Global, randomized, phase III 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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Background: RATIONALE-306 (NCT03783442) is the first global study to investigate anti-programmed cell death protein 1 therapy in combination with different chemotherapy (chemo) options in the first-line (1L) treatment of advanced/metastatic esophageal squamous cell carcinoma (ESCC). At interim analysis (IA), tislelizumab (TIS) plus chemo demonstrated a statistically significant, clinically meaningful improvement in overall survival (OS) versus placebo (PBO) plus chemo, with a

manageable safety profile. Here, we report updated efficacy and safety data with minimum 3 years' follow-up after study unblinding at IA.

Methods: Adults with unresectable locally advanced recurrent/metastatic ESCC and no prior systemic treatment for advanced disease were enrolled and randomized (1:1; stratified by region, prior definitive therapy, and investigator [INV]-chosen chemo) to receive TIS 200 mg (Arm A) or PBO (Arm B) IV every 3 weeks plus chemo (platinum plus fluoropyrimidine or platinum plus paclitaxel), until disease progression or intolerable toxicity. The primary endpoint was OS in the intent-to-treat population. Secondary endpoints included progression-free survival (PFS), objective response rate (ORR), and duration of response (DoR), all per INV, and safety.

Results: In total, 649 patients (pts) were randomized (Arm A, n=326; Arm B, n=323). At a minimum study follow-up of 36.0 months, improvements in OS, PFS, and DoR in Arm A versus B (**Table**) were maintained relative to the IA. The hazard ratio (HR) for OS with TIS plus chemo versus PBO plus chemo was 0.70 (95% confidence interval: 0.59, 0.83). Similar to the 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; treatment-emergent adverse events leading to treatment discontinuation were higher in Arm A (32.1%) versus B (22.1%). In Arm A versus B, respectively, serious TRAEs occurred in 29.9% vs 19.6% of pts; TRAEs leading to death occurred in 1.9% and 1.2%.

Conclusions: After minimum 3 years' follow-up, 1L TIS plus chemo continued to demonstrate clinically meaningful improvements in OS and PFS and durable antitumor response benefit versus PBO plus chemo in pts with advanced/metastatic ESCC, with no new safety signals.

	Arm A: TIS + chemo (n=326)	**Arm B: PBO + chemo (n=323)**
Median OS, mo (95% CI)	17.2 (15.8, 20.1)	10.6 (9.3, 12.0)
24-mo OS, % (95% CI)	37.9 (32.5, 43.2)	24.8 (20.1, 29.8)
36-mo OS, % (95% CI)	22.1 (17.6, 27.0)	14.1 (10.4, 18.4)
24-mo PFS, % (95% CI)	18.1 (13.6, 23.1)	7.2 (4.4, 11.0)
36-mo PFS, % (95% CI)	15.0 (10.8, 19.9)	2.9 (1.1, 6.2)
24-mo DoR, % (95% CI)[a]	19.9 (14.3, 26.3)	10.1 (5.0, 17.1)
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)