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for the
Oncologic Drugs Advisory Committee

BLA 761417

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
5-FU	5-fluorouracil
AE	adverse event
BLA	Biologics License Application
BOR	best overall response
CBR	clinical benefit rate
CI	confidence interval
CPS	combined positive score
CR	complete response
DCR	disease control rate
DOR	duration of response
ECOG	Eastern Cooperative Oncology Group
EOP2	end-of-phase 2
ESCC	esophageal cancer
FA	final analysis
FDA	Food and Drug Administration
GC	gastric cancer
GEA	gastroesophageal adenocarcinoma
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
NE	not estimable
ORR	overall response rate
OS	overall survival
PBO+C	placebo + investigator's choice chemotherapy
PD	progressive disease
PD-L1	programmed death ligand 1
PDUFA	Prescription Drug User Fee Act

Abbreviation	Definition
PFS	progression-free survival
PR	partial response
PT	preferred term
Q3W	every 3 weeks
RECIST	Response Evaluation Criteria in Solid Tumors
SAE	serious adverse event
SD	stable disease
TAP	tumor area positivity
TIS+C	tislelizumab + investigator's choice chemotherapy
TTR	time to response
US	United States

1. EXECUTIVE SUMMARY

RATIONALE-305 is a global, multicenter, randomized, double-blind, placebo-controlled, pivotal Phase 3 study evaluating the efficacy and safety of tislelizumab + chemotherapy (TIS+C) versus placebo + chemotherapy (PBO+C) in the first line setting in 997 patients with locally advanced unresectable or metastatic G/GEJ cancer.

PD-L1 expression was prospectively assessed in a central laboratory using the TAP scoring algorithm with the VENTANA PD-L1 (SP263) Assay.

Efficacy Summary

- At the pre-specified interim analysis, Study 305 demonstrated a statistically significant and clinically meaningful improvement in OS with TIS+C versus PBO+C in patients with PD-L1 score ≥ 5%. The treatment benefit in OS was accompanied by improvements in the secondary endpoints of PFS and ORR.
- At the final analysis, in patients with PD-L1 score ≥ 5%, the updated OS results were consistent with the primary results at the interim analysis in this population and continued to show a meaningful OS improvement after additional long-term follow up. In the ITT Analysis Set, treatment with TIS+C showed superior OS to PBO+C.
- Subgroup analysis by PD-L1 expression indicated an association between efficacy and PD-L1 expression levels, with a more pronounced treatment benefit for the subgroups with higher level of PD-L1 expression.
  - Subgroup analyses of OS by PD-L1 expression level ≥ 5% (ie, PD-L1 score ≥ 5%, ≥ 5% to < 10% and ≥ 10% subgroups) showed a trend in survival improvement favoring TIS+C over PBO+C.
  - PD-L1 score of 5% was prespecified as stratification factor in the study design and OS in the patients with PD-L1 score ≥ 5% was evaluated as primary endpoint.
- Efficacy results of Study 305, including the primary efficacy analysis in patients with PD-L1 score ≥ 5% and ITT, and further exploratory analyses examining additional PD-L1 expression are comparable with the results seen in other agents in this class.

Safety Summary

- TIS+C showed a tolerable and acceptable safety profile in the first-line treatment of patients with locally advanced unresectable or metastatic G/GEJ adenocarcinoma, which was also consistent with the known safety profile of tislelizumab and other checkpoint inhibitors in combination with chemotherapy.
  - The safety profile of treatment with TIS+C across PD-L1 subgroups of TAP < 5% and ≥ 5% was generally consistent with that reported for the overall population, revealing no increased safety risks or new safety signals for these subgroups.

Company Position

- Study 305 supports a favorable benefit/risk assessment for tislelizumab in combination with platinum and fluoropyrimidine based chemotherapy as 1L

treatment in patients with unresectable, locally advanced or metastatic G/GEJ cancer with tumors with PD-L1 score ≥ 5%.

- 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 Gastric Cancer

GC is the fifth most common cancer worldwide and the fifth leading cause of cancer-related death in 2022.[1] Notably, the prevalence is higher in Eastern Asia than in the rest of world. Worldwide, approximately half of GC cases and deaths are estimated to occur in East Asia, especially in China, which accounted for approximately 40% of diagnoses and deaths (Table 1). In the US, GC is the 16th most common cancer and the 16th most common cause of cancer-related deaths; the incidence has decreased substantially over the past several decades,[2] making GC a relatively uncommon disease in the US.

Adenocarcinoma is the dominant histologic subtype of GC worldwide (approximately 90%), and approximately 75% of the patients with G/GEJ are HER2 negative.[3,4,5] Approximately 80% are true GCs (non-cardia), and the remainder are GEJ cancers (cardia) (the 2 types are referred to together as G/GEJ cancer hereafter, unless otherwise specified).[6]

The prognosis of GC, as a serious and life-threatening malignancy, is poor.[7,8] In most areas worldwide, the overall 5-year relative survival (the ratio of the proportion of observed survivors to the proportion of expected survivors in a comparable set of cancer-free individuals) of GC is about 20% to 30%, except in Japan and South Korea, where early detection screening is widely performed. In the US, fewer than 25% of patients present with early stage (localized disease) GC at diagnosis,[9] and the 5-year survival rate has been 32% if the cancer has extended into the gastric wall or metastasized to locoregional lymph nodes, and only 6% if the tumor has metastasized to distant sites.[10]

Table 1: Summary of GC-related Cases and Deaths in Major Countries/Regions in 2022

Country	New Cases n (%)	Deaths n (%)
World-wide	968,784 (100)	660,175 (100)
China	358,672 (37.0)	260,372 (39.4)
Japan	126,724 (13.1)	43,807 (6.6)
South Korea	29,267 (3.0)	8,517 (1.3)
United States	**25,554 (2.6)**	**10,976 (1.7)**
Europe	135,610 (14.0)	95,431 (14.5)

Source: GLOBOCON 2022[1]

2.2. Current Treatment Options in G/GEJ Cancer

International treatment guidelines are generally consistent in their approach to the treatment of GC. Patient management depends on patient and disease characteristics, mainly the tumor-node-metastasis stage.[3,11,12,13]

For HER2-negative unresectable advanced or metastatic G/GEJ cancer, platinum- and fluoropyrimidine-based chemotherapy regimens formed the backbone therapy in the first line setting in the past decades.[14,15,16,17] However, the efficacy of chemotherapy regimens

resulted in a median PFS of only 5 to 7 months and median OS less than 12 months.[16,18,19,20,21]

In recent years, immune checkpoint inhibitors such as anti-PD-1 antibodies have advanced the treatment of G/GEJ cancer. In 1L settings, nivolumab and pembrolizumab plus platinum- and fluoropyrimidine-based chemotherapy have demonstrated survival benefit over chemotherapy alone both in patients with PD-L1 high expression and in all randomized patients in Phase 3 studies CheckMate-649 and KEYNOTE-859.[22,23] Results from those Phase 3 studies led to approval by the US FDA of nivolumab in combination with chemotherapy as 1L treatment in April 2021 (advanced or metastatic G/GEJ cancer and esophageal adenocarcinoma), and pembrolizumab in combination with chemotherapy in November 2023 (locally advanced unresectable or metastatic HER2-negative GC or GEJ adenocarcinoma).

The subgroup data by PD-L1 status in CheckMate-649 and KEYNOTE-859, however, indicated that PD-L1 expression affects the efficacy of anti-PD-1 antibodies in terms of the magnitude of treatment benefit that was enhanced with increasing PD-L1 expression levels (Table 9). This finding resulted in a debatable benefit/risk assessment in patients with low PD-L1 expression. Therefore, although the FDA has approved nivolumab + chemotherapy and pembrolizumab + chemotherapy for 1L treatment of G/GEJ cancer for an all-comer population, the EMA restricted the indications to patients with PD-L1 CPS ≥ 1 for pembrolizumab + chemotherapy and PD-L1 CPS ≥ 5 for nivolumab + chemotherapy. In addition, NCCN guidelines recommend patients with certain PD-L1 expression levels receive nivolumab + chemotherapy or pembrolizumab + chemotherapy as 1L treatment of G/GEJ cancer, ie, pembrolizumab plus chemotherapy is a Category 1 treatment for patients with PD-L1 CPS ≥ 10 and a Category 2B treatment for patients with PD-L1 CPS 1 to < 10. Nivolumab plus chemotherapy is a Category 1 treatment for patients with PD-L1 CPS ≥ 5.[11]

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 G/GEJ cancer, there is still a need for additional alternative therapeutic options with the potential to prolong OS. BeiGene, Ltd initiated RATIONALE-305 (Study BGB-A317-305; hereafter Study 305) in 2018 as part of the wave of clinical development of immune checkpoint inhibitors for the treatment of this disease. Study 305 showed efficacy and safety results similar to those of nivolumab and pembrolizumab. The option of 1L 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 G/GEJ cancer.

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 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.[25]

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

The clinical development of tislelizumab in G/GEJ cancer 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), both including patients with GC and other solid tumors. The program for tislelizumab plus chemotherapy as 1L treatment of GC started with Phase 2 Study BGB-A317-205, which showed a manageable safety profile and preliminary anticancer activity.

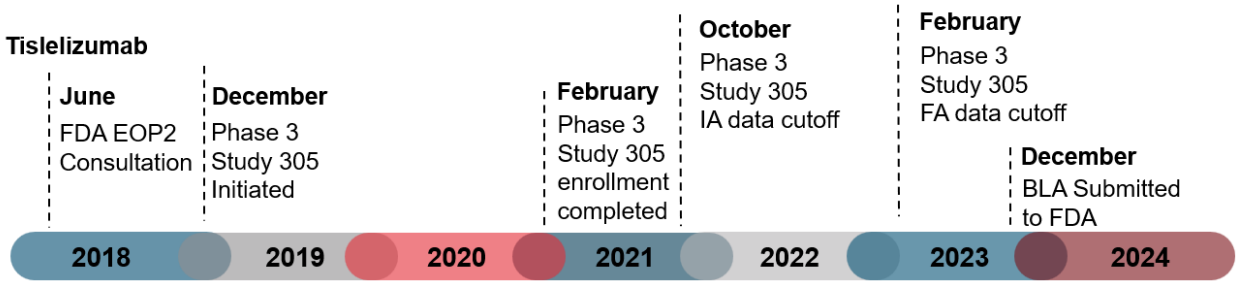
Subsequently, the global pivotal Phase 3 Study 305, initiated in 2018, evaluated the efficacy and safety of tislelizumab + chemotherapy (TIS+C) versus placebo + chemotherapy (PBO+C) in the first line setting in 997 patients with locally advanced unresectable or metastatic G/GEJ cancer.

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 FDA review:

- BLA for the first-line treatment of patients with unresectable recurrent locally advanced or metastatic ESCC (pivotal Study BGB-A317-306, 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 305, submitted on 28 December 2023 and currently under review [PDUFA date: 28 December 2024]).

Figure 1: Tislelizumab Clinical and Regulatory History in GC



4. EVALUATION OF EFFICACY IN STUDY 305

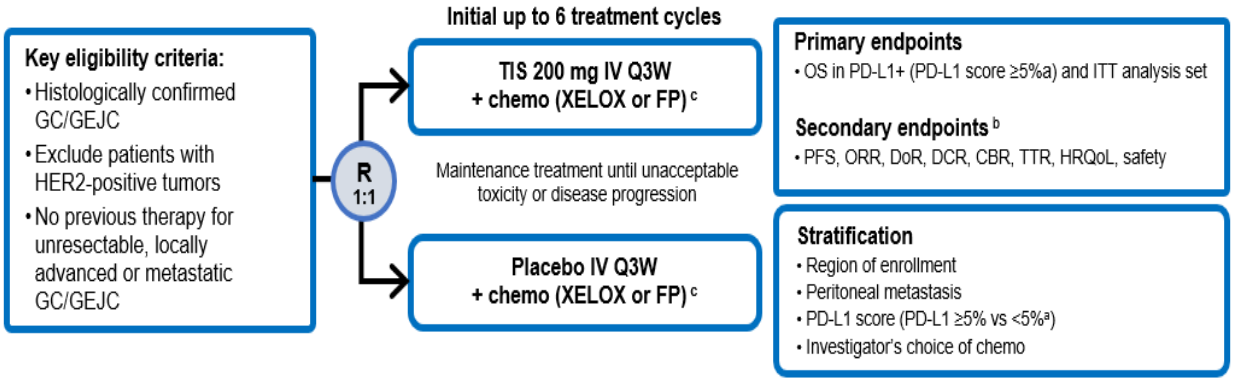
The efficacy of TIS+C for the treatment of patients with advanced unresectable or metastatic G/GEJ cancer is primarily based on data from the prespecified interim analysis of Study 305 and further supported by the final analysis.

4.1. Study 305 Design and Methods

4.1.1. Study Design

Study 305 is a global, multicenter, randomized, double-blind, placebo-controlled, Phase 3 study conducted in 141 clinical sites in 13 countries/regions across Asia, Europe, and North America (Figure 2). Enrolled patients had a histologically confirmed diagnosis of locally advanced unresectable or metastatic G/GEJ cancer and were required to have an ECOG PS score of ≤ 1 and adequate organ function. Patients were enrolled regardless of their tumor PD-L1 expression level.

Figure 2: Study 305 Design



[a] PD-L1 expression status was determined by PD-L1 tumor area positivity (TAP) score 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.
XELOX: Oxaliplatin 130 mg/m^2 IV on Day 1 + capecitabine 1000 mg/m^2 BID Days 1 to 14, Q3W. Oxaliplatin was administered for up to 6 cycles and capecitabine was administered as maintenance therapy at investigator's discretion until disease progression or intolerable toxicity.
FP: Cisplatin 80 mg/m^2 IV Day 1 + 5-FU 800 mg/m^2/day CIV Days 1 to 5, Q3W. Cisplatin and 5-FU were given for up to 6 cycles.

Dual primary endpoints:

- OS in the PD-L1 Positive and ITT Analysis Sets
  - OS was defined as the time from the date of randomization to the date of death due to any cause
  - PD-L1 Positive Set was defined as PD-L1 TAP score ≥ 5%
  - The ITT Analysis Set included all randomized patients

Select secondary endpoints:

- PFS per RECIST v1.1 as assessed by investigators in the PD-L1 Positive and ITT Analysis Sets
  - PFS was defined as the time from the randomization date to disease progression or death, whichever occurred first
- ORR and DOR, per RECIST v1.1 as assessed by investigators

  - ORR was defined as the number of patients whose BOR was confirmed CR or PR divided by the number of randomized patients in each arm.
    - BOR was defined as the best response recorded from randomization until data cut or the start of new anticancer treatment
  - DOR was defined as progression/death-event-free time counted from the first objective response date to the first documented radiological disease progression date/or death date, whichever occurred first
- Safety and tolerability profile of tislelizumab or placebo plus chemotherapy

When a patient reached a 24-month duration of study treatment, 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 during the study treatment period was not allowed.

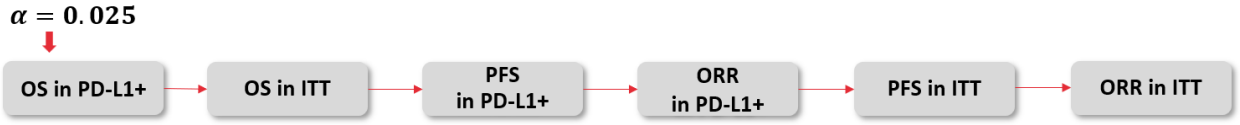
At the pre-specified interim analysis (data cutoff date: 08 October 2021), Study 305 met one of the dual primary endpoints of improved OS with TIS+C in the PD-L1 Positive Analysis Set but not in the ITT Analysis Set. At the planned final analysis (data cutoff date: 28 February 2023), Study 305 met the other dual primary endpoint of OS in the ITT Analysis Set.

4.1.2. Statistical Analysis Methods

The dual primary endpoints were OS in the PD-L1 Positive Set (TAP score ≥ 5% using VENTANA PD-L1 [SP263] Assay) and the ITT Analysis Set (all randomized patients).

Assuming OS true HR of 0.75 in the PD-L1 Positive and 0.8 in the ITT Analysis Sets (with median OS in the control group of 11.5 months) and a 50% PD-L1 Positive prevalence rate, 384 and 768 deaths were required to have 80% and 87% power for superiority testing in the PD-L1 Positive and ITT Analysis Sets, respectively. Assuming a roughly 5% dropout rate, approximately 980 patients were to be enrolled.

OS analysis was performed in the PD-L1 Positive Analysis Set first. OS analysis in the ITT Analysis Set was to be performed only if the OS analysis in the PD-L1 Positive Analysis Set was statistically significant favoring TIS+C. Hypothesis testing of PFS and ORR in the PD-L1 Positive and ITT Analysis Set was to be performed sequentially in the order below. The inferential test would be stopped at the first nonsignificant endpoint.



The study had 1 interim analysis of OS for both efficacy, and futility was planned to be performed when approximately 269 deaths in the PD-L1 Positive Analysis Set and 538 deaths in the ITT Analysis Set (70% of the target number of OS events in each analysis set) had occurred.

Analyses of OS/PFS using the logrank test and a Cox model, which were stratified by region of enrollment (east Asia vs US/EU), presence of peritoneal metastasis (yes vs no), and PD-L1 expression (positive: TAP ≥ 5% vs negative: TAP < 5%, for ITT only). The Cochran Mantel Haenszel test stratified by the same stratification factors above was used to compare the ORR between the 2 treatment arms. Unless otherwise noted, stratified analysis result is reported for

endpoints in the prespecified hypothesis testing sequence, whereas unstratified analysis results are reported for exploratory subgroup analyses of those endpoints.

Exploratory analyses of efficacy and safety endpoints in various PD-L1 subgroups were conducted. Note that this study was neither designed to nor powered for testing treatment benefit in any PD-L1 subgroup except the PD-L1 ≥ 5% subgroup.

4.1.3. PD-L1 Expression Testing

PD-L1 expression was prospectively assessed in a central laboratory using the TAP scoring 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 VENTANA PD-L1 (SP263) Assay.

Selection of the PD-L1 ≥ 5% cutoff was based on a post-hoc analysis of tumors from patients with gastroesophageal adenocarcinoma who were treated with tislelizumab (GEA cohort from Study 001) exclusive of Study 305. The cutoff selection was based on receiver operating characteristic analysis (Youden index optimal cutoff = 5.5, AUC = 0.75 [95% CI = 0.52, 0.99]) and statistical parameters relative to clinical response (confirmed CR/PR) (Sensitivity = 85.7%, Specificity = 54.3%, Positive predictive value = 15.8%, Negative predictive value = 97.4%). At the data cutoff of 26 August 2020 for Study 001, improved ORR, DCR, OS, and PFS were observed in patients with a PD-L1 score ≥ 5% versus PD-L1 < 5 % (Table 2).

Table 2: Clinical Performance With PD-L1 ≥ 5% Cutoff in GEA Cohort of BGB-A317-Study_001 With an Evaluable PD-L1 Score (N = 77)

	TAP score ≥ 5% (n = 38)	TAP score < 5% (n = 39)
ORR (95% CI)	**15.8%** (6.0, 31.3)	**2.6%** (0.1, 13.5)
DCR (95% CI)	**39.5%** (24.0, 56.6)	**20.5%** (9.3, 36.5)
mOS (95% CI)	**6.2** (3.8, 14.7)	**5.3** (3.4, 7.6)
mPFS (95% CI)	**2.1** (1.9, 3.8)	**1.9** (1.5, 2.1)
Sensitivity/Specificity	**85.7% / 54.3%**	
PPV/NPV	**15.8% / 97.4%**	

Data cutoff: 26AUG2020.
ORR = CR+PR, DCR = CR+PR+SD (Non-CR/Non-PD).
Exact Clopper-Pearson 2-sided confidence interval.
Sensitivity = No. of confirmed responders in patients with PD-L1 score ≥ 5% / Total No. of responder
Specificity = No. of non-responders in patients with PD-L1 score < 5% / Total No. of non-responder
PPV = Positive predictive value; Percent of responders within patients with PD-L1 score ≥ 5%
NPV = Negative predictive value; Percent of non-responders within patients with PD-L1 score < 5%

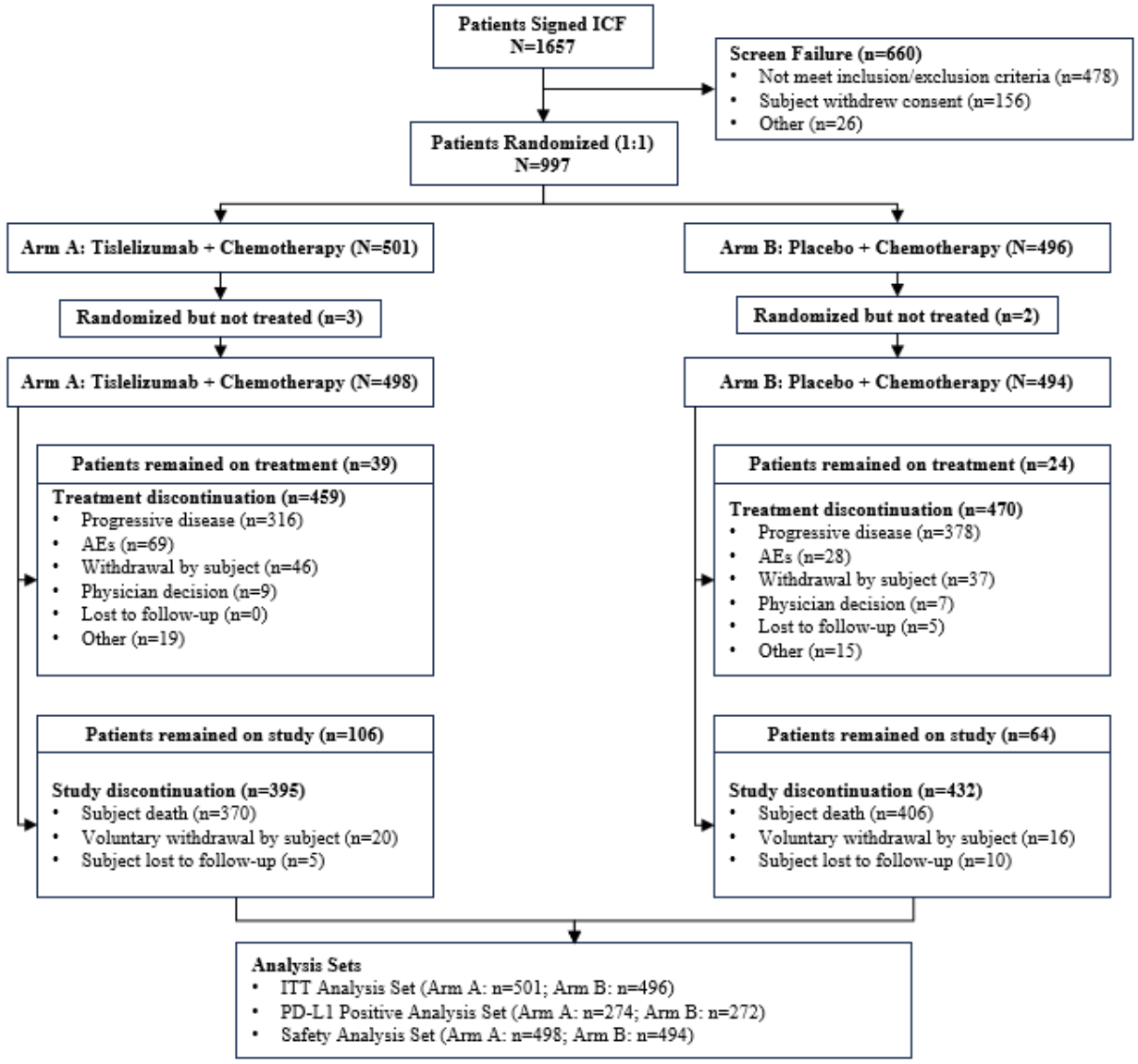
Prior to assessment of PD-L1 status in the BGB-A317-305 study, which used PD-L1 status as a stratification factor, the VENTANA PD-L1 (SP263) IHC Assay using a ≥ 5% cutoff was analytically validated for G/GEJ cancer in order to demonstrate the assay robustness for the intended patient population. While the VENTANA PD-L1 (SP263) Assay is FDA-approved in multiple indications, the assay is currently not FDA-approved for use in G/GEJ cancer.[25]

4.2. Study 305 Patient Disposition

The study randomized 997 patients (ITT Analysis Set) to treatment with TIS+C or PBO+C (Figure 3). Approximately 55% of patients had tumors with a PD-L1 score ≥ 5% (ie, the PD-L1 Positive Analysis Set).

