RATIONALE-305: Exploratory Analysis of Patient Baseline Characteristics, Efficacy, and Safety in Long-Term Survivors

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CONCLUSIONS

- In patients with advanced gastric cancer or gastroesophageal junction cancer (GC/GEJC) from the RATIONALE-305 trial (NCT03777657), **30.7% who received tislelizumab + chemotherapy survived ≥24 months**
- Although **patients without baseline peritoneal metastases and those with fewer than 3 metastatic sites were more likely to survive beyond 24 months**, no present mechanism can reliably identify these patients at baseline
- Objective response rate (ORR) and time to response were similar between patients who survived ≥15 months and ≥24 months, but greater than those in the intent to treat (ITT) population
- No new safety signals were observed among the subgroup of long-term survivors
- **Further validation of baseline characteristics and survival results using real-world data would provide meaningful insights for both patients and clinicians**

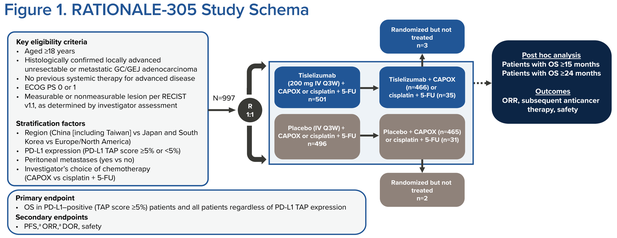
INTRODUCTION

- A subset of patients with advanced GC/GEJC who have received anti–programmed cell death 1 (PD-1) antibody + chemotherapy in Phase 3 studies achieve long-term survival[1-6]
- Tislelizumab is a high-affinity immune checkpoint inhibitor targeting PD-1 and is specifically engineered to minimize Fcγ receptor binding on macrophages[7,8]
- In the phase 3 RATIONALE-305 trial, patients with human epidermal growth factor receptor 2 (HER2)-negative advanced GC/GEJC were randomized to first-line tislelizumab or placebo + chemotherapy[9]
  - As of 28 February 2023, tislelizumab + chemotherapy improved OS vs placebo + chemotherapy in all randomized patients and those with programmed cell death 1 ligand 1 (PD-L1) tumor area positivity (TAP) score ≥5%
  - The median OS for all randomized patients who received tislelizumab + chemotherapy was 15.0 months
  - Unlike other PD-1 inhibitor trials, the RATIONALE-305 trial did not limit tislelizumab treatment at 2 years when clinical benefits were still observed; patients remained on therapy until disease progression or unacceptable toxicity
- Given the poor outcomes of patients with advanced GC/GEJC, characterization of those patients who achieve longer survival when receiving tislelizumab therapy may help to optimize treatment regimens
- Here we present a post hoc analysis from the RATIONALE-305 study, evaluating patients with advanced GC/GEJC who received tislelizumab + chemotherapy who survived longer than the median OS of 15.0 months

METHODS

- The study schema for RATIONALE-305, a randomized, double-blind, placebo-controlled phase 3 trial, is shown in **Figure 1**[9]
- Eligible patients with HER2-negative disease were randomized 1:1 to receive tislelizumab + chemotherapy or placebo + chemotherapy (chemotherapy was administered for up to six cycles)
  - Chemotherapy regimens included:
    - CAPOX: oxaliplatin 130 mg/m^2 Day 1 + capecitabine 1000 mg/m^2 twice daily on Days 1-14, every 3 weeks (Q3W)
    - FP: cisplatin 80 mg/m^2 Day 1 + 5-fluorouracil 800 mg/m^2/day intravenous on Days 1-5, Q3W
  - Capecitabine continuation with tislelizumab or placebo was at the investigator's discretion

Figure 1. RATIONALE-305 Study Schema



[a] Investigator assessed per RECIST v1.1.

Abbreviations: 5-FU, 5-fluorouracil; CAPOX, oxaliplatin + capecitabine; DOR, duration of response; ECOG PS, Eastern Cooperative Oncology Group performance status; GC/GEJ, gastric cancer or gastroesophageal junction; IV, intravenous; ORR, objective 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.

Post Hoc Analysis

- The objective of this post hoc analysis was to identify baseline characteristics associated with long-term survival in patients who received tislelizumab + chemotherapy; additionally, efficacy and safety data were examined for numerical differences from the ITT population
- The following two time points were selected for this analysis:
  - OS ≥15 months: the median OS observed in all randomized patients; this timepoint allows for contextualization of patients with survival at or above the 50% percentile
  - OS ≥24 months: a clinically meaningful milestone that is beyond the expected treatment benefit with this combination
- Outcomes from patients treated with subsequent immunotherapy were included
- Efficacy endpoints were measured from the time of enrollment
- For context, baseline characteristics, as well as efficacy and safety data were compared with the ITT population
- The data cutoff date for this analysis was 28 February 2024

