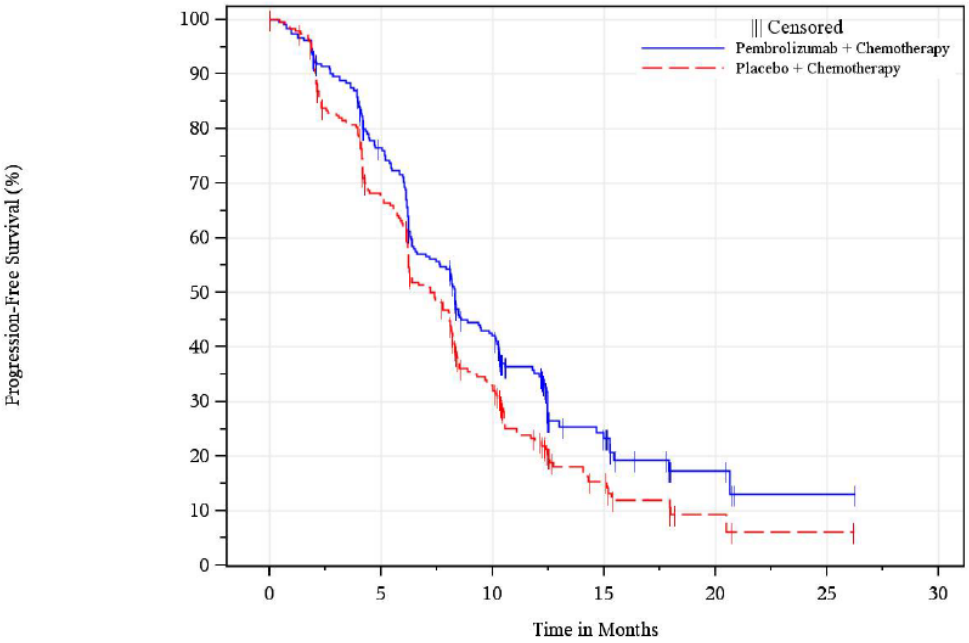
[a] From product-limit (Kaplan-Meier) method for censored data.

[b] Based on Cox regression model with Efron's method of tie handling with treatment as a covariate stratified by planned bevacizumab use in the study (yes vs no), region (US vs EU vs ROW) and PD-L1 status (CPS <1 vs CPS 1 to <10 vs CPS >=10) with small strata collapsed as pre-specified in the sSAP.

[c] One-sided p-value based on log-rank test stratified by planned bevacizumab use in the study (yes vs no), region (US vs EU vs ROW) and PD-L1 status (CPS <1 vs CPS 1 to <10 vs CPS >=10) with small strata collapsed as pre-specified in the sSAP.

Database Cutoff Date: 03APR2024

Figure 6 Kaplan-Meier Plot of Progression-Free Survival (Primary Censoring Rule) Based on Investigator Assessment per RECIST 1.1 Population With PD-L1 CPS>=1 (ITT Population) IA1

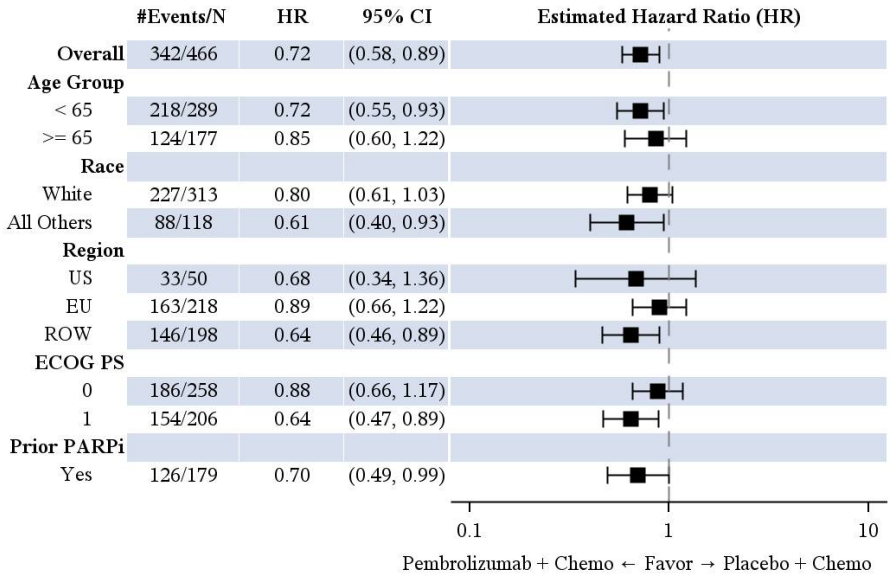


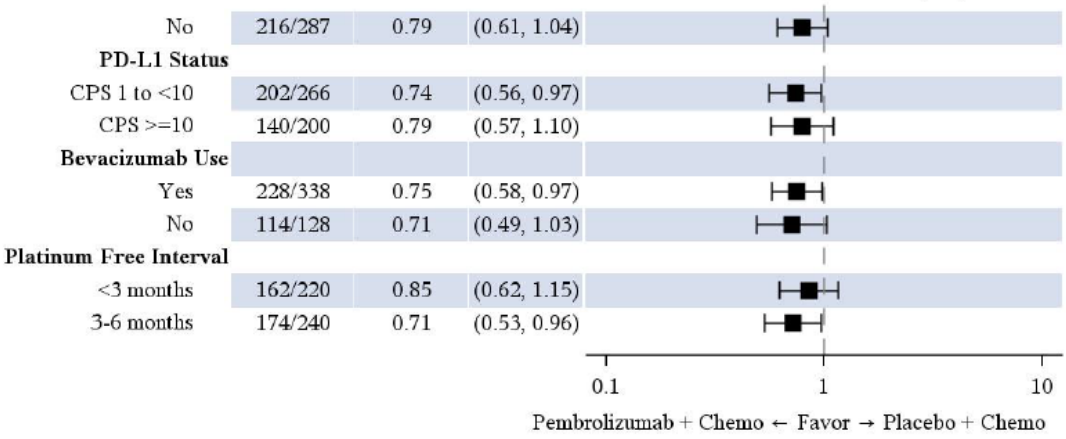
Number of participants at risk

Pembrolizumab + Chemotherapy	234	170	87	21	5	1	0
Placebo + Chemotherapy	232	150	64	16	3	1	0

Database Cutoff Date: 03APR2024.

Figure 7 Forest Plot of Progression-Free Survival Hazard Ratio by Subgroup Factors Based on Investigator Assessments per RECIST 1.1 (Primary Censoring Rule) Population With PD-L1 CPS⩾1 (ITT Population) IA1





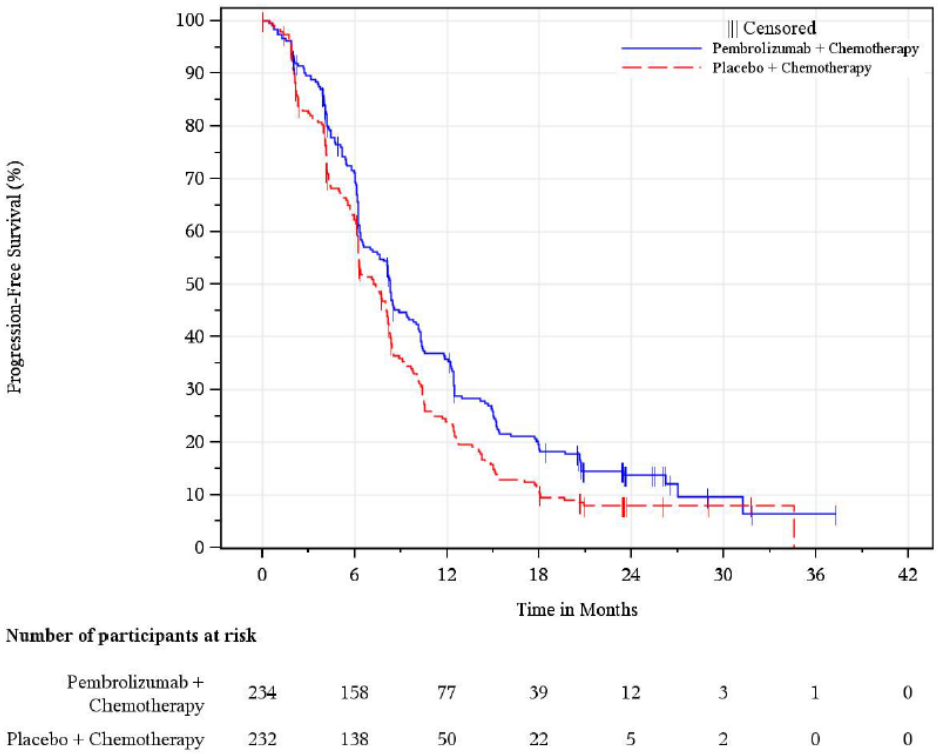
Subgroup analyses are based on unstratified Cox regression model with Efron's method of tie handling with treatment as a covariate.
Platinum free interval is from last platinum therapy to subsequent progression.
Database Cutoff Date: 03APR2024.

Table 25 Analysis of Progression-Free Survival (Primary Censoring Rule) Based on Investigator Assessment per RECIST 1.1 All Participants With PD-L1 CPS>=1 (ITT Population) at IA2

	Pembrolizumab + Chemotherapy (N=234)	Placebo + Chemotherapy (N=232)
Number of Events (%)	191 (81.6)	201 (86.6)
Death	20 (8.5)	19 (8.2)
Documented progression	171 (73.1)	182 (78.4)
Number of Censored (%)	43 (18.4)	31 (13.4)
Last assessment prior to missing >=2 consecutive assessments immediately before event	6 (2.6)	3 (1.3)
Last assessment prior to new anti-cancer therapy showing no progression	9 (3.8)	12 (5.2)
Last assessment showing no progression	27 (11.5)	14 (6.0)
Randomization	1 (0.4)	2 (0.9)
Kaplan-Meier Estimates (months)[a]		
Median (95% CI)	8.3 (7.0, 9.5)	7.2 (6.2, 8.1)
[Q1, Q3]	[5.2, 15.0]	[4.1, 11.2]
Person-months	2360.2	1934.3
Event Rate / 100 Person-months	8.1	10.4
vs Placebo + Chemotherapy		
Hazard Ratio (95% CI)[b]	0.75 (0.61, 0.91)	
p-value[c]	0.0022	
PFS Rate at month 6 (%) (95% CI)	71.1 (64.7, 76.5)	62.3 (55.6, 68.3)
PFS Rate at month 12 (%) (95% CI)	35.9 (29.6, 42.2)	23.9 (18.4, 29.8)
PFS Rate at month 18 (%) (95% CI)	18.7 (13.8, 24.2)	10.5 (6.8, 15.1)
PFS Rate at month 24 (%) (95% CI)	13.8 (9.4, 19.0)	7.9 (4.7, 12.2)
PFS Rate at month 30 (%) (95% CI)	9.6 (4.8, 16.6)	7.9 (4.7, 12.2)

[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 planned bevacizumab use in the study (yes vs no), region (US vs EU vs ROW) and PD-L1 status (CPS <1 vs CPS 1 to <10 vs CPS >=10) with small strata collapsed as pre-specified in the sSAP.
[c] One-sided p-value based on log-rank test stratified by planned bevacizumab use in the study (yes vs no), region (US vs EU vs ROW) and PD-L1 status (CPS <1 vs CPS 1 to <10 vs CPS >=10) with small strata collapsed as pre-specified in the sSAP.
Database Cutoff Date: 05MAR2025

Figure 8 Kaplan-Meier Plot of Progression-Free Survival (Primary Censoring Rule) Based on Investigator Assessment per RECIST 1.1 All Participants With PD-L1 CPS>=1 (ITT Population) at IA2



Database Cutoff Date: 05MAR2025.

Preplanned PFS sensitivity analyses in PD-L1 CPS≥1 at IA2 showed an HR of 0.73 (95%CI 0.60, 0.89) according to Censoring Rule 1, and an HR of 0.75 (95%CI 0.61, 0.90) according to Censoring Rule 2.

Time to discontinuation of study treatment (TDT) in PD-L1 CPS≥1 at IA2 was an HR of 0.79 (0.65, 0.96), median 7.5 (6.7, 8.6) vs 7.0 (6.0, 7.7) months.

Table 26 Analysis of Progression-Free Survival (Primary Censoring Rule) Based on Investigator Assessment per RECIST 1.1 All Participants With PD-L1 CPS>=1 (ITT Population) – Final analysis

	Pembrolizumab + Chemotherapy (N=234)	Placebo + Chemotherapy (N=232)
Number of Events (%)	198 (84.6)	206 (88.8)
Death	20 (8.5)	19 (8.2)
Documented progression	178 (76.1)	187 (80.6)
Number of Censored (%)	36 (15.4)	26 (11.2)
Last assessment prior to missing >=2 consecutive assessments immediately before event	7 (3.0)	3 (1.3)
Last assessment prior to new anti-cancer therapy showing no progression	9 (3.8)	12 (5.2)
Last assessment showing no progression	19 (8.1)	9 (3.9)

Randomization	1 (0.4)	2 (0.9)
Kaplan-Meier Estimates (months)[a]		
Median (95% CI)	8.3 (7.0, 9.5)	7.2 (6.2, 8.1)
(Q1, Q3)	(5.2, 15.0)	(4.1, 11.2)
Person-months	2498.9	2011.8
Event Rate / 100 Person-months	7.9	10.2
vs Placebo + Chemotherapy		
Hazard Ratio (95% CI)[b]	0.76 (0.62, 0.93)	
p-value[c]	0.0036	
PFS Rate at month 6 (%) (95% CI)	71.1 (64.7, 76.5)	62.3 (55.6, 68.3)
PFS Rate at month 12 (%) (95% CI)	35.9 (29.6, 42.2)	23.9 (18.4, 29.8)
PFS Rate at month 18 (%) (95% CI)	18.7 (13.8, 24.2)	10.5 (6.8, 15.1)
PFS Rate at month 24 (%) (95% CI)	13.8 (9.5, 18.8)	8.0 (4.9, 12.2)
PFS Rate at month 30 (%) (95% CI)	10.3 (6.6, 14.9)	4.7 (2.1, 8.9)
PFS Rate at month 36 (%) (95% CI)	8.0 (4.4, 12.9)	2.4 (0.3, 8.5)
PFS Rate at month 42 (%) (95% CI)	8.0 (4.4, 12.9)	0.0 (NR, NR)

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

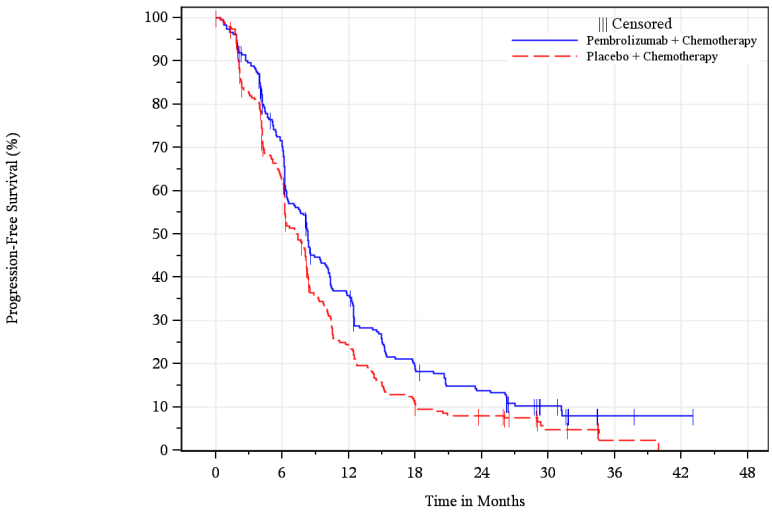
[b] Based on Cox regression model with Efron's method of tie handling with treatment as a covariate stratified by planned bevacizumab use in the study (yes vs no), region (US vs EU vs ROW) and PD-L1 status (CPS <1 vs CPS 1 to <10 vs CPS >=10) with small strata collapsed as pre-specified in the sSAP.

[c] One-sided p-value based on log-rank test stratified by planned bevacizumab use in the study (yes vs no), region (US vs EU vs ROW) and PD-L1 status (CPS <1 vs CPS 1 to <10 vs CPS >=10) with small strata collapsed as pre-specified in the sSAP.

NR = Not reached.

Database Cutoff Date: 05SEP2025

Figure 9 Kaplan-Meier Plot of Progression-Free Survival (Primary Censoring Rule) Based on Investigator Assessment per RECIST 1.1 All Participants With PD-L1 CPS>=1 (ITT Population) - final analysis



Number of participants at risk

Pembrolizumab + Chemotherapy	234	158	77	39	28	10	2	1	0
Placebo + Chemotherapy	232	138	50	22	15	5	1	0	0

Database Cutoff Date: 05SEP2025.

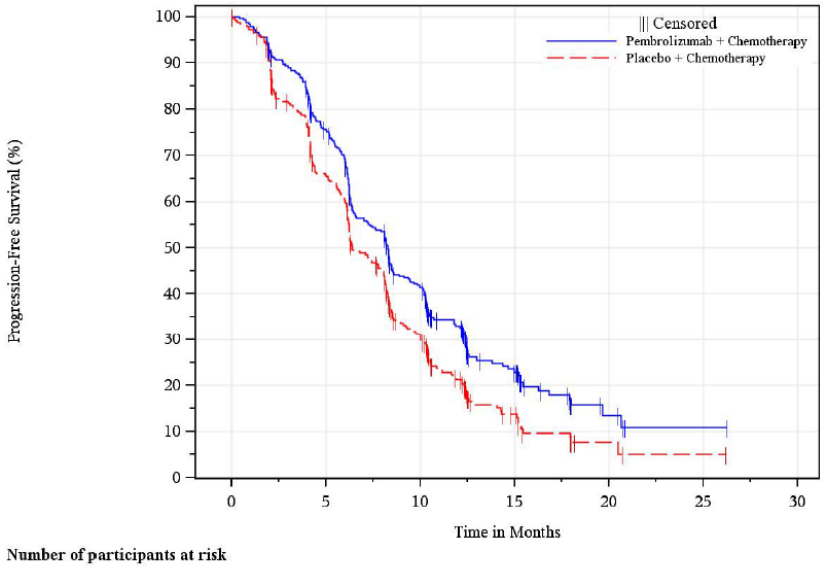
PFS in the all-comers population

Table 27 Analysis of Progression-Free Survival (Primary Censoring Rule) Based on Investigator Assessment per RECIST 1.1 (ITT Population) IA1

	Pembrolizumab + Chemotherapy (N=322)	Placebo + Chemotherapy (N=321)
Number of Events (%)	231 (71.7)	253 (78.8)
Death	37 (11.5)	31 (9.7)
Documented progression	194 (60.2)	222 (69.2)
Number of Censored (%)	91 (28.3)	68 (21.2)
Last assessment prior to missing >=2 consecutive assessments immediately before event	5 (1.6)	4 (1.2)
Last assessment prior to new anti-cancer therapy showing no progression	12 (3.7)	13 (4.0)
Last assessment showing no progression	73 (22.7)	48 (15.0)
Randomization	1 (0.3)	3 (0.9)
Kaplan-Meier Estimates (months)[a]		
Median (95% CI)	8.3 (7.2, 8.6)	6.4 (6.2, 8.1)
[Q1, Q3]	[5.2, 13.8]	[4.1, 10.6]
Person-months	2658.9	2248.2
Event Rate / 100 Person-months	8.7	11.3
vs Placebo + Chemotherapy		
Hazard Ratio (95% CI)[b]	0.70 (0.58, 0.84)	
p-value[c]	<0.0001	
PFS Rate at month 6 (%) (95% CI)	69.2 (63.8, 74.0)	60.5 (54.8, 65.6)
PFS Rate at month 12 (%) (95% CI)	33.1 (27.7, 38.5)	21.3 (16.6, 26.4)
PFS Rate at month 18 (%) (95% CI)	15.8 (10.7, 21.8)	7.7 (4.1, 12.7)

[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 planned bevacizumab use in the study (yes vs no), region (US vs EU vs ROW) and PD-L1 status (CPS <1 vs CPS 1 to <10 vs CPS >=10) with small strata collapsed as pre-specified in the sSAP.
[c] One-sided p-value based on log-rank test stratified by planned bevacizumab use in the study (yes vs no), region (US vs EU vs ROW) and PD-L1 status (CPS <1 vs CPS 1 to <10 vs CPS >=10) with small strata collapsed as pre-specified in the sSAP.
Database Cutoff Date: 03APR2024

Figure 10 Kaplan-Meier Plot of Progression-Free Survival (Primary Censoring Rule) Based on Investigator Assessment per RECIST 1.1 (ITT Population) IA1



Number of participants at risk

Pembrolizumab + Chemotherapy	322	233	119	34	6	1	0
Placebo + Chemotherapy	321	200	84	19	3	1	0

Database Cutoff Date: 03APR2024.

Figure 11 Forest Plot of Progression-Free Survival Hazard Ratio by Subgroup Factors Based on Investigator Assessments per RECIST 1.1 (Primary Censoring Rule) (ITT Population) IA1

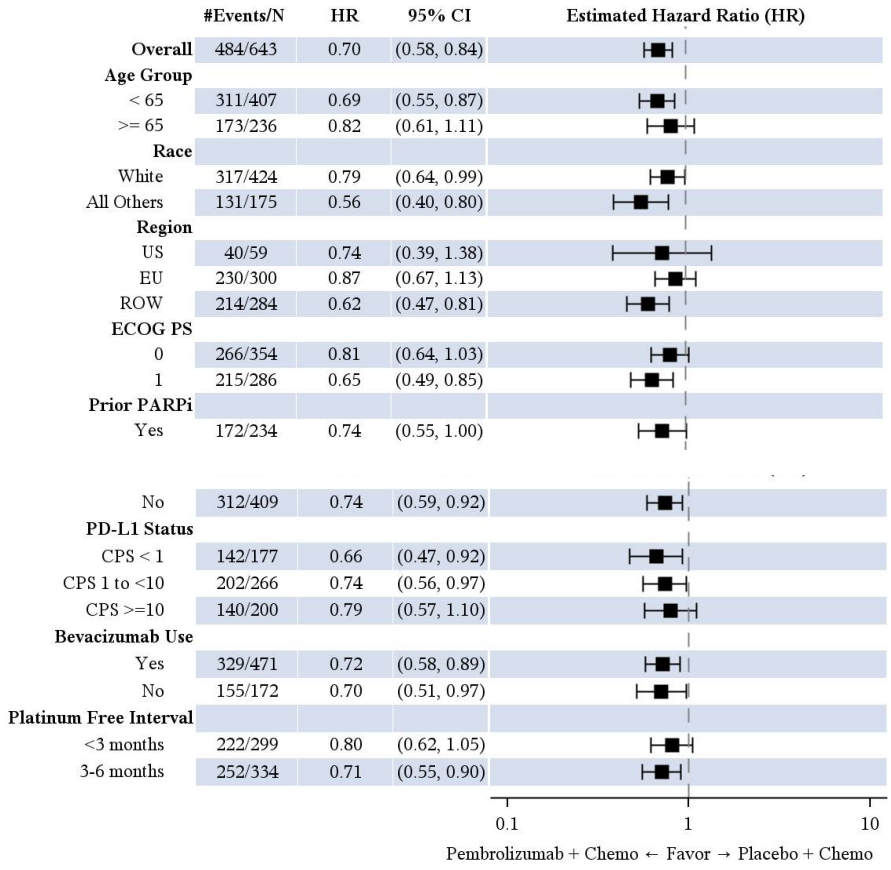


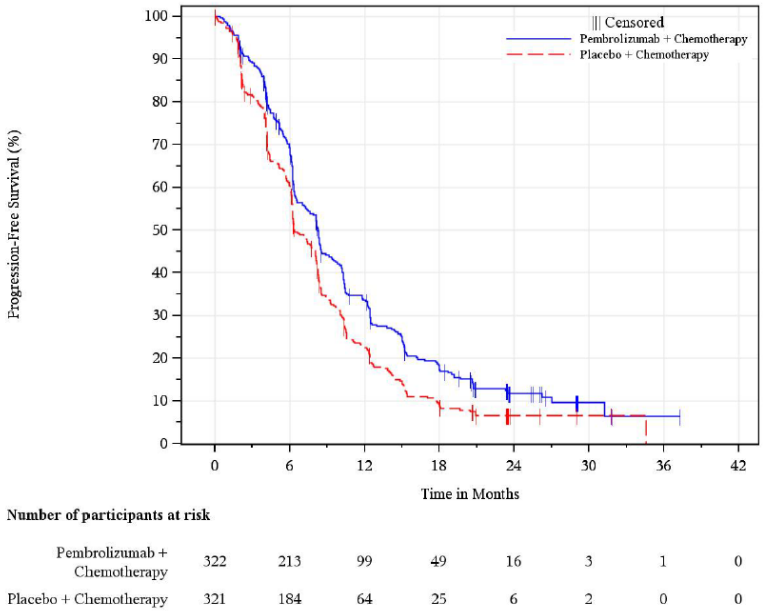
Table 28 Analysis of Progression-Free Survival (Primary Censoring Rule) Based on Investigator Assessment per RECIST 1.1 All Participants (ITT Population) IA2

	Pembrolizumab + Chemotherapy (N=322)	Placebo + Chemotherapy (N=321)
Number of Events (%)	268 (83.2)	280 (87.2)
Death	40 (12.4)	32 (10.0)
Documented progression	228 (70.8)	248 (77.3)
Number of Censored (%)	54 (16.8)	41 (12.8)
Last assessment prior to missing >=2 consecutive assessments immediately before event	7 (2.2)	4 (1.2)
Last assessment prior to new anti-cancer therapy showing no progression	13 (4.0)	17 (5.3)
Last assessment showing no progression	33 (10.2)	17 (5.3)
Randomization	1 (0.3)	3 (0.9)
Kaplan-Meier Estimates (months)[a]		
Median (95% CI)	8.3 (7.2, 8.6)	6.4 (6.2, 8.1)
[Q1, Q3]	[5.2, 15.0]	[4.1, 10.6]
Person-months	3175.4	2548.6
Event Rate / 100 Person-months	8.4	11.0
vs Placebo + Chemotherapy		
Hazard Ratio (95% CI)[b]	0.73 (0.62, 0.86)	
p-value[c]	0.0001	
PFS Rate at month 6 (%) (95% CI)	69.2 (63.8, 74.0)	60.5 (54.8, 65.6)
PFS Rate at month 12 (%) (95% CI)	33.7 (28.4, 39.0)	22.5 (17.9, 27.4)
PFS Rate at month 18 (%) (95% CI)	17.3 (13.2, 21.9)	9.0 (6.0, 12.6)
PFS Rate at month 24 (%) (95% CI)	11.8 (8.3, 15.9)	6.6 (4.1, 9.9)

PFS Rate at month 30 (%) (95% CI)	9.6 (6.0, 14.3)	6.6 (4.1, 9.9)

[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 planned bevacizumab use in the study (yes vs no), region (US vs EU vs ROW) and PD-L1 status (CPS <1 vs CPS 1 to <10 vs CPS >=10) with small strata collapsed as pre-specified in the sSAP.
[c] One-sided p-value based on log-rank test stratified by planned bevacizumab use in the study (yes vs no), region (US vs EU vs ROW) and PD-L1 status (CPS <1 vs CPS 1 to <10 vs CPS >=10) with small strata collapsed as pre-specified in the sSAP.
Database Cutoff Date: 05MAR2025

Figure 12 Kaplan-Meier Plot of Progression-Free Survival (Primary Censoring Rule) Based on Investigator Assessment per RECIST 1.1 All Participants (ITT Population) IA2



Database Cutoff Date: 05MAR2025.

At IA2, preplanned PFS sensitivity analyses in all-comers showed an HR of 0.73 (95%CI 0.62, 0.86) according to Censoring Rule 1, and an HR of 0.74 (95%CI 0.63, 0.87) according to Censoring Rule 2.

Table 29 Analysis of Progression-Free Survival (Primary Censoring Rule) Based on Investigator Assessment per RECIST 1.1 All Participants (ITT Population) – Final Analysis

	Pembrolizumab + Chemotherapy (N=322)	Placebo + Chemotherapy (N=321)
Number of Events (%)	276 (85.7)	286 (89.1)
Death	40 (12.4)	32 (10.0)
Documented progression	236 (73.3)	254 (79.1)
Number of Censored (%)	46 (14.3)	35 (10.9)
Last assessment prior to missing >=2 consecutive assessments immediately before event	9 (2.8)	4 (1.2)
Last assessment prior to new anti-cancer therapy showing no progression	12 (3.7)	17 (5.3)
Last assessment showing no progression	24 (7.5)	11 (3.4)

Randomization	1 (0.3)	3 (0.9)
Kaplan-Meier Estimates (months)[a]		
Median (95% CI)	8.3 (7.2, 8.6)	6.4 (6.2, 8.1)
(Q1, Q3)	(5.2, 15.0)	(4.1, 10.6)
Person-months	3339.0	2640.0
Event Rate / 100 Person-months	8.3	10.8
vs Placebo + Chemotherapy		
Hazard Ratio (95% CI)[b]	0.73 (0.62, 0.87)	
p-value[c]	0.0001	
PFS Rate at month 6 (%) (95% CI)	69.2 (63.8, 74.0)	60.5 (54.8, 65.6)
PFS Rate at month 12 (%) (95% CI)	33.7 (28.4, 39.0)	22.5 (17.9, 27.4)
PFS Rate at month 18 (%) (95% CI)	17.3 (13.2, 21.9)	9.0 (6.0, 12.6)
PFS Rate at month 24 (%) (95% CI)	11.8 (8.4, 15.9)	6.7 (4.2, 10.1)
PFS Rate at month 30 (%) (95% CI)	9.2 (6.2, 12.9)	4.5 (2.3, 7.7)
PFS Rate at month 36 (%) (95% CI)	7.8 (4.8, 11.6)	1.5 (0.2, 6.1)
PFS Rate at month 42 (%) (95% CI)	5.2 (1.8, 11.4)	0.0 (NR, NR)

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

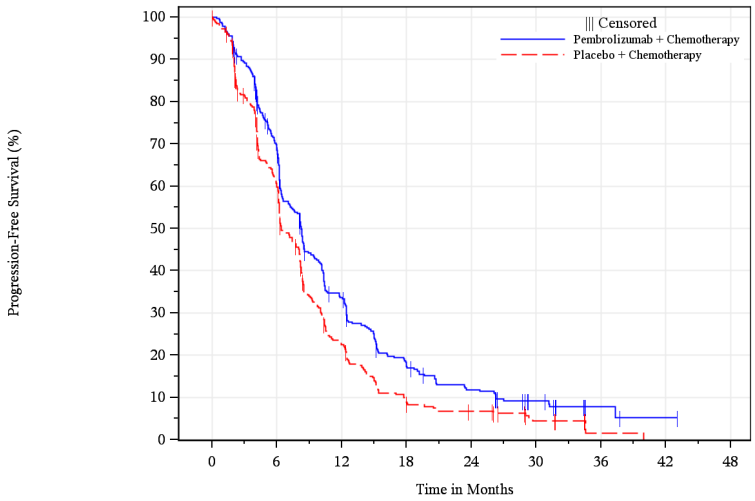
[b] Based on Cox regression model with Efron's method of tie handling with treatment as a covariate stratified by planned bevacizumab use in the study (yes vs no), region (US vs EU vs ROW) and PD-L1 status (CPS <1 vs CPS 1 to <10 vs CPS >=10) with small strata collapsed as pre-specified in the sSAP.

