EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

20 July 2023
EMA/359366/2023
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Keytruda

International non-proprietary name: pembrolizumab

Procedure No. EMEA/H/C/003820/II/0133

Note

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

Official address Domenico Scarlattilaan 6 ● 1083 HS Amsterdam ● The Netherlands
Address for visits and deliveries Refer to www.ema.europa.eu/how-to-find-us
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List of abbreviations

Abbreviation	Definition
3L+	Third-line therapy (participants who have received 2 prior therapies)
5-FU	5-fluorouracil
AE	Adverse event
AEOSI	Adverse event of special interest
APaT	All participants as treated
AST	Aspartate aminotransferase
BICR	Blinded independent central review
CAPOX	Capecitabine plus oxaliplatin
CE	Confirmatory Europe
CI	Confidence interval
CPS	Combined positive score
DCO	Data cutoff
DCR	Disease control rate
DOR	Duration of response
EC_{50}	Half-maximal effective concentration
ECOG	Eastern Cooperative Oncology Group
EMA	European Medicines Agency
EORTC QLQ-C30	European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-C30
EORTC QLQ-STO22	European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-STO22
EQ-5D-5L	EuroQoL-5 Dimension Questionnaire
E-R	Exposure-response
EU	European Union
FDA	Food and Drug Administration
FP	cisplatin plus 5-fluorouracil
GCP	Good Clinical Practice
GEJ	Gastroesophageal junction
HER2	Human epidermal growth factor receptor 2
HNSCC	Head and neck squamous cell carcinoma
HR	Hazard ratio
IA	Interim analysis
IFNγ	Interferon gamma
IgG4	Immunoglobulin G4

Abbreviation	Definition
IHC	Immunohistochemical
IL-2	Interleukin 2
ITT	Intention to treat
KM	Kaplan-Meier
LS	Least square
LVEF	Left ventricular ejection fraction
mAb	Monoclonal antibody
NCCN	National Comprehensive Cancer Network
NK	Natural killer
NSCLC	Non-small cell lung cancer
ORR	Objective response rate
OS	Overall survival
PD-1	Programmed cell death 1
PD-L1	Programmed cell death ligand 1
PD-L2	Programmed cell death ligand 2
PFS	Progression-free survival
PK	Pharmacokinetic(s)
PRO	Patient-reported outcome
Q3W	Every 3 weeks
Q6W	Every 6 weeks
RECIST	Response evaluation criteria in solid tumors
ROC	Receiver operating characteristic
RSD	Reference safety dataset
SAE	Serious adverse event
SOC	Standard-of-care
SOX	Oxaliplatin + S-1
sSAP	Supplemental statistical analysis plan
TNBC	Triple-negative breast cancer
TNFα	Tumor necrosis factor alpha
ToGA	Trastuzumab in gastric cancer
TTP	Time to progression
TTR	Time to response
UC	Urothelial cancer
vs	Versus

1. Background information on the procedure

1.1. Type II variation

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, Merck Sharp & Dohme B.V. submitted to the European Medicines Agency on 8 February 2023 an application for a variation.

The following variation was requested:

Variation requested	Type	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 trastuzumab, fluoropyrimidine and platinum-containing chemotherapy for treatment of locally advanced unresectable or metastatic HER2- positive gastric or gastro-oesophageal junction adenocarcinoma for Keytruda in adults whose tumours express PD-L1 with a CPS ≥ 1, based on interim results from study KEYNOTE-811, an ongoing Phase 3, double-blind trial comparing trastuzumab plus chemotherapy and pembrolizumab with trastuzumab plus chemotherapy and placebo as first-line treatment in participants with HER2-positive advanced gastric or gastro-oesophageal junction adenocarcinoma; As a consequence, sections 4.1, 4.8, and 5.1 of the SmPC are updated. The Package Leaflet and Labelling are updated in accordance. Version 40.1 of the RMP has also been submitted.

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).

At the time of submission of the application, the PIP was completed.

Information relating to orphan market exclusivity

Similarity

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

Scientific advice

The MAH did not seek Scientific Advice at the CHMP.

1.2. Steps taken for the assessment of the product

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

Rapporteur: Armando Genazzani Co-Rapporteur: N/A

Timetable	Actual dates
Submission date	8 February 2023
Start of procedure	25 February 2023
CHMP Rapporteur's preliminary assessment report circulated on	24 April 2023
PRAC Rapporteur's preliminary assessment report circulated on	26 April 2023
PRAC RMP advice and assessment overview adopted by PRAC on	12 May 2023
CHMP Rapporteur's updated assessment report circulated on	19 May 2023
Request for supplementary information adopted by the CHMP on	25 May 2023
MAH's responses submitted to the CHMP on	30 May 2023
PRAC Rapporteur's preliminary assessment report on the MAH's responses circulated on	26 June 2023
CHMP Rapporteur's preliminary assessment report on the MAH's responses circulated on	05 July 2023
PRAC RMP advice and assessment overview adopted by PRAC on	6 July 2023
CHMP Rapporteur's updated assessment report on the MAH's responses circulated on	14 July 2023
CHMP opinion adopted on	20 July 2023

2. Scientific discussion

2.1. Introduction

2.1.1. Problem statement

Disease or condition

Locally advanced unresectable or metastatic HER2- positive gastric or gastro-oesophageal junction adenocarcinoma.

State the claimed therapeutic indication

KEYTRUDA, in combination with trastuzumab, fluoropyrimidine and platinum-containing chemotherapy, is indicated for the first-line treatment of locally advanced unresectable or metastatic HER2-positive gastric or gastro-oesophageal junction adenocarcinoma in adults whose tumours express PD-L1 with a CPS $\geq$ 1.

Epidemiology and risk factors, screening tools/prevention

The gastric and gastro-oesophageal junction cancer are two different clinical entities, representing the 4th and 6th most common cause of cancer-related mortalities according with the GLOBOCAN 2020

database. While the gastric cancer incidence has been declining in Western countries thanks to economic development, preventative programs focused on dietary habits, and better food preservation practices, recent studies have reported an increase in younger age groups (<50 years), and a rise in the incidence of the gastro-oesophageal junction disease has also been observed. Asia is the leading geographic area for incidence and mortality of the disease, with 48.6% of all global deaths occurring in China alone.
Genetic predisposition has been recognised in a minority of cases of gastric cancer (10%), while diet-related factors, smoking habit, H. pylori infection, together with excess body weight, gastroesophageal reflux disease and oesophageal intestinal metaplasia are among the key risk factors. Considering the modifiable nature of the most important etiopathogenetic factors for gastric and gastro-oesophageal cancer, prevention has a relevant impact on burden of disease.

Biologic features, Aetiology and pathogenesis

Approximately 90% of gastric cancers are adenocarcinomas (ACs). Adenocarcinoma accounts for roughly two-thirds of oesophageal cancer cases. In terms of biological features, gastric and junctional cancer are highly heterogeneous. Among molecular hallmarks, the HER-2 over-expression provides a marker for selecting patients who benefit from a targeted-therapeutic approach in addition to chemotherapy.

Clinical presentation, diagnosis and stage/prognosis

Patients are generally asymptomatic in the early stages. In advanced disease, they can present with non-specific symptoms including dysphagia, asthenia, indigestion, vomiting, weight loss, early satiety and/or iron deficiency anaemia. Because of the silent progression, diagnosis is often delayed so that the majority of patients are at an advanced stage of disease at presentation, and this compromises the curative potential of available treatments. Endoscopic examination and biopsies are the gold standard for diagnosis. Prognosis is generally poor, with an overall mortality at 1 year.
The current 5-year survival rate for advanced gastric cancer, diagnosed at the distant/metastatic stage is 5.9% and therefore represents an area of high unmet medical need for a treatment regimen that improves upon outcomes for these patients. Cancer. 2020; 126: 4553-4562; Gut. 2020; 69: 823-829; CA Cancer J Clin. 2021; : caac.21660; World J Gastroenterol. 2018; 24: 2818-2832

Management

In HER-2-positive advanced tumours, the use of trastuzumab in addition to chemotherapy demonstrated survival advantage over chemotherapy alone, based on the phase III ToGA study (HR 0.74; 95% CI 0.60-0.91; P =0.0046 in OS). The current recommended management of patients is illustrated below, according with current ESMO guidelines (Annals of Oncology 2022;33(10):1005).

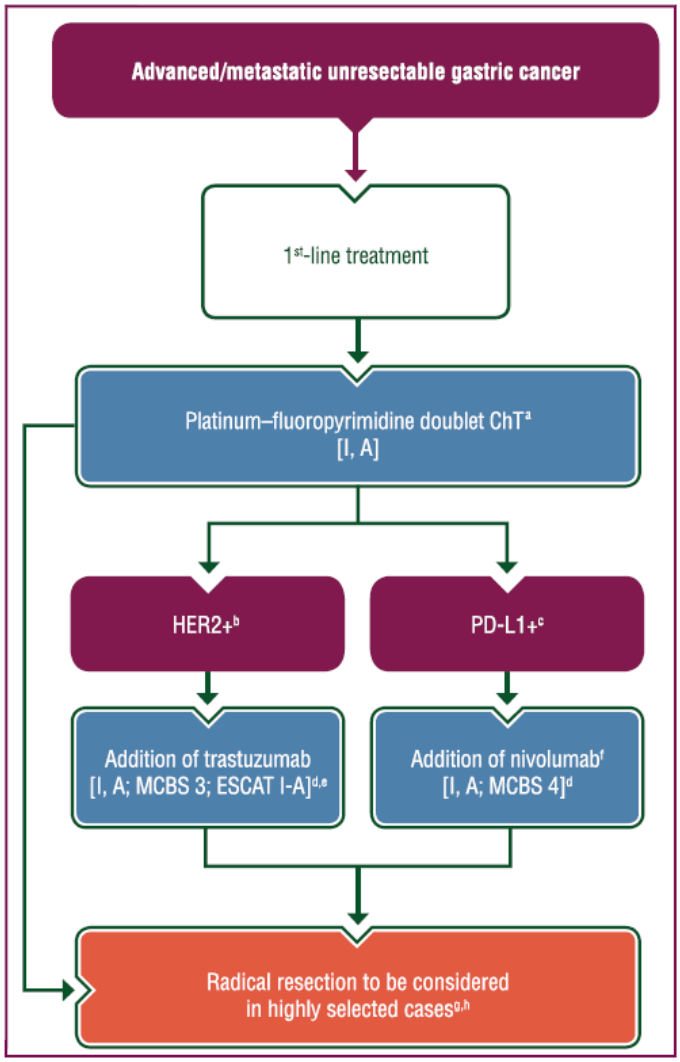


Figure 2. Treatment algorithm for first-line treatment of advanced/metastatic unresectable gastric cancer.

Purple: general categories or stratification; red: surgery; white: other aspects of management; blue: systemic anticancer therapy.

5-FU, 5-fluorouracil; ChT, chemotherapy; CPS, combined positive score; EMA, European Medicines Agency; ESCAT, ESMO Scale for Clinical Actionability of Molecular Targets; FDA, Food and Drug Administration; HER2, human epidermal growth factor receptor 2; IHC, immunohistochemistry; MCBS, ESMO-Magnitude of Clinical Benefit Scale; PD-L1, programmed death-ligand 1; S-1, tegafur—gimeracil—oteracil.

[a]Recommended platinum compounds are oxaliplatin or cisplatin. Oxaliplatin is preferred, especially for older patients. Recommended fluoropyrimidines are intravenous 5-FU, oral capecitabine or oral S-1. Irinotecan—5-FU can be considered an alternative option for patients who do not tolerate platinum compounds.

[b]HER2 IHC 3+ or IHC 2+/FISH-positive.

[c]PD-L1 status should be reported according to the CPS.

[d]ESMO-MCBS v1.1[112] was used to calculate scores for therapies/indications approved by the EMA or FDA. The scores have been calculated by the ESMO-MCBS Working Group and validated by the ESMO Guidelines Committee (https://www.esmo.org/guidelines/esmo-mcbs/esmo-mcbs-evaluation-forms).

[e]ESCAT scores apply to genomic alterations only. These scores have been defined by the guideline authors and validated by the ESMO Translational Research and Precision Medicine Working Group.[111]

[f]Nivolumab—ChT is recommended for advanced, untreated gastric cancer with a PD-L1 CPS score ≥5 (FDA approved without PD-L1 CPS restriction, EMA approved for PD-L1 CPS ≥5).

[g]Gastrectomy is not recommended in metastatic gastric cancer unless required for palliation of symptoms.

[h]Resection of metastases cannot be recommended in general, but might be considered as an individual approach in highly selected cases with oligometastatic disease and response to ChT.

2.1.2. About the product

Keytruda (pembrolizumab) is a humanized mAb IgG4/kappa isotype directed against PD-1. By blocking the interaction between PD-1 and its ligands PD-L1/2, pembrolizumab enhances T cell lymphocyte activity with consequent stimulation of the immune-mediated anti-tumour activity. Pembrolizumab also modulates the level of IL-2, TNFα, IFNγ, and other cytokines. The antibody potentiates existing immune responses in the presence of antigen only; it does not non-specifically activate T cells.

Junttila et al demonstrated that combining trastuzumab-based bispecific antibody HER2-TDB with anti-PD-L1 yielded a combination immunotherapy that enhanced tumor growth inhibition, increasing the rates and durability of therapeutic response (Junttila et al. Antitumor efficacy of a bispecific antibody that targets HER2 and activates T cells. Cancer Res. 2014 Oct 1;74(19):5561-7). In addition, nonclinical studies have shown that a mAb against PD-1 substantially boosts the efficacy of anti-HER2 treatment and shows improved activity (Junttila et al. Antitumor efficacy of a bispecific antibody that targets HER2 and activates T cells. Cancer Res. 2014 Oct 1;74(19):5561-7).

Pembrolizumab is already approved as monotherapy or in combination with chemotherapeutic agents across a wide range of clinical indications. Within the clinical setting of gastroesophageal disease, Keytruda has been approved, in combination with chemotherapy, for the first-line treatment of the oesophagus or HER-2 negative gastroesophageal junction adenocarcinoma with CPS≥10.

The applied and approved indication is:

Gastric or gastro-oesophageal junction (GEJ) adenocarcinoma

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

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.

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

No scientific advice was sought on study KEYNOTE-811 pivotal for this application.

2.1.4. General comments on compliance with GCP

The Clinical trials were performed in accordance with GCP as claimed by the MAH. The MAH has provided a statement to the effect that clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

2.2. Non-clinical aspects

No new non-clinical data have been submitted in this application, which is considered acceptable.

2.2.1. Ecotoxicity/environmental risk assessment

Keytruda is a protein and is therefore exempt from the ERA requirements. This is compliant to the current Guideline on the Environmental Risk Assessment of Medicinal Products for Human Use (EMEA/CHMP/SWP/4447/00).

2.3. Clinical aspects

2.3.1. Introduction

GCP

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

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

- Tabular overview of clinical studies

Table 2.5-gastric5: 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, multi-cohort, 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 and 3: 1L, 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=296)	PFS, OS
KEYNOTE-063 Study discontinued[a]	Phase 3, randomized, open-label	Advanced gastric/GEJ adenocarcinoma in Asian participants; 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=256) 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 Days 1-14 Q3W (N=257) 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 Days 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	Cohort 1: Pembrolizumab 200 mg Q3W IV + TS-1 BID continuous oral administration for 14 days followed by a recovery period of 7 days + oxaliplatin 130 mg/m^2 Q3W IV (N=54) Cohort 2: Pembrolizumab 200 mg Q3W IV + TS 1 BID continuous oral administration for 14 days followed by a recovery period of 7 days + cisplatin 60 mg/m^2 Q3W IV (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 (N=350) OR Placebo in combination with trastuzumab + cisplatin + 5-FU or oxaliplatin + capecitabine (N=348)	PFS, OS

Study Number Status	Study Design	Study Population	Number of Participants by Intervention Group	Primary Endpoint(s)
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 (N=790) OR Placebo in combination with cisplatin + 5-FU or oxaliplatin + capecitabine (N=789)	OS
LEAP-015 Ongoing	Phase 3, randomized, open-label	HER2-negative participants with advanced or metastatic gastric or GEJ adenocarcinoma in the 1L setting	Pembrolizumab 400 mg Q6W × 2 + lenvatinib 8 mg QD + CAPOX (Q3W) or mFOLFOX6 (Q2W) (induction), then pembrolizumab 400 mg + lenvatinib 20 mg QD (consolidation) OR CAPOX (Q3W) or mFOLFOX6 (Q2W) Approximately 880 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 + 5-FU + 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 to be enrolled to FLOT safety cohort.	EFS, OS, pCR

1L=first-line; 2L=second-line; 3L+=third line plus; 5-FU=5 fluorouracil; BID=twice daily; CAPOX=capecitabine and oxaliplatin; CR=complete response; EFS=event-free survival; FOLFOX=5-FU + oxaliplatin + leucovorin; GEJ=gastroesophageal junction; HER2=human endothelial growth factor receptor 2; IV=intravenous; 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; QD=once daily; TS-1=tegafur + gimeracil + oteracil.

[a] KEYNOTE-063 was discontinued to enrollment once it was determined that a similar study in the gastric pembrolizumab program, KEYNOTE-061, failed to meet its primary efficacy endpoint.

2.3.2. Pharmacokinetics

Substantial characterization of the PK and immunogenicity of pembrolizumab have been provided in previous submissions. In particular, pembrolizumab PK disposition has been characterized via pooled population PK analyses using serum concentration-time data contributed from subjects across various clinical studies using a time-dependent PK (TDPK) model. The PK reference dataset for monotherapy includes all available PK data from subjects enrolled on KEYNOTE-001, KEYNOTE-002, KEYNOTE-006,

KEYNOTE-010, and KEYNOTE-024, with an overall sample size of 2993. This serves as the PK reference analysis to support descriptions of pembrolizumab pharmacokinetics in the USPI and EU SmPC.

An additional dosing regimen of 400 mg Q6W has been approved in certain regions, including in the US for all adult indications in the monotherapy and combination therapy settings. In addition to the dosing regimens of 200 mg Q3W or 2 mg/kg Q3W, the 400 mg Q6W dosing regimen was also approved in the EU for all adult monotherapy indications (procedure number EMEA/H/C/003820/II/0062) and for all adult indications in combination with other anticancer agents (procedure number EMEA/H/C/003820/II/0102).

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

Considering that an extensive characterization of the PK and immunogenicity profile of pembrolizumab have been provided in previous submissions, in this submission the focus is on the data related to the characterization of the pharmacology for the combination of pembrolizumab with trastuzumab plus chemotherapy (hereafter referred to as pembrolizumab plus SOC) from KEYNOTE-811 IA2.

The study includes a Global Cohort, in which the chemotherapy is composed by Fluoropyrimidine (FP) or Oxaliplatin and capecitabine (CAPOX), and a Japan-specific S-1 and oxaliplatin (SOX) Cohort, in which the chemotherapy is composed by S-1 plus oxaliplatin. Clinical pharmacology results from the global cohort are presented herein. The clinical pharmacology results from Japan-specific SOX cohort are not presented. Clinical pharmacology results from global cohort specific to this submission include:

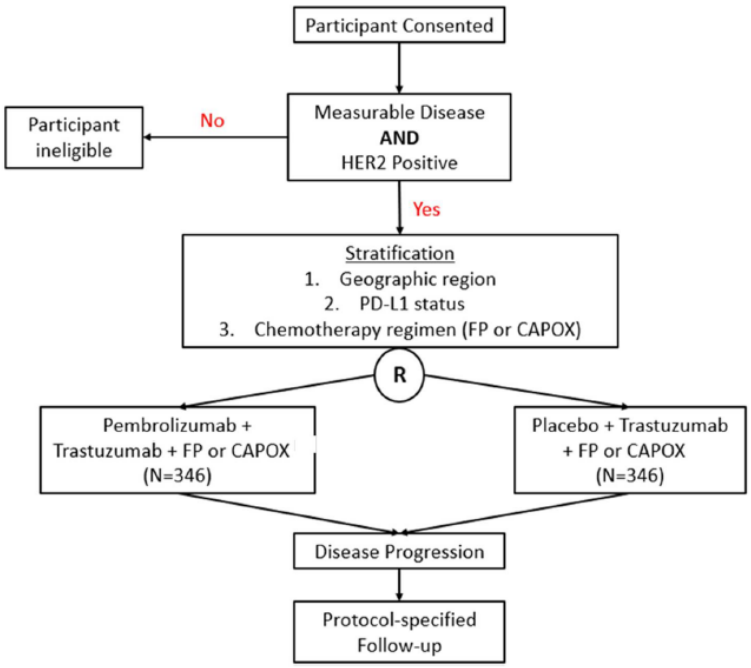
- PK and (Antidrug antibody) ADA data of pembrolizumab at 200 mg Q3W for pembrolizumab plus SOC treatment.

- PK and ADA data of trastuzumab at 8 mg/kg loading dose followed by 6 mg/kg Q3W maintenance doses for pembrolizumab plus SOC and SOC treatments.

PK Data Keynote-811

Keynote-811 is a phase III, Randomized, Double-blind Trial Comparing Trastuzumab Plus Chemotherapy and Pembrolizumab With Trastuzumab Plus Chemotherapy and Placebo as First-line Treatment in Participants with HER2 Positive Advanced Gastric or Gastroesophageal Junction Adenocarcinoma".

Figure 2.7.3-gastric5: 1
KEYNOTE-811 Study Design (Global Cohort)



Abbreviations: 5-FU=5 fluorouracil; CAPOX=capecitabine + oxaliplatin; FP=cisplatin + 5-FU; HER2=human epidermal growth factor receptor 2; N=number; PD-L1=programmed cell death-ligand 1; R=randomized.

PK Analysis Pembrolizumab

Table 1 Overview of Cohorts Included in KEYNOTE-811 Pembrolizumab PK Analysis

Study/Cohort	Cancer Type	Treatment	Analyte	Number of subjects providing PK[b]
KEYNOTE-811 Global Cohort	(HER2) positive with advanced gastric or GEJ adenocarcinoma	Pembrolizumab (200 mg Q3W) plus SOC[a]	Pembrolizumab	350

SOC = Standard of care treatment: Trastuzumab plus either cisplatin plus 5-FU (FP) or oxaliplatin plus capecitabine (CAPOX)
[a] At Cycle 1, Trastuzumab 8 mg/kg loading dose was administered and then 6 mg/kg maintenance thereafter (Q3W).
[b] Unique subjects providing an evaluable pk sample; PK samples from patients dosed with placebo were not analyzed.
HER2 = Human epidermal growth factor receptor 2
Q3W = Every 3 weeks

Source: [082S3M: adpcpem]

PK sampling schedule in KEYNOTE-811 for pembrolizumab: pre infusion pembrolizumab serum concentrations (Ctrough) were obtained within 24 hours prior to dosing at Cycle 1, 2, 4 and 8 and every 4 cycles thereafter. Post-dose samples (Cmax) were drawn at Cycle 1 and 8, approximately 30 minutes after the end of pembrolizumab infusion.

Phoenix™ WinNonlin® (Version 8.1.1.279) software was used for pharmacokinetic analysis.

Summary descriptive statistics of the predose concentrations by cycle are presented in the following table:

Table 2 **Summary Statistics of Pembrolizumab Predose (C_{trough}) and Postdose (C_{max}) Serum Concentration Values for Pembrolizumab plus SOC Group Following Administration of Multiple I.V. doses of 200 mg Q3W Pembrolizumab in KEYNOTE-811, Global Cohort**

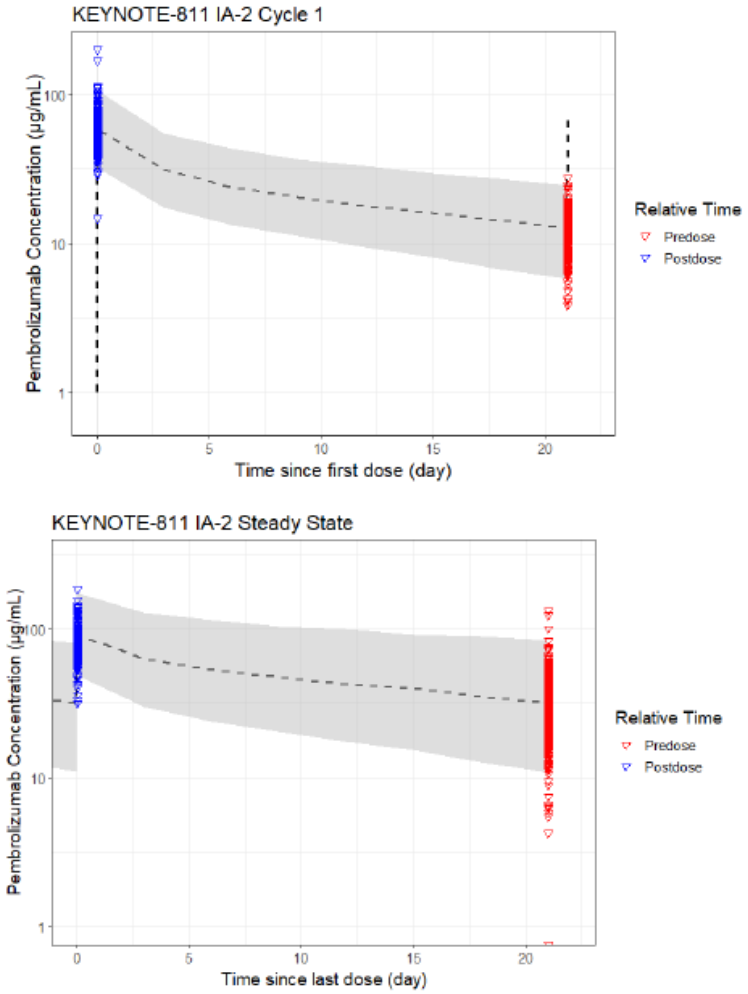
Cycle	NOMTAFD (day)	N	GM (%CV)	AM (SD)	Min	Median	Max
			(µg/mL)				
Predose (C_{trough})							
Cycle 1 (Week 0)	0.00	339	-	0.00 (0)	0.00	0.00	0.00
Cycle 2 (Week 3)	21.0	328	11.0 (36.2)	11.7 (3.8)	3.58	11.5	27.6
Cycle 4 (Week 9)	63.0	290	21.1 (39.3)	22.6 (8.3)	6.75	22.0	64.4
Cycle 8 (Week 21)	147	223	26.7 (43.4)	28.9 (11)	4.27	27.8	63.7
Cycle 12 (Week 33)	231	169	-	31.4 (13.7)	0.00	29.6	101
Cycle 16 (Week 45)	315	125	30.6 (41.7)	32.8 (11.2)	5.53	32.0	75.5
Cycle 20 (Week 57)	399	89	31.6 (42.5)	34.2 (15.1)	9.19	33.2	133
Cycle 24 (Week 69)	483	65	31.4 (46.8)	34.5 (16.8)	9.88	31.8	124
Cycle 28 (Week 81)	567	48	36.4 (32.4)	38.1 (11.6)	16.9	38.4	72.5
Cycle 32 (Week 93)	651	37	35.0 (32.1)	36.7 (11.6)	16.4	34.6	72.8
Postdose (C_{max})							
Cycle 1 (Week 0)	0.0210	323	56.6 (27.3)	58.8 (18)	14.7	56.2	201
Cycle 8 (Week 21)	147	218	79.9 (30.2)	83.4 (24.5)	31.7	78.9	185

AM = Arithmetic Mean; CV% = Geometric Coefficient of Variation; GM = Geometric Mean; Min = Minimum; Max = Maximum; NOMTAFD = Nominal time after first administration; SD = Standard Deviation;
Results reported for time points with N ≥ 3.

Source: [082S3M: adpcpem]

Observed pembrolizumab concentration data in KEYNOTE-811 Global Cohort for pembrolizumab plus SOC group are overlaid on the simulated profile using the reference PK model as shown in Figure 3

Figure 3 **Observed Pembrolizumab Concentration Data in KEYNOTE-811 for Pembrolizumab plus SOC Group, Global Cohort Subjects Receiving 200 mg Q3W with Reference Model-Predicted Pharmacokinetic Profile for 200 mg Q3W Dose Regimen at Cycle 1 and Steady State (at and after Cycle 8)**



Note: Pembrolizumab model predictions and observed concentration data for KEYNOTE-811 subjects of the Global Cohort. a) After 1st dose; b) at and after cycle 8 (21 weeks), with a 28 day time since last dose sample cut off. Symbols are individual observed data (nominal time); black dashed line is median predicted concentrations from the model for a regimen of 200 mg Q3W and the grey shaded area represents the 90% prediction interval; plots are displayed on log scale.

Source: [082S3M: adpcpem]

Tabular summaries of descriptive statistics and boxplots from early drug treatment at Cycle 1 end of infusion (post-dose) and at pre-dose Cycle 2 and Cycle 8, comparing observed pembrolizumab concentrations of 200 mg (Q3W) from participants with advanced gastric or GEJ adenocarcinoma in KEYNOTE-811 and monotherapy trials in non-small cell lung cancer (NSCLC, KEYNOTE-024), urothelial cancer (UC, KEYNOTE-045 and KEYNOTE- 052), head and neck squamous cell cancer (HNSCC, KEYNOTE-048 and KEYNOTE-055),

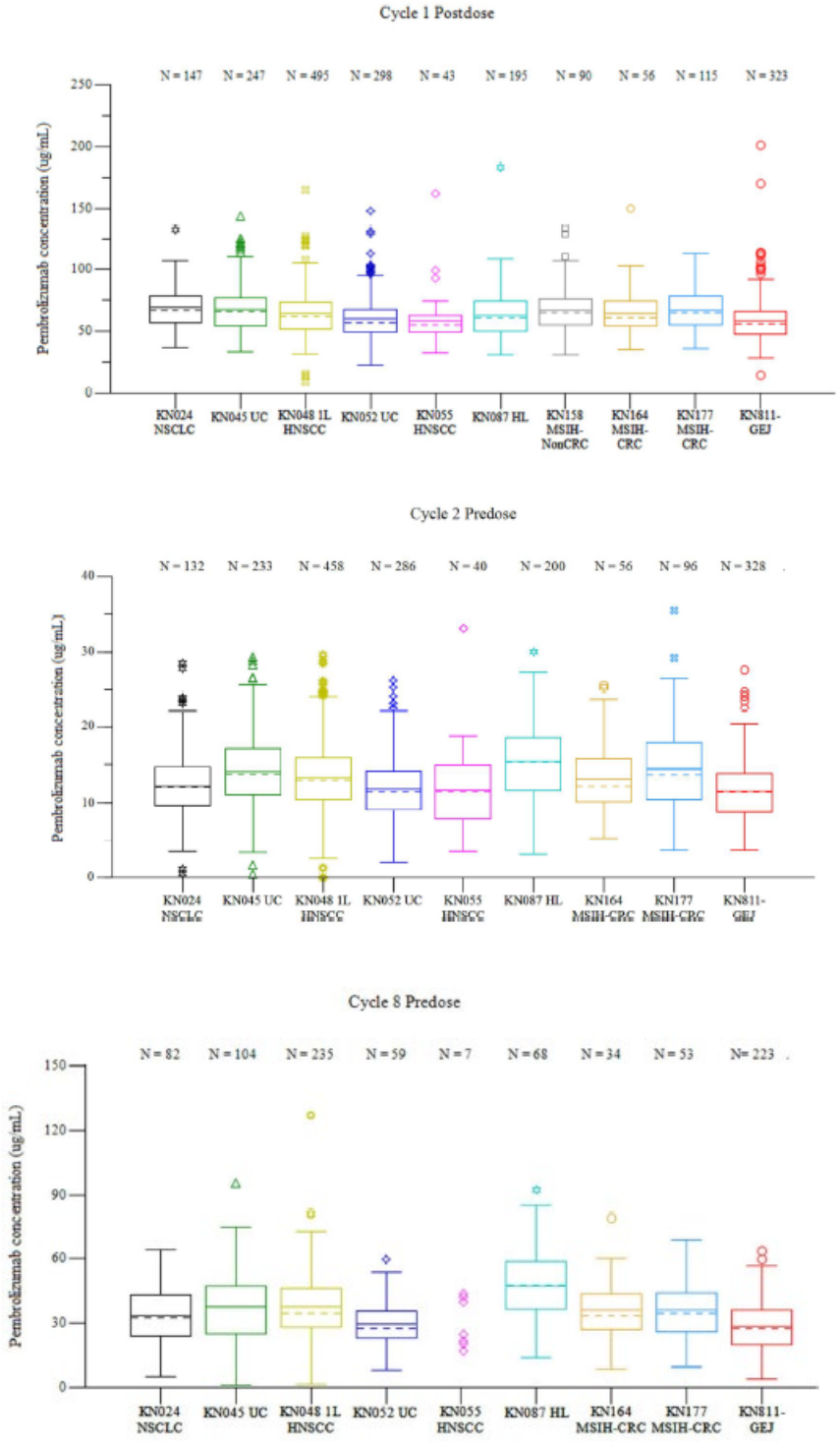
classical Hodgkin Lymphoma (HL, KEYNOTE-087), microsatellite instability-high cancer (MSIH, KEYNOTE-158) and MSIH colorectal cancer (MSIH-CRC, KEYNOTE-164 and KEYNOTE-177), are presented in Table 3 and Figure 4 reported below.

Table 3 **Summary Statistics of Observed Pembrolizumab Concentrations at Cycle 1 Postdose, Cycle 2 and Cycle 8 Predose in Various Monotherapy Trials (KEYNOTE-024, -045, -048, -052, -055, -087, 158 MSIH non CRC, -164, -177) and KEYNOTE-811 Advanced Gastric or GEJ Adenocarcinoma**

Time point	Dose (mg)	Study / Indication	N	GM(CV%) (µg/mL)	AM(SD) (µg/mL)	Min (µg/mL)	Median (µg/mL)	Max (µg/mL)
Cycle 1 Postdose	200	KN024 NSCLC	147	67.5 (23.1)	69.3 (16.2)	36.6	66.8	132
	200	KN045 UC	247	65.7 (26.2)	67.9 (18.2)	33.9	65.9	144
	200	KN048 1L HNSCC	495	61.8 (28.7)	64.2 (17.6)	9.48	61.7	165
	200	KN052 UC	298	58.0 (27.9)	60.2 (17.3)	22.8	57.4	148
	200	KN055 HNSCC	43	56.5 (27.8)	58.9 (20.7)	33.1	54.9	162
	200	KN087 HL	195	60.7 (28)	63.1 (18.3)	31.2	61.3	183
	200	KN158 MSIH-NonCRC	90	64.4 (27)	66.7 (18.3)	31.2	65.2	133
	200	KN164 MSIH-CRC	56	62.2 (27.8)	64.6 (19.1)	34.9	61.2	150
	200	KN177 MSIH-CRC	115	65.0 (25.7)	67.1 (17.1)	36.4	65.7	113
	200	KN811-GEJ	323	56.6 (27.3)	58.8 (18)	14.7	56.2	201
Cycle 2 Predose	200	KN024 NSCLC	132	11.1 (54.1)	12.3 (4.7)	0.535	12.2	28.5
	200	KN045 UC	233	13.1 (47.2)	14.2 (4.9)	0.475	13.9	29.3
	200	KN048 1L HNSCC	458		13.4 (4.6)	0.00	13.2	29.6
	200	KN052 UC	286	11.1 (42.3)	11.9 (4.4)	2.07	11.5	26.2
	200	KN055 HNSCC	40	10.7 (47.2)	11.8 (5.2)	3.45	11.6	33.1
	200	KN087 HL	200	14.4 (39.5)	15.4 (5.1)	3.06	15.3	30.0
	200	KN164 MSIH-CRC	56	12.5 (35.3)	13.2 (4.6)	5.44	12.4	25.6
	200	KN177 MSIH-CRC	96	13.2 (45.7)	14.4 (5.9)	3.64	13.9	35.5
	200	KN811-GEJ	328	11.0 (36.2)	11.7 (3.8)	3.58	11.5	27.6
Cycle 8 Predose	200	KN024 NSCLC	82	30.6 (49.6)	33.6 (13.3)	5.26	32.7	64.1
	200	KN045 UC	104	33.4 (63.7)	37.8 (16.5)	1.13	37.5	95.6
	200	KN048 1L HNSCC	235	34.2 (50.3)	37.5 (15.1)	1.77	34.8	127
	200	KN052 UC	59	28.0 (38.4)	29.9 (10.4)	8.15	27.9	59.8
	200	KN055 HNSCC	7	27.8 (41)	29.6 (11.4)	16.8	24.5	43.3
	200	KN087 HL	68	43.9 (43.5)	47.4 (17)	13.9	47.5	92.4
	200	KN164 MSIH-CRC	34	33.6 (43.1)	36.2 (13.8)	8.40	33.7	78.8
	200	KN177 MSIH-CRC	53	32.9 (49.2)	36.2 (15.1)	9.76	34.7	68.5
	200	KN811-GEJ	223	26.7 (43.4)	28.9 (11)	4.27	27.8	63.7

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; GEJ = Gastroesophageal Junction.

Figure 4 **Pembrolizumab Observed Pembrolizumab Concentrations at Cycle 1 Postdose, Cycle 2 and Cycle 8 Predose in Various Monotherapy Trials (KEYNOTE-024, -045, -048, -052, -055, -087, 158 MSIH non CRC, -164, -177) and KEYNOTE-811**



PK Analysis Trastuzumab

Table 5 Overview of Cohorts Included in KEYNOTE-811 Trastuzumab PK Analysis

Study/Cohort	Cancer Type	Treatment	Analyte	Number of subjects providing PK[b]
KEYNOTE-811 Global Cohort	(HER2) positive with advanced gastric or GEJ adenocarcinoma	Pembrolizumab (200 mg Q3W) plus SOC[a]	Trastuzumab	350
		SOC[a]	Trastuzumab	346

SOC = Standard of care treatment: Trastuzumab plus either cisplatin plus 5-FU (FP) or oxaliplatin plus capecitabine (CAPOX)

[a] At Cycle 1, Trastuzumab 8 mg/kg loading dose was administered and then 6 mg/kg maintenance thereafter (Q3W).

[b] Unique subjects providing an evaluable pk sample;

HER2 = Human epidermal growth factor receptor 2; Q3W = Every 3 weeks

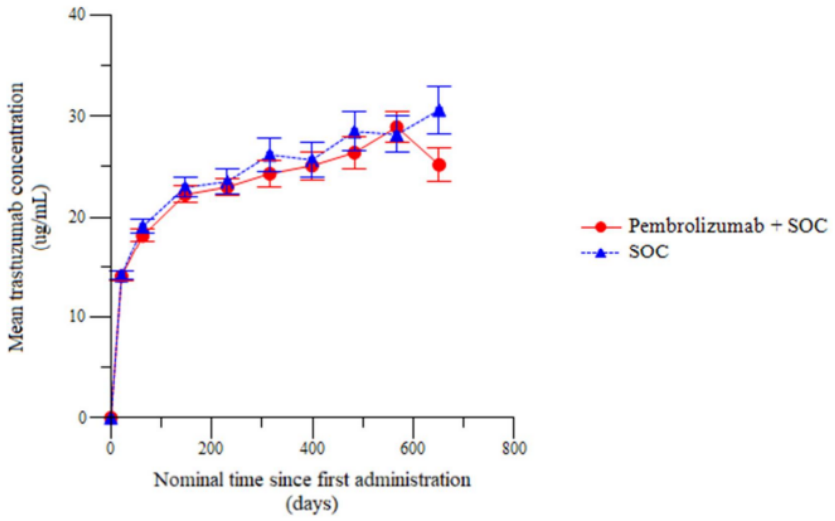
Source: [082S3M: adpctra]

PK sampling schedule in KEYNOTE-811 for trastuzumab: pre infusion trastuzumab serum concentrations (Ctrough) were obtained within 24 hours prior to dosing at Cycle 1, 2, 4 and 8 and every 4 cycles thereafter. Postdose samples (Cmax) were drawn at Cycle 1 and 8, approximately 30 minutes after the end of trastuzumab infusion.

Phoenix™ WinNonlin® (Version 8.1.1.279) software was used for pharmacokinetic analysis.

Mean predose serum trastuzumab concentration-time profiles stratified by treatment groups are shown in Figure 6.

Figure 6 Arithmetic Mean (SE) Trastuzumab Predose Concentration -Time Profiles Following Administration of Multiple I.V. doses of 6 mg/kg Q3W Trastuzumab in KEYNOTE-811, Global Cohort, Stratified by Treatment Groups (Linear scale)



Note: Error bars are associated +/- SE (Standard Error).

Source: [082S3M: adpctra]

Summary descriptive statistics of the predose and postdose concentration by Cycle and stratified by treatment groups after multiple I.V. doses of 6 mg/kg Q3W for pembrolizumab plus SOC and SOC groups are presented in Table 6.

