First-Line Tislelizumab Plus Chemotherapy in Gastric/Gastroesophageal Junction Cancer: RATIONALE-305 Asian Subgroup

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Conclusions

- **In Asian patients in the RATIONALE-305 study**
  - **Tislelizumab plus chemotherapy showed an improvement in overall survival (OS) versus placebo plus chemotherapy in both the intent-to-treat (ITT) and programmed death-ligand 1 (PD-L1) score ≥5% populations**
  - **Additionally, tislelizumab plus chemotherapy demonstrated improved progression-free survival (PFS), favorable response rates, and more durable antitumor responses versus placebo plus chemotherapy**
  - **Tislelizumab plus chemotherapy also showed a manageable safety profile, with no new safety signals identified**
- **The efficacy and safety results in the Asian patient subgroup were consistent with the results in the overall study population, suggesting this combination may be a first-line treatment option for Asian patients with advanced gastric/gastroesophageal junction cancer (GC/GEJC)[1]**

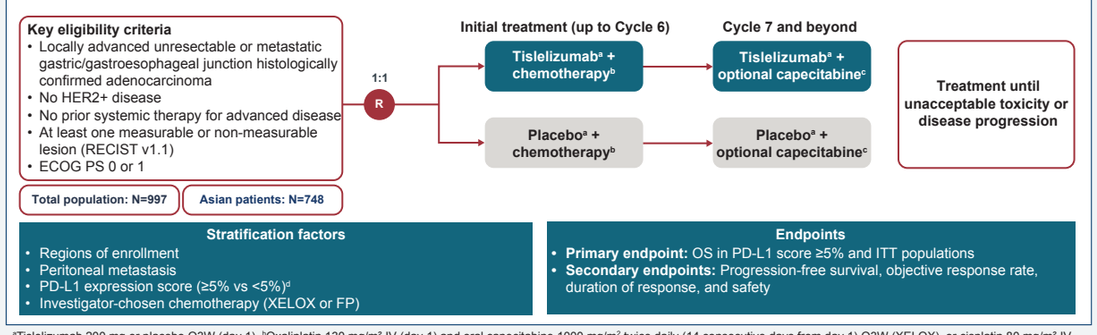
Introduction

- Gastric cancer is one of the leading causes of cancer-related deaths worldwide; Asia has a notably higher incidence and mortality rate of GC, and the disease is of particular concern in China, South Korea, and Japan[2-5]
- Prior to the introduction of immunotherapy, platinum plus fluoropyrimidine chemotherapy was the standard first-line therapy for advanced GC/GEJC, with a median OS of less than 12 months[6-8]
- The RATIONALE-305 study (NCT03777657) met its primary endpoint, showing significant improvement in OS with tislelizumab plus chemotherapy versus placebo plus chemotherapy in the PD-L1 ≥5% population at interim analysis, and in the ITT population at final analysis, with favorable PFS[1,9]
- Overall, results of the final analysis supported tislelizumab plus chemotherapy as a potential first-line treatment option for patients with advanced GC/GEJC[1]
- Here, we present results from the Asian patient subgroup of the RATIONALE-305 study at final analysis

Methods

- Of 997 randomized patients, 748 (tislelizumab with chemotherapy: n=376; placebo with chemotherapy: n=372) were enrolled from Asia, of whom 403 had a PD-L1 score of ≥5% (**Figure 1**)
- The Asian subgroup comprised patients from China (including Taiwan), Japan, and South Korea
- As of the data cutoff for the final analysis (February 28, 2023), median study follow-up in the Asian subgroup was 14.5 months (range, 0.1-50.1) and minimum study follow-up in this subgroup was 24.6 months

Figure 1. Study Design and Patient Population



[a]Tislelizumab 200 mg or placebo Q3W (day 1). [b]Oxaliplatin 130 mg/m² IV (day 1) and oral capecitabine 1000 mg/m² twice daily (14 consecutive days from day 1) Q3W (XELOX), or cisplatin 80 mg/m² IV (day 1) and FP 800 mg/m²/day IV (days 1-5) Q3W. [c]Capecitabine as maintenance therapy was optional and only for XELOX-treated patients. [d]PD-L1 score was determined using the VENTANA PD-L1 (SP263) assay by tumor area positivity score.
ECOG PS, Eastern Cooperative Oncology Group Performance Status; FP, 5-fluorouracil; HER2, human epidermal growth factor receptor 2; ITT, intent-to-treat; IV, intravenous; OS, overall survival; PD-L1, programmed death-ligand 1; Q3W, once every 3 weeks; R, randomized; RECIST v1.1, Response Evaluation Criteria in Solid Tumors version 1.1.

