FDA Briefing Document

Immune checkpoint inhibitors in patients with metastatic or unresectable HER2-negative gastric adenocarcinoma

Oncology Advisory Committee Meeting

September 26, 2024

Division of Oncology 3/Office of Oncologic Drugs

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 HER2-negative gastric adenocarcinoma 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.

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Glossary

ACS	American Cancer Society
AE	Adverse event
BD	Briefing Document
BICR	Blinded independent central review
BRF	Benefit-Risk Framework
BMS	Bristol-Myers Squibb
CAPOX	Capecitabine and oxaliplatin
CDER	Center for Drug Evaluation and Research
CDRH	Center for Devices and Radiological Health
CDTL	Cross-Discipline Team Leader
CM-649	CheckMate-649
CPS	Combined Positive Score
CT	Computed tomography scan
CTLA4	Cytotoxic T-lymphocyte associated protein-4
dMMR	Deficient mismatch repair
DO3	Division of Oncology 3
DOR	Duration of response
ESCC	Esophageal squamous cell carcinoma
FDA	Food and Drug Administration
FOLFOX	Fluorouracil, leucovorin and oxaliplatin
GC	Gastric cancer
GEA	Gastroesophageal adenocarcinoma
GEJ	Gastroesophageal junction
HR	Hazard ratio
IA	Interim analysis
IHC	Immunohistochemistry
IV	Intravenous
KN-859	KEYNOTE-859
MRI	Magnetic resonance imaging
MSI-H	Microsatellite instability-high

ODAC	Oncologic Drugs Advisory Committee
OOD	Office of Oncologic Diseases
ORR	Overall response rate
OS	Overall survival
PD-1	Programmed death receptor-1
PD-L1	Programmed death ligand-1
PD-L2	Programmed death ligand-2
PFS	Progression-free survival
pMMR	Proficient Mismatch Repair
REMS	risk evaluation and mitigation strategy
RN-305	RATIONALE-305
RPM	Regulatory Project Manager
RT	Radiotherapy
SAP	Statistical Analysis Plan
sBLA	Supplemental Biologic License Application
SOC	Standard of care
TAP	Tumor Area Positivity
XELOX	Capecitabine and Oxaliplatin

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 advanced human epidermal growth factor (HER)-2 negative gastric adenocarcinoma at different levels of programmed death ligand 1 (PD-L1) protein expression. Labeling for approved checkpoint inhibitors for the treatment of patients with HER2-negative gastric cancer reflects approvals in the intent to treat patient populations agnostic of 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 HER2-negative gastric adenocarcinoma as well as the data submitted to support 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 in this patient population, 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 ICI in combination with chemotherapy for the first line treatment of HER-2 negative and microsatellite stable (or mismatch repair proficient) gastric adenocarcinoma should require patient selection based on PD-L1 expression levels (e.g., ≥1 or ≥10).

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 assessing tumor PD-L1 expression as a predictive biomarker for identifying patients likely to benefit from the use of ICI varies considerably by tumor histology (Patel and Kurzrock 2015). The data from the three pivotal studies that are the subject of the ODAC discussion utilized three separate PD-L1 immunohistochemistry (IHC) assays, scoring algorithms, and specified different cutoffs both for patient stratification and for the hierarchical testing when assessing the endpoint of overall survival. Although there have been attempts at assessing the interoperability of these assays (Ahn and Kim 2021; Klempner et al. 2024; Yeong et al. 2022), 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 nivolumab (based on CHECKMATE-649 [CM-649]) and pembrolizumab (based on KEYNOTE-859 [KN-859]) in combination with chemotherapy for the first line treatment of gastric cancer is agnostic of PD-L1 expression status. The studies that led to these approvals and the trial of

tislelizumab currently under review (RATIONALE-305, [RN305]) 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, US professional guidelines recommend use of these products based on PD-L1 expression cutoffs (CPS ≥1-9 [category 2B] or CPS ≥10 [category 1] for pembrolizumab and CPS ≥5 for nivolumab) which were based on the assay and the statistical design of each trial (NCCN 2024; Shah et al. 2023). Furthermore, the European Medicines Agency's (EMA's) Committee for Medicinal Products for Human Use (CHMP) approved pembrolizumab only for patients with gastric/GEJ adenocarcinoma whose tumors express PD-L1 with a CPS ≥ 1 (EMA 2023), and nivolumab for patients with CPS ≥ 5% (EMA 2021).

In the US, the use of pembrolizumab for patients with HER-2 positive gastric/GEJ adenocarcinoma is restricted to patients with PD-L1 combined positive score (CPS) ≥1. This restriction was based on a prespecified interim analysis of Study KEYNOTE-811 demonstrating lack of benefit and possible harm in patients with a PD-L1 CPS expression level <1 (KEYTRUDA 2024).

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 gastric cancer 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 gastric cancer. 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 gastric cancer 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 HER2-negative gastric adenocarcinoma 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 3). Similar results were also reported in a published meta-analysis (that included these and other studies) (Yoon et al. 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 HER-2 negative (and MSS) gastric/GEJ adenocarcinoma.
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 is appropriate.

2 Introduction and Background

2.1 Background of the Condition/Standard of Clinical Care

Gastric cancer is the fifth most frequently diagnosed cancer and the fifth leading cause of cancer related mortality worldwide (Bray et al. 2024). There are significant differences in regional incidences of gastric cancer due to the prevailing risk factors in a given population. In the United States, an estimated 27,000 new diagnoses of gastric cancer will be made with an expected 10,000 deaths in 2024 (Siegel, Giaquinto, and Jemal 2024). The current 5-year survival estimate for patients diagnosed with advanced disease is 7% and this continues to be a population with unmet medical need (ACS 2024).

The predominant histologic subtype in gastric cancer is adenocarcinoma accounting for approximately 95% of cases (Ajani et al. 2017). Gastric cancers are also classified based on the topographic anatomy (Siewert and Stein 1998). These anatomic distinctions were designed to allow for standardized therapeutic strategies, especially when choosing surgical approaches. There is considerable variability in the inclusion of patients with esophageal adenocarcinoma (EAC) with gastric/GEJ adenocarcinoma when designing studies addressing the management of patients with advanced disease. However, there is reasonable consensus and data to suggest that esophageal and gastric adenocarcinomas share sufficient similarities based on histology for these patients to be combined in such studies, irrespective of anatomic location (Salem et al. 2018; Smyth et al. 2017).

The treatment of patients with advanced unresectable gastric/GEJ adenocarcinoma requires the use of systemic therapies and is stratified by HER2 expression status. The pivotal studies CM-649, KN-859, and RN-305 are described in detail in Section 2.2 and Section 3, in addition there are published meta-analyses outlining global studies that have evaluated the use of ICIs in this patient population (Yoon et al. 2022).

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 the programmed death 1 (PD-1) receptor 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.

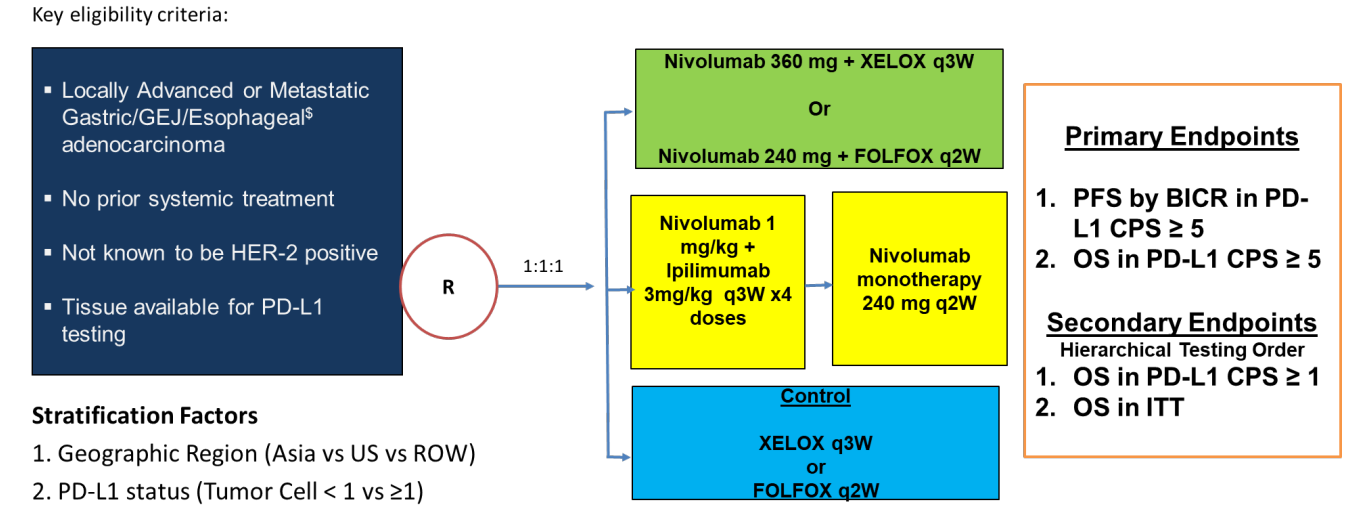
Both nivolumab and pembrolizumab are approved for the treatment of multiple cancers. Tislelizumab is approved for the treatment of unresectable or metastatic esophageal squamous cell carcinoma (ESCC) after prior systemic chemotherapy that did not include a PD-(L)1 inhibitor.

Study Designs

CheckMate-649 (CM-649) Study Design

CM-649 was an international, multicenter, randomized, open-label, three arm study of nivolumab plus chemotherapy (nivolumab, oxaliplatin, and fluoropyrimidine) or nivolumab plus ipilimumab versus chemotherapy (oxaliplatin and fluoropyrimidine) (Figure 1). The clinical protocol for CM-649 underwent multiple revisions from initially a two-arm study evaluating nivolumab plus ipilimumab versus chemotherapy to a 3-arm study. Enrollment into the nivolumab plus ipilimumab arm, however, was closed early following the recommendations of the Data Monitoring Committee, owing to an increased rate of adverse events and early deaths relative to the other two study groups.

Figure 1: CheckMate-649 Study Design



Source: Adapted from CheckMate-649 Protocol

$CheckMate-649 protocol was amended (version 4) to allow for the inclusion of patients with esophageal adenocarcinoma.

Abbreviations: BICR: blinded independent central review; CPS: Combined Positive Score; ECOG: Eastern Cooperative Oncology Group; FOLFOX: 5-fluorouracil, leucovorin, and oxaliplatin; HER2: Human Epidermal Growth Factor-2; OS: Overall Survival; PD-L1: Programmed Death Ligand -1; PFS: Progression Free Survival; ROW: Rest of World; XELOX: capecitabine and oxaliplatin.

Over the course of CM-649, a combination of unpublished internal data from other trials available to BMS and data from published studies evaluating the use of ICI in latter lines for patients with gastric/GEJ adenocarcinoma therapies suggested that CPS had improved performance characteristics as a predictive biomarker compared to tumor proportion score (TPS).