Table 6 **Summary Statistics of Trastuzumab Concentration Values Following Administration of Multiple I.V. doses of 6 mg/kg Q3W Trastuzumab in KEYNOTE-811, Global Cohort, Stratified by Treatment**

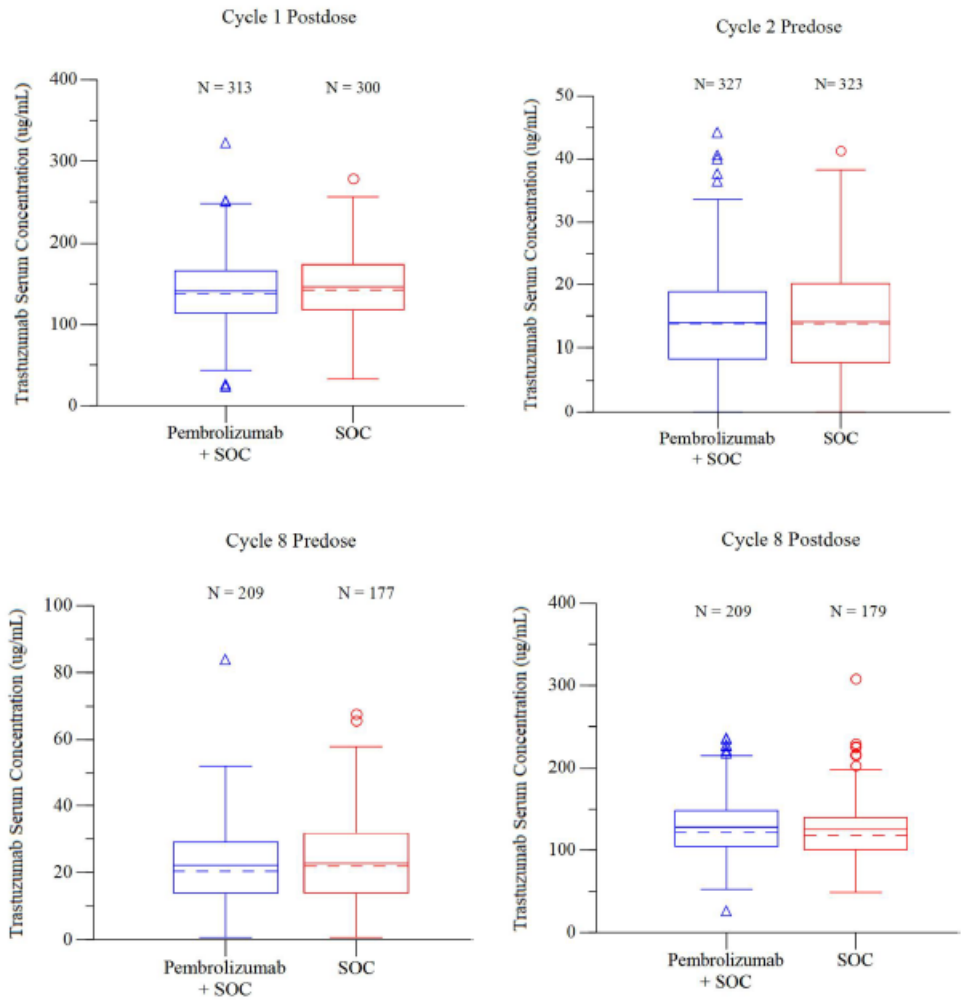
			Pembrolizumab plus SOC					SOC				
Relative Time	Cycle	NOMTAFD (Day)	N	GM (%CV) (µg/mL)	AM (SD) (µg/mL)	Median (µg/mL)	Ranges (µg/mL)	N	GM (%CV) (µg/mL)	AM (SD) (µg/mL)	Median (µg/mL)	Ranges (µg/mL)
Predose	Cycle 1	0	338		0.00 (0)	0.00	0.00 ~ 0.00	336		0.00 (0)	0.00	0.00 ~ 0.00
	Cycle 2	21.0	327		14.0 (8.1)	13.8	0.00 ~ 44.2	323		14.1 (8.3)	13.9	0.00 ~ 41.2
	Cycle 4	63.0	289		18.2 (10.5)	17.3	0.00 ~ 66.1	281	14.7 (120)	19.1 (12.1)	16.9	0.0409 ~ 93.2
	Cycle 8	147	209	18.6 (78)	22.2 (12)	20.3	0.642 ~ 83.9	177	18.8 (85)	22.9 (12.6)	22.0	0.519 ~ 67.5
	Cycle 12	231	167		23.0 (11.4)	21.6	0.00 ~ 67.4	140	18.7 (97)	23.5 (14.4)	20.2	0.238 ~ 91.6
	Cycle 16	315	126		24.3 (15.4)	23.0	0.00 ~ 111	96	20.9 (90)	26.2 (16.1)	24.1	1.20 ~ 101
	Cycle 20	399	87	20.2 (96)	25.1 (13)	25.7	0.928 ~ 63.7	72	20.2 (112)	25.7 (14.6)	23.4	0.127 ~ 76.6
	Cycle 24	483	60	22.1 (89)	26.4 (12.2)	24.7	0.864 ~ 50.4	54	24.6 (68)	28.5 (13.9)	26.2	2.16 ~ 71.6
	Cycle 28	567	50	26.9 (41)	28.9 (11.2)	26.5	9.39 ~ 59.8	43	24.9 (67)	28.2 (11.8)	24.3	1.26 ~ 57.9
	Cycle 32	651	39	22.9 (51)	25.2 (10.2)	23.8	4.86 ~ 45.8	33	27.4 (56)	30.6 (13.6)	29.5	4.55 ~ 65.4
Postdose	Cycle 1	0.0210	313	134 (35)	141 (42.0)	138	23.7 ~ 323	300	140 (32)	146 (41.3)	142	33.2 ~ 278
	Cycle 8	147	209	123 (30)	128 (36.2)	121	26.5 ~ 237	179	120 (30)	125 (37.9)	119	48.2 ~ 308

AM = Arithmetic Mean; CV% = Geometric Coefficient of Variation; GM = Geometric Mean; NOMTAFD = Nominal time after first trastuzumab administration; SD = Standard Deviation; Results reported for time points with N ≥ 3.

Source: [082W2B: adpctra]

Comparison boxplots using observed trastuzumab concentration data from both pembrolizumab plus SOC and SOC treatment groups in KEYNOTE-811 Global Cohort were provided in Figure 7.

Figure 7 **Boxplots with Serum Concentration Values of Trastuzumab Following Administration of Multiple I.V. doses of 6 mg/kg Q3W Trastuzumab in KEYNOTE-811, Global Cohort, Stratified by Treatment Groups**



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.

IMMUNOGENICITY

The existing immunogenicity assessment for pembrolizumab for the monotherapy setting is based on a sufficiently large dataset of patients across several indications, with very low observed rates of total treatment emergent ADA (1.4 - 3.8%) as well as of neutralizing antibodies (0.4 – 1.6%).

In total 337 subjects from study KEYNOTE-811 were included in the immunogenicity assessment for pembrolizumab and 672 subjects were included in the immunogenicity assessment for the SOC component trastuzumab.

Overview of Subjects Included in the Immunogenicity Analysis after Pembrolizumab plus SOC or SOC Treatments in Subjects with HER2 Positive Advanced Gastric or GEJ Adenocarcinoma (KEYNOTE-811)

Study	Treatment	Analyte	Subjects		
			Subjects Providing ADA Samples	Subjects Dosed with MK-3475	Assessable Subjects Dosed with MK-3475 and Post Treatment Samples
Keynote-811	MK-3475 (200 mg Q3W) plus SOC[a]	MK-3475	350	350	337
		Trastuzumab	350	350	338
	SOC[a]	Trastuzumab	346	346	334

SOC = Standard of care treatment: Trastuzumab plus either cisplatin plus 5-FU (FP) or oxaliplatin plus capecitabine (CAPOX).
a: At Cycle 1, Trastuzumab 8 mg/kg loading dose was administered and then 6 mg/kg maintenance thereafter (Q3W).

Data source: [085ZRS: analysis-adadapem, analysis-adadatra]

The overall immunogenicity incidence was defined as the proportion of treatment emergent positive subjects to the total number of evaluable subjects (treatment emergent positive, nontreatment emergent positive and negative immunogenicity status).

Pembrolizumab

For pembrolizumab (200 mg MK-3475 Q3W) plus SOC treatment ADA samples were available from 350 subjects (ADA cut-off date of 20 April 2022).

A subset of the subjects was not assessable for drug-induced immunogenicity analysis, because only a pre-treatment ADA sample was available (N=13). The remaining 337 subjects were assessable for drug-induced immunogenicity analysis.

Out of the 337 subjects included in the immunogenicity assessment, 11 subjects were inconclusive, resulting in 326 evaluable subjects. The observed incidence of treatment emergent ADA in evaluable subjects with HER2 positive advanced gastric or GEJ adenocarcinoma is 2.1% (7 out of 326), based on

7 subjects with treatment emergent positive status, and 319 with negative immunogenicity status. Out of the 7 treatment emergent positive subjects, one subject had antibodies with neutralizing capacity, resulting in a treatment emergent neutralizing positive incidence rate of 0.3% (1 out of 326).

An overview of the immunogenicity status of all assessable subjects is presented in the table below.

Summary of Subject Immunogenicity Results for Pembrolizumab after Pembrolizumab plus SOC Treatment in Subjects with HER2 Positive Advanced Gastric or GEJ Adenocarcinoma (KEYNOTE-811)

Pembrolizumab Immunogenicity	
Immunogenicity status	**Total**
Assessable subjects[a]	337
Inconclusive subjects[b]	11
Evaluable subjects[c]	**326**
Negative[d]	319 (97.9%)
Non-Treatment emergent positive[d]	0
Neutralizing negative	0
Neutralizing positive	0
Treatment emergent positive[d]	7 (2.1%)
Neutralizing missing	1 (0.3%)
Neutralizing negative	5 (1.5%)
Neutralizing positive	1 (0.3%)

a: Included are subjects with at least one ADA sample available after treatment with pembrolizumab
b: Inconclusive subjects are the number of subjects with no positive ADA samples present and the drug concentration in the last sample above the drug tolerance level.
c: Evaluable subjects are the total number of negative and positive subjects (non-treatment emergent and treatment emergent.
d: Denominator was total number of evaluable subjects.

Data source: [085ZRS: analysis-adadapem]

The immunogenicity incidence of treatment emergent positive subjects for pembrolizumab after treatment with pembrolizumab plus SOC in subjects with HER2 positive advanced gastric or GEJ adenocarcinoma is 2.1% (7 out of 326) with 0.3% of neutralizing antibodies (1 out of 326).

Trastuzumab

For SOC component trastuzumab, ADA samples for trastuzumab were available from 696 subjects, of which 350 were treated with pembrolizumab plus SOC and 346 were treated with SOC. (ADA cut-off date of 22 March 2022)

A subset of the subjects was not assessable for drug-induced immunogenicity analysis, because only a pre-treatment ADA sample was available (N=24). The remaining 672 subjects were assessable for drug-induced immunogenicity analysis, 338 were in the pembrolizumab plus SOC group and 334 were in the SOC group.

Out of the 672 subjects included in the immunogenicity assessment, 16 subjects were inconclusive, resulting in 656 evaluable subjects.

The incidence of trastuzumab treatment emergent ADA in evaluable subjects after pembrolizumab plus SOC therapy is 3.1% (10 out of 327), based on 10 subjects with treatment emergent positive status, 6 subjects with non-treatment emergent positive status and 311 with negative immunogenicity status.

The incidence of trastuzumab treatment emergent ADA in evaluable subjects after SOC therapy is 2.4% (8 out of 329), based on 8 subjects with treatment emergent positive status, 13 subjects with non-treatment emergent positive status and 308 with negative immunogenicity status.

No Nab analysis was performed for trastuzumab ADA positive samples.

An overview of the immunogenicity status of all assessable subjects is presented in the following table:

Summary of Subject Immunogenicity Results for Trastuzumab after Pembrolizumab plus SOC and SOC Treatments in Subjects with HER2 Positive Advanced Gastric or GEJ Adenocarcinoma (KEYNOTE-811)

Trastuzumab Immunogenicity			
Immunogenicity status	**Total**	**Pembrolizumab plus SOC**	**SOC**
Assessable subjects[a]	672	338	334
Inconclusive subjects[b]	16	11	5
Evaluable subjects[c]	**656**	**327**	**329**
Negative[d]	619 (94.4%)	311 (95.1%)	308 (93.6%)
Non-Treatment emergent positive[d]	19 (2.9%)	6 (1.8%)	13 (4.0%)
Treatment emergent positive[d]	18 (2.7%)	10 (3.1%)	8 (2.4%)

a: Included are subjects with at least one ADA sample available after treatment with trastuzumab
b: Inconclusive subjects are the number of participants with no positive ADA samples present and the drug concentration in the last sample above the drug tolerance level.
c: Evaluable subjects are the total number of negative and positive subjects (non-treatment emergent and treatment emergent.
d: Denominator was total number of evaluable subjects.

Data source: [085ZRS: analysis-adadatra]

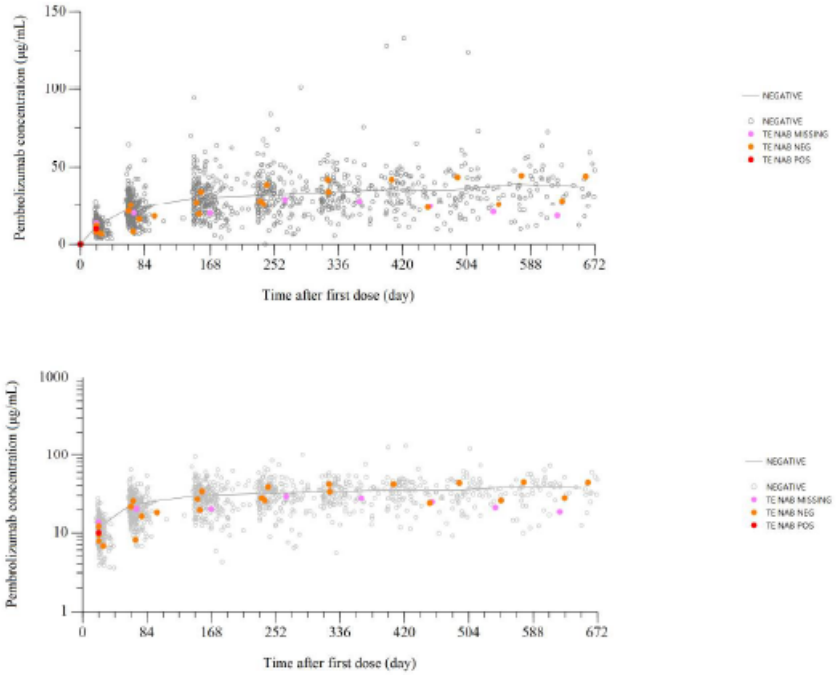
IMPACT OF ANTI-DRUG ANTIBODIES ON EXPOSURE

Pembrolizumab

The effect of ADA on pembrolizumab levels, for the subjects with ADA positive samples, is compared with the subjects treated with the same regimen that only have ADA negative samples.

For the ADA positive subjects, the pembrolizumab exposure was comparable with the exposures observed for the negative subjects treated with the same regimen (see figure below).

Effect of ADA on Pembrolizumab Exposure after Pembrolizumab plus SOC Therapy in Subjects with HER2 Positive Advanced Gastric or GEJ Adenocarcinoma (KEYNOTE-811), Linear Scale (top) and Log Scale (bottom)



Footnote: Figure includes ADA samples with corresponding PK concentrations. Samples taken > 42 days after last dose (> 2 times the scheduled time) are excluded. Pembrolizumab concentrations for samples with Cycle 1 predose PK concentrations >0 were set to missing as their results are unreliable.

Individual pembrolizumab concentrations for the ADA negative subjects (grey circles), mean value of the negative subjects (grey line), treatment emergent neutralizing missing subjects (pink dot), treatment emergent neutralizing negative subjects (orange dot), treatment emergent neutralizing positive subjects (red dot).
If a subject is determined to be ADA positive (non-TE or TE, based on one or more positive samples), all data-points belonging to that subject are shown in the color of the corresponding ADA status group.

TE nAB missing: treatment emergent positive neutralizing antibody missing subject.
TE nAB Neg: treatment emergent positive neutralizing antibody negative subject.
TE nAB Pos: treatment emergent positive neutralizing antibody positive subject.

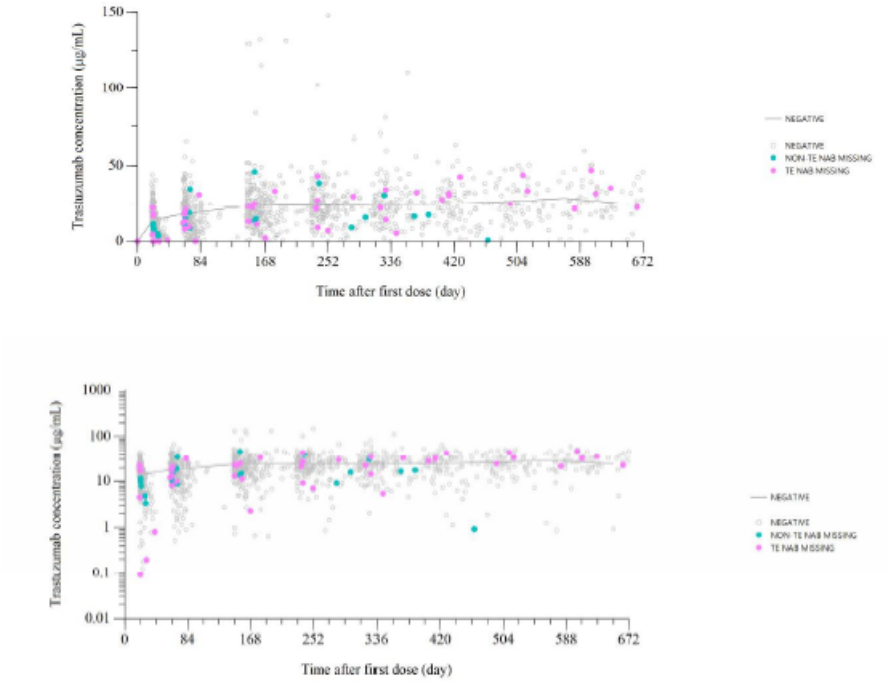
Data source: [085ZRS: analysis-adadapem]

Trastuzumab

The effect of ADA on trastuzumab levels, for the subjects with ADA positive samples, is compared with the subjects treated with the same regimen that only have ADA negative samples. No Nab analysis was performed for trastuzumab ADA positive samples.

For the ADA positive subjects, the trastuzumab exposure was comparable with the exposures observed for the negative subjects treated with the same regimen figures below:

Effect of ADA on Trastuzumab Exposure after Pembrolizumab plus SOC Therapy in Subjects with HER2 Positive Advanced Gastric or GEJ Adenocarcinoma (KEYNOTE-811), Linear Scale (top) and Log Scale (bottom)



Footnote: Figure includes ADA samples with corresponding PK concentrations. Samples taken > 42 days after last dose (> 2 times the scheduled time) are excluded. Trastuzumab concentrations for samples with Cycle 1 predose PK concentrations >0 were set to missing as their results are unreliable.

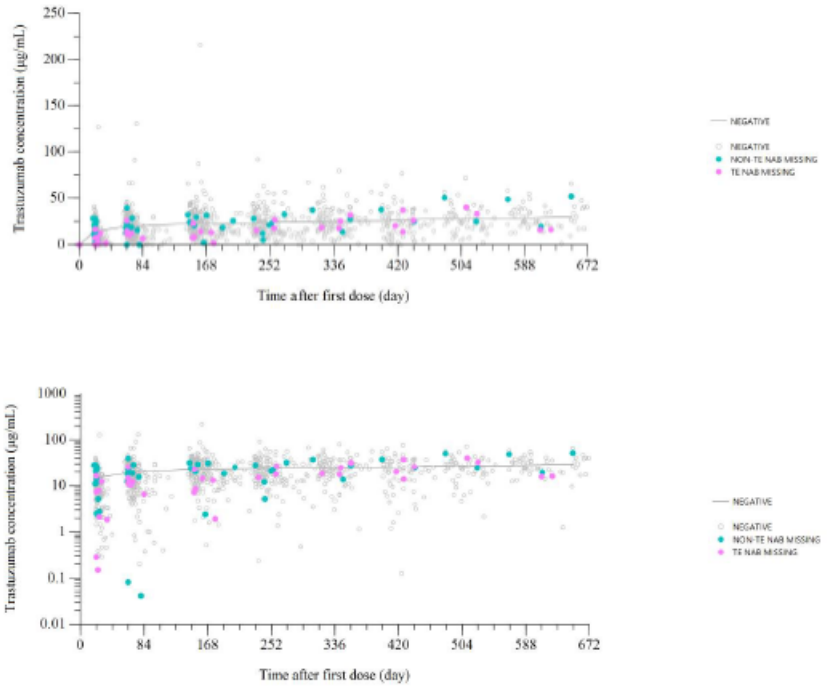
Individual trastuzumab concentrations for the ADA negative subjects (grey circles), mean value of the negative subjects (grey line), non-treatment emergent neutralizing missing subjects (green/blue dot), treatment emergent neutralizing missing subjects (pink dot).

If a subject is determined to be ADA positive (non-TE or TE, based on one or more positive samples), all data-points belonging to that subject are shown in the color of the corresponding ADA status group.

Non-TE nAB missing: non-treatment emergent positive neutralizing antibody missing subject.
TE nAB missing: treatment emergent positive neutralizing antibody missing subject.

Data source: [085ZRS: analysis-adadatra]

Effect of ADA on Trastuzumab Exposure after SOC Therapy in Subjects with HER2 Positive Advanced Gastric or GEJ Adenocarcinoma (KEYNOTE-811), Linear Scale (top) and Log Scale (bottom)



Footnote: Figure includes ADA samples with corresponding PK concentrations. Samples taken > 42 days after last dose (> 2 times the scheduled time) are excluded. Trastuzumab concentrations for samples with Cycle 1 predose PK concentrations >0 were set to missing as their results are unreliable.

Individual trastuzumab concentrations for the ADA negative subjects (grey circles), mean value of the negative subjects (grey line), non-treatment emergent neutralizing missing subjects (green/blue dot), treatment emergent neutralizing missing subjects (pink dot).
If a subject is determined to be ADA positive (non-TE or TE, based on one or more positive samples), all data-points belonging to that subject are shown in the color of the corresponding ADA status group.

Non-TE nAB missing: non-treatment emergent positive neutralizing antibody missing subject.
TE nAB missing: treatment emergent positive neutralizing antibody missing subject.

Data source: [085ZRS: analysis-adadatra]

2.3.4. PK/PD modelling

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

2.3.5. Discussion on clinical pharmacology

In this application, the focus is on PK and immunogenicity data related to the combination of pembrolizumab with trastuzumab plus chemotherapy (hereafter referred to as pembrolizumab plus SOC) from KEYNOTE-811 IA2. The study includes a Global Cohort, in which the chemotherapy is composed by FP or CAPOX, and a Japan-specific SOX Cohort, in which the chemotherapy is composed by S-1 plus oxaliplatin. Clinical pharmacology results from the global cohort are presented herein.

PK data from KEYNOTE-811 show that the observed pembrolizumab serum concentration values in subjects with advanced gastric or GEJ adenocarcinoma are contained within the 90% CI of the

reference PK model, which indicate consistency with the historical data, in both cycle 1 postdose and cycle 8 predose (at steady state).

In addition, tabular summaries of descriptive statistics and boxplots from early drug treatment at Cycle 1 end of infusion (post-dose) and at pre-dose Cycle 2 and Cycle 8 show that observed pembrolizumab concentrations of 200 mg (Q3W) in combination with SOC (including Trastuzumab) from participants with advanced gastric or GEJ adenocarcinoma in KEYNOTE-811 are similar to the observed pembrolizumab concentration when administered as monotherapy in other trials.

In conclusion, pembrolizumab PK disposition is not affected by the coadministration with SOC including trastuzumab and chemotherapy and in the same way, the PK disposition of the SOC component trastuzumab is not affected by the coadministration of pembrolizumab. Similar exposures for trastuzumab are reported in the SOC arm as well as in the Pembrolizuma SOC arm.

The immunogenicity incidence of treatment emergent ADA positive subjects for pembrolizumab after treatment with pembrolizumab plus SOC in subjects with HER2 positive advanced gastric or GEJ adenocarcinoma is 2.1% (7 out of 326) with 0.3% of neutralizing antibodies (1 out of 326). This incidence rate is comparable to the historical incidence rate reported after pembrolizumab monotherapy, (1.8%) with 0.4% of neutralizing antibodies.

The incidence of trastuzumab treatment emergent ADA in evaluable subjects is similar between pembrolizumab plus SOC arm (3.1%) and SOC arm (2.4%).

No Nab analysis was performed for trastuzumab ADA positive samples. This is considered acceptable since this lack of Nab characterisation for trastuzumab does not impact on pembrolizumab's SmPC.

2.3.6. Conclusions on clinical pharmacology

Pembrolizumab PK disposition is not affected by the coadministration with SOC including trastuzumab and chemotherapy and, in the same way, the PK disposition of the SOC component trastuzumab is not affected by the coadministration of pembrolizumab. Similar exposures for trastuzumab are reported in the SOC arm as well as in the Pembrolizumab + SOC arm.

The immunogenicity incidence of treatment emergent ADA positive subjects for pembrolizumab after treatment with pembrolizumab plus SOC in subjects with HER2 positive advanced gastric or GEJ adenocarcinoma is similar to the historical incidence rate reported after pembrolizumab monotherapy.

The incidence of trastuzumab treatment emergent ADA in evaluable subjects is similar between pembrolizumab plus SOC arm and SOC arm.

2.4. Clinical efficacy

The current submission is based on a single pivotal study (KEYNOTE-811).

KEYNOTE-811 is an ongoing, Phase 3, randomized, double-blind, placebo-controlled, multicentre study to evaluate the efficacy and safety of pembrolizumab in combination with trastuzumab + chemotherapy (cisplatin and 5-FU or oxaliplatin and capecitabine) versus trastuzumab + chemotherapy alone as 1L treatment in participants with unresectable or metastatic HER-2-positive gastric/gastroesophageal junction (GEJ) adenocarcinoma.

Results are submitted from the IA2 of KEYNOTE-811 (DCO date: 25-MAY-2022) that was triggered approximately 9 months after the last participant was randomized, when 484 PFS events had occurred (80% information fraction).

2.4.1. Dose response study(ies)

No dose-response studies were submitted as part of this application.

2.4.2. Main study

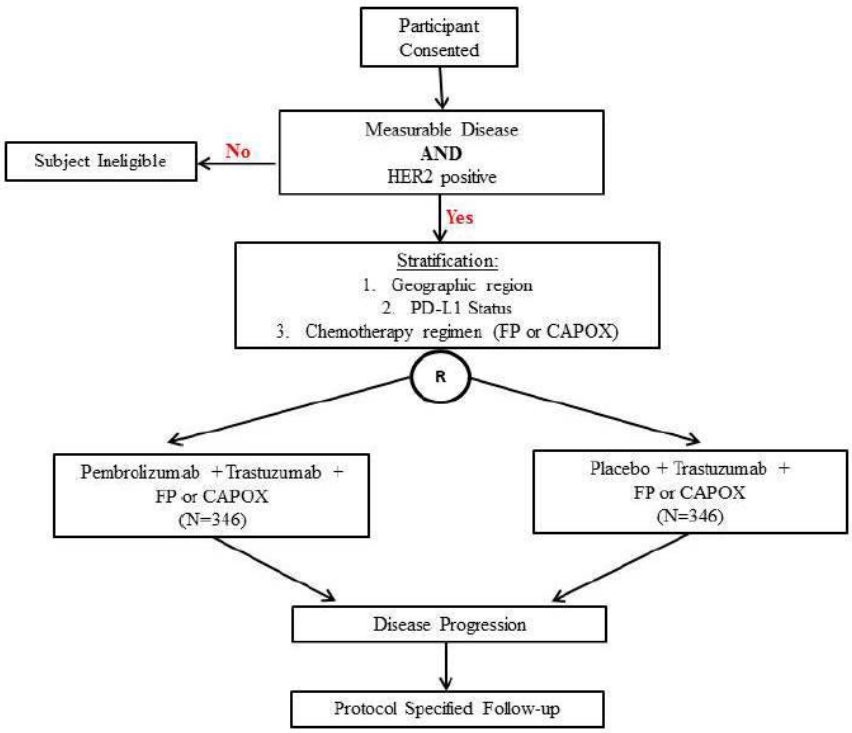
Title of Study

A Phase III, Randomized, Double-blind Trial Comparing Trastuzumab Plus Chemotherapy and Pembrolizumab With Trastuzumab Plus Chemotherapy and Placebo as First-line Treatment in Participants With HER2 Positive Advanced Gastric or Gastroesophageal Junction Adenocarcinoma (KEYNOTE-811)

Methods

The overall study design of study KEYNOTE-811 is illustrated below. The study included a Global Cohort (planned 692 individuals) and an additional Japan-specific SOX Cohort (40 participants) randomised 1:1 to pembrolizumab or placebo, each in combination with chemotherapy plus trastuzumab. Only efficacy data from the Global Cohort are presented herein. The efficacy data from the Japan-specific SOX Cohort are not presented in the current application.

Figure 9-1
Study Design (Global Cohort)



CAPOX = capecitabine/oxaliplatin; FP = cisplatin plus 5 fluorouracil; HER2 = human epidermal growth factor receptor 2; PD-L1 = programmed cell death ligand 1; R = randomization.

Study participants

Inclusion criteria

Participants were eligible to be included in the study only if all of the following criteria applied:

1. Be male/female who were at least 18 years of age on the day of signing the informed consent with histologically or cytologically confirmed diagnosis of previously untreated, locally advanced unresectable or metastatic HER2-positive gastric or GEJ adenocarcinoma.

2. Be HER2-positive defined as either IHC 3+ or IHC 2+ in combination with ISH+ (or FISH), as assessed by central review on primary or metastatic tumor.

3. Had measurable disease as defined by RECIST 1.1 by scans with IV contrast, as determined by the site investigator.

4. If male, agreed to use an adequate method of contraception, as outlined in Appendix 3 of the study protocol [16.1.1], for the course of the study through 7 months after the last dose of all study treatments.

5. If female, not pregnant (see Appendix 3 of the study protocol [16.1.1]), not breastfeeding, and had at least one of the following conditions apply:

a.) Not a WOCBP as defined in Appendix 3 of the study protocol [16.1.1]

OR

b.) Not a WOCBP who agreed to follow the contraceptive guidance in Appendix 3 of the study protocol [16.1.1] during the treatment period and for at least 7 months after the last dose of study treatment.

6. Provided written informed consent for the study.

7. Had a performance status of 0 or 1 on the ECOG Performance Scale within 3 days prior to the first dose of study treatment.

8. Had a life expectancy of greater than 6 months.

9. Had a 12-lead ECG and ECHO or MUGA scan performed by the investigator or other qualified person to evaluate cardiac function prior to enrollment in the study.

10. Provided tumor tissue sample deemed adequate for PD-L1 and MSI biomarker analysis.

11. Had adequate organ function as defined in Table 2 of the study protocol [16.1.1].

Exclusion Criteria

Participants were excluded from the study if any of the following criteria applied:

1. Had previous therapy for locally advanced unresectable or metastatic gastric/GEJ cancer.

2. Had major surgery, open biopsy or significant traumatic injury within 28 days prior to randomization, or anticipation of the need for major surgery during the course of study treatment.

3. Had radiotherapy within 14 days of randomization.

4. Had a known additional malignancy that was progressing or had required active treatment within the past 5 years.

5. Had known active CNS metastases and/or carcinomatous meningitis.

6. Had an active autoimmune disease that had required systemic treatment in past 2 years (ie, with use of disease modifying agents, corticosteroids or immunosuppressive drugs).

7. Had a diagnosis of immunodeficiency or was receiving chronic systemic steroid therapy (in dosing exceeding 10 mg daily of prednisone equivalent) or any other form of immunosuppressive therapy within 7 days prior the first dose of trial drug.

8. Had a history of (noninfectious) pneumonitis that required steroids or had pneumonitis.

9. Had a known history of active TB.

10. Had an active infection requiring systemic therapy.

11. Had poorly controlled diarrhea (eg, watery stool, uncontrollable bowel movement with drugs, Grade ≥2 and number of defecations, ≥5/day).

12. Had accumulation of pleural, ascitic, or pericardial fluid requiring drainage or diuretic drugs within 2 weeks prior to enrollment.

13. Had a history or current evidence of any condition, therapy, or laboratory abnormality that might confound the results of the study, interfered with the participant's participation for the full duration of the study, or was not in the best interest of the participant to participate, in the opinion of the treating investigator.

14. Had peripheral neuropathy > Grade 1.

15. Had a known psychiatric or substance abuse disorder that would interfere with cooperation with the requirements of the study.

16. Was a WOCBP who had a positive urine pregnancy test within 24 hours prior to randomization or treatment allocation (see Appendix 3 of the study protocol [16.1.1]).

17. Removed.

18. Had active or clinically significant cardiac disease.

19. Had a known history of HIV.

20. Had a known history of hepatitis B or known active hepatitis C virus infection.

21. Had severe hypersensitivity (≥Grade 3) to pembrolizumab, trastuzumab, study chemotherapy agents and/or to any excipients, murine proteins, or platinum-containing products.

22. Had an allogeneic tissue/solid organ transplant.

23. Had 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 (eg, CTLA-4, OX 40, CD137).

24. Had received a live vaccine within 30 days prior to the first dose of study treatment.

25. Was participating in or had participated in a study of an investigational agent or had used an investigational device within 4 weeks prior to the first dose of study treatment.

Treatments

Table 9-1 Study Treatments

Study Treatment Name	Dose Formulation	Unit Dose Strength(s)[b]	Dosage Level(s)	Route of Administration	Use	IMP/NIMP	Sourcing
Pembrolizumab/Placebo							
Pembrolizumab (MK-3475)[a]	Vial	25 mg/mL vial	200 mg on Day 1 of each cycle (Q3W)	IV infusion via infusion pump	Experimental	IMP	Provided centrally by the Sponsor
Placebo	Solution for infusion, refer to the Pharmacy Manual	N/A	On Day 1 of each cycle (Q3W)	IV infusion via infusion pump	Placebo	IMP	Provided locally by the study site, subsidiary, or designee
FP							
Cisplatin[c]	Vial	1 mg/mL vial 20 mg vial	80 mg/m^2 on Day 1 of each cycle (Q3W)	IV infusion	Comparator regimen and combination agent	NIMP	Provided centrally by the Sponsor or locally by the study site, subsidiary, or designee
5-FU	Vial	25 mg/mL vial 50 mg/mL vial	800 mg/m^2/day continuous on Days 1-5 of each cycle (Q3W) (120 hours, or per local standard)	IV infusion	Comparator regimen and combination agent	NIMP	Provided centrally by the Sponsor or locally by the study site, subsidiary, or designee
CAPOX							
Oxaliplatin[d]	Vial	5 mg/mL vial 50 mg vial	130 mg/m^2 on Day 1 of each cycle (Q3W) over 2 hours	IV infusion	Comparator regimen and combination agent	NIMP	Provided centrally by the Sponsor or locally by the study site, subsidiary, or designee
Capecitabine	Tablet	150 mg tablet 500 mg tablet	1000 mg/m^2 bid on Days 1-14 of each cycle (Q3W)	Oral	Comparator regimen and combination agent	NIMP	Provided centrally by the Sponsor or locally by the study site, subsidiary, or designee
SOX (Japan only)							
S-1	Capsule	20 mg capsule 25 mg capsule	<1.25 m^2 BSA 40 mg bid on Days 1-14 of each cycle (Q3W). 1.25 to <1.5 m^2 BSA 50 mg bid on Days 1-14 of each cycle (Q3W). ≥1.5 m^2 BSA 60 mg bid on Days 1-14 of each cycle (Q3W).	Oral	Comparator regimen and combination agent	NIMP	Provided locally by the study site, subsidiary, or designee
Oxaliplatin	Vial	5 mg/mL vial 50 mg vial	130 mg/m^2 on Day 1 of each cycle (Q3W) over 2 hours	IV infusion	Comparator regimen and combination agent	NIMP	Provided locally by the study site, subsidiary, or designee
Trastuzumab[a]							
Trastuzumab	Vial	60 mg vial (Japan only) 150 mg vial 440 mg vial 600 mg vial	8 mg/kg loading dose, and then 6 mg/kg maintenance thereafter (Q3W)	IV infusion	Comparator regimen and combination agent	NIMP	Provided centrally by the Sponsor or locally by the study site, subsidiary, or designee

5-FU=5-fluorouracil; bid=2 times a day; BSA=body surface area; CAPOX=capecitabine/oxaliplatin; CDHP=5-chloro-2,4-dihydroxypyridine; FP= 5-fluorouracil plus cisplatin; IMP=Investigational Medicinal Product; IV=intravenous; N/A=not applicable; NIMP=Non-Investigational Medicinal Product; Oxo=potassium oxonate; Q3W=every 3 weeks; S-1=combination product containing tegafur, a prodrug of 5-FU, and 2 types of enzyme inhibitors, CDHP and Oxo; SOX=S-1 plus oxaliplatin.

[a] Pembrolizumab/trastuzumab will be administered until disease progression or other withdrawal criteria are met.

[b] The strength of treatment may vary depending on the source. The table captures the current available strengths, but could vary depending on availability.

[c] Duration of cisplatin treatment may be capped at 6 cycles as per local country guidelines; however, treatment with 5-FU may continue per protocol.

[d] Duration of oxaliplatin may be capped at 6 or 8 cycles as per local country guidelines; however, treatment with capecitabine may continue per protocol.

Definition of IMP and NIMP are based on guidance issued by the European Commission. Regional and/or Country differences of the definition of IMP/NIMP may exist. In these circumstances, local legislation is followed.

Objectives/Outcomes/Endpoints

Objective/Hypothesis	Endpoint
Primary	
• Objective: To compare PFS between treatment groups. • Hypothesis (H1): Pembrolizumab in combination with trastuzumab plus chemotherapy is superior to trastuzumab plus chemotherapy alone in terms of PFS per RECIST 1.1 as assessed by blinded independent central review (BICR).	• PFS: The time from randomization to the first documented disease progression or death due to any cause, whichever occurs first.

• Objective: To compare OS between treatment groups. • Hypothesis (H2): Pembrolizumab in combination with trastuzumab plus chemotherapy is superior to trastuzumab plus chemotherapy alone in terms of OS.	• OS: The time from randomization to death due to any cause.
Secondary	
• Objective: To compare ORR between treatment groups. Hypothesis (H3): Pembrolizumab in combination with trastuzumab plus chemotherapy is superior to trastuzumab plus chemotherapy alone per RECIST 1.1 as assessed by BICR in terms of ORR.	• Objective Response (OR): Complete response (CR) or partial response (PR)
• Objective: To estimate DOR, per RECIST 1.1 as assessed by BICR for each treatment group.	• DOR: The time from first response (CR or PR) to subsequent disease progression or death from any cause, whichever occurs first.
• Objective: To assess the safety and tolerability of pembrolizumab in combination with trastuzumab plus chemotherapy by proportion of adverse events (AEs).	• Adverse events • Discontinuation of study treatment due to AEs
Tertiary/Exploratory	
• Objective: To compare the change from baseline in health-related quality of life using the EORTC QLQ-C30 and the EORTC QLQ-STO22 among participants when treated with pembrolizumab in combination with trastuzumab plus chemotherapy compared to trastuzumab plus chemotherapy alone.	• EORTC QLQ-C30 and EORTC QLQ-STO22 score.

Objective/Hypothesis	Endpoint
• Objective: To characterize utilities using EuroQoL EQ-5D among participants when treated with pembrolizumab in combination with trastuzumab plus chemotherapy compared to trastuzumab plus chemotherapy alone.	• Health utility scores assessed from the EQ-5D-5L
• Objective: To evaluate the genetic and genomic correlates of treatment in pre- and post-treatment blood samples where available.	• Expression of PD-1, PD-L1 and PD-L2 by IHC or ribonucleic acid (RNA) sequencing. • Genetic alterations in PD-1, PD-L1 and PD-L2 on chromosome 9p24.1 by fluorescent in situ hybridization (FISH).
• Objective: 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	• Germline genetic variation, genetic (DNA) mutations from tumor, tumor and blood RNA variation, proteomics and IHC, and other biomarkers
• To compare PFS and ORR using modified RECIST 1.1 for immune-based therapeutics (iRECIST), as assessed by the investigator, following administration of pembrolizumab versus placebo when each is combined with chemotherapy	• PFS using iRECIST • OR using iRECIST

Sample size

The study was planned to randomize approximately 692 participants in the Global Cohort in a 1:1 ratio to receive either pembrolizumab or placebo in combination with trastuzumab plus chemotherapy (FP or CAPOX). An additional 40 participants were planned to be randomized in the study as a Japan-specific SOX Cohort in a 1:1 ratio between the 2 arms. Data from this cohort has been analyzed separately from the Japanese Global Cohort participants, who were randomized as part of the Global Cohort and follow the FP or CAPOX treatment regimens to which they are assigned.

