Tislelizumab With or Without Capecitabine Continuation in Gastric or Gastro-oesophageal Junction Cancer: RATIONALE-305 Post Hoc Analysis

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CONCLUSIONS

- In advanced gastric or gastro-oesophageal junction cancer (GC/GEJC), patients who completed six cycles of tislelizumab plus CAPOX (capecitabine plus oxaliplatin) or placebo plus CAPOX and continued capecitabine had substantially longer survival vs those who discontinued capecitabine (median overall survival [OS]: 21.0 months vs 10.2 months with tislelizumab; 18.1 months vs 12.3 months with placebo)
- Patients who received tislelizumab with capecitabine continuation demonstrated significantly longer OS compared with those who received placebo with capecitabine continuation (21.0 vs 18.1 months; hazard ratio [HR]=0.78; nominal *P*=.0071)
- Tislelizumab with capecitabine continuation treatment showed significant improvements in OS, progression-free survival (PFS), and objective response rate (ORR) vs placebo with capecitabine continuation
- Continuation of capecitabine with tislelizumab did not result in any new safety signals, making this a suitable option after tislelizumab plus CAPOX in patients with locally advanced or metastatic GC/GEJC
- Investigators had a strong preference to administer capecitabine continuation when patients were eligible
- Among patients who received CAPOX without capecitabine continuation, PFS and ORR were numerically higher with tislelizumab vs placebo, but not statistically significant, and no OS advantage was observed

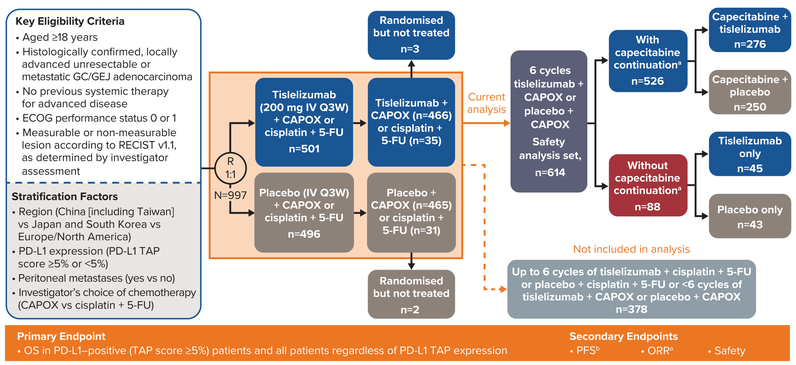
INTRODUCTION

- Standard systemic therapy for GC/GEJC typically includes fluoropyrimidines (5-fluorouracil [5-FU] or capecitabine), platinum agents (oxaliplatin or cisplatin), and, in the modern era, immune checkpoint inhibitors (ICIs) for advanced disease[1-3]
- Tislelizumab, an anti–programmed cell death protein-1 (PD-1) monoclonal antibody, demonstrated improved OS when combined with chemotherapy in the phase 3 RATIONALE-305 trial (NCT03777657), which evaluated tislelizumab or placebo with CAPOX or cisplatin plus 5-FU[4]
- Preclinical studies suggest that oxaliplatin-based regimens may synergise more effectively with PD-1 inhibitors like tislelizumab compared with other platinum agents through immunogenic cell death mechanisms[5]
- No high-level evidence has been generated for continuation therapy with ICIs alone or with capecitabine after CAPOX induction for advanced GC/GEJC, although small retrospective studies have suggested potential benefits of capecitabine maintenance.[6-8] Continuation strategies may have significant implications for patients' quality of life, highlighting the importance of evaluating patient values in maintenance therapy decision-making[9]
- Here we present the first post hoc analysis of a phase 3 trial evaluating the efficacy and safety of tislelizumab with capecitabine continuation or placebo with capecitabine continuation after induction treatment with six cycles of tislelizumab plus CAPOX or placebo plus CAPOX in patients with human epidermal growth factor receptor 2 (HER2)-negative, advanced GC/GEJC

