Global, randomized, phase 3 study of tislelizumab plus chemotherapy versus placebo plus chemotherapy as first-line treatment for advanced/metastatic esophageal squamous cell carcinoma (RATIONALE-306 update): minimum 3-year survival follow-up

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ABSTRACT

Background: RATIONALE-306 (NCT03783442) is the first global study to investigate anti-programmed cell death protein-1 (PD-1) therapy in combination with different chemotherapy (CT) options in the first-line (1L) treatment of advanced/metastatic esophageal squamous cell carcinoma (ESCC). At interim analysis (IA), tislelizumab (TIS; anti-PD-1 mAb) + CT demonstrated a statistically significant, clinically meaningful improvement in OS vs placebo (PBO) + CT, with a manageable safety profile. Here, we report updated efficacy and safety data with minimum 3 years' follow-up (FU) after unblinding at IA.

Materials (Patients) and Methods: Eligible adults with previously untreated unresectable locally advanced recurrent/metastatic ESCC were randomized (1:1; stratified by region, prior definitive therapy, and investigator [INV]-chosen CT) to receive TIS 200 mg (Arm A) or PBO (Arm B) IV every 3 weeks + CT (platinum + fluoropyrimidine or platinum + paclitaxel), until disease progression or intolerable toxicity. The primary endpoint was OS in the ITT population. Secondary endpoints included PFS, ORR, and DoR, all per INV, and safety.

Results: In total, 649 pts were randomized (Arm A, n=326; Arm B, n=323). At a minimum study FU of 36.0 months, improvements in OS, PFS, and DoR in Arm A vs B (**Table**) were maintained, similar to IA. The HR for OS with TIS + CT vs PBO + CT was 0.70 (95% CI, 0.59-0.83). Similar to IA, incidences of any-grade (96.6% vs 96.3%) or grade ≥3 (67.0% vs 64.5%) treatment-related adverse events (TRAEs) were comparable between Arms A and B, respectively. In Arm A versus B, TRAEs leading to death occurred in 1.9% and 1.2%, respectively.

Conclusions: After minimum 3 years' FU, 1L TIS + CT continued to demonstrate clinically meaningful improvements in OS and PFS and durable antitumor response benefit vs PBO + CT in pts with advanced/metastatic ESCC, with no new safety signals.

Table.

	Arm A: TIS + CT (n=326)	Arm B: PBO + CT (n=323)
Median OS, mo (95% CI)	17.2 (15.8, 20.1)	10.6 (9.3, 12.0)
36-mo OS, % (95% CI)	22.1 (17.6, 27.0)	14.1 (10.4, 18.4)
36-mo PFS, % (95% CI)	15.0 (10.8, 19.9)	2.9 (1.1, 6.2)
36-mo DoR, % (95% CI)[a]	17.7 (12.3, 24.0)	5.0 (1.5, 11.8)

[a]Among responders (Arm A, n=207; Arm B, n=137)
mo, month(s)