Randomized, Global, Phase 3 Study of Tislelizumab + Chemotherapy Versus Placebo + Chemotherapy as First-line Treatment for Advanced/Metastatic Esophageal Squamous Cell Carcinoma: 2-year Follow-up From RATIONALE-306

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Conclusions

Tislelizumab (TIS) plus chemotherapy (chemo) showed clinically meaningful improvements in overall survival (OS) and progression-free survival (PFS), and durable antitumor response, compared with placebo (PBO) plus chemo in the first-line (1L) treatment of advanced or metastatic esophageal squamous cell carcinoma (ESCC) after a minimum of 2 years of follow-up in RATIONALE-306.

Consistent with the results of the interim analysis (IA), the results of the 2-year follow-up provide additional evidence of sustained efficacy and a manageable safety profile, supporting the treatment benefit of TIS plus chemo compared with PBO plus chemo in the 1L treatment of ESCC.

Background

ESCC is the predominant histologic subtype of esophageal cancer, accounting for 85% of cases worldwide.[1] Platinum-based chemo has been used for 1L treatment of advanced or metastatic ESCC,[2-4] but median survival remains poor at <1 year.[2-5] TIS is a monoclonal antibody with high affinity and binding specificity for programmed cell death protein 1 (PD-1).[6,7] Anti-PD-1 antibodies in combination with chemotherapy have demonstrated superior survival benefit vs chemo alone as 1L treatment for ESCC.[2,8-11]

At IA, the randomized, double-blind, phase 3 RATIONALE-306 trial (NCT03783442) of 1L TIS plus chemo demonstrated a statistically significant, clinically meaningful improvement in OS (stratified hazard ratio [HR]=0.66, 95% confidence interval [CI]: 0.54, 0.80) vs PBO plus chemo, with a manageable safety profile, in patients with advanced/metastatic ESCC.[12] Here, we report updated efficacy and safety data, with a minimum of 2 years of follow-up.

Methods

- The study design has been described previously.[12] For full details of the study design and primary analysis results, please read the primary publication at the QR code
- Systemic therapy-naïve adults with unresectable locally advanced recurrent/metastatic ESCC were randomized to receive either TIS 200 mg or PBO intravenously every 3 weeks plus investigator-chosen chemo (ICC)
- The primary endpoint was OS in the intent-to-treat (ITT) population; secondary endpoints included investigator-assessed PFS, objective response rate (ORR), duration of response (DoR), OS in the subgroup with programmed death-ligand 1 (PD-L1) tumor area positivity (TAP) score ≥10%, and safety

Results

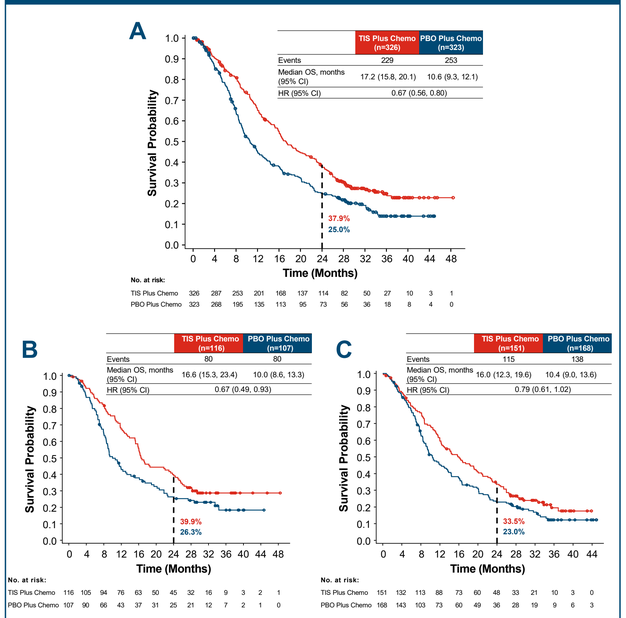
Patient Disposition and Baseline Characteristics

- Baseline characteristics were generally balanced between both arms, as described previously[12]
- At data cutoff (December 31, 2022), minimum study follow-up time (defined as the difference between the date of cutoff and the date of last patient randomized) was 25.2 months
- A total of 626 (96.5%) patients discontinued from treatment (TIS plus chemo: 306 [93.9%]; PBO plus chemo: 320 [99.1%]) and 530 (81.7%) patients discontinued from the study (TIS plus chemo: 251 [77.0%]; PBO plus chemo: 279 [86.4%])

Efficacy

- A clinically meaningful improvement in OS was seen with TIS plus chemo vs PBO plus chemo in all patients (**Figure 1A**), including those with PD-L1 TAP score ≥10% (**Figure 1B**) and <10% (**Figure 1C**), similar to results of the IA[12]
- An OS benefit in favor of TIS plus chemo vs PBO plus chemo was seen across the predefined subgroups evaluated (**Figure 2**) and the findings were similar to those reported in the IA[12]
- Improvements in PFS, ORR, and DoR with TIS plus chemo vs PBO plus chemo (**Table 1**) were also maintained relative to the IA[12]

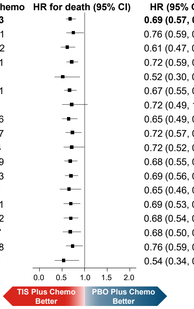
Figure 1. Kaplan-Meier Curves of OS for (A) All Patients; (B) Patients With PD-L1 TAP Score ≥10%; and (C) <10% (ITT Analysis Set)



Data cutoff: December 31, 2022. A total of 59 (TIS plus chemo) vs 48 (PBO plus chemo) patients had unknown PD-L1 status at baseline. Stratified HR based on Cox regression model including treatment regimen as a covariate and pooled geographic region (Asia vs RoW), prior definitive therapy (yes vs no), and ICC option as strata. **Abbreviations**: Chemo, chemotherapy; CI, confidence interval; HR, hazard ratio; ICC, investigator-chosen chemo; ITT, intent-to-treat; OS, overall survival; PBO, placebo; PD-L1, programmed death-ligand 1; RoW, rest of world; TAP, tumor area positivity; TIS, tislelizumab.

