Modeling Analysis of RATIONALE-305: Impact of Peritoneal Metastasis Representation on Clinical Outcomes in Patients Treated With Tislelizumab Plus Chemotherapy With Gastric Cancer/Gastroesophageal Junction Cancer

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CONCLUSIONS

- Our analysis showed that lowering peritoneal metastasis (PM) representation in the model marginally improved overall survival (OS), progression-free survival (PFS), and objective response rate (ORR), underscoring the poor prognosis of peritoneal disease
- In RATIONALE-305, patients with human epidermal growth factor receptor 2 (HER2)-negative unresectable locally advanced or metastatic gastric cancer/gastroesophageal junction carcinoma (GC/GEJC) who received tislelizumab plus chemotherapy had clinically meaningful responses and survival benefits irrespective of PM, with higher response rates in those who were programmed death-ligand 1 (PD-L1) positive
- Response rates were lower in patients with PM than in those without PM across all PD-L1 expression levels

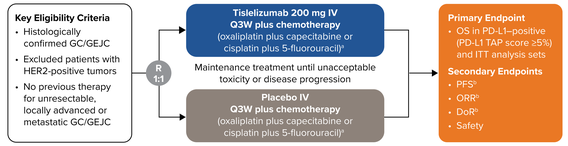
INTRODUCTION

- In the phase 3 RATIONALE-305 trial (NCT03777657), patients with HER2-negative locally advanced unresectable or metastatic GC/GEJC who received first-line treatment with tislelizumab plus chemotherapy experienced significantly improved efficacy outcomes compared with those who received placebo plus chemotherapy in both the intent-to-treat (ITT) population and the population with Tumor Area Positivity (TAP) score ≥5%[1,2]
- RATIONALE-305 enrolled the highest proportion of patients with PM among similar phase 3 randomized controlled trials,[3,4] and stratified patients by presence of PM
  - An improvement in median OS with tislelizumab plus chemotherapy vs placebo plus chemotherapy was observed consistently among patients with PM in the ITT population and those with PD-L1 TAP scores ≥5% and ≥1% (**Figure 1**)[5]
- We used statistical modeling to evaluate the impact of varying PM levels on efficacy outcomes with tislelizumab plus chemotherapy

METHODS

- RATIONALE-305 was a randomized, double-blind, global phase 3 trial comparing tislelizumab plus chemotherapy with placebo plus chemotherapy in systemic treatment-naive patients with locally advanced unresectable or metastatic HER2-negative GC/GEJC
- The study design for RATIONALE-305 is presented in **Figure 2**[5]
- TAP score was evaluated in tumor tissue using the VENTANA PD-L1 (SP263) Assay (Roche Diagnostics, Indianapolis, IN, USA)[7]
- Method of moments was used to weight patients and to match a hypothetical population to the ITT population, with the same marginal distribution of sex, primary tumor location, PD-L1 (TAP score <5% vs ≥5%), number of metastatic sites (0-2 vs 3+), liver metastasis, and a determinist PM proportion to enable PM representation
- PM representation was set from 20% to 45%
- Weighted OS, PFS, and ORR assessed by investigator were analyzed

Figure 2. Study Design



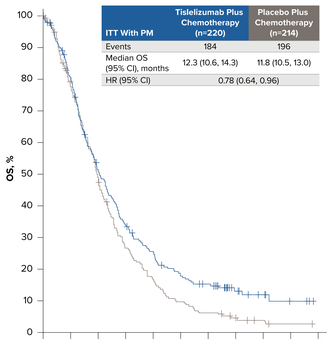
Stratification Factors:
- Regions of enrollment: China (including Taiwan) vs Japan and South Korea vs US and Europe and other regions
- PD-L1 expression (PD-L1 score ≥5% vs PD-L1 score <5%)
- Presence of peritoneal metastasis (yes vs no)
- Investigator-chosen chemotherapy (oxaliplatin plus capecitabine or cisplatin plus 5-fluorouracil)

[a]Chemotherapy: oxaliplatin 130 mg/m² on day 1 plus capecitabine 1000 mg/m² twice daily on days 1-14, Q3W; cisplatin 80 mg/m² on day 1 plus 5-fluorouracil 800 mg/m²/d on days 1-5, Q3W. [b]Investigator assessed per Response Evaluation Criteria in Solid Tumors v1.1.
Abbreviations: DoR, duration of response; IV, intravenous; Q3W, once every 3 weeks; R, randomized.

