# Impact of Tislelizumab on Health-Related Quality of Life in Asian Patients with Esophageal Squamous Cell Carcinoma

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**Sung-Bae Kim, MD[1]; Eric Van Cutsem, MD[2]; Jaffer Ajani, MD[3]; Lin Shen, MD[4]; Gisoo Barnes, PhD[5]; Ningning Ding, MD[6]; Aiyang Tao, PhD[7]; Tianyu Xia, MS[6]; Lin Zhan, MS[5]; Ken Kato, MD[8]**

[1]Department of Oncology, Asan Medical Center, University of Ulsan College of Medicine, Seoul, South Korea; [2]University Hospitals Gasthuisberg Leuven and KU Leuven, Leuven, Belgium; [3]University of Texas MD Anderson Cancer Center, Houston, Texas; [4]Department of Gastrointestinal Oncology, Key Laboratory of Carcinogenesis and Translational Research (Ministry of Education/Beijing), Peking University Cancer Hospital & Institute, Beijing, China; [5]BeiGene, Ltd., Emeryville, CA, USA; [6]BeiGene (Beijing) Co., Ltd., Beijing, China; [7]BeiGene, Ltd., Ridgefield Park, NJ, USA; [8]National Cancer Center Hospital, Tokyo, Japan

## Introduction

- Although incidence of esophagus adenocarcinoma is highest among White adults, incidence of esophageal squamous cell carcinoma (ESCC) is highest in Asian adults[1]
  - The incidence of esophageal cancer is the highest in Eastern Asia (12.2 per 100,000 people)[2]
  - Globally, the Asian continent accounts for 78% of all esophageal cancer deaths[2]
- Individuals with ESCC experience severe symptom burden and associated reductions in health-related quality of life (HRQoL) at diagnosis as well as with advancing disease severity[3-6]
- Tislelizumab, a monoclonal antibody against programmed cell death protein-1 (PD-1), was specifically engineered to minimize binding to 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
- RATIONALE-302 was a global, open-label, randomized, phase 3 study (NCT03430843) that investigated tislelizumab compared with investigator-chosen chemotherapy (ICC) as second-line treatment for patients with advanced or metastatic ESCC[7]
  - Overall survival was significantly improved with tislelizumab vs ICC (median, 8.6 vs 6.3 months; hazard ratio [HR] 0.70 [95% CI 0.57–0.85], *P*=0.0001)
  - Treatment with tislelizumab was associated with higher objective response rate (20.3% vs 9.8%) and a more durable anti-tumor response (median, 7.1 months vs 4.0 months) vs ICC
  - Fewer patients experienced Grade ≥3 treatment-related adverse events (18.8% vs 55.8%) with tislelizumab as compared to ICC
  - Analysis of the intent-to-treat (ITT) population of RATIONALE-302 found overall HRQoL, fatigue, and physical functioning were maintained in patients receiving tislelizumab while worsening in patients receiving ICC[8]
- Given the heavy disease burden of ESCC in the Asian population, the current post-hoc analysis examined whether tislelizumab could improve HRQoL and reduce symptom burden compared with chemotherapy in the Asian subgroup of patients in RATIONALE-302

## 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) or ICC of the following single-agent chemotherapies: paclitaxel, docetaxel, or irinotecan. Tislelizumab was administered intravenously every three weeks until no further clinical benefit was observed
- HRQoL was a secondary endpoint and was assessed using patient-reported outcomes (PROs) via three validated PRO instruments:
  - The European Organisation for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire Core 30 items (QLQ-C30)
  - The EORTC Quality of Life Questionnaire Esophageal Cancer Module OES18 (QLQ-OES18)[7]
  - The EuroQoL Five-Dimensions Five-Levels (EQ-5D-5L) Visual Analogue Score (VAS)[8]

### HRQoL Assessments and Endpoints

- The PRO measures were collected at baseline, and at every cycle through Cycle 6 or until treatment discontinuation (whichever occured first)
- The key PRO endpoints included:
  - EORTC QLQ-C30 Global Health Status/Quality of Life (GHS/QoL), physical functioning, and fatigue scales
  - EORTC QLQ-OES18 index score (total symptoms), dysphagia, reflux, eating, and pain symptom scores
- Higher scores in GHS/QoL and physical functioning and lower scores in fatigue scales and OES18 symptoms scores indicated better HRQoL outcomes