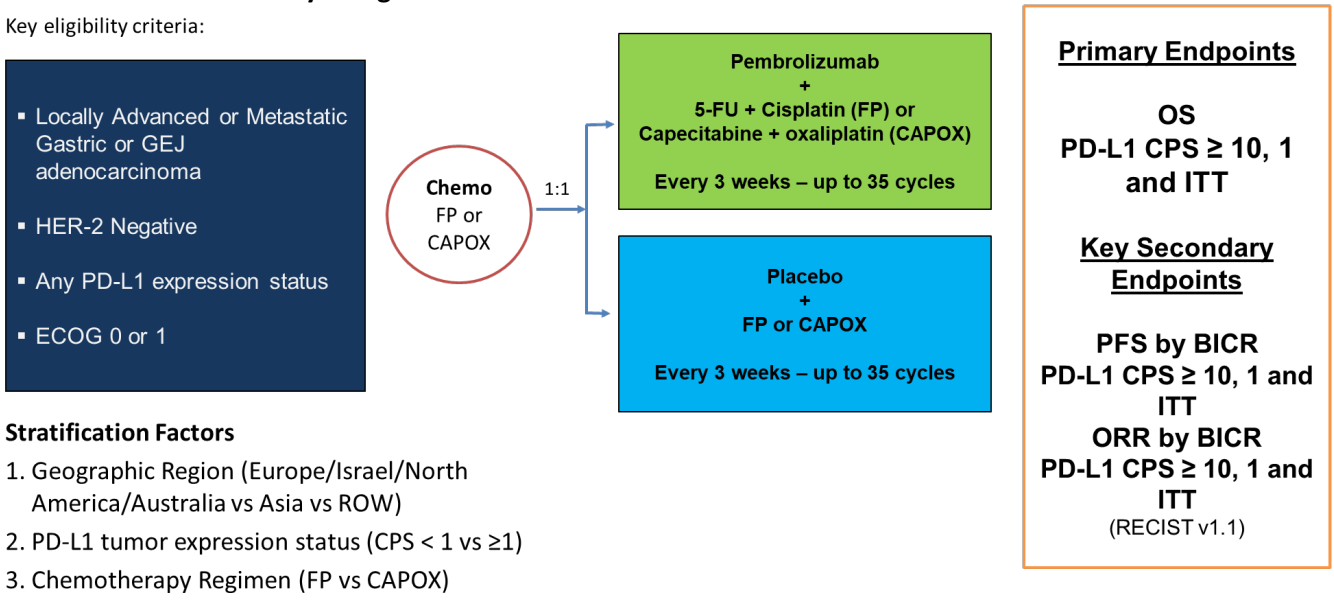
PD-L1 expression was determined by a central lab using the Agilent/Dako PD-L1 IHC 28-8 pharmDx test. Stratification for randomization remained based on TPS; however, efficacy analyses were conducted using PD-L1 CPS, which were generated centrally by rescoring the PD-L1 stained slides using the central lab DAKO CPS algorithm. All but 20 patients (8 in the nivolumab plus chemotherapy arm and 12 in the chemotherapy arm) had CPS values available.

BMS provided data demonstrating the lower prevalence of PD-L1 ≥1 by TPS which was used to define the original PD-L1 expressing population in the original protocol. The protocol and sample size calculation were revised to define the primary population using PD-L1 ≥5 by CPS. The primary endpoints of the trial were subsequently revised to progression-free survival (PFS) per RECIST v1.1 as assessed by a blinded independent central review (BICR) in patients with PD-L1 CPS ≥5 and OS in patients with PD-L1 CPS ≥5. Additional efficacy outcome measures tested in hierarchical order were OS in patients with PD-L1 CPS ≥1 and OS in all patients.

KEYNOTE-859 Study Design

KN-859 was an international, multicenter, randomized (1:1), double-blind, placebo-controlled trial (Figure 2).

Figure 2: KEYNOTE-859 Study Design



Source: Adapted from KEYNOTE-859 Protocol

Abbreviations: BICR: blinded independent central review; CAPOX: capecitabine and oxaliplatin; CPS: Combined Positive Score; ECOG: Eastern Cooperative Oncology Group; FP: 5-fluorouracil, cisplatin; HER2: Human Epidermal Growth Factor-2; ITT: Intent to Treat; ORR: Objective Response Rate OS: Overall Survival; PD-L1: Programmed Death Ligand -1; PFS: Progression Free Survival; ROW: Rest of World

The clinical protocol for KN-859 underwent multiple revisions from the design of the initial trial with an estimated sample size of 780 patients with a dual primary endpoint of PFS and OS in the ITT population, to 1542 patients to power the study for the PD-L1 CPS ≥10, CPS ≥1, and ITT populations with an OS primary endpoint and PFS as a key secondary endpoint as outlined in Figure 2.

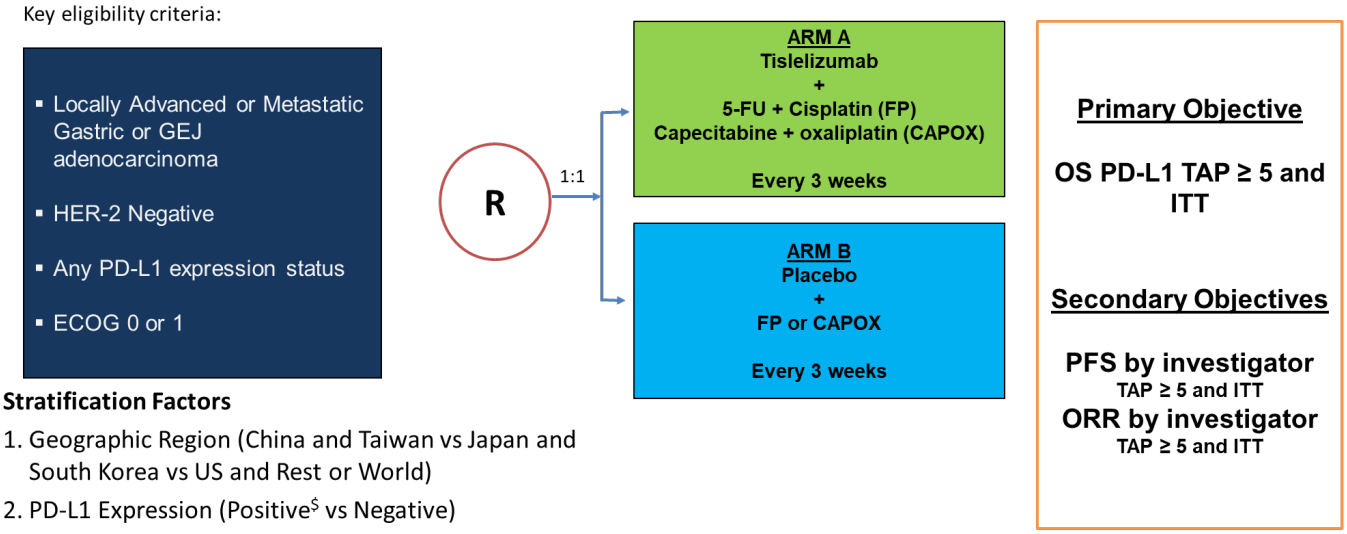
PD-L1 status was centrally determined in tumor specimens in patients using the Agilent PD-L1 IHC 22C3 pharmDx assay.

The primary endpoints of the trial sequentially evaluated OS in patients with CPS ≥10, CPS ≥1 and ITT. Key secondary endpoints evaluated PFS by BICR according to RECIST v1.1 and ORR by BICR according to RECIST v1.1 sequentially in patients with CPS ≥10, CPS ≥1 and ITT.

RATIONALE-305 Study Design

RN-305 is an international, randomized (1:1), double-blind, placebo-controlled trial (Figure 3).

Figure 3: RATIONALE-305 Study Design



Stratification Factors

1. Geographic Region (China and Taiwan vs Japan and South Korea vs US and Rest or World)
2. PD-L1 Expression (Positive[$] vs Negative)
3. Chemotherapy Regimen (FP vs CAPOX)
4. Presence of peritoneal metastasis (Yes vs No)

Source: Adapted from RATIONALE-305 Protocol

[$]PD-L1 positive were classified as patients with TAP ≥ 5

Abbreviations CAPOX: capecitabine and oxaliplatin; ECOG: Easter Cooperative Oncology Group; FP: 5-fluorouracil, cisplatin; HER2: Human Epidermal Growth Factor-2; ITT: Intent to Treat; ORR: Objective Response Rate OS: Overall Survival; PD-L1: Programmed Death Ligand -1; PFS: Progression Free Survival; ROW: Rest of World; TAP: Tumor Area Positivity.

The clinical protocol for RN-305 underwent multiple revisions from the initial submission. PFS was changed from a co-primary endpoint to a key secondary endpoint and the use of blinded independent central review (BICR) was removed (Figure 3).

PD-L1 expression in tumor specimens was assessed in patients using the VENTANA PD-L1 IHC SP264 CDx assay using the tumor area positivity (TAP) scoring system.

The primary endpoints of the trial sequentially evaluated OS in patients with TAP ≥5, and ITT. Key secondary endpoints evaluated PFS by investigator and ORR by investigator sequentially in patients with TAP ≥5, and ITT.

Study Populations

The demographic and clinical characteristics of patients randomized into the CM-649, KN-859, and RN-305 are outlined in Table 1: . Across the three studies, patients had a similar age and sex distribution, a greater proportion of patients enrolled in KN-859 and RN-305 were Asian compared to CM-649, and the differences in the studies by the country and regions of enrollment are outlined in the Appendix Table 4.

Notable differences in clinical characteristics between patients enrolled into CM-649, compared to KN-859 and RN-305 are the inclusion of patients with esophageal adenocarcinoma (EAC) and the proportions of patients who had undetermined/unknown or positive HER2 status; CM-649 excluded patients who were known to be HER2 positive although patients with undetermined HER2 status were included. All three studies enrolled patients irrespective of microsatellite instability (MSI) status: there were small differences in terms of patients who were MSI-H, microsatellite stable (MSS), or in those where the MSI status was not available.

To account for these differences, the FDA pooled analyses, which aims to provide estimates of efficacy across different subpopulations defined by PD-L1 cutoffs, excluded patients with EAC and was limited to patients who are known to be MSS (or pMMR). All pooled analyses in this document, unless otherwise specified, refer to the population of patients with gastric/GEJ adenocarcinoma that are MSS (or pMMR).

Table 1: Demographics and Clinical Characteristics of Overall Populations in CM-649, KN-859, and RN-305 (FDA Analyses)

	CheckMate-649				KEYNOTE-859				RATIONALE-305			
	Nivo + Chemo		Chemo		Pembro+Chemo		Chemo		Tis + Chemo		Chemo	
Randomized	**N=789**	**(%)**	**N = 792**	**(%)**	**N=790**	**(%)**	**N=789**	**(%)**	**N=501**	**(%)**	**N=496**	**(%)**
Age (median, range) (years)	62 (18, 88)		61 (21, 90)		61 (23, 86)		62 (21, 85)		60 (23, 86)		61 (25, 86)	
Sex (%)												
Male	540	68	560	71	527	67	544	69	346	69	346	70
Female	249	32	232	29	263	33	245	31	155	31	150	30
Primary Tumor Location												
Gastric Cancer	554	70	556	70	640	81	603	76	405	81	395	80
GEJ	132	17	128	16	149	19	185	23	96	19	100	20
EAC	103	13	108	14								
Race												
American Indian or Alaskan Native	12	1.5	14	1.8	31	3.9	36	4.6				
Asian	186	24	189	24	270	34	269	34	376	75	372	75
Black or African American	7	0.9	11	1.4	12	1.5	9	1.1				
Multiple					43	5.4	30	3.8				
Native Hawaiian or Pacific Islander					1	0.1	2	0.3				
White	556	71	541	68	426	54	435	55	116	23	107	22
Missing/Not Reported/Other	28	3.5	36	4.5	7	0.9	8	1	9	1.8	17	3.4
Ethnicity												
Hispanic or Latino	115	15	98	12	175	22	157	20	2	0.4	6	1.2
Not Hispanic or Latino	313	40	300	38	590	75	615	78	492	98	474	96

Unknown/Not Reported	361	46	394	50	25	3.2	17	2.2	7	1.4	16	3.2
ECOG PS												
0	326	41	336	42	281	36	301	38	169	33	154	31
1	462	59	452	57	509	64	488	62	332	66	342	69
HER2 Status												
Negative	459	58	472	60	790	100	789	100	500	100	493	99
Positive	3	0.4	4	0.5					0	0	1	0.2
Unknown/Not Reported	327	41	316	40					1	0.2	2	0.4
PD-L1 cutoffs (prespecified)												
CPS or TAP ≥ 1	641	81	655	82	618	78	617	78				
CPS or TAP ≥ 5	473	60	482	61					274	55	272	55
CPS or TAP ≥ 10					279	35	272	35				
MSI Status												
MSI High (or dMMR)	23	3	21	3	39	5	35	4	16	3	24	5
MSS	695	88	682	86	641	81	639	81	448	89	439	89
Not Reported/Invalid	71	9	89	11	110	14	115	15	37	7	33	7
Chemo Arm												
- CAPOX/XELOX	365	46	370	47	682	86	681	86	466	93	465	94
- FOLFOX	424	54	422	53								
- FP					108	14	108	14	35	7	31	6

Abbreviations CAPOX/XELOX: capecitabine and oxaliplatin; CPS: Combined Positive Score ECOG PS: Eastern Cooperative Oncology Group Performance Status; FOLFOX: 5-fluorouracil, leucovorin, and oxaliplatin; FP: 5-fluorouracil, cisplatin; HER2: Human Epidermal Growth Factor-2; PD-L1: Programmed Death Ligand -1; TAP: Tumor Area Positivity.