At the interim (data cutoff: 08 October 2021) and final analyses (data cutoff: 28 February 2023), the minimum study follow-up time (ie, the time between the date of the last patient randomized and the data cut-off) was 7.9 months and 24.6 months, respectively.

Figure 3: Study 305 Patient Disposition at the Final Analysis



Data cutoff: 28FEB2023.

4.3. Study 305 Demographics and Baseline Characteristic

The enrolled patients were representative of the target patient population. Specifically, the age (median 61.0 years), sex distribution (69.4% male), and primary cancer site (stomach: 80.2%) were generally in line with the epidemiology of G/GEJ cancer globally. Reflective of the geographic incidence of G/GEJ, the majority of patients (75.0%) were enrolled from East Asia.

Baseline characteristics were generally balanced between treatment arms, without noteworthy differences (Table 3).

Table 3: Baseline Characteristics at the Final Analysis (ITT Analysis Set)

Parameter	PD-L1 Score ≥ 5%			ITT Analysis Set		
	TIS+C (N = 274)	PBO+C (N = 272)	Total (N = 546)	TIS+C (N = 501)	PBO+C (N = 496)	Total (N = 997)
Age Group, ≥ 65 years, n (%)	99 (36.1)	115 (42.3)	214 (39.2)	161 (32.1)	183 (36.9)	344 (34.5)
Age median, years	61.0	62.0	62.0	60.0	61.0	61.0
Sex, n (%)						
Female	81 (29.6)	71 (26.1)	152 (27.8)	155 (30.9)	150 (30.2)	305 (30.6)
Male	193 (70.4)	201 (73.9)	394 (72.2)	346 (69.1)	346 (69.8)	692 (69.4)
ECOG Status, n (%)						
0	98 (35.8)	86 (31.6)	184 (33.7)	169 (33.7)	154 (31.0)	323 (32.4)
1	176 (64.2)	186 (68.4)	362 (66.3)	332 (66.3)	342 (69.0)	674 (67.6)
Race, n (%)						
Asian	202 (73.7)	201 (73.9)	403 (73.8)	376 (75.0)	372 (75.0)	748 (75.0)
White	64 (23.4)	62 (22.8)	126 (23.1)	116 (23.2)	107 (21.6)	223 (22.4)
Not Reported	7 (2.6)	8 (2.9)	15 (2.7)	8 (1.6)	16 (3.2)	24 (2.4)
Other/Unknown	1 (0.4)	1 (0.4)	2 (0.4)	1 (0.2)	1 (0.2)	2 (0.2)
Region, n (%)						
East Asia	202 (73.7)	201 (73.9)	403 (73.8)	376 (75.0)	372 (75.0)	748 (75.0)
China (including Taiwan)	133 (48.5)	132 (48.5)	265 (48.5)	259 (51.7)	257 (51.8)	516 (51.8)
Japan	38 (13.9)	35 (12.9)	73 (13.4)	50 (10.0)	51 (10.3)	101 (10.1)
South Korea	31 (11.3)	34 (12.5)	65 (11.9)	67 (13.4)	64 (12.9)	131 (13.1)
US/Europe	72 (26.3)	71 (26.1)	143 (26.2)	125 (25.0)	124 (25.0)	249 (25.0)
US	5 (1.8)	8 (2.9)	13 (2.4)	10 (2.0)	15 (3.0)	25 (2.5)
Europe	67 (24.5)	63 (23.2)	130 (23.8)	115 (23.0)	109 (22.0)	224 (22.5)
Time from Initial Diagnosis to Study Entry, median (months)	1.3	1.4	1.4	1.5	1.6	1.6
Metastatic Disease at Screening, n (%)	270 (98.5)	268 (98.5)	538 (98.5)	494 (98.6)	490 (98.8)	984 (98.7)
Primary Location, n (%)						
Gastro-Esophageal Junction	51 (18.6)	59 (21.7)	110 (20.1)	96 (19.2)	100 (20.2)	196 (19.7)
Stomach	223 (81.4)	213 (78.3)	436 (79.9)	405 (80.8)	395 (79.6)	800 (80.2)
Had Liver Metastases, n (%)	121 (44.2)	117 (43.0)	238 (43.6)	190 (37.9)	188 (37.9)	378 (37.9)
Had Presence of Peritoneal Metastasis, n (%)	110 (40.1)	107 (39.3)	217 (39.7)	220 (43.9)	214 (43.1)	434 (43.5)

Parameter	PD-L1 Score ≥ 5%			ITT Analysis Set		
	TIS+C (N = 274)	PBO+C (N = 272)	Total (N = 546)	TIS+C (N = 501)	PBO+C (N = 496)	Total (N = 997)
Number of Metastatic Sites at Study Entry, n (%)						
0 - 2	183 (66.8)	180 (66.2)	363 (66.5)	335 (66.9)	335 (67.5)	670 (67.2)
≥ 3	91 (33.2)	92 (33.8)	183 (33.5)	166 (33.1)	160 (32.3)	326 (32.7)
Prior Gastrectomy/ Esophagectomy, n (%)	50 (18.2)	56 (20.6)	106 (19.4)	133 (26.5)	139 (28.0)	272 (27.3)
Patients With at Least One Prior Adjuvant/Neo-Adjuvant Systemic Therapy for Cancer, n (%)	39 (14.2)	38 (14.0)	77 (14.1)	107 (21.4)	100 (20.2)	207 (20.8)
ICC Option per IRT, n (%)						
Oxaliplatin + Capecitabine	254 (92.7)	254 (93.4)	508 (93.0)	466 (93.0)	465 (93.8)	931 (93.4)
Cisplatin + 5-Fluorouracil	20 (7.3)	18 (6.6)	38 (7.0)	35 (7.0)	31 (6.3)	66 (6.6)

Data cutoff: 28FEB2023.

4.4. Study 305 Efficacy Results in the Prespecified Analysis Sets

4.4.1. Primary Endpoint: Overall Survival

Protocol-Planned Interim Analysis

- TIS+C demonstrated a statistically significant and clinically meaningful improvement in OS compared with PBO+C in patients with PD-L1 score ≥ 5% (Table 4; Figure 4a).
- Stratified HR: 0.74 (95% CI: 0.59 to 0.94), representing a 26% reduction in the risk of death
- 1-sided p-value: 0.0056 (stratified log-rank test)
- Median OS was prolonged by 4.6 months (17.2 vs 12.6 months)

This benefit in OS was seen even though fewer patients treated with TIS+C than PBO+C were reported as having received subsequent chemotherapy (41.2% vs 51.8%), targeted therapy (24.1% vs 31.3%), and immunotherapy (6.9% vs 14.0%).

Protocol-Planned Final Analysis

TIS+C demonstrated a clinically meaningful and statistically significant improvement in OS compared with PBO+C in the ITT Analysis Set (Table 4; Figure 4c).

- Stratified HR: 0.80 (95% CI: 0.70 to 0.92), representing a 20% reduction in the risk of death
- 1-sided p-value: 0.0011 (stratified log-rank test)
- Median OS was prolonged by 2.1 months (15.0 vs 12.9 months)

Similar to the observation in patients with PD-L1 score ≥ 5% at the interim analysis, fewer patients treated with TIS+C than PBO+C received subsequent chemotherapy (50.1% vs 56.5%), targeted therapy (29.9% vs 32.3%), and immunotherapy (12.4% vs 18.1%).

In patients with PD-L1 score ≥ 5% at final analysis, the updated OS results were consistent with the interim analysis. The data continued to show a meaningful OS improvement with TIS+C versus PBO+C, indicating a sustained OS benefit with TIS+C in patients with PD-L1 score ≥ 5% (Table 4; Figure 4b).

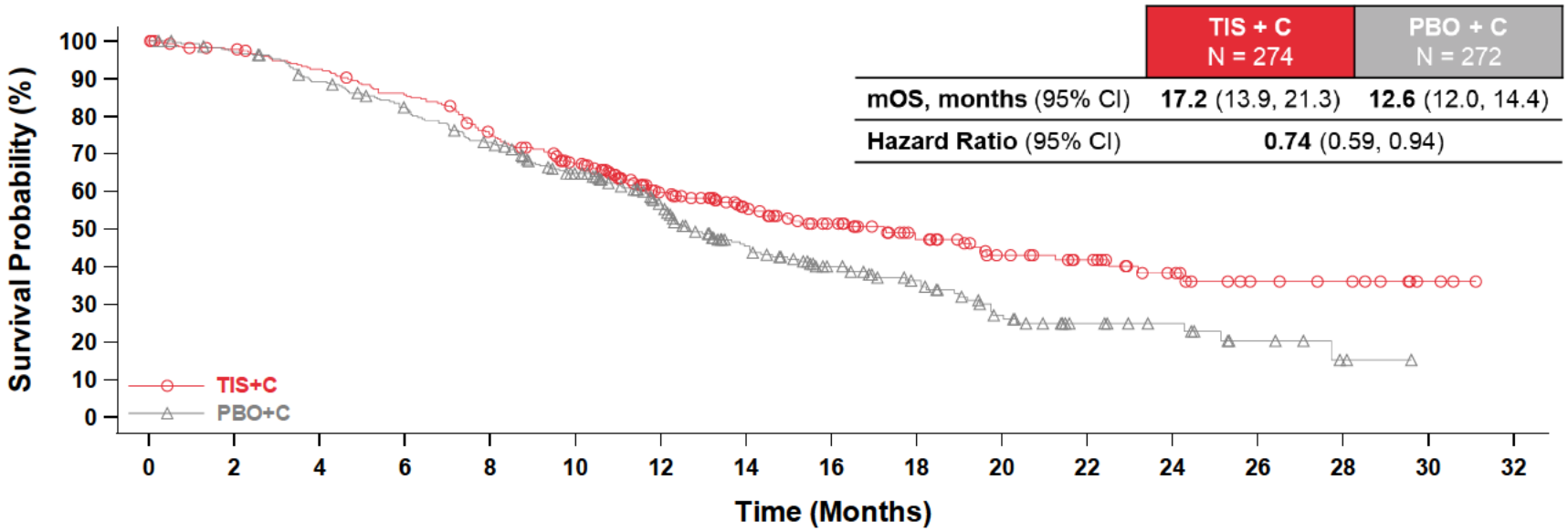
Table 4: Summary of Primary Endpoint: Overall Survival in the PD-L1 Positive and ITT Analysis Sets

	PD-L1 Score ≥ 5% (Interim Analysis)		PD-L1 Score ≥ 5% (Final Analysis)		ITT Analysis Set (Final Analysis)	
	TIS+C (N = 274)	PBO+C (N = 272)	TIS+C (N = 274)	PBO+C (N = 272)	TIS+C (N = 501)	PBO+C (N = 496)
Number of Patients						
Death, n (%)	130 (47.4)	161 (59.2)	192 (70.1)	219 (80.5)	370 (73.9)	406 (81.9)
One-Sided Stratified Log-Rank Test P-value	0.0056		-		0.0011	
Stratified Hazard Ratio (95% CI)	0.74 (0.59, 0.94)		0.71 (0.58, 0.86)		0.80 (0.70, 0.92)	
Median OS (95% CI), months	17.2 (13.9, 21.3)	12.6 (12.0, 14.4)	16.4 (13.6, 19.1)	12.8 (12.0, 14.5)	15.0 (13.6, 16.5)	12.9 (12.1, 14.1)
OS Rate at, % (95% CI)						
12 months	59.8 (53.4, 65.5)	56.7 (50.3, 62.6)	59.3 (53.2, 65.0)	56.4 (50.2, 62.2)	57.9 (53.4, 62.2)	55.3 (50.8, 59.7)
24 months	38.3 (29.9, 46.6)	24.9 (18.1, 32.3)	37.8 (31.9, 43.6)	21.1 (16.3, 26.3)	32.7 (28.5, 36.9)	23.4 (19.7, 27.3)
36 months	36.1 (27.1, 45.0)	NE (NE, NE)	25.6 (20.0, 31.5)	14.7 (10.4, 19.6)	21.3 (17.4, 25.5)	12.9 (9.8, 16.4)

Interim Analysis: Data cutoff: 08OCT2021. Final Analysis: Data cutoff: 28FEB2023.
Percentages were based on N.

Figure 4: Kaplan-Meier Plots of Overall Survival at the Interim and Final Analyses (PD-L1 Positive and ITT Analysis Sets)

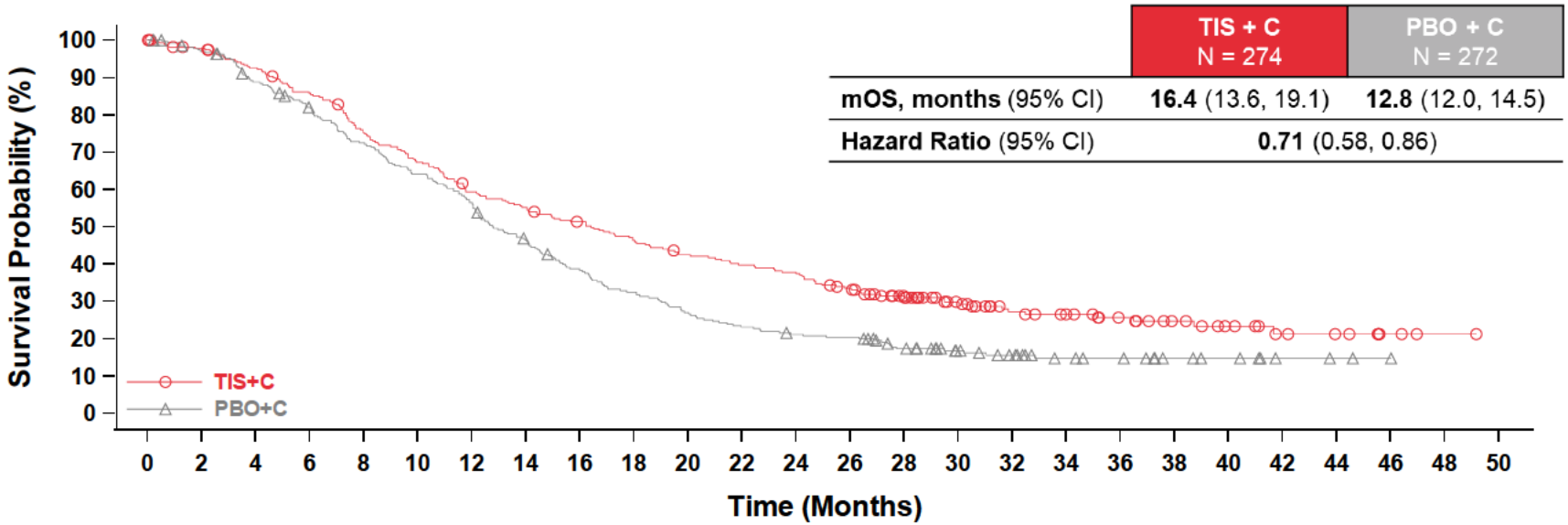
a) PD-L1 Tap Score ≥ 5% (Interim Analysis)



No. At Risk:

TIS+C	274	262	246	227	196	167	122	93	70	52	38	30	19	11	9	3	0
PBO+C	272	261	237	215	189	156	118	80	57	44	26	16	12	6	2	0	0

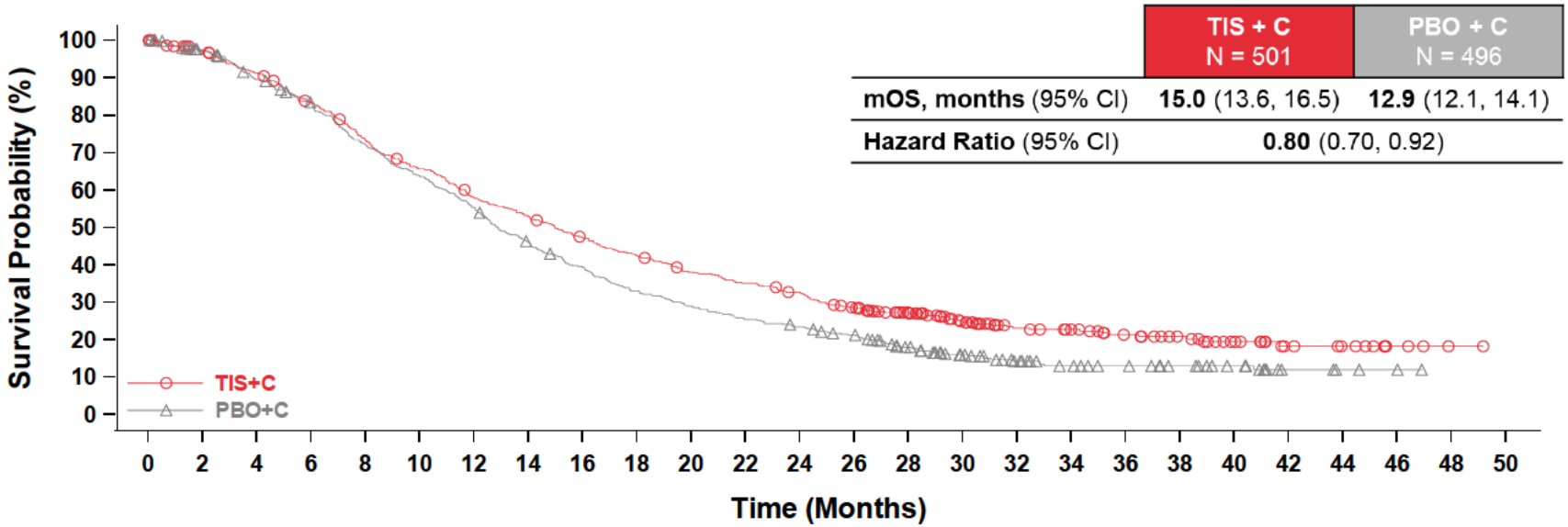
b) PD-L1 TAP Score ≥ 5% (Final Analysis)



No. At Risk:

TIS+C	274	263	247	228	199	178	156	145	133	120	109	102	97	84	68	50	38	34	27	19	14	9	7	3	1	0
PBO+C	272	261	236	215	190	168	148	120	99	83	69	59	53	51	39	29	23	16	14	9	7	3	2	1	0	0

c) ITT Analysis Set (Final Analysis)



No. At Risk:

TIS+C	501	477	445	404	355	316	278	254	226	202	179	165	152	130	107	77	59	53	43	31	22	13	10	4	1	0
PBO+C	496	472	431	398	344	304	264	218	186	155	136	119	109	96	73	52	39	29	25	20	15	6	3	2	0	0

Interim Analysis: Data cutoff: 08OCT2021. Final Analysis: Data cutoff: 28FEB2023.

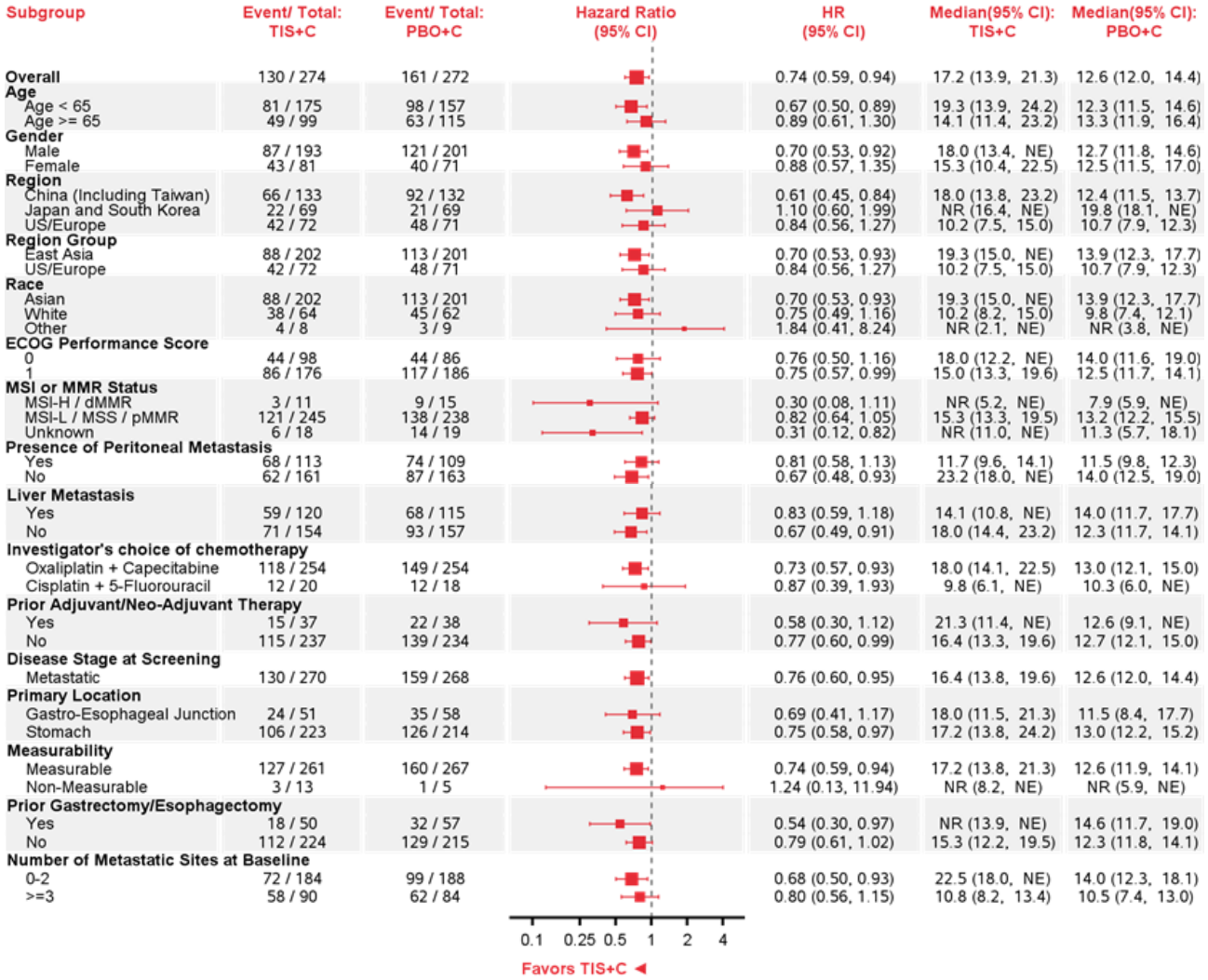
4.4.1.1. Overall Survival by Predefined Subgroups

At the interim analysis, a consistent trend in OS favoring TIS+C over PBO+C (ie, HR < 1) was observed across most of the predefined subgroups within the patients with PD-L1 score ≥ 5% (Figure 5). The inconsistent results observed in the non-measurable subgroup and the subgroup of "other race" were likely chance observations due to small subgroup sample size. The inconsistent OS result in the subgroup of "Japan and South Korea" was probably impacted by lower maturity at the interim analysis.

Moreover, after longer follow-up beyond the interim analysis, the inconsistent findings in the HR of OS observed in a few subgroups at the interim analysis change to favor TIS+C (ie, HR changed from > 1 to < 1) at the final analysis, including in the subgroup of "Japan and South Korea" and the subgroup of "other race" (Figure 14).

At the final analysis, a consistent direction in OS favoring TIS+C over PBO+C (ie, HR < 1) was observed across most prespecified subgroups in the ITT Analysis Set, including subgroups of ICC options (oxaliplatin plus capecitabine vs cisplatin plus 5-FU), regions (East Asia vs US/Europe and China vs Japan and South Korea vs US/Europe), and baseline PD-L1 score (PD-L1 score ≥ 5% vs PD-L1 score < 5%) (Figure 13).

Figure 5: Forest Plot of Overall Survival - Subgroup Analysis at the Interim Analysis (PD-L1 Positive Analysis Set)



Data cutoff: 08OCT2021. Hazard ratio (TIS+C vs. PBO+C) was based on unstratified Cox regression model only including treatment as a covariate, except for Overall population for which stratified hazard ratio is displayed.

4.4.2. Secondary Endpoints: PFS, ORR, and DOR

Interim Analysis

According to the prespecified testing hierarchy of the secondary endpoints (Section 4.1.2), PFS analysis in patients with PD-L1 score ≥ 5% was conducted using data from the interim analysis at the time of final analysis.

In patients with PD-L1 score ≥ 5%, a statistically significant and clinically meaningful improvement in PFS with TIS+C over PBO+C was observed, with a stratified HR of 0.67 (95% CI: 0.55 to 0.83), a 1-sided p-value < 0.0001 from stratified log-rank test; and median PFS of 7.2 versus 5.9 months (Table 5; Figure 6).

TIS+C showed a greater antitumor response than PBO+C in patients with PD-L1 score ≥ 5%. The ORR as assessed by the investigator was higher with TIS+C than PBO+C (50.4% vs 43.0%) (Table 5).

