Recurrent Patient-Reported Outcome (PRO)-Based Symptomatic Deterioration Predicts Progression-Free Survival (PFS): Results from RATIONALE-305

Markus Moehler,[1] Daniel Serrano,[2] Hui Xu,[3] Tao Sheng,[4] Liyun Li,[3] Bryant Barnes,[4] Gisoo Barnes,[4] Do-Youn Oh[5]

[1]Johannes Gutenberg-University Clinic, Department of Internal Medicine, Mainz, Germany; [2]The Psychometrics Team, Sheridan, WY, USA; [3]BeiGene (Beijing) Co., Ltd, Beijing, China; [4]BeiGene USA, Inc., San Mateo, CA, USA; [5]Seoul National University Hospital, Cancer Research Institute, Seoul, Korea

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Conclusions

After predicting progression-free survival (PFS) from the risk of recurrent symptomatic deterioration events, the tislelizumab arm remained superior to the placebo arm, with estimated hazard ratios (HRs) for the tislelizumab arm between 0.70 to 0.78, reflecting a 30% to 22% reduced risk of disease progression

Recurrent patient-reported outcome (PRO) symptomatic deterioration in appetite, fatigue, pain/discomfort, and upper gastrointestinal [UGI] symptoms) were leading predictors for risk of disease progression, indicating a potential need for increased clinical monitoring

These preliminary analyses provide a mechanism for modeling PRO data in oncology clinical trials that may help illuminate additional clinically interpretable treatment effects that might enhance clinician-patient dialogue

Background

- PRO-based symptom endpoints are routinely employed in time to deterioration (TTD) analyses
  - However, these endpoints are rarely associated with treatment efficacy in oncology trials involving patients with G/GEJ adenocarcinoma
- In contrast to outcomes with a clear terminal event, such as PFS, recurrent PRO symptom deterioration may result in endpoints with "transient" terminal event times, better addressed by recurrent event survival models than the single-event TTD framework
- The objective of the current analyses was to develop a joint survival model linking time to recurrent PRO-based deterioration and disease progression (defined as PFS events) within the RATIONALE-305 trial population

Methods

Study Design and Patients

- These analyses were conducted using data from RATIONALE-305 (NCT03777657), 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

PRO Measures

- PRO-based symptoms were assessed using the European Organisation for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire – Core 30 (QLQ-C30) and Gastric Cancer Module (QLQ-STO22)[1]
  - Two QLQ-C30 domains were analyzed: appetite loss and fatigue
  - Four QLQ-STO22 domains were analyzed: dietary restrictions, dysphagia, pain/discomfort, and UGI symptoms
- Both the QLQ-C30 and QLQ-STO22 were administered at baseline and then every 3-week cycle until the end of treatment

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
- Change from baseline (CFBL) scores in each symptom domain were analyzed for up to 21 cycles between cycle 2 and cycle 38 (≈114 weeks)
- A recurrent deterioration event was defined as a CFBL score ≥10 points[2], and recurrent events defined as 2 events had to be separated by non-events
  - For a deterioration event to qualify as recurrent, it had to be a unique event
  - Patients without recurrent deterioration events or disease progression to end of study were censored
- Treatment effect was coded as tislelizumab arm versus placebo arm with tislelizumab arm as the effect group
- The terminal survival event was investigator-assessed PFS
- A joint survival model was specified for PRO symptom deterioration and PFS terminal events that linked the following components:
  - PRO symptom deterioration was modeled via a recurrent events frailty Cox model, to account for time to recurrent deterioration events, with treatment arm and stratification factor covariates
  - PFS terminal events were modeled via a Cox proportional hazards model to evaluate the recurrent deterioration frailty prediction of PFS
- The joint model provides a comprehensive adjustment for missing data bias, allowing for deeper exploration into later treatment cycles
- This model was 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 were evaluated using trace and density plots, survival model HRs, and the $\hat{R}$ statistic

Results

- ITT population (N=997; tislelizumab arm, n=501; placebo arm, n=496), cut-off date =February 28, 2023
  - Patient demographics and baseline disease characteristics were generally balanced across the arms, with 465 patients in the tislelizumab arm and 467 patients in the placebo arm completing the questionnaires
- The number of recurrent deterioration events ranged from 0 (censored) to 5 (see **Table 1** for the number of recurrent UGI deterioration events as an example)
  - A total of 42.3% of the sample had at least 1 recurrent event

Table 1. Observed Number of Recurrent QLQ-STO22 Upper Gastrointestinal Symptom Deterioration Events up to Cycle 38[a]

