Randomized, Global, Phase 3 Study of Tislelizumab Plus Chemotherapy versus Chemotherapy as First-line Treatment for Advanced or Metastatic Esophageal Squamous Cell Carcinoma (RATIONALE-306): China Subgroup Analysis

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Conclusions

Tislelizumab plus chemotherapy showed a clinically meaningful improvement in overall survival (OS) compared with placebo plus chemotherapy as first-line (1L) treatment in patients with advanced or metastatic esophageal squamous cell carcinoma (ESCC) in the China subgroup of RATIONALE-306.

Tislelizumab plus chemotherapy had a manageable safety profile as 1L treatment for advanced or metastatic ESCC, with no new safety signals identified in the China subgroup.

The treatment benefit and the safety profile of tislelizumab plus chemotherapy in the China subgroup were consistent with the published results in the overall study population.

Background

Esophageal cancer is the eighth most commonly diagnosed cancer worldwide, with more than half of new cases occurring in China, and with ESCC being the predominant histologic subtype.[1] Platinum-based chemotherapy has been used for first-line (1L) treatment of advanced or metastatic ESCC, but median survival remains poor at ~1 year.[2-4]

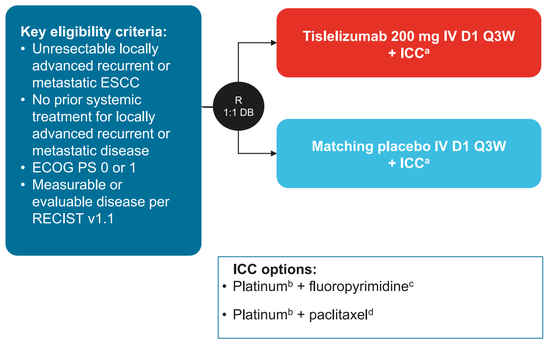
Tislelizumab is a monoclonal antibody with high affinity and binding specificity for programmed cell death protein 1.[5,6] In the interim analysis of the overall population of the phase 3 RATIONALE-306 study (NCT03783442), tislelizumab plus chemotherapy demonstrated a statistically significant and clinically meaningful overall survival (OS) benefit as 1L treatment in patients with advanced or metastatic ESCC, compared with placebo plus chemotherapy.[7]

Here, we report interim analysis results for the China subgroup of RATIONALE-306.

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]Treatment until disease progression, intolerable toxicity, or withdrawal for other reasons. [b]Cisplatin was used in China, Taiwan, and Japan, where oxaliplatin substitution was not permitted. [c]5-fluorouracil 750-800 mg/m² IV on Days 1-5 Q3W or capecitabine 1000 mg/m² orally BID on Days 1-14. [d]Paclitaxel 175 mg/m² IV Q3W.
Abbreviations: BID, twice daily; D, day; DB, double-blind; DoR, duration of response; ECOG PS, Eastern Cooperative Oncology Group performance status; ESCC, esophageal squamous cell carcinoma; HRQoL, health-related quality of life; ICC, investigator-chosen chemotherapy; ITT, intent-to-treat; IV, intravenously; ORR, objective response rate; OS, overall survival; PD-L1, programmed death-ligand 1; PFS, progression-free survival; Q3W, every 3 weeks; R, randomized; RECIST, Response Evaluation Criteria in Solid Tumors version 1.1.

Results

Patient Disposition and Baseline Characteristics

- Of 649 randomized patients, 370 (57.0%) patients were enrolled from China (tislelizumab + ICC, n=182; placebo + ICC, n=188)
- Baseline characteristics were generally balanced between treatment arms (**Table 1**)
- As of February 28, 2022, median study follow-up was 15.8 months (mo) in the tislelizumab + ICC arm vs 10.6 mo in the placebo + ICC arm

Table 1. Baseline Characteristics

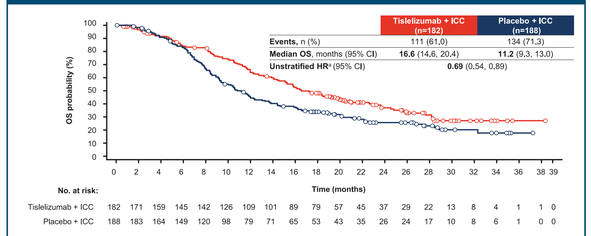
	Tislelizumab + ICC (n=182)	Placebo + ICC (n=188)
Median age, years (range)	63 (57-68)	64 (57-69)
Sex, male	157 (86.3)	170 (90.4)
Race, Chinese	182 (100.0)	188 (100.0)
ECOG PS 0/1	43 (23.6)/139 (76.4)	44 (23.4)/144 (76.6)
Disease status at study entry		
Metastatic/locally advanced	158 (86.8)/24 (13.2)	171 (91.0)/17 (9.0)
PD-L1 score		
≥10%/<10%/unknown	65 (35.7)/87 (47.8)/30 (16.5)	75 (39.9)/95 (50.5)/18 (9.6)
ICC option		
Platinum + fluoropyrimidine	41[a] (22.5)	37 (19.7)
Platinum + paclitaxel	140 (76.9)	151 (80.3)
Posttreatment systemic therapy/ immunotherapy	79 (43.4)/25 (13.7)	103 (54.8)/36 (19.1)

