Impact of Tislelizumab + Chemotherapy Versus Placebo + Chemotherapy on Patient-Reported Symptoms and Disease Progression by Programmed Death-Ligand 1 Expression in Gastroesophageal Adenocarcinoma: A Post Hoc Analysis of the RATIONALE-305 Trial

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Poster 365. Presented at the American Society of Clinical Oncology (ASCO) Gastrointestinal Cancers Symposium; January 23–25, 2025; San Francisco, CA, USA

Conclusions

- **Tislelizumab + chemotherapy (T+C) was associated with a significantly lower risk of PFS for all PRO domains compared with placebo + chemotherapy (P+C)**
- **T+C demonstrated greater efficacy in the PD-L1 ≥1% subgroup for pain/discomfort, upper GI symptoms, and dietary restriction and in the PD-L1 ≥5% subgroup for GHS/QoL and dietary restriction, compared with P+C**
- **PRO-based recurrent symptomatic deterioration (RS-D) in GHS/QoL, physical functioning, fatigue, dysphagia-odynophagia, pain/discomfort, and dietary restriction in the PD-L1 ≥1% subgroup, and in GHS/QoL, pain/discomfort, and dietary restriction in the PD-L1 ≥5% subgroup, were leading predictors of disease progression, irrespective of treatment arm**
- **The joint survival model analyses suggest that patients' self-reported HRQoL can provide independent prognostic evidence for disease progression**

Background

- Gastric/gastroesophageal junction (G/GEJ) adenocarcinoma is an aggressive solid tumor with poor prognosis, including substantial negative impacts on health-related quality of life (HRQoL)
- Although patient-reported outcomes (PRO) are frequently collected in randomized clinical trials in oncology to measure HRQoL, they have not been fully examined for their potential prognostic capabilities, particularly in patients with G/GEJ adenocarcinoma
- The objectives of the current analyses were to apply a joint survival model to assess the prognostic associations between PRO-based treatment effects, RS-D events, and disease progression (defined as progression-free survival [PFS] events) in programmed death-ligand 1 (PD-L1) subgroups (≥1% and ≥5%) from the RATIONALE-305 trial population

Methods

Study Design and Patients

- RATIONALE-305 (NCT03777657) was a phase 3, randomized, double-blind, placebo-controlled trial assessing T+C as first-line treatment for patients with locally advanced, unresectable, or metastatic G/GEJ adenocarcinoma, regardless of PD-L1 expression

Measures

- PRO-based symptoms were assessed using the European Organisation for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire – Core (QLQ-C30) and Gastric Cancer Module (QLQ-STO22),[1] a questionnaire designed to assess gastric cancer-specific symptoms
  - Three QLQ-C30 domains were analyzed:
    - Global health status/quality of life (GHS/QoL), physical functioning, and fatigue
  - Four QLQ-STO22 domains were analyzed:
    - Dysphagia/odynophagia, pain/discomfort, upper gastrointestinal (GI) symptoms, and dietary restrictions
  - Both QLQ-C30 and QLQ-STO22 were administered at baseline and then every 3-week cycle until the end of treatment
- Investigator-assessed PFS was the terminal event measure, an RS-D event was defined as any change from baseline (CFBL) score ≥10[2] for both QLQ-C30 and QLQ-STO22
- For a deterioration event to qualify as a recurrent event, it had to be a unique event (eg, 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
- Analyses were conducted using the JMBayes2 package in R (version 4.3.2)

Results

- At data cutoff (February 28, 2023), the overall ITT population consisted of a total of 997 patients (N=501, T+C vs N=496, P+C)
- The joint model analytic samples included a total of 779 patients in the PD-L1 expression ≥1% subgroup (n=378, T+C vs n=401, P+C) and a total of 475 patients in the PD-L1 expression ≥5% subgroup (n=238, T+C vs n=237, P+C)
  - In the PD-L1 ≥1% and ≥5% subgroups, male participants comprised 70.8% (T+C) and 69.0% (P+C), and 75.9% (T+C) and 68.9% (P+C) of the subgroups, respectively, while female participants accounted for 29.2% and 31.0%, and 24.1% and 31.1%, respectively
  - The observed number of RS-D events ranged from 0 to 7, with approximately half of the analytic samples having at least 1 recurrent event

