ONCOLOGIC DRUGS ADVISORY COMMITTEE (ODAC) MEETING

PEMBROLIZUMAB IN FIRST-LINE GASTRIC CANCER

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MERCK SHARP & DOHME LLC

RAHWAY, NJ USA

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

Abbreviation/Term	Definition
1L	First-line
2L	Second-line
3L(+)	Third-line (or greater)
5-FU	5-fluorouracil
advGastric EDM	Advanced Gastric/Esophageal/GEJ Enhanced Datamart
AE	Adverse event
APaT	All-Participants-as-Treated
BICR	Blinded independent central review
BLA/sBLA	Biologics License Application/supplemental Biologics License Application
CAPOX	Capecitabine + oxaliplatin
CI	Confidence interval
CIN	Chromosomal instability
CPS	Combined positive score
CR	Complete response
DOR	Duration of response
EC_{50}	Half-maximal effective concentration
ECOG	Eastern Cooperative Oncology Group
EHR	Electronic health record
EORTC QLQ-C30	European Organisation for the Research and Treatment of Cancer Quality of life Questionnaire Core 30
EORTC QLQ-STO22	European Organisation for the Research and Treatment of Cancer Quality of life Questionnaire for Gastric Cancer
ErbB2	Erb-B2 receptor tyrosine kinase 2
ESCC	Esophageal squamous cell carcinoma
ESMO	European Society for Medical Oncology
EU	European Union
FA	Final analysis
FAS	Full analysis set
FDA	Food and Drug Administration
FGFR2b	Fibroblast growth factor receptor 2b
FHRD	Flatiron Health Research Database
FP	5-FU + cisplatin
GEJ	Gastroesophageal junction
H	Hypothesis
HER2	Human epidermal growth factor receptor 2
HNSCC	Head and neck squamous cell carcinoma
HR	Hazard ratio
HRQoL	Health-related quality of life

Abbreviation/Term	**Definition**
IA1	First interim analysis
IA2	Second interim analysis
IA3	Third interim analysis
ICD	International Classification of Diseases
ICI	Immune checkpoint inhibitor
IFNγ	Interferon gamma
IgG4	Immunoglobulin 4
IHC	Immunohistochemistry
IL-2	Interleukin-2
ITT	Intent-to-treat
KM	Kaplan-Meier
LOT	Line(s) of therapy
LS	Least squares
mAb	Monoclonal antibody
NCCN	National Comprehensive Cancer Network
NSCLC	Non-small cell lung cancer
ODAC	Oncology Drugs Advisory Committee
ORR	Objective response rate
OS	Overall survival
PD-1	Programmed cell death protein 1
PD-L1	Programmed cell death 1 ligand 1
PD-L2	Programmed cell death 1 ligand 2
PFS	Progression-free survival
PR	Partial response
PRO	Patient-reported Outcome
Q-TWiST	Quality-adjusted time without symptoms of disease progression or toxicity of treatment
q3w	Every 3 weeks
q6w	Every 6 weeks
QoL	Quality of life
RECIST 1.1	Response Evaluation Criteria in Solid Tumors version 1.1
REL	Relapse
ROC	Receiver operating characteristic
RSD	Reference safety dataset
RWE	Real-world evidence
SAE	Serious adverse event
SAP	Statistical analysis plan
SOC	Standard of care
sSAP	Supplemental statistical analysis plan

Abbreviation/Term	**Definition**
TCGA	The Cancer Genome Atlas
TNBC	Triple-negative breast cancer
TNFα	Tumor necrosis factor alpha
TOX	Toxicity
TPS	Tumor proportion score
TWiST	Time without symptoms of disease progression or toxicity of treatment
US	United States
USPI	United States Prescribing Information
XP	Capecitabine plus cisplatin

1 EXECUTIVE SUMMARY

The FDA is convening this ODAC to discuss the approach to selection of PD-L1 expression cut-points within gastric cancer clinical studies based on the clinical data results from completed Phase 3 studies that supported approval of 1L indications for anti-PD-(L)1 agents in the US.

Merck conducted 2 double-blinded, placebo-controlled, pivotal Phase 3 clinical studies to evaluate pembrolizumab (KEYTRUDA®) for the 1L treatment of locally advanced unresectable or metastatic HER2-negative (KEYNOTE-859) and HER2-positive (KEYNOTE-811) gastric or GEJ adenocarcinoma (hereafter referred to as gastric cancer) compared with SOC alone. Based on the FDA-agreed protocol and protocol-specified analysis plans for these studies, the addition of pembrolizumab to SOC treatment resulted in statistically significant and clinically meaningful improvements in OS, PFS, and ORR in all patients enrolled in these studies. On the basis of these findings, pembrolizumab was granted 2 separate indications for the 1L treatment of locally advanced unresectable or metastatic HER2-negative and HER2-positive gastric or GEJ adenocarcinoma.

Based on the totality of the clinical data from pembrolizumab gastric cancer studies, and to ensure that patients who may benefit from the addition of pembrolizumab to chemotherapy have appropriate access in the US, the currently approved indications in patients with locally advanced and metastatic HER2-negative and HER2-positive gastric and GEJ cancer should be retained. To support this position, this briefing document summarizes the benefit:risk profile in support of the current indications and provides information on the biological basis for combinations of chemotherapy and immunotherapy. The briefing document also explains the PD-L1 biomarker cut-point selection process and how this biomarker knowledge was incorporated into the clinical studies evaluating pembrolizumab for the treatment of gastric cancer.

Gastric Cancer

As the fifth most common cancer and the fifth leading cause of cancer deaths globally [1], gastric cancer is a major health problem worldwide and remains a disease with high unmet need. In the US, the number of new cases and deaths from gastric cancer in 2024 are estimated to be 26,890 and 10,880, respectively [2]. The 5-year relative survival rate for those with distant disease is only 7.0% [3]. For decades, the only available treatment option for locally advanced unresectable or metastatic gastric or GEJ cancer was doublet chemotherapy, which was associated with survival of approximately 12 to 14 months [4] [5] [6] [7] [8].

With a greater understanding of the biology of gastric cancer, the disease has become divided into distinct biological subtypes, in particular HER2-negative and HER2-positive, and novel therapies, including checkpoint inhibitors have been approved [9] [10]. Approximately 80% of gastric cancers are HER2-negative [8] [11], with fluoropyrimidine/platinum doublet regimens containing 5-FU or capecitabine and cisplatin or oxaliplatin recognized worldwide as standard 1L chemotherapy regimens for these patients.

Approximately 20% of gastric cancers are HER2-positive [12]. Patients with gastric cancers that overexpress HER2 benefit from HER2-directed therapy (eg, trastuzumab) and represent a distinct biologic population of gastric adenocarcinoma. Systemic chemotherapy with trastuzumab has been the mainstay of treatment for advanced and metastatic gastric cancer [13] [14]. HER2-positive cancers are most commonly seen in the CIN TCGA subgroup and are associated with intestinal-type pathology and a proximal tumor location [15].

The recent approvals of pembrolizumab and nivolumab have changed the treatment paradigm for patients with newly diagnosed gastric cancer, which improved median OS when added to SOC [Sec. 4.6.1.2] [Sec. 4.7.1.2] [9]. Therefore, ICIs offer patients an opportunity for durable responses and long-term survival, which are not commonly observed with historic chemotherapy regimens for gastric cancer. Despite the benefit of adding ICIs to 1L treatment, almost all patients will experience disease progression. Upon progression, it is estimated that fewer than 50% of patients in the US in 2024 receive subsequent therapy in the 2L setting, where ICIs are not currently available [16].

Considering the global health burden of gastric cancer and poor 5-year survival rate for patients with distant/metastatic disease, there continues to be a high unmet medical need for this patient population. Continuing to provide patients with locally advanced and metastatic HER2-negative and HER2-positive gastric and GEJ cancer access to pembrolizumab in the 1L setting, as currently labelled, allows these patients to have the best chance of benefiting from this practice-changing therapy.

Pembrolizumab – Monotherapy and Combination Studies in Gastric Cancer

Pembrolizumab is a monoclonal antibody that binds to the PD-1 receptor and blocks its interaction with PD-L1 and PD-L2, releasing PD-1-pathway-mediated inhibition of the immune response, including the antitumor immune response. This blockade enhances functional activity of the target lymphocytes to facilitate tumor regression and, ultimately, immune rejection. The Sponsor was a pioneer in exploring immunotherapy in gastric cancer, a rare disease for which the FDA has granted pembrolizumab Orphan Drug Designation. The program started with KEYNOTE-012, which was a Phase 1b basket study evaluating pembrolizumab monotherapy and included participants with recurrent or metastatic gastric cancer that started enrolling participants in 2013. To date, approximately 3000 participants with gastric cancer have been treated with pembrolizumab as either monotherapy or in combination with chemotherapy in clinical studies spanning from perioperative therapy to heavily pretreated (3L+) gastric cancer.

An important component of the program has been evaluation of approaches to identify patient populations that may be more likely to benefit from treatment with pembrolizumab. Early monotherapy studies of pembrolizumab and other anti-PD-(L)1 agents suggested that PD-L1 expression might enrich for benefit in several tumor types, including gastric and GEJ cancer (HER2-negative and HER2-positive) [17] [18] [19] [20]. However, PD-L1 expression does not clearly discriminate between those who will versus those who will not benefit from the addition of pembrolizumab, as some patients whose tumors do not express PD-L1 (PD-L1 negative) do respond when pembrolizumab is administered as monotherapy or in combination (KEYTRUDA USPI [accessed 21-AUG-2024]).

Chemotherapy augments the antitumor immune response by several mechanisms, including immunogenic cell death, increasing T-cell infiltration in the tumor microenvironment, and reducing immunosuppressive cells [21]. In several tumor types, combining pembrolizumab with chemotherapy eliminated the need to restrict pembrolizumab to a population of patients whose tumors express PD-L1 (eg, TPS ≥50% in NSCLC) or enhanced the antitumor activity of pembrolizumab monotherapy across a broad spectrum of PD-L1 expression levels, including PD-L1 negative (eg, NSCLC) [22] [23] [24] [Sec. 4.5]. Similar results have been observed in TNBC and HNSCC [25] [26] [27].

KEYNOTE-859 and KEYNOTE-811 Study Design and CPS Cut-point Selection

KEYNOTE-859 and KEYNOTE-811 were rigorously designed, Phase 3 studies that evaluated the addition of pembrolizumab to SOC in participants enrolled across all levels of tumor PD-L1 expression, including no PD-L1 expression (ie, the ITT population). Prior to starting both studies, the FDA was consulted on the clinical study design, endpoints, study population, statistical analyses, and biomarker evaluation plan. The studies met the success criteria for the hypotheses of the primary and key secondary endpoints in the overall ITT population.

The PD-L1 all-comer study designs were based on a number of factors: 1) chemotherapy augments the antitumor immune response; 2) PD-1 inhibition enhances the positive immune effects of chemotherapy; 3) the results of 2 investigator-initiated studies suggested PD-L1 expression was not a predictor of response to pembrolizumab plus chemotherapy in HER2-positive gastric cancer [28] [29]; and 4) potential extension of benefit of pembrolizumab to those patients whose tumors are PD-L1 negative.

Accumulating experience with pembrolizumab as monotherapy in several cancer types where PD-L1 expression enriched for improved efficacy, including gastric cancer, led to the incorporation of CPS cut-points as stratification factors in both KEYNOTE-859 and KEYNOTE-811. The selection of the CPS cut-points was based on an analysis of training set data from the Sponsor's initial clinical studies with pembrolizumab monotherapy in later lines of treatment for gastric cancer (ie, KEYNOTE-012 and KEYNOTE-059). The analysis aimed to assess potential PD-L1 expression cut-point values for enrichment (tumor response rates observed in PD-L1 positive patients), sensitivity (number of responders captured by a potential cut-point), and the prevalence of PD-L1 expression. The CPS cut-point of ≥1 was identified and added as a stratification factor for both studies. As further data emerged from other gastric studies, KEYNOTE-859 incorporated the CPS ≥1 and CPS ≥10 cut-points into the analyses of the primary and secondary endpoints. Incorporating PD-L1 CPS cut-points into the designs of these studies provided additional information regarding efficacy at higher PD-L1 levels. Of note, there are no analytical validation data at CPS ≥5 for the PD-L1 IHC 22C3 pharmDx™ in any tumor type across the pembrolizumab development program.

KEYNOTE-859 Summary

In KEYNOTE-859, pembrolizumab plus chemotherapy demonstrated a statistically significant and clinically meaningful improvement in OS, PFS, and ORR compared with placebo plus chemotherapy as a 1L treatment of HER2-negative, advanced gastric or GEJ

cancer in all participants enrolled [Sec. 4.6.1], which led to FDA approval based on their assessment of the favorable benefit:risk profile in the 1L setting for patients with any level of PD-L1 expression on 16-NOV-2023.

At the request of the FDA in preparation for this ODAC, the Sponsor conducted exploratory post-hoc analyses at additional CPS cut-points. Many of the requested PD-L1 subgroups were not prespecified and the study was not powered to definitively demonstrate efficacy in the requested populations. The results should be interpreted with caution. These exploratory analyses indicate that all CPS subgroups had HR point estimates <1 [Sec. 4.6.1] and suggest that there is a potential for benefit across all PD-L1 expression levels, supporting the current indication for KEYNOTE-859.

KEYNOTE-811 Summary

KEYNOTE-811 was the first global Phase 3 study in HER2-positive gastric cancer to show that the combination of an ICI with SOC (ie, trastuzumab plus chemotherapy) significantly and meaningfully improves OS, PFS, and ORR, results in durable responses, and provides an improved therapeutic option for patients [Sec. 4.7.1]. The FDA granted accelerated approval on 05-MAY-2021 for patients with any level of PD-L1 expression based on ORR and DOR from the first 264 randomized participants at IA1.

At IA2, PFS was statistically significant in the ITT population, while the OS data were not mature (information fraction: 73%) and did not reach statistical significance. Based on the OS HR in the CPS <1 subgroup, which was greater than 1 with a lower bound of the 95% CI almost excluding unity, the benefit was considered to be greater in patients with PD-L1 CPS ≥1. The Sponsor proactively engaged with FDA to limit the approved indication to only those patients whose tumors express PD-L1 with a CPS ≥1. The indication was updated to the CPS-enriched population on 07-NOV-2023 and is the currently approved indication in the US. The Sponsor announced on 01-MAY-2024 that the KEYNOTE-811 study met the success criteria for the hypothesis of the dual primary endpoint of OS at the FA in the ITT study population. A supplemental BLA to convert the accelerated approval to a traditional approval for the current indication is under review at FDA.

At the request of the FDA in preparation for this ODAC, the Sponsor conducted exploratory post-hoc analyses at additional CPS cut-points, as described above for KEYNOTE-859. These exploratory analyses indicate that the benefit of pembrolizumab plus trastuzumab and chemotherapy is greater in participants with CPS ≥1; however, there is no further increase in efficacy observed at higher PD-L1 expression cut-points [Sec. 4.7.1]. These data support the current indication for KEYNOTE-811 in the US.

Health-related Quality of Life and Safety

In both KEYNOTE-859 and KEYNOTE-811, the changes from baseline in HRQoL scores were similar between the pembrolizumab plus SOC group and the SOC group throughout the course of treatment, suggesting that there was no decrement in HRQoL with addition of pembrolizumab to SOC [Sec. 4.6.1.5] [Sec. 4.7.1.5]. As gastric cancer progresses, patients

would be expected to experience diminished HRQoL, therefore, maintenance of HRQoL may be considered a meaningful outcome [30] [31].

The safety profile observed in both studies was manageable and generally consistent with the individual established safety profiles of the chemotherapy administered and pembrolizumab monotherapy and primarily consisted of the addition of immune-mediated AEs (due to pembrolizumab) to the safety profile of chemotherapy [Sec. 4.6.2] [Sec. 4.7.2]. There is no biologic rationale to suggest that the safety profile of pembrolizumab would change based on the level of PD-L1 expression. The Sponsor has evaluated the safety of pembrolizumab in combination with chemotherapy by PD-L1 subgroups across participants with gastric cancer and has not identified clinically significant differences in the safety profile across different PD-L1 expression cut-points.

Summary and Conclusions

KEYNOTE-859 and KEYNOTE-811 were designed with pembrolizumab in combination with chemotherapy to address different populations with gastric cancer. Based on the available data, the approved indications for KEYNOTE-859 and KEYNOTE-811 are supported by the study designs and results. These studies were agreed upon with the FDA, and appropriately capture patients who may receive benefit from adding pembrolizumab to SOC treatment in 1L HER2-negative and HER2-positive gastric cancer, respectively. The disease biology of HER2-negative and HER2-positive gastric cancer is distinct; therefore, it is possible that there may be differences in the clinical activity of pembrolizumab. Alternatively, the differences seen between KEYNOTE-859 and KEYNOTE-811 may have been due to chance, particularly with the smaller sample size of the PD-L1 CPS <1 subgroup (n=52 in each treatment arm) in KEYNOTE-811 which may have led to more variability in the outcomes.

Based on the prevalence of PD-L1 expression from KEYNOTE-859, restricting the approved all-comer indication to a CPS ≥1 or CPS ≥10 population would result in the exclusion of approximately 22% and 65% of the estimated new patients with metastatic, HER2-negative gastric cancer [Sec. 4.8.1], respectively [8] [11] [2]. Similarly, based on the expected prevalence of PD-L1 expression from KEYNOTE-811, further restricting the approved indication to a CPS ≥10 population, where there was no added benefit observed with further PD-L1 expression beyond the CPS ≥1 cut-point, would result in the exclusion of approximately 54% of the estimated new patients with metastatic, HER2-positive gastric cancer [12] [2].

An analysis of Flatiron Health electronic health record-derived data of adult patients with advanced/metastatic gastric and GEJ cancer who initiated 1L treatment after FDA approvals of immunotherapy found that about 25% of patients were not being tested for PD-L1 expression prior to initiation of therapy. Additionally, many patients with HER2-negative and HER2-positive gastric cancer did not receive FDA-approved ICI-based therapies in the 1L setting [Sec. 8.3], which have demonstrated long-term survival. As there are no currently approved immunotherapies available for gastric cancer in the 2L setting, the best opportunity to receive an immunotherapy is in the 1L setting where patients have the greatest chance to benefit.

For these separate disease subtypes, the current all-comer indication for patients with locally advanced and metastatic HER2-negative gastric and GEJ cancer and the current CPS ≥1-restricted indication for patients with HER2-positive gastric and GEJ cancer should be retained to ensure that all patients who may benefit from the addition of pembrolizumab to chemotherapy do not lose access to this foundational therapeutic option.

2 OVERVIEW OF GASTRIC CANCER AND TREATMENT OPTIONS

Gastric cancer, including cancer arising from the GEJ, remains a major health problem worldwide. Most gastric cancers are adenocarcinomas, which are typically classified based on anatomical location (cardia or non-cardia) and histology (intestinal or diffuse) [32]. Gastric cancer is the fifth most common cancer in the world and is a major cause of cancer-related death [1]. In the US, the estimated number of new cases and deaths from gastric cancer in 2024 will be 26,890 and 10,880, respectively [2]. Approximately 29% of gastric cancers are diagnosed as localized, 25% as regional, and 36% as distant. In 2024, it is estimated that approximately 10,760 patients will be diagnosed with locally advanced or metastatic gastric cancer in the US [2]. The 5-year relative survival rates for regional and distant disease remain dismal at 35.8%, and 7.0%, respectively, highlighting the tremendous unmet need in these patients [3].

Systemic chemotherapy, with or without immunotherapy, is the mainstay of treatment for advanced and metastatic gastric cancer according to both NCCN and ESMO clinical practice guidelines [13] [14]. With a greater understanding of the biology of gastric cancer, the disease has become divided into distinct biological subtypes, in particular HER2-negative and HER2-positive, and novel therapies, including ICIs, have been approved [9] [10].

Approximately 80% of gastric cancers are HER2-negative [8] [11] with fluoropyrimidine/platinum doublet regimens containing 5-FU or capecitabine and cisplatin or oxaliplatin recognized worldwide as standard 1L chemotherapy regimens for these patients. The most commonly used doublet regimens are XP, FP, CAPOX, and 5-FU/oxaliplatin (known as FOLFOX) [13] [14]. However, these treatment regimens result in limited benefit to patients, with median PFS ranging from 4 to 7 months, and median OS typically of 8 to 14 months [4] [5] [6] [7]. The treatment landscape has been evolving rapidly, in particular with the introduction of immunotherapy combined with SOC chemotherapy regimens for the 1L treatment of advanced gastric and GEJ adenocarcinoma [9] [10].

For HER2-negative gastric and GEJ cancers, additional biomarker-directed therapies targeting Claudin 18.2 and FGFR2b in combination with chemotherapy are being investigated for locally advanced unresectable or metastatic gastric or GEJ cancers [33] [34] [35]. However, these will likely only be options for select patients that express these biomarkers.

Patients with gastric cancer that overexpresses the tyrosine kinase receptor HER2 represent a distinct biologic subtype, with an estimated prevalence of approximately 20% [12], and benefit from HER2-directed therapy, such as trastuzumab. HER2-positive gastric cancers are most commonly seen in the “CIN” TCGA subgroup and are associated with intestinal-type pathology and a proximal tumor location [15]. Recent studies suggest that HER2 positivity is

not independently prognostic of outcome, although it is predictive of response to HER2-directed therapies [36]. Interestingly, there may be an association between HER2 positivity and lower tumor mutational burden [37], while other studies have shown that trastuzumab upregulates the expression of PD-1 and its ligand, PD-L1 [38]. A growing body of preclinical and clinical evidence shows that the immune system contributes substantially to the therapeutic effects of trastuzumab in solid tumors [39] [40]. As a consequence, the PD-1/PD-L1 pathway is an attractive target for therapeutic intervention in HER2-positive gastric and GEJ cancer.

The standard 1L treatment for patients with HER2-positive advanced gastric cancer is trastuzumab in combination with a fluoropyrimidine and platinum-containing doublet regimen, which is recommended by both NCCN and ESMO Guidelines [13] [14]. However, the majority of patients treated with trastuzumab plus fluoropyrimidine and platinum-containing chemotherapy relapse or become refractory to treatment historically within approximately 7 months [8].

The approvals of pembrolizumab and nivolumab have changed the treatment paradigm for patients with newly diagnosed gastric cancer, which improved median OS when added to SOC [Sec. 4.6.1.2] [Sec. 4.7.1.2] [9]. Therefore, ICIs offer patients an opportunity for durable responses and long-term survival, which are not commonly observed with historic chemotherapy regimens for gastric cancer. Despite the benefit of adding ICIs to 1L treatment, almost all patients will experience disease progression. Upon progression, fewer than 50% of patients in the US receive subsequent therapy in the 2L setting, where ICIs are currently not available [16].

Considering the global health burden of gastric cancer and poor 5-year survival rate for distant/metastatic stage, there continues to be a high unmet medical need to provide broad access to immunotherapies for this patient population.

3 PEMBROLIZUMAB AND TESTING FOR PD-L1 EXPRESSION

Pembrolizumab is a potent and highly selective humanized mAb of the IgG4/kappa isotype designed to directly block the interaction between PD-1 and its ligands, PD-L1 and PD-L2. This blockade enhances functional activity of the target lymphocytes to facilitate tumor regression and, ultimately, immune rejection. The antibody potentiates existing immune responses in the presence of antigen only; it does not nonspecifically activate T cells.

3.1 PD-L1 IHC 22C3 PharmDx Background

The PD-L1 IHC 22C3 pharmDx assay has been utilized in the pembrolizumab clinical development program for testing tumor tissue for PD-L1 expression. The PD-L1 IHC 22C3 pharmDx is an immunohistochemical assay using monoclonal mouse anti-PD-L1, Clone 22C3 intended for use in the detection of PD-L1 protein in FFPE tissues using EnVision FLEX visualization system on Autostainer Link 48.

PD-L1 IHC 22C3 pharmDx is currently FDA-approved as a companion diagnostic to aid in identifying patients with NSCLC, ESCC, cervical cancer, HNSCC, TNBC, and gastric or GEJ cancer for treatment with KEYTRUDA.

PD-L1 expression in most solid tumors, including gastric or GEJ adenocarcinoma, is determined by CPS, which is the number of PD-L1 staining cells (tumor cells, lymphocytes, macrophages) divided by the total number of viable tumor cells, multiplied by 100. Although the result of the calculation can exceed 100, the maximum score is defined as CPS 100. CPS is defined as follows:

$$\text{CPS} = \frac{\text{\# PD-L1 staining cells (tumor cells, lymphocytes, macrophages)}}{\text{Total \# of viable tumor cells}} \times 100$$

3.2 Selection of PD-L1 Expression Cut-points

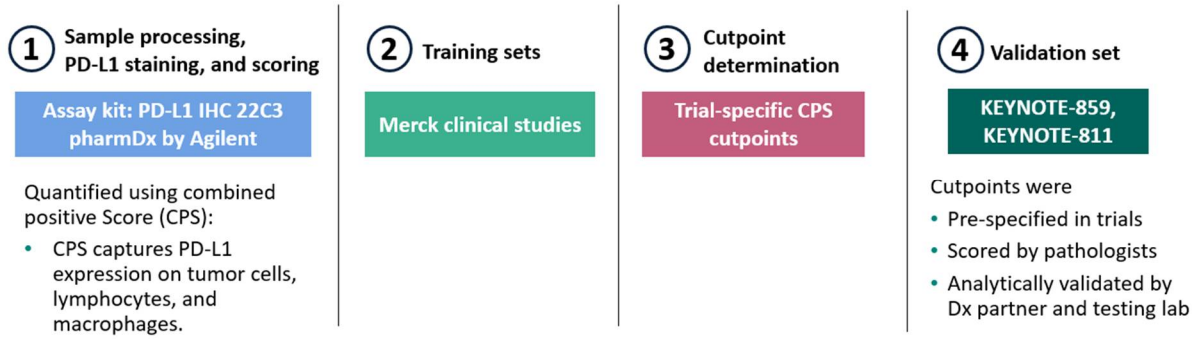
The selection of cut-points for the PD-L1 IHC 22C3 pharmDx assay in gastric cancer was based on an analysis of training set data from the Sponsor's initial clinical studies of pembrolizumab monotherapy in later lines of treatment for gastric cancer. The analysis assessed the clinical utility of potential cut-point values for (1) enrichment of tumor response rates, (2) sensitivity to identify responders, and (3) prevalence of patients in subgroups defined by cut-points based on PD-L1 expression. The selection of cut-points was adapted further as additional information on the relationship between PD-L1 levels and long-term efficacy of pembrolizumab versus SOC became available from ongoing studies. This adaptation ensured that the chosen cut-points were based on robust evidence and reflected the clinical outcomes observed in patients treated with pembrolizumab.

Input from pathologists was also incorporated in cut-point selection to enable accurate and reproducible PD-L1 scoring across different testing sites and pathologists, both in clinical studies, and subsequently, in clinical practice.

Once the cut-points were identified, they were prespecified and incorporated into subsequent randomized clinical studies evaluating pembrolizumab, as appropriate (refer to [Sec. 8.1.1] and [Sec. 8.2.1]). An overview of the cut-point selection process is in [Figure 1].

Details for the justification of the cut-points selected for gastric care are provided in [Sec. 4.2] [Sec. 4.3].

Figure 1
Robust Process for Selection of Cut-points into Merck Randomized Studies



CPS=combined positive score; Dx=diagnostic; IHC=immunohistochemistry; PD-L1=programmed cell death 1 ligand 1.

4 PEMBROLIZUMAB DEVELOPMENT PROGRAM IN GASTRIC CANCER

The clinical development program for pembrolizumab for the treatment of locally advanced or metastatic gastric cancer is presented in [Table 1] and illustrates the Sponsor's commitment to improving treatment options for patients living with gastric cancer.

Data from early studies (KEYNOTE-012, KEYNOTE-059 [Cohort 1]) established the importance of PD-L1 expression for enrichment of response to pembrolizumab as monotherapy in later lines of therapy. Additionally, data from 2 of the Sponsor's clinical studies (KEYNOTE-059 [Cohorts 2 and 3] and KEYNOTE-062) established initial evidence to support the clinical activity of pembrolizumab in combination with chemotherapy for the treatment of metastatic gastric and GEJ adenocarcinoma in the 1L setting [41] [19] [42] [43].