2.3 PD-L1 Expression and Immune Checkpoint Inhibition in Gastric Cancer

Multiple immunohistochemistry (IHC) assays and scoring systems are available to assess PD-L1 in gastric cancers 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 may 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) gastric cancer were specifically included in the statistical testing hierarchy. PD-L1-negative or low subgroups were not specifically tested. 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 CM-649 and KN-859 were positive studies in the overall population, professional guidance recommendations for the first-line treatment for patients with unresectable or metastatic gastric cancer are based on subgroup analyses of the PD-L1 cutoffs of each individual study (Table 2). Of note, the 2023 ASCO Guidelines below did not include discussion on the results of Study KEYNOTE-859.

Table 2: ASCO, NCCN, and ESMO guidelines for the first-line treatment of HER2 negative Gastric or Gastroesophageal Cancer

ASCO Guidelines: Advanced Gastroesophageal Cancer

• Recommendation 1.1 – For patients with HER2-negative gastric adenocarcinoma and PD-L1 CPS ≥5, nivolumab plus fluoropyrimidine- and platinum-based chemotherapy is recommended (evidence quality medium, strong recommendation).
  ○ For HER2-negative patients with gastric adenocarcinoma and PD-L1 CPS 1-5, first-line therapy with nivolumab in combination with fluoropyrimidine- and platinum-based chemotherapy may be considered on a case-by-case basis.
  ○ For patients with gastric adenocarcinoma and PD-L1 CPS 0, first-line therapy with fluoropyrimidine-and platinum-based chemotherapy, without the addition of nivolumab, is recommended.
• Recommendation 1.2 – For patients with HER2-negative esophageal or gastroesophageal junction adenocarcinoma, first-line therapy with nivolumab for patients with PD-L1 CPS ≥ 5, or pembrolizumab for PD-L1 CPS ≥ 10, in combination with fluoropyrimidine- and platinum-based chemotherapy is recommended (Type: Evidence based; benefits outweigh harms; Evidence quality: Low; Strength of recommendation: Strong)
  ○ For HER2-negative patients with esophageal or GEJ adenocarcinoma, first-line therapy with nivolumab for patients with PD-L1 CPS 1-5, or pembrolizumab for patients with PD-L1 CPS 1-10, in combination with fluoropyrimidine- and platinum-based CT may be recommended on a case-by-case basis.

○ For HER2-negative patients with gastric adenocarcinoma and PD-L1 CPS 0 or PD-L1 tumor proportion score (TPS) 0%, first-line therapy with fluoropyrimidine- and platinum-based CT, without the addition of programmed cell death protein 1 inhibitors, is recommended.
NCCN 2024 V4 Guidelines (HER2 negative, non-MSI-H)
Preferred Regimens • Fluoropyrimidine (fluorouracil or capecitabine), oxaliplatin, and nivolumab for PD-L1 CPS ≥ 5 (category 1) • Fluoropyrimidine (fluorouracil or capecitabine), oxaliplatin or cisplatin, and pembrolizumab for PD-L1 CPS ≥ 1 (category 1 for PD-L1 CPS ≥10; category 2B for PD-L1 CPS 1 < 10) • Fluoropyrimidine (fluorouracil or capecitabine) and oxaliplatin (category 2A) • Fluoropyrimidine (fluorouracil or capecitabine) and cisplatin (category 2A) Relevant NCCN Categories of Evidence and Consensus Category 1: Based upon high-level evidence (≥1 randomized phase 3 trials or high-quality, robust meta-analyses), there is uniform NCCN consensus (≥85% support of the Panel) that the intervention is appropriate. Category 2A: Based upon lower-level evidence, there is uniform NCCN consensus (≥85% support of the Panel) that the intervention is appropriate. Category 2B: Based upon lower-level evidence, there is NCCN consensus (≥50%, but <85% support of the Panel) that the intervention is appropriate.
ESMO Guidelines
• All patients: platinum-fluoropyrimidine doublet (IA) • HER2-negative PD-L1 positive (CPS ≥ 5): nivolumab-chemotherapy (IA) 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. Relevant ESMO Categories for Grades of Recommendation ○ A: Strong evidence for efficacy with a substantial clinical benefit, strongly recommended

Source: Adapted from (Lordick et al. 2022; NCCN 2024; Shah et al. 2023)

A systematic review and meta-analysis of randomized clinical trials in gastroesophageal cancers (including gastric and esophageal adenocarcinomas and ESCC) was conducted to evaluate the OS benefit from ICIs based on high vs. absent or low PD-L1 expression (Yoon et al. 2022). 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, 6,099 had adenocarcinoma (most gastric/GEJ) and of these, 3,919 were enrolled in first line setting trials (including reports of trials conducted solely in Asia). Of note, the meta-analysis was based on published trial-level data. Per the report, among patients with adenocarcinoma (all lines), PD-L1 combined positive score (CPS) was the strongest predictor of ICI benefit after microsatellite instability high status (CPS "high"; however, was dependent on the trial design and varied between 1, 5, or 10 in the different trials):

- CPS “high” OS HR 0.73 (95% CI 0.66, 0.81)
- CPS “non-high” OS HR 0.95 (95% CI 0.84, 1.07)

The authors also described consistent results based on the cutoff of CPS10 across trials. The 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 3 trials submitted to FDA: CM-649, KN-859, and RN-305 (Table 3).

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

3 Summary of Data for the AC

3.1 Efficacy

PD-L1 Distribution

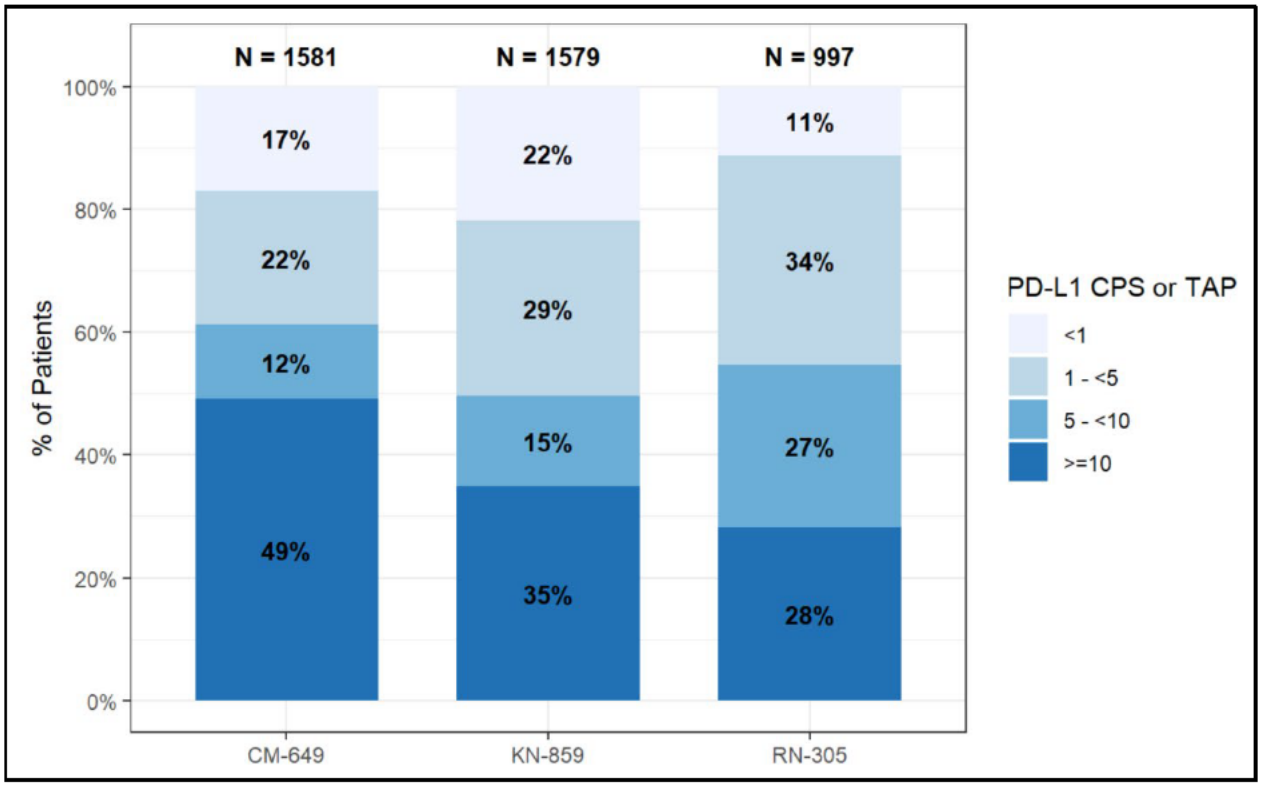
FDA analyses of proportion of randomized patients at PD-L1 cutoffs across the three studies are outlined in Figure 4. In this analysis, if a particular cutoff was not prespecified in a study, the raw CPS/TAP score was used to provide patient classification. All patients were placed in mutually exclusive PD-L1 strata.

CM-649 randomized the greatest proportion of patients classified as having PD-L1 CPS ≥ 10 (N=768 [49%], all values assessed using raw scores), with the PD-L1 < 10 subgroup accounting for 51% of the patient population (PD-L1 CPS <10 and ≥ 5 N=187 [12%], CPS <5 and ≥ 1 N=341 [22%], CPS < 1 N=265 [17%]). Patients with EAC (N=211 [13%]) are included in this analysis with their distribution of PD-L1 expression being similar to the overall population (PD-L1 CPS ≥ 10 N=99 [47%], PD-L1 CPS <10 and ≥ 5 N=19 [9%], CPS <5 and ≥ 1 N=55 [26%], and CPS < 1 N= 31 [15%]). The PD-L1 CPS score was not available in 20 patients.

KN-859 randomized 35% (N=551) who were classified as having PD-L1 CPS ≥ 10. PD-L1 CPS of 5 was not prespecified in the KN-859 protocol and classification of patients in different strata with PD-L1 CPS ≥ 1 and < 10 are based on raw scores, with 15% (N=232) having PD-L1 CPS <10 and ≥ 5, 29% (N=452) having CPS <5 and ≥ 1, and 22% (N=344) CPS < 1.

RN-305, which assessed PD-L1 expression using the TAP scoring method, enrolled the lowest proportion of patients with a PD-L1 TAP ≥ 10 (N=281 [28%], assessed using raw TAP values), with 27% (N=265) having PD-L1 TAP <10 and ≥ 5, 34% (N=339) having TAP <5 and ≥ 1, and 11% (N=112) TAP < 1.

Figure 4: PD-L1 Distribution Across Studies (FDA Analysis)



Abbreviations: CM-649: CheckMate-649; CPS: Combined Positive Score; KN-859: KEYNOTE-859; PD-L1: Programmed Death Ligand-1; TAP: Tumor Area Positivity. Note: 20 patients with missing PD-L1 status in Study CM-649 were not included in this figure.

