Tislelizumab Versus Chemotherapy as Second-Line Treatment for Advanced or Metastatic Esophageal Squamous Cell Carcinoma (Rationale 302): Impact on Health-Related Quality of Life

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Background (1)

- ESCC is the most common histological subtype of esophageal cancer, accounting for more than 85% of esophageal cancers worldwide[1,2]
- Standard second-line therapy for advanced or metastatic ESCC typically consists of single-agent taxane or irinotecan
  - The efficacy of this therapy is limited, with marginal antitumor activity, poor long-term survival, and significant toxicities[2-6]
- Tislelizumab, a monoclonal antibody against PD-1, was specifically engineered to minimize binding to the Fcγ receptor on macrophages in order to abrogate antibody-dependent phagocytosis, a mechanism of T-cell clearance and potential resistance to anti-PD-1 therapy

ESCC Esophageal squamous cell carcinoma; PD-1, Programmed cell death protein 1.

1. Wang QL, et al. *Clin Epidemiol.* 2018;10:717-728; 2. Huang J, et al. *Lancet Oncol.* 2020;21:832-842; 3. Assersohn L, et al. *Lancet Oncol.* 2014;15:78-86; 4. Ford HE, et al. *Lancet Oncol.* 2014;15:78-86; 5. Kato K, et al. *Lancet Oncol.* 2019;20:1506-1517; 6. Kojima T, et al. *J Clin Oncol.* 2020;38:4138-4148.

Background (2)

- RATIONALE 302 was a global, open-label, randomized, phase 3 study (NCT03430843) that investigated tislelizumab compared with ICC as second-line treatment for patients with advanced or metastatic ESCC
  - Overall survival was significantly improved with tislelizumab versus ICC (median, 8.6 vs 6.3 months; hazard ratio, 0.70 [95% CI, 0.57-0.85]; P = .0001)
  - Treatment with tislelizumab was associated with a higher objective response rate (20.3% vs 9.8%) and a more durable antitumor response (median, 7.1 months vs 4.0 months) versus ICC
  - Fewer patients experienced Grade ≥ 3 treatment-related adverse events with tislelizumab compared with ICC (18.8% vs 55.8%)

ESCC Esophageal squamous cell carcinoma; ICC, investigator-chosen chemotherapy; PD-1, Programmed cell death protein 1.

Methods

- The study population consisted of adult patients (aged ≥ 18 years) with histologically confirmed ESCC who had advanced or metastatic disease which progressed during or after first-line systemic treatment
  - Eligible patients were randomized (1:1) to receive tislelizumab (200 mg) IV every 3 weeks or ICC of the following single-agent chemotherapies: paclitaxel, docetaxel, or irinotecan IV on defined schedules
  - Treatment discontinuation was triggered upon disease progression, intolerable toxicity, or withdrawal for other reasons
- HRQoL was a secondary endpoint and was assessed using PROs via 3 validated PRO instruments:
  - The EORTC QLQ-C30
  - The EORTC QLQ-OES18[1]
  - The EQ-5D-5L VAS[2]

EORTC, European Organization for Research and Treatment of Cancer; ESCC, Esophageal squamous cell carcinoma; EQ-5D-5L, EuroQoL Five-Dimensions Five-Levels; HRQoL, Health-related quality of life; ICC, investigator-chosen chemotherapy; PD-1, Programmed cell death protein 1; PROs, patient reported outcomes; QLQ-C30, Quality of Life Questionnaire Core 30 items; QLQ-OES18, Quality of Life Questionnaire Esophageal Cancer Module OES18; VAS, visual analogue scale.

