RATIONALE-306 Subgroup Analysis of Patients With Advanced/Metastatic Esophageal Squamous Cell Cancer and Tumor Area Positivity Score ≥5%

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CONCLUSIONS

- The median overall survival (OS) of 19.1 months with tislelizumab plus chemotherapy in the tumor programmed death-ligand 1 (PD-L1) ≥5% population sets a new bar for efficacy in this group of patients with advanced/metastatic esophageal squamous cell carcinoma (ESCC) and should be considered in shared decision-making
- Efficacy benefits and safety outcomes remained consistent with primary analysis and 3-year follow-up data, showing sustained improvement with no new safety signals

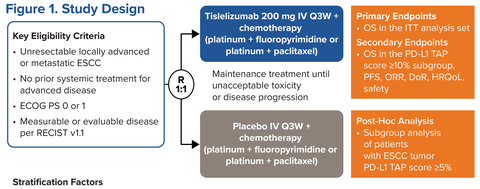
INTRODUCTION

- Tislelizumab, in combination with platinum-based chemotherapy, is approved by the European Medicines Agency for the first-line treatment of adults with unresectable, locally advanced or metastatic ESCC with tumor PD-L1 Tumor Area Positivity (TAP) score ≥5%[1]
- In the CheckMate 648 trial, patients with unresectable advanced, recurrent or metastatic ESCC and tumor PD-L1 combined positive score (CPS) ≥5 showed an improvement in OS with nivolumab plus chemotherapy vs chemotherapy alone (hazard ratio [HR]=0.78) after a 29-month minimum follow-up[2]
- The RATIONALE-306 trial demonstrated significant OS benefit for first-line treatment with tislelizumab plus chemotherapy compared with placebo plus chemotherapy in patients with advanced ESCC, both at primary analysis[3] and at the minimum 3-year follow-up[4]
  - At the 3-year follow-up, OS results showed a stratified HR of 0.70 for all patients in the intent-to-treat (ITT) population[4]
  - In patients with tumor PD-L1 TAP score ≥10% and ≥5%, the HRs were 0.70[4] and 0.62, respectively, at the 3-year follow-up
- Here, we report the study close-out analysis (August 22, 2024) of RATIONALE-306 in the subgroup with tumor PD-L1 TAP score ≥5%

METHODS

- RATIONALE-306 (NCT03783442) is a randomized, double-blind, global, phase 3 trial evaluating the efficacy and safety of tislelizumab plus chemotherapy, compared with placebo plus chemotherapy, as a first-line treatment for metastatic or unresectable ESCC (**Figure 1**)

Figure 1. Study Design



Stratification Factors
- Geographic region (Asia [excluding Japan] vs Japan vs rest of world)
- Prior definitive therapy (yes vs no)
- Investigator-chosen chemotherapy (platinum + fluoropyrimidine vs platinum + paclitaxel)

Abbreviations: DoR, duration of response; ECOG PS, Eastern Cooperative Oncology Group performance status; HRQoL, health-related quality of life; ITT, intent-to-treat; IV, intravenous; ORR, objective response rate; PFS, progression-free survival; Q3W, once every 3 weeks; R, randomized; RECIST, Response Evaluation Criteria in Solid Tumours.

METHODS (CONT.)

- Patients were enrolled regardless of their tumor PD-L1 expression at screening
  - Samples were stained for PD-L1 using the VENTANA PD-L1 (SP263) Assay (Roche) and expression was determined by TAP score
  - For exploratory purposes, pathologists in the central laboratory scored the same stained samples according to CPS

RESULTS

Patient Disposition and Baseline Characteristics

- Of 649 patients randomized (tislelizumab plus chemotherapy n=326; placebo plus chemotherapy n=323), 358 (55.2%) had a tumor PD-L1 TAP score ≥5% (tislelizumab plus chemotherapy n=172; placebo plus chemotherapy n=186) (**Table 1**)
- Baseline characteristics of patients with tumor PD-L1 TAP score ≥5% were consistent with the ITT population
- At data cutoff (August 22, 2024), the minimum study follow-up time was 45.2 months (range: 0.4-63.6)
- In the tislelizumab plus chemotherapy arm, 106 patients (61.6%) vs 126 (67.7%) in the placebo plus chemotherapy arm received post-treatment systemic therapy, of whom 27 (25.5%) vs 44 (34.9%), respectively, had systemic immunotherapy

