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ORIGINAL RESEARCH

First-Line Tislelizumab Plus Chemotherapy for Advanced Gastric Cancer with Programmed Death-Ligand 1 Expression ≥ 1%: A Retrospective Analysis of RATIONALE-305

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ABSTRACT

Introduction: Tislelizumab plus investigator-chosen chemotherapy (ICC) demonstrated a statistically significant improvement in overall survival (OS) versus placebo plus ICC in RATIONALE-305 in patients with locally advanced unresectable or metastatic human epidermal growth factor receptor 2 (HER2)-negative gastric cancer/gastroesophageal junction cancer (GC/GEJC) in the intent-to-treat population and in patients with programmed death-ligand 1 (PD-L1) Tumor Area Positivity (TAP) score ≥ 5%. The United States Food and Drug Administration Oncologic Drugs Advisory Committee voted (September 2024) against first-line treatment with programmed cell death protein-1 inhibitors in this setting in patients with a PD-L1 combined positive score < 1 or TAP score < 1%, due to an unfavorable benefit–risk profile. Thus, we retrospectively analyzed data

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from RATIONALE-305 in patients with a PD-L1 TAP score ≥ 1%.

***Methods*:** Adult patients with locally advanced unresectable or metastatic HER2-negative GC/GEJC were randomized to tislelizumab 200 mg or placebo with ICC every 3 weeks. Efficacy and safety outcomes of tislelizumab plus ICC versus placebo plus ICC were retrospectively assessed in those with a PD-L1 TAP score ≥ 1%.

***Results*:** At the final analysis cutoff (February 28, 2023), 432 patients received tislelizumab plus ICC and 453 received placebo plus ICC, and had a PD-L1 TAP score ≥ 1%. Clinically meaningful improvements to OS were observed with tislelizumab plus ICC compared with placebo plus ICC [15.0 months (95% confidence interval [CI] 13.3–16.7) vs. 12.8 months (95% CI 12.1–14.1), respectively; stratified hazard ratio 0.77 (95% CI 0.67–0.90)]. Progression-free survival, overall response rate, duration of response, and disease control rate, were also improved. OS improvements were maintained at a 3-year data cutoff (February 28, 2024). Tislelizumab plus ICC had an acceptable safety profile with no new safety signals.

***Conclusions*:** Tislelizumab plus ICC is an effective and tolerable first-line treatment for patients with locally advanced unresectable or metastatic HER2-negative GC/GEJC with a PD-L1 TAP score ≥ 1%.

***Trial registration number*:** NCT03777657.

Keywords: Clinical trial; Gastric cancer; Gastroesophageal junction cancer; Immunotherapy; PD-1 inhibitor; Tislelizumab

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Key Summary Points

Why carry out this study?

Tislelizumab plus investigator-chosen chemotherapy (ICC) demonstrated improved survival outcomes compared with placebo plus ICC in patients with locally advanced unresectable or metastatic human epidermal growth factor receptor 2 (HER2)-negative gastric cancer/gastroesophageal junction cancer (GC/GEJC) in the RATIONALE-305 final analysis in both the intent-to-treat population and in patients whose tumors had a programmed cell death-ligand 1 (PD-L1) Tumor Area Positivity (TAP) score ≥ 5%.

The United States Food and Drug Administration Oncologic Drugs Advisory Committee voted in September 2024 against the use of programmed cell death protein-1 treatment in patients with locally advanced unresectable or metastatic HER2-negative GC/GEJC and a PD-L1 TAP score < 1% or combined positive score < 1.

This retrospective analysis was conducted to evaluate the efficacy and safety of tislelizumab + ICC in the RATIONALE-305 trial in patients with a PD-L1 TAP score ≥ 1%.

What was learned from the study?

Overall survival, progression-free survival, overall response rate, duration of response, and disease control rate were all numerically improved with tislelizumab plus ICC compared with placebo plus ICC in patients with a PD-L1 TAP score ≥ 1%.

Adverse events were consistent with the known safety profiles for the individual components.

This study showed a favorable benefit–risk profile for patients with locally advanced unresectable or metastatic HER2-negative GC/GEJC whose tumors had a PD-L1 TAP score ≥ 1%.

INTRODUCTION

Gastric cancer (GC) is the fifth most common cancer worldwide and the fifth leading cause of cancer death; it is approximately twice as common in men compared with women [1]. After the results of the CheckMate 649 phase 3 trial [2], and later the KEYNOTE-859 phase 3 trial [3], both of which showed improvement in overall survival (OS) and progression-free survival (PFS) with the addition of immunotherapy to chemotherapy in patients with locally advanced unresectable or metastatic human epidermal growth factor receptor 2 (HER2)-negative GC/gastroesophageal junction cancer (GEJC), the United States Food and Drug Administration (FDA) approved nivolumab and pembrolizumab for first-line treatment of GC/GEJC [4, 5]. CheckMate 649 and KEYNOTE-859, along with RATIONALE-305 [6], which showed similar survival benefits for tislelizumab, included pre-specified programmed death-ligand 1 (PD-L1) expression cutoffs, although both the cutoffs and evaluation methods varied. All three trials randomized patients to immune checkpoint inhibitor plus chemotherapy or chemotherapy alone, and included all patients regardless of PD-L1 status. CheckMate 649 was stratified by tumor cell PD-L1 status (≥ 1% vs. < 1% or indeterminate), and the protocol was later amended to investigate the primary endpoint in patients with a PD-L1 combined positive score (CPS) of ≥ 5 [2]. KEYNOTE-859 used a PD-L1 CPS of 1 as a stratification factor and was powered to assess the outcomes in all patients within the intent-to-treat (ITT) population, as well as those with a PD-L1 CPS ≥ 1 and ≥ 10 [3], and RATIONALE-305 was powered to assess the study endpoints in all patients in the ITT population and in those with a PD-L1 Tumor Area Positivity (TAP) score of ≥ 5% [6].

An evaluation in September 2024 conducted by the FDA Oncologic Drugs Advisory Committee (ODAC) determined that the results from these trials support the use of PD-L1 expression

as a predictive biomarker for benefit in the selection of patients for treatment with programmed cell death protein-1 (PD-1) inhibitors [7]. The FDA ODAC also voted that PD-1 inhibitors should not be administered as first-line treatment for advanced HER2-negative GC/GEJC in patients with negative or low PD-L1 expression (TAP score < 1%/CPS < 1), as these patients may not benefit from these therapies and may experience added adverse events unnecessarily [7]. In December 2024, the FDA approved tislelizumab for the first-line treatment of unresectable or metastatic HER2-negative GC/GEJC in adult patients whose tumors express PD-L1 ≥ 1 based on the findings of the RATIONALE-305 trial [8].

RATIONALE-305 was a global, randomized, double-blind, phase 3 trial that assessed the efficacy and safety of tislelizumab plus investigator-chosen chemotherapy (ICC), compared with placebo plus ICC, as a first-line treatment for locally advanced unresectable or metastatic HER2-negative GC/GEJC [6]. The primary endpoint was OS, with prespecified hierarchy testing for the PD-L1–high (TAP score ≥ 5%) population followed by the ITT population. At final analysis, at a minimum follow up of 24.6 months, OS was significantly improved with tislelizumab plus ICC versus placebo plus ICC in patients with a PD-L1 TAP score ≥ 5% (median: 16.4 months vs. 12.8 months; hazard ratio [HR] 0.71 (95% confidence interval (CI) 0.58–0.86)] and in the ITT population [median: 15.0 months vs. 12.9 months; HR 0.80 (0.70–0.92); $p = 0.001$] [6]. A retrospective analysis of patients with a PD-L1 TAP score cutoff of ≥ 1% was also conducted. PD-L1 expression was determined by using an analytically validated assay of PD-L1 (SP263) and measured by TAP score. Here, we conducted a retrospective analysis of the RATIONALE-305 trial, to evaluate the efficacy and safety of tislelizumab plus ICC in the first-line treatment of HER2-negative, advanced or metastatic GC/GEJC observed at the final analysis, and 3-year follow-up data cutoffs among patients with a PD-L1 TAP score ≥ 1%.