[c] One-sided p-value based on log-rank test stratified by planned bevacizumab use in the study (yes vs no), region (US vs EU vs ROW) and PD-L1 status (CPS <1 vs CPS 1 to <10 vs CPS >=10) with small strata collapsed as pre-specified in the sSAP.

NR = Not reached.

Database Cutoff Date: 05SEP2025

Figure 13 Kaplan-Meier Plot of Progression-Free Survival (Primary Censoring Rule) Based on Investigator Assessment per RECIST 1.1 All Participants (ITT Population) at FA



Number of participants at risk

Pembrolizumab + Chemotherapy	322	213	99	49	32	14	3	1	0
Placebo + Chemotherapy	321	184	64	25	17	7	1	0	0

Database Cutoff Date: 05SEP2025.

Secondary endpoint: OS

Results for OS in participants with PD-L1 positive tumours (CPS ≥1) did not cross the prespecified efficacy boundary (p=0.0084, p-value boundary at 0.0021) at IA1; therefore, OS in the all-comer population was not tested at IA1 per prespecified multiplicity strategy.

At IA2, statistically significant OS improvement was shown in participants with PD-L1 CPS≥1 (observed p-value of 0.0053 crossed the prespecified p-value boundary of 0.0083). OS in all-comers was not statistically significant at IA2. OS in all participants was re-tested at FA when it reached statistical significance in the ITT population (observed p-value of 0.0115 in all-comers for OS at FA crossed the prespecified p-value boundary of 0.0242) meeting success criterion. Since the OS hypothesis in participants with PD-L1 CPS≥1 was successful at IA2, OS was not statistically tested at FA, thus the OS analysis in participants with PD-L1 CPS≥1 is descriptive and p-value provided at FA is nominal.

OS results from IA2 and final analysis for CPS≥1 and OS results from FA for all-comers are reported below.

OS in the CPS≥1 population

Table 30 Analysis of Overall Survival All Participants With PD-L1 CPS⩾1 (ITT Population) IA2

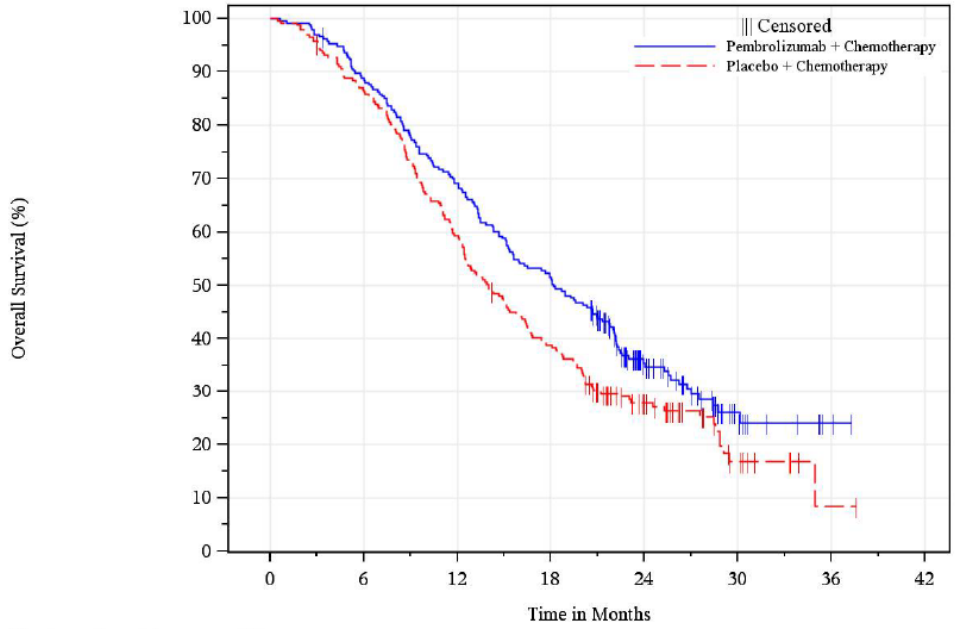
	Pembrolizumab + Chemotherapy (N=234)	Placebo + Chemotherapy (N=232)
Number of Events (%)	157 (67.1)	175 (75.4)
Kaplan-Meier Estimates (months)[a]		
Median (95% CI)	18.2 (15.3, 21.0)	14.0 (12.5, 16.1)
[Q1, Q3]	[9.6, 30.1]	[8.7, 28.5]
Person-months	4046.1	3545.6
Event Rate / 100 Person-months	3.9	4.9
vs Placebo + Chemotherapy		
Hazard Ratio (95% CI)[b]	0.76 (0.61, 0.94)	
p-value[c]	0.0053	
OS Rate at month 6 (%) (95% CI)	88.9 (84.1, 92.3)	86.6 (81.5, 90.4)
OS Rate at month 12 (%) (95% CI)	69.1 (62.7, 74.6)	59.3 (52.7, 65.3)
OS Rate at month 18 (%) (95% CI)	51.5 (44.9, 57.7)	38.9 (32.6, 45.1)
OS Rate at month 24 (%) (95% CI)	35.5 (29.2, 41.9)	27.8 (22.1, 33.8)
OS Rate at month 30 (%) (95% CI)	26.0 (19.3, 33.2)	16.8 (10.6, 24.2)
OS Rate at month 36 (%) (95% CI)	24.0 (16.9, 31.8)	8.4 (1.2, 25.1)

[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 planned bevacizumab use in the study (yes vs no), region (US vs EU vs ROW) and PD-L1 status (CPS <1 vs CPS 1 to <10 vs CPS >=10) with small strata collapsed as pre-specified in the sSAP.
[c] One-sided p-value based on log-rank test stratified by planned bevacizumab use in the study (yes vs no), region (US vs EU vs ROW) and PD-L1 status (CPS <1 vs CPS 1 to <10 vs CPS >=10) with small strata collapsed as pre-specified in the sSAP.
Database Cutoff Date: 05MAR2025

Table 31 Summary of Censoring Reason for Overall Survival Analysis All Participants with PD-L1 CPS>=1 and without Overall Survival Events (ITT Population)

	Pembrolizumab + Chemotherapy		Placebo + Chemotherapy	
	n	(%)	n	(%)
Participants in population	77		57	
Censoring Reason				
Censored at last known alive date	54	(70.1)	41	(71.9)
Censored at data cutoff date due to confirmed survival status post data cutoff	23	(29.9)	16	(28.1)
Database Cutoff Date: 05MAR2025.				

Figure 14 Kaplan-Meier Plot of Overall Survival All Participants With PD-L1 CPS>=1 (ITT Population) IA2



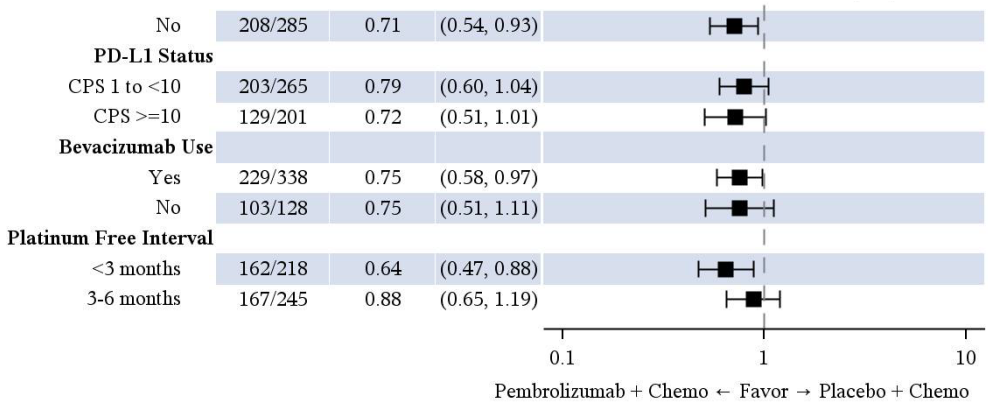
Number of participants at risk

Pembrolizumab + Chemotherapy	234	207	161	120	49	13	3	0
Placebo + Chemotherapy	232	200	137	89	41	10	1	0

Database Cutoff Date: 05MAR2025.

Figure 15 Forest Plot of Overall Survival Hazard Ratio by Subgroup Factors All Participants With PD-L1 CPS>=1 (ITT Population) IA2

	#Events/N	HR	95% CI	Estimated Hazard Ratio (HR)
Overall	332/466	0.76	(0.61, 0.94)	
Age Group				
< 65	206/289	0.73	(0.55, 0.96)	
>= 65	126/177	0.82	(0.58, 1.16)	
Race				
White	213/313	0.78	(0.60, 1.02)	
All Others	90/118	0.70	(0.46, 1.06)	
Region				
US	35/50	0.82	(0.42, 1.59)	
EU	148/218	0.90	(0.65, 1.24)	
ROW	149/198	0.63	(0.46, 0.88)	
ECOG PS				
0	170/258	0.83	(0.61, 1.12)	
1	160/206	0.72	(0.53, 0.99)	
Prior PARPi				
Yes	124/181	0.85	(0.59, 1.20)	



Subgroup analyses are based on unstratified Cox regression model with Efron's method of tie handling with treatment as a covariate.
Platinum free interval is from last platinum therapy to subsequent progression.
Database Cutoff Date: 05MAR2025.

Table 32 Analysis of Overall Survival All Participants With PD-L1 CPS>=1 (ITT Population) – Final analysis

	Pembrolizumab + Chemotherapy (N=234)	Placebo + Chemotherapy (N=232)
Number of Events (%)	174 (74.4)	192 (82.8)
Kaplan-Meier Estimates (months)[a]		
Median (95% CI)	18.2 (15.3, 21.3)	14.0 (12.5, 16.1)
(Q1, Q3)	(9.6, 30.8)	(8.7, 25.8)
Person-months	4437.3	3812.9
Event Rate / 100 Person-months	3.9	5.0
vs Placebo + Chemotherapy		
Hazard Ratio (95% CI)[b]	0.76 (0.62, 0.93)	
p-value[c]	0.0045	
OS Rate at month 6 (%) (95% CI)	88.9 (84.1, 92.3)	86.6 (81.5, 90.4)
OS Rate at month 12 (%) (95% CI)	69.1 (62.7, 74.6)	59.3 (52.7, 65.3)
OS Rate at month 18 (%) (95% CI)	51.5 (44.9, 57.7)	38.9 (32.6, 45.1)
OS Rate at month 24 (%) (95% CI)	35.6 (29.5, 41.8)	26.6 (21.1, 32.5)
OS Rate at month 30 (%) (95% CI)	26.8 (21.0, 32.8)	18.1 (13.3, 23.5)
OS Rate at month 36 (%) (95% CI)	21.4 (15.7, 27.8)	12.0 (6.9, 18.5)
OS Rate at month 42 (%) (95% CI)	21.4 (15.7, 27.8)	8.0 (2.6, 17.5)

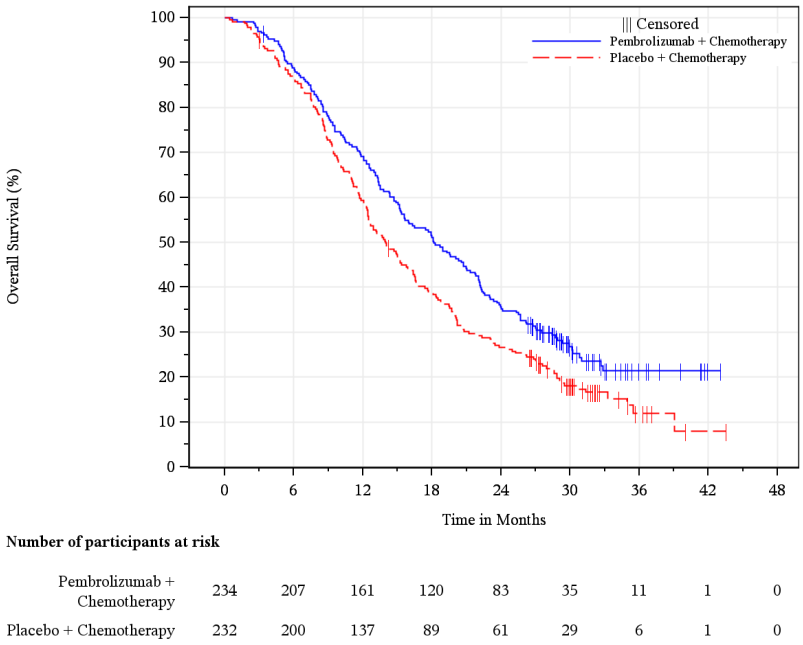
[a] From product-limit (Kaplan-Meier) method for censored data.

[b] Based on Cox regression model with Efron's method of tie handling with treatment as a covariate stratified by planned bevacizumab use in the study (yes vs no), region (US vs EU vs ROW) and PD-L1 status (CPS <1 vs CPS 1 to <10 vs CPS >=10) with small strata collapsed as pre-specified in the sSAP.

[c] One-sided p-value based on log-rank test stratified by planned bevacizumab use in the study (yes vs no), region (US vs EU vs ROW) and PD-L1 status (CPS <1 vs CPS 1 to <10 vs CPS >=10) with small strata collapsed as pre-specified in the sSAP.

Database Cutoff Date: 05SEP2025

Figure 16 Kaplan-Meier Plot of Overall Survival All Participants With PD-L1 CPS≥1 (ITT Population) at FA



Database Cutoff Date: 05SEP2025.

OS in the all-comers population

Table 33 Analysis of Overall Survival All Participants (ITT Population) – Final analysis

	Pembrolizumab + Chemotherapy (N=322)	Placebo + Chemotherapy (N=321)
Number of Events (%)	247 (76.7)	266 (82.9)
Kaplan-Meier Estimates (months)[a]		
Median (95% CI)	17.7 (15.2, 19.2)	14.0 (12.5, 15.6)
(Q1, Q3)	(9.2, 29.5)	(8.6, 25.8)
Person-months	5871.7	5223.2
Event Rate / 100 Person-months	4.2	5.1
vs Placebo + Chemotherapy		
Hazard Ratio (95% CI)[b]	0.82 (0.69, 0.97)	

p-value[c]	0.0115	
OS Rate at month 6 (%) (95% CI)	86.3 (82.0, 89.6)	85.0 (80.6, 88.5)
OS Rate at month 12 (%) (95% CI)	66.0 (60.6, 70.9)	59.9 (54.3, 65.0)
OS Rate at month 18 (%) (95% CI)	49.1 (43.6, 54.5)	39.1 (33.8, 44.5)
OS Rate at month 24 (%) (95% CI)	32.9 (27.8, 38.0)	27.1 (22.4, 32.1)
OS Rate at month 30 (%) (95% CI)	24.2 (19.5, 29.2)	17.9 (13.7, 22.5)
OS Rate at month 36 (%) (95% CI)	20.0 (15.4, 25.2)	12.3 (8.1, 17.6)
OS Rate at month 42 (%) (95% CI)	18.7 (13.8, 24.2)	6.9 (2.2, 15.4)

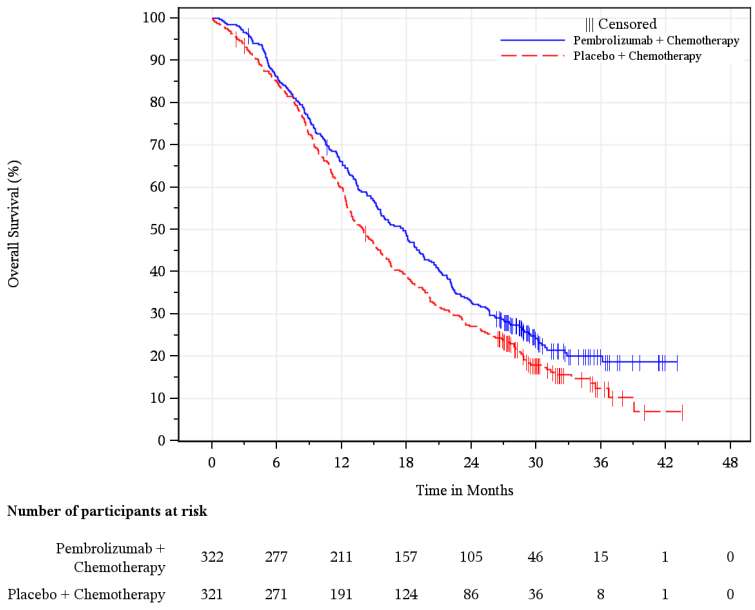
[a] From product-limit (Kaplan-Meier) method for censored data.

[b] Based on Cox regression model with Efron's method of tie handling with treatment as a covariate stratified by planned bevacizumab use in the study (yes vs no), region (US vs EU vs ROW) and PD-L1 status (CPS <1 vs CPS 1 to <10 vs CPS >=10) with small strata collapsed as pre-specified in the sSAP.

[c] One-sided p-value based on log-rank test stratified by planned bevacizumab use in the study (yes vs no), region (US vs EU vs ROW) and PD-L1 status (CPS <1 vs CPS 1 to <10 vs CPS >=10) with small strata collapsed as pre-specified in the sSAP.

Database Cutoff Date: 05SEP2025

Figure 17 Kaplan-Meier Plot of Overall Survival All



Database Cutoff Date: 05SEP2025.

Secondary endpoint: PFS by BICR

Table 34 Analysis of Progression-Free Survival (Primary Censoring Rule) Based on BICR per RECIST 1.1 All Participants With PD-L1 CPS>=1 (ITT Population) IA2

	Pembrolizumab + Chemotherapy (N=234)	Placebo + Chemotherapy (N=232)
Number of Events (%)	154 (65.8)	164 (70.7)
Death	27 (11.5)	27 (11.6)
Documented progression	127 (54.3)	137 (59.1)
Number of Censored (%)	80 (34.2)	68 (29.3)
Last assessment prior to missing >=2 consecutive assessments immediately before event	10 (4.3)	5 (2.2)
Last assessment prior to new anti-cancer therapy showing no progression	41 (17.5)	47 (20.3)
Last assessment showing no progression	26 (11.1)	12 (5.2)
Randomization	3 (1.3)	4 (1.7)
Kaplan-Meier Estimates (months)[a]		
Median (95% CI)	8.5 (8.1, 10.4)	7.6 (6.2, 8.3)
[Q1, Q3]	[5.6, 18.0]	[4.3, 12.2]
Person-months	2221.4	1772.9
Event Rate / 100 Person-months	6.9	9.3
vs Placebo + Chemotherapy		
Hazard Ratio (95% CI)[b]	0.75 (0.60, 0.93)	
p-value[c]	0.0051	
PFS Rate at month 6 (%) (95% CI)	74.3 (68.0, 79.6)	66.1 (59.2, 72.0)
PFS Rate at month 12 (%) (95% CI)	39.3 (32.4, 46.2)	26.7 (20.4, 33.3)
PFS Rate at month 18 (%) (95% CI)	25.8 (19.5, 32.5)	15.5 (10.3, 21.6)
PFS Rate at month 24 (%) (95% CI)	18.9 (13.2, 25.5)	10.5 (5.9, 16.5)
PFS Rate at month 30 (%) (95% CI)	12.2 (5.2, 22.4)	7.0 (2.2, 15.5)

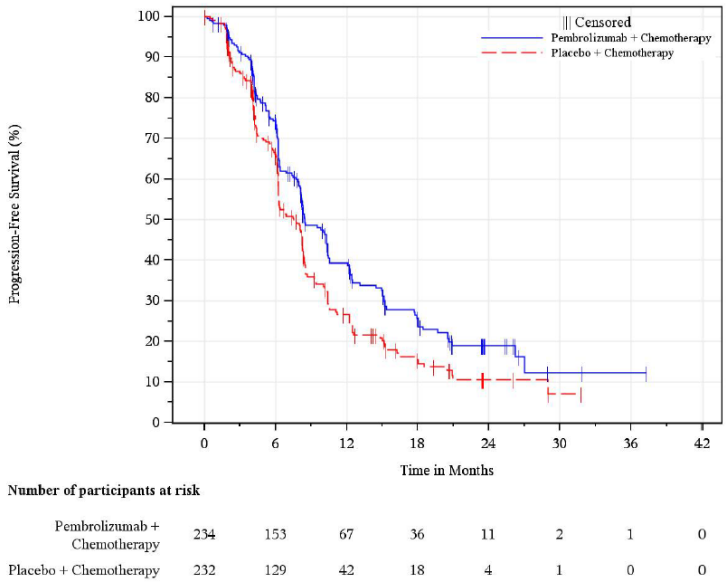
[a] From product-limit (Kaplan-Meier) method for censored data.

[b] Based on Cox regression model with Efron's method of tie handling with treatment as a covariate stratified by planned bevacizumab use in the study (yes vs no), region (US vs EU vs ROW) and PD-L1 status (CPS <1 vs CPS 1 to <10 vs CPS >=10) with small strata collapsed as pre-specified in the sSAP.

[c] One-sided p-value based on log-rank test stratified by planned bevacizumab use in the study (yes vs no), region (US vs EU vs ROW) and PD-L1 status (CPS <1 vs CPS 1 to <10 vs CPS >=10) with small strata collapsed as pre-specified in the sSAP.

Database Cutoff Date: 05MAR2025

Figure 18 Kaplan-Meier Plot of Progression-Free Survival (Primary Censoring Rule) Based on BICR per RECIST 1.1 All Participants With PD-L1 CPS>=1 (ITT Population) at IA2



Database Cutoff Date: 05MAR2025.

PFS Based on BICR per RECIST 1.1 - All Participants: HR = 0.74 (0.61, 0.89)

Tertiary/Exploratory Endpoints

ORR and DOR

Results from IA2 for CPS≥1 and all-comers are reported below.

Table 35 Summary of Best Objective Response (Confirmed) Based on Investigator Assessment per RECIST 1.1 All Participants With PD-L1 CPS>=1 and Measurable Disease at Baseline (ITT Population)

Response Evaluation	Pembrolizumab + Chemotherapy			Placebo + Chemotherapy		
	n	%	95% CI[a]	n	%	95% CI[a]
Participants in population	202			204		
Complete Response (CR)	20	9.9	(6.2, 14.9)	16	7.8	(4.5, 12.4)
Partial Response (PR)	87	43.1	(36.1, 50.2)	79	38.7	(32.0, 45.8)
Overall Response (CR+PR)	**107**	**53.0**	**(45.8, 60.0)**	**95**	**46.6**	**(39.6, 53.7)**
Stable Disease (SD)	76	37.6	(30.9, 44.7)	72	35.3	(28.7, 42.3)
Disease Control (CR+PR+SD)	**183**	**90.6**	**(85.7, 94.2)**	**167**	**81.9**	**(75.9, 86.9)**
Progressive Disease (PD)	17	8.4	(5.0, 13.1)	29	14.2	(9.7, 19.8)
No Assessment	2	1.0	(0.1, 3.5)	8	3.9	(1.7, 7.6)

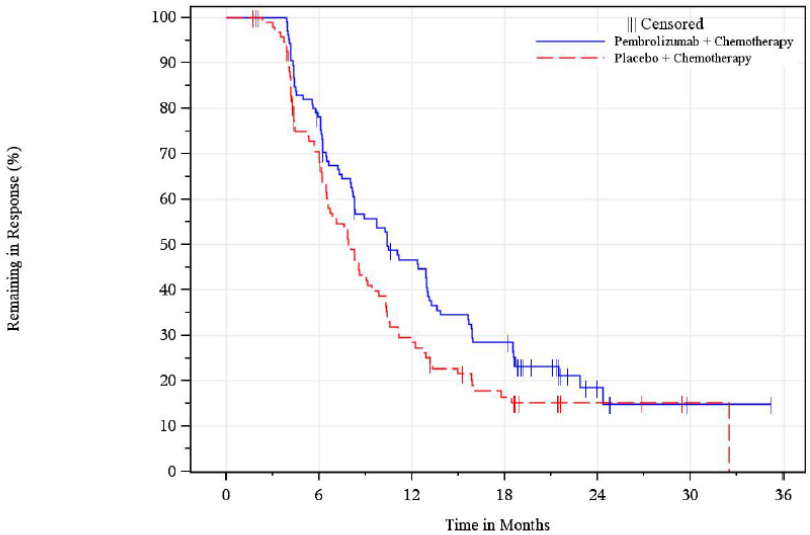
[a] Based on the exact method for binomial data.
Responses are based on investigator assessment per RECIST 1.1.
Database Cutoff Date: 05MAR2025.

Table 36 Summary of Time to Response and Duration of Response Based on Investigator Assessment per RECIST 1.1 in Participants with Confirmed Response All Participants With PD-L1 CPS>=1 and Measurable Disease at Baseline (ITT Population)

	Pembrolizumab + Chemotherapy (N=202)	Placebo + Chemotherapy (N=204)
Number of participants with response[a]	107	95
Time to Response (months)		
Mean (SD)	2.6 (1.3)	2.8 (1.7)
Median (Range)	2.1 (1.9 to 12.5)	2.1 (1.8 to 10.3)
Response Duration[b] (months)		
Median (95% CI)	10.4 (8.3, 12.9)	8.1 (6.5, 9.4)
Range	1.9+ to 35.2+	1.7+ to 32.5
Number (%[b]) of Participants with Extended Response Duration		
≥6 months	81 (78.1)	63 (70.5)
≥9 months	56 (55.7)	38 (43.2)
≥12 months	46 (46.7)	26 (29.6)
≥18 months	28 (28.4)	13 (16.4)

[a] Includes participants with confirmed 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: 05MAR2025

Figure 19 Kaplan-Meier Plot of Duration of Response Based on Investigator Assessment per RECIST 1.1 in Participants With Confirmed Response All Participants With PD-L1 CPS>=1 and Measurable Disease at Baseline (ITT Population)



Database Cutoff Date: 05MAR2025.

ORR based on investigator assessment per RECIST 1.1 – All participants with measurable disease at baseline: 50.4% (44.3, 56.4) vs 40.8% (35.0, 46.8); CR 8.3% (5.4, 12.2), vs 6% (3.6, 9.5).

DOR – All participants: 10.4 (8.3, 12.9) vs 7.9 (6.5, 8.6) months.

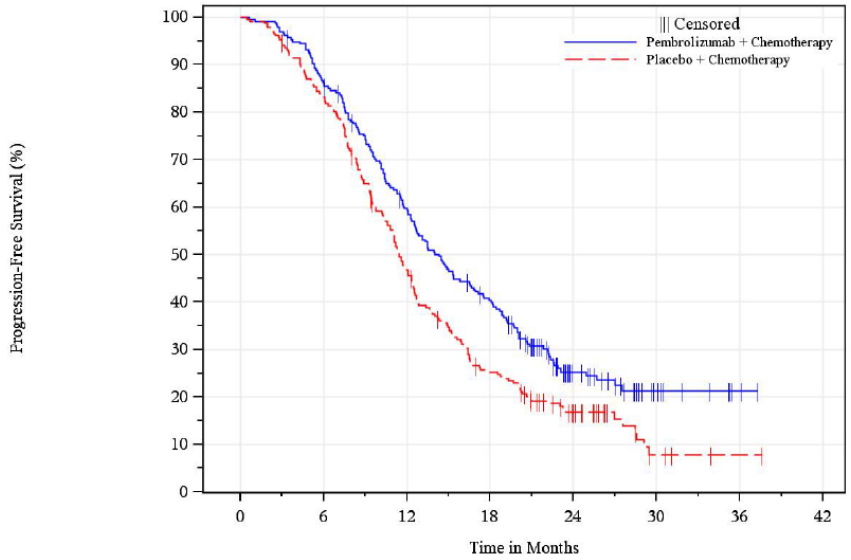
Progression Free Survival 2

Table 37 Analysis of Progression-Free Survival After Next-line Treatment (PFS2) Based on Investigator Assessment All Participants With PD-L1 CPS>=1 (ITT Population) at IA2

	Pembrolizumab + Chemotherapy (N=234)	Placebo + Chemotherapy (N=232)
Number of Events (%)	171 (73.1)	193 (83.2)
Death	76 (32.5)	94 (40.5)
Progression after next-line therapy	95 (40.6)	99 (42.7)
Number of Censored (%)	63 (26.9)	39 (16.8)
Last known alive date	54 (23.1)	32 (13.8)
Second next-line therapy start date	9 (3.8)	7 (3.0)
Kaplan-Meier Estimates (months)[a]		
Median (95% CI)	14.3 (12.6, 16.6)	11.4 (10.6, 12.5)
[Q1, Q3]	[9.0, 24.9]	[7.6, 18.5]
Person-months	3552.7	2993.0
Event Rate / 100 Person-months	4.8	6.4
vs Placebo + Chemotherapy		
Hazard Ratio (95% CI)[b]	0.70 (0.57, 0.86)	
p-value[c]	0.0004	

[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 planned bevacizumab use in the study (yes vs no), region (US vs EU vs ROW) and PD-L1 status (CPS <1 vs CPS 1 to <10 vs CPS >=10).
[c] One-sided p-value based on log-rank test stratified by planned bevacizumab use in the study (yes vs no), region (US vs EU vs ROW) and PD-L1 status (CPS <1 vs CPS 1 to <10 vs CPS >=10).
Database Cutoff Date: 05MAR2025

Figure 20 Kaplan-Meier Plot of Progression-Free Survival After Next-line Treatment (PFS2) Based on Investigator Assessment All Participants With PD-L1 CPS>=1 (ITT Population) at IA2



Number of participants at risk

Pembrolizumab + Chemotherapy	234	201	136	90	32	10	2	0
Placebo + Chemotherapy	232	192	106	55	24	4	1	0

Database Cutoff Date: 05MAR2025.

PFS2 – All participants: HR 0.75 (0.62, 0.89).

