Tislelizumab (TIS) Plus Chemotherapy (CT) vs Placebo (PBO) Plus CT as First-Line (1L) Treatment of Advanced Gastric or Gastroesophageal Junction Adenocarcinoma (GC/GEJC): Final Analysis (FA) Results of the RATIONALE-305 Study

Lorenzo Fornaro, MD,[1] Rui-Hua Xu,[2] Do-Youn Oh,[3] Ken Kato,[4] Hendrik-Tobias Arkenau,[5] Josep Tabernero,[6] Marcia Cruz Correa,[7] Anastasia V. Zimina,[8] Yuxian Bai,[9] Jianhua Shi,[10] Keun-Wook Lee,[11] Hidekazu Hirano,[4] David R. Spigel,[12] Lucjan Wyrwicz,[13] Roberto Pazo Cid,[14] Liyun Li,[15]* Yaling Xu,[16] M. Brent McHenry,[17] Silu Yang,[15] Markus Moehler[18]

[1]Azienda Ospedaliero Universitaria Pisana, Pisa, Italy; [2]Sun Yat-sen University Cancer Center State Key Laboratory of Oncology in South China, Collaborative Innovation Center of Cancer Medicine, Department of Medical Oncology, Guangzhou, China; [3]Seoul National University Hospital Cancer Research Institute, Seoul National University College of Medicine, Department of Internal Medicine, Seoul, Republic of Korea; [4]National Cancer Center Hospital, Department of Gastrointestinal Medical Oncology, Tokyo, Japan; [5]Sarah Cannon Research Institute, Department of Drug Development, University College London, Cancer Institute, London, United Kingdom; [6]Vall d'Hebron Hospital Campus and Institute of Oncology (VHIO), Department of Medical Oncology, Barcelona, Spain; [7]University of Puerto Rico, School of Medicine, San Juan, Puerto Rico; [8]BIH of Omsk Region, Department of Oncology, Clinical Oncology Dispensary, Omsk Oblast, Russia; [9]Harbin Medical University Cancer Hospital, Department of Gastrointestinal Oncology, Harbin, China; [10]Linyi Cancer Hospital, Department II of Medical Oncology, Linyi, China; [11]Seoul National University Bundang Hospital, Seoul National University College of Medicine, Department of Internal Medicine, Seongnam, Republic of Korea; [12]Tennessee Oncology, Department of Thoracic Medical Oncology, Nashville, TN, United States; [13]Maria Sklodowska-Curie National Cancer Center and Institute of Oncology, Department of Oncology and Radiotherapy, Warsaw, Poland; [14]Hospital Universitario Miguel Servet, Department of Medical Oncology, Zaragoza, Spain; [15]BeiGene (Beijing) Co., Ltd., Beijing, China; [16]BeiGene (Shanghai) Co., Ltd., Shanghai, China; [17]BeiGene USA, Inc., Cambridge, MA, United States; [18]Johannes Gutenberg-University Clinic, Department of Internal Medicine I, Mainz, Germany
* Affiliation at the time of study

Poster No: A27 Presented at XXVI Italian Medical Oncology Association (AIOM); November 8-10, 2024; Rome, Italy

Conclusions

- **Tislelizumab (TIS) + chemotherapy (CT) produced a statistically significant and clinically meaningful improvement in overall survival (OS) versus placebo (PBO) + CT as first-line treatment in patients with advanced or metastatic gastric or gastroesophageal junction adenocarcinoma (GC/GEJC) in the intent-to-treat (ITT) population**
  - **Median OS was 15.0 months (95% confidence interval [CI], 13.6-16.5) versus 12.9 months (95% CI, 12.1-14.1), respectively**
  - **Stratified hazard ratio (HR) was 0.80 (95% CI, 0.70-0.92; *P*=0.0011)**
- **TIS + CT continued to demonstrate clinically meaningful improvement in OS in patients with programmed death-ligand 1 (PD-L1) score ≥5% with longer follow-up at the final analysis**
  - **Median OS was 16.4 months (95% CI, 13.6-19.1) versus 12.8 months (95% CI, 12.0-14.5), respectively**
  - **Stratified HR was 0.71 (95% CI, 0.58-0.86)**
- **The safety profile of TIS + CT was manageable, with no new safety signals identified**
- **These data suggest that TIS + CT presents a potential new first-line treatment option for patients with advanced GC/GEJC**