Final Analysis

TIS+C showed an improvement in PFS compared with PBO+C (stratified HR: 0.78 [95% CI: 0.67 to 0.90], median PFS: 6.9 months vs 6.2 months) in ITT analysis set (Table 5; Figure 6).

TIS+C showed a greater antitumor response than PBO+C in the ITT Analysis Set at the final analysis (ORR: 47.3% in TIS+C vs 40.5% in PBO+C) (Table 5).

The updated secondary endpoints of PFS and ORR in patients with PD-L1 score ≥ 5% at final analysis remained consistent with those of the interim analysis after additional long-term follow-up, and continued to show improvements in PFS and ORR with TIS+C over PBO+C (Table 5; Figure 6).

Median DOR in different PD-L1 subgroups are presented in Table 5.

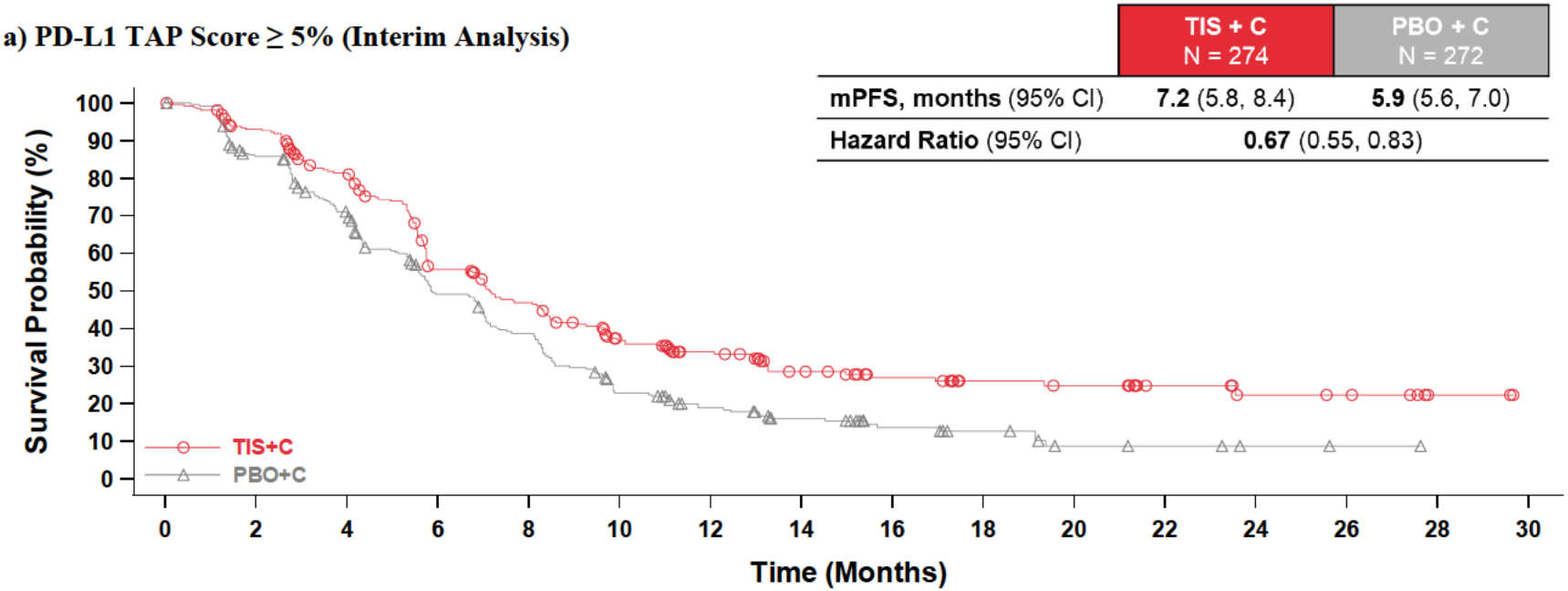
Table 5: Summary of Secondary Efficacy Endpoints at the Interim and Final Analyses (PD-L1 Positive and ITT Analysis Sets)

	PD-L1 Score ≥ 5% (Interim Analysis)		PD-L1 Score ≥ 5% (Final Analysis)		ITT Analysis Set (Final Analysis)	
	TIS+C (N = 274)	PBO+C (N = 272)	TIS+C (N = 274)	PBO+C (N = 272)	TIS+C N = 501	PBO+C N = 496
PFS per investigator						
Events, n (%)	169 (61.7)	206 (75.7)	189 (69.0)	216 (79.4)	361 (72.1)	391 (78.8)
One-Sided Stratified Log-Rank Test P-value	< 0.0001		-		-	
Stratified Hazard Ratio (95% CI)	0.67 (0.55, 0.83)		0.68 (0.56, 0.83)		0.78 (0.67, 0.90)	
Median PFS (95% CI) months	7.2 (5.8, 8.4)	5.9 (5.6, 7.0)	7.2 (5.8, 8.4)	5.9 (5.6, 7.0)	6.9 (5.7, 7.2)	6.2 (5.6, 6.9)
ORR, n	138	117	141	116	237	201
% (95% CI)	50.4 (44.3, 56.4)	43.0 (37.1, 49.1)	51.5 (45.4, 57.5)	42.6 (36.7, 48.8)	47.3 (42.9, 51.8)	40.5 (36.2, 45.0)
Odds Ratio, (95% CI)	1.36 (0.97, 1.92)		1.45 (1.03, 2.04)		1.33 (1.03, 1.72)	
Difference, % (95% CI)	7.4 (-0.8, 15.6)		8.9 (0.7, 17.0)		6.8 (0.8, 12.9)	
DOR, n	138	117	141	116	237	201
Events, n (%)	72 (52.2)	78 (66.7)	92 (65.2)	84 (72.4)	158 (66.7)	148 (73.6)
Median (95% CI) months	9.0 (8.2, 19.4)	7.1 (5.7, 8.3)	10.0 (8.2, 16.8)	6.9 (5.7, 8.5)	8.6 (7.9, 11.1)	7.2 (6.0, 8.5)

Interim Analysis: Data cutoff: 08OCT2021. Final Analysis: Data cutoff: 28FEB2023.
Percentages were based on N. Percentages for events in the duration of response were based on number of confirmed responders (CR and PR)

Figure 6: Kaplan-Meier Plot of Progression-Free Survival at the Interim and Final Analyses (PD-L1 Positive and ITT Analysis Sets)

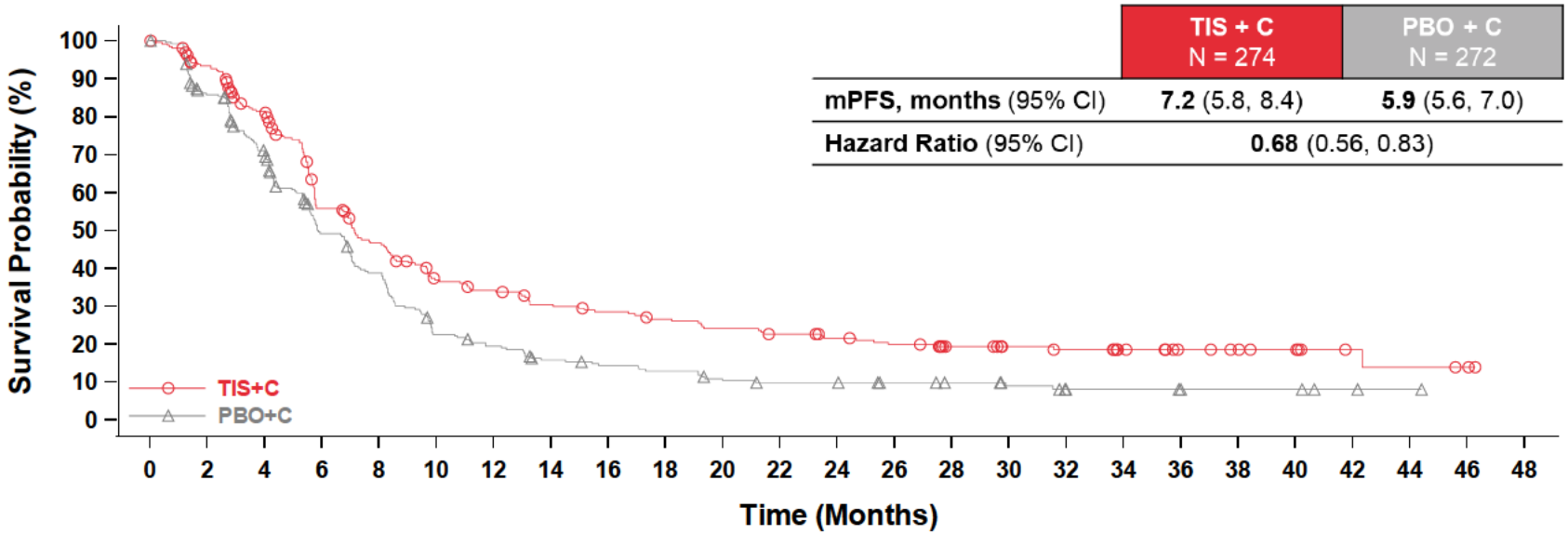
a) PD-L1 TAP Score ≥ 5% (Interim Analysis)



No. At Risk:

TIS+C	274	236	199	130	106	74	57	40	31	21	19	12	8	7	2	0
PBO+C	272	219	176	114	89	50	35	25	15	11	5	4	2	1	0	0

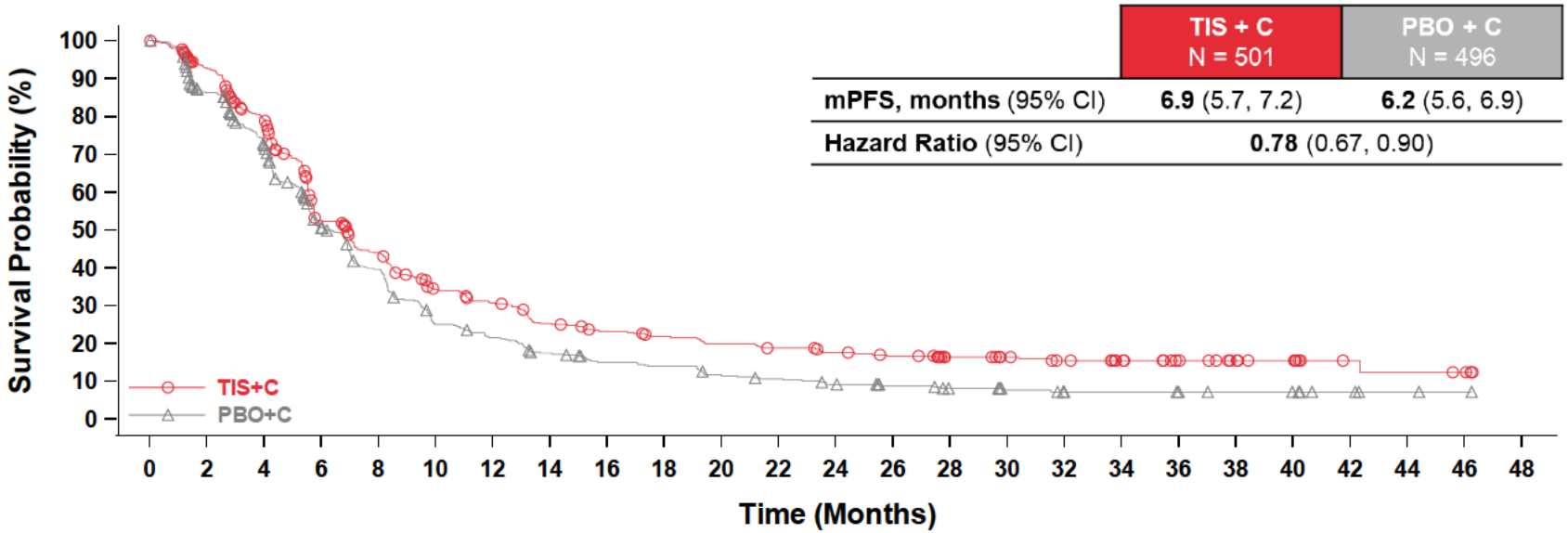
b) PD-L1 TAP Score ≥ 5% (Final Analysis)



No. At Risk:

TIS+C	274	237	200	131	107	81	74	64	59	54	49	45	40	36	28	24	22	18	13	11	8	4	3	2	0
PBO+C	272	219	176	114	89	51	43	33	29	26	21	18	18	15	13	10	7	6	5	4	4	2	1	0	0

c) ITT Analysis Set (Final Analysis)



No. At Risk:

TIS+C	501	434	361	226	184	136	120	97	86	79	72	67	60	55	41	37	32	27	21	16	12	5	4	3	0
PBO+C	496	399	327	211	161	100	85	67	55	51	42	37	31	26	21	16	13	11	10	8	7	4	2	1	0

Interim Analysis: Data cutoff: 08OCT2021. Final Analysis: Data cutoff: 28FEB2023.

4.5. Study 305 Efficacy Results in Patients by PD-L1 Expression Assessed by TAP Assay

In support of the treatment benefit/risk assessment of TIS+C in patients with advanced or metastatic G/GEJ cancer, exploratory subgroup analyses were performed by PD-L1 TAP score of 1% and 10%, as well as ≥ 1% to < 5% and ≥ 5% to < 10%, using the data from the final analysis (data cutoff date: 28 February 2023).

4.5.1. Patient Distribution

All patients had evaluable PD-L1 expression status (Table 6). One of the randomization stratification factors was PD-L1 TAP score ≥ 5% and < 5%.

Table 6: Patient Distribution by PD-L1 TAP Expression

PD-L1 subgroup	Total (N = 997) n (%)
< 1%	112 (11.2)
≥ 1%	885 (88.8)
< 5%	451 (45.2)
≥ 5%	546 (54.8)
< 10%	716 (71.8)
≥ 10%	281 (28.2)
≥ 1% to < 5%	339 (34.0)
≥ 5% to < 10%	265 (26.6)

4.5.2. Demographics and Baseline Characteristic in PD-L1 TAP Score Subgroups

Although because of the limitation of sample size in the exploratory PD-L1 subgroups, a few random imbalances in baseline characteristics were noted between arms in a small number of subgroups, the demographics and key baseline characteristics were generally balanced between treatment arms across most of PD-L1 subgroups (Table 10Table). A multivariate adjustment analysis to adjust the baseline numerical unbalances between treatment arms is presented in Section 4.5.3.2.

4.5.3. Efficacy Results

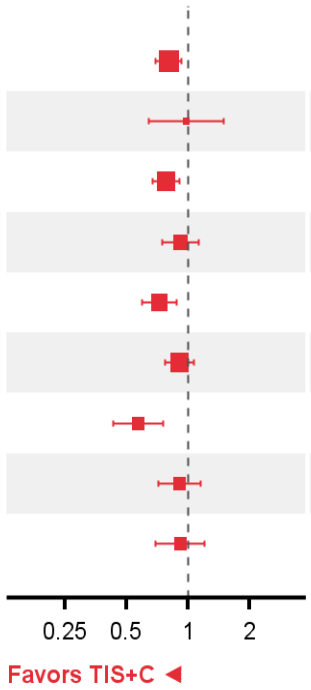
4.5.3.1. Overall Survival

The magnitude of OS improvement with the treatment of TIS+C over PBO+C was enhanced with increasing PD-L1 expression levels (Figure 7). Kaplan-Meier curves by baseline PD-L1 scores are provided in Figure 4, Figure 15, Figure 16, Figure 17, and Figure 18. Specifically, subgroup analyses of OS by PD-L1 expression levels ≥ 5% (ie, PD-L1 score ≥ 5%, 5% to < 10% and ≥ 10% subgroups) showed a trend in survival improvement favoring TIS+C over PBO+C:

Similar to the observation in patients with PD-L1 TAP score ≥ 5% and the ITT Analysis Set, the proportion of patients in the TIS+C treatment arm who received subsequent immunotherapy was numerically lower than in the PBO+C treatment arm in all PD-L1 subgroups (Table 11).

Figure 7: Forest Plot of Overall Survival by Baseline PD-L1 TAP Score at the Final Analysis

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	370 / 501	406 / 496	0.80 (0.70, 0.92)	15.0 (13.6, 16.5)	12.9 (12.1, 14.1)
< 1%	52 / 69	36 / 43	0.98 (0.64, 1.50)	15.4 (8.4, 19.2)	13.8 (10.2, 17.8)
>= 1%	318 / 432	370 / 453	0.78 (0.67, 0.90)	15.0 (13.3, 16.7)	12.8 (12.1, 14.1)
< 5%	178 / 227	187 / 224	0.91 (0.74, 1.12)	14.1 (11.9, 15.6)	12.9 (11.3, 14.7)
>= 5%	192 / 274	219 / 272	0.72 (0.59, 0.88)	16.4 (13.6, 19.1)	12.8 (12.0, 14.5)
< 10%	286 / 365	288 / 351	0.91 (0.77, 1.07)	14.0 (12.0, 15.3)	13.0 (12.1, 14.3)
>= 10%	84 / 136	118 / 145	0.57 (0.43, 0.76)	22.5 (16.4, 26.4)	12.3 (11.3, 14.9)
1% - < 5%	126 / 158	151 / 181	0.90 (0.71, 1.14)	13.8 (11.5, 15.6)	12.9 (10.8, 14.7)
5% - < 10%	108 / 138	101 / 127	0.91 (0.70, 1.20)	13.8 (10.8, 16.2)	13.3 (12.0, 15.0)



Data cutoff: 28FEB2023. Hazard ratio (TIS+C vs. PBO+C) was based on unstratified Cox regression model only including treatment as a covariate, except for Overall population for which stratified hazard ratio is displayed.

4.5.3.2. Overall Survival Analysis Adjusted for Baseline Covariates

A multivariate adjusted analysis was performed using an unstratified Cox regression model that adjusted for treatment, ECOG PS, liver metastasis, number of metastatic organs (0-2 vs ≥ 3), prior gastrectomy/esophagectomy (yes vs no), regions (east Asia vs US/Europe), and presence of peritoneal metastasis as covariates to assess the impact of those numerical imbalances observed between the 2 treatment arms (as described in Section 4.5.1). The analysis found no major impact caused by baseline numerical imbalances between arms to the OS results in any of the PD-L1 subgroups (Table 13).

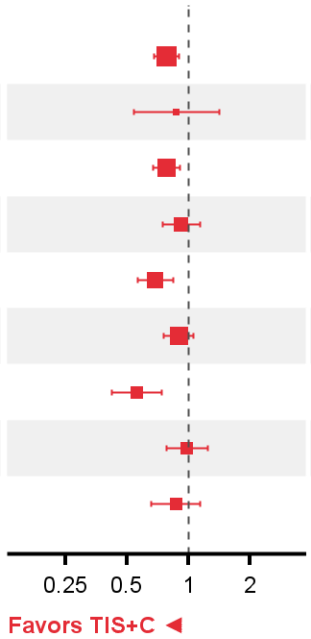
4.5.3.3. Other Secondary Endpoints by PD-L1 Status: PFS, ORR, and DOR

4.5.3.3.1. Progression-Free Survival

Similar to OS, the magnitude of PFS improvement with TIS+C over PBO+C was enhanced with increasing PD-L1 expression levels (Figure 8). Kaplan-Meier curves by baseline PD-L1 expression levels are provided in Figure 6, Figure 19, Figure 20, Figure 21, and Figure 22. Specifically, subgroup analyses of PFS by PD-L1 expression levels ≥ 5% (ie, PD-L1 score ≥ 5%, ≥ 5% to < 10% and ≥ 10% subgroups) showed a numerical improvement in PFS favoring TIS+C over PBO+C:

Figure 8: Forest Plot of Progression-Free Survival by Baseline PD-L1 TAP Score at the Final Analysis

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	361 / 501	391 / 496	0.78 (0.67, 0.90)	6.9 (5.7, 7.2)	6.2 (5.6, 6.9)
< 1%	45 / 69	27 / 43	0.87 (0.54, 1.41)	7.9 (5.6, 9.7)	6.9 (5.6, 15.0)
>= 1%	316 / 432	364 / 453	0.78 (0.67, 0.91)	6.9 (5.7, 7.2)	5.9 (5.6, 6.9)
< 5%	172 / 227	175 / 224	0.92 (0.75, 1.14)	5.7 (5.6, 7.0)	6.5 (5.5, 7.1)
>= 5%	189 / 274	216 / 272	0.69 (0.57, 0.84)	7.2 (5.8, 8.4)	5.9 (5.6, 7.0)
< 10%	273 / 365	272 / 351	0.90 (0.76, 1.06)	5.7 (5.6, 7.0)	6.9 (5.7, 7.1)
>= 10%	88 / 136	119 / 145	0.56 (0.42, 0.74)	9.0 (7.0, 12.1)	5.7 (4.5, 6.9)
1% - < 5%	127 / 158	148 / 181	0.98 (0.78, 1.25)	5.6 (5.1, 6.9)	6.2 (5.5, 7.1)
5% - < 10%	101 / 138	97 / 127	0.86 (0.65, 1.14)	5.8 (5.6, 7.7)	6.9 (5.7, 8.3)



Data cutoff: 28FEB2023. Hazard ratio (TIS+C vs. PBO+C) was based on unstratified Cox regression model only including treatment as a covariate, except for Overall population for which stratified hazard ratio is displayed.

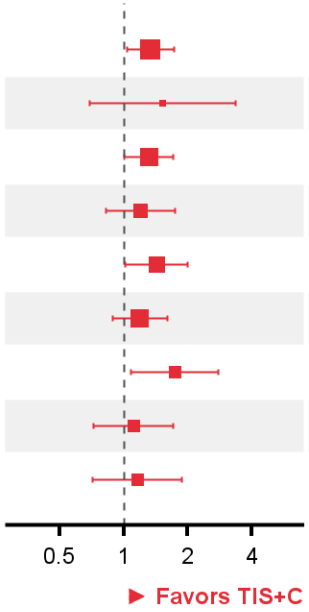
4.5.3.3.2. **Objective Response Rate and Duration of Response**

Numerically higher ORR with TIS+C over PBO+C was observed in all prespecified and exploratory PD-L1 subgroups (Figure 9).

Median DOR in different PD-L1 subgroups are presented in Table 12.

Figure 9: Forest Plot of Overall Response Rate by Baseline PD-L1 TAP Score at the Final Analysis

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	237 / 501	201 / 496	1.33 (1.03, 1.72)	47.3 (42.9, 51.8)	40.5 (36.2, 45.0)
< 1%	31 / 69	15 / 43	1.52 (0.69, 3.34)	44.9 (32.9, 57.4)	34.9 (21.0, 50.9)
>= 1%	206 / 432	186 / 453	1.31 (1.00, 1.71)	47.7 (42.9, 52.5)	41.1 (36.5, 45.7)
< 5%	96 / 227	85 / 224	1.20 (0.82, 1.75)	42.3 (35.8, 49.0)	37.9 (31.6, 44.7)
>= 5%	141 / 274	116 / 272	1.43 (1.02, 2.00)	51.5 (45.4, 57.5)	42.6 (36.7, 48.8)
< 10%	164 / 365	143 / 351	1.19 (0.88, 1.60)	44.9 (39.8, 50.2)	40.7 (35.6, 46.1)
>= 10%	73 / 136	58 / 145	1.74 (1.08, 2.79)	53.7 (44.9, 62.3)	40.0 (32.0, 48.5)
1% - < 5%	65 / 158	70 / 181	1.11 (0.72, 1.71)	41.1 (33.4, 49.2)	38.7 (31.5, 46.2)
5% - < 10%	68 / 138	58 / 127	1.16 (0.71, 1.87)	49.3 (40.7, 57.9)	45.7 (36.8, 54.7)



Data cutoff: 28FEB2023. Odds ratio (TIS+C vs. PBO+C) was based on unstratified Cochran-Mantel-Haenszel method, except for Overall population for which stratified odds ratio is displayed.

4.6. Exploratory Analysis by PD-L1 Expression Using CPS

Beyond PD-L1 assessment by TAP score per Study 305 protocol, CPS has also been used in clinical trials investigating PD-1 inhibitors in G/GEJ cancer. Both the TAP and CPS scoring methods assess PD-L1 expression on tumor cells and immune cells, with the 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 305 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 974 evaluable patients for PD-L1 by CPS (Table 7); 23 patients with evaluable TAP score were not evaluable for CPS scoring mainly because of insufficient tumor cells, tissue falling off, and staining fading.

The proportion of patients by baseline PD-L1 CPS cutoffs (1, 5 and 10) and by PD-L1 CPS categories (≥ 1 to < 5 and ≥ 5 to < 10) were similar to those for PD-L1 TAP (Table 6).

