Oncologic Drugs Advisory Committee (ODAC) Meeting

Pembrolizumab in First-line Esophageal Cancer

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ADVISORY COMMITTEE BRIEFING MATERIALS: AVAILABLE FOR PUBLIC RELEASE

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

Abbreviation	Definition
1L	First-line
2L	Second-line
3L+	third-line or higher
5-FU	5-fluorouracil
advGastric EDM	Advanced Gastric/Esophageal/GEJ Enhanced Datamart
AE	Adverse event
CPS	Combined positive score
CR	Complete responders
DOR	Duration of response
EAC	Esophageal adenocarcinoma
EDM	Enhanced datamart
EHR	Electronic health record
EORTC QLQ-C30	European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30
EORTC QLQ-OES18	European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire in Oesophageal Cancer 18
EQ-5D-5L	EuroQoL 5 Dimensions 5 Level
ESCC	esophageal squamous cell carcinoma
FAS	Full Analysis Set
FDA	Food and Drug Administration
FFPE	formalin-fixed, paraffin-embedded
FHRD	Flatiron Health Research Database
GEJ	Gastroesophageal junction
H	Hypothesis
HNSCC	Head and neck squamous cell carcinoma
HR	Hazard ratio
HRQoL	Health-related quality-of-life
ICD	International Classification of Diseases
ICI	Immune checkpoint inhibitor
IgG4	Immunoglobulin G4
IHC	Immunohistochemistry
ITT	Intent-to-treat
KM	Kaplan-Meier
LOT	Line of therapy
LS	Least squares
mAb	Monoclonal antibody
NPV	Negative predictive value
NSCLC	Non-small cell lung cancer

Abbreviation	Definition
ODAC	Oncology Drugs Advisory Committee
ORR	Objective response rate
OS	Overall survival
PD-1	Programmed cell death-1
PD-L1	Programmed cell death-1 ligand-1
PD-L2	Programmed cell death-1 ligand-2
PFS	Progression-free survival
PPV	Positive predictive value
PRO	Patient-reported outcomes
Q-TWiST	Quality-adjusted time without symptoms of disease progression or toxicity of treatment
RECIST 1.1	Response Evaluation Criteria in Solid Tumors version 1.1
REL	Relapse
ROC	Receiver operating characteristic
RMST	Restricted mean survival time
RSD	Reference safety dataset
SAE	Serious AE
SOC	Standard of care
TNBC	Triple negative breast cancer
TOX	Toxicity
TPS	Tumor proportion score
TWiST	Time without symptoms of disease progression or toxicity of treatment
US	United States

1 EXECUTIVE SUMMARY

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

Merck conducted KEYNOTE-590, a Phase 3 study of pembrolizumab versus placebo on a background of standard cisplatin and 5-FU in patients with locally advanced unresectable or metastatic esophageal carcinoma (adenocarcinoma or squamous cell carcinoma of the esophagus or Siewert type 1 adenocarcinoma of the GEJ). Based on the FDA-agreed protocol and statistical plan for this study, addition of pembrolizumab to standard chemotherapy resulted in statistically significant and clinically meaningful improvements in OS, PFS, and ORR versus chemotherapy in this patient population. On the basis of these findings, pembrolizumab in combination with platinum- and fluoropyrimidine-based chemotherapy is approved for the treatment of patients with locally advanced or metastatic esophageal cancer regardless of PD-L1 expression in the tumor. To ensure that patients who may benefit from the addition of pembrolizumab to chemotherapy have appropriate access in the US, the currently approved indication in patients with locally advanced and metastatic esophageal cancer should be retained.

To support this position, this briefing document provides the primary results of KEYNOTE-590. Additionally, this briefing document summarizes information on the Sponsor's pembrolizumab monotherapy program in esophageal cancer, and the biological basis for combinations of chemotherapy and immunotherapy. It also explains the PD-L1 biomarker cut-point selection process and how this biomarker knowledge was incorporated into the Sponsor's esophageal cancer clinical development program.

Esophageal Cancer

Esophageal cancer is the 11th most commonly diagnosed cancer and the 7th leading cause of cancer-related deaths worldwide [1] (see [Sec. 2]). In the US, over 22,000 cases of esophageal cancer are diagnosed annually, with over 16,000 deaths [2]. There are 2 main histological subtypes: ESCC and EAC, with ESCC more common globally, and EAC more common in the US [3] [4]. Most patients with esophageal cancer are diagnosed at the regional or distant stage (71%), with an overall 5-year survival rate of 28% and 5%, respectively [5]. For decades, doublet chemotherapy was the only treatment option for these patients, with median survivals of under 1 year [6] [7].

Studies of the ICIs pembrolizumab and nivolumab in front-line advanced/metastatic esophageal cancer have demonstrated anti-cancer effects and benefits in overall survival. Thus, these agents have been incorporated in the treatment paradigm for patients with newly diagnosed esophageal cancer. ICIs also offer patients an opportunity for durable responses and long-term survival, which are not commonly observed with historic chemotherapy regimens for esophageal cancer. Despite the benefit of adding ICIs to 1L treatment, most patients with esophageal cancer experience primary disease progression. Real-world treatment data show that only about 40% of patients treated in the 1L setting receive 2L

therapy [CMP: CancerMPact® PM Dashboards, Oracle Life Sciences. Available from www.cancermpact.com (Accessed 19-JUL-2024)]. Considering the global health burden of esophageal cancer and poor 5-year survival rate for those with advanced disease, there continues to be a high unmet medical need for this patient population (see [Sec. 2]). Notably, since the approval of immunotherapy in combination with chemotherapy, there have been no additional advances in systemic treatment options for patients with esophageal cancer that resulted in new marketing approvals.

Pembrolizumab – Monotherapy and Combination Studies in Esophageal Cancer

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.

Four studies evaluated the efficacy of pembrolizumab, with or without concomitant chemotherapy, in 1521 subjects with locally advanced/metastatic esophageal cancer. An important component of the program has been an 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 some tumors, including esophageal cancer (KEYNOTE-028, KEYNOTE-180, KEYNOTE-181). However, some patients with CPS <1 did respond to pembrolizumab monotherapy (KEYTRUDA USPI [accessed 09-MAY-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 [8]. In several tumor types (eg, NSCLC), 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)[9] [10] [11] (see [Sec. 4.5]). Similar results have been observed in TNBC [12] [13] and HNSCC [14].

KEYNOTE-590 was a randomized, double-blind, Phase 3 trial evaluating pembrolizumab plus chemotherapy compared with placebo plus chemotherapy for the 1L treatment of 749 patients with locally advanced or metastatic esophageal carcinoma. It is one of the largest Phase 3 studies of esophageal cancer conducted to date. KEYNOTE-590 included both histological subtypes (ESCC and EAC), which allows generalization of the study data to a Western population where EAC is the more common subtype. Patients were enrolled regardless of PD-L1 status.

KEYNOTE-590 Study Design and CPS Cut-point Selection

The study design for KEYNOTE-590 was based on prior observations that the addition of chemotherapy might allow broadening the patient population with respect to PD-L1

expression. The study followed prespecified statistical analyses to test pembrolizumab plus chemotherapy versus chemotherapy for the 1L treatment of patients with locally advanced or metastatic esophageal carcinoma in the overall ITT population. During the course of the KEYNOTE-590 study, data from later line studies of esophageal cancer showed enrichment of efficacy of pembrolizumab monotherapy at the PD-L1 CPS ≥10 cut point. Because of these findings, a prespecified statistical analysis in the PD-L1 CPS ≥10 subgroup was incorporated into the design to provide additional information regarding efficacy at higher PD-L1 levels.

In KEYNOTE-590, 1L therapy with pembrolizumab plus chemotherapy provided a statistically significant and clinically meaningful improvement versus chemotherapy in OS in the ITT population. The median OS was 12.4 months (95% CI: 10.5, 14.0) compared with 9.8 months (95% CI: 8.8, 10.8) in the pembrolizumab plus chemotherapy arm compared with the control arm (placebo plus chemotherapy) (HR = 0.73 [95% CI: 0.62, 0.86; $p<0.0001$]). Further, the 2-year OS rate was 28% compared with 16% in the pembrolizumab plus chemotherapy arm compared with the control arm, supporting the potential for pembrolizumab to enhance long-term survival in some patients. PFS and ORR based on investigator assessment per RECIST 1.1 in the overall ITT population (n = 749) also showed statistically significant and clinically meaningful improvement in the pembrolizumab plus chemotherapy arm with a HR of 0.65 (95% CI: 0.55, 0.76; p<0.0001) and a response difference of 15.8% ($p<0.0001$), respectively, compared to the control arm (see [Sec. 4.6.1.3.1] and [Sec. 4.6.1.4.1]). All of these data support the current labelled indication for KEYNOTE-590.

Efficacy results in the CPS ≥10 subgroup (n = 383), were also statistically significant and clinically meaningful in favor of pembrolizumab plus chemotherapy versus chemotherapy and consistent with results in the overall ITT population (see [Sec. 4.6.1.2.1] and [Sec. 4.6.1.3.1]). However, the higher PD-L1 expression cut-point of CPS ≥10 includes only 51% of participants. Restricting the indication to this CPS cut-point would deny access to almost half of patients who could potentially benefit from treatment with pembrolizumab plus chemotherapy.

KEYNOTE-590 was rigorously designed, included consultation with the FDA on the clinical study design, study endpoints, study population, statistical analyses, and biomarker evaluation plan, and met all primary and key secondary endpoints in the overall ITT population. Based on the results of KEYNOTE-590, pembrolizumab plus chemotherapy was approved by the FDA upon its review of the positive benefit/risk profile in March 2021 for the treatment of all patients with locally advanced or metastatic esophageal or GEJ (tumors with epicenter 1 to 5 centimeters above the GEJ) carcinoma that is not amenable to surgical resection or definitive chemoradiation, in combination with platinum- and fluoropyrimidine-based chemotherapy. This was the first approval for ICIs in this indication, and it changed the standard of care in this underserved malignancy.

At the request of the FDA in preparation for this ODAC, the Sponsor conducted exploratory post hoc analyses at additional CPS cut-points, which, with the exception of CPS ≥ 10, were not prespecified. As such, the study was not powered to definitively demonstrate efficacy in the FDA requested PD-L1 subgroups. These analyses indicate that all CPS subgroups had

HR point estimates <1 and overlapping confidence intervals with those in the ITT population (see [Sec. 4.6.1.2.3]). Efficacy results by histology in KEYNOTE-590 were also consistent with results in the overall ITT population. Results in the prespecified ESCC subgroup in KEYNOTE-590 were consistent with results in the overall ITT population: 1L therapy with pembrolizumab plus chemotherapy provided a statistically significant and clinically meaningful improvement versus chemotherapy in OS (HR = 0.72 [95% CI: 0.60, 0.88; p=0.0006]) and PFS (HR = 0.65 [95% CI: 0.54, 0.78; p<0.0001]) in ESCC participants (see [Sec. 4.6.1.2.2] and [Sec. 4.6.1.3.2]). The 2-year OS rate was higher for pembrolizumab plus chemotherapy (28.6%) versus chemotherapy (17.3%) in ESCC participants. The observed long-term benefit for the ESCC subgroup in KEYNOTE-590 is characteristic of treatment with checkpoint inhibitors. Results from the EAC subgroup were also consistent with the results in the ITT population.

Health-related Quality of Life and Safety

As esophageal cancer progresses, patients would be expected to experience diminished HRQoL. Therefore, maintenance of HRQoL may be considered a meaningful outcome [15]. The changes from baseline in HRQoL scores were similar between the pembrolizumab plus chemotherapy group and the chemotherapy group throughout the course of treatment, suggesting that there was no decrement in HRQoL with addition of pembrolizumab to chemotherapy in KEYNOTE-590 (see [Sec. 4.6.3]).

The safety profile of pembrolizumab plus chemotherapy in KEYNOTE-590 was generally consistent with the individual established safety profiles of the chemotherapy administered (cisplatin and 5-FU) and pembrolizumab. There is no biological rationale to suggest that the safety profile of pembrolizumab would change based on the level of PD-L1 expression, and no differences in the safety profile were observed based on PD-L1 expression in analyses of pooled safety data from the first line esophageal and gastric studies (see [Sec. 4.7.1]).

Summary and Conclusions

In summary, data from KEYNOTE-590 established pembrolizumab in combination with chemotherapy as a paradigm-changing 1L treatment option that offers a clinically meaningful survival benefit for 1L esophageal cancer patients. These patients have tremendous unmet need, and previously had only doublet chemotherapy as a treatment option. Based on KEYNOTE-590 and other studies, immune checkpoint inhibitors in combination with chemotherapy have become the SOC in esophageal cancer [6] [7] [9] [16].

Consistent with the approved indication for all-comers and data presented in this briefing document, the benefits of pembrolizumab treatment in combination with chemotherapy demonstrated in KEYNOTE-590 outweigh the risks. Similar HRQoL compared to chemotherapy alone and a manageable safety profile in patients with locally advanced unresectable or metastatic carcinoma of the esophagus and GEJ (Siewert Type 1) all underscore the positive benefit/risk ratio of pembrolizumab plus chemotherapy in the currently labelled indication. Because the patient population in KEYNOTE-590 represents the global distribution of the disease and includes both histologic subtypes, the approved all-

comers indication facilitates access to immuno-oncology therapy for patients with either EAC or ESCC.

The Sponsor considers that the current PD-L1 all-comer indication for metastatic esophageal cancer, as evaluated in the ITT population of KEYNOTE-590, should remain as it is in the best interest of patients in the US. The observed efficacy of pembrolizumab plus chemotherapy in participants with CPS <1 is generally consistent with that observed in the ITT population, albeit the magnitude of benefit is less (see [Sec. 4.6.1.2.3], [Sec. 4.6.1.3.3], and [Sec. 4.6.1.4.3]). Real-world data suggest that many patients are not currently being treated with ICI-based regimens, which have demonstrated long-term survival (based on Flatiron Health electronic medical record data (see [Sec. 4.9]). Applying the prevalence of PD-L1 expression from KEYNOTE-590 to the estimated number of new metastatic esophageal cancer cases in the US in 2024, restricting the approved indication to the CPS ≥10 cut-point or the CPS ≥1 cut-point, may exclude 48% and 11% of patients, respectively, from receiving a foundational, potentially life-extending treatment option. Given the high unmet need and lack of alternative options for patients with esophageal cancer, US patients and physicians should have the ability to make an informed choice on treatment and the current labeling informs and enables that decision.

2 OVERVIEW OF ESOPHAGEAL CANCER AND TREATMENT OPTIONS

Esophageal cancer is the 11th most diagnosed cancer and the 7th leading cause of cancer-related deaths worldwide [1]. There are 2 main histological subtypes (ESCC and EAC) [3] [4]; ESCC typically occurs in the proximal two -thirds of the esophagus, while EAC is usually found in the distal third of the esophagus and at the GEJ. Key risk factors for EAC are gastroesophageal reflux disease, abdominal obesity, and cigarette smoking, while alcohol consumption and cigarette smoking are predominant for ESCC [4]. Most patients are diagnosed at the regional or distant stage (71%), with an overall 5-year survival rate of 28% and 5%, respectively [5].

There is distinct geographic variation in the distribution of ESCC and EAC. ESCC is the predominant histological subtype globally contributing to an estimated 85% of esophageal cancer cases while approximately 15% of esophageal cancer cases worldwide are adenocarcinomas [4] [17]. In the US, Canada, and Northern and Western Europe, EAC is the dominant histologic subtype and comprises about 63% of cases in the US [17].

Given the high incidence and mortality worldwide and the lack of effective therapeutic options, patients with advanced esophageal cancer have a high unmet medical need. Prior to the introduction of immunotherapy, doublet chemotherapy was the only treatment option for these patients, which provided limited benefit [7]. Median overall survival with cisplatin and 5-FU combinations, the most common chemotherapy doublet used for 1L treatment of patients with esophageal cancer, ranges from 8 to 11 months [18] [19] [20] [21] [22]. Of patients who receive systemic treatment in the 1L setting, only 35% to 40% go on to receive 2L treatment, emphasizing the importance of giving the most effective therapy up front [23] [CMP: CancerMPact ® PM Dashboards, Oracle Life Sciences. Available from www.cancermpact.com (Accessed 19-JUL-2024)].

There had been no major advancements in the development of systemic therapy for the 1L treatment of esophageal cancer before study KEYNOTE-590 [6]. The FDA approval for pembrolizumab plus chemotherapy in the 1L treatment of esophageal cancer in March 2021 was the first approval of an ICI in combination with chemotherapy for esophageal cancer in the 1L setting (KEYTRUDA USPI [accessed 09-MAY-2024]) [6]. Subsequent to the approval of pembrolizumab and chemotherapy for 1L, nivolumab in combination with ipilimumab or with chemotherapy was approved for the treatment of ESCC, while nivolumab in combination with chemotherapy was approved for the treatment of EAC (OPDIVO USPI [accessed 17-AUG-2024]) [22] [24].

3 PEMBROLIZUMAB AND 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 and does not lead to nonspecific activation of T cells.

3.1 PD-L1 IHC 22C3 PharmDx

PD-L1 IHC 22C3 pharmDx has been utilized in the pembrolizumab clinical development program for testing tumor tissue for PD-L1 expression. The PD-L1 IHC 22C3 pharmDx is a 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.

Esophageal and gastric cancers have a significant immune infiltration component, so capturing expression of PD-L1 in both tumor and immune cells by using the combined positive score (CPS), which captures expression in tumor cells and immune cells, is clinically relevant. CPS 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:

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

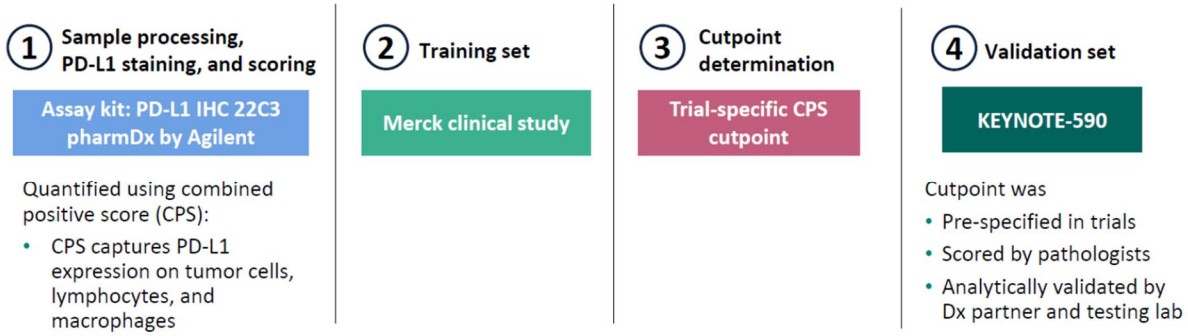
3.2 Selection of PD-L1 Expression Cut-point

Across the pembrolizumab development program, the selection of cut-points for the PD-L1 IHC 22C3 pharmDx assay for evaluation in randomized studies in each malignancy was based on an analysis of training set data from earlier studies in each respective tumor type. The analysis assessed the clinical utility of potential cut-points for (1) enrichment of tumor response rates, (2) sensitivity to identify responders, and (3) prevalence of participants in subgroups defined by cutoffs on PD-L1 expression.

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 in subsequent clinical practice.

An overview of the cut-point selection process is in [Figure 1].

Figure 1
Robust Process for Selection of Cut-points into the Sponsor's Randomized Trials



4 PEMBROLIZUMAB DEVELOPMENT PROGRAM IN ESOPHAGEAL CANCER

The Sponsor has conducted several clinical studies of pembrolizumab in esophageal cancer and continues to explore new treatments options for patients with this malignancy as shown in [Table 1].

Table 1
Summary of the Esophageal Cancer Clinical Development Program

Study Number/ Status	Design	Population	Dosage, Regimen	Primary Efficacy Endpoint(s)
KEYNOTE-028 Completed for esophageal cohort	Phase 1 Multi-center, non-randomized, single-arm, multi-cohort	PD-L1 positive participants* Cohort A4 of advanced/metastatic esophageal cancer participants N=23	Pembrolizumab monotherapy (10 mg/kg Q2W)	ORR
KEYNOTE-180 Completed, reached predefined data cutoffs and analyses	Phase 2 Multi-center, non-randomized, single-arm, multi-cohort	PD-L1 CPS ≥10 and <10 subgroups PD-L1 CPS ≥1 and <1 subgroups Advanced/metastatic esophageal cancer participants, 3L+ N=121	Pembrolizumab monotherapy (200 mg Q3W)	ORR
KEYNOTE-181 Completed, reached predefined data cutoffs and analyses	Phase 3 Multi-center, randomized, open label	PD-L1 CPS ≥10 and <10 subgroups Advanced/metastatic esophageal cancer, 2L N=628 randomized	Pembrolizumab monotherapy (200 mg Q3W) or investigator's choice of paclitaxel, docetaxel, or irinotecan	OS
KEYNOTE-590 Completed, reached predefined data cutoffs and analyses	Phase 3 Multi-center, randomized, double-blind, placebo-controlled	PD-L1 CPS ≥10 and <10 subgroups Locally advanced unresectable or metastatic esophageal cancer, 1L N=749 randomized	Pembrolizumab (200 mg Q3W) or placebo in combination with chemotherapy	OS, PFS
KEYNOTE-975 Ongoing, not yet reached predefined data cutoffs and analyses; enrollment complete	Phase 3 Multi-center, randomized, double-blind, placebo-controlled	cTX N + M0 or cT2-T4aNXM0 ESCC (as defined by AJCC 8th edition), Siewert Type I adenocarcinoma of the GEJ, or EAC Target N =700; Actual randomized N = 703	Pembrolizumab (200 mg Q3W, 8 cycles) and then 400 mg Q6W (5 cycles) with dCRT or placebo with dCRT	OS, EFS

Study Number/ Status	Design	Population	Dosage, Regimen	Primary Efficacy Endpoint(s)
LEAP-014 Ongoing, not yet reached predefined data cutoffs and analyses	Phase 3 Multi-center, randomized, active controlled, open label. Run-in cohorts followed by Main study	Metastatic esophageal cancer, 1L Target N = 12 (FP and TP run-in cohorts) and N = 850 (main study)	Run-in: Pembrolizumab 400 mg Q6W + lenvatinib 8 mg once daily + FP Q3W; or Pembrolizumab 400 mg Q6W + lenvatinib 8 mg once daily + TP Q3W. Main study: Pembrolizumab 400 mg Q6W + lenvatinib 8 mg once daily + Investigator Choice (FP Q3W or TP Q3W or mFOLFOX6 Q2W) for Induction Phase followed by Pembrolizumab 400 mg Q6W + lenvatinib 20 mg once daily for Consolidation Phase; or Pembrolizumab 400 mg Q6W + Investigator Choice (FP Q3W or TP Q3W or mFOLFOX6 Q2W)	PFS OS

* A prototype immunohistochemical assay was used to determine PD-L1 positivity for KEYNOTE-028. This prototype assay was used before the PD-L1 IHC 22C3 pharmDx assay and quantification by CPS score.

Abbreviations: 1L = first line; 2L = second line; 3L+ = third line or later; AJCC = American Joint Committee on Cancer; cTX = chemotherapy; dCRT = definitive chemoradiotherapy; EAC = esophageal adenocarcinoma; EFS = event-free survival; ESCC = esophageal squamous cell carcinoma; FP = cisplatin + 5-flurouracil (5-FU); mFOLFOX6 = oxaliplatin + 5-FU + leucovorin; GEJ=gastroesophageal junction; ORR = objective response ratio or rate; OS = overall survival; PD L1 = programmed cell death-1 ligand-1; PFS = progression-free survival; Q2W = once every 2 weeks; Q3W = once every 3 weeks; Q6W = once every 6 weeks; TP = paclitaxel + cisplatin.

4.1 Regulatory History in Esophageal Cancer

The Sponsor received pre-Phase 3 feedback on the KEYNOTE-590 clinical trial and formal advice several times from the FDA during the study to align on the clinical trial design, endpoints, population, statistical analyses, and biomarker evaluation plan ([Table 12] in [Sec. 7.1]). At the interim analysis, the primary and key secondary efficacy endpoints for KEYNOTE-590 met the prespecified criteria for statistical significance in the PD-L1 all-comers population and upon FDA review, the Agency approved the following indication in March 2021: *pembrolizumab in combination with platinum- and fluoropyrimidine-based chemotherapy for the treatment of patients with locally advanced or metastatic esophageal or GEJ (tumors with epicenter 1 to 5 centimeters above the GEJ) carcinoma that is not amenable to surgical resection or definitive chemoradiation.*

Pembrolizumab monotherapy is also approved by the FDA in the 2L or greater settings for ESCC patients in CPS ≥10 based on results of KEYNOTE-181 and KEYNOTE-180.

These approvals fulfill a high unmet need for patients with advanced esophageal cancer.

4.2 Pembrolizumab Monotherapy Studies in Locally Advanced/Metastatic Esophageal Cancer – KEYNOTE-028, KEYNOTE-180, and KEYNOTE-181

KEYNOTE-028 was a Phase 1, non-randomized, single-arm study of pembrolizumab monotherapy in participants with advanced/metastatic esophageal cancer and who were PD-L1 positive as determined by a prototype assay [25]. A total of 23 participants received pembrolizumab in KEYNOTE-028. Treatment with pembrolizumab resulted in a clinically meaningful ORR (by BICR) of 18.2% (95% CI 5.2, 40.3) in KEYNOTE-028 (P028V02MK3475 clinical study report).

KEYNOTE-180 was a Phase 2, single-arm, open-label, multi-center study of pembrolizumab monotherapy in participants with previously treated, advanced/metastatic esophageal cancer. Participants were required to have been previously treated with ≥2 lines of therapy (3L+ setting). In this study, 121 participants were treated with pembrolizumab.

KEYNOTE-181 was a Phase 3 randomized, multi-center, open-label study of pembrolizumab monotherapy versus standard-of-care chemotherapy (investigator's choice of paclitaxel, docetaxel, or irinotecan) in participants with advanced/metastatic esophageal cancer. Participants were required to have been previously treated with 1 prior line of systemic therapy (2L setting). A total of 628 participants were randomized in this study (n = 314 in the pembrolizumab group and n = 314 in the chemotherapy group).

Data from these 3 studies established evidence to support the clinical benefit of pembrolizumab as monotherapy in esophageal cancer. Results of KEYNOTE-028, KEYNOTE-180 and KEYNOTE-181 are consistent with studies of pembrolizumab monotherapy in other tumors, which suggested that PD-L1 expression could be used to enrich for benefit [26]. As shown in [Table 2], ORR generally increased for participants with higher PD-L1 CPS scores, and in KEYNOTE-181, results for OS and PFS were consistent with ORR outcomes. Importantly, responses were observed in participants across PD-L1

CPS subgroups, even in participants with PD-L1 CPS <1. These data indicate that it is not possible to accurately predict which patients will benefit based on PD-L1 expression.

KEYNOTE-181 and KEYNOTE-180 results led to approvals for pembrolizumab monotherapy in the US in the 2L and 3L+ settings for patients with ESCC who have PD-L1 CPS ≥10.

