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for the
Oncologic Drugs Advisory Committee

BLA 761380

TEVIMBRA (tislelizumab)

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ADVISORY COMMITTEE BRIEFING MATERIALS: AVAILABLE FOR PUBLIC RELEASE

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LIST OF ABBREVIATIONS

Abbreviation	Definition
1L	first-line
2L	second-line
5-FU	5-fluorouracil
AE	adverse event
AUS	Australia
BOR	best overall response
CI	confidence interval
CPI	checkpoint inhibitor
CPS	combined positive score
CRF	case report form
DCO	data cutoff
DOR	duration of response
EC	esophageal squamous cell carcinoma
ESCC	esophageal cancer
ESMO	European Society for Medical Oncology
EOP2	end-of-phase 2
EU	Europe
FDA	Food and Drug Administration
GEJ	gastroesophageal junction
HR	hazard ratio
HRQoL	health-related quality of life
IA	interim analysis
ICC	investigator's choice chemotherapy
IHC	immunohistochemistry
imAE	immune-mediated adverse event
IRT	Interactive Response Technology
ITT	intent to treat
IV	intravenous
mOS	median overall survival
mPFS	median progression-free survival
NCCN	National Comprehensive Cancer Network
ORR	overall response rate
OS	overall survival
PBO+C	placebo + investigator's choice chemotherapy
PD-L1	programmed death ligand 1
PDUFA	Prescription Drug User Fee Act
PFS	progression-free survival
PS	performance status

Abbreviation	Definition
PT	Preferred Term
Q3W	every 3 weeks
RECIST	Response Evaluation Criteria in Solid Tumors
SAE	serious adverse event
TAP	tumor area positivity
TEAE	treatment-emergent adverse event
TIS+C	tislelizumab + investigator's choice chemotherapy
US	United States

1. EXECUTIVE SUMMARY

RATIONALE-306 is a global, multicenter Phase 3 study, which enrolled 649 patients from 16 countries, evaluated the efficacy and safety of tislelizumab combined with chemotherapy as a first-line treatment compared to chemotherapy alone in patients with locally advanced or metastatic ESCC. Patients were enrolled regardless of their tumor PD-L1 expression level, and PD-L1 expression was retrospectively assessed in a central laboratory using the TAP scoring algorithm with the VENTANA PD-L1 (SP263) Assay.

Efficacy Summary

- Tislelizumab plus chemotherapy was superior to placebo plus chemotherapy for the primary OS endpoint, with a statistically significant 34% reduction in the risk of death (stratified HR: 0.66 [95% CI: 0.54 to 0.80]; 1-sided p-value of < 0.0001) and a clinically meaningful improvement in median OS by 6.6 months (median OS: 17.2 vs 10.6 months). This benefit was consistent across all prespecified subgroups, including by baseline PD-L1 expression ≥ 10% and < 10%.
- **Exploratory PD-L1 Subgroup Analysis:**
  - For patients with PD-L1 scores ≥ 1%, there was a 34% reduction in the risk of death and a 7.2-month improvement in median OS.
  - In PD-L1 expression subgroups of 1% to < 5% and 5%-10%, OS showed a numerical improvement, with the benefit becoming more pronounced with longer follow up.
  - For patients with PD-L1 < 1%, the small sample size and high median OS in the control group complicate the interpretation, precluding a definitive conclusion.
- **Secondary Endpoints:**
  - **PFS:** Tislelizumab plus chemotherapy significantly reduced the risk of disease progression or death by 38% and improved median PFS by 1.7 months in the overall population-, PFS benefits were observed across all PD-L1 subgroups and, benefits increased with higher PD-L1 expression.
  - **ORR:** A higher tumor response rate was observed in patients receiving tislelizumab plus chemotherapy, with consistent benefit across PD-L1 subgroups, except for a less reliable result in the PD-L1 <1% subgroup potentially confounded by small sample size.

Safety Summary

TIS+C showed a tolerable and acceptable safety profile in the first-line treatment of patients with locally advanced or metastatic ESCC, which was also consistent with the known safety profile of tislelizumab and other checkpoint inhibitors in combination with chemotherapy.

In PD-L1 subgroups, the safety profile of treatment with TIS+C in the subgroups of PD-L1 ≥ 1% and PD-L1 < 1% was consistent with that reported for the overall population, revealing no increased safety risks or new safety signals for this subgroup.

Company Position

Study 306 confirms the efficacy and safety of tislelizumab plus chemotherapy as a first-line treatment for patients with unresectable, locally advanced, or metastatic ESCC. The most favorable benefit/risk was observed in patients with a PD-L1 score ≥ 1%.

- BeiGene supports efforts in gaining consistency in labeling and testing across the class of anti-PD-1 agents as it would help provide clarity among the medical community and would better support treatment decisions in clinical practice, along with harmonizing the use of PD-L1 testing, with these agents.

2. DISEASE BACKGROUND

2.1. Brief Overview of ESCC

EC constitutes a major global health problem, especially in low- and middle-income countries.[1] Globally in 2022, there were an estimated 511,054 new cases resulting in 443,391 deaths (Table 1), making EC the 11th most frequently diagnosed cancer and the eighth leading cause of cancer-related deaths in the world.[2] Esophageal cancer is more common in Asia than North America or Western Europe, accounting for 75% of diagnoses and 74% of deaths worldwide.[2] In 2022, an estimated 18,747 new cases of EC are expected to be diagnosed and approximately 16,469 patients are predicted to die of this disease in the US, making esophageal cancer the 19th most frequently diagnosed cancer and the 11th leading cause of cancer-related death in the US.[3]

In the US (2014 to 2020), 50% of patients diagnosed with EC presented with early/middle stage (localized or spread to regional lymph node) and 38% have metastasized to distant sites. The outcome of patients with distant metastatic esophageal cancer remains poor, with a 5-year survival rate of 5.3%.[4]

Esophageal cancers are histologically classified as squamous cell carcinoma or adenocarcinoma, which differ in their pathology, tumor location, and prognosis.[5] Esophageal squamous cell carcinoma is the predominant histological subtype of esophageal cancer worldwide (approximately 90%).

Table 1: Summary of EC-Related Cases and Deaths in Major Countries/Regions in 2022

Country	New Cases n (%)	Deaths n (%)
World-wide	511,054 (100)	443,391 (100)
China	224,012 (43.8)	187,467 (42.1)
Japan	19,826 (3.9)	12,161 (2.7)
South Korea	2,437 (0.4)	1,521 (0.3)
United States	**18,747 (3.7)**	**16,469 (3.7)**
Europe	53,513 (10.5)	47,212 (10.6)

2.2. Current Treatment Options in ESCC

International treatment guidelines, such as NCCN and ESMO guidelines, are consistent in the approach for the treatment of ESCC, with management dependent on the characteristics of the patient (including performance status and overall health status) and those of the tumor, mainly the Tumor Node Metastasis stage.[6,7,8]

More than 30% of patients with ESCC are diagnosed at an advanced or metastatic stage[9] and are ineligible for curative interventions. Patients with advanced or metastatic (including unresectable, or recurrent after curative therapy) ESCC receive 1L palliative chemotherapy.[7] Platinum-based chemotherapy doublets, which include either platinum agents (cisplatin, oxaliplatin, or carboplatin) plus fluoropyrimidine (5-FU or capecitabine) or taxanes (paclitaxel or

docetaxel) are recommended.[6,7] First-line palliation is associated with an ORR of 29% to 58% and a median OS of 8.8 to 13.5 months. These data indicate the need for additional efficacious and tolerable therapies for ESCC in the 1L setting.[10,11,12]

In recent years, immune checkpoint inhibitors, such as anti-PD-1/PD-L1 antibodies, have advanced the treatment of ESCC. Several anti-PD-1 antibodies in combination with chemotherapy have demonstrated survival improvement over chemotherapy alone in the first-line treatment of ESCC, such as the findings from global studies of the KEYNOTE-590 study of pembrolizumab plus chemotherapy compared to chemotherapy and the CHECKMATE-648 study of nivolumab plus chemotherapy compared to chemotherapy.[10,13,14] Those results indicate that ESCC, as an immunogenic tumor type, is sensitive to immunotherapy. Based on the survival benefit, pembrolizumab plus chemotherapy was approved in the US in March 2021 (locally advanced or metastatic esophageal or GEJ carcinoma that is not amenable to surgical resection or definitive chemoradiation), and in the EU in June 2021 (the first-line treatment of locally advanced unresectable or metastatic carcinoma of oesophagus or HER-2 negative GEJ adenocarcinoma with tumors PD-L1 CPS ≥ 10); nivolumab plus ipilimumab and nivolumab plus fluoropyrimidine- and platinum-based chemotherapy was approved in the US in May 2022 (the first-line treatment of unresectable advanced or metastatic ESCC) and in the EU in April 2022 (the first-line treatment of unresectable advanced, recurrent or metastatic ESCC with tumor cell PD-L1 expression ≥ 1%).

NCCN guidelines for 1L treatment of ESCC are pembrolizumab plus chemotherapy at category 1 for patients with PD-L1 CPS ≥ 10 and at category 2B for patients with PD-L1 CPS < 1, while nivolumab plus chemotherapy is recommended for all comers.[8,14]

Considering the poor prognosis and the limited availability of effective treatment choices in the first-line setting in the past decades for advanced or metastatic ESCC, there is still a need for more alternative therapeutic options that could prolong OS. BeiGene, Ltd initiated Rationale-306 (Study BGB-A317-306; hereafter Study 306) in 2018 as part of the wave of the clinical development of immune checkpoint inhibitors for the treatment of this disease in 2018 and showed efficacy and safety results similar to those with nivolumab and pembrolizumab. The option of first-line treatment with tislelizumab in combination with chemotherapy offers a promising strategy for improving survival in this target population, and overall strengthens the treatment armamentarium for ESCC.

3. OVERVIEW OF TISLELIZUMAB

3.1. Mechanism of Action

Tislelizumab is a humanized monoclonal IgG4 kappa antibody that binds to the extracellular domain of human PD-1 with high specificity and affinity (dissociation constant = 0.15 nM). It competitively blocks the binding of both PD-L1 and PD-L2, inhibiting PD-1-mediated negative signaling and enhancing the functional activity of T cells in in vitro cell-based assays.

Tislelizumab was engineered to minimize FcγR1 binding on macrophages, limiting antibody-dependent cellular cytotoxicity or complement-dependent cytotoxicity, which has been shown to compromise the antitumor activity of other anti-PD-1 monoclonal antibodies through activation of antibody-dependent, macrophage-mediated killing of T effector cells.[15]

3.2. Clinical Development and Regulatory Status of Tislelizumab in the United States

The clinical development of tislelizumab in ESCC was initiated based on the clinical evidence of tislelizumab monotherapy in the first-in-human dose-escalation/expansion study BGB-A317_Study_001 (hereafter Study 001) and the dose verification/expansion study BGB-A317-102 (hereafter Study 102), both including patients with ESCC and other solid tumors. The program for tislelizumab plus chemotherapy as 1L treatment of ESCC started with Phase 2 Study 205, which showed a manageable safety profile and preliminary anticancer activity.

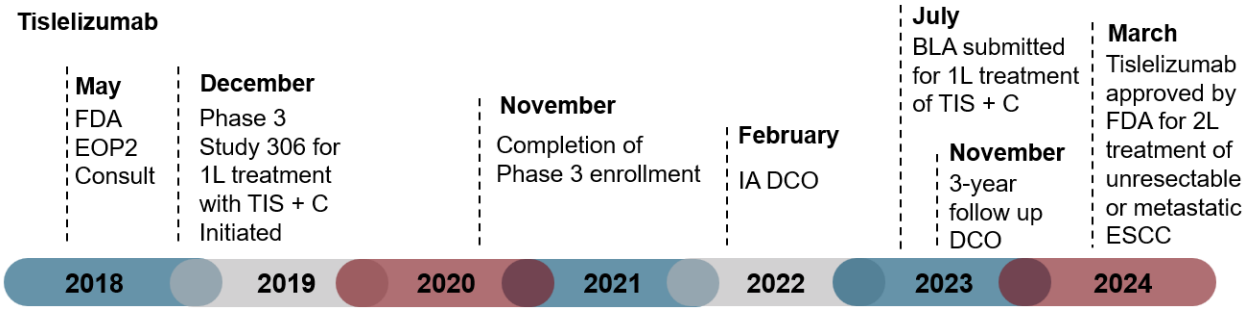
Subsequently, the global pivotal Phase 3 Study 306, initiated in 2018, evaluated the efficacy and safety of tislelizumab + chemotherapy (TIS+C) versus placebo + chemotherapy (PBO+C) in the first-line setting in patients with locally advanced unresectable or metastatic ESCC.

The US FDA approved tislelizumab on 14 March 2024 to treat patients with unresectable or metastatic ESCC after prior systemic chemotherapy that did not include a PD-(L)1 inhibitor.

Two marketing applications are currently under review:

- BLA for the first-line treatment of patients with unresectable recurrent locally advanced or metastatic ESCC (pivotal Study 306; submitted on 18 July 2023). As of 18 July 2024, the US FDA has deferred approval because of a delay in scheduling clinical site inspections.
- BLA for the first-line treatment of adult patients with locally advanced, unresectable, or metastatic gastric or gastroesophageal junction adenocarcinoma (pivotal study BGB-A317-305; submitted on 28 December 2023 and currently under review [PDUFA date: 28 December 2024]).

Figure 1: Tislelizumab Clinical and Regulatory History in ESCC



4. EVALUATION OF EFFICACY IN STUDY 306

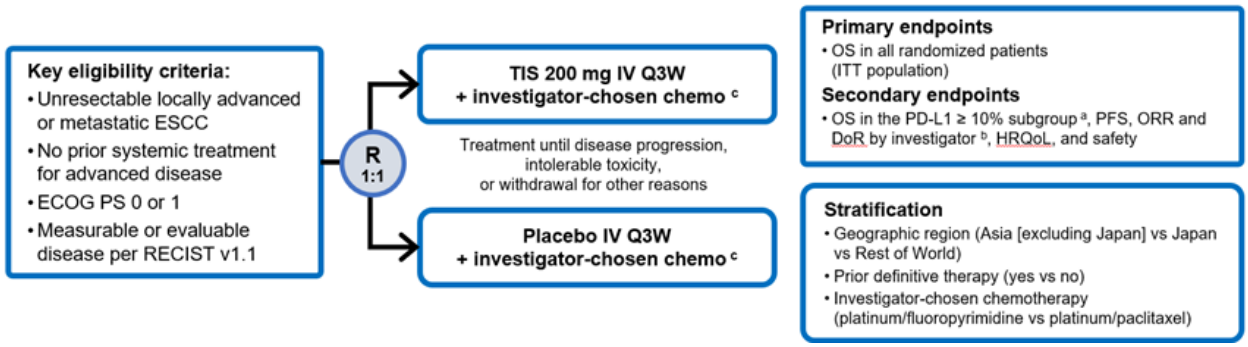
The efficacy of TIS+C for the treatment of patients with advanced or metastatic ESCC is primarily based on data from the prespecified interim analysis of Study 306 and further supported by an updated analysis with a 3-year follow-up.

4.1. Study 306 Design and Methods

4.1.1. Study Design

Study 306 is a multicenter, randomized, placebo-controlled, double-blind, Phase 3 study conducted in 162 clinical sites in 16 countries/regions across Asia, Europe, North America, and Australia (Figure 2). Enrolled patients had a histologically confirmed diagnosis of ESCC with metastatic or locally advanced disease that was not amenable to definitive surgery or radiotherapy and were required to have at least one evaluable lesion per RECIST v1.1 and ECOG PS score of ≤ 1.

Figure 2: Study 306 Design



[a] PD-L1 tumor area positivity (TAP) score was determined using the VENTANA PD-L1 (SP263) Assay. TAP score was previously called visually-estimated combined positive score (vCPS) or tumor immune cell (TIC) score. TAP, vCPS, and TIC score refer to the same scoring method.
[b] All tumor response assessments were performed by the investigator per RECIST v1.1.
[c] Tislelizumab 200 mg IV on Day 1, every 3 weeks.
Option A: Platinum (cisplatin [60 to 80 mg/m^2 IV, on Day 1] or oxaliplatin [130 mg/m^2 IV, on Day 1]) and a fluoropyrimidine (5-FU [750 to 800 mg/m^2 IV, on Days 1 to 5] or capecitabine [1000 mg/m^2 orally twice daily, on Days 1 to 14]), or
Option B: Platinum (cisplatin [60 to 80 mg/m^2 IV, on Day 1 or 2] or oxaliplatin [130 mg/m^2 IV, on Day 1 or 2]) and paclitaxel (175 mg/m^2 IV, on Day 1).

Primary endpoint:

- OS in the ITT Analysis Set
  - OS was defined as the time from the date of randomization to the date of death due to any cause
  - ITT Analysis Set included all randomized patients

Select secondary endpoints:

- PFS per RECIST v1.1 as assessed by investigators
  - PFS was defined as the time from the date of randomization to the date of first documentation of disease progression or death, whichever occurred first
- ORR and DOR per RECIST v1.1 as assessed by investigators
  - ORR was defined as the proportion of patients whose BOR was complete response or partial response

  - BOR was defined as the best response recorded from randomization until data cutoff or the start of new anticancer treatment
- DOR was defined as the time from the first determination of an objective response until the first documentation of progression or death, whichever occurred first

- OS in the PD-L1 ≥ 10% subgroup
- Safety and tolerability profile of tislelizumab or placebo plus chemotherapy

When a patient reached a 24-month treatment duration of tislelizumab or placebo, the patient could continue or stop study treatment based on the investigator's assessment of clinical benefit and potential risks. Cross-over between treatment arms or between fluoropyrimidine and paclitaxel during the study treatment period was not allowed.

The study met its primary endpoint at the time of the interim analysis and was subsequently unblinded.

4.1.2. Statistical Analyses

The primary endpoint was OS in the ITT Population. Assuming the OS HR to be 0.74 at the time of final analysis after an initial 1-month delayed treatment effect and the median OS for the PBO+C arm is 9 months, the number of deaths required for the final analysis is approximately 488 with 90% power.

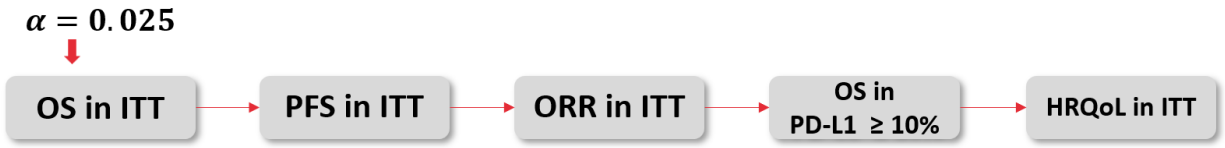
One interim analysis of OS utilizing the O'Brien-Fleming boundary approximated by Hwang-Shih-DeCani spending function was planned when approximately 423 death events (87% of the target number of OS events) among the 2 treatment arms occurred.

OS was compared between the 2 treatment arms using a one-sided log-rank test stratified by pooled geographic region (Asia vs US/Europe/Australia), prior definitive therapy (yes vs no), and ICC option (platinum with fluoropyrimidine vs platinum with paclitaxel). The HR and its 2-sided 95% CI were estimated from a stratified Cox regression model with the same stratification factors as above.

The hypothesis testing and analysis methods for PFS and OS in patients with PD-L1 scores ≥ 10% were similar to those for the primary endpoint OS in the ITT Population.

The Cochran Mantel Haenszel test stratified by the same stratification factors as above was used to compare the ORR between the 2 treatment arms.

Using the graphic approach of Bretz et al,[16] if the null hypothesis for OS in the ITT Analysis Set was rejected, the corresponding alpha would be shifted to the hypothesis tests of the secondary endpoints: PFS by the investigator in the ITT Analysis Set, ORR by the investigator in the ITT Analysis Set, OS in the PD-L1 score ≥ 10% subgroup, and health-related quality of life in the ITT Analysis Set, which were tested sequentially. The inferential test was to be stopped at the first nonsignificant endpoint.



Exploratory analyses of efficacy and safety endpoints in various PD-L1 subgroups were conducted post hoc. Note that this study was neither designed nor powered for testing treatment benefit in any of these PD-L1 subgroups (except the PD-L1 ≥ 10% subgroup). Unless otherwise noted, stratified analysis result is reported for endpoints in the prespecified hypothesis testing sequence (except quality of life endpoints), whereas the unstratified analysis result is reported for exploratory subgroup analyses of those endpoints.

4.1.3. PD-L1 Expression Testing

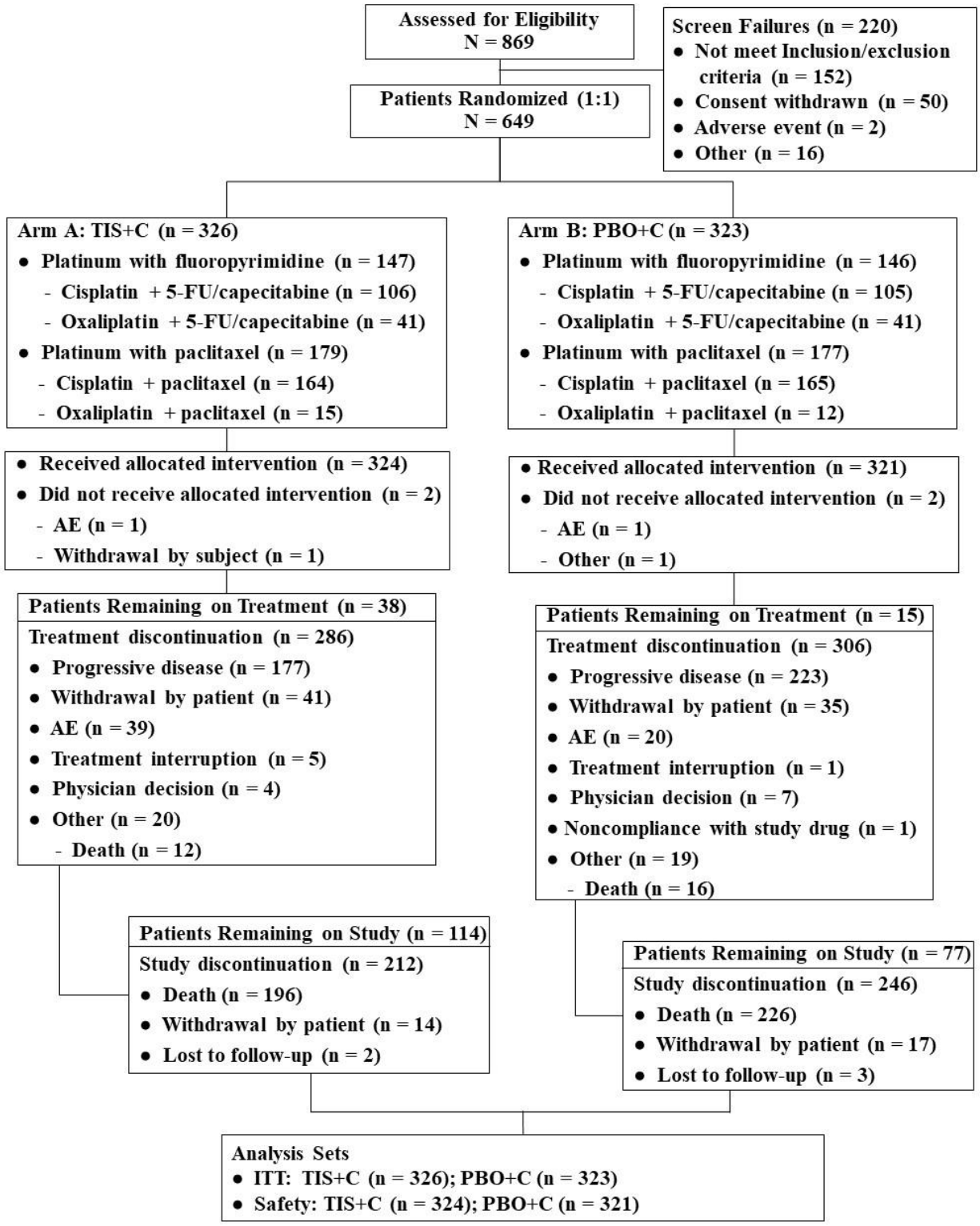
PD-L1 expression was retrospectively assessed in a central laboratory using the TAP algorithm, defined as the total percentage of the tumor area (tumor and any desmoplastic stroma) covered by tumor cells with PD-L1 membrane staining (any intensity) and tumor-associated immune cells with PD-L1 staining (any intensity), visually estimated by trained and certified pathologists using the VENTANA PD-L1 (SP263) Assay.

