SPONSOR BRIEFING DOCUMENT
FOR THE
ONCOLOGIC DRUGS ADVISORY COMMITTEE

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OPDIVO® (nivolumab)
BLA 125554/S-105 and BLA 125554/S-106

YERVOY® (ipilimumab)
BLA 125377/S-122

Meeting Date: 26-Sep-2024

OPDIVO (nivolumab), in combination with fluoropyrimidine- and platinum-containing chemotherapy, for the first-line treatment of adult patients with unresectable advanced or metastatic esophageal squamous cell carcinoma (ESCC).

OPDIVO (nivolumab), in combination with YERVOY (ipilimumab), for the first-line treatment of adult patients with unresectable advanced or metastatic ESCC.

ADVISORY COMMITTEE BRIEFING MATERIALS AVAILABLE FOR PUBLIC RELEASE

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LIST OF ABBREVIATIONS

Abbreviation	Term
1L	First line
2L	Second line
3L	Third line
5-FU	5-fluorouracil
AE	Adverse event
AJCC	American Joint Committee on Cancer
BICR	Blinded independent central reviewer
BMS	Bristol Myers Squibb
CI	Confidence interval
Chemo	Chemotherapy
CMH	Cochran-Mantel-Haenszel
CPS	Combined positive score
CR	Complete response
DBL	Database lock
DC	Discontinue
DoR	Duration of response
EAC	Esophageal adenocarcinoma
EC	Esophageal cancer
ECOG	Eastern Cooperative Oncology Group
ESCC	Esophageal squamous cell carcinoma
FDA	Food & Drug Administration
Gr	Grade
HR	Hazard ratio
IC	Immune cell
ICI	Immune checkpoint inhibitor
IHC	Immunohistochemistry
IMAE	Immune-mediated adverse event
IMM	Immune-modulating medication
IO	Immuno-oncology
Ipi	Ipilimumab
IRT	Interactive response technology
ITT	Intention-to-treat
IV	Intravenous
HCP	Healthcare provider

LPLV	Last patient last visit
NCCN	National Comprehensive Care Network
NIH	National Institute of Health
Nivo	Nivolumab
NPA	Negative percent agreement
NPV	Negative predictive value
ODAC	Oncologic Drugs Advisory Committee
OESI	Other Event of Special Interest
OPA	Overall percent agreement
ORR	Objective response rate
OS	Overall survival
PD-1	Programmed death protein 1
PD-L1	Programmed death ligand 1
PFS	Progression-free survival
PPA	Positive percent agreement
PPV	Positive predictive value
PR	Partial response
PS	Performance score
QxW	Every x weeks
RECIST	Response Evaluation Criteria in Solid Tumours
SAE	Serious adverse event
SAP	Statistical Analysis Plan
TAP	Tumor area positivity
TC	Tumor cell
TPS	Tumor proportion score
US	United States
USPI	United States Prescribing Information

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, by PD-L1 expression level, focusing on the treatment of advanced ESCC.

1.1 CURRENT INDICATIONS AND REGULATORY HISTORY - 1L ESCC

On 30-May-2022, nivolumab, a PD-1 inhibitor, was approved by FDA for two indications in ESCC without a PD-L1 biomarker restriction based on data from the primary analysis of pivotal study CHECKMATE-648.

Table 1.1-1: FDA-Approved 1L ESCC Nivolumab Indications and Dosing based on CHECKMATE-648

Indication (OPDIVO®)[1]	Dosing
Treatment of adult patients with unresectable advanced or metastatic ESCC as first-line treatment in combination with fluoropyrimidine- and platinum-containing chemotherapy	240 mg every 2 weeks or 480 mg every 4 weeks in combination with chemotherapy regimen of fluoropyrimidine- and platinum-containing chemotherapy
Treatment of adult patients with unresectable advanced or metastatic ESCC as first-line treatment in combination with ipilimumab	3 mg/kg every 2 weeks or 360 mg every 3 weeks with ipilimumab 1 mg/kg every 6 weeks

CHECKMATE-648 showed statistically significant and clinically meaningful OS benefit vs chemotherapy with nivo+chemo or nivo+ipi in patients with PD-L1 TPS ≥ 1% (primary analysis population) and in all randomized patients (formally tested secondary population).

Although exploratory analyses of PD-L1 subgroups using scoring methods TPS and CPS (see Section 1.1.1) showed a higher likelihood of OS benefit in patients with PD-L1 expression compared to patients without PD-L1 expression regardless of the scoring system used for PD-L1 counting, CHECKMATE-648 results overall supported a positive benefit-risk assessment for the approved unrestricted indications. NCCN recommendations for nivolumab combinations in 1L ESCC are aligned with the FDA approved indications, with no recommendation to restrict treatment based on PD-L1 expression level.[2]

To help inform individual patient treatment decisions by HCPs based on potential level of benefit, OS subgroup data based on the Agilent/Dako PD-L1 IHC 28-8 pharmDx test are provided in Section 14 of the USPI for CHECKMATE-648 patients with PD-L1 TPS ≥ 1% and for exploratory subgroups of patients with PD-L1 TPS < 1%, CPS < 1, and CPS ≥ 1 (see Section 2.1).

Since the approvals of nivo+chemo and nivo+ipi in 1L ESCC, longer-term follow up (45 months) results for CHECKMATE-648 have become available. These show consistency and no meaningful changes compared with the primary analysis. Over the last several years, more 1L ICI combination studies in ESCC have expanded the body of data on PD-L1 expression and its potential relationship with ICI efficacy. However, individual studies have used different methods to assess PD-L1

expression levels and different cutoffs to define PD-L1 positivity.[3,4] The FDA has not thus far included restriction based on PD-L1 expression level in labeling for other ICIs in 1L ESCC.[3]

Based on Flatiron Health Oncology real-world US data, more than half (59.4%) of all diagnosed ESCC patients (1L) are currently being tested for PD-L1 expression even without a requirement to do so. This suggests that many treating physicians incorporate PD-L1 testing into their clinical decision making. Most testing in practice is done using the CPS methodology rather than the TPS methodology (see Section 1.4).

The totality of available data has led to the question of whether 1L ESCC patients should be selected for ICI combination treatment based on PD-L1 expression status and whether harmonization is feasible. The Sponsor's goal is to ensure that each 1L ESCC patient has every appropriate therapy available to them, and to ensure that the guidance to inform choice of treatment is clear. Therefore, the purpose of this briefing document is to:

1) Discuss the present-day treatment landscape in 1L ESCC (Section 1.2)
2) Describe clinical data by PD-L1 TPS and CPS subgroups for nivo+chemo and nivo+ipi from primary and longer-term (45 months) analyses of CHECKMATE-648 (Section 1.3)
3) Review PD-L1 utilization (Section 1.4) and challenges of PD-L1 quantification and interpretation of results (Section 1.5) in clinical practice
4) Discuss advantages and disadvantages (Section 1.6) of two potential labeling options for harmonization, developed by the Sponsor for consideration at this ODAC meeting:

- **Option 1**: Maintain the PD-L1 unrestricted 1L ESCC indications with subgroup data in labels showing levels of benefit based on PD-L1 expression, as is currently done.
- **Option 2**: In the event of a class labeling change, modify the indications to PD-L1 positive patients using the most appropriate testing method and threshold, which the Sponsor would propose to be the lowest threshold by any PD-L1 test validated within upper GI malignancies (ie, CPS ≥ 1 or TPS ≥ 1%).

The Sponsor understands the desire to harmonize patient selection based on a PD-L1 expression criterion to move closer to the goal of providing treatment to those most likely to benefit. Clinical trial data support that patients with some level of PD-L1 expression appear more likely to have survival benefit than those without PD-L1 expression. However, given the challenges of PD-L1 quantification and interpretation in clinical practice, restriction could also leave some patients with potential to benefit without an important treatment option.

The Sponsor proposes that maintaining the existing indications offers providers necessary flexibility, leaving decision-making in the hands of the treating physician and permitting opportunity for all patients to be considered for 1L ICI therapy. Since ~90% of ESCC patients show PD-L1 expression (CPS ≥ 1) and would be considered more likely to derive benefit from ICI therapy per NCCN[2], introducing the clinical burden of mandatory testing may, at a population level, result in denying treatment to more patients who might have benefited than preventing treatment of relatively few patients with true lack of PD-L1 expression.

1.1.1 PD-L1 Scoring Methods

At present, two main scoring methods, TPS (also known as the percentage of tumor cell expression [%TC]) and CPS are used to assess PD-L1 expression in tumor samples.[5] CPS is presently the most commonly utilized PD-L1 test scoring algorithm in the US for upper GI cancers, including ESCC (Section 1.4).

- TPS (%TC) is a scoring method that 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 PD-L1 IHC 22C3 pharmDx assay association with TPS and PD-L1 IHC 28-8 pharmDx assay association with tumor cell (%TC) PD-L1, both use the same scoring algorithm. This scoring method will be referred to as 'TPS' throughout this document.
- CPS is defined as the sum of PD-L1+ cells (tumor cells, lymphocytes, and macrophages) divided by the total number of viable tumor cells and multiplied by 100.

A third method, tumor area positivity (TAP) score, was used with the VENTANA SP263 assay in the RATIONALE-306 study which evaluated tislelizumab+chemo vs chemo in 1L ESCC.[4] TAP is defined as percentage of PD-L1 positive tumor cells and immune cells divided by tumor area.[6]

1.2 FIRST-LINE TREATMENT OF ADVANCED OR METASTATIC ESCC

As described in Sections 2.2.1 and 2.2.3, ESCC is a rare disease in the US with a high mortality rate. Palliative radiation and/or standard of care chemotherapy were the only treatment options for unresectable, advanced, or metastatic disease up until several years ago when ICI combination treatments (nivo+chemo, nivo+ipi, pembrolizumab+chemo) were FDA approved with PD-L1 unrestricted indications. As of August 2024, an application by BeiGene, Ltd. for tislelizumab plus chemotherapy in 1L ESCC is under FDA review.

The superior OS over chemotherapy alone shown by ICI+chemo combinations is a meaningful treatment advance for patients in 1L able to receive chemotherapy vs the previous chemo-only SOC. As the only approved dual-IO treatment for 1L ESCC, nivo+ipi provides an option for patients who may not be good candidates for chemotherapy due to comorbidity or unwillingness to receive cytotoxic drugs. A limited number of ESCC patients proceed to 2L treatment and survival in this group is generally less than 1 year (Section 2.2.5); considering this, effective treatment should be used when possible in the 1L setting and should not be deferred.

PD-L1 expression tends to be higher in SCCs than in ACs; this phenomenon is seen in EC and in other tumor types.[7,8] The majority of ESCC patients express some level of PD-L1, as defined by the scoring method and cutoff CPS $\geq$ 1.[9] Approximately 91% of ESCC patients in CHECKMATE-648 scored PD-L1 CPS $\geq$ 1 and approximately 50% scored PD-L1 TPS $\geq$ 1%.[10] Similarly, approximately 89% (480/537 [CPS-evaluable]) of ESCC patients in RATIONALE-306 scored PD-L1 CPS $\geq$ 1.[11]

Additionally (see Section 2.2.2), SCC differs from AC in that SCC involves a comparatively more chronically inflamed tumor microenvironment dominated by exhausted T cells, and suppressive

cell populations such as Tregs, MDSCs, and M2-type, suppressive macrophages.[12,13,14] This suggests that ESCC patients may have greater sensitivity to ICI therapy than AC patients.

1.3 CHECKMATE-648

At the primary analysis (data cutoff 18-Jan-2021), significant OS benefit was demonstrated in CHECKMATE-648 in all randomized patients and in the PD-L1 TPS ≥ 1% subgroup, both of which were statistically powered to show difference between nivo+chemo vs chemo and nivo+ipi vs chemo. These improvements were maintained, with upper threshold of 95% CI < 1, at 45 months follow-up.

- In exploratory subgroup analyses of OS by additional PD-L1 TPS categories, consistent benefit was seen across all cutoffs ≥ 1%, with the PD-L1 TPS < 1% subgroup OS HR point estimate close to 1. No further enrichment (ie, improved HR) was seen at cutoffs ≥ 5% or ≥ 10% compared with the cutoff ≥ 1%.
- In exploratory subgroup analyses of OS by PD-L1 CPS categories, consistent benefit was seen across all cutoffs ≥ 1, with the PD-L1 CPS < 1 subgroup OS HR point estimate close to 1 (nivo+chemo vs chemo) or equal to 1 (nivo+ipi vs chemo).
- OS improvements (TPS ≥ 1% and CPS ≥ 1) observed at the primary analysis were maintained at 45 months follow-up, with upper threshold of 95% CI < 1.
- The overall safety profile of nivo+chemo and of nivo+ipi in previously untreated patients with advanced or metastatic ESCC was manageable with established treatment algorithms. The overall safety profile of nivo+ipi was consistent with the established safety profile of immunotherapy, which is distinct from chemo. No new safety concerns were identified with either regimen. No increase in treatment-related mortality (ie, study drug toxicity-related deaths) was observed with nivo+chemo or nivo+ipi compared with chemo alone.
- No meaningful differences in safety were observed by PD-L1 subgroups.

Results (primary and 45-month) of CHECKMATE-648 are presented in Section 2.3.

1.4 UTILIZATION OF PD-L1 TESTING IN CLINICAL PRACTICE

In clinical practice, PD-L1 testing in ESCC starts with obtaining a tissue sample from biopsy or resection. Not all PD-L1 assays and test types are widely available across all clinical practices and HCPs might not choose to request a specific scoring method when ordering a PD-L1 test.

Although IO labeling does not currently mandate PD-L1 testing, more than half of all diagnosed ESCC patients are being tested in practice, according to real-world data. Data on PD-L1 testing in US clinical practice was obtained from a retrospective observational analysis of the Flatiron Health Oncology database (BMS Data on File). Among patients diagnosed with advanced ESCC who received 1L treatment from May 2022 to June 2024 (N=170), 59.4% received any PD-L1 test (TPS or CPS) and 40.6% were not tested. Of patients who were tested, a larger proportion received a CPS than a TPS test (Figure 2.4-1). In the same analysis, the assay most frequently used for CPS and TPS testing was Dako PD-L1 IHC 22C3 pharmDx. The next most frequently used type was 'lab-developed test' which inherently implies a high degree of variability (Figure 2.4-2).

Looking at treatment patterns, BMS internal chart audit (physician survey) data (N=219) suggest the presence of a positive test result leads to greater numbers of patients being treated with IO

combination treatment; (Figure 2.4-3). Approximately half (48.0%) of untested patients or those with unknown test results are treated with an IO combination; this is considered by the Sponsor to be appropriate since an unknown/untested patient is more likely to be PD-L1 positive than negative, with approximately 90% of ESCC patients PD-L1 positive per a CPS ≥ 1 cutoff.[10,11]

1.5 CHALLENGES OF PD-L1 QUANTIFICATION AND INTERPRETATION OF RESULTS

Many challenges exist in precisely and reliably quantifying 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.[15]
- Tumor tissue fixation: Poor fixation of tissue specimens may hamper PD-L1 evaluation due to morphologic alterations and unreliable PD-L1 staining.[16,17]
- Tumor heterogeneity in 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 (ie, one metastatic site may be positive and another metastatic site negative). Variable concordance data[18,19,20,21] suggest that the assessment of PD-L1 from biopsy samples may not always be representative of the real status of the biomarker in the tumor.
- Dynamic nature of PD-L1 expression: Chemoradiation or radiation can change PD-L1 expression levels.[22,23] PD-L1 status may also change after chemotherapy in ESCC,[24] meaning that PD-L1 expression may differ in the same patient prior to, early in ICI+chemo treatment, and later in ICI+chemo treatment.
- Quantification based on pathologist interpretation: At a population level, PD-L1 has been shown to be a useful enrichment tool. However, at an individual patient level, there is inherent pathologist variability in determining actual scores/values.
- Variability among antibodies/assays and scoring methods: Interlaboratory variability in PD-L1 assessment is seen due to the use of different diagnostic assays and antibody clones with different staining patterns.[25]
- Application of study results to real-world practice: Each of the pivotal studies CHECKMATE-648, KEYNOTE-590, and RATIONALE-306 used a different PD-L1 scoring method 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 2.5. Given the challenges with PD-L1 quantification and interpretation outlined, it would be difficult to anticipate a certain clinical outcome based on any specific numerical PD-L1 score, which may fall only slightly outside of a given cutoff range. Patients who score above a certain cutoff by one scoring method/assay may not by another. Patients who score PD-L1 negative by one sample may not by another sample due

to variability within a given block of tissue or among tumor sites. This can lead to confusion and ambiguity in using PD-L1 test results alone to make treatment decisions.

