Tislelizumab First-Line Gastric/Gastroesophageal Junction (G/GEJ) Adenocarcinoma Treatment Efficacy on Patient-Reported Outcome (PRO)-Based Symptom Endpoints Adjusting for Informative Missing Data Bias: Results from RATIONALE-305

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Conclusions

- **The use of joint models to adjust for informative missing data bias provides promising evidence that tislelizumab + chemotherapy (tislelizumab arm) was associated with lower deterioration for select key gastric/gastroesophageal junction (G/GEJ) adenocarcinoma symptoms (i.e., dysphagia, dietary restrictions, pain, and upper gastrointestinal [GI] symptoms) compared with placebo + chemotherapy (placebo arm) in RATIONALE-305 for both progression-free survival (PFS) and overall survival (OS)**
- **These preliminary analyses provide a mechanism for modeling patient-reported outcome (PRO) data in oncology clinical trials that may help illuminate additional patient-centric therapeutic benefits. This approach enables analysis of PRO data collected throughout the course of the trial, as opposed to commonly employed analyses which restrict analysis to early cycles out of fear of missing data bias**
- **To our knowledge, this method has not previously been used for PROs in the oncology therapeutic domain**

Background

- PRO-based symptom endpoints are rarely associated with treatment efficacy in oncology trials, including those in patients with G/GEJ adenocarcinoma
- One barrier to PRO efficacy detection may lie in restricting analyses to early treatment cycles because of later cycle data becoming missing not at random (MNAR)
  - The informative process thought to induce MNAR data is that those who experience a terminal event leave the study having not contributed data reflecting their subjective health status, thereby biasing the characterization of PRO data
- However, separation between arms on other efficacy endpoints (e.g., OS) typically occurs at cycles subsequent to the analysis period cutoff for PRO-based endpoints
- To protect against MNAR bias associated with later cycles, joint models may be used to link linear mixed models for change from baseline in PRO symptom scores with each patient's PFS or OS terminal event times – this approach adjusts the linear mixed model PRO data for both data missing at random (MAR) and MNAR
- The joint model was augmented with a recurrent symptomatic deterioration event survival model
- The objective of the current analyses was to develop joint models in order to evaluate treatment efficacy on PRO-based change from baseline symptom scores in treatment cycles occurring later than typically analyzed and OS events within the RATIONALE-305 trial population

Methods

Study Design and Patients

- These analyses were conducted using data from the RATIONALE-305 trial
  - RATIONALE-305 (NCT03777657) was a phase 3, randomized, double-blind, placebo-controlled trial assessing the addition of tislelizumab to chemotherapy as first-line treatment for patients with locally advanced, unresectable, or metastatic G/GEJ adenocarcinoma
  - Patients were randomized 1:1 to receive tislelizumab 200 mg or placebo intravenously once every 3 weeks plus investigator's choice of chemotherapy regimen until disease progression, unacceptable toxicity, or patient withdrawal
  - The study was carried out in accordance with Good Clinical Practice Guidelines, the principles of the Declaration of Helsinki, and local laws and regulations

Measures

- PRO-based symptoms were assessed using the European Organisation for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire – Cancer Module (QLQ-C30) and Gastric Cancer Module (QLQ-STO22),[1] a questionnaire designed to assess gastric cancer-specific symptoms
  - Two QLQ-C30 domains were analyzed:
    - Appetite, fatigue
  - Four QLQ-STO22 domains were analyzed:
    - Dietary restrictions, dysphagia/odynophagia, pain/discomfort, and upper GI symptoms
  - Both QLQ-C30 and QLQ-STO22 were administered at baseline and then every 3-week cycle until the end of treatment
- Two terminal event measures were analyzed:
  - Investigator-assessed PFS and OS
- For both QLQ-C30 and QLQ-STO22, a recurrent deterioration event (RDE) was defined as any change-from-baseline (CFBL) score ≥10[2]
  - For a deterioration event to qualify as a recurrent event, it had to be a unique event: 2 events had to be separated by non-events to qualify as recurrent

