SPONSOR BRIEFING DOCUMENT
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OPDIVO® (nivolumab)
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Meeting Date: 26-Sep-2024

OPDIVO (nivolumab), in combination with fluoropyrimidine- and platinum-containing chemotherapy, for first-line treatment of adult patients with advanced or metastatic gastric cancer, gastroesophageal junction cancer, and esophageal adenocarcinoma.

ADVISORY COMMITTEE BRIEFING MATERIALS AVAILABLE FOR PUBLIC RELEASE

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LIST OF ABBREVIATIONS

Abbreviation	Term
1L	First line
5-FU	5-fluorouracil
AC	Adenocarcinoma
AE	Adverse event
BICR	Blinded independent central reviewer
BMS	Bristol-Myers Squibb
CI	Confidence interval
Chemo	Chemotherapy
CPS	Combined positive score
DBL	Database lock
DC	Discontinue/discontinuation
dMMR	Mismatch repair deficient
DOR	Duration of response
EAC	Esophageal adenocarcinoma
EBV	Epstein-Barr virus
EC	Esophageal cancer
ECOG	Eastern Cooperative Oncology Group
ESCC	Esophageal squamous cell carcinoma
FDA	Food and Drug Administration
FOLFOX	Leucovorin plus oxaliplatin plus 5-fluorouracil
GEJC	Gastroesophageal junction cancer
GES	Gene expression signature
HCP	Health care provider
HR	Hazard ratio
ICC	Intraclass correlation
ICI	Immune checkpoint inhibitor
IHC	Immunohistochemistry
IMAE	Immune-mediated adverse event
IO	Immuno-oncology
Ipi	Ipilimumab
ITT	Intent to Treat
IV	Intravenous
HCP	Healthcare provider
MSI-H	Microsatellite instability-high
NCCN	National Comprehensive Care Network
Nivo	Nivolumab
ODAC	Oncologic Drugs Advisory Committee
OESI	Other events of special interest
ORR	Objective response rate
OS	Overall survival

PD-1	Programmed death protein 1
PD-L1	Programmed death ligand 1
PFS	Progression-free survival
PRO	Patient reported outcomes
PS	Performance score
QxW	Every x weeks
ROW	Rest of world
SAE	Serious adverse event
TAP	Tumor Area Positivity
TC	Tumor cell
Tisle	Tislelizumab
TMB	Tumor mutation burden
TMB-H	Tumor mutation burden-high
TPS	Tumor proportion score
US/USA	United States of America
USPI	United States Prescribing Information
XELOX	Oxaliplatin plus capecitabine

1 EXECUTIVE SUMMARY

This session of the 26-Sep-2024 ODAC meeting is being convened to discuss the emerging benefit-risk analysis on use of ICIs as a class, including nivolumab, focusing on the treatment of advanced gastroesophageal adenocarcinoma by PD-L1 expression levels.

1.1 CURRENT INDICATION AND REGULATORY HISTORY - FIRST-LINE GC/GEJC/EAC (GASTROESOPHAGEAL ADENOCARCINOMA)

On 16-Apr-2021, nivolumab (a PD-1 immune checkpoint inhibitor) was approved by the FDA for the below indication in GC/GEJC/EAC (without restriction by PD-L1 expression level) based on the totality of data from the primary analysis of the pivotal CHECKMATE-649 study[1]:

Indication (nivolumab [OPDIVO®])	Dosing
Treatment of adult patients with advanced or metastatic gastric cancer, gastroesophageal junction cancer, and esophageal adenocarcinoma in combination with fluoropyrimidine- and platinum-containing chemotherapy.	• 360 mg every 3 weeks with fluoropyrimidine- and platinum-containing chemotherapy every 3 weeks • 240 mg every 2 weeks with fluoropyrimidine- and platinum-containing chemotherapy every 2 weeks

CHECKMATE-649 demonstrated a statistically significant and clinically meaningful OS benefit with nivolumab in combination with chemotherapy (hereafter nivo+chemo) in the primary population of patients with PD-L1 CPS ≥ 5 and in the formally tested secondary populations of patients with PD-L1 CPS ≥ 1 and all randomized patients with GC/GEJC/EAC. Although across PD-L1 CPS subgroups higher likelihood of benefit was seen at or above the cutoffs of 1, 5, and 10 compared to below, overall, the results supported a positive benefit-risk assessment for the approved indication. Information on PD-L1 subgroups (including exploratory subgroups of PD-L1 CPS < 5 and < 1) is included in the Clinical Studies Section (14.13) of the USPI to adequately inform treatment decisions by prescribers.

Since the approval of nivo+chemo in first-line GC/GEJC/EAC, results of long-term (4 -year) follow-up for CHECKMATE-649 have become available, showing consistency with the results of the primary analysis. Additional first-line ICI combination studies in gastroesophageal adenocarcinoma have increased the body of data on tumor PD-L1 expression and its potential relationship with ICI efficacy. However, it is important to note that individual studies have used different methods to assess PD-L1 expression levels.

The available data have led to the question of whether first-line gastroesophageal adenocarcinoma patients should be selected for ICI combination treatment based on PD-L1 expression status and whether harmonization is possible and feasible.

Therefore, the purpose of this briefing document is to:

1) discuss the present-day treatment landscape in first-line gastroesophageal adenocarcinoma

2) describe the available clinical data by PD-L1 CPS subgroups for nivo+chemo from the primary analysis and long-term follow-up analyses from CHECKMATE-649

3) review PD-L1 testing and treatment patterns, as well as challenges of PD-L1 testing, in current clinical practice

4) discuss the advantages and disadvantages of two potential options for harmonization, developed by the Sponsor for consideration at this ODAC meeting:

- **Option 1**: Maintain the current unrestricted indication with inclusion of PD-L1 subgroup data in the label highlighting the efficacy based on PD-L1 expression, as is presently the case.
- **Option 2**: In the event of a class label change, modify the indication to PD-L1 positive patients using the most appropriate threshold, which the Sponsor would propose to be CPS ≥ 1.

The clinical data from CHECKMATE-649, as well as from other ICI+chemo studies, show enriched survival benefit of the combination vs chemo alone by PD-L1 expression level (Section 1.2.1). To reserve treatment for those most likely to benefit and allow for potential harmonization across the ICI class, one option would be to modify the indication to PD-L1 positive patients using the most appropriate threshold (which the Sponsor considers would be CPS ≥ 1; see Sections 1.6 and 2.6). However, this approach would leave some potential responders untreated due to practical considerations. The lack of PD--L1 testing or inconclusive test results in some patients (due to tumor tissue inadequacy/poor quality), as well as the complexity around PD--L1 CPS scoring (Section 2.5), support keeping the flexibility of the current PD-L1 unrestricted indication and leaving the clinical decision-making in the hands of the treating physician, as is the case today. Flexibility is especially important when making treatment decisions in the first-line setting since many patients do not go on to receive later line therapy and, when they do, their choices are limited.

1.1.1 PD-L1 Scoring Methods

At present, two main scoring methods, TPS and CPS, are used to assess PD-L1 expression in tumor samples.[2] CPS is presently the most commonly utilized PD-L1 scoring method in the US for upper GI cancers.[3]

- TPS (also referred to as Percent Tumor Cell, %TC) evaluates the percentage of viable tumor cells showing partial or complete membrane staining at any intensity and is expressed as a percentage on a scale of 0-100%. While TPS and %TC differ in name based on 22C3 pharmDx assay association with TPS and 28-8 pharmDx assay association with %TC, both use the same scoring algorithm. This scoring method will be referred to as TPS within the document.
- CPS evaluates the combination of tumor cells with tumor membrane staining and immune cells with cytoplasmic staining and is defined as the sum of PD-L1 positive cells (tumor cells, lymphocytes and macrophages) divided by the total number of viable tumor cells and multiplied by 100. CPS is used with both PD-L1 IHC pharmDx assays, 22C3 and 28-8.

A third method, tumor area positivity (TAP) score, was used with the VENTANA SP263 assay in the RATIONALE-305 study which evaluated tislelizumab+chemo vs chemo in first-line GC/GEJC.[4] TAP is defined as the percentage of PD-L1 positive tumor cells and immune cells divided by tumor area.[5]

1.2 GC/GEJC/EAC (GASTROESOPHAGEAL ADENOCARCINOMA)

1.2.1 Disease Background, First-Line Treatments, and PD-L1 Expression

As described in Section 2.2.1 advanced or metastatic GC/GEJC/EAC (also collectively termed gastroesophageal adenocarcinoma) are lethal diseases with a high mortality. Platinum compounds (oxaliplatin and cisplatin) and fluoropyrimidines (5-fluorouracil [5-FU], or capecitabine) were long considered the only first-line standard-of-care treatments for HER2-negative, metastatic gastroesophageal adenocarcinoma across geographic regions. However, first-line chemo treatment was associated with poor outcomes in this disease setting, with a median OS of <1 year.[6,7,8]

Following CHECKMATE-649, which demonstrated the survival benefit of nivo+chemo relative to chemo alone in the first-line treatment of advanced/metastatic gastroesophageal adenocarcinoma in 2020, other prospective Phase 3 clinical studies investigating the use of ICIs with chemo vs chemo in this disease/setting have also confirmed the improved efficacy of these combination regimens. A summary of OS with nivo+chemo vs chemo (CHECKMATE-649)[9], pembrolizumab+chemo vs chemo (KEYNOTE-859) [10], and tislelizumab+chemo vs chemo (RATIONALE-305)[4] is provided in Table 2.2.1-1, including PD-L1 subgroup data. Although these studies demonstrated the benefit of ICI+chemo vs chemo in the ITT population (ie, overall population), they also demonstrated that patients with relatively higher PD-L1 expression (by various scoring methods and cutoffs) showed more pronounced benefit than patients with relatively lower PD-L1 expression. While OS HR point estimates were < 1.0 in the subgroups of patients with lower PD-L1 expression, the point estimates were closer to 1.0 and the upper bounds of the 95% CIs encompassed 1.

An important complexity in comparing and interpreting results across studies is that each study used different methods of scoring PD-L1, different assays, and evaluated different PD-L1 expression level cutoffs. In addition, PD-L1 testing in clinical practice has known limitations that make it challenging to accurately determine levels of PD-L1 expression (see Section 1.5). Given the above-mentioned complexity, establishing harmonization is challenging.

1.2.2 GC/GEJC/EAC (Gastroesophageal Adenocarcinoma) Treatment in the Second-Line Setting and Beyond

There are no approved ICI treatment options in the second-line setting and beyond for most of the HER-2 negative population with gastroesophageal adenocarcinoma.[11,12,13,14] Ramucirumab (with or without paclitaxel) and monotherapy with chemo agents (paclitaxel, docetaxel, or irinotecan) are the current standards of care for second-line gastroesophageal carcinoma, but are associated with poor outcomes.[15]

A limited number of patients with gastroesophageal adenocarcinoma go on to receive second-line therapy: ~60% based on clinical practice data[16] and ~40% based on clinical study data[17].

The limited number of patients with gastroesophageal adenocarcinoma who proceed to second-line treatment, as well as the few and suboptimally effective treatment options available in that setting, underscore the need for use of effective therapies in the first-line setting.

1.3 STUDY CHECKMATE-649 (CA209649)

- At the primary analysis (data cutoff: 27-May-2020), CHECKMATE-649 demonstrated statistically significant and clinically meaningful OS benefit with nivo+chemo vs chemo in patients with PD-L1 CPS ≥ 5 (primary endpoint), as well as in patients with PD-L1 CPS ≥ 1 and all randomized patients (formally tested secondary endpoints).
  - Exploratory subgroup analyses by PD-L1 CPS showed that survival benefit was increased in subgroups at or above each cutoff (CPS ≥ 1, ≥ 5, and ≥ 10) compared with below each cutoff (CPS < 1, < 5, and < 10) or with CPS ranges of 1 - < 5, 1 - < 10 and 5 - <10. For the PD-L1 CPS < 1 subgroup, the OS HR point estimate was above 0.9 and the upper bound of the 95% CI encompassed 1.
- Long-term follow-up data (up to 4 years) demonstrated the consistency of OS results with the primary analysis, highlighting the durable efficacy of nivo+chemo.
  - Although the most pronounced OS benefit was observed in the PD-L1 CPS subgroup of ≥ 10, with longer-term follow-up (4 years), there was a trend toward OS benefit in some subgroups, including in the PD-L1 CPS 1- <10 subgroup.
- The overall safety profile of nivo+chemo in previously untreated patients with advanced or metastatic gastroesophageal adenocarcinoma was manageable with established treatment algorithms. No new safety concerns were identified. As anticipated, AEs of immune-mediated etiology (IMAEs) were reported more frequently in the nivo+ chemo arm; the majority of events were of low-grade (Grade 1-2) and the frequencies were consistent with those of nivolumab monotherapy.
- No meaningful differences in safety were observed by PD-L1 subgroups.

Results (primary and longer-term follow-up) of CHECKMATE-649 are presented in Section 2.3.

1.4 PD-L1 TESTING AND TREATMENT PATTERNS IN CLINICAL PRACTICE

The majority of patients with gastroesophageal adenocarcinoma are PD-L1 positive based on CPS assessment: ~80% with CPS ≥ 1, ~60% with CPS ≥ 5, and ~50% with CPS ≥ 10 according to the prevalence observed in CHECKMATE-649.

Real-world data from the US Flatiron database[3](see Section 2.4 for more details), which is derived largely from community treatment centers, suggests that more than half of gastroesophageal adenocarcinoma patients (~60%) are tested for PD-L1 CPS (Figure 2.4-1), even without a requirement to do so per the ICI drug labeling. PD-L1 testing may be even more common in academic treatment centers. Importantly, the testing rates are ~73% for patients receiving first-line nivo+chemo, demonstrating that most decisions to treat with nivo+chemo are informed by a test result. Of the tested patients who received first line nivo+chemo, 83.4% had CPS ≥ 1 and 14.6% had CPS < 1 (which is consistent with the prevalence of PD-L1 CPS ≥ 1 and < 1 observed in CHECKMATE-649), and for 2% the CPS was unknown.[3]

An examination of treatment patterns (using Flatiron database) showed that a positive test result was associated with a larger proportion of patients being treated with first-line ICI-containing regimens (47.6% vs 28.9% of patients with PD-L1 CPS ≥ 1 vs < 1, respectively); Figure 2.4-2. This is consistent with clinical practice guidelines denoting the strength of recommendations for

ICI+chemo by PD-L1 score.[12,13] Per the Flatiron data, 32.3% patients with untested/unknown CPS results are treated with ICI+chemo.[3] Given the high prevalence of PD-L1 positivity described above, most patients without a test result would be considered PD-L1 positive if tested.

In conclusion, a high degree of PD-L1 testing is already occurring in patients treated with nivolumab, and test results are being used to guide treatment decisions with ICI+chemo in gastroesophageal adenocarcinoma clinical practice.

