Tislelizumab Plus Chemotherapy Versus Placebo Plus Chemotherapy in Advanced Gastric or Gastroesophageal Junction Cancer: A RATIONALE-305 Subgroup Analysis of Patients Treated with Capecitabine Plus Oxaliplatin

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CONCLUSIONS

- In patients with advanced gastric cancer and gastroesophageal junction cancer (GC/GEJC), tislelizumab + capecitabine and oxaliplatin (CAPOX) improved efficacy outcomes vs placebo + CAPOX, including longer median overall survival (mOS; 15.3 vs 13.0 months; hazard ratio [HR], 0.78; 95% CI, 0.68-0.90), longer median progression-free survival (mPFS; 7.0 vs 6.5 months; HR, 0.77; 95% CI, 0.67-0.90), and higher overall response rate (ORR; 48.3% vs 41.3%)
- The magnitude of survival benefit with tislelizumab + CAPOX increased with higher programmed cell death 1 ligand 1 (PD-L1) expression score cutoffs, supporting an enhanced treatment effect in biomarker-enriched populations
- Among patients with peritoneal metastases, tislelizumab + CAPOX was associated with a higher mOS (HR, 0.78; 95% CI, 0.63-0.96), mPFS (HR, 0.79; 95% CI, 0.63-0.98), and ORR (43.6% vs 32.5%) vs placebo + CAPOX, despite the historically poor prognosis associated with peritoneal disease
- No new safety signals were identified, and the safety profile of tislelizumab + CAPOX was consistent with the known safety profiles of the individual agents
- These data support the favorable benefit-risk profile of tislelizumab + CAPOX in advanced GC/GEJC

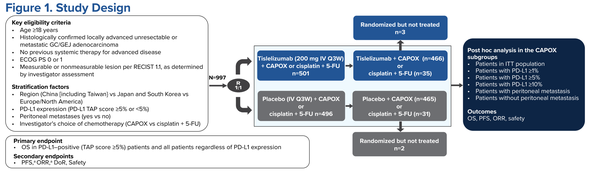
INTRODUCTION

- Fluoropyrimidine- and platinum-based chemotherapy remains a standard first-line treatment backbone for advanced GC/GEJC;[1,2] however, CAPOX is more commonly used in clinical practice than cisplatin + 5-fluorouracil (5-FU) because of its favorable tolerability and convenience profile
- Tislelizumab is a high-affinity immune checkpoint inhibitor targeting programmed cell death protein 1 (PD-1) and is specifically engineered to minimize Fcγ receptor binding on macrophages[3,4]
- Tislelizumab demonstrated a significant OS benefit when combined with chemotherapy in the phase 3 RATIONALE-305 trial (NCT03777657), which evaluated tislelizumab or placebo combined with CAPOX or cisplatin + 5-FU in patients with human epidermal growth factor receptor 2 (HER2)–negative, advanced GC/GEJC[5]
- Preclinical and translational studies suggest that oxaliplatin-based regimens may enhance antitumor immune responses and synergize with PD-1 inhibitors through induction of immunogenic cell death and modulation of the tumor microenvironment[6]
- Here, we present a post hoc analysis of RATIONALE-305 evaluating efficacy and safety outcomes among patients who received tislelizumab or placebo in combination with CAPOX

METHODS

- In the RATIONALE-305 trial, patients underwent 1:1 randomization to receive tislelizumab (200 mg intravenously every 3 weeks) or placebo in combination with CAPOX or cisplatin + 5-FU for up to six cycles, followed by tislelizumab or placebo, with optional capecitabine continuation at the investigator's discretion in patients who received CAPOX (**Figure 1**)
- All efficacy endpoints were assessed from the time of randomization
- This exploratory post hoc analysis included the randomized subgroup of patients assigned to receive tislelizumab or placebo in combination with CAPOX and was not designed or powered for formal statistical comparisons
- OS, PFS by investigator, ORR by investigator, and safety were evaluated in the overall population, in patients with PD-L1 tumor area positivity scores ≥1% and ≥5%, and in patients with and without peritoneal metastasis

Figure 1. Study Design



[a]Investigator assessed per RECIST v1.1.

Abbreviations: 5-FU, 5-fluorouracil; CAPOX, capecitabine and oxaliplatin; DoR, duration of response; ECOG PS, Eastern Cooperative Oncology Group performance status; GC, gastric cancer; GEJ, gastroesophageal junction; ITT, intent-to-treat; IV, intravenous; ORR, overall response rate; OS, overall survival; PD-L1, programmed cell death 1 ligand 1; PFS, progression-free survival; Q3W, every 3 weeks; R, randomization; RECIST, Response Evaluation Criteria in Solid Tumors; TAP, tumor area positivity.

