Examining the Impact of Tislelizumab Added to Chemotherapy on Health-Related Quality of Life (HRQoL) Outcomes in Patients With Advanced or Metastatic Esophageal Squamous Cell Carcinoma (ESCC): The RATIONALE-306 Study

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Jianming Xu,[1] Paula Jimenez-Fonseca,[2] Ken Kato,[3] Yongqian Shu,[4] Sook Ryun Park,[5] Richard Hubner,[6] Eric Raymond,[7] Harry H Yoon,[8] Sebastian Yan,[9] Bryant Barnes,[9] Alberto Prieto Patron,[10] Silvy Mardiguian,[9] Gisoo Barnes[9]

[1]Fifth Medical Center, Chinese PLA General Hospital, Beijing, China; [2]Central University Hospital of Asturias, ISPA, Oviedo, Spain; [3]National Cancer Center Hospital, Tokyo, Japan; [4]The First Affiliated Hospital of Nanjing Medical University, Nanjing, China; [5]Asan Medical Center, University of Ulsan College of Medicine, Seoul, South Korea; [6]Department of Medical Oncology, The Christie NHS Foundation Trust/Division of Cancer Sciences, University of Manchester, Manchester, UK; [7]Centre Hospitalier Paris Saint-Joseph, Paris, France; [8]Department of Oncology, Mayo Clinic, Rochester, MN, USA; [9]BeiGene USA, Inc., San Mateo, CA, USA; [10]BeiGene Switzerland GmbH, Basel, Switzerland

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Conclusions

- **At Cycle 6, compared with patients receiving placebo plus chemotherapy, those receiving tislelizumab plus chemotherapy experienced clinically meaningful improvement in pain and less worsening in physical functioning. Both arms showed reduction in pain at Cycle 8, with a greater reduction observed in the tislelizumab plus chemotherapy arm**
- **Key PRO symptoms were better or comparable in patients receiving tislelizumab plus chemotherapy versus those receiving placebo plus chemotherapy**
- **These results, alongside the clinical benefits such as PFS and OS, support the use of 1L treatment with tislelizumab plus chemotherapy in patients with unresectable, locally advanced, recurrent, or metastatic ESCC**

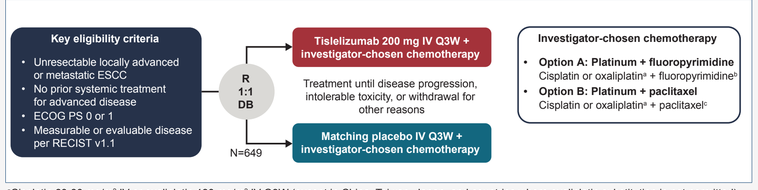
Background

- Esophageal squamous cell carcinoma is the most common histological subtype of esophageal cancers (EC), accounting for more than 85% of EC worldwide[1,2]
- Individuals with ESCC experience severe symptom burden and associated reductions in HRQoL[3-6]
- In the global, randomized, Phase 3 RATIONALE-306 trial (NCT03783442), first-line (1L) treatment with tislelizumab plus chemotherapy (T+C) demonstrated statistically significant and clinically meaningful improvement in overall survival versus placebo plus chemotherapy (P+C) in patients with unresectable, locally advanced, recurrent, or metastatic ESCC
  - Patients receiving T+C experienced significant improvements in progression-free survival (PFS) and overall response rate (ORR), with a more durable tumor response compared with P+C
- In RATIONALE-306, HRQoL was a secondary endpoint measured by patient-reported outcomes (PROs). The purpose of the current analysis was to assess HRQoL in patients treated with T+C in the RATIONALE-306 study

Methods

- Patients were randomized to receive either tislelizumab 200 mg intravenously (IV) every 3 weeks (Q3W) plus investigator-chosen chemotherapy (ICC), or placebo IV Q3W plus ICC (**Figure 1**)

