Impact of Tislelizumab + Chemotherapy Versus Placebo + Chemotherapy on Patient-Reported Symptoms and Overall Survival by Programmed Death-Ligand 1 Expression in Advanced or Metastatic Esophageal Squamous Cell Carcinoma: A Post Hoc Analysis of the RATIONALE-306 Trial

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Conclusions

- Tislelizumab + chemotherapy (T+C) demonstrated greater efficacy in patient-reported physical functioning (PD-L1 ≥5% subgroup) and pain symptoms (PD-L1 ≥1% and ≥5% subgroups) compared with placebo + chemotherapy (P+C)
- T+C showed significantly lower risk of death across all PRO domains in the PD-L1 ≥1% and ≥5% subgroups compared with P+C
- Statistically significant associations were observed between PRO-based recurrent symptomatic deterioration (RS-D) events and longitudinal symptom trajectories, irrespective of treatment arm
- These findings suggest that patients' self-reported HRQoL may provide independent prognostic value for OS, reinforcing the role of T+C as a standard first-line therapy for advanced or metastatic ESCC

Background

- Esophageal squamous cell carcinoma (ESCC) is an aggressive solid tumor with poor prognosis,[1] often associated with debilitating patient-reported symptoms that negatively impact health-related quality of life (HRQoL)[2–4]
- Improved overall survival (OS) has been previously demonstrated;[5] however, the independent prognostic value of patient-reported outcome (PRO)-based symptom endpoints for survival outcomes in patients with ESCC has not been extensively examined
- The objectives of the current analyses were to apply a joint survival model framework to assess the prognostic associations between PRO-based treatment effects, RS-D events, and OS in PD-L1 subgroups (≥1% and ≥5%) with ESCC from the RATIONALE-306 trial population

Methods

Study Design and Patients

- The RATIONALE-306 (NCT03783442) study was a randomized, double-blind, placebo-controlled, global phase 3 trial assessing T+C as first-line treatment for patients with unresectable, locally advanced recurrent or metastatic ESCC

Measures

- PRO-based symptoms were assessed using the European Organisation for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire – Core (QLQ-C30)[6] and the Oesophageal Cancer Module (QLQ-OES18),[7] a questionnaire designed to assess esophageal cancer symptoms
  - Three QLQ-C30 domains were analyzed:
    - Global health status/quality of life (GHS/QoL), physical functioning, and fatigue
  - Four QLQ-OES18 domains were analyzed:
    - Reflux, trouble with eating, pain, and dysphagia
  - Both QLQ-C30 and QLQ-OES18 were administered at baseline and at every treatment cycle (up to 6 cycles), then every other cycle, and at safety follow-up
- OS was the terminal event measure, an RS-D event for both QLQ-C30 and QLQ-OES18 was defined as a change from baseline (CFBL) score of ≥10[8] indicating worsening
- 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-OES18 were eligible
- Analyses were conducted using the JMBayes2 package in R (version 4.3.2)

Results

- At data cutoff (February 28, 2022), the overall ITT population consisted of a total of 649 patients (n=326, T+C vs n=323, P+C)
- The joint survival model analytic samples included a total of 468 patients in the PD-L1 expression ≥1% subgroup (n=226, T+C vs n=242, P+C) and a total of 216 patients in the PD-L1 expression ≥5% subgroup (n=113, T+C vs n=103, P+C)
  - In the PD-L1 ≥1% and ≥5% subgroups, male participants comprised 88.4% (T+C) and 85.0% (P+C), and 88.8% (T+C) and 82.1% (P+C) of the subgroups, respectively, while female participants accounted for 11.6% and 15.0%, and 11.2% and 17.9%, respectively
  - The observed number of RS-D events ranged from 0 to 5; 167 patients (99.4%) in the T+C Arm and 173 patients (97.2%) in the P+C Arm experienced ≥1 recurrent event

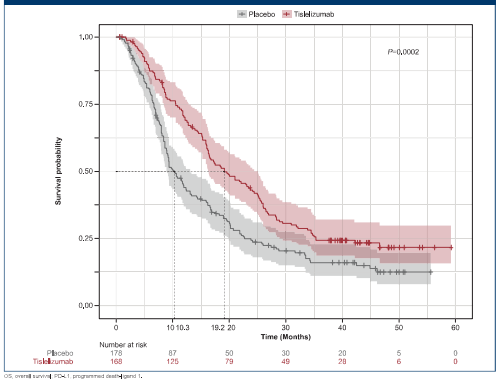
Kaplan-Meier Plot for OS

- Statistically significant (*P*=0.0002) 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** as an illustration of the QLQ-C30 physical function domain for OS)

Joint Model Evidence

- Patients in the T+C Arm experienced significantly greater reductions in pain symptom scores (PD-L1 expression ≥1% and ≥5% subgroups; **Tables 1** and **2**) as well as significantly greater improvement in physical functioning (PD-L1 expression ≥5% subgroup; **Table 2**) compared with the P+C Arm
- Increasing PRO symptom scores (fatigue, reflux, trouble with eating, pain, and dysphagia) and decreasing physical functioning for both the 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 death were observed across each of the PRO domains, reflecting a 32%–39% (hazard ratio [HR] range: 0.68–0.65) reduction for the PD-L1 expression ≥1% subgroup (**Table 1**) and a 32%–45% (HR range: 0.68–0.55) reduction for the PD-L1 expression ≥5% subgroup (**Table 2**)

Figure 1. Kaplan-Meier Plot for Physical Functioning Adjusted for OS in the Joint Survival Model in Patients with PD-L1 Expression ≥5% (Illustration)



OS, overall survival; PD-L1, programmed death-ligand 1.

