FDA Briefing Document

Immune checkpoint inhibitors in patients with metastatic or unresectable esophageal squamous cell carcinoma

Oncologic Drugs Advisory Committee Meeting

September 26, 2024

Division of Oncology 3/Office of Oncologic Diseases

DISCLAIMER STATEMENT

The attached package contains background information prepared by the Food and Drug Administration (FDA) for the panel members of the Advisory Committee. The FDA background package often contains assessments and/or conclusions and recommendations written by individual FDA reviewers. Such conclusions and recommendations do not necessarily represent the final position of the individual reviewers, nor do they necessarily represent the final position of the Review Division or Office. We have brought the use of immune checkpoint inhibitors in patients with metastatic or unresectable esophageal squamous cell carcinoma to this Advisory Committee in order to gain the Committee's insights and opinions, and the background package may not include all issues relevant to the final regulatory recommendation and instead is intended to focus on issues identified by the Agency for discussion by the Advisory Committee. The FDA will not issue a final determination on the issues at hand until input from the Advisory Committee process has been considered and all reviews have been finalized. The final determination may be affected by issues not discussed at the Advisory Committee meeting.

Table of Contents

Table of Tables

Table of Figures

Glossary

ASCO	American Society of Clinical Oncology
BMS	Bristol Myers Squibb
BD	Briefing Document
BICR	Blinded Independent Central Review
BLA	Biologics License Application
CDER	Center for Drug Evaluation and Research
CI	confidence interval
CHMP	Committee for Medicinal Products for Human Use
CPS	Combined Positive Score
CTL4	cytotoxic T-lymphocyte antigen 4
dMMR	deficient mismatch repair
DOR	duration of response
EAC	esophageal adenocarcinoma
EGFR	endothelial growth factor receptor
EMA	European Medicines Agency
ESCC	esophageal squamous cell carcinoma
ESMO	European Society for Medical Oncology
FDA	Food and Drug Administration
GEJ	gastroesophageal junction
GLOBOCAN	Global Cancer Observatory, International Agency for Research in Cancer
HR	hazard ratio
IA	integrated assessment
ICIs	immune checkpoint inhibitors
IHC	immunohistochemistry
ITT	Intent-to-Treat
IV	intravenously
MSI-H	microsatellite instability-high
NCCN	National Comprehensive Cancer Network
ODAC	Oncologic Drugs Advisory Committee
ORR	Overall Response Rate

OS	Overall Survival
PD-1	Programmed Death Cell Receptor-1
PD-L1	Programmed Death Ligand-1
PFS	Progression-Free Survival
Q2W	every 2 weeks
Q3W	every 3 weeks
SEER	Surveillance, Epidemiology, and End Results Program
SAP	Statistical Analysis Plan
SD	standard deviation
TC	Tumor Cell
TAP	Tumor Area Positivity
TPS	Tumor Proportion Score
vCPS	visually Combined Positive Score

1 Executive Summary/Draft Points for Consideration by the Advisory Committee

1.1 Purpose/Objective of the AC Meeting

The FDA is convening this Oncologic Drugs Advisory Committee (ODAC) meeting to discuss the risk benefit assessment of the use of immune checkpoint inhibitors (ICI) in combination with chemotherapy for the first line treatment of patients with unresectable or metastatic esophageal squamous cell carcinoma (ESCC) at different levels of programmed death ligand 1 (PD-L1) protein expression. Labeling for approved immune checkpoint inhibitors (ICIs) for the treatment of patients with ESCC reflects approvals in the intent to treat patient (ITT) populations agnostic of programmed death cell ligand-1 (PD-L1) expression. Cumulative data across independent trials and ICI products have shown that PD-L1 expression appears to be a predictive biomarker of treatment efficacy in this patient population; however, clinical trials have used different assays to assess PD-L1 expression and different thresholds to define PD-L1 positivity.

This document discusses the relevant data from individual studies leading to the approvals of nivolumab and pembrolizumab for the first-line treatment of unresectable or metastatic ESCC, as well as the data submitted to support the approval of tislelizumab for the same indication. The aggregated experience with these independent trials and products provides a framework to discuss the strength of evidence for PD-L1 expression as a predictive biomarker for patient selection, differing risk-benefit assessments in different subpopulations defined by PD-L1 expression, and adequacy of the cumulative data to restrict the approvals of immune checkpoint inhibitors based on PD-L1 expression.

FDA would like the Committee to discuss whether the respective indications for the use of ICIs in combination with chemotherapy for the first line treatment of ESCC should require patient selection based on PD-L1 expression levels (e.g., ≥1).

FDA will consider the discussion of these key topics and any (non-binding) recommendations provided by the Committee to determine whether to revise the existing approved indications and when considering labeling of the submitted tislelizumab application.

1.2 Context for Issues to Be Discussed at the AC

The utility of tumor PD-L1 expression as a predictive biomarker for identifying patients likely to benefit from ICIs varies considerably by tumor histology (Patel S, 2015). Assessment of PD-L1 via immunohistochemistry (IHC) may differ across drug products due to the availability of multiple IHC assays, scoring algorithms, and cutoffs. Although there have been attempts at assessing the interoperability of these assays in gastroesophageal tumors (Ahn S, 2021; Yeong J, 2022; Yoon H, 2022; Wang L, 2024; Wang X, 2024; Klempner S, 2024) and it appears that there is significant overlap, it is unclear that the same populations are being selected with each assay and these studies are not designed to address clinical outcome comparisons.

The US FDA approvals of pembrolizumab (based on KEYNOTE-590 [KN-590]) and nivolumab (based on CHECKMATE-648 [CM-648]) in combination with chemotherapy for the first line treatment of ESCC is agnostic of PD-L1 expression status. The studies that led to these approvals and the trial of tislelizumab currently under review (RATIONALE-306, [RN-306]) have demonstrated an improvement in overall survival (OS) both in protocol-specified (see below) PD-L1 positive populations and in the intent-to-treat

(ITT) unselected populations. Analyses in the PD-L1 *negative or low* populations were considered exploratory analyses and not necessarily powered to demonstrate a treatment effect.

Although the FDA did not restrict labeling based on PD-L1 status following the review of the results of each trial on its own merits, results are now available across multiple trials which may make inferences based on subgroups more reliable. As an example, in December 2008, FDA held an Advisory Committee meeting to discuss *KRAS* as a predictive biomarker for EGFR inhibitors cetuximab and panitumumab for the treatment of metastatic colorectal cancer using retrospective analyses of multiple trials to support decision making. Important factors when considering subgroup effects included sample ascertainment and consistency of subgroup effects across trials. Following the ODAC, labeling for panitumumab and cetuximab was amended in July 2009 to recommend against treatment of patients with *KRAS* mutant tumors. Similarly, after an ODAC meeting held on April 2023, the approval of olaparib in combination with abiraterone was restricted to patients with BRCA-mutated metastatic castration-resistant prostate cancer, where in a randomized study a statistically significant improvement in the primary outcome was observed in the ITT population but this improvement was primarily attributable to the results in a subgroup of patients with BRCA mutations.

At the time of decision making for the nivolumab and pembrolizumab approvals, analyses of results by PD-L1 cutoffs were conducted and incorporated into labeling, acknowledging the exploratory nature of these analyses and the relatively small number of patients enrolled with negative or low PD-L1 expression. However, based on subgroup analyses of these trials, the majority of the benefit appears to be attributable to patients with PD-L1 ≥1 expression, with increasing benefit in patients with PD-L1 ≥10 and no apparent benefit in patients with PD-L1 <1. Based on these findings, US professional guidelines (NCCN 2024, ASCO [Shah M, 2023]; and ESMO [Obermannova R et al, 2022]) recommend use of these products based on PD-L1 expression cutoffs. The selected cutoffs are based on the assay and statistical plan used in each clinical trial. Furthermore, the European Medicines Agency's (EMA's) Committee for Medicinal Products for Human Use (CHMP) approved pembrolizumab (EMA, 2021) only for patients with esophageal carcinoma whose tumors express PD-L1 with a CPS ≥ 10, and nivolumab (EMA, 2022) for patients with ESCC with TC PD-L1 ≥ 1%.

Although the approach to restrict use of ICIs based on the trial design methodology (PD-L1 testing, stratification, and statistical analysis plans) is straight forward with respect to assessment of benefit in the protocol-specified biomarker positive populations, analysis of data is more challenging in the biomarker negative populations due to considerations regarding statistical power in each trial. Labeling different PD-L1 cut-points for different drugs has implications on future drug development (e.g., an add-on therapy must consider which partner anti-PD-1 to use and which test to use). There also may be logistical considerations of different PD-L1 cut-points with respect to insurance coverage and specific tests used at each clinical site.

Although there may be methodological limitations to analyses based on PD-L1 across different drugs based on differences in statistical methodology and testing across clinical trials, consistency in the approach to the treatment of patients with ESCC may foster improved outcomes overall by ensuring appropriate patient selection and by facilitating the design of future trials intended to improve outcomes in patients with ESCC. FDA believes a contemporary risk:benefit discussion evaluating the

available data is required to further define the indication for these products for the treatment of ESCC to better match patients with a treatment that is likely to provide them benefit.

As stated above, efficacy data from the three pivotal randomized controlled studies evaluating the use of anti PD-1 monoclonal antibodies in combination with chemotherapy for the first line treatment of patients with ESCC submitted to FDA suggest that PD-L1 tumor expression is a predictive biomarker in identifying patients most likely to benefit from the use of ICIs. In these three studies, the OS benefit observed in the ITT population appears to be predominantly attributable to subgroups of patients with higher PD-L1 expression, with limited efficacy in terms of OS benefit observed in patients with low or no PD-L1 expression (Table 4). Similar results were also reported in a published meta-analysis (that included these and other studies) (Yoon H, 2022).

The FDA review team requests the Committee to discuss:

1. The data supporting PD-L1 expression via IHC as a predictive biomarker to select patients for the use of ICI for the first line treatment of ESCC.
2. The risk benefits of the use of ICI in different subpopulations, as identified by the PD-L1 cutoffs.
3. If a favorable risk-benefit assessment is not warranted at specific PD-L1 cutoffs, whether class labeling based on a specific cutoff (e.g., PD-L1 <1) is appropriate.

2 Introduction and Background

2.1 Background of the Condition/Standard of Clinical Care

Esophageal cancer is the eleventh most common cancer and the seventh leading cause of cancer deaths worldwide, accounting for more than 445,000 deaths each year (Globocan 2022). In the US, it is estimated that 22,370 new cases will be diagnosed in 2024 (SEER, 2024). ESCC and esophageal adenocarcinoma (EAC) are the two main histological subtypes and have distinct epidemiology. Although globally ESCC is the most common (85%), in the US, adenocarcinoma is more common (Uhlenhopp D, 2020). In a retrospective analysis of the Surveillance Epidemiology and End Results (SEER) database, the overall age adjusted incidence rate for adenocarcinoma and squamous cell carcinoma in the US from 2004 – 2015 was 3.2 and 1.9 per 100,000 respectively (Then EO, 2020).

For patients with locally advanced disease not amenable to surgery or definitive chemoradiation and/or metastatic ESCC, treatment is limited to palliative systemic therapy. Based on the trials described below, nivolumab and pembrolizumab (both antibodies targeting PD-1) are now incorporated into the first-line treatment of patients with unresectable or metastatic ESCC as add-ons to standard of care chemotherapy (platinum and fluoropyrimidine). In addition, nivolumab in combination with ipilimumab (a cytotoxic T-lymphocyte 4 antigen [CTLA-4] targeting monoclonal antibody, another checkpoint inhibitor) is approved for this indication.

2.2 Pertinent Drug Development and Regulatory History

Nivolumab (Opdivo, Bristol Myers Squibb [BMS]), pembrolizumab (Keytruda, Merck), and tislelizumab (Tevimbra, BeiGene) are humanized monoclonal antibodies of the IgG4/kappa (IgG4κ) isotype that bind to PD-1 and directly block the interaction between PD-1 and its ligands, PD-L1 and PD-L2, releasing the PD-1 pathway-mediated inhibition of the immune response, including the anti-tumor immune response.

Both nivolumab and pembrolizumab are approved for the treatment of multiple cancers. Tislelizumab is approved for the treatment of unresectable or metastatic ESCC after prior systemic chemotherapy that did not include a PD-(L)1 inhibitor. Ipilimumab is a monoclonal antibody that binds to CTLA-4 and blocks the interaction of CTLA-4 with its ligands, CD80/CD86, increasing T-cell activation and proliferation. Ipilimumab is approved for the treatment of multiple cancers.

Study Designs

Pembrolizumab approval in esophageal carcinoma

On March 22, 2021, FDA approved pembrolizumab, in combination with platinum- and fluoropyrimidine-based chemotherapy, for the treatment of patients with locally advanced or metastatic esophageal or gastroesophageal junction (GEJ) carcinoma (BLA125514 S-096). The study supporting this approval was KEYNOTE-590 (KN-590). The following summarizes the key study elements:

- Design: international, two-arm, randomized (1:1), double-blind, placebo-controlled trial. Randomization was stratified by tumor histology (squamous cell carcinoma vs. adenocarcinoma), geographic region (Asia vs. non-Asia), and ECOG performance status (0 vs. 1).
- Population: patients with previously untreated metastatic or locally advanced esophageal carcinoma, irrespective of histology.
- PD-L1 status: centrally determined in tumor specimens in all patients using the PD-L1 IHC 22C3 pharmDx kit.
- Treatments:
    - Pembrolizumab 200 mg intravenous (IV) every 3 weeks (Q3W), combined with cisplatin 80 mg/m^2 IV Q3W and 5-fluorouracil (5-FU) 800 mg/m^2/day continuous IV infusion on each of Days 1 to 5 Q3W (total of 4000 mg/m^2 per 3-week cycle) (FP regimen), or
    - Saline placebo 200 mg IV, combined with FP.

  Treatment with pembrolizumab or chemotherapy continued until unacceptable toxicity or disease progression. Patients could be treated with pembrolizumab for up to 24 months in the absence of disease progression.
- Endpoints: the primary endpoints of the trial were progression-free survival (PFS) per RECIST v1.1 (modified to allow a maximum of 10 target lesions in total and 5 per organ) as assessed by the investigator, and overall survival (OS). The study pre-specified multiple analyses including OS in patients with ESCC combined positive score (CPS) ≥10, OS in all patients with ESCC, and PFS in all patients with ESCC and by combined positive score (CPS) ≥10. Additional analyses were prespecified in all patients and for ORR.

A total of 749 patients were randomized, 373 patients into the pembrolizumab arm and 376 patients into the placebo arm. Seventy-three percent of patients had a tumor histology of squamous cell carcinoma, and 27% had adenocarcinoma. Demographic and disease characteristics of patients *with ESCC* can be found in Table 1. All pre-specified analyses of Study KN-590 included in the statistical plan for which type I error and hierarchical testing were specified were determined to be statistically significant (KEYNOTE-590 Table 5 and Table 6). For the purposes of this ODAC meeting, the discussion will be centered only in the population of patients with ESCC. Results in the ESCC populations are summarized in Table 4.

Nivolumab approval in ESCC

On May 27, 2022, FDA approved nivolumab, in combination with fluoropyrimidine-and platinum-containing chemotherapy for the first-line treatment of patients with unresectable advanced or metastatic ESCC (BLA 125554 S-105). In addition, on May 27, 2022, FDA approved the combination of nivolumab and ipilimumab (BLA 125514 S-106 and BLA 125377 S-130 respectively) for the same indication. These approvals were supported by the results of Study CA209648 (CHECKMATE-648 or CM-648). The following summarizes the key study elements:

- Design: three-arm randomized (1:1:1), international, open-label trial. Randomization was stratified by tumor cell (TC, also called PD-L1 tumor proportion score [TPS]) PD-L1 status (≥ 1% vs < 1% [including indeterminate]), geographic region (East Asia [Japan, Korea, Taiwan] vs. rest of Asia [China, Hong Kong, Singapore] vs. Rest of the World), ECOG performance status (0 vs. 1), and number of organs with metastases (≤ 1 vs. ≥2).
- Population: patients with previously untreated locally advanced unresectable or metastatic ESCC.
- PD-L1 status: centrally assessed using the PD-L1 IHC 28-8 pharmDx assay and a retrospective scoring of a patient's tumor PD-L1 status using CPS was also conducted using the PD-L1-stained tumor specimens used for randomization.
- Treatments:
    - Nivolumab 240 mg Q2W in combination with cisplatin 80 mg/m^2 IV Q3W and 5-fluorouracil (5-FU) 800 mg/m^2/day continuous IV infusion on each of Days 1 to 5 Q3W (total of 4000 mg/m^2 per 3-week cycle) (FP)
    - Nivolumab 3 mg/kg Q2W in combination with ipilimumab 1 mg/kg Q6W, or
    - Chemotherapy (FP) alone.