RESULTS

- As of 28 February 2024, 931 patients were included (tislelizumab + CAPOX, n=466; placebo + CAPOX, n=465)
- Baseline characteristics were generally balanced between treatment arms (**Table 1**)
  - Median age was 61.0 years; 65.6% of patients were aged <65 years, 69.5% were male, and 43.7% had peritoneal metastases

Table 1. Baseline Demographic and Disease Characteristics

Characteristic	Overall N=931	Tislelizumab + CAPOX n=466	Placebo + CAPOX n=465
Age (range), years	61.0 (23-86)	60.0 (23-86)	61.0 (25-86)
Age, n (%)			
<65 years	611 (65.6)	318 (68.2)	293 (63.0)
≥65 years	320 (34.4)	148 (31.8)	172 (37.0)
Male, n (%)	647 (69.5)	320 (68.7)	327 (70.3)
Asian race, n (%)	737 (79.2)	370 (79.4)	367 (78.9)
Geographic region, n (%)			
East Asia	737 (79.2)	370 (79.4)	367 (78.9)
Other	194 (20.8)	96 (20.6)	98 (21.1)
ECOG PS at baseline, n (%)			
0	289 (31.0)	152 (32.6)	137 (29.5)
1	642 (69.0)	314 (67.4)	328 (70.5)
Primary site, n (%)			
Stomach	758 (81.4)	382 (82.0)	376 (80.9)
Gastroesophageal junction	173 (18.6)	84 (18.0)	89 (19.1)
PD-L1 TAP score, n (%)			
0	423 (45.4)	212 (45.5)	211 (45.4)
1	508 (54.6)	254 (54.5)	254 (54.6)
Metastatic sites, n (%)			
0-2 sites	626 (67.2)	308 (66.1)	318 (68.4)
≥3 sites	305 (32.8)	158 (33.9)	147 (31.6)
Liver metastasis, n (%)	354 (38.0)	179 (38.4)	175 (37.6)
Peritoneal metastasis, n (%)	407 (43.7)	204 (43.8)	203 (43.7)

Abbreviations: CAPOX, capecitabine and oxaliplatin; ECOG PS, Eastern Cooperative Oncology Group performance status; PD-L1, programmed cell death 1 ligand 1; TAP, tumor area positivity.

Survival Outcomes in the CAPOX-Treated Intent-to-Treat Population

- Tislelizumab + CAPOX improved survival outcomes vs placebo + CAPOX in the overall population
  - mOS: 15.3 vs 13.0 months (HR, 0.78; 95% CI, 0.68-0.90; **Table 2**); 4-year OS rates (17.1% vs 8.7%; **Figure 2**)
  - mPFS: 7.0 vs 6.5 months (HR, 0.77; 95% CI, 0.67-0.90; **Table 2**); 4-year PFS rates (13.9% vs 7.3%)
  - ORR: 48.3% vs 41.3%

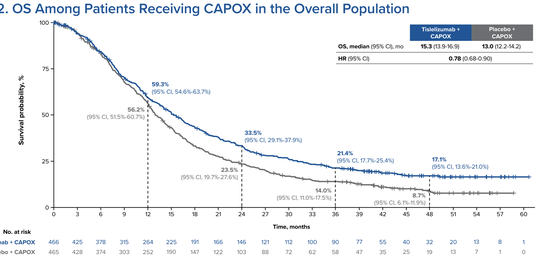
Table 2. Survival Outcomes Among All Patients Receiving CAPOX