The studies that are the topic of discussion for this ODAC share common characteristics in design and population i.e., all being randomized, global studies, predominantly in Ga/GEJ adenocarcinoma, which stratified patients based on PD-L1 expression status and had OS as a primary endpoint. However, each of the studies utilized a unique PD-L1 assay and cutoff when prespecifying statistical analysis plans and endpoints. FDA analyses above have outlined the key differences in the demographic and clinical characteristics in the respective patient populations, including the difference in distribution of PD-L1 expression that should be taken into account when discussing the observed efficacy in each study alone and in the pooled analyses.

Efficacy

Although the primary study OS results were statistically significant for the anti PD-L1-containing arms 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 tumors with PD-L1 <10 (which included patients with PD-L1 <1). Although these results are exploratory, and uncertainty exits for each trial (as the 95% CIs cross one), strong evidence does not appear to support the use of anti-PD-L1 drugs in patients with low PD-L1 expression (Table 3). The tables and figures below provide a summary of FDA's efficacy analyses for OS that were observed in each study and the prespecified and exploratory analysis populations at specific PD-L1 cutoffs were outlined. The efficacy analyses were derived from the primary data that was used to support each sBLA.

Table 3: Highlights of (FDA) OS analyses by PD-L1 cutoffs (FDA Analyses)

	All Patients		PD-L1 ≥ 1		PD-L1 ≥5		PD-L1 ≥ 10		PD-L1 <1		PD-L1 <5		PD-L1 <10	
CM649	**N+CHT**	**CHT**	**N+CHT**	**CHT**	**N+CHT**	**CHT**	**N+CHT**	**CHT**	**N+CHT**	**CHT**	**N+CHT**	**CHT**	**N+CHT**	**CHT**
N	**789**	**792**	**641**	**655**	**473**	**482**	**375**	**393**	**140**	**125**	**308**	**298**	**406**	**387**
mOS (95% CI)	13.8 (12.6, 14.6	11.6 (10.9, 12.5)	14.0 (12.6, 15)	11.3 (10.6, 12.3)	14.4 (13.1, 16.2)	11.1 (10.0, 12.1)	15.0 (13.8, 16.8)	10.9 (9.8, 11.8)	13.1 (9.8, 16.7)	12.5 (10.1, 13.8)	12.4 (10.6, 14.3)	12.3 (11.0, 13.2)	12.6 (11.1, 14.2)	12.5 (11.2, 13.3)
OS HR (95% CI)	**0.79 (0.70, 0.89)**		**0.76 (0.67, 0.87)**		**0.70 (0.60, 0.81)**		**0.65 (0.55, 0.78)**		**0.92 (0.70, 1.23)**		**0.94 (0.78, 1.13)**		**0.94 (0.80, 1.1)**	
KN859	**P+CHT**	**CHT**	**P+CHT**	**CHT**	**P+CHT**	**CHT**	**P+CHT**	**CHT**	**P+CHT**	**CHT**	**P+CHT**	**CHT**	**P+CHT**	**CHT**
N	**790**	**789**	**618**	**617**	**390**	**393**	**279**	**272**	**172**	**172**	**400**	**396**	**511**	**517**
mOS (95% CI)	12.9 (11.9, 14.0)	11.5 (10.6, 12.1)	13.0 (11.6, 14.2)	11.4 (10.5, 12.0)	14.0 (12.1, 15.4)	11.5 (10.3, 12.5)	15.7 (13.8, 19.3)	11.8 (10.3, 12.7)	12.7 (11.4, 15.0)	12.2 (9.5, 14.0)	12.0 (11.1, 13.5)	11.4 (10.0, 12.2)	11.7 (10.7, 12.8)	11.2 (10.0, 12.1)
OS HR (95% CI)	**0.77 (0.69, 0.86)**		**0.73 (0.65, 0.83)**		**0.70 (0.60, 0.82)**		**0.64 (0.52, 0.77)**		**0.92 (0.73 ,1.17)**		**0.85 (0.73, 0.98)**		**0.86 (0.75, 0.98)**	
RN306	**T+CHT**	**CHT**	**T+CHT**	**CHT**	**T+CHT**	**CHT**	**T+CHT**	**CHT**	**T+CHT**	**CHT**	**T+CHT**	**CHT**	**T+CHT**	**CHT**
N	**501**	**496**	**432**	**453**	**274**	**272**	**136**	**145**	**69**	**43**	**227**	**224**	**365**	**351**
mOS (95% CI)	15.0 (13.6, 16.5)	12.9 (12.1, 14.1)	15.0 (13.3, 16.7)	12.8 (12.1, 14.1)	16.4 (13.6, 19.1)	12.8 (12.0, 14.5)	22.5 (16.4, 26.4)	12.3 (11.3, 14.9)	15.4 (8.4, 19.2)	13.8 (10.2, 17.8)	14.1 (11.9, 15.6)	12.9 (11.3, 14.7)	14.0 (12.0, 15.3)	13.0 (12.1, 14.3)
OS HR (95% CI)	**0.80 (0.69, 0.92)**		**0.78 (0.67, 0.91)**		**0.72 (0.59, 0.88)**		**0.57 (0.43, 0.76)**		**0.98 (0.64, 1.50)**		**0.91 (0.74, 1.12)**		**0.91 (0.77, 1.07)**	

Abbreviations: CHT: Chemotherapy; CI: Confidence Interval; HR: Hazard Ratio; N: Nivolumab; OS: Overall Survival; P: Pembrolizumab; T: Tislelizumab.

Note: The PD-L1 cutoffs used in the trial prespecified analysis are highlighted. All FDA analyses are exploratory. HRs were estimated by Cox proportional hazards models with treatment arm as the only covariate and Efron method handling ties (methodology for this table and in Forrest Plots below may have differed from that used in the original study analyses and therefore results may differ compared to product labeling); Twenty patients with missing CPS status in CM-649 were included in the all patients analysis but were not included in the subgroup analyses.

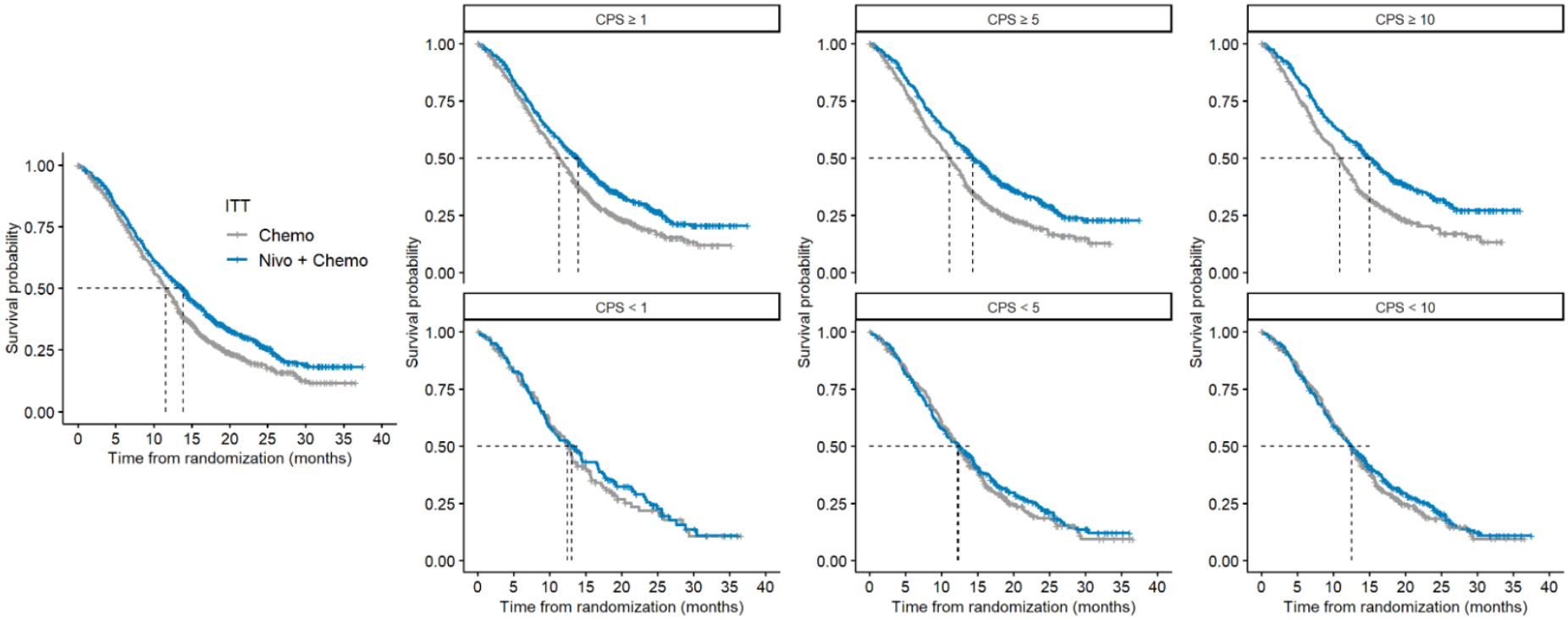
CheckMate-649

All pre-specified significance levels were met at the planned analysis (data cutoff date October 3, 2022) with OS improvement in all randomized patients, PD-L1 CPS ≥ 1 (82% of the total population) and ≥ 5 (60% of the total population). However, most of the patients within these subgroups had PD-L1 CPS ≥ 10 (49% of total population).

The study was not specifically designed to assess treatment effects in PD-L1 low populations; however, exploratory analyses in patients with PD-L1 low (e.g., CPS <1 or <5) tumors did not appear to demonstrate similar point estimates for the treatment effect as compared to patients with PD-L1 higher (e.g., ≥1 or ≥ 5) tumors.

Consistent with the summary results of CM-649 summarized in Table 3 above, the KM curves appear to show that the treatment effect appears to be attributable to patients with PD-L1 high tumors.

Figure 5: Kaplan-Meier estimates of Overall Survival in CheckMate-649 (FDA Analyses)



Abbreviations: CPS: Combined Positive Score; ITT: Intent to Treat

Efficacy by PD-L1 Expression in CheckMate-649

FDA conducted additional exploratory analyses of efficacy, evaluating OS, at intermediate PD-L1 cutoffs e.g., PD-L1 CPS ≥1, <5; PD-L1 CPS ≥5, <10; and PD-L1 CPS ≥1, <10. Collectively these subgroups are presented in Figure 6. These analyses were conducted to show, for example, whether lack of an effect in patients with CPS <10 tumors could be attributable to patients with CPS <1 tumors.

Figure 6: Forest Plot of Overall Survival at PD-L1 cutoffs in CheckMate-649 (FDA Analyses)

		Nivo + Chemo	Chemo			Nivo + Chemo	Chemo
Subgroup	**% of Pts**	**Evt / N**	**Evt / N**	**HR (95% CI)**		**Median (95% CI)**	**Median (95% CI)**
Overall	**100**	**544/789**	**591/792**	**0.79 (0.7 ,0.89)**		**13.8 (12.6, 14.6)**	**11.6 (10.9, 12.5)**
CPS <1	17	103/140	91/125	0.92 (0.7 ,1.23)		13.1 (9.8, 16.7)	12.5 (10.1, 13.8)
CPS >=1	82	434/641	492/655	0.76 (0.67 ,0.87)		14 (12.6, 15)	11.3 (10.6, 12.3)
CPS <5	38	228/308	221/298	0.94 (0.78 ,1.13)		12.4 (10.6, 14.3)	12.3 (11, 13.2)
CPS >=5	60	309/473	362/482	0.7 (0.6 ,0.81)		14.4 (13.1, 16.2)	11.1 (10, 12.1)
CPS <10	50	302/406	288/387	0.94 (0.8 ,1.1)		12.6 (11.1, 14.2)	12.5 (11.2, 13.3)
CPS >=10	49	235/375	295/393	0.65 (0.55 ,0.78)		15 (13.8, 16.8)	10.9 (9.8, 11.8)
CPS 1-<5	22	125/168	130/173	0.97 (0.76 ,1.24)		12.3 (9.6, 14.3)	12 (10.9, 13.9)
CPS 5-<10	12	74/98	67/89	0.92 (0.66 ,1.28)		12.6 (10.7, 16.2)	12.9 (9.4, 14.4)
CPS 1-<10	33	199/266	197/262	0.95 (0.78 ,1.16)		12.4 (10.8, 14.2)	12.6 (11, 13.7)

Abbreviations: CPS: Combined Positive Score; Chemo: Chemotherapy; CI: Confidence Interval; HR: Hazard Ratio; Nivo: Nivolumab; OS: Overall Survival. Note: Twenty patients with missing CPS status were included in the overall population analysis but were not included in the subgroup analyses. HRs were estimated by Cox proportional hazards models with treatment arm as the only covariate and Efron method handling ties.