METHODS

- RATIONALE-305 was a randomised, double-blind, placebo-controlled phase 3 trial comparing tislelizumab plus chemotherapy with chemotherapy alone in treatment-naive patients with locally advanced or metastatic GC/GEJC[4,10]
- Eligible patients with HER2-negative, unresectable locally advanced or metastatic GC/GEJC were randomised 1:1 to receive tislelizumab or placebo in combination with CAPOX or cisplatin plus 5-FU for up to six cycles. Capecitabine continuation with tislelizumab or placebo was at the investigator's discretion (**Figure 1**)
- This analysis included patients who received tislelizumab plus CAPOX or placebo plus CAPOX and who were alive and remained on study after completing six cycles of chemotherapy
- A sensitivity analysis was conducted, excluding patients who had experienced disease progression after six cycles, to assess the robustness of findings
- The primary endpoint was OS in patients with programmed death-ligand 1 (PD-L1)–positive Tumor Area Positivity (TAP) score ≥5% and in all patients regardless of PD-L1 expression
- All efficacy endpoints (OS, PFS, ORR) were measured from the time of enrollment; all *P*-values are nominal

Figure 1. Study Design



[a]Continuation of capecitabine was at the discretion of the investigator and per their clinical judgement. [b]Investigator assessed per RECIST v1.1.
Abbreviations: ECOG, Eastern Cooperative Oncology Group; IV, intravenous; Q3W, every 3 weeks; RECIST, Response Evaluation Criteria in Solid Tumors.

RESULTS

Patient Disposition and Baseline Characteristics

- A total of 997 patients were randomised, of whom 931 (93.4%) received tislelizumab plus CAPOX or placebo plus CAPOX; 614 (61.6%) received all six cycles of tislelizumab plus CAPOX or placebo plus CAPOX and were eligible for continuation therapy
- Among these 614 eligible patients, 526 (85.7%) received tislelizumab plus capecitabine or placebo plus capecitabine as continuation therapy (tislelizumab: n=276, placebo: n=250)
- Nearly all patients eligible for continuation therapy (608/614; 99.0%) had metastatic disease at baseline
- Median study follow-up time was 46.4 months (95% confidence interval [CI]: 44.2, 49.5) for tislelizumab and 47.3 months (95% CI: 43.7, 51.9) for placebo in the capecitabine continuation group, and 51.5 months (95% CI: 45.2, not evaluated [NE]) for tislelizumab and 53.2 months (95% CI: 45.2, NE) for placebo in the group without capecitabine continuation

RESULTS (CONT.)

- Baseline demographics and disease characteristics were similar across treatment arms (**Table 1**)

Table 1. Patient Baseline Demographics and Characteristics (Safety Analysis Set)

	With Capecitabine Continuation		Without Capecitabine Continuation	
	Tislelizumab (n=276)	Placebo (n=250)	Tislelizumab (n=45)	Placebo (n=43)
Median age, years	60.0	61.0	57.0	61.0
<65, n (%)	195 (70.7)	155 (62.0)	36 (80.0)	27 (62.8)
Sex, n (%)				
Male	188 (68.1)	174 (69.6)	30 (66.7)	36 (83.7)
Female	88 (31.9)	76 (30.4)	15 (33.3)	7 (16.3)
Region, n (%)				
East Asia[a]	232 (84.1)	206 (82.4)	33 (73.3)	33 (76.7)
Rest of world[b]	44 (15.9)	44 (17.6)	12 (26.7)	10 (23.3)
ECOG performance status, n (%)				
0	96 (34.8)	71 (28.4)	16 (35.6)	15 (34.9)
1	180 (65.2)	179 (71.6)	29 (64.4)	28 (65.1)
Primary location, n (%)				
Gastro-oesophageal junction	42 (15.2)	33 (13.2)	9 (20.0)	12 (27.9)
Stomach	234 (84.8)	217 (86.8)	36 (80.0)	31 (72.1)
PD-L1 TAP expression, n (%)				
<5%	121 (43.8)	120 (48.0)	18 (40.0)	17 (39.5)
≥5%	155 (56.2)	130 (52.0)	27 (60.0)	26 (60.5)

[a]Includes China, Taiwan, Japan, and South Korea. [b]Includes the United States and Europe.