Selection of the PD-L1 ≥ 10% cutoff was based on a post-hoc analysis of tumors from patients with ESCC who were treated with tislelizumab (ESCC cohort from Studies 001 and 102) based on pathological feasibility, assay reproducibility, assay performance (sensitivity, specificity, positive predictive value, and negative predictive value), and clinical outcomes in patients with PD-L1 TAP ≥ 10%, as well as PD-L1 positive prevalence. PD-L1 TAP ≥ 10% was analytically validated for ESCC before PD-L1 scoring in Study 306. While the VENTANA PD-L1 (SP263) Assay is FDA-approved in multiple indications, the assay is currently not FDA-approved for use in ESCC.[17]

4.2. Study 306 Patient Disposition

The study randomized 649 patients to treatment with TIS+C or PBO+C (Figure 3). As of the interim analysis (28 February 2022), the median follow-up time was 16.3 months for the TIS+C arm and 9.8 months for the PBO+C arm, and the minimum follow-up duration (time between the data cutoff date and the date of last patient randomized) was 15.2 months for all patients in the ITT Analysis Set.

Figure 3: Study 306 Patient Disposition



Data cutoff: 28FEB2022.

4.3. Study 306 Demographics and Baseline Characteristic

The enrolled patients were representative of the target patient population. Specifically, the age (median: 64 years) and sex distribution (86.7% male) were consistent with the epidemiology of ESCC. Most patients (86.4%) had metastatic disease at study entry. Reflective of the geographic incidence of ESCC, the majority of patients (74.9%) were enrolled from Asia.

Baseline characteristics were generally balanced between treatment arms, without noteworthy differences (Table 2).

Table 2: Summary of Demographics and Baseline Characteristics (ITT Analysis Set)

	TIS+C (N = 326)	PBO+C (N = 323)	Total (N = 649)
Age Group, ≥ 65 years, n (%)	150 (46.0)	162 (50.2)	312 (48.1)
Median Age, years	64.0	65.0	64.0
Sex, n (%)			
Female	44 (13.5)	42 (13.0)	86 (13.3)
Male	282 (86.5)	281 (87.0)	563 (86.7)
ECOG Status, n (%)			
0	109 (33.4)	104 (32.2)	213 (32.8)
1	217 (66.6)	219 (67.8)	436 (67.2)
Tobacco Consumption, n (%)			
Never	68 (20.9)	81 (25.1)	149 (23.0)
Former	200 (61.3)	181 (56.0)	381 (58.7)
Current	47 (14.4)	50 (15.5)	97 (14.9)
Missing	11 (3.4)	11 (3.4)	22 (3.4)
Race, n (%)			
Asian	243 (74.5)	243 (75.2)	486 (74.9)
White	79 (24.2)	76 (23.5)	155 (23.9)
American Indian or Alaska Native	0 (0.0)	1 (0.3)	1 (0.2)
Not Reported/Unknown	4 (1.2)	3 (0.9)	7 (1.1)
Region, n (%)			
Asia	243 (74.5)	243 (75.2)	486 (74.9)
China (including Taiwan)	182 (55.8)	188 (58.2)	370 (57.0)
Japan	33 (10.1)	33 (10.2)	66 (10.2)
Korea	28 (8.6)	22 (6.8)	50 (7.7)
US/Europe/Australia	83 (25.5)	80 (24.8)	163 (25.1)
Europe	79 (24.2)	77 (23.8)	156 (24.0)
Australia	3 (0.9)	2 (0.6)	5 (0.8)
US	1 (0.3)	1 (0.3)	2 (0.3)
Time From Initial Diagnosis to Study Entry (months)	2.04	2.33	2.30
Metastatic Disease Status at Study Entry, n (%)	279 (85.6)	282 (87.3)	561 (86.4)
Number of Metastatic Sites at Study Entry, n (%)			
0 – 2	272 (83.4)	264 (81.7)	536 (82.6)
> 2	54 (16.6)	59 (18.3)	113 (17.4)
Patients with at Least One Prior Definitive Therapy, n (%)	143 (43.9)	141 (43.7)	284 (43.8)

	TIS+C (N = 326)	PBO+C (N = 323)	Total (N = 649)
ICC Option per IRT, n (%)			
Platinum with paclitaxel	179 (54.9)	177 (54.8)	356 (54.9)
Platinum with fluoropyrimidine	147 (45.1)	146 (45.2)	293 (45.1)

Data cutoff: 28FEB2022.

4.4. Study 306 Efficacy Results in the ITT Analysis Set

4.4.1. Primary Endpoint: Overall Survival at the Interim Analysis

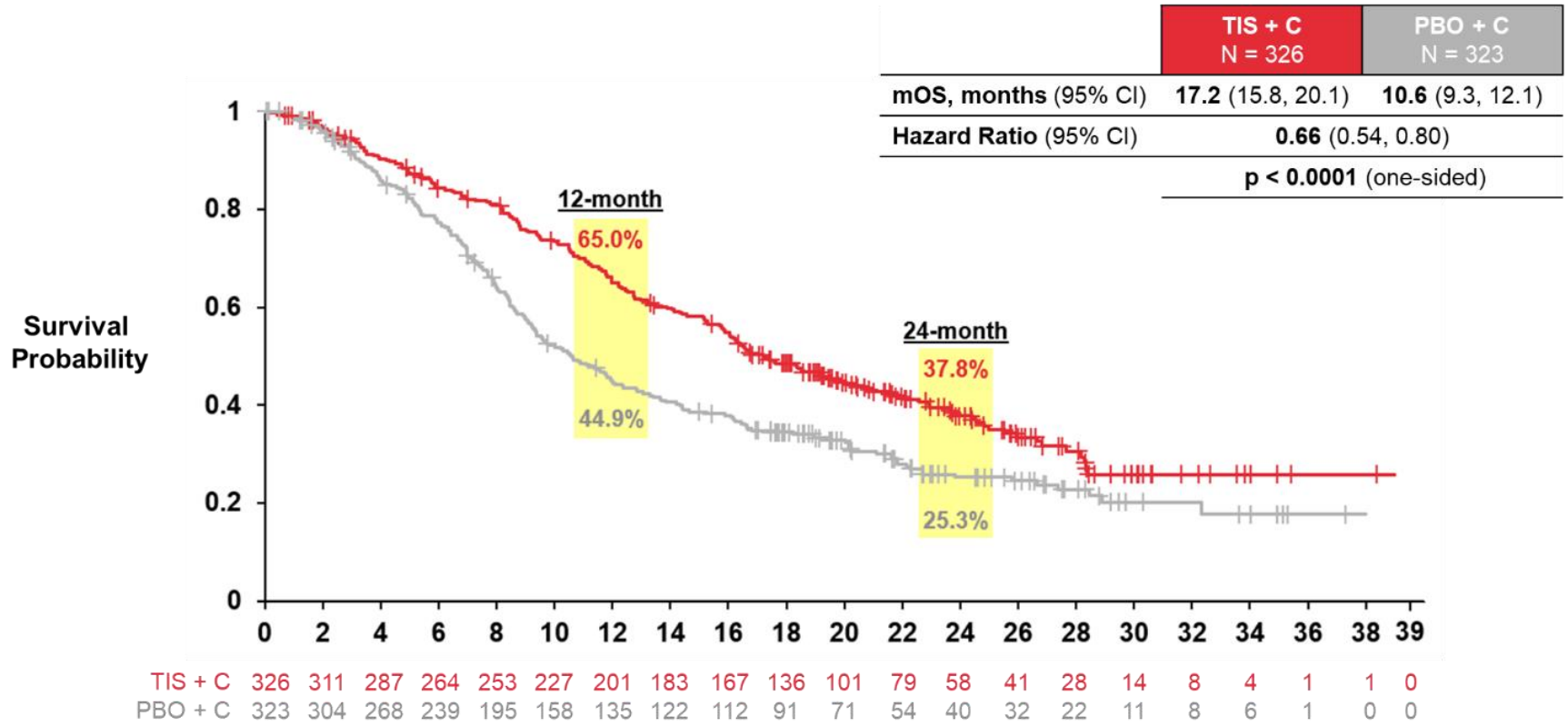
Study 306 met its primary endpoint at the interim analysis (data cutoff: 28 February 2022), demonstrating a statistically significant and clinically meaningful benefit with TIS+C compared to PBO+C (HR: 0.66 [95% CI: 0.54 to 0.80]; $p < 0.0001$) (Table 3; Figure 4). The median OS was prolonged by 6.6 months with TIS+C versus PBO+C. After the positive interim analysis, the study was unblinded.

Table 3: Overall Survival at the Interim Analysis (ITT Analysis Set)

	TIS+C (N = 326)	PBO+C (N = 323)
Number of Patients		
Death, n (%)	196 (60.1)	226 (70.0)
One-Sided Stratified Log-Rank Test P-value	< 0.0001	
Stratified Hazard Ratio (95% CI)	0.66 (0.54, 0.80)	
OS (months)		
Median (95% CI)	17.2 (15.8, 20.1)	10.6 (9.3, 12.1)
OS rate at, % (95% CI)		
12 months	65.0 (59.4, 70.0)	44.9 (39.2, 50.3)
24 months	37.8 (31.9, 43.6)	25.3 (20.1, 30.7)
30 months	25.9 (19.3, 33.0)	20.2 (14.6, 26.4)

Data cutoff: 28FEB2022.
Percentages were based on N.

Figure 4: Kaplan-Meier Plot of Overall Survival at the Interim Analysis (ITT Analysis Set)

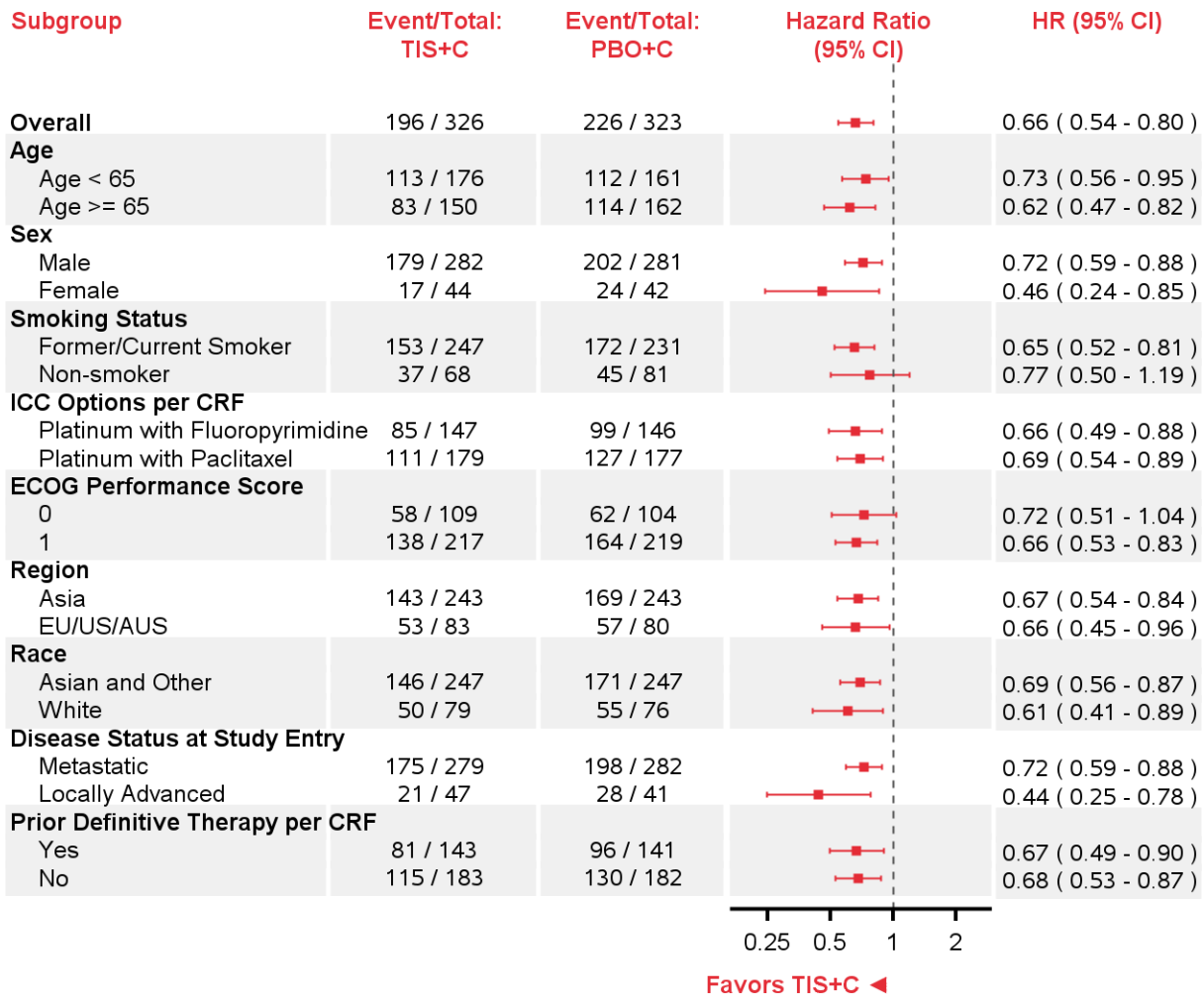


Data cutoff: 28FEB2022.

4.4.1.1. Overall Survival by Predefined Subgroups

The OS benefit of TIS+C over PBO+C was observed across all prespecified subgroups (Figure 5).

Figure 5: Forest Plot of Overall Survival at the Interim Analysis (ITT Analysis Set)



Data cutoff: 28FEB2022.
Notes: Hazard ratio was based on unstratified Cox regression model except that the stratified hazard ratio was provided for the overall population.
The race subcategory Other includes American Indian or Alaska Native, Not Reported, and Unknown.

4.4.2. Secondary Endpoints: PFS, ORR, and DOR at the Interim Analysis

The efficacy results favoring TIS+C were also observed in the secondary endpoints of PFS and ORR as assessed by the investigator (Table 4).

Table 4: Summary of Secondary Efficacy Endpoints at the Interim Analysis (ITT Analysis Set)

	TIS+C N = 326	PBO+C N = 323
PFS per Investigator		
Events, n (%)	220 (67.5)	254 (78.6)
One-Sided Stratified Log-Rank Test P-value	< 0.0001	
Stratified Hazard Ratio (95% CI)	0.62 (0.52, 0.75)	
PFS (months)		
Median (95% CI)	7.3 (6.9, 8.3)	5.6 (4.9, 6.0)
PFS rate at, % (95% CI)		
6 months	61.1 (55.3, 66.5)	44.5 (38.6, 50.2)
12 months	30.0 (24.6, 35.6)	15.7 (11.5, 20.4)
Confirmed ORR, n	184	117
% (95% CI)	56.4 (50.9, 61.9)	36.2 (31.0, 41.7)
Odds Ratio, (95% CI)	2.31 (1.68, 3.17)	
Difference, % (95% CI)	20.3 (12.8, 27.8)	
Duration of confirmed response, n	184	117
Events, n (%)	123 (66.8)	86 (73.5)
Median (95% CI), months	7.4 (6.9, 8.5)	6.6 (5.6, 8.3)

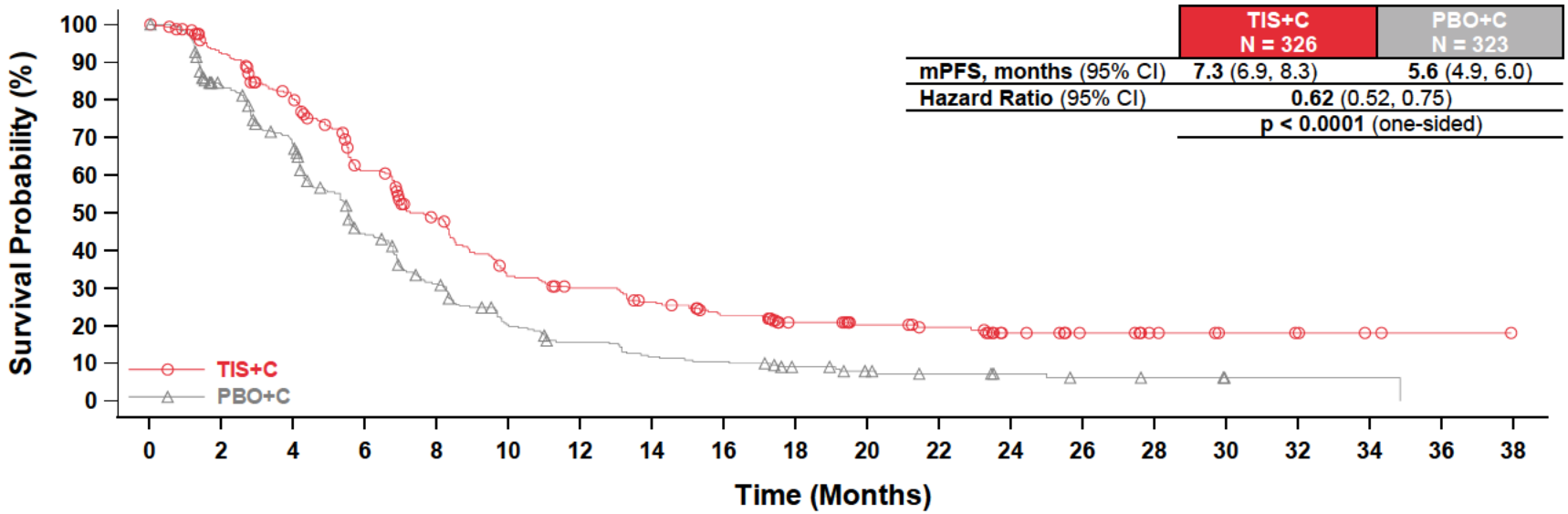
Percentages were based on N. Percentages for events in the duration of response were based on number of confirmed responders (CR and PR)

4.4.2.1. Progression-Free Survival

After rejecting the null hypothesis for the primary endpoint of OS in the ITT Analysis Set, PFS per the investigator in the ITT Analysis Set was tested. A statistically significant and clinically meaningful improvement in PFS with TIS+C over PBO+C was demonstrated (Table 4 and Figure 6).

- Estimated HR: 0.62 (95% CI: 0.52 to 0.75), corresponding to a 38% reduction in the risk of experiencing a PFS event for patients receiving TIS+C
- One-sided p-value: < 0.0001
- Median PFS was longer with TIS+C than with PBO+C

Figure 6: Kaplan-Meier Plot of Progression-Free Survival by the Investigator at the Interim Analysis (ITT Analysis Set)



No. At Risk:

TIS+C	326	283	236	168	125	84	73	62	50	38	32	27	18	12	8	5	4	2	1	0
PBO+C	323	248	196	119	80	49	36	27	24	17	12	9	7	4	3	1	1	1	0	0

Data cutoff: 28FEB2022.

4.4.2.2. Objective Response Rate

- There was a statistically significant and clinically relevant higher tumor response (unconfirmed) in patients receiving TIS+C over PBO+C (63.5% vs 42.4%), with a difference of 21.2%, an odds ratio for ORR of 2.38 and a two-sided p-value of < 0.0001.
  - Complete responses were observed for 15 patients (4.6%) following treatment with TIS+C versus 8 patients (2.5%) following treatment with PBO+C.
- The results of the analysis of ORR based on confirmed tumor response showed results consistent with those of the primary analysis.
  - The confirmed ORR was higher in the TIS+C arm than in the PBO+C arm (56.4% vs 36.2%), with a difference of 20.3%, an odds ratio of 2.31 between the 2 treatment arms (Table 4).

4.4.2.3. Duration of Response

- The median DOR (unconfirmed) per investigator assessment was 7.1 months in the TIS+C arm and 5.7 months in the PBO+C arm.
- Similar results were obtained in the analysis of DOR based on confirmed responses.

4.4.3. Updated Efficacy Results From 3-Year Follow-up

Updated efficacy results from the recently available long-term 3-year follow-up (data cutoff: 24 November 2023) reinforce the sustained clinical response and treatment continued to favor TIS+C in the overall population. This analysis provided an additional 20.8 months of follow-up and 92 deaths, with a minimum follow-up duration of 36 months for all patients in the ITT Analysis Set.

- HR of OS: 0.70 (95% CI: 0.59 to 0.83)
- HR of PFS: 0.60 (95% CI: 0.50 to 0.72)

4.5. Study 306 Efficacy Results in Patients by PD-L1 Status Assessed by TAP Assay

In support of the treatment benefit/risk assessment of TIS+C in patients with advanced or metastatic ESCC, subgroup analyses were performed per the prespecified analysis plan for subgroups by PD-L1 TAP score of 10%. In addition, post-hoc exploratory analyses were performed for subgroups by 1% and 5%, as well as ≥ 1% to < 5% and ≥ 5% to < 10%, using both data from the interim analysis (data cutoff: 28 February 2022) and updated analysis with 3-year follow up (data cutoff: 24 November 2023).

4.5.1. Patient Distribution

Baseline PD-L1 expression status was available in 542 (83.5%) patients; 107 (16.5%) patients had an unknown PD-L1 expression status because of the absence of sample collection, samples being not evaluable at baseline, or having provided an unqualified sample (Table 5).

Table 5: Patient Distribution by Baseline PD-L1 TAP Expression

Baseline PD-L1 Status	All Randomized Patients (N = 649) n (%)	Patients With Available Baseline PD-L1 Status (n = 542) n (%)
≥ 10%	223 (34.4)	223 (41.1)
< 10%	319 (49.2)	319 (58.9)
≥ 5%	358 (55.2)	358 (66.1)
< 5%	184 (28.4)	184 (33.9)
≥ 1%	481 (74.1)	481 (88.7)
< 1%	61 (9.4)	61 (11.3)
≥ 1% to < 5%	123 (19.0)	123 (22.7)
≥ 5% to < 10%	135 (20.8)	135 (24.9)
Unknown	107 (16.5)	N/A

Data cutoff: 28FEB2022.
Notes: 107 (16.5%) patients in the ITT Analysis Set had unknown PD-L1 TAP expression due to the absence of sample collection, samples being not evaluable at baseline, or having provided an unqualified sample. The percentages in the "All Randomized Patients" column were based on the number of randomized patients regardless if the patient had an unknown PD-L1 TAP expression or not; the percentages in the "Patients With Available PD-L1 Status" column were based on the number of patients with available PD-L1 TAP expression.

A multivariate adjusted analysis was performed to evaluate the impact of the imbalances on the analyses of OS (Section 4.5.2).

4.5.2. Efficacy Results

4.5.2.1. Overall Survival at the Interim Analysis

PD-L1 ≥ 10%: OS in PD-L1 ≥ 10% subgroup is a predefined secondary endpoint. TIS+C demonstrated a statistically significant and clinically meaningful improvement in OS compared with PBO+C (stratified HR = 0.63; 95% CI: 0.45 to 0.89; 1-sided p-value = 0.0042), with a median OS of 16.6 months (95% CI: 15.3 to 24.4 months) in the T+C Arm and 10.0 months (95% CI: 8.6 to 13.3 months) in the P+C Arm at interim analysis (Figure 7).

PD-L1 < 10%: OS in PD-L1 score < 10% subgroup was a predefined subgroup for OS analysis. Treatment with TIS+C showed OS benefit compared with PBO+C (HR = 0.75; 95% CI: 0.58 to 0.98), with a median OS of 15.8 months (95% CI: 12.3 to 19.6 months) in the TIS+C Arm and 10.4 months (95% CI: 9.0 to 13.4 months) in the PBO+C Arm (Figure 7).

PD-L1 ≥ 5%: Treatment with TIS+C also showed OS benefit compared with PBO+C (HR = 0.58; 95% CI: 0.45, 0.76), with a median OS of 19.6 months (95% CI: 16.1 to 25.0 months) in the TIS+C Arm and 10.0 months (95% CI: 8.6 to 11.9 months) in the PBO+C Arm (Figure 7).

PD-L1 < 5%: the HR of OS was 1.04 (95% CI: 0.74 to 1.46), with a median OS of 12.3 months (95% CI: 10.8 to 16.0 months) in the TIS+C Arm and 10.6 months (95% CI: 8.7 to 14.4 months) in the PBO+C Arm (Figure 7).