Table 2
Objective Response Rate Based on RECIST 1.1 per BICR in KEYNOTE-180 and KEYNOTE-181

	KEYNOTE-180		KEYNOTE-181			
	Pembrolizumab Monotherapy		Pembrolizumab Monotherapy		Chemotherapy	
ORR	**N**	**% (95% CI)**	**n**	**% (95% CI)**	**n**	**% (95% CI)**
All participants	121	9.9 (5.2, 16.7)	314	13.1 (9.5, 17.3)	314	6.7 (4.2, 10.0)
PD-L1 CPS ≥10	58	13.8 (6.1, 25.4)	107	21.5 (14.1, 30.5)	115	6.1 (2.5, 12.1)
PD-L1 CPS <10	63	6.3 (1.8, 15.50	201	8.0 (4.6, 12.6)	196	7.1 (4.0, 11.7)
PD-L1 CPS ≥1*	104	8.7 (4.0, 15.8)	239	13.8 (9.7, 18.8)	242	6.2 (3.5, 10.0)
PD-L1 CPS <1	17	11.8 (1.5, 36.4)	69	8.7 (3.3, 18.0)	69	8.7 (3.3, 18.0)

CPS=combined positive score; CSR=clinical study report; ORR=objective response rate; PD-L1=programmed cell death-1 ligand-1

Source: P180V01MK3475 CSR, data cutoff 30JUL2018; P181V01MK3475 CSR, data cutoff 15OCT2018; KEYNOTE-181 supplemental tables: e19orr0bicr.rtf; e21orr0bicr0pdl1.rtf; e19orr0bicr0pdl1n.rtf

4.3 CPS ≥10 Cut-point Selection Based on Data from Initial Studies of Pembrolizumab Monotherapy in Esophageal Cancer

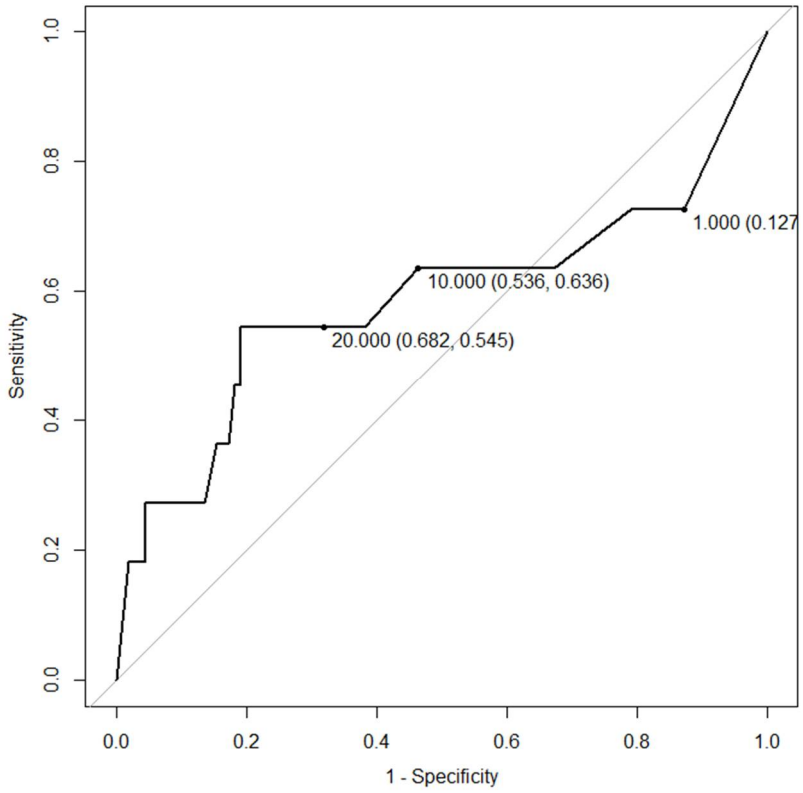
The PD-L1 expression cut-point of CPS ≥10 for PD-L1 IHC 22C3 pharmDx in esophageal cancer was determined and confirmed based on an analysis of data from study KEYNOTE-180.

The evaluation of the association between CPS and ORR (by central review) in KEYNOTE-180 was investigated via standard logistic regression, rank sum tests, and ROC curve analysis. The potential for an improved alternate to a CPS ≥1 cut-point involved a review of how the PPV (response rate in those above a cut-point), NPV (nonresponse rate in those below the cut-point), and fraction of participants having higher PD-L1 expression change as a function of increasing cut-points and whether there was evidence for a relative improvement in clinical utility relative to the CPS ≥1 cut-point. CPS ranges containing potential cut-points were also gauged in the context of practical implementation and interpretation by pathologists in clinical practice.

The KEYNOTE-180 trial enrolled 121 participants, all with evaluable PD-L1 data. These 121 participants were used to evaluate the association between CPS and response at an interim analysis to establish an enriching cut-off for utilization in ongoing randomized studies. The analysis included evaluation at the CPS ≥1 cut-point as well as evaluating the potential for an improved alternate cut-point. Eleven of the 121 participants were considered confirmed responders (partial or complete responders) via RECIST 1.1 (central review) at the

time of the analysis. Some evidence for an association between CPS score and higher probability of response was observed (one-sided p-values: p = 0.022 logistic regression, p = 0.171 rank sum test). [Figure 2] displays the ROC curve with the location of the CPS 1, 10, and 20 points and the associated specificity and sensitivity labeled in the figure. The area under the ROC curve was 0.59 (95% CI: 0.35, 0.82). [Table 3] shows various performance measures for CPS cut-points 1, 10, and 20.

Figure 2
ROC Curve for CPS in 121 Participants from KEYNOTE-180



Note: Points on ROC curve are labeled as (specificity, sensitivity).

Table 3
Performance Measures for Several CPS Cut-points in KEYNOTE-180 (N=121)

	CPS Cut-point		
Performance Measure:	**≥1**	**≥10**	**≥20**
%PPV/NPV	7.7/82.5	12.1/93.7	14.6/93.8
%Sens./Spec.	72.7/12.7	63.6/53.6	54.5/68.2
%Prevalence	86.0	47.9	33.9
PPV = response rate at or above cut-point; NPV = non-response rate below cut-point Prevalence = percent of patients with tumors score at or above cut-point			

The cut-point of CPS ≥1 did not suggest enrichment of response to pembrolizumab monotherapy in this population of esophageal cancer patients, with an ORR = 7.7% (8/104 participants) compared with the ORR of 9.1% (11/121 participants) in the all-participants population and an ORR of 17.6% (3/17 participants) in the CPS <1 group. At CPS ≥10, ORR increased to 12.1% (7/58). As shown in [Table 3], while the ORR was similar at CPS ≥20, there was a drop in sensitivity, with 1 additional responding participant who was not captured using CPS ≥20 (n=5 responders not captured) relative to CPS ≥10 (n=4 responders not captured), and a drop in prevalence compared to CPS ≥10. [Table 4] provides a summary of the best overall response (with confirmation) based on central imaging assessment per RECIST 1.1 using the CPS ≥10 cut-point.

Table 4
Best Response Summary Data for the CPS ≥10 Cut-point in KEYNOTE-180

	PD-L1 CPS≥10 (N=58)		**PD-L1 CPS<10 (N=63)**	
	N (%)	95% CI†	N (%)	95% CI†
Objective Response	7 (12.1)	(5.0, 23.3)	4 (6.3)	(1.8, 15.5)
Stable Disease (SD)	14 (24.1)	(13.9, 37.2)	12 (19.0)	(10.2, 30.9)

CPS=combined positive score; PD-L1=programmed cell death-1 ligand-1
† Based on binomial exact CI method
Database Cutoff Date: 17JUL2017

Given the large percentage of esophageal cancer observed to be CPS ≥1 and lack of clear enrichment in this late-line monotherapy study (which may reflect the limited sample size of the training set), the PPV, sensitivity and prevalence profile of KEYNOTE-180 favored CPS ≥10 as a potential biomarker for enrichment of response to pembrolizumab monotherapy, and subsequently it was prespecified and incorporated into randomized clinical studies evaluating pembrolizumab in esophageal cancer, including KEYNOTE-181 and KEYNOTE-590.

In KEYNOTE-590, participants were not stratified based on PD-L1 CPS score because the correlation of efficacy and PD-L1 expression at CPS ≥10 in patients with esophageal cancer was not established until after the study was initiated; however, the statistical analysis plan was adjusted in a later amendment of the KEYNOTE-590 protocol to formally test hypotheses in the CPS ≥10 population and the overall ITT population. Although CPS ≥1 was not a prespecified cut-point in KEYNOTE-590, this cut-point has been utilized in previous esophageal studies, and it continues to be used in our ongoing esophageal studies. Pathologists at our testing laboratories were previously trained and certified at this cut-point, and the testing laboratory had validated this cut-point, establishing reproducibility and repeatability. In addition, pathologists have indicated that it is easier to score around the CPS 1 cut-point, because it is intuitive to determine no expression versus some expression in the tumor area. Due to all these factors, the Sponsor has confidence in the accuracy of these data at the CPS 1 cut-point.

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

To ensure the robustness of the selected cut-points, the Sponsor has worked with its diagnostic partner and testing laboratories to analytically validate CPS ≥1 and CPS ≥10 in esophageal cancer specimens through internal and external analytical studies. No other cut-point has been analytically validated for 22C3 pharmDx in this tumor type. This validation process aimed to confirm the accuracy, precision, and robustness of the assay in measuring PD-L1 expression levels. Pathologists are trained to score samples at the cut-points specified in the study ensuring consistency and accuracy in the classification of patients into those subgroups. In addition, the pathologists have been trained to capture raw CPS scores (based on a continuous scoring system) as accurately and precisely as possible. The pathologists successfully completed training per a prespecified training plan, prior to evaluation PD-L1 expression in KEYNOTE-590.

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 [8]. 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 [27] [28] [29]. 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 [30] [31] [32]. Therefore, the combination of PD-(L)1 inhibitors plus chemotherapy can enhance anti-tumor effects [27]. Pembrolizumab plus chemotherapy has demonstrated efficacy across various tumor types [6] [33] [9] [11] [13] [14] [34] [14] [11] (KEYTRUDA USPI [accessed 09-MAY-2024]).

While early studies with pembrolizumab monotherapy and other anti-PD-(L)1 agents suggested that PD-L1 expression might enrich for benefit in several tumors, including esophageal cancer (KEYNOTE-028, KEYNOTE-180, KEYNOTE-181), limiting treatment to those whose tumors express PD-L1 may not be needed when combined with chemotherapy. For example, as a 1L treatment for NSCLC, pembrolizumab monotherapy showed substantial clinical activity in participants whose tumors expressed high levels of PD-L1 (TPS ≥50%) whereas moderate activity was observed in participants with TPS <1% or 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) [10] [35] [11] [Table 5]. Similar results have been observed in TNBC [12] [13] and HNSCC [14]. While these cross-study comparisons in different diseases 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 areas.

Table 5
Cross-study Comparison of Efficacy Results 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; 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 includes 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: [10] [9]

In locally advanced/metastatic esophageal cancer, data from KEYNOTE-181 established evidence to support the clinical benefit of pembrolizumab as monotherapy in this setting. From preclinical and clinical studies, chemotherapy augments the antitumor immune response and PD-(L)1 inhibition enhances the positive immune effects of chemotherapy [8] [27] [28] [29]. While PD-L1 expression may enrich for response, PD-L1 expression does not granularly predict who will have benefit, and it is known that some individual patients with CPS <1 tumors do respond to pembrolizumab monotherapy (see [Sec. 4.6.1.2.3], [Sec. 4.6.1.3.3], and [Sec. 4.6.1.4.3] and KEYTRUDA USPI [accessed 09-MAY-2024]).

4.6 KEYNOTE-590 Efficacy Results

Given the above data, the global, Phase 3, randomized, double-blind, placebo-controlled, multisite study, KEYNOTE-590, was designed with pembrolizumab in combination with chemotherapy (cisplatin and 5-FU) to enable meaningful response and survival in all participants across all levels of PD-L1 expression (ie, the ITT population) versus chemotherapy (cisplatin with 5-FU) as 1L treatment in participants with locally advanced unresectable metastatic adenocarcinoma or squamous cell carcinoma of the esophagus or advanced/metastatic Siewert type 1 adenocarcinoma of the GEJ ([Figure 24] in [Sec. 7.1]) [6].

As indicated previously, KEYNOTE-590 was initiated based on results from the pembrolizumab monotherapy study KEYNOTE-028 that showed that pembrolizumab induced anti-tumor responses in esophageal cancer patients (78% and 22% of participants in KEYNOTE-028 were ESCC and EAC, respectively). Following initiation of the KEYNOTE-590 study, data from KEYNOTE-180 indicated that CPS ≥10 was a potential cut-point that might be predictive for increased benefit. Therefore, the statistical testing plan was adjusted to formally test hypotheses in the CPS ≥10 population and the overall ITT population.

The prespecified multiplicity strategy ([Figure 25] in [Sec. 7.2]) for alpha allocation and hypothesis testing included OS and PFS as assessed by the investigator per RECIST 1.1 (dual primary endpoints) in the following populations: for both OS and PFS in all participants (overall ITT population); participants with PD-L1 CPS ≥10; participants with ESCC; and additionally for OS in participants with ESCC and PD-L1 CPS ≥10. The prespecified multiplicity strategy also included testing of ORR as determined by investigator per RECIST 1.1 in all participants (key secondary endpoint).

Additional secondary endpoints included change from baseline in HRQoL using the EORTC QLQ-C30 and EORTC QLQ-OES18 in all participants and in participants whose tumors express PD-L1 CPS ≥10, participants with ESCC, and in participants with ESCC whose tumors express PD-L1 CPS ≥10.

Prespecified statistical hypotheses in the PD-L1 CPS ≥10 population were included in the KEYNOTE-590 protocol in order to provide additional information regarding efficacy at higher PD-L1 levels. However, participants were not stratified based on PD-L1 CPS score because efficacy data analysis of the cut-point was not confirmed at the start of the study. Based on the prevalence of PD-L1 expression and the relatively large sample size, balance between treatment groups in KEYNOTE-590 was expected even though this was not a stratification factor. Baseline characteristics in KEYNOTE-590 showed that the percentages of participants by PD-L1 status were well balanced between treatment groups (see [Sec. 4.6.1.1]).

KEYNOTE-590 was designed in consultation with the FDA on the study design, endpoints, study population, statistical analyses, and biomarker evaluation plan. At the preplanned interim analysis (an interim analysis and final analysis were planned in the protocol), KEYNOTE-590 met statistical success criteria for all primary and key secondary endpoints in the overall ITT population regardless of PD-L1 expression establishing a new standard of care for the treatment of patients with advanced esophageal cancer in the first line setting. KEYNOTE-590 was the first study to show that an anti-PD-1/PD-L1 improved outcomes in this malignancy.

4.6.1 KEYNOTE-590: Key Efficacy Results

4.6.1.1 KEYNOTE-590: Disposition, Demographics and Baseline Characteristics

Participants with previously untreated locally advanced unresectable or metastatic carcinoma of the esophagus and gastroesophageal junction were enrolled in KEYNOTE-590. Among the 749 participants in the ITT population, 373 and 376 participants were randomized to the

pembrolizumab plus chemotherapy group and the chemotherapy group, respectively. As of 02-JUL-2020 (data cutoff), the median follow-up duration was longer for participants in the pembrolizumab plus chemotherapy group compared with the chemotherapy group (12.6 months vs 9.8 months).

The baseline characteristics of participants are representative of the global population of patients with unresectable or metastatic esophageal carcinoma ([Table 13] in [Sec. 7.3]). The primary diagnosis was ESCC in 73% of participants and EAC in 27% of participants, which were well balanced between treatment groups. This observed distribution by histology is expected for a global study of esophageal cancer [17]. Approximately 51% and 46% of participants had a PD-L1 status of PD-L1 CPS ≥10 and PD-L1 CPS <10, respectively, and 86.4% and 11.1% were PD-L1 CPS ≥1 and PD-L1 CPS <1, respectively (PD-L1 CPS score was missing for 19 participants at baseline). The percentages of participants by PD-L1 status were well balanced between treatment groups (ie, in the CPS ≥10, CPS <10, CPS ≥1, CPS <1 subgroups).

4.6.1.2 KEYNOTE-590: Overall Survival

Pembrolizumab plus chemotherapy met the success criteria for the hypotheses of the primary endpoint in OS, showing statistically significant and clinically meaningful improvement in OS compared with chemotherapy in previously untreated locally advanced unresectable or metastatic carcinoma of the esophagus and gastroesophageal junction across all prespecified populations (all participants [ITT population] [H4], PD-L1 CPS ≥10 participants [H3], ESCC participants [H2], and ESCC PD-L1 CPS ≥10 participants [H1]) [Table 6] [Sec. 4.6.1.2.1] [Sec. 4.6.1.2.2] (see ([Figure 25] in [Sec. 7.2]) for alpha allocation and hypothesis testing). This supports the current labelled indication for KEYNOTE-590.

Table 6
KEYNOTE-590: Summary of Overall Survival
(ITT Population)

Endpoints & Hypotheses (Pembrolizumab + Chemotherapy vs. Chemotherapy)		Number of Events Observed	Observed HR (95% CI)	p-value Crossing Boundary	Observed p-Value	Outcome
Primary	OS in all participants (H4)	571	0.73 (0.62, 0.86)[a]	0.01421	<0.0001[d]	Statistically significant
	OS in CPS ≥10 (H3)	289	0.62 (0.49, 0.78)[b]	0.01414	<0.0001[e]	Statistically significant
	OS in ESCC Participants (H2)	412	0.72 (0.60, 0.88)[c]	0.01003	0.0006[f]	Statistically significant
	OS in ESCC Participants with CPS ≥10 (H1)	215	0.57 (0.43, 0.75)[c]	0.0067	<0.0001[f]	Statistically significant

CI=confidence interval; CPS=combined positive score; ECOG: Eastern Cooperative Oncology Group; ESCC= esophageal squamous cell carcinoma; H=hypothesis; HR=hazard ratio; OS=overall survival; PD-L1=programmed cell death ligand 1.

a. Based on Cox regression model with Efron's method of tie handling with treatment as a covariate stratified by geographic region (Asia versus Rest of the World) and tumor histology (Adenocarcinoma versus Squamous Cell Carcinoma) and ECOG performance status (0 versus 1).
b. Based on Cox regression model with Efron's method of tie handling with treatment as a covariate stratified by geographic region (Asia versus Rest of the World) and tumor histology (Adenocarcinoma versus Squamous Cell Carcinoma).
c. Based on Cox regression model with Efron's method of tie handling with treatment as a covariate stratified by geographic region (Asia versus Rest of the World and ECOG performance status (0 versus 1).
d. One-sided p-value based on log-rank test stratified by geographic region (Asia versus Rest of the World) and tumor histology (Adenocarcinoma versus Squamous Cell Carcinoma) and ECOG performance status (0 versus 1).
e. One-sided p-value based on log-rank test stratified by geographic region (Asia versus Rest of the World) and tumor histology (Adenocarcinoma versus Squamous Cell Carcinoma).
f. One-sided p-value based on log-rank test stratified by geographic region (Asia versus Rest of the World) and ECOG performance status (0 versus 1).

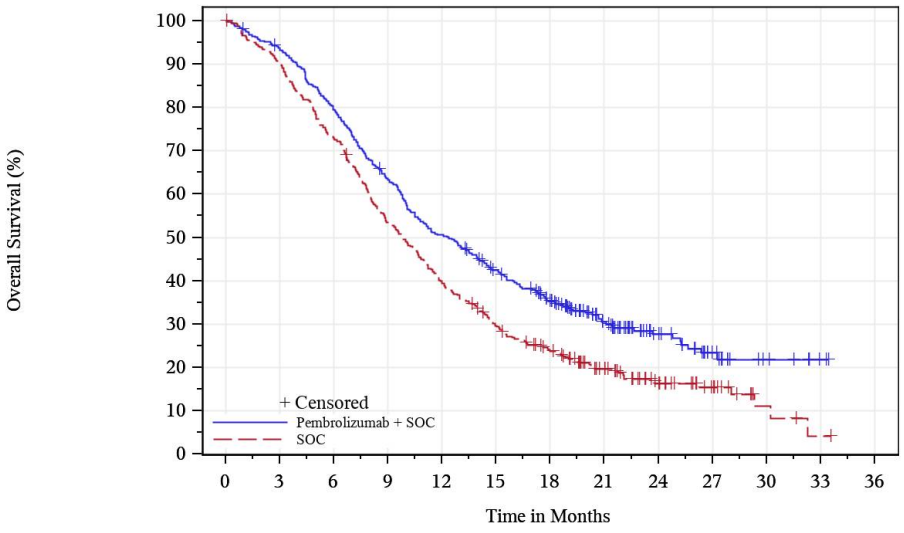
Database Cutoff Date: 02JUL2020

4.6.1.2.1 Overall Survival in ITT Population and Per Protocol CPS Cut-point Population

Pembrolizumab plus chemotherapy was superior to chemotherapy for the primary endpoint of OS in all participants (ITT population) [Figure 3] ([Table 14] in [Sec. 7.3]). The HR for OS was 0.73 (95% CI: 0.62, 0.86), with $p<0.0001$, which is less than the p-value crossing boundary of 0.01421 for statistical significance in favor of pembrolizumab plus chemotherapy compared to chemotherapy. This represents a 27% reduction in the risk of death. The median OS was 12.4 months (95% CI: 10.5, 14.0) and 9.8 months (95% CI: 8.8, 10.8) for pembrolizumab plus chemotherapy and chemotherapy alone arms, respectively. The 2-year OS rate (KM estimates) was higher for pembrolizumab plus chemotherapy (27.7%) versus chemotherapy (16.3%) ([Table 15] in [Sec. 7.3]). As described above, the observed long-term benefit in KEYNOTE-590 is characteristic of treatment with checkpoint inhibitors and is not commonly seen with chemotherapy alone in this population.

In addition, pembrolizumab plus chemotherapy was superior to chemotherapy for the primary endpoint of OS in participants with PD-L1 CPS ≥10 [Figure 4] ([Table 16] in [Sec. 7.3]). The HR for OS was 0.62 (95% CI: 0.49, 0.78), with $p<0.0001$, which is less than the p-value crossing boundary of 0.01414 for statistical significance in favor of pembrolizumab plus chemotherapy compared to chemotherapy. This represents a 38% reduction in the risk of death. The median OS was 13.5 months (95% CI: 11.1, 15.6) and 9.4 months (95% CI: 8.0, 10.7) for pembrolizumab plus chemotherapy and chemotherapy, respectively.

Figure 3
KEYNOTE-590 - Kaplan-Meier Estimates of Overall Survival
(ITT Population)

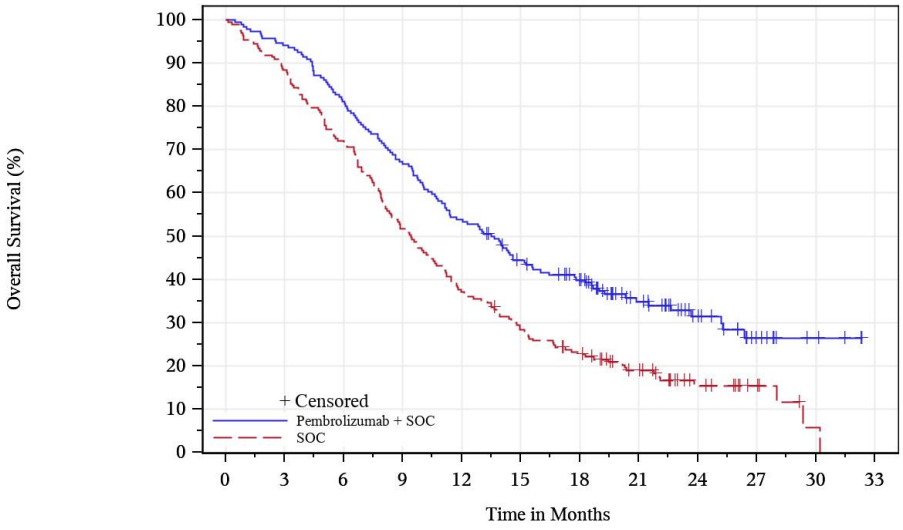


Number of Subjects at Risk

Pembrolizumab + SOC	373	348	295	235	187	151	118	68	36	17	7	2	0
SOC	376	338	274	200	147	108	82	51	28	15	4	1	0

Database Cutoff Date: 02JUL2020
Source: [P590V01MK3475: adam-adsl; adtte]

Figure 4
KEYNOTE-590 - Kaplan-Meier Estimates of Overall Survival
(Participants with PD-L1 CPS >= 10, ITT Population)



Number of Subjects at Risk

Pembrolizumab + SOC	186	175	151	125	100	79	66	40	23	10	4	0
SOC	197	174	142	102	73	55	42	28	13	6	1	0

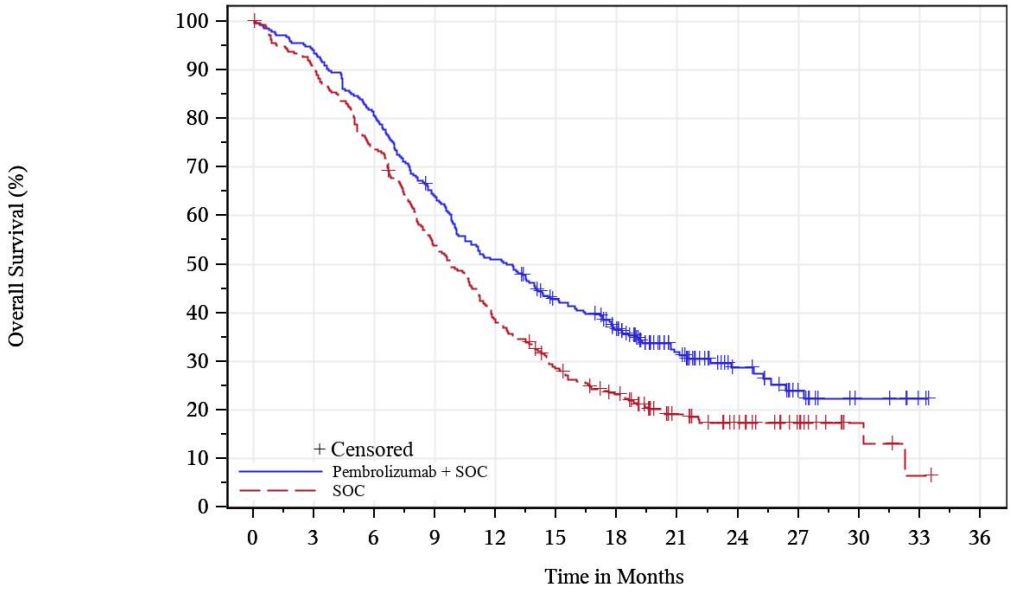
Database Cutoff Date: 02JUL2020
Source: [P590V01MK3475: adam-adsl; adtte]

4.6.1.2.2 Overall Survival by Histology Subgroup

Pembrolizumab plus chemotherapy was also superior to chemotherapy for the primary endpoint of OS in ESCC participants [Figure 5] ([Table 17] in [Sec. 7.3]). The HR for OS was 0.72 (95% CI: 0.60, 0.88), with p=0.0006, which is less than the p-value crossing boundary of 0.01003 for statistical significance in favor of pembrolizumab plus chemotherapy compared to chemotherapy. This represents a 28% reduction in the risk of death. The median OS was 12.6 months (95% CI: 10.2, 14.3) and 9.8 months (95% CI: 8.6, 11.1) for pembrolizumab plus chemotherapy and chemotherapy, respectively. The 2-year OS rate (KM estimates) was higher for pembrolizumab plus chemotherapy (28.6%) versus chemotherapy (17.3%) ([Table 18] in [Sec. 7.3]). The observed long-term benefit for the ESCC subgroup in KEYNOTE-590 is characteristic of treatment with checkpoint inhibitors.

Pembrolizumab plus chemotherapy was also superior to chemotherapy for the primary endpoint of OS in ESCC participants with PD-L1 CPS ≥10 [Figure 6] ([Table 17] in [Sec. 7.3]). The HR for OS was 0.57 (95% CI: 0.43, 0.75), with $p<0.0001$, which is less than the p-value crossing boundary of 0.0067 for statistical significance in favor of pembrolizumab plus chemotherapy compared to chemotherapy. This represents a 43% reduction in the risk of death. The median OS was 13.9 months (95% CI: 11.1, 17.7) and 8.8 months (95% CI: 7.8, 10.5) for pembrolizumab plus chemotherapy and chemotherapy, respectively.