1.6 EVALUATION OF POTENTIAL LABELING OPTIONS IN 1L ESCC AND 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 esophageal cancer, the Sponsor has developed two potential labeling options for consideration. See Table 2.6-1 for a detailed evaluation of these summarized in tabular format.

With **Option 1** (***Maintain the PD-L1-unrestricted 1L ESCC indications with subgroup data included in labels showing levels of benefit based on PD-L1 expression, as is currently done)***, 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), and retaining ICI as a treatment option for patients who may be unable to receive a PD-L1 test, those with insufficient/inadequate tumor tissue for testing, or those who may score PD-L1 negative due to testing variability/limitations of testing precision in a disease where the large majority (> 90%) of patients are PD-L1 positive, ie, CPS ≥ 1. 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, as well as the current lack of incentive for HCPs to perform PD-L1 testing, which, while an imperfect biomarker for the reasons described can be a useful tool in clinical decision making.

With **Option 2** (***In the event of a class labeling change, modify the indications to PD-L1 positive patients using the most appropriate testing method and threshold, which the Sponsor would propose to be the lowest threshold by any PD-L1 test validated within upper GI malignancies [ie, CPS ≥ 1 or TPS ≥ 1%]***), 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 but could be missed simply due to limitations of testing. 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 ESCC 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. The Sponsor shares the FDA's desire to ensure that patients for whom benefit might reasonably be expected receive therapies and that information provided to HCPs is clear.

Based on the assessment of each approach, the Sponsor's conclusion is that the totality of data for nivolumab in 1L ESCC supports the current approved labeling as the most justified option.

2 SPONSOR BRIEFING DOCUMENT

2.1 CURRENT INDICATIONS AND REGULATORY HISTORY - 1L ESCC

As described in Section 1.1, since the approvals of nivo+chemo and nivo+ipi in 1L ESCC, results of long-term follow up (45 months) for CHECKMATE-648 have become available (Section 2.3.4), showing consistency and no meaningful changes compared with the results of the primary analysis. Additional 1L ICI combination studies in ESCC have also 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 1L ESCC patients should be selected for ICI combination treatment based on PD-L1 expression status and whether harmonization is feasible.

To help inform individual patient treatment decisions by HCPs based on potential level of benefit, OS subgroup data 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 and nivo+ipi for CHECKMATE-648 patients with PD-L1 TPS ≥ 1% (primary analysis population) and for exploratory subgroups of patients with PD-L1 TPS < 1%, PD-L1 CPS < 1, and PD-L1 CPS ≥ 1.

Current prescribing information (Section 14.12 of the USPI) is as follows:

Table 74: Efficacy Results - CHECKMATE-648

	OPDIVO with Cisplatin and Fluorouracil (n=321)	OPDIVO and Ipilimumab (n=325)	Cisplatin and Fluorouracil (n=324)	OPDIVO with Cisplatin and Fluorouracil (n=158)	OPDIVO and Ipilimumab (n=158)	Cisplatin and Fluorouracil (n=157)
	All Patients			TC PD-L1 expression ≥1%		
Overall Survival						
Deaths (%)	209 (65)	216 (66)	232 (72)	98 (62)	106 (67)	121 (77)
Median (months) (95% CI)	13.2 (11.1, 15.7)	12.8 (11.3, 15.5)	10.7 (9.4, 11.9)	15.4 (11.9, 19.5)	13.7 (11.2, 17.0)	9.1 (7.7, 10)
Hazard ratio (95% CI)[b]	0.74 (0.61, 0.90)	0.78 (0.65, 0.95)	-	0.54 (0.41, 0.71)	0.64 (0.49, 0.84)	-
p-value[c]	0.0021[S1]	0.0110[S2]	-	<0.0001[S3]	0.0010[S4]	-

Exploratory subgroup analyses of patients with TC PD-L1 expression <1% (N=492)

- OPDIVO with Chemotherapy (n = 163) vs. Chemotherapy (n = 165): unstratified OS HR was 0.99 (95% CI: 0.76, 1.29) with median OS of 12 months (95% CI: 9.9, 15.5) on the OPDIVO with Chemotherapy arm and 12.2 months (95% CI: 10.7, 14) on the Chemotherapy arm.
- OPDIVO with Ipilimumab (n = 164) vs. Chemotherapy (n = 165): unstratified OS HR was 0.97 (95% CI: 0.74, 1.26) with median OS of 12 months (95% CI: 10.1, 16.0) on the OPDIVO with Ipilimumab arm and 12.2 months (95% CI: 10.7, 14) on the Chemotherapy arm.

Exploratory subgroup analyses were also conducted by PD-L1 status per CPS (≥1 and <1)

- OPDIVO with Chemotherapy vs. Chemotherapy: unstratified OS HR was 0.69 (95% CI: 0.56, 0.84) for PD-L1 CPS ≥1 subgroup and 0.98 (95% CI: 0.50, 1.95) for PD-L1 CPS <1 subgroup.
- OPDIVO with Ipilimumab vs. Chemotherapy: unstratified OS HR was 0.76 (95% CI: 0.62, 0.93) for PD-L1 CPS ≥1 subgroup and 1.0 (95% CI: 0.52, 1.94) for PD-L1 CPS <1 subgroup.

2.2 FIRST-LINE TREATMENT OF ADVANCED OR METASTATIC ESCC

2.2.1 Incidence and Prevalence in the United States

The American Cancer Society estimates that in 2024 in the US there will be approximately 22,340 new EC cases diagnosed and about 16,120 deaths from EC.[26] EC consists of two major histological types: ESCC and EAC.

In the US, ESCC is now considered a rare disease. Per an NIH analysis, in the US, ESCC comprises ~35% of ECs while EAC comprises ~62%; the remaining ~3% are signet ring cancers.[27] According to a SEER database analysis (2020), among an estimated 13,919 total ESCC patients in the US, 41% (~4,736) presented at an early stage (Stage I/II) and 59% (~6,822) presented to clinic at a later stage (Stage III/IV) of disease.[27]

Perhaps related to decreases in smoking rates in the US, incidence of ESCC in the US has been steadily decreasing over time, so that now a community oncologist may be unlikely to encounter many of these patients in practice. SEER21 data showed that ESCC incidence has declined from 2000 to 2018 by an annual percentage change of -2.80 (95% CI: -3.0 to -2.6).[28]

2.2.2 Biology of Disease - Squamous Cell Carcinoma

There are biological differences within subtypes of esophageal cancer. PD-L1 expression tends to be higher in SCCs than in ACs; this phenomenon is seen in esophageal cancer and in other tumor types.[7,8] The majority of ESCC patients appear to express some level of PD-L1, as defined by the scoring method and cutoff PD-L1 CPS $\geq$ 1.[9] Approximately 91% of ESCC patients in CHECKMATE-648 scored PD-L1 CPS $\geq$ 1 and approximately 50% scored PD-L1 TPS $\geq$ 1%.[10] Similarly, approximately 89% (480/537 [CPS-evaluable]) of ESCC patients in RATIONALE-306 scored PD-L1 CPS $\geq$ 1.[11]

Additionally, SCC differs from AC in that SCC involves a comparatively more chronically inflamed tumor microenvironment dominated by exhausted T cells, and suppressive cell populations such as Tregs, MDSCs, and M2-type, suppressive macrophages.[12,13,14] This chronic inflammation likely stems from exposure to the more common risk factors for ESCC, smoking and alcohol intake, which lead to the production of reactive oxygen species (ROS), which subsequently induces DNA damage and activation of multiple cancer-associated pathways such as the nuclear factor-κB (NF-κB) pathway in the esophagus. This suggests that ESCC patients may have greater sensitivity to ICI therapy than AC patients.

Further, given a chronically inflamed tumor microenvironment, PD-L1 expression may not be the only indicator to determine which patients with ESCC will respond to ICI therapy. The Sponsor has investigated multiple additional biomarkers as possible predictors of response in ESCC. Results of an exploratory analysis of CHECKMATE-648 by baseline gene expression signature (data cutoff: 17-May-2022; minimum follow-up of 29 months) demonstrated that, regardless of PD-L1 expression, higher inflammation and lower β-catenin GES scores were associated with improved OS benefit with nivo+chemo and nivo+ipi vs chemo, while lower stromal GES scores were associated with improved OS benefit with nivo+ipi vs chemo.[29]

2.2.3 Historical Standard of Care Treatments and Survival Outcomes

Patients with advanced or metastatic ESCC are generally treated with chemotherapy and with localized treatments, such as radiotherapy or endoscopic therapies such as stents, for the symptomatic treatment of obstruction and dysphagia.[2,30] At the time of presentation to clinic, patients with advanced or metastatic ESCC are often frail and may have difficulty taking in adequate nutrition. In some cases, patients may proceed directly to palliative radiation therapy to improve symptoms and nutritional status before a systemic treatment decision is made.

Chemotherapy is typically offered to select patients with good PS. For previously untreated patients, combination chemotherapies (ie, fluoropyrimidine [5-FU or capecitabine] with a platinum agent [cisplatin or oxaliplatin]) are routinely used. ESCC carries a poor prognosis. For

decades, cytotoxic chemotherapy was the only recommended 1L systemic treatment for metastatic ESCC, resulting in median OS < 1 year.[31,32,33,34]

2.2.4 ICI Combination Treatments and PD-L1 Expression

Within the last several years, several IO regimens have been approved for 1L treatment of ESCC: pembrolizumab in combination with chemotherapy for treatment of advanced or metastatic EC/GEJC in 2021 based on KEYNOTE-590, and nivo+chemo and nivo+ipi for treatment of advanced or metastatic ESCC in 2022 based on CHECKMATE-648. These 3 indications are for PD-L1 unrestricted patient populations based on statistically significant improvements observed in the pivotal studies in all randomized (ITT) populations.

As of August 2024, an application by BeiGene, Ltd. for tislelizumab plus chemo as treatment of advanced/metastatic ESCC is under FDA review based on a similar PD-L1 unrestricted ITT patient population as the currently approved agents. Several other recent phase III trials have shown benefit of IO+chemo in all randomized populations, including ESCORT-1[35] (camrelizumab + carboplatin/paclitaxel), ORIENT-15[36] (sintilimab + cisplatin/paclitaxel), and JUPITER-06[37] (toripalimab + cisplatin/paclitaxel), with OS benefit seen regardless of PD-L1 status.

Meta-analyses in the literature report various findings on the potential relevance of PD-L1 expression and its association with outcomes with ICI treatment in ESCC. Rogers, et al.[9] concluded "The relevance of PD-L1 expression remains in question. ESCC patients with low expressing PD-L1 expression have shown benefit with ICI therapy, and the bulk of ESCC patients appear to express PD-L1 CPS ≥ 1. Therefore, we feel this marker for ESCC patients is likely not the key indicator to determine who will respond to ICI therapy (dual checkpoint) or anti-PD-1 plus upfront chemotherapy. We feel more work is needed to establish other predictive/prognostic biomarkers."

A summary of OS data for nivo+chemo or nivo+ipi vs chemo[1], pembrolizumab+chemo vs chemo[3], and tislelizumab+chemo[4] vs chemo is provided in Table 2.2.4-1, with PD-L1 subgroup data as available. The CHECKMATE-648, KEYNOTE-590, and RATIONALE-306 studies each demonstrated survival benefit of ICI combination treatment vs chemotherapy in an ITT or ESCC-only population. While in general, the 3 studies demonstrated that patients with higher PD-L1 expression showed more pronounced benefit than patients with lower or no PD-L1 expression, CHECKMATE-648 and RATIONALE-306 showed comparable and clinically meaningful OS HRs at relatively lower (1-<10) and relatively higher (≥10) exploratory CPS cutoffs, suggesting that OS benefit observed in the CPS ≥ 1 subgroup in these two studies is not solely driven by higher CPS cutoffs. Results by PD-L1 CPS cutoff intervals 1-<10 are not available in the literature for KEYNOTE-590 (ITT or ESCC only).

Any interpretation of results across studies must acknowledge the limitations of cross-trial comparison given potential differences in patient demographic and disease characteristics, geographic footprint, and other possible confounding factors. Each trial used a different method (not interchangeable) of scoring PD-L1, with different antibodies/assays (also not interchangeable). This results in variations in frequency of patients with PD-L1 expression at given

cutoffs among the pivotal studies. As an example, as all three reported CPS results, the percentage of patients with PD-L1 CPS ≥ 10 ranged across the 3 studies: 41.9% (ITT [ESCC only]) in CHECKMATE-648[10], 42.5% (ITT [ESCC only]) in RATIONALE-306[11], and 51.1% (ITT) and 52.2% (ESCC only) in KEYNOTE-590.[38]

Table 2.2.4-1: IO Therapies (Approved and under FDA Review) in Metastatic or Advanced Esophageal Cancer - OS HR (Investigational Therapy vs Comparator) - ITT and by PD-L1 Subgroup

IO Therapy	Studied/ Indicated Population	Study Information	OS HR [Investigative therapy vs Comparator] (All Randomized)	OS HR [Investigative therapy vs Comparator] (by PD-L1 Subgroup)
Nivo + Chemo (ITT n=321)	1L Adv/ Metastatic ESCC	**CHECKMATE-648** [1] Comparator: Chemo (ITT n=324) PD-L1 Scoring: TPS (Exploratory CPS subgroups ≥ and < 1 also shown in USPI) Median f/u (Primary Analysis): 23.5 mos (nivo); 23.7 mos (chemo)	ITT (n=645): 0.74 (95% CI: 0.61, 0.90)	TPS ≥1% (n=314): 0.54 (95% CI: 0.41, 0.71) TPS <1% (n=329): 0.99 (95% CI: 0.76, 1.29) CPS ≥1 (n=558): 0.69 (95% CI: 0.56, 0.84) CPS <1 (n=51): 0.98 (95% CI: 0.50, 1.95) (Additional CPS cutoffs: see Figure 2.3.2.1-4)
Nivo + Ipi (ITT n=325)	1L Adv/ Metastatic ESCC	**CHECKMATE-648** [1] Comparator: Chemo (ITT n=324) PD-L1 Scoring: TPS (Exploratory CPS subgroups ≥ and < 1 also shown in USPI) Median f/u (Primary Analysis): 23.9 mos (nivo); 23.7 mos (chemo)	ITT (n=649): 0.78 (95% CI: 0.65, 0.95)	TPS ≥1% (n=314): 0.64 (95% CI: 0.49, 0.84) TPS <1% (n=330): 0.97 (95% CI: 0.74, 1.26) CPS ≥1 (n=546): 0.76 (95% CI: 0.62, 0.93) CPS <1 (n=55): 1.0 (95% CI: 0.52, 1.94) (Additional CPS cutoffs: see Figure 2.3.2.2-4)
Pembro + Chemo (ITT n=373)	1L Adv/ Metastatic EC (EAC/ESCC) or GEJC siewert type 1	**KEYNOTE-590** [3,39] Comparator: Chemo (ITT, n=376) PD-L1 Scoring: CPS Median f/u (Primary Analysis): 22.6 mos	ITT (n=749): 0.73 (95% CI: 0.62, 0.86) ESCC only (n=548):[38] 0.72 (95% CI: 0.60, 0.88)	CPS ≥10 (n=383): 0.62 (95% CI: 0.49, 0.78) CPS <10 (n=347): 0.86 (95% CI: 0.68, 1.10) ESCC only: CPS ≥10 (n=286): 0.57 (95% CI: 0.43, 0.75) CPS <10 (n=247): 0.99 (95% CI: 0.74, 1.32)
Tisle + Chemo (ITT n=326)	Under FDA review, trial comprised 1L Adv/ Metastatic ESCC	**RATIONALE-306** [4] Comparator: Chemo (ITT n=323) PD-L1 Scoring: TAP (Exploratory CPS) Median f/u (Primary Analysis): 16.3 mos (tisle); 9.8 mos (chemo)	ITT (n=649): 0.66 (95% CI: 0.54, 0.80)	TAP ≥10% (n=223): 0.62 (95% CI: 0.44, 0.87) TAP <10% (n=319): 0.77 (95% CI: 0.59, 1.01) Minimum 3-year follow up:* TAP ≥10% (n=223): 0.71 (95% CI: 0.53, 0.95) TAP 5-<10% (n=135): 0.50 (95% CI: 0.33, 0.75) TAP 1-<5% (n=123): 0.86 (95% CI: 0.59, 1.26) TAP <1% (n=61): 1.21 (95% CI: 0.70, 2.08) CPS ≥10 (n=228): 0.64 (95% CI: 0.48, 0.86) CPS 5-<10 (n=115): 0.72 (95% CI: 0.47, 1.09) CPS 1-<5 (n=137): 0.71 (95% CI: 0.49, 1.03) CPS <1 (n=57): 1.36 (95% CI: 0.78, 2.38)