Sample Size and Power Calculations for PFS and OS

The study includes dual-primary efficacy endpoints: 1) PFS per RECIST 1.1 as assessed by BICR and 2) OS.

The sample size (number of participants) calculations were based on the following assumptions: (1) the enrollment period was 28 months and the ramp-up period of enrolment was 6 months; (2) the duration of PFS and OS is assumed to follow an exponential distribution; (3) median PFS was assumed

to be 6.7 months in the control group with a true HR of 0.7; (4) median OS was assumed to be 13.8 months in the control group with a true HR ratio of 0.75.

Progression-free Survival

It was expected that with approximately 606 PFS events at final analysis (FA), the study has approximately 95% power for detecting a HR of 0.7 at an initially assigned 0.003 (1-sided) significance level.

Overall Survival

It was expected that with approximately 551 deaths at FA, the study has approximately 90% power for detecting an HR of 0.75 at an initially assigned 0.020 (1-sided) significance level.

Software used for sample size calculation

Power and interim analyses calculations were performed using the gsDesign R package.

Randomisation

Treatment allocation/randomization occurred centrally using an interactive response technology (IRT) system. There are 2 study treatment arms. Participants were assigned randomly in a 1:1 ratio to pembrolizumab and saline placebo, respectively.

Treatment randomization was stratified based on the following criteria:

1. For Global cohort only:
   - Geographic region (Europe/Israel/North America/Australia versus Asia versus Rest of the World including South America)
   - PD-L1 status (positive (CPS≥1) versus negative (CPS<1))
   - Chemotherapy regimen (FP or CAPOX), which was chosen prior to randomization in the study.
2. Japan-specific SOX cohort:
   - Disease status (ECOG 0 versus ECOG 1)

Blinding (masking)

This study has been conducted as a double-blind study under in-house blinding procedures. The participant and the investigator who were involved in the study treatment administration or clinical evaluation of the participants were unaware of the group assignments. Pembrolizumab and placebo were prepared and/or dispensed in a blinded fashion by an unblinded pharmacist or other qualified site personnel dispensed in a blinded fashion by an unblinded pharmacist or unblinded qualified study site.

The official, final database has not been unblinded until medical/scientific review has been performed, protocol deviations have been identified, and data have been declared final and complete. Related to the planned interim analyses, an external Data Monitoring Committee (DMC) served as the primary reviewer of the results of the interim analyses of the study and had the role to make (if needed) recommendations for discontinuation or protocol modifications to an executive committee of the Sponsor who might have been unblinded to results at treatment level in order to act on these recommendations.

Statistical methods

Protocol Amendments involving statistical methods

The protocol was subject to eight amendments, of which Amendment 5 (20-May-2020), Amendment 6 (07-Jul-2020) and Amendment 8 (07-Apr-2022) modified the SAP language as follows.

Amendment 5 (20-May-2020): PFS endpoint was added to the first interim analysis (IA1) as an administrative look and futility analysis for ORR was removed from the IA1. The protocol was also updated to clarify how to handle with participants with positive response to study treatment resulting in the opportunity to have curative surgical resection. Among these patients, only patients who had CR or PR prior to the curative surgical resection were used for ORR endpoint. In addition, the associated primary censoring rules of PFS were updated and a sensitivity analysis of PFS in which participants were censored at the time of curative surgical resection were added.

Amendment 6 (07-Jul-2020): Based on Regulatory Authority input, the data might have been immature for PFS at time of IA1 since the enrolment was not completed. For this reason the PFS endpoint was removed from IA1.

Amendment 8 (07-APR-2022): To accommodate the situation in case of significantly slower than anticipated accrual of PFS and/or OS events, greater flexibility of the timing of second interim analysis (IA2), third interim analysis (IA3) and FA has been introduced, allowing the Sponsor to conduct the analyses with up to 3 additional months of follow-up than the minimal follow-up as described above, or when the specified number of events are observed, whichever comes first. In addition, a clarification regarding the alpha spending at FA for PFS and OS hypothesis testing has been added; only the remaining Type I error that has not been spent at earlier analyses can be used during the FA.

The table below shows the history of changes.

Document	Date of Issue	Overall Rationale
Amendment 8	07-APR-2022	To update SAP language for the flexibility of the timing of the interim and final efficacy analyses in case of significantly slower than anticipated accrual of PFS and/or OS events
Amendment 7	24-JUN-2021	To update the pembrolizumab dose-modification and toxicity-management guidelines for irAEs and update protocol language to allow option for standard of care treatment beyond 35 cycles.
Amendment 6	07-JUL-2020	Update SAP language to remove PFS analysis for IA1 in response to Regulatory Authority Input.
Amendment 5	20-MAY-2020	Update protocol and SAP language regarding the definition of the curative surgical resection and modification of PFS primary censoring rule associated with the curative surgical resection, remove the ORR futility analysis for IA1, and add a PFS analysis for IA1.
Amendment 4	27-FEB-2019	Update Biomarker Collection Information.
Amendment 3	24-JAN-2019	Response to Regulatory Authority Input.
Amendment 2	16-AUG-2018	Response to Regulatory Authority Input.
Amendment 1	31-MAY-2018	Response to Regulatory Authority Input.
Original Protocol	11-APR-2018	N/A

Interim Analyses

There are three planned interim analyses (IA) in addition to the final analysis (FA) for this study. The efficacy analyses in this submission are based on IA2. The timing and the purpose of each analysis are summarized in the table below.

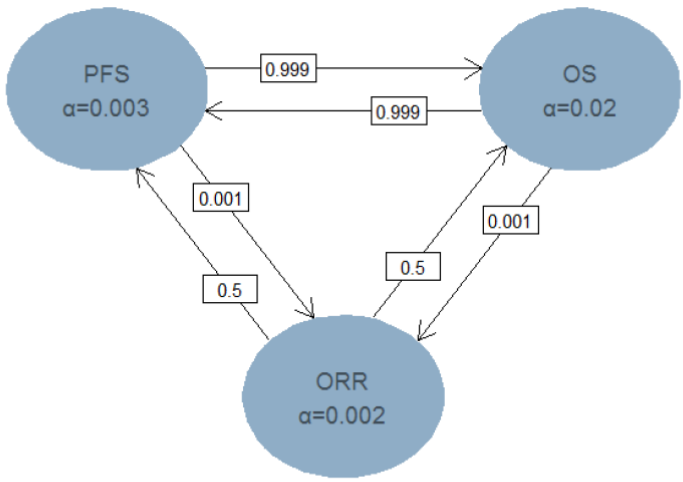
Analysis	**Timing**	**Estimated time after first Participant Randomized**	**Primary Purpose of Analysis**
IA1	The first 260 participants with approximately 8.5 months follow-up.	~ 22.5 months	• Efficacy analysis of OR
IA2[a]	**Approximately 542 PFS events have occurred and ~ 9 months after the last participant has been randomized.**	**~ 37 months**	• **Efficacy analysis for PFS and OS**
IA3[a]	Approximately 18 months after the last participant has been randomized AND ~ 606 PFS events have been observed. This is final PFS analysis.	~ 46 months	• Efficacy analysis for PFS and OS

Final Analysis[a]	Final OS analysis to be performed until approximately 28 months after the last participant has been randomized AND ~ 551 deaths have occurred.	~ 56 months	• Efficacy analysis for OS
ORR = Objective Response Rate; OS= Overall Survival; PFS = Progression-free Survival [a]Note for IA2, IA3, and FA, if the events accrue slower than expected, the Sponsor may conduct the analysis with up to 3 additional months of follow-up than the minimal follow-up as described above, or when the specified number of events are observed, whichever comes first.			

At the time of data cutoff (25-MAY-2022) for IA2, approximately 484 PFS events (234 in the pembrolizumab plus SOC group and 250 in the SOC group) and 415 OS events (202 in the pembrolizumab plus SOC group and 213 in the SOC group) occurred. Median duration of follow-up in the ITT population (N=698) was 16.1 months (range: 0.6 to 41.6 months) and 14.8 months (range: 0.3, 41.2 months) in the pembrolizumab plus SOC group and SOC group, respectively. For CPS ≥1, the median duration of follow-up of participants was 17.0 months (range: 0.6 to 41.6 months) and 13.9 months (range: 0.3 to 41.2 months) in the pembrolizumab plus SOC group and SOC group, respectively, which was consistent with the ITT population.

Error probabilities, adjustment for multiplicity

The trial used an extension of the graphical method of Maurer and Bretz to provide strong multiplicity control for multiple hypotheses while making the interim and final analysis timing be more flexible. 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 rate among the multiple hypotheses was strongly controlled at 2.5% (one-sided). Figure below shows the Type I Error Reallocation Strategy according to Protocol Amendment 8.



Note: If both PFS and OS null hypotheses are rejected, the reallocation strategy allows re-testing of ORR at alpha=0.025 based on the p-value at IA1.

IA1=interim analysis 1; ORR=objective response rate; OS=overall survival; PFS=progression-free survival.

The initial 1-sided alpha allocation for each hypothesis in the ellipse representing the hypothesis. The weights for reallocation from each hypothesis to the others are represented in the boxes on the lines connecting hypotheses. The extended graphical method spends alpha as a function of the minimum of the actual event information fraction and the expected event information fraction. This ensures that

the actual spending will be no more aggressive than the planned, while at the same time ensuring that not all alpha is spent prior to final planned event counts.

ORR

The study initially allocated alpha=0.002, 1-sided, to test ORR, and ORR was tested only at the IA1. However, if the test did not reach statistical significance at IA1, the p-value from IA1 could has been compared to an updated alpha-level if the null hypotheses for both PFS and OS were rejected at a later time. Power at the possible alpha-levels as well as the approximate treatment difference required to reach the bound (ORR difference) at Interim Analysis 1 are shown in the table below.

Alpha	ORR difference	Power
0.002	~ 0.17	0.90
0.025	~ 0.11	0.99

PFS

The initial alpha-level for testing PFS was 0.003. If the null hypothesis for ORR was rejected, half of its alpha was reallocated to PFS hypothesis testing. If the null hypothesis for OS was rejected, then alpha=0.02 was essentially fully reallocated to PFS hypothesis testing. Thus, the PFS null hypothesis might be tested at alpha=0.003, alpha=0.004 (if the ORR null hypothesis was rejected but not the OS null hypothesis), alpha=0.023 (if the OS null hypothesis was rejected but not the ORR null hypothesis), or alpha=0.025 (if both the ORR and OS null hypotheses were rejected). Table below shows the boundary properties for each of these alpha-levels for the interim analyses, which were derived using a Lan-DeMets O'Brien-Fleming spending function based on predicted number of events at the planned time of interim analysis. The final row indicates the total power to reject the null hypothesis for PFS at each alpha-level.

Analysis	Value	α=0.003	α=0.004	α=0.023	α=0.025
IA 2: 90%[a] N: 692 Events: 542 Month: 37	Z	2.927	2.826	2.137	2.1
	p (1-sided)[b]	0.0017	0.0024	0.0163	0.0179
	HR at bound[c]	0.7777	0.7849	0.8326	0.8353
	P(Cross) if HR=1[d]	0.0017	0.0024	0.0163	0.0179
	P(Cross) if HR=0.7[e]	0.8915	0.9091	0.9785	0.9804
IA 3: 100%[a] N: 692 Events: 606 Month: 46	Z	2.807	2.714	2.086	2.052
	p (1-sided)[b]	0.0025	0.0033	0.0185	0.0201
	HR at bound[c]	0.796	0.8024	0.8444	0.8467
	P(Cross) if HR=1[d]	0.003	0.004	0.023	0.025
	P(Cross) if HR=0.7[e]	0.9475	0.9569	0.9909	0.9917

HR = Hazard Ratio; IA = interim analysis
[a] Percentage of expected number of events at final analysis
[b] p (1-sided) is the nominal alpha for testing.
[c] HR at bound is the approximate HR required to reach an efficacy bound
[d] P(Cross if HR=1) is the cumulative probability of crossing a bound under the null hypothesis
[e] P(Cross if HR=0.7) is the cumulative probability of crossing a bound under the alternative hypothesis

The event counts for all analyses was used to compute correlations. Also note that if the OS or ORR null hypothesis was rejected at an interim or final analysis, each PFS interim and final analysis test might be compared to its updated bounds considering the alpha reallocation from the OS or ORR hypothesis.

OS

The OS hypothesis may be tested at alpha=0.02 (initially allocated alpha), alpha=0.023 (if the PFS but not the ORR null hypothesis was rejected), alpha=0.021(if the ORR but not the PFS null hypothesis was rejected), or alpha=0.025 (if both the ORR and PFS null hypotheses weree rejected). Table below shows the bounds and boundary properties for OS hypothesis testing derived using a Lan-DeMets O'Brien-Fleming spending function based on the predicted number of events at the planned time of interim analysis.

Analysis	Value	α=0.02	α=0.021	α=0.023	α=0.025
IA 2: 73%[a] N: 692 Events: 401 Month: 37	Z	2.493	2.47	2.426	2.385
	p (1-sided)[b]	0.0063	0.0068	0.0076	0.0085
	HR at bound[c]	0.7794	0.7815	0.7849	0.7881
	P(Cross) if HR=1[d]	0.0063	0.0068	0.0076	0.0085
	P(Cross) if HR=0.75[e]	0.6513	0.6598	0.6757	0.6902
IA 3: 89%[a] N: 692 Events: 488 Month: 46	Z	2.272	2.252	2.213	2.178
	p (1-sided)[b]	0.0115	0.0122	0.0134	0.0147
	HR at bound[c]	0.814	0.8158	0.8186	0.8212
	P(Cross) if HR=1[d]	0.0134	0.0142	0.0157	0.0172
	P(Cross) if HR=0.75[e]	0.8263	0.8316	0.8413	0.85
Final N: 692 Events: 551 Month: 56	Z	2.152	2.133	2.097	2.064
	p (1-sided)[b]	0.0157	0.0165	0.018	0.0195
	HR at bound[c]	0.8325	0.834	0.8366	0.8389
	P(Cross) if HR=1[d]	0.02	0.021	0.023	0.025
	P(Cross) if HR=0.75[e]	0.9001	0.9035	0.9097	0.9151

HR = Hazard Ratio; IA = interim analysis
[a] Percentage of expected number of events at final analysis
[b] p (1-sided) is the nominal α for testing.
[c] HR at bound is the approximate HR required to reach an efficacy bound.
[d] P(Cross if HR=1) is the cumulative probability of crossing a bound under the null hypothesis.
[e] P(Cross if HR=0.75) is the cumulative probability of crossing a bound under the alternative hypothesis.

The event counts for all analyses were used to compute correlations. Also note that if the PFS or ORR null hypothesis were rejected at an interim or final analysis, each OS interim and final analysis test might be compared to its updated bounds considering the alpha reallocation from the PFS or ORR hypothesis.

Efficacy analyses

The Intention-to-Treat (ITT) population, which consisted of all 698 randomized participants, served as the population for primary efficacy analyses. Any participant who receives a randomization number was considered to have been randomized. Participants were included in the treatment group to which they are randomized, regardless of whether they received study treatment. The ITT population excluding MSI-H participants served as the sensitivity analysis for the endpoints of PFS per RECIST 1.1 by BICR, OS, and ORR per RECIST 1.1 per BICR.

A summary of the analysis strategy for key efficacy endpoints as well as censoring rules for primary and sensitivity analyses of PFS are presented in the following tables:

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

PFS = Progression-free survival; OS = Overall survival; ORR = Objective response rate; ITT = Intention to treat.

† Statistical models are described in further detail in the text. For stratified analyses, the stratification factors used for randomization (Protocol Section 6.3.1.1) will be applied to the analysis. Small strata will be combined in a way specified by a blinded statistician prior to the analysis.

†† Miettinen and Nurminen method

Table 1 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 anti-cancer 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 anti-cancer therapy, if any	Censored at last disease assessment prior to the earlier date of ≥ 2 consecutive missed disease assessment and new anti-cancer 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 treatment or completed study treatment.
No PD and no death; new anticancer treatment is initiated	Censored at last disease assessment before new anticancer treatment	Censored at last disease assessment	Progressed at date of initiation of new anticancer treatment or discontinuation of treatment due to reasons other than complete response, whichever occurs later

New anti-cancer therapy: excluding curative surgical resections (the detailed definition in Protocol Section 6.5.3).

Table 2 Censoring Rules for DOR

Situation	Date of Progression or Censoring	Outcome
No progression nor death, no new anti-cancer therapy initiated	Last adequate disease assessment	Censor (non-event)
No progression nor death, new anti-cancer therapy[#] initiated	Last adequate disease assessment before new anti-cancer therapy initiated	Censor (non-event)
Death or progression immediately after ≥ 2 consecutive missed disease assessments or after new anti-cancer therapy[#], if any	Earlier date of last adequate disease assessment prior to ≥ 2 missed adequate disease assessments and new anti-cancer therapy, if any	Censor (non-event)
Death or progression after ≤ 1 missed disease assessments and before new anti-cancer therapy[#], if any	PD or death	End of response (Event)
A missed disease assessment includes any assessment that is not obtained or is considered inadequate for evaluation of response. [#]new anti-cancer therapy: excluding curative surgical resections (the detailed definition in Protocol Section 6.5.3).		

The non-parametric Kaplan-Meier method was used to estimate the PFS and OS curve in each treatment group. The treatment difference in PFS and OS was assessed by the stratified log-rank test. For PFS and OS a stratified Cox proportional hazard model with Efron's method of tie handling was used to assess the magnitude of the treatment difference between the treatment arms. The hazard ratio (HR) and its 95% confidence interval (CI) from the stratified Cox model with Efron's method of tie handling and with a single treatment covariate was reported. The same stratification factors used for randomization were applied to both the stratified log-rank test and the stratified Cox model.

For OS analysis, participants without documented death at the time of analysis will be censored at the date of last contact.

In order to evaluate the robustness of the PFS endpoint, one primary and two sensitivity analyses with a different set of censoring rules were performed. The censoring rules for primary and sensitivity analyses are summarized in Table 1.

Sensitivity analyses to adjust for the effect of treatment switching to other PD-1 or other new anticancer therapies on OS may be performed as model assumptions permit. Three recognized methods may be included: 1) the Rank Preserving Structural Failure Time (RPSFT) model proposed by Robins and Tsiatis (1989); 2) the two-stage model proposed by Latimer; and 3) the Inverse-Probability-of-Censoring Weighting (IPCW) model in which an examination of the appropriateness of the data to the assumptions is required by the methods. Other sensitivity analyses described for the PFS endpoint were applied to OS endpoint as appropriate.

The stratified Miettinen and Nurminen method was used for the comparison of the ORR between the two treatment groups. The difference in ORR and its 95% confidence interval from the stratified Miettinen and Nurminen method with strata weighting by sample size was reported. The stratification factors used for randomization were applied to the analysis. The same strategy of combination of small strata defined for the PFS analysis was used for the ORR analysis. The descriptive analysis of ORR based on all participants was performed after IA1. No formal hypothesis testing was conducted.

DOR was summarised descriptively using Kaplan-Meier medians and quartiles. Only the subset of patients who show a complete response (CR) or partial response (PR) were included in this analysis. For each DOR analysis, a corresponding summary of the censoring reasons for responding participant were also provided. Responding subjects who were alive, had not progressed, had not initiated new anti-cancer treatment, had not been determined to be lost to follow-up, and had a disease assessment

within ~5 months of the data cutoff date were considered ongoing responders at the time of analysis. If a subject met multiple criteria for censoring, the censoring criterion that occurs earliest was applied. Censoring rules for DOR are summarized in Table 2.

Subgroup analyses

Subgroup Analyses and Effect of Baseline Factors are planned. To determine whether the treatment effect is consistent across various subgroups, the between-group treatment effect for PFS and OS (with a nominal 95% CI) was estimated and plotted by treatment group within each category of the following classification variables: Age category: (<65 versus ≥65 years); Sex: (female, male); Race: (Asian versus non-Asian); Region: Europe/Israel/North America/Australia versus Asia versus Rest of World (including South America); PD-L1: Positive versus Negative: MSI status; Primary location: Stomach versus GEJ; Histological subtype: Diffuse versus intestinal versus indeterminate; Tumor Burden: ≥ median versus <median; Number of Metastases: ≤2 versus ≥3; Prior Gastrectomy/Esophagectomy: yes versus no; Baseline ECOG : 0 versus 1; Region: US versus ex-US; Chemotherapy regimen: FP or CAPOX.

The consistency of the treatment effect was assessed descriptively via summary statistics by category for the classification variables listed above. If any level of a subgroup variable had fewer than 20 participants, above analysis could not be performed for that level of the subgroup variable. The subgroup analyses for PFS and OS were conducted using an unstratified Cox model, and the subgroup analyses for ORR were conducted using the unstratified Miettinen and Nurminen method.

Safety analyses

Safety analyses were based on the APaT population, which included all 696 randomized participants who received at least 1 dose of study intervention. The analysis of safety results followed a tiered approach as shown in the table below. There were no Tier 1 endpoints in this study, and Tier 2 parameters were assessed via point estimates with 95% CIs provided for provided for between group comparisons; only point estimates by intervention arm were provided for Tier 3 safety parameters. Because many 95% CIs were provided without adjustment for multiplicity, the analysis represents a helpful descriptive measure to be used in review, not a formal method for assessing the statistical significance of the between-group differences. These analyses were performed using the Miettinen and Nurminen method, an unconditional, asymptotic method.

Table 4 Analysis Strategy for Safety Parameters

Safety Tier	Safety Endpoint	95% CI for Treatment Comparison	Descriptive Statistics
Tier 2	AEs (≥10% of participants in one of the treatment groups)	X	X
	Grade 3-5 AEs (≥5% of participants in one of the treatment groups)	X	X
	SAEs (5% of participants in one of the treatment groups)	X	X
	AEs (<10% of participants in one of the treatment groups)		X
Tier 3	Discontinuation due to AE		X
	Change from Baseline Results (laboratory test toxicity grade)		X
X = results will be provided.			

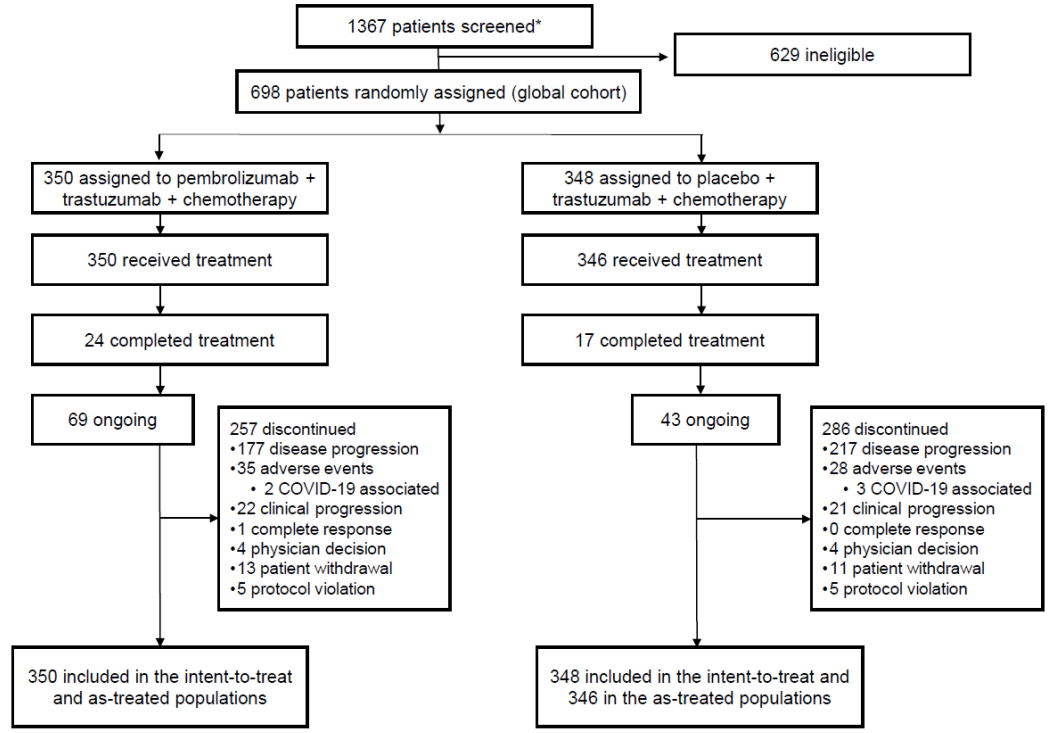
PRO analyses

The patient-reported outcomes were exploratory objectives in KEYNOTE 811, and thus no formal hypotheses were formulated. 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 participants in the ITT population who had at least 1 PRO assessment and received at least 1 dose of study intervention.

Results

Participant flow



* Patients screened includes both Global and Japan cohorts

Recruitment

A total of 1367 participants were screened in the study and 698 were randomized across 92 study sites in 19 countries.

All nonrandomized participants were screen failures.

Table 10-2
Disposition of Participants
(Global Cohort)
(ITT Population)

	Pembrolizumab + SOC		SOC	
	n	(%)	n	(%)
Participants in population	350		348	
Status for Study Medication of Treatment Phase				
Started	350		346	
Completed	24	(6.9)	17	(4.9)
Discontinued	257	(73.4)	286	(82.7)
Adverse Event	35	(10.0)	28	(8.1)
Associated with COVID-19	2	(0.6)	3	(0.9)
Clinical Progression	22	(6.3)	21	(6.1)
Complete Response	1	(0.3)	0	(0.0)
Non-Study Anti-Cancer Therapy	5	(1.4)	5	(1.4)
Physician Decision	4	(1.1)	4	(1.2)
Progressive Disease	177	(50.6)	217	(62.7)
Withdrawal By Subject	13	(3.7)	11	(3.2)
Participants Ongoing	69	(19.7)	43	(12.4)
Status for Trial				
Discontinued	202	(57.7)	214	(61.5)
Death	201	(57.4)	211	(60.6)
Associated with COVID-19	2	(0.6)	3	(0.9)
Withdrawal By Subject	1	(0.3)	3	(0.9)
Not Associated with COVID-19, No Further Information	0	(0.0)	1	(0.3)
Not Associated with COVID-19, Subsequently Died	1	(0.3)	2	(0.6)
Participants Ongoing	148	(42.3)	134	(38.5)

If the overall count of participants is calculated and displayed within a section in the first row, then it is used as the denominator for the percentage calculation. Otherwise, participants in population is used as the denominator for the percentage calculation.
For the status for study medication of treatment phase, participants treated with study medication is used as the denominator for percentage calculation.
For the status for trial, participants in population is used as the denominator for percentage calculation.
Database Cutoff Date: 25MAY2022

Source: [P811V02MK3475: adam-adsl]

Table 10-3
Summary of Follow-up Duration
(Global Cohort)
(ITT Population)

Follow-up duration (months)[a]	Pembrolizumab + SOC (N=350)	SOC (N=348)	Total (N=698)
Median (Range)	16.1 (0.6, 41.6)	14.8 (0.3, 41.2)	15.4 (0.3, 41.6)
Mean (SD)	17.7 (10.0)	16.4 (10.0)	17.1 (10.0)

[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.
N is the number of participants in population.
Database Cutoff Date: 25MAY2022

Source: [P811V02MK3475: adam-adsl]

Conduct of the study

Important protocol deviations were reported for 35 and 27 participants in the pembrolizumab plus SOC and SOC groups, respectively. Of these, 4 participants in the pembrolizumab plus SOC group and 1 participant in the SOC group had important protocol deviations that were considered to be clinically important. The 4 participants in the pembrolizumab plus SOC group had clinically important protocol deviations related to study intervention as described in the table below.

Table 10-4
Summary of Important Protocol Deviations Considered to be Clinically Important
(Global Cohort)
(ITT Population)

	Pembrolizumab + SOC		SOC	
	n	(%)	n	(%)
Participants in population	350		348	
with one or more clinically important protocol deviations	4	(1.1)	1	(0.3)
with no clinically important protocol deviations	346	(98.9)	347	(99.7)
Study Intervention	**4**	**(1.1)**	**0**	**(0.0)**
Participant was administered improperly stored study intervention that was deemed unacceptable for use.	2	(0.6)	0	(0.0)
Participant was dispensed study intervention other than what was assigned in the allocation schedule, i.e. incorrect medication or potential cross-treatment.	2	(0.6)	0	(0.0)
Trial Procedures	**0**	**(0.0)**	**1**	**(0.3)**
Failure to conduct key safety or efficacy assessments	0	(0.0)	1	(0.3)

Every participant is counted a single time for each applicable row and column.
Database Cutoff Date: 25MAY2022.

Source: [P811V02MK3475: adam-adsl] [P811V02MK3475: sdtm-dv; suppdv]

Baseline data

Table 10-5
Participant Characteristics
(Global Cohort)
(ITT Population)

	Pembrolizumab + SOC		SOC		Total	
	n	(%)	n	(%)	n	(%)
Participants in population	350		348		698	
Sex						
Male	284	(81.1)	280	(80.5)	564	(80.8)
Female	66	(18.9)	68	(19.5)	134	(19.2)
Age (Years)						
< 65	205	(58.6)	192	(55.2)	397	(56.9)
>= 65	145	(41.4)	156	(44.8)	301	(43.1)
Mean	60.4		61.7		61.0	
SD	11.8		10.8		11.3	
Median	62.0		63.0		63.0	
Range	19 to 85		32 to 85		19 to 85	
Race						
American Indian Or Alaska Native	5	(1.4)	6	(1.7)	11	(1.6)
Asian	119	(34.0)	121	(34.8)	240	(34.4)
Black Or African American	2	(0.6)	2	(0.6)	4	(0.6)
Multiple	6	(1.7)	5	(1.4)	11	(1.6)
White	217	(62.0)	209	(60.1)	426	(61.0)
Missing	1	(0.3)	5	(1.4)	6	(0.9)
Ethnicity						
Hispanic Or Latino	38	(10.9)	45	(12.9)	83	(11.9)
Not Hispanic Or Latino	309	(88.3)	292	(83.9)	601	(86.1)
Not Reported	1	(0.3)	10	(2.9)	11	(1.6)
Unknown	2	(0.6)	1	(0.3)	3	(0.4)
Age Group (Years)						
18-39	19	(5.4)	14	(4.0)	33	(4.7)
40-49	44	(12.6)	30	(8.6)	74	(10.6)
50-59	73	(20.9)	99	(28.4)	172	(24.6)
60-69	135	(38.6)	109	(31.3)	244	(35.0)
70-79	74	(21.1)	88	(25.3)	162	(23.2)
>=80	5	(1.4)	8	(2.3)	13	(1.9)

	Pembrolizumab + SOC		SOC		Total	
	n	(%)	n	(%)	n	(%)
Age Group 2 (Years)						
< 65	205	(58.6)	192	(55.2)	397	(56.9)
65 - 74	117	(33.4)	121	(34.8)	238	(34.1)
75 - 84	27	(7.7)	34	(9.8)	61	(8.7)
85+	1	(0.3)	1	(0.3)	2	(0.3)
Geographic Region of Enrolling Site						
Western Europe/Israel/North America/Australia	113	(32.3)	111	(31.9)	224	(32.1)
Asia	118	(33.7)	119	(34.2)	237	(34.0)
Rest of the World	119	(34.0)	118	(33.9)	237	(34.0)
ECOG Performance Scale						
0	146	(41.7)	145	(41.7)	291	(41.7)
1	204	(58.3)	202	(58.0)	406	(58.2)
Missing	0	(0.0)	1	(0.3)	1	(0.1)
Primary Location at Diagnosis						
Adenocarcinoma of the gastroesophageal junction	110	(31.4)	122	(35.1)	232	(33.2)
Adenocarcinoma of the stomach	240	(68.6)	226	(64.9)	466	(66.8)
Current Disease Overall Stage						
IIB	1	(0.3)	0	(0.0)	1	(0.1)
IIIA	2	(0.6)	1	(0.3)	3	(0.4)
IIIB	5	(1.4)	2	(0.6)	7	(1.0)
IIIC	2	(0.6)	3	(0.9)	5	(0.7)
IV	340	(97.1)	342	(98.3)	682	(97.7)
Disease Status						
Locally advanced	10	(2.9)	7	(2.0)	17	(2.4)
Metastatic	340	(97.1)	341	(98.0)	681	(97.6)
Number of Metastatic Sites						
0-2	182	(52.0)	200	(57.5)	382	(54.7)
>=3	168	(48.0)	148	(42.5)	316	(45.3)

	Pembrolizumab + SOC		SOC		Total	
	n	(%)	n	(%)	n	(%)
Histological Subtype (Lauren classification)						
Diffuse	70	(20.0)	58	(16.7)	128	(18.3)
Intestinal	197	(56.3)	185	(53.2)	382	(54.7)
Indeterminate	83	(23.7)	105	(30.2)	188	(26.9)
Prior Gastrectomy/Esophagectomy						
Yes	51	(14.6)	64	(18.4)	115	(16.5)
No	299	(85.4)	284	(81.6)	583	(83.5)
PD-L1 Status (CPS>=1)						
Positive	298	(85.1)	296	(85.1)	594	(85.1)
Negative	52	(14.9)	52	(14.9)	104	(14.9)
Tumor Burden						
< Median	161	(46.0)	166	(47.7)	327	(46.8)
>= Median	172	(49.1)	170	(48.9)	342	(49.0)
Missing	17	(4.9)	12	(3.4)	29	(4.2)
HER2 Status						
IHC 1+	1	(0.3)	1	(0.3)	2	(0.3)
IHC 2+ ISH Equivocal	0	(0.0)	1	(0.3)	1	(0.1)
IHC 2+ ISH Negative	1	(0.3)	1	(0.3)	2	(0.3)
IHC 2+ ISH Positive	62	(17.7)	84	(24.1)	146	(20.9)
IHC 3+	286	(81.7)	261	(75.0)	547	(78.4)
MSI Status						
MSI High	6	(1.7)	2	(0.6)	8	(1.1)
non-MSI-High	326	(93.1)	329	(94.5)	655	(93.8)
Unknown	18	(5.1)	17	(4.9)	35	(5.0)
Chemotherapy Regimen						
CAPOX	297	(84.9)	299	(85.9)	596	(85.4)
FP	53	(15.1)	49	(14.1)	102	(14.6)

Western Europe includes Belgium, France, Germany, Spain, Italy, United Kingdom, Ireland, Latvia, Lithuania, which is consistent with the 'Europe' region defined in the protocol for stratification.
Database Cutoff Date: 25MAY2022.

Source: [P811V02MK3475: adam-adsl]

Numbers analysed

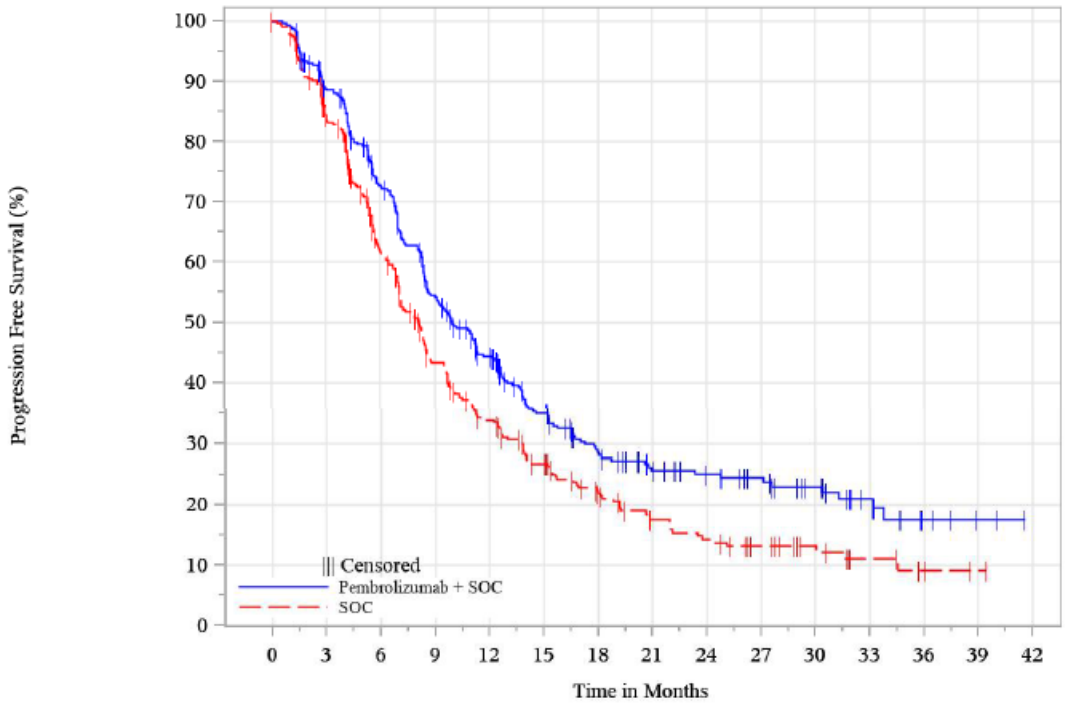
The ITT population, which consisted of all 698 randomized participants, whether or not treatment was administered, served as the population for primary efficacy analyses.

Outcomes and estimation

Primary Endpoints

Progression Free Survival (PFS)

Figure 11-1
Kaplan-Meier Estimates of Progression-Free Survival (Primary Analysis)
Based on BICR Assessment per RECIST 1.1
(Global Cohort)
(ITT Population)



Number of Subjects at Risk

Pembrolizumab + SOC	350	296	234	171	129	90	65	50	42	34	26	14	5	2	0
SOC	348	273	183	120	90	66	47	32	26	19	13	7	3	1	0

Database Cutoff Date: 25MAY2022.

Source: [P811V02MK3475: adam-adsl; adtte]

Table 11-1
Analysis of Progression-Free Survival (Primary Analysis)
Based on BICR Assessment per RECIST 1.1
(Global Cohort)
(ITT Population)

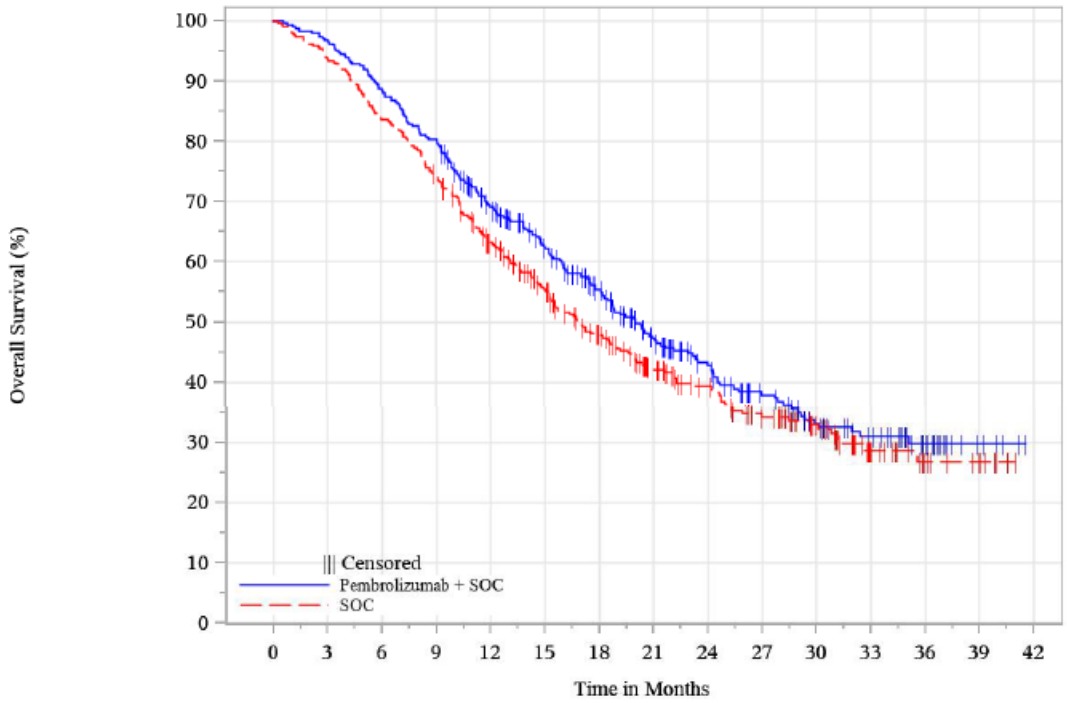
	Pembrolizumab + SOC (N=350)	SOC (N=348)
Number of Events (%)	234 (66.9)	250 (71.8)
DEATH	36 (10.3)	33 (9.5)
DOCUMENTED PROGRESSION	198 (56.6)	217 (62.4)
Kaplan-Meier Estimates (months)[a]		
Median (95% CI)	10.0 (8.6, 11.7)	8.1 (7.0, 8.5)
[Q1, Q3]	[5.6, 24.7]	[4.3, 15.6]
Person-months	4000.4	3181.8
Event Rate / 100 Person-months	5.8	7.9
vs SOC		
Hazard Ratio (95% CI)[b]	0.72 (0.60, 0.87)	
p-value[c]	0.0002	
PFS Rate at month 6 (%) (95% CI)	72.7 (67.6, 77.2)	62.0 (56.4, 67.2)
PFS Rate at month 12 (%) (95% CI)	44.3 (38.8, 49.7)	33.8 (28.4, 39.2)
PFS Rate at month 18 (%) (95% CI)	28.6 (23.4, 34.0)	22.0 (17.2, 27.1)
PFS Rate at month 24 (%) (95% CI)	25.1 (20.1, 30.5)	14.2 (10.1, 19.1)

[a] From product-limit (Kaplan-Meier) method for censored data.
[b] Based on Cox regression model with Efron's method of tie handling with treatment as a covariate stratified by Geographic region (Western Europe/Israel/North America/Australia, Asia and Rest of the World), PD-L1 status (positive vs. negative), 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 (positive vs. negative), and Chemotherapy regimen (FP or CAPOX) with small strata collapsed as pre-specified in the sSAP.
Western Europe includes Belgium, France, Germany, Spain, Italy, United Kingdom, Ireland, Latvia, Lithuania, which is consistent with the 'Europe' region defined in the protocol for stratification.
BICR = Blinded Independent Central Review.
Database Cutoff Date: 25MAY2022

Source: [P811V02MK3475: adam-adsl; adtte]

Overall Survival (OS)

Figure 11-3
Kaplan-Meier Estimates of Overall Survival
(Global Cohort)
(ITT Population)



Number of Subjects at Risk

Pembrolizumab + SOC	350	339	311	281	227	192	152	115	90	68	52	39	21	5	0
SOC	348	327	292	258	207	170	133	99	80	63	46	22	11	6	0

Database Cutoff Date: 25MAY2022.