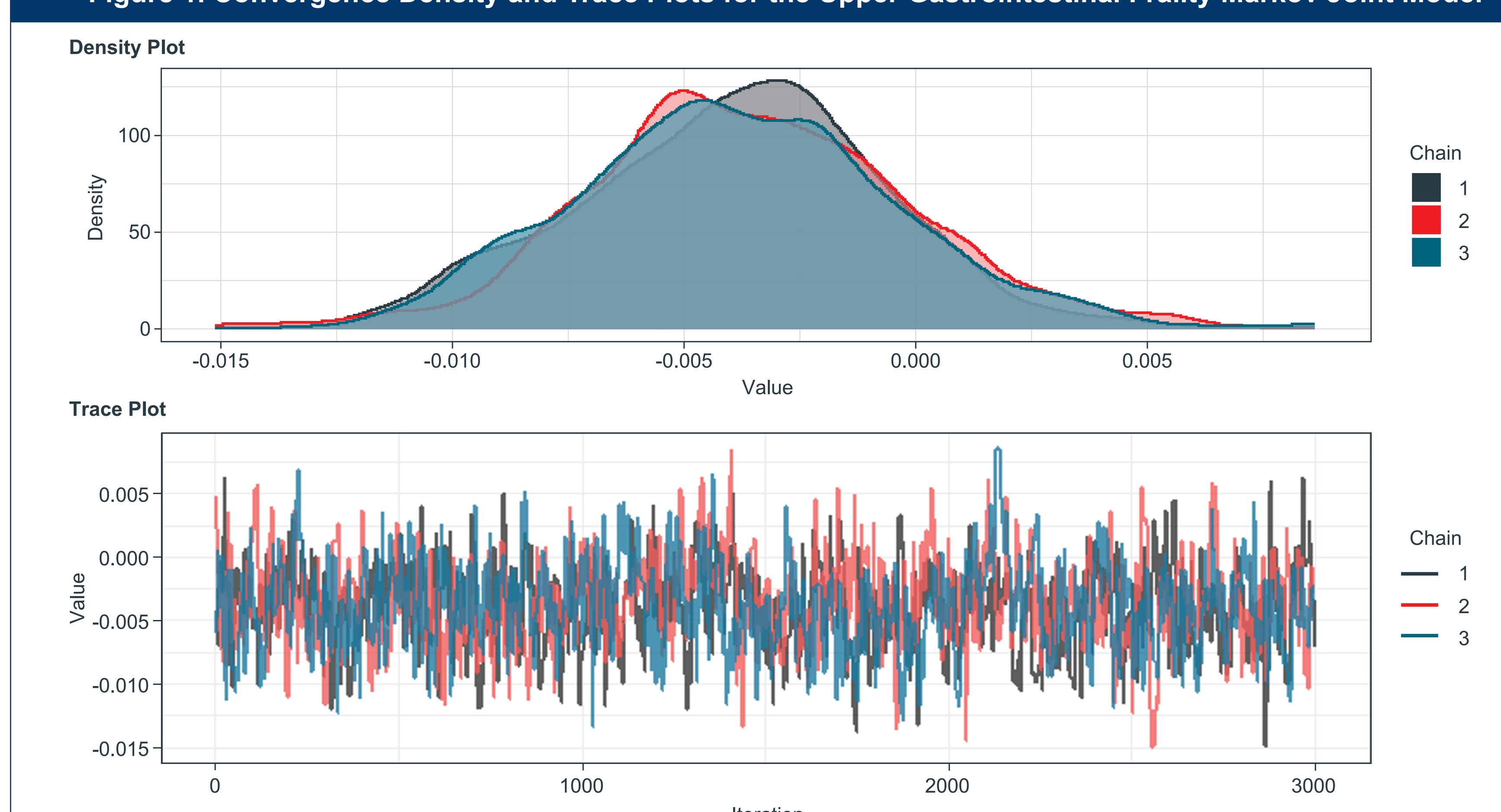
Number of Recurrent Events	Patients, N (%)	Cumulative N (%)
0	514 (57.4)	514 (57.4)
1	254 (28.3)	768 (85.7)
2	83 (9.3)	851 (95.0)
3	26 (2.9)	877 (97.9)
4	16 (1.8)	893 (99.7)
5	3 (0.3)	896 (100)

[a]Patients who completed baseline and ≥1 post-baseline QLQ-C30 and QLQ-STO22 were eligible.
QLQ-C30, Quality of Life Questionnaire – Core 30; QLQ-STO22, Quality of Life Questionnaire – Gastric Cancer Module.