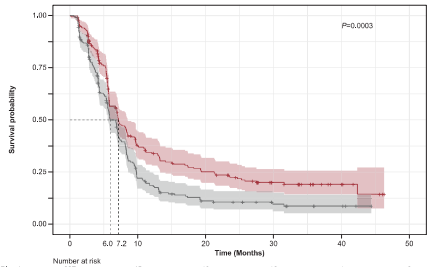
Kaplan-Meier Plot for PFS

- A statistically significant (*P*=0.0003) improvement in survival was observed for patients treated with T+C compared with P+C in the PD-L1 expression ≥5% subgroup (see **Figure 1** for a depiction of the QLQ-STO22 pain/discomfort domain for PFS)

Joint Model Evidence

- Patients in the T+C Arm experienced significantly greater symptom reductions in pain/discomfort, upper GI symptoms, and dietary restriction symptom scores (PD-L1 expression ≥1% subgroup; **Table 1**), as well as significantly greater improvement in GHS/QoL and significantly greater reduction in dietary restriction symptom scores (PD-L1 expression ≥5% subgroup; **Table 2**) compared with the P+C Arm
- Increasing CFBL in all PRO symptom scores and decreasing functional scores for both PD-L1 expression ≥1% and ≥5% subgroups were prognostic of an increased risk of RS-D events, irrespective of treatment, reflected by the recurrent – longitudinal parameter (**Tables 1** and **2**)
- Statistically significant reductions in the risk of PFS events was observed across all PRO domains, with a 24% to 31% reduced risk of disease progression for the PD-L1 expression ≥1% subgroup (**Table 1**) and a 35% to 45% reduced risk of disease progression for the PD-L1 expression ≥5% subgroup (**Table 2**)
- In the frailty Cox proportional hazards models, increasing RS-D events for GHS/QoL, physical functioning, fatigue, dysphagia-odynophagia, pain/discomfort, and dietary restriction symptom scores in the PD-L1 expression ≥1% subgroup (**Table 1**), and for GHS/QoL, pain/discomfort, and dietary restriction symptom scores in the PD-L1 expression ≥5% subgroup (**Table 2**), were strongly predictive of the risk of PFS, irrespective of treatment

Figure 1. Kaplan-Meier Plot for Pain/Discomfort Adjusted for PFS in the Joint Survival Model in Patients with PD-L1 Expression ≥5%



PD-L1, programmed death-ligand 1; PFS, progression-free survival.

Table 1. Joint Survival Models for QLQ-C30 and QLQ-STO22 Domain Scores Adjusted for PFS (Terminal Event), CFBL Treatment Effect, and RS-D in Patients with PD-L1 Expression ≥1%