Table 38 Participants With Subsequent Oncologic Therapies (Incidence > 0% in One or More Treatment Groups) All Participants (ITT Population) at IA2

	Pembrolizumab + Chemotherapy		Placebo + Chemotherapy	
	n	(%)	n	(%)
Participants in population	322		321	
with one or more Subsequent Oncologic Therapies	168	(52.2)	194	(60.4)
with no Subsequent Oncologic Therapies	154	(47.8)	127	(39.6)
ANTIINFECTIVES FOR SYSTEMIC USE				
VACCINES	**0**	**(0.0)**	**1**	**(0.3)**
MRNA VACCINES, PREVENTIVE	0	(0.0)	1	(0.3)
ANTINEOPLASTIC AND IMMUNOMODULATING AGENTS				
ANTINEOPLASTIC AGENTS	**166**	**(51.6)**	**190**	**(59.2)**
ABEMACICLIB	0	(0.0)	1	(0.3)
ADAVOSERTIB	0	(0.0)	1	(0.3)
ANTINEOPLASTIC AGENTS	0	(0.0)	3	(0.9)
ATEZOLIZUMAB	1	(0.3)	2	(0.6)
AZACITIDINE	1	(0.3)	0	(0.0)
AZENOSERTIB	1	(0.3)	0	(0.0)
BELOTECAN	3	(0.9)	5	(1.6)
BEVACIZUMAB	25	(7.8)	25	(7.8)
BEVACIZUMAB AWWB	1	(0.3)	2	(0.6)
BEVACIZUMAB BVZR	1	(0.3)	1	(0.3)
BL B01D1	0	(0.0)	1	(0.3)
CAPECITABINE	4	(1.2)	0	(0.0)
CARBOPLATIN	36	(11.2)	49	(15.3)
CATEQUENTINIB HYDROCHLORIDE	1	(0.3)	2	(0.6)
CDX 1140	1	(0.3)	0	(0.0)
CEDIRANIB	1	(0.3)	0	(0.0)
CELECOXIB	0	(0.0)	1	(0.3)
CEMIPLIMAB	1	(0.3)	2	(0.6)
CEMIPLIMAB RWLC	0	(0.0)	1	(0.3)
CERALASERTIB	1	(0.3)	0	(0.0)
CISPLATIN	16	(5.0)	20	(6.2)
CISPLATIN;GEMCITABINE	1	(0.3)	0	(0.0)
CYCLOPHOSPHAMIDE	9	(2.8)	18	(5.6)
CYH 33	0	(0.0)	1	(0.3)
DATOPOTAMAB DERUXTECAN	0	(0.0)	1	(0.3)
DISITAMAB VEDOTIN	1	(0.3)	1	(0.3)

	Pembrolizumab + Chemotherapy		Placebo + Chemotherapy	
	n	(%)	n	(%)
ANTINEOPLASTIC AND IMMUNOMODULATING AGENTS				
ANTINEOPLASTIC AGENTS	**166**	**(51.6)**	**190**	**(59.2)**
DOCETAXEL	0	(0.0)	5	(1.6)
DOXORUBICIN	25	(7.8)	29	(9.0)
DOXORUBICIN HYDROCHLORIDE	13	(4.0)	17	(5.3)
DURVALUMAB	1	(0.3)	0	(0.0)
ELU 001	1	(0.3)	0	(0.0)
EPIRUBICIN HYDROCHLORIDE	0	(0.0)	1	(0.3)
ETOPOSIDE	6	(1.9)	12	(3.7)
FARLETUZUMAB ECTERIBULIN	2	(0.6)	0	(0.0)
GEMCITABINE	66	(20.5)	63	(19.6)
GEMCITABINE HYDROCHLORIDE	11	(3.4)	14	(4.4)
GEN 1047	0	(0.0)	1	(0.3)
HS 20089	1	(0.3)	0	(0.0)
IFOSFAMIDE	0	(0.0)	3	(0.9)
INVESTIGATIONAL ANTINEOPLASTIC DRUGS	1	(0.3)	0	(0.0)
IRINOTECAN	0	(0.0)	1	(0.3)
IRINOTECAN HYDROCHLORIDE	1	(0.3)	2	(0.6)
JK 08	0	(0.0)	1	(0.3)
LOBAPLATIN	1	(0.3)	0	(0.0)
MELPHALAN	0	(0.0)	1	(0.3)
MIRVETUXIMAB SORAVTANSINE	3	(0.9)	5	(1.6)
MIRVETUXIMAB SORAVTANSINE GYNX	1	(0.3)	3	(0.9)
NEDAPLATIN	1	(0.3)	2	(0.6)
NIRAPARIB	1	(0.3)	0	(0.0)
NIRAPARIB TOSYLATE MONOHYDRATE	2	(0.6)	0	(0.0)
NIVOLUMAB	0	(0.0)	1	(0.3)
OLAPARIB	0	(0.0)	1	(0.3)
OTHER ANTINEOPLASTIC AGENTS	1	(0.3)	1	(0.3)
OTHER MONOCLONAL ANTIBODIES AND ANTIBODY DRUG CONJUGATES	3	(0.9)	5	(1.6)
OXALIPLATIN	1	(0.3)	2	(0.6)
PACLITAXEL	16	(5.0)	12	(3.7)
PACLITAXEL NANOPARTICLE ALBUMIN-BOUND	4	(1.2)	15	(4.7)

	Pembrolizumab + Chemotherapy		Placebo + Chemotherapy	
	n	(%)	n	(%)
ANTINEOPLASTIC AND IMMUNOMODULATING AGENTS				
ANTINEOPLASTIC AGENTS	**166**	**(51.6)**	**190**	**(59.2)**
PEGYLATED LIPOSOMAL DOXORUBICIN HYDROCHLORIDE	38	(11.8)	44	(13.7)
PEMBROLIZUMAB	2	(0.6)	6	(1.9)
PEMETREXED DISODIUM	2	(0.6)	1	(0.3)
PEMETREXED DISODIUM HEPTAHYDRATE	0	(0.0)	1	(0.3)
PEP 010	1	(0.3)	0	(0.0)
PHI 101	0	(0.0)	1	(0.3)
PREXASERTIB	1	(0.3)	0	(0.0)
PROTEIN KINASE INHIBITORS	1	(0.3)	0	(0.0)
RALUDOTATUG DERUXTECAN	2	(0.6)	0	(0.0)
RINATABART SESUTECAN	1	(0.3)	0	(0.0)
RIVOCERANIB MESYLATE	0	(0.0)	1	(0.3)
SERPLULIMAB	0	(0.0)	1	(0.3)
SINTILIMAB	0	(0.0)	1	(0.3)
SIROLIMUS NANOPARTICLE ALBUMIN-BOUND	0	(0.0)	1	(0.3)
SL 172154	1	(0.3)	4	(1.2)
TEMOZOLOMIDE	1	(0.3)	0	(0.0)
TOPOTECAN	18	(5.6)	25	(7.8)
TOPOTECAN HYDROCHLORIDE	1	(0.3)	5	(1.6)
TRABECTEDIN	1	(0.3)	0	(0.0)
TRAMETINIB	0	(0.0)	1	(0.3)
TRAMETINIB DIMETHYL SULFOXIDE	0	(0.0)	1	(0.3)
TRASTUZUMAB	1	(0.3)	0	(0.0)
TREOSULFAN	1	(0.3)	1	(0.3)
TULMIMETOSTAT	0	(0.0)	1	(0.3)
UBAMATAMAB	1	(0.3)	4	(1.2)
VINORELBINE TARTRATE	3	(0.9)	3	(0.9)
VISMODEGIB	1	(0.3)	0	(0.0)
XB 002	1	(0.3)	0	(0.0)
ENDOCRINE THERAPY	**12**	**(3.7)**	**6**	**(1.9)**
ANASTROZOLE	2	(0.6)	1	(0.3)
LETROZOLE	6	(1.9)	2	(0.6)

	Pembrolizumab + Chemotherapy		Placebo + Chemotherapy	
	n	(%)	n	(%)
ANTINEOPLASTIC AND IMMUNOMODULATING AGENTS				
ENDOCRINE THERAPY	**12**	**(3.7)**	**6**	**(1.9)**
TAMOXIFEN	5	(1.6)	3	(0.9)
IMMUNOSTIMULANTS	**2**	**(0.6)**	**5**	**(1.6)**
INTERLEUKINS	1	(0.3)	1	(0.3)
LENTINAN	1	(0.3)	0	(0.0)
NEMVALEUKIN ALFA	0	(0.0)	3	(0.9)
NOCARDIA RUBRA CELL WALL SKELETON	0	(0.0)	1	(0.3)
IMMUNOSUPPRESSANTS	**9**	**(2.8)**	**19**	**(5.9)**
CYCLOPHOSPHAMIDE	9	(2.8)	18	(5.6)
TOCILIZUMAB	0	(0.0)	1	(0.3)
CARDIOVASCULAR SYSTEM				
CARDIAC THERAPY	**16**	**(5.0)**	**12**	**(3.7)**
PACLITAXEL	16	(5.0)	12	(3.7)
MUSCULO-SKELETAL SYSTEM				
ANTIINFLAMMATORY AND ANTIRHEUMATIC PRODUCTS	**0**	**(0.0)**	**1**	**(0.3)**
CELECOXIB	0	(0.0)	1	(0.3)
DRUGS FOR TREATMENT OF BONE DISEASES	**1**	**(0.3)**	**0**	**(0.0)**
ZOLEDRONIC ACID MONOHYDRATE	1	(0.3)	0	(0.0)
SENSORY ORGANS				
OPHTHALMOLOGICALS	**25**	**(7.8)**	**25**	**(7.8)**
BEVACIZUMAB	25	(7.8)	25	(7.8)
SYSTEMIC HORMONAL PREPARATIONS, EXCL. SEX HORMONES AND INSULINS				
CORTICOSTEROIDS FOR SYSTEMIC USE	**0**	**(0.0)**	**2**	**(0.6)**
RELACORILANT	0	(0.0)	2	(0.6)
VARIOUS				
ALL OTHER THERAPEUTIC PRODUCTS	**2**	**(0.6)**	**3**	**(0.9)**
OTHER THERAPEUTIC PRODUCTS	2	(0.6)	3	(0.9)

	Pembrolizumab + Chemotherapy		Placebo + Chemotherapy	
	n	(%)	n	(%)
VARIOUS				
INVESTIGATIONAL DRUG	**18**	**(5.6)**	**22**	**(6.9)**
ADAVOSERTIB	0	(0.0)	1	(0.3)
AZENOSERTIB	1	(0.3)	0	(0.0)
BL B01D1	0	(0.0)	1	(0.3)
CDX 1140	1	(0.3)	0	(0.0)
CERALASERTIB	1	(0.3)	0	(0.0)
CYH 33	0	(0.0)	1	(0.3)
DATOPOTAMAB DERUXTECAN	0	(0.0)	1	(0.3)
ELU 001	1	(0.3)	0	(0.0)
FARLETUZUMAB ECTERIBULIN	2	(0.6)	0	(0.0)
GEN 1047	0	(0.0)	1	(0.3)
HS 20089	1	(0.3)	0	(0.0)
INVESTIGATIONAL ANTINEOPLASTIC DRUGS	1	(0.3)	0	(0.0)
INVESTIGATIONAL DRUG	3	(0.9)	1	(0.3)
JK 08	0	(0.0)	1	(0.3)
NEMVALEUKIN ALFA	0	(0.0)	3	(0.9)
PEP 010	1	(0.3)	0	(0.0)
PHI 101	0	(0.0)	1	(0.3)
PREXASERTIB	1	(0.3)	0	(0.0)
RALUDOTATUG DERUXTECAN	2	(0.6)	0	(0.0)
RELACORILANT	0	(0.0)	2	(0.6)
RINATABART SESUTECAN	1	(0.3)	0	(0.0)
SL 172154	1	(0.3)	4	(1.2)
TULMIMETOSTAT	0	(0.0)	1	(0.3)
UBAMATAMAB	1	(0.3)	4	(1.2)
XB 002	1	(0.3)	0	(0.0)

Every participant is counted a single time for each applicable specific subsequent therapy. A participant with multiple subsequent therapies within a therapy category is counted a single time for that category. Each specific subsequent therapy is listed under all relevant therapy classes based on the therapy's generic name, regardless of route of administration or reason for use.
Database Cutoff Date: 05MAR2025.

Patient reported outcomes (PROs)

At IA2, the assessment of the secondary PRO endpoints showed that pembrolizumab plus chemotherapy was not accompanied by any substantial deterioration in HRQoL compared with placebo plus chemotherapy in participants with PD-L1 positive tumors (CPS ≥1) and in all-comers.

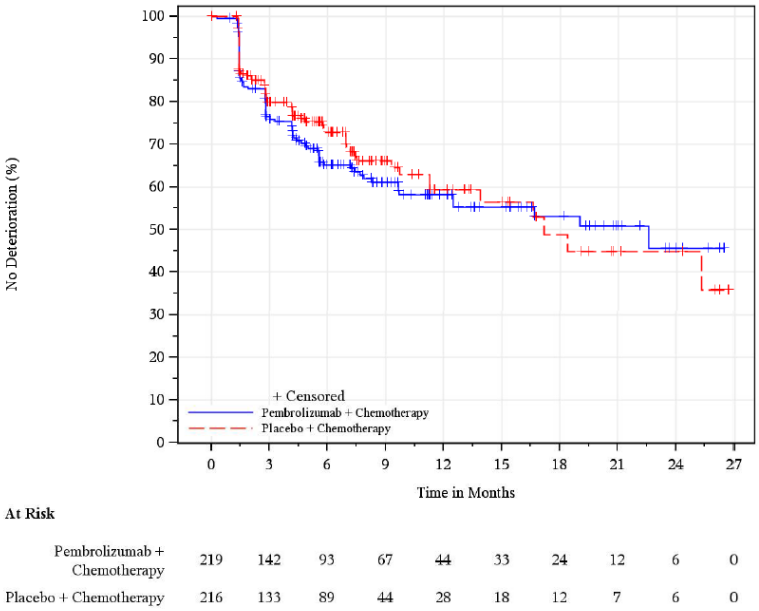
Table 39 Analysis of Change from Baseline to Week 24 in EORTC QLQ-C30 Global Health Status/QoL (PRO FAS Population With PD-L1 CPS >=1)

Treatment	Baseline		Week 24		Change from Baseline to Week 24	
	N	Mean (SD)	N	Mean (SD)	N	LS Mean (95% CI)[a]
Pembrolizumab + Chemotherapy	219	66.78 (21.38)	160	63.28 (20.27)	227	-5.02 (-8.19, -1.84)
Placebo + Chemotherapy	216	63.81 (22.31)	139	65.29 (20.28)	227	-3.63 (-6.97, -0.29)

Pairwise Comparison	Difference in LS Means[a] (95% CI)	p-Value[a]
Pembrolizumab + Chemotherapy vs. Placebo + Chemotherapy	-1.38 (-5.62, 2.85)	0.5205

[a] Based on a cLDA model with the PRO scores as the response variable with covariates for treatment by study visit interaction, and stratification factors by planned bevacizumab use in the study (yes vs no), region (US vs EU vs ROW) and PD-L1 status (CPS <1 vs CPS 1 to <10 vs CPS >=10) as pre-specified in the sSAP.
P-value is two-sided.
For baseline and Week 24, N is the number of participants in each treatment group with non-missing assessments at the specific time point; for change from baseline, N is the number of participants in the analysis population in each treatment group.
Database Cutoff Date: 05MAR2025

Figure 21 Kaplan-Meier Plot of Time to Deterioration in EORTC QLQ-C30 Global Health Status/QoL (PRO FAS Population With PD-L1 CPS >=1 With Baseline)



Database Cutoff Date: 05MAR2025.

Table 40 Analysis of Change from Baseline to Week 24 in EORTC QLQ-OV28 Abdominal/GI Symptoms (PRO FAS Population With PD-L1 CPS >=1)

Treatment	Baseline		Week 24		Change from Baseline to Week 24	
	N	Mean (SD)	N	Mean (SD)	N	LS Mean (95% CI)[a]
Pembrolizumab + Chemotherapy	212	24.84 (19.74)	158	20.43 (18.25)	227	-2.29 (-4.90, 0.33)
Placebo + Chemotherapy	209	23.24 (19.81)	139	21.51 (18.19)	227	-0.28 (-3.05, 2.49)

Pairwise Comparison	Difference in LS Means[a] (95% CI)	p-Value[a]
Pembrolizumab + Chemotherapy vs. Placebo + Chemotherapy	-2.01 (-5.58, 1.56)	0.2691

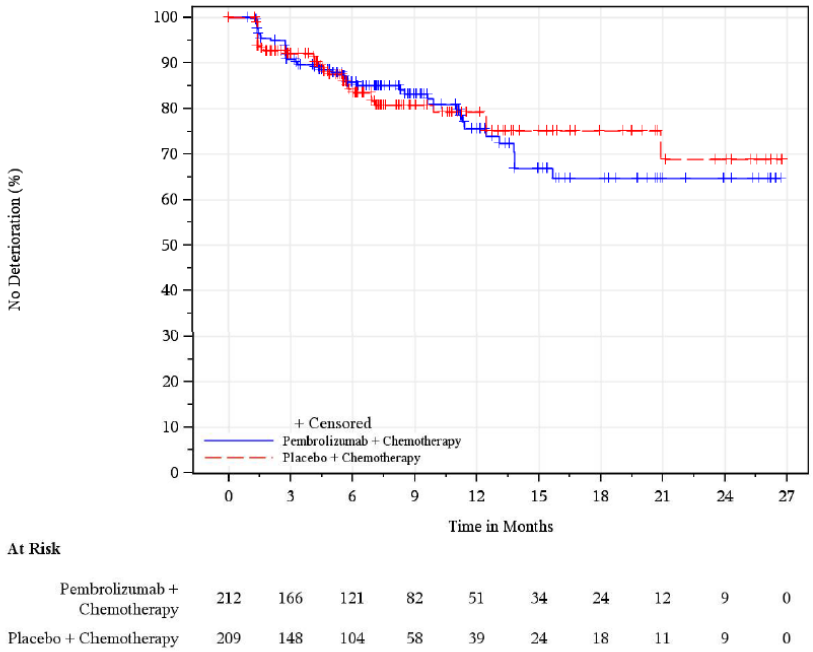
[a] Based on a cLDA model with the PRO scores as the response variable with covariates for treatment by study visit interaction, and stratification factors by planned bevacizumab use in the study (yes vs no), region (US vs EU vs ROW) and PD-L1 status (CPS <1 vs CPS 1 to <10 vs CPS >=10) as pre-specified in the sSAP.

P-value is two-sided.

For baseline and Week 24, N is the number of participants in each treatment group with non-missing assessments at the specific time point; for change from baseline, N is the number of participants in the analysis population in each treatment group.

Database Cutoff Date: 05MAR2025

Figure 22 Kaplan-Meier Plot of Time to Deterioration in EORTC QLQ-OV28 Abdominal/GI Symptoms (PRO FAS Population With PD-L1 CPS >=1 With Baseline)



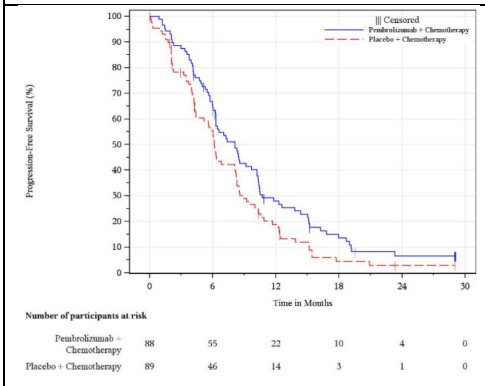
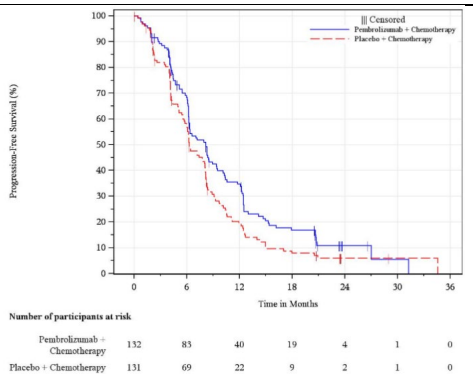
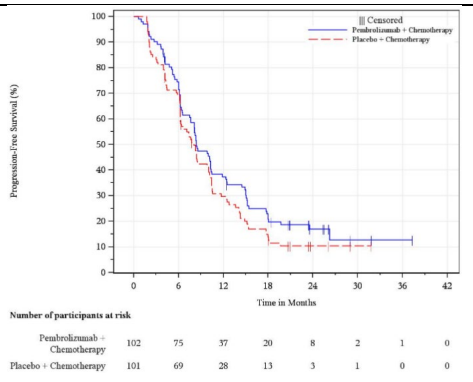
Database Cutoff Date: 05MAR2025.

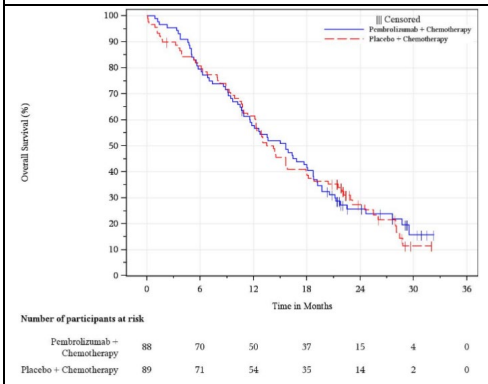
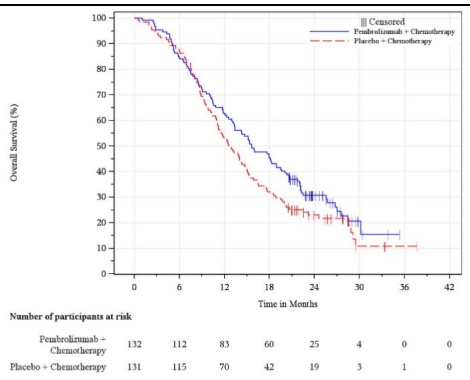
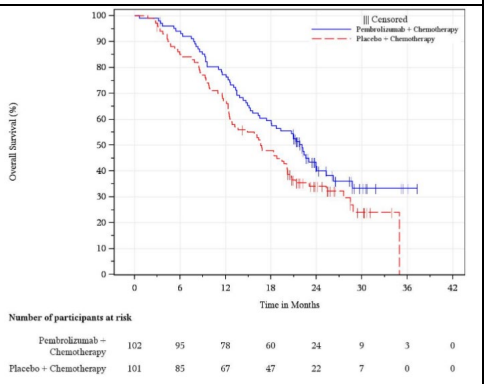
Ancillary analyses

The following subgroups were not powered and intended solely for hypothesis generation.

Efficacy by PD-L1 expression

Table 41 results by PD-L1 expression

PFS by inv		
CPS<1	**CPS 1-10**	**CPS ≥10**
		
HR=0.71 (0.51, 0.97) median 8.1 vs 6.1 months	HR=0.75 (0.57, 0.97) median 8.2 vs 6.3 months	HR=0.80 (0.59, 1.08) median 8.4 vs 8.1 months
OS		

CPS<1	CPS 1-10	CPS ≥10
		
HR=0.97 (0.69, 1.35) median 15.6 vs 14.3 months	HR=0.79 (0.60, 1.04) median 15.6 vs 12.6 months	HR=0.71 (0.50, 1.01) median 22.1 vs 16.6 months
ORR by inv 43.2% vs 25.6% **DOR** median 9.6 vs 6.8 months		

Data cut-off date: 5 MAR 2025

Efficacy by age

Table 42 Progression-Free Survival by Subgroup Factors Based on Investigator Assessments per RECIST 1.1 (Primary Censoring Rule) Point Estimate and Nominal 95% Confidence Interval All Participants With PD-L1 CPS>=1 (ITT Population)

	Pembrolizumab + Chemotherapy (N=234)			Placebo + Chemotherapy (N=232)			Pembrolizumab + Chemotherapy vs. Placebo + Chemotherapy
	N	Number of Events	(%)	N	Number of Events	(%)	Hazard Ratio (95% CI)
Overall	234	191	(81.6)	232	201	(86.6)	0.75 (0.61, 0.91)
Age (Years)							
< 65	145	122	(84.1)	144	129	(89.6)	0.74 (0.58, 0.95)
65 - 74	69	53	(76.8)	66	55	(83.3)	0.80 (0.55, 1.17)
75 - 84	19	15	(78.9)	22	17	(77.3)	0.80 (0.39, 1.63)

Subgroup analyses are based on unstratified Cox regression model with Efron's method of tie handling with treatment as a covariate.
Database Cutoff Date: 05MAR2025.

Table 43 Overall Survival by Subgroup Factors Point Estimate and Nominal 95% Confidence Interval All Participants With PD-L1 CPS>=1 (ITT Population)

	Pembrolizumab + Chemotherapy (N=234)			Placebo + Chemotherapy (N=232)			Pembrolizumab + Chemotherapy vs. Placebo + Chemotherapy
	N	Number of Events	(%)	N	Number of Events	(%)	Hazard Ratio (95% CI)
Overall	234	157	(67.1)	232	175	(75.4)	0.76 (0.61, 0.94)
Age (Years)							
< 65	145	96	(66.2)	144	110	(76.4)	0.73 (0.55, 0.96)
65 - 74	69	46	(66.7)	66	47	(71.2)	0.80 (0.53, 1.20)
75 - 84	19	14	(73.7)	22	18	(81.8)	0.91 (0.45, 1.86)
Subgroup analyses are based on unstratified Cox regression model with Efron's method of tie handling with treatment as a covariate. Database Cutoff Date: 05MAR2025.							

Efficacy by histology

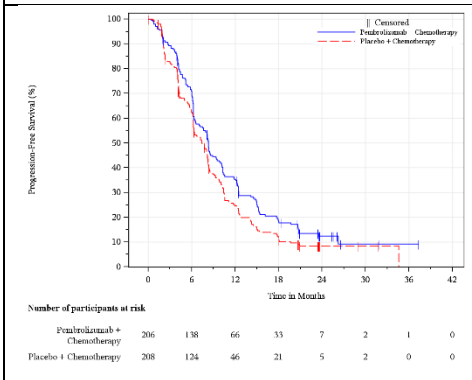
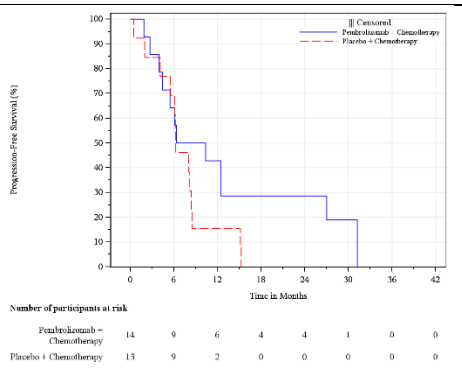
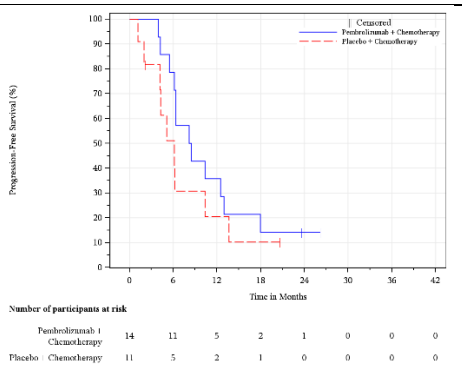
Histology was not a stratification factor, although distribution is similar between treatment arms: in the CPS≥1 population, 88% vs 89.7% (206 vs 208) were HGS, 6% vs 5.6% (14 vs 13) were clear cell, 6% vs 5.3% (14 vs 11) other histologies.

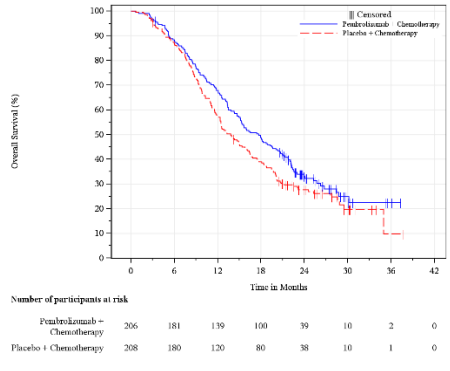
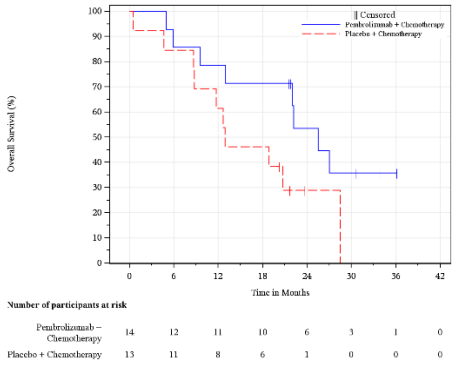
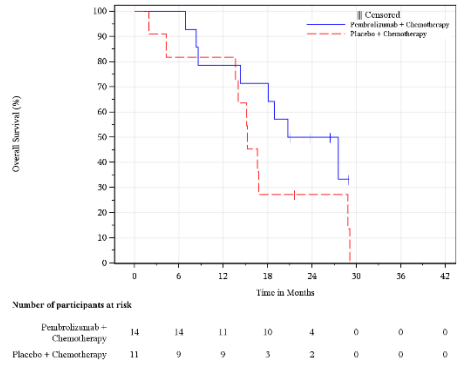
Results in subgroups by histology in the **CPS≥1 population** showed:

- HGS: OS 0.81 (0.64, 1.01); PFS 0.79 (0.64, 0.98)
- clear cell: OS 0.42 (0.16, 1.11); PFS 0.53 (0.23, 1.24)
- other histologies: OS 0.55 (0.21, 1.44); PFS 0.64 (0.27, 1.54)

[all CPS≥1 OS 0.76 (0.61, 0.94); PFS 0.75 (0.61, 0.91)].

