12 October 2023
EMA/506795/2023
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Keytruda

International non-proprietary name: pembrolizumab

Procedure No. EMEA/H/C/003820/II/0135

Note

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

Official address Domenico Scarlattilaan 6 ● 1083 HS Amsterdam ● The Netherlands
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List of abbreviations

Abbreviation	Definition
1L	First-line
5-FU	5-fluorouracil
ADA	antidrug antibodies
AE	adverse event
AEOSI	adverse events of special interest
APaT	all participants as treated
ASaT	all subjects as treated
AST	aspartate aminotransferase
BICR	blinded independent central review
CAPOX	capecitabine and oxaliplatin
CI	confidence interval
CPS	combined positive score
CSR	Clinical Study Report
DCO	data cutoff
DDI	drug-drug interaction
DILI	drug-induced liver injury
DOR	duration of response
ECOG	Eastern Cooperative Oncology Group
EORTC QLQ	European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire
E-R	exposure/dose-response
ESMO	European Society for Medical Oncology
FAS	full analysis set
FP	5-FU plus cisplatin
GEJ	gastroesophageal junction
HER2	human epidermal growth factor receptor 2
HR	hazard ratio
HRQoL	health-related quality of life
IA	interim analysis
ITT	intent to treat
KM	Kaplan-Meier

KN859	KEYNOTE-859
LS	Least-squares
mAb	monoclonal antibody
NR	not reached
ORR	objective response rate
OS	overall survival
PD-1	programmed cell death-1
PD-L1	programmed cell death-1 ligand-1
PD-L2	programmed cell death-1 ligand-2
PFS	progression-free survival
PK	pharmacokinetics
PPK	population pharmacokinetics
PR	partial response
PRO	patient-reported outcomes
PS	performance scale
Q2W	every 2 weeks
Q3W	every 3 weeks
Q6W	every 6 weeks
QoL	Quality of Life
RECIST	Response Evaluation Criteria in Solid Tumours
RSD	Reference Safety Dataset
SAE	serious adverse event
sSAP	supplemental statistical analysis plan
SOC	standard-of-care
TTR	time to response
VAS	visual analog scale

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 6 March 2023 an application for a variation.

The following variation was requested:

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

Extension of indication to include in combination with chemotherapy the first-line treatment of locally advanced unresectable or metastatic HER2-negative gastric or gastrooesophageal junction adenocarcinoma in adults based on study KEYNOTE-859, a randomized, double-blind phase 3 trial, evaluating KEYTRUDA in combination with chemotherapy compared to placebo in combination with chemotherapy for the first-line treatment of patients with HER2-negative locally advanced unresectable or metastatic gastric or GEJ adenocarcinoma. As a consequence sections 4.1 and 5.1 of the SmPC are updated. The Package Leaflet and Annex II are updated in accordance. Version 42.1 of the RMP has also been submitted.

The variation requested amendments to the Summary of Product Characteristics, Annex II 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(s) P/0043/2018 on the agreement of a paediatric investigation plan (PIP). The PIP (EMEA-001474-PIP01-13-M01) covering the condition 'Treatment of all conditions included in the category of malignant neoplasms (except nervous system, haematopoietic and lymphoid tissue) and the final compliance check have been provided. Additionally, the PIP covering the condition 'Treatment of Hodgkin Lymphoma' (EMEA -001474-PIP02-16-M01) and the partial compliance check, completed on 1 February 2019, has been also provided.

Information relating to orphan market exclusivity

Similarity

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

Scientific advice

The MAH did not seek Scientific Advice at the CHMP.

1.2. Steps taken for the assessment of the product

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

Rapporteur: N/A Co-Rapporteur: Jan Mueller-Berghaus

Timetable	Actual dates
Submission date	6 March 2023
Start of procedure	25 March 2023
CHMP Co-Rapporteur's preliminary assessment report circulated on	17 May 2023
PRAC Rapporteur's preliminary assessment report circulated on	25 May 2023
PRAC RMP advice and assessment overview adopted by PRAC on	8 June 2023
CHMP Co-Rapporteur's updated assessment report circulated on	15 June 2023
Request for supplementary information adopted by the CHMP on	22 June 2023
MAH's responses submitted to the CHMP on	11 July 2023
Re-start of procedure	17 July 2023
CHMP Co-Rapporteur's preliminary assessment report on the MAH's responses circulated on	14 August 2023
CHMP Co-Rapporteur's updated assessment report on the MAH's responses circulated on	7 September 2023
2nd request for supplementary information adopted by the CHMP on	14 September 2023
MAH's responses submitted to the CHMP on	18 September 2023
Re-start of procedure	20 September 2023
CHMP Co-Rapporteur's preliminary assessment report on the MAH's responses circulated on	26 September 2023
CHMP opinion adopted on	12 October 2023

2. Scientific discussion

2.1. Introduction

2.1.1. Problem statement

Disease or condition

The proposed new indication for Keytruda in this procedure is:

"KEYTRUDA, in combination with fluoropyrimidine and platinum-containing chemotherapy, is indicated for the first-line treatment of locally advanced unresectable or metastatic HER2-negative gastric or gastro-oesophageal junction adenocarcinoma in adults."

Epidemiology and risk factors, screening tools/prevention

Gastric cancer remains a major health problem worldwide. Gastric cancer is the fifth most common cancer in the world and the fourth leading cause of cancer death globally [1], with more than 1 million new cases estimated in 2020, resulting in 768,793 deaths [2]. In the EU, the incidences of new cases and mortality for gastric cancer were estimated at 136,038 and 96,997, respectively in 2020 [1]. The highest gastric cancer incidence rates occur in Northeast Asia, South and Central America, and Eastern Europe, with rates being particularly high in Japan and Korea, where gastric cancer is the most commonly diagnosed cancer in men.

Biologic features

The majority of gastric cancers are HER2-negative, with the estimated prevalence of HER2- positive gastric cancer ranging from 6% to 34% [3,4].

Clinical presentation, diagnosis and stage/prognosis

Approximately 37% of new gastric cancer cases are diagnosed at the distant/metastatic stage, contributing to a poor 5-year relative survival rate of 6% [5].

Management

Systemic chemotherapy, with or without immunotherapy, is the mainstay of treatment for advanced and metastatic gastric cancer according to both NCCN and ESMO guidelines. Despite a large number of randomised studies, there is no globally accepted standard 1L chemotherapy regimen in HER2 negative, advanced, unresectable and/or metastatic gastric and GEJ adenocarcinoma. Fluoropyrimidine/platinum doublet regimens containing cisplatin or oxaliplatin and 5-fluorouracil (5-FU) or capecitabine are the most frequently used worldwide as 1L chemotherapy regimens for patients with metastatic gastric/GEJ disease.

The treatment landscape is evolving rapidly with the introduction of immunotherapy combined with standard-of-care chemotherapy regimens in 1L advanced gastric cancer. For example, the combination of nivolumab and fluoropyrimidine- and platinum-containing chemotherapy was recently approved for the treatment of HER2-negative advanced or metastatic gastric, GEJ, and esophageal adenocarcinoma in several regions, including the EU and US [see Table 1]. In the EU, this indication was restricted to patients whose tumours express PD-L1 with a combined positive score (CPS) ≥ 5.

Considering the poor 5-year relative survival rate of 5.5% in metastatic gastric cancer, there continues to be a high unmet medical need for providing new effective and safe therapies for this patient population.

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[1] International Agency for Research on Cancer. Stomach. Lyon (France): International Agency for Research on Cancer (IARC); 2020. 2 p. Available from: https://gco.iarc.fr/today/fact-sheetscancers.
[2] Lordick F, Carneiro F, Cascinu S, Fleitas T, Haustermans K, Piessen G, et al. Gastric cancer: ESMO clinical practice guideline for diagnosis, treatment and follow-up. Ann Oncol. 2022;33(10):1005-20.
[3] Bang YJ, Van Cutsem E, Feyereislova A, Chung HC, Shen L, Sawaki A, et al. Trastuzumab in combination with chemotherapy versus chemotherapy alone for treatment of HER2-positive advanced gastric or gastro-oesophageal junction cancer (ToGA): a phase 3, open-label, randomised controlled trial. Lancet. 2010 Aug 28;376(9742):687-97.
[4] Kelly CM, Janjigian YY. The genomics and therapeutics of HER2-positive gastric cancer-from trastuzumab and beyond. J Gastrointest Oncol. 2016 Oct;7(5):750-762.
[5] Surveillance, Epidemiology, and End Results Program [Internet]. Bethesda (MD): National Cancer Institute (NCI). Cancer stat facts: stomach cancer; [cited 2022 Jul 6]; [about 18 screens]. Available from: https://seer.cancer.gov/statfacts/html/stomach.html.

Table 1 First-Line Therapies for HER2-negative Gastric or GEJ Adenocarcinoma – Preferred Treatment Regimens per NCCN and ESMO Guidelines

Approved Therapies	Median Overall Survival	Median Progression-free Survival	Objective Response Rates	Reference
Fluoropyrimidine (fluorouracil or capecitabine) + Platinum-based chemotherapy (**cisplatin**)	8.8 months[a] 10.5 months[b]	3.9 months[a] 5.6 months[b]	24.5%[a] 46%[b]	Enzinger et al, JCO 2016; Kim et al, EJC 2012
Fluoropyrimidine (fluorouracil or capecitabine) + Platinum-based chemotherapy (**oxaliplatin**)	10.7 months[c] 11.8 months[d] 13.3 months[b]	5.8 months[c] 6.8 months[d] 7.2 months[b] (TTP)	34.8%[c] 54.3%[d] 44%[b]	Enzinger et al, JCO 2016; Kim et al, EJC 2012
Fluoropyrimidine (fluorouracil or capecitabine) + Platinum-based chemotherapy (oxaliplatin) + nivolumab	13.8 months	7.7 months	58%	Moehler et al, JCO 2021

Abbreviations: GEJ = gastroesophageal junction; ESMO = European Society of Medical Oncology; HER2 = human epidermal growth factor receptor 2; NCCN = National Comprehensive Cancer Network; TTP = time to progression.

[a] Metastatic Gastroesophageal Adenocarcinoma
[b] Advanced Gastric Cancer
[c] Metastatic Gastroesophageal Carcinoma
[d] Metastatic Esophageal and Gastroesophageal Junction Cancers

2.1.2. About the product

Pembrolizumab is a highly selective humanized monoclonal antibody that binds to human programmed cell death 1 (PD 1) and blocks the interaction between the PD-1 pathway receptor and its ligands, programmed cell death 1 ligand 1 (PD-L1) and 2 (PD-L2) on antigen presenting tumour cells.

In the EU, pembrolizumab is currently approved (as monotherapy and in combination with other agents) for the treatment of melanoma, non-small cell lung carcinoma (NSCLC), classical Hodgkin lymphoma (cHL), urothelial cancer, head and neck squamous cell carcinoma (HNSCC), renal cell carcinoma (RCC), Microsatellite instability high (MSI-H) or mismatch repair deficient (dMMR) cancers, oesophageal carcinoma, triple negative breast cancer (TNBC), endometrial carcinoma (EC) and cervical cancer.

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.

The applied indication is:

"KEYTRUDA, in combination with fluoropyrimidine and platinum-containing chemotherapy, is indicated for the first-line treatment of locally advanced unresectable or metastatic HER2-negative gastric or gastrooesophageal junction adenocarcinoma in adults", based on study KEYNOTE-859.

The approved indications is:

"KEYTRUDA, in combination with fluoropyrimidine and platinum-containing chemotherapy, is indicated for the first-line treatment of locally advanced unresectable or metastatic HER2-negative gastric or gastro-oesophageal junction adenocarcinoma in adults whose tumours express PD-L1 with a CPS ≥ 1 (see section 5.1). "

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

Regarding the proposed indication, the MAH did not seek Scientific advice at the CHMP. A pre-submission teleconference with EMA and the (Co-)Rapporteurs was held on 02 February 2023.

An overview of the clinical development program for gastric/GEJ adenocarcinoma is provided in Table 2, in section 2.3.1.

2.1.4. General comments on compliance with GCP

The assessment of the clinical study data did not raise any specific concerns questioning GCP compliance.

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

According to the Guideline on the Environmental Risk Assessment of Medicinal Products for Human Use (EMEA/CHMP/SWP/4447/00) proteins are exempted from the submission of ERA studies because they are unlikely to result in significant risk to the environment. Pembrolizumab is a protein, therefore an ERA has not been submitted by the MAH. This is acceptable.

2.3. Clinical aspects

2.3.1. Introduction

GCP

The Clinical trials were performed in accordance with GCP as claimed by the applicant.

The applicant 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 Overview of the Pembrolizumab Clinical Development Program in Gastric or GEJ Adenocarcinoma

Study Number Status	Study Design	Study Population	Number of Participants by Intervention Group	Primary Endpoint(s)
2L +Treatment				
KEYNOTE-012 Final analyses completed	Phase 1B, multicohort, nonrandomized, multicenter	Cohort D: PD-L1 positive Gastric/GEJ adenocarcinoma	Cohort D: Pembrolizumab 10 mg/kg IV Q2W (N=39)	ORR
KEYNOTE-059 Final analyses completed	Phase 2, multisite, nonrandomized, open-label	Recurrent and/or metastatic gastric/GEJ adenocarcinoma; Cohort 1: 3L+, HER2-negative or HER2-positive and previously treated with trastuzumab; Cohorts 2: 1L, HER2-negative Cohort 3: 1L, PD-L1 positive, HER2-negative	Cohort 1: Pembrolizumab 200 mg Q3W (N=259) Cohort 2: Pembrolizumab 200 mg Q3W + cisplatin and 5-FU (or capecitabine in Japan) (N=25) Cohort 3: Pembrolizumab 200 mg Q3W (N=31)	ORR
KEYNOTE-061 Final analyses completed	Phase 3, randomized, open-label, active comparator	Advanced gastric/GEJ adenocarcinoma; HER2-negative or HER2-positive and previously treated with trastuzumab	Pembrolizumab 200 mg Q3W (N=296) OR Paclitaxel 80 mg/m^2 on Days 1, 8, and 15 of every 28-day (4-week) cycle (N=276)	PFS, OS
KEYNOTE-063 Study discontinued [a]	Phase 3, randomized, open-label	Advanced gastric/GEJ adenocarcinoma in Asian subjects; HER2-negative or HER2-positive and previously treated with trastuzumab	Pembrolizumab 200 mg Q3W (N=47) OR Paclitaxel 80 mg/m^2 on Days 1, 8, and 15 of every 28-day (4-week) cycle (N=47)	PFS, OS
1L Treatment				
KEYNOTE-062 Final analyses completed	Phase 3, randomized, active-controlled, partially blinded	Advanced gastric/GEJ adenocarcinoma; HER2-negative	Pembrolizumab 200 mg Q3W (N=254) OR Pembrolizumab 200 mg Q3W+ Cisplatin 80 mg/m^2 Q3W+5-FU 800 mg/m^2/day continuous IV infusion Days 1-5 (120 hours) or capecitabine (in place of 5-FU) 1000 mg/m^2 BID Day1-14 Q3W (N=256) OR Placebo Q3W + cisplatin 80 mg/m^2 Q3W+5-FU 800 mg/m^2/day continuous IV infusion Days 1-5 (120 hours) or capecitabine (in place of 5-FU) 1000 mg/m^2 BID Day 1-14 Q3W (N=250)	PFS, OS
KEYNOTE-659 Final analysis completed	Phase 2b, single-arm, open-label	HER2-negative participants with advanced gastric/GEJ adenocarcinoma in Japan	Cohort 1: Pembrolizumab 200 mg Q3W + oxaliplatin + TS-1 (N=54) Cohort 2: Pembrolizumab 200 mg Q3W + cisplatin + TS-1 (N=46)	ORR
KEYNOTE-811 Ongoing	Phase 3, randomized, double-blind	Unresectable or metastatic HER2-positive gastric/GEJ adenocarcinoma	Pembrolizumab 200 mg Q3W in combination with trastuzumab + cisplatin + 5-FU OR oxaliplatin + capecitabine OR Placebo in combination with trastuzumab + cisplatin + 5-FU OR oxaliplatin + capecitabine (N=738)	PFS, OS
KEYNOTE-859 Ongoing	Phase 3, randomized, double-blind	Unresectable or metastatic HER2-negative gastric/GEJ adenocarcinoma	Pembrolizumab 200 mg Q3W in combination with cisplatin + 5-FU OR oxaliplatin + capecitabine OR Placebo in combination with cisplatin + 5-FU OR oxaliplatin + capecitabine (N=1579)	OS
LEAP-015 Ongoing	Phase 3, randomized, open-label	Participants with advanced or metastatic gastric, GEJ, or esophageal adenocarcinoma	Pembrolizumab 400 mg Q6W x 2 + Lenvatinib 8 mg QD + CAPOX (Q3W) or mFOLFOX (Q2W) (induction), then pembrolizumab 400 mg + lenvatinib 20 mg QD (consolidation) OR CAPOX (Q3W) or mFOLFOX (Q2W) Approximately 890 participants to be enrolled	PFS, OS

Neoadjuvant/Adjuvant Treatment				
KEYNOTE-585 Ongoing	Phase 3, randomized, double-blind	Neoadjuvant/adjuvant treatment for participants with gastric/GEJ adenocarcinoma	Neoadjuvant Combination therapy (3 cycles): Pembrolizumab 200 mg Q3W + cisplatin +5-FU or capecitabine OR Placebo + cisplatin + 5-FU or capecitabine Adjuvant Combination therapy (3 cycles): Pembrolizumab 200 mg Q3W + cisplatin + 5-FU or capecitabine OR Placebo + cisplatin + 5-FU or capecitabine Monotherapy (11 cycles) Pembrolizumab 200 mg Q3W OR Placebo FLOT Safety Cohort Neoadjuvant Combination therapy (3 cycles): Pembrolizumab 200 mg Q3W + FLOT (docetaxel + oxaliplatin + leucovorin) OR Placebo Q3W + FLOT (docetaxel + oxaliplatin + 5-FU + leucovorin [calcium folinate]) FLOT Safety Cohort Adjuvant Combination therapy (3 cycles): Pembrolizumab 200 mg Q3W + FLOT (docetaxel + oxaliplatin + 5-FU + leucovorin) OR Placebo + FLOT (docetaxel + oxaliplatin + 5-FU + leucovorin [calcium folinate]) FLOT Safety Cohort Monotherapy (11 cycles) Pembrolizumab 200 mg Q3W OR Placebo Approximately 800 participants to be enrolled and an additional 200 participants enrolled to FLOT safety cohort.	EFS, OS, pCR

Abbreviations: 1L=first-line; 2L=second-line; 5-FU=5 fluorouracil; BID=dis in die (twice daily); CAPOX=Capecitabine 1000 mg/m^2 BID for 14 days Q3W for 4 cycles + Oxaliplatin 130 mg/m^2 Once Q3W for 4 cycles; CR=complete response; EFS=event-free survival; GEJ=gastroesophageal junction; HER2=human endothelial growth factor receptor 2; IV=intravenous; mFOLFOX=Oxaliplatin 85 mg/m^2 Once Q2W + 5-FU 400 mg/m^2 (bolus) plus 2400 mg/m^2 (continuous) Q2W; N=number; ORR=objective response rate; OS=overall survival; pCR = pathological complete response; PD-L1=Programmed cell death Ligand 1; PFS=progression-free survival; Q2W=every 2 weeks; Q3W= every 3 weeks; TS-1=Tegafur+gimeracil+oteracil.

[a] KEYNOTE-063 was discontinued to enrollment based on efficacy results from a similar study KEYNOTE-061.

2.3.2. Pharmacokinetics

Substantial characterization of the pharmacokinetics (PK) of pembrolizumab had been provided in previous applications as monotherapy and in combination with small molecules or chemotherapy. Therefore, PK and antidrug antibodies (ADA) collection were not planned for study KEYNOTE-859.

The focus of the clinical pharmacology data to support the current submission is on the clinical PK data from participants with advanced gastric or GEJ adenocarcinoma in KEYNOTE-062 (a Phase III clinical trial designed to evaluate the efficacy and safety of pembrolizumab as monotherapy and in combination with cisplatin + 5-FU or cisplatin + capecitabine as 1L treatment in subjects with advanced gastric or GEJ adenocarcinoma).

Pembrolizumab PK data in KEYNOTE-062 was obtained from 502 participants with advanced gastric or GEJ adenocarcinoma treated with pembrolizumab as monotherapy (n=252) or in combination with cisplatin + 5-FU or cisplatin + capecitabine (n=250).

The key clinical pharmacology characteristics are summarized in the current KEYTRUDA EU SmPC.

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 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

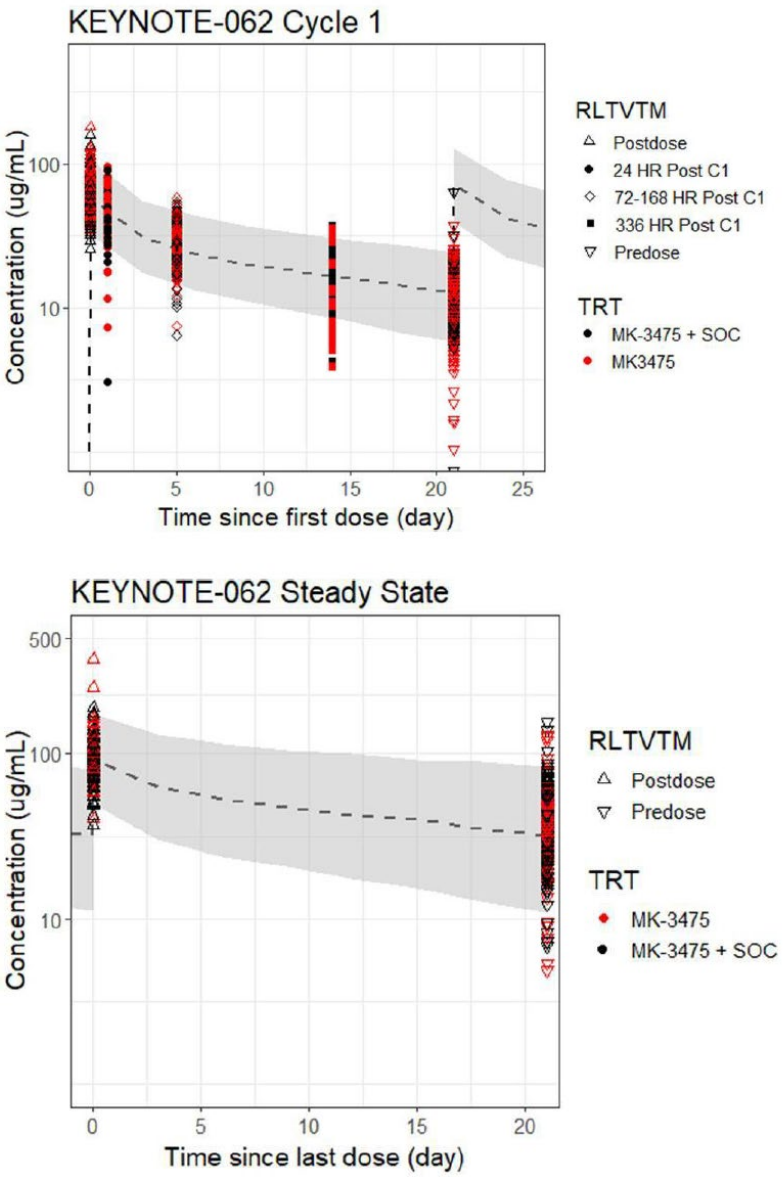
Based on the existing characterization of pembrolizumab PK, a comparison of observed PK for advanced gastric or GEJ adenocarcinoma with the predictions from the historical reference PK model developed with pembrolizumab monotherapy data was provided.

The observed and predicted pembrolizumab concentration-time profiles following 200 mg Q3W administration at Cycle 1 and at Steady State (at or after Cycle 8) are illustrated in Figure 1 with the observed concentrations from KEYNOTE-062 overlaid on the model predicted median concentrations and 90% prediction interval (PI).

The PK in subjects with advanced gastric or GEJ adenocarcinoma follows a similar profile as predicted based on the PK reference model over the dosing interval, in both Cycle 1 and Steady State. The majority of the observed PK data are contained within the 90% PI based on the PK reference model.

In addition, observed pembrolizumab serum concentration values in KEYNOTE-062 are found to be consistent with other globally approved studies in different cancer indications (KEYNOTE-024 in NSCLC, KEYNOTE-045 and KEYNOTE-052 in UC, KEYNOTE-048 and KEYNOTE-055 in HNSCC, KEYNOTE-087 in cHL, KEYNOTE-158 in MSI-H nonCRC, KEYNOTE-164 and KEYNOTE-177 in MSI-H-CRC) following administration of 200 mg Q3W as shown in Table 3 and Figure 2.

Figure 1 Observed Concentration Data in KEYNOTE-062 Subjects Receiving Pembrolizumab 200 mg Q3W as Monotherapy or in Combination with Standard of Care Treatment (Stratified by Treatment) with Reference Model-Predicted Pharmacokinetic Profile for 200 mg Q3W Dose Regimen at Cycle 1 and Steady State



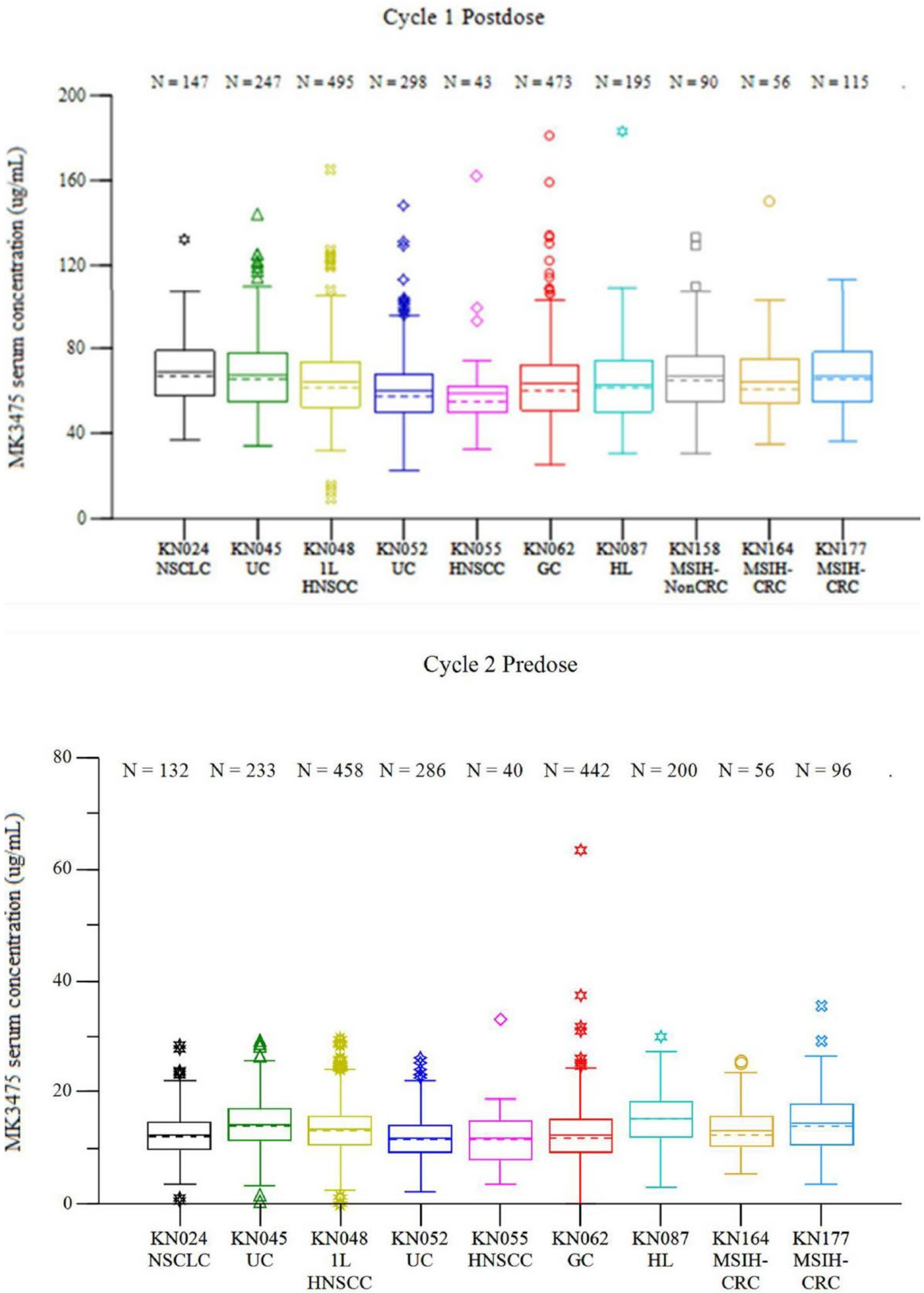
Note: Pembrolizumab at first dose and steady state (at and after Cycle 8) on log scale. Symbols are individual observed data within 24 hours prior to dosing (Predose), at approximately 30 minutes after the end of the infusion (Postdose), at 24 hours after cycle 1 dose (24 HR Post C1), between 72 to 168 hours after cycle 1 dose (72-168 HR Post C1), and at 336 hours after cycle 1 dose (336 HR Post C1) from subjects in KEYNOTE-062. Black dashed line is median predicted concentrations from the model for a regimen of 200 mg Q3W monotherapy and the grey shaded area represents the 90% prediction interval.
RLTVTM= Relative time to dose; TRT=Treatment; SOC= Standard of Care (for KEYNOTE-062: cisplatin + 5-FU or cisplatin + capecitabine).

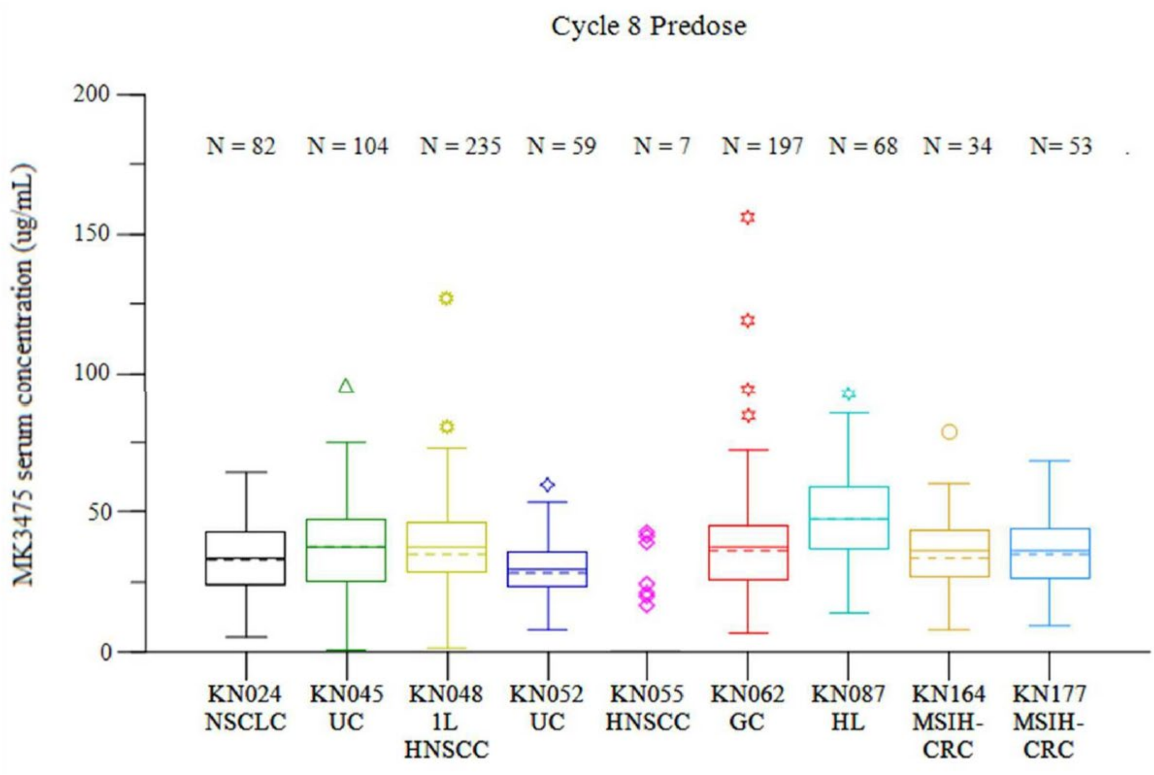
Table 3 Summary Statistics of Observed Pembrolizumab Concentrations at Cycle 1 Postdose, Cycle 2 and Cycle 8 (Steady State) Predose in Various Monotherapy Trials (KEYNOTE-024, -045, -048, -052, -055, -087, -158, -164, -177) and KEYNOTE-062

Time point	dose	Study / Indication	N	GM(CV%) (µg/mL)	AM(SD) (µg/mL)	Min (µg/mL)	Median (µg/mL)	Max (µg/mL)
Cycle 1 Postdose	200mg	KN024 NSCLC	147	67.5 (23)	69.3 (16)	36.6	66.8	132
	200mg	KN045 UC	247	65.7 (26)	67.9 (18)	33.9	65.9	144
	200mg	KN048 1L HNSCC	495	61.8 (29)	64.2 (18)	9.48	61.7	165
	200mg	KN052 UC	298	58.0 (28)	60.2 (17)	22.8	57.4	148
	200mg	KN055 HNSCC	43	56.5 (28)	58.9 (21)	33.1	54.9	162
	200mg	KN062 GC	473	61.5 (26)	63.6 (18)	25.8	60.3	181
	200mg	KN087 HL	195	60.7 (28)	63.1 (18)	31.2	61.3	183
	200mg	KN158 MSIH-NonCRC	90	64.4 (27)	66.7 (18)	31.2	65.2	133
	200mg	KN164 MSIH-CRC	56	62.2 (28)	64.6 (19)	34.9	61.2	150
	200mg	KN177 MSIH-CRC	115	65.0 (26)	67.1 (17)	36.4	65.7	113
Cycle 2 Predose	200mg	KN024 NSCLC	132	11.1 (54)	12.3 (4.7)	0.535	12.2	28.5
	200mg	KN045 UC	233	13.1 (47)	14.2 (4.9)	0.475	13.9	29.3
	200mg	KN048 1L HNSCC	458		13.4 (4.6)	0.00	13.2	29.6
	200mg	KN052 UC	286	11.1 (42)	11.9 (4.4)	2.07	11.5	26.2
	200mg	KN055 HNSCC	40	10.7 (47)	11.8 (5.2)	3.45	11.6	33.1
	200mg	KN062 GC	442		12.4 (5.5)	0.00	11.7	63.4
	200mg	KN087 HL	200	14.4 (40)	15.4 (5.1)	3.06	15.3	30.0
	200mg	KN164 MSIH-CRC	56	12.5 (35)	13.2 (4.6)	5.44	12.4	25.6
	200mg	KN177 MSIH-CRC	96	13.2 (46)	14.4 (5.9)	3.64	13.9	35.5
Cycle 8 Predose	200mg	KN024 NSCLC	82	30.6 (50)	33.6 (13)	5.26	32.7	64.1
	200mg	KN045 UC	104	33.4 (64)	37.8 (17)	1.13	37.5	95.6
	200mg	KN048 1L HNSCC	235	34.2 (50)	37.5 (15)	1.77	34.8	127
	200mg	KN052 UC	59	28.0 (38)	29.9 (10)	8.15	27.9	59.8
	200mg	KN055 HNSCC	7	27.8 (41)	29.6 (11)	16.8	24.5	43.3
	200mg	KN062 GC	197	34.1 (47)	37.5 (18)	6.88	35.9	156
	200mg	KN087 HL	68	43.9 (43)	47.4 (17)	13.9	47.5	92.4
	200mg	KN164 MSIH-CRC	34	33.6 (43)	36.2 (14)	8.40	33.7	78.8
	200mg	KN177 MSIH-CRC	53	32.9 (49)	36.2 (15)	9.76	34.7	68.5

GM = Geometric Mean; %CV = Geometric Coefficient of Variation; AM = Arithmetic Mean; SD = Standard Deviation; NSCLC = non-small cell lung cancer; UC = urothelial cancer; HNSCC = head and neck squamous cell carcinoma;
HL = Hodgkin lymphoma; MSIH CRC= micro satellite instability high cancer colorectal cancer; GC = Gastric Cancer

Figure 2 Observed Pembrolizumab Concentrations at Cycle 1 Postdose and Predose Cycle 2 and Cycle 8 (Steady State) in Various Monotherapy Trials (KEYNOTE-024, -045, -048, -052, -055, -087, -158, -164, -177) and KEYNOTE-062





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.

Dose regimen

The 200 mg Q3W dosing regimen is approved for use in multiple indications globally as monotherapy as well as in combination with small molecule or chemotherapy based on a large, integrated body of evidence at this dose level across indications. An additional dosing regimen of 400 mg Q6W has been approved in the US and EU for all adult indications in the monotherapy and combination therapy settings. These approvals were mainly supported by a modelling and simulation-based approach, bridging PK and exposure/dose-response (E-R) data, and by clinical efficacy, safety, and PK data from KEYNOTE-555, Cohort B study.

2.3.4. PK/PD modelling

No new information regarding PK/PD modelling for pembrolizumab is available within this application.

Immunogenicity

No new ADA data are provided in this submission based on the characterization of immunogenicity potential with trials in monotherapy setting.

2.3.5. Discussion on clinical pharmacology

Clinical pharmacology results in support of the current extension of indication of pembrolizumab in combination with chemotherapy for the treatment of advanced gastric or GEJ adenocarcinoma are provided from Study KEYNOTE-062. PK data in KEYNOTE-062 was obtained from 502 participants with advanced gastric or GEJ adenocarcinoma treated with pembrolizumab as monotherapy (n=252) or in combination with cisplatin + 5-FU or cisplatin + capecitabine (n=250).

The MAH provided a comparison between the observed PK data in KEYNOTE-062 and the predictions from the historical reference PK model that had been developed with pembrolizumab monotherapy data.

The observed and predicted pembrolizumab concentration-time profiles following 200 mg Q3W administration at Cycle 1 and at Steady State (at or after Cycle 8) overlaid on the model predicted median concentrations and 90% prediction interval (PI). The PK in subjects with advanced gastric or GEJ adenocarcinoma followed a similar profile as predicted based on the PK reference model over the dosing interval, in both Cycle 1 and Steady State. The majority of the observed PK data were contained within the 90% PI based on the PK reference model.

In addition, observed pembrolizumab serum concentration values in KEYNOTE- 062 were found to be consistent with other globally approved studies in different cancer indications following administration of 200 mg Q3W.

In view of the robust characterization of immunogenicity it is considered acceptable that no new immunogenicity data have been provided to support the current application.

Overall, the PK data from KEYNOTE-062 are supportive of the proposed pembrolizumab dose of 200 mg Q3W for the 1L treatment of locally advanced unresectable or metastatic HER2-negative gastric or GEJ adenocarcinoma in adults. Given the integrated body of evidence, the 400 mg Q6W dosing regimen is expected to have a similar benefit-risk profile as 200 mg Q3W and can be accepted as an additional dosing regimen also for the 1L treatment of locally advanced unresectable or metastatic HER2-negative gastric or GEJ adenocarcinoma in combination with fluoropyrimidine- and platinum-containing chemotherapy.

2.3.6. Conclusions on clinical pharmacology

Overall, the PK in participants with advanced gastric or GEJ adenocarcinoma as shown with KEYNOTE-062 data is generally consistent with monotherapy PK, as previously established.

Given the totality of data available from KEYNOTE-062 and the similarity between KEYNOTE-062 and KEYNOTE-859 study populations and treatments, pembrolizumab PK characterization in KEYNOTE-062 is considered suitable to be extended to KEYNOTE-859 population.

2.4. Clinical efficacy

2.4.1. Dose response study

No dose response studies were included in this application.

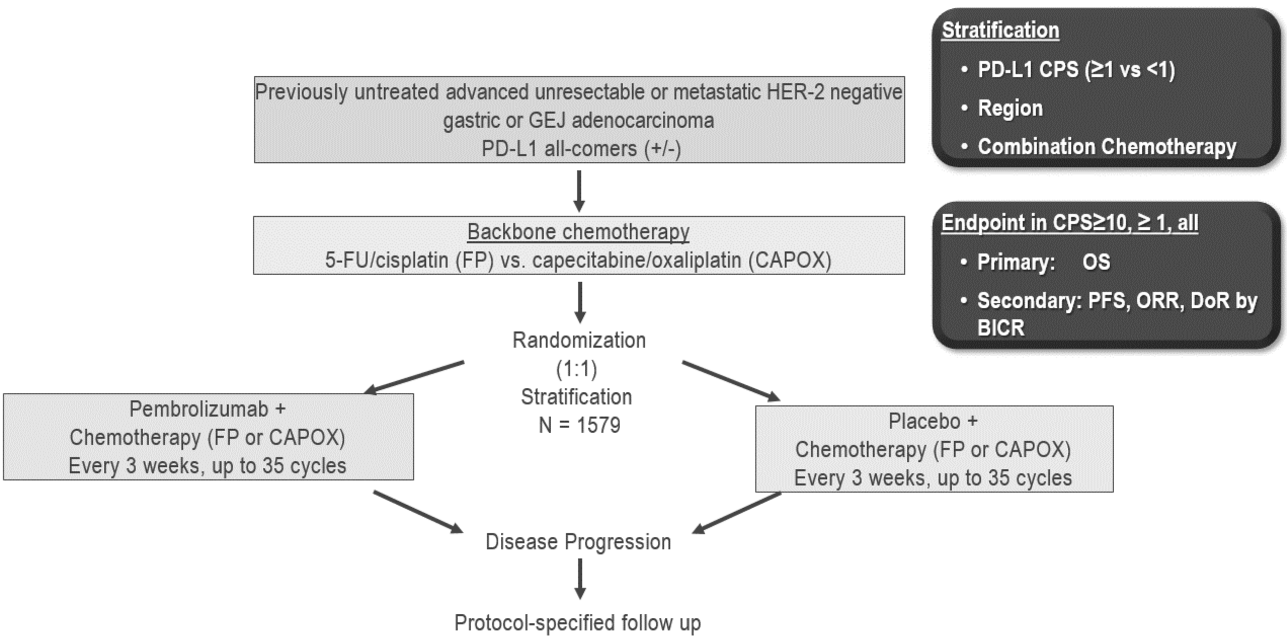
2.4.2. Main study

Title of Study - KEYNOTE-859

A Phase 3, randomised, double-blind clinical study of pembrolizumab (MK-3475) plus chemotherapy versus placebo plus chemotherapy as first-line treatment in participants with HER2 negative, previously untreated, unresectable or metastatic gastric or gastroesophageal junction adenocarcinoma

Methods

Figure 3 KEYNOTE-859 Study Design



HER2=human epidermal growth factor receptor 2; GEJ=gastroesophageal junction; CAPOX=capecitabine and oxaliplatin; FP=cisplatin and 5-fluorouracil; PD-L1=programmed cell death-1 ligand-1; CPS=combined positive score; OS=overall survival; PFS=progression free survival; ORR=objective response rate; DoR=duration of response; BICR=blinded independent central review

The 2 chemotherapy regimen choices, FP or CAPOX, had to be chosen before randomisation in the study. Participants were stratified by PD-L1 tumour expression status (CPS <1, ≥1), combination chemotherapy (FP or CAPOX), and geographic region (Europe/Israel/North America/Australia vs Asia vs Rest of the World [including South America]). The study was double-blind with respect to randomised study intervention (pembrolizumab/placebo). Participants continued on the type of chemotherapy regimen chosen before randomisation throughout the study.

Imaging was performed every 6 weeks (± 7 days) after randomisation to assess response to treatment using RECIST 1.1.

Study participants

Main inclusion criteria:

- Had histologically or cytologically confirmed diagnosis of locally advanced unresectable or metastatic gastric or GEJ adenocarcinoma, with known PD-L1 expression status.
- Had HER2-negative cancer.
- Was at least 18 years of age at the time of providing documented informed consent (or acceptable age according to local regulations, whichever is older).
- Had measurable disease per RECIST 1.1 as assessed by investigator assessment. Lesions situated in a previously irradiated area are considered measurable if progression has been demonstrated in such lesions.
- Had provided archival tumour tissue sample or newly obtained core, incisional or excisional biopsy of a tumour lesion not previously irradiated.
- Had provided tumour tissue sample deemed adequate for PD-L1 biomarker analysis.
- Had provided tumour tissue sample for MSI biomarker analysis.
- Had an ECOG performance status of 0 or 1 (within 3 days prior to the start of study intervention).
- Had adequate organ function (as defined in the protocol)
- Had to agree to follow contraceptive guidance

Main exclusion criteria:

- Had squamous cell or undifferentiated gastric cancer.
- Had major surgery, open biopsy, or significant traumatic injury within 28 days prior to randomisation, or anticipation of the need for major surgery during the course of study intervention.
- Had pre-existing peripheral neuropathy >Grade 1.
- Had previous therapy for locally advanced, unresectable or metastatic gastric/GEJ cancer. Participants may have received prior neoadjuvant and/or adjuvant therapy as long as it was completed at least 6 months prior to randomisation.
- Received prior therapy with an anti-PD-1, anti-PD-L1, or anti-PD-L2 agent or with an agent directed to another stimulatory or coinhibitory T-cell receptor (e.g., CTLA-4, OX 40, CD137).
- Had received a live vaccine within 30 days prior to the first dose of study intervention.
- Had a diagnosis of immunodeficiency or is receiving chronic systemic steroid therapy (≥10 mg daily of prednisone equivalent) or any other form of immunosuppressive therapy within 7 days prior to the first dose of study intervention.
- Had an active autoimmune disease that had required systemic treatment in past 2 years.
- Had a history of (non-infectious) pneumonitis that required steroids or had current pneumonitis.
- Had known active CNS metastases and/or carcinomatous meningitis. Participants with previously treated, stable brain metastases without requirement of steroid treatment were allowed to participate.
- Had an active infection requiring systemic therapy.

Biomarker evaluation

According to the protocol all participants were required to supply a tumour tissue specimen. Newly obtained endoscopic biopsy or core biopsy of a metastatic site, if obtained as part of normal clinical practice, was preferred to archived samples. Both formalin solution and formalin-fixed, paraffin embedded (FFPE) block specimens were acceptable. If submitting unstained slides, newly cut slides should have been received by the testing laboratory within 14 days from the date slides are cut, otherwise a new specimen was requested.

HER2 testing

HER2 negative was defined as: IHC (0, or 1+) or fluorescence in situ hybridization (FISH) negative (HER2:CEP17 ratio <2 with an average *HER2* copy number <4.0 signals/cell). FISH could be replaced with locally available in situ hybridization (ISH) methods acceptable as per institutional guidelines (e.g., DISH).

HER2 testing was conducted either by local or central testing laboratory. *HER2* assay for local testing was clinical instruction's choice. The assays used for *HER2* central laboratory testing were the FDA-approved and EU-CE Marked Dako (Agilent) HercepTest (IHC) and Dako (Agilent) HER2 IQFISH pharmDx Kit (Reflex FISH testing for *HER2* IHC 2+ samples).

PD-L1 testing

Per inclusion criteria all participants needed to provide tumour tissue sample deemed adequate for PD-L1 biomarker analysis and tumour PD-L1 expression status had to be available prior to randomisation.

The assay used for tumour PD-L1 testing was the Agilent PD-L1 IHC 22C3 pharmDx kit and testing was conducted at a central laboratory. This kit has been analytically validated to determine PD-L1 expression status in gastric tumours.

MSI biomarker analysis

Both tumour tissue samples and blood will be collected for MSI analyses and are required to perform central MSI testing by polymerase chain reaction (PCR). In order to perform MSI analysis by PCR, blood and tumour tissue was required. A blood sample was collected to extract normal DNA for comparison testing to tumour DNA in MSI analysis.

Treatments

Table 4 Study Intervention

Group Name	Intervention Name	Dose Strength	Dose Frequency	Route of Admin	Use
Pembrolizumab	Pembrolizumab (MK-3475)	200 mg on Day 1 of each cycle	Q3W	IV	Experimental
Placebo	Placebo	Day 1 of each cycle	Q3W	IV	Placebo
Backbone chemotherapy					
FP	Cisplatin	80 mg/m^2 on Day 1 of each cycle	Q3W*	IV	Comparator regimen and combination agent
	5-FU	800 mg/m^2/day continuous on Days 1 to 5 of each cycle (120 hours, or per local standard)	Q3W	IV	Comparator regimen and combination agent
CAPOX	Oxaliplatin	130 mg/m^2 on Day 1 of each cycle	Q3W*	IV	Comparator regimen and combination agent
	Capecitabine	1000 mg/m^2 twice daily on Days 1 to 14 of each cycle	Q3W	Oral	Comparator regimen and combination agent

5-FU=5-fluorouracil; Admin=administration; CAPOX=capecitabine and oxaliplatin; FP=cisplatin and 5-fluorouracil; IV=intravenous; Q3W=every 3 weeks

*Duration of cisplatin or oxaliplatin treatment may be capped at 6 cycles as per local country guidelines; however, treatment with 5-FU/capecitabine may continue per protocol.

Investigator decision regarding the type of backbone chemotherapy (FP or CAPOX) should be determined prior to randomization.

Participants should continue on the type of backbone chemotherapy chosen prior to randomization throughout the study. Exceptions may be permitted after consultation with the Sponsor.

Participants who are randomized to placebo are not allowed to crossover to pembrolizumab treatment.

Pembrolizumab or placebo had to be administered as a 30-minute IV infusion Q3W (-5 min/+10 min).

Study intervention administration continued until confirmed progressive disease (PD) by BICR, unacceptable AE(s), intercurrent illness that prevented further administration of treatment, investigator's decision to discontinue the participant, administrative reasons requiring cessation of treatment, or until the participant had received 35 administrations (approximately 2 years) of treatment. The investigator could elect to implement modified RECIST 1.1 for immune-based therapeutics (iRECIST).