Endpoint	ITT		PD-L1 TAP ≥1%		PD-L1 TAP ≥5%		PD-L1 TAP ≥10%		With peritoneal metastasis		Without peritoneal metastasis	
	TIS n=466	PBO n=465	TIS n=402	PBO n=424	TIS n=254	PBO n=254	TIS n=127	PBO n=134	TIS n=204	PBO n=203	TIS n=262	PBO n=262
mOS (95% CI), mo	15.3 (13.9-16.9)	13.0 (12.2-14.2)	15.3 (13.8-17.3)	12.9 (12.1-14.2)	16.7 (13.9-19.5)	13.0 (12.1-14.6)	23.2 (16.2-28.0)	12.3 (11.3-14.9)	12.6 (11.1-15.3)	11.9 (11.0-13.3)	18.2 (15.0-21.1)	14.1 (12.7-16.0)
HR (95% CI)	0.78 (0.68-0.90)		0.76 (0.65-0.89)		0.71 (0.58-0.86)		0.55 (0.41-0.73)		0.78 (0.63-0.96)		0.78 (0.64-0.94)	
mPFS (95% CI), mo[a]	7.0 (5.8-8.2)	6.5 (5.7-7.0)	7.0 (5.7-8.1)	6.4 (5.6-7.0)	7.3 (5.8-9.0)	6.5 (5.6-7.1)	9.3 (6.9-13.0)	5.7 (4.5-6.9)	6.7 (5.6-7.9)	5.7 (5.3-6.9)	7.1 (6.1-8.8)	6.9 (5.8-8.1)
HR (95% CI)	0.77 (0.67-0.90)		0.77 (0.66-0.90)		0.70 (0.57-0.85)		0.56 (0.42-0.74)		0.79 (0.63-0.98)		0.75 (0.62-0.92)	

[a]By investigator.

Abbreviations: CAPOX, capecitabine and oxaliplatin; HR, hazard ratio; ITT, intent-to-treat; mOS, median overall survival; mPFS, median progression-free survival; PBO, placebo; PD-L1, programmed cell death 1 ligand 1; TAP, tumor area positivity; TIS, tislelizumab.

Figure 2. OS Among Patients Receiving CAPOX in the Overall Population

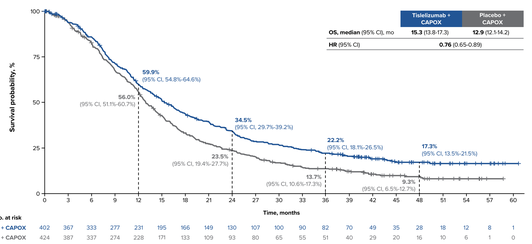


Abbreviations: CAPOX, capecitabine and oxaliplatin; HR, hazard ratio; OS, overall survival.

Survival Outcomes in the CAPOX-Treated PD-L1 ≥1% Population

- Tislelizumab + CAPOX improved survival outcomes vs placebo + CAPOX in the PD-L1 ≥1% population
  - mOS: 15.3 vs 12.9 months (HR, 0.76; 95% CI, 0.65-0.89; **Table 2**); 4-year OS rates (17.3% vs 9.3%; **Figure 3**)
  - mPFS: 7.0 vs 6.4 months (HR, 0.77; 95% CI, 0.66-0.90; **Table 2**); 4-year PFS rates (14.1% vs 7.1%)
  - ORR: 48.8% vs 41.7%

Figure 3. OS Among Patients Receiving CAPOX in the PD-L1 ≥1% Population

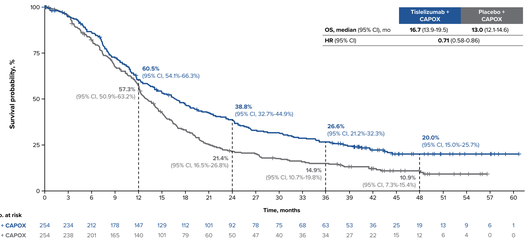


Abbreviations: CAPOX, capecitabine and oxaliplatin; HR, hazard ratio; OS, overall survival; PD-L1, programmed cell death 1 ligand 1.

Survival Outcomes in the CAPOX-Treated PD-L1 ≥5% Population

- Tislelizumab + CAPOX improved survival outcomes vs placebo + CAPOX in the PD-L1 ≥5% population
  - mOS: 16.7 vs 13.0 months (HR, 0.71; 95% CI, 0.58-0.86; **Table 2**); 4-year OS rates (20.0% vs 10.9%; **Figure 4**)
  - mPFS: 7.3 vs 6.7 months (HR, 0.70; 95% CI, 0.57-0.85; **Table 2**); 4-year PFS rates (16.2% vs 8.7%)
  - ORR: 52.4% vs 43.3%

Figure 4. OS Among Patients Receiving CAPOX in the PD-L1 ≥5% Population

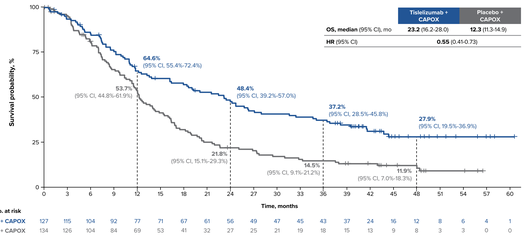


Abbreviations: CAPOX, capecitabine and oxaliplatin; HR, hazard ratio; OS, overall survival; PD-L1, programmed cell death 1 ligand 1.