Table 7: Patient Distribution by PD-L1 CPS Expression

PD-L1 subgroup	Total (N = 974) n (%)
< 1	120 (12.3)
≥ 1	854 (87.7)
< 5	451 (46.3)
≥ 5	523 (53.7)
< 10	685 (70.3)
≥ 10	289 (29.7)
≥ 1 to < 5	331 (34.0)
≥ 5 to < 10	234 (24.0)

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

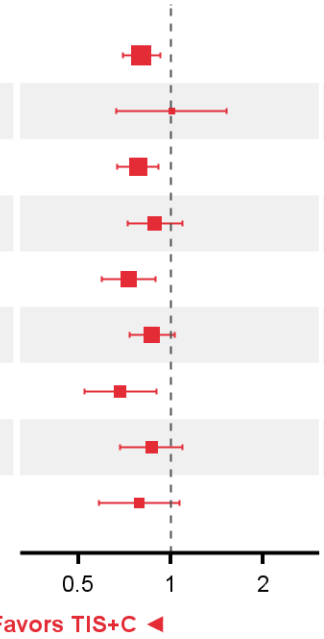
In general, efficacy results of OS and PFS by PD-L1 subgroups defined by CPS are similar to those of PD-L1 subgroups defined by TAP.

4.6.2.1. Overall Survival by PD-L1 CPS Status

Similar to subgroups of PD-L1 by TAP (Figure 7), the magnitude of OS improvement with the treatment of TIS+C over PBO+C was enhanced with increasing CPS expression levels. Moreover, subgroup analyses of OS by PD-L1 CPS levels ≥ 5 (ie, CPS ≥ 5, ≥ 5 to < 10 and ≥ 10 subgroups) showed a numerical improvement in survival favoring TIS+C over PBO+C (Figure 10).

Figure 10: Forest Plot of Overall Survival by Baseline PD-L1 CPS Expression at the Final Analysis

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	370 / 501	406 / 496	0.80 (0.70, 0.92)	15.0 (13.6, 16.5)	12.9 (12.1, 14.1)
< 1	53 / 71	39 / 49	1.01 (0.66, 1.52)	15.6 (8.4, 19.2)	15.3 (10.2, 21.6)
>= 1	308 / 420	356 / 434	0.78 (0.67, 0.91)	15.1 (13.6, 17.2)	12.9 (12.1, 14.1)
< 5	186 / 237	184 / 214	0.89 (0.72, 1.09)	13.6 (11.3, 15.6)	13.0 (11.5, 15.1)
>= 5	175 / 254	211 / 269	0.73 (0.60, 0.89)	17.8 (14.8, 20.8)	13.2 (12.1, 14.6)
< 10	261 / 340	284 / 345	0.87 (0.73, 1.03)	14.6 (12.6, 16.2)	13.1 (12.1, 14.6)
>= 10	100 / 151	111 / 138	0.68 (0.52, 0.90)	18.0 (13.6, 23.2)	12.9 (11.5, 15.5)
1 - < 5	133 / 166	145 / 165	0.86 (0.68, 1.09)	12.6 (10.6, 15.3)	12.8 (11.0, 14.7)
5 - < 10	75 / 103	100 / 131	0.79 (0.58, 1.07)	17.3 (13.8, 21.0)	13.3 (11.7, 15.4)



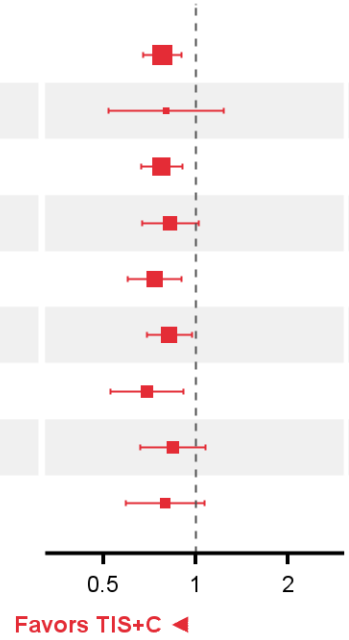
Data cutoff: 28FEB2023. Hazard ratio (TIS+C vs. PBO+C) was based on unstratified Cox regression model only including treatment as a covariate, except for Overall population for which stratified hazard ratio is displayed.

4.6.2.2. Progression-free Survival by PD-L1 CPS Expression

PFS results in all PD-L1 CPS subgroups numerically favored TIS+C over PBO+C. In additional, numerical improvement in PFS with TIS+C over PBO+C was observed in subgroup analyses by the baseline PD-L1 CPS levels ≥ 5 (ie, CPS ≥ 5, ≥ 5 to < 10 and ≥ 10 subgroups) (Figure 11), which was similar to that in subgroups of PD-L1 by TAP (Figure 8).

Figure 11: Forest Plot of Progression-Free Survival by Baseline PD-L1 CPS Expression at the Final Analysis

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	361 / 501	391 / 496	0.78 (0.67, 0.90)	6.9 (5.7, 7.2)	6.2 (5.6, 6.9)
< 1	49 / 71	36 / 49	0.80 (0.52, 1.23)	7.0 (5.6, 8.5)	6.1 (5.5, 8.3)
>= 1	303 / 420	348 / 434	0.77 (0.66, 0.90)	7.0 (5.7, 7.7)	6.4 (5.6, 6.9)
< 5	173 / 237	172 / 214	0.82 (0.67, 1.02)	5.7 (5.6, 7.0)	6.1 (5.5, 7.1)
>= 5	179 / 254	212 / 269	0.73 (0.60, 0.90)	7.2 (6.9, 8.8)	6.7 (5.6, 7.0)
< 10	250 / 340	277 / 345	0.82 (0.69, 0.97)	6.0 (5.7, 7.2)	6.8 (5.6, 7.0)
>= 10	102 / 151	107 / 138	0.69 (0.53, 0.91)	7.7 (6.9, 9.7)	5.7 (5.4, 7.0)
1 - < 5	124 / 166	136 / 165	0.84 (0.66, 1.07)	5.6 (5.3, 6.9)	6.2 (4.6, 7.1)
5 - < 10	77 / 103	105 / 131	0.79 (0.59, 1.06)	7.1 (5.7, 8.8)	6.9 (5.5, 8.1)



Data cutoff: 28FEB2023. Hazard ratio (TIS+C vs. PBO+C) was based on unstratified Cox regression model only including treatment as a covariate, except for Overall population for which stratified hazard ratio is displayed.

4.6.3. Concordance Between TAP and CPS in Study 305

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 = 974).

Overall, the TAP score and CPS showed substantial concordance at matched cutoff (TAP ≥ 1% vs CPS ≥ 1, TAP ≥ 5% vs CPS ≥ 5, TAP ≥ 10% vs CPS ≥ 10), with OPA of 95%, 82%, and 85%, with Cohen's Kappa of 0.78, 0.64, and 0.64, respectively (Table 8).

Table 8: Concordance Agreement Between TAP Score and CPS Results

	TAP ≥ 1% vs CPS ≥ 1	
	n/N	Agreement % (95% CI)
PPA	838/854	98 (97-99)
NPA	91/120	76 (68-83)
OPA	929/974	95 (94-97)
Cohen's kappa	0.78 (0.71-0.84)	
	TAP ≥ 5% vs CPS ≥ 5	
	n/N	Agreement % (95% CI)
PPA	443/523	85 (81-88)
NPA	359/451	80 (76-83)
OPA	802/974	82 (80-85)
Cohen's kappa	0.64 (0.60-0.69)	
	TAP ≥ 10% vs CPS ≥ 10	
	n/N	Agreement % (95% CI)
PPA	208/289	72 (66-77)
NPA	622/685	91 (89-93)
OPA	830/974	85 (83-87)
Cohen's kappa	0.64 (0.59-0.69)	

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

Study 305 demonstrated a statistically significant and clinically meaningful improvement in OS with TIS+C versus PBO+C in patients with PD-L1 TAP score ≥ 5% and in the ITT Analysis Set. The treatment benefit in OS was accompanied by improvements in the secondary endpoints of PFS and ORR.

The prespecified and exploratory PD-L1 subgroups indicated an association between efficacy and of PD-L1 expression levels with more pronounced treatment benefit for the subgroups with higher level of PD-L1 expression. Subgroup analyses by PD-L1 expression levels ≥ 5% (ie, PD-L1 score ≥ 5%, 5% to < 10% and ≥ 10% subgroups) showed a trend of treatment benefit with TIS+C over PBO+C across OS, PFS and ORR.

5. STUDY 305 SAFETY RESULTS

The safety of TIS+C for the treatment of patients with advanced unresectable or metastatic G/GEJ cancer is based primarily on results from the final analysis (in all treated randomized patients) of Study 305.

5.1. Safety Results in the Overall Population

Among the 997 randomized patients, 992 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 locally advanced unresectable or metastatic G/GEJ adenocarcinoma. 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 (99.4%) or PBO+C (98.4%) (Table 14). The most common TEAEs (incidence ≥ 20%) were generally similar between the 2 treatment arms.
- The incidence of TEAEs of ≥ Grade 3 was similar between arms (TIS+C: 69.3% vs PBO+C: 65.6%; Table 14). The most common TEAEs of ≥ Grade 3 (incidence ≥ 2%) were generally similar between the 2 treatment arms.
- More patients treated with TIS+C versus PBO+C experienced serious TEAEs (42.2% vs 36.0%, respectively; Table 16). 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 similar between the 2 arms (TIS+C: 4.2%; PBO+C: 3.6%; Table 14).
- The incidence of AEs leading to any treatment discontinuation was higher with TIS+C (22.9%) than with PBO+C (13.6%) (Table 17). The incidence of exposure-adjusted AEs leading to any treatment discontinuation was comparable between 2 arms (2.69 vs 2.01 per 100 person-months).
- As anticipated, more of patients receiving TIS+C reported ≥ 1 imAE than patients receiving PBO+C (30.9% vs 11.7%; Table 19); of those, 7.6% of patients with TIS+C and 2.0% of patients with PBO+C experienced ≥ Grade 3 imAEs.

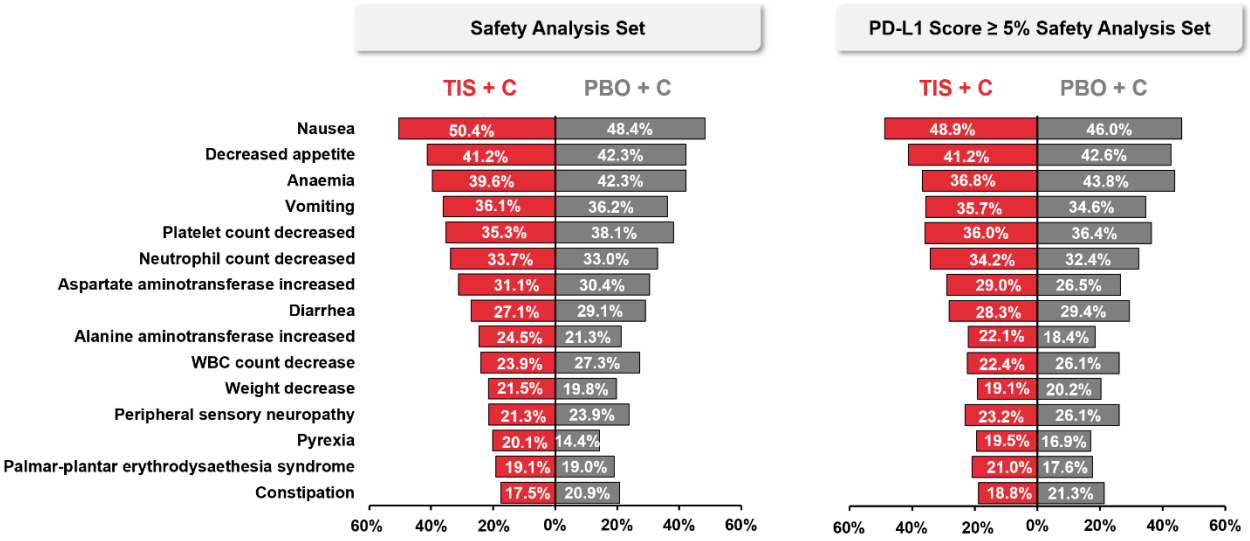
5.2. Safety Results in Subgroups by PD-L1 Cutoff of 5%

Exploratory safety analyses were performed for subgroups of PD-L1 score ≥ 5% using the Safety Analysis Set at final analysis, to explore if there was any increased safety risk associated with tislelizumab plus chemotherapy treatment in PD-L1 subgroups.

Overall, no consistent and clinically meaningful difference in the safety profile of TIS+C was observed in the subgroups by PD-L1 score cutoff of ≥ 5% versus overall Safety Analysis Set. Numerical differences in the incidence of TEAEs and imAEs with TIS+C between subgroups should be interpreted with caution. BeiGene Ltd considers these not clinically meaningful

because the differences are not biologically plausible. They are, therefore, likely to have arisen by chance.

Figure 12: Most Common (incidence ≥ 20%) TEAEs Similar Between Tislelizumab Plus Chemotherapy and Placebo Plus Chemotherapy in Patients With PD-L1 Score ≥ 5% and Overall Patients (Safety Analysis Set)



Data cutoff: 28FEB2023.

5.3. Safety Conclusion

In conclusion, TIS+C showed a tolerable and acceptable safety profile in the first-line treatment of patients with locally advanced unresectable or metastatic G/GEJ adenocarcinoma. The addition of tislelizumab to chemotherapy did not impact the tolerability and safety of chemotherapy or tislelizumab. No new safety signal was identified.

No consistent or clinically meaningful difference in the safety profile of TIS+C was identified within PD-L1 score cutoff of 5% that would give rise to clinical concern or result in changes of treatment-strategy.

6. BENEFIT/RISK ASSESSMENT

6.1. Benefit Assessment

The medical practice and treatment recommendation for 1L treatment of advanced or metastatic GC are unified globally, including in the US, supporting the conduct of a global multicenter pivotal study to investigate the efficacy and safety of an additional1L treatment option in advanced or metastatic GC.

The global, multicenter, pivotal Phase 3 Study 305 enrolled 997 patients regardless of PD-L1 expression. Of those randomized, 249 (25.0%) of patients enrolled were from the US and Europe, with the remainder of patients (748 [75.0%]) enrolled from East Asia, reflective of the geographic incidence of the disease.

BeiGene conducted exploratory analyses by PD-L1 expression and assessed the benefit and risk of tislelizumab in the target population. The data from pivotal Study 305 supports a favorable benefit-risk assessment for tislelizumab in combination with chemotherapy in patients with PD-L1 score ≥ 5%.

6.1.1. Benefit in Overall Survival

Study 305 demonstrated a statistically significant and clinically meaningful improvement in OS with TIS+C versus PBO+C in patients with PD-L1 score ≥ 5%. The trend of treatment benefit in OS was consistently observed in subgroups of PD-L1 expression levels ≥ 5% (ie, PD-L1 score ≥ 5%, ≥ 5% to < 10% and ≥ 10% subgroups).

- At the interim analysis, in patients with PD-L1 score ≥ 5%, TIS+C showed a statistically significant and clinically meaningful improvement in OS over PBO+C (stratified HR: 0.74 [95% CI: 0.59 to 0.94]; one-sided p value of 0.0056; median OS of 17.2 months for TIS+C vs 12.6 months for PBO+C). OS favored TIS+C across most prespecified subgroups, including subgroups by region (East Asia and US/Europe) and race (Asian and White).
- At the final analysis, the updated OS results in patients with PD-L1 score ≥ 5%, were consistent with the interim analysis. The data continued to show a meaningful OS improvement after additional long-term follow up (stratified HR: 0.71 [95% CI: 0.58 to 0.86]; median OS of 16.4 months vs 12.8 months).
- In PD-L1 subgroup analysis using the data from the final analysis, the magnitude of OS improvement with the treatment of TIS+C over PBO+C was enhanced with increasing PD-L1 expression levels. Subgroup analyses of OS by PD-L1 expression levels ≥ 5% (ie, PD-L1 score ≥ 5%, ≥ 5% to < 10% and ≥ 10% subgroups) all showed a trend in survival improvement favoring TIS+C over PBO+C.

Additionally, in the ITT Analysis Set, at the final analysis, treatment with TIS+C showed superior OS to PBO+C (stratified HR of 0.80; 95% CI: 0.70, 0.92; 1-sided p value of 0.0011; median OS of 15.0 months for TIS+C vs 12.9 months for PBO+C).

6.1.2. Other Benefits

Treatment with TIS+C also resulted in favorable effects in the secondary endpoints across the patients with PD-L1 score ≥ 5% and subgroups of PD-L1 expression levels ≥ 5% (ie, PD-L1 score ≥ 5%, ≥ 5% to < 10% and ≥ 10% subgroups), supporting the superior survival benefit demonstrated in patients with PD-L1 score ≥ 5%.

- In patients with PD-L1 score ≥ 5%, TIS+C showed a statistically significant and clinically meaningful improvement in PFS over PBO+C (stratified HR of 0.67 [95% CI: 0.55 to 0.83], 1-sided p-value < 0.0001; median PFS of 7.2 months in TIS+C versus 5.9 months in PBO+C) in the analysis using data from the interim analysis at the time of final analysis. In addition, that data showed a greater antitumor response, as evidenced by higher ORR (50.4% vs 43.0%).

- At the final analysis, updated secondary endpoints of PFS and ORR in patients with PD-L1 score ≥ 5% remained consistent with those of the interim analysis after additional long-term follow-up, indicating a sustained treatment benefit.
- In PD-L1 subgroup analysis using the data from the final analysis, subgroups of PD-L1 expression levels ≥ 5% (ie, PD-L1 score ≥ 5%, ≥ 5% to < 10% and ≥ 10% subgroups) showed a trend of improvement across PFS and ORR favoring TIS+C over PBO+C.

These data, including primary efficacy analysis in patients with PD-L1 score ≥ 5% and ITT, and further exploratory analyses examining additional cut offs and categories for PD-L1 scores, are comparable with the results seen in other agents in this class (eg, nivolumab and pembrolizumab) (Table 9).

Table 9: Summary of Clinical Efficacy for PD-1 CPIs in Combination with Chemotherapy for the First-line Treatment of Patients with G/GEJ

Study	**Study 305**	**KEYNOTE-859** [23],[26]	**CHECKMATE 649** [22][27]
Design	Global, randomized, double-blind	Global, randomized, double-blind	Global, randomized, open-label
Patient Population	Untreated, unresectable, advanced, and metastatic G/GEJ adenocarcinoma, HER2-	Untreated, unresectable, advanced, and metastatic G/GEJ adenocarcinoma, HER2-	Untreated, unresectable, advanced, and metastatic G/GEJ adenocarcinoma, HER2-f
Treatment	Tisle+Chemo vs Placebo+Chemo	Pembro+Chemo vs Placebo+Chemo	Nivo+Chemo vs Chemo
PD-L1 Expression Assay	Ventana PD-L1 (SP263) Assay	PD-L1 IHC 22C3 pharmDx	PD-L1 IHC 28-8 pharmDx
ITT	N = 501 vs 496	N = 790 vs 789	N = 789 vs 792
Median Follow-up (months)	14.1 vs 12.6	31.0 [a]	13.1 vs 11.1
Primary Endpoint	OS in PD-L1+ (PD-L1 TAP ≥ 5%) and ITT	OS in PD-L1+ (CPS ≥ 1 and CPS ≥ 10) and in ITT	PFS assessed by IRC and OS in PD-L1+ (CPS ≥ 5)
ITT Population	N = 997 (100%)	N = 1,579 (100%)	N = 1,581 (100%)
mOS, months HR (95% CI)	15.0 vs 12.9 *HR = 0.80 (0.70,0.92)[b], p = 0.0011*	12.9 vs 11.5 *HR = 0.78 (0.70, 0.87), p < 0.0001*	13.8 vs 11.6 *HR = 0.80 (0.68,0.94), p < 0.0002*
mPFS, months HR (95% CI)	6.9 vs 6.2 HR = 0.78 (0.67, 0.90)	6.9 vs 5.6 *HR = 0.76 (0.67, 0.85), p < 0.0001*	7.7 vs 6.9 HR = 0.77 (0.68,0.87)
ORR, %	47.3 vs 40.5 Δ 6.8 (0.8, 12.9)	51.3 vs 42.0 *Δ 9.3 (4.4-14.1), p = 0.00009*	58.0 vs 46.1 Δ 12.8
Median DOR, months	8.6 vs 7.2	8.0 vs 5.7	8.5 vs 6.9
PD-L1 TAP ≥1% or CPS ≥1[d]	N = 885 (89%)	N = 1,235 (78%)	N = 1,296 (82%)
mOS, months HR (95% CI)	15.0 vs 12.8 HR = 0.78 (0.67, 0.90)	13.0 vs 11.4 *HR = 0.74 (0.65, 0.84), p < 0.0001*	14.0 vs 11.3 *HR = 0.77 (0.64,0.92), p < 0.0001*
mPFS, months HR (95% CI)	6.9 vs 5.9 HR = 0.78 (0.67, 0.91)	6.9 vs 5.6 *HR = 0.72 (0.64, 0.82), p < 0.0001*	7.5 vs 6.9 HR = 0.74 (0.65,0.85)
ORR, %	47.7 vs 41.1	52.1 vs 42.6 *Δ 9.5 (3.9-15.0), p = 0.00041*	59.5 vs 46.4
PD-L1 TAP <1% or CPS <1[d]	N = 112 (11%)	N = 344 (22%)	N = 265 (17%)
mOS, months HR (95% CI)	15.4 vs 13.8 HR = 0.98 (0.64, 1.50)	12.7 vs 12.2 HR = 0.92 (0.73, 1.17)	13.1 vs 12.5 HR = 0.92 (0.70,1.23)
mPFS, months HR (95% CI)	7.9 vs 6.9	7.2 vs 5.8	8.7 vs 8.1

	HR = 0.87 (0.54,1.41)	HR = 0.90 (0.70, 1.15)	HR = 0.93 (0.69,1.26)
ORR, %	44.9 vs 34.9	48.3 vs 39.5	50.5 vs 41.2
PD-L1 TAP ≥5% or CPS ≥5 [d]	N = 546 (55%)	N = 767 (49%)	N = 955 (60%)
mOS, months HR (95% CI)	17.2 vs 12.6 *HR = 0.74 (0.59,0.94), p=0.0056*	14.0 vs 11.5 HR = 0.70 (0.60, 0.82)	14.4 vs 11.1 *HR = 0.71 (0.59,0.86), p < 0.0001*
mPFS, months HR (95% CI)	7.2 vs 5.9 [c] *HR = 0.67 (0.55, 0.83) , p< 0.0001* [c]	7.1 vs 5.6 HR = 0.69 (0.58, 0.81)	7.7 vs 6.05 *HR = 0.68 (0.56,0.81), p < 0.0001*
ORR, %	50.4 vs 43.0	55.1 vs 44.1	59.8 vs 45.3
PD-L1 TAP<5% or CPS<5 [d]	N = 451 (45%)	N = 812 (51%)	N = 606 (38%)
mOS, months HR (95% CI)	14.1 vs 12.9 HR = 0.92 (0.75, 1.13)	12.1 vs 11.4 HR = 0.84 (0.72, 0.98)	12.4 vs 12.3 HR = 0.94 (0.78,1.13)
mPFS, months HR (95% CI)	5.7 vs 6.5 HR = 0.91 (0.74, 1.13)	6.9 vs 5.6 HR = 0.83 (0.71, 0.98)	7.5 vs 8.2 HR = 0.93 (0.76,1.12)
ORR, %	42.3 vs 37.9	47.7 vs 39.9	55.3 vs 46.4
PD-L1 TAP ≥10% or CPS ≥10 [d]	N = 281 (28%)	N = 551 (35%)	N = 768 (49%)
mOS, months HR (95% CI)	22.5 vs 12.3 HR = 0.57 (0.43, 0.76)	15.7 vs 11.8 *HR = 0.65 (0.53, 0.79), p < 0.0001*	15.0 vs 10.9 HR = 0.65 (0.55, 0.78)
mPFS, months HR (95% CI)	9.0 vs 5.7 HR = 0.56 (0.42, 0.74)	8.1 vs 5.6 *HR = 0.62 (0.51, 0.76), p < 0.0001*	8.3 vs 5.8 HR = 0.65 (0.55, 0.77)
ORR, %	53.7 vs 40.0	60.6 vs 43.0 *Δ 17.5 (9.3-25.5), p < 0.00002*	58.3 vs 44.2
PD-L1 TAP <10% or CPS <10 [d]	N = 716 (72%)	N = 1,026 (65%)	N = 793 (50%)
mOS, months HR (95% CI)	14.0 vs 13.0 HR = 0.91 (0.77, 1.07)	11.7 vs 11.2 HR = 0.86 (0.75, 0.98)	12.6 vs 12.5 HR = 0.94 (0.80, 1.10)
mPFS, months HR (95% CI)	5.7 vs 6.9 HR = 0.90 (0.76, 1.06)	6.8 vs 5.6 HR = 0.85 (0.74, 0.98)	7.5 vs 7.7 HR = 0.91 (0.77, 1.08)
ORR, %	44.9 vs 40.7	46.2 vs 41.4	57.9 vs 47.3

Data in PD-L1 TAP ≥5% of Study 305 are from interim analysis. Data in other PD-L1 subgroups of Study 305 are from final analysis.