Figure 2. Forest Plot of OS by Subgroup (ITT Analysis Set)

Subgroup		Event/Total: TIS Plus Chemo	Event/Total: PBO Plus Chemo	HR for death (95% CI)	HR (95% CI)
Overall		**229/326**	**253/323**		**0.69 (0.57, 0.82)**
Age	<65 years	129/176	121/161		0.76 (0.59, 0.97)
	≥65 years	100/150	132/162		0.61 (0.47, 0.80)
Sex	Male	205/282	224/281		0.72 (0.59, 0.87)
	Female	24/44	29/42		0.52 (0.30, 0.90)
Smoking status	Former/Current smoker	179/247	188/231		0.67 (0.55, 0.83)
	Non-smoker	43/68	55/81		0.72 (0.49, 1.08)
ICC options per CRF	Platinum with fluoropyrimidine	101/147	117/146		0.65 (0.49, 0.84)
	Platinum with paclitaxel	128/179	136/177		0.72 (0.57, 0.92)
ECOG PS	0	73/109	77/104		0.72 (0.52, 0.99)
	1	156/217	176/219		0.68 (0.55, 0.84)
Region	Asia	169/243	188/243		0.69 (0.56, 0.86)
	Rest of World	60/83	65/80		0.65 (0.46, 0.92)
Prior Definitive Therapy per CRF	Yes	98/143	108/141		0.69 (0.53, 0.91)
	No	131/183	145/182		0.68 (0.54, 0.86)
Baseline PD-L1 status	PD-L1 score ≥10%	80/116	80/107		0.68 (0.50, 0.93)
	PD-L1 score <10%	115/151	138/168		0.76 (0.59, 0.97)
	Unknown	34/59	35/48		0.54 (0.34, 0.87)



Data cutoff: December 31, 2022. HR was based on unstratified Cox regression model including treatment as a covariate.
Abbreviations: Chemo, chemotherapy; CI, confidence interval; CRF, case report form; ECOG PS, Eastern Cooperative Oncology Group performance status; HR, hazard ratio; ICC, investigator-chosen chemo; ITT, intent-to-treat; OS, overall survival; PBO, placebo; PD-L1, programmed death-ligand 1; TIS, tislelizumab.

Table 1. Efficacy Endpoints (ITT Analysis Set)

	TIS Plus Chemo (n=326)	PBO Plus Chemo (n=323)
Median PFS (95% CI), months	7.3 (6.9, 8.3)	5.6 (4.9, 6.0)
HR (95% CI)	0.61 (0.51, 0.73)	
24-month PFS rate, % (95% CI)	18.1 (13.6, 23.1)	7.2 (4.4, 11.0)
ORR, % (95% CI)	63.5 (58.0, 68.7)	42.4 (37.0, 48.0)
Median DoR (95% CI), months	7.1 (6.1, 8.1)	5.7 (4.4, 7.1)
24-month DoR rate, % (95% CI)	19.6 (13.9, 25.9)	10.1 (5.0, 17.1)

Data cutoff: December 31, 2022. Listed endpoints assessed by investigator. **Abbreviations**: Chemo, chemotherapy; CI, confidence interval; DoR, duration of response; HR, hazard ratio; ITT, intent-to-treat; ORR, objective response rate; OS, overall survival; PBO, placebo; PFS, progression-free survival; TIS, tislelizumab.

Safety

- Median exposure was longer for TIS plus chemo (6.4 months, range: 0.1-48.4) than for PBO plus chemo (4.9 months, range: 0.6-36.4), with 39 (12.0%) and 10 (3.1%) patients treated with TIS plus chemo and PBO plus chemo for ≥24 months, respectively
- Incidence of any-grade and grade ≥3 treatment-related adverse events (TRAEs) was similar between treatment arms (**Table 2**)
- Serious TRAEs and treatment-emergent adverse events leading to any treatment discontinuation occurred more frequently with TIS plus chemo vs PBO plus chemo
- The most common grade ≥3 TRAEs in the TIS plus chemo vs PBO plus chemo arms, respectively, were decreased neutrophil count (30.6% vs 32.7%), anemia (14.5% vs 12.8%), and decreased white blood cell count (10.8% vs 15.6%)
- 164 (50.3%) patients in the TIS plus chemo arm vs 186 (57.6%) in the PBO plus chemo arm received posttreatment systemic therapy, of whom 48 (14.7%) vs 76 (23.5%), respectively, had posttreatment immunotherapy

Table 2. Summary of TEAEs and TRAEs (Safety Analysis Set)

	TIS Plus Chemo (n=324)	PBO Plus Chemo (n=321)
Patients with at least one TRAE, n (%)	313 (96.6)	309 (96.3)
Grade ≥3	216 (66.7)	207 (64.5)
Serious	95 (29.3)	63 (19.6)
Leading to death	6 (1.9)	4 (1.2)
Patients with at least one TEAE leading to any treatment discontinuation, n (%)	103 (31.8)	71 (22.1)
Patients with at least one TEAE leading to any dose modification, n (%)	247 (76.2)	229 (71.3)

Data cutoff: December 31, 2022. TRAEs include TEAEs that were considered by the investigator to be related to study drug or TEAEs with a missing causality.
Abbreviations: Chemo, chemotherapy; PBO, placebo; TEAE, treatment-emergent adverse event; TIS, tislelizumab; TRAE, treatment-related adverse event.

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