Table 1
Overview of the Global Pembrolizumab Clinical Development Program in Locally Advanced or Metastatic Gastric or Gastroesophageal Junction Adenocarcinoma

Study Number and Status	Study Design	Study Population	Number of Participants by Intervention Group	Primary Endpoint(s)
2L+ Treatment				
KEYNOTE-012 FA complete	Phase 1B, multicohort, nonrandomized, multicenter	Cohort D: PD-L1 positive gastric/GEJ adenocarcinoma based on a prototype PD-L1 assay.	Cohort D: Pembrolizumab 10 mg/kg IV Q2W (N=39)	ORR
KEYNOTE-059 FA complete	Phase 2, multicenter, nonrandomized, open-label	Recurrent and/or metastatic gastric/GEJ adenocarcinoma; Cohort 1: HER2-negative or HER2-positive, and previously treated with trastuzumab; Cohorts 2 and 3: HER2-negative Participants were enrolled at all levels of PD-L1 expression in Cohorts 1 and 2; Cohort 3 enrolled only CPS ≥1	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 FA complete	Phase 3, randomized, open-label, active comparator	Advanced gastric/GEJ adenocarcinoma; HER2-negative or HER2-positive and previously treated with trastuzumab. Participants were enrolled at all levels of PD-L1 expression[a]; statistical analyses prespecified for CPS ≥1.	Pembrolizumab 200 mg Q3W (N=294) OR Paclitaxel 80 mg/m^2 on Days 1, 8, and 15 of every 28 day (4-week) cycle (N=276)	PFS, OS

Study Number and Status	Study Design	Study Population	Number of Participants by Intervention Group	Primary Endpoint(s)
1L Treatment				
KEYNOTE-062 FA complete	Phase 3, randomized, active-controlled, partially blinded	Advanced gastric/GEJ adenocarcinoma; HER2-negative. Only PD-L1 CPS ≥1 participants were enrolled; statistical analyses prespecified for CPS ≥1 and CPS ≥10.	Pembrolizumab 200 mg Q3W (N=254) OR Pembrolizumab 200 mg Q3W + cisplatin 80 mg/m^2 Q3W + 5-FU 800 mg/m^2/day continuous IV infusion Days 1-5 (120 hours) or capecitabine (in place of 5-FU) 1000 mg/m^2 BID Day1 to 14 Q3W (N=256) OR Placebo Q3W + cisplatin 80 mg/m^2 Q3W + 5-FU 800 mg/m^2/day continuous IV infusion Days 1-5 (120 hours) or capecitabine (in place of 5-FU) 1000 mg/m^2 BID Day 1 to 14 Q3W (N=250)	PFS, OS
KEYNOTE-811 FA Complete	Phase 3, randomized, double-blind	Unresectable or metastatic HER2-positive gastric/GEJ adenocarcinoma. Participants were enrolled at all levels of PD-L1 expression.	Pembrolizumab 200 mg Q3W in combination with trastuzumab + cisplatin + 5-FU or oxaliplatin + capecitabine OR Placebo in combination with trastuzumab + cisplatin + 5-FU or oxaliplatin + capecitabine Approximately 692 participants to be enrolled	PFS, OS
KEYNOTE-859 FA Complete	Phase 3, randomized, double-blind	Unresectable or metastatic HER2-negative gastric/GEJ adenocarcinoma. Participants were enrolled at all levels of PD-L1 expression; statistical analyses prespecified for ITT, CPS ≥1 and CPS ≥10.	Pembrolizumab 200 mg Q3W OR Placebo in combination with cisplatin + 5-FU or oxaliplatin + capecitabine Approximately 1542 participants to be enrolled	OS

Study Number and Status	Study Design	Study Population	Number of Participants by Intervention Group	Primary Endpoint(s)
LEAP-015 Ongoing	Phase 3, randomized, open-label	HER2-negative participants with advanced or metastatic gastric or GEJ adenocarcinoma. Participants were enrolled at all levels of PD-L1 expression; statistical analyses prespecified for ITT and CPS ≥1.	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 780 participants to be enrolled	PFS, OS

1L=first-line; 2L=second-line; 5-FU=5 fluorouracil; BID=twice daily; CAPOX=capecitabine and oxaliplatin; CR=complete response; EFS=event-free survival; FA=final analysis; GEJ=gastroesophageal junction; HER2=human endothelial growth factor receptor 2; IV=intravenous; mFOLFOX=5-FU + oxaliplatin + leucovorin; N=number; ORR=objective response rate; OS=overall survival; pCR=pathological complete response; PD-L1=programmed cell death-ligand 1; PFS=progression-free survival; Q2W=every 2 weeks; Q3W=every 3 weeks; QD=once daily; TS-1=tegafur+gimeracil+oteracil.

a. The study originally allowed participants whose tumors were negative for PD-L1 expression. Based on a recommendation from the DMC, the protocol was amended to only allow participants with PD-L1 positive tumors.

4.1 KEYTRUDA Regulatory Status and History in 1L Gastric Cancer

Pembrolizumab was granted Orphan Drug Designation (#15-4817) for "treatment of gastric and gastroesophageal junction adenocarcinoma" on 16-JUN-2015.

There are currently 2 approved indications in the US for KEYTRUDA in gastric and GEJ adenocarcinoma, one for patients with 1L HER2-negative disease and one for those with 1L HER2-positive disease:

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

- KEYTRUDA, in combination with trastuzumab, fluoropyrimidine- and platinum-containing chemotherapy, is indicated for the first-line treatment of adults with locally advanced unresectable or metastatic HER2-positive gastric or gastroesophageal junction (GEJ) adenocarcinoma whose tumors express PD-L1 (CPS ≥1) as determined by an FDA-approved test. This indication is approved under accelerated approval based on tumor response rate and durability of response. Continued approval of this indication may be contingent upon verification and description of clinical benefit in the confirmatory trials.

The Sponsor received FDA feedback at the outset of the KEYNOTE-859 study as well as formal advice during clinical development to align on the clinical study design, endpoints, study population, statistical analyses, and biomarker evaluation plan [Appendix Table 2]. At a preplanned IA, KEYNOTE-859 met the success criteria for the hypotheses of the primary and key secondary endpoints by demonstrating a statistically significant and clinically meaningful improvement in OS, PFS and ORR in the ITT population. FDA granted approval for the HER2-negative indication on 16-NOV-2023 based on their positive benefit:risk assessment of KEYNOTE-859 in the ITT population.

The Sponsor received pre-Phase 3 feedback on KEYNOTE-811 and received FDA advice during clinical development to align on the study design, endpoints, study population, statistical analyses, and biomarker evaluation plan [Appendix Table 18]. At the preplanned IA1, KEYTRUDA was granted accelerated approval by the FDA on 05-MAY-2021 "in combination with trastuzumab, fluoropyrimidine- and platinum-containing chemotherapy, for the 1L treatment of patients with locally advanced unresectable or metastatic HER2-positive gastric or gastroesophageal junction (GEJ) adenocarcinoma." The accelerated approval was based on ORR and DOR results in the first 264 participants randomized across all levels of PD-L1 expression. Based on the results at IA2 and IA3, the Sponsor proactively engaged with FDA to limit the approved indication to only those patients whose tumors express PD-L1 with a CPS ≥1 which FDA approved on 07-NOV-2023. The accompanying companion diagnostic PD-L1 IHC 22C3 pharmDx was approved on the same day.

The final analysis of KEYNOTE-811 has recently been carried out; the success criteria for all the primary and key secondary endpoints were met, demonstrating a statistically significant and clinically meaningful improvement in OS, PFS and ORR in the ITT population. A supplemental BLA is under review at the FDA to convert the accelerated approval to a traditional approval for the currently approved indication.

4.2 CPS ≥1 Cut-point Selection Based on Data from Initial Studies of Pembrolizumab Monotherapy in Gastric Cancer

The PD-L1 expression cut-point of CPS ≥1 for PD-L1 IHC 22C3 pharmDx in gastric or GEJ cancer was determined and confirmed based on analysis of data from participants with gastric cancer in the Sponsor's clinical studies KEYNOTE-012 and KEYNOTE-059, respectively. These initial studies enrolled patients regardless of HER2 status (ie, negative and positive) and were not designed to determine the potential immunologic differences between the 2 subtypes.

KEYNOTE-012 was a multicenter, non-randomized, multi-cohort study of pembrolizumab monotherapy that included 39 participants with 2L+ gastric cancer whose tumors expressed PD-L1 enrolled in Cohort D. Eligibility for KEYNOTE-012 was determined using a prototype PD-L1 IHC test (which uses the same primary antibody as the Agilent PD-L1 IHC 22C3 pharmDx) developed at Qualtek. PD-L1 positivity for the purposes of screening KEYNOTE-012 participants was defined as membrane staining in at least 1% of tumor or stromal cells or the presence of a distinctive interface pattern of mononuclear immune cells. The primary efficacy endpoint was ORR by central imaging assessment based on RECIST 1.1. Samples were retrospectively tested with the Agilent PD-L1 IHC 22C3 assay using the CPS scoring system when data from 38 participants were available.

[Table 2] separates the gastric cohort responders from the non-responders (RECIST 1.1 per investigator assessment) based on their PD-L1 IHC 22C3 pharmDx PD-L1 status at a CPS ≥1 cut-point in KEYNOTE-012. Ten of the 12 responders were identified using the CPS ≥1 cut-point, indicating the potential of this cut-point to enrich for response to pembrolizumab; however, these data also show that 2 participants with tumors with CPS <1 did respond to pembrolizumab. Based on these results, CPS ≥1 was chosen as the cut-point for further assessment of pembrolizumab efficacy by PD-L1 status for participants with gastric cancer in subsequent studies, potentially enhancing the ability of future studies to demonstrate the efficacy of pembrolizumab by evaluation in a PD-L1 positive subgroup.

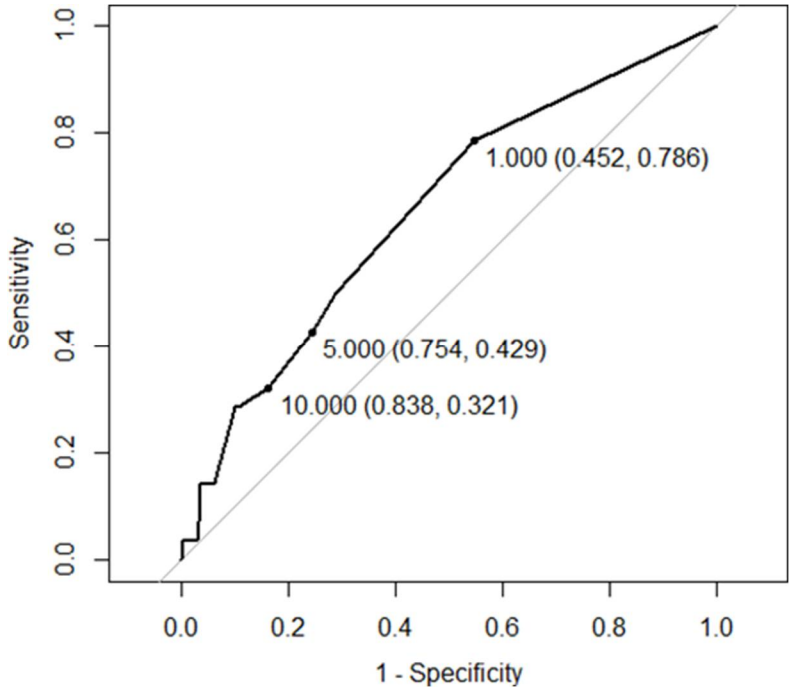
Table 2
Responders vs. Non-responders to Pembrolizumab Monotherapy
by PD-L1 CPS Status in KEYNOTE-012

	Non-responder	Responder
CPS < 1	6	2
CPS ≥ 1	20	10
CPS=combined positive score; PD-L1=programmed cell death 1 ligand 1.		

KEYNOTE-059 is a completed non-randomized, multi-site, open-label study of pembrolizumab monotherapy in participants with gastric or GEJ adenocarcinoma eligible for 3L+ treatment (N=259 in Cohort 1). The study further validated CPS ≥1 as a PD-L1 expression cut-point enriching for improved clinical outcome for gastric and GEJ cancer. PD-L1 testing for participants in KEYNOTE-059 was performed using the Agilent PD-L1 IHC 22C3 pharmDx at a central laboratory. CPS was used for scoring the samples.

ROC analysis of 256 participants from Cohort 1 of KEYNOTE-059 with best overall response data determined by central review [Figure 2] demonstrated a Youden index of CPS 1 with an area under the curve of 0.65, and 95% CIs of 0.55, 0.76. Youden index analysis facilitates the identification of a cut-point that provides an optimal tradeoff between sensitivity and specificity [44] [45]. Six of the 28 responders were not captured (sensitivity of 78.6%) using CPS ≥1 and using any cut-point higher than CPS 1 had a negative impact on both sensitivity and prevalence for only a modest gain in positive predictive value (enrichment of response) [Table 3]. These data from the KEYNOTE-059 study further supported selection of CPS ≥1 as the optimal cut-point in patients treated with pembrolizumab monotherapy [Table 4].

Figure 2
Receiver Operating Characteristics Curve for Participants from KEYNOTE-059 Cohort 1



Points on ROC curve labeled as (specificity, sensitivity)

Table 3
KEYNOTE-059 Performance Characteristics of PD-L1 IHC Assay at Different CPS Cut-points

	CPS Cut-point	
Performance Measure:	1	10
PPV (response rate)/NPV	15.0/94.5	19.6/91.0
Sens./Spec.	78.6/45.2	32.1/83.8
Prevalence	57.4	18.0
CPS=combined positive score; IHC=immunohistochemistry; NPV=negative predictive value; PD-L1=programmed cell death 1 ligand 1; PPV=positive predictive value; Sens=sensitivity; Spec=specificity.		

Table 4
Responders vs. Non-responders by PD-L1 CPS Status* in KEYNOTE-059

	Non-responder	Responder
CPS <1	103	6
CPS ≥1	125	22
CPS=combined positive score; PD-L1=programmed cell death 1 ligand 1.		

*Response rate irrespective of PD-L1 status = 28/256=10.9%

Collectively, the data from KEYNOTE-012 and KEYNOTE-059 suggest that PD-L1 CPS ≥1 served as an enrichment marker for pembrolizumab monotherapy efficacy in gastric or GEJ adenocarcinoma. This expression cut-point was subsequently prespecified as a stratification factor (CPS ≥1 vs CPS <1) in both KEYNOTE-811 and KEYNOTE-859, as well as a primary analysis objective in KEYNOTE-859.

4.3 CPS ≥10 Cut-point Selection Based on Additional Data from Clinical Studies of Pembrolizumab Monotherapy in Gastric Cancer

As the clinical development program moved into evaluating pembrolizumab in earlier lines of advanced gastric cancer, the Sponsor also evaluated the additional CPS cut-point of ≥10. Post-hoc evaluation of OS data from a study in 2L gastric cancer (KEYNOTE-061) demonstrated that, while activity is observed with pembrolizumab monotherapy across a range of PD-L1 IHC 22C3 expression levels, a more robust OS treatment effect for pembrolizumab, relative to SOC, was observed as PD-L1 IHC 22C3 expression level increased.

KEYNOTE-061 was a global Phase 3 study of single-agent pembrolizumab versus single-agent paclitaxel in the 2L treatment setting of advanced gastric and GEJ adenocarcinoma that progressed after 1L therapy with both a platinum and fluoropyrimidine agent [20]. The OS HR for the CPS ≥1 population was 0.82 (95% CI: 0.66, 1.03) and for CPS ≥10 was 0.64 (95% CI: 0.41, 1.02). Based on these clinical data, the Sponsor added CPS ≥10 as an additional PD-L1 expression cut-point to the SAP for KEYNOTE-859. Further, data at CPS ≥10 in KEYNOTE-062 [42] [43], another study of pembrolizumab in gastric cancer, also supported the addition of CPS ≥10 to KEYNOTE-859.

4.4 Robustness of PD-L1 Testing in the Sponsor's Clinical Studies

To ensure the robustness of the selected PD-L1 expression cut-points, the Sponsor worked with its diagnostic partner and testing laboratories to analytically validate CPS ≥1 and CPS ≥10 through internal and external analytical studies. This validation process aimed to confirm the accuracy, precision, and robustness of the assay in measuring PD-L1 expression levels. The pathologists at the testing laboratories were trained to record the PD-L1 results based on a pre-specified CPS cut-point and to capture raw CPS scores (based on a continuous scoring system). Pathologists successfully completed training per a pre-specified training plan, prior to evaluation of KEYNOTE-811 and KEYNOTE-859 specimens. No other CPS cut-point has been analytically validated for 22C3 pharmDx in gastric cancer.

4.5 Rationale for Pembrolizumab in Combination with Chemotherapy

Chemotherapy augments the antitumor immune response, possibly by inducing immunogenic cell death, enhancing the maturation and activation of dendritic cells, increasing T-cell penetrance and function in the tumor, improving the presentation of tumor antigens, and eliminating immunosuppressive cells (T regulatory cells, myeloid-derived suppressor cells, and M2 macrophages) [21]. PD-(L)1 inhibitors enhance the positive immune effects of chemotherapy such as antigen presentation, activation of innate immunity, and favorable effects on immune regulatory cells [46] [47] [48]. In addition, the negative immune effects of chemotherapy (eg, post-chemotherapy induction of immune regulatory receptors, ligands and unfavorable effects on immune regulatory cells) may be countered by PD-(L)1 inhibitors [49] [48] [50]. Therefore, the combination of PD-(L)1 inhibitors plus chemotherapy can enhance antitumor effects [46]. Pembrolizumab plus chemotherapy has demonstrated efficacy across various tumor types [51] [52] [53] [27] [25] [24]. Other immunotherapies in combination with chemotherapy have demonstrated efficacy in gastric cancer [9] [10].

While early studies with pembrolizumab monotherapy or other anti-PD-(L)1 agents suggested that PD-L1 expression (by either CPS or TPS) could be used to enrich for benefit in several tumors, including gastric and GEJ cancer [17] [18] [19] [20], limiting treatment to those whose tumors express PD-L1 may not be needed when combined with chemotherapy. For example, in 1L treatment for NSCLC, pembrolizumab monotherapy showed substantial clinical activity in participants whose tumors expressed PD-L1 TPS ≥50% and modest activity in participants with TPS <1% or PD-L1 TPS 1-49% [Table 5]. In contrast, combining pembrolizumab with chemotherapy in NSCLC, as in KEYNOTE-189 and KEYNOTE-407, showed substantial clinical activity in participants with PD-L1 TPS <1%, thereby eliminating the need to restrict pembrolizumab to a population of patients with PD-L1 expression and enhanced the antitumor activity of pembrolizumab monotherapy across all levels of PD-L1 expression (ie, when compared to KEYNOTE-001) [22] [23] [24] [Table 5]. Similar results have been observed in TNBC [26] [27] and HNSCC [25]. While these are cross-study comparisons across different diseases and should be interpreted with caution, these data demonstrate that chemotherapy combined with pembrolizumab can induce durable benefit for patients whose tumors have low levels of PD-L1 in multiple disease types.

Table 5
Cross-study Comparison of Objective Response Rate in Participants with NSCLC Eligible for First-line Treatment

	KEYNOTE-001[a]		KEYNOTE-189[b]			
	Pembrolizumab Monotherapy[c]		Pembrolizumab + Chemotherapy[d]		Chemotherapy[d]	
ORR	**n**	**% (95% CI)**	**n**	**% (95% CI)**	**n**	**% (95% CI)**
TPS <1%	6	16.7 (0.4, 64.7)	127	32.3 (24.3, 41.2)	63	14.3 (6.7, 25.4)
TPS 1-49%	26	19.2 (6.6, 39.4)	128	48.4 (39.5, 57.4)	58	20.7 (11.2, 33.4)
TPS ≥50%	16	50.0 (24.7, 75.3)	132	61.4 (52.5, 69.7)	70	22.9 (13.7, 34.4)

ALK=ALK tyrosine kinase receptor; AUC=area under the concentration-time curve; CI=confidence interval; EGFR= epidermal growth factor receptor; NSCLC=non-small cell lung cancer; ORR=objective response rate; q2w=every 2 weeks; q3w=every 3 weeks; TPS=tumor proportion score.

a. Cohort F1: participants with treatment-naïve NSCLC treated with pembrolizumab monotherapy. Data presented include the biomarker-evaluable population.
b. Participants with advanced or metastatic nonsquamous NSCLC who had not previously received systemic therapy for advanced disease and in whom EGFR- or ALK-directed therapy was not indicated.
c. Participants were randomly assigned in a 1:1:1 ratio to receive pembrolizumab 2 mg/kg q3w (n=6), 10 mg/kg q3w (n=49), or 10 mg/kg q2w (n=46).
d. Participants were randomly assigned in a 2:1 ratio to receive:
   - pembrolizumab (200 mg) + pemetrexed 500 mg/m^2 (with vitamin supplementation) + cisplatin 75 mg/m^2 OR carboplatin AUC 5 q3w for 4 cycles followed by pembrolizumab 200 mg + pemetrexed 500 mg/m^2 q3w until progression
   - saline placebo + pemetrexed 500 mg/m^2 (with vitamin supplementation) + cisplatin 75 mg/m^2 OR carboplatin AUC 5 q3w for 4 cycles followed by saline placebo + pemetrexed 500 mg/m^2 q3w until progression.

Data cutoff: KN001 29AUG2014; KN189 08NOV2017.

Source: [22] [23]

Given the data above, KEYNOTE-859 and KEYNOTE-811 were designed to evaluate the benefit of the addition of pembrolizumab to SOC chemotherapy in all participants. Based on the Sponsor's prior experience with pembrolizumab monotherapy in gastric cancers, CPS cut-points were included as stratification factors in both KEYNOTE-859 and KEYNOTE-811, and to the formal testing of endpoints by CPS cut-point in KEYNOTE-859. Incorporating PD-L1 cut points into the designs of these studies provided additional information regarding efficacy at higher PD-L1 levels. These studies were designed with pembrolizumab in combination with chemotherapy to enable meaningful response and survival in patients across all levels of PD-L1 expression (ie, the ITT population).

4.6 KEYNOTE-859

KEYNOTE-859 is an ongoing, Phase 3, randomized, placebo-controlled, double-blind study designed to assess pembrolizumab in combination with chemotherapy as treatment in participants with HER2-negative advanced gastric or GEJ adenocarcinoma [Appendix Figure 1].

KEYNOTE-859 was designed to test the effect of adding pembrolizumab to SOC chemotherapy in the ITT population [Sec. 8.1.1.1]. PD-L1 status (CPS ≥1 and CPS <1) was included as a stratification factor to ensure balanced baseline characteristics if differences in efficacy based on PD-L1 expression were observed in the study, as seen in previous HER2-negative gastric cancer studies with pembrolizumab monotherapy [19]. The SAP

included testing of both the CPS ≥1 and the ITT population. Following initiation of the study, results from KEYNOTE-061 and KEYNOTE-062 became available that suggested there was potential for further increased enrichment at CPS ≥10, so the SAP was adjusted to formally test a hypothesis in this population as well. The FDA agreed with the study design, including the planned analyses.

At the preplanned IA [Appendix Table 1], KEYNOTE-859 met the success criteria for the hypotheses of the primary endpoint of OS and the secondary endpoints of PFS and ORR; ie, pembrolizumab plus chemotherapy was superior to chemotherapy with respect to OS, PFS, and ORR in participants whose tumors express PD-L1 (CPS ≥10 [H1, H4, H7] and CPS ≥1 [H2, H5, H8]) and in all participants (H3, H6, H9) [Appendix Figure 2]. These results led to FDA approval based on their assessment of a favorable benefit:risk profile in the 1L setting for patients with locally advanced unresectable or metastatic HER2-negative gastric with any level of PD-L1 expression.

4.6.1 KEYNOTE-859: Key Efficacy Results

4.6.1.1 KEYNOTE-859: Disposition, Demographics, and Baseline Characteristics

The baseline characteristics were generally well balanced between both treatment groups and are reflective of patients with previously untreated, HER2-negative, advanced gastric or GEJ adenocarcinoma. At baseline, 78.2% of participants had a PD-L1 status of CPS ≥1 and 34.9% had a PD-L1 status of CPS ≥10 [Appendix Table 3]. When assessed by PD-L1 status (CPS ≥1 and CPS ≥10), the demographics and disease characteristics were generally well balanced between the 2 treatment groups and consistent with those of the ITT population [Appendix Table 4] [Appendix Table 5].

4.6.1.2 KEYNOTE-859: Overall Survival

4.6.1.2.1 Overall Survival

At the preplanned IA, KEYNOTE-859 met the success criteria for the hypotheses of the primary endpoint of OS; ie, pembrolizumab plus chemotherapy was superior to chemotherapy with respect to OS in participants whose tumors express PD-L1 (CPS ≥10 [H1] and CPS ≥1 [H2]) and, importantly, in all participants (H3) [Appendix Figure 2]. There was a trend toward increased benefit with increasing PD-L1 expression (CPS ≥1 and CPS ≥10) [Table 6] [Appendix Figure 3] [Appendix Figure 4]. However, the results of KEYNOTE-859 show a statistically significant and clinically meaningful improvement in OS in all participants enrolled across all levels of PD-L1 expression (ie, the approved population) [Table 6] [Figure 3].

Table 6
KEYNOTE-859: Summary of Overall Survival
(ITT Population)

Endpoints & Hypotheses (Pembrolizumab + Chemotherapy vs. Chemotherapy)		Number of Events Observed	Observed HR[a] (95% CI)	p-value Crossing Boundary	Observed p-Value[b]	Outcome
Primary	OS in all participants (H3)	1269	0.78 (0.70, 0.87)	0.006079	<0.0001	Statistically significant
	OS in CPS ≥1 (H2)	990	0.74 (0.65, 0.84)	0.020556	<0.0001	Statistically significant
	OS in CPS ≥10 (H1)	414	0.65 (0.53, 0.79)	0.011603	<0.0001	Statistically significant

CAPOX=capecitabine + oxaliplatin; CI=confidence interval; CPS=combined positive score; FP=5-FU + cisplatin; H=hypothesis; HR=hazard ratio; OS=overall survival; PD-L1=programmed cell death ligand 1; sSAP=supplementary statistical analysis plan.

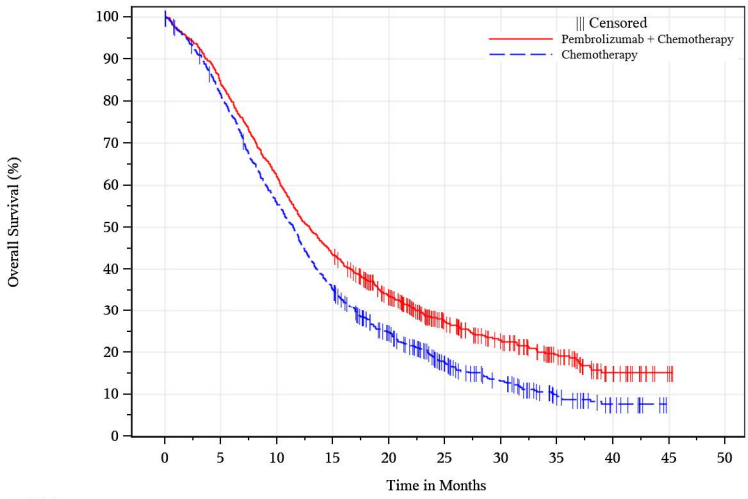
a. Based on Cox regression model with Efron's method of tie handling with treatment as a covariate stratified by Geographic region (Western Europe/Israel/North America/Australia, Asia and Rest of the World), PD-L1 status (CPS <1 vs. CPS ≥1), and Chemotherapy regimen (FP or CAPOX) with small strata collapsed as pre-specified in the sSAP.

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

Database Cutoff Date: 03OCT2022

Source: [Appendix Table 6] [Appendix Table 7] [Appendix Table 8]

Figure 3
KEYNOTE-859: Kaplan-Meier Plot of Overall Survival
(ITT Population)



At Risk

Pembrolizumab + Chemotherapy	790	663	490	343	240	143	95	55	19	3	0
Chemotherapy	789	636	434	274	169	95	58	26	10	0	0

Database Cutoff Date: 03OCT2022

Source: [P859V01MK3475: adam-adsl; adtte]

4.6.1.2.2 Exploratory Analysis of Overall Survival by CPS Cut-point

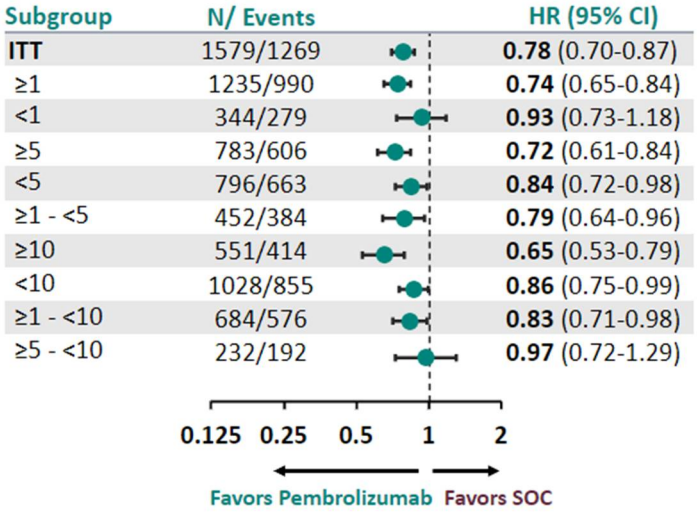
In preparation for this ODAC, the FDA requested information on subgroups using different CPS cut-points. Many of the requested PD-L1 subgroups were not prespecified and the study was not powered to definitively demonstrate efficacy in the requested populations. Pathologists are trained to score samples at the cut-points specified in the protocols (ie, CPS ≥1 and/or CPS ≥10), ensuring consistency and accuracy in the classification of participants into those subgroups. There are no analytical validation data at the CPS ≥5 cut-point for the PD-L1 IHC 22C3 pharmDx in any tumor type; therefore, results need to be interpreted with caution due to the uncertainty around the precision and reproducibility at the CPS 5 cut-point. PD-L1 raw scores were used to derive the subgroups for performing the requested analyses by CPS cut-point that were not prespecified in the study. Therefore, assessment of PD-L1 expression determined at an analytically validated cut-point is considered more reliable than the raw score value.

The HR, 95% CI of HR, and SE of log(HR) for OS were estimated for the ITT population and the PD-L1 subpopulations with formal hypothesis testing (CPS ≥1 and CPS ≥10). As pre-specified in the protocol and SAP, the protocol-specified analysis used a stratified Cox regression model with Efron's method of tie handling with treatment as a covariate and was stratified by stratification factors for randomization. Therefore, for this requested exploratory analysis, a stratified analysis was performed for all PD-L1 subpopulations to ensure consistency with the statistical model used for the ITT population and to account for the

potential prognostic effect of the stratification factors. Small strata in all stratified analyses were pooled based on an sSAP pre-specified algorithm.

Pembrolizumab in combination with chemotherapy shows a favorable trend with respect to point estimate of OS HR when compared with chemotherapy at all CPS cut-points requested by FDA. Although the HRs for OS suggest that patients whose tumors express higher levels of PD-L1 may have a higher probability to receive a benefit, all CPS subgroups analyzed indicated the potential for patients to benefit from pembrolizumab plus chemotherapy with a point estimate of HR <1 [Figure 4].

Figure 4
KEYNOTE-859: Exploratory Analysis: Forrest Plot of OS HR by CPS Cut-point (ITT Population)



Database cutoff: 03OCT2022.
Source: [Appendix Table 9]

4.6.1.3 KEYNOTE-859: Progression-free Survival

4.6.1.3.1 Progression-free Survival

KEYNOTE-859 met the success criteria for the hypotheses of the secondary endpoint of PFS. Pembrolizumab plus chemotherapy was superior to chemotherapy with respect to PFS in participants whose tumors express PD-L1 (CPS ≥10 [H4] and CPS ≥1 [H5]) and, importantly, in all participants (H6) [Appendix Figure 2]. There was a trend towards increased benefit with increasing CPS cut-point (CPS ≥1 and CPS ≥10) [Table 7]. However, as with OS, there was a statistically significant and clinically meaningful improvement in PFS in all participants enrolled across all levels of PD-L1 expression (ie, the approved population) [Table 7] [Figure 5].