Objectives

Primary and secondary efficacy objectives were evaluated in participants with **PD-L1 CPS ≥10**, **PD-L1 CPS ≥1**, and in **all participants** following administration of pembrolizumab versus placebo when each is combined with chemotherapy:

Primary efficacy objective:

- To compare the **OS**

Secondary efficacy objectives:

- To compare the **PFS** per RECIST 1.1, as assessed by BICR
- To compare the **ORR** per RECIST 1.1, as assessed by BICR
- To describe the **DOR** per RECIST 1.1, as assessed by BICR

Tertiary/Exploratory objective:

- To compare the changes from baseline in **health-related quality-of-life** assessments, using the EORTC-QLQ C30 and the EORTC-QLQ STO22
- To characterize utilities, using the EQ-5D™
- To compare PFS and ORR using modified RECIST 1.1 for iRECIST
- To identify molecular (genomic, metabolic, and/or proteomic) biomarkers that may be indicative of clinical response/resistance, safety, pharmacodynamic activity, and/or the mechanism of action of pembrolizumab and other treatments (Germline genetic variation, genetic (DNA) mutations from tumour, tumour and blood RNA variation, proteomics and IHC, and other biomarkers)

Outcomes/endpoints

Primary efficacy endpoint:

OS, defined as the time from randomisation to death due to any cause.

Secondary endpoints:

PFS, defined as the time from randomisation to the first documented disease progression as measured by BICR per RECIST 1.1 or death due to any cause, whichever occurs first.

ORR, defined as the proportion of participants in the analysis population who had a response (CR or PR) as measured by BICR per RECIST 1.1.

DOR, defined as the time from the first documented evidence of CR or PR until disease progression or death due to any cause, whichever occurred first.

Sample size

The overall sample size of the study (i.e., all participants) was planned to be approximately 1579. The sample size for the CPS ≥10 participants was projected to be ~551 based on a prevalence rate of ~ 35% of the CPS ≥10 participants among all participants. The sample size of the CPS ≥1 participants was projected to be ~ 1235 based on a prevalence rate of ~ 78% of the CPS ≥1 participants among all participants.

Sample size calculation

To account for the potential delayed treatment effect, a piecewise hazard ratio (HR) was assumed for both PFS and OS in subpopulations of CPS ≥10, 1≤ CPS ≤9, and CPS <1 with HR=1 in the delayed period and HR <1 afterwards. The CPS ≥1 population comprised of the subpopulations of CPS ≥10 and 1≤ CPS ≤9 combined; the all participants population comprised of the subpopulations of CPS ≥10, 1≤ CPS ≤9, and CPS <1 combined. Based on HRs assumed for OS and PFS, an average hazard ratio (AHR) at the planed final analysis time (~43 months for PFS and ~54 months for OS) was estimated for each study population: CPS ≥10, CPS ≥1, and all participants. The AHR is the geometric mean of the underlying piecewise hazard ratio in each interval weighted by the expected number of events observed in the interval.

Overall Survival

Given the above assumptions, the study has ~ 87% power for detecting an AHR=0.73 in CPS ≥10 participants with 463 OS events at the final analysis (expected ~54 months) with an initially assigned 0.017 (1-sided) significance level.

It was assumed that there will be ~ 1057 OS events in CPS ≥1 participants at the OS final analysis. With 1057 OS events, the study has ~ 90% power for detecting an AHR=0.81 in CPS ≥1 participants at the final analysis (expected ~54 months) with an (1-sided) significance level of 0.017 (alpha=0.017 can be passed from H1 to H2 if H1 is rejected).

It was estimated that there will be ~ 1358 OS events in all participants at the OS final analysis. With 1358 OS events, the study has ~ 84% power for detecting an AHR=0.83 in all participants at the final analysis (expected ~54 months) with an initially assigned 0.008 (1-sided) significance level.

Progression Free Survival

It was estimated that there will be ~ 478 events in CPS ≥10 participants at the PFS analysis (i.e., the interim analysis of the study). With 478 PFS events, the study has ~ 99% power for detecting an AHR=0.68 in CPS ≥10 participants at 0.025 (1-sided) significance level (after H1, H2, and H3 are all rejected).

It was assumed that there will be ~ 1095 events in CPS ≥1 participants at the PFS analysis. With 1095 PFS events, the study has ~ 99% power for detecting an AHR=0.78 in CPS ≥1 participants at a significance level of 0.025 (1-sided) if H1 to H4 were previously rejected.

It was assumed that there will be ~ 1407 events in all participants at the PFS analysis. With 1407 PFS events, the study has ~ 98% power for detecting an AHR=0.80 in all participants at a significance level of 0.025 (1-sided) if H1 to H5 were previously rejected.

Overall Response Rate

With the planned sample size of ~ 551 randomised for CPS ≥10 participants, the study has ~99% power to detect a difference of 20% in ORR (37% ORR in the control arm and 57% ORR in the experimental arm in CPS ≥10 participants) under alpha=0.025 after H1 to H6 were previously rejected. The ORR difference required for significance of H7 is ~ 8.3% under alpha=0.025.

With the planned sample size of ~ 1235 randomised for CPS ≥1 participants, the study has ~ 99% power to detect a difference of 16% in ORR (37% ORR in the control arm and 53% ORR in the experimental arm in CPS ≥1 participants) under alpha=0.025 after H1 to H7 were previously rejected. The ORR difference required for significance of H8 is ~ 5.5% under alpha=0.025.

With the planned sample size of ~1579 randomised for all participants, the study has ~99% power to detect a difference of 13% in ORR (37% ORR in the control arm and 50% in the experimental arm in all participants) under alpha=0.025 after H1 to H8 were previously rejected. The ORR difference required for significance of H9 is ~ 4.9% under alpha=0.025. Randomisation

Treatment allocation/randomisation occurred centrally using an interactive response technology (IRT) system. Participants were assigned randomly in a 1:1 ratio to pembrolizumab or placebo, respectively. Participants were stratified by geographic region (Europe/Israel/North America/Australia, Asia or Rest of the World (including South America)), PD-L1 tumour expression status (CPS <1 or ≥1), and combination chemotherapy (FP or CAPOX), which was chosen prior to randomisation in the study. There were 12 combinations of categories of all stratification factors (3 × 2 × 2=12 strata). Within each stratum, the block size of 4 was used.

Blinding (masking)

The trial was double-blinded. Pembrolizumab and placebo were prepared and/or dispensed in a blinded fashion by an unblinded pharmacist or qualified study site personnel. PD-L1 expression was masked to the site.

An external DMC served as the primary reviewer of the results of the interim analysis (or potential safety analyses) of the study and made recommendations for discontinuation of the study or protocol modifications to the Sponsor. If the DMC recommended modifications to the design of the protocol or discontinuation of the study, this executive committee (and potentially other limited Sponsor personnel) may be unblinded to results at the treatment-level in order to act on these recommendations. The extent to which individuals were unblinded with respect to results of interim analyses was to be documented. Additional logistical details were to be provided in the DMC Charter. Treatment-level results from the interim analysis were provided to the DMC by the external unblinded statistician. Prior to final study unblinding, the external unblinded statistician was not to be involved in any discussions regarding modifications to the protocol, statistical methods.

Statistical methods

Analysis population

The Intent-to-Treat (ITT) population was defined as all randomised participants, whether or not treatment was administered. The ITT was the primary analysis population for efficacy endpoints.

The safety analysis population 'all participants as treated' (APaT) was defined as all randomised participants who received at least 1 dose of study intervention. The APaT was used for safety analyses.

Analysis method and censoring rules

The analysis strategy for key efficacy endpoints is displayed in the following table:

Table 5 Analysis Strategy for Key Efficacy Endpoints

Endpoint	Statistical Method [a]	Analysis Population	Missing Data Approach
Primary Endpoint			
OS	Test: Stratified log-rank test Estimation: Stratified Cox model with Efron's tie handling method	ITT (CPS ≥10, CPS ≥1, and all participants)	Censored at the last known alive date
Key Secondary Endpoints			
PFS per RECIST 1.1 by BICR	Test: Stratified log-rank test Estimation: Stratified Cox model with Efron's tie handling method	ITT (CPS ≥10, CPS ≥1, and all participants)	• Primary censoring rule • Sensitivity analysis 1 • Sensitivity analysis 2 (More details are provided in Table 16, Censoring Rules for Primary and Sensitivity Analyses of PFS)
ORR per RECIST 1.1 by BICR	Test and Estimation: Stratified M&N method with sample size weight	ITT (CPS ≥10, CPS ≥1, and all participants)	Participants without assessments are considered nonresponders and conservatively included in the denominator

BICR=blinded independent central review; CPS=combined positive score; ITT=Intention-to-Treat; M&N=Miettinen and Numinen; ORR=objective response rate; OS=overall survival; PFS=progression-free survival; RECIST=Response Evaluation Criteria in Solid Tumors

a. Statistical models are described in further detail in the text. For stratified analyses, the stratification factors used for randomization (Section 6.3.2) will be applied to the analysis. Small strata will be combined in a way specified by a blinded statistician prior to the analysis.

For PFS, the date of disease progression was approximated by the date of the first assessment of PD per RECIST 1.1 by BICR. Death was considered as a PD event. The following censoring rules were applied for the primary and sensitivity analyses:

Table 6 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 therapy, if any	Progressed at date of documented PD or death	Progressed at date of documented PD or death	Progressed at date of documented PD or death
PD or death documented immediately after ≥2 consecutive missed disease assessments or after new anticancer therapy, if any	Censored at last disease assessment prior to the earlier date of ≥2 consecutive missed disease assessment and new anticancer therapy, 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 intervention or completed study intervention
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

PD=progressive disease; PFS=progression-free survival

Stratified analyses were based on collapsed strata by combining strata with small number of participants or events. The collapsed strata will be based on blinded data taking into considerations of both clinical relevance and actual counts of subjects/events.

Interim Analysis

One interim analysis was planned for the study. It was planned to be performed after approximately 403 OS events have occurred in CPS ≥ 10 participants and approximately 12 months after the last participant was randomised. An interim analysis for OS and final analysis for PFS and ORR was planned for the interim analysis.

The following tables show the Lan-DeMets O'Brien-Fleming spending function based on the predicted number of events at the planned time of analysis:

Table 7 Efficacy Boundaries and Properties for OS Analysis in CPS≥10 Participants

Analysis	Value	α=0.017	α=0.025
IA: 87% [a] N: 551 Events: 403 Month: 43	Z	2.3072	2.1373
	p (1-sided)[b]	0.0105	0.0163
	HR at bound [c]	0.7946	0.8082
	Power [d]	0.7326	0.7854
Final N: 551 Events: 463 Month: 54	Z	2.1969	2.0449
	p (1-sided)[b]	0.0140	0.0204
	HR at bound [c]	0.8153	0.8269
	Power [d]	0.8723	0.9018

HR=hazard ratio; IA=interim analysis; OS=overall survival
a. Percentage of expected number of events at final analysis
b. The nominal α for testing
c. HR at bound is the approximate HR required to reach an efficacy bound
d. Power is the cumulative probability of crossing a bound under the alternative hypothesis

Table 8 Efficacy Boundaries and Properties for OS Analysis in CPS≥1 Participants

Analysis	Value	α=0.017	α=0.025
IA: 87% [a] N: 1235 Events: 923 Month: 43	Z	2.3028	2.1332
	p (1-sided)[b]	0.0106	0.0165
	HR at bound [c]	0.8593	0.8690
	Power [d]	0.7611	0.8104
Final N: 1235 Events: 1057 Month: 54	Z	2.1977	2.0457
	p (1-sided)[b]	0.0140	0.0204
	HR at bound [c]	0.8736	0.8818
	Power [d]	0.8963	0.9214

HR=hazard ratio; IA=interim analysis; OS=overall survival
a. Percentage of expected number of events at final analysis
b. The nominal α for testing.
c. HR at bound is the approximate HR required to reach an efficacy bound
d. Power is the cumulative probability of crossing a bound under the alternative hypothesis

Table 9 Efficacy Boundaries and Properties for OS Analysis in All Participants

Analysis	Value	α=0.008	α=0.025
IA: 87% [a] N: 1579 Events: 1187 Month: 43	Z	2.6074	2.1316
	p (1-sided)[b]	0.0046	0.0165
	HR at bound [c]	0.8596	0.8836
	Power [d]	0.6545	0.8088
Final N: 1579 Events: 1358 Month: 54	Z	2.4739	2.0460
	p (1-sided)[b]	0.0067	0.0204
	HR at bound [c]	0.8744	0.8949
	Power [d]	0.8355	0.9207

HR=hazard ratio; IA=interim analysis; OS=overall survival
a. Percentage of expected number of events at final analysis
b. The nominal α for testing
c. HR at bound is the approximate HR required to reach an efficacy bound
d. Power is the cumulative probability of crossing a bound under the alternative hypothesis

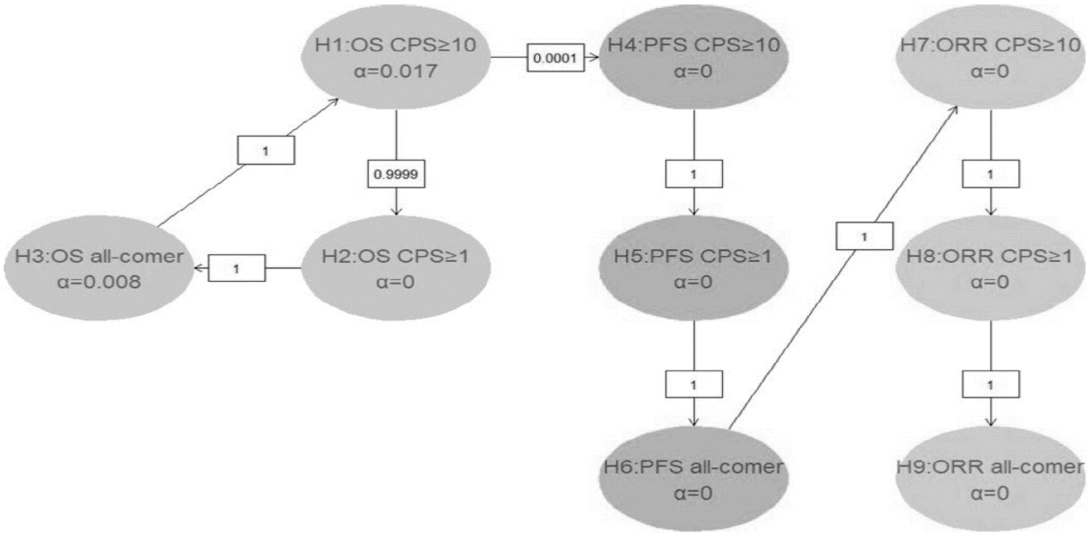
The actual spending function was based the actual information fraction of the observed number of OS events at the interim analyses relative to the expected number of OS events at the final analysis.

Multiplicity

The study used an extension of the graphical method of Maurer and Bretz [Maurer, W. and Bretz, F. 2013] to provide strong multiplicity control for multiple hypotheses while making the interim and final analysis timing be more flexible [Anderson, K. M. 2018]. According to the Maurer and Bretz approach, study hypotheses may be tested in a group sequential fashion, and when a particular null hypothesis is rejected, the alpha allocated to that hypothesis can be reallocated to other hypothesis tests.

The overall type I error at 2.5% (1-sided) was assigned to the primary and secondary endpoints as follows: 1.7% was assigned to OS in CPS >= 10 (H1) and 0.8% to OS in all participants (H3). OS in CPS >= 1 (H2) could be tested with alpha that was recycled once H1 and/or H3 was tested significant. If H1, H2 and H3 were tested significant, then PFS could be tested, followed by ORR.

Figure 4 Multiplicity Strategy

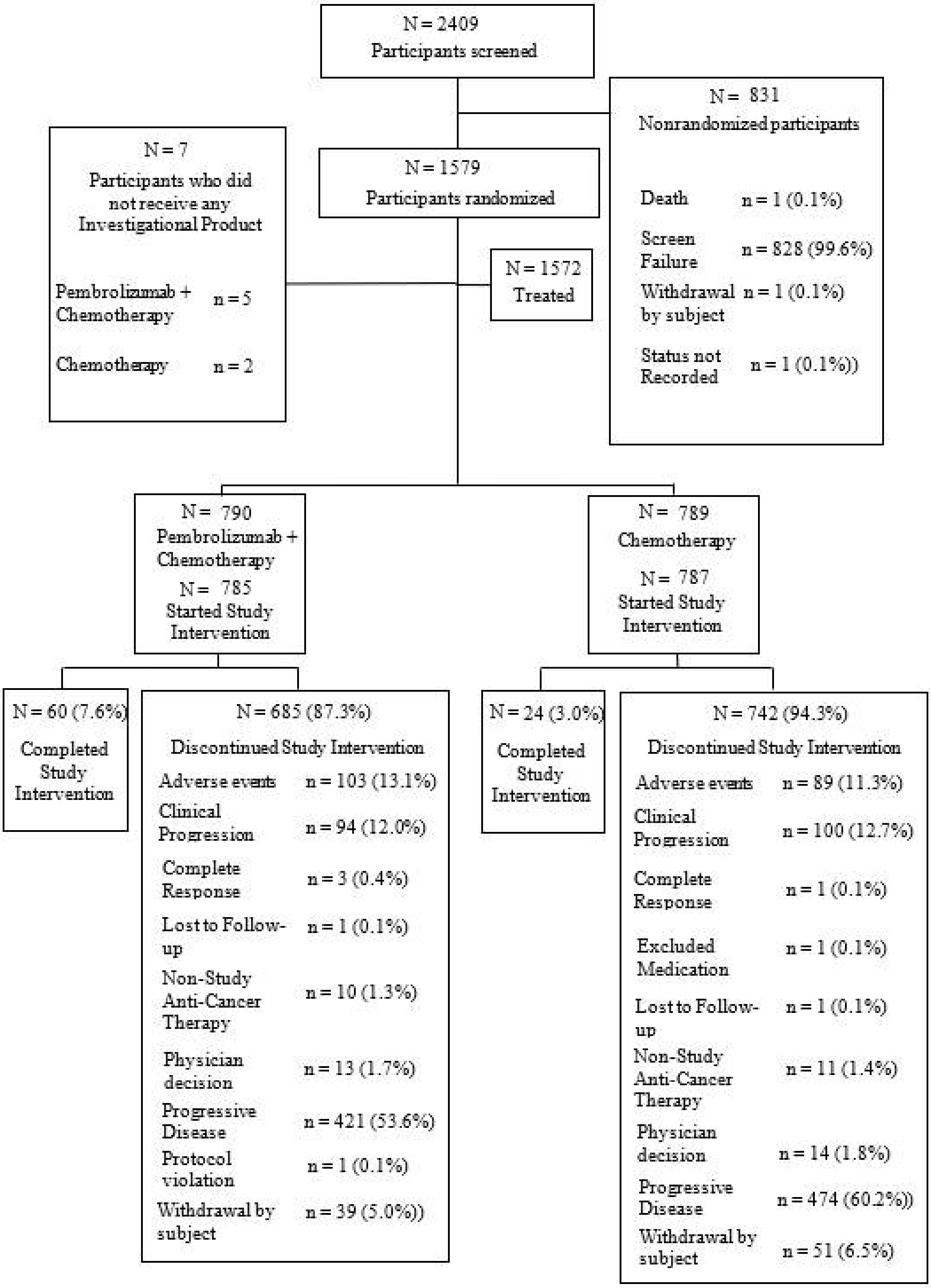


Note: There is no initial alpha assigned to any PFS or ORR hypotheses. The testing for PFS or ORR hypotheses (H4-9) to be performed only at IA after all OS null hypotheses (H1, H2, and H3) are rejected, and the testing alpha bound is 0.025.

Results

Participant flow

Figure 5 CONSORT Diagram Flowchart (ITT Population)



Participants analysed N = 1579; participants excluded from analysis N=0.

About a third of all screened participants were screen failures. The most prevalent reason for screen failure was related to the inclusion criteria of having an adequate organ function, as defined per protocol and collection of specimens within 10 days prior to the start of study intervention.

At the time of DCO (03 Oct 2022), 181 (22.9%) participants were ongoing in the study in the pembrolizumab plus chemotherapy group vs 112 (14.2%) in the chemotherapy group. 40 (5.1%) participants remained on treatment in the pembrolizumab plus chemotherapy group vs 21 (2.7%) participants in the control group.

Follow-up duration

*Table 10 Summary of Follow-up Duration (**ITT** Population)*

Follow-up duration (months)[a]	Pembrolizumab + Chemotherapy (N=790)	Chemotherapy (N=789)	Total (N=1579)
Median (Range)	12.9 (0.2, 45.9)	11.6 (0.1, 45.5)	12.0 (0.1, 45.9)
Mean (SD)	15.5 (10.7)	13.6 (9.6)	14.6 (10.2)

[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: 03OCT2022

*Table 11 Summary of Follow-up Duration (**CPS ≥1** Population)*

Follow-up duration (months)[a]	Pembrolizumab + Chemotherapy (N=618)	Chemotherapy (N=617)	Total (N=1235)
Median (Range)	13.0 (0.2, 45.9)	11.5 (0.1, 45.5)	11.9 (0.1, 45.9)
Mean (SD)	15.7 (11.0)	13.3 (9.5)	14.5 (10.3)

*Table 12 Summary of Follow-up Duration (**CPS ≥10** Population)*

Follow-up duration (months)[a]	Pembrolizumab + Chemotherapy (N=279)	Chemotherapy (N=272)	Total (N=551)
Median (Range)	15.4 (0.4, 45.9)	11.8 (0.3, 45.5)	13.3 (0.3, 45.9)
Mean (SD)	17.7 (11.8)	14.1 (10.4)	16.0 (11.2)

Recruitment

This study was conducted at 215 centres in 33 countries (number of participants)

Asia: China (237), South Korea (150), Japan (101), Taiwan (23), Hong Kong (15)

Western Europe: Spain (67), Poland (62), France (52), UK (53), Ireland (19), Italy (18), Germany (12), Switzerland (11), Denmark (10); Israel (46); North America: USA (33), Canada (18)

Rest of the Word:

- Chile (79), Brazil (71), Guatemala (45), Colombia (39), Mexico (27), Peru (25), Costa Rica (24), Argentina (21)
- Ukraine (99), Russia (45), Hungary (14), Czech Republic (12)
- Turkey (92)
- Australia (27), New Zealand (7)
- South Africa (22)

The first subject was enrolled on **08 Nov 2018**;

The first subject was randomized/treated on **25 Nov 2018**;

The last subject was enrolled on **11 June 2021**;

The last subject was randomized/treated on **24 June 2021**.

This study is ongoing; the data cutoff for the provided first interim analysis was the **03 Oct 2022**.

Conduct of the study

Protocol amendments

Original protocol Version **00** (12 Jul 2018)

- Approximately 780 participants will be randomised.
- The primary efficacy endpoints in this study are OS and PFS.
- One interim analysis is planned in this study after ~539 OS events in all participants and ~11 months after last participant randomised. Primary purpose: efficacy analysis for ORR, PFS, and OS in all participants and in participants with CPS ≥1.
- Final analysis to be performed after ~649 OS events have occurred in all participants, ~386 OS events have occurred in CPS ≥1 participants, and ~22 months after last participant randomised. Primary purpose: efficacy analysis for OS in all participants and participants with CPS ≥1.
- Multiplicity: The overall type I error over the primary and secondary hypotheses is strongly controlled at 2.5% (1-sided), with initially 0.9% to OS in all participants (H1), 1.4% to OS in CPS1 (H2), 0.1% to PFS in all participants (H3), and 0.1% to PFS in CPS1 (H4). By using the graphical approach of Mauer and Bretz, if one hypothesis is rejected, the alpha will be shifted to other hypotheses.

Protocol Amendment Version **01** (20 Nov 2018)

Clarified inclusion/exclusion criteria and updated country-specific requirements

Protocol Amendment Version **02** (12 Dec 2019)

- Changed the hypotheses of the study:
  - added PFS/OS/ORR hypotheses in PD-L1 CPS ≥10 population (CPS ≥10 becomes the primary analysis Population)
  - added a primary OS objective for MSI-high, conditional upon meeting enrolment target.

Rationale: Refocus study on patient population thought to have an increased likelihood of response. Study redesign informed by recent study results with pembrolizumab. Clinically meaningful improvement in ORR, DOR, and PFS was observed in CPS ≥10 participants.

- Changed target enrolment from 780 to 1542 participants.

Rationale: Study is powered for PD-L1 CPS ≥10 population and enrolment duration is now driven by PD-L1 CPS ≥10 population, as a result, the target enrolment in PD-L1 all-comer population is increased.

- Duration of study changed from 5.5 years to 6 years.

Rationale: Updated duration of study based upon increased target enrolment of 1542 participants.

- Changed the Interim Analysis, Multiplicity, and Power and Sample Size with new design details.
    1. Updated interim/final analysis timing.
    2. Updated alpha passing strategy.
    3. Updated efficacy boundaries and properties.

Rationale:

1. The primary analysis population is changed to PD-L1 CPS ≥10 (then step down to CPS ≥1, then further to all participants) and thus reaching targeted number of events in PD-L1 CPS ≥10 population together with the minimum follow-up requirement will drive timing of the analysis in the new design.
2. The alpha passing strategy was updated to account for new hypotheses added in CPS ≥10 population and MSI-H population and allow for alpha to be stepped down to CPS ≥1 and further to all participants should preceding hypothesis is positive.
3. The efficacy boundary and properties were updated to reflect the change in hypotheses and in the alpha splitting/passing strategy.
4. Underlying assumption for treatment effect size was updated due potential delayed treatment effect in both PFS and OS; as a result, power and sample size calculations were updated.

- Added additional subgroup analyses variables (ECOG, Disease status, Primary location, and Histologic subtype).

<u>Protocol Amendment Version **03**</u> (11 Jan 2021)

- Moved PFS objectives and hypotheses (H4, H5, and H6) from the primary hypothesis to the secondary objectives.
- Eliminated MSI-H OS hypothesis (H2)

Rationale:

In response to the published CM649 study which demonstrated statistically significant OS benefit in all examined PD-L1 CPS subgroups, the KN859 protocol was redesigned to focus initial alpha allocation on the OS endpoint and test PFS in a conditional step-down manner. Since initial alpha spending on PFS in PD-L1 CPS ≥10 was removed, the PFS hypotheses were changed from primary to secondary hypotheses.

The MSI-H OS hypothesis was removed and the alpha reallocated to other OS hypotheses in order to maximize statistical power for these needed hypotheses. A sensitivity analysis assessing the impact of MSI-H was planned and was prespecified in the sSAP. Because formal statistical testing of the PFS endpoint was conditional on demonstration of OS significance, there was the possibility that PFS may not be formally tested. For all these reasons, PFS was amended from a primary to a secondary endpoint.

- The total study enrolment was specified to be 1542 PD-L1 CPS "all-comer" participants. Previously, the total study enrolment was driven by the requirement for a minimum of 416 PD-L1 CPS participants; accordingly, the study was projected to enrol 1542 subjects based upon an estimated 27% prevalence of CPS ≥10

Rationale:

The prevalence of PD-L1 CPS ≥10 to date noted in the study was higher than expected (35% vs. 27%). Per protocol, this would result in fewer than 1542 PD-L1 CPS "all-comer" participants being enrolled in the study. Specifying a total study enrolment of 1542 PD-L1 CPS "all-comer" participants could increase enrolment of PDL1 CPS ≥10 participants (the primary analysis population), thus maximizing statistical power for hypothesis testing in this primary analysis population without changing the targeted enrolment in the “all-comer” population.”

- Changed the Interim Analysis, Multiplicity, and Statistical Power with new design outlined below.
    1. Changed PFS to the secondary endpoint from the primary endpoint.
    2. The trigger of IA was updated.
    3. Updated alpha passing strategy.
    4. Updated efficacy boundaries and properties.
    5. Updated the assumed magnitude of OS benefit and OS median in the control group after incorporating the recently available study result information.

Rationale:

Study redesign was as a result of available study results of CM649 and ATTRACTION-4.

1. Primary hypotheses included only OS (OS in PDL1 CPS ≥10, ≥1 and “all-comers”) and not PFS (PFS hypotheses to be tested in a conditional step-down manner only if OS in PD-L1 CPS “all-comers” shows statistical significance). For this reason, PFS was changed to a secondary endpoint.
2. The targeted number of OS events (instead of PFS events) in PD-L1 CPS ≥10 population together with the minimum follow-up requirement would drive timing of the first interim analysis.
3. The alpha passing strategy was updated by allocating the initial alpha to OS hypotheses in CPS ≥10 population and all-comer population. Only if all 3 null hypotheses of OS endpoint were rejected, PFS and ORR hypotheses were to be tested subsequently.
4. The efficacy boundary and properties were updated to reflect the changes in hypotheses and in the alpha splitting/passing strategy.
5. Data from ATTRACTION-4 (conducted in Japan, Korea and Taiwan) suggested longer-than-expected OS median for the SOC control arm and a smaller-than-expected OS treatment effect for the combination of nivolumab + SOC chemotherapy vs. SOC chemotherapy alone. It was expected that ~17% of participants were enrolled from Japan, Korea and Taiwan in this study. The prevalence of CPS ≥10 was also updated from 27% to 35% as observed in already enrolled participants in the study. As a result, power calculations were updated given the targeted sample size and new assumptions mentioned above.

Protocol Amendment Version **04** (07 Jun 2021)

The dose modification and toxicity management guidelines for immune related adverse events were updated.

Protocol Amendment Version **05** (30 Nov 2021)

The enrolment period was divided into 2 periods: the Global portion of the study and the China mainland extension. After enrolment of the Global portion of the study was completed, the study remained open to enrolment in China mainland until the target number of participants were enrolled to meet local regulatory requirements. With Protocol Amendment 05 the Global portion of the study and China mainland extension portion were combined into one Global Study.

Rationale:
Due to 1) short interval of date of Last Participant Randomised between Global portion of the study and China mainland extension portion (44 days); and 2) the small number of randomised participants in China mainland extension portion relative to the Global portion of the study (35 of 1579 participants).

Protocol Amendment Version **06** (28 Sep 2022)

Merck Sharp & Dohme Corp. underwent an entity name and address change to Merck Sharp & Dohme LLC, Rahway, NJ, USA. This conversion resulted only in an entity name change and update to the address

Impact of COVID-19 pandemic

Measures implemented by the Sponsor to manage key aspects of study conduct during the COVID-19 pandemic are summarised in the following table (implementation/end date shown in parentheses). Not all measures were implemented at all study sites due to differences in local conditions and impact of the pandemic.

Table 13 Measures Implemented by the Sponsor to Manage Study Conduct During the COVID-19 Pandemic for KEYNOTE-859

Process	**Measure (Date Implemented)**
Study site monitoring	• Modifications to the frequency of on-site and remote monitoring were allowed due to national and local travel restrictions and/or study site restrictions to on-site monitoring (21-MAR-2020). • Redacted/alternate methods for source data review and verification for critical data points in absence of remote access to electronic medical records were allowed under documented circumstances (06-MAR-2020). • Source data review and/or verification before database lock was/were waived for this study when it was not possible to perform the process (13-MAR-2020). • Critical data points for SDV were reassessed and the SMP updated without the usual approval workflow approval for resumption of on-site monitoring (01-MAY-2020).
Protocol deviations	• Study sites were not queried as to the relationship of reported deviations to the COVID-19 pandemic; however, any impact to study procedures related to COVID-19 were documented as protocol deviations (20-MAR-2020).
AE reporting	• COVID-19 infection was to be reported following the protocol's AE and SAE reporting instructions.
Clinical supplies (including study intervention)	• Direct shipping of ambient drug, without temperature monitoring, from the study site to study participants was allowed under specific circumstances (eg, stability data support transit time) (30-MAR-2020).
Data management	• Alternative procedures were allowed for study sites using shared electronic devices to complete clinical outcome assessments (08-APR-2020). One Brazilian Site had participants who completed ePRO data via telephone. Subsequent review by CQOM determined this was not an SQI. All data completed in this manner will be corrected to reflect MISS MODE. • Study sites were queried, and responses documented about the relationship of the following to the COVID-19 pandemic (08-APR-2020): - Missing participant study visits and data. - Participants who discontinued study intervention and/or the study.
Clinical laboratory and other facilities	• Alternate clinical laboratory facilities were allowed for collection of samples for study participants unable to visit the study site (16-APR-2020). • Delayed schedules for study site imaging were allowed for protocol-required imaging (each to be reported as a protocol deviation) (24-MAR-2020).
Informed consent	• Oral confirmation of participant consent (eg, via telephone) was allowed when in-person discussion and signature were not possible (30-MAR-2020).

There were no changes in the planned analyses of the study due to the COVID-19 pandemic. No protocol deviations associated with the pandemic were considered important or clinically important.

Protocol Deviations

Important protocol deviations: those that may significantly impact the quality or integrity of key study data or that may significantly affect a participant´s rights, safety, or well-being.

Clinically important protocol deviations: deviations that may compromise critical data analyses pertaining to primary efficacy and/or safety endpoints or the participant´s safety.

Table 14 Summary of Important Protocol Deviations (ITT Population)

	Pembrolizumab + Chemotherapy		Chemotherapy	
	n	(%)	n	(%)
Participants in population	790		789	
with one or more important protocol deviations	57	(7.2)	43	(5.4)
with no important protocol deviations	733	(92.8)	746	(94.6)
Discontinuation Criteria	**3**	**(0.4)**	**3**	**(0.4)**
Participant developed study intervention discontinuation criteria, but was not discontinued from study intervention.	2	(0.3)	1	(0.1)
Participant developed trial specific discontinuation criteria but was not discontinued from the trial.	1	(0.1)	2	(0.3)
Inclusion/ Exclusion Criteria	**2**	**(0.3)**	**4**	**(0.5)**
Participants entered into the trial who did not have the correct tumor histology per the I/E criteria, including the correct presence/absence of molecular aberrations/mutations and the correct tumor stage.	2	(0.3)	4	(0.5)
Informed Consent	**3**	**(0.4)**	**1**	**(0.1)**
Participant had no documented initial consent to enter the trial.	3	(0.4)	1	(0.1)
Prohibited Medications	**3**	**(0.4)**	**1**	**(0.1)**
Antineoplastic systemic chemotherapy, biologic therapy, immunotherapy, other investigational agents given while on treatment or before study entry during screening (unless allowed per protocol).	3	(0.4)	1	(0.1)
Safety Reporting	**41**	**(5.2)**	**32**	**(4.1)**
Participant had a reportable Safety Event and/or follow up Safety Event information that was not reported per the timelines outlined in the protocol.	41	(5.2)	32	(4.1)
Study Intervention	**5**	**(0.6)**	**5**	**(0.6)**
Participant was administered improperly stored study intervention that was deemed unacceptable for use.	1	(0.1)	2	(0.3)
Participant was dispensed study intervention other than what was assigned in the allocation schedule, i.e. incorrect medication or potential cross-treatment.	4	(0.5)	3	(0.4)

Every participant is counted a single time for each applicable row and column.
Database Cutoff Date: 03OCT2022

Table 15 Summary of Important Protocol Deviations Considered to be Clinically Important (ITT Population)

	Pembrolizumab + Chemotherapy		Chemotherapy	
	n	(%)	n	(%)
Participants in population	790		789	
with one or more clinically important protocol deviations	0	(0.0)	2	(0.3)
with no clinically important protocol deviations	790	(100.0)	787	(99.7)
Inclusion/ Exclusion Criteria	**0**	**(0.0)**	**2**	**(0.3)**
Participants entered into the trial who did not have the correct tumor histology per the I/E criteria, including the correct presence/absence of molecular aberrations/mutations and the correct tumor stage.	0	(0.0)	2	(0.3)

Every participant is counted a single time for each applicable row and column.
Database Cutoff Date: 03OCT2022

Baseline data

Table 16 Participant Characteristics (ITT Population)

	Pembrolizumab + Chemotherapy		Chemotherapy		Total	
	n	(%)	n	(%)	n	(%)
Participants in population	790		789		1,579	
Sex						
Male	527	(66.7)	544	(68.9)	1,071	(67.8)
Female	263	(33.3)	245	(31.1)	508	(32.2)

	Pembrolizumab + Chemotherapy		Chemotherapy		Total	
	n	(%)	n	(%)	n	(%)
Participants in population	790		789		1,579	
Age Category 1 (Years)						
< 65	486	(61.5)	479	(60.7)	965	(61.1)
>= 65	304	(38.5)	310	(39.3)	614	(38.9)
Mean	59.3		60.0		59.6	
SD	11.9		11.8		11.8	
Median	61.0		62.0		62.0	
Range	23 to 86		21 to 85		21 to 86	
Age Category 2 (Years)						
< 65	486	(61.5)	479	(60.7)	965	(61.1)
>= 65 to <75	247	(31.3)	250	(31.7)	497	(31.5)
>= 75 to <85	55	(7.0)	59	(7.5)	114	(7.2)
>= 85	2	(0.3)	1	(0.1)	3	(0.2)
Age Category 3 (Years)						
18-39	57	(7.2)	49	(6.2)	106	(6.7)
40-49	102	(12.9)	99	(12.5)	201	(12.7)
50-59	184	(23.3)	186	(23.6)	370	(23.4)
60-69	302	(38.2)	284	(36.0)	586	(37.1)
70-79	132	(16.7)	152	(19.3)	284	(18.0)
>=80	13	(1.6)	19	(2.4)	32	(2.0)
Race						
American Indian Or Alaska Native	31	(3.9)	36	(4.6)	67	(4.2)
Asian	270	(34.2)	269	(34.1)	539	(34.1)
Black Or African American	12	(1.5)	9	(1.1)	21	(1.3)
Multiple	43	(5.4)	30	(3.8)	73	(4.6)
Native Hawaiian Or Other Pacific Islander	1	(0.1)	2	(0.3)	3	(0.2)
White	426	(53.9)	435	(55.1)	861	(54.5)
Missing	7	(0.9)	8	(1.0)	15	(0.9)
Ethnicity						
Hispanic Or Latino	175	(22.2)	157	(19.9)	332	(21.0)
Not Hispanic Or Latino	590	(74.7)	615	(77.9)	1,205	(76.3)
Not Reported	14	(1.8)	14	(1.8)	28	(1.8)
Unknown	7	(0.9)	3	(0.4)	10	(0.6)
Missing	4	(0.5)	0	(0.0)	4	(0.3)
Geographic Region for Randomisation						
Western Europe/Israel/North America/Australia	201	(25.4)	202	(25.6)	403	(25.5)
Asia	263	(33.3)	262	(33.2)	525	(33.2)
Rest of the World	326	(41.3)	325	(41.2)	651	(41.2)
Combination Chemotherapy for Randomisation						
CAPOX	682	(86.3)	681	(86.3)	1,363	(86.3)
FP	108	(13.7)	108	(13.7)	216	(13.7)
PD-L1 Status for Randomisation						
CPS >= 1	619	(78.4)	616	(78.1)	1,235	(78.2)
CPS < 1	171	(21.6)	173	(21.9)	344	(21.8)
Baseline PD-L1 Status (CPS Cut Point: 1)						
CPS >= 1	618	(78.2)	617	(78.2)	1,235	(78.2)
CPS < 1	172	(21.8)	172	(21.8)	344	(21.8)
Baseline PD-L1 Status (CPS Cut Point: 10)						
CPS >= 10	279	(35.3)	272	(34.5)	551	(34.9)
CPS < 10	509	(64.4)	517	(65.5)	1,026	(65.0)
Missing	2	(0.3)	0	(0.0)	2	(0.1)
MSI Status						
MSI-High	39	(4.9)	35	(4.4)	74	(4.7)
non-MSI-High	641	(81.1)	639	(81.0)	1,280	(81.1)
Unknown	0	(0.0)	1	(0.1)	1	(0.1)

	Pembrolizumab + Chemotherapy		Chemotherapy		Total	
	n	(%)	n	(%)	n	(%)
Participants in population	790		789		1,579	
Missing	110	(13.9)	114	(14.4)	224	(14.2)
ECOG Performance Scale						
0	281	(35.6)	301	(38.1)	582	(36.9)
1	509	(64.4)	488	(61.9)	997	(63.1)
Primary Location						
Adenocarcinoma of the gastroesophageal junction	149	(18.9)	185	(23.4)	334	(21.2)
Adenocarcinoma of the stomach	640	(81.0)	603	(76.4)	1,243	(78.7)
Other	0	(0.0)	1	(0.1)	1	(0.1)
Missing	1	(0.1)	0	(0.0)	1	(0.1)
Overall Stage						
IIA	0	(0.0)	1	(0.1)	1	(0.1)
IIB	0	(0.0)	2	(0.3)	2	(0.1)
IIIA	2	(0.3)	9	(1.1)	11	(0.7)
IIIB	11	(1.4)	10	(1.3)	21	(1.3)
IIIC	9	(1.1)	5	(0.6)	14	(0.9)
IV	767	(97.1)	762	(96.6)	1,529	(96.8)
Missing	1	(0.1)	0	(0.0)	1	(0.1)
Disease Status						
Locally advanced	28	(3.5)	30	(3.8)	58	(3.7)
Metastatic	761	(96.3)	759	(96.2)	1,520	(96.3)
Missing	1	(0.1)	0	(0.0)	1	(0.1)
Histological Subtype (Lauren classification)						
Diffuse	318	(40.3)	301	(38.1)	619	(39.2)
Intestinal	284	(35.9)	273	(34.6)	557	(35.3)
Indeterminate	186	(23.5)	215	(27.2)	401	(25.4)
Unknown	1	(0.1)	0	(0.0)	1	(0.1)
Missing	1	(0.1)	0	(0.0)	1	(0.1)
Number of Metastasis						
0-2	438	(55.4)	421	(53.4)	859	(54.4)
>=3	351	(44.4)	368	(46.6)	719	(45.5)
Missing	1	(0.1)	0	(0.0)	1	(0.1)
Tumour Burden						
>= Median	387	(49.0)	357	(45.2)	744	(47.1)
< Median	358	(45.3)	384	(48.7)	742	(47.0)
Missing	45	(5.7)	48	(6.1)	93	(5.9)
Liver Metastases						
Yes	314	(39.7)	311	(39.4)	625	(39.6)
No	475	(60.1)	478	(60.6)	953	(60.4)
Missing	1	(0.1)	0	(0.0)	1	(0.1)
Prior Gastrectomy/Esophagectomy						
Yes	172	(21.8)	162	(20.5)	334	(21.2)
No	613	(77.6)	622	(78.8)	1,235	(78.2)
Missing	5	(0.6)	5	(0.6)	10	(0.6)

CAPOX: Backbone chemotherapy oxaliplatin + capecitabine.
FP: Backbone chemotherapy cisplatin + 5-FU.
Database Cutoff Date: 03OCT2022

Table 17 Table Participants with prior oncologic therapies (ITT)

	Pembrolizumab + Chemotherapy (N=790)		Chemotherapy (N=789)	
	n	(%)	n	(%)
Received Any Prior Oncological Therapy	208	(26.3)	205	(26.0)
Prior Systemic Oncological Drug	108	(13.7)	110	(13.9)
Neo Adjuvant	48	(6.1)	56	(7.1)
Adjuvant	81	(10.3)	79	(10.0)
Not Applicable[a]	0	(0.0)	1	(0.1)
Prior Oncological Radiation	31	(3.9)	31	(3.9)
Neo-Adjuvant	11	(1.4)	16	(2.0)
Adjuvant	20	(2.5)	15	(1.9)
Prior Oncological Surgery	193	(24.4)	195	(24.7)

[a]Not applicable: a locally approved Chinese non-chemotherapy Brucea Javanica Oil.
Every participant is counted a single time for each applicable row and column.
Database Cutoff Date: 03OCT2022

The baseline characteristics in the CPS ≥1 and CPS ≥10 populations were generally consistent with all participants, and balanced between both treatment groups.

Table 18 Participant Characteristics (ITT Population with CPS ⩾1)

	Pembrolizumab + Chemotherapy		Chemotherapy		Total	
	n	(%)	n	(%)	n	(%)
Participants in population	618		617		1,235	
Sex						
Male	422	(68.3)	448	(72.6)	870	(70.4)
Female	196	(31.7)	169	(27.4)	365	(29.6)
Age Category 1 (Years)						
< 65	377	(61.0)	364	(59.0)	741	(60.0)
>= 65	241	(39.0)	253	(41.0)	494	(40.0)
Mean	59.8		60.5		60.1	
SD	11.8		11.6		11.7	
Median	62.0		63.0		62.0	
Range	24 to 86		25 to 85		24 to 86	
Age Category 2 (Years)						
< 65	377	(61.0)	364	(59.0)	741	(60.0)
>= 65 to <75	195	(31.6)	203	(32.9)	398	(32.2)
>= 75 to <85	44	(7.1)	49	(7.9)	93	(7.5)
>= 85	2	(0.3)	1	(0.2)	3	(0.2)
Age Category 3 (Years)						
18-39	42	(6.8)	34	(5.5)	76	(6.2)
40-49	70	(11.3)	75	(12.2)	145	(11.7)
50-59	150	(24.3)	141	(22.9)	291	(23.6)
60-69	236	(38.2)	230	(37.3)	466	(37.7)
70-79	110	(17.8)	121	(19.6)	231	(18.7)
>=80	10	(1.6)	16	(2.6)	26	(2.1)
Race						
American Indian Or Alaska Native	24	(3.9)	29	(4.7)	53	(4.3)
Asian	206	(33.3)	203	(32.9)	409	(33.1)
Black Or African American	7	(1.1)	9	(1.5)	16	(1.3)
Multiple	32	(5.2)	25	(4.1)	57	(4.6)
Native Hawaiian Or Other Pacific Islander	1	(0.2)	1	(0.2)	2	(0.2)
White	342	(55.3)	343	(55.6)	685	(55.5)
Missing	6	(1.0)	7	(1.1)	13	(1.1)

	Pembrolizumab + Chemotherapy		Chemotherapy		Total	
	n	(%)	n	(%)	n	(%)
Ethnicity						
Hispanic Or Latino	135	(21.8)	124	(20.1)	259	(21.0)
Not Hispanic Or Latino	461	(74.6)	480	(77.8)	941	(76.2)
Not Reported	12	(1.9)	11	(1.8)	23	(1.9)
Unknown	7	(1.1)	2	(0.3)	9	(0.7)
Missing	3	(0.5)	0	(0.0)	3	(0.2)
Geographic Region for Randomization						
Western Europe/Israel/North America/Australia	166	(26.9)	166	(26.9)	332	(26.9)
Asia	201	(32.5)	200	(32.4)	401	(32.5)
Rest of the World	251	(40.6)	251	(40.7)	502	(40.6)
Combination Chemotherapy for Randomization						
CAPOX	528	(85.4)	528	(85.6)	1,056	(85.5)
FP	90	(14.6)	89	(14.4)	179	(14.5)
PD-L1 Status for Randomization						
CPS >= 1	618	(100.0)	616	(99.8)	1,234	(99.9)
CPS < 1	0	(0.0)	1	(0.2)	1	(0.1)
Baseline PD-L1 Status (CPS Cut Point: 10)						
CPS >= 10	279	(45.1)	272	(44.1)	551	(44.6)
CPS < 10	337	(54.5)	345	(55.9)	682	(55.2)
Missing	2	(0.3)	0	(0.0)	2	(0.2)
MSI Status						
MSI-High	35	(5.7)	31	(5.0)	66	(5.3)
non-MSI-High	503	(81.4)	500	(81.0)	1,003	(81.2)
Unknown	0	(0.0)	1	(0.2)	1	(0.1)
Missing	80	(12.9)	85	(13.8)	165	(13.4)
ECOG Performance Scale						
0	223	(36.1)	228	(37.0)	451	(36.5)
1	395	(63.9)	389	(63.0)	784	(63.5)
Primary Location						

	Pembrolizumab + Chemotherapy		Chemotherapy		Total	
	n	(%)	n	(%)	n	(%)
Adenocarcinoma of the gastroesophageal junction	123	(19.9)	164	(26.6)	287	(23.2)
Adenocarcinoma of the stomach	494	(79.9)	453	(73.4)	947	(76.7)
Missing	1	(0.2)	0	(0.0)	1	(0.1)
Overall Stage						
IIA	0	(0.0)	1	(0.2)	1	(0.1)
IIB	0	(0.0)	2	(0.3)	2	(0.2)
IIIA	2	(0.3)	7	(1.1)	9	(0.7)
IIIB	10	(1.6)	7	(1.1)	17	(1.4)
IIIC	9	(1.5)	5	(0.8)	14	(1.1)
IV	596	(96.4)	595	(96.4)	1,191	(96.4)
Missing	1	(0.2)	0	(0.0)	1	(0.1)
Disease Status						
Locally advanced	26	(4.2)	24	(3.9)	50	(4.0)
Metastatic	591	(95.6)	593	(96.1)	1,184	(95.9)
Missing	1	(0.2)	0	(0.0)	1	(0.1)
Histological Subtype (Lauren classification)						
Diffuse	236	(38.2)	220	(35.7)	456	(36.9)
Intestinal	239	(38.7)	215	(34.8)	454	(36.8)
Indeterminate	141	(22.8)	182	(29.5)	323	(26.2)
Unknown	1	(0.2)	0	(0.0)	1	(0.1)
Missing	1	(0.2)	0	(0.0)	1	(0.1)
Number of Metastasis						
0-2	345	(55.8)	329	(53.3)	674	(54.6)
>=3	272	(44.0)	288	(46.7)	560	(45.3)
Missing	1	(0.2)	0	(0.0)	1	(0.1)
Tumor Burden						
>= Median	308	(49.8)	285	(46.2)	593	(48.0)
< Median	277	(44.8)	299	(48.5)	576	(46.6)
Missing	33	(5.3)	33	(5.3)	66	(5.3)
Liver Metastases						
Yes	258	(41.7)	253	(41.0)	511	(41.4)

	Pembrolizumab + Chemotherapy		Chemotherapy		Total	
	n	(%)	n	(%)	n	(%)
No	359	(58.1)	364	(59.0)	723	(58.5)
Missing	1	(0.2)	0	(0.0)	1	(0.1)
Prior Gastrectomy/Esophagectomy						
Yes	109	(17.6)	105	(17.0)	214	(17.3)
No	506	(81.9)	508	(82.3)	1,014	(82.1)
Missing	3	(0.5)	4	(0.6)	7	(0.6)
CAPOX: Backbone chemotherapy oxaliplatin + capecitabine. FP: Backbone chemotherapy cisplatin + 5-FU. Database Cutoff Date: 03OCT2022						

Subsequent therapies

Table 19 Participants with subsequent oncologic therapies (ITT Population)

	Pembrolizumab + Chemotherapy (N=790)	Chemotherapy (N=789)
Started Study Treatment	785 (99.4)	787 (99.7)
Discontinued Study Treatment	685 (86.7)	742 (94.0)
Received Any Subsequent Systemic Anti-Cancer Therapy	355 (44.9)	369 (46.8)
Subsequent Systemic Therapy by Type		
Chemotherapy	339 (42.9)	346 (43.9)
Any PD1/PD-L1 checkpoint inhibitor	66 (8.4)	72 (9.1)
Any VEGF/VEGFR inhibitor	137 (17.3)	138 (17.5)
Other	92 (11.6)	96 (12.2)
Subsequent Systemic Therapy by Lines		
1 subsequent line	352 (44.6)	364 (46.1)
2 subsequent lines	145 (18.4)	138 (17.5)
>=3 subsequent lines	66 (8.4)	58 (7.4)
Every participant is counted a single time for each applicable specific anti-cancer treatment. A participant with multiple anti-cancer treatments within a therapy category is counted a single time for that category. Database cutoff date: 03OCT2022.		

