Tislelizumab + Chemotherapy vs Placebo + Chemotherapy in HER2-negative Advanced or Metastatic Gastric or Gastro-esophageal Junction Adenocarcinoma (GC/GEJC): RATIONALE-305 Study Minimum 3-year Survival Follow-up

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CONCLUSIONS

- After a minimum 3 years follow-up, tislelizumab (TIS; BGB-A317) plus chemotherapy (CT) as first-line treatment for gastric or gastro-esophageal junction adenocarcinoma (GC/GEJC) continued to demonstrate clinically meaningful improvements in overall survival (OS), progression-free survival (PFS), and duration of response (DoR) compared with placebo (PBO) plus CT, with no new safety signals
- These long-term data further support TIS plus CT as a new first-line treatment option for advanced human epidermal growth factor receptor 2 (HER2)-negative GC/GEJC

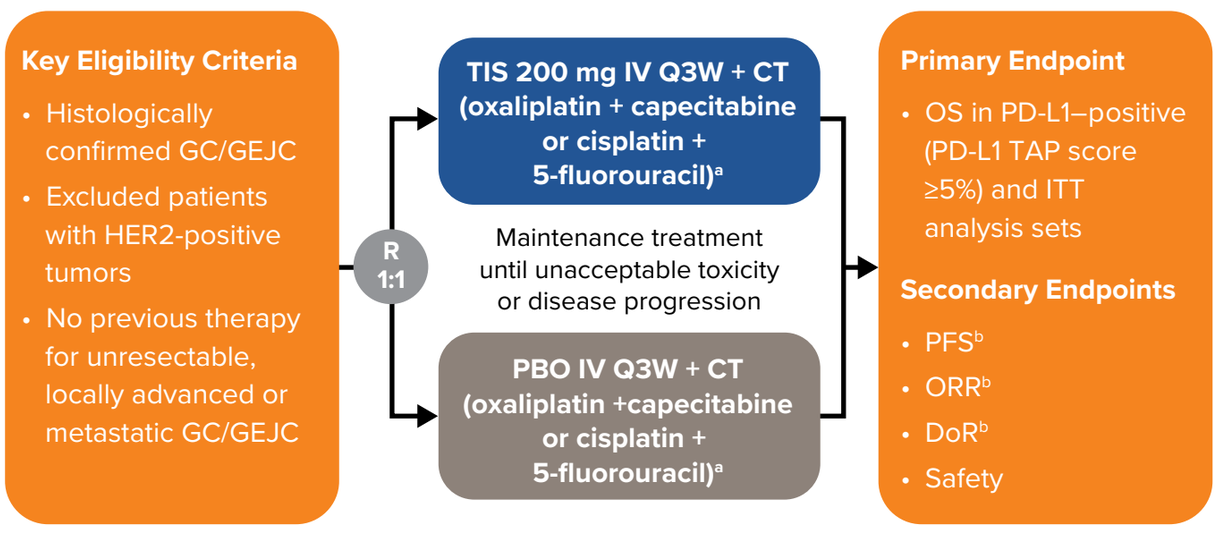
BACKGROUND

- GC/GEJC are among the most common cancer types worldwide, representing the 5th and 7th most common causes of death due to cancer for gastric and esophageal cancers, respectively.[1] Checkpoint inhibition with anti–programmed cell death protein-1 (PD-1) inhibitors in combination with CT has shown improved survival in GC/GEJC over chemotherapy alone[2-4]
- TIS (an anti–PD-1 antibody) plus CT demonstrated significant OS benefit vs PBO plus CT as first-line therapy for advanced GC/GEJC in all randomized patients (hazard ratio [HR]=0.80; at final analysis) and in patients with programmed death-ligand 1 (PD-L1) Tumor Area Positivity (TAP) score ≥5% (HR=0.74; at the interim analysis) in the phase 3 RATIONALE-305 study (NCT03777657).[2] Two-year OS rates for TIS plus CT vs PBO plus CT in the RATIONALE-305 study were 32.7% vs 23.4%, respectively.[5] Here, we report efficacy and safety from RATIONALE-305 after a minimum 3-year follow-up

METHODS

- The RATIONALE-305 study is a randomized, double-blind, global phase 3 study (**Figure 1**)
- TAP score was evaluated in tumor tissue using the VENTANA PD-L1 (SP263) assay

Figure 1. Study Design



Stratification Factors:

- Regions of enrolment: China (including Taiwan) vs Japan and South Korea vs US and Europe and other regions
- PD-L1 expression (PD-L1 score ≥5% vs PD-L1 score <5%)
- Presence of peritoneal metastasis (yes vs no)
- Investigator-chosen CT (oxaliplatin + capecitabine or cisplatin + 5-fluorouracil)