RESULTS

Patients

- 501 patients who received tislelizumab + chemotherapy (ITT) were included in the analysis; the median follow-up was 14.1 (range, 0.1-62.1) months
- A total of 238 patients (47.5%) survived for ≥15 months and 154 (30.7%) patients survived for ≥24 months (**Table 1**)
  - Baseline characteristics were similar between patients with OS ≥15 and ≥24 months
- Compared with the ITT population, patients who survived longer had a greater proportion with a PD-L1 TAP score ≥5% (ITT, 54.7%; OS ≥15 months, 57.6%; OS ≥24 months, 63.0%), and fewer than 3 sites of metastases (ITT, 66.9%; OS ≥15 months, 79.4%; OS ≥24 months, 81.2%)
  - Baseline peritoneal metastases were also rarer for those with a longer survival vs ITT (ITT, 43.9%; OS ≥15 months, 37.4%; OS ≥24 months, 33.8%)
- Median treatment duration with tislelizumab was 12.3 (range, 0.7-59.0) months in the OS ≥15-month group and 18.2 (0.7-59.0) months in the OS ≥24-month group (**Table 2**)

Table 1. Baseline Demographic and Disease Characteristics

Characteristic	ITT (N=501)	OS ≥15 mo (n=238)	OS ≥24 mo (n=154)
Age, median (range), y	60 (23-86)	61 (28-81)	61 (31-80)
Sex, n (%)			
Male	346 (69.1)	163 (68.5)	104 (67.5)
Female	155 (30.9)	75 (31.5)	50 (32.5)
ECOG PS, n (%)			
0	169 (33.7)	91 (38.2)	60 (39.0)
1	332 (66.3)	147 (61.8)	94 (61.0)
Geographic region, n (%)			
East Asia	376 (75.0)	193 (81.1)	122 (79.2)
Rest of world	125 (25.0)	45 (18.9)	32 (20.8)
PD-L1 TAP score, n (%)			
TAP <5%	227 (45.3)	101 (42.4)	57 (37.0)
TAP ≥5%	274 (54.7)	137 (57.6)	97 (63.0)
Liver metastasis, n (%)	190 (37.9)	80 (33.6)	58 (37.7)
Peritoneal metastasis, n (%)	220 (43.9)	89 (37.4)	52 (33.8)
≥3 Metastatic sites, n (%)	166 (33.1)	49 (20.6)	29 (18.8)
Primary metastatic location, n (%)			
GEJ	96 (19.2)	47 (19.7)	29 (18.8)
Stomach	405 (80.8)	191 (80.3)	125 (81.2)
Prior definitive treatment/surgery, n (%)			
Yes	163 (32.5)	88 (37.0)	51 (33.1)
No	338 (67.5)	150 (63.0)	103 (66.9)

Data cutoff date: 28 February 2024.

Abbreviations: ECOG PS, Eastern Cooperative Oncology Group performance status; GEJ, gastroesophageal junction; ITT, intent to treat; mo, month; OS, overall survival; PD-L1, programmed cell death 1 ligand 1; TAP, tumor area positivity.

Table 2. Tislelizumab and Chemotherapy Exposure

Treatment	ITT (n=498)	OS ≥15 mo (n=238)	OS ≥24 mo (n=154)
	Median exposure, mo (range)		
Tislelizumab exposure	5.9 (0.1-59.0)	12.3 (0.7-59.0)	18.2 (0.7-59.0)
CAPOX regimen, n (%)	463 (93.0)	225 (94.5)	146 (94.8)
Capecitabine exposure	5.8[a] (0.3-57.4)	11.0 (0.7-57.4)	14.8 (0.7-57.4)
Oxaliplatin exposure	4.2 (0.1-8.0)	4.3 (0.7-8.0)	4.4 (0.7-7.6)
FP regimen, n (%)	35 (7.0)	13 (5.5)	8 (5.2)
5-fluorouracil exposure	4.2 (0.3-5.3)	4.2 (0.7-5.3)	4.3 (3.7-4.9)
Cisplatin exposure	4.1 (0.3-5.3)	4.1 (0.7-5.3)	4.3 (3.7-4.9)

[a] Ten patients discontinued before receiving capecitabine; therefore, data are based on n=453.

Data cutoff date: 28 February 2024.

Abbreviations: CAPOX, capecitabine + oxaliplatin; FP, fluoropyrimidine + platinum; ITT, intent to treat; mo, months; OS, overall survival.

Efficacy

Best Overall Response

- Greater ORRs were observed for patients with OS ≥15 months and OS ≥24 months, than those in the ITT population (67.2%, 74.0%, and 47.3%, respectively)
  - Disease control rates showed a similar relationship (**Table 3**)
- The median time to response was the same for both OS subgroups (1.5 months)

Table 3. Best Overall Response

Response	ITT (n=501)	OS ≥15 mo (n=238)	OS ≥24 mo (n=154)
ORR, % (95% CI)	47.3 (42.9-51.8)	67.2 (60.9-73.2)	74.0 (66.4-80.8)
CR, n (%)	19 (3.8)	18 (7.6)	17 (11.0)
PR, n (%)	218 (43.5)	142 (59.7)	97 (63.0)
SD, n (%)	185 (36.9)	54 (22.7)	27 (17.5)
PD, n (%)	23 (4.6)	4 (1.7)	2 (1.3)
DCR, % (95% CI)	89.8 (86.8-92.3)	89.9 (85.4-93.4)	91.6 (86.0-95.4)

Data cutoff date: 28 February 2024.

