RATIONALE-305: Phase 3 Study of Tislelizumab Plus Chemotherapy Versus Placebo + Chemotherapy as First-Line Treatment of Advanced Gastric or Gastroesophageal Junction Adenocarcinoma

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Conclusions

In RATIONALE-305, tislelizumab (TIS) plus investigator-chosen chemotherapy (ICC) demonstrated statistically significant and clinically meaningful improvement in overall survival (OS) vs placebo (PBO) plus ICC as first-line (1L) treatment in patients with programmed death-ligand 1 (PD-L1)-positive (+) gastric cancer or gastroesophageal junction adenocarcinoma (GC/GEJC).

OS benefit with TIS plus ICC was accompanied by improvements in progression-free survival (PFS), objective response rate (ORR), and duration of response (DoR), and generally better health-related quality of life (HRQoL) compared with PBO plus ICC. TIS plus ICC had a manageable safety profile with no new safety signals.

RATIONALE-305 results offer TIS plus ICC as a new 1L treatment option for patients with PD-L1+ GC/GEJC. The study continues to be double-blinded towards OS final analysis in the intention-to-treat (ITT) population, the results of which will be presented later this year.

Background

GC is the fifth most common cancer globally[1] and is more prevalent in Eastern Asia than rest of world.[2] The prognosis for patients with advanced unresectable or metastatic GC/GEJC treated with standard-of-care ICC remains unsatisfying,[3] but the addition of anti-programmed cell death protein 1 (PD-1) antibodies to ICC improved survival.[4]

Nivolumab plus ICC has been approved as 1L treatment for GC/GEJC in many countries/regions for patients with different levels of PD-L1 expression.[5-7] In a phase 2 study, TIS, an anti-PD-1 monoclonal antibody,[8] plus ICC demonstrated durable antitumor activity as 1L treatment for patients in China with GC/GEJC.[9]

The global phase 3 RATIONALE-305 study assessed the efficacy and safety of 1L TIS or PBO plus ICC in unresectable, locally advanced or metastatic GC/GEJC.

Here we report results from the interim analysis performed in the PD-L1+ patient population.

Methods

- RATIONALE-305 was a randomized, double-blind, global phase 3 study (NCT03777657; **Figure 1**).

Figure 1. Study Design

Key eligibility criteria
- Histologically confirmed GC/GEJC
- Exclude patients with HER2+ tumors
- No previous therapy for unresectable, locally advanced or metastatic GC/GEJC

TIS 200 mg IV Q3W + ICC (XELOX or FP)

R 1:1[a]

Initial up to six treatment cycles[b]

PBO IV Q3W + ICC (XELOX or FP)

Maintenance treatment until unacceptable toxicity or disease progression

Primary endpoints
- OS in PD-L1+ (PD-L1 TAP score ≥5%[c]) and ITT analysis set

Secondary endpoints[d]
- PFS, ORR, DoR, DCR, HRQoL, and safety

Statistical considerations
- If OS in the PD-L1+ analysis set was statistically significant, OS in the ITT analysis set was tested hierarchically
- An interim analysis was performed based on 291 observed events for the PD-L1+ analysis set, and the updated, one-sided *P* value boundary was 0.0092

[a]Patients were stratified by region of enrolment, peritoneal metastasis, PD-L1 TAP score (PD-L1 ≥5% vs <5%[c]), and ICC;

[b]ICC of doublet regimen (XELOX or FP) administered up to six cycles; capecitabine as optional maintenance therapy only for XELOX regimen administered until disease progression, intolerable toxicity, or another treatment discontinuation criterion was met. TIS (or PBO) was administered until disease progression, intolerable toxicity, or another treatment discontinuation criterion was met;

[c]PD-L1 score was determined using the VENTANA SP263 assay;

[d]All tumor response assessments were performed by investigator per RECIST v1.1.

Abbreviations: BID, twice daily; DCR, disease control rate; DoR, duration of response; FP, cisplatin 80 mg/m² IV Day 1 + 5-fluorouracil 800 mg/m²/day continuous IV Days 1-5 Q3W; GC/GEJC, gastric cancer or gastroesophageal junction adenocarcinoma; HER2, human epidermal growth factor receptor 2; HRQoL, health-related quality of life; ICC, investigator-chosen chemotherapy; ITT, intention-to-treat; IV, intravenously; ORR, objective response rate; OS, overall survival; PBO, placebo; PO, orally; PD-L1, programmed death-ligand 1; PFS, progression-free survival; Q3W, every three weeks; R, randomized; RECIST v1.1, Response Evaluation Criteria in Solid Tumors version 1.1; TAP, tumor area positivity; TIS, tislelizumab; XELOX, oxaliplatin 130 mg/m² IV Day 1 + capecitabine 1000 mg/m² PO BID Days 1-14 Q3W.