Results

- Improved OS differences of 2.1 and 4.6 months in favor of tislelizumab plus chemotherapy versus placebo plus chemotherapy were observed in the overall ITT and PD-L1 score ≥5% populations at final and interim analysis, respectively (**Figure 2**)[9]

Figure 2. Overall Survival: Overall Population

ITT Population at Final Analysis[1]

	Events, n (%)	Median OS (95% CI), Months[a]	HR (95% CI)[a] *P* Value[b]
TIS + chemo (n=501)	370 (73.9)	15.0 (13.6-16.5)	0.80 (0.70-0.92)
PBO + chemo (n=496)	406 (81.9)	12.9 (12.1-14.1)	0.0011

PD-L1 Score ≥5% Population at Interim Analysis[9]

	Events, n (%)	Median OS (95% CI), Months[c]	HR (95% CI)[c] *P* Value[b]
TIS + chemo (n=274)	130 (47.4)	17.2 (13.9-21.3)	0.74 (0.59-0.94)
PBO + chemo (n=272)	161 (59.2)	12.6 (12.0-14.4)	0.0056

[a]Cox regression model was stratified by regions (east Asia vs rest of the world), PD-L1 expression, and presence of peritoneal metastasis. [b]*P* values are one-sided and based on the stratified log-rank test. [c]Cox regression model was stratified by regions (east Asia vs rest of the world) and presence of peritoneal metastasis.
Chemo, chemotherapy; HR, hazard ratio; ITT, intent-to-treat; OS, overall survival; PBO, placebo; PD-L1, programmed death-ligand 1; TIS, tislelizumab.

- Demographics and baseline characteristics of patients in the Asian subgroup were similar to those of the overall ITT population (**Table 1**)

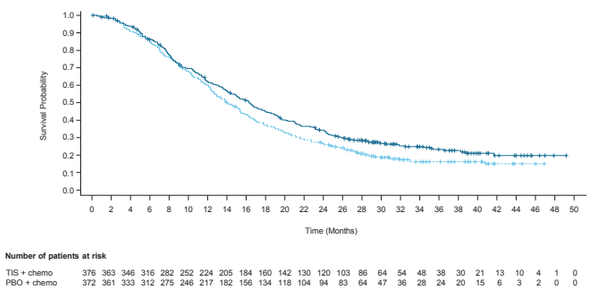
Table 1. Demographics and Baseline Disease Characteristics

	Asian Subgroup ITT Population		Overall ITT Population	
	Tislelizumab + Chemotherapy (n=376)	Placebo + Chemotherapy (n=372)	Tislelizumab + Chemotherapy (n=501)	Placebo + Chemotherapy (n=496)
Age, median (range), years	59.0 (23.0-86.0)	61.0 (25.0-83.0)	60.0 (23.0-86.0)	61.0 (25.0-86.0)
Sex, male, n (%)	258 (68.6)	261 (70.2)	346 (69.1)	346 (69.8)
ECOG PS, n (%)				
0	120 (31.9)	102 (27.4)	169 (33.7)	154 (31.0)
1	256 (68.1)	270 (72.6)	332 (66.3)	342 (69.0)
Primary tumor location, n (%)[a]				
Stomach	329 (87.5)	319 (85.8)	405 (80.8)	395 (79.6)
GEJ	47 (12.5)	52 (14.0)	96 (19.2)	100 (20.2)
PD-L1 TAP score, n (%)				
≥5%	202 (53.7)	201 (54.0)	274 (54.7)	272 (54.8)
<5%	174 (46.3)	171 (46.0)	227 (45.3)	224 (45.2)
Metastatic disease, n (%)	373 (99.2)	369 (99.2)	494 (98.6)	490 (98.8)
Peritoneal metastasis, n (%)	165 (43.9)	160 (43.0)	220 (43.9)	214 (43.1)
Investigator-chosen chemo, n (%)				
Oxaliplatin/capecitabine	370 (98.4)	367 (98.7)	466 (93.0)	465 (93.8)
Cisplatin/5-fluorouracil	6 (1.6)	5 (1.3)	35 (7.0)	31 (6.3)

Data cutoff: February 28, 2023.
[a]The diagnosis of 1 patient was updated from gastric adenocarcinoma to pancreatic cancer after randomization and the patient remained in the ITT population.
Chemo, chemotherapy; ECOG PS, Eastern Cooperative Oncology Group Performance Status; GEJ, gastroesophageal junction; ITT, intent-to-treat; PBO, placebo; PD-L1, programmed death-ligand 1; TAP, tumor area positivity; TIS, tislelizumab.