[a] Defined as time from randomization to the data cutoff date

[b] In italics indicated the results have statistical significance.

[c] The analysis using IA dataset was conducted at final analysis.

[d] TAP is for Study 305; CPS is for CHEMKMATE-649 and KEYNOTE-859.

6.2. Risk Assessment

In the risk evaluation, following important risks were observed:

- TEAE: The incidence between TIS+C and PBO+C was similar (difference ≤ 5%) for TEAEs of ≥ Grade 3 (69.3% in TIS+C vs 65.6% in PBO+C) and TEAEs leading to death (4.2% vs 3.6%). The incidence observed was higher (difference ≥ 5%) in TIS+C than PBO+C for TEAE leading to treatment discontinuation of any study drug (22.9% vs 13.6%). The incidence of exposure-adjusted TEAE leading to any treatment discontinuation was similar between the 2 arms (2.69 vs 2.01 per 100 person-months).
- imAE: As expected for a PD-1 CPI, the incidence of imAEs was higher with TIS+C than PBO+C. Most imAEs were of Grade 1 or 2 in severity. The imAE in TIS+C was generally in line with the known safety profile for tislelizumab monotherapy.

Overall, TIS+C showed a tolerable and acceptable safety profile in the first-line treatment of patients with locally advanced unresectable or metastatic G/GEJ adenocarcinoma. The findings are consistent with the known safety profile of tislelizumab and other checkpoint inhibitors in combination with chemotherapy [22] [23]. The safety profile of treatment with TIS+C across PD-L1 subgroups of TAP <5% and ≥ 5% was generally consistent with that reported for the overall population, revealing no increased safety risks or new safety signals for these subgroups.

6.3. Conclusions of the Benefit-Risk Assessment

Study 305 is a global Phase 3 study, like other recent global Phase 3 studies (KEYNOTE-859 and CHECKMATE 649), that evaluated immune CPIs plus chemotherapy as 1L treatment of G/GEJ cancer to address the unmet medical need for additional effective treatment options for this indication. Study 305 results substantiate the value of tislelizumab plus chemotherapy as an effective and safe option for 1L treatment in G/GEJ cancer patients with tumors that express a PD-L1 score of ≥ 5%. The study showed TIS+C provided a statistically significant benefit over PBO+C by prolonging survival with a positive benefit/risk ratio for patients with locally advanced, metastatic G/GEJ cancer with tumors that express a PD-L1 score of ≥ 5%.

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.

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[27] Human medicine European public assessment report (EPAR)_ Procedure No. EMEA/H/C/003985/II/0096 _ 16 September 2021.

APPENDIX 1. SUPPLEMENTAL TABLES AND FIGURES

Table 10: Key Demographics and Baseline Characteristics by Baseline PD-L1 TAP Expression Cuts and Categories

Baseline PD-L1 Status	< 1%		≥ 1%		< 5%		≥ 5%		< 10%		≥ 10%		≥ 1% to < 5%		≥ 5% to < 10%	
	T+C (N = 69)	P+C (N = 43)	T+C (N = 432)	P+C (N = 453)	T+C (N = 227)	P+C (N = 224)	T+C (N = 274)	P+C (N = 272)	T+C (N = 365)	P+C (N = 351)	T+C (N = 136)	P+C (N = 145)	T+C (N = 158)	P+C (N = 181)	T+C (N = 138)	P+C (N = 127)
Age Group, ≥ 65 years, %	17.4	34.9	34.5	37.1	27.3	30.4	36.1	42.3	31.2	35.3	34.6	40.7	31.6	29.3	37.7	56 (44.1)
Gender, %																
Female	40.6	30.2	29.4	30.2	32.6	35.3	29.6	26.1	29.9	31.9	33.8	26.2	29.1	36.5	25.4	26.0
Region, %																
East Asia	73.9	79.1	75.2	74.6	76.7	76.3	73.7	73.9	76.4	76.4	71.3	71.7	77.8	75.7	76.1	76.4)
US/Europe	26.1	20.9	24.8	25.4	23.3	23.7	26.3	26.1	23.6	23.6	28.7	28.3	22.2	24.3	23.9	23.6
ECOG Status, %																
0	29.0	20.9	34.5	32.0	31.3	30.4	35.8	31.6	32.9	30.5	36.0	32.4	32.3	32.6	35.5	30.7
1	71.0	79.1	65.5	68.0	68.7	69.6	64.2	68.4	67.1	69.5	64.0	67.6	67.7	67.4	64.5	69.3
Metastatic Disease at Screening, %	98.6	95.3	98.6	99.1	98.7	99.1	98.5	98.5	99.2	98.9	97.1	98.6	98.7	100.0	100.0	98.4
Number of Metastatic Sites at Study Entry, %																
0 - 2	65.2	86.0	67.1	65.8	67.0	69.2	66.8	66.2	65.8	68.9	69.9	64.1	67.7	65.2	63.8	68.5
≥ 3	34.8	14.0	32.9	34.0	33.0	30.4	33.2	33.8	34.2	30.8	30.1	35.9	32.3	34.3	36.2	31.5
Primary Location, %																
Gastro-Esophageal Junction	15.9	18.6	19.7	20.3	19.8	18.3	18.6	21.7	19.2	19.4	19.1	22.1	21.5	18.2	18.1	21.3
Stomach	84.1	79.1	80.3	79.7	80.2	81.3	81.4	78.3	80.8	80.3	80.9	77.9	78.5	81.8	81.9	78.7
Had Liver Metastases, %	29.0	18.6	39.4	39.7	30.4	31.7	44.2	43.0	35.9	36.5	43.4	41.4	31.0	34.8	44.9	44.9

Baseline PD-L1 Status	< 1%		≥ 1%		< 5%		≥ 5%		< 10%		≥ 10%		≥ 1% to < 5%		≥ 5% to < 10%	
	T+C (N = 69)	P+C (N = 43)	T+C (N = 432)	P+C (N = 453)	T+C (N = 227)	P+C (N = 224)	T+C (N = 274)	P+C (N = 272)	T+C (N = 365)	P+C (N = 351)	T+C (N = 136)	P+C (N = 145)	T+C (N = 158)	P+C (N = 181)	T+C (N = 138)	P+C (N = 127)
Had Presence of Peritoneal Metastasis, %	43.5	41.9	44.0	43.3	48.5	47.8	40.1	39.3	46.0	44.2	38.2	40.7	50.6	49.2	42.0	37.8
Prior Gastrectomy/ Esophagectomy %	31.9	41.9	25.7	26.7	36.6	37.1	18.2	20.6	29.3	31.6	19.1	19.3	38.6	35.9	17.4	22.0
Patients With at Least One Prior Adjuvant/Neo-Adjuvant Systemic Therapy for Cancer, %	26.1	34.9	20.6	18.8	30.0	27.7	14.2	14.0	24.1	23.4	14.0	12.4	31.6	26.0	14.5	15.7

Data cutoff: 28FEB2023.
Abbreviations: P+C, placebo + chemotherapy; PD-L1, programmed cell death protein ligand-1; T+C, tislelizumab + chemotherapy; TAP, tumor area positive.
PD-L1 TAP score was determined with VENTANA PD-L1 (SP263) Assay.
Percentages were based on N.

Table 11: Post-Treatment Subsequent Anti-Cancer Systemic Therapies by Baseline PD-L1 TAP at the Final Analysis (ITT Analysis Set)

Baseline PD-L1 Status	< 1%		≥ 1%		< 5%		≥ 5%		< 10%		≥ 10%		≥ 1% to < 5%		≥ 5% to < 10%	
	T+C (N = 69)	P+C (N = 43)	T+C (N = 432)	P+C (N = 453)	T+C (N = 227)	P+C (N = 224)	T+C (N = 274)	P+C (N = 272)	T+C (N = 365)	P+C (N = 351)	T+C (N = 136)	P+C (N = 145)	T+C (N = 158)	P+C (N = 181)	T+C (N = 138)	P+C (N = 127)
Patients With Any Subsequent Anti-Cancer Systemic Therapy, n (%)	33 (47.8)	24 (55.8)	232 (53.7)	270 (59.6)	129 (56.8)	133 (59.4)	136 (49.6)	161 (59.2)	198 (54.2)	204 (58.1)	67 (49.3)	90 (62.1)	96 (60.8)	109 (60.2)	69 (50.0)	71 (55.9)
Targeted Therapy	18 (26.1)	13 (30.2)	132 (30.6)	147 (32.5)	69 (30.4)	67 (29.9)	81 (29.6)	93 (34.2)	113 (31.0)	106 (30.2)	37 (27.2)	54 (37.2)	51 (32.3)	54 (29.8)	44 (31.9)	39 (30.7)
Chemotherapy	31 (44.9)	22 (51.2)	220 (50.9)	258 (57.0)	120 (52.9)	124 (55.4)	131 (47.8)	156 (57.4)	188 (51.5)	194 (55.3)	63 (46.3)	86 (59.3)	89 (56.3)	102 (56.4)	68 (49.3)	70 (55.1)
Immunotherapy	10 (14.5)	8 (18.6)	52 (12.0)	82 (18.1)	30 (13.2)	35 (15.6)	32 (11.7)	55 (20.2)	47 (12.9)	60 (17.1)	15 (11.0)	30 (20.7)	20 (12.7)	27 (14.9)	17 (12.3)	25 (19.7)
Other Therapies	3 (4.3)	4 (9.3)	11 (2.5)	14 (3.1)	8 (3.5)	10 (4.5)	6 (2.2)	8 (2.9)	13 (3.6)	13 (3.7)	1 (0.7)	5 (3.4)	5 (3.2)	6 (3.3)	5 (3.6)	3 (2.4)

Data cutoff: 28FEB2023.
Abbreviations: ITT, intent to treat; P+C, placebo + chemotherapy; PD-L1, programmed cell death protein ligand-1; T+C, tislelizumab + chemotherapy; TAP, tumor area positive.
PD-L1 TAP score was determined with VENTANA PD-L1 (SP263) Assay.

Table 12: Duration of Response by Baseline PD-L1 TAP at the Final Analysis (ITT Analysis Set)

Baseline PD-L1 Status	< 1%		≥ 1%		< 5%		≥ 5%		< 10%		≥ 10%		≥ 1% to < 5%		≥ 5% to < 10%	
	T+C (N = 69)	P+C (N = 43)	T+C (N = 432)	P+C (N = 453)	T+C (N = 227)	P+C (N = 224)	T+C (N = 274)	P+C (N = 272)	T+C (N = 365)	P+C (N = 351)	T+C (N = 136)	P+C (N = 145)	T+C (N = 158)	P+C (N = 181)	T+C (N = 138)	P+C (N = 127)
Number of Responders	31	15	206	186	96	85	141	116	164	143	73	58	65	70	68	58
Events, n (%)	18 (58.1)	8 (53.3)	140 (68.0)	140 (75.3)	66 (68.8)	64 (75.3)	92 (65.2)	84 (72.4)	114 (69.5)	104 (72.7)	44 (60.3)	44 (75.9)	48 (73.8)	56 (80.0)	48 (70.6)	40 (69.0)
DOR Median (months) (95% CI)	11.8 (4.3, NE)	18.0 (2.8, NE)	8.6 (7.8, 10.4)	7.2 (5.8, 8.3)	7.1 (5.5, 9.7)	8.0 (5.7, 11.6)	10.0 (8.2, 16.8)	6.9 (5.7, 8.5)	7.8 (5.9, 9.7)	7.2 (5.8, 9.3)	16.8 (8.4, 24.1)	7.2 (5.4, 9.8)	6.8 (4.8, 9.5)	7.2 (5.6, 10.5)	8.2 (5.8, 10.4)	6.9 (5.6, 9.3)

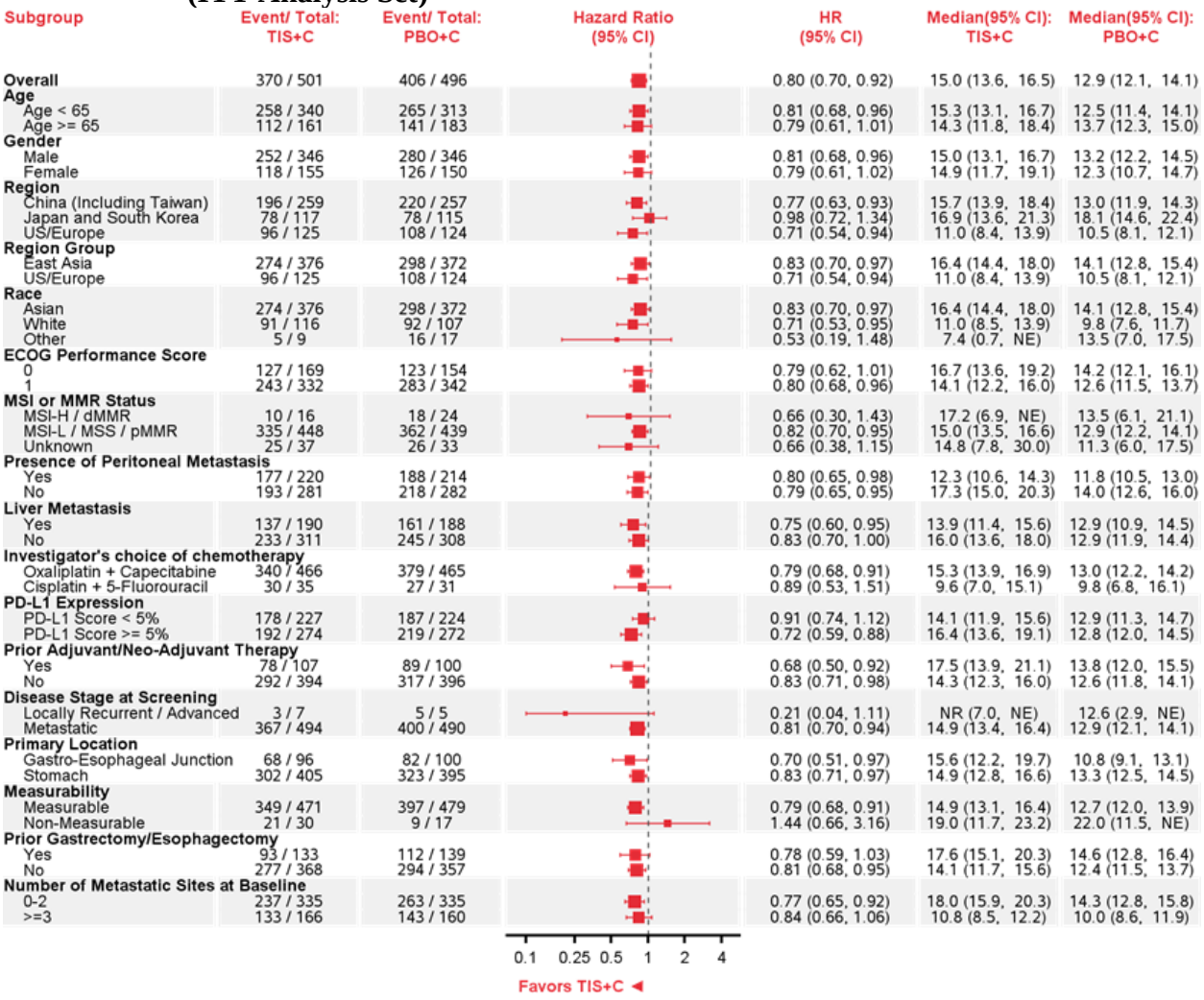
Data cutoff: 28FEB2023.
Abbreviations: CI, confidence interval; DOR, duration of response; ITT, intent to treat; NE, not estimable; P+C, placebo + chemotherapy; PD-L1, programmed cell death protein ligand-1; T+C, tislelizumab + chemotherapy; TAP, tumor area positive.
PD-L1 TAP score was determined with VENTANA PD-L1 (SP263) Assay.
Duration of response analysis included patients with confirmed CR or PR.
Median was estimated by Kaplan-Meier method with 95% CIs estimated using the method of Brookmeyer and Crowley.

Table 13: Overall Survival by Baseline PD-L1 of TAP at the Final Analysis (ITT Analysis Set)

Baseline PD-L1 Status	< 1%		≥ 1%		< 5%		≥ 5%		< 10%		≥ 10%		≥ 1% to < 5%		≥ 5% to < 10%	
	T+C (N = 69)	P+C (N = 43)	T+C (N = 432)	P+C (N = 453)	T+C (N = 227)	P+C (N = 224)	T+C (N = 274)	P+C (N = 272)	T+C (N = 365)	P+C (N = 351)	T+C (N = 136)	P+C (N = 145)	T+C (N = 158)	P+C (N = 181)	T+C (N = 138)	P+C (N = 127)
Number of Patients Death, n (%)	52 (75.4)	36 (83.7)	318 (73.6)	370 (81.7)	178 (78.4)	187 (83.5)	192 (70.1)	219 (80.5)	286 (78.4)	288 (82.1)	84 (61.8)	118 (81.4)	126 (79.7)	151 (83.4)	108 (78.3)	101 (79.5)
Stratified Hazard Ratio (95% CI) [a]	0.93 (0.60, 1.44)	-	0.77 (0.67, 0.90)	-	0.92 (0.75, 1.13)	-	0.71 (0.58, 0.86)	-	0.91 (0.77, 1.07)	-	0.55 (0.42, 0.74)	-	0.92 (0.72, 1.16)	-	0.90 (0.69, 1.19)	-
Unstratified Hazard Ratio (95% CI) [b]	0.98 (0.64, 1.50)	-	0.78 (0.67, 0.90)	-	0.91 (0.74, 1.12)	-	0.72 (0.59, 0.88)	-	0.91 (0.77, 1.07)	-	0.57 (0.43, 0.76)	-	0.90 (0.71, 1.14)	-	0.91 (0.70, 1.20)	-
Multivariate Adjusted Unstratified Hazard Ratio (95% CI) [c]	0.82 (0.53, 1.28)	-	0.77 (0.67, 0.90)	-	0.89 (0.72, 1.09)	-	0.72 (0.59, 0.87)	-	0.88 (0.74, 1.03)	-	0.58 (0.44, 0.77)	-	0.91 (0.72, 1.16)	-	0.89 (0.68, 1.17)	-

Data cutoff: 28FEB2023.
Abbreviations: CI, confidence interval; P+C, placebo + chemotherapy; PD-L1, programmed cell death protein ligand-1; T+C, tislelizumab + chemotherapy; TAP, tumor area positive.
PD-L1 TAP score was determined with VENTANA PD-L1 (SP263) Assay.
Percentages were based on N.
[a] Primary OS analysis: Stratified by regions (east Asia vs US/Europe) and presence of peritoneal metastasis.
[b] Unstratified OS sensitivity analysis: Hazard ratio was estimated from Cox model with Arm B (placebo + chemotherapy) as the reference group.
[c] Multivariate adjusted unstratified hazard ratio was based on unstratified Cox regression model including treatment, ECOG PS, liver metastasis, number of metastatic organs (0-2 vs. >=3), prior gastrectomy/esophagectomy (yes vs. no), regions (east Asia versus US/Europe) and presence of peritoneal metastasis as covariates.

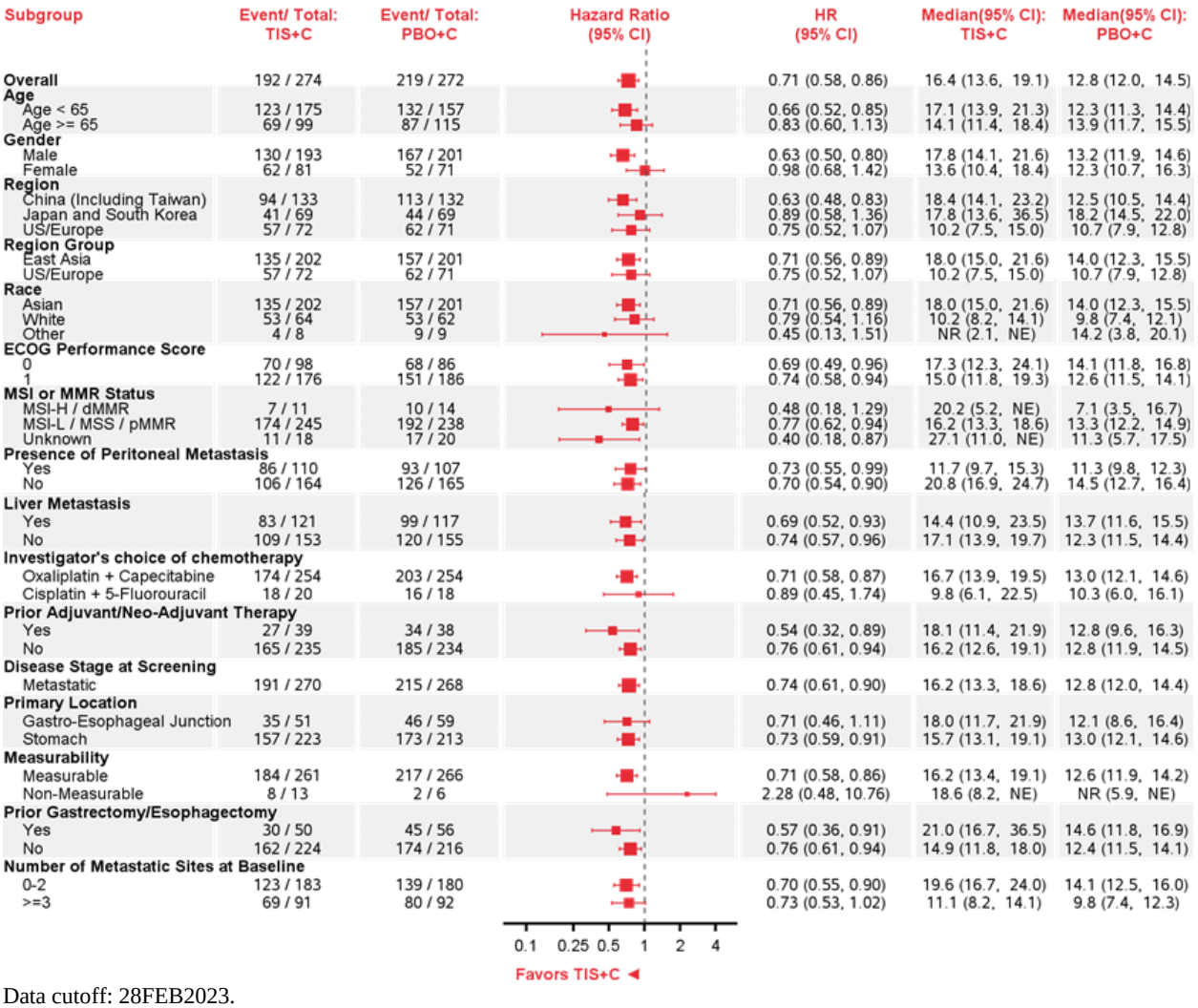
Figure 13: Forest Plot of Overall Survival - Subgroup Analysis at the Final Analysis (ITT Analysis Set)



Data cutoff: 28FEB2023.
Abbreviation: CI, confidence interval; NE, not estimable; NR, not reached; PBO+C, placebo + chemotherapy; TIS+C, tislelizumab + chemotherapy.

Any subset with fewer than 10 patients would not be shown. The race subcategory 'Other' includes Not Reported, Unknown, and Other; 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. The range of x-axis for HR is (0.1, 4), extreme values lower than 0.1 are not shown in the plot.

Figure 14: Forest Plot of Overall Survival - Subgroup Analysis at the Final Analysis (PD-L1 Positive Analysis Set)



Data cutoff: 28FEB2023.

Abbreviation: CI, confidence interval; NE, not estimable; NR, not reached; PBO+C, placebo + chemotherapy; TIS+C, tislelizumab + chemotherapy.

Any subset with fewer than 10 patients would not be shown. The race subcategory 'Other' includes Not Reported, Unknown, and Other; 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. The range of x-axis for HR is (0.1, 4), extreme values greater than 4 are not shown in the plot.