1. Blazeby JM, et al. *Eur J Cancer.* 2003;39:1384-1394; 2. Pickard AS, et al. *Med Care.* 2007;45:259-263.

HRQoL Assessments and Endpoints

- The PRO measures were collected at baseline and at every cycle through Cycle 6 or until treatment discontinuation (whichever occurred first)
- The key PRO endpoints included:
  - EORTC QLQ-C30 GHS/QoL, physical functioning, and fatigue scales
  - EORTC QLQ-OES18 index score (total symptoms) dysphagia, reflux, eating, and pain symptom scores
  - Additionally, EQ-5D-5L VAS scores were included in the analysis
- Higher scores in GHS/QoL, physical functioning, and VAS, and lower scores in fatigue scales and OES18 symptom scores indicated better HRQoL outcomes

EORTC, European Organization for Research and Treatment of Cancer; GHS/QoL, Global Health Status/Quality of Life; HRQoL, Health-related quality of life; QLQ-C30, Quality of Life Questionnaire Core 30 items; QLQ-OES18, Quality of Life Questionnaire Esophageal Cancer Module OES18; VAS, visual analogue scale.

Statistical Analysis

- All analyses were conducted using the data cutoff of December 1, 2020
- The completion rate was defined as the number of patients who completed the questionnaire out of the total number of patients in the relevant treatment arm
- The adjusted completion rate was defined as the proportion of patients who completed the questionnaire out of the total number of patients in the study at the relevant visit in the relevant treatment arm
- LS mean score change from baseline to Cycle 4 and Cycle 6 were assessed using a mixed model for repeated measurement with the change from baseline in the key PRO endpoints score as the response variable
  - Study visit, treatment by study visit interaction, baseline mean score by study visit interaction, and randomization stratification factors (ECOG performance status [0 vs 1] and ICC option [paclitaxel vs docetaxel vs irinotecan]) were covariates based upon the “missing at random” assumption
- Mean change from baseline in the EQ-VAS was analyzed descriptively
- Time to deterioration was defined as time to first onset of a ≥ 10-point change in direction of worsening from baseline with confirmation by a subsequent decrease from baseline using the Kaplan-Meier method
  - A stratified Cox model with Efron’s method of tie handling was used to assess between-group differences
- Nominal p values are reported here

ECOG, Eastern Cooperative Oncology Group; EQ-VAS, visual analogue scale; ICC, investigator-chosen chemotherapy; LS, least squares; PRO, patient-reported outcome.

Demographics and Baseline Characteristics (ITT)

	Tislelizumab (n = 256)	ICC (n = 256)
Median age, years (range)	62.0 (40-86)	63.0 (35-81)
Patients < 65 years, n (%)	157 (61.3)	161 (62.9)
Patients ≥ 65 years, n (%)	99 (38.7)	95 (37.1)
Sex		
Male	217 (84.8)	215 (84.0)
Female	39 (15.2)	41 (16.0)
Geographic region		
Asia	201 (78.5)	203 (79.3)
Europe/North America	55 (21.5)	53 (20.7)
ECOG performance status, n (%)		
0	66 (25.8)	60 (23.4)
1	190 (74.2)	196 (76.6)
Smoking status, n (%)		
Never	68 (26.6)	63 (24.6)
Former/Current	188 (73.4)	192 (75.0)
Missing	0 (0.0)	1 (0.4)
Previous therapies, n (%)		
Surgery	94 (36.7)	99 (38.7)
Radiotherapy	169 (66.0)	163 (63.7)
Platinum-based chemotherapy	249 (97.3)	252 (98.4)
Disease stage at study entry, n (%)		
Locally advanced	5 (2.0)	20 (7.8)
Metastatic	251 (98.0)	236 (92.2)

ECOG, Eastern Cooperative Oncology Group; ITT, intent-to-treat; PD-L1, programmed death-ligand 1; vCPS, visually estimated combined positive score.

Completion Rates

- QLQ-C30, QLQ-OES18, and EQ-5D-5L completion rates at baseline were 93.8% or greater
  - At Cycle 4, the completion rate dropped to 57% in the tislelizumab arm and 30% in the ICC arm
  - At Cycle 6, the completion rate declined to 39% in the tislelizumab arm and 15% in the ICC arm
- For all 3 measures, the adjusted completion rates remained consistent and were 92% or greater across all assessments