Figure 5
KEYNOTE-590 - Kaplan-Meier Estimates of Overall Survival
(Participants with Squamous Cell Carcinoma, ITT Population)

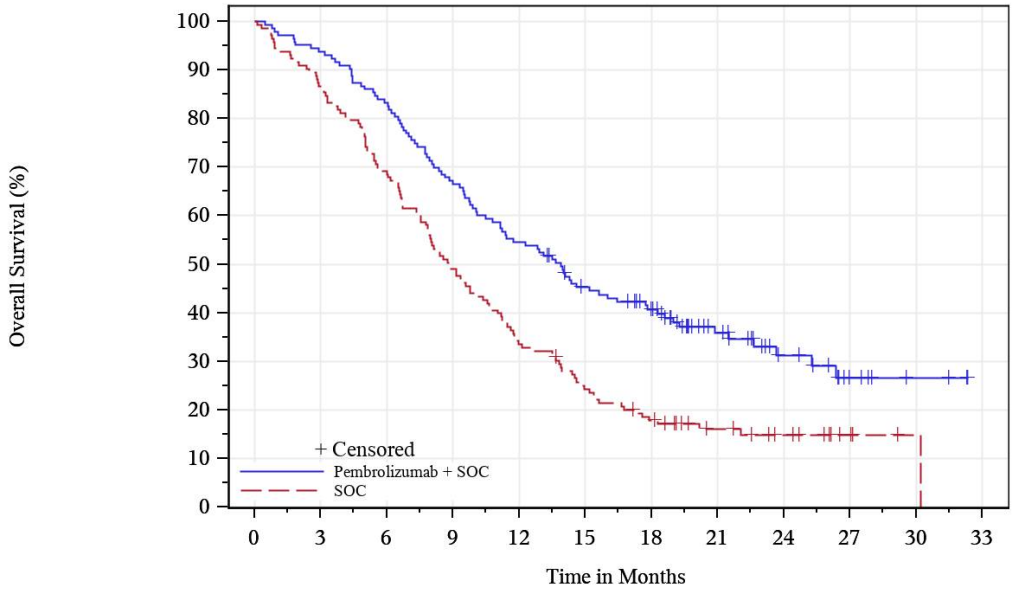


Number of Subjects at Risk

Pembrolizumab + SOC	274	258	221	175	139	111	89	50	27	14	6	2	0
SOC	274	247	203	146	103	75	57	34	23	13	4	1	0

Database Cutoff Date: 02JUL2020
Source: [P590V01MK3475: adam-adsl; adtte]

Figure 6
KEYNOTE-590 - Kaplan-Meier Estimates of Overall Survival
(Participants with Squamous Cell Carcinoma and PD-L1 CPS >= 10, ITT Population)



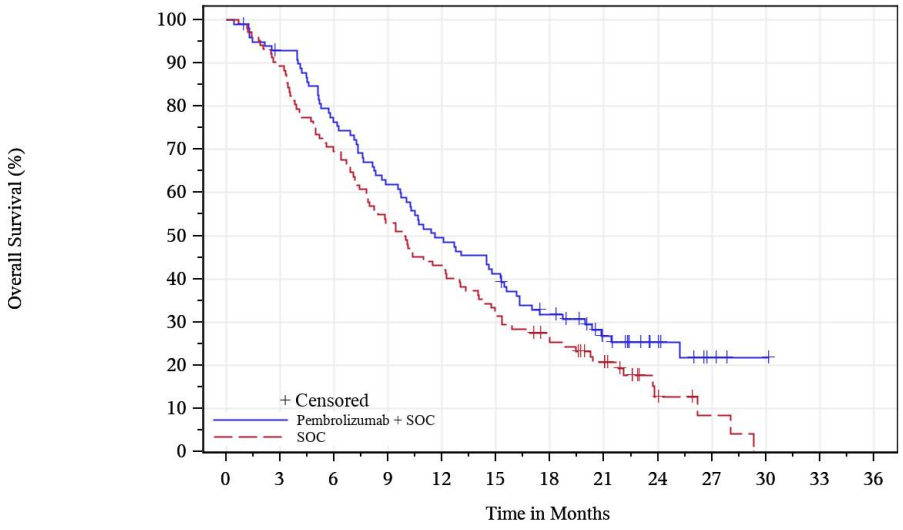
Number of Subjects at Risk

Pembrolizumab + SOC	143	134	119	96	78	61	51	29	16	7	3	0
SOC	143	124	99	70	48	34	24	15	10	4	1	0

Database Cutoff Date: 02JUL2020
Source: [P590V01MK3475: adam-adsl; adtte]

OS results in participants with EAC were also consistent with results in all participants and participants with ESCC. In EAC participants, the HR was 0.74 (95% CI: 0.54, 1.02) in favor of pembrolizumab plus chemotherapy versus chemotherapy [Figure 7] ([Table 20] in [Sec. 7.3]). The median OS was 11.6 months (95% CI: 9.7, 15.2) and 9.9 months (95% CI: 7.8, 12.3) for pembrolizumab plus chemotherapy and chemotherapy, respectively. The prespecified multiplicity strategy for alpha allocation and hypothesis testing did not include analysis of OS in the EAC subgroup in KEYNOTE-590 ([Table 13] in [Sec. 7.3]). The number of participants in the EAC subgroup (n = 201) was also smaller compared to the ESCC subgroup (n = 548).

Figure 7
KEYNOTE-590 - Kaplan-Meier Estimates of Overall Survival
(Participants with Adenocarcinoma, ITT Population)



Number of Subjects at Risk

Pembrolizumab + SOC	99	90	74	60	48	40	29	18	9	3	1	0	0
SOC	102	91	71	54	44	33	25	17	5	2	0	0	0

Database Cutoff Date: 02JUL2020
Source: [P590V01MK3475: adam-adsl; adtte]

4.6.1.2.3 Exploratory Analysis of Overall Survival by CPS Cut-point

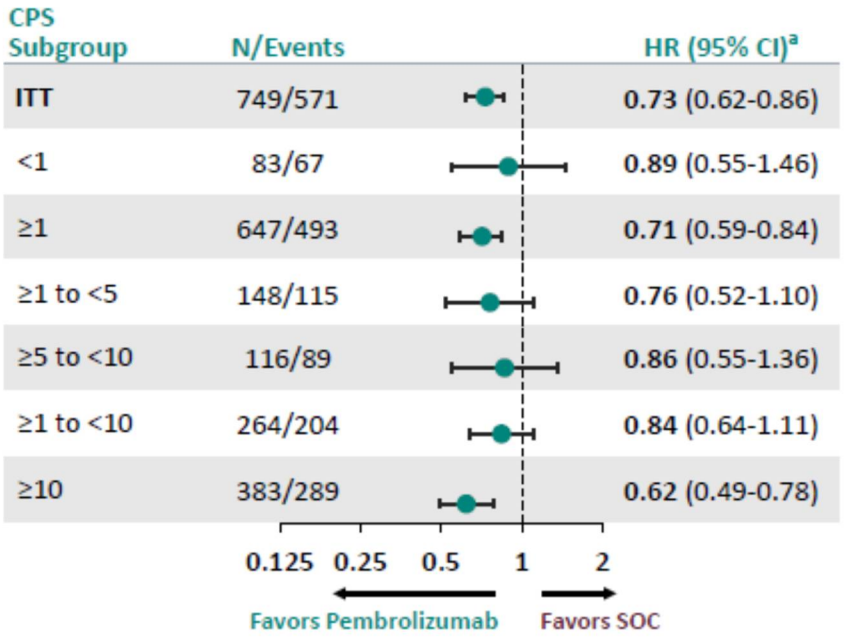
In preparation for this ODAC, the FDA requested information on subgroups using different CPS cut-points. Many of the requested PD-L1 subgroups were not prespecified and the study was not powered to definitively demonstrate statistically significant efficacy in the requested subgroups. The analyses are post hoc and exploratory, and there are small numbers of participants in some subgroups.

Pathologists were trained to score samples at the cut-point specified in the KEYNOTE-590 protocol (CPS ≥10), ensuring consistency and accuracy in the classification of patients into those subgroups. There are no analytical validation data at the CPS ≥5 cutoff for the PD-L1 IHC 22C3 pharmDx kit in any tumor type studied at Merck, and therefore precision and reproducibility around this cutoff are uncertain. PD-L1 raw scores were used to derive the subgroups by CPS cut-points that were not prespecified. Of note, there is inconsistency in results with the ≥1 to <5 and ≥5 to <10 subgroups, with better OS HR observed in the ≥1 to <5 subgroup. This may reflect variability of small subgroups based on raw scores at the CPS 5 cut-point.

In KEYNOTE-590, a greater magnitude of benefit is observed in the prespecified CPS ≥10 subgroup relative to the overall ITT population as noted above in [Sec. 4.6.1.2.1], but a consistent treatment effect, directionally aligned with the result in the ITT population, was observed in all PD-L1 CPS subgroups ([Figure 8] and [Table 21] in [Sec. 7.3]). The observed

HR point estimates for all subgroups were less than 1 with confidence intervals overlapping the results in the ITT population.

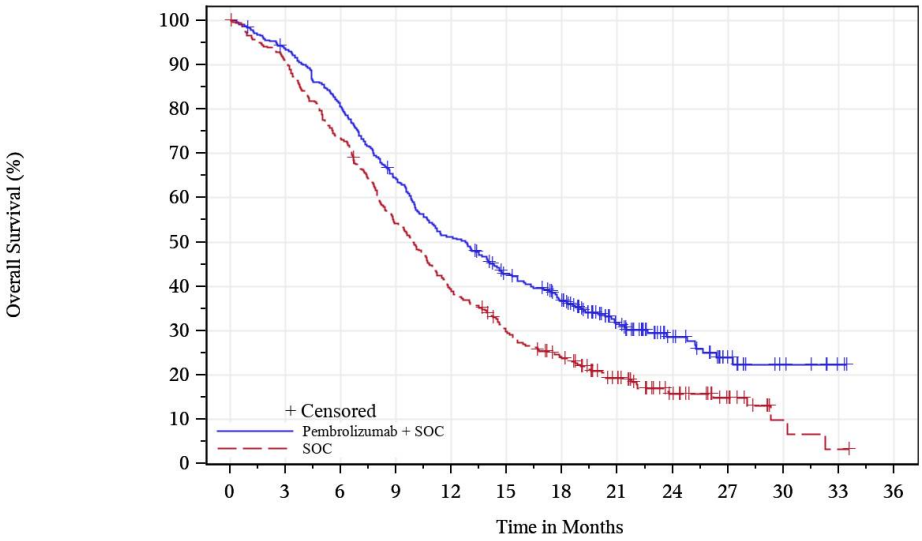
Figure 8
KEYNOTE-590 – Forest Plot of OS Hazard Ratio by PD-L1 CPS Subgroup (ITT Population)



[a]Based on stratified Cox regression model with small strata collapsed as pre-specified in the sSAP.
Database Cutoff Date: 02JUL2020
Source tables: prot590_final_gecko_os_22MAR2024.rtf

At the PD-L1 CPS ≥1 cut-point (which includes 86% of participants in the overall ITT population), results favored pembrolizumab plus chemotherapy; the improvement in OS in the pembrolizumab plus chemotherapy group versus the chemotherapy group was directionally consistent with the overall ITT population and support a favorable benefit to risk ratio in the ITT population In PD-L1 CPS ≥1 participants, the OS HR was 0.71 (95% CI: 0.59, 0.84) [Figure 9] ([Table 22] in [Sec. 7.3]).

Figure 9
KEYNOTE-590 - Kaplan-Meier Estimates of Overall Survival
(Participants with PD-L1 CPS >= 1, ITT Population)



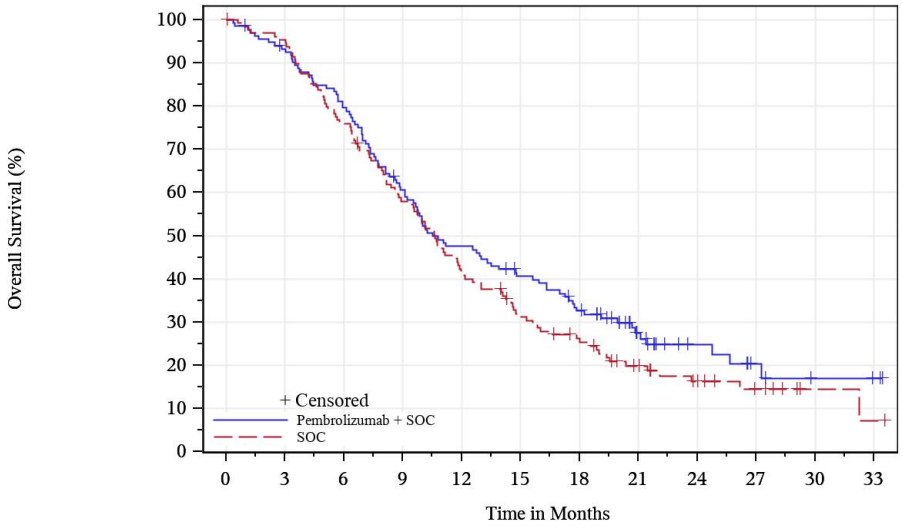
Number of Subjects at Risk

Pembrolizumab + SOC	320	298	256	204	162	130	106	61	34	16	7	2	0
SOC	327	297	240	176	126	94	72	47	25	13	3	1	0

Database Cutoff Date: 02JUL2020
Source: [P590V01MK3475: adam-adsl; adtte]

In the PD-L1 CPS ≥1 to <10 subgroup, OS results also support improved treatment benefit for participants who received pembrolizumab plus chemotherapy versus chemotherapy [Figure 10] ([Table 23] in [Sec. 7.3]). The OS HR was 0.84 (95% CI: 0.64, 1.11).

Figure 10
Kaplan-Meier Estimates of Overall Survival
(Participants with PD-L1 1 <= CPS < 10, ITT Population)



Number of Subjects at Risk

Pembrolizumab + SOC	134	123	105	79	62	51	40	21	11	6	3	2
SOC	130	123	98	74	53	39	30	19	12	7	2	1

Database Cutoff Date: 02JUL2020
Source: [P590V01MK3475: adam-adsl; adtte]

There were very few participants with PD-L1 CPS <1 (n = 41 and n = 42 in the pembrolizumab plus chemotherapy and chemotherapy groups, respectively) and this subgroup analysis was not powered to detect a statistically significant or clinically meaningful treatment difference as in all participants. Despite the limited sample size, the observed efficacy with chemotherapy combined with pembrolizumab was directionally consistent with the ITT population with overlapping confidence intervals, acknowledging that the observed magnitude of benefit is less than in the ITT population, with an OS HR of 0.89 (95% CI: 0.55, 1.46) ([Table 24], [Figure 26] in [Sec. 7.3]).

Overall, KEYNOTE-590 met its prespecified endpoints in the all-comers population. Although the data suggest that PD-L1 expression cut-points may allow for enrichment of the probability to benefit from pembrolizumab plus chemotherapy, the level of PD-L1 expression as measured by CPS score does not predict which patients will have benefit. Pembrolizumab plus chemotherapy is anticipated to enable meaningful responses, including for some patients who have tumors with PD-L1 CPS <10 or PD-L1 CPS <1 at baseline. The data continue to support the positive benefit-risk assessment for the currently approved US indication: overall ITT population (all participants) for KEYNOTE-590.

4.6.1.3 KEYNOTE-590: Progression-free Survival

Pembrolizumab plus chemotherapy met the success criteria for the hypotheses of the primary endpoint in PFS, showing statistically significant and clinically meaningful improvement in in PFS as assessed by the investigator per RECIST 1.1 across all prespecified populations (all

participants [ITT population] [H7], PD-L1 CPS ≥10 participants [H6], and ESCC participants [H5] [Sec. 4.6.1.3.1] and [Sec. 4.6.1.3.2]) (see ([Figure 25] in [Sec. 7.2]) for alpha allocation and hypothesis testing), again supporting the current indication for KEYNOTE-590.

Table 7
KEYNOTE-590: Summary of Progression-free Survival (Primary Censoring Rule) Based on Investigator Assessment Per RECIST 1.1 (ITT Population)

Endpoints & Hypotheses (Pembrolizumab + Chemotherapy vs. Chemotherapy)		Number of Events Observed	Observed HR (95% CI)	p-value Crossing Boundary	Observed p-Value	Outcome
Primary	PFS in all participants (H7)	630	0.65 (0.55, 0.76)[a]	0.02477	<0.0001[d]	Statistically significant
	PFS in CPS ≥10 (H6)	314	0.51 (0.41, 0.65)[b]	0.002	<0.0001[e]	Statistically significant
	PFS in ESCC Participants (H5)	463	0.65 (0.54, 0.78)[c]	0.002	<0.0001[f]	Statistically significant

CI=confidence interval; CPS=combined positive score; ECOG: Eastern Cooperative Oncology Group; ESCC= esophageal squamous cell carcinoma; H=hypothesis; HR=hazard ratio; PFS=progression-free survival; PD-L1=programmed cell death ligand 1.

a. Based on Cox regression model with Efron's method of tie handling with treatment as a covariate stratified by geographic region (Asia versus Rest of the World) and tumor histology (Adenocarcinoma versus Squamous Cell Carcinoma) and ECOG performance status (0 versus 1).
b. Based on Cox regression model with Efron's method of tie handling with treatment as a covariate stratified by geographic region (Asia versus Rest of the World) and tumor histology (Adenocarcinoma versus Squamous Cell Carcinoma).
c. Based on Cox regression model with Efron's method of tie handling with treatment as a covariate stratified by geographic region (Asia versus Rest of the World) and ECOG performance status (0 versus 1).
d. One-sided p-value based on log-rank test stratified by geographic region (Asia versus Rest of the World) and tumor histology (Adenocarcinoma versus Squamous Cell Carcinoma) and ECOG performance status (0 versus 1).
e. One-sided p-value based on log-rank test stratified by geographic region (Asia versus Rest of the World) and tumor histology (Adenocarcinoma versus Squamous Cell Carcinoma).
f. One-sided p-value based on log-rank test stratified by geographic region (Asia versus Rest of the World) and ECOG performance status (0 versus 1).

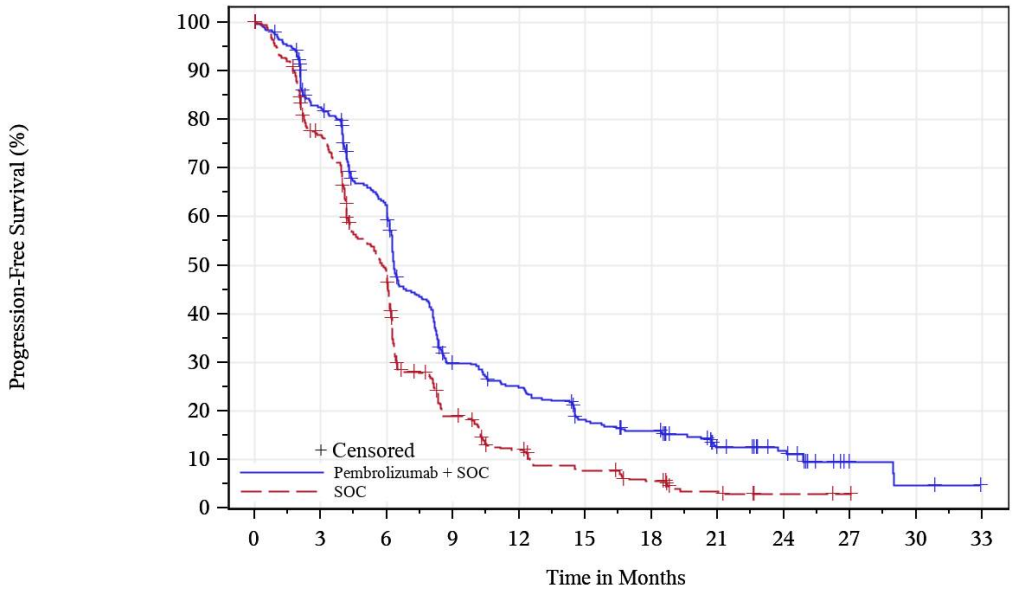
Database Cutoff Date: 02JUL2020

4.6.1.3.1 Progression-free Survival in ITT Population and Per Protocol CPS Cut-point Population

Pembrolizumab plus chemotherapy was superior to chemotherapy for the primary endpoint of PFS as assessed by the investigator per RECIST 1.1 in all participants (ITT population) [Figure 11] ([Table 25] in [Sec. 7.3]). The HR for PFS based on investigator assessment per RECIST 1.1 was 0.65 (95% CI: 0.55, 0.76; p<0.0001, which is less than the p-value crossing boundary of 0.02477 for statistical significance) in favor of pembrolizumab compared to chemotherapy, representing a 35% reduction in the risk of progression or death compared with chemotherapy. The median PFS was 6.3 months (95% CI: 6.2, 6.9) and 5.8 months (95% CI: 5.0, 6.0) for pembrolizumab plus chemotherapy and chemotherapy, respectively. The 18-month PFS rate (KM estimates) was higher for pembrolizumab plus chemotherapy (15.8%) versus chemotherapy (5.5%) ([Table 26] in [Sec. 7.3]). The observed long-term benefit in KEYNOTE-590 is characteristic of treatment with checkpoint inhibitors.

Pembrolizumab plus chemotherapy was also superior to chemotherapy for the primary endpoint of PFS as assessed by the investigator in PD-L1 CPS ≥10 participants [Figure 12] ([Table 27] in [Sec. 7.3]). The HR for PFS based on investigator assessment per RECIST 1.1 was 0.51 (95% CI: 0.41, 0.65; $p<0.0001$, which is less than the p-value crossing boundary of 0.002 for statistical significance) in favor of pembrolizumab compared to chemotherapy, representing a 49% reduction in the risk of progression or death compared with chemotherapy. Median PFS was 7.5 months (95% CI: 6.2, 8.2) and 5.5 months (95% CI: 4.3, 6.0) for pembrolizumab plus chemotherapy and chemotherapy, respectively.

Figure 11
KEYNOTE-590 - Kaplan-Meier Estimates of Progression-Free Survival Based on Investigator Assessment Per RECIST 1.1 (Primary Censoring Rule) (ITT Population)

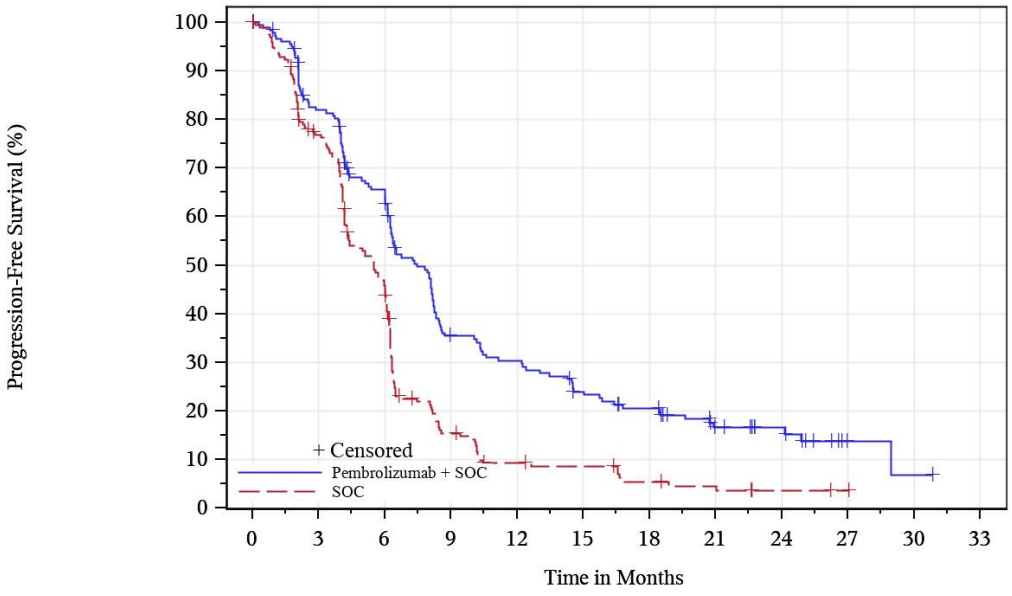


Number of Subjects at Risk

Pembrolizumab + SOC	373	289	210	96	79	55	45	25	17	4	2	0
SOC	376	278	172	62	36	22	14	6	2	1	0	0

Database Cutoff Date: 02JUL2020
Source: [P590V01MK3475: adam-adsl; adtte]

Figure 12
KEYNOTE-590 - Kaplan-Meier Estimates of Progression-Free Survival Based on Investigator Assessment Per RECIST 1.1 (Primary Censoring Rule)
(Participants with PD-L1 CPS >= 10, ITT Population)



Number of Subjects at Risk

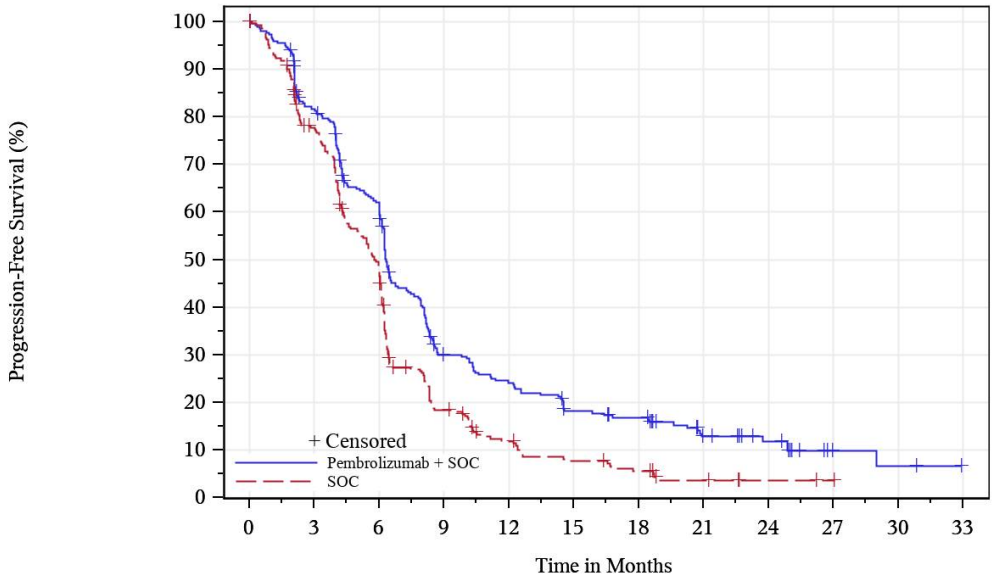
Pembrolizumab + SOC	186	143	109	56	48	36	29	17	12	2	1	0
SOC	197	145	85	26	14	12	7	5	2	1	0	0

Database Cutoff Date: 02JUL2020
Source: [P590V01MK3475: adam-adsl; adtte]

4.6.1.3.2 Progression-free Survival by Histology Subgroup

Pembrolizumab plus chemotherapy is superior to chemotherapy for the primary endpoint of PFS as assessed by the investigator in ESCC participants [Figure 13] ([Table 28] in [Sec. 7.3]). The median PFS was 6.3 months (95% CI: 6.2, 6.9) for the pembrolizumab plus chemotherapy group and 5.8 months (95% CI: 5.0, 6.1) for the chemotherapy group. The PFS HR was 0.65 (95% CI: 0.54, 0.78; p<0.0001, which is less than the p-value crossing boundary of 0.002 for statistical significance) in favor of pembrolizumab compared to chemotherapy, representing a 35% reduction in the risk of disease progression or death.

Figure 13
KEYNOTE-590 - Kaplan-Meier Estimates of Progression-Free Survival Based on Investigator Assessment Per RECIST 1.1 (Primary Censoring Rule) (Participants with Squamous Cell Carcinoma, ITT Population)



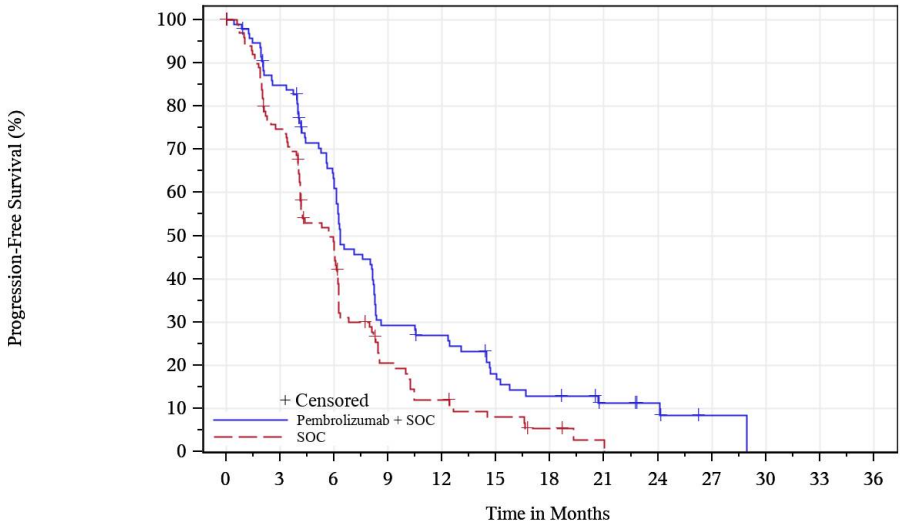
Number of Subjects at Risk

Pembrolizumab + SOC	274	211	156	71	57	41	35	19	13	3	2	0
SOC	274	205	127	45	26	16	11	5	2	1	0	0

Database Cutoff Date: 02JUL2020
Source: [P590V01MK3475: adam-adsl; adtte]

PFS results in participants with EAC were consistent with results in all participants and participants with ESCC. In participants with EAC, the PFS HR was 0.63 (95% CI: 0.46, 0.87) in favor of pembrolizumab plus chemotherapy versus chemotherapy [Figure 14] ([Table 29] in [Sec. 7.3]). The median PFS was 6.3 months (95% CI: 6.0, 8.1) and 5.7 months (95% CI: 4.1, 6.2) in the pembrolizumab plus chemotherapy and chemotherapy groups, respectively. The prespecified multiplicity strategy for alpha allocation and hypothesis testing did not include analysis of PFS in the EAC subgroup in KEYNOTE-590.