### Statistical Analyses

- All analyses were conducted using the data cutoff of 15 January 2021
- Completion rate was defined as the number of patients that completed the questionnaire from the total number of patients in the relevant treatment arm
- Adjusted completion rate was defined as the proportion of patients that completed the questionnaire from the total number of patients in the study at the relevant visit in the relevant treatment arm
- Least-squares (LS) mean score change from baseline to Week 12 and Week 18 was assessed using a mixed model for repeated measures with the change from baseline in PRO key endpoints score as the response variable, and treatment, 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]) as covariates, based on the missing at random assumption

## Conclusions

- **Tislelizumab monotherapy as a second-line treatment for Asian patients with advanced or metastatic ESCC was associated with more favorable HRQoL outcomes than ICC**
- **The results of this post-hoc analysis of the Asian subgroup largely mirrored those previously reported in the ITT population of RATIONALE-302**
  - **For the EORTC QLQ-C30, like in the ITT population, the Asian subgroup that received tislelizumab demonstrated maintenance in GHS/QoL at Weeks 12 and 18 while ICC-treated patients declined**
  - **Similar to the ITT population, the Asian subgroup receiving tislelizumab experienced less fatigue than the ICC arm at Weeks 12 and 18**
  - **Maintenance in problem eating and dysphagia, and improvements in reflux symptoms in the tislelizumab arm relative to the ICC arm were observed, which was also observed in the ITT population**
- **These HRQoL results in Asian patients support the HRQoL findings in the ITT population, indicating tislelizumab is a potential new second-line treatment option for patients with advanced or metastatic ESCC**

## Results

### Patient Characteristics

- Patient demographics and baseline disease characteristics are presented in **Table 1**
  - Like the ITT population, the proportion of patients with metastatic disease was slightly higher in the Asian Subgroup receiving tislelizumab than ICC

**Table 1. Patient Demographics and Baseline Characteristics**

| | Asian Subgroup | | ITT Population | |
|---|---|---|---|---|
| | Tislelizumab (n = 201) | ICC (n = 203) | Tislelizumab (n = 256) | ICC (n = 256) |
| **Age** | | | | |
| Median, years (range) | 61.0 (40-83) | 62.0 (41-81) | 62.0 (40-86) | 63.0 (35-81) |
| <65 years, n (%) | 132 (65.7) | 137 (67.5) | 157 (61.3) | 161 (62.9) |
| ≥65 years, n (%) | 69 (34.3) | 66 (32.5) | 99 (38.7) | 95 (37.1) |
| **Sex, n (%)** | | | | |
| Male | 180 (89.6) | 179 (88.2) | 217 (84.8) | 215 (84.0) |
| Female | 21 (10.4) | 24 (11.8) | 39 (15.2) | 41 (16.0) |
| **Race, n (%)** | | | | |
| Asian Indian | 0 (0.0) | 0 (0.0) | 0 (0.0) | 3 (1.2) |
| Chinese | 161 (80.1) | 162 (79.8) | 161 (62.9) | 163 (63.7) |
| Japanese | 25 (12.4) | 25 (12.3) | 25 (9.8) | 25 (9.8) |
| Korean | 15 (7.5) | 16 (7.9) | 15 (5.9) | 16 (6.3) |
| White/Caucasian | 0 (0.0) | 0 (0.0) | 53 (20.7) | 44 (17.2) |
| Black/African American | 0 (0.0) | 0 (0.0) | 0 (0.0) | 2 (0.8) |
| Not Reported | 0 (0.0) | 0 (0.0) | 1 (0.4) | 0 (0.0) |
| Unknown | 0 (0.0) | 0 (0.0) | 1 (0.4) | 2 (0.8) |
| **Ethnicity** | | | | |
| Hispanic or Latino | 0 (0.0) | 0 (0.0) | 2 (0.8) | 2 (0.8) |
| Not Hispanic or Latino | 201 (100.0) | 203 (100.0) | 252 (98.4) | 252 (98.4) |
| Unknown/not reported | 0 (0.0) | 0 (0.0) | 2 (0.8) | 2 (0.8) |
| **ECOG performance status, n (%)** | | | | |
| 0 | 43 (21.4) | 42 (20.7) | 66 (25.8) | 60 (23.4) |
| 1 | 158 (78.6) | 161 (79.3) | 190 (74.2) | 196 (76.6) |
| **Smoking status, n (%)** | | | | |
| Never | 55 (27.4) | 48 (23.6) | 68 (26.6) | 63 (24.6) |
| Former | 135 (67.2) | 136 (67.0) | 162 (63.3) | 159 (62.1) |
| Current | 11 (5.5) | 18 (8.9) | 26 (10.2) | 33 (12.9) |
| Missing | 0 (0.0) | 1 (0.5) | 0 (0.0) | 1 (0.4) |
| **Previous therapies, n (%)** | | | | |
| Chemotherapy | 71 (35.3) | 80 (39.4) | 94 (36.7) | 101 (39.5) |
| Chemo-Radiotherapy | 129 (64.2) | 123 (60.6) | 161 (62.9) | 155 (60.5) |
| Other | 1 (0.5) | 0 (0.0) | 1 (0.4) | 0 (0.0) |
| **Disease stage at study entry, n (%)** | | | | |
| Locally advanced | 3 (1.5) | 14 (6.9) | 5 (2.0) | 20 (7.8) |
| Metastatic | 198 (98.5) | 189 (93.1) | 251 (98.0) | 236 (92.2) |