Background

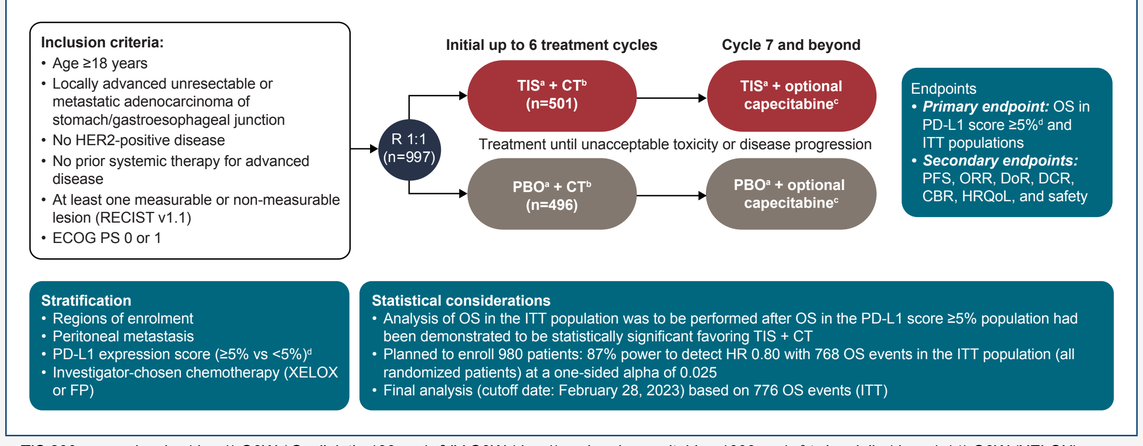
- Gastric cancer is the fifth most common cancer globally[1] and is more prevalent in Eastern Asia[2]
- The prognosis for patients with advanced unresectable or metastatic GC/GEJC treated with standard-of-care CT remains unsatisfying[3]
- The addition of anti-programmed cell death protein-1 (PD-1) antibodies to CT demonstrated improved survival,[4] and nivolumab plus CT has been approved as first-line (1L) treatment in GC/GEJC in many countries/regions for patients with different PD-L1 expression[5-7]
- Tislelizumab is an anti-PD-1 monoclonal antibody engineered to minimize binding to FcγR on macrophages.[8] In a phase 2 study, 1L TIS + CT demonstrated durable antitumor activity in GC/GEJC patients[9]
- In the global, phase 3 RATIONALE-305 study (NCT03777657), TIS + CT demonstrated significant OS benefit versus PBO + CT as 1L treatment in patients with advanced GC/GEJC at a pre-specified interim analysis of the PD-L1-positive (tumor area positivity score ≥5%) population[10]
- Here, we present the primary analysis results in the ITT population at the pre-specified final analysis

Methods

Study Design

- RATIONALE-305 was a randomized, open-label, multicenter, multiregional phase 3 study (**Figure 1**)
- The study population consisted of adults (aged ≥18 years) with previously untreated HER2-negative, locally advanced, unresectable or metastatic GC/GEJC
- Eligible patients were randomized 1:1 to receive TIS 200 mg or PBO intravenously once every 3 weeks plus investigator's choice of CT regimen until disease progression, unacceptable toxicity, or patient withdrawal
- The primary endpoints were OS in PD-L1-positive and ITT populations
- Secondary endpoints included progression-free survival (PFS), objective response rate (ORR), and duration of response (DoR) by investigator per RECIST v1.1, and safety