Numbers analysed

Efficacy Analysis Population

OS, PFS, ORR, and DOR were analysed in the ITT population (referenced as all participants; n=1579) and in participants with tumour PD-L1 expression of CPS ≥1 (n=1235) and CPS ≥10 (n=551).

Safety Analysis Population

Safety analyses were based on the APaT population, which included all 1572 randomised participants who received at least 1 dose of study intervention according to the study intervention they received PRO was analysed in the FAS population.

Patient-reported Outcome Analysis Population

PRO analyses for the EORTC-QLQ-C30, EORTC-QLQ-STO22, and EQ-5D-5L questionnaires were based on the PRO FAS population, which included all 1543 (EORTC-QLQ-C30 and EQ-5D-5L) and 1528 (EORTC-QLQ-STO22) randomised participants who had at least 1 PRO assessment available for the specific endpoint and have received at least 1 dose of study intervention.

Outcomes and estimation

Efficacy results are presented from the IA of Study KEYNOTE-859 as of the DCO date of 03-OCT-2022 with approximately 15 months of follow-up after the last participant was randomised (interim OS analysis and final analyses for PFS and ORR). At this IA, the study met the predefined superiority criteria for all efficacy hypotheses: pembrolizumab in combination with chemotherapy provided statistically significant improvements in OS, PFS by BICR, and ORR by BICR in CPS ≥ 10, CPS ≥ 1 and ITT when compared with chemotherapy alone.

Table 20 Summary of Efficacy Results for KEYNOTE-859

	All Participants		**PD-L1 CPS ≥1**		**PD-L1 CPS ≥10**	
Efficacy Endpoint	**P+C (N=790)**	**C (N=789)**	**P+C (N=618)**	**C (N=617)**	**P+C (N=279)**	**C (N=272)**
Primary Efficacy Outcome: OS						
Number of events (%)	603 (76.3)	666 (84.4)	464 (75.1)	526 (85.3)	188 (67.4)	226 (83.1)
Median OS, months (95% CI)	12.9 (11.9, 14.0)	11.5 (10.6, 12.1)	13.0 (11.6, 14.2)	11.4 (10.5, 12.0)	15.7 (13.8, 19.3)	11.8 (10.3, 12.7)
HR (95% CI)	0.78 (0.70, 0.87)		0.74 (0.65, 0.84)		0.65 (0.53, 0.79)	
p-Value *	<0.0001		<0.0001		<0.0001	
OS rate, % (95% CI) at 12 Months	52.7 (49.1, 56.1)	46.7 (43.2, 50.2)	52.4 (48.4, 56.3)	45.7 (41.7, 49.6)	60.6 (54.6, 66.0)	47.8 (41.7, 53.6)
OS rate, % (95% CI) at 24 Months	28.2 (25.0, 31.5)	18.9 (16.1, 21.9)	29.6 (25.9, 33.3)	17.7 (14.7, 21.0)	37.9 (32.0, 43.7)	20.9 (16.2, 26.1)
OS rate, % (95% CI) at 30 Months	22.8 (19.6, 26.1)	13.1 (10.6, 15.9)	23.9 (20.3, 27.6)	12.3 (9.6, 15.4)	32.4 (26.6, 38.3)	16.5 (12.0, 21.6)
Secondary Efficacy Outcome: PFS (BICR per RECIST 1.1)						
Number of events (%)	572 (72.4)	608 (77.1)	443 (71.7)	483 (78.3)	190 (68.1)	210 (77.2)
Median PFS (95% CI), months	6.9 (6.3, 7.2)	5.6 (5.5, 5.7)	6.9 (6.0, 7.2)	5.6 (5.4, 5.7)	8.1 (6.8, 8.5)	5.6 (5.4, 6.7)
HR (95% CI)‡	0.76 (0.67, 0.85)		0.72 (0.63, 0.82)		0.62 (0.51, 0.76)	
p-Value *	<0.0001		<0.0001		<0.0001	
PFS rate, % (95% CI) at 12 Months†	28.9 (25.5, 32.4)	19.3 (16.3, 22.4)	29.4 (25.5, 33.3)	18.4 (15.1, 21.9)	36.6 (30.5, 42.6)	20.0 (14.9, 25.5)
PFS rate, % (95% CI) at 24 Months	17.8 (14.8, 20.9)	9.4 (7.0, 12.2)	19.5 (16.1, 23.2)	7.9 (5.3, 11.0)	25.4 (20.0, 31.2)	7.7 (4.2, 12.5)

	All Participants		PD-L1 CPS ≥1		PD-L1 CPS ≥10	
Efficacy Endpoint	**P+C (N=790)**	**C (N=789)**	**P+C (N=618)**	**C (N=617)**	**P+C (N=279)**	**C (N=272)**
Secondary Efficacy Outcomes: ORR and DOR (BICR per RECIST 1.1)						
ORR						
ORR, % (95% CI)	51.3 (47.7, 54.8)	42.0 (38.5, 45.5)	52.1 (48.1, 56.1)	42.6 (38.7, 46.6)	60.6 (54.6, 66.3)	43.0 (37.1, 49.1)
p-Value*	0.00009		0.00041		0.00002	
Complete Response (CR), n (%)	75 (9.5%)	49 (6.2%)	61 (9.9%)	36 (5.8%)	36 (12.9%)	14 (5.1%)
Partial Response (PR), n (%)	330 (41.8%)	282 (35.7%)	261 (42.2%)	227 (36.8%)	133 (47.7%)	103 (37.9%)
DOR (CR or PR)						
Number of responders	405	331	322	263	169	117
Median DOR, months (range)	8.0 (1.2+ - 41.5+)	5.7 (1.3+ - 34.7+)	8.3 (1.2+ - 41.5+)	5.6 (1.3+ - 34.2+)	10.9 (1.2+ - 41.5+)	5.8 (1.4+ - 31.2+)

Abbreviations: BICR=Blinded independent central review; CI=Confidence interval; CPS=Combined positive score; DOR=Duration of response; HR=Hazard ratio; ITT=Intention to treat; ORR=Objective response rate; OS=Overall survival; PFS=Progression-free survival; RECIST 1.1=Response Evaluation Criteria in Solid Tumours Version 1.1.
* *p*-value crossing boundary for statistical significance; OS in all participants = 0.006079, OS in CPS ≥1 = 0.020556, OS in CPS ≥10 = 0.011603, PFS and ORR difference = 0.025 (all participants, CPS ≥1, and CPS ≥10).
Database cutoff date: 03-OCT-2022

Primary endpoint

OS

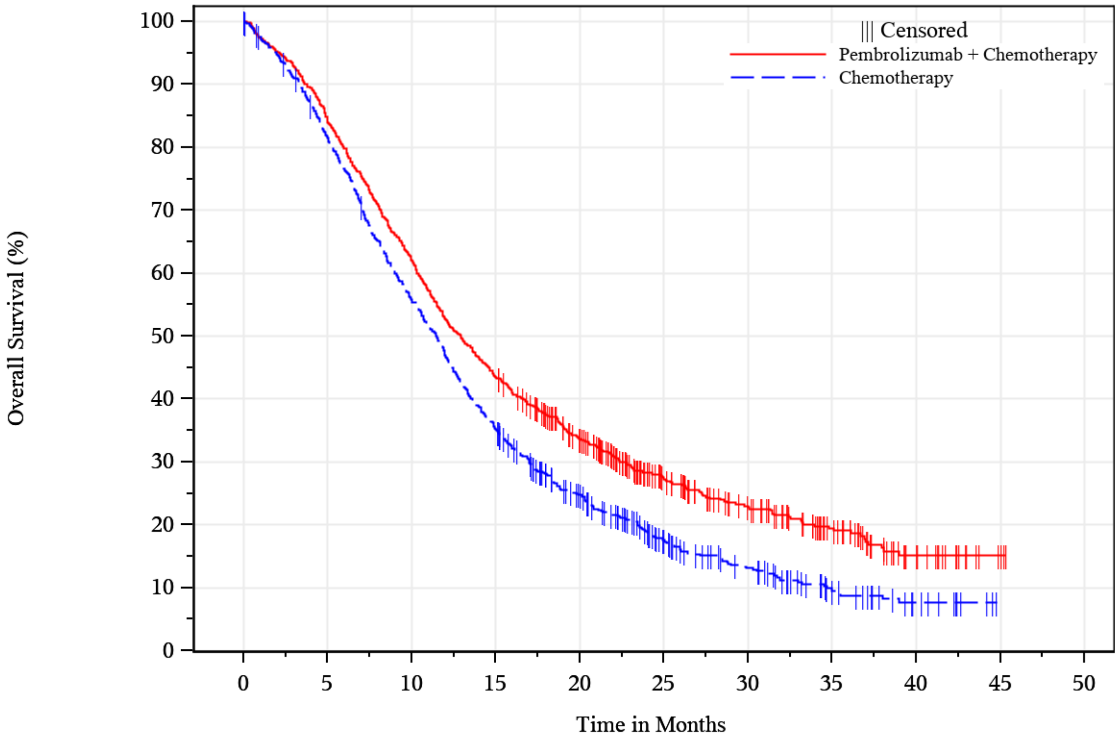
- **All participants**

Table 21 Analysis of Overall Survival (ITT Population)

	Pembrolizumab + Chemotherapy (N=790)	Chemotherapy (N=789)
Number of Events (%)	603 (76.3)	666 (84.4)
Kaplan-Meier Estimates (months)[a]		
Median (95% CI)	12.9 (11.9, 14.0)	11.5 (10.6, 12.1)
[Q1, Q3]	[7.1, 27.2]	[6.3, 19.8]
Person-months	12213.0	10438.9
Event Rate / 100 Person-months	4.9	6.4
vs Chemotherapy		
Hazard Ratio (95% CI)[b]	0.78 (0.70, 0.87)	
p-value[c]	<0.0001	
OS Rate at month 6 (%) (95% CI)	79.9 (76.9, 82.5)	76.6 (73.5, 79.4)
OS Rate at month 12 (%) (95% CI)	52.7 (49.1, 56.1)	46.7 (43.2, 50.2)
OS Rate at month 18 (%) (95% CI)	37.5 (34.1, 40.9)	28.1 (25.0, 31.4)
OS Rate at month 24 (%) (95% CI)	28.2 (25.0, 31.5)	18.9 (16.1, 21.9)
OS Rate at month 30 (%) (95% CI)	22.8 (19.6, 26.1)	13.1 (10.6, 15.9)

[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 Geographic region (Western Europe/Israel/North America/Australia, Asia and Rest of the World), PD-L1 status (CPS<1 vs. CPS>=1), and Chemotherapy regimen (FP or CAPOX) with small strata collapsed as pre-specified in the sSAP.
[c] One-sided p-value based on log-rank test stratified by Geographic region (Western Europe/Israel/North America/Australia, Asia and Rest of the World), PD-L1 status (CPS<1 vs. CPS>=1), and Chemotherapy regimen (FP or CAPOX) with small strata collapsed as pre-specified in the sSAP.
Western Europe includes France, Germany, Spain, Italy, United Kingdom, Ireland, Switzerland, Czech Republic, Denmark and Hungary, which is consistent with the ''Europe'' region defined in the protocol for stratification.
Database Cutoff Date: 03OCT2022

Figure 6 Kaplan-Meier Plot of Overall Survival (ITT Population)



At Risk

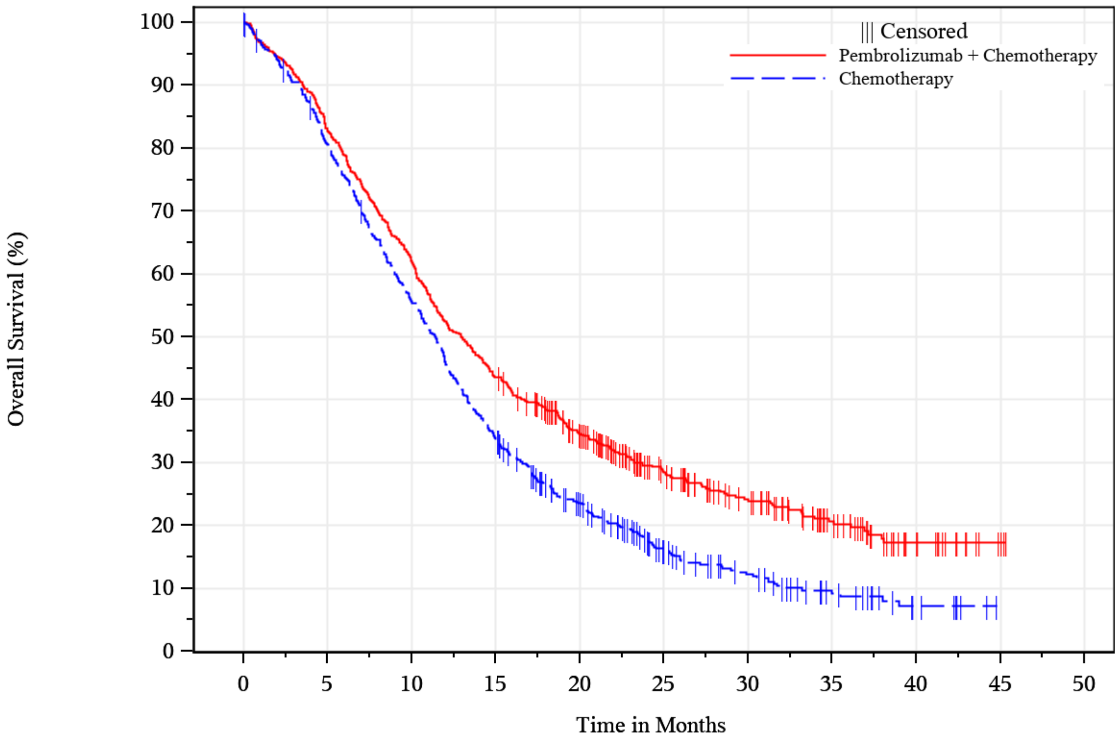
	0	5	10	15	20	25	30	35	40	45	50
Pembrolizumab + Chemotherapy	790	663	490	343	240	143	95	55	19	3	0
Chemotherapy	789	636	434	274	169	95	58	26	10	0	0

- **CPS ≥1**

Table 22 Analysis of Overall Survival (ITT Population with CPS ≥1)

	Pembrolizumab + Chemotherapy (N=618)	Chemotherapy (N=617)
Number of Events (%)	464 (75.1)	526 (85.3)
Kaplan-Meier Estimates (months)[a]		
Median (95% CI)	13.0 (11.6, 14.2)	11.4 (10.5, 12.0)
[Q1, Q3]	[6.9, 28.7]	[6.2, 18.6]
Person-months	9644.5	8008.1
Event Rate / 100 Person-months	4.8	6.6
vs Chemotherapy		
Hazard Ratio (95% CI)[b]	0.74 (0.65, 0.84)	
p-value[c]	<0.0001	
OS Rate at month 6 (%) (95% CI)	79.0 (75.5, 82.0)	75.7 (72.1, 78.9)
OS Rate at month 12 (%) (95% CI)	52.4 (48.4, 56.3)	45.7 (41.7, 49.6)
OS Rate at month 18 (%) (95% CI)	38.4 (34.6, 42.3)	26.6 (23.2, 30.2)
OS Rate at month 24 (%) (95% CI)	29.6 (25.9, 33.3)	17.7 (14.7, 21.0)
OS Rate at month 30 (%) (95% CI)	23.9 (20.3, 27.6)	12.3 (9.6, 15.4)

Figure 7 Kaplan-Meier Plot of Overall Survival (ITT Population with CPS ≥ 1)



At Risk

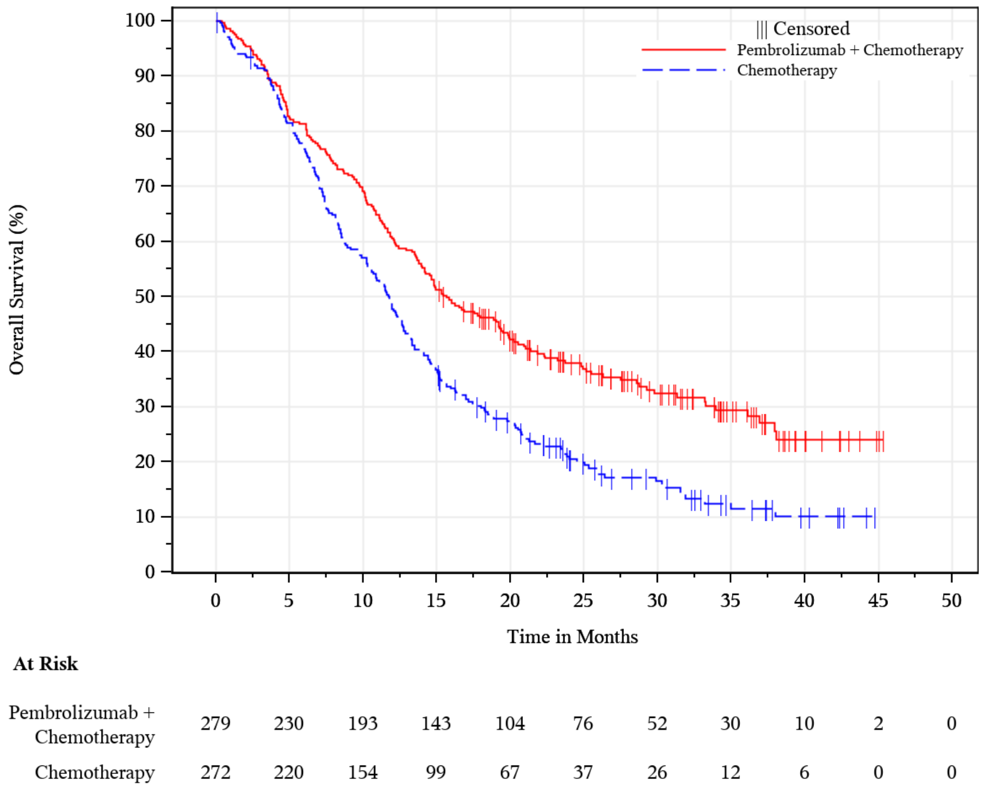
Pembrolizumab + Chemotherapy	618	511	383	269	192	121	81	46	17	3	0
Chemotherapy	617	493	339	206	126	66	41	20	7	0	0

- **CPS ≥10**

Table 23 Analysis of Overall Survival (ITT Population with CPS ≥ 10)

	Pembrolizumab + Chemotherapy (N=279)	Chemotherapy (N=272)
Number of Events (%)	188 (67.4)	226 (83.1)
Kaplan-Meier Estimates (months)[a]		
Median (95% CI)	15.7 (13.8, 19.3)	11.8 (10.3, 12.7)
[Q1, Q3]	[7.8, 38.1]	[6.3, 20.7]
Person-months	4926.5	3747.2
Event Rate / 100 Person-months	3.8	6.0
vs Chemotherapy		
Hazard Ratio (95% CI)[b]	0.65 (0.53, 0.79)	
p-value[c]	<0.0001	
OS Rate at month 6 (%) (95% CI)	81.4 (76.3, 85.5)	77.1 (71.6, 81.6)
OS Rate at month 12 (%) (95% CI)	60.6 (54.6, 66.0)	47.8 (41.7, 53.6)
OS Rate at month 18 (%) (95% CI)	46.1 (40.2, 51.9)	30.2 (24.8, 35.7)
OS Rate at month 24 (%) (95% CI)	37.9 (32.0, 43.7)	20.9 (16.2, 26.1)
OS Rate at month 30 (%) (95% CI)	32.4 (26.6, 38.3)	16.5 (12.0, 21.6)

Figure 8 Kaplan-Meier Plot of Overall Survival (ITT Population with CPS ≥ 10)



Secondary endpoints

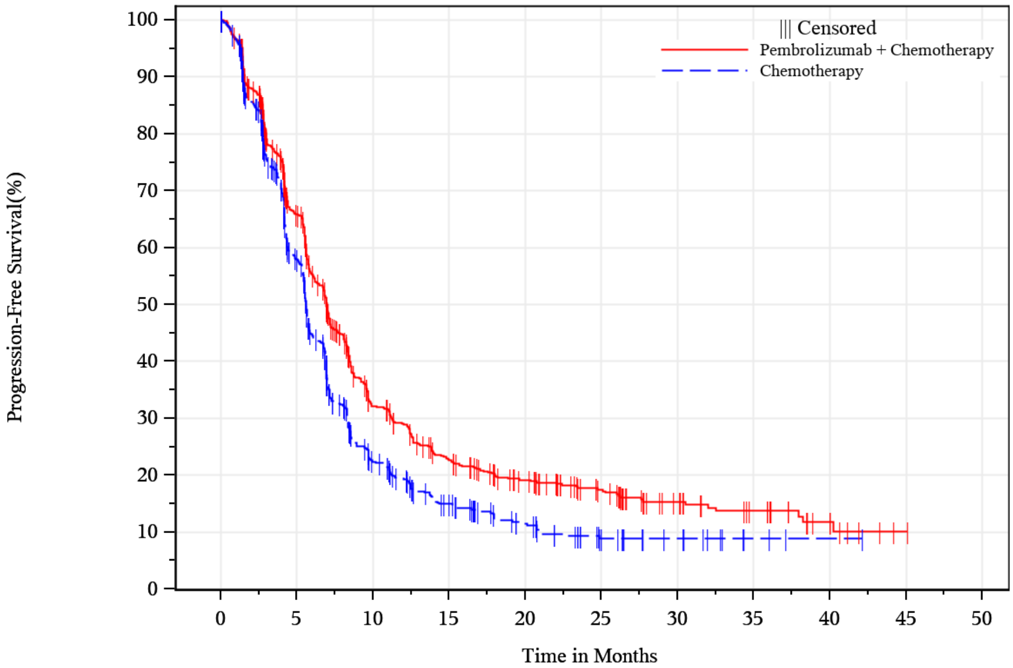
PFS

- **All participants**

Table 24 Analysis of PFS (Primary Analysis) by BICR per RECIST 1.1 (ITT Population)

	Pembrolizumab + Chemotherapy (N=790)	Chemotherapy (N=789)
Number of Events (%)	572 (72.4)	608 (77.1)
Death	109 (13.8)	114 (14.4)
Documented progression	463 (58.6)	494 (62.6)
Kaplan-Meier Estimates (months)[a]		
Median (95% CI)	6.9 (6.3, 7.2)	5.6 (5.5, 5.7)
[Q1, Q3]	[4.0, 13.8]	[3.0, 9.5]
Person-months	6918.5	5241.6
Event Rate / 100 Person-months	8.3	11.6
vs Chemotherapy		
Hazard Ratio (95% CI)[b]	0.76 (0.67, 0.85)	
p-value[c]	<0.0001	
PFS Rate at month 6 (%) (95% CI)	55.3 (51.6, 58.9)	44.8 (41.1, 48.4)
PFS Rate at month 12 (%) (95% CI)	28.9 (25.5, 32.4)	19.3 (16.3, 22.4)
PFS Rate at month 18 (%) (95% CI)	20.1 (17.1, 23.4)	12.3 (9.7, 15.2)
PFS Rate at month 24 (%) (95% CI)	17.8 (14.8, 20.9)	9.4 (7.0, 12.2)
PFS Rate at month 30 (%) (95% CI)	15.3 (12.4, 18.6)	9.0 (6.5, 11.8)

Figure 9 KM Plot of PFS (Primary Analysis) by BICR per RECIST 1.1 (ITT Population)



At Risk

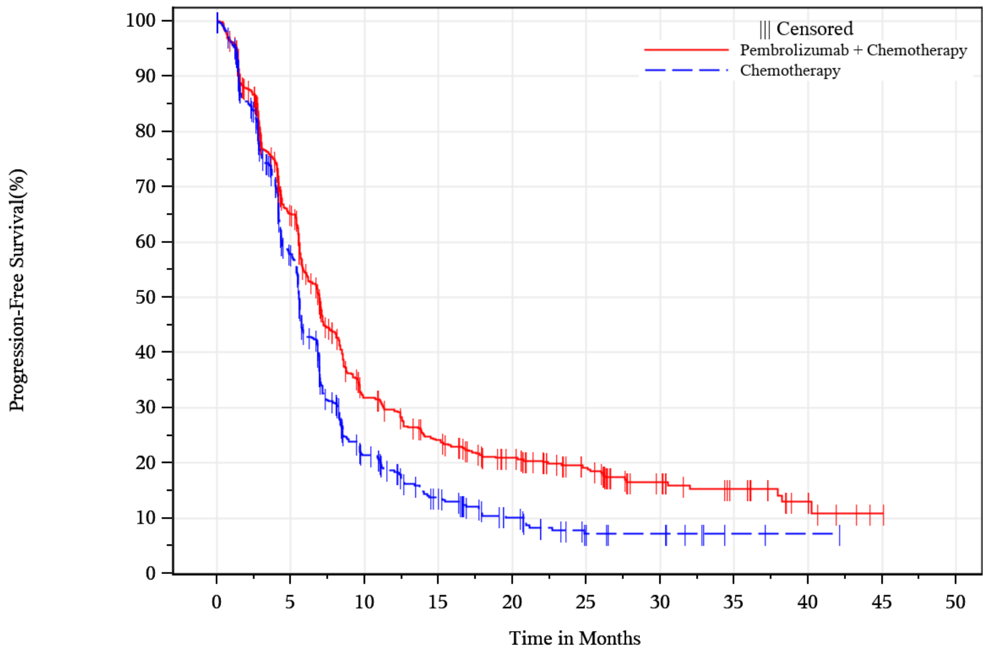
Pembrolizumab + Chemotherapy	790	461	199	131	94	63	36	22	9	1	0
Chemotherapy	789	407	130	71	41	19	11	3	1	0	0

- **CPS ≥1**

Table 25 Analysis of PFS Based on BICR Assessment per RECIST 1.1 (ITT Population with CPS ≥1)

	Pembrolizumab + Chemotherapy (N=618)	Chemotherapy (N=617)
Number of Events (%)	443 (71.7)	483 (78.3)
Death	91 (14.7)	92 (14.9)
Documented progression	352 (57.0)	391 (63.4)
Kaplan-Meier Estimates (months)[a]		
Median (95% CI)	6.9 (6.0, 7.2)	5.6 (5.4, 5.7)
[Q1, Q3]	[3.9, 14.0]	[3.2, 8.6]
Person-months	5538.1	3987.5
Event Rate / 100 Person-months	8.0	12.1
vs Chemotherapy		
Hazard Ratio (95% CI)[b]	0.72 (0.63, 0.82)	
p-value[c]	<0.0001	
PFS Rate at month 6 (%) (95% CI)	54.4 (50.1, 58.4)	43.4 (39.3, 47.5)
PFS Rate at month 12 (%) (95% CI)	29.4 (25.5, 33.3)	18.4 (15.1, 21.9)
PFS Rate at month 18 (%) (95% CI)	21.2 (17.7, 24.9)	10.4 (7.7, 13.6)
PFS Rate at month 24 (%) (95% CI)	19.5 (16.1, 23.2)	7.9 (5.3, 11.0)
PFS Rate at month 30 (%) (95% CI)	16.6 (13.2, 20.3)	7.3 (4.7, 10.5)

Figure 10 KM Plot of PFS by BICR Assessment per RECIST 1.1 (ITT Population with CPS ≥1)



At Risk

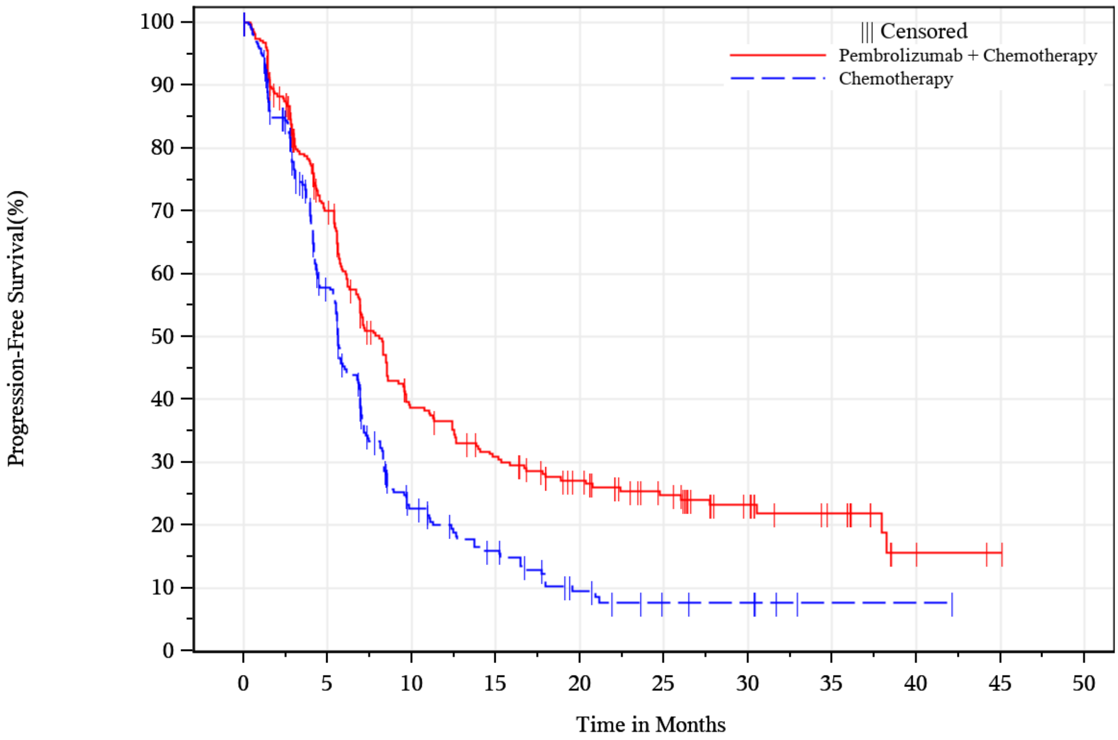
Pembrolizumab + Chemotherapy	618	356	156	112	82	57	33	21	8	1	0
Chemotherapy	617	317	97	51	26	11	8	2	1	0	0

- **CPS ≥10**

Table 26 Analysis of PFS by BICR Assessment per RECIST 1.1 (ITT Population with CPS ≥10)

	Pembrolizumab + Chemotherapy (N=279)	Chemotherapy (N=272)
Number of Events (%)	190 (68.1)	210 (77.2)
Death	33 (11.8)	36 (13.2)
Documented progression	157 (56.3)	174 (64.0)
Kaplan-Meier Estimates (months)[a]		
Median (95% CI)	8.1 (6.8, 8.5)	5.6 (5.4, 6.7)
[Q1, Q3]	[4.2, 24.7]	[3.0, 9.5]
Person-months	2962.0	1797.7
Event Rate / 100 Person-months	6.4	11.7
vs Chemotherapy		
Hazard Ratio (95% CI)[b]	0.62 (0.51, 0.76)	
p-value[c]	<0.0001	
PFS Rate at month 6 (%) (95% CI)	60.4 (54.1, 66.1)	45.2 (38.9, 51.3)
PFS Rate at month 12 (%) (95% CI)	36.6 (30.5, 42.6)	20.0 (14.9, 25.5)
PFS Rate at month 18 (%) (95% CI)	27.6 (22.1, 33.4)	10.2 (6.3, 15.1)
PFS Rate at month 24 (%) (95% CI)	25.4 (20.0, 31.2)	7.7 (4.2, 12.5)
PFS Rate at month 30 (%) (95% CI)	23.2 (17.8, 29.1)	7.7 (4.2, 12.5)

Figure 11 KM Plot of PFS Based on BICR Assessment per RECIST 1.1 (ITT Population with CPS ≥10)



At Risk

Pembrolizumab + Chemotherapy	279	176	90	69	52	37	23	14	3	1	0
Chemotherapy	272	138	44	27	12	6	5	1	1	0	0

ORR and DOR

Table 27 Analysis of Objective Response (Confirmed) and Duration of Response Based on BICR Assessment per RECIST 1.1

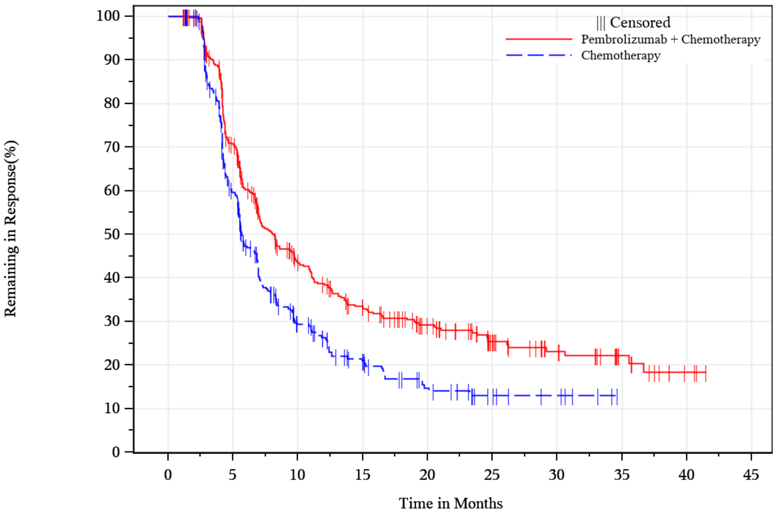
	All Participants		PD-L1 CPS ≥1		PD-L1 CPS ≥10	
Efficacy Endpoint	**P+C (N=790)**	**C (N=789)**	**P+C (N=618)**	**C (N=617)**	**P+C (N=279)**	**C (N=272)**
ORR						
Number of obj. responses	405	331	322	263	169	117
ORR, % (95% CI)	51.3 (47.7, 54.8)	42.0 (38.5, 45.5)	52.1 (48.1, 56.1)	42.6 (38.7, 46.6)	60.6 (54.6, 66.3)	43.0 (37.1, 49.1)
Difference in % (95% CI)[a]	9.3 (4.4, 14.1)		9.5 (3.9, 15.0)		17.5 (9.3, 25.5)	
p-Value[b]	0.00009		0.00041		0.00002	
Complete Response, n (%)	75 (9.5%)	49 (6.2%)	61 (9.9%)	36 (5.8%)	36 (12.9%)	14 (5.1%)
Partial Response, n (%)	330 (41.8%)	282 (35.7%)	261 (42.2%)	227 (36.8%)	133 (47.7%)	103 (37.9%)
Stable Disease, n (%)	256 (32.4%)	314 (39.8%)	194 (31.4%)	243 (39.4%)	70 (25.1%)	105 (38.6%)
Progressive Disease, n (%)	73 (9.2%)	87 (11.0%)	54 (8.7%)	64 (10.4%)	24 (8.6%)	28 (10.3%)
DOR (CR or PR)						
Number of responders	405	331	322	263	169	117
Median DOR, months (range)	8.0 (1.2+ - 41.5+)	5.7 (1.3+ - 34.7+)	8.3 (1.2+ - 41.5+)	5.6 (1.3+ - 34.2+)	10.9 (1.2+ - 41.5+)	5.8 (1.4+ - 31.2+)

[a] Based on Miettinen & Nurminen method stratified by Geographic region (Western Europe/Israel/North America/Australia, Asia and Rest of the World), PD-L1 status (CPS<1 vs. CPS>=1) and Chemotherapy regimen (FP or CAPOX) with small strata collapsed as pre-specified in the sSAP.
Western Europe includes France, Germany, Spain, Italy, United Kingdom, Ireland, Switzerland, Czech Republic, Denmark and Hungary, which is consistent with the ''Europe'' region defined in the protocol for stratification.
[b] One-sided p-value for testing. H0: difference in % = 0 versus H1: difference in % > 0.
Responses are based on BICR assessment per RECIST 1.1.
Database Cutoff Date: 03OCT2022

In the ITT population (all participants), a small and comparable proportion of patients were "not evaluable" (post-baseline assessment(s) available however not being evaluable) or had no post-baseline assessment available for response evaluation (0.9% and 6.2% "not evaluable" and "no assessment" in the pembrolizumab + chemotherapy group vs 1.6% and 5.6% in the chemotherapy group).

*Figure 12 KM Plots of **DOR** by BICR per RECIST 1.1 in Participants with a Confirmed Response*

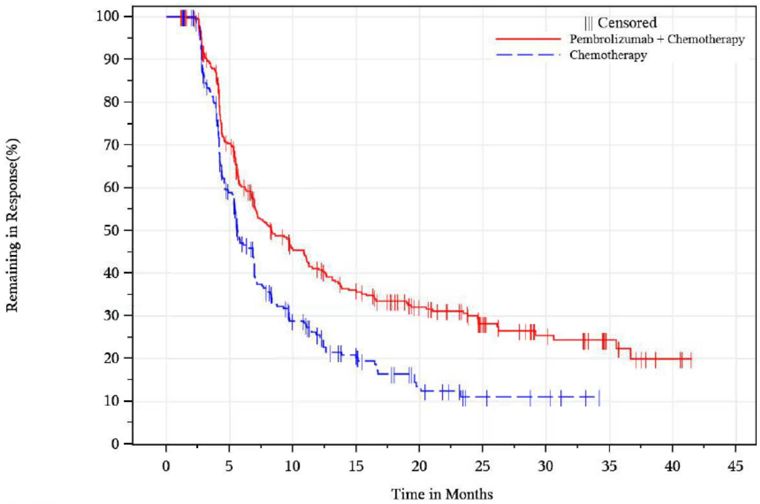
All participants



At Risk

Pembrolizumab + Chemotherapy	405	262	139	101	71	42	26	13	3	0
Chemotherapy	331	180	70	39	21	10	6	0	0	0

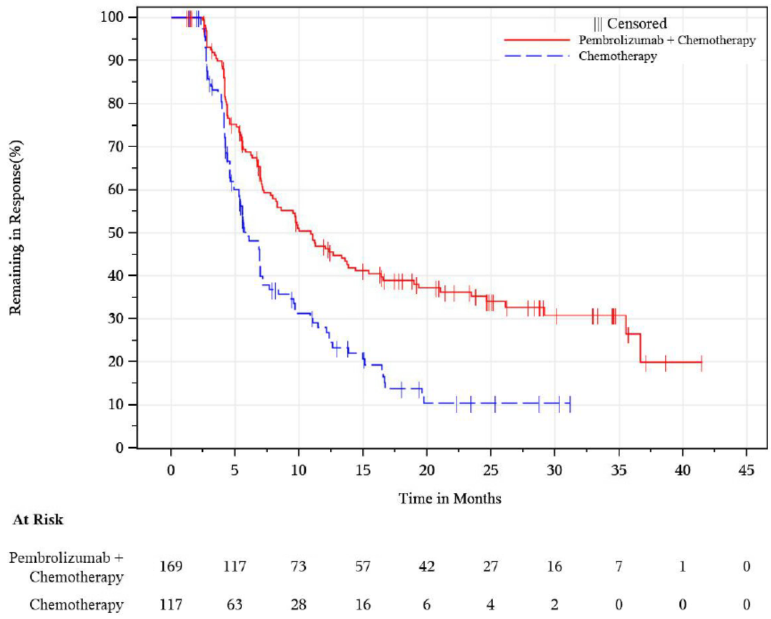
CPS ≥1



At Risk

Pembrolizumab + Chemotherapy	322	206	118	90	66	40	24	12	3	0
Chemotherapy	263	139	56	30	14	6	4	0	0	0

CPS ≥10



The **median time to response** was 1.5 months in both intervention groups for all participants and in the CPS ≥1 and CPS ≥10 subgroups.

Exploratory endpoints

PRO

Based on criteria for compliance and completion rates prespecified in the sSAP, Week 18 was selected as the time point for analysing changes from baseline for the EORTC QLQC30, QLQ-STO22, and EQ-5D-5L.

Compliance rates for all PROs, in the PRO FAS, CPS ≥1 and CPS ≥10 populations, were >90% at baseline and >80% after 18 weeks of follow-up in both treatment groups.

Baseline scores were similar in both intervention groups (for all prespecified items and across the PRO FAS, CPS ≥1 and CPS ≥10 populations).

EORTC QLQ-C30 (data not shown)

Prespecified scales: *GHS/QoL, physical functioning, role functioning, nausea/vomiting symptom scale, and appetite loss*

- At Week 18, the observed LS mean changes from baseline in scores for all these scales were similar in both intervention groups.
- There was a higher proportion of participants who improved (as defined in the sSAP) in the pembrolizumab plus chemotherapy group compared with the chemotherapy group for the GHS/QoL scale in the PRO FAS and CPS ≥10 populations, and for appetite loss, nausea and vomiting, and role functioning scale in the CPS ≥ 10 population (no difference for other scales and no difference for the proportion of participants who were considered improved and/or stable).
- The time to deterioration was similar in both intervention groups for all prespecified scales across all populations.

EORTC- QLQ-STO22 Scores (data not shown)

Prespecified symptom scale: *pain*

At Week 18, favourable effects for the symptom scale pain were observed for the pembrolizumab plus chemotherapy group compared with the chemotherapy group across all populations regarding

- the observed LS mean changes from baseline
- a higher proportion of participants whose symptom scale pain was improved

  (PRO FAS: 36.5% vs 31.1%; CPS ≥1: 37.3% vs 31.5%; CPS ≥10: 39.4% vs 29.3%)
- a higher proportion of participants whose symptom scale pain was improved and/or stable
- a prolonged time to deterioration

EuroQoL EQ-5D-5L Scores *(data not shown)*

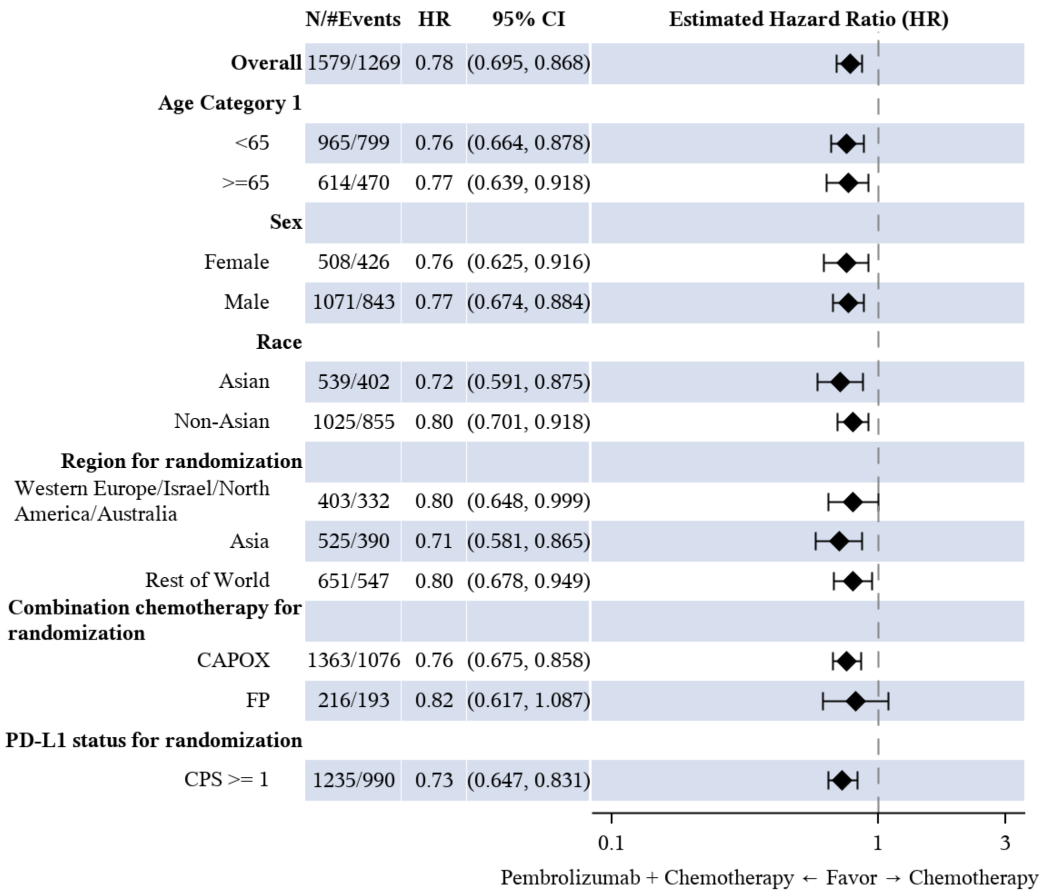
At Week 18, the observed LS mean change from baseline in EQ-5D-5L VAS was similar in both intervention groups across all populations.

Ancillary analyses

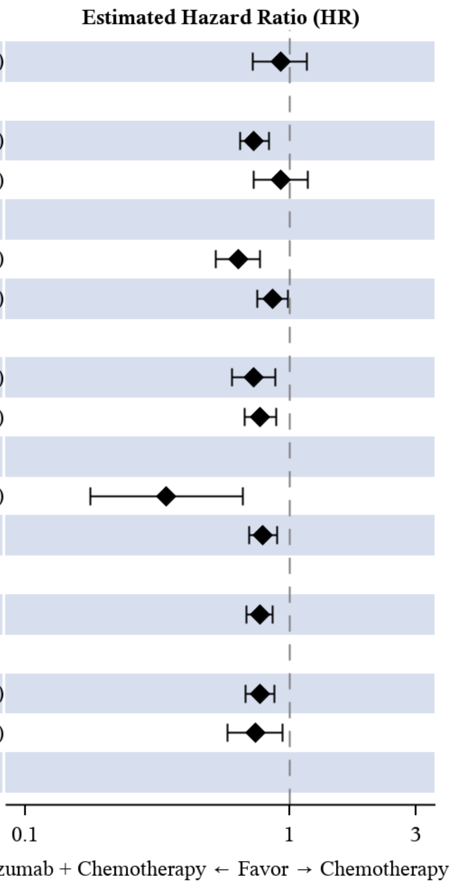
Subgroup analyses

- Overall survival

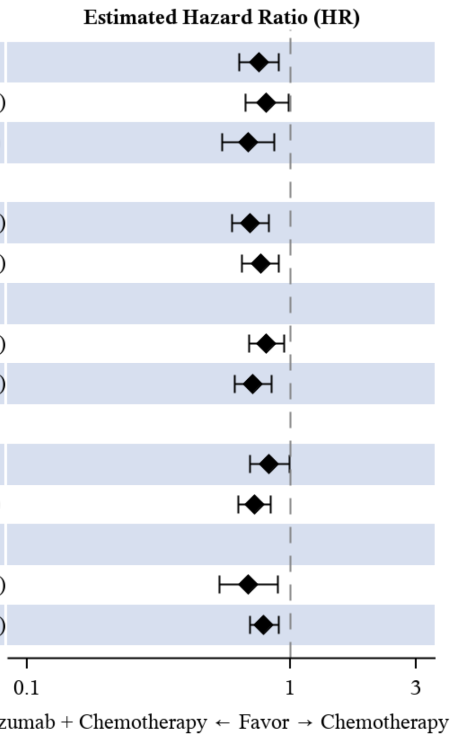
Figure 13 Forest Plot of OS Hazard Ratio by Subgroup Factors (ITT Population)



	N/#Events	HR	95% CI
CPS < 1	344/279	0.92	(0.726, 1.162)
Baseline PD-L1 status (CPS<1 vs >=1)			
CPS >= 1	1235/990	0.73	(0.647, 0.831)
CPS < 1	344/279	0.92	(0.729, 1.167)
Baseline PD-L1 status (CPS<10 vs >=10)			
CPS >= 10	551/414	0.64	(0.523, 0.772)
CPS < 10	1026/853	0.86	(0.751, 0.983)
ECOG Performance Status			
0	582/439	0.73	(0.602, 0.879)
1	997/830	0.77	(0.675, 0.886)
MSI Status			
MSI High	74/39	0.34	(0.176, 0.663)
non-MSI-High	1280/1037	0.79	(0.7, 0.894)
Disease status			
Metastatic	1520/1225	0.77	(0.686, 0.86)
Primary location			
Stomach	1243/992	0.77	(0.681, 0.874)
GEJ	334/276	0.74	(0.582, 0.941)
Histologic subtype			



	N/#Events	HR	95% CI
Diffuse	619/528	0.76	(0.639, 0.9)
Intestinal	557/430	0.81	(0.672, 0.982)
Indeterminate	401/309	0.69	(0.55, 0.865)
Tumor Burden			
>= Median	744/611	0.70	(0.599, 0.824)
< Median	742/585	0.77	(0.652, 0.904)
Number of metastases			
<=2	859/670	0.81	(0.698, 0.946)
>=3	719/598	0.72	(0.612, 0.845)
Liver metastases			
Yes	625/512	0.83	(0.7, 0.99)
No	953/756	0.73	(0.631, 0.84)
Prior gastrectomy/esophagectomy			
Yes	334/238	0.69	(0.538, 0.897)
No	1235/1022	0.79	(0.703, 0.899)



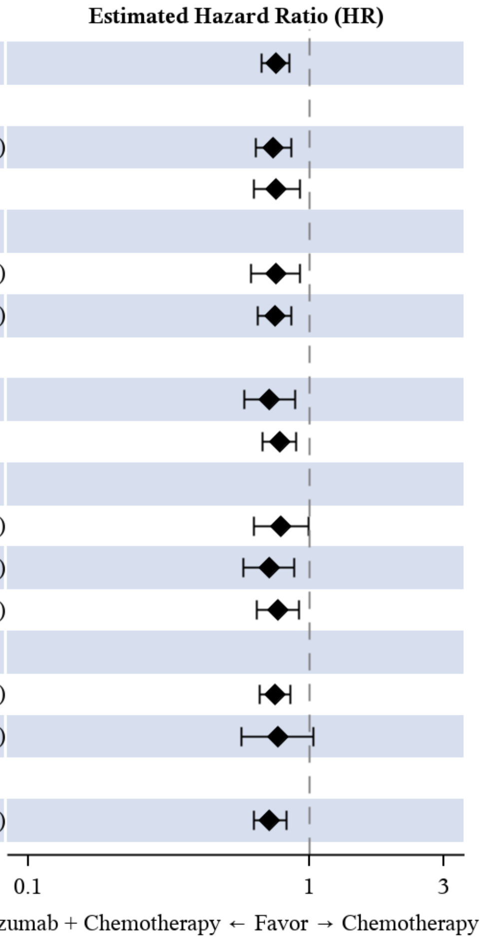
For overall population, analysis is based on Cox regression model with treatment as a covariate stratified by Geographic region (Western Europe/Israel/North America/Australia, Asia and Rest of the World), PD-L1 status (CPS<1 vs. CPS>=1), and Chemotherapy regimen (FP or CAPOX) with small strata collapsed as pre-specified in the sSAP.
Western Europe includes France, Germany, Spain, Italy, United Kingdom, Ireland, Switzerland, Czech Republic, Denmark and Hungary, which is consistent with the ''Europe'' region defined in the protocol for stratification.
For subgroups, analysis is based on unstratified Cox regression model with treatment as a covariate.