* At 3-year follow up, Raymond, et al. concluded that OS improvement was seen in all randomized patients and in PD-L1 subgroups with TAP ≥ 1% or CPS ≥ 1.[11]

2.2.5 Post-First-Line Treatments and Outcomes in ESCC

In clinical practice, a limited number of patients with ESCC go beyond 1L treatment. In an analysis of real-world treatment patterns, 374 patients with advanced/metastatic ESCC were identified. Of these, 263 (70.3%) received ≥ 1L therapy, 86 (23.0%) received ≥ 2L therapy, and 29 (7.8%) received ≥ 3L therapy.[40] Among patients with advanced/metastatic ESCC who do proceed to 2L+ therapy, survival is generally less than a year. In real-world analyses published in 2020, median overall survival with taxane treatment in the 2L setting was approximately 7 months and with a non-taxane treatment was approximately 5 months.[40]

In 2L+ ESCC, nivolumab[1] and tislelizumab[41] are approved as monotherapy without PD-L1 restriction. Pembrolizumab is approved as monotherapy as 2L+ treatment for patients with tumors of squamous cell histology that express PD-L1 (CPS ≥ 10) as determined by an FDA-approved test.[3] ICI treatments in 2L+ ESCC have improved survival over chemotherapy although outcomes remain modest, with median OS ranging from 8-11 months with ICI treatment and 6-8 months with chemotherapy.[42,43,44] Real-world Flatiron database analyses published in 2022 report a median OS of 10.3 months with nivolumab and 10.8 months with pembrolizumab.[45]

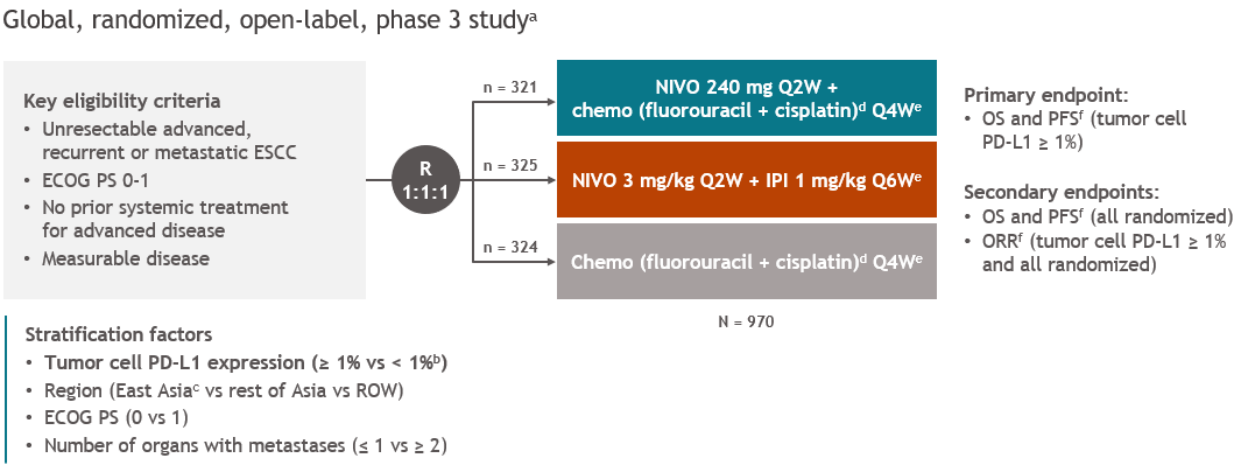
2.3 CHECKMATE-648

This section provides an overview of CHECKMATE-648, which provided pivotal evidence for the approved nivolumab indications in 1L ESCC. Results from the primary analysis are presented, with focus on PD-L1 subgroups, to support the ODAC discussion. Long-term (45 months) data are also presented and are consistent with results of the primary analysis.

2.3.1 Study Overview

CHECKMATE-648 is a global, open-label, randomized Phase 3 study of a two-IO-agent combination (nivo+ipi) or nivo+chemo (fluorouracil plus cisplatin) compared with chemo (fluorouracil plus cisplatin) in adult (≥ 18 years) male and female patients with unresectable advanced, recurrent, or metastatic ESCC (Figure 2.3.1-1).

Figure 2.3.1-1: CHECKMATE-648 Study Schematic



[a] ClinicalTrials.gov NCT3143153; [b] < 1% includes indeterminate tumor cell PD-L1 (ie, PD-L1 TPS) expression, determined by PD-L1 IHC 28-8 pharmDx assay (Dako); [c] East Asia includes patients from Japan, Korea, and Taiwan; [d] Fluorouracil 800 mg/m2 IV daily (days 1-5) and cisplatin 80 mg/m2 IV (day 1); [e] until documented disease progression (unless consented to treatment beyond progression for nivo+ipi or nivo+chemo), discontinuation due to toxicity, withdrawal of consent, or study end. Nivo is given alone or in combination with Ipi for a maximum of 2 years; [f] Per BICR.

2.3.1.1 Key Dates and Follow-Up

Table 2.3.1.1-1: Key Dates and Follow up (CHECKMATE-648)

	Primary Analysis	Long-Term Follow up
LPLV (Data cutoff date)	18-Jan-2021	25-Sep-2023
DBL	01-Mar-2021	27-Oct-2023
Minimum follow-up for OS	12.9 months (nivo+chemo vs chemo), 13.1 months (nivo+ipi vs chemo)	45.1 months (nivo+chemo vs chemo), 45.3 months (nivo+ipi vs chemo)
Median follow-up	23.5 months (nivo+chemo), 23.9 months (nivo+ipi), 23.7 months (chemo)	55.7 months (nivo+chemo), 56.1 months (nivo+ipi), 55.9 months (chemo)

2.3.1.2 Key Endpoints and Statistical Considerations

Key objectives/endpoints for nivo+chemo vs chemo and nivo+ipi vs chemo comparisons were identical and are listed in Table 2.3.1.2-1.

Table 2.3.1.2-1: Key Objectives/Endpoints (CHECKMATE-648)

Study Arm Comparisons	Endpoints
Nivo+Chemo vs Chemo and Nivo+Ipi vs Chemo	**Primary** • OS in all randomized patients with tumor cell PD-L1 (ie, TPS) ≥ 1% • PFS by BICR in all randomized patients with tumor cell PD-L1 (ie, TPS) ≥ 1%
	Secondary • OS in all randomized patients • PFS by BICR in all randomized patients • ORR by BICR in all randomized patients with tumor cell PD-L1 (ie, TPS) ≥ 1% and in all randomized patients
	Key Exploratory • DoR per BICR in all randomized patients with tumor cell PD-L1 (ie, TPS) ≥ 1% and in all randomized patients • Safety and tolerability

The primary and secondary endpoints were tested by following a hierarchical testing strategy as prespecified. All 4 primary endpoints were statistically tested; secondary endpoints were statistically tested only if corresponding primary endpoint above them in the hierarchy was significant.[10]

2.3.1.3 PD-L1 Testing Methods and Analyses

PD-L1 IHC 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. PD-L1 TPS at the 1% cutoff was a stratification factor in CHECKMATE-648.

To be randomized, patients were required to have an evaluable tumor cell PD-L1 (TPS) expression classification (≥ 1%, < 1%, or indeterminate) as determined by the central lab. The Agilent/Dako PD-L1 IHC 28-8 pharmDx assay was validated at the TPS 1% cutoff.

As described in Table 2.3.1.3-1, only the PD-L1 subgroup TPS ≥ 1% was evaluated in CHECKMATE-648 as a primary analysis population. All PD-L1 TPS subgroup analyses at cutoffs other than ≥ 1% and all PD-L1 CPS subgroup analysis were exploratory. CPS data was generated centrally at HistoGeneX by rescoring the slides originally stained for PD-L1 and scored by TPS at LabCorp.

Table 2.3.1.3-1: PD-L1 Analysis Methods and Assay Validation Status in CHECKMATE-648

PD-L1 Assay	PD-L1 Scoring Method	PD-L1-based Stratification Factor	PD-L1-based Statistical Analysis Populations	Predefined[b] PD-L1 Subgroups for Exploratory Analysis	PD-L1 Assay Cutoff Development Status	Testing Laboratory
Agilent/ Dako PD-L1 IHC 28-8 pharmDx	TPS	≥ 1%, < 1%[a]	TPS ≥ 1% (primary)	TPS: <1%, <5%, ≥5%, <10%, ≥10%	Validated for investigational use at 1%	LabCorp
Agilent/ Dako PD-L1 IHC 28-8 pharmDx	CPS	NA	NA	CPS: <1, ≥1, <5, ≥5, <10, ≥10	N/A	HistoGeneX

[a] < 1% includes indeterminate PD-L1 TPS expression. [b] Additional (not predefined in CHECKMATE-648 SAP) exploratory analyses were performed for PD-L1 TPS and CPS subgroups at cutoffs: 1-<5(%), 1-<10(%), and 5-<10(%).

Rationale for selection of TPS in CHECKMATE-648: CHECKMATE-648 enrolled patients with ESCC (not AC) regardless of PD-L1 expression, and randomization was stratified by tumor-cell PD-L1 expression (TPS) of ≥ 1% vs < 1%. When CHECKMATE-648 was designed, PD-L1 TPS data from the ATTRACTION-1 study showed that ESCC patients with higher tumor-cell PD-L1 expression (TPS ≥ 1%) had numerically higher response rate compared with patients who had lower PD-L1 expression (TPS < 1%) (ORR of 23.8% vs. 12.5%, respectively).[46] Conversely, CHECKMATE-649 enrolled patients with GC, GEJC, and EAC. PD-L1 CPS has generally been used in AC of the stomach, GEJ, and esophagus. PD-L1 expression by CPS has shown better enrichment for efficacy of ICIs than tumor-cell PD-L1 (TPS) expression in gastric, GEJ, and EAC in the CHECKMATE-032 study. The primary endpoints of CHECKMATE-649 were amended because PD-L1 CPS has been shown to be a more appropriate scoring method than tumor cell PD-L1 (TPS) expression in predicting the efficacy of ICI-based therapies for gastroesophageal adenocarcinoma. The primary endpoints of CHECKMATE-648 were not amended to measure PD-L1 CPS because, unlike in AC, there was no evidence demonstrating an advantage of CPS over TPS in predicting efficacy of ICIs in ESCC patients.

2.3.1.4 Patient Population

Baseline demographic and disease characteristics in all randomized patients were representative of the advanced or metastatic ESCC population and balanced between the treatment arms. The study population was reflective of the geographic prevalence of ESCC.[10]

2.3.2 Efficacy (Primary Analysis; Data Cutoff 18-Jan-2021)

2.3.2.1 Nivolumab + Chemotherapy

At the primary analysis, statistically significant and clinically meaningful improvements in OS were observed with nivo+chemo vs chemo in:

- **All randomized patients with PD-L1 TPS ≥ 1%** (primary endpoint)
- **All randomized patients** (formally tested and pre-specified secondary endpoint)

Results for additional endpoints (PFS, ORR, DOR) in the primary (PD-L1 TPS ≥ 1%) and secondary (all randomized) analysis populations are shown in Table 2.3.2.1-1.

Key efficacy results for nivo+chemo vs chemo by PD-L1 subgroups (TPS and CPS) are summarized in Table 2.3.2.1-2.

OS benefit with nivo+chemo vs chemo was observed at the lowest PD-L1 positive cutoffs evaluated: in the PD-L1 TPS ≥ 1% subgroup, as noted above, and in the PD-L1 CPS ≥ 1 subgroup (HR = 0.69 [95% CI: 0.56, 0.84]).

Table 2.3.2.1-1: Summary of Key Efficacy Results - Nivo+Chemo vs Chemo - All Randomized Patients with PD-L1 TPS ≥ 1% and All Randomized Patients (CHECKMATE-648)

	All Randomized Patients with PD-L1 TPS ≥ 1%		All Randomized Patients	
Efficacy Parameter	**Nivo+Chemo N = 158**	**Chemo N = 157**	**Nivo+Chemo N= 321**	**Chemo N = 324**
OS	**Primary Endpoint**		**Secondary Endpoint**	
Events, n (%)	98 (62.0)	121 (77.1)	209 (65.1)	232 (71.6)
HR (95% CI)[a]	0.54 (0.41, 0.71)		0.74 (0.61, 0.90)	
Stratified 2-sided log-rank test p-value[b]	< 0.0001		0.0021	
Median OS, mo (95% CI)[c]	15.44 (11.93, 19.52)	9.07 (7.69, 9.95)	13.21 (11.14, 15.70)	10.71 (9.40, 11.93)
PFS per BICR	**Primary Endpoint**		**Secondary Endpoint**	
Events, n (%)	117 (74.1)	100 (63.7)	235 (73.2)	210 (64.8)
HR (95% CI)[a]	0.65 (0.49, 0.86)		0.81 (0.67, 0.99)	
Stratified 2-sided log-rank test p-value[b]	0.0023		0.0355	
Median PFS, mo. (95% CI)[c]	6.93 (5.68, 8.34)	4.44 (2.89, 5.82)	5.82 (5.55, 7.00)	5.59 (4.27, 5.88)
ORR per BICR	**Secondary Endpoint**		**Secondary Endpoint**	
N Responders (ORR%)[d]	84 (53.2)	31 (19.7)	152 (47.4)	87 (26.9)
95% CI	(45.1, 61.1)	(13.8, 26.8)	(41.8, 53.0)	(22.1, 32.0)
Difference (95% CI)[e]	33.4 (23.5, 43.4)		20.6 (13.4, 27.7)	
DOR per BICR	**Exploratory Endpoint**		**Exploratory Endpoint**	
n Events/N Responders (%)	55/84 (65.5)	17/31 (54.8)	96/152 (63.2)	51/87 (58.6)
Median, mo. (95% CI)[c]	8.38 (6.90, 12.35)	5.68 (4.40, 8.67)	8.18 (6.90, 9.69)	7.13 (5.65, 8.21)
Proportion (95% CI)[c] with DOR of:				
≥12 mo.	0.40 (0.28, 0.51)	0.13 (0.02, 0.33)	0.39 (0.30, 0.47)	0.23 (0.13, 0.34)

[a] Stratified Cox proportional hazards model. HR is Nivo+Chemo over Chemo.

[b] Log-rank test stratified by ECOG PS (0 vs 1) and number of organs with metastases (≤1 vs ≥2) as recorded in IRT for All Randomized Patients with Tumor Cell PD-L1 ≥1%, and stratified by ECOG PS, number of organs with metastases, and tumor cell PD-L1 expression (≥1% or <1% and indeterminate) as recorded in IRT for All Randomized Patients.

[c] Based on Kaplan-Meier estimates.

[d] CR or PR per RECIST 1.1. CI based on the Clopper and Pearson method.

[e] Strata adjusted difference in objective response rate (Nivo+Chemo - Chemo) based on CMH method of weighting. Stratified by ECOG PS (0 vs 1) and number of organs with metastases (≤1 vs ≥2) as recorded in IRT for All Randomized Patients with Tumor Cell PD-L1 ≥1%, and stratified by ECOG PS, number of organs with metastases, and tumor cell PD-L1 expression (≥1% or <1% and indeterminate) as recorded in IRT for All Randomized Patients.