  Patients were treated until disease progression, unacceptable toxicity, or 2 years of nivolumab or nivolumab+ipilimumab treatment.

- Endpoints: the primary endpoints of the trial were OS in patients with TC PD-L1 ≥ 1% and PFS per RECIST v1.1 as assessed by a blinded independent central review (BICR) in patients with TC PD-L1 ≥ 1%. Additional efficacy outcome measures tested were OS and PFS in all patients, and ORR by BIRC in patients with TC PD-L1 ≥ 1% and in all patients. For the purposes of this ODAC meeting, the discussion will be centered on the results of the comparison of nivolumab and chemotherapy vs. chemotherapy alone. FDA's analyses of outcomes for the nivolumab + ipilimumab arm (including exploratory analyses) can be found in the Appendices section, Subsection 5.2.2).

A total of 970 patients were randomized, 321 patients into the nivolumab in combination with FP arm, 325 patients into the nivolumab and ipilimumab arm, and 324 patients to the FP alone arm. Demographic and disease characteristics can be found in Table 1. All pre-specified OS analyses of Study CM-648 included in the statistical plan for which type I error and hierarchical testing were specified were determined to be statistically significant (Table 7). FDA's exploratory analyses limited to patients with ESSC are summarized below in Table 4.

Tislelizumab BLA submission for ESCC

On July 18, 2023, BLA 761380 (BeiGene) was submitted for tislelizumab in combination with platinum-containing chemotherapy, for the first line treatment of patients with unresectable advanced or

metastatic ESCC. The study supporting this BLA is BGB-A317-306 (RATIONALE-306, RN-306). The following summarizes the key study elements:

- Design: international, two-arm, randomized (1:1), double-blind, placebo-controlled trial. Randomization was stratified by geographic region (Asia [excluding Japan] vs. Japan vs. Rest of the World), prior definitive therapy (yes vs. no), and investigator's choice of chemotherapy (platinum with fluoropyrimidine vs. platinum with paclitaxel).
- Population: patients with previously untreated metastatic or locally advanced ESCC.
- PD-L1 status: centrally assessed as visually estimated combined positive score (vCPS or TAP) using the Ventana SP263 assay.
- Treatments:
    - Tislelizumab 200 mg Q3W in combination with investigator's choice of chemotherapy. Investigator's choice of therapy was combination platinum and fluoropyrimidine (cisplatin 60-80 mg/m^2 IV or oxaliplatin 130 mg/m^2 IV with fluorouracil 750-800 mg/m^2 IV x 5 consecutive days or capecitabine 1000 mg/m^2 orally twice daily on Days 1-14 of each 21-day cycle) or paclitaxel 175 mg/m^2 on Day 1 of each 21-day cycle in combination with platinum (cisplatin or oxaliplatin as described above).
    - Placebo 200 mg Q3W with investigator's choice of therapy as described above.

  Patients were treated with tislelizumab or placebo until disease progression or unacceptable toxicity. Platinum therapy could be stopped after 6 cycles, per site or investigator preference or standard practice.
- Endpoints: the primary endpoint of the trial was OS in all patients. Additional efficacy outcome measures tested in hierarchical order were PFS per RECIST v1.1 as assessed by investigator in all patients, ORR per RECIST v1.1 as assessed by investigator in all patients, and OS in the PD-L1 ≥ 10% subpopulation.

A total of 649 patients were randomized, 326 patients into the tislelizumab in combination with chemotherapy arm and 323 patients into the placebo and chemotherapy arm. Demographic and disease characteristics can be found in Table 1. All pre-specified OS analyses of Study KN-306 included in the statistical plan for which type I error and hierarchical testing were specified were determined to be statistically significant (RATIONALE-306 Table 10). In the overall population (n = 649), tislelizumab in combination with chemotherapy provided a statistically significant improvement in OS compared with placebo and chemotherapy.

Patient Populations

Throughout this document (unless highlighted), all FDA analyses summarize results on patients with ESCC only. The ESCC population therefore differs from the ITT populations (described in labeling) as follows:

- KN-590: exclusion of 201 patients with adenocarcinoma
- CM-648: exclusion of 16 patients, 15 of whom had adenosquamous-cell carcinoma and 1 patient with histology "other"; no patients enrolled in the nivolumab + ipilimumab arm are included
- RN-306: exclusion of 1 patient with histology "other"

Table 1 summarizes the key demographic and disease characteristics of patients with ESCC enrolled in the trials described above. Highlighted are the PD-L1 cutoffs for which there were prespecified statistical analyses. In general, the characteristics of patients across the trials were comparable with respect to sex

(all studies >80% men), age (median age 63 to 64 years), and race (two-thirds to three-fourths of the patients were Asian). There was one known patient with an MSI-H/dMMR tumor enrolled in RN-306 and none in KN-590; however, the status of the tumor in most patients in these trials was unknown.

Table 1. Demographic and Disease Characteristics of Patients with ESCC (FDA Analyses)

Characteristic	KN-590 N = 548	CM-648 N = 629	RN-306 N = 648	Overall N = 1,825
Sex				
Female	94 (17.2%)	116 (18.4%)	86 (13.3%)	296 (16.2%)
Male	454 (82.8%)	513 (81.6%)	562 (86.7%)	1,529 (83.8%)
Age				
Median (Range)	63.0 (32.0, 94.0)	64.0 (26.0, 86.0)	64.0 (26.0, 84.0)	64.0 (26.0, 94.0)
≥ 65 y.o.	240 (43.8%)	305 (48.5%)	311 (48.0%)	856 (46.9%)
Race				
Asian	364 (66.4%)	452 (71.9%)	485 (74.8%)	1,301 (71.3%)
White	139 (25.4%)	157 (25.0%)	155 (23.9%)	451 (24.7%)
Black/African American	5 (0.9%)	6 (1.0%)	0 (0.0%)	11 (0.6%)
Multiple	8 (1.5%)	0 (0.0%)	0 (0.0%)	8 (0.4%)
Not reported	17 (3.1%)	0 (0.0%)	7 (1.1%)	24 (1.3%)
Other	15 (2.7%)	14 (2.2%)	1 (0.2%)	30 (1.6%)
Ethnicity				
Hispanic/Latino	69 (12.6%)	30 (4.8%)	6 (0.9%)	105 (5.8%)
Not Hispanic/Latino	456 (83.2%)	263 (41.8%)	637 (98.3%)	1,356 (74.3%)
Not reported	23 (4.2%)	336 (53.4%)	5 (0.8%)	364 (19.9%)
ECOG				
0	208 (38.0%)	296 (47.1%)	213 (32.9%)	717 (39.3%)
1	340 (62.0%)	332 (52.8%)	435 (67.1%)	1,107 (60.7%)
Not reported	0 (0.0%)	1 (0.2%)	0 (0.0%)	1 (0.1%)
Disease status				
Metastatic	497 (90.7%)	363 (57.7%)	560 (86.4%)	1,420 (77.8%)
Recurrent	0 (0.0%)	175 (27.8%)	0 (0.0%)	175 (9.6%)
Unresectable	51 (9.3%)	91 (14.5%)	88 (13.6%)	230 (12.6%)
PD-L1 Group				
<1	55 (10.0%)	48 (7.6%)	61 (9.4%)	164 (9.0%)
≥ 1	478 (87.2%)	546 (86.8%)	481 (74.2%)	1,505 (82.5%)
1 - <5	113 (20.6%)	133 (21.1%)	123 (19.0%)	369 (20.2%)
5 - <10	79 (14.4%)	138 (21.9%)	135 (20.8%)	352 (19.3%)
≥10	286 (52.2%)	275 (43.7%)	223 (34.4%)	784 (43.0%)
Not Reported	15 (2.7%)	35 (5.6%)	106 (16.4%)	156 (8.5%)

Notes: The PD-L1 cutoffs used in the trial prespecified analyses are highlighted.

2.3 PD-L1 Expression and Immune Checkpoint Inhibition in ESCC

Multiple immunohistochemistry (IHC) assays and scoring systems are available to assess PD-L1 in ESCC and the clinical trials described above used different testing methodologies and had different prespecified cut-offs to assess treatment effect. Although the studies used pre-specified analyses in different PD-L1 positive populations, the treatment effects in the PD-L1-negative (or low) populations would be considered exploratory analyses.

In clinical research, the safety and efficacy of an experimental treatment is usually assessed by the average treatment effect in the entire patient population. However, efficacy might vary across patient subpopulations due to differences in some patient or disease characteristics and in the three trials subgroups of patients with PD-L1-positive (using different cutoffs) ESCC were specifically included in the statistical testing hierarchy. PD-L1-negative or low subgroups were not specifically tested (with alpha allocated to the analyses). Based on a single trial it can be difficult to assess whether a result in a subgroup is based on chance alone or a real finding; however, consistency of subgroup effects over multiple trials as well as biological plausibility can increase confidence in the subgroup results.

Although, as summarized above, both KN-590 and CM-648 were positive studies in the overall population, professional guidance recommendations for the first-line treatment for patients with unresectable or metastatic ESCC (NCCN, 2024; Shah M, 2023; Obermannova R, 2022) are based on subgroup analyses of the PD-L1 cutoffs of each individual study as follows (Table 2):

Table 2. ASCO, NCCN, and ESMO guidelines for the first-line treatment of ESCC

ASCO 2023 Guidelines
• Recommendation 1.3 – For patients with ESCC and PD-L1 CPS ≥10, pembrolizumab plus fluoropyrimidine- and platinum-based chemotherapy is recommended (evidence quality high, strong recommendation) • Recommendation 1.4 – For patients with ESCC and TPS ≥1%, nivolumab plus fluoropyrimidine- and platinum-based chemotherapy, or nivolumab plus ipilimumab are recommended (evidence quality medium, strong recommendation). o Qualifying statement: Data from the primary analysis of CHECKMATE-648 supports Recommendation 1.4 in patients with ESCC and PD-L1 TPS ≥1%. Additional exploratory analyses from CHECKMATE-648 found that 91% of patients across three study arms had PD-L1 CPS ≥1%, therefore CPS ≥1% can be used as threshold for treatment decision-making if TPS is not available. o Qualifying statement: The PD-L1 cutoffs in Recommendations 1.1-1.4 are based on subgroup analyses presented in included studies. All possible cutoffs have not been assessed; therefore, optimal PD-L1 cutoffs are unknown.
NCCN 2024 V3 Guidelines (non-MSI-H)
<u>Preferred Regimens</u> • Fluoropyrimidine (fluorouracil or capecitabine), oxaliplatin, and nivolumab (category 1)

- Fluoropyrimidine (fluorouracil or capecitabine), oxaliplatin, and pembrolizumab (category 2A for PD-L1 CPS ≥10; category 2B for PD-L1 CPS <10)
- Fluoropyrimidine (fluorouracil or capecitabine) and oxaliplatin (category 1)
- Fluoropyrimidine (fluorouracil or capecitabine), cisplatin, and nivolumab (category 1)
- Fluoropyrimidine (fluorouracil or capecitabine), cisplatin, and pembrolizumab (category 1 for PD-L1 CPS ≥10; category 2B for PD-L1 CPS <10))
- Fluoropyrimidine (fluorouracil or capecitabine) and cisplatin (category 1)
- Nivolumab and ipilimumab

Relevant NCCN Categories of Evidence and Consensus

- Category 1: Based upon high-level evidence, there is uniform NCCN consensus that the intervention is appropriate
- Category 2A: Based upon lower-level evidence, there is uniform NCCN consensus that the intervention is appropriate
- Category 2B: Based upon lower-level evidence, there is NCCN consensus that the intervention is appropriate
- Category 3: Based upon any level of evidence, there is major NCCN disagreement that the intervention is appropriate.

All recommendations are category 2A unless otherwise indicated.

ESMO 2022 Guidelines

- PD-L1 CPS ≥ 10: pembrolizumab-chemotherapy (IA)
- PD-L1 TPS ≥ 1:
  - nivolumab-chemotherapy (IA)
  - nivolumab-ipilimumab (IB)
- PD-L1 negative/low: chemotherapy (IIA)

Relevant ESMO Categories for Levels of Evidence

- I: Evidence from at least one large randomized, controlled trial of good methodological quality (low potential for bias) or meta-analyses of well- conducted randomized trials without heterogeneity.
- II: Small randomized trials or large randomized trials with a suspicion of bias (lower methodological quality) or meta-analyses of such trials or of trials with demonstrated heterogeneity

Relevant ESMO Categories for Grades of Recommendation

- A: Strong evidence for efficacy with a substantial clinical benefit, strongly recommended
- B: Strong or moderate evidence for efficacy but with a limited clinical benefit, generally recommended

A systematic review and meta-analysis (Yoon H, 2022) of randomized clinical trials in gastroesophageal cancers (including gastric and esophageal adenocarcinomas and ESCC) was conducted to evaluate OS benefit from ICIs based on high vs. absent or low PD-L1 expression. The authors identified 17 randomized trials that assessed the results of immune checkpoint inhibitors (including anti-PD-1/L1 drugs not approved in the US) in gastric cancer or ESCC, including trials in the first-line and second-line settings. Of the 11,166 participants included, 5067 had ESCC and of these, 2739 were enrolled in first line setting trials (including reports of trials conducted solely in Asia). The meta-analysis was based on published trial-level data. Per the report, among patients with ESCC (all lines), PD-L1 tumor proportion score (TPS) was the strongest predictor of ICI benefit (TPS "high" was defined as TPS of 1 or greater except in one trial which used TPS ≥10):

- TPS "high" OS HR 0.60 (95% CI 0.53, 0.68)
- TPS "non-high" OS HR 0.84 (95% CI 0.75, 0.95)

The second strongest predictor was CPS "high" (defined as CPS ≥10 in all trials except one trial which used a CPS ≥ 1 cutoff):

- CPS "high" OS HR 0.62 (95% CI 0.54, 0.69)
- CPS "non-high" OS HR 0.82 (95% CI 0.72, 0.94)

This trend to improved efficacy outcomes in patients whose tumors express "high" PD-L1 expression – or even lack of clinically meaningful activity in patients with tumors with low PD-L1 expression is also observed in the three trials submitted to FDA: KN-590, CM-648, and RN-306 (Table 4).

Section 3 will summarize the trials results and exploratory analyses, including results in different cut-offs based on PD-L1 status.

3 Summary of Data for the AC

3.1 Efficacy

FDA conducted patient-level analyses of the randomized controlled studies described in Section 2.2 (KEYNOTE-590, CHECKMATE-648, and RATIONALE-306) in the relevant patient population (ESCC). All three studies evaluated ICIs in combination with chemotherapy versus chemotherapy alone; CHECKMATE-648 also evaluated the combination of 2 ICIs (nivolumab and ipilimumab) vs. chemotherapy but this comparison will not be the subject of this ODAC meeting.

Each trial used different assays for the assessment of PD-L1 expression, different scoring algorithms, and different cutoffs for patient stratification and/or hierarchical testing of outcomes. Assay concordance and assessments of the comparability of assays and scoring algorithms in patients with ESCC (Wang L, 2023; Wang X., 2024) have been limited to single sites with a limited number of patients and comparisons were not designed to address clinical outcome comparisons.

Table 3 summarizes the assays and scoring algorithms used for assessment of PD-L1 status, the role of PD-L1 status as a stratification factor, and the hierarchical testing order for primary and secondary endpoints of relevance for this discussion.