Figure 1. Kaplan-Meier Plots of OS Outcomes in the (A) ITT, (B) PD-L1 TAP Score ≥5%, and (C) PD-L1 TAP Score ≥1% Subgroups[5]

A

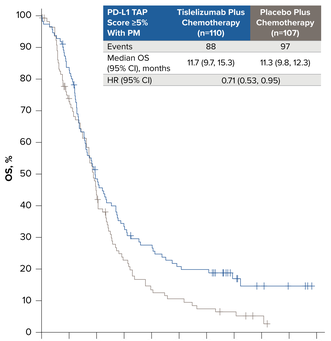
ITT With PM	Tislelizumab Plus Chemotherapy (n=220)	Placebo Plus Chemotherapy (n=214)
Events	184	196
Median OS (95% CI), months	12.3 (10.6, 14.3)	11.8 (10.5, 13.0)
HR (95% CI)	0.78 (0.64, 0.96)	



No. at risk											
Tislelizumab plus chemotherapy	220	174	108	71	52	35	28	13	8	3	0
Placebo plus chemotherapy	214	161	99	53	33	19	12	7	3	1	0

B

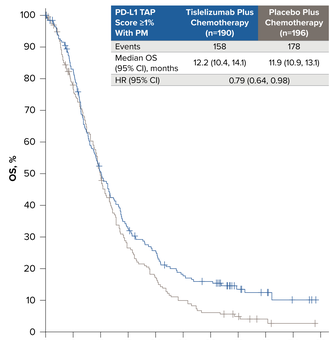
PD-L1 TAP Score ≥5% With PM	Tislelizumab Plus Chemotherapy (n=110)	Placebo Plus Chemotherapy (n=107)
Events	88	97
Median OS (95% CI), months	11.7 (9.7, 15.3)	11.3 (9.8, 12.3)
HR (95% CI)	0.71 (0.53, 0.95)	



No. at risk											
Tislelizumab plus chemotherapy	110	91	51	35	28	21	20	9	5	3	0
Placebo plus chemotherapy	107	76	46	22	13	10	7	5	2	0	0

C

PD-L1 TAP Score ≥1% With PM	Tislelizumab Plus Chemotherapy (n=190)	Placebo Plus Chemotherapy (n=196)
Events	158	178
Median OS (95% CI), months	12.2 (10.4, 14.1)	11.9 (10.9, 13.1)
HR (95% CI)	0.79 (0.64, 0.98)	



No. at risk											
Tislelizumab plus chemotherapy	190	153	92	59	45	30	26	12	8	3	0
Placebo plus chemotherapy	196	145	92	48	31	18	11	7	3	1	0

Abbreviations: CI, confidence interval; HR, hazard ratio.

RESULTS

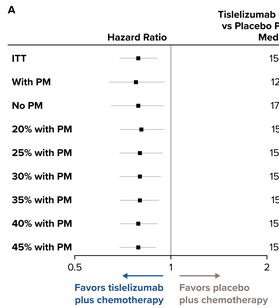
Patient Disposition

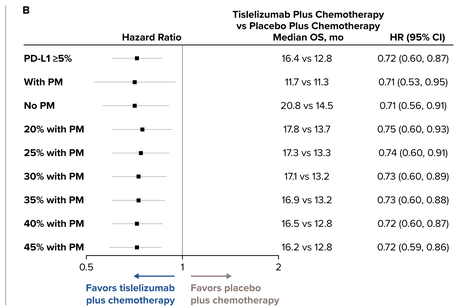
- As of the data cutoff (February 28, 2024; minimum study follow-up: 36.6 months), 43.5% of patients in the ITT population had PM; 54.8% of patients had PD-L1 TAP scores ≥5%; 39.7% of those had PM. Among the 88.9% patients with TAP scores ≥1%, 43.6% had PM (**Table 1**)
- A higher proportion of female patients had PM (with PM: 41.2%, without PM: 22.4%; **Table 1**)
- Patients with PM, compared with those without PM, were less likely to have PD-L1 ≥5% tumors (50% vs 58.4%) and were more likely to have primary stomach tumors (86.6% vs 75.5%)
- Patients with PM, compared with those without PM, were also more likely to have ≥3 metastatic sites (49.1% vs 20.1%), and less likely to have liver metastases (24.9% vs 48.0%)
- Baseline demographics and disease characteristics were generally similar across treatment arms