**Abbreviations:** ECOG, Eastern Cooperative Oncology Group; ICC, investigator-chosen chemotherapy; ITT, intent-to-treat.

### Completion Rates

- For the QLQ-C30 and the QLQ-OES18, the completion rates and adjusted completion rates for the Asian subgroup were comparable to that of the ITT population
- In the Asian subgroup at baseline the completion rates were ≥95.5%, as were the adjusted completion rates (**Table 2**)
  - At Weeks 12 and 18 the completion rates and the adjusted completion rates remained high (≥96.4%)

**Table 2. Completion Rates for HRQoL Assessments**

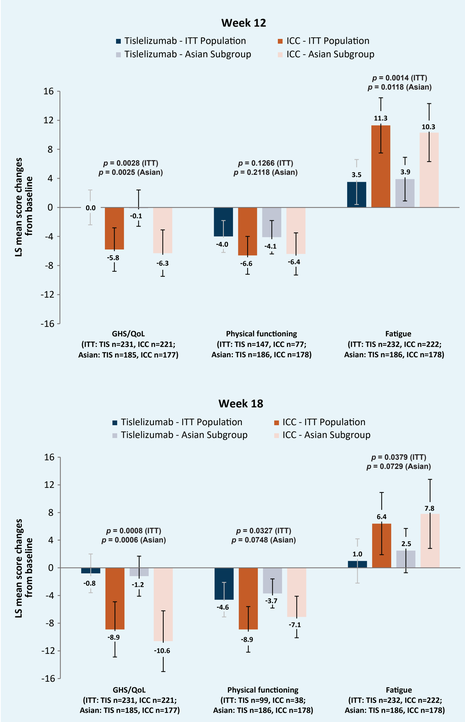
| | Asian Subgroup | | ITT Population | |
|---|---|---|---|---|
| | Tislelizumab (n = 201) | ICC (n = 203) | Tislelizumab (n = 256) | ICC (n = 256) |
| **EORTC QLQ-C30** | | | | |
| **Baseline** | | | | |
| Patients in study at visit, n | 201 | 203 | 256 | 256 |
| Patients completed questionnaire, n | 192 | 200 | 242 | 247 |
| Completion rate[a] (%) | 95.5 | 98.5 | 94.5 | 96.5 |
| Adjusted completion rate[b] (%) | 95.5 | 98.5 | 94.5 | 96.5 |
| **Week 12** | | | | |
| Patients in study at visit, n | 122 | 61 | 157 | 83 |
| Patients completed questionnaire, n | 120 | 59 | 147 | 77 |
| Completion rate[a] (%) | 59.7 | 29.1 | 57.4 | 30.1 |
| Adjusted completion rate[b] (%) | 98.4 | 96.7 | 93.6 | 92.8 |
| **Week 18** | | | | |
| Patients in study at visit, n | 78 | 28 | 100 | 39 |
| Patients completed questionnaire, n | 78 | 27 | 99 | 38 |
| Completion rate[a] (%) | 38.8 | 13.3 | 38.7 | 14.8 |
| Adjusted completion rate[b] (%) | 100.0 | 96.4 | 99.0 | 97.4 |
| **EORTC QLQ-OES18** | | | | |
| **Baseline** | | | | |
| Patients in study at visit, n | 201 | 203 | 256 | 256 |
| Patients completed questionnaire, n | 192 | 200 | 240 | 248 |
| Completion rate[a] (%) | 95.5 | 98.5 | 93.8 | 96.9 |
| Adjusted completion rate[b] (%) | 95.5 | 98.5 | 93.8 | 96.9 |
| **Week 12** | | | | |
| Patients in study at visit, n | 122 | 61 | 157 | 83 |
| Patients completed questionnaire, n | 119 | 59 | 146 | 76 |
| Completion rate[a] (%) | 59.2 | 29.1 | 57.0 | 29.7 |
| Adjusted completion rate[b] (%) | 97.5 | 96.7 | 93.0 | 91.6 |
| **Week 18** | | | | |
| Patients in study at visit, n | 78 | 28 | 100 | 39 |
| Patients completed questionnaire, n | 77 | 27 | 99 | 37 |
| Completion rate[a] (%) | 38.3 | 13.3 | 38.7 | 14.5 |
| Adjusted completion rate[b] (%) | 98.7 | 96.4 | 99.0 | 94.9 |