METHODS

Study Design and Patients

RATIONALE-305 is a randomized, double-blind, global, phase 3 trial comparing the efficacy and safety of tislelizumab plus ICC versus placebo plus ICC in adults (aged ≥ 18 years) with previously untreated, locally advanced unresectable or metastatic HER2-negative GC/GEJC. Patients may have received prior neoadjuvant or adjuvant therapy for earlier stage GC/GEJC as long as this was completed and patients had experienced no recurrence or disease progression for at least 6 months. The trial was conducted in compliance with Good Clinical Practice guidelines and the principles of the Declaration of Helsinki, and was approved by the relevant institutional review board/independent ethics committee for each study site. Written informed consent was obtained from patients before study participation. The trial design and patient eligibility criteria have been presented previously [6].

Briefly, eligible patients were randomized 1:1 to receive either tislelizumab 200 mg or matching placebo intravenously in combination with ICC every 3 weeks. Patients were stratified by geographical regions of enrollment, PD-L1 expression (positive or negative, where positive is PD-L1 TAP score ≥ 5%), presence of peritoneal metastasis, and ICC. Patients received capecitabine 1000 mg/m^2 twice daily on days 1–14 and oxaliplatin 130 mg/m^2 on day 1 or 5-fluorouracil 800 mg/m^2 on days 1–5 and cisplatin 80 mg/m^2 on day 1 for up to six cycles. Patients continued treatment with either tislelizumab or placebo, with optional maintenance capecitabine (only permitted for patients who initially received capecitabine and oxaliplatin), until disease progression, unacceptable toxicity, or investigator decision after 2 years of study treatment. Crossover between the treatment arms or between chemotherapy regimens was prohibited.

Endpoints and Assessments

The study endpoints and assessments have been detailed previously [6]. The primary endpoint was OS; key secondary endpoints were

investigator-assessed PFS, overall response rate (ORR), duration of response (DoR), and disease control rate. Safety was also assessed based on the incidence and severity of adverse events. In the current study, a retrospective analysis of these endpoints was conducted in patients with a PD-L1 expression of ≥ 1% as measured by TAP score. A secondary subgroup analysis was also performed in patients with a PD-L1 TAP score 1% to < 5%. PD-L1 expression was assessed retrospectively by a central laboratory and visually estimated by pathologists using an investigational use-only version of the VENTANA PD-L1 (SP263) CDx Assay (Roche Diagnostics, Indianapolis, IN, USA).

This assay was originally termed "visually estimated CPS" [9]. TAP score was defined as the total percentage of the tumor area (tumor and any desmoplastic stroma) covered by tumor cells with PD-L1 membrane staining at any intensity and tumor-associated immune cells with PD-L1 staining at any intensity, as visually estimated. Efficacy and safety were also evaluated in the centrally assessed population of patients with a tumor PD-L1 expression of ≥ 1 as measured by CPS using samples previously stained per the SP263 assay protocol. CPS was defined as the number of PD-L1-expressing tumor cells, lymphocytes, and macrophages divided by the total number of viable tumor cells, multiplied by 100 [10].

Statistical Analysis

The statistical methodology has been previously presented [6]. Retrospective efficacy analyses were conducted in randomized patients with a PD-L1 TAP score ≥ 1%. Patients with a PD-L1 TAP score < 1% were excluded from this analysis due to cumulative data suggesting no benefit in this patient population. The OS and PFS analyses were performed using both an unstratified and a stratified Cox proportional hazard regression model, stratified by geographical regions of enrollment (East Asia vs. rest of the world) and presence of peritoneal metastasis. OS and PFS HRs and associated two-sided 95% CIs were estimated. The median and cumulative probabilities of time-to-event endpoints were estimated using the Kaplan–Meier method. OS was assessed in prespecified subgroups by region and several other baseline demographic and disease characteristics. Investigator-assessed confirmed ORR, disease control rate, and DoR were analyzed. Confirmed ORR along with Clopper–Pearson two-sided 95% CIs were calculated and compared between treatment arms. Because this study was not designed to assess the statistical significance of the PD-L1 TAP score ≥ 1% treatment effect, *p* values included in this analysis are descriptive only. The secondary subgroup analysis in the PD-L1 TAP score 1% to < 5% and CPS ≥ 1 populations employed the same methodology as that used in the statistical analysis of the PD-L1 TAP score ≥ 1% population.

RESULTS

Patient Demographic and Baseline Characteristics

A total of 997 patients were randomly assigned to receive tislelizumab plus ICC ($n = 501$) or placebo and ICC ($n = 496$) [6]; at the final analysis data cutoff of February 28, 2023, median study follow-up was 13.2 months (IQR 7.1–24.6) (Supplementary Fig. S1). Of those in the ITT population, 432 (86.2%) and 158 (31.9%) patients in the tislelizumab plus ICC arm and 453 (91.3%) and 181 (36.1%) in the placebo plus ICC arm had PD-L1 TAP scores ≥ 1% and 1% to < 5%, respectively, at baseline. Baseline and disease characteristics in the ITT population have been previously reported [6] and were generally balanced between treatment arms for the PD-L1 TAP score ≥ 1% population (Table 1) and PD-L1 TAP score 1 to < 5% population (Supplementary Table S1). Baseline and disease characteristics in the PD-L1 TAP score ≥ 1% population were similar to those of the ITT population [6], and comparable with the CPS ≥ 1 population (Supplementary Table S1). Enrichment of patients with peritoneal metastatic disease was observed in the PD-L1 TAP score 1% to < 5% population compared with the ITT population. Data cutoff for the 3-year survival follow-up was February 28, 2024, and minimum study follow-up

Table 1 Patient demographic and baseline characteristics in the PD-L1 TAP score ≥ 1% population

Demographic/characteristics	Tislelizumab plus ICC (*n* = 432)	Placebo plus ICC (*n* = 453)
Age		
Median (range)	61.0 (23.0–86.0)	61.0 (25.0–86.0)
≥ 65 years, *n* (%)	149 (34.5)	168 (37.1)
Sex, *n* (%)		
Female	127 (29.4)	137 (30.2)
Male	305 (70.6)	316 (69.8)
Race/ethnicity, *n* (%)		
Asian	325 (75.2)	338 (74.6)
Chinese	217 (50.2)	230 (50.8)
Korean	59 (13.7)	58 (12.8)
Japanese	49 (11.3)	50 (11.0)
White	98 (22.7)	100 (22.1)
Other[a]	9 (2.1)	15 (3.3)
Region, *n* (%)		
East Asia	325 (75.2)	338 (74.6)
China (including Taiwan)	217 (50.2)	229 (50.6)
South Korea	59 (13.7)	59 (13.0)
Japan	49 (11.3)	50 (11.0)
North America/Europe	107 (24.8)	115 (25.4)
ECOG performance status, *n* (%)		
0	149 (34.5)	145 (32.0)
1	283 (65.5)	308 (68.0)
Time from initial diagnosis to study entry, median (range), months[b]	1.5 (0.3–442.1)	1.6 (0.2–190.2)
Metastatic disease status at study entry, *n* (%)	426 (98.6)	449 (99.1)
Number of metastatic sites at study entry, *n* (%)[c]		
0–2	290 (67.1)	298 (65.8)
≥ 3	142 (32.9)	154 (34.0)
Liver metastases, *n* (%)	170 (39.4)	180 (39.7)
Peritoneal metastases, *n* (%)	190 (44.0)	196 (43.3)

Table 1 continued

Demographic/characteristics	Tislelizumab plus ICC (*n* = 432)	Placebo plus ICC (*n* = 453)
Primary tumor location, *n* (%)[d]		
Stomach	347 (80.3)	361 (79.7)
Gastro-esophageal junction	85 (19.7)	92 (20.3)
Histologic type (Lauren classification), *n* (%)		
Diffuse type	88(20.4)	93 (20.5)
Intestinal type	73 (16.9)	82 (18.1)
Mixed type	24 (5.6)	31 (6.8)
Unknown	247 (57.2)	247 (54.5)
MSI or MMR status, *n* (%)		
MSI-H/dMMR	16 (3.7)	20 (4.4)
MSI-L/MSS/pMMR	385 (89.1)	401 (88.5)
Unknown	31 (7.2)	32 (7.1)
Previous adjuvant/neoadjuvant treatment, *n* (%)[e]	89 (20.6)	85 (18.8)
Previous gastrectomy/esophagectomy, *n* (%)	111 (25.7)	121 (26.7)
ICC, *n* (%)		
Oxaliplatin and capecitabine	402 (93.1)	424 (93.6)
Cisplatin and 5-fluouracil	30 (6.9)	29 (6.4)

dMMR mismatch repair deficient, *ECOG* Eastern Cooperative Oncology Group, *ICC* investigator-chosen chemotherapy, *MSI-H/L* microsatellite instability-high/low, *MSS* microsatellite stable, *PD-L1* programmed death-ligand 1, *pMMR* mismatch repair proficient, *TAP* Tumor Area Positivity

[a]Includes not reported, unknown, and other

[b]Study entry date refers to randomization date

[c]One patient in the placebo plus chemotherapy arm had the metastatic site removed by surgery before study entry

[d]The diagnosis of one patient the placebo plus chemotherapy arm was updated from gastric adenocarcinoma to pancreatic cancer after randomization

[e]Patients were permitted to have received prior neoadjuvant or adjuvant therapy for earlier stage GC/GEJC as long as this was completed and patients had experienced no recurrence or disease progression for at least 6 months

duration (defined as the difference between the date of data cutoff and the date of last patient randomized) was 36.6 months.