Table 7
KEYNOTE-859: Summary of Progression-free Survival (Primary Analysis)
Based on BICR Assessment per RECIST 1.1
(ITT Population)

Endpoints & Hypotheses (Pembrolizumab + Chemotherapy vs. Chemotherapy)		Number of Events Observed	Observed HR[a] (95% CI)	p-value Crossing Boundary	Observed p-Value[b]	Outcome
Key Secondary	PFS in all participants (H6)	1180	0.76 (0.67, 0.85)	.025	<0.0001	Statistically significant
	PFS in CPS ≥1 (H5)	926	0.72 (0.63, 0.82)	.025	<0.0001	Statistically significant
	PFS in CPS ≥10 (H4)	400	0.62 (0.51, 0.76)	.025	<0.0001	Statistically significant

CAPOX=capecitabine + oxaliplatin; CI=confidence interval; CPS=combined positive score; FP=5-FU + cisplatin; H=hypothesis; HR=hazard ratio; PD-L1=programmed cell death ligand 1; PFS=progression-free survival; sSAP=supplementary statistical analysis plan.

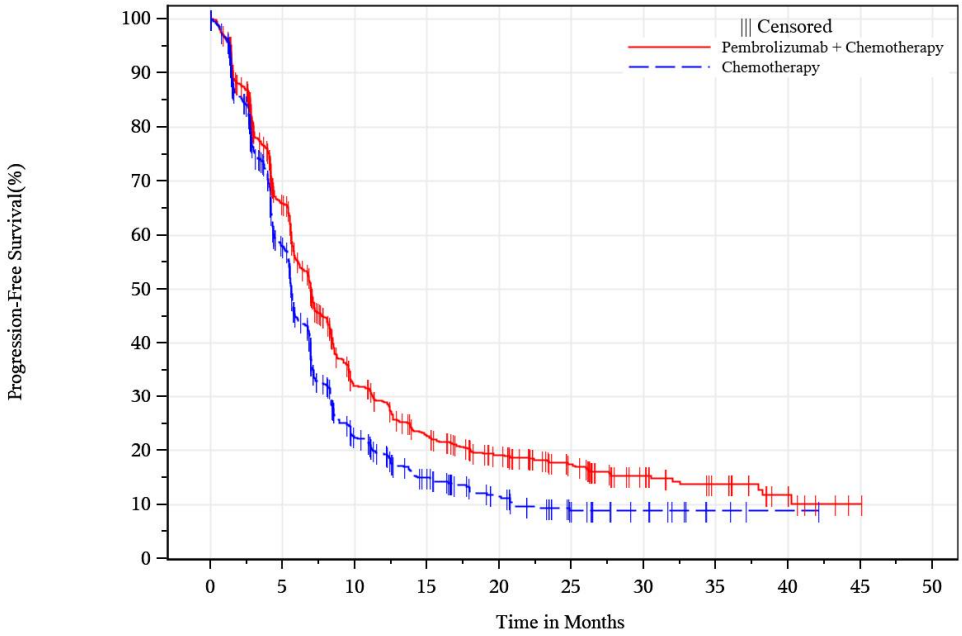
a. Based on Cox regression model with Efron's method of tie handling with treatment as a covariate stratified by Geographic region (Western Europe/Israel/North America/Australia, Asia and Rest of the World), PD-L1 status (CPS<1 vs. CPS ≥1), and Chemotherapy regimen (FP or CAPOX) with small strata collapsed as pre-specified in the sSAP.

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

Database Cutoff Date: 03OCT2022

Source: [Appendix Table 10] [Appendix Table 11] [Appendix Table 12]

Figure 5
KEYNOTE-859: Kaplan-Meier Plot of Progression-Free Survival (Primary Analysis)
Based on BICR Assessment per RECIST 1.1
(ITT Population)



At Risk

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

Database Cutoff Date: 03OCT2022

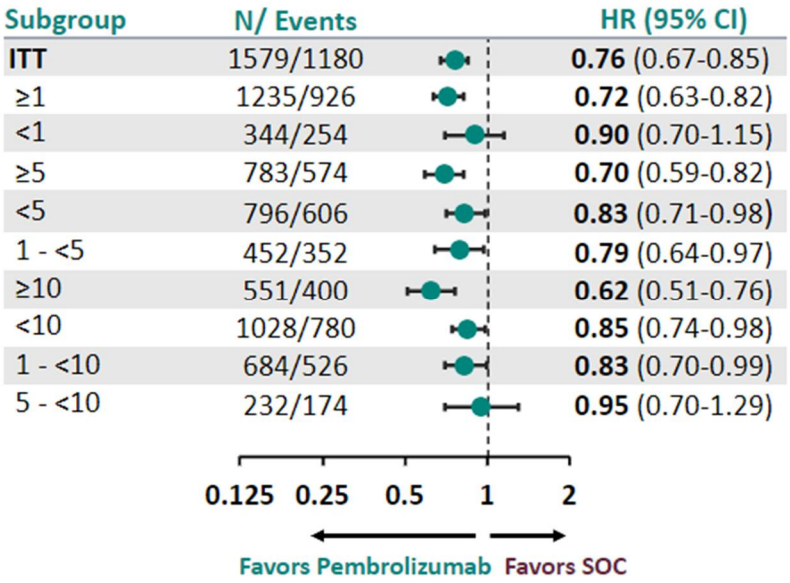
Source: [P859V01MK3475: adam-adsl; adtte]

4.6.1.3.2 Exploratory Analysis of Progression-free Survival by CPS Cut-point

As noted in [Sec. 4.6.1.2.2], exploratory post-hoc analyses using different CPS cut-points were performed for PFS in response to the FDA request. The analyses were performed as described above for OS.

Pembrolizumab in combination with chemotherapy shows a favorable trend in PFS when compared with chemotherapy at all CPS cut-points requested by FDA. Although the HRs for PFS suggest that patients whose tumors express higher levels of PD-L1 may have a higher probability to receive a benefit, all CPS subgroups analyzed indicated the potential for patients to benefit from pembrolizumab plus chemotherapy with a point estimate of HR <1 [Figure 6].

Figure 6
KEYNOTE-859: Exploratory Analysis: Forrest Plot of PFS HR by CPS Cut-point (ITT Population)



Database cutoff: 03OCT2022.
Source: [Appendix Table 13]

4.6.1.4 KEYNOTE-859: Objective Response Rate and Duration of Response

4.6.1.4.1 Objective Response Rate and Duration of Response

KEYNOTE-859 met the success criteria for the hypotheses of the secondary endpoint of ORR; ie, pembrolizumab plus chemotherapy was superior to chemotherapy with respect to ORR in participants whose tumors express PD-L1 (CPS ≥10 [H7] and CPS ≥1 [H8]) and in all participants (H9) [Appendix Figure 2]. The trend for benefit was greater with increasing CPS cut-point (CPS ≥1 and CPS ≥10) [Table 8]. However, the results of KEYNOTE-859 show a statistically significant and clinically meaningful improvement in ORR in all participants (ie, the approved population) [Table 8].

Table 8
KEYNOTE-859: Summary of Objective Response Rate
Based on BICR Assessment per RECIST 1.1
(ITT Population)

Endpoints & Hypotheses (Pembrolizumab + Chemotherapy vs. Chemotherapy)		Number of Events Observed	ORR Difference (95% CI)[a]	p-value Crossing Boundary	Observed p-Value[b]	Outcome
Key Secondary	ORR in all participants (H9)	736	9.3 (4.4, 14.1)	.025	0.00009	Statistically significant
	ORR in CPS ≥1 (H8)	585	9.5 (3.9, 15.0)	.025	0.00041	Statistically significant
	ORR in CPS ≥10 (H7)	286	17.5 (9.3, 25.5)	.025	0.00002	Statistically significant

CAPOX=capecitabine + oxaliplatin; CI=confidence interval; CPS=combined positive score; FP=5-FU + cisplatin; H=hypothesis; ORR=objective response rate; PD-L1=programmed cell death ligand 1; sSAP=supplementary statistical analysis plan.

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

b. One-sided p-value for testing. H0: difference in % = 0 versus H1: difference in % > 0.

Database Cutoff Date: 03OCT2022

Source [Appendix Table 14] [Appendix Table 15] [Appendix Table 16]

4.6.1.4.2 Exploratory Analysis of Objective Response Rate by CPS Cut-point

As noted in [Sec. 4.6.1.2.2], exploratory post-hoc analyses by CPS cut-point were performed for ORR in response to the FDA request.

The results of these exploratory analyses are generally consistent with the prespecified analyses for ORR. Pembrolizumab in combination with chemotherapy shows a favorable trend for increased ORR when compared with chemotherapy in all CPS subgroups with the exception of CPS 5 to <10, where the control group had an unexpectedly high ORR and the experimental group had an unexpectedly low ORR. This is likely due to the small sample size and small number of responders in this subgroup [Table 9].

Table 9
KEYNOTE-859: Exploratory Analysis of Objective Response Rate by CPS Cut-point
Based on BICR Assessment per RECIST 1.1
(ITT Population; Data Cutoff 03-OCT-2022)

Baseline PD-L1 Status[a]	Number of Participants		Number of Complete Responses		Number of Partial Responses		ORR[b] (%) (95% CI)[c]	
	Pembro + Chemo	Chemo	Pembro + Chemo	Chemo	Pembro + Chemo	Chemo	Pembro + Chemo	Chemo
ITT	790	789	75	49	330	282	51.3 (47.7, 54.8)	42.0 (38.5, 45.5)
CPS <1	172	172	14	13	69	55	48.3 (40.6, 56.0)	39.5 (32.2, 47.3)
CPS 1 - <5	228	224	17	15	91	74	47.4 (40.7, 54.1)	39.7 (33.3, 46.5)
CPS <5	400	396	31	28	160	129	47.8 (42.8, 52.8)	39.6 (34.8, 44.7)
CPS 1 - <10	339	345	25	22	128	124	45.1 (39.8, 50.6)	42.3 (37.0, 47.7)
CPS 5 - <10	111	121	8	7	37	50	40.5 (31.3, 50.3)	47.1 (38.0, 56.4)
CPS <10	511	517	39	35	197	179	46.2 (41.8, 50.6)	41.4 (37.1, 45.8)
CPS ≥1	618	617	61	36	261	227	52.1 (48.1, 56.1)	42.6 (38.7, 46.6)
CPS ≥5	390	393	44	21	170	153	54.9 (49.8, 59.9)	44.3 (39.3, 49.3)
CPS ≥10	279	272	36	14	133	103	60.6 (54.6, 66.3)	43.0 (37.1, 49.1)

BICR=blinded independent central review; chemo=chemotherapy; CI=confidence interval; ITT=intent-to-treat; ORR=objective response rate; PD-L1=programmed death-ligand 1; pembro=pembrolizumab.

a. Data analyses at CPS ≥1 and CPS ≥10 were pre-specified, and data collected at the validated CPS ≥1 and CPS ≥10 cut-points were used for analyses. Remaining analyses at other CPS cut-points were not pre-specified and CPS raw scores were used in addition to CPS ≥10 cut-point information to ensure mutual exclusivity.
b. Determined by Blinded Independent Central Review.
c. Based on Clopper-Pearson method.

Database cutoff date: 03OCT2022

4.6.1.5 Patient-reported Outcomes

In KEYNOTE-859, PRO data analyses were based on the FAS population, which included all participants in the ITT population who had at least 1 completed PRO assessment and received at least 1 dose of study intervention. In this population, the addition of pembrolizumab to chemotherapy (either FP or CAPOX) resulted in similar HRQoL scores as those on chemotherapy alone. These results provide further support for the favorable benefit:risk profile for the addition of pembrolizumab as part of the SOC in 1L treatment of patients with HER2-negative advanced gastric or GEJ adenocarcinoma.

For the prespecified EORTC QLQ-C30 Global Health Status/QoL scale, baseline scores were similar for pembrolizumab plus chemotherapy and chemotherapy treatment groups (LS means [SD]: 65.51 [20.74] and 66.48 [21.00], respectively, out of a 0-100 scale, with a higher score representing better QoL). The analysis of change from baseline at Week 18 showed no meaningful difference between the 2 treatment groups (difference in LS means: 1.25 points [95% CI: -1.07, 3.58]). In addition, changes from baseline at Week 18 results in prespecified scales of physical functioning, role functioning, and nausea/vomiting, as well as symptom of appetite loss were similar between the 2 treatment groups. The analysis of change from baseline for the prespecified EORTC QLQ-STO22 pain symptom scale at Week 18 favored pembrolizumab plus chemotherapy versus chemotherapy (difference in LS means: -2.57 points; [95% CI: -4.72, -0.41]). Week 18 was selected as the latest analysis time point at which predefined rates of completion (≥60%) and compliance (≥80%) were met based on blinded data review. Results across the CPS subgroups were generally consistent with PRO FAS analyses results. Stability in PRO endpoints may be considered a meaningful goal in patients with advanced gastric cancer, as patients typically progress rapidly and would be expected to experience precipitous declines in HRQoL [30] [31]. These data provide reassurance that adding pembrolizumab to chemotherapy will not adversely affect HRQoL and may help to mitigate worsening of some symptoms.

4.6.1.6 Efficacy Summary and Conclusions

The results from KEYNOTE-859 showed that pembrolizumab plus chemotherapy provides a statistically significant and clinically meaningful improvement in OS, PFS, and ORR in participants across all levels of PD-L1 expression (ie, the ITT population), as well as in the prespecified CPS ≥1 and CPS ≥10 populations, when compared with chemotherapy. While there is a trend toward increased benefit in the CPS ≥1 and CPS ≥10 populations as compared with the ITT population, a consistent treatment effect, directionally aligned with the result in the ITT population, was observed in all PD-L1 CPS subgroups analyzed. The exploratory post-hoc analyses provide additional support that, for patients with HER2-negative gastric cancer, the results were generally consistent with the ITT population. Furthermore, there was no observed detriment in HRQoL with the addition of pembrolizumab to chemotherapy. Taken together, pembrolizumab plus chemotherapy may provide a benefit for all HER2-negative gastric cancer patients.

4.6.2 KEYNOTE-859: Key Safety Results

The safety profile of pembrolizumab plus chemotherapy was generally consistent with the individual established safety profiles of the SOC regimen (either FP or CAPOX) and pembrolizumab monotherapy. The safety profile of pembrolizumab plus chemotherapy was similar across PD-L1 subgroups.

The incidences of AEs, drug-related AEs, Grade 3 to 5 AEs, SAEs, and discontinuations due to an AE or SAE were generally similar (≤10% difference) between the pembrolizumab plus chemotherapy and the chemotherapy groups in KEYNOTE-859 [Table 10].

Compared with the pembrolizumab monotherapy RSD, there were higher incidences of AE parameters in the pembrolizumab plus chemotherapy group [Table 10]. This was anticipated due to the combination of pembrolizumab with chemotherapy (CAPOX or FP) versus pembrolizumab monotherapy. In KEYNOTE-859, immune-mediated AEs were generally low grade and manageable, with some events such as endocrinopathies requiring long-term hormone replacement. No new safety concerns were identified for pembrolizumab.

The Sponsor has evaluated the safety of pembrolizumab monotherapy and pembrolizumab in combination with chemotherapy by PD-L1 subgroups across a number of tumor types within the development program and has not identified differences in the safety profile at different PD-L1 expression cut-points. For purposes of this ODAC, the Sponsor pooled data from the 3 key studies for the gastric (KEYNOTE-859 and KEYNOTE-811) and esophageal indications (KEYNOTE-590), as these studies included tumor types with relatively similar histopathology that are expected to express PD-L1 in an analogous manner and are treated with comparable chemotherapy regimens. The safety profile of pembrolizumab and chemotherapy is generally similar across PD-L1 CPS subgroups in the pooled data for the 3 key studies for gastric and esophageal indications (KEYNOTE-811, KEYNOTE-859, and KEYNOTE-590) with pembrolizumab and chemotherapy [Table 11].

Table 10
KEYNOTE-859: Summary of Overall Adverse Events and Immune-mediated Reactions and Infusion Reactions (APaT Population)

	Pembrolizumab + Chemotherapy (n=785)	Chemotherapy (n=787)	Reference Safety Dataset for Pembrolizumab Monotherapy (N=2799)
Overall Adverse Events, n (%)			
One or more AEs	776 (98.9)	771 (98.0)	2727 (97.4)
Grade 3-5 AEs	591 (75.3)	548 (69.6)	1273 (45.5)
Serious AEs	355 (45.2)	316 (40.2)	1042 (37.2)
Deaths due to AEs	64 (8.2)	58 (7.4)	110 (3.9)
AEs leading to discontinuation	257 (32.7)	204 (25.9)	334 (11.9)
Immune-mediated reactions and infusion reactions, n (%)			
One or more AEs	242 (30.8)	105 (13.3)	600 (21.4)
Grade 3-5 AEs	74 (9.4)	17 (2.2)	155 (5.5)
Serious AEs	61 (7.8)	13 (1.7)	162 (5.8)
Deaths due to AEs	1 (0.1)	1 (0.1)	4 (0.1)
AEs leading to discontinuation	40 (5.1)	14 (1.8)	85 (3.0)

AE=adverse event; APaT=All Participants as Treated.
KEYNOTE-859 Database Cutoff Date: 03OCT2022
Source: KN859 Filing Module 2.7.4, Table 2.7.4-gastric6: 5 and Table 2.7.4-gastric6: 14

Table 11
Summary of Overall Adverse Events and Immune-mediated Reactions and Infusion Reactions by CPS Cut-point (APaT Population)

	Pembrolizumab + SOC/Chemotherapy KN811 +KN859 + KN590				
	All Participants (n=1505)	CPS <1 (n=263)	CPS ≥1 (n=1231)	CPS <10 (n=921)	CPS ≥10 (n=573)
Overall Adverse Events, n (%)					
One or more AEs	1494 (99.3)	262 (99.6)	1221 (99.2)	912 (99.0)	571 (99.7)
Grade 3-5 AEs	1162 (77.2)	196 (74.5)	957 (77.7)	700 (76.0)	453 (79.1)
Serious AEs	723 (48.0)	104 (39.5)	612 (49.7)	422 (45.8)	294 (51.3)
Deaths due to AEs	115 (7.6)	21 (8.0)	94 (7.6)	79 (8.6)	36 (6.3)
AEs leading to discontinuation	497 (33.0)	84 (31.9)	411 (33.4)	299 (32.5)	196 (34.2)
imAEs and IRRs, n (%)					
One or more AEs	490 (32.6)	87 (33.1)	400 (32.5)	291 (31.6)	196 (34.2)
Grade 3-5 AEs	144 (9.6)	23 (8.7)	120 (9.7)	87 (9.4)	56 (9.8)
Serious AEs	131 (8.7)	19 (7.2)	110 (8.9)	77 (8.4)	52 (9.1)
Deaths due to AEs	6 (0.4)	1 (0.4)	5 (0.4)	5 (0.5)	1 (0.2)
AEs leading to discontinuation	85 (5.6)	12 (4.6)	73 (5.9)	47 (5.1)	38 (6.6)

AE=adverse event; APaT=All Participants as Treated; CPS=combined positive score; imAEs=immune-mediated adverse events; IRR=infusion-related reaction; KN=KEYNOTE; SOC=standard-of-care.
Database cutoff date: for KN811: 20MAR2024; for KN859: 03OCT2022; for KN590: 02JUL2020.

Source: [ISS: adam-adsl; adae]

4.6.3 KEYNOTE-859: Q-TWiST Analysis

In order to better understand the benefit:risk profile of adding pembrolizumab to chemotherapy for the 1L treatment of HER2-negative gastric cancer, a post-hoc Q-TWiST analysis was performed to evaluate the quality (ie, patient health utilities) and quantity (ie, OS, PFS, and AEs) of survival in participants who received pembrolizumab plus chemotherapy versus chemotherapy in KEYNOTE-859 [Sec. 8.1.1.2]. Recent publications have reported the utility of Q-TWiST analyses of studies of an ICI in NSCLC and RCC [54] [55].

Q-TWiST combines efficacy, safety, and quality of life in a single measure. In this analysis, the OS time is partitioned into 3 health states:

- TOX: time spent with all-cause Grade 3+ AEs starting from randomization and before disease progression based on RECIST 1.1 by investigator assessment or death
- TWiST: time spent without Grade 3+ AEs starting from randomization to disease progression or death
- REL: time from disease progression to death

Utility values (range 0 to 1) come from the EQ-5D-5L questionnaire collected from KEYNOTE-859 for each health state. Q-TWiST was calculated as the sum of the time spent in each health state, multiplied by its corresponding utility weight:

$$\text{Q-TWiST} = (\text{TOX} * U_{\text{TOX}}) + (\text{TWiST} * U_{\text{TWIST}}) + (\text{PROG} * U_{\text{PROG}})$$

Relative gain in Q-TWiST is presented as a percentage and is defined as the difference in Q-TWiST between the pembrolizumab plus chemotherapy arm and the chemotherapy arm divided by the restricted mean OS of the chemotherapy arm. A relative gain of 10 percentage points is considered clinically important, and a gain of 15 percentage points is considered clearly clinically important [56].

In KEYNOTE-859, there was a relative gain in Q-TWiST of 20.9% (CI: 12.49, 30.56), 25.3% (CI: 16.04, 36.26), and 38.1% (CI: 23.21, 56.59) in the ITT, CPS ≥1, and CPS ≥10 populations, respectively. These data emphasize the favorable benefit:risk profile with a "clearly clinically important" positive relative Q-TWiST gain over 56 months for pembrolizumab + chemotherapy versus chemotherapy in the ITT population.

4.7 KEYNOTE-811

KEYNOTE-811 is an ongoing, Phase 3, randomized, placebo-controlled, double-blind study designed to assess pembrolizumab in combination with trastuzumab plus chemotherapy as 1L treatment in participants with HER2-positive advanced gastric or GEJ adenocarcinoma [Appendix Figure 6].

KEYNOTE-811 was designed to test the effect of adding pembrolizumab to SOC in the ITT population [Sec. 8.2.1.1]. PD-L1 status (CPS ≥1 and CPS <1) was included as a stratification factor to ensure balanced baseline characteristics if differences in efficacy based on PD-L1 expression were observed in the study, as seen in previous HER2-negative gastric cancer studies with pembrolizumab monotherapy [19]. The FDA agreed with the study design, including the planned analyses.

KEYNOTE-811 met the success criteria for the hypotheses of the primary endpoints of OS (at the FA) and PFS (at IA2) and the secondary endpoint of ORR at IA1 [Appendix Table 17] [Appendix Figure 6]. Accelerated approval was granted based on ORR and DOR after IA1 and supported an approval for all HER2-positive patients. At IA2 and IA3, the observed HR for OS in the CPS <1 subgroup, which was greater than 1 with a lower bound of the 95% CI almost excluding unity. The Sponsor proactively engaged with FDA to limit the approved indication to only those patients whose tumors express PD-L1 with a CPS ≥1 cut-point. At the FA, the OS HR for the CPS <1 subgroup has improved, reflecting the challenge of isolating the precise treatment effect in this subgroup. However, the data continue to support the approved indication for patients whose tumors express PD-L1 with CPS ≥1.

4.7.1 KEYNOTE-811: Key Efficacy Results

4.7.1.1 KEYNOTE-811: Disposition, Demographics, and Baseline Characteristics

The baseline characteristics were generally well balanced between both treatment groups and are reflective of patients with locally advanced unresectable or metastatic HER2-positive gastric or GEJ adenocarcinoma. At baseline, 85% of participants had a PD-L1 status of CPS ≥1 [Appendix Table 19]. When assessed by PD-L1 status (CPS ≥1), the demographics and disease characteristics were generally well balanced between the 2 treatment groups and consistent with those of the ITT population [Appendix Table 20].

4.7.1.2 KEYNOTE-811: Overall Survival

4.7.1.2.1 Overall Survival

At the FA (data cutoff 20-MAR-2024), pembrolizumab in combination with SOC provided a statistically significant and clinically meaningful improvement in OS when compared with SOC in all participants (ie, ITT population) [Table 12] [Figure 7].

- The HR for OS was 0.80 (95% CI: 0.67, 0.94; *p*=0.0040, which was less than the *p*-value boundary of 0.0201), representing a 20% reduction in the risk of death [Table 12].
    - Although not powered to demonstrate improvement in subgroups, pembrolizumab plus SOC resulted in a clinically meaningful improvement in OS in participants whose tumors were CPS ≥1; HR: 0.79 (95% CI: 0.66, 0.95) [Appendix Table 24] [Appendix Figure 8].
    - In participants whose tumors were CPS <1, the OS HR estimate was 1.10 with a wide 95% CI [Appendix Figure 8]. Due to the smaller number of participants with CPS <1 (n=104 [14.9%]) [Appendix Table 19] and few events observed (n=85), the CIs are wide in the analyses of the CPS <1 subgroup, reflecting the challenge of isolating the precise treatment effect in this subgroup.
    - By KM estimation, the OS rates were higher for the pembrolizumab plus SOC group compared with the SOC group at 6, 12, 18, 24, and 48 months, supporting the potential for pembrolizumab to enhance long-term survival in some participants [Table 12].

Table 12
KEYNOTE-811: Analysis of Overall Survival
(Global Cohort)
(ITT Population)

	Pembrolizumab + SOC (N=350)	SOC (N=348)
Number of Events (%)	267 (76.3)	288 (82.8)
DEATH	267 (76.3)	288 (82.8)
Kaplan-Meier Estimates (months)[a]		
Median (95% CI)	20.0 (17.8, 22.1)	16.8 (14.9, 18.7)
[Q1, Q3]	[10.2, 39.9]	[8.7, 33.0]
Person-months	8489.9	7601.1
Event Rate / 100 Person-months	3.1	3.8
vs SOC		
Hazard Ratio (95% CI)[b]	0.80 (0.67, 0.94)	
p-value[c]	0.0040	
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)	69.4 (64.3, 74.0)	63.2 (57.9, 68.0)
OS Rate at month 18 (%) (95% CI)	54.9 (49.5, 59.9)	47.4 (42.1, 52.5)
OS Rate at month 24 (%) (95% CI)	41.1 (36.0, 46.2)	36.2 (31.1, 41.2)
OS Rate at month 30 (%) (95% CI)	33.1 (28.3, 38.1)	29.5 (24.8, 34.4)
OS Rate at month 36 (%) (95% CI)	28.0 (23.4, 32.8)	22.8 (18.5, 27.3)
OS Rate at month 42 (%) (95% CI)	24.1 (19.7, 28.8)	20.8 (16.7, 25.3)
OS Rate at month 48 (%) (95% CI)	23.3 (18.9, 28.0)	16.3 (12.4, 20.6)

[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 .

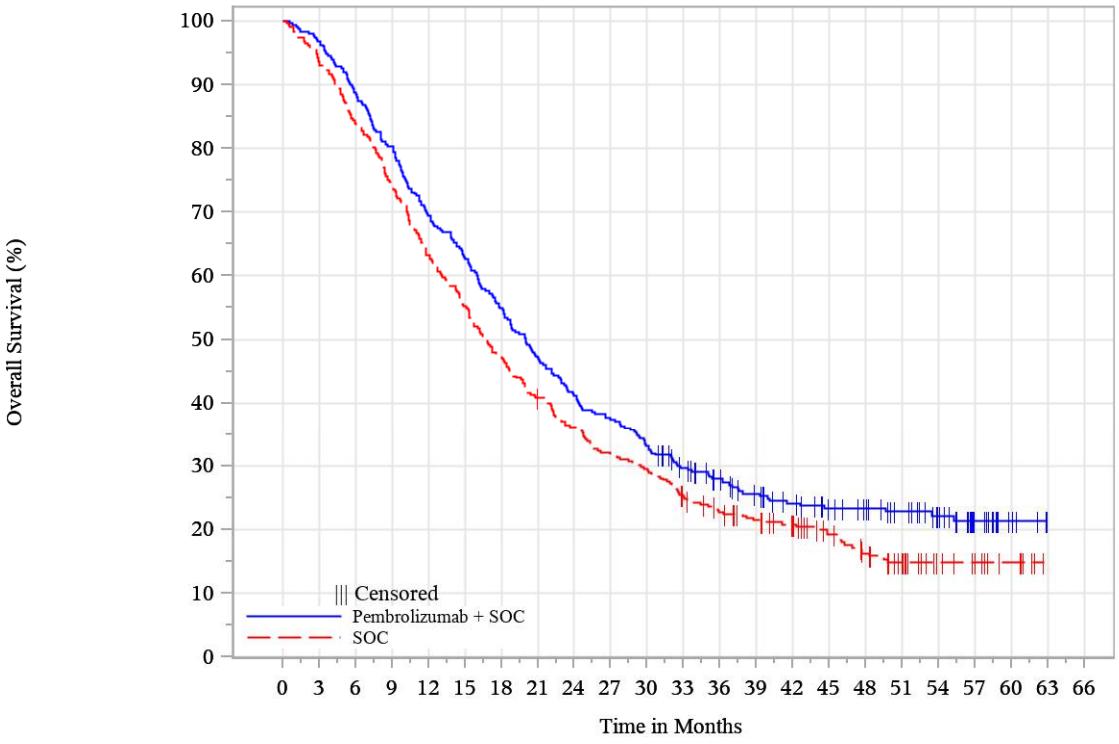
[c] One-sided p-value based on log-rank test stratified by Geographic region (Western Europe/Israel/North America/Australia, Asia and Rest of the World), PD-L1 status (positive vs. negative), and Chemotherapy regimen (FP or CAPOX) with small strata collapsed as pre-specified in the sSAP .

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.