Table 1. Joint Survival Models for QLQ-C30 and QLQ-OES18 Domain Scores Adjusted for OS, CFBL Treatment Effect, and RS-D Events 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]	1.56 (-0.60, 3.70)	0.1539	1.002	NA
RS-D event – longitudinal effect	0.00 (-0.00, 0.01)	0.5927	1.026	1.00 (0.10, 1.01)
Terminal event – T+C effect[b]	-0.39 (-0.64, -0.16)	**0.0015**	1.007	0.68 (0.53, 0.86)
Terminal event – RS-D event (frailty)	-0.25 (-5.69, 4.34)	0.9609	1.022	0.78 (0.00, 76.88)[c]
Physical Functioning				
CFBL – T+C effect[b]	1.68 (-0.11, 3.49)	0.0647	1.001	NA
RS-D event – longitudinal effect	0.03 (0.02, 0.04)	**<0.0001**	1.013	1.03 (1.02, 1.04)
Terminal event – T+C effect[b]	-0.43 (-0.87, -0.09)	**0.0093**	1.095	0.65 (0.42, 0.91)
Terminal event – RS-D event (frailty)	-4.28 (-8.40, 3.32)	0.2732	1.296	0.01 (0.00, 27.60)[c]
Fatigue				
CFBL – T+C effect[b]	-1.91 (-4.21, 0.32)	0.0964	1.002	NA
RS-D event – longitudinal effect	0.01 (0.01, 0.02)	**<0.0001**	1.162	1.01 (1.01, 1.02)
Terminal event – T+C effect[b]	-0.42 (-0.73, -0.17)	**0.0005**	1.016	0.66 (0.48, 0.84)
Terminal event – RS-D event (frailty)	-0.01 (-5.95, 6.32)	0.9873	1.024	0.99 (0.00, 553.09)[c]
Reflux				
CFBL – T+C effect[b]	-1.39 (-3.18, 0.38)	0.1252	1.002	NA
RS-D event – longitudinal effect	0.05 (0.04, 0.06)	**<0.0001**	1.101	1.05 (1.04 1.06)
Terminal event – T+C effect[b]	-0.45 (-0.81, -0.18)	**0.0011**	1.074	0.64 (0.45, 0.84)
Terminal event – RS-D event (frailty)	-1.52 (-6.32, 4.18)	0.5943	1.127	0.22 (0.00, 65.25)[c]
Trouble with Eating				
CFBL – T+C effect[b]	-0.09 (-0.18, 0.01)	0.0924	1.001	N/A
RS-D event – longitudinal effect	1.24 (0.99, 1.51)	**<0.0001**	1.040	3.46 (2.70, 4.52)
Terminal event – T+C effect[b]	-0.49 (-0.94, -0.18)	**0.0004**	1.110	0.61 (0.39, 0.83)
Terminal event – RS-D event (frailty)	1.62 (-4.67, 6.72)	0.6647	1.129	5.05 (0.01, 832.34)[c]
Pain				
CFBL – T+C effect[b]	-2.35 (-3.85, -0.87)	**0.0028**	1.001	NA
RS-D event – longitudinal effect	0.04 (0.03, 0.05)	**<0.0001**	1.146	1.04 (1.03, 1.05)
Terminal event – T+C effect[b]	-0.44 (-0.79, -0.18)	**0.0004**	1.005	0.65 (0.46, 0.84)
Terminal event – RS-D event (frailty)	-0.80 (-6.57, 5.06)	0.8185	1.001	0.45 (0.00, 157.47)[c]
Dysphagia				
CFBL – T+C effect[b]	1.37 (-2.81, 5.48)	0.5173	1.001	NA
RS-D event – longitudinal effect	0.02 (0.02, 0.03)	**<0.0001**	1.091	1.02 (1.02, 1.03)
Terminal event – T+C effect[b]	-0.46 (-0.76, -0.21)	**0.0007**	1.007	0.63 (0.47, 0.81)
Terminal event – RS-D event (frailty)	0.01 (-5.25, 6.07)	0.9803	1.025	1.01 (0.01, 433.61)[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 not an HR.
Each model was adjusted for stratification factors, significant effects are highlighted in bold and *P*-values are presented in full.
CFBL, change from baseline; CI, confidence interval; GHS/QoL, global health status/quality of life; HR, hazard ratio; NA, not assessed; OS, overall survival; P+C, placebo + chemotherapy; PD-L1, programmed death-ligand 1; QLQ-C30, Quality of Life Questionnaire – Core; QLQ-OES18, Quality of Life Questionnaire – Oesophageal Cancer Module; RS-D, recurrent symptomatic deterioration; T+C, tislelizumab + chemotherapy.

