Tislelizumab (TIS) + chemotherapy (CT) vs placebo (PBO) + CT in advanced or metastatic esophageal squamous cell carcinoma (ESCC): PD-L1 biomarker analysis from RATIONALE-306

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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 ESCC in all randomized patients (pts; stratified HR 0.66) and pts with PD-L1 Tumor Area Positivity (TAP) score ≥10% (stratified HR 0.62) (RATIONALE-306; NCT03783442). Sustained survival benefit was observed at 3 yrs follow-up. Here we report exploratory analyses of OS by PD-L1 expression status and concordance of PD-L1 TAP and combined positive score (CPS).

Methods: Adults with advanced ESCC were randomized (1:1) to IV TIS 200 mg or PBO every 3 wks + investigator-chosen CT (platinum + fluoropyrimidine or platinum + paclitaxel) until disease progression or intolerable toxicity. The primary endpoint was OS. Tissue samples were stained using the VENTANA PD-L1 (SP263) assay. PD-L1 expression was assessed by TAP and rescored post hoc by CPS. OS with different PD-L1 cutoffs, concordance between TAP and CPS at multiple cutoffs, interclass correlation coefficient (ICC), and Cohen's Kappa were investigated.

Results: Among 647 randomized pts, PD-L1 status was evaluable in 542 for TAP and 537 for CPS. 223/34%, 135/21%, 123/19% and 61/9% of pts had PD-L1 TAP score ≥10%, 5 to <10%, 1 to <5% and <1%, respectively. After a minimum 3-yr follow-up, OS improvement with TIS + CT vs PBO + CT was seen in PD-L1 subgroups with TAP score ≥1%, while small subgroup size with TAP score <1% limited interpretation (**Table**). OS results defined by TAP and CPS were similar. ICC between TAP and CPS was 0.85 (95% CI 0.80–0.88). TAP and CPS scores showed substantial concordance in overall percentage agreement and Cohen's Kappa.

Conclusions: Exploratory PD-L1 subgroup results with prior results from all randomized pts, support TIS + CT as a new 1L treatment option for pts with advanced ESCC. The concordance of TAP and CPS scoring methods indicate that both are viable clinical measurements of PD-L1 expression in pts with ESCC.

PD-L1 status	Event/total		OS, unstratified hazard ratio (95% CI)
	TIS + CT	PBO + CT	
TAP score			
≥10%	90/116	85/107	0.71 (0.53–0.95)
5 to <10%	38/56	66/79	0.50 (0.33–0.75)
1 to <5%	50/59	56/64	0.86 (0.59–1.26)
<1%	32/36	22/25	1.21 (0.70–2.08)
Unknown	40/59	35/48	0.65 (0.41–1.02)
CPS			
≥10	85/115	93/113	0.64 (0.48–0.86)
5 to <10	39/54	51/61	0.72 (0.47–1.09)
1 to <5	52/64	60/73	0.71 (0.49–1.03)
<1	28/31	23/26	1.36 (0.78–2.38)
Unknown	43/62	37/50	0.66 (0.42–1.02)
PD-L1 concordance between TAP and CPS	**Overall % agreement, (95% CI)**		**Cohen's Kappa, (95% CI)**
TAP 1% vs CPS 1	97 (96–98)		0.85 (0.77–0.92)
TAP 5% vs CPS 5	85 (82–88)		0.67 (0.60–0.73)
TAP 10% vs CPS 10	89 (87–92)		0.78 (0.72–0.83)