Tislelizumab Plus Chemotherapy Vs Placebo Plus Chemotherapy as First-Line Treatment for Locally Advanced, Unresectable Esophageal Squamous Cell Carcinoma: PD-L1 Tumor Area Positivity Score ≥1% Subgroup Analysis of RATIONALE-306

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CONCLUSIONS

- In patients with locally advanced unresectable esophageal squamous cell carcinoma (ESCC) with programmed death ligand 1 (PD-L1) Tumor Area Positivity (TAP) score ≥1%, tislelizumab plus chemotherapy demonstrated clinically meaningful improvements in efficacy outcomes vs placebo plus chemotherapy, with median overall survival (OS) exceeding 2 years
- Benefit in the metastatic subgroup (median OS 16.4 months) was similar to that in the overall PD-L1 ≥1% population (16.8 months)
- The tislelizumab regimen was well tolerated, with no new safety signals, supporting its use as a first-line treatment option for patients who have locally advanced unresectable or metastatic ESCC with a PD-L1 TAP score ≥1%

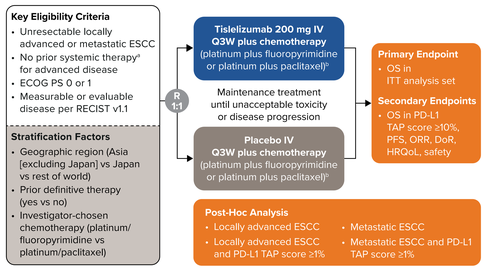
INTRODUCTION

- In RATIONALE-306, patients with locally advanced unresectable or metastatic ESCC who received tislelizumab plus chemotherapy (platinum plus fluoropyrimidine or paclitaxel) demonstrated statistically significant OS improvement compared with those who received placebo plus chemotherapy at the primary analysis; this improvement was maintained after a ≥3-year follow-up[1]
- Analyses of the PD-L1 TAP score ≥1% subgroup found clinically meaningful improvement with tislelizumab plus chemotherapy,[2] which supported the US Food and Drug Administration approval for first-line treatment of advanced/metastatic ESCC for patients with tumor PD-L1 expression ≥1[3]

METHODS

- RATIONALE-306 was a randomized, double-blind, global phase 3 trial comparing tislelizumab plus chemotherapy with placebo plus chemotherapy in patients with no prior systemic therapy for locally advanced unresectable or metastatic ESCC
- The study design for RATIONALE-306 is presented in **Figure 1**
- Patients were randomized 1:1 to receive tislelizumab 200 mg or placebo intravenously (IV) every 3 weeks (Q3W) plus investigator-chosen chemotherapy (platinum plus fluoropyrimidine or paclitaxel)
- PD-L1 TAP score was evaluated in tumor tissue using the VENTANA PD-L1 (SP263) Assay (Roche Diagnostics, Indianapolis, IN, USA)[4]
- This analysis evaluated patients with PD-L1 TAP score ≥1% in the locally advanced unresectable ESCC and metastatic ESCC subgroups

Figure 1. Study Design



[a]Patients with prior systemic concurrent chemotherapy in concurrent chemoradiotherapy were eligible. If there was prior neoadjuvant/adjuvant therapy with platinum-based chemotherapy, a treatment-free interval of at least 6 months was required. [b]Chemotherapy: cisplatin 60-80 mg/m² on day 1 or oxaliplatin 130 mg/m² on day 1 plus fluoropyrimidine (5-FU 750-800 mg/m²/day on days 1-5 or capecitabine 1000 mg/m² twice daily on days 1-14), Q3W; or cisplatin 60-80 mg/m² on day 1 or oxaliplatin 130 mg/m² on day 1 plus paclitaxel 175 mg/m² on day 1, Q3W.

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

RESULTS

Patient Disposition

- Baseme demographics and disease characteristics were generally similar across treatment arms (**Table 1**)
- At the primary analysis (data cutoff: February 28, 2022), of the 63 patients with locally advanced ESCC and PD-L1 TAP score ≥1%, 41.3% had TAP scores ≥10%. Among the 418 patients with metastatic ESCC and PD-L1 TAP score ≥1%, 47.1% had TAP scores ≥10%
- A higher percentage of patients with locally advanced ESCC and PD-L1 TAP score ≥1% received prior definitive therapy (61.9%) compared with patients with metastatic ESCC and PD-L1 TAP score ≥1% (40.0%) at the data cutoff of February 28, 2022

Table 1. Patient Baseline Demographics and Characteristics at Primary Analysis (Data Cutoff: February 28, 2022 [PD-L1 TAP Score ≥1%; ITT Analysis Set])