Database Cutoff Date: 20MAR2024

Source: [P811V04MK3475: adam-adsl; adtte]

Figure 7
KEYNOTE-811: Kaplan-Meier Estimates of Overall Survival
(Global Cohort)
(ITT Population)



At Risk

Pembrolizumab + SOC	350	339	311	281	243	220	192	165	144	131	116	97	84	72	62	53	49	42	32	18	5	0	0
SOC	348	326	292	259	220	192	165	142	125	110	102	85	74	66	59	47	37	25	16	12	6	0	0

Database Cutoff Date: 20MAR2024.

Source: [P811V04MK3475: adam-adsl; adtte]

4.7.1.2.2 Exploratory Analysis of Overall Survival by CPS Cut-point

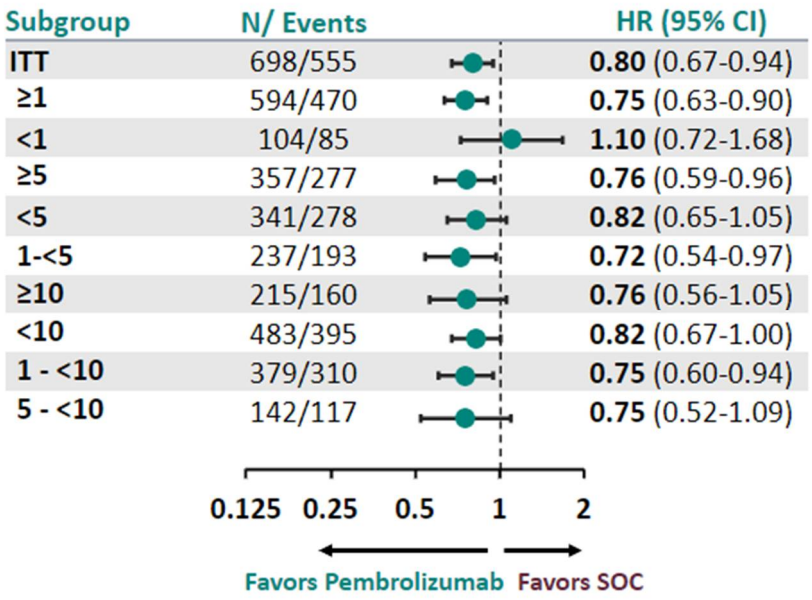
Exploratory post-hoc analyses using different CPS cut-points was performed for OS in response to the FDA request. Many of the requested PD-L1 subgroups were not prespecified and the study was not powered to definitively demonstrate efficacy in the requested populations. The analyses were performed as described in [Sec. 4.6.1.2.2].

The results of this exploratory analysis illustrate that pembrolizumab in combination with SOC shows a favorable trend in OS when compared with SOC except for those with CPS<1. At the CPS <1 cut-point, there was an improvement in OS HR between IA2 (OS HR: 1.61 [95% CI: 0.95, 2.64]) and the FA (OS HR: 1.10 [95% CI: 0.72, 1.68]) with overlapping 95% CIs, reflecting the challenge of isolating the precise treatment effect in this subgroup. These results also indicate that there is no additional benefit with increasing level of PD-L1 expression beyond the cut-point of CPS ≥1:

- The HR for OS favors pembrolizumab plus SOC in all PD-L1 subgroups with the exception of CPS <1 [Figure 8].

- Compared with CPS ≥1 (HR: 0.75 [95% CI: 0.63, 0.90]), there is no trend for improved OS with increase in PD-L1 expression when using either the CPS ≥5 (HR: 0.76 [95% CI: 0.59, 0.96]) or CPS ≥10 (HR: 0.76 [95% CI: 0.56, 1.05]) cut-points [Figure 8].

Figure 8
KEYNOTE-811 – Exploratory Analysis: Forrest Plot of OS HR by CPS Cut-point
(Global Cohort)
(ITT Population)



Database cutoff date: 20MAR2024.
Source: [Appendix Table 25]

4.7.1.3 KEYNOTE-811: Progression-free Survival

4.7.1.3.1 Progression-free Survival

At IA2 (data cutoff 25-MAY-2022), pembrolizumab in combination with SOC provided a statistically significant and clinically meaningful improvement in PFS per RECIST 1.1 as assessed by BICR when compared with SOC in all participants (ie, ITT population) [Table 13]. The PFS at the FA, which was not formally tested because PFS met the criteria for statistical significance at IA2, continues to show a clinically meaningful improvement in the pembrolizumab + SOC group compared with the placebo + SOC group [Table 13] [Figure 9]:

- At the FA (data cutoff 20-MAR-2024), the PFS HR was 0.73 ([95% CI: 0.61, 0.87]; nominal p-value=0.0002) in favor of pembrolizumab plus SOC, representing a 27% reduction in the risk of disease progression or death [Table 13].

- Although not powered to demonstrate improvement in subgroups, pembrolizumab plus SOC resulted in a clinically meaningful improvement in PFS in participants whose tumors were CPS ≥1 [Appendix Table 23] [Appendix Figure 7].

  - In participants whose tumors express low levels of PD-L1 (CPS <1), the PFS HR estimate was 0.99 with a wide 95% CI [Appendix Figure 7]. Due to the smaller number of participants with CPS <1 (n=104 [14.9%]) [Appendix Table 19] and few events observed (n=74), the CIs are wide in the analyses of the CPS <1 subgroup, reflecting the challenge of isolating the precise treatment effect in this subgroup.

Table 13
KEYNOTE-811: Summary of Progression-Free Survival (Primary Analysis)
Based on BICR Assessment per RECIST 1.1
(Global Cohort)
(ITT Population)

Endpoint	**Pembrolizumab + SOC (N=350)**	**SOC (N=348)**
PFS at IA2		
Median PFS, months (95% CI)[a]	10.0 (8.6, 11.7)	8.1 (7.0, 8.5)
HR (95% CI)[b], *p*-value [c, d]	0.72 (0.60, 0.87), 0.0002	
PFS at the FA		
Median PFS, months (95% CI)[a]	10.0 (8.6, 12.2)	8.1 (7.0, 8.5)
HR (95% CI)[b], nominal *p*-value[c]	0.73 (0.61, 0.87), 0.0002	

Abbreviations: CI = confidence interval; FA=final analysis; HR = hazard ratio; IA2=interim analysis 2; ITT = intent-to-treat; PFS = progression-free survival.

[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.

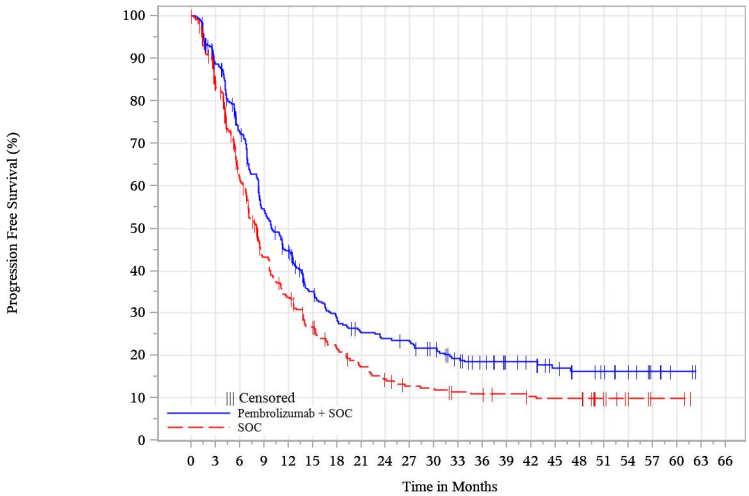
Western Europe includes Belgium, France, Germany, Spain, Italy, United Kingdom, Ireland, Latvia, Lithuania, which is consistent with the 'Europe' region defined in the protocol for stratification.

[d] The multiplicity-adjusted one-sided nominal alpha level was 0.0012795.

Data cutoff: IA2: 25MAY2022; FA: 20MAR2024

Data Source: [Appendix Table 21] [Appendix Table 22]

Figure 9
Kaplan-Meier Estimates of Progression-Free Survival (Primary Analysis)
Based on BICR Assessment per RECIST 1.1
(Global Cohort)
(ITT Population)



Database Cutoff Date: 20MAR2024.

Source: [P811V04MK3475: adam-adsl; adtte]

4.7.1.3.2 Exploratory Analysis of Progression-free Survival by CPS Cut-point

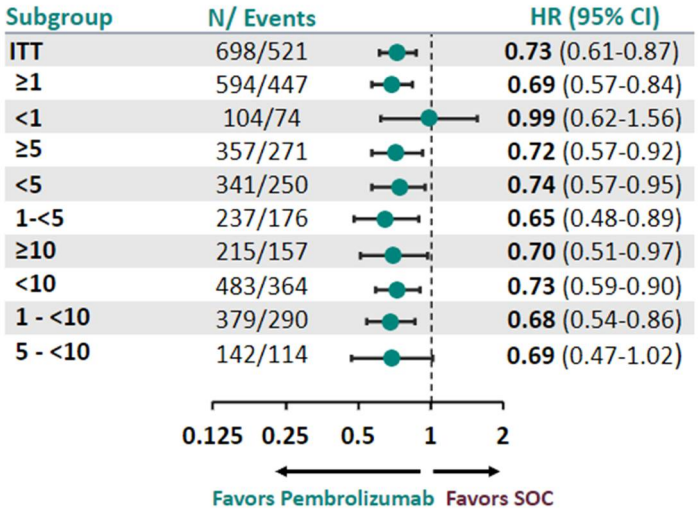
As described in [Sec. 4.6.1.2.2], exploratory post-hoc analyses by CPS cut-point were performed for PFS in response to the FDA request.

The results of these exploratory analyses illustrate that pembrolizumab in combination with SOC shows a favorable trend in PFS when compared with SOC at all CPS cut-points. These results also indicate that there is no additional benefit with increasing level of PD-L1 expression beyond the cut-point of CPS ≥1:

- The HR for PFS favors pembrolizumab plus SOC in all PD-L1 subgroups with the exception of CPS <1, where the HR is close to 1 [Figure 10].

- Compared with CPS ≥1 (HR: 0.69 [95% CI: 0.57, 0.84]), there is not a trend for improved PFS with increase in PD-L1 expression when using either the CPS ≥5 (HR: 0.72 [95% CI: 0.57, 0.92]) or CPS ≥10 (HR: 0.70 [95% CI: 0.51, 0.97]) cut-points [Figure 10].

Figure 10
KEYNOTE-811: Exploratory Analysis: Forrest Plot of PFS HR by CPS Cut-point
(Global Cohort)
(ITT Population)



Database cutoff date: 20MAR2024.
Source: [Appendix Table 23]

4.7.1.4 KEYNOTE-811: Objective Response Rate and Duration of Response

4.7.1.4.1 Objective Response Rate

At IA1 (data cutoff 17-JUN-2020), based on BICR assessment per RECIST 1.1, pembrolizumab in combination with SOC provided a statistically significant and clinically meaningful improvement in ORR compared with SOC alone (p=0.00006) in the first 264 participants randomized [Table 14]. The ORR results at the FA in the ITT population continue to show a clinically meaningful improvement in ORR in the pembrolizumab + chemotherapy group compared with the placebo + chemotherapy group [Table 14].

Table 14
KEYNOTE-811: Results for Objective Response with Confirmation and Duration of Response Based on BICR Assessment per RECIST 1.1 in Participants with Confirmed Response
(Global Cohort)
(ITT Population)

Endpoint	Pembrolizumab + SOC	SOC
Objective Response at IA1[a]		
Number of Participants	133	131
ORR % (95% CI)	74.4 (66.2, 81.6)	51.9 (43.0, 60.7)
ORR Difference % (95% CI)[b], *p*-value[c]	22.7 (11.2, 33.7), p=0.00006	
DOR (months), median (range)	10.6 (1.1+ to 16.5+)	9.5 (1.4+ to 15.4+)
Objective Response at the FA		
Number of Participants	350	348
ORR % (95% CI)	72.6 (67.6, 77.2)	60.1 (54.7, 65.2)
ORR Difference % (95% CI)[a], nominal *p*-value	12.6 (5.6, 19.4), 0.00020	
DOR (months), median (range)[d]	11.3 (1.1+ to 60.8+)	9.5 (1.4+ to 60.5+)

Abbreviations: CI = confidence interval; DOR = duration of response; ITT = intent-to-treat; ORR = objective response rate; PD-L1 = programmed cell death 1 ligand 1.
Confirmed responses are included.
"+" indicates there is no progressive disease by the time of last disease assessment.
[a] Includes the first 264 participants randomized in the ITT population.
[b] 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.
[c] One-sided p-value for testing. H0: difference in % = 0 versus H1: difference in % > 0. One-sided p-value boundary=0.002.
[d] From product-limit (Kaplan-Meier) method for censored data. DOR includes participants with best objective response as confirmed complete response or partial response.
Data cutoff: IA1: 17JUN2020; FA: 20MAR2024

Data Source: [Appendix Table 26] [Appendix Table 27] [Appendix Table 28] [Appendix Table 29]

4.7.1.4.2 Exploratory Analysis of Objective Response Rate by CPS Cut-point

As noted in [Sec. 4.6.1.2.2], exploratory post-hoc analyses by CPS cut-point were performed for ORR in response to the FDA request.

The results of these exploratory analyses using data from the FA are consistent with the results observed at the primary analysis (ie, IA1). Pembrolizumab in combination with SOC shows a favorable trend in ORR when compared with SOC. At the CPS <1 cut-point, there was no difference in ORR between the pembrolizumab plus SOC and SOC treatment groups. These results also indicate that there is no additional benefit of pembrolizumab with increasing level of PD-L1 expression beyond the cut-point of CPS ≥1 [Table 15].

Table 15
KEYNOTE-811: Exploratory Analysis of Objective Response Rate by CPS Cut-point
Based on BICR Assessment per RECIST 1.1
(Global Cohort)
(ITT Population; Data Cutoff 20-MAR-2024)

Baseline PD-L1 Status[a]	**Number of Participants**		**Number of Complete Responses**		**Number of Partial Responses**		**ORR[b] (%) (95% CI)**	
	Pembro + SOC	**SOC**	**Pembro + SOC**	**SOC**	**Pembro + SOC**	**SOC**	**Pembro + SOC**	**SOC**
ITT	350	348	60	41	194	168	72.6 (67.6, 77.2)	60.1 (54.7, 65.2)
CPS <1	52	52	9	10	27	26	69.2 (54.9, 81.3)	69.2 (54.9, 81.3)
CPS 1 - <5	112	125	14	11	70	60	75.0 (65.9, 82.7)	56.8 (47.6, 65.6)
CPS <5	164	177	23	21	97	86	73.2 (65.7, 79.8)	60.5 (52.8, 67.7)
CPS 1 - <10	189	190	28	14	115	94	75.7 (68.9, 81.6)	56.8 (49.5, 64.0)
CPS 5 - <10	77	65	14	3	45	34	76.6 (65.6, 85.5)	56.9 (44.0, 69.2)
CPS < 10	241	242	37	24	142	120	74.3 (68.3, 79.7)	59.5 (53.0, 65.7)
CPS ≥1	298	296	51	31	167	142	73.2 (67.7, 78.1)	58.4 (52.6, 64.1)
CPS ≥5	186	171	37	20	97	82	72.0 (65.0, 78.4)	59.6 (51.9, 67.1)
CPS ≥10	109	106	23	17	52	48	68.8 (59.2, 77.3)	61.3 (51.4, 70.6)

BICR=blinded independent central review; CI=confidence interval; CPS=combined positive score; ITT=intent-to-treat; ORR=objective response rate; PD-L1=programmed death-ligand 1; pembro=pembrolizumab; SOC=standard of care.

a. Data analysis at CPS ≥1 was pre-specified, and data collected at validated CPS ≥1 cut-point were used for analyses. Remaining analyses at other CPS cut-points were not pre-specified, and CPS raw scores were used.

b. Determined by Blinded Independent Central Review.

Database cutoff date: 20MAR2024

4.7.1.5 KEYNOTE-811: Patient-reported Outcomes

In the PRO FAS population of KEYNOTE-811, the addition of pembrolizumab to SOC chemotherapy (trastuzumab plus either FP or CAPOX) resulted in similar HRQoL as those on SOC alone. These results provide further support of the favorable benefit:risk profile for the addition of pembrolizumab as part of the SOC in 1L treatment of patients with HER2-positive advanced gastric or GEJ adenocarcinoma.

The analyses presented here were performed at IA2. For the prespecified EORTC QLQ-C30 Global Health Status/QoL scale, baseline scores were similar for pembrolizumab plus SOC and SOC treatment groups (LS means [SD]: 68.91 [19.17] and 67.26 [20.59], respectively, out of a 0 -100 scale, with a higher score representing better QoL). The analysis of change from baseline at Week 24 showed no meaningful difference between the 2 treatment groups (difference in LS means: -1.16 points [95% CI: -4.23, 1.91]). In addition, changes from baseline at Week 24 in the prespecified scales of physical functioning and nausea/vomiting, and symptom of appetite loss scores were similar between the 2 treatment groups. The analysis of change from baseline for the prespecified EORTC QLQ-STO22 pain symptom scale at Week 24 also showed no difference between the 2 treatment groups (difference in LS means: -0.01 points [95% CI: -2.60, 2.57]). Week 24 was selected as the latest analysis time point at which predefined rates of completion (≥60%) and compliance (≥80%) were met based on blinded data review.

Results across the CPS subgroups were generally consistent with PRO FAS. In addition, the results observed at the FA were consistent with those reported at IA2. As with HER2-negative gastric cancer, maintenance of HRQoL may be considered a meaningful goal in patients with advanced disease [30] [31], and these data provide reassurance that the addition of pembrolizumab does not adversely affect HRQoL.

4.7.1.6 KEYNOTE-811: Efficacy Summary and Conclusions

In KEYNOTE-811, 1L therapy with pembrolizumab plus SOC (trastuzumab and chemotherapy) provided a statistically significant and clinically meaningful improvement versus placebo plus SOC in OS, PFS, and ORR in all patients with locally advanced and metastatic HER2-positive gastric and GEJ cancer. Furthermore, there was no observed detriment in HRQoL with the addition of pembrolizumab to SOC (trastuzumab plus chemotherapy).

As discussed above, HER2-positive gastric cancer is a unique subtype of gastric cancer, with distinct pathophysiological characteristics. The totality of the data generated in KEYNOTE-811 indicate that greater benefit of pembrolizumab plus trastuzumab and chemotherapy is observed in participants with CPS ≥1. The HR for OS was greater than 1 in the PD-L1 CPS <1 subgroup at both IA2 and IA3, with a lower bound of the 95% CI close to 1. Based on these data, the Sponsor proactively restricted the label to CPS ≥1. With additional follow-up, there was an improvement in the OS HR at the FA in this subgroup, indicating the challenge of isolating the precise treatment effect of adding pembrolizumab to trastuzumab and chemotherapy. Exploratory post-hoc analyses looking at different CPS

cut-points show that there is no additional benefit with PD-L1 expression at levels above CPS ≥1 (ie, CPS ≥10).

These data continue to support the current indication for patients with locally advanced and metastatic HER2-positive gastric and GEJ cancer whose tumors express PD-L1 at CPS ≥1.

4.7.2 KEYNOTE-811: Key Safety Results

The safety profile of pembrolizumab plus SOC was generally consistent with the individual established safety profiles of the SOC regimen (trastuzumab + either FP or CAPOX) and pembrolizumab monotherapy. The safety profile of pembrolizumab plus SOC was similar across PD-L1 subgroups.

The incidences of AEs, drug-related AEs, Grade 3 to 5 AEs, SAEs, and discontinuations due to an AE or SAE were generally similar (≤10% difference) between the pembrolizumab plus SOC and the SOC groups in KEYNOTE-811 [Table 16].

Compared with the pembrolizumab monotherapy RSD, there were higher incidences of most AE parameters in the pembrolizumab plus SOC group [Table 16]. This was anticipated due to the combination of pembrolizumab with trastuzumab plus chemotherapy (CAPOX or FP) versus pembrolizumab monotherapy. Immune-mediated AEs were generally low grade and manageable in KEYNOTE-811, though some events such as endocrinopathies may require long-term hormone replacement. No new safety concerns were identified for pembrolizumab.

The safety profile of pembrolizumab and SOC is generally similar across PD-L1 CPS subgroups in the pooled data for the 3 key studies for gastric and esophageal indications (KEYNOTE-811, KEYNOTE-859, and KEYNOTE-590) [Sec. 4.6.2] with pembrolizumab and chemotherapy [Table 11].

Table 16
KEYNOTE-811: Summary of Overall Adverse Events and Immune-mediated Reactions and Infusion Reactions (APaT Population)

	Pembrolizumab + SOC (n=350)	SOC (n=346)	Reference Safety Dataset for Pembrolizumab Monotherapy (N=2799)
Overall Adverse Events, n (%)			
One or more AEs	348 (99.4)	346 (100)	2727 (97.4)
Grade 3-5 AEs	253 (72.3)	228 (65.9)	1273 (45.5)
Serious AEs	163 (46.6)	159 (46.0)	1042 (37.2)
Deaths due to AEs	23 (6.6)	22 (6.4)	110 (3.9)
AEs leading to discontinuation	150 (42.9)	136 (39.3)	334 (11.9)
Immune-mediated reactions and infusion reactions, n (%)			
One or more AEs	140 (40.0)	86 (24.9)	600 (21.4)
Grade 3-5 AEs	41 (11.7)	12 (3.5)	155 (5.5)
Serious AEs	37 (10.6)	15 (4.3)	162 (5.8)
Deaths due to AEs	3 (0.9)	1 (0.3)	4 (0.1)
AEs leading to discontinuation	27 (7.7)	14 (4.0)	85 (3.0)

pembro=pembrolizumab; SOC=standard-of-care.
KEYNOTE-811 Database Cutoff Date: 20MAR2024
Source: Pembro RSD data from KN-811 IA2 2.7.4, Table 2.7.4-gastric5: 5 and Table 2.7.4-gastric5: 12

4.7.3 KEYNOTE-811: Q-TWiST Analysis

In order to better understand the benefit:risk of adding pembrolizumab to SOC for the 1L treatment of HER2-positive gastric cancer, a post-hoc Q-TWiST analysis was performed to evaluate the quality (ie, patient health utilities) and quantity (ie, OS, PFS, and AEs) of survival in participants who received pembrolizumab plus SOC versus SOC in KEYNOTE-811 [Sec. 8.2.1.2]. Recent publications have reported the utility of Q-TWiST analyses of studies of an ICI in NSCLC and RCC [54] [55].

In this analysis, the OS time is partitioned into 3 health states: TOX, TWiST, and REL [Sec. 4.6.3]. Q-TWiST was calculated as the sum of the time spent in each health state, multiplied by its corresponding utility weight. Relative gain in Q-TWiST is presented as a percentage and is defined as the difference in Q-TWiST between the pembrolizumab plus SOC arm and the SOC arm divided by the restricted mean OS of the SOC arm. A relative gain of 10 percentage points is considered clinically important and a gain of 15 percentage points is considered clearly clinically important [56].

In KEYNOTE-811, there was a relative gain in Q-TWiST of 13.1% (95% CI: 2.90, 25.58) and 16.6% (95% CI: 5.18, 30.40) in the ITT and CPS ≥1 populations, respectively. These data emphasize the favorable benefit:risk profile with a clearly clinically important positive

relative Q-TWiST gain over 56 months for pembrolizumab + SOC versus SOC at the CPS ≥1 cut-point.

4.8 Real-world PD-L1 Testing and ICI Usage

The PD-L1 IHC 22C3 pharmDx is the primary assay used for patient selection or treatment decisions within the pembrolizumab program [Sec. 3.1]. The Sponsor has not conducted any comparison studies in gastric cancer with different PD-L1 assays. Understanding of the potential clinical utility of ICIs in the 1L setting of gastric cancer is relatively recent, with 2 different ICIs (pembrolizumab and nivolumab) approved in gastric cancer based on Phase 3 studies that used 2 different PD-L1 assays (22C3 or 28-8 based PD-L1 clones). The Sponsor has reviewed and continues to review the research data available in the public domain regarding the concordance between the 2 assays, and based on the data seen to date, the results are inconsistent. The PD-L1 IHC 22C3 pharmDx is currently the only PD-L1 test that is FDA-approved for guiding treatment decisions for pembrolizumab in gastric cancer.

Despite the rigor built into the Sponsor's clinical studies, it is acknowledged that PD-L1 testing is varied in routine clinical practice. To investigate PD-L1 testing and treatment patterns among patients with advanced/metastatic gastric cancer, a retrospective observational study was conducted using Flatiron Health electronic health record-derived de-identified database of adult (≥18 years of age) patients with locally advanced unresectable/metastatic HER2-negative and HER2-positive gastric/GEJ cancer who initiated 1L systemic treatment primarily in the community oncology setting in the US after the first FDA approval of ICIs for these indications in 2021. A description of the database and the methods of the retrospective study are provided in [Sec. 8.3]. A high-level summary of the results is presented below.

4.8.1 HER2-negative gastric cancer

Of the 546 patients with HER2-negative disease treated in the 1L setting, 77% had evidence of an evaluation for PD-L1 expression, indicating a significant proportion of patients may not be tested in clinical practice despite guideline recommendations supporting testing. The most commonly used assay was the Dako PD-L1 IHC 22C3 pharmDx (~50%), followed by laboratory developed tests (~20%). Of those with PD-L1 CPS data available (n=341 based on various assays), 74% were CPS ≥1 and 29% were CPS ≥10 (data on file).

Among the overall HER2-negative gastric cancer population receiving 1L therapy identified in the database (N=546), only 46% were treated with ICI-based regimens. Of the patients with available PD-L1 CPS data (based on various assays), 59% with CPS ≥1 and 30% with CPS <1 received ICI-containing therapy in the 1L. Notably, 35% of patients whose tumors were CPS ≥10 did not receive an ICI.

Approximately 40% of HER2-negative gastric cancer patients receive any treatment in the 2L setting (data on file). Yet, as there are no approved ICIs in 2L+ setting in the US, there is no opportunity to receive an ICI beyond 1L. For this reason, it is crucial that patients have access to the best treatment in 1L.

In 2024, it is estimated that approximately 10,760 patients will be diagnosed with metastatic gastric cancer in the US [2], of which, approximately 8600 patients would have HER2-negative disease [8] [11]. Should the indication for gastric cancer in the 1L setting be restricted to a CPS cut-point, even more patients will lose the opportunity to benefit from pembrolizumab. Specifically, based on PD-L1 expression from KEYNOTE-859, an estimated 22% (~1900 patients) and 65% (~5600 patients) of patients with HER2-negative gastric cancer in the US may be deprived of a potentially effective treatment with a cut-point of CPS ≥1 or CPS ≥10, respectively. Maintaining an all-comers indication for pembrolizumab will allow providers and patients to individualize treatment for each patient and allow eligible patients to receive recommended therapy with ICI-based combinations in the 1L, where patients have the greatest chance to benefit.

4.8.2 HER2-positive gastric cancer

Of the 204 patients with HER2-positive disease treated in the 1L setting, 75% had evidence of an evaluation for PD-L1 expression, indicating a significant proportion of patients may not be tested in clinical practice despite guideline recommendations supporting testing. Similar to HER2-negative patients, the Dako PD-L1 IHC 22C3 pharmDx was the most frequently used assay (~60%), followed by laboratory developed tests (~24%) among those patients with testing information. Of those with PD-L1 CPS data available (N=132 based on various assays), 77% were CPS ≥1 and 30% were CPS ≥10 (data on file).

Among the overall HER2-positive gastric cancer population receiving 1L therapy identified in the database (N=204), only 44% were treated with ICI-containing regimens, while 22% received HER2-inhibitor-containing therapy, and 33% received chemotherapy-based regimens only. Of the patients with available PD-L1 CPS data (based on various assays), only about 50% with CPS ≥1 (~50%) or CPS ≥10 (~54%) received ICI-containing therapy in the 1L, suggesting that a substantial proportion of the patient population who may benefit are not receiving an ICI. Among patients with CPS <1, approximately 35% received ICI-containing therapy. Like HER2-negative gastric cancer, only about 48% of HER2-positive gastric cancer patients were found to receive any treatment in the 2L setting (data on file), emphasizing that the best treatment options should be available upfront in 1L for patients.

In summary, despite guideline recommendations, PD-L1 testing may not be routinely performed prior to starting an ICI for the 1L treatment of advanced/metastatic gastric cancer. Many patients are not receiving appropriate ICI-based therapy, even at higher PD-L1 expression cut-points. Further restricting labelled indications may exclude patients that may benefit from pembrolizumab in this setting. For those with CPS <1, physicians are likely weighing risks and benefits when discussing treatment options with their patients. As there are no currently approved immunotherapies available for gastric cancer in the 2L setting, the best opportunity to receive an immunotherapy is in the 1L setting where patients have the greatest chance to benefit. Together, these data support maintaining the currently labeled KEYNOTE-859 and KEYNOTE-811 indications to allow access to pembrolizumab for the most appropriate patients.

5 BENEFIT:RISK ASSESSMENT

5.1 KEYNOTE-859: Benefit:Risk Assessment

KEYNOTE-859 met the prespecified success criteria for all primary and key secondary hypotheses including the primary OS endpoint and the secondary PFS and ORR endpoints in the ITT, CPS ≥1, and CPS ≥10 populations. These results led to FDA approval based on their assessment of the favorable benefit:risk profile in the 1L setting for patients with locally advanced unresectable or metastatic HER2-negative gastric with any level of PD-L1 expression.

The addition of pembrolizumab to chemotherapy provides a statistically significant and clinically meaningful improvement in OS, PFS, and ORR in the ITT population and the CPS ≥1 and CPS ≥10 populations compared with chemotherapy. There was no observed detriment in HRQoL with the addition of pembrolizumab to chemotherapy, and a "clearly clinically important" positive relative Q-TWiST gain for pembrolizumab plus chemotherapy versus chemotherapy in the ITT population. The results from KEYNOTE-859 demonstrate that pembrolizumab in combination with chemotherapy has a tolerable and manageable safety profile that is consistent with the safety profile of a commonly used chemotherapy regimen for the 1L treatment of patients with locally advanced unresectable or metastatic HER2-negative gastric or GEJ adenocarcinoma and the known safety profile of pembrolizumab.

Limiting the labeled population to CPS ≥1 or CPS ≥10 would exclude 22% and 65%, respectively, of patients who might otherwise be eligible to receive pembrolizumab, further restricting access to a treatment that could help provide a durable benefit to patients.