Figure 1. RATIONALE-306 Study Design



[a]Cisplatin 60-80 mg/m² IV or oxaliplatin 130 mg/m² IV Q3W (except in China, Taiwan, Japan, and countries where oxaliplatin substitution is not permitted) according to site or investigator preference or standard practice. Platinum therapy may be stopped after 6 cycles, per site or investigator preference or standard practice. If platinum treatment is stopped, the non-platinum agent may continue at the regular schedule.
[b]5-fluorouracil 750-800 mg/m² IV on Days 1-5 Q3W or capecitabine 1000 mg/m² orally BID on Days 1-14.
[c]Paclitaxel 175 mg/m² IV Q3W.
BID, twice daily; DB, double-blind; ECOG PS, Eastern Cooperative Oncology Group Performance Status; ESCC, esophageal squamous cell carcinoma; IV, intravenously; Q3W, every 3 weeks; R, randomized; RECIST, Response Evaluation Criteria in Solid Tumors; v, version.

Assessments

- PROs were assessed at baseline (Day 1 of Cycle 1) and the key clinical cycles 6 and 8
- The following key PRO endpoints were pre-selected based on their relevance to ESCC and treatment side effects, as well as their use in previous studies[4-6]
  - European Organisation for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire – Core 30 (QLQ-C30): global health status/quality of life (GHS/QoL), physical functioning, and fatigue symptom scales
    - Higher scores on the GHS/QoL and physical functioning scales indicate better HRQoL or functioning, whereas a higher score on the fatigue symptom scale suggests worse symptoms
  - EORTC QLQ – Oesophageal Cancer 18 question module (QLQ-OES18): dysphagia, difficulty eating, reflux, pain symptoms, and the index score
    - Higher scores on the QLQ-OES18 indicate worse symptoms or problems

Statistical Analyses

- The data cut-off date was February 28, 2022, and all randomized patients who completed the baseline and at least 1 post-baseline PRO questionnaire were included in the analyses
- Adjusted completion rates, defined as the ratio of the number of patients who completed the questionnaires at each visit divided by the number still undergoing treatment, were reported
- Change from baseline in each key PRO endpoint to Cycle 6 and Cycle 8 was analyzed using a constrained longitudinal data analysis model
  - The model included baseline score, stratification factors, treatment arm, visit, and treatment arm by visit interaction as fixed effects and visit as a repeated measure
  - Between-group comparisons were reported as differences in the least squares (LS) mean change from baseline with 95% confidence intervals (CI)
  - A clinically meaningful change was defined as a ≥5-point mean change from baseline[7-9]
- Time to deterioration (TTD) was defined as time to first onset of a ≥10-point change in the worsening direction from baseline with confirmation by a subsequent worsening in the following cycle

Results

- A total of 649 patients were randomized to receive T+C (n=326) or P+C (n=323)
- Patient demographics and baseline disease characteristics were generally balanced across treatment arms (**Table 1**)
- In both arms, most patients were male (87%), from Asian countries and Asian race (75%), current or former smokers (76% [T+C], 72% [P+C])

Adjusted Completion Rates

- The adjusted completion rates were >92% and consistent across treatment arms at each assessment timepoint

Change From Baseline to Cycle 6

- At Cycle 6, the difference in LS mean between the arms on the GHS/QoL was significant (3.3 [95% CI, 0.4-6.2]) with the T+C arm maintaining and the P+C arm declining (**Figure 2**)
- For physical functioning, both arms experienced worsening but change from baseline was greater in the P+C arm (2.6 [95% CI, 0.0-5.1])
- Patients receiving T+C experienced a clinically meaningful reduction in mean pain symptoms at Cycle 6 (-5.2 [95% CI, -6.7 to -3.7])

Change From Baseline to Cycle 8

- Changes from baseline on the key domains were generally maintained in patients treated with T+C (**Figure 3**)
- Both arms experienced similar clinically meaningful worsening in physical functioning and fatigue
- Both arms showed reduction in pain at Cycle 8, with a greater reduction observed in the T+C arm