- An improvement in OS was observed with tislelizumab plus chemotherapy versus placebo plus chemotherapy in the ITT population (**Figure 3**)

Figure 3. Overall Survival: Asian Subgroup (ITT Population)

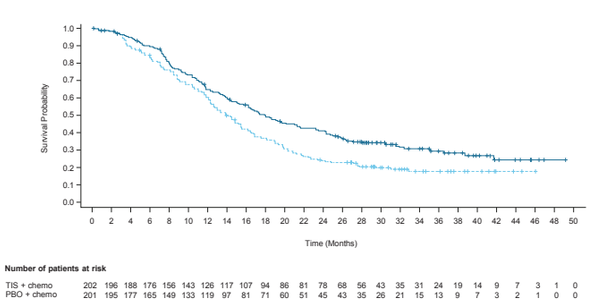


	Events, n (%)	Median OS (95% CI), Months[a]	HR (95% CI)[a]
TIS + chemo (n=376)	274 (72.9)	16.4 (14.4-18.0)	0.83 (0.70-0.97)
PBO + chemo (n=372)	298 (80.1)	14.1 (12.8-15.4)	

Data cutoff: February 28, 2023.
[a]HR and 95% CIs were estimated from an unstratified Cox regression model including treatment as a covariate.
Chemo, chemotherapy; HR, hazard ratio; ITT, intent-to-treat; OS, overall survival; PBO, placebo; TIS, tislelizumab.

- An improvement in OS was also observed with tislelizumab plus chemotherapy versus placebo plus chemotherapy in the PD-L1 score ≥5% population (**Figure 4**)

Figure 4. Overall Survival: Asian Subgroup (PD-L1 Score ≥5% Population)



	Events, n (%)	Median OS (95% CI), Months[a]	HR (95% CI)[a]
TIS + chemo (n=202)	135 (66.8)	18.0 (15.0-21.6)	0.71 (0.56-0.89)
PBO + chemo (n=201)	157 (78.1)	14.0 (12.3-15.5)	

Data cutoff: February 28, 2023.
[a]HR and 95% CIs were estimated from an unstratified Cox regression model including treatment as a covariate.
Chemo, chemotherapy; CI, confidence interval; HR, hazard ratio; OS, overall survival; PBO, placebo; PD-L1, programmed death-ligand 1; TIS, tislelizumab.

- Improved PFS was observed with tislelizumab plus chemotherapy versus placebo plus chemotherapy in the ITT and PD-L1 score ≥5% populations (**Figure 5**)

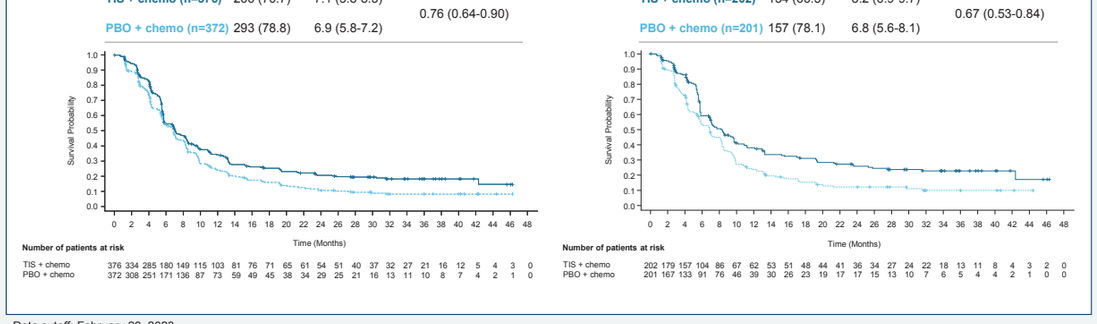
Figure 5. Progression-Free Survival: Asian Subgroup

ITT Population

	Events, n (%)	Median PFS (95% CI), Months	HR (95% CI)[a]
TIS + chemo (n=376)	266 (70.7)	7.1 (5.8-8.3)	0.76 (0.64-0.90)
PBO + chemo (n=372)	293 (78.8)	6.9 (5.8-7.2)	

PD-L1 Score ≥5% Population

	Events, n (%)	Median PFS (95% CI), Months	HR (95% CI)[a]
TIS + chemo (n=202)	134 (66.3)	8.2 (6.9-9.7)	0.67 (0.53-0.84)
PBO + chemo (n=201)	157 (78.1)	6.8 (5.6-8.1)	



Data cutoff: February 28, 2023.
[a]HR was based on an unstratified Cox regression model.
Chemo, chemotherapy; HR, hazard ratio; ITT, intent-to-treat; PBO, placebo; PD-L1, programmed death-ligand 1; PFS, progression-free survival; TIS, tislelizumab.