Source: [P811V02MK3475: adam-adsl; adtte]

Table 11-2
Analysis of Overall Survival
(Global Cohort)
(ITT Population)

	Pembrolizumab + SOC (N=350)	SOC (N=348)
Number of Events (%)	202 (57.7)	213 (61.2)
DEATH	202 (57.7)	213 (61.2)
Kaplan-Meier Estimates (months)[a]		
Median (95% CI)	20.0 (17.8, 23.2)	16.9 (15.0, 19.8)
[Q1, Q3]	[10.2,]	[8.7,]
Person-months	6182.2	5672.8
Event Rate / 100 Person-months	3.3	3.8
vs SOC		
Hazard Ratio (95% CI)[b]	0.87 (0.72, 1.06)	
p-value[c]	0.0842	
OS Rate at month 6 (%) (95% CI)	88.9 (85.1, 91.7)	83.9 (79.6, 87.4)
OS Rate at month 12 (%) (95% CI)	69.2 (64.0, 73.7)	63.2 (57.9, 68.1)
OS Rate at month 18 (%) (95% CI)	55.3 (49.8, 60.6)	48.1 (42.6, 53.5)
OS Rate at month 24 (%) (95% CI)	42.9 (37.1, 48.5)	39.3 (33.7, 44.8)

[a] From product-limit (Kaplan-Meier) method for censored data.
[b] Based on Cox regression model with Efron's method of tie handling with treatment as a covariate stratified by Geographic region (Western Europe/Israel/North America/Australia, Asia and Rest of the World), PD-L1 status (positive vs. negative), 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 (positive vs. negative), and Chemotherapy regimen (FP or CAPOX) with small strata collapsed as pre-specified in the sSAP .
NR = Not reached.
Western Europe includes Belgium, France, Germany, Spain, Italy, United Kingdom, Ireland, Latvia, Lithuania, which is consistent with the 'Europe' region defined in the protocol for stratification.
Database Cutoff Date: 25MAY2022

Source: [P811V02MK3475: adam-adsl; adtte]

Secondary Endpoints

ORR

Table 11-3
Analysis of Objective Response with Confirmation
Based on BICR Assessment per RECIST 1.1
(Global Cohort)
(ITT Population)

Treatment	N	Number of Objective Responses	Objective Response Rate (%) (95% CI)	Difference in % Pembrolizumab + SOC vs. SOC	
				Estimate(95% CI)[a]	p-Value[b]
Pembrolizumab + SOC	350	254	72.6 (67.6, 77.2)	12.8 (5.9, 19.7)	0.00015
SOC	348	208	59.8 (54.4, 65.0)		

[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 (positive vs. negative), and Chemotherapy regimen (FP or CAPOX) with small strata collapsed as pre-specified in the sSAP. Western Europe includes Belgium, France, Germany, Spain, Italy, United Kingdom, Ireland, Latvia, Lithuania, 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.
BICR = Blinded Independent Central Review.
Database Cutoff Date: 25MAY2022.

Source: [P811V02MK3475: adam-adsl; adrs]

Table 11-4
Summary of Objective Response with Confirmation
Based on BICR Assessment per RECIST 1.1
(Global Cohort)
(ITT Population)

	Pembrolizumab + SOC			SOC		
	n	(%)	(95% CI)	n	(%)	(95% CI)
Number of Subjects in Population	350			348		
Complete Response (CR)	49	14.0	(10.5, 18.1)	38	10.9	(7.8, 14.7)
Partial Response (PR)	205	58.6	(53.2, 63.8)	170	48.9	(43.5, 54.2)
Overall Response (CR+PR)	**254**	**72.6**	**(67.6, 77.2)**	**208**	**59.8**	**(54.4, 65.0)**
Stable Disease (SD)	67	19.1	(15.2, 23.7)	96	27.6	(23.0, 32.6)
Disease Control (CR+PR+SD)	**321**	**91.7**	**(88.3, 94.4)**	**304**	**87.4**	**(83.4, 90.7)**
Progressive Disease (PD)	19	5.4	(3.3, 8.3)	23	6.6	(4.2, 9.8)
Not Evaluable (NE[a])	1	0.3	(0.0, 1.6)	5	1.4	(0.5, 3.3)
No Assessment[b]	9	2.6	(1.2, 4.8)	16	4.6	(2.7, 7.4)

Responses are based on BICR assessment per RECIST 1.1.
BICR = Blinded independent central review.
Stable disease includes SD, Non-CR/Non-PD, and NED.
NED: No lesions were identified at baseline assessment and there remained no lesions at post baseline assessment(s).
[a]NE: post-baseline assessment(s) available however not being evaluable.
[b]No Assessment: no post-baseline assessment available for response evaluation.
Database Cutoff Date: 25MAY2022.

Source: [P811V02MK3475: adam-adsl; adrs]

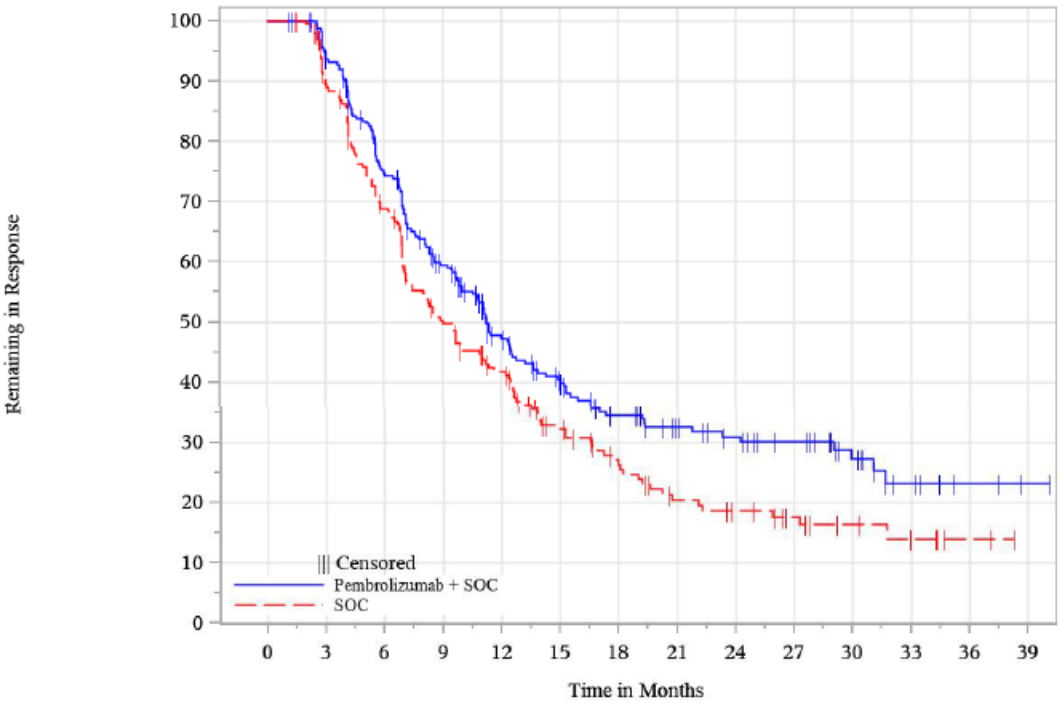
Table 11-5
Summary of Time to Response and Duration of Response
Based on BICR Assessment per RECIST 1.1 in Participants with Confirmed Response
(Global Cohort)

	Pembrolizumab + SOC (N=350)	SOC (N=348)
Number of participants with response[a]	254	208
Time to Response (months)		
Mean (SD)	1.9 (1.3)	2.0 (1.1)
Median (Range)	1.4 (0.9-15.2)	1.5 (0.7-7.0)
Response Duration[b] (months)		
Median (Range)	11.2 (1.1+ - 40.1+)	9.0 (1.4+ - 38.3+)
Number (%[b]) of Participants with Extended Response Duration:		
≥3 months	234 (94.0)	173 (89.9)
≥6 months	179 (74.7)	129 (68.9)
≥9 months	136 (59.5)	90 (50.3)
≥12 months	94 (47.8)	70 (41.7)

[a] Includes participants with best objective response as confirmed complete response or partial response
[b] From product-limit (Kaplan-Meier) method for censored data.
"+" indicates there is no progressive disease by the time of last disease assessment.
BICR = Blinded independent central review.
Database Cutoff Date: 25MAY2022

Source: [P811V02MK3475: adam-adsl; adtte]

Figure 11-7
Kaplan-Meier Estimates of Duration of Response
Based on BICR Assessment per RECIST 1.1
(Global Cohort)
(In Participants with Confirmed Response)



Number of Subjects at Risk

Pembrolizumab + SOC	254	234	179	136	94	73	54	44	36	28	18	8	3	1
SOC	208	173	129	90	70	47	34	23	19	13	9	6	2	0

Database Cutoff Date: 25MAY2022.

Source: [P811V02MK3475: adam-adsl; adtte]

Patient Reported Outcomes

Table 11-11
Analysis of Change from Baseline in EORTC QLQ-C30 Global Health Status/QoL to Week 24
(PRO FAS Population)

Treatment	Baseline		Week 24		Change from Baseline to Week 24	
	N	Mean (SD)	N	Mean (SD)	N	LS Mean (95% CI)†
Pembrolizumab + SOC	320	68.91 (19.17)	231	70.67 (17.65)	344	1.18 (-1.12, 3.49)
SOC	322	67.26 (20.59)	190	72.46 (17.25)	339	2.34 (-0.14, 4.82)
Pairwise Comparison					Difference in LS Means† (95% CI)	p-Value†
Pembrolizumab + SOC vs. SOC					-1.16 (-4.23, 1.91)	0.4595

† Based on a cLDA model with the PRO scores as the response variable with covariates for treatment by study visit interaction and stratification factors (Geographic region (Western Europe/Israel/North America/Australia, Asia and Rest of the World), PD-L1 status (positive vs. negative), and Chemotherapy regimen (FP or CAPOX)).

Western Europe includes Belgium, France, Germany, Spain, Italy, United Kingdom, Ireland, Latvia, Lithuania, which is consistent with the 'Europe' region defined in the protocol for stratification.

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

Two-sided p-value is based on t test.

Database Cutoff Date: 25MAY2022

Source: [P811V02MK3475: adam-adsl; adpro]

Table 14.2-52
Analysis of Time to True Deterioration for EORTC QLQ-STO22 Symptom Scale Pain
(PRO FAS Population with Baseline)

Treatment	N	Number of Events (%)	Median Time to True Deterioration [a] (months) (95% CI)	Time to True Deterioration Rate at 12 months in % [a] (95% CI)
Pembrolizumab + SOC	319	36 (11.3)	NR (NR, NR)	86.5 (81.6, 90.2)
SOC	320	34 (10.6)	NR (NR, NR)	87.8 (83.2, 91.1)
Pairwise Comparisons			Hazard Ratio[b] (95% CI)[b]	p-Value
Pembrolizumab + SOC vs. SOC			0.99 (0.62, 1.58)	0.9681[d]

[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 (positive vs. negative), and Chemotherapy regimen (FP or CAPOX)).

[d] Two-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 (positive vs. negative), and Chemotherapy regimen (FP or CAPOX)).

NR = Not reached.

Western Europe includes Belgium, France, Germany, Spain, Italy, United Kingdom, Ireland, Latvia, Lithuania, which is consistent with the 'Europe' region defined in the protocol for stratification.

True deterioration is defined as the time to first onset of a 10 points or more deterioration (i.e., increase in score) from baseline with confirmation by the subsequent visit of a 10 points or more deterioration from baseline under right-censoring rule.

Database Cutoff Date: 25MAY2022.

Source: [P811V02MK3475: adam-adsl; adprotte]

Table 14.2-53
Analysis of Change from Baseline in EQ-5D-5L VAS to Week 24
(PRO FAS Population)

Treatment	Baseline		Week 24		Change from Baseline to Week 24	
	N	Mean (SD)	N	Mean (SD)	N	LS Mean (95% CI)†
Pembrolizumab + SOC	324	76.33 (16.82)	232	78.66 (14.35)	344	0.95 (-0.87, 2.76)
SOC	324	75.93 (18.61)	191	80.16 (14.40)	339	1.63 (-0.30, 3.56)

Pairwise Comparison	Difference in LS Means† (95% CI)	p-Value†
Pembrolizumab + SOC vs. SOC	-0.69 (-3.06, 1.68)	0.5698

† Based on a cLDA model with the PRO scores as the response variable with covariates for treatment by study visit interaction and stratification factors (Geographic region (Western Europe/Israel/North America/Australia, Asia and Rest of the World), PD-L1 status (positive vs. negative), and Chemotherapy regimen (FP or CAPOX)).

Western Europe includes Belgium, France, Germany, Spain, Italy, United Kingdom, Ireland, Latvia, Lithuania, which is consistent with the 'Europe' region defined in the protocol for stratification.

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

Two-sided p-value is based on t test.

Database Cutoff Date: 25MAY2022

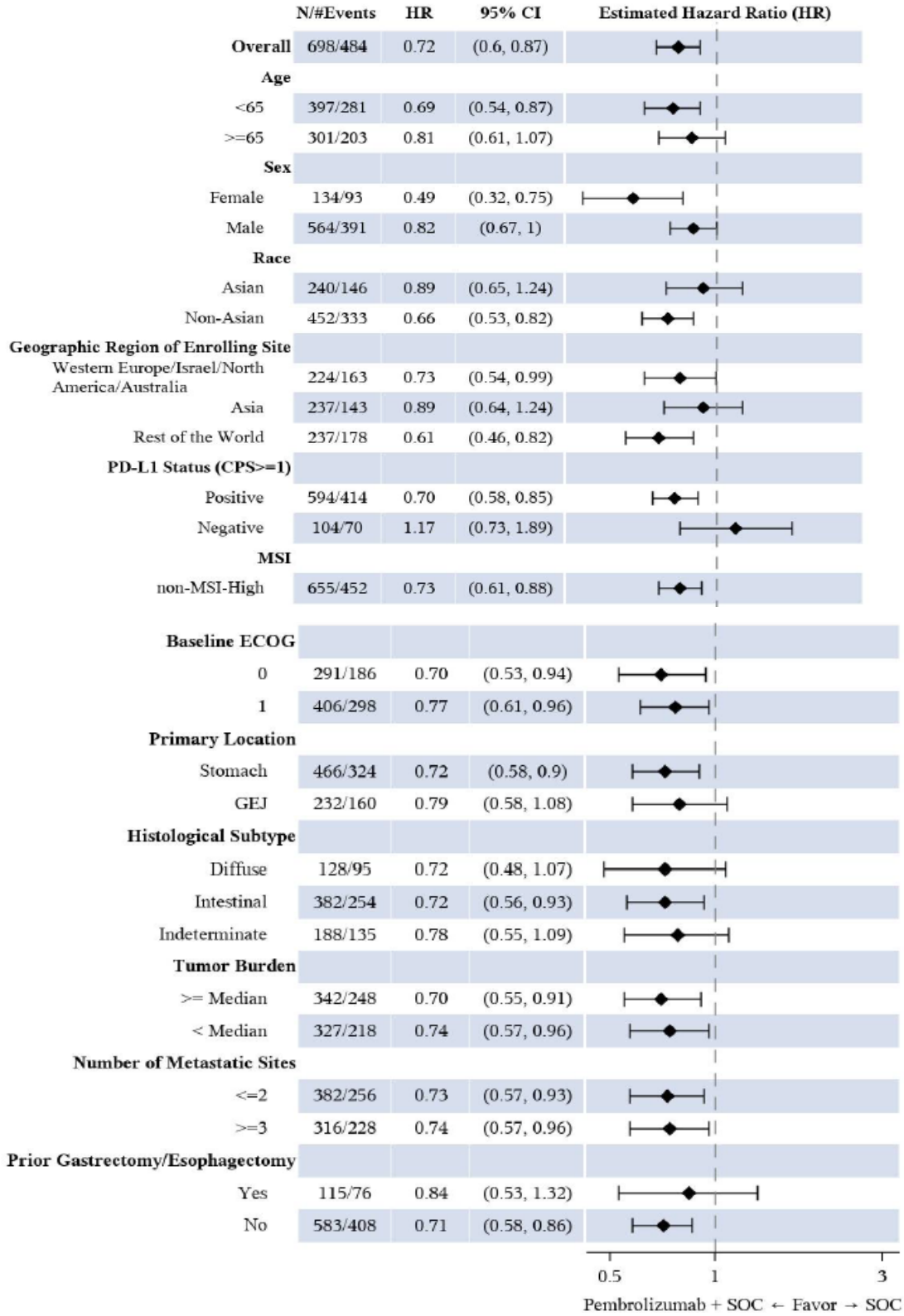
Source: [P811V02MK3475: adam-adsl; adpro]

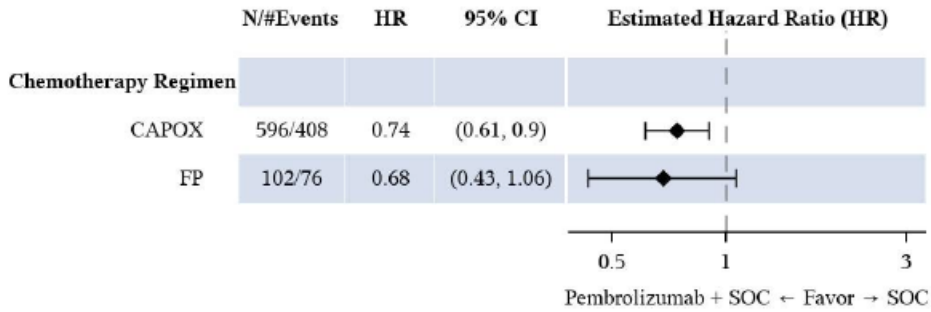
Ancillary analyses

Subgroup analysis

PFS

Figure 11-2: Forest plot of progression-free survival hazard ratio by subgroup factors based on BICR assessment per RECIST 1.1 (primary analysis) (global cohort) (ITT population)



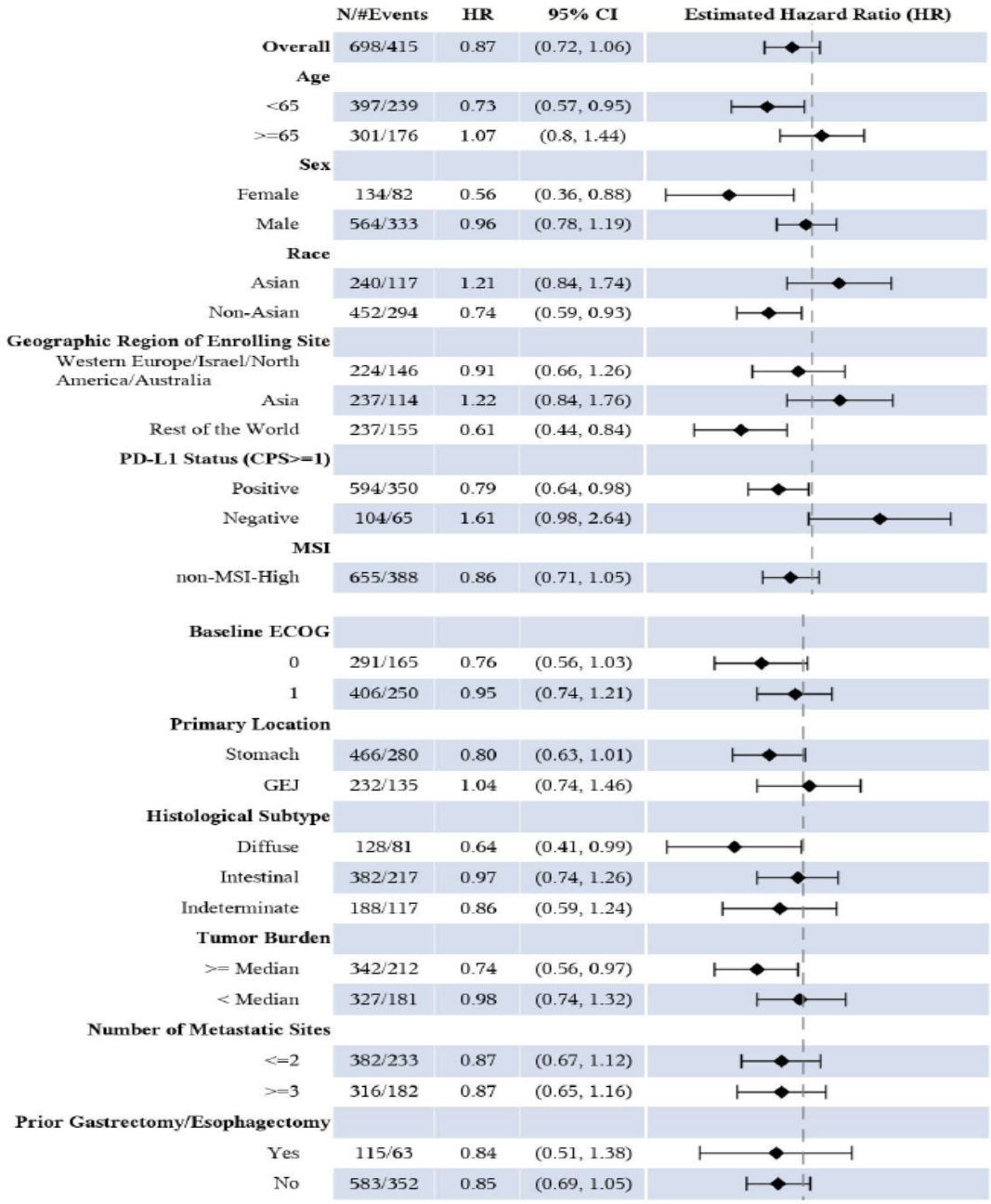


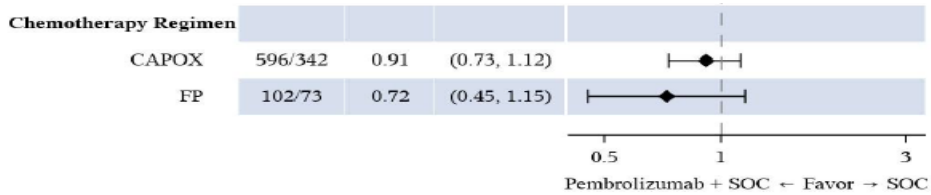
For overall population, analysis is based on Cox regression model with Efron's method of tie handling with treatment as a covariate stratified by Geographic region (Western Europe/Israel/North America/Australia, Asia and Rest of the World), PD-L1 status (positive vs. negative), and Chemotherapy regimen (FP or CAPOX) with small strata collapsed as pre-specifiedin the sSAP.
Western Europe includes Belgium, France, Germany, Spain, Italy, United Kingdom, Ireland, Latvia, Lithuania, 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 a subgroup variable has two levels and one level of the subgroup variable has fewer than 20 participants, then this subgroup is not displayed in the plot.
Database Cutoff Date: 25MAY2022.

Source: [P811V02MK3475: adam-adsl; adtte]

OS

Figure 11-4: Forest plot of overall survival hazard ratio by subgroup factors (global cohort) (ITT population)





For overall population, analysis is 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 (positive vs. negative), and Chemotherapy regimen (FP or CAPOX) with small strata collapsed as pre-specifiedin the sSAP.
Western Europe includes Belgium, France, Germany, Spain, Italy, United Kingdom, Ireland, Latvia, Lithuania, 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 a subgroup variable has two levels and one level of the subgroup variable has fewer than 20 participants, then this subgroup is not displayed in the plot.
Database Cutoff Date: 25MAY2022.

Source: [P811V02MK3475: adam-adsl; adtte]

Analysis by PD-L1 status

CPS≥1

Patient characteristics

Table 14.1-16
Participant Characteristics
(CPS>=1 Participants)
(Global Cohort)
(ITT Population)

	Pembrolizumab + SOC		SOC		Total	
	n	(%)	n	(%)	n	(%)
Participants in population	298		296		594	
Sex						
Male	240	(80.5)	237	(80.1)	477	(80.3)
Female	58	(19.5)	59	(19.9)	117	(19.7)
Age (Years)						
< 65	174	(58.4)	165	(55.7)	339	(57.1)
>= 65	124	(41.6)	131	(44.3)	255	(42.9)
Mean	60.6		61.4		61.0	
SD	11.8		10.8		11.3	
Median	63.0		63.0		63.0	
Range	19 to 85		32 to 85		19 to 85	
Race						
American Indian Or Alaska Native	5	(1.7)	6	(2.0)	11	(1.9)
Asian	97	(32.6)	97	(32.8)	194	(32.7)
Black Or African American	2	(0.7)	2	(0.7)	4	(0.7)
Multiple	5	(1.7)	4	(1.4)	9	(1.5)
White	188	(63.1)	184	(62.2)	372	(62.6)
Missing	1	(0.3)	3	(1.0)	4	(0.7)
Ethnicity						
Hispanic Or Latino	36	(12.1)	41	(13.9)	77	(13.0)
Not Hispanic Or Latino	259	(86.9)	249	(84.1)	508	(85.5)
Not Reported	1	(0.3)	5	(1.7)	6	(1.0)
Unknown	2	(0.7)	1	(0.3)	3	(0.5)
Age Group (Years)						
18-39	16	(5.4)	12	(4.1)	28	(4.7)
40-49	34	(11.4)	27	(9.1)	61	(10.3)
50-59	59	(19.8)	86	(29.1)	145	(24.4)
60-69	118	(39.6)	92	(31.1)	210	(35.4)
70-79	67	(22.5)	73	(24.7)	140	(23.6)
>=80	4	(1.3)	6	(2.0)	10	(1.7)

	Pembrolizumab + SOC		SOC		Total	
	n	(%)	n	(%)	n	(%)
Age Group 2 (Years)						
< 65	174	(58.4)	165	(55.7)	339	(57.1)
65 - 74	101	(33.9)	104	(35.1)	205	(34.5)
75 - 84	22	(7.4)	26	(8.8)	48	(8.1)
85+	1	(0.3)	1	(0.3)	2	(0.3)
Geographic Region of Enrolling Site						
Western Europe/Israel/North America/Australia	97	(32.6)	96	(32.4)	193	(32.5)
Asia	96	(32.2)	96	(32.4)	192	(32.3)
Rest of the World	105	(35.2)	104	(35.1)	209	(35.2)
ECOG Performance Scale						
0	127	(42.6)	121	(40.9)	248	(41.8)
1	171	(57.4)	174	(58.8)	345	(58.1)
Missing	0	(0.0)	1	(0.3)	1	(0.2)
Primary Location at Diagnosis						
Adenocarcinoma of the gastroesophageal junction	97	(32.6)	99	(33.4)	196	(33.0)
Adenocarcinoma of the stomach	201	(67.4)	197	(66.6)	398	(67.0)
Current Disease Overall Stage						
IIB	1	(0.3)	0	(0.0)	1	(0.2)
IIIA	2	(0.7)	1	(0.3)	3	(0.5)
IIIB	5	(1.7)	1	(0.3)	6	(1.0)
IIIC	0	(0.0)	3	(1.0)	3	(0.5)
IV	290	(97.3)	291	(98.3)	581	(97.8)
Disease Status						
Locally advanced	8	(2.7)	6	(2.0)	14	(2.4)
Metastatic	290	(97.3)	290	(98.0)	580	(97.6)
Number of Metastatic Sites						
0-2	149	(50.0)	172	(58.1)	321	(54.0)

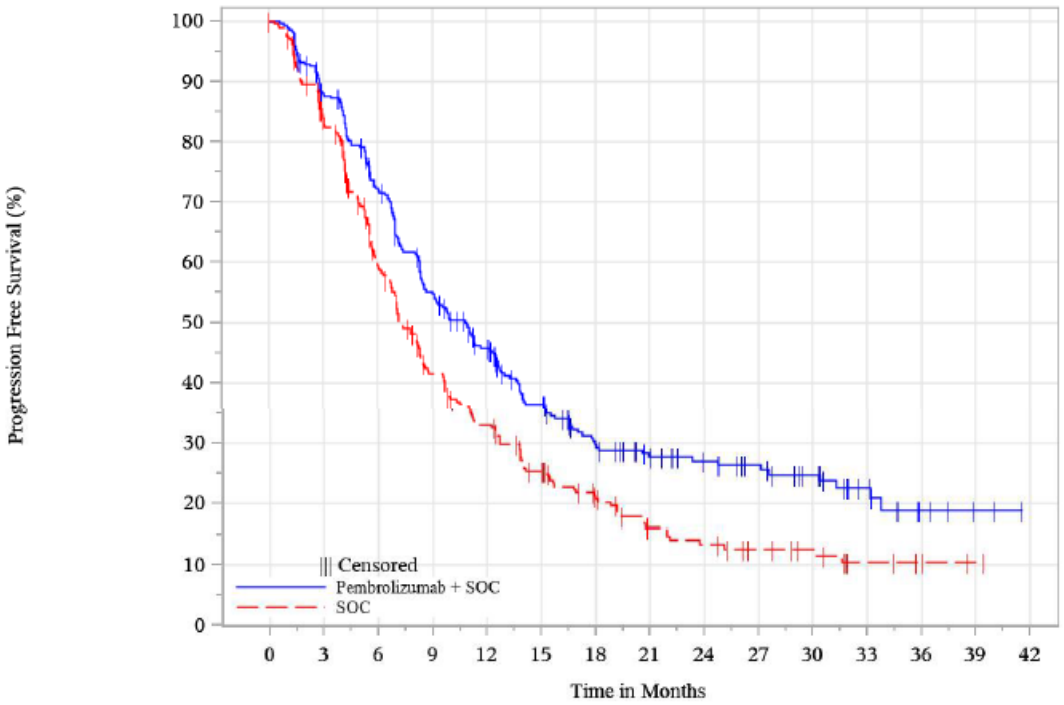
	Pembrolizumab + SOC		SOC		Total	
	n	(%)	n	(%)	n	(%)
>=3	149	(50.0)	124	(41.9)	273	(46.0)
Histological Subtype (Lauren classification)						
Diffuse	56	(18.8)	49	(16.6)	105	(17.7)
Intestinal	169	(56.7)	158	(53.4)	327	(55.1)
Indeterminate	73	(24.5)	89	(30.1)	162	(27.3)
Prior Gastrectomy/Esophagectomy						
Yes	36	(12.1)	48	(16.2)	84	(14.1)
No	262	(87.9)	248	(83.8)	510	(85.9)
PD-L1 Status (CPS>=1)						
Positive	298	(100.0)	296	(100.0)	594	(100.0)
Tumor Burden						
< Median	139	(46.6)	139	(47.0)	278	(46.8)
>= Median	147	(49.3)	146	(49.3)	293	(49.3)
Missing	12	(4.0)	11	(3.7)	23	(3.9)
HER2 Status						
IHC 1+	1	(0.3)	1	(0.3)	2	(0.3)
IHC 2+ ISH Equivocal	0	(0.0)	1	(0.3)	1	(0.2)
IHC 2+ ISH Negative	1	(0.3)	1	(0.3)	2	(0.3)
IHC 2+ ISH Positive	51	(17.1)	68	(23.0)	119	(20.0)
IHC 3+	245	(82.2)	225	(76.0)	470	(79.1)
MSI Status						
MSI High	6	(2.0)	2	(0.7)	8	(1.3)
non-MSI-High	282	(94.6)	280	(94.6)	562	(94.6)
Unknown	10	(3.4)	14	(4.7)	24	(4.0)
Chemotherapy Regimen						
CAPOX	251	(84.2)	253	(85.5)	504	(84.8)
FP	47	(15.8)	43	(14.5)	90	(15.2)

Western Europe includes Belgium, France, Germany, Spain, Italy, United Kingdom, Ireland, Latvia, Lithuania, which is consistent with the 'Europe' region defined in the protocol for stratification.
Database Cutoff Date: 25MAY2022.

Source: [P811V02MK3475: adam-adsl]

PFS

Figure 11-8
Kaplan-Meier Estimates of Progression-Free Survival (Primary Analysis)
Based on BICR Assessment per RECIST 1.1
(CPS>=1 Participants)
(Global Cohort)
(ITT Population)



Number of Subjects at Risk

Pembrolizumab + SOC	298	250	200	150	116	84	61	48	40	33	26	14	5	2	0
SOC	296	231	150	98	76	54	38	24	20	15	12	6	3	1	0

Database Cutoff Date: 25MAY2022.

Source: [P811V02MK3475: adam-adsl; adtte]

Table 11-6
Analysis of Progression-Free Survival (Primary Analysis)
Based on BICR Assessment per RECIST 1.1
(CPS>=1 Participants)
(Global Cohort)
(ITT Population)

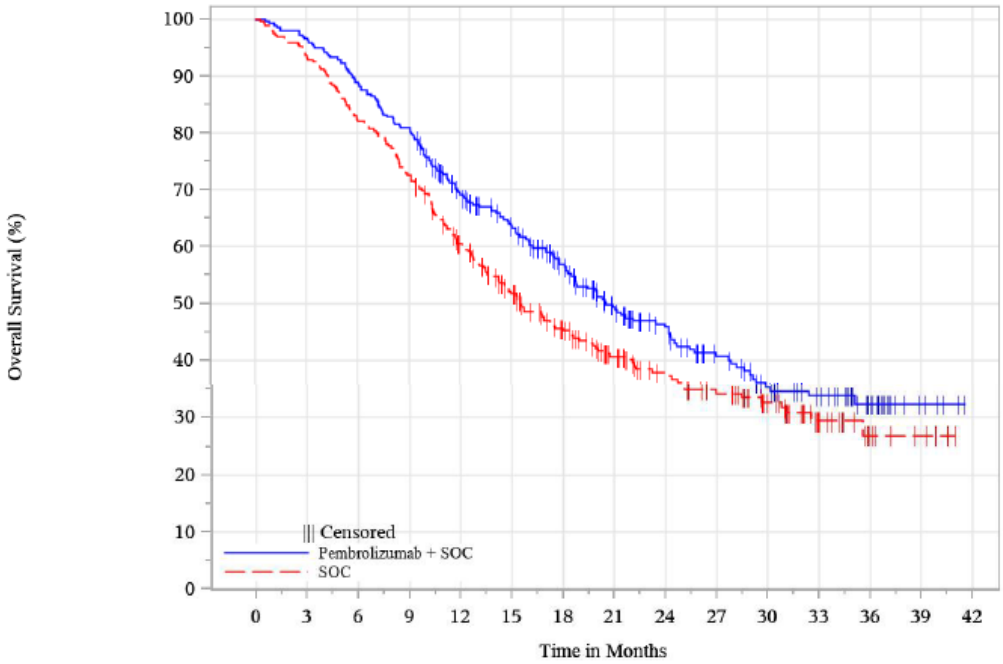
	Pembrolizumab + SOC (N=298)	SOC (N=296)
Number of Events (%)	199 (66.8)	215 (72.6)
DEATH	29 (9.7)	30 (10.1)
DOCUMENTED PROGRESSION	170 (57.0)	185 (62.5)
Kaplan-Meier Estimates (months)[a]		
Median (95% CI)	10.8 (8.5, 12.5)	7.2 (6.8, 8.4)
[Q1, Q3]	[5.6, 27.6]	[4.3, 15.2]
Person-months	3530.2	2644.1
Event Rate / 100 Person-months	5.6	8.1
vs SOC		
Hazard Ratio (95% CI)[b]	0.70 (0.58, 0.85)	
p-value[c]	0.0001	
PFS Rate at month 6 (%) (95% CI)	72.3 (66.7, 77.1)	59.9 (53.7, 65.5)
PFS Rate at month 12 (%) (95% CI)	45.7 (39.7, 51.5)	32.9 (27.2, 38.8)
PFS Rate at month 18 (%) (95% CI)	29.8 (24.2, 35.6)	20.7 (15.7, 26.2)
PFS Rate at month 24 (%) (95% CI)	27.0 (21.5, 32.8)	13.3 (9.0, 18.5)

[a] From product-limit (Kaplan-Meier) method for censored data.
[b] Based on Cox regression model with Efron's method of tie handling with treatment as a covariate.
[c] One-sided p-value based on log-rank test.
BICR = Blinded Independent Central Review.
Database Cutoff Date: 25MAY2022

Source: [P811V02MK3475: adam-adsl; adtte]

OS

Figure 11-9: Kaplan-Meier estimates of overall survival (CPS ≥1 participants) (global cohort) (ITT population)



Number of Subjects at Risk

Pembrolizumab + SOC	298	288	265	241	194	169	134	103	83	64	49	37	20	5	0
SOC	296	277	244	215	169	136	106	79	62	52	38	19	8	4	0

Database Cutoff Date: 25MAY2022.

Source: [P811V02MK3475: adam-adsl; adtte]

Table 11-7: Analysis of overall survival (CPS ≥1 participants) (global cohort) (ITT population)

	Pembrolizumab + SOC (N=298)	SOC (N=296)
Number of Events (%)	167 (56.0)	183 (61.8)
DEATH	167 (56.0)	183 (61.8)
Kaplan-Meier Estimates (months)[a]		
Median (95% CI)	20.5 (18.2, 24.3)	15.6 (13.5, 18.6)
[Q1, Q3]	[10.3,]	[8.4,]
Person-months	5383.7	4684.2
Event Rate / 100 Person-months	3.1	3.9
vs SOC		
Hazard Ratio (95% CI)[b]	0.79 (0.64, 0.98)	
p-value[c]	0.0143	
OS Rate at month 6 (%) (95% CI)	88.9 (84.8, 92.0)	82.4 (77.6, 86.3)
OS Rate at month 12 (%) (95% CI)	69.2 (63.6, 74.1)	60.6 (54.7, 65.9)
OS Rate at month 18 (%) (95% CI)	56.9 (50.9, 62.5)	45.6 (39.7, 51.4)
OS Rate at month 24 (%) (95% CI)	45.8 (39.5, 51.8)	37.8 (31.8, 43.8)

[a] From product-limit (Kaplan-Meier) method for censored data.
[b] Based on Cox regression model with Efron's method of tie handling with treatment as a covariate.
[c] One-sided p-value based on log-rank test.
NR = Not reached.
Database Cutoff Date: 25MAY2022

Source: [P811V02MK3475: adam-adsl; adtte]

ORR

Table 11-8
Analysis of Objective Response Wwith Confirmation
Based on BICR Assessment per RECIST 1.1
(CPS>=1 Participants) (Global Cohort)
(ITT Population)

Treatment	N	Number of Objective Responses	Objective Response Rate (%) (95% CI)	Difference in % Pembrolizumab + SOC vs. SOC Estimate(95% CI)[a]	p-Value[b]
Pembrolizumab + SOC	298	218	73.2 (67.7, 78.1)	14.7 (7.1, 22.2)	0.00008
SOC	296	173	58.4 (52.6, 64.1)		

[a] Based on unstratified Miettinen & Nurminen method.
[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.
BICR = Blinded Independent Central Review.
Database Cutoff Date: 25MAY2022.