Results

- A total of 997 patients were enrolled from 13 countries, of whom 546 (54.8%) were included in the PD-L1+ analysis set (**Table 1**).
- At data cutoff (October 8, 2021), median follow-up was 11.8 months for TIS plus ICC and 11.7 months for PBO plus ICC.

Table 1. Baseline Characteristics (PD-L1+ Analysis Set)

		TIS + ICC (n=274)	PBO + ICC (n=272)
Median age, years (range)		61.0 (23.0-83.0)	62.0 (30.0-84.0)
Male sex, n (%)		193 (70.4)	201 (73.9)
Region, n (%)	East Asia[a]	202 (73.7)	201 (73.9)
	Rest of world[b]	72 (26.3)	71 (26.1)
ECOG PS, n (%)	0	98 (35.8)	86 (31.6)
	1	176 (64.2)	186 (68.4)
Primary location, n (%)	Stomach	223 (81.4)	214 (78.7)
	GEJC	51 (18.6)	58 (21.3)
ICC, n (%)	XELOX	254 (92.7)	254 (93.4)
	FP	20 (7.3)	18 (6.6)
Metastatic disease, n (%)		270 (98.5)	268 (98.5)
Peritoneal metastasis, n (%)		113 (41.2)	109 (40.1)
Prior adjuvant/neoadjuvant treatment, n (%)		37 (13.5)	38 (14.0)

In the ITT population, 54.7% of patients in the TIS + ICC arm and 54.8% in the PBO + ICC arm had a PD-L1 score of ≥5% and were included in the PD-L1+ analysis set.
[a]East Asia includes China (including Taiwan), Japan, and South Korea; [b]Rest of world includes US and EU.
Abbreviations: ECOG PS, Eastern Cooperative Oncology Group performance status; EU, European Union; FP, cisplatin + 5-fluorouracil; GEJC, gastroesophageal junction adenocarcinoma; ICC, investigator-chosen chemotherapy; ITT, intention-to-treat; PBO, placebo; PD-L1, programmed death-ligand 1; TIS, tislelizumab; US, United States; XELOX, oxaliplatin + capecitabine.

Efficacy

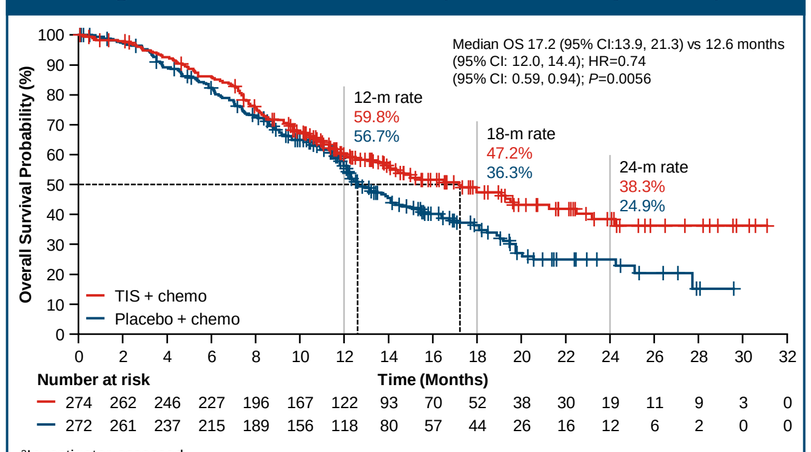
- TIS plus ICC demonstrated statistically significant improvement in OS vs PBO plus ICC in the PD-L1+ analysis set.
  - Median OS 17.2 months (95% confidence interval [CI]:13.9, 21.3) vs 12.6 months (95% CI: 12.0, 14.4); hazard ratio (HR)=0.74 (95% CI: 0.59, 0.94); *P*=0.0056 (**Figure 2**).
- OS benefit with TIS plus ICC was observed across prespecified subgroups.
- In the PD-L1+ analysis set, TIS plus ICC improved PFS over PBO plus ICC in the PD-L1+ analysis set (median PFS 7.2 months [95% CI: 5.8, 8.4] vs 5.9 months [95% CI: 5.6, 7.0]; HR=0.67 [95% CI: 0.55, 0.83]; **Figure 3**).
- TIS plus ICC was associated with a numerically higher ORR and more durable response vs PBO plus ICC (**Table 2**).