Survival Outcomes in the CAPOX-Treated PD-L1 ≥10% Population

- Tislelizumab + CAPOX improved survival outcomes vs placebo + CAPOX in the PD-L1 ≥10% population
  - mOS: 23.2 vs 12.3 months (HR, 0.55; 95% CI, 0.41-0.73; **Table 2**); 4-year OS rates (27.9% vs 11.9%; **Figure 5**)
  - mPFS: 9.3 vs 5.7 months (HR, 0.56; 95% CI, 0.42-0.74; **Table 2**); 4-year PFS rates (20.2% vs 8.0%)
  - ORR: 53.5% vs 40.3%

Figure 5. OS Among Patients Receiving CAPOX in the PD-L1 ≥10% Population

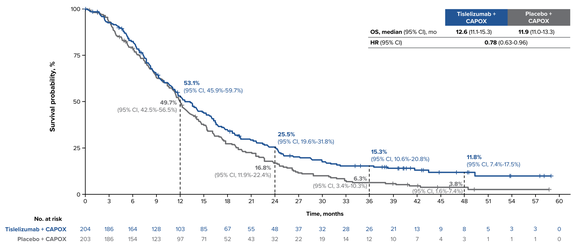


Abbreviations: CAPOX, capecitabine and oxaliplatin; HR, hazard ratio; OS, overall survival; PD-L1, programmed cell death 1 ligand 1.

Survival Outcomes in the CAPOX-Treated Patients With and Without Peritoneal Metastasis

- Tislelizumab + CAPOX improved survival outcomes vs placebo + CAPOX in patients with peritoneal metastasis
  - mOS: 12.6 vs 11.9 months (HR, 0.78; 95% CI, 0.63-0.96; **Table 2**); 4-year OS rates (11.8% vs 3.8%; **Figure 6**)
  - mPFS: 6.7 vs 5.7 months (HR, 0.79; 95% CI, 0.63-0.98; **Table 2**); 4-year PFS rates (8.0% vs 4.5%)
  - ORR: 43.6% vs 32.5%
- Tislelizumab + CAPOX improved survival outcomes vs placebo + CAPOX in patients without peritoneal metastasis
  - mOS: 18.2 vs 14.1 months (HR, 0.78; 95% CI, 0.64-0.94; **Table 2**); 4-year OS rates (21.1% vs 12.7%)
  - mPFS: 7.1 vs 6.9 months (HR, 0.75; 95% CI, 0.62-0.92; **Table 2**); 4-year PFS rates (18.5% vs 9.5%)
  - ORR: 51.9% vs 48.1%

Figure 6. OS Among Patients Receiving CAPOX With Peritoneal Metastasis



Abbreviations: CAPOX, capecitabine and oxaliplatin; HR, hazard ratio; OS, overall survival.

Treatment-Related Adverse Events Across Patient Populations

- Grade ≥3 treatment-related adverse events occurred in 53.9% and 48.4% of patients in the tislelizumab and placebo arms, respectively, with generally similar incidence across all subgroups (**Table 3**)

Table 3. TRAE Safety Summary

Adverse Event	Tislelizumab + CAPOX	Placebo + CAPOX
Overall Population, n	466	465
Any TRAE, n (%)	451 (96.8)	445 (95.7)
Grade ≥3 TRAE, n (%)	251 (53.9)	225 (48.4)
PD-L1 ≥1%, n	402	424
Any TRAE, n (%)	387 (96.3)	405 (95.5)
Grade ≥3 TRAE, n (%)	215 (53.5)	201 (47.4)
PD-L1 ≥5%, n	254	254
Any TRAE, n (%)	244 (96.1)	243 (95.7)
Grade ≥3 TRAE, n (%)	139 (54.7)	125 (49.2)
PD-L1 ≥10%, n	127	134
Any TRAE, n (%)	123 (96.9)	127 (94.8)
Grade ≥3 TRAE, n (%)	67 (52.8)	66 (49.3)
With Peritoneal Metastasis, n	204	203
Any TRAE, n (%)	197 (96.6)	191 (94.1)
Grade ≥3 TRAE, n (%)	118 (57.8)	97 (47.8)
Without Peritoneal Metastasis, n	262	262
Any TRAE, n (%)	254 (96.9)	254 (96.9)
Grade ≥3 TRAE, n (%)	133 (50.8)	128 (48.9)

Abbreviations: CAPOX, capecitabine and oxaliplatin; PD-L1, programmed cell death 1 ligand 1; TRAE, treatment-related adverse event.

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