Table 2. Joint Survival Models for QLQ-C30 and QLQ-OES18 Domain Scores Adjusted for OS, CFBL Treatment Effect, and RS-D Events 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]	1.87 (-0.72, 4.45)	0.1553	1.001	NA
RS-D event – longitudinal effect	-0.00 (-0.01, 0.01)	0.9409	1.002	1.00 (0.99, 1.01)
Terminal event – T+C effect[b]	-0.45 (-0.73, -0.19)	**0.0007**	1.000	0.64 (0.48, 0.83)
Terminal event – RS-D event (frailty)	0.07 (-4.53, 4.90)	0.9820	1.011	1.07 (0.01, 134.53)[c]
Physical Functioning				
CFBL – T+C effect[b]	2.21 (0.02, 4.41)	**0.0476**	1.002	NA
RS-D event – longitudinal effect	0.02 (0.02, 0.03)	**<0.0001**	1.002	1.02 (1.02, 1.03)
Terminal event – T+C effect[b]	-0.39 (-0.71, -0.10)	**0.0071**	1.005	0.68 (0.49, 0.91)
Terminal event – RS-D event (frailty)	-0.61 (-5.79, 4.08)	0.8480	1.011	0.54 (0.00, 59.12)[c]
Fatigue				
CFBL – T+C effect[b]	-2.24 (-5.09, 0.59)	0.1216	1.002	NA
RS-D event – longitudinal effect	0.01 (0.01, 0.02)	**0.0003**	1.042	1.01 (1.01, 1.02)
Terminal event – T+C effect[b]	-0.53 (-0.87, -0.24)	**<0.0001**	1.001	0.59 (0.42, 0.79)
Terminal event – RS-D event (frailty)	-0.41 (-5.52, 4.16)	0.8947	1.001	0.67 (0.00, 64.25)[c]
Reflux				
CFBL – T+C effect[b]	-1.06 (-3.11, 1.04)	0.3229	1.006	NA
RS-D event – longitudinal effect	0.05 (0.04, 0.06)	**<0.0001**	1.018	1.05 (1.04, 1.06)
Terminal event – T+C effect[b]	-0.52 (-0.90, -0.21)	**0.0008**	1.046	0.60 (0.41, 0.81)
Terminal event – RS-D event (frailty)	-0.34 (-5.91, 5.50)	0.9059	1.019	0.71 (0.00, 245.11)[c]
Trouble with Eating				
CFBL – T+C effect[b]	-0.08 (-0.20, 0.04)	0.1913	1.000	NA
RS-D event – longitudinal effect	1.28 (0.97, 1.64)	**<0.0001**	1.102	3.60 (2.65, 5.13)
Terminal event – T+C effect[b]	-0.61 (-1.10, -0.24)	**0.0009**	1.051	0.55 (0.33, 0.78)
Terminal event – RS-D event (frailty)	-1.62 (-6.13, 5.53)	0.5403	1.205	0.20 (0.00, 251.54)[c]
Pain				
CFBL – T+C effect[b]	-2.43 (-4.38, -0.48)	**0.0149**	1.008	NA
RS-D event – longitudinal effect	0.03 (0.02, 0.05)	**<0.0001**	1.053	1.04 (1.02, 1.05)
Terminal event – T+C effect[b]	-0.53 (-0.97, -0.21)	**0.0001**	1.031	0.59 (0.38, 0.82)
Terminal event – RS-D event (frailty)	-1.03 (-6.38, 5.21)	0.7329	1.147	0.36 (0.00, 182.96)[c]
Dysphagia				
CFBL – T+C effect[b]	1.35 (-3.48, 6.19)	0.5877	1.002	NA
RS-D event – longitudinal effect	0.03 (0.02, 0.03)	**<0.0001**	1.035	1.03 (1.02, 1.03)
Terminal event – T+C effect[b]	-0.61 (-1.12, -0.27)	**<0.0001**	1.020	0.55 (0.33, 0.77)
Terminal event – RS-D event (frailty)	1.43 (-4.38, 6.48)	0.6808	1.003	4.17 (0.01, 648.82)[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 not an HR.
Each model was adjusted for stratification factors, significant effects are highlighted in bold and *P*-values are presented in full.
CFBL, change from baseline; CI, confidence interval; GHS/QoL, global health status/quality of life; HR, hazard ratio; NA, not assessed; OS, overall survival; P+C, placebo + chemotherapy; PD-L1, programmed death-ligand 1; QLQ-C30, Quality of Life Questionnaire – Core; QLQ-OES18, Quality of Life Questionnaire – Oesophageal Cancer Module; RS-D, recurrent symptomatic deterioration; T+C, tislelizumab + chemotherapy.

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