PD-L1 ≥ 1%: Treatment with TIS+C showed OS benefit compared with PBO+C (HR = 0.66; 95% CI: 0.53, 0.82), with a median OS of 16.8 months (95% CI: 15.3 to 20.8 months) in the TIS+C Arm and 9.6 months (95% CI: 8.9 to 11.8 months) in the PBO+C Arm (Figure 7).

PD-L1 < 1%: the HR of OS was 1.34 (95% CI: 0.73 to 2.46), with a median OS of 11.8 months (95% CI: 6.2 to 16.3 months) in the TIS+C Arm versus 16.1 months (95% CI: 10.4 to 28.9 months) in the PBO+C Arm. Given these historical data and the small samples size of the < 1% subgroup, the results should be interpreted with caution. Several factors could have possibly confounded the results and thus precludes making a reliable conclusion in this subgroup (refer to Section 4.5.3 for more detailed discussion).

PD-L1 unknown: the HR of OS was 0.53 (95% CI: 0.32 to 0.88), with a 12.0 month improvement in median OS (TIS+C: 23.7 months; PBO+C: 11.7 months).

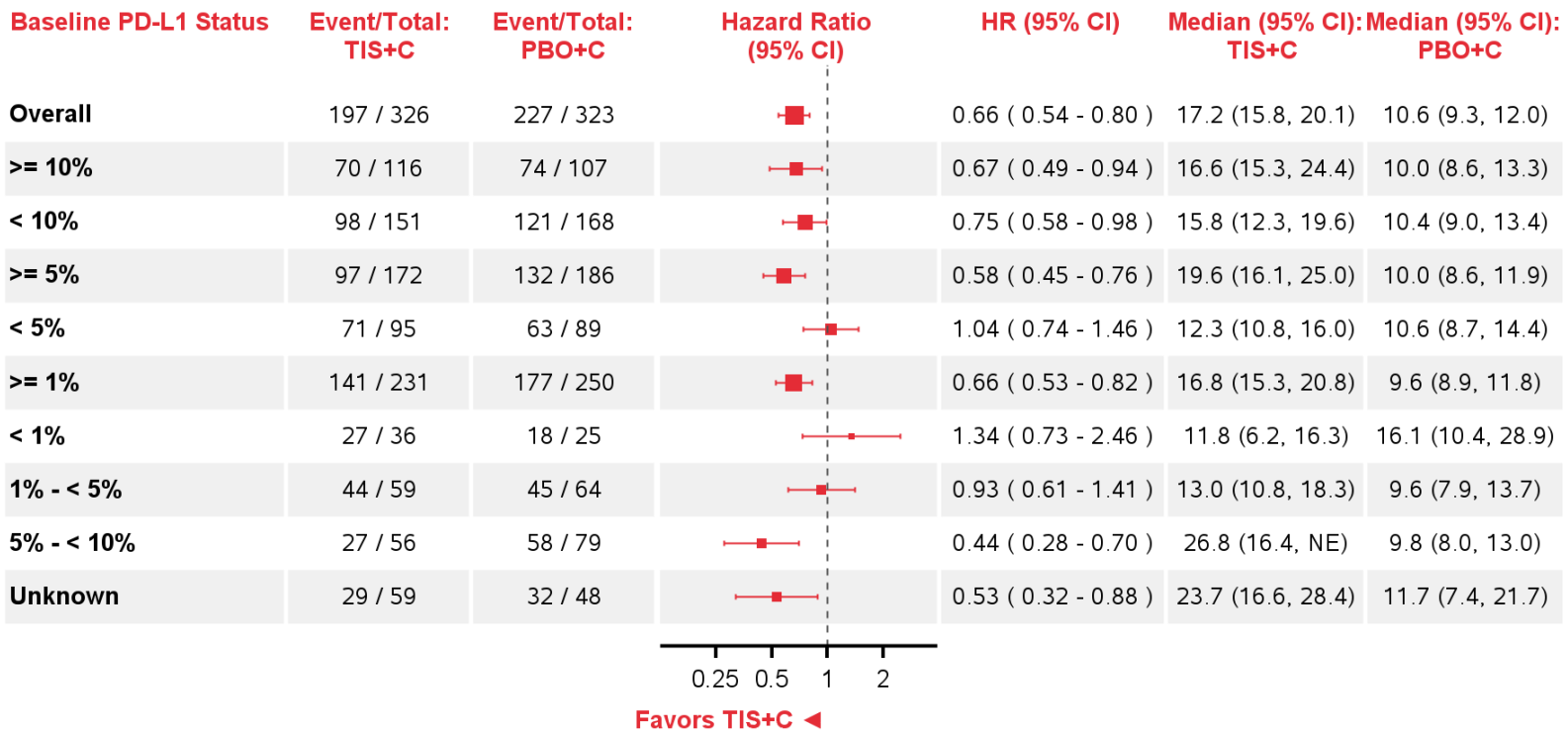
To explore the potential relationship between OS and PD-L1 expression further, additional exploratory analyses were performed in specific PD-L1 subgroups of PD-L1 ≥ 5% to < 10% and PD-L1 ≥ 1% to < 5%. An OS improvement in patients receiving TIS+C over PBO+C was still observed in each subgroup.

PD-L1 ≥ 5% to < 10%: the HR was 0.44 (95% CI: 0.28 to 0.70), with a 17.0 month improvement in median OS (TIS+C: 26.8 months; PBO+C: 9.8 months).

PD-L1 ≥ 1% to < 5%: the HR of OS was 0.93 (95% CI: 0.61 to 1.41), with a 3.4 month improvement in median OS (TIS+C: 13.0 months; PBO+C: 9.6 months). The Kaplan-Meier curves of OS separated at around 4 months, clearly in favor of the TIS+C Arm, and the separation was maintained thereafter until around 23 months.

-

Figure 7: Forest Plot of Overall Survival by Baseline PD-L1 TAP Score at the Interim Analysis (ITT Analysis Set)



Data cutoff: 28FEB2022.
Notes: Hazard ratio (TIS+C vs PBO+C) was based on unstratified Cox regression model except that the stratified hazard ratio was provided for the overall population. Updated death data for three patients were incorporated.

4.5.2.1.1. Overall Survival Analysis Adjusted for Baseline Covariates- at the Interim Analysis

The baseline characteristics, including demographics, disease history, and prior anticancer therapy, were generally balanced between the 2 treatment arms across PD-L1 low expression subgroups and similar to those observed in the overall population (Table 9).

A multivariate adjusted analysis was performed to assess the impact of the numerical imbalances observed between the 2 treatment arms.

The adjusted HR (TIS+C vs PBO+C) was based on an unstratified Cox regression model including treatment group, as well as prespecified key baseline characteristics and prognostic factors of age (< 65 years, ≥ 65 years), sex (male, female), smoking status (former, current, never, missing), ECOG PS (0, 1), disease stage (locally advanced, metastatic), and stratification factors (pooled geographic region per IRT, prior definitive therapy per IRT, and ICC option per IRT) as covariates.

Results of the multivariate adjusted analysis in the PD-L1 < 5% and PD-L1 ≥ 1% to < 5% subgroups were:

- **PD-L1 < 5% subgroup:** HR was 0.95 (95% CI: 0.67 to 1.35).
- **PD-L1 ≥ 1% to < 5% subgroup:** HR was 0.78 (95% CI: 0.51 to 1.22).

4.5.2.2. Posttreatment Subsequent Anticancer Therapy

In general, within each PD-L1 subgroup, the proportion of patients receiving PBO+C who received subsequent anticancer therapy, such as radiotherapy, surgery, or systemic therapies (including immunotherapy), was consistently higher than with TIS+C (Table 10). When comparing across subgroups, more striking differences in subsequent anticancer therapy were observed between the 2 arms in the PD-L1 < 1% subgroup, with a particular emphasis on subsequent immunotherapy. These noticeable differences could have confounded the OS results in the PD-L1 < 1% subgroup more than overall population and in other exploratory subgroups by PD-L1 status in this document.

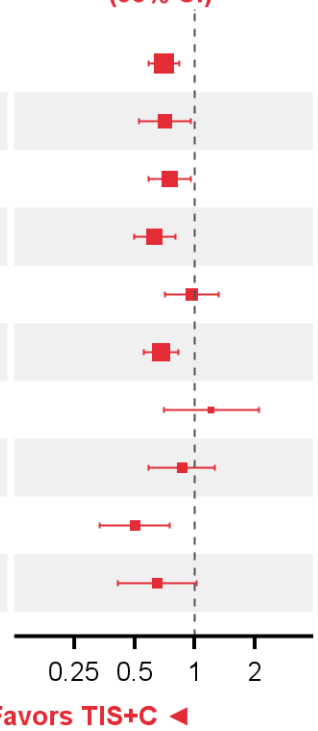
4.5.2.3. Overall Survival at 3-Year Survival Follow-up

To better support the benefit and risk assessment for treatment with TIS+C in exploratory PD-L1 subgroups, updated OS results from the recently available long-term 3-year follow-up (data cutoff on 24 November 2023) were provided for all PD-L1 subgroups (Figure 8 and Table 6).

Overall, the updated OS results from a minimum 3-year follow-up were consistent with those at the interim analysis. It is worthwhile to note that the favorable trend for OS HR in the PD-L1 ≥ 1% to < 5% subgroup became more pronounced with longer follow-up, providing additional supportive evidence for the treatment benefit with TIS+C in this subgroup. Consequently, the HR of OS dropped below 1 in the PD-L1 < 5% subgroup.

Figure 8: Forest Plot of Overall Survival by Baseline PD-L1 TAP Score at the 3-Year Follow-up (ITT Analysis Set)

Baseline PD-L1 Status	Event/Total: TIS+C	Event/Total: PBO+C	HR (95% CI)	Median (95% CI): TIS+C	Median (95% CI): PBO+C
Overall	250 / 326	264 / 323	0.70 (0.59 - 0.83)	17.2 (15.8, 20.1)	10.6 (9.3, 12.0)
>= 10%	90 / 116	85 / 107	0.71 (0.53 - 0.95)	16.6 (15.3, 23.4)	10.0 (8.6, 13.3)
< 10%	120 / 151	144 / 168	0.74 (0.58 - 0.95)	16.0 (12.3, 19.6)	10.4 (9.0, 13.4)
>= 5%	128 / 172	151 / 186	0.63 (0.49 - 0.79)	19.1 (16.1, 24.1)	10.0 (8.6, 11.9)
< 5%	82 / 95	78 / 89	0.96 (0.71 - 1.31)	12.3 (10.8, 16.0)	10.6 (8.7, 14.4)
>= 1%	178 / 231	207 / 250	0.68 (0.55 - 0.83)	16.8 (15.3, 20.8)	9.6 (8.9, 11.8)
< 1%	32 / 36	22 / 25	1.21 (0.70 - 2.08)	11.8 (6.2, 16.3)	16.1 (10.4, 27.1)
1% - < 5%	50 / 59	56 / 64	0.86 (0.59 - 1.26)	13.0 (10.8, 18.3)	9.6 (7.9, 13.7)
5% - < 10%	38 / 56	66 / 79	0.50 (0.33 - 0.75)	23.1 (16.4, 28.3)	9.8 (8.0, 13.0)
Unknown	40 / 59	35 / 48	0.65 (0.41 - 1.02)	23.7 (16.6, 29.1)	11.7 (7.4, 21.7)



Data cutoff: 24NOV2023.
Notes: Hazard ratio (TIS+C vs PBO+C) was based on unstratified Cox regression model except that the stratified hazard ratio was provided for the overall population. Updated death data for three patients were incorporated.

Table 6: Overall Survival by Baseline PD-L1 TAP at the Interim Analysis and 3-Year Follow-up (ITT Analysis Set)

	Interim Analysis				3-Year Follow-up			
	Death Events				Death Events			
Baseline PD-L1 Status	TIS+C n/N (%)	PBO+C n/N (%)	OS HR (95% CI)	OS Adjusted HR (95% CI)	TIS+C n/N (%)	PBO+C n/N (%)	OS HR (95% CI)	OS Adjusted HR (95% CI)
≥ 10%	70/116 (60.3)	74/107 (69.2)	0.67 (0.49, 0.94)	0.67 (0.48, 0.94)	90/116 (77.6)	85/107 (79.4)	0.71 (0.53, 0.95)	0.74 (0.54, 1.01)
< 10%	98/151 (64.9)	121/168 (72.0)	0.75 (0.58, 0.98)	0.74 (0.57, 0.97)	120/151 (79.5)	144/168 (85.7)	0.74 (0.58, 0.95)	0.74 (0.58, 0.95)
≥ 5%	97/172 (56.4)	132/186 (71.0)	0.58 (0.45, 0.76)	0.58 (0.44, 0.76)	128/172 (74.4)	151/186 (81.2)	0.63 (0.49, 0.79)	0.63 (0.50, 0.81)
< 5%	71/95 (74.7)	63/89 (70.8)	1.04 (0.74, 1.46)	0.95 (0.67, 1.35)	82/95 (86.3)	78/89 (87.6)	0.96 (0.71, 1.31)	0.90 (0.65, 1.23)
≥ 1%	141/231 (61.0)	177/250 (70.8)	0.66 (0.53, 0.82)	0.64 (0.51, 0.80)	178/231 (77.1)	207/250 (82.8)	0.68 (0.55, 0.83)	0.66 (0.54, 0.81)
< 1%	27/36 (75.0)	18/25 (72.0)	1.34 (0.73, 2.46)	1.47 (0.76, 2.84)	32/36 (88.9)	22/25 (88.0)	1.21 (0.70, 2.08)	1.34 (0.73, 2.45)
≥ 5% to < 10%	27/56 (48.2)	58/79 (73.4)	0.44 (0.28, 0.70)	0.41 (0.25, 0.66)	38/56 (67.9)	66/79 (83.5)	0.50 (0.33, 0.75)	0.45 (0.29, 0.69)
≥ 1% to < 5%	44/59 (74.6)	45/64 (70.3)	0.93 (0.61, 1.41)	0.78 (0.51, 1.22)	50/59 (84.7)	56/64 (87.5)	0.86 (0.59, 1.26)	0.76 (0.50, 1.13)
Unknown	29/59 (49.2)	32/48 (66.7)	0.53 (0.32, 0.88)	0.58 (0.34, 0.99)	40/59 (67.8)	35/48 (72.9)	0.65 (0.41, 1.02)	0.63 (0.38, 1.04)

Interim Analysis: Data cutoff: 28FEB2022. 3-Year Follow-up: Data cutoff: 24NOV2023.

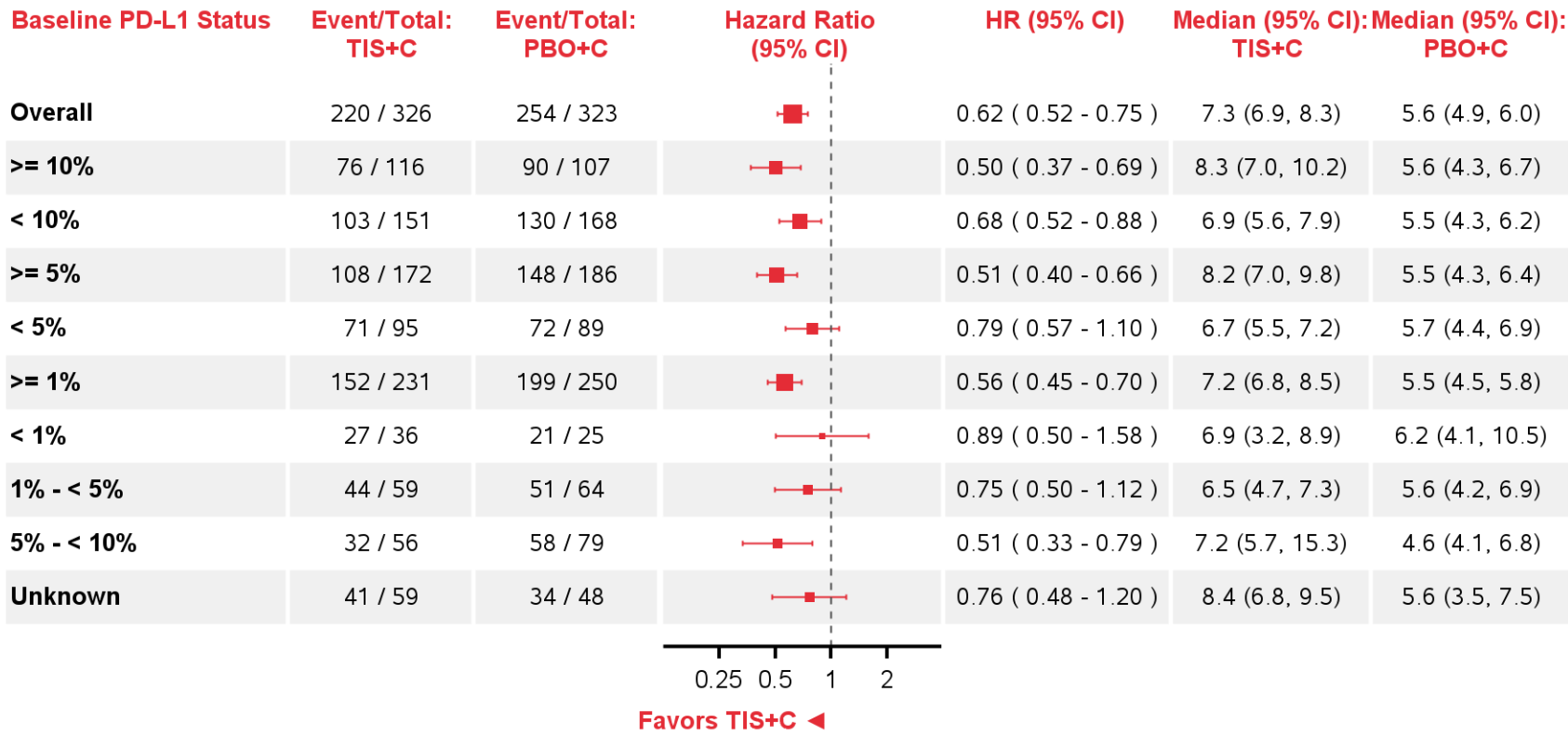
Notes: Hazard ratio (TIS+C vs PBO+C) was based on unstratified Cox regression model. Adjusted hazard ratio (TIS+C vs PBO+C) was based on unstratified Cox regression model including treatment group, age (< 65, ≥ 65), sex (Male, Female), smoking (Former, Current, Never, Missing), ECOG status (0, 1), metastatic (locally advanced vs metastatic), pooled geographic region (Asia [including Japan] vs US/Europe/Australia) per IRT, prior definitive therapy (Yes vs No) per IRT, and ICC option (Investigator's choice of chemotherapy [platinum with fluoropyrimidine vs platinum with paclitaxel]) per IRT as covariates. Updated death data for three patients were incorporated.

4.5.2.4. Other Secondary Endpoints by PD-L1 Status at the Interim Analysis: PFS, ORR, and DOR

4.5.2.4.1. Progression-Free Survival

In all the exploratory PD-L1 expression subgroups, favorable PFS results were observed with TIS+C compared with PBO+C (Figure 9), accompanied by numerical improvements in median PFS. The magnitude of PFS benefit was enhanced with increasing PD-L1 expression.

Figure 9: Forest Plot of Progression-Free Survival by Baseline PD-L1 TAP Expression at the Interim Analysis (ITT Analysis Set)



Data cutoff: 28FEB2022.

Notes: Hazard ratio (TIS + C vs PBO + C) was based on unstratified Cox regression model except that the stratified hazard ratio was provided for the overall population. Updated death data for three patients were incorporated.

4.5.2.4.2. Objective Response Rate

A higher ORR was observed in patients receiving TIS+C than PBO+C in the subgroups of PD-L1 ≥ 1% (Figure 10).

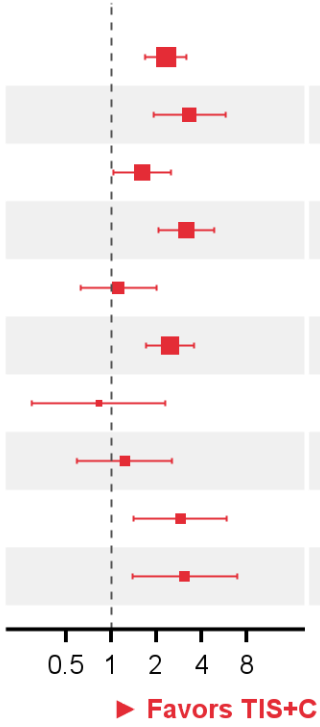
For the PD-L1 < 1% subgroup:

- The ORR in patients receiving PBO+C in this subgroup (52.0%) was much higher than those observed with PBO+C across other PD-L1 subgroups (35.5% to 36.7%) and higher than those reported in other recently completed first-line ESCC studies.[13,18]

Considering the small sample size of the PD-L1 < 1% subgroup, these high ORRs with PBO+C could have possibly arisen by chance; therefore, the comparation of ORRs between treatment arms in this subgroup should be interpreted with caution.

Figure 10: Forest Plot of Overall Response Rate by Baseline PD-L1 TAP Score at the Interim Analysis (ITT Analysis Set)

Baseline PD-L1 Status	Responder/Total: TIS+C	Responder/Total: PBO+C	Odds Ratio (95% CI)	ORR (95% CI): TIS+C	ORR (95% CI): PBO+C
Overall	184 / 326	117 / 323	2.31 (1.68, 3.17)	56.4 (50.9, 61.9)	36.2 (31.0, 41.7)
>= 10%	75 / 116	38 / 107	3.32 (1.92, 5.75)	64.7 (55.2, 73.3)	35.5 (26.5, 45.4)
< 10%	76 / 151	65 / 168	1.61 (1.03, 2.51)	50.3 (42.1, 58.6)	38.7 (31.3, 46.5)
>= 5%	110 / 172	67 / 186	3.15 (2.05, 4.85)	64.0 (56.3, 71.1)	36.0 (29.1, 43.4)
< 5%	41 / 95	36 / 89	1.12 (0.62, 2.01)	43.2 (33.0, 53.7)	40.4 (30.2, 51.4)
>= 1%	134 / 231	90 / 250	2.46 (1.70, 3.55)	58.0 (51.4, 64.5)	36.0 (30.0, 42.3)
< 1%	17 / 36	13 / 25	0.83 (0.30, 2.29)	47.2 (30.4, 64.5)	52.0 (31.3, 72.2)
1% - < 5%	24 / 59	23 / 64	1.22 (0.59, 2.53)	40.7 (28.1, 54.3)	35.9 (24.3, 48.9)
5% - < 10%	35 / 56	29 / 79	2.87 (1.41, 5.84)	62.5 (48.5, 75.1)	36.7 (26.1, 48.3)
Unknown	33 / 59	14 / 48	3.08 (1.38, 6.91)	55.9 (42.4, 68.8)	29.2 (17.0, 44.1)



Data cutoff: 28FEB2022.
Notes: Crude odds ratio of confirmed overall response rate was presented except that the stratified odds ratio was provided for the overall population.

4.5.2.4.3. Duration of Response

Median DOR observed in all prespecified and exploratory PD-L1 subgroups are provided in Table 11.

4.5.3. The Interpretability of the Treatment Benefit in Subgroups With PD-L1 Expression Level Less Than TAP Score 5%

The treatment benefit in patients with PD-L1 TAP score < 5% is specifically discussed for those with PD-L1 TAP score ≥ 1% to < 5% and with PD-L1 TAP score < 1% separately below:

- **In the PD-L1 ≥ 1% to < 5% subgroup,** as summarized above, HR of OS at the interim analysis was 0.93 (95% CI: 0.61 to 1.41) and reduced to 0.86 (95% CI: 0.59 to 1.26) with 3-year follow-up. The favorable OS results observed in this subgroup were further supported by an analysis to adjust the impact from the numerical imbalances of baseline characteristics most notably in the PD L1 ≥ 1% to < 5% subgroup.
  - At the interim analysis, the crossing of the TIS+C and PBO+C curves was mainly due to the very small number of patients with follow-up time ≥ 23 months. The curves are sensitive to any event change. In the updated analysis with a minimum 3-year follow-up, the separation of the Kaplan-Meier curves in favor of TIS+C was maintained until approximately 24 months. An overlapping of Kaplan-Meier curves was observed after 24 months, which could have been due to the use of subsequent immunotherapy with PBO+C: 7 of those 14 patients who were followed up for ≥ 24 months with PBO+C received subsequent immunotherapy.
  - In the multivariate adjusted analysis, the adjusted HR of OS was 0.78 (95% CI: 0.51 to 1.22) at the interim analysis and 0.76 (95% CI: 0.50 to 1.13) in the 3-year follow-up, further supporting the favorable OS results observed in this subgroup after adjusting the impact from the numerical imbalances of baseline characteristics most notably in the PD-L1 ≥ 1% to < 5% subgroup.
  - Favorable PFS (HR: 0.75; [95% CI: 0.50 to 1.12]) and ORR (40.7% with TIS+C vs 35.9% with PBO+C) were observed in this subgroup, in support of the treatment benefit with TIS+C.