Figure 14
KEYNOTE-590 - Progression-Free Survival Based on Investigator Assessment per RECIST 1.1 (Primary Censoring Rule) (Participants with Adenocarcinoma, ITT Population)



Number of Subjects at Risk

Pembrolizumab + SOC	99	78	54	25	22	14	10	6	4	1	0	0	0
SOC	102	73	45	17	10	6	3	1	0	0	0	0	0

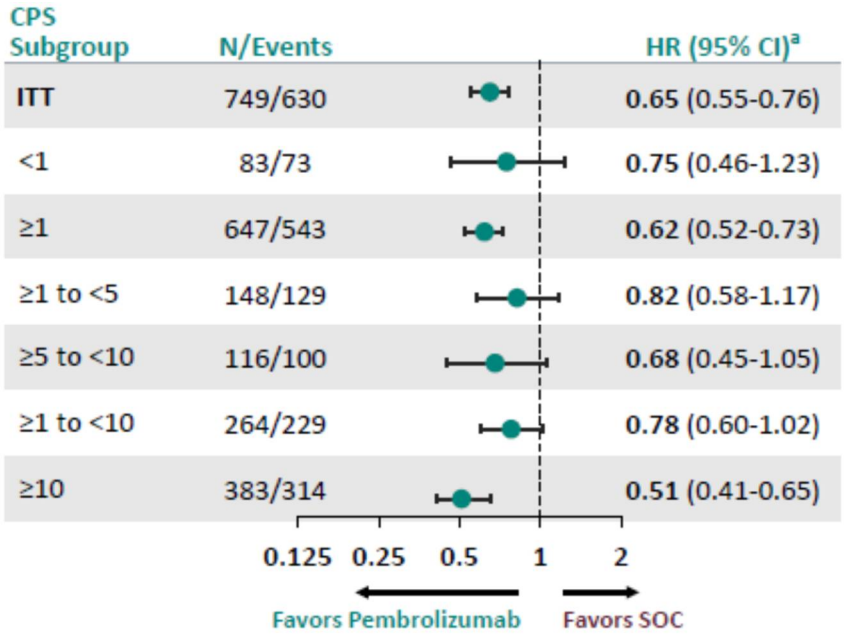
Progression-free survival is defined as time from randomization to disease progression, or death, whichever occurs first.
Database Cutoff Date: 02JUL2020
Source: [P590V01MK3475: adam-adsl; adtte]

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

As noted in [Sec. 4.6.1.2.3], an exploratory analysis using different CPS cut-points was performed for PFS in response to the FDA request. The analyses were performed as described above for OS.

In KEYNOTE-590, pembrolizumab in combination with chemotherapy shows a favorable trend in PFS when compared with chemotherapy at all CPS cut-points. A consistent treatment effect, directionally aligned with the result in the overall ITT population, was observed in all PD-L1 CPS subgroups [Figure 15] ([Table 30] in [Sec. 7.3]). The observed HR point estimates for all subgroups were less than 1 with confidence intervals overlapping the results in the ITT population.

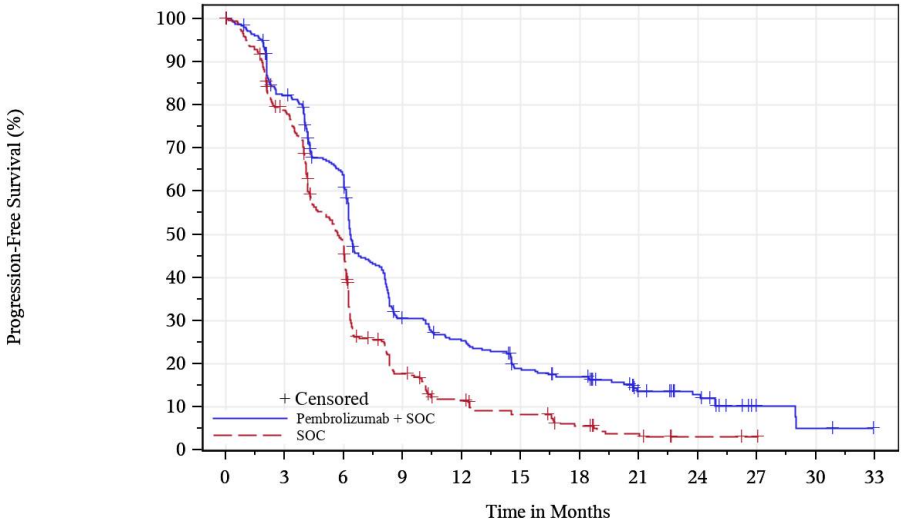
Figure 15
KEYNOTE-590 - Forest Plot of PFS Hazard Ratio by PD-L1 CPS Subgroup Based on Investigator Assessment per RECIST 1.1 (Primary Censoring Rule)
(ITT Population)



Database Cutoff Date: 02JUL2020
Source tables: prot590_final_gecko_pfs_22MAR2024.rtf

At the PD-L1 CPS ≥1 cut-point (which includes 86% of participants in the overall ITT population), results favored pembrolizumab plus chemotherapy; the improvement in PFS in the pembrolizumab plus chemotherapy group versus the chemotherapy group was clinically meaningful and directionally consistent with the overall ITT population and support a favorable benefit to risk ratio in the ITT population. In PD-L1 CPS ≥1 participants, the PFS HR was 0.62 (95% CI: 0.52, 0.73); [Figure 16] ([Table 31] in [Sec. 7.3]).

Figure 16
KEYNOTE-590 - Kaplan-Meier Estimates of Progression-Free Survival Based on Investigator Assessment per RECIST 1.1 (Primary Censoring Rule)
(Participants with PD-L1 CPS >= 1, ITT Population)



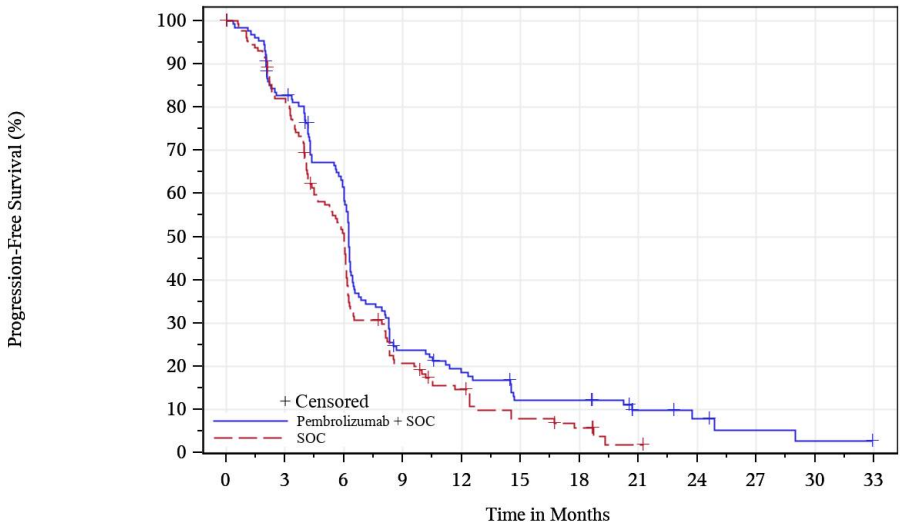
Number of Subjects at Risk

Pembrolizumab + SOC	320	247	184	84	69	49	42	23	16	4	2	0
SOC	327	249	148	51	30	20	12	6	2	1	0	0

Database Cutoff Date: 02JUL2020
Source: [P590V01MK3475: adam-adsl; adtte]

In the PD-L1 CPS ≥1 to <10 subgroup, PFS results also support improved treatment benefit for participants who received pembrolizumab plus chemotherapy versus chemotherapy [Figure 17] ([Table 32] in [Sec. 7.3]). The PFS HR was 0.78 (95% CI: (0.60, 1.02).

Figure 17
Kaplan-Meier Estimates of Progression-Free Survival Based on Investigator Assessment per RECIST 1.1
(Primary Censoring Rule)
(Participants with PD-L1 1 <= CPS < 10, ITT Population)



Number of Subjects at Risk

Pembrolizumab + SOC	134	104	75	28	21	13	13	6	4	2	1	0
SOC	130	104	63	25	16	8	5	1	0	0	0	0

Database Cutoff Date: 02JUL2020
Source: [P590V01MK3475: adam-adsl; adtte]

In the PD-L1 CPS <1 subgroup, despite the limited sample size (n = 41 and n = 42 in the pembrolizumab plus chemotherapy and chemotherapy groups, respectively), the observed efficacy with chemotherapy combined with pembrolizumab is directionally consistent with the ITT population with overlapping confidence intervals, acknowledging that the observed magnitude of benefit is less than in the ITT population. In the PD-L1 CPS <1 subgroup, the PFS HR was 0.75 (95% CI: 0.46, 1.23) ([Table 33], [Figure 27] in [Sec. 7.3]).

KEYNOTE-590 met the prespecified PFS endpoint in the all-comers population. Although the data suggest that PD-L1 expression cut-points may allow for enrichment of the probability to benefit from pembrolizumab plus chemotherapy, the level of PD-L1 expression as measured by CPS score does not predict which individual patients will have benefit. The data continue to support the positive benefit/risk ratio for the currently approved US indication: overall ITT population (all participants) for KEYNOTE-590.

4.6.1.4 KEYNOTE-590: Objective Response Rate and Duration of Response

The prespecified multiplicity strategy for hypothesis testing included ORR (key secondary endpoint) in all participants (see ([Figure 25] in [Sec. 7.2])). Results for ORR and DOR (a secondary endpoint) are presented in the sections below.

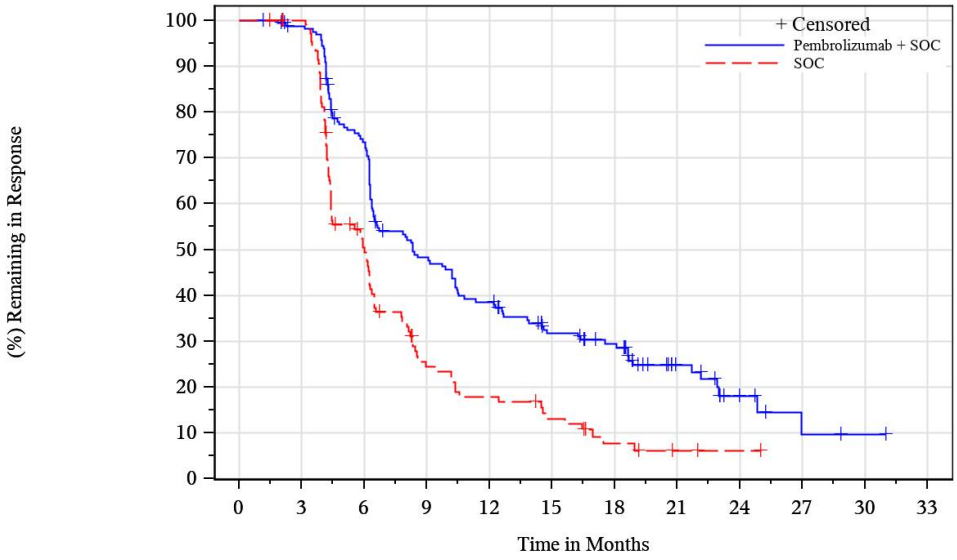
In all participants (the overall ITT population), pembrolizumab plus chemotherapy, compared with chemotherapy, provided a statistically significant and clinically meaningful improvement in confirmed ORR based on investigator assessment per RECIST 1.1.

4.6.1.4.1 Objective Response Rate and Duration of Response in ITT Population and Per Protocol CPS Cut-point Population

Pembrolizumab plus chemotherapy is superior to chemotherapy for the key secondary endpoint of ORR based on investigator assessment per RECIST 1.1 in all participants ([Table 34] in [Sec. 7.3]). The confirmed ORR was 45.0% versus 29.3%, reflecting a statistically significant and clinically meaningful 15.8% improvement ($p<0.0001$, which is less than the p-value boundary of 0.025 for statistical significance) in the pembrolizumab plus chemotherapy group versus the chemotherapy group. Median DOR was also longer for the pembrolizumab plus chemotherapy group (8.3 months) compared with the chemotherapy group (6.0 months), and a higher percentage of participants in the pembrolizumab plus chemotherapy group than in the chemotherapy group had extended responses for ≥24 months (18.1% vs 6.1% [KM estimation]) [Figure 18] ([Table 35] in [Sec. 7.3]). These data emphasize the durable responses which can be seen with immunotherapy, and which are less characteristic of chemotherapy alone.

In PD-L1 CPS ≥10 participants, ORR was also higher in the pembrolizumab plus chemotherapy group versus the chemotherapy group (51.1% vs 26.9%) ([Table 36] in [Sec. 7.3]). The median DOR was approximately 2-fold longer in the pembrolizumab plus chemotherapy group versus the chemotherapy group, and a higher percentage of participants had extended responses for ≥24 months (24.0% vs 7.8% [KM estimation]) [Figure 19] ([Table 37] in [Sec. 7.3]).

Figure 18
KEYNOTE-590 - Kaplan-Meier Estimates of Duration of Response in Participants with Confirmed Response Based on Investigator Assessment per RECIST 1.1 (ITT Population)

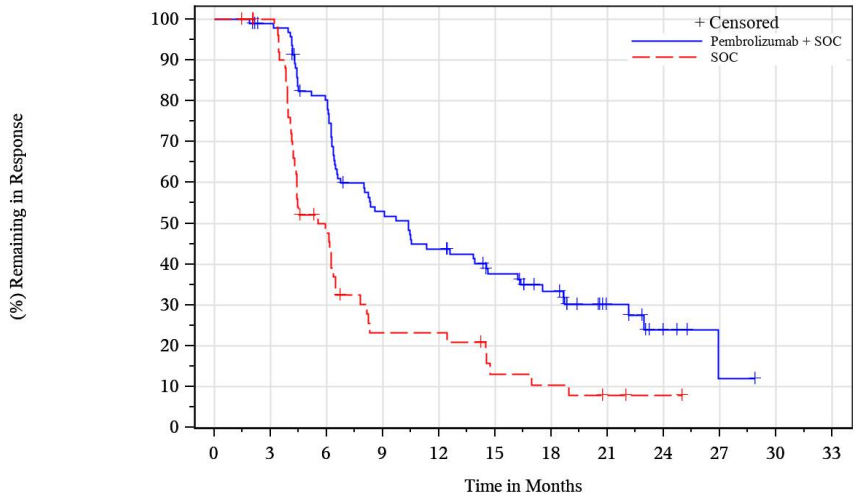


Number of subjects at risk

Pembrolizumab + SOC	168	162	117	75	60	43	35	16	6	2	1	0
SOC	110	106	50	22	16	11	5	2	1	0	0	0

Database Cutoff Date: 02JUL2020
Source: [P590V01MK3475: adam-adsl; adtte]

Figure 19
KEYNOTE-590 - Kaplan-Meier Estimates of Duration of Response in Participants with Confirmed Response Based on Investigator Assessment per RECIST 1.1
(Participants with PD-L1 CPS >= 10, ITT Population)



Number of subjects at risk

Pembrolizumab + SOC	95	91	71	46	38	29	22	11	4	1	0	0
SOC	53	50	22	10	10	5	4	2	1	0	0	0

Database Cutoff Date: 02JUL2020
Source: [P590V01MK3475: adam-adsl; adtte]

4.6.1.4.2 Objective Response Rate and Duration of Response by Histology

ORR and DOR results in participants with ESCC and EAC were consistent with results in all participants. In participants with ESCC, ORR was higher in the pembrolizumab plus chemotherapy group versus the chemotherapy group (43.8% vs 31.0%) ([Table 38] in [Sec. 7.3]). Median DOR was longer in the pembrolizumab plus chemotherapy group versus the chemotherapy group, and a higher percentage of participants had extended responses for ≥18 months (32.1% vs 8.7% [KM estimation]) ([Table 39] and [Figure 28] in [Sec. 7.3]).

In participants with EAC, ORR was higher in the pembrolizumab plus chemotherapy group versus the chemotherapy group (48.5% vs 24.5%) ([Table 40] in [Sec. 7.3]). Median DOR was longer in the pembrolizumab plus chemotherapy group versus the chemotherapy group, and a higher percentage of participants had extended responses for ≥18 months (22.7% vs 5.0% [KM estimation]) ([Table 41] and [Figure 29] in [Sec. 7.3])

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

As noted in [Sec. 4.6.1.2.3], an exploratory analysis using different CPS cut-points was performed for ORR in response to the FDA request. The results of this exploratory analysis 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 (including CPS <1) [Table 8].

Table 8
KEYNOTE-590: Exploratory Analysis of Objective Response
with Confirmation Based on Investigator Assessment per RECIST 1.1 by CPS Cut-point
(ITT Population; data cutoff: 02-JUL-2020)

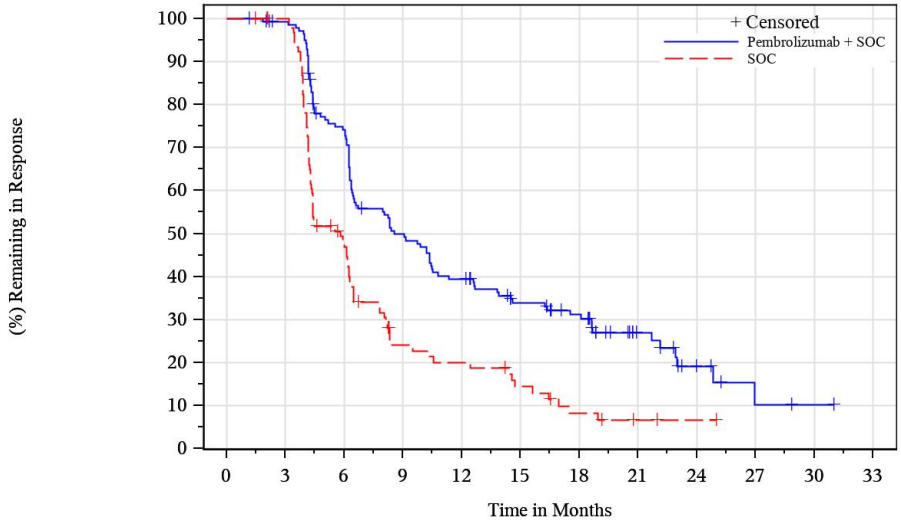
Baseline PD-L1 Status*	Number of participants**		Number of complete responses		Number of partial responses		ORR[#] (%) (95% CI)[†]	
	Pembro + Chemo	Chemo	Pembro + Chemo	Chemo	Pembro + Chemo	Chemo	Pembro + Chemo	Chemo
ITT	373	376	24	9	144	101	45.0 (39.9, 50.2)	29.3 (24.7, 34.1)
< 1	41	42	4	0	14	14	43.9 (28.5, 60.3)	33.3 (19.6, 49.5)
1 - <5	80	68	6	2	21	14	33.8 (23.6, 45.2)	23.5 (14.1, 35.4)
< 5	121	110	10	2	35	28	37.2 (28.6, 46.4)	27.3 (19.2, 36.6)
1 - <10	134	130	8	4	42	37	37.3 (29.1, 46.1)	31.5 (23.7, 40.3)
5 - <10	54	62	2	2	21	23	42.6 (29.2, 56.8)	40.3 (28.1, 53.6)
< 10	175	172	12	4	56	51	38.9 (31.6, 46.5)	32.0 (25.1, 39.5)
≥ 1	320	327	19	9	126	85	45.3 (39.8, 50.9)	28.7 (23.9, 34.0)
≥ 5	240	259	13	7	105	71	49.2 (42.7, 55.7)	30.1 (24.6, 36.1)
≥ 10	186	197	11	5	84	48	51.1 (43.7, 58.5)	26.9 (20.8, 33.7)

* Data analyses at CPS ≥10 were prespecified, and data collected at the validated CPS ≥10 cut-point were used for analyses. Remaining analyses at other CPS cut-points were not prespecified and CPS raw scores were used.
** CPS data were not available for 19 patients.
[#] Determined by Investigator Review
[†] Based on Clopper-Pearson method

CI: confidence interval; CPS: combined positive score; ITT: intent-to-treat; ORR: objective response rate; PD-L1: programmed death-ligand 1.

At the PD-L1 CPS ≥1 cut-point (which includes 86% of participants in the overall ITT population), results favored pembrolizumab plus chemotherapy; the improvements in ORR, and DOR in the pembrolizumab plus chemotherapy group versus the chemotherapy group were directionally consistent with the overall ITT population and support a favorable benefit to risk ratio in the ITT population. In PD-L1 CPS ≥1 participants, ORR was 45.3% (95% CI: 39.8, 50.9) versus 28.7% (95% CI: 23.9, 34.0) in the pembrolizumab plus chemotherapy versus chemotherapy groups, respectively; and median DOR was 8.6 months (range, 1.2+ to 31.0+) versus 5.8 months (range, 1.5+ to 25.0+) in the pembrolizumab plus chemotherapy versus chemotherapy groups, respectively [Figure 20] ([Table 42] [Table 43] in [Sec. 7.3]).

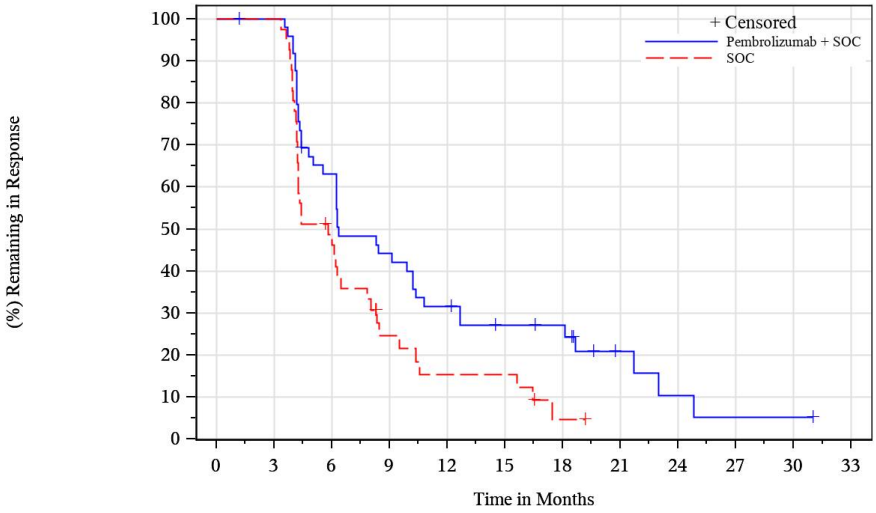
Figure 20
KEYNOTE-590 - Kaplan-Meier Estimates of Duration of Response in Participants with Confirmed Response Based on Investigator Assessment per RECIST 1.1
(Participants with PD-L1 CPS >= 1, ITT Population)



Database Cutoff Date: 02JUL2020
Source: [P590V01MK3475: adam-adsl; adtte]

In the PD-L1 CPS ≥1 to <10 subgroup, ORR and DOR results support treatment benefit for participants who received pembrolizumab plus chemotherapy versus chemotherapy [Figure 21] ([Table 44], [Table 45] in [Sec. 7.3]). The ORR in the pembrolizumab plus chemotherapy group (37.3% [95% CI: 29.1, 46.1]) was higher compared with the chemotherapy group (31.5% [95% CI: 23.7, 40.3]) ([Table 44] in [Sec. 7.3]).

Figure 21
KEYNOTE-590 - Kaplan-Meier Estimates of Duration of Response in Subjects with Confirmed Response
Based on Investigator Assessment per RECIST 1.1
(Participants with PD-L1 1 <= CPS < 10, ITT Population)



Number of subjects at risk

Pembrolizumab + SOC	50	49	30	21	15	11	10	4	2	1	1	0
SOC	41	41	19	8	5	5	1	0	0	0	0	0

Database Cutoff Date: 02JUL2020
Source: [P590V01MK3475: adam-adsl; adtte]

Despite the limited sample size in the PD-L1 CPS <1 subgroup (n = 41 and n = 42 in the pembrolizumab plus chemotherapy and chemotherapy groups, respectively), the ORR with chemotherapy combined with pembrolizumab was generally consistent with the ITT population acknowledging that the difference in ORR between treatment groups was less than in the ITT population. The ORR was higher for the pembrolizumab plus chemotherapy group (43.9% [95% CI: 28.5, 60.3]) versus the chemotherapy group (33.3% [95% CI: 19.6, 49.5]) ([Table 46] and [Table 47] in [Sec. 7.3]). In the PD-L1 CPS <1 subgroup, there were 4 CRs in the pembrolizumab plus chemotherapy group versus no CRs in the chemotherapy group ([Table 47] in [Sec. 7.3]). Although the sample size is small, these ORR results in the PD-L1 CPS <1 subgroup may support benefit for some patients in this subgroup ([Table 46], [Table 47], [Table 48], and [Figure 30] in [Sec. 7.3]).

KEYNOTE-590 met the secondary ORR endpoint in the all-comers population. Although the data suggest that PD-L1 expression cut-points may allow for enrichment of the probability to benefit from pembrolizumab plus chemotherapy, the level of PD-L1 expression as measured by CPS score does not predict which patients will have benefit. The data continue to support the positive benefit/risk ratio for the currently approved US indication: overall ITT population (all participants) for KEYNOTE-590.

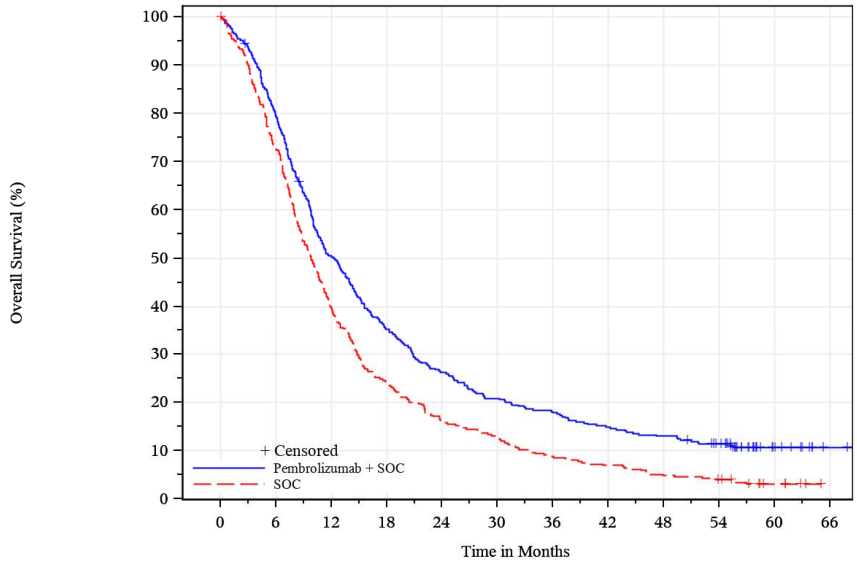
4.6.2 KEYNOTE-590 5-Year Follow-up Results for OS and PFS

Long-term results at approximately 5 years of follow-up (median follow-up was 58.8 months [range, 49.2 to 70.6 months], 10-JUL-2023 data cutoff) for KEYNOTE-590 show consistency with the original analyses (02-JUL-2020 data cutoff) [36]. The OS HR was 0.72 (95% CI: 0.62, 0.84) in favor of pembrolizumab plus chemotherapy group versus chemotherapy in all participants [Figure 22] ([Table 49] in [Sec. 7.3]). Median OS was 12.3 months (95% CI: 10.5, 14.0) and 9.8 months (95% CI: 8.8, 11.0) for pembrolizumab plus chemotherapy and chemotherapy, respectively. The 5-year OS rate (KM estimates) was >3-fold higher for pembrolizumab plus chemotherapy (10.6%) versus chemotherapy (3.0%) ([Table 50] in [Sec. 7.3]).

The PFS HR was 0.64 (94% CI: 0.54, 0.75) in favor of pembrolizumab plus chemotherapy versus chemotherapy in all participants [Figure 23] ([Table 51] in [Sec. 7.3]). Median PFS was 6.3 months (95% CI: 6.2, 7.1) and 5.8 months (95% CI: 5.0, 6.0) for pembrolizumab plus chemotherapy group and chemotherapy, respectively.