Treatment Exposure

At the final analysis cutoff in the PD-L1 TAP score ≥ 1% population, median duration of exposure to tislelizumab was 5.9 months (minimum, maximum, 0.1, 47.0), and 5.7 months (0.3, 46.9) for placebo. Median duration of

Table 2 Subsequent anticancer therapy in the PD-L1 TAP score ≥ 1% population

Anticancer therapy, *n* (%)	Tislelizumab plus ICC (*n* = 432)	Placebo plus ICC (*n* = 453)
Any subsequent anticancer systemic therapy	232 (53.7)	270 (59.6)
Chemotherapy	220 (50.9)	258 (57.0)
Targeted therapy	132 (30.6)	147 (32.5)
Immunotherapy	52 (12.0)	82 (18.1)
Other	11 (2.5)	14 (3.1)

Data cutoff: February 28, 2023. Percentages were based on *n*. PD-L1 TAP score was determined by an investigational use-only version of the VENTANA PD-L1 (SP263) CDx Assay

ICC investigator-chosen chemotherapy, *PD-L1* programmed death-ligand 1, *TAP* Tumor Area Positivity

exposure to the different chemotherapy doublets among patients who received at least one dose of study treatment and the numbers of patients who received capecitabine maintenance treatment were similar between treatment arms. At final analysis in the PD-L1 TAP score ≥ 1% population, 397 (91.9%) patients in the tislelizumab plus ICC arm and 429 (94.7%) in the placebo plus ICC arm had discontinued or completed treatment per protocol. After study treatment discontinuation, 232 (53.7%) of 432 patients in the tislelizumab plus ICC arm and 270 (59.6%) of 453 patients in the placebo plus ICC arm received subsequent systemic anticancer therapies (Table 2).

Efficacy Outcomes

OS

At the final analysis cutoff in the PD-L1 TAP score ≥ 1% population, median OS was numerically higher in the tislelizumab plus ICC arm versus the placebo plus ICC arm [15.0 months (95% CI 13.3–16.7) vs. 12.8 months (12.1–14.1), respectively; stratified HR 0.77 (95% CI 0.67–0.90), one-sided nominal *p* value 0.0004; unstratified HR 0.78 (95% CI 0.67–0.90), one-sided nominal *p* value 0.0005] in patients with a PD-L1 TAP score ≥ 1% (Fig. 1). A numerical improvement was also observed in median OS with tislelizumab plus ICC versus placebo plus ICC across key patient subgroups (Fig. 2). Similar OS outcomes were observed between the arms and across key subgroups in the CPS ≥ 1 population at the final analysis cutoff (Supplementary Figs. S2A and S3). No clinically significant improvement in median OS was observed between the arms in the PD-L1 TAP score 1% to < 5% population (Supplementary Fig. S4).

At the 3-year data cutoff, improvements were maintained with tislelizumab plus ICC versus placebo plus ICC in median OS [15.0 months (95% CI 13.3–16.7) vs. 12.8 months (12.0–14.1), respectively; stratified HR 0.77 (95% CI 0.66–0.89); unstratified HR 0.77 (95% CI 0.67–0.90)]. The estimated 12-month OS rate was 58.2% (95% CI 53.3–62.8) in the tislelizumab plus ICC arm and 55.0% (95% CI 50.2–59.5) in the placebo plus ICC arm. The estimated 24- and 36-month OS rates were 33.4% (95% CI 28.9–38.0) versus 23.1% (95% CI 19.2–27.2) and 21.3% (95% CI 17.5–25.4) versus 13.1% (95% CI 10.1–16.5), respectively. Similar OS outcomes were observed in the CPS ≥ 1 population at the 3-year data cutoff (Supplementary Fig. S2B).

Investigator-Assessed PFS

Similar to the OS results, median PFS was also numerically improved in the tislelizumab plus ICC arm versus the placebo plus ICC arm in all randomized patients in the PD-L1 TAP score ≥ 1% population [6.9 months (95% CI 5.7–7.2) vs. 5.9 months (95% CI 5.6–6.9); stratified HR 0.77 (95% CI 0.67–0.90); unstratified HR 0.78 (95% CI 0.67–0.91)] (Fig. 3). The estimated 12-month PFS rate was 30.3% (95% CI 25.7–35.0) in the tislelizumab plus ICC arm and 20.7% (95% CI 16.8–24.9) in the placebo plus ICC arm. The estimated 24- and 36-month PFS rates were 17.1% (95% CI 13.3–21.2) versus 9.1% (95% CI 6.4–12.4) and 15.2% (95% CI 11.6–19.3) versus 7.0% (95% CI 4.5–10.2), respectively. A numerical improvement was also observed in