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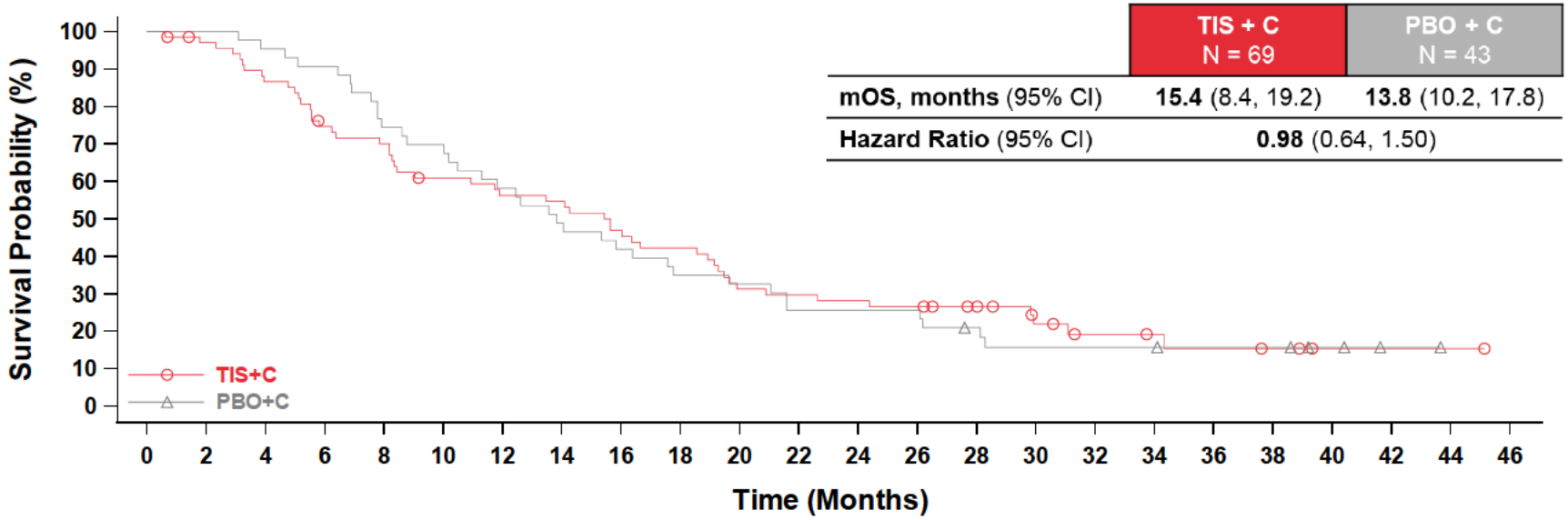
Figure 15: Kaplan-Meier Plot of Overall Survival of Baseline PD-L1 Subgroups with TAP Cutoff of 1% at the Final Analysis (ITT Analysis Set)

PD-L1 Status: TAP < 1%

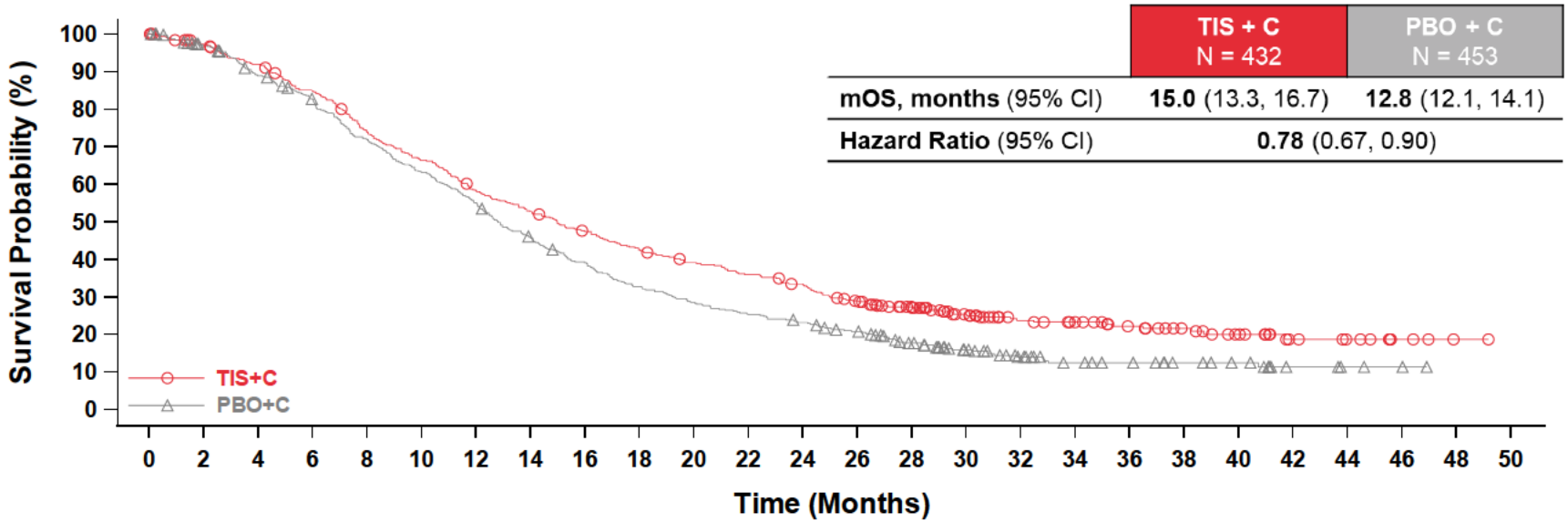


No. At Risk:

TIS+C	69	65	58	49	46	39	36	35	30	27	20	19	18	17	14	9	6	5	4	3	1	1	1	0
PBO+C	43	43	41	39	32	30	25	21	18	15	14	11	11	11	8	6	6	6	5	5	3	1	0	0

Data cutoff: 28FEB2023.
Abbreviations: CI, confidence interval; mOS, median overall survival; PBO+C, placebo + chemotherapy; PD-L1, programmed cell death protein ligand-1; TAP, tumor area positive; TIS+C, tislelizumab + chemotherapy.
PD-L1 TAP score was determined with VENTANA PD-L1 (SP263) Assay.
Hazard ratio was based on unstratified Cox regression model.
'+' = censored.

PD-L1 Status: TAP ≥ 1%



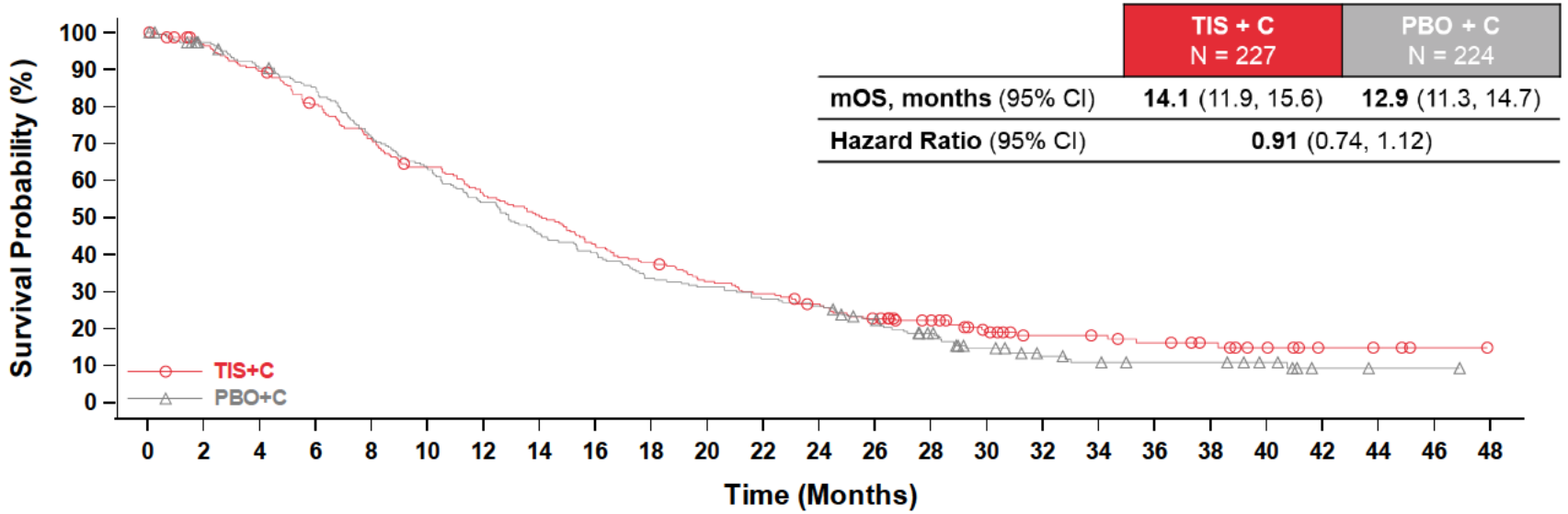
No. At Risk:

TIS+C	432	412	387	355	309	277	242	219	196	175	159	146	134	113	93	68	53	48	39	28	21	12	9	4	1	0
PBO+C	453	429	390	359	312	274	239	197	168	140	122	108	98	85	65	46	33	23	20	15	12	5	3	2	0	0

Data cutoff: 28FEB2023.
Abbreviations: CI, confidence interval; mOS, median overall survival; PBO+C, placebo + chemotherapy; PD-L1, programmed cell death protein ligand-1; TAP, tumor area positive; TIS+C, tislelizumab + chemotherapy.
PD-L1 TAP score was determined with VENTANA PD-L1 (SP263) Assay.
Hazard ratio was based on unstratified Cox regression model.
'+' = censored.

Figure 16: Kaplan-Meier Plot of Overall Survival of Baseline PD-L1 Subgroups with TAP < 5% at the Final Analysis (ITT Analysis Set)

PD-L1 Status: TAP < 5%



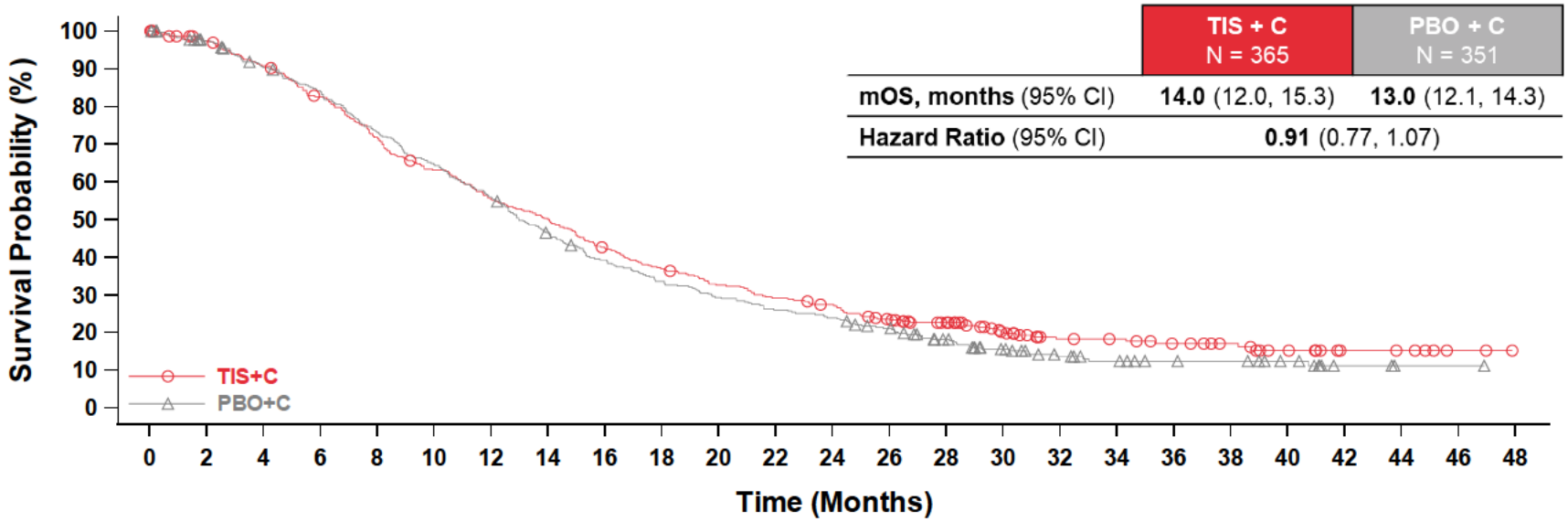
No. At Risk:

TIS+C	227	214	198	176	156	138	122	109	93	82	70	63	55	46	39	27	21	19	16	12	8	4	3	1	0
PBO+C	224	211	195	183	154	136	116	98	87	72	67	60	56	45	34	23	16	13	11	11	8	3	1	1	0

Data cutoff: 28FEB2023.
Abbreviations: CI, confidence interval; mOS, median overall survival; PBO+C, placebo + chemotherapy; PD-L1, programmed cell death protein ligand-1; TAP, tumor area positive; TIS+C, tislelizumab + chemotherapy.
PD-L1 TAP score was determined with VENTANA PD-L1 (SP263) Assay.
Hazard ratio was based on unstratified Cox regression model.
'+' = censored.

Figure 17: Kaplan-Meier Plot of Overall Survival of Baseline PD-L1 Subgroups with TAP Cutoff of 10% at the Final Analysis (ITT Analysis Set)

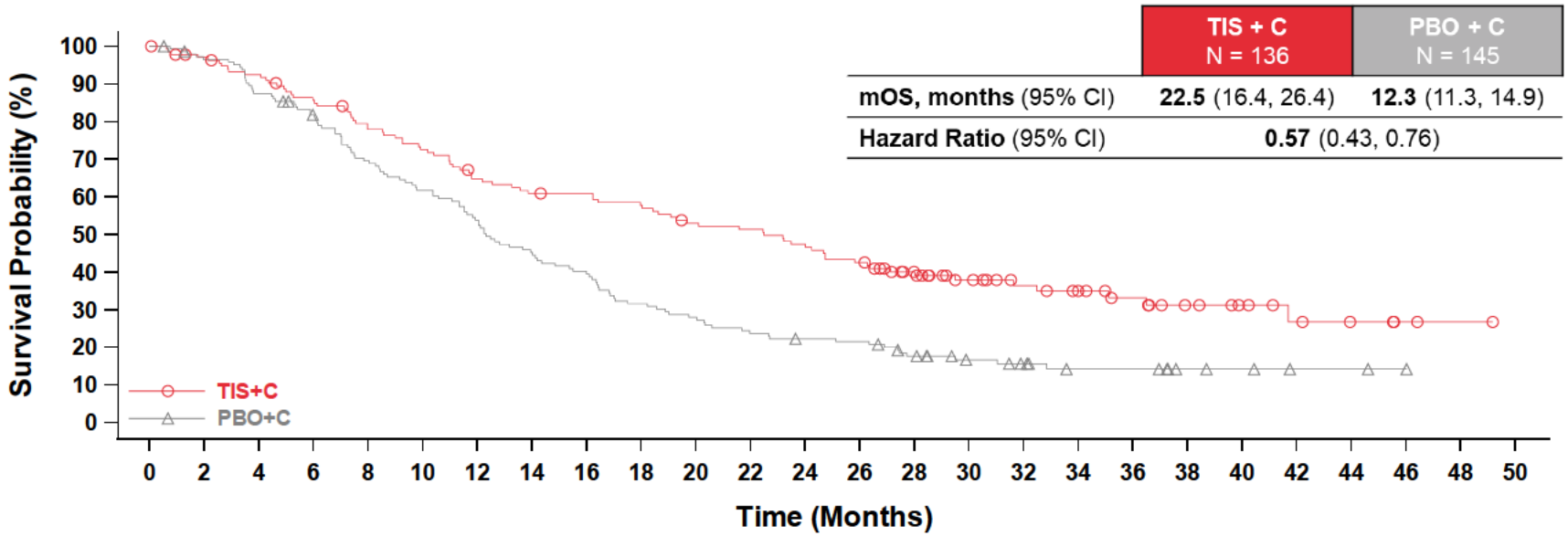
PD-L1 Status: TAP < 10%



No. At Risk:

TIS+C	365	348	323	292	254	222	195	176	149	129	113	101	93	77	66	46	34	31	26	19	13	7	6	2	0
PBO+C	351	334	306	284	247	218	189	155	130	111	97	86	79	67	51	36	26	20	16	15	11	4	1	1	0

PD-L1 Status: TAP ≥ 10%



No. At Risk:

TIS+C	136	129	122	112	101	94	83	78	77	73	66	64	59	53	41	31	25	22	17	12	9	6	4	2	1	0
PBO+C	145	138	125	114	97	86	75	63	56	44	39	33	30	29	22	16	13	9	9	5	4	2	2	1	0	0

Data cutoff: 28FEB2023.

Abbreviations: CI, confidence interval; mOS, median overall survival; PBO+C, placebo + chemotherapy; PD-L1, programmed cell death protein ligand-1; TAP, tumor area positive; TIS+C, tislelizumab + chemotherapy.

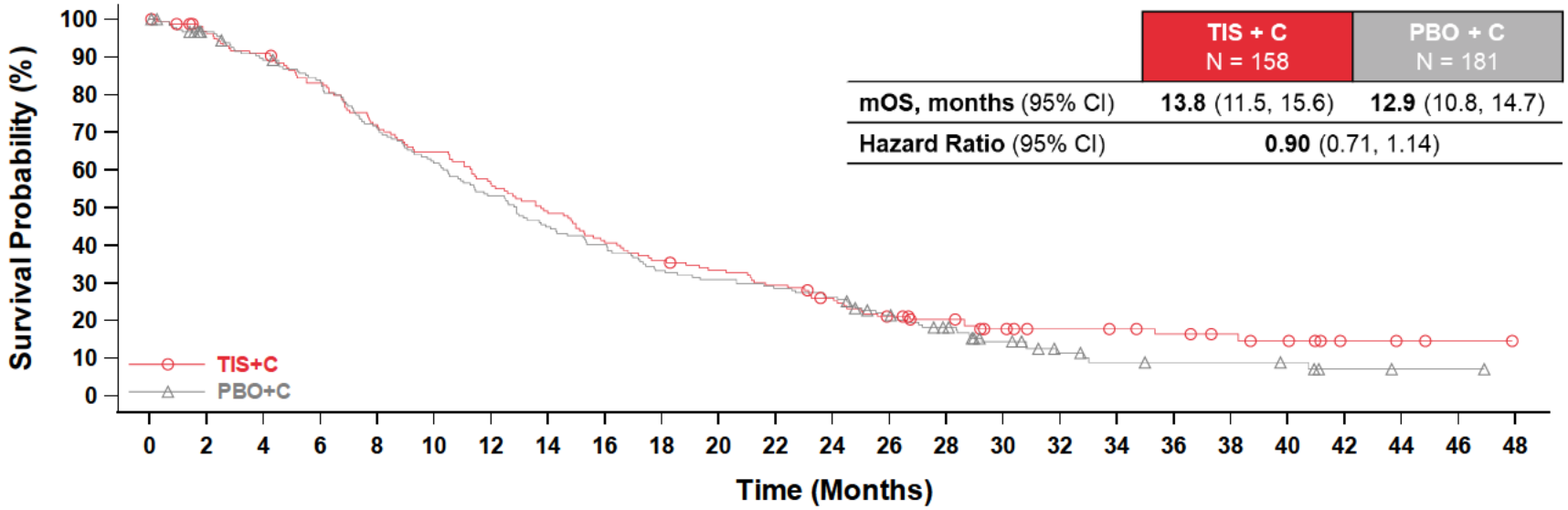
PD-L1 TAP score was determined with VENTANA PD-L1 (SP263) Assay.

Hazard ratio was based on unstratified Cox regression model.

'+' = censored.

Figure 18: Kaplan-Meier Plot of Overall Survival of Baseline PD-L1 Categories of TAP at the Final Analysis (ITT Analysis Set)

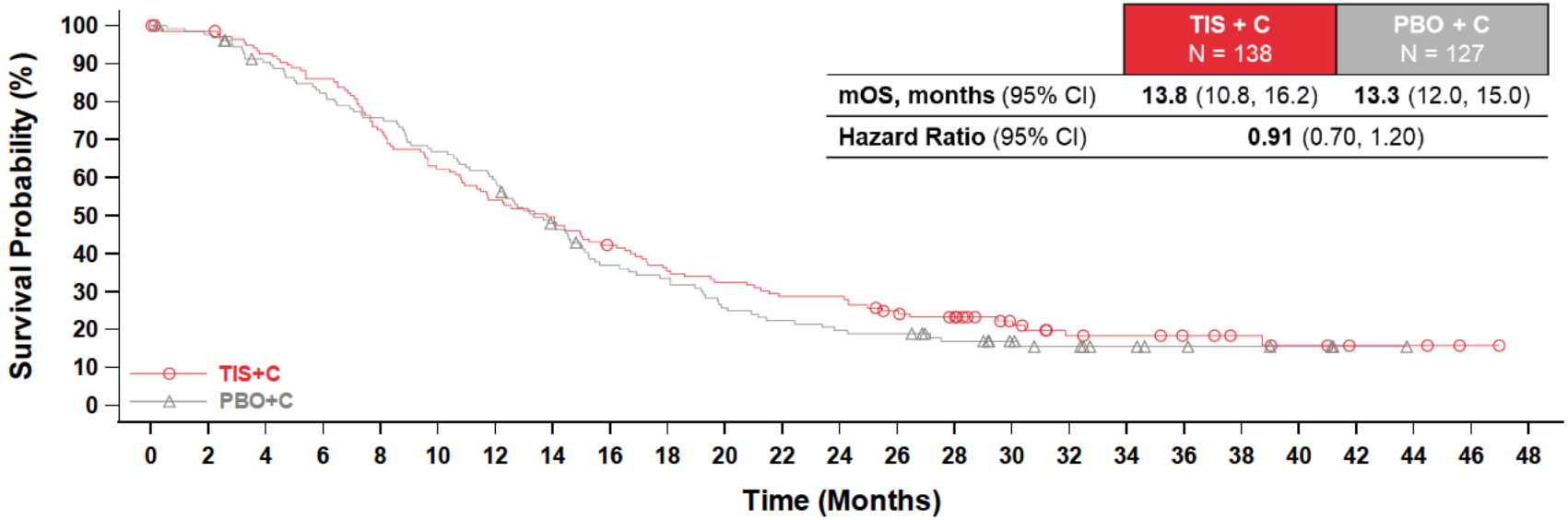
PD-L1 Status: TAP Score ≥ 1% - < 5%



No. At Risk:

TIS+C	158	149	140	127	110	99	86	74	63	55	50	44	37	29	25	18	15	14	12	9	7	3	2	1	0
PBO+C	181	168	154	144	122	106	91	77	69	57	53	49	45	34	26	17	10	7	6	6	5	2	1	1	0

PD-L1 Status: TAP Score ≥ 5% - < 10%



No. At Risk:

TIS+C	138	134	125	116	98	84	73	67	56	47	43	38	38	31	27	19	13	12	10	7	5	3	3	1	0
PBO+C	127	123	111	101	93	82	73	57	43	39	30	26	23	22	17	13	10	7	5	4	3	1	0	0	0

Data cutoff: 28FEB2023.

Abbreviations: CI, confidence interval; mOS, median overall survival; PBO+C, placebo + chemotherapy; PD-L1, programmed cell death protein ligand-1; TAP, tumor area positive; TIS+C, tislelizumab + chemotherapy.

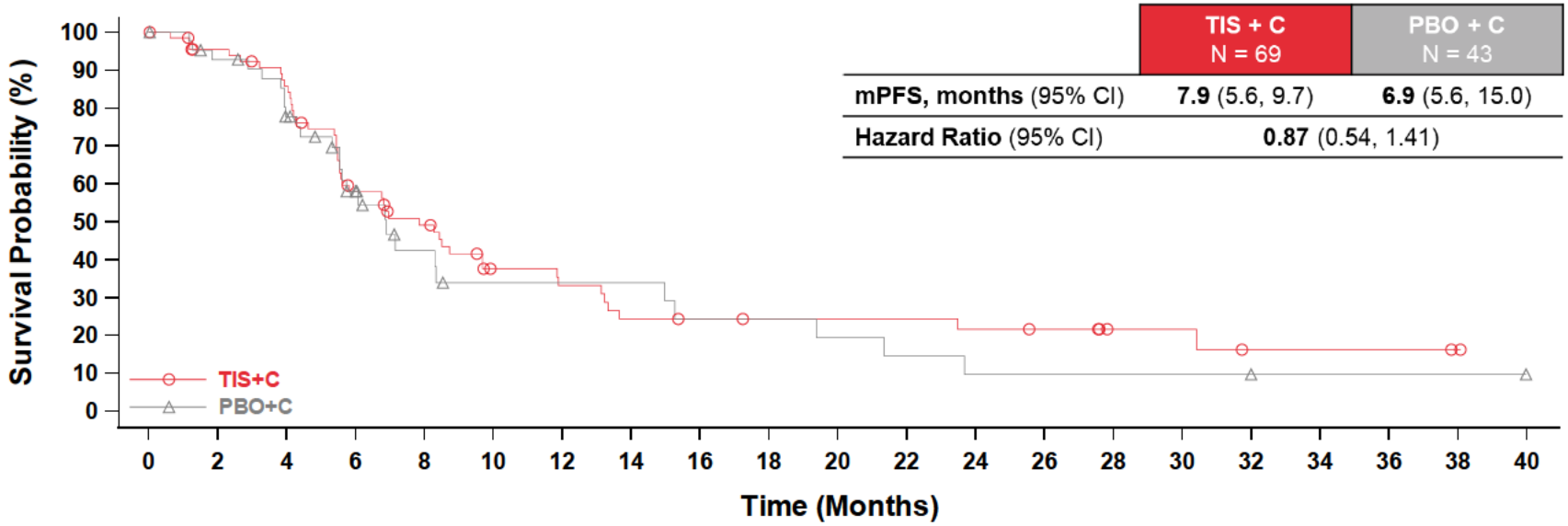
PD-L1 TAP score was determined with VENTANA PD-L1 (SP263) Assay.