Abbreviations: CR, complete response; DCR, disease control rate; ITT, intent to treat; mo, months; ORR, objective response rate; OS, overall survival; PD, progressive disease; PR, partial response; SD, stable disease.

Subsequent Anti-Cancer Therapy

- The proportion of patients who received subsequent anti-cancer therapies following tislelizumab + chemotherapy treatment were similar between the ITT population, and those who survived ≥24 months (both 54.5%); patients who survived ≥15 months were more likely to have received a subsequent therapy (65.1%) (**Table 4**)
- Patients in both long survivors subgroups were more likely to receive 2 or more subsequent anti-cancer therapies
- In all groups, chemotherapy was the most common subsequent anti-cancer therapy (ITT, 51.5%; OS ≥15 months, 63.4%; OS ≥24 months, 51.9%)

Table 4. Subsequent Anti-Cancer Therapy

Parameter, n (%)	ITT (N=501)	OS ≥15 mo (n=238)	OS ≥24 mo (n=154)
Any Subsequent Therapy	273 (54.5)	155 (65.1)	84 (54.5)
Targeted Therapy	156 (31.1)	91 (38.2)	55 (35.7)
Chemotherapy	258 (51.5)	151 (63.4)	80 (51.9)
Immunotherapy	65 (13.0)	49 (20.6)	32 (20.8)
Other Therapies	15 (3.0)	10 (4.2)	5 (3.2)
1st subsequent therapy	273 (54.5)	155 (65.1)	84 (54.5)
2nd subsequent therapy	118 (23.6)	86 (36.1)	52 (33.8)
3rd subsequent therapy	50 (10.0)	44 (18.5)	25 (16.2)
≥4th subsequent therapy	18 (3.6)	15 (6.3)	10 (6.5)

Data cutoff date: 28 February 2024.

Abbreviations: mo, months; ITT, intent to treat.

Safety

- Rates of treatment-emergent adverse events were similar for patients in the OS ≥15-month group (grade ≥3, 64.3%) and OS ≥24-month group (grade ≥3, 65.6%), with no new safety signals identified (**Table 5**)

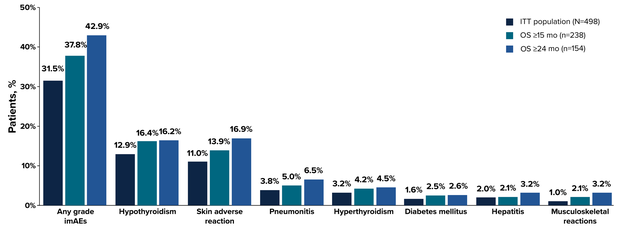
Table 5. Safety Summary

Category	ITT (n=498)	OS ≥15 mo (n=238)	OS ≥24 mo (n=154)
Any grade TEAEs, n (%)	495 (99.4)	238 (100)	154 (100)
Grade ≥3 TEAEs	346 (69.5)	153 (64.3)	101 (65.6)
Serious TEAEs	211 (42.4)	77 (32.4)	49 (31.8)
TEAEs leading to death	47 (9.4)	1 (0.4)	0

Abbreviations: mo, months; TEAE, treatment-emergent adverse event.

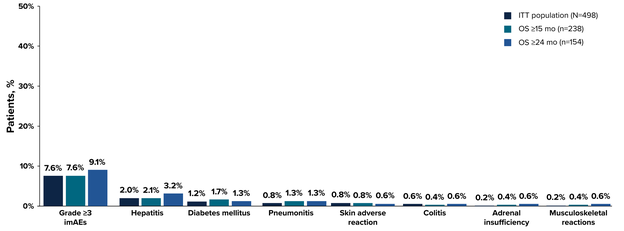
- The rate of any grade imAEs (**Figure 2**) and grade ≥3 imAEs (**Figure 3**) were similar for both OS subgroups

Figure 2. Any Grade imAEs (incidence ≥2%)



Abbreviations: imAE, immune-mediated adverse event; ITT, intent to treat; mo, months; OS, overall survival.

Figure 3. Grade ≥3 imAEs



Abbreviations: imAE, immune-mediated adverse event; ITT, intent to treat; mo, months; OS, overall survival.

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DISCLOSURES

MM: Advisory board: BMS, Servier, Amgen, Lilly, Bayer, BeOne Medicines, Ltd, Novartis, Taiho, Daiichi Sankyo, Amgen, MD;
Honoraria: MSD, BMS, Falk Foundation, AIO, BeOne Medicines, Ltd, Amgen;
Expert testimony: Sanofi;
Other: EORTC Chair.

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