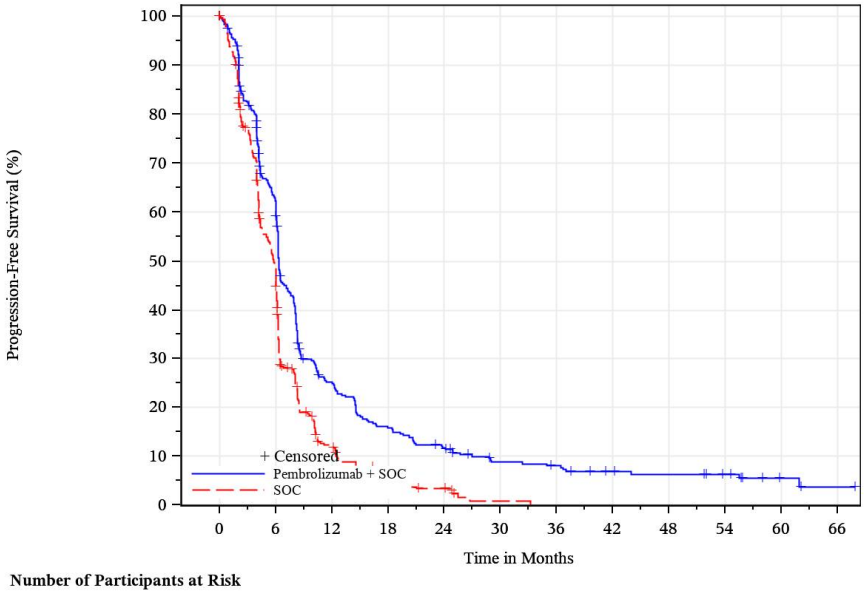
In summary, long-term data from KEYNOTE-590 continue to show durable and robust efficacy after 5 years of follow-up in the ITT population. These data support the current labeling indication based on the KEYNOTE-590 all-comers population.

Figure 22
KEYNOTE-590 - Kaplan-Meier Estimates of Overall Survival (ITT Population) – 5-year Follow-up



Database Cutoff Date: 10JUL2023
Source: [P590MK3475: adam-adsl; adtte]

Figure 23
KEYNOTE-590 - Kaplan-Meier Estimates of Progression-Free Survival Based on Investigator Assessment per RECIST 1.1 (Primary Censoring Rule) (ITT Population) – 5-year Follow-up



Number of Participants at Risk

Pembrolizumab + SOC	373	210	79	50	36	23	20	14	12	9	3	1
SOC	376	172	36	15	8	1	0	0	0	0	0	0

Database Cutoff Date: 10JUL2023
Source: [P590MK3475: adam-adsl; adtte]

4.6.3 KEYNOTE-590: Patient-Reported Outcomes – KEYNOTE-590

Changes from baseline in HRQoL scores based on prespecified EORTC QLQ-C30 and EORTC QLQ-OES18 scales and items were secondary efficacy endpoints in the KEYNOTE-590 study.

In the PRO FAS population, the changes from baseline in EORTC QLQ-C30 GHS/QoL scores remained stable and were similar between the pembrolizumab plus chemotherapy group and the chemotherapy group throughout the course of treatment, suggesting no decrement in HRQoL with the addition of pembrolizumab to chemotherapy in KEYNOTE-590 [Figure 31] in [Sec. 7.3].

The baseline GHS/QoL scores were similar for pembrolizumab plus chemotherapy and chemotherapy treatment groups (LS means [SD]: 64.37 [21.23] and 65.66 [20.06], respectively, out of a 0 to 100 scale, with a higher score representing better QoL). The LS mean difference in change from baseline between treatment groups was -0.10 points (95% CI: -3.40, 3.20) at Week 18 in GHS/QoL score ([Table 52] in [Sec. 7.3]). 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. In addition, changes from baseline in scores for prespecified EORTC QLQ-30 physical functioning and EORTC QLQ-OES18 reflux scales were similar between the 2 treatment groups ([Table 54] and [Table 53]

in [Sec. 7.3]). The prespecified change from baseline in QLQ-OES18 dysphagia (LS mean difference, 5.54; 95% CI, 10.93 to 0.16) and pain (LS mean difference, 2.94; 95% CI, 5.86 to 0.02) scales favored pembrolizumab plus chemotherapy over placebo plus chemotherapy ([Table 55] and [Table 56] in [Sec. 7.3]) [37].

Results were generally similar across PD-L1 expression subgroups compared with the overall PRO FAS population ([Table 57], [Table 58], [Table 59], [Figure 32], [Figure 33], and [Figure 34] in [Sec. 7.3]).

As esophageal cancer progresses, patients would be expected to experience diminished HRQoL, therefore maintenance of HRQoL may be considered a meaningful outcome. Patients and providers may be reassured that the addition of pembrolizumab does not decrease QoL, and may offer some benefit for specific symptoms, as described above [15].

4.7 Overview of Clinical Safety

4.7.1 Safety Results – KEYNOTE-590

The safety profile of pembrolizumab plus chemotherapy was generally consistent with the individual safety profiles of chemotherapy (cisplatin and 5-FU) and pembrolizumab monotherapy [Table 9]. The safety profile of pembrolizumab plus chemotherapy is similar across PD-L1 subgroups [Table 10].

The incidences of AEs, Grade 3 to 5 AEs, SAEs, and discontinuations due to an AE were generally similar (≤10% difference) between the pembrolizumab plus chemotherapy and the chemotherapy groups in KEYNOTE-590 [Table 9].

Compared with the pembrolizumab monotherapy RSD, there were higher incidences of most AE parameters in the pembrolizumab plus chemotherapy group [Table 9]. This was anticipated due to the combination of pembrolizumab with chemotherapy versus pembrolizumab monotherapy [Table 9]. Immune-mediated AEs were generally low grade and manageable in KEYNOTE-590, though some events such as endocrinopathies may require 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 across the development program and has not identified differences in the safety profile across 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 a 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 10].

Table 9
Summary of Overall Adverse Events and Immune-mediated Reactions and Infusion Reactions (ASaT Population)

	KN590 Data for Pembrolizumab + Chemotherapy (n=370)	KN590 Data for Placebo + Chemotherapy (n=370)	Reference Safety Dataset for Pembrolizumab Monotherapy (n=2799)
Overall Adverse Events			
One or more AEs	370 (100.0)	368 (99.5)	2727 (97.4)
Grade 3-5 AEs	318 (85.9)	308 (83.2)	1273 (45.5)
Serious AEs	205 (55.4)	204 (55.1)	1042 (37.2)
Deaths due to AEs	28 (7.6)	38 (10.3)	110 (3.9)
AEs leading to discontinuation	90 (24.3)	74 (20.0)	334 (11.9)
Immune-mediated reactions and infusion reactions			
One or more AEs	95 (25.7)	43 (11.6)	599 (21.4)
Grade 3-5 AEs	26 (7.0)	8 (2.2)	156 (5.6)
Serious AEs	30 (8.1)	7 (1.9)	163 (5.8)
Deaths due to AEs	2 (0.5)	1 (0.3)	4 (0.1)
AEs leading to discontinuation	16 (4.3)	2 (0.5)	85 (3.0)

KEYNOTE-590 Database Cutoff Date: 02JUL2020
Source tables: Table 2.7.4-esophageal3:5; Table 2.7.4-esophageal3:12

Source: [ISS: adam-adsl; adae]

Table 10
Summary of Overall Adverse Events and Immune-mediated Reactions and Infusion Reactions by PD-L1 CPS Subgroups (ASaT 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; chemo=chemotherapy; 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]

4.8 Q-TWiST Analysis

In order to better understand the benefit/risk ratio of adding pembrolizumab to chemotherapy for the 1L treatment of locally advanced/metastatic esophageal 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-590. Recent publications report results of Q-TWiST analyses of checkpoint inhibitor studies in NSCLC and renal cell carcinoma [38] [39]. 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 (for details of analysis methods, see [Sec. 7.2.1]):

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 all-cause Grade 3+ AEs starting from randomization to disease progression or death

REL (relapse): time from disease progression to death

Utility values (range 0 to 1) come from the EQ-5D-5L questionnaire collected from KEYNOTE-590 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 based on the EQ-5D questionnaire included in KEYNOTE-590:

Q-TWiST = (TOX*UTOX) + (TWiST*UTWiST) +(PROG*UPROG)

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. Published criteria consider a relative gain of 10 percentage points as clinically important and a gain of 15 percentage points as clearly clinically important [40].

In KEYNOTE-590, there was a relative gain in Q-TWiST of 18.73% (CI: 10.23, 28.82), 20.53% (CI: 11.14, 30.35), and 28.24% (CI: 15.13, 44.49) in the ITT, CPS ≥1, and CPS ≥10 populations, respectively. These data suggest a favorable benefit/risk ratio with a positive relative Q-TWiST gain over 33 months for pembrolizumab plus chemotherapy versus chemotherapy in all CPS cut-points, but notably a "clearly clinically important" benefit in the all-comers population.

4.9 Real World PD-L1 Testing

The PD-L1 IHC 22C3 pharmDx is the primary assay used for patient selection or treatment decisions within the pembrolizumab program. Understanding of the potential clinical utility of ICIs in the 1L setting in esophageal cancer is relatively recent, pembrolizumab and nivolumab were approved in esophageal cancer based on Phase 3 studies that used 2 different PD-L1 assays, 22C3 and 28-8 based PD-L1 clones, respectively. 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 which is minimal, the results are questionable. The PD-L1 IHC 22C3 pharmDx is currently the only PD-L1 test that is FDA-approved for guiding treatment decisions for pembrolizumab in esophageal squamous cell carcinoma.

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 advanced/metastatic esophageal cancer patients, a retrospective observational study was conducted using Flatiron Health EHR-derived de-identified database of adult (≥18 years of age) patients with advanced/metastatic esophageal cancer who initiated 1L systemic treatment in the primarily community oncology setting after March 22, 2021, the date of the first ICI approval for esophageal cancer in the US (see [Sec. 7.2.2] for analysis methods).

Of the 670 patients with advanced/metastatic esophageal cancer treated in the 1L setting identified, 66% had evidence of an evaluation for PD-L1 expression, indicating that a significant proportion are not tested in clinical practice as per guideline recommendations. The most commonly utilized assay was the Agilent PD-L1 IHC 22C3 (~50%) followed by lab developed tests (~20%). Of those with available PD-L1 CPS data (n = 396), 74% of the tumors were CPS ≥1 and 35% were CPS ≥10 [data on file].

Amongst the overall population receiving 1L therapy within this database (N = 670), 41% were treated with immune checkpoint inhibitor-based regimens and a significant proportion received chemotherapy only (58%) [data on file].

Of the population with available tumor PD-L1 CPS data (utilizing any of the available assays), only about 55% with CPS ≥10 and 49% with CPS ≥1 received IO-containing therapy. Amongst the population with tumor PD-L1 CPS <1, only 43% received ICI containing therapy indicating that investigators are likely discussing treatment options with patients. These data suggest that a significant proportion of the population who may benefit from IO are not currently being treated appropriately with chemotherapy in combination with immunotherapy and, potentially, that physicians and patients are weighing risks and benefits when considering available treatment options.

Only 41% of patients with advanced/metastatic esophageal cancer received any treatment in the 2L setting. Therefore, the best treatment should be available upfront.

Should the indication in 1L be restricted to a CPS cut point, this will further decrease the population receiving ICI in any line, depriving a sizeable proportion from a potentially effective therapy. Specifically, an estimated 48% and 11% of patients with esophageal cancer in the US may be deprived of a potentially effective treatment utilizing a cut-point of CPS ≥10 or CPS ≥1, respectively.[1]

Maintaining an all-comers indication for pembrolizumab plus chemotherapy allows more eligible patients to receive recommended therapy with ICI-based combinations in the 1L, where patients have the greatest chance to benefit, after discussions with their physicians.

5 BENEFIT-RISK ASSESSMENT

The totality of the data continue to support a favorable benefit/risk ratio for pembrolizumab plus chemotherapy as a standard-of-care 1L treatment in patients with locally advanced unresectable or metastatic esophageal or GEJ (Siewert Type I) carcinoma across PD-L1 expression levels.

[Table 11] presents the benefit-risk assessment for pembrolizumab plus chemotherapy for 1L treatment of patients with esophageal cancer.

[1] Based on the expected PD-L1 CPS prevalence from the KEYNOTE-590 trial (N = 730), approximately 89% and 52% of metastatic cancer patients are estimated to be CPS ≥1 and CPS ≥10, which when applied to the estimated number of new esophageal cancer cases in the US in 2024 (N =22,370) [2], diagnosed at the distant (metastatic) stage (~40%) [5] is approximately 7964 and 6085 who are CPS ≥1 and CPS ≥10, respectively. The estimated number and proportion of patients potentially excluded by CPS cut-point was calculated by subtracting the estimated number of patients at each CPS cut-point (CPS ≥1 and CPS ≥10) from the estimated new distant (metastatic) esophageal cancer cases in the US (N = 8948)

Table 11
Benefit-risk Assessment

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• Esophageal cancer is the 11th most diagnosed cancer and the 7th leading cause of cancer-related death worldwide. • Most patients are diagnosed at an advanced stage, and the prognosis for metastatic esophageal cancer is poor, with an overall 5-year survival rate of 5.3%.	• 1L esophageal cancer is a serious and life-threatening condition with limited treatment options
Current Treatment Options	• Prior to the introduction of immunotherapy, doublet chemotherapy was the only treatment option for patients with esophageal cancer and there were no systemic therapy advancements in 1L treatment of esophageal cancer for approximately 40 years before study KEYNOTE-590. Almost all patients with esophageal cancer experience primary disease progression with doublet chemotherapy in 1L and real-world data show that only 40% of patients treated in the 1L setting receive 2L therapy and majority do not receive further therapy.	• For patients who do not receive immunotherapy, doublet chemotherapy is the only option for most patients with esophageal cancer and prognosis is poor.
Benefit	• Statistically significant and clinically meaningful improvements were observed in OS, PFS, and ORR for pembrolizumab plus chemotherapy versus chemotherapy in the overall ITT population. • In the CPS ≥10 subgroup (n = 383), efficacy results were also statistically significant and clinically meaningful in favor of pembrolizumab plus chemotherapy versus chemotherapy and consistent with results in the overall ITT population. Results in the CPS ≥1 subgroup (n = 647), although exploratory without prespecified alpha control, showed clinically meaningful improvement in OS, PFS and ORR favoring pembrolizumab plus chemotherapy versus chemotherapy and are directionally consistent with the overall ITT population. The higher PD-L1 expression cut-point of CPS ≥10 includes only 51% of participants. Restricting the indication to this CPS cut-point would deny access to almost half of patients who could potentially benefit from treatment with pembrolizumab plus chemotherapy. • Efficacy results by histology subgroup ESCC and EAC in KEYNOTE-590 were consistent with results in the overall ITT population. • As esophageal cancer progresses, patients would be expected to experience diminished HRQoL, therefore maintenance of HRQoL may be considered a meaningful outcome. Changes from baseline in HRQoL scores were similar between the pembrolizumab plus chemotherapy group and the chemotherapy group throughout the course of treatment, suggesting that there was no decrement in HRQoL with addition of pembrolizumab to chemotherapy in KEYNOTE-590. • Post-hoc Q-TWiST analyses indicate a favorable benefit:risk 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 demonstrated benefit for patients with esophageal cancer including both ESCC and EAC in the 1L setting.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Risk and Risk Management	• The safety profile of pembrolizumab plus chemotherapy was generally consistent with the known safety profiles of either chemotherapy regimen alone and pembrolizumab monotherapy. • The safety profile of pembrolizumab plus chemotherapy was primarily the addition of immune-mediated AEs due to pembrolizumab added to the safety profile of chemotherapy. • Immune-mediated AEs were mostly low grade and manageable, although some may require long-term hormone replacement. • There is no biological rationale to suggest that the safety profile of pembrolizumab would change based on the level of PD-L1 expression, and 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	• Data from KEYNOTE-590 established pembrolizumab in combination with chemotherapy as a paradigm-changing 1L treatment option that offers a clinically meaningful survival benefit for 1L esophageal cancer patients. These patients have tremendous unmet need, and previously had only double chemotherapy as a treatment option. Based on KEYNOTE-590 and other studies, immune checkpoint inhibitors in combination with chemotherapy have become the SOC in esophageal cancer. • Consistent with the approved indication for all comers, the benefits of pembrolizumab treatment in combination with chemotherapy demonstrated in KEYNOTE-590 outweigh the risks. Similar HRQoL compared to chemotherapy alone, Q-TWiST analyses supporting the ITT population, and a manageable safety profile in patients with locally advanced unresectable or metastatic carcinoma of the esophagus and gastroesophageal junction (Siewert Type 1) all underscore the positive benefit/risk ratio of pembrolizumab plus chemotherapy in the currently labelled indication. Because the patient population in KEYNOTE-590 represented the global distribution of the disease and included both histologic subtypes, the approved all-comers indication also facilitates access to immunotherapy for patients with either EAC or ESCC. • The Sponsor considers that the current PD-L1 all-comer indication for metastatic esophageal cancer, as evaluated in the ITT population of KEYNOTE-590, should remain as it is in the best interest of patients in the US. The observed efficacy of pembrolizumab plus chemotherapy in participants with CPS <1 is generally consistent with that observed in the ITT population, albeit the magnitude of benefit is less. Real-world data suggest that many patients are not currently being treated with ICI-based regimens, which have demonstrated long-term survival (based on Flatiron data). Applying the prevalence of PD-L1 expression from KEYNOTE-590 to the estimated number of new metastatic esophageal cancer cases in the US in 2024, restricting the approved indication to the CPS ≥10 cut-point or the CPS ≥1 cut-point, may exclude 48% and 11% of patients, respectively, from receiving a foundational, potentially life-extending treatment option. • Patients who have access to 1L treatment will have the best likelihood of longer survival, and therefore increased opportunity for receiving subsequent therapy as an available option, if needed. • Given the high unmet need and lack of alternative options for patients with esophageal cancer, US patients and physicians should have the ability to make an informed choice on treatment and the current labeling informs and enables that decision.	

6 POINTS FOR THE ADVISORY COMMITTEE TO CONSIDER

Study design

- KEYNOTE-590 study was rigorously designed based on data available at initiation of the study. The study design was adjusted via protocol amendment with data from other trial(s) while maintaining study integrity.
- Key aspects of the protocol (clinical study design, study endpoints, study population, statistical analyses, and biomarker evaluation plan) were aligned during multiple interactions with the FDA.

- Prespecification of statistical analysis plan is crucial for achieving reliable interpretations of clinical data [41]. Information to support the label should be based on the pivotal study that supported registration.

- KEYNOTE-590 prespecified endpoints were statistically tested with multiplicity control for family-wise error rate.

Study results

Efficacy

- Study results were statistically significant and demonstrated clinically meaningful improvement for the pembrolizumab plus chemotherapy group versus the chemotherapy group in the overall ITT population and for predefined subgroups.

- A generally consistent treatment effect was observed across PD-L1 CPS subgroups. Some subgroups were evaluated by post hoc exploratory analyses, which were under-powered to detect statistically significant treatment differences and were not controlled for multiplicity.

- Although the data suggest that PD-L1 expression cut-points may allow for enrichment of the probability to benefit from pembrolizumab monotherapy, the level of PD-L1 expression as measured by CPS score does not predict which patients will have benefit. Further, the KEYNOTE-590 trial was designed with pembrolizumab in combination with chemotherapy to enable meaningful response and survival in all patients across all levels of PD-L1 expression (ie, the ITT population), which is not commonly observed with traditional chemotherapy regimens.

- Patient-reported outcome results also support no detriment for the pembrolizumab plus chemotherapy group at different PD-L1 CPS subgroups.

- The relative gain in Q-TWiST of 18.73% in the all-comers population is considered “clearly clinically important” [40].

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

- Real-world data suggest that many patients are not currently being treated with ICI-based regimens, which have demonstrated long-term survival (based on Flatiron data). Applying the prevalence of PD-L1 expression from KEYNOTE-590 to the estimated number of new metastatic esophageal cancer cases in the US in 2024, restricting the approved indication to the CPS ≥10 cut-point or the CPS ≥1 cut-point, may exclude 48% and 11% of patients, respectively, from receiving a foundational, potentially life-extending treatment option.

Indication and Label

- The current all-comer indication for pembrolizumab plus chemotherapy in 1L locally advanced or metastatic esophageal cancer that includes both EAC and ESCC is appropriate based on the KEYNOTE-590 study design and results. In addition, pembrolizumab plus chemotherapy was approved by the FDA upon its review of the positive benefit/risk profile in the current indication.

- Given the high unmet need and lack of alternative options for treatment of esophageal cancer, US patients and physicians should have the opportunity to decide the best course of treatment and current labeling informs of potential benefits, risks and subgroup data and enables that decision.

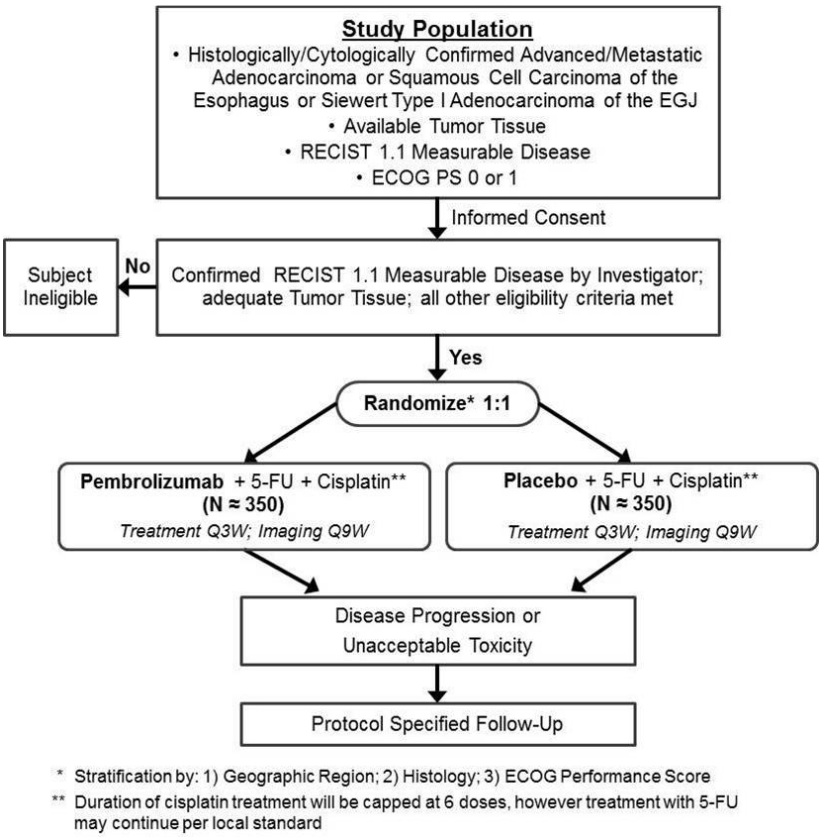
7 APPENDICES

7.1 KEY Sponsor/FDA Interactions and KEYNOTE-590 Study Design

Table 12
Key Sponsor/FDA Interactions Related to KEYNOTE-590

Date	Regulatory Interaction/Outcome
27-Feb-2017	On 27-FEB-2017, feedback was received from the FDA Type C Pre-Phase 3 meeting for KEYNOTE-590. FDA generally agreed with the proposed study population, stratification factors, choice of comparator, and original SAP. The Agency suggested having a planned subgroup analysis by histological subtype for all efficacy endpoints.
28-Mar-2017	Merck submission of new protocol, KEYNOTE-590 for first line esophageal cancer treatment.
15-Jun-2017	FDA grants Orphan Drug Designation to pembrolizumab for treatment of "esophageal carcinoma" (Designation number #17-5787).
16-Feb-2018	On 16-FEB-2018, regarding KEYNOTE-590 advice sought on MSI-H status, the FDA commented that it would be acceptable to determine MSI-H/dMMR tumor status only in those patients with esophageal cancer who achieve a complete or partial response per RECIST 1.1.
28-Jan-2019	Submission of sBLA for KEYTRUDA for patients with recurrent locally advanced or metastatic esophageal cancer whose tumors express PD-L1 (Combined Positive Score [CPS] ≥10), as determined by an FDA-approved test, with disease progression after one or more prior lines of systemic therapy based on the results of KEYNOTE-181 and KEYNOTE-180.
30-Jul-2019	FDA approved indication based on sBLA (S-55 and S-56) for KEYNOTE-180 and KEYNOTE-181as: KEYTRUDA is indicated for the treatment of patients with recurrent locally advanced or metastatic squamous cell carcinoma of the esophagus whose tumors express PD-L1 [Combined Positive Score (CPS) ≥10] as determined by an FDA-approved test, with disease progression after one or more prior lines of systemic therapy.
11-Oct-2019	KEYNOTE-590 feedback was received from the FDA in which the Agency agreed with the Sponsor's plan to: add additional primary hypotheses to the primary endpoint for participants with squamous cell carcinoma, including OS in ESCC PD-L1 CPS≥10 participants and OS and PFS in ESCC participants.
18-Apr-2020	KEYNOTE-590 feedback was received from the FDA in which the Agency agreed with the Sponsor's plan to: - Amend the study to include only a single IA (final analyses for PFS) at Month 35 relative to the first participant enrolled. - Amend the primary endpoint for PFS from BICR to investigator assessment.
02-Oct-2020	FDA preliminary comments for KEYNOTE-590Type B Pre-sBLA meeting was received. FDA indicated that the results from the interim analysis can potentially support the filing of an sBLA and that the indication statement and the intended population will be determined at the time of review. Merck accepts preliminary comments and the pre-sBLA meeting was cancelled.
13-Oct-2020	Submission of the KEYNOTE-590 sBLA
22-Mar-2021	FDA approved the KEYNOTE-590 indication: KEYTRUDA is indicated for the treatment of patients with locally advanced or metastatic esophageal or gastroesophageal (GEJ) (tumors with epicenter 1 to 5 centimeters above the GEJ) carcinoma that is not amenable to surgical resection or definitive chemoradiation, in combination with platinum- and fluoropyrimidine-based chemotherapy.

Figure 24
Study Design for KEYNOTE-590



5-FU=5-fluorouracil; ECOG PS=Eastern Cooperative Oncology Group; EGJ=esophagogastric junction; PS=performance status; Q3W=every 3 weeks; Q9W=every 9 weeks; RECIST 1.1=Response Evaluation Criteria in Solid Tumors version 1.1.

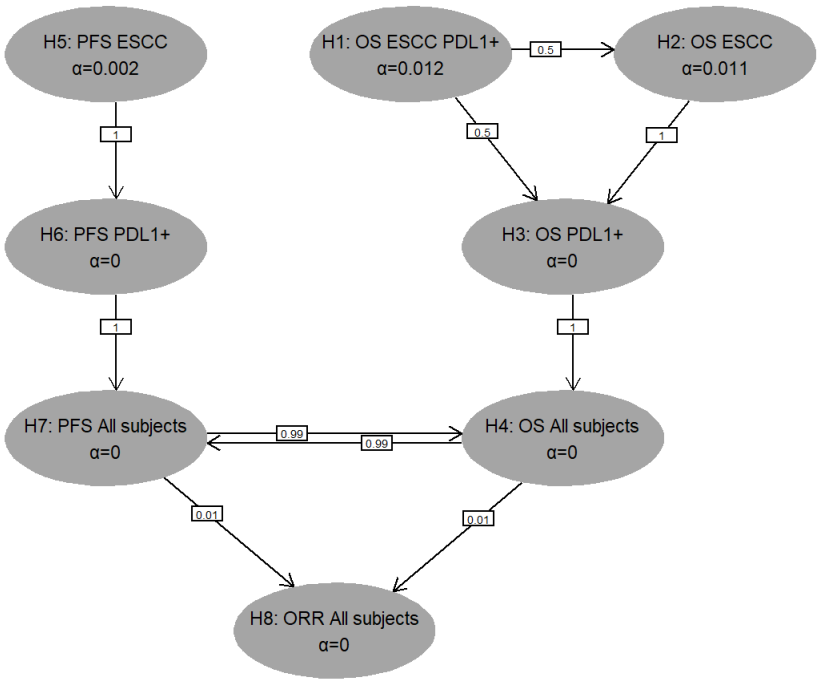
7.2 KEYNOTE-590 Statistical Methods

Statistical methods for OS, PFS, and ORR are the following. The ITT population was the efficacy analysis population. The primary endpoints of OS and PFS per RECIST 1.1 by investigator assessment were each tested by the stratified log-rank test and estimated by the stratified Cox model with Efron's tie handling method. OS data were censored at participant's last known alive date. PFS data were censored according to rules defined in the study protocol. The key secondary endpoint of ORR was tested and estimated by the stratified Miettinen and Nurminen method. Participants with missing ORR data were considered nonresponders.