If any level of a subgroup variable has fewer than approximately 5% of the ITT population, subgroup analysis is not performed in that level of the subgroup variable.
Database Cutoff Date: 03OCT2022

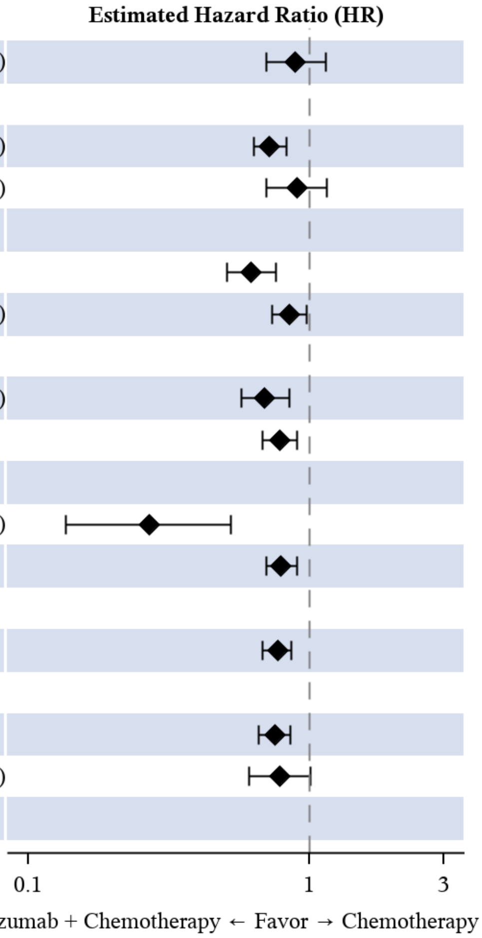
- Progression free survival

Figure 14 Forest Plot of PFS Hazard Ratio by Subgroup Factors Based on BICR Assessment per RECIST 1.1 (Primary Analysis) (ITT Population)

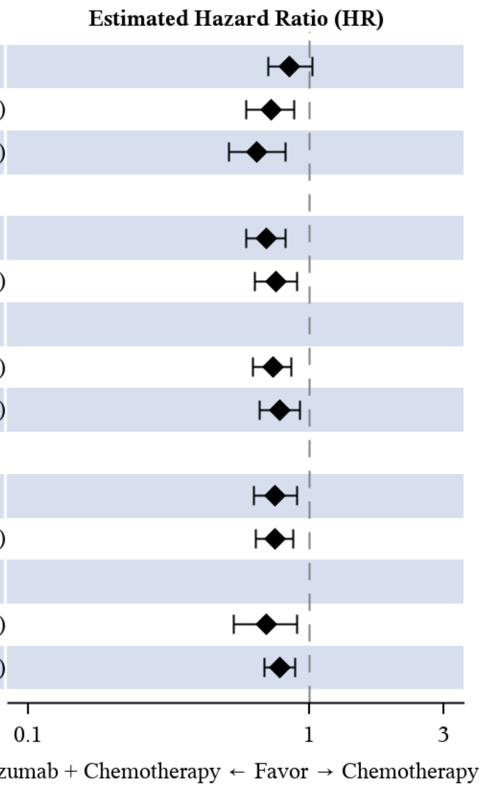
	N/#Events	HR	95% CI
Overall	1579/1180	0.76	(0.675, 0.85)
Age Category 1			
<65	965/735	0.74	(0.643, 0.862)
>=65	614/445	0.76	(0.633, 0.92)
Sex			
Female	508/385	0.76	(0.619, 0.926)
Male	1071/795	0.75	(0.652, 0.863)
Race			
Asian	539/357	0.72	(0.586, 0.89)
Non-Asian	1025/813	0.78	(0.68, 0.897)
Region for randomization			
Western Europe/Israel/North America/Australia	403/310	0.79	(0.632, 0.992)
Asia	525/347	0.72	(0.579, 0.884)
Rest of World	651/523	0.77	(0.646, 0.913)
Combination chemotherapy for randomization			
CAPOX	1363/995	0.75	(0.663, 0.852)
FP	216/185	0.77	(0.574, 1.029)
PD-L1 status for randomization			
CPS >= 1	1235/926	0.72	(0.635, 0.824)



	N/#Events	HR	95% CI
CPS < 1	344/254	0.89	(0.699, 1.144)
Baseline PD-L1 status (CPS<1 vs >=1)			
CPS >= 1	1235/926	0.72	(0.635, 0.824)
CPS < 1	344/254	0.90	(0.701, 1.148)
Baseline PD-L1 status (CPS<10 vs >=10)			
CPS >= 10	551/400	0.62	(0.51, 0.759)
CPS < 10	1026/779	0.85	(0.738, 0.978)
ECOG Performance Status			
0	582/413	0.69	(0.571, 0.845)
1	997/767	0.78	(0.68, 0.904)
MSI Status			
MSI High	74/38	0.27	(0.136, 0.526)
non-MSI-High	1280/973	0.79	(0.699, 0.9)
Disease status			
Metastatic	1520/1141	0.77	(0.681, 0.86)
Primary location			
Stomach	1243/922	0.75	(0.66, 0.856)
GEJ	334/257	0.78	(0.609, 1.007)
Histologic subtype			



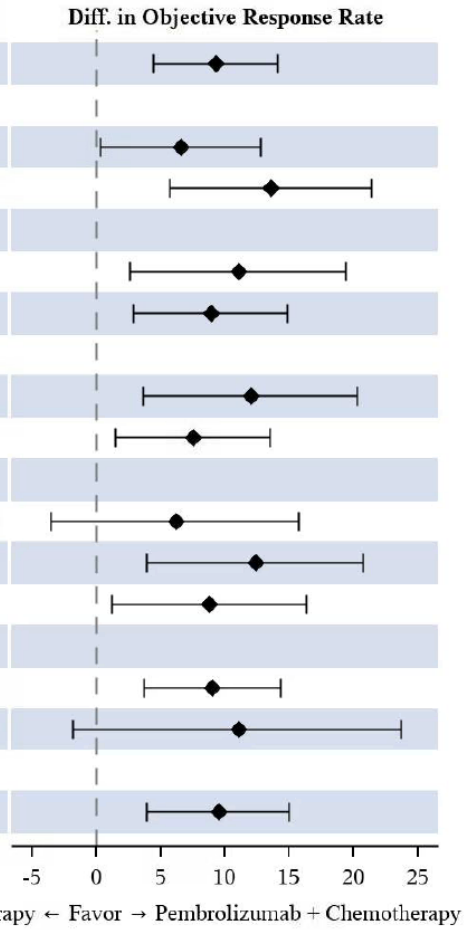
	N/#Events	HR	95% CI
Diffuse	619/473	0.85	(0.71, 1.02)
Intestinal	557/409	0.73	(0.596, 0.883)
Indeterminate	401/297	0.65	(0.518, 0.822)
Tumor Burden			
>= Median	744/597	0.70	(0.593, 0.82)
< Median	742/524	0.76	(0.636, 0.899)
Number of metastases			
<=2	859/608	0.74	(0.627, 0.863)
>=3	719/571	0.78	(0.662, 0.921)
Liver metastases			
Yes	625/503	0.75	(0.633, 0.9)
No	953/676	0.75	(0.645, 0.874)
Prior gastrectomy/esophagectomy			
Yes	334/228	0.70	(0.535, 0.903)
No	1235/944	0.78	(0.689, 0.891)

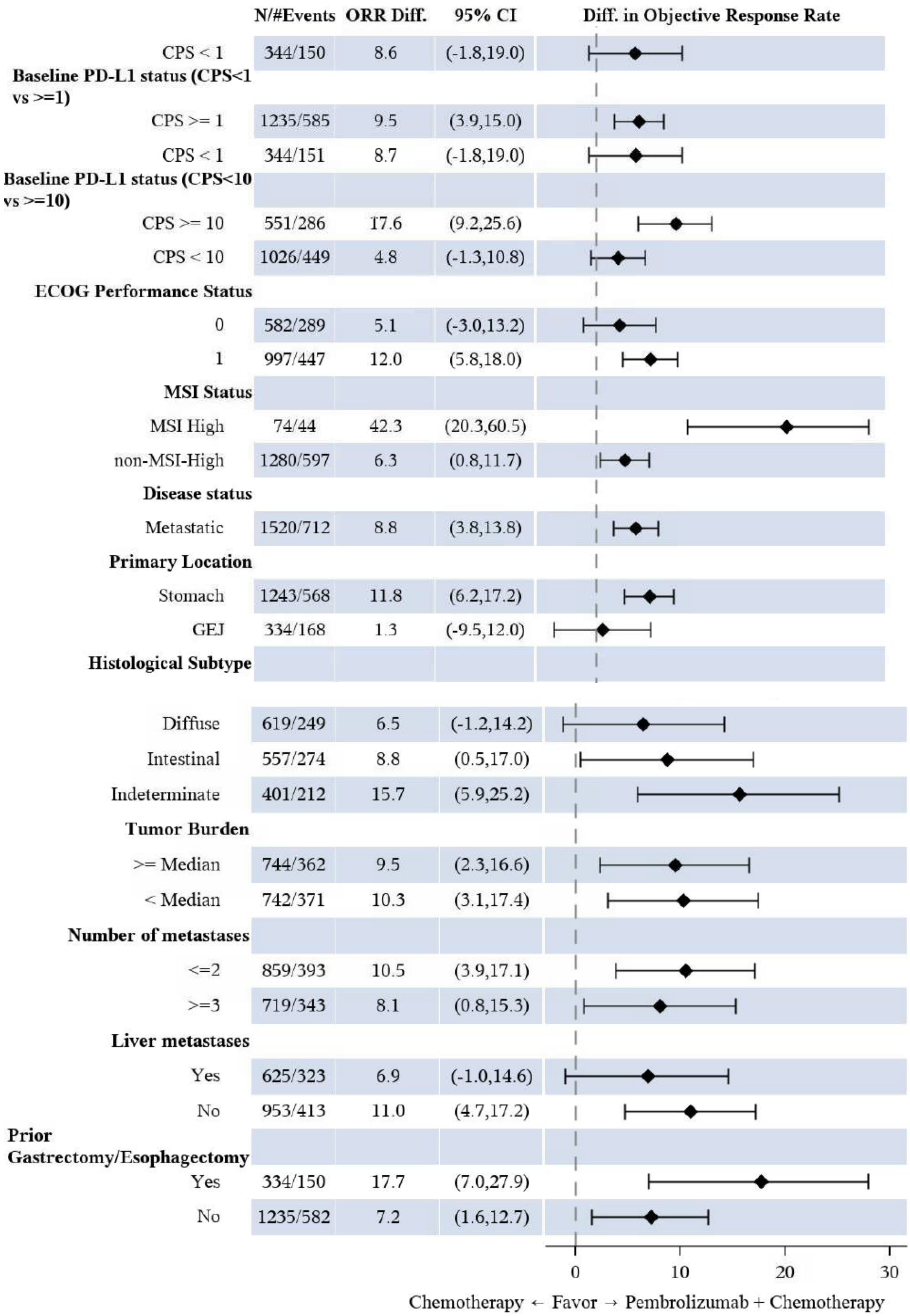


- <u>Objective Response Rate</u>

Figure 15 Forest Plot of Difference in Objective Response Rate (Confirmed) by Subgroup Factors Based on BICR Assessment per RECIST 1.1 (ITT Population)

	N/#Events	ORR Diff.	95% CI
Overall	1579/736	9.3	(4.4,14.1)
Age Category 1			
<65 years	965/443	6.6	(0.3,12.8)
>=65 years	614/293	13.6	(5.7,21.4)
Sex			
Female	508/195	11.1	(2.6,19.4)
Male	1071/541	8.9	(2.9,14.8)
Race			
Asian	539/295	12.0	(3.6,20.3)
Non-Asian	1025/437	7.5	(1.5,13.5)
Region for randomization			
Western Europe/Israel/North America/Australia	403/174	6.2	(-3.5,15.7)
Asia	525/289	12.4	(3.9,20.7)
Rest of the World	651/273	8.8	(1.2,16.3)
Combination chemotherapy for randomization			
CAPOX	1363/656	9.0	(3.7,14.3)
FP	216/80	11.1	(-1.8,23.7)
PD-L1 status for randomization			
CPS >= 1	1235/586	9.5	(3.9,15.0)





These analyses are post hoc and not prespecified. Exploratory subgroups were not individually powered to demonstrate treatment effect.

Efficacy by PD-L1 expression – complementary analyses

- **CPS <1**

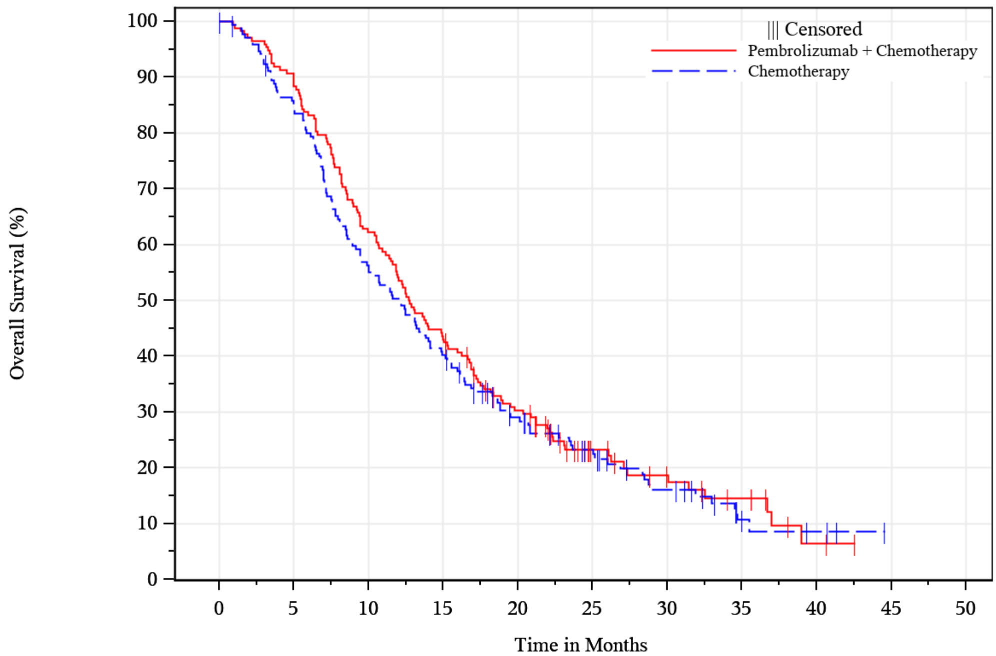
<u>Overall Survival</u>

Table 28 Analysis of Overall Survival (ITT Population with CPS <1)

	Pembrolizumab + Chemotherapy (N=172)	Chemotherapy (N=172)
Number of Events (%)	139 (80.8)	140 (81.4)
Kaplan-Meier Estimates (months)[a]		
Median (95% CI)	12.7 (11.4, 15.0)	12.2 (9.5, 14.0)
[Q1, Q3]	[7.7, 22.4]	[6.8, 23.5]
Person-months	2568.4	2430.8
Event Rate / 100 Person-months	5.4	5.8
vs Chemotherapy		
Hazard Ratio (95% CI)[b]	0.92 (0.73, 1.17)	
p-value[c]	0.2497	
OS Rate at month 6 (%) (95% CI)	83.1 (76.7, 88.0)	79.9 (73.1, 85.2)
OS Rate at month 12 (%) (95% CI)	53.5 (45.8, 60.6)	50.3 (42.6, 57.6)
OS Rate at month 18 (%) (95% CI)	34.1 (27.0, 41.2)	33.6 (26.6, 40.8)
OS Rate at month 24 (%) (95% CI)	23.3 (17.0, 30.1)	23.2 (17.0, 30.1)
OS Rate at month 30 (%) (95% CI)	18.7 (12.6, 25.8)	16.0 (10.4, 22.7)

[a] From product-limit (Kaplan-Meier) method for censored data.
[b] based on unstratified cox regression model with Efron's method of tie handling with treatment as a covariate.
[c] One-sided p-value based on unstratified log-rank test.
Database Cutoff Date: 03OCT2022

Figure 16 Kaplan-Meier Plot of Overall Survival (ITT Population with CPS <1)



At Risk

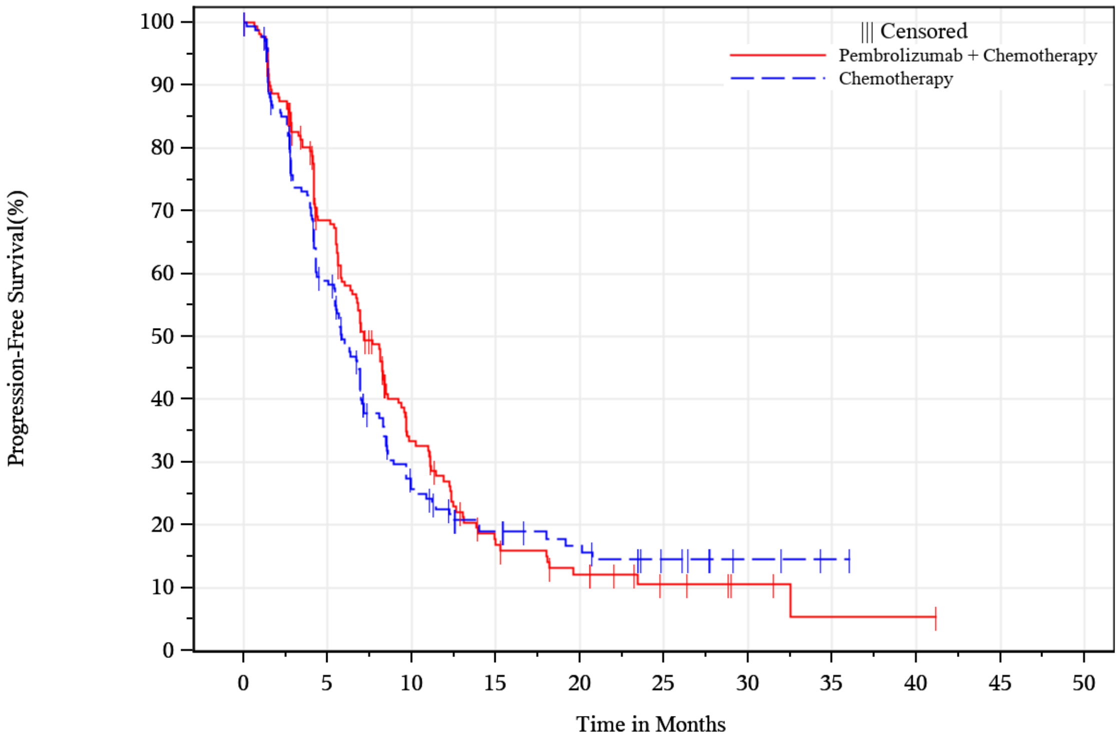
Pembrolizumab + Chemotherapy	172	152	107	74	48	22	14	9	2	0	0
Chemotherapy	172	143	95	68	43	29	17	6	3	0	0

<u>Progression-free Survival</u>

Table 29 Analysis of PFS (Primary Analysis) by BICR per RECIST 1.1 (ITT Population with CPS <1)

	Pembrolizumab + Chemotherapy (N=172)	Chemotherapy (N=172)
Number of Events (%)	129 (75.0)	125 (72.7)
Death	18 (10.5)	22 (12.8)
Documented progression	111 (64.5)	103 (59.9)
Kaplan-Meier Estimates (months)		
Median (95% CI)	7.2 (6.0, 8.5)	5.8 (5.4, 6.9)
[Q1, Q3]	[4.2, 12.4]	[3.0, 10.2]
Person-months	1380.4	1254.1
Event Rate / 100 Person-months	9.3	10.0
vs Chemotherapy		
Hazard Ratio (95% CI)	0.90 (0.70, 1.15)	
p-value	0.1950	
PFS Rate at month 6 (%) (95% CI)	58.7 (50.6, 65.9)	49.6 (41.5, 57.1)
PFS Rate at month 12 (%) (95% CI)	27.0 (19.9, 34.5)	22.6 (16.0, 29.8)
PFS Rate at month 18 (%) (95% CI)	16.0 (10.2, 22.9)	18.9 (12.8, 26.0)
PFS Rate at month 24 (%) (95% CI)	10.6 (5.7, 17.3)	14.5 (8.8, 21.5)
PFS Rate at month 30 (%) (95% CI)	10.6 (5.7, 17.3)	14.5 (8.8, 21.5)

Figure 17 KM Plot of PFS (Primary Analysis) by BICR per RECIST 1.1 (ITT Population with CPS <1)



At Risk

Pembrolizumab + Chemotherapy	172	105	43	19	12	6	3	1	1	0	0
Chemotherapy	172	90	33	20	15	8	3	1	0	0	0

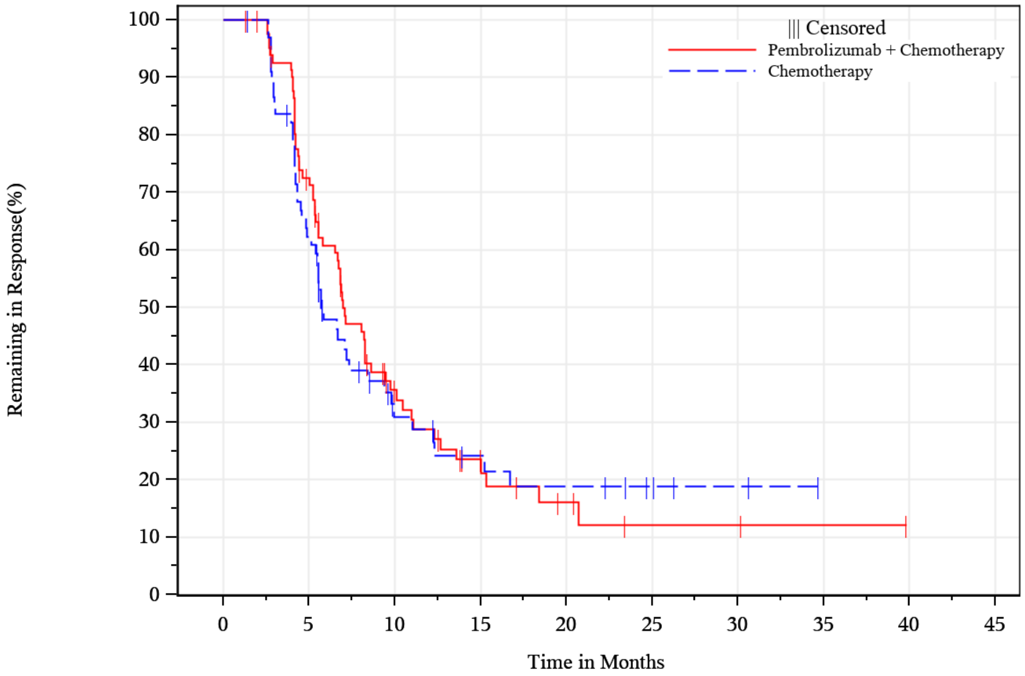
<u>Objective Response Rate</u>

Table 30 Summary of Best Objective Response (Confirmed) by BICR per RECIST 1.1 (ITT Population with CPS<1)

	Pembrolizumab + Chemotherapy			Chemotherapy		
	n	(%)	(95% CI)	n	(%)	(95% CI)
Number of Participants in Population	172			172		
Complete Response (CR)	14	8.1	(4.5, 13.3)	13	7.6	(4.1, 12.6)
Partial Response (PR)	69	40.1	(32.7, 47.9)	55	32.0	(25.1, 39.5)
Overall Response (CR+PR)	**83**	**48.3**	**(40.6, 56.0)**	**68**	**39.5**	**(32.2, 47.3)**
Stable Disease (SD)	62	36.0	(28.9, 43.7)	71	41.3	(33.8, 49.0)
Disease Control (CR+PR+SD)	**145**	**84.3**	**(78.0, 89.4)**	**139**	**80.8**	**(74.1, 86.4)**
Progressive Disease (PD)	19	11.0	(6.8, 16.7)	23	13.4	(8.7, 19.4)
Not Evaluable (NE)	2	1.2	(0.1, 4.1)	1	0.6	(0.0, 3.2)
No Assessment	6	3.5	(1.3, 7.4)	9	5.2	(2.4, 9.7)

Duration of Response

Figure 18 KM Plot of DoR by BICR per RECIST 1.1 in Participants with a Confirmed Response (CPS<1)



At Risk

Pembrolizumab + Chemotherapy	83	56	21	11	5	2	2	1	0	0
Chemotherapy	68	41	14	9	7	4	2	0	0	0

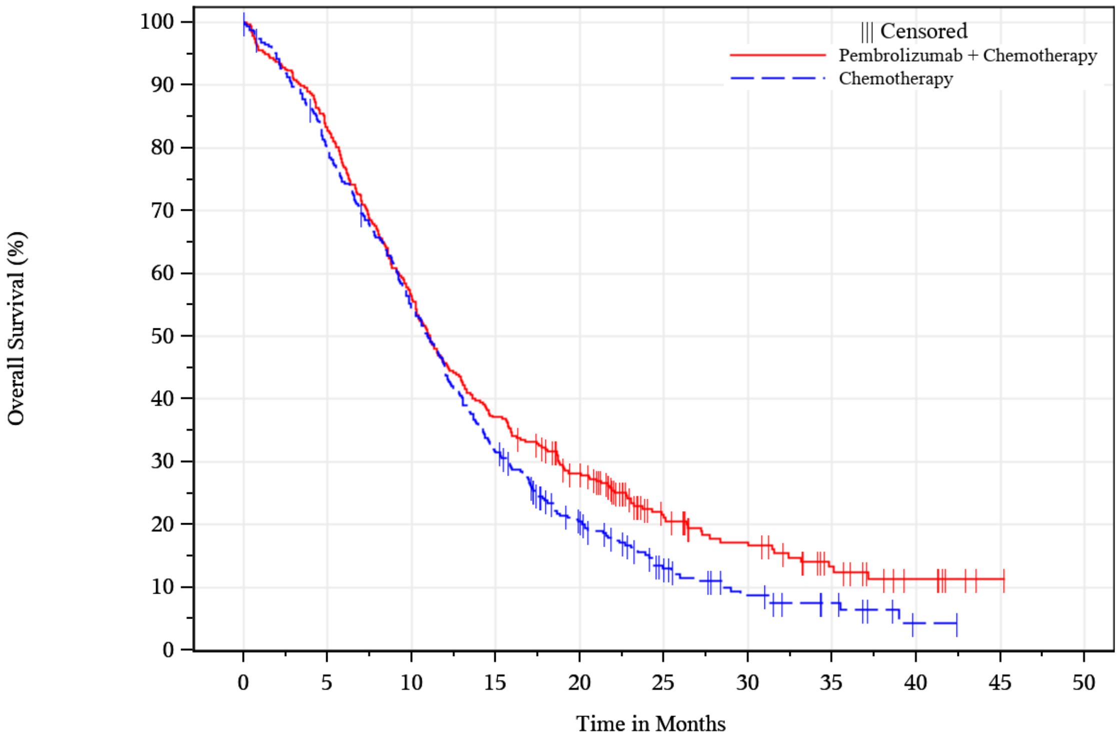
- **CPS ≥1 to <10**

Overall Survival

Table 31 Analysis of Overall Survival (ITT Population with CPS ≥1 to <10)

	Pembrolizumab + Chemotherapy (N=337)	Chemotherapy (N=345)
Number of Events (%)	274 (81.3)	300 (87.0)
Kaplan-Meier Estimates (months)[a]		
Median (95% CI)	11.1 (10.2, 12.2)	10.9 (9.9, 12.0)
[Q1, Q3]	[6.3, 22.7]	[5.8, 17.3]
Person-months	4685.5	4260.9
Event Rate / 100 Person-months	5.8	7.0
vs Chemotherapy		
Hazard Ratio (95% CI)[b]	0.83 (0.70, 0.98)	
p-value[c]	0.0134	
OS Rate at month 6 (%) (95% CI)	76.9 (72.0, 81.0)	74.6 (69.6, 78.9)
OS Rate at month 12 (%) (95% CI)	45.7 (40.3, 50.9)	44.1 (38.7, 49.3)
OS Rate at month 18 (%) (95% CI)	32.0 (27.1, 37.0)	23.8 (19.4, 28.5)
OS Rate at month 24 (%) (95% CI)	22.5 (18.0, 27.3)	15.1 (11.4, 19.4)
OS Rate at month 30 (%) (95% CI)	16.6 (12.3, 21.5)	8.7 (5.6, 12.7)

Figure 19 Kaplan-Meier Plot of Overall Survival (ITT Population with CPS ≥1 to <10)



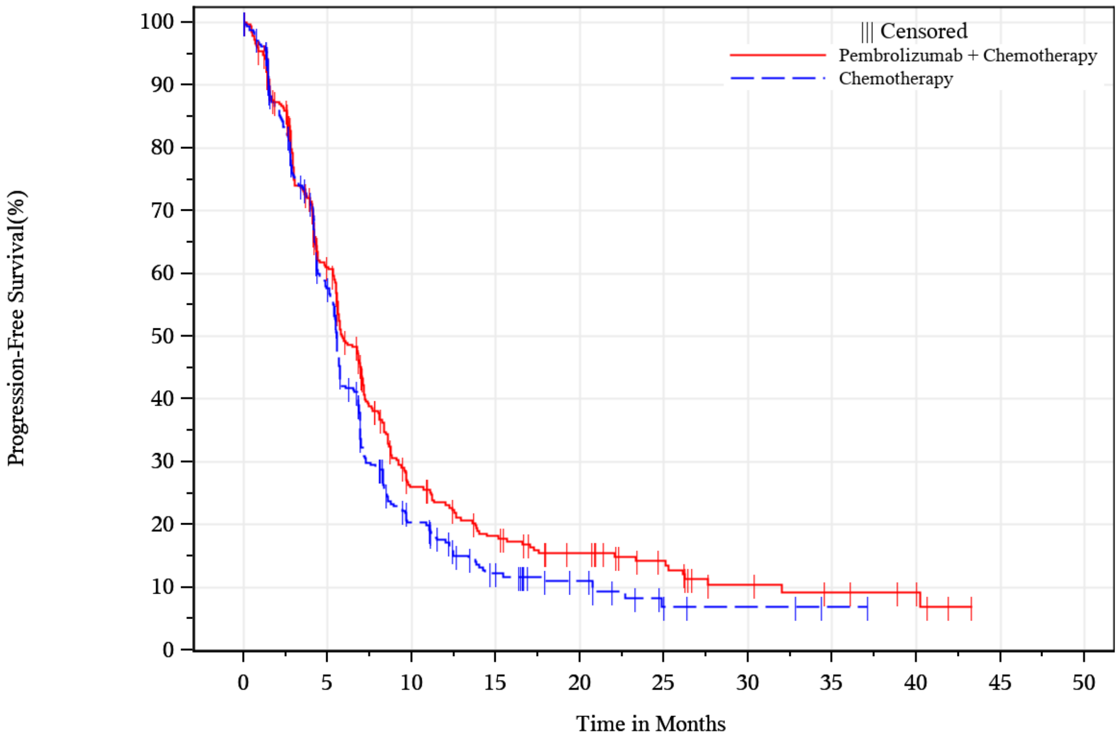
At Risk											
Pembrolizumab + Chemotherapy	337	279	189	125	87	44	29	16	7	1	0
Chemotherapy	345	273	185	107	59	29	15	8	1	0	0

<u>Progression-free Survival</u>

Table 32 Analysis of PFS (Primary Analysis) by BICR per RECIST 1.1 (ITT with CPS ≥1 to <10)

	Pembrolizumab + Chemotherapy (N=337)	Chemotherapy (N=345)
Number of Events (%)	252 (74.8)	273 (79.1)
Death	58 (17.2)	56 (16.2)
Documented progression	194 (57.6)	217 (62.9)
Kaplan-Meier Estimates (months)[a]		
Median (95% CI)	5.9 (5.6, 7.0)	5.6 (5.3, 5.7)
[Q1, Q3]	[3.0, 11.2]	[3.2, 8.5]
Person-months	2566.0	2189.8
Event Rate / 100 Person-months	9.8	12.5
vs Chemotherapy		
Hazard Ratio (95% CI)[b]	0.83 (0.70, 0.99)	
p-value[c]	0.0170	
PFS Rate at month 6 (%) (95% CI)	49.3 (43.5, 54.8)	42.1 (36.6, 47.4)
PFS Rate at month 12 (%) (95% CI)	23.1 (18.3, 28.3)	17.1 (13.0, 21.8)
PFS Rate at month 18 (%) (95% CI)	15.4 (11.3, 20.1)	11.0 (7.5, 15.3)
PFS Rate at month 24 (%) (95% CI)	14.2 (10.1, 18.9)	8.3 (4.8, 12.8)
PFS Rate at month 30 (%) (95% CI)	10.4 (6.5, 15.2)	6.9 (3.5, 11.8)

Figure 20 KM Plot of PFS (Primary Analysis) by BICR per RECIST 1.1 (ITT with CPS ≥1 to <10)



At Risk

Pembrolizumab + Chemotherapy	337	179	66	43	30	20	10	7	5	0	0
Chemotherapy	345	179	53	24	14	5	3	1	0	0	0

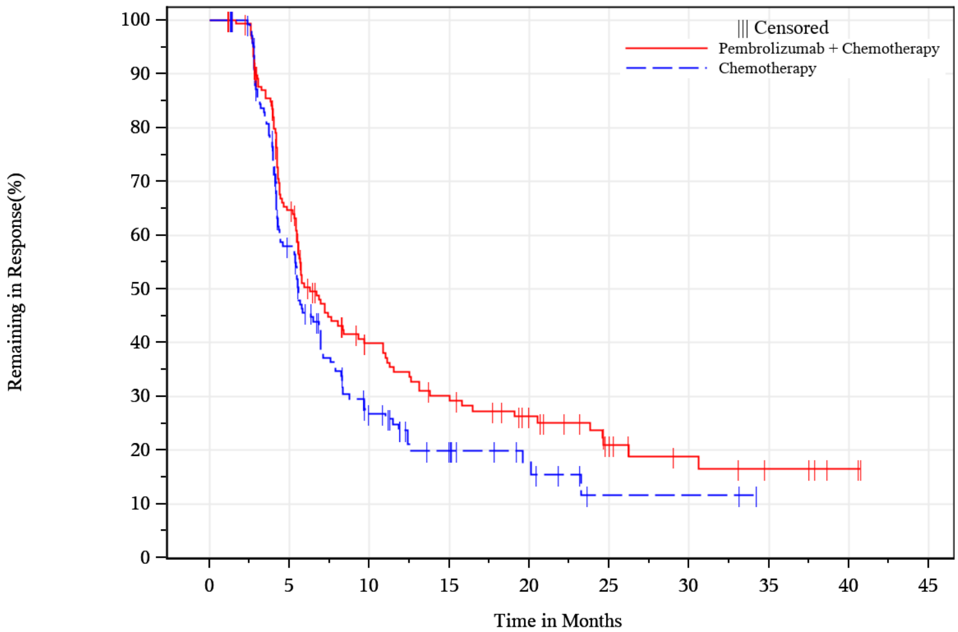
<u>Objective Response Rate</u>

Table 33 Best Objective Response (Confirmed) by BICR per RECIST 1.1 (CPS ⩾1 to <10)

	Pembrolizumab + Chemotherapy			Chemotherapy		
	n	(%)	(95% CI)	n	(%)	(95% CI)
Number of Participants in Population	337			345		
Complete Response (CR)	25	7.4	(4.9, 10.8)	22	6.4	(4.0, 9.5)
Partial Response (PR)	127	37.7	(32.5, 43.1)	124	35.9	(30.9, 41.3)
Overall Response (CR+PR)	**152**	**45.1**	**(39.7, 50.6)**	**146**	**42.3**	**(37.0, 47.7)**
Stable Disease (SD)	123	36.5	(31.3, 41.9)	138	40.0	(34.8, 45.4)
Disease Control (CR+PR+SD)	**275**	**81.6**	**(77.0, 85.6)**	**284**	**82.3**	**(77.9, 86.2)**
Progressive Disease (PD)	30	8.9	(6.1, 12.5)	36	10.4	(7.4, 14.2)
Not Evaluable (NE)	2	0.6	(0.1, 2.1)	7	2.0	(0.8, 4.1)
No Assessment	30	8.9	(6.1, 12.5)	18	5.2	(3.1, 8.1)

Duration of Response

Figure 21 KM Plot of DoR by BICR per RECIST 1.1 (CPS ≥1 to <10)



At Risk										
Pembrolizumab + Chemotherapy	152	89	45	33	24	13	8	5	2	0
Chemotherapy	146	76	28	14	8	2	2	0	0	0

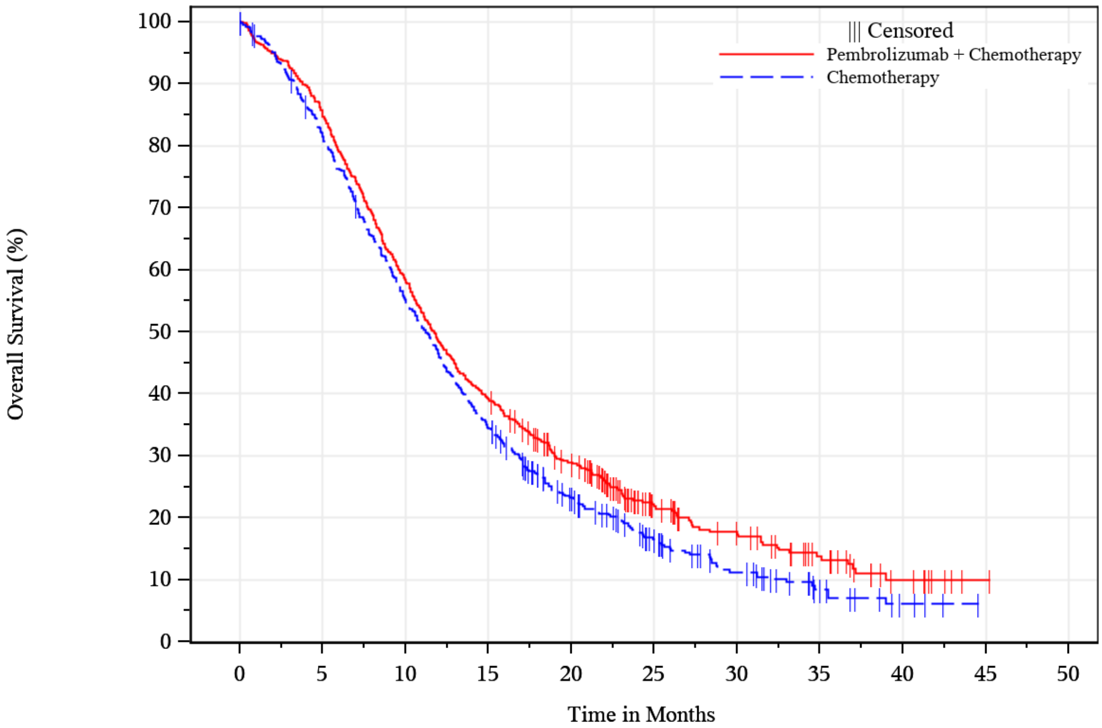
- **CPS <10**

Overall Survival

Table 34 Analysis of Overall Survival (ITT Population with CPS <10)

	Pembrolizumab + Chemotherapy (N=509)	Chemotherapy (N=517)
Number of Events (%)	413 (81.1)	440 (85.1)
Kaplan-Meier Estimates (months)[a]		
Median (95% CI)	11.7 (10.7, 12.8)	11.2 (10.0, 12.1)
[Q1, Q3]	[6.9, 22.4]	[6.3, 18.8]
Person-months	7254.0	6691.8
Event Rate / 100 Person-months	5.7	6.6
vs Chemotherapy		
Hazard Ratio (95% CI)[b]	0.86 (0.75, 0.98)	
p-value[c]	0.0135	
OS Rate at month 6 (%) (95% CI)	79.0 (75.2, 82.3)	76.4 (72.4, 79.8)
OS Rate at month 12 (%) (95% CI)	48.3 (43.9, 52.6)	46.1 (41.8, 50.4)
OS Rate at month 18 (%) (95% CI)	32.7 (28.7, 36.8)	27.1 (23.3, 31.0)
OS Rate at month 24 (%) (95% CI)	22.8 (19.1, 26.7)	17.8 (14.5, 21.5)
OS Rate at month 30 (%) (95% CI)	17.3 (13.8, 21.3)	11.2 (8.3, 14.6)

Figure 22 Kaplan-Meier Plot of Overall Survival (ITT Population with CPS <10)



At Risk

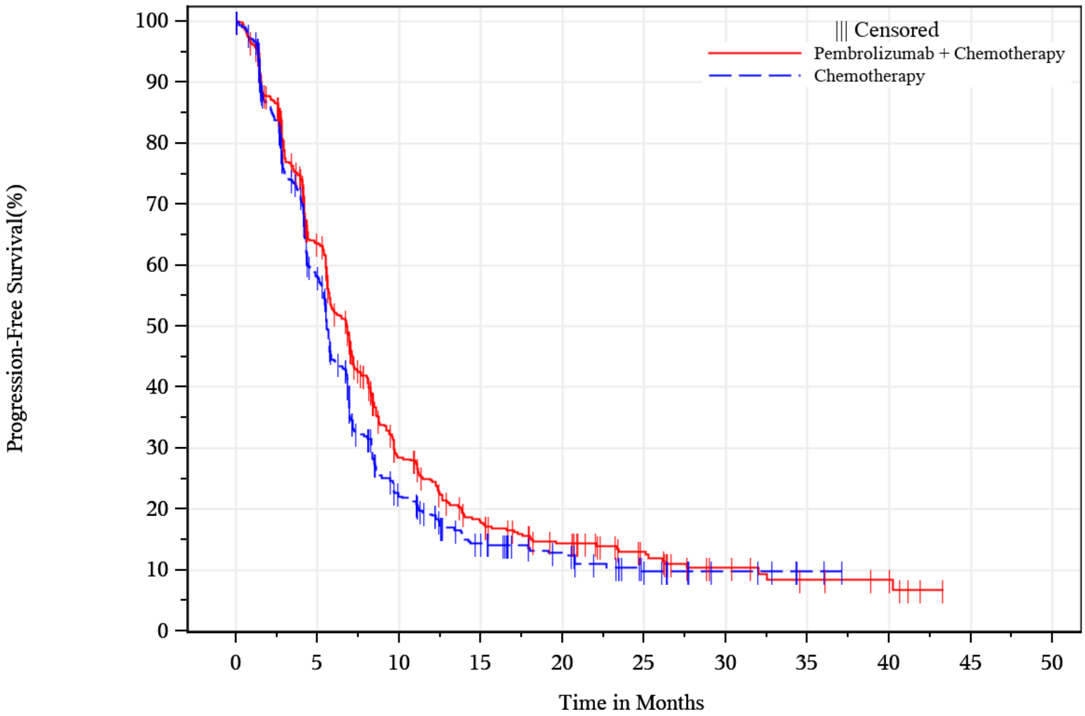
Pembrolizumab + Chemotherapy	509	431	296	199	135	66	43	25	9	1	0
Chemotherapy	517	416	280	175	102	58	32	14	4	0	0

Progression-free Survival

Table 35 Analysis of PFS (Primary Analysis) by BICR per RECIST 1.1 (ITT Population with CPS <10)

	Pembrolizumab + Chemotherapy (N=509)	Chemotherapy (N=517)
Number of Events (%)	381 (74.9)	398 (77.0)
Death	76 (14.9)	78 (15.1)
Documented progression	305 (59.9)	320 (61.9)
Kaplan-Meier Estimates (months)[a]		
Median (95% CI)	6.8 (5.7, 7.1)	5.6 (5.5, 5.8)
[Q1, Q3]	[3.8, 11.9]	[3.0, 9.5]
Person-months	3946.4	3443.9
Event Rate / 100 Person-months	9.7	11.6
vs Chemotherapy		
Hazard Ratio (95% CI)[b]	0.85 (0.74, 0.98)	
p-value[c]	0.0121	
PFS Rate at month 6 (%) (95% CI)	52.5 (47.9, 57.0)	44.5 (40.0, 49.0)
PFS Rate at month 12 (%) (95% CI)	24.5 (20.4, 28.7)	18.9 (15.3, 22.8)
PFS Rate at month 18 (%) (95% CI)	15.7 (12.2, 19.5)	13.7 (10.4, 17.3)
PFS Rate at month 24 (%) (95% CI)	13.0 (9.7, 16.8)	10.5 (7.4, 14.1)
PFS Rate at month 30 (%) (95% CI)	10.3 (7.2, 14.2)	9.8 (6.7, 13.5)

Figure 23 KM Plot of PFS (Primary Analysis) by BICR per RECIST 1.1 (ITT Population with CPS <10)



At Risk

Pembrolizumab + Chemotherapy	509	284	109	62	42	26	13	8	6	0	0
Chemotherapy	517	269	86	44	29	13	6	2	0	0	0

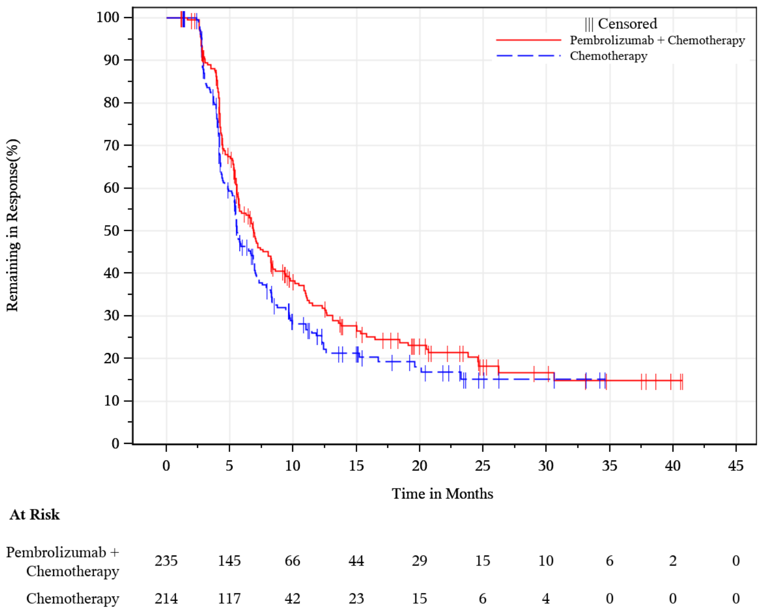
<u>Objective Response Rate</u>

Table 36 Best Objective Response (Confirmed) by BICR per RECIST 1.1 (ITT with CPS <10)

	Pembrolizumab + Chemotherapy			Chemotherapy		
	n	(%)	(95% CI)	n	(%)	(95% CI)
Number of Participants in Population	509			517		
Complete Response (CR)	39	7.7	(5.5, 10.3)	35	6.8	(4.8, 9.3)
Partial Response (PR)	196	38.5	(34.3, 42.9)	179	34.6	(30.5, 38.9)
Overall Response (CR+PR)	**235**	**46.2**	**(41.8, 50.6)**	**214**	**41.4**	**(37.1, 45.8)**
Stable Disease (SD)	185	36.3	(32.2, 40.7)	209	40.4	(36.2, 44.8)
Disease Control (CR+PR+SD)	**420**	**82.5**	**(78.9, 85.7)**	**423**	**81.8**	**(78.2, 85.0)**
Progressive Disease (PD)	49	9.6	(7.2, 12.5)	59	11.4	(8.8, 14.5)
Not Evaluable (NE)	4	0.8	(0.2, 2.0)	8	1.5	(0.7, 3.0)
No Assessment	36	7.1	(5.0, 9.7)	27	5.2	(3.5, 7.5)

Duration of Response

Figure 24 KM Plot of DoR by BICR per RECIST 1.1 in Participants with a Confirmed Response (CPS<10)



Summary of efficacy for complementary PD-L1 subgroups

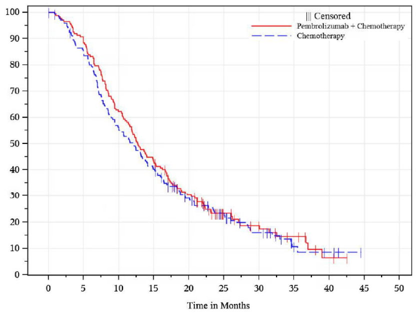
Table 37 Summary of efficacy for complementary PD-L1 subgroups CPS <1, CPS ≥ 1 to <10 and CPS <10

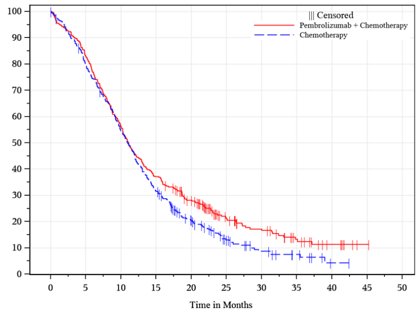
Efficacy Endpoint	PD-L1 CPS < 1		PD-L1 CPS ≥ 1 to <10		PD-L1 CPS < 10	
	P+C (N=172)	C (N=172)	P+C (N=337)	C (N=345)	P+C (N=509)	C (N=517)
OS						
Number of events (%)	139 (80.8)	140 (81.4)	274 (81.3)	300 (87.0)	413 (81.1)	440 (85.1)
Median OS, months (95% CI)	12.7 (11.4, 15.0)	12.2 (9.5, 14.0)	11.1 (10.2, 12.2)	10.9 (9.9, 12.0)	11.7 (10.7, 12.8)	11.2 (10.0, 12.1)
HR (95% CI)	0.92 (0.73, 1.17)		0.83 (0.70, 0.98)		0.86 (0.75, 0.98)	
p-Value *	0.2497		0.0134		0.0135	
PFS (BICR per RECIST 1.1)						
Number of events (%)	129 (75.0)	125 (72.7)	252 (74.8)	273 (79.1)	381 (74.9)	398 (77.0)
Median PFS (95% CI), months	7.2 (6.0, 8.5)	5.8 (5.4, 6.9)	5.9 (5.6, 7.0)	5.6 (5.3, 5.7)	6.8 (5.7, 7.1)	5.6 (5.5, 5.8)
HR (95% CI)	0.90 (0.70, 1.15)		0.83 (0.70, 0.99)		0.85 (0.74, 0.98)	
p-Value *	0.1950		0.0170		0.0121	
ORR (BICR per RECIST 1.1)						
ORR, % (95% CI)	48.3 (40.6, 56.0)	39.5 (32.2, 47.3)	45.1 (39.7, 50.6)	42.3 (37.0, 47.7)	46.2 (41.8, 50.6)	41.4 (37.1, 45.8)
ORR difference (%)	8.5		2.8		4.8	

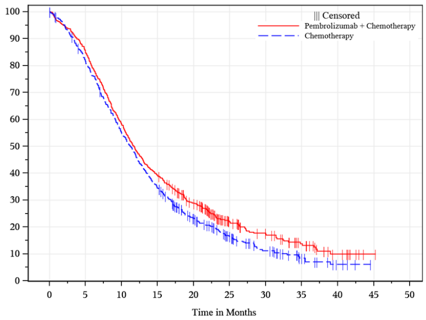
Figure 25 KM Plots of OS and PFS for complementary PD-L1 subgroups CPS <1, CPS ≥ 1 to <10 and CPS <10

CPS <1 **CPS ≥ 1 to <10** **CPS < 10**

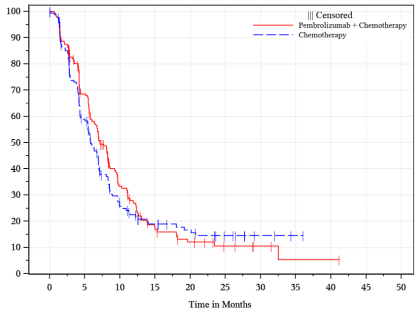
OS

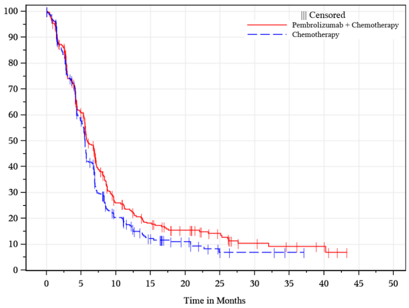


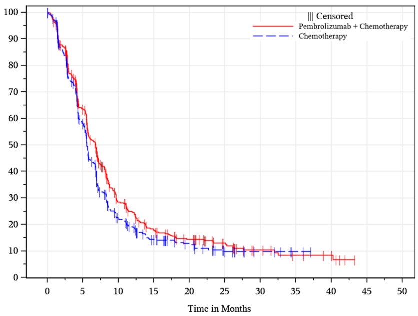




PFS







Note: Please see discussion on clinical efficacy for comments on PD-L1 subgroup results

Table 38 Analysis of Association between PD-L1 CPS and Overall Survival (ITT Population)

Treatment	N	Event n (%)	Hazard Ratio for Square Root of CPS†	
			Hazard Ratio (95% CI)	p-Value‡
Pembrolizumab + Chemotherapy	790	603 (76.3%)	0.929 (0.893, 0.966)	0.0002
Chemotherapy	789	666 (84.4%)	0.987 (0.956, 1.020)	0.4411

† From a Cox regression model with Efron's method of tie handling using PD-L1 CPS on the square root scale as a continuous covariate. Each treatment group was analysed separately. Hazard ratio (HR) represents ratio of the hazard rates for the event as CPS increases by 1 on the square root scale. A HR of 1 indicates that CPS does not affect the hazard rate. A HR of greater than 1 indicates that there is higher hazard as CPS increases. A HR of less than 1 indicates that there is lower hazard as CPS increases.
‡ Two-sided p-value from the Cox regression model.
Database Cutoff Date: 03OCT2022

Table 39 Table Analysis of Association between PD-L1 CPS and PFS by BICR per RECIST 1.1 (ITT Population)

Treatment	N	Event n (%)	Hazard Ratio for Square Root of CPS†	
			Hazard Ratio (95% CI)	p-Value‡
Pembrolizumab + Chemotherapy	790	572 (72.4%)	0.940 (0.904, 0.978)	0.0021
Chemotherapy	789	608 (77.1%)	1.006 (0.973, 1.040)	0.7166

† From a Cox regression model with Efron's method of tie handling using PD-L1 CPS on the square root scale as a continuous covariate. Each treatment group was analysed separately. Hazard ratio (HR) represents ratio of the hazard rates for the event as CPS increases by 1 on the square root scale. A HR of 1 indicates that CPS does not affect the hazard rate. A HR of greater than 1 indicates that there is higher hazard as CPS increases. A HR of less than 1 indicates that there is lower hazard as CPS increases.
‡ Two-sided p-value from the Cox regression model.
Database Cutoff Date: 03OCT2022

Exploratory analyses based on a CPS 5 cutpoint

During the procedure the MAH provided post-hoc exploratory efficacy results based on the PD-L1 CPS cutpoints of CPS <5 and CPS ≥5, CPS ≥1 to <5, and CPS ≥5 to <10 (see Table 40 below). The CPS 5 cutpoint was not analytically validated and no pathologist training was conducted for this cutpoint.