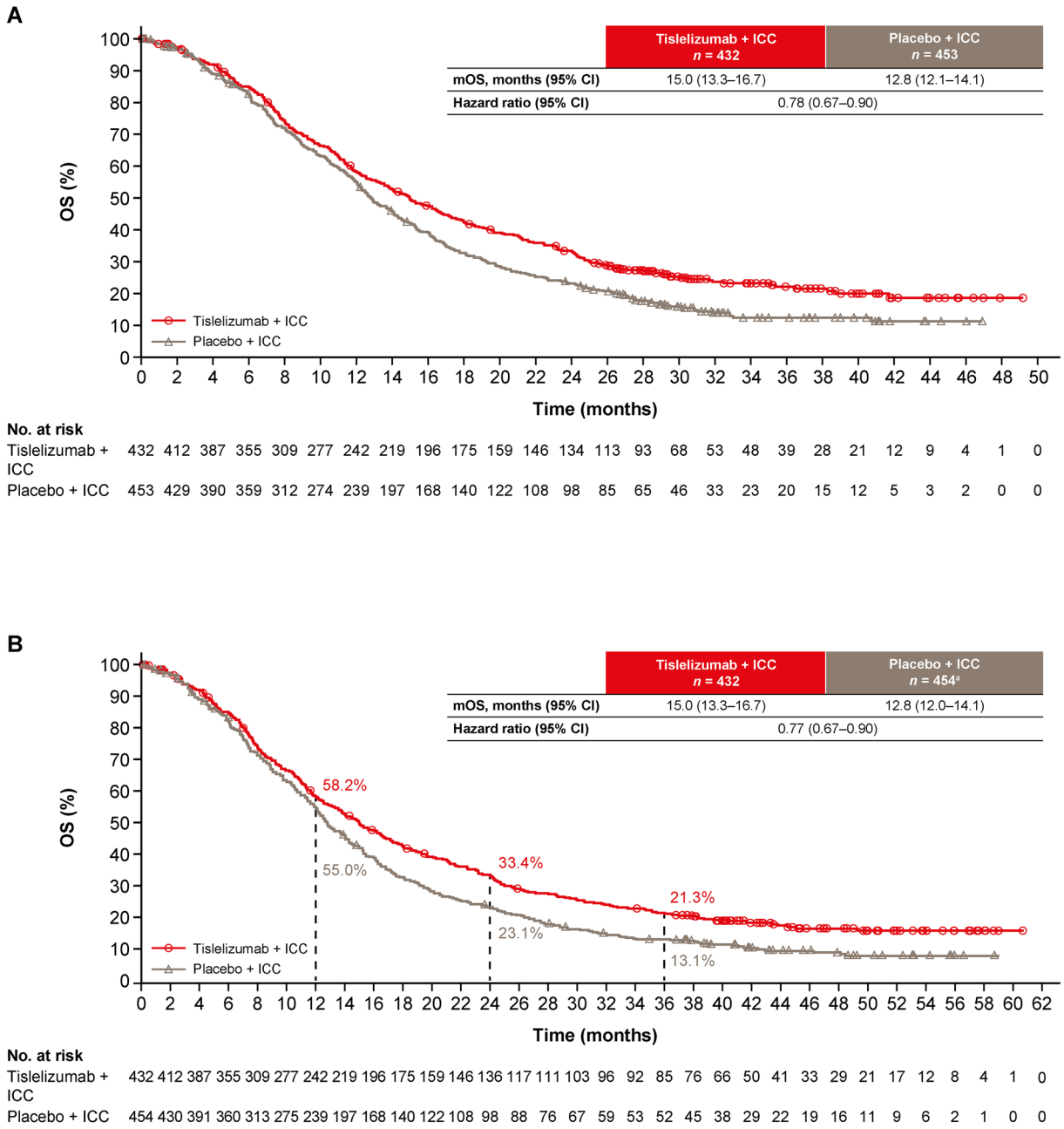

Fig. 1 Kaplan–Meier curve of OS by baseline PD-L1 TAP score of ≥ 1% at the final analysis (**A**) and 3-year follow-up (**B**). PD-L1 TAP score was determined with an investigational use-only version of the VENTANA PD-L1 (SP263) CDx Assay. Unstratified hazard ratios were based on a Cox regression model. The *red circles* and *gray triangles* represent censored patients. *A* The data cutoff was February 28, 2023. *B* The data cutoff was February 28, 2024. [a]One patient in the placebo plus ICC arm had an updated PD-L1 reading after final analysis. Overall survival rates were estimated by Kaplan–Meier method, with 95% CIs estimated using Greenwood's formula. *CI* confidence interval, *ICC* investigator-chosen chemotherapy, *(m)OS* (median) overall survival, *PD-L1* programmed death-ligand 1, *TAP* Tumor Area Positivity

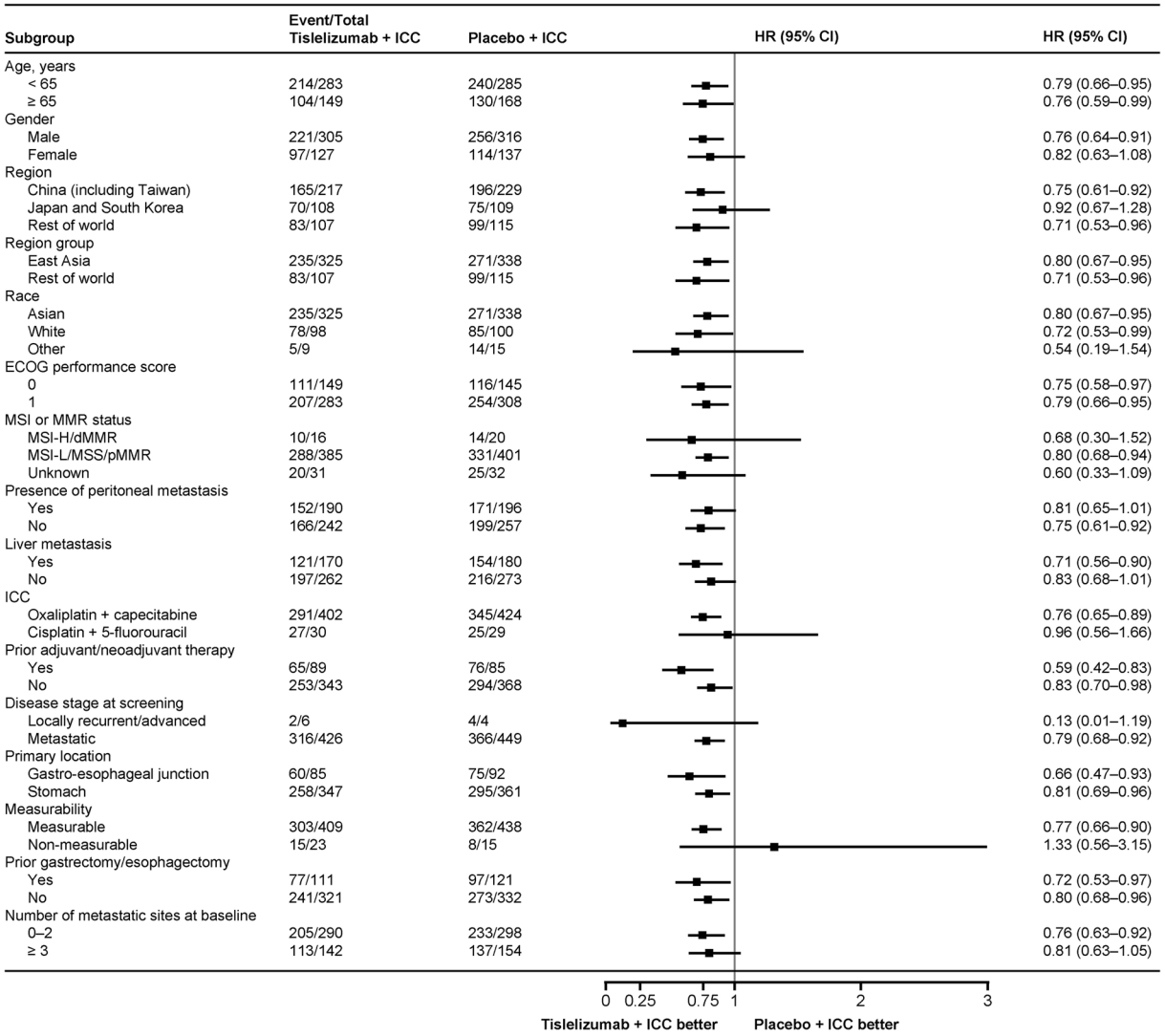

Fig. 2 Subgroup analysis of OS by baseline PD-L1 TAP score ≥ 1% at the final analysis (efficacy-evaluable population). The data cutoff was February 28, 2023. Medians were estimated by Kaplan–Meier method, with 95% CIs estimated using the method of Brookmeyer and Crowley using log–log transformation. The HR and its 95% CI were estimated from an unstratified Cox regression model including treatment as a covariate. The race subcategory *Other* includes not reported, unknown, and other. The range of the *x*-axis for HR is (0–3) and some extreme 95% CI values > 3 are not shown in the plot. Patients were permitted to have received prior neoadjuvant or adjuvant therapy for earlier stage GC/GEJC as long as this was completed and patients had experienced no recurrence or disease progression for at least 6 months. *CI* confidence interval, *dMMR* mismatch repair deficient, *HR* hazard ratio, *ICC* investigator-chosen chemotherapy, *MSI-H/L* microsatellite instability high/low, *MSS* microsatellite stable, *PD-L1* programmed death-ligand 1, *pMMR* mismatch repair proficient, *TAP* Tumor Area Positivity

PFS with tislelizumab plus ICC versus placebo plus ICC across key subgroups (Fig. 4). PFS observed in the CPS ≥ 1 population was similar to that reported for the TAP score ≥ 1% population (Supplementary Table S2). No difference in median PFS was observed between the arms in the PD-L1 TAP score 1% to < 5% population (Supplementary Table S2).