Given the high unmet need and limited treatment options for these patients, the totality of the data continues to support a favorable benefit:risk profile for pembrolizumab plus chemotherapy as a standard-of-care 1L treatment in the all-comers patient population, consistent with the currently approved FDA label [Table 17].

Table 17
Benefit:Risk Assessment for KEYNOTE-859

Dimension	Evidence and Uncertainty	Conclusion and Reasons
Analysis of Condition	• There will be 26,890 estimated new cases and 10,880 deaths from gastric cancer in the US in 2024. • 36% of cases will be diagnosed at the metastatic or locally advanced stage. • The 5-year estimated survival rate for gastric cancer diagnosed at the locally advanced or metastatic stage prior to introduction of immunotherapy is 7%. • About 80% of gastric cancer is HER2-negative. • In KN-859, ~22% of HER2-negative gastric cancer was PD-L1 negative (CPS <1). • RWE indicates less than 50% of patients treated in the 1L setting will go on to receive 2L treatment.	• 1L metastatic HER2-negative gastric cancer is a serious and life-threatening condition with limited treatment options.
Current Treatment Options	• Systemic chemotherapy, with or without immunotherapy, is the current treatment option for 1L advanced and metastatic HER2-negative gastric cancer. • Clinical studies with novel mechanisms of action are ongoing and present an additional option. • ICIs are only available in the 1L setting in the US and are not an option for patients who progress and need 2L treatment.	• Chemotherapy is the only available option outside of clinical studies for HER2-negative patients who cannot receive immunotherapy with an anti-PD-(L)1 agent.
Benefit	• Statistically significant and clinically meaningful improvement in OS, PFS, and ORR was observed in all participants enrolled, which included all levels of PD-L1 expression. • Post-hoc exploratory analyses show that OS, PFS, and ORR favor pembrolizumab plus chemotherapy in all CPS subgroups analyzed. • No detriment in health-related quality of life was observed in all CPS subgroups. • Post-hoc Q-TWiST analyses indicate a favorable benefit:risk profile with a positive relative Q-TWiST gain that is clearly clinically important for the ITT population.	• A carefully designed and well-controlled Phase 3 global study that was aligned with the FDA showed benefit for all patients enrolled, which included all levels of PD-L1 expression.

Dimension	Evidence and Uncertainty	Conclusion and Reasons
Risk and Risk Management	• The safety profile of pembrolizumab plus chemotherapy was generally consistent with the known safety profiles of chemotherapy alone and pembrolizumab monotherapy. • The safety profile of pembrolizumab plus chemotherapy was primarily the addition of expected immune-mediated AEs due to pembrolizumab added to the safety profile of chemotherapy. • Immune-mediated AEs were generally low grade and manageable, although some may require long-term hormone replacement. • The safety profile for pembrolizumab plus chemotherapy does not change when assessed at different CPS cut-points.	• The AEs associated with pembrolizumab and doublet chemotherapy are well known by treating oncologists. The combination has a manageable profile.
Conclusions Regarding Benefit:Risk	• The benefit:risk profile for pembrolizumab plus chemotherapy is favorable. • Labeling clarifies that patients with CPS <1 had a lower observed benefit in KN-859 based on point estimate of the OS hazard ratio. This will allow treating physicians to choose the optimal treatment for patients with advanced gastric cancer patients at their clinical discretion. • **The availability of pembrolizumab plus chemotherapy as a treatment choice in 1L advanced gastric cancer patients across all levels of PD-L1 expression can help address the unmet need in this patient population**.	

1L=first-line; 2L=second-line; AE=adverse event; CPS=combined positive score; FDA=Food and Drug-Administration; HER2=human epidermal growth factor receptor 2; ICI=immune checkpoint inhibitor; ITT=intent-to-treat; KN=KEYNOTE; ORR=objective response rate; OS=overall survival; PD-L1=programmed cell death ligand 1; PFS=progression-free survival; Q-TWIST= quality-adjusted time without symptoms of disease progression or toxicity of treatment; RWE=real-world evidence; US=United States.

5.2 KEYNOTE-811: Benefit:Risk Assessment

In KEYNOTE-811, the addition of pembrolizumab to SOC provides a statistically significant and clinically meaningful improvement in OS, PFS, and ORR in all participants (ITT population) compared with SOC. The benefit of pembrolizumab plus trastuzumab and chemotherapy is greater in participants with CPS ≥1; however, there is no further increase in efficacy observed at higher PD-L1 expression cut-points. There was no observed detriment in HRQoL observed with the addition of pembrolizumab to chemotherapy, and the relative gain in Q-TWiST is considered "clearly clinically important" for the current indication. The results from KEYNOTE-811 demonstrate that pembrolizumab in combination with chemotherapy has a tolerable and manageable safety profile that is consistent with the safety profile of a commonly used chemotherapy regimen for the 1L treatment of patients with locally advanced unresectable or metastatic HER2-positive gastric or GEJ adenocarcinoma and the known safety profile of pembrolizumab.

Further limiting the indication to the CPS ≥10 population would exclude an estimated 54% of patients who might otherwise be eligible and would have an opportunity for durable benefit with chemotherapy, trastuzumab, and pembrolizumab.

Given the high unmet need and limited treatment options for these patients, the totality of the data continues to support a favorable benefit:risk profile for pembrolizumab plus trastuzumab and chemotherapy as a standard-of-care 1L treatment in this patient population whose tumors express PD-L1 (CPS ≥1) [Table 18].

Table 18
Benefit:Risk Assessment for KEYNOTE-811

Dimension	Evidence and Uncertainty	Conclusion and Reasons
Analysis of Condition	• There will be 26,890 estimated new cases and 10,880 deaths from gastric cancer in the US in 2024. • 36% of cases will be diagnosed at the metastatic or locally advanced stage. • The 5-year estimated survival rate for gastric cancer diagnosed at the locally advanced or metastatic stage prior to introduction of immunotherapy was 7%. • About 20% of gastric cancer is HER2-positive. • In KN-811, ~15% of HER2-positive gastric cancer was PD-L1 negative (CPS <1). • RWE indicates less than 50% of patients treated in the 1L setting will go on to receive 2L treatment.	• 1L metastatic HER2-positive gastric cancer is a serious and life-threatening condition with limited treatment options.
Current Treatment Options	• Systemic chemotherapy plus trastuzumab, with or without immunotherapy, is the current treatment option for advanced and metastatic HER2-positive gastric cancer. • ICIs are only available in the 1L setting and are not an option for patients who progress and need 2L treatment.	• Chemotherapy plus trastuzumab, approved almost 15 years ago, is the only available option outside of clinical studies for patients who cannot receive immunotherapy with an anti-PD-(L)1 agent.
Benefit	• Statistically significant and clinically meaningful improvement in OS, PFS, and ORR was observed in all participants enrolled, which included all levels of PD-L1 expression. • Post-hoc exploratory analyses show that OS, PFS, and ORR favor pembrolizumab plus chemotherapy in all CPS subgroups ≥1 and there is no further increase in efficacy at CPS cut-points >1. • No detriment in health-related quality of life was observed in all CPS subgroups. • Post-hoc Q-TWiST analyses indicate a favorable benefit:risk profile with positive relative Q-TWiST gains that are clearly clinically important for those with CPS ≥1.	• A carefully designed and well-controlled Phase 3 global study that was aligned with the FDA showed benefit for all patients enrolled, which included all levels of PD-L1 expression. • Given that the HR for OS for those with CPS <1 was greater than 1 at IA2 and IA3, the Sponsor proactively worked with FDA to limit the indication. The OS HR for CPS <1 improved at FA; however, the challenge of isolating the precise treatment effect in this subgroup supports the current indication of CPS ≥1.

Dimension	Evidence and Uncertainty	Conclusion and Reasons
Risk and Risk Management	• The safety profile of pembrolizumab plus SOC was generally consistent with the known safety profiles of the chemotherapy regimen alone, trastuzumab, and pembrolizumab monotherapy. • The safety profile of pembrolizumab plus SOC was primarily the addition of expected immune-mediated AEs due to pembrolizumab added to the safety profile of chemotherapy and trastuzumab. • Immune-mediated AEs were generally low grade and manageable, although some may require long-term hormone replacement. • The safety profile for pembrolizumab plus SOC does not change when assessed at different CPS cut-points.	• The AEs associated with pembrolizumab, trastuzumab, and doublet chemotherapy are well known by treating oncologists. The combination has a manageable profile.
Conclusions Regarding Benefit:Risk	• The benefit:risk profile for pembrolizumab plus trastuzumab and chemotherapy is favorable in patients whose tumors express PD-L1 with CPS ≥1. • **The availability of pembrolizumab plus trastuzumab and chemotherapy as a treatment choice in 1L advanced HER2-positive gastric cancer patients can help address the unmet need in this patient population.**	

1L=first-line; 2L=second-line; AE=adverse event; CPS=combined positive score; FA=final analysis; FDA=Food and Drug Administration; HER2=human epidermal growth factor receptor 2; HR=hazard ratio; IA-interim analysis; ITT=intent-to-treat; ICI=immune checkpoint inhibitor; KN=KEYNOTE; ORR=objective response rate; OS=overall survival; PD-L1=programmed cell death ligand 1; PFS=progression-free survival; Q TWIST= quality-adjusted time without symptoms of disease progression or toxicity of treatment; RWE=real-world evidence; SOC=standard of care; US=United States.

6 POINTS FOR THE ADVISORY COMMITTEE TO CONSIDER

Study Design:

- HER2-negative and HER2-positive tumors are biologically distinct subtypes of gastric and GEJ cancer with different clinical and molecular characteristics.

- KEYNOTE-859 and KEYNOTE-811 were rigorously designed based on data available at the time the studies were initiated and included predefined endpoints that were statistically tested with multiplicity control for family-wise error rate. The FDA agreed on the study design and planned analyses.

- The CPS cut-points (ie, CPS ≥1 and CPS ≥10 for KEYNOTE-859 and CPS ≥1 for KEYNOTE-811) were chosen based on the possibility to enrich for benefit with pembrolizumab as monotherapy. However, these biomarkers do not granularly predict who will have benefit, and it is known that some individual patients with CPS <1 do respond to pembrolizumab monotherapy.

- KEYNOTE-859 and KEYNOTE-811 were designed with pembrolizumab in combination with chemotherapy to enable meaningful response and survival in all patients, which is not commonly observed with historic chemotherapy regimens, including those patients whose tumors have low PD-L1 expression.

Study Results:

<u>Efficacy:</u>

- KEYNOTE-859 and KEYNOTE-811 met the success criteria for the hypotheses of the primary and key secondary endpoints in the ITT population (OS, PFS, and ORR). The FDA has requested exploratory examination of subgroups at different levels of PD-L1 expression, which are neither multiplicity controlled nor powered for analysis.

    - Pathologists are trained to score samples at the cut-points specified in the protocols (CPS ≥1 and/or CPS ≥10), ensuring consistency and accuracy in the classification of patients into those subgroups. PD-L1 raw scores were used to derive the subgroups for performing the analyses by CPS cut-points that were not pre-specified in the studies. Assessment of PD-L1 expression determined at a specified cut-point is considered more reliable than the raw score value.

    - The Sponsor has no analytical validation data at the CPS ≥5 cut-point for the PD-L1 IHC 22C3 pharmDx kit in any tumor type, and therefore precision and reproducibility around this cut-point are uncertain.

- In KEYNOTE-859 a consistent treatment effect, directionally aligned with the result in the ITT population, was observed in all PD-L1 CPS subgroups analyzed.

- In KEYNOTE-811, the data continue to support a favorable benefit:risk profile for the currently labeled CPS ≥1 population.

  - The result for OS in the CPS <1 population at both IA2 and IA3, where the HR was above 1 with a lower bound of the 95% confidence interval of the HR close to 1, led the Sponsor to proactively restrict the indication. With additional follow-up, there was an improvement in the OS HR at the FA in this subgroup, reflecting the challenge of isolating the true treatment effect of adding pembrolizumab to trastuzumab and chemotherapy.

  - Exploratory analyses looking at different CPS cut-points do not suggest that there is additional benefit with a further increase in PD-L1 expression at levels above CPS ≥1.

- Additional exploratory evaluation requested at CPS 5, a cut-point not validated for the 22C3 assay, reveals that the point estimates of the PFS and OS HRs for these subgroups in each study are generally consistent with the ITT population with overlapping confidence intervals; it does not represent a better cut-point than those evaluated within the studies.

- PRO data analyses show no detriment for pembrolizumab plus SOC at any CPS level.

- Q-TWiST analyses indicates that there is a favorable benefit:risk profile for the ITT and the preplanned CPS subgroups in both KEYNOTE-859 and KEYNOTE-811.

Safety:

- The safety profile for pembrolizumab plus chemotherapy does not change across PD-L1 CPS subgroups, is well characterized, and manageable by the treating oncologist.

Real World ICI Usage:

- Based on Flatiron Health electronic health record-derived data, many patients with HER2-negative and HER2-positive gastric cancer are not receiving FDA-approved ICI-based therapy in the 1L setting, which has demonstrated long-term survival. Only 59% and 50% of patients with HER2-negative and HER2-positive gastric cancer whose tumors express CPS ≥1 received ICI-based therapy, respectively. In contrast, only 30% of patients with HER2-negative gastric cancer whose tumors express CPS <1 received ICI-based therapy. These data suggest that physicians and patients are likely weighing the risks and benefits when considering available treatment options.

Indication and Label:

- Cross-study comparisons with other drugs using different diagnostic tests are not scientifically valid and should not override FDA's previous analysis of results based on design of individual studies. Information in a drug's label should be based on the pivotal study that supported registration.

- The current indications in patients with locally advanced and metastatic HER2-negative and HER2-positive gastric and GEJ cancer are appropriate based on the study designs and results from KEYNOTE-859 and KEYNOTE-811.

  - Restricting the label for HER2-negative patients to only CPS ≥1 or CPS ≥10 in KEYNOTE-859 would preclude access for approximately 22% or 65% of patients with a significant unmet need, respectively. Based on the estimated prevalence of metastatic HER2-negative gastric cancer in 2024 and the prevalence of PD-L1 expression in KEYNOTE-859, this equates to approximately 1900 and 5600 US patients per year losing access to pembrolizumab, respectively.

  - The data do not support selecting a CPS cut-point other than CPS ≥1 for HER2-positive patients in KEYNOTE-811. Restricting the label to CPS ≥10 would preclude access for approximately 54% of patients with a significant unmet medical need. Based on the estimated prevalence of metastatic HER2-positive gastric cancer in 2024 and the prevalence of PD-L1 expression in KEYNOTE-811, this equates to approximately 1200 US patients per year losing access to pembrolizumab.

- Information currently included in labeling will inform the conversation between the patient and physician to determine if pembrolizumab is the right option for an individual patient.

- There are no approved ICIs in the 2L setting; therefore, the opportunity to receive an ICI is in the 1L setting, where patients have the greatest chance to benefit.

- Patients with metastatic gastric cancer have a poor prognosis, and they should have continued access to pembrolizumab in accordance with current labelling. This will allow patients and their providers to make informed decisions together for their gastric cancer therapy. Pembrolizumab has transformed the treatment landscape for advanced gastric cancer and should remain as a cornerstone of therapy for appropriate patients.

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8 APPENDICES

8.1 KEYNOTE-859

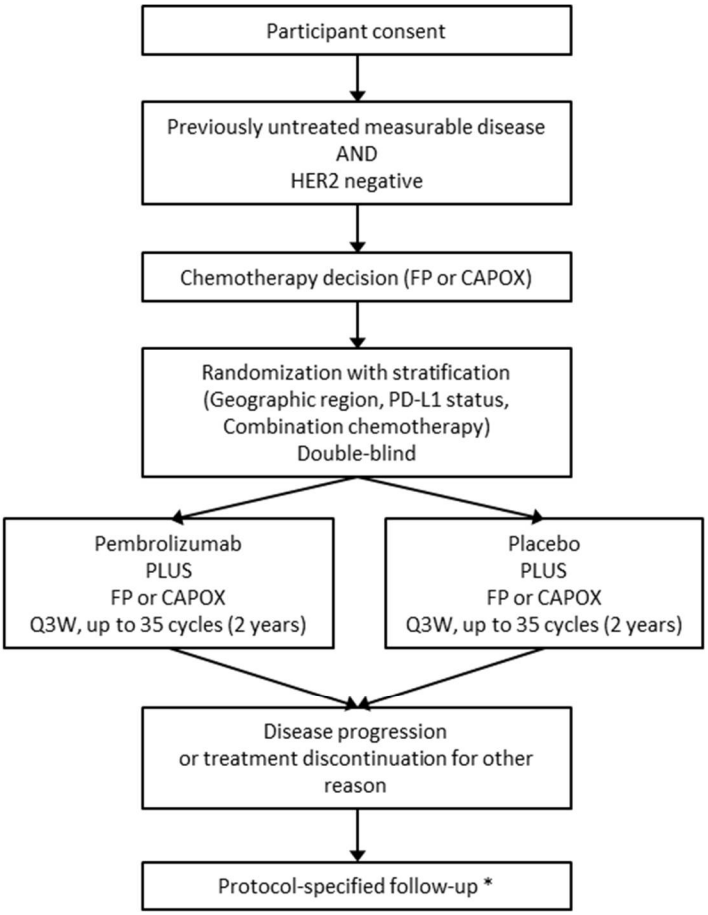
8.1.1 KEYNOTE-859: Study Design

KEYNOTE-859 is an ongoing, Phase 3, randomized, placebo-controlled, double-blind study designed to assess pembrolizumab in combination with chemotherapy as treatment in participants with HER2-negative advanced gastric or GEJ adenocarcinoma [Appendix Figure 1]. There were 1579 participants randomized in a 1:1 ratio to receive:

- Pembrolizumab plus chemotherapy (n=790)
- Placebo plus chemotherapy (hereafter referred to as the chemotherapy group; n=789)

The investigators had 2 chemotherapy regimen choices, FP or CAPOX, which had to be chosen before randomization in the study. Participants were stratified by geographic region, PD-L1 tumor expression status (CPS <1 vs CPS ≥1), and combination chemotherapy (FP or CAPOX). KEYNOTE-859 was designed based on information available from pembrolizumab monotherapy studies, which indicated that CPS ≥1 was a potential cut-point to explore as predictive for increased benefit. Therefore, the study was stratified around the CPS 1 cut-point and the statistical testing plan was designed to test both the CPS ≥1 and the ITT population. Following initiation of the study, results from KEYNOTE-061 and KEYNOTE-062 became available that indicated there was potential for increased benefit at CPS ≥10. Therefore, the statistical plan was adjusted to formally test a hypothesis in this population as well [Sec. 8.1.1.1].

Appendix Figure 1
Study Design for KEYNOTE-859



* Safety follow-up, follow-up , and survival follow-up per protocol procedures.
CAPOX=capecitabine and oxaliplatin; FP=cisplatin and 5-fluorouracil; HER2=human epidermal growth factor receptor 2; Q3W=every 3 weeks

CAPOX=capecitabine/oxaliplatin; FP=cisplatin plus 5-fluorouracil; HER2=human epidermal growth factor receptor 2; PD-L1=programmed cell death ligand 1; Q3W=every 3 weeks.

8.1.1.1 Statistical Methods

The primary efficacy endpoint was OS. OS is defined as the time from randomization to death due to any cause. The key secondary endpoints were PFS and ORR per RECIST 1.1 assessed by BICR. PFS is defined as the time from randomization to the first documented disease progression per RECIST 1.1 by BICR or death due to any cause, whichever occurs first. ORR is defined as the proportion of participants who have confirmed CR or PR per RECIST 1.1 by BICR.

One IA was planned in this study [Appendix Table 1]. The nonparametric Kaplan-Meier method was used to estimate the OS and PFS (per RECIST 1.1 by BICR) curves. The treatment difference in OS and PFS was assessed by the stratified log-rank test. A stratified

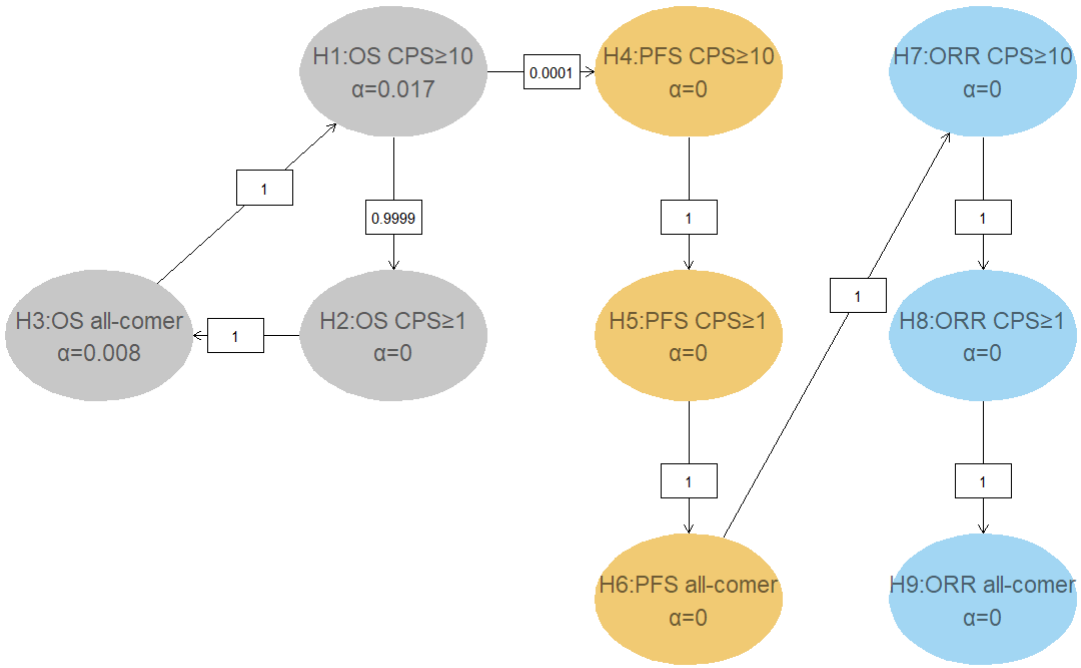
Cox proportional hazard model with Efron's method of tie handling was used to assess the magnitude of the treatment difference (the HR). The stratification factors used for randomization were applied to the stratified Miettinen and Nurminen method. [Appendix Figure 2] shows the initial 1-sided α-allocation for each hypothesis in the ellipse representing the hypotheses. The study uses the graphical method of Maurer and Bretz [57] to provide strong multiplicity control for multiple hypotheses as well as interim analysis.

Appendix Table 1
Timing, Sample Size, and Decision Guidance for KEYNOTE-859 Analyses

Analyses	Timing	Estimated Months After First Participant Randomized	Primary Purpose of Analysis	Data Cutoff Date
Interim Analysis	~ 403 OS events have occurred in CPS ≥10 participants AND ~ 12 months after the last participant has been randomized. If there are fewer than ~1187 OS events in all participants at the time, then the analysis may be delayed for up to 2 months or when the targeted OS event number is reached, whichever occurs first. This is the final analysis of PFS and ORR.	~ 43 months	Efficacy analysis for ORR, PFS, and OS in CPS ≥10, in CPS ≥1, and in all participants.	03-OCT-2022
Final Analysis[a]	~ 463 OS events have occurred in CPS ≥10 participants AND ~ 23 months after the last participant has been randomized. If there are fewer than ~1358 OS events in all participants at the time, then the analysis may be delayed for up to 2 months or when the targeted OS event number is reached, whichever occurs first.	~ 54 months	Efficacy analysis for OS in CPS ≥10, in CPS ≥1, in all participants.	22-AUG-2023

CPS=combined positive score; ORR=objective response rate; OS=overall survival; PFS=progression-free survival.
a. At the pre-planned IA, KEYNOTE-859 met the success criteria for the hypotheses of the primary endpoint of OS and the secondary endpoints of PFS and ORR; therefore, the FA was not needed; however, a descriptive analysis was performed.

Appendix Figure 2
Multiplicity Strategy – KEYNOTE-859



CPS=combined positive score; ORR=objective response rate; OS=overall survival; PFS=progression-free survival
Note: If all OS (H1, H2, and H3) 3 null hypotheses are rejected at FA, the reallocation strategy allows testing of PFS and ORR at alpha=0.025 based on the *p*-value at IA.

8.1.1.2 Statistical Methods – Q-TWiST Analysis

8.1.1.2.1 EQ-5D Health Utility Weights

The EuroQoL EQ-5D-5L is a standardized instrument for use as a measure of health outcome and will provide data for use in economic models and analyses including developing health utilities or quality-adjusted life-years. The 5 health state dimensions in this instrument include the following: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Each dimension is rated on a 5-point scale from 1 (no problem) to 5 (extreme problem). The EuroQoL EQ-5D-5L also includes a graded (0 to 100) vertical visual analog scale on which the subject rates his or her general state of health at the time of the assessment. The EuroQoL EQ-5D-5L was completed electronically by participants first, prior to completing any other ePRO.

EQ-5D-5L scores were collected at Cycle 1 to Cycle 5, and every 2 cycles thereafter (eg, Cycle 7, Cycle 9, etc.), at the Treatment Discontinuation Visit, and at the 30-day Safety Follow-up Visit.

Only post-baseline EQ-5D-5L scores through 24 months are considered in this analysis and are mapped using US algorithm [58]. In case that a participant completed multiple EQ-5D questionnaires on the same date, the questionnaire with the latest entry time is considered in the analysis.

A post-baseline EQ-5D assessment is considered to have the progression-free status by investigator assessment, if it was completed prior to the date of the first documented disease progression per RECIST 1.1 based on investigator assessment or the date of death, or if it was completed no later than the censoring date of PFS. Among these EQ-5D assessments, the ones completed while participants were experiencing a Grade 3 to 5 AE are reported under health state TOX, and the corresponding average EQ-5D utility score across treatment arms is considered as U_{TOX}. The ones completed while participants were experiencing a Grade 1 or 2 AE or without an AE are reported under health state TWiST, and the corresponding average EQ-5D utility score across treatment arms is considered as U_{TWiST}.

The post-baseline EQ-5D score, which was collected at or after the date of the first documented disease progression per RECIST 1.1 based on investigator assessment, is reported under REL health state, and the corresponding average EQ-5D utility score across treatment arms is considered as U_{REL}.

8.1.1.2.2 Overall Survival/ Progression-free Survival /Toxicity

The Kaplan-Meier method is used to estimate the survival curves for OS, PFS, and toxicity for the pembrolizumab + chemotherapy arm and the chemotherapy arm.

8.1.1.2.2.1 Restricted Mean Survival Time

RMST is a measure of average survival from time 0 to a specified time point (t*), and this equals to the area under the survival curve S(t) from time 0 to specified time point (t*).

$$\text{RMST}(t^*)=\int_0^{t^*} S(t)dt$$

For each given time point t*, all survival times beyond time point t* are censored at t*, with the KM estimation then using data up to t* to estimate the RMST and its standard error.

RMST is used to perform analysis of OS, TOX, TWiST, REL and Q-TWiST. Median follow-up time (12 months) and maximum follow-up time (56 months) is used as the cutoff timepoint (t*) for the above analysis.

8.1.1.2.2.2 Toxicity (TOX)

The restricted mean duration in Toxicity is derived using RMST, equivalent to the area under the KM curves of TOX over the time interval of [0, 12 months], and [0, 56 months], for each treatment arm. All RMST values are presented in months.

The difference in TOX between the 2 treatment arms and its corresponding 95% CIs are then calculated. The 95% CI of TOX difference is obtained based on 1000 bootstrapped samples, as follows:

1. Draw a bootstrap sample from the original dataset, with replacement. The bootstrap is stratified by treatment arm (pembrolizumab + chemotherapy arm and chemotherapy arm).

2. Estimate the TOX difference of pembrolizumab + chemotherapy arm versus chemotherapy arm for each bootstrapped sample.

3. The 95% CI of TOX difference is estimated by using the lower 2.5 percentile and the upper 97.5 percentile of the distribution of TOX differences from these 1000 bootstrapped samples.

8.1.1.2.2.3 Time Without Symptoms or Toxicities (TWiST)

The restricted mean duration in TWiST is equivalent to the difference between the area under KM curves of PFS and TOX over the time interval of [0, 12 months] and [0, 56 months], for each treatment arm. All RMST values are presented in months.

8.1.1.2.2.4 Relapse (REL)

The restricted mean duration in REL is equivalent to the difference between the area under KM curves of OS and PFS over the time interval of [0, 12 months], and [0, 56 months], for each treatment arm. All RMST values are presented in months.

8.1.1.2.2.5 EQ-5D Health Utility Weights

The mean, standard error and its 95% CI are presented for EQ-5D utility weights in different health states.

The post-baseline EQ-5D assessments from the same participant are treated as independent, and the correlation within participants is not considered for the EQ-5D utility weights estimation, and consequently may produce CIs that are too narrow. The post-baseline utility weights estimation should be treated with caution.

8.1.1.2.2.6 Quality-adjusted Time Without Symptoms of Disease Progression or Toxicity of Treatment (Q-TWiST)

At each specified timepoint (ie, 12 months and 56 months), restricted mean Q-TWiST is calculated for each treatment arm using the formula:

$$\text{Q-TWiST} = (\text{TOX} * U_{\text{TOX}}) + (\text{TWiST} * U_{\text{TWiST}}) + (\text{REL} * U_{\text{REL}})$$

Where U_{TOX}, U_{TWiST} and U_{REL} denote the utility weight for each health state

8.1.1.2.2.7 Relative Gain in Q-TWiST

At each specified timepoint (ie, 12 months and 56 months), the relative gain in Q-TWiST for pembrolizumab + chemotherapy arm versus chemotherapy arm and its corresponding 95%CI are provided using the same method as TOX described in [Sec. 8.1.1.2.2.2].