Efficacy

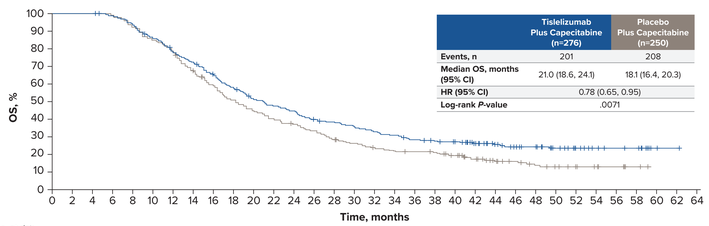
- Median treatment duration was longer in patients receiving capecitabine continuation than in those without continuation (tislelizumab: 10.0 vs 4.4 months; placebo: 9.6 vs 4.4 months)
- At data cutoff (August 27, 2024), patients who received tislelizumab with capecitabine continuation showed significant improvements in efficacy outcomes compared with those who received placebo with capecitabine continuation (**Table 2**):
  - Patients who received tislelizumab with capecitabine continuation demonstrated significantly longer OS compared with those who received placebo with capecitabine continuation (**Figure 2**)
    - Small numbers of patients in the group without capecitabine continuation limit the interpretation
  - PFS was significantly improved with tislelizumab vs placebo in patients with capecitabine continuation and numerically improved with tislelizumab vs placebo in patients without capecitabine continuation (**Figure 3**)
  - ORR was higher with tislelizumab vs placebo, both in patients with capecitabine continuation and without capecitabine continuation

Table 2. Efficacy Outcomes (Safety Analysis Set)

	With Capecitabine Continuation		Without Capecitabine Continuation	
	Tislelizumab (n=276)	Placebo (n=250)	Tislelizumab (n=45)	Placebo (n=43)
Median OS, months (95% CI)	21.0 (18.6, 24.1)	18.1 (16.4, 20.3)	10.2 (7.2, 14.1)	12.3 (11.1, 15.2)
HR (95% CI)	0.78 (0.65, 0.95)		1.24 (0.80, 1.92)	
Median PFS[a], months (95% CI)	10.1 (9.0, 12.9)	9.5 (8.3, 9.8)	4.7 (4.2, 5.5)	4.3 (4.1, 4.5)
HR (95% CI)	0.79 (0.65, 0.96)		0.82 (0.52, 1.32)	
ORR[a], % (95% CI)	71.4 (65.7, 76.6)	66.8 (60.6, 72.6)	57.8 (42.2, 72.3)	48.8 (33.3, 64.5)

[a]PFS and ORR were derived from tumour assessments by investigators.

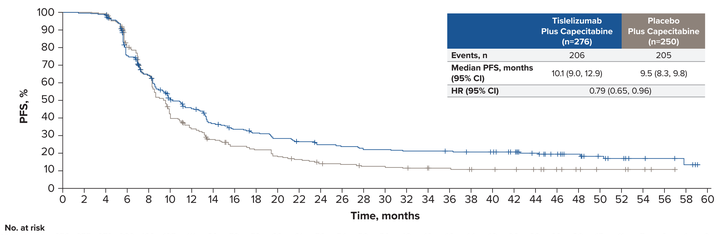
Figure 2. Kaplan–Meier Plot of OS With Capecitabine Continuation (Safety Analysis Set)



No. at risk

Tislelizumab plus capecitabine	276	276	276	271	256	234	212	196	176	154	136	126	119	105	100	92	85	80	73	69	65	56	44	37	30	24	16	12	10	9	2	1	0
Placebo plus capecitabine	250	250	250	247	231	213	196	167	146	125	110	97	90	81	69	63	55	51	50	48	41	34	26	22	17	14	11	9	6	2	0	0	0

Figure 3. Kaplan–Meier Plot of PFS With Capecitabine Continuation (Safety Analysis Set)



No. at risk

Tislelizumab plus capecitabine	276	275	273	202	169	125	111	89	79	73	66	61	56	54	50	50	48	48	46	44	42	36	30	23	20	15	11	7	6	4	0
Placebo plus capecitabine	250	250	247	192	151	93	78	62	52	48	40	35	29	27	24	23	22	19	19	16	16	15	13	10	8	6	6	4	1	0	0

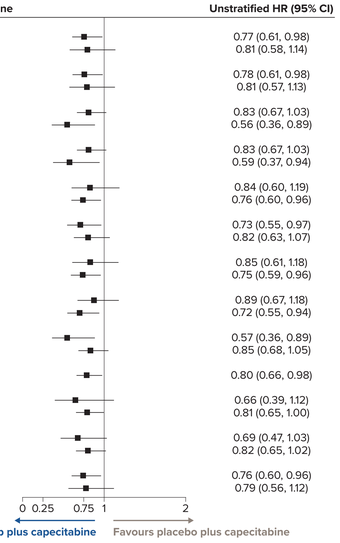
- In PD-L1 subgroup analyses with capecitabine continuation, greater treatment benefit was observed among patients with higher tumour PD-L1 expression (PD-L1 TAP score ≥1% and ≥5%) receiving tislelizumab vs placebo (**Table 3**)
- OS results were consistent across all prespecified subgroups (**Figure 4**)

