Tislelizumab Plus Chemotherapy Versus Placebo Plus Chemotherapy as First-Line Treatment for Locally Advanced Unresectable or Metastatic Gastric or Gastroesophageal Junction Adenocarcinoma: RATIONALE-305 European/North American Patient Subgroup

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Conclusions

In the European/North American (Eu/NA) patient subgroup analysis of RATIONALE-305, tislelizumab (TIS) plus chemotherapy showed overall survival (OS) improvement in the intent-to-treat (ITT) analysis set and programmed death-ligand 1-positive (PD-L1+) analysis set compared with placebo plus chemotherapy, as first-line treatment of locally advanced unresectable or metastatic gastric or gastroesophageal junction adenocarcinoma (GC/GEJC).

OS improvement with TIS plus chemotherapy in the Eu/NA patient subgroup was accompanied by favorable progression-free survival (PFS), objective response rate (ORR), and median duration of response (DoR). TIS plus chemotherapy had a manageable safety profile. These results are consistent with previously published results in the overall study population.

Background

GC is the fifth most common cancer globally.[1] The prognosis for patients with advanced unresectable or metastatic GC/GEJC treated with standard-of-care chemotherapy remains unsatisfactory,[2] but the addition of anti-programmed cell death protein 1 (PD-1) antibodies to chemotherapy has been shown to improve survival.[3]

TIS, an anti-PD-1 monoclonal antibody, plus chemotherapy, demonstrated significant OS benefit versus placebo plus chemotherapy (hazard ratio [HR]=0.80, 95% confidence interval [CI]: 0.70, 0.92) as first-line therapy in patients with advanced GC/GEJC in the randomized, double-blind, global, phase 3 RATIONALE-305 study (NCT03777657).[4]

Here, we present the efficacy and safety results from the Eu/NA patient subgroup analysis from the RATIONALE-305 study.

Methods

- The design of the double-blind, global, phase 3 RATIONALE-305 study has been previously described[4]
- Eligible patients were randomized (1:1) to receive TIS 200 mg or placebo intravenously once every 3 weeks plus investigator-chosen chemotherapy (5-fluorouracil + cisplatin or capecitabine + oxaliplatin)
- The primary endpoint was OS in both the ITT analysis set and the PD-L1+ analysis set (patients with tumor area positivity score ≥5%)
- Secondary endpoints included PFS, ORR, DoR, and safety

Results

Patient Baseline Characteristics

- A total of 997 patients were enrolled in the study, of whom 249 (25.0%) were included in the Eu/NA patient subgroup analysis (TIS plus chemotherapy, n=125; placebo plus chemotherapy, n=124)
- Patient baseline characteristics were generally balanced between treatment arms (**Table 1**)
- At data cutoff (February 28, 2023), minimum follow-up in the overall population was 24.6 months for TIS plus chemotherapy and 25.0 months for placebo plus chemotherapy

Efficacy

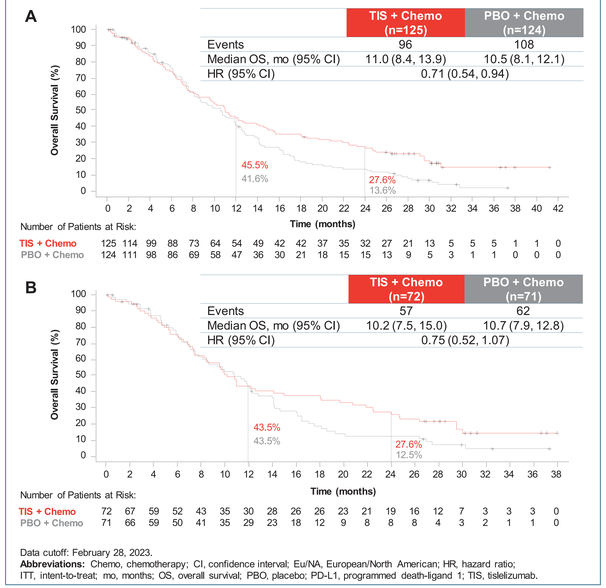
- In the Eu/NA subgroup, TIS plus chemotherapy improved OS compared with placebo plus chemotherapy in the ITT analysis set (HR=0.71, 95% CI: 0.54, 0.94) and PD-L1+ analysis set (HR=0.75, 95% CI: 0.52, 1.07) (the HR results for OS in this subgroup should be interpreted with caution) (**Figure 1**)
- OS rates at 24 months were higher with TIS plus chemotherapy versus placebo plus chemotherapy in the ITT analysis set (27.6% vs 13.6%) and PD-L1+ analysis set (27.6% vs 12.5%)
- TIS plus chemotherapy resulted in favorable PFS, numerically higher ORR, and longer DoR versus placebo plus chemotherapy (**Table 2**)