The graphical method of Maurer and Bretz [42] was used to provide strong multiplicity control for multiple hypotheses as well as interim analyses [Figure 25]. There was 1 interim analysis and a final analysis planned in the study protocol.

Hypotheses in the top row (see [Figure 25]) were tested first and in parallel. Remaining hypotheses were tested only if the preceding hypothesis was positive.

Figure 25
Primary Endpoints and Key Secondary Endpoint Hypothesis Testing in KEYNOTE-590



Abbreviations: C=chemotherapy; CPS=combined positive score; ESCC=esophageal squamous cell carcinoma; H=hypothesis; ITT=intent-to-treat; ORR=objective response rate; OS=overall survival; PD-L1+ = PD-L1 CPS ≥10; PFS=progression-free survival; P=pembrolizumab.

7.2.1 Q-TWiST Analysis

Overall Survival/Progression Free Survival/Toxicity

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

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 Kaplan-Meier 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.

Toxicity (TOX)

The restricted mean duration in TOX is derived using RMST, equivalent to the area under the KM curves of TOX over the time interval of [0, 12 months], and [0, 33 months], for each treatment arm.

Difference in TOX between two treatment arms and its corresponding 95%CI 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.

The 95% CI of TOX difference is 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.

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, 33 months], for each treatment arm.

Relapse

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, 33 months], for each treatment arm.

EQ-5D Health Utility Weights

The EQ-5D-5L is a standardized instrument for use as a measure of health outcome and will provide data to develop health utilities for use in health economic analyses [43]. The 5 health state dimensions in the EQ-5D-5L 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 (unable to/extreme problems). The EQ-5D-5L also includes a graded (0 to 100) vertical visual analog scale on which the participant rates his or her general state of health at the time of the assessment. This instrument has been used extensively in cancer studies and published results from these studies support its validity and reliability [44].

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 confidence intervals that are too narrow. The post baseline utility weights estimation should be treated with caution.

Quality-adjusted Time Without Symptoms of disease progression or Toxicity of treatment (Q-TWiST)

At each specified timepoint, ie, 12 months and 33 months, restricted mean Q-TWiST is calculated for each treatment arm.

Relative Gain in Q-TWiST

At each specified timepoint, ie, 12 months and 33 months, the relative gain in Q-TWiST for pembrolizumab + SOC arm versus SOC arm and its corresponding 95%CI are provided using the same method as TOX.

7.2.2 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 post FDA approval of immune checkpoint inhibitors in three 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 oesophageal carcinoma (reflective of KEYNOTE-590).

The study populations were sourced from the Flatiron Health 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 a hash of a 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 1 January 2011. For esophageal/GEJ cancer patients, advanced disease is defined as patients with distant metastases at diagnosis or with one of the following on or after 1 January 2011,

1. distant recurrence,
2. any locoregional recurrence,
3. no surgical resection of the primary tumor, or
4. incomplete resection

Other inclusion criteria include evidence of adenocarcinoma or squamous cell carcinoma histological subtype and initiated 1L systemic treatment after FDA approval of KEYNOTE-590 (22 March 2021). Patients with evidence of treatment with a clinical study drug after 1L treatment start, a secondary malignancy prior to or during 1L treatment or who were unfit, refused or did not receive surgery for other or unknown reasons were excluded.

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 EDM at time of analysis on 31 March 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 1L 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 advanced/metastatic esophageal cancer patients receiving 1L treatment post FDA approval of KEYNOTE-590 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.

7.3 Tables and Figures

Demographics and Baseline Characteristics

Table 13
KEYNOTE-590 - Participant Characteristics
(ITT Population)

	Pembrolizumab + SOC		SOC		Total	
	n	(%)	n	(%)	n	(%)
Participants in population	373		376		749	
Gender						
Male	306	(82.0)	319	(84.8)	625	(83.4)
Female	67	(18.0)	57	(15.2)	124	(16.6)
Age (Years)						
Mean	62.8		62.0		62.4	
SD	9.8		9.2		9.5	
Median	64.0		62.0		63.0	
Range	28 to 94		27 to 89		27 to 94	
Race						
American Indian Or Alaska Native	9	(2.4)	12	(3.2)	21	(2.8)
Asian	201	(53.9)	199	(52.9)	400	(53.4)
Black Or African American	5	(1.3)	2	(0.5)	7	(0.9)
Multiple	5	(1.3)	9	(2.4)	14	(1.9)
American Indian Or Alaska Native, White	3	(0.8)	6	(1.6)	9	(1.2)
Black Or African American, White	2	(0.5)	3	(0.8)	5	(0.7)
White	139	(37.3)	139	(37.0)	278	(37.1)
Missing	14	(3.8)	15	(4.0)	29	(3.9)
Region						
Asia	196	(52.5)	197	(52.4)	393	(52.5)
Rest of World	177	(47.5)	179	(47.6)	356	(47.5)
Primary Diagnosis						
Squamous Cell Carcinoma of the Esophagus	274	(73.5)	274	(72.9)	548	(73.2)
Adenocarcinoma of the Esophagus	58	(15.5)	52	(13.8)	110	(14.7)
Adenocarcinoma of the Gastroesophageal Junction, Siewert Type I	41	(11.0)	50	(13.3)	91	(12.1)
ECOG Performance Scale						
0	149	(39.9)	150	(39.9)	299	(39.9)
1	223	(59.8)	225	(59.8)	448	(59.8)
2	1	(0.3)	1	(0.3)	2	(0.3)
Histology						
Adenocarcinoma	99	(26.5)	102	(27.1)	201	(26.8)
Squamous Cell Carcinoma	274	(73.5)	274	(72.9)	548	(73.2)
Disease Status						
Metastatic	344	(92.2)	339	(90.2)	683	(91.2)
Unresectable - Locally Advanced	29	(7.8)	37	(9.8)	66	(8.8)
PD-L1 Status						
CPS >= 10	186	(49.9)	197	(52.4)	383	(51.1)
CPS < 10	175	(46.9)	172	(45.7)	347	(46.3)
Not evaluable	6	(1.6)	6	(1.6)	12	(1.6)
Missing	6	(1.6)	1	(0.3)	7	(0.9)
Database Cutoff Date: 02JUL2020						

Source: [P590V01MK3475: adam-adsl]

Overall Survival in ITT Population and Per Protocol CPS Cut-point Population

Table 14
KEYNOTE-590 - Analysis of Overall Survival
(ITT Population)

Treatment	N	Number of Events (%)	Person-Months	Event Rate/ 100 Person-Months	Median OS † (Months) (95% CI)	OS Rate at Month 12 in % † (95% CI)
Pembrolizumab + SOC	373	262 (70.2)	4935.1	5.3	12.4 (10.5, 14.0)	50.6 (45.4, 55.6)
SOC	376	309 (82.2)	4301.2	7.2	9.8 (8.8, 10.8)	39.4 (34.4, 44.3)
Pairwise Comparisons					Hazard Ratio‡ (95% CI)‡	p-Value
Pembrolizumab + SOC vs. SOC					0.73 (0.62, 0.86)	<0.0001§

† From product-limit (Kaplan-Meier) method for censored data.
‡ Based on Cox regression model with Efron's method of tie handling with treatment as a covariate stratified by geographic region (Asia versus Rest of the World) and tumor histology (Adenocarcinoma versus Squamous Cell Carcinoma) and ECOG performance status (0 versus 1).
§ One-sided p-value based on log-rank test stratified by geographic region (Asia versus Rest of the World) and tumor histology (Adenocarcinoma versus Squamous Cell Carcinoma) and ECOG performance status (0 versus 1).
Database Cutoff Date: 02JUL2020.

Source: [P590V01MK3475: adam-adsl; adtte]

Table 15
KEYNOTE-590 - Overall Survival Rate
(ITT Population)

	Pembrolizumab + SOC (N=373)	SOC (N=376)
OS rate at 3 Months in (95% CI)†	93.8 (90.8, 95.9)	90.1 (86.6, 92.8)
OS rate at 6 Months in (95% CI)†	79.5 (75.1, 83.3)	73.1 (68.3, 77.3)
OS rate at 9 Months in (95% CI)†	63.6 (58.5, 68.3)	53.5 (48.4, 58.4)
OS rate at 12 Months in (95% CI)†	50.6 (45.4, 55.6)	39.4 (34.4, 44.3)
OS rate at 18 Months in (95% CI)†	35.3 (30.4, 40.2)	24.0 (19.8, 28.5)
OS rate at 24 Months in (95% CI)†	27.7 (22.7, 32.8)	16.3 (12.4, 20.6)

† From the product-limit (Kaplan-Meier) method for censored data.
Database Cutoff Date: 02JUL2020

Source: [P590V01MK3475: adam-adsl; adtte]

Table 16
KEYNOTE-590 - Analysis of Overall Survival
(Participants with PD-L1 CPS >= 10, ITT Population)

Treatment	N	Number of Events (%)	Person-Months	Event Rate/ 100 Person-Months	Median OS † (Months) (95% CI)	OS Rate at Month 12 in % † (95% CI)
Pembrolizumab + SOC	186	124 (66.7)	2594.2	4.8	13.5 (11.1, 15.6)	53.8 (46.3, 60.6)
SOC	197	165 (83.8)	2201.1	7.5	9.4 (8.0, 10.7)	37.1 (30.3, 43.8)
Pairwise Comparisons					Hazard Ratio‡ (95% CI)‡	p-Value
Pembrolizumab + SOC vs. SOC					0.62 (0.49, 0.78)	<0.0001§

† From product-limit (Kaplan-Meier) method for censored data.
‡ Based on Cox regression model with Efron's method of tie handling with treatment as a covariate stratified by geographic region (Asia versus Rest of the World) and tumor histology (Adenocarcinoma versus Squamous Cell Carcinoma).
§ One-sided p-value based on log-rank test stratified by geographic region (Asia versus Rest of the World) and tumor histology (Adenocarcinoma versus Squamous Cell Carcinoma).
Database Cutoff Date: 02JUL2020.

Overall Survival by Histology Subgroup

Table 17
KEYNOTE-590 - Analysis of Overall Survival
(Participants with Squamous Cell Carcinoma, ITT Population)

Treatment	N	Number of Events (%)	Person-Months	Event Rate/ 100 Person-Months	Median OS † (Months) (95% CI)	OS Rate at Month 12 in % † (95% CI)
Pembrolizumab + SOC	274	190 (69.3)	3667.2	5.2	12.6 (10.2, 14.3)	51.0 (44.9, 56.8)
SOC	274	222 (81.0)	3129.7	7.1	9.8 (8.6, 11.1)	37.9 (32.2, 43.7)
Pairwise Comparisons					Hazard Ratio‡ (95% CI)‡	p-Value
Pembrolizumab + SOC vs. SOC					0.72 (0.60, 0.88)	0.0006§

† From product-limit (Kaplan-Meier) method for censored data.
‡ Based on Cox regression model with Efron's method of tie handling with treatment as a covariate stratified by geographic region (Asia versus Rest of the World) and ECOG performance status (0 versus 1).
§ One-sided p-value based on log-rank test stratified by geographic region (Asia versus Rest of the World) and ECOG performance status (0 versus 1).
Database Cutoff Date: 02JUL2020.

Source: [P590V01MK3475: adam-adsl; adtte]

Table 18
Overall Survival Rate
(Subjects with Squamous Cell Carcinoma, ITT Population)

	Pembrolizumab + SOC (N=274)	SOC (N=274)
OS rate at 3 Months in (95% CI)[†]	94.2 (90.6, 96.4)	90.5 (86.3, 93.4)
OS rate at 6 Months in (95% CI)[†]	80.7 (75.5, 84.9)	74.4 (68.7, 79.1)
OS rate at 9 Months in (95% CI)[†]	64.2 (58.2, 69.6)	53.8 (47.7, 59.5)
OS rate at 12 Months in (95% CI)[†]	51.0 (44.9, 56.8)	37.9 (32.2, 43.7)
OS rate at 18 Months in (95% CI)[†]	36.5 (30.8, 42.3)	23.1 (18.3, 28.4)
OS rate at 24 Months in (95% CI)[†]	28.6 (22.7, 34.8)	17.3 (12.9, 22.4)

[†] From the product-limit (Kaplan-Meier) method for censored data.
Database Cutoff Date: 02JUL2020

Source: [P590V01MK3475: adam-adsl; adtte]

Table 19
KEYNOTE-590 - Analysis of Overall Survival
(Participants with Squamous Cell Carcinoma and PD-L1 CPS >= 10, ITT Population)

Treatment	N	Number of Events (%)	Person-Months	Event Rate/ 100 Person-Months	Median OS [†] (Months) (95% CI)	OS Rate at Month 12 in % [†] (95% CI)
Pembrolizumab + SOC	143	94 (65.7)	1997.6	4.7	13.9 (11.1, 17.7)	54.5 (46.0, 62.3)
SOC	143	121 (84.6)	1505.6	8.0	8.8 (7.8, 10.5)	33.6 (26.0, 41.3)
Pairwise Comparisons					Hazard Ratio[‡] (95% CI)[‡]	p-Value
Pembrolizumab + SOC vs. SOC					0.57 (0.43, 0.75)	<0.0001[§]

[†] From product-limit (Kaplan-Meier) method for censored data.
[‡] Based on Cox regression model with Efron's method of tie handling with treatment as a covariate stratified by geographic region (Asia versus Rest of the World) and ECOG performance status (0 versus 1).
[§] One-sided p-value based on log-rank test stratified by geographic region (Asia versus Rest of the World) and ECOG performance status (0 versus 1).
Database Cutoff Date: 02JUL2020.

Source: [P590V01MK3475: adam-adsl; adtte]

Table 20
KEYNOTE-590 - Analysis of Overall Survival
(Participants with Adenocarcinoma, ITT Population)

Treatment	N	Number of Events (%)	Person-Months	Event Rate/ 100 Person-Months	Median OS † (Months) (95% CI)	OS Rate at Month 12 in % † (95% CI)
Pembrolizumab + SOC	99	72 (72.7)	1268.0	5.7	11.6 (9.7, 15.2)	49.5 (39.3, 59.0)
SOC	102	87 (85.3)	1171.4	7.4	9.9 (7.8, 12.3)	43.1 (33.4, 52.5)
Pairwise Comparisons					Hazard Ratio‡ (95% CI)‡	p-Value
Pembrolizumab + SOC vs. SOC					0.74 (0.54, 1.02)	0.0309§

† From product-limit (Kaplan-Meier) method for censored data.
‡ Based on Cox regression model with Efron's method of tie handling with treatment as a covariate stratified by geographic region (Asia versus Rest of the World) and ECOG performance status (0 versus 1).
§ One-sided p-value based on log-rank test stratified by geographic region (Asia versus Rest of the World) and ECOG performance status (0 versus 1).
Database Cutoff Date: 02JUL2020.

Source: [P590V01MK3475: adam-adsl; adtte]

Exploratory Analysis of Overall Survival by CPS Cut-point

Table 21
OS data for KEYNOTE-590 (data cutoff: 02-JUL-2020)

Baseline PD-L1 Status*	Number of patients**		Number of deaths		Median OS (95% CI)		Hazard Ratio †		
	Pembro + Chemo	Chemo	Pembro + Chemo	Chemo	Pembro + Chemo	Chemo	HR	95% CI of HR	SE of log(HR)
ITT	373	376	262	309	12.4 (10.5, 14.0)	9.8 (8.8, 10.8)	0.730	0.618, 0.861	0.085
< 1	41	42	34	33	10.5 (7.1, 15.1)	10.2 (7.0, 12.8)	0.895	0.549, 1.459	0.250
1 - <5	80	68	60	55	12.6 (9.7, 16.3)	9.8 (7.4, 11.1)	0.757	0.524, 1.096	0.188
< 5	121	110	94	88	11.6 (9.8, 14.8)	9.8 (7.7, 11.4)	0.826	0.616, 1.107	0.149
1 - <10	134	130	98	106	10.5 (9.2, 14.8)	10.6 (8.8, 12.0)	0.843	0.637, 1.114	0.143
5 - <10	54	62	38	51	10.0 (7.1, 14.8)	12.0 (9.4, 14.5)	0.862	0.546, 1.362	0.233
< 10	175	172	132	139	10.5 (9.7, 13.5)	10.6 (8.8, 12.0)	0.865	0.679, 1.101	0.123
≥ 1	320	327	222	271	12.7 (10.5, 14.4)	9.8 (8.8, 10.8)	0.706	0.591, 0.844	0.091
≥ 5	240	259	162	216	12.8 (10.5, 14.6)	10.0 (8.8, 11.2)	0.684	0.557, 0.839	0.105
≥ 10	186	197	124	165	13.5 (11.1, 15.6)	9.4 (8.0, 10.7)	0.618	0.488, 0.783	0.120

* Data analyses at CPS ≥10 were prespecified, and data collected at validated CPS ≥10 cut-point were used for analyses. Remaining analyses at other CPS cut-points were not prespecified, and CPS raw scores were used.
** CPS data were not available for 19 patients.
† 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 prespecified in sSAP. The pooled stratification variables used are ADSL.STRATAR for ITT and ADSL.STRAGR9 for the rest of the subgroups.
CI: confidence interval; CPS: combined positive score; HR: hazard ratio; ITT: intent-to-treat; OS: overall survival; PD-L1: programmed death-ligand 1; SE: standard error; sSAP: supplemental statistical analysis plan.

Table 22
KEYNOTE-590 - Analysis of Overall Survival
(Participants with PD-L1 CPS >= 1, ITT Population)

Treatment	N	Number of Events (%)	Person-Months	Event Rate/ 100 Person-Months	Median OS † (Months) (95% CI)	OS Rate at Month 12 in % † (95% CI)
Pembrolizumab + SOC	320	222 (69.4)	4303.2	5.2	12.7 (10.5, 14.4)	51.2 (45.6, 56.5)
SOC	327	271 (82.9)	3763.6	7.2	9.8 (8.8, 10.8)	38.8 (33.5, 44.1)
Pairwise Comparisons					Hazard Ratio‡ (95% CI)‡	p-Value
Pembrolizumab + SOC vs. SOC					0.71 (0.59, 0.84)	<0.0001§

† From product-limit (Kaplan-Meier) method for censored data.
‡ Based on Cox regression model with Efron's method of tie handling with treatment as a covariate stratified by geographic region (Asia versus Rest of the World) and tumor histology (Adenocarcinoma versus Squamous Cell Carcinoma).
§ One-sided p-value based on log-rank test stratified by geographic region (Asia versus Rest of the World) and tumor histology (Adenocarcinoma versus Squamous Cell Carcinoma).
Database Cutoff Date: 02JUL2020.

Source: [P590V01MK3475: adam-adsl; adtte]

Table 23
KEYNOTE-590 - Analysis of Overall Survival
(Participants with PD-L1 1 <= CPS < 10, ITT Population)

Treatment	N	Number of Events (%)	Person-Months	Event Rate/ 100 Person-Months	Median OS † (Months) (95% CI)	OS Rate at Month 12 in % † (95% CI)
Pembrolizumab + SOC	134	98 (73.1)	1709.0	5.7	10.5 (9.2, 14.8)	47.6 (38.8, 55.8)
SOC	130	106 (81.5)	1562.5	6.8	10.6 (8.8, 12.0)	41.5 (33.0, 49.9)
Pairwise Comparisons					Hazard Ratio‡ (95% CI)‡	p-Value
Pembrolizumab + SOC vs. SOC					0.84 (0.64, 1.11)	0.1143§

† From product-limit (Kaplan-Meier) method for censored data.
‡ Based on Cox regression model with Efron's method of tie handling with treatment as a covariate stratified by geographic region (Asia versus Rest of the World) and tumor histology (Adenocarcinoma versus Squamous Cell Carcinoma).
§ One-sided p-value based on log-rank test stratified by geographic region (Asia versus Rest of the World) and tumor histology (Adenocarcinoma versus Squamous Cell Carcinoma).
Database Cutoff Date: 02JUL2020.

Source: [P590V01MK3475: adam-adsl; adtte]

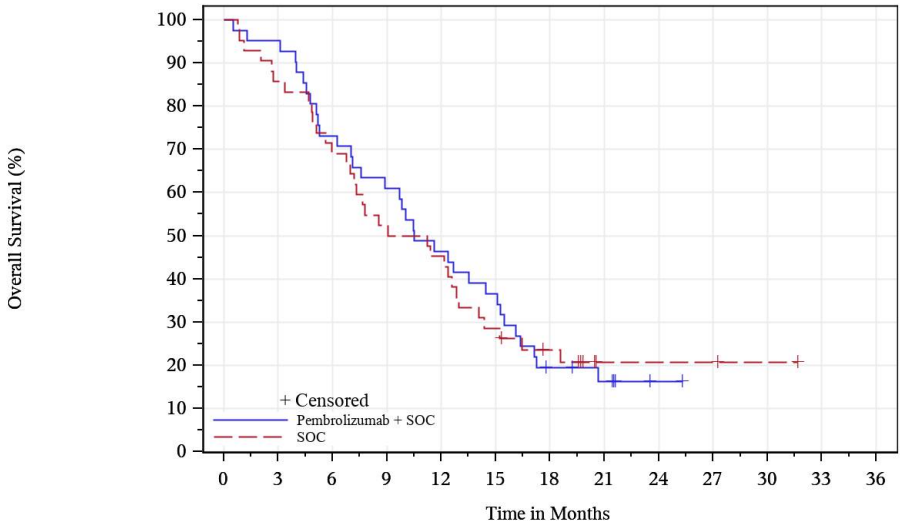
Table 24
KEYNOTE-590 - Analysis of Overall Survival
(Participants with PD-L1 CPS < 1, ITT Population)

Treatment	N	Number of Events (%)	Person-Months	Event Rate/ 100 Person-Months	Median OS † (Months) (95% CI)	OS Rate at Month 12 in % † (95% CI)
Pembrolizumab + SOC	41	34 (82.9)	478.2	7.1	10.5 (7.1, 15.1)	46.3 (30.7, 60.6)
SOC	42	33 (78.6)	462.3	7.1	10.2 (7.0, 12.8)	45.2 (29.9, 59.4)
Pairwise Comparisons					Hazard Ratio‡ (95% CI)‡	p-Value
Pembrolizumab + SOC vs. SOC					0.89 (0.55, 1.46)	0.3277§

† From product-limit (Kaplan-Meier) method for censored data.
‡ Based on Cox regression model with Efron's method of tie handling with treatment as a covariate stratified by geographic region (Asia versus Rest of the World) and tumor histology (Adenocarcinoma versus Squamous Cell Carcinoma).
§ One-sided p-value based on log-rank test stratified by geographic region (Asia versus Rest of the World) and tumor histology (Adenocarcinoma versus Squamous Cell Carcinoma).
Database Cutoff Date: 02JUL2020.

Source: [P590V01MK3475: adam-adsl; adtte]

Figure 26
KEYNOTE-590 - Kaplan-Meier Estimates of Overall Survival
(Participants with PD-L1 CPS < 1, ITT Population)



Database Cutoff Date: 02JUL2020
Source: [P590V01MK3475: adam-adsl; adtte]

Progression-free Survival in ITT Population and Per Protocol CPS Cut-point Population

Table 25
KEYNOTE-590 - Analysis of Progression-Free Survival Based on Investigator Assessment Per RECIST 1.1 (Primary Censoring Rule) (ITT Population)

Treatment	N	Number of Events (%)	Person-Months	Event Rate/ 100 Person-Months	Median PFS † (Months) (95% CI)	PFS Rate at Month 6 in % † (95% CI)
Pembrolizumab + SOC	373	297 (79.6)	2981.5	10.0	6.3 (6.2, 6.9)	62.4 (57.1, 67.3)
SOC	376	333 (88.6)	2235.1	14.9	5.8 (5.0, 6.0)	48.7 (43.4, 53.7)
Pairwise Comparisons					Hazard Ratio‡ (95% CI)‡	p-Value
Pembrolizumab + SOC vs. SOC					0.65 (0.55, 0.76)	<0.0001§

† From product-limit (Kaplan-Meier) method for censored data.
‡ Based on Cox regression model with Efron's method of tie handling with treatment as a covariate stratified by geographic region (Asia versus Rest of the World) and tumor histology (Adenocarcinoma versus Squamous Cell Carcinoma) and ECOG performance status (0 versus 1).
§ One-sided p-value based on log-rank test stratified by geographic region (Asia versus Rest of the World) and tumor histology (Adenocarcinoma versus Squamous Cell Carcinoma) and ECOG performance status (0 versus 1).
Progression-free survival is defined as time from randomization to disease progression, or death, whichever occurs first.
Database Cutoff Date: 02JUL2020.

Source: [P590V01MK3475: adam-adsl; adtte]

Table 26
Summary of PFS Rate Over Time Based on Investigator Assessment per RECIST 1.1 (ITT Population)

	Pembrolizumab + SOC (N=373)	SOC (N=376)
PFS rate at 3 Months in (95% CI)†	82.5 (78.2, 86.1)	76.9 (72.3, 80.9)
PFS rate at 6 Months in (95% CI)†	62.4 (57.1, 67.3)	48.7 (43.4, 53.7)
PFS rate at 9 Months in (95% CI)†	29.9 (25.1, 34.8)	18.9 (15.0, 23.2)
PFS rate at 12 Months in (95% CI)†	24.9 (20.4, 29.6)	11.9 (8.7, 15.7)
PFS rate at 15 Months in (95% CI)†	18.2 (14.2, 22.5)	7.8 (5.1, 11.1)
PFS rate at 18 Months in (95% CI)†	15.8 (12.0, 20.0)	5.5 (3.3, 8.5)

† From the product-limit (Kaplan-Meier) method for censored data.
Database Cutoff Date: 02JUL2020

Source: [P590V01MK3475: adam-adsl; adtte]

Table 27
KEYNOTE-590 - Analysis of Progression-Free Survival Based on Investigator Assessment Per RECIST 1.1 (Primary Censoring Rule) (Participants with PD-L1 CPS >= 10, ITT Population)

Treatment	N	Number of Events (%)	Person-Months	Event Rate/ 100 Person-Months	Median PFS † (Months) (95% CI)	PFS Rate at Month 6 in % † (95% CI)
Pembrolizumab + SOC	186	140 (75.3)	1618.4	8.7	7.5 (6.2, 8.2)	65.6 (58.0, 72.1)
SOC	197	174 (88.3)	1125.6	15.5	5.5 (4.3, 6.0)	45.9 (38.6, 52.8)
Pairwise Comparisons					Hazard Ratio‡ (95% CI)‡	p-Value
Pembrolizumab + SOC vs. SOC					0.51 (0.41, 0.65)	<0.0001§

† From product-limit (Kaplan-Meier) method for censored data.
‡ Based on Cox regression model with Efron's method of tie handling with treatment as a covariate stratified by geographic region (Asia versus Rest of the World) and tumor histology (Adenocarcinoma versus Squamous Cell Carcinoma).
§ One-sided p-value based on log-rank test stratified by geographic region (Asia versus Rest of the World) and tumor histology (Adenocarcinoma versus Squamous Cell Carcinoma).
Progression-free survival is defined as time from randomization to disease progression, or death, whichever occurs first.
Database Cutoff Date: 02JUL2020.

Source: [P590V01MK3475: adam-adsl; adtte]

Progression-free Survival by Histology Subgroup

Table 28
KEYNOTE-590 - Analysis of Progression-Free Survival Based on Investigator Assessment Per RECIST 1.1 (Primary Censoring Rule)
(Participants with Squamous Cell Carcinoma, ITT Population)

Treatment	N	Number of Events (%)	Person-Months	Event Rate/ 100 Person-Months	Median PFS † (Months) (95% CI)	PFS Rate at Month 6 in % † (95% CI)
Pembrolizumab + SOC	274	219 (79.9)	2202.6	9.9	6.3 (6.2, 6.9)	62.1 (55.8, 67.7)
SOC	274	244 (89.1)	1645.9	14.8	5.8 (5.0, 6.1)	48.8 (42.6, 54.6)
Pairwise Comparisons					Hazard Ratio‡ (95% CI)‡	p-Value
Pembrolizumab + SOC vs. SOC					0.65 (0.54, 0.78)	<0.0001§

† From product-limit (Kaplan-Meier) method for censored data.
‡ Based on Cox regression model with Efron's method of tie handling with treatment as a covariate stratified by geographic region (Asia versus Rest of the World) and ECOG performance status (0 versus 1).
§ One-sided p-value based on log-rank test stratified by geographic region (Asia versus Rest of the World) and ECOG performance status (0 versus 1).
Progression-free survival is defined as time from randomization to disease progression, or death, whichever occurs first.
Database Cutoff Date: 02JUL2020.