Table 1. Patient Demographic and Baseline Characteristics

	Tislelizumab Plus Chemotherapy (n=172)	Placebo Plus Chemotherapy (n=186)
Median age, years (range)	62.0 (41-81)	64.0 (40-84)
≥65, n (%)	72 (41.9)	88 (47.3)
Male, n (%)	141 (82.0)	163 (87.6)
ECOG PS, n (%)		
0	50 (29.1)	57 (30.6)
1	122 (70.9)	129 (69.4)
Primary site of esophageal cancer, n (%)		
Cervical	9 (5.2)	9 (4.8)
Upper thoracic	30 (17.4)	38 (20.4)
Middle thoracic	74 (43.0)	78 (41.9)
Lower thoracic	59 (34.3)	61 (32.8)
Metastatic disease at study entry, n (%)	147 (85.5)	166 (89.2)
Number of metastatic sites at study entry, n (%)		
0	25 (14.5)	20 (10.8)
1	75 (43.6)	87 (46.8)
2	46 (26.7)	45 (24.2)
>2	26 (15.1)	34 (18.3)
Patients who received at least one prior definitive therapy, n (%)[a]	68 (39.5)	73 (39.2)
Prior anticancer systemic therapy, n (%)	46 (26.7)	59 (31.7)
Prior radiotherapy, n (%)	35 (20.3)	41 (22.0)
Prior anticancer surgery, n (%)	54 (31.4)	60 (32.3)

[a]A patient was counted only once within each category but may be counted in multiple categories.

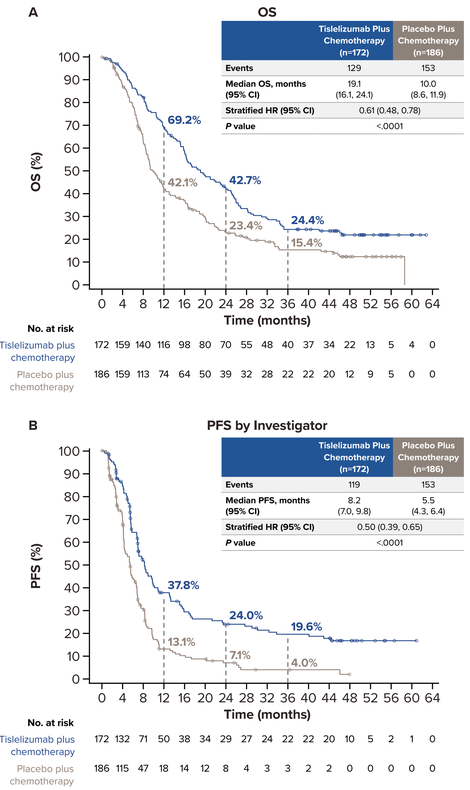
Efficacy

- Clinically meaningful improvements in OS (**Figure 2A**) and investigator-assessed PFS (**Figure 2B**) were observed with tislelizumab plus chemotherapy compared to placebo plus chemotherapy
  - OS benefit was observed across all prespecified subgroups, as shown in **Figure 3**

RESULTS (CONT.)

- A higher ORR and improved DoR were observed with tislelizumab plus chemotherapy vs placebo plus chemotherapy, as shown in **Table 2**

Figure 2. Kaplan–Meier Plots of (A) OS and (B) PFS by Investigator



Medians and other quartiles were estimated by Kaplan–Meier method, with 95% CIs estimated using the method of Brookmeyer and Crowley. OS rates (cumulative probability of OS) were estimated by Kaplan–Meier method, with 95% CIs estimated using Greenwood's formula. One-sided *P* value was estimated from a log-rank test stratified by pooled geographic region (Asia vs rest of world) per IRT, prior definitive therapy (yes vs no) per IRT, and chemotherapy option (investigator choice) per IRT. HR was based on a Cox regression model including treatment as a covariate and pooled geographic region (Asia vs rest of world) per IRT, prior definitive therapy (yes vs no) per IRT, and chemotherapy (investigator choice) per IRT as strata.
Abbreviations: CI, confidence interval; IRT, interactive response technology; PD, progressive disease.

PD-L1 TAP Score vs CPS Concordance

- TAP score 5% and CPS 5 cutoffs had 84.9% overall percent agreement[5], showing substantial concordance (**Figure 4**)

