RATIONALE 302: RANDOMIZED, PHASE 3 STUDY OF TISLELIZUMAB VS CHEMOTHERAPY AS SECOND-LINE TREATMENT FOR ADVANCED UNRESECTABLE/METASTATIC ESOPHAGEAL SQUAMOUS CELL CARCINOMA (ESCC)

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ABSTRACT

Introduction: Tislelizumab (tis) ± chemotherapy had antitumor activity in patients (pts) with solid tumors, including ESCC (NCT03469557 and CTR20160872).

Methods: RATIONALE 302 was a global Phase 3 study (NCT03430843) in adults with advanced/unresectable or metastatic ESCC that progressed on/after prior systemic therapy, ≥1 evaluable lesion per RECIST v1.1, and Eastern Cooperative Oncology Group performance score (ECOG PS) ≤1. Pts were randomized 1:1 to receive tis 200 mg intravenously every 3 weeks or investigator-chosen standard chemotherapy (ICC; paclitaxel, docetaxel, or irinotecan) until disease progression, unacceptable toxicity, or withdrawal. Stratification factors included ICC option, region, and ECOG PS. The primary endpoint was overall survival (OS) in all pts (ITT population). The key secondary endpoint was OS in programmed death-ligand 1 positive (PD-L1+; visually-estimated combined positive score [vCPS] ≥10% by VENTANA SP263 assay) pts. Other secondary endpoints were progression-free survival, overall response rate (ORR), duration of response (DoR), and safety.

Results: 512 pts (median age: 62 y; range 35-86 y) from 132 sites in 10 countries in Asia (n=404, 79%) and Europe or North America (n=108, 21%) were randomized to tis (n=256) or ICC (n=256); 157 pts (tis [n=89], ICC [n=68]) were PD-L1+. On 1Dec2020 (data cut-off), median follow-up was 8.5 mo (tis) and 5.8 mo (ICC). Primary endpoint was met: tis improved OS vs ICC in the ITT population (median OS: 8.6 vs 6.3 mo; HR 0.70, 95% CI 0.57-0.85, *P*=.0001). Tis also improved OS vs ICC in PD-L1+ pts (median OS: 10.3 vs 6.8 mo; HR 0.54, 95% CI: 0.36-0.79, *P*=.0006). Survival benefit was consistently observed across predefined subgroups, including baseline PD-L1 status and region. Tis was also associated with a higher ORR (20.3% vs 9.8%) and more durable responses (median DoR: 7.1 vs 4.0 mo; HR 0.42, 95% CI 0.23-0.75) than ICC in the ITT population. Fewer pts had ≥Grade 3 treatment-emergent adverse events (AEs) with tis vs ICC (46% vs 68%) and fewer ≥Grade 3 AEs were treatment-related (TR) with tis vs ICC (19% vs 56%). Fewer discontinuations due to TRAEs occurred with tis vs ICC (7% vs 14%).

Conclusion: Tis demonstrated statistically significant and clinically meaningful OS improvement vs ICC in pts with advanced or metastatic ESCC with progression on or after first-line systemic therapy. Tis showed a higher response rate, longer duration of responses, and a more favorable safety profile vs ICC.