RATIONALE-305: Phase 3 study of tislelizumab (TIS) plus chemotherapy vs placebo (P) plus chemotherapy as first-line (1L) treatment of advanced gastric or gastroesophageal junction adenocarcinoma (GC/GEJC)

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Introduction and Objectives: In a phase 2 study, TIS, an anti-PD-1 monoclonal antibody, plus chemotherapy demonstrated durable 1L antitumor activity in GC/GEJC patients (Xu et al, 2020). RATIONALE-305 (NCT03777657) was a global, double-blind, phase 3 study comparing 1L TIS plus investigator-chosen chemotherapy (TIS+ICC) vs P+ICC in GC/GEJC patients. Results from the interim analysis in the PD-L1+ (TAP score ≥5%) population are presented.

Materials and Methods: Adults with previously untreated, unresectable locally advanced or metastatic GC/GEJC, regardless of PD-L1 expression, were randomized (1:1) to receive TIS (200 mg IV Q3W) plus ICC (oxaliplatin and capecitabine, or cisplatin and 5-fluorouracil) or P+ICC. Randomization was stratified by region, PD-L1 expression, peritoneal metastasis, and ICC. Patients with known HER2+ status were excluded. RATIONALE-305 had dual primary endpoints of OS in the PD-L1+ and ITT analysis set. Secondary endpoints include PFS, ORR and DoR per RECIST 1.1, HRQoL, and safety profile.

Results: Of 546 PD-L1+ patients enrolled from 13 countries/regions (73.8% Asia; 26.2% Europe/ North America), 274 received TIS+ICC and 272 received P+ICC. In Spain, 27 patients (TIS+ICC [n=14], P+ICC [n=13]) were enrolled at 11 sites. At Oct 2021, median follow-up was 11.8 (TIS+ICC) and 11.7 mo (P+ICC). TIS+ICC showed statistically significant and clinically meaningful OS improvement vs P+ICC (HR 0.74 [95% CI: 0.59-0.94], mOS 17.2 vs 12.6 mo; 1-sided *P*=.0056). Compared with P+ICC, TIS+ICC also had longer PFS (mPFS 7.2 vs 5.9 mo; HR 0.67 [95% CI: 0.55-0.83]), higher ORR (50.4% vs

43.0%), and more durable response (mDoR 9.0 vs 7.1 mo). Patients treated with TIS+ICC reported better HRQoL than those with P+ICC per EORTC-QLQ-C30 and QLQST022 scores. No new safety signals were observed with TIS+ICC or P+ICC. While TEAEs leading to discontinuation of any treatment were higher with TIS+ICC than P+ICC (22.4% vs 12.1%), incidence rates of grade ≥3 TEAEs (64.7% vs 62.9%), serious TEAEs (42.3% vs 36.8%), and TEAEs leading to death (8.8% vs 7.7%) were comparable between arms.

Conclusion: In RATIONALE-305, TIS+ICC provided significant and clinically meaningful improvement in OS vs P+ICC with acceptable safety as 1L in PD-L1+ patients with advanced GC/GEJC. These data suggest this combination is a new 1L option for this patient population.