Title: RATIONALE-306: Randomized, multi-regional, Phase 3 study of tislelizumab plus chemotherapy versus chemotherapy as first-line treatment for locally advanced unresectable or metastatic esophageal squamous cell carcinoma (ESCC)

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Abstract text:

Background: Tislelizumab, an anti-programmed cell death protein 1 antibody, has demonstrated a survival benefit as second-line treatment in ESCC. Here, we report interim analysis (IA) data from the multi-regional Phase 3 RATIONALE-306 study, which evaluated the efficacy and safety of tislelizumab plus chemotherapy vs chemotherapy alone in patients with locally advanced unresectable or metastatic ESCC in the first-line setting.

Methods: In this randomized, double-blind study, adults with histologically confirmed ESCC were enrolled regardless of programmed death-ligand 1 (PD-L1) expression status. Patients were randomized (1:1) to receive tislelizumab 200 mg (Arm A) or placebo (Arm B) intravenously once every three weeks, both in combination with investigator-chosen chemotherapy (ICC; platinum [cisplatin or oxaliplatin] and fluoropyrimidine [capecitabine or 5-FU] or platinum and paclitaxel) until disease progression per RECIST v1.1, unacceptable toxicity, or withdrawal. Randomization was stratified by geographic region, prior definitive therapy and ICC. The primary endpoint was overall survival (OS) in the intent-to-treat (ITT) population. Hierarchical sequentially-tested secondary endpoints were progression-free survival (PFS) and objective response rate (ORR) by the investigator, OS in the PD-L1 score ≥10% subgroup, and health-related quality of life. Other secondary endpoints included duration of response (DoR) by the investigator, and safety.

Results: Of 649 patients enrolled from 16 countries/regions (74.9% and 25.1% from Asia and non-Asian countries [Europe, Oceania, and North America]), 326 and 323 patients were randomized to Arms A and B, respectively (ITT population). At data cutoff (Feb 28, 2022), median follow-up was 16.3 and 9.8 months in Arms A and B, respectively. The study met its primary endpoint at IA by demonstrating statistically significant improvement in OS in Arm A vs Arm B (median OS: 17.3 vs 10.6 months; HR 0.66 [95% CI 0.54–0.80], p<0.0001). Improvement in OS was consistently observed across prespecified subgroups including ICC option, region, and PD-L1 expression status. In patients with PD-L1 score ≥10%, Arm A also demonstrated significant improvement in OS vs Arm B (median OS: 16.8 vs 10.0 months, HR 0.61 [95% CI 0.44–0.85], p=0.0017). A significant improvement in PFS was observed in Arm A vs Arm B (median PFS: 7.3 vs 5.6 months; HR 0.62 [95% CI 0.52–0.75], p<0.0001). Arm A was associated with a higher ORR (63.5% vs 42.4%, odds ratio 2.38 [95% CI 1.73–3.27], p<0.0001) and more durable response (median DoR: 7.1 [95% CI 6.1–8.1] vs 5.7 months [95% CI 4.4–7.1]) than Arm B. Overall, a similar proportion of patients had ≥1 treatment-related adverse event (TRAE; 96.6% and 96.3%) and ≥Grade 3 TRAEs (66.7% vs 64.5%) in Arms A and B, respectively.

Serious TRAEs occurred in 28.7% vs 19.3%, and TRAEs leading to death were similar in Arms A vs B (1.9% vs 1.2%). Treatment-emergent AEs leading to discontinuation occurred in 31.8% vs 22.4% in Arms A vs B.

Conclusions: Tislelizumab plus chemotherapy as first-line treatment demonstrated a statistically significant and clinically meaningful improvement in OS over chemotherapy alone in patients with advanced or metastatic ESCC, with a manageable safety profile.