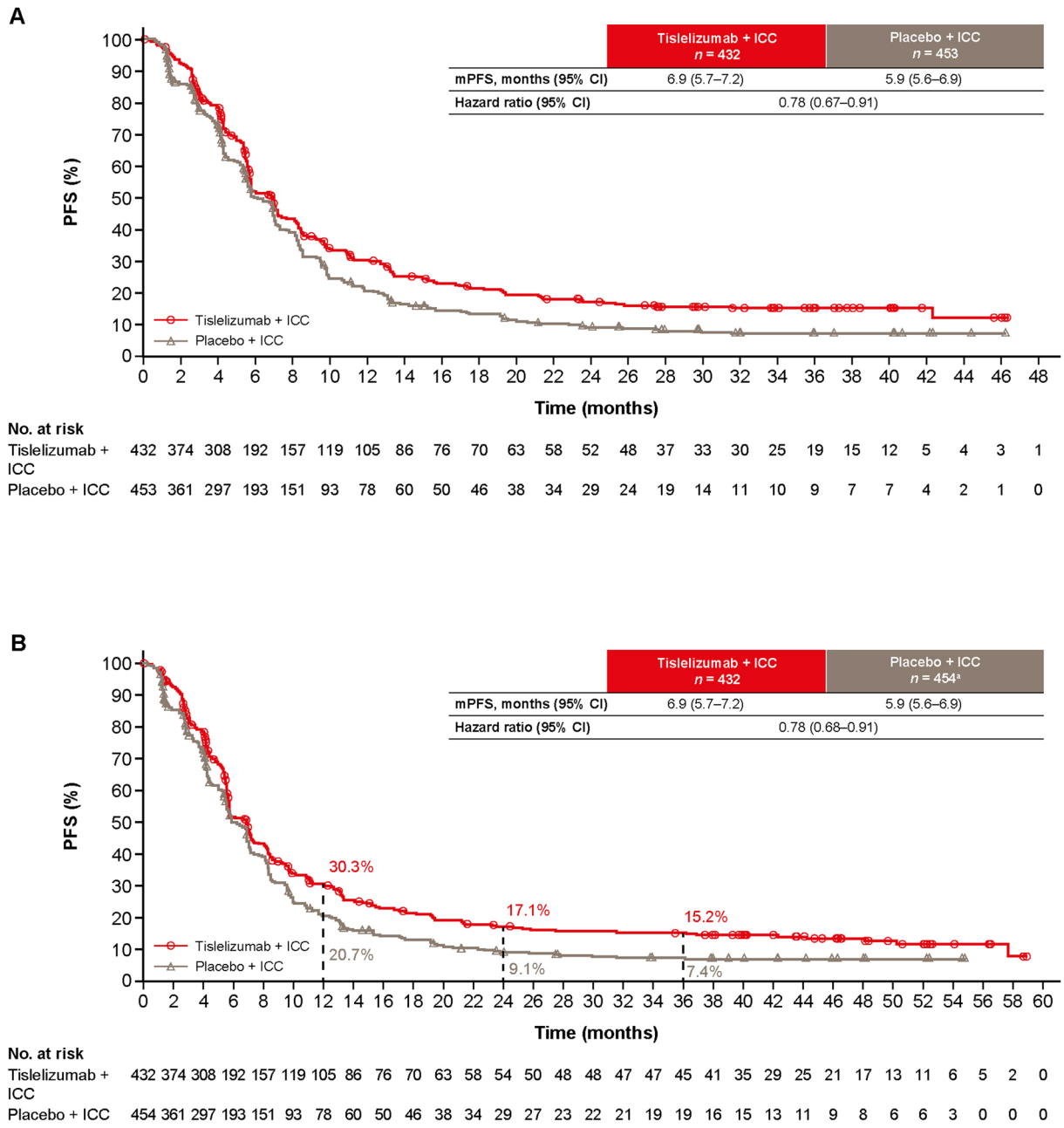

Fig. 3 Kaplan–Meier curve of PFS by baseline PD-L1 TAP score ≥ 1% at the final analysis (**A**) and 3-year follow-up (**B**). PD-L1 TAP score was determined with an investigational use-only version of the VENTANA PD-L1 (SP263) CDx Assay. Unstratified hazard ratios were based on a Cox regression model. The *red circles* and *gray triangles* represent censored patients. **A** The data cutoff was February 28, 2023. **B** The data cutoff was February 28, 2024. [a]One patient in the placebo plus ICC arm had an updated PD-L1 reading after final analysis. Progression free survival rates were estimated by Kaplan-Meier method, with 95% CIs estimated using Greenwood's formula. *CI* confidence interval, *ICC* investigator-chosen chemotherapy, *(m)PFS* (median) progression-free survival, *PD-L1* programmed death-ligand 1, *TAP* Tumor Area Positivity

Investigator-Assessed Antitumor Activity

At the final analysis cutoff, the confirmed ORR was numerically higher in the tislelizumab plus ICC arm [47.7% (95% CI 42.9–52.5)] versus the placebo plus ICC arm [41.1% (95% CI 36.5–45.7), stratified odds ratio, 1.31 (95% CI 1.00–1.72)]. The median DoR was 8.6 months (95% CI 7.8–10.4) in the tislelizumab plus ICC arm versus 7.2 months (95% CI 5.8–8.3) in the placebo plus ICC arm. The disease control rate was also higher in the tislelizumab plus ICC arm [89.6% (95% CI 86.3–92.3)] versus the placebo plus ICC arm [82.3% (95% CI 78.5–85.7)]. The ORR and median DoR were comparable between the treatment arms in the PD-L1 TAP score 1% to < 5% population; however, there was a numerical improvement in disease control rate for patients treated with tislelizumab plus ICC versus placebo plus ICC (Supplementary Table S2). At 3 years, 24.6% (95% CI 18.6–31.2) of patients remained in response in the tislelizumab plus ICC arm versus 14.0% (95% CI 8.9–20.3) in the placebo plus ICC arm. ORR, disease control rate, and DoR in the CPS ≥ 1 population were similar to those reported for the TAP score ≥ 1% population (Supplementary Table S2).

Safety and Tolerability

At the final analysis cutoff in the PD-L1 TAP score ≥ 1% population, at least one treatment-emergent adverse event (TEAE) was reported in 426 (99.3%) of 429 patients in the tislelizumab plus ICC arm and in 444 (98.2%) of 452 patients in the placebo plus ICC arm. Grade ≥ 3 TEAEs were reported in 295 (68.8%) patients in the tislelizumab plus ICC arm and in 297 (65.7%) patients in the placebo plus ICC arm. More patients in the tislelizumab plus ICC arm compared with the placebo plus ICC arm had serious TEAEs: 188 (43.8%) versus 169 (37.4%). TEAEs led to discontinuation of any treatment component in 103 (24.0%) patients in the tislelizumab plus ICC arm versus 64 (14.2%) in the placebo plus ICC arm. Discontinuation of tislelizumab or placebo due to TEAEs was reported in 69 (16.1%) and 36 (8.0%) patients, respectively. Dose modifications of any treatment component due to TEAEs occurred in 329 (76.7%) patients receiving tislelizumab plus ICC versus 343 (75.9%) receiving placebo plus ICC. Dose modifications of tislelizumab or placebo due to TEAEs were reported in 211 (49.2%) patients in the tislelizumab plus ICC arm and in 215 (47.6%) in the placebo plus ICC arm. Infusion-related reactions occurred in 17 (4.0%) patients in the tislelizumab plus ICC arm and in 16 (3.5%) in the placebo plus ICC arm. Of these, only two (0.5%) patients in the tislelizumab plus ICC arm experienced grade ≥ 3 TEAEs. At least one immune-mediated adverse event was reported by 136 (31.7%) patients receiving tislelizumab plus ICC and 54 (11.9%) patients receiving placebo plus ICC. Of these, 32 (7.5%) and 9 (2.0%) patients experienced grade ≥ 3 immune-mediated adverse events, respectively.

Grade ≥ 3 treatment-related adverse events (TRAEs) in the PD-L1 TAP score ≥ 1% population were reported in 295 (68.8%) patients in the tislelizumab plus ICC arm and in 297 (65.7%) patients in the placebo plus ICC arm (Table 3). The most common TRAEs were nausea [222 (51.7%) in the tislelizumab plus ICC arm vs. 222 (49.1%) in the placebo plus ICC arm], decreased appetite [185 (43.1%) vs. 191 (42.3%)], anemia [160 (37.3%) vs. 189 (41.8%)], vomiting [151 (35.2%) vs. 163 (36.1%)], platelet count decreased [146 (34.0%) vs. 171 (37.8%)], and neutrophil count decreased [143 (33.3%) vs. 148 (32.7%)]; the most common grade ≥ 3 TRAEs were neutrophil count decreased [53 (12.4%) vs. 51 (11.3%)], platelet count decreased (46 (10.7%) vs. 50 (11.1%)], anemia [32 (7.5%) vs. 47 (10.4%)], and neutropenia [30 (7.0%) vs. 26 (5.8%)]. The adverse events reported were consistent with the known safety profiles of the individual agents.