Table 2.3.2.1-2: Summary of Efficacy Results by PD-L1 Subgroups (TPS and CPS) - Nivo+Chemo vs Chemo (CHECKMATE-648)

Endpoint	PD-L1 TPS Subgroups	PD-L1 CPS Subgroups
OS	• Consistent benefit was seen across all cutoffs ≥ 1%. However, no enrichment (ie, improved HR) was seen at cutoffs ≥ 5% or ≥ 10% vs the cutoff ≥ 1% (Figure 2.3.2.1-1). • The PD-L1 TPS < 1% subgroup HR point estimate was close to 1. • HR point estimates for additional TPS cutoff intervals ≥ 1% (1-<5% [0.39], 1<10% [0.42], and 5<10% [0.58]) were lower, in favor of nivo+chemo, than the HR point estimate for TPS ≥ 10% (0.62), further suggesting that it is not only patients with the highest levels of PD-L1 expression driving OS benefit in the TPS ≥ 1% subgroup. It should be noted that sample sizes and number of events were small for the cutoff intervals 1-<5% 1-<10%, and 5-<10%. • Median OS was longer across all cutoff intervals with nivo+chemo than with chemo, except for TPS < 1%.	• Consistent benefit was seen across all cutoffs ≥ 1, with comparable HR point estimates across cutoff intervals (Figure 2.3.2.1-4). • The < 1 subgroup HR point estimate was close to 1. Sample size for < 1 subgroup was very small (n=27 [nivo+chemo]; n=24 [chemo]), number of events was small, and 95% CI was wide; therefore, results should be interpreted with caution. • HR point estimates for additional CPS cutoff intervals ≥ 1 (1-<5 [0.63], 1<10 [0.75], and 5<10 [0.81]) were clinically meaningful in favor of nivo+chemo and, for CPS 1-5, equal to the HR point estimate for CPS ≥ 10 (0.63), suggesting that the OS benefit seen in the CPS ≥ 1 subgroup is not driven only by patients with high CPS scores. • Median OS was longer across all cutoff intervals with nivo+chemo than with chemo, except for CPS < 1.
PFS per BICR	• Consistent benefit was seen across all cutoffs ≥ 1%. However, no enrichment (ie, improved HR) was seen at cutoffs ≥ 5% or ≥ 10% vs the cutoff ≥ 1% (Figure 2.3.2.1-2). • The PD-L1 TPS < 1% subgroup HR point estimate was close to 1.	• Broadly similar HR point estimates, favoring nivo+chemo, were observed across all CPS cutoffs (Figure 2.3.2.1-5).
ORR per BICR	• Higher ORR per BICR with nivo+chemo vs chemo was observed across all TPS subgroups, including < 1% (Figure 2.3.2.1-3). • Numerically higher ORR with nivo+chemo vs chemo across PD-L1 TPS subgroups was due to more CRs and PRs with nivo+chemo. • In the PD-L1 TPS ≥ 1% subgroup there were 26 [16.5%] CRs and 58 [36.7%] PRs with nivo+chemo vs 8 [5.1%] CRs and 23 [14.7%] PRs with chemo.	• Higher ORR per BICR with nivo+chemo vs chemo was observed across all CPS subgroups, including < 1 (Figure 2.3.2.1-6). • Numerically higher ORR with nivo+chemo vs chemo across PD-L1 CPS subgroups was due to more CRs and PRs with nivo+chemo. • In the PD-L1 CPS ≥ 1 subgroup there were 39 [14.0%] CRs and 96 [34.5%] PRs with nivo+chemo vs 18 [6.4%] CRs and 58 [20.7%] PRs with chemo.
DOR per BICR	• Among responders with PD-L1 TPS ≥ 1%, nivo+chemo showed longer median DOR and more patients with ≥ 12 months DOR vs chemo (Table 2.3.2.1-1).	• Among all randomized responders, nivo+chemo showed similar median DOR but more patients with ≥ 12 months DOR vs chemo (Table 2.3.2.1-1). As responders in the PD-L1 CPS ≥ 1 subgroup comprised a large majority of the all randomized population

Table 2.3.2.1-2: Summary of Efficacy Results by PD-L1 Subgroups (TPS and CPS) - Nivo+Chemo vs Chemo (CHECKMATE-648)

Endpoint	PD-L1 TPS Subgroups	PD-L1 CPS Subgroups
		(135/152 [88.8%] nivo+chemo; 76/87 [87.4%] chemo), a similar trend was observed in this subgroup. • Among responders with PD-L1 CPS ≥ 1, slightly longer median DOR was observed (8.18 months [95% CI: 6.70, 11.07]) with nivo+chemo than with chemo (6.90 months [95% CI: 5.65, 8.21]).

Except OS and PFS per BICR analyses which were formally tested in the PD-L1 TPS ≥ 1% subgroup, all PD-L1 TPS subgroup analyses at other cutoffs were exploratory (not formally tested) in CHECKMATE-648. All PD-L1 CPS subgroup analyses were exploratory (not formally tested) in CHECKMATE-648.

Figure 2.3.2.1-1: OS by PD-L1 TPS Subgroup - Nivo+Chemo vs Chemo (CHECKMATE-648)

PD-L1	Nivo + Chemo N	Nivo + Chemo Events	Nivo + Chemo Median, months	Chemo N	Chemo Events	Chemo Median, months	HR (95% CI)
All Randomized	321	209	13.21	324	232	10.71	**0.74** (0.61, 0.90)
TPS <1%	163	111	11.96	166	111	12.16	**0.98** (0.76, 1.28)
TPS ≥1% and <5%	38	20	19.45	41	35	7.79	**0.39** (0.22, 0.68)
TPS <5%	201	131	12.81	207	146	11.14	**0.82** (0.65, 1.04)
TPS ≥1% and <10%	56	32	16.46	59	50	7.89	**0.42** (0.27, 0.67)
TPS ≥5% and <10%	18	12	8.67	18	15	8.11	**0.58** (0.27, 1.29)
TPS <10%	219	143	12.29	225	161	10.84	**0.79** (0.63, 0.99)
TPS ≥1%	158	98	15.44	156	120	9.20	**0.55** (0.42, 0.72)
TPS ≥5%	120	78	13.67	115	85	9.49	**0.61** (0.45, 0.83)
TPS ≥10%	102	66	14.69	97	70	9.49	**0.62** (0.44, 0.87)

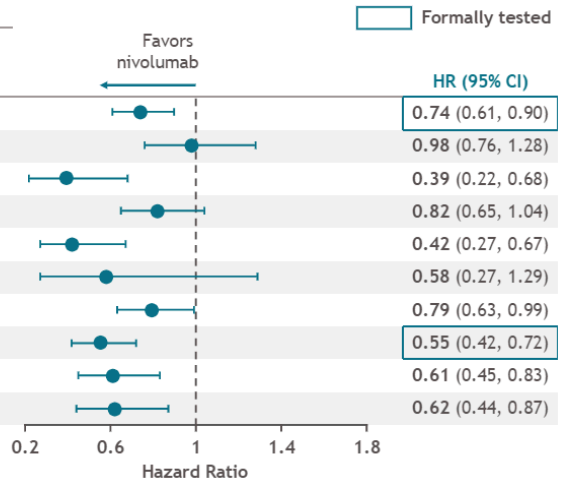


Figure 2.3.2.1-2: PFS per BICR by PD-L1 TPS Subgroup - Nivo+Chemo vs Chemo (CHECKMATE-648)

PD-L1	Nivo + Chemo N	Nivo + Chemo Events	Nivo + Chemo Median, months	Chemo N	Chemo Events	Chemo Median, months	HR (95% CI)
All Randomized	321	235	5.82	324	210	5.59	**0.79** (0.65, 0.95)
TPS <1%	163	118	5.55	166	108	5.75	**0.95** (0.73, 1.24)
TPS ≥1% and <5%	38	24	8.34	41	26	4.44	**0.49** (0.27, 0.88)
TPS <5%	201	142	5.75	207	134	5.68	**0.85** (0.67, 1.08)
TPS ≥1% and <10%	56	37	7.62	59	39	4.17	**0.41** (0.25, 0.68)
TPS ≥5% and <10%	18	13	7.33	18	13	4.17	**0.31** (0.13, 0.77)
TPS <10%	219	155	5.78	225	147	5.65	**0.80** (0.63, 1.00)
TPS ≥1%	158	117	6.93	156	100	4.44	**0.64** (0.48, 0.84)
TPS ≥5%	120	93	6.80	115	74	4.40	**0.68** (0.50, 0.93)
TPS ≥10%	102	80	6.80	97	61	4.50	**0.77** (0.55, 1.09)

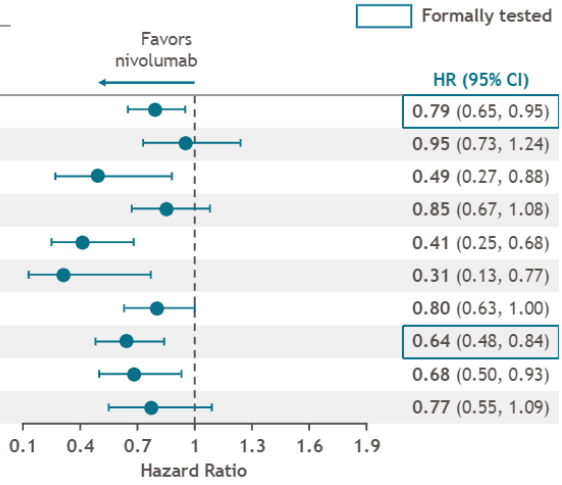


Figure 2.3.2.1-3: ORR per BICR by PD-L1 TPS Subgroup - Nivo+Chemo vs Chemo (CHECKMATE-648)

Population	Nivo + Chemo N	Nivo + Chemo N Responders	Nivo + Chemo ORR%	Chemo N	Chemo N Responders	Chemo ORR%	ORR Difference, % (95% CI)
All Randomized	321	152	47.35	324	87	26.85	**20.50** (13.09, 27.60)
TPS <1%	163	68	41.72	166	56	33.73	**7.98** (-2.47, 18.21)
TPS ≥1% - <5%	38	22	57.89	41	8	19.51	**38.38** (17.01, 55.39)
TPS <5%	201	90	44.78	207	64	30.92	**13.86** (4.45, 22.94)
TPS ≥1% - <10%	56	33	58.83	59	10	16.95	**41.98** (24.58, 56.04)
TPS ≥5% - <10%	18	11	61.11	18	2	11.11	**50.00** (18.75, 70.24)
TPS <10%	219	101	46.12	225	66	29.33	**16.79** (7.78, 25.43)
TPS ≥1%	158	84	53.16	156	31	19.87	**33.29** (22.87, 42.69)
TPS ≥5%	120	62	51.67	115	23	20.00	**31.67** (19.58, 42.44)
TPS ≥10%	102	51	50.00	97	21	21.65	**28.35** (15.11, 40.19)

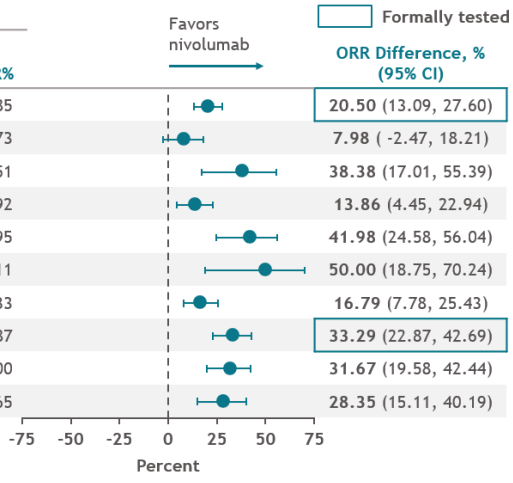


Figure 2.3.2.1-4: OS by PD-L1 CPS Subgroup - Nivo+Chemo vs Chemo (CHECKMATE-648)

	Nivo + Chemo			Chemo			
PD-L1	N	Events	Median, months	N	Events	Median, months	HR (95% CI)
All Randomized	321	209	13.21	324	232	10.71	**0.74** (0.61, 0.90)
CPS <1	27	19	9.86	24	16	12.09	**0.98** (0.50, 1.95)
CPS ≥1 - <5	70	43	11.99	67	50	8.90	**0.63** (0.42, 0.95)
CPS <5	97	62	11.96	91	66	9.40	**0.74** (0.52, 1.04)
CPS ≥1 - <10	143	96	12.06	135	102	9.40	**0.75** (0.57, 0.99)
CPS ≥5 - <10	73	53	12.09	68	52	10.78	**0.81** (0.55, 1.20)
CPS <10	170	115	12.06	159	118	9.69	**0.78** (0.60, 1.01)
CPS ≥1	278	177	13.77	280	205	9.76	**0.69** (0.56, 0.84)
CPS ≥5	208	134	15.18	213	155	11.14	**0.69** (0.55, 0.87)
CPS ≥10	135	81	16.13	145	103	11.63	**0.63** (0.47, 0.84)

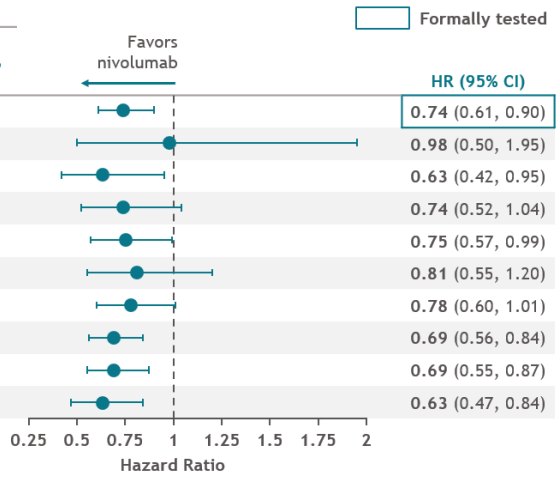


Figure 2.3.2.1-5: PFS per BICR by PD-L1 CPS Subgroup - Nivo+Chemo vs Chemo (CHECKMATE-648)

	Nivo + Chemo			Chemo			
PD-L1	N	Events	Median, months	N	Events	Median, months	HR (95% CI)
All Randomized	321	235	5.82	324	210	5.59	**0.79** (0.65, 0.95)
CPS <1	27	21	6.31	24	14	5.68	**0.79** (0.39, 1.60)
CPS ≥1 - <5	70	45	5.68	67	42	4.17	**0.71** (0.47, 1.09)
CPS <5	97	66	5.75	91	56	4.27	**0.74** (0.51, 1.06)
CPS ≥1 - <10	143	100	5.55	135	85	4.50	**0.82** (0.61, 1.09)
CPS ≥5 - <10	73	55	5.45	68	43	4.76	**0.91** (0.60, 1.36)
CPS <10	170	121	5.55	159	99	4.76	**0.81** (0.62, 1.06)
CPS ≥1	278	201	5.78	280	184	5.55	**0.78** (0.64, 0.95)
CPS ≥5	208	156	6.80	213	142	5.62	**0.79** (0.63, 1.00)
CPS ≥10	135	101	7.03	145	99	5.78	**0.74** (0.56, 0.98)

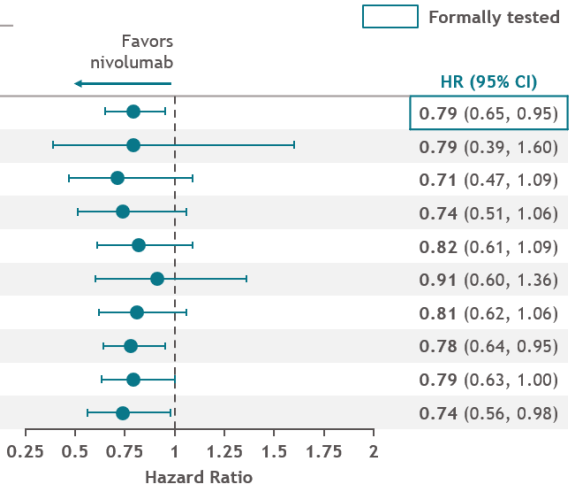
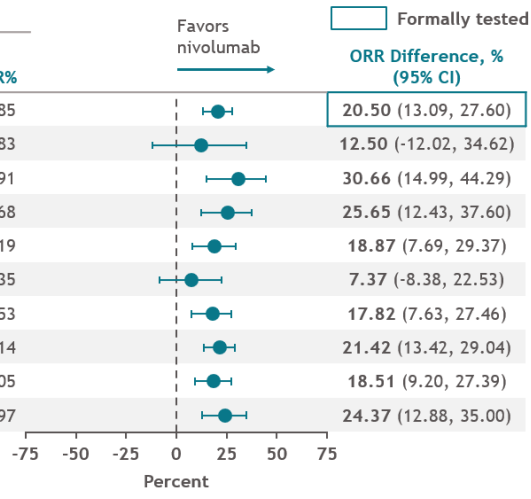


Figure 2.3.2.1-6: ORR per BICR by PD-L1 CPS Subgroup - Nivo+Chemo vs Chemo (CHECKMATE-648)

	Nivo + Chemo			Chemo			
Population	N	N Responders	ORR%	N	N Responders	ORR%	ORR Difference, % (95% CI)
All Randomized	321	152	47.35	324	87	26.85	**20.50** (13.09, 27.60)
CPS <1	27	9	33.33	24	5	20.83	**12.50** (-12.02, 34.62)
CPS ≥1 - <5	70	34	48.57	67	12	17.91	**30.66** (14.99, 44.29)
CPS <5	97	43	44.33	91	17	18.68	**25.65** (12.43, 37.60)
CPS ≥1 - <10	143	63	44.06	135	34	25.19	**18.87** (7.69, 29.37)
CPS ≥5 - <10	73	29	39.73	68	22	32.35	**7.37** (-8.38, 22.53)
CPS <10	170	72	42.35	159	39	24.53	**17.82** (7.63, 27.46)
CPS ≥1	278	135	48.56	280	76	27.14	**21.42** (13.42, 29.04)
CPS ≥5	208	101	48.56	213	64	30.05	**18.51** (9.20, 27.39)
CPS ≥10	135	72	53.33	145	42	28.97	**24.37** (12.88, 35.00)



2.3.2.2 *Nivolumab + Ipilimumab*

At the primary analysis, statistically significant and clinically meaningful improvements in OS were observed with nivo+ipi vs chemo in:

- **All randomized patients with PD-L1 TPS ≥ 1%** (primary endpoint)
- **All randomized patients** (formally tested and pre-specified secondary endpoint)

Results for additional endpoints (PFS, ORR, DOR) in the primary (PD-L1 TPS ≥ 1%) and secondary (all randomized) analysis populations are shown in Table 2.3.2.2-1.