Hazard ratio was based on unstratified Cox regression model.

'+' = censored.

Figure 19: Kaplan-Meier Plot of Progression-Free Survival of Baseline PD-L1 Subgroups with TAP Cutoff of 1% at the Final Analysis (ITT Analysis Set)

PD-L1 Status: TAP < 1%



No. At Risk:

TIS+C	69	60	53	34	27	17	15	11	10	9	9	9	8	7	4	4	2	2	2	1	0
PBO+C	43	38	30	18	10	7	7	7	5	5	4	3	2	2	2	2	2	1	1	1	0

Data cutoff: 28FEB2023.

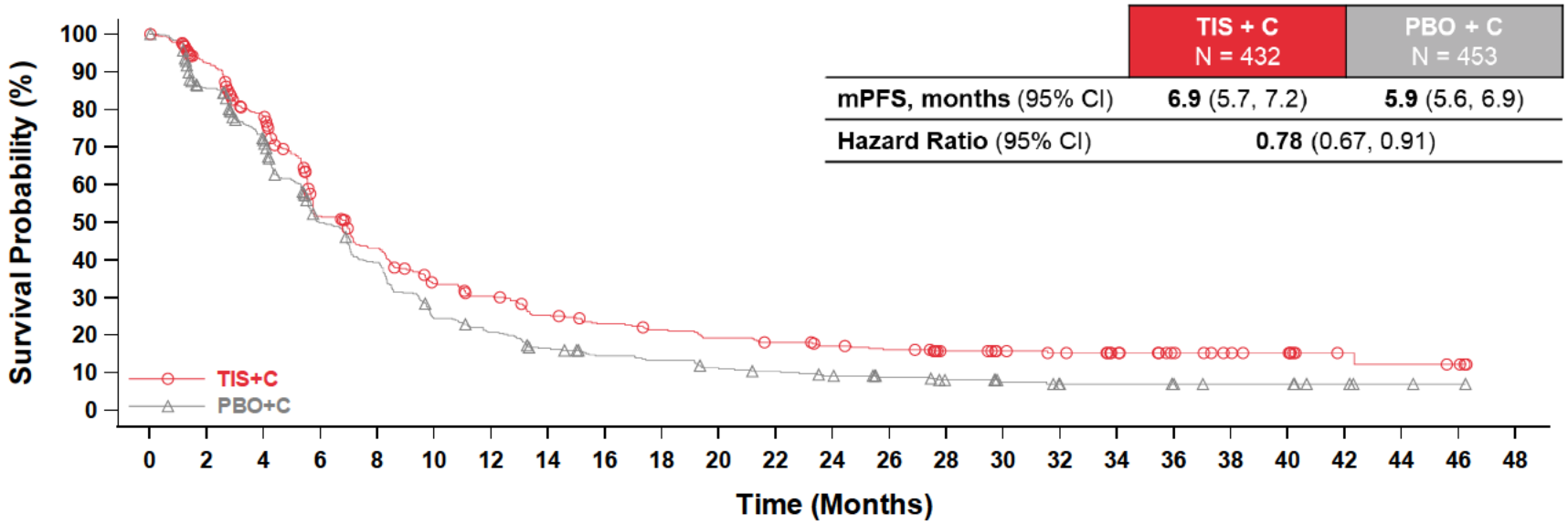
Abbreviations: CI, confidence interval; mPFS, median progression-free survival; PBO+C, placebo + chemotherapy; PD-L1, programmed cell death protein ligand-1; TAP, tumor area positive; TIS+C, tislelizumab + chemotherapy.

PD-L1 TAP score was determined with VENTANA PD-L1 (SP263) Assay.

Hazard ratio was based on unstratified Cox regression model.

'+' = censored.

PD-L1 Status: TAP ≥ 1%



	TIS + C N = 432	PBO + C N = 453
mPFS, months (95% CI)	**6.9** (5.7, 7.2)	**5.9** (5.6, 6.9)
Hazard Ratio (95% CI)	**0.78** (0.67, 0.91)	

No. At Risk:

TIS+C	432	374	308	192	157	119	105	86	76	70	63	58	52	48	37	33	30	25	19	15	12	5	4	3	0
PBO+C	453	361	297	193	151	93	78	60	50	46	38	34	29	24	19	14	11	10	9	7	7	4	2	1	0

Data cutoff: 28FEB2023.

Abbreviations: CI, confidence interval; mPFS, median progression-free survival; PBO+C, placebo + chemotherapy; PD-L1, programmed cell death protein ligand-1; TAP, tumor area positive; TIS+C, tislelizumab + chemotherapy.

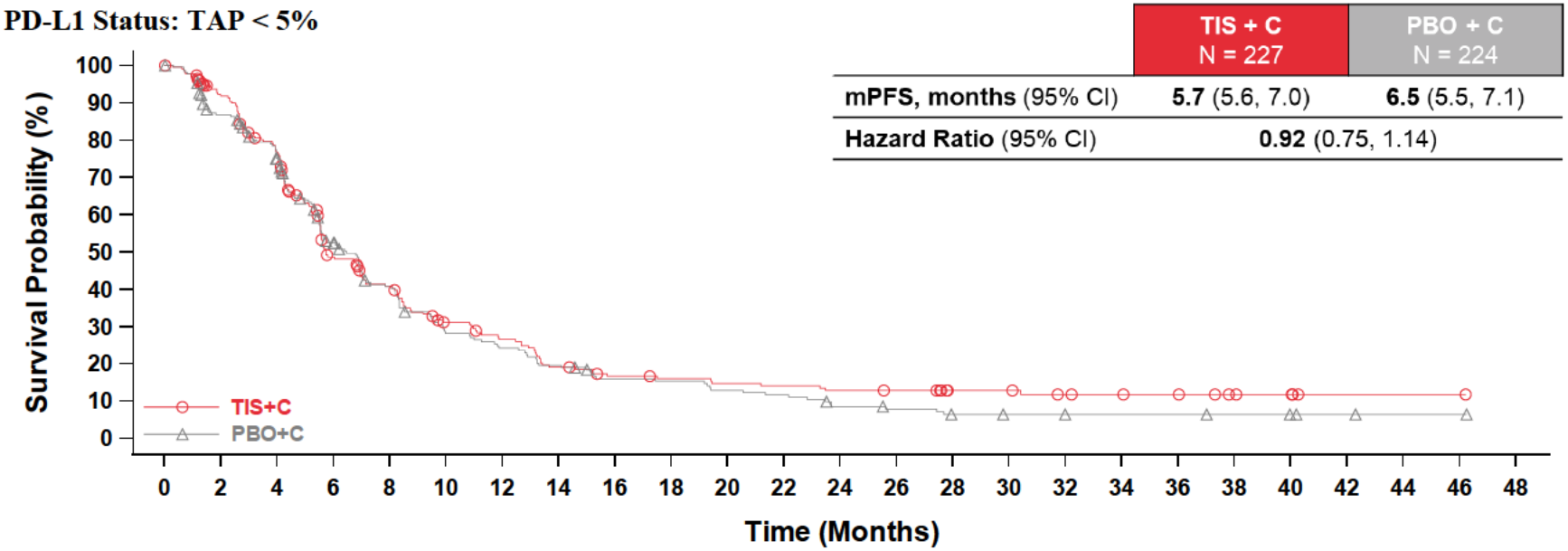
PD-L1 TAP score was determined with VENTANA PD-L1 (SP263) Assay.

Hazard ratio was based on unstratified Cox regression model.

'+' = censored.

Figure 20: Kaplan-Meier Plot of Progression-Free Survival of Baseline PD-L1 Subgroups with TAP < 5% at the Final Analysis (ITT Analysis Set)

PD-L1 Status: TAP < 5%



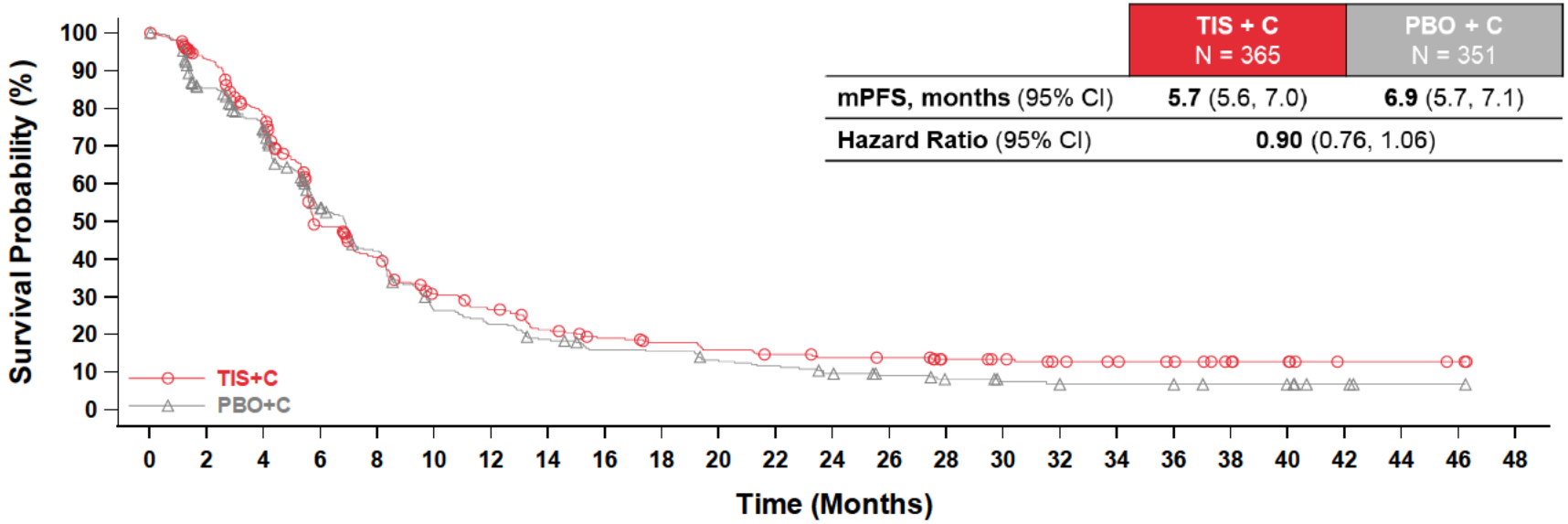
No. At Risk:

TIS+C	227	197	161	95	77	55	46	33	27	25	23	22	20	19	13	13	10	9	8	5	4	1	1	1	0
PBO+C	224	180	151	97	72	49	42	34	26	25	21	19	13	11	8	6	6	5	5	4	3	2	1	1	0

Data cutoff: 28FEB2023.
Abbreviations: CI, confidence interval; mPFS, median progression-free survival; PBO+C, placebo + chemotherapy; PD-L1, programmed cell death protein ligand-1; TAP, tumor area positive; TIS+C, tislelizumab + chemotherapy.
PD-L1 TAP score was determined with VENTANA PD-L1 (SP263) Assay.
Hazard ratio was based on unstratified Cox regression model.
'+' = censored.

Figure 21: Kaplan-Meier Plot of Progression-Free Survival of Baseline PD-L1 Subgroups with TAP Cutoff of 10% at the Final Analysis (ITT Analysis Set)

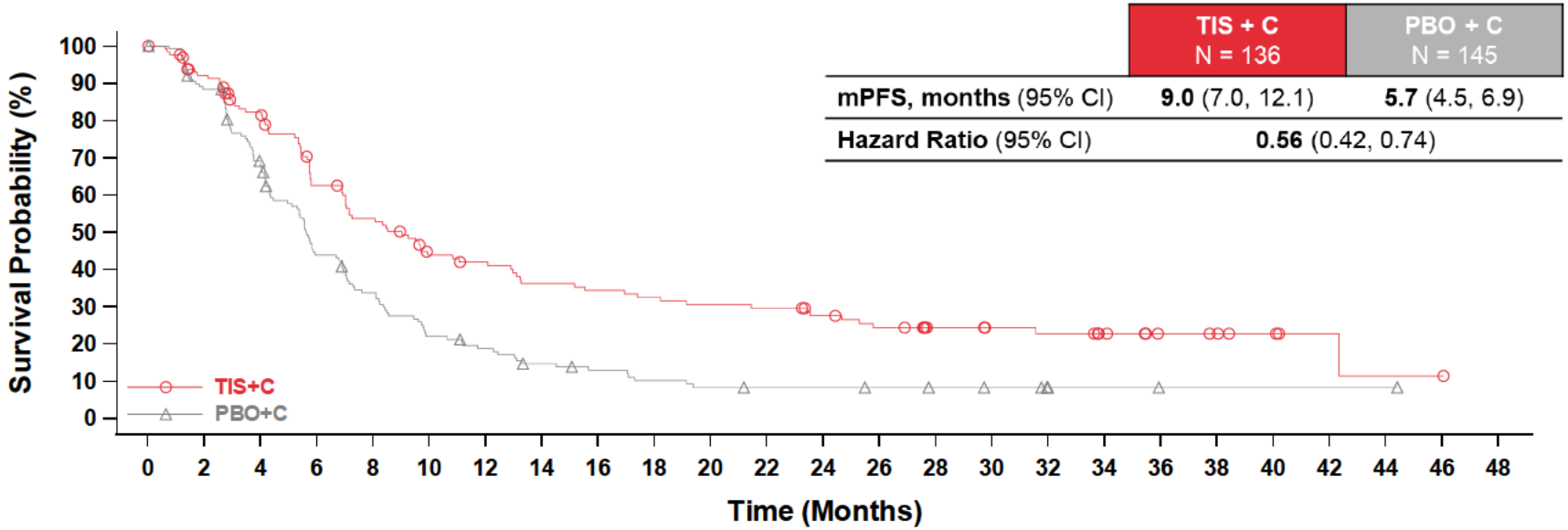
PD-L1 Status: TAP < 10%



No. At Risk:

TIS+C	365	320	263	154	123	89	76	59	50	45	40	36	33	32	24	22	18	16	14	10	8	3	3	2	0
PBO+C	351	278	235	154	118	72	62	50	41	40	33	29	23	19	15	11	10	9	9	7	6	3	1	1	0

PD-L1 Status: TAP ≥ 10%



No. At Risk:

TIS+C	136	114	98	72	61	47	44	38	36	34	32	31	27	23	17	15	14	11	7	6	4	2	1	1	0
PBO+C	145	121	92	57	43	28	23	17	14	11	9	8	8	7	6	5	3	2	1	1	1	1	1	0	0

Data cutoff: 28FEB2023.

Abbreviations: CI, confidence interval; mPFS, median progression-free survival; PBO+C, placebo + chemotherapy; PD-L1, programmed cell death protein ligand-1; TAP, tumor area positive; TIS+C, tislelizumab + chemotherapy.

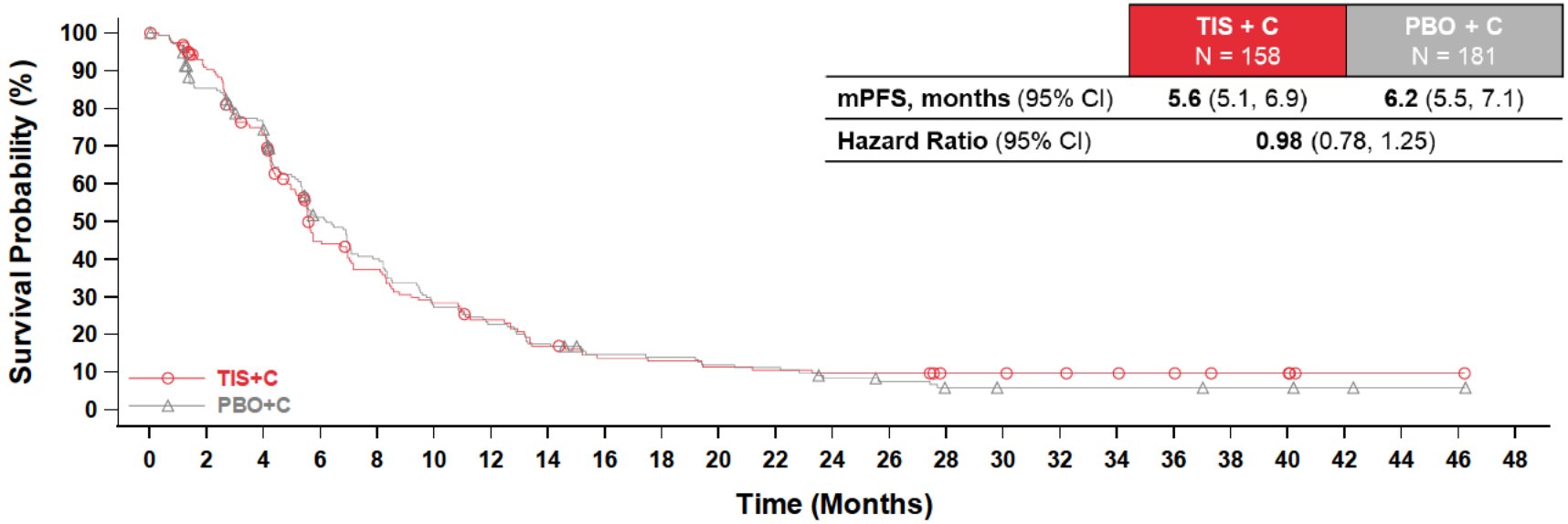
PD-L1 TAP score was determined with VENTANA PD-L1 (SP263) Assay.

Hazard ratio was based on unstratified Cox regression model.

'+' = censored.

Figure 22: Kaplan-Meier Plot of Progression-Free Survival of Baseline PD-L1 Category of TAP at the Final Analysis (ITT Analysis Set)

PD-L1 Status: TAP Score ≥ 1% - < 5%



	TIS + C N = 158	PBO + C N = 181
mPFS, months (95% CI)	**5.6** (5.1, 6.9)	**6.2** (5.5, 7.1)
Hazard Ratio (95% CI)	**0.98** (0.78, 1.25)	

No. At Risk:

TIS+C	158	137	108	61	50	38	31	22	17	16	14	13	12	12	9	9	8	7	6	4	4	1	1	1	0
PBO+C	181	142	121	79	62	42	35	27	21	20	17	16	11	9	6	4	4	4	4	3	3	2	1	1	0

Data cutoff: 28FEB2023.

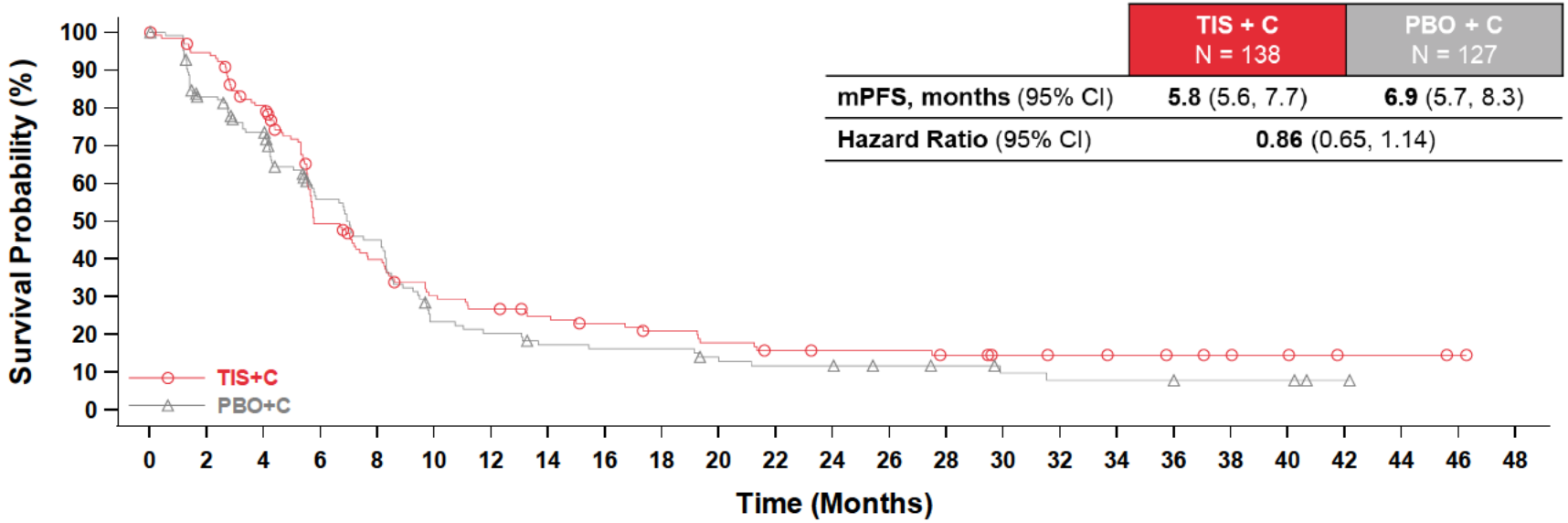
Abbreviations: CI, confidence interval; mPFS, median progression-free survival; PBO+C, placebo + chemotherapy; PD-L1, programmed cell death protein ligand-1; TAP, tumor area positive; TIS+C, tislelizumab + chemotherapy.

PD-L1 TAP score was determined with VENTANA PD-L1 (SP263) Assay.

Hazard ratio was based on unstratified Cox regression model.

'+' = censored.

PD-L1 Status: TAP Score ≥ 5% - < 10%



	TIS + C N = 138	PBO + C N = 127
mPFS, months (95% CI)	**5.8** (5.6, 7.7)	**6.9** (5.7, 8.3)
Hazard Ratio (95% CI)	**0.86** (0.65, 1.14)	

No. At Risk:

TIS+C	138	123	102	59	46	34	30	26	23	20	17	14	13	13	11	9	8	7	6	5	4	2	2	1	0
PBO+C	127	98	84	57	46	23	20	16	15	15	12	10	10	8	7	5	4	4	4	3	3	1	0	0	0

Data cutoff: 28FEB2023.
Abbreviations: CI, confidence interval; mPFS, median progression-free survival; PBO+C, placebo + chemotherapy; PD-L1, programmed cell death protein ligand-1; TAP, tumor area positive; TIS+C, tislelizumab + chemotherapy.
PD-L1 TAP score was determined with VENTANA PD-L1 (SP263) Assay.
Hazard ratio was based on unstratified Cox regression model.
'+' = censored.