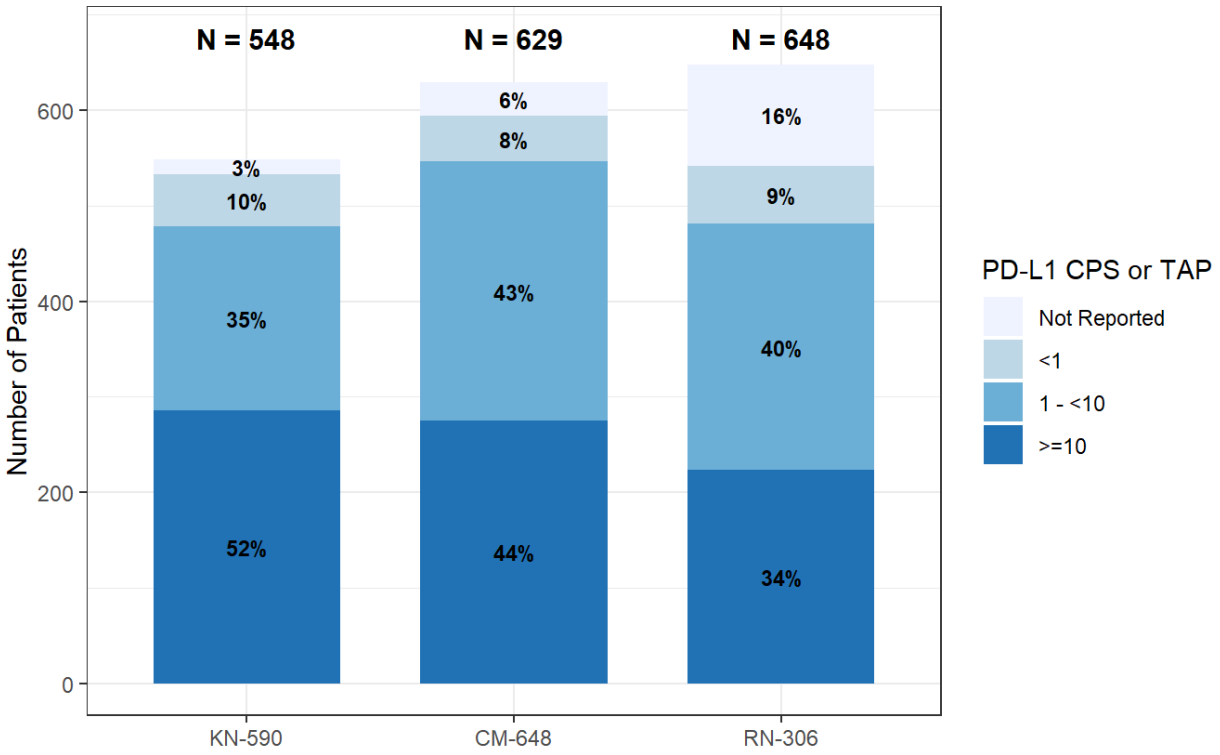
Table 3. Summary of PD-L1 testing and role of cutoff in statistical analysis plan

	KN-590 (pembrolizumab)	CM-648 (nivolumab)	RN-306 (tislelizumab)
Assay	22C3 pharmDx	28-8 pharmDx	SP263
Algorithm	CPS	TC and retrospective CPS	vCPS (TAP)
PD-L1 as a stratification factor	No	TC PD-L1 status (≥ 1% vs < 1% [including indeterminate])	No
Endpoints tested per SAP*	1. OS ESCC CPS ≥10 2. OS ESCC. 3. PFS (investigator) ESCC 4. PFS (investigator) CPS ≥10	1. OS TC ≥ 1 2. PFS (BICR) TC ≥ 1 3. OS all patients 4. PFS (BICR) all patients	1. OS all patients 2. PFS (investigator) all patients 3. OS TAP ≥10

*The cells do not necessarily represent the complete list of all endpoints tested (e.g., ORR).

FDA analyses of the proportion of patients at PD-L1 cutoffs across the three studies are outlined in Figure 1 and in Table 1. As shown in Table 1, PD-L1 status was not available in 3%, 6%, and 16% of patients in KN-590, CM-648, and RN-306, respectively; the figure shows CPS scoring for KN-590 and CM-648 and TAP for RN-306. The greatest proportion (52%) of patients with PD-L1 ≥10 was enrolled in KN-590, followed by CM-648 (44%), and RN-306 (34%). The proportion of patients with tumors that were PD-L1 <1 was similar across studies, ranging from 8-10%.

Figure 1. PD-L1 Distribution Across Studies (FDA Analyses)



Exploratory analyses with small sample sizes create the potential for imbalance in baseline covariates. For the observed covariates analyzed, it does not appear that there were meaningful differences in the

demographic and disease baseline characteristics for each trial based on PD-L1 cutoffs (Table 11, Appendices section).

Although the primary OS results were statistically significant for the anti-PD-L1-containing arm in all three trials, the point estimates for the treatment effect appeared not favorable in patients with PD-L1 < 1 and intermediate in patients with PD-L1 < 10 (which included patients with PD-L1 less than 1). Although these results are exploratory, and uncertainty exists for each trial (as the 95% CIs cross 1, strong evidence does not appear to support the use of anti-PD-L1 drugs in patients who are PD-L1 <1).

Table 4 below summarizes the results by PD-L1 cutoff (for Studies KN-590 and CM-648, the cutoffs displayed are based on PD-L1 as assessed by CPS, for study RN 306, the cutoffs displayed are based on PD-L1 as assessed by TAP).

Table 4. Highlights of (FDA) OS analyses by PD-L1 cutoff (FDA Analyses)

	All ESCC		PD-L1 ≥ 1		PD-L1 ≥ 10		PD-L1 <1		PD-L1 <10	
KN-590	**Pembro+CHT**	**Placebo+CHT**	**Pembro+CHT**	**Placebo+CHT**	**Pembro+CHT**	**Placebo+CHT**	**Pembro+CHT**	**Placebo+CHT**	**Pembro+CHT**	**Placebo+CHT**
N	**274**	**274**	**238**	**240**	**143**	**143**	**26**	**29**	**121**	**126**
mOS (95% CI)	12.6 (10.2, 14.3)	9.8 (8.6, 11.1)	12.6 (10.1, 14.3)	9.8 (8.4, 10.8)	13.9 (11.1, 17.7)	8.8 (7.8, 10.5)	11.4 (7.0, 17.1)	11.4 (7.0, 16.5)	10.5 (9.2, 13.5)	11.1 (9.1, 12.4)
OS HR (95% CI)	0.72 (0.59, 0.87)		0.69 (0.56, 0.85)		0.57 (0.44, 0.75)		1.00 (0.54, 1.85)		0.95 (0.71, 1.26)	
CM-648	**Nivo+CHT**	**CHT**	**Nivo+CHT**	**CHT**	**Nivo+CHT**	**CHT**	**Nivo+CHT**	**CHT**	**Nivo+CHT**	**CHT**
N	**311**	**318**	**271**	**275**	**133**	**142**	**25**	**23**	**163**	**156**
mOS (95% CI)	13.4 (11.7, 15.8)	10.8 (9.4, 12.1)	13.8 (12.0, 16.5)	9.9 (8.9, 11.7)	16.1 (12.3, 21.9)	11.6 (9.0, 13.7)	10.2 (7.7, 21.8)	12.5 (9.3, 17.1)	12.1 (10.6, 15.7)	9.7 (8.8, 11.1)
OS HR (95% CI)	0.73 (0.60, 0.88)		0.69 (0.56, 0.84)		0.62 (0.46, 0.84)		0.93 (0.46, 1.91)		0.77 (0.60, 1.01)	
RN-306	**Tisle+CHT**	**Placebo+CHT**	**Tisle+CHT**	**Placebo+CHT**	**Tisle+CHT**	**Placebo+CHT**	**Tisle+CHT**	**Placebo+CHT**	**Tisle+CHT**	**Placebo+CHT**
N	**325**	**323**	**231**	**250**	**116**	**107**	**36**	**25**	**151**	**168**
mOS (95% CI)	17.2 (15.8, 20.1)	10.6 (9.3, 12.1)	16.8 (15.3, 20.8)	9.6 (8.9, 11.8)	16.6 (15.3, 24.4)	10.0 (8.6, 13.3)	11.8 (6.2, 16.3)	16.1 (10.4, 28.9)	15.8 (12.3, 19.6)	10.4 (9.0, 13.6)
OS HR (95% CI)	0.68 (0.56, 0.82)		0.66 (0.52, 0.82)		0.66 (0.48, 0.92)		1.34 (0.73, 2.46)		0.76 (0.58, 0.99)	

Abbreviations: Pembro = pembrolizumab, Nivo = nivolumab, Tisle = tislelizumab, CHT = chemotherapy, mOS = median OS, CI = confidence interval; HR = hazard ratio

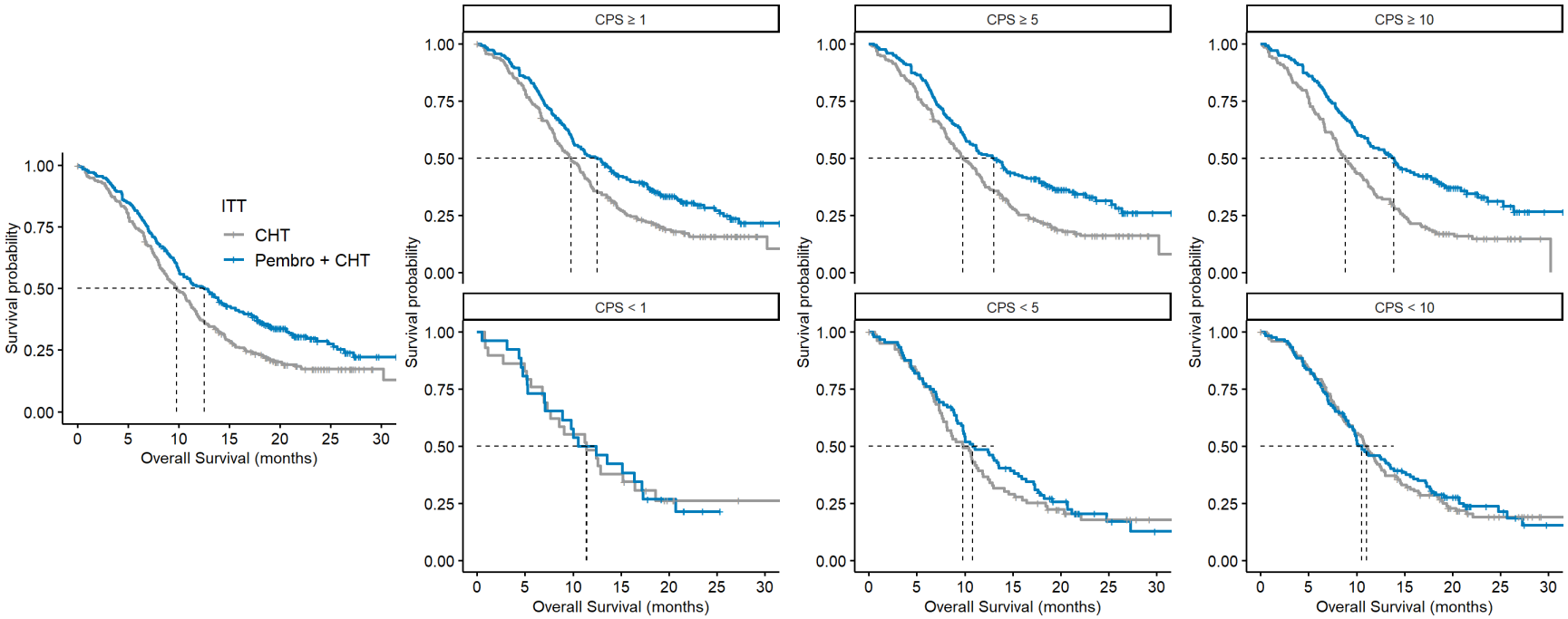
Highlighted the trial prespecified cutoffs.

Notes: The PD-L1 cutoffs used in the trial prespecified analysis are highlighted. All FDA analyses are exploratory, and the analysis population includes only patients with ESCC. HRs were estimated by Cox proportional hazards models using treatment arm as the only covariate and the Efron method for handling ties (methodology for this table and the forest plots below may differ from that was used in the original analyses and therefore results may differ modestly compared to product labeling).

Figure 2, Figure 3, and Figure 4 below display the overall survival Kaplan-Meier estimates by PD-L1 cutoff for the ESCC populations by study. Analyses of other cutoffs and groupings for each individual study can be found in Figure 5, Figure 6, and Figure 7 below.

For KN-590, the Kaplan-Meier OS plots for all patients with ESCC (Figure 2) show separation of the curves in all patients with PD-L1 CPS ≥1, with increased separation with higher cutoffs.

Figure 2. KN-590: OS Kaplan-Meier Estimates by PD-L1 status (CPS), ESCC population (FDA Analyses)

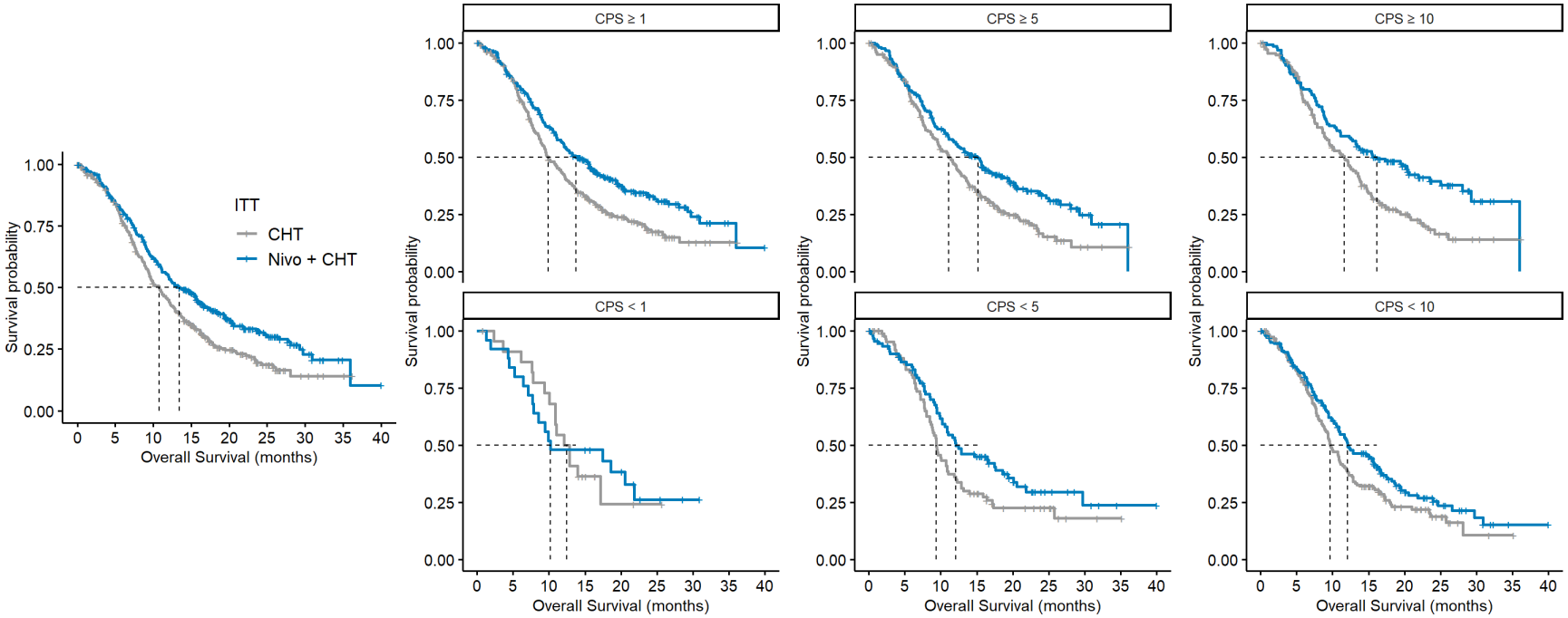


Abbreviation: Pembro = pembrolizumab, CHT = chemotherapy

However, when exploring the treatment effect in patients with PD-L1 <1, 5, and 10, the curves appear super imposed or demonstrate a smaller treatment effect.

Similarly, to KN-590, the CM-648 OS Kaplan-Meier curves (Figure 3) show separation of the curves in all patients with PD-L1 CPS ≥1, with increased separation with higher cutoffs, which appear to derive the greatest benefit. In CM-648, curves cross over in patients with CPS <1, while are close to each other in patients with CPS <10 (acknowledging that this group includes patients with CPS <1).

