

First-line (1L) tislelizumab (TIS) plus chemotherapy (CT) vs placebo (PBO) plus CT in advanced/metastatic esophageal squamous cell carcinoma (ESCC): RATIONALE-306 Japanese subgroup analysis with longer follow-up

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ABSTRACT

Background: In the global phase 3 RATIONALE-306 study (NCT03783442), TIS + CT showed a significant overall survival (OS) benefit vs PBO + CT as 1L therapy for advanced/metastatic ESCC. After a minimum 3-year follow-up, the hazard ratio (HR) for OS was 0.70 for all randomized patients (pts) and for pts with programmed death-ligand 1 (PD-L1) Tumor Area Positivity (TAP) score $\geq 10\%$. We report results for the Japanese subgroup.

Methods: Eligible pts enrolled in Japan were randomized (1:1) to receive intravenous TIS 200 mg or PBO every 3 weeks + investigator-chosen CT (platinum + fluoropyrimidine/paclitaxel) until disease progression or intolerable toxicity. The primary endpoint was OS in the intent-to-treat (ITT) population. Secondary endpoints included progression-free survival (PFS), objective response rate (ORR), safety, and OS in pts with PD-L1 TAP score $\geq 10\%$.

Results: Of 649 randomized pts, 66 (10.2%) were Japanese, median age was 67 years, 89.4% were male, and 28.8% had PD-L1 TAP score $\geq 10\%$. At study entry, Eastern Cooperative Oncology Group performance status was 0 for 77.3% pts and 97.0% had metastatic disease. As of Nov 24, 2023, 78.8% vs 84.8% Japanese pts on TIS + CT vs PBO + CT received post-systemic therapy (ITT: 51.5% vs 57.9%). After a minimum follow-up of 37.9 months, TIS + CT showed improvements vs PBO + CT in median OS (24.5 vs 15.1 months [mo]; HR: 0.75) in all pts and in pts with PD-L1 TAP score $\geq 10\%$ (HR: 0.79), median PFS (HR: 0.77) and ORR (63.6% vs 45.5%) (Table). Treatment-related adverse events (TRAEs) with TIS + CT vs PBO + CT in Japanese pts were 45.5% vs 36.4% for any grade (ITT: 69.8% vs 60.7%); 27.3% vs 6.1% for grade ≥ 3 (ITT: 32.1% vs 20.2%); 24.2% vs 3.0% for serious TRAEs (ITT: 19.8% vs 8.4%); TRAEs led to treatment discontinuation in 3.0% vs 6.1% (ITT: 13.3% vs 6.5%). No TRAEs leading to death were reported in Japanese pts (ITT: 1.5% vs 0.6%).

Conclusions: After 3 years, TIS + CT continued to demonstrate robust efficacy and a tolerable safety profile in Japanese pts as 1L therapy for advanced/metastatic ESCC in the RATIONALE-306 study, consistent with the overall population.

Table. Efficacy outcomes

	Japan TIS + CT (n=33)	Japan PBO + CT (n=33)	Overall TIS + CT (n=326)	Overall PBO + CT (n=323)
Median OS, mo (95% CI)	24.5 (17.6, 26.9)	15.1 (8.0, 22.5)	17.2 (15.8, 20.1)	10.6 (9.3, 12.1)
HR (95% CI)	0.75 (0.43, 1.30)	-	0.70 (0.59, 0.83) ^b	-
PD-L1 TAP score ≥10%, n (%)	12 (36.4)	7 (21.2)	116 (35.6)	107 (33.1)
Median OS by PD-L1 TAP score ≥10%, mo (95% CI)	25.5 (10.9, NE)	16.8 (0.9, NE)	16.6 (15.3, 23.4)	10.0 (8.6, 13.3)
HR (95% CI)	0.79 (0.26, 2.36)	-	0.70 (0.52, 0.95) ^b	-
Median PFS^a, mo (95% CI)	6.8 (4.4, 8.5)	4.5 (4.1, 6.7)	7.3 (6.9, 8.3)	5.6 (4.9, 6.0)
HR (95% CI)	0.77 (0.45, 1.32)	-	0.60 (0.50, 0.72) ^b	-
ORR^a, n (%)	21 (63.6)	15 (45.5)	207 (63.5)	137 (42.4)

^aInvestigator assessed. ^bStratified. CI, confidence interval; NE, not estimable.