Source: [P590V01MK3475: adam-adsl; adtte]

Table 29
KEYNOTE-590 - Analysis of Progression-Free Survival Based on Investigator Assessment per RECIST 1.1 (Primary Censoring Rule)
(Participants with Adenocarcinoma, ITT Population)

Treatment	N	Number of Events (%)	Person-Months	Event Rate/ 100 Person-Months	Median PFS † (Months) (95% CI)	PFS Rate at Month 12 in % † (95% CI)
Pembrolizumab + SOC	99	78 (78.8)	778.8	10.0	6.3 (6.0, 8.1)	27.0 (18.1, 36.6)
SOC	102	89 (87.3)	589.2	15.1	5.7 (4.1, 6.2)	12.0 (6.3, 19.9)
Pairwise Comparisons					Hazard Ratio‡ (95% CI)‡	p-Value
Pembrolizumab + SOC vs. SOC					0.63 (0.46, 0.87)	0.0019§

† From product-limit (Kaplan-Meier) method for censored data.
‡ Based on Cox regression model with Efron's method of tie handling with treatment as a covariate stratified by geographic region (Asia versus Rest of the World) and ECOG performance status (0 versus 1).
§ One-sided p-value based on log-rank test stratified by geographic region (Asia versus Rest of the World) and ECOG performance status (0 versus 1).
Database Cutoff Date: 02JUL2020.

Source: [P590V01MK3475: adam-adsl; adtte]

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

Table 30
PFS data for KEYNOTE-590 (data cutoff: 02-JUL-2020)

Baseline PD-L1 Status*	Number of patients**		Number of events		Median PFS[#] (95% CI)		Hazard Ratio [†]		
	Pembro + Chemo	Chemo	Pembro + Chemo	Chemo	Pembro + Chemo	Chemo	HR	95% CI of HR	SE of log(HR)
ITT	373	376	297	333	6.3 (6.2, 6.9)	5.8 (5.0, 6.0)	0.645	0.550, 0.757	0.082
< 1	41	42	36	37	6.1 (4.4, 8.2)	6.2 (3.4, 8.4)	0.753	0.461, 1.231	0.251
1 - <5	80	68	71	58	6.2 (5.9, 6.4)	5.8 (4.0, 6.2)	0.821	0.575, 1.172	0.182
< 5	121	110	107	95	6.2 (5.8, 6.5)	6.0 (4.1, 6.3)	0.846	0.638, 1.120	0.144
1 - <10	134	130	112	117	6.2 (6.0, 6.4)	6.0 (4.6, 6.1)	0.781	0.600, 1.018	0.135
5 - <10	54	62	41	59	6.2 (5.6, 6.6)	6.0 (4.7, 6.2)	0.684	0.447, 1.048	0.217
< 10	175	172	148	154	6.2 (6.0, 6.4)	6.0 (5.0, 6.2)	0.801	0.636, 1.008	0.117
≥ 1	320	327	252	291	6.3 (6.2, 7.1)	5.7 (4.6, 6.0)	0.616	0.519, 0.733	0.088
≥ 5	240	259	181	233	6.5 (6.2, 8.1)	5.7 (4.6, 6.0)	0.552	0.451, 0.676	0.103
≥ 10	186	197	140	174	7.5 (6.2, 8.2)	5.5 (4.3, 6.0)	0.514	0.407, 0.649	0.119

* Data analyses at CPS ≥10 were prespecified, and data collected at validated CPS ≥10 cut-point were used for analyses. Remaining analyses at other CPS cut-points were not prespecified, and CPS raw scores were used.
** CPS data were not available for 19 patients.
[#] Determined by Investigator Review
[†] 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 prespecified in sSAP. The pooled stratification variables used are ADSL.STRATAR for ITT and ADSL.STRAGR9 for the rest of the subgroups.
CI: confidence interval; CPS: combined positive score; HR: hazard ratio; ITT: intent-to-treat; PD-L1: programmed death-ligand 1; PFS: progression-free survival; SE: standard error; sSAP: supplemental statistical analysis plan.

Table 31
KEYNOTE-590 - Analysis of Progression-Free Survival Based on Investigator Assessment per RECIST 1.1 (Primary Censoring Rule)
(Participants with PD-L1 CPS >= 1, ITT Population)

Treatment	N	Number of Events (%)	Person-Months	Event Rate/ 100 Person-Months	Median PFS † (Months) (95% CI)	PFS Rate at Month 6 in % † (95% CI)
Pembrolizumab + SOC	320	252 (78.8)	2602.5	9.7	6.3 (6.2, 7.1)	63.9 (58.1, 69.0)
SOC	327	291 (89.0)	1946.3	15.0	5.7 (4.6, 6.0)	47.9 (42.2, 53.3)
Pairwise Comparisons					Hazard Ratio‡ (95% CI)‡	p-Value
Pembrolizumab + SOC vs. SOC					0.62 (0.52, 0.73)	<0.0001§

† From product-limit (Kaplan-Meier) method for censored data.
‡ Based on Cox regression model with Efron's method of tie handling with treatment as a covariate stratified by geographic region (Asia versus Rest of the World) and tumor histology (Adenocarcinoma versus Squamous Cell Carcinoma).
§ One-sided p-value based on log-rank test stratified by geographic region (Asia versus Rest of the World) and tumor histology (Adenocarcinoma versus Squamous Cell Carcinoma).
Progression-free survival is defined as time from randomization to disease progression, or death, whichever occurs first.
Database Cutoff Date: 02JUL2020.

Source: [P590V01MK3475: adam-adsl; adtte]

Table 32
KEYNOTE-590 - Analysis of Progression-Free Survival Based on Investigator Assessment per RECIST 1.1
(Primary Censoring Rule)
(Participants with PD-L1 1 <= CPS < 10, ITT Population)

Treatment	N	Number of Events (%)	Person-Months	Event Rate/ 100 Person-Months	Median PFS † (Months) (95% CI)	PFS Rate at Month 6 in % † (95% CI)
Pembrolizumab + SOC	134	112 (83.6)	984.0	11.4	6.2 (6.0, 6.4)	61.5 (52.4, 69.4)
SOC	130	117 (90.0)	820.8	14.3	6.0 (4.6, 6.1)	50.9 (41.9, 59.2)
Pairwise Comparisons					Hazard Ratio‡ (95% CI)‡	p-Value
Pembrolizumab + SOC vs. SOC					0.78 (0.60, 1.02)	0.0313§

† From product-limit (Kaplan-Meier) method for censored data.
‡ Based on Cox regression model with Efron's method of tie handling with treatment as a covariate stratified by geographic region (Asia versus Rest of the World) and tumor histology (Adenocarcinoma versus Squamous Cell Carcinoma).
§ One-sided p-value based on log-rank test stratified by geographic region (Asia versus Rest of the World) and tumor histology (Adenocarcinoma versus Squamous Cell Carcinoma).
Progression-free survival is defined as time from randomization to disease progression, or death, whichever occurs first.
Database Cutoff Date: 02JUL2020.

Source: [P590V01MK3475: adam-adsl; adtte]

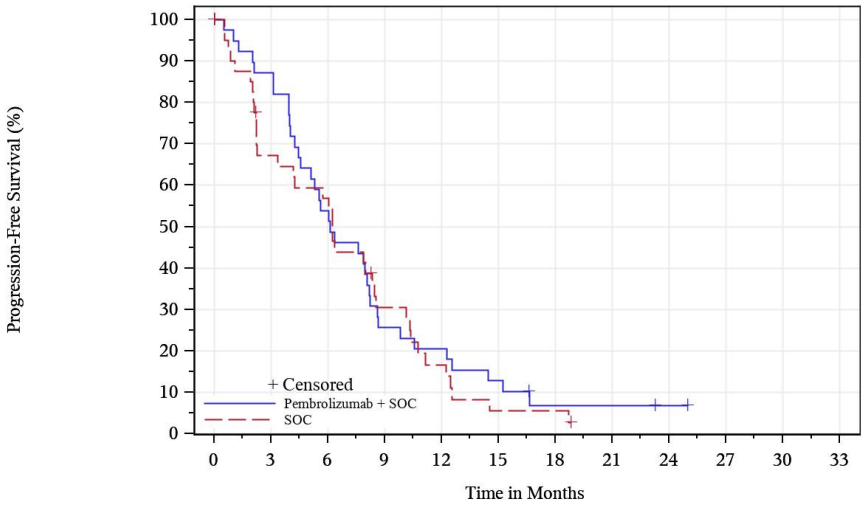
Table 33
KEYNOTE-590 - Analysis of Progression-Free Survival Based on Investigator Assessment per RECIST 1.1 (Primary Censoring Rule)
(Participants with PD-L1 CPS < 1, ITT Population)

Treatment	N	Number of Events (%)	Person-Months	Event Rate/ 100 Person-Months	Median PFS † (Months) (95% CI)	PFS Rate at Month 6 in % † (95% CI)
Pembrolizumab + SOC	41	36 (87.8)	304.2	11.8	6.1 (4.4, 8.2)	53.8 (37.2, 67.9)
SOC	42	37 (88.1)	263.3	14.1	6.2 (3.4, 8.4)	56.8 (40.0, 70.6)
Pairwise Comparisons					Hazard Ratio‡ (95% CI)‡	p-Value
Pembrolizumab + SOC vs. SOC					0.75 (0.46, 1.23)	0.1313§

† From product-limit (Kaplan-Meier) method for censored data.
‡ Based on Cox regression model with Efron's method of tie handling with treatment as a covariate stratified by geographic region (Asia versus Rest of the World) and tumor histology (Adenocarcinoma versus Squamous Cell Carcinoma).
§ One-sided p-value based on log-rank test stratified by geographic region (Asia versus Rest of the World) and tumor histology (Adenocarcinoma versus Squamous Cell Carcinoma).
Progression-free survival is defined as time from randomization to disease progression, or death, whichever occurs first.
Database Cutoff Date: 02JUL2020.

Source: [P590V01MK3475: adam-adsl; adtte]

Figure 27
KEYNOTE-590 - Kaplan-Meier Estimates of Progression-Free Survival Based on Investigator Assessment per RECIST 1.1 (Primary Censoring Rule)
(Participants with PD-L1 CPS < 1, ITT Population)



Database Cutoff Date: 02JUL2020
Source: [P590V01MK3475: adam-adsl; adtte]

Objective Response Rate and Duration of Response in ITT Population and Per Protocol CPS Cut-point Population

Table 34
KEYNOTE-590 - Analysis of Objective Response with Confirmation Based on Investigator Assessment per RECIST 1.1 (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	373	168	45.0 (39.9, 50.2)	15.8 (9.0, 22.5)	<0.0001
SOC	376	110	29.3 (24.7, 34.1)		

[†] Based on Miettinen & Nurminen method stratified by geographic region (Asia versus Rest of the World) and tumor histology (Adenocarcinoma versus Squamous Cell Carcinoma) and ECOG performance status (0 versus 1).
[††] One-sided p-value for testing. H0: difference in % = 0 versus H1: difference in % > 0.
Responses are based on Investigator Assessment per RECIST 1.1 with confirmation.
Database Cutoff Date: 02JUL2020

Source: [P590V01MK3475: adam-adsl; adrs]

Table 35
KEYNOTE-590 - Summary of Time to Response and Duration of Response Based on Investigator Assessment per RECIST 1.1 in Participants with Confirmed Response (ITT Population)

	Pembrolizumab + SOC (N=373)	SOC (N=376)
Number of participants with response[†]	168	110
Time to Response[†] (months)		
Mean (SD)	2.3 (0.9)	2.4 (1.2)
Median (Range)	2.1 (1.1-8.3)	2.1 (1.3-12.6)
Response Duration[‡] (months)		
Median (Range)	8.3 (1.2+ - 31.0+)	6.0 (1.5+ - 25.0+)
Number (%[‡]) of Participants with Extended Response Duration:		
≥3 months	162 (98.8)	106 (100.0)
≥6 months	117 (73.5)	50 (50.4)
≥9 months	75 (48.2)	22 (24.5)
≥12 months	60 (38.6)	16 (17.8)
≥18 months	35 (29.4)	5 (7.7)
≥24 months	6 (18.1)	1 (6.1)

[†] Includes participants with 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.
Database Cutoff Date: 02JUL2020

Source: [P590V01MK3475: adam-adsl; adtte]

Table 36
KEYNOTE-590 - Analysis of Objective Response with Confirmation Based on Investigator Assessment per RECIST 1.1 (Participants with PD-L1 CPS ≥ 10, 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	186	95	51.1 (43.7, 58.5)	24.0 (14.3, 33.2)	<0.0001
SOC	197	53	26.9 (20.8, 33.7)		

[†] Based on Miettinen & Nurminen method stratified by geographic region (Asia versus Rest of the World) and tumor histology (Adenocarcinoma versus Squamous Cell Carcinoma).
[††] One-sided p-value for testing. H0: difference in % = 0 versus H1: difference in % > 0.
Responses are based on Investigator Assessment per RECIST 1.1 with confirmation.
Database Cutoff Date: 02JUL2020

Source: [P590V01MK3475: adam-adsl; adrs]

Table 37
KEYNOTE-590 - Summary of Time to Response and Duration of Response Based on Investigator Assessment per RECIST 1.1 in Participants with Confirmed Response (Participants with PD-L1 CPS ≥ 10, ITT Population)

	Pembrolizumab + SOC (N=186)	SOC (N=197)
Number of participants with response[†]	95	53
Time to Response[†] (months)		
Mean (SD)	2.3 (1.0)	2.3 (0.6)
Median (Range)	2.1 (1.4-8.3)	2.1 (1.3-4.3)
Response Duration[‡] (months)		
Median (Range)	10.4 (1.9 - 28.9+)	5.6 (1.5+ - 25.0+)
Number (%[‡]) of Participants with Extended Response Duration:		
≥3 months	91 (98.9)	50 (100.0)
≥6 months	71 (80.2)	22 (47.7)
≥9 months	46 (52.9)	10 (23.2)
≥12 months	38 (43.7)	10 (23.2)
≥18 months	22 (33.4)	4 (10.4)
≥24 months	4 (24.0)	1 (7.8)

[†] Includes participants with 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.
Database Cutoff Date: 02JUL2020

Source: [P590V01MK3475: adam-adsl; adtte]

Objective Response Rate and Duration of Response by Histology

Table 38
KEYNOTE-590
Analysis of Objective Response with Confirmation Based on Investigator Assessment per RECIST 1.1 (Subjects with Squamous Cell Carcinoma, 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	274	120	43.8 (37.8, 49.9)	12.8 (4.7, 20.7)	0.0009
SOC	274	85	31.0 (25.6, 36.9)		

[†] Based on Miettinen & Nurminen method stratified by geographic region (Asia versus Rest of the World) and ECOG performance status (0 versus 1).
[††] One-sided p-value for testing. H0: difference in % = 0 versus H1: difference in % > 0.
Responses are based on Investigator Assessment per RECIST 1.1 with confirmation.
Database Cutoff Date: 02JUL2020

Source: [P590V01MK3475: adam-adsl; adrs]

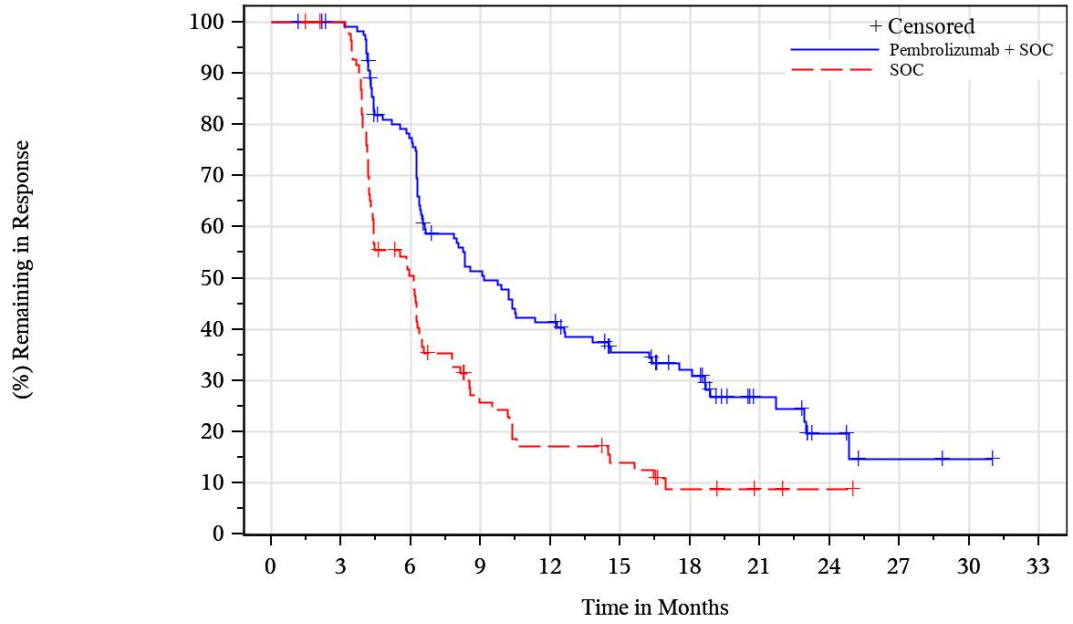
Table 39
Summary of Time to Response and Duration of Response
Based on Investigator Assessment per RECIST 1.1 in Subjects with Confirmed Response
(Subjects with Squamous Cell Carcinoma, ITT Population)

	Pembrolizumab + SOC (N=274)	SOC (N=274)
Number of subjects with response[†]	120	85
Time to Response[†] (months)		
Mean (SD)	2.2 (0.8)	2.3 (1.2)
Median (Range)	2.1 (1.1-8.3)	2.1 (1.3-12.6)
Response Duration[‡] (months)		
Median (Range)	9.1 (1.2+ - 31.0+)	6.1 (1.5+ - 25.0+)
Number (%[‡]) of Subjects with Extended Response Duration:		
≥3 months	117 (100.0)	83 (100.0)
≥6 months	87 (77.5)	40 (50.4)
≥9 months	56 (51.4)	18 (25.6)
≥12 months	45 (41.3)	12 (17.1)
≥18 months	26 (32.1)	4 (8.7)
≥24 months	5 (19.6)	1 (8.7)

[†] Includes subjects with 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.
Database Cutoff Date: 02JUL2020

Source: [P590V01MK3475: adam-adsl; adtte]

Figure 28
Kaplan-Meier Estimates of Duration of Response in Subjects with Confirmed Response Based on Investigator Assessment per RECIST 1.1
(Subjects with Squamous Cell Carcinoma, ITT Population)



Number of subjects at risk

Pembrolizumab + SOC	120	117	87	56	45	34	26	12	5	2	1	0
SOC	85	83	40	18	12	9	4	2	1	0	0	0

Database Cutoff Date: 02JUL2020
Source: [P590V01MK3475: adam-adsl; adtte]

Table 40
Analysis of Objective Response with Confirmation Based on Investigator Assessment per RECIST 1.1 (Subjects with Adenocarcinoma, 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	99	48	48.5 (38.3, 58.7)	24.3 (11.1, 36.7)	0.0002
SOC	102	25	24.5 (16.5, 34.0)		

[†] Based on Miettinen & Nurminen method stratified by geographic region (Asia versus Rest of the World) and ECOG performance status (0 versus 1).
[††] One-sided p-value for testing. H0: difference in % = 0 versus H1: difference in % > 0.
Responses are based on Investigator Assessment per RECIST 1.1 with confirmation.
Database Cutoff Date: 02JUL2020

Source: [P590V01MK3475: adam-adsl; adrs]

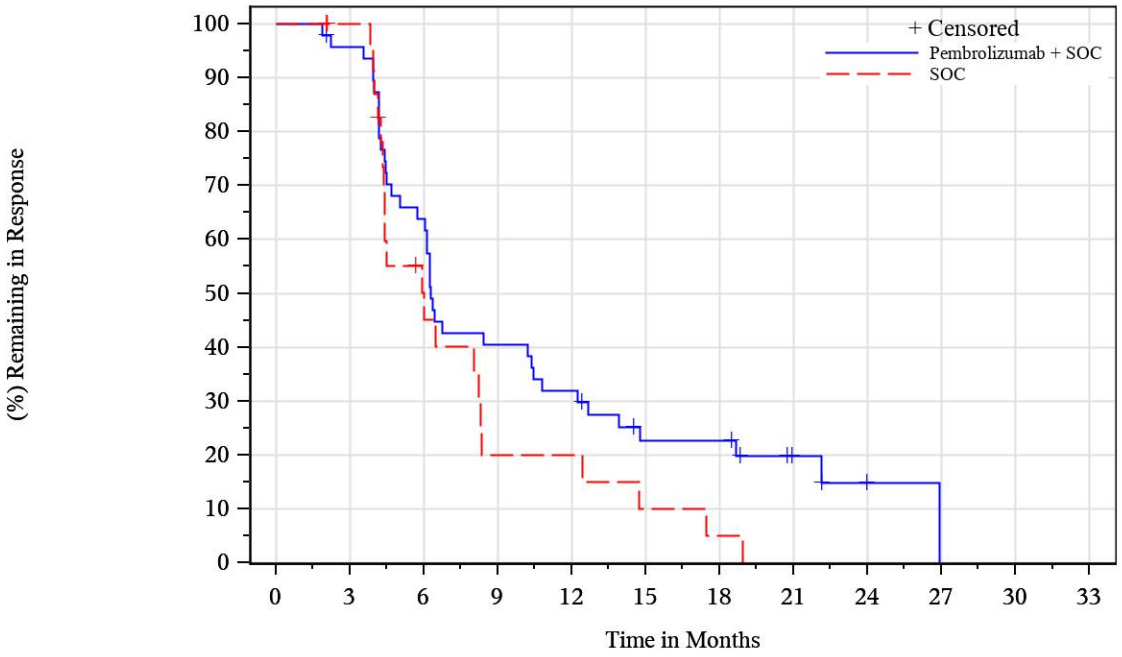
Table 41
Summary of Time to Response and Duration of Response
Based on Investigator Assessment per RECIST 1.1 in Subjects with Confirmed Response
(Subjects with Adenocarcinoma, ITT Population)

	Pembrolizumab + SOC (N=99)	SOC (N=102)
Number of subjects with response[†]	48	25
Time to Response[†] (months)		
Mean (SD)	2.5 (1.1)	2.4 (0.9)
Median (Range)	2.1 (1.8-8.3)	2.0 (1.4-4.3)
Response Duration[‡] (months)		
Median (Range)	6.3 (1.9 - 26.9)	6.0 (2.1+ - 19.0)
Number (%[‡]) of Subjects with Extended Response Duration:		
≥3 months	45 (95.8)	23 (100.0)
≥6 months	30 (63.9)	10 (50.1)
≥9 months	19 (40.4)	4 (20.0)
≥12 months	15 (31.9)	4 (20.0)
≥18 months	9 (22.7)	1 (5.0)
≥24 months	1 (14.9)	0 (NR)

[†] Includes subjects with 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.
NR = Not Reached.
Database Cutoff Date: 02JUL2020

Source: [P590V01MK3475: adam-adsl; adtte]

Figure 29
Kaplan-Meier Estimates of Duration of Response in Subjects with Confirmed Response Based on Investigator Assessment per RECIST 1.1
(Subjects with Adenocarcinoma, ITT Population)



Number of subjects at risk

Pembrolizumab + SOC	48	45	30	19	15	9	9	4	1	0	0	0
SOC	25	23	10	4	4	2	1	0	0	0	0	0

Database Cutoff Date: 02JUL2020
Source: [P590V01MK3475: adam-adsl; adtte]

Exploratory Analysis of Objective Response Rate by CPS Cut-point

Table 42
KEYNOTE-590 - Analysis of Objective Response with Confirmation Based on Investigator Assessment per RECIST 1.1 (Participants with PD-L1 CPS >= 1, 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	320	145	45.3 (39.8, 50.9)	16.6 (9.2, 23.8)	<0.0001
SOC	327	94	28.7 (23.9, 34.0)		

[†] Based on Miettinen & Nurminen method stratified by geographic region (Asia versus Rest of the World) and tumor histology (Adenocarcinoma versus Squamous Cell Carcinoma).
[††] One-sided p-value for testing. H0: difference in % = 0 versus H1: difference in % > 0.
Responses are based on Investigator Assessment per RECIST 1.1 with confirmation.
Database Cutoff Date: 02JUL2020

Source: [P590V01MK3475: adam-adsl; adrs]

Table 43
KEYNOTE-590 - Summary of Time to Response and Duration of Response Based on Investigator Assessment per RECIST 1.1 in Participants with Confirmed Response (Participants with PD-L1 CPS ≥ 1, ITT Population)

	Pembrolizumab + SOC (N=320)	SOC (N=327)
Number of participants with response[†]	145	94
Time to Response[†] (months)		
Mean (SD)	2.3 (0.9)	2.4 (1.2)
Median (Range)	2.1 (1.1-8.3)	2.1 (1.3-12.6)
Response Duration[‡] (months)		
Median (Range)	8.6 (1.2+ - 31.0+)	5.8 (1.5+ - 25.0+)
Number (%[‡]) of Participants with Extended Response Duration:		
≥3 months	140 (99.3)	91 (100.0)
≥6 months	101 (74.2)	41 (48.2)
≥9 months	67 (49.9)	18 (24.0)
≥12 months	53 (39.5)	15 (20.0)
≥18 months	32 (31.2)	5 (8.2)
≥24 months	6 (19.1)	1 (6.6)

[†] Includes participants with 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.
Database Cutoff Date: 02JUL2020

Source: [P590V01MK3475: adam-adsl; adtte]

Table 44
KEYNOTE-590 - Analysis of Objective Response with Confirmation Based on Investigator Assessment per RECIST 1.1
(Participants with PD-L1 1 <= CPS < 10, 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	134	50	37.3 (29.1, 46.1)	6.0 (-5.6, 17.3)	0.1554
SOC	130	41	31.5 (23.7, 40.3)		

[†] Based on Miettinen & Nurminen method stratified by geographic region (Asia versus Rest of the World) and tumor histology (Adenocarcinoma versus Squamous Cell Carcinoma).
[††] One-sided p-value for testing. H0: difference in % = 0 versus H1: difference in % > 0.
Responses are based on Investigator Assessment per RECIST 1.1 with confirmation.
Database Cutoff Date: 02JUL2020

Source: [P590V01MK3475: adam-adsl; adrs]

Table 45
KEYNOTE-590 - Summary of Time to Response and Duration of Response Based on Investigator Assessment per RECIST 1.1 in Subjects with Confirmed Response (Participants with PD-L1 1 <= CPS < 10, ITT Population)

	Pembrolizumab + SOC (N=134)	SOC (N=130)
Number of subjects with response[†]	50	41
Time to Response[†] (months)		
Mean (SD)	2.3 (0.7)	2.5 (1.7)
Median (Range)	2.1 (1.1-4.3)	2.1 (1.3-12.6)
Response Duration[‡] (months)		
Median (Range)	6.4 (1.2+ - 31.0+)	5.8 (3.4 - 19.2+)
Number (%[‡]) of Subjects with Extended Response Duration:		
≥3 months	49 (100.0)	41 (100.0)
≥6 months	30 (63.1)	19 (48.7)
≥9 months	21 (44.2)	8 (24.6)
≥12 months	15 (31.5)	5 (15.4)
≥18 months	10 (27.0)	1 (4.6)
≥24 months	2 (10.4)	0 (NR)

[†] Includes subjects with 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.
NR = Not Reached.
Database Cutoff Date: 02JUL2020

Source: [P590V01MK3475: adam-adsl; adtte]

Table 46
KEYNOTE-590 - Analysis of Objective Response with Confirmation Based on Investigator Assessment per RECIST 1.1 (Participants with PD-L1 CPS < 1, 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	41	18	43.9 (28.5, 60.3)	10.3 (-10.9, 30.6)	0.1706
SOC	42	14	33.3 (19.6, 49.5)		

[†] Based on Miettinen & Nurminen method stratified by geographic region (Asia versus Rest of the World) and tumor histology (Adenocarcinoma versus Squamous Cell Carcinoma).
[††] One-sided p-value for testing. H0: difference in % = 0 versus H1: difference in % > 0.
Responses are based on Investigator Assessment per RECIST 1.1 with confirmation.
Database Cutoff Date: 02JUL2020

Source: [P590V01MK3475: adam-adsl; adrs]

Table 47
KEYNOTE-590 - Summary of Best Overall Response Based on Investigator Assessment per RECIST 1.1 with Confirmation (Participants with PD-L1 CPS < 1, ITT Population)