Table 40 Summary of exploratory efficacy results for PD-L1 subgroups CPS <5 and CPS ⩾5

	PD-L1 CPS < 5		**PD-L1 CPS ≥ 5**	
Efficacy Endpoint	**P+C (N=411)**	**C (N=401)**	**P+C (N=379)**	**C (N=388)**
OS				
Number of events (%)	334 (81.3)	341 (85)	269 (71.0)	325 (83.8)
Median OS (95% CI), months	12.1 (11.2, 13.5)	11.4 (10.0, 12.2)	14.0 (12.1, 5.4)	11.5 (10.3, 12.5)
HR (95% CI) *	**0.84** (0.72, 0.98)		**0.70** (0.60, 0.82)	
p-Value **	0.0132		<0.0001	
PFS (BICR per RECIST 1.1)				
Number of events (%)	309 (75.2)	308 (76.8)	263 (69.4)	300 (77.3)
Median PFS (95% CI), months	6.9 (5.8,7.2)	5.6 (5.5, 5.8)	7.1 (6.1, 8.3)	5.6 (5.4, 5.9)
HR (95% CI) *	**0.83** (0.71, 0.98)		**0.69** (0.58, 0.81)	
p-Value **	0.0119		<0.0001	
ORR (BICR per RECIST 1.1)				
ORR, % (95% CI)	47.7 (42.8, 52.6)	39.9 (35.1, 44.9)	55.1 (50.0, 60.2)	44.1 (39.1, 49.2)
ORR difference (%)	7.8 (1.0, 14.5)		11.1 (4.0, 18.0)	

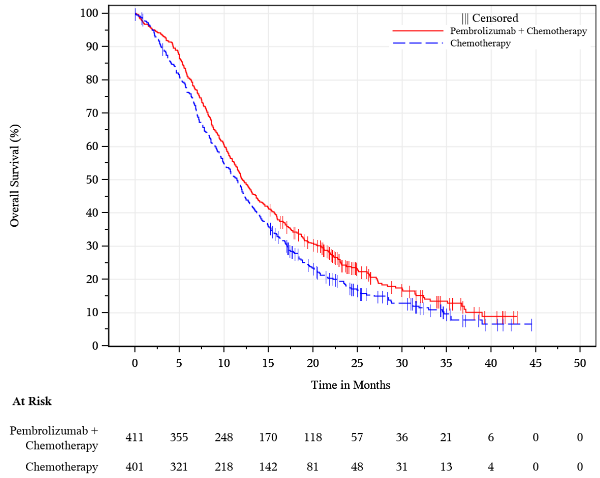
* based on unstratified cox regression model with Efron's method of tie handling with treatment as a covariate.

** One-sided p-value based on unstratified log-rank test.

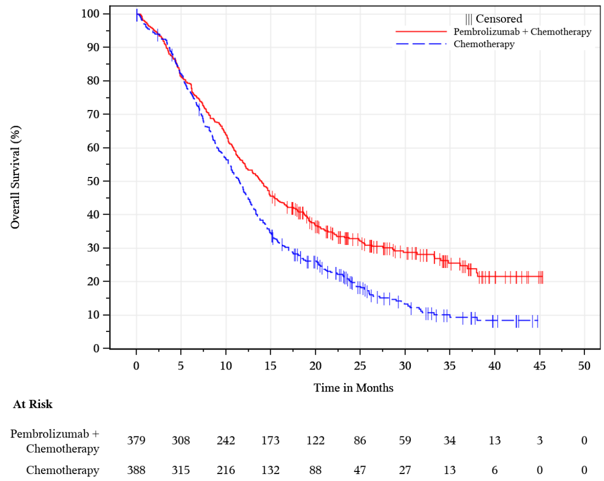
Figure 26 KM Plots of OS and PFS for PD-L1 subgroups CPS <5 and CPS ≥5

CPS <5

OS

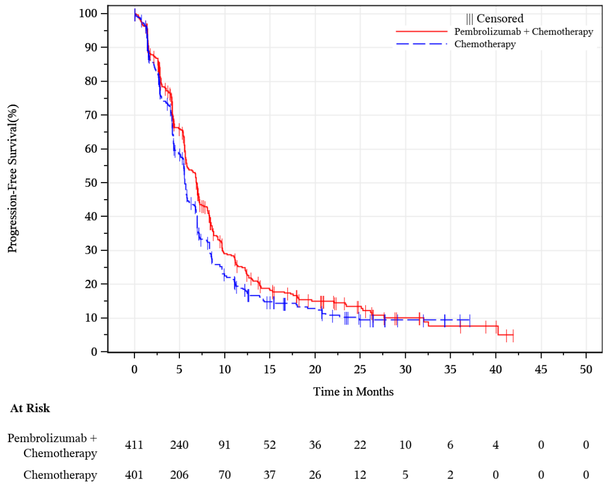


CPS ≥5



CPS <5

PFS



CPS ≥5

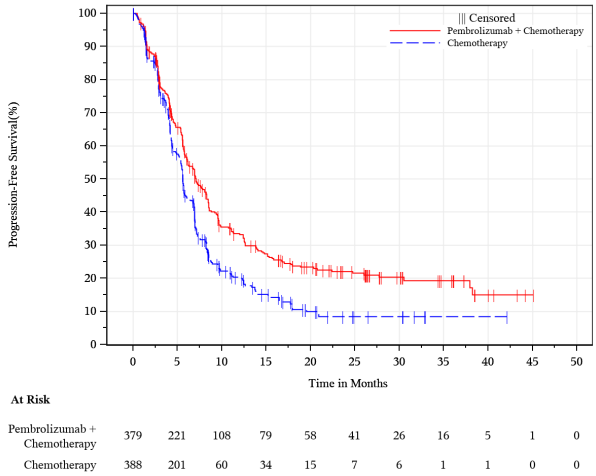


Table 41 Summary of exploratory efficacy results for PD-L1 subgroups CPS ⩾1 to <5 and CPS ⩾5 to <10

Efficacy Endpoint	PD-L1 CPS ≥ 1 to < 5		PD-L1 CPS ≥ 5 to < 10	
	P+C (N=239)	C (N=229)	P+C (N=110)	C (N=121)
OS				
Number of events (%)	195 (81.6)	201 (87.8)	88 (80.0)	103 (85.1)
Median OS (95% CI), months	11.5 (10.3, 13.5)	11.1 (9.7, 12.0)	10.2 (8.2, 12.1)	10.7 (9.5, 13.0)
HR (95% CI) *	**0.78** (0.64, 0.95)		**0.94** (0.71, 1.25)	
p-Value **	0.0075		0.3323	
PFS (BICR per RECIST 1.1)				
Number of events (%)	180 (75.3)	183 (79.9)	80 (72.7)	94 (77.7)
Median PFS (95% CI), months	6.7 (5.6, 7.1)	5.6 (5.2, 5.7)	5.7 (4.3, 7.3)	5.6 (4.6, 6.9)

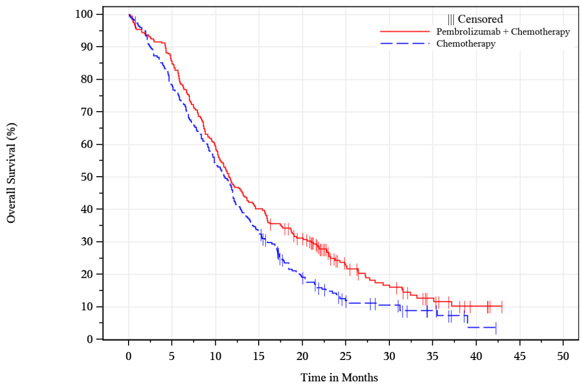
	PD-L1 CPS ≥ 1 to < 5		PD-L1 CPS ≥ 5 to < 10	
Efficacy Endpoint	**P+C (N=239)**	**C (N=229)**	**P+C (N=110)**	**C (N=121)**
HR (95% CI) *	**0.78** (0.64, 0.96)		**0.93** (0.69, 1.25)	
p-Value **	0.0107		0.3207	
ORR (BICR per RECIST 1.1)				
ORR, % (95% CI)	47.3 (40.8, 53.8)	40.2 (33.8, 46.8)	40.0 (30.8, 49.8)	47.1 (38.0, 56.4)
ORR difference (%)	7.1 (-1.9, 16.0)		-7.1 (-19.7, 5.7)	

* based on unstratified cox regression model with Efron's method of tie handling with treatment as a covariate.
** One-sided p-value based on unstratified log-rank test.

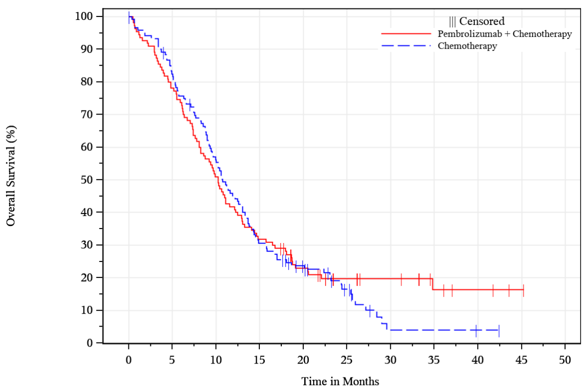
Figure 27 KM Plots of OS and PFS for PD-L1 subgroups CPS ≥1 to <5 and CPS ≥5 to <10

CPS ≥ 1 to < 5 **CPS ≥ 5 to < 10**

OS

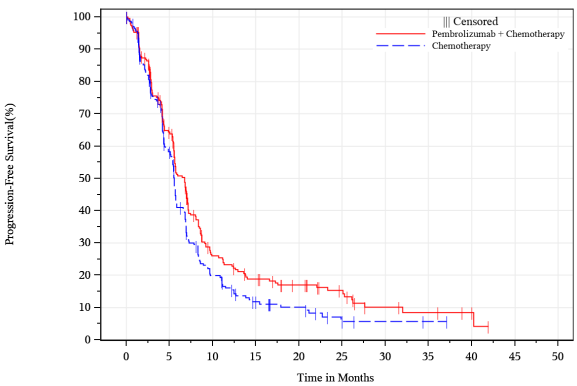


At Risk	0	5	10	15	20	25	30	35	40	45	50
Pembrolizumab + Chemotherapy	239	203	141	96	70	35	22	12	4	0	0
Chemotherapy	229	178	123	74	38	19	14	7	1	0	0

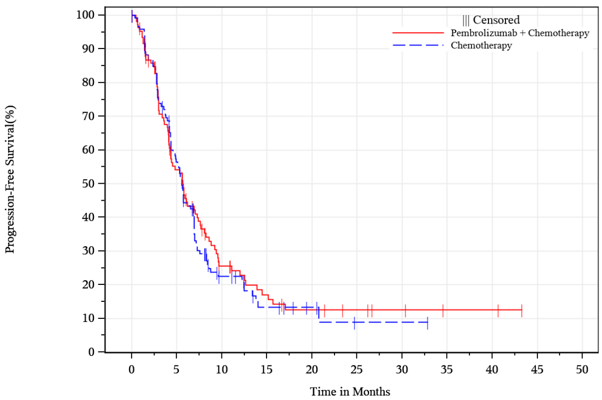


At Risk	0	5	10	15	20	25	30	35	40	45	50
Pembrolizumab + Chemotherapy	110	86	56	35	22	13	10	5	3	1	0
Chemotherapy	121	98	65	36	23	12	2	2	1	0	0

PFS



At Risk	0	5	10	15	20	25	30	35	40	45	50
Pembrolizumab + Chemotherapy	239	135	48	33	24	16	7	5	3	0	0
Chemotherapy	229	116	37	17	11	4	2	1	0	0	0



At Risk	0	5	10	15	20	25	30	35	40	45	50
Pembrolizumab + Chemotherapy	110	51	20	12	8	6	4	2	2	0	0
Chemotherapy	121	65	18	8	4	1	1	0	0	0	0

- **Association Between PD-L1 CPS Score and Efficacy**

Table 42 Analysis of Association between PD-L1 Score (CPS ≥1, CPS ≥5 and CPS ≥10) and Efficacy (OS and PFS)

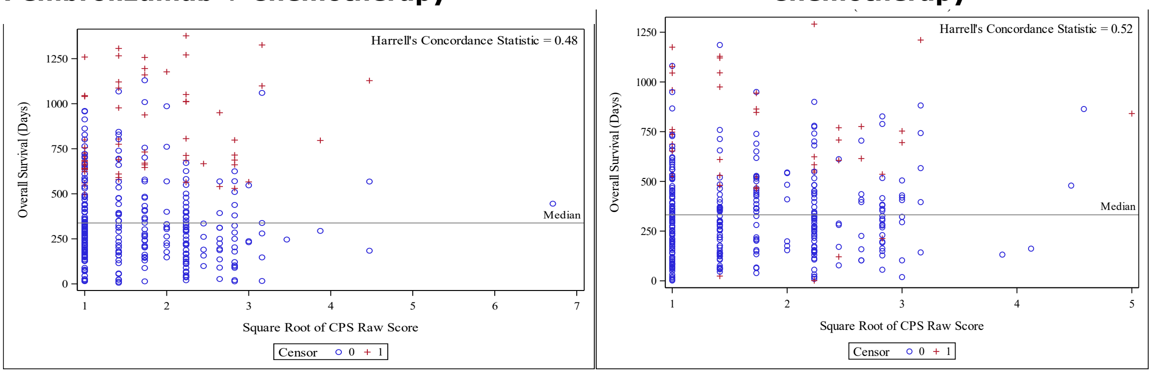
CPS subgroup	End-point	Treatment	N	Event n (%)	Hazard Ratio for Square Root of CPS†	
					Hazard Ratio (95% CI)	p-Value‡
CPS ≥1	OS	Pembro + Chemo	618	464 (75.1%)	0.911 (0.867, 0.958)	0.0003
		Chemotherapy	617	526 (85.3%)	0.962 (0.924, 1.002)	0.0605
	PFS	Pembro + Chemo	618	443 (71.7%)	0.921 (0.877, 0.968)	0.0011
		Chemotherapy	617	483 (78.3%)	0.988 (0.949, 1.028)	0.5444
CPS ≥5	OS	Pembro + Chemo	379	269 (71.0%)	0.916 (0.856, 0.981)	0.0126
		Chemotherapy	388	325 (83.8%)	0.966 (0.917, 1.018)	0.1973
	PFS	Pembro + Chemo	379	263 (69.4%)	0.927 (0.867, 0.991)	0.0256
		Chemotherapy	388	300 (77.3%)	0.996 (0.947, 1.048)	0.8810
CPS ≥10	OS	Pembro + Chemo	279	188 (67.4%)	0.962 (0.895, 1.033)	0.2850
		Chemotherapy	272	226 (83.1%)	0.984 (0.929, 1.042)	0.5798
	PFS	Pembro + Chemo	279	190 (68.1%)	0.952 (0.887, 1.022)	0.1774
		Chemotherapy	272	210 (77.2%)	0.997 (0.942, 1.056)	0.9257

† From a Cox regression model with Efron's method of tie handling using PD-L1 CPS on the square root scale as a continuous covariate. Each treatment group was analysed separately. Hazard ratio (HR) represents ratio of the hazard rates for the event as CPS increases by 1 on the square root scale. A HR of 1 indicates that CPS does not affect the hazard rate. A HR of greater than 1 indicates that there is higher hazard as CPS increases. A HR of less than 1 indicates that there is lower hazard as CPS increases.
‡ Two-sided p-value from the Cox regression model.
Database Cutoff Date: 03OCT2022

Figure 28 Graphical presentation of Association between PD-L1 Score (⩾1 CPS <10) and Efficacy (OS and PFS)

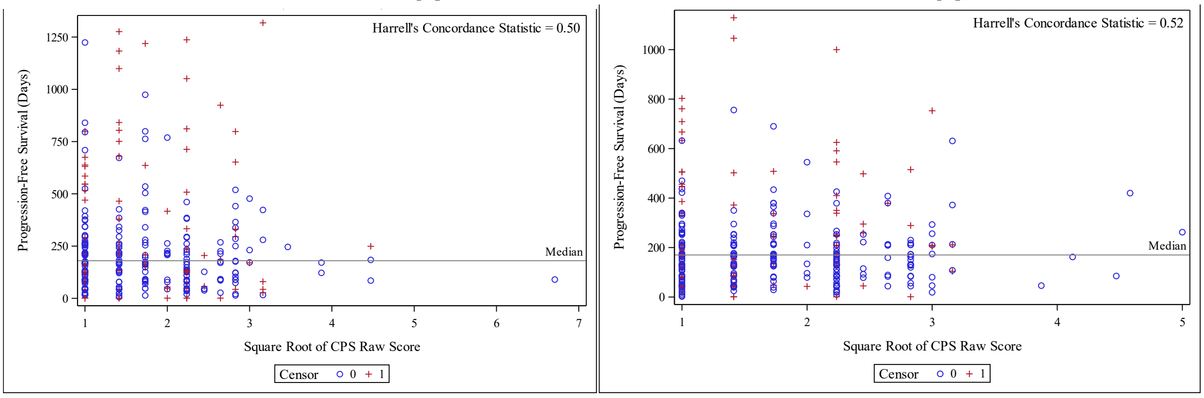
CPS Score in Relation to **Overall Survival** (**⩾1 CPS <10**)

Pembrolizumab + Chemotherapy **Chemotherapy**



CPS Score in Relation to **Progression-free Survival** (⩾**1 CPS <10**)

Pembrolizumab + Chemotherapy **Chemotherapy**



Additional efficacy analyses

Efficacy by Age

Subgroup analyses by age category (<65, ≥65 to <75, and ≥75 years) for OS, PFS and ORR are shown in the tables below. Because there were only 3 participants in the ⩾85 age category, the ⩾75 to <85 and ⩾85 age categories were combined for the analyses.

Table 43 Subgroup Analysis of ***Overall Survival*** *by Age Categories (ITT Population)*

	Pembrolizumab + Chemotherapy (N=790)			Chemotherapy (N=789)			Pembrolizumab + Chemotherapy vs. Chemotherapy
	N	Number (%) of Events		N	Number (%) of Events		Hazard Ratio (95% CI)
Overall	790	603	(76.3)	789	666	(84.4)	0.78 (0.695, 0.868)
Age (Years)							
<65	486	383	(78.8)	479	416	(86.8)	0.76 (0.664, 0.878)
>=65 to <75	247	184	(74.5)	250	196	(78.4)	0.85 (0.698, 1.044)
>=75	57	36	(63.2)	60	54	(90.0)	0.49 (0.321, 0.751)

Table 44 Subgroup Analysis of ***PFS*** *by Age Categories by BICR per RECIST 1.1 (Primary Analysis)*

	Pembrolizumab + Chemotherapy (N=790)			Chemotherapy (N=789)			Pembrolizumab + Chemotherapy vs. Chemotherapy
	N	Number (%) of Events		N	Number (%) of Events		Hazard Ratio (95% CI)
Overall	790	572	(72.4)	789	608	(77.1)	0.76 (0.675, 0.85)
Age (Years)							
<65	486	357	(73.5)	479	378	(78.9)	0.74 (0.643, 0.862)
>=65 to <75	247	180	(72.9)	250	183	(73.2)	0.85 (0.688, 1.039)
>=75	57	35	(61.4)	60	47	(78.3)	0.53 (0.341, 0.83)

*Table 45 Subgroup analysis of **ORR** (Confirmed) by BICR per RECIST 1.1 by age categories (ITT Population)*

	Pembrolizumab + Chemotherapy (N=790)				Chemotherapy (N=789)				Difference	
	N	n	(%)	95% CI (%)	N	n	(%)	95% CI (%)	(%)	95% CI (%)
Overall	790	405	(51.3)	(47.7, 54.8)	789	331	(42.0)	(38.5, 45.5)	(9.3)	(4.4,14.1)
Age (Years)										
<65	486	239	(49.2)	(44.6, 53.7)	479	204	(42.6)	(38.1, 47.2)	(6.6)	(0.3,12.8)
>=65 to <75	247	136	(55.1)	(48.6, 61.4)	250	106	(42.4)	(36.2, 48.8)	(12.7)	(3.9,21.3)
>=75	57	30	(52.6)	(39.0, 66.0)	60	21	(35.0)	(23.1, 48.4)	(17.6)	(-0.4,34.6)

Efficacy for Non-MSI-H Tumours

According to baseline characteristics 4.7% of study participants had MSI-high, 81.8% had non-MSI-high tumours and MSI status was missing for 14.2%. Most of the participants with missing MSI status (134/236) were enrolled in China, where biomarker sample collection was dependent on approval by HGRAC (22-DEC-2020; enrolment in study from Nov 2018 until Jun 2021). Outside China only 6.7% of participants had missing MSI data. Baseline characteristics were generally similar between the treatment arms (and similar compared to the overall study population) (data not shown).

Table 46 OS, PFS, ORR and DOR for All Participants and Participants with Non-MSI-High Tumours

	All Participants		**Participants with Non-MSI-High Tumours**	
Efficacy Endpoint	**P+C (N=790)**	**C (N=789)**	**P+C (N=641)**	**C (N=639)**
Primary Efficacy Outcome: **OS**				
Number of events (%)	603 (76.3)	666 (84.4)	497 (77.5)	540 (84.5)
Median OS, months (95% CI)	12.9 (11.9, 14.0)	11.5 (10.6, 12.1)	12.8 (11.5, 14.0)	11.6 (10.6, 12.3)
HR (95% CI)	0.78 (0.70, 0.87)		0.79 (0.70, 0.89)	
p-Value *	<0.0001		<0.0001	
Secondary Efficacy Outcome: **PFS** (BICR per RECIST 1.1)				
Number of events (%)	572 (72.4)	608 (77.1)	475 (74.1)	498 (77.9)
Median PFS (95% CI), months	6.9 (6.3, 7.2)	5.6 (5.5, 5.7)	6.9 (6.2, 7.2)	5.7 (5.6, 6.3)
HR (95% CI)‡	0.76 (0.67, 0.85)		0.79 (0.70, 0.90)	
p-Value *	<0.0001		0.0002	
Secondary Efficacy Outcomes: **ORR** (BICR per RECIST 1.1)				
ORR, % (95% CI)	51.3 (47.7, 54.8)	42.0 (38.5, 45.5)	49.8 (45.8, 53.7)	43.5 (39.6, 47.5)

Efficacy for the Global population excluding the China extension

Results of the analysis of OS, PFS and ORR for the Global population excluding the China extension portion of the study are presented below:

Table 47 Efficacy Results for the Global population excluding the China Extension portion

	All Participants Excluding China Extension		PD-L1 CPS ≥1 Excluding China Extension		PD-L1 CPS ≥10 Excluding China Extension	
Efficacy Endpoint	**P+C (N=773)**	**C (N=771)**	**P+C (N=604)**	**C (N=604)**	**P+C (N=272)**	**C (N=266)**
OS						
Median OS, months (95% CI)	12.9 (11.9, 14.1)	11.4 (10.5, 12.0)	13.0 (11.7, 14.3)	11.4 (10.3, 11.9)	15.9 (14.0, 19.5)	11.8 (10.3, 12.7)
HR (95% CI)	0.77 (0.69, 0.86)		0.73 (0.64, 0.83)		0.64 (0.52, 0.78)	
PFS (BICR per RECIST 1.1)						
Median PFS (95% CI), months	6.9 (6.4, 7.2)	5.6 (5.5, 5.7)	6.9 (6.1, 7.2)	5.6 (5.4, 5.7)	7.7 (6.7, 8.5)	5.6 (5.3, 6.7)
HR (95% CI)[‡]	0.75 (0.67, 0.85)		0.72 (0.63, 0.82)		0.62 (0.50, 0.76)	
ORR (BICR per RECIST 1.1)						
ORR, % (95% CI)	51.0 (47.7, 54.5)	42.2 (38.6, 45.7)	51.8 (47.8, 55.9)	42.9 (38.9, 46.9)	59.9 (53.8, 65.8)	42.9 (36.8, 49.0)

Additional PFS Analyses

Table 48 PFS sensitivity analysis by BICR and PFS primary analysis based on investigator assessment

	All Participants		PD-L1 CPS ≥1		PD-L1 CPS ≥10	
	P+C (N=790)	**C (N=789)**	**P+C (N=618)**	**C (N=617)**	**P+C (N=279)**	**C (N=272)**
PFS HR (95% CI)						
Primary analysis (BICR)	0.76 (0.67, 0.85)		0.72 (0.63, 0.82)		0.62 (0.51, 0.76)	
Sensitivity analysis 1 (BICR)	0.76 (0.69, 0.85)		0.73 (0.64, 0.82)		0.62 (0.51, 0.75)	
Sensitivity analysis 2 (BICR)	0.78 (0.70, 0.86)		0.73 (0.65, 0.82)		0.62 (0.51, 0.74)	
Primary analysis (Investigator)	0.72 (0.65, 0.81)		0.68 (0.60, 0.77)		0.56 (0.46, 0.69)	
Sensitivity analysis 1 (Investigator)	0.73 (0.65, 0.81)		0.69 (0.61, 0.77)		0.56 (0.46, 0.67)	

ORR Analyses by Investigator

Table 49 Objective Response (confirmed) based on Investigator Assessment per RECIST 1.1

	All Participants		PD-L1 CPS ≥1		PD-L1 CPS ≥10	
Efficacy Endpoint	**P+C (N=790)**	**C (N=789)**	**P+C (N=618)**	**C (N=617)**	**P+C (N=279)**	**C (N=272)**
ORR (BICR per RECIST 1.1)						
ORR, % (95% CI)	51.3 (47.7, 54.8)	42.0 (38.5, 45.5)	52.1 (48.1, 56.1)	42.6 (38.7, 46.6)	60.6 (54.6, 66.3)	43.0 (37.1, 49.1)
Difference in % (95% CI)	9.3 (4.4, 14.1)		9.5 (3.9, 15.0)		17.5 (9.3, 25.5)	
ORR (based on Investigator Assessment per RECIST 1.1)						
ORR, % (95% CI)	50.4 (46.8, 53.9)	45.9 (42.4, 49.4)	51.8 (47.8, 55.8)	46.0 (42.0, 50.1)	57.3 (51.3, 63.2)	47.1 (41.0, 53.2)
Difference in % (95% CI)	4.5 (-0.4, 9.4)		5.7 (0.2, 11.3)		9.9 (1.6, 18.1)	

Efficacy by prior oncological radiation

Table 50 Subgroup analysis of OS by prior oncological radiation (ITT Population)

	Pembrolizumab + Chemotherapy (N=790)			Chemotherapy (N=789)			Pembrolizumab + Chemotherapy vs. Chemotherapy
	N	Number of Events	(%)	N	Number of Events	(%)	Hazard Ratio (95% CI)
Overall	790	603	(76.3)	789	666	(84.4)	0.78 (0.695, 0.868)
Prior Oncological Radiation							
Yes	31	24	(77.4)	31	23	(74.2)	1.12 (0.63, 1.987)
No	759	579	(76.3)	758	643	(84.8)	0.76 (0.675, 0.846)
For subgroups, analysis is based on unstratified Cox regression model with treatment as a covariate. Database Cutoff Date: 03OCT2022							

Summary of main study

The following table summarises the efficacy results from the main study supporting the present application. This summary should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Table 51 Summary of Efficacy for trial KEYNOTE-859

Title: A Phase 3, randomised, double-blind clinical study of pembrolizumab (MK-3475) plus chemotherapy versus placebo plus chemotherapy as first-line treatment in participants with HER2 negative, previously untreated, unresectable or metastatic gastric or gastroesophageal junction adenocarcinoma (KEYNOTE-859)		
Study identifier	P859V01MK3475 (MK-3475-859-06; EudraCT: 2018-001757-27; IND: 123,482; NCT: 03675737)	
Design	Phase 3, Multicenter, efficacy, safety, parallel-assignment, double-blinded, placebo-controlled intervention	
	Duration of main phase:	The first participant first visit occurred on 08-NOV-2018; Data cutoff: 03-OCT-2022; Study is ongoing
	Duration of Run-in phase:	Not applicable
	Duration of Extension phase:	Not applicable
Hypothesis	Superiority	
Treatments groups	Pembrolizumab PLUS FP or CAPOX (Pembrolizumab + Chemotherapy) N=790	**Pembrolizumab:** 200 mg on Day 1 of each cycle, intravenous (IV), every 3 weeks (Q3W), up to 35 cycles **Placebo:** On Day 1 of each cycle, IV, Q3W, up to 35 cycles **FP Backbone Chemotherapy:**
	Placebo PLUS FP or CAPOX (Chemotherapy) N=789	

Endpoints and definitions	Primary endpoint	Overall Survival (OS)	OS is defined as the time from randomisation to death due to any cause. Evaluated in: • Intent to treat population (ITT Population). • ITT population with PD-L1 positive tumours defined by CPS ≥1 (PD-L1 CPS ≥1 Population). • ITT population with PD-L1 positive tumours defined by CPS ≥10 (PD-L1 CPS ≥10 Population).
	Secondary endpoint	Progression-free survival (PFS) per RECIST 1.1 assessed by blinded independent central review (BICR)	PFS is defined as the time from randomisation to the first documented disease progression per RECIST 1.1 by BICR or death due to any cause, whichever occurs first. Evaluated in: • Intent to treat population (ITT Population). • ITT population with PD-L1 positive tumours defined by CPS ≥1 (PD-L1 CPS ≥1 Population). • ITT population with PD-L1 positive tumours defined by CPS ≥10 (PD-L1 CPS ≥10
	Secondary endpoint	Objective Response Rate (ORR) per RECIST 1.1 by BICR	OR defined as complete response (CR) or a partial response (PR). Evaluated in: • Intent to treat population (ITT Population). • ITT population with PD-L1 positive tumours defined by CPS ≥1 (PD-L1 CPS ≥1 Population). • ITT population with PD-L1 positive tumours defined by CPS ≥10 (PD-L1 CPS ≥10 Population).
	Secondary endpoint	Duration of Response (DOR) per RECIST 1.1 by BICR	For participants who demonstrated CR or PR, DOR is defined as the time from first response (CR or PR) to subsequent disease progression or death from any cause, whichever occurs first. Evaluated in responders in: • Intent to treat population (ITT Population). • ITT population with PD-L1 positive tumours defined by CPS ≥1 (PD-L1 CPS ≥1 Population). • ITT population with PD-L1 positive tumours defined by CPS ≥10 (PD-L1 CPS ≥10 Population).
Database lock	04-NOV-2022		
Results and Analysis			
Analysis description	**Primary Analysis of OS in All Participants (Primary Endpoint)**		
Analysis population and time point description	ITT Population (all randomised participants) = 1579 participants. Interim Analysis (IA) data cutoff: 03-OCT-2022		
Descriptive statistics and estimate variability	Treatment group	Pembrolizumab + Chemotherapy	Chemotherapy
	Number of participants	790	789
	ITT Population Median OS (months)	12.9	11.5
	95% Confidence Interval (CI)	11.9, 14.0	10.6, 12.1

	ITT Population OS Rate at Month 12 (%)	52.7	46.7
	95% CI	49.1, 56.1	43.2, 50.2
Effect estimate per comparison	OS	Comparison groups	Pembrolizumab + Chemotherapy
		Hazard ratio (HR)	0.78
		95% CI	0.70, 0.87
		P-value	<0.0001[a]
Notes	[a] The result reached statistically significance compared with the prespecified p-value crossing boundary of 0.006079.		
Analysis description	**Primary Analysis of OS in the PD-L1 CPS ≥1 Population (Primary Endpoint)**		
Analysis population and time point description	PD-L1 CPS ≥1 Population = 1235 participants. IA data cutoff: 03-OCT-2022		
Descriptive statistics and estimate variability	Treatment group	Pembrolizumab + Chemotherapy	Chemotherapy
	Number of participants	618	617
	PD-L1 CPS ≥1 Population Median OS (months)	13.0	11.4
	95% CI	11.6, 14.2	10.5, 12.0
	PD-L1 CPS ≥1 Population OS Rate at Month 12 (%)	52.4	45.7
	95% CI	48.4, 56.3	41.7, 49.6
Effect estimate per comparison	OS	Comparison groups	Pembrolizumab + Chemotherapy Chemotherapy
		HR	0.74
		95% CI	0.65, 0.84
		P-value	<0.0001[b]
Notes	[b] The result reached statistically significance compared with the prespecified p-value crossing boundary of 0.020556.		
Analysis description	**Primary Analysis of OS in the PD-L1 CPS ≥10 Population (Primary Endpoint)**		
Analysis population and time point description	PD-L1 CPS ≥10 Population = 551 participants. IA data cutoff: 03-OCT-2022		
Descriptive statistics and estimate variability	Treatment group	Pembrolizumab + Chemotherapy	Chemotherapy
	Number of participants	279	272
	PD-L1 CPS ≥10 Population Median OS (months)	15.7	11.8
	95% CI	13.8, 19.3	10.3, 12.7

	PD-L1 CPS ≥10 Population OS Rate at Month 12 (%)	60.6	47.8
	95% CI	54.6, 66.0	41.7, 53.6
Effect estimate per comparison	OS	Comparison groups	Pembrolizumab + Chemotherapy
		HR	0.65
		95% CI	0.53, 0.79
		P-value	<0.0001[c]
Notes	[c] The result reached statistically significance compared with the prespecified p-value crossing boundary of 0.011603.		
Analysis description	**Primary analysis of PFS in All Participant (Secondary Endpoint)**		
Analysis population and time point description	ITT Population (all randomised participants) = 1579 participants. IA data cutoff: 03-OCT-2022		
Descriptive statistics and estimate variability	Treatment group	Pembrolizumab + Chemotherapy	Chemotherapy
	Number of participants	790	789
	ITT Population Median PFS (months)	6.9	5.6
	95% CI	6.3, 7.2	5.5, 5.7
	ITT Population PFS Rate at Month 12 (%)	28.9	19.3
	95% CI	25.5, 32.4	16.3, 22.4
Effect estimate per comparison	PFS	Comparison groups	Pembrolizumab + Chemotherapy
		HR	0.76
		95% CI	0.67, 0.85
		P-value	<0.0001[d]
Notes	[d] The result reached statistically significance compared with the prespecified p-value crossing boundary of 0.025.		
Analysis description	**Primary Analysis of PFS in the PD-L1 CPS ≥1 Population (Secondary Endpoint)**		
Analysis population and time point description	PD-L1 CPS ≥1 Population = 1235 participants. IA data cutoff: 03-OCT-2022		
Descriptive statistics and estimate variability	Treatment group	Pembrolizumab + Chemotherapy	Chemotherapy
	Number of participants	618	617
	PD-L1 CPS ≥1 Population Median PFS (months)	6.9	5.6
	95% CI	6.0, 7.2	5.4, 5.7
	PD-L1 CPS ≥1 Population PFS Rate at Month 12 (%)	29.4	18.4
	95% CI	(25.5, 33.3)	(15.1, 21.9)

Effect estimate per comparison	PFS	Comparison groups	Pembrolizumab + Chemotherapy
		HR	0.72
		95% CI	0.63, 0.82
		P-value	<0.0001[e]
Notes	[e] The result reached statistically significance compared with the prespecified p-value crossing boundary of 0.025.		
Analysis description	**Primary Analysis of PFS in the PD-L1 CPS ≥10 Population (Secondary Endpoint)**		
Analysis population and time point description	PD-L1 CPS ≥10 Population = 551 participants. IA data cutoff: 03-OCT-2022		
Descriptive statistics and estimate variability	Treatment group	Pembrolizumab + Chemotherapy	Chemotherapy
	Number of participants	279	272
	PD-L1 CPS ≥10 Population Median PFS (months)	8.1	5.6
	95% CI	6.8, 8.5	5.4, 6.7
	PD-L1 CPS ≥10 Population PFS Rate at Month 12 (%)	36.6	20.0
	95% CI	(30.5, 42.6)	(14.9, 25.5)
Effect estimate per comparison	PFS	Comparison groups	Pembrolizumab + Chemotherapy
		HR	0.62
		95% CI	0.51, 0.76
		P-value	<0.0001[f]
Notes	[f] The result reached statistically significance compared with the prespecified p-value crossing boundary of 0.025.		
Analysis description	**Primary analysis of ORR in All Participant (Secondary Endpoint)**		
Analysis population and time point description	ITT Population (all randomised participants) = 1579 participants. IA data cutoff: 03-OCT-2022		
Descriptive statistics and estimate variability	Treatment group	Pembrolizumab + Chemotherapy	Chemotherapy
	Number of participants	790	789
	ITT Population Confirmed ORR rate (%)	51.3	42.0
	95% CI	47.7, 54.8	38.5, 45.5
Effect estimate per comparison	ORR	Comparison groups	Pembrolizumab + Chemotherapy
		Difference (%)	9.3
		95% CI	4.4, 14.1
		P-value	0.00009[g]
Notes	[g] The result reached statistically significance compared with the prespecified p-value crossing boundary of 0.025.		

Analysis description	**Primary analysis of ORR in the PD-L1 CPS ≥1 Population (Secondary Endpoint)**		
Analysis population and time point description	PD-L1 CPS ≥1 Population = 1235 participants. IA data cutoff: 03-OCT-2022		
Descriptive statistics and estimate variability	Treatment group	Pembrolizumab + Chemotherapy	Chemotherapy
	Number of participants	618	617
	PD-L1 CPS ≥1 Population Confirmed ORR rate (%)	52.1	42.6
	95% CI	48.1, 56.1	38.7, 46.6
Effect estimate per comparison	ORR	Comparison groups	Pembrolizumab + Chemotherapy
		Difference (%)	9.5
		95% CI	3.9, 15.0
		P-value	0.00041[h]
Notes	[h] The result reached statistically significance compared with the prespecified p-value crossing boundary of 0.025.		
Analysis description	**Primary Analysis of ORR in the PD-L1 CPS ≥10 Population (Secondary Endpoint)**		
Analysis population and time point description	PD-L1 CPS ≥10 Population = 551 participants. IA data cutoff: 03-OCT-2022		
Descriptive statistics and estimate variability	Treatment group	Pembrolizumab + Chemotherapy	Chemotherapy
	Number of participants	279	272
	PD-L1 CPS ≥10 Population Confirmed ORR rate (%)	60.6	43.0
	95% CI	54.6, 66.3	37.1, 49.1
Effect estimate per comparison	ORR	Comparison groups	Pembrolizumab + Chemotherapy
		Difference (%)	17.5
		95% CI	9.3, 25.5
		P-value	0.00002[i]
Notes	[i] The result reached statistically significance compared with the prespecified p-value crossing boundary of 0.025.		
Analysis description	**Primary analysis of DOR in All Responders (Secondary Endpoint)**		
Analysis population and time point description	ITT Population (all randomised participants) = 1579 participants. IA data cutoff: 03-OCT-2022		
Descriptive statistics and estimate variability	Treatment group	Pembrolizumab + Chemotherapy	Chemotherapy
	Number of participants	790	789
	Number of participants with response	405	331
	All Responders Median DOR (months)	8.0	5.7
	Range	1.2+ - 41.5+	1.3+ - 34.7+

Analysis description	**Primary analysis of DOR in the PD-L1 CPS ≥1 Population (Secondary Endpoint)**		
Analysis population and time point description	PD-L1 CPS ≥1 Population = 1235 participants. IA data cutoff: 03-OCT-2022		
Descriptive statistics and estimate variability	Treatment group	Pembrolizumab + Chemotherapy	Chemotherapy
	Number of participants	618	617
	Number of participants with response	322	263
	PD-L1 CPS ≥1 Population Median DOR (months)	8.3	5.6
	Range	1.2+ - 41.5+	1.3+ - 34.2+
Analysis description	**Primary analysis of DOR in the PD-L1 CPS ≥10 Population (Secondary Endpoint)**		
Analysis population and time point description	PD-L1 CPS ≥10 Population = 551 participants. IA data cutoff: 03-OCT-2022		
Descriptive statistics and estimate variability	Treatment group	Pembrolizumab + Chemotherapy	Chemotherapy
	Number of participants	279	272
	Number of participants with response	169	117
	PD-L1 CPS ≥10 Population Median DOR (months)	10.9	5.8
	Range	1.2+ - 41.5+	1.4+ - 31.2+

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

Not applicable.

Clinical studies in special populations

Not applicable.

Supportive studies

The phase 3 Study **KEYNOTE-062** failed to demonstrate a statistically significant benefit for the addition of pembrolizumab to chemotherapy in the 1L treatment of advanced HER2-negative

GEJ/gastric adenocarcinoma. The MAH presented these negative study results in the context of the current application (data not shown).

Table 52 KEYNOTE-062 study design

Study Number Status	Study Design	Study Population	Number of Participants by Intervention Group	Primary Endpoint(s)
1L Treatment				
KEYNOTE-062 Final analyses completed	Phase 3, randomized, active-controlled, partially blinded	Advanced gastric/GEJ adenocarcinoma; HER2-negative	Pembrolizumab 200 mg Q3W (N=254) OR Pembrolizumab 200 mg Q3W+ Cisplatin 80 mg/m^2 Q3W+5-FU 800 mg/m^2/day continuous IV infusion Days 1-5 (120 hours) or capecitabine (in place of 5-FU) 1000 mg/m^2 BID Day1-14 Q3W (N=256) OR Placebo Q3W + cisplatin 80 mg/m^2 Q3W+5-FU 800 mg/m^2/day continuous IV infusion Days 1-5 (120 hours) or capecitabine (in place of 5-FU) 1000 mg/m^2 BID Day 1-14 Q3W (N=250)	PFS, OS

Table 53 Clinical studies of pembrolizumab in gastric cancer

Study	Phase	Intervention
KN012	1B	Pembrolizumab in PD-L1 positive participants
KN059	2	Pembrolizumab (Cohort 1, 3L treatment), pembrolizumab plus cisplatin and 5-FU or capecitabine (Cohort 2, 1L treatment), pembrolizumab (Cohort 3, 1L treatment)
KN061	3	Pembrolizumab versus paclitaxel, 2L treatment
KN062	3	Pembrolizumab versus pembrolizumab plus FP, placebo plus FP, 1L treatment in PD-L1 positive participants
KN063	3	Pembrolizumab versus paclitaxel, 2L treatment

2.4.3. Discussion on clinical efficacy

With the current variation application, the MAH initially sought the following new indication:

"KEYTRUDA, in combination with fluoropyrimidine and platinum-containing chemotherapy, is indicated for the first-line treatment of locally advanced unresectable or metastatic HER2-negative gastric or gastro-oesophageal junction adenocarcinoma in adults."

Design and conduct of clinical studies

The extension of indication is based on the double-blinded, global study KEYNOTE-859 that randomised participants with previously untreated, HER2-negative, advanced gastric or GEJ adenocarcinoma to receive pembrolizumab or placebo in combination with chemotherapy (FP [cisplatin/5-FU] or CAPOX [capecitabine and oxaliplatin]).

Patients had not received previous therapy for advanced disease, but participants may have received prior neoadjuvant and/or adjuvant therapy as long as it was completed at least 6 months prior to randomisation. No pre-treatment with a checkpoint inhibitor was allowed.

Participants were eligible regardless of PD-L1 or MSI status; however, all participants needed to provide tumour tissue samples for central PD-L1 testing with the Agilent PD-L1 IHC 22C3 pharmDx assay and for central MSI analysis by PCR. HER2 testing was conducted either by local or central testing laboratory.

Participants were stratified by geographic region, PD-L1 tumour expression status (CPS <1 or ≥1), and combination chemotherapy (FP or CAPOX), which was chosen prior to randomisation in the study.

The choice of FP or CAPOX as chemotherapy backbone regimens and the applied dosing regimens are in line with recommended standard of care treatment options and reflect different regional practice. Of note, the majority of patients (86%) received CAPOX as investigator´s choice.

Baseline characteristics were generally balanced between treatment arms and are overall reflective of patients with advanced gastric /GEJ adenocarcinoma apart from the typical limitations of eligibility criteria that restrict the study population to patients with good performance status and adequate organ function. The majority of participants (61%) were <65 years of age (median age was 62.0 years) and only 7.4% were enrolled with an age above 75 years. Participants were primarily male (68%), the majority had an ECOG PS of 1 (63%) and were white (55%) or Asian (34%). Most participants had adenocarcinoma of the stomach (78.7%) and had not received prior gastrectomy/esophagectomy (78.2%). Nearly all had metastatic disease (96.3%) with about 40% with liver metastases.

The majority of participants (78.2%) had PD-L1 tumour expression status of CPS ≥1 and 34.9% had CPS ≥10.

After several relevant design modifications during the study conduct, overall survival was finally determined as sole primary efficacy endpoint with PFS, ORR and DOR (measured by BICR per RECIST 1.1) as secondary endpoints. Primary and secondary efficacy endpoints were hierarchically tested in participants with PD-L1 CPS ≥10, PD-L1 CPS ≥1, and in all participants.