- Tislelizumab plus chemotherapy showed a favorable objective response rate and duration of response compared with placebo plus chemotherapy in the ITT and PD-L1 score ≥5% populations (**Figure 6**)

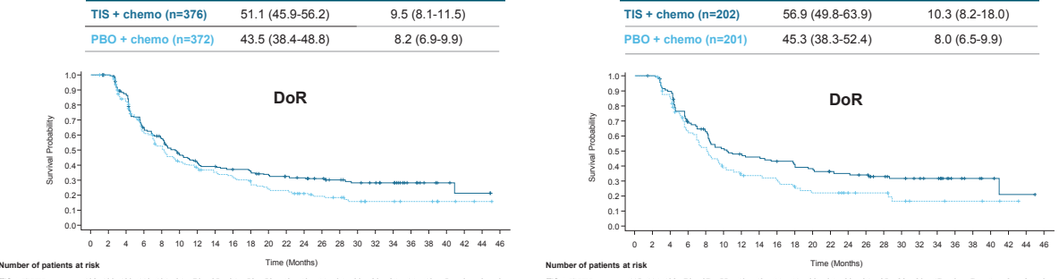
Figure 6. Disease Response and Duration of Response: Asian Subgroup

ITT Population

	ORR % (95% CI)[a,b]	Median DoR (95% CI), Months[c]
TIS + chemo (n=376)	51.1 (45.9-56.2)	9.5 (8.1-11.5)
PBO + chemo (n=372)	43.5 (38.4-48.8)	8.2 (6.9-9.9)

PD-L1 Score ≥5% Population

	ORR % (95% CI)[a,b]	Median DoR (95% CI), Months[d]
TIS + chemo (n=202)	56.9 (49.8-63.9)	10.3 (8.2-18.0)
PBO + chemo (n=201)	45.3 (38.3-52.4)	8.0 (6.5-9.9)

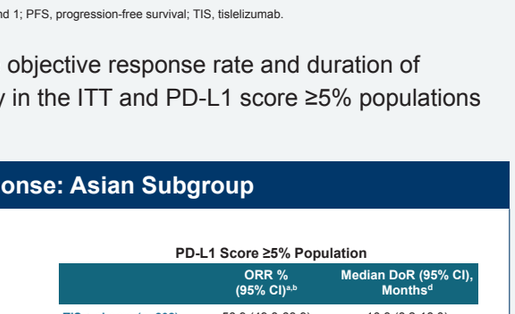


Data cutoff: February 28, 2023.
[a]ORR was calculated using the unstratified Cochran-Mantel-Haenszel method. [b]ORR is defined as the proportion of patients with a confirmed complete response or partial response. [c]DoR analysis performed on 192 patients in the TIS + chemo arm and 162 patients in the PBO + chemo arm. [d]DoR analysis performed on 115 patients in the TIS + chemo arm and 91 patients in the PBO + chemo arm.
Chemo, chemotherapy; DoR, duration of response; ORR, objective response rate; PBO, placebo; PD-L1, programmed death-ligand 1; TIS, tislelizumab.

- No new safety signals with tislelizumab plus chemotherapy were identified in the Asian subgroup (**Figure 7**)

Figure 7. Safety Summary: Asian Subgroup (Safety Analysis Population)

	Tislelizumab + Chemotherapy (n=375)	Placebo + Chemotherapy (n=370)
Patients with at least one TRAE	366 (97.6)	360 (97.3)
Grade ≥3 TRAEs	208 (55.5)	185 (50.0)
Serious TRAEs	97 (25.9)	55 (14.9)
TRAE leading to death	9 (2.4)	3 (0.8)
TRAE leading to treatment discontinuation	64 (17.1)	33 (8.9)



Data cutoff: February 28, 2023. Data are n (%).
Chemo, chemotherapy; PBO, placebo; TIS, tislelizumab; TRAE, treatment-related adverse event.

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Presenter Disclosures

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