

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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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/GJ) 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/GJ 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/GJ 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-SC22).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-SC22 domains were analyzed:
 - Dysphagia/odynophagia, pain/discomfort, upper gastrointestinal (GI) symptoms, and dietary restrictions
 - Both QLQ-C30 and QLQ-SC22 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 (CBFL) score ≥10² for both QLQ-C30 and QLQ-SC22
 - 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-SC22 were eligible
 - Analyses were conducted using the JMBayes2 package in R (version 4.3.2)

Results

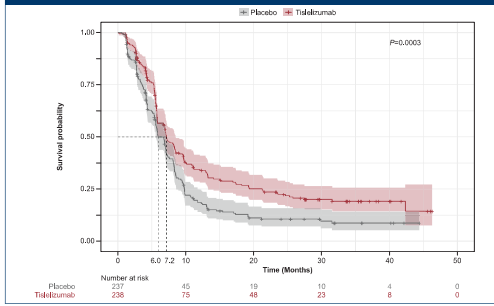
- At data cutoff (February 28, 2023), the overall ITT population consisted of a total of 997 patients (N=501, T+C vs N=496, P+C)

- 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-SC22 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 CBFL 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%



References
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2. Osoba D et al. J Clin Oncol. 1998;16(1):139-44.

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Table 1. Joint Survival Models for QLQ-C30 and QLQ-SC22 Domain Scores Adjusted for PFS (Terminal Event), CBFL Treatment Effect, and RS-D in Patients with PD-L1 Expression ≥1%

Parameter	β (95% CI)	P-value	R ²	HR (95% CI)
GHS/QoL				
CBFL – T+C effect ^a	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	0.89 (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				
CBFL – T+C effect ^a	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				
CBFL – T+C effect ^a	-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				
CBFL – T+C effect ^a	-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)	1.28 (0.16, 3.42)	0.0240	1.080	3.62 (1.17, 30.60) ^c

Pain/Discomfort				
CBFL – T+C effect ^a	-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	1.08 (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				
CBFL – T+C effect ^a	-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				
CBFL – T+C effect ^a	-1.75 (-3.37, -0.12)	0.0362	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)	1.89 (0.21, 4.28)	0.0157	1.162	5.40 (1.23, 72.05) ^c

^aSee Appendix Table 1 for all 22 symptom scores. ^bSee Appendix Table 2 for all 22 symptom scores. ^cSee Appendix Table 3 for all 22 symptom scores. ^dSee Appendix Table 4 for all 22 symptom scores. ^eSee Appendix Table 5 for all 22 symptom scores. ^fSee Appendix Table 6 for all 22 symptom scores. ^gSee Appendix Table 7 for all 22 symptom scores. ^hSee Appendix Table 8 for all 22 symptom scores. ⁱSee Appendix Table 9 for all 22 symptom scores. ^jSee Appendix Table 10 for all 22 symptom scores. ^kSee Appendix Table 11 for all 22 symptom scores. ^lSee Appendix Table 12 for all 22 symptom scores. ^mSee Appendix Table 13 for all 22 symptom scores. ⁿSee Appendix Table 14 for all 22 symptom scores. ^oSee Appendix Table 15 for all 22 symptom scores. ^pSee Appendix Table 16 for all 22 symptom scores. ^qSee Appendix Table 17 for all 22 symptom scores. ^rSee Appendix Table 18 for all 22 symptom scores. ^sSee Appendix Table 19 for all 22 symptom scores. ^tSee Appendix Table 20 for all 22 symptom 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