Table 44 results by histology

PFS by inv (CPS≥1)		
High grade serous	**Clear Cell**	**Other histology**
		
HR=0.79 (0.64, 0.98) median 8.3 vs 7.4 months	HR=0.53 (0.23, 1.24) median 8.4 vs 6.2 months	HR=0.64 (0.27, 1.54) median 8.3 vs 6.2 months
***OS* (CPS ≥1)**		
High grade serous	**Clear Cell**	**Other histology**

		
HR=0.81 (0.64, 1.01) median 17.7 vs 13.8 months	HR=0.42 (0.16, 1.11) median 25.5 vs 12.9 months	HR=0.55 (0.21, 1.44) median 24.1 vs 15.2 months

Data cut-off date: 05 MAR 2025

Efficacy by prior bevacizumab use in patients treated with bevacizumab

Table 45 Progression-Free Survival Based on Investigator Assessment per RECIST 1.1 (Primary Censoring Rule) by Prior Bevacizumab Use Point Estimate and Nominal 95% Confidence Interval All Participants with PD-L1 CPS>=1 and Treated with Bevacizumab (ITT Population)

	Pembrolizumab + Chemotherapy (N=169)			Placebo + Chemotherapy (N=169)			Pembrolizumab + Chemotherapy vs. Placebo + Chemotherapy
	N	Number of Events	(%)	N	Number of Events	(%)	Hazard Ratio (95% CI)
Overall	169	133	(78.7)	169	143	(84.6)	0.76 (0.60, 0.97)
Prior Bevacizumab							
Yes	68	57	(83.8)	66	61	(92.4)	0.71 (0.49, 1.03)
No	101	76	(75.2)	103	82	(79.6)	0.77 (0.56, 1.06)
Subgroup analyses are based on unstratified Cox regression model with Efron's method of tie handling with treatment as a covariate. Database Cutoff Date: 05MAR2025.							

Table 46 Overall Survival by Prior Bevacizumab Use Point Estimate and Nominal 95% Confidence Interval All Participants with PD-L1 CPS>=1 and Treated with Bevacizumab (ITT Population)

	Pembrolizumab + Chemotherapy (N=169)			Placebo + Chemotherapy (N=169)			Pembrolizumab + Chemotherapy vs. Placebo + Chemotherapy
	N	Number of Events	(%)	N	Number of Events	(%)	Hazard Ratio (95% CI)
Overall	169	107	(63.3)	169	122	(72.2)	0.75 (0.58, 0.97)
Prior Bevacizumab							
Yes	68	45	(66.2)	66	49	(74.2)	0.86 (0.58, 1.30)
No	101	62	(61.4)	103	73	(70.9)	0.68 (0.49, 0.96)

Subgroup analyses are based on unstratified Cox regression model with Efron's method of tie handling with treatment as a covariate.
Database Cutoff Date: 05MAR2025.

Efficacy by Region

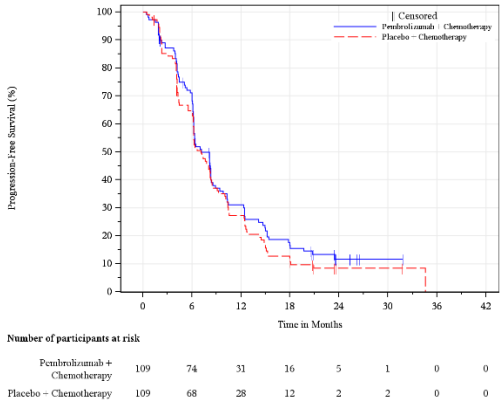
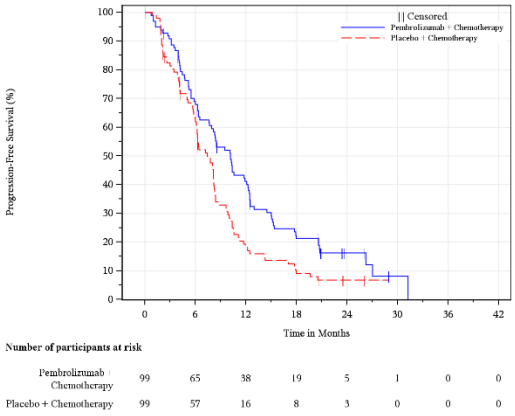
Region (EU vs US vs ROW) was a stratification factor. EU represents 47% of the CPS≥1 population (109 vs 109 patients), followed by ROW (42.5%, 99 vs 99 patients) and US (10.7%, 26 vs 24 patients).

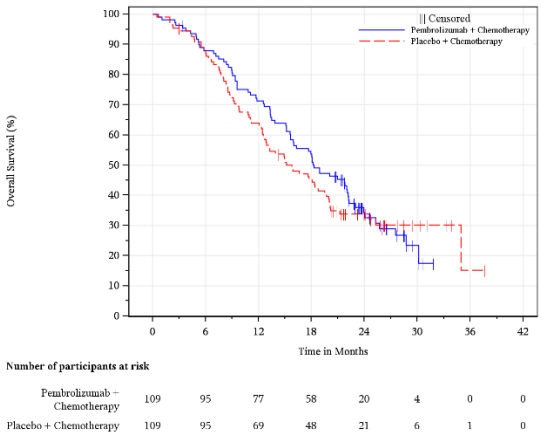
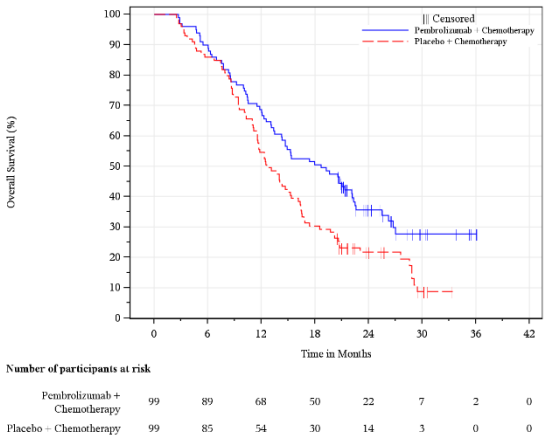
Results in subgroups EU/ROW by Region in the **CPS≥1 population** showed:

- EU: OS 0.90 (0.65, 1.24); PFS 0.88 (0.66, 1.17); ORR 54.2% vs 50.5%
- ROW: OS 0.63 (0.46, 0.88); PFS 0.65 (0.47, 0.88), ORR 51.8% vs 41.4%.

[all CPS≥1 OS 0.76 (0.61, 0.94); PFS 0.75 (0.61, 0.91)].

Table 47 results by region

PFS by inv (CPS≥1)	
EU	**ROW**
	
HR 0.88 (0.66, 1.17) Median 7.2 vs 7.1 months	HR 0.65 (0.47, 0.88) Median 10.2 vs 7.4 months
OS (CPS≥1)	
EU	**ROW**

	
HR 0.90 (0.65, 1.24) Median 18.3 vs 15.2 months	HR 0.63 (0.46, 0.88) Median 18.7 vs 12.6 months

Summary of main study

The following table summarises 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 later sections).

Table 48 Summary of Efficacy for trial KEYNOTE-B96

Title: A Phase 3, Randomized, Double-Blind Study of Pembrolizumab versus Placebo in Combination With Paclitaxel With or Without Bevacizumab for the Treatment of Platinum-resistant Recurrent Ovarian Cancer (KEYNOTE-B96 / ENGOT-ov65)			
Study identifier	IND: 126191; EudraCT: 2020-005027-37; EU CT: 2023-506177-35; NCT:		
Design	Phase 3, randomized, placebo-controlled, parallel-group, multisite, double-blind placebo-controlled, interventional study		
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:		Approximately 2 years Not applicable Not applicable
Hypothesis	Superiority		
Treatments groups	Pembrolizumab + Chemotherapy (pembrolizumab + paclitaxel ± bevacizumab)		Pembrolizumab 400 mg q6w for 18 cycles PLUS paclitaxel 80 mg/m^2 on Days 1, 8, and 15 of each q3w cycle (with or without bevacizumab 10 mg/kg q2w) (approximately 2 years) 322 participants randomized (ITT population)
	Placebo + Chemotherapy (placebo + paclitaxel ± bevacizumab)		Placebo q6w for 18 cycles PLUS paclitaxel 80 mg/m^2 on Days 1, 8, and 15 of each q3w cycle (with or without bevacizumab 10 mg/kg q2w) 321 participants randomized (ITT population)
Endpoints and definitions	Primary endpoint	PFS (Investigator assessed)	Time from randomization to the first documented disease progression as assessed by investigator per RECIST 1.1, or death due to any cause, whichever occurs first.
	Secondary Endpoint	OS	Time from randomization to the time of death due to any cause.

	Secondary Endpoint	PFS by BICR	Time from randomization to the first documented disease progression per RECIST 1.1 as assessed by BICR, or death due to any cause, whichever occurs first.	
	Secondary Endpoint	PRO	Defined as the change from baseline and TTD of the EORTC QLQ-C30 GHS/QOL (items 29,30) and the EORTC QLQ-OV28 Abdominal/GI symptoms (items 31-36)	
Database lock	02-APR-2025			
Results and Analysis				
Analysis description	**Analyses of primary and secondary endpoints in participants with PD-L1 positive tumours [CPS ≥1] and in all-comer participants**			
Analysis population and time point description	ITT at IA1 Data cutoff: 03-APR-2024; IA2: data cutoff: 05-MAR-2025; FA: 05-SEP-2025.			
Descriptive statistics and estimate variability	Treatment group		Pembrolizumab + Chemotherapy	Placebo + Chemotherapy
	CPS ≥1 Participants			
	Number of subjects (ITT population)		234	232
	PFS (Investigator Assessed) at IA1			
	Median, months (95% CI)		8.3 (7.0, 9.4)	7.2 (6.2, 8.1)
	OS at IA2			
	Median, months (95% CI)		18.2 (15.3, 21.0)	14.0 (12.5, 16.1)
	All-comer Participants			
	Number of subjects (ITT population)		322	321
	PFS (Investigator Assessed) at IA1			
	Median, months (95% CI)		8.3 (7.2, 8.6)	6.4 (6.2, 8.1)
	OS at FA			
	Median, months (95% CI)		17.7 (15.2, 19.2)	14.0 (12.5, 15.6)
Effect estimate per comparison	**Endpoints**		**Comparison groups**	**Pembrolizumab + Chemotherapy vs Placebo + Chemotherapy**
	CPS ≥1 Participants			
	Primary endpoint: PFS (Investigator Assessed) at IA1		Hazard ratio	0.72
			95% CI	(0.58, 0.89)
			p-value	0.0014
	Secondary endpoint: OS at IA2		Hazard ratio	0.76
			95% CI	(0.61, 0.94)
			p-value	0.0053
	All-comer Participants			
			Hazard ratio	0.70

Primary endpoint: PFS (Investigator Assessed) at IA1	95% CI	(0.58, 0.84)
	p-value	<0.0001
Secondary endpoint: OS at FA	Hazard ratio	0.82
	95% CI	(0.69, 0.97)
	p-value	0.0115

Notes: the family-wise Type I error rate for this study was controlled for multiple hypothesis and interim analyses, at 0.025 (one-sided) across the 2 primary hypotheses on PFS (CPS≥1 and all-comers) and the 2 key secondary hypotheses on OS (CPS≥1 and all-comers). The study was considered a success if PFS in participants with PD-L1 CPS ≥1 or PFS in all-comers was statistically significant under multiplicity control.

The primary endpoint PFS by investigator assessment was met at IA1 in both CPS≥1 and all-comers populations. The secondary endpoint OS was statistically significant at IA2 in the CPS≥1 population, and at FA in the all-comers population.

Clinical studies in special populations

Table 49 Clinical studies in special populations

	Controlled Trials	Non-controlled trials
Renal impairment* patients (Subjects number /total number)	0/643	0
Hepatic impairment** patients (Subjects number /total number)	0/643	0
Paediatric patients <18 years (Subjects number /total number)	0/643	0
Age 65-74 (Subjects number /total number)	178/643	0
Age 75-84 (Subjects number /total number)	57/643	0
Age 85+ (Subjects number /total number)	1/643	0
Other (Subjects number /total number)	0/643	0

* Renal impairment is defined as having creatinine clearance <60mL/min.

** Hepatic impairment is defined as having moderate or severe liver dysfunction, where moderate dysfunction = (total bilirubin > 1.5 to 3x ULN) and severe dysfunction = (total bilirubin > 3x ULN). Hepatic impairment is defined per National Cancer Institute Organ Dysfunction Working Group Criteria for Hepatic Dysfunction.

In vitro biomarker test for patient selection for efficacy

PD-L1 testing was conducted using the PD-L1 IHC 22C3 pharmDx (Agilent Technologies). The combined positive score (CPS) was assessed at a central laboratory and defined as the number of PD-L1 CPS ≥1 cells (tumour cells, lymphocytes, macrophages) divided by the total number of tumour cells x 100.

Supportive study

Not applicable.

2.4.3. Discussion on clinical efficacy

The results of the pivotal trial KEYNOTE-B96 have been submitted to support an extension of indication for Keytruda in combination with paclitaxel with or without bevacizumab for adult patients with platinum-resistant epithelial ovarian, fallopian tube, or primary peritoneal carcinoma expressing PD-L1 CPS ≥ 1 and who have received one or two prior systemic treatment regimens.

Design and conduct of clinical studies

KEYNOTE-B96 / ENGOT-ov65 is an international phase 3, randomized 1:1, double-blind study, recruiting a population of adult female patients with histologically confirmed epithelial ovarian/fallopian tube/primary peritoneal cancer, who were platinum-resistant, but excluding platinum-refractory, i.e. with disease progression between 1 and 6 months after the last dose of platinum-based chemotherapy. Only 1 or 2 prior lines of systemic therapy were allowed, including at least one platinum-based chemotherapy. Those criteria reflect a population for whom non-platinum options is indicated, although select a specific subset of patients with a better prognosis (not platinum refractory, no more than 2 prior lines of systemic treatment). This information on the eligible population is described section 5.1 of the SmPC, and the wording of the indication in section 4.1 of the SmPC specifies that patients have received 1 or 2 prior systemic treatment regimens.

The study allowed inclusion of different histological subtype of epithelial ovarian cancer (EOC), not only the most common high grade serous, but also rarer subtype as low grade serous, clear cell, carcinosarcoma and endometrioid, although excluding the mucinous subtype, possibly due to its unique features including poor response to chemotherapy[33]. As expected, most patients in KEYNOTE-B96 had high grade serous EOC (85%). Histologies were balanced between treatment arms.

Only patients with ECOG 0 and 1 were eligible. Literature data report, however, that approximately 13-14% of patients with advanced OC may have ECOG ≥2 in clinical setting[34] [35], thus raising the issue of the representativeness of the study population.

The comparator was weekly paclitaxel, with or without bevacizumab. Weekly paclitaxel is one of the recommended chemotherapy options in the PROC setting; furthermore, the addition of bevacizumab to second- or third-line non-platinum chemotherapy, based on the results of the AURELIA trial, is included in clinical guidelines[36]. The comparator is therefore deemed acceptable. Docetaxel was used in place of paclitaxel only in case of hypersensitivity/AE leading to discontinuing paclitaxel, but this was needed only in few patients and similarly in each arm (3.5%), thus not raising issue. The investigator's choice of using bevacizumab was made before randomization, which is acceptable. From an assessment's perspective, the use of the same backbone regimen in the two treatment arms of the KEYNOTE-B96 study allows the evaluation of pembrolizumab as add-on treatment. The indication in section 4.1 of the SmPC specifies that pembrolizumab is to be associated with paclitaxel with or without bevacizumab,

[33] Morice P, Gouy S, Leary A. Mucinous Ovarian Carcinoma. N Engl J Med. 2019 Mar 28;380(13):1256-1266
[34] Quindós-Varela M, Soto de Prado-Otero D, Gallego A, García Y, Guerra E, Estévez-García P, Barretina-Ginesta MP, Borraz P, González-Martín A, Rubio MJ. Management and Clinical Outcomes of Patients with Advanced Ovarian Cancer in Routine Clinical Practice in Spain: The OVOC Study. Oncol Ther. 2025 Sep;13(3):631-648
[35] Roncolato FT, Joly F, O'Connell R, Lanceley A, Hilpert F, Buizen L, Okamoto A, Aotani E, Pignata S, Donnellan P, Oza A, Avall-Lundqvist E, Berek JS, Heitz F, Feeney A, Berton-Rigaud D, Stockler MR, King M, Friedlander M; GCIG Symptom Benefit group. Reducing Uncertainty: Predictors of Stopping Chemotherapy Early and Shortened Survival Time in Platinum Resistant/Refractory Ovarian Cancer-The GCIG Symptom Benefit Study. Oncologist. 2017 Sep;22(9):1117-1124
[36] González-Martín A, Harter P, Leary A, Lorusso D, Miller RE, Pothuri B, Ray-Coquard I, Tan DSP, Bellet E, Oaknin A, Ledermann JA; ESMO Guidelines Committee. Newly diagnosed and relapsed epithelial ovarian cancer: ESMO Clinical Practice Guideline for diagnosis, treatment and follow-up. Ann Oncol. 2023 Oct;34(10):833-848.

which is appropriate. Pembrolizumab was administered at 400 mg Q6W IV, which is acceptable as being one of the currently approved IV dose regimen of pembrolizumab.

The expression of PD-L1 according to CPS score was prospectively and centrally evaluated and included as stratification factor, since prior evidence from the KEYNOTE-100 study showed a trend toward higher ORR with increasing PD-L1 CPS[37]. Data on BRCA and HRD status were collected only if available prior to enrolment, thus the status is unknown in 40% and 65% of the population respectively; approximately 8% of patients in both arms were both BRCA or HRD positive. Data on MSI status were not collected.

Two global amendments were issued. Of those, protocol amendment 04 (31 January 2024), which was released between the end of recruitment (3 July 2023) and the first interim analysis (3 April 2024), updated the target number of events for interim/final analyses and sample size and power calculations, by using the same assumptions and methodologies as in the original protocol, after a blinded data review resulting in CPS≥1 prevalence larger than initially expected. The number of subjects enrolled was larger than the planned sample size (643 vs 616), resulted in higher statistical power as a higher-than-expected number of participants were screened. Important protocol deviations occurred at a similar rate in both arms, with a limited number of clinically important deviations (approximately 3% in each arm), thus not raising concern.

Overall, all statistical methodologies and blinding procedures appear acceptable.

PFS per RECIST 1.1 by investigator was the primary endpoint, assessed in the CPS≥1 and in the all-comer populations. The study was considered a success if PFS in participants with CPS≥1 or PFS in all participants was shown to be statistically significant under multiplicity control. The study being blinded, investigator's assessment of PFS can be accepted. In particular, it is of relevance that a review of PFS by BICR was conducted to support PFS by investigator. OS in the CPS≥1 and in the all-comer populations were secondary endpoints, adjusted for multiplicity. In view of the dismal prognosis of PROC, and the lack of effective subsequent treatment, OS is considered the most relevant outcome of clinical trials in this disease setting.

Efficacy data and additional analyses

A total of 643 patients were randomized; of those, 466 participants had a tumour status of PD-L1 CPS ≥1 (234 participants in the pembrolizumab plus chemotherapy group and 232 participants in the placebo plus chemotherapy group). Baseline patient's and disease characteristics appear overall well balanced between the two treatment arms. In the CPS≥1 population, all participants were female with median age of 61.4 years, 55.4% with ECOG 0. Most participants (67.2%) were White, and 46.8% enrolled in the EU. At the time of initial diagnosis, the majority had Stage IIIC/IVB diagnosis, high-grade serous histology (88.8%), and had received mainly 2 (63.5%) lines of prior therapy (51.8% two lines of prior platinum in all participants); only few (2.2%) were previously treated with anti-PD(L)-1, while 36.5% received prior PARP-inhibitors and 45.9% prior bevacizumab. The characteristics of the CPS ≥1 population were overall similar to the all participants population. In KEYNOTE-B96, approximately 73% of the overall population received bevacizumab in both treatment arms. Patients who did not receive prior bevacizumab and were treated with bevacizumab in the study (i.e. according to bevacizumab EU label) were balanced between treatment arms (43% vs 44%).

The study met its primary endpoints of **PFS** in both CPS ≥1 and ITT population at the first interim analysis (IA1). In the **CPS ≥1** population (i.e. the sought indication), PFS HR was 0.72 (0.58, 0.89; p

[37] Matulonis UA, Shapira-Frommer R, Santin AD, Lisyanskaya AS, Pignata S, Vergote I, Raspagliesi F, Sonke GS, Birrer M, Provencher DM, Sehouli J, Colombo N, González-Martín A, Oaknin A, Ottevanger PB, Rudaitis V, Katchar K, Wu H, Keefe S, Ruman J, Ledermann JA. Antitumor activity and safety of pembrolizumab in patients with advanced recurrent ovarian cancer: results from the phase II KEYNOTE-100 study. Ann Oncol. 2019 Jul 1;30(7):1080-1087.

0.0014), with median survival follow-up time of 12.0 months [range: 0.5 to 27.0 months]), with most patients experiencing a PFS event (69.2% vs 77.6%). The absolute gain in median PFS was however limited: median PFS 8.3 (7, 9.4) vs 7.2 (6.2, 8.1) months (IA1), further corroborated by the shape of the KM curves. Pre-planned sensitivity PFS analyses and PFS assessed by BICR were overall consistent with the primary analysis, as well as descriptive updated PFS analyses conducted at IA2 (HR 0.75) and at the time of the final analysis (HR 0.76). Regarding BICR assessment, the overall concordance rate was 70.7% between INV and BICR in progression events. The early discordance rate was 31% and late discordance rate was 43.9%. According to the MAH, the level of discordance seen in this study is similar to other trials in ovarian cancer. Reassuringly, the rate of concordance/discordance is comparable in both treatment arms. Considering the overall PFS results provided, the clinical relevance of the PFS improvement observed in the KEYNOTE-B96 study by adding pembrolizumab to weekly paclitaxel, is questionable.

OS in the **CPS ≥1** population met statistical significance at the IA2. After a median survival follow-up of 15.8 months (range 0.5, 38), with 67.1 vs 75.4% of participants experiencing a death event, OS HR was 0.76 (0.61, 0.94, p=0.0053). Median OS was 18.2 (15.3, 21) vs 14 (12.5, 16.1) months in the pembrolizumab plus chemotherapy vs placebo plus chemotherapy group. The improvement in OS rate was higher at 18 months (51.5% vs 38.9%), however curves tend to converge afterwards. Considering the high number of events and the follow-up time in the poor prognostic setting of PROC with limited survival, the OS data can be considered sufficiently mature, and the observed benefit can be considered of clinical relevance. The descriptive updated OS result at final analysis provided during the procedure showed consistent hazard ratio, with OS curves remaining separated with longer follow-up (OS Rate at month 24: 35.6% vs 26.6%).

In the **CPS ≥1** population, the added activity of pembrolizumab to chemotherapy is limited in terms of response rate (**ORR** 53% vs 46.6%), although with longer median **DOR** (10.4 vs 8.1 months), as expected for immunotherapy. **PFS2** however is considered supportive of OS results (HR 0.70, medians 14.3 vs 11.4 months). More patients in the control arm (52.2% vs 60.4% in the ITT population) received one or more subsequent oncologic therapies after study treatment. Most commonly used treatments were gemcitabine (24.2% vs 24%), pegylated liposomal doxorubicin (11.8% vs 13.7%), doxorubicin (11.8% vs 14.3%), carboplatin (11.2% vs 15.3%) and cisplatin (5.3% vs 6.2%), bevacizumab (8.4% vs 8.7%), topotecan (5.9% vs 9.4%), paclitaxel (5% vs 3.7%) and paclitaxel nanoparticle albumin bound (1.2% vs 4.7%). The use of mirvetuximab soravtansine was limited in both arms (1.2% vs 2.5%), likely due to the recent approval with respect to the time when the trial was conducted. Also, according to clinical guidelines, platinum re-challenge could be considered following treatment with a non-platinum regimen[38]. Therefore, no specific concern regarding post-study treatments is raised.

The MAH has also collected **PRO** data, overall suggesting no substantial deterioration in HRQoL in the pembrolizumab containing arm compared with control.

As for the CPS ≥1 population, **PFS** was statistically significant at IA1 also in the **all-comers population** (HR 0.70, 95%CI 0.58-0.84, p<0.0001, median PFS 8.3 vs 6.4 months, median survival follow up time of 11.8 months [range: 0.1 to 27.0 months]), with slightly worse HR (0.73) at IA2. OS did reach statistical significance in the all-comers population only at the final analysis with an HR 0.82, 95%CI 0.69-0.97, p=0.0115, p-value boundary 0.0242, median OS 17.7 vs 14 months with median survival follow-up time of 15.6 months (range: 0.1 to 44.1 months). Pre-planned subgroup analyses by

[38] Colombo N, Sessa C, du Bois A, Ledermann J, McCluggage WG, McNeish I, Morice P, Pignata S, Ray-Coquard I, Vergote I, Baert T, Belaroussi I, Dashora A, Olbrecht S, Planchamp F, Querleu D; ESMO-ESGO Ovarian Cancer Consensus Conference Working Group. ESMO-ESGO consensus conference recommendations on ovarian cancer: pathology and molecular biology, early and advanced stages, borderline tumours and recurrent disease. Ann Oncol. 2019 May 1;30(5):672-705.

PD-L1 CPS score (<1 vs 1-10 vs >10), which was a stratification factor, showed consistent PFS results across PD-L1 expression, but no survival advantage in the PD-L1 negative population, representing 27.5% of the all-comers (HR=0.97, 95%CI 0.69, 1.35); on the contrary, a positive survival trend is shown in the PD-L1 positive subgroups. The MAH is seeking an indication only for the PD-L1 positive (i.e. CPS≥1) disease.

With regard to **subgroup analyses**, at IA2, the direction of the PFS and OS estimated effect was the same in all subgroups analysed within the CPS≥1 population, including by use of bevacizumab. However, the magnitude of the estimated treatment effect shows some differences by age, race, region, ECOG score, prior PARPi and PFI. Moreover, some inconsistencies among PFS and OS subgroup analyses by ECOG score, and by PFI were observed. However, results of the interaction test show that differences in treatment effect among strata for each variable requested were not significant. In a post-hoc subgroup analysis for patients who received bevacizumab but were not treated with bevacizumab before (i.e. according to EU label), results were consistent with the primary analysis.

It was however observed an apparent lower survival benefit from the addition of pembrolizumab to weekly paclitaxel in the EU enrolled population (OS HR 0.90, 95%CI 0.65, 1.24), in older subjects (≥65y) (65-74y: OS HR 0.80, 95%CI 0.53, 1.20; 75-84y: HR 0.91 95%CI 0.45, 1.86) and in patients with high-grade serous histology (OS HR 0.81, 95%CI 0.64, 1.01), as compared to the entire population.

Ovarian cancer is known to be a heterogeneous disease. Post-hoc subgroup analyses based on histology suggest improved benefit from the addition of pembrolizumab to chemotherapy in rarer histologies, thus the OS benefit in the largest part of the population (high grade serous) seems more limited (OS 0.81, 95%CI 0.64 1.01). However, the limited number of patients with rarer type of EOC other than high grade serous (HGS) included in the study (approximately 5.5% clear cell and 5.5% other histologies) should be noted; further, histology was not a stratification factor, although distribution was similar between treatment arms. Therefore, no definitive conclusion can be drawn. Some literature data may suggest increased sensitivity of clear cell ovarian cancer to ICI[39] [40] [41] [42] [43], but not in other studies[44] [45].

Of note, results in subgroups by Region in the CPS≥1 population suggest a lower benefit in the EU population: OS HR 0.90 (0.65, 1,24), PFS HR 0.88 (0.66, 1.17), ORR 54.2% vs 50.5%. Region (EU vs US vs ROW) was a stratification factor and EU represents 47% of the overall study population. When compared to ROW region, patients enrolled in the EU included a higher percentage of elderly

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[45] Ngoi NYL, Choi CH, Zhu J, Lim D, Tan TZ, Sun H, et al. Durvalumab versus physician's choice chemotherapy in recurrent ovarian clear cell adenocarcinoma (MOCCA/APGOT-OV2/GCGS-OV3): a multicenter, randomized, phase 2 trial. Clin Cancer Res. 2025 Sep 15;31(18):3907-15.

participants (median age 64 vs 57, <65y 55.7% vs 73.9% in EU vs ROW), less use of bevacizumab (65% vs 82.4%), more patients exposed to prior PARP inhibitors (44% vs 27.5%), and less clear cell (5.3% vs 9.9%)/other histologies (5.7% vs 7.5%). Also, more frequent use of post-study treatments was reported in the EU (67% vs 64.2% in the pembrolizumab vs SOC arm) as compared to ROW region (47.5% vs 57.6%). Apparently, the SOC arm in the EU group performed better than the SOC arm in the ROW. According to the MAH, the observed regional differences in treatment benefits were likely due to multiple factors, including variations in participant characteristics across regions and use of post-study treatments. This is acknowledged. These subgroup results are difficult to interpret as the study is not powered for subgroups, also it is not possible to disentangle the effects of imbalances in baseline/ disease characteristics like age, histology, or prior/post-progression therapies and conclude whether the results of the EU study population are truly representative of Europeans in clinical practice. It is of reassurance that no detriment is suggested in the EU in any of the endpoint analysed. In conclusion, although the magnitude of benefit in the real-world population expected in an European context may be uncertain, without a biological rationale for possible regional differences in the treatment effect of pembrolizumab, the global ITT estimate should guide the assessment of treatment benefit.

The MAH was requested during the assessment to discuss the positive results of the KEYNOTE-B96 study in the context of several negative results of clinical trials testing anti-PD(L)1 antibodies for the treatment of ovarian cancer in various setting and lines, indeed there are no approved immunotherapy for patients with OC so far[46][47]. The MAH considered that the combination of chemotherapy and immune-checkpoint blockade may be a rational approach for the treatment of recurrent OC and chose the combination of weekly paclitaxel and bevacizumab yielding superior efficacy in the AURELIA trial[48]. In particular, the combination of paclitaxel and pembrolizumab, especially with chemotherapy given weekly (metronomic), can result in synergistic treatment, and also synergistic activity may also occur between antiangiogenic therapy and immunotherapy. The MAH's justification is acknowledged, although still remains speculative.

2.4.4. Conclusions on the clinical efficacy

In the KEYNOTE-B96 study, the addition of pembrolizumab to standard treatment weekly paclitaxel with or without bevacizumab for patients with platinum-resistant ovarian cancer who have received prior 1 or 2 lines of therapy showed statistically significant results in the primary endpoint PFS by investigator in the PD-L1 CPS ≥1 population, for which the indication is sought, supported by sensitivity analyses and PFS by BICR, although the clinical relevance of such improvement is questionable. The activity of pembrolizumab in terms of response rate in this disease seem marginal, although prolonging the duration of responses. The secondary endpoint OS was statistically significant in the CPS ≥1 population, and the observed absolute magnitude of survival improvement is considered of clinical relevance in the context of the poor prognosis of PROC and the limited treatment options.