	Tislelizumab (n = 256)	ICC (n = 256)
EORTC QLQ-C30		
Baseline		
Patients in study at visit, n	256	256
Completion rate[a], n (%)	242 (94.5)	247 (96.5)
Adjusted completion rate (%)[b]	94.5	96.5
Cycle 4		
Patients in study at visit, n	157	83
Completion rate[a], n (%)	147 (57.4)	77 (30.1)
Adjusted PRO completion rate (%)[b]	93.6	92.8
Cycle 6		
Patients in study at visit, n	100	39
Completion rate[a], n (%)	99 (38.7)	38 (14.8)
Adjusted completion rate (%)[b]	99.0	97.4

	Tislelizumab (n = 256)	ICC (n = 256)
EORTC QLQ-OES18		
Baseline		
Patients in study at visit, n	256	256
Completion rate[a], n (%)	240 (93.8)	248 (96.9)
Adjusted completion rate (%)[b]	93.8	96.9
Cycle 4		
Patients in study at visit, n	157	83
Completion rate[a], n (%)	146 (57.0)	76 (29.7)
Adjusted completion rate (%)[b]	93.0	91.6
Cycle 6		
Patients in study at visit, n	100	39
Completion rate[a], n (%)	99 (38.7)	37 (14.5)
Adjusted completion rate (%)[b]	99.0	94.9

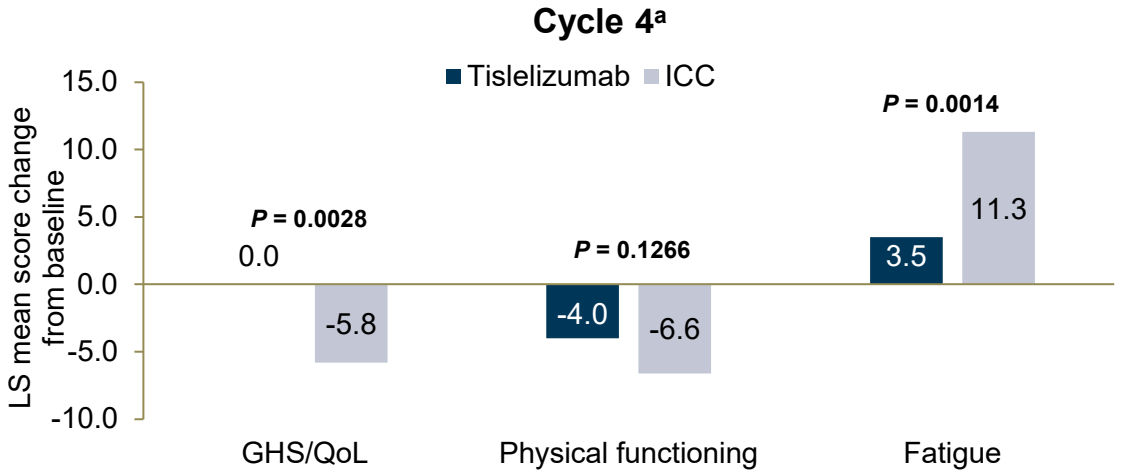
	Tislelizumab (n = 256)	ICC (n = 256)
EQ-5D-5L		
Baseline		
Patients in study at visit, n	256	256
Completion rate[a], n (%)	242 (94.5)	248 (96.9)
Adjusted completion rate (%)[b]	94.5	96.9
Cycle 4		
Patients in study at visit, n	157	83
Completion rate[a], n (%)	147 (57.4)	77 (30.1)
Adjusted completion rate (%)[b]	93.6	92.8
Cycle 6		
Patients in study at visit, n	100	39
Completion rate[a], n (%)	99 (38.7)	37 (14.5)
Adjusted completion rate (%)[b]	99.0	94.9