Source: [P811V02MK3475: adam-adsl; adrs]

Table 11-9
Summary of Objective Response with Confirmation
Based on BICR Assessment per RECIST 1.1
(CPS>=1 Participants) (Global Cohort)
(ITT Population)

	Pembrolizumab + SOC			SOC		
	n	(%)	(95% CI)	n	(%)	(95% CI)
Number of Subjects in Population	298			296		
Complete Response (CR)	42	14.1	(10.4, 18.6)	29	9.8	(6.7, 13.8)
Partial Response (PR)	176	59.1	(53.2, 64.7)	144	48.6	(42.8, 54.5)
Overall Response (CR+PR)	**218**	**73.2**	**(67.7, 78.1)**	**173**	**58.4**	**(52.6, 64.1)**
Stable Disease (SD)	55	18.5	(14.2, 23.3)	83	28.0	(23.0, 33.5)
Disease Control (CR+PR+SD)	**273**	**91.6**	**(87.9, 94.5)**	**256**	**86.5**	**(82.1, 90.2)**
Progressive Disease (PD)	16	5.4	(3.1, 8.6)	22	7.4	(4.7, 11.0)
Not Evaluable (NE[a])	1	0.3	(0.0, 1.9)	5	1.7	(0.6, 3.9)
No Assessment[b]	8	2.7	(1.2, 5.2)	13	4.4	(2.4, 7.4)

Responses are based on BICR assessment per RECIST 1.1.
BICR = Blinded independent central review.
Stable disease includes SD, Non-CR/Non-PD, and NED.
NED: No lesions were identified at baseline assessment and there remained no lesions at post baseline assessment(s).
[a]NE: post-baseline assessment(s) available however not being evaluable.
[b]No Assessment: no post-baseline assessment available for response evaluation.
Database Cutoff Date: 25MAY2022.

Source: [P811V02MK3475: adam-adsl; adrs]

DoR

Table 11-10
Summary of Time to Response and Duration of Response
Based on BICR Assessment per RECIST 1.1 in Participants with Confirmed Response
(CPS>=1 Participants)
(Global Cohort)

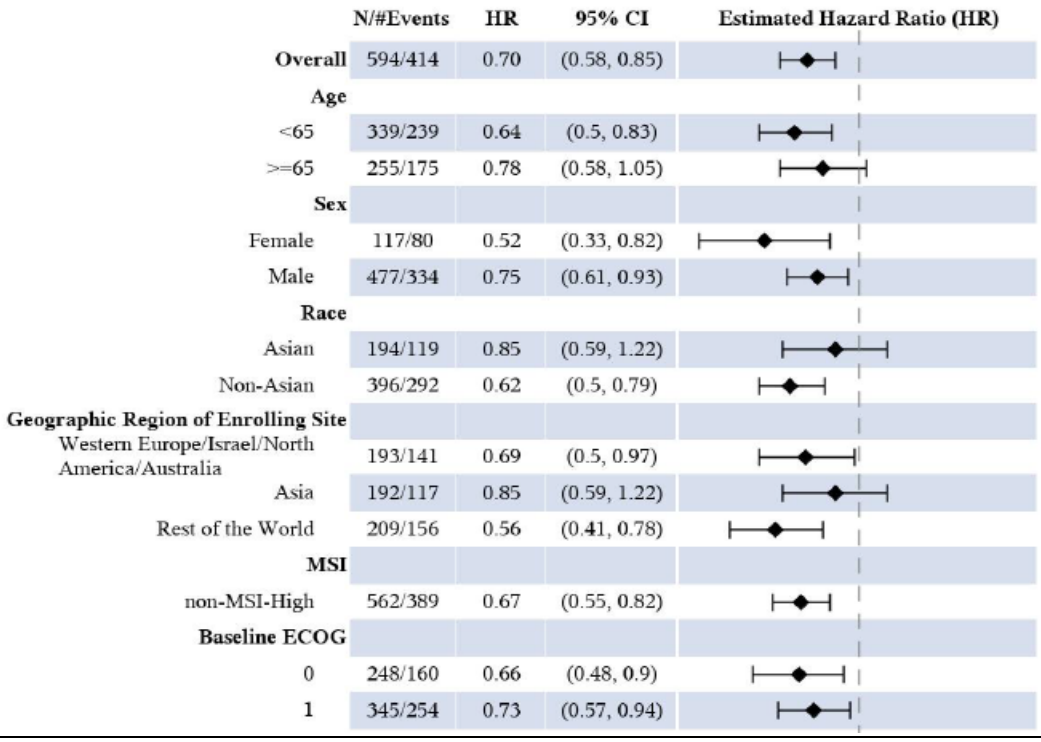
	Pembrolizumab + SOC (N=298)	SOC (N=296)
Number of participants with response[a]	218	173
Time to Response (months)		
Mean (SD)	1.9 (1.4)	1.9 (1.1)
Median (Range)	1.4 (0.9-15.2)	1.5 (1.0-7.0)
Response Duration[b] (months)		
Median (Range)	11.3 (1.1+ - 40.1+)	9.5 (1.4+ - 38.3+)
Number (%[b]) of Participants with Extended Response Duration:		
≥3 months	201 (93.9)	141 (89.1)
≥6 months	155 (74.5)	104 (67.3)
≥9 months	122 (60.9)	74 (50.2)
≥12 months	86 (49.2)	58 (41.2)

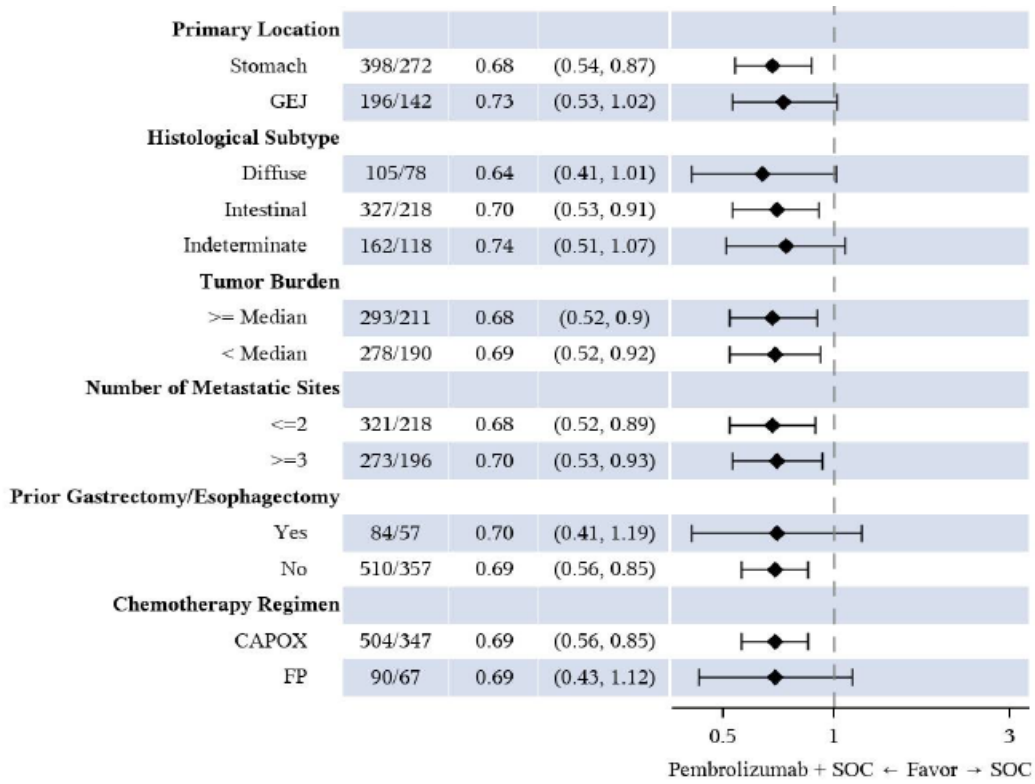
[a] Includes participants with best objective response as confirmed complete response or partial response
[b] From product-limit (Kaplan-Meier) method for censored data.
"+" indicates there is no progressive disease by the time of last disease assessment.
BICR = Blinded independent central review.
Database Cutoff Date: 25MAY2022

Source: [P811V02MK3475: adam-adsl; adtte]

Forest plots for PFS in CPS≥1

Figure 14.2-42: Forest plot of progression-free survival hazard ratio by subgroup factors based on BICR assessment per RECIST 1.1 (primary analysis) (CPS ≥1 participants) (global cohort) (ITT population)





For overall population and subgroups, analyses are based on unstratified Cox regression model with Efrons method of tie handling with treatment as a covariate.
If a subgroup variable has two levels and one level of the subgroup variable has fewer than 20 participants, then this subgroup is not displayed in the plot.
Database Cutoff Date: 25MAY2022.

CPS<1

Patient characteristics

Table 14.1-17
Participant Characteristics
(CPS<1 Participants)
(Global Cohort)
(ITT Population)

	Pembrolizumab + SOC		SOC		Total	
	n	(%)	n	(%)	n	(%)
Participants in population	52		52		104	
Sex						
Male	44	(84.6)	43	(82.7)	87	(83.7)
Female	8	(15.4)	9	(17.3)	17	(16.3)
Age (Years)						
< 65	31	(59.6)	27	(51.9)	58	(55.8)
>= 65	21	(40.4)	25	(48.1)	46	(44.2)
Mean	59.2		63.0		61.1	
SD	12.0		10.9		11.5	
Median	59.0		64.0		62.0	
Range	34 to 84		32 to 80		32 to 84	
Race						
Asian	22	(42.3)	24	(46.2)	46	(44.2)
Multiple	1	(1.9)	1	(1.9)	2	(1.9)
White	29	(55.8)	25	(48.1)	54	(51.9)
Missing	0	(0.0)	2	(3.8)	2	(1.9)
Ethnicity						
Hispanic Or Latino	2	(3.8)	4	(7.7)	6	(5.8)
Not Hispanic Or Latino	50	(96.2)	43	(82.7)	93	(89.4)
Not Reported	0	(0.0)	5	(9.6)	5	(4.8)
Age Group (Years)						
18-39	3	(5.8)	2	(3.8)	5	(4.8)
40-49	10	(19.2)	3	(5.8)	13	(12.5)
50-59	14	(26.9)	13	(25.0)	27	(26.0)
60-69	17	(32.7)	17	(32.7)	34	(32.7)
70-79	7	(13.5)	15	(28.8)	22	(21.2)
>=80	1	(1.9)	2	(3.8)	3	(2.9)
Age Group 2 (Years)						
< 65	31	(59.6)	27	(51.9)	58	(55.8)

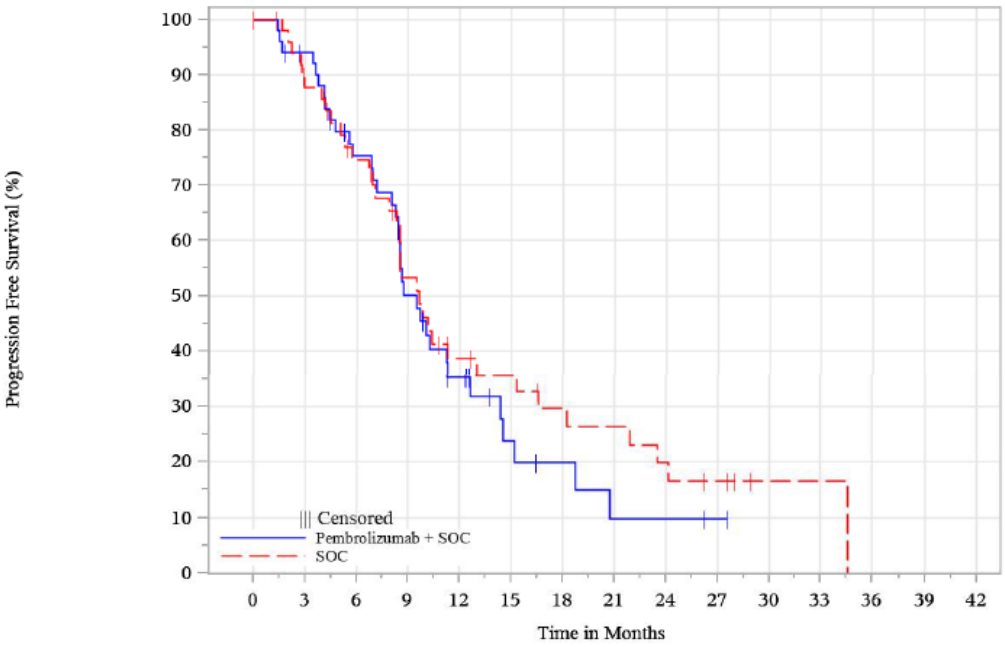
	Pembrolizumab + SOC		SOC		Total	
	n	(%)	n	(%)	n	(%)
65 - 74	16	(30.8)	17	(32.7)	33	(31.7)
75 - 84	5	(9.6)	8	(15.4)	13	(12.5)
Geographic Region of Enrolling Site						
Western Europe/Israel/North America/Australia	16	(30.8)	15	(28.8)	31	(29.8)
Asia	22	(42.3)	23	(44.2)	45	(43.3)
Rest of the World	14	(26.9)	14	(26.9)	28	(26.9)
ECOG Performance Scale						
0	19	(36.5)	24	(46.2)	43	(41.3)
1	33	(63.5)	28	(53.8)	61	(58.7)
Primary Location at Diagnosis						
Adenocarcinoma of the gastroesophageal junction	13	(25.0)	23	(44.2)	36	(34.6)
Adenocarcinoma of the stomach	39	(75.0)	29	(55.8)	68	(65.4)
Current Disease Overall Stage						
IIIB	0	(0.0)	1	(1.9)	1	(1.0)
IIIC	2	(3.8)	0	(0.0)	2	(1.9)
IV	50	(96.2)	51	(98.1)	101	(97.1)
Disease Status						
Locally advanced	2	(3.8)	1	(1.9)	3	(2.9)
Metastatic	50	(96.2)	51	(98.1)	101	(97.1)
Number of Metastatic Sites						
0-2	33	(63.5)	28	(53.8)	61	(58.7)
>=3	19	(36.5)	24	(46.2)	43	(41.3)
Histological Subtype (Lauren classification)						
Diffuse	14	(26.9)	9	(17.3)	23	(22.1)
Intestinal	28	(53.8)	27	(51.9)	55	(52.9)
Indeterminate	10	(19.2)	16	(30.8)	26	(25.0)
Prior Gastrectomy/Esophagectomy						
Yes	15	(28.8)	16	(30.8)	31	(29.8)
No	37	(71.2)	36	(69.2)	73	(70.2)
PD-L1 Status (CPS>=1)						
Negative	52	(100.0)	52	(100.0)	104	(100.0)
Tumor Burden						
< Median	21	(40.4)	28	(53.8)	49	(47.1)
>= Median	26	(50.0)	23	(44.2)	49	(47.1)
Missing	5	(9.6)	1	(1.9)	6	(5.8)
HER2 Status						
IHC 2+ ISH Positive	11	(21.2)	16	(30.8)	27	(26.0)
IHC 3+	41	(78.8)	36	(69.2)	77	(74.0)
MSI Status						
non-MSI-High	44	(84.6)	49	(94.2)	93	(89.4)
Unknown	8	(15.4)	3	(5.8)	11	(10.6)
Chemotherapy Regimen						
CAPOX	46	(88.5)	46	(88.5)	92	(88.5)
FP	6	(11.5)	6	(11.5)	12	(11.5)

Western Europe includes Belgium, France, Germany, Spain, Italy, United Kingdom, Ireland, Latvia, Lithuania, which is consistent with the 'Europe' region defined in the protocol for stratification.
Database Cutoff Date: 25MAY2022.

Source: [P811V02MK3475: adam-adsl]

PFS

Figure 14.2-20: Kaplan-Meier estimates of progression-free survival based on BICR assessment per RECIST 1.1 (primary analysis) (CPS <1 participants) (global cohort) (ITT population)



Number of Subjects at Risk

Pembrolizumab + SOC	52	46	34	21	13	6	4	2	2	1	0	0	0	0	0
SOC	52	42	33	22	14	12	9	8	6	4	1	1	0	0	0

Database Cutoff Date: 25MAY2022.

Table 14.2-24: Analysis of progression-free survival based on BICR assessment per RECIST 1.1 (primary analysis) (CPS <1 participants) (global cohort) (ITT population)

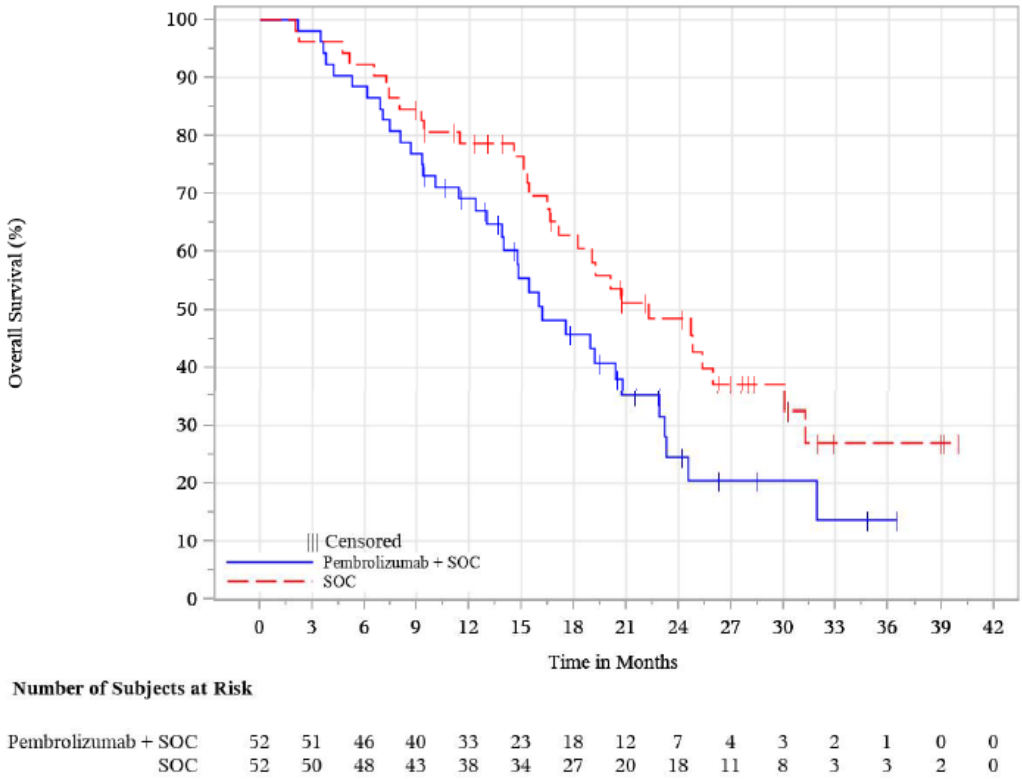
	Pembrolizumab + SOC (N=52)	SOC (N=52)
Number of Events (%)	35 (67.3)	35 (67.3)
DEATH	7 (13.5)	3 (5.8)
DOCUMENTED PROGRESSION	28 (53.8)	32 (61.5)
Kaplan-Meier Estimates (months)[a]		
Median (95% CI)	9.5 (8.3, 11.3)	9.6 (7.9, 13.0)
[Q1, Q3]	[6.9, 14.5]	[5.7, 21.9]
Person-months	470.2	537.7
Event Rate / 100 Person-months	7.4	6.5
vs SOC		
Hazard Ratio (95% CI)[b]	1.17 (0.73, 1.89)	
p-value[c]	0.7432	
PFS Rate at month 6 (%) (95% CI)	75.3 (60.6, 85.2)	74.6 (59.6, 84.7)
PFS Rate at month 12 (%) (95% CI)	35.3 (21.4, 49.4)	38.6 (24.2, 52.8)
PFS Rate at month 18 (%) (95% CI)	19.8 (8.2, 35.1)	29.7 (16.4, 44.2)
PFS Rate at month 24 (%) (95% CI)	9.9 (2.0, 25.4)	19.8 (8.7, 34.2)

[a] From product-limit (Kaplan-Meier) method for censored data.
[b] Based on Cox regression model with Efron's method of tie handling with treatment as a covariate.
[c] One-sided p-value based on log-rank test.
BICR = Blinded Independent Central Review.
Database Cutoff Date: 25MAY2022

Source: [P811V02MK3475: adam-adsl; adtte]

OS

Figure 14.2-22: Kaplan-Meier estimates of overall survival (CPS <1 participants) (global cohort) (ITT population)



Database Cutoff Date: 25MAY2022.

Table 14.2-26: Analysis of overall survival (CPS <1 participants) (global cohort) (ITT population)

	Pembrolizumab + SOC (N=52)	SOC (N=52)
Number of Events (%)	35 (67.3)	30 (57.7)
DEATH	35 (67.3)	30 (57.7)
Kaplan-Meier Estimates (months)[a]		
Median (95% CI)	16.1 (13.9, 20.8)	22.3 (16.6, 30.1)
[Q1, Q3]	[9.3, 23.3]	[15.1,]
Person-months	798.5	988.5
Event Rate / 100 Person-months	4.4	3.0
vs SOC		
Hazard Ratio (95% CI)[b]	1.61 (0.98, 2.64)	
p-value[c]	0.9722	
OS Rate at month 6 (%) (95% CI)	88.5 (76.1, 94.6)	92.3 (80.8, 97.0)
OS Rate at month 12 (%) (95% CI)	69.1 (54.5, 79.8)	78.6 (64.7, 87.5)
OS Rate at month 18 (%) (95% CI)	45.7 (31.0, 59.3)	62.8 (47.4, 74.8)
OS Rate at month 24 (%) (95% CI)	24.5 (12.0, 39.4)	48.4 (33.2, 62.0)

[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.
[c] One-sided p-value based on log-rank test.
NR = Not reached.
Database Cutoff Date: 25MAY2022

Source: [P811V02MK3475: adam-adsl; adtte]

ORR

Table 14.2-32
Summary of Objective Response with Confirmation
Based on BICR Assessment per RECIST 1.1
(CPS<1 Participants) (Global Cohort)
(ITT Population)

	Pembrolizumab + SOC			SOC		
	n	(%)	(95% CI)	n	(%)	(95% CI)
Number of Subjects in Population	52			52		
Complete Response (CR)	7	13.5	(5.6, 25.8)	9	17.3	(8.2, 30.3)
Partial Response (PR)	29	55.8	(41.3, 69.5)	26	50.0	(35.8, 64.2)
Overall Response (CR+PR)	**36**	**69.2**	**(54.9, 81.3)**	**35**	**67.3**	**(52.9, 79.7)**
Stable Disease (SD)	12	23.1	(12.5, 36.8)	13	25.0	(14.0, 38.9)
Disease Control (CR+PR+SD)	**48**	**92.3**	**(81.5, 97.9)**	**48**	**92.3**	**(81.5, 97.9)**
Progressive Disease (PD)	3	5.8	(1.2, 15.9)	1	1.9	(0.0, 10.3)
Not Evaluable (NE[a])	0	0.0	(0.0, 6.8)	0	0.0	(0.0, 6.8)
No Assessment[b]	1	1.9	(0.0, 10.3)	3	5.8	(1.2, 15.9)

Responses are based on BICR assessment per RECIST 1.1.
BICR = Blinded independent central review.
Stable disease includes SD, Non-CR/Non-PD, and NED.
NED: No lesions were identified at baseline assessment and there remained no lesions at post baseline assessment(s).
[a]NE: post-baseline assessment(s) available however not being evaluable.
[b]No Assessment: no post-baseline assessment available for response evaluation.
Database Cutoff Date: 25MAY2022.

Source: [P811V02MK3475: adam-adsl; adrs]

DoR

Table 14.2-33
Summary of Time to Response and Duration of Response
Based on BICR Assessment per RECIST 1.1 in Participants with Confirmed Response
(CPS<1 Participants)
(Global Cohort)

	Pembrolizumab + SOC (N=52)	SOC (N=52)
Number of participants with response[a]	36	35
Time to Response (months)		
Mean (SD)	2.0 (1.1)	2.2 (1.2)
Median (Range)	1.5 (1.2-7.1)	1.6 (0.7-5.8)
Response Duration[b] (months)		
Median (Range)	8.9 (2.6+ - 26.0+)	9.0 (1.4+ - 31.8)
Number (%[b]) of Participants with Extended Response Duration:		
≥3 months	33 (94.3)	32 (94.1)
≥6 months	24 (76.0)	25 (76.3)
≥9 months	14 (49.2)	16 (50.9)
≥12 months	8 (36.9)	12 (44.1)

[a] Includes participants with best objective response as confirmed complete response or partial response
[b] From product-limit (Kaplan-Meier) method for censored data.
"+" indicates there is no progressive disease by the time of last disease assessment.
BICR = Blinded independent central review.
Database Cutoff Date: 25MAY2022

Source: [P811V02MK3475: adam-adsl; adtte]

Summary of main study(ies)

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

Table 1. Summary of Efficacy for trial KEYNOTE-811

Title: A Phase III, Randomized, Double-blind Trial Comparing Trastuzumab Plus Chemotherapy and Pembrolizumab With Trastuzumab Plus Chemotherapy and Placebo as First-line Treatment in Participants With HER2 Positive Advanced Gastric or Gastroesophageal Junction Adenocarcinoma (KEYNOTE-811)			
Study identifier	IND: 123,482; EudraCT: 2018-000224-34		
Design	Phase 3, randomized, double-blind, placebo-controlled		
Hypothesis	Superiority		
Treatments groups	Pembrolizumab + SOC		Pembrolizumab 200 mg Q3W + CAPOX (Oxaliplating 130 mg/m2 and Capecitabine 1000 mg/m2 BID Q3W) or FP (Cisplatin 80 mg/m2 Q3W and 5-FU 800 mg/m2 Q3W) + Trastuzumab 8 mg/kg loading dose, 6 mg/kg maintenance Q3W N=350 participants
	SOC		CAPOX (Oxaliplating 130 mg/m2 and Capecitabine 1000 mg/m2 BID Q3W) or FP (Cisplatin 80 mg/m2 Q3W and 5-FU 800 mg/m2 Q3W) + Trastuzumab 8 mg/kg loading dose, 6 mg/kg maintenance Q3W N=348 participants
Endpoints and definitions	Dual primary endpoints	PFS	Time from randomization to PD, based upon RECIST 1.1 by BICR, or death, whichever occurred earlier
		OS	Time from randomization to death due to any cause
	Secondary endpoint	ORR	proportion of subjects who have a CR or a PR by BICR
		DoR	time from first documented evidence of CR or PR until disease progression or death
Database lock	25-MAY-2022		

Results and Analysis

Analysis description	**Primary Analysis**		
Analysis population and time point description	Intent to treat		
Descriptive statistics and estimate variability	Treatment group	Pembrolizumab +SOC	SOC <group descriptor>
	Number of subject	350	348
	PFS (median months)	10	8.1
	95% CI	8.6, 11.7	7, 8.5
	OS (median months)	20	16.9
	95% CI	17.8, 23.2	15, 19.8
	ORR (CR+PR) (%) 95% CI **DOR** (median months)	72.6 67.6, 77.2 11.2 (1.1+ - 40.1+)	59.8 54.4, 65.0 9.0 (1.4+ – 38.3+)
Effect estimate per comparison	Primary endpoint	Pembrolizumab + SOC vs SOC	**PFS**
		HR	0.72
		95% CI	0.60; 0.87
		P-value	0.0002
	Primary endpoint	Pembrolizumab + SOC vs SOC	**OS**
		HR	0.87

		95% CI	0.72; 1.06
		P-value	0.0842
Notes	<free text>		
Analysis description	**Analysis by CPS**		
	CPS⩾1	Pembrolizumab +SOC	SOC
	Number of subject	298	296
	PFS (median months)	10.8	7.2
	95% CI	8.5, 12.5	6.8, 8.4
	OS (median months)	20.5	15.6
	95% CI	18.2, 24.3	13.5, 18.6
	ORR (CR+PR) (%) 95% CI **DOR** (months)	73.2 67.7, 78.1 11.3 (1.1+ - 40.1+)	58.4 52.6, 64.1 9.5 (1.4+ – 38.3+)
	Primary endpoint	Pembrolizumab + SOC vs SOC	**PFS**
		HR	0.70
		95% CI	0.58; 0.85
		P-value	0.0001
	Primary endpoint	Pembrolizumab + SOC vs SOC	**OS**
		HR	0.79
		95% CI	0.64; 0.98
		P-value	0.0143

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

N/A

Clinical studies in special populations

N/A

Supportive study(ies)

N/A

2.4.3. Discussion on clinical efficacy

Design and conduct of clinical studies

KEYNOTE-811 was a Phase 3, randomized, double-blind study of pembrolizumab vs placebo on top of chemotherapy and trastuzumab in first line HER2-positive gastric or GEJ adenocarcinoma at an advanced disease status (unresectable or metastatic tumours). In support of the sought indication, data derived from the IA2 (cutoff date of 25-MAY-2022) of the Phase 3 trial KEYNOTE-811 are presented.

The study population included relatively fit patients (ECOG 0-1 and adequate organ function). Among the inclusion/exclusion criteria, attention was given to the cardiac function in consideration of the indication to treatment with the HER2-targeted agent trastuzumab and the associated cardiotoxicity.

Availability of the tissue sample was an additional requirement for study entry in view of the PD-L1-based stratification scheme.

Pembrolizumab was administrated at a dose of 200 mg Q3W on top of a background therapy including two distinct chemotherapeutic regimens, namely a CAPOX (oxaliplatin+capecitabine) or FP (cisplatin+5 fluorouracil) combination, in addition to the HER2-targeted drug trastuzumab. The tested treatments are in line with the current clinical recommendations for the front-line approach to advanced/metastatic disease, the adopted drug combinations are considered equally effective and the dose of pembrolizumab can also be deemed appropriate since it is approved in both monotherapy and chemotherapy combined regimens across different indications. The choice of placebo as add-on to chemotherapy plus HER2-targeted therapy as comparator is adequate given the current therapeutic landscape for the intended indication.

The study included dual-primary efficacy endpoints based on PFS per RECIST 1.1 as assessed by BICR and OS. A sample size of 692 participants was calculated based on the assumptions that (1) the enrolment period was 28 months and the ramp-up period of enrolment was 6 months; (2) the duration of PFS and OS followed an exponential distribution; (3) a median PFS of 6.7 months in the control group with a true HR of 0.7; (4) a median OS of 13.8 months in the control group with a true HR ratio of 0.75. The calculation is comprehensible and reproducible, and the assumptions made for median PFS and median OS in the control arm are in line with the available historical data of chemotherapy in the 1L setting. The eight amendments to the protocol did not affect the sample size and power calculation. Only data from the Global Cohort has been used in the present analysis, data from the Japan-specific SOX Cohort remains outside the aim of the present report.

In the Global Cohort, randomization was stratified according to geographic region, PD-L1 status and chemotherapy regimen. The combination of these categories resulted in 3x2x2=12 strata. In the first version of the protocol dated 11-Apr-2018, patients were stratified according to geographic region, disease status and chemotherapy regimen. After the General Amendment n. 1, dated 31-May-2018 the stratification criterion of disease status (ECOG 0 versus ECOG 1) was removed and replaced with the PD-L1 status (positive versus negative, where positive was defined as CPS $\geq$1 and negative was defined as CPS <1). This change should not have inflated the balance of demographic and disease related characteristics at baseline between the two treatment groups, since the first patient, first visit was performed on 05-Oct-2018. It is understood that results from the Phase 1b study KEYNOTE-012 and Phase 2 KEYNOTE-059 in gastric cancer informed the CPS cut-off level (≥1 and <1) used in the current trial. Of note, the assay used for PD-L1 testing in KEYNOTE-811 was the Agilent PD-L1 IHC 22C3 pharmDx kit, which has been analytically validated to determine PD-L1 expression status in gastric tumors. This kit is CE marked as a companion diagnostic for KEYTRUDA in NSCLC, HNSCC, UC, esophageal cancer, TNBC, and cervical cancer. KEYNOTE-811 data will be utilized to seek approval of the kit as a companion diagnostic for gastric cancer.

The demographic and baseline disease characteristics were compared to evaluate balance between the 2 treatment groups and consistency with those of the all-comer participants (ITT).

As of the data cutoff date for IA2, 9 participants (2 in the pembrolizumab + SOC group and 7 in the placebo + SOC group) were inadvertently unblinded to their treatment assignment at the Sponsor level due to unblinded information being revealed by different modes of communication to blinded team members. Overall, 7 out of the 9 participants were unblinded after discontinuation from treatment. Two participants in the pembrolizumab plus SOC group were still on treatment when premature unblinding occurred. These unblinding incidents were reviewed via the Sponsor's Significant Quality Issues process and concluded not to have impacted the quality of the data.

The ITT population served as the population for the primary efficacy analyses. All randomly assigned participants were included in this population. The IA2 was the first analysis of PFS and OS. Statistical methods were well reported in the protocol section and in the supplemental Statistical Analysis Plan (sSAP), and considered appropriate: the overall type I error over the primary endpoints (PFS and OS) and the key secondary endpoint (ORR) is strongly controlled at 2.5% (one-sided), with initially 0.2% allocated to ORR, 0.3% to PFS and 2% to OS. PFS was tested using a hierarchical strategy and prespecified analysis plan allows alpha from successful hypotheses to be passed to other hypotheses.

There were eight protocol amendments over the study course, of these only amendments 5, 6 and 8 affected the SAP language. The rationale for these amendments was exhaustively explained. Altogether these amendments did not affect the consistency of study results, however some issues are addressed. Just before the first data cut-off (17-Jun-2020), the protocol was amended to add the PFS endpoint at IA1 as an administrative look (amendment 5 of 20-May-2020). Upon health authority feedback, after the DCO of 17-Jun-2020 (but before the database was locked on 14-July-2020) the protocol was amended again to remove PFS from the IA1 analysis (amendment 6 of 07-Jul-2020). The MAH confirmed that these changes were not based on internal data from the study.

Part of the study was conducted during the coronavirus disease 2019 (COVID-19) pandemic. There were no changes in the planned analyses following study unblinding and/or no post-hoc analyses were performed due to the COVID-19 pandemic or any other reason.

Sensitivity analyses were adequate.

At IA1 the stratified analyses were based only on 6 collapsed strata due to the small number of participants or events in some strata. The collapsed strata were based on blinded data taking into considerations both clinical relevance and counts of subjects/events. The same strata, used in the stratified log-rank test and the stratified Cox model, were used consistently at IA2.

Efficacy data and additional analyses

At the time of IA2 the number of randomized patients in the ITT population was 698 (350 to pembrolizumab + SOC and 348 to placebo + SOC), slightly higher than the planned number of 692 patients, and 696 were started on treatment. At time of data cut-off, only 484 PFS events over 542 required for IA2 were reached, while 415 OS events occurred, more than the expected 401 OS events, representing the 75.3% of information fraction. The median duration of follow-up was 15.4 months (range: 0.3 to 41.6 months).

Discontinuation from study intervention was registered in 78.0% of participants. The frequency of discontinuation from study intervention was higher in the control arm (73.4% and 82.7% in the pembrolizumab and placebo group, respectively), with the most common reason for discontinuation from study intervention being progressive disease (50.6% and 62.7% in the pembrolizumab and placebo group, respectively). Treatment was ongoing in more participants in the pembrolizumab plus SOC group compared with the SOC group (19.7% vs 12.4%).

The treatment arms were overall comparable in their demographic and disease characteristics. The majority of the study population included male patients (80.8% vs 19.2% of male and female subjects, respectively) aged 63 years in median, with equal representation of the different age categories according with disease epidemiology, with the exception of >75 year group that accounted for only 8% of the total population. An equal contribution to recruitment can be noted for the different geographic areas (Eastern Europe, Asia and rest of the World, around 30% each). Metastatic disease was prevailing over a locally advanced stage (97.6% vs 2.4%), mainly including gastric adenocarcinoma (66.8% vs 33.2% of gastroesophageal junction adenocarcinoma). The PD-L1 status was mostly

positive (85.1% CPS≥1 vs 14.9% of CPS<1), and the backbone therapy was more frequently a CAPOX combination (85.4% vs 14.6% of FP combination). Overall, the study population can be considered representative of the targeted indication, although very elderly patients were poorly represented and only relatively fit patients without significant cardiac conditions were recruited.

The efficacy analysis in the ITT population, showed advantage of pembrolizumab over placebo in terms of PFS (HR=0.72; 95% CI 0.60; 0.87; p<0.0002) with a 2-month gain in disease progression (10 vs 8.1 months in median in the pembrolizumab and control arm, respectively), but no benefit was demonstrated in OS (HR=0.87; 95% CI 0.72;1.06; p<0.0842). With a 75.3% of information fraction in OS events at the time of IA2, data can be considered overall mature.

Among the pre-specified subgroup analysis, the PD-L1 status emerged as the only effect modifier. Specifically, the PFS was unfavourably impacted by pembrolizumab in patients with CPS<1 (HR=1.17; 95% CI 0.73, 1.89), and actually the number of deaths was higher in the pembrolizumab arm relative to control (67.3% vs 57.7%) within this subgroup, leading to a negative effect of treatment on OS (HR=1.61; 95% CI 0.98,2.64; p=0.9722). For the counterpart CPS ≥1, pembrolizumab showed advantage over placebo in PFS (HR=0.70; 95% CI 0.58, 0.85) and OS (HR=0.79; 95% CI 0.64, 0.98; p=0.0143), with a gain in median PFS of 3 months (10.8 vs 7.2) and median OS of 5 months (20.5 vs 15.6). All the remaining strata were consistent with the ITT population.

As regards the analysis by PD-L1 status, it should be noted that the effect of pembrolizumab was almost similar in the two CPS categories for what concerns PFS (10.8 and 9.5 months in median in the CPS ≥1 and CPS<1 group, respectively); superiority in the CPS≥1 subgroup was mainly driven by the lower performance of the backbone therapy compared to the effect observed in CPS<1 (7.2 and 9.6 months in median PFS in the placebo arm for the CPS ≥1 and CPS<1 group, respectively). The OS results showed a similar trend, although more deaths were registered with pembrolizumab among patients with CPS<1 than those reported in the CPS≥1 group (67.3% vs 56%); on the contrary, placebo performed slightly better in the CPS<1 than CPS≥1 group (57.7% vs 61%). Overall, the superior effect of pembrolizumab over placebo in the CPS ≥1 seems to result from a slightly better performance of pembrolizumab and a lower efficacy of chemotherapy in this group. Acknowledging the limited value of subgroups analyses within subgroups, patients aged ≥65 years, and Asians within the CPS≥1 population apparently gained no OS benefit. Upon request, the MAH provided additional data for subgroup analysis. The increased frequency in the use of subsequent oncologic therapies in the Asian population may have contributed to differences in OS compared to non-Asians. Concerning the age categories, the subgroup 65-74 year-old patients shows an unfavourable outcome in OS but this was not confirmed in the oldest age group (≥75), although this latter is numerically limited for a proper analysis. A reduced magnitude of effect based on OS results was also noted for GEJ cancer compared to gastric cancer; no definitive conclusions can be made at the moment given the limited sample size of this subgroup. In any case, a detrimental effect is not envisaged in the GEJ cancer, with a HR=0.94 in OS, and the HR=0.73 in PFS that is similar to the ITT population value.

Based on these data, the MAH seeks indication limited to the CPS≥1 subgroup. Although being a stratification factor, efficacy by PD-L1 score was not incorporated in the multiplicity strategy of the study design. The non-confirmatory nature of these analyses should be considered implying that an effect on both PFS and OS has not been formally demonstrated in CPS ≥1 patients. However, plausibility of a PD-L1 dependent effect of pembrolizumab, and balanced distribution of baseline characteristics between the two CPS categories by virtue of the stratification scheme, provides a good rationale and reliability to the observed results. According to the EMA guidelines on subgroup analysis (EMA/CHMP/539146/2013), the trial was formally successful since a statistically significant effect in the ITT population on one of the two components of the dual endpoint has emerged; however, the therapeutic efficacy or risk-benefit is borderline and clearly not proven in the CPS<1 population, thus

configuring Scenario 2 of the guideline. A restriction of indication based on PD-L1 status can therefore be supported. Considering the single pivotal trial, replication of subgroup findings from other relevant trials should be considered, as stated by the EMA guidelines. In this regard, PD-L1 dependency in response to treatment has emerged in other clinical indications; and KEYNOTE-590 offers a relevant precedent in this specific clinical setting where benefit of treatment in the HER-2 negative gastric disease was demonstrated in the subgroup of patients with CPS≥10. The MAH has provided further analyses demonstrating that unlike precedent trials in other gastrointestinal cancer types, a CPS cut-off of 1 clearly distinguishes between favourable and no effect of treatment in this clinical setting, which makes the CPS ≥1 in the clinical indication uncontroversial.