Additional efficacy data evaluating PFS and ORR by BICR per RECIST v1.1, using the same PD-L1 CPS cutoffs outlined above are available in the Appendix Figure 13 and Appendix Table 5.

Among the PD-L1 expression cutoffs evaluated, the greatest estimated magnitude of benefit for OS was observed in patients with PD-L1 CPS ≥ 10 (HR 0.65 [95% CI: 0.55, 0.78]). Conversely, patients with PD-L1 CPS < 1 demonstrated only a marginal (and uncertain) improvement in OS (HR 0.92 [95% CI: 0.71, 1.23], as did the patients with PD-L1 CPS < 5 (HR 0.94 [95% CI: 0.78, 1.13]), and PD-L1 CPS < 10 (HR 0.94 [95% CI: 0.8, 1.1). When evaluating the observed efficacy, across exploratory subgroups of patients with PD-L1 CPS ≥ 1 to < 10, CPS ≥ 1 to < 5, CPS ≥ 5 to < 10, these subgroups derived similar magnitude of benefit as the patients with PD-L1 CPS < 1.

KEYNOTE-859

All pre-specified significance levels were met at the planned analysis (data cutoff date October 3, 2022) with OS improvements in all randomized patients, PD-L1 ≥ 10 (35% of the total population) and PD-L1 ≥ 1 (78% of total population). KN-859 also allocated alpha for hypothesis testing of key secondary endpoints of PFS and ORR by BICR per RECIST v1.1, at PD-L1 cutoffs outlined above and the ITT, all being statistically significant (Appendix Figure 14 and Table 6 provide exploratory subgroup analyses of PFS and ORR by BICR).

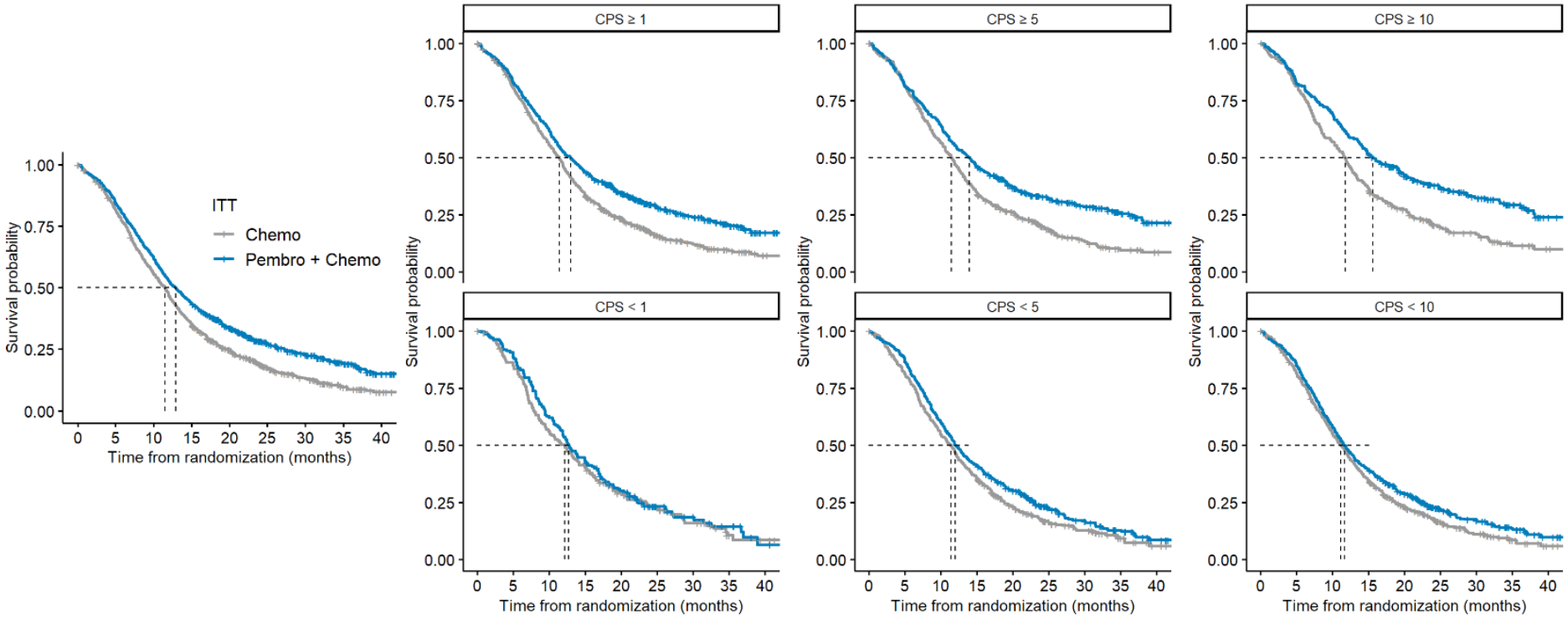
Efficacy by PD-L1 Expression in KEYNOTE-859

Like CM-649, KN-859 was not specifically designed to assess treatment effects in PD-L1 low populations; however, exploratory analyses in patients with PD-L1 low (e.g., CPS < 10) tumors did not demonstrate similar point estimates for the treatment effect as compared to patients with PD-L1 ≥10 tumors (Table 3, Figure 7, and Figure 8). FDA exploratory analyses at the CPS 5 cut-offs used raw CPS scores using the PD-L1 IHC 22C3 assay, with no analytic validation around the cut point of 5; therefore, there is notable uncertainty on the reproducibility and inferences that can be ascertained from this particular cut point, when using this assay.

Patients with PD-L1 CPS < 1, accounting for 22% of the total population, demonstrated a marginal and uncertain estimated improvement in OS (HR 0.92 [95% CI: 0.73, 1.17). Patients with PD-L1 CPS < 5 and < 10, derived marginally greater however still modest improvement in OS.

Consistent with the summary results of KN-859 above, the KM curves appear to show that the treatment effect appears to be attributable to patients with PD-L1 high tumors.

Figure 7: Kaplan-Meier estimates of Overall Survival in KEYNOTE-859 (FDA Analyses)



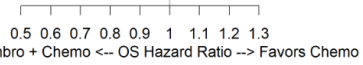
Abbreviations: CPS: Combined Positive Score; ITT: Intent to Treat

With respect to the analyses in the intermediate subgroups (CPS 1 to <5 and CPS 5 to <10), these findings appear to represent an outlier with respect to the more consistent findings of stepwise (estimated) improvement in efficacy observed with higher PD-L1 expression cutoffs. Such findings may represent the limitations of performing these post-hoc exploratory analyses around the CPS 5 cutoff point with the PD-L1 IHC 22C3 assay (or represent a chance finding) (Figure 8).

Overall, the findings of KN-859 demonstrate that the observed average treatment effect seen in patients with CPS ≥1, is primarily attributable to patients who are CPS ≥10, with greater uncertainty on the utility of CPS ≥5 being an acceptable cutoff with the assay used. Notably, patients in between the pre-specified cutoffs of CPS ≥1 and CPS ≥10, had a point estimate consistent with an intermediate effect. There was no evidence to suggest clear detriment in OS at any PD-L1 CPS threshold assessed.

Figure 8: Forest Plot of Overall Survival at PD-L1 cutoffs in KEYNOTE-859 (FDA Analyses)

		Pembro + Chemo	Chemo			Pembro + Chemo	Chemo
Subgroup	**% of Pts**	**Evt / N**	**Evt / N**	**HR (95% CI)**		**Median (95% CI)**	**Median (95% CI)**
Overall	**100**	**603/790**	**666/789**	**0.77 (0.69 ,0.86)**		**12.9 (11.9, 14)**	**11.5 (10.6, 12.1)**
CPS <1	22	139/172	140/172	0.92 (0.73 ,1.17)		12.7 (11.4, 15)	12.2 (9.5, 14)
CPS >=1	78	464/618	526/617	0.73 (0.65 ,0.83)		13 (11.6, 14.2)	11.4 (10.5, 12)
CPS <5	50	326/400	337/396	0.85 (0.73 ,0.98)		12 (11.1, 13.5)	11.4 (10, 12.2)
CPS >=5	50	277/390	329/393	0.7 (0.6 ,0.82)		14 (12.1, 15.4)	11.5 (10.3, 12.5)
CPS <10	65	415/511	440/517	0.86 (0.75 ,0.98)		11.7 (10.7, 12.8)	11.2 (10, 12.1)
CPS >=10	35	188/279	226/272	0.64 (0.52 ,0.77)		15.7 (13.8, 19.3)	11.8 (10.3, 12.7)
CPS 1-<5	29	187/228	197/224	0.78 (0.64 ,0.96)		11.5 (10.3, 13.3)	11 (9.7, 12)
CPS 5-<10	15	89/111	103/121	0.93 (0.7 ,1.24)		10.3 (8.2, 12.2)	10.7 (9.5, 13)
CPS 1-<10	43	276/339	300/345	0.83 (0.7 ,0.98)		11.1 (10.2, 12.2)	10.9 (9.9, 12)



Abbreviations: CPS: Combined Positive Score; Chemo: Chemotherapy; CI: Confidence Interval; HR: Hazard Ratio; Pembro: Pembrolizumab; OS: Overall Survival. Note: HRs were estimated by Cox proportional hazards models with treatment arm as the only covariate and Efron method handling ties.

RATIONALE-305

Pre-specified significance levels for OS analysis were met in patients with PD-L1 TAP ≥5 (55% of total population) at the planned interim analysis (data cutoff date October 8, 2021) and in all randomized patients at the planned final analysis (data cutoff date February 28, 2023). The final analysis data cutoff was used for the exploratory subgroup analyses conducted by the FDA. Secondary endpoints included PFS and ORR by investigator per RECIST v1.1, at PD-L1 TAP ≥ 5 and the ITT. Exploratory subgroup analyses of PFS and ORR are outlined in Appendix Figure 15 and Table 7.