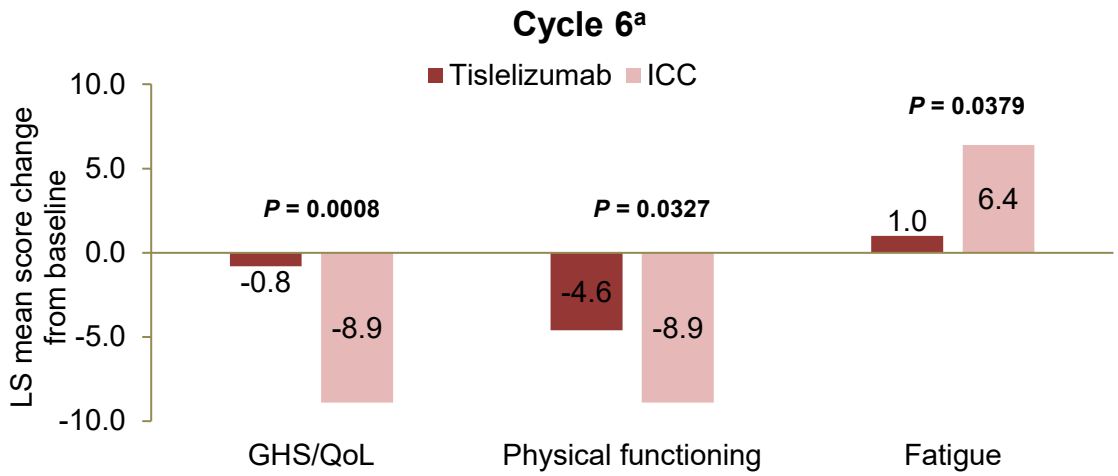
[a]Completion rate = number of patients with completed questionnaire/total number of patients in relevant treatment arm. [b]Adjusted completion rate = number of patients with completed questionnaire/total number of patients in study at relevant visits in relevant treatment arm.

EORTC, European Organization for Research and Treatment of Cancer; EQ-5D-5L, EuroQoL Five-Dimensions Five-Levels; HRQoL, health-related quality of life; ICC, investigator-chosen chemotherapy; PRO, patient-reported outcome; QLQ-C30, Quality of Life Questionnaire Core 30; QLQ-OES18, Quality of Life Questionnaire Esophageal Cancer Module OES18.

Change from Baseline for EORTC QLQ-C30 Scores

- Changes from baseline in GHS/QoL were significantly less at Cycles 4 and 6 in tislelizumab-treated patients compared to the ICC arm
- There were no differences in change from baseline between the arms at Cycle 4 in physical functioning
  - At Cycle 6, the decline in physical functioning from baseline was significantly less in the tislelizumab arm compared with the ICC arm
- Fatigue increased at Cycles 4 and 6 for both tislelizumab and ICC arms
  - At both cycles the increase in fatigue was significantly less in the tislelizumab arm