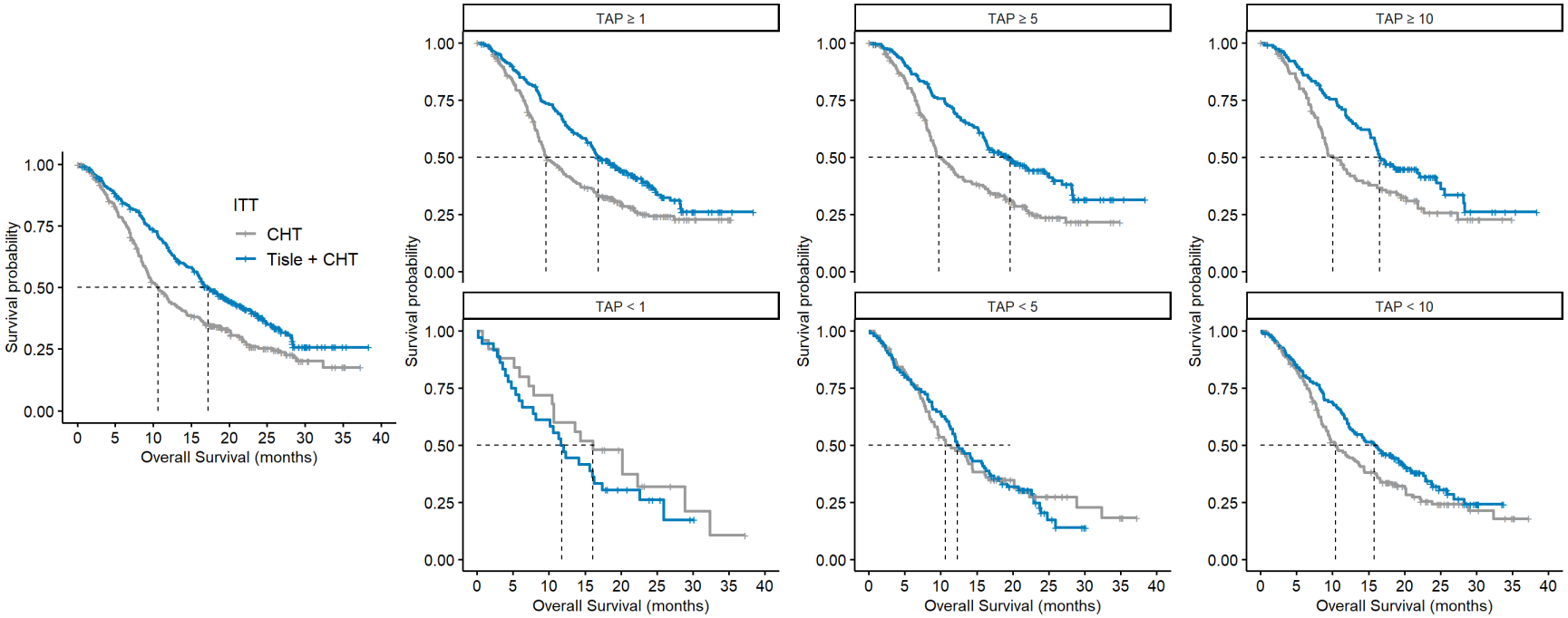
Figure 3. CM-648: OS Kaplan-Meier Estimates by PD-L1 status (CPS), ESCC Population (FDA Analyses)



Abbreviation: CHT = chemotherapy, Nivo = nivolumab

As in the previous 2 studies, in the OS Kaplan-Meier plots for RN-306, the curves separate in the overall population and patients with PD-L1 >1 (Figure 4), appearing to favor the addition of tislelizumab to chemotherapy (acknowledging that these curves include the population that appear to derive the greatest benefit [PD-L1 ≥ 10]). Unlike the previous studies, the tislelizumab arm KM curve is below the control arm in the CPS <1 population, while crosses or is closer to the control arm with cutoffs of 5 or 10, consistent with an intermediate effect (again acknowledging that these curves include the PD-L1 <1 population).

Figure 4. RN-306: OS Kaplan-Meier Estimates by PD-L1 cutoff (TAP), ESCC Population (FDA Analyses)



Abbreviation: CHT = chemotherapy, Tisle = tislelizumab

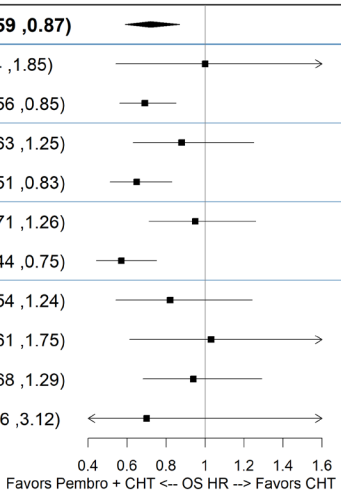
Consistent with the results displayed in Table 4, the OS Kaplan-Meier curves in the PD-L1 ≥10 population show the greatest degree of separation between arms, representing the increased magnitude of effect in this subgroup.

To further explore the utility of PD-L1 expression as a predictive biomarker, FDA conducted additional exploratory analyses of efficacy evaluating OS, at intermediate PD-L1 cutoffs. Figure 5 displays the forest plot for patients with ESCC enrolled in KN-590. As shown previously, acknowledging the small sample size, based on the point estimate, no benefit is observed in patients with PD-L1 CPS <1 (HR 1.00; 95% CI 0.54, 1.85). The analysis below shows the results, for example, of patients with tumors who have PD-L1 expression between 1 and 10 (to contextualize whether the subgroup of patients with PD-L1 less than 10 is driven by patients with tumors that are PD-L1 less than one).

Some of the subgroups appeared to show inconsistency in results (particularly the analyses of intermediate scores) which may be due to chance, lack of power of the analysis to detect a true difference, or technical difficulties in ascertainment of PD-L1 expression for reduced variability strata (for example, scoring a tumor between 1 and 4 may be more technically challenging than scoring a tumor between 1 and 10).

Figure 5. KN-590: Overall Survival Forest Plot by PD-L1 Cutoff (CPS), ESCC Population (FDA Analyses)

Subgroup	% of Pts	Pembro + CHT Evt / N	CHT Evt / N	HR (95% CI)	Pembro + CHT Median (95% CI)	CHT Median (95% CI)
Overall	**100.0**	**190/274**	**222/274**	**0.72 (0.59 ,0.87)**	**12.6 (10.2, 14.3)**	**9.8 (8.6, 11.1)**
CPS < 1	10.0	20/26	21/29	1 (0.54 ,1.85)	11.4 (7, 17.1)	11.4 (7, 16.5)
CPS ≥ 1	87.2	166/238	198/240	0.69 (0.56 ,0.85)	12.6 (10.1, 14.3)	9.8 (8.4, 10.8)
CPS < 5	30.7	69/88	63/80	0.88 (0.63 ,1.25)	10.8 (9.2, 14.8)	9.8 (7.8, 11.4)
CPS ≥ 5	66.6	117/176	156/189	0.65 (0.51 ,0.83)	13 (10.2, 15.6)	9.8 (8.4, 11.5)
CPS < 10	45.1	92/121	98/126	0.95 (0.71 ,1.26)	10.5 (9.2, 13.5)	11.1 (9.1, 12.4)
CPS ≥ 10	52.2	94/143	121/143	0.57 (0.44 ,0.75)	13.9 (11.1, 17.7)	8.8 (7.8, 10.5)
CPS 1 - < 5	20.6	49/62	42/51	0.82 (0.54 ,1.24)	10.8 (9.1, 14.8)	9.2 (7.4, 10.8)
CPS 5 - < 10	14.4	23/33	35/46	1.03 (0.61 ,1.75)	10 (6.9, 17.7)	12.6 (10.1, 16.6)
CPS 1 - < 10	35.0	72/95	77/97	0.94 (0.68 ,1.29)	10.2 (9.1, 13.5)	10.8 (8.9, 12.1)
Not Reported	2.7	4/10	3/5	0.7 (0.16 ,3.12)	NA (0.1, NA)	8.9 (7.2, NA)

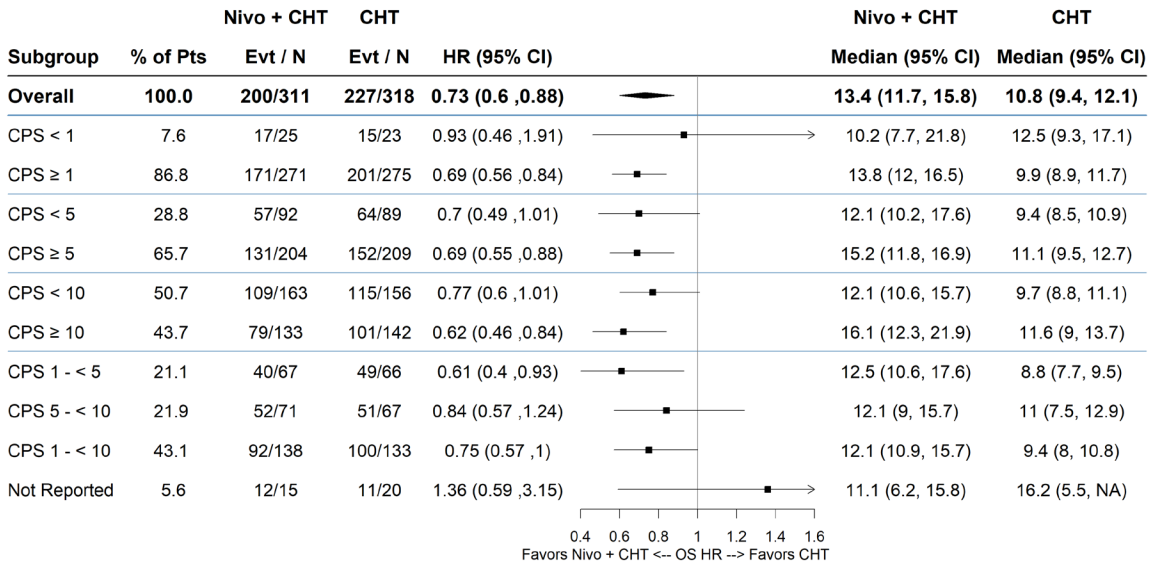


Abbreviations: Pembro = pembrolizumab, CHT = chemotherapy, Evt = event, HR = hazard ratio, CI = confidence interval

Note: HRs were estimated by Cox proportional hazards models using treatment arm as the only covariate and the Efron method for handling ties.

Figure 6 displays the forest plot for patients with ESCC enrolled in CM-648 (only patients in the nivolumab + chemotherapy and chemotherapy arms). The HR in patients with CPS ≥ 1 is 0.69 (95% CI 0.56, 0.84) while is 0.93 (0.46, 1.91) in patients with CPS < 1. As in KN-590, intermediate strata analyses show some inconsistencies.

Figure 6. CM-648: Overall Survival Forest Plot by PD-L1 Cutoff (CPS), ESCC Population (FDA Analyses)

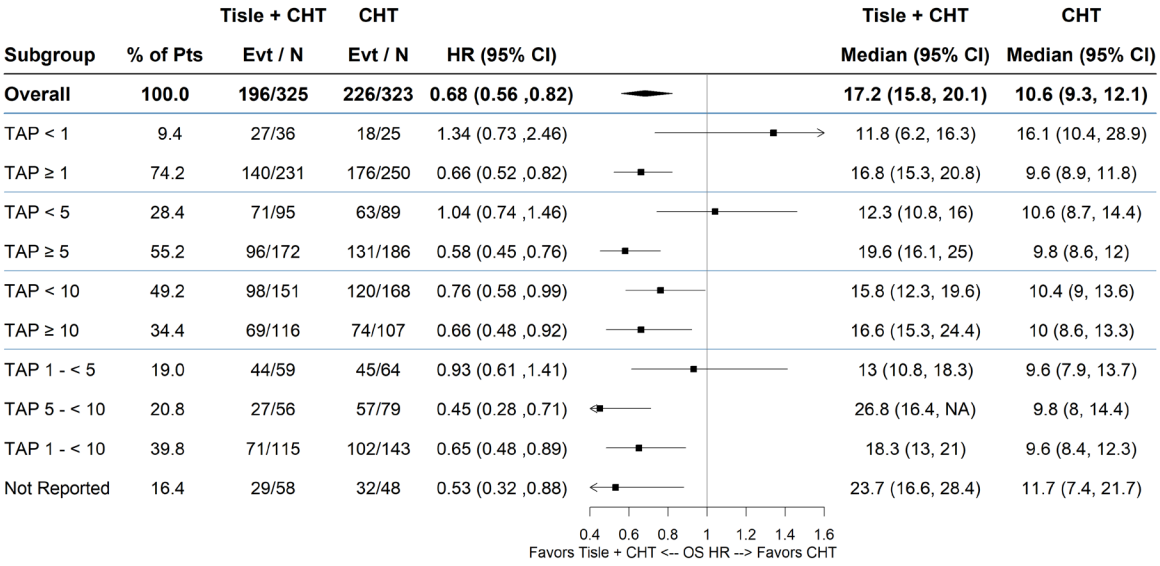


Abbreviations: Nivo = nivolumab, CHT = chemotherapy, Evt = event, HR = hazard ratio, CI = confidence interval

Note: HRs were estimated by Cox proportional hazards models using treatment arm as the only covariate and the Efron method for handling ties.

Figure 7 displays the OS forest plot for patients with ESCC enrolled in RN-306. In this study, there is potential detriment for patients with PD-L1 expression (as determined by TAP) < 1, with a HR 1.34 (95% CI 0.73, 2.46). For patients with PD-L1 ≥ 1, the HR is 0.66 (95% CI 0.52, 0.82).

Figure 7. RN-306: Overall Survival Forest Plot by PD-L1 Cutoff (TAP), ESCC Population (FDA Analyses)



Abbreviations: Tisle = tislelizumab, CHT = chemotherapy, Evt = event, HR = hazard ratio, CI = confidence interval

Note: HRs were estimated by Cox proportional hazards models using treatment arm as the only covariate and the Efron method for handling ties.

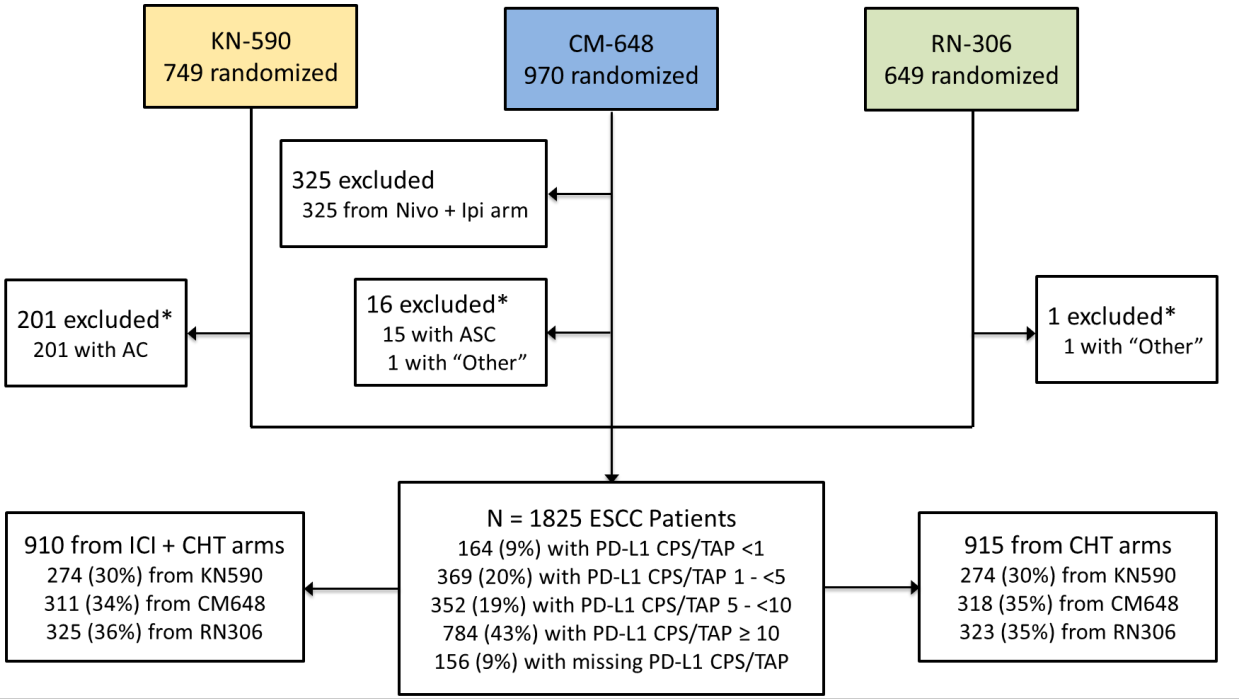
To summarize:

- Improvement in survival with the addition of a checkpoint inhibitor was greatest in patients with higher PD-L1 expression (≥ 10) in all three trials. The following FDA ESCC analyses in different PD-L1 positive groups were also positive in all three trials (in the pre-specified analysis). These were the pre-specified cut-off points for PD-L1 used in the original trial designs.
    - For pembrolizumab, the prespecified PD-L1 level with alpha allocation was OS in patients with CPS ≥ 10, which represented 52% of the overall ESCC population with a HR of 0.57 (95% CI 0.44, 0.75)
    - For nivolumab, the prespecified PD-L1 level with alpha allocation was OS in patients with PD-L1 ≥ 1 (HR 0.69 [95% CI 0.56, 0.84]), which represented 87% of the overall ESCC population (44% had CPS ≥ 10)
    - For tislelizumab, the prespecified PD-L1 level with alpha allocation was OS in patients with TAP ≥ 10, which represented 34% of the overall ESCC population with a HR of 0.66 (95% CI 0.48, 0.92)
- Although sample sizes were limited, the point estimates (1.00 for pembrolizumab; 0.93 for nivolumab; and 1.34 for tislelizumab) for treatment effect did not appear consistent with a beneficial effect of ICI in patients with tumors that were PD-L1 < 1.
- The treatment effect in patients with PD-L1 < 10 (or in the subgroup of patients with PD-L1 ≥ 1 to less than 10) appeared intermediate with a hazard ratio close to 1 (0.95) in one study (pembrolizumab) and less than 0.80 in two studies. This difference may be a chance finding considering the limitations in sample size or due to other factors (e.g., sampling assessment).