Among the secondary endpoints, ORR analysis showed advantage of pembrolizumab over placebo in the ITT population (72.6% vs 59.8%) with a slightly better response duration in pembrolizumab than control arm (11.2 vs 9 months in median); a higher rate of participants with extended duration was achieved in the pembrolizumab arm compared to the control arm at all time points. The results were consistent in the subgroup with CPS≥1.

The PROs showed similar results between treatment arms.

Additional expert consultation

None.

Assessment of paediatric data on clinical efficacy

Not applicable

2.4.4. Conclusions on the clinical efficacy

In KEYNOTE-811, a statistically significant advantage of pembrolizumab versus placebo in addition to SOC was demonstrated in PFS but not OS, in the ITT population. However, an unfavourable effect of pembrolizumab relative to placebo emerges in the CPS<1 subgroup. An indication restricted to the CPS≥1 group can be considered, as proposed by the MAH, since data indicate superiority of pembrolizumab versus placebo in both PFS and OS in this category of patients.

2.5. Clinical safety

Introduction

Safety results are presented for 4 datasets (see table below):

- Safety results from IA2 of KEYNOTE-811 (DCO date: 25 MAY-2022). Safety analyses were based on the APaT population, which included all randomized participants who received at least 1 dose of study intervention.

- Pooled safety data from studies of pembrolizumab in combination with chemotherapy, as a point of reference. This group is comprised of non-gastric studies (ie, NSCLC, HNSCC, TNBC, esophageal, and cervical) with participants who received a variety of single agent or combination chemotherapies, thus comparisons of safety data may be limited due to the differences in the chemotherapeutic regimens, indications, time of exposure, underlying disease and severity of disease, and demographics between these datasets.

- Pooled safety data from pembrolizumab monotherapy studies, comprising the pembrolizumab monotherapy RSD, to enable a comparison of the safety profile of pembrolizumab plus SOC observed in KEYNOTE-811 to the established safety profile for pembrolizumab monotherapy.

Table 2: Safety Datasets and Nomenclature

Datasets	Population	Nomenclature in Tables	Nomenclature in Text
KEYNOTE-811 pembrolizumab plus SOC safety dataset	(**N=350**): Safety data from participants with gastric/GEJ adenocarcinoma who received pembrolizumab in combination with trastuzumab plus platinum/fluoropyrimidine doublet chemotherapy (FP or CAPOX) in KEYNOTE-811 (global cohort[a])	KN-811 Pembro + SOC	Pembrolizumab plus SOC
KEYNOTE-811 SOC safety dataset	(**N=346**): Safety data from participants with gastric/GEJ adenocarcinoma who received placebo plus trastuzumab plus chemotherapy (FP or CAPOX) in KEYNOTE-811 (global cohort[a])	KN-811 SOC	SOC
Pembrolizumab plus chemo pooled	(**N=3123**): Pooled safety data from participants who received at least 1 dose of pembrolizumab chemotherapy combo therapy in KN021 Cohort A, C and G, KN048, KN189, KN355, KN407, KN522, KN590 and KN826[b]	Pembro + Chemo Pooled Dataset	Pembrolizumab plus chemo pooled
Pembrolizumab monotherapy reference safety dataset	(**N=7631**): Pooled safety data from participants treated with pembrolizumab monotherapy, who received at least 1 dose of pembrolizumab in KN001 Part B1, B2, B3, D, C, F1, F2, F3, KN002 (original phase), KN006, KN010, KN012 Cohort B and B2, KN013 Cohort 3, KN024, KN040, KN042, KN045, KN048, KN052, KN054, KN055, KN087, KN177, KN204, KN564 and KN716	Pembrolizumab Monotherapy Reference Safety Dataset	Pembrolizumab monotherapy RSD

CAPOX=capecitabine plus oxaliplatin; FP=cisplatin plus 5-fluorouracil; GEJ=gastroesophageal junction; N=number; NSCLC=non–small cell lung cancer; Pembro = pembrolizumab; RSD=reference safety dataset; SOC=standard of care.

[a] Global cohort=approximately 692 participants were randomized in the global cohort in a 1:1 ratio to receive pembrolizumab or placebo each in combination with chemotherapy plus trastuzumab. The investigator had 2 chemotherapy regimen choices, FP or CAPOX, which were chosen prior to randomization in the trial.

[b] 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

Patients enrolled in KN811 study received study intervention as per table below. Pembrolizumab/trastuzumab were given until PD, completion of 35 cycles, or other discontinuation criteria were met. Duration of cisplatin in FP may be capped at 6 cycles, while oxaliplatin in CAPOX may be capped at 6 or 8 cycles as per local country guidelines; however, treatment with 5-FU or capecitabine may continue per protocol. Participants have the option to receive up to 1 additional year of trastuzumab and capecitabine or 5-FU or S1 beyond 35 administrations of pembrolizumab/placebo at the discretion of the investigator and after Sponsor consultation.

Table 3: treatments in KEYNOTE-811

Arm Name	Arm Type	Intervention Name	Intervention Type	Dose Formulation	Unit Dose Strength(s)[c]	Dosage Level(s)	Route of Adminis-tration	Regimen/ Treatment Period/ Vaccination Regimen	Use	IMP or NIMP/ AxMP	Sourcing
Pembrolizumab	Experimental	Pembrolizumab (MK-3475)	Biological/ Vaccine	Vial	25 mg/mL	200 mg	IV Infusion	Day 1 of each cycle (Q3W)	Test Product	IMP	Central
Placebo	Placebo Comparator	Placebo	Drug	Solution for Infusion	N/A	N/A	IV Infusion	Day 1 of each cycle (Q3W)	Placebo	IMP	Local
FP[a]	Experimental	Cisplatin[b]	Drug	Vial	1 mg/mL	80 mg/m^2	IV Infusion	Day 1 of each cycle (Q3W)	Background Treatment	NIMP/AxMP	Central or Local
FP[a]	Experimental	5-FU	Drug	Vial	25 mg/mL	800 mg/m^2	IV Infusion	Continuous on Days 1 to 5 of each cycle (Q3W) (120 hours, or per local standard)	Background Treatment	NIMP/AxMP	Central or Local
CAPOX[d]	Experimental	Oxaliplatin[b]	Drug	Vial	5 mg/mL	130 mg/m^2	IV Infusion	Day 1 of each cycle (Q3W) over 2 hours	Background Treatment	NIMP/AxMP	Central or Local
CAPOX[d]	Experimental	Capecitabine[b]	Drug	Tablet	150 mg or 500 mg	1000 mg/m^2 BID	Oral	Days 1 to 14 of each cycle (Q3W)	Background Treatment	NIMP/AxMP	Central or Local
SOX (Japan Only)	Experimental	S1[b]	Drug	Capsule	20 mg or 25 mg	40 mg (<1.25 m^2 BSA) 50 mg BID (1.25 to <1.5 m^2) 60 mg (≥1.5 m^2 BSA)	Oral	Days 1 to 14 of each cycle (Q3W) BID Days 1 to 14 of each cycle (Q3W).	Background Treatment	NIMP/AxMP	Local
SOX (Japan Only)	Experimental	Oxaliplatin	Drug	Vial	5 mg/mL	130 mg/m^2	IV Infusion	Day 1 of each cycle (Q3W) over 2 hours	Background Treatment	NIMP/AxMP	Local
All Cohorts	Experimental	Trastuzumab[b]	Drug	Vial	60 mg Japan only) 150 mg 420 mg 440 mg 600 mg	8 mg/kg loading dose, 6 mg/kg maintenance	IV Infusion	Day 1 of each cycle (Q3W)	Background Treatment	NIMP/AxMP	Central or Local

5-FU=5 fluorouracil; AxMP = auxiliary medicinal product, BID=twice daily; BSA=body surface area; CAPOX=capecitabine/oxaliplatin; FP=cisplatin plus 5 fluorouracil; IMP=investigational medicinal product; IV=intravenous; Q3W=every 3 weeks; S1=combination product containing tegafur, a prodrug of 5-FU, and 2 types of enzyme inhibitors, CDHP and Oxo; SOX=S1 plus oxaliplatin.

Definitions of IMP, NIMP, and AxMP are based on guidance issues by the European Commission. Regional and/or country differences of the definition of IMP and NIMP/AxMP may exist. In these circumstances, local legislation is followed.

Pembrolizumab/trastuzumab will be administered until disease progression, completion of 35 cycles, or other discontinuation criteria are met.

Participants have the option to receive up to 1 additional year of trastuzumab and capecitabine or 5-FU or S1 beyond 35 administrations of pembrolizumab/placebo at the discretion of the investigator and after Sponsor consultation. Pembrolizumab/placebo treatment is not allowed beyond 35 administrations in the initial treatment course. Participants who stop pembrolizumab/placebo treatment after 35 administrations, for reasons other than disease progression or intolerability, or participants who attain a CR and stop trial treatment, may be eligible for up to 17 additional administrations of pembrolizumab upon experiencing disease progression if they are randomized to the pembrolizumab arm.

a FP: Duration of cisplatin treatment may be capped at 6 cycles as per local country guidelines; however, treatment with 5-FU may continue per protocol.
b Chemotherapy options and trastuzumab are used in both the experimental and placebo arms.
c The strength of treatment may vary depending on the source. The table captures the current available strengths but could vary depending on availability.
d CAPOX: duration of oxaliplatin may be capped at 6 or 8 cycles as per local country guidelines; however, treatment with capecitabine may continue per protocol.

Table 4: Summary of Drug Exposure (APaT Population)

	KN811 Pembrolizumab + SOC (N=350)	KN811 SOC (N=346)	Pembro + Chemo Pooled Dataset[i] (N=3123)	Pembrolizumab Monotherapy Reference Safety Dataset[j] (N=7631)
Duration On Therapy (month)				
Mean	11.60	10.01	9.85	7.85
Median	9.59	7.31	7.89	5.78
SD	8.495	7.998	7.291	6.907
Range	0.33 to 36.60	0.03 to 36.11	0.03 to 48.00	0.03 to 38.01
Number of Cycles				
Mean	15.87	13.81	13.23	12.31
Median	13.00	10.00	11.00	9.00
SD	11.389	10.899	9.649	10.098
Range	1.00 to 51.00	1.00 to 49.00	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.				

Table 5: Drug Exposure by Duration (APaT Population)

	KN811 Pembrolizumab + SOC (N=350)			KN811 SOC (N=346)			Pembro + Chemo Pooled Dataset[i] (N=3123)			Pembrolizumab Monotherapy Reference Safety Dataset[j] (N=7631)		
	n	(%)	Person-years	n	(%)	Person-years	n	(%)	Person-years	n	(%)	Person-years
Duration of exposure												
>0 m	350	(100.0)	(338.4)	346	(100.0)	(288.7)	3,118	(99.8)	(2,558.5)	7,631	(100.0)	(4,995.0)
>=1 m	334	(95.4)	(337.6)	330	(95.4)	(288.2)	2,889	(92.5)	(2,550.9)	6,637	(87.0)	(4,962.4)
>=3 m	299	(85.4)	(331.9)	283	(81.8)	(280.4)	2,535	(81.2)	(2,488.4)	5,023	(65.8)	(4,693.1)
>=6 m	241	(68.9)	(310.0)	206	(59.5)	(251.2)	1,847	(59.1)	(2,225.8)	3,781	(49.5)	(4,240.0)
>=12 m	141	(40.3)	(236.7)	105	(30.3)	(179.3)	1,192	(38.2)	(1,760.0)	1,673	(21.9)	(2,558.8)
Each participant is counted once on each applicable duration category row. Duration of Exposure is calculated as last dose date - first dose date + 1.												

Table 6: Participant Characteristics (APaT Population)

	KN811 Pembrolizumab + SOC		KN811 SOC		Pembro + Chemo Pooled Dataset[i]		Pembrolizumab Monotherapy Reference Safety Dataset[j]	
	n	(%)	n	(%)	n	(%)	n	(%)
Participants in population	350		346		3,123		7,631	
Sex								
Male	284	(81.1)	278	(80.3)	1,042	(33.4)	4,889	(64.1)
Female	66	(18.9)	68	(19.7)	2,081	(66.6)	2,742	(35.9)
Age (Years)								
<65	205	(58.6)	190	(54.9)	2,176	(69.7)	4,524	(59.3)
>=65	145	(41.4)	156	(45.1)	947	(30.3)	3,107	(40.7)
Mean	60.4		61.7		56.6		59.9	
SD	11.8		10.8		12.5		13.4	
Median	62.0		63.0		58.0		62.0	
Range	19 to 85		32 to 85		20 to 94		15 to 94	
Race								
American Indian Or Alaska Native	5	(1.4)	6	(1.7)	55	(1.8)	59	(0.8)
Asian	119	(34.0)	121	(35.0)	686	(22.0)	826	(10.8)

Black Or African American	2	(0.6)	2	(0.6)	108	(3.5)	146	(1.9)
Multiracial	6	(1.7)	5	(1.4)	64	(2.0)	86	(1.1)
Native Hawaiian Or Other Pacific Islander	0	(0.0)	0	(0.0)	2	(0.1)	5	(0.1)
White	217	(62.0)	207	(59.8)	2,088	(66.9)	5,838	(76.5)
Missing	1	(0.3)	5	(1.4)	120	(3.8)	671	(8.8)
Ethnicity								
Hispanic Or Latino	38	(10.9)	44	(12.7)	429	(13.7)	604	(7.9)
Not Hispanic Or Latino	309	(88.3)	291	(84.1)	2,502	(80.1)	6,064	(79.5)
Not Reported	1	(0.3)	10	(2.9)	105	(3.4)	808	(10.6)
Unknown	2	(0.6)	1	(0.3)	66	(2.1)	145	(1.9)
Missing	0	(0.0)	0	(0.0)	21	(0.7)	10	(0.1)
ECOG Performance Scale								
[0] Normal Activity	146	(41.7)	144	(41.6)	1,768	(56.6)	4,016	(52.6)
[1] Symptoms, but ambulatory	204	(58.3)	201	(58.1)	1,349	(43.2)	3,440	(45.1)
Other/Missing	0	(0.0)	1	(0.3)	6	(0.2)	175	(2.3)
Geographic Region								
Western Europe	98	(28.0)	91	(26.3)	1,118	(35.8)	2,856	(37.4)
Ex-Western Europe	252	(72.0)	255	(73.7)	2,005	(64.2)	4,775	(62.6)
Western Europe includes countries in the European Economic Area, United Kingdom, and Switzerland.								

Adverse events

AEs were coded using MedDRA version 25.0 and reported according to NCI CTCAE version 4.03.

Table 7: Adverse Event Summary (APaT Population)

	KN811 Pembrolizumab + SOC		KN811 SOC		Pembro + Chemo Pooled Dataset[i]		Pembrolizumab Monotherapy Reference Safety Dataset[j]	
	n	(%)	n	(%)	n	(%)	n	(%)
Participants in population	350		346		3,123		7,631	
with one or more adverse events	347	(99.1)	346	(100.0)	3,097	(99.2)	7,375	(96.6)
with no adverse event	3	(0.9)	0	(0.0)	26	(0.8)	256	(3.4)
with drug-related[a] adverse events	341	(97.4)	334	(96.5)	3,020	(96.7)	5,462	(71.6)
with toxicity grade 3-5 adverse events	248	(70.9)	225	(65.0)	2,479	(79.4)	3,514	(46.0)
with toxicity grade 3-5 drug-related adverse events	204	(58.3)	176	(50.9)	2,099	(67.2)	1,208	(15.8)
with serious adverse events	157	(44.9)	157	(45.4)	1,456	(46.6)	2,742	(35.9)
with serious drug-related adverse events	88	(25.1)	79	(22.8)	910	(29.1)	840	(11.0)
who died	22	(6.3)	20	(5.8)	160	(5.1)	346	(4.5)
who died due to a drug-related adverse event	4	(1.1)	3	(0.9)	49	(1.6)	42	(0.6)
discontinued any drug due to an adverse event	142	(40.6)	126	(36.4)	900	(28.8)	1,066	(14.0)
discontinued pembrolizumab or placebo	45	(12.9)	36	(10.4)	548	(17.5)	1,066	(14.0)
discontinued any chemotherapy	135	(38.6)	124	(35.8)	636	(20.4)	NA	
discontinued all drugs	22	(6.3)	23	(6.6)	143	(4.6)	1,066	(14.0)
discontinued any drug due to a drug-related adverse event	124	(35.4)	108	(31.2)	747	(23.9)	639	(8.4)
discontinued pembrolizumab or placebo	29	(8.3)	17	(4.9)	405	(13.0)	639	(8.4)
discontinued any chemotherapy	115	(32.9)	106	(30.6)	528	(16.9)	NA	
discontinued all drugs	11	(3.1)	9	(2.6)	86	(2.8)	639	(8.4)
discontinued any drug due to a serious adverse event	45	(12.9)	42	(12.1)	472	(15.1)	714	(9.4)
discontinued pembrolizumab or placebo	34	(9.7)	35	(10.1)	382	(12.2)	714	(9.4)
discontinued any chemotherapy	39	(11.1)	39	(11.3)	307	(9.8)	NA	
discontinued all drugs	20	(5.7)	23	(6.6)	127	(4.1)	714	(9.4)
discontinued any drug due to a serious drug-related adverse event	30	(8.6)	21	(6.1)	343	(11.0)	347	(4.5)
discontinued pembrolizumab or placebo	21	(6.0)	16	(4.6)	261	(8.4)	347	(4.5)

discontinued any chemotherapy	24	(6.9)	18	(5.2)	213	(6.8)	NA	
discontinued all drugs	10	(2.9)	9	(2.6)	73	(2.3)	347	(4.5)

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

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

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

Table 8: Exposure-Adjusted Adverse Event Summary (Including Multiple Occurrences of Events) (APaT Population)

	Event Count and Rate (Events/100 person-months)[a]			
	KN811 Pembrolizumab + SOC	KN811 SOC	Pembro + Chemo Pooled Dataset[i]	Pembrolizumab Monotherapy Reference Safety Dataset[j]
Number of subjects exposed	350	346	3123	7631
Total exposure[b] in person-months	4354.61	3773.18	34084.64	66840.89
Total events (rate)				
adverse events	5904 (135.58)	5325 (141.13)	66128 (194.01)	76878 (115.02)
drug-related[c] adverse events	3953 (90.78)	3565 (94.48)	40032 (117.45)	24542 (36.72)
toxicity grade 3-5 adverse events	724 (16.63)	615 (16.30)	9548 (28.01)	7463 (11.17)
toxicity grade 3-5 drug-related adverse events	439 (10.08)	363 (9.62)	6869 (20.15)	1770 (2.65)
serious adverse events	312 (7.16)	257 (6.81)	2903 (8.52)	4801 (7.18)
serious drug-related adverse events	145 (3.33)	116 (3.07)	1477 (4.33)	1093 (1.64)
adverse events leading to death	22 (0.51)	20 (0.53)	166 (0.49)	353 (0.53)
drug-related adverse events leading to death	4 (0.09)	3 (0.08)	50 (0.15)	42 (0.06)
adverse events resulting in drug discontinuation	188 (4.32)	152 (4.03)	1097 (3.22)	1165 (1.74)
drug-related adverse events resulting in drug discontinuation	160 (3.67)	125 (3.31)	907 (2.66)	703 (1.05)
serious adverse events resulting in drug discontinuation	50 (1.15)	45 (1.19)	534 (1.57)	753 (1.13)
serious drug-related adverse events resulting in drug discontinuation	34 (0.78)	21 (0.56)	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.

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

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

For KN001 and KN054, a new AE episode was recorded when there was any AE change in grade, relationship, or seriousness. If the episode date ranges were continuous, then these records were counted as one AE episode.

Grades are based on NCI CTCAE version 4.03.

All adverse events

Table 9: Participants With Adverse Events (Incidence ≥ 10% in One or More Treatment Groups) By Decreasing Frequency of Preferred Term (APaT Population)

	KN811 Pembrolizumab + SOC		KN811 SOC		Pembro + Chemo Pooled Dataset[i]		Pembrolizumab Monotherapy Reference Safety Dataset[j]	
	n	(%)	n	(%)	n	(%)	n	(%)
Participants in population	350		346		3,123		7,631	
with one or more adverse events	347	(99.1)	346	(100.0)	3,097	(99.2)	7,375	(96.6)
with no adverse events	3	(0.9)	0	(0.0)	26	(0.8)	256	(3.4)
Diarrhoea	183	(52.3)	160	(46.2)	1,071	(34.3)	1,678	(22.0)
Nausea	168	(48.0)	167	(48.3)	1,695	(54.3)	1,534	(20.1)
Anaemia	157	(44.9)	159	(46.0)	1,704	(54.6)	982	(12.9)
Vomiting	113	(32.3)	99	(28.6)	885	(28.3)	945	(12.4)
Decreased appetite	110	(31.4)	111	(32.1)	850	(27.2)	1,312	(17.2)
Neutrophil count decreased	96	(27.4)	85	(24.6)	621	(19.9)	53	(0.7)
Platelet count decreased	95	(27.1)	98	(28.3)	377	(12.1)	95	(1.2)
Aspartate aminotransferase increased	85	(24.3)	63	(18.2)	490	(15.7)	538	(7.1)
Peripheral sensory neuropathy	85	(24.3)	73	(21.1)	393	(12.6)	83	(1.1)
Fatigue	81	(23.1)	77	(22.3)	1,197	(38.3)	2,368	(31.0)
Palmar-plantar erythrodysaesthesia syndrome	79	(22.6)	77	(22.3)	34	(1.1)	24	(0.3)
Weight decreased	73	(20.9)	59	(17.1)	365	(11.7)	628	(8.2)
Neuropathy peripheral	65	(18.6)	65	(18.8)	465	(14.9)	146	(1.9)
Alanine aminotransferase increased	63	(18.0)	48	(13.9)	564	(18.1)	572	(7.5)
Constipation	59	(16.9)	68	(19.7)	1,107	(35.4)	1,179	(15.5)

Neutropenia	59	(16.9)	57	(16.5)	1,111	(35.6)	82	(1.1)
White blood cell count decreased	55	(15.7)	42	(12.1)	464	(14.9)	70	(0.9)
Hypokalaemia	54	(15.4)	41	(11.8)	335	(10.7)	324	(4.2)
Pyrexia	53	(15.1)	46	(13.3)	630	(20.2)	934	(12.2)
Hypoalbuminaemia	52	(14.9)	55	(15.9)	154	(4.9)	209	(2.7)
Blood bilirubin increased	50	(14.3)	34	(9.8)	64	(2.0)	163	(2.1)
Asthenia	47	(13.4)	66	(19.1)	661	(21.2)	880	(11.5)
Thrombocytopenia	43	(12.3)	47	(13.6)	572	(18.3)	117	(1.5)
Infusion related reaction	41	(11.7)	34	(9.8)	122	(3.9)	75	(1.0)
Abdominal pain	38	(10.9)	42	(12.1)	323	(10.3)	674	(8.8)
Stomatitis	38	(10.9)	31	(9.0)	451	(14.4)	201	(2.6)
Hypothyroidism	37	(10.6)	15	(4.3)	434	(13.9)	937	(12.3)
Pneumonia	37	(10.6)	15	(4.3)	241	(7.7)	487	(6.4)
Cough	29	(8.3)	19	(5.5)	659	(21.1)	1,392	(18.2)
Oedema peripheral	28	(8.0)	27	(7.8)	347	(11.1)	630	(8.3)
Pruritus	28	(8.0)	18	(5.2)	468	(15.0)	1,435	(18.8)
Rash	28	(8.0)	15	(4.3)	644	(20.6)	1,175	(15.4)
Mucosal inflammation	27	(7.7)	26	(7.5)	363	(11.6)	111	(1.5)
Arthralgia	23	(6.6)	14	(4.0)	660	(21.1)	1,436	(18.8)
Back pain	21	(6.0)	22	(6.4)	365	(11.7)	847	(11.1)
Insomnia	21	(6.0)	16	(4.6)	400	(12.8)	528	(6.9)
Dizziness	19	(5.4)	12	(3.5)	363	(11.6)	564	(7.4)
Headache	19	(5.4)	20	(5.8)	572	(18.3)	946	(12.4)
Dysgeusia	17	(4.9)	16	(4.6)	328	(10.5)	150	(2.0)
Dyspnoea	15	(4.3)	13	(3.8)	425	(13.6)	1,130	(14.8)
Leukopenia	12	(3.4)	23	(6.6)	367	(11.8)	52	(0.7)
Myalgia	12	(3.4)	7	(2.0)	361	(11.6)	575	(7.5)
Urinary tract infection	12	(3.4)	13	(3.8)	343	(11.0)	511	(6.7)
Alopecia	8	(2.3)	6	(1.7)	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.

Adverse Events Related to Study Intervention

Table 10: Participants in KN811 With Drug-Related Adverse Events by Decreasing Incidence (Incidence ≥ 5% in One or More Treatment Groups) (Global Cohort) (APaT Population)

	Pembrolizumab + SOC		SOC	
	n	(%)	n	(%)
Participants in population	350		346	
with one or more adverse events	341	(97.4)	334	(96.5)
with no adverse events	9	(2.6)	12	(3.5)
Diarrhoea	165	(47.1)	145	(41.9)
Nausea	154	(44.0)	152	(43.9)
Anaemia	109	(31.1)	113	(32.7)
Neutrophil count decreased	92	(26.3)	83	(24.0)
Decreased appetite	91	(26.0)	91	(26.3)
Platelet count decreased	89	(25.4)	93	(26.9)
Vomiting	88	(25.1)	86	(24.9)
Peripheral sensory neuropathy	84	(24.0)	73	(21.1)
Palmar-plantar erythrodysaesthesia syndrome	78	(22.3)	72	(20.8)
Fatigue	69	(19.7)	57	(16.5)
Aspartate aminotransferase increased	66	(18.9)	50	(14.5)
Neuropathy peripheral	60	(17.1)	63	(18.2)
Neutropenia	59	(16.9)	54	(15.6)
White blood cell count decreased	53	(15.1)	41	(11.8)
Alanine aminotransferase increased	51	(14.6)	41	(11.8)
Weight decreased	42	(12.0)	24	(6.9)
Infusion related reaction	41	(11.7)	34	(9.8)
Thrombocytopenia	40	(11.4)	44	(12.7)
Asthenia	39	(11.1)	50	(14.5)
Blood bilirubin increased	39	(11.1)	27	(7.8)
Stomatitis	36	(10.3)	31	(9.0)
Hypothyroidism	29	(8.3)	15	(4.3)
Malaise	25	(7.1)	25	(7.2)
Paraesthesia	25	(7.1)	21	(6.1)
Pruritus	25	(7.1)	9	(2.6)
Constipation	23	(6.6)	28	(8.1)
Mucosal inflammation	22	(6.3)	25	(7.2)
Blood creatinine increased	21	(6.0)	6	(1.7)
Hypokalaemia	21	(6.0)	15	(4.3)
Pyrexia	20	(5.7)	19	(5.5)
Rash	20	(5.7)	6	(1.7)
Leukopenia	11	(3.1)	21	(6.1)

Every participant is counted a single time for each applicable row and column.
A specific adverse event appears on this report only if its incidence in one or more of the columns meets the incidence criterion in the report title, after rounding.
Non-serious adverse events up to 30 days of last dose and serious adverse events up to 90 days of last dose are included.
Database Cutoff Date: 25MAY2022.

All Grade 3 to 5 Adverse Events

Table 11: Participants With Grade 3-5 Adverse Events (Incidence ≥ 1% in One or More Treatment Groups) By Decreasing Frequency of Preferred Term (APaT Population)

	KN811 Pembrolizumab + SOC		KN811 SOC		Pembro + Chemo Pooled Dataset[i]		Pembrolizumab Monotherapy Reference Safety Dataset[j]	
	n	(%)	n	(%)	n	(%)	n	(%)
Participants in population	350		346		3,123		7,631	
with one or more adverse events	248	(70.9)	225	(65.0)	2,479	(79.4)	3,514	(46.0)
with no adverse events	102	(29.1)	121	(35.0)	644	(20.6)	4,117	(54.0)
Anaemia	44	(12.6)	35	(10.1)	620	(19.9)	275	(3.6)
Diarrhoea	34	(9.7)	29	(8.4)	102	(3.3)	114	(1.5)
Neutrophil count decreased	29	(8.3)	30	(8.7)	443	(14.2)	10	(0.1)
Neutropenia	23	(6.6)	18	(5.2)	727	(23.3)	21	(0.3)
Platelet count decreased	22	(6.3)	24	(6.9)	114	(3.7)	10	(0.1)
Hypokalaemia	20	(5.7)	20	(5.8)	96	(3.1)	70	(0.9)

Vomiting	17	(4.9)	11	(3.2)	101	(3.2)	52	(0.7)
Fatigue	16	(4.6)	9	(2.6)	158	(5.1)	166	(2.2)
Nausea	14	(4.0)	19	(5.5)	108	(3.5)	58	(0.8)
Decreased appetite	13	(3.7)	14	(4.0)	61	(2.0)	77	(1.0)
Peripheral sensory neuropathy	13	(3.7)	7	(2.0)	26	(0.8)	2	(0.0)
Pneumonia	13	(3.7)	7	(2.0)	148	(4.7)	270	(3.5)
Thrombocytopenia	13	(3.7)	8	(2.3)	201	(6.4)	23	(0.3)
Pulmonary embolism	11	(3.1)	10	(2.9)	58	(1.9)	101	(1.3)
Aspartate aminotransferase increased	10	(2.9)	3	(0.9)	81	(2.6)	95	(1.2)
Asthenia	10	(2.9)	11	(3.2)	112	(3.6)	70	(0.9)
Blood bilirubin increased	8	(2.3)	3	(0.9)	6	(0.2)	27	(0.4)
Hyponatraemia	8	(2.3)	10	(2.9)	114	(3.7)	169	(2.2)
Neuropathy peripheral	8	(2.3)	10	(2.9)	33	(1.1)	4	(0.1)
Alanine aminotransferase increased	7	(2.0)	3	(0.9)	120	(3.8)	97	(1.3)
Dysphagia	7	(2.0)	9	(2.6)	40	(1.3)	31	(0.4)
Weight decreased	7	(2.0)	4	(1.2)	41	(1.3)	35	(0.5)
Colitis	6	(1.7)	4	(1.2)	27	(0.9)	74	(1.0)
Hypertension	6	(1.7)	5	(1.4)	92	(2.9)	148	(1.9)
Infusion related reaction	6	(1.7)	2	(0.6)	17	(0.5)	1	(0.0)
Pneumonitis	6	(1.7)	0	(0.0)	46	(1.5)	97	(1.3)
Acute kidney injury	5	(1.4)	2	(0.6)	59	(1.9)	65	(0.9)
COVID-19	5	(1.4)	1	(0.3)	2	(0.1)	0	(0.0)
Dehydration	5	(1.4)	5	(1.4)	45	(1.4)	70	(0.9)
Ejection fraction decreased	5	(1.4)	3	(0.9)	0	(0.0)	0	(0.0)
Palmar-plantar erythrodysaesthesia syndrome	5	(1.4)	5	(1.4)	3	(0.1)	1	(0.0)
Upper gastrointestinal haemorrhage	5	(1.4)	4	(1.2)	6	(0.2)	6	(0.1)
White blood cell count decreased	5	(1.4)	6	(1.7)	218	(7.0)	5	(0.1)
Gamma-glutamyltransferase increased	4	(1.1)	5	(1.4)	34	(1.1)	56	(0.7)
Gastric haemorrhage	4	(1.1)	5	(1.4)	4	(0.1)	5	(0.1)
Gastrointestinal haemorrhage	4	(1.1)	3	(0.9)	4	(0.1)	9	(0.1)
Hypoalbuminaemia	4	(1.1)	4	(1.2)	12	(0.4)	33	(0.4)
Hypomagnesaemia	4	(1.1)	2	(0.6)	19	(0.6)	5	(0.1)
Lymphocyte count decreased	4	(1.1)	4	(1.2)	60	(1.9)	33	(0.4)
Mucosal inflammation	4	(1.1)	3	(0.9)	55	(1.8)	10	(0.1)
Stomatitis	4	(1.1)	6	(1.7)	63	(2.0)	9	(0.1)
Hyperglycaemia	3	(0.9)	3	(0.9)	35	(1.1)	83	(1.1)
Hypophosphataemia	3	(0.9)	5	(1.4)	35	(1.1)	52	(0.7)
Sepsis	3	(0.9)	2	(0.6)	48	(1.5)	60	(0.8)
COVID-19 pneumonia	2	(0.6)	5	(1.4)	1	(0.0)	2	(0.0)
Febrile neutropenia	2	(0.6)	4	(1.2)	259	(8.3)	11	(0.1)
Hypotension	2	(0.6)	1	(0.3)	31	(1.0)	35	(0.5)
Leukopenia	2	(0.6)	4	(1.2)	145	(4.6)	7	(0.1)
Back pain	1	(0.3)	4	(1.2)	22	(0.7)	72	(0.9)
Dyspnoea	1	(0.3)	1	(0.3)	50	(1.6)	145	(1.9)
Malaise	1	(0.3)	4	(1.2)	8	(0.3)	5	(0.1)
Neurotoxicity	1	(0.3)	4	(1.2)	0	(0.0)	0	(0.0)
Rash maculo-papular	1	(0.3)	0	(0.0)	37	(1.2)	23	(0.3)
Syncope	1	(0.3)	0	(0.0)	43	(1.4)	43	(0.6)
Abdominal pain	0	(0.0)	4	(1.2)	20	(0.6)	65	(0.9)
Lymphopenia	0	(0.0)	0	(0.0)	32	(1.0)	20	(0.3)
Pleural effusion	0	(0.0)	0	(0.0)	29	(0.9)	73	(1.0)
Rash	0	(0.0)	0	(0.0)	37	(1.2)	44	(0.6)
Urinary tract infection	0	(0.0)	2	(0.6)	60	(1.9)	85	(1.1)

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

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

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

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

Grade 3 to 5 Adverse Events Related to Study Intervention

Table 12: 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)

	KN811 Pembrolizumab + SOC		KN811 SOC		Pembro + Chemo Pooled Dataset[i]		Pembrolizumab Monotherapy Reference Safety Dataset[j]	
	n	(%)	n	(%)	n	(%)	n	(%)
Participants in population	350		346		3,123		7,631	
with one or more adverse events	204	(58.3)	176	(50.9)	2,099	(67.2)	1,208	(15.8)
with no adverse events	146	(41.7)	170	(49.1)	1,024	(32.8)	6,423	(84.2)
Diarrhoea	31	(8.9)	27	(7.8)	74	(2.4)	75	(1.0)
Neutrophil count decreased	28	(8.0)	30	(8.7)	428	(13.7)	6	(0.1)
Neutropenia	22	(6.3)	16	(4.6)	710	(22.7)	13	(0.2)
Platelet count decreased	22	(6.3)	23	(6.6)	110	(3.5)	2	(0.0)
Anaemia	21	(6.0)	20	(5.8)	524	(16.8)	33	(0.4)
Nausea	14	(4.0)	15	(4.3)	96	(3.1)	13	(0.2)
Vomiting	14	(4.0)	10	(2.9)	77	(2.5)	12	(0.2)
Peripheral sensory neuropathy	13	(3.7)	7	(2.0)	26	(0.8)	2	(0.0)
Fatigue	12	(3.4)	8	(2.3)	133	(4.3)	75	(1.0)
Decreased appetite	11	(3.1)	11	(3.2)	49	(1.6)	23	(0.3)
Hypokalaemia	11	(3.1)	10	(2.9)	41	(1.3)	12	(0.2)
Thrombocytopenia	11	(3.1)	6	(1.7)	185	(5.9)	11	(0.1)
Neuropathy peripheral	8	(2.3)	9	(2.6)	33	(1.1)	2	(0.0)
Asthenia	7	(2.0)	9	(2.6)	82	(2.6)	26	(0.3)
Aspartate aminotransferase increased	6	(1.7)	1	(0.3)	63	(2.0)	47	(0.6)
Colitis	6	(1.7)	4	(1.2)	26	(0.8)	67	(0.9)
Infusion related reaction	6	(1.7)	2	(0.6)	15	(0.5)	1	(0.0)
Palmar-plantar erythrodysaesthesia syndrome	5	(1.4)	5	(1.4)	3	(0.1)	1	(0.0)
Pneumonitis	5	(1.4)	0	(0.0)	42	(1.3)	91	(1.2)
Weight decreased	5	(1.4)	2	(0.6)	22	(0.7)	8	(0.1)
Ejection fraction decreased	4	(1.1)	3	(0.9)	0	(0.0)	0	(0.0)
Gamma-glutamyltransferase increased	4	(1.1)	3	(0.9)	19	(0.6)	25	(0.3)
Stomatitis	4	(1.1)	6	(1.7)	60	(1.9)	5	(0.1)
Acute kidney injury	3	(0.9)	0	(0.0)	37	(1.2)	16	(0.2)
Alanine aminotransferase increased	3	(0.9)	1	(0.3)	96	(3.1)	56	(0.7)
Dehydration	3	(0.9)	4	(1.2)	18	(0.6)	9	(0.1)
Hyponatraemia	3	(0.9)	6	(1.7)	53	(1.7)	32	(0.4)
Mucosal inflammation	3	(0.9)	2	(0.6)	53	(1.7)	6	(0.1)
Pneumonia	3	(0.9)	1	(0.3)	39	(1.2)	17	(0.2)
White blood cell count decreased	3	(0.9)	6	(1.7)	211	(6.8)	2	(0.0)
Hypertension	2	(0.6)	1	(0.3)	32	(1.0)	15	(0.2)
Leukopenia	2	(0.6)	3	(0.9)	142	(4.5)	3	(0.0)
Lymphocyte count decreased	2	(0.6)	4	(1.2)	51	(1.6)	9	(0.1)
Febrile neutropenia	1	(0.3)	3	(0.9)	245	(7.8)	0	(0.0)
Neurotoxicity	1	(0.3)	4	(1.2)	0	(0.0)	0	(0.0)
Rash maculo-papular	1	(0.3)	0	(0.0)	31	(1.0)	21	(0.3)
Rash	0	(0.0)	0	(0.0)	31	(1.0)	37	(0.5)

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

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

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

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

Serious adverse event/deaths/other significant events

SAE

Table 13: Participants With Serious Adverse Events (Incidence ≥1% in One or More Treatment Groups) By Decreasing Frequency of Preferred Term (APaT Population)

	KN811 Pembrolizumab + SOC		KN811 SOC		Pembro + Chemo Pooled Dataset[i]		Pembrolizumab Monotherapy Reference Safety Dataset[j]	
	n	(%)	n	(%)	n	(%)	n	(%)
Participants in population	350		346		3,123		7,631	
with one or more adverse events	157	(44.9)	157	(45.4)	1,456	(46.6)	2,742	(35.9)
with no adverse events	193	(55.1)	189	(54.6)	1,667	(53.4)	4,889	(64.1)
Pneumonia	18	(5.1)	7	(2.0)	145	(4.6)	272	(3.6)
Diarrhoea	17	(4.9)	16	(4.6)	47	(1.5)	70	(0.9)
Pulmonary embolism	10	(2.9)	7	(2.0)	43	(1.4)	78	(1.0)
Infusion related reaction	7	(2.0)	2	(0.6)	11	(0.4)	5	(0.1)
Pneumonitis	7	(2.0)	1	(0.3)	54	(1.7)	136	(1.8)
Vomiting	7	(2.0)	9	(2.6)	41	(1.3)	32	(0.4)
Acute kidney injury	6	(1.7)	3	(0.9)	55	(1.8)	65	(0.9)
Upper gastrointestinal haemorrhage	6	(1.7)	5	(1.4)	5	(0.2)	6	(0.1)
COVID-19	5	(1.4)	4	(1.2)	2	(0.1)	0	(0.0)
Dysphagia	5	(1.4)	7	(2.0)	21	(0.7)	18	(0.2)
Fatigue	5	(1.4)	3	(0.9)	14	(0.4)	22	(0.3)
Gastrointestinal haemorrhage	5	(1.4)	2	(0.6)	4	(0.1)	12	(0.2)
Anaemia	4	(1.1)	3	(0.9)	86	(2.8)	65	(0.9)
Colitis	4	(1.1)	3	(0.9)	28	(0.9)	71	(0.9)
Gastric haemorrhage	4	(1.1)	5	(1.4)	4	(0.1)	4	(0.1)
Nausea	4	(1.1)	4	(1.2)	28	(0.9)	30	(0.4)
Pyrexia	4	(1.1)	6	(1.7)	73	(2.3)	79	(1.0)
COVID-19 pneumonia	3	(0.9)	5	(1.4)	1	(0.0)	2	(0.0)
Sepsis	3	(0.9)	2	(0.6)	43	(1.4)	56	(0.7)
Decreased appetite	2	(0.6)	4	(1.2)	16	(0.5)	20	(0.3)
Dehydration	2	(0.6)	4	(1.2)	21	(0.7)	44	(0.6)
Platelet count decreased	2	(0.6)	6	(1.7)	19	(0.6)	0	(0.0)
Febrile neutropenia	1	(0.3)	2	(0.6)	217	(6.9)	8	(0.1)
Hypokalaemia	1	(0.3)	6	(1.7)	20	(0.6)	9	(0.1)
Thrombocytopenia	1	(0.3)	6	(1.7)	43	(1.4)	10	(0.1)
Dyspnoea	0	(0.0)	1	(0.3)	18	(0.6)	91	(1.2)
Neutropenia	0	(0.0)	1	(0.3)	50	(1.6)	3	(0.0)
Pleural effusion	0	(0.0)	0	(0.0)	31	(1.0)	88	(1.2)
Urinary tract infection	0	(0.0)	1	(0.3)	33	(1.1)	67	(0.9)

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.

