Tislelizumab (TIS) plus chemotherapy (CT) vs placebo (PBO) plus CT in HER2-negative advanced or metastatic gastric or gastro-esophageal junction adenocarcinoma (GC/GEJC): PD-L1 biomarker analysis from RATIONALE-305

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ABSTRACT

Background: TIS (an anti–PD-1 antibody) + CT demonstrated significant overall survival (OS) benefit vs PBO + CT as first-line (1L) therapy for advanced GC/GEJC in all randomized patients (pts; HR=0.80) and pts 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).

Methods: Adults with GC/GEJC were randomized (1:1) to IV 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 pts and in pts 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 pts 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 (min follow-up: 24.6 mo), OS improvement with TIS + CT vs PBO + CT was observed in subgroups of PD-L1 TAP score ≥10% and ≥1% (**Table**). ICC between TAP and CPS was 0.81 (95% CI 0.79–0.83). TAP and CPS scores showed substantial concordance in terms of overall percentage agreement and Cohen's Kappa (N=974).

Conclusions: The addition of TIS to CT as 1L treatment for GC/GEJC improved OS in pts with PD-L1 TAP ≥10% and ≥1%. These data, with prior data from pts with PD-L1 TAP ≥5% and all randomized pts, 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 pts with GC/GEJC.

PD-L1 status	Events/total		OS unstratified, HR (95% CI)
	TIS + CT	PBO + CT	
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 vs CPS	Overall % agreement, (95% CI)	Cohen's Kappa, (95% CI)
1% vs 1	95 (94–97)	0.78 (0.71–0.84)
5% vs 5	82 (80–85)	0.64 (0.60–0.69)
10% vs 10	85 (83–87)	0.64 (0.59–0.69)