In addition to the analyses summarized above, FDA conducted exploratory pooled analyses, acknowledging that patients were included using different assays and scoring algorithms in terms of PD-L1 expression. Although there have been attempts to cross validate scoring algorithms in gastric and esophageal cancers, the acceptability of doing so has not been determined (Ahn S, 2021; Yeong J, 2022; Yoon H, 2022; Wang L, 2024; Wang X, 2024; Klempner S, 2024). FDA's analyses include patient-level data and are therefore limited to the studies that were submitted to FDA for review; FDA's pooled patient-level analysis does not include data from other published studies either positive or negative, which may introduce bias. However, in the context of published trial-level meta-analysis that demonstrate PD-L1 expression to be a predictive biomarker in this patient population (Yoon H, 2022), FDA believes that a pooled analysis of patient-level data may provide the advisory committee with additional context for the risk-benefit discussion for ICIs in relationship to PD-L1 expression in patients with ESCC.

To provide the most pertinent data for discussion, the primary population for the pooled analysis was limited to patients with ESCC (e.g., excluding patients with esophageal adenocarcinoma enrolled in KN-590, adenosquamous histology enrolled in CM-648, and one patient with histology "other" in RN-306) and study arms comparing anti-PD1 agents in combination with chemotherapy vs. chemotherapy (i.e., excluding patients enrolled in the nivolumab and ipilimumab arm of CM-648). Sensitivity analyses including all populations were conducted and available in the Appendices Section (Subsections 5.1, 5.2, 5.3, 5.4). The primary population included in the pooled analyses is outlined below, in Figure 8.

Figure 8. Consort Diagram of Patients Included in Pooled Analyses (FDA Analyses)

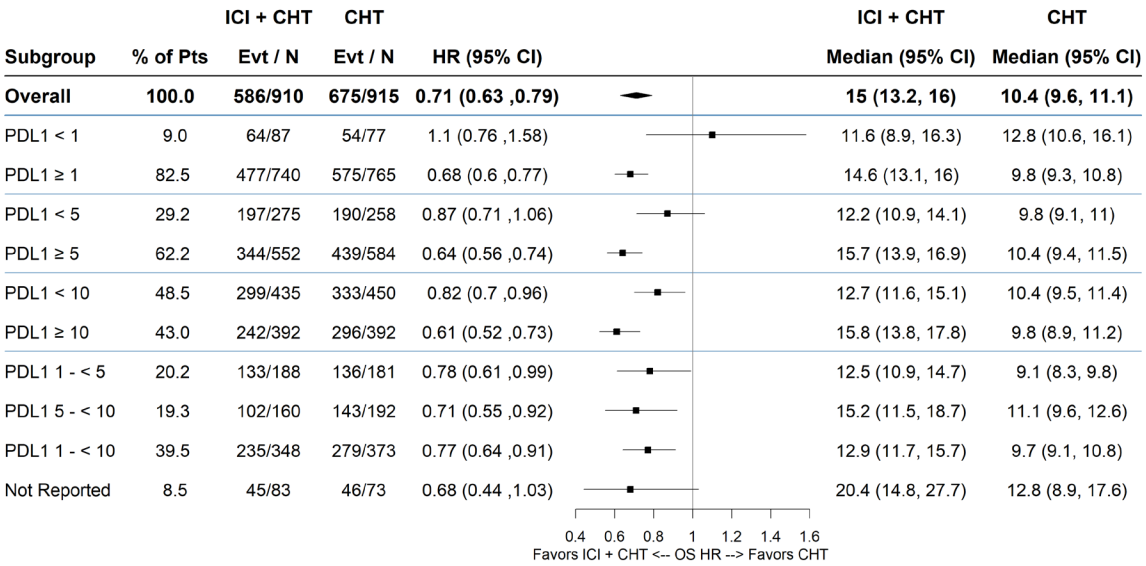


Abbreviation: ASC = Adenosquamous carcinoma, AC = Adenocarcinoma, ESCC = Esophageal squamous carcinoma
*Exclusion based on histology

Figure 9 below displays the forest plot for OS of the pooled population based on PD-L1 cutoffs (CPS for KN-590 and CM-648 and TAP for RN-306).

Like the analyses for each individual study, the magnitude of benefit of the addition of PD-1 monoclonal antibodies appears to increase with increasing PD-L1 expression; however, more importantly is that the apparent effect in the PD-L1 negative (< 1) subgroup is not consistent with evidence of benefit [HR 1.10 (95% CI 0.76, 1.58)]. The HR in patients with PD-L1 between 1 and 10 was 0.77 (0.64, 0.91), consistent with the potential for modest benefit in these patients.

Figure 9. Overall Survival Forest Plot by PD-L1 Cutoff – ESCC Pooled Population (FDA Analyses)



Abbreviations: ICI = immune checkpoint inhibitor, CHT = chemotherapy, Evt = event, HR = hazard ratio, CI = confidence interval

Note: HRs were estimated by Cox proportional hazards models stratified by study, using treatment arm as the only covariate and the Efron method for handling ties.

FDA acknowledges that the pooled analysis has certain limitations. The analysis was not pre-specified prior to the conduct of the three trials and patients in the PD-L1 defined subgroups are identified by different testing assays across trials. Nevertheless, the pooled analysis provides a framework that appears to show that patients with higher PD-L1 expression derived the most benefit, and that patients who are PD-L1 negative appear not to benefit. In ESCC, most patients (~90%) have some PD-L1 expression and therefore excluding only patients who are PD-L1 negative would change management for a minority of patients. If these patients (without PD-L1 expression) are not expected to benefit based on the available data, then administering anti-PD-1 therapy has the potential for harm including serious immune related adverse events on top of a malignancy that can markedly affect a patient's quality of life.

As indicated above, the treatment effect appears intermediate in patients with PD-L1 levels between 1 and 10; however, the effect is consistent with the potential for benefit.

3.1.1 Summary

Typically, drugs approved by the FDA are indicated for use in the total patient population studied; subgroup analyses have an important role in regulatory decision-making to ensure there are consistent treatment effects across important study subgroups. However, there are examples of restriction of indications to a subgroup of patients despite positive study results in the entire study population. Such an approach was taken retrospectively based on cumulative data for EGFR inhibitors in *RAS*-mutated colorectal cancer and prospectively for restriction of the indication for olaparib in combination with abiraterone for *BRCA*-mutated metastatic castration-resistant prostate cancer, where in a randomized study a statistically significant improvement in the primary outcome was observed in the ITT population

but this improvement was primarily driven by the results in a subgroup of patients with *BRCA* mutations (Fallah J, 2023).

The current US FDA approvals of ICIs in combination with chemotherapy for the first line treatment of ESCC is agnostic of PD-L1 expression status; however, consistently across 3 different applications, FDA's patient-level pooled population, and in a trial level meta-analysis (Yoon H, 2022), a predictive role of PD-L1 expression emerged and approvals for all randomized patients may not be in the best interest of patients with tumors with low PD-L1 expression. Addition of ICIs to standard of care chemotherapy for the treatment of patients with ESCC PD-L1 < 1 does not appear to result in benefit. Patients with tumors PD-L1 ≥ 10 appear to have the greatest magnitude of benefit. Patients with PD-L1 within these two cutoffs appear to benefit, although the magnitude of this benefit may be of decreased magnitude when compared to patients with PD-L1 ≥ 10.

In this document, FDA provided analyses of efficacy across a range of PD-L1 expression levels and stated the notable caveats of assessing efficacy across these populations. FDA is concerned with the lack of benefit observed across patients with ESCC who have lower (or negative) PD-L1 scores (defined post-hoc for 2 of the studies and using different assays), which would expose these patients to the incremental added toxicity of anti-PD-1 monoclonal antibodies, warranting a more contemporary discussion on the risk benefit profile in a biomarker selected patient population.

FDA would like the committee to discuss the risk and benefits from the addition of immune checkpoint inhibitors to chemotherapy based on PD-L1 status and whether labeling should be amended so that patients are selected based on PD-L1 levels (e.g., PD-L1 ≥ 1 for ESCC).

As stated in the introduction, one approach to amend labeling (if taken) could solely consider the specific testing and statistical analysis plan in each trial. Although this approach would be statistically sound, this would result in different PD-L1 cut-offs for each drug resulting in obstacles to the consistent treatment of patients with ESCC in the United States *and* in the conduct of future trials to improve outcomes of patients with ESCC. Alternatively, one could amend labeling using the totality of data to select a single cut-off, acknowledging some differences in available PD-L1 tests.

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5 Appendices

5.1 KEYNOTE-590

Table 5. KN-590: ITT primary outcomes

Efficacy Endpoint	Pembrolizumab + chemotherapy (N=373)	Placebo + chemotherapy (N=376)
OS		
Number of events (%)	262 (70.2)	309 (82.2)
Median OS, months (95% CI) [1]	12.4 (10.5, 14.0)	9.8 (8.8, 10.8)
HR (95% CI)[2], p value[3]	0.73 (0.62, 0.86), <0.0001	
PFS (Investigator Assessed per RECIST 1.1)		
Number of events (%)	297 (79.6)	333 (88.6)
Median PFS (95% CI), months[1]	6.3 (6.2, 6.9)	5.8 (5.0, 6.0)
HR (95% CI)[2], p-value[3]	0.65 (0.55, 0.76), <0.0001	
[1] Kaplan-Meier method; [2] Stratified Cox proportional hazard model; [3] Stratified log-rank test		

Table 6. KN-590: Prespecified OS and PFS analysis in non-ITT populations

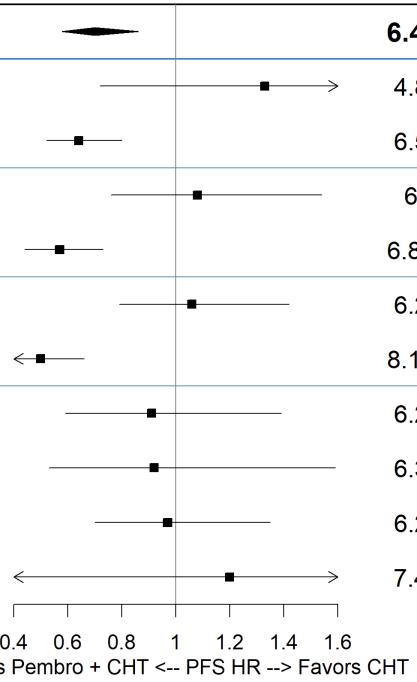
Population	Progression-free Survival (investigator)		Overall Survival	
	Pembrolizumab + chemotherapy N=373	Placebo + chemotherapy N=376	Pembrolizumab + chemotherapy N=373	Placebo + chemotherapy N=376
ESCC PD-L1 ≥10, N	**143**	**143**	**143**	**143**
Events (%)	109 (76.2)	127 (88.8)	94 (65.7)	121 (84.6)
Median, months (95% CI)[1]	7.3 (6.2, 8.2)	5.4 (4.2, 6.0)	13.9 (11.1, 17.7)	8.8 (7.8, 10.5)
Hazard Ratio (95% CI)[2]	0.53 (0.40, 0.69)		0.57 (0.43, 0.75)	
p-value[3]	Not tested		<0.0001	
ESCC, N	**274**	**274**	**274**	**274**
Events (%)	219 (79.9)	244 (89.1)	190 (69.3)	222 (81.0)

Median, months (95% CI)[1]	6.3 (6.2, 6.9)	5.8 (5.0, 6.1)	12.6 (10.2, 14.3)	9.8 (8.6, 11.1)
Hazard Ratio (95% CI)[2]	0.65 (0.54, 0.78)		0.72 (0.60, 0.88)	
p-value[3]	<0.0001		0.0006	
PD-L1 ≥10, N	**186**	**197**	**186**	**197**
Events (%)	140 (75.3)	174 (88.3)	124 (66.7)	165 (83.8)
Median, months (95% CI)[1]	7.5 (6.2, 8.2)	5.5 (4.3, 6.0)	13.5 (11.1, 15.6)	9.4 (8.0, 10.7)
Hazard Ratio (95% CI)[2]	0.51 (0.41, 0.65)		0.62 (0.49, 0.78)	
p-value[3]	<0.0001		<0.0001	

[1] Kaplan-Meier method; [2] Stratified Cox proportional hazard model; [3] Stratified log-rank test; NA: not evaluated for statistical significance as per pre-specified hierarchical testing procedure

Figure 10. KN-590: BICR-assessed PFS Forest Plot by PD-L1 Cutoff (CPS), ESCC Population (FDA Analyses)

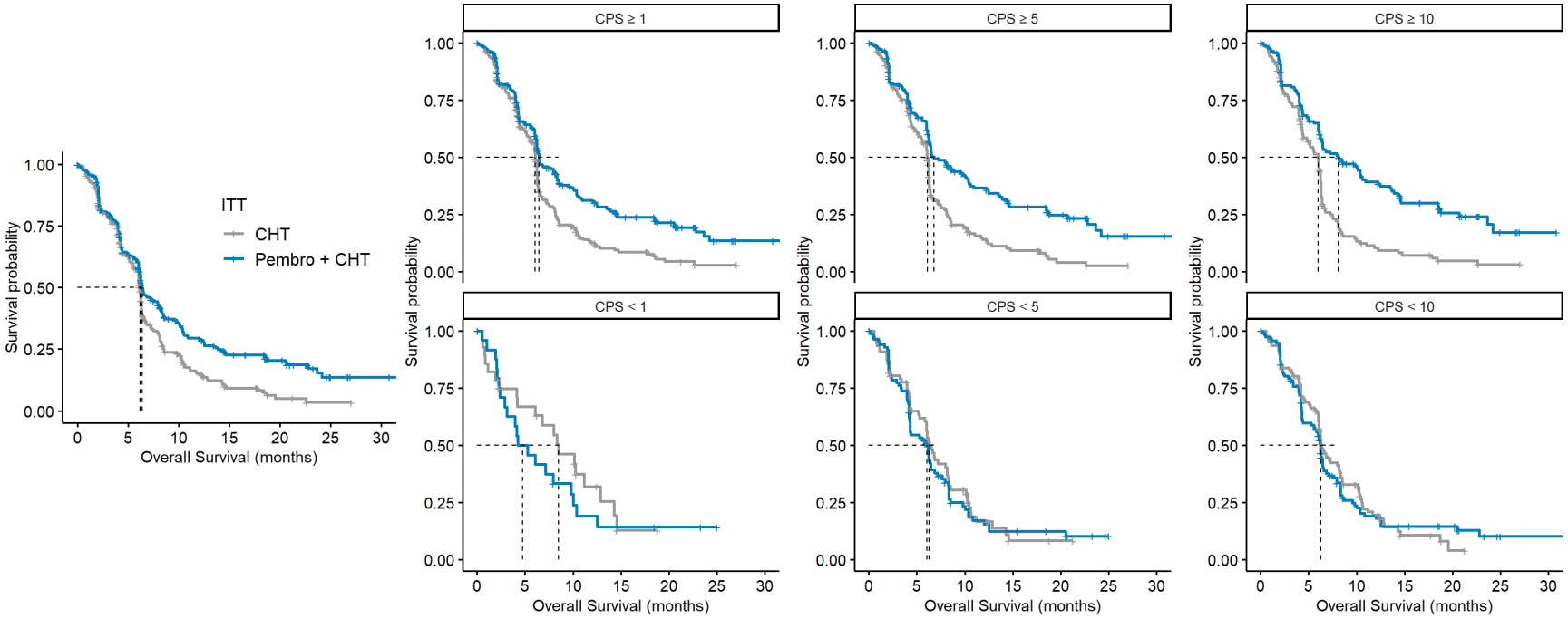
Subgroup	% of Pts	Pembro + CHT Evt / N	CHT Evt / N	HR (95% CI)	Pembro + CHT Median (95% CI)	CHT Median (95% CI)
Overall	**100.0**	**189/274**	**210/274**	**0.7 (0.58 ,0.86)**	**6.4 (6.2, 7.9)**	**6.2 (6, 6.3)**
CPS < 1	10.0	20/26	20/29	1.33 (0.72 ,2.49)	4.8 (2.4, 9.8)	8.5 (4.2, 12.8)
CPS ≥ 1	87.2	162/238	188/240	0.64 (0.52 ,0.8)	6.5 (6.2, 8.1)	6.1 (5.7, 6.2)
CPS < 5	30.7	69/88	58/80	1.08 (0.76 ,1.54)	6 (4.2, 6.5)	6.3 (5.3, 8.2)
CPS ≥ 5	66.6	113/176	150/189	0.57 (0.44 ,0.73)	6.8 (6.2, 10.1)	6.1 (5.5, 6.2)
CPS < 10	45.1	92/121	90/126	1.06 (0.79 ,1.42)	6.2 (5.3, 6.5)	6.3 (6, 8.1)
CPS ≥ 10	52.2	90/143	118/143	0.5 (0.37 ,0.66)	8.1 (6.2, 10.6)	6 (4.4, 6.2)
CPS 1 - < 5	20.6	49/62	38/51	0.91 (0.59 ,1.39)	6.2 (4.3, 6.9)	6 (4.4, 6.9)
CPS 5 - < 10	14.4	23/33	32/46	0.92 (0.53 ,1.59)	6.3 (5.9, 8.7)	6.2 (6.1, 10.3)
CPS 1 - < 10	35.0	72/95	70/97	0.97 (0.7 ,1.35)	6.2 (5.6, 6.5)	6.2 (6, 7.2)
Not Reported	2.7	7/10	2/5	1.2 (0.24 ,6.05)	7.4 (0.1, NA)	NA (1.9, NA)