Parameter	β (95% CI)	*P*-value	$\hat{R}^a$	HR (95% CI)
GHS/QoL				
CFBL – T+C effect[b]	1.69 (-0.04, 3.41)	0.0555	1.001	N/A
RS-D – longitudinal	-0.04 (-0.04, -0.03)	**<0.0001**	1.007	0.96 (0.96, 0.97)
Terminal event – T+C effect[b]	-0.37 (-0.69, -0.08)	**0.0105**	1.007	0.69 (0.50, 0.92)
Terminal event – RS-D (frailty)	5.30 (3.31, 7.73)	**<0.0001**	1.019	199.98 (27.32, 2278.15)[c]
Physical Functioning				
CFBL – T+C effect[b]	1.31 (-0.20, 2.84)	0.0936	1.006	N/A
RS-D – longitudinal	-0.02 (-0.03, -0.01)	**<0.0001**	1.032	0.98 (0.98, 0.99)
Terminal event – T+C effect[b]	-0.34 (-0.68, -0.05)	**0.0228**	1.009	0.71 (0.51, 0.96)
Terminal event – RS-D (frailty)	5.82 (3.73, 8.29)	**<0.0001**	1.020	335.55 (41.58, 3984.81)[c]
Fatigue				
CFBL – T+C effect[b]	-1.22 (-3.31, 0.91)	0.2537	1.001	N/A
RS-D – longitudinal	0.08 (0.07, 0.09)	**<0.0001**	1.005	1.08 (1.07, 1.09)
Terminal event – T+C effect[b]	-0.32 (-0.60, -0.06)	**0.0165**	1.006	0.73 (0.55, 0.94)
Terminal event – RS-D (frailty)	3.94 (1.59, 6.43)	**0.0083**	1.026	51.62 (4.89, 621.92)[c]
Dysphagia/Odynophagia				
CFBL – T+C effect[b]	-0.94 (-2.17, 0.31)	0.1383	1.001	N/A
RS-D – longitudinal	0.14 (0.12, 0.17)	**<0.0001**	1.009	1.15 (1.13, 1.18)
Terminal event – T+C effect[b]	-0.27 (-0.51, -0.06)	**0.0107**	1.007	0.76 (0.60, 0.94)
Terminal event – RS-D (frailty)	1.29 (0.16, 3.42)	**0.0240**	1.080	3.62 (1.17, 30.60)[c]
Pain/Discomfort				
CFBL – T+C effect[b]	-1.87 (-3.62, -0.12)	**0.0376**	1.005	N/A
RS-D – longitudinal	0.09 (0.08, 0.10)	**<0.0001**	1.008	1.09 (1.08, 1.10)
Terminal event – T+C effect[b]	-0.34 (-0.63, -0.08)	**0.0113**	1.004	0.71 (0.53, 0.92)
Terminal event – RS-D (frailty)	3.84 (1.90, 5.87)	**<0.0001**	1.002	46.59 (6.68, 354.27)[c]
Upper GI Symptoms				
CFBL – T+C effect[b]	-1.20 (-3.47, -0.52)	**0.0088**	1.004	N/A
RS-D – longitudinal	0.11 (0.10, 0.13)	**<0.0001**	1.042	1.12 (1.10, 1.13)
Terminal event – T+C effect[b]	-0.29 (-0.54, -0.07)	**0.0104**	1.005	0.75 (0.58, 0.94)
Terminal event – RS-D (frailty)	2.38 (-2.03, 5.51)	0.2325	1.068	10.75 (0.13, 247.39)[c]
Dietary Restrictions				
CFBL – T+C effect[b]	-1.75 (-3.37, -0.12)	**0.0352**	1.002	N/A
RS-D – longitudinal	0.10 (0.08, 0.11)	**<0.0001**	1.035	1.10 (1.09, 1.12)
Terminal event – T+C effect[b]	-0.28 (-0.53, -0.06)	**0.0131**	1.003	0.76 (0.59, 0.94)
Terminal event – RS-D (frailty)	1.69 (0.21, 4.28)	**0.0157**	1.162	5.40 (1.23, 72.05)[c]

[a]An $\hat{R}$ statistic with a value of 1.2 indicated acceptable convergence. [b]Treatment effect was coded as T+C versus P+C with the former as the effect group. [c]Association parameter and not HR.
Each model was adjusted for stratification factors. Significant effects are highlighted in **bold**.
CFBL, change from baseline; CI, confidence interval; GHS/QoL, global health status/quality of life; GI, gastrointestinal; HR, hazard ratio; NA, not applicable; P+C, placebo + chemotherapy; PD-L1, programmed death-ligand 1; PFS, progression-free survival; QLQ-C30, Quality of Life Questionnaire—Core; QLQ-STO22, Quality of Life Questionnaire—Gastric Cancer Module; RS-D, recurrent symptomatic deterioration; T+C, tislelizumab + chemotherapy.

Table 2. Joint Survival Models for QLQ-C30 and QLQ-STO22 Domain Scores Adjusted for PFS (Terminal Event), CFBL Treatment Effect, and R-SD in Patients with PD-L1 Expression ≥5%