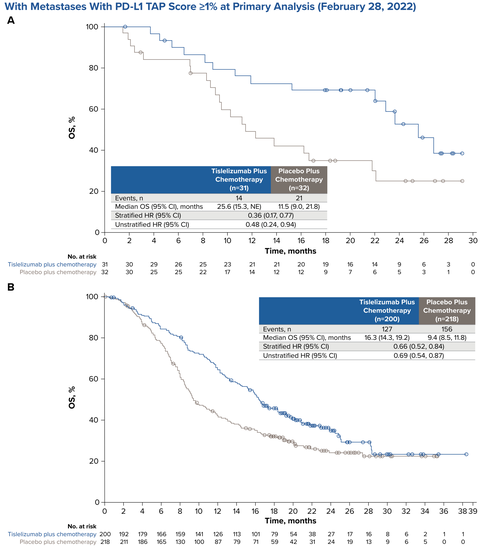
	Locally Advanced ESCC (N=63)		Metastatic ESCC (N=418)	
Baseline Characteristics	Tislelizumab Plus Chemotherapy (n=31)	Placebo Plus Chemotherapy (n=32)	Tislelizumab Plus Chemotherapy (n=200)	Placebo Plus Chemotherapy (n=218)
Median age, years (range)	66.0 (51-75)	68.5 (50-79)	62.0 (38-81)	64.0 (40-84)
≥65 years	18 (58.1)	22 (68.8)	82 (41.0)	105 (48.2)
Sex, n (%)				
Male	26 (83.9)	28 (87.5)	170 (85.0)	191 (87.6)
Region, n (%)				
Asia	22 (71.0)	16 (50.0)	151 (75.5)	176 (80.7)
Rest of the world	9 (29.0)	16 (50.0)	49 (24.5)	42 (19.3)
ECOG PS, n (%)				
0	12 (38.7)	14 (43.8)	63 (31.5)	74 (33.9)
1	19 (61.3)	18 (56.3)	137 (68.5)	144 (66.1)
TAP status, n (%)				
TAP score ≥10%	15 (48.4)	11 (34.4)	101 (50.5)	96 (44.0)
TAP score <10%	16 (51.6)	21 (65.6)	99 (49.5)	122 (56.0)
Prior definitive therapy, n (%)				
Definitive radiotherapy	10 (32.3)	7 (21.9)	19 (9.5)	25 (11.5)
Definitive surgery	11 (35.5)	14 (43.8)	64 (32.0)	64 (29.4)
Definitive surgery and radiotherapy[a]	1 (3.2)	2 (6.3)	2 (1.0)	3 (1.4)
No previous definitive therapy	11 (35.5)	13 (40.6)	119 (59.5)	132 (60.6)

[a]A patient would be counted once if the patient had both prior definitive surgery and radiotherapy.

Efficacy

- At the primary analysis (data cutoff: February 28, 2022), tislelizumab plus chemotherapy demonstrated an OS benefit in patients with locally advanced ESCC and PD-L1 TAP score ≥1% (25.6 vs 11.5 months) (**Figure 2A**)
- An OS benefit with tislelizumab was also observed in patients with metastatic ESCC and PD-L1 TAP score ≥1% (16.3 vs 9.4 months) (**Figure 2B**)
- These OS benefits were maintained at the 3-year follow-up (data cutoff: November 24, 2023), with tislelizumab plus chemotherapy continuing to show improved survival in patients with locally advanced ESCC (median OS: 25.6 vs 12.3 months) (**Figure 3A**) and in patients with metastatic ESCC (16.4 vs 9.4 months) (**Figure 3B**)
- At the primary analysis (data cutoff: February 28, 2022), tislelizumab plus chemotherapy demonstrated improved PFS and ORR compared with placebo plus chemotherapy in patients with locally advanced ESCC with PD-L1 TAP score ≥1% and in patients with metastatic ESCC with PD-L1 TAP score ≥1% (**Table 2**)
  - Median time to response was similar between treatment arms in both subgroups (approximately 1.4-1.5 months)
- These efficacy benefits were maintained or improved at the 3-year follow-up (data cutoff: November 24, 2023) (**Table 3**)
  - As of the 3-year follow-up DCO (November 24, 2023), median DoR was longer with tislelizumab plus chemotherapy in both locally advanced (22.1 vs 5.7 months) and metastatic (6.2 vs 5.4 months) subgroups, with 63.8% vs 15.6% of responders with locally advanced disease maintaining response at 12 months

Figure 2. Kaplan-Meier Plot of OS for (A) Patients With Locally Advanced Disease and (B) Patients With Metastases With PD-L1 TAP Score ≥1% at Primary Analysis (February 28, 2022)



Abbreviations: CI, confidence interval; HR, hazard ratio.