Abbreviations: Pembro = pembrolizumab, CHT = chemotherapy, Evt = event, HR = hazard ratio, CI = confidence interval

Note: HRs were estimated by Cox proportional hazards models using treatment arm as the only covariate and the Efron method for handling ties.

Figure 11. KN-590: BICR-assessed PFS Kaplan-Meier Estimates by PD-L1 cutoff (CPS), ESCC Population (FDA Analyses)



Abbreviation: Pembro = pembrolizumab, CHT = chemotherapy

Figure 12. KN-590: BICR-assessed ORR by PD-L1 Cutoff (CPS), ESCC population (FDA Analyses)

	Pembro + CHT			CHT		
	n/N	**ORR (95% CI)**	**median DoR (95% CI)**	**n/N**	**ORR (95% CI)**	**median DoR (95% CI)**
Overall	117/274	42.7 (36.8, 48.8)	9.9 (8.1, 16.5)	83/274	30.3 (24.9, 36.1)	5.4 (4.4, 6.2)
CPS < 1	8/26	30.8 (14.3, 51.8)	8.3 (4.1, NA)	11/29	37.9 (20.7, 57.7)	9 (5.8, 11)
CPS ≥ 1	104/238	43.7	10.5	71/240	29.6	4.7

		(37.3, 50.3)	(8.1, 16.6)		(23.9, 35.8)	(4.3, 6.1)
CPS < 5	27/88	30.7 (21.3, 41.4)	7.9 (6, 18.6)	25/80	31.2 (21.3, 42.6)	6.2 (5.1, 9)
CPS ≥ 5	85/176	48.3 (40.7, 55.9)	11.8 (8.3, 18.7)	57/189	30.2 (23.7, 37.2)	4.4 (4.2, 6.1)
CPS < 10	44/121	36.4 (27.8, 45.6)	7.9 (5.9, 18.6)	42/126	33.3 (25.2, 42.3)	6.2 (5.1, 9)
CPS ≥ 10	68/143	47.6 (39.1, 56.1)	12.5 (8.3, 22.1)	40/143	28 (20.8, 36.1)	4.4 (4.2, 5.4)
CPS 1 - < 5	19/62	30.6 (19.6, 43.7)	6.2 (5.6, 10.5)	14/51	27.5 (15.9, 41.7)	5.9 (3.8, 8.5)
CPS 5 - < 10	17/33	51.5 (33.5, 69.2)	5.9 (4.2, NA)	17/46	37 (23.2, 52.5)	6.4 (4.2, NA)
CPS 1 - < 10	36/95	37.9 (28.1, 48.4)	6.2 (5.6, 10.5)	31/97	32 (22.9, 42.2)	5.9 (4.3, 8.5)

Abbreviations: Pembro = pembrolizumab, CHT = Chemotherapy, ORR = objective response rate, DoR = duration of response, CI = confidence interval

5.2 CHECKMATE-648

5.2.1 Nivolumab + chemotherapy vs. chemotherapy

Table 7. CM-648 (nivolumab + chemotherapy and control arms): Primary outcomes

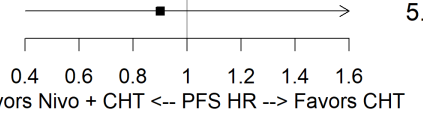
	Tumor Cell PD-L1 ≥1%		**All Randomized Subjects**	
Efficacy Parameter	**Nivolumab + chemotherapy N = 158**	**Chemotherapy N = 157**	**Nivolumab + chemotherapy N= 321**	**Chemotherapy N = 324**
OS	**Primary Endpoint**		**Secondary Endpoint**	
Events, n (%)	98 (62.0)	121 (77.1)	209 (65.1)	232 (71.6)
Median OS, mo (95% CI)[1]	15.44 (11.93, 19.52)	9.07 (7.69, 9.95)	13.21 (11.14, 15.70)	10.71 (9.40, 11.93)
HR (95% CI)[2]	0.54 (0.41, 0.71)		0.74 (0.61, 0.90)	
Stratified log-rank p-value[3]	<0.0001		0.0021	
PFS per BICR	**Primary Endpoint**		**Secondary Endpoint**	
Events, n (%)	117 (74.1)	100 (63.7)	235 (73.2)	210 (64.8)
Median PFS, mo. (95% CI)[1]	6.93 (5.68, 8.34)	4.44 (2.89, 5.82)	5.82 (5.55, 7.00)	5.59 (4.27, 5.88)

	Tumor Cell PD-L1 ≥1%		All Randomized Subjects	
Efficacy Parameter	**Nivolumab + chemotherapy N = 158**	**Chemotherapy N = 157**	**Nivolumab + chemotherapy N= 321**	**Chemotherapy N = 324**
HR (95% CI)[2]	0.65 (0.49, 0.86)		0.81 (0.67, 0.99)	
Stratified log-rank p-value[3]	0.0023		0.0355 (not significant)	

[1] Kaplan-Meier method; [2] Stratified Cox proportional hazard model; [3] Stratified log-rank test; NA: not evaluated for statistical significance as per pre-specified hierarchical testing procedure

Figure 13. CM-648 (nivolumab + chemotherapy and chemotherapy arms): BICR-assessed PFS Forest Plots by PD-L1 Cutoff (CPS), ESCC Population (FDA Analyses)

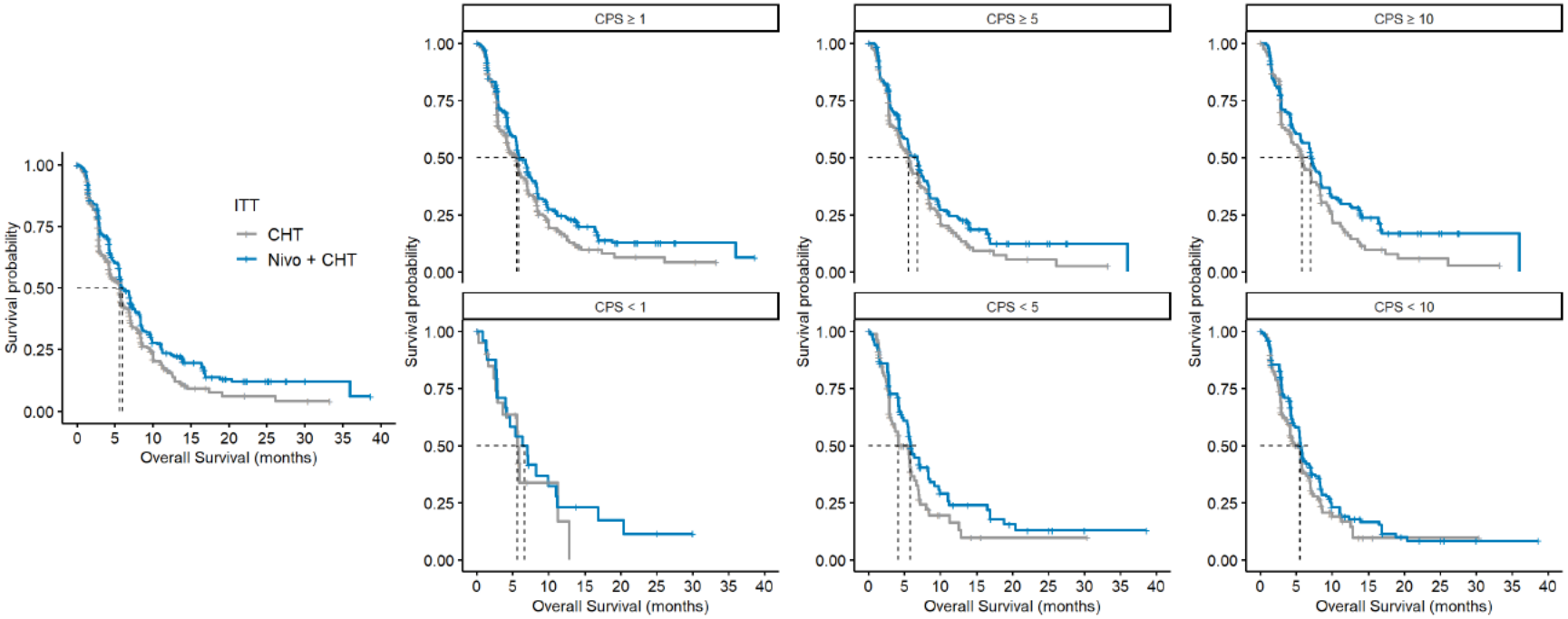
Subgroup	% of Pts	Nivo + CHT Evt / N	CHT Evt / N	HR (95% CI)	Nivo + CHT Median (95% CI)	CHT Median (95% CI)
Overall	**100.0**	**227/311**	**205/318**	**0.79 (0.65 ,0.95)**	**5.9 (5.6, 7)**	**5.6 (4.3, 5.9)**
CPS < 1	7.6	20/25	13/23	0.79 (0.38 ,1.64)	6.7 (2.8, 11)	5.7 (2.6, 11.2)
CPS ≥ 1	86.8	195/271	180/275	0.78 (0.64 ,0.96)	5.8 (5.5, 7)	5.6 (4.2, 5.8)
CPS < 5	28.8	62/92	54/89	0.71 (0.49 ,1.04)	5.8 (4.8, 8.2)	4.2 (3.1, 5.9)
CPS ≥ 5	65.7	153/204	139/209	0.81 (0.64 ,1.02)	6.8 (5.5, 7.2)	5.6 (4.3, 6.9)
CPS < 10	50.7	116/163	97/156	0.82 (0.62 ,1.07)	5.6 (4.8, 6.8)	5.5 (4.2, 5.7)
CPS ≥ 10	43.7	99/133	96/142	0.74 (0.56 ,0.99)	7 (5.6, 8.3)	5.8 (4.3, 7.1)
CPS 1 - < 5	21.1	42/67	41/66	0.68 (0.44 ,1.05)	5.8 (4.8, 8.3)	4.2 (2.8, 6.4)
CPS 5 - < 10	21.9	54/71	43/67	0.97 (0.65 ,1.46)	5.5 (4.2, 6.8)	4.8 (4.2, 6.9)
CPS 1 - < 10	43.1	96/138	84/133	0.82 (0.61 ,1.1)	5.6 (4.6, 6)	4.4 (3.8, 5.7)
Not Reported	5.6	12/15	12/20	0.9 (0.4 ,2.03)	5.8 (2.8, 8.8)	6.8 (2.8, 10.9)



Abbreviations: Nivo = nivolumab, CHT = chemotherapy, Evt = event, HR = hazard ratio, CI = confidence interval

Note: HRs were estimated by Cox proportional hazards models using treatment arm as the only covariate and the Efron method for handling ties.

Figure 14. CM-648 (nivolumab + chemotherapy and chemotherapy arms): BICR-assessed PFS Kaplan-Meier Estimates by PD-L1 Cutoff (CPS), ESCC Population (FDA Analyses)



Abbreviation: Nivo = nivolumab, CHT = chemotherapy

Figure 15. CM-648 (nivolumab + chemotherapy and chemotherapy arms): BICR-assessed ORR by PD-L1 cutoff (CPS), ESCC Population (FDA Analyses)

	Nivo + CHT			CHT		
	n/N	ORR (95% CI)	median DoR (95% CI)	n/N	ORR (95% CI)	median DoR (95% CI)
Overall	150/311	48.2 (42.6, 53.9)	8.2 (6.9, 9.7)	84/318	26.4 (21.7, 31.6)	7.1 (5.7, 8.7)
CPS < 1	9/25	36 (18, 57.5)	15.2 (2.7, NA)	4/23	17.4 (5, 38.8)	9.8 (4.2, NA)

CPS ≥ 1	133/271	49.1 (43, 55.2)	8.2 (6.7, 9.7)	74/275	26.9 (21.8, 32.6)	6.9 (5.7, 8.5)
CPS < 5	43/92	46.7 (36.3, 57.4)	8.3 (4.4, 15.6)	15/89	16.9 (9.8, 26.3)	5.7 (4.2, 10.1)
CPS ≥ 5	99/204	48.5 (41.5, 55.6)	8.2 (6.8, 11.4)	63/209	30.1 (24, 36.9)	7.1 (5.7, 8.7)
CPS < 10	71/163	43.6 (35.8, 51.5)	7.1 (5.7, 9.7)	37/156	23.7 (17.3, 31.2)	7.1 (5.5, 10.1)
CPS ≥ 10	71/133	53.4 (44.5, 62.1)	8.4 (6.7, 13.8)	41/142	28.9 (21.6, 37.1)	6.9 (5.6, 8.7)
CPS 1 - < 5	34/67	50.7 (38.2, 63.2)	6.7 (4.2, 17.1)	11/66	16.7 (8.6, 27.9)	5.7 (3.4, NA)
CPS 5 - < 10	28/71	39.4 (28, 51.7)	6.9 (5.1, 9.5)	22/67	32.8 (21.8, 45.4)	7.1 (5.5, NA)
CPS 1 - < 10	62/138	44.9 (36.5, 53.6)	6.9 (5.1, 9.5)	33/133	24.8 (17.7, 33)	7.1 (5.4, 10.9)

Abbreviations: Nivo = nivolumab, CHT = Chemotherapy, DoR = duration of response, ORR = objective response rate

5.2.2 Nivolumab + ipilimumab vs. chemotherapy

Table 8. CM-648 (nivolumab + ipilimumab arm): PD-L1 Expression (FDA Analyses)

PD-L1 expression (CPS)	Nivolumab + ipilimumab (N=322)[1]; n (%)
<1	30 (9)
1 - <5	74 (23)
5 - <10	65 (20)
≥ 10	125 (39)
Not reported	28 (9)

[1] Three subjects with adenosquamous carcinoma were excluded.