Time to Deterioration

- Results from TTD analyses showed that the risk of clinically meaningful worsening across all PRO endpoints were similar between treatment arms (**Table 2**)

Table 1. Baseline Demographic and Clinical Characteristics (Intent-to-Treat Population)

	Tislelizumab + Chemotherapy (n=326)	Placebo + Chemotherapy (n=323)
Age, years		
Median (IQR)	64.0 (59.0-68.0)	65.0 (58.0-70.0)
<65	176 (54)	161 (50)
≥65	150 (46)	162 (50)
Sex		
Male	282 (87)	281 (87)
Female	44 (13)	42 (13)
Geographical region		
Asia	243 (75)	243 (75)
Europe	79 (24)	77 (24)
North America	1 (<1)	1 (<1)
Oceania	3 (1)	2 (1)
Race		
Asian	243 (75)	243 (75)
White	79 (24)	76 (24)
American Indian or Alaska Native	0 (0)	1 (<1)
Not reported or unknown	4 (1)	3 (1)
BMI, kg/m² (IQR)	21.2 (19.4-23.4)	21.2 (18.9-24.1)
ECOG performance status		
0	109 (33)	104 (32)
1	217 (67)	219 (68)
Smoking status		
Never	68 (21)	81 (25)
Current or former	247 (76)	231 (72)
Missing	11 (3)	11 (3)
Disease status at study entry		
Locally advanced	47 (14)	41 (13)
Metastatic	279 (86)	282 (87)
Number of metastatic sites at study entry		
0	47 (14)	41 (13)
1	144 (44)	143 (44)
2	81 (25)	80 (25)
>2	54 (17)	59 (18)
Histological type		
Squamous cell carcinoma	325 (>99)	323 (100)
Other	1 (<1)	0
PD-L1 expression		
TAP score ≥10%	116 (36)	107 (33)
TAP score <10%	151 (46)	168 (52)
Unknown	59 (18)	48 (15)

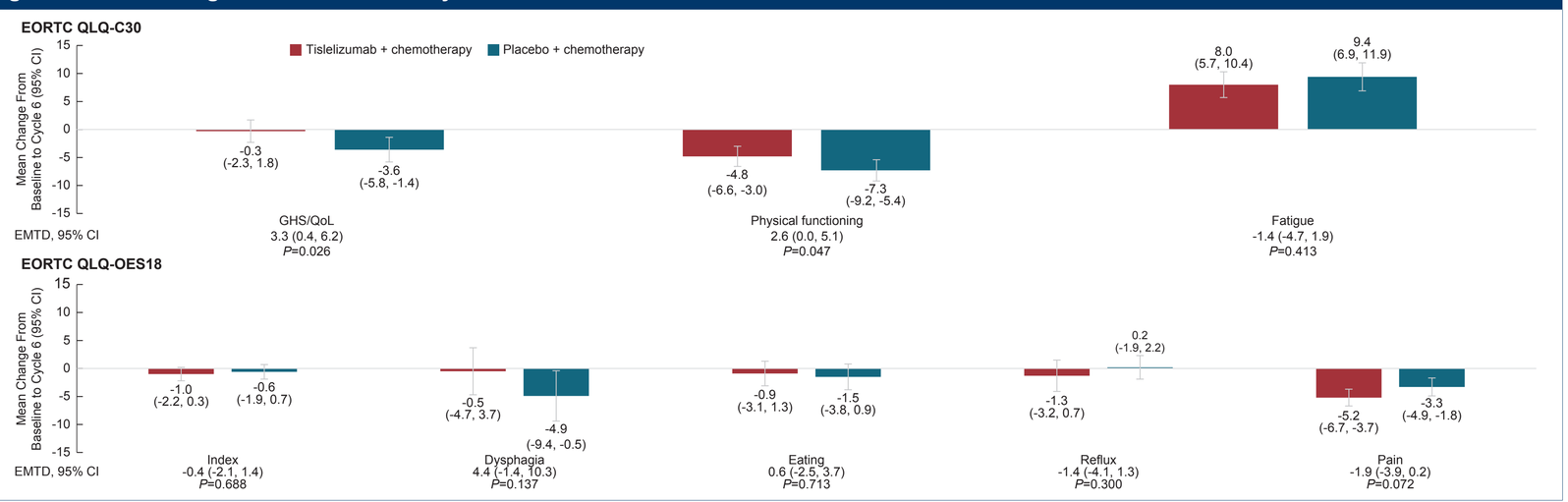
Data are presented as n (%) unless otherwise indicated.
BMI, body mass index; ECOG, Eastern Cooperative Oncology Group; IQR, interquartile range; PD-L1, programmed death-ligand 1; TAP, tumor area positivity.

