

RATIONALE 305: Phase 3 Study of Tislelizumab Plus Chemotherapy vs Placebo Plus Chemotherapy as First-line Treatment (1L) of Advanced Gastric or Gastroesophageal Junction Adenocarcinoma (GC/GEJC)

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Background: In a phase 2 study, tislelizumab (TIS), an anti-PD-1 monoclonal antibody, plus chemotherapy (chemo) demonstrated durable antitumour activity as 1L in Chinese GC/GEJC patients (pts). RATIONALE 305 (NCT03777657) was a global, double-blind, phase 3 study comparing 1L TIS plus investigator-chosen chemo (TIS+ICC) vs placebo plus ICC (P+ICC) in GC/GEJC. Results from interim analysis (IA) in PD-L1+ pts are presented; ITT population outcomes will be presented after final analysis.

Methods: Adults with previously untreated, unresectable, locally advanced or metastatic GC/GEJC, regardless of PD-L1 expression, were randomised (1:1) to TIS (200 mg IV Q3W) + ICC (oxaliplatin [130 mg/m² IV Q3W] and oral capecitabine [1,000 mg/m² BID, Days 1-14 Q3W] or cisplatin [80 mg/m² IV Q3W] and 5-fluorouracil [800 mg/m²/day IV, Days 1-5 Q3W]) or P+ICC. Randomisation was stratified by region, PD-L1 expression, peritoneal metastasis, and ICC. Pts with HER2-positive status were excluded. RATIONALE 305 had dual primary endpoints of OS in the PD-L1+ (TAP score ≥5% [VENTANA SP263 assay] assessed by blinded independent central laboratory) and ITT analysis sets. Secondary endpoints included PFS, ORR and DoR per RECIST v1.1, HRQoL, and safety. Prespecified IA was conducted after ~70% of total OS events had occurred.

Results: Of 546 PD-L1+ pts enrolled from 13 countries (73.8 % Asia; 26.2% Europe/North America), 274 were randomised to TIS+ICC and 272 to P+ICC. As of 8 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 $P=0.0056$). Compared with P+ICC, TIS+ICC 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). Pts treated with TIS+ICC reported better HRQoL than pts treated with P+ICC, as indicated by EORTC-QLQ-C30 global health status and physical functioning scores, and QLQST022 index score. No new safety signals were observed. While TEAEs leading to any treatment discontinuation were higher with TIS+ICC than P+ICC (22.4% vs 12.1%), 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.

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