Efficacy and safety of tislelizumab + chemotherapy vs placebo + chemotherapy in HER2-negative advanced or metastatic gastric or gastroesophageal junction adenocarcinoma: RATIONALE-305 study Chinese subgroup analysis

Authors: Miao-Zhen Qiu,[1] Yuxian Bai,[2] Jianhua Shi,[3] Jufeng Wang,[4] Hongming Pan,[5] Ruixing Zhang,[6] Yang Yang,[7] Tao Zhang,[8] Zenqing Guo,[9] Yi Ba,[10] Lei Yang,[11] Changzheng Li,[12] Xi Shi,[13] Yee Chao,[14] Lin Shen,[15] Mengyue Shi,[16] Tao Sheng,[17] Silu Yang,[18] Liyun Li,[18] and Rui-Hua Xu[1]* on behalf of the RATIONALE-305 Investigators
**Presenting author*

Affiliations: [1]Department of Medical Oncology, Sun Yat-sen University Cancer Center State Key Laboratory of Oncology in South China, Guangzhou, China; [2]Harbin Medical University Cancer Hospital, Harbin, China; [3]Linyi Cancer Hospital, Linyi, China; [4]The Affiliated Cancer Hospital of Zhengzhou University and Henan Cancer Hospital, Zhengzhou, China; [5]Sir Run Run Shaw Hospital, Zhejiang University School of Medicine, Hangzhou, China; [6]Fourth Hospital of Hebei Medical University, Shijiazhuang, China; [7]Nanjing Drum Tower Hospital, The Affiliated Hospital of Nanjing University Medical School, Nanjing, China; [8]Union Hospital of Tongji Medical College, Huazhong University of Science and Technology, Wuhan, China; [9]Fujian Cancer Hospital, Fuzhou, China; [10]Tianjin Medical University Cancer Institute & Hospital, Tianjin, China; [11]Nantong Cancer Hospital, Nantong, China; [12]Shandong First Medical University Affiliated Cancer Hospital, Jinan, China; [13]The First Affiliated Hospital of Fujian Medical University, Fuzhou, China; [14]Taipei Veterans General Hospital, Taipei, Taiwan; [15]Peking University Cancer Hospital & Institute, Beijing, China; [16]BeiGene (Shanghai) Co., Ltd., Shanghai, China; [17]BeiGene USA, Inc., San Mateo, CA, USA; [18]BeiGene (Beijing) Co., Ltd., Beijing, China

ABSTRACT

Objective: Advanced gastric or gastroesophageal junction adenocarcinoma (GC/GEJC) remains a significant cause of cancer-related mortality globally and in China. Patients diagnosed with advanced GC/GEJC have a poor prognosis with conventional chemotherapy (chemo) alone. In the RATIONALE-305 randomized, double-blind, phase 3 study (NCT03777657), tislelizumab (TIS; an anti–programmed cell death protein 1 antibody) + chemo demonstrated statistically significant and clinically meaningful improvements in overall survival (OS) compared with placebo (PBO) + chemo as first-line therapy for advanced GC/GEJC, not only in patients with a programmed death-ligand 1 (PD-L1) Tumor Area Positivity (TAP) score ≥5% (hazard ratio [HR], 0.74; *P*=0.006), but also in all randomized patients (HR, 0.80; *P*=0.001). This abstract reports the efficacy and safety of TIS + chemo vs PBO + chemo in Chinese patients from the RATIONALE-305 study.

Methods: Adults with locally advanced, non-resectable or metastatic human epidermal growth factor receptor 2 (HER2)-negative, untreated GC/GEJC were randomized (1:1) to intravenous TIS 200 mg or PBO every 3 weeks plus investigator-chosen chemo (oxaliplatin + capecitabine or cisplatin + 5-fluorouracil). The primary endpoint in the main study was OS in all randomized patients and patients with PD-L1 TAP score ≥5% (PD-L1 positive). TAP score was evaluated in tumor tissues using the VENTANA PD-L1 (SP263) assay. Secondary endpoints included investigator-assessed progression-free survival (PFS), objective response rate (ORR), duration of response per Response Evaluation Criteria in Solid Tumors v1.1, and safety assessments.