Figure 3. Forest Plot of OS by Subgroup Analysis

Subgroup	Event/Total: Tislelizumab Plus Chemotherapy	Event/Total: Placebo Plus Chemotherapy	Unstratified HR (95% CI)
Overall	129/172	153/186	0.62 (0.49, 0.78)
Age			
<65	74/100	77/98	0.66 (0.48, 0.91)
≥65	55/72	76/88	0.58 (0.41, 0.82)
Sex			
Male	111/141	136/163	0.68 (0.53, 0.87)
Female	18/31	17/23	0.45 (0.23, 0.87)
Smoking status			
Former/current smoker	102/131	113/132	0.60 (0.46, 0.78)
Non-smoker	23/35	32/45	0.70 (0.41, 1.20)
ECOG PS			
0	36/50	43/57	0.61 (0.39, 0.95)
1	93/122	110/129	0.62 (0.47, 0.82)
Geographic region analysis			
Asia	99/133	122/147	0.61 (0.47, 0.80)
Rest of world	30/39	31/39	0.65 (0.39, 1.08)
Race			
Asian and other	99/133	124/150	0.62 (0.47, 0.80)
White	30/39	29/36	0.62 (0.37, 1.04)
Disease status at study entry			
Metastatic	113/147	137/166	0.66 (0.51, 0.85)
Locally advanced	16/25	16/20	0.42 (0.21, 0.86)
Prior definitive therapy – IRT			
Yes	47/70	68/80	0.46 (0.32, 0.67)
No	82/102	85/106	0.76 (0.56, 1.03)

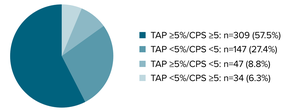
HR was based on an unstratified Cox regression model including treatment as covariate. The race subcategory "Other" includes American Indian or Alaska Native, Not Reported, and Unknown.
Abbreviations: CRF, case report form.

Table 2. Efficacy Outcomes

	Tislelizumab Plus Chemotherapy (n=172)	Placebo Plus Chemotherapy (n=186)
ORR[a], n (%) [95% CI][b]	123 (71.5) [64.1, 78.1]	77 (41.4) [34.2, 48.8]
Median DoR[c], months [95% CI][d]	7.1 [5.8, 9.7]	5.4 [4.1, 5.8]

[a]Investigator assessed. ORR is unconfirmed and defined as the proportion of patients with PR or CR, as assessed by the investigator per RECIST v1.1. [b]95% CI was estimated using the Clopper–Pearson method. [c]Duration of response analysis included patients with unconfirmed objective response. Medians and other quartiles were estimated by Kaplan–Meier method. [d]95% CI was estimated using the method of Brookmeyer and Crowley.
Abbreviations: CR, complete response; PR, partial response.

Figure 4. PD-L1 TAP Score vs CPS Concordance



TAP/CPS[5] 5%/5	n/N	Agreement, % (95% CI)
PPA	309/343	90.1 (87, 93)
NPA	147/194	75.8 (70, 81)
OPA	456/537	84.9 (82, 88)
Cohen's Kappa (95% CI)	0.67 (0.60, 0.73)	
Strength of agreement (Kappa)		
Slight (0.01-0.20)	Fair (0.21-0.40)	Moderate (0.41-0.60)	Substantial (0.61-0.80)	Almost perfect (0.81-1.0)

Abbreviations: NPA, negative percent agreement; OPA, overall percent agreement; PPA, positive percent agreement.

Safety/Tolerability Profile

- Treatment-related adverse events (TRAEs) were observed in most patients across both cohorts, with similar any-grade rates. A higher incidence of grade ≥3 and serious TRAEs were observed with tislelizumab plus chemotherapy (**Table 3**)
  - Grade ≥3 TRAEs occurring in ≥10% of patients with tislelizumab plus chemotherapy vs placebo plus chemotherapy included decreased neutrophil count (35.1% vs 31.9%), decreased white blood cell count (12.3% vs 17.8%), and anemia (13.5% vs 11.4%)
- More TRAEs leading to death (2.9% vs 1.6%) and treatment-emergent adverse events (TEAEs) leading to any treatment discontinuation (34.5% vs 23.2%) occurred in the tislelizumab plus chemotherapy arm than in the placebo plus chemotherapy arm
- Immune-mediated adverse events (imAEs) were observed in both arms. The incidence of grade ≥3 imAEs was higher with tislelizumab plus chemotherapy vs placebo plus chemotherapy (8.8% vs 2.2%) (**Table 3**)

Table 3. Safety Summary (Safety Analysis Set)

	Tislelizumab Plus Chemotherapy (n=171)	Placebo Plus Chemotherapy (n=185)
Patients with ≥1 TRAEs, n (%)	167 (97.7)	182 (98.4)
Grade ≥3	120 (70.2)	123 (66.5)
Serious	50 (29.2)	38 (20.5)
Leading to death	5 (2.9)	3 (1.6)
Patients with ≥1 TEAEs leading to any treatment discontinuation, n (%)	59 (34.5)	43 (23.2)
Patients with any imAEs, n (%)	73 (42.7)	40 (21.6)
Grade ≥3	15 (8.8)	4 (2.2)

Adverse event grades were evaluated based on Common Terminology Criteria for Adverse Events version 4.03. Adverse event terms were coded using Medical Dictionary for Drug Regulatory Affairs version 24.0. TRAEs include events considered by the investigator to be related to study treatments or with missing assessment of the causal relationship. Deaths here exclude those caused by disease under study.

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DISCLOSURES

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