1.5 CHALLENGES OF PD-L1 TESTING IN CLINICAL PRACTICE

Although PD-L1 testing is occurring in clinical practice, there are challenges in precisely and reliably determining PD-L1 expression:

- Tissue adequacy for PD-L1 scoring: A collected sample must be of adequate quantity and quality to make a PD-L1 expression determination.
- Type of tissue sample: Whether a sample is collected via mucosal biopsy or tumor resection impacts the size of sample and each has technical considerations related to PD-L1 scoring.[18]
- Tumor tissue fixation: Poor fixation of tissue specimens may hamper PD-L1 evaluation due to morphologic alterations and unreliable PD-L1 staining.[19,20]
- Tumor heterogeneity of PD-L1 expression: PD-L1 expression is characterized by a high degree of spatial and temporal tumor heterogeneity; variability within the tumor sample itself that was biopsied and/or vs metastases that may show different PD-L1 expression. Different CPS is not infrequently seen in clinical practice when different sites of disease are evaluated.[21,22,23,24]
- Dynamic nature of PD-L1 expression: In GC, PD-L1 is expressed predominantly by immune cells (ie, macrophages) present in the invasive margin.[25] PD-L1 expression, particularly by immune cells, is highly inducible.[26]
- Interobserver variability: At a population level, PD-L1 has been shown to be a useful enrichment tool. However, at an individual patient level, there is inherent inter-pathologist variability for actual scores/values.
- Interlaboratory variability in PD-L1 assessment: Interlaboratory variability in PD-L1 assessment is seen due to the use of different diagnostic assays and antibody clones with different staining patterns.[27,28,29]
- Application of study results to real-world practice: Each pivotal study (CHECKMATE-649, KEYNOTE-859, and RATIONALE-305) used a different PD-L1 scoring methods and antibody. Data suggest that this variation makes cross-trial interpretation of results challenging and also suggests difficulty in drawing a conclusion on use of a given treatment when in practice a patient receives a test by a different scoring method/antibody than was used in the pivotal study for that treatment.

Detail on the above issues is provided in Section 2.4. Given the challenges above, it is difficult to anticipate a certain clinical outcome based on any specific numerical PD-L1 score which might fall only slightly outside of a given cutoff range. Patients who score above a specific numerical cutoff with one scoring method/assay may not by another. Patients who score PD-L1 negative (ie, CPS < 1) by one sample/test may not always score negative by another sample/test due to

variability within a given block of tissue or among tumor sites.[30] This can lead to confusion and ambiguity in using specific numerical scores to make treatment decisions.

1.6 EVALUATION OF POTENTIAL LABELING OPTIONS IN FIRST-LINE GASTROESOPHAGEAL ADENOCARCINOMA AND THE SPONSOR'S CONCLUSION

In accordance with the FDA's intent of this ODAC to discuss the emerging risk-benefit analysis of ICIs as a class in gastroesophageal adenocarcinoma, the Sponsor has developed two potential labeling options for consideration. See Table 2.6-1 for a detailed evaluation of both options.

With **Option 1** (***Maintain the current unrestricted indication with inclusion of PD-L1 subgroup data in the label highlighting the efficacy based on PD-L1 expression, as is presently the case***), the key advantages are providing HCPs with the opportunity to continue making informed treatment decisions on an individual patient basis using the efficacy data by PD-L1 expression level in the USPI (Section 14.13) and retaining ICI as a treatment option for patients who may be unable to receive a PD-L1 test or have inconclusive test results (due to inadequate/poor quality tumor tissue) as the majority (80%) of such patients would be PD-L1 positive (ie, CPS ≥ 1). The limited number of patients with gastroesophageal adenocarcinoma who proceed to second-line treatment, as well as the few and suboptimally effective treatment options available in that setting (ie, no ICI options for vast majority of patients), underscore the need for use of effective therapies in the first-line setting. In the Sponsor's interactions with expert panels and patient advocacy organizations, retaining options for treatment and removing barriers to treatment are communicated as being of critical importance. However, the potential exposure to ICI safety risks without high likelihood of benefit in patients without PD-L1 expression should be recognized.

With **Option 2** ***(In the event of a class label change, modify the indication to PD-L1 positive patients using the most appropriate threshold, which the Sponsor would propose to be CPS ≥ 1)***, the key advantages are allowing for treatment of patients with evidence of PD-L1 expression, as they have the greatest likelihood for benefit, and avoiding safety risks of ICI treatment in those without evidence of PD-L1 expression. However, mandatory PD-L1 testing could lead to treatment delay or reduced access for some patients who may have potential to benefit. The Sponsor proposes that a cutoff of CPS ≥1 is the most reasonable choice to ensure continued access for the greatest number of patients with potential to benefit from nivo+chemo based on clinical data from CHECKMATE-649, and accounting for interobserver variability in CPS scoring and other PD-L1 testing limitations in clinical practice. In the Sponsor's consideration, implementing a required PD-L1 cutoff would only facilitate clinical practice if labeling modifications were done across ICIs as a class for the gastroesophageal adenocarcinoma indication, with consistency in cutoff and test type requirements. Otherwise, individual product labeling modifications would introduce even more complexity for prescribers and might inadvertently limit the use of some drugs based on unintended factors such as test type availability and reimbursement.

In summary, this is a challenging situation for which multiple solutions could be considered. Overall, the Sponsor concludes that the existing labelling adequately informs prescribers on the potential benefits and risks of nivo+chemo in GC/GEJC/EAC, including on the clinical efficacy by PD-L1 expression level. The existing labelling leaves the decision-making in the hands of the

treating physician and increases the chance for patients who may potentially benefit, including those without a test result, to be considered for treatment with ICIs in the first-line setting. This flexibility is especially important when making treatment decisions in the first-line setting since many patients do not go on to receive later line therapy and, when they do, their choices are limited.

2 SPONSOR BRIEFING DOCUMENT

2.1 CURRENT INDICATION AND REGULATORY BACKGROUND - FIRST-LINE GC/GEJC/EAC (GASTROESOPHAGEAL ADENOCARCINOMA)

As described in Section 1.1, since the approval of nivo+chemo in first-line GC/GEJC/EAC, results of long-term follow up (4-year) for CHECKMATE-649 have become available (Sections 2.3.2.2 and 2.3.3.3), showing consistency with the results of the primary analysis. Additional first-line ICI combination studies in gastroesophageal adenocarcinoma have increased the body of data on PD-L1 expression and its potential relationship with ICI efficacy.

The available data have led to the question of whether first-line gastroesophageal adenocarcinoma patients should be selected for ICI combination treatment based on PD-L1 expression status and whether harmonization is possible and feasible.

To help inform individual patient treatment decisions by HCPs based on potential likelihood of benefit, OS data in PD-L1 CPS subgroups based on the Agilent/Dako PD-L1 IHC 28-8 pharmDx test are currently provided in the Clinical Studies section of the USPI for nivo+chemo vs chemo in CHECKMATE-649. The PD-L1 CPS subgroups presented include the CPS ≥ 5 (primary analysis population), CPS ≥ 1 (formally tested secondary analysis population), as well as exploratory subgroups of CPS < 5 and < 1.

Current prescribing information (Section 14.13 of the USPI) is as follows:

Table 76: Efficacy Results - CHECKMATE-649

	OPDIVO and mFOLFOX6 or CapeOX (n=789)	mFOLFOX6 or CapeOX (n=792)	OPDIVO and mFOLFOX6 or CapeOX (n=641)	mFOLFOX6 or CapeOX (n=655)	OPDIVO and mFOLFOX6 or CapeOX (n=473)	mFOLFOX6 or CapeOX (n=482)
	All Patients		PD-L1 CPS ≥1		PD-L1 CPS ≥5	
Overall Survival						
Deaths (%)	544 (69)	591 (75)	434 (68)	492 (75)	309 (65)	362 (75)
Median (months) (95% CI)	13.8 (12.6, 14.6)	11.6 (10.9, 12.5)	14.0 (12.6, 15.0)	11.3 (10.6, 12.3)	14.4 (13.1, 16.2)	11.1 (10.0, 12.1)
Hazard ratio (95% CI)[a]	0.80 (0.71, 0.90)		0.77 (0.68, 0.88)		0.71 (0.61, 0.83)	
p-value[b]	0.0002		<0.0001		<0.0001	

In an exploratory analysis in patients with PD-L1 CPS <1 (n = 265), the median OS was 13.1 months (95% CI: 9.8, 16.7) for the OPDIVO and chemotherapy arm and 12.5 months (95% CI: 10.1, 13.8) for the chemotherapy arm, with a stratified HR of 0.85 (95% CI: 0.63, 1.15).

In an exploratory analysis in patients with PD-L1 CPS <5 (n = 606), the median OS was 12.4 months (95% CI: 10.6, 14.3) for the OPDIVO and chemotherapy arm and 12.3 months (95% CI: 11.0, 13.2) for the chemotherapy arm, with a stratified HR of 0.94 (95% CI: 0.78, 1.14).

[a] Based on stratified Cox proportion hazard model; [b] Based on stratified log-rank test

2.2 GC/GEJC/EAC (GASTROESOPHAGEAL ADENOCARCINOMA)

2.2.1 Disease Background, First-line Treatments, and PD-L1 Expression

GC is the 5th leading cancer and the 5th leading cause of cancer-related deaths worldwide.[31] GC/GEJC/EAC (also collectively referred to as gastroesophageal adenocarcinoma) remains a leading cause of cancer-related mortality globally, with an estimated 1 million deaths in 2018.[32] In the US, GC is a relatively rare cancer (ranked 15th by prevalence/mortality among the cancer types),[33] with 26,890 new cases and 10,880 deaths from this disease estimated in 2024[34]. As GC, GEJC, and EAC are considered similar diseases, the same treatment approach is recommended.[12,13,35,36,37] Up until several years ago, standard-of-care chemo was the only first-

line treatment option for HER2-negative, advanced/ metastatic GC/GEJC/EAC, but was associated with poor outcomes.[6,7,8]

In recent years, several prospective Phase 3 clinical studies investigating the use of ICI+chemo have confirmed the improved efficacy of these combination regimens relative to chemo alone in the first-line treatment of advanced/metastatic gastroesophageal adenocarcinoma (Table 2.2.1-1). Based on the positive results of the CHECKMATE-649 and KEYNOTE-859 studies, nivo+chemo and pembrolizumab+chemo were approved by the FDA in 2021 and 2023, respectively, for the first-line treatment of advanced/metastatic HER2-negative gastroesophageal adenocarcinomas (regardless of PD-L1 status) and have become the first-line standards of care in this disease setting. Recently, the RATIONALE-305 study also reported statistically significant and clinically meaningful improvement in OS with first-line tislelizumab+chemo vs chemo in patients with GC/GEJC.[4] On the basis of the RATIONALE-305 study, a tislelizumab BLA for the treatment of gastroesophageal carcinoma has been submitted and is under review by the FDA. The overall safety profile of ICI+chemo was reflective of the combined toxicities of the individual components (ie, typical chemo-based toxicities and immune-mediated AEs).

Although the CHECKMATE-649, KEYNOTE-859, and RATIONALE-305 studies demonstrated the benefit of ICI+chemo vs chemo in the ITT population (ie, overall population), they also demonstrated that patients with relatively higher PD-L1 expression (by various scoring methods and cutoffs) showed more pronounced benefit than patients with relatively lower PD-L1 expression. While OS HR point estimates were < 1.0 in the subgroups of patients with lower PD-L1 expression, the point estimates were closer to 1.0 and the upper bounds of the 95% CIs encompassed 1 (Table 2.2.1-1). A meta-analysis of Phase 2/3 ICI+chemo studies demonstrated the superiority of ICI+chemo vs chemo alone for OS in patients with positive PD-L1 expression (ie, CPS ≥ 1): HR 0.81 (95% CI: 0.73, 0.90).[38] Another meta-analysis reported that the OS effect with ICI+chemo vs chemo was more pronounced in PD-L1 positive patients (HR 0.69 [95% CI: 0.58, 0.81]) compared to PD-L1 negative patients (HR 0.84 [95% CI: 0.75, 0.94]).[39].

Medical societies have addressed the Phase 3 ICI+chemo study data as it emerged (Table 2.2.1-2). The NCCN guidelines' approach for nivo+chemo in gastroesophageal adenocarcinoma is complementary with the approach used in the current OPDIVO labelling. The guidelines do not limit the recommendations by PD-L1 expression level but use different categorizations/weights of evidence for the PD-L1 CPS cutoffs of ≥ 5 vs < 5, thereby leaving the ultimate treatment decisions in the hands of the informed prescribers.

An important complexity in comparing and interpreting results across studies is that each study used a different method of scoring PD-L1, different assays, and evaluated different PD-L1 expression level cutoffs. In addition, PD-L1 testing in clinical practice has known limitations that make it challenging to accurately quantify levels of PD-L1 expression (see Section 2.4). Given the above-mentioned complexity, establishing harmonization is challenging.