Key efficacy results for nivo+ipi vs chemo by PD-L1 subgroups (TPS and CPS) are summarized in Table 2.3.2.2-2.

OS benefit with nivo+ipi vs chemo was observed at the lowest PD-L1 positive cutoffs evaluated: in the PD-L1 TPS ≥ 1% subgroup, as noted above, and in the PD-L1 CPS ≥ 1 subgroup (HR = 0.76 [95% CI: 0.62, 0.93]).

Table 2.3.2.2-1: Summary of Key Efficacy Results - Nivo+Ipi vs Chemo - All Randomized Patients with PD-L1 TPS ≥ 1% and All Randomized Patients (CHECKMATE-648)

	All Randomized Patients with PD-L1 TPS ≥1%		All Randomized Patients	
Efficacy Parameter	**Nivo+Ipi N = 158**	**Chemo N = 157**	**Nivo+Ipi N = 325**	**Chemo N = 324**
OS	**Primary Endpoint**		**Secondary Endpoint**	
Events, n (%)	106 (67.1)	121 (77.1)	216 (66.5)	232 (71.6)
HR (95% CI)[a]	0.64 (0.49, 0.84)		0.78 (0.62, 0.98)	
Stratified 2-sided log-rank test p-value[b]	0.0010		0.0110	
Median OS, mo (95% CI)[c]	13.70 (11.24, 17.02)	9.07 (7.69, 9.95)	12.75 (11.27, 15.47)	10.71 (9.40, 11.93)
PFS per BICR	**Primary Endpoint**		**Secondary Endpoint**	
Events, n (%)	123 (77.8)	100 (63.7)	258 (79.4)	210 (64.8)
HR (95% CI)[a]	1.02 (0.78, 1.34)		1.26 (1.04, 1.52)	
Stratified 2-sided log-rank test p-value[b]	0.8958		NA	
Median PFS, mo. (95% CI)[c]	4.04 (2.40, 4.93)	4.44 (2.89, 5.82)	2.92 (2.66, 4.17)	5.59 (4.27, 5.88)
ORR per BICR	**Secondary Endpoint**		**Secondary Endpoint**	
N Responders (%)[d]	56 (35.4)	31 (19.7)	90 (27.7)	87 (26.9)
95% CI	(28.0, 43.4)	(13.8, 26.8)	(22.9, 32.9)	(22.1, 32.0)
ORR Difference (95% CI)[e]	15.7 (5.9, 25.4)		0.9 (-5.9, 7.6)	
DOR per BICR	**Exploratory Endpoint**		**Exploratory Endpoint**	
n events/N responders (%)	31/56 (55.4)	17/31 (54.8)	53/90 (58.9)	51/87 (58.6)

Table 2.3.2.2-1: Summary of Key Efficacy Results - Nivo+Ipi vs Chemo - All Randomized Patients with PD-L1 TPS ≥ 1% and All Randomized Patients (CHECKMATE-648)

	All Randomized Patients with PD-L1 TPS ≥1%		All Randomized Patients	
Efficacy Parameter	**Nivo+Ipi N = 158**	**Chemo N = 157**	**Nivo+Ipi N = 325**	**Chemo N = 324**
Median, mo. (95% CI)	11.83 (7.10, 27.43)	5.68 (4.40, 8.67)	11.07 (8.31, 14.00)	7.13 (5.65, 8.21)
Proportion (95% CI)[c] with DOR of:				
≥12 mo.	0.49 (0.35, 0.62)	0.13 (0.02, 0.33)	0.48 (0.36, 0.58)	0.23 (0.13, 0.34)

[a] Stratified Cox proportional hazards model. HR is Nivo+Ipi over Chemo.

[b] Log-rank test stratified by ECOG PS (0 vs 1) and number of organs with metastases (≤ 1 vs ≥ 2) as recorded in IRT for All Randomized Patients with Tumor Cell PD-L1 ≥1%, and stratified by ECOG PS, number of organs with metastases, and tumor cell PD-L1 expression (≥1% or <1% and indeterminate) as recorded in IRT for All Randomized Patients.

[c] Based on Kaplan-Meier estimates.

[d] CR or PR per RECIST 1.1. CI based on the Clopper and Pearson method.

[e] Strata adjusted difference in objective response rate (nivo+ipi - chemo) based on CMH method of weighting. Stratified by ECOG PS (0 vs 1) and number of organs with metastases (≤1 vs ≥2) per IRT for all randomized patients with tumor cell PD-L1 ≥1%, and stratified by ECOG PS, number of organs with metastases, and tumor cell PD-L1 expression (≥1% or <1% and indeterminate) per IRT for all randomized patients.

Table 2.3.2.2-2: Summary of Efficacy Results by PD-L1 Subgroups (TPS and CPS) - Nivo+Ipi vs Chemo (CHECKMATE-648)

Endpoint	PD-L1 TPS Subgroups	PD-L1 CPS Subgroups
OS	• Consistent benefit was seen across all cutoffs ≥ 1%. However, no enrichment (ie, improved HR) was seen at cutoffs ≥ 5% or ≥ 10% vs the cutoff ≥ 1% (Figure 2.3.2.2-1). • The < 1% subgroup HR point estimate was close to 1. • HR point estimates for additional TPS cutoff intervals ≥ 1% (1-<5% [0.52], 1-<10% [0.48], and 5-<10% [0.41]) were lower, in favor of nivo+ipi, than the HR point estimate for TPS ≥ 10% (0.71), further suggesting that it is not only patients with the highest levels of PD-L1 expression driving OS benefit in the TPS ≥ 1% subgroup. It should be noted that sample sizes and number of events were small for the cutoff intervals 1-<5% 1-<10%, and 5-<10%. • Median OS was longer across all cutoff intervals with nivo+ipi than with chemo, except for TPS < 1%.	• Consistent benefit was seen across all cutoffs ≥ 1, with comparable HR point estimates across cutoff intervals (Figure 2.3.2.2-4). • The < 1 subgroup HR point estimate was equal to 1. The sample size for the < 1 subgroup was very small (n=31 [nivo+ipi]; n=24 [chemo]), number of events was small, and 95% CI was wide; therefore, results should be interpreted with caution. • Although the HR point estimate was lowest (0.64) in the subgroup with highest CPS (≥ 10), HR point estimates for additional CPS cutoff intervals ≥ 1 (1-<5 [0.83] and 1-<10 [0.88]) were clinically meaningful in favor of nivo+ipi, suggesting that the OS benefit seen in the CPS ≥ 1 subgroup is not driven only by patients with high CPS scores. • Median OS was longer across most cutoff intervals with nivo+ipi than with chemo, except for CPS < 1. Median OS was similar with nivo+ipi vs chemo at the interval CPS 5-<10, with HR point estimate of 0.93.
PFS per BICR	• Subgroup analysis showed no clear benefit of nivo+ipi over chemo across all TPS cutoffs (Figure 2.3.2.2-2).	• No benefit was observed with nivo+ipi vs chemo across the cutoffs. The HR point estimate was > 1.0 across all subgroups except ≥ 10 (Figure 2.3.2.2-5). • As the mechanism of action of ICIs is different than that of chemo, it is known that PFS may not correlate well with OS.[47] Although improved PFS was not seen with nivo+ipi, this did not preclude the improved OS observed. As noted, among nivo+ipi responders, longer DOR was observed than with chemo.
ORR per BICR	• Higher ORRs per BICR with nivo+ipi vs chemo were observed in the subgroups ≥ 1%, ≥ 5%, ≥ 10%, 1-<5%, 1-<10%, and 5-<10% (Figure 2.3.2.2-3). • Numerically higher ORR with nivo+ipi vs chemo in these subgroups was due to more CRs with nivo+ipi. • In the PD-L1 TPS ≥ 1% subgroup there was improved ORR with nivo+ipi vs chemo and more CRs with nivo+ipi: 28 [17.7%] (nivo+ipi) and 8 [5.1%] (chemo)	• While ORR were broadly similar with nivo+ipi vs chemo across CPS cutoffs (Figure 2.3.2.2-6), patients treated with nivo+ipi had more CRs than patients treated with chemo. • In the PD-L1 CPS ≥ 1 subgroup there was similar ORR with nivo+ipi vs chemo but more CRs with nivo+ipi: 32 [12.0%] (nivo+ipi) and 18 [6.4%] (chemo).

Table 2.3.2.2-2: Summary of Efficacy Results by PD-L1 Subgroups (TPS and CPS) - Nivo+Ipi vs Chemo (CHECKMATE-648)

Endpoint	PD-L1 TPS Subgroups	PD-L1 CPS Subgroups
DOR per BICR	• Among responders with PD-L1 TPS ≥ 1%, nivo+ipi showed longer median DOR and more patients with ≥ 12 months DOR vs chemo (Table 2.3.2.2-1).	• Among all randomized responders, nivo+ipi showed longer median DOR and more patients with ≥ 12 months DOR vs chemo (Table 2.3.2.2-1). As patients in the PD-L1 CPS ≥ 1 subgroup comprised a large majority of the all randomized population (74/90 [82.2%] nivo+ipi; 76/87 [87.4%] chemo), a similar trend was observed in this subgroup. • Among responders with PD-L1 CPS ≥ 1, approximately 5 months longer median DOR was observed (11.83 months [95% CI: 7.10, 23.62]) with nivo+ipi than with chemo (6.90 months [95% CI: 5.65, 8.21]).

Except OS and PFS per BICR analyses formally tested in the PD-L1 TPS ≥ 1% subgroup, all PD-L1 TPS subgroup analyses at other cutoffs were exploratory (not formally tested) in CHECKMATE-648. All PD-L1 CPS subgroup analyses were exploratory (not formally tested) in CHECKMATE-648.

Figure 2.3.2.2-1: OS by PD-L1 TPS Subgroup - Nivo+Ipi vs Chemo (CHECKMATE-648)

	Nivo + Ipi			Chemo			
PD-L1	N	Events	Median, months	N	Events	Median, months	HR (95% CI)
All Randomized	325	216	12.75	324	232	10.71	0.78 (0.65, 0.95)
TPS <1%	164	108	11.96	166	111	12.16	0.96 (0.74, 1.25)
TPS ≥1% - <5%	38	26	14.62	41	35	7.79	0.52 (0.31, 0.87)
TPS <5%	202	134	12.42	207	146	11.14	0.86 (0.68, 1.09)
TPS ≥1% - <10%	55	37	14.62	59	50	7.89	0.48 (0.31, 0.75)
TPS ≥5% - <10%	17	11	13.82	18	15	8.11	0.41 (0.18, 0.93)
TPS <10%	219	145	12.52	225	161	10.84	0.82 (0.65, 1.02)
TPS ≥1%	158	106	13.70	156	120	9.20	0.63 (0.48, 0.82)
TPS ≥5%	120	80	13.04	115	85	9.49	0.66 (0.48, 0.90)
TPS ≥10%	103	69	13.04	97	70	9.49	0.71 (0.51, 1.00)

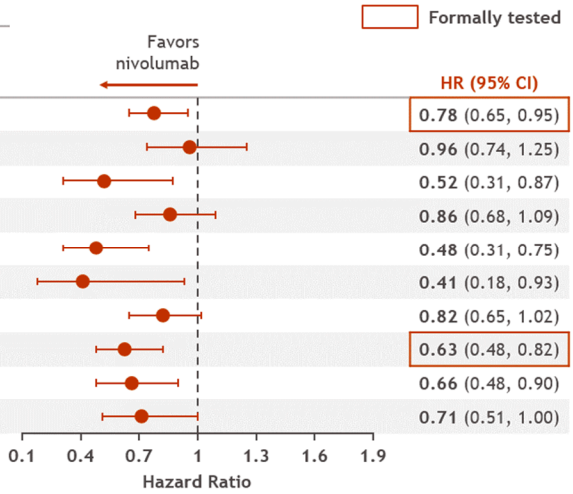


Figure 2.3.2.2-2: PFS per BICR by PD-L1 TPS Subgroup - Nivo+Ipi vs Chemo (CHECKMATE-648)

	Nivo + Ipi			Chemo			
PD-L1	N	Events	Median, months	N	Events	Median, months	HR (95% CI)
All Randomized	325	258	2.92	324	210	5.59	1.20 (1.00, 1.45)
TPS <1%	164	132	2.83	166	108	5.75	1.45 (1.13, 1.88)
TPS ≥1% - <5%	38	29	2.25	41	26	4.44	1.08 (0.63, 1.87)
TPS <5%	202	161	2.79	207	134	5.68	1.35 (1.07, 1.70)
TPS ≥1% - <10%	55	43	2.79	59	39	4.17	0.99 (0.64, 1.55)
TPS ≥5% - <10%	17	14	4.14	18	13	4.17	0.75 (0.34, 1.65)
TPS <10%	219	175	2.83	225	147	5.65	1.30 (1.04, 1.62)
TPS ≥1%	158	123	4.04	156	100	4.44	0.98 (0.75, 1.29)
TPS ≥5%	120	94	4.24	115	74	4.40	0.95 (0.70, 1.30)
TPS ≥10%	103	80	4.24	97	61	4.50	0.98 (0.70, 1.39)

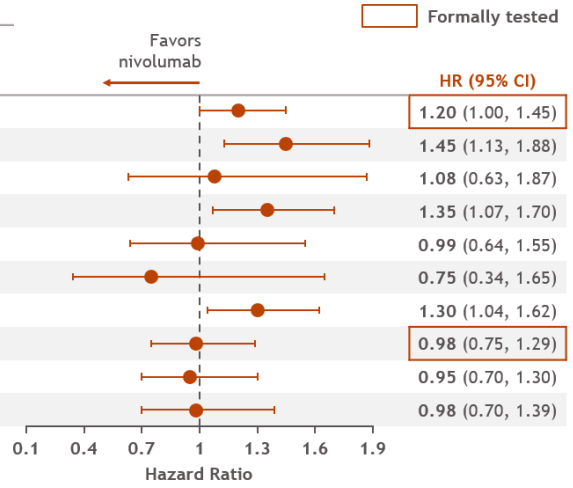


Figure 2.3.2.2-3: ORR per BICR by PD-L1 TPS Subgroup - Nivo+Ipi vs Chemo (CHECKMATE-648)

	Nivo + Ipi			Chemo			
Population	N	N Responders	ORR%	N	N Responders	ORR%	ORR Difference, % (95% CI)
All Randomized	325	90	27.69	324	87	26.85	0.84 (-6.00, 7.67)
TPS <1%	164	33	20.12	166	56	33.73	-13.61 (-22.86, -4.04)
TPS ≥1% - <5%	38	12	31.58	41	8	19.51	12.07 (-7.07, 30.46)
TPS <5%	202	45	22.28	207	64	30.92	-8.64 (-17.03, -0.06)
TPS ≥1% - <10%	55	18	32.73	59	10	16.95	15.78 (-0.09, 30.92)
TPS ≥5% - <10%	17	6	35.29	18	2	11.11	24.18 (-3.99, 48.92)
TPS <10%	219	51	23.29	225	66	29.33	-6.05 (-14.12, 2.16)
TPS ≥1%	158	56	35.44	156	31	19.87	15.57 (5.68, 25.06)
TPS ≥5%	120	44	36.67	115	23	20.00	16.67 (5.13, 27.57)
TPS ≥10%	103	38	36.89	97	21	21.65	15.24 (2.60, 27.17)