Considering the increased evidence to support OS benefit in the PD-L1 ≥ 1% to < 5% subgroup with longer follow up and multivariate adjusted analysis, the HR of OS observed in the PD-L1 < 5% subgroup is considered primarily driven by results in the PD-L1 < 1% subgroup.

- **In the PD-L1 < 1% subgroup,** results in this subgroup should be interpreted with caution, as several factors could have possibly confounded the results and thus preclude a reliable conclusion to be made in this subgroup:
  - The sample size in both arms was very small (36 patients [11.0%] receiving TIS+C and 25 patients [7.7%] receiving PBO+C), leading to an estimate with high variability, as indicated by a wide CI. These small sample sizes make this subgroup more sensitive to random imbalances in the distribution of baseline

characteristics and to the numbers of observed deaths between treatment arms (27 events with TIS+C vs 18 events with PBO+C).

- The median OS in patients receiving PBO+C was 16.1 months, which was much higher than that in the overall population of Study 306 and the historical median OS with chemotherapy alone in 1L ESCC for PD-L1 high expression and low expression,[10,13,14,19,20,21] and an ORR of 52.0%, which was again unexpected and higher than those reported in other recently completed first-line ESCC studies.
- A noticeably higher proportion of patients receiving PBO+C than TIS+C received subsequent immunotherapy (28.0% vs 8.3%), which could have contributed to the longer OS in the PBO+C arm. This explanation is also supported by the favorable results in the secondary endpoints of PFS within this subgroup (refer to Section 4.4.2 for PFS results), which are not impacted by subsequent anticancer therapies.

The above factors could have possibly confounded the OS results in the PD-L1< 1% subgroup, and therefore results should be interpreted with caution.

4.6. Exploratory Analysis by PD-L1 Expression Using CPS at the Interim Analysis

Beyond PD-L1 assessment by TAP score per Study 306 protocol, CPS has also been used in clinical studies investigating PD-1 inhibitors in ESCC. Both the TAP and CPS scoring methods assess PD-L1 expression on tumor cells and immune cells, with TAP score utilizing a visual estimation-based approach and CPS utilizing a cell counting-based approach.

To understand the concordance between TAP score and CPS and the relationship between PD-L1 status with Study 306 clinical outcomes, a post-hoc exploratory analysis of CPS was conducted, where pathologists in the central laboratory rescored the same stained samples (stained with the VENTANA PD-L1 [SP263] Assay) using CPS.

4.6.1. Patient Distribution

There were 537 evaluable patients for PD-L1 by CPS (Table 7).

The proportion of patients by baseline PD-L1 CPS levels (≥ 1, < 1, ≥ 5, < 5, ≥ 10 and < 10) and by PD-L1 CPS categories (1 to < 5 and 5 to < 10) were similar with those for PD-L1 TAP Table 5).

Table 7: Patient Distribution by Baseline PD-L1 CPS Expression

Baseline PD-L1 Status	All Randomized Patients (N = 649) n (%)	Patients With Available Baseline PD-L1 Status (N = 537) n (%)
≥ 10	228 (35.1)	228 (42.5)
< 10	309 (47.6)	309 (57.5)
≥ 5	343 (52.9)	343 (63.9)
< 5	194 (29.9)	194 (36.1)

Baseline PD-L1 Status	All Randomized Patients (N = 649) n (%)	Patients With Available Baseline PD-L1 Status (N = 537) n (%)
≥ 1	480 (74.0)	480 (89.4)
< 1	57 (8.8)	57 (10.6)
1 to < 5	137 (21.1)	137 (25.5)
5 to < 10	115 (17.7)	115 (21.4)
Unknown	112 (17.3)	NA

Data cutoff: 28FEB2022.
Abbreviations: CPS, combined positive score; PD-L1, programmed death ligand 1.
Notes: 112 (17.3%) patients in the ITT Analysis Set had an unknown PD-L1 CPS expression due to the absence of sample collection, samples being not evaluable at baseline, or having provided an unqualified sample. The percentages in the "All Randomized Patients" column was based on the number of randomized patients regardless if the patient had an unknown PD-L1 CPS expression or not; the percentages in the "Patients With Available PD-L1 Status" column was based on the number of patients with available PD-L1 CPS expression.

4.6.2. Efficacy Results by PD-L1 Subgroups Defined by CPS

In general, efficacy results of OS and PFS by PD-L1 subgroups defined by CPS are similar to those of PD-L1 subgroups defined by TAP.

4.6.2.1. Overall Survival by PD-L1 CPS Status

Overall, OS results by baseline PD-L1 CPS status were similar to those observed by baseline PD-L1 TAP score, in support of the finding that OS benefit was enhanced with increase of PD-L1 expression except subgroups of PD-L1 CPS < 5 and 1 to < 5 which showed more substantial OS benefit (Figure 11).

PD-L1 < 5 subgroup

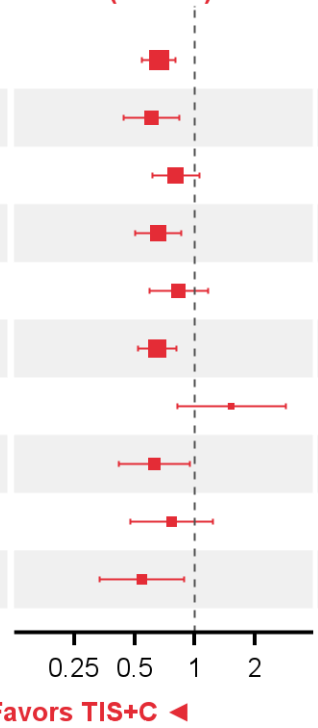
- HR: 0.83 (95% CI: 0.59 to 1.16)
- Median OS: TIS+C: 14.1 months; PBO+C:10.6 months.

PD-L1 1 to < 5 subgroup

- HR: 0.62 (95% CI: 0.41 to 0.94)
- Median OS: TIS+C: 16.7 months; PBO+C: 9.5 months.

Figure 11: Forest Plot of Overall Survival by Baseline PD-L1 CPS Expression at the Interim Analysis (ITT Analysis Set)

Baseline PD-L1 Status	Event/Total: TIS+C	Event/Total: PBO+C	HR (95% CI)	Median (95% CI): TIS+C	Median (95% CI): PBO+C
Overall	197 / 326	227 / 323	0.66 (0.54 - 0.80)	17.2 (15.8, 20.1)	10.6 (9.3, 12.0)
>= 10	69 / 115	82 / 113	0.61 (0.44 - 0.83)	17.2 (15.3, 25.0)	9.4 (8.5, 12.3)
< 10	96 / 149	111 / 160	0.80 (0.61 - 1.06)	15.8 (12.5, 19.2)	10.6 (9.1, 13.8)
>= 5	100 / 169	121 / 174	0.66 (0.50 - 0.85)	16.8 (15.8, 23.9)	10.0 (8.7, 12.4)
< 5	65 / 95	72 / 99	0.83 (0.59 - 1.16)	14.1 (12.0, 18.4)	10.6 (8.4, 14.4)
>= 1	141 / 233	175 / 247	0.65 (0.52 - 0.81)	16.8 (15.3, 20.8)	9.6 (8.9, 11.8)
< 1	24 / 31	18 / 26	1.52 (0.81 - 2.84)	11.6 (6.2, 16.3)	18.1 (10.4, 28.9)
1 - < 5	41 / 64	54 / 73	0.62 (0.41 - 0.94)	16.7 (12.3, 20.8)	9.5 (7.7, 13.7)
5 - < 10	31 / 54	39 / 61	0.76 (0.48 - 1.23)	16.8 (11.2, 28.3)	10.8 (8.0, 18.2)
Unknown	32 / 62	34 / 50	0.54 (0.34 - 0.88)	22.9 (16.6, 27.7)	10.9 (7.4, 16.4)

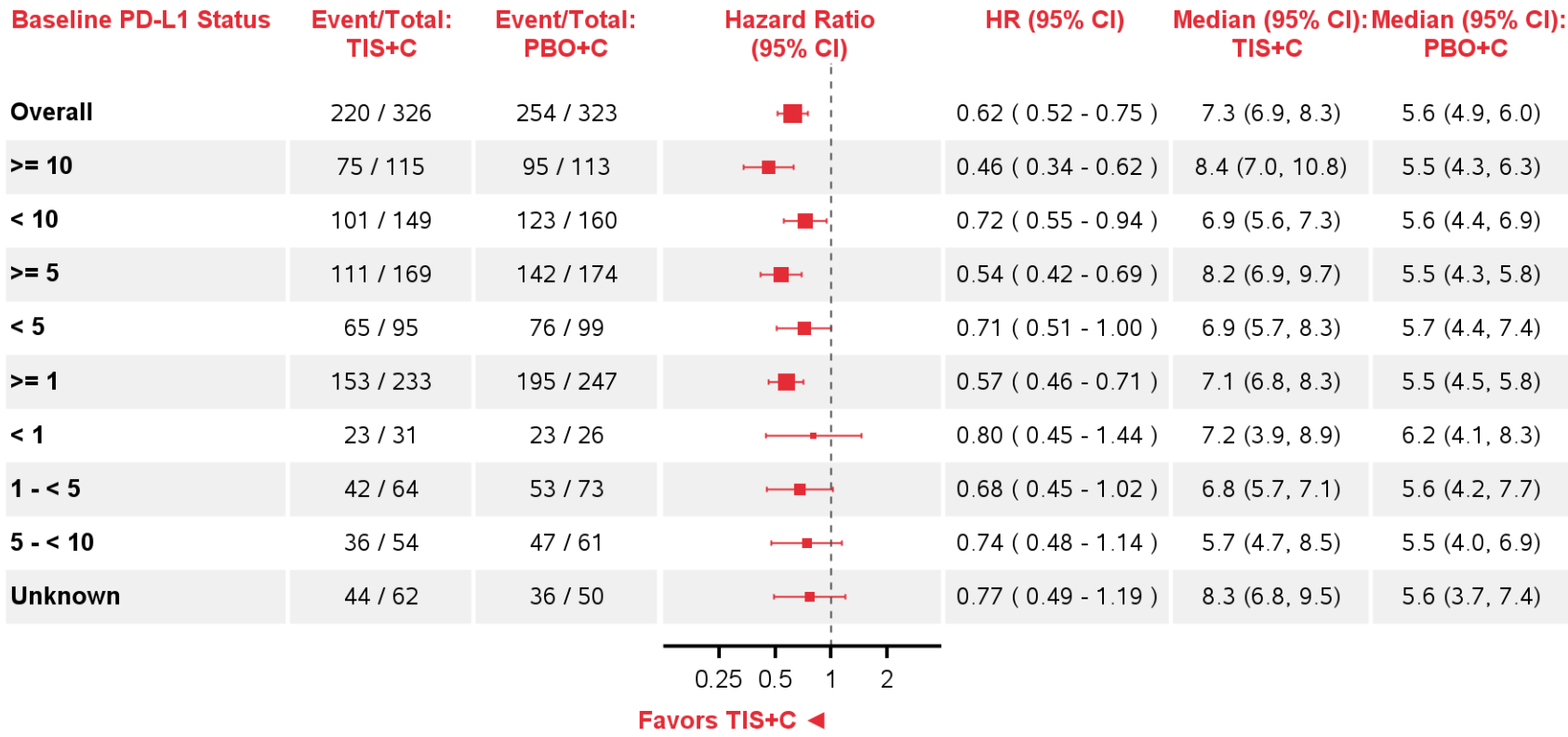


Data cutoff: 28FEB2022.
Notes: Hazard ratio (TIS+C vs PBO+C) was based on unstratified Cox regression model except that the stratified hazard ratio was provided for the overall population. Updated death data for three patients were incorporated.

4.6.2.2. Progression-Free Survival by PD-L1 CPS Status

PFS results in all PD-L1 CPS subgroups showed a favorable findings in TIS+C over PBO+C (ie, HR < 1) in all the subgroups of PD-L1 expression, which was similar to those in subgroups of PD-L1 by TAP (Figure 12).

Figure 12: Forest Plot of Progression-Free Survival by Baseline PD-L1 CPS Expression at the Interim Analysis (ITT Analysis Set)



Data cutoff: 28FEB2022.
Notes: Hazard ratio (TIS+C vs PBO+C) was based on unstratified Cox regression model except that the stratified hazard ratio was provided for the overall population. Updated death data for three patients were incorporated.

4.6.3. Concordance Between TAP and CPS in ESCC

To investigate the analytical concordance between TAP and CPS, an exploratory agreement analysis was performed on samples with both TAP and CPS evaluable results (N = 537).

Overall, the TAP score and CPS showed substantial concordance at matched cutoffs (TAP ≥ 1% vs CPS ≥ 1, TAP ≥ 5% vs CPS ≥ 5, TAP ≥ 10% vs CPS ≥ 10), with OPA of 97%, 85%, and 89% and Cohen's Kappa values of 0.85, 0.67, and 0.78, respectively (Table 8).

Table 8: Concordance Between TAP and CPS Results

	TAP ≥ 1% vs CPS ≥ 1	
	n/N	Agreement % (95% CI)
PPA	470/480	98 (96, 99)
NPA	51/57	89 (81, 96)
OPA	521/537	97 (96, 98)
Cohen's Kappa	0.85 (0.77, 0.92)	
	TAP ≥ 5% vs CPS ≥ 5	
	n/N	Agreement % (95% CI)
PPA	309/343	90 (87, 93)
NPA	147/194	76 (70, 81)
OPA	456/537	85 (82, 88)
Cohen's Kappa	0.67 (0.60, 0.73)	
	TAP ≥ 10% vs CPS ≥ 10	
	n/N	Agreement % (95% CI)
PPA	196/228	86 (81, 90)
NPA	283/309	92 (88, 94)
OPA	479/537	89 (86, 92)
Cohen's Kappa	0.78 (0.72, 0.83)	

Abbreviations: CPS, combined positive score; NPA, negative percentage agreement; OPA, overall percentage agreement; PPA, positive percentage agreement; TAP, tumor area positivity.
Notes: PPA, NPA, OPA, and Cohen's Kappa (K) were calculated from 2 × 2 contingency tables by categorizing individual samples as PD-L1 positive or PD-L1 negative according to each cutoff and using CPS score as the reference.

4.7. Efficacy Conclusion

The study met its primary endpoint at its preplanned interim analysis by demonstrating a statistically significant and clinically meaningful improvement in OS in patients receiving TIS+C, with a 34% risk reduction for death and a median OS improved by 6.6 months. The OS benefit favoring TIS+C over PBO+C was observed across subgroups of baseline demographic and disease characteristics, including region, ICC options, and race. The benefit of TIS+C was also observed as significant improvements in PFS, superior ORR, and more durable tumor responses, without an increase of patients' symptom burden.

Efficacy results from prespecified or post-hoc exploratory subgroups by baseline PD-L1 expression levels using PD-L1 cutoffs of 10%, 5%, and 1% showed enhancing treatment effect with increasing PD-L1 expression levels with TIS+C compared with PBO+C. Caution should be

taken when interpreting results from exploratory subgroups and subgroups with limited sample size.

5. SAFETY RESULTS

The safety of TIS+C for the treatment of patients with advanced or metastatic ESCC is based primarily on results from the interim analysis (in all treated randomized patients) of Study 306.

5.1. Safety Results in the Safety Analysis Set

Among the 649 randomized patients, 645 received at least one dose of either TIS+C or PBO+C and constituted the Safety Analysis Set.

Overall, TIS+C showed a tolerable and acceptable safety profile in the first-line treatment of patients with advanced or metastatic ESCC. The safety profile of TIS+C was consistent with the known risks of each treatment agent and the underlying diseases under investigation.

Nearly all patients experienced at least one TEAE with TIS+C (99.7%) or PBO+C (99.4%) (Table 12). The most common TEAEs (≥ incidence 20%), generally similar between the 2 treatment arms) (Table 13).

The incidence of ≥ Grade 3 TEAEs was similar in the 2 arms (78.4% vs 77.6%, respectively; Table 14), while more patients treated with TIS+C versus PBO+C experienced serious TEAEs (48.1% vs 39.6%, respectively). The higher overall incidence of serious TEAEs with TIS+C than PBO+C was not driven by a specific AE type, and most of these events generally reflected the known safety profile of study drugs and the underlying condition of the disease under study.

The incidence of TEAEs leading to death was also similar between the 2 arms (TIS+C: 5.2%; PBO+C: 5.3%; Table 15).

TEAEs leading to discontinuation of any treatment component occurred in 31.8% of treated with TIS+C and 22.4% with PBO+C.

35.2% of patients treated with TIS+C versus 18.7% of patients treated with PBO+C reported ≥ 1 imAE. 29 patients (9.0%) treated with TIS+C versus 4 patients (1.2%) treated with PBO+C experienced ≥ Grade 3 imAEs (Table 12).

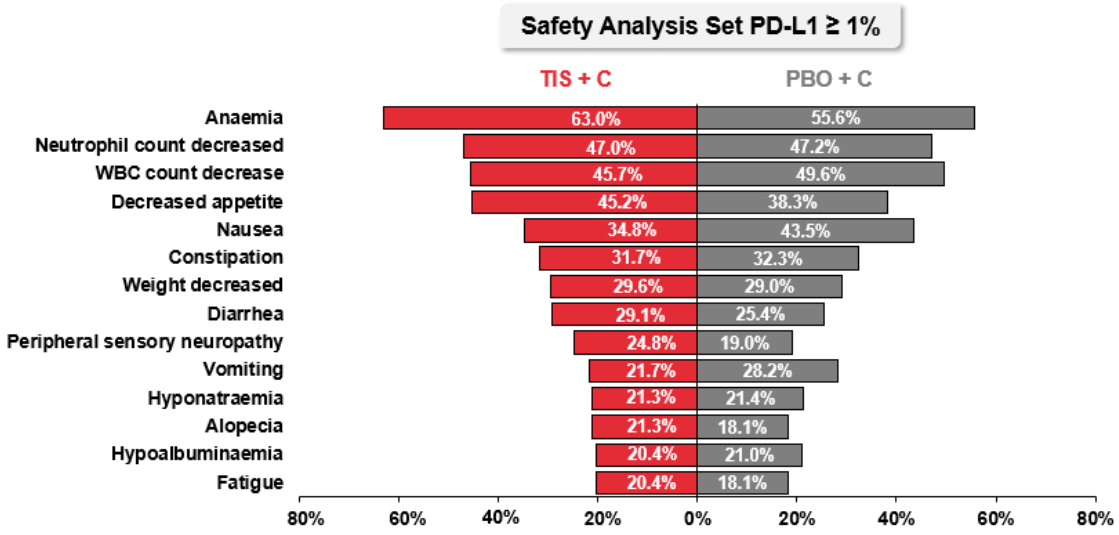
5.2. Safety Results in PD-L1 Subgroups

Exploratory safety analyses were performed for PD-L1 subgroups by TAP 1% (≥ 1% vs < 1%) using the Safety Analysis Set to explore if there was any increased safety risk associated with PD-L1 expression following the treatment of TIS+C, especially in the PD-L1 < 1% subgroup (Table 12, Table 13, Table 14, and Table 15).

The safety data remained similar among the PD-L1 subgroups by TAP 1% (≥ 1% vs < 1%), with slight differences observed in the 2 treatment arms. These differences were not clinically relevant and were similar to the Safety Analysis Set. The most common TEAEs by PT reported in these subgroups in both treatment arms are in line with the known toxicity of chemotherapy agents and the underlying disease.

- For PD-L1 TAP ≥ 1%, most patients in both arms experienced ≥ 1 TEAE (TIS+C: 99.6% vs PBO+C: 100.0%; Figure 13).
  - The incidence of ≥ Grade 3 TEAEs (TIS+C: 78.3% vs PBO+C: 77.4%), serious TEAEs (TIS+C: 46.5% vs PBO+C: 39.1%), TEAEs leading to death (TIS+C: 6.1% vs PBO+C: 5.2%), and TEAEs leading to discontinuation of any treatment component (TIS+C: 35.2% vs PBO+C: 22.2%), were generally consistent with the overall population.
- For PD-L1 TAP < 1%, most patients in both arms experienced ≥ 1 TEAE (TIS+C: 100.0% vs PBO+C: 96.0%).
  - Fewer patients treated with TIS+C compared with PBO+C experienced ≥ Grade 3 TEAEs (77.8% vs 84.0%).
  - Although the incidence of SAEs with TIS+C (58.3%) was higher than with PBO+C (32.0%), as well as higher with TIS+C in the overall population (48.1%), the incidences of SAEs related to any component of the study treatment or tislelizumab-/placebo-related SAEs in patients receiving TIS+C were similar to those in the overall population. Most of these events generally reflected the underlying condition of the disease or the known safety profile of chemotherapy.
  - Two patients (5.6%) receiving TIS+C experienced TEAEs leading to death, with the PT of Death and Myocarditis, while no such events were reported with PBO+C. The incidence in patients receiving TIS+C was similar to those receiving TIS+C in the overall population (5.2%). The between-arm difference was mainly driven by the lower incidence of TEAEs leading to death with PBO+C.

Figure 13: Most Common TEAEs (≥ 20%) Similar Between Tislelizumab Plus Chemotherapy and Placebo Plus Chemotherapy in Patients With PD-L1 Score ≥ 1% (Safety Analysis Set)



Data cutoff: 28FEB2022.

5.3. Safety Conclusion

Tislelizumab in combination with chemotherapy demonstrated an acceptable safety profile in the pivotal Study 306, which is consistent with the known safety profile of PD-1 inhibitors and/or the underlying disease condition of adult patients with locally advanced unresectable or metastatic ESCC.

In PD-L1 subgroups, the safety profile of treatment with TIS+C in the subgroups of PD-L1 ≥ 1% and PD-L1 < 1% was consistent with that reported for the overall population, revealing no increased safety risks or new safety signals for this subgroup.

6. BENEFIT-RISK ASSESSMENT

6.1. Benefit

Advanced ESCC is a rapidly progressing and symptomatic disease with poor clinical outcomes. The overall 5-year survival is 4.6% for patients with distant metastatic diseases.[22]

The global, multicenter, pivotal Phase 3 Study 306 enrolled 649 patients from 16 countries/ regions in Asia, Europe, North America, and Australia, making it one of the largest global studies conducted to evaluate the efficacy and safety of tislelizumab in combination with chemotherapy versus chemotherapy alone as the first-line treatment in ESCC. Results of Study 306 demonstrated a statistically significant and clinically meaningful improvement in OS with tislelizumab in combination with chemotherapy as a first-line treatment compared with chemotherapy alone in patients with locally advanced or metastatic ESCC. The OS benefit with tislelizumab plus chemotherapy over placebo plus chemotherapy (ie, HR < 1) was consistently observed -across all prespecified subgroups of baseline demographics and disease characteristics. Superior efficacy results favoring tislelizumab plus chemotherapy were also observed in the secondary endpoints of PFS and ORR. Acknowledging the caveat of cross-study comparison, the benefit seen in the TIS+C arm of Study 306 compared favorably with the benefit seen in the pembrolizumab + chemotherapy arm of KEYNOTE-590 or the benefits seen in the nivolumab + chemotherapy arm of CheckMate-648, with a greater magnitude of improvement in median OS.[13,14]

6.1.1. Benefit in OS by PD-L1 Subgroups

For patients with a PD-L1 score ≥ 10%, TIS+C was superior to PBO+C with a statistically significant and clinically meaningful risk reduction for death (37%) and an improvement in median OS by 6.6 months. The HR was 0.63 (95% CI: 0.45 to 0.89) and the 1-sided stratified log-rank test p-value was 0.0042, lower than the prespecified alpha of 0.025 for secondary endpoint.

For patients with PD-L1 low expression, favorable treatment effects for OS were observed in PD-L1 subgroups of 5% to < 10% and 1% to < 5% with TIS+C compared with PBO+C were observed:

- In patients with baseline PD-L1 expression ≥ 5% to < 10% and ≥ 1% to < 5%, a numerical OS improvement in patients receiving TIS+C was observed. This was

evidenced by a favorable trend in HR of OS and by improvement in both median OS and landmark OS rates after the first 6 months.