[a]CT: oxaliplatin 130 mg/m² on day 1 + capecitabine 1000 mg/m² twice daily on days 1-14, Q3W; cisplatin 80 mg/m² on day 1 + 5-fluorouracil 800 mg/m²/day on days 1-5, Q3W. [b]Investigator assessed per Response Evaluation Criteria In Solid Tumors v1.1.
Abbreviations: CT, chemotherapy; DoR, duration of response; GC/GEJC, gastric or gastro-oesophageal junction adenocarcinoma; HER2, human epidermal growth factor receptor 2; ITT, intent-to-treat; IV, intravenous; ORR, objective response rate; OS, overall survival; PBO, placebo; PD-L1, programmed death-ligand 1; PFS, progression-free survival; Q3W, once every 3 weeks; R, randomized; TAP, Tumor Area Positivity; TIS, tislelizumab.

RESULTS

Patient Disposition

- Among 1657 patients assessed for eligibility, a total of 997 patients were randomized (TIS plus CT, n=501; PBO plus CT, n=496)
- At 3-year follow-up (minimum follow-up, 36.6 months), 23 (4.6%) patients treated with TIS plus CT and 10 (2.0%) patients treated with PBO plus CT remain on treatment

Efficacy

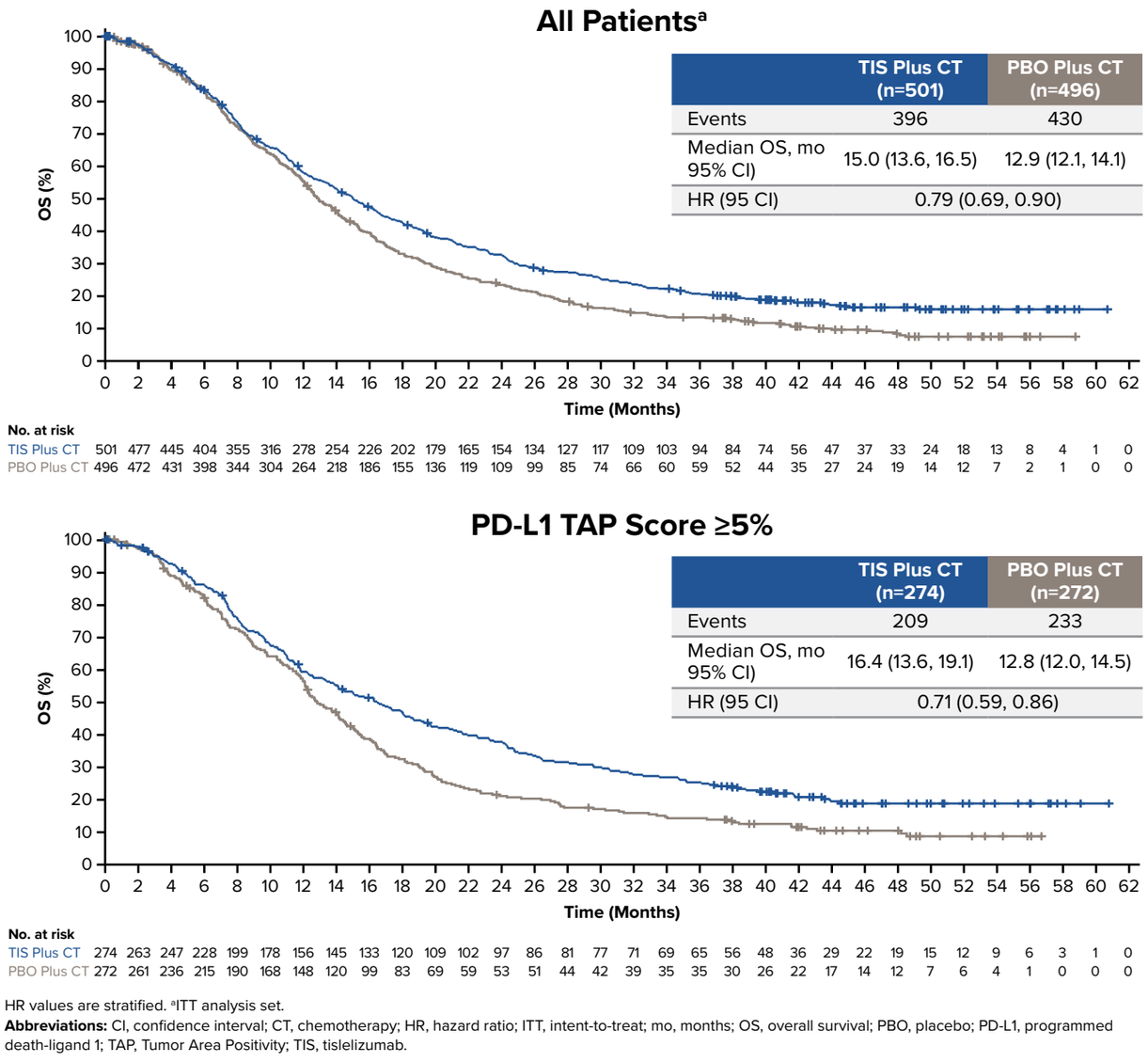
- Improvements in OS, PFS, and DoR with TIS plus CT vs PBO plus CT were maintained at 3-year follow-up (**Table 1**)
- In all patients, and at the prespecified PD-L1 TAP score cutoff points, OS was improved with TIS plus CT vs PBO plus CT (**Figure 2**)
- OS benefit was observed across all prespecified subgroups (**Figure 3**)
- Among the 273 (54.5%) patients treated with TIS plus CT vs 300 (60.5%) patients treated with PBO plus CT who received subsequent anticancer therapies, 258 (51.5%) vs 286 (57.7%) received chemotherapy, 156 (31.1%) vs 165 (33.3%) received targeted therapy, 65 (13.0%) vs 98 (19.8%) received immunotherapy, and 15 (3.0%) vs 19 (3.8%) received other therapies, respectively