EORTC, European Organisation for Research and Treatment of Cancer; ICC, investigator-chosen chemotherapy; ITT, intent-to-treat; QLQ-C30, Quality of Life Questionnaire Core 30 items; QLQ-OES18, Quality of Life Questionnaire Esophageal Cancer Module.
[a]Completion rate = number of patients completed questionnaire / total number of patients in relevant treatment arm.
[b]Adjusted completion rate = number of patients completed questionnaire / total number of patients in study at relevant visits in relevant treatment arm.

### EORTC QLQ-C30: Change From Baseline

- Changes from baseline in GHS/QoL in the Asian Subgroup (**Figure 1**) were less pronounced at Weeks 12 and 18 in tislelizumab-treated patients compared with ICC-treated patients
- Worsening of physical functioning from baseline was less in the tislelizumab arm at both weeks in the Asian Subgroup
- The worsening of fatigue was less in the tislelizumab arm compared with the ICC arm at both weeks, particularly at Week 12 in the Asian Subgroup

**Figure 1. Change from Baseline for EORTC QLQ-C30 at Week 12 and Week 18**

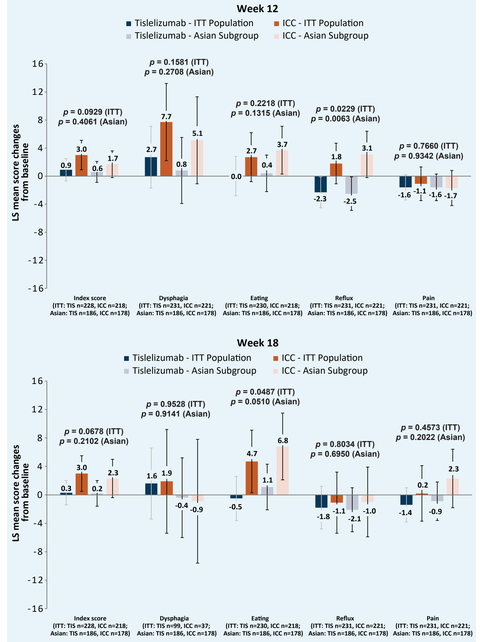



*n* = Patients with baseline and at least 1 post-baseline measurement. Reported P values are nominal.
**Abbreviations:** EORTC, European Organisation for Research and Treatment of Cancer; GHS, global health status; ICC, investigator-chosen chemotherapy; ITT, intent-to-treat; LS, least square; QLQ-C30, Quality of Life Questionnaire Core 30; QOL, quality of life; TIS, tislelizumab.

### EORTC QLQ-OES18: Change From Baseline

- The QLQ-OES18 symptom index scale score (**Figure 2**) was maintained in the tislelizumab arm at both Weeks 12 and 18, while the ICC arm experienced maintenance at Week 12 and worsening at Week 18
- Dysphagia symptoms at Week 12 remained stable in the tislelizumab arm and worsened in the ICC arm
- At Weeks 12 and 18, there was a difference in change from baseline in eating problems, with the tislelizumab arm demonstrating maintenance and the ICC arm experiencing worsening
- For reflux symptoms at Week 12, there was a difference in change from baseline, with the tislelizumab arm demonstrating a reduction compared with the ICC arm, which experienced a worsening in reflux
- For pain symptoms, tislelizumab-treated patients consistently maintained their scores at both Weeks 12 and 18; the ICC-treated patients' pain scores maintained at week 12, but slightly worsened at week 18

**Figure 2. Change from Baseline for QLQ-OES18 Scores at Week 12 and Week 18**




n = Patients with baseline and at least 1 post-baseline measurement. Reported P values are nominal.
**Abbreviations:** ICC, investigator-chosen chemotherapy; ITT, intention to treat; LS, least square; QLQ-OES18, Quality of Life Questionnaire - Oesophageal Cancer Module; TIS, tislelizumab.

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**Email: sbkim3@amc.seoul.kr**