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)

Authors: Markus Moehler[1]; Ken Kato[2]; Tobias Arkenau[3]; Do-Youn Oh[4]; Josep Tabernero[5]; Marcia Cruz Correa[6]; Hongwei Wang[7], Hui Xu[8]; Jiang Li[9]; Silu Yang[8]; Rui-Hua Xu[10]

Affiliations: [1]Johannes Gutenberg-University Clinic, Mainz, Germany; [2]National Cancer Center Hospital, Tokyo, Japan; [3]Sarah Cannon Research, London, England; [4]Seoul National University Hospital, Cancer Research Institute, Seoul National University College of Medicine; [5]Vall d'Hebron University Hospital, Barcelona, Spain; [6]University of Puerto Rico, San Juan, Puerto Rico; [7]BeiGene, Ltd, Boston, MA, United States; [8]BeiGene (Beijing) Co., Ltd, Beijing, China; [9]BeiGene, Ltd., Ridgefield Park, NJ, United States; [10]Sun Yat-sen University Cancer Center State Key Laboratory of Oncology in South China, Collaborative Innovation Center of Cancer Medicine, Guangzhou, China

Background: In a phase 2 study, tislelizumab (TIS), an anti-PD-1 monoclonal antibody, plus chemotherapy demonstrated durable antitumor activity as 1L in Chinese 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 placebo plus ICC (P+ICC) in GC/GEJC patients. Results from the interim analysis (IA) in the PD-L1+ population 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 randomized (1:1) to receive TIS (200 mg IV Q3W) plus 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. Randomization was stratified by region, PD-L1 expression, peritoneal metastasis, and ICC. Patients with known HER2-positive status were excluded. RATIONALE 305 had dual primary endpoints of OS in the PD-L1+ and ITT analysis set; PD-L1+ was defined as PD-L1 TAP score ≥5% (VENTANA SP263 assay) assessed by blinded independent central laboratory. Secondary endpoints include PFS, ORR and DoR per RECIST 1.1, HRQoL, and safety profile. The prespecified IA was conducted after ~70% of total OS events had occurred.

Results: Of 546 PD-L1+ patients enrolled from 13 counties/regions (73.8 % Asia; 26.2% Europe/ North America), 274 were randomized to receive TIS+ICC and 272 to receive 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*=.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 patients treated with P+ICC, as indicated by EORTC-QLQ-C30 global health status and physical functioning scores as well as the QLQST022 index score. 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 both arms.

Conclusions: In RATIONALE 305, TIS+ICC provided significant and clinically meaningful improvement in OS vs P+ICC with well 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

---