Statistical Analyses

- All randomized patients in the intent-to-treat (ITT) population who completed the baseline and ≥1 post-baseline QLQ-C30 and QLQ-STO22 were eligible
- CFBL in each symptom domain was analyzed for up to 21 cycles between cycles 2 and 38, representing approximately 114 weeks from the first treatment
- Treatment efficacy for the QLQ-C30 and QLQ-STO22 endpoints was evaluated using 3-part joint models (treatment effect was coded as tislelizumab arm vs placebo arm with tislelizumab arm as the effect group)
  - For each PRO endpoint, the 3-part joint models linked:
    - A linear mixed model for symptom domain CFBL
    - A Cox proportional hazards model for PFS or OS (terminal event)
    - A frailty Cox proportional hazard model for time to recurrent symptom deterioration
    - The time metric for all 3 models was months since baseline.
- Missing data adjustment: The joint model provides a comprehensive adjustment for missing data bias
  - The linear mixed model directly adjusts for data MAR
  - The terminal event survival models adjusted the linear mixed model for data MNAR
- Model Adjustment
  - All models were adjusted for the following randomization factors: geographic region (Asia vs non-Asia), programmed death-ligand 1 (PD-L1) expression status (tumor area positivity ≥5% vs <5%), and presence of peritoneal metastasis (yes vs no)
- Analyses were conducted using the JMBayes2 package in R (version 4.3.2)
  - Model and parameter convergence evaluated using trace and density plots and the $\hat{R}$ statistic (reported in last column in **Tables 2** and **3**)
- Linear-mixed model efficacy for endpoints is reported for joint models adjusting for PFS and OS separately
  - Covariate effects are not reported
  - Survival model hazard ratios and frailty association parameters are not reported here but have been submitted for presentation elsewhere

Results

- At data cutoff (February 28, 2023), the ITT population consisted of a total of 997 patients (tislelizumab arm, N=501; placebo arm, N=496)
  - Patient demographics and baseline disease characteristics were generally balanced across the arms
- At baseline, 465 patients in the tislelizumab arm and 467 patients in the placebo arm completed the QLQ-STO22
  - The number of patients who contributed QLQ-C30 and QLQ-STO22 symptom data in each cycle stratified by treatment arm are presented in **Table 1**

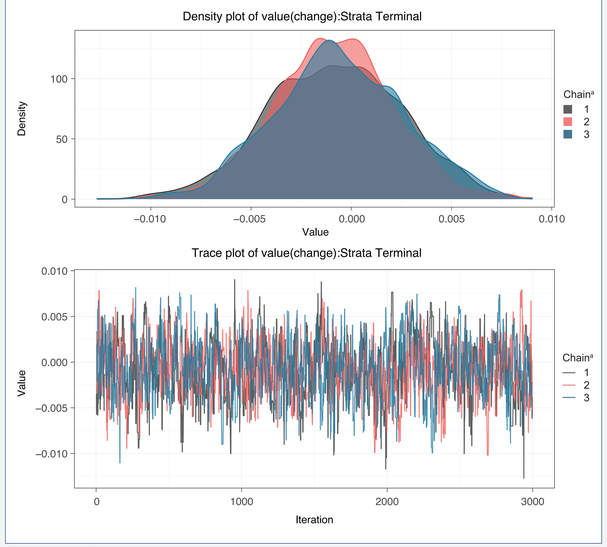
Joint Models

- Convergence plots for the joint models indicated satisfactory convergence of the Bayesian integral-based marginalization (**Figure 1**)
- Adjusting for OS, recurrent symptomatic deterioration, and stratification factors, tislelizumab arm was associated with significantly lower symptom deterioration compared with placebo arm for the following domains: dysphagia, dietary restrictions, pain, and upper GI symptoms (**Table 2**)
  - The treatment by study month interaction was not statistically significant, indicating that the treatment arms did not have differential rates of change across treatment cycles

Table 1. Number of Patients per Cycle

Treatment Cycle, n (%)	Tislelizumab Arm (N=465)	Placebo Arm (N=467)
Baseline	465 (100)	467 (100)
2	464 (99.8)	456 (97.6)
3	419 (90.1)	402 (86.1)
4	387 (83.2)	379 (81.2)
5	352 (75.7)	330 (70.7)
6	358 (77.0)	339 (72.6)
8	280 (60.2)	244 (52.2)
10	226 (48.6)	198 (42.4)
12	183 (39.4)	158 (33.8)
14	152 (32.7)	120 (25.7)
16	131 (28.2)	107 (22.9)
18	117 (25.2)	79 (16.9)
20	98 (21.1)	69 (14.8)
22	89 (19.1)	70 (15.0)
24	89 (19.1)	58 (12.4)
26	80 (17.2)	47 (10.1)
28	74 (15.9)	49 (10.5)
30	66 (14.2)	39 (8.4)
32	69 (14.8)	39 (8.4)
34	63 (13.5)	34 (7.3)
36	52 (11.2)	31 (6.6)
38	46 (9.9)	28 (6.0)

Figure 1. Convergence Plots for the Joint Models



[a]Chains are sampling elements for Markov chains, autocorrelated samples from a posterior distribution.