Parameter	β (95% CI)	*P*-value	$\hat{R}^a$	HR (95% CI)
GHS/QoL				
CFBL – T+C effect[b]	2.91 (0.80, 5.06)	**0.0080**	1.002	N/A
RS-D – longitudinal	0.04 (-0.04, -0.03)	**<0.0001**	1.026	0.96 (0.96, 0.97)
Terminal event – T+C effect[b]	-0.60 (-1.03, -0.22)	**0.0024**	1.007	0.55 (0.36, 0.80)
Terminal event – RS-D (frailty)	4.46 (2.42, 6.84)	**0.0004**	1.012	86.42 (11.24, 932.03)[c]
Physical Functioning				
CFBL – T+C effect[b]	1.54 (-0.30, 3.38)	0.1003	1.006	N/A
RS-D – longitudinal	-0.02 (-0.03, -0.01)	**<0.0001**	1.028	0.98 (0.98, 0.99)
Terminal event – T+C effect[b]	-0.49 (-0.89, -0.17)	**0.0013**	1.008	0.61 (0.41, 0.85)
Terminal event – RS-D (frailty)	3.67 (-1.66, 6.94)	0.1396	1.081	39.19 (0.19, 1031.83)[c]
Fatigue				
CFBL – T+C effect[b]	-0.94 (-3.44, 1.54)	0.4485	1.001	N/A
RS-D – longitudinal	0.08 (0.07, 0.09)	**<0.0001**	1.018	1.08 (1.07, 1.10)
Terminal event – T+C effect[b]	-0.47 (-0.85, -0.18)	**0.0004**	1.032	0.63 (0.43, 0.84)
Terminal event – RS-D (frailty)	2.35 (-2.36, 5.69)	0.2573	1.079	10.44 (0.10, 296.34)[c]
Dysphagia/Odynophagia				
CFBL – T+C effect[b]	-0.85 (-2.41, 0.74)	0.2989	1.002	N/A
RS-D – longitudinal	0.12 (0.09, 0.15)	**<0.0001**	1.090	1.12 (1.10, 1.16)
Terminal event – T+C effect[b]	-0.45 (-0.74, -0.19)	**0.0008**	1.003	0.64 (0.48, 0.83)
Terminal event – RS-D (frailty)	0.68 (-0.12, 2.02)	0.0916	1.025	1.97 (0.89, 7.50)[c]
Pain/Discomfort				
CFBL – T+C effect[b]	-1.04 (-3.12, 1.06)	0.3273	1.012	N/A
RS-D – longitudinal	0.09 (0.08, 0.11)	**<0.0001**	1.052	1.10 (1.08, 1.12)
Terminal event – T+C effect[b]	-0.54 (-0.93, -0.21)	**0.0001**	1.008	0.58 (0.40, 0.81)
Terminal event – RS-D (frailty)	3.25 (1.26, 5.69)	**0.0051**	1.008	25.71 (3.52, 295.10)[c]
Upper GI Symptoms				
CFBL – T+C effect[b]	-1.44 (-3.15, 0.29)	0.1032	1.001	N/A
RS-D – longitudinal	0.11 (0.09, 0.13)	**<0.0001**	1.042	1.12 (1.10, 1.14)
Terminal event – T+C effect[b]	-0.43 (-0.71, -0.17)	**0.0008**	1.001	0.65 (0.49, 0.84)
Terminal event – RS-D (frailty)	0.94 (-3.27, 4.78)	0.6253	1.003	2.56 (0.04, 118.60)[c]
Dietary Restrictions				
CFBL – T+C effect[b]	-1.94 (-3.86, -0.03)	**0.0475**	1.002	N/A
RS-D – longitudinal	0.08 (0.06, 0.10)	**<0.0001**	1.053	1.08 (1.07, 1.10)
Terminal event – T+C effect[b]	-0.49 (-0.84, -0.20)	**0.0011**	1.031	0.61 (0.43, 0.82)
Terminal event – RS-D (frailty)	1.49 (0.34, 3.34)	**0.0077**	1.249	4.44 (1.40, 28.20)[c]

[a]An $\hat{R}$ statistic with a value of 1.2 indicated acceptable convergence. [b]Treatment effect was coded as T+C versus P+C with the former as the effect group. [c]Association parameter and not HR.
Each model was adjusted for stratification factors. Significant effects are highlighted in **bold**.
CFBL, change from baseline; CI, confidence interval; GHS/QoL, global health status/quality of life; GI, gastrointestinal; HR, hazard ratio; NA, not applicable; P+C, placebo + chemotherapy; PD-L1, programmed death-ligand 1; PFS, progression-free survival; QLQ-C30, Quality of Life Questionnaire—Core; QLQ-STO22, Quality of Life Questionnaire—Gastric Cancer Module; RS-D, recurrent symptomatic deterioration; T+C, tislelizumab + chemotherapy.

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Acknowledgments

We would like to thank the investigators, site support staff, and especially the patients for participating in this study. This study was sponsored by BeiGene, Ltd. Medical writing support, under the direction of the authors, was provided by Jason Allaire, PhD of Generativity Solutions Group and was funded by BeiGene. Editorial support, under the direction of the authors, was provided by Envision Pharma Inc., and was funded by BeiGene.

Presenter Disclosures

Marcia Cruz Correa holds patents and royalties from Johns Hopkins University; Research funding from AbbVie, BeiGene, Bristol-Myers Squibb/Celgene, Genentech/Roche, GENFIT, HUYA Bioscience International, Janssen, Lilly, Merck, Pfizer, Regeneron, VMO; Stock and other ownership from Pan American Center for Oncology Trials.

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