Tislelizumab + chemotherapy vs placebo + chemotherapy in patients with locally advanced esophageal squamous cell carcinoma: RATIONALE-306 subgroup analysis

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Introduction: In RATIONALE-306 (NCT03783442), patients (pts) with metastatic/locally advanced esophagus squamous cell carcinoma (ESCC) were randomized to IV TIS 200 mg or PBO every 3 weeks + investigator-chosen CT (platinum + fluoropyrimidine/paclitaxel) until disease progression, unacceptable toxicity, death, or withdrawal of consent, whichever occurred first. There was improvement in overall survival (OS) in the intent-to-treat (ITT) population (primary endpoint) and a subgroup of pts with PD-L1 Tumor Area Positivity (TAP) score ≥10% (secondary endpoint). At 3-year follow-up, improvement was sustained vs PBO + CT with TIS + CT in both the ITT population (HR=0.70, 95% CI: 0.59, 0.83), and the ≥10% PD-L1 subgroup population (HR=0.70, 95% CI: 0.52, 0.95). We report a post hoc analysis of the RATIONALE-306 data in pts with locally advanced (la) ESCC regardless of PD-L1 expression as well as those patients with a tumor PD-L1 TAP score of ≥5%.

Patients and Methods: Patients with la ESCC, with non-metastatic disease and deemed unfit for surgery or definitive chemoradiation, were retrospectively selected and included in this analysis. Efficacy outcomes (OS, PFS, objective response rate [ORR]) and safety were analysed. PD-L1 was assessed using VENTANA (SP263) assay and scored by TAP.

Results: Of the 649 pts randomized to treatment (TIS + CT, n=326; PBO + CT, n=323), 88 had la ESCC (TIS + CT n=49; PBO + CT n=39). In total, 46.6% of pts (TIS + CT, 42.9%; PBO + CT, 51.3%) had subsequent anticancer therapy and 23.9% (TIS + CT, 18.4%; PBO + CT, 30.8%) had subsequent radiation therapy, consistent with the ITT population.

At data cutoff (Aug 22, 2024), where median follow-up with TIS + CT was 49.8 mo and PBO +CT was 51.2 mo, efficacy with TIS + CT was improved in pts with la ESCC compared with PBO +CT. Similar improvements in efficacy with TIS + CT vs PBO + CT were observed in a subgroup of patients with locally advanced disease and a tumor PD-L1 TAP score ≥5% (Table).

The safety/tolerability profile of TIS + CT in the la ESCC subgroup was consistent with the ITT population, with no new safety signals. Treatment-related adverse events (TRAEs) with TIS + CT vs PBO + CT were 100% vs 92.3% (any grade), 59.2% vs 59.0% (grade ≥3), and 28.6% vs 20.5% (serious). The most common grade ≥3 TRAE was neutropenia in both the TIS + CT (26.5%) and PBO + CT (10.3%) treatment arms, consistent with the ITT population. Immune-mediated adverse events with TIS + CT vs PBO + CT were 40.8% vs 12.8%.

Conclusions: In this subgroup analysis of patients with la ESCC, first-line tislelizumab plus chemotherapy showed substantial and clinically meaningful improvements in efficacy, regardless of PD-L1 expression, consistent with the primary and 3-year long-term follow-up

analyses. These findings further support the use of tislelizumab plus chemotherapy as a first-line treatment option for patients with la ESCC.

Table

LOCALLY ADVANCED ESCC SUBGROUP		
	TIS + CT (n=49)	**PBO + CT (n=39)**
Median OS, mo (95% CI)	25.6 (19.4, 36.3)	12.3 (9.0, 21.7)
HR (95% CI)	0.49 (0.29, 0.84)	-
Median PFS[a], mo (95% CI)	9.7 (6.9, 19.6)	6.9 (4.2, 9.7)
HR (95% CI)	0.56 (0.31, 1.01)	-
ORR[a], n (%)	30 (61.2)	15 (38.5)
Time to response[a], mo (range)	1.4 (1.2-23.3)	2.6 (1.2-4.2)
LOCALLY ADVANCED ESCC SUBGROUP AND PD-L1 TAP SCORE ≥5% SUBGROUP		
	TIS + CT (n=25)	**PBO + CT (n=20)**
Median OS, mo (95% CI)	26.4 (15.3, NE)	11.5 (8.6, 19.8)
HR (95% CI)	0.37 (0.16, 0.83)	-
Median PFS[a], mo (95% CI)	13.2 (6.8, 30.2)	6.7 (4.2, 8.6)
HR (95% CI)	0.44 (0.19, 1.02)	-
ORR[a], n (%)	17 (68.0)	6 (30.0)
Time to response[a], mo (range)	1.5 (1.2-23.3)	2.0 (1.2-2.7)

[a]Investigator assessed. ESCC, esophageal squamous cell carcinoma; ORR, objective response rate; OS, overall survival; PD-L1, programmed death-ligand 1; PFS, progression-free survival.