By redesigning the study to include the PD-L1 CPS ≥10 population as the primary analysis population, the target enrolment was increased from 780 to 1542 participants and the timing of the interim/final analysis were updated amongst other changes with protocol amendment 02. With amendment 03, PFS was amended from a primary to a secondary endpoint and the interim analysis, multiplicity and statistical power were revised again. Protocol amendment 03 occurred about 5 months prior to recruitment of the last participant. These changes concern central elements of the study design, which raised concerns during the assessment of the application. The MAH confirmed that changes made to the study design in Protocol Amendments 2 and 3 resulted from data external to KEYNOTE-859 study data that emerged after the start of the study. The MAH clarified that results from KEYNOTE-062, which evaluated pembrolizumab monotherapy or pembrolizumab in combination with chemotherapy versus chemotherapy alone in participants with HER2-negative PD-L1-positive advanced gastric cancer or GEJ adenocarcinoma, indicated a greater PFS benefit for the PD-L1 CPS ≥10 population. This led to the addition of PD-L1 CPS ≥10 as the primary analysis population and the changing of the order of testing of OS and PFS hypotheses in accordance with the CPS level in Amendment 2. The sample size in KEYNOTE-859 was increased from 780 to 1542 participants to maintain >80% power for the analysis of OS in the PD-L1 CPS ≥10 population.

Protocol Amendment 3 was also informed by the results of CheckMate-649 study that evaluated nivolumab in a similar patient population and demonstrated statistically significant OS benefit in all examined PD-L1 CPS subgroups. Given the importance of the OS endpoint, the KEYNOTE-859 protocol design was updated to assign all initial alpha to the primary OS endpoint and test PFS in a step-down manner.

The reasons for the implemented changes based on the outlined external data are considered plausible and can be followed. Also considering that the study has been conducted with a double-blind design, it appears sufficiently reasonable to accept that the amendments were not triggered by knowledge of internal study data.

Efficacy data and additional analyses

Efficacy results were provided from the IA of Study KEYNOTE-859 as of the data cutoff date of 03-OCT-2022 with a median follow-up time of 12 months (representing the interim OS analysis and final analyses for PFS and ORR). At this IA, the study met the predefined superiority criteria for all efficacy hypotheses: pembrolizumab in combination with chemotherapy provided statistically significant improvements in OS, PFS by BICR, and ORR by BICR in CPS ≥ 10, CPS ≥ 1 and ITT when compared with chemotherapy alone.

In the **ITT** population (all 1579 randomised participants), an improvement of median survival was observed from 11.5 months in the chemotherapy group to 12.9 months in the pembrolizumab + chemotherapy group (OS HR 0.78; 95% CI 0.70, 0.87). Median PFS was 5.6 months vs 6.9 months (PFS HR 0.76; 95% CI 0.67, 0.85) and ORR improved from 42% to 51.3% in the chemotherapy vs pembrolizumab + chemotherapy group, respectively. Median DOR was not statistically tested but favoured also the pembrolizumab + chemotherapy group (median DOR 5.7 months vs 8.0 months).

The exploratory analyses of PRO endpoints did overall not show clinically meaningful differences between both treatment arms. A positive trend was seen for selected items only in selected analyses of EORTC QLQ-C30 in the highest PD-L1 expression group, whereas an improvement in pain (measured by the EORTC- QLQ-STO22) was consistently observed in favour of the pembrolizumab plus chemotherapy group in all populations.

Efficacy by PD-L1 expression

In line with the known predictive value of PD-L1 expression in gastric/GEJ adenocarcinoma, an association of PD-L1 status with efficacy outcomes was observed in KEYNOTE-859. The largest difference between the prespecified analysis populations with the most meaningful benefit could be observed for the highest PD-L1 expression group **CPS ≥10**, representing 35% of the study population. In this subgroup, the addition of pembrolizumab to standard chemotherapy led to an improvement of median OS of 3.9 months (OS HR 0.65; 95% CI 0.53, 0.79), a delay in median disease progression (median PFS) of 2.5 months and an improvement of ORR of 17.5%.

On the contrary, the efficacy results for the positive PD-L1 group with **CPS ≥1** were only slightly better compared to the all participants population (ITT). In the CPS ≥1 subpopulation: OS HR 0.74 (95% CI 0.65, 084) and PFS HR 0.72 (95% CI 0.63, 0.82) in favour of the pembrolizumab + chemotherapy group vs the chemotherapy group; while in the ITT population: OS HR 0.78 (95% CI 0.70, 0.87) and PFS HR 0.76 (0.67, 0.85).

It is acknowledged that the study demonstrated statistically significant and consistent improvements in OS, PFS and ORR, not only in the predefined PD-L1 positive subgroups, but also in the ITT (all participants) population. Although the magnitude of the improvements is not overwhelming in the overall study population, it could be regarded as clinically meaningful; however, the benefit is driven by participants with higher PD-L1 expression levels, concealing the lack of benefit for patients with low PD-L1 status in the ITT analyses. With this regard, the complementary analyses that have been provided are considered relevant, though they are retrospective and exploratory (given the design of the prespecified hypothesis testing).

Efficacy analysis in the subgroup of participants with PD-L1 **CPS <1** (21.8% of KEYNOTE-859 study population) did not show a meaningful benefit regarding OS or PFS for the addition of pembrolizumab: OS HR 0.92 (95% CI 0.73, 1.17), PFS HR 0.90 (95% CI 0.70, 1.15). The KM curves largely overlap for

OS, PFS and DOR. Considering the amount of external clinical data supporting the predictive relevance of PD-L1 expression in gastric/GEJ adenocarcinoma, the fact that all patients were centrally tested with a validated assay for this disease setting and that PD-L1 CPS </≥1 was a stratification factor, the subgroup results are considered reliable. Given the lack of benefit in OS and PFS and in view of the additional toxicity of the immunochemotherapy combination, the B/R balance is not considered favourable in this subgroup. Therefore, the indication wording was revised to restrict the target population to adults whose tumours express PD-L1 with a CPS ≥ 1.

Subgroup results in the PD-L1 **CPS <10** population similarly suggest only a modest benefit: OS HR 0.86 [95% 0.75, 0.98] with a late and small separation of KM curves (max. 6% difference in OS rate); PFS HR 0.85 (95% CI 0.74, 0.98). Nonetheless, the CPS <10 population needs to be seen as a composite of patients with CPS <1 and patients with PD-L1 CPS ≥1 to <10, and results for the **CPS ≥1 to <10** population (43% of study population) are considered relevant for the decision on the most appropriate target population. For patients with PD-L1 CPS ≥1 to <10, a slightly more pronounced benefit is observed: OS HR 0.83 (95% CI 0.70, 0.98 with an 8% difference in OS rate), PFS HR 0.83 (95% CI 0.70, 0.99). Taking the modest, but clear separation of OS and PFS KMs (and the upper confidence intervals) into account, a restriction of an indication excluding these patients does not appear to be justified.

Given, however, the considerably smaller benefit in the subgroup of patients with PD-L1 CPS ≥1 to <10 compared to CPS ≥10, subgroup results of patients with PD-L1 CPS ≥1 to <10 compared to CPS ≥ 10 were reflected in SmPC 5.1, as this information is considered relevant for physicians if weighing the B/R for individual patients when deciding on adding pembrolizumab to chemotherapy.

Moreover, in order to get further information regarding the impact of PD-L1 expression of efficacy (especially in low expression groups), the MAH was asked to provide a more granular analysis by PD-L1 score by using CPS as a continuous variable and to present efficacy results for a subgroup analysis based on an exploratory PD-L1 CPS cutpoint of 5 specifically. The MAH assessed the association between PD-L1 CPS and efficacy (OS and PFS) by using CPS as a continuous score (after square root transformation) in a Cox regression model. Though exploratory and post-hoc, these analyses in the ITT suggest an association between higher CPS scores and PFS or OS in the pembrolizumab plus chemotherapy group (HR (95% CI): 0.929 (0.893, 0.966), nominal 2-sided p value = 0.0002 for OS and HR (95% CI): 0.940 (0.904, 0.978), nominal p-value = 0.0021 for PFS). Thus, higher CPS scores suggest higher treatment effect. Based on the provided hazard ratio estimate and confidence intervals of CPS as a continuous score, no optimal cutpoint for CPS can be concluded. The MAH did not perform PD-L1 IHC 22C3 analyses at a **CPS ≥5** cutpoint, since there is no analytical validation data at the CPS ≥5 cutpoint for the PD-L1 22C3 pharmDx kit in gastric or GEJ adenocarcinoma and therefore precision and reproducibility around this cutpoint is uncertain and the PD-L1 IHC 22C3 analyses would be potentially unreliable at a CPS ≥5 cutpoint.

Upon request, the MAH provided post-hoc exploratory efficacy results based on the PD-L1 CPS cutpoints of CPS <5 and CPS ≥5, CPS ≥1 to <5, and CPS ≥5 to <10. The MAH reiterated that the CPS 5 cutpoint was neither a prespecified endpoint nor a stratification factor, it was not analytically validated and no pathologist training was conducted for this cutpoint; thus, these factors may negatively impact the accuracy of the PD-L1 raw scores at CPS 5. Therefore, the results of these exploratory analyses should be interpreted with caution.

Indeed, the provided results of the analyses based on the CPS 5 cutpoint were not fully plausible. As expected, a greater benefit was observed for the subgroup of patients with CPS ≥5 as compared to CPS <5 (OS HR of 0.70 [95% CI 0.60, 0.82] vs 0.84 [95% CI 0.72, 0.98]; PFS HR 0.69 [95% CI 0.58, 0.81] vs 0.83 [95% CI 0.71, 0.98] for CPS ≥5 vs CPS <5, respectively). A benefit was also observed in the CPS ≥1 to <5 subgroup (n=468) with an OS HR of 0.78 [95% CI: 0.64, 0.95] and a PFS HR of

0.78 [95% CI: 0.64, 0.96] with 7% higher response rates in the pembrolizumab plus chemotherapy arm. However, less favourable results were reported for the smallest subgroup of subjects with CPS ≥5 to <10 (n=231; OS HR 0.94 [95% CI 0.71, 1.25); PFS HR 0.93 [95% CI 0.69, 1.25]) with even 7% higher response rates in the chemotherapy control arm. The lack of benefit in the comparatively higher PD-L1 expression group is not biologically plausible and might be questioned in the context of the above discussed methodological limitations.

The MAH also provided analyses of association between PD-L1 CPS and efficacy (OS and PFS) using CPS as a continuous score (after square root transformation) in a Cox regression model, for CPS ≥1, CPS ≥10 as well as for CPS ≥5 subpopulations. These data suggest an association between higher CPS scores and efficacy in the pembrolizumab plus chemotherapy group in the CPS ≥1 subpopulation, the same trend was also observed in the CPS ≥5 subgroup, but not in the CPS ≥10 population.

In addition, the MAH provided graphical presentations of the relation of CPS score (square root transformed) to OS and PFS. The graphs did not suggest a correlation between CPS scores and OS or PFS (Harrell's concordance statistics were close to 0.5).

The methodological limitations of the exploratory analyses around the CPS 5 cutpoint are acknowledged; nonetheless, these results as a whole are considered supportive to select the CPS ≥1 cutpoint as the most appropriate one in the proposed indication. Patients likely derive a greater benefit with increasing PD-L1 expression levels; available data do however not support CPS 5 as an alternative cutpoint. In view of the large subgroup of patients with PD-L1 CPS ≥1 to <10 it is considered important not to ignore the potential to improve the B/R assessment for patients with advanced cancer in a palliative setting. Therefore, depending on the PD-L1 expression data in a given indication, the MAH might consider for future studies to prospectively validate and integrate additional cutpoints into the study design to be able to provide more reliable data by PD-L1 status.

There was an overlap of the currently applied indication and the previously approved indication in patients with HER-2 negative gastroesophageal junction (GEJ) adenocarcinoma (EMEA/H/C/003820/II/0097) which was restricted to patients whose tumours express PD L1 with a CPS ≥10 (study KEYNOTE-590). The HER-2 negative GEJ adenocarcinoma indication was therefore removed from the oesophageal carcinoma indication in section 4.1 of the SmPC and included in the gastric cancer KEYNOTE-859 indication (i.e., in adults whose tumours express PD-L1 with a CPS ≥1).

KEYNOTE-859 enrolled a larger and broader group of participants that was more representative of the subgroup of patients with GEJ adenocarcinoma, including 334 participants with GEJ adenocarcinoma (21.2% of ITT population) as compared to 91 participants (12.1% of ITT population) in KEYNOTE-590. Moreover, KEYNOTE-859 enrolled participants with all subtypes of GEJ adenocarcinoma (Siewert type 1-3), whereas KEYNOTE-590 only enrolled those with Siewert type 1.

Among participants with GEJ adenocarcinoma in KEYNOTE-859, the point estimates for OS HR and PFS HR favoured pembrolizumab plus chemotherapy over chemotherapy in the ITT population (OS HR 0.74, 95% CI: 0.582, 0.941; PFS HR 0.78, 95% CI: 0.609, 1.007) and for participants whose tumours express PD L1 CPS ≥1 (OS HR 0.74, 95% CI: 0.65, 0.84; PFS HR 0.72, 95% CI: 0.63, 0.82). These results were generally consistent with the overall study population.

Among participants with GEJ adenocarcinoma in KEYNOTE-590, the point estimates for OS HR and PFS HR also favoured pembrolizumab plus chemotherapy in the ITT population (OS HR 0.73, 95% CI: 0.45, 1.17; PFS HR 0.73, 95% CI: 0.45, 1.18) and among participants whose tumours express PD L1 CPS ≥1 (OS HR 0.68, 95% CI: 0.40, 1.18; PFS HR 0.72, 95% CI: 0.42, 1.24).

Of note, the efficacy analyses among participants with GEJ adenocarcinoma in KEYNOTE-590 whose tumours express PD L1 CPS ≥1 were post-hoc exploratory analyses using raw score values for PD-L1

IHC 22C3 expression at CPS ≥1. Results were based on relatively small numbers and the CIs are wide. On the contrary, the CPS ≥ 1 cutpoint was prespecified in the KEYNOTE-859 efficacy analyses.

Given these rather consistent efficacy results across both studies among participants with GEJ adenocarcinoma whose tumours express PD L1 CPS ≥1, CHMP agreed on the proposed CPS ≥1 cutpoint for the GEJ adenocarcinoma indication.

Subgroups

Subgroup analyses of OS, PFS and ORR showed overall consistent results across different subgroups with the exception of MSI status. Subjects with MSI high (4.7% of study population) had substantially better efficacy results compared to subjects with non-MSI-high status: OS HR 0.34 vs 0.79, PFS HR 0.27 vs 0.79, ORR 42.3 vs 6.3 for the comparison of MSI high vs non-MSI-high; 95% CI were non-overlapping across all endpoints. Given the small sample size of the MSI-high population, ancillary analysis in subjects with non-MSI-high status were consistent with the primary analysis in the ITT (All participants) population.

Post-hoc subgroup analysis of OS by prior oncological radiation did not show a benefit in the subgroup of participants who did receive previous radiotherapy (OS HR 1.12, 95% CI: 0.63, 1.987). It is acknowledged that no reliable conclusions can be drawn from these post-hoc exploratory analyses, considering the small sample size (n=62 of 1579; 4%) and the wide CI. It is however noted this has been similarly observed for nivolumab in study CheckMate649, where the benefit of Nivo+Chemo over chemo appeared less clear in patients with previously untreated advanced or metastatic gastric, gastroesophageal junction cancer or oesophageal adenocarcinoma who had received prior radiotherapy (OS HR 0.92; 95% CI: 0.64, 1.33; 9.6% of study population) (EMEA/H/C/003985/II/0096).

3.7% of patients had locally advanced unresectable disease (28 and 30 participants in both treatment arms) with disease stage between IIA and IIIC (according to baseline characteristics). The MAH did not provide efficacy data by disease status, since subgroup analysis was not performed if any level of a subgroup variable had fewer than approximately 5% of the ITT population. It is acknowledged that no reliable conclusions could be drawn based on efficacy analysis of this small sample size and a similar treatment effect might be assumed for locally advanced and metastatic disease. According to ESMO Clinical Practice Guidelines, multimodality treatment including pre- and post-operative chemotherapy is recommended for localised gastric cancer (Stage IB-III >T1 and/or ≥ NO MO) *(Lordick et al. Annals of Oncology 07/2022).* For patients with locally advanced adenocarcinoma of the gastroesophageal junction perioperative chemotherapy as well as neoadjuvant chemoradiotherapy is recommended (*Obermannová, Annals of Oncology 07/2022*). Since the inclusion criteria for Study KN859 only specified "diagnosis of locally advanced unresectable or metastatic gastric or GEJ adenocarcinoma", the MAH provided further clarification that recruitment occurred in high-volume centres and resectability was determined by individual patient case assessments by experienced multidisciplinary teams that included consulting surgeons and oncologists.

Subgroup analyses by age category (<65, ≥65 to <75, and ≥75 years) showed improved results for OS, PFS and ORR in all 3 age categories with pembrolizumab plus chemotherapy when compared with chemotherapy.

Cross-study comparisons were not made due to study differences between KEYNOTE-859 and other gastric studies in treatment regimens, monotherapy versus combination therapy, patient population enrolled in the studies (line of therapy), study design, and biomarker selection.

Additional efficacy analyses

PFS and ORR analysis results per INV assessments were provided as supportive analyses, which showed consistent treatment effects that favoured pembrolizumab plus chemotherapy.

Supportive studies

The phase 3 Study **KEYNOTE-062** failed to demonstrate a statistically significant benefit for the addition of pembrolizumab to chemotherapy in the 1L treatment of advanced HER2-negative GEJ/gastric adenocarcinoma. The MAH presented these negative study results in the context of the current application.

The MAH provided the following discussion: The first evidence of activity of pembrolizumab in advanced gastric cancer was obtained from KEYNOTE-059 in the 3L setting. Building on these data, KEYNOTE-061 and KEYNOTE-062 were initiated in 2015 and sought to evaluate the activity of pembrolizumab in previously treated and untreated patients, respectively. At the time, the activity of pembrolizumab as a monotherapy, and other anti-PD-1 inhibitors, was demonstrated in melanoma and lung cancer and being explored in a multitude of other tumours. KEYNOTE-061 and KEYNOTE-062 were designed as such without a chemotherapy backbone, except for 1 arm in KEYNOTE-062, which was pembrolizumab plus chemotherapy. As more data became available from the overall pembrolizumab development program coupled with external data in gastric cancer, it was evident that chemotherapy had to be a backbone for certain tumour types and that the magnitude of benefit with the addition of an anti-PD-1 could vary by tumour type.

Subsequently KEYNOTE-859 was designed to evaluate treatment with a chemotherapy backbone plus the addition of pembrolizumab in advanced and unresectable gastric cancer patients who have not received prior therapy (1L) and its design reflects an updated understanding of the role of anti-PD-1 inhibition in gastric cancer.

KEYNOTE-062 and KEYNOTE-859 both enrolled untreated, locally advanced/unresectable or metastatic gastric of GEJ adenocarcinoma, however, there were some distinguishing characteristics for each study.

1. KEYNOTE-062 was a 3-arm study of pembrolizumab vs. chemotherapy, and pembrolizumab plus chemotherapy vs. chemotherapy, while KEYNOTE-859 was a 2-arm study of pembrolizumab plus chemotherapy vs. chemotherapy.
2. KEYNOTE-062 enrolled patients with tumour PD-L1 expression of CPS ≥1 while KEYNOTE-859 was an all-comer population with stratification according to CPS ≥1. PD-L1 CPS ≥10 hypotheses were added in KEYNOTE-859 protocol amendment 2 in addition to PD-L1 CPS ≥1. This change was based on KEYNOTE-062 data.
3. KEYNOTE-062 statistical assumptions and design were modelled after early studies with pembrolizumab in melanoma and lung cancer (KEYNOTE-001, KEYNOTE-002, KEYNOTE-006, KEYNOTE-010) and in retrospect may have been too aggressive for gastric cancer as it is a different tumour type. In addition, the KEYNOTE-062 results and external studies showed a delayed treatment effect for OS and PFS for pembrolizumab. Based on these learnings, KEYNOTE-859 was amended to update the HR assumptions and incorporate piecewise modelling assumptions (ie, nonproportional hazard model).

Therefore, KEYNOTE-859, which is a large, randomised, global, double-blind, Phase 3 pivotal study further establishes the benefit of pembrolizumab plus chemotherapy in the 1L setting compared with chemotherapy for patients with advanced or unresectable gastric cancer.

2.4.4. Conclusions on the clinical efficacy

In previously untreated patients with advanced HER2 negative gastric or GEJ adenocarcinoma, data from KEYNOTE-859 demonstrated statistically significant improvements in OS, PFS, and ORR for pembrolizumab in combination with chemotherapy compared with chemotherapy alone. However, the benefit in the overall study population is driven by participants with higher PD-L1 expression levels.

Considering the totality of efficacy data by PD-L1 expression, the most pronounced benefit is observed for patients with PD-L1 CPS ≥10, whereas data in patients with CPS <10 show only a marginal improvement. However, among the CPS <10 population, patients with PD-L1 CPS <1 are those who do not seem to derive meaningful benefit from the addition of pembrolizumab to chemotherapy. As a result, the target population was restricted to adults whose tumours express PD-L1 with a CPS ≥1. Subgroup results of patients with PD-L1 CPS ≥1 to <10 compared to CPS ≥10 are reflected in SmPC 5.1 as this information is considered relevant for physicians.

2.5. Clinical safety

Introduction

Safety results are based on data from the IA of the KEYNOTE-859 study for the pembrolizumab plus chemotherapy and placebo plus chemotherapy (hereafter chemotherapy) groups (DCO date of 03-OCT-2022). This IA includes 1269 OS events as of the DCO date of 03-OCT-2022, with approximately 12 months of follow-up after last participant was randomised.

Safety analyses were based on the 'all participants as treated' (APaT) population, which included all randomised participants who received at least 1 dose of study intervention.

Pooled safety data from studies of pembrolizumab monotherapy in approved indications in the EU (pembrolizumab monotherapy Reference Safety Dataset (RSD)) are included to enable a comparison of the safety profile of pembrolizumab plus chemotherapy observed in KEYNOTE-859 to the established safety profile for pembrolizumab monotherapy. Pooled safety data from studies of pembrolizumab in combination with chemotherapy (the pooled pembrolizumab plus chemo dataset) represents a heterogeneous group of participants with different indications and chemotherapeutic regimens compared with participants in KEYNOTE-859.

Table 54 Safety results are presented for the 4 datasets:

Datasets	Population	Nomenclature in Tables	Nomenclature in Text
KEYNOTE-859 pembrolizumab plus chemotherapy safety dataset	(N=785): Safety data from participants with HER2-negative unresectable or metastatic gastric or GEJ adenocarcinoma who received pembrolizumab in combination with chemotherapy (FP or CAPOX) in KEYNOTE-859	KN-859 Pembrolizumab + Chemotherapy	Pembrolizumab plus chemotherapy
KEYNOTE-859 placebo plus chemotherapy safety dataset	(N=787): Safety data from participants with HER2-negative unresectable or metastatic gastric or GEJ adenocarcinoma who received placebo in combination with chemotherapy (FP or CAPOX) in KEYNOTE-859	KN-859 Placebo + Chemotherapy	Chemotherapy
Pooled pembrolizumab plus chemotherapy safety dataset[a]	(N=3123): Pooled safety data from participants treated with pembrolizumab plus chemotherapy, including participants with NSCLC in KEYNOTE-021 Cohorts A, C, and G, KEYNOTE-189 and KEYNOTE-407, HNSCC in KEYNOTE-048, TNBC in KEYNOTE-355 and KEYNOTE-522, esophageal carcinoma in KEYNOTE-590, and cervical in KEYNOTE-826	Pembrolizumab + Chemo Pooled Dataset	Pooled pembrolizumab plus chemo dataset
Pembrolizumab monotherapy reference safety dataset	(N=7631): Pooled safety data from participants treated with pembrolizumab monotherapy, including participants with advanced melanoma in KEYNOTE-001 Part B1, B2, B3, D, C, F1, F2, and F3, KEYNOTE-002, KEYNOTE-006, KEYNOTE-054, and KEYNOTE-716, NSCLC in KEYNOTE-001 Part B1, B2, B3, D, C, F1, F2, and F3, KEYNOTE-010, KEYNOTE-024, and KEYNOTE-042, HNSCC in KEYNOTE-012 Cohort B, and B2, KEYNOTE-040, KEYNOTE-048, KEYNOTE-055, cHL in KEYNOTE-013 Cohort 3, KEYNOTE-087, and KEYNOTE-204, bladder in KEYNOTE-045 and KEYNOTE-052, MSI-H in KEYNOTE-158 Cohort K, colorectal in KEYNOTE-164 Cohort A, B, and KEYNOTE-177, and RCC in KEYNOTE-564	Pembrolizumab Monotherapy RSD	Pembrolizumab monotherapy RSD

Abbreviations: CAPOX=capecitabine and oxaliplatin; cHL=classical Hodgkin Lymphoma; FP=cisplatin and 5-fluorouracil; GEJ=gastroesophageal junction; HER2= human epidermal growth factor receptor 2; HNSCC=head and neck squamous cell carcinoma; N=number; NSCLC=non–small cell lung cancer; RCC=renal cell carcinoma; RSD=reference safety dataset; TNBC=triple negative breast cancer.

[a]Chemotherapy combo therapies = KN021 Cohort A, C, G (NSCLC): pemetrexed plus cisplatin or carboplatin/carboplatin plus paclitaxel or nab-paclitaxel; KN189 (NSCLC): pemetrexed plus cisplatin or carboplatin; KN407 (NSCLC): carboplatin plus paclitaxel or nab-paclitaxel; KN048 (HNSCC): carboplatin or cisplatin plus 5-FU; KN355 (TNBC): nab-paclitaxel or paclitaxel, or gemcitabine plus carboplatin; KN590 (esophageal): cisplatin plus 5-FU; KN826 (cervical): paclitaxel plus cisplatin or carboplatin ± bevacizumab; KN522 (TNBC): carboplatin plus paclitaxel followed by doxorubicin plus cyclophosphamide.

Patient exposure

As of the DCO date (03-OCT-2022) of KEYNOTE-859, a total of 785 participants in the pembrolizumab plus chemotherapy group and 787 participants in the chemotherapy group had received at least 1 dose of study treatment.

Table 55 Summary of Drug Exposure (APaT Populatioon)

	KN859 Pembrolizumab + Chemotherapy (N=785)	KN859 Placebo + Chemotherapy (N=787)	Pembrolizumab + Chemo Pooled Dataset (N=3123)	Pembrolizumab Monotherapy Reference Safety Dataset (N=7631)
Duration of exposure (month)				
n	785	787	3118	7631
Mean (SD)	9.07 (7.55)	7.21 (5.96)	9.85 (7.29)	7.85 (6.91)
Median	6.70	5.59	7.89	5.78
Range	0.03 to 33.68	0.03 to 29.70	0.03 to 48.00	0.03 to 38.01
Number of cycles				
n	785	787	3118	7631
Mean (SD)	12.57 (10.26)	10.11 (8.01)	13.23 (9.65)	12.31 (10.10)
Median	9.00	8.00	11.00	9.00
Range	1.00 to 36.00	1.00 to 35.00	1.00 to 68.00	1.00 to 59.00

Each participant is counted once on each applicable duration category row.

Duration of exposure is calculated as last dose date - first dose date + 1.

Database cutoff date for KN859: 03OCT2022.

Table 56 Exposure by Duration (APaT Population)

	KN859 Pembrolizumab + Chemotherapy (N=785)			KN859 Placebo + Chemotherapy (N=787)			Pembrolizumab + Chemo Pooled Dataset (N=3123)			Pembrolizumab Monotherapy Reference Safety Dataset (N=7631)		
	n	(%)	Person-months	n	(%)	Person-months	n	(%)	Person-months	n	(%)	Person-months
Duration of exposure (month)												
>0	785	(100.0)	7,123.0	787	(100.0)	5,673.8	3,118	(99.8)	30,701.6	7,631	(100.0)	59,940.3
>=1	720	(91.7)	7,093.7	731	(92.9)	5,648.7	2,889	(92.5)	30,611.0	6,637	(87.0)	59,548.3
>=3	619	(78.9)	6,892.8	592	(75.2)	5,362.7	2,535	(81.2)	29,860.4	5,023	(65.8)	56,316.8
>=6	426	(54.3)	6,008.4	362	(46.0)	4,303.0	1,847	(59.1)	26,709.6	3,781	(49.5)	50,879.4
>=12	203	(25.9)	4,114.5	128	(16.3)	2,361.1	1,192	(38.2)	21,120.5	1,673	(21.9)	30,706.1
>=18	130	(16.6)	3,032.6	60	(7.6)	1,368.0	433	(13.9)	10,048.9	783	(10.3)	17,970.0
>=24	62	(7.9)	1,580.6	24	(3.0)	615.3	151	(4.8)	3,986.4	186	(2.4)	4,739.1

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 KN859: 03OCT2022.

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 57 Participant Characteristics (APaT Population)

	KN859 Pembrolizumab + Chemotherapy		KN859 Placebo + Chemotherapy		Pembrolizumab + Chemo Pooled Dataset		Pembrolizumab Monotherapy Reference Safety Dataset	
	n	(%)	n	(%)	n	(%)	n	(%)
Participants in population	785		787		3,123		7,631	
Sex								
Male	522	(66.5)	542	(68.9)	1,042	(33.4)	4,889	(64.1)
Female	263	(33.5)	245	(31.1)	2,081	(66.6)	2,742	(35.9)
Age (Years)								
<65	483	(61.5)	478	(60.7)	2,176	(69.7)	4,524	(59.3)
>=65	302	(38.5)	309	(39.3)	947	(30.3)	3,107	(40.7)
Mean	59.2		60.0		56.6		59.9	
SD	11.9		11.8		12.5		13.4	
Median	61.0		62.0		58.0		62.0	
Range	23 to 86		21 to 85		20 to 94		15 to 94	
Race								
American Indian Or Alaska Native	31	(3.9)	36	(4.6)	55	(1.8)	59	(0.8)
Asian	269	(34.3)	269	(34.2)	686	(22.0)	826	(10.8)
Black Or African American	12	(1.5)	8	(1.0)	108	(3.5)	146	(1.9)
Multiracial	43	(5.5)	30	(3.8)	64	(2.0)	86	(1.1)
Native Hawaiian Or Other Pacific Islander	1	(0.1)	2	(0.3)	2	(0.1)	5	(0.1)
White	422	(53.8)	434	(55.1)	2,088	(66.9)	5,838	(76.5)
Missing	7	(0.9)	8	(1.0)	120	(3.8)	671	(8.8)
Ethnicity								
Hispanic Or Latino	174	(22.2)	157	(19.9)	429	(13.7)	604	(7.9)
Not Hispanic Or Latino	586	(74.6)	613	(77.9)	2,502	(80.1)	6,064	(79.5)
Not Reported	14	(1.8)	14	(1.8)	105	(3.4)	808	(10.6)
Unknown	7	(0.9)	3	(0.4)	66	(2.1)	145	(1.9)
Missing	4	(0.5)	0	(0.0)	21	(0.7)	10	(0.1)
Age Category (Years)								
<65	483	(61.5)	478	(60.7)	2,176	(69.7)	4,524	(59.3)
65-74	246	(31.3)	249	(31.6)	767	(24.6)	2,173	(28.5)
75-84	54	(6.9)	59	(7.5)	175	(5.6)	824	(10.8)
>=85	2	(0.3)	1	(0.1)	5	(0.2)	110	(1.4)
ECOG Performance Scale								
[0] Normal Activity	281	(35.8)	300	(38.1)	1,768	(56.6)	4,016	(52.6)
[1] Symptoms, but ambulatory	504	(64.2)	487	(61.9)	1,349	(43.2)	3,440	(45.1)
Other/Missing	0	(0.0)	0	(0.0)	6	(0.2)	175	(2.3)
Geographic Region								
Western Europe	166	(21.1)	166	(21.1)	1,118	(35.8)	2,856	(37.4)
Ex-Western Europe	619	(78.9)	621	(78.9)	2,005	(64.2)	4,775	(62.6)

Western Europe includes countries in the European Economic Area, United Kingdom, and Switzerland.
Database cutoff date for KN859: 03OCT2022.

Adverse events

Adverse events (AEs) were coded using MedDRA version 25.0 and reported according to NCI CTCAE version 4.03.

Table 58 Adverse Event Summary (APaT Population)

	KN859 Pembrolizumab + Chemotherapy		KN859 Placebo + Chemotherapy		Pembrolizumab + Chemo Pooled Dataset		Pembrolizumab Monotherapy Reference Safety Dataset	
	n	(%)	n	(%)	n	(%)	n	(%)
Participants in population	785		787		3,123		7,631	
with one or more adverse events	776	(98.9)	771	(98.0)	3,097	(99.2)	7,375	(96.6)
with no adverse event	9	(1.1)	16	(2.0)	26	(0.8)	256	(3.4)
with drug-related[a] adverse events	751	(95.7)	736	(93.5)	3,020	(96.7)	5,462	(71.6)
with toxicity grade 3-5 adverse events	591	(75.3)	548	(69.6)	2,479	(79.4)	3,514	(46.0)
with toxicity grade 3-5 drug-related adverse events	**466**	**(59.4)**	402	(51.1)	2,099	(67.2)	1,208	(15.8)
with serious adverse events	355	(45.2)	316	(40.2)	1,456	(46.6)	2,742	(35.9)
with serious drug-related adverse events	**184**	**(23.4)**	146	(18.6)	910	(29.1)	840	(11.0)
with dose modification[b] due to an adverse event	**679**	**(86.5)**	660	(83.9)	2,477	(79.3)	2,719	(35.6)
who died	**64**	**(8.2)**	**58**	**(7.4)**	160	(5.1)	346	(4.5)
who died due to a drug-related adverse event	8	(1.0)	16	(2.0)	49	(1.6)	42	(0.6)
discontinued due to an adverse event	**257**	**(32.7)**	**204**	**(25.9)**	900	(28.8)	1,066	(14.0)
discontinued MK-3475/PLACEBO	116	(14.8)	86	(10.9)	548	(17.5)	1,066	(14.0)
discontinued any chemotherapy	237	(30.2)	197	(25.0)	644	(20.6)	0	(0.0)
discontinued all drugs	67	(8.5)	59	(7.5)	143	(4.6)	1,066	(14.0)
discontinued due to a drug-related adverse event	207	(26.4)	158	(20.1)	747	(23.9)	639	(8.4)
discontinued MK-3475/PLACEBO	68	(8.7)	40	(5.1)	405	(13.0)	639	(8.4)
discontinued any chemotherapy	190	(24.2)	155	(19.7)	537	(17.2)	0	(0.0)
discontinued all drugs	33	(4.2)	26	(3.3)	86	(2.8)	639	(8.4)
discontinued due to a serious adverse event	104	(13.2)	79	(10.0)	472	(15.1)	714	(9.4)
discontinued MK-3475/PLACEBO	93	(11.8)	73	(9.3)	382	(12.2)	714	(9.4)
discontinued any chemotherapy	83	(10.6)	74	(9.4)	314	(10.1)	0	(0.0)
discontinued all drugs	54	(6.9)	54	(6.9)	127	(4.1)	714	(9.4)
discontinued due to a serious drug-related adverse event	56	(7.1)	35	(4.4)	343	(11.0)	347	(4.5)
discontinued MK-3475/PLACEBO	48	(6.1)	29	(3.7)	261	(8.4)	347	(4.5)
discontinued any chemotherapy	41	(5.2)	34	(4.3)	221	(7.1)	0	(0.0)
discontinued all drugs	23	(2.9)	22	(2.8)	73	(2.3)	347	(4.5)

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

[b] Defined as an action taken of dose reduced, drug interrupted or drug withdrawn.

Grades are based on NCI CTCAE version 4.03.

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 v25.0 preferred terms "Neoplasm Progression", "Malignant Neoplasm Progression" and "Disease Progression" not related to the drug are excluded.
Database cutoff date for KN859: 03OCT2022.

Table 59 Exposure-Adjusted Adverse Event Summary (Including Multiple Occurrences of Events) - (APaT Population)

	Event Count and Rate (Events/100 person-months)[a]			
	KN859 Pembrolizumab + Chemotherapy	KN859 Placebo + Chemotherapy	Pembrolizumab + Chemo Pooled Dataset	Pembrolizumab Monotherapy Reference Safety Dataset
Number of participants exposed	785	787	3123	7631
Total exposure[b] in person-months	7866.95	6432.96	34084.64	66844.27
Total events (rate)				
adverse events	12096 (153.76)	9936 (154.45)	66128 (194.01)	76878 (115.01)
drug-related[c] adverse events	7726 (98.21)	6371 (99.04)	40032 (117.45)	24542 (36.72)
toxicity grade 3-5 adverse events	1647 (20.94)	1389 (21.59)	9548 (28.01)	7463 (11.16)
toxicity grade 3-5 drug-related adverse events	947 (12.04)	779 (12.11)	6869 (20.15)	1770 (2.65)
serious adverse events	627 (7.97)	531 (8.25)	2903 (8.52)	4801 (7.18)
serious drug-related adverse events	262 (3.33)	207 (3.22)	1477 (4.33)	1093 (1.64)
adverse events resulting in dose modification[d]	2407 (30.60)	1993 (30.98)	8960 (26.29)	4783 (7.16)
adverse events leading to death	**64 (0.81)**	**58 (0.90)**	166 (0.49)	353 (0.53)
drug-related adverse events leading to death	8 (0.10)	16 (0.25)	50 (0.15)	42 (0.06)
adverse events resulting in drug discontinuation	331 (4.21)	242 (3.76)	1097 (3.22)	1165 (1.74)
drug-related adverse events resulting in drug discontinuation	268 (3.41)	189 (2.94)	907 (2.66)	703 (1.05)
serious adverse events resulting in drug discontinuation	117 (1.49)	85 (1.32)	534 (1.57)	753 (1.13)
serious drug-related adverse events resulting in drug discontinuation	66 (0.84)	38 (0.59)	386 (1.13)	363 (0.54)

[a] Event rate per 100 person-months of exposure=event count *100/person-months of exposure.

[b] Drug exposure is defined as the time from the first dose date to the earlier of the last dose date + 30 or the database cut-off date.

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

[d] Defined as an action taken of dose reduced, drug interrupted or drug withdrawn.

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 v25.0 preferred terms "Neoplasm progression", "Malignant neoplasm progression" and "Disease progression" not related to the drug are excluded.

Grades are based on NCI CTCAE version 4.03.

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 KN859: 03OCT2022.

Table 60 Participants With Adverse Events (Incidence ≥ 10% in One or More Treatment Groups) By Decreasing Frequency of Preferred Term (APaT Population)

	KN859	KN859 Placebo	Pembrolizumab	Pembrolizumab

	Pembrolizumab + Chemotherapy		+ Chemotherapy		+ Chemo Pooled Dataset		Monotherapy Reference Safety Dataset	
	n	(%)	n	(%)	n	(%)	n	(%)
Participants in population	785		787		3,123		7,631	
with one or more adverse events	776	(98.9)	771	(98.0)	3,097	(99.2)	7,375	(96.6)
with no adverse events	9	(1.1)	16	(2.0)	26	(0.8)	256	(3.4)
Nausea	364	(46.4)	364	(46.3)	1,695	(54.3)	1,534	(20.1)
Anaemia	329	(41.9)	286	(36.3)	1,704	(54.6)	982	(12.9)
Diarrhoea	280	(35.7)	254	(32.3)	1,071	(34.3)	1,678	(22.0)
Vomiting	264	(33.6)	210	(26.7)	885	(28.3)	945	(12.4)
Decreased appetite	231	(29.4)	225	(28.6)	850	(27.2)	1,312	(17.2)
Platelet count decreased	209	(26.6)	188	(23.9)	377	(12.1)	95	(1.2)
Neutrophil count decreased	198	(25.2)	175	(22.2)	621	(19.9)	53	(0.7)
Fatigue	197	(25.1)	194	(24.7)	1,197	(38.3)	2,368	(31.0)
Palmar-plantar erythrodysaesthesia syndrome	195	(24.8)	171	(21.7)	34	(1.1)	24	(0.3)
Aspartate aminotransferase increased	184	(23.4)	137	(17.4)	490	(15.7)	538	(7.1)
Constipation	170	(21.7)	165	(21.0)	1,107	(35.4)	1,179	(15.5)
Neuropathy peripheral	157	(20.0)	175	(22.2)	465	(14.9)	146	(1.9)
Weight decreased	157	(20.0)	146	(18.6)	365	(11.7)	628	(8.2)
Hypoalbuminaemia	147	(18.7)	106	(13.5)	154	(4.9)	209	(2.7)
Neutropenia	147	(18.7)	142	(18.0)	1,111	(35.6)	82	(1.1)
Peripheral sensory neuropathy	140	(17.8)	136	(17.3)	393	(12.6)	83	(1.1)
Abdominal pain	139	(17.7)	118	(15.0)	323	(10.3)	674	(8.8)
Alanine aminotransferase increased	132	(16.8)	96	(12.2)	564	(18.1)	572	(7.5)
Asthenia	129	(16.4)	124	(15.8)	661	(21.2)	880	(11.5)
Hypothyroidism	120	(15.3)	34	(4.3)	434	(13.9)	937	(12.3)
Hypokalaemia	117	(14.9)	87	(11.1)	335	(10.7)	324	(4.2)
Blood bilirubin increased	106	(13.5)	71	(9.0)	64	(2.0)	163	(2.1)
White blood cell count decreased	106	(13.5)	93	(11.8)	464	(14.9)	70	(0.9)
Thrombocytopenia	93	(11.8)	84	(10.7)	572	(18.3)	117	(1.5)
Pyrexia	89	(11.3)	59	(7.5)	630	(20.2)	934	(12.2)
Blood alkaline phosphatase increased	81	(10.3)	69	(8.8)	176	(5.6)	322	(4.2)
Rash	72	(9.2)	40	(5.1)	644	(20.6)	1,175	(15.4)
Pruritus	65	(8.3)	21	(2.7)	468	(15.0)	1,435	(18.8)
Oedema peripheral	59	(7.5)	54	(6.9)	347	(11.1)	630	(8.3)
Stomatitis	57	(7.3)	48	(6.1)	451	(14.4)	201	(2.6)
Back pain	53	(6.8)	46	(5.8)	365	(11.7)	847	(11.1)
Dizziness	53	(6.8)	38	(4.8)	363	(11.6)	564	(7.4)
Mucosal inflammation	51	(6.5)	41	(5.2)	363	(11.6)	111	(1.5)
Dysgeusia	48	(6.1)	37	(4.7)	328	(10.5)	150	(2.0)
Leukopenia	47	(6.0)	42	(5.3)	367	(11.8)	52	(0.7)
Insomnia	43	(5.5)	52	(6.6)	400	(12.8)	528	(6.9)
Dyspnoea	42	(5.4)	32	(4.1)	425	(13.6)	1,130	(14.8)
Urinary tract infection	40	(5.1)	22	(2.8)	343	(11.0)	511	(6.7)
Cough	38	(4.8)	25	(3.2)	659	(21.1)	1,392	(18.2)
Arthralgia	34	(4.3)	27	(3.4)	660	(21.1)	1,436	(18.8)
Headache	28	(3.6)	34	(4.3)	572	(18.3)	946	(12.4)
Myalgia	21	(2.7)	13	(1.7)	361	(11.6)	575	(7.5)
Alopecia	19	(2.4)	15	(1.9)	1,099	(35.2)	118	(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 v25.0 preferred terms "Neoplasm Progression", "Malignant Neoplasm Progression" and "Disease Progression"

not related to the drug are excluded.
Database cutoff date for KN859: 03OCT2022.

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

	KN859 Pembrolizumab + Chemotherapy		KN859 Placebo + Chemotherapy		Pembrolizumab + Chemo Pooled Dataset		Pembrolizumab Monotherapy Reference Safety Dataset	
	n	(%)	n	(%)	n	(%)	n	(%)
Participants in population	785		787		3,123		7,631	
with one or more adverse events	751	(95.7)	736	(93.5)	3,020	(96.7)	5,462	(71.6)
with no adverse events	34	(4.3)	51	(6.5)	103	(3.3)	2,169	(28.4)
Nausea	325	(41.4)	326	(41.4)	1,513	(48.4)	675	(8.8)
Diarrhoea	252	(32.1)	214	(27.2)	745	(23.9)	904	(11.8)
Anaemia	243	(31.0)	212	(26.9)	1,465	(46.9)	234	(3.1)
Vomiting	215	(27.4)	175	(22.2)	693	(22.2)	248	(3.2)
Platelet count decreased	196	(25.0)	177	(22.5)	363	(11.6)	43	(0.6)
Neutrophil count decreased	193	(24.6)	170	(21.6)	603	(19.3)	34	(0.4)
Palmar-plantar erythrodysaesthesia syndrome	189	(24.1)	166	(21.1)	34	(1.1)	19	(0.2)
Decreased appetite	168	(21.4)	168	(21.3)	661	(21.2)	525	(6.9)
Fatigue	157	(20.0)	164	(20.8)	1,039	(33.3)	1,476	(19.3)
Neuropathy peripheral	150	(19.1)	164	(20.8)	409	(13.1)	54	(0.7)
Neutropenia	142	(18.1)	135	(17.2)	1,076	(34.5)	49	(0.6)
Aspartate aminotransferase increased	139	(17.7)	102	(13.0)	386	(12.4)	312	(4.1)
Peripheral sensory neuropathy	137	(17.5)	131	(16.6)	371	(11.9)	35	(0.5)
Hypothyroidism	107	(13.6)	32	(4.1)	377	(12.1)	810	(10.6)
Alanine aminotransferase increased	101	(12.9)	68	(8.6)	454	(14.5)	336	(4.4)
White blood cell count decreased	101	(12.9)	87	(11.1)	442	(14.2)	34	(0.4)
Asthenia	94	(12.0)	79	(10.0)	522	(16.7)	491	(6.4)
Thrombocytopenia	83	(10.6)	77	(9.8)	535	(17.1)	56	(0.7)
Blood bilirubin increased	78	(9.9)	51	(6.5)	40	(1.3)	71	(0.9)
Weight decreased	67	(8.5)	70	(8.9)	189	(6.1)	148	(1.9)
Constipation	62	(7.9)	55	(7.0)	509	(16.3)	184	(2.4)
Rash	56	(7.1)	29	(3.7)	496	(15.9)	884	(11.6)
Stomatitis	53	(6.8)	42	(5.3)	408	(13.1)	103	(1.3)
Hypoalbuminaemia	52	(6.6)	41	(5.2)	56	(1.8)	23	(0.3)
Hypokalaemia	50	(6.4)	44	(5.6)	129	(4.1)	43	(0.6)
Mucosal inflammation	49	(6.2)	37	(4.7)	330	(10.6)	57	(0.7)
Pruritus	47	(6.0)	18	(2.3)	347	(11.1)	1,143	(15.0)
Dysgeusia	44	(5.6)	35	(4.4)	294	(9.4)	79	(1.0)
Leukopenia	44	(5.6)	35	(4.4)	345	(11.0)	32	(0.4)
Paraesthesia	44	(5.6)	30	(3.8)	140	(4.5)	63	(0.8)
Abdominal pain	42	(5.4)	31	(3.9)	125	(4.0)	148	(1.9)
Pyrexia	33	(4.2)	15	(1.9)	291	(9.3)	314	(4.1)
Blood creatinine increased	28	(3.6)	16	(2.0)	211	(6.8)	105	(1.4)
Alopecia	14	(1.8)	14	(1.8)	1,072	(34.3)	57	(0.7)
Arthralgia	8	(1.0)	7	(0.9)	314	(10.1)	661	(8.7)
Epistaxis	8	(1.0)	6	(0.8)	155	(5.0)	6	(0.1)
Headache	8	(1.0)	6	(0.8)	190	(6.1)	250	(3.3)
Myalgia	7	(0.9)	3	(0.4)	272	(8.7)	312	(4.1)
Febrile neutropenia	3	(0.4)	7	(0.9)	250	(8.0)	0	(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.
Database cutoff date for KN859: 03OCT2022.