Joint Models

- Convergence plots for the joint models indicated satisfactory convergence of the Bayesian integral-based marginalization (illustrated by examples from the UGI frailty parameter in **Figure 1**)

Figure 1. Convergence Density and Trace Plots for the Upper Gastrointestinal Frailty Markov Joint Model



Chain 1
- Represents one sequence of sampled values starting from an initial value
- Essentially used to explore the parameter space independently of the other chains

Chain 2
- Represents another independent sequence of sampled values from a different starting point
- Provides an additional path through the parameter space for comparison

Chain 3
- Represents a third independent sequence of sampled values
- Helps ensure robustness and thorough exploration of the parameter space

- The prediction of PFS was statistically significant for the appetite loss, fatigue, pain/discomfort, and UGI symptoms domains, with higher rates of recurrent deterioration events predicting increased risk of progression (**Table 2**)
- The tislelizumab arm demonstrated statistically significant greater protection against PFS compared with the placebo arm
- The association parameter for CFBL in symptomatic PRO scores and risk of recurrent corresponding symptomatic deterioration was statistically significant for all domains (as is to be expected); however, the association parameter for CFBL in symptomatic PRO scores and risk of PFS was not statistically significant

Table 2. Joint Survival Model for Recurrent Symptomatic Deterioration and PFS Adjusting for CFBL in PRO Domains, Treatment Arm, and Stratification Factors

Domain	Effect	HR (95% CI)	P	$\hat{R}$[a]
Appetite	TIS arm versus PBO arm: R-Det	1.20 (0.85, 1.71)	0.3176	1.0206
	TIS arm versus PBO arm: PFS	0.74 (0.57, 0.95)	0.0216	1.0570
	CFBL: R-Det	1.08 (1.07, 1.09)	0.0000	1.0819
	CFBL: PFS	1.00 (1.00, 1.01)	0.3864	1.0020
	R-Det frailty: PFS[b]	20.49 (2.84, 259.82)	0.0000	**1.6812**
Dysphagia	TIS arm versus PBO arm: R-Det	1.07 (0.70, 1.68)	0.7762	1.0252
	TIS arm versus PBO arm: PFS	0.78 (0.65, 0.93)	0.0069	1.0223
	CFBL: R-Det	1.16 (1.13, 1.19)	0.0000	1.1233
	CFBL: PFS	1.00 (0.99, 1.01)	0.9533	1.0118
	R-Det frailty: PFS[b]	2.77 (0.18, 87.03)	0.3433	1.2353
Dietary restrictions	TIS arm versus PBO arm: R-Det	0.89 (0.61, 1.31)	0.5584	1.0198
	TIS arm versus PBO arm: PFS	0.78 (0.63, 0.94)	0.0116	1.0070
	CFBL: R-Det	1.10 (1.08, 1.11)	0.0000	1.1874
	CFBL: PFS	1.01 (1.00, 1.01)	0.0978	1.0106
	R-Det frailty: PFS[b]	3.81 (0.98, 20.66)	0.0516	1.2261
Fatigue	TIS arm versus PBO arm: R-Det	0.96 (0.73, 1.27)	0.7724	1.0210
	TIS arm versus PBO arm: PFS	0.72 (0.55, 0.93)	0.0162	1.0224
	CFBL: R-Det	1.08 (1.07, 1.09)	0.0000	1.0212
	CFBL: PFS	1.00 (1.00, 1.01)	0.3002	1.0269
	R-Det frailty: PFS[b]	53.06 (10.11, 375.30)	0.0000	1.2619
Pain/discomfort	TIS arm versus PBO arm: R-Det	1.01 (0.75, 1.37)	0.9200	1.0287
	TIS arm versus PBO arm: PFS	0.70 (0.53, 0.92)	0.0084	1.1073
	CFBL: R-Det	1.10 (1.08, 1.11)	0.0000	1.0739
	CFBL: PFS	1.00 (0.99, 1.01)	0.6702	1.0482
	R-Det frailty: PFS[b]	52.39 (7.68, 864.09)	0.0000	**1.3480**
UGI symptoms	TIS arm versus PBO arm: R-Det	0.88 (0.65, 1.20)	0.4804	1.0215
	TIS arm versus PBO arm: PFS	0.73 (0.56, 0.94)	0.0073	1.0020
	CFBL: R-Det	1.11 (1.10, 1.13)	0.0000	1.0443
	CFBL: PFS	1.00 (0.99, 1.01)	0.7827	1.0189
	R-Det frailty: PFS[b]	29.35 (2.94, 400.21)	0.0000	1.0687

[a]Based on $\hat{R}$ statistic with values of 1 indicating acceptable convergence; all estimates except some frailty predictions (highlighted in bold) achieved acceptable convergence. [b]Association parameter and not HR. Significant effects are highlighted in blue.
CFBL, change from baseline; CI, confidence interval; HR, hazard ratio; PBO, placebo; PFS: progression-free survival; PRO, patient-reported outcomes; TIS, tislelizumab; R-Det, recurrent deterioration; UGI, upper gastrointestinal.

References

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