Table 14: Overall Summary of TEAEs in Patients With PD-L1 Score < 5%, PD-L1 Score ≥ 5%, and Overall Patients (Safety Analysis Set)

	PD-L1 score < 5%		PD-L1 score ≥ 5%		Overall Patients	
	TIS+C (N = 226) n (%)	PBO+C (N = 222) n (%)	TIS+C (N = 272) n (%)	PBO+C (N = 272) n (%)	TIS+C (N = 498) n (%)	PBO+C (N = 494) n (%)
Patients with at Least One TEAE	224 (99.1)	220 (99.1)	271 (99.6)	266 (97.8)	495 (99.4)	486 (98.4)
Treatment-Related TEAE for Any Treatment Component	219 (96.9)	215 (96.8)	264 (97.1)	261 (96.0)	483 (97.0)	476 (96.4)
TIS- or PBO-Related TEAE	144 (63.7)	107 (48.2)	177 (65.1)	154 (56.6)	321 (64.5)	261 (52.8)
Any Chemo Component Related TEAE	217 (96.0)	214 (96.4)	262 (96.3)	261 (96.0)	479 (96.2)	475 (96.2)
TEAE of ≥ Grade 3	159 (70.4)	147 (66.2)	186 (68.4)	177 (65.1)	345 (69.3)	324 (65.6)
Treatment-Related TEAE of ≥ Grade 3 for Any Treatment Component	117 (51.8)	110 (49.5)	151 (55.5)	136 (50.0)	268 (53.8)	246 (49.8)
TIS- or PBO-Related TEAE of ≥ Grade 3	53 (23.5)	36 (16.2)	79 (29.0)	58 (21.3)	132 (26.5)	94 (19.0)
Any Chemo Component Related TEAE of ≥ Grade 3	108 (47.8)	108 (48.6)	137 (50.4)	133 (48.9)	245 (49.2)	241 (48.8)
Serious TEAE	85 (37.6)	78 (35.1)	125 (46.0)	100 (36.8)	210 (42.2)	178 (36.0)
Treatment-Related Serious TEAE for Any Treatment Component	40 (17.7)	28 (12.6)	73 (26.8)	44 (16.2)	113 (22.7)	72 (14.6)
TIS- or PBO-Related Serious TEAE	32 (14.2)	15 (6.8)	51 (18.8)	23 (8.5)	83 (16.7)	38 (7.7)
Any Chemo Component Related Serious TEAE	27 (11.9)	25 (11.3)	62 (22.8)	42 (15.4)	89 (17.9)	67 (13.6)
TEAE Leading to Death	11/226 (4.9)	9/222 (4.1)	10/272 (3.7)	9/272 (3.3)	21 (4.2)	18 (3.6)
Treatment-Related TEAE Leading to Death for Any Treatment Component	3/226 (1.3)	2/222 (0.9)	3/272 (1.1)	0/272 (0.0)	6 (1.2)	2 (0.4)
TIS- or PBO-Related TEAE Leading to Death	3/226 (1.3)	2/222 (0.9)	2/272 (0.7)	0/272 (0.0)	5 (1.0)	2 (0.4)
Any Chemo Component Related TEAE Leading to Death	3/226 (1.3)	2/222 (0.9)	2/272 (0.7)	0/272 (0.0)	5 (1.0)	2 (0.4)
TEAE Leading to Discontinuation of Any Treatment Component	48 (21.2)	31 (14.0)	66 (24.3)	36 (13.2)	114 (22.9)	67 (13.6)
TEAE Leading to Discontinuation of TIS or PBO	34 (15.0)	16 (7.2)	44 (16.2)	20 (7.4)	78 (15.7)	36 (7.3)

	PD-L1 score < 5%		PD-L1 score ≥ 5%		Overall Patients	
	TIS+C (N = 226) n (%)	PBO+C (N = 222) n (%)	TIS+C (N = 272) n (%)	PBO+C (N = 272) n (%)	TIS+C (N = 498) n (%)	PBO+C (N = 494) n (%)
TEAE Leading to Discontinuation of Any Chemo Component	45 (19.9)	29 (13.1)	59 (21.7)	33 (12.1)	104 (20.9)	62 (12.6)
TEAE Leading to Dose Modification of Any Treatment Component [a]	169 (74.8)	175 (78.8)	212 (77.9)	200 (73.5)	381 (76.5)	375 (75.9)
TEAE Leading to Dose Modification of TIS or PBO	102 (45.1)	117 (52.7)	142 (52.2)	122 (44.9)	244 (49.0)	239 (48.4)
TEAE Leading to Dose Modification of Any Chemo Component	169 (74.8)	175 (78.8)	209 (76.8)	197 (72.4)	378 (75.9)	372 (75.3)
Immune-Mediated AEs	76 (33.6)	24 (10.8)	78 (28.7)	34 (12.5)	154 (30.9)	58 (11.7)
Immune-Mediated AEs of Grade 3 or Higher	17 (7.5)	5 (2.3)	21 (7.7)	5 (1.8)	38 (7.6)	10 (2.0)

Data cutoff: 28FEB2023.
Abbreviations: PBO+C, placebo + chemotherapy; TIS+C, tislelizumab + chemotherapy; TEAE, treatment-emergent adverse event.
Percentages were based on N.
TEAE definition includes any AE which occurred on or after the first dose of study drug (tislelizumab/placebo or chemotherapy) up to 30 days following study drug (any component of combination treatment, whichever is last) or initiation of new anticancer therapy.
For each row category, a patient with 2 or more adverse events in that category is counted only once.
Adverse events terms are coded using Medical Dictionary for Regulatory Activities (MedDRA) version 24.0 and graded per NCI-CTCAE v5.0
[a] The types of dose modification include dose delay, dose interruption, dose reduction, and infusion rate decreased for chemotherapy and dose delay, dose interruption, and infusion rate decreased for tislelizumab/placebo.

Table 15: Treatment-Emergent Adverse Events With ≥ Grade 3 and an Incidence ≥ 2% by Preferred Term in Patients With PD-L1 Score < 5%, PD-L1 Score ≥ 5%, and Overall Patients at the Final Analysis (Safety Analysis Set)

	PD-L1 Score < 5%		PD-L1 Score ≥ 5%		Overall	
Preferred Term	TIS+C (N = 226) n (%)	PBO+C (N = 222) n (%)	TIS+C (N = 272) n (%)	PBO+C (N = 272) n (%)	TIS+C (N = 498) n (%)	PBO+C (N = 494) n (%)
Patients with at Least One ≥ Grade 3 TEAE	159 (70.4)	147 (66.2)	186 (68.4)	177 (65.1)	345 (69.3)	324 (65.6)
Neutrophil count decreased	20 (8.8)	26 (11.7)	39 (14.3)	32 (11.8)	59 (11.8)	58 (11.7)
Platelet count decreased	26 (11.5)	25 (11.3)	31 (11.4)	34 (12.5)	57 (11.4)	59 (11.9)
Anaemia	16 (7.1)	20 (9.0)	24 (8.8)	33 (12.1)	40 (8.0)	53 (10.7)
Neutropenia	14 (6.2)	19 (8.6)	19 (7.0)	15 (5.5)	33 (6.6)	34 (6.9)
Hypokalaemia	6 (2.7)	8 (3.6)	15 (5.5)	7 (2.6)	21 (4.2)	15 (3.0)
Decreased appetite	6 (2.7)	6 (2.7)	13 (4.8)	12 (4.4)	19 (3.8)	18 (3.6)
Aspartate aminotransferase increased	5 (2.2)	5 (2.3)	12 (4.4)	0 (0.0)	17 (3.4)	5 (1.0)
Nausea	5 (2.2)	4 (1.8)	9 (3.3)	7 (2.6)	14 (2.8)	11 (2.2)
White blood cell count decreased	6 (2.7)	3 (1.4)	9 (3.3)	5 (1.8)	15 (3.0)	8 (1.6)
Asthenia	5 (2.2)	9 (4.1)	8 (2.9)	4 (1.5)	13 (2.6)	13 (2.6)
Diarrhoea	6 (2.7)	3 (1.4)	8 (2.9)	8 (2.9)	14 (2.8)	11 (2.2)
Fatigue	4 (1.8)	3 (1.4)	8 (2.9)	5 (1.8)	12 (2.4)	8 (1.6)
Palmar-plantar erythrodysaesthesia syndrome	7 (3.1)	7 (3.2)	8 (2.9)	4 (1.5)	15 (3.0)	11 (2.2)
Blood bilirubin increased	5 (2.2)	4 (1.8)	7 (2.6)	3 (1.1)	12 (2.4)	7 (1.4)
Vomiting	5 (2.2)	6 (2.7)	7 (2.6)	7 (2.6)	12 (2.4)	13 (2.6)
Alanine aminotransferase increased	5 (2.2)	3 (1.4)	6 (2.2)	2 (0.7)	11 (2.2)	5 (1.0)
Pneumonia	3 (1.3)	7 (3.2)	6 (2.2)	7 (2.6)	9 (1.8)	14 (2.8)
Ascites	10 (4.4)	4 (1.8)	5 (1.8)	1 (0.4)	15 (3.0)	5 (1.0)
Death	5 (2.2)	3 (1.4)	5 (1.8)	2 (0.7)	10 (2.0)	5 (1.0)
Leukopenia	1 (0.4)	5 (2.3)	5 (1.8)	2 (0.7)	6 (1.2)	7 (1.4)
Thrombocytopenia	12 (5.3)	4 (1.8)	4 (1.5)	11 (4.0)	16 (3.2)	15 (3.0)
Hyponatraemia	6 (2.7)	2 (0.9)	2 (0.7)	3 (1.1)	8 (1.6)	5 (1.0)
Blood alkaline phosphatase increased	1 (0.4)	6 (2.7)	0 (0.0)	2 (0.7)	1 (0.2)	8 (1.6)

Data cutoff: 28FEB2023.
Abbreviations: PBO+C, placebo + chemotherapy; TIS+C, tislelizumab + chemotherapy; TEAE, treatment-emergent adverse event.
PD-L1 TAP score was determined with VENTANA PD-L1 (SP263) Assay. Percentages were based on N.
Patients with two or more adverse events in the same preferred term are counted only once for that preferred term.

Adverse events terms are coded using Medical Dictionary for Regulatory Activities (MedDRA) version 24.0
Adverse events are sorted by decreasing frequency in the TIS+C column of PD-L1 score ≥5% group.

Table 16: Serious Treatment-Emergent Adverse Events With an Incidence ≥ 1% by Preferred Term in Patients With PD-L1 Score < 5%, PD-L1 Score ≥ 5%, and Overall Patients (Safety Analysis Set)

	PD-L1 Score < 5%		PD-L1 Score ≥ 5%		Overall	
Preferred Term	**TIS+C (N = 226) n (%)**	**PBO+C (N = 222) n (%)**	**TIS+C (N = 272) n (%)**	**PBO+C (N = 272) n (%)**	**TIS+C (N = 498) n (%)**	**PBO+C (N = 494) n (%)**
Patients with at Least One Serious TEAE	85 (37.6)	78 (35.1)	125 (46.0)	100 (36.8)	210 (42.2)	178 (36.0)
Platelet count decreased	7 (3.1)	7 (3.2)	9 (3.3)	10 (3.7)	16 (3.2)	17 (3.4)
Decreased appetite	0 (0.0)	1 (0.5)	7 (2.6)	4 (1.5)	7 (1.4)	5 (1.0)
Pneumonia	5 (2.2)	8 (3.6)	7 (2.6)	6 (2.2)	12 (2.4)	14 (2.8)
Diarrhoea	0 (0.0)	2 (0.9)	6 (2.2)	2 (0.7)	6 (1.2)	4 (0.8)
Cholangitis	1 (0.4)	1 (0.5)	5 (1.8)	0 (0.0)	6 (1.2)	1 (0.2)
Death	5 (2.2)	3 (1.4)	5 (1.8)	2 (0.7)	10 (2.0)	5 (1.0)
Aspartate aminotransferase increased	1 (0.4)	1 (0.5)	4 (1.5)	0 (0.0)	5 (1.0)	1 (0.2)
COVID-19 pneumonia	0 (0.0)	0 (0.0)	4 (1.5)	0 (0.0)	4 (0.8)	0 (0.0)
Gastric haemorrhage	2 (0.9)	0 (0.0)	4 (1.5)	1 (0.4)	6 (1.2)	1 (0.2)
General physical health deterioration	2 (0.9)	2 (0.9)	4 (1.5)	5 (1.8)	6 (1.2)	7 (1.4)
Hepatic function abnormal	0 (0.0)	0 (0.0)	4 (1.5)	1 (0.4)	4 (0.8)	1 (0.2)
Nausea	0 (0.0)	3 (1.4)	4 (1.5)	2 (0.7)	4 (0.8)	5 (1.0)
Pyrexia	2 (0.9)	4 (1.8)	4 (1.5)	2 (0.7)	6 (1.2)	6 (1.2)
Vomiting	3 (1.3)	2 (0.9)	4 (1.5)	3 (1.1)	7 (1.4)	5 (1.0)
Acute kidney injury	2 (0.9)	1 (0.5)	3 (1.1)	1 (0.4)	5 (1.0)	2 (0.4)
Gastrointestinal haemorrhage	3 (1.3)	1 (0.5)	3 (1.1)	1 (0.4)	6 (1.2)	2 (0.4)
Immune-mediated hepatitis	2 (0.9)	1 (0.5)	3 (1.1)	0 (0.0)	5 (1.0)	1 (0.2)
Pneumonitis	1 (0.4)	0 (0.0)	3 (1.1)	0 (0.0)	4 (0.8)	0 (0.0)
Pulmonary embolism	2 (0.9)	2 (0.9)	3 (1.1)	2 (0.7)	5 (1.0)	4 (0.8)
Sepsis	3 (1.3)	1 (0.5)	3 (1.1)	1 (0.4)	6 (1.2)	2 (0.4)
Upper gastrointestinal haemorrhage	1 (0.4)	3 (1.4)	3 (1.1)	4 (1.5)	4 (0.8)	7 (1.4)
Anaemia	2 (0.9)	4 (1.8)	2 (0.7)	6 (2.2)	4 (0.8)	10 (2.0)
Ascites	3 (1.3)	3 (1.4)	2 (0.7)	2 (0.7)	5 (1.0)	5 (1.0)
Enterocolitis	0 (0.0)	0 (0.0)	1 (0.4)	3 (1.1)	1 (0.2)	3 (0.6)
Ileus	4 (1.8)	3 (1.4)	1 (0.4)	1 (0.4)	5 (1.0)	4 (0.8)

Preferred Term	PD-L1 Score < 5%		PD-L1 Score ≥ 5%		Overall	
	TIS+C (N = 226) n (%)	PBO+C (N = 222) n (%)	TIS+C (N = 272) n (%)	PBO+C (N = 272) n (%)	TIS+C (N = 498) n (%)	PBO+C (N = 494) n (%)
Stomatitis	1 (0.4)	0 (0.0)	1 (0.4)	3 (1.1)	2 (0.4)	3 (0.6)
Tumour haemorrhage	1 (0.4)	0 (0.0)	1 (0.4)	4 (1.5)	2 (0.4)	4 (0.8)
Biliary obstruction	0 (0.0)	3 (1.4)	0 (0.0)	0 (0.0)	0 (0.0)	3 (0.6)
Febrile neutropenia	0 (0.0)	1 (0.5)	0 (0.0)	3 (1.1)	0 (0.0)	4 (0.8)
Obstruction gastric	1 (0.4)	3 (1.4)	0 (0.0)	2 (0.7)	1 (0.2)	5 (1.0)
Respiratory failure	4 (1.8)	0 (0.0)	0 (0.0)	0 (0.0)	4 (0.8)	0 (0.0)
Thrombocytopenia	0 (0.0)	0 (0.0)	0 (0.0)	3 (1.1)	0 (0.0)	3 (0.6)

Data cutoff: 28FEB2023.
Abbreviations: PBO+C, placebo + chemotherapy; PD-L1, programmed death ligand 1; TEAE, treatment-emergent adverse event; TIS+C, tislelizumab + chemotherapy.
PD-L1 TAP score was determined with VENTANA PD-L1 (SP263) Assay. Percentages were based on N.
Patients with two or more adverse events in the same preferred term are counted only once for that preferred term.
Adverse events terms are coded using Medical Dictionary for Regulatory Activities (MedDRA) version 24.0
Adverse events are sorted by decreasing frequency in the TIS+C column of PD-L1 score ≥5% group.

Table 17: Treatment-Emergent Adverse Events Leading to Treatment Discontinuation With an Incidence ≥ 1% by Preferred Term in Patients With PD-L1 Score < 5%, PD-L1 Score ≥ 5%, and Overall Patients (Safety Analysis Set)

Preferred Term	PD-L1 Score < 5%		PD-L1 Score ≥ 5%		Overall	
	TIS+C (N = 226) n (%)	PBO+C (N = 222) n (%)	TIS+C (N = 272) n (%)	PBO+C (N = 272) n (%)	TIS+C (N = 498) n (%)	PBO+C (N = 494) n (%)
Patients with at Least One TEAE Leading to Treatment Discontinuation	48 (21.2)	31 (14.0)	66 (24.3)	36 (13.2)	114 (22.9)	67 (13.6)
Death	2 (0.9)	1 (0.5)	4 (1.5)	1 (0.4)	6 (1.2)	2 (0.4)
Peripheral sensory neuropathy	2 (0.9)	0 (0.0)	3 (1.1)	2 (0.7)	5 (1.0)	2 (0.4)
Platelet count decreased	2 (0.9)	4 (1.8)	3 (1.1)	3 (1.1)	5 (1.0)	7 (1.4)
Pneumonitis	2 (0.9)	0 (0.0)	3 (1.1)	0 (0.0)	5 (1.0)	0 (0.0)
General physical health deterioration	0 (0.0)	0 (0.0)	2 (0.7)	3 (1.1)	2 (0.4)	3 (0.6)
Neutrophil count decreased	2 (0.9)	3 (1.4)	1 (0.4)	2 (0.7)	3 (0.6)	5 (1.0)
Anaemia	0 (0.0)	2 (0.9)	0 (0.0)	3 (1.1)	0 (0.0)	5 (1.0)
Blood bilirubin increased	3 (1.3)	0 (0.0)	0 (0.0)	0 (0.0)	3 (0.6)	0 (0.0)
Gastrointestinal haemorrhage	3 (1.3)	0 (0.0)	0 (0.0)	0 (0.0)	3 (0.6)	0 (0.0)

Data cutoff: 28FEB2023.
Abbreviations: PBO+C, placebo + chemotherapy; PD-L1, programmed death ligand 1; TEAE, treatment-emergent adverse event; TIS+C, tislelizumab + chemotherapy.
PD-L1 TAP score was determined with VENTANA PD-L1 (SP263) Assay. Percentages were based on N.
Patients with two or more adverse events in the same preferred term are counted only once for that preferred term.
Adverse events terms are coded using Medical Dictionary for Regulatory Activities (MedDRA) version 24.0
Adverse events are sorted by decreasing frequency in the TIS+C column of PD-L1 score ≥5% group.

Table 18: Treatment-Emergent Adverse Events Leading to Death by Preferred Term in Patients With PD-L1 Score < 5%, PD-L1 Score ≥ 5%, and Overall Patients (Safety Analysis Set)

Preferred Term	PD-L1 Score < 5%		PD-L1 Score ≥ 5%		Overall	
	TIS+C (N = 226) n (%)	PBO+C (N = 222) n (%)	TIS+C (N = 272) n (%)	PBO+C (N = 272) n (%)	TIS+C (N = 498) n (%)	PBO+C (N = 494) n (%)
Patients with at Least One TEAE Leading to Death	11 (4.9)	9 (4.1)	10 (3.7)	9 (3.3)	21 (4.2)	18 (3.6)
Death	4 (1.8)	1 (0.5)	4 (1.5)	1 (0.4)	8 (1.6)	2 (0.4)
Pneumonia	0 (0.0)	2 (0.9)	1 (0.4)	0 (0.0)	1 (0.2)	2 (0.4)
Pulmonary embolism	1 (0.4)	1 (0.5)	1 (0.4)	1 (0.4)	2 (0.4)	2 (0.4)
Sepsis	2 (0.9)	0 (0.0)	1 (0.4)	1 (0.4)	3 (0.6)	1 (0.2)
Shock haemorrhagic	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)	1 (0.2)	0 (0.0)
Subdural haematoma	0 (0.0)	0 (0.0)	1 (0.4)	1 (0.4)	1 (0.2)	1 (0.2)
Sudden death	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)	1 (0.2)	0 (0.0)
Arteriosclerosis	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)	1 (0.2)
Brain herniation	0 (0.0)	1 (0.5)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)
COVID-19	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)	1 (0.2)
Cardiopulmonary failure	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)	1 (0.2)
Cerebrovascular accident	0 (0.0)	1 (0.5)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)
Colitis	1 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)
Completed suicide	0 (0.0)	1 (0.5)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)
Gallbladder obstruction	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)	1 (0.2)
Hepatic failure	0 (0.0)	1 (0.5)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)
Left ventricular failure	0 (0.0)	1 (0.5)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)
Peritonitis	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)	1 (0.2)
Pneumonia bacterial	1 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)
Respiratory failure	2 (0.9)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.4)	0 (0.0)
Respiratory tract infection viral	1 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)

Data cutoff: 28FEB2023.
Abbreviations: PBO+C, placebo + chemotherapy; PD-L1, programmed death ligand 1; TEAE, treatment-emergent adverse event; TIS+C, tislelizumab + chemotherapy.
Percentages were based on N. Patients with two or more adverse events in the same preferred term are counted only once for that preferred term.
Adverse events terms are coded using Medical Dictionary for Regulatory Activities (MedDRA) version 24.0

Adverse events are sorted by decreasing frequency in the TIS+C column of PD-L1 score ≥5% group.
Those death events due to disease under study are not included as TEAEs leading to Death. 'Disease Under Study' is one of the primary death causes which can be found in CRF page 'Subject Discontinuation from the Study'.

Table 19: Immune-Mediated Adverse Events by Category in Patients With PD-L1 Score < 5%, PD-L1 Score ≥ 5%, and Overall Patients (Safety Analysis Set)

Category	PD-L1 Score < 5%		PD-L1 Score ≥ 5%		Overall	
	TIS+C (N = 226) n (%)	PBO+C (N = 222) n (%)	TIS+C (N = 272) n (%)	PBO+C (N = 272) n (%)	TIS+C (N = 498) n (%)	PBO+C (N = 494) n (%)
Patients with at Least One Immune-Mediated Adverse Events	76 (33.6)	24 (10.8)	78 (28.7)	34 (12.5)	154 (30.9)	58 (11.7)
Immune-mediated pneumonitis	8 (3.5)	1 (0.5)	11 (4.0)	1 (0.4)	19 (3.8)	2 (0.4)
Immune-mediated hepatitis	4 (1.8)	2 (0.9)	6 (2.2)	0 (0.0)	10 (2.0)	2 (0.4)
Immune-mediated skin adverse reaction	25 (11.1)	5 (2.3)	28 (10.3)	10 (3.7)	53 (10.6)	15 (3.0)
Immune-mediated colitis	2 (0.9)	3 (1.4)	4 (1.5)	7 (2.6)	6 (1.2)	10 (2.0)
Immune-mediated myositis/rhabdomyolysis	3 (1.3)	1 (0.5)	0 (0.0)	1 (0.4)	3 (0.6)	2 (0.4)
Immune-mediated endocrinopathies (hypothyroidism)	30 (13.3)	8 (3.6)	33 (12.1)	7 (2.6)	63 (12.7)	15 (3.0)
Immune-mediated endocrinopathies (hyperthyroidism)	7 (3.1)	3 (1.4)	9 (3.3)	2 (0.7)	16 (3.2)	5 (1.0)
Immune-mediated endocrinopathies (thyroiditis)	0 (0.0)	1 (0.5)	3 (1.1)	1 (0.4)	3 (0.6)	2 (0.4)
Immune-mediated endocrinopathies (adrenal insufficiency)	1 (0.4)	0 (0.0)	2 (0.7)	2 (0.7)	3 (0.6)	2 (0.4)
Immune-mediated endocrinopathies (hypophysitis)	1 (0.4)	0 (0.0)	1 (0.4)	1 (0.4)	2 (0.4)	1 (0.2)
Immune-mediated endocrinopathies (diabetes mellitus)	3 (1.3)	0 (0.0)	5 (1.8)	1 (0.4)	8 (1.6)	1 (0.2)
Immune-mediated nephritis and renal dysfunction	1 (0.4)	0 (0.0)	2 (0.7)	0 (0.0)	3 (0.6)	0 (0.0)
Immune-mediated myocarditis/pericarditis	2 (0.9)	0 (0.0)	2 (0.7)	1 (0.4)	4 (0.8)	1 (0.2)
Other immune-mediated reactions (pancreatitis)	2 (0.9)	1 (0.5)	0 (0.0)	0 (0.0)	2 (0.4)	1 (0.2)
Other immune-mediated reactions (CNS)	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)	1 (0.2)	0 (0.0)
Other immune-mediated reactions (blood dyscrasias)	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)	1 (0.2)	0 (0.0)
Other immune-mediated reactions (musculoskeletal)	2 (0.9)	0 (0.0)	3 (1.1)	0 (0.0)	5 (1.0)	0 (0.0)
Other immune-mediated reactions (other)	2 (0.9)	3 (1.4)	0 (0.0)	2 (0.7)	2 (0.4)	5 (1.0)

Data cutoff: 28FEB2023.
Abbreviations: imAE, immune-mediated adverse event; PBO+C, placebo + chemotherapy; PD-L1, programmed death ligand 1; TEAE, treatment-emergent adverse event; TIS+C, tislelizumab + chemotherapy.

Percentages were based on N. imAE categories are presented by a pre-specified order. Patients with multiple events for a given category were counted only once.
Immune-mediated AEs are identified from all AEs that had an onset date or a worsening in severity from baseline (pretreatment) on or after the first dose of study drug and up to 90 days from the last dose of study drug, regardless of whether the patient starts a new anticancer therapy.
Adverse events terms are coded using Medical Dictionary for Regulatory Activities (MedDRA) version 24.0. imAE identified based on imAE CCQ v2.2.

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