8.1.2 KEYNOTE-859: Regulatory Interactions

Appendix Table 2
Key Sponsor/FDA Interactions Related to KEYNOTE-859

Date	Regulatory Interaction/Outcome
27-JUL-2018	Submission of new protocol KEYNOTE-859 for 1L HER2 negative gastric cancer.
17-OCT-2018	FDA provided feedback on the initial protocol for KEYNOTE-859. FDA agreed with the study design, provided comments on the required magnitude of benefit and timing of analysis of PFS to support a regulatory approval, and provided content and format recommendations for a future sBLA submission based on the results of the study.
17-Dec-2019	Submission of KEYNOTE-859 amendment 02 which added the CPS ≥10 cut-point to the statistical plan and increased sample size.
17-JAN-2020	Received FDA Type C Meeting Written Response Only (WRO) feedback regarding KEYNOTE-859 amendment 02. FDA agreed with the proposed increase in study size in amendment 02 to power the study for primary hypotheses in the CPS ≥10 population and with the Sponsor's proposal to re-test slides at CPS ≥10 from patients enrolled prior to implementation of the amendment. FDA also provided recommendations for sensitivity analyses to include with an eventual sBLA to account for any imbalances or bias introduced by these changes.
25-JAN-2023	Preliminary FDA comments were received for a pre-sBLA Type B meeting to discuss a filing based on KEYNOTE-859. FDA indicated that the results from the KEYNOTE-859 interim analysis are adequate to support the filing of an sBLA and that the indication statement and the intended population will ultimately be determined based on the benefit:risk assessment at the time of review.
16-FEB-2023	Submission of KEYNOTE-859 sBLA.
14-NOV-2023	FDA approved KEYTRUDA, in combination with fluoropyrimidine- and platinum-containing chemotherapy, is indicated for the 1L treatment of adults with locally advanced unresectable or metastatic HER2-negative gastric or gastroesophageal junction (GEJ) adenocarcinoma.

1L=first-line; CPS=combined positive score; HER2=human epidermal growth factor receptor 2; PFS=progression-free survival; sBLA=supplemental Biologics License Application.

8.1.3 KEYNOTE-859: Disposition, Demographics, and Baseline Characteristics

All Participants	
[Appendix Table 3]	Participant Characteristics; (ITT Population)
Participants with PD-L1 (CPS ≥1)	
[Appendix Table 4]	Participant Characteristics (ITT Population with CPS ≥1 Participants)
Participants with PD-L1 (CPS ≥10)	
[Appendix Table 5]	Participant Characteristics (ITT Population with CPS ≥10 Participants)

Appendix Table 3
KEYNOTE-859: Participant Characteristics (ITT Population)

	Pembrolizumab + Chemotherapy		Chemotherapy		Total	
	n	(%)	n	(%)	n	(%)
Participants in population	790		789		1,579	
Sex						
Male	527	(66.7)	544	(68.9)	1,071	(67.8)
Female	263	(33.3)	245	(31.1)	508	(32.2)
Age Category 1 (Years)						
< 65	486	(61.5)	479	(60.7)	965	(61.1)
>= 65	304	(38.5)	310	(39.3)	614	(38.9)
Mean	59.3		60.0		59.6	
SD	11.9		11.8		11.8	
Median	61.0		62.0		62.0	
Range	23 to 86		21 to 85		21 to 86	
Age Category 2 (Years)						
< 65	486	(61.5)	479	(60.7)	965	(61.1)
>= 65 to <75	247	(31.3)	250	(31.7)	497	(31.5)
>= 75 to <85	55	(7.0)	59	(7.5)	114	(7.2)
>= 85	2	(0.3)	1	(0.1)	3	(0.2)
Age Category 3 (Years)						
18-39	57	(7.2)	49	(6.2)	106	(6.7)
40-49	102	(12.9)	99	(12.5)	201	(12.7)
50-59	184	(23.3)	186	(23.6)	370	(23.4)
60-69	302	(38.2)	284	(36.0)	586	(37.1)
70-79	132	(16.7)	152	(19.3)	284	(18.0)
>=80	13	(1.6)	19	(2.4)	32	(2.0)
Race						
American Indian Or Alaska Native	31	(3.9)	36	(4.6)	67	(4.2)
Asian	270	(34.2)	269	(34.1)	539	(34.1)
Black Or African American	12	(1.5)	9	(1.1)	21	(1.3)
Multiple	43	(5.4)	30	(3.8)	73	(4.6)
Native Hawaiian Or Other Pacific Islander	1	(0.1)	2	(0.3)	3	(0.2)
White	426	(53.9)	435	(55.1)	861	(54.5)
Missing	7	(0.9)	8	(1.0)	15	(0.9)

KEYNOTE-859: Participant Characteristics (ITT Population)

	Pembrolizumab + Chemotherapy		Chemotherapy		Total	
	n	(%)	n	(%)	n	(%)
Ethnicity						
Hispanic Or Latino	175	(22.2)	157	(19.9)	332	(21.0)
Not Hispanic Or Latino	590	(74.7)	615	(77.9)	1,205	(76.3)
Not Reported	14	(1.8)	14	(1.8)	28	(1.8)
Unknown	7	(0.9)	3	(0.4)	10	(0.6)
Missing	4	(0.5)	0	(0.0)	4	(0.3)
Geographic Region for Randomization						
Western Europe/Israel/North America/Australia	201	(25.4)	202	(25.6)	403	(25.5)
Asia	263	(33.3)	262	(33.2)	525	(33.2)
Rest of the World	326	(41.3)	325	(41.2)	651	(41.2)
Combination Chemotherapy for Randomization						
CAPOX	682	(86.3)	681	(86.3)	1,363	(86.3)
FP	108	(13.7)	108	(13.7)	216	(13.7)
PD-L1 Status for Randomization						
CPS >= 1	619	(78.4)	616	(78.1)	1,235	(78.2)
CPS < 1	171	(21.6)	173	(21.9)	344	(21.8)
Baseline PD-L1 Status (CPS Cut Point: 1)						
CPS >= 1	618	(78.2)	617	(78.2)	1,235	(78.2)
CPS < 1	172	(21.8)	172	(21.8)	344	(21.8)
Baseline PD-L1 Status (CPS Cut Point: 10)						
CPS >= 10	279	(35.3)	272	(34.5)	551	(34.9)
CPS < 10	509	(64.4)	517	(65.5)	1,026	(65.0)
Missing	2	(0.3)	0	(0.0)	2	(0.1)
MSI Status						
MSI-High	39	(4.9)	35	(4.4)	74	(4.7)
non-MSI-High	641	(81.1)	639	(81.0)	1,280	(81.1)
Unknown	0	(0.0)	1	(0.1)	1	(0.1)
Missing	110	(13.9)	114	(14.4)	224	(14.2)
ECOG Performance Scale						

KEYNOTE-859: Participant Characteristics (ITT Population)

	Pembrolizumab + Chemotherapy		Chemotherapy		Total	
	n	(%)	n	(%)	n	(%)
0	281	(35.6)	301	(38.1)	582	(36.9)
1	509	(64.4)	488	(61.9)	997	(63.1)
Primary Location						
Adenocarcinoma of the gastroesophageal junction	149	(18.9)	185	(23.4)	334	(21.2)
Adenocarcinoma of the stomach	640	(81.0)	603	(76.4)	1,243	(78.7)
Other	0	(0.0)	1	(0.1)	1	(0.1)
Missing	1	(0.1)	0	(0.0)	1	(0.1)
Overall Stage						
IIA	0	(0.0)	1	(0.1)	1	(0.1)
IIB	0	(0.0)	2	(0.3)	2	(0.1)
IIIA	2	(0.3)	9	(1.1)	11	(0.7)
IIIB	11	(1.4)	10	(1.3)	21	(1.3)
IIIC	9	(1.1)	5	(0.6)	14	(0.9)
IV	767	(97.1)	762	(96.6)	1,529	(96.8)
Missing	1	(0.1)	0	(0.0)	1	(0.1)
Disease Status						
Locally advanced	28	(3.5)	30	(3.8)	58	(3.7)
Metastatic	761	(96.3)	759	(96.2)	1,520	(96.3)
Missing	1	(0.1)	0	(0.0)	1	(0.1)
Histological Subtype (Lauren classification)						
Diffuse	318	(40.3)	301	(38.1)	619	(39.2)
Intestinal	284	(35.9)	273	(34.6)	557	(35.3)
Indeterminate	186	(23.5)	215	(27.2)	401	(25.4)
Unknown	1	(0.1)	0	(0.0)	1	(0.1)
Missing	1	(0.1)	0	(0.0)	1	(0.1)
Number of Metastasis						
0-2	438	(55.4)	421	(53.4)	859	(54.4)
>=3	351	(44.4)	368	(46.6)	719	(45.5)
Missing	1	(0.1)	0	(0.0)	1	(0.1)
Tumor Burden						
>= Median	387	(49.0)	357	(45.2)	744	(47.1)

KEYNOTE-859: Participant Characteristics (ITT Population)

	Pembrolizumab + Chemotherapy		Chemotherapy		Total	
	n	(%)	n	(%)	n	(%)
< Median	358	(45.3)	384	(48.7)	742	(47.0)
Missing	45	(5.7)	48	(6.1)	93	(5.9)
Liver Metastases						
Yes	314	(39.7)	311	(39.4)	625	(39.6)
No	475	(60.1)	478	(60.6)	953	(60.4)
Missing	1	(0.1)	0	(0.0)	1	(0.1)
Prior Gastrectomy/Esophagectomy						
Yes	172	(21.8)	162	(20.5)	334	(21.2)
No	613	(77.6)	622	(78.8)	1,235	(78.2)
Missing	5	(0.6)	5	(0.6)	10	(0.6)

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

Source: [P859V01MK3475: adam-adsl; adbase]

Appendix Table 4
KEYNOTE-859: Participant Characteristics
(ITT Population with CPS>=1)

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

KEYNOTE-859: Participant Characteristics (ITT Population with CPS>=1)

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

KEYNOTE-859: Participant Characteristics (ITT Population with CPS>=1)

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

KEYNOTE-859: Participant Characteristics (ITT Population with CPS>=1)

	Pembrolizumab + Chemotherapy		Chemotherapy		Total	
	n	(%)	n	(%)	n	(%)
No	359	(58.1)	364	(59.0)	723	(58.5)
Missing	1	(0.2)	0	(0.0)	1	(0.1)
Prior Gastrectomy/Esophagectomy						
Yes	109	(17.6)	105	(17.0)	214	(17.3)
No	506	(81.9)	508	(82.3)	1,014	(82.1)
Missing	3	(0.5)	4	(0.6)	7	(0.6)

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

Source: [P859V01MK3475: adam-adsl; adbase]

Appendix Table 5
KEYNOTE-859: Participant Characteristics
(ITT Population with CPS>=10)

	Pembrolizumab + Chemotherapy		Chemotherapy		Total	
	n	(%)	n	(%)	n	(%)
Participants in population	279		272		551	
Sex						
Male	193	(69.2)	205	(75.4)	398	(72.2)
Female	86	(30.8)	67	(24.6)	153	(27.8)
Age Category 1 (Years)						
< 65	161	(57.7)	159	(58.5)	320	(58.1)
>= 65	118	(42.3)	113	(41.5)	231	(41.9)
Mean	60.6		60.8		60.7	
SD	11.6		11.1		11.3	
Median	63.0		63.0		63.0	
Range	26 to 84		25 to 82		25 to 84	
Age Category 2 (Years)						
< 65	161	(57.7)	159	(58.5)	320	(58.1)
>= 65 to <75	96	(34.4)	92	(33.8)	188	(34.1)
>= 75 to <85	22	(7.9)	21	(7.7)	43	(7.8)
Age Category 3 (Years)						
18-39	16	(5.7)	12	(4.4)	28	(5.1)
40-49	30	(10.8)	35	(12.9)	65	(11.8)
50-59	68	(24.4)	61	(22.4)	129	(23.4)
60-69	99	(35.5)	104	(38.2)	203	(36.8)
70-79	61	(21.9)	54	(19.9)	115	(20.9)
>=80	5	(1.8)	6	(2.2)	11	(2.0)
Race						
American Indian Or Alaska Native	7	(2.5)	11	(4.0)	18	(3.3)
Asian	98	(35.1)	89	(32.7)	187	(33.9)
Black Or African American	2	(0.7)	5	(1.8)	7	(1.3)
Multiple	16	(5.7)	8	(2.9)	24	(4.4)
Native Hawaiian Or Other Pacific Islander	1	(0.4)	0	(0.0)	1	(0.2)
White	155	(55.6)	157	(57.7)	312	(56.6)
Missing	0	(0.0)	2	(0.7)	2	(0.4)
Ethnicity						

KEYNOTE-859: Participant Characteristics (ITT Population with CPS>=10)

	Pembrolizumab + Chemotherapy		Chemotherapy		Total	
	n	(%)	n	(%)	n	(%)
Hispanic Or Latino	59	(21.1)	51	(18.8)	110	(20.0)
Not Hispanic Or Latino	211	(75.6)	215	(79.0)	426	(77.3)
Not Reported	6	(2.2)	5	(1.8)	11	(2.0)
Unknown	3	(1.1)	1	(0.4)	4	(0.7)
Geographic Region for Randomization						
Western Europe/Israel/North America/Australia	78	(28.0)	64	(23.5)	142	(25.8)
Asia	96	(34.4)	88	(32.4)	184	(33.4)
Rest of the World	105	(37.6)	120	(44.1)	225	(40.8)
Combination Chemotherapy for Randomization						
CAPOX	242	(86.7)	235	(86.4)	477	(86.6)
FP	37	(13.3)	37	(13.6)	74	(13.4)
PD-L1 Status for Randomization						
CPS >= 1	279	(100.0)	271	(99.6)	550	(99.8)
CPS < 1	0	(0.0)	1	(0.4)	1	(0.2)
MSI Status						
MSI-High	20	(7.2)	16	(5.9)	36	(6.5)
non-MSI-High	227	(81.4)	224	(82.4)	451	(81.9)
Unknown	0	(0.0)	1	(0.4)	1	(0.2)
Missing	32	(11.5)	31	(11.4)	63	(11.4)
ECOG Performance Scale						
0	99	(35.5)	103	(37.9)	202	(36.7)
1	180	(64.5)	169	(62.1)	349	(63.3)
Primary Location						
Adenocarcinoma of the gastroesophageal junction	65	(23.3)	73	(26.8)	138	(25.0)
Adenocarcinoma of the stomach	214	(76.7)	199	(73.2)	413	(75.0)
Overall Stage						
IIA	0	(0.0)	1	(0.4)	1	(0.2)
IIB	0	(0.0)	2	(0.7)	2	(0.4)
IIIA	2	(0.7)	3	(1.1)	5	(0.9)

KEYNOTE-859: Participant Characteristics (ITT Population with CPS>=10)

	Pembrolizumab + Chemotherapy		Chemotherapy		Total	
	n	(%)	n	(%)	n	(%)
IIIB	8	(2.9)	2	(0.7)	10	(1.8)
IIIC	4	(1.4)	2	(0.7)	6	(1.1)
IV	265	(95.0)	262	(96.3)	527	(95.6)
Disease Status						
Locally advanced	14	(5.0)	11	(4.0)	25	(4.5)
Metastatic	265	(95.0)	261	(96.0)	526	(95.5)
Histological Subtype (Lauren classification)						
Diffuse	102	(36.6)	89	(32.7)	191	(34.7)
Intestinal	111	(39.8)	99	(36.4)	210	(38.1)
Indeterminate	65	(23.3)	84	(30.9)	149	(27.0)
Unknown	1	(0.4)	0	(0.0)	1	(0.2)
Number of Metastasis						
0-2	151	(54.1)	144	(52.9)	295	(53.5)
>=3	128	(45.9)	128	(47.1)	256	(46.5)
Tumor Burden						
>= Median	141	(50.5)	127	(46.7)	268	(48.6)
< Median	127	(45.5)	131	(48.2)	258	(46.8)
Missing	11	(3.9)	14	(5.1)	25	(4.5)
Liver Metastases						
Yes	119	(42.7)	110	(40.4)	229	(41.6)
No	160	(57.3)	162	(59.6)	322	(58.4)
Prior Gastrectomy/Esophagectomy						
Yes	48	(17.2)	40	(14.7)	88	(16.0)
No	231	(82.8)	231	(84.9)	462	(83.8)
Missing	0	(0.0)	1	(0.4)	1	(0.2)

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

Source: [P859V01MK3475: adam-adsl; adbase]

8.1.4 KEYNOTE-859: Efficacy

8.1.4.1 Overall Survival

All Participants	
[Appendix Table 6]	Analysis of Overall Survival; (ITT Population)
Participants with PD-L1 (CPS ≥1)	
[Appendix Table 7]	Analysis of Overall Survival; (ITT Population with CPS ≥1)
[Appendix Figure 3]	Kaplan-Meier Plot of Overall Survival; (ITT Population with CPS>=1)
Participants with PD-L1 (CPS ≥10)	
[Appendix Table 8]	Analysis of Overall Survival; (ITT Population with CPS ≥10)
[Appendix Figure 4]	Kaplan-Meier Plot of Overall Survival; (ITT Population with CPS>=10)
Exploratory Analyses	
[Appendix Table 9]	KEYNOTE-859: Exploratory Analysis of Overall Survival by CPS Cut-point (ITT Population; Data Cutoff 03-OCT-2022)

Appendix Table 6
KEYNOTE-859: Analysis of Overall Survival
(ITT Population)

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

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

[b] Based on Cox regression model with Efron's method of tie handling with treatment as a covariate stratified by Geographic region (Western Europe/Israel/North America/Australia, Asia and Rest of the World), PD-L1 status (CPS<1 vs. CPS>=1), and Chemotherapy regimen (FP or CAPOX) with small strata collapsed as pre-specified in the sSAP.

[c] One-sided p-value based on log-rank test stratified by Geographic region (Western Europe/Israel/North America/Australia, Asia and Rest of the World), PD-L1 status (CPS<1 vs. CPS>=1), and Chemotherapy regimen (FP or CAPOX) with small strata collapsed as pre-specified in the sSAP.

Western Europe includes France, Germany, Spain, Italy, United Kingdom, Ireland, Switzerland, Czech Republic, Denmark and Hungary, which is consistent with the 'Europe' region defined in the protocol for stratification.

Database Cutoff Date: 03OCT2022

Source: [P859V01MK3475: adam-adsl; adtte]

Appendix Table 7
KEYNOTE-859: Analysis of Overall Survival
(ITT Population with CPS>=1)

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

[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) and Chemotherapy regimen (FP or CAPOX) with small strata collapsed as pre-specified in the sSAP.

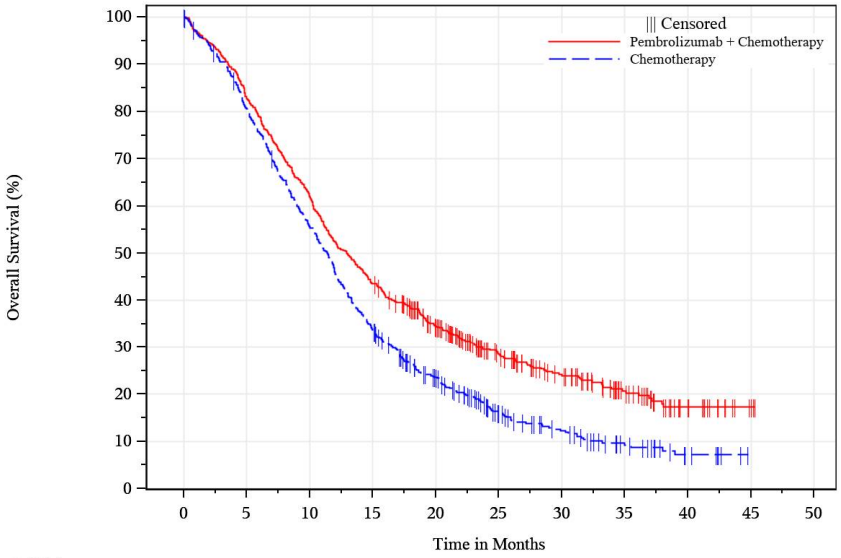
[c] One-sided p-value based on log-rank test stratified by Geographic region (Western Europe/Israel/North America/Australia, Asia and Rest of the World) and Chemotherapy regimen (FP or CAPOX) with small strata collapsed as pre-specified in the sSAP.

Western Europe includes France, Germany, Spain, Italy, United Kingdom, Ireland, Switzerland, Czech Republic, Denmark and Hungary, which is consistent with the 'Europe' region defined in the protocol for stratification.

Database Cutoff Date: 03OCT2022

Source: [P859V01MK3475: adam-adsl; adtte]

Appendix Figure 3
KEYNOTE-859: Kaplan-Meier Plot of Overall Survival
(ITT Population with CPS>=1)



At Risk

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

Database Cutoff Date: 03OCT2022

Source: [P859V01MK3475: adam-adsl; adtte]

Appendix Table 8
KEYNOTE-859: Analysis of Overall Survival
(ITT Population with CPS>=10)

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

[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) and Chemotherapy regimen (FP or CAPOX) with small strata collapsed as pre-specified in the sSAP.

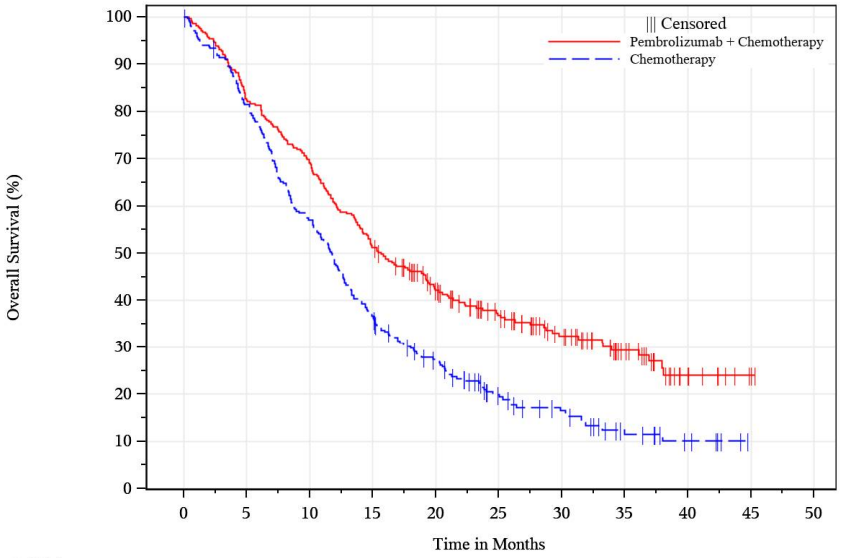
[c] One-sided p-value based on log-rank test stratified by Geographic region (Western Europe/Israel/North America/Australia, Asia and Rest of the World) and Chemotherapy regimen (FP or CAPOX) with small strata collapsed as pre-specified in the sSAP.

Western Europe includes France, Germany, Spain, Italy, United Kingdom, Ireland, Switzerland, Czech Republic, Denmark and Hungary, which is consistent with the 'Europe' region defined in the protocol for stratification.

Database Cutoff Date: 03OCT2022

Source: [P859V01MK3475: adam-adsl; adtte]

Appendix Figure 4
KEYNOTE-859: Kaplan-Meier Plot of Overall Survival
(ITT Population with CPS>=10)



At Risk

Pembrolizumab + Chemotherapy	279	230	193	143	104	76	52	30	10	2	0
Chemotherapy	272	220	154	99	67	37	26	12	6	0	0

Database Cutoff Date: 03OCT2022

Source: [P859V01MK3475: adam-adsl; adtte]

Appendix Table 9
KEYNOTE-859: Exploratory Analysis of Overall Survival by CPS Cut-point
(ITT Population; Data Cutoff 03-OCT-2022)

Baseline PD-L1 Status[a]	Number of Participants		Number of Deaths		Median OS (95% CI)		Hazard Ratio[b]		
	Pembro + Chemo	Chemo	Pembro + Chemo	Chemo	Pembro + Chemo	Chemo	HR	95% CI of HR	SE of log(HR)
ITT	790	789	603	666	12.9 (11.9, 14.0)	11.5 (10.6, 12.1)	0.777	0.695, 0.868	0.057
CPS <1	172	172	139	140	12.7 (11.4, 15.0)	12.2 (9.5, 14.0)	0.929	0.732, 1.177	0.121
CPS 1 - <5	228	224	187	197	11.5 (10.3, 13.3)	11.0 (9.7, 12.0)	0.786	0.641, 0.963	0.104
CPS <5	400	396	326	337	12.0 (11.1, 13.5)	11.4 (10.0, 12.2)	0.842	0.721, 0.983	0.079
CPS 1 - <10	339	345	276	300	11.1 (10.2, 12.2)	10.9 (9.9, 12.0)	0.833	0.706, 0.982	0.084
CPS 5 - <10	111	121	89	103	10.3 (8.2, 12.2)	10.7 (9.5, 13.0)	0.966	0.723, 1.290	0.148
CPS <10	511	517	415	440	11.7 (10.7, 12.8)	11.2 (10.0, 12.1)	0.862	0.753, 0.987	0.069
CPS ≥1	618	617	464	526	13.0 (11.6, 14.2)	11.4 (10.5, 12.0)	0.739	0.652, 0.838	0.064
CPS ≥5	390	393	277	329	14.0 (12.1, 15.4)	11.5 (10.3, 12.5)	0.715	0.609, 0.840	0.082
CPS ≥10	279	272	188	226	15.7 (13.8, 19.3)	11.8 (10.3, 12.7)	0.647	0.532, 0.787	0.100

chemo=chemotherapy; CI=confidence interval; CPS=combined positive score; HR=hazard ratio; ITT=intent-to-treat; OS=overall survival; PD-L1=programmed death-ligand 1; pembro=pembrolizumab; SE=standard error; sSAP=supplemental statistical analysis plan.

a. Data analyses at CPS ≥1 and CPS ≥10 were pre-specified, and data collected at the validated CPS ≥1 and CPS ≥10 cut-points were used for analyses. Remaining analyses at other CPS cut-points were not pre-specified and CPS raw scores were used in addition to CPS ≥10 cut-point information to ensure mutual exclusivity.

b. HR was based on a Cox regression model with Efron's method of tie handling with treatment as a covariate stratified by stratification factors for randomization with small strata collapsed as pre-specified in sSAP. The pooled stratification variables used are ADSL.STRATAP for ITT, CPS <5, and CPS <10 subgroups, and ADSL.STRATA1 for the rest of the subgroups.

Database cutoff date: 03OCT2022

8.1.4.2 Progression-free Survival

All Participants	
[Appendix Table 10]	Analysis of Progression-Free Survival (Primary Analysis) Based on BICR Assessment per RECIST 1.1; (ITT Population)
Participants with PD-L1 (CPS ≥1)	
[Appendix Table 11]	Analysis of Progression-Free Survival (Primary Analysis) Based on BICR Assessment per RECIST 1.1; (ITT Population with CPS ≥1)
Participants with PD-L1 (CPS ≥10)	
[Appendix Table 12]	Analysis of Progression-Free Survival (Primary Analysis) Based on BICR Assessment per RECIST 1.1; (ITT Population with CPS ≥10)
Exploratory Analysis	
[Appendix Table 13]	KEYNOTE-859: Exploratory Analysis of Progression-free Survival by CPS Cut-point; Based on BICR Assessment per RECIST 1.1; (ITT Population; Data Cutoff 03-OCT-2022)

Appendix Table 10
KEYNOTE-859: Analysis of Progression-Free Survival (Primary Analysis) Based on BICR Assessment per RECIST 1.1
(ITT Population)

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

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

[b] Based on Cox regression model with Efron's method of tie handling with treatment as a covariate stratified by Geographic region (Western Europe/Israel/North America/Australia, Asia and Rest of the World), PD-L1 status (CPS<1 vs. CPS>=1), and Chemotherapy regimen (FP or CAPOX) with small strata collapsed as pre-specified in the sSAP.

[c] One-sided p-value based on log-rank test stratified by Geographic region (Western Europe/Israel/North America/Australia, Asia and Rest of the World), PD-L1 status (CPS<1 vs. CPS>=1), and Chemotherapy regimen (FP or CAPOX) with small strata collapsed as pre-specified in the sSAP.

Western Europe includes France, Germany, Spain, Italy, United Kingdom, Ireland, Switzerland, Czech Republic, Denmark and Hungary, which is consistent with the 'Europe' region defined in the protocol for stratification.

Database Cutoff Date: 03OCT2022

Source: [P859V01MK3475: adam-adsl; adtte]

Appendix Table 11
KEYNOTE-859: Analysis of Progression-Free Survival (Primary Analysis) Based on BICR Assessment per RECIST 1.1
(ITT Population with CPS>=1)

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

[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) 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) and Chemotherapy regimen (FP or CAPOX) with small strata collapsed as pre-specified in the sSAP.

Western Europe includes France, Germany, Spain, Italy, United Kingdom, Ireland, Switzerland, Czech Republic, Denmark and Hungary, which is consistent with the 'Europe' region defined in the protocol for stratification.

Database Cutoff Date: 03OCT2022

Source: [P859V01MK3475: adam-adsl; adtte]

Appendix Table 12
KEYNOTE-859: Analysis of Progression-Free Survival (Primary Analysis) Based on BICR Assessment per RECIST 1.1
(ITT Population with CPS>=10)

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

[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) 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) and Chemotherapy regimen (FP or CAPOX) with small strata collapsed as pre-specified in the sSAP.

Western Europe includes France, Germany, Spain, Italy, United Kingdom, Ireland, Switzerland, Czech Republic, Denmark and Hungary, which is consistent with the 'Europe' region defined in the protocol for stratification.