Efficacy by PD-L1 Expression in RATIONALE-305

The study was not specifically designed to assess treatment effects in PD-L1 low populations; however, consistent with CM-649 and KN-859, FDA evaluated the overall survival benefits from the addition of

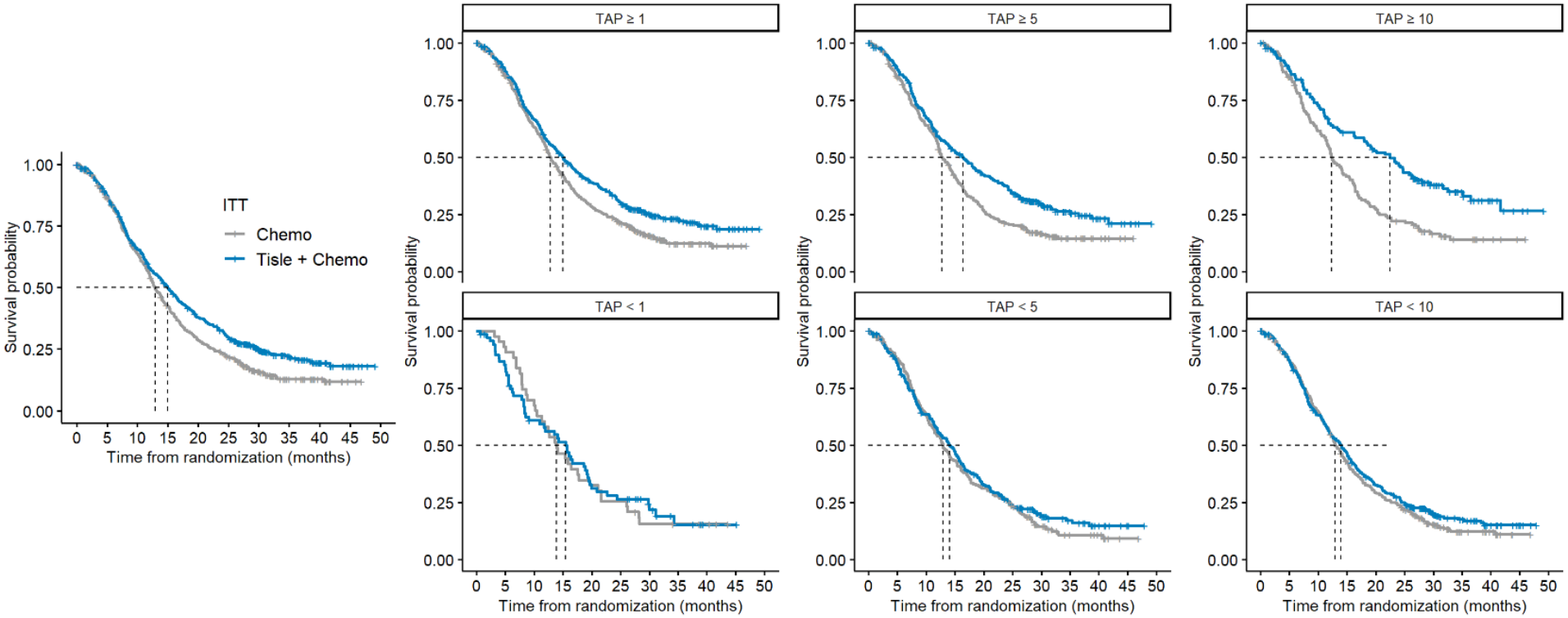
tislelizumab to chemotherapy at the same intermediate PD-L1 TAP values as was used for CM-649 an KN-859 (Figure 10).

A prominent difference with RN-305, compared to CM-649 and KN-859, is the use of VENTANA PD-L1 IHC SP264 CDx assay at a cutoff of TAP ≥5 to define the patient population that were 'positive' for PD-L1 expression. However, consistent with the findings from CM-649 and KN-859, the greatest magnitude of benefit is observed in patients with TAP ≥10 (HR 0.57 [95% CI: 0.43, 0.76). Patients who were defined in a post-hoc exploratory analyses with TAP <1, accounting for 11% of the total population, had crossing of the Kaplan-Meier curves with the point estimate for the OS HR demonstrating no benefit from the addition of tislelizumab to chemotherapy in this patient population. Patients with TAP <5 and <10, had identical point estimates for OS HR, suggesting a marginal to no benefit in terms of OS in this patient population.

The point estimates (in FDA's exploratory analysis) for patients with TAP ≥1 to <10 (61% of total population) demonstrated a marginal and uncertain benefit in terms of OS, especially when compared to the magnitude observed in patients with TAP ≥10 (Figure 10 below).

Although limited by lack of pre-specification and different scoring algorithm (i.e., TAP) to define the patient population within this study, the finding of improved efficacy with higher TAP scores is consistent with the studies using CPS. Another consistent finding is that average treatment effect seen in patients with TAP ≥1 and TAP ≥5 appears attributable to patients with TAP ≥10. There is no evidence to suggest any benefit in terms of OS for patients with TAP <1, and the benefit for patients with TAP ≥1 and <10, if present, is modest.

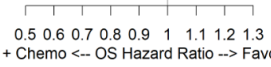
Figure 9: Kaplan-Meier estimates of Overall Survival in RATIONALE-305 (FDA Analyses)



Abbreviations: TAP: Tumor Area Positivity; ITT: Intent to Treat

Figure 10: Forest Plot of Overall Survival at PD-L1 cutoffs in RATIONALE-305 (FDA Analyses)

Subgroup	% of Pts	Tisle + Chemo Evt / N	Chemo Evt / N	HR (95% CI)	Tisle + Chemo Median (95% CI)	Chemo Median (95% CI)
Overall	**100**	**370/501**	**406/496**	**0.8 (0.69 ,0.92)**	**15 (13.6, 16.5)**	**12.9 (12.1, 14.1)**
TAP <1	11	52/69	36/43	0.98 (0.64 ,1.5)	15.4 (8.4, 19.2)	13.8 (10.2, 17.8)
TAP >=1	89	318/432	370/453	0.78 (0.67 ,0.91)	15 (13.3, 16.7)	12.8 (12.1, 14.1)
TAP <5	45	178/227	187/224	0.91 (0.74 ,1.12)	14.1 (11.9, 15.6)	12.9 (11.3, 14.7)
TAP >=5	55	192/274	219/272	0.72 (0.59 ,0.88)	16.4 (13.6, 19.1)	12.8 (12, 14.5)
TAP <10	72	286/365	288/351	0.91 (0.77 ,1.07)	14 (12, 15.3)	13 (12.1, 14.3)
TAP >=10	28	84/136	118/145	0.57 (0.43 ,0.76)	22.5 (16.4, 26.4)	12.3 (11.3, 14.9)
TAP 1-<5	34	126/158	151/181	0.9 (0.71 ,1.14)	13.8 (11.5, 15.6)	12.9 (10.8, 14.7)
TAP 5-<10	27	108/138	101/127	0.91 (0.7 ,1.2)	13.8 (10.8, 16.2)	13.3 (12, 15)
TAP 1-<10	61	234/296	252/308	0.9 (0.76 ,1.08)	13.8 (11.9, 15)	12.9 (11.9, 14.3)



Abbreviations: TAP: Tumor Area Positivity; Chemo: Chemotherapy; CI: Confidence Interval; HR: Hazard Ratio; Tisle: Tislelizumab; OS: Overall Survival. Note: HRs were estimated by Cox proportional hazards models with treatment arm as the only covariate and Efron method handling ties.

Pooled Analyses

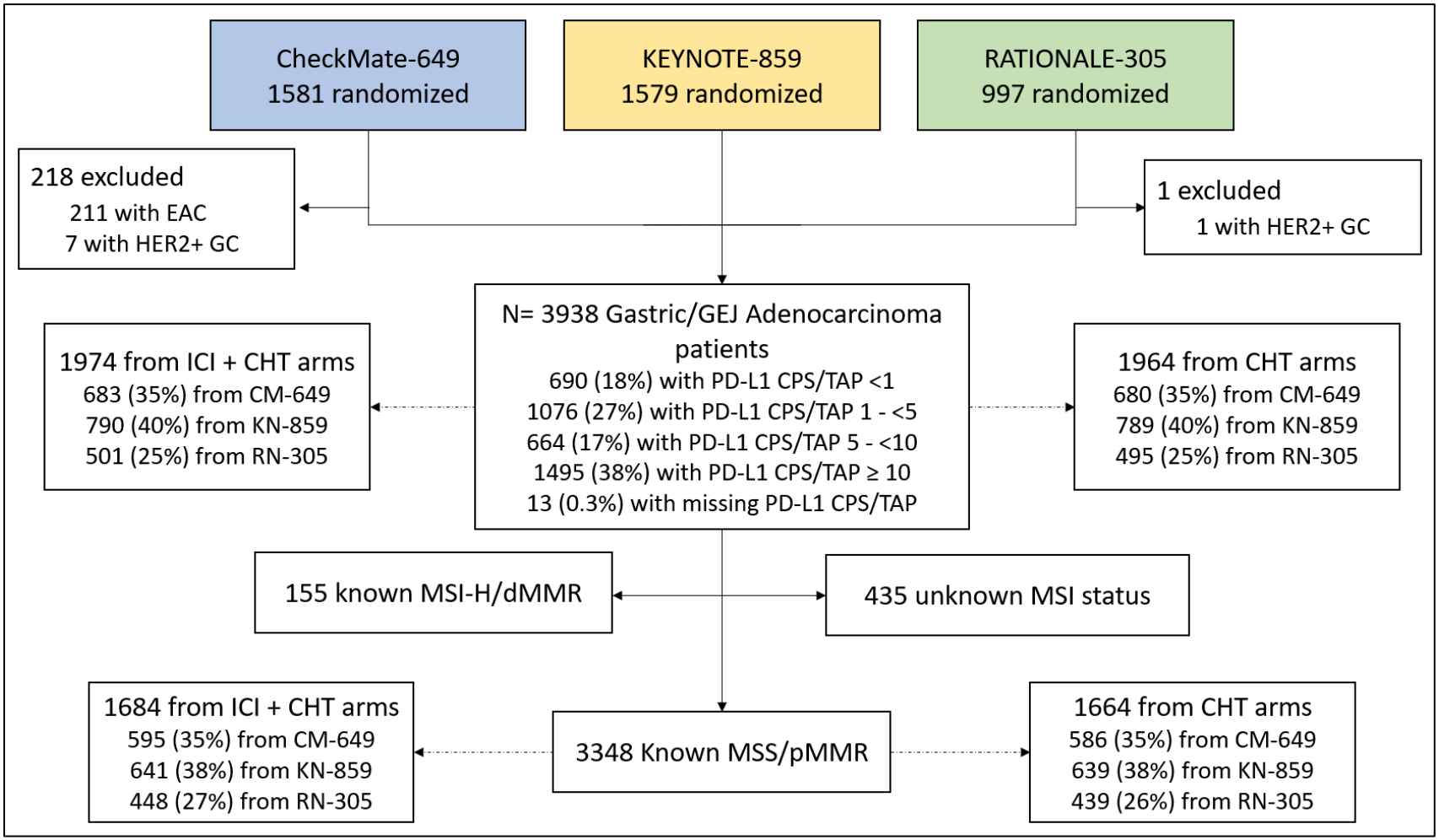
In addition to the analyses summarized above, FDA conducted exploratory pooled analyses, acknowledging that patients were included using different assays and scoring algorithms in terms of PD-L1 expression. Although there have been attempts to cross validate scoring algorithms, the acceptability of doing so has not been determined (Klempner et al. 2024; Yeong et al. 2022; Yoon et al. 2022; Ahn and Kim 2021). Another major caveat to these analyses is that this is limited to the global studies that were submitted to FDA for review and does not include data from other published studies either positive or negative, which may introduce bias. However, in the context of published meta-analyses that demonstrate PD-L1 expression to be a predictive biomarker in this patient population (Yoon et al. 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 gastric cancer.

<u>Patient Population included in Primary Analysis</u>

All three studies included patients who are mismatch repair deficient (dMMR) or microsatellite instability high (MSI-H). The efficacy of ICI in this patient population is well established and over the course of the conduct of the pivotal studies discussed in this ODAC, the first US FDA approval agnostic of cancer site was in this patient population (Lemery, Keegan, and Pazdur 2017). To provide the most pertinent data for discussion, the primary population for the pooled analysis was limited to patients with microsatellite stable (MSS) tumors, excluding patients who are either MSI-H or have not had their mismatch repair status determined. Similarly, FDA excluded patients with esophageal adenocarcinoma

from the primary analysis. Sensitivity analyses including all populations were conducted and are available in the Appendix Figure 16. The primary population included in the pooled analyses is outlined in Figure 11. The hazard ratios were estimated by Cox proportional hazards models stratified by each study with treatment arm as the only covariate and Efron method handling ties.