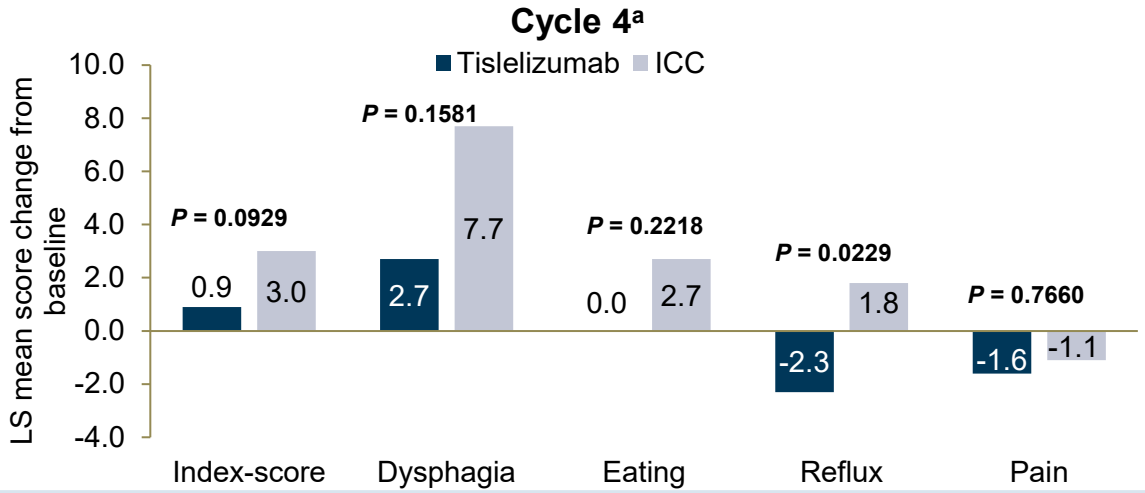


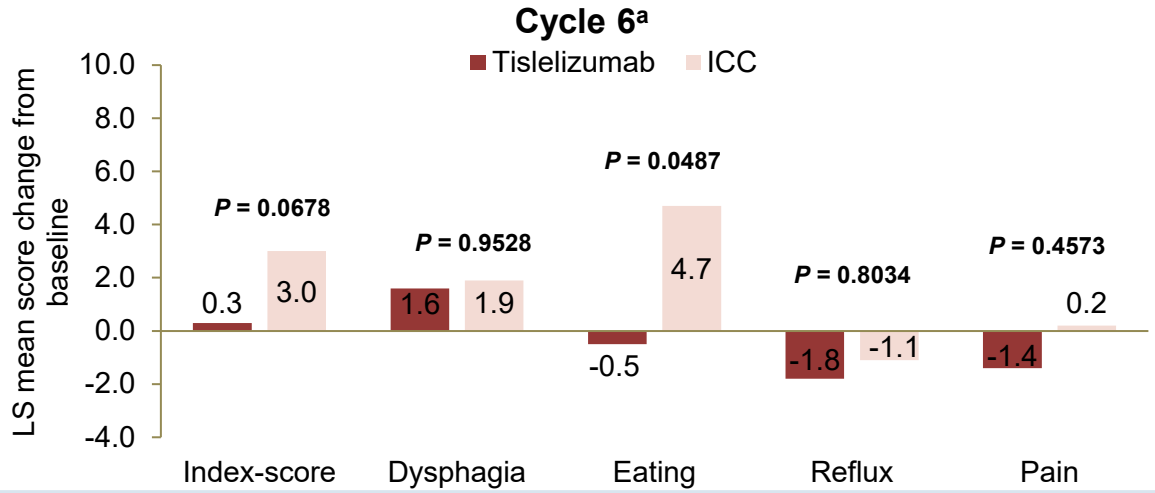


[a]Patients with baseline and at least one post-baseline measurement.
CI, confidence interval; EORTC, European Organization for Research and Treatment of Cancer; ICC, investigator-chosen chemotherapy; GHS/QoL, Global Health Status/Quality of Life; LS, least square; QLQ-OES18, Quality of Life Questionnaire Esophageal Cancer Module.

Change from Baseline for EORTC QLQ-OES18 Scores

- Change from baseline in the OES18 index, dysphagia, and pain did not differ between the 2 arms at Cycles 4 and 6
- Patients in the tislelizumab arm experienced similar eating symptoms at Cycle 4, but had improvement at Cycle 6 when compared to the ICC arm
- For reflux at Cycle 4, change from baseline was significant, with patients in the tislelizumab arm experiencing fewer reflux symptoms at Cycle 4 compared with the ICC arm
  - At Cycle 6, patients in both arms experienced similar and slight decreases from baseline in reflux





[a]Patients with baseline and at least one post-baseline measurement.
CI, confidence interval; ICC, investigator-chosen chemotherapy; LS, least square; QLQ-OES18, Quality of Life Questionnaire Esophageal Cancer Module.

Change from Baseline for EQ-5D-5L VAS Scores

- At Cycle 4, patients in the tislelizumab arm experienced less decrease in health status according to the VAS score compared with the ICC arm
- At Cycle 6, patients in the tislelizumab arm continued to experience less decrease in health status compared with the ICC Arm

	Tislelizumab (n = 256)		ICC (n = 256)	
	Observed mean (SD)	Change from baseline mean (SD)	Observed mean (SD)	Change from baseline mean (SD)
Baseline	73.7 (17.05)		72.5 (18.13)	
Cycle 4	77.5 (14.77)	-0.2 (10.91)	70.8 (17.01)	-1.8 (14.17)
Cycle 6	78.5 (16.03)	-0.6 (14.81)	73.8 (16.32)	-5.9 (16.34)

EQ-5D-5L VAS, EuroQoL Five-Dimensions Five-Level visual analogue scale; ICC, investigator-chosen chemotherapy; SD, standard deviation.