Table 1. Efficacy Outcomes at 3-year Follow-up[a]

	TIS Plus CT n=501	PBO Plus CT n=496
Median OS, mo (95% CI)	15.0 (13.6, 16.5)	12.9 (12.1, 14.1)
HR (95% CI)[b]	0.79 (0.69, 0.90)	
OS rate at 36 mo, % (95% CI)	20.7 (17.1, 24.4)	13.4 (10.5, 16.6)
Median PFS, mo (95% CI)[c]	6.9 (5.7, 7.2)	6.2 (5.6, 6.9)
HR (95% CI)[b]	0.79 (0.68, 0.91)	
PFS rate at 36 mo, % (95% CI)	15.0 (11.6, 18.8)	7.5 (5.1, 10.5)
Confirmed ORR, % (95% CI)[c]	47.3 (42.9, 51.8)	40.5 (36.2, 45.0)
Median DoR (confirmed responders), mo (95% CI)	8.6 (7.9, 11.1)	7.2 (6.0, 8.5)
Remaining in response at 36 mo, % (95% CI)	24.5 (18.8, 30.6)	14.4 (9.3, 20.5)

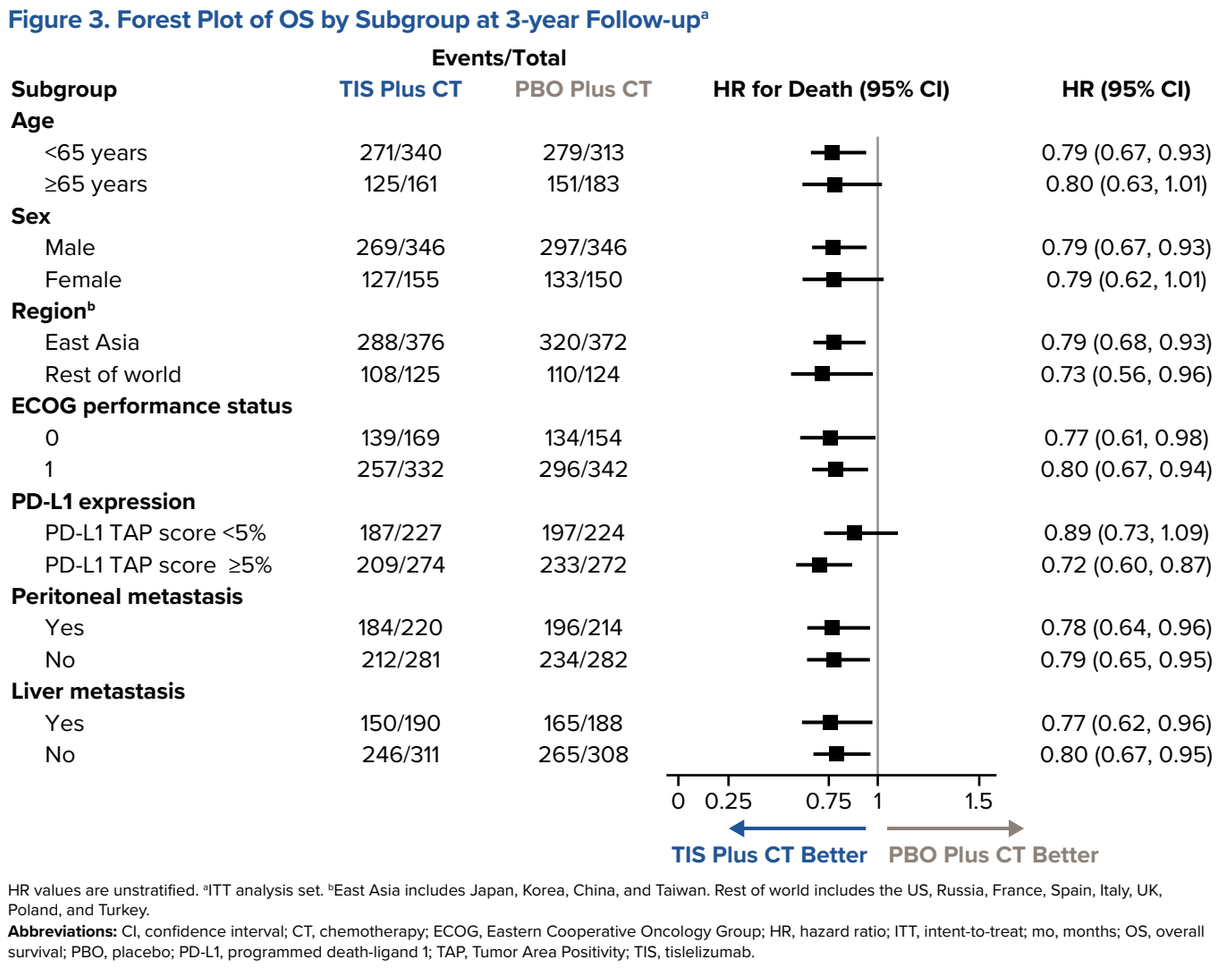
[a]ITT analysis set. [b]Stratified by region (East Asia vs rest of world), PD-L1 expression, and presence of peritoneal metastasis. [c]Investigator evaluated.
Abbreviations: CI, confidence interval; CT, chemotherapy; DoR, duration of response; HR, hazard ratio; ITT, intent-to-treat; mo, months; ORR, objective response rate; OS, overall survival; PBO, placebo; PD-L1, programmed death-ligand 1; PFS, progression-free survival; TIS, tislelizumab.