Table 62 Participants With Grade 3-5 Adverse Events (Incidence ⩾ 1% in One or More Treatment Groups)
By Decreasing Frequency of Preferred Term (APaT Population)

	KN859 Pembrolizumab + Chemotherapy		KN859 Placebo + Chemotherapy		Pembrolizumab + Chemo Pooled Dataset		Pembrolizumab Monotherapy Reference Safety Dataset	
	n	(%)	n	(%)	n	(%)	n	(%)
Participants in population	785		787		3,123		7,631	
with one or more adverse events	591	(75.3)	548	(69.6)	2,479	(79.4)	3,514	(46.0)
with no adverse events	194	(24.7)	239	(30.4)	644	(20.6)	4,117	(54.0)
Anaemia	95	(12.1)	76	(9.7)	620	(19.9)	275	(3.6)
Neutrophil count decreased	77	(9.8)	64	(8.1)	443	(14.2)	10	(0.1)
Neutropenia	58	(7.4)	68	(8.6)	727	(23.3)	21	(0.3)
Platelet count decreased	56	(7.1)	39	(5.0)	114	(3.7)	10	(0.1)
Diarrhoea	50	(6.4)	40	(5.1)	102	(3.3)	114	(1.5)
Hypokalaemia	50	(6.4)	31	(3.9)	96	(3.1)	70	(0.9)
Vomiting	41	(5.2)	42	(5.3)	101	(3.2)	52	(0.7)
Fatigue	39	(5.0)	40	(5.1)	158	(5.1)	166	(2.2)
Hyponatraemia	29	(3.7)	22	(2.8)	114	(3.7)	169	(2.2)
Nausea	29	(3.7)	35	(4.4)	108	(3.5)	58	(0.8)
Decreased appetite	26	(3.3)	20	(2.5)	61	(2.0)	77	(1.0)
Pneumonia	26	(3.3)	13	(1.7)	148	(4.7)	270	(3.5)
Palmar-plantar erythrodysaesthesia syndrome	24	(3.1)	14	(1.8)	3	(0.1)	1	(0.0)
Weight decreased	23	(2.9)	21	(2.7)	41	(1.3)	35	(0.5)
Asthenia	22	(2.8)	31	(3.9)	112	(3.6)	70	(0.9)
Peripheral sensory neuropathy	22	(2.8)	8	(1.0)	26	(0.8)	2	(0.0)
Pulmonary embolism	20	(2.5)	24	(3.0)	58	(1.9)	101	(1.3)
Aspartate aminotransferase increased	18	(2.3)	12	(1.5)	81	(2.6)	95	(1.2)
Blood bilirubin increased	18	(2.3)	8	(1.0)	6	(0.2)	27	(0.4)
Abdominal pain	17	(2.2)	18	(2.3)	20	(0.6)	65	(0.9)
Colitis	16	(2.0)	4	(0.5)	27	(0.9)	74	(1.0)
Hypoalbuminaemia	16	(2.0)	12	(1.5)	12	(0.4)	33	(0.4)
White blood cell count decreased	16	(2.0)	11	(1.4)	218	(7.0)	5	(0.1)
Alanine aminotransferase increased	15	(1.9)	12	(1.5)	120	(3.8)	97	(1.3)
Blood alkaline phosphatase increased	15	(1.9)	12	(1.5)	15	(0.5)	65	(0.9)
Acute kidney injury	14	(1.8)	14	(1.8)	59	(1.9)	65	(0.9)
Hypophosphataemia	14	(1.8)	8	(1.0)	35	(1.1)	52	(0.7)
Ascites	13	(1.7)	14	(1.8)	2	(0.1)	21	(0.3)
Gamma-glutamyltransferase increased	13	(1.7)	4	(0.5)	34	(1.1)	56	(0.7)
Lymphocyte count decreased	13	(1.7)	5	(0.6)	60	(1.9)	33	(0.4)
Thrombocytopenia	13	(1.7)	18	(2.3)	201	(6.4)	23	(0.3)
Hypertension	12	(1.5)	9	(1.1)	92	(2.9)	148	(1.9)
Death	11	(1.4)	4	(0.5)	18	(0.6)	49	(0.6)
Dysphagia	10	(1.3)	16	(2.0)	40	(1.3)	31	(0.4)
Neuropathy peripheral	10	(1.3)	26	(3.3)	33	(1.1)	4	(0.1)
Lymphopenia	9	(1.1)	3	(0.4)	32	(1.0)	20	(0.3)
Pleural effusion	9	(1.1)	2	(0.3)	29	(0.9)	73	(1.0)
Sepsis	9	(1.1)	7	(0.9)	48	(1.5)	60	(0.8)
Dehydration	8	(1.0)	7	(0.9)	45	(1.4)	70	(0.9)

Gastrointestinal haemorrhage	8	(1.0)	9	(1.1)	4	(0.1)	9	(0.1)
Hypotension	8	(1.0)	4	(0.5)	31	(1.0)	35	(0.5)
Intestinal obstruction	8	(1.0)	5	(0.6)	5	(0.2)	20	(0.3)
Pneumonitis	8	(1.0)	2	(0.3)	46	(1.5)	97	(1.3)
Upper gastrointestinal haemorrhage	8	(1.0)	8	(1.0)	6	(0.2)	6	(0.1)
Stomatitis	7	(0.9)	1	(0.1)	63	(2.0)	9	(0.1)
Urinary tract infection	7	(0.9)	4	(0.5)	60	(1.9)	85	(1.1)
Dyspnoea	6	(0.8)	3	(0.4)	50	(1.6)	145	(1.9)
Hyperglycaemia	6	(0.8)	4	(0.5)	35	(1.1)	83	(1.1)
Mucosal inflammation	6	(0.8)	8	(1.0)	55	(1.8)	10	(0.1)
Syncope	6	(0.8)	9	(1.1)	43	(1.4)	43	(0.6)
Gastric haemorrhage	5	(0.6)	8	(1.0)	4	(0.1)	5	(0.1)
Rash	5	(0.6)	1	(0.1)	37	(1.2)	44	(0.6)
Rash maculo-papular	5	(0.6)	0	(0.0)	37	(1.2)	23	(0.3)
Febrile neutropenia	4	(0.5)	10	(1.3)	259	(8.3)	11	(0.1)
Leukopenia	4	(0.5)	2	(0.3)	145	(4.6)	7	(0.1)
Obstruction gastric	3	(0.4)	9	(1.1)	0	(0.0)	1	(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.

Grades are based on NCI CTCAE version 4.03.

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 v25.0 preferred terms "Neoplasm Progression", "Malignant Neoplasm Progression" and "Disease Progression" not related to the drug are excluded.

Database cutoff date for KN859: 03OCT2022.

Table 63 Participants With Grade 3-5 Drug-Related Adverse Events (Incidence ⩾ 1% in One or More Treatment Groups) - By Decreasing Frequency of Preferred Term (APaT Population)

	KN859 Pembrolizumab + Chemotherapy		KN859 Placebo + Chemotherapy		Pembrolizumab + Chemo Pooled Dataset		Pembrolizumab Monotherapy Reference Safety Dataset	
	n	(%)	n	(%)	n	(%)	n	(%)
Participants in population	785		787		3,123		7,631	
with one or more adverse events	466	(59.4)	402	(51.1)	2,099	(67.2)	1,208	(15.8)
with no adverse events	319	(40.6)	385	(48.9)	1,024	(32.8)	6,423	(84.2)
Neutrophil count decreased	72	(9.2)	58	(7.4)	428	(13.7)	6	(0.1)
Anaemia	64	(8.2)	51	(6.5)	524	(16.8)	33	(0.4)
Neutropenia	55	(7.0)	60	(7.6)	710	(22.7)	13	(0.2)
Platelet count decreased	55	(7.0)	36	(4.6)	110	(3.5)	2	(0.0)
Diarrhoea	46	(5.9)	37	(4.7)	74	(2.4)	75	(1.0)
Vomiting	35	(4.5)	32	(4.1)	77	(2.5)	12	(0.2)
Fatigue	27	(3.4)	32	(4.1)	133	(4.3)	75	(1.0)
Hypokalaemia	26	(3.3)	18	(2.3)	41	(1.3)	12	(0.2)
Nausea	26	(3.3)	29	(3.7)	96	(3.1)	13	(0.2)
Palmar-plantar erythrodysaesthesia syndrome	24	(3.1)	14	(1.8)	3	(0.1)	1	(0.0)
Peripheral sensory neuropathy	22	(2.8)	8	(1.0)	26	(0.8)	2	(0.0)
Colitis	16	(2.0)	4	(0.5)	26	(0.8)	67	(0.9)
Decreased appetite	15	(1.9)	14	(1.8)	49	(1.6)	23	(0.3)
Asthenia	13	(1.7)	16	(2.0)	82	(2.6)	26	(0.3)
Hyponatraemia	13	(1.7)	9	(1.1)	53	(1.7)	32	(0.4)
Thrombocytopenia	12	(1.5)	18	(2.3)	185	(5.9)	11	(0.1)
White blood cell count decreased	12	(1.5)	9	(1.1)	211	(6.8)	2	(0.0)
Aspartate aminotransferase increased	11	(1.4)	8	(1.0)	63	(2.0)	47	(0.6)
Alanine aminotransferase increased	10	(1.3)	7	(0.9)	96	(3.1)	56	(0.7)

Lymphocyte count decreased	10	(1.3)	2	(0.3)	51	(1.6)	9	(0.1)
Neuropathy peripheral	10	(1.3)	25	(3.2)	33	(1.1)	2	(0.0)
Blood bilirubin increased	9	(1.1)	3	(0.4)	4	(0.1)	5	(0.1)
Pneumonitis	7	(0.9)	2	(0.3)	42	(1.3)	91	(1.2)
Mucosal inflammation	6	(0.8)	8	(1.0)	53	(1.7)	6	(0.1)
Stomatitis	6	(0.8)	0	(0.0)	60	(1.9)	5	(0.1)
Acute kidney injury	5	(0.6)	5	(0.6)	37	(1.2)	16	(0.2)
Hypertension	5	(0.6)	3	(0.4)	32	(1.0)	15	(0.2)
Rash	5	(0.6)	1	(0.1)	31	(1.0)	37	(0.5)
Rash maculo-papular	5	(0.6)	0	(0.0)	31	(1.0)	21	(0.3)
Leukopenia	4	(0.5)	1	(0.1)	142	(4.5)	3	(0.0)
Pneumonia	4	(0.5)	1	(0.1)	39	(1.2)	17	(0.2)

Table 64 Participants With Grade 3-5 Drug-Related Adverse Events (Incidence ≥ 1% in One or More Treatment Groups) - By Decreasing Frequency of Preferred Term (APaT Population)

	KN859 Pembrolizumab + Chemotherapy		KN859 Placebo + Chemotherapy		Pembrolizumab + Chemo Pooled Dataset		Pembrolizumab Monotherapy Reference Safety Dataset	
	n	(%)	n	(%)	n	(%)	n	(%)
Febrile neutropenia	3	(0.4)	7	(0.9)	245	(7.8)	0	(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.

Grades are based on NCI CTCAE version 4.03.

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 KN859: 03OCT2022.

Table 65 Adverse Event Summary - By Backbone Therapy (APaT Population)

	Pembrolizumab + CAPOX		Pembrolizumab + FP		CAPOX		FP	
	n	(%)	n	(%)	n	(%)	n	(%)
Participants in population	674		106		679		107	
with one or more adverse events	666	(98.8)	105	(99.1)	663	(97.6)	107	(100.0)
with no adverse event	8	(1.2)	1	(0.9)	16	(2.4)	0	(0.0)
with drug-related[a] adverse events	644	(95.5)	102	(96.2)	636	(93.7)	100	(93.5)
with toxicity grade 3-5 adverse events	501	(74.3)	87	(82.1)	457	(67.3)	90	(84.1)
with toxicity grade 3-5 drug-related adverse events	389	(57.7)	74	(69.8)	333	(49.0)	69	(64.5)
with serious adverse events	309	(45.8)	45	(42.5)	257	(37.8)	58	(54.2)
with serious drug-related adverse events	167	(24.8)	16	(15.1)	116	(17.1)	30	(28.0)
with dose modification[b] due to an adverse event	586	(86.9)	88	(83.0)	565	(83.2)	94	(87.9)
who died	50	(7.4)	14	(13.2)	39	(5.7)	18	(16.8)
who died due to a drug-related adverse event	7	(1.0)	1	(0.9)	11	(1.6)	5	(4.7)
discontinued due to an adverse event	228	(33.8)	27	(25.5)	172	(25.3)	31	(29.0)
discontinued MK-3475/PLACEBO	106	(15.7)	10	(9.4)	66	(9.7)	19	(17.8)
discontinued any chemotherapy	212	(31.5)	23	(21.7)	167	(24.6)	30	(28.0)
discontinued all drugs	63	(9.3)	4	(3.8)	44	(6.5)	15	(14.0)
discontinued due to a drug-related adverse event	188	(27.9)	17	(16.0)	137	(20.2)	21	(19.6)
discontinued MK-	66	(9.8)	2	(1.9)	31	(4.6)	9	(8.4)

3475/PLACEBO								
discontinued any chemotherapy	173	(25.7)	15	(14.2)	135	(19.9)	20	(18.7)
discontinued all drugs	33	(4.9)	0	(0.0)	20	(2.9)	6	(5.6)
discontinued due to a serious adverse event	92	(13.6)	12	(11.3)	60	(8.8)	18	(16.8)
discontinued MK-3475/PLACEBO	84	(12.5)	9	(8.5)	56	(8.2)	16	(15.0)
discontinued any chemotherapy	75	(11.1)	8	(7.5)	56	(8.2)	18	(16.8)
discontinued all drugs	51	(7.6)	3	(2.8)	40	(5.9)	14	(13.1)
discontinued due to a serious drug-related adverse event	52	(7.7)	4	(3.8)	27	(4.0)	8	(7.5)
discontinued MK-3475/PLACEBO	46	(6.8)	2	(1.9)	23	(3.4)	6	(5.6)
discontinued any chemotherapy	39	(5.8)	2	(1.9)	26	(3.8)	8	(7.5)
discontinued all drugs	23	(3.4)	0	(0.0)	17	(2.5)	5	(4.7)

[a] Determined by the investigator to be related to the drug.
[b] Defined as an action taken of dose reduced, drug interrupted or drug withdrawn.
Participants with at least one chemotherapy is summarized in this table.
Grades are based on NCI CTCAE version 4.03.
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 V25.0 preferred terms "Neoplasm progression", "Malignant neoplasm progression" and "Disease progression" not related to the drug are excluded.
CAPOX: Backbone chemotherapy oxaliplatin + capecitabine.
FP: Backbone chemotherapy cisplatin + 5-FU.
Database Cutoff Date: 03OCT2022

Table 66 Exposure-Adjusted Adverse Event Summary (Including Multiple Occurrences of Events) by Backbone Therapy (APaT Population in Chemotherapy Arm)Adverse Event Summary By Backbone Therapy (APaT Population)

	Event Count and Rate (Events/100 person-months)[a]			
	CAPOX		FP	
Number of Participants exposed	679		107	
Total exposure[b] in person-months	5656.69		775.25	
Total events (rate)				
adverse events	8,528	(150.76)	1,407	(181.49)
drug-related[c] adverse events	5,595	(98.91)	776	(100.10)
toxicity grade 3-5 adverse events	1,096	(19.38)	292	(37.67)
toxicity grade 3-5 drug-related adverse events	623	(11.01)	156	(20.12)
serious adverse events	412	(7.28)	118	(15.22)
serious drug-related adverse events	155	(2.74)	52	(6.71)
adverse events resulting in dose modification[d]	1,746	(30.87)	246	(31.73)
adverse events leading to death	39	(0.69)	18	(2.32)
drug-related adverse events leading to death	11	(0.19)	5	(0.64)
adverse events resulting in drug discontinuation	206	(3.64)	35	(4.51)
drug-related adverse events resulting in drug discontinuation	165	(2.92)	24	(3.10)
serious adverse events resulting in drug discontinuation	65	(1.15)	19	(2.45)
serious drug-related adverse events resulting in drug discontinuation	30	(0.53)	8	(1.03)

[a] Event rate per 100 person-months of exposure = event count *100/person-months of exposure.
[b] Drug exposure is defined as the between the first dose date + 1 day and the earlier of the last dose date + 30 or the database cutoff date.
[c] Determined by the investigator to be related to the drug.
[d] Defined as an action taken of dose reduced, drug interrupted or drug withdrawn.
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 V25.0 preferred terms "Neoplasm progression", "Malignant neoplasm progression" and "Disease progression" not related to the drug are excluded.
Grades are based on NCI CTCAE version 4.03.
Database Cutoff Date: 03OCT2022

Serious adverse event/deaths/other significant events

Table 67 Participants With Serious Adverse Events (Incidence ⩾ 1% in One or More Treatment Groups) By Decreasing Frequency of Preferred Term (APaT Population)

	KN859 Pembrolizumab + Chemotherapy		KN859 Placebo + Chemotherapy		Pembrolizumab + Chemo Pooled Dataset		Pembrolizumab Monotherapy Reference Safety Dataset	
	n	(%)	n	(%)	n	(%)	n	(%)
Participants in population	785		787		3,123		7,631	
with one or more adverse events	355	(45.2)	316	(40.2)	1,456	(46.6)	2,742	(35.9)
with no adverse events	430	(54.8)	471	(59.8)	1,667	(53.4)	4,889	(64.1)
Diarrhoea	31	(3.9)	25	(3.2)	47	(1.5)	70	(0.9)
Pneumonia	30	(3.8)	14	(1.8)	145	(4.6)	272	(3.6)
Vomiting	19	(2.4)	23	(2.9)	41	(1.3)	32	(0.4)
Colitis	16	(2.0)	4	(0.5)	28	(0.9)	71	(0.9)
Pulmonary embolism	15	(1.9)	6	(0.8)	43	(1.4)	78	(1.0)
Nausea	14	(1.8)	11	(1.4)	28	(0.9)	30	(0.4)
Abdominal pain	12	(1.5)	9	(1.1)	9	(0.3)	43	(0.6)
Acute kidney injury	12	(1.5)	11	(1.4)	55	(1.8)	65	(0.9)
Pyrexia	12	(1.5)	9	(1.1)	73	(2.3)	79	(1.0)
Death	11	(1.4)	4	(0.5)	18	(0.6)	49	(0.6)
Decreased appetite	9	(1.1)	10	(1.3)	16	(0.5)	20	(0.3)
Gastrointestinal haemorrhage	9	(1.1)	8	(1.0)	4	(0.1)	12	(0.2)
Upper gastrointestinal haemorrhage	9	(1.1)	8	(1.0)	5	(0.2)	6	(0.1)
Anaemia	8	(1.0)	8	(1.0)	86	(2.8)	65	(0.9)
Dysphagia	8	(1.0)	15	(1.9)	21	(0.7)	18	(0.2)
Hypokalaemia	8	(1.0)	6	(0.8)	20	(0.6)	9	(0.1)
Intestinal obstruction	8	(1.0)	6	(0.8)	5	(0.2)	19	(0.2)
Pleural effusion	8	(1.0)	2	(0.3)	31	(1.0)	88	(1.2)
Pneumonitis	8	(1.0)	2	(0.3)	54	(1.7)	136	(1.8)
Sepsis	7	(0.9)	7	(0.9)	43	(1.4)	56	(0.7)
Ascites	5	(0.6)	9	(1.1)	1	(0.0)	8	(0.1)
Febrile neutropenia	3	(0.4)	7	(0.9)	217	(6.9)	8	(0.1)
Obstruction gastric	3	(0.4)	9	(1.1)	0	(0.0)	1	(0.0)
Thrombocytopenia	3	(0.4)	1	(0.1)	43	(1.4)	10	(0.1)
Urinary tract infection	3	(0.4)	2	(0.3)	33	(1.1)	67	(0.9)
Dyspnoea	1	(0.1)	2	(0.3)	18	(0.6)	91	(1.2)
Neutropenia	1	(0.1)	1	(0.1)	50	(1.6)	3	(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.

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

MedDRA v25.0 preferred terms "Neoplasm Progression", "Malignant Neoplasm Progression" and "Disease Progression" not related to the drug are excluded.

Database cutoff date for KN859: 03OCT2022.

Table 68 Participants With Drug-Related Serious Adverse Events (Incidence ⩾ 1% in One or More Treatment Groups) - By Decreasing Frequency of Preferred Term (APaT Population)

	KN859 Pembrolizumab + Chemotherapy		KN859 Placebo + Chemotherapy		Pembrolizumab + Chemo Pooled Dataset		Pembrolizumab Monotherapy Reference Safety Dataset	
	n	(%)	n	(%)	n	(%)	n	(%)
Participants in population	785		787		3,123		7,631	
with one or more adverse events	184	(23.4)	146	(18.6)	910	(29.1)	840	(11.0)

with no adverse events	601	(76.6)	641	(81.4)	2,213	(70.9)	6,791	(89.0)
Diarrhoea	31	(3.9)	24	(3.0)	34	(1.1)	44	(0.6)
Colitis	16	(2.0)	4	(0.5)	27	(0.9)	63	(0.8)
Vomiting	14	(1.8)	17	(2.2)	30	(1.0)	9	(0.1)
Nausea	12	(1.5)	7	(0.9)	26	(0.8)	7	(0.1)
Pneumonitis	7	(0.9)	2	(0.3)	49	(1.6)	129	(1.7)
Pneumonia	6	(0.8)	2	(0.3)	38	(1.2)	19	(0.2)
Decreased appetite	5	(0.6)	8	(1.0)	16	(0.5)	6	(0.1)
Acute kidney injury	4	(0.5)	4	(0.5)	36	(1.2)	19	(0.2)
Anaemia	4	(0.5)	7	(0.9)	68	(2.2)	6	(0.1)
Pyrexia	3	(0.4)	3	(0.4)	39	(1.2)	22	(0.3)
Thrombocytopenia	3	(0.4)	1	(0.1)	41	(1.3)	6	(0.1)
Febrile neutropenia	2	(0.3)	4	(0.5)	208	(6.7)	0	(0.0)
Neutropenia	1	(0.1)	0	(0.0)	46	(1.5)	1	(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.

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

Database cutoff date for KN859: 03OCT2022.

Table 69 Participants With Adverse Events Resulting in Death (Incidence > 0% in KN859 Treatment groups) - By Decreasing Frequency of Preferred Term (APaT Population)

	KN859 Pembrolizumab + Chemotherapy		KN859 Placebo + Chemotherapy		Pembrolizumab + Chemo Pooled Dataset		Pembrolizumab Monotherapy Reference Safety Dataset	
	n	(%)	n	(%)	n	(%)	n	(%)
Participants in population	785		787		3,123		7,631	
with one or more adverse events	**64**	**(8.2)**	**58**	**(7.4)**	160	(5.1)	346	(4.5)
with no adverse events	721	(91.8)	729	(92.6)	2,963	(94.9)	7,285	(95.5)
Death	11	(1.4)	4	(0.5)	18	(0.6)	49	(0.6)
Pneumonia	7	(0.9)	6	(0.8)	16	(0.5)	40	(0.5)
Pulmonary embolism	4	(0.5)	2	(0.3)	4	(0.1)	10	(0.1)
Sepsis	4	(0.5)	5	(0.6)	9	(0.3)	11	(0.1)
Sudden death	4	(0.5)	1	(0.1)	1	(0.0)	2	(0.0)
Intestinal obstruction	3	(0.4)	1	(0.1)	0	(0.0)	1	(0.0)
Aspiration	2	(0.3)	0	(0.0)	0	(0.0)	4	(0.1)
Cerebrovascular accident	2	(0.3)	1	(0.1)	2	(0.1)	5	(0.1)
Gastrointestinal haemorrhage	2	(0.3)	1	(0.1)	0	(0.0)	0	(0.0)
Respiratory failure	2	(0.3)	3	(0.4)	5	(0.2)	17	(0.2)
Septic shock	2	(0.3)	5	(0.6)	8	(0.3)	11	(0.1)
Urosepsis	2	(0.3)	1	(0.1)	0	(0.0)	5	(0.1)
Acute kidney injury	1	(0.1)	1	(0.1)	4	(0.1)	3	(0.0)
Acute myocardial infarction	1	(0.1)	4	(0.5)	3	(0.1)	1	(0.0)
COVID-19	1	(0.1)	1	(0.1)	1	(0.0)	0	(0.0)
COVID-19 pneumonia	1	(0.1)	1	(0.1)	0	(0.0)	1	(0.0)
Cachexia	1	(0.1)	0	(0.0)	0	(0.0)	3	(0.0)
Cardiac arrest	1	(0.1)	1	(0.1)	10	(0.3)	9	(0.1)
Cardiac tamponade	1	(0.1)	0	(0.0)	0	(0.0)	1	(0.0)
Cerebral infarction	1	(0.1)	0	(0.0)	1	(0.0)	0	(0.0)
Cholangitis infective	1	(0.1)	0	(0.0)	0	(0.0)	0	(0.0)
Diarrhoea	1	(0.1)	1	(0.1)	1	(0.0)	1	(0.0)
Hypercalcaemia	1	(0.1)	0	(0.0)	0	(0.0)	0	(0.0)
Ileus	1	(0.1)	0	(0.0)	0	(0.0)	0	(0.0)
Myocardial infarction	1	(0.1)	0	(0.0)	4	(0.1)	6	(0.1)
Peripheral embolism	1	(0.1)	0	(0.0)	0	(0.0)	0	(0.0)
Pneumonitis	1	(0.1)	1	(0.1)	5	(0.2)	8	(0.1)

Pneumoperitoneum	1	(0.1)	0	(0.0)	0	(0.0)	0	(0.0)
Pulmonary haemorrhage	1	(0.1)	0	(0.0)	2	(0.1)	5	(0.1)
Thrombotic thrombocytopenic purpura	1	(0.1)	0	(0.0)	0	(0.0)	0	(0.0)
Weight decreased	1	(0.1)	0	(0.0)	0	(0.0)	0	(0.0)
Abdominal infection	0	(0.0)	1	(0.1)	0	(0.0)	0	(0.0)
Acute coronary syndrome	0	(0.0)	1	(0.1)	0	(0.0)	1	(0.0)
Acute respiratory failure	0	(0.0)	1	(0.1)	1	(0.0)	5	(0.1)
Biliary sepsis	0	(0.0)	1	(0.1)	0	(0.0)	0	(0.0)
Cardio-respiratory arrest	0	(0.0)	1	(0.1)	3	(0.1)	4	(0.1)
Cerebral haemorrhage	0	(0.0)	1	(0.1)	0	(0.0)	1	(0.0)
Cholestasis	0	(0.0)	1	(0.1)	0	(0.0)	0	(0.0)
Completed suicide	0	(0.0)	1	(0.1)	0	(0.0)	3	(0.0)
Gastric perforation	0	(0.0)	1	(0.1)	0	(0.0)	0	(0.0)
Gastrointestinal perforation	0	(0.0)	1	(0.1)	0	(0.0)	2	(0.0)
Hepatic function abnormal	0	(0.0)	1	(0.1)	0	(0.0)	0	(0.0)
Hypoglycaemia	0	(0.0)	1	(0.1)	0	(0.0)	0	(0.0)
Klebsiella sepsis	0	(0.0)	1	(0.1)	0	(0.0)	0	(0.0)
Multiple organ dysfunction syndrome	0	(0.0)	1	(0.1)	5	(0.2)	6	(0.1)
Neurotoxicity	0	(0.0)	1	(0.1)	0	(0.0)	0	(0.0)
Pneumonia aspiration	0	(0.0)	1	(0.1)	5	(0.2)	8	(0.1)
Spinal fracture	0	(0.0)	0	(0.0)	1	(0.0)	0	(0.0)
Ulcer haemorrhage	0	(0.0)	1	(0.1)	0	(0.0)	0	(0.0)
Upper gastrointestinal haemorrhage	0	(0.0)	1	(0.1)	1	(0.0)	1	(0.0)

Deaths considered drug-related by investigator were:

- Eight AEs resulting in death in the pembrolizumab plus SOC group: death, diarrhoea, peripheral embolism, pneumonitis, pulmonary haemorrhage, sepsis and septic shock.

- Sixteen AEs resulting in death in the SOC group: 2 patients died from acute myocardial infarction and 4 due to sepsis or septic shock.

Table 70 Adverse Event Summary Adverse Events Of Special Interest (APaT Population)

	KN859 Pembrolizumab + Chemotherapy		KN859 Placebo + Chemotherapy		Pembrolizumab + Chemo Pooled Dataset		Pembrolizumab Monotherapy Reference Safety Dataset	
	n	(%)	n	(%)	n	(%)	n	(%)
Participants in population	785		787		3,123		7,631	
with one or more adverse events	242	(30.8)	105	(13.3)	1,052	(33.7)	2,042	(26.8)
with no adverse event	543	(69.2)	682	(86.7)	2,071	(66.3)	5,589	(73.2)
with drug-related[a] adverse events	224	(28.5)	92	(11.7)	943	(30.2)	1,790	(23.5)
with toxicity grade 3-5 adverse events	**74**	**(9.4)**	**17**	**(2.2)**	**326**	**(10.4)**	**523**	**(6.9)**
with toxicity grade 3-5 drug-related adverse events	**68**	**(8.7)**	**15**	**(1.9)**	**297**	**(9.5)**	**462**	**(6.1)**
with serious adverse events	**61**	**(7.8)**	**13**	**(1.7)**	251	(8.0)	502	(6.6)
with serious drug-related adverse events	56	(7.1)	11	(1.4)	230	(7.4)	449	(5.9)
with dose modification[b] due to an adverse event	**106**	**(13.5)**	**41**	**(5.2)**	473	(15.1)	747	(9.8)
who died	1	(0.1)	1	(0.1)	9	(0.3)	13	(0.2)
who died due to a drug-related adverse event	1	(0.1)	1	(0.1)	9	(0.3)	13	(0.2)
discontinued due to an	40	(5.1)	14	(1.8)	228	(7.3)	354	(4.6)

adverse event								
discontinued MK-3475/PLACEBO	30	(3.8)	6	(0.8)	176	(5.6)	354	(4.6)
discontinued any chemotherapy	27	(3.4)	11	(1.4)	120	(3.8)	0	(0.0)
discontinued all drugs	8	(1.0)	1	(0.1)	20	(0.6)	354	(4.6)
discontinued due to a drug-related adverse event	39	(5.0)	13	(1.7)	224	(7.2)	349	(4.6)
discontinued MK-3475/PLACEBO	29	(3.7)	5	(0.6)	172	(5.5)	349	(4.6)
discontinued any chemotherapy	25	(3.2)	11	(1.4)	118	(3.8)	0	(0.0)
discontinued all drugs	8	(1.0)	1	(0.1)	20	(0.6)	349	(4.6)
discontinued due to a serious adverse event	29	(3.7)	5	(0.6)	144	(4.6)	226	(3.0)
discontinued MK-3475/PLACEBO	26	(3.3)	5	(0.6)	132	(4.2)	226	(3.0)
discontinued any chemotherapy	18	(2.3)	3	(0.4)	67	(2.1)	0	(0.0)
discontinued all drugs	7	(0.9)	1	(0.1)	17	(0.5)	226	(3.0)
discontinued due to a serious drug-related adverse event	28	(3.6)	5	(0.6)	141	(4.5)	224	(2.9)
discontinued MK-3475/PLACEBO	25	(3.2)	5	(0.6)	129	(4.1)	224	(2.9)
discontinued any chemotherapy	17	(2.2)	3	(0.4)	65	(2.1)	0	(0.0)
discontinued all drugs	7	(0.9)	1	(0.1)	17	(0.5)	224	(2.9)

[a] Determined by the investigator to be related to the drug.
[b] Defined as an action taken of dose reduced, drug interrupted or drug withdrawn.
Grades are based on NCI CTCAE version 4.03.
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 KN859: 03OCT2022.

Table 71 Participants With Adverse Events of Special Interest (Incidence > 0% in One or More Treatment Groups) - By AEOSI Category and Preferred Term (APaT Population)

	KN859 Pembrolizumab + Chemotherapy		KN859 Placebo + Chemotherapy		Pembrolizumab + Chemo Pooled Dataset		Pembrolizumab Monotherapy Reference Safety Dataset	
	n	(%)	n	(%)	n	(%)	n	(%)
Participants in population	785		787		3,123		7,631	
with one or more adverse events	242	(30.8)	105	(13.3)	1,052	(33.7)	2,042	(26.8)
with no adverse events	543	(69.2)	682	(86.7)	2,071	(66.3)	5,589	(73.2)
Adrenal Insufficiency	**10**	**(1.3)**	**1**	**(0.1)**	**40**	**(1.3)**	**74**	**(1.0)**
Adrenal insufficiency	10	(1.3)	1	(0.1)	39	(1.2)	69	(0.9)
Addison's disease	0	(0.0)	0	(0.0)	1	(0.0)	2	(0.0)
Adrenocortical insufficiency acute	0	(0.0)	0	(0.0)	0	(0.0)	2	(0.0)
Secondary adrenocortical insufficiency	0	(0.0)	0	(0.0)	0	(0.0)	2	(0.0)
Cholangitis Sclerosing	**0**	**(0.0)**	**0**	**(0.0)**	**2**	**(0.1)**	**0**	**(0.0)**
Cholangitis sclerosing	0	(0.0)	0	(0.0)	1	(0.0)	0	(0.0)
Immune-mediated cholangitis	0	(0.0)	0	(0.0)	1	(0.0)	0	(0.0)
Colitis	**26**	**(3.3)**	**14**	**(1.8)**	**84**	**(2.7)**	**159**	**(2.1)**
Colitis	20	(2.5)	14	(1.8)	64	(2.0)	134	(1.8)
Immune-mediated enterocolitis	4	(0.5)	0	(0.0)	2	(0.1)	6	(0.1)
Enterocolitis	3	(0.4)	0	(0.0)	14	(0.4)	11	(0.1)
Autoimmune colitis	0	(0.0)	0	(0.0)	4	(0.1)	6	(0.1)

Colitis microscopic	0	(0.0)	0	(0.0)	1	(0.0)	4	(0.1)
Encephalitis	**0**	**(0.0)**	**0**	**(0.0)**	**5**	**(0.2)**	**5**	**(0.1)**
Encephalitis	0	(0.0)	0	(0.0)	2	(0.1)	4	(0.1)
Encephalitis autoimmune	0	(0.0)	0	(0.0)	3	(0.1)	1	(0.0)
Guillain-Barre Syndrome	**0**	**(0.0)**	**0**	**(0.0)**	**2**	**(0.1)**	**6**	**(0.1)**
Axonal neuropathy	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)
Demyelinating polyneuropathy	0	(0.0)	0	(0.0)	1	(0.0)	1	(0.0)
Guillain-Barre syndrome	0	(0.0)	0	(0.0)	1	(0.0)	4	(0.1)
Hepatitis	**9**	**(1.1)**	**4**	**(0.5)**	**40**	**(1.3)**	**80**	**(1.0)**
Hepatitis	5	(0.6)	2	(0.3)	14	(0.4)	34	(0.4)
Autoimmune hepatitis	3	(0.4)	0	(0.0)	16	(0.5)	35	(0.5)
Immune-mediated hepatitis	1	(0.1)	1	(0.1)	11	(0.4)	3	(0.0)
Drug-induced liver injury	0	(0.0)	1	(0.1)	0	(0.0)	8	(0.1)
Hepatitis acute	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)
Hyperthyroidism	**44**	**(5.6)**	**13**	**(1.7)**	**173**	**(5.5)**	**398**	**(5.2)**
Hyperthyroidism	44	(5.6)	13	(1.7)	171	(5.5)	398	(5.2)
Basedow's disease	0	(0.0)	0	(0.0)	2	(0.1)	0	(0.0)
Hypoparathyroidism	**1**	**(0.1)**	**0**	**(0.0)**	**1**	**(0.0)**	**1**	**(0.0)**
Hypoparathyroidism	1	(0.1)	0	(0.0)	1	(0.0)	1	(0.0)
Hypophysitis	**3**	**(0.4)**	**0**	**(0.0)**	**28**	**(0.9)**	**52**	**(0.7)**
Hypopituitarism	3	(0.4)	0	(0.0)	11	(0.4)	19	(0.2)
Hypophysitis	0	(0.0)	0	(0.0)	17	(0.5)	32	(0.4)
Lymphocytic hypophysitis	0	(0.0)	0	(0.0)	0	(0.0)	2	(0.0)
Hypothyroidism	**120**	**(15.3)**	**34**	**(4.3)**	**434**	**(13.9)**	**939**	**(12.3)**
Hypothyroidism	120	(15.3)	34	(4.3)	434	(13.9)	937	(12.3)
Autoimmune hypothyroidism	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)
Immune-mediated hypothyroidism	0	(0.0)	0	(0.0)	1	(0.0)	0	(0.0)
Myxoedema	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)
Primary hypothyroidism	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)
Infusion Reactions	**44**	**(5.6)**	**37**	**(4.7)**	**246**	**(7.9)**	**165**	**(2.2)**
Infusion related reaction	27	(3.4)	23	(2.9)	122	(3.9)	75	(1.0)
Hypersensitivity	9	(1.1)	7	(0.9)	76	(2.4)	49	(0.6)
Anaphylactic reaction	5	(0.6)	2	(0.3)	10	(0.3)	10	(0.1)
Drug hypersensitivity	4	(0.5)	7	(0.9)	41	(1.3)	24	(0.3)
Anaphylactoid reaction	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)
Cytokine release syndrome	0	(0.0)	0	(0.0)	5	(0.2)	8	(0.1)
Infusion related hypersensitivity reaction	0	(0.0)	1	(0.1)	0	(0.0)	0	(0.0)
Serum sickness	0	(0.0)	0	(0.0)	1	(0.0)	0	(0.0)
Myasthenic Syndrome	**1**	**(0.1)**	**0**	**(0.0)**	**1**	**(0.0)**	**8**	**(0.1)**
Myasthenia gravis	1	(0.1)	0	(0.0)	1	(0.0)	5	(0.1)
Myasthenic syndrome	0	(0.0)	0	(0.0)	0	(0.0)	3	(0.0)
Myelitis	**0**	**(0.0)**	**0**	**(0.0)**	**0**	**(0.0)**	**3**	**(0.0)**
Myelitis	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)
Myelitis transverse	0	(0.0)	0	(0.0)	0	(0.0)	2	(0.0)
Myocarditis	**0**	**(0.0)**	**1**	**(0.1)**	**8**	**(0.3)**	**9**	**(0.1)**
Autoimmune myocarditis	0	(0.0)	0	(0.0)	1	(0.0)	0	(0.0)
Immune-mediated myocarditis	0	(0.0)	1	(0.1)	0	(0.0)	0	(0.0)
Myocarditis	0	(0.0)	0	(0.0)	7	(0.2)	9	(0.1)
Myositis	**1**	**(0.1)**	**0**	**(0.0)**	**13**	**(0.4)**	**34**	**(0.4)**
Myositis	1	(0.1)	0	(0.0)	6	(0.2)	22	(0.3)
Autoimmune myositis	0	(0.0)	0	(0.0)	1	(0.0)	0	(0.0)
Dermatomyositis	0	(0.0)	0	(0.0)	1	(0.0)	0	(0.0)
Myopathy	0	(0.0)	0	(0.0)	5	(0.2)	8	(0.1)
Necrotising myositis	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)
Rhabdomyolysis	0	(0.0)	0	(0.0)	0	(0.0)	3	(0.0)
Nephritis	**4**	**(0.5)**	**0**	**(0.0)**	**25**	**(0.8)**	**37**	**(0.5)**
Tubulointerstitial nephritis	2	(0.3)	0	(0.0)	10	(0.3)	14	(0.2)
Immune-mediated nephritis	1	(0.1)	0	(0.0)	0	(0.0)	0	(0.0)

Nephritis	1	(0.1)	0	(0.0)	14	(0.4)	10	(0.1)
Acute kidney injury	0	(0.0)	0	(0.0)	0	(0.0)	2	(0.0)
Autoimmune nephritis	0	(0.0)	0	(0.0)	2	(0.1)	5	(0.1)
Glomerulonephritis	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)
Glomerulonephritis acute	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)
Glomerulonephritis membranous	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)
Nephrotic syndrome	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)
Renal failure	0	(0.0)	0	(0.0)	0	(0.0)	2	(0.0)
Pancreatitis	**3**	**(0.4)**	**3**	**(0.4)**	**15**	**(0.5)**	**28**	**(0.4)**
Pancreatitis	3	(0.4)	2	(0.3)	11	(0.4)	24	(0.3)
Autoimmune pancreatitis	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)
Pancreatitis acute	0	(0.0)	1	(0.1)	5	(0.2)	4	(0.1)
Pneumonitis	**25**	**(3.2)**	**7**	**(0.9)**	**124**	**(4.0)**	**324**	**(4.2)**
Pneumonitis	20	(2.5)	5	(0.6)	112	(3.6)	291	(3.8)
Immune-mediated lung disease	3	(0.4)	1	(0.1)	1	(0.0)	4	(0.1)
Interstitial lung disease	2	(0.3)	1	(0.1)	10	(0.3)	29	(0.4)
Organising pneumonia	0	(0.0)	0	(0.0)	1	(0.0)	3	(0.0)
Sarcoidosis	**0**	**(0.0)**	**0**	**(0.0)**	**1**	**(0.0)**	**20**	**(0.3)**
Cutaneous sarcoidosis	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)
Pulmonary sarcoidosis	0	(0.0)	0	(0.0)	0	(0.0)	2	(0.0)
Sarcoidosis	0	(0.0)	0	(0.0)	1	(0.0)	18	(0.2)
Severe Skin Reactions	**16**	**(2.0)**	**1**	**(0.1)**	**96**	**(3.1)**	**130**	**(1.7)**
Rash	5	(0.6)	1	(0.1)	37	(1.2)	44	(0.6)
Rash maculo-papular	5	(0.6)	0	(0.0)	37	(1.2)	23	(0.3)
Erythema multiforme	2	(0.3)	0	(0.0)	6	(0.2)	8	(0.1)
Cutaneous vasculitis	1	(0.1)	0	(0.0)	0	(0.0)	0	(0.0)
Dermatitis bullous	1	(0.1)	0	(0.0)	8	(0.3)	9	(0.1)
Pemphigoid	1	(0.1)	0	(0.0)	1	(0.0)	3	(0.0)
Pruritus	1	(0.1)	0	(0.0)	6	(0.2)	16	(0.2)
Dermatitis exfoliative	0	(0.0)	0	(0.0)	0	(0.0)	5	(0.1)
Dermatitis exfoliative generalised	0	(0.0)	0	(0.0)	4	(0.1)	2	(0.0)
Exfoliative rash	0	(0.0)	0	(0.0)	0	(0.0)	2	(0.0)
Lichen planus	0	(0.0)	0	(0.0)	0	(0.0)	6	(0.1)
Oral lichen planus	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)
Pemphigus	0	(0.0)	0	(0.0)	0	(0.0)	2	(0.0)
Pruritus genital	0	(0.0)	0	(0.0)	0	(0.0)	2	(0.0)
Rash erythematous	0	(0.0)	0	(0.0)	1	(0.0)	1	(0.0)
Rash pruritic	0	(0.0)	0	(0.0)	1	(0.0)	4	(0.1)
Rash pustular	0	(0.0)	0	(0.0)	1	(0.0)	2	(0.0)
Skin necrosis	0	(0.0)	0	(0.0)	0	(0.0)	2	(0.0)
Stevens-Johnson syndrome	0	(0.0)	0	(0.0)	1	(0.0)	4	(0.1)
Toxic skin eruption	0	(0.0)	0	(0.0)	2	(0.1)	4	(0.1)
Thyroiditis	**9**	**(1.1)**	**1**	**(0.1)**	**41**	**(1.3)**	**74**	**(1.0)**
Autoimmune thyroiditis	4	(0.5)	0	(0.0)	12	(0.4)	22	(0.3)
Thyroiditis	3	(0.4)	1	(0.1)	28	(0.9)	50	(0.7)
Silent thyroiditis	1	(0.1)	0	(0.0)	0	(0.0)	0	(0.0)
Thyroid disorder	1	(0.1)	0	(0.0)	0	(0.0)	3	(0.0)
Immune-mediated thyroiditis	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)
Thyroiditis acute	0	(0.0)	0	(0.0)	1	(0.0)	0	(0.0)
Type 1 Diabetes Mellitus	**5**	**(0.6)**	**1**	**(0.1)**	**11**	**(0.4)**	**34**	**(0.4)**
Type 1 diabetes mellitus	3	(0.4)	1	(0.1)	9	(0.3)	25	(0.3)
Diabetic ketoacidosis	2	(0.3)	0	(0.0)	3	(0.1)	15	(0.2)
Uveitis	**1**	**(0.1)**	**0**	**(0.0)**	**3**	**(0.1)**	**25**	**(0.3)**
Uveitis	1	(0.1)	0	(0.0)	2	(0.1)	16	(0.2)
Chorioretinitis	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)
Iridocyclitis	0	(0.0)	0	(0.0)	1	(0.0)	5	(0.1)
Iritis	0	(0.0)	0	(0.0)	0	(0.0)	4	(0.1)
Vasculitis	**2**	**(0.3)**	**1**	**(0.1)**	**23**	**(0.7)**	**5**	**(0.1)**
Vasculitis	2	(0.3)	1	(0.1)	22	(0.7)	4	(0.1)
Central nervous system	0	(0.0)	0	(0.0)	1	(0.0)	0	(0.0)

vasculitis								
Giant cell arteritis	0	(0.0)	0	(0.0)	0	(0.0)	1	(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.								
Database cutoff date for KN859: 03OCT2022.								

Adverse drug reactions (ADRs)

Section 4.8 of the SmPC has been updated to reflect the addition of the KEYNOTE-859 population of gastric and gastro-oesophageal junction adenocarcinoma patients, receiving pembrolizumab in combination with fluoropyrimidine and platinum-containing chemotherapy, into the current 'pembrolizumab in combination with chemotherapy' pooled dataset (N=4258).

Table 72 Adverse reactions in patients treated with pembrolizumab in combination with chemotherapy

		Combination Therapy (N=4258)	
		All AEs % (n)	Gr 3-5 AEs n
Infections and infestations			
Common	Pneumonia	7.8% (333)	187
Blood and lymphatic system disorders			
Very common	Neutropenia	30.9% (1317)	808
Very common	Anaemia	51.4% (2190)	759
Very common	Thrombocytopenia	16.6% (708)	227
Very common	Leukopenia	10.0% (426)	151
Common	Febrile Neutropenia	6.5% (275)	265
Common	Lymphopenia	3.1% (133)	41
Uncommon	Eosinophilia	0.6% (26)	2
Rare	Haemolytic Anaemia	0.05% (2)	1
Rare	Immune Thrombocytopenia	0.02% (1)	0
Immune system disorders			
Common	Infusion Reactions[a]	8.1% (346)	62
Rare	Sarcoidosis	0.02% (1)	0
Endocrine disorders			
Very common	Hypothyroidism[b]	13.9% (591)	15
Common	Adrenal Insufficiency[c]	1.3% (54)	23
Common	Thyroiditis[d]	1.3% (54)	6
Common	Hyperthyroidism[e]	5.4% (231)	5
Uncommon	Hypophysitis[f]	0.8% (35)	18
Rare	Hypoparathyroidism	0.05% (2)	0
Metabolism and nutrition disorders			
Very common	Hypokalaemia	11.9% (506)	166
Very common	Decreased Appetite	28.0% (1191)	100
Common	Hyponatraemia	7.4% (317)	151
Common	Hypocalcaemia	4.6% (196)	30
Uncommon	Type 1 Diabetes Mellitus[g]	0.4% (17)	16

		Combination Therapy (N=4258)	
		All AEs % (n)	Gr 3-5 AEs n
Psychiatric disorders			
Very common	Insomnia	10.9% (464)	5
Nervous system disorders			
Very common	Neuropathy Peripheral	16.1% (687)	51
Very common	Dizziness	10.2% (435)	14
Very common	Headache	14.5% (619)	13
Common	Dysgeusia	9.2% (393)	2
Common	Lethargy	1.2% (49)	2
Uncommon	Encephalitis[h]	0.1% (5)	5
Uncommon	Epilepsy	0.1% (6)	3
Rare	Guillain-Barre Syndrome[i]	0.05% (2)	2
Rare	Myasthenic Syndrome	0.05% (2)	2
Eye disorders			
Common	Dry Eye	3.3% (140)	1
Uncommon	Uveitis[j]	0.1% (5)	0
Cardiac disorders			
Common	Cardiac Arrhythmia (Including Atrial Fibrillation)[k]	3.8% (163)	42
Uncommon	Myocarditis[l]	0.2% (8)	6
Uncommon	Pericardial Effusion	0.4% (16)	5
Uncommon	Pericarditis	0.1% (6)	1
Vascular disorders			
Common	Hypertension	6.1% (261)	110
Uncommon	Vasculitis[m]	0.7% (29)	4
Respiratory, thoracic and mediastinal disorders			
Very common	Dyspnoea	11.3% (482)	57
Very common	Cough	17.1% (726)	5
Common	Pneumonitis[n]	4.0% (170)	66

		Combination Therapy (N=4258)	
		All AEs % (n)	Gr 3-5 AEs n
Gastrointestinal disorders			
Very common	Diarrhoea	36.0% (1534)	186
Very common	Vomiting	29.6% (1262)	159
Very common	Nausea	52.3% (2227)	151
Very common	Abdominal Pain[o]	18.9% (803)	55
Very common	Constipation	31.4% (1336)	15
Common	Colitis[p]	3.0% (127)	63
Common	Gastritis	2.1% (88)	8
Common	Dry Mouth	4.8% (206)	1
Uncommon	Pancreatitis[q]	0.4% (18)	14
Uncommon	Gastrointestinal Ulceration[r]	0.4% (18)	2
Rare	Small Intestinal Perforation	0.05% (2)	2
Hepatobiliary disorders			
Common	Hepatitis[s]	1.2% (51)	40
Rare	Cholangitis Sclerosing[t]	0.05% (2)	2
Skin and subcutaneous tissue disorders			
Very common	Alopecia	26.4% (1126)	6
Very common	Rash[u]	21.5% (915)	4
Very common	Pruritus[v]	14.1% (600)	4
Common	Severe Skin Reactions[w]	2.7% (115)	99
Common	Erythema	4.1% (176)	3
Common	Dry Skin	5.4% (232)	2
Common	Dermatitis Acneiform	2.1% (91)	2
Common	Dermatitis	1.6% (69)	2
Common	Eczema	1.3% (54)	1
Uncommon	Psoriasis	0.4% (18)	4
Uncommon	Lichenoid Keratosis[x]	0.1% (5)	1
Uncommon	Vitiligo[y]	0.6% (26)	0
Uncommon	Papule	0.2% (9)	0
Rare	Stevens-Johnson Syndrome	0.02% (1)	1
Rare	Erythema Nodosum	0.07% (3)	0

		Combination Therapy (N=4258)	
		All AEs % (n)	Gr 3-5 AEs n
Rare	Hair Colour Changes	0.02% (1)	0
Musculoskeletal and connective tissue disorders			
Very common	Musculoskeletal Pain[z]	14.5% (616)	33
Very common	Arthralgia	16.8% (717)	30
Common	Myositis[aa]	9.5% (404)	16
Common	Pain In Extremity	7.4% (314)	9
Common	Arthritis[bb]	1.6% (68)	6
Uncommon	Tenosynovitis[cc]	0.4% (17)	1
Rare	Sjogren's Syndrome	0.02% (1)	0
Renal and urinary disorders			
Common	Acute Kidney Injury	3.5% (150)	78
Uncommon	Nephritis[dd]	0.8% (33)	19
Uncommon	Cystitis Noninfective	0.2% (8)	0
General disorders and administration site conditions			
Very common	Fatigue	34.6% (1475)	213
Very common	Asthenia	19.7% (837)	144
Very common	Pyrexia	18.1% (772)	28
Common	Oedema[ee]	4.7% (200)	8
Common	Influenza Like Illness	2.8% (119)	1
Common	Chills	3.0% (127)	0
Investigations			
Very common	Alanine Aminotransferase Increased	17.8% (759)	142
Very common	Aspartate Aminotransferase Increased	17.8% (759)	109
Common	Blood Alkaline Phosphatase Increased	6.5% (275)	32
Common	Blood Bilirubin Increased	5.2% (220)	32
Common	Blood Creatinine Increased	8.9% (378)	23
Common	Hypercalcaemia	1.7% (71)	17

		Combination Therapy (N=4258)	
		All AEs % (n)	Gr 3-5 AEs n
Uncommon	Amylase Increased	0.6% (25)	8

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

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

b. Hypothyroidism (Hypothyroidism, Immune-Mediated Hypothyroidism)

c. Adrenal Insufficiency (Addison's Disease, Adrenal Insufficiency)

d. Thyroiditis (Autoimmune Thyroiditis, Silent Thyroiditis, Thyroid Disorder, Thyroiditis, Thyroiditis Acute)

e. Hyperthyroidism (Basedow's Disease, Hyperthyroidism)

f. Hypophysitis (Hypophysitis, Hypopituitarism)

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

h. Encephalitis (Encephalitis, Encephalitis Autoimmune)

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

j. Uveitis (Iridocyclitis, Uveitis)

k. 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)

l. Myocarditis (Autoimmune Myocarditis, Myocarditis)

m. Vasculitis (Central Nervous System Vasculitis, Vasculitis)

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

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

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

q. Pancreatitis (Pancreatitis, Pancreatitis Acute)

r. Gastrointestinal Ulceration (Duodenal Ulcer, Gastric Ulcer)

s. Hepatitis (Autoimmune Hepatitis, Hepatitis, Immune-Mediated Hepatitis)

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

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

v. Pruritus (Pruritus, Urticaria)

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

x. Lichenoid Keratosis (Lichen Planus, Lichenoid Keratosis)

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

z. Musculoskeletal Pain (Back Pain, Musculoskeletal Chest Pain, Musculoskeletal Discomfort, Musculoskeletal Pain, Musculoskeletal Stiffness)

aa. Myositis (Myalgia, Myopathy, Myositis, Polymyalgia Rheumatica, Rhabdomyolysis)

bb. Arthritis (Arthritis, Joint Effusion, Joint Swelling, Polyarthritis)

cc. Tenosynovitis (Synovitis, Tendon Pain, Tendonitis, Tenosynovitis)

dd. Nephritis (Autoimmune Nephritis, Immune-Mediated Nephritis, Nephritis, Tubulointerstitial Nephritis)

ee. Oedema (Eyelid Oedema, Face Oedema, Fluid Retention, Generalised Oedema, Lip Oedema, Localised Oedema, Oedema, Periorbital Oedema)

Includes all participants who received at least one dose of pembrolizumab combo therapy in KN021-A/C/G, KN048, KN189, KN355, KN407, KN522, KN590, KN826, KN811 and KN859.