  - In the PD-L1 ≥ 1% to < 5% subgroup, although the HR of OS appeared marginal at 0.93 (95% CI: 0.61 to 1.41) at the interim analysis, in a 3-year follow-up analysis, OS data showed the HR of OS improved to 0.86 (95% CI: 0.59 to 1.26), which continued to show an OS benefit in patients with PD-L1 levels ≥ 1% to < 5% with the magnitude of benefit becoming clearer and more substantial.
  - The conclusion was further supported by multivariate adjusted analysis that revealed that this result was influenced by numerical imbalances in key baseline characteristics and prognostic factors. The adjusted HR improved to 0.78 (95% CI: 0.51 to 1.22) at the interim analysis and 0.76 (95% CI: 0.50 to 1.13) at the 3-year follow-up.
  - The results above suggest that in patients whose tumors express PD-L1 ≥ 1%, a clinically relevant OS benefit can be observed-.

- In patients with baseline PD-L1 expression levels < 1%, although an OS HR of > 1.0 was observed, it is important to note that the sample size was small in this subgroup, and the median OS in the PBO+C arm (16.1 months) in PD-L1 < 1% subgroup was higher than the median OS in control arm (10.6 months) observed in the overall population of 306 study and the historical median OS with chemotherapy alone in 1L ESCC (< 12 months).

6.1.2. Other Benefits

6.1.2.1. Progression-Free Survival

In the overall population, patients receiving TIS+C showed superior PFS to PBO+C, with a statistically significant and clinically relevant 38% reduction in the risk of disease progression or death (HR of 0.62 [95% CI: 0.52 to 0.75]; p-value of < 0.0001) and an improvement in median PFS by 1.7 months (7.3 months [95% CI: 6.9 to 8.3] with TIS+C vs 5.6 months [95% CI: 4.9 to 6.0] with PBO+C).

In all the exploratory PD-L1 expression subgroups, favorable PFS results were observed in patients receiving TIS+C compared with PBO+C, accompanied by numerical improvements in median PFS. The magnitude of the PFS benefit was enhanced with the increase of PD-L1 expression.

- In the PD-L1 ≥ 1% subgroup, the HR of PFS was 0.56 (95% CI: 0.45 to 0.70), with a 1.7-month improvement of median PFS; in the PD-L1 < 1% subgroup, the HR of PFS was 0.89 (95% CI: 0.50 to 1.58), with a 0.7-month improvement of median PFS.

6.1.2.2. Overall Response Rate

In the overall population, the ORR assessed by the investigator showed a statistically significant and clinically relevant benefit in tumor response rate favoring TIS+C over PBO+C. The stratified ORR odds ratio was 2.38 (95% CI: 1.73 to 3.27). Analyses of ORR based on confirmed tumor response displayed also results benefiting patients receiving TIS+C.

In the subgroups of PD-L1 ≥ 1%, a higher ORR was observed in patients receiving TIS+C than PBO+C. For the PD-L1 < 1% subgroup, the ORR in patients receiving PBO+C was much higher than those observed in patients receiving PBO+C across other PD-L1 subgroups and higher than those reported in other recently completed first-line ESCC studies. Large variability of estimation due to the small sample size in this subgroup might attribute to the high ORR observed in patients receiving PBO+C, which could potentially lead to unreliable comparation for the 2 arms.

6.2. Risks

The safety profiles of TIS+C were in line with the known safety profiles of PD-1/PD-L1 CPIs and chemotherapy agents. The incidence of ≥ Grade 3 TEAEs and TEAEs leading to death were also similar in the 2 arms. As expected for a PD-1 CPI, more patients experienced TEAEs leading to treatment discontinuation and SAEs with TIS+C versus PBO+C.

In line with the known safety profile of monoclonal antibodies against PD-1, imAEs were more frequent in patients receiving TIS+C. Most of these imAEs were Grade 1 or 2.

The safety data was similar for the exploratory PD-L1 subgroups. Differences observed in the TIS+C and PBO+C arms were relatively minor. In both arms, the most common TEAEs reported in these subgroups are consistent with the known toxicity of platinum-based chemotherapy and the underlying disease.

6.3. Conclusion of Benefit-Risk Assessment

Study 306 is a global Phase 3 study that joins other recent global Phase 3 studies (KEYNOTE-590 and CHECKMATE-648) that evaluated immune CPIs plus chemotherapy as 1L treatment of ESCC to address the unmet medical need for more effective treatment options for this indication. Study 306 results substantiate the value of tislelizumab plus chemotherapy as an effective and safe treatment option for patients with ESCC as a first-line treatment. These results support the first-line treatment with tislelizumab plus chemotherapy, providing a positive benefit/risk ratio for patients with unresectable, locally advanced or metastatic ESCC. The most favorable benefit/risk was observed in patients with a PD-L1 score ≥ 1%.

BeiGene supports efforts in gaining consistency in labeling and testing across the class of anti-PD-1 agents as it would help provide clarity among the medical community and would better support treatment decisions in clinical practice, along with harmonizing the use of PD-L1 testing, with these agents.

7. REFERENCES

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APPENDIX 1. SUPPLEMENTAL TABLES AND FIGURES

Table 9: Key Demographics and Baseline Characteristics by PD-L1 TAP Expression Cuts and Categories (ITT Analysis Set)

Baseline PD-L1 Status	≥ 10%		<10%		≥ 5%		<5%		≥ 1%		< 1%		≥ 1% to < 5%		≥ 5% to <10%	
	TIS+C (N = 116)	PBO+C (N = 107)	TIS+C (N = 151)	PBO+C (N = 168)	TIS+C (N = 172)	PBO+C (N = 186)	TIS+C (N = 95)	PBO+C (N = 89)	TIS+C (N = 231)	PBO+C (N = 250)	TIS+C (N = 36)	PBO+C (N = 25)	TIS+C (N = 59)	PBO+C (N = 64)	TIS+C (N = 56)	PBO+C (N = 79)
Age Group, ≥ 65 years, %	43.1	48.6	44.4	51.8	41.9	47.3	47.4	57.3	43.3	50.8	47.2	48.0	47.5	60.9	39.3	45.6
Sex, %																
Female	19.0	10.3	9.9	13.1	18.0	12.4	6.3	11.2	15.2	12.4	5.6	8.0	6.8	12.5	16.1	15.2
Male	81.0	89.7	90.1	86.9	82.0	87.6	93.7	88.8	84.8	87.6	94.4	92.0	93.2	87.5	83.9	84.8
ECOG Status, %																
0	31.0	30.8	35.8	36.9	29.1	30.6	42.1	42.7	32.5	35.2	41.7	28.0	42.4	48.4	25.0	30.4
1	80 69.0	74 69.2	97 64.2	106 63.1	122 70.9	129 69.4	55 57.9	51 57.3	156 67.5	162 64.8	21 58.3	18 72.0	34 57.6	33 51.6	42 75.0	55 69.6
Tobacco Consumption, %																
Never	20.7	22.4	19.2	25.0	20.3	24.2	18.9	23.6	19.5	24.0	22.2	24.0	16.9	23.4	19.6	26.6
Former	60.3	53.3	60.3	57.7	60.5	55.4	60.0	57.3	60.2	56.4	61.1	52.0	59.3	59.4	60.7	58.2
Current	15.5	17.8	15.9	15.5	15.7	15.6	15.8	18.0	16.5	16.0	11.1	20.0	18.6	17.2	16.1	12.7
Missing	4 3.4	7 6.5	7 4.6	3 1.8	6 3.5	9 4.8	5 5.3	1 1.1	9 3.9	9 3.6	2 5.6	1 4.0	3 5.1	0 0.0	2 3.6	2 2.5
Region, %																
Asia	74.1	84.1	77.5	73.2	77.3	79.0	73.7	74.2	74.9	76.8	83.3	84.0	67.8	70.3	83.9	72.2
China including Taiwan	56.0	70.1	57.6	56.5	58.1	64.5	54.7	56.2	56.3	60.8	61.1	72.0	50.8	50.0	62.5	57.0
Japan	10.3	6.5	11.3	12.5	9.9	8.6	12.6	13.5	10.4	10.4	13.9	8.0	11.9	15.6	8.9	11.4
Korea	7.8	7.5	8.6	4.2	9.3	5.9	6.3	4.5	8.2	5.6	8.3	4.0	5.1	4.7	12.5	3.8
US/Europe/Australia	25.9	15.9	22.5	26.8	22.7	21.0	26.3	25.8	25.1	23.2	16.7	16.0	32.2	29.7	16.1	27.8
Europe	25.9	15.0	21.2	25.6	22.7	19.9	24.2	24.7	24.2	22.0	16.7	16.0	28.8	28.1	16.1	26.6
Australia	0.0	0.9	1.3	0.6	0.0	1.1	2.1	0.0	0.9	0.8	0.0	0.0	3.4	0.0	0.0	1.3

Baseline PD-L1 Status	≥ 10%		<10%		≥ 5%		<5%		≥ 1%		< 1%		≥ 1% to < 5%		≥ 5% to <10%	
	TIS+C (N = 116)	PBO+C (N = 107)	TIS+C (N = 151)	PBO+C (N = 168)	TIS+C (N = 172)	PBO+C (N = 186)	TIS+C (N = 95)	PBO+C (N = 89)	TIS+C (N = 231)	PBO+C (N = 250)	TIS+C (N = 36)	PBO+C (N = 25)	TIS+C (N = 59)	PBO+C (N = 64)	TIS+C (N = 56)	PBO+C (N = 79)
US	0.0	0.0	0.0	0.6	0.0	0.0	0.0	1.1	0.0	0.4	0.0	0.0	0.0	1.6	0.0	0.0
Time from Initial Diagnosis to Study Entry months																
Median	1.59	1.84	4.96	2.40	1.58	1.66	8.61	10.55	2.00	1.87	1.63	15.44	8.97	6.57	1.58	1.48
Min, Max	0.3, 152.7	0.3, 68.8	0.1, 100.8	0.2, 116.8	0.3, 152.7	0.2, 83.1	0.1, 100.8	0.2, 116.8	0.2, 152.7	0.2, 116.8	0.1, 79.3	0.4, 61.9	0.2, 100.8	0.2, 116.8	0.3, 84.4	0.2, 83.1
Disease Status at Study Entry, Metastatic, %	87.1	89.7	88.1	85.7	86.0	89.2	90.5	83.1	86.6	87.2	94.4	88.0	88.1	81.3	83.9	88.6
Number of Metastatic Sites at Study Entry, %																
0 – 2	85.3	81.3	80.8	72.7	84.9	81.7	78.9	83.1	83.1	81.2	80.6	92.0	78.0	79.7	83.9	82.3
> 2	14.7	18.7	19.2	17.3	15.1	18.3	21.1	16.9	16.9	18.8	19.4	8.0	22.0	20.3	16.1	17.7
Patients with at Least One Prior Definitive Therapy, %	37.1	39.3	47.7	45.8	39.5	39.2	49.5	51.7	43.7	42.0	38.9	56.0	55.9	50.0	44.6	39.2
ICC Option per IRT, %																
Platinum with fluoropyrimidine	42.2	39.3	44.4	48.8	40.1	41.9	49.5	51.7	43.3	46.8	44.4	28.0	52.5	60.9	35.7	45.6
Platinum with paclitaxel	57.8	60.7	55.6	51.2	59.9	58.1	50.5	48.3	56.7	53.2	55.6	72.0	47.5	39.1	64.3	43 54.4

Data cutoff: 28FEB2022.

Abbreviations: ECOG, Eastern Cooperative Oncology Group; ICC, investigator's choice chemotherapy; IRT, Interactive Response Technology; ITT, intent to treat; PBO+C, placebo + chemotherapy; PD-L1, programmed death ligand 1; TIS+C, tislelizumab + chemotherapy.

Table 10: Subsequent Systemic Anticancer Therapy by PD-L1 TAP Expression (ITT Analysis Set)

Baseline PD-L1 Status	≥ 10%		< 10%		≥ 5%		< 5%		≥ 1%		< 1%		≥ 1% to < 5%		≥ 5% to < 10%	
	TIS+C (N = 116)	PBO+C (N = 107)	TIS+C (N = 151)	PBO+C (N = 168)	TIS+C (N = 172)	PBO+C (N = 186)	TIS+C (N = 95)	PBO+C (N = 89)	TIS+C (N = 231)	PBO+C (N = 250)	TIS+C (N = 36)	PBO+C (N = 25)	TIS+C (N = 59)	PBO+C (N = 64)	TIS+C (N = 56)	PBO+C (N = 79)
Patients with Any Subsequent Anticancer Therapy	62 (53.4)	67 (62.6)	77 (51.0)	112 (66.7)	92 (53.5)	120 (64.5)	47 (49.5)	59 (66.3)	121 (52.4)	161 (64.4)	18 (50.0)	18 (72.0)	29 (49.2)	41 (64.1)	30 (53.6)	53 (67.1)
Radiotherapy	24 (20.7)	23 (21.5)	22 (14.6)	46 (27.4)	32 (18.6)	44 (23.7)	14 (14.7)	25 (28.1)	40 (17.3)	64 (25.6)	6 (16.7)	5 (20.0)	8 (13.6)	20 (31.3)	8 (14.3)	21 (26.6)
Procedure or Surgery	5 (4.3)	3 (2.8)	3 (2.0)	9 (5.4)	6 (3.5)	6 (3.2)	2 (2.1)	6 (6.7)	8 (3.5)	9 (3.6)	0 (0.0)	3 (12.0)	2 (3.4)	3 (4.7)	1 (1.8)	3 (3.8)
Systemic Therapy	56 (48.3)	62 (57.9)	75 (49.7)	94 (56.0)	85 (49.4)	108 (58.1)	46 (48.4)	48 (53.9)	113 (48.9)	140 (56.0)	18 (50.0)	16 (64.0)	28 (47.5)	32 (50.0)	29 (51.8)	46 (58.2)
Immunotherapy	15 (12.9)	20 (18.7)	22 (14.6)	40 (23.8)	24 (14.0)	40 (21.5)	13 (13.7)	20 (22.5)	34 (14.7)	53 (21.2)	3 (8.3)	7 (28.0)	10 (16.9)	13 (20.3)	9 (16.1)	20 (25.3)

Data cutoff: 28FEB2022.
Abbreviations: ITT, intent to treat; PBO+C, placebo + chemotherapy; PD-L1, programmed death ligand 1; TAP, tumor area positivity; TIS+C, tislelizumab + chemotherapy
Notes: Anticancer surgeries/procedures performed after all study treatments were permanently discontinued were captured as Procedure or Surgery in the eCRF.

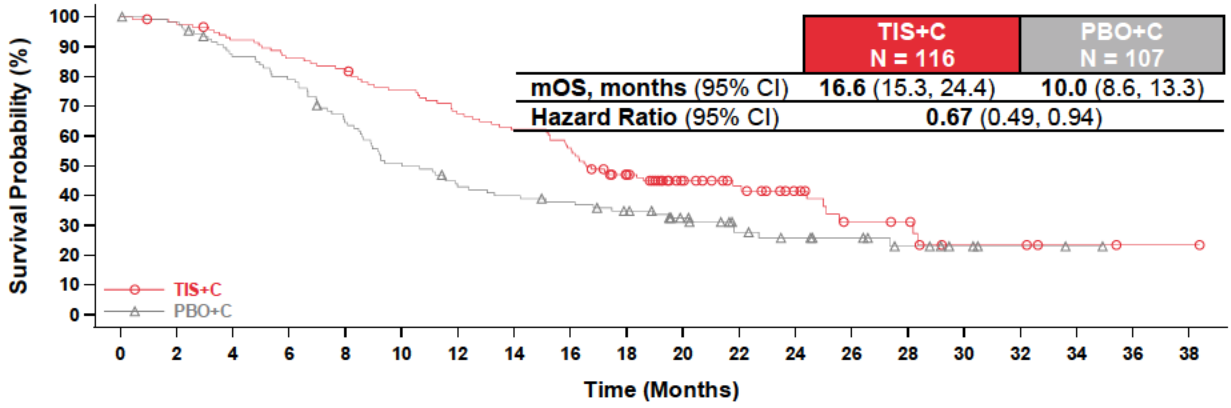
Table 11: Progression Free Survival, Objective Response Rate, and Duration of Response by Baseline PD-L1 Status (ITT Analysis Set)

Baseline PD-L1 Status	≥ 10%		<10%		≥ 5%		<5%		≥ 1%		< 1%		≥ 1% to < 5%		≥ 5% to < 10%	
	TIS+C (N = 116)	PBO+C (N = 107)	TIS+C (N = 151)	PBO+C (N = 168)	TIS+C (N = 172)	PBO+C (N = 186)	TIS+C (N = 95)	PBO+C (N = 89)	TIS+C (N = 231)	PBO+C (N = 250)	TIS+C (N = 36)	PBO+C (N = 25)	TIS+C (N = 59)	PBO+C (N = 64)	TIS+C (N = 56)	PBO+C (N = 79)
PFS Events, n (%)	76 (65.5)	90 (84.1)	103 (68.2)	130 (77.4)	108 (62.8)	148 (79.6)	71 (74.7)	72 (80.9)	152 (65.8)	199 (79.6)	27 (75.0)	21 (84.0)	44 (74.6)	51 (79.7)	32 (57.1)	58 (73.4)
Progressive Disease	66 (56.9)	76 (71.0)	82 (54.3)	112 (66.7)	94 (54.7)	126 (67.7)	54 (56.8)	62 (69.7)	129 (55.8)	169 (67.6)	19 (52.8)	19 (76.0)	35 (59.3)	43 (67.2)	28 (50.0)	50 (63.3)
Death	10 (8.6)	14 (13.1)	21 (13.9)	18 (10.7)	14 (8.1)	22 (11.8)	17 (17.9)	10 (11.2)	23 (10.0)	30 (12.0)	8 (22.2)	2 (8.0)	9 (15.3)	8 (12.5)	4 (7.1)	8 (10.1)
Unstratified PFS Hazard Ratio (95% CI)	0.50 (0.37, 0.69)		0.68 (0.52, 0.88)		0.51 (0.40, 0.66)		0.79 (0.57, 1.10)		0.56 (0.45, 0.70)		0.89 (0.50, 1.58)		0.75 (0.50, 1.12)		0.51 (0.33, 0.79)	
Median PFS (95% CI), months	8.3 (7.0, 10.2)	5.6 (4.3, 6.7)	6.9 (5.6, 7.9)	5.5 (4.3, 6.2)	8.2 (7.0, 9.8)	5.5 (4.3, 6.4)	6.7 (5.5, 7.2)	5.7 (4.4, 6.9)	7.2 (6.8, 8.5)	5.5 (4.5, 5.8)	6.9 (3.2, 8.9)	6.2 (4.1, 10.5)	6.5 (4.7, 7.3)	5.6 (4.2, 6.9)	7.2 (5.7, 15.3)	4.6 (4.1, 6.8)
Confirmed ORR, n	75	38	76	65	110	67	41	36	134	90	17	13	24	23	35	29
% (95% CI)	64.7 (55.2, 73.3)	35.5 (26.5, 45.4)	50.3 (42.1, 58.6)	38.7 (31.3, 46.5)	64.0 (56.3, 71.1)	36.0 (29.1, 43.4)	43.2 (33.0, 53.7)	40.4 (30.2, 51.4)	58.0 (51.4, 64.5)	36.0 (30.0, 42.3)	47.2 (30.4, 64.5)	52.0 (31.3, 72.2)	40.7 (28.1, 54.3)	35.9 (24.3, 48.9)	62.5 (48.5, 75.1)	36.7 (26.1, 48.3)
Confirmed DOR,																
Median (95% CI), months	7.6 (6.8, 9.8)	5.4 (4.1, 6.6)	8.3 (5.3, 12.6)	7.1 (5.6, 8.6)	8.4 (6.9, 11.4)	5.6 (4.2, 7.1)	6.7 (4.4, 10.3)	7.5 (5.4, 10.0)	7.2 (6.2, 9.6)	5.7 (4.4, 7.3)	9.8 (4.4, NE)	9.2 (4.2, 12.5)	6.0 (4.2, 9.6)	7.3 (4.4, 9.6)	8.5 (4.4, NE)	5.7 (4.3, 8.6)
DOR rate at, % (95% CI)																
6 Months	65.9 (53.5, 75.7)	37.0 (21.5, 52.6)	56.0 (43.8, 66.5)	54.5 (40.7, 66.4)	63.5 (53.4, 71.9)	41.6 (29.0, 53.8)	53.8 (37.0, 67.9)	59.6 (40.8, 74.2)	60.6 (51.6, 68.5)	43.9 (32.8, 54.4)	62.5 (34.9, 81.1)	75.0 (40.8, 91.2)	48.2 (27.2, 66.5)	50.4 (27.5, 69.5)	58.5 (40.2, 73.0)	47.6 (27.1, 65.5)
12 Months	35.0 (23.8, 46.4)	13.5 (4.4, 27.7)	39.2 (27.7, 50.5)	21.0 (10.8, 33.4)	39.3 (29.6, 48.8)	17.7 (8.8, 29.1)	31.4 (17.4, 46.5)	19.8 (7.5, 36.2)	36.6 (28.0, 45.2)	15.2 (7.8, 24.8)	41.7 (17.7, 64.3)	38.9 (12.6, 65.0)	25.1 (9.6, 44.1)	6.9 (0.5, 26.4)	48.8 (31.0, 64.4)	22.8 (8.0, 42.1)

Data cutoff: 28FEB2022.
Abbreviations: DOR, duration of response; ITT, intent to treat; ORR, overall response rate; PD-L1, programmed death ligand 1; PFS, progression-free survival.
Notes: Updated death data for three patients were incorporated.

Figure 14: Kaplan-Meier Plot of OS by Baseline PD-L1 TAP Score of 10% at the Interim Analysis (ITT Analysis Set)

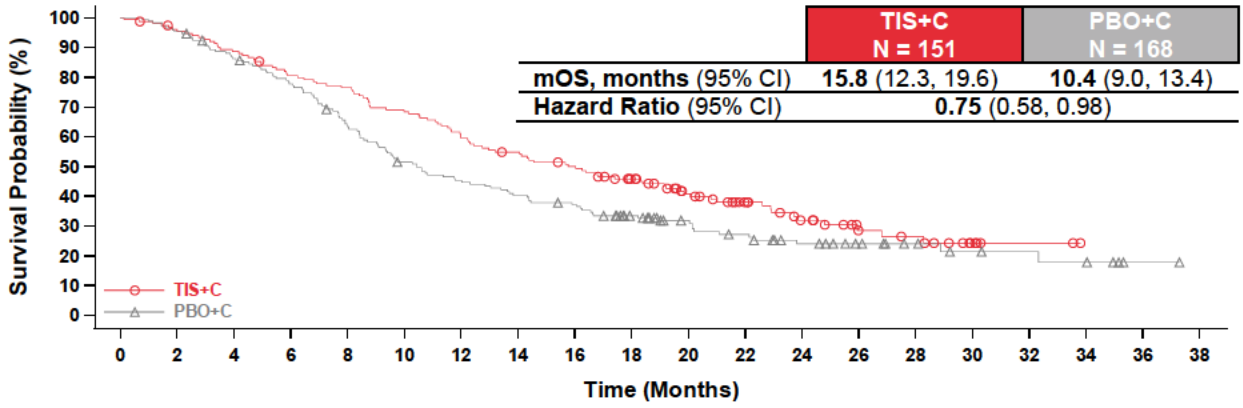
a) PD-L1 ≥ 10%



No. At Risk:

TIS+C	116	113	105	98	94	85	76	70	63	48	33	25	18	11	9	4	4	2	1	1
PBO+C	107	104	90	82	66	52	43	40	37	32	24	16	13	11	7	4	2	1	0	0

b) PD-L1 < 10%



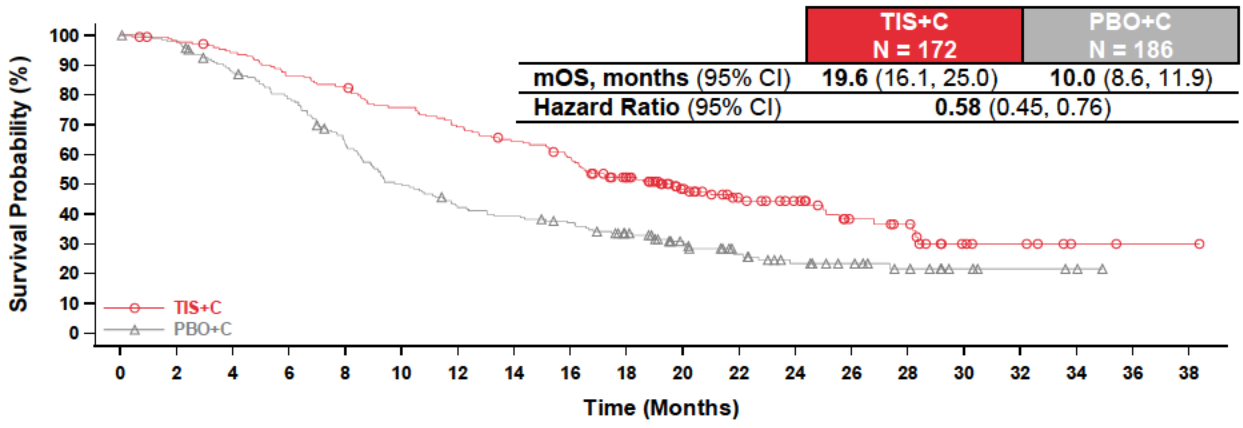
No. At Risk:

TIS+C	151	143	132	119	113	101	88	80	72	60	45	34	23	14	12	5	2	0	0	0
PBO+C	168	160	143	128	104	83	73	65	59	46	34	28	20	15	10	7	6	5	1	0

Data cutoff: 28FEB2022.
Abbreviations: CI, confidence interval; ITT, intent to treat; mOS, median overall survival; PBO+C, placebo + chemotherapy; PD-L1, programmed death ligand 1; TAP, tumor area positivity; TIS+C, tislelizumab + chemotherapy.
Notes: Hazard ratio (TIS+C vs PBO+C) was based on unstratified Cox regression model. Updated death data for three patients were incorporated.

