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): Programmed death-ligand 1 (PD-L1) biomarker analysis from RATIONALE-305 study

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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 PD-L1 tumor area positivity (TAP) score ≥5% (HR, 0.71) (phase 3 RATIONALE-305 study, NCT03777657). Here, we report exploratory analyses of OS subgroup results by PD-L1 expression status and concordance between PD-L1 TAP score and combined positive score (CPS).

Patients and Methods: Adults with 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). The primary endpoint was OS in all randomized patients and in those with PD-L1 TAP ≥5%. Tissue samples were stained using the VENTANA PD-L1 (SP263) assay. PD-L1 expression was prospectively assessed by TAP and rescored post hoc by CPS. OS with exploratory PD-L1 score cutoffs (TAP: 1%, 10%; CPS: 1, 5, 10), concordance between TAP and CPS at multiple cutoffs, and interclass correlation coefficient (ICC) were investigated.

Results: Of 997 patients randomized (TIS + CT, n=501; PBO + CT, n=496), 281 (28.2%) and 885 (88.8%) had baseline PD-L1 TAP ≥10% and ≥1%, respectively. At final analysis (minimum follow-up: 24.6 months), OS improvement with TIS + CT versus PBO + CT was observed in subgroups of PD-L1 TAP score ≥10% and ≥1% (**Table**). ICC between TAP and CPS was 0.81 (95% confidence interval [CI], 0.79-0.83). TAP and CPS scores showed substantial concordance in terms of overall percentage agreement and Cohen's Kappa (N=974).

Conclusion: The addition of TIS to CT as 1L treatment for GC/GEJC improved OS in patients with PD-L1 TAP ≥10% and ≥1%. These data, with prior data from patients with PD-L1 TAP ≥5% and all randomized patients, support TIS + CT as a new 1L treatment option for advanced HER2-negative GC/GEJC. Concordant TAP and CPS results suggest both methods are viable for clinical PD-L1 expression measurement in patients with GC/GEJC.

Table

PD-L1 Status	Events/Total TIS + CT	Events/Total PBO + CT	OS Unstratified, HR (95% CI)
TAP			
≥1%	318/432	370/453	0.78 (0.67-0.90)
<1%	52/69	36/43	0.98 (0.64-1.50)
≥5%	192/274	219/272	0.72 (0.59-0.88)
<5%	178/227	187/224	0.91 (0.74-1.12)
≥10%	84/136	118/145	0.57 (0.43-0.76)
<10%	286/365	288/351	0.91 (0.77-1.07)
CPS			
≥1	308/420	356/434	0.78 (0.67-0.91)
<1	53/71	39/49	1.01 (0.66-1.52)
≥5	175/254	211/269	0.73 (0.60-0.89)
<5	186/237	184/214	0.89 (0.72-1.09)
≥10	100/151	111/138	0.68 (0.52-0.90)
<10	261/340	284/345	0.87 (0.73-1.03)

PD-L1 concordance of TAP versus CPS	Overall % Agreement, (95% CI)	Cohen's Kappa, (95% CI)
1% versus 1	95 (94-97)	0.78 (0.71-0.84)
5% versus 5	82 (80-85)	0.64 (0.60-0.69)
10% versus 10	85 (83-87)	0.64 (0.59-0.69)