Table 2. Time to Deterioration (TTD)

		Tislelizumab + Chemotherapy (n=326)	Placebo + Chemotherapy (n=323)
EORTC QLQ-C30			
GHS/QoL	**Patients**		
	Worsened	109 (33.4)	98 (30.3)
	Censored	217 (66.6)	225 (69.7)
	Median TTD, months (95% CI)[a]	27.1 (14.6-NE)	NR (9.5-NE)
	One-sided stratified log-rank test *P*-value[b]	0.4290	
	Stratified HR (95% CI)[c]	0.98 (0.74-1.29)	
Physical functioning	**Patients**		
	Worsened	106 (32.5)	103 (31.9)
	Censored	220 (67.5)	220 (68.1)
	Median TTD, months (95% CI)[a]	NR (11.9-NE)	18.8 (8.1-NE)
	One-sided stratified log-rank test *P*-value[b]	0.0448	
	Stratified HR (95% CI)[c]	0.79 (0.60-1.04)	
EORTC QLQ-OES18			
Dysphagia	**Patients**		
	Worsened	112 (34.4)	106 (32.8)
	Censored	214 (65.6)	217 (67.2)
	Median TTD, months (95% CI)[a]	NR (13.6-NE)	NR (8.9-NE)
	One-sided stratified log-rank test *P*-value[b]	0.2647	
	Stratified HR (95% CI)[c]	0.92 (0.70-1.20)	
Eating	**Patients**		
	Worsened	77 (23.6)	67 (20.7)
	Censored	249 (76.4)	256 (79.3)
	Median TTD, months (95% CI)[a]	NR (NE-NE)	26.7 (19.6-NE)
	One-sided stratified log-rank test *P*-value[b]	0.4881	
	Stratified HR (95% CI)[c]	1.00 (0.72-1.39)	
Reflux	**Patients**		
	Worsened	83 (25.5)	64 (19.8)
	Censored	243 (74.5)	259 (80.2)
	Median TTD, months (95% CI)[a]	NR (NE-NE)	NR (17.3-NE)
	One-sided stratified log-rank test *P*-value[b]	0.7985	
	Stratified HR (95% CI)[c]	1.15 (0.83-1.60)	
Pain	**Patients**		
	Worsened	63 (19.3)	64 (19.8)
	Censored	263 (80.7)	259 (80.2)
	Median TTD, months (95% CI)[a]	NR (NE-NE)	24.4 (24.4-NE)
	One-sided stratified log-rank test *P*-value[b]	0.0976	
	Stratified HR (95% CI)[c]	0.79 (0.56-1.13)	