Table 2. Antitumor Response (PD-L1+ Analysis Set)

	TIS + ICC (n=274)	PBO + ICC (n=272)
ORR[a], % (95% CI[b])	50.4 (44.3, 56.4)	43.0 (37.1, 49.1)
Best overall response, n (%)		
CR	9 (3.3)	5 (1.8)
PR	129 (47.1)	112 (41.2)
SD[c]	104 (38.0)	109 (40.1)
PD	12 (4.4)	32 (11.8)
Undetermined[d]	20 (7.3)	14 (5.1)
Disease control rate, % (95% CI[b])	88.3 (83.9, 91.9)	83.1 (78.1, 87.3)
Median DoR, months (95% CI)	9.0 (8.2, 19.4)	7.1 (5.7, 8.3)

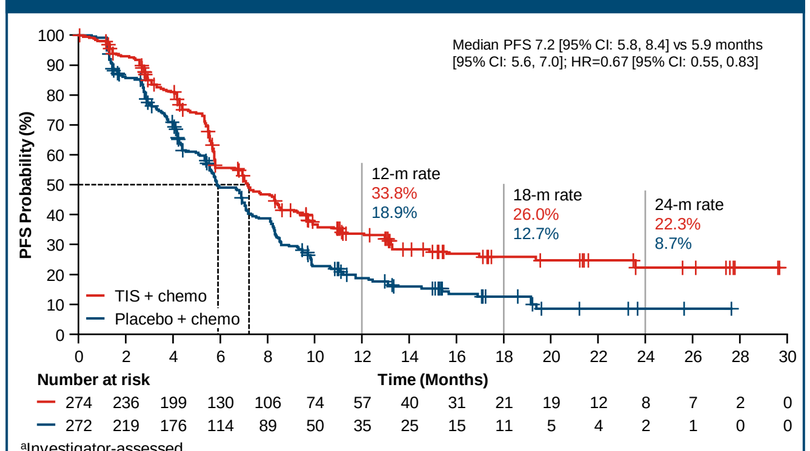
[a]ORR is defined as the percentage of patients with confirmed CR/PR; [b]Exact Clopper-Pearson two-sided CI; [c]SD includes non-CR and non-PD; [d]Best overall response of 'undetermined' included patients who had postbaseline tumor assessments, none of which were evaluable; or patients who had no postbaseline tumor assessment due to death, withdrawal of consent, loss to follow-up, or any other reason.
Abbreviations: CI, confidence interval; CR, complete response; DoR, duration of response; ICC, investigator-chosen chemotherapy; ORR, objective response rate; PBO, placebo; PD, progressive disease; PD-L1, programmed death-ligand 1; PR, partial response; SD, stable disease; TIS, tislelizumab.

Figure 2. Overall Survival[a] (PD-L1+ Analysis Set)



[a]Investigator-assessed.
Abbreviations: Chemo, chemotherapy; CI, confidence interval; HR, hazard ratio; m, months; OS, overall survival; PD-L1, programmed death-ligand 1;TIS, tislelizumab.

Figure 3. Progression-Free Survival[a] (PD-L1+ Analysis Set)



[a]Investigator-assessed.
Abbreviations: Chemo, chemotherapy; CI, confidence interval; HR, hazard ratio; m, months; PD-L1, programmed death ligand; PFS, progression-free survival; TIS, tislelizumab.

Health-Related Quality of Life

- Patients receiving TIS plus ICC generally reported better HRQoL, as indicated by maintenance of EORTC-QLQ-C30 global health status, physical functioning scores, and QLQST022 index score, and greater reductions in symptoms of fatigue, pain/discomfort, dysphagia, and upper gastrointestinal symptoms.

Safety

- TIS plus ICC had a manageable safety profile in patients with unresectable, locally advanced or metastatic GC/GEJC (**Table 3**).
- The profile of treatment-emergent adverse events with TIS plus ICC was consistent with the known profile of each treatment agent, with no new safety signals identified.

Table 3. Summary of TEAEs and TRAEs (PD-L1+ Safety Analysis Set)

Category, n (%)	TIS + ICC (n=272)	PBO + ICC (n=272)
Median duration of TIS/PBO treatment, weeks (range)	27.9 (0.6-135.3)	24.4 (2.3-128.6)
Any TEAE	271 (99.6)	266 (97.8)
Treatment-related	264 (97.1)	261 (96.0)
TEAE ≥grade 3	176 (64.7)	171 (62.9)
Treatment-related	143 (52.6)	132 (48.5)
Serious TEAE	115 (42.3)	100 (36.8)
Treatment-related	70 (25.7)	45 (16.5)
TEAE leading to discontinuation of any treatment	61 (22.4)	33 (12.1)
TEAE leading to discontinuation of TIS/PBO	39 (14.3)	18 (6.6)
TEAE leading to discontinuation of any ICC component	54 (19.9)	31 (11.4)
TEAE leading to death	24 (8.8)	21 (7.7)
Treatment-related	6 (2.2)	2 (0.7)

For each row category, a patient with two or more AEs in that category was counted only once. AE grades were evaluated based on National Cancer Institute–Common Terminology Criteria for Adverse Events (version 5.0). AE terms were coded using Medical Dictionary for Drug Regulatory Affairs version 24.0.
Abbreviations: AE, adverse event; ICC, investigator-chosen chemotherapy; PBO, placebo; PD-L1, programmed death ligand-1;TEAEs, treatment-emergent adverse events; TIS, tislelizumab; TRAEs, treatment-related adverse events.

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