Randomized, Global, Phase 3 Study of Tislelizumab + Chemotherapy vs Placebo + Chemotherapy as First-line (1L) Treatment for Advanced/Metastatic Esophageal Squamous Cell Carcinoma (ESCC): RATIONALE-306 Update

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Background: At interim analysis (IA) of RATIONALE-306 (NCT03783442), 1L tislelizumab + chemotherapy demonstrated a statistically significant, clinically meaningful improvement in overall survival (OS) vs placebo +

chemotherapy, with a manageable safety profile, in patients with advanced/metastatic ESCC. Here, we report updated efficacy and safety data with minimum 2 years' follow-up.

Methods: Adults with unresectable locally advanced recurrent/metastatic ESCC and no prior systemic treatment for advanced disease were enrolled and randomized 1:1 to receive tislelizumab 200 mg (Arm A) or placebo (Arm B) IV Q3W + chemotherapy (platinum + fluoropyrimidine or platinum + paclitaxel), until disease progression, toxicity, or withdrawal. Primary endpoint was OS in the intent-to-treat population; secondary endpoints included progression-free survival (PFS), objective response rate (ORR), duration of response (DoR) per investigator, and safety.

Results: 649 pts were randomized (Arm A n=326, Arm B n=323). At data cutoff (December 31, 2022), minimum study follow-up was 25.2 months. Improvements in OS, PFS, ORR, and DoR in Arm A vs B were maintained relative to the IA. Median OS was 17.2 months and 10.6 months (hazard ratio [HR]: 0.67; 95% CI: 0.56, 0.80) with 24-month OS rates of 37.9% and 25.0% in Arms A and B, respectively. Median PFS in Arm A vs B was 7.3 months vs 5.6 months (HR: 0.61; 95% CI: 0.51, 0.73). ORR was 63.5% and 42.4% and median DoR was 7.1 months and 5.7 months in Arms A and B, respectively. Similar to the IA, incidences of any-grade (96.6% vs 96.3%) or grade ≥3 (66.7% 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 (31.8%) vs B (22.1%). In Arm A vs B, serious TRAEs occurred in 29.3% vs 19.6% of patients; TRAEs leading to death were reported in 1.9% and 1.2% of patients.

Conclusions: After minimum 2 years' follow-up, 1L tislelizumab + chemotherapy continued to demonstrate clinically meaningful improvements in OS and PFS and durable tumor response benefit vs placebo + chemotherapy in patients with advanced/metastatic ESCC, with no new safety signals.