Database Cutoff Date: 03OCT2022

Source: [P859V01MK3475: adam-adsl; adtte]

Appendix Table 13
KEYNOTE-859: Exploratory Analysis of Progression-free Survival by CPS Cut-point
Based on BICR Assessment per RECIST 1.1
(ITT Population; Data Cutoff 03-OCT-2022)

Baseline PD-L1 Status[a]	Number of Participants		Number of Events		Median PFS[b] (95% CI)		Hazard Ratio[c]		
	Pembro + Chemo	Chemo	Pembro + Chemo	Chemo	Pembro + Chemo	Chemo	HR	95% CI of HR	SE of log(HR)
ITT	790	789	572	608	6.9 (6.3, 7.2)	5.6 (5.5, 5.7)	0.758	0.675, 0.850	0.059
CPS <1	172	172	129	125	7.2 (6.0, 8.5)	5.8 (5.4, 6.9)	0.897	0.701, 1.149	0.126
CPS 1 - <5	228	224	173	179	6.7 (5.6, 7.1)	5.6 (5.2, 5.7)	0.788	0.637, 0.975	0.109
CPS <5	400	396	302	304	6.9 (5.8, 7.2)	5.6 (5.5, 5.8)	0.832	0.708, 0.978	0.082
CPS 1 - <10	339	345	253	273	5.8 (5.6, 7.0)	5.6 (5.3, 5.7)	0.831	0.699, 0.989	0.088
CPS 5 - <10	111	121	80	94	5.7 (4.3, 7.3)	5.6 (4.6, 6.9)	0.953	0.704, 1.291	0.155
CPS <10	511	517	382	398	6.8 (5.7, 7.1)	5.6 (5.5, 5.8)	0.852	0.739, 0.982	0.072
CPS ≥1	618	617	443	483	6.9 (6.0, 7.2)	5.6 (5.4, 5.7)	0.723	0.634, 0.824	0.067
CPS ≥5	390	393	270	304	7.1 (6.1, 8.3)	5.6 (5.4, 5.9)	0.695	0.588, 0.822	0.085
CPS ≥10	279	272	190	210	8.1 (6.8, 8.5)	5.6 (5.4, 6.7)	0.620	0.506, 0.759	0.103

BICR=blinded independent central review; chemo=chemotherapy; CI=confidence interval; CPS=combined positive score; HR=hazard ratio; ITT=intent-to-treat; PD-L1=programmed death-ligand 1; pembro=pembrolizumab; PFS=progression-free survival; SE=standard error; sSAP=supplemental statistical analysis plan.

a. Data analyses at CPS ≥1 and CPS ≥10 were pre-specified, and data collected at the validated CPS ≥1 and CPS ≥10 cut-points were used for analyses. Remaining analyses at other CPS cut-points were not pre-specified and CPS raw scores were used in addition to CPS ≥10 cut-point information to ensure mutual exclusivity
b. Determined by Blinded Independent Central Review.
c. HR was based on a Cox regression model with Efron's method of tie handling with treatment as a covariate stratified by stratification factors for randomization with small strata collapsed as pre-specified in sSAP. The pooled stratification variables used are ADSL.STRATAP for ITT, CPS <5, and CPS <10 subgroups, and ADSL.STRATA1 for the rest of the subgroups.

Database cutoff date: 03OCT2022

8.1.4.3 Objective Response Rate and Duration of Response

All Participants	
[Appendix Table 14]	Analysis of Objective Response (Confirmed) Based on BICR Assessment per RECIST 1.1 (ITT Population)
Participants with PD-L1 (CPS ≥1)	
[Appendix Table 15]	Analysis of Objective Response (Confirmed) Based on BICR Assessment per RECIST 1.1 (ITT Population with CPS ≥1)
Participants with PD-L1 (CPS ≥10)	
[Appendix Table 16]	Analysis of Objective Response (Confirmed) Based on BICR Assessment per RECIST 1.1 (ITT Population with CPS ≥10)

Appendix Table 14
KEYNOTE-859: Analysis of Objective Response (Confirmed) Based on BICR Assessment per RECIST 1.1 (ITT Population)

Treatment	N	Number of Objective Responses	Objective Response Rate (%) (95% CI)	Difference in % Pembrolizumab + Chemotherapy vs. Chemotherapy	
				Estimate (95% CI)[a]	p-Value[b]
Pembrolizumab + Chemotherapy	790	405	51.3 (47.7, 54.8)	9.3 (4.4, 14.1)	0.00009
Chemotherapy	789	331	42.0 (38.5, 45.5)		

[a] Based on Miettinen & Nurminen method stratified by Geographic region (Western Europe/Israel/North America/Australia, Asia and Rest of the World), PD-L1 status (CPS<1 vs. CPS>=1) and Chemotherapy regimen (FP or CAPOX) with small strata collapsed as pre-specified in the sSAP.

Western Europe includes France, Germany, Spain, Italy, United Kingdom, Ireland, Switzerland, Czech Republic, Denmark and Hungary, which is consistent with the 'Europe' region defined in the protocol for stratification.

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

Responses are based on BICR assessment per RECIST 1.1.

BICR = Blinded Independent Central Review.

Database Cutoff Date: 03OCT2022

Source: [P859V01MK3475: adam-adsl; adrs]

Appendix Table 15
KEYNOTE-859: Analysis of Objective Response (Confirmed) Based on BICR Assessment per RECIST 1.1 (ITT Population with CPS>=1)

Treatment	N	Number of Objective Responses	Objective Response Rate (%) (95% CI)	Difference in % Pembrolizumab + Chemotherapy vs. Chemotherapy	
				Estimate (95% CI)[a]	p-Value[b]
Pembrolizumab + Chemotherapy	618	322	52.1 (48.1, 56.1)	9.5 (3.9, 15.0)	0.00041
Chemotherapy	617	263	42.6 (38.7, 46.6)		

[a] Based on Miettinen & Nurminen method stratified by Geographic region (Western Europe/Israel/North America/Australia, Asia and Rest of the World) and Chemotherapy regimen (FP or CAPOX) with small strata collapsed as pre-specified in the sSAP.

Western Europe includes France, Germany, Spain, Italy, United Kingdom, Ireland, Switzerland, Czech Republic, Denmark and Hungary, which is consistent with the 'Europe' region defined in the protocol for stratification.

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

Responses are based on BICR assessment per RECIST 1.1.

BICR = Blinded Independent Central Review.

Database Cutoff Date: 03OCT2022

Source: [P859V01MK3475: adam-adsl; adrs]

Appendix Table 16
KEYNOTE-859: Analysis of Objective Response (Confirmed) Based on BICR Assessment per RECIST 1.1 (ITT Population with CPS>=10)

Treatment	N	Number of Objective Responses	Objective Response Rate (%) (95% CI)	Difference in % Pembrolizumab + Chemotherapy vs. Chemotherapy	
				Estimate (95% CI)[a]	p-Value[b]
Pembrolizumab + Chemotherapy	279	169	60.6 (54.6, 66.3)	17.5 (9.3, 25.5)	0.00002
Chemotherapy	272	117	43.0 (37.1, 49.1)		

[a] Based on Miettinen & Nurminen method stratified by Geographic region (Western Europe/Israel/North America/Australia, Asia and Rest of the World) and Chemotherapy regimen (FP or CAPOX) with small strata collapsed as pre-specified in the sSAP.

Western Europe includes France, Germany, Spain, Italy, United Kingdom, Ireland, Switzerland, Czech Republic, Denmark and Hungary, which is consistent with the 'Europe' region defined in the protocol for stratification.

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

Responses are based on BICR assessment per RECIST 1.1.

BICR = Blinded Independent Central Review.

Database Cutoff Date: 03OCT2022

Source: [P859V01MK3475: adam-adsl; adrs]

8.2 KEYNOTE-811

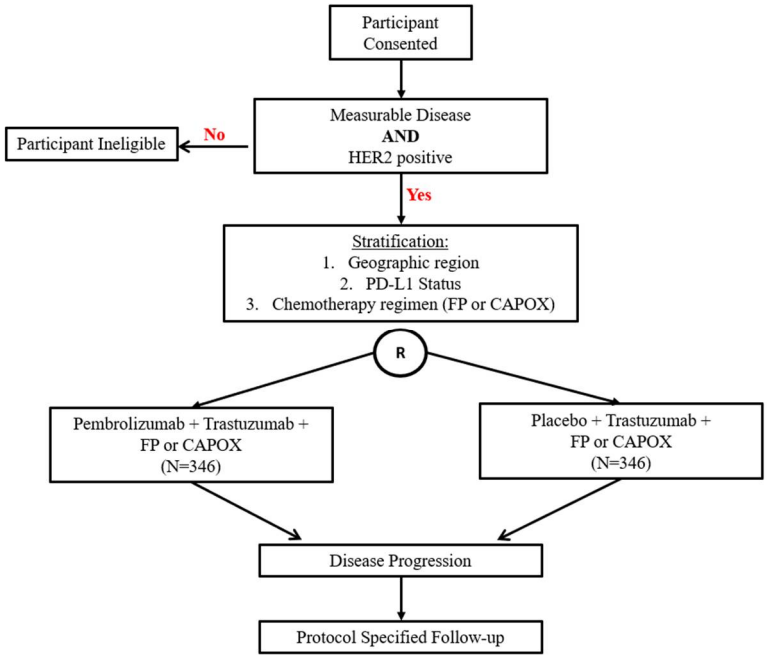
8.2.1 KEYNOTE-811: Study Design

KEYNOTE-811 is an ongoing, Phase 3, randomized, placebo-controlled, double-blind study designed to assess pembrolizumab in combination with trastuzumab plus chemotherapy as 1L treatment in participants with HER2-positive advanced gastric or GEJ adenocarcinoma [Appendix Figure 5]. There were 698 participants randomized in a 1:1 ratio to receive:

- Pembrolizumab plus SOC (n=350)
- Placebo plus SOC (hereafter referred to as SOC; n=348)

The investigators had 2 chemotherapy regimen choices, FP or CAPOX, which had to be chosen before randomization in the study. Treatment randomization for the Global Cohort was stratified by geographic region (Europe/Israel/North America/Australia vs Asia vs rest of world), PD-L1 status (CPS ≥1 vs CPS <1), and chemotherapy regimen (FP vs CAPOX). KEYNOTE-811 was developed based on 2 investigator-initiated studies that showed the promise of adding pembrolizumab to trastuzumab and chemotherapy [28] [29]. In these studies, there was no evidence of increased efficacy by PD-L1 status; therefore, KEYNOTE-811 was designed to test the effect of adding pembrolizumab to SOC in the ITT population [Sec. 8.2.1.1]. PD-L1 status (CPS ≥1 [positive] and CPS <1 [negative]) was included as a stratification factor to ensure balanced baseline characteristics if differences in efficacy based on PD-L1 expression were to be observed in the study, as seen in previous HER2-negative gastric cancer studies with pembrolizumab monotherapy [19].

Appendix Figure 5
Study Design for KEYNOTE-811 – Global Cohort



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

8.2.1.1 Statistical Methods

The dual primary efficacy endpoints are PFS per RECIST 1.1 assessed by BICR and OS. PFS is defined as the time from randomization to the first documented disease progression per RECIST 1.1 by BICR or death due to any cause, whichever occurs first. OS is defined as the time from randomization to death due to any cause.

The key secondary endpoint is ORR per RECIST 1.1. ORR is defined as the proportion of participants who have confirmed CR or PR.

The timing, criteria, and decision guidance for the 3 IAs and FA are provided in [Appendix Table 17].

The non-parametric KM method was used to estimate the PFS and OS curves. The treatment difference in PFS and OS was assessed by the stratified log-rank test. A stratified Cox proportional hazard model with Efron's method of tie handling was used to assess the magnitude of the treatment difference (ie, the HR). The HR and its 95% CI from the Cox model, with Efron's method of tie handling and with a single treatment covariate, was reported. The stratification factors used for randomization were applied to both the stratified log-rank test and the stratified Cox model. The graphical method of Maurer and Bretz [59] was applied to provide strong multiplicity control for multiple hypotheses as well as interim

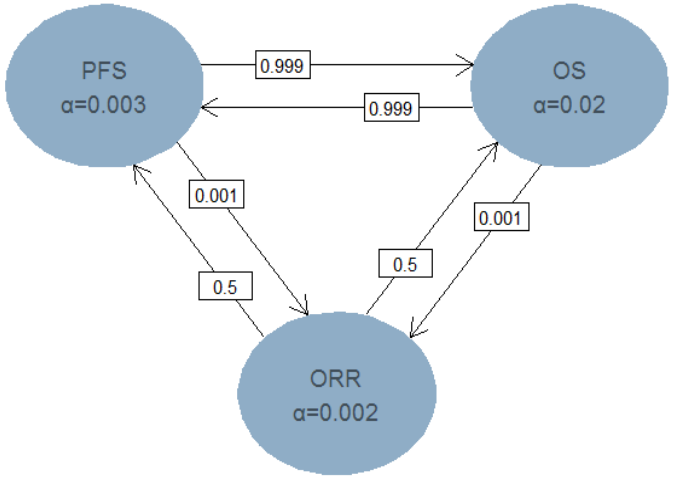
analyses. [Appendix Figure 6] shows the initial one-sided α-allocation for each hypothesis in the ellipse representing the hypotheses.

Appendix Table 17
Timing, Sample Size, and Decision Guidance for KEYNOTE-811 Analyses

Analyses	Timing	Estimated Time After First Participant Randomized	Primary Purpose of Analysis	Data Cutoff Date
IA1	The first 260 participants with opportunity for at least 8.5 months follow-up.	~22.5 months	Efficacy analysis of ORR (hypothesis testing)	17-JUN-2020
IA2[a]	At least 542 PFS events have occurred and ~9 months after the last participant has been randomized.	~37 months	Efficacy analysis for PFS and OS	25-MAY-2022
IA3[a]	At least 18 months after the last participant has been randomized AND at least 606 PFS events have been observed. This is final PFS analysis.	~46 months	Efficacy analysis for PFS and OS	29-MAR-2023
Final Analysis[a]	Final OS analysis to be performed until at least 28 months after the last participant has been randomized AND at least ~551 deaths have occurred.	~56 months	Efficacy analysis for OS	20-MAR-2024

Abbreviations: IA=interim analysis; ORR=objective response rate; OS=overall survival; PFS=progression-free survival.
[a] Note for IA2, IA3, and final analyses, 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.

Appendix Figure 6
Multiplicity Strategy – KEYNOTE-811



Abbreviations: α=alpha; ORR=objective response rate; OS=overall survival; PFS=progression-free survival.

8.2.1.2 Statistical Methods – Q-TWiST Analysis

8.2.1.2.1 EQ-5D Health Utility Weights

The EuroQoL EQ-5D-5L is a standardized instrument for use as a measure of health outcome and will provide data for use in economic models and analyses, including developing health utilities or quality-adjusted life-years. The 5 health state dimensions in this instrument include the following: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Each dimension is rated on a 5-point scale from 1 (no problem) to 5 (extreme problem). The EuroQoL EQ-5D-5L also includes a graded (0 to 100) vertical visual analog scale on which the subject rates his or her general state of health at the time of the assessment. The EuroQoL EQ-5D-5L was completed electronically by participants first, prior to completing any other ePRO.

EQ-5D-5L scores were collected at Cycle 1 to Cycle 5, and then every 2 cycles after Cycle 5 (12 weeks) for up to 35 cycles (about 2 years) or until end of treatment, whichever came first, at time of discontinuation, and at the 30-day post-treatment discontinuation follow-up visit.

Only post-baseline EQ-5D-5L scores are considered in this analysis and are mapped using US algorithm [58]. In case a participant completed multiple EQ-5D questionnaires on the same date, the questionnaire with the latest entry time is considered in the analysis.

A post-baseline EQ-5D assessment is considered to have the progression-free status by the investigator, if it was completed prior to the date of the first documented disease progression per RECIST 1.1 based on investigator assessment or the date of death, or if it was completed no later than the censoring date of PFS. Among these EQ-5D assessments, the ones completed while participants experiencing an AEs whose worst Grade is 3+, are reported under health state TOX, and the corresponding average EQ-5D utility score across treatment

arms is considered as U_{TOX}. The ones completed while participants were without AEs whose worst Grade is 3+ are reported under health state TWiST, and the corresponding average EQ-5D utility score across treatment arms is considered as U_{TWiST}.

The post-baseline EQ-5D score, which was collected at or after the date of the first documented disease progression per RECIST 1.1 based on investigator, is reported under REL health state, and the corresponding average EQ-5D utility score across treatment arms is considered as U_{REL}.

8.2.1.2.2 Overall Survival/ Progression-free Survival /Toxicity

The Kaplan-Meier method is used to estimate the survival curves for OS, PFS, and toxicity (TOX) for the pembrolizumab + SOC arm and the SOC arm.

8.2.1.2.2.1 Restricted Mean Survival Time

RMST is a measure of average survival from time 0 to a specified time point (t*), and this equals to the area under the survival curve S(t) from time 0 to specified time point (t*).

$$\text{RMST}(t^*)=\int_0^{t^*} S(t)dt$$

For each given time point t*, all survival times beyond time point t* are censored at t*, with the KM estimation then using data up to t* to estimate the RMST and its standard error.

RMST is used to perform analysis of OS, TOX, TWiST, REL and Q-TWiST. Maximum follow-up time (63 months) is used as the cutoff timepoint (t*) for the above analysis.

8.2.1.2.2.2 Toxicity (TOX)

The restricted mean duration in Toxicity is derived using RMST, equivalent to the area under the KM curves of TOX over the time interval of [0, 63 months], for each treatment arm. All RMST values are presented in months.

The difference in TOX between the 2 treatment arms and its corresponding 95% CIs are then calculated. The 95% CI of TOX difference is obtained based on 1000 bootstrapped samples, as follows:

1. Draw a bootstrap sample from the original dataset, with replacement. The bootstrap is stratified by treatment arm (pembrolizumab + SOC arm and SOC arm).

2. Estimate the TOX difference of pembrolizumab + SOC arm versus SOC arm for each bootstrapped sample.

3. The 95% CIs of TOX difference are estimated by using the lower 2.5th percentile and the upper 97.5th percentile of the distribution of TOX differences from these 1000 bootstrapped samples.

8.2.1.2.2.3 Time Without Symptoms or Toxicities (TWiST)

The restricted mean duration in TWiST is equivalent to the difference between the area under KM curves of PFS and TOX over the time interval of [0, 63 months], for each treatment arm. All RMST values are presented in months.

8.2.1.2.2.4 Relapse (REL)

The restricted mean duration in REL is equivalent to the difference between the area under KM curves of OS and PFS over the time interval of [0, 63 months], for each treatment arm. All RMST values are presented in months.

8.2.1.2.2.5 EQ-5D Health Utility Weights

The mean, standard error and its 95% CI are presented for EQ-5D utility weights in different health states.

The post-baseline EQ-5D assessments from the same participant are treated as independent, and the correlation within participants is not considered for the EQ-5D utility weights estimation, and consequently may produce CIs that are too narrow. The post-baseline utility weights estimation should be treated with caution.

8.2.1.2.2.6 Quality-adjusted Time Without Symptoms of Disease Progression or Toxicity of Treatment (Q-TWiST)

At the specified timepoint (ie, 63 months), restricted mean Q-TWiST is calculated for each treatment arm using the formula:

$$\text{Q-TWiST} = (\text{TOX} * U_{TOX}) + (\text{TWiST} * U_{TWiST}) + (\text{REL} * U_{REL})$$

With U_{TOX}, U_{TWiST} and U_{REL} denote the utility weight for each health state

8.2.1.2.2.7 Relative Gain in Q-TWiST

At the specified timepoint (ie, 63 months), the relative gain in Q-TWiST for the pembrolizumab + SOC arm versus the SOC arm and its corresponding 95% CIs are provided using the same method as TOX described in [Sec. 8.2.1.2.2.2].

8.2.2 KEYNOTE-811: Regulatory Interactions

Appendix Table 18
Key Sponsor/FDA Interactions Related to KEYNOTE-811

Date	Regulatory Interaction/Outcome
02-MAY-2018	Type B EOP Meeting to discuss the design of KEYNOTE-811. FDA agreed with the overall proposed study design and noted the uncertain relationship between PD-L1 status and treatment outcome. FDA strongly recommended including PD-L1 status as a stratification factor, which the Sponsor employed in the study prior to randomization of the first patient.
02-NOV-2020	Type B pre-sBLA meeting to discuss a potential sBLA based on results of KEYNOTE-811 at IA1. FDA agreed that the results could potentially support filing of an sBLA for accelerated approval. FDA noted that the indication statement and the intended population would be a review issue and they requested subgroup analyses by PD-L1 status and tumor location.
06-NOV-2020	Submission of KEYNOTE-811 sBLA based on results from IA1.
05-MAY-2021	FDA approved KEYTRUDA, in combination with trastuzumab, fluoropyrimidine- and platinum-containing chemotherapy, is indicated for the 1L treatment of adults with locally advanced unresectable or metastatic HER2-positive gastric or gastroesophageal junction (GEJ) adenocarcinoma. This indication was approved under accelerated approval based on tumor response rate and durability of response. Continued approval of this indication may be contingent upon verification and description of clinical benefit in the confirmatory trials.
06-SEP-2022	Informal teleconference between the Sponsor and FDA to discuss a potential sBLA submission based on KEYNOTE-811 at IA2. FDA indicated they wanted to wait for more mature data before taking action.
12-JUN-2023	Informal teleconference between the Sponsor and FDA to discuss a potential sBLA submission based on KEYNOTE-811 at IA3. FDA indicated they would accept an efficacy supplement to update the indication to include only those patients whose tumors express PD-L1 with CPS ≥1.
04-AUG-2023	Submission of KEYNOTE-811 sBLA based on results from IA3 to restrict the indication to only those patients whose tumors express PD-L1 with a CPS ≥1.
07-NOV-2023	FDA approved KEYTRUDA, in combination with trastuzumab, fluoropyrimidine- and platinum-containing chemotherapy, is indicated for the 1L treatment of adults with locally advanced unresectable or metastatic HER2-positive gastric or gastroesophageal junction (GEJ) adenocarcinoma whose tumors express PD-L1 (CPS ≥1) as determined by an FDA-approved test. This indication is approved under accelerated approval based on tumor response rate and durability of response. Continued approval of this indication may be contingent upon verification and description of clinical benefit in the confirmatory trials.
07-NOV-2023	CDRH approved the PMA for the PD-L1 IHC 22C3 pharmDx assay as a companion diagnostic for KEYTRUDA in gastric and gastroesophageal junction adenocarcinoma at a PD-L1 expression cut-point of CPS ≥1.
10-JUL-2024	Type B pre-sBLA meeting to discuss a potential sBLA based on results of KEYNOTE-811 at Final Analysis. FDA agreed with the Sponsor's plan for submission.
18-JUL-2024	Submission of the KEYNOTE-811 sBLA based on results from Final Analysis to convert the accelerated approval to a traditional approval.

1L=first-line; CDRH=Center for Devices and Radiological Health; CPS=combined positive score; EOP=end of phase; HER2=human epidermal growth factor receptor 2; IA1=interim analysis 1; IA2=interim analysis 2; IA3=interim analysis 3; IHC=immunohistochemistry; PD-L1=programmed cell death ligand 1; PMA=premarket approval; sBLA=supplemental Biologics License Application.

8.2.3 KEYNOTE-811: Disposition, Demographics, and Baseline Characteristics

All Participants	
[Appendix Table 19]	Participant Characteristics (Global Cohort); (ITT Population)
Participants with PD-L1 (CPS ≥1)	
[Appendix Table 20]	Participant Characteristics (CPS ≥1 Participants); (Global Cohort); (ITT Population)

Appendix Table 19
KEYNOTE-811: 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)

KEYNOTE-811: Participant Characteristics (Global Cohort) (ITT Population)

	Pembrolizumab + SOC		SOC		Total	
	n	(%)	n	(%)	n	(%)
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)
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)

KEYNOTE-811: Participant Characteristics (Global Cohort) (ITT Population)

	Pembrolizumab + SOC		SOC		Total	
	n	(%)	n	(%)	n	(%)
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]

Appendix Table 20
KEYNOTE-811: 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)

KEYNOTE-811: Participant Characteristics (CPS≥1 Participants) (Global Cohort) (ITT Population)

	Pembrolizumab + SOC		SOC		Total	
	n	(%)	n	(%)	n	(%)
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)
>=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)

KEYNOTE-811: Participant Characteristics (CPS≥1 Participants) (Global Cohort) (ITT Population)

	Pembrolizumab + SOC		SOC		Total	
	n	(%)	n	(%)	n	(%)
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]

8.2.4 KEYNOTE-811: Efficacy

8.2.4.1 Progression-free Survival

All Participants at IA2	
[Appendix Table 21]	Analysis of Progression-Free Survival (Primary Analysis) at IA2; Based on BICR Assessment per RECIST 1.1; (Global Cohort); (ITT Population)
All Participants at the FA	
[Appendix Table 22]	Analysis of Progression-Free Survival (Primary Analysis) at the FA; Based on BICR Assessment per RECIST 1.1; (Global Cohort); (ITT Population)
[Appendix Figure 7]	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)
Exploratory Analysis	
[Appendix Table 23]	KEYNOTE-811: Exploratory Analysis of Progression-Free Survival (Primary Analysis) by CPS Cut-point; Based on BICR Assessment per RECIST 1.1; (Global Cohort); (ITT Population; Data Cutoff 20-MAR-2024)

Appendix Table 21
KEYNOTE-811: Analysis of Progression-Free Survival (Primary Analysis) at IA2 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]

Appendix Table 22
KEYNOTE-811: Analysis of Progression-Free Survival (Primary Analysis) at the FA Based on BICR Assessment per RECIST 1.1
(Global Cohort)
(ITT Population)

	Pembrolizumab + SOC (N=350)	SOC (N=348)
Number of Events (%)	258 (73.7)	263 (75.6)
DEATH	40 (11.4)	34 (9.8)
DOCUMENTED PROGRESSION	218 (62.3)	229 (65.8)
Kaplan-Meier Estimates (months)[a]		
Median (95% CI)	10.0 (8.6, 12.2)	8.1 (7.0, 8.5)
[Q1, Q3]	[5.6, 22.7]	[4.3, 15.4]
Person-months	5064.8	3764.1
Event Rate / 100 Person-months	5.1	7.0
vs SOC		
Hazard Ratio (95% CI)[b]	0.73 (0.61, 0.87)	
p-value[c]	0.0002	
PFS Rate at month 6 (%) (95% CI)	72.7 (67.6, 77.2)	62.0 (56.4, 67.1)
PFS Rate at month 12 (%) (95% CI)	44.7 (39.2, 50.1)	33.6 (28.3, 39.1)
PFS Rate at month 18 (%) (95% CI)	28.8 (23.8, 33.9)	21.6 (16.9, 26.6)
PFS Rate at month 24 (%) (95% CI)	23.8 (19.2, 28.8)	14.4 (10.5, 18.9)
PFS Rate at month 30 (%) (95% CI)	21.7 (17.2, 26.5)	12.3 (8.6, 16.6)
PFS Rate at month 36 (%) (95% CI)	18.4 (14.2, 23.1)	10.9 (7.5, 15.1)

[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.

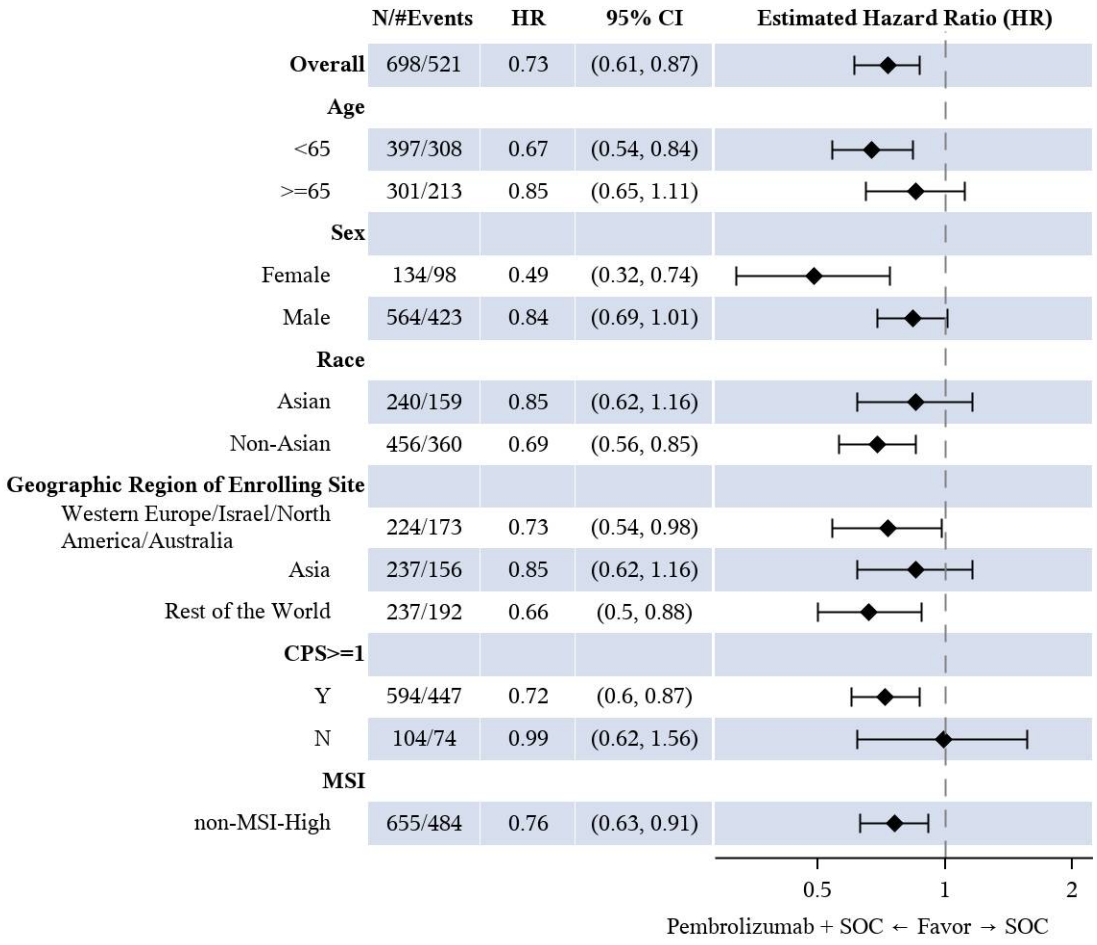
Western Europe includes Belgium, France, Germany, Spain, Italy, United Kingdom, Ireland, Latvia, Lithuania, which is consistent with the 'Europe' region defined in the protocol for stratification.

BICR = Blinded Independent Central Review.