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3. Clinical safety

Introduction

Safety data have been submitted from the phase 3 KEYNOTE-B96 study investigating pembrolizumab vs placebo in combination with paclitaxel with or without bevacizumab in participants with PRROC who had received ≤2 prior lines of therapy. Paclitaxel was replaced with docetaxel for participants who discontinued or had a severe hypersensitivity reaction to paclitaxel. Pembrolizumab was administered at 400 mg Q6W for 18 cycles, while paclitaxel and/or bevacizumab could be continued until disease progression, prohibitive toxicity, other protocol-defined reason for discontinuation, or the participant had received the maximum duration (if applicable) per the respective approved label or local practice.

Safety analyses were conducted using the APaT population, defined as all randomized participants who received at least 1 dose of study treatment and whose safety data were analyzed according to the study treatment they actually received.

The safety profile of pembrolizumab plus paclitaxel with or without bevacizumab in the KEYNOTE-B96 study was also compared with the established safety profile of pembrolizumab plus chemotherapy (using pooled safety data from studies in which participants received pembrolizumab in combination with single agent or combination chemotherapies, including platinum-based chemotherapy, 5-fluorouracil, paclitaxel/nab-paclitaxel, and pemetrexed) and pembrolizumab monotherapy (using pooled safety data from pembrolizumab monotherapy studies).

Table 50 Summary of Clinical Safety Datasets and Nomenclature

Dataset	Population	Treatment	Dataset Nomenclature in Tables	Nomenclature in Text
KEYNOTE-B96 pembrolizumab plus paclitaxel with or without bevacizumab[a]	**N=320**: Safety data from participants with PRROC who received at least 1 dose of pembrolizumab in combination with chemotherapy with or without bevacizumab in KEYNOTE-B96	Pembrolizumab plus chemotherapy (paclitaxel) with or without bevacizumab	KN-B96 Pembrolizumab + Chemotherapy	Pembrolizumab + chemotherapy
KEYNOTE-B96 placebo plus paclitaxel with or without bevacizumab[a]	**N=318**: Safety data from participants with PRROC who received at least 1 dose of placebo in combination with chemotherapy with or without bevacizumab in KEYNOTE-B96	Placebo plus chemotherapy (paclitaxel) with or without bevacizumab	KN-B96 Placebo + Chemotherapy	Placebo + chemotherapy
Pembrolizumab plus chemotherapy	**N=5711**: Pooled safety data from participants treated with pembrolizumab in combination with approved platinum-based chemotherapy	Pembrolizumab plus chemotherapy	Pooled Safety Dataset for Pembrolizumab plus Chemotherapy	Pooled pembrolizumab plus chemotherapy dataset
Pembrolizumab monotherapy global reference safety dataset	**N=7631**: Pooled safety data from participants treated with pembrolizumab monotherapy	Pembrolizumab monotherapy	Pembrolizumab Monotherapy Reference Safety Dataset	RSD

KN=KEYNOTE; N=number; PPROC= platinum-resistant recurrent ovarian cancer; RSD=reference safety dataset.

[a] Database Cutoff Date: 05-MAR-2025

Patient exposure

Table 51 Summary of Drug Exposure (APaT Population)

	KN-B96 Pembrolizumab + Chemotherapy (N=320)	KN-B96 Placebo + Chemotherapy (N=318)	Pooled Safety Dataset for Pembrolizumab + Chemotherapy (N=5711)	Pembrolizumab Monotherapy Reference Safety Dataset (N=7631)
Duration on Therapy (months)				
n	320	318	5706	7631
Mean (SD)	9.74 (7.25)	8.14 (6.53)	10.45 (8.01)	7.85 (6.91)
Median	7.47	6.34	8.38	5.78
Range	0.03 to 35.91	0.03 to 33.84	0.03 to 56.90	0.03 to 38.01
Number of Cycle				
n	320	318	5706	7631
Mean (SD)	7.36 (5.06)	6.33 (4.61)	12.83 (10.14)	12.31 (10.10)
Median	6.00	5.00	10.00	9.00
Range	1.00 to 26.00	1.00 to 24.00	1.00 to 70.00	1.00 to 59.00

Duration on therapy (months) is calculated as (last dose date - first dose date + 1) / 30.4367.
Database cutoff date for KN-B96: 05MAR2025.

Table 52 Exposure by Duration (APaT Population)

	KN-B96 Pembrolizumab + Chemotherapy (N=320)			KN-B96 Placebo + Chemotherapy (N=318)			Pooled Safety Dataset for Pembrolizumab + Chemotherapy (N=5711)			Pembrolizumab Monotherapy Reference Safety Dataset (N=7631)		
	n	(%)	Person-years	n	(%)	Person-years	n	(%)	Person-years	n	(%)	Person-years
Duration of Exposure (months)												
> 0	320	(100.0)	259.8	318	(100.0)	215.6	5,706	(99.9)	4,971.1	7,631	(100.0)	4,995.0
≥ 1	303	(94.7)	259.0	300	(94.3)	214.9	5,320	(93.2)	4,957.6	6,637	(87.0)	4,962.4
≥ 3	271	(84.7)	253.4	256	(80.5)	207.6	4,661	(81.6)	4,844.7	5,023	(65.8)	4,693.1
≥ 6	203	(63.4)	227.6	176	(55.3)	178.4	3,516	(61.6)	4,412.6	3,781	(49.5)	4,240.0
≥ 12	103	(32.2)	159.0	65	(20.4)	101.3	2,211	(38.7)	3,481.7	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 KN-B96: 05MAR2025.
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.

Adverse events

Table 53 Adverse Event Summary (APaT Population)

	KN-B96 Pembrolizumab + Chemotherapy		KN-B96 Placebo + Chemotherapy		Pooled Safety Dataset for Pembrolizumab + Chemotherapy		Pembrolizumab Monotherapy Reference Safety Dataset	
	n	(%)	n	(%)	n	(%)	n	(%)
Participants in population	320		318		5,711		7,631	
with one or more adverse events	319	(99.7)	316	(99.4)	5,666	(99.2)	7,375	(96.6)
with no adverse event	1	(0.3)	2	(0.6)	45	(0.8)	256	(3.4)
with drug-related[a] adverse events	313	(97.8)	303	(95.3)	5,500	(96.3)	5,462	(71.6)
with toxicity grade 3-5 adverse events	264	(82.5)	225	(70.8)	4,441	(77.8)	3,514	(46.0)
with toxicity grade 3-5 drug-related AE	216	(67.5)	176	(55.3)	3,692	(64.6)	1,208	(15.8)
with serious adverse events	178	(55.6)	122	(38.4)	2,589	(45.3)	2,742	(35.9)
with serious drug-related adverse events	106	(33.1)	62	(19.5)	1,481	(25.9)	840	(11.0)

who died	15	(4.7)	14	(4.4)	313	(5.5)	346	(4.5)
who died due to a drug-related adverse event	3	(0.9)	5	(1.6)	75	(1.3)	42	(0.6)
discontinued any drug due to an AE	132	(41.3)	108	(34.0)	1,657	(29.0)	1,066	(14.0)
discontinued pembrolizumab or placebo	48	(15.0)	30	(9.4)	923	(16.2)	1,066	(14.0)
discontinued any chemotherapy	123	(38.4)	107	(33.6)	1,251	(21.9)	0	(0.0)
discontinued any drug due to a drug-related AE	115	(35.9)	89	(28.0)	1,362	(23.8)	639	(8.4)
discontinued pembrolizumab or placebo	37	(11.6)	18	(5.7)	653	(11.4)	639	(8.4)
discontinued any chemotherapy	106	(33.1)	88	(27.7)	1,025	(17.9)	0	(0.0)
discontinued any drug due to a serious AE	56	(17.5)	41	(12.9)	795	(13.9)	714	(9.4)
discontinued pembrolizumab or placebo	38	(11.9)	23	(7.2)	658	(11.5)	714	(9.4)
discontinued any chemotherapy	45	(14.1)	39	(12.3)	532	(9.3)	0	(0.0)
discontinued any drug due to a serious drug-related AE	44	(13.8)	26	(8.2)	537	(9.4)	347	(4.5)
discontinued pembrolizumab or placebo	29	(9.1)	13	(4.1)	423	(7.4)	347	(4.5)
discontinued any chemotherapy	33	(10.3)	24	(7.5)	336	(5.9)	0	(0.0)

[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 PTs "Neoplasm Progression", "Malignant Neoplasm Progression" and "Disease Progression" not related to the drug are excluded.

For KN-B96, grades are based on NCI CTCAE version 5.0.

Database cutoff date for KN-B96: 05MAR2025.

Table 54 Exposure-Adjusted Adverse Event Summary (Including Multiple Occurrences of Events) (APaT Population)

	Event Count and Rate (Events/100 person-months)[a]							
	KN-B96 Pembrolizumab + Chemotherapy		KN-B96 Placebo + Chemotherapy		Pooled Safety Dataset for Pembrolizumab + Chemotherapy		Pembrolizumab Monotherapy Reference Safety Dataset	
Number of participants exposed	320		318		5,711		7,631	
Total exposure[b] in person-months	3407.24		2875.48		65347.98		66570.95	
Total events (rate)								
adverse events	8,553	(251.02)	6,770	(235.44)	111,439	(170.53)	76,878	(115.48)
drug-related[c] adverse events	5,122	(150.33)	4,034	(140.29)	68,207	(104.38)	24,542	(36.87)
toxicity grade 3-5 adverse events	1,074	(31.52)	789	(27.44)	15,999	(24.48)	7,463	(11.21)
toxicity grade 3-5 drug-related adverse events	743	(21.81)	559	(19.44)	11,103	(16.99)	1,770	(2.66)
serious adverse events	351	(10.30)	209	(7.27)	5,033	(7.70)	4,801	(7.21)
serious drug-related adverse events	172	(5.05)	88	(3.06)	2,334	(3.57)	1,093	(1.64)
adverse events leading to death	15	(0.44)	14	(0.49)	321	(0.49)	353	(0.53)
drug-related adverse events leading to death	3	(0.09)	5	(0.17)	76	(0.12)	42	(0.06)
adverse events resulting in drug discontinuation	181	(5.31)	139	(4.83)	2,061	(3.15)	1,165	(1.75)
drug-related adverse events resulting in drug discontinuation	156	(4.58)	114	(3.96)	1,689	(2.58)	703	(1.06)
serious adverse events resulting in drug discontinuation	62	(1.82)	45	(1.56)	894	(1.37)	753	(1.13)
serious drug-related adverse events resulting in drug discontinuation	50	(1.47)	26	(0.90)	605	(0.93)	363	(0.55)

[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 and the earliest of the last dose date + 30, death date or the database cutoff date, then + 1 day since the first dose date is Day 1.

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

For KN-B96, 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 KN-B96: 05MAR2025.

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 55 Participants With Adverse Events by Maximum Toxicity Grade All Participants – KEYNOTE-B96 (APaT Population)

	Pembrolizumab + Chemotherapy		Placebo + Chemotherapy	
	n	(%)	n	(%)
Participants in population	320		318	
with one or more adverse events	319	(99.7)	316	(99.4)
Grade 1	5	(1.6)	9	(2.8)
Grade 2	50	(15.6)	82	(25.8)
Grade 3	187	(58.4)	165	(51.9)
Grade 4	62	(19.4)	46	(14.5)
Grade 5	15	(4.7)	14	(4.4)
with no adverse events	1	(0.3)	2	(0.6)

Table 56 Participants With Adverse Events by Decreasing Frequency of Preferred Term (Incidence ⩾ 10% in One or More Treatment Groups) (APaT Population)

	KN-B96 Pembrolizumab + Chemotherapy		KN-B96 Placebo + Chemotherapy		Pooled Safety Dataset for Pembrolizumab + Chemotherapy		Pembrolizumab Monotherapy Reference Safety Dataset	
	n	(%)	n	(%)	n	(%)	n	(%)
Participants in population	320		318		5,711		7,631	
with one or more adverse events	319	(99.7)	316	(99.4)	5,666	(99.2)	7,375	(96.6)
with no adverse events	1	(0.3)	2	(0.6)	45	(0.8)	256	(3.4)
Anaemia	174	(54.4)	152	(47.8)	3,041	(53.2)	982	(12.9)
Diarrhoea	142	(44.4)	126	(39.6)	2,025	(35.5)	1,678	(22.0)
Fatigue	132	(41.3)	119	(37.4)	1,892	(33.1)	2,368	(31.0)
Nausea	132	(41.3)	115	(36.2)	3,010	(52.7)	1,534	(20.1)
Neuropathy peripheral	126	(39.4)	104	(32.7)	743	(13.0)	146	(1.9)
Alopecia	122	(38.1)	112	(35.2)	1,231	(21.6)	118	(1.5)
Epistaxis	103	(32.2)	80	(25.2)	319	(5.6)	106	(1.4)
Neutrophil count decreased	92	(28.8)	72	(22.6)	1,585	(27.8)	53	(0.7)
Urinary tract infection	88	(27.5)	73	(23.0)	577	(10.1)	511	(6.7)
White blood cell count decreased	78	(24.4)	59	(18.6)	1,055	(18.5)	70	(0.9)
Abdominal pain	76	(23.8)	84	(26.4)	694	(12.2)	671	(8.8)
Constipation	76	(23.8)	81	(25.5)	1,798	(31.5)	1,179	(15.5)
Decreased appetite	76	(23.8)	62	(19.5)	1,551	(27.2)	1,312	(17.2)
Neutropenia	76	(23.8)	81	(25.5)	1,443	(25.3)	82	(1.1)
Vomiting	76	(23.8)	73	(23.0)	1,629	(28.5)	945	(12.4)
Pyrexia	66	(20.6)	39	(12.3)	1,052	(18.4)	934	(12.2)
Rash	66	(20.6)	42	(13.2)	951	(16.7)	1,175	(15.4)
Cough	65	(20.3)	49	(15.4)	865	(15.1)	1,392	(18.2)
Hypertension	64	(20.0)	59	(18.6)	368	(6.4)	416	(5.5)
Asthenia	61	(19.1)	66	(20.8)	1,063	(18.6)	880	(11.5)
Alanine aminotransferase increased	57	(17.8)	33	(10.4)	1,023	(17.9)	572	(7.5)
Hypothyroidism	57	(17.8)	19	(6.0)	803	(14.1)	937	(12.3)
Stomatitis	57	(17.8)	33	(10.4)	627	(11.0)	201	(2.6)
Arthralgia	56	(17.5)	47	(14.8)	870	(15.2)	1,449	(19.0)
Oedema peripheral	56	(17.5)	44	(13.8)	580	(10.2)	630	(8.3)
Dyspnoea	55	(17.2)	46	(14.5)	624	(10.9)	1,130	(14.8)
Hypomagnesaemia	53	(16.6)	48	(15.1)	573	(10.0)	184	(2.4)
Nail disorder	49	(15.3)	42	(13.2)	48	(0.8)	11	(0.1)
Back pain	48	(15.0)	46	(14.5)	580	(10.2)	847	(11.1)
COVID-19	48	(15.0)	49	(15.4)	151	(2.6)	6	(0.1)
Aspartate aminotransferase increased	47	(14.7)	32	(10.1)	1,002	(17.5)	538	(7.1)
Hyponatraemia	46	(14.4)	30	(9.4)	470	(8.2)	387	(5.1)
Hypoalbuminaemia	43	(13.4)	22	(6.9)	451	(7.9)	209	(2.7)

Peripheral sensory neuropathy	42	(13.1)	37	(11.6)	671	(11.7)	83	(1.1)
Proteinuria	40	(12.5)	27	(8.5)	138	(2.4)	80	(1.0)
Myalgia	39	(12.2)	34	(10.7)	470	(8.2)	575	(7.5)
Onycholysis	38	(11.9)	32	(10.1)	41	(0.7)	7	(0.1)
Weight decreased	38	(11.9)	15	(4.7)	762	(13.3)	628	(8.2)
Headache	36	(11.3)	54	(17.0)	787	(13.8)	946	(12.4)
Dysgeusia	35	(10.9)	33	(10.4)	481	(8.4)	150	(2.0)
Hypokalaemia	35	(10.9)	28	(8.8)	700	(12.3)	324	(4.2)
Insomnia	34	(10.6)	36	(11.3)	610	(10.7)	528	(6.9)
Mucosal inflammation	34	(10.6)	27	(8.5)	474	(8.3)	111	(1.5)
Dizziness	33	(10.3)	25	(7.9)	550	(9.6)	564	(7.4)
Pruritus	33	(10.3)	28	(8.8)	727	(12.7)	1,435	(18.8)
Upper respiratory tract infection	33	(10.3)	35	(11.0)	386	(6.8)	514	(6.7)
Leukopenia	24	(7.5)	27	(8.5)	581	(10.2)	52	(0.7)
Platelet count decreased	18	(5.6)	10	(3.1)	1,086	(19.0)	95	(1.2)
Thrombocytopenia	6	(1.9)	10	(3.1)	789	(13.8)	117	(1.5)

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

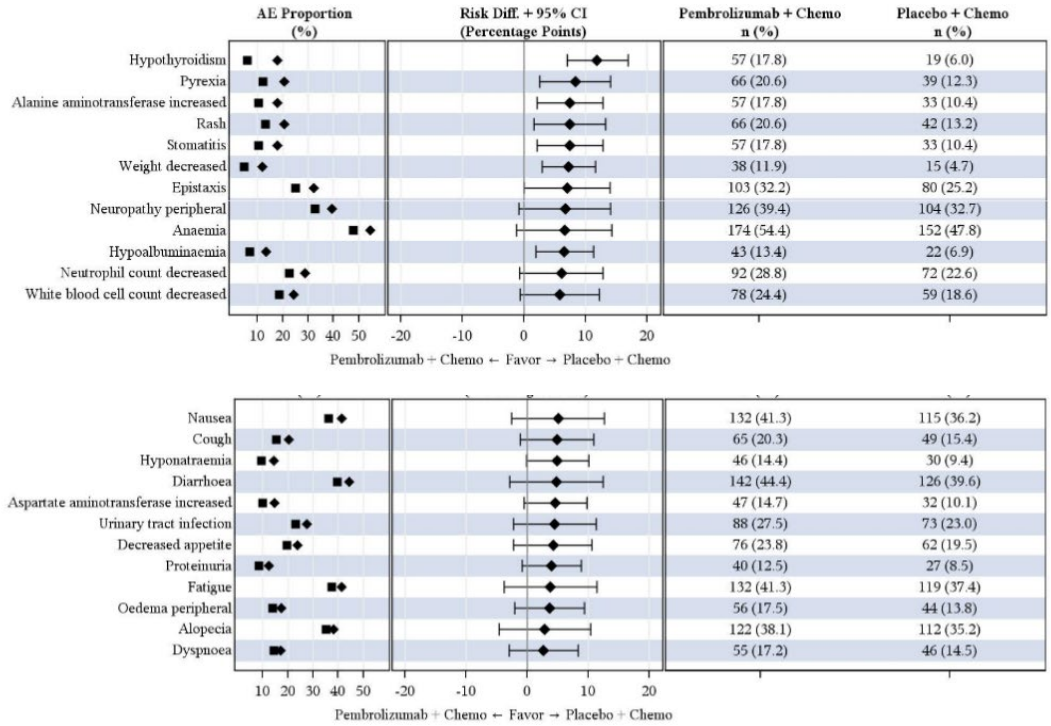
A specific adverse event appears on this report only if its incidence in one or more of the columns meets the incidence criterion in the report title, after rounding.

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

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

Database cutoff date for KN-B96: 05MAR2025.

Figure 23 Between-Treatment Comparisons in Adverse Events Selected Adverse Events (>= 10% Incidence) and Sorted by Risk Difference All Participants (APaT Population)



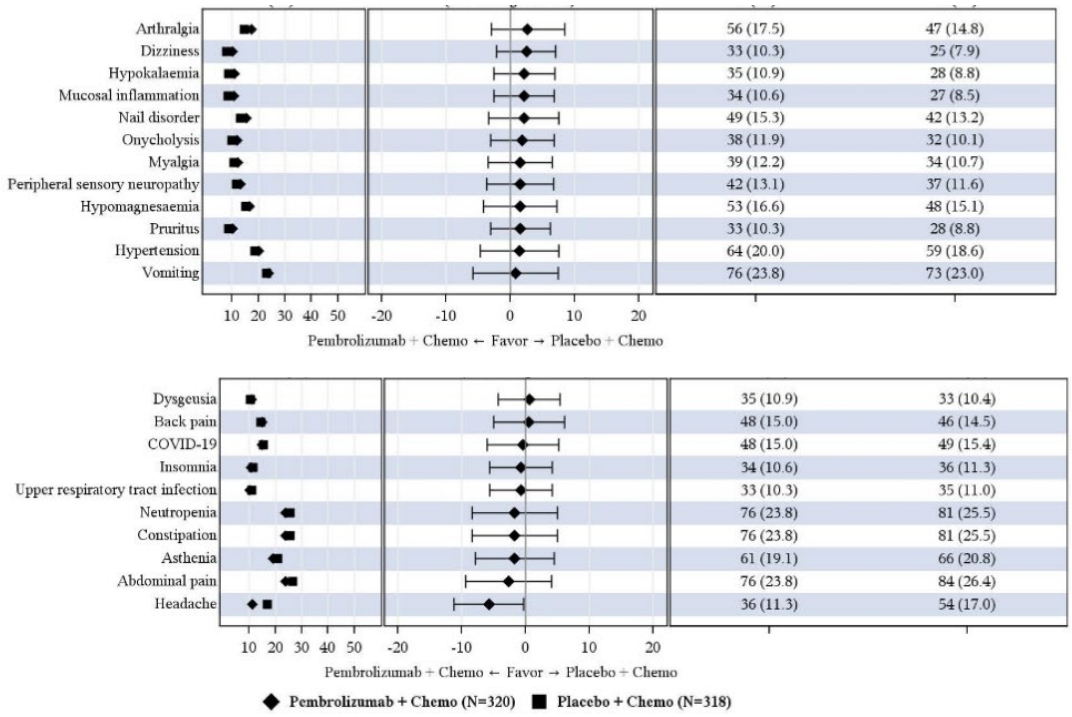


Table 57 Participants With Drug-Related Adverse Events by Decreasing Frequency of Preferred Term (Incidence ⩾ 5% in One or More Treatment Groups) (APaT Population)

	KN-B96 Pembrolizumab + Chemotherapy		KN-B96 Placebo + Chemotherapy		Pooled Safety Dataset for Pembrolizumab + Chemotherapy		Pembrolizumab Monotherapy Reference Safety Dataset	
	n	(%)	n	(%)	n	(%)	n	(%)
Participants in population	320		318		5,711		7,631	
with one or more adverse events	313	(97.8)	303	(95.3)	5,500	(96.3)	5,462	(71.6)
with no adverse events	7	(2.2)	15	(4.7)	211	(3.7)	2,169	(28.4)
Anaemia	159	(49.7)	134	(42.1)	2,556	(44.8)	234	(3.1)
Neuropathy peripheral	124	(38.8)	99	(31.1)	662	(11.6)	54	(0.7)
Alopecia	121	(37.8)	108	(34.0)	1,189	(20.8)	57	(0.7)
Fatigue	113	(35.3)	105	(33.0)	1,612	(28.2)	1,476	(19.3)
Nausea	100	(31.3)	87	(27.4)	2,707	(47.4)	675	(8.8)
Epistaxis	94	(29.4)	69	(21.7)	190	(3.3)	6	(0.1)
Diarrhoea	93	(29.1)	79	(24.8)	1,539	(26.9)	904	(11.8)
Neutrophil count decreased	92	(28.8)	71	(22.3)	1,536	(26.9)	34	(0.4)
White blood cell count decreased	75	(23.4)	57	(17.9)	1,021	(17.9)	34	(0.4)
Neutropenia	73	(22.8)	78	(24.5)	1,394	(24.4)	49	(0.6)
Decreased appetite	54	(16.9)	41	(12.9)	1,202	(21.0)	525	(6.9)
Rash	53	(16.6)	33	(10.4)	722	(12.6)	884	(11.6)
Asthenia	51	(15.9)	56	(17.6)	828	(14.5)	491	(6.4)
Hypothyroidism	50	(15.6)	16	(5.0)	708	(12.4)	810	(10.6)
Stomatitis	48	(15.0)	28	(8.8)	560	(9.8)	103	(1.3)
Nail disorder	46	(14.4)	39	(12.3)	38	(0.7)	8	(0.1)
Hypertension	45	(14.1)	49	(15.4)	109	(1.9)	44	(0.6)
Vomiting	44	(13.8)	39	(12.3)	1,295	(22.7)	248	(3.2)
Peripheral sensory neuropathy	42	(13.1)	36	(11.3)	633	(11.1)	35	(0.5)
Alanine aminotransferase increased	41	(12.8)	21	(6.6)	802	(14.0)	336	(4.4)
Constipation	39	(12.2)	37	(11.6)	858	(15.0)	184	(2.4)
Onycholysis	35	(10.9)	30	(9.4)	37	(0.6)	4	(0.1)
Aspartate aminotransferase increased	34	(10.6)	20	(6.3)	753	(13.2)	312	(4.1)

Dysgeusia	33	(10.3)	28	(8.8)	435	(7.6)	79	(1.0)
Proteinuria	32	(10.0)	19	(6.0)	99	(1.7)	24	(0.3)
Myalgia	31	(9.7)	28	(8.8)	331	(5.8)	312	(4.1)
Mucosal inflammation	29	(9.1)	26	(8.2)	429	(7.5)	57	(0.7)
Arthralgia	28	(8.8)	33	(10.4)	401	(7.0)	672	(8.8)
Hypomagnesaemia	26	(8.1)	20	(6.3)	357	(6.3)	37	(0.5)
Urinary tract infection	25	(7.8)	18	(5.7)	115	(2.0)	15	(0.2)
Lymphocyte count decreased	23	(7.2)	16	(5.0)	263	(4.6)	64	(0.8)
Paronychia	23	(7.2)	23	(7.2)	27	(0.5)	3	(0.0)
Pruritus	23	(7.2)	18	(5.7)	537	(9.4)	1,143	(15.0)
Pyrexia	23	(7.2)	12	(3.8)	447	(7.8)	314	(4.1)
Leukopenia	22	(6.9)	26	(8.2)	550	(9.6)	32	(0.4)
Oedema peripheral	22	(6.9)	21	(6.6)	210	(3.7)	126	(1.7)
Abdominal pain	21	(6.6)	24	(7.5)	234	(4.1)	147	(1.9)
Nail discolouration	21	(6.6)	16	(5.0)	67	(1.2)	2	(0.0)
Dyspnoea	20	(6.3)	12	(3.8)	170	(3.0)	232	(3.0)
Weight decreased	20	(6.3)	8	(2.5)	383	(6.7)	148	(1.9)
Headache	19	(5.9)	27	(8.5)	266	(4.7)	250	(3.3)
Malaise	19	(5.9)	13	(4.1)	260	(4.6)	55	(0.7)
Paraesthesia	19	(5.9)	20	(6.3)	248	(4.3)	63	(0.8)
Dizziness	18	(5.6)	12	(3.8)	203	(3.6)	120	(1.6)
Hypoaesthesia	17	(5.3)	12	(3.8)	114	(2.0)	16	(0.2)
Hyperthyroidism	16	(5.0)	2	(0.6)	282	(4.9)	352	(4.6)
Blood creatinine increased	14	(4.4)	3	(0.9)	398	(7.0)	105	(1.4)
Hypokalaemia	14	(4.4)	8	(2.5)	310	(5.4)	43	(0.6)
Platelet count decreased	14	(4.4)	10	(3.1)	1,037	(18.2)	43	(0.6)
Palmar-plantar erythrodysaesthesia syndrome	11	(3.4)	10	(3.1)	304	(5.3)	19	(0.2)
Thrombocytopenia	6	(1.9)	9	(2.8)	733	(12.8)	56	(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.

Database cutoff date for KN-B96: 05MAR2025.

Table 58 Participants With Grade 3-5 Adverse Events by Decreasing Frequency of Preferred Term (Incidence ⩾ 5% in One or More Treatment Groups) (APaT Population)

	KN-B96 Pembrolizumab + Chemotherapy		KN-B96 Placebo + Chemotherapy		Pooled Safety Dataset for Pembrolizumab + Chemotherapy		Pembrolizumab Monotherapy Reference Safety Dataset	
	n	(%)	n	(%)	n	(%)	n	(%)
Participants in population	320		318		5,711		7,631	
with one or more adverse events	264	(82.5)	225	(70.8)	4,441	(77.8)	3,514	(46.0)
with no adverse events	56	(17.5)	93	(29.2)	1,270	(22.2)	4,117	(54.0)
Neutrophil count decreased	59	(18.4)	46	(14.5)	975	(17.1)	10	(0.1)
Neutropenia	47	(14.7)	45	(14.2)	870	(15.2)	21	(0.3)
Anaemia	43	(13.4)	33	(10.4)	1,073	(18.8)	275	(3.6)
White blood cell count decreased	39	(12.2)	30	(9.4)	428	(7.5)	5	(0.1)
Fatigue	22	(6.9)	20	(6.3)	251	(4.4)	166	(2.2)
Hypertension	22	(6.9)	17	(5.3)	158	(2.8)	148	(1.9)
Urinary tract infection	20	(6.3)	9	(2.8)	101	(1.8)	85	(1.1)
Diarrhoea	16	(5.0)	4	(1.3)	234	(4.1)	114	(1.5)
Neuropathy peripheral	16	(5.0)	19	(6.0)	54	(0.9)	4	(0.1)
Febrile neutropenia	7	(2.2)	3	(0.9)	287	(5.0)	11	(0.1)
Platelet count decreased	2	(0.6)	3	(0.9)	332	(5.8)	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.

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 KN-B96, grades are based on NCI CTCAE version 5.0.

Database cutoff date for KN-B96: 05MAR2025.

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

	KN-B96 Pembrolizumab + Chemotherapy		KN-B96 Placebo + Chemotherapy		Pooled Safety Dataset for Pembrolizumab + Chemotherapy		Pembrolizumab Monotherapy Reference Safety Dataset	
	n	(%)	n	(%)	n	(%)	n	(%)
Participants in population	320		318		5,711		7,631	
with one or more adverse events	216	(67.5)	176	(55.3)	3,692	(64.6)	1,208	(15.8)
with no adverse events	104	(32.5)	142	(44.7)	2,019	(35.4)	6,423	(84.2)
Neutrophil count decreased	59	(18.4)	43	(13.5)	937	(16.4)	6	(0.1)
Neutropenia	45	(14.1)	43	(13.5)	844	(14.8)	13	(0.2)
Anaemia	38	(11.9)	25	(7.9)	863	(15.1)	33	(0.4)
White blood cell count decreased	38	(11.9)	28	(8.8)	412	(7.2)	2	(0.0)
Hypertension	18	(5.6)	16	(5.0)	50	(0.9)	15	(0.2)
Fatigue	17	(5.3)	19	(6.0)	203	(3.6)	75	(1.0)
Neuropathy peripheral	16	(5.0)	19	(6.0)	52	(0.9)	2	(0.0)
Platelet count decreased	0	(0.0)	3	(0.9)	318	(5.6)	2	(0.0)

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 KN-B96, grades are based on NCI CTCAE version 5.0.