Table 2.2.1-1: ICI+Chemo Combinations (Approved and under FDA Review) in Advanced or Metastatic HER2-negative Gastroesophageal Cancer - OS HR (Investigative Therapy vs Comparator) - ITT and PD-L1 Subgroups

Therapy/ Data Source	Indicated Population	Study Information	OS HR (Investigative Therapy vs Comparator) (All Randomized [ITT])	OS HR (Investigative Therapy vs Comparator) (by PD-L1 Subgroup)
Nivo + Chemo (n=789) (USPI)[1]	1L GC/GEJC/EAC	CHECKMATE-649 Comparator: chemo (n=792) PD-L1 Scoring: CPS (primary analysis population) and TPS Minimum Follow-up: 12.1 months	ITT: 0.80 (95% CI: 0.71, 0.90)	PD-L1 CPS ≥ 5: 0.71 (95% CI: 0.61, 0.83) PD-L1 CPS < 5: 0.94 (95% CI: 0.78, 1.14) PD-L1 CPS ≥ 1: 0.77 (95% CI: 0.68, 0.88) PD-L1 CPS < 1: 0.85 (95% CI: 0.63, 1.15)
Pembro + Chemo (n=790) (USPI)[11]	1L GC/GEJC	KEYNOTE-859 Comparator: placebo + chemo (n=789) PD-L1 Scoring: CPS (primary analysis population) Minimum Follow-up: 15.3 months	ITT: 0.78 (95% CI: 0.70, 0.87)	PD-L1 CPS ≥ 10: 0.65 (95% CI: 0.53, 0.79) PD-L1 CPS ≥ 1: 0.74 (95% CI: 0.65, 0.84) PD-L1 CPS < 1: 0.92 (95% CI: 0.73, 1.17)
Tisle + Chemo (n=501) (Publication[4] and Presentation[40])	Under FDA Review/ Study population: 1L GC/GEJC	RATIONALE-305 Comparator: placebo + chemo (n=496) PD-L1 Scoring: TAP (primary analysis population). Post hoc CPS scoring was also performed. Minimum Follow-up (Interim Analysis): 7.9 months Minimum Follow-up (Final Analysis): 24.6 months	ITT: 0.80 (95% CI: 0.70, 0.92)	PD-L1 TAP ≥ 5: 0.74 (95% CI: 0.59, 0.94) PD-L1 TAP < 5: 0.92 (95% CI: 0.75, 1.13) Post hoc CPS Analysis PD-L1 CPS ≥ 5: 0.72 (95% CI: 0.59, 0.88) PD-L1 CPS < 5: 0.89 (95% CI: 0.72, 1.09) PD-L1 CPS ≥ 1: 0.78 (95% CI: 0.67, 0.91) PD-L1 CPS < 1: 1.01 (95% CI: 0.66, 1.52)

Table 2.2.1-2: USPI and NCCN Guidelines Recommendations - FDA Approved ICI Treatments in Gastroesophageal Cancer

Histology (Line)	Recommended Regimen	USPI[1,11]	NCCN[12,13]
GC/GEJC/EAC (1L)	**Nivolumab** + fluoropyrimidine and platinum-containing chemo	PD-L1-unrestricted	PD-L1 CPS ≥ 5 (Category 1) PD-L1 CPS < 5 (Category 2B)
	Pembrolizumab + fluoropyrimidine and platinum-containing chemo	PD-L1-unrestricted	PD-L1 CPS ≥ 10 (Category 1) PD-L1 CPS 1-9 (Category 2B)

2.2.2 GC/GEJC/EAC (Gastroesophageal Adenocarcinoma) Treatment in the Second-Line Setting and Beyond

A limited number of patients with gastroesophageal adenocarcinoma proceed to second-line therapy and few treatment options (with modest outcomes) are available for these patients, highlighting the need for use of effective therapies in the first-line setting. There are no approved ICI treatment options in the second-line setting and beyond for most of the HER2-negative population with gastroesophageal adenocarcinoma (although pembrolizumab is approved in the US for small populations of patients with gastroesophageal tumors that are MSI-H/dMMR or TMB-H).[11,12,13,14] Ramucirumab (with or without paclitaxel) and monotherapy with chemo agents (paclitaxel, docetaxel, or irinotecan) are the current standards of care for second-line gastroesophageal carcinoma, but are associated with poor outcomes.[15]

In clinical practice, ~60% of patients with GC/GEJC/EAC go on to receive second-line treatment. This data was obtained from a retrospective analysis of patients with advanced GC/GEJC/EAC in the US Flatiron database who initiated first-line treatment between Jan-2013 and Apr-2018 (N=3850).[41] A smaller proportion of patients (~40%) was reported to progress to second-line treatment based on data from CHECKMATE-649.[17]

Some analyses have indicated that ICI treatment in the first-line setting may have longer-term benefit that may affect outcomes in the second-line setting and beyond. A retrospective analysis of medical records[42] and a subgroup analysis of the RINDBeRG trial[43] indicated that prior exposure to ICIs may improve outcomes with second-line (or later line) ramucirumab in GC/GEJC.

2.3 CHECKMATE-649 (CA209649)

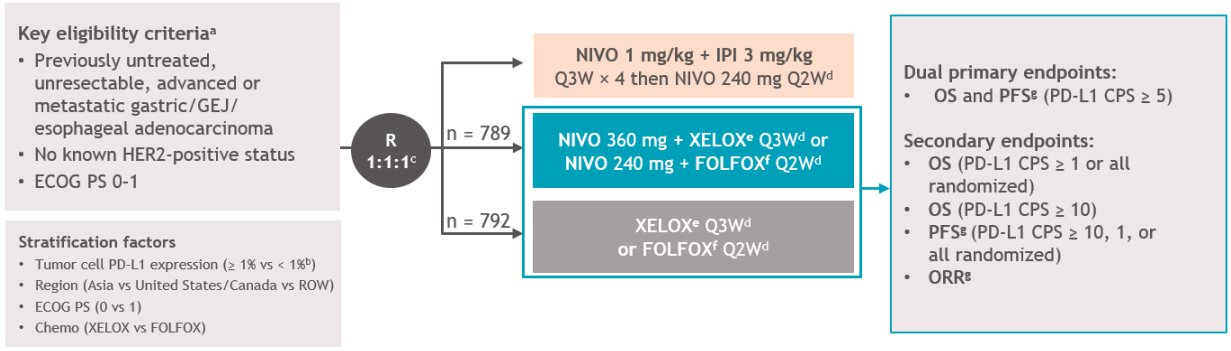
2.3.1 Study Overview

2.3.1.1 Study Design

CHECKMATE-649 is an open-label, 3-arm, randomized Phase 3 study of nivo+ipi or nivo+chemo vs chemo in patients with previously untreated advanced or metastatic GC/GEJC/EAC (Figure 2.3.1.1-1). This briefing document focuses on efficacy results of patients concurrently

randomized to the nivo+chemo and chemo treatment arms, which formed the basis for the approved indication.

Figure 2.3.1.1-1: CHECKMATE-649 (CA209649) Study Design Schematic



[a]ClinicalTrials.gov number. NCT02872116; [b]PD-L1 < 1% includes indeterminate tumor cell PD-L1 expression; determined by PD-L1 IHC 28-8 pharmDx assay (Dako); [c]Enrollment into the nivo+ipi arm was closed early; randomization (1:1) into the nivo+chemo and chemo arms proceeded ; [d]Until documented disease progression (unless consented to treatment beyond progression for nivo + chemo), discontinuation due to toxicity, withdrawal of consent, or study end. Nivo is given for a maximum of 2 years; [e]Oxaliplatin 130 mg/m^2 IV (day 1) and capecitabine 1000 mg/m^2 orally twice daily (days 1–14); [f]Oxaliplatin 85 mg/m^2, leucovorin 400 mg/m^2, and FU 400 mg/m^2 IV (day 1) and FU 1200 mg/m^2 IV daily (days 1–2); [g]BICR assessed.

2.3.1.2 Objectives and Endpoints

Table 2.3.1.2-1: Key Objectives/Endpoints for Nivo+Chemo vs Chemo

Primary Endpoints	• OS in randomized patients with PD-L1 CPS ≥ 5 • PFS by BICR in randomized patients with PD-L1 CPS ≥ 5
Secondary Endpoints (in hierarchical testing order)	• OS in randomized patients with PD-L1 CPS ≥ 1 • OS in all randomized patients.
Secondary Endpoints (descriptive)	• OS in randomized patients with PD-L1 CPS ≥ 10 • PFS by BICR in randomized patients with PD-L1 CPS ≥ 10, 1 or all randomized patients • ORR by BICR in randomized patients with PD-L1 CPS ≥ 10, 5, 1 or all randomized patients
Exploratory Endpoints	• ORR[a] and DOR[b] per BICR • OS, PFS, ORR[a] per BICR in randomized patients across PD-L1 CPS and TPS cutoffs • PRO • Biomarkers, safety and tolerability, and immunogenicity

[a] ORR in all randomized patients and in patients with measurable disease.

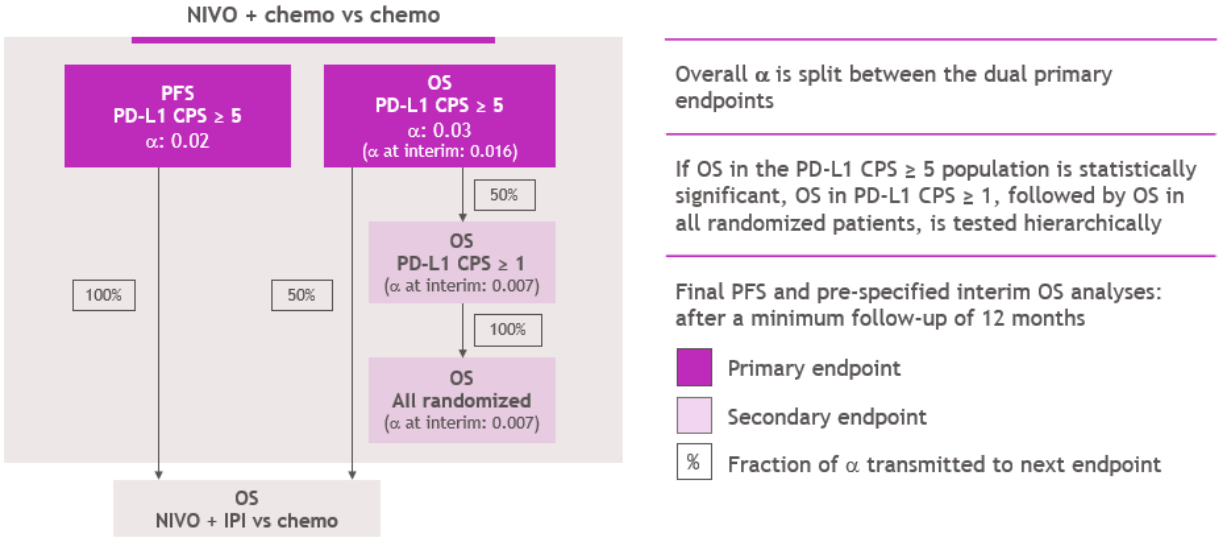
[b] DOR in all randomized patients and in patients with measurable disease.

2.3.1.3 Statistical Considerations

The hierarchical testing strategy described in Figure 2.3.1.3-1 ensured a strong control of type I error (family-wise error rate) at a 2-sided significance (alpha) level of 5% for the primary and key

secondary endpoints. For the dual primary endpoints of OS and PFS in the comparison of nivo+chemo vs chemo in randomized patients with PD-L1 CPS ≥ 5, a 2-sided significance level of 3% was allocated to OS and 2% was allocated to PFS. If the OS comparison in patients with PD-L1 CPS ≥ 5 between nivo+chemo vs chemo was significant, then OS in patients with PD-L1 CPS ≥ 1 and OS in all randomized were planned to be sequentially tested.

Figure 2.3.1.3-1: Hierarchical Testing Strategy for Primary and Secondary Endpoints in CheckMate-649 (CA209649)



2.3.1.4 PD-L1 Methods and Analyses

PD-L1 TPS testing was conducted at a central laboratory (LabCorp) using the Agilent/Dako PD-L1 IHC 28-8 pharmDx test (labeled as investigational use only) according to the manufacturer's instructions with the DAKO Autostainer Link-48 system (Table 2.3.1.4-1). Per protocol, patients were eligible for randomization if they had an evaluable PD-L1 test result of their tumor tissue as determined by a central lab. Approximately 15% of screen failures in the study did not have a conclusive/evaluable PD-L1 test result.

PD-L1 TPS at the 1% cutoff was validated for investigational use and was used as a stratification factor (based on the available data/knowledge of PD-L1 testing in GC at the time of the study design). In the original study protocol, the primary analysis population comprised patients with PD-L1 TPS ≥ 1%, and all randomized patients was a secondary analysis population. During the course of the study, as emerging internal and external data indicated that CPS is a more relevant scoring method for predicting efficacy of immune checkpoint blockade in GC,[44,45,46] PD-L1 CPS cutoffs of 5 and 1 were analytically validated for investigational use and were used to define the primary (CPS ≥ 5) and secondary (CPS ≥ 1) analysis populations, respectively. The change in the primary analysis population to CPS ≥ 5 occurred after patient enrollment had already started; therefore, PD-L1 TPS at the 1% cutoff remained unchanged as a stratification factor for consistency. PD-L1 CPS cutoff of 10 was also validated retrospectively. CPS data was generated centrally by rescoring the slides originally stained for PD-L1 and scored by TPS. The primary,

secondary, and pre-specified exploratory PD-L1 analyses subgroups are shown in Table 2.3.1.4-1.

Table 2.3.1.4-1: PD-L1 Testing Summary in CHECKMATE-649

PD-L1 Assay	PD-L1 Scoring Method	PD-L1 Stratification	Primary and Secondary Analysis Population (PD-L1 Subgroup)	Exploratory Analysis Subgroup by PD-L1 Cutoff	PD-L1 Assay Cutoff Development Status	Testing Laboratory
28-8	TPS	≥ 1%, < 1%[a]	NA	TPS[c] < 1%, ≥ 1%, < 5%, ≥ 5%, < 10%, ≥ 10%	Validated: TPS 1% Exploratory: TPS 5%, 10%	LabCorp
28-8	CPS	NA	CPS ≥ 5[b] (primary) CPS ≥ 1[b] (secondary)	CPS[c] < 1, ≥ 1, < 5, ≥ 5, < 10, ≥ 10	Validated: CPS 1, 5, 10[d]	LabCorp

[a] PD-L1 TPS < 1% stratification factor category included patients with indeterminate expression.

[b] Patients with PD-L1 CPS ≥ 5 and CPS ≥ 1 were the primary and secondary analysis populations, respectively, used for formal statistical analyses.

[c] Pre-specified exploratory analyses of efficacy endpoints (OS, PFS, ORR and DOR) by PD-L1 CPS and TPS subgroups at the cutoffs of 1, 5, and 10 were performed. For the CPS ≥ 10 subgroup analyses, OS, PFS per BICR and ORR per BICR were secondary endpoints, while ORR and PFS per investigator were exploratory endpoints.

[d] PD-L1 CPS cutoff of 10 was not validated at the time of the primary analysis and was retrospectively validated.

2.3.1.5 Key Dates and Follow-up for the Primary Analysis

The primary analysis, which formed the basis for the approved indication and is included in the OPDIVO USPI,[1] was based on data from 1581 patients concurrently randomized to the nivo+chemo or chemo arms from 17-Apr-2017 (first patient randomized) to 27-May-2019 (last patient randomized).