Table 1. Patient Baseline Characteristics (ITT Analysis Set)

	Eu/NA Patient Subgroup		
	TIS + Chemo (n=125)	PBO + Chemo (n=124)	Total (n=249)
Median age, years (range)	61.0 (23.0-83.0)	62.5 (30.0-86.0)	62.0 (23.0-86.0)
Male, n (%)	88 (70.4)	85 (68.5)	173 (69.5)
ECOG PS, n (%)			
0	49 (39.2)	52 (41.9)	101 (40.6)
1	76 (60.8)	72 (58.1)	148 (59.4)
Primary tumor location, n (%)			
Stomach	76 (60.8)	76 (61.3)	152 (61.0)
GEJ	49 (39.2)	48 (38.7)	97 (39.0)
Metastatic disease,[a] n (%)	121 (96.8)	121 (97.6)	242 (97.2)
Peritoneal metastasis, n (%)	55 (44.0)	54 (43.5)	109 (43.8)
Prior adjuvant/neoadjuvant treatment, n (%)	23 (18.4)	17 (13.7)	40 (16.1)
PD-L1 score, n (%)			
<5%	53 (42.4)	53 (42.7)	106 (42.6)
≥5%	72 (57.6)	71 (57.3)	143 (57.4)

Data cutoff: February 28, 2023. [a]Disease stage rating at screening was based on American Joint Committee on Cancer TNM Staging Classification for Carcinoma of the Stomach and for Carcinoma of the Esophagus and Esophagogastric Junction (8th ed., 2017).
Abbreviations: Chemo, chemotherapy; ECOG PS, Eastern Cooperative Oncology Group performance status; Eu/NA, European/North American; GEJ, gastroesophageal junction; ITT, intent-to-treat; PBO, placebo; PD-L1, programmed death-ligand 1; TIS, tislelizumab.

Figure 1. OS in the Eu/NA Patient Subgroup in the (A) ITT Analysis Set and (B) PD-L1+ Analysis Set



Data cutoff: February 28, 2023.
Abbreviations: Chemo, chemotherapy; CI, confidence interval; Eu/NA, European/North American; HR, hazard ratio; ITT, intent-to-treat; mo, months; OS, overall survival; PBO, placebo; PD-L1, programmed death-ligand 1; TIS, tislelizumab.

Table 2. Efficacy Endpoints (ITT Analysis Set)

	Eu/NA Patient Subgroup	
	TIS + Chemo (n=125)	PBO + Chemo (n=124)
Median PFS, mo (95% CI)	5.6 (4.4, 7.0)	5.4 (4.3, 5.9)
Hazard ratio	0.84 (0.63, 1.11)	
ORR,[a] % (95% CI)[b]	36.0 (27.6, 45.1)	31.5 (23.4, 40.4)
Median DoR,[a] mo (95% CI)	7.5 (4.4, 12.0)	5.0 (3.9, 6.7)

Data cutoff: February 28, 2023. Medians were estimated by the Kaplan–Meier method with 95% CIs estimated using the method of Brookmeyer and Crowley. [a]Among patients with a confirmed partial or complete response per RECIST version 1.1. [b]Exact Clopper–Pearson 2-sided CI.
Abbreviations: Chemo, chemotherapy; CI, confidence interval; DoR, duration of response; Eu/NA, European/North American; ITT, intent-to-treat; mo, months; ORR, objective response rate; PBO, placebo; PFS, progression-free survival; RECIST, Response Evaluation Criteria in Solid Tumors; TIS, tislelizumab.

Safety

- Incidences of grade ≥3 treatment-related adverse events (TRAEs) (48.8% vs 49.2%) and TRAEs leading to death (1.6% vs 0.8%) were similar between arms, while more patients discontinued treatment (13.0% vs 5.6%) due to TRAEs with TIS plus chemotherapy versus placebo plus chemotherapy, respectively
- Overall, the safety profile of TIS plus chemotherapy was manageable in patients with locally advanced unresectable or metastatic GC/GEJC in the Eu/NA subgroup (**Table 3**)

Table 3. Safety Summary (Safety Analysis Set)

	Eu/NA Patient Subgroup	
	TIS + Chemo (n=123)	PBO + Chemo (n=124)
TRAE of any grade, n (%)	117 (95.1)	116 (93.5)
TRAE of grade ≥3, n (%)	60 (48.8)	61 (49.2)
TRAE leading to discontinuation,[a] n (%)	16 (13.0)	7 (5.6)
TRAE leading to death, n (%)	2 (1.6)	1 (0.8)

Data cutoff: February 28, 2023. [a]Discontinuation of any treatment component.
Abbreviations: Chemo, chemotherapy; Eu/NA, European/North American; PBO, placebo; TIS, tislelizumab; TRAE, treatment-related treatment-emergent adverse event.

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