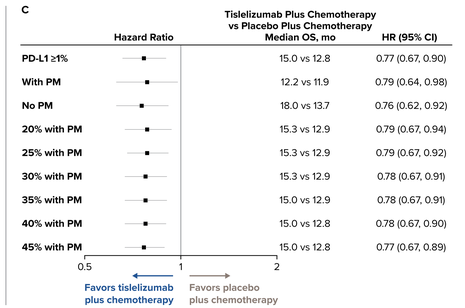
Table 1. Patient Baseline Demographics and Characteristics (ITT Analysis Set)

Baseline Characteristics	All (n=434)	With PM		Without PM		
		Tislelizumab Plus Chemotherapy (n=220)	Placebo Plus Chemotherapy (n=214)	All (n=563)	Tislelizumab Plus Chemotherapy (n=281)	Placebo Plus Chemotherapy (n=282)
Sex, n (%)						
Male	255 (58.8)	136 (61.8)	119 (55.6)	437 (77.6)	210 (74.7)	227 (80.5)
Female	179 (41.2)	84 (38.2)	95 (44.4)	126 (22.4)	71 (25.3)	55 (19.5)
Disease site, n (%)						
GEJ	58 (13.4)	24 (10.9)	34 (15.9)	138 (24.5)	72 (25.6)	66 (23.4)
Stomach	376 (86.6)	196 (89.1)	180 (84.1)	425 (75.5)	209 (74.4)	216 (76.6)
PD-L1 TAP score, n (%)						
<5%	217 (50.0)	110 (50.0)	107 (50.0)	234 (41.6)	117 (41.6)	117 (41.5)
≥5%	217 (50.0)	110 (50.0)	107 (50.0)	329 (58.4)	164 (58.4)	165 (58.5)
<1%	48 (11.1)	30 (13.6)	18 (8.4)	63 (11.2)	39 (13.9)	24 (8.5)
≥1%	386 (88.9)	190 (86.4)	196 (91.6)	500 (88.8)	242 (86.1)	258 (91.5)
Number of metastatic sites, n (%)						
0-2	221 (50.9)	112 (50.9)	109 (50.9)	450 (79.9)	223 (79.4)	227 (80.5)
≥3	213 (49.1)	108 (49.1)	105 (49.1)	113 (20.1)	58 (20.6)	55 (19.5)
Liver metastases, n (%)						
Yes	108 (24.9)	55 (25.0)	53 (24.8)	270 (48.0)	135 (48.0)	135 (47.9)
No	326 (75.1)	165 (75.0)	161 (75.2)	293 (52.0)	146 (52.0)	147 (52.1)

Figure 3. Forest Plots of OS Outcomes in the (A) ITT, (B) PD-L1 TAP Score ≥5%, and (C) PD-L1 TAP Score ≥1% Subgroups







Efficacy

- An improvement in median OS and higher ORR, with tislelizumab plus chemotherapy vs placebo plus chemotherapy was observed consistently among patients with or without PM and regardless of the proportion of PM modeled, which ranged from 20% to 45% in the ITT population (**Figure 3A**, **Table 2**)
  - Difference in ORR between treatment arms was more pronounced in patients with PM than without PM
  - Patients with higher PD-L1 TAP score showed a greater difference in ORR between treatment arms
- Similar improvements in PFS were also observed (data not shown)
- This improvement across all measures of efficacy regardless of the proportion of PM modeled was also consistent among patients with different PD-L1 cutoffs, including TAP score PD-L1 ≥5% (**Figure 3B**, **Table 2**), and TAP score PD-L1 ≥1% (**Figure 3C**, **Table 2**)