Clinical Cutoff Date	27-May-2020
DBL	10-Jul-2020
Minimum Follow-up,[a] months	12.1

[a] Defined as time from the last patient's randomization date to the clinical cutoff date

2.3.1.6 Patient Population (Primary Analysis Data Cutoff: 27-May-2020)

Baseline demographic and disease characteristics in all randomized patients were representative of the advanced or metastatic GC/GEJC/EAC population and balanced between the nivo+chemo and chemo arms.[9] The study population included approximately 70% of patients with GC and 30% of patients with GEJC and EAC (~13% with EAC and ~16% with GEJC), which is representative of the global epidemiological data for these cancers. Approximately 17% of all randomized patients were from US/Canada. Tumor tissue was collected from all patients for the assessment of PD-L1 expression, primarily through biopsies (~74% of patients). For most patients (~79%), tumor tissue was collected from the primary tumor site rather than from metastatic sites

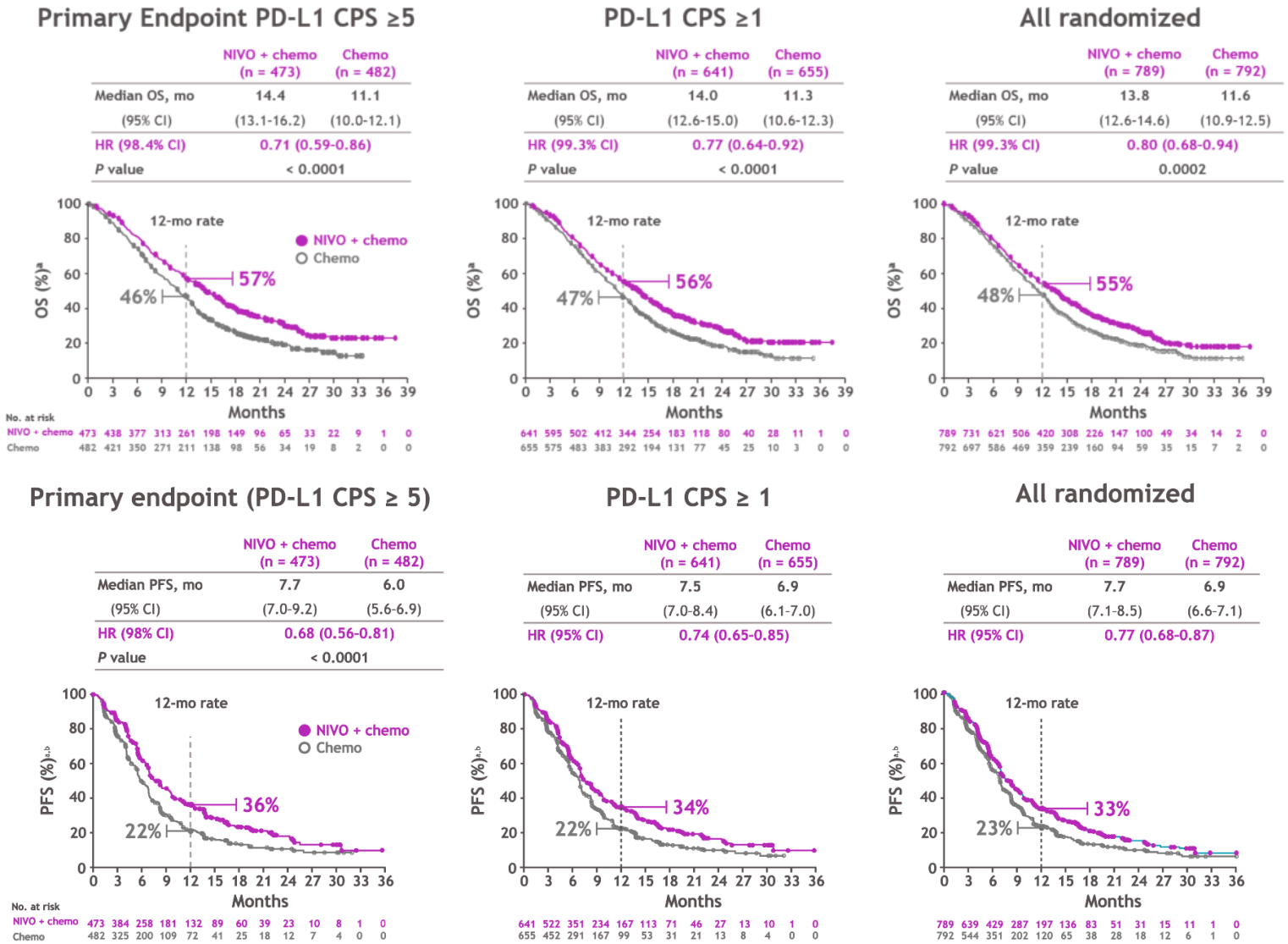
(21%). In patients with quantifiable PD-L1 CPS at baseline, approximately 60% had CPS ≥ 5 and approximately 80% had CPS ≥ 1.

2.3.2 EFFICACY in CHECKMATE-649 (CA209649)

2.3.2.1 Efficacy in All Randomized Patients and CPS Subgroups (Primary Analysis Data Cutoff: 27-May-2020)

- In patients with previously untreated advanced or metastatic GC/GEJC/EAC, nivo+chemo provided statistically significant and clinically meaningful improvements in **PFS per BICR and OS in patients with PD-L1 CPS ≥ 5** (primary endpoints); Figure 2.3.2.1-1:
  - PFS per BICR in patients with PD-L1 CPS ≥ 5: HR = 0.68 (98% CI: 0.56, 0.81)
  - OS in patients with PD-L1 CPS ≥ 5: HR = 0.71 (98.4% CI: 0.59, 0.86)
- Nivo+chemo also demonstrated statistically significant and clinically meaningful improvements in **OS in patients with PD-L1 CPS ≥ 1 and all randomized patients** (formally tested secondary endpoints); Figure 2.3.2.1-1
  - OS in patients with PD-L1 CPS ≥ 1: HR = 0.77 (99.3% CI: 0.64, 0.92)
  - OS in all randomized patients: HR = 0.80 (99.3% CI: 0.68, 0.94)
- An improvement in **PFS per BICR in patients with PD-L1 CPS ≥ 1 and all randomized patients** (secondary endpoints; not formally tested) was also observed with nivo+chemo compared to chemo, with HR (95% CI) < 1 in both populations (Figure 2.3.2.2-1).

Figure 2.3.2.1-1: OS and PFS Kaplan Meier Plots - Primary and Secondary Endpoints



[a]Minimum follow-up: 12. 1 months; [b]PFS per BICR.

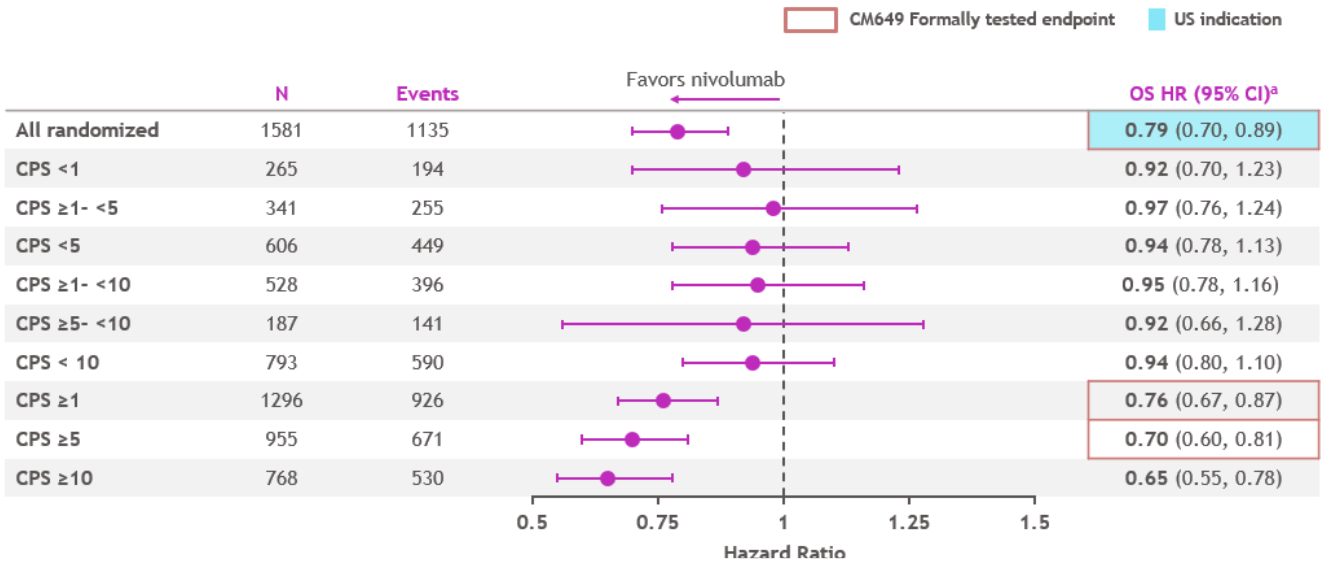
Exploratory Analyses by CPS Subgroups

In addition to the formal statistical tests in the PD-L1 CPS ≥ 5 and CPS ≥ 1 primary and secondary analyses, exploratory analyses of efficacy endpoints (eg, OS, PFS, ORR) by CPS subgroups were also performed and were descriptive in nature. PD-L1 CPS cutoffs of 1, 5, and 10 were pre-specified for the primary analysis. PD-L1 CPS cutoffs of 1 - <5, 1 - < 10, and 5 - < 10 were evaluated post hoc.

In the subgroup analyses of **OS and PFS per BICR** by PD-L1 CPS, HRs favored nivo+chemo over chemo (HR [95% CI] <1) in the CPS ≥ 1, ≥ 5, ≥ 10 subgroups (Figure 2.3.2.1-2 and Figure 2.3.2.1-3). Although across the CPS ≥ 1, ≥ 5, ≥ 10 subgroups, some improvement in nivo+chemo vs chemo HRs was seen at higher vs lower cutoffs, the 95% CIs for the HRs largely overlapped. Less OS and PFS improvement with nivo+chemo vs chemo was seen in the subgroups of CPS < 1, 1 - <5, 1 - < 10, < 5, 5 - < 10 and <10; the HRs for nivo+chemo vs chemo ranged from 0.88 to 0.97 and the upper bounds of the 95% CIs encompassed 1.

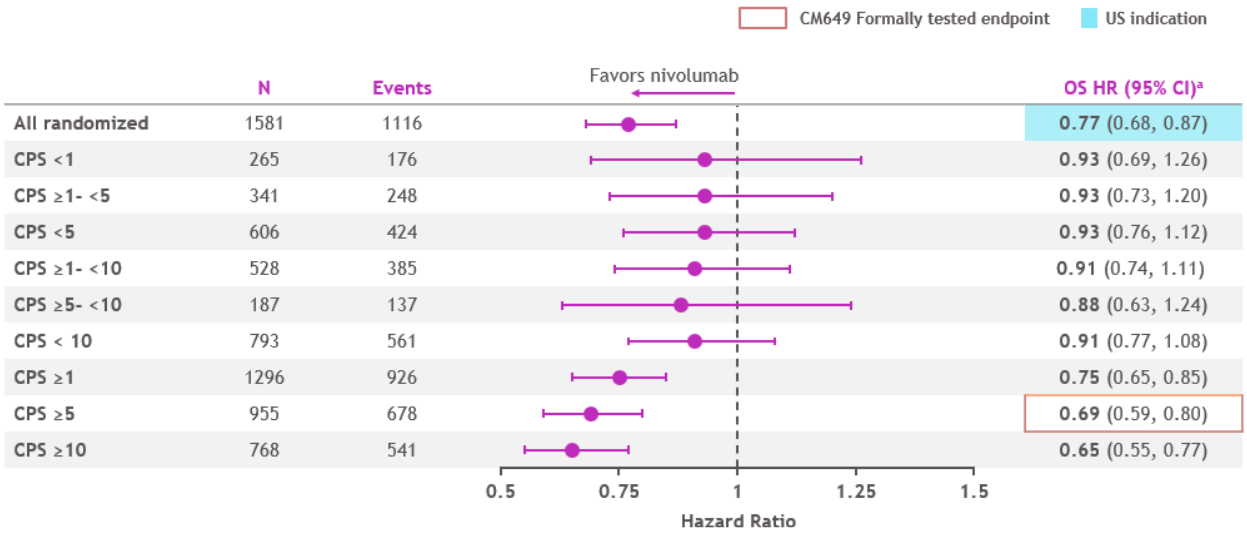
Higher **ORRs per BICR** with nivo+chemo vs chemo were observed across all CPS subgroups (Figure 2.3.2.1-4). The numerical improvement in ORR with nivo+chemo vs chemo was broadly similar across the CPS cutoffs.

Figure 2.3.2.1-2: OS by PD-L1 CPS Subgroups



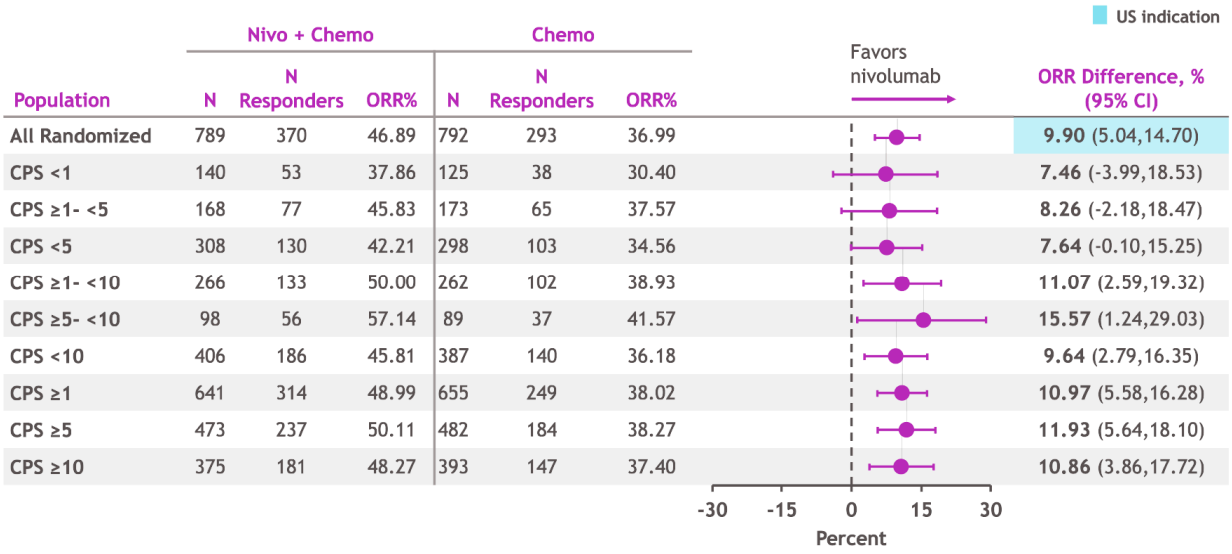
[a]Unstratified hazard ratio. HR is not computed for subset category with less than 10 patients per treatment group. Minimum follow-up: 12.1 months.

Figure 2.3.2.1-3: PFS per BICR by PD-L1 CPS Subgroups



[a]Unstratified hazard ratio. HR is not computed for subset category with less than 10 patients per treatment group. Minimum follow-up: 12.1 months.