Figure 15: Kaplan- Meier Plot of OS by Baseline PD-L1 TAP Score of 5% at the Interim Analysis (ITT Analysis Set)

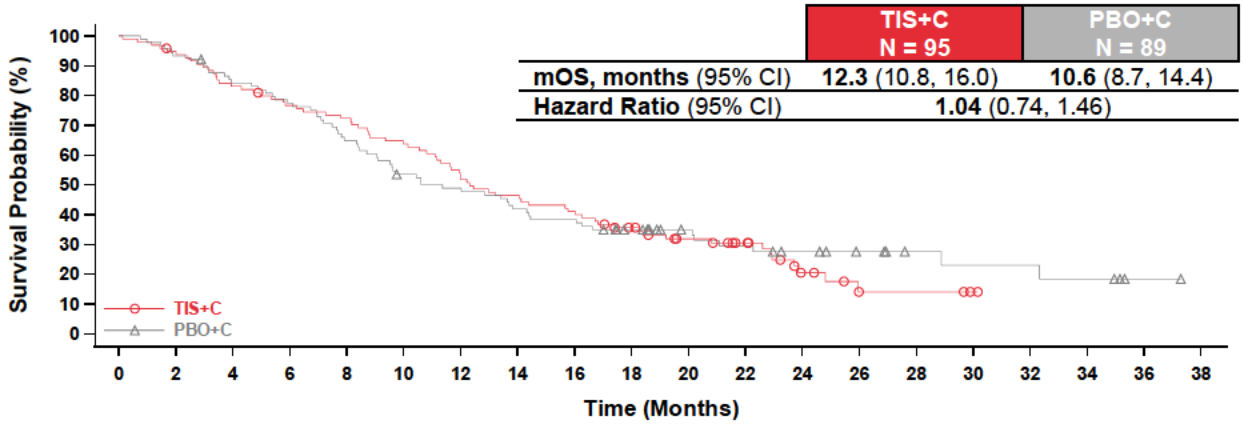
a) PD-L1 ≥ 5%



No. At Risk:

TIS+C	172	167	159	146	140	127	116	107	97	78	55	41	33	22	18	8	6	2	1	1
PBO+C	186	181	159	142	113	89	74	69	63	52	39	28	20	16	11	6	3	2	0	0

b) PD-L1 < 5%



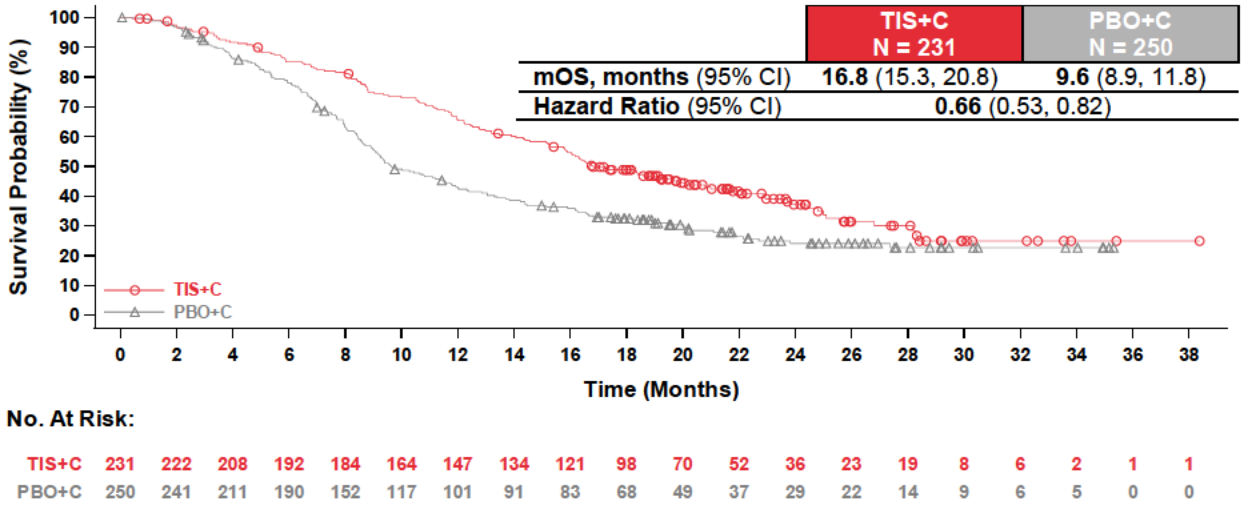
No. At Risk:

TIS+C	95	89	78	71	67	59	48	43	38	30	23	18	8	3	3	1	0	0	0	0
PBO+C	89	83	74	68	57	46	42	36	33	26	19	16	13	10	6	5	5	4	1	0

Data cutoff: 28FEB2022.
Abbreviations: CI, confidence interval; ITT, intent to treat; mOS, median overall survival; PBO+C, placebo + chemotherapy; PD-L1, programmed death ligand 1; TAP, tumor area positivity; TIS+C, tislelizumab + chemotherapy.
Notes: Hazard ratio (TIS+C vs PBO+C) was based on unstratified Cox regression model. Updated death data for three patients were incorporated.

Figure 16: Kaplan-Meier Plot of OS by Baseline PD-L1 TAP Score of 1% at the Interim Analysis (ITT Analysis Set)

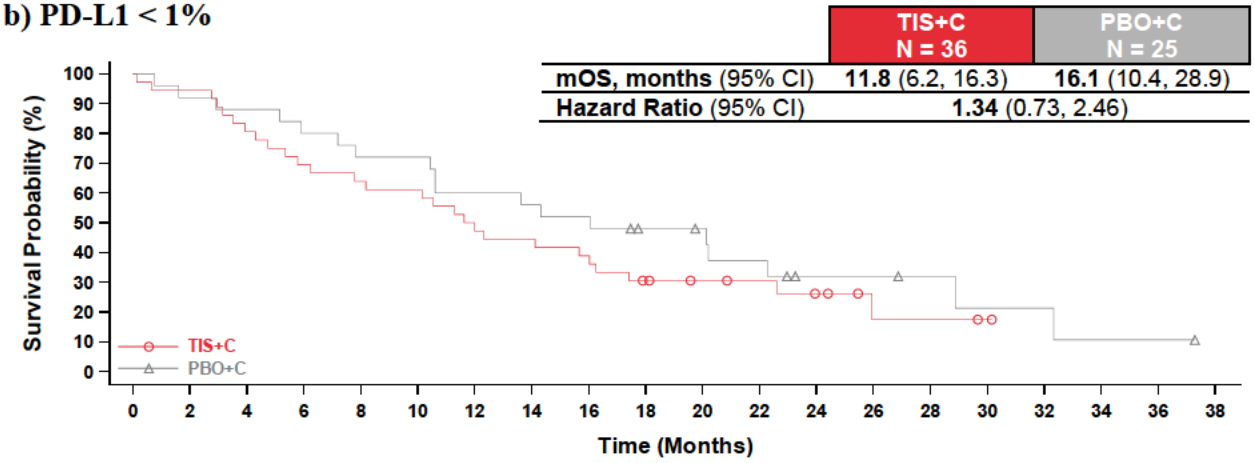
a) PD-L1 ≥ 1%



No. At Risk:

TIS+C	231	222	208	192	184	164	147	134	121	98	70	52	36	23	19	8	6	2	1	1
PBO+C	250	241	211	190	152	117	101	91	83	68	49	37	29	22	14	9	6	5	0	0

b) PD-L1 < 1%



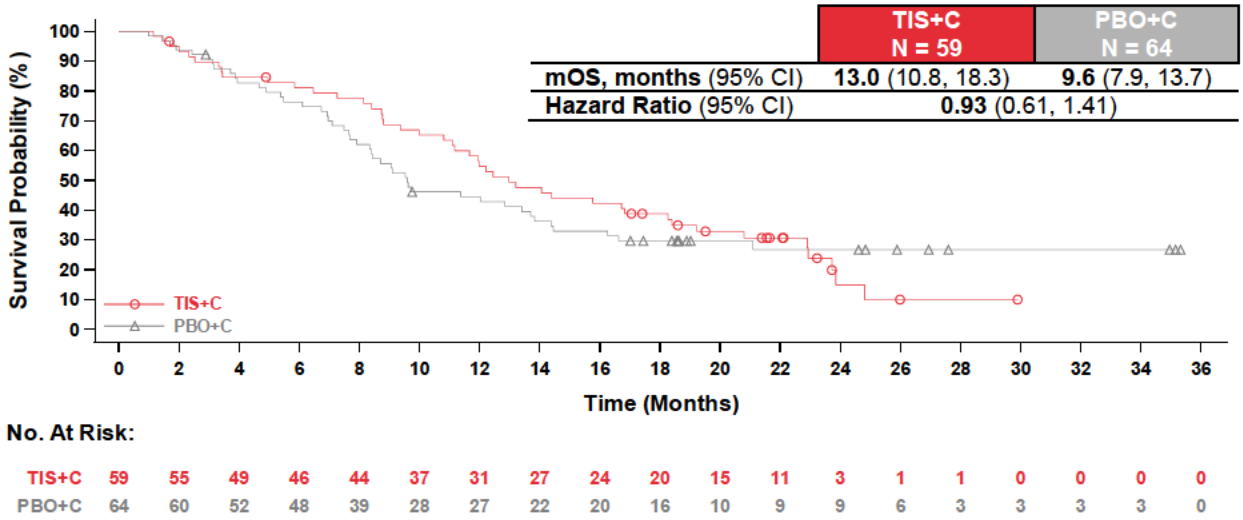
No. At Risk:

TIS+C	36	34	29	25	23	22	17	16	14	10	8	7	5	2	2	1	0	0	0	0
PBO+C	25	23	22	20	18	18	15	14	13	10	9	7	4	4	3	2	2	1	1	0

Data cutoff: 28FEB2022.
Abbreviations: CI, confidence interval; ITT, intent to treat; mOS, median overall survival; PBO+C, placebo + chemotherapy; PD-L1, programmed death ligand 1; TAP, tumor area positivity; TIS+C, tislelizumab + chemotherapy.
Notes: Hazard ratio (TIS+C vs PBO+C) was based on unstratified Cox regression model. Updated death data for three patients were incorporated.

Figure 17: Kaplan-Meier Plot of OS by Baseline PD-L1 TAP Score Categories at the Interim Analysis (ITT Analysis Set)

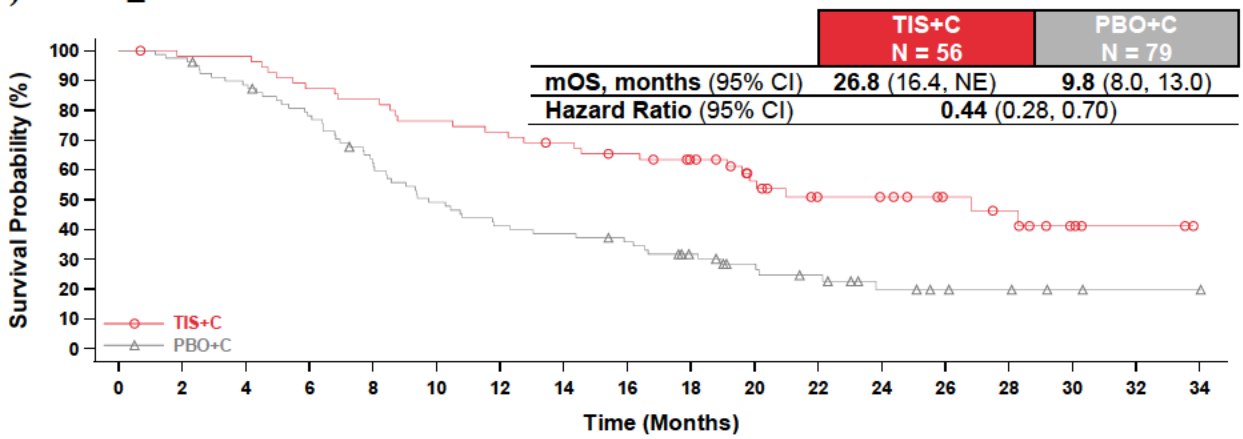
a) PD-L1 ≥ 1% - < 5%



No. At Risk:

TIS+C	59	55	49	46	44	37	31	27	24	20	15	11	3	1	1	0	0	0	0
PBO+C	64	60	52	48	39	28	27	22	20	16	10	9	9	6	3	3	3	3	0

b) PD-L1 ≥ 5% - < 10%



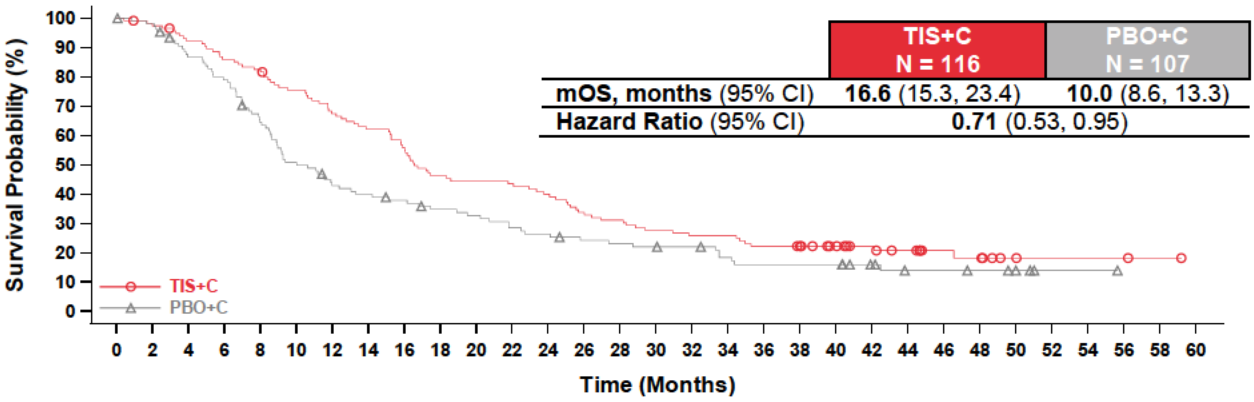
No. At Risk:

TIS+C	56	54	54	48	46	42	40	37	34	30	22	16	15	11	9	4	2	0	
PBO+C	79	77	69	60	47	37	31	29	26	20	15	12	7	5	4	2	1	1	

Data cutoff: 28FEB2022.
Abbreviations: CI, confidence interval; ITT, intent to treat; mOS, median overall survival; PBO+C, placebo + chemotherapy; PD-L1, programmed death ligand 1; TAP, tumor area positivity; TIS+C, tislelizumab + chemotherapy.
Notes: Hazard ratio (TIS+C vs PBO+C) was based on unstratified Cox regression model. Updated death data for three patients were incorporated.

Figure 18: Kaplan-Meier Plot of OS by Baseline PD-L1 TAP Score of 10% at the 3-Year Follow-up (ITT Analysis Set)

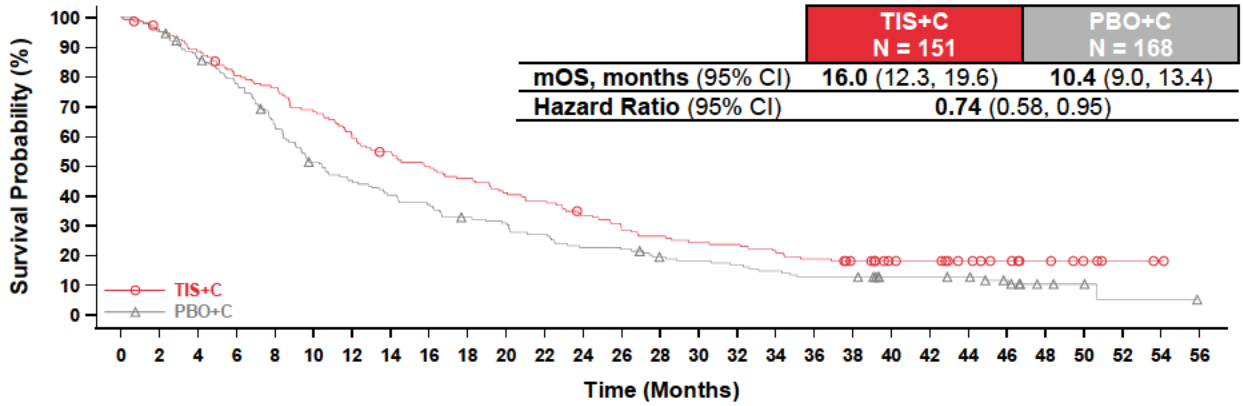
a) PD-L1 ≥ 10%



No. At Risk:

TIS+C	116	113	105	98	94	85	76	70	63	52	50	49	45	38	35	31	29	29	25	24	19	15	12	8	7	3	2	2	2	1	0
PBO+C	107	104	90	82	66	52	43	40	37	33	31	27	25	22	21	20	19	15	13	13	13	9	6	6	5	4	1	1	0	0	0

b) PD-L1 < 10%



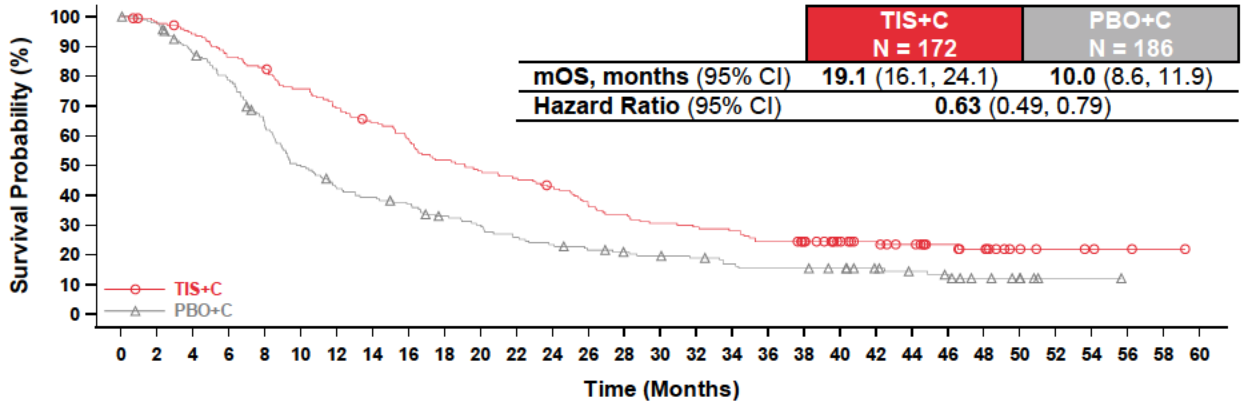
No. At Risk:

TIS+C	151	143	132	119	113	101	88	80	73	67	60	56	48	41	38	35	34	31	27	23	18	17	13	10	7	4	2	1	0
PBO+C	168	160	143	128	104	83	73	65	60	52	49	43	36	35	29	27	25	22	19	19	14	14	13	9	4	3	1	1	0

Data cutoff: 24NOV2023.
Abbreviations: CI, confidence interval; ITT, intent to treat; mOS, median overall survival; PBO+C, placebo + chemotherapy; PD-L1, programmed death ligand 1; TAP, tumor area positivity; TIS+C, tislelizumab + chemotherapy.
Notes: Hazard ratio (TIS+C vs PBO+C) was based on unstratified Cox regression model. Updated death data for three patients were incorporated.

Figure 19: Kaplan-Meier Plot of OS by Baseline PD-L1 TAP Score of 5% at the 3-Year Follow-up (ITT Analysis Set)

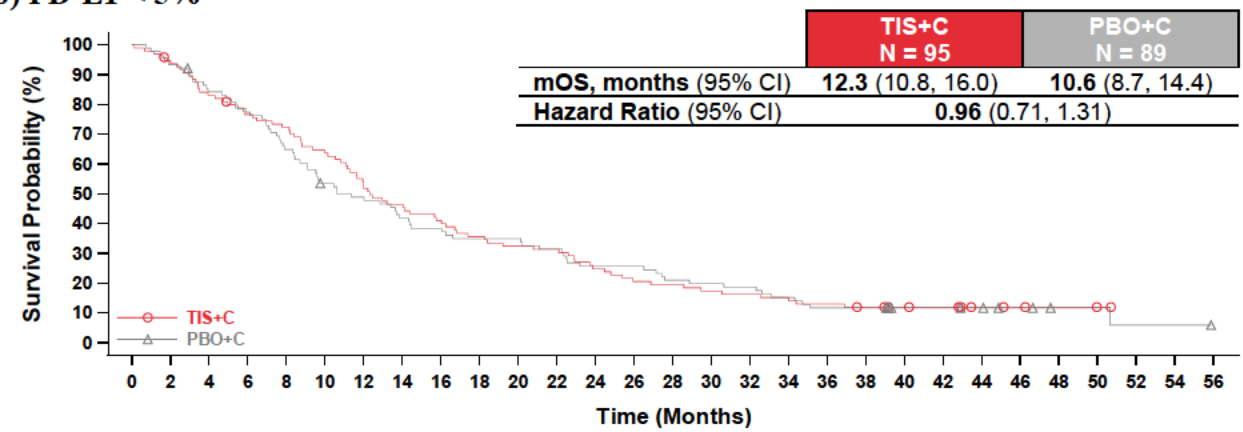
a) PD-L1 ≥ 5%



No. At Risk:

TIS+C	172	167	159	146	140	127	116	107	98	86	80	76	70	60	55	50	48	46	40	37	29	25	21	15	12	6	4	3	2	1	0
PBO+C	186	181	159	142	113	89	74	69	64	55	50	43	39	35	32	30	28	24	22	22	20	16	13	11	7	5	1	1	0	0	0

b) PD-L1 < 5%



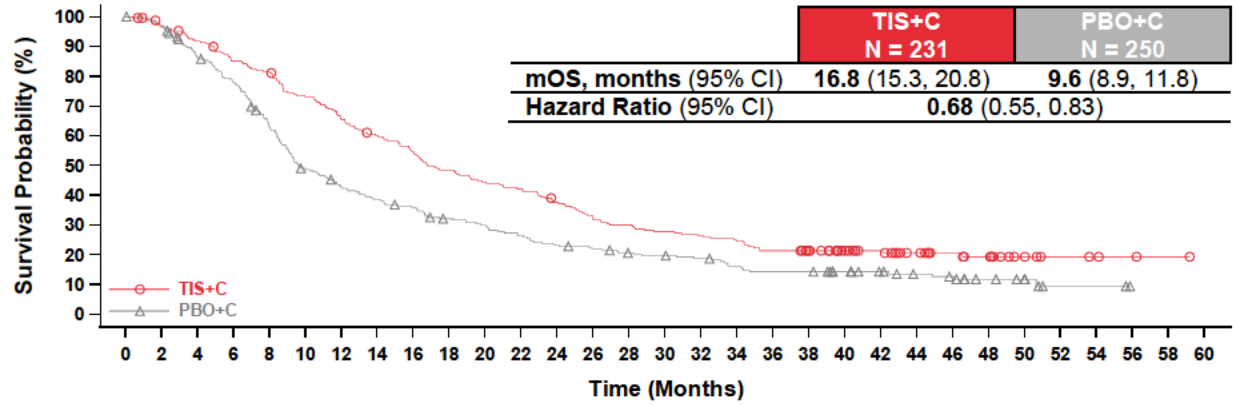
No. At Risk:

TIS+C	95	89	78	71	67	59	48	43	38	33	30	29	23	19	18	16	15	14	12	10	8	7	4	3	2	1	0	0	0
PBO+C	89	83	74	68	57	46	42	36	33	30	30	27	22	22	18	17	16	13	10	10	7	7	6	4	2	2	1	1	0

Data cutoff: 24NOV2023.
Abbreviations: CI, confidence interval; ITT, intent to treat; mOS, median overall survival; PBO+C, placebo + chemotherapy; PD-L1, programmed death ligand 1; TAP, tumor area positivity; TIS+C, tislelizumab + chemotherapy.
Notes: Hazard ratio (TIS+C vs PBO+C) was based on unstratified Cox regression model. Updated death data for three patients were incorporated.