Figure 1. RATIONALE-305 Study Design



[a]TIS 200 mg or placebo (day 1) Q3W. [b]Oxaliplatin 130 mg/m² IV Q3W (day 1) and oral capecitabine 1000 mg/m² twice daily (days 1-14) Q3W (XELOX), or cisplatin 80 mg/m² IV Q3W (day 1) and 5-fluorouracil 800 mg/m²/day IV (days 1-5) Q3W (FP). [c]Capecitabine as maintenance therapy was optional and only for XELOX-treated patients. [d]PD-L1 score was determined using the VENTANA PD-L1 (SP263) assay by tumor area positivity (TAP) score.
CBR, clinical benefit rate; CT, chemotherapy; DCR, disease control rate; DoR, duration of response; ECOG PS, Eastern Cooperative Oncology Group performance status; HER2, human epidermal growth factor receptor 2; HR, hazard ratio; HRQoL, health-related quality of life; ITT, intent-to-treat; IV, intravenous; ORR, objective response rate; OS, overall survival; PBO, placebo; PD-L1, programmed death-ligand 1; PFS, progression-free survival; Q3W, every 3 weeks; R, randomization; RECIST v1.1, Response Evaluation Criteria in Solid Tumors version 1.1; TIS, tislelizumab.

Results

- At data cutoff (February 28, 2023), 997 patients were randomized to receive either TIS + CT (n=501) or PBO + CT (n=496)
- Minimum study follow-up was 24.6 months
- Patient demographics and baseline disease characteristics were generally balanced across treatment arms (**Table 1**)

Table 1. Baseline Characteristics (ITT Population)

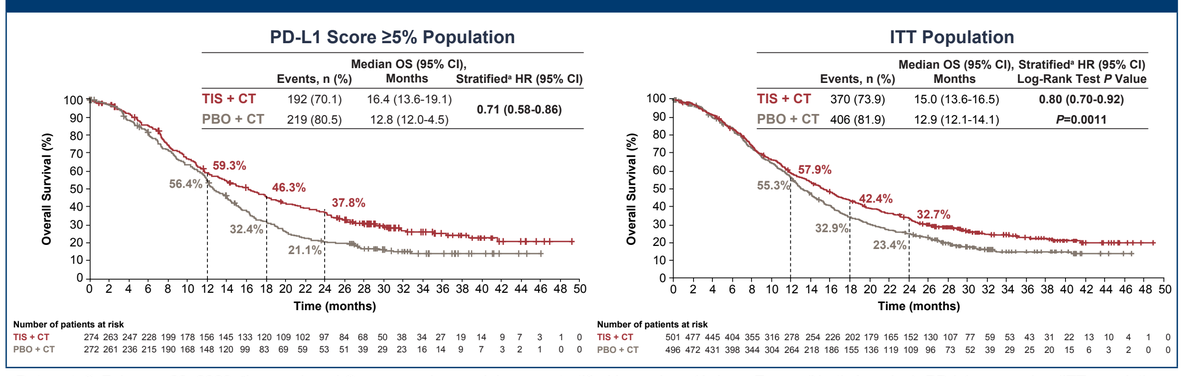
	TIS + CT (n=501)	PBO + CT (n=496)
Median age, years (range)	60.0 (23.0-86.0)	61.0 (25.0-86.0)
Sex, male	346 (69.1)	346 (69.8)
Region		
Asia[a]	376 (75.0)	372 (75.0)
Europe/North America	125 (25.0)	124 (25.0)
ECOG PS 1	332 (66.3)	342 (69.0)
Primary tumor location		
Stomach	405 (80.8)	395 (79.6)
GEJ	96 (19.2)	100 (20.2)[b]
Metastatic disease	494 (98.6)	490 (98.8)
Peritoneal metastasis	220 (43.9)	214 (43.1)
Prior adjuvant/neoadjuvant treatment	107 (21.4)	100 (20.2)
PD-L1 score		
<5%	227 (45.3)	224 (45.2)
≥5%	274 (54.7)	272 (54.8)
Investigator-chosen chemotherapy		
Oxaliplatin/capecitabine	466 (93.0)	465 (93.8)
Cisplatin/5-fluorouracil	35 (7.0)	31 (6.3)

Data cutoff: February 28, 2023. Minimum study follow-up time (defined as from the date of last patient randomized to the data cutoff): 24.6 months. Median study follow-up duration (defined as from randomization to data cutoff, death, or study discontinuation due to other reasons, whichever came first for all patients) was 13.2 months (IQR, 7.1-24.6). All data are n (%) unless otherwise stated. [a]Asia comprises China (including Taiwan), Japan, and South Korea; [b]The diagnosis of one patient was updated from gastric adenocarcinoma to be pancreatic cancer after randomization and the patient remained in the ITT population.
CT, chemotherapy; ECOG PS, Eastern Cooperative Oncology Group performance status; GEJ, gastroesophageal junction; IQR, interquartile range; ITT, intent-to-treat; PD-L1, programmed death-ligand 1; PBO, placebo; TIS, tislelizumab.