	Pembrolizumab + SOC		SOC	
	n	%	n	%
Number of Participants in Population	41		42	
Complete Response (CR)	4	9.8	0	0.0
Partial Response (PR)	14	34.1	14	33.3
Best Overall Response (CR+PR)	**18**	**43.9**	**14**	**33.3**
Stable Disease (SD)	15	36.6	13	31.0
Disease Control (CR + PR + SD)	**33**	**80.5**	**27**	**64.3**
Progressive Disease (PD)	3	7.3	9	21.4
Not Evaluable (NE)	1	2.4	1	2.4
No Assessment	4	9.8	5	11.9

Responses are based on Investigator Assessment best assessment across timepoints, with confirmation.
NE: post-baseline assessment(s) available however not being evaluable (i.e., all post-baseline assessment(s) being NOT EVALUABLE or CR/PR/SD < 6 weeks from randomization).
No Assessment: no post-baseline assessment available for response evaluation.
Database Cutoff Date: 02JUL2020

Source: [P590V01MK3475: adam-adsl; adrs]

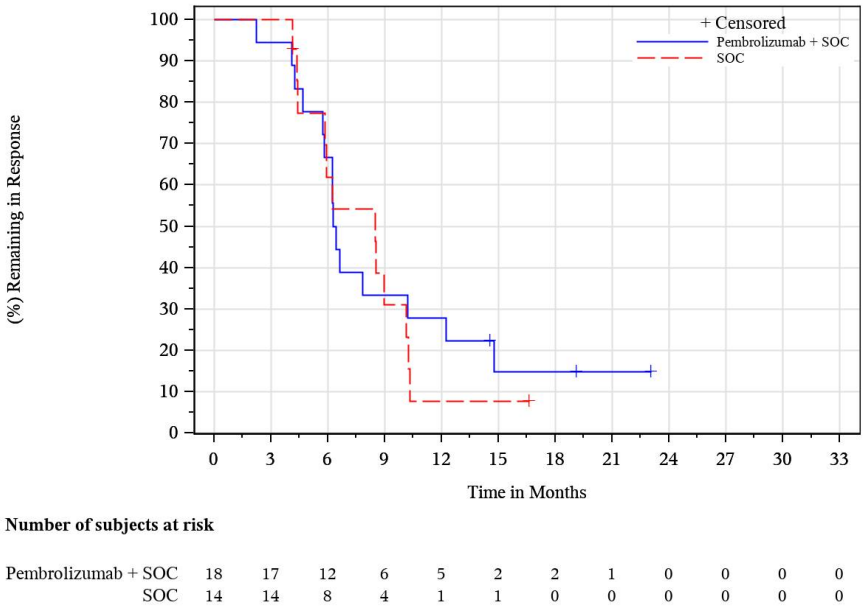
Table 48
KEYNOTE-590 - Summary of Time to Response and Duration of Response Based on Investigator Assessment per RECIST 1.1 in Participants with Confirmed Response (Participants with PD-L1 CPS < 1, ITT Population)

	Pembrolizumab + SOC (N=41)	SOC (N=42)
Number of participants with response[†]	18	14
Time to Response[†] (months)		
Mean (SD)	2.4 (0.8)	2.4 (0.8)
Median (Range)	2.1 (1.8-4.2)	2.2 (1.9-4.2)
Response Duration[‡] (months)		
Median (Range)	6.4 (2.2 - 23.1+)	8.5 (4.1 - 16.6+)
Number (%[‡]) of Participants with Extended Response Duration:		
≥3 months	17 (94.4)	14 (100.0)
≥6 months	12 (66.7)	8 (61.9)
≥9 months	6 (33.3)	4 (31.0)
≥12 months	5 (27.8)	1 (7.7)
≥18 months	2 (14.8)	0 (NR)

[†] Includes participants with 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.
NR = Not Reached.
Database Cutoff Date: 02JUL2020

Source: [P590V01MK3475: adam-adsl; adtte]

Figure 30
KEYNOTE-590 - Kaplan-Meier Estimates of Duration of Response in Participants with Confirmed Response Based on Investigator Assessment per RECIST 1.1 (Participants with PD-L1 CPS < 1, ITT Population)



Database Cutoff Date: 02JUL2020
Source: [P590V01MK3475: adam-adsl; adtte]

5-Year Follow-up Results for OS and PFS

Table 49
KEYNOTE-590 - Analysis of Overall Survival (ITT Population) – 5-year Follow-up

Treatment	N	Number of Events (%)	Person-Months	Event Rate/ 100 Person-Months	Median OS [a] (Months) (95% CI)	OS Rate at Month 12 in % [a] (95% CI)
Pembrolizumab + SOC	373	331 (88.7)	7134.1	4.6	12.3 (10.5, 14.0)	50.5 (45.3, 55.4)
SOC	376	363 (96.5)	5396.5	6.7	9.8 (8.8, 11.0)	39.5 (34.5, 44.4)
Pairwise Comparisons					Hazard Ratio[b] (95% CI)[b]	p-Value
Pembrolizumab + SOC vs. SOC					0.72 (0.62, 0.84)	<0.0001[c]

[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 (Asia versus Rest of the World) and tumor histology (Adenocarcinoma versus Squamous Cell Carcinoma) and ECOG performance status (0 versus 1).
[c] One-sided p-value based on log-rank test stratified by geographic region (Asia versus Rest of the World) and tumor histology (Adenocarcinoma versus Squamous Cell Carcinoma) and ECOG performance status (0 versus 1).
Database Cutoff Date: 10JUL2023.

Source: [P590MK3475: adam-adsl; adtte]

Table 50
KEYNOTE-590 - Overall Survival Rate
(ITT Population) – 5-year Follow-up

	Pembrolizumab + SOC (N=373)	SOC (N=376)
OS rate at 3 Months in (95% CI)[a]	93.8 (90.9, 95.9)	90.1 (86.6, 92.8)
OS rate at 6 Months in (95% CI)[a]	79.6 (75.1, 83.3)	73.1 (68.3, 77.3)
OS rate at 9 Months in (95% CI)[a]	63.7 (58.6, 68.4)	53.6 (48.4, 58.5)
OS rate at 12 Months in (95% CI)[a]	50.5 (45.3, 55.4)	39.5 (34.5, 44.4)
OS rate at 18 Months in (95% CI)[a]	35.1 (30.3, 40.0)	24.0 (19.8, 28.4)
OS rate at 24 Months in (95% CI)[a]	26.2 (21.8, 30.7)	16.0 (12.5, 19.9)
OS rate at 30 Months in (95% CI)[a]	20.8 (16.8, 25.1)	12.8 (9.7, 16.4)
OS rate at 36 Months in (95% CI)[a]	17.8 (14.1, 21.9)	8.8 (6.2, 11.9)
OS rate at 48 Months in (95% CI)[a]	13.0 (9.8, 16.6)	4.8 (3.0, 7.3)
OS rate at 60 Months in (95% CI)[a]	10.6 (7.7, 14.0)	3.0 (1.6, 5.2)

[a] From the product-limit (Kaplan-Meier) method for censored data.
Database Cutoff Date: 10JUL2023

Source: [P590MK3475: adam-adsl; adtte]

Table 51
KEYNOTE-590 - Analysis of Progression-Free Survival Based on Investigator Assessment per RECIST 1.1 (Primary Censoring Rule)
(ITT Population) – 5-year Follow-up

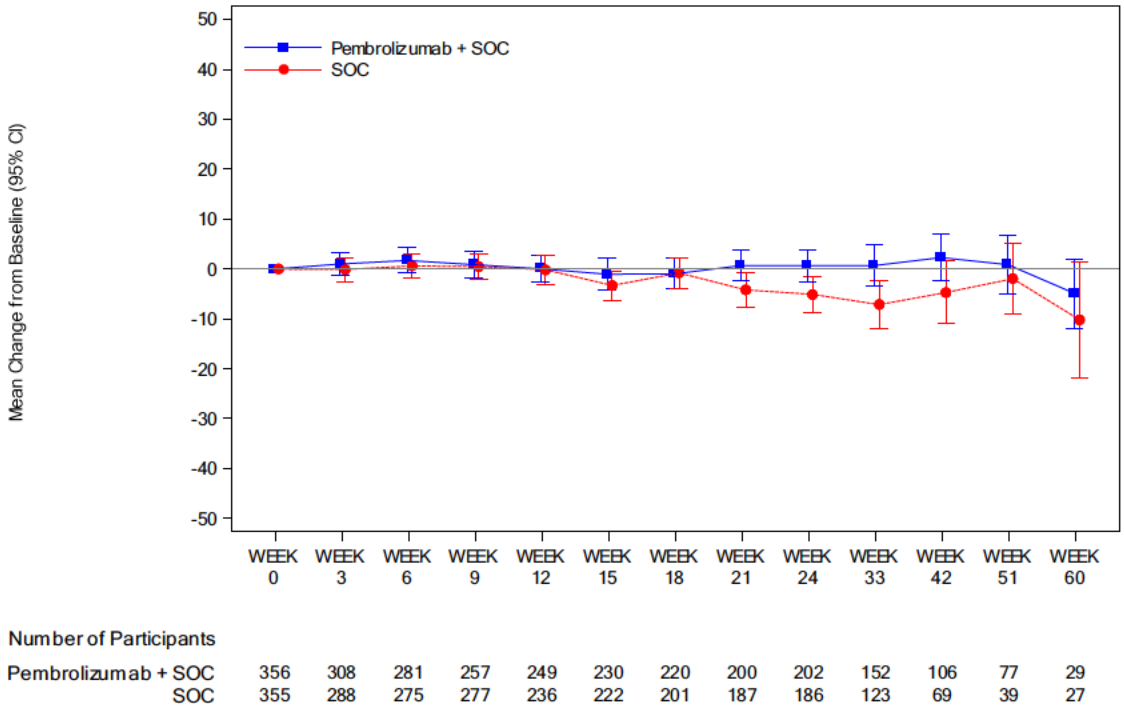
Treatment	N	Number of Events (%)	Person-Months	Event Rate/ 100 Person-Months	Median PFS [a] (Months) (95% CI)	PFS Rate at Month 6 in % [a] (95% CI)
Pembrolizumab + SOC	373	313 (83.9)	3614.8	8.7	6.3 (6.2, 7.1)	62.4 (57.1, 67.3)
SOC	376	339 (90.2)	2272.7	14.9	5.8 (5.0, 6.0)	48.7 (43.4, 53.7)
Pairwise Comparisons					Hazard Ratio[b] (95% CI)[b]	p-Value
Pembrolizumab + SOC vs. SOC					0.64 (0.54, 0.75)	<0.0001[c]

[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 (Asia versus Rest of the World) and tumor histology (Adenocarcinoma versus Squamous Cell Carcinoma) and ECOG performance status (0 versus 1).
[c] One-sided p-value based on log-rank test stratified by geographic region (Asia versus Rest of the World) and tumor histology (Adenocarcinoma versus Squamous Cell Carcinoma) and ECOG performance status (0 versus 1).
Progression-free survival is defined as time from randomization to disease progression, or death, whichever occurs first.
Database Cutoff Date: 10JUL2023.

Source: [P590MK3475: adam-adsl; adtte]

Patient-reported Outcomes

Figure 31
KEYNOTE-590 - Empirical Mean Change from Baseline and 95% CI for the EORTC QLQ-C30 Global Health Status/QoL Over Time by Treatment Group
(FAS Population)



Number of Participants													
Pembrolizumab + SOC	356	308	281	257	249	230	220	200	202	152	106	77	29
SOC	355	288	275	277	236	222	201	187	186	123	69	39	27

Database Cutoff Date: 02JUL2020
Source: [P590V01MK3475: adam-adsl; adpro]

Table 52
KEYNOTE-590 - Analysis of Change from Baseline in EORTC QLQ-C30 Global Health Status/QoL to Week 18 (FAS Population)

	Baseline		Week 18		Change from Baseline to Week 18	
Treatment	N	Mean (SD)	N	Mean (SD)	N	LS Mean (95% CI)†
Pembrolizumab + SOC	356	64.37 (21.23)	225	65.00 (20.80)	366	-1.74 (-4.24, 0.75)
SOC	355	65.66 (20.06)	206	66.42 (18.59)	363	-1.64 (-4.21, 0.92)

Pairwise Comparison	Difference in LS Means† (95% CI)	p-Value†
Pembrolizumab + SOC vs. SOC	-0.10 (-3.40, 3.20)	0.9530

† Based on a cLDA model with the PRO scores as the response variable with covariates for treatment by study visit interaction, stratification factors geographic region (Asia versus Rest of the World) and tumor histology (Adenocarcinoma versus Squamous Cell Carcinoma) and ECOG performance status (0 versus 1).

For baseline and Week 18, N is the number of participants in each treatment group with non-missing assessments at the specific time point; for change from baseline, N is the number of participants in the analysis population in each treatment group.

Database Cutoff Date: 02JUL2020

Source: [P590V01MK3475: adam-adsl; adpro]

Table 53
Analysis of Change from Baseline in EORTC QLQ-C30 Physical Functioning to Week 18
(FAS Population)

	Baseline		Week 18		Change from Baseline to Week 18	
Treatment	N	Mean (SD)	N	Mean (SD)	N	LS Mean (95% CI)†
Pembrolizumab + SOC	356	82.66 (18.78)	225	78.46 (21.95)	366	-7.24 (-9.70, -4.77)
SOC	355	82.44 (19.93)	206	79.09 (20.58)	363	-8.09 (-10.62, -5.56)

Pairwise Comparison	Difference in LS Means† (95% CI)	p-Value†
Pembrolizumab + SOC vs. SOC	0.85 (-2.56, 4.27)	0.6244

† Based on a cLDA model with the PRO scores as the response variable with covariates for treatment by study visit interaction, stratification factors geographic region (Asia versus Rest of the World) and tumor histology (Adenocarcinoma versus Squamous Cell Carcinoma) and ECOG performance status (0 versus 1).

For baseline and Week 18, N is the number of subjects in each treatment group with non-missing assessments at the specific time point; for change from baseline, N is the number of subjects in the analysis population in each treatment group.

Database Cutoff Date: 02JUL2020

Source: [P590V01MK3475: adam-adsl; adpro]

Table 54
Analysis of Change from Baseline in OES-18 Reflux to Week 18
(FAS Population)

	Baseline		Week 18		Change from Baseline to Week 18	
Treatment	N	Mean (SD)	N	Mean (SD)	N	LS Mean (95% CI)†
Pembrolizumab + SOC	355	15.96 (21.78)	224	14.88 (19.95)	366	-0.22 (-2.81, 2.36)
SOC	350	16.10 (21.63)	204	16.09 (21.40)	359	0.71 (-1.96, 3.38)

Pairwise Comparison	Difference in LS Means† (95% CI)	p-Value†
Pembrolizumab + SOC vs. SOC	-0.93 (-4.36, 2.49)	0.5932

† Based on a cLDA model with the PRO scores as the response variable with covariates for treatment by study visit interaction, stratification factors geographic region (Asia versus Rest of the World) and tumor histology (Adenocarcinoma versus Squamous Cell Carcinoma) and ECOG performance status (0 versus 1).

For baseline and Week 18, N is the number of subjects in each treatment group with non-missing assessments at the specific time point; for change from baseline, N is the number of subjects in the analysis population in each treatment group.

Database Cutoff Date: 02JUL2020

Source: [P590V01MK3475: adam-adsl; adpro]

Table 55
Analysis of Change from Baseline in OES-18 Dysphagia to Week 18
(FAS Population)

	Baseline		Week 18		Change from Baseline to Week 18	
Treatment	N	Mean (SD)	N	Mean (SD)	N	LS Mean (95% CI)[†]
Pembrolizumab + SOC	355	33.18 (30.93)	224	29.27 (34.06)	366	-3.18 (-7.19, 0.82)
SOC	350	37.87 (32.82)	204	36.76 (35.43)	359	2.36 (-1.77, 6.49)

Pairwise Comparison	Difference in LS Means[†] (95% CI)	p-Value[†]
Pembrolizumab + SOC vs. SOC	-5.54 (-10.93, -0.16)	0.0436

[†] Based on a cLDA model with the PRO scores as the response variable with covariates for treatment by study visit interaction, stratification factors geographic region (Asia versus Rest of the World) and tumor histology (Adenocarcinoma versus Squamous Cell Carcinoma) and ECOG performance status (0 versus 1).

For baseline and Week 18, N is the number of subjects in each treatment group with non-missing assessments at the specific time point; for change from baseline, N is the number of subjects in the analysis population in each treatment group.

Database Cutoff Date: 02JUL2020

Source: [P590V01MK3475: adam-adsl; adpro]

Table 56
Analysis of Change from Baseline in OES-18 Pain to Week 18
(FAS Population)

	Baseline		Week 18		Change from Baseline to Week 18	
Treatment	N	Mean (SD)	N	Mean (SD)	N	LS Mean (95% CI)[†]
Pembrolizumab + SOC	355	15.43 (18.51)	224	10.02 (15.85)	366	-4.78 (-7.01, -2.56)
SOC	350	17.30 (20.03)	204	13.13 (17.79)	359	-1.85 (-4.14, 0.45)

Pairwise Comparison	Difference in LS Means[†] (95% CI)	p-Value[†]
Pembrolizumab + SOC vs. SOC	-2.94 (-5.86, -0.02)	0.0487

[†] Based on a cLDA model with the PRO scores as the response variable with covariates for treatment by study visit interaction, stratification factors geographic region (Asia versus Rest of the World) and tumor histology (Adenocarcinoma versus Squamous Cell Carcinoma) and ECOG performance status (0 versus 1).

For baseline and Week 18, N is the number of subjects in each treatment group with non-missing assessments at the specific time point; for change from baseline, N is the number of subjects in the analysis population in each treatment group.

Database Cutoff Date: 02JUL2020

Source: [P590V01MK3475: adam-adsl; adpro]

Table 57
KEYNOTE-590 - Analysis of Change from Baseline in EORTC QLQ-C30 Global Health Status/QoL to Week 18 (Participants with PD-L1 CPS ≥ 10, FAS Population)

	Baseline		Week 18		Change from Baseline to Week 18	
Treatment	N	Mean (SD)	N	Mean (SD)	N	LS Mean (95% CI)†
Pembrolizumab + SOC	179	64.57 (21.16)	109	64.76 (21.30)	184	-1.73 (-5.50, 2.04)
SOC	185	65.23 (19.16)	105	67.38 (18.20)	191	0.04 (-3.77, 3.85)

Pairwise Comparison	Difference in LS Means† (95% CI)	p-Value†
Pembrolizumab + SOC vs. SOC	-1.77 (-6.71, 3.17)	0.4810

† Based on a cLDA model with the PRO scores as the response variable with covariates for treatment by study visit interaction, stratification factors geographic region (Asia versus Rest of the World) and tumor histology (Adenocarcinoma versus Squamous Cell Carcinoma).

For baseline and Week 18, N is the number of participants in each treatment group with non-missing assessments at the specific time point; for change from baseline, N is the number of participants in the analysis population in each treatment group.

Database Cutoff Date: 02JUL2020

Source: [P590V01MK3475: adam-adsl; adpro]

Table 58
KEYNOTE-590 - Analysis of Change from Baseline in EORTC QLQ-C30 Global Health Status/QoL to Week 18 (Participants with PD-L1 CPS >= 1, FAS Population)

	Baseline		Week 18		Change from Baseline to Week 18	
Treatment	N	Mean (SD)	N	Mean (SD)	N	LS Mean (95% CI)†
Pembrolizumab + SOC	311	64.17 (21.31)	195	64.70 (21.11)	317	-2.01 (-4.70, 0.68)
SOC	310	65.22 (20.12)	181	66.39 (18.17)	317	-1.32 (-4.07, 1.42)

Pairwise Comparison	Difference in LS Means† (95% CI)	p-Value†
Pembrolizumab + SOC vs. SOC	-0.69 (-4.25, 2.87)	0.7049

† Based on a cLDA model with the PRO scores as the response variable with covariates for treatment by study visit interaction , stratification factors geographic region (Asia versus Rest of the World) and tumor histology (Adenocarcinoma versus Squamous Cell Carcinoma).

For baseline and Week 18, N is the number of participants in each treatment group with non-missing assessments at the specific time point; for change from baseline, N is the number of participants in the analysis population in each treatment group.

Database Cutoff Date: 02JUL2020

Source: [P590V01MK3475: adam-adsl; adpro]

Table 59
KEYNOTE-590 - Analysis of Change from Baseline in EORTC QLQ-C30 Global Health Status/QoL to Week 18 (Participants with PD-L1 CPS < 1, FAS Population)

	Baseline		Week 18		Change from Baseline to Week 18	
Treatment	N	Mean (SD)	N	Mean (SD)	N	LS Mean (95% CI)†
Pembrolizumab + SOC	35	65.48 (22.34)	23	62.68 (17.20)	39	-2.80 (-10.54, 4.94)
SOC	38	69.96 (19.90)	22	67.42 (22.41)	39	-4.19 (-12.01, 3.63)

Pairwise Comparison	Difference in LS Means† (95% CI)	p-Value†
Pembrolizumab + SOC vs. SOC	1.39 (-8.90, 11.68)	0.7879

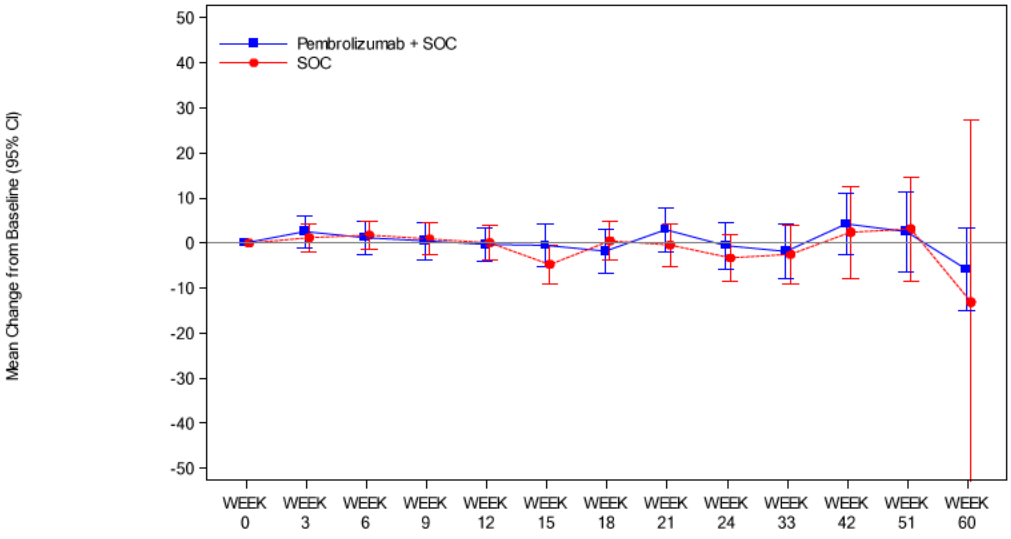
† Based on a cLDA model with the PRO scores as the response variable with covariates for treatment by study visit interaction , unstratified.

For baseline and Week 18, N is the number of participants in each treatment group with non-missing assessments at the specific time point; for change from baseline, N is the number of participants in the analysis population in each treatment group.

Database Cutoff Date: 02JUL2020

Source: [P590V01MK3475: adam-adsl; adpro]

Figure 32
KEYNOTE-590 - Empirical Mean Change from Baseline and 95% CI for the EORTC QLQ-C30 Global Health Status/QoL Over Time by Treatment Group (Participants with PD-L1 CPS >= 10, FAS Population)

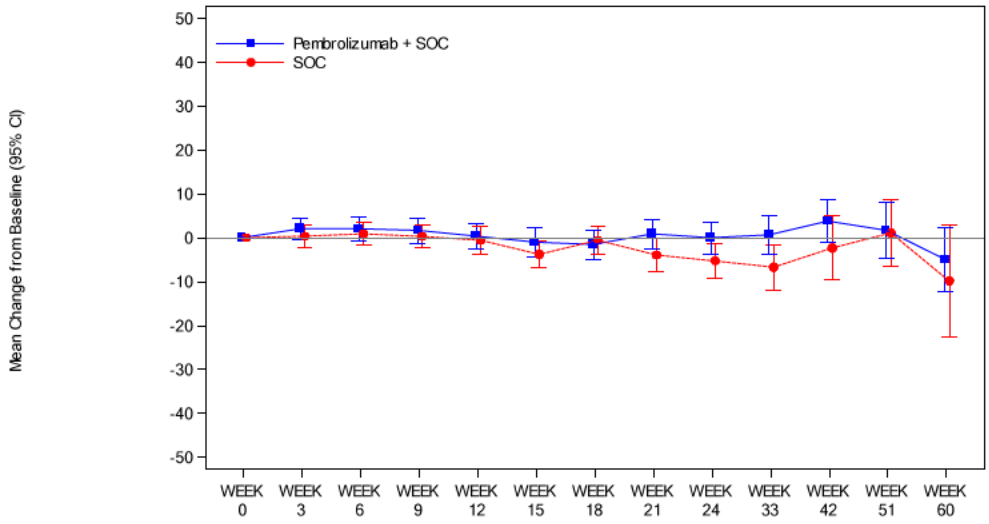


Number of Participants	WEEK 0	WEEK 3	WEEK 6	WEEK 9	WEEK 12	WEEK 15	WEEK 18	WEEK 21	WEEK 24	WEEK 33	WEEK 42	WEEK 51	WEEK 60
Pembrolizumab + SOC	179	153	138	128	130	113	107	101	103	84	61	46	20
SOC	185	144	149	139	129	118	102	95	91	60	31	16	7

Database Cutoff Date: 02JUL2020

Source: [P590V01MK3475: adam-adsl; adpro]

Figure 33
KEYNOTE-590 - Empirical Mean Change from Baseline and 95% CI for the EORTC QLQ-C30 Global Health Status/QoL Over Time by Treatment Group
(Participants with PD-L1 CPS >= 1, FAS Population)

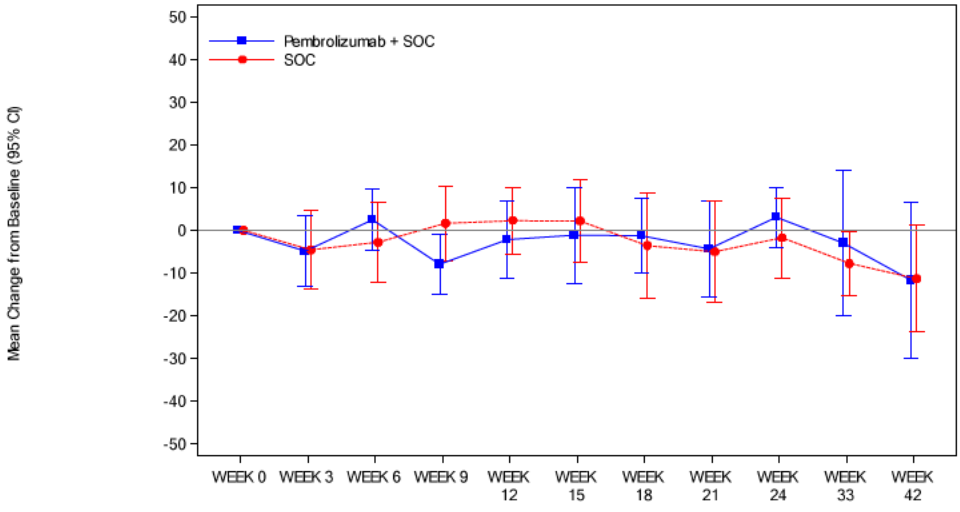


Number of Participants

	WEEK 0	WEEK 3	WEEK 6	WEEK 9	WEEK 12	WEEK 15	WEEK 18	WEEK 21	WEEK 24	WEEK 33	WEEK 42	WEEK 51	WEEK 60
Pembrolizumab + SOC	311	269	245	228	214	201	193	175	177	133	93	69	27
SOC	310	252	244	247	211	200	177	164	165	107	54	30	22

Database Cutoff Date: 02JUL2020
Source: [P590V01MK3475: adam-adsl; adpro]

Figure 34
KEYNOTE-590 - Empirical Mean Change from Baseline and 95% CI for the EORTC QLQ-C30 Global Health Status/QoL Over Time by Treatment Group
(Participants with PD-L1 CPS < 1, FAS Population)



Number of Participants

	WEEK 0	WEEK 3	WEEK 6	WEEK 9	WEEK 12	WEEK 15	WEEK 18	WEEK 21	WEEK 24	WEEK 33	WEEK 42
Pembrolizumab + SOC	35	29	27	22	27	22	20	21	19	14	10
SOC	38	31	27	25	22	19	21	20	19	14	14

Database Cutoff Date: 02JUL2020
Source: [P590V01MK3475: adam-adsl; adpro]

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