Database cutoff date for KN-B96: 05MAR2025.

Serious adverse event/deaths/other significant events

Serious Adverse Events

Table 60 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)

	KN-B96 Pembrolizumab + Chemotherapy		KN-B96 Placebo + Chemotherapy		Pooled Safety Dataset for Pembrolizumab + Chemotherapy		Pembrolizumab Monotherapy Reference Safety Dataset	
	n	(%)	n	(%)	n	(%)	n	(%)
Participants in population	320		318		5,711		7,631	
with one or more adverse events	178	(55.6)	122	(38.4)	2,589	(45.3)	2,742	(35.9)
with no adverse events	142	(44.4)	196	(61.6)	3,122	(54.7)	4,889	(64.1)
Urinary tract infection	15	(4.7)	6	(1.9)	64	(1.1)	67	(0.9)
Pneumonia	14	(4.4)	4	(1.3)	224	(3.9)	272	(3.6)
Pulmonary embolism	9	(2.8)	7	(2.2)	91	(1.6)	78	(1.0)
Hyponatraemia	8	(2.5)	2	(0.6)	26	(0.5)	43	(0.6)
Pyrexia	8	(2.5)	2	(0.6)	141	(2.5)	79	(1.0)
Abdominal pain	7	(2.2)	2	(0.6)	27	(0.5)	43	(0.6)

Adrenal insufficiency	7	(2.2)	0	(0.0)	25	(0.4)	30	(0.4)
Anaemia	7	(2.2)	6	(1.9)	135	(2.4)	65	(0.9)
COVID-19	7	(2.2)	2	(0.6)	24	(0.4)	0	(0.0)
Diarrhoea	7	(2.2)	1	(0.3)	114	(2.0)	70	(0.9)
Febrile neutropenia	7	(2.2)	1	(0.3)	237	(4.1)	8	(0.1)
Neutrophil count decreased	7	(2.2)	5	(1.6)	32	(0.6)	1	(0.0)
Small intestinal obstruction	7	(2.2)	4	(1.3)	8	(0.1)	19	(0.2)
Vomiting	7	(2.2)	3	(0.9)	80	(1.4)	32	(0.4)
Intestinal obstruction	6	(1.9)	11	(3.5)	18	(0.3)	19	(0.2)
Sepsis	6	(1.9)	3	(0.9)	75	(1.3)	56	(0.7)
Colitis	5	(1.6)	0	(0.0)	56	(1.0)	71	(0.9)
Device related infection	4	(1.3)	2	(0.6)	17	(0.3)	5	(0.1)
Immune-mediated enterocolitis	4	(1.3)	0	(0.0)	5	(0.1)	4	(0.1)
Intestinal perforation	4	(1.3)	2	(0.6)	5	(0.1)	5	(0.1)
Pneumonitis	3	(0.9)	2	(0.6)	85	(1.5)	136	(1.8)
Acute kidney injury	2	(0.6)	2	(0.6)	85	(1.5)	65	(0.9)
Nausea	2	(0.6)	1	(0.3)	55	(1.0)	30	(0.4)
Pleural effusion	2	(0.6)	1	(0.3)	45	(0.8)	88	(1.2)
Dyspnoea	1	(0.3)	0	(0.0)	24	(0.4)	91	(1.2)

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

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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.

Database cutoff date for KN-B96: 05MAR2025.

Table 61 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)

	KN-B96 Pembrolizumab + Chemotherapy		KN-B96 Placebo + Chemotherapy		Pooled Safety Dataset for Pembrolizumab + Chemotherapy		Pembrolizumab Monotherapy Reference Safety Dataset	
	n	(%)	n	(%)	n	(%)	n	(%)
Participants in population	320		318		5,711		7,631	
with one or more adverse events	106	(33.1)	62	(19.5)	1,481	(25.9)	840	(11.0)
with no adverse events	214	(66.9)	256	(80.5)	4,230	(74.1)	6,791	(89.0)
Anaemia	7	(2.2)	4	(1.3)	101	(1.8)	6	(0.1)
Diarrhoea	7	(2.2)	1	(0.3)	96	(1.7)	44	(0.6)
Febrile neutropenia	7	(2.2)	1	(0.3)	227	(4.0)	0	(0.0)
Neutrophil count decreased	7	(2.2)	5	(1.6)	31	(0.5)	0	(0.0)
Adrenal insufficiency	6	(1.9)	0	(0.0)	24	(0.4)	25	(0.3)
Pneumonia	6	(1.9)	1	(0.3)	57	(1.0)	19	(0.2)
Urinary tract infection	6	(1.9)	2	(0.6)	12	(0.2)	0	(0.0)
Colitis	5	(1.6)	0	(0.0)	54	(0.9)	63	(0.8)
Pulmonary embolism	5	(1.6)	5	(1.6)	23	(0.4)	7	(0.1)
Pyrexia	5	(1.6)	1	(0.3)	65	(1.1)	22	(0.3)
Vomiting	5	(1.6)	1	(0.3)	60	(1.1)	9	(0.1)
Immune-mediated enterocolitis	4	(1.3)	0	(0.0)	5	(0.1)	4	(0.1)
Pneumonitis	2	(0.6)	2	(0.6)	76	(1.3)	129	(1.7)

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.

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

Database cutoff date for KN-B96: 05MAR2025.

Deaths

Table 62 Participants With Adverse Events Resulting in Death Up to 90 Days of Last Dose by Decreasing Frequency of Preferred Term (Incidence > 0% in One or More Treatment Groups of KN-B96) (APaT Population)

	KN-B96 Pembrolizumab + Chemotherapy		KN-B96 Placebo + Chemotherapy		Pooled Safety Dataset for Pembrolizumab + Chemotherapy		Pembrolizumab Monotherapy Reference Safety Dataset	
	n	(%)	n	(%)	n	(%)	n	(%)
Participants in population	320		318		5,711		7,631	
with one or more adverse events	15	(4.7)	14	(4.4)	313	(5.5)	346	(4.5)
with no adverse events	305	(95.3)	304	(95.6)	5,398	(94.5)	7,285	(95.5)
Assisted suicide	2	(0.6)	0	(0.0)	1	(0.0)	0	(0.0)
Death	2	(0.6)	1	(0.3)	38	(0.7)	49	(0.6)
Intestinal perforation	2	(0.6)	2	(0.6)	2	(0.0)	1	(0.0)
Sepsis	2	(0.6)	0	(0.0)	20	(0.4)	11	(0.1)
COVID-19	1	(0.3)	0	(0.0)	7	(0.1)	0	(0.0)
Cardio-respiratory arrest	1	(0.3)	0	(0.0)	4	(0.1)	4	(0.1)
Colitis	1	(0.3)	0	(0.0)	0	(0.0)	0	(0.0)
Duodenal obstruction	1	(0.3)	0	(0.0)	0	(0.0)	1	(0.0)
Embolic stroke	1	(0.3)	0	(0.0)	1	(0.0)	0	(0.0)
Gastrointestinal haemorrhage	1	(0.3)	0	(0.0)	3	(0.1)	0	(0.0)
Interstitial lung disease	1	(0.3)	0	(0.0)	2	(0.0)	1	(0.0)
Aspiration	0	(0.0)	1	(0.3)	2	(0.0)	4	(0.1)
Cardiac failure	0	(0.0)	1	(0.3)	3	(0.1)	4	(0.1)
Cardiopulmonary failure	0	(0.0)	1	(0.3)	2	(0.0)	2	(0.0)
Cerebrovascular accident	0	(0.0)	1	(0.3)	5	(0.1)	5	(0.1)
Large intestine perforation	0	(0.0)	3	(0.9)	1	(0.0)	2	(0.0)
Multiple organ dysfunction syndrome	0	(0.0)	1	(0.3)	6	(0.1)	6	(0.1)
Pneumonia bacterial	0	(0.0)	1	(0.3)	0	(0.0)	0	(0.0)
Respiratory failure	0	(0.0)	1	(0.3)	9	(0.2)	17	(0.2)
Sudden death	0	(0.0)	1	(0.3)	6	(0.1)	2	(0.0)

Every participant is counted a single time for each applicable row and column.
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.
Database cutoff date for KN-B96: 05MAR2025.

In the KEYNOTE-B96 study, of the total deaths due to AE, **8 deaths** were **considered to be drug-related** by the investigator, 3 in the experimental arm and 5 in the control arm. In the pembrolizumab plus chemotherapy group, these included colitis (n=1), interstitial lung disease (n=1), and intestinal perforation (n=1). In the placebo plus chemotherapy group, these included large intestine perforation (n=2), intestinal perforation (n=2), and cardiac failure (n=1).

Adverse Events of Special Interest

Adverse Events of Special Interest (AEOSI) for pembrolizumab are immune-mediated events and infusion-related reactions causally associated with pembrolizumab.

Table 63 Adverse Event Summary for AEOSI (APaT Population)

	KN-B96 Pembrolizumab + Chemotherapy		KN-B96 Placebo + Chemotherapy		Pooled Safety Dataset for Pembrolizumab + Chemotherapy		Pembrolizumab Monotherapy Reference Safety Dataset	
	n	(%)	n	(%)	n	(%)	n	(%)
Participants in population	320		318		5,711		7,631	
with one or more adverse events	125	(39.1)	60	(18.9)	1,927	(33.7)	2,095	(27.5)
with no adverse event	195	(60.9)	258	(81.1)	3,784	(66.3)	5,536	(72.5)
with drug-related[a] adverse events	108	(33.8)	49	(15.4)	1,699	(29.7)	1,815	(23.8)
with toxicity grade 3-5 adverse events	37	(11.6)	11	(3.5)	546	(9.6)	543	(7.1)
with toxicity grade 3-5 drug-related adverse events	32	(10.0)	10	(3.1)	494	(8.6)	475	(6.2)
with serious adverse events	35	(10.9)	7	(2.2)	437	(7.7)	527	(6.9)
with serious drug-related adverse events	32	(10.0)	7	(2.2)	394	(6.9)	462	(6.1)
who died	2	(0.6)	0	(0.0)	17	(0.3)	13	(0.2)
who died due to a drug-related adverse event	2	(0.6)	0	(0.0)	15	(0.3)	13	(0.2)
discontinued any drug due to an adverse event	22	(6.9)	8	(2.5)	366	(6.4)	363	(4.8)
discontinued pembrolizumab or placebo	15	(4.7)	4	(1.3)	287	(5.0)	363	(4.8)
discontinued any chemotherapy	16	(5.0)	6	(1.9)	190	(3.3)	0	(0.0)
discontinued any drug due to a drug-related adverse event	21	(6.6)	8	(2.5)	357	(6.3)	356	(4.7)
discontinued pembrolizumab or placebo	15	(4.7)	4	(1.3)	280	(4.9)	356	(4.7)
discontinued any chemotherapy	15	(4.7)	6	(1.9)	184	(3.2)	0	(0.0)
discontinued any drug due to a serious adverse event	16	(5.0)	5	(1.6)	236	(4.1)	231	(3.0)
discontinued pembrolizumab or placebo	14	(4.4)	4	(1.3)	215	(3.8)	231	(3.0)
discontinued any chemotherapy	11	(3.4)	3	(0.9)	114	(2.0)	0	(0.0)
discontinued any drug due to a serious drug-related adverse event	16	(5.0)	5	(1.6)	228	(4.0)	229	(3.0)
discontinued pembrolizumab or placebo	14	(4.4)	4	(1.3)	209	(3.7)	229	(3.0)
discontinued any chemotherapy	11	(3.4)	3	(0.9)	109	(1.9)	0	(0.0)

[a] Determined by the investigator to be related to the drug.
For KN-B96, 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.
Database cutoff date for KN-B96: 05MAR2025.
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 64 Exposure-Adjusted Adverse Event Summary for AEOSI (Including Multiple Occurrences of Events) (APaT Population)

	Event Count and Rate (Events/100 person-months)[a]							
	KN-B96 Pembrolizumab + Chemotherapy		KN-B96 Placebo + Chemotherapy		Pooled Safety Dataset for Pembrolizumab + Chemotherapy		Pembrolizumab Monotherapy Reference Safety Dataset	
Number of participants exposed	320		318		5,711		7,631	
Total exposure[b] in person-months	3407.24		2875.48		65347.98		66570.95	
Total events (rate)								
adverse events	192	(5.64)	78	(2.71)	2,975	(4.55)	2,979	(4.47)
drug-related[c] adverse events	162	(4.75)	64	(2.23)	2,512	(3.84)	2,539	(3.81)
toxicity grade 3-5 adverse events	43	(1.26)	13	(0.45)	620	(0.95)	620	(0.93)
toxicity grade 3-5 drug-related adverse events	38	(1.12)	12	(0.42)	563	(0.86)	538	(0.81)
serious adverse events	40	(1.17)	7	(0.24)	490	(0.75)	591	(0.89)
serious drug-related adverse events	37	(1.09)	7	(0.24)	442	(0.68)	520	(0.78)
adverse events leading to death	2	(0.06)	0	(0.00)	17	(0.03)	13	(0.02)
drug-related adverse events leading to death	2	(0.06)	0	(0.00)	15	(0.02)	13	(0.02)
adverse events resulting in drug discontinuation	24	(0.70)	8	(0.28)	379	(0.58)	372	(0.56)
drug-related adverse events resulting in drug discontinuation	22	(0.65)	8	(0.28)	368	(0.56)	365	(0.55)
serious adverse events resulting in drug discontinuation	17	(0.50)	5	(0.17)	240	(0.37)	237	(0.36)
serious drug-related adverse events resulting in drug discontinuation	17	(0.50)	5	(0.17)	232	(0.36)	235	(0.35)

[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 and the earliest of the last dose date + 30, death date or the database cutoff date, then + 1 day since the first dose date is Day 1.
[c] Determined by the investigator to be related to the drug.
For KN-B96, 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 KN-B96: 05MAR2025.
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 65 Participants With Adverse Events of Special Interest by Maximum Toxicity Grade (APaT Population)

	KN-B96 Pembrolizumab + Chemotherapy		KN-B96 Placebo + Chemotherapy		Pooled Safety Dataset for Pembrolizumab + Chemotherapy		Pembrolizumab Monotherapy Reference Safety Dataset	
	n	(%)	n	(%)	n	(%)	n	(%)
Participants in population	320		318		5,711		7,631	
with one or more adverse events	125	(39.1)	60	(18.9)	1,927	(33.7)	2,095	(27.5)
Grade 1	19	(5.9)	16	(5.0)	484	(8.5)	496	(6.5)
Grade 2	69	(21.6)	33	(10.4)	897	(15.7)	1,056	(13.8)
Grade 3	33	(10.3)	11	(3.5)	465	(8.1)	465	(6.1)
Grade 4	2	(0.6)	0	(0.0)	64	(1.1)	65	(0.9)
Grade 5	2	(0.6)	0	(0.0)	17	(0.3)	13	(0.2)
with no adverse events	195	(60.9)	258	(81.1)	3,784	(66.3)	5,536	(72.5)

Table 66 Participants With Adverse Events of Special Interest by AEOSI Category (Incidence > 0% in One or More Treatment Groups) (APaT Population)

	KN-B96 Pembrolizumab + Chemotherapy		KN-B96 Placebo + Chemotherapy		Pooled Safety Dataset for Pembrolizumab + Chemotherapy		Pembrolizumab Monotherapy Reference Safety Dataset	
	n	(%)	n	(%)	n	(%)	n	(%)
Participants in population	320		318		5,711		7,631	
with one or more adverse events	125	(39.1)	60	(18.9)	1,927	(33.7)	2,095	(27.5)
with no adverse events	195	(60.9)	258	(81.1)	3,784	(66.3)	5,536	(72.5)
Adrenal Insufficiency	**15**	**(4.7)**	**0**	**(0.0)**	**64**	**(1.1)**	**74**	**(1.0)**
Arthritis	**1**	**(0.3)**	**0**	**(0.0)**	**1**	**(0.0)**	**5**	**(0.1)**
Cholangitis Sclerosing	**0**	**(0.0)**	**0**	**(0.0)**	**2**	**(0.0)**	**0**	**(0.0)**
Colitis	**14**	**(4.4)**	**4**	**(1.3)**	**157**	**(2.7)**	**159**	**(2.1)**
Encephalitis	**0**	**(0.0)**	**0**	**(0.0)**	**8**	**(0.1)**	**5**	**(0.1)**
Exocrine Pancreatic Insufficiency	**0**	**(0.0)**	**0**	**(0.0)**	**0**	**(0.0)**	**5**	**(0.1)**
Gastritis	**7**	**(2.2)**	**5**	**(1.6)**	**129**	**(2.3)**	**57**	**(0.7)**
Guillain-Barre Syndrome	**0**	**(0.0)**	**0**	**(0.0)**	**3**	**(0.1)**	**6**	**(0.1)**
Haemolytic Anaemia	**2**	**(0.6)**	**1**	**(0.3)**	**8**	**(0.1)**	**2**	**(0.0)**
Hepatitis	**1**	**(0.3)**	**0**	**(0.0)**	**65**	**(1.1)**	**80**	**(1.0)**
Hyperthyroidism	**16**	**(5.0)**	**2**	**(0.6)**	**334**	**(5.8)**	**398**	**(5.2)**
Hypoparathyroidism	**0**	**(0.0)**	**0**	**(0.0)**	**2**	**(0.0)**	**1**	**(0.0)**
Hypophysitis	**3**	**(0.9)**	**0**	**(0.0)**	**40**	**(0.7)**	**52**	**(0.7)**
Hypothyroidism	**57**	**(17.8)**	**19**	**(6.0)**	**804**	**(14.1)**	**939**	**(12.3)**
Infusion Reactions	**19**	**(5.9)**	**15**	**(4.7)**	**369**	**(6.5)**	**165**	**(2.2)**
Myasthenic Syndrome	**1**	**(0.3)**	**0**	**(0.0)**	**4**	**(0.1)**	**8**	**(0.1)**
Myelitis	**0**	**(0.0)**	**0**	**(0.0)**	**0**	**(0.0)**	**3**	**(0.0)**
Myocarditis	**2**	**(0.6)**	**0**	**(0.0)**	**10**	**(0.2)**	**9**	**(0.1)**
Myositis	**1**	**(0.3)**	**2**	**(0.6)**	**18**	**(0.3)**	**34**	**(0.4)**
Nephritis	**3**	**(0.9)**	**2**	**(0.6)**	**39**	**(0.7)**	**37**	**(0.5)**
Optic Neuritis	**0**	**(0.0)**	**0**	**(0.0)**	**1**	**(0.0)**	**2**	**(0.0)**
Pancreatitis	**3**	**(0.9)**	**1**	**(0.3)**	**26**	**(0.5)**	**28**	**(0.4)**
Pericarditis	**0**	**(0.0)**	**0**	**(0.0)**	**8**	**(0.1)**	**11**	**(0.1)**
Pneumonitis	**15**	**(4.7)**	**6**	**(1.9)**	**231**	**(4.0)**	**324**	**(4.2)**
Sarcoidosis	**1**	**(0.3)**	**0**	**(0.0)**	**3**	**(0.1)**	**20**	**(0.3)**
Severe Skin Reactions	**5**	**(1.6)**	**5**	**(1.6)**	**140**	**(2.5)**	**130**	**(1.7)**
Thyroiditis	**1**	**(0.3)**	**2**	**(0.6)**	**73**	**(1.3)**	**74**	**(1.0)**
Type 1 Diabetes Mellitus	**3**	**(0.9)**	**0**	**(0.0)**	**18**	**(0.3)**	**34**	**(0.4)**
Uveitis	**1**	**(0.3)**	**0**	**(0.0)**	**8**	**(0.1)**	**25**	**(0.3)**
Vasculitis	**0**	**(0.0)**	**0**	**(0.0)**	**32**	**(0.6)**	**5**	**(0.1)**

Every participant is counted a single time for each applicable row and column.
Non-serious adverse events up to 30 days of last dose and serious adverse events up to 90 days of last dose are included.
Database cutoff date for KN-B96: 05MAR2025.
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 67 Time to Onset and Duration of AEOSI (APaT Population)

	KN-B96 Pembrolizumab + Chemotherapy	KN-B96 Placebo + Chemotherapy	Pooled Safety Dataset for Pembrolizumab + Chemotherapy	Pembrolizumab Monotherapy Reference Safety Dataset
Participants in population	320	318	5711	7631
Participants with AEOSI, n (%)	125 (39.1)	60 (18.9)	1927 (33.7)	2095 (27.5)
Time to Onset of First AEOSI (days)[a]				
Mean (SD)	139.9 (126.8)	121.1 (114.4)	129.8 (134.5)	118.8 (121.6)
Median	101.0	84.5	88.0	78.0
Range	1 to 700	1 to 476	1 to 878	1 to 796
Total episodes of AEOSI	192	78	2975	2979
Average number of episodes of AEOSI per participant	1.5	1.3	1.5	1.4
Episode Durations (days)[b]				
Median	184.0	44.0	73.0	103.0
Range	1 to 1087	1 to 965	1 to 2448+	1 to 1915+

Table 68 Summary of Concomitant Corticosteroid Use for AEOSI (APaT Population)

	KN-B96 Pembrolizumab + Chemotherapy		KN-B96 Placebo + Chemotherapy		Pooled Safety Dataset for Pembrolizumab + Chemotherapy		Pembrolizumab Monotherapy Reference Safety Dataset	
	n	(%)	n	(%)	n	(%)	n	(%)
Participants in population	320		318		5711		7631	
Participants with one or more events	125		60		1927		2095	
Treated with systemic corticosteroid	56	(44.8)	20	(33.3)	742	(38.5)	730	(34.8)
High starting dose	24	(19.2)	10	(16.7)	505	(26.2)	530	(25.3)
Low starting dose	32	(25.6)	10	(16.7)	231	(12.0)	197	(9.4)
Missing starting dose	0	(0.0)	0	(0.0)	6	(0.3)	3	(0.1)
Not treated with systemic corticosteroid	69	(55.2)	40	(66.7)	1185	(61.5)	1365	(65.2)

Table 69 Participants With Adverse Events of Special Interest by Outcome (APaT Population)

	Outcome	KN-B96 Pembrolizumab + Chemotherapy	KN-B96 Placebo + Chemotherapy	Pooled Safety Dataset for Pembrolizumab + Chemotherapy	Pembrolizumab Monotherapy Reference Safety Dataset
		n (%)	n (%)	n (%)	n (%)
Participants in population		320	318	5711	7631
With one or more AEOSI	**Overall**	**125 (39.1)**	**60 (18.9)**	**1927 (33.7)**	**2095 (27.5)**
	Fatal	2 (1.6)	0 (0.0)	17 (0.9)	13 (0.6)
	Not Resolved	59 (47.2)	18 (30.0)	675 (35.0)	909 (43.4)
	Resolving	15 (12.0)	6 (10.0)	274 (14.2)	182 (8.7)
	Unknown	1 (0.8)	0 (0.0)	5 (0.3)	30 (1.4)
	Sequelae	2 (1.6)	0 (0.0)	51 (2.6)	67 (3.2)
	Resolved	46 (36.8)	36 (60.0)	905 (47.0)	894 (42.7)

Adverse Drug Reactions (ADR) in the SmPC

Section 4.8 of the SmPC is updated to include the KEYNOTE-B96 population of platinum-resistant recurrent ovarian cancer patients, receiving pembrolizumab in combination with paclitaxel, with or without bevacizumab, into the current 'pembrolizumab in combination with chemotherapy, radiation therapy or chemoradiotherapy' pooled safety dataset.

The below encompasses the adverse reactions included in Table 2 of the SmPC with related frequency categories and incidence percentages from the latest pooled dataset from combination therapy (pembrolizumab plus chemotherapy or radiation therapy or chemoradiotherapy) studies as follows:

- Non small cell lung cancer: KEYNOTE-021 (Cohorts A, C, and G), KEYNOTE-189, KEYNOTE-407 and KEYNOTE-671
- Head and neck squamous cell carcinoma: KEYNOTE-048 and KEYNOTE-689
- Gastric, oesophageal or gastroesophageal cancer: KEYNOTE-590, KEYNOTE-811 and KEYNOTE-859
- Triple negative breast cancer: KEYNOTE-355 and KEYNOTE-522
- Cervical cancer: KEYNOTE-826 and KEYNOTE-A18
- Biliary tract carcinoma: KEYNOTE-966
- Endometrial cancer: KEYNOTE-868
- Malignant pleural mesothelioma: KEYNOTE-483
- Ovarian cancer: KEYNOTE-B96.

Of note the 'pembrolizumab in combination with chemotherapy' pooled safety dataset increased from N=5711 at time of submission of this extension of indication to N= 6695 with the approval of Keytruda EMA/VR/0000248795 extension of indication in locally advanced head and neck squamous cell carcinoma (EC decision issued on 24 October 2025).

As a consequence of the updated 'pembrolizumab in combination with chemotherapy' pooled safety dataset, the frequency of the ADR 'epilepsy' has been revised in section 4.8 of the SmPC from 'uncommon' to 'rare'.

Table 70 Adverse Reactions in Patients Treated with Pembrolizumab in Combination with Chemotherapy (Approved in the Current EUPI Plus New Population under Review) (APaT Population)

		Combination Therapy (N=7015)	
		All AEs % (n)	Gr 3-5 AEs n
Infections and infestations			
Common	Pneumonia	6.8% (477)	260
Blood and lymphatic system disorders			
Very common	Anaemia	50.7% (3557)	1220
Very common	Neutropenia	22.0% (1543)	932
Very common	Thrombocytopenia	11.6% (811)	242
Common	Febrile Neutropenia	4.8% (334)	323
Common	Leukopenia	8.7% (612)	243
Common	Lymphopenia	3.0% (211)	94
Uncommon	Haemolytic Anaemia[a]	0.1% (10)	9
Uncommon	Eosinophilia	0.8% (54)	4
Rare	Immune Thrombocytopenia	0.04% (3)	2
Immune system disorders			
Common	Infusion Reactions[b]	6.7% (473)	83
Rare	Sarcoidosis	0.06% (4)	0
Endocrine disorders			
Very common	Hypothyroidism[c]	14.5% (1019)	18
Common	Adrenal Insufficiency[d]	1.3% (92)	40
Common	Hyperthyroidism[e]	5.9% (411)	8
Common	Thyroiditis[f]	1.1% (76)	7
Uncommon	Hypophysitis[g]	0.7% (48)	26
Rare	Hypoparathyroidism	0.04% (3)	0
Metabolism and nutrition disorders			
Very common	Hypokalaemia	11.9% (836)	246
Very common	Decreased Appetite	25.8% (1808)	132
Common	Hyponatraemia	8.8% (618)	231
Common	Hypocalcaemia	4.8% (334)	53
Uncommon	Type 1 Diabetes Mellitus[h]	0.3% (23)	22
Psychiatric disorders			
Very common	Insomnia	11.2% (783)	12
Nervous system disorders			
Very common	Neuropathy Peripheral	14.2% (997)	73
Very common	Headache	13.4% (941)	22
Common	Dizziness	9.8% (685)	17
Common	Dysgeusia	9.1% (635)	3
Uncommon	Encephalitis[i]	0.1% (9)	9
Uncommon	Lethargy	0.96% (67)	2
Rare	Myasthenic Syndrome[j]	0.09% (6)	6
Rare	Guillain-Barre Syndrome[k]	0.06% (4)	4
Rare	Myelitis	0.01% (1)	1
Rare	Optic Neuritis	0.01% (1)	1
Rare	Epilepsy	0.0998% (7)	3
Rare	Meningitis (Aseptic)	0.01% (1)	1

		Combination Therapy (N=7015)	
		All AEs % (n)	Gr 3-5 AEs n
Eye disorders			
Common	Dry Eye	2.9% (203)	1
Uncommon	Uveitis[l]	0.2% (15)	0
Cardiac disorders			
Common	Cardiac Arrhythmia (Including Atrial Fibrillation)[m]	4.0% (283)	65
Uncommon	Myocarditis[n]	0.2% (14)	11
Uncommon	Pericarditis[o]	0.1% (8)	3
Uncommon	Pericardial Effusion	0.4% (28)	10
Vascular disorders			
Common	Hypertension	7.5% (524)	205
Uncommon	Vasculitis[p]	0.5% (35)	6
Respiratory, thoracic and mediastinal disorders			
Very common	Dyspnoea	12.2% (855)	90
Very common	Cough	15.1% (1061)	5
Common	Pneumonitis[q]	4.0% (282)	97
Gastrointestinal disorders			
Very common	Diarrhoea	35.2% (2467)	271
Very common	Nausea	50.5% (3541)	209
Very common	Vomiting	27.1% (1903)	199
Very common	Abdominal Pain[r]	18.9% (1328)	94
Very common	Constipation	31.7% (2223)	25
Common	Colitis[s]	2.8% (193)	97
Common	Gastritis[t]	2.1% (144)	12
Common	Dry Mouth	5.3% (374)	6
Uncommon	Pancreatitis[u]	0.5% (37)	25
Uncommon	Gastrointestinal Ulceration[v]	0.4% (28)	6
Rare	Exocrine Pancreatic Insufficiency	(0)	0
Rare	Small Intestinal Perforation	0.04% (3)	3
Rare	Coeliac Disease	(0)	0
Hepatobiliary disorders			
Common	Hepatitis[w]	1.1% (74)	55
Rare	Cholangitis Sclerosing[x]	0.03% (2)	2