MK-3475 Database Cutoff Date for Lung (KN021: 19AUG2019, KN189: 20MAY2019, KN407: 09MAY2019)

MK-3475 Database Cutoff Date for HNSCC (KN048: 25FEB2019)

MK-3475 Database Cutoff Date for Gastroesophageal (KN859: 03OCT2022, KN811: 25MAY2022, KN590: 02JUL2020)

MK-3475 Database Cutoff Date for TNBC (KN355: 11DEC2019, KN522: 23MAR2021)

MK-3475 Database Cutoff Date for Cervical (KN826: 03MAY2021)

Laboratory findings

The incidence of the most frequently reported laboratory abnormalities was similar between the pembrolizumab plus chemotherapy and chemotherapy groups (data not shown). The most common (≥ 55% incidence) laboratory abnormalities (all grades) in the pembrolizumab plus chemotherapy group were decreased haemoglobin, decreased platelets, decreased neutrophils, decreased leukocytes, decreased lymphocytes, increased AST, and decreased albumin.

A total of 3 participants in the pembrolizumab plus chemotherapy group and 2 participants in the chemotherapy group met one of the prespecified laboratory criteria for potential drug-induced liver injury (DILI) (increase in ALT or AST ≥3× ULN and bilirubin ≥2× ULN and alkaline phosphatase <2× ULN), but no participant met the full criteria for the AE of DILI.

Safety in special populations

Table 73 Adverse Event Summary by Age Category (< 65, ≥ 65 Years) (APaT Population)

	KN859 Pembrolizumab + Chemotherapy				KN859 Placebo + Chemotherapy				Pembrolizumab + Chemo Pooled Dataset			
	<65		>=65		<65		>=65		<65		>=65	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Participants in population	483		302		478		309		2,176		947	
with one or more adverse events	478	(99.0)	298	(98.7)	472	(98.7)	299	(96.8)	2,158	(99.2)	939	(99.2)
with no adverse event	5	(1.0)	4	(1.3)	6	(1.3)	10	(3.2)	18	(0.8)	8	(0.8)
with drug-related[a] adverse events	458	(94.8)	293	(97.0)	453	(94.8)	283	(91.6)	2,107	(96.8)	913	(96.4)
with toxicity grade 3-5 adverse events	347	(71.8)	244	(80.8)	318	(66.5)	230	(74.4)	1,721	(79.1)	758	(80.0)
with toxicity grade 3-5 drug-related adverse events	269	(55.7)	197	(65.2)	238	(49.8)	164	(53.1)	1,464	(67.3)	635	(67.1)
with serious adverse events	195	(40.4)	160	(53.0)	175	(36.6)	141	(45.6)	935	(43.0)	521	(55.0)
with serious drug-related adverse events	93	(19.3)	91	(30.1)	82	(17.2)	64	(20.7)	592	(27.2)	318	(33.6)
with any dose modification[b] due to an adverse event	411	(85.1)	268	(88.7)	390	(81.6)	270	(87.4)	1,693	(77.8)	784	(82.8)
who died	36	(7.5)	28	(9.3)	26	(5.4)	32	(10.4)	72	(3.3)	88	(9.3)
who died due to a drug-related adverse event	3	(0.6)	5	(1.7)	12	(2.5)	4	(1.3)	20	(0.9)	29	(3.1)
discontinued any drug due to an adverse event	149	(30.8)	108	(35.8)	110	(23.0)	94	(30.4)	567	(26.1)	333	(35.2)
discontinued MK-3475/PLACEBO	65	(13.5)	51	(16.9)	45	(9.4)	41	(13.3)	332	(15.3)	216	(22.8)
discontinued any chemotherapy	135	(28.0)	102	(33.8)	104	(21.8)	93	(30.1)	387	(17.8)	257	(27.1)
discontinued all drugs	37	(7.7)	30	(9.9)	29	(6.1)	30	(9.7)	71	(3.3)	72	(7.6)
discontinued any drug due to a drug-related adverse event	121	(25.1)	86	(28.5)	92	(19.2)	66	(21.4)	493	(22.7)	254	(26.8)
discontinued MK-3475/PLACEBO	38	(7.9)	30	(9.9)	28	(5.9)	12	(3.9)	261	(12.0)	144	(15.2)

discontinued any chemotherapy	109	(22.6)	81	(26.8)	89	(18.6)	66	(21.4)	344	(15.8)	193	(20.4)
discontinued all drugs	19	(3.9)	14	(4.6)	19	(4.0)	7	(2.3)	45	(2.1)	41	(4.3)
discontinued any drug due to a serious adverse event	53	(11.0)	51	(16.9)	36	(7.5)	43	(13.9)	270	(12.4)	202	(21.3)
discontinued MK-3475/PLACEBO	47	(9.7)	46	(15.2)	34	(7.1)	39	(12.6)	210	(9.7)	172	(18.2)
discontinued any chemotherapy	39	(8.1)	44	(14.6)	34	(7.1)	40	(12.9)	167	(7.7)	147	(15.5)
discontinued all drugs	27	(5.6)	27	(8.9)	25	(5.2)	29	(9.4)	63	(2.9)	64	(6.8)

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

[b] Defined as an action taken of dose reduced, drug interrupted or drug withdrawn

Table 74 Adverse Event Summary by Age Category (< 65, 65-74, 75-84, ≥ 85 Years) (APaT Population)

	KN859 Pembrolizumab + Chemotherapy								KN859 Placebo + Chemotherapy								Pembrolizumab + Chemo Pooled Dataset							
	<65		65-74		75-84		>=85		<65		65-74		75-84		>=85		<65		65-74		75-84		>=85	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Participants in population	483		246		54		2		478		249		59		1		2,176		767		175		5	
with one or more adverse events	478	(99.0)	244	(99.2)	52	(96.3)	2	(100.0)	472	(98.7)	241	(96.8)	57	(96.6)	1	(100.0)	2,158	(99.2)	760	(99.1)	174	(99.4)	5	(100.0)
with no adverse event	5	(1.0)	2	(0.8)	2	(3.7)	0	(0.0)	6	(1.3)	8	(3.2)	2	(3.4)	0	(0.0)	18	(0.8)	7	(0.9)	1	(0.6)	0	(0.0)
with drug-related[a] adverse events	458	(94.8)	241	(98.0)	50	(92.6)	2	(100.0)	453	(94.8)	229	(92.0)	53	(89.8)	1	(100.0)	2,107	(96.8)	742	(96.7)	167	(95.4)	4	(80.0)
with toxicity grade 3-5 adverse events	347	(71.8)	195	(79.3)	47	(87.0)	2	(100.0)	318	(66.5)	181	(72.7)	48	(81.4)	1	(100.0)	1,721	(79.1)	608	(79.3)	145	(82.9)	5	(100.0)
with toxicity grade 3-5 drug-related adverse events	269	(55.7)	161	(65.4)	35	(64.8)	1	(50.0)	238	(49.8)	132	(53.0)	32	(54.2)	0	(0.0)	1,464	(67.3)	520	(67.8)	111	(63.4)	4	(80.0)
with serious adverse events	195	(40.4)	126	(51.2)	33	(61.1)	1	(50.0)	175	(36.6)	108	(43.4)	32	(54.2)	1	(100.0)	935	(43.0)	415	(54.1)	102	(58.3)	4	(80.0)
with serious drug-related adverse events	93	(19.3)	69	(28.0)	21	(38.9)	1	(50.0)	82	(17.2)	52	(20.9)	12	(20.3)	0	(0.0)	592	(27.2)	255	(33.2)	60	(34.3)	3	(60.0)
with any dose modification[b] due to an adverse event	411	(85.1)	217	(88.2)	50	(92.6)	1	(50.0)	390	(81.6)	217	(87.1)	52	(88.1)	1	(100.0)	1,693	(77.8)	632	(82.4)	147	(84.0)	5	(100.0)
who died	36	(7.5)	23	(9.3)	4	(7.4)	1	(50.0)	26	(5.4)	22	(8.8)	9	(15.3)	1	(100.0)	72	(3.3)	54	(7.0)	30	(17.1)	4	(80.0)
who died due to a drug-related adverse event	3	(0.6)	3	(1.2)	1	(1.9)	1	(50.0)	12	(2.5)	2	(0.8)	2	(3.4)	0	(0.0)	20	(0.9)	18	(2.3)	8	(4.6)	3	(60.0)
discontinued any drug due to an adverse event	149	(30.8)	88	(35.8)	19	(35.2)	1	(50.0)	110	(23.0)	78	(31.3)	15	(25.4)	1	(100.0)	567	(26.1)	259	(33.8)	70	(40.0)	4	(80.0)
discontinued MK-3475/PLACEBO	65	(13.5)	39	(15.9)	11	(20.4)	1	(50.0)	45	(9.4)	32	(12.9)	8	(13.6)	1	(100.0)	332	(15.3)	159	(20.7)	53	(30.3)	4	(80.0)
discontinued any chemotherapy	135	(28.0)	84	(34.1)	17	(31.5)	1	(50.0)	104	(21.8)	77	(30.9)	15	(25.4)	NA		387	(17.8)	198	(25.8)	55	(31.4)	4	(80.0)
discontinued all drugs	37	(7.7)	24	(9.8)	6	(11.1)	0	(0.0)	29	(6.1)	21	(8.4)	8	(13.6)	1	(100.0)	71	(3.3)	46	(6.0)	22	(12.6)	4	(80.0)

The AE summary profile based on sex in the pembrolizumab plus chemotherapy group was generally similar between participants who were male and female (data not shown).

The AE summary profile based on ECOG PS in the pembrolizumab plus chemotherapy group was generally similar between participants with an ECOG PS of 0 or 1 (data not shown).

Table 75 Adverse Event Summary by Region (Western Europe, Ex-Western Europe) (APaT Population)

	KN859 Pembrolizumab + Chemotherapy				KN859 Placebo + Chemotherapy				Pembrolizumab + Chemo Pooled Dataset			
	Western Europe		Ex-Western Europe		Western Europe		Ex-Western Europe		Western Europe		Ex-Western Europe	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Participants in population	166		619		166		621		1,118		2,005	
with one or more adverse events	164	(98.8)	612	(98.9)	163	(98.2)	608	(97.9)	1,105	(98.8)	1,992	(99.4)
with no adverse event	2	(1.2)	7	(1.1)	3	(1.8)	13	(2.1)	13	(1.2)	13	(0.6)
with drug-related[a] adverse events	161	(97.0)	590	(95.3)	158	(95.2)	578	(93.1)	1,070	(95.7)	1,950	(97.3)
with toxicity grade 3-5 adverse events	127	(76.5)	464	(75.0)	118	(71.1)	430	(69.2)	876	(78.4)	1,603	(80.0)
with toxicity grade 3-5 drug-related adverse events	106	(63.9)	360	(58.2)	90	(54.2)	312	(50.2)	727	(65.0)	1,372	(68.4)
with serious adverse events	89	(53.6)	266	(43.0)	80	(48.2)	236	(38.0)	548	(49.0)	908	(45.3)
with serious drug-related adverse events	54	(32.5)	130	(21.0)	30	(18.1)	116	(18.7)	340	(30.4)	570	(28.4)
with any dose modification[b] due to an adverse event	145	(87.3)	534	(86.3)	144	(86.7)	516	(83.1)	898	(80.3)	1,579	(78.8)
who died	8	(4.8)	56	(9.0)	8	(4.8)	50	(8.1)	56	(5.0)	104	(5.2)
who died due to a drug-related adverse event	2	(1.2)	6	(1.0)	2	(1.2)	14	(2.3)	12	(1.1)	37	(1.8)
discontinued any drug due to an adverse event	66	(39.8)	191	(30.9)	55	(33.1)	149	(24.0)	383	(34.3)	517	(25.8)
discontinued MK-3475/PLACEBO	24	(14.5)	92	(14.9)	19	(11.4)	67	(10.8)	237	(21.2)	311	(15.5)
discontinued any chemotherapy	61	(36.7)	176	(28.4)	53	(31.9)	144	(23.2)	269	(24.1)	375	(18.7)
discontinued all drugs	13	(7.8)	54	(8.7)	11	(6.6)	48	(7.7)	52	(4.7)	91	(4.5)
discontinued any drug due to a drug-related adverse event	59	(35.5)	148	(23.9)	45	(27.1)	113	(18.2)	320	(28.6)	427	(21.3)
discontinued MK-3475/PLACEBO	18	(10.8)	50	(8.1)	8	(4.8)	32	(5.2)	173	(15.5)	232	(11.6)
discontinued any chemotherapy	54	(32.5)	136	(22.0)	44	(26.5)	111	(17.9)	228	(20.4)	309	(15.4)
discontinued all drugs	8	(4.8)	25	(4.0)	4	(2.4)	22	(3.5)	29	(2.6)	57	(2.8)
discontinued any drug due to a serious adverse event	23	(13.9)	81	(13.1)	17	(10.2)	62	(10.0)	199	(17.8)	273	(13.6)
discontinued MK-3475/PLACEBO	18	(10.8)	75	(12.1)	17	(10.2)	56	(9.0)	165	(14.8)	217	(10.8)
discontinued any chemotherapy	19	(11.4)	64	(10.3)	16	(9.6)	58	(9.3)	129	(11.5)	185	(9.2)
discontinued all drugs	10	(6.0)	44	(7.1)	11	(6.6)	43	(6.9)	49	(4.4)	78	(3.9)

Safety related to drug-drug interactions and other interactions

As pembrolizumab is an IgG antibody that is administered parenterally and cleared by catabolism, food and drug-drug interaction (DDI) are not anticipated to influence exposure.

Studies evaluating pharmacodynamic drug interactions with pembrolizumab have not been conducted. However, as systemic corticosteroids may be used in combination with pembrolizumab to ameliorate potential side effects, the potential for a PK DDI with pembrolizumab as a victim was assessed as part of the population pharmacokinetics (PPK) analysis (data not shown). No relationship was observed between prolonged use of systemic corticosteroids and pembrolizumab exposure. Nevertheless, the use of systemic corticosteroids or other immunosuppressants before the start of pembrolizumab treatment should be avoided because of their potential interference with the pharmacodynamic activity and efficacy of pembrolizumab. However, systemic corticosteroids or other immunosuppressants can be used after starting pembrolizumab treatment to treat immune-mediated adverse reactions. Corticosteroids can also be used as premedication, when pembrolizumab is used in combination with chemotherapy, as antiemetic prophylaxis and/or to alleviate chemotherapy-related adverse reactions (see section 4.5 of the SmPC).

Discontinuation due to adverse events

Table 76 Participants With Adverse Events Resulting in Treatment Discontinuation of Pembrolizumab/Placebo (Incidence > 0% in KN859 Pembro+Chemo Treatment group) By Decreasing Frequency of Preferred Term (APaT Population)

	KN859 Pembrolizumab + Chemotherapy		KN859 Placebo + Chemotherapy		Pembrolizumab + Chemo Pooled Dataset		Pembrolizumab Monotherapy Reference Safety Dataset	
	n	(%)	n	(%)	n	(%)	n	(%)
Participants in population	785		787		3,123		7,631	
with one or more adverse events	116	(14.8)	86	(10.9)	548	(17.5)	1,066	(14.0)
with no adverse events	669	(85.2)	701	(89.1)	2,575	(82.5)	6,565	(86.0)
Diarrhoea	8	(1.0)	2	(0.3)	8	(0.3)	19	(0.2)
Colitis	6	(0.8)	2	(0.3)	17	(0.5)	39	(0.5)
Pneumonia	6	(0.8)	4	(0.5)	20	(0.6)	34	(0.4)
Pneumonitis	5	(0.6)	2	(0.3)	42	(1.3)	115	(1.5)
Pulmonary embolism	5	(0.6)	1	(0.1)	7	(0.2)	14	(0.2)
Acute kidney injury	4	(0.5)	1	(0.1)	19	(0.6)	14	(0.2)
Sepsis	4	(0.5)	6	(0.8)	6	(0.2)	10	(0.1)
Sudden death	4	(0.5)	1	(0.1)	1	(0.0)	2	(0.0)
Alanine aminotransferase increased	3	(0.4)	3	(0.4)	40	(1.3)	35	(0.5)
Anaemia	3	(0.4)	0	(0.0)	3	(0.1)	3	(0.0)
Death	3	(0.4)	2	(0.3)	10	(0.3)	27	(0.4)
Intestinal obstruction	3	(0.4)	2	(0.3)	1	(0.0)	0	(0.0)
Rash maculo-papular	3	(0.4)	0	(0.0)	4	(0.1)	1	(0.0)
Abdominal pain	2	(0.3)	0	(0.0)	1	(0.0)	1	(0.0)
Anaphylactic reaction	2	(0.3)	0	(0.0)	1	(0.0)	0	(0.0)
Aspiration	2	(0.3)	0	(0.0)	0	(0.0)	2	(0.0)
Blood bilirubin increased	2	(0.3)	2	(0.3)	1	(0.0)	5	(0.1)
Decreased appetite	2	(0.3)	0	(0.0)	2	(0.1)	4	(0.1)
Gastrointestinal haemorrhage	2	(0.3)	0	(0.0)	0	(0.0)	1	(0.0)
Ileus	2	(0.3)	1	(0.1)	0	(0.0)	0	(0.0)
Immune-mediated lung disease	2	(0.3)	0	(0.0)	0	(0.0)	3	(0.0)
Platelet count decreased	2	(0.3)	1	(0.1)	3	(0.1)	0	(0.0)
Tubulointerstitial nephritis	2	(0.3)	0	(0.0)	9	(0.3)	6	(0.1)
Urosepsis	2	(0.3)	1	(0.1)	0	(0.0)	5	(0.1)
Vomiting	2	(0.3)	2	(0.3)	1	(0.0)	2	(0.0)
Abdominal distension	1	(0.1)	0	(0.0)	0	(0.0)	1	(0.0)
Abdominal pain upper	1	(0.1)	0	(0.0)	1	(0.0)	1	(0.0)
Acute myocardial infarction	1	(0.1)	3	(0.4)	2	(0.1)	2	(0.0)
Aortic dissection	1	(0.1)	0	(0.0)	0	(0.0)	0	(0.0)
Arrhythmia	1	(0.1)	0	(0.0)	1	(0.0)	0	(0.0)
Arthritis	1	(0.1)	0	(0.0)	3	(0.1)	7	(0.1)
Aspartate aminotransferase increased	1	(0.1)	2	(0.3)	25	(0.8)	28	(0.4)
Asthenia	1	(0.1)	1	(0.1)	5	(0.2)	5	(0.1)
Autoimmune haemolytic anaemia	1	(0.1)	0	(0.0)	0	(0.0)	1	(0.0)
Autoimmune hepatitis	1	(0.1)	0	(0.0)	14	(0.4)	18	(0.2)

	KN859 Pembrolizumab + Chemotherapy		KN859 Placebo + Chemotherapy		Pembrolizumab + Chemo Pooled Dataset		Pembrolizumab Monotherapy Reference Safety Dataset	
	n	(%)	n	(%)	n	(%)	n	(%)
Back pain	1	(0.1)	0	(0.0)	0	(0.0)	4	(0.1)
COVID-19 pneumonia	1	(0.1)	0	(0.0)	0	(0.0)	0	(0.0)
Cachexia	1	(0.1)	0	(0.0)	1	(0.0)	2	(0.0)
Cardiac arrest	1	(0.1)	1	(0.1)	8	(0.3)	7	(0.1)
Cerebral infarction	1	(0.1)	0	(0.0)	1	(0.0)	0	(0.0)
Chest pain	1	(0.1)	0	(0.0)	0	(0.0)	0	(0.0)
Confusional state	1	(0.1)	0	(0.0)	0	(0.0)	1	(0.0)
Constipation	1	(0.1)	0	(0.0)	0	(0.0)	0	(0.0)
Cutaneous vasculitis	1	(0.1)	0	(0.0)	0	(0.0)	0	(0.0)
Dehydration	1	(0.1)	0	(0.0)	0	(0.0)	0	(0.0)
Dyspnoea	1	(0.1)	0	(0.0)	2	(0.1)	17	(0.2)
Enterocolitis	1	(0.1)	0	(0.0)	1	(0.0)	4	(0.1)
Fatigue	1	(0.1)	0	(0.0)	2	(0.1)	19	(0.2)
Gastric dilatation	1	(0.1)	0	(0.0)	0	(0.0)	0	(0.0)
Gastrointestinal obstruction	1	(0.1)	0	(0.0)	0	(0.0)	0	(0.0)
Hepatic cytolysis	1	(0.1)	0	(0.0)	0	(0.0)	0	(0.0)
Hepatic vein thrombosis	1	(0.1)	0	(0.0)	0	(0.0)	0	(0.0)
Hypercalcaemia	1	(0.1)	0	(0.0)	0	(0.0)	3	(0.0)
Hypertransaminasaemia	1	(0.1)	0	(0.0)	0	(0.0)	1	(0.0)
Immune-mediated enterocolitis	1	(0.1)	0	(0.0)	2	(0.1)	1	(0.0)
Immune-mediated hepatitis	1	(0.1)	1	(0.1)	7	(0.2)	3	(0.0)
Immune-mediated nephritis	1	(0.1)	0	(0.0)	0	(0.0)	0	(0.0)
Infusion related reaction	1	(0.1)	0	(0.0)	5	(0.2)	4	(0.1)
Insomnia	1	(0.1)	0	(0.0)	0	(0.0)	0	(0.0)
Mesenteric vein thrombosis	1	(0.1)	0	(0.0)	0	(0.0)	0	(0.0)
Mucosal inflammation	1	(0.1)	0	(0.0)	0	(0.0)	1	(0.0)
Myasthenia gravis	1	(0.1)	0	(0.0)	1	(0.0)	3	(0.0)
Myocardial infarction	1	(0.1)	0	(0.0)	5	(0.2)	8	(0.1)
Nausea	1	(0.1)	3	(0.4)	0	(0.0)	0	(0.0)
Nephritis	1	(0.1)	0	(0.0)	5	(0.2)	4	(0.1)
Optic neuritis	1	(0.1)	0	(0.0)	0	(0.0)	2	(0.0)
Pancreatitis	1	(0.1)	0	(0.0)	6	(0.2)	4	(0.1)
Peripheral artery occlusion	1	(0.1)	0	(0.0)	0	(0.0)	2	(0.0)
Peripheral nerve injury	1	(0.1)	0	(0.0)	0	(0.0)	0	(0.0)
Peripheral sensory neuropathy	1	(0.1)	0	(0.0)	5	(0.2)	2	(0.0)
Pneumoperitoneum	1	(0.1)	0	(0.0)	0	(0.0)	0	(0.0)
Rash	1	(0.1)	0	(0.0)	5	(0.2)	14	(0.2)
Renal failure	1	(0.1)	1	(0.1)	3	(0.1)	6	(0.1)
Respiratory failure	1	(0.1)	1	(0.1)	5	(0.2)	16	(0.2)
Septic encephalopathy	1	(0.1)	0	(0.0)	0	(0.0)	0	(0.0)
Septic shock	1	(0.1)	5	(0.6)	5	(0.2)	9	(0.1)
Small intestinal obstruction	1	(0.1)	0	(0.0)	0	(0.0)	0	(0.0)
Thrombocytopenia	1	(0.1)	0	(0.0)	2	(0.1)	4	(0.1)
Thrombotic thrombocytopenic purpura	1	(0.1)	0	(0.0)	0	(0.0)	0	(0.0)
Vanishing bile duct syndrome	1	(0.1)	0	(0.0)	0	(0.0)	0	(0.0)
Weight decreased	1	(0.1)	0	(0.0)	1	(0.0)	2	(0.0)
White blood cell count decreased	1	(0.1)	0	(0.0)	0	(0.0)	0	(0.0)

<u>Intervention Interruption due to Adverse Events</u>

The overall percentage of participants with a drug-related AE leading to interruption of any drug in the pembrolizumab plus chemotherapy group was 66.0% compared with 56.4% in the chemotherapy group.

- The percentage of participants with drug-related AEs leading to interruption of pembrolizumab/placebo in the pembrolizumab plus chemotherapy group was higher than the chemotherapy group (54.4% vs 42.7%).
- The most common drug-related AEs (≥5% of participants) leading to treatment interruption of pembrolizumab in the pembrolizumab plus chemotherapy group were decreased neutrophil count, decreased platelet count, neutropenia, and diarrhoea.

Post marketing experience

The safety profile of pembrolizumab was summarized in the Periodic Safety Update Report covering the period 04-SEP-2021 through 03-SEP-2022, specifically Appendix 20.3. No revocation or withdrawal of pembrolizumab registration for safety reasons has occurred in any country.

2.5.1. Discussion on clinical safety

The evaluation of the safety profile of pembrolizumab for the indication of 1st line treatment of patients with locally advanced unresectable or metastatic HER2-negative gastric or GEJ adenocarcinoma was primarily based on the pivotal study KEYNOTE-859 (KN859) (n=785 in the pembrolizumab+ chemotherapy group vs n=787 in the placebo +chemotherapy group). Data from the interim analysis IA with data cutoff of 03-OCT-2022 were submitted. Comparisons of the pembrolizumab + chemo pooled dataset (n=3123) and the pembrolizumab monotherapy reference safety dataset (RSD) (n=7631) were included.

The median duration of exposure was 6.7 months in the KN859 pembrolizumab + chemotherapy arm and 5.59 months in the KN859 chemotherapy arm. 203 (25.9%) subjects in the pembrolizumab + chemotherapy arm and 128 (16.3 %) subjects in the chemotherapy arm received treatment for ≥ 12 months.

With regards to **demographics and disease characteristics**, KN859 study arms were well balanced between the two treatment groups, more participants in KEYNOTE-859 were male and Asian, and fewer participants were enrolled from EU sites as compared to pembrolizumab combo and pembrolizumab monotherapy datasets, as expected based on the epidemiology of gastric/GEJ cancer.

The **Adverse Event Summary** demonstrated similar incidences of AEs between the pembrolizumab +chemotherapy group and chemotherapy group. The observed incidence of SAEs (45.2 % versus 40.2%), drug-related SAEs (23.4 vs 18.6%) and drug-related Grade 3-5 AEs (59.4% vs 51.1%) was slightly higher for the pembrolizumab + chemotherapy.

In KN859 a comparison of the frequencies of the **most common AEs** by treatment group showed high incidences of nausea, anaemia, vomiting, and diarrhoea (>30%). AEs reported at higher frequencies for pembrolizumab compared to chemotherapy were anaemia, vomiting, aspartate aminotransferase increased, pruritus and hypothyroidism (difference at least 5%).

The overall incidences of AEs in the KEYNOTE-859 Dataset was similar compared to the pooled pembro+chemo Reference Safety Dataset.

Regarding **drug-related AEs** pembrolizumab + chemotherapy could be regarded as comparable to placebo+chemotherapy; most frequently reported (≥20% incidence) were nausea, diarrhoea, anaemia, vomiting, platelet count decreased, neutrophil count decreased, palmar-plantar erythrodysaesthesia syndrome, decreased appetite and fatigue.

Overall analysis of **Grade 3 to 5 AEs** was slightly elevated in the pembrolizumab group; Grade 3 to 5 AEs were reported in 75.3 % of subjects in the pembrolizumab +chemotherapy arm and 69.6 % in the placebo+chemotherapy arm. Anaemia (12.1% vs. 9.7%), Neutrophil count decreased (9.8% vs. 8.1%) and neutropenia (7.4% vs. 8.6%) were the preferred terms with the highest incidences in the pembrolizumab + chemotherapy arm as well as in the placebo+ chemotherapy arm. When compared with the pembrolizumab + Chemo RSD, the analysis of Grade 3 to 5 AEs by SOC demonstrated lower rates.

Analysis of **drug-related Grade 3-5 AEs** revealed a similar picture. The overall incidence of drug-related Grade 3 to 5 AEs was higher in the pembrolizumab arm (59.4%) compared with the chemotherapy arm (51.1%). The most frequently reported drug-related Grade 3 to 5 AEs in both treatment arms were decreased neutrophil count, anaemia and neutropenia.

The incidence of serious adverse events (SAEs) was slightly higher in the pembrolizumab + chemotherapy group (45.2 %) compared to the placebo+chemotherapy group (40.2 %) in KN859. The most frequently reported SAEs (≥2% incidence) in the pembrolizumab plus chemo group were diarrhea, pneumonia, vomiting and colitis. The most frequently reported drug-related SAE (≥3% incidence) in both the pembrolizumab plus chemo and chemo groups was diarrhea (3.9% and 3.0% of participants, respectively).

A total of 64 vs 58 patients died due to AEs in the investigational vs control arm of KN859 study. Of those, 8 AEs in the pembro +chemo group and 16 AEs in the placebo+chemo group were treatment-related according to investigator or sponsor, i.e. diarrhoea (2 cases) and pneumonitis (2 cases). Pneumonitis is a known ADR for pembrolizumab.

As anticipated, the incidence of **Adverse events of special interests (AEOSIs)** was higher in the pembrolizumab +chemotherapy arm of KN859 compared to the placebo+chemotherapy arm (30.8% vs. 13.3%). When comparing KN859 to the other datasets, frequency of AEOSI was comparable to both Reference Safety Dataset (33.7% in pembrolizumab + chemo combo pooled dataset and 26.8% in pembrolizumab monotherapy dataset). The frequency of each AEOSI observed in the KN859 population was comparable to the Reference Safety Dataset chemo combo and monotherapy). Overall, most AEOSI were Grade 1 or 2 in severity and nonserious. Grade 5 AEOSI occurred in 1 patient in the pembrolizumab plus chemo group (pneumonitis). The most common (>3% incidence) AEOSI categories reported in the pembrolizumab plus chemo group were hypothyroidism (15.3%), infusion reactions (5.6%), hyperthyroidism (5.6%), colitis (3.3%) and pneumonitis (3.2%). The frequency and severity of AEOSI categories in the pembrolizumab plus SOC group were generally consistent with the pembrolizumab plus chemo pooled group and monotherapy RSD.

The most common AEs (≥1% incidence) leading to discontinuation of pembrolizumab in the pembrolizumab plus SOC group were diarrhoea (1.0%) colitis and pneumonia (0.8%). The most common AEs (≥5% incidence) leading to treatment interruption of any drug in the pembrolizumab plus chemo group were neutrophil count, decreased platelet count, neutropenia, and diarrhoea.

With regard to laboratory value, the MAH reported three participants in the pembrolizumab plus SOC arm meeting the prespecified laboratory criteria for drug-induced liver injury (vs 2 in the control arm). Further, it is noted a higher incidence of ALT, AST and bilirubin increase as AEs in the experimental vs the control arm, also as compared to the pembro combo pooled dataset.

The adverse event summary showed similar incidence in the pembrolizumab plus SOC arm between patients <65 years and ≥ 65 years, however SAEs (40.4% vs 53. 0%), Grade 3-5 AEs (71.8% vs 80.8%) and death due to AEs (0.6% vs 1.7%) and discontinuation due to AEs (30.8% vs 35.8%) were more frequent in patients ≥ 65 years. A similar pattern is however observed also in the SOC arm, as well as in the pembro combo pooled dataset. The same observation is made according to age categories <65, 65-74 and 75-84. Only 56 patients were older than 75 years, considering the dataset as too limited in this subgroup.

The frequency of ADRs in patients treated with pembrolizumab + chemotherapy has been updated in section 4.8 of the SmPC to reflect the data on the ‘pembrolizumab in combination with chemotherapy’ pooled dataset including the KEYNOTE-859 population.

2.5.2. Conclusions on clinical safety

The safety profile of pembrolizumab in combination with chemotherapy (FP/CAPOX) in previously untreated participants with locally advanced unresectable or metastatic HER2-negative gastric or GEJ adenocarcinoma in KEYNOTE-859 overall reflects the established safety profiles of the chemotherapy regimen administered and pembrolizumab monotherapy. No new safety concerns were identified.

2.5.3. PSUR cycle

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

2.6. Risk management plan

The MAH submitted an updated RMP version 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 40.0 is acceptable.

The CHMP endorsed the Risk Management Plan version 40.0 with the following content:

Safety concerns

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

Pharmacovigilance plan

Areas Requiring Further Investigation	Proposed Routine and Additional Pharmacovigilance Activities	Objectives
Important Identified risk: Immune-Related Adverse Reactions (including immune-related pneumonitis; colitis; hepatitis; nephritis and endocrinopathies)		
In order to monitor for and better characterize the occurrence of immune-related adverse reactions the MAH monitors and evaluates reports of immune-related adverse reactions received in the postmarketing and clinical environment.	Routine pharmacovigilance including: Additional pharmacovigilance including: • Safety monitoring in all ongoing MAH-sponsored clinical trials for pembrolizumab in various tumour types	To monitor, identify and evaluate reports of immune-related adverse reactions in patients treated with pembrolizumab
Important Potential Risk: For hematologic malignancies: increased risk of severe complications of allogeneic SCT in patients who have previously received pembrolizumab		
In order to monitor for and better characterize the occurrence (for hematologic malignancies) of an increased risk of severe complications of allogeneic SCT in patients who have previously received pembrolizumab, the MAH monitors and evaluates reports of severe complications of allogeneic SCT in patients who have previously received pembrolizumab from both the postmarketing and clinical environment.	Routine pharmacovigilance Additional pharmacovigilance including: • Safety monitoring in the ongoing HL trial (KN204)	To monitor, identify and evaluate for hematologic malignancies: reports of severe complications of allogeneic SCT in patients who have previously received pembrolizumab
Important Potential Risk: Graft versus host disease (GVHD) after pembrolizumab administration in patients with a history of allogeneic stem cell transplant (SCT)		
In order to monitor for and better characterize the occurrence of GVHD after pembrolizumab administration in patients with a history of allogeneic SCT, the MAH monitors and evaluates reports of GVHD after pembrolizumab administration in patients with a history of allogeneic SCT from both the postmarketing and clinical trial environment.	Routine pharmacovigilance Additional pharmacovigilance including: • Safety monitoring in all ongoing MAH-sponsored clinical trials for pembrolizumab in various tumour types	To monitor, identify and evaluate reports of GVHD after pembrolizumab administration in patients with a history of allogeneic SCT

Risk minimisation measures

Safety Concern	Risk Minimisation Measure	Pharmacovigilance Activities
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 tumour 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).
GVHD after pembrolizumab administration in patients with a history of allogeneic SCT	Routine risk minimisation measures: • GVHD after pembrolizumab administration in patients with a history of allogeneic SCT is described in the SmPC, Section 4.4 and appropriate advice is provided to the prescriber to minimize the risk. No additional risk minimisation measures warranted	Routine pharmacovigilance activities Additional pharmacovigilance including: • Safety monitoring in all ongoing MAH-sponsored clinical trials for pembrolizumab in various tumour types

2.7. Update of the Product information

As a result of this variation, sections 4.1, 4.8 and 5.1 of the SmPC are being updated. Section 4 of the Package Leaflet (PL) is updated accordingly.

Please refer to Attachment 1 which includes all agreed changes to the Product Information.

2.7.1. User consultation

A justification for not performing a full user consultation with target patient groups on the package leaflet has been submitted by the MAH and has been found acceptable for the following reasons:

The changes in the package leaflet are related to the extension of the indication "a kind of stomach cancer called gastric or gastro-oesophageal junction adenocarcinoma" in section 1 "What KEYTRUDA is and what it is used for". There are no other proposed changes to the content of the package leaflet. In particular the key messages for the safe use of the medicinal product are not impacted. Furthermore, the design, layout and format of the package leaflet will not be affected by the proposed revisions.

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

The finally approved indications is:

KEYTRUDA, in combination with fluoropyrimidine and platinum-containing chemotherapy, is indicated for the first-line treatment of locally advanced unresectable or metastatic HER2-negative gastric or gastro-oesophageal junction adenocarcinoma in adults whose tumours express PD L1 with a CPS ≥ 1 (see section 5.1).

3.1.2. Available therapies and unmet medical need

Fluoropyrimidine/platinum doublet regimens containing cisplatin or oxaliplatin and 5-FU or capecitabine are the most frequently used as 1L chemotherapy regimens for patients with metastatic gastric/GEJ disease worldwide [6]. Recently, the combination of nivolumab and fluoropyrimidine- and platinum-containing chemotherapy was approved for the treatment of HER2-negative advanced or metastatic gastric, GEJ, and esophageal adenocarcinoma whose tumours express PD-L1 with a combined positive score (CPS) ≥ 5 (Opdivo II/96).

[6]- Al-Batran SE, Hartmann JT, Probst S, Schmalenberg H, Hollerbach S, Hofheinz R, et al. Phase III trial in metastatic gastroesophageal adenocarcinoma with fluorouracil, leucovorin plus either oxaliplatin or cisplatin: a study of the Arbeitsgemeinschaft Internistische Onkologie. J Clin Oncol. 2008 Mar 20;26(9):1435-42.
- Kang YK, Kang WK, Shin DB, Chen J, Xiong J, Wang J, et al. Capecitabine/cisplatin versus 5-fluorouracil/cisplatin as first-line therapy in patients with advanced gastric cancer: a randomised phase III noninferiority trial. Ann Oncol. 2009 Apr;20(4):666- 73.
- Enzinger PC, Burtness BA, Niedzwiecki D, Ye X, Douglas K, Ilson DH, et al. CALGB 80403 (Alliance)/E1206: a randomized phase II study of three chemotherapy regimens plus cetuximab in metastatic esophageal and gastroesophageal junction cancers. J Clin Oncol. 2016 Aug 10;34(23):2736-42.
- Kim GM, Jeung HC, Rha SY, Kim HS, Jung I, Nam BH, et al. A randomized phase II trial of S-1-oxaliplatin versus capecitabineoxaliplatin in advanced gastric cancer. Eur J Cancer. 2012 Mar;48(4):518-26.

3.1.3. Main clinical studies

The extension of indication is based on the double-blinded, global study KEYNOTE-859 that randomised 1579 participants with previously untreated, HER2-negative, advanced gastric or GEJ adenocarcinoma to receive pembrolizumab or placebo in combination with chemotherapy (cisplatin/5-FU or capecitabine and oxaliplatin).

3.1. Favourable effects

At the IA, the study met the predefined superiority criteria for all efficacy hypotheses: pembrolizumab in combination with chemotherapy provided statistically significant improvements in OS, PFS, and ORR in CPS ≥ 10, CPS ≥ 1 and ITT when compared with chemotherapy alone:

- The efficacy analysis in the **ITT population** showed advantage of pembrolizumab plus chemotherapy over placebo plus chemotherapy in the primary endpoint OS (0.78 (95% CI 0.70, 0.87), median OS 12.9 vs 11.5 months). Efficacy was also shown on the secondary endpoints PFS (0.76 (95% CI 0.67, 0.85), median PFS 6.9 vs 5.6 months) and ORR (51% vs 42%, difference 9%).

- The efficacy analysis in the population with expression of PD-L1 **CPS ≥1** (78% of study population), also showed advantage of pembrolizumab plus chemotherapy over placebo plus chemotherapy in the primary endpoint OS (HR 0.74 (95% CI 0.65, 0.84); median OS 13.0 vs 11.4 months). Efficacy was also shown on the secondary endpoints PFS (HR 0.72 (95% CI 0.63, 0.82), median PFS 6.9 vs 5.6 months) and ORR (52% vs 43%, difference 9.5%).

- In the population with expression of PD-L1 **CPS ≥10** (35% of study population), pembrolizumab plus chemotherapy also showed superiority over placebo plus chemotherapy in OS (HR 0.65 (95% CI 0.53, 0.79), median OS 15.7 vs 11.8 months), PFS (HR 0.62 (95% CI 0.51, 0.76), median PFS 8.1 vs 5.6 months) and ORR (61% vs 43%, difference 17.5%).

3.2. Uncertainties and limitations about favourable effects

Efficacy analysis in the subgroup of participants with PD-L1 **CPS <1** (21.8% of study population) did not show a meaningful benefit regarding OS or PFS for the addition of pembrolizumab: OS HR 0.92 (95% CI 0.73, 1.17), PFS HR 0.90 (95% CI 0.70, 1.15). Patients with PD-L1 CPS <1 are those that most clearly do not derive any meaningful benefit by the addition of pembrolizumab to chemotherapy and for these patients the additional toxicity is not considered justified.

Subgroup results in the PD-L1 **CPS <10** population similarly suggest only a modest benefit: OS HR 0.86 [95% 0.75, 0.98] and PFS HR 0.85 (95% CI 0.74, 0.98). For patients with PD-L1 **CPS ≥1 to <10** (43% of study population), a slightly more pronounced benefit is observed: OS HR 0.83 (95% CI 0.70, 0.98 with an 8% difference in OS rate), PFS HR 0.83 (95% CI 0.70, 0.99). These results are reflected in SmPC section 5.1 for the awareness of the prescriber.

3.3. Unfavourable effects

The observed incidence of **SAEs (**45.2 % versus 40.2%), drug-**related SAEs** (23.4 vs 18.6%) and drug-related **Grade 3-5 AEs** (59.4% vs 51.1%) was slightly higher for the pembrolizumab chemo combo.

In KN859 a comparison of the frequencies of the **most common AEs** by treatment group showed high incidences of nausea, anaemia, vomiting, and diarrhoea (>30%). AEs reported at higher frequencies for pembrolizumab compared to chemotherapy were anaemia, vomiting, aspartate aminotransferase increased, pruritus and hypothyroidism (difference at least 5%).

Most frequently reported **drug-related AEs** (≥20% incidence) were nausea, diarrhoea, anaemia, vomiting, platelet count decreased, neutrophil count decreased, palmar-plantar erythrodysaesthesia syndrome, decreased appetite and fatigue.

Anaemia (12.1% vs. 9.7%), Neutrophil count decreased (9.8% vs. 8.1%) and neutropenia (7.4% vs. 8.6%) were the preferred terms with the highest incidences of **Grade 3-5 AEs.**

The most frequently reported **drug-related Grade 3 to 5 AEs** in both treatment arms were decreased neutrophil count, anaemia and neutropenia.

The most frequently reported **SAEs** (≥2% incidence) in the pembrolizumab plus chemo group were diarrhea, pneumonia, vomiting and colitis. The most frequently reported **drug-related SAE** (≥3% incidence) in both the pembrolizumab plus chemo and chemo groups was diarrhea (3.9% and 3.0% of participants, respectively).

A total of **64 vs 58 patients died due to AEs** in the investigational vs control arm of KN859 study. Of those, 8 AEs in the pembro +chemo group and 16 AEs in the placebo+chemo group were treatment-related according to investigator or sponsor, i.e. diarrhoea (2 cases) and pneumonitis (2 cases), Pneumonitis is a known ADR for pembrolizumab

As anticipated, the incidence of **Adverse events of special interests (AEOSIs)** was higher in the pembrolizumab +chemotherapy arm of KN859 compared to the placebo+chemotherapy arm (30.8% vs. 13.3%). When comparing KN859 to the other datasets, frequency of AEOSI was comparable to both Reference Safety Dataset (33.7% in pembrolizumab + chemo combo pooled dataset and 26.8% in pembrolizumab monotherapy dataset). Reference Safety Dataset (22.7%). The most common (>3% incidence) AEOSI categories reported in the pembrolizumab plus chemo group were hypothyroidism (15.3%), infusion reactions (5.6%), hyperthyroidism (5.6%), colitis (3.3%) and pneumonitis (3.2%)

The most common AEs (≥1% incidence) leading to discontinuation of pembrolizumab in the pembrolizumab plus SOC group were diarrhoea (1.0%) colitis and pneumonia (0.8%). The most common AEs (≥5% incidence) leading to treatment interruption of any drug in the pembrolizumab plus chemo group were neutrophil count, decreased platelet count, neutropenia, and diarrhoea.

3.4. Uncertainties and limitations about unfavourable effects

Dataset in patients older than 75 years is limited and a statement is included in section 4.4 of the SmPC to reflect this limitation.

3.5. Effects Table

Effects Table for Keytruda in combination with fluoropyrimidine and platinum-containing chemotherapy for 1L treatment of advanced HER2-negative gastric or gastro-oesophageal junction adenocarcinoma in adults with PD L1 expression (CPS ⩾ 1) (data cut-off: 03-OCT-2022)

Effect	Short description	Unit	Treatment	Control	Uncertainties / Strength of evidence	References
Favourable Effects (PD-L1 CPS ⩾ 1 population)						
OS	duration of survival from randomisation to death regardless of cause	months (95% CI)	13.0 (11.6, 14.2)	11.4 (10.5, 12.0)	Benefit in CPS<1 population not considered clinically	CSR, SCE
		HR	0.74 (0.65, 0.84)			

Effect	Short description	Unit	Treatment	Control	Uncertainties / Strength of evidence	References
		(95% CI)			meaningful: OS HR 0.92 (95% 0.73, 1.17); PFS HR 0.90 (95% 0.70, 1.15)	
PFS	duration of survival without progression from randomisation to PD or death whichever occurred first	months (95% CI)	6.9 (6.0, 7.2)	5.6 (5.4, 5.7)		
		HR (95% CI)	0.72 (0.63, 0.82)			
ORR	Confirmed CR + PR	%	52	43		
Unfavourable Effects						
summary	G3-5 AEs	%	75.3	69.6	No new safety concerns identified	KN-859
	SAE	%	45.2	40.2		
	Death	%	8.2	7.4		
	Discontinuation due to AEs	%	32.7	25.9		
	AEOSI	%	30.8	13.3		
	- hypothyroidism	%	15.3	4.3		
	-hyperthyroidism	%	5.6	1.7		
	-IRR	%	5.6	4.7		
	-colitis	%	3.3	1.8		
	- pneumonitis	%	3.2	0.9		

3.6. Benefit-risk assessment and discussion

3.6.1. Importance of favourable and unfavourable effects

Data from the double-blinded study KEYNOTE-859 demonstrated statistically significant improvements in OS, PFS, and ORR for pembrolizumab in combination with chemotherapy versus chemotherapy alone in previously untreated participants with advanced HER2 negative gastric or GEJ adenocarcinoma. However, the benefit in the overall study population is driven by participants with higher PD-L1 expression levels.

Overall, the safety profile of pembrolizumab in combination with chemotherapy (FP/CAPOX) reflects the established safety profile of the chemotherapy regimens administered and pembrolizumab monotherapy. No new safety concerns have been identified.

3.6.2. Balance of benefits and risks

Considering the totality of efficacy data by PD-L1 expression, the most pronounced benefit is observed for patients with PD-L1 CPS ≥10, whereas data in patients with CPS <10 show a marginal improvement. For patients with PD-L1 CPS ≥1 to <10, a slightly more pronounced benefit is observed: OS HR 0.83 (95% CI 0.70, 0.98 with an 8% difference in OS rate), PFS HR 0.83 (95% CI 0.70, 0.99); in addition OS and PFS KMs clearly separate in this patient population.

Considering the clear benefit to patients in relation to an established safety profile, it can be concluded that the benefits of Keytruda in combination with fluoropyrimidine and platinum containing chemotherapy outweigh its risks in the 1L treatment of advanced HER2-negative gastric or GEJ adenocarcinoma patients whose tumours express PD-L1 with a CPS ≥1.

3.6.3. Additional considerations on the benefit-risk balance

None

3.7. Conclusions

The overall B/R of Keytruda is positive.

4. Recommendations

Outcome

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

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

Extension of indication to include in combination with chemotherapy the first-line treatment of locally advanced unresectable or metastatic HER2-negative gastric or gastrooesophageal junction adenocarcinoma in adults whose tumours express PD-L1 with a CPS ≥ 1 based on study KEYNOTE-859, a randomised, double-blind phase 3 trial, evaluating KEYTRUDA in combination with chemotherapy compared to placebo in combination with chemotherapy for the first-line treatment of patients with HER2-negative locally advanced unresectable or metastatic gastric or GEJ adenocarcinoma. As a consequence sections 4.1, 4.8 and 5.1 of the SmPC are updated. The Package Leaflet is updated in accordance. Version 40.0 of the RMP has also been submitted.

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

Amendments to the marketing authorisation

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

Conditions or restrictions with regard to the safe and effective use of the medicinal product

Risk management plan (RMP)

The Marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

In addition, an updated RMP should be submitted:

At the request of the European Medicines Agency;

Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

5. EPAR changes

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

Scope

Please refer to the Recommendations section above.

Summary

Please refer to Scientific Discussion 'Keytruda-H-C-003820-II-0135'