Figure 11: Consort Diagram of Patients included in Pooled Analyses

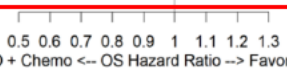


Abbreviations: CHT: Chemotherapy; CPS: Combined Positive Score; dMMR: Deficient Mismatch Repair; GC: Gastric Cancer; HER2: Human Epidermal Growth Factor-2; ICI: Immune Checkpoint Inhibitor; MSS: Microsatellite Stable; MSI-H: Microsatellite instability High; PD-L1: Programmed Death Ligand -1; pMMR: Proficient Mismatch Repair.

Acknowledging the caveats when interpreting the OS benefits of adding ICIs to chemotherapy at 'PD-L1 expression levels' in first line MSS gastric/GEJ adenocarcinoma that are outlined in Figure 12, there is a consistent theme on the greatest magnitude of benefit being in patients with PD-L1 expression ≥ 10, and that there is an incremental improvement at each higher PD-L1 cutoff that is analyzed. Similarly, the efficacy in patients with PD-L1 expression <1 or <10 is modest (and uncertain). Evaluating the efficacy in patient populations ≥1 to <5 and ≥5 to <10 is challenging given the variability in analytic techniques used and assigning patients to a particular PD-L1 stratum. As stated above this may represent the broader caveats when analyzing this pooled patient population or the caveats with respect to PD-L1 assignment at or below 5 described above for KN-859.

Figure 12: Forest Plot for Overall Survival in Pooled MSS/pMMR Patient population (FDA Analyses)

Subgroup	% of Pts	IO + Chemo Evt / N	Chemo Evt / N	HR (95% CI)	IO + Chemo Median (95% CI)	Chemo Median (95% CI)
Overall	**100**	**1246/1684**	**1340/1664**	**0.8 (0.74 ,0.87)**	**13.8 (12.9, 14.4)**	**12 (11.4, 12.5)**
PDL1 <1	17	233/306	218/274	0.91 (0.75 ,1.09)	13.4 (11.5, 15)	12.4 (10.6, 13.2)
PDL1 >=1	83	1011/1376	1120/1387	0.78 (0.71 ,0.85)	13.8 (12.9, 14.6)	12 (11.4, 12.5)
PDL1 <5	45	597/752	610/740	0.89 (0.8 ,1)	12.6 (11.6, 13.7)	11.9 (11, 12.6)
PDL1 >=5	55	647/930	728/921	0.73 (0.66 ,0.82)	14.6 (13.8, 16.2)	12.1 (11.3, 12.6)
PDL1 <10	62	834/1049	827/1014	0.92 (0.84 ,1.01)	12.4 (11.5, 13.1)	12.3 (11.6, 12.8)
PDL1 >=10	38	410/633	511/647	0.64 (0.56 ,0.73)	16.5 (14.9, 18.3)	11.5 (10.7, 12.3)
PDL1 1-<5	27	364/446	392/466	0.88 (0.76 ,1.02)	12.2 (11.1, 13.6)	11.8 (10.8, 12.6)
PDL1 5-<10	17	237/297	217/274	1.01 (0.84 ,1.22)	11.7 (10.4, 13)	13 (12.1, 14)
PDL1 1-<10	44	601/743	609/740	0.93 (0.83 ,1.04)	12 (11.1, 12.9)	12.3 (11.4, 12.9)



Abbreviations: Chemo: Chemotherapy; IO: Immunotherapy; HR: Hazard Ratio; OS: Overall Survival. Note: HRs were estimated by Cox proportional hazards models stratified by study, with treatment arm as the only covariate, and Efron method handling ties.

The three pivotal studies, which have predominantly evaluated the addition of ICI to chemotherapy in HER2 negative Ga/GEJ adenocarcinoma have shown a statistically significant improvement in overall survival in the ITT populations.

Although not defined consistently across studies, most of the benefit seems to be derived from patients who have PD-L1 expression levels ≥ 10 (either CPS or TAP). Patients with PD-L1 <1 have marginal evidence of benefit if at all, but no evidence to suggest worsened survival. The patients who are within the 1 to 10 threshold pose a challenging therapeutic and regulatory decision, given the variability of testing (and patient populations) and given that the data are not proportionally better at increasing PD-L1 levels.

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 is consistency of treatment effect across the study subgroups. However, there are examples of restriction to a subgroup of patients despite positive study results in the entire study population. Such an approach was taken retrospectively based on cumulating data for EGFR inhibitors in colorectal cancer and PARP inhibitors in prostate cancer.

The current US FDA approvals of ICIs in combination with chemotherapy for the first line treatment of Ga/GEJ adenocarcinoma 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 et al. 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 PD-L1 <1 does not appear to result in benefit. Benefit for patients with PD-L1 ≥10 have the greatest magnitude of benefit. Benefit is unclear in patients with PD-L1 levels less than 10 across the class; however, data interpretation is challenging. If patients with low or no PD-L1 expression are not expected to benefit based on the available data, then administering anti-PD1 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.

In this document, FDA provided the prespecified and exploratory 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 that the efficacy observed across patient populations defined at different PD-L1 thresholds is modest, and these patients are exposed to the incremental added toxicity of ICI, 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 or PD-L1 ≥10 for Ga/GEJ adenocarcinoma).

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 Ga/GEJ adenocarcinoma in the United States and in the conduct of future trials to improve outcomes of patients with gastric/GEJ adenocarcinoma. Alternatively, one could amend labeling using the totality of data to select a single cut-off, acknowledging differences in available PD-L1 tests.

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5 Appendix

Table 4: Country/Region of Enrollment by Study

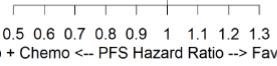
	CheckMate-649		KEYNOTE - 859		RATIONALE-305	
	N = 1581		N = 1579		N = 997	
Country	**N**	**%Total**	**N**	**% Total**	**N**	**% Total**
China	208	13	236	15	516	52
Japan	109	7	101	6	101	10
South Korea	8	0.5	150	9	131	13
Taiwan	6	0.4	23	1		
Europe	419	27	616	39	224	23
USA	203	13	33	2	25	3
Rest of World	628	40	420	27		

Additional Efficacy Results

The Figures and Tables below outline additional efficacy data (FDA exploratory analyses) from CM-649, KN-859, and RN-305 including data on PFS and objective response rate (ORR) submitted in the sBLA supporting the approval in this indication. The subgroup analysis populations of PFS and ORR are consistent with the OS subgroup analyses of each study. It is noted that PFS and ORR in CM-649 and KN-859 were assessed by BICR while they were assessed by investigators in RN-305.

Figure 13: Forest Plot of Progression-Free Survival at PD-L1 cutoffs in CheckMate-649 (FDA Analyses)

		Nivo + Chemo	Chemo		Nivo + Chemo	Chemo
Subgroup	**% of Pts**	**Evt / N**	**Evt / N**	**HR (95% CI)**	**Median (95% CI)**	**Median (95% CI)**
Overall	**100**	**559/789**	**557/792**	**0.77 (0.68 ,0.87)**	**7.7 (7.1, 8.5)**	**6.9 (6.6, 7.1)**
CPS <1	17	99/140	77/125	0.93 (0.69 ,1.26)	8.7 (6.9, 9.7)	8.1 (6.9, 9.8)
CPS >=1	82	454/641	472/655	0.75 (0.65 ,0.85)	7.5 (7, 8.4)	6.9 (6.1, 7)
CPS <5	38	225/308	199/298	0.93 (0.77 ,1.12)	7.5 (7, 8.7)	8.1 (7.1, 8.7)
CPS >=5	60	328/473	350/482	0.69 (0.59 ,0.8)	7.7 (7, 9.2)	6 (5.6, 6.9)
CPS <10	50	301/406	260/387	0.91 (0.77 ,1.08)	7.5 (7, 8.4)	7.7 (7, 8.3)
CPS >=10	49	252/375	289/393	0.65 (0.55 ,0.77)	8.3 (7, 9.7)	5.8 (5.5, 6.9)
CPS 1-<5	22	126/168	122/173	0.93 (0.73 ,1.2)	7.2 (6.8, 8.4)	8.1 (7, 9.1)
CPS 5-<10	12	76/98	61/89	0.88 (0.63 ,1.24)	7.5 (6.5, 9.6)	6.5 (5.6, 8.3)
CPS 1-<10	33	202/266	183/262	0.91 (0.74 ,1.11)	7.3 (6.9, 8.3)	7.2 (6.9, 8.3)



Abbreviations: Chemo: Chemotherapy; HR: Hazard Ratio; Nivo: Nivolumab; PFS: Progression free survival; Note: HRs were estimated by Cox proportional hazards models with treatment arm as the only covariate and Efron method handling ties.

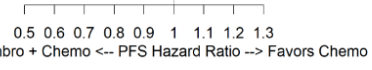
Table 5: Objective Response Rate at PD-L1 cutoffs in CheckMate-649 (FDA Analyses)

	Nivo + Chemo			Chemo		
	n/N	ORR (95% CI)	Median DoR (95% CI)	n/N	ORR (95% CI)	Median DoR (95% CI)
Overall	370/789	46.9 (43.4, 50.4)	8.5 (7.2, 9.9)	293/792	37 (33.6, 40.5)	6.9 (5.8, 7.2)
CPS <1	53/140	37.9 (29.8, 46.4)	7 (5.7, 11.8)	38/125	30.4 (22.5, 39.3)	7.1 (5.5, 10.9)
CPS >=1	314/641	49 (45.1, 52.9)	8.5 (7.7, 10.3)	249/655	38 (34.3, 41.9)	6.9 (5.8, 7.6)
CPS <5	130/308	42.2 (36.6, 47.9)	7.7 (6.3, 8.6)	103/298	34.6 (29.2, 40.3)	7 (5.7, 8.3)
CPS >=5	237/473	50.1 (45.5, 54.7)	9.5 (8.1, 11.9)	184/482	38.2 (33.8, 42.7)	6.9 (5.6, 7.9)
CPS <10	186/406	45.8 (40.9, 50.8)	7.7 (6.6, 8.5)	140/387	36.2 (31.4, 41.2)	6.9 (5.7, 7.8)
CPS >=10	181/375	48.3 (43.1, 53.5)	9.9 (8.2, 12.5)	**147/393**	37.4 (32.6, 42.4)	7 (5.7, 8.3)
CPS 1-<5	77/168	45.8 (38.1, 53.7)	7.7 (6.2, 10.3)	65/173	37.6 (30.3, 45.2)	6.8 (5.6, 8.3)
CPS 5-<10	56/98	57.1 (46.7, 67.1)	8.3 (5.6, 10.2)	37/89	41.6 (31.2, 52.5)	5.4 (4.5, 8.3)
CPS 1-<10	133/266	50 (43.8, 56.2)	7.9 (6.6, 8.6)	102/262	38.9 (33, 45.1)	6.8 (5.5, 7.6)

Abbreviations: Chemo: Chemotherapy DoR: Duration of Response; Nivo: Nivolumab; ORR: Objective Response Rate;

Figure 14: Forest Plot of Progression-Free Survival at PD-L1 cutoffs in KEYNOTE-859 (FDA Analyses)

		Pembro + Chemo	Chemo		Pembro + Chemo	Chemo
Subgroup	% of Pts	Evt / N	Evt / N	HR (95% CI)	Median (95% CI)	Median (95% CI)
Overall	**100**	**572/790**	**608/789**	**0.76 (0.67 ,0.85)**	**6.9 (6.3, 7.2)**	**5.6 (5.5, 5.7)**
CPS <1	22	129/172	125/172	0.9 (0.7 ,1.15)	7.2 (6, 8.5)	5.8 (5.4, 6.9)
CPS >=1	78	443/618	483/617	0.72 (0.63 ,0.82)	6.9 (6, 7.2)	5.6 (5.4, 5.7)
CPS <5	50	302/400	304/396	0.83 (0.71 ,0.98)	6.9 (5.8, 7.2)	5.6 (5.5, 5.8)
CPS >=5	50	270/390	304/393	0.69 (0.59 ,0.82)	7.1 (6.1, 8.3)	5.6 (5.4, 5.9)
CPS <10	65	382/511	398/517	0.85 (0.74 ,0.98)	6.8 (5.7, 7.1)	5.6 (5.5, 5.8)
CPS >=10	35	190/279	210/272	0.62 (0.51 ,0.76)	8.1 (6.8, 8.5)	5.6 (5.4, 6.7)
CPS 1-<5	29	173/228	179/224	0.79 (0.64 ,0.97)	6.7 (5.6, 7.1)	5.6 (5.2, 5.7)
CPS 5-<10	15	80/111	94/121	0.92 (0.68 ,1.24)	5.7 (4.3, 7.3)	5.6 (4.6, 6.9)
CPS 1-<10	43	253/339	273/345	0.83 (0.7 ,0.98)	5.8 (5.6, 7)	5.6 (5.3, 5.7)



Abbreviations: Chemo: Chemotherapy; HR: Hazard Ratio; Pembro: Pembrolizumab; PFS: Progression free survival. Note: HRs were estimated by Cox proportional hazards models with treatment arm as the only covariate and Efron method handling ties.