DISCUSSION

In this retrospective analysis, patients with locally advanced unresectable or metastatic HER2-negative GC/GEJC with PD-L1 TAP score ≥ 1% experienced improved survival outcomes for tislelizumab plus ICC. PD-L1 positivity defined by a TAP score of ≥ 1% is an excellent

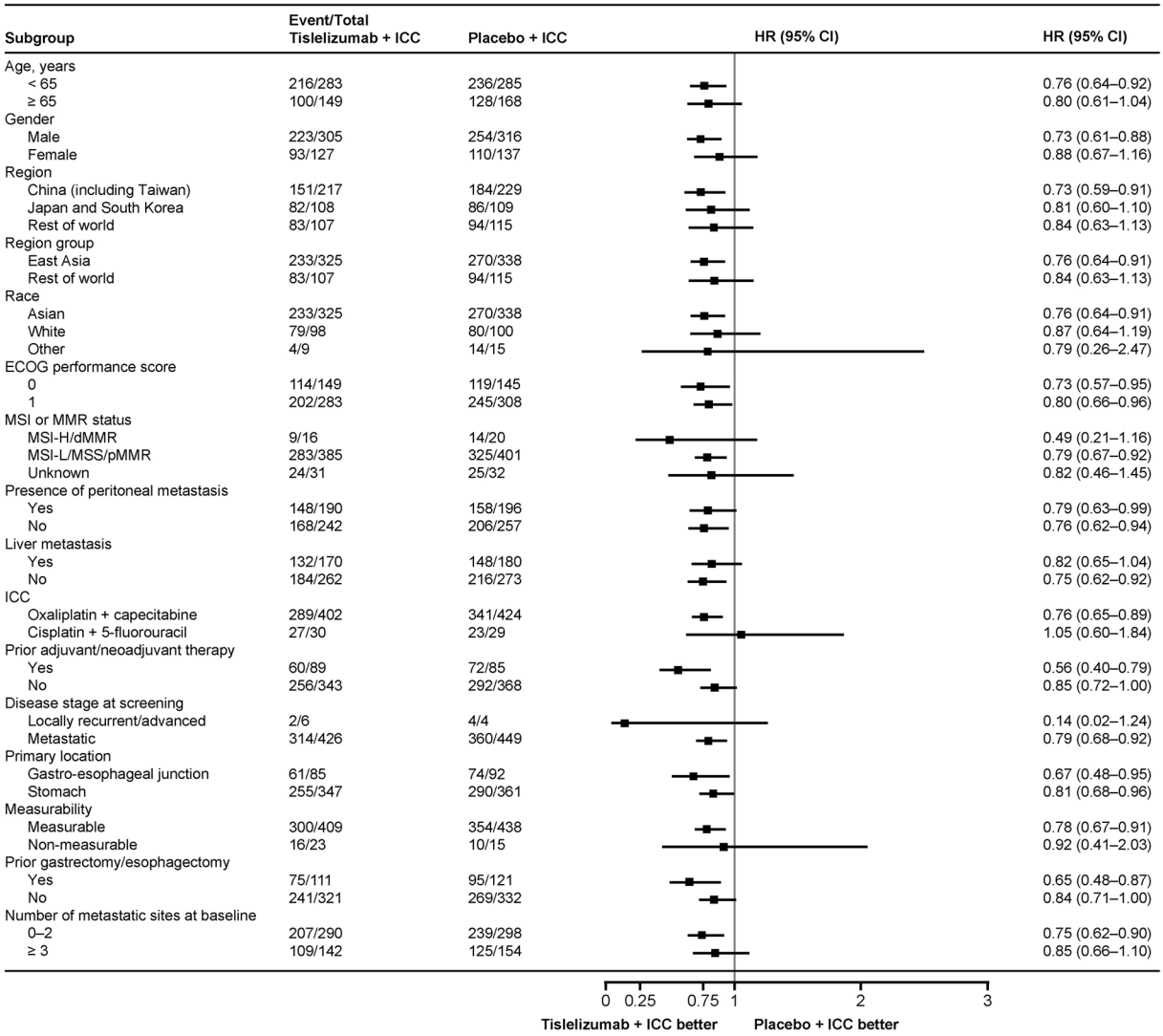

Fig. 4 Subgroup analysis of PFS by baseline PD-L1 TAP score ≥ 1% at the final analysis (efficacy-evaluable population). The data cutoff was February 28, 2023. Medians were estimated by Kaplan–Meier method, with 95% CIs estimated using the method of Brookmeyer and Crowley using log–log transformation. The HR and its 95% CI were estimated from an unstratified Cox regression model including treatment as a covariate. The race subcategory 'Other' includes not reported, unknown, and other. The range of the *x*-axis for HR is (0–3), some extreme values greater than three are not shown in the plot. *CI* confidence interval, *dMMR* mismatch repair deficient, *ECOG* Eastern Cooperative Oncology Group, *HR* hazard ratio, *ICC* investigator-chosen chemotherapy, *MSI-H/L* microsatellite instability high/low, *MSS* microsatellite stable, *PD-L1* programmed death-ligand 1, *pMMR* mismatch repair proficient, *TAP* Tumor Area Positivity

biomarker of response and survival in GC/GEJC and is comparable with PD-L1 positivity defined by CPS [10, 12]. Treatment guidelines for first-line locally advanced unresectable or metastatic GC/GEJC recommend PD-1 immunotherapy with chemotherapy for patients with HER2-negative, PD-L1-positive disease [13, 14]. Thus, nivolumab, pembrolizumab, and tislelizumab in combination with chemotherapy are approved by the FDA for first-line treatment of locally advanced unresectable or metastatic GC/GEJC [4, 5, 8]. In September 2024, the FDA

Table 3 Treatment-related adverse events with an incidence of ≥ 5% in the PD-L1 TAP score ≥ 1% population (safety analysis set) by preferred term: all grades and grade ≥ 3

System organ class preferred term, *n* (%)	Tislelizumab plus ICC (*n* = 429)		Placebo plus ICC (*n* = 452)	
	All Grades	Grade ≥ 3	All Grades	Grade ≥ 3
Patients with ≥ 1 TRAE	426 (99.3)	295 (68.8)	444 (98.2)	297 (65.7)
Nausea	222 (51.7)	13 (3.0)	222 (49.1)	11 (2.4)
Decreased appetite	185 (43.1)	18 (4.2)	191 (42.3)	18 (4.0)
Anemia	160 (37.3)	32 (7.5)	189 (41.8)	47 (10.4)
Vomiting	151 (35.2)	10 (2.3)	163 (36.1)	12 (2.7)
Platelet count decreased	146 (34.0)	46 (10.7)	171 (37.8)	50 (11.1)
Neutrophil count decreased	143 (33.3)	53 (12.4)	148 (32.7)	51 (11.3)
Aspartate aminotransferase increased	127 (29.6)	16 (3.7)	139 (30.8)	4 (0.9)
Diarrhea	124 (28.9)	13 (3.0)	130 (28.8)	11 (2.4)
Alanine aminotransferase increased	99 (23.1)	9 (2.1)	98 (21.7)	5 (1.1)
White blood cell count decreased	98 (22.8)	13 (3.0)	122 (27.0)	7 (1.5)
Peripheral sensory neuropathy	96 (22.4)	1 (0.2)	112 (24.8)	3 (0.7)
Weight decreased	92 (21.4)	7 (1.6)	87 (19.2)	2 (0.4)
Pyrexia	87 (20.3)	7 (1.6)	67 (14.8)	3 (0.7)
Palmar-plantar erythrodysesthesia syndrome	84 (19.6)	15 (3.5)	86 (19.0)	9 (2.0)
Constipation	79 (18.4)	1 (0.2)	94 (20.8)	1 (0.2)
Asthenia	78 (18.2)	12 (2.8)	74 (16.4)	11 (2.4)
Hypoalbuminemia	73 (17.0)	3 (0.7)	83 (18.4)	2 (0.4)
Fatigue	73 (17.0)	10 (2.3)	70 (15.5)	8 (1.8)
Hypokalemia	72 (16.8)	20 (4.7)	49 (10.8)	14(3.1)
Abdominal pain	68 (15.9)	6 (1.4)	78 (17.3)	6 (1.3)
Endocrine disorders	66 (15.4)	2 (0.5)	18 (4.0)	0 (0.0)
Blood bilirubin increased	65 (15.2)	10 (2.3)	63 (13.9)	5 (1.1)
Neutropenia	62 (14.5)	30 (7.0)	71 (15.7)	26 (5.8)
Hypothyroidism	55 (12.8)	1 (0.2)	11 (2.4)	0 (0.0)
Thrombocytopenia	52 (12.1)	13 (3.0)	55 (12.2)	15 (3.3)
Hypoesthesia	49 (11.4)	1 (0.2)	54 (11.9)	0 (0.0)
Abdominal pain upper	43 (10.0)	1 (0.2)	46 (10.2)	1 (0.2)