		Combination Therapy (N=7015)	
		All AEs % (n)	Gr 3-5 AEs n
Skin and subcutaneous tissue disorders			
Very common	Alopecia	22.6% (1585)	6
Very common	Pruritus[y]	13.9% (977)	6
Very common	Rash[z]	20.4% (1432)	4
Common	Severe Skin Reactions[aa]	2.5% (175)	140
Common	Dermatitis	1.8% (125)	6
Common	Erythema	3.3% (234)	5
Common	Dry Skin	5.2% (367)	3
Common	Dermatitis Acneiform	2.0% (142)	2
Common	Eczema	1.2% (86)	2
Uncommon	Psoriasis	0.6% (41)	6
Uncommon	Lichenoid Keratosis[bb]	0.1% (10)	1
Uncommon	Vitiligo[cc]	0.5% (36)	0
Uncommon	Papule	0.2% (12)	0
Rare	Stevens-Johnson Syndrome	0.04% (3)	3
Rare	Erythema Nodosum	0.07% (5)	0
Rare	Hair Colour Changes	0.01% (1)	0
Musculoskeletal and connective tissue disorders			
Very common	Arthralgia	15.7% (1098)	47
Very common	Musculoskeletal Pain[dd]	13.2% (926)	45
Common	Myositis[ee]	8.8% (617)	28
Common	Pain In Extremity	7.2% (503)	13
Common	Arthritis[ff]	1.7% (119)	11
Uncommon	Tenosynovitis[gg]	0.4% (26)	2
Rare	Sjogren's Syndrome	0.03% (2)	0
Renal and urinary disorders			
Common	Acute Kidney Injury	3.2% (223)	115
Uncommon	Nephritis[hh]	0.7% (49)	27
Uncommon	Cystitis Noninfective	0.3% (18)	0
General disorders and administration site conditions			
Very common	Fatigue	35.8% (2514)	301
Very common	Asthenia	16.8% (1179)	177
Very common	Pyrexia	17.8% (1247)	52
Very common	Oedema[ii]	13.7% (960)	31
Common	Influenza Like Illness	3.0% (208)	2
Common	Chills	2.9% (203)	0
Investigations			
Very common	Alanine Aminotransferase Increased	17.0% (1195)	205
Very common	Aspartate Aminotransferase Increased	16.3% (1145)	168
Common	Blood Bilirubin Increased	4.4% (312)	52
Common	Blood Alkaline Phosphatase Increased	6.6% (465)	51
Common	Blood Creatinine Increased	9.7% (680)	38
Common	Hypercalcaemia	1.8% (126)	25

		Combination Therapy (N=7015)	
		All AEs % (n)	Gr 3-5 AEs n
Uncommon	Amylase Increased	0.7% (47)	10

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

a. Haemolytic Anaemia (Autoimmune Haemolytic Anaemia, Coombs Negative Haemolytic Anaemia, Haemolytic Anaemia)

b. Infusion Reactions (Anaphylactic Reaction, Cytokine Release Syndrome, Drug Hypersensitivity, Hypersensitivity, Infusion Related Hypersensitivity Reaction, Infusion Related Reaction, Serum Sickness)

c. Hypothyroidism (Autoimmune Hypothyroidism, Hypothyroidism, Immune-Mediated Hypothyroidism)

d. Adrenal Insufficiency (Addison's Disease, Adrenal Insufficiency, Primary Adrenal Insufficiency, Secondary Adrenocortical Insufficiency)

e. Hyperthyroidism (Graves' Disease, Hyperthyroidism)

f. Thyroiditis (Autoimmune Thyroiditis, Immune-Mediated Thyroiditis, Silent Thyroiditis, Thyroid Disorder, Thyroiditis, Thyroiditis Acute)

g. Hypophysitis (Hypophysitis, Hypopituitarism)

h. Type 1 Diabetes Mellitus (Diabetic Ketoacidosis, Type 1 Diabetes Mellitus)

i. Encephalitis (Encephalitis, Encephalitis Autoimmune)

j. Myasthenic Syndrome (Myasthenia Gravis, Myasthenic Syndrome)

k. Guillain-Barre Syndrome (Demyelinating Polyneuropathy, Guillain-Barre Syndrome)

l. Uveitis (Iridocyclitis, Iritis, Uveitis)

m. Cardiac Arrhythmia (Including Atrial Fibrillation) (Arrhythmia, Atrial Fibrillation, Atrial Flutter, Atrial Tachycardia, Atrioventricular Block, Atrioventricular Block First Degree, Atrioventricular Block Second Degree, Bundle Branch Block, Cardiac Flutter, Electrocardiogram Qt Prolonged, Electrocardiogram Repolarisation Abnormality, Extrasystoles, Heart Rate Irregular, Sinus Arrhythmia, Sinus Bradycardia, Sinus Node Dysfunction, Sinus Tachycardia, Supraventricular Extrasystoles, Supraventricular Tachycardia, Ventricular Arrhythmia, Ventricular Extrasystoles, Ventricular Tachycardia)

n. Myocarditis (Autoimmune Myocarditis, Immune-Mediated Myocarditis, Myocarditis)

o. Pericarditis (Myopericarditis, Pericarditis)

p. Vasculitis (Central Nervous System Vasculitis, Vasculitis)

q. Pneumonitis (Autoimmune Lung Disease, Immune-Mediated Lung Disease, Interstitial Lung Disease, Organising Pneumonia, Pneumonitis)

r. Abdominal Pain (Abdominal Discomfort, Abdominal Pain, Abdominal Pain Lower, Abdominal Pain Upper)

s. Colitis (Autoimmune Colitis, Colitis, Colitis Microscopic, Enterocolitis, Immune-Mediated Enterocolitis)

t. Gastritis (Gastritis, Gastritis Erosive, Immune-Mediated Gastritis)

u. Pancreatitis (Autoimmune Pancreatitis, Pancreatitis, Pancreatitis Acute)

v. Gastrointestinal Ulceration (Duodenal Ulcer, Gastric Ulcer)

w. Hepatitis (Autoimmune Hepatitis, Drug-Induced Liver Injury, Hepatitis, Hepatitis Acute, Immune-Mediated Hepatitis)

x. Cholangitis Sclerosing (Cholangitis Sclerosing, Immune-Mediated Cholangitis)

y. Pruritus (Pruritus, Pruritus Genital, Urticaria)

z. Rash (Genital Rash, Rash, Rash Erythematous, Rash Follicular, Rash Macular, Rash Maculo-Papular, Rash Papular, Rash Pruritic, Rash Vesicular)

aa. Severe Skin Reactions (Cutaneous Vasculitis, Dermatitis Bullous, Dermatitis Exfoliative, Dermatitis Exfoliative Generalised, Erythema Multiforme, Exfoliative Rash, Pemphigoid, Pruritus, Rash, Rash Erythematous, Rash Maculo-Papular, Rash Pruritic, Rash Pustular, Skin Necrosis, Stevens-Johnson Syndrome, Toxic Skin Eruption)

bb. Lichenoid Keratosis (Lichen Planus, Lichenoid Keratosis)

cc. Vitiligo (Skin Depigmentation, Skin Hypopigmentation, Vitiligo)

dd. Musculoskeletal Pain (Back Pain, Musculoskeletal Chest Pain, Musculoskeletal Discomfort, Musculoskeletal

Laboratory findings

The most frequently (>50% incidence) reported laboratory abnormalities in the KEYNOTE-B96 study were:

- Pembrolizumab plus chemotherapy: hemoglobin decreased (84.3%), leukocytes decreased (83.4%), neutrophils decreased (71.5%), lymphocytes decreased (59.2%), sodium decreased (51.1%), and albumin decreased (50.9%)
- Placebo plus chemotherapy: hemoglobin decreased (78.5%), leukocytes decreased (78.4%), neutrophils decreased (67.2%), and lymphocytes decreased (60.2%)

The most frequently reported worsening to Grade 3 to 4 events of protocol-specified laboratory tests (≥10% incidence) were:

- Pembrolizumab plus chemotherapy: decreased neutrophils (38.9%), decreased lymphocytes (26.6%), and decreased leukocytes (23.8%), and decreased hemoglobin (15.4%)
- Placebo plus chemotherapy: decreased neutrophils (31.8%), decreased leukocytes (20%), decreased lymphocytes (18.5%), and decreased hemoglobin (10.8%).

Table 71 Participants With Liver Function Laboratory Findings That Met Predetermined Criteria All Participants – KEYNOTE-B96 (APaT Population)

Criteria	Pembrolizumab + Chemotherapy		Placebo + Chemotherapy	
	n/m	(%)	n/m	(%)
Participants in population	320		318	
Alanine Aminotransferase				
≥3 x ULN	38/318	(11.9)	20/315	(6.3)
≥5 x ULN	22/318	(6.9)	6/315	(1.9)
≥10 x ULN	7/318	(2.2)	0/315	(0.0)
≥20 x ULN	1/318	(0.3)	0/315	(0.0)
Aspartate Aminotransferase				
≥3 x ULN	33/318	(10.4)	20/315	(6.3)
≥5 x ULN	14/318	(4.4)	5/315	(1.6)
≥10 x ULN	5/318	(1.6)	2/315	(0.6)
≥20 x ULN	2/318	(0.6)	0/315	(0.0)
Aminotransferase (ALT or AST)				
≥3 x ULN	47/318	(14.8)	31/315	(9.8)
≥5 x ULN	25/318	(7.9)	10/315	(3.2)
≥10 x ULN	8/318	(2.5)	2/315	(0.6)
≥20 x ULN	2/318	(0.6)	0/315	(0.0)
Bilirubin				
≥2 x ULN	15/318	(4.7)	17/315	(5.4)
Alkaline Phosphatase				
≥1.5 x ULN	73/318	(23.0)	67/314	(21.3)
Aminotransferase (ALT or AST) and Bilirubin				
AT ≥3 x ULN and BILI ≥1.5 x ULN	5/318	(1.6)	6/315	(1.9)
AT ≥3 x ULN and BILI ≥2 x ULN	4/318	(1.3)	4/315	(1.3)
Aminotransferase (ALT or AST) and Bilirubin and Alkaline Phosphatase				
AT ≥3 x ULN and BILI ≥2 x ULN and ALP <2 x ULN	0/318	(0.0)	0/315	(0.0)

n = Number of participants with postbaseline test results (or combination of test results from the same day) that met predetermined criteria.
m = Number of participants with at least one postbaseline test result or combination of test results from the same day.
ALP = Alkaline phosphatase; ALT = Alanine aminotransferase; AST = Aspartate aminotransferase; AT = Aminotransferase (ALT or AST); BILI = Bilirubin; ULN = Upper limit of normal range.
Database Cutoff Date: 05MAR2025.

Safety in special populations

Table 72 Adverse Event Summary by Age Category (< 65, 65-74, >= 75 Years) (APaT Population)

	KN-B96 Pembrolizumab + Chemotherapy						KN-B96 Placebo + Chemotherapy					
	<65		65-74		>=75		<65		65-74		>=75	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Participants in population	200		90		30		207		85		26	
with one or more adverse events	199	(99.5)	90	(100.0)	30	(100.0)	206	(99.5)	85	(100.0)	25	(96.2)
with no adverse event	1	(0.5)	0	(0.0)	0	(0.0)	1	(0.5)	0	(0.0)	1	(3.8)
with drug-related[a] adverse events	196	(98.0)	88	(97.8)	29	(96.7)	195	(94.2)	84	(98.8)	24	(92.3)
with toxicity grade 3-5 adverse events	158	(79.0)	78	(86.7)	28	(93.3)	148	(71.5)	58	(68.2)	19	(73.1)
with toxicity grade 3-5 drug-related adverse events	132	(66.0)	63	(70.0)	21	(70.0)	115	(55.6)	45	(52.9)	16	(61.5)
with non-serious adverse events	199	(99.5)	90	(100.0)	30	(100.0)	203	(98.1)	85	(100.0)	25	(96.2)
with serious adverse events	108	(54.0)	47	(52.2)	23	(76.7)	80	(38.6)	30	(35.3)	12	(46.2)
with serious drug-related adverse events	63	(31.5)	29	(32.2)	14	(46.7)	39	(18.8)	17	(20.0)	6	(23.1)
who died	4	(2.0)	7	(7.8)	4	(13.3)	10	(4.8)	3	(3.5)	1	(3.8)
who died due to a drug-related adverse event	1	(0.5)	1	(1.1)	1	(3.3)	5	(2.4)	0	(0.0)	0	(0.0)
discontinued any drug due to an adverse event	65	(32.5)	49	(54.4)	18	(60.0)	58	(28.0)	38	(44.7)	12	(46.2)
discontinued pembrolizumab or placebo	25	(12.5)	15	(16.7)	8	(26.7)	17	(8.2)	8	(9.4)	5	(19.2)
discontinued any chemotherapy	58	(29.0)	47	(52.2)	18	(60.0)	57	(27.5)	38	(44.7)	12	(46.2)
discontinued any drug due to a drug-related adverse event	59	(29.5)	40	(44.4)	16	(53.3)	48	(23.2)	33	(38.8)	8	(30.8)
discontinued pembrolizumab or placebo	21	(10.5)	10	(11.1)	6	(20.0)	11	(5.3)	4	(4.7)	3	(11.5)
discontinued any chemotherapy	52	(26.0)	38	(42.2)	16	(53.3)	47	(22.7)	33	(38.8)	8	(30.8)
discontinued any drug due to a serious adverse event	27	(13.5)	18	(20.0)	11	(36.7)	22	(10.6)	12	(14.1)	7	(26.9)
discontinued pembrolizumab or placebo	17	(8.5)	14	(15.6)	7	(23.3)	12	(5.8)	7	(8.2)	4	(15.4)
discontinued any chemotherapy	20	(10.0)	15	(16.7)	10	(33.3)	20	(9.7)	12	(14.1)	7	(26.9)
discontinued any drug due to a serious drug-related adverse event	22	(11.0)	14	(15.6)	8	(26.7)	14	(6.8)	8	(9.4)	4	(15.4)
discontinued pembrolizumab or placebo	14	(7.0)	10	(11.1)	5	(16.7)	8	(3.9)	3	(3.5)	2	(7.7)
discontinued any chemotherapy	15	(7.5)	11	(12.2)	7	(23.3)	12	(5.8)	8	(9.4)	4	(15.4)

	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	3,823		1,527		361		4,524		2,173		934	
with one or more adverse events	3,791	(99.2)	1,517	(99.3)	358	(99.2)	4,364	(96.5)	2,097	(96.5)	914	(97.9)
with no adverse event	32	(0.8)	10	(0.7)	3	(0.8)	160	(3.5)	76	(3.5)	20	(2.1)
with drug-related[a] adverse events	3,677	(96.2)	1,482	(97.1)	341	(94.5)	3,231	(71.4)	1,552	(71.4)	679	(72.7)
with toxicity grade 3-5 adverse events	2,946	(77.1)	1,196	(78.3)	299	(82.8)	1,917	(42.4)	1,071	(49.3)	526	(56.3)
with toxicity grade 3-5 drug-related adverse events	2,450	(64.1)	1,011	(66.2)	231	(64.0)	629	(13.9)	391	(18.0)	188	(20.1)
with non-serious adverse events	3,767	(98.5)	1,508	(98.8)	351	(97.2)	4,282	(94.7)	2,051	(94.4)	889	(95.2)
with serious adverse events	1,589	(41.6)	783	(51.3)	217	(60.1)	1,457	(32.2)	839	(38.6)	446	(47.8)
with serious drug-related adverse events	928	(24.3)	430	(28.2)	123	(34.1)	451	(10.0)	265	(12.2)	124	(13.3)
who died	140	(3.7)	117	(7.7)	56	(15.5)	158	(3.5)	113	(5.2)	75	(8.0)
who died due to a drug-related adverse event	32	(0.8)	28	(1.8)	15	(4.2)	21	(0.5)	13	(0.6)	8	(0.9)
discontinued any drug due to an adverse event	1,000	(26.2)	513	(33.6)	144	(39.9)	554	(12.2)	327	(15.0)	185	(19.8)
discontinued pembrolizumab or placebo	532	(13.9)	290	(19.0)	101	(28.0)	554	(12.2)	327	(15.0)	185	(19.8)
discontinued any chemotherapy	690	(18.0)	392	(25.7)	116	(32.1)	0	(0.0)	0	(0.0)	0	(0.0)
discontinued any drug due to a drug-related adverse event	857	(22.4)	406	(26.6)	99	(27.4)	333	(7.4)	206	(9.5)	100	(10.7)
discontinued pembrolizumab or placebo	404	(10.6)	195	(12.8)	54	(15.0)	333	(7.4)	206	(9.5)	100	(10.7)
discontinued any chemotherapy	593	(15.5)	307	(20.1)	75	(20.8)	0	(0.0)	0	(0.0)	0	(0.0)
discontinued any drug due to a serious adverse event	437	(11.4)	263	(17.2)	95	(26.3)	366	(8.1)	214	(9.8)	134	(14.3)
discontinued pembrolizumab or placebo	354	(9.3)	217	(14.2)	87	(24.1)	366	(8.1)	214	(9.8)	134	(14.3)
discontinued any chemotherapy	258	(6.7)	182	(11.9)	73	(20.2)	0	(0.0)	0	(0.0)	0	(0.0)
discontinued any drug due to a serious drug-related adverse event	321	(8.4)	164	(10.7)	52	(14.4)	177	(3.9)	113	(5.2)	57	(6.1)
discontinued pembrolizumab or placebo	245	(6.4)	134	(8.8)	44	(12.2)	177	(3.9)	113	(5.2)	57	(6.1)
discontinued any chemotherapy	178	(4.7)	107	(7.0)	35	(9.7)	0	(0.0)	0	(0.0)	0	(0.0)

[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 KN-B96, grades are based on NCI CTCAE version 5.0.
Database cutoff date for KN-B96: 05MAR2025.
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 Adverse Event Summary for Elderly Participants by Age All Participants (APaT Population)

	Age (Years)															
	Pembrolizumab + Chemotherapy								Placebo + Chemotherapy							
	< 65		65 - 74		75 - 84		85+		< 65		65 - 74		75 - 84		85+	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Participants in Population	200		90		29		1		207		85		26		0	
with one or more adverse events	199	(99.5)	90	(100.0)	29	(100.0)	1	(100.0)	206	(99.5)	85	(100.0)	25	(96.2)	0	(NA)
who died	4	(2.0)	7	(7.8)	4	(13.8)	0	(0.0)	10	(4.8)	3	(3.5)	1	(3.8)	0	(NA)
with serious adverse events	108	(54.0)	47	(52.2)	23	(79.3)	0	(0.0)	80	(38.6)	30	(35.3)	12	(46.2)	0	(NA)
discontinued drug due to an adverse event	65	(32.5)	49	(54.4)	17	(58.6)	1	(100.0)	58	(28.0)	38	(44.7)	12	(46.2)	0	(NA)
CNS (confusion/extrapyramidal)	28	(14.0)	16	(17.8)	6	(20.7)	0	(0.0)	23	(11.1)	16	(18.8)	3	(11.5)	0	(NA)
AE related to falling	30	(15.0)	16	(17.8)	5	(17.2)	0	(0.0)	18	(8.7)	9	(10.6)	1	(3.8)	0	(NA)
CV events	77	(38.5)	34	(37.8)	14	(48.3)	0	(0.0)	79	(38.2)	35	(41.2)	8	(30.8)	0	(NA)
Cerebrovascular events	2	(1.0)	3	(3.3)	1	(3.4)	0	(0.0)	3	(1.4)	2	(2.4)	2	(7.7)	0	(NA)
Infections	135	(67.5)	67	(74.4)	21	(72.4)	0	(0.0)	150	(72.5)	58	(68.2)	9	(34.6)	0	(NA)

AEs were followed to 30 days after last dose of study treatment; SAEs were followed to 90 days after last dose of study treatment.
Grades are based on NCI CTCAE version 5.
MedDRA V27.1 preferred terms "Neoplasm progression", "Malignant neoplasm progression" and "Disease progression" not related to the drug are excluded.
Database Cutoff Date: 05MAR2025.

Table 74 Adverse Event Summary by Bevacizumab Use All Participants (APaT Population)

	Pembrolizumab + Chemotherapy				Placebo + Chemotherapy			
	With Bevacizumab Use		Without Bevacizumab Use		With Bevacizumab Use		Without Bevacizumab Use	
	n	(%)	n	(%)	n	(%)	n	(%)
Participants in population	235		85		236		82	
with one or more adverse events	234	(99.6)	85	(100.0)	236	(100.0)	80	(97.6)
with no adverse event	1	(0.4)	0	(0.0)	0	(0.0)	2	(2.4)
with drug-related[a] adverse events	232	(98.7)	81	(95.3)	228	(96.6)	75	(91.5)
with toxicity grade 3-5 adverse events	199	(84.7)	65	(76.5)	174	(73.7)	51	(62.2)
with toxicity grade 3-5 drug-related[a] adverse events	168	(71.5)	48	(56.5)	139	(58.9)	37	(45.1)
with serious adverse events	139	(59.1)	39	(45.9)	95	(40.3)	27	(32.9)
with serious drug-related[a] adverse events	88	(37.4)	18	(21.2)	55	(23.3)	7	(8.5)
who died	9	(3.8)	6	(7.1)	10	(4.2)	4	(4.9)
who died due to a drug-related[a] adverse event	2	(0.9)	1	(1.2)	4	(1.7)	1	(1.2)
discontinued any drug due to an adverse event	111	(47.2)	21	(24.7)	96	(40.7)	12	(14.6)
discontinued MK-3475/PLACEBO	38	(16.2)	10	(11.8)	25	(10.6)	5	(6.1)
discontinued PACLITAXEL (DOCETAXEL)	81	(34.5)	17	(20.0)	76	(32.2)	12	(14.6)
discontinued BEVACIZUMAB	59	(25.1)	0	(0.0)	44	(18.6)	0	(0.0)
discontinued any drug due to a drug-related[a] adverse event	96	(40.9)	19	(22.4)	80	(33.9)	9	(11.0)
discontinued MK-3475/PLACEBO	30	(12.8)	7	(8.2)	16	(6.8)	2	(2.4)
discontinued PACLITAXEL (DOCETAXEL)	73	(31.1)	15	(17.6)	67	(28.4)	9	(11.0)
discontinued BEVACIZUMAB	43	(18.3)	0	(0.0)	30	(12.7)	0	(0.0)
discontinued any drug due to a serious adverse event	49	(20.9)	7	(8.2)	36	(15.3)	5	(6.1)
discontinued MK-3475/PLACEBO	31	(13.2)	7	(8.2)	18	(7.6)	5	(6.1)
discontinued PACLITAXEL (DOCETAXEL)	22	(9.4)	5	(5.9)	18	(7.6)	5	(6.1)
discontinued BEVACIZUMAB	34	(14.5)	0	(0.0)	30	(12.7)	0	(0.0)
discontinued any drug due to a serious drug-related[a] adverse event	39	(16.6)	5	(5.9)	24	(10.2)	2	(2.4)
discontinued MK-3475/PLACEBO	24	(10.2)	5	(5.9)	11	(4.7)	2	(2.4)
discontinued PACLITAXEL (DOCETAXEL)	16	(6.8)	3	(3.5)	10	(4.2)	2	(2.4)
discontinued BEVACIZUMAB	24	(10.2)	0	(0.0)	19	(8.1)	0	(0.0)

[a] Determined by the investigator to be related to any drug.
Grades are based on NCI CTCAE version 5.
Non-serious adverse events up to 30 days of last treatment and serious adverse events up to 90 days of last treatment are included.
MedDRA V27.1 preferred terms "Neoplasm progression", "Malignant neoplasm progression" and "Disease progression" not related to the drug are excluded.
Database Cutoff Date: 05MAR2025.

Table 75 Adverse Event Summary by ECOG Status Category (0, 1) (APaT Population)

	KN-B96 Pembrolizumab + Chemotherapy				KN-B96 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	179		141		173		143		3,085		2,619		4,016		3,440	
with one or more adverse events	178	(99.4)	141	(100.0)	173	(100.0)	141	(98.6)	3,065	(99.4)	2,594	(99.0)	3,883	(96.7)	3,324	(96.6)
with no adverse event	1	(0.6)	0	(0.0)	0	(0.0)	2	(1.4)	20	(0.6)	25	(1.0)	133	(3.3)	116	(3.4)
with drug-related[a] adverse events	175	(97.8)	138	(97.9)	164	(94.8)	137	(95.8)	2,987	(96.8)	2,507	(95.7)	3,072	(76.5)	2,295	(66.7)
with toxicity grade 3-5 adverse events	144	(80.4)	120	(85.1)	120	(69.4)	103	(72.0)	2,386	(77.3)	2,048	(78.2)	1,540	(38.3)	1,866	(54.2)
with toxicity grade 3-5 drug-related adverse events	119	(66.5)	97	(68.8)	102	(59.0)	72	(50.3)	2,033	(65.9)	1,655	(63.2)	623	(15.5)	555	(16.1)
with non-serious adverse events	178	(99.4)	141	(100.0)	172	(99.4)	139	(97.2)	3,049	(98.8)	2,570	(98.1)	3,845	(95.7)	3,214	(93.4)
with serious adverse events	96	(53.6)	82	(58.2)	64	(37.0)	58	(40.6)	1,302	(42.2)	1,280	(48.9)	1,157	(28.8)	1,491	(43.3)
with serious drug-related adverse events	60	(33.5)	46	(32.6)	32	(18.5)	30	(21.0)	776	(25.2)	702	(26.8)	442	(11.0)	381	(11.1)
who died	4	(2.2)	11	(7.8)	8	(4.6)	6	(4.2)	110	(3.6)	202	(7.7)	93	(2.3)	237	(6.9)
who died due to a drug-related adverse event	1	(0.6)	2	(1.4)	5	(2.9)	0	(0.0)	34	(1.1)	41	(1.6)	13	(0.3)	29	(0.8)
discontinued any drug due to an adverse event	75	(41.9)	57	(40.4)	66	(38.2)	42	(29.4)	896	(29.0)	760	(29.0)	515	(12.8)	522	(15.2)
discontinued pembrolizumab or placebo	28	(15.6)	20	(14.2)	17	(9.8)	13	(9.1)	479	(15.5)	443	(16.9)	515	(12.8)	522	(15.2)
discontinued any chemotherapy	71	(39.7)	52	(36.9)	65	(37.6)	42	(29.4)	610	(19.8)	587	(22.4)	0	(0.0)	0	(0.0)
discontinued any drug due to a drug-related adverse event	69	(38.5)	46	(32.6)	58	(33.5)	31	(21.7)	782	(25.3)	580	(22.1)	379	(9.4)	247	(7.2)
discontinued pembrolizumab or placebo	25	(14.0)	12	(8.5)	12	(6.9)	6	(4.2)	378	(12.3)	275	(10.5)	379	(9.4)	247	(7.2)
discontinued any chemotherapy	64	(35.8)	42	(29.8)	57	(32.9)	31	(21.7)	536	(17.4)	439	(16.8)	0	(0.0)	0	(0.0)
discontinued any drug due to a serious adverse event	29	(16.2)	27	(19.1)	23	(13.3)	18	(12.6)	387	(12.5)	407	(15.5)	296	(7.4)	397	(11.5)
discontinued pembrolizumab or placebo	21	(11.7)	17	(12.1)	13	(7.5)	10	(7.0)	319	(10.3)	338	(12.9)	296	(7.4)	397	(11.5)
discontinued any chemotherapy	21	(11.7)	24	(17.0)	21	(12.1)	18	(12.6)	226	(7.3)	286	(10.9)	0	(0.0)	0	(0.0)
discontinued any drug due to a serious drug-related adverse event	26	(14.5)	18	(12.8)	17	(9.8)	9	(6.3)	296	(9.6)	241	(9.2)	184	(4.6)	156	(4.5)
discontinued pembrolizumab or placebo	19	(10.6)	10	(7.1)	10	(5.8)	3	(2.1)	236	(7.6)	187	(7.1)	184	(4.6)	156	(4.5)
discontinued any chemotherapy	18	(10.1)	15	(10.6)	15	(8.7)	9	(6.3)	166	(5.4)	154	(5.9)	0	(0.0)	0	(0.0)

[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 KN-B96, grades are based on NCI CTCAE version 5.0.
Database cutoff date for KN-B96: 05MAR2025.
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 Region (North America, Western Europe, ROW) All Participants (APaT Population)

	Pembrolizumab + Chemotherapy						Placebo + Chemotherapy					
	North America		Western Europe		ROW		North America		Western Europe		ROW	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Participants in population	57		118		145		68		125		125	
with one or more adverse events	57	(100.0)	118	(100.0)	144	(99.3)	67	(98.5)	125	(100.0)	124	(99.2)
with no adverse event	0	(0.0)	0	(0.0)	1	(0.7)	1	(1.5)	0	(0.0)	1	(0.8)
with drug-related[a] adverse events	57	(100.0)	113	(95.8)	143	(98.6)	66	(97.1)	119	(95.2)	118	(94.4)
with toxicity grade 3-5 adverse events	37	(64.9)	96	(81.4)	131	(90.3)	57	(83.8)	77	(61.6)	91	(72.8)
with toxicity grade 3-5 drug-related[a] adverse events	28	(49.1)	76	(64.4)	112	(77.2)	46	(67.6)	59	(47.2)	71	(56.8)
with serious adverse events	31	(54.4)	55	(46.6)	92	(63.4)	30	(44.1)	38	(30.4)	54	(43.2)
with serious drug-related[a] adverse events	16	(28.1)	31	(26.3)	59	(40.7)	16	(23.5)	16	(12.8)	30	(24.0)
who died	4	(7.0)	2	(1.7)	9	(6.2)	2	(2.9)	5	(4.0)	7	(5.6)
who died due to a drug-related[a] adverse event	1	(1.8)	0	(0.0)	2	(1.4)	1	(1.5)	1	(0.8)	3	(2.4)
discontinued drug due to an adverse event	19	(33.3)	48	(40.7)	65	(44.8)	19	(27.9)	45	(36.0)	44	(35.2)
discontinued drug due to a drug-related[a] adverse event	14	(24.6)	41	(34.7)	60	(41.4)	16	(23.5)	37	(29.6)	36	(28.8)
discontinued drug due to a serious adverse event	7	(12.3)	19	(16.1)	30	(20.7)	9	(13.2)	13	(10.4)	19	(15.2)
discontinued drug due to a serious drug-related[a] adverse event	3	(5.3)	16	(13.6)	25	(17.2)	8	(11.8)	7	(5.6)	11	(8.8)

[a] Determined by the investigator to be related to any drug.
Grades are based on NCI CTCAE version 5
Non-serious adverse events up to 30 days of last treatment and serious adverse events up to 90 days of last treatment are included.
MedDRA V27.1 preferred terms "Neoplasm progression", "Malignant neoplasm progression" and "Disease progression" not related to the drug are excluded.
Western Europe includes countries in the European Economic Area, United Kingdom, and Switzerland.
Database Cutoff Date: 05MAR2025.

Safety related to drug-drug interactions and other interactions

General considerations made about DDI for pembrolizumab are valid also for this extension of indication. 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 improve potential side effects, the potential for a pharmacokinetic DDI with pembrolizumab as a victim was previously assessed as part of the population pharmacokinetic analysis in previous procedures.