Table 2. Efficacy Outcomes in Patients With PD-L1 TAP Score ≥1% at Primary Analysis

	Locally Advanced ESCC (N=63)		Metastatic ESCC (N=418)	
Endpoint	Tislelizumab Plus Chemotherapy (n=31)	Placebo Plus Chemotherapy (n=32)	Tislelizumab Plus Chemotherapy (n=200)	Placebo Plus Chemotherapy (n=218)
Median PFS, months (95% CI)	13.2 (6.8, NE)	6.7 (4.2, 9.7)	7.1 (6.8, 8.3)	5.5 (4.3, 5.8)
HR (95% CI)[a]	0.46 (0.22, 0.96)		0.59 (0.47, 0.74)	
ORR, n (%) (95% CI)	18 (58.1) (39.1, 75.5)	10 (31.3) (16.1, 50.0)	134 (67.0) (60.0, 73.5)	95 (43.6) (36.9, 50.4)
ORR difference, % (95% CI)[b]	32.6 (8.1, 57.1)		23.5 (14.2, 32.8)	
Odds ratio (95% CI)[b]	3.92 (1.25, 12.32)		2.64 (1.77, 3.94)	
Time to response				
Median (IQR), months	1.5 (1.4, 4.1)	1.5 (1.3, 2.7)	1.4 (1.3, 2.7)	1.4 (1.3, 2.7)
Median DoR, months (95% CI)	NR (8.4, NE)	5.7 (1.5, 9.6)	6.2 (5.2, 7.1)	5.4 (4.1, 5.7)
12-month DoR rate, % (95% CI)	66.2 (36.5, 84.5)	15.6 (0.8, 49.1)	28.8 (21.0, 37.1)	13.0 (6.4, 21.9)

Data cutoff: February 28, 2022.

[a]Stratified hazard ratio (tislelizumab plus chemotherapy vs placebo plus chemotherapy) was based on Cox regression model including treatment arm as a 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.

[b]Objective response rate, objective response rate differences, and odds ratios between arms were calculated using the Cochran-Mantel-Haenszel method, 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.

Abbreviations: ICC, investigators choice of chemotherapy; IRT, interactive response technology; NE, not estimable; NR, not reached; IQR, interquartile range.

Figure 3. Kaplan-Meier Plot of OS for (A) Patients With Locally Advanced Disease and (B) Patients With Metastases With PD-L1 TAP Score ≥1% at the 3-Year Follow-up (November 24, 2023)

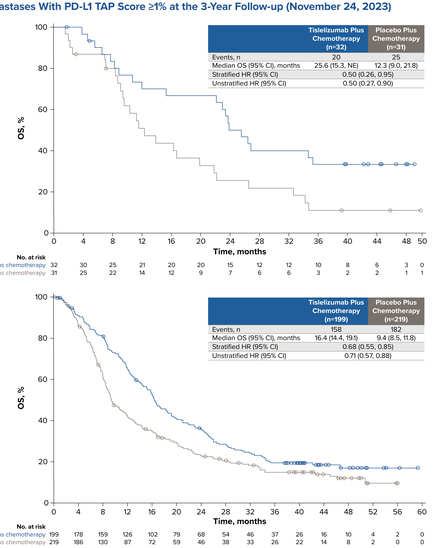


Table 3. Efficacy Outcomes in Patients With PD-L1 TAP Score ≥1% at 3-Year Follow-up

	Locally Advanced ESCC (N=63)		Metastatic ESCC (N=418)	
Endpoint	Tislelizumab Plus Chemotherapy (n=32)	Placebo Plus Chemotherapy (n=31)	Tislelizumab Plus Chemotherapy (n=199)	Placebo Plus Chemotherapy (n=219)
Median PFS, months (95% CI)	13.2 (6.8, 27.7)	6.7 (4.2, 9.7)	7.0 (6.7, 8.3)	5.5 (4.3, 5.8)
HR (95% CI)[a]	0.47 (0.23, 0.96)		0.56 (0.45, 0.71)	
ORR, n (%) (95% CI)	19 (59.4) (40.6, 76.3)	10 (32.3) (16.7, 51.4)	133 (66.8) (59.8, 73.3)	95 (43.4) (36.7, 50.2)
ORR difference, % (95% CI)[b]	33.1 (8.9, 57.2)		23.5 (14.2, 32.8)	
Odds ratio (95% CI)[b]	4.00 (1.28, 12.48)		2.65 (1.77, 3.95)	
Time to response				
Median (IQR), months	1.5 (1.4, 4.1)	1.5 (1.3, 2.7)	1.4 (1.3, 2.7)	1.4 (1.4, 2.7)
Median DoR, months (95% CI)	22.1 (6.1, NE)	5.7 (1.5, 9.6)	6.2 (5.2, 7.1)	5.4 (4.1, 5.7)
12-month DoR rate, % (95% CI)	63.8 (36.2, 81.9)	15.6 (0.8, 49.1)	29.2 (21.3, 37.5)	13.3 (6.6, 22.4)

Data cutoff: November 24, 2023.