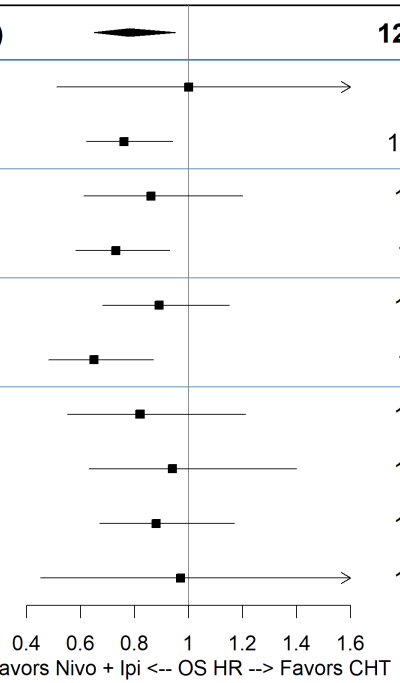
Table 9. CM-648 (nivolumab + ipilimumab and control arms): Primary outcomes

Efficacy Parameter	Tumor Cell PD-L1 ≥1%		All Randomized Subjects	
	Nivolumab + Ipilimumab N = 158	Chemotherapy N = 157	Nivolumab + Ipilimumab N = 325	Chemotherapy N = 324
OS	**Primary Endpoint**		**Secondary Endpoint**	
Events, n (%)	106 (67.1)	121 (77.1)	216 (66.5)	232 (71.6)
Median OS, mo (95% CI)[1]	13.70 (11.24, 17.02)	9.07 (7.69, 9.95)	12.75 (11.27, 15.47)	10.71 (9.40, 11.93)
HR (95% CI)[2]	0.64 (0.49, 0.84)		0.78 (0.65, 0.95)	
Stratified log-rank p-value[3]	0.0010		0.0110	
PFS per BICR	**Primary Endpoint**		**Secondary Endpoint**	
Events, n (%)	123 (77.8)	100 (63.7)	258 (79.4)	210 (64.8)
Median PFS, mo. (95% CI)[1]	4.04 (2.40, 4.93)	4.44 (2.89, 5.82)	2.92 (2.66, 4.17)	5.59 (4.27, 5.88)
HR (95% CI)[2]	1.02 (0.78, 1.34)		1.26 (1.04, 1.52)	
Stratified log-rank p-value[3]	0.8958 (not significant)		NA	

[1] Kaplan-Meier method; [2] Stratified Cox proportional hazard model; [3] Stratified log-rank test; NA: not evaluated for statistical significance as per pre-specified hierarchical testing procedure

Figure 16. CM-648 (nivolumab + ipilimumab and chemotherapy arms): OS Forest Plots by PD-L1 Cutoff (CPS), ESCC patients (FDA Analyses)

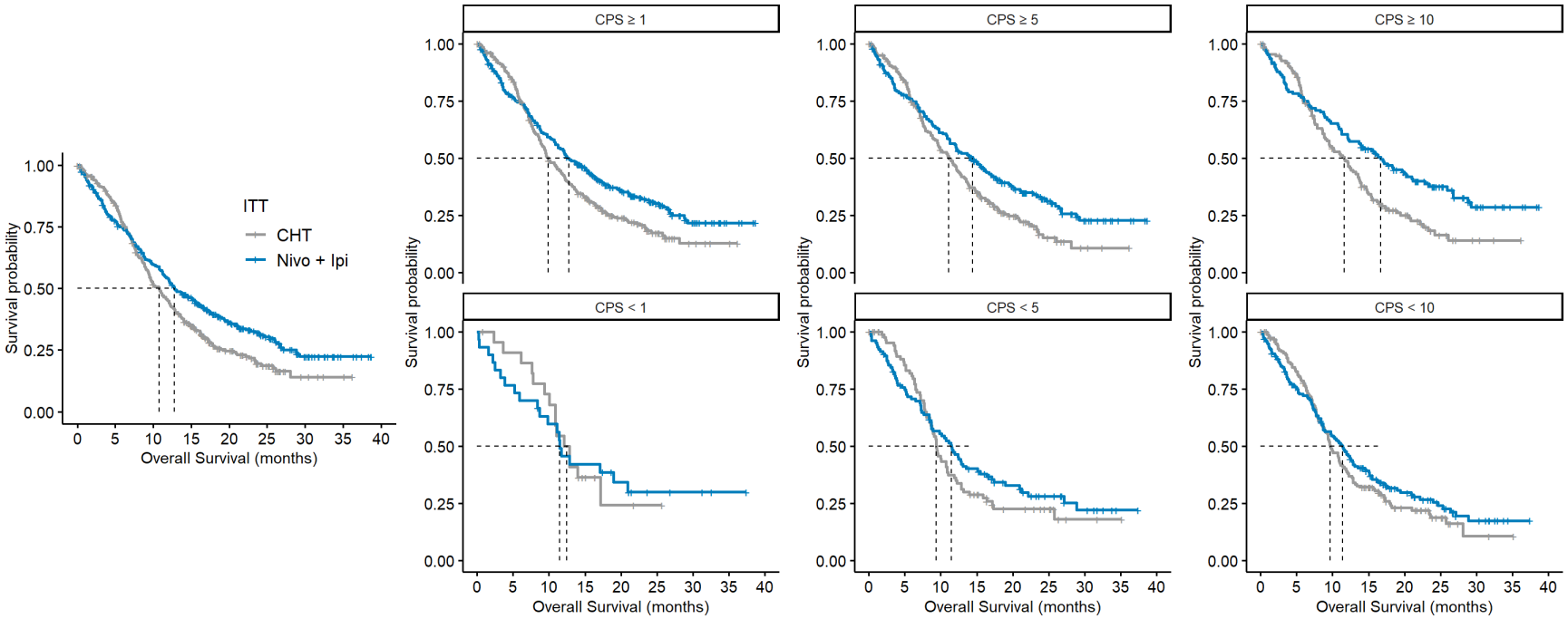
Subgroup	% of Pts	Nivo + Ipi Evt / N	CHT Evt / N	HR (95% CI)	Nivo + Ipi Median (95% CI)	CHT Median (95% CI)
Overall	**100.0**	**214/322**	**227/318**	**0.78 (0.65 ,0.95)**	**12.8 (11.3, 15.5)**	**10.8 (9.4, 12.1)**
CPS < 1	8.3	20/30	15/23	1 (0.51 ,1.97)	11.5 (8.3, 21)	12.5 (9.3, 17.1)
CPS ≥ 1	84.2	178/264	201/275	0.76 (0.62 ,0.94)	12.7 (10.9, 15.5)	9.9 (8.9, 11.7)
CPS < 5	30.2	71/104	64/89	0.86 (0.61 ,1.2)	11.5 (8.7, 13.5)	9.4 (8.5, 10.9)
CPS ≥ 5	62.3	127/190	152/209	0.73 (0.58 ,0.93)	14.4 (11.2, 17)	11.1 (9.5, 12.7)
CPS < 10	50.8	119/169	115/156	0.89 (0.68 ,1.15)	11.4 (8.7, 12.9)	9.7 (8.8, 11.1)
CPS ≥ 10	41.7	79/125	101/142	0.65 (0.48 ,0.87)	16.7 (12.1, 21)	11.6 (9, 13.7)
CPS 1 - < 5	21.9	51/74	49/66	0.82 (0.55 ,1.21)	10.7 (7.6, 15.1)	8.8 (7.7, 9.5)
CPS 5 - < 10	20.6	48/65	51/67	0.94 (0.63 ,1.4)	10.9 (7.7, 14.6)	11 (7.5, 12.9)
CPS 1 - < 10	42.5	99/139	100/133	0.88 (0.67 ,1.17)	10.9 (8.4, 13.1)	9.4 (8, 10.8)
Not Reported	7.5	16/28	11/20	0.97 (0.45 ,2.1)	18.8 (7.3, 26.1)	16.2 (5.5, NA)



Abbreviations: Nivo = nivolumab, Ipi = ipilimumab, CHT = chemotherapy, Evt = event, HR = hazard ratio, CI = confidence interval

Note: HRs were estimated by Cox proportional hazards models using treatment arm as the only covariate and the Efron method for handling ties.

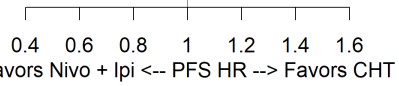
Figure 17. CM-648 (nivolumab + ipilimumab and chemotherapy arms): OS Kaplan-Meier Estimates by PD-L1 Cutoff (CPS), ESCC patients (FDA Analyses)



Abbreviation: Nivo = nivolumab, Ipi = ipilimumab, CHT = chemotherapy

Figure 18. CM-648 (nivolumab + ipilimumab and chemotherapy arms): BICR-assessed PFS Forest Plot by PD-L1 Cutoff (CPS), ESCC Population (FDA Analyses)

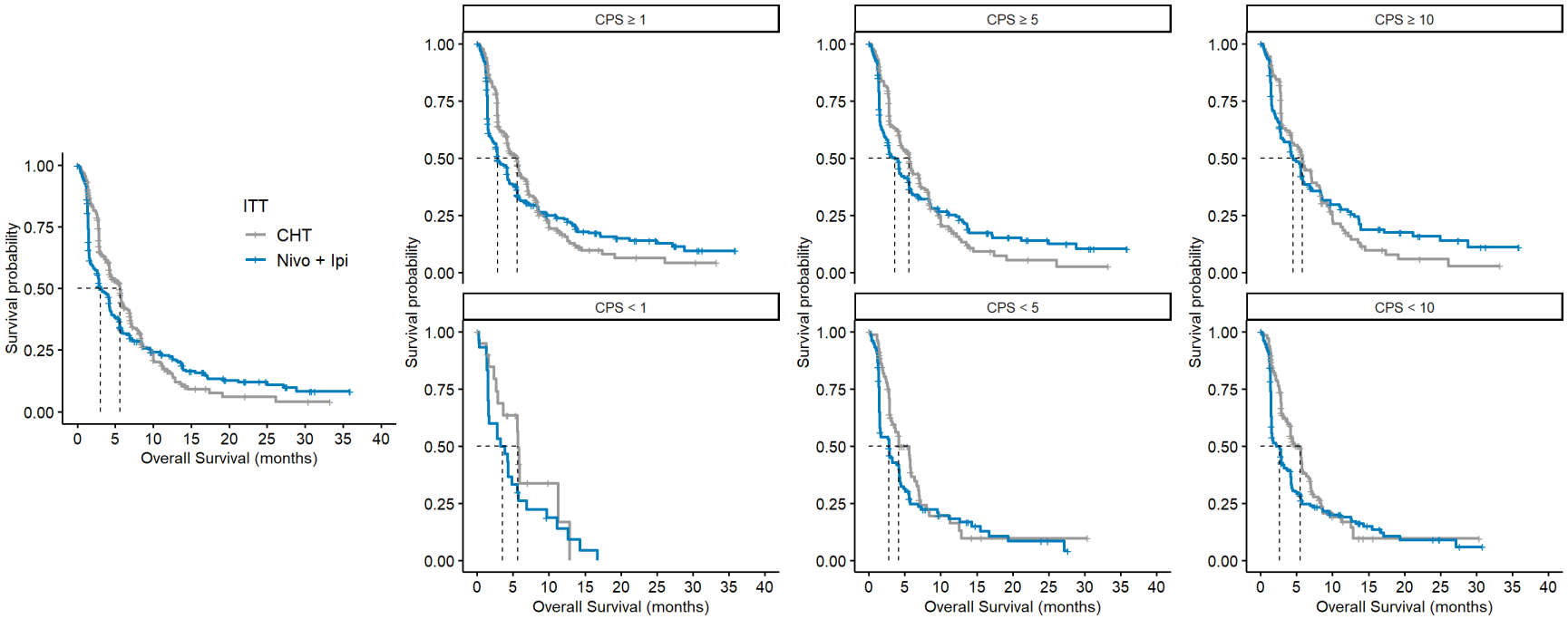
Subgroup	% of Pts	Nivo + Ipi Evt / N	CHT Evt / N	HR (95% CI)	Nivo + Ipi Median (95% CI)	CHT Median (95% CI)
Overall	**100.0**	**255/322**	**205/318**	**1.2 (1 ,1.45)**	**3.1 (2.7, 4.2)**	**5.6 (4.3, 5.9)**
CPS < 1	8.3	28/30	13/23	1.5 (0.77 ,2.92)	3.5 (1.5, 5.6)	5.7 (2.6, 11.2)
CPS ≥ 1	84.2	204/264	180/275	1.18 (0.96 ,1.45)	2.8 (2.6, 4.2)	5.6 (4.2, 5.8)
CPS < 5	30.2	86/104	54/89	1.4 (0.99 ,1.97)	2.8 (1.5, 4.2)	4.2 (3.1, 5.9)
CPS ≥ 5	62.3	146/190	139/209	1.11 (0.88 ,1.41)	3.6 (2.6, 4.4)	5.6 (4.3, 6.9)
CPS < 10	50.8	136/169	97/156	1.44 (1.11 ,1.88)	2.6 (1.5, 2.9)	5.5 (4.2, 5.7)
CPS ≥ 10	41.7	96/125	96/142	0.98 (0.74 ,1.31)	4.5 (2.8, 5.8)	5.8 (4.3, 7.1)
CPS 1 - < 5	21.9	58/74	41/66	1.38 (0.92 ,2.06)	2.8 (1.4, 4.1)	4.2 (2.8, 6.4)
CPS 5 - < 10	20.6	50/65	43/67	1.51 (0.99 ,2.28)	1.6 (1.4, 3)	4.8 (4.2, 6.9)
CPS 1 - < 10	42.5	108/139	84/133	1.45 (1.09 ,1.94)	1.7 (1.4, 2.8)	4.4 (3.8, 5.7)
Not Reported	7.5	23/28	12/20	1.15 (0.56 ,2.35)	4.2 (1.4, 7.2)	6.8 (2.8, 10.9)



Abbreviations: Nivo = nivolumab, Ipi = ipilimumab, CHT = chemotherapy, Evt = event, HR = hazard ratio, CI = confidence interval

Note: HRs were estimated by Cox proportional hazards models using treatment arm as the only covariate and the Efron method for handling ties.

Figure 19. CM-648 (nivolumab + ipilimumab and chemotherapy arms): BICR-assessed PFS Kaplan-Meier Estimates by PD-L1 Cutoff (CPS), ESCC Population (FDA Analyses)



Abbreviation: Nivo = nivolumab, Ipi = ipilimumab, CHT = Chemotherapy

Figure 20. CM-648 (nivolumab + ipilimumab and chemotherapy arms): BICR-assessed ORR by PD-L1 Cutoff (CPS), ESCC Population (FDA Analyses)

	Nivo + Ipi			CHT		
	n/N	**ORR (95% CI)**	**median DoR (95% CI)**	**n/N**	**ORR (95% CI)**	**median DoR (95% CI)**
Overall	90/322	28 (23.1, 33.2)	11.1 (8.3, 14)	84/318	26.4 (21.7, 31.6)	7.1 (5.7, 8.7)
CPS < 1	7/30	23.3 (9.9, 42.3)	10.3 (2.8, NA)	4/23	17.4 (5, 38.8)	9.8 (4.2, NA)
CPS ≥ 1	74/264	28	11.8	74/275	26.9	6.9

		(22.7, 33.9)	(7.1, 23.6)		(21.8, 32.6)	(5.7, 8.5)
CPS < 5	21/104	20.2 (13, 29.2)	11.1 (3.9, NA)	15/89	16.9 (9.8, 26.3)	5.7 (4.2, 10.1)
CPS ≥ 5	60/190	31.6 (25, 38.7)	10.8 (7.1, 23.6)	63/209	30.1 (24, 36.9)	7.1 (5.7, 8.7)
CPS < 10	34/169	20.1 (14.4, 27)	11.8 (5.9, NA)	37/156	23.7 (17.3, 31.2)	7.1 (5.5, 10.1)
CPS ≥ 10	47/125	37.6 (29.1, 46.7)	10.3 (6.7, 23.6)	41/142	28.9 (21.6, 37.1)	6.9 (5.6, 8.7)
CPS 1 - < 5	14/74	18.9 (10.7, 29.7)	16.7 (3.9, NA)	11/66	16.7 (8.6, 27.9)	5.7 (3.4, NA)
CPS 5 - < 10	13/65	20 (11.1, 31.8)	14.3 (2.9, NA)	22/67	32.8 (21.8, 45.4)	7.1 (5.5, NA)
CPS 1 - < 10	27/139	19.4 (13.2, 27)	16.7 (5.9, NA)	33/133	24.8 (17.7, 33)	7.1 (5.4, 10.9)

Abbreviations: Nivo = nivolumab, Ipi = ipilimumab, CHT = Chemotherapy, DoR = duration of response, ORR = objective response rate