Figure 2.3.2.1-4: ORR per BICR by PD-L1 CPS Subgroups



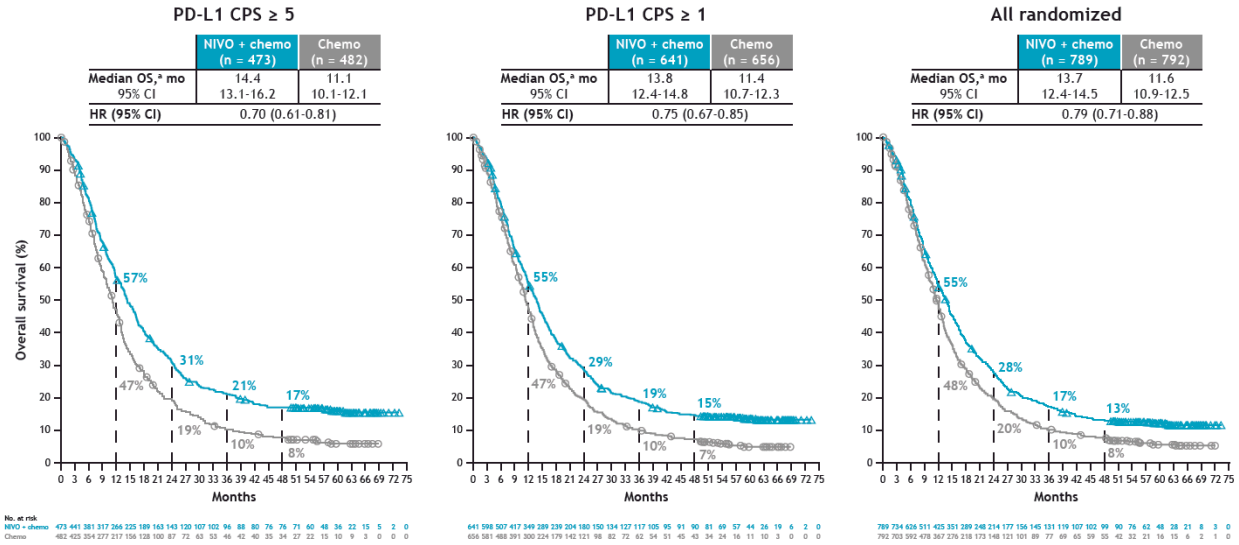
ORR difference is not computed for subset category with less than 10 patients per treatment group. Two-sided 95% confidence interval for ORR based on the Clopper and Pearson method.

Minimum follow-up: 12.1 months.

2.3.2.2 Efficacy at Longer-Term Follow-up

At 2, 3, and 4 years of minimum follow-up, efficacy results remained consistent with those of the primary analysis (minimum follow-up of ~1 year).[17,47,48] Clinically meaningful improvements in OS (Figure 2.3.2.2-1) and PFS per BICR (Figure 2.3.2.2-2) with nivo+chemo vs chemo were maintained across the PD-L1 CPS ≥ 5, ≥ 1, and all randomized populations at 4 years of minimum follow-up.

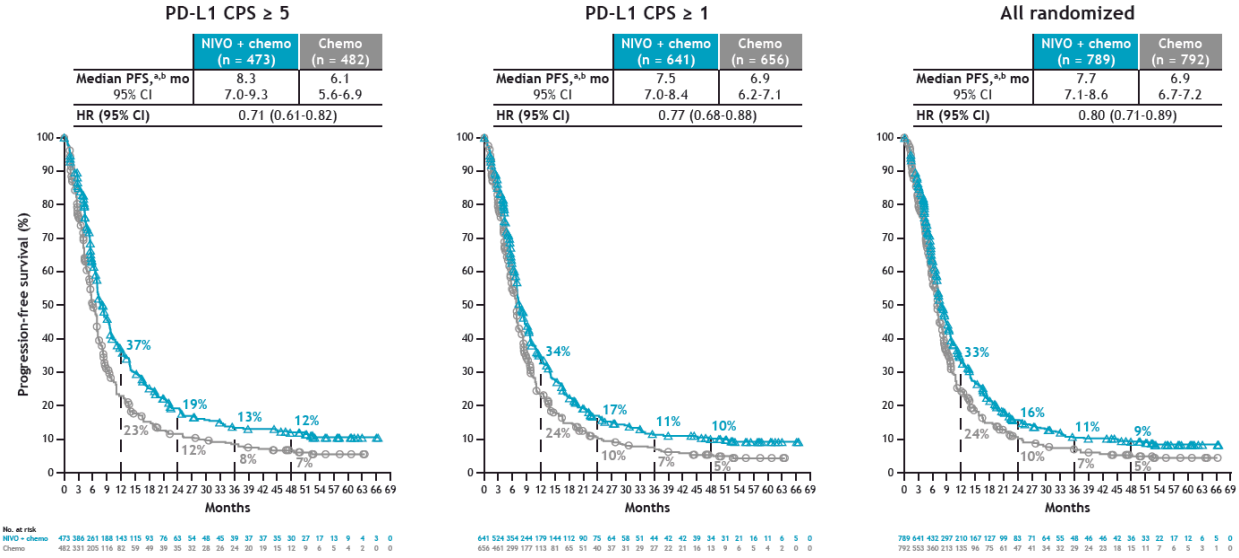
Figure 2.3.2.2-1: OS in Patients with PD-L1 CPS ≥ 5, ≥ 1, and All Randomized Patients - 4-year Follow-up



Minimum follow-up: 48.1 months

Source: Shitara et al.[48]

Figure 2.3.2.2-2: PFS per BICR in Patients with PD-L1 CPS ≥ 5, ≥ 1, and All Randomized Patients - 4-year Follow-up



Minimum follow-up: 48.1 months

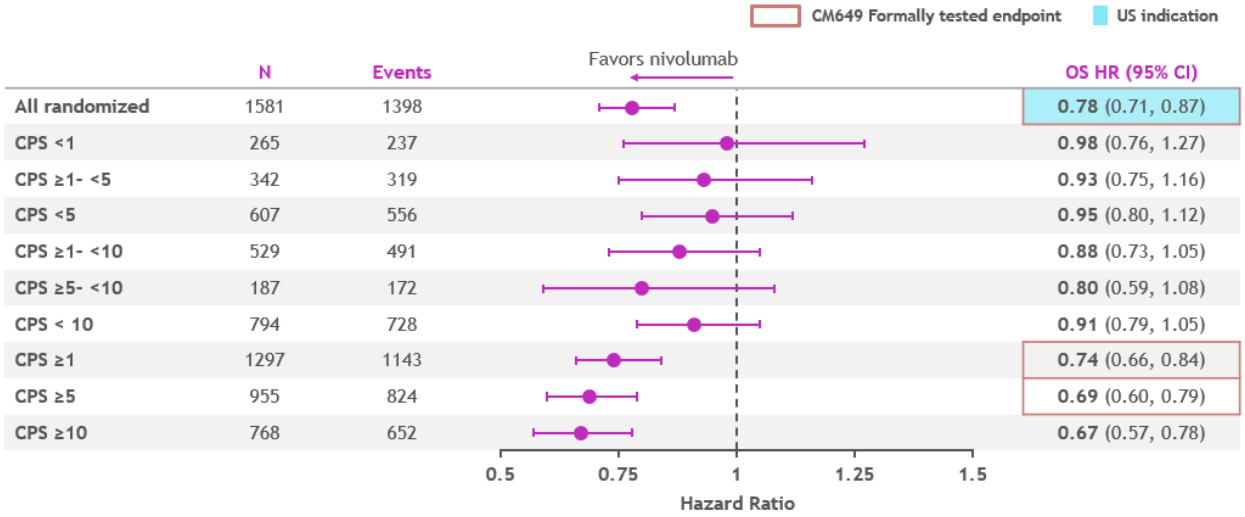
Source: Shitara et al.[48]

Analyses by PD-L1 CPS Subgroups

Four-year data in PD-L1 CPS subgroups remained generally consistent with the primary analysis (Figure 2.3.2.2-3). Results of the primary analysis and follow-up showed that the OS benefit with nivo+chemo vs chemo was most pronounced in the PD-L1 CPS ≥ 10 subgroup. Of note, with long-

term follow-up, there was a trend toward OS benefit in the PD-L1 CPS 1 - <10 subgroup: HR of 0.88 (95% CI: 0.73, 1.05) at 4 years of follow-up. Taken together, the improved OS HR in the PD-L1 CPS 1- <10 subgroup and the sustained improvement in OS with nivo+chemo vs chemo in the CPS ≥ 1 subgroup at 4 years of minimum follow-up (HR=0.74 [95% CI: 0.66, 0.84]), indicate that patients with PD-L1 CPS ≥ 1 derive OS benefit with nivo+chemo.

Figure 2.3.2.2-3: OS in PD-L1 CPS Subgroups - 4-year Follow-up



Minimum follow-up: 48.1 months

2.3.2.3 Non-PD-L1 Biomarkers as Predictors of Treatment Benefit

Other biomarkers beyond PD-L1 (including MSI, TMB, EBV)[12,13,49] may also influence treatment benefit of ICI. Testing for MSI and TMB status is recommended/considered in the gastroesophageal carcinoma treatment guidelines.[12,13,49] The prevalence of MSI-H and TMB-H is relatively low in GC, but patients with these biomarkers have been shown to derive benefit, independent of PD-L1 CPS.

In a CHECKMATE-649 exploratory analysis, greater survival benefit with nivo+chemo vs chemo was seen in patients with MSI-H or TMB-H status, with improved OS HRs compared to the all-randomized population. It should be noted that the MSI-H and TMB-H patient populations within the study were small; therefore, the results should be interpreted with caution.

- For the 44 (2.8%) patients who were MSI-H in CHECKMATE-649, OS HR for nivo+chemo vs chemo was 0.37 (95% CI: 0.16, 0.87)
- For the 57 patients who were TMB-H in CHECKMATE-649, OS HR for nivo+chemo vs chemo was 0.48 (95% CI: 0.25, 0.93)

In addition, an exploratory gene expression analysis in CHECKMATE-649 showed that patients with favorable stromal features in tumor tissue (eg, with low angiogenesis gene expression signature scores) may benefit from nivo+chemo vs chemo regardless of PD-L1 CPS status (ie, CPS < 5 or CPS ≥ 5).[50]

2.3.3 SAFETY in CHECKMATE-649 (CA209649)

2.3.3.1 Safety in All Treated Patients (Primary Analysis Data Cutoff: 27-May-2020)

Safety data from 782 patients treated with first-line nivo+chemo from CHECKMATE-649 were used to characterize the safety profile of this combination regimen in patients with advanced or metastatic GC/GEJC/EAC. The safety profile of nivo+chemo in this population/setting was reflective of the known safety profiles of the immunotherapy and chemo components and manageable with established treatment algorithms (Table 2.3.3.1-1).

- No new safety signals or toxicities were identified with nivo+chemo in all treated patients relative to each agent's safety profile as monotherapy or in combination.
- The number of treated patients who died in the nivo+chemo arm was numerically lower compared with the chemo arm.
  - Disease progression was the most frequently reported cause of death in both the nivo+chemo and chemo arms.
  - Among 16 deaths attributed to study drug toxicity in the nivo+chemo arm[1] (4 of which originally had causality attribution of "other reasons", but were updated by investigators after the database lock), 9 were related to nivo alone or to nivo+chemo and 7 were related to chemo alone per the investigator assessment. In the chemo arm, 4 deaths were attributed to study drug toxicity per the investigator.
- The overall frequencies of all causality and drug-related SAEs and AEs leading to discontinuation were numerically higher with nivo+chemo vs chemo; however, the majority of the events were consistent with typical chemo toxicities.
- As anticipated, AEs of immune-mediated etiology (IMAEs) were reported more frequently in the nivo+ chemo arm and the frequencies were consistent with those of nivolumab monotherapy. The majority of IMAEs in the nivo+chemo arm were Grade 1-2. Across IMAE categories, the majority of events were manageable using the established management algorithms, with resolution occurring when immune-modulating medications (mostly systemic corticosteroids) were administered (Table 2.3.3.1-2). Most IMAEs reported with nivo+chemo treatment had resolved at the time of clinical data cutoff, except for some endocrine events that were not considered resolved due to continuing need for hormone replacement therapy.

Table 2.3.3.1-1: Summary of Safety - All Treated Patients

Safety Parameters	No. of Patients (%)	
	Nivo + Chemo (N = 782)	Chemo (N = 767)
Deaths	538 (68.8)	572 (74.6)
Primary Reason for Death		
Disease	465 (59.5)	506 (66.0)
Study Drug Toxicity[a]	12 (1.5)	4 (0.5)
Unknown	12 (1.5)	18 (2.3)
Other[b]	49 (6.3)	44 (5.7)

	Adverse Event Grades			
	Any Grade	Grade 3-4	Any Grade	Grade 3-4
All-causality SAEs	423 (54.1)	281 (35.9)	335 (43.7)	229 (29.9)
Drug-related SAEs	172 (22.0)	131 (16.8)	93 (12.1)	77 (10.0)
All-causality AEs leading to DC	371 (47.4)	194 (24.8)	251 (32.7)	113 (14.7)
Drug-Related AEs leading to DC	284 (36.3)	132 (16.9)	181 (23.6)	67 (8.7)
All-causality AEs	776 (99.2)	540 (69.1)	752 (98.0)	456 (59.5)
Drug-related AEs	738 (94.4)	462 (59.1)	679 (88.5)	341 (44.5)
≥ 15% of Patients in Any Treatment Group				
Nausea	323 (41.3)	20 (2.6)	292 (38.1)	19 (2.5)
Diarrhea	253 (32.4)	35 (4.5)	206 (26.9)	24 (3.1)
Neuropathy Peripheral	221 (28.3)	31 (4.0)	190 (24.8)	22 (2.9)
Anaemia	203 (26.0)	47 (6.0)	171 (22.3)	21 (2.7)
Fatigue	202 (25.8)	30 (3.8)	173 (22.6)	17 (2.2)
Vomiting	195 (24.9)	17 (2.2)	166 (21.6)	24 (3.1)
Neutropenia	191 (24.4)	118 (15.1)	181 (23.6)	93 (12.1)
Neutrophil Count Decreased	158 (20.2)	83 (10.6)	118 (15.4)	67 (8.7)
Thrombocytopenia	157 (20.1)	19 (2.4)	145 (18.9)	13 (1.7)
Decreased Appetite	157 (20.1)	14 (1.8)	139 (18.1)	13 (1.7)
Platelet Count Decreased	156 (19.9)	20 (2.6)	115 (15.0)	19 (2.5)
Peripheral Sensory Neuropathy	137 (17.5)	16 (2.0)	119 (15.5)	14 (1.8)
Aspartate Aminotransferase Increased	122 (15.6)	12 (1.5)	69 (9.0)	5 (0.7)
All-causality Select AEs				
Endocrine	117 (15.0)	7 (0.9)	14 (1.8)	1 (0.1)
Gastrointestinal	315 (40.3)	48 (6.1)	260 (33.9)	29 (3.8)
Hepatic	267 (34.1)	45 (5.8)	186 (24.3)	29 (3.8)
Pulmonary	41 (5.2)	14 (1.8)	6 (0.8)	1 (0.1)
Renal	58 (7.4)	11 (1.4)	24 (3.1)	7 (0.9)
Skin	262 (33.5)	27 (3.5)	137 (17.9)	7 (0.9)
Hypersensitivity/Infusion Reactions	118 (15.1)	19 (2.4)	45 (5.9)	11 (1.4)
Drug-Related Select AEs				
Endocrine	107 (13.7)	5 (0.6)	3 (0.4)	0
Gastrointestinal	262 (33.5)	43 (5.5)	207 (27.0)	25 (3.3)
Hepatic	203 (26.0)	29 (3.7)	134 (17.5)	16 (2.1)
Pulmonary	40 (5.1)	14 (1.8)	4 (0.5)	1 (0.1)