[a]Stratified hazard ratio (tislelizumab plus chemotherapy vs placebo plus chemotherapy) was based on Cox regression model including treatment arm as a 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.

[b]Objective response rate, objective response rate differences, and odds ratios between arms were calculated using the Cochran-Mantel-Haenszel method, 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.

- The safety profile of tislelizumab plus chemotherapy was generally consistent with the known safety profiles of the individual agents, with no new safety signals identified at the 3-year follow-up (**Table 4**)
- In both locally advanced and metastatic ESCC populations, higher incidences of serious tislelizumab-/placebo-related adverse events and tislelizumab-/placebo-related treatment-emergent adverse events (TEAEs) leading to treatment discontinuation were observed in the tislelizumab plus chemotherapy arm compared with the placebo plus chemotherapy arm
- In the population with locally advanced ESCC, a higher incidence of grade ≥3 treatment-related adverse events (TRAEs) was observed in the placebo plus chemotherapy arm compared with the tislelizumab plus chemotherapy arm. Serious TRAEs and TRAEs leading to treatment discontinuation were more frequent in the tislelizumab arm than in the placebo arm

Table 4. Safety Summary in Patients With PD-L1 TAP Score ≥1% at 3-Year Follow-up

	Locally Advanced ESCC (N=63)		Metastatic ESCC (N=415)	
	Tislelizumab Plus Chemotherapy (n=32)	Placebo Plus Chemotherapy (n=31)	Tislelizumab Plus Chemotherapy (n=198)	Placebo Plus Chemotherapy (n=217)
Patients with at least 1 TEAE, n (%)	32 (100.0)	31 (100.0)	197 (99.5)	217 (100.0)
Any study treatment component–related TEAEs	32 (100.0)	30 (96.8)	191 (96.5)	211 (97.2)
Tislelizumab-/Placebo-related TEAEs	19 (59.4)	18 (58.1)	143 (72.2)	136 (62.7)
Any chemotherapy component–related TEAEs	32 (100.0)	30 (96.8)	191 (96.5)	210 (96.8)
TEAEs of grade 3 or higher, n (%)	18 (56.3)	23 (74.2)	162 (81.8)	169 (77.9)
Any study treatment component–related TEAEs of grade 3 or higher	15 (46.9)	19 (61.3)	139 (70.2)	141 (65.0)
Tislelizumab-/Placebo-related TEAEs of grade 3 or higher	7 (21.9)	9 (29.0)	68 (34.3)	41 (18.9)
Any chemotherapy component–related TEAEs of grade 3 or higher	13 (40.6)	17 (54.8)	129 (65.2)	139 (64.1)
Serious TEAEs, n (%)	13 (40.6)	16 (51.6)	96 (48.5)	82 (37.8)
Any study treatment component–related serious TEAEs	8 (25.0)	7 (22.6)	59 (29.8)	44 (20.3)
Tislelizumab-/Placebo-related serious TEAEs	6 (18.8)	3 (9.7)	42 (21.2)	18 (8.3)
Any chemotherapy component–related serious TEAEs	5 (15.6)	6 (19.4)	40 (20.2)	41 (18.9)
TEAEs leading to death, n (%)	3 (9.4)	0 (0.0)	10 (5.1)	13 (6.0)
Any study treatment component–related TEAEs leading to death	2 (6.3)	0 (0.0)	3 (1.5)	4 (1.8)
TEAEs leading to treatment discontinuation, n (%)	13 (40.6)	11 (35.5)	69 (34.8)	43 (19.8)
TEAEs leading to discontinuation of tislelizumab/placebo	6 (18.8)	2 (6.5)	24 (12.1)	15 (6.9)
TEAEs leading to discontinuation of any chemotherapy component	12 (37.5)	11 (35.5)	64 (32.3)	42 (19.4)
Tislelizumab-/Placebo-related TEAEs leading to discontinuation of tislelizumab/placebo	4 (12.5)	1 (3.2)	19 (9.6)	1 (0.5)

Data cutoff: November 24, 2023.

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