Discontinuation due to adverse events

Table 77 discontinuation due to AE – KEYNOTE-B96 (excerpt)

	Pembrolizumab + Chemotherapy		Placebo + Chemotherapy	
	n	(%)	n	(%)
Participants in population	320		318	
discontinued any drug due to an adverse event	132	(41.3)	108	(34.0)
discontinued MK-3475/PLACEBO	48	(15.0)	30	(9.4)
discontinued PACLITAXEL (DOCETAXEL)	98	(30.6)	88	(27.7)
discontinued BEVACIZUMAB	59	(18.4)	44	(13.8)
discontinued any drug due to a drug-related[a] adverse event	115	(35.9)	89	(28.0)
discontinued MK-3475/PLACEBO	37	(11.6)	18	(5.7)
discontinued PACLITAXEL (DOCETAXEL)	88	(27.5)	76	(23.9)
discontinued BEVACIZUMAB	43	(13.4)	30	(9.4)
discontinued any drug due to a serious adverse event	56	(17.5)	41	(12.9)
discontinued MK-3475/PLACEBO	38	(11.9)	23	(7.2)
discontinued PACLITAXEL (DOCETAXEL)	27	(8.4)	23	(7.2)
discontinued BEVACIZUMAB	34	(10.6)	30	(9.4)
discontinued any drug due to a serious drug-related[a] adverse event	44	(13.8)	26	(8.2)
discontinued MK-3475/PLACEBO	29	(9.1)	13	(4.1)
discontinued PACLITAXEL (DOCETAXEL)	19	(5.9)	12	(3.8)

In both study groups, discontinuations of any study drug were caused most frequently by PTs within the SOCs of Gastrointestinal disorders, General disorders and administration site conditions, Infections and infestations, Nervous system disorders, Respiratory, thoracic and mediastinal disorders, and Skin and subcutaneous tissue disorders.

Post marketing experience

Since the first approval of pembrolizumab on 17 July 2015 through 03 September 2024 (the DCO of the latest PBRER), the estimated cumulative patient exposure was 1,518,204 patient-years.

3.1.1. Discussion on clinical safety

Safety data have been presented for the two arms of the pivotal phase 3 double blind randomized KEYNOTE-B96 study in adult females with PROC evaluating pembrolizumab or placebo added to weekly paclitaxel with or without bevacizumab (N=320 vs 318). To contextualise the safety data of the experimental combination and evaluate the consistency with the known toxicity of pembrolizumab, safety data from KEYNOTE-B96 have been presented also side by side with the pembrolizumab plus chemotherapy pooled dataset (N=5711) and with the pembrolizumab monotherapy reference safety dataset (N=7631).

The median duration of **exposure** to study drug in the KEYNOTE-B96 study was numerically longer in the pembrolizumab plus chemotherapy group compared with the placebo plus chemotherapy group

(median 7.47 vs 6.34 months), with about two-thirds of the patients in the pembrolizumab plus chemotherapy group receiving more than 6 months of therapy.

The **overall** incidence of AEs was similar between participants in the pembrolizumab plus chemotherapy group and the placebo plus chemotherapy group of the KEYNOTE-B96 study (99.7% vs 99.4%), although a higher incidence of participants with Grade 3-5 AEs (82.5% vs 70.8% all causality, 67.5% vs 55.3% drug related) and SAE (55.6% vs 38.4% all causality, 33.1% vs 19.5% drug related), as well as discontinuation due to AE (41.3% vs 34%)/drug-related AE (35.9% vs 28%)/SAE (17.5% vs 12.9%) was observed in the pembrolizumab plus chemotherapy arm vs the placebo plus chemotherapy arm, which is also confirmed after adjusting for exposure. This increased toxicity is however expected, due to the addition of pembrolizumab to SOC.

The **most frequently reported AEs** (incidence ≥10%) were overall consistent between the pembrolizumab plus chemotherapy group and the placebo plus chemotherapy group, although overall a tendency toward increased incidences of AEs is noted. In particular, the AEs with greater risk for the pembrolizumab plus chemotherapy group compared with the placebo plus chemotherapy were hypothyroidism (17.8% vs 6%), pyrexia (20.6% vs 12.3%), ALT increased (17.8% vs 10.4%), rash (20.6% vs 13.2%), stomatitis (17.8% vs 10.4%), and weight decreased (11.9% vs 4.7%). While hypothyroidism and rash are known immune-mediated AEs associated with pembrolizumab, stomatitis is known to be associated with paclitaxel and bevacizumab, therefore the addition of pembrolizumab may increase the toxicity of the associated drugs. When compared with the pooled pembrolizumab plus chemotherapy pooled dataset, a higher incidence is noted in some AEs such as neuropathy peripheral (39.4% vs 13%), alopecia (38.1% vs 21.6%), epistaxis (32.2% vs 5.6%), stomatitis 17.8% vs 11%), nail disorder (15.3% vs 0.8%), onycholysis (11.9% vs 0.7%), proteinuria (12.5% vs 2.4%), hypertension (20% vs 6.4%), which is expected, as those AEs are commonly related to paclitaxel and bevacizumab. When compared with the pembrolizumab monotherapy RSD, there was a higher incidence of participants in the pembrolizumab plus chemotherapy group of most PTs, consistently with the addition of paclitaxel +/- bevacizumab.

The most common **grade 3-5 adverse events** in both arms of the KEYNOTE-B96 study were haematological toxicity including neutrophil count decreased (18.4% vs 14.5%) and neutropenia (14.7% vs 14.2%), anaemia (13.4% vs 10.4%), and white blood cell decreased (12.2% vs 9.4%), slightly higher in the pembrolizumab containing arm as compared to the control arm. Diarrhoea (5% vs 1.3%) and urinary tract infection (6.3% vs 2.8%) were the AEs with greater risk in the pembrolizumab plus chemotherapy arm. The most frequently reported AEs were generally consistent between the pembrolizumab plus chemotherapy group and the pooled pembrolizumab plus chemotherapy dataset, although still with higher incidence of hypertension (6.9% vs 2.8%), neuropathy peripheral (5% vs 0.9%), and UTI (6.3% vs 1.8%), AEs which are related to paclitaxel and bevacizumab and also to the underlying disease. This finding is confirmed also considering the G3-5 drug-related AEs. When compared with the monotherapy RSD, there was a higher incidence of participants in the pembrolizumab plus chemotherapy group with most PTs reported as Grade 3 to 5 AEs, consistent with the addition of paclitaxel +/- bevacizumab.

More **SAE** occurred in the experimental arm of the KEYNOTE-B96 study: the most common SAEs were UTI (4.7% vs 1.9%) and pneumonia (4.4% vs 1.3%) in the pembrolizumab plus chemotherapy arm and intestinal obstruction (1.9% vs 3.5%) in the placebo plus chemotherapy arm. The SAEs with greater risk for the pembrolizumab plus chemotherapy group versus the placebo plus chemotherapy were pneumonia (4.4% vs 1.3%) and adrenal insufficiency (2.2% vs 0%). The most frequently reported drug-related SAEs (incidence ≥1%) were generally consistent between the pembrolizumab plus chemotherapy group and the placebo plus chemotherapy group, and expected based on the established safety profiles of pembrolizumab monotherapy, paclitaxel, and bevacizumab.

The **AEs resulting in death** occurred at a similar rate in both groups of the KEYNOTE-B96 study (4.7% vs 4.4%), and also as compared to the pooled pembrolizumab combination dataset (5.5%) and monotherapy RSD (4.5%). Death due to drug-related AEs were low and similar in both arms (0.9% vs 1.6%). In the pembrolizumab arm, the 3 deaths considered to be drug-related where due to colitis, interstitial lung disease, and intestinal perforation. Colitis was considered related to pembrolizumab by the investigator: this is included among immune-related events and already reported in the SmPC. ILD was considered related to pembrolizumab and paclitaxel by the investigator and considered an AEOSI by the MAH; interstitial lung disease is included under "pneumonitis" in section 4.8 of the SmPC. Intestinal perforation was considered by the investigator related to bevacizumab, but not to pembrolizumab and paclitaxel. This is indeed a known risk of bevacizumab. The MAH reviewed all fatal events and did not identify any trends in AEs resulting in death suggesting any safety concerns for the use of pembrolizumab plus chemotherapy with or without bevacizumab. Based on the data provided, no new concern is indeed raised.

The percentages of participants with postbaseline **laboratory abnormalities** in the pembrolizumab plus chemotherapy group were generally slightly higher than the placebo plus chemotherapy group, but overall consistent with the pooled pembrolizumab plus chemotherapy group and higher than those in the RSD. Abnormalities were overall consistent with the known toxicity profiles of pembrolizumab and chemotherapy (weekly paclitaxel with or without bevacizumab). In both groups of the KEYNOTE-B96 study, most shifts in toxicity grade from baseline to worst postbaseline values were Grades 1 or 2.The review of the laboratory abnormalities did not reveal unexpected findings.

With regard to the **AEOSI**, which are immune-mediated events and infusion-related reactions causally associated with pembrolizumab, as expected those occurred more commonly in the pembrolizumab plus chemo arm of the KYENOTE-B96 study as compared to the control arm (39.1% vs 18.9%). AEOSI occurred also slightly more commonly than in the pooled combination safety dataset (33.7%) and the monotherapy RSD (27.5%), although the difference is reduced when adjusted for exposure. As compared to the other two datasets, it can be observed a higher incidence as compared to the pooled pembrolizumab combination and pembrolizumab mono dataset of AEOSI especially in the category adrenal insufficiency (4.7% vs 1.1% vs 1%), hypothyroidism (17.8% vs 14.1% vs 12.3%), and infusion reactions (5.9% vs 6.5% vs 2.2%). Hypothyroidism may be related to the fact that all participants were female, while for the infusion-related reactions, this may have been secondary to chemotherapy administration (indeed, similar incidence was observed in the pembrolizumab combination pooled dataset). With regard to adrenal insufficiency, the review of these events (15) found that the majority of events (8) were Grade 1 to 2, with no fatal events. Of the Grade 3 events, the majority were managed with corticosteroids or dose interruptions, while one event required withdrawal of pembrolizumab. Of the 15 events, 13 were in participants who were treated with bevacizumab. A total of 3 events were considered resolved, while 5 events each (33%) were not resolved or resolving. Although no specific cause is found for the unexpected higher incidence of adrenal insufficiency in this study, adrenal insufficiency is an expected event associated with pembrolizumab, already reported in the SmPC. Therefore, no additional change to the SmPC is considered needed in this regard.

With regard to **safety in special populations**, in the pembrolizumab plus chemotherapy group a general worse safety profile is observed in participants ≥65 years old, in particular for treatment discontinuation. However, a similar trend is observed also in the placebo plus chemotherapy group, and it is consistent with the reference pooled datasets of pembrolizumab. Toxicity is also increased in the pembrolizumab plus chemotherapy arm in patients who also receive bevacizumab as compared to patients who do not receive it. However, the same trend is observed in the control arm, which is therefore consistent with the addition of another drug, therefore no concern is raised. No difference in

safety is noted based on ECOG Performance Status 0 vs 1. With regard to region, safety seems better in Western Europe as compared to ROW.

More **treatment discontinuation due to AE** occurred in the pembrolizumab plus chemotherapy arm than in the placebo plus chemotherapy arm of the KEYNOTE-B96 study. Paclitaxel was more commonly discontinued, although this occurred similarly in both arm (30.6% vs 27.7%). The type of AEs leading to discontinuation are overall consistent with the established safety profiles of pembrolizumab monotherapy, paclitaxel, and bevacizumab. The number of patients who discontinued any treatment due to AE was higher in the pembrolizumab plus chemotherapy arm (41.3%) as compared to the pooled safety pembrolizumab plus chemotherapy dataset (29%), which may be partly attributed to the different chemotherapy products included in the study groups, and, as expected, was higher than the pembrolizumab monotherapy RSD (14%).

3.1.2. Conclusions on clinical safety

The toxicity of pembrolizumab plus weekly paclitaxel with or without bevacizumab in patients with PROC treated in the KEYNOTE-B96 study is consistent with the well-established safety profiles of pembrolizumab monotherapy, paclitaxel and bevacizumab. As expected, the addition of pembrolizumab to SOC increases the overall toxicity, which however is known and considered overall manageable. No new safety concern has been identified.

3.1.3. 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.

3.2. Risk management plan

The MAH submitted an updated RMP version with this application.

The CHMP received the following PRAC Advice on the submitted Risk Management Plan:

The PRAC considered that the risk management plan version 47.0 is acceptable.

The CHMP endorsed the Risk Management Plan version 47.0 with the following content:

Safety concerns

Table 78 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

No new safety concerns were identified as a result of the review the data from this extension of indication.

Pharmacovigilance plan

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

Risk minimisation measures

Table 79 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		
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).
	Routine risk minimisation measures:	Routine pharmacovigilance activities

Safety Concern	Risk minimisation Measures	Pharmacovigilance Activities
GVHD after pembrolizumab administration in patients with a history of allogeneic SCT	• 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	Additional pharmacovigilance including: • Safety monitoring in all ongoing MAH-sponsored clinical trials for pembrolizumab in various tumor types

3.3. 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.

In addition, the MAH took the opportunity to replace 'kit' with 'assay' after the PD-L1 IHC 22C3 pharmDx in section 5.1 of the SmPC and to remove Organon as Manufacturer of Keytruda solution for injection from the Package Leaflet as requested by EMA.

3.3.1. 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: no changes of the package leaflet are foreseen impacting the safe use of the medicinal product.

4. Benefit-Risk Balance

4.1. Therapeutic Context

4.1.1. Disease or condition

The recommended indication reflecting the data evaluated is:

KEYTRUDA, in combination with paclitaxel, with or without bevacizumab, is indicated for the treatment of platinum resistant epithelial ovarian, fallopian tube, or primary peritoneal carcinoma in adults whose tumours express PD L1 with a CPS ≥1 and who have received one or two prior systemic treatment regimens.

4.1.2. Available therapies and unmet medical need

Ovarian cancer (OC) is the most lethal gynaecological cancer: in 2022, 40,714 new cases were diagnosed in the EU [49], and, although mortality has been declining, in 2025, 26,900 deaths are estimated in the EU for this disease, with an overall 5-year survival rate less than 40%[50]. Epithelial OC represents a heterogeneous spectrum of disease entities at a clinical, pathological and molecular level,

[49] ECIS - European Cancer Information System. Available at https://ecis.jrc.ec.europa.eu. Accessed October 6, 2025.
[50] Wojtyla C, Bertuccio P, Giermaziak W, Santucci C, Odone A, Ciebiera M, et al. European trends in ovarian cancer mortality, 1990-2020 and predictions to 2025. Eur J Cancer. 2023;194:113350.

with high-grade serous carcinoma the most common subtype[51]. Diagnosis is usually made at advanced stages due to lack of effective screening methods and the absence of tumour-specific symptoms[52].

First line treatment includes either cytoreductive surgery, followed by platinum- and taxane-based, adjuvant/neoadjuvant chemotherapy, with maintenance PARPi +/- bevacizumab in eligible patients. Despite high responses to platinum-based treatment, most patients relapse, and are generally classified as platinum-refractory, platinum-resistant or platinum-sensitive based on the platinum-free interval. In patients for whom platinum is not an option, common treatment options are monotherapy with non-platinum compounds, which have shown generally modest (<20%) response rates[53] [54]. Bevacizumab is recommended in combination with weekly paclitaxel, PLD or topotecan in patients without contraindications to bevacizumab and not previously exposed to bevacizumab[55]. Recently, mirvetuximab soravtansine was approved for FR-α positive platinum-resistant OC[56]. In OC, the results of trials with ICIs have been disappointing so far, including addition of anti-PD1 to chemotherapy in the specific PROC setting [57] [58] , with no ICIs receiving regulatory approval to date for this tumour type[59] [60]. Prognosis of PROC is generally poor, with mOS around 16-22 months and mPFS around 4-8 months[61] [62], therefore novel and effective therapies are still necessary in this advanced setting.

4.1.3. Main clinical studies

The pivotal study supporting this application is KEYNOTE-B96, a phase 3 randomized multicenter double-blind study in adult female patients with epithelial ovarian/fallopian tube/primary peritoneal cancer platinum-resistant (excluding platinum-refractory, i.e. with disease progression 1-6 months after the last dose of platinum-based chemotherapy), after 1 or 2 prior lines of systemic therapy. A total of 643 patients were randomized 1:1 to receive pembrolizumab 400 mg Q6W (max 18 cycles) plus weekly paclitaxel with or without bevacizumab, vs placebo plus weekly paclitaxel with or without bevacizumab. Bevacizumab was given at investigator's discretion and was one of the stratification factors, together with PD-L1 status (CPS<1 vs 1 to <10 vs ≥10) and region (US vs EU vs ROW).

The primary endpoint was PFS per RECIST 1.1 according to investigator in the CPS ≥1 and in all comers, multiplicity adjusted secondary endpoint was OS in CPS ≥1 and in all comers.

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[51] Matulonis UA. Management of newly diagnosed or recurrent ovarian cancer. Clin Adv Hematol Oncol. 2018 Jun;16(6):426-39.
[52] Lheureux S, Braunstein M, Oza AM. Epithelial ovarian cancer: evolution of management in the era of precision medicine. CA Cancer J Clin. 2019;69:280-304.
[53] National Comprehensive Cancer Network. NCCN clinical practice guidelines in oncology: ovarian cancer including fallopian tube cancer and primary peritoneal cancer; version 3.2024. Plymouth Meeting (PA): National Comprehensive Cancer Network (NCCN); 2024. 241 p.
[54] González-Martín A, Harter P, Leary A, Lorusso D, Miller RE, Pothuri B, Ray-Coquard I, Tan DSP, Bellet E, Oaknin A, Ledermann JA; ESMO Guidelines Committee. Newly diagnosed and relapsed epithelial ovarian cancer: ESMO Clinical Practice Guideline for diagnosis, treatment and follow-up. Ann Oncol. 2023 Oct;34(10):833-848.
[55] González-Martín A, Harter P, Leary A, Lorusso D, Miller RE, Pothuri B, Ray-Coquard I, Tan DSP, Bellet E, Oaknin A, Ledermann JA; ESMO Guidelines Committee. Newly diagnosed and relapsed epithelial ovarian cancer: ESMO Clinical Practice Guideline for diagnosis, treatment and follow-up. Ann Oncol. 2023 Oct;34(10):833-848.
[56] EMA/473768/2024 - Elahere CHMP EPAR EMEA/H/C/005036/0000, https://www.ema.europa.eu/en/documents/assessment-report/elahere-epar-public-assessment-report_en.pdf
[57] Pujade-Lauraine E, Fujiwara K, Ledermann JA, et al. Avelumab alone or in combination with chemotherapy versus chemotherapy alone in platinum-resistant or platinum-refractory ovarian cancer (JAVELIN Ovarian 200): an open-label, three-arm, randomised, phase 3 study. Lancet Oncol. 2021 Jul;22(7):1034-1046. doi: 10.1016/S1470-2045(21)00216-3.
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[61] Xiong Z, Ha C, Li R, Wu M, Wei M. Related clinical factors of platinum-based chemotherapy resistance in patients with epithelial ovarian cancer. Gynecol Obstet Invest. 2024;89:469-77.
[62] Chase DM, Patton G, Annavarapu S, Shi J, Szamreta EA, Monberg M. Factors associated with platinum sensitivity (PST) and related outcomes in patients with ovarian cancer (OC) in a US community oncology setting: looking beyond [abstract]. Presented at: 2023 American Society of Clinical Oncology (ASCO) Annual Meeting; 2023 Jun 2-6; Chicago, IL. J Clin Oncol. 2023;41(6 suppl).

Results come from pre-planned study analyses: IA1 (data cut-off 03 April 2024, median FU 12 months in CPS≥1), IA2 (data cut-off 05 March 2025, median FU 15.8 months in CPS≥1, range 0.5, 38), and the final analysis (data cut-off date 05 September 2025, median FU 15.8 months in CPS ≥1, range 0.5, 44.1).

The PFS endpoint was met in both populations, CPS ≥1 and all-comers, at IA1; OS endpoint was met in the CPS≥1 population at IA2 and in the all-comers at FA. The MAH is seeking an indication limited to tumours expressing PD-L1 with a CPS ≥1, representing 72.5% of the overall population of the KEYNOTE-B96 study (N=234 vs 232).

4.2. Favourable effects

- The primary endpoint PFS per RECIST 1.1 by investigator reached statistical significance at IA1 in the CPS≥1 (HR 0.72, 95%CI 0.58, 0.89, p<0.0014) population. Results of PFS by BICR are consistent with the results by investigator.
- The secondary endpoint OS was adjusted for multiplicity and met statistical significance at IA2 in the CPS≥1 population (HR 0.76, 95%CI 0.61, 0.94, p=0.0053). Median OS was 18.2 (15.3, 21) vs 14 (12.5, 16.1) months, for an absolute gain in median OS of 4.2 months. The maximum improvement in OS rate was from 38.9% to 51.5% at 18 months, although KM curves tend to converge afterwards (but still censored). Updated descriptive OS at final analysis showed consistent result, with OS curves remaining separated with longer follow-up (OS Rate at month 24: 35.6% vs 26.6%). Overall, the magnitude of OS benefit shown by the addition of pembrolizumab is considered clinically relevant.

4.3. Uncertainties and limitations about favourable effects

- The study enrolled more patients than planned resulting in higher statistical power, and the obtained results showed lower estimated effects than values assumed in sample size calculation, allowing the detection of statistical significance for treatment effects lower than expected.
- The apparent numerical difference in the treatment effect observed in the EU subgroup (OS HR 0.90, 95%CI 0.65, 1.24) may reflect random variation or differences in baseline characteristics, and post-progression management. However, no formal evidence of a treatment-by-region interaction was identified. As subgroup analyses are not powered for definitive conclusions, and without a biological rationale for possible regional difference in the treatment effect of pembrolizumab, the global ITT estimate should guide the assessment of treatment benefit.

4.4. Unfavourable effects

- In the KEYNOTE-B96 study, the AEs were similar in the two arms (99.7% vs 99.4%), however the addition of pembrolizumab to SOC increases the rate of Grade 3-5 AEs (82.5% vs 70.8% all causality, 67.5% vs 55.3% drug related) and SAEs (55.6% vs 38.4% all causality, 33.1% vs 19.5% drug related), as well as the discontinuation due to AEs (41.3% vs 34%)/drug-related AEs (35.9% vs 28%)/SAE (17.5% vs 12.9%).
- **AEs** with a greater risk for the pembrolizumab plus chemotherapy group compared with the placebo plus chemotherapy were hypothyroidism (17.8% vs 6%), pyrexia (20.6% vs 12.3%), ALT increased (17.8% vs 10.4%), rash (20.6% vs 13.2%), stomatitis (17.8% vs 10.4%), and weight decreased (11.9% vs 4.7%).

- The most common **grade 3-5 adverse events** in both arms of the KEYNOTE-B96 study were haematological toxicity, with diarrhoea (5% vs 1.3%) and urinary tract infection (6.3% vs 2.8%) the AEs with greater risk in the pembrolizumab plus chemotherapy arm.
- The most common **SAEs** were UTI (4.7% vs 1.9%) and pneumonia (4.4% vs 1.3%) in the pembrolizumab plus chemotherapy arm.
- **Death due to drug-related AEs** were low and similar in both arms (0.9% vs 1.6%). In the pembrolizumab arm, the 3 deaths considered to be drug-related where due to colitis, interstitial lung disease, and intestinal perforation (this attributed to bevacizumab). Colitis and interstitial lung disease are already included in the SmPC.
- **AEOSI:** a higher incidence of AEOSI was observed in the pooled pembrolizumab combination than in the pembrolizumab monotherapy dataset especially in the category Adrenal Insufficiency (4.7% vs 1.1% vs 1%), hypothyroidism (17.8% vs 14.1% vs 12.3%), and infusion reactions (5.9% vs 6.5% vs 2.2%). Although no specific cause is found for the unexpected higher incidence of adrenal insufficiency in the KEYNOTE-B96 study, adrenal insufficiency is an expected event associated with pembrolizumab which is already well covered in the SmPC.
- With regards to **safety in special populations**, in the pembrolizumab plus chemotherapy group, a generally worse safety profile is observed in participants ≥65 years old, in particular for treatment discontinuation, although this trend is similar to the placebo plus chemotherapy group, and consistent with the reference pooled datasets of pembrolizumab. Toxicity is also increased in both treatment arms in patients who receive bevacizumab as compared to patients who do not receive it, which is consistent with the addition of another drug.

4.5. Uncertainties and limitations about unfavourable effects

None.

4.6. Effects Table

Table 80 Effects Table for Keytruda with weekly paclitaxel with or without bevacizumab in patients with PROC after 1-2 lines of prior treatment, population PD-L1 CPS≥1 (data cut-off: 5 March 2025, IA2)

Effect	Short description	Unit	Treatment	Control	Uncertainties / Strength of evidence	References
Favourable Effects						
PFS by investigator per RECIST 1.1	Time from randomization to the first documented disease progression or death due to any cause, whichever occurs first	Months	8.3 (7.0, 9.4) HR 0.72 (0.58, 0.89) p= 0.0014	7.2 (6.2, 8.1)	Questionable clinical relevance / Statistical significance met at IA1; consistent PFS results by BICR	CSR KEYNOTE-B96

Effect	Short description	Unit	Treatment	Control	Uncertainties / Strength of evidence	References
OS	Time from randomization to death due to any cause	Months	18.2 (15.3, 21) HR 0.76 (0.61, 0.94) p=0.0053	14 (12.5,16.1)	Statistical significance met at IA2, supportive PFS2, supportive updated OS results at FA	
Unfavourable Effects						
G3-5 AE		%	82.5	70.5	Increased toxicity of the combination due to the addition of pembrolizumab / toxicity consistent with safety profile of each drug, no new safety concerns	CSR KEYNOTE-B96
SAE		%	55.6	38.4		
Discontinuation due to AE		%	41.3	34		
Deaths due treatment-related AE		%	0.9	1.6		
AEOSI		%	39.1	18.9		

Abbreviations: CRS = clinical study report; PFS=progression free survival; OS=overall survival; RECIST= Response Evaluation Criteria In Solid Tumors; BICR=blinded independent central review; HR=hazard ratio; IA=interim analysis; AE=adverse event; SAE=serious adverse event; AEOSI=adverse event of special interest; CSR=clinical study report.

4.7. Benefit-risk assessment and discussion

4.7.1. Importance of favourable and unfavourable effects

The KEYNOTE-B96 double blind pivotal RCT demonstrated at IA1 a statistically significant PFS by investigator improvement in the PD-L1 positive population, defined as CPS≥1, by adding pembrolizumab to weekly paclitaxel with or without bevacizumab in patients with PROC, although the absolute benefit is considered of questionable clinical relevance, especially in the context of an add-on trial. OS, although a secondary endpoint, was adjusted for multiplicity; in the CPS≥1 population, at the subsequent preplanned interim analysis IA2, statistical significance was reached also for OS. The absolute survival gain is considered of clinical relevance, especially in a setting like PROC with dismal prognosis and limited treatment options. The improvement in ORR was limited, although responses were more durable in the pembrolizumab containing arm. The KEYNOTE-B96 study enrolled a specific population with expected better outcome (i.e. not platinum refractory, no more than 2 prior lines of systemic treatment) and also quite fit (only ECOG 0-1), which limits the representativeness of the study, thus results may be difficult to generalize to a more general patient population with PROC. The limit of 1-2 prior lines of systemic treatment is however specified in the wording of the indication in 4.1 of the SmPC, and the population included in this study is adequately described in section 5.1 of the SmPC, which is considered acceptable. Some doubts are raised on subgroup analyses results: the magnitude of effect might not be as large as in the overall population for patients expected to be treated in the real European context; however, it is not possible to disentangle the effects of imbalances in baseline/ disease characteristics like age, histology, or prior/post-progression therapies, also without a biological rationale for regional difference in pembrolizumab treatment effect, thus making subgroup results, for which the study is not powered

for, difficult to interpret. As the overall KEYNOTE-B96 study results are positive and there is no suggestion of detriment in any of the subgroups analysed, the global ITT estimate should guide the assessment of treatment benefit. Subgroup results are reflected in this report (see section 2.4.2).

The toxicity of the experimental combination pembrolizumab plus weekly paclitaxel with or without bevacizumab was worse than weekly paclitaxel with or without bevacizumab, as expected from an add-on treatment, although the overall toxicity was consistent with the known safety profile of each drug, pembrolizumab, paclitaxel and bevacizumab, and generally considered manageable, with no new safety findings identified.

4.7.2. Balance of benefits and risks

In the context of a disease like PROC with dismal prognosis and limited treatment options, a statistically significant and clinically relevant OS benefit was observed in the KEYNOTE-B96 study in the CPS≥1 population for pembrolizumab plus weekly paclitaxel with or without bevacizumab as compared to placebo plus weekly paclitaxel with or without bevacizumab, which was accompanied by a PFS improvement, which was, although statistically significant, of questionable clinical relevance. In the quite selected PROC patient population of this trial (i.e. not platinum refractory, no more than 2 prior lines of systemic treatment, only ECOG 0-1), the survival improvement is considered outweighing the risk of the increased toxicity given by the addition of pembrolizumab to weekly paclitaxel with or without bevacizumab, toxicity which is however considered as expected from the safety profile of each drug of the combination, with no new safety signals identified.

4.8. Conclusions

Overall, the B/R balance of Keytruda in the new claimed indication is considered positive.

5. Recommendations

Outcome

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

Variation(s) requested		**Type**
C.I.6.a	C.I.6.a Addition of a new therapeutic indication or modification of an approved one	Variation type II

Extension of indication to include in combination with paclitaxel, with or without bevacizumab, the treatment of platinum-resistant epithelial ovarian, fallopian tube, or primary peritoneal carcinoma in adults whose tumours express PD-L1 with a CPS ≥ 1 and who have received one or two prior systemic treatment regimens for KEYTRUDA, based on the results from study PB96V01MK3475 (KEYNOTE-B96); this is a Phase 3, randomized, double-blind study of pembrolizumab in combination with paclitaxel with or without bevacizumab for the treatment of platinum-resistant recurrent ovarian cancer. As a consequence, sections 4.1, 4.8 and 5.1 of the SmPC are updated. The Package Leaflet is updated in accordance. Version 47.0 of the RMP has also been agreed. In addition, the MAH took the opportunity to replace 'kit' with 'assay' after the PD-L1 IHC 22C3 pharmDx in section 5.1 of the SmPC and to

remove Organon as Manufacturer of Keytruda solution for injection from the Package Leaflet as requested by EMA.

The variation leads to amendments to the annexes I and IIIB 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.

Similarity with authorised orphan medicinal products

The CHMP by consensus is of the opinion that Keytruda is not similar to Zejula and Elahere within the meaning of Article 3 of Commission Regulation (EC) No. 847/200.