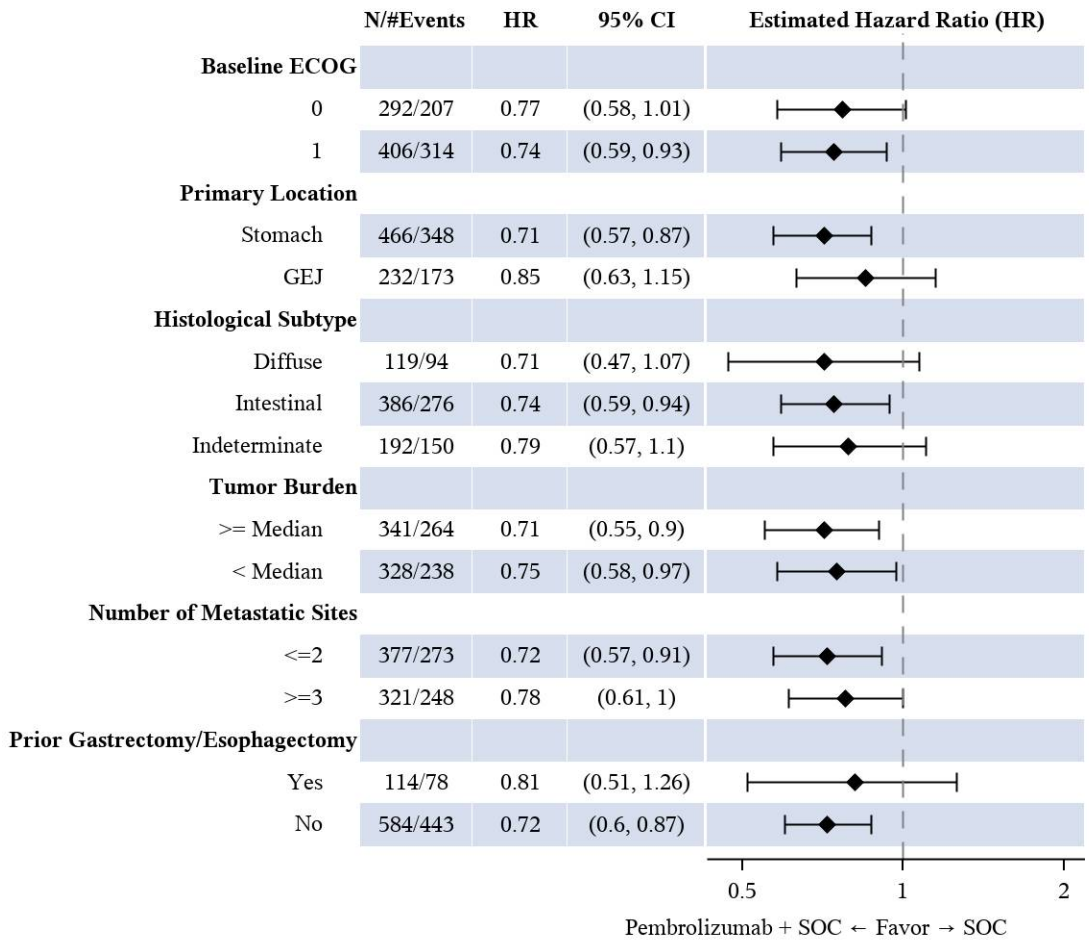
Database Cutoff Date: 20MAR2024

Source: [P811V04MK3475: adam-adsl; adtte]

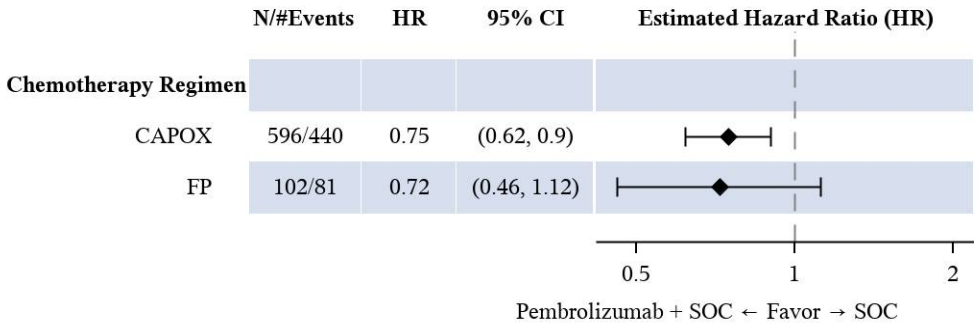
Appendix Figure 7
KEYNOTE-811: Forest Plot of Progression-Free Survival Hazard Ratio by Subgroup Factors Based on BICR Assessment per RECIST 1.1(Primary Analysis)
(Global Cohort)
(ITT Population)



KEYNOTE-811: 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) (Continued)



KEYNOTE-811: 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) (Continued)



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: 20MAR2024.

Source: [P811V04MK3475: adam-adsl; adtte]

Appendix Table 23
KEYNOTE-811: Exploratory Analysis of Progression-Free Survival (Primary Analysis) by CPS Cut-point
Based on BICR Assessment per RECIST 1.1 (Global Cohort)
(ITT Population; Data Cutoff 20-MAR-2024)

Baseline PD-L1 Status[a]	Number of Participants		Number of Events		Median PFS[b] (95% CI)		Hazard Ratio[c]		
	Pembro + SOC	SOC	Pembro + SOC	SOC	Pembro + SOC	SOC	HR	95% CI of HR	SE of log(HR)
ITT	350	348	258	263	10.0 (8.6, 12.2)	8.1 (7.0, 8.5)	0.729	0.612, 0.868	0.089
CPS <1	52	52	37	37	9.5 (8.3, 12.6)	9.5 (7.9, 13.0)	0.987	0.624, 1.560	0.234
CPS 1 - <5	112	125	83	93	9.9 (8.3, 12.8)	7.1 (5.6, 8.5)	0.652	0.480, 0.885	0.156
CPS <5	164	177	120	130	9.8 (8.5, 12.5)	8.1 (6.9, 9.6)	0.740	0.574, 0.955	0.130
CPS 1 - <10	189	190	145	145	9.9 (8.5, 12.4)	7.1 (5.9, 8.2)	0.679	0.536, 0.859	0.120
CPS 5 - <10	77	65	62	52	9.8 (8.3, 12.2)	6.8 (5.7, 8.4)	0.690	0.469, 1.016	0.197
CPS <10	241	242	182	182	9.8 (8.5, 11.3)	7.8 (6.8, 8.5)	0.734	0.595, 0.905	0.107
CPS ≥1	298	296	221	226	10.9 (8.5, 12.5)	7.3 (6.8, 8.4)	0.693	0.573, 0.837	0.096
CPS ≥5	186	171	138	133	10.9 (8.3, 13.0)	8.1 (6.8, 9.7)	0.721	0.565, 0.920	0.124
CPS ≥10	109	106	76	81	11.7 (7.2, 13.9)	9.6 (7.0, 11.3)	0.699	0.506, 0.966	0.165

CI=confidence interval; CPS=combined positive score; HR=hazard ratio; ITT=intent-to-treat; PD-L1=programmed death-ligand 1; pembro=pembrolizumab; PFS=progression-free survival; SE=standard error; SOC=standard of care; sSAP=supplemental statistical analysis plan.

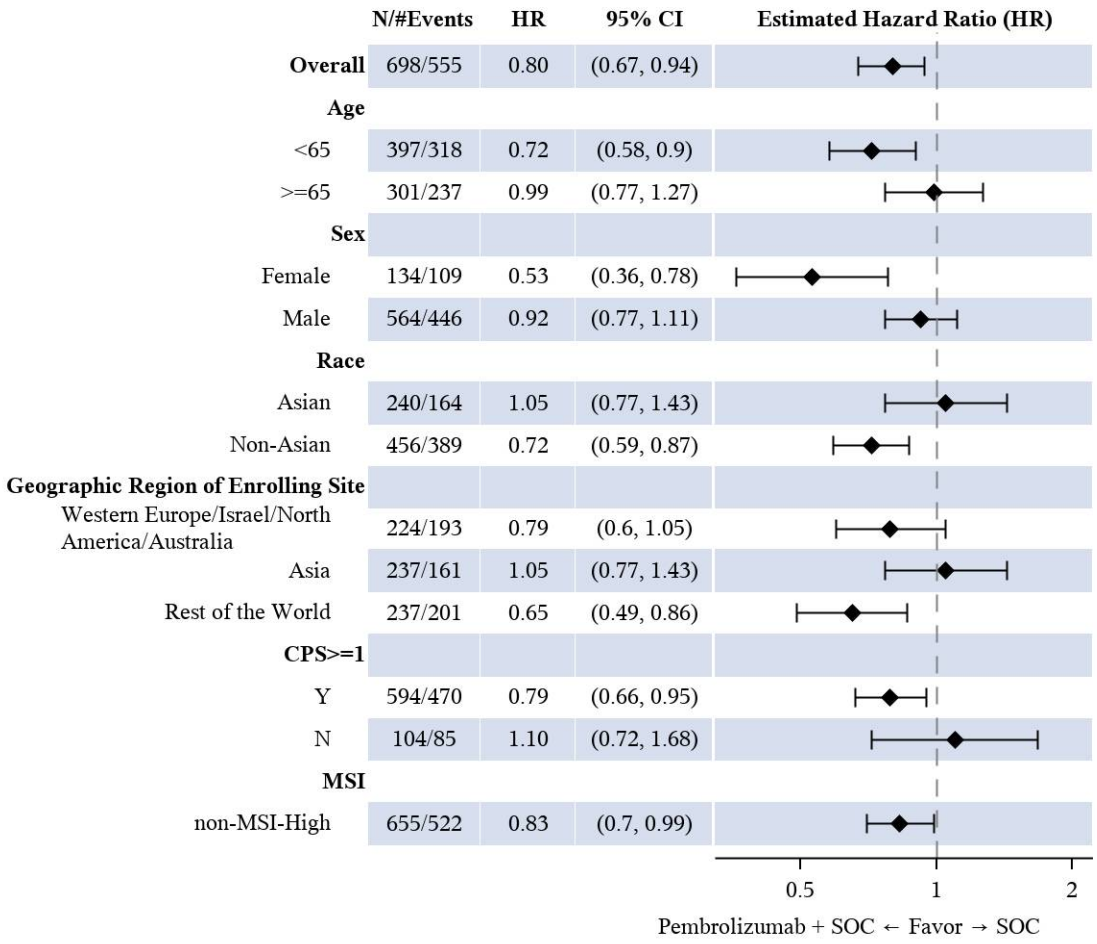
a. Data analysis at CPS ≥1 was pre-specified, and data collected at validated CPS ≥1 cut-point were used for analyses. Remaining analyses at other CPS cut-points were not pre-specified, and CPS raw scores were used.
b. Determined by Blinded Independent Central Review.
c. HR was based on Cox regression model with Efon's method of tie handling with treatment as a covariate stratified by stratification factors for randomization with small strata collapsed as pre-specified in sSAP. The pooled stratification variable used is ADSL.STRATA1.

Database cutoff date: 20MAR2024

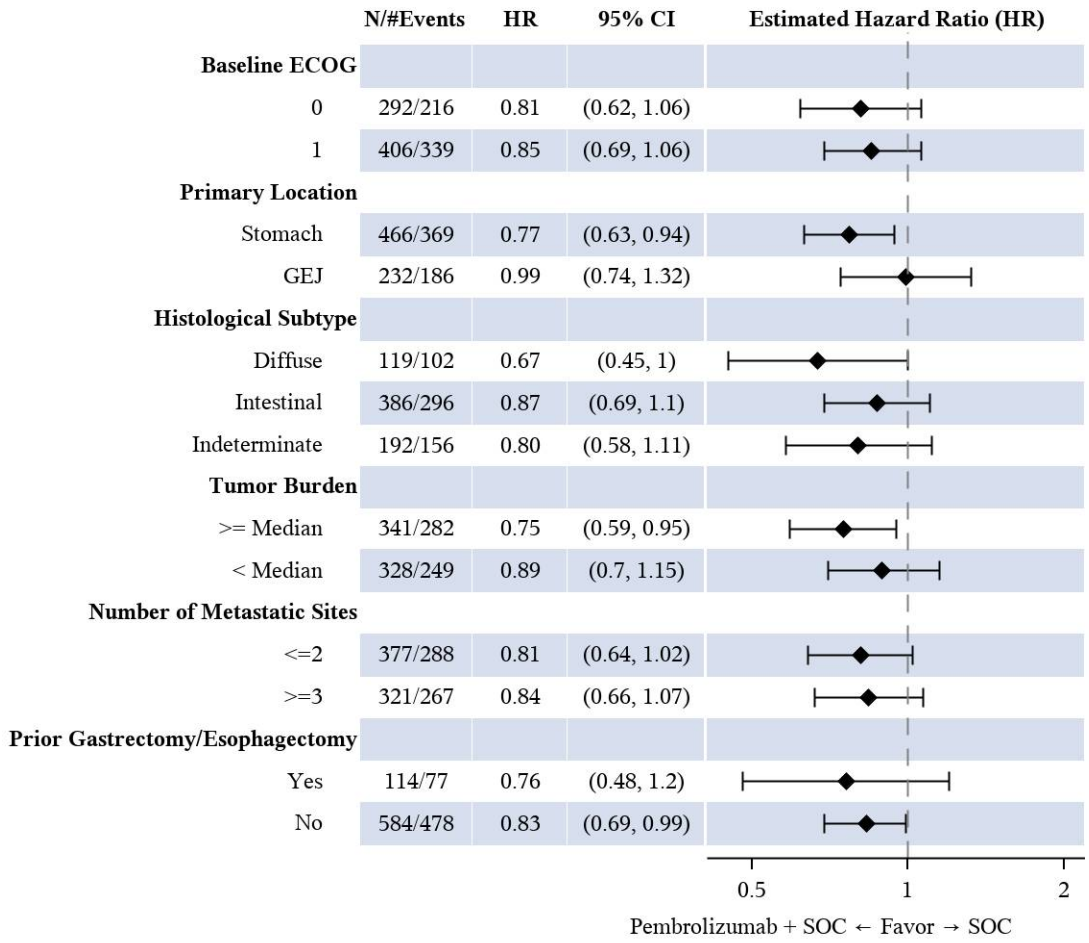
8.2.4.2 Overall Survival

All Participants	
[Appendix Figure 8]	Forest Plot of Overall Survival Hazard Ratio by Subgroup Factors; (Global Cohort); (ITT Population)
Participants with PD-L1 (CPS ≥1)	
[Appendix Table 24]	Analysis of Overall Survival; (CPS ≥1 Participants); (Global Cohort); (ITT Population)
Exploratory Analysis	
[Appendix Table 25]	KEYNOTE-811: Exploratory Analysis of Overall Survival by CPS Cut-point; (Global Cohort); (ITT Population; Data Cutoff 20-MAR-2024)

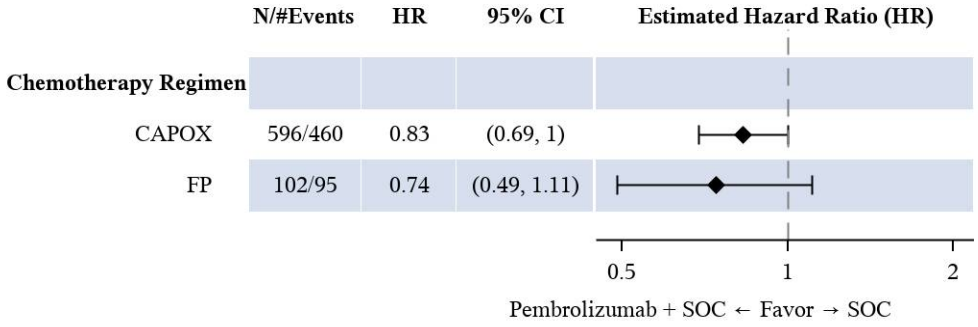
Appendix Figure 8
KEYNOTE-811: Forest Plot of Overall Survival Hazard Ratio by Subgroup Factors
(Global Cohort)
(ITT Population)



KEYNOTE-811: Forest Plot of Overall Survival Hazard Ratio by Subgroup Factors
(Global Cohort)
(ITT Population) (Continued)



KEYNOTE-811: Forest Plot of Overall Survival Hazard Ratio by Subgroup Factors (Global Cohort) (ITT Population) (Continued)



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: 20MAR2024.

Source: [P811V04MK3475: adam-adsl; adtte]

Appendix Table 24
KEYNOTE-811: Analysis of Overall Survival
(CPS>=1 Participants)
(Global Cohort)
(ITT Population)

	Pembrolizumab + SOC (N=298)	SOC (N=296)
Number of Events (%)	226 (75.8)	244 (82.4)
DEATH	226 (75.8)	244 (82.4)
Kaplan-Meier Estimates (months)[a]		
Median (95% CI)	20.1 (17.9, 22.9)	15.7 (13.5, 18.5)
[Q1, Q3]	[10.3, 42.6]	[8.4, 33.2]
Person-months	7433.4	6323.2
Event Rate / 100 Person-months	3.0	3.9
vs SOC		
Hazard Ratio (95% CI)[b]	0.79 (0.66, 0.95)	
p-value[c]	0.0062	
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)	69.5 (63.9, 74.4)	60.8 (55.0, 66.1)
OS Rate at month 18 (%) (95% CI)	55.7 (49.9, 61.1)	45.6 (39.9, 51.2)
OS Rate at month 24 (%) (95% CI)	42.6 (37.0, 48.2)	35.4 (30.0, 40.9)
OS Rate at month 30 (%) (95% CI)	34.2 (28.9, 39.6)	29.0 (23.9, 34.2)
OS Rate at month 36 (%) (95% CI)	29.0 (23.9, 34.2)	23.0 (18.4, 28.0)
OS Rate at month 42 (%) (95% CI)	25.1 (20.3, 30.3)	21.4 (16.9, 26.3)
OS Rate at month 48 (%) (95% CI)	24.2 (19.4, 29.3)	16.3 (12.0, 21.1)

[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.
[c] One-sided p-value based on log-rank test.
Database Cutoff Date: 20MAR2024

Source: [P811V04MK3475: adam-adsl; adtte]

Appendix Table 25
KEYNOTE-811: Exploratory Analysis of Overall Survival by CPS Cut-point
(Global Cohort)
(ITT Population; Data Cutoff 20-MAR-2024)

Baseline PD-L1 Status[a]	Number of Participants		Number of Deaths		Median OS (95% CI)		Hazard Ratio[b]		
	Pembro + SOC	SOC	Pembro + SOC	SOC	Pembro + SOC	SOC	HR	95% CI of HR	SE of log(HR)
ITT	350	348	267	288	20.0 (17.8, 22.1)	16.8 (14.9, 18.7)	0.797	0.673, 0.943	0.086
CPS <1	52	52	41	44	18.2 (13.9, 22.9)	20.4 (16.4, 24.7)	1.099	0.717, 1.685	0.218
CPS 1 - <5	112	125	87	106	19.7 (16.3, 22.2)	14.7 (11.4, 19.0)	0.721	0.539, 0.966	0.149
CPS <5	164	177	128	150	19.0 (16.1, 22.1)	17.3 (14.6, 19.9)	0.823	0.647, 1.048	0.123
CPS 1 - <10	189	190	149	161	20.5 (17.8, 22.9)	14.4 (11.8, 18.1)	0.751	0.599, 0.941	0.115
CPS 5 - <10	77	65	62	55	21.7 (17.4, 26.6)	13.7 (11.2, 18.6)	0.754	0.520, 1.094	0.190
CPS <10	241	242	190	205	20.1 (17.5, 22.2)	16.5 (14.2, 18.6)	0.815	0.667, 0.996	0.102
CPS ≥1	298	296	226	244	20.1 (17.9, 22.9)	15.7 (13.5, 18.5)	0.752	0.626, 0.903	0.093
CPS ≥5	186	171	139	138	20.8 (18.1, 24.5)	16.0 (13.7, 19.9)	0.756	0.595, 0.960	0.122
CPS ≥10	109	106	77	83	19.9 (15.2, 28.2)	17.1 (14.6, 24.2)	0.764	0.555, 1.051	0.163

CI=confidence interval; CPS=combined positive score; HR=hazard ratio; ITT=intent-to-treat; OS=overall survival; PD-L1=programmed death-ligand 1; Pembro=pembrolizumab; SE=standard error; SOC=standard of care; sSAP=supplemental statistical analysis plan.

a. Data analysis at CPS ≥1 was pre-specified, and data collected at validated CPS ≥1 cut-point were used for analyses. Remaining analyses at other CPS cut-points were not pre-specified, and CPS raw scores were used.

b. HR was based on Cox regression model with Efon's method of tie handling with treatment as a covariate stratified by stratification factors for randomization with small strata collapsed as pre-specified in sSAP. The pooled stratification variable used is ADSL.STRATA1.

Database cutoff date: 20MAR2024

8.2.4.3 Objective Response Rate and Duration of Response

All Participants at IA1	
[Appendix Table 26]	Analysis of Objective Response with Confirmation at IA1; Based on BICR Assessment per RECIST 1.1; (Global Cohort); (First 264 Patients Randomized in ITT Population)
[Appendix Table 27]	Summary of Time to Response and Duration of Response at IA1; Based on BICR Assessment per RECIST 1.1 in Subjects with Confirmed Response; (Global Cohort); (First 264 Patients Randomized in ITT Population)
All Participants at the FA	
[Appendix Table 28]	Analysis of Objective Response with Confirmation at the FA; Based on BICR Assessment per RECIST 1.1; (Global Cohort); (ITT Population)
[Appendix Table 29]	Summary of Time to Response and Duration of Response at the FA; Based on BICR Assessment per RECIST 1.1 in Participants with Confirmed Response; (Global Cohort); (ITT Population)

Appendix Table 26
KEYNOTE-811: Analysis of Objective Response with Confirmation at IA1
Based on BICR Assessment per RECIST 1.1
(Global Cohort)
(First 264 Patients Randomized in ITT Population)

Treatment	N	Number of Objective Responses	Objective Response Rate (%) (95% CI)	Difference in % Pembrolizumab + SOC vs. SOC	
				Estimate(95% CI)[†]	p-Value[††]
Pembrolizumab + SOC	133	99	74.4 (66.2, 81.6)	22.7 (11.2, 33.7)	0.00006
SOC	131	68	51.9 (43.0, 60.7)		

[†] Based on Miettinen & Nurminen method stratified by Geographic region (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.

[††] 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: 17JUN2020.

Source: [P811V01MK3475: adam-adsl; adrs]

Appendix Table 27
KEYNOTE-811: Summary of Time to Response and Duration of Response at IA1
Based on BICR Assessment per RECIST 1.1 in Subjects with Confirmed Response
(Global Cohort)
(First 264 Patients Randomized in ITT Population)

	Pembrolizumab + SOC (N=133)	SOC (N=131)
Number of subjects with response[†]	99	68
Time to Response (months)		
Mean (SD)	1.8 (0.7)	1.9 (1.0)
Median (Range)	1.4 (1.2-5.6)	1.5 (1.0-5.5)
Response Duration[‡] (months)		
Median (Range)	10.6 (1.1+ - 16.5+)	9.5 (1.4+ - 15.4+)
Number (%[‡]) of Subjects with Extended Response Duration:		
≥3 months	89 (92.7)	57 (89.3)
≥6 months	64 (70.3)	36 (61.4)
≥9 months	36 (58.4)	20 (51.1)

[†] Includes subjects with best objective response as confirmed complete response or partial response.
[‡] 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: 17JUN2020.

Source: [P811V01MK3475: adam-adsl; adtte]

Appendix Table 28
KEYNOTE-811: Analysis of Objective Response with Confirmation at the FA
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)	12.6 (5.6, 19.4)	0.00020
SOC	348	209	60.1 (54.7, 65.2)		

[a] Based on Miettinen & Nurminen method stratified by Geographic region (Western Europe/Israel/North America/Australia, Asia and Rest of the World), PD-L1 status (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: 20MAR2024.

Source: [P811V04MK3475: adam-adsl; adrs]

Appendix Table 29
KEYNOTE-811: Summary of Time to Response and Duration of Response at the FA Based on BICR Assessment per RECIST 1.1 in Participants with Confirmed Response
(Global Cohort)
(ITT Population)

	Pembrolizumab + SOC (N=350)	SOC (N=348)
Number of participants with response[a]	254	209
Time to Response (months)		
Mean (SD)	1.9 (1.3)	1.9 (1.0)
Median (Range)	1.4 (0.9-15.2)	1.5 (0.7-7.0)
Response Duration[b] (months)		
Median (Range)	11.3 (1.1+ - 60.8+)	9.5 (1.4+ - 60.5+)
Number (%[b]) of Participants with Extended Response Duration:		
≥3 months	234 (94.0)	176 (90.5)
≥6 months	181 (74.8)	131 (69.2)
≥9 months	143 (59.5)	93 (50.8)
≥12 months	109 (48.0)	73 (41.9)

[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: 20MAR2024

Source: [P811V04MK3475: adam-adsl; adtte]

8.3 Electronic Health Record-based Study (Flatiron Health Research Database)

The Sponsor is investigating the real-world use of systemic therapies in advanced/metastatic gastric, GEJ and esophageal cancers in the United States using FHRD, a US-based, EHR-derived de-identified database. FHRD is a longitudinal database comprising patient-level structured and unstructured data from approximately 280 US cancer clinics (~800 sites of care) across the US. These analyses are part of an ongoing retrospective observational cohort study of treatment patterns for patients initiating 1L treatment after FDA approval of ICIs in 3 study populations: 1) HER2-positive advanced gastric or GEJ adenocarcinoma (reflective of KEYNOTE-811), 2) HER2-negative advanced gastric or GEJ adenocarcinoma (reflective of KEYNOTE-859), and 3) advanced esophageal carcinoma (reflective of KEYNOTE-590).

The study populations were sourced from the advGastric EDM, which contains a probabilistic sample from all patients in the FHRD meeting specified inclusion and exclusion criteria for the database. Patients are probabilistically sampled based on an algorithmically assigned unique patient identifier that is not linked to patient characteristics (eg, demographics) or clinical outcomes (eg, treatments received). Sampling is used to limit the number of patients for whom charts are reviewed and data curated.

Patients included in advGastric EDM must be at least 18 years of age at advanced diagnosis, have an ICD diagnosis of advanced gastric/esophageal cancer (ICD-9 150.x or 151.x or ICD-10 C15.x or C16.x) with pathology consistent with gastric/esophageal/GEJ cancer and at least 2 documented clinical visits, on different days in the Flatiron database on or after 01-JAN-2011. For patients with gastric cancer, advanced disease is defined as patients with metastatic disease at diagnosis or with one of the following on or after 01-JAN-2011:

1. distant recurrence,
2. a second locoregional recurrence,
3. a first locoregional recurrence that was not completely resected
4. no surgical resection of the primary tumor, or
5. incomplete resection

For patients with GEJ, the criteria above are the same except patients with any locoregional recurrence are included.

Additional inclusion criteria for the study cohorts reflective of KEYNOTE-811 and KEYNOTE-859 are described below.

KEYNOTE-811 study population:

- Has evidence of adenocarcinoma histology

- Has evidence of HER2 positive biomarker status defined as: [ERBB2 amplification, HER2 (2-3+)] for gastric or GEJ cancer with test results no more than 180 days prior to 1L systemic treatment initiation and no more than 30 days after 1L treatment initiation, or received HER2 directed therapy at any point after diagnosis

- Initiated 1L systemic treatment after FDA approval of KEYNOTE-811 (05-MAY-2021)

KEYNOTE-859 study population:

- Has evidence of adenocarcinoma histology
- Has evidence of at least one HER2-negative biomarker result and has no evidence of having a HER2 positive biomarker status at any time
- Has no evidence of treatment with a HER2-targeted therapy at any time, defined as any medication administration or non-canceled order of any HER2 targeted therapy
- Initiated 1L systemic treatment after the first FDA approval of ICI in 1L HER2-negative gastric cancer (16-APR-2021)

For all cohorts, patients were excluded if they had evidence of treatment with a clinical study drug after 1L treatment start, evidence of a secondary primary malignancy prior to or during 1L treatment, or did not receive surgery because they were unfit, refused or for other or unknown reasons.

The index date was defined as the start date for 1L systemic treatment. The follow-up time for each patient in this study extends from the start of 1L systemic therapy through the date of death (if available) or last confirmed activity prior to the data cutoff date of the advGastric EDM at time of analysis 31-MAR-2024. Study variables examined using the data available during the study period included patient demographic and disease characteristics as well as HER2 status and PD-L1 testing, assay used and CPS value obtained from clinician documentation, pathology reports, or lab reports.

The Flatiron Health LOT algorithm developed for the advGastric EDM defined the start of the first line of therapy as the first episode of an eligible therapy that was given within 14 days of advanced gastroesophageal cancer diagnosis as identified rom EHR. Regimen components given within 28 days after the first eligible drug episode are considered part of that LOT. The treatment line was advanced to the next line if a patient has a gap of more than 120-days in drug episodes (i.e., administration of a non-canceled order of the therapy).

In addition, the following substitutions or additions in therapy or combination therapy did <u>not</u> advance the line of therapy:

- Substitution of cisplatin for carboplatin or vice-versa
- Substitution of fluorouracil for capecitabine or vice-versa
- Substitution of leucovorin for levoleucovorin or vice-versa
- Substitution of paclitaxel for paclitaxel protein-bound or vice-versa

- Substitution of trastuzumab for its biosimilar (eg, trastuzumab-anns for trastuzumab) or vice-versa

- Substitution of bevacizumab for its biosimilar (eg, bevacizumab-awwb for bevacizumab) or vice-versa

- Addition of leucovorin or levoleucovorin

- Addition of trastuzumab or trastuzumab biosimilar to a chemo/targeted therapy background within the first 2 months after the start of the line

- Addition of bevacizumab or bevacizumab biosimilar to a chemo/targeted therapy background within the first 2 months after the start of the line

- Drug component suppression" of one or more drugs within a combination regimen that is subsequently reintroduced

The results presented in this document on treatment patterns and PD-L1 testing in patients with advanced/metastatic gastric/GEJ cancer receiving 1L treatment since first FDA approvals of an ICI in HER2-positive and HER2-negative gastric cancer are reported based on the preliminary analysis of an ongoing study with additional results pending. It should be noted that there may be variation in the final results presented.