Results: A total of 516 Chinese patients were randomized (TIS + chemo, n=259; PBO + chemo, n=257). The median age was 59.0 years and 69.4% were male. At study entry, 99.0% (511/516) of patients had metastatic disease, with ≥3 metastatic sites in 37.2% (192/516) of patients and peritoneal metastasis in 39.9% (206/516) of patients. 133 (51.4%) patients in the TIS + chemo group

and 132 (51.4%) patients in the PBO + chemo group had PD-L1 TAP score ≥5% (PD-L1 positive analysis set). After a minimum follow-up of 27.5 months, TIS + chemo vs PBO + chemo resulted in a median OS of 15.7 months (95% CI: 13.9, 18.4) vs 13.0 months (95% CI: 11.9, 14.3), HR, 0.77; 95% CI: 0.63, 0.93 (**Table**). A PFS improvement was observed in the TIS + chemo group vs the PBO + chemo group (HR, 0.73; 95% CI: 0.60, 0.89). TIS + chemo also demonstrated an OS benefit vs PBO + chemo in patients with PD-L1 TAP score ≥5%, with a median OS of 18.4 months (95% CI: 14.1, 23.2) vs 12.5 months (95% CI: 10.5, 14.4), HR, 0.63; 95% CI: 0.48, 0.83 (**Table**). Additional main efficacy results are presented in the **Table**. Grade ≥3 treatment-related adverse events (TRAEs) related to TIS/PBO were similar between groups, occurring in 25.6% (66/258) of patients receiving TIS + chemo and 21.6% (55/255) of patients receiving PBO + chemo. TRAEs leading to discontinuation were reported in 17.4% (45/258) vs 9.8% (25/255) of patients in the TIS + chemo and the PBO + chemo groups, and TRAEs leading to death, excluding death due to disease under study, were reported in 1.6% (4/258) and 0.8% (2/255) of patients in the TIS + chemo and the PBO + chemo groups, respectively.

Conclusions: In the subgroup of Chinese patients with advanced GC/GEJC from the RATIONALE-305 study, TIS + chemo demonstrated clinically meaningful improvements in OS, PFS, and ORR compared with PBO + chemo, with no new safety signals. These findings are consistent with published results in the overall study population.

Table: Efficacy Outcomes in the Chinese Subgroup

	Chinese Subgroup (N=516)			
	All Patients		**PD-L1–Positive Analysis Set**	
	TIS + Chemo (n=259)	**PBO + Chemo (n=257)**	**TIS + Chemo (n=133)**	**PBO + Chemo (n=132)**
Median OS, months (95% CI)	15.7 (13.9, 18.4)	13.0 (11.9, 14.3)	18.4 (14.1, 23.2)	12.5 (10.5, 14.4)
HR (95% CI)[a]	0.77 (0.63, 0.93)		0.63 (0.48, 0.83)	
Median PFS, months (95% CI)[b]	6.8 (5.7, 7.4)	6.8 (5.6, 7.1)	7.0 (5.7, 8.5)	6.8 (5.5, 8.2)
HR (95% CI)[a]	0.73 (0.60, 0.89)		0.66 (0.49, 0.88)	
ORR, n (%)[b]	132 (51.0)	110 (42.8)	73 (54.9)	58 (43.9)
Median DoR, months (95% CI)[b]	8.5 (6.0, 12.2)	8.0 (6.0, 9.8)	8.4 (5.6, 18.0)	8.0 (5.7, 10.3)

[a]Unstratified. [b]Investigator-evaluated. Data cutoff: 28 February 2023. CI, confidence interval; chemo, chemotherapy; DoR, duration of response; HR, hazard ratio; ORR, objective response rate; OS, overall survival; PBO, placebo; PD-L1, programmed death-ligand 1; PFS, progression-free survival; TIS, tislelizumab.