Figure 20: Kaplan-Meier Plot of OS by Baseline PD-L1 TAP Score of 1% at the 3-Year Follow-up (ITT Analysis Set)

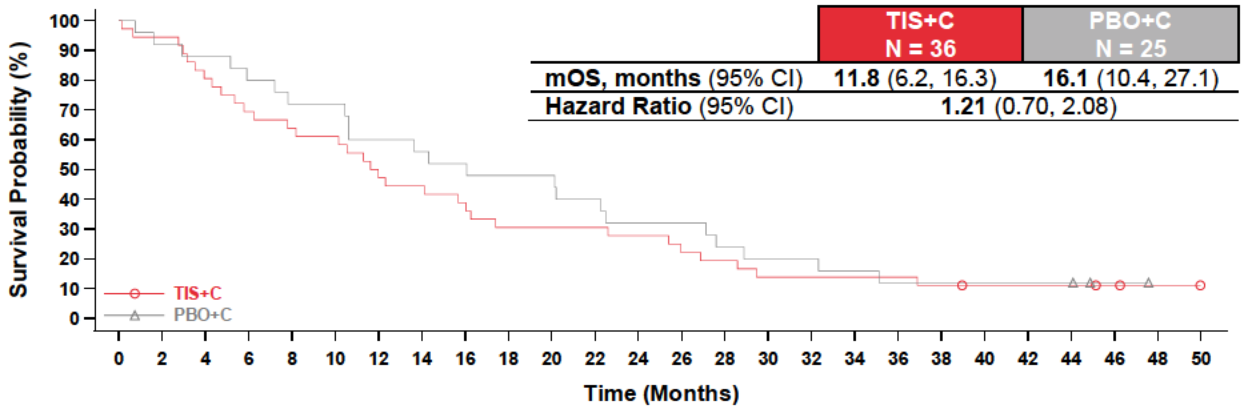
a) PD-L1 ≥ 1%



No. At Risk:

TIS+C	231	222	208	192	184	164	147	134	122	108	99	94	83	71	66	61	58	55	47	43	34	29	22	16	13	7	4	3	2	1	0
PBO+C	250	241	211	190	152	117	101	91	84	73	68	60	53	49	44	42	39	33	29	29	24	20	16	14	9	7	2	2	0	0	0

b) PD-L1 < 1%



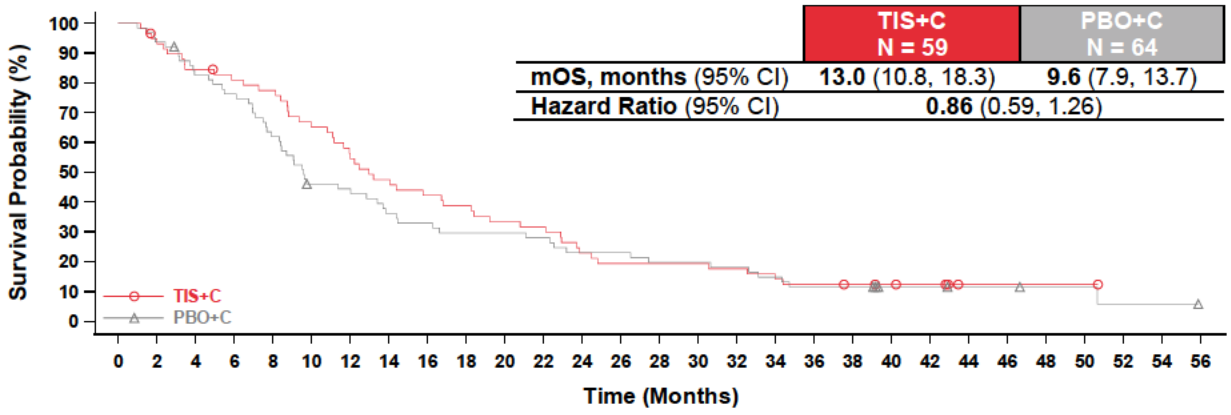
No. At Risk:

TIS+C	36	34	29	25	23	22	17	16	14	11	11	11	10	8	7	5	5	5	5	4	3	3	3	2	1	0			
PBO+C	25	23	22	20	18	18	15	14	13	12	12	10	8	8	6	5	5	4	3	3	3	3	3	1	0	0			

Data cutoff: 24NOV2023.
Abbreviations: CI, confidence interval; ITT, intent to treat; mOS, median overall survival; PBO+C, placebo + chemotherapy; PD-L1, programmed death ligand 1; TAP, tumor area positivity; TIS+C, tislelizumab + chemotherapy.
Notes: Hazard ratio (TIS+C vs PBO+C) was based on unstratified Cox regression model. Updated death data for three patients were incorporated.

Figure 21: Kaplan-Meier Plot of OS by Baseline PD-L1 TAP Score Categories at the 3-Year Follow-up (ITT Analysis Set)

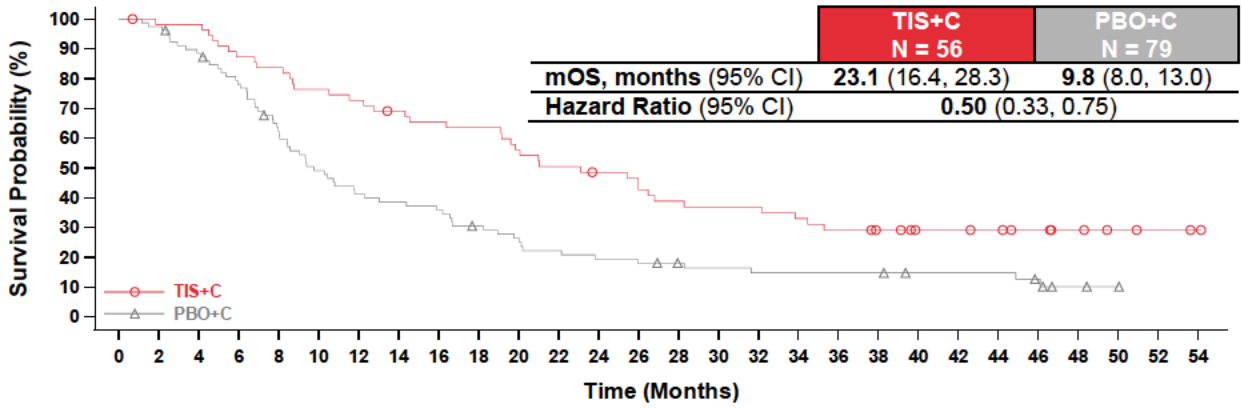
a) PD-L1 ≥ 1% - < 5%



No. At Risk:

TIS+C	59	55	49	46	44	37	31	27	24	22	19	18	13	11	11	11	10	9	7	6	5	4	1	1	1	1	0	0	0
PBO+C	64	60	52	48	39	28	27	22	20	18	18	17	14	14	12	12	11	9	7	7	4	4	3	3	2	2	1	1	0

b) PD-L1 ≥ 5% - < 10%



No. At Risk:

TIS+C	56	54	54	48	46	42	40	37	35	34	30	27	25	22	20	19	19	17	15	13	10	10	9	7	5	3	2	1
PBO+C	79	77	69	60	47	37	31	29	27	22	19	16	14	13	11	10	9	9	9	9	7	7	7	5	2	1	0	0

Data cutoff: 24NOV2023.
Abbreviations: CI, confidence interval; ITT, intent to treat; mOS, median overall survival; PBO+C, placebo + chemotherapy; PD-L1, programmed death ligand 1; TAP, tumor area positivity; TIS+C, tislelizumab + chemotherapy.
Notes: Hazard ratio (TIS+C vs PBO+C) was based on unstratified Cox regression model. Updated death data for three patients were incorporated.

Table 12: Overall Summary of TEAEs for Baseline PD-L1 TAP Cutoff of 1% (Safety Analysis Set)

	PD-L1 < 1%		PD-L1 ≥ 1%		Overall	
	TIS+C (N = 36) n (%)	PBO+C (N = 25) n (%)	TIS+C (N = 230) n (%)	PBO+C (N = 248) n (%)	TIS+C (N = 324) n (%)	PBO+C (N = 321) n (%)
Patients with at Least One TEAE	36 (100.0)	24 (96.0)	229 (99.6)	248 (100.0)	323 (99.7)	319 (99.4)
Any Study Treatment Component Related TEAEs	33 (91.7)	22 (88.0)	223 (97.0)	241 (97.2)	313 (96.6)	309 (96.3)
TIS- or PBO-Related TEAEs	25 (69.4)	15 (60.0)	161 (70.0)	154 (62.1)	224 (69.1)	195 (60.7)
Any Chemo Component-Related TEAEs	33 (91.7)	22 (88.0)	223 (97.0)	240 (96.8)	313 (96.6)	308 (96.0)
TEAEs of Grade 3 or Higher	28 (77.8)	21 (84.0)	180 (78.3)	192 (77.4)	254 (78.4)	249 (77.6)
Any Study Treatment Component-Related TEAEs of ≥ Grade 3	22 (61.1)	19 (76.0)	154 (67.0)	160 (64.5)	216 (66.7)	207 (64.5)
TIS- or PBO-Related TEAEs of ≥ Grade 3	12 (33.3)	8 (32.0)	75 (32.6)	50 (20.2)	103 (31.8)	65 (20.2)
Any Chemo Component-Related TEAEs of ≥ Grade 3	22 (61.1)	19 (76.0)	142 (61.7)	156 (62.9)	203 (62.7)	202 (62.9)
Serious TEAEs	21 (58.3)	8 (32.0)	107 (46.5)	97 (39.1)	156 (48.1)	127 (39.6)
Any Study Treatment Component-Related Serious TEAEs	11 (30.6)	4 (16.0)	64 (27.8)	50 (20.2)	93 (28.7)	62 (19.3)
TIS- or PBO-Related Serious TEAEs	8 (22.2)	2 (8.0)	46 (20.0)	21 (8.5)	61 (18.8)	27 (8.4)
Any Chemo Component-Related Serious TEAEs	10 (27.8)	4 (16.0)	44 (19.1)	46 (18.5)	70 (21.6)	57 (17.8)
TEAEs Leading to Death [a]	2 (5.6)	0 (0.0)	14 (6.1)	13 (5.2)	17 (5.2)	17 (5.3)
Any Study Treatment Component-Related TEAEs Leading to Death	1 (2.8)	0 (0.0)	5 (2.2)	4 (1.6)	6 (1.9)	4 (1.2)
TIS- or PBO-Related TEAEs Leading to Death	1 (2.8)	0 (0.0)	4 (1.7)	2 (0.8)	5 (1.5)	2 (0.6)
Any Chemo Component-Related TEAEs Leading to Death	0 (0.0)	0 (0.0)	3 (1.3)	4 (1.6)	3 (0.9)	4 (1.2)
TEAEs Leading to Any Treatment Discontinuation	10 (27.8)	4 (16.0)	81 (35.2)	55 (22.2)	103 (31.8)	72 (22.4)
TEAEs Leading to Discontinuation of TIS or PBO	7 (19.4)	0 (0.0)	29 (12.6)	17 (6.9)	42 (13.0)	21 (6.5)
TEAEs Leading to Discontinuation of Any Chemo Component	9 (25.0)	4 (16.0)	75 (32.6)	54 (21.8)	95 (29.3)	70 (21.8)
TEAEs Leading to Any Dose Modification [b]	27 (75.0)	15 (60.0)	173 (75.2)	178 (71.8)	247 (76.2)	229 (71.3)
TEAEs Leading to Dose Modification of TIS or PBO	19 (52.8)	8 (32.0)	116 (50.4)	100 (40.3)	170 (52.5)	128 (39.9)
TEAEs Leading to Dose Modification of Any Chemo Component	27 (75.0)	14 (56.0)	168 (73.0)	173 (69.8)	239 (73.8)	220 (68.5)
Immune-Mediated AEs	8 (22.2)	3 (12.0)	89 (38.7)	50 (20.2)	114 (35.2)	60 (18.7)
Immune-Mediated AEs of ≥ Grade 3	2 (5.6)	0 (0.0)	22 (9.6)	4 (1.6)	29 (9.0)	4 (1.2)

Data cutoff: 28FEB2022.

Abbreviations: AE, adverse event; chemo, chemotherapy; PBO, placebo; PBO+C, placebo + chemotherapy; TEAE, treatment-emergent adverse event; TIS+C, tislelizumab + chemotherapy; TIS, tislelizumab.

Notes: Percentages were based on N.

Adverse event grades were evaluated based on NCI-CTCAE (Version 4.03).

A TEAE is defined as an AE that had an onset date or a worsening in severity from baseline (pretreatment) on or after the first dose of study treatment up to 30 days following study treatment discontinuation or initiation of new anticancer therapy, whichever occurred first.

For each row category, a patient with two or more adverse events in that category was counted only once.

Treatment-related TEAEs included TEAEs that were considered by the investigator to be related to the study treatment or TEAEs with a missing causality.
[a] The death event due to disease progression of ESCC is requested to be reported as an adverse event if the death occurred ≤30 days after the last dose of study treatment per the protocol. Those events were not included as TEAE leading to death.
[b] The types of dose modification include dose delay, infusion interruption, infusion rate decreased and dose reduction for chemotherapy; dose delay, infusion interruption, and infusion rate decreased for tislelizumab/placebo.

Table 13: Treatment-Emergent Adverse Events With an Incidence ≥ 10% by Preferred Term (Safety Analysis Set)

	PD-L1 < 1%		PD-L1 ≥ 1%		Overall	
Preferred Term	TIS+C (N = 36) n (%)	PBO+C (N = 25) n (%)	TIS+C (N = 230) n (%)	PBO+C (N = 248) n (%)	TIS+C (N = 324) n (%)	PBO+C (N = 321) n (%)
Patients with at Least One TEAE	36 (100.0)	24 (96.0)	229 (99.6)	248 (100.0)	323 (99.7)	319 (99.4)
Anaemia	17 (47.2)	19 (76.0)	145 (63.0)	138 (55.6)	197 (60.8)	180 (56.1)
Neutrophil count decreased	19 (52.8)	19 (76.0)	108 (47.0)	117 (47.2)	154 (47.5)	156 (48.6)
Decreased appetite	16 (44.4)	8 (32.0)	104 (45.2)	95 (38.3)	144 (44.4)	125 (38.9)
White blood cell count decreased	17 (47.2)	17 (68.0)	105 (45.7)	123 (49.6)	143 (44.1)	157 (48.9)
Nausea	16 (44.4)	11 (44.0)	80 (34.8)	108 (43.5)	123 (38.0)	136 (42.4)
Constipation	11 (30.6)	7 (28.0)	73 (31.7)	80 (32.3)	98 (30.2)	100 (31.2)
Weight decreased	13 (36.1)	5 (20.0)	68 (29.6)	72 (29.0)	94 (29.0)	89 (27.7)
Diarrhoea	6 (16.7)	7 (28.0)	67 (29.1)	63 (25.4)	91 (28.1)	78 (24.3)
Peripheral sensory neuropathy	6 (16.7)	4 (16.0)	57 (24.8)	47 (19.0)	75 (23.1)	62 (19.3)
Hypoalbuminaemia	10 (27.8)	5 (20.0)	47 (20.4)	52 (21.0)	74 (22.8)	60 (18.7)
Hyponatraemia	7 (19.4)	3 (12.0)	49 (21.3)	53 (21.4)	72 (22.2)	60 (18.7)
Vomiting	11 (30.6)	8 (32.0)	50 (21.7)	70 (28.2)	72 (22.2)	88 (27.4)
Hypokalaemia	9 (25.0)	5 (20.0)	40 (17.4)	46 (18.5)	65 (20.1)	55 (17.1)
Fatigue	9 (25.0)	1 (4.0)	47 (20.4)	45 (18.1)	64 (19.8)	57 (17.8)
Stomatitis	4 (11.1)	2 (8.0)	45 (19.6)	37 (14.9)	63 (19.4)	48 (15.0)
Platelet count decreased	7 (19.4)	7 (28.0)	44 (19.1)	41 (16.5)	62 (19.1)	55 (17.1)
Alopecia	5 (13.9)	6 (24.0)	49 (21.3)	45 (18.1)	60 (18.5)	63 (19.6)
Neutropenia	6 (16.7)	2 (8.0)	33 (14.3)	40 (16.1)	53 (16.4)	47 (14.6)
Aspartate aminotransferase increased	4 (11.1)	3 (12.0)	35 (15.2)	24 (9.7)	52 (16.0)	37 (11.5)
Pyrexia	7 (19.4)	2 (8.0)	35 (15.2)	34 (13.7)	52 (16.0)	39 (12.1)
Cough	8 (22.2)	5 (20.0)	32 (13.9)	30 (12.1)	51 (15.7)	38 (11.8)
Alanine aminotransferase increased	5 (13.9)	6 (24.0)	34 (14.8)	29 (11.7)	50 (15.4)	42 (13.1)

Preferred Term	PD-L1 < 1%		PD-L1 ≥ 1%		Overall	
	TIS+C (N = 36) n (%)	PBO+C (N = 25) n (%)	TIS+C (N = 230) n (%)	PBO+C (N = 248) n (%)	TIS+C (N = 324) n (%)	PBO+C (N = 321) n (%)
Blood creatinine increased	6 (16.7)	4 (16.0)	30 (13.0)	21 (8.5)	45 (13.9)	30 (9.3)
Dysphagia	7 (19.4)	2 (8.0)	25 (10.9)	22 (8.9)	44 (13.6)	35 (10.9)
Asthenia	2 (5.6)	4 (16.0)	28 (12.2)	35 (14.1)	43 (13.3)	45 (14.0)
Malaise	0 (0.0)	4 (16.0)	37 (16.1)	41 (16.5)	43 (13.3)	52 (16.2)
Pruritus	5 (13.9)	1 (4.0)	29 (12.6)	17 (6.9)	43 (13.3)	21 (6.5)
Pneumonia	8 (22.2)	5 (20.0)	29 (12.6)	25 (10.1)	42 (13.0)	35 (10.9)
Rash	3 (8.3)	1 (4.0)	29 (12.6)	19 (7.7)	37 (11.4)	23 (7.2)
Hypochloraemia	4 (11.1)	3 (12.0)	23 (10.0)	26 (10.5)	36 (11.1)	31 (9.7)
Hypoaesthesia	4 (11.1)	4 (16.0)	25 (10.9)	33 (13.3)	34 (10.5)	40 (12.5)
Leukopenia	5 (13.9)	4 (16.0)	22 (9.6)	24 (9.7)	34 (10.5)	30 (9.3)
Hypothyroidism	2 (5.6)	2 (8.0)	24 (10.4)	11 (4.4)	33 (10.2)	14 (4.4)
Hyperglycaemia	5 (13.9)	3 (12.0)	18 (7.8)	21 (8.5)	32 (9.9)	27 (8.4)
Hypomagnesaemia	5 (13.9)	3 (12.0)	19 (8.3)	21 (8.5)	31 (9.6)	29 (9.0)
Insomnia	5 (13.9)	3 (12.0)	19 (8.3)	19 (7.7)	29 (9.0)	25 (7.8)
Arthralgia	5 (13.9)	4 (16.0)	22 (9.6)	24 (9.7)	28 (8.6)	32 (10.0)
Hyperuricaemia	2 (5.6)	3 (12.0)	20 (8.7)	22 (8.9)	27 (8.3)	25 (7.8)
Thrombocytopenia	5 (13.9)	2 (8.0)	18 (7.8)	16 (6.5)	27 (8.3)	23 (7.2)
Abdominal pain	1 (2.8)	3 (12.0)	20 (8.7)	8 (3.2)	25 (7.7)	13 (4.0)
Pain in extremity	2 (5.6)	2 (8.0)	20 (8.7)	28 (11.3)	25 (7.7)	31 (9.7)
Productive cough	5 (13.9)	3 (12.0)	17 (7.4)	13 (5.2)	25 (7.7)	18 (5.6)
Blood urea increased	4 (11.1)	1 (4.0)	14 (6.1)	13 (5.2)	24 (7.4)	16 (5.0)
Hiccups	1 (2.8)	3 (12.0)	18 (7.8)	22 (8.9)	22 (6.8)	28 (8.7)
Amylase increased	1 (2.8)	3 (12.0)	11 (4.8)	13 (5.2)	20 (6.2)	18 (5.6)
Headache	5 (13.9)	2 (8.0)	9 (3.9)	12 (4.8)	15 (4.6)	15 (4.7)
Malnutrition	4 (11.1)	0 (0.0)	3 (1.3)	2 (0.8)	8 (2.5)	2 (0.6)
Sinus tachycardia	0 (0.0)	3 (12.0)	4 (1.7)	1 (0.4)	4 (1.2)	4 (1.2)

Data cutoff: 28FEB2022.
Abbreviations: PBO+C, placebo + chemotherapy; TEAE, treatment-emergent adverse event; TIS+C, tislelizumab + chemotherapy.
Notes: Percentages were based on N.
Patients with multiple events for a given Preferred Term were counted only once for the Preferred Term.
PTs filtered by incidence ≥ 10% in any column.
Adverse events terms were coded using Medical Dictionary for Drug Regulatory Affairs Version 24.0.
Adverse events were sorted by descending frequency of Preferred Term in the Tislelizumab + Chemotherapy column.