Table 3. Efficacy Outcomes by PD-L1 Expression TAP Score Level (With Capecitabine Continuation, Safety Analysis Set)

	TAP Score ≥1% Subgroup		TAP Score ≥5% Subgroup	
	Tislelizumab (n=238)	Placebo (n=225)	Tislelizumab (n=155)	Placebo (n=130)
Median OS, months (95% CI)	21.2 (18.1, 24.4)	18.1 (16.4, 20.3)	23.5 (18.4, 27.1)	18.1 (15.5, 20.0)
HR (95% CI)	0.77 (0.63, 0.95)		0.72 (0.55, 0.94)	
Median PFS[a], months (95% CI)	10.0 (8.6, 12.9)	9.5 (8.4, 9.9)	11.1 (9.3, 14.1)	9.4 (8.3, 9.9)
HR (95% CI)	0.80 (0.65, 0.98)		0.75 (0.58, 0.99)	
ORR[a], % (95% CI)	73.1 (67.0, 78.6)	68.4 (61.9, 74.5)	76.8 (69.3, 83.2)	70.8 (62.2, 78.4)

[a]PFS and ORR were derived from tumour assessments by investigators.

Figure 4. Forest Plot of OS With Capecitabine Continuation (Safety Analysis Set)



- Sensitivity analysis of patients without disease progression after six cycles (tislelizumab: n=267, placebo: n=240) confirmed the treatment benefit observed in the main analysis (data not shown)

Safety

- Nearly all patients experienced at least one treatment-emergent adverse event (TEAE) across treatment groups, with treatment-related adverse events (TRAEs) reported in most patients (**Table 4**)
- Serious TRAEs were more frequent in the tislelizumab-containing arms, both with capecitabine continuation and without capecitabine continuation
- Grade ≥3 TRAEs occurred at similar rates in patients receiving tislelizumab with capecitabine continuation vs tislelizumab alone and at higher rates in patients receiving placebo with capecitabine continuation vs placebo alone
- TRAEs leading to treatment discontinuation were more frequent with tislelizumab than placebo, both with capecitabine continuation and without capecitabine continuation
- TRAEs leading to dose modifications occurred at similar rates across treatment arms, and the overall safety profile was consistent with known profiles of the individual treatment components

Table 4. Overall Safety Summary (Safety Analysis Set)

	With Capecitabine Continuation		Without Capecitabine Continuation	
n (%)	Tislelizumab (n=276)	Placebo (n=250)	Tislelizumab (n=45)	Placebo (n=43)
Patients with ≥1 TEAE	275 (99.6)	249 (99.6)	45 (100.0)	43 (100.0)
TRAE for any treatment component	272 (98.6)	247 (98.8)	45 (100.0)	43 (100.0)
Serious TRAEs for any treatment component	56 (20.3)	36 (14.4)	11 (24.4)	2 (4.7)
Grade ≥3 TRAEs for any treatment component	152 (55.1)	133 (53.2)	27 (60.0)	17 (39.5)
TRAEs leading to any treatment discontinuation	45 (16.3)	19 (7.6)	8 (17.8)	0
TRAEs leading to dose modification of any treatment component	227 (82.2)	206 (82.4)	34 (75.6)	34 (79.1)
TRAEs leading to death	4 (1.4)	2 (0.8)	1 (2.2)	0

REFERENCES

1. Lordick F, et al. *Ann Oncol.* 2022;33:1005-1020.
2. Kono K, et al. *Gastric Cancer.* 2020;23:565-578.
3. Grivas P, et al. *Target Oncol.* 2019;14:505-525.
4. Qiu M, et al. *BMJ.* 2024;385:e078876.
5. Liu P, et al. *Oncoimmunology.* 2022;11:2093518.
6. Oyan B, et al. *J Clin Oncol.* 2014;32(Suppl 15):e15003.
7. Qiu MZ, et al. *Tumor Biol.* 2014;35:4369-4375.
8. Moehler M, et al. *J Clin Oncol.* 2021;39:966-977.
9. Theis S, et al. *Front Oncol.* 2025;15:1588721.
10. Cruz-Correa M, et al. *Curr Med Res Opin.* 2025;41:1007-1016.

DISCLOSURES

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