Tislelizumab (TIS) + chemotherapy (CT) versus placebo (PBO) + CT in human epidermal growth factor receptor 2 (HER2)-negative advanced or metastatic gastric or gastroesophageal junction adenocarcinoma (GC/GEJC): RATIONALE-305 study minimum 3-year survival follow-up

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ABSTRACT

Introduction: TIS (an anti–programmed cell death protein-1 antibody) + CT demonstrated significant overall survival (OS) benefit versus PBO + CT as first-line (1L) therapy for advanced GC/GEJC in all randomized patients (hazard ratio [HR], 0.80) and patients with programmed death-ligand 1 (PD-L1) tumor area positivity (TAP) score ≥5% (HR, 0.71) in the phase 3 RATIONALE-305 study (NCT03777657). Two-year OS rates for TIS + CT versus PBO + CT were 32.7% versus 23.4%, respectively. We report efficacy and safety after a minimum 3-year follow-up.

Patients and Methods: Adults with locally advanced, non-resectable or metastatic, HER2-negative, untreated GC/GEJC were randomized (1:1) to intravenous TIS 200 mg or PBO every 3 weeks + investigator-chosen CT (oxaliplatin + capecitabine or cisplatin + 5-fluorouracil). TAP score was evaluated in tumor tissue using the VENTANA PD-L1 (SP263) assay. Primary endpoint was OS in all randomized patients and in those with PD-L1 TAP ≥5%. Secondary endpoints included investigator-assessed progression-free survival (PFS), objective response rate, duration of response (DoR) per Response Evaluation Criteria in Solid Tumors version 1.1, and safety.

Results: A total of 997 patients were randomized (TIS + CT, n=501; PBO + CT, n=496). At 3-year follow-up (minimum: 36.6 months), improvements in OS, PFS, and DoR in TIS + CT versus PBO + CT (**Table**) were maintained. Grade ≥3 treatment-related adverse events (TRAEs) were similar in both arms, occurring in 269/498 patients (54.0%) with TIS + CT and 246/494 patients (49.8%) with PBO +

CT. TRAEs led to any treatment discontinuation in 16.7% versus 8.1% of patients and led to death in 1.2% versus 0.4% of patients in the TIS + CT and PBO + CT arms, respectively.

Conclusion: After a minimum 3-year follow-up, TIS + CT as 1L treatment for GC/GEJC continued to demonstrate clinically meaningful improvements in OS, PFS, and DoR compared with PBO + CT, with no new safety signals. These long-term data further support TIS + CT as a new 1L treatment option for advanced HER2-negative GC/GEJC.

Table

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

[a]Stratified.
[b]Investigator evaluated.
CI, confidence interval