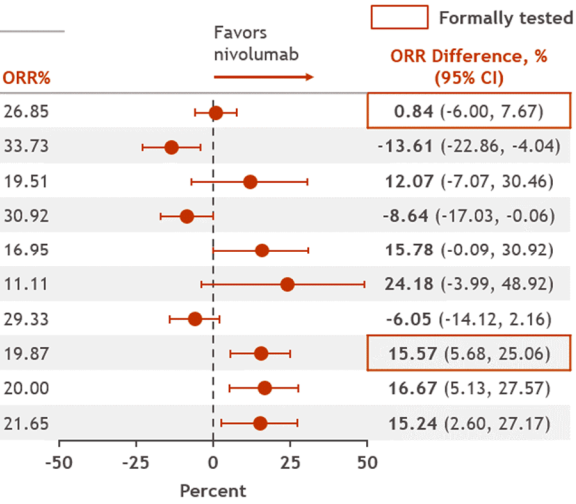


Figure 2.3.2.2-4: OS by PD-L1 CPS Subgroup - Nivo+Ipi vs Chemo (CHECKMATE-648)

	Nivo + Ipi			Chemo			
PD-L1	N	Events	Median, months	N	Events	Median, months	HR (95% CI)
All Randomized	325	216	12.75	324	232	10.71	0.78 (0.65, 0.95)
CPS <1	31	21	11.47	24	16	12.09	1.00 (0.52, 1.94)
CPS ≥1 - <5	75	52	10.74	67	50	8.90	0.83 (0.56, 1.23)
CPS <5	106	73	11.43	91	66	9.40	0.87 (0.62, 1.21)
CPS ≥1 - <10	140	100	10.74	135	102	9.40	0.88 (0.67, 1.16)
CPS ≥5 - <10	65	48	10.87	68	52	10.78	0.93 (0.62, 1.37)
CPS <10	171	121	11.24	159	118	9.69	0.89 (0.69, 1.14)
CPS ≥1	266	179	12.75	280	205	9.76	0.76 (0.62, 0.93)
CPS ≥5	191	127	14.52	213	155	11.14	0.72 (0.57, 0.91)
CPS ≥10	126	79	16.69	145	103	11.63	0.64 (0.47, 0.86)

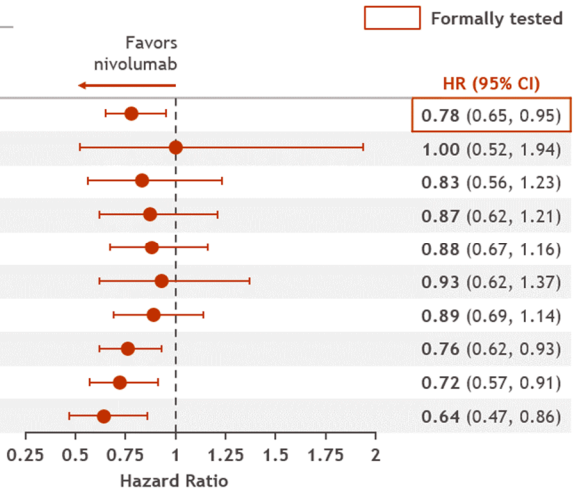


Figure 2.3.2.2-5: PFS per BICR by PD-L1 CPS Subgroup - Nivo+Ipi vs Chemo (CHECKMATE-648)

	Nivo + Ipi			Chemo			
PD-L1	N	Events	Median, months	N	Events	Median, months	HR (95% CI)
All Randomized	325	258	2.92	324	210	5.59	1.20 (1.00, 1.45)
CPS <1	31	29	3.22	24	14	5.68	1.49 (0.78, 2.85)
CPS ≥1 - <5	75	59	2.79	67	42	4.17	1.39 (0.93, 2.07)
CPS <5	106	88	2.79	91	56	4.27	1.41 (1.00, 1.97)
CPS ≥1 - <10	140	109	1.74	135	85	4.50	1.45 (1.09, 1.94)
CPS ≥5 - <10	65	50	1.58	68	43	4.76	1.51 (0.99, 2.28)
CPS <10	171	138	2.60	159	99	4.76	1.45 (1.11, 1.88)
CPS ≥1	266	206	2.83	280	184	5.55	1.18 (0.97, 1.45)
CPS ≥5	191	147	3.65	213	142	5.62	1.11 (0.88, 1.40)
CPS ≥10	126	97	4.44	145	99	5.78	0.98 (0.73, 1.30)

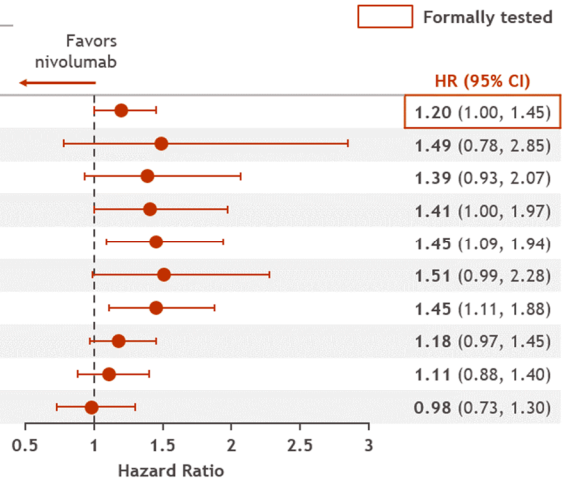
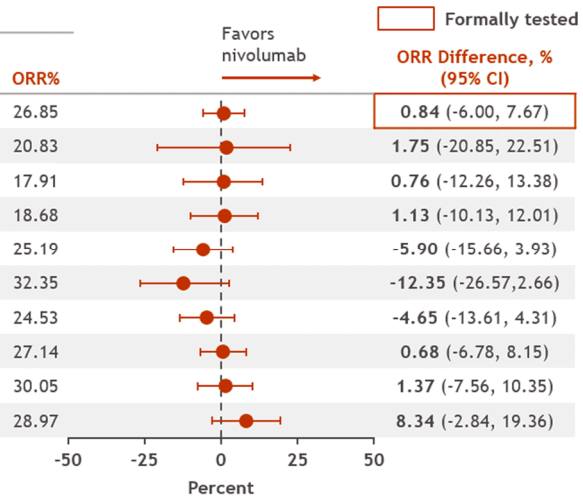


Figure 2.3.2.2-6: ORR per BICR by PD-L1 CPS Subgroup - Nivo+Ipi vs Chemo (CHECKMATE-648)

	Nivo + Ipi			Chemo			
Population	N	N Responders	ORR%	N	N Responders	ORR%	ORR Difference, % (95% CI)
All Randomized	325	90	27.69	324	87	26.85	0.84 (-6.00, 7.67)
CPS <1	31	7	22.58	24	5	20.83	1.75 (-20.85, 22.51)
CPS ≥1 - <5	75	14	18.67	67	12	17.91	0.76 (-12.26, 13.38)
CPS <5	106	21	19.81	91	17	18.68	1.13 (-10.13, 12.01)
CPS ≥1 - <10	140	27	19.29	135	34	25.19	-5.90 (-15.66, 3.93)
CPS ≥5 - <10	65	13	20.00	68	23	32.35	-12.35 (-26.57,2.66)
CPS <10	171	34	19.88	159	39	24.53	-4.65 (-13.61, 4.31)
CPS ≥1	266	74	27.82	280	76	27.14	0.68 (-6.78, 8.15)
CPS ≥5	191	60	31.41	213	64	30.05	1.37 (-7.56, 10.35)
CPS ≥10	126	47	37.30	145	42	28.97	8.34 (-2.84, 19.36)



2.3.3 *Safety (Primary Analysis; Data Cutoff 18-Jan-2021)*

The safety profile of nivo+chemo and of nivo+ipi in previously untreated patients with advanced or metastatic ESCC was manageable with established treatment algorithms. The safety profile of nivo+ipi was consistent with the established safety profile of immunotherapy, which is distinct from chemo. No new safety concerns were identified with either regimen. No increase in treatment-related mortality (ie, study drug toxicity-related deaths) was observed with nivo+chemo or nivo+ipi compared with chemo alone.

As anticipated, AEs of immune-mediated etiology (IMAEs) were reported more frequently in the IO-containing regimens (nivo+chemo and nivo+ipi) than with chemotherapy alone. Overall, the majority of IMAEs were Grade 1-2. Most IMAEs, including those that were Grade 3-4, were manageable using the established treatment algorithms for nivolumab +/- ipilimumab, with resolution occurring when IMMs (mostly systemic corticosteroids) were administered (Table 2.3.3-2). Some patients' endocrine IMAEs were not considered resolved due to the continuing need for hormone replacement therapy. OESIs were infrequent, and most events resolved.

As shown in Table 2.3.3-3 (nivo+chemo) and Table 2.3.3-4 (nivo+ipi), safety was similar across PD-L1 TPS subgroups (≥ 1% or < 1%) and consistent with safety in all treated patients (Table 2.3.3-1). Safety was not evaluated for PD-L1 CPS subgroups ≥ 1 and < 1 due to very small sample size in the < 1 group and the ≥ 1 subgroup comprising a large majority of the all-treated population.

Table 2.3.3-1: Summary of Safety - All Treated Patients (CHECKMATE-648)

	No. of Patients (%)					
Safety Parameter	**Nivo+Chemo (N=310)**		**Nivo+Ipi (N=322)**		**Chemo (N=304)**	
Deaths	200 (64.5)		215 (66.8)		224 (73.7)	
Primary Reason for Death						
Disease	168 (54.2)		176 (54.7)		204 (67.1)	
Study Drug Toxicity[a]	5 (1.6)		5 (1.6)		4 (1.3)	
Unknown	10 (3.2)		12 (3.7)		8 (2.6)	
Other	17 (5.5)		22 (6.8)		8 (2.6)	
	Any Grade	**Grade 3-4**	**Any Grade**	**Grade 3-4**	**Any Grade**	**Grade 3-4**
All-causality SAEs	180 (58.1)	132 (42.6)	214 (66.5)	146 (45.3)	128 (42.1)	96 (31.6)
Drug-related SAEs	74 (23.9)	57 (18.4)	103 (32.0)	73 (22.7)	49 (16.1)	38 (12.5)
All-causality AEs leading to DC	126 (40.6)	51 (16.5)	81 (25.2)	54 (16.8)	77 (25.3)	28 (9.2)
Drug-Related AEs leading to DC	106 (34.2)	29 (9.4)	57 (17.7)	41 (12.7)	59 (19.4)	14 (4.6)
All-causality AE	308 (99.4)	216 (69.7)	316 (98.1)	192 (59.6)	301 (99.0)	165 (54.3)
Drug-related AEs	297 (95.8)	147 (47.4)	256 (79.5)	102 (31.7)	275 (90.5)	108 (35.5)
≥ 15% Drug-related AEs in Any Treatment						
Rash	24 (7.7)	1 (0.3)	55 (17.1)	7 (2.2)	5 (1.6)	0

Table 2.3.3-1: Summary of Safety - All Treated Patients (CHECKMATE-648)

	No. of Patients (%)					
Safety Parameter	**Nivo+Chemo (N=310)**		**Nivo+Ipi (N=322)**		**Chemo (N=304)**	
	Any Grade	**Grade 3-4**	**Any Grade**	**Grade 3-4**	**Any Grade**	**Grade 3-4**
Diarrhoea	60 (19.4)	3 (1.0)	32 (9.9)	2 (0.6)	46 (15.1)	6 (2.0)
Fatigue	61 (19.7)	7 (2.3)	29 (9.0)	4 (1.2)	50 (16.4)	11 (3.6)
Nausea	182 (58.7)	11 (3.5)	26 (8.1)	1 (0.3)	158 (52.0)	8 (2.6)
Decreased appetite	132 (42.6)	13 (4.2)	19 (5.9)	5 (1.6)	130 (42.8)	9 (3.0)
Vomiting	56 (18.1)	7 (2.3)	18 (5.6)	4 (1.2)	49 (16.1)	9 (3.0)
Stomatitis	98 (31.6)	20 (6.5)	14 (4.3)	0	71 (23.4)	5 (1.6)
Anaemia	93 (30.0)	30 (9.7)	12 (3.7)	2 (0.6)	67 (22.0)	17 (5.6)
Malaise	50 (16.1)	1 (0.3)	12 (3.7)	0	45 (14.8)	0
Constipation	59 (19.0)	2 (0.6)	7 (2.2)	1 (0.3)	66 (21.7)	1 (0.3)
Neutrophil count decreased	65 (21.0)	25 (8.1)	2 (0.6)	0	52 (17.1)	24 (7.9)
Hiccups	42 (13.5)	0	2 (0.6)	0	53 (17.4)	0
All-causality IMAEs within 100 d of last dose treated with IMM by Category						
Diarrhea/Colitis	6 (1.9)	4 (1.3)	11 (3.4)	4 (1.2)	0	0
Hepatitis	2 (0.6)	1 (0.3)	13 (4.0)	9 (2.8)	0	0
Pneumonitis	10 (3.2)	2 (0.6)	12 (3.7)	7 (2.2)	0	0
Nephritis/Renal Dysfunction	3 (1.0)	3 (1.0)	4 (1.2)	2 (0.6)	0	0
Rash	16 (5.2)	1 (0.3)	44 (13.7)	8 (2.5)	2 (0.7)	1 (0.3)
Hypersensitivity/Infusion Reactions	0	0	1 (0.3)	0	0	0
All-causality Endocrine IMAEs within 100 d of last dose by Category						
Adrenal Insufficiency	5 (1.6)	1 (0.3)	18 (5.6)	7 (2.2)	0	0
Hypophysitis	2 (0.6)	1 (0.3)	21 (6.5)	10 (3.1)	0	0
Hypothyroidism/Thyroiditis	19 (6.1)	0	50 (15.5)	1 (0.3)	0	0
Diabetes Mellitus	3 (1.0)	3 (1.0)	5 (1.6)	2 (0.6)	0	0
Hyperthyroidism	7 (2.3)	0	19 (5.9)	2 (0.6)	1 (0.3)	0
All-causality OESIs within 100 d of last dose with/without IMM by Category[b]						
Pancreatitis	0	0	5 (1.6)	4 (1.2)	0	0
Encephalitis	0	0	3 (0.9)	3 (0.9)	0	0
Myositis/Rhabdomyolysis	2 (0.6)	1 (0.3)	2 (0.6)	0	0	0
Uveitis	2 (0.6)	0	2 (0.6)	1 (0.3)	0	0
Myocarditis	0	0	2 (0.6)	0	0	0

MedDRA version 23.1 CTCAE version 4.0. All events are within 30 days of the last dose of study drug, unless otherwise indicated (eg, any time for deaths, 100 days for IMAEs and OESIs).

Footnotes from previous page:

[a] **In the nivo+chemo arm** two events (pneumonitis [2]) were reported related to nivo only, one (pneumatosis intestinalis [1]) was reported related to nivo and to chemo, and two (pneumonia [1] and acute kidney injury [1]) were reported related to chemo only.
In the nivo+ipi arm events reported related to nivo and ipi were pneumonitis [2], interstitial lung disease [1], pulmonary embolism [1], and acute respiratory distress syndrome [1] (note: while this death was attributed to study drug toxicity, the causality of this fatal SAE was reported on the AE eCRF as not related to study therapy by the investigator).
In the chemo arm events reported related to chemo were septic shock [1], sepsis [1], acute kidney injury [1], and pneumonia [1].

[b] **In the nivo+chemo arm**: OESIs were reported in 4 patients (6 events), of which 4 events resolved (2 with IMM).
In the nivo+ipi arm: OESIs were reported in 14 patients (23 events), of which 19 events resolved (11 with IMM).