Efficacy

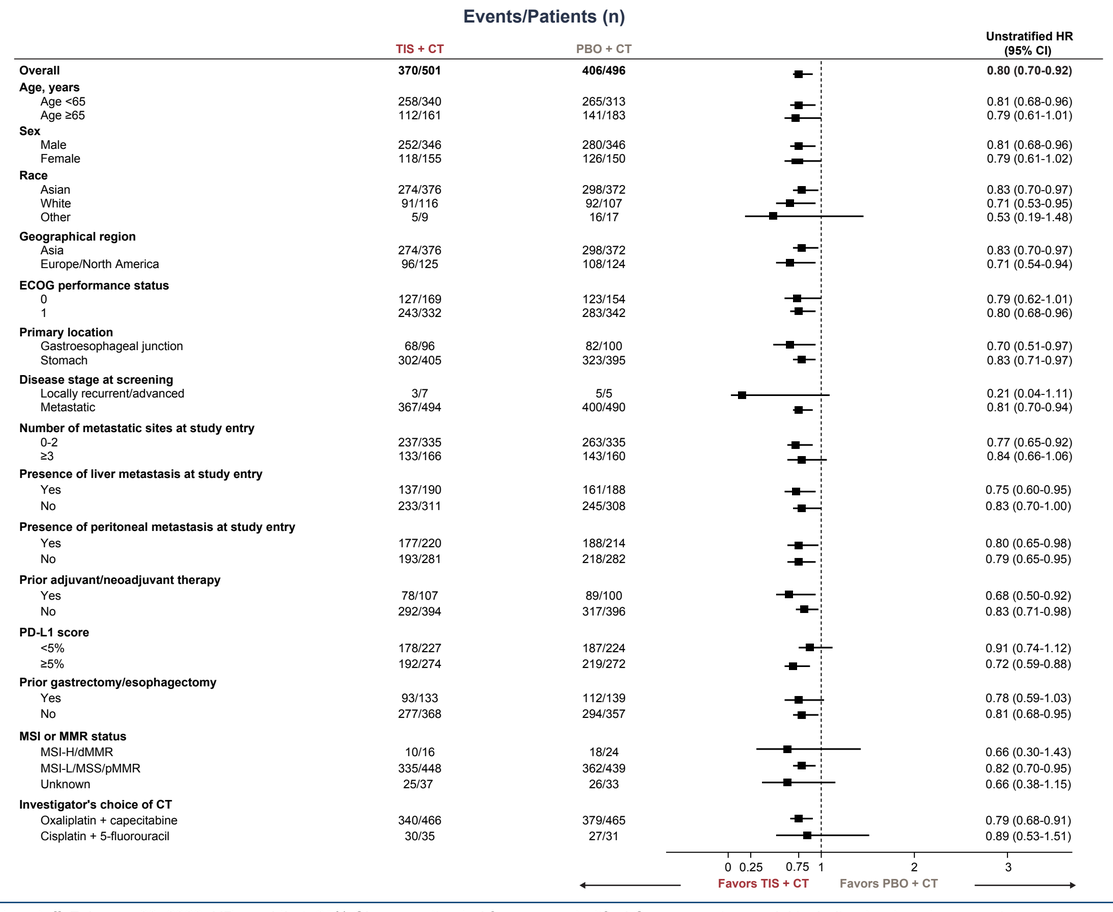
- TIS + CT as 1L treatment of advanced GC/GEJC demonstrated a statistically significant and clinically meaningful improvement in OS over PBO + CT in the ITT population at the final analysis (**Figure 2**)
- Updated OS results in the PD-L1 score ≥5% population remained consistent with those observed at the interim analysis (HR 0.74 [95% CI, 0.59-0.94]; *P*=0.0056) after an additional 17 months of follow-up, showing a clinically meaningful improvement in OS
- OS benefit of TIS + CT was observed across multiple patient subgroups (**Figure 3**)
- TIS + CT was associated with improved PFS, higher ORR, and a more durable response versus PBO + CT (**Figure 4**)