Table 2. Tislelizumab Arm vs Placebo Arm Efficacy for CFBL in QLQ-C30 and QLQ-STO22 Domains Adjusting for OS and Recurrent Symptomatic Deterioration in 3-part Recurrent Event Joint Model

EORTC Domain	Effect	β (95% CI)	*P*	$\hat{R}$
Appetite	TIS arm vs PBO arm	-2.07 (-4.64-0.42)	0.1020	1.0040
	Study month	-0.69 (-0.86 to -0.52)	<0.00001	1.0474
	TIS arm vs PBO arm x study month	0.13 (-0.08-0.33)	0.2378	1.0025
Dysphagia	TIS arm vs PBO arm	-1.72 (-2.97 to -0.50)	0.0060	1.0069
	Study month	-0.12 (-0.23 to -0.01)	0.0322	1.0517
	TIS arm vs PBO arm x study month	0.08 (-0.06-0.21)	0.2558	1.0034
Diet Restriction	TIS arm vs PBO arm	-1.83 (-3.47 to -0.25)	0.0253	1.0056
	Study month	-0.23 (-0.39 to -0.06)	0.0062	1.0193
	TIS arm vs PBO arm x study month	0.13 (-0.07-0.34)	0.1967	1.0087
Fatigue	TIS arm vs PBO arm	-1.75 (-3.71-0.16)	0.0709	1.0058
	Study month	-0.37 (-0.56 to -0.19)	<0.00001	1.1124
	TIS arm vs PBO arm x study month	0.02 (-0.19-0.22)	0.7936	1.0139
Pain/Discomfort	TIS arm vs PBO arm	-2.24 (-3.9 to -0.63)	0.0078	1.0040
	Study month	-0.25 (-0.36 to -0.13)	<0.00001	1.0130
	TIS arm vs PBO arm x study month	-0.01 (-0.17-0.13)	0.8867	1.0179
Upper GI Symptoms	TIS arm vs PBO arm	-2.59 (-3.98 to -1.25)	0.0004	1.0056
	Study month	-0.21 (-0.32 to -0.11)	<0.00001	1.0052
	TIS arm vs PBO arm x study month	0.07 (-0.06-0.19)	0.2809	1.0001

CFBL, change-from-baseline; CI, confidence interval; EORTC, European Organisation for Research and Treatment of Cancer; GI, gastrointestinal; PBO, placebo; QLQ-C30, Quality of Life Questionnaire – Cancer Module; QLQ-STO22, Quality of Life Questionnaire – Gastric Cancer Module; TIS, tislelizumab.

- Adjusting for PFS, recurrent symptomatic deterioration, and stratification factors, tislelizumab arm was associated with significantly lower symptom deterioration compared with placebo arm for the following domains: dysphagia, dietary restrictions, pain, and upper GI symptoms (**Table 3**)
  - The treatment by study month interaction was not statistically significant, indicating that the treatment arms do not have differential rates of change across treatment cycles

Table 3. Tislelizumab Arm vs Placebo Arm Efficacy for CFBL in QLQ-C30 and QLQ-STO22 Domains Adjusting for PFS and Recurrent Symptomatic Deterioration in 3-part Recurrent Event Joint Model

EORTC Domain	Effect	β (95% CI)	*P*	$\hat{R}$
Appetite	TIS arm vs PBO arm	-1.30 (-3.71-1.10)	0.3038	1.0055
	Study month	-0.52 (-0.70 to -0.35)	<0.00001	1.0085
	TIS arm vs PBO arm x study month	0.03 (-0.20-0.25)	0.8338	1.0140
Dysphagia	TIS arm vs PBO arm	-1.37 (-2.53 to -0.23)	0.0162	1.0027
	Study month	-0.07 (-0.17-0.01)	0.1047	1.0075
	TIS arm vs PBO arm x study month	0.02 (-0.10-0.15)	0.7089	1.0062
Diet Restriction	TIS arm vs PBO arm	-1.70 (-3.22 to -0.18)	0.0289	1.0019
	Study month	-0.16 (-0.32-0.01)	0.0651	1.0585
	TIS arm vs PBO arm x study month	0.09 (-0.12-0.31)	0.3956	1.0078
Fatigue	TIS arm vs PBO arm	-1.17 (-3.10-0.75)	0.2440	1.0099
	Study month	-0.27 (-0.45 to -0.09)	0.0016	1.0359
	TIS arm vs PBO arm x study month	-0.08 (-0.32-0.16)	0.5133	1.0367
Pain/Discomfort	TIS arm vs PBO arm	-2.08 (-3.68 to -0.50)	0.0082	1.0053
	Study month	-0.14 (-0.24 to -0.02)	0.0169	1.0313
	TIS arm vs PBO arm x study month	-0.06 (-0.21-0.08)	0.4444	1.0102
Upper GI Symptoms	TIS arm vs PBO arm	-2.15 (-3.54 to -0.80)	0.0013	1.0053
	Study month	-0.15 (-0.24 to -0.05)	0.0024	1.0149
	TIS arm vs PBO arm x study month	0.03 (-0.10-0.15)	0.6747	1.0103

CFBL, change-from-baseline; CI, confidence interval; EORTC, European Organisation for Research and Treatment of Cancer; GI, gastrointestinal; PBO, placebo; PFS, progression-free survival; QLQ-C30, Quality of Life Questionnaire – Cancer Module; QLQ-STO22, Quality of Life Questionnaire – Gastric Cancer Module; TIS, tislelizumab.

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