Table 2.3.3.1-1: Summary of Safety - All Treated Patients

Safety Parameters	No. of Patients (%)			
	Nivo + Chemo (N = 782)		Chemo (N = 767)	
	Adverse Event Grades			
	Any Grade	Grade 3-4	Any Grade	Grade 3-4
Renal	26 (3.3)	6 (0.8)	8 (1.0)	1 (0.1)
Skin	214 (27.4)	26 (3.3)	105 (13.7)	6 (0.8)
Hypersensitivity/Infusion Reactions	111 (14.2)	17 (2.2)	42 (5.5)	11 (1.4)
All-causality IMAEs within 100 days of last dose				
Treated with Immune Modulating Medication				
Diarrhea/Colitis	26 (3.3)	17 (2.2)	0	0
Hepatitis	19 (2.4)	13 (1.7)	0	0
Pneumonitis	33 (4.2)	15 (1.9)	0	0
Nephritis/Renal Dysfunction	4 (0.5)	2 (0.3)	0	0
Rash	51 (6.5)	11 (1.4)	4 (0.5)	0
Hypersensitivity/Infusion Reactions	6 (0.8)	1 (0.1)	0	0
All-causality Endocrine IMAEs within 100 days of last dose				
With or Without Immune Modulating Medication				
Adrenal Insufficiency	5 (0.6)	1 (0.1)	2 (0.3)	2 (0.3)
Hypophysitis	6 (0.8)	3 (0.4)	0	0
Hypothyroidism/Thyroiditis	74 (9.5)	0	6 (0.8)	0
Diabetes Mellitus	2 (0.3)	1 (0.1)	0	0
Hyperthyroidism	23 (2.9)	0	2 (0.3)	0
All-causality OESIs within 100 days of last dose				
With or Without Immune Modulating Medication				
Pancreatitis	3 (0.4)	2 (0.3)	2 (0.3)	1 (0.1)
Encephalitis	1 (0.1)	1 (0.1)	0	0
Myositis/Rhabdomyolysis	0	0	2 (0.3)	2 (0.3)
Myasthenic Syndrome	0	0	0	0
Demyelination	0	0	0	0
Guillain-Barre Syndrome	1 (0.1)	1 (0.1)	0	0
Uveitis	1 (0.1)	1 (0.1)	0	0
Myocarditis	2 (0.3)	1 (0.1)	0	0
Graft Versus Host Disease	0	0	0	0

[a] The causes of death per investigator: **nivo+chemo arm:** interstitial lung disease and pneumonitis in 2 patients (due to nivo); infection and gastrointestinal toxicity (due to nivo and chemo); neutropenic fever, intestinal mucositis, stroke, gastrointestinal bleeding, septic shock, pneumonia, and febrile neutropenia (due to chemo) and **chemo arm**: pulmonary thromboembolism, asthenia/hiporexy severe, diarrhea, and interstitial pneumonia.

[b] An additional 4 deaths in the nivo+chemo arm, which were due to other reasons, were reported as related to study drug(s) (nivo, chemo, or both) per the investigator (thrombosis mesenteric vessel, disseminated intravascular coagulation, cerebral infarction, and pneumonitis); 1 of the 4 deaths, pneumonitis, was considered related to nivolumab; the other 3 events were reported as related to both nivo and chemo per the investigator.

MedDRA version 23.0 CTCAE version 4.0. All events are within 30 days of the last dose of study drug, unless otherwise indicated (e.g. any time for deaths, 100 days for IMAEs and OESIs).

Table 2.3.3.1-2: Onset, Management, and Resolution of All-Causality IMAEs Within 100 Days of Last Dose - Nivo+Chemo Treated Patients (N = 782)

IMAE Category	% Subj. with Any Grade/ Grade 3-4 IMAEs	% Subj. with IMAE leading to DC / Dose Delay	% Subj. with IMAEs Receiving IMM / High-dose Corticosteroids [a]	Median Duration IMM (range), wks	% Subj. with Resolution of IMAE [b,c]
Pneumonitis	4.2 / 1.9	1.8 / 2.0	100 / 84.8	9.29 (0.1 - 94.1)	63.6
Diarrhea/Colitis	3.3 / 2.2	2.0 / 1.5	100 / 69.2	6.71 (0.3 - 63.9)	84.6
Hepatitis	2.4 / 1.7	0.8 / 1.2	100 / 78.9	6.14 (0.1 - 100.6)	89.5
Nephritis/Renal Dysfunction	0.5 / 0.3	0.4 / 0.4	100 / 50	11.43 (6.1 - 14.4)	75.0
Rash	6.5 / 1.4	0.1 / 1.3	100 / 23.5	7.14 (0.4 - 97.0)	78.4
Hypersensitivity	0.8 / 0.1	0.1 / 0	100 / 83.3	0.21 (0.1 - 6.0)	100
Adrenal Insufficiency	0.6 / 0.1	0 / 0.1	60 / 0	35.86 (15.1 - 41.0)	20.0
Hypophysitis	0.8 / 0.4	0 / 0.5	83.3 / 33.3	24.57 (4.7 - 63.1)	66.7
Hypothyroidism/ Thyroiditis	9.5 / 0	0.3 / 0.9	5.4 / 5.4	4.64 (0.4 - 5.1)	36.5
Hyperthyroidism	2.9 / 0	0 / 0.3	4.3 / 0	16.00 (16.0 - 16.0)	78.3
Diabetes Mellitus	0.3 / 0.1	0 / 0	50 / 0	0.43 (0.4 - 0.4)	0

[a] Denominator is based on the number of patients who experienced the event

[b] Patients who experienced IMAE without worsening from baseline grade were excluded from time to resolution analysis

[c] Events without a stop date or with a stop date equal to the death as well as grade 5 events are considered unresolved

2.3.3.2 Safety in PD-L1 CPS Subgroups (Primary Analysis Data Cutoff: 27-May-2020)

The safety profile of nivo+chemo was similar in treated patients with PD-L1 CPS ≥ 5 or CPS < 5 (Table 2.3.3.2-1) and consistent with the safety profile in all treated patients (Table 2.3.3.1-1). The numerically higher frequencies of all causality and drug-related SAEs, AEs leading to discontinuation and IMAEs that were reported with nivo+chemo vs chemo in all treated patients, were also reported in the PD-L1 CPS ≥ 5 and < 5 subgroups.

The safety profile of nivo+chemo was also similar in patients with PD-L1 CPS ≥ 1 or CPS < 1 (Table 2.3.3.2-2).

Table 2.3.3.2-1: Summary of Safety - Patients with PD-L1 CPS ≥ 5 and Patients with PD-L1 CPS < 5

	Number (%) of Patients			
	Patients with PD-L1 CPS ≥ 5		Patients with PD-L1 CPS < 5	
Safety Parameters	**Nivo + Chemo N = 468**	**Chemo N = 465**	**Nivo + Chemo N = 306**	**Chemo N = 290**
Deaths	305 (65.2)	350 (75.3)	226 (73.9)	214 (73.8)
Primary Reason for Death				
Disease	260 (55.6)	306 (65.8)	199 (65.0)	193 (66.6)
Due to Study Drug Toxicity[a]	8 (1.7)	4 (0.9)	3 (1.0)	0
Unknown	8 (1.7)	11 (2.4)	4 (1.3)	7 (2.4)
Other	29 (6.2)	29 (6.2)	20 (6.5)	14 (4.8)
	Adverse Event Grades			
	Any Grade	**Grade 3-4**	**Any Grade**	**Grade 3-4**	**Any Grade**	**Grade 3-4**	**Any Grade**	**Grade 3-4**
All Causality SAEs	250 (53.4)	162 (34.6)	211 (45.4)	141 (30.3)	170 (55.6)	116 (37.9)	119 (41.0)	83 (28.6)
Drug-related SAEs	112 (23.9)	81 (17.3)	64 (13.8)	53 (11.4)	57 (18.6)	47 (15.4)	29 (10.0)	24 (8.3)
All Causality AEs leading to DC	228 (48.7)	120 (25.6)	160 (34.4)	74 (15.9)	139 (45.4)	70 (22.9)	86 (29.7)	38 (13.1)
Drug-Related AEs leading to DC	178 (38.0)	85 (18.2)	115 (24.7)	44 (9.5)	102 (33.3)	43 (14.1)	61 (21.0)	22 (7.6)
All Causality AEs	466 (99.6)	319 (68.2)	456 (98.1)	278 (59.8)	302 (98.7)	215 (70.3)	284 (97.9)	172 (59.3)
Drug-Related AEs	444 (94.9)	277 (59.2)	407 (87.5)	203 (43.7)	286 (93.5)	179 (58.5)	262 (90.3)	135 (46.6)
All Causality Select AEs								
Endocrine	80 (17.1)	7 (1.5)	10 (2.2)	1 (0.2)	37 (12.1)	0	4 (1.4)	0
Gastrointestinal	183 (39.1)	25 (5.3)	163 (35.1)	15 (3.2)	129 (42.2)	23 (7.5)	91 (31.4)	14 (4.8)
Hepatic	162 (34.6)	31 (6.6)	114 (24.5)	18 (3.9)	105 (34.3)	14 (4.6)	71 (24.5)	11 (3.8)
Pulmonary	22 (4.7)	9 (1.9)	4 (0.9)	1 (0.2)	16 (5.2)	3 (1.0)	2 (0.7)	0
Renal	41 (8.8)	9 (1.9)	18 (3.9)	5 (1.1)	17 (5.6)	2 (0.7)	5 (1.7)	2 (0.7)
Skin	161 (34.4)	18 (3.8)	75 (16.1)	4 (0.9)	98 (32.0)	8 (2.6)	60 (20.7)	3 (1.0)
Hypersensitivity/Infusion Reactions	68 (14.5)	13 (2.8)	26 (5.6)	9 (1.9)	48 (15.7)	5 (1.6)	19 (6.6)	2 (0.7)
Drug-Related Select AEs								
Endocrine	72 (15.4)	5 (1.1)	3 (0.6)	0	35 (11.4)	0	0	0
Gastrointestinal	152 (32.5)	21 (4.5)	128 (27.5)	15 (3.2)	108 (35.3)	22 (7.2)	73 (25.2)	10 (3.4)

Table 2.3.3.2-1: Summary of Safety - Patients with PD-L1 CPS ≥ 5 and Patients with PD-L1 CPS < 5

	Number (%) of Patients							
	Patients with PD-L1 CPS ≥ 5				Patients with PD-L1 CPS < 5			
Safety Parameters	Nivo + Chemo N = 468		Chemo N = 465		Nivo + Chemo N = 306		Chemo N = 290	
	Adverse Event Grades							
	Any Grade	Grade 3-4	Any Grade	Grade 3-4	Any Grade	Grade 3-4	Any Grade	Grade 3-4
Hepatic	130 (27.8)	20 (4.3)	79 (17.0)	9 (1.9)	73 (23.9)	9 (2.9)	54 (18.6)	7 (2.4)
Pulmonary	21 (4.5)	9 (1.9)	3 (0.6)	1 (0.2)	16 (5.2)	3 (1.0)	1 (0.3)	0
Renal	18 (3.8)	6 (1.3)	5 (1.1)	0	8 (2.6)	0	2 (0.7)	1 (0.3)
Skin	134 (28.6)	17 (3.6)	61 (13.1)	3 (0.6)	77 (25.2)	8 (2.6)	43 (14.8)	3 (1.0)
Hypersensitivity/Infusion Reactions	64 (13.7)	11 (2.4)	25 (5.4)	9 (1.9)	45 (14.7)	5 (1.6)	17 (5.9)	2 (0.7)
All Causality IMAEs within 100 days of last dose Treated with Immune Modulating Medication								
Diarrhea/Colitis	17 (3.6)	11 (2.4)	0	0	9 (2.9)	6 (2.0)	0	0
Hepatitis	14 (3.0)	10 (2.1)	0	0	5 (1.6)	3 (1.0)	0	0
Pneumonitis	19 (4.1)	11 (2.4)	0	0	12 (3.9)	2 (0.7)	0	0
Nephritis/Renal Dysfunction	3 (0.6)	2 (0.4)	0	0	1 (0.3)	0	0	0
Rash	35 (7.5)	9 (1.9)	4 (0.9)	0	16 (5.2)	2 (0.7)	0	0
Hypersensitivity/Infusion Reactions	3 (0.6)	1 (0.2)	0	0	3 (1.0)	0	0	0
All Causality Endocrine IMAEs within 100 days of last dose With or Without Immune Modulating Medication								
Adrenal Insufficiency	5 (1.1)	1 (0.2)	1 (0.2)	1 (0.2)	0	0	1 (0.3)	1 (0.3)
Hypophysitis	3 (0.6)	3 (0.6)	0	0	3 (1.0)	0	0	0
Hypothyroidism/Thyroiditis	48 (10.3)	0	5 (1.1)	0	27 (8.8)	0	1 (0.3)	0
Hyperthyroidism	17 (3.6)	0	2 (0.4)	0	6 (2.0)	0	0	0
Diabetes Mellitus	2 (0.4)	1 (0.2)	0	0	0	0	0	0
All-causality OESIs within 100 days of last dose With or Without Immune Modulating Medication								
Pancreatitis	1 (0.2)	1 (0.2)	2 (0.4)	1 (0.2)	2 (0.7)	1 (0.3)	0	0
Encephalitis	1 (0.2)	1 (0.2)	0	0	0	0	0	0

Table 2.3.3.2-1: Summary of Safety - Patients with PD-L1 CPS ≥ 5 and Patients with PD-L1 CPS < 5

	Number (%) of Patients							
	Patients with PD-L1 CPS ≥ 5				Patients with PD-L1 CPS < 5			
Safety Parameters	Nivo + Chemo N = 468		Chemo N = 465		Nivo + Chemo N = 306		Chemo N = 290	
	Adverse Event Grades							
	Any Grade	Grade 3-4	Any Grade	Grade 3-4	Any Grade	Grade 3-4	Any Grade	Grade 3-4
Myositis/ Rhabdomyolysis	0	0	1 (0.2)	1 (0.2)	0	0	1 (0.3)	1 (0.3)
Guillain-Barre Syndrome	0	0	0	0	1 (0.3)	1 (0.3)	0	0
Uveitis	1 (0.2)	1 (0.2)	0	0	0	0	0	0
Myocarditis	1 (0.2)	0	0	0	1 (0.3)	1 (0.3)	0	0

[a] 8 patients categorized as CPS PD-L1 indeterminate and are not included in this table. One patient had death attributed to study drug toxicity.
MedDRA version 23.0 CTCAE version 4.0. All events are within 30 days of the last dose of study drug, unless otherwise indicated.