Table 3 continued

System organ class preferred term, *n* (%)	Tislelizumab plus ICC (*n* = 429)		Placebo plus ICC (*n* = 452)	
	All Grades	Grade ≥ 3	All Grades	Grade ≥ 3
Abdominal distension	40 (9.3)	0 (0.0)	49 (10.8)	0 (0.0)
Insomnia	38 (8.9)	0 (0.0)	47 (10.4)	1 (0.2)
Stomatitis	38 (8.9)	7 (1.6)	35 (7.7)	6 (1.3)
Pruritus	37 (8.6)	0 (0.0)	13 (2.9)	0 (0.0)
Leukopenia	34 (7.9)	6 (1.4)	40 (8.8)	4 (0.9)
Malaise	34 (7.9)	2 (0.5)	38 (8.4)	0 (0.0)
Edema peripheral	34 (7.9)	0 (0.0)	32 (7.1)	2 (0.4)
Rash	34 (7.9)	0 (0.0)	15 (3.3)	0 (0.0)
Hyponatremia	31 (7.2)	7 (1.6)	27 (6.0)	4 (0.9)
Dizziness	30 (7.0)	1 (0.2)	36 (8.0)	1 (0.2)
Dyspnea	27 (6.3)	1 (0.2)	30 (6.6)	1 (0.2)
Pneumonia	26 (6.1)	8 (1.9)	25 (5.5)	13 (2.9)
Productive cough	25 (5.8)	0 (0.0)	20 (4.4)	0 (0.0)
Back pain	24 (5.6)	1 (0.2)	35 (7.7)	1 (0.2)
Dysgeusia	23 (5.4)	0 (0.0)	16 (3.5)	0 (0.0)
Upper respiratory tract infection	23 (5.4)	3 (0.7)	9 (2.0)	0 (0.0)
Weight increased	22 (5.1)	2 (0.5)	8 (1.8)	1 (0.2)
Cough	21 (4.9)	0 (0.0)	26 (5.8)	0 (0.0)
Dyspepsia	19 (4.4)	0(0.0)	28 (6.2)	1 (0.2)
Hypoproteinemia	19 (4.4)	0 (0.0)	24 (5.3)	2 (0.4)
Arthralgia	18 (4.2)	0 (0.0)	23 (5.1)	0 (0.0)
Gastro-esophageal reflux disease	15 (3.5)	1 (0.2)	23 (5.1)	0 (0.0)

Percentages were based on *n*. Patients with two or more adverse events in the same preferred term were counted only once for that preferred term. Adverse events were sorted by decreasing frequency in the tislelizumab plus ICC column. Adverse event terms were coded using Medical Dictionary for Regulatory Activities version 24.0 and graded per National Cancer Institute Common Terminology Criteria for Adverse Events version 5.0

ICC investigator-chosen chemotherapy, *PD-L1* programmed death-ligand 1, *TAP* Tumor Area Positivity, *TRAE* treatment-related adverse event

ODAC conducted a pooled analysis of patient data from RATIONALE-305, CheckMate 649, and KEYNOTE-859, which examined whether PD-L1 expression is a suitable candidate biomarker for determining which patients would benefit from immunotherapy. Based on this analysis, the FDA ODAC recommended that PD-1 inhibitors had an unfavorable benefit–risk profile for patients with negative PD-L1 (a PD-L1 TAP score < 1% or PD-L1 CPS < 1). It is important to note that the FDA ODAC recommendation excluded patients with microsatellite instability-high (MSI-H)

tumors. These patients should receive immunotherapy regardless of their PD-L1 expression status, as tumors with MSI-H status are known to be responsive to treatment with PD-1 inhibitors [15].

In response to the FDA ODAC recommendations, we evaluated PD-L1 further as a predictive biomarker of the potential to benefit from immunotherapy in GC/GEJC. The results of this retrospective analysis highlight the favorable benefit–risk profile for tislelizumab plus ICC as first-line treatment for patients with locally advanced unresectable or metastatic HER2-negative GC/GEJC with a PD-L1 TAP score ≥ 1%. At the final analysis cutoff, median OS in the ITT population was 15.0 months in the tislelizumab plus ICC arm and 12.9 months in the placebo plus ICC arm (HR 0.80), while median OS in the PD-L1 TAP score ≥ 5% population was 16.4 months in the tislelizumab plus ICC arm and 12.8 months in the placebo plus ICC arm (HR 0.71) [6]. In this retrospective analysis, median OS in the PD-L1 TAP score ≥ 1% population was 15.0 months in the tislelizumab arm and 12.8 months in the placebo arm (stratified HR 0.77). Similar benefit was observed for PFS and antitumor activity. For all subgroups in the PD-L1 TAP score ≥ 1% population, numerical improvements in PFS and OS were observed with tislelizumab plus ICC. Improvements in median OS were maintained at the 3-year follow-up cutoff, as observed for the ITT and PD-L1 TAP score ≥ 5% populations. At the 3-year follow-up, median OS in the ITT population was 15.0 months in the tislelizumab plus ICC arm and 12.9 months in the placebo plus ICC arm (stratified/unstratified HR 0.79), and median OS in the PD-L1 TAP score ≥ 5% population was 16.4 months in the tislelizumab plus ICC arm and 12.8 months in the placebo plus ICC arm (stratified HR 0.71; unstratified HR 0.72) [16]. In this retrospective analysis, median OS at 3-year follow up in the PD-L1 TAP score ≥ 1% population was 15.0 months in the tislelizumab plus ICC arm and 12.8 months in the placebo plus ICC arm (stratified/unstratified HR 0.77). As expected, all efficacy outcomes in the CPS ≥ 1 population were similar to those observed in the TAP score ≥ 1% population, given the known concordance between PD-L1 expression determined by the TAP score and CPS assays [11, 12].

Even with variation in the follow-up interval, which impacts HR, similar survival benefits have been reported in phase 3 trials of nivolumab (CheckMate 649) and pembrolizumab (KEYNOTE-859) as those seen in RATIONALE-305. In CheckMate 649, at a median OS follow-up of 13.1 months and 11.1 months for nivolumab plus chemotherapy and chemotherapy alone, respectively, the nivolumab group showed an improvement in OS versus the chemotherapy-alone group in patients with a PD-L1 CPS ≥ 1 (HR 0.77) [2]. In KEYNOTE-859, with a median follow-up at the data cutoff of 31 months, median OS was longer in patients with a PD-L1 CPS ≥ 1 with pembrolizumab plus chemotherapy than placebo plus chemotherapy [HR 0.74 (95% CI 0.65–0.84); $p < 0.0001$] [3]. In RATIONALE-305, at the final analysis cutoff (median study follow-up 13.2 months), median OS was longer in patients with a PD-L1 CPS ≥ 1 treated with tislelizumab plus ICC versus placebo plus ICC [HR 0.78 (95% CI 0.67–0.91)] [12]. These studies all show that, with longer follow-up, HR for PD-1 inhibitors improves, demonstrating the long-term benefits of these therapies.