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

Table 14: Participants With Drug-Related Serious Adverse Events (Incidence ≥ 1% in One or More Treatment Groups) By Decreasing Frequency of Preferred Term (APaT Population)

	KN811 Pembrolizumab + SOC		KN811 SOC		Pembro + Chemo Pooled Dataset[i]		Pembrolizumab Monotherapy Reference Safety Dataset[j]	
	n	(%)	n	(%)	n	(%)	n	(%)
Participants in population	350		346		3,123		7,631	
with one or more adverse events	88	(25.1)	79	(22.8)	910	(29.1)	840	(11.0)
with no adverse events	262	(74.9)	267	(77.2)	2,213	(70.9)	6,791	(89.0)

Diarrhoea	16	(4.6)	15	(4.3)	34	(1.1)	44	(0.6)
Infusion related reaction	7	(2.0)	2	(0.6)	10	(0.3)	5	(0.1)
Pneumonia	7	(2.0)	1	(0.3)	38	(1.2)	19	(0.2)
Pneumonitis	6	(1.7)	1	(0.3)	49	(1.6)	129	(1.7)
Vomiting	6	(1.7)	8	(2.3)	30	(1.0)	9	(0.1)
Acute kidney injury	4	(1.1)	1	(0.3)	36	(1.2)	19	(0.2)
Colitis	4	(1.1)	3	(0.9)	27	(0.9)	63	(0.8)
Fatigue	4	(1.1)	3	(0.9)	10	(0.3)	7	(0.1)
Nausea	4	(1.1)	4	(1.2)	26	(0.8)	7	(0.1)
Dehydration	2	(0.6)	4	(1.2)	8	(0.3)	5	(0.1)
Platelet count decreased	2	(0.6)	6	(1.7)	18	(0.6)	0	(0.0)
Pyrexia	2	(0.6)	2	(0.6)	39	(1.2)	22	(0.3)
Anaemia	1	(0.3)	2	(0.6)	68	(2.2)	6	(0.1)
Febrile neutropenia	1	(0.3)	2	(0.6)	208	(6.7)	0	(0.0)
Hypokalaemia	1	(0.3)	5	(1.4)	11	(0.4)	3	(0.0)
Thrombocytopenia	1	(0.3)	5	(1.4)	41	(1.3)	6	(0.1)
Neutropenia	0	(0.0)	1	(0.3)	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.

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

Deaths

Table 15: Participants With Adverse Events Resulting in Death By Decreasing Frequency of Preferred Term (APaT Population) – at least 1 event in one of the KN811 arm

	KN811 Pembrolizumab + SOC		KN811 SOC		Pembro + Chemo Pooled Dataset[i]		Pembrolizumab Monotherapy Reference Safety Dataset[j]	
	n	(%)	n	(%)	n	(%)	n	(%)
Participants in population	350		346		3,123		7,631	
with one or more adverse events	22	(6.3)	20	(5.8)	160	(5.1)	346	(4.5)
with no adverse events	328	(93.7)	326	(94.2)	2,963	(94.9)	7,285	(95.5)
Pneumonia	3	(0.9)	1	(0.3)	16	(0.5)	40	(0.5)
COVID-19	2	(0.6)	1	(0.3)	1	(0.0)	0	(0.0)
Death	2	(0.6)	1	(0.3)	18	(0.6)	49	(0.6)
Pneumonitis	2	(0.6)	0	(0.0)	5	(0.2)	8	(0.1)
Abdominal infection	1	(0.3)	0	(0.0)	0	(0.0)	0	(0.0)
Acute respiratory failure	1	(0.3)	0	(0.0)	1	(0.0)	5	(0.1)
Cardiac failure chronic	1	(0.3)	0	(0.0)	0	(0.0)	0	(0.0)
Cerebral infarction	1	(0.3)	0	(0.0)	1	(0.0)	0	(0.0)
Gastric haemorrhage	1	(0.3)	0	(0.0)	0	(0.0)	2	(0.0)
Hepatitis	1	(0.3)	0	(0.0)	0	(0.0)	0	(0.0)
Multiple organ dysfunction syndrome	1	(0.3)	1	(0.3)	5	(0.2)	6	(0.1)
Myocardial infarction	1	(0.3)	0	(0.0)	4	(0.1)	6	(0.1)
Peritonitis	1	(0.3)	0	(0.0)	1	(0.0)	0	(0.0)
Pneumonia aspiration	1	(0.3)	0	(0.0)	5	(0.2)	8	(0.1)
Pulmonary embolism	1	(0.3)	1	(0.3)	4	(0.1)	10	(0.1)
Sepsis	1	(0.3)	0	(0.0)	9	(0.3)	11	(0.1)
Sudden death	1	(0.3)	1	(0.3)	1	(0.0)	2	(0.0)
Aspiration	0	(0.0)	2	(0.6)	0	(0.0)	4	(0.1)
COVID-19 pneumonia	0	(0.0)	2	(0.6)	0	(0.0)	1	(0.0)
Cholangitis	0	(0.0)	1	(0.3)	0	(0.0)	0	(0.0)
Completed suicide	0	(0.0)	1	(0.3)	0	(0.0)	3	(0.0)
Craniocerebral injury	0	(0.0)	1	(0.3)	0	(0.0)	0	(0.0)
Gastric cancer	0	(0.0)	1	(0.3)	0	(0.0)	0	(0.0)
Intestinal ischaemia	0	(0.0)	1	(0.3)	2	(0.1)	1	(0.0)
Ischaemic stroke	0	(0.0)	1	(0.3)	2	(0.1)	1	(0.0)
Myocarditis	0	(0.0)	1	(0.3)	0	(0.0)	1	(0.0)

Respiratory tract infection	0	(0.0)	1	(0.3)	0	(0.0)	1	(0.0)
Subdural haematoma	0	(0.0)	1	(0.3)	0	(0.0)	0	(0.0)
Upper gastrointestinal haemorrhage	0	(0.0)	1	(0.3)	1	(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.

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

Deaths considered drug-related by investigator were:

- Four AEs resulting in death in the pembrolizumab plus SOC group: pneumonitis, hepatitis, sepsis, and cerebral infarction (of the AEs resulting in death, it is noted in the narrative that an additional case of pneumonitis, which was considered unrelated by the investigator, was instead assessed as drug-related based on the sponsor's review).

- Three AEs resulting in death in the SOC group: myocarditis, pulmonary embolism, and cholangitis.

Adverse Events of Special Interest (AEOSI)

AEOSI are immune-mediated events and infusion-related AEs causally associated with pembrolizumab.

Table 16: Adverse Event Summary AEOSI (APaT Population)

	KN811 Pembrolizumab + SOC		KN811 SOC		Pembro + Chemo Pooled Dataset[i]		Pembrolizumab Monotherapy Reference Safety Dataset[j]	
	n	(%)	n	(%)	n	(%)	n	(%)
Participants in population	350		346		3,123		7,631	
with one or more adverse events	132	(37.7)	83	(24.0)	1,052	(33.7)	2,042	(26.8)
with no adverse event	218	(62.3)	263	(76.0)	2,071	(66.3)	5,589	(73.2)
with drug-related[a] adverse events	122	(34.9)	78	(22.5)	943	(30.2)	1,790	(23.5)
with toxicity grade 3-5 adverse events	36	(10.3)	12	(3.5)	326	(10.4)	523	(6.9)
with toxicity grade 3-5 drug-related adverse events	34	(9.7)	12	(3.5)	297	(9.5)	462	(6.1)
with serious adverse events	32	(9.1)	15	(4.3)	251	(8.0)	502	(6.6)
with serious drug-related adverse events	29	(8.3)	15	(4.3)	230	(7.4)	449	(5.9)
who died	3	(0.9)	1	(0.3)	9	(0.3)	13	(0.2)
who died due to a drug-related adverse event	2	(0.6)	1	(0.3)	9	(0.3)	13	(0.2)
discontinued any drug due to an adverse event	24	(6.9)	13	(3.8)	228	(7.3)	354	(4.6)
discontinued pembrolizumab or placebo	14	(4.0)	6	(1.7)	176	(5.6)	354	(4.6)
discontinued any chemotherapy	20	(5.7)	11	(3.2)	118	(3.8)	NA	
discontinued all drugs	8	(2.3)	4	(1.2)	20	(0.6)	354	(4.6)
discontinued any drug due to a drug-related adverse event	23	(6.6)	13	(3.8)	224	(7.2)	349	(4.6)
discontinued pembrolizumab or placebo	13	(3.7)	6	(1.7)	172	(5.5)	349	(4.6)
discontinued any chemotherapy	19	(5.4)	11	(3.2)	116	(3.7)	NA	
discontinued all drugs	7	(2.0)	4	(1.2)	20	(0.6)	349	(4.6)
discontinued any drug due to a serious adverse event	16	(4.6)	6	(1.7)	144	(4.6)	226	(3.0)
discontinued pembrolizumab or placebo	13	(3.7)	6	(1.7)	132	(4.2)	226	(3.0)
discontinued any chemotherapy	13	(3.7)	4	(1.2)	65	(2.1)	NA	
discontinued all drugs	8	(2.3)	4	(1.2)	17	(0.5)	226	(3.0)

discontinued any drug due to a serious drug-related adverse event	15	(4.3)	6	(1.7)	141	(4.5)	224	(2.9)
discontinued pembrolizumab or placebo	12	(3.4)	6	(1.7)	129	(4.1)	224	(2.9)
discontinued any chemotherapy	12	(3.4)	4	(1.2)	63	(2.0)	NA	
discontinued all drugs	7	(2.0)	4	(1.2)	17	(0.5)	224	(2.9)

Table 17: Participants With Adverse Events of Special Interest (Incidence > 0% in One or More Treatment Groups) By AEOSI Category and Preferred Term (APaT Population)

	KN811 Pembrolizumab + SOC		KN811 SOC		Pembro + Chemo Pooled Dataset[1]		Pembrolizumab Monotherapy Reference Safety Dataset[2]	
	n	(%)	n	(%)	n	(%)	n	(%)
Participants in population	350		346		3,123		7,631	
with one or more adverse events	132	(37.7)	83	(24.0)	1,052	(33.7)	2,042	(26.8)
with no adverse events	218	(62.3)	263	(76.0)	2,071	(66.3)	5,589	(73.2)
Adrenal Insufficiency	**4**	**(1.1)**	**0**	**(0.0)**	**40**	**(1.3)**	**74**	**(1.0)**
Adrenal insufficiency	4	(1.1)	0	(0.0)	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	**17**	**(4.9)**	**10**	**(2.9)**	**84**	**(2.7)**	**159**	**(2.1)**
Colitis	13	(3.7)	6	(1.7)	64	(2.0)	134	(1.8)
Enterocolitis	2	(0.6)	2	(0.6)	14	(0.4)	11	(0.1)
Immune-mediated enterocolitis	2	(0.6)	2	(0.6)	2	(0.1)	6	(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)**	**1**	**(0.3)**	**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)	1	(0.3)	1	(0.0)	1	(0.0)
Guillain-Barre syndrome	0	(0.0)	0	(0.0)	1	(0.0)	4	(0.1)
Hepatitis	**2**	**(0.6)**	**4**	**(1.2)**	**40**	**(1.3)**	**80**	**(1.0)**
Hepatitis	2	(0.6)	3	(0.9)	14	(0.4)	34	(0.4)
Autoimmune hepatitis	0	(0.0)	0	(0.0)	16	(0.5)	35	(0.5)
Drug-induced liver injury	0	(0.0)	0	(0.0)	0	(0.0)	8	(0.1)
Hepatitis acute	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)
Immune-mediated hepatitis	0	(0.0)	1	(0.3)	11	(0.4)	3	(0.0)
Hyperthyroidism	**14**	**(4.0)**	**11**	**(3.2)**	**173**	**(5.5)**	**398**	**(5.2)**
Hyperthyroidism	14	(4.0)	11	(3.2)	171	(5.5)	398	(5.2)
Basedow's disease	0	(0.0)	0	(0.0)	2	(0.1)	0	(0.0)
Hypoparathyroidism	**0**	**(0.0)**	**0**	**(0.0)**	**1**	**(0.0)**	**1**	**(0.0)**
Hypoparathyroidism	0	(0.0)	0	(0.0)	1	(0.0)	1	(0.0)
Hypophysitis	**4**	**(1.1)**	**0**	**(0.0)**	**28**	**(0.9)**	**52**	**(0.7)**
Hypophysitis	4	(1.1)	0	(0.0)	17	(0.5)	32	(0.4)
Hypopituitarism	0	(0.0)	0	(0.0)	11	(0.4)	19	(0.2)
Lymphocytic hypophysitis	0	(0.0)	0	(0.0)	0	(0.0)	2	(0.0)
Hypothyroidism	**37**	**(10.6)**	**15**	**(4.3)**	**434**	**(13.9)**	**939**	**(12.3)**
Hypothyroidism	37	(10.6)	15	(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	**56**	**(16.0)**	**45**	**(13.0)**	**246**	**(7.9)**	**165**	**(2.2)**
Infusion related reaction	41	(11.7)	34	(9.8)	122	(3.9)	75	(1.0)
Hypersensitivity	10	(2.9)	7	(2.0)	76	(2.4)	49	(0.6)
Drug hypersensitivity	5	(1.4)	4	(1.2)	41	(1.3)	24	(0.3)
Anaphylactic reaction	1	(0.3)	0	(0.0)	10	(0.3)	10	(0.1)
Anaphylactoid reaction	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)
Cytokine release syndrome	0	(0.0)	0	(0.0)	5	(0.2)	8	(0.1)
Serum sickness	0	(0.0)	0	(0.0)	1	(0.0)	0	(0.0)
Myasthenic Syndrome	**0**	**(0.0)**	**0**	**(0.0)**	**1**	**(0.0)**	**8**	**(0.1)**
Myasthenia gravis	0	(0.0)	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**	**(0.3)**	**8**	**(0.3)**	**9**	**(0.1)**
Autoimmune myocarditis	0	(0.0)	0	(0.0)	1	(0.0)	0	(0.0)
Myocarditis	0	(0.0)	1	(0.3)	7	(0.2)	9	(0.1)
Myositis	**1**	**(0.3)**	**0**	**(0.0)**	**13**	**(0.4)**	**34**	**(0.4)**
Rhabdomyolysis	1	(0.3)	0	(0.0)	0	(0.0)	3	(0.0)
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)

Myositis	**1**	**(0.3)**	**0**	**(0.0)**	**13**	**(0.4)**	**34**	**(0.4)**
Myopathy	0	(0.0)	0	(0.0)	5	(0.2)	8	(0.1)
Myositis	0	(0.0)	0	(0.0)	6	(0.2)	22	(0.3)
Necrotising myositis	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)
Nephritis	**4**	**(1.1)**	**0**	**(0.0)**	**25**	**(0.8)**	**37**	**(0.5)**
Nephritis	3	(0.9)	0	(0.0)	14	(0.4)	10	(0.1)
Tubulointerstitial nephritis	1	(0.3)	0	(0.0)	10	(0.3)	14	(0.2)
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	**0**	**(0.0)**	**1**	**(0.3)**	**15**	**(0.5)**	**28**	**(0.4)**
Autoimmune pancreatitis	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)
Pancreatitis	0	(0.0)	1	(0.3)	11	(0.4)	24	(0.3)
Pancreatitis acute	0	(0.0)	0	(0.0)	5	(0.2)	4	(0.1)
Pneumonitis	**21**	**(6.0)**	**5**	**(1.4)**	**124**	**(4.0)**	**324**	**(4.2)**
Pneumonitis	19	(5.4)	5	(1.4)	112	(3.6)	291	(3.8)
Interstitial lung disease	2	(0.6)	0	(0.0)	10	(0.3)	29	(0.4)
Autoimmune lung disease	1	(0.3)	0	(0.0)	0	(0.0)	0	(0.0)
Immune-mediated lung disease	0	(0.0)	0	(0.0)	1	(0.0)	4	(0.1)
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	**3**	**(0.9)**	**0**	**(0.0)**	**96**	**(3.1)**	**130**	**(1.7)**
Dermatitis exfoliative generalised	1	(0.3)	0	(0.0)	4	(0.1)	2	(0.0)
Pruritus	1	(0.3)	0	(0.0)	6	(0.2)	16	(0.2)
Rash maculo-papular	1	(0.3)	0	(0.0)	37	(1.2)	23	(0.3)
Dermatitis bullous	0	(0.0)	0	(0.0)	8	(0.3)	9	(0.1)
Dermatitis exfoliative	0	(0.0)	0	(0.0)	0	(0.0)	5	(0.1)
Erythema multiforme	0	(0.0)	0	(0.0)	6	(0.2)	8	(0.1)
Severe Skin Reactions	**3**	**(0.9)**	**0**	**(0.0)**	**96**	**(3.1)**	**130**	**(1.7)**
Exfoliative rash	0	(0.0)	0	(0.0)	0	(0.0)	2	(0.0)
Lichen planus	0	(0.0)	0	(0.0)	0	(0.0)	6	(0.1)
Oral lichen planus	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)
Pemphigoid	0	(0.0)	0	(0.0)	1	(0.0)	3	(0.0)
Pemphigus	0	(0.0)	0	(0.0)	0	(0.0)	2	(0.0)
Pruritus genital	0	(0.0)	0	(0.0)	0	(0.0)	2	(0.0)
Rash	0	(0.0)	0	(0.0)	37	(1.2)	44	(0.6)
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	**4**	**(1.1)**	**0**	**(0.0)**	**41**	**(1.3)**	**74**	**(1.0)**
Thyroid disorder	2	(0.6)	0	(0.0)	0	(0.0)	3	(0.0)
Autoimmune thyroiditis	1	(0.3)	0	(0.0)	12	(0.4)	22	(0.3)
Thyroiditis	1	(0.3)	0	(0.0)	28	(0.9)	50	(0.7)
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	**1**	**(0.3)**	**0**	**(0.0)**	**11**	**(0.4)**	**34**	**(0.4)**
Type 1 diabetes mellitus	1	(0.3)	0	(0.0)	9	(0.3)	25	(0.3)
Diabetic ketoacidosis	0	(0.0)	0	(0.0)	3	(0.1)	15	(0.2)
Uveitis	**1**	**(0.3)**	**1**	**(0.3)**	**3**	**(0.1)**	**25**	**(0.3)**
Uveitis	1	(0.3)	1	(0.3)	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	**4**	**(1.1)**	**1**	**(0.3)**	**23**	**(0.7)**	**5**	**(0.1)**
Vasculitis	4	(1.1)	1	(0.3)	22	(0.7)	4	(0.1)
Central nervous system vasculitis	0	(0.0)	0	(0.0)	1	(0.0)	0	(0.0)
Giant cell arteritis	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)

Every participant is counted a single time for each applicable row and column.
A bolded term or specific adverse event appears on this report only if its incidence in one or more of the columns meets the incidence criterion in the report title, after rounding.
Non-serious adverse events up to 30 days of last dose and serious adverse events up to 90 days of last dose are included.

Participants With Adverse Events of Special Interest (AEOSI) by Maximum Toxicity Grade
(Incidence > 0% in One or More Treatment Groups)
(APaT Population)

	KN811 Pembrolizumab + SOC		KN811 SOC		Pembro + Chemo Pooled Dataset[i]		Pembrolizumab Monotherapy Reference Safety Dataset[j]	
	n	(%)	n	(%)	n	(%)	n	(%)
Participants in population	350		346		3,123		7,631	
with one or more adverse events	132	(37.7)	83	(24.0)	1,052	(33.7)	2,042	(26.8)
Grade 1	35	(10.0)	28	(8.1)	252	(8.1)	485	(6.4)
Grade 2	61	(17.4)	43	(12.4)	474	(15.2)	1,034	(13.5)
Grade 3	30	(8.6)	11	(3.2)	274	(8.8)	447	(5.9)
Grade 4	3	(0.9)	0	(0.0)	43	(1.4)	63	(0.8)
Grade 5	3	(0.9)	1	(0.3)	9	(0.3)	13	(0.2)
with no adverse events	218	(62.3)	263	(76.0)	2,071	(66.3)	5,589	(73.2)

Summary of Concomitant Corticosteroid Use for AEOSI (APaT Population)

	KN811 Pembrolizumab + SOC		KN811 SOC		Pembro + Chemo Pooled Dataset[i]		Pembrolizumab Monotherapy Reference Safety Dataset[j]	
	n	(%)	n	(%)	n	(%)	n	(%)
Participants in population	350		346		3123		7631	
Participants with one or more events	132		83		1052		2042	
Treated with systemic corticosteroid	68	(51.5)	32	(38.6)	460	(43.7)	713	(34.9)
Not treated with systemic corticosteroid	64	(48.5)	51	(61.4)	592	(56.3)	1329	(65.1)

Summary of Outcome for Participants With AEOSI (Incidence > 0% in One or More Treatment Groups) (APaT Population)

	Outcome	KN811 Pembrolizumab + SOC		KN811 SOC		Pembro + Chemo Pooled Dataset[i]		Pembrolizumab Monotherapy Reference Safety Dataset[j]	
		n	(%)	n	(%)	n	(%)	n	(%)
Participants in population		350		346		3123		7631	
With one or more AEOSI	**Overall**	**132**	**(37.7)**	**83**	**(24.0)**	**1052**	**(33.7)**	**2042**	**(26.8)**
	Fatal	3	(2.3)	1	(1.2)	9	(0.9)	13	(0.6)
	Not Resolved	36	(27.3)	10	(12.0)	354	(33.7)	884	(43.3)
	Resolving	14	(10.6)	8	(9.6)	131	(12.5)	178	(8.7)
	Unknown	0	(0.0)	0	(0.0)	2	(0.2)	30	(1.5)
	Sequelae	2	(1.5)	1	(1.2)	37	(3.5)	64	(3.1)
	Resolved	77	(58.3)	63	(75.9)	519	(49.3)	873	(42.8)

Time to Onset and Duration of AEOSI (APaT Population)

	KN811 Pembrolizumab + SOC	KN811 SOC	Pembro + Chemo Pooled Dataset[i]	Pembrolizumab Monotherapy Reference Safety Dataset[j]
Participants in population	350	346	3123	7631
Participants with AEOSI, n (%)	132 (37.7)	83 (24.0)	1052 (33.7)	2042 (26.8)
Time to Onset of First AEOSI[a] (day)				
Mean (SD)	104.6 (117.0)	78.0 (127.6)	120.9 (127.6)	118.1 (121.4)
Median	67.0	21.0	83.0	77.0
Range	1 to 584	1 to 703	1 to 825	1 to 796
Total number of episodes of AEOSI	205	110	1648	2883
Average number of episodes of AEOSI per participant	1.6	1.3	1.6	1.4
Episode Duration[b] (day)				
Median	41.0	2.0	58.0	105.0
Range	1 to 1066+	1 to 994+	1 to 1748+	1 to 1915+

Other or Indication-specific Adverse Events

Trastuzumab can cause cardiomyopathy, and there is a 4- to 6-fold increase in the incidence of symptomatic myocardial dysfunction among participants receiving treatment as a single agent or in combination therapy. As a result, a review of Grade 3 to 5 AEs of cardiac disorders and LVEF <50% and ≥10% decrease from baseline was performed for each treatment group.

The proportion of participants with baseline and postbaseline measurements who experienced decreases from baseline in LVEF was similar between the pembrolizumab plus SOC and SOC treatment groups.

Summary of Participants with Myocardial Dysfunction (by LVEF)
(Global Cohort)
(APaT Population)

	Pembrolizumab + SOC		SOC	
	n	(%)	n	(%)
Participants in population	350		346	
Participants with Baseline and Post-baseline Measurements	324		314	
LVEF <50% and Absolute Decrease from Baseline				
LVEF <50%	12	(3.7)	16	(5.1)
LVEF <50% and >=10% Decrease from Baseline	9	(2.8)	12	(3.8)
LVEF <50% and >=16% Decrease from Baseline	5	(1.5)	6	(1.9)
Absolute LVEF Decrease from Baseline				
<20% and >=10%	46	(14.2)	53	(16.9)
>=20%	5	(1.5)	5	(1.6)

Number of participants with at least one baseline and post-baseline laboratory measurement is used as the denominator in percentage calculation.
LVEF: Left Ventricular Ejection Fraction
Database Cutoff Date: 25MAY2022

Three participants in the pembrolizumab plus SOC group experienced Grade 3 SAEs of cardiac disorders and LVEF <50% and ≥10% decrease from baseline: 1 congestive cardiac failure (unrelated), 1 cardiac failure (related), and 1 acute myocardial infarction (related). For both SAEs considered related to study intervention by the investigator, study treatment was discontinued. In the SOC group, 1 participant experienced a Grade 3 SAE of acute myocardial infarction, considered unrelated to study intervention.

The incidence of AEs by SOC "cardiac disorder" is reported below:

	KN811 Pembrolizumab + SOC		KN811 SOC		Pembro + Chemo Pooled Dataset[i]		Pembrolizumab Monotherapy Reference Safety Dataset[i]	
	n	(%)	n	(%)	n	(%)	n	(%)
Cardiac disorders	**39**	**(11.1)**	**34**	**(9.8)**	**350**	**(11.2)**	**584**	**(7.7)**

The incidence of drug-related AEs by SOC "cardiac disorder" is reported below:

	KN811 Pembrolizumab + SOC		KN811 SOC		Pembro + Chemo Pooled Dataset[i]		Pembrolizumab Monotherapy Reference Safety Dataset[i]	
	n	(%)	n	(%)	n	(%)	n	(%)

Cardiac disorders	**18**	**(5.1)**	**21**	**(6.1)**	**117**	**(3.7)**	**74**	**(1.0)**
Acute coronary syndrome	0	(0.0)	0	(0.0)	1	(0.0)	0	(0.0)
Acute myocardial infarction	1	(0.3)	0	(0.0)	0	(0.0)	1	(0.0)
Angina pectoris	0	(0.0)	1	(0.3)	2	(0.1)	1	(0.0)
Angina unstable	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)
Aortic valve calcification	0	(0.0)	1	(0.3)	0	(0.0)	0	(0.0)
Aortic valve disease	0	(0.0)	1	(0.3)	0	(0.0)	1	(0.0)
Aortic valve incompetence	1	(0.3)	2	(0.6)	2	(0.1)	0	(0.0)
Arrhythmia	2	(0.6)	0	(0.0)	3	(0.1)	1	(0.0)
Arteriospasm coronary	0	(0.0)	0	(0.0)	1	(0.0)	0	(0.0)
Atrial fibrillation	2	(0.6)	2	(0.6)	4	(0.1)	7	(0.1)
Atrial flutter	0	(0.0)	0	(0.0)	1	(0.0)	0	(0.0)
Atrioventricular block	1	(0.3)	0	(0.0)	1	(0.0)	0	(0.0)
Atrioventricular block complete	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)
Atrioventricular block first degree	0	(0.0)	0	(0.0)	2	(0.1)	1	(0.0)
Autoimmune myocarditis	0	(0.0)	0	(0.0)	1	(0.0)	0	(0.0)
Autoimmune pericarditis	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)
Bradycardia	1	(0.3)	1	(0.3)	1	(0.0)	0	(0.0)
Bundle branch block left	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)
Cardiac arrest	0	(0.0)	0	(0.0)	1	(0.0)	0	(0.0)
Cardiac failure	1	(0.3)	1	(0.3)	6	(0.2)	3	(0.0)
Cardiac failure acute	0	(0.0)	0	(0.0)	0	(0.0)	2	(0.0)
Cardiac failure chronic	0	(0.0)	0	(0.0)	1	(0.0)	0	(0.0)
Cardiac failure congestive	0	(0.0)	0	(0.0)	1	(0.0)	1	(0.0)
Cardiac tamponade	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)
Cardio-respiratory arrest	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)
Cardiomyopathy	0	(0.0)	0	(0.0)	1	(0.0)	0	(0.0)
Cardiotoxicity	0	(0.0)	1	(0.3)	0	(0.0)	0	(0.0)
Cardiovascular disorder	0	(0.0)	0	(0.0)	1	(0.0)	0	(0.0)
Cardiovascular insufficiency	0	(0.0)	0	(0.0)	2	(0.1)	0	(0.0)
Diastolic dysfunction	1	(0.3)	0	(0.0)	0	(0.0)	0	(0.0)
Extrasystoles	0	(0.0)	0	(0.0)	1	(0.0)	0	(0.0)
Left atrial enlargement	1	(0.3)	2	(0.6)	0	(0.0)	0	(0.0)
Left ventricular dilatation	0	(0.0)	0	(0.0)	1	(0.0)	0	(0.0)
Left ventricular dysfunction	2	(0.6)	3	(0.9)	3	(0.1)	0	(0.0)
Left ventricular hypertrophy	0	(0.0)	0	(0.0)	1	(0.0)	0	(0.0)
Mitral valve disease	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)
Mitral valve incompetence	5	(1.4)	1	(0.3)	3	(0.1)	0	(0.0)
Myocardial infarction	0	(0.0)	0	(0.0)	4	(0.1)	3	(0.0)
Myocardial ischaemia	0	(0.0)	0	(0.0)	1	(0.0)	0	(0.0)
Myocarditis	0	(0.0)	1	(0.3)	7	(0.2)	9	(0.1)
Myopericarditis	0	(0.0)	0	(0.0)	1	(0.0)	0	(0.0)
Palpitations	0	(0.0)	2	(0.6)	25	(0.8)	15	(0.2)
Paroxysmal arrhythmia	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)
Pericardial effusion	0	(0.0)	1	(0.3)	4	(0.1)	17	(0.2)
Pericarditis	2	(0.6)	0	(0.0)	1	(0.0)	5	(0.1)
Pleuropericarditis	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)
Pulmonary valve incompetence	1	(0.3)	1	(0.3)	1	(0.0)	0	(0.0)
Right ventricular failure	0	(0.0)	0	(0.0)	1	(0.0)	0	(0.0)
Right ventricular hypertrophy	0	(0.0)	0	(0.0)	1	(0.0)	0	(0.0)
Sinus arrhythmia	0	(0.0)	1	(0.3)	0	(0.0)	0	(0.0)
Sinus bradycardia	1	(0.3)	0	(0.0)	1	(0.0)	0	(0.0)
Sinus tachycardia	1	(0.3)	0	(0.0)	20	(0.6)	4	(0.1)
Supraventricular extrasystoles	1	(0.3)	1	(0.3)	1	(0.0)	1	(0.0)
Supraventricular tachycardia	0	(0.0)	1	(0.3)	3	(0.1)	0	(0.0)
Tachyarrhythmia	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)
Tachycardia	0	(0.0)	0	(0.0)	21	(0.7)	8	(0.1)
Tachycardia paroxysmal	0	(0.0)	0	(0.0)	1	(0.0)	0	(0.0)
Tricuspid valve incompetence	2	(0.6)	0	(0.0)	0	(0.0)	0	(0.0)
Ventricular arrhythmia	1	(0.3)	0	(0.0)	1	(0.0)	0	(0.0)
Ventricular extrasystoles	0	(0.0)	1	(0.3)	1	(0.0)	0	(0.0)
Ventricular hypertrophy	0	(0.0)	0	(0.0)	1	(0.0)	0	(0.0)
Ventricular hypokinesia	0	(0.0)	1	(0.3)	0	(0.0)	0	(0.0)
Ventricular remodelling	0	(0.0)	0	(0.0)	1	(0.0)	0	(0.0)
Ventricular tachycardia	0	(0.0)	0	(0.0)	1	(0.0)	0	(0.0)
Wolff-Parkinson-White syndrome	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)

The incidence of Grade 3-5 AEs by SOC "cardiac disorder" is reported below:

	KN811 Pembrolizumab + SOC		KN811 SOC		Pembro + Chemo Pooled Dataset[i]		Pembrolizumab Monotherapy Reference Safety Dataset[j]	
	n	(%)	n	(%)	n	(%)	n	(%)
Cardiac disorders	**9**	**(2.6)**	**9**	**(2.6)**	**105**	**(3.4)**	**201**	**(2.6)**

The incidence of drug-related Grade 3-5 AEs by SOC "cardiac disorder" is reported below:

	KN811 Pembrolizumab + SOC		KN811 SOC		Pembro + Chemo Pooled Dataset[i]		Pembrolizumab Monotherapy Reference Safety Dataset[j]	
	n	(%)	n	(%)	n	(%)	n	(%)
Cardiac disorders	**3**	**(0.9)**	**5**	**(1.4)**	**32**	**(1.0)**	**37**	**(0.5)**

The incidence of SAE by SOC "cardiac disorder" is reported below:

	KN811 Pembrolizumab + SOC		KN811 SOC		Pembro + Chemo Pooled Dataset[i]		Pembrolizumab Monotherapy Reference Safety Dataset[j]	
	n	(%)	n	(%)	n	(%)	n	(%)
Cardiac disorders	**10**	**(2.9)**	**9**	**(2.6)**	**99**	**(3.2)**	**202**	**(2.6)**

Adverse reactions included in the SmPC

The MAH has updated Section 4.8 of the SmPC to include the KEYNOTE-811 population of gastric and gastro-oesophageal junction adenocarcinoma patients, receiving pembrolizumab in combination with trastuzumab plus chemotherapy, into the current 'pembrolizumab in combination with chemotherapy' pooled dataset. This dataset includes all pembrolizumab plus chemotherapy combination indications currently approved in the EU. Supportive table is shown below:

Table 18: Adverse Reactions in Patients Treated with Pembrolizumab in Combination with Chemotherapy

		Combination Therapy (N=3473)	
		All AEs % (n)	Gr 3-5 AEs n
Infections and infestations			
Common	Pneumonia	8.0% (278)	161
Blood and lymphatic system disorders			
Very common	Neutropenia	33.7% (1170)	750
Very common	Anaemia	53.6% (1861)	664
Very common	Thrombocytopenia	17.7% (615)	214
Very common	Leukopenia	10.9% (379)	147
Common	Febrile Neutropenia	7.8% (271)	261
Common	Lymphopenia	3.0% (105)	32
Uncommon	Eosinophilia	0.6% (20)	2
Rare	Haemolytic Anaemia	0.03% (1)	1
Rare	Immune Thrombocytopenia	0.03% (1)	0
Immune system disorders			
Common	Infusion Reactions[a]	8.7% (302)	50
Rare	Sarcoidosis	0.03% (1)	0
Endocrine disorders			
Very common	Hypothyroidism[b]	13.6% (471)	14
Common	Adrenal Insufficiency[c]	1.3% (44)	19
Common	Thyroiditis[d]	1.3% (45)	6
Common	Hyperthyroidism[e]	5.4% (187)	5
Uncommon	Hypophysitis[f]	0.9% (32)	17
Rare	Hypoparathyroidism	0.03% (1)	0
Metabolism and nutrition disorders			
Very common	Hypokalaemia	11.2% (389)	116
Very common	Decreased Appetite	27.6% (960)	74
Common	Hyponatraemia	7.1% (245)	122
Common	Hypocalcaemia	4.2% (146)	24
Uncommon	Type 1 Diabetes Mellitus[g]	0.3% (12)	11

Psychiatric disorders			
Very common	Insomnia	12.1% (421)	5
Nervous system disorders			
Very common	Neuropathy Peripheral	15.3% (530)	41
Very common	Headache	17.0% (591)	13
Very common	Dizziness	11.0% (382)	11
Common	Lethargy	1.4% (47)	2
Common	Dysgeusia	9.9% (345)	1
Uncommon	Encephalitis[h]	0.1% (5)	5
Uncommon	Epilepsy	0.2% (6)	3
Rare	Guillain-Barre Syndrome[i]	0.06% (2)	2
Rare	Myasthenic Syndrome	0.03% (1)	1
Eye disorders			
Common	Dry Eye	3.8% (132)	1
Uncommon	Uveitis[j]	0.1% (4)	0
Cardiac disorders			
Common	Cardiac Arrhythmia (Including Atrial Fibrillation)[k]	4.2% (145)	38
Uncommon	Myocarditis[l]	0.2% (8)	6
Uncommon	Pericardial Effusion	0.3% (11)	3
Uncommon	Pericarditis	0.2% (6)	1
Vascular disorders			
Common	Hypertension	6.8% (237)	98
Uncommon	Vasculitis[m]	0.8% (27)	3
Respiratory, thoracic and mediastinal disorders			
Very common	Dyspnoea	12.7% (440)	51
Very common	Cough	19.8% (688)	5
Common	Pneumonitis[n]	4.2% (145)	56
Gastrointestinal disorders			
Very common	Diarrhoea	36.1% (1254)	136
Very common	Nausea	53.6% (1863)	122
Very common	Vomiting	28.7% (998)	118
Very common	Abdominal Pain[o]	17.5% (608)	33
Very common	Constipation	33.6% (1166)	11
Common	Colitis[p]	2.9% (101)	44
Common	Gastritis	2.3% (79)	7
Common	Dry Mouth	4.9% (169)	1
Uncommon	Pancreatitis[q]	0.4% (15)	11
Uncommon	Gastrointestinal Ulceration[r]	0.5% (16)	2
Rare	Small Intestinal Perforation	0.03% (1)	1
Hepatobiliary disorders			
Common	Hepatitis[s]	1.2% (42)	37
Rare	Cholangitis Sclerosing[t]	0.06% (2)	2
Skin and subcutaneous tissue disorders			
Very common	Alopecia	31.9% (1107)	6
Very common	Rash[u]	23.8% (828)	4
Very common	Pruritus[v]	15.3% (530)	4
Common	Severe Skin Reactions[w]	2.9% (99)	87
Common	Erythema	4.9% (170)	3
Common	Dry Skin	5.8% (201)	2
Common	Dermatitis Acneiform	2.5% (88)	2
Common	Dermatitis	1.8% (63)	2
Common	Eczema	1.5% (51)	1
Uncommon	Psoriasis	0.5% (18)	4
Uncommon	Lichenoid Keratosis[x]	0.1% (5)	1
Uncommon	Vitiligo[y]	0.6% (21)	0
Uncommon	Papule	0.2% (8)	0
Rare	Stevens-Johnson Syndrome	0.03% (1)	1
Rare	Erythema Nodosum	0.09% (3)	0

Rare	Hair Colour Changes	0.03% (1)	0
Musculoskeletal and connective tissue disorders			
Very common	Arthralgia	19.7% (683)	27
Very common	Musculoskeletal Pain[z]	15.9% (551)	27
Very common	Myositis[aa]	11.0% (382)	15
Common	Pain In Extremity	8.5% (296)	9
Common	Arthritis[bb]	1.8% (62)	4
Uncommon	Tenosynovitis[cc]	0.5% (16)	1
Rare	Sjogren's Syndrome	0.03% (1)	0
Renal and urinary disorders			
Common	Acute Kidney Injury	3.8% (131)	64
Uncommon	Nephritis[dd]	0.8% (29)	15
Uncommon	Cystitis Noninfective	0.2% (7)	0
General disorders and administration site conditions			
Very common	Fatigue	36.8% (1278)	174
Very common	Asthenia	20.4% (708)	122
Very common	Pyrexia	19.7% (683)	25
Common	Oedema[ee]	5.3% (185)	7
Common	Influenza Like Illness	3.2% (112)	1
Common	Chills	3.3% (115)	0
Investigations			
Very common	Alanine Aminotransferase Increased	18.1% (627)	127
Very common	Aspartate Aminotransferase Increased	16.6% (575)	91
Common	Blood Creatinine Increased	9.5% (330)	20
Common	Blood Alkaline Phosphatase Increased	5.6% (194)	17
Common	Blood Bilirubin Increased	3.3% (114)	14
Common	Hypercalcaemia	1.8% (64)	14

Uncommon	Amylase Increased	0.5% (16)	5

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, 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, 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 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 (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, 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 and KN811.

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 (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 most frequently reported laboratory abnormalities were generally consistent between the pembrolizumab plus SOC and SOC treatment groups. Most laboratory abnormalities in the pembrolizumab plus SOC group were Grade 1 or 2.

