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 monoclonal antibody) + CT demonstrated a statistically significant, clinically meaningful improvement in overall survival (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 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 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 progression-free survival (PFS), objective response rate (ORR), and duration of response (DoR), all per INV, and safety.

Results: In total, 649 pts were randomized (Arm A, n=326; Arm B, n=323); in Korea, the study enrolled 50 patients across 10 sites. At a minimum study FU of 36.0 months (mo), improvements in 36-month OS (22.1 vs 14.1 mo), PFS (15.0 vs 2.9 mo), and DoR among responders (Arm A, n=207; Arm B, n=137; 17.7 vs 5.0 mo) in Arm A vs B, respectively, were maintained relative to the IA. The

hazard ratio (HR) for OS with TIS + CT vs PBO + CT was 0.70 (95% CI, 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%) vs B (22.1%). In Arm A vs 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' 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.