Time to Deterioration

- Deterioration in physical functioning was experienced by fewer patients in the tislelizumab arm than in the ICC arm
  - Time to deterioration in physical functioning was significantly longer with tislelizumab than chemotherapy
- Deterioration in reflux was experienced by fewer patients in the tislelizumab arm than in the ICC arm
  - Time to deterioration in reflux was significantly longer with tislelizumab than chemotherapy
- There were no significant differences in time to deterioration for GHS/QoL, dysphagia, eating, or pain

		Tislelizumab (n = 256)	ICC (n = 256)
QLQ-C30 GHS/QoL	Patients with event, n (%)	59 (23.0)	47 (18.4)
	Median time to deterioration, months (95% CI)	NR (NE, NE)	NR (NE, NE)
	Stratified[1] hazard ratio, 95% CI	0.96 (0.65, 1.41)	
	Stratified[1] log-rank test P value	0.4156	
QLQ-C30 Physical Functioning	Patients with event, n (%)	47 (18.4)	52 (20.3)
	Median time to deterioration, months (95% CI)	NR (NE, NE)	10.0 (4.5, NE)
	Stratified[1] hazard ratio, 95% CI	0.67 (0.45, 1.00)	
	Stratified[1] log-rank test P value	0.0239	
QLQ-OES18 Dysphagia	Patients with event, n (%)	63 (24.6)	63 (24.6)
	Median time to deterioration, months (95% CI)	NR (NE, NE)	NR (3.7, NE)
	Stratified[1] hazard ratio, 95% CI	0.76 (0.53, 1.07)	
	Stratified[1] log-rank test P value	0.0562	
QLQ-OES18 Eating	Patients with event, n (%)	35 (13.7)	27 (10.5)
	Median time to deterioration, months (95% CI)	NR (NE, NE)	NR (NE, NE)
	Stratified[1] hazard ratio, 95% CI	1.06 (0.64, 1.75)	
	Stratified[1] log-rank test P value	0.4158	
QLQ-OES18 Reflux	Patients with event, n (%)	32 (12.5)	45 (17.6)
	Median time to deterioration, months (95% CI)	NR (15.1, NE)	NR (NE, NE)
	Stratified[1] hazard ratio, 95% CI	0.50 (0.32, 0.80)	
	Stratified[1] log-rank test P value	0.0014	
QLQ-OES18 Pain	Patients with event, n (%)	49 (19.1)	44 (17.2)
	Median time to deterioration, months (95% CI)	NR (NE, NE)	NR (NE, NE)
	Stratified[1] hazard ratio, 95% CI	0.89 (0.59, 1.35)	
		0.2969	

CI, confidence interval; EORTC, European Organization for Research and Treatment of Cancer; GHS/QoL, Global Health Status/Quality of Life; ICC, investigator-chosen chemotherapy; NE, not estimated; NR, not reached; QLQ-C30, Quality of Life Questionnaire Core 30; QLQ-OES18, Quality of Life Questionnaire Esophageal Cancer Module.

Conclusions

- Tislelizumab as a second-line treatment for patients with advanced or metastatic ESCC was associated with more favorable HRQoL outcomes than investigator-chosen chemotherapy
- The general health and QoL of tislelizumab-treated patients remained stable while ICC-treated patients experienced a decline
  - In addition, tislelizumab-treated patients experienced less worsening in physical functioning and fatigue than ICC patients
- Improvements were observed in the disease-specific symptoms of eating and reflux in the tislelizumab arm relative to the ICC arm
- Time to deterioration analysis showed that through the course of treatment, patients in the tislelizumab arm were at lower risk of worsening of physical functioning and the disease-related symptom of reflux
- While the results of this study are encouraging, they should be considered alongside the following limitations:
  - First, the study was open-label and had limited follow-up time (eg, through 6 cycles) to assess change in patients' HRQoL
  - Second, the completion rate of the QLQ-C30 and QLQ-OES18 at Cycles 4 and 6 were markedly lower than at baseline
- These HRQoL data, together with the efficacy and safety results from the RATIONALE 302 trial, support the favorable risk-benefit ratio for tislelizumab as a second-line therapy for patients with advanced or metastatic ESCC

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