Three participants met the criteria for drug-induced liver injury (2 [0.6%] in the pembrolizumab plus SOC group and 1 [0.3%] in the SOC group): ALT or AST ≥3 x ULN and bilirubin ≥2 x ULN and ALP <2 x ULN.

Safety in special populations

The safety findings in the pembrolizumab plus SOC group based on sex and ECOG performance status were balanced in the pembrolizumab + generally consistent with the established safety profiles of trastuzumab, chemotherapy components, and pembrolizumab monotherapy. The overall summary of AEs in the pembrolizumab plus SOC group was similar between male and female and between patients with ECOG 0 and 1 (data not shown).

Table 19: Adverse Event Summary by Age Category (< 65, ≥ 65 Years) (APaT Population)

	KN811 Pembrolizumab + SOC				KN811 SOC				Pembro + Chemo Pooled Dataset[1]			
	<65		>=65		<65		>=65		<65		>=65	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Participants in population	205		145		190		156		2,176		947	
with one or more adverse events	203	(99.0)	144	(99.3)	190	(100.0)	156	(100.0)	2,158	(99.2)	939	(99.2)
with no adverse event	2	(1.0)	1	(0.7)	0	(0.0)	0	(0.0)	18	(0.8)	8	(0.8)
with drug-related[a] adverse events	201	(98.0)	140	(96.6)	184	(96.8)	150	(96.2)	2,107	(96.8)	913	(96.4)
with toxicity grade 3-5 adverse events	151	(73.7)	97	(66.9)	110	(57.9)	115	(73.7)	1,721	(79.1)	758	(80.0)
with toxicity grade 3-5 drug-related adverse events	122	(59.5)	82	(56.6)	85	(44.7)	91	(58.3)	1,464	(67.3)	635	(67.1)
with serious adverse events	96	(46.8)	61	(42.1)	80	(42.1)	77	(49.4)	935	(43.0)	521	(55.0)
with serious drug-related adverse events	52	(25.4)	36	(24.8)	38	(20.0)	41	(26.3)	592	(27.2)	318	(33.6)
who died	8	(3.9)	14	(9.7)	8	(4.2)	12	(7.7)	72	(3.3)	88	(9.3)
who died due to a drug-related adverse event	2	(1.0)	2	(1.4)	0	(0.0)	3	(1.9)	20	(0.9)	29	(3.1)
discontinued any drug due to an adverse event	73	(35.6)	69	(47.6)	49	(25.8)	77	(49.4)	567	(26.1)	333	(35.2)
discontinued pembrolizumab/placebo	16	(7.8)	29	(20.0)	14	(7.4)	22	(14.1)	332	(15.3)	216	(22.8)
discontinued any chemotherapy	68	(33.2)	67	(46.2)	48	(25.3)	76	(48.7)	383	(17.6)	253	(26.7)
discontinued all drugs	9	(4.4)	13	(9.0)	9	(4.7)	14	(9.0)	71	(3.3)	72	(7.6)
discontinued any drug due to a drug-related adverse event	65	(31.7)	59	(40.7)	39	(20.5)	69	(44.2)	493	(22.7)	254	(26.8)
discontinued pembrolizumab/placebo	12	(5.9)	17	(11.7)	4	(2.1)	13	(8.3)	261	(12.0)	144	(15.2)
discontinued any chemotherapy	60	(29.3)	55	(37.9)	38	(20.0)	68	(43.6)	340	(15.6)	188	(19.9)
discontinued all drugs	6	(2.9)	5	(3.4)	1	(0.5)	8	(5.1)	45	(2.1)	41	(4.3)
discontinued any drug due to a serious adverse event	17	(8.3)	28	(19.3)	15	(7.9)	27	(17.3)	270	(12.4)	202	(21.3)
discontinued pembrolizumab/placebo	11	(5.4)	23	(15.9)	13	(6.8)	22	(14.1)	210	(9.7)	172	(18.2)
discontinued any chemotherapy	16	(7.8)	23	(15.9)	14	(7.4)	25	(16.0)	164	(7.5)	143	(15.1)
discontinued all drugs	8	(3.9)	12	(8.3)	9	(4.7)	14	(9.0)	63	(2.9)	64	(6.8)
discontinued any drug due to a serious drug-related adverse event	12	(5.9)	18	(12.4)	5	(2.6)	16	(10.3)	211	(9.7)	132	(13.9)
discontinued pembrolizumab/placebo	7	(3.4)	14	(9.7)	3	(1.6)	13	(8.3)	154	(7.1)	107	(11.3)
discontinued any chemotherapy	11	(5.4)	13	(9.0)	4	(2.1)	14	(9.0)	126	(5.8)	87	(9.2)

Table 20: Adverse Event Summary by Age Category (< 65, 65-74, 75-84, >=85 Years) (APaT Population)

	KN811 Pembrolizumab + SOC								KN811 SOC							
	<65		65-74		75-84		>=85		<65		65-74		75-84		>=85	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Participants in population	205		117		27		1		190		121		34		1	
with one or more adverse events	203	(99.0)	116	(99.1)	27	(100.0)	1	(100.0)	190	(100.0)	121	(100.0)	34	(100.0)	1	(100.0)
with no adverse event	2	(1.0)	1	(0.9)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
with drug-related[a] adverse events	201	(98.0)	114	(97.4)	25	(92.6)	1	(100.0)	184	(96.8)	116	(95.9)	33	(97.1)	1	(100.0)
with toxicity grade 3-5 adverse events	151	(73.7)	79	(67.5)	17	(63.0)	1	(100.0)	110	(57.9)	90	(74.4)	24	(70.6)	1	(100.0)
with toxicity grade 3-5 drug-related adverse events	122	(59.5)	67	(57.3)	14	(51.9)	1	(100.0)	85	(44.7)	71	(58.7)	19	(55.9)	1	(100.0)
with serious adverse events	96	(46.8)	45	(38.5)	15	(55.6)	1	(100.0)	80	(42.1)	60	(49.6)	16	(47.1)	1	(100.0)
with serious drug-related adverse events	52	(25.4)	25	(21.4)	10	(37.0)	1	(100.0)	38	(20.0)	34	(28.1)	7	(20.6)	0	(0.0)
who died	8	(3.9)	8	(6.8)	5	(18.5)	1	(100.0)	8	(4.2)	6	(5.0)	6	(17.6)	0	(0.0)
who died due to a drug-related adverse event	2	(1.0)	2	(1.7)	0	(0.0)	0	(0.0)	0	(0.0)	2	(1.7)	1	(2.9)	0	(0.0)
discontinued any drug due to an adverse event	73	(35.6)	53	(45.3)	15	(55.6)	1	(100.0)	49	(25.8)	59	(48.8)	17	(50.0)	1	(100.0)
discontinued pembrolizumab/placebo	16	(7.8)	20	(17.1)	8	(29.6)	1	(100.0)	14	(7.4)	16	(13.2)	6	(17.6)	0	(0.0)
discontinued any chemotherapy	68	(33.2)	52	(44.4)	14	(51.9)	1	(100.0)	48	(25.3)	58	(47.9)	17	(50.0)	1	(100.0)
discontinued all drugs	9	(4.4)	6	(5.1)	6	(22.2)	1	(100.0)	9	(4.7)	11	(9.1)	3	(8.8)	0	(0.0)
discontinued any drug due to a drug-related adverse event	65	(31.7)	48	(41.0)	11	(40.7)	0	(0.0)	39	(20.5)	54	(44.6)	14	(41.2)	1	(100.0)
discontinued pembrolizumab/placebo	12	(5.9)	13	(11.1)	4	(14.8)	0	(0.0)	4	(2.1)	12	(9.9)	1	(2.9)	0	(0.0)
discontinued any chemotherapy	60	(29.3)	45	(38.5)	10	(37.0)	0	(0.0)	38	(20.0)	53	(43.8)	14	(41.2)	1	(100.0)
discontinued all drugs	6	(2.9)	3	(2.6)	2	(7.4)	0	(0.0)	1	(0.5)	8	(6.6)	0	(0.0)	0	(0.0)
discontinued any drug due to a serious adverse event	17	(8.3)	18	(15.4)	9	(33.3)	1	(100.0)	15	(7.9)	18	(14.9)	9	(26.5)	0	(0.0)
discontinued pembrolizumab/placebo	11	(5.4)	14	(12.0)	8	(29.6)	1	(100.0)	13	(6.8)	16	(13.2)	6	(17.6)	0	(0.0)
discontinued any chemotherapy	16	(7.8)	14	(12.0)	8	(29.6)	1	(100.0)	14	(7.4)	16	(13.2)	9	(26.5)	0	(0.0)
discontinued all drugs	8	(3.9)	5	(4.3)	6	(22.2)	1	(100.0)	9	(4.7)	11	(9.1)	3	(8.8)	0	(0.0)

Table 21: Adverse Event Summary by Age Category (< 65, 65-74, 75-84, ≥85 Years) AEOSI

	KN811 Pembrolizumab + SOC								KN811 SOC							
	<65		65-74		75-84		>=85		<65		65-74		75-84		>=85	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Participants in population	205		117		27		1		190		121		34		1	
with one or more adverse events	80	(39.0)	43	(36.8)	9	(33.3)	0	(0.0)	45	(23.7)	32	(26.4)	5	(14.7)	1	(100.0)
with no adverse event	125	(61.0)	74	(63.2)	18	(66.7)	1	(100.0)	145	(76.3)	89	(73.6)	29	(85.3)	0	(0.0)
with drug-related[a] adverse events	75	(36.6)	39	(33.3)	8	(29.6)	0	(0.0)	42	(22.1)	30	(24.8)	5	(14.7)	1	(100.0)
with toxicity grade 3-5 adverse events	25	(12.2)	7	(6.0)	4	(14.8)	0	(0.0)	7	(3.7)	5	(4.1)	0	(0.0)	0	(0.0)
with toxicity grade 3-5 drug-related adverse events	24	(11.7)	7	(6.0)	3	(11.1)	0	(0.0)	7	(3.7)	5	(4.1)	0	(0.0)	0	(0.0)
with serious adverse events	20	(9.8)	8	(6.8)	4	(14.8)	0	(0.0)	8	(4.2)	7	(5.8)	0	(0.0)	0	(0.0)
with serious drug-related adverse events	18	(8.8)	8	(6.8)	3	(11.1)	0	(0.0)	8	(4.2)	7	(5.8)	0	(0.0)	0	(0.0)
who died	2	(1.0)	0	(0.0)	1	(3.7)	0	(0.0)	0	(0.0)	1	(0.8)	0	(0.0)	0	(0.0)
who died due to a drug-related adverse event	2	(1.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.8)	0	(0.0)	0	(0.0)
discontinued any drug due to an adverse event	10	(4.9)	10	(8.5)	4	(14.8)	0	(0.0)	5	(2.6)	8	(6.6)	0	(0.0)	0	(0.0)
discontinued pembrolizumab/placebo	4	(2.0)	6	(5.1)	4	(14.8)	0	(0.0)	1	(0.5)	5	(4.1)	0	(0.0)	0	(0.0)
discontinued any chemotherapy	10	(4.9)	8	(6.8)	2	(7.4)	0	(0.0)	4	(2.1)	7	(5.8)	0	(0.0)	0	(0.0)
discontinued all drugs	4	(2.0)	2	(1.7)	2	(7.4)	0	(0.0)	0	(0.0)	4	(3.3)	0	(0.0)	0	(0.0)
discontinued any drug due to a drug-related adverse event	10	(4.9)	10	(8.5)	3	(11.1)	0	(0.0)	5	(2.6)	8	(6.6)	0	(0.0)	0	(0.0)
discontinued pembrolizumab/placebo	4	(2.0)	6	(5.1)	3	(11.1)	0	(0.0)	1	(0.5)	5	(4.1)	0	(0.0)	0	(0.0)
discontinued any chemotherapy	10	(4.9)	8	(6.8)	1	(3.7)	0	(0.0)	4	(2.1)	7	(5.8)	0	(0.0)	0	(0.0)
discontinued all drugs	4	(2.0)	2	(1.7)	1	(3.7)	0	(0.0)	0	(0.0)	4	(3.3)	0	(0.0)	0	(0.0)
discontinued any drug due to a serious adverse event	7	(3.4)	5	(4.3)	4	(14.8)	0	(0.0)	1	(0.5)	5	(4.1)	0	(0.0)	0	(0.0)
discontinued pembrolizumab/placebo	4	(2.0)	5	(4.3)	4	(14.8)	0	(0.0)	1	(0.5)	5	(4.1)	0	(0.0)	0	(0.0)
discontinued any chemotherapy	7	(3.4)	4	(3.4)	2	(7.4)	0	(0.0)	0	(0.0)	4	(3.3)	0	(0.0)	0	(0.0)

Table 22: Adverse Event Summary by Region (Western Europe, Ex-Western Europe) (APaT Population)

	KN811 Pembrolizumab + SOC				KN811 SOC				Pembro + Chemo Pooled Dataset[i]			
	Western Europe		Ex-Western Europe		Western Europe		Ex-Western Europe		Western Europe		Ex-Western Europe	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Participants in population	98		252		91		255		1,118		2,005	
with one or more adverse events	96	(98.0)	251	(99.6)	91	(100.0)	255	(100.0)	1,105	(98.8)	1,992	(99.4)
with no adverse event	2	(2.0)	1	(0.4)	0	(0.0)	0	(0.0)	13	(1.2)	13	(0.6)
with drug-related[a] adverse events	93	(94.9)	248	(98.4)	88	(96.7)	246	(96.5)	1,070	(95.7)	1,950	(97.3)
with toxicity grade 3-5 adverse events	74	(75.5)	174	(69.0)	69	(75.8)	156	(61.2)	876	(78.4)	1,603	(80.0)
with toxicity grade 3-5 drug-related adverse events	65	(66.3)	139	(55.2)	53	(58.2)	123	(48.2)	727	(65.0)	1,372	(68.4)
with serious adverse events	54	(55.1)	103	(40.9)	66	(72.5)	91	(35.7)	548	(49.0)	908	(45.3)
with serious drug-related adverse events	33	(33.7)	55	(21.8)	31	(34.1)	48	(18.8)	340	(30.4)	570	(28.4)
who died	2	(2.0)	20	(7.9)	8	(8.8)	12	(4.7)	56	(5.0)	104	(5.2)
who died due to a drug-related adverse event	0	(0.0)	4	(1.6)	2	(2.2)	1	(0.4)	12	(1.1)	37	(1.8)
discontinued any drug due to an adverse event	36	(36.7)	106	(42.1)	37	(40.7)	89	(34.9)	383	(34.3)	517	(25.8)
discontinued pembrolizumab/placebo	11	(11.2)	34	(13.5)	12	(13.2)	24	(9.4)	237	(21.2)	311	(15.5)
discontinued any chemotherapy	34	(34.7)	101	(40.1)	37	(40.7)	87	(34.1)	266	(23.8)	370	(18.5)
discontinued all drugs	6	(6.1)	16	(6.3)	7	(7.7)	16	(6.3)	52	(4.7)	91	(4.5)
discontinued any drug due to a drug-related adverse event	33	(33.7)	91	(36.1)	33	(36.3)	75	(29.4)	320	(28.6)	427	(21.3)
discontinued pembrolizumab/placebo	9	(9.2)	20	(7.9)	6	(6.6)	11	(4.3)	173	(15.5)	232	(11.6)
discontinued any chemotherapy	30	(30.6)	85	(33.7)	33	(36.3)	73	(28.6)	224	(20.0)	304	(15.2)
discontinued all drugs	4	(4.1)	7	(2.8)	4	(4.4)	5	(2.0)	29	(2.6)	57	(2.8)
discontinued any drug due to a serious adverse event	16	(16.3)	29	(11.5)	16	(17.6)	26	(10.2)	199	(17.8)	273	(13.6)
discontinued pembrolizumab/placebo	10	(10.2)	24	(9.5)	12	(13.2)	23	(9.0)	165	(14.8)	217	(10.8)
discontinued any chemotherapy	13	(13.3)	26	(10.3)	16	(17.6)	23	(9.0)	126	(11.3)	181	(9.0)
discontinued all drugs	6	(6.1)	14	(5.6)	7	(7.7)	16	(6.3)	49	(4.4)	78	(3.9)
discontinued any drug due to a serious drug-related adverse event	13	(13.3)	17	(6.7)	9	(9.9)	12	(4.7)	142	(12.7)	201	(10.0)
discontinued pembrolizumab/placebo	8	(8.2)	13	(5.2)	6	(6.6)	10	(3.9)	108	(9.7)	153	(7.6)
discontinued any chemotherapy	10	(10.2)	14	(5.6)	9	(9.9)	9	(3.5)	88	(7.9)	125	(6.2)

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 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 PPK analysis. 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.

Discontinuation due to adverse events

Table 23: Participants With Drug-Related Adverse Events Resulting in Treatment Discontinuation of Any Drug by Decreasing Incidence (at least 1 event in the pembrolizumab+SOC group of KN-811) (Global Cohort) (APaT Population)

	Pembrolizumab + SOC		SOC	
	n	(%)	n	(%)
Participants in population	350		346	
with one or more adverse events	124	(35.4)	108	(31.2)
with no adverse events	226	(64.6)	238	(68.8)
Peripheral sensory neuropathy	18	(5.1)	15	(4.3)
Neuropathy peripheral	17	(4.9)	19	(5.5)
Platelet count decreased	11	(3.1)	13	(3.8)
Palmar-plantar erythrodysaesthesia syndrome	10	(2.9)	5	(1.4)
Neutrophil count decreased	7	(2.0)	5	(1.4)
Nausea	5	(1.4)	4	(1.2)
Pneumonitis	5	(1.4)	1	(0.3)
Vomiting	5	(1.4)	3	(0.9)
Blood creatinine increased	4	(1.1)	0	(0.0)
Decreased appetite	4	(1.1)	3	(0.9)
Infusion related reaction	4	(1.1)	5	(1.4)
Neutropenia	4	(1.1)	4	(1.2)
Colitis	3	(0.9)	0	(0.0)
Diarrhoea	3	(0.9)	5	(1.4)
Ejection fraction decreased	3	(0.9)	1	(0.3)
Hypersensitivity	3	(0.9)	1	(0.3)
Thrombocytopenia	3	(0.9)	3	(0.9)
Alanine aminotransferase increased	2	(0.6)	0	(0.0)
Aspartate aminotransferase increased	2	(0.6)	0	(0.0)
Enterocolitis	2	(0.6)	0	(0.0)
Fatigue	2	(0.6)	2	(0.6)
Hepatic function abnormal	2	(0.6)	0	(0.0)
Pneumonia	2	(0.6)	0	(0.0)
Acute kidney injury	1	(0.3)	1	(0.3)
Acute myocardial infarction	1	(0.3)	0	(0.0)
Anaemia	1	(0.3)	0	(0.0)
Anaphylactic reaction	1	(0.3)	0	(0.0)
Anxiety	1	(0.3)	0	(0.0)
Asthenia	1	(0.3)	0	(0.0)
Autoimmune haemolytic anaemia	1	(0.3)	0	(0.0)
Autoimmune lung disease	1	(0.3)	0	(0.0)
Blood alkaline phosphatase increased	1	(0.3)	0	(0.0)
Blood bilirubin increased	1	(0.3)	0	(0.0)
Cardiac failure	1	(0.3)	0	(0.0)
Cerebral infarction	1	(0.3)	0	(0.0)
Delirium	1	(0.3)	0	(0.0)
Disseminated intravascular coagulation	1	(0.3)	0	(0.0)
Drug hypersensitivity	1	(0.3)	1	(0.3)
Dysaesthesia	1	(0.3)	1	(0.3)
Epistaxis	1	(0.3)	0	(0.0)
Gamma-glutamyltransferase increased	1	(0.3)	0	(0.0)
Granulocytopenia	1	(0.3)	0	(0.0)
Hepatitis	1	(0.3)	1	(0.3)
Herpes zoster	1	(0.3)	0	(0.0)
Hyperbilirubinaemia	1	(0.3)	0	(0.0)
Hypoacusis	1	(0.3)	0	(0.0)
Hypoaesthesia	1	(0.3)	0	(0.0)
Neurotoxicity	1	(0.3)	4	(1.2)
Paraesthesia	1	(0.3)	1	(0.3)
Polyneuropathy	1	(0.3)	1	(0.3)
Pyrexia	1	(0.3)	1	(0.3)
Rash	1	(0.3)	0	(0.0)
Renal failure	1	(0.3)	0	(0.0)
Respiratory failure	1	(0.3)	0	(0.0)
Rhabdomyolysis	1	(0.3)	0	(0.0)
Sepsis	1	(0.3)	0	(0.0)
Stomatitis	1	(0.3)	1	(0.3)
Tubulointerstitial nephritis	1	(0.3)	0	(0.0)

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. No revocation or withdrawal of pembrolizumab registration for safety reasons has occurred in any country.

2.5.1. Discussion on clinical safety

The MAH provided safety data from KN811 study (n=350 experimental treatment, n=346 control), and included for comparisons the pooled chemo combo dataset (n=3123) and the pembrolizumab monotherapy reference safety dataset (RSD) (n=7631).

It should be noted that data from 3,473 patients is the sum of the previous pooled combo dataset (3,123) plus the newly added pembro+chemo arm in KEYNOTE-811 (350).

Regarding exposure, in KEYNOTE-811 the median duration of therapy in the pembrolizumab plus SOC was longer than all other datasets. The percentage of participants with ≥6 and ≥12 months duration of exposure was longer in the pembrolizumab plus SOC as compared to the control group, while similar to the pembro combo dataset.

While the demographic and baseline characteristics in KEYNOTE-811 were generally well balanced between the two treatment groups, more participants in KEYNOTE-811 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 AE rates in the pembrolizumab + SOC group were generally consistent with the control arm, although few more G3-5 AEs (all-causality and drug-related) were observed. There were little more discontinuations due to AEs, drug-related AEs and drug-related SAE. When adjusted for exposure, however, the differences between the two treatment arms of KN-811 do not seem relevant. As compared to the pembro combo dataset, increased rate of discontinuation is observed, which is however mostly due to discontinuation of chemotherapy. As expected, the pembrolizumab+SOC group of KN811 presented safety profile reflective of AEs for the combination of trastuzumab, chemotherapy and pembrolizumab in comparison with pembrolizumab monotherapy.

In the pembrolizumab plus SOC group, the most frequently reported AEs regardless of causality (≥20% incidence) were diarrhoea, nausea, anaemia, vomiting, decreased appetite, neutrophil count decreased, platelet count decreased, AST increased, peripheral sensory neuropathy, fatigue, palmar-plantar erythrodysaesthesia syndrome, and weight decreased, which were reported with similar incidences in SOC group.

The most frequently reported drug-related AEs (≥20% incidence) in the pembrolizumab plus SOC group were diarrhea, nausea, anemia, neutrophil count decreased, decreased appetite, platelet count decreased, vomiting, peripheral sensory neuropathy, and palmar-plantar erythrodysaesthesia syndrome, with similar incidences reported in the SOC group.

The most common Grade 3 to 5 AEs regardless of causality (>5% incidence) in the pembrolizumab plus SOC group were anaemia, diarrhoea, neutrophil count decreased, neutropenia, platelet count decreased, and hypokalaemia, which were reported with similar incidences in SOC group.

The most frequently reported drug-related Grade 3 to 5 events (≥5% incidence) in the pembrolizumab plus SOC group were diarrhoea, neutrophil count decreased, neutropenia, platelet count decreased, and anaemia, with similar incidences in the SOC group.

The most frequently reported SAEs (≥2% incidence) in the pembrolizumab plus SOC group were pneumonia, diarrhea, pulmonary embolism, infusion-related reaction, pneumonitis, and vomiting.

The most frequently reported drug-related SAE (≥3% incidence) in both the pembrolizumab plus SOC and SOC groups was diarrhea (4.6% and 4.3% of participants, respectively).

The most common AEs (≥1% incidence) leading to discontinuation of pembrolizumab in the pembrolizumab plus SOC group were pneumonitis (1.7%) and pneumonia (1.1%), and the most common drug-related AE leading to discontinuation of any drug were peripheral sensory neuropathy/neuropathy peripheral in both arms (about 10%), while the leading AE for discontinuation of pembrolizumab was pneumonitis (1.4%). The most common AEs (≥10% incidence) leading to treatment interruption of any drug in the pembrolizumab plus SOC group were neutrophil count decreased, diarrhoea, platelet count decreased, and neutropenia, with similar incidences in the SOC group.

With regard to laboratory value, the MAH reported two participants in the pembrolizumab plus SOC arm meeting the laboratory criteria for drug-induced liver injury (vs 1 in the control arm). Furthermore, a higher incidence of ALT, AST and bilirubin increase as AEs was noted in the experimental vs the control arm, and in some cases also as compared to the pembrolizumab combo pooled dataset. Upon request, the MAH reviewed the hepatic toxicity in KEYNOTE-811. Based on the data provided, it is agreed that the hepatic-related AEs require neither a change in the characterization of this risk for pembrolizumab nor an update of the SmPC.

A total of 22 vs 20 patients died due to AEs in the investigational vs control arm of KN811 study. Of those, 5 AEs were treatment-related according to investigator or sponsor, i.e. pneumonitis (2 cases), hepatitis, sepsis and cerebral infarction. Pneumonitis is a known ADR for pembrolizumab. Cerebral infarction was considered by the investigator related to pembrolizumab, but not to chemotherapy nor trastuzumab. Cerebral infarction it is not a known AE of pembrolizumab. At request of the CHMP, a review of cerebral infarction events was performed in the Company Global Safety Database. Based on the data provided, it is agreed that causality assessment was confounded by pre-existing or concurrent conditions that represent known risk factors for cerebral infarction, i.e. hypertension, hyperlipidemia, diabetes, atherosclerosis, coagulation abnormality associated with underlying malignancy. Based on the data provided, no changes in the SmPC are considered warranted at this stage. This event should be monitored in the future.

As expected, the overall incidence of AEOSI was higher in the pembrolizumab plus SOC group compared with the SOC group, but overall similar to pembrolizumab + chemotherapy dataset. The median time to onset of the first AEOSI in the pembrolizumab plus SOC group was 67 days, similar to both pembrolizumab combo and pembrolizumab mono datasets. Median duration of AEOSI episodes (41 days) is similar to the pembrolizumab combo dataset but shorter than pembrolizumab monotherapy. Overall, most AEOSI were Grade 1 or 2 in severity and nonserious. Grade 5 AEOSI occurred in 3 (0.9%) participants in the pembrolizumab plus SOC group (2 patients with pneumonitis and 1 with hepatitis). Most of the AEOSI in the pembrolizumab plus SOC arm resolved (58.3%). The most common (>5% incidence) AEOSI categories reported in the pembrolizumab plus SOC group were infusion reactions, hypothyroidism, and pneumonitis (16.0%, 10.6%, and 6.0%, respectively). 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, with the exceptions of pneumonitis (6% vs 1.4% vs 4% vs 4.2%) and infusion-related reactions (16% vs 13% vs 7.9% vs 2.2%). A higher frequency of pneumonitis and infusion-related reactions was expected with the addition of trastuzumab and oxaliplatin to pembrolizumab since these are known risks of the SOC combination, as well as due to longer exposure, based on exposure-adjusted data (not shown). A higher incidence of colitis as AEOSI category is noted as compared to the other datasets (4.9% vs

2.9% vs 2.7% vs 2.1%), but no meaningful difference is observed after adjusting for exposure. Overall, no additional warnings regarding these toxicities are considered needed in the SmPC.

Taking into account the known cardiotoxicity of trastuzumab, the MAH provided data specific for such toxicity as well as an evaluation of LVEF decrease. The MAH noted that the prescribing information for trastuzumab shows 2% of patients experiencing congestive heart failure events and a range from 4% (for monotherapy) to 28% (in combination with chemotherapy) of patients experiencing cardiac dysfunction following treatment with trastuzumab. Based on the data provided, it is agreed that the frequency of cardiac events observed in KEYNOTE-811 is consistent with these results, and no increase in cardiac events for the combination of pembrolizumab with trastuzumab is envisaged.

The adverse event summary showed similar incidence in the pembrolizumab plus SOC arm between patients <65 years and ≥ 65 years, with the exception of death due to AEs and discontinuation due to AEs. A similar pattern is however observed also in the SOC arm, as well as in the pembrolizumab combo pooled dataset. The same observation is made according to age categories <65, 65-74 and 75-84. Only 28 patients however were over 75 in the experimental arm.

The MAH was requested by the CHMP to review the AEs occurring in the CPS<1 subset, as the pattern of crossing OS curves raised concern from a safety perspective, acknowledging that this PD-L1 negative patients are nevertheless excluded from the indication. Based on the data provided, the events of death due to AEs (in terms of frequency and causes), do not raise additional safety concern that may impact on the indication for the combination.

2.5.2. Conclusions on clinical safety

The safety profile of pembrolizumab in combination with chemotherapy (FP/CAPOX) and trastuzumab in previously untreated participants with locally advanced unresectable or metastatic HER2-positive gastric or GEJ adenocarcinoma in KEYNOTE-811 overall reflects the established safety profiles of the chemotherapy regimen administered and pembrolizumab monotherapy. The addition of pembrolizumab does not appear to increase cardiac toxicity associated with the established safety profile of trastuzumab and the SOC regimens. 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/was requested to submit 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 38 is acceptable.

The main proposed RMP changes were the following:

- Addition of a new indication for pembrolizumab in combination with trastuzumab, fluoropyrimidine- and platinum-containing chemotherapy for the first-line treatment of locally advanced unresectable or metastatic HER2-positive gastric or gastro-oesophageal junction adenocarcinoma in adults whose tumours express PD-L1 with a CPS ≥ 1.

- Addition of study KEYNOTE-811 in Modules SIII, SVII and SVIII.
- Renaming the Important Identified Risk of "Immune-related adverse reactions (including immune-related pneumonitis, colitis, hepatitis, nephritis, and endocrinopathies" to "Immune-mediated adverse reactions" as per European Medicines Agency (EMA) request.
- Update to Part V Risk Minimisation Measures (including Evaluation of the Effectiveness of Risk Minimisation Activities) and Annex 6 Details of Proposed Additional Risk Minimisation Activities to include additional symptoms of diabetic ketoacidosis (DKA) in line with the update to the Package leaflet as part of PSUSA/00010403/202109, to retire the Patient Brochure as part of PSUSA/00010403/202209 and to update the Patient Alert Card, to be used as a single document..

Safety concerns

Table SVIII.1: Summary of Safety Concerns

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

Pharmacovigilance plan

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

Risk minimisation measures

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

Safety Concern	Risk minimisation Measures	Pharmacovigilance Activities
Important Identified Risks: Immune-Mediated Adverse Reactions		
Immune-mediated adverse reactions	Routine risk minimisation measures: ▪ The risk of the immune-mediated adverse reactions associated with the use of pembrolizumab is described in the SmPC, Section 4.2, 4.4, 4.8 and appropriate advice is provided to the prescriber to minimize the risk.	Routine pharmacovigilance activities Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: Targeted questionnaire for spontaneous postmarketing reports of all adverse events

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

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

2.7. Update of the Product information

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

2.7.1. User consultation

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

There are two changes in the package leaflet for this submission: section 1 (addition of new indication) and in section 4 (minor changes to align to update in 4.8 section of the SmPC). The key messages for the safe use of the medicinal product are however not impacted. Furthermore, the design, layout and format of the package leaflet will not be affected by the proposed revisions. Therefore, the proposed revision does not constitute significant changes that would require the need to conduct a new user consultation.

3. Benefit-Risk Balance

3.1. Therapeutic Context

HER-2-positive gastric or GEJ adenocarcinoma at an advanced stage of disease.

3.1.1. Disease or condition

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

3.1.2. Available therapies and unmet medical need

Chemotherapy plus trastuzumab represents the current SOC for the front-line approach to locally advanced and metastatic HER-2-positive gastric or GEJ adenocarcinoma (ESMO guidelines 2022). However, prognosis remains poor with survival generally below 1 year, which makes development of new therapies a high unmet medical need.

3.1.3. Main clinical studies

The current variation is supported by data from KEYNOTE-811, a Phase 3, randomised, double-blind, placebo-controlled trial Comparing Trastuzumab Plus Chemotherapy and Pembrolizumab With Trastuzumab Plus Chemotherapy and Placebo as First-line Treatment in Participants With HER2 Positive Advanced Gastric or Gastroesophageal Junction Adenocarcinoma.

3.2. Favourable effects

-The efficacy analysis in the ITT population, showed advantage of pembrolizumab over placebo in the primary endpoint PFS (HR=0.72; 95% CI 0.60;0.87; p<0.0002) with a 2-month gain in disease progression (10 vs 8.1 months in median in the pembrolizumab and control arm, respectively)

-In the CPS ≥1 subgroup, pembrolizumab showed superiority over placebo in PFS (HR=0.70; 95% CI 0.58, 0.85) and OS (HR=0.79; 95% CI 0.64,0.98; p=0.0143), with a gain in median PFS and OS of 3 months (10.8 vs 7.2) and 5 months (20.5 vs 15.6), respectively.

-The ORR analysis showed advantage of pembrolizumab over placebo in the ITT population (72.6% vs 59.8%) with a slightly better response duration (11.2 vs 9 months in median)

3.3. Uncertainties and limitations about favourable effects

None.

3.4. Unfavourable effects

- In the pembrolizumab plus SOC group, the most frequently reported AEs regardless of causality (≥ 20% incidence) were diarrhoea, nausea, anaemia, vomiting, decreased appetite, neutrophil count decreased, platelet count decreased, AST increased, peripheral sensory neuropathy, fatigue, palmar-plantar erythrodysaesthesia syndrome, and weight decreased, with similar incidences reported in the SOC group, suggesting that the overall safety profile of the proposed combination is mostly influenced by the common chemotherapy backbone. The overall pattern of drug-related AEs was consistent with the overall safety analysis.

- The pattern of Grade 3-5 AEs (all causality and drug related) was similar in the two treatment arms. The most common all-causality Grade 3 to 5 AEs (>5% incidence) in the pembrolizumab plus SOC group were anaemia, diarrhoea, neutrophil count decreased, neutropenia, platelet count decreased, and hypokalaemia.

- SAEs were observed in similar percentage between treatment arms, with diarrhoea being the most common treatment-related SAE in both arms.

- There were few more discontinuation of study drugs due to adverse events in the pembrolizumab+SOC arm as compared to the control arm (40.6% vs 36.4%), although mostly leading to discontinuation of chemotherapy.

- Pembrolizumab is characterized by the occurrence of immune-mediated adverse events. The rate of AEOSI was, as expected, higher in the pembrolizumab containing arm as compared to the control arm (37.7% vs 24%), but not very different to the pembro+chemo pooled dataset (33.7%). Most common (>5%) AEOSI were infusion related reactions (11.7%), hypothyroidism (10.6%) and pneumonitis (5.4%). Infusion-related reaction AEOSI were reported in a similar proportion in both treatment arms, but were more common than in the reference safety datasets of both pembro combo and pembro mono. This may be likely related to the contribution of trastuzumab and oxaliplatin, having known risks of infusion-related reactions. Pneumonitis and hypothyroidism AEOSI were both higher in the pembrolizumab plus SOC group compared with the SOC group. However, pneumonitis was also more commonly reported than in the pembrolizumab reference datasets, possibly due to trastuzumab which has known risk of pneumonitis, while incidence of hypothyroidism was similar to the reference datasets.

- Deaths due to AEs occurred in 6.3% vs 5.8% of patients in the pembrolizumab+SOC vs placebo+SOC arm of KEYNOTE-811. Treatment-related deaths were due to pneumonitis, hepatitis, sepsis, and cerebral infarction in the pembrolizumab + SOC arm. Both pneumonitis and hepatitis are known ADR for pembrolizumab.

3.5. Uncertainties and limitations about unfavourable effects

- Similar incidence of AEs are observed in the pembrolizumab plus SOC arm according to age categories, with the exception of death due to AEs and discontinuation due to AEs. A similar pattern is however observed also in the SOC arm, as well as in the pembro combo pooled dataset. Only 28 patients however were over 75 in the experimental arm, limiting conclusion in this subset.

3.6. Effects Table

Table 24. Effects Table for [Keytruda in combination with trastuzumab, fluoropyrimidine- and platinum-containing chemotherapy, for the first-line treatment of locally advanced unresectable or metastatic HER2-positive gastric or gastro-oesophageal junction adenocarcinoma with CPS⩾1] (data cut-off: 25-

MAY-2022)

Effect	Short description	Unit	Treatment	Control	Uncertainties / Strength of evidence	References
Favourable Effects						
OS	duration of survival from randomization to death regardless of cause	months (95% CI)	20.5 (18.2, 24.3)	15.6 (13.5,18.6)		CSR
PFS	duration of survival without progression from randomization to PD or death whichever occurred first	months (95% CI)	10.8 (8.5, 12.5)	7.2 (6.8, 8.4)		
ORR	Confirmed CR + PR	%	73.2	58.4		
DoR	Duration of CR/PR until documented PD	months (95% CI)	11.3 (1.1+ -40.1+)	9.5 (1.4+ –38.3+)		
Unfavourable Effects						
summary	G3-5 AEs	%	70.9	65	No new safety concerns identified	KN-811
	SAE	%	44.9	45.4		
	Death	%	6.3	5.8		
	Discontinuation due to AEs	%	40.6	36.4		
	AEOSI	%	37.7	24		
	- IRR	%	11.7	9.8		
	- hypothyroidism	%	10.6	4.3		
	- pneumonitis	%	5.4	1.4		

Abbreviations: AE= adverse event; SAE=serious adverse event; AEOSI= adverse event of special interest; IRR=infusion related reaction; CSR=clinical study report

Notes: DCO 25-MAY-2022

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

In the ITT population, pembrolizumab as add-on to chemotherapy and trastutzumab demonstrated a statistically significant improvement in median PFS but not in median OS compared to the control arm. In the subgroup of patients with CPS<1 no benefit from the addition of pembrolizumab was observed. The MAH's proposal for a restriction of the indication to the CPS ≥1 population is in line with the EMA guidelines on the investigation of subgroups in confirmatory clinical trials. Indeed, the study was formally successful since a statistically significant effect in the ITT population on one of the two components of the dual endpoint was demonstrated; however, the therapeutic efficacy or risk-benefit is borderline and clearly not proven in the CPS<1 group, thus reflecting Scenario 2 of the guideline. In patients with CPS ≥1, the addition of pembrolizumab to trastuzumab plus chemotherapy improved the median PFS (HR=0.70; 95% CI 0.58, 0.85, with a 3-month gain compared to placebo) and the median OS (HR=0.79; 95% CI 0.64, 0.98; p=0.0143, with a 5-month gain compared to placebo).

Overall, the safety profile of pembrolizumab in combination with chemotherapy (FP/CAPOX) and trastuzumab in the first line treatment of patients with locally advanced unresectable or metastatic HER2-positive gastric or GEJ adenocarcinoma in KEYNOTE-811 reflects the established safety profiles of the chemotherapy regimen administered and pembrolizumab monotherapy. No new safety concerns have been identified.

3.7.2. Balance of benefits and risks

Considering the poor prognosis of patients in the intended indication, the improved median PFS and OS demonstrated by pembrolizumab as add-on to SOC in the CPS≥1 subgroup can be considered of clinical relevance. From a safety perspective, the increased toxicity associated to treatment compared to placebo appears manageable.

3.7.3. Additional considerations on the benefit-risk balance

N/A

3.7.4. Conclusions

The overall B/R of Keytruda in combination with trastuzumab, fluoropyrimidine and platinum-containing chemotherapy, for the first-line treatment of locally advanced unresectable or metastatic HER2-positive gastric or gastro-oesophageal junction adenocarcinoma in adults whose tumours express PD-L1 with a CPS ⩾ 1 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, II and IIIB

Extension of indication to include in combination with trastuzumab, fluoropyrimidine and platinum-containing chemotherapy for treatment of locally advanced unresectable or metastatic HER2- positive gastric or gastro-oesophageal junction adenocarcinoma for Keytruda in adults whose tumours express PD-L1 with a CPS ≥ 1, based on interim results from study KEYNOTE-811, an ongoing Phase 3, double-blind trial comparing trastuzumab plus chemotherapy and pembrolizumab with trastuzumab plus chemotherapy and placebo as first-line treatment in participants with HER2-positive advanced gastric or gastro-oesophageal junction adenocarcinoma; As a consequence, sections 4.1, 4.8, and 5.1 of the SmPC are updated. The Annex II, Package Leaflet and Labelling are updated in accordance. Version 38 of the RMP has also been submitted.

Amendments to the marketing authorisation

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

5. EPAR changes

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

Scope

Please refer to the Recommendations section above.

Summary

Please refer to Scientific Discussion 'Keytruda-H-C-3820-II-0133'