Table 2. ORR

Treatment Arm	All Patients	With PM	No PM	20% with PM	25% with PM	30% with PM	35% with PM	40% with PM	45% with PM
ITT									
Tislelizumab plus chemotherapy	47.3 (42.9, 51.8)	43.6 (37.0, 50.5)	50.2 (44.2, 56.2)	48.0 (42.9, 53.1)	47.8 (42.9, 52.7)	47.7 (43.0, 52.4)	47.5 (43.0, 52.1)	47.4 (42.9, 51.9)	47.3 (42.8, 51.8)
Placebo plus chemotherapy	40.5 (36.2, 45.0)	32.2 (26.0, 39.0)	46.8 (40.9, 52.8)	43.1 (38.1, 48.3)	42.6 (37.8, 47.5)	42.1 (37.5, 46.8)	41.5 (37.1, 46.1)	40.9 (36.6, 45.4)	40.3 (36.0, 44.8)
ORR difference	6.8 (0.6, 12.9)	11.4 (2.3, 20.3)	3.4 (-4.9, 11.6)	4.9 (-2.2, 11.9)	5.2 (-1.5, 11.9)	5.6 (-0.9, 12.0)	6.0 (-0.3, 12.2)	6.4 (0.3, 12.6)	6.9 (0.8, 13.0)
PD-L1 ≥5% analysis set									
Tislelizumab plus chemotherapy	51.5 (45.4, 57.5)	47.3 (37.7, 57.0)	54.3 (46.3, 62.1)	52.1 (45.1, 59.0)	52.0 (45.3, 58.5)	51.8 (45.5, 58.2)	51.7 (45.5, 57.9)	51.6 (45.5, 57.6)	51.4 (45.3, 57.5)
Placebo plus chemotherapy	42.6 (36.7, 48.8)	30.8 (22.3, 40.5)	50.3 (42.4, 58.2)	46.5 (39.6, 53.5)	45.8 (39.2, 52.5)	45.0 (38.7, 51.5)	44.2 (38.1, 50.4)	43.3 (37.3, 49.4)	42.4 (36.4, 48.5)
ORR difference	8.8 (0.4, 17.1)	16.4 (3.4, 28.9)	4.0 (-6.8, 14.7)	5.6 (-4.0, 15.0)	6.2 (-3.0, 15.2)	6.8 (-2.0, 15.5)	7.5 (-1.0, 15.9)	8.3 (-0.2, 16.6)	9.1 (0.7, 17.3)
PD-L1 ≥1% analysis set									
Tislelizumab plus chemotherapy	47.7 (42.9, 52.5)	44.2 (37.0, 51.6)	50.4 (43.9, 56.9)	48.1 (42.5, 53.6)	48.0 (42.8, 53.3)	47.9 (42.9, 53.0)	47.9 (43.0, 52.8)	47.8 (42.9, 52.6)	47.7 (42.9, 52.5)
Placebo plus chemotherapy	41.0 (36.4, 45.6)	33.2 (26.6, 40.2)	46.9 (40.7, 53.2)	43.6 (38.3, 49.0)	43.1 (38.0, 48.2)	42.5 (37.7, 47.4)	42.0 (37.3, 46.7)	41.4 (36.8, 46.1)	40.8 (36.2, 45.5)
ORR difference	6.7 (0.2, 13.2)	11.0 (1.3, 20.6)	3.5 (-5.2, 12.2)	4.5 (-3.1, 12.0)	5.0 (-2.2, 12.1)	5.4 (-1.4, 12.3)	5.9 (-0.8, 12.5)	6.4 (-0.2, 12.9)	6.9 (0.3, 13.4)

Values are % (95% CI).

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DISCLOSURES

MBS: Received honoraria from Novartis and declares other financial or nonfinancial interests with Lilly and Taiho Oncology.

ACKNOWLEDGMENTS

The authors thank the patients and their families, investigators, co-investigators, and the study teams at each of the participating centers. This study was sponsored by BeOne Medicines, Ltd. Medical writing support was provided by Lauren Van Wassenhove, PhD, of Parexel, and supported by BeOne Medicines.

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Presented at ASCO GI, January 8-10, 2026, San Francisco, CA, USA