5.3 RATIONALE-306

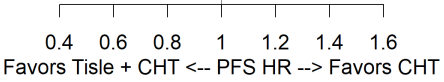
Table 10. RN-306: Primary Outcomes

Efficacy Parameter	**All Randomized Subjects**		**PD-L1 ≥ 10**	
	Tislelizumab + Chemotherapy N=326	**Placebo + Chemotherapy N=323**	**Tislelizumab + Chemotherapy N=116**	**Placebo + Chemotherapy N=107**
OS				
Events, n (%)	196 (60.1)	226 (70.0)	69 (59.5)	74 (69.2)
Median OS (95% CI), months[1]	17.2 (15.8, 20.1)	10.6 (9.3, 12.1)	16.6 (15.3, 24.4)	10.0 (8.6, 13.3)
HR[2] (95% CI)	0.66 (0.54, 0.80)		0.62 (0.44, 0.87)	
p-value[3] (stratified)	<0.0001		0.002949	
PFS by investigator				
Events, n (%)	220 (67.5)	254 (78.6)	-	-
Median PFS (95% CI), months	7.3 (6.9, 8.3)	5.6 (4.9, 6.0)	-	-
HR[2] (95% CI)	0.62 (0.52, 0.75)		-	-

p-value[3] (stratified)	<0.0001	-	-
[1] Kaplan-Meier method; [2] Stratified Cox proportional hazard model; [3] one-sided p value from stratified log-rank test			

Figure 21. RN-306: BICR-assessed PFS Forest Plot by PD-L1 Cutoff (TAP), ESCC Population (FDA Analyses)

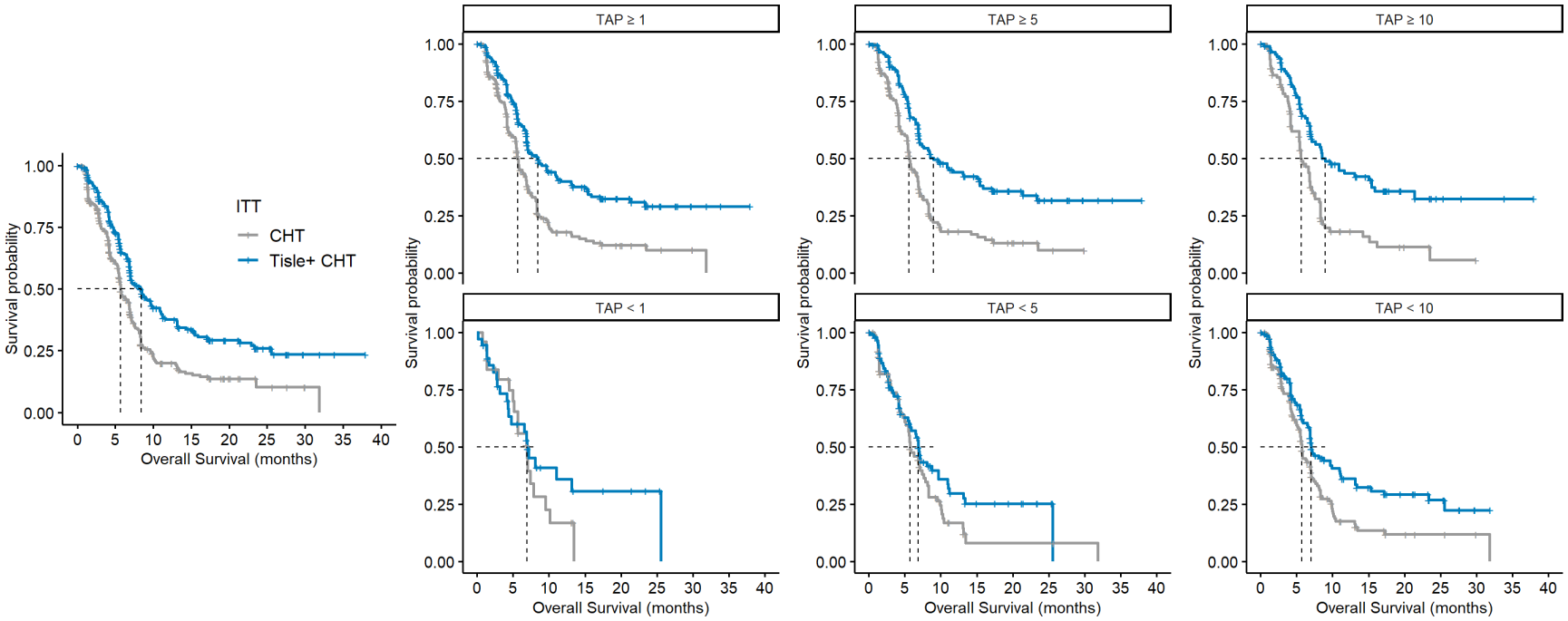
Subgroup	% of Pts	Tisle + CHT Evt / N	CHT Evt / N	HR (95% CI)	Tisle + CHT Median (95% CI)	CHT Median (95% CI)
Overall	**100.0**	**177/325**	**208/323**	**0.6 (0.49 ,0.73)**	**8.4 (7, 9.7)**	**5.7 (5.5, 6.8)**
TAP < 1	9.4	21/36	18/25	0.74 (0.39 ,1.4)	6.9 (4.3, 13.2)	6.9 (5, 7.9)
TAP ≥ 1	74.2	121/231	165/250	0.54 (0.43 ,0.68)	8.5 (6.9, 10.9)	5.7 (5.4, 6.7)
TAP < 5	28.4	54/95	61/89	0.75 (0.52 ,1.09)	6.9 (5.6, 9.7)	5.7 (5, 7.4)
TAP ≥ 5	55.2	88/172	122/186	0.49 (0.37 ,0.65)	9 (7, 15)	5.6 (5.3, 6.8)
TAP < 10	49.2	82/151	108/168	0.64 (0.48 ,0.86)	7 (6.6, 9.9)	5.7 (5.2, 6.9)
TAP ≥ 10	34.4	60/116	75/107	0.48 (0.34 ,0.67)	9 (7, 15.4)	5.7 (5.3, 6.8)
TAP 1 - < 5	19.0	33/59	43/64	0.74 (0.47 ,1.18)	6.9 (5.4, 9.7)	5.7 (4.2, 8.1)
TAP 5 - < 10	20.8	28/56	47/79	0.52 (0.32 ,0.83)	9.9 (6.9, 23.3)	5.6 (4.3, 6.9)
TAP 1 - < 10	39.8	61/115	90/143	0.62 (0.44 ,0.86)	7 (5.9, 10.9)	5.7 (4.5, 6.4)
Not Reported	16.4	35/58	25/48	0.88 (0.52 ,1.47)	8.5 (6.8, 9.9)	6.9 (3.5, 12.9)



Abbreviations: Tisle = tislelizumab, CHT = chemotherapy, Evt = event, HR = hazard ratio, CI = confidence interval

Note: HRs were estimated by Cox proportional hazards models using treatment arm as the only covariate and the Efron method for handling ties.

Figure 22. RN-306: BICR-assessed PFS Kaplan-Meier Estimates by PD-L1 Cutoff (TAP), ESCC Population (FDA Analyses)



Abbreviation: Tisle = tislelizumab, CHT = chemotherapy

Figure 23. RN-306: BICR-assessed ORR by PD-L1 Cutoff (TAP), ESCC Population (FDA Analyses)

	Tisle + CHT			CHT		
	n/N	**ORR (95% CI)**	**median DoR (months) (95% CI)**	**n/N**	**ORR (95% CI)**	**median DoR (months) (95% CI)**
Overall	199/325	61.2 (55.7, 66.6)	9.7 (8.2, 14)	134/323	41.5 (36.1, 47.1)	5.7 (5.5, 7)
TAP < 1	18/36	50 (32.9, 67.1)	24.1 (4.4, NA)	15/25	60 (38.7, 78.9)	5.6 (4.2, 8.7)
TAP ≥ 1	144/231	62.3 (55.7, 68.6)	11.7 (8.2, 20.1)	102/250	40.8 (34.6, 47.2)	5.7 (5.1, 7.1)
TAP < 5	44/95	46.3	9.6	38/89	42.7	5.9

		(36, 56.8)	(6.7, NA)		(32.3, 53.6)	(5, 8.5)
TAP ≥ 5	118/172	68.6 (61.1, 75.5)	11.8 (7.3, 20.7)	79/186	42.5 (35.3, 49.9)	5.6 (4.6, 7)
TAP < 10	84/151	55.6 (47.3, 63.7)	12 (8.2, 24.1)	71/168	42.3 (34.7, 50.1)	5.7 (5.1, 7.3)
TAP ≥ 10	78/116	67.2 (57.9, 75.7)	11.7 (7.1, NA)	46/107	43 (33.5, 52.9)	5.6 (4.2, 7)
TAP 1 - < 5	26/59	44.1 (31.2, 57.6)	9 (5.8, NA)	23/64	35.9 (24.3, 48.9)	6.9 (4.5, 9)
TAP 5 - < 10	40/56	71.4 (57.8, 82.7)	14 (5.7, NA)	33/79	41.8 (30.8, 53.4)	5.7 (4.2, 8.6)
TAP 1 - < 10	66/115	57.4 (47.8, 66.6)	11.8 (6.1, NA)	56/143	39.2 (31.1, 47.7)	5.7 (4.9, 8.5)

Abbreviations: Tisle = tislelizumab, CHT = Chemotherapy, DoR = duration of response, ORR = objective response rate

5.4 Additional Tables

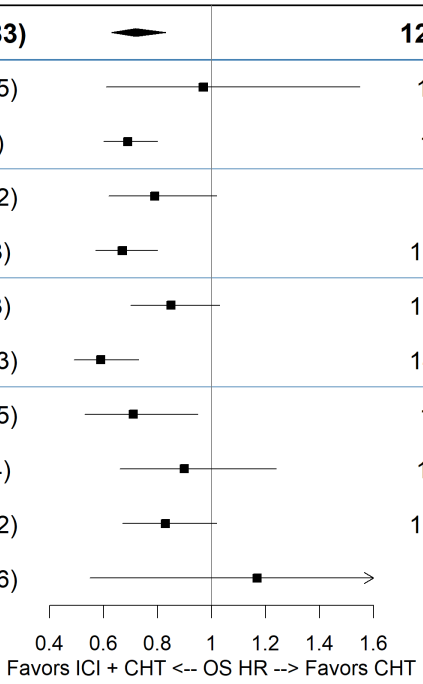
Table 11. Demographic and baseline disease characteristics by PD-L1 status, ESCC population (FDA analyses)

	KN-590 (N = 548)			CM-648 (N = 629)			RN-306 (N = 648)		
	PD-L1 <1	**PD-L1 1-<10**	**PD-L1 ≥10**	**PD-L1 <1**	**PD-L1 1-<10**	**PD-L1 ≥10**	**PD-L1 <1**	**PD-L1 1-<10**	**PD-L1 ≥10**
N (%)	55 (10.0)	192 (35.0)	286 (52.2)	48 (7.6)	271 (43.1)	275 (43.7)	61 (9.4)	258 (39.8)	223 (34.4)
Sex									
F	9 (16.4)	25 (13.0)	56 (19.6)	7 (14.6)	48 (17.7)	57 (20.7)	4 (6.6)	33 (12.8)	33 (14.8)
M	46 (83.6)	167 (87.0)	230 (80.4)	41 (85.4)	223 (82.3)	218 (79.3)	57 (93.4)	225 (87.2)	190 (85.2)
Age									
Median (range)	65.0 (44.0, 94.0)	63.0 (40.0, 82.0)	63.0 (32.0, 89.0)	65.0 (36.0, 78.0)	63.0 (40.0, 85.0)	64.0 (26.0, 84.0)	64.0 (42.0, 84.0)	64.0 (38.0, 84.0)	64.0 (40.0, 82.0)
≥ 65 yo	30 (54.5)	82 (42.7)	120 (42.0)	26 (54.2)	126 (46.5)	133 (48.4)	29 (47.5)	125 (48.4)	102 (45.7)
Race									
Asian	32 (58.2)	126 (65.6)	197 (68.9)	32 (66.7)	188 (69.4)	205 (74.5)	51 (83.6)	189 (73.3)	176 (78.9)
Other	1 (1.8)	3 (1.6)	11 (3.8)	2 (4.2)	4 (1.5)	7 (2.5)	0 (0.0)	1 (0.4)	0 (0.0)
White	17 (30.9)	54 (28.1)	62 (21.7)	14 (29.2)	76 (28.0)	60 (21.8)	9 (14.8)	64 (24.8)	46 (20.6)
Black or AA	0 (0.0)	3 (1.6)	2 (0.7)	0 (0.0)	3 (1.1)	3 (1.1)	0 (0.0)	0 (0.0)	0 (0.0)
Multiple	1 (1.8)	1 (0.5)	6 (2.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Not reported	4 (7.3)	5 (2.6)	8 (2.8)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.6)	4 (1.6)	1 (0.4)
Ethnicity									
Hispanic	8 (14.5)	26 (13.5)	32 (11.2)	4 (8.3)	12 (4.4)	13 (4.7)	0 (0.0)	5 (1.9)	1 (0.4)
ECOG									
0	17 (30.9)	68 (35.4)	115 (40.2)	18 (37.5)	130 (48.0)	134 (48.7)	22 (36.1)	94 (36.4)	69 (30.9)
1	38 (69.1)	124 (64.6)	171 (59.8)	30 (62.5)	141 (52.0)	140 (50.9)	39 (63.9)	164 (63.6)	154 (69.1)
Disease status									
Metastatic	50 (90.9)	172 (89.6)	262 (91.6)	24 (50.0)	173 (63.8)	146 (53.1)	56 (91.8)	221 (85.7)	197 (88.3)
Recurrent	0 (0.0)	0 (0.0)	0 (0.0)	21 (43.8)	59 (21.8)	85 (30.9)	0 (0.0)	0 (0.0)	0 (0.0)
Unresectable	5 (9.1)	20 (10.4)	24 (8.4)	3 (6.3)	39 (14.4)	44 (16.0)	5 (8.2)	37 (14.3)	26 (11.7)

Abbreviations: F = female, M = male, AA = African American

Figure 24. Overall Survival Forest Plot - Pooled Data Based on CPS Scoring (KN-590 and CM-648) (FDA Analyses)

Subgroup	% of Pts	ICI + CHT Evt / N	CHT Evt / N	HR (95% CI)	ICI + CHT Median (95% CI)	CHT Median (95% CI)
Overall	**100.0**	**390/585**	**449/592**	**0.72 (0.63 ,0.83)**	**12.9 (11.4, 14.8)**	**10.1 (9.4, 11.1)**
CPS < 1	8.8	37/51	36/52	0.97 (0.61 ,1.55)	10.5 (7.8, 17.3)	12.1 (9.3, 15.2)
CPS ≥ 1	87.0	337/509	399/515	0.69 (0.6 ,0.8)	13.1 (11.6, 15)	9.8 (9.1, 10.8)
CPS < 5	29.7	126/180	127/169	0.79 (0.62 ,1.02)	12 (10, 14.7)	9.5 (8.6, 10.8)
CPS ≥ 5	66.1	248/380	308/398	0.67 (0.57 ,0.8)	13.8 (11.6, 15.7)	10.6 (9.5, 11.6)
CPS < 10	48.1	201/284	213/282	0.85 (0.7 ,1.03)	11.8 (10.2, 13.5)	10.6 (9.4, 11.4)
CPS ≥ 10	47.7	173/276	222/285	0.59 (0.49 ,0.73)	14.3 (12.5, 18.3)	9.8 (8.6, 11.2)
CPS 1 - < 5	20.9	89/129	91/117	0.71 (0.53 ,0.95)	12.1 (10, 14.8)	8.8 (8, 9.8)
CPS 5 - < 10	18.4	75/104	86/113	0.9 (0.66 ,1.24)	11.2 (8.9, 15.7)	11.7 (9.8, 13.4)
CPS 1 - < 10	39.3	164/233	177/230	0.83 (0.67 ,1.02)	11.8 (10.2, 13.5)	9.8 (8.9, 11.1)
Not Reported	4.2	16/25	14/25	1.17 (0.55 ,2.46)	11.9 (8.8, NA)	16.2 (7.4, NA)



Abbreviations: ICI = immune checkpoint inhibitor, CHT = chemotherapy, Evt = event, HR = hazard ratio, CI = confidence interval

Note: HRs were estimated by Cox proportional hazards models stratified by study, using treatment arm as the only covariate and the Efron method for handling ties.