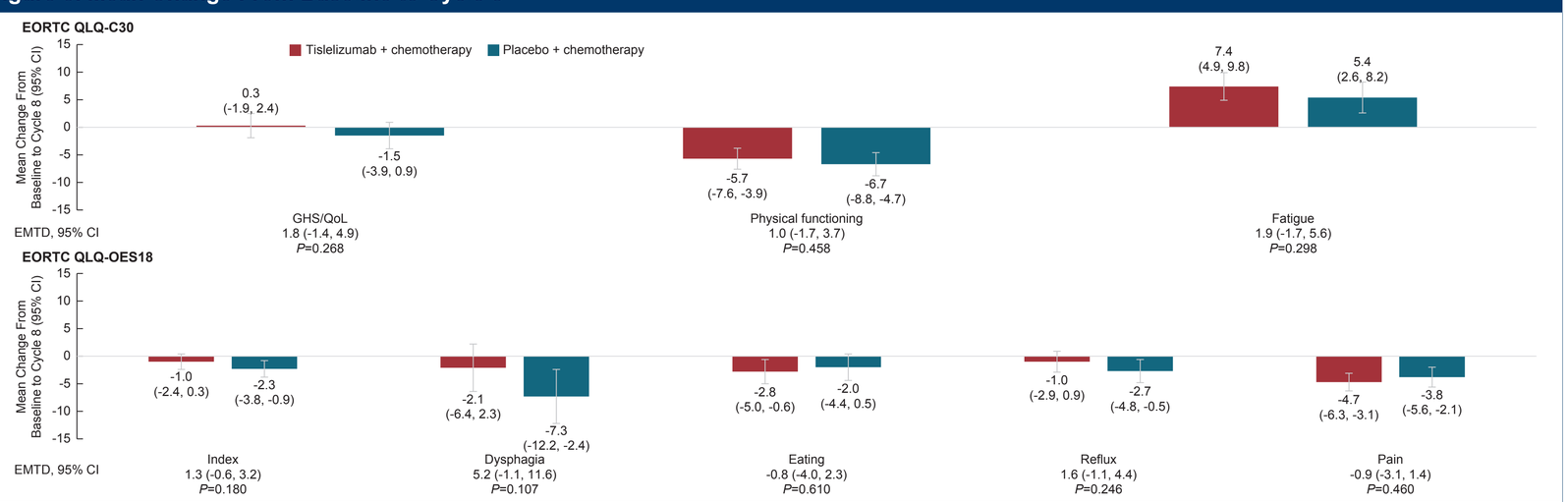
Data are presented as n (%) unless otherwise indicated. Event free rates were estimated by Kaplan-Meier method with 95% CIs estimated using the Greenwood's formula.
[a]Estimates are based on Kaplan-Meier method.
[b]One-sided *P*-value was estimated from log rank test stratified by pooled geographic region (Asia vs Rest of World) per IRT, prior definitive therapy (Yes vs No) per IRT, and ICC option (Investigator choice of chemotherapy [platinum with fluoropyrimidine vs platinum with paclitaxel]) per IRT, for descriptive purpose only.
[c]Hazard ratio is based on Cox regression model including treatment as covariate and stratified by pooled geographic region (Asia vs Rest of World) per IRT, prior definitive therapy (Yes vs No) per IRT, and ICC option (Investigator choice of chemotherapy [platinum with fluoropyrimidine vs platinum with paclitaxel]) per IRT.
CI, confidence interval; EORTC QLQ-C30, European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire – Core 30; EORTC QLQ-OES18, European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire – Oesophageal Cancer 18 question module; GHS/QoL, global health status/quality of life; HR, hazard ratio; IRT, interactive response technology; NE, not estimable; NR, not reached; TTD, time to deterioration.

Figure 2. Mean Change From Baseline to Cycle 6



Higher scores on the GHS/QoL and physical functioning scales indicate better HRQoL or functioning, whereas a higher score on the fatigue symptom scale suggests worse symptoms. Higher scores on the QLQ-OES18 indicate worse symptoms or problems.
CI, confidence interval; EMTD, estimated mean treatment difference; EORTC QLQ-C30, European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire – Core 30; EORTC QLQ-OES18, European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire – Oesophageal Cancer 18 question module; GHS/QoL, global health status/quality of life.

Figure 3. Mean Change From Baseline to Cycle 8



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Presenter Disclosures

Alberto Prieto Patron is employed by BeiGene and may hold stock or other ownership.

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Contact: gisoo.barnes@beigene.com (Gisoo Barnes)