Table 2.3.3.2-2: Summary of Safety - Patients with PD-L1 CPS ≥ 1 and Patients with PD-L1 CPS < 1

	Number (%) of Patients			
	Patients with PD-L1 CPS ≥ 1		Patients with PD-L1 CPS < 1	
Safety Parameters	**Nivo + Chemo N = 635**	**Chemo N = 633**	**Nivo + Chemo N = 139**	**Chemo N = 122**
Deaths	429 (67.6)	476 (75.2)	102 (73.4)	88 (72.1)
Primary Reason for Death				
Disease	370 (58.3)	422 (66.7)	89 (64.0)	77 (63.1)
Due to Study Drug Toxicity[a]	8 (1.3)	4 (0.6)	3 (2.2)	0
Unknown	10 (1.6)	14 (2.2)	2 (1.4)	4 (3.3)
Other	41 (6.5)	36 (5.7)	8 (5.8)	7 (5.7)
	Adverse Event Grades			
	Any Grade	**Grade 3-4**	**Any Grade**	**Grade 3-4**	**Any Grade**	**Grade 3-4**	**Any Grade**	**Grade 3-4**
All Causality SAEs	349 (55.0)	231 (36.4)	284 (44.9)	191 (30.2)	71 (51.1)	47 (33.8)	46 (37.7)	33 (27.0)
Drug-related SAEs	148 (23.3)	111 (17.5)	78 (12.3)	63 (10.0)	21 (15.1)	17 (12.2)	15 (12.3)	14 (11.5)
All Causality AEs leading to DC	312 (49.1)	164 (25.8)	210 (33.2)	99 (15.6)	55 (39.6)	26 (18.7)	36 (29.5)	13 (10.7)
Drug-Related AEs leading to DC	238 (37.5)	110 (17.3)	148 (23.4)	58 (9.2)	42 (30.2)	18 (12.9)	28 (23.0)	8 (6.6)
All Causality AEs	631 (99.4)	442 (69.6)	622 (98.3)	381 (60.2)	137 (98.6)	92 (66.2)	118 (96.7)	69 (56.6)
Drug-Related AEs	602 (94.8)	380 (59.8)	557 (88.0)	283 (44.7)	128 (92.1)	76 (54.7)	112 (91.8)	55 (45.1)

[a] 8 patients categorized as CPS PD-L1 indeterminate and are not included in this table. One patient had death attributed to study drug toxicity.

MedDRA version 23.0 CTCAE version 4.0. All events are within 30 days of the last dose of study drug.

2.3.3.3 Safety at Longer-Term Follow-Up

With longer follow-up (minimum follow-up of 2, 3, and 4 years), the safety profile of nivo+chemo in all treated patients remained consistent with that observed in the primary analysis (Table 2.3.3.3-1).[17,47,48] No new safety concerns were identified.

Table 2.3.3.3-1: Drug-related AEs and Deaths at 4 Years of Follow-up - All Treated Patients

	Nivo +Chemo N = 782		Chemo N = 767	
	Any Grade n (%)	Grade 3-4 n (%)	Any Grade n (%)	Grade 3-4 n (%)
Drug-related AEs	739 (95)	473 (60)	682 (89)	346 (45)
Drug-related SAEs	176 (23)	134 (17)	95 (12)	78 (10)
Drug-related AEs leading DC	331 (42)	147 (19)	198 (26)	73 (10)
Deaths Due to Study Drug Toxicity	16 (2)[a]		4 (< 1)[b]	

[a] Included 4 events of pneumonitis, 2 events of febrile neutropenia or neutropenic fever, 2 events of acute cerebral infarction or stroke, and 1 event each of disseminated intravascular coagulation, GI bleeding, GI toxicity, infection, intestinal mucositis, mesenteric thrombosis, pneumonia, and septic shock. The 16 deaths include 12 deaths due to study drug toxicity reported in the primary analysis and 4 deaths reported as due to "other" reasons but considered related to the study drug by the investigator at the primary analysis for which the causality was later updated by the investigator as due to study drug toxicity. All 16 deaths are included in the nivolumab (OPDIVO) USPI.[1]

[b] Included 1 event each of asthenia and severe hyporexia, diarrhea, pneumonitis, and pulmonary thromboembolism

Table includes AEs reported during treatment and for up to 30 days after the last dose of the study treatment. Deaths due to study drug toxicity are reported regardless of the timeframe.

Source: Shitara et al. 2024[48]

2.4 PD-L1 TESTING AND TREATMENT PATTERNS IN CLINICAL PRACTICE

In clinical practice, PD-L1 testing in gastroesophageal adenocarcinoma typically starts with obtaining a biopsy, which must have sufficient tissue and tumor content for PD-L1 expression determination. The biopsy sample is sent to a laboratory where PD-L1 expression is assessed by a board-certified pathologist. The results of the testing are, on average, available for the HCP approximately 1 week after submitting the samples to pathology.[51] Turnaround time can be more rapid if within an institution (eg, 2-3 days) or ≤ 2 weeks if an external laboratory is used.

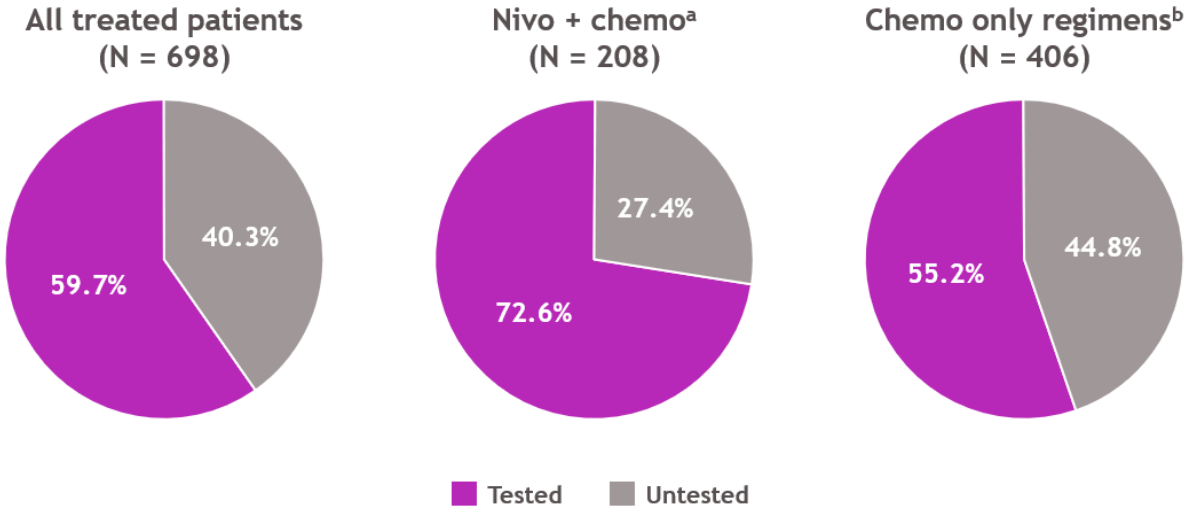
The majority of patients with gastroesophageal adenocarcinoma are PD-L1 positive based on CPS assessment: ~80% with CPS ≥ 1, ~60% with CPS ≥ 5, and ~50% with CPS ≥ 10 according to the prevalence observed in CHECKMATE-649.

Real-world data from the US Flatiron database (see description below), which is derived largely from community treatment centers, suggests that more than half of gastroesophageal adenocarcinoma patients (~60%) are tested for PD-L1 CPS, even without a requirement to do so per the drug labeling. PD-L1 testing may be even more common in academic treatment centers.

Importantly, the testing rates are ~73% for patients receiving first-line nivo+chemo, demonstrating that most decisions to treat with nivo+chemo are informed by a test result.

- Real-world data on PD-L1 testing patterns in the US was obtained from a retrospective observational study of electronic health records in the US Flatiron Health oncology database.[3] Of all treated patients with advanced/metastatic GC/GEJC/EAC (N = 698), 59.7% were tested for PD-L1 CPS (Figure 2.4-1).
  - Among the patients who received first-line nivo+chemo (N = 208), the majority (72.6%) were tested for PD-L1 CPS (Figure 2.4-1). Of the tested patients who received first line nivo+chemo (N = 151), 83.4% had CPS ≥ 1 and 14.6% had CPS < 1 (which is consistent with the prevalence of PD-L1 CPS ≥ 1 and < 1 observed in CHECKMATE-649), and for 2% the CPS was unknown.[3]

Figure 2.4-1: PD-L1 CPS Testing Patterns among Advanced/Metastatic GC/GEJC/EAC Patients Diagnosed from Jan-2023 to Mar-2024 - US Flatiron Data



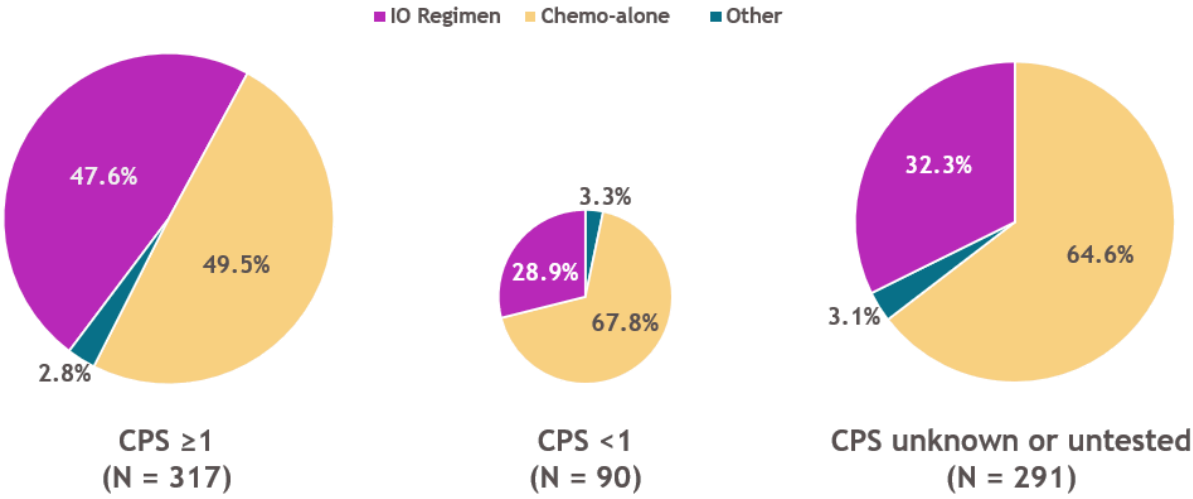
[a]Chemo regimens in this group included FOLFOX/CAPEOX/FP/XP.

[b]Chemo-only regimens included FOLFOX/CAPEOX/FP/XP and other chemo groups.

Source: Data on file[3]

An examination of treatment patterns based on the data from the Flatiron database showed that a positive test result is leading to a greater number of patients being treated with ICI+chemo regimens (47.6% vs 28.9% of patients with PD-L1 CPS ≥ 1 vs < 1, respectively); Figure 2.4-2. This is consistent with clinical practice guidelines denoting the strength of recommendations for ICI+chemo by PD-L1 score.[12,13] Per the Flatiron data, 32.3% patients with untested/unknown CPS results are treated with ICI+chemo.[3] Given the high prevalence of PD-L1 positivity described above, most patients without a test result would be considered PD-L1 positive if tested.

Figure 2.4-2: Treatment Patterns (Combined ICI Regimens) among Advanced/Metastatic GC/GEJC/EAC Patients Diagnosed from Jan-2023 to Mar-2024 - US Flatiron Data (N = 698)



Source: Data on file[3]

In summary, real-world data shows that, at present, more than half of all patients are tested for PD-L1 expression using CPS. Among those ultimately treated with nivo+chemo, approximately 73% of patients are tested for PD-L1, with most (~83%) of the treated patients having a positive PD-L1 test result. Based on these data, a high degree of PD-L1 testing is already occurring in patients treated with nivolumab, and test results are being used to guide treatment decisions with ICI+chemo in gastroesophageal adenocarcinoma clinical practice.

2.5 CHALLENGES OF PD-L1 TESTING IN CLINICAL PRACTICE

Although PD-L1 testing is occurring in clinical practice, there are challenges in precisely and reliably testing PD-L1 expression.

Tissue adequacy for PD-L1 scoring: In clinical practice, PD-L1 testing starts with obtaining a biopsy or tissue resection which must provide a sufficient amount and quality of tissue for PD-L1 expression determination. To be randomized in CHECKMATE-649, patients were required to have an evaluable PD-L1 test result of their tumor tissue as determined by a central lab. In CHECKMATE-649, approximately 15% of screen failures did not have a conclusive/evaluable PD-L1 test result (due to inadequate tissue/inability to test for PD-L1). As even in a controlled study setting PD-L1 expression could not be evaluated for a meaningful percentage of patients, it is expected that some patients in clinical practice may also not be evaluable for PD-L1 expression.

Type of tissue sample: Endoscopic mucosal biopsies are challenging for accurate PD-L1 expression assessment as they only sample a small and superficial area of the tumor. Assessment of such a small tumor area can increase the potential for false negative results.[18] On the other hand, tumor resections have large areas for PD-L1 expression evaluation. However, accurate scoring of

resections using CPS can be very challenging, if not impossible, due to the need to manually count very large numbers of stained tumor cells and immune cells.

Tumor tissue fixation: In gastroesophageal adenocarcinoma, poor fixation of tissue specimens may hamper PD-L1 evaluation due to morphologic alterations and unreliable PD-L1 staining.[52] Poor fixation can influence the staining of IHC biomarkers, including PD-L1, causing false-negative staining, edge effect and non-specific cytoplasmic staining.[53]

Tumor heterogeneity of PD-L1 expression: PD-L1 expression is characterized by a high degree of intra- and inter-tumor heterogeneity. Tissue-based assays are limited by the size and quality of specimens biopsied. Heterogeneity may refer to variability within the tumor sample itself that was biopsied (intra-tumor heterogeneity) and/or to metastases that may show different PD-L1 expression from the primary tumor or between each metastatic site (inter-tumor heterogeneity). Different CPS is not infrequently seen in clinical practice when different sites of disease are evaluated.[21,22,23,24]

Dynamic nature of PD-L1 expression: In GC, PD-L1 is expressed predominantly by immune cells (ie, macrophages) present in the invasive margin.[25] The enumeration of macrophages to determine the CPS score per the algorithm can be very challenging.[54] PD-L1 expression, particularly by immune cells, is highly inducible.[26] Cytokine-mediated upregulation is the major mechanism driving PD-L1 expression in immune cells.