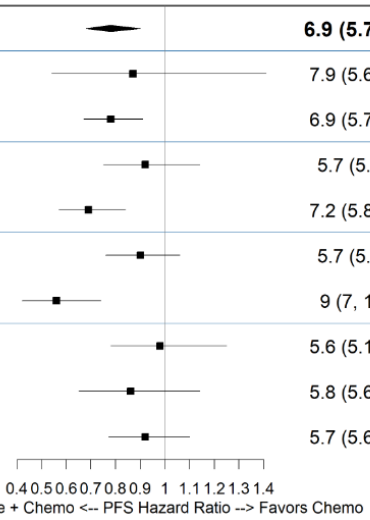
Table 6: Objective Response Rate at PD-L1 cutoffs in KEYNOTE-859 (FDA Analyses)

	Pembro + Chemo			Chemo		
	n/N	**ORR (95% CI)**	**Median DoR (95% CI)**	**n/N**	**ORR (95% CI)**	**Median DoR (95% CI)**
Overall	405/790	51.3 (47.7, 54.8)	8 (7, 9.7)	331/789	42 (38.5, 45.5)	5.7 (5.5, 6.9)
CPS <1	83/172	48.3 (40.6, 56)	7 (5.8, 8.6)	68/172	39.5 (32.2, 47.3)	5.7 (4.9, 8.4)
CPS >=1	322/618	52.1 (48.1, 56.1)	8.3 (7, 10.9)	263/617	42.6 (38.7, 46.6)	5.6 (5.4, 6.9)
CPS <5	191/400	47.8 (42.8, 52.8)	6.8 (5.7, 8.2)	157/396	39.6 (34.8, 44.7)	5.7 (5.2, 6.9)
CPS >=5	214/390	54.9 (49.8, 59.9)	9.8 (7.8, 13.1)	174/393	44.3 (39.3, 49.3)	5.7 (5.4, 6.9)
CPS <10	236/511	46.2 (41.8, 50.6)	6.9 (5.7, 8.2)	214/517	41.4 (37.1, 45.8)	5.6 (5.4, 6.9)
CPS >=10	169/279	60.6 (54.6, 66.3)	10.9 (8, 13.8)	117/272	43 (37.1, 49.1)	5.8 (5.3, 7)
CPS 1-<5	108/228	47.4 (40.7, 54.1)	5.7 (5.5, 8.4)	89/224	39.7 (33.3, 46.5)	5.6 (4.3, 6.9)
CPS 5-<10	45/111	40.5 (31.3, 50.3)	8 (4.9, 13.1)	57/121	47.1 (38, 56.4)	5.5 (4.3, 8.2)
CPS 1-<10	153/339	45.1 (39.8, 50.6)	6.3 (5.6, 8.4)	146/345	42.3 (37, 47.7)	5.6 (4.4, 6.9)

Abbreviations: Chemo: Chemotherapy DoR: Duration of Response; ORR: Objective Response Rate; Pembro: Pembrolizumab

Figure 15: Forest Plot of Progression-Free Survival at PD-L1 cutoffs in RATIONALE-305 (Analyses)

Subgroup	% of Pts	Tisle + Chemo Evt / N	Chemo Evt / N	HR (95% CI)	Tisle + Chemo Median (95% CI)	Chemo Median (95% CI)
Overall	**100**	**361/501**	**391/496**	**0.78 (0.68 ,0.9)**	**6.9 (5.7, 7.2)**	**6.2 (5.6, 6.9)**
TAP <1	11	45/69	27/43	0.87 (0.54 ,1.41)	7.9 (5.6, 9.7)	6.9 (5.6, 15)
TAP >=1	89	316/432	364/453	0.78 (0.67 ,0.91)	6.9 (5.7, 7.2)	5.9 (5.6, 6.9)
TAP <5	45	172/227	175/224	0.92 (0.75 ,1.14)	5.7 (5.6, 7)	6.5 (5.5, 7.1)
TAP >=5	55	189/274	216/272	0.69 (0.57 ,0.84)	7.2 (5.8, 8.4)	5.9 (5.6, 7)
TAP <10	72	273/365	272/351	0.9 (0.76 ,1.06)	5.7 (5.6, 7)	6.9 (5.7, 7.1)
TAP >=10	28	88/136	119/145	0.56 (0.42 ,0.74)	9 (7, 12.1)	5.7 (4.5, 6.9)
TAP 1-<5	34	127/158	148/181	0.98 (0.78 ,1.25)	5.6 (5.1, 6.9)	6.2 (5.5, 7.1)
TAP 5-<10	27	101/138	97/127	0.86 (0.65 ,1.14)	5.8 (5.6, 7.7)	6.9 (5.7, 8.3)
TAP 1-<10	61	228/296	245/308	0.92 (0.77 ,1.1)	5.7 (5.6, 6.9)	6.8 (5.6, 7.1)



Abbreviations: Chemo: Chemotherapy; HR: Hazard Ratio; PFS: Progression free survival; TAP: Tumor Area Positivity; Tisle: Tislelizumab. Note: HRs were estimated by Cox proportional hazards models with treatment arm as the only covariate and Efron method handling ties.

Table 7: Objective Response Rate at PD-L1 cutoffs in RATIONALE-305 (FDA Analyses)

	Tisle + Chemo			Chemo		
	n/N	**ORR (95% CI)**	**Median DoR (95% CI)**	**n/N**	**ORR (95% CI)**	**Median DoR (95% CI)**
Overall	237/501	47.3 (42.9, 51.8)	8.6 (7.9, 11.1)	201/496	40.5 (36.2, 45)	7.2 (6, 8.5)
TAP <1	31/69	44.9 (32.9, 57.4)	11.8 (4.3, NA)	15/43	34.9 (21, 50.9)	18 (2.8, NA)
TAP >=1	206/432	47.7 (42.9, 52.5)	8.6 (7.8, 10.4)	186/453	41.1 (36.5, 45.7)	7.2 (5.8, 8.3)
TAP <5	96/227	42.3 (35.8, 49)	7.1 (5.5, 9.7)	85/224	37.9 (31.6, 44.7)	8 (5.7, 11.6)
TAP >=5	141/274	51.5 (45.4, 57.5)	10 (8.2, 16.8)	116/272	42.6 (36.7, 48.8)	6.9 (5.7, 8.5)
TAP <10	164/365	44.9 (39.8, 50.2)	7.8 (5.9, 9.7)	143/351	40.7 (35.6, 46.1)	7.2 (5.8, 9.3)
TAP >=10	73/136	53.7 (44.9, 62.3)	16.8 (8.4, 24.1)	58/145	40 (32, 48.5)	7.2 (5.4, 9.8)
TAP 1-<5	65/158	41.1 (33.4, 49.2)	6.8 (4.8, 9.5)	70/181	38.7 (31.5, 46.2)	7.2 (5.6, 10.5)
TAP 5-<10	68/138	49.3 (40.7, 57.9)	8.2 (5.8, 10.4)	58/127	45.7 (36.8, 54.7)	6.9 (5.6, 9.3)
TAP 1-<10	133/296	44.9 (39.2, 50.8)	7.5 (5.8, 9)	128/308	41.6 (36, 47.3)	7.1 (5.7, 8.4)

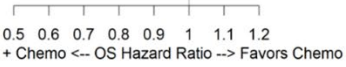
Abbreviations: Chemo: Chemotherapy DoR: Duration of Response; ORR: Objective Response Rate; TAP: Tumor Area Positivity: TIsle: Tislelizumab

Pooled Sensitivity Analyses

The primary FDA pooled analyses excluded patients with MSI-H/dMMR tumors and unknown MSI status from the pooled HER2- gastric/GEJ adenocarcinoma patient population. The sensitivity analyses where these patients were included are outlined in Appendix Figure 16. Although there are differences in the point estimates at each of the exploratory subgroups evaluated, in general the observations are consistent with the findings demonstrated in the primary analyses outlined in Figure 12.

Figure 16 Forest Plot for Overall Survival in Pooled Overall Patient population (FDA Analyses)

		IO + Chemo	Chemo		IO + Chemo	Chemo
Subgroup	**% of Pts**	**Evt / N**	**Evt / N**	**HR (95% CI)**	**Median (95% CI)**	**Median (95% CI)**
Overall	**100**	**1444/1974**	**1582/1964**	**0.78 (0.73 ,0.84)**	**13.8 (13, 14.4)**	**11.9 (11.4, 12.4)**
PDL1 <1	18	277/363	258/327	0.92 (0.78 ,1.09)	13.6 (11.9, 15)	12.5 (10.8, 13.6)
PDL1 >=1	82	1161/1605	1319/1630	0.76 (0.7 ,0.82)	13.8 (12.9, 14.6)	11.9 (11.3, 12.3)
PDL1 <5	45	697/890	716/876	0.89 (0.8 ,0.99)	12.7 (11.8, 13.7)	12 (11.4, 12.8)
PDL1 >=5	55	741/1078	861/1081	0.7 (0.64 ,0.78)	14.6 (13.8, 16)	11.9 (11.1, 12.5)
PDL1 <10	62	966/1229	978/1201	0.9 (0.82 ,0.99)	12.4 (11.7, 13.1)	12.2 (11.6, 12.8)
PDL1 >=10	38	472/739	599/756	0.62 (0.55 ,0.7)	16.4 (14.8, 18.3)	11.5 (10.7, 12.2)
PDL1 1-<5	27	420/527	458/549	0.87 (0.76 ,1)	12.1 (11.1, 13.4)	11.8 (11, 12.8)
PDL1 5-<10	17	269/339	262/325	0.94 (0.79 ,1.12)	11.8 (10.7, 13.1)	12.6 (11.1, 13.4)
PDL1 1-<10	44	689/866	720/874	0.9 (0.81 ,1)	12 (11.3, 12.9)	12 (11.4, 12.8)



Abbreviations: Chemo: Chemotherapy; HR: Hazard Ratio; IO: Immunotherapy; OS: Overall Survival: PDL1: Programmed Death Ligand 1; Note: HRs were estimated by Cox proportional hazards models stratified by study, with treatment arm as the only covariate, and Efron method handling ties.

MSI-H

The pooled patient efficacy data of patients with MSI-H Ga/GEJ adenocarcinoma appears to show that the use of ICI is highly efficacious in this patient population (Table 8).

Table 8: Overall Survival in Pooled MSI-H/dMMR Patient Population (FDA Analyses)

Subgroup	IO + Chemo		Chemo		OS HR (95% CI)
	Event / N	Median (95% CI)	Event / N	Median (95% CI)	
MSI-H	32/77	37.1 (24.7, NA)	57/78	12.5 (8.3, 16.6)	0.42 (0.27, 0.66)

Abbreviations: Chemo: Chemotherapy; MSI-H: Microsatellite instability-high; IO: Immunotherapy; OS: Overall Survival