Table 14: Treatment-Emergent Adverse Events With Grade 3 or Higher and an Incidence ≥ 2% by Preferred Term (Safety Analysis Set)

	PD-L1 < 1%		PD-L1 ≥ 1%		Overall	
Preferred Term	TIS+C (N = 36) n (%)	PBO+C (N = 25) n (%)	TIS+C (N = 230) n (%)	PBO+C (N = 248) n (%)	TIS+C (N = 324) n (%)	PBO+C (N = 321) n (%)
Patients with at Least One TEAE	28 (77.8)	21 (84.0)	180 (78.3)	192 (77.4)	254 (78.4)	249 (77.6)
Neutrophil count decreased	14 (38.9)	15 (60.0)	71 (30.9)	78 (31.5)	100 (30.9)	107 (33.3)
Anaemia	7 (19.4)	5 (20.0)	34 (14.8)	40 (16.1)	56 (17.3)	50 (15.6)
Hyponatraemia	2 (5.6)	2 (8.0)	24 (10.4)	14 (5.6)	36 (11.1)	18 (5.6)
White blood cell count decreased	6 (16.7)	5 (20.0)	26 (11.3)	39 (15.7)	35 (10.8)	50 (15.6)
Hypokalaemia	3 (8.3)	2 (8.0)	17 (7.4)	19 (7.7)	28 (8.6)	22 (6.9)
Neutropenia	3 (8.3)	2 (8.0)	13 (5.7)	27 (10.9)	24 (7.4)	32 (10.0)
Dysphagia	3 (8.3)	1 (4.0)	12 (5.2)	8 (3.2)	20 (6.2)	13 (4.0)
Pneumonia	3 (8.3)	2 (8.0)	13 (5.7)	16 (6.5)	19 (5.9)	20 (6.2)
Decreased appetite	4 (11.1)	0 (0.0)	11 (4.8)	6 (2.4)	18 (5.6)	7 (2.2)
Fatigue	2 (5.6)	1 (4.0)	12 (5.2)	6 (2.4)	17 (5.2)	9 (2.8)
Diarrhoea	2 (5.6)	1 (4.0)	9 (3.9)	3 (1.2)	14 (4.3)	6 (1.9)
Stomatitis	2 (5.6)	0 (0.0)	7 (3.0)	6 (2.4)	13 (4.0)	7 (2.2)
Peripheral sensory neuropathy	0 (0.0)	1 (4.0)	9 (3.9)	5 (2.0)	10 (3.1)	7 (2.2)
Hypertension	0 (0.0)	0 (0.0)	7 (3.0)	5 (2.0)	9 (2.8)	6 (1.9)
Leukopenia	2 (5.6)	2 (8.0)	5 (2.2)	7 (2.8)	9 (2.8)	10 (3.1)
Nausea	1 (2.8)	0 (0.0)	6 (2.6)	3 (1.2)	9 (2.8)	5 (1.6)
Platelet count decreased	0 (0.0)	1 (4.0)	7 (3.0)	2 (0.8)	9 (2.8)	3 (0.9)
Amylase increased	1 (2.8)	0 (0.0)	4 (1.7)	3 (1.2)	8 (2.5)	3 (0.9)
Oesophageal stenosis	2 (5.6)	0 (0.0)	5 (2.2)	2 (0.8)	8 (2.5)	2 (0.6)
Aspartate aminotransferase increased	0 (0.0)	0 (0.0)	7 (3.0)	2 (0.8)	7 (2.2)	4 (1.2)
Asthenia	0 (0.0)	1 (4.0)	5 (2.2)	2 (0.8)	7 (2.2)	3 (0.9)
Lymphocyte count decreased	3 (8.3)	0 (0.0)	3 (1.3)	6 (2.4)	7 (2.2)	7 (2.2)
Rash	0 (0.0)	0 (0.0)	6 (2.6)	0 (0.0)	7 (2.2)	0 (0.0)
Gamma-glutamyltransferase increased	0 (0.0)	0 (0.0)	5 (2.2)	3 (1.2)	6 (1.9)	3 (0.9)
Hyperkalaemia	1 (2.8)	0 (0.0)	4 (1.7)	5 (2.0)	6 (1.9)	5 (1.6)
Lipase increased	0 (0.0)	1 (4.0)	4 (1.7)	6 (2.4)	6 (1.9)	7 (2.2)
Weight decreased	2 (5.6)	0 (0.0)	3 (1.3)	2 (0.8)	6 (1.9)	2 (0.6)
Febrile neutropenia	0 (0.0)	1 (4.0)	4 (1.7)	5 (2.0)	5 (1.5)	7 (2.2)

Preferred Term	PD-L1 < 1%		PD-L1 ≥ 1%		Overall	
	TIS+C (N = 36) n (%)	PBO+C (N = 25) n (%)	TIS+C (N = 230) n (%)	PBO+C (N = 248) n (%)	TIS+C (N = 324) n (%)	PBO+C (N = 321) n (%)
Hypotension	1 (2.8)	0 (0.0)	4 (1.7)	0 (0.0)	5 (1.5)	1 (0.3)
Oesophageal obstruction	0 (0.0)	2 (8.0)	5 (2.2)	3 (1.2)	5 (1.5)	5 (1.6)
Vomiting	2 (5.6)	1 (4.0)	3 (1.3)	5 (2.0)	5 (1.5)	8 (2.5)
Hypochloraemia	1 (2.8)	0 (0.0)	2 (0.9)	1 (0.4)	4 (1.2)	1 (0.3)
Hypophosphataemia	1 (2.8)	0 (0.0)	2 (0.9)	5 (2.0)	4 (1.2)	5 (1.6)
Thrombocytopenia	0 (0.0)	1 (4.0)	4 (1.7)	4 (1.6)	4 (1.2)	6 (1.9)
Colitis	1 (2.8)	0 (0.0)	0 (0.0)	0 (0.0)	3 (0.9)	0 (0.0)
Death	2 (5.6)	0 (0.0)	1 (0.4)	3 (1.2)	3 (0.9)	4 (1.2)
Lymphopenia	1 (2.8)	0 (0.0)	2 (0.9)	1 (0.4)	3 (0.9)	1 (0.3)
Oesophageal fistula	2 (5.6)	0 (0.0)	1 (0.4)	2 (0.8)	3 (0.9)	2 (0.6)
Palmar-plantar erythrodysaesthesia syndrome	1 (2.8)	0 (0.0)	1 (0.4)	3 (1.2)	3 (0.9)	3 (0.9)
Pulmonary embolism	1 (2.8)	0 (0.0)	1 (0.4)	2 (0.8)	3 (0.9)	3 (0.9)
Septic shock	2 (5.6)	0 (0.0)	1 (0.4)	1 (0.4)	3 (0.9)	1 (0.3)
Cataract	1 (2.8)	0 (0.0)	1 (0.4)	1 (0.4)	2 (0.6)	1 (0.3)
Malnutrition	1 (2.8)	0 (0.0)	1 (0.4)	1 (0.4)	2 (0.6)	1 (0.3)
Paraesthesia	1 (2.8)	0 (0.0)	1 (0.4)	1 (0.4)	2 (0.6)	1 (0.3)
Abscess limb	1 (2.8)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)	0 (0.0)
Bacteraemia	1 (2.8)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)	0 (0.0)
Cachexia	1 (2.8)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)	0 (0.0)
Carbuncle	1 (2.8)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)	0 (0.0)
Cardiac failure	0 (0.0)	1 (4.0)	1 (0.4)	0 (0.0)	1 (0.3)	1 (0.3)
Depression	1 (2.8)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)	0 (0.0)
Hypomagnesaemia	0 (0.0)	1 (4.0)	1 (0.4)	1 (0.4)	1 (0.3)	2 (0.6)
Myocarditis	1 (2.8)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)	0 (0.0)
Oesophagobronchial fistula	1 (2.8)	0 (0.0)	0 (0.0)	1 (0.4)	1 (0.3)	1 (0.3)
Pneumothorax	1 (2.8)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)	0 (0.0)
Post procedural pneumonia	1 (2.8)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)	0 (0.0)
Hepatic failure	0 (0.0)	1 (4.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)

Data cutoff: 28FEB2022.
Abbreviations: PBO+C, placebo + chemotherapy; TEAE, treatment-emergent adverse event; TIS+C, tislelizumab + chemotherapy.
Notes: Percentages were based on N.
Adverse events terms were coded using Medical Dictionary for Drug Regulatory Affairs Version 24.0. Adverse event grades were evaluated based on NCI-CTCAE (Version 4.03).

Patients with multiple events for a given Preferred Term were counted only once at the worst severity for the Preferred Term. PTs filtered by incidence ≥ 2% in any column. Adverse events were sorted by descending frequency of Preferred Term in the Tislelizumab + Chemotherapy column.

Table 17: Serious Treatment-Emergent Adverse Events With an Incidence ≥ 1% by Preferred Term (Safety Analysis Set)

	PD-L1 < 1%		PD-L1 ≥ 1%		Overall	
Preferred Term	**TIS+C (N = 36) n (%)**	**PBO+C (N = 25) n (%)**	**TIS+C (N = 230) n (%)**	**PBO+C (N = 248) n (%)**	**TIS+C (N = 324) n (%)**	**PBO+C (N = 321) n (%)**
Patients with at Least One TEAE	21 (58.3)	8 (32.0)	107 (46.5)	97 (39.1)	156 (48.1)	127 (39.6)
Dysphagia	2 (5.6)	0 (0.0)	10 (4.3)	6 (2.4)	17 (5.2)	8 (2.5)
Pneumonia	3 (8.3)	3 (12.0)	11 (4.8)	16 (6.5)	17 (5.2)	22 (6.9)
Diarrhoea	1 (2.8)	0 (0.0)	5 (2.2)	1 (0.4)	7 (2.2)	3 (0.9)
Oesophageal stenosis	1 (2.8)	0 (0.0)	5 (2.2)	2 (0.8)	7 (2.2)	2 (0.6)
Acute kidney injury	0 (0.0)	0 (0.0)	6 (2.6)	0 (0.0)	6 (1.9)	0 (0.0)
Anaemia	0 (0.0)	0 (0.0)	4 (1.7)	3 (1.2)	6 (1.9)	6 (1.9)
Decreased appetite	1 (2.8)	0 (0.0)	4 (1.7)	1 (0.4)	6 (1.9)	2 (0.6)
Hyponatraemia	1 (2.8)	0 (0.0)	3 (1.3)	2 (0.8)	6 (1.9)	2 (0.6)
Pneumonitis	1 (2.8)	0 (0.0)	4 (1.7)	3 (1.2)	6 (1.9)	4 (1.2)
Vomiting	3 (8.3)	1 (4.0)	3 (1.3)	4 (1.6)	6 (1.9)	6 (1.9)
Febrile neutropenia	0 (0.0)	1 (4.0)	3 (1.3)	3 (1.2)	5 (1.5)	5 (1.6)
General physical health deterioration	1 (2.8)	0 (0.0)	4 (1.7)	4 (1.6)	5 (1.5)	4 (1.2)
Malaise	0 (0.0)	0 (0.0)	5 (2.2)	2 (0.8)	5 (1.5)	3 (0.9)
Nausea	1 (2.8)	0 (0.0)	2 (0.9)	2 (0.8)	5 (1.5)	2 (0.6)
Stomatitis	2 (5.6)	0 (0.0)	1 (0.4)	0 (0.0)	5 (1.5)	0 (0.0)
Colitis	1 (2.8)	0 (0.0)	0 (0.0)	0 (0.0)	4 (1.2)	0 (0.0)
Neutrophil count decreased	0 (0.0)	0 (0.0)	3 (1.3)	2 (0.8)	4 (1.2)	3 (0.9)
Pneumonia aspiration	0 (0.0)	0 (0.0)	4 (1.7)	3 (1.2)	4 (1.2)	4 (1.2)
Pyrexia	0 (0.0)	0 (0.0)	4 (1.7)	1 (0.4)	4 (1.2)	1 (0.3)
Sepsis	0 (0.0)	0 (0.0)	3 (1.3)	2 (0.8)	4 (1.2)	2 (0.6)
Upper gastrointestinal haemorrhage	0 (0.0)	0 (0.0)	4 (1.7)	1 (0.4)	4 (1.2)	2 (0.6)
Acquired tracheo-oesophageal fistula	0 (0.0)	0 (0.0)	3 (1.3)	3 (1.2)	3 (0.9)	3 (0.9)
Death	2 (5.6)	0 (0.0)	1 (0.4)	3 (1.2)	3 (0.9)	4 (1.2)
Hypercalcaemia	0 (0.0)	0 (0.0)	3 (1.3)	2 (0.8)	3 (0.9)	2 (0.6)
Hypokalaemia	0 (0.0)	0 (0.0)	2 (0.9)	4 (1.6)	3 (0.9)	4 (1.2)
Oesophageal fistula	2 (5.6)	1 (4.0)	1 (0.4)	2 (0.8)	3 (0.9)	3 (0.9)

Preferred Term	PD-L1 < 1%		PD-L1 ≥ 1%		Overall	
	TIS+C (N = 36) n (%)	PBO+C (N = 25) n (%)	TIS+C (N = 230) n (%)	PBO+C (N = 248) n (%)	TIS+C (N = 324) n (%)	PBO+C (N = 321) n (%)
Respiratory failure	0 (0.0)	0 (0.0)	2 (0.9)	4 (1.6)	3 (0.9)	4 (1.2)
Septic shock	2 (5.6)	0 (0.0)	1 (0.4)	1 (0.4)	3 (0.9)	1 (0.3)
Malnutrition	1 (2.8)	0 (0.0)	1 (0.4)	0 (0.0)	2 (0.6)	0 (0.0)
Oesophageal obstruction	0 (0.0)	2 (8.0)	2 (0.9)	0 (0.0)	2 (0.6)	2 (0.6)
Abscess limb	1 (2.8)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)	0 (0.0)
Cachexia	1 (2.8)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)	0 (0.0)
Carbuncle	1 (2.8)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)	0 (0.0)
Dehydration	1 (2.8)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)	0 (0.0)
Depression	1 (2.8)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)	0 (0.0)
Leukopenia	0 (0.0)	0 (0.0)	1 (0.4)	4 (1.6)	1 (0.3)	4 (1.2)
Myocarditis	1 (2.8)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)	0 (0.0)
Neutropenia	0 (0.0)	0 (0.0)	1 (0.4)	6 (2.4)	1 (0.3)	7 (2.2)
Oesophagobronchial fistula	1 (2.8)	0 (0.0)	0 (0.0)	1 (0.4)	1 (0.3)	1 (0.3)
Pneumothorax	1 (2.8)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)	0 (0.0)
Post procedural pneumonia	1 (2.8)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)	0 (0.0)
Renal injury	1 (2.8)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)	0 (0.0)
Tumour associated fever	1 (2.8)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)	0 (0.0)
Cardiac failure	0 (0.0)	1 (4.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)
Chest discomfort	0 (0.0)	0 (0.0)	0 (0.0)	3 (1.2)	0 (0.0)	3 (0.9)
Constipation	0 (0.0)	1 (4.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)
Hepatic failure	0 (0.0)	1 (4.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)
Ileus	0 (0.0)	0 (0.0)	0 (0.0)	3 (1.2)	0 (0.0)	3 (0.9)
Peripheral arterial occlusive disease	0 (0.0)	1 (4.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)
Platelet count decreased	0 (0.0)	1 (4.0)	0 (0.0)	2 (0.8)	0 (0.0)	3 (0.9)

Data cutoff: 28FEB2022.
Abbreviations: PBO+C, placebo + chemotherapy; TEAE, treatment-emergent adverse event; TIS+C, tislelizumab + chemotherapy.
Percentages were based on N.
Patients with multiple events for a given preferred term were counted only once for the preferred term.
Adverse Events terms were coded using Medical Dictionary for Drug Regulatory Affairs (MedDRA) version 24.0.
Adverse Events are sorted by descending frequency of preferred term in Tislelizumab + Chemotherapy column of overall group.

Table 18: Treatment-Emergent Adverse Events Leading to Treatment Discontinuation With an Incidence ≥ 1% by Preferred Term (Safety Analysis Set)

	PD-L1 < 1%		PD-L1 ≥ 1%		Overall	
Preferred Term	TIS+C (N = 36) n (%)	PBO+C (N = 25) n (%)	TIS+C (N = 230) n (%)	PBO+C (N = 248) n (%)	TIS+C (N = 324) n (%)	PBO+C (N = 321) n (%)
Patients with at Least One TEAE	10 (27.8)	4 (16.0)	81 (35.2)	55 (22.2)	103 (31.8)	72 (22.4)
Peripheral sensory neuropathy	0 (0.0)	0 (0.0)	22 (9.6)	6 (2.4)	23 (7.1)	8 (2.5)
Anaemia	0 (0.0)	0 (0.0)	5 (2.2)	1 (0.4)	8 (2.5)	1 (0.3)
Pneumonitis	1 (2.8)	0 (0.0)	5 (2.2)	1 (0.4)	7 (2.2)	2 (0.6)
Hypoaesthesia	0 (0.0)	1 (4.0)	6 (2.6)	5 (2.0)	6 (1.9)	7 (2.2)
Neurotoxicity	0 (0.0)	0 (0.0)	4 (1.7)	3 (1.2)	5 (1.5)	3 (0.9)
Blood creatinine increased	1 (2.8)	0 (0.0)	2 (0.9)	1 (0.4)	4 (1.2)	4 (1.2)
Fatigue	2 (5.6)	1 (4.0)	2 (0.9)	2 (0.8)	4 (1.2)	4 (1.2)
Malaise	0 (0.0)	0 (0.0)	4 (1.7)	0 (0.0)	4 (1.2)	0 (0.0)
Drug hypersensitivity	0 (0.0)	0 (0.0)	3 (1.3)	1 (0.4)	3 (0.9)	1 (0.3)
Paraesthesia	2 (5.6)	0 (0.0)	1 (0.4)	2 (0.8)	3 (0.9)	2 (0.6)
Pneumonia	0 (0.0)	0 (0.0)	2 (0.9)	4 (1.6)	3 (0.9)	4 (1.2)
Chills	1 (2.8)	0 (0.0)	1 (0.4)	1 (0.4)	2 (0.6)	1 (0.3)
Neutrophil count decreased	0 (0.0)	1 (4.0)	2 (0.9)	1 (0.4)	2 (0.6)	2 (0.6)
Pyrexia	2 (5.6)	0 (0.0)	0 (0.0)	1 (0.4)	2 (0.6)	1 (0.3)
Renal injury	1 (2.8)	0 (0.0)	1 (0.4)	0 (0.0)	2 (0.6)	0 (0.0)
Myocarditis	1 (2.8)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)	0 (0.0)
Oesophageal fistula	1 (2.8)	0 (0.0)	0 (0.0)	1 (0.4)	1 (0.3)	1 (0.3)
Pain in extremity	0 (0.0)	1 (4.0)	0 (0.0)	1 (0.4)	1 (0.3)	2 (0.6)
Palmar-plantar erythrodysaesthesia syndrome	0 (0.0)	0 (0.0)	1 (0.4)	3 (1.2)	1 (0.3)	3 (0.9)
Pruritus	1 (2.8)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)	0 (0.0)
Renal impairment	0 (0.0)	0 (0.0)	1 (0.4)	3 (1.2)	1 (0.3)	3 (0.9)
Weight decreased	1 (2.8)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)	0 (0.0)

Data cutoff: 28FEB2022.
Abbreviations: PBO+C, placebo + chemotherapy; TEAE, treatment-emergent adverse event; TIS+C, tislelizumab + chemotherapy.
Percentages were based on N.
Patients with multiple events for a given preferred term were counted only once for the preferred term.
Adverse Events terms were coded using Medical Dictionary for Drug Regulatory Affairs (MedDRA) version 24.0.
Adverse Events are sorted by descending frequency of preferred term in Tislelizumab + Chemotherapy column of overall group.

Table 15: Treatment-Emergent Adverse Events Leading to Death by Preferred Term (Safety Analysis Set)

Preferred Term	PD-L1 < 1%		PD-L1 ≥ 1%		Overall	
	TIS+C (N = 36) n (%)	PBO+C (N = 25) n (%)	TIS+C (N = 230) n (%)	PBO+C (N = 248) n (%)	TIS+C (N = 324) n (%)	PBO+C (N = 321) n (%)
Patients with at Least One TEAE	2 (5.6)	0 (0.0)	14 (6.1)	13 (5.2)	17 (5.2)	17 (5.3)
Death	1 (2.8)	0 (0.0)	1 (0.4)	3 (1.2)	2 (0.6)	4 (1.2)
Acquired tracheo-oesophageal fistula	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)	1 (0.3)	0 (0.0)
Brain injury	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)	1 (0.3)	0 (0.0)
Electrolyte imbalance	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)	1 (0.3)	0 (0.0)
Gastrointestinal haemorrhage	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)	1 (0.3)	0 (0.0)
Multiple organ dysfunction syndrome	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)	0 (0.0)
Myocarditis	1 (2.8)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)	0 (0.0)
Pneumonia	0 (0.0)	0 (0.0)	1 (0.4)	3 (1.2)	1 (0.3)	4 (1.2)
Pneumonia aspiration	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)	1 (0.3)	0 (0.0)
Pulmonary embolism	0 (0.0)	0 (0.0)	1 (0.4)	1 (0.4)	1 (0.3)	2 (0.6)
Pulmonary tuberculosis	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)	1 (0.3)	0 (0.0)
Respiratory failure	0 (0.0)	0 (0.0)	1 (0.4)	1 (0.4)	1 (0.3)	1 (0.3)
Sepsis	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)	1 (0.3)	0 (0.0)
Sudden death	0 (0.0)	0 (0.0)	1 (0.4)	1 (0.4)	1 (0.3)	1 (0.3)
Traumatic intracranial haemorrhage	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)	1 (0.3)	0 (0.0)
Upper gastrointestinal haemorrhage	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)	1 (0.3)	0 (0.0)
Accidental death	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)	1 (0.3)
Asphyxia	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)	1 (0.3)
COVID-19 pneumonia	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)	2 (0.6)
Septic shock	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)	1 (0.3)

Data cutoff: 28FEB2022.
Abbreviations: PBO+C, placebo + chemotherapy; TEAE, treatment-emergent adverse event; TIS+C, tislelizumab + chemotherapy.
Percentages were based on N.
Patients with multiple events for a given preferred term were counted only once for the preferred term.
Adverse Events terms were coded using Medical Dictionary for Drug Regulatory Affairs (MedDRA) version 24.0.
Adverse Events are sorted by descending frequency of preferred term in Tislelizumab + Chemotherapy column of overall group.
The death event due to disease progression of ESCC is requested to be reported as an AE if the death event occurred <=30 days after the last dose of study drug per protocol. Those events are not included as TEAE leading to Death.

Table 20: Immune-Mediated Adverse Events by Category (Safety Analysis Set)

Category	PD-L1 < 1%		PD-L1 ≥ 1%		Overall	
	TIS+C (N = 36) n (%)	PBO+C (N = 25) n (%)	TIS+C (N = 230) n (%)	PBO+C (N = 248) n (%)	TIS+C (N = 324) n (%)	PBO+C (N = 321) n (%)
Patients with at Least One Immune-Mediated Adverse Event	8 (22.2)	3 (12.0)	89 (38.7)	50 (20.2)	114 (35.2)	60 (18.7)
Immune-mediated skin adverse reaction	2 (5.6)	0 (0.0)	34 (14.8)	20 (8.1)	41 (12.7)	22 (6.9)
Immune-mediated endocrinopathies (hypothyroidism)	2 (5.6)	2 (8.0)	29 (12.6)	12 (4.8)	38 (11.7)	16 (5.0)
Immune-mediated pneumonitis	4 (11.1)	0 (0.0)	18 (7.8)	12 (4.8)	26 (8.0)	14 (4.4)
Immune-mediated endocrinopathies (hyperthyroidism)	1 (2.8)	1 (4.0)	8 (3.5)	4 (1.6)	9 (2.8)	5 (1.6)
Other immune-mediated reactions (other)	1 (2.8)	0 (0.0)	5 (2.2)	2 (0.8)	6 (1.9)	2 (0.6)
Immune-mediated colitis	1 (2.8)	0 (0.0)	1 (0.4)	0 (0.0)	5 (1.5)	0 (0.0)
Immune-mediated endocrinopathies (adrenal insufficiency)	0 (0.0)	0 (0.0)	4 (1.7)	0 (0.0)	5 (1.5)	0 (0.0)
Other immune-mediated reactions (pancreatitis)	1 (2.8)	0 (0.0)	3 (1.3)	0 (0.0)	5 (1.5)	0 (0.0)
Immune-mediated hepatitis	0 (0.0)	0 (0.0)	3 (1.3)	0 (0.0)	4 (1.2)	0 (0.0)
Immune-mediated endocrinopathies (hypophysitis)	0 (0.0)	0 (0.0)	3 (1.3)	0 (0.0)	3 (0.9)	0 (0.0)
Other immune-mediated reactions (musculoskeletal)	0 (0.0)	0 (0.0)	2 (0.9)	0 (0.0)	3 (0.9)	0 (0.0)
Other immune-mediated reactions (ocular)	0 (0.0)	0 (0.0)	2 (0.9)	1 (0.4)	3 (0.9)	1 (0.3)
Immune-mediated endocrinopathies (diabetes mellitus)	0 (0.0)	0 (0.0)	2 (0.9)	1 (0.4)	2 (0.6)	1 (0.3)
Immune-mediated myocarditis/pericarditis	1 (2.8)	0 (0.0)	1 (0.4)	0 (0.0)	2 (0.6)	0 (0.0)
Immune-mediated endocrinopathies (thyroiditis)	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)	1 (0.3)	0 (0.0)
Immune-mediated myositis/rhabdomyolysis	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)	1 (0.3)	0 (0.0)
Immune-mediated nephritis and renal dysfunction	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)

Data cutoff: 28FEB2022.
Abbreviations: PBO+C, placebo + chemotherapy; TEAE, treatment-emergent adverse event; TIS+C, tislelizumab + chemotherapy.
Percentages were based on N.
Patients with multiple events for a given category and preferred term were counted only once at the worst severity for each category.
Adverse Events terms were coded using Medical Dictionary for Drug Regulatory Affairs (MedDRA) version 24.0.

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