Figure 2. Kaplan-Meier Curves of OS at 3-year Follow-up



HR values are stratified. [a]ITT analysis set.
Abbreviations: CI, confidence interval; CT, chemotherapy; HR, hazard ratio; ITT, intent-to-treat; mo, months; OS, overall survival; PBO, placebo; PD-L1, programmed death-ligand 1; TAP, Tumor Area Positivity; TIS, tislelizumab.

Figure 3. Forest Plot of OS by Subgroup at 3-year Follow-up[a]



HR values are unstratified. [a]ITT analysis set. [b]East Asia includes Japan, Korea, China, and Taiwan. Rest of world includes the US, Russia, France, Spain, Italy, UK, Poland, and Turkey.
Abbreviations: CI, confidence interval; CT, chemotherapy; ECOG, Eastern Cooperative Oncology Group; HR, hazard ratio; ITT, intent-to-treat; mo, months; OS, overall survival; PBO, placebo; PD-L1, programmed death-ligand 1; TAP, Tumor Area Positivity; TIS, tislelizumab.

Safety

- Safety was maintained at 3-year follow-up (**Table 2**)
- The numbers of treatment-related adverse events (TRAEs), grade ≥3 TRAEs, and treatment-emergent adverse events leading to dose modification were similar in both arms
- The most common grade ≥3 TRAEs were neutrophil and platelet count decreased

Table 2. Safety at 3-year Follow-up[a]

n (%)	TIS Plus CT n=498	PBO Plus CT n=494
Patients with ≥1 TRAE for any treatment component	483 (97.0)	476 (96.4)
Grade ≥3 TRAEs	269 (54.0)	246 (49.8)
Occurring at ≥5% incidence		
Neutrophil count decreased	59 (11.8)	57 (11.5)
Platelet count decreased	56 (11.2)	57 (11.5)
Neutropenia	33 (6.6)	34 (6.9)
Anemia	25 (5.0)	37 (7.5)
Serious TRAEs for any treatment component	113 (22.7)	72 (14.6)
TRAEs leading to any treatment discontinuation	83 (16.7)	40 (8.1)
TEAEs leading to dose modification of any treatment component	381 (76.5)	375 (75.9)
TRAEs leading to death[b]	6 (1.2)[c]	2 (0.4)[d]

[a]Patients with ≥2 events for the same preferred term were counted only once for the preferred term. [b]Excludes death due to disease progression. [c]Death (n=4), colitis (n=1), sepsis (n=1), subdural hematoma (n=1). [d]Pneumonia (n=2).
Abbreviations: CT, chemotherapy; PBO, placebo; TEAE, treatment-emergent adverse event; TIS, tislelizumab; TRAE, treatment-related adverse event.

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DISCLOSURES

KK reports consulting fees from ONO, Bristol Myers Squibb, BeOne Medicines/Novartis, AstraZeneca, Roche, Bayer, Merck & Co., Merck Bio, and Janssen; payment for expert testimony from ONO and Bristol Myers Squibb; and participation on a data safety monitoring or advisory board for ONO and Bristol Myers Squibb.

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