No clinically significant benefit was observed in the PD-L1 TAP score 1% to < 5% population in the current study or in the CPS 1 to < 5 population in the CheckMate 649 trial [2]. Notably, neither trial evaluated these populations in a prospective manner, making the findings of both studies subject to the limitations of a retrospective analysis [2]. For example, in RATIONALE-305, the lack of clinical benefit in patients with a PD-L1 TAP score between 1% to < 5% could also be due to imbalance in prognostic factors, such as presence of peritoneal metastasis [17]. In comparison, KEYNOTE-859 (where results were prospectively assessed according to CPS ≥ 1) reported a clinically meaningful OS benefit in the retrospectively assessed CPS 1 to 9 population, which provides support for the utility of immunotherapy in this population [3]. Survival benefit with immunotherapy has also been reported among patients with low PD-L1 expression (i.e., CPS 1–4) in a patient-level meta-analysis [18].

Among the notable findings of this analysis of RATIONALE-305 is the difference of 10% in the PFS rate (30.3% with TIS plus ICC vs. 20.7% with placebo plus ICC) at 12 months in the PD-L1 TAP score ≥ 1% population. This difference was sustained at 3-year follow-up with a PFS rate of 17.1% in the tislelizumab plus ICC arm, compared with placebo plus ICC at 9.1% at 24 months. This response is durable, with 15.2% of patients in the tislelizumab plus ICC arm still in response at 36 months, which is more than double that observed in the placebo plus ICC arm (7.4%). These long-term survivors with their disease under control highlight the impact of immunotherapy on the natural history of GC/GEJC and the potential for a cure in this population.

Tislelizumab plus ICC was well tolerated in patients with a PD-L1 TAP score ≥ 1%, similar to observations among all randomized patients and those with a PD-L1 TAP score ≥ 5%. No new safety findings were reported.

As a retrospective analysis, the PD-L1 TAP score ≥ 1% was not included in the original analysis plan, thus formal statistical tests cannot be performed in this group. Additionally, this retrospective study was not statistically powered to detect differences between arms. Finally, the study population of RATIONALE-305 was representative of the real-world prevalence based on sex. However, the strength of this analysis and of the RATIONALE-305 data overall is the consistency of these data with historical data such as that observed in the CheckMate 649 and KEYNOTE-859 trials on analysis of this patient subgroup.

CONCLUSION

The results of this retrospective analysis support the use of tislelizumab plus ICC as an effective first-line treatment for patients with locally advanced unresectable or metastatic HER2-negative GC/GEJC and tumor PD-L1 expression defined by a TAP score ≥ 1% or CPS ≥ 1.

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Data Availability. On request, and subject to certain criteria, conditions, and expectations, BeiGene, Ltd., will provide access to individual de-identified participant data from BeiGene-sponsored global interventional clinical studies conducted (1) for indications that have been approved based BeiGene data sharing policy or (2) in programs that have been terminated.

BeiGene shares data only when permitted by applicable data privacy and security laws and regulations, shares when it is feasible to do so without compromising the privacy of study participants, and other considerations. Data requests may be submitted to ClinicalTrials@beigene.com.

Declarations

Conflict of Interest. Markus Moehler reports consulting or advisory roles for Bayer, Merck Sharp & Dohme, Merck Serono, Amgen, Taiho Pharmaceutical, Pfizer, Roche, Lilly, Servier, BeiGene, Bristol Myers Squibb, AstraZeneca, Astellas, Dragonfly, Novartis; reports honoraria from Amgen, Genentech/F. Hoffmann-La Roche Ltd, Merck Serono, Merck Sharp & Dohme, Bristol Myers Squibb, AstraZeneca/MedImmune, Servier, Pierre Fabre, Sanofi, Falk Foundation, Transcenta, Daiichi Sankyo, Astellas, and Nordic; and has received grant or research funding from Amgen, Leap Therapeutics, Merck Serono, and Merck Sharp & Dohme; and reports other renumeration from Amgen, Merck Serono, F. Hoffmann-La Roche Ltd, Bayer, ASCO, German Cancer Society, Merck Sharp & Dohme, ESMO, BeiGene, and EORTC. Do-Youn Oh has received honoraria from AstraZeneca, Novartis, Array Biopharma, Lilly, Servier, BeiGene, Merck Sharp & Dohme, and Handok, and has participated on data safety monitoring boards or advisory boards for AstraZeneca, Novartis, Genentech/F. Hoffmann-La Roche Ltd, Merck Serono, Bayer, Taiho Pharmaceutical, Aslan, Halozyme, Zymeworks, Celgene, Basilea, BeiGene, Yunan, Arcus Biosciences, Turning Point Therapeutics, IQVIA, and Merck Sharp & Dohme. Ken Kato has received consulting fees from AstraZeneca, Bayer, BeiGene, Bristol Myers Squibb, Janssen, Merck Bio, Merck & Co., Novartis, Ono Pharmaceutical, and F. Hoffmann-La Roche Ltd; has received payment for expert testimony from Bristol Myers Squibb and Ono Pharmaceutical; and has participated on data safety monitoring boards or advisory boards for Bristol Myers Squibb, Chugai, Merck & Co., and Ono Pharmaceutical. Tobias Arkenau has received consulting fees from Further and EDX Medical; has received honoraria from Servier; and owns stock or stock options in Ellipses Pharma and Careforme. Josep Tabernero owns stocks in Oniria Therapeutics; has received honoraria from Imedex/HMP, Medscape Education, MJH Life Sciences, and PeerView Institute for Medical Education and Physicians Education; and has received consulting fees from Array Biopharma, AstraZeneca, Bayer, Boehringer Ingelheim, Cardiff Oncology, Chugai, Daiichi Sankyo, Genentech/F. Hoffmann-La Roche Ltd, HalioDX SAS, Hutchison MediPharma International, Ikena Oncology, Inspirna Inc, IQVIA, Lilly, Menarini, Merck Serono, Merus, Merck Sharp & Dohme, Mirati, Neophore, Novartis, Ona Therapeutics, Orion Biotechnology, Peptomyc, Pfizer, Pierre Fabre, Samsung Bioepis, Sanofi, Scandion Oncology, Scorpion Therapeutics, Seattle Genetics, Servier, Sotio Biotech, Taiho Pharmaceutical, TheraMyc, and Tolremo Therapeutics. Keun-Wook Lee has received grants or contracts for conducting clinical trials from BeiGene, AstraZeneca, Ono Pharmaceutical, Merck Sharp & Dohme, Merck KGaA, F. Hoffmann-La Roche Ltd, Pfizer, Leap Therapeutics, ALX Oncology, Zymeworks, Astellas, Macrogenics, Amgen, Seagen, Bolt Therapeutics, Trishula Therapeutics, Oncologie, Pharmacyclics, MedPacto, Green Cross Corp, ABLBIO, Y-BIOLOGICS, Daiichi Sankyo, Taiho Pharmaceutical, InventisBio, Elevar Therapeutics, Metafines, Idience, Genome & Company, and Exelixis. Hidekazu Hirano has received institutional research grants from PPD, Daiichi Sankyo, Nippon Boehringer Ingelheim, Novartis, BeiGene, Taiho Pharmaceutical, Amgen, ALX Oncology, and Bristol Myers Squibb, and reports speaker honorarium from FUJIFILM Toyama Chemical, Chugai Pharmaceutical, Bristol Myers Squibb, Taiho Pharmaceutical, Novartis, Teijin Pharma, and Ono Pharmaceutical. Sun Young Rha has received grants from Amgen, Astellas, AstraZeneca, Arcus, Daiichi Sankyo, Eisai, Merck & Co., F. Hoffmann-La Roche Ltd, Gilead, Zymeworks, Indivumed, Merck Sharp & Dohme, Ono Pharmaceutical/Bristol Myers Squibb, ABL Bio, Taiho Pharmaceutical, Lilly, SN Bioscience, Boehringer Ingelheim, and YH Corp; consulting fees from Amgen, ABL Bio, Astellas, AstraZeneca, Daiichi Sankyo, Eisai, Indivumed Therapeutics, LG BioChem, Merck Sharp & Dohme,

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Ethical Approval. RATIONALE-305 was conducted in compliance with Good Clinical Practice guidelines and the principles of the Declaration of Helsinki and its later amendments, and was approved by the relevant institutional review board/independent ethics committee for each study site. Written informed consent was obtained before study participation. Full ethics committee information is available in the supplemental materials.

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