Figure 2. Overall Survival



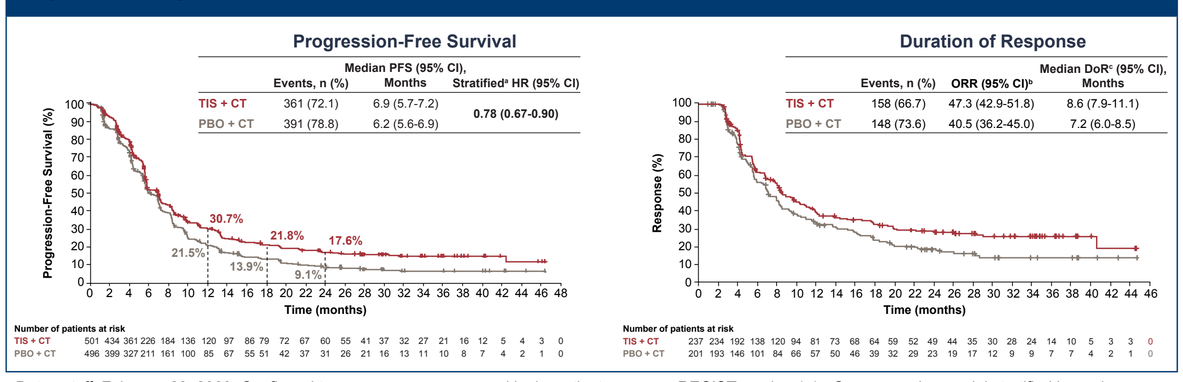
Data cutoff: February 28, 2023. [a]Log-rank and Cox regression models were stratified by regions (Asia vs Europe/North America), PD-L1 expression (ITT population analysis only), and presence of peritoneal metastasis. *P* values are one-sided and based on the stratified log-rank test. *P* value boundary at final analysis is 0.0226. Medians were estimated by the Kaplan-Meier method with 95% CIs estimated using the method of Brookmeyer and Crowley. OS rates were estimated by the Kaplan-Meier method.
CT, chemotherapy; CI, confidence interval; GC/GEJC, gastric or gastroesophageal junction adenocarcinoma; HR, hazard ratio; ITT, intent-to-treat; OS, overall survival; PBO, placebo; PD-L1, programmed death-ligand 1; TIS, tislelizumab.

Figure 3. Overall Survival: Subgroup Analysis (ITT Population)



Data cutoff: February 28, 2023. HRs and their 95% CI were estimated from an unstratified Cox regression model including treatment as covariate.
The race subcategory 'Other' includes Not Reported, Unknown, and Other.
CT, chemotherapy; dMMR, deficient mismatch repair; ECOG, Eastern Cooperative Oncology Group; HR, hazard ratio; MSI-L/H, microsatellite instability low/high; MSS, microsatellite stable; PBO, placebo; PD-L1, programmed death-ligand 1; pMMR, proficient mismatch repair; TIS, tislelizumab

Figure 4. Progression-Free Survival and Tumor Responses (ITT Population)[a]



Data cutoff: February 28, 2023. Confirmed tumor responses assessed by investigators as per RECIST version 1.1. [a]Cox regression model stratified by regions (Asia vs Europe/North America), PD-L1 expression and presence of peritoneal metastasis. [b]Exact Clopper-Pearson two-sided CI. [c]Among patients who achieved a confirmed CR or PR only. Medians were estimated by Kaplan-Meier method with 95% CIs estimated using the method of Brookmeyer and Crowley. PFS rates were estimated by Kaplan-Meier method.
CT, chemotherapy; CI, confidence interval; DoR, duration of response; HR, hazard ratio; ITT, intent-to-treat; ORR, objective response rate; PBO, placebo; PFS, progression-free survival; RECIST, Response Evaluation Criteria in Solid Tumors; TIS, tislelizumab.