Table 2.3.3-2: All-Causality IMAEs within 100 days of Last Dose - All Patients Treated with Nivo+Chemo or Nivo+Ipi (CHECKMATE-648)

	Nivo+Chemo (N=310)			Nivo+Ipi (N=322)		
IMAE Category	**% Pt. with Any Grade/ Grade 3-4 IMAEs**	**% Pt. with IMAE leading to DC / Dose Delay**	**% Pt. with Resolution of IMAE[a,b,c]**	**% Pt. with Any Grade/ Grade 3-4 IMAEs**	**% Pt. with IMAE leading to DC / Dose Delay**	**% Pt. with Resolution of IMAE[a,b,c]**
Pneumonitis	3.2 / 0.6	2.3 / 0.6	70.0	3.7 / 2.2	2.8 / 0.3	50.0
Diarrhea/Colitis	1.9 / 1.3	1.0 / 0.6	83.3	3.4 / 1.2	1.2 / 1.6	100
Hepatitis	0.6 / 0.3	0.3 / 0.3	100	4.0 / 2.8	1.9 / 2.2	84.6
Nephritis/Renal Dysfunction	1.0 / 1.0	0.6 / 0	66.7	1.2 / 0.6	0 / 0.6	75.0
Rash	5.2 / 0.3	0 / 1.0	62.5	13.7 / 2.5	0.6 / 2.8	68.2
Hypersensitivity	0 / 0	NA	NA	0.3 / 0	0 / 0	100
Adrenal Insufficiency	1.6 / 0.3	0.3 / 1.0	0	5.6 / 2.2	1.6 / 2.8	16.7
Hypophysitis	0.6 / 0.3	0 / 0.6	0	6.5 / 3.1	0.9 / 4.3	23.8
Hypothyroidism/ Thyroiditis	6.1 / 0	0 / 2.3	10.5	15.5 / 0.3	0.6 / 3.1	26.0
Hyperthyroidism	2.3/ 0	0 / 1.0	71.4	5.9 / 0.6	0.3 / 1.2	78.9
Diabetes Mellitus	1.0 / 1.0	0.3 / 0.3	0	1.6 / 0.6	0.6 / 0.9	0

MedDRA Version: 23.1. CTC Version 4.0. Includes events reported between first dose and 100 days after last dose of study therapy.

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

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

[c] For each patient, the longest duration of immune-mediated AEs where immune modulation is considered.

Table 2.3.3-3: Safety Summary - Nivo+Chemo vs Chemotherapy - All Treated Patients by PD-L1 Subgroups TPS < 1% and ≥ 1% (CHECKMATE-648)

	Patients, n (%)			
	PD-L1 TPS ≥ 1%		PD-L1 TPS < 1%	
	Nivo + Chemo (N=155)	Chemo (N=145)	Nivo + Chemo (N=155)	Chemo (N=158)
All grade, all causality AEs	155 (100.0)	144 (99.3)	153 (98.7)	156 (98.7)
Grade 3/4 drug-related AEs	77 (49.7)	60 (41.4)	70 (45.2)	46 (29.1)
Grade 3/4 drug-related SAEs	32 (20.6)	18 (12.4)	25 (16.1)	18 (11.4)
Drug-related Gr 3/4 AEs leading to DC	18 (11.6)	6 (4.1)	11 (7.1)	8 (5.1)
Study drug-related deaths	5 (3.2)	1 (0.7)	0	3 (1.9)

Table 2.3.3-4: Safety Summary - Nivo+Ipi vs Chemotherapy - All Treated Patients by PD-L1 Subgroups TPS < 1% and ≥ 1% (CHECKMATE-648)

	Patients, n (%)			
	PD-L1 TPS ≥ 1%		PD-L1 TPS < 1%	
	Nivo + Ipi (N=158)	Chemo (N=145)	Nivo + Ipi (N=161)	Chemo (N=158)
All grade, all causality AEs	155 (98.1)	144 (99.3)	158 (98.1)	156 (98.7)
Grade 3/4 drug-related AEs	49 (31.0)	60 (41.4)	52 (32.3)	46 (29.1)
Grade 3/4 drug-related SAEs	36 (22.8)	18 (12.4)	37 (23.0)	18 (11.4)
Drug-related Gr 3/4 AEs leading to DC	25 (15.8)	6 (4.1)	16 (9.9)	8 (5.1)
Study drug-related deaths	1 (0.6)	1 (0.7)	4 (2.5)	3 (1.9)

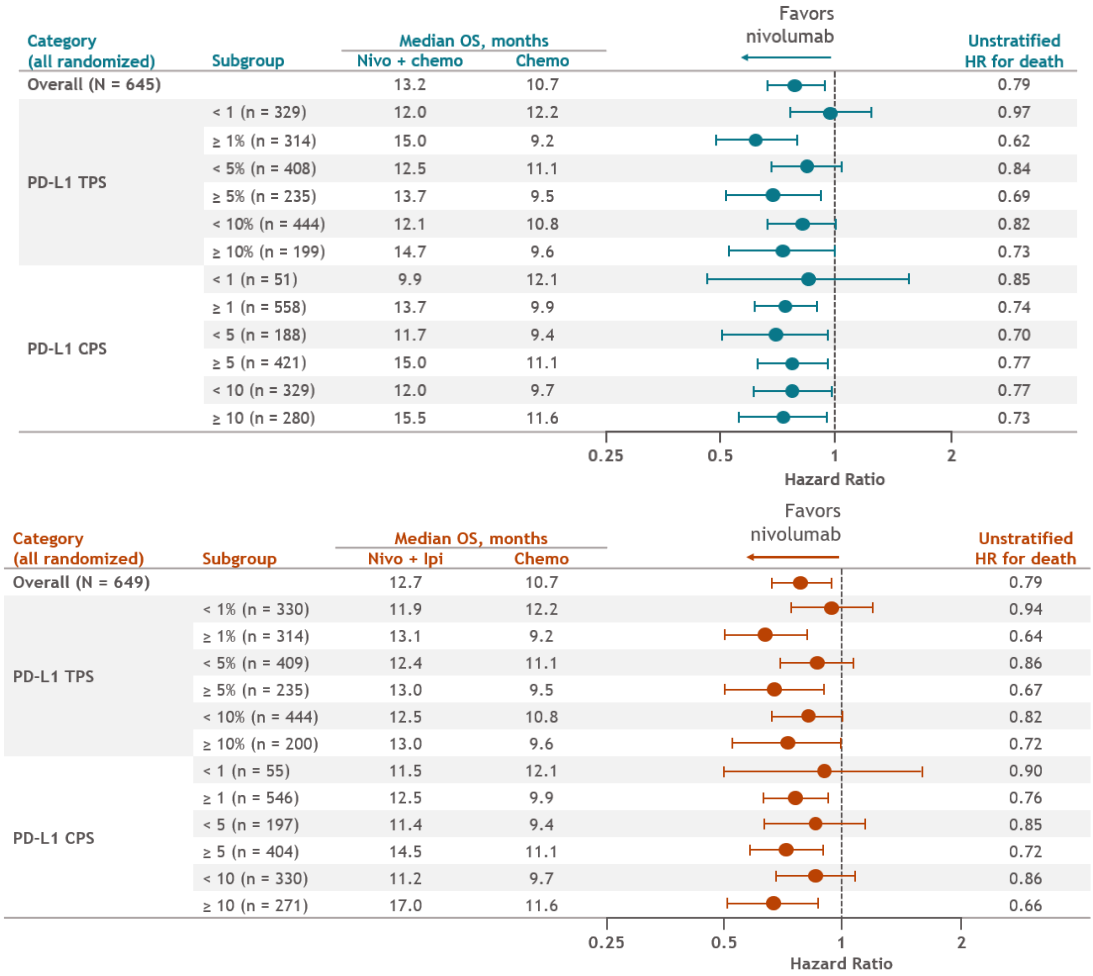
2.3.4 Long-Term Follow-up (Data Cutoff 25-Sep-2023)

Efficacy: At 45 months follow-up, nivo+chemo and nivo+ipi continued to show OS benefit vs chemo among PD-L1 TPS ≥ 1% and all randomized patients, consistent with results of the primary analysis of CHECKMATE-648 (minimum follow-up of ~ 1 year). [48]

OS results across baseline PD-L1 status subgroups (TPS and CPS) were generally consistent with those reported at the primary analysis for nivo+chemo vs chemo and nivo+ipi vs chemo (Figure 2.3.4-1).

Improvement in OS vs chemo (HR point estimate < 1 with upper bound of 95% CI < 1) continued to be seen with nivo+chemo and with nivo+ipi among patients at the lowest PD-L1 cutoffs evaluated (TPS ≥ 1% and CPS ≥ 1). The HR point estimate in patients with CPS < 1 improved numerically to 0.85 from 0.98 with nivo+chemo vs chemo and to 0.90 from 1.0 with nivo+ipi vs chemo with longer follow-up, reflecting the well-known durable effect of immunotherapy.

Figure 2.3.4-1: OS by Prespecified PD-L1 TPS and CPS Subgroups, Nivo+Chemo vs Chemo and Nivo+Ipi vs Chemo (CHECKMATE-648) - Long-term Follow-up



Source: Chau, et al., 2024[48] Minimum follow-up: 45 months.
Tumor cell PD-L1 (TPS) expression indeterminate, not evaluable, or missing: Nivo+ipi, n=3; Chemo, n=2.
PD-L1 CPS expression indeterminate, not evaluable, or missing: Nivo+chemo, n=16; Nivo+ipi, n=28; Chemo, n=20.

Safety: The incidence of drug-related AEs in all treated patients (Table 2.3.4-1) remained consistent with that previously reported. As observed at the primary analysis, the most frequently reported any-grade drug-related AEs with nivo+chemo were AEs commonly associated with chemotherapy and the most frequently reported drug-related AEs with nivo+ipi were IMAEs. No increase in treatment-related mortality (ie, study drug toxicity-related deaths) was observed with nivo+chemo or nivo+ipi compared with chemo alone with long term follow-up.

The most frequently reported any-grade drug-related AEs included:

- Nivo+chemo: nausea (59%), decreased appetite (43%), and stomatitis (32%)
- Nivo+ipi: rash (17%), pruritis (13%), and hypothyroidism (13%)
- Chemo: nausea (52%), decreased appetite (43%), and stomatitis (23%)

Table 2.3.4-1: Drug-related Adverse Events - All Treated Patients (CHECKMATE-648) - Long-term Follow-up

All treated, n (%)	Nivo+chemo (n=310)		Nivo+ipi (n=322)		Chemo (n=304)	
	Any Grade	Grade 3/4	Any Grade	Grade 3/4	Any Grade	Grade 3/4
Any drug-related AEs	297 (96)	151 (49)	256 (80)	105 (33)	275 (90)	111 (37)
Serious drug-related AEs	74 (24)	58 (19)	105 (33)	75 (23)	49 (16)	41 (13)
Drug-related AEs leading to DC	107 (35)	30 (10)	60 (19)	44 (14)	63 (21)	18 (6)
Study drug toxicity deaths[a]	5 (2)		6 (2)		5 (2)	

Source: Chau, et al., 2024.[48] Minimum follow-up: 45 months.

Patients who received ≥ 1 dose of study drug. All events are within 30 days of the last dose of study drug, unless otherwise indicated (eg, any time for deaths). Drug-related AEs leading to discontinuation refer to discontinuation of any drug in the regimen.

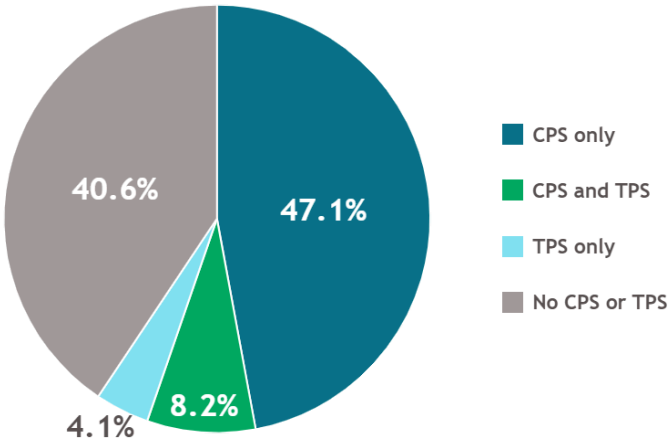
[a] **In the nivo+chemo arm**: comprises same study drug toxicity events as reported at primary analysis. **In the nivo+ipi arm**: comprises events reported at primary analysis (pneumonitis [2], interstitial lung disease [1], and pulmonary embolism [1]), 1 event (internal haemorrhage) that was changed from 'other' to 'drug-related' after the primary analysis DBL, and 1 new event (pneumonitis) that occurred after the primary analysis DBL. One event reported as a study-drug toxicity death at primary analysis (acute respiratory distress syndrome) was reclassified from 'drug-related' to 'other' after the primary analysis DBL and no longer attributed to study drug toxicity. **In the chemo arm**: comprises events reported at primary analysis (septic shock [1], sepsis [1], acute kidney injury [1], and pneumonia [1]) and 1 event, myocardial infarction that was changed from 'other' to 'drug-related' after the primary analysis DBL.

2.4 UTILIZATION OF PD-L1 TESTING IN CLINICAL PRACTICE

In clinical practice, PD-L1 testing in ESCC starts with obtaining a tissue sample from biopsy or resection which must have sufficient tissue 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.[49] Turnaround time can be more rapid if occurring within an institution (eg, 2-3 days) or up to a couple of weeks if an external lab is used. Not all PD-L1 assessment assays and scoring methods are widely available across all clinical practices. Additionally, HCPs might not choose to request a specific scoring approach when ordering a PD-L1 test.

Although IO labeling does not currently mandate PD-L1 testing, more than half of all diagnosed ESCC patients (1L) are being tested in practice, according to real-world data. Data on PD-L1 testing in US clinical practice was obtained from a retrospective observational analysis of the Flatiron Health Oncology database. Among patients diagnosed with advanced ESCC who received 1L treatment from May 2022 to June 2024 (N=170), 59.4% received any PD-L1 test (TPS or CPS) and 40.6% were not tested. Of the patients who were tested, a larger proportion received a CPS than a TPS test (Figure 2.4-1).

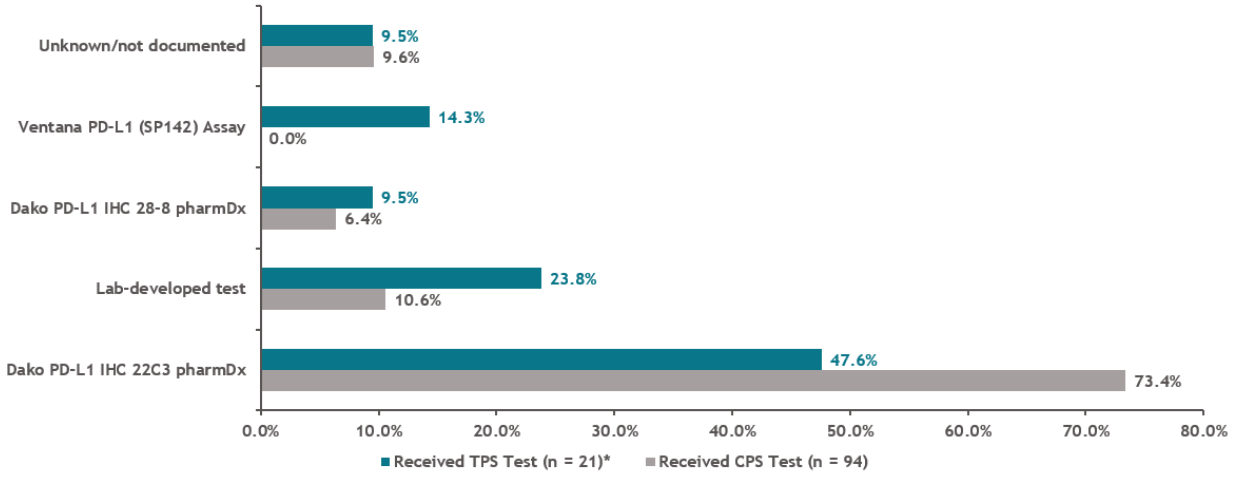
Figure 2.4-1: PD-L1 CPS and TPS Testing Patterns among Patients with Advanced ESCC who Received 1L Treatment from May 2022 to June 2024 (N=170) - US Flatiron Analysis



Source: Data on File. The percentages above reflect patients who received a test, not necessarily a test result.

In the same retrospective observational analysis of the Flatiron Health Oncology database, there was a high degree of variability in PD-L1 assays used for testing, although the assay most frequently used for CPS and TPS testing was Dako PD-L1 IHC 22C3 pharmDx. The next most frequently used type was 'lab-developed test' which inherently implies a high degree of variability (Figure 2.4-2).