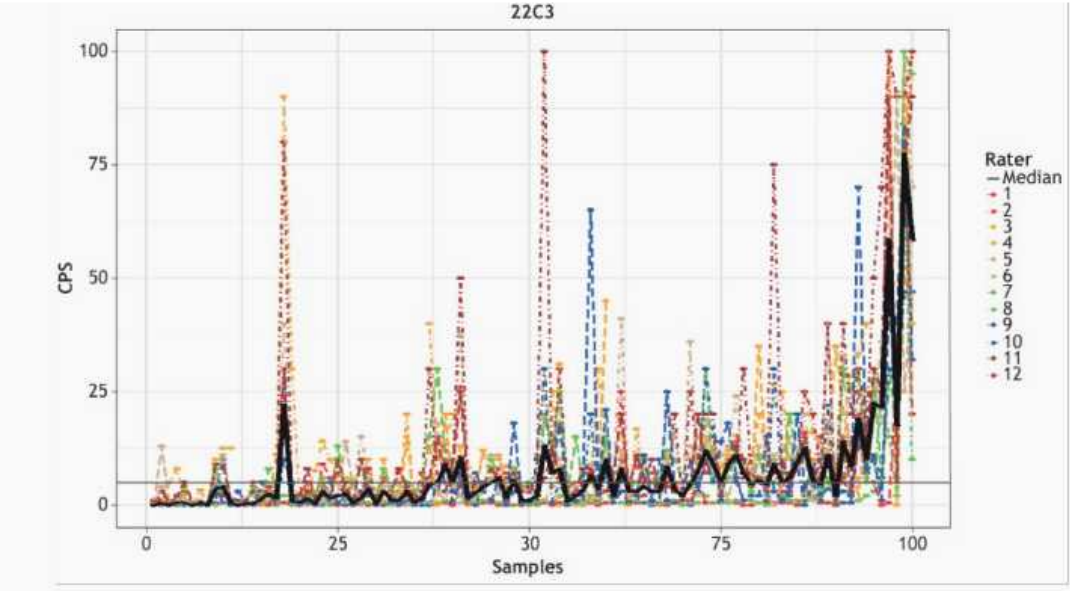
Interobserver variability: PD-L1 is considered an informative biomarker at the population level, as increased efficacy of certain treatments is observed with higher PD-L1 expression cutoffs. As such, PD-L1 functions more as a qualitative biomarker, often deployed in a binary manner (eg, CPS ≥ 1) to determine treatment eligibility. Pathologists in the real world face significant challenges in quantitatively discerning CPS values, such as differentiating between scores of 1, 3, and 7. This inter-pathologist variability can lead to inconsistencies in treatment paradigms, as the interpretation of PD-L1 expression may vary depending on the pathologist. In controlled studies[55] as well as real-world data[56], it is not uncommon to see disagreement amongst pathologists when quantitating CPS. In a real-world study, comparison of exact CPS value recorded by 12 pathologists demonstrated only fair inter-pathologist agreement, with ICCs of 0.45 (95% CI: 0.38, 0.53) for the 28-8 assay and 0.55 (95% CI: 0.47, 0.63) for the 22C3 assay.[56] Marked variability in CPS scoring was demonstrated regardless of CPS cutoff (ie, 1, 5 or 10); Figure 2.5-1. As an illustrative example, 4 pathologists may score the same tumor sample differently, with one pathologist scoring CPS 1, another CPS 3, the third CPS 5, and the fourth CPS 7. Using an example cutoff of CPS 5, would mean that a patient would not be eligible for treatment if scored by the first 2 pathologists (ie, at CPS 1 or 3, both of which are below the example treatment threshold of CPS ≥ 5), but would be eligible for treatment if scored by the last 2 pathologists (ie, at CPS 5 or 7, both of which meet the treatment threshold of CPS ≥ 5).

Based on the prevalence data alone from CHECKMATE-649 (see Section 2.4), more stringent cutoffs of CPS ≥ 5 or ≥ 10 would exclude ~40% or ~50% patients from treatment with nivo+chemo, whereas a cutoff of CPS ≥ 1 would exclude ~20% from treatment based on the

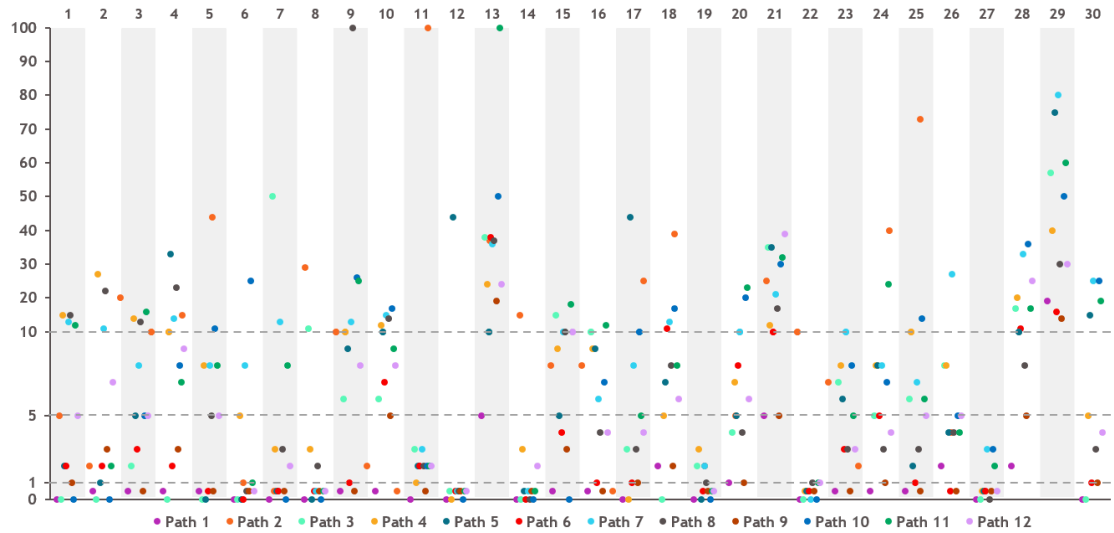
overall patient population. These analytical considerations, in conjunction with the clinical data from CHECKMATE-649, would support a cutoff of CPS ≥ 1 as to not unnecessarily limit patients who have the potential to benefit from nivo+chemo.

Figure 2.5-1: Interobserver Variability Among Pathologists Evaluating PD-L1 Expression by CPS on GC Biopsies (22C3 PharmDx Assay)

Panel A: Interobserver variability for the total 100 evaluated samples



Panel B: Interobserver variability around the CPS cutoffs of 1, 5, and 10 (dotted lines) for the first 30 samples analyzed (of the 100 samples shown in Panel A).



Source: Robert M et al [56,57]

Interlaboratory variability in PD-L1 assessment: There is also a certain degree of interlaboratory variability in PD-L1 assessment due to the use of different diagnostic assays and antibody clones with different staining patterns. Pivotal ICI studies in gastroesophageal

adenocarcinoma have used a variety of PD-L1 antibodies and assay platforms. CheckMate-649 used the Agilent/Dako PD-L1 IHC 28-8 pharmDx assay, while KEYNOTE-859 used the Agilent/Dako PD-L1 IHC 22C3 pharmDx assay, and RATIONALE-306 used the VENTANA SP263 assay. Real-world data similarly reflects a variety of assays/antibodies used in clinical practice. The Agilent/Dako PD-L1 22C3 assay is most commonly utilized in clinical practice. Per a real-world data analysis from the US Flatiron Database, of the 898 patients with advanced/metastatic GC/GEJC/EAC, 54.7% received the Agilent/Dako PD-L1 22C3 assay, 18.8% received lab-developed assays, and 9.0% received the Agilent/Dako PD-L1 28-8 assay.[58] Assay type was unknown in 17.6% of patients.

Variable levels of concordance are reported for the 28-8 and 22C3 assays with respect to CPS in the clinical setting. Yeong et al. reported that the percentages of PD-L1-positive samples at clinically relevant CPS cutoffs of ≥ 1, ≥ 5, and ≥ 10 were approximately 2-fold higher for the 28-8 assay than for the 22C3 assay.[27] Narita et al. found that 28-8 and 22C3 assay concordance improved at higher CPS cutoffs (at 5 and 10 vs 1), with a strong concordance at CPS cutoffs of 5 and 10 (kappa score = 0.881 and 0.837, respectively).[28] Kim et al. found suboptimal concordance between 28-8 and 22C3 PD-L1 assays.[29]

Application of study results to real-world practice: Additionally, there are challenges in applying pivotal study results and findings reported in the literature to real world practice. As described in Section 2.2, each of the pivotal studies CHECKMATE-649, KEYNOTE-859, and RATIONALE-305 used a different PD-L1 scoring method and antibody. Results of these studies cannot easily be used to draw a conclusion about what the data might mean when perhaps in practice a patient receives a test by a different scoring method/antibody than was used in the pivotal study of the treatment being considered. Across the literature, there are challenges in interpretation as many publications may describe results based on using lab-developed tests with the antibodies versus approved tests, amongst other variables. Also, some approaches/studies are tightly controlled (eg, 3 pathologists at the same institute) versus others that are more reflective of real-world data that may be generated (eg, multiple institutes, pathologists).

Given the challenges above, it is difficult to anticipate a certain clinical outcome based on any specific numerical PD-L1 score which might fall only slightly outside of a given cutoff range. Patients who score above a specific numerical cutoff with one scoring method/assay may not by another. Patients who score PD-L1 negative (ie, < 1) by one sample/test may not always score negative by another sample/test due to variability within a given block of tissue or among tumor sites.[30] This can lead to confusion and ambiguity in using specific numerical scores to make treatment decisions.

2.6 EVALUATION OF POTENTIAL LABELING OPTIONS IN FIRST-LINE GASTROESOPHAGEAL ADENOCARCINOMA AND THE SPONSOR'S CONCLUSION

Currently, PD-L1 testing is not mandated for use of ICI combination treatment in gastroesophageal adenocarcinoma. While across the current body of ICI combination therapy data, including CHECKMATE-649, greater benefit appears to be seen in first-line gastroesophageal

adenocarcinoma patients expressing PD-L1 (by various study-defined scoring methods and cutoffs), there are challenges around PD-L1 testing in clinical practice and the dilemma that any implemented cutoff may result in some patients who might benefit from ICIs not having access to them.

In accordance with the FDA's intent for this ODAC to discuss the emerging benefit-risk analysis of ICIs as a class in advanced gastroesophageal adenocarcinoma, the Sponsor has developed two potential labeling options for consideration, with the advantages and disadvantages of each approach summarized in Table 2.6-1.

Table 2.6-1: Assessment of Potential Indication Options in First-line Gastroesophageal Adenocarcinoma

	Advantages	Disadvantages
Option 1: Maintain the current unrestricted indication with inclusion of PD-L1 subgroup data in the label highlighting the likelihood of benefit based on PD-L1 expression, as is presently the case	• Provides HCPs and patients with opportunity to continue making informed treatment decisions on an individual patient basis, based on the USPI and NCCN guidelines. – For CHECKMATE-649, efficacy data in PD-L1 CPS subgroups are currently provided in the Clinical Studies section 14.13 of the USPI. – Real-world data from the US Flatiron database shows that a high degree of PD-L1 testing is occurring in gastroesophageal adenocarcinoma patients treated with nivolumab, and that test results are being used to guide treatment decisions. This is in line with the NCCN guidelines. • Provides flexibility (in terms of access to ICI treatment) for patients with inadequate/poor-quality tumor tissue for PD-L1 testing or inconclusive test results. Based on the prevalence (~80% of patients with CPS ≥ 1 in CHECKMATE-649), the majority of these patients would be classified as PD-L1 positive if test results were available. • A limited number of patients proceed to second-line treatment, where survival outcomes are modest and there are no ICI treatment options for most patients. Therefore, there is a public health need for accessible, effective treatments in the first-line setting. In the Sponsor's interactions with expert panels and patient advocacy organizations, retaining options for treatment and removing barriers to treatment are communicated as being of critical importance.	• Concern about exposing patients who are less likely to benefit to the safety risks of ICI treatment (mainly IMAEs which can be managed with treatment algorithms), in addition to the safety risks of chemo.
Option 2: In the event of a class label change, modify the indication to PD-L1 positive patients using the most appropriate threshold, which the Sponsor would propose to be CPS ≥ 1	• Approach would limit treatment to patients most likely to benefit based on clinical study data. – In CHECKMATE-649, KEYNOTE-859, and RATIONALE-305, significant OS improvements with ICI+chemo vs chemo were observed in patients with PD-L1 CPS ≥ 1; for patients with CPS < 1, the HRs were closer to 1 and the upper bound of the 95% CI encompassed 1. • The Sponsor proposes that a cutoff of CPS ≥1 is the most reasonable choice to ensure continued access for the greatest number of patients with potential to benefit from nivo+chemo based on clinical data from CHECKMATE-649 and accounting for interobserver variability in CPS scoring and other PD-L1 testing limitations in clinical practice.	• Mandatory PD-L1 testing could lead to treatment delay or reduced access for some patients who may have potential to benefit. – PD-L1 is a dynamic biomarker and expression is heterogeneous; therefore, some patients may be incorrectly identified as PD-L1 negative. – Some patients may have inadequate/poor quality tumor tissue for biomarker testing or inconclusive test results and new biopsies may not be possible.

Table 2.6-1: Assessment of Potential Indication Options in First-line Gastroesophageal Adenocarcinoma

	Advantages	Disadvantages
	– Although in CHECKMATE-649, the CPS ≥ 5 and ≥ 10 subgroups showed more pronounced survival benefit with nivo+chemo vs chemo, the pre-specified PD-L1 CPS ≥ 1 subgroup also showed significant and durable survival benefit and there was a trend toward OS benefit in the CPS 1 - <10 subgroup with long-term follow-up (4 years). – Implementation of a CPS-based treatment threshold could lead to exclusion of patients with potential to benefit due to high interobserver variability in CPS scoring between pathologists, and other limitations of PD-L1 testing as described in Section 2.5. The same patient may receive a CPS score from a pathologist that would make them ineligible for treatment, whereas with a different pathologist's interpretation they may be considered eligible. A cutoff of CPS ≥1 helps avoid inadvertently excluding patients who may potentially benefit from nivo+chemo treatment, given this limitation of CPS testing. – In the event of a class labeling modification, CPS is proposed by the Sponsor as the most appropriate method, as it is the most frequently used scoring method in gastroesophageal adenocarcinoma. TPS and TAP are not commonly used in this disease setting.	– Choice of a cutoff is challenging since PD-L1 expression is a continuum. – If a higher cutoff such as CPS ≥ 5 or ≥ 10 was chosen, these disadvantages would be more pronounced. For example, when considering the CHECKMATE-649 clinical data and the real-world PD-L1 CPS testing limitations (described on the left), there would be a risk of excluding an even larger proportion of patients from treatment with nivo+chemo (~40-50% at higher cutoffs), whereas a cutoff of CPS ≥ 1 would exclude ~20% from treatment based on the overall patient population.

In summary, this is a challenging situation for which multiple solutions could be considered. Overall, the Sponsor concludes that the existing labelling adequately informs prescribers on the potential benefits and risks of nivo+chemo in GC/GEJC/EAC, including on the clinical efficacy by PD-L1 expression level. The existing labelling leaves the decision-making in the hands of the treating physician and increases the chance for patients who may potentially benefit, including those without a test result, to be considered for treatment with ICIs in the first line setting. This flexibility is especially important when making treatment decisions in the first-line setting since many patients do not go on to receive later line therapy and, when they do, their choices are limited.

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