Safety

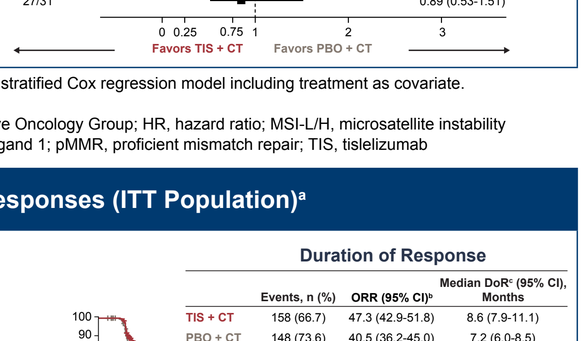
- TIS + CT had a manageable safety profile (**Table 2**)
- The most common treatment-related adverse events were consistent with the known safety profiles of the individual study treatment components (**Figure 5**)

Table 2. Summary of AE Incidence

n (%)	TIS + CT (n=498)	PBO + CT (n=494)
Any TRAE	483 (97.0)	476 (96.4)
Grade ≥3 TRAEs	268 (53.8)	246 (49.8)
Serious TRAEs	113 (22.7)	72 (14.6)
Any immune-mediated AE	154 (30.9)	58 (11.7)
TRAEs leading to treatment discontinuation	80 (16.1)	40 (8.1)
TRAEs leading to death[a]	6 (1.2)	2 (0.4)

[a]Excluding death due to disease under study.

Figure 5. TRAEs of Any Grade With Incidence ≥30%



Data cutoff: February 28, 2023.
AE, adverse event; CT, chemotherapy; PBO, placebo; TIS, tislelizumab; TRAE, treatment-related adverse event.

References

1. Global Cancer Observatory: Cancer Today, Lyon, France: International Agency for Research on Cancer. Available at: https://gco.iarc.fr/today/data/factsheets/cancers/39-All-cancers-fact-sheet.pdf.
2. WHO International Agency for Research on Cancer. Oesophagus. GLOBOCAN 2020b. Available at: https://gco.iarc.fr/today/data/factsheets/populations/160-china-fact-sheets.pdf .
3. Patel TH, Cecchini M. *Curr Treat Options Oncol*. 2020;21(9):70.
4. Janjigian Y, et al. *Lancet*. 2021;398:27-40.
5. U.S. Food and Drug Administration. Available at: https://fda.gov/drugs/resources-information-approved-drugs/fda-approves-nivolumab-combination-chemotherapy-metastatic-gastric-cancer-and-esophageal.
6. PPF. Available at: https://www.ppf.eu/insights/biotech-market/september-2021-review-of-news-from-the-most-innovative-therapeutic-areas-and-the/opdivo-approved-as-first-immunotherapy-for-first-line-advanced-gastric-cancer-in. Accessed September 23, 2024.
7. Bristol Myers Squibb Press Release. Available at: https://news.bms.com/news/corporate-financial/2021/Bristol-Myers-Squibb-Receives-European-Commission-Approval-for-Opdivo-nivolumab--Chemotherapy-for-Patients-with-HER2-Negative-Advanced-or-Metastatic-Gastric-Gastroesophageal-Junction-or-Esophageal-Adenocarcinoma-/default.aspx. Accessed September 23, 2024.
8. Zhang T, et al. *Cancer Immunol Immunother*. 2018;67:1079-1090.
9. Xu J, et al. *Clin. Cancer Res*. 2020;26:4542-4250.
10. Qiu M-Z, et al. *BMJ* 2024;385:e078876.

Acknowledgments
We would like to thank the investigators, site support staff, and especially the patients, for participating in this study. This study was sponsored by BeiGene, Ltd. Medical writing support, under the direction of the authors, was provided by Simon Lancaster, BSc, of Ashfield MedComms, an Inizio company, and was funded by BeiGene. Editorial support, under the direction of the authors, was provided by Envision Pharma Inc., and was funded by BeiGene. Reused with permission from the European Society for Medical Oncology (ESMO). This abstract was accepted and previously presented by Rui-Hua Xu et al. at the ESMO Congress 2023, FPN (Final Publication Number): LBA80, *Annals of Oncology*, Volume 34, 2023 Supplement 2. All rights reserved.

Presenter Disclosures
Lorenzo Fornaro has no interests to disclose.

Contact: lorenzo.fornaro@gmail.com (Lorenzo Fornaro)