Figure 2.4-2: PD-L1 Assays Used among Patients with Advanced ESCC who Received 1L Treatment from May 2022 to June 2024 (N=170) - US Flatiron Analysis

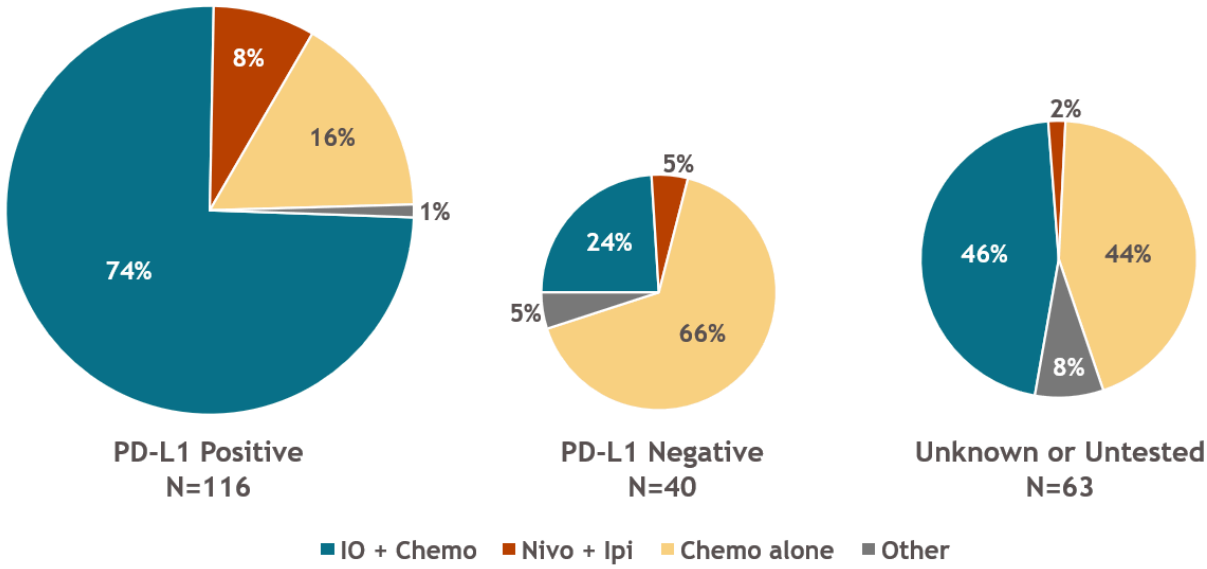


Source: Data on File.
*One patient received 2 different assay types.

Looking also at treatment patterns, BMS internal chart audit (physician survey) data (N=219) suggest that the presence of a positive test result leads to greater numbers of patients being treated with an IO combination treatment (IO+chemo or nivo+ipi); see Figure 2.4-3. Data also show that approximately half (48.0%) of untested patients or patients with unknown test results are treated

with an IO combination treatment (IO+chemo or nivo+ipi); this is considered by the Sponsor to be appropriate since an unknown or untested patient is more likely to be PD-L1 positive than negative, with approximately 90% of ESCC patients considered PD-L1 positive when using a CPS ≥ 1 cutoff.[10,11]

Figure 2.4-3: Treatment Patterns in ESCC - BMS Internal Chart Audit (Physician Survey) Data (N=219)



Source: Data on File - BMS Monthly Chart Audit, new patients, weighted by patient volume and setting type. Lookback period: September 2023-March 2024. The information presented is an estimate derived from BMS Chart Audit proprietary surveys on a rolling 6-month basis and is recent as of March 2024. Full survey data are collected via an internet-based survey and are checked for quality and weighted for epidemiology and processed internally within BMS. Participating physicians must be board-certified oncologists who spend a majority of time in direct patient care and have initiated a new patient on therapy within the measurement month.

2.5 CHALLENGES OF PD-L1 QUANTIFICATION AND INTERPRETATION OF RESULTS

Many challenges exist in precisely and reliably quantifying PD-L1 expression, such as:

Tissue adequacy for PD-L1 scoring

- A tumor tissue sample of adequate quantity and quality is needed to make a PD-L1 expression determination. There were 12.7% (42/330) of patients in CHECKMATE-648 who were enrolled but could not be randomized due to inadequate tissue/inability to test for PD-L1. In RATIONALE-306, 16.5% (107/649) of patients had unknown PD-L1 status due to inability to collect sample or conduct a PD-L1 assessment.[4] Based on these rates in clinical trials, a meaningful percentage of patients in practice may likewise have insufficient/inadequate tumor tissue for PD-L1 testing.

Type of tissue sample

- Endoscopic mucosal biopsies may be biased for 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.[15] Tumor resections have large areas

for PD-L1 expression evaluation. However, accurate scoring of resections can be challenging due to the need to manually count very large numbers of cells.

Tumor tissue fixation

- Poor fixation of tissue specimens may hamper PD-L1 evaluation due to morphologic alterations and unreliable PD-L1 staining.[16] Poor fixation can influence the staining of IHC biomarkers, including PD-L1, causing false-negative staining, edge effect and non-specific cytoplasmic staining.[17]

Tumor heterogeneity

- PD-L1 expression is characterized by a high degree of spatial and temporal 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 (inter-tumor heterogeneity, ie, one metastatic site may be positive and another metastatic site negative).
- Variable data exist on the concordance of PD-L1 expression within specimen blocks, between blocks taken from the same surgical sample and between those taken from primary versus metastatic tumors[18,19,20,21] and suggest that the assessment of PD-L1 from biopsy samples may not always be representative of the real status of the biomarker in the tumor.
  - Wang, et al.[19] reported that intra-tumoral heterogeneity, particularly PD-L1 heterogeneity, differed markedly among ESCC specimens. The concordance rates of PD-L1 (CPS and TPS) status among three different areas sampled were 71.6%, 74.6%, and 73.1%.
  - In a prospective study by Yu, et al.[20] of 30 patients with treatment-naive, stage II-III ESCC, multi-region sampling was taken from 4 regions (proximal, distal, midpoint of tumor surface, and internal center, respectively). PD-L1 expression was evaluated by IHC using CPS, with PD-L1 (+) defined as CPS $\geq$ 1 and PD-L1 (-) defined as CPS < 1. PD-L1 positive/negative discordance rate of the 4 sampling regions was 66.7%, with poor concordance (kappa = 0.206). The authors concluded that PD-L1 expression is spatially heterogeneous in ESCC, and a single region cannot reflect the PD-L1 status of the tumor, consistent with observations in the literature of suboptimal prediction of PD-L1 expression for ESCC immunotherapy.

Dynamic PD-L1 expression

- PD-L1 evaluation in the primary tumor may change following chemoradiation or radiation therapy.[22,23] As noted in Section 2.2.3, some patients with 1L ESCC proceed directly to palliative radiotherapy, prior to a systemic treatment decision being made. However, it is medically challenging to obtain a tumor sample from patients previously treated with radiation. Ng, et al.[24] reported PD-L1 status changes by chemotherapy in ESCC, meaning that PD-L1 expression may differ in the same patient prior to, early in ICI+chemo treatment, and later in ICI+chemo treatment.

Quantification based on pathologist interpretation

- PD-L1 expression is a continuous variable, meaning it exists along a spectrum rather than as a binary (yes/no) value. PD-L1 test results are described as more qualitative than quantitative in the product labels of currently marketed assays including PD-L1 IHC 28-8

pharmDx[50] and PD-L1 IHC 22C3 pharmDx.[51] In clinical trials, researchers often set cutoffs to categorize patients based on PD-L1 expression. These qualitative cutoffs can vary due to different diagnostic assays, antibody clones with different staining patterns and the perceived benefit-risk rationale at the proposed cutoff for treatment eligibility. At an individual patient level, there is inherent pathologist variability in determining actual scores/values.

- Wang, et al. evaluated concordance of PD-L1 interpretation and the impact on interobserver reproducibility by analyzing different antibody clones, and assays.[25] Overall percent agreement varied from 81.7% (95% CI: 79.4%-84.0%) to 90.8% (95% CI: 89.6%-91.9%). The study found lower concordance than expected due to diverse field of experiences of numerous pathologists, an observation likely reflective of real-world practice. The authors believed that the results of this study did not support the interchangeability of antibody clones to determine PD-L1 expression in ESCC.
- In a controlled analysis of the Agilent PD-L1 IHC 28-8 pharmDx assay when used to evaluate ESCC samples [BMS/Laboratory Corporation of America; Data on File], after adjusting for prevalence at a CPS 1 cutoff (prevalence: 87%), the positive predictive value was high at 98.2% (97.2% to 98.8%) and the negative predictive value was relatively low at 67.2% (53.6% to 78.5%). This indicates a strong probability that a positive result (CPS $\geq$ 1) is positive but a weaker probability that a negative result (CPS $<$ 1) is negative.

Variability among antibodies/assays and scoring methods

- Interlaboratory variability in PD-L1 assessment has been seen due to the use of different diagnostic assays and antibody clones with different staining patterns.
  - Wang, et al.[25] evaluated concordance among the VENTANA SP263, Agilent/Dako 22C3, and Agilent/Dako 28-8 assays, with assays performed in a College of American Pathologists accredited central laboratory using 145 archival ESCC tumor samples from 131 Taiwanese patients scored for PD-L1 staining using multiple metrics including TC score, IC score, CPS, or TAP. Classification concordance was calculated pairwise between assays by PPA, NPA, and OPA at cutoff values $\geq$ 1, $\geq$ 5, and $\geq$ 10. Both NPA and PPA were highly variable. PPA ranged from 54%-95% and NPA ranged from 15%-94%, illustrating the inherent variability that can be seen across assays and cutoffs. The SP263 and 22C3 assays appeared more sensitive, assigning a higher proportion of patients as PD-L1 positive or high, compared to the 28-8 assay. The authors concluded that the SP263, 22C3, and 28-8 assays and their corresponding clinical algorithms identify different but overlapping ESCC patient populations.

Application of study results to real-world practice

- Pivotal ICI studies of EC/ESCC have used a variety of PD-L1 antibodies, scoring methods, and assay platforms. CHECKMATE-648 used the Agilent/Dako PD-L1 IHC 28-8 pharmDx assay, while KEYNOTE-590 used the Agilent/Dako PD-L1 IHC 22C3 pharmDx assay, and RATIONALE-306 used the VENTANA SP263 assay. Data above from Wang, et al.[25] 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. Real-world data shows a variety of assays/antibodies used in clinical practice, including lab-developed tests (see Section 2.4).

- Across the literature, many publications describe results based on using lab-developed tests rather than approved tests. Some approaches for slide reading and quantification described in the literature are tightly controlled (eg, 3 pathologists at the same institute) whereas others are more reflective of real-world data that may be generated (eg, multiple institutes, pathologists, etc.).

Given the challenges with PD-L1 quantification and interpretation outlined, it would be difficult to anticipate a certain clinical outcome based on any specific numerical PD-L1 score, which may fall only slightly outside of a given cutoff range. Patients who score above a certain cutoff by one scoring method/assay may not by another. Patients who score PD-L1 negative by one sample may not by another sample due to variability within a given block of tissue or among tumor sites. This can lead to confusion and ambiguity in using PD-L1 test results alone to make treatment decisions.

2.6 EVALUATION OF POTENTIAL LABELING OPTIONS IN 1L ESCC AND SPONSOR'S CONCLUSION

Currently, PD-L1 testing is not mandated for use of ICI combination treatment in ESCC, and the Sponsor proposes there are valid reasons why this remains appropriate. While across the current body of ICI combination therapy data, greater benefit appears to be seen in 1L ESCC patients expressing PD-L1 (by various study-defined scoring methods and cutoffs), there are challenges around precise PD-L1 quantification 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 of this ODAC to discuss the emerging risk-benefit analysis of ICIs as a class in esophageal cancer, the Sponsor has developed two potential labeling options for consideration, described in Table 2.6-1, with the advantages and disadvantages of each approach summarized.

Table 2.6-1: Assessment of Potential Indication Options in 1L ESCC

	Advantages	Disadvantages
Option 1: ***Maintain the PD-L1 unrestricted 1L ESCC indications with subgroup data included in labels showing levels of benefit based on PD-L1 expression, as is currently done.***	• This approach provides HCPs with the opportunity to continue making informed treatment decisions on an individual patient basis, using efficacy data by PD-L1 expression level in the USPI. – OS subgroup data based on the Agilent/Dako PD-L1 IHC 28-8 pharmDx test are provided in the USPI for CHECKMATE-648 patients with PD-L1 TPS ≥ 1% (primary analysis population) and in exploratory subgroups of patients with PD-L1 TPS < 1%, CPS < 1, and CPS ≥ 1. – The Sponsor believes this approach transparently discloses the differential benefit that may be anticipated at clinically relevant cutoff levels using two scoring methods: TPS (method validated in CHECKMATE-648) and CPS (method most common in practice), but the Sponsor is open to discussing further labeling revisions if FDA determines that additional clarifications would be helpful for physicians. • This approach retains ICI as a treatment option for patients who may be unable to receive a PD-L1 test, those with insufficient/inadequate tumor tissue for testing, or those who may score PD-L1 negative due to testing variability/ limitations of testing precision. – As described in Section 2.5, in a controlled analysis of the Agilent PD-L1 IHC 28-8 pharmDx assay used to evaluate ESCC samples at a CPS 1 cutoff, PPV was high at 98.2% and NPV was relatively low at 67.2%. A test that aims to identify a small minority (< 10%) of patients who are PD-L1 negative should require a high NPV; otherwise, the risk of excluding positive patients may outweigh the benefit of identifying true negative patients. – NCCN notes the high level of PD-L1 expression (>90%) in ESCC as rationale for the nivo+chemo and nivo+ipi unrestricted indications and recommends the regimens irrespective of CPS score.[2] • Advanced ESCC is an aggressive disease and a limited number of ESCC patients proceed to 2L treatment, where survival outcomes are modest. Therefore, there is a public health need for accessible, effective treatments. 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.	• HCPs may wish to avoid exposing patients less likely to benefit to the safety risks of ICI treatment. – Safety risks, although generally manageable with treatment algorithms and not shown associated with increased treatment-related mortality, include IMAEs and AEs which are distinct from chemotherapy. • If there remains no requirement to perform PD-L1 testing per drug label, there is less incentive for HCPs to perform PD-L1 testing. – Although an imperfect biomarker for the reasons described, PD-L1 expression can be a useful tool in clinical decision making.

Table 2.6-1: Assessment of Potential Indication Options in 1L ESCC

	Advantages	Disadvantages
Option 2: ***In the event of a class labeling change, modify the indications to PD-L1 positive patients using the most appropriate testing method and threshold, which the Sponsor would propose to be the lowest threshold by any PD-L1 test validated within upper GI malignancies (ie, CPS ≥ 1 or TPS ≥ 1%).***	• Would allow for treatment of patients with evidence of PD-L1 expression, as they have the greatest likelihood for benefit, and avoids safety risks of ICIs in patients without evidence of PD-L1 expression. – CHECKMATE-648 showed OS benefit at the lowest PD-L1 positive (TPS ≥ 1%/ CPS ≥ 1) cutoffs. CHECKMATE-648 showed clinically meaningful OS HRs at relatively lower (1-<10) and relatively higher (≥10) exploratory CPS cutoffs, suggesting that benefit observed in the CPS ≥ 1 subgroup is not solely driven by patients with high CPS scores. – These clinical data support selection of the lowest threshold as an indicator of PD-L1 expression in the event of a class labeling change. Use of the lowest threshold is also justified due to the many challenges with PD-L1 quantification and interpretation. – Allowing any PD-L1 test validated within upper GI malignancies to be used reduces complexity in practice and avoids excluding patients who might only be offered a certain test type. The Sponsor does not consider restriction using only a TPS ≥ 1% cutoff as a viable option; this would likely add an additional hurdle to testing and harmonization as TPS is infrequently used for upper GI cancers.	• Mandatory PD-L1 testing could lead to treatment delay or reduced access for some patients who might have potential to benefit. – This approach risks excluding patients who test negative for PD-L1 due to tumor heterogeneity, the dynamic nature of PD-L1 expression, etc., but who may have some level of expression. It also excludes patients who have insufficient/inadequate tumor tissue for biomarker testing. – A patient's classification as PD-L1 positive or negative can vary depending on testing method (eg, a given patient could test PD-L1 [-] per TPS test and be considered ineligible for treatment; the same patient might test PD-L1 [+] per CPS and be eligible for treatment if a different scoring method is chosen by their HCP/laboratory). – Variable concordance among tests/ assays/ antibodies can produce the same problem of potentially missing patients for treatment due to limitations of testing. – 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 ESCC 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. The Sponsor shares the FDA's desire to ensure that patients for whom benefit might reasonably be expected receive therapies and that the information provided to HCPs is clear.

Based on the assessment of each approach, the Sponsor's conclusion is that the totality of data for nivolumab in 1L ESCC supports the current approved labeling as the most justified option.

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