Data are n (%), unless otherwise stated. [a]One patient did not receive ICC treatment.
Abbreviations: ECOG PS, Eastern Cooperative Oncology Group performance status; ICC, investigator-chosen chemotherapy; PD-L1, programmed death-ligand 1.

Efficacy

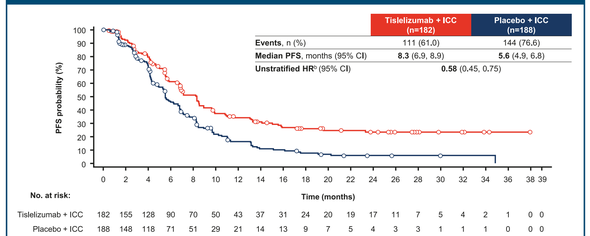
- Median OS was 16.6 mo in the tislelizumab + ICC arm vs 11.2 mo in the placebo + ICC arm (unstratified hazard ratio [HR]=0.69; 95% confidence interval [CI]: 0.54, 0.89; **Figure 2**)
- Median progression-free survival (PFS) was 8.3 mo in the tislelizumab + ICC arm vs 5.6 mo in the placebo + ICC arm (unstratified HR=0.58; 95% CI: 0.45, 0.75; **Figure 3**)
- Median duration of response was longer with tislelizumab + ICC than placebo + ICC (7.4 mo [95% CI: 5.6, 9.5] vs 5.7 mo [95% CI: 4.3, 7.5]), respectively (**Table 2**)

Figure 2. OS (China Subgroup)



Data cutoff: February 28, 2022. [a]HR was based on an unstratified Cox regression model including only treatment as a covariate.
Abbreviations: CI, confidence interval; HR, hazard ratio; ICC, investigator-chosen chemotherapy; OS, overall survival.

Figure 3. PFS[a] (China Subgroup)



Data cutoff: February 28, 2022. [a]PFS assessed by investigator per Response Evaluation Criteria in Solid Tumors version 1.1. [b]HR was based on an unstratified Cox regression model including only treatment as a covariate.
Abbreviations: CI, confidence interval; HR, hazard ratio; ICC, investigator-chosen chemotherapy; PFS, progression-free survival.

Table 2. Disease Response

	Tislelizumab + ICC (n=182)	Placebo + ICC (n=188)
ORR, % (95% CI)	64.8 (57.4, 71.8)	44.1 (36.9, 51.6)
Complete response, n (%)	3 (1.6)	3 (1.6)
Partial response, n (%)	115 (63.2)	80 (42.6)
Stable disease, n (%)	42 (23.1)	75 (39.9)
Progressive disease, n (%)	8 (4.4)	20 (10.6)
Not evaluable[a]/not assessable, n (%)	14 (7.7)	10 (5.3)
Median DoR, months (95% CI)	7.4 (5.6, 9.5)	5.7 (4.3, 7.5)

[a]Based on Response Evaluation Criteria in Solid Tumors version 1.1.
Abbreviations: CI, confidence interval; DoR, duration of response; ICC, investigator-chosen chemotherapy; ORR, objective response rate.

Safety

- A summary of the safety findings is shown in **Table 3**
- For tislelizumab + ICC and placebo + ICC, respectively, treatment-related adverse events (TRAEs) occurring in ≥30% of patients in either arm were anemia (70.7% vs 66.0%), neutrophil count decreased (66.3% vs 66.5%), white blood cell count decreased (63.5% vs 67.6%), decreased appetite (40.3% vs 38.8%), and nausea (33.7% vs 37.8%)
- The most common ≥grade 3 TRAEs (occurring in ≥10% of patients in either arm) in the tislelizumab + ICC and placebo + ICC arms, respectively, were neutrophil count decreased (44.2% vs 46.8%), white blood cell count decreased (18.2% vs 23.4%), and anemia (17.1% vs 16.5%)

Table 3. Safety Summary (Safety Analysis Set)

n (%)	Tislelizumab + ICC (n=181)	Placebo + ICC (n=188)
Patients with ≥1 TRAE	179 (98.9)	186 (98.9)
≥grade 3	129 (71.3)	137 (72.9)
Serious	50 (27.6)	39 (20.7)
Leading to death	5 (2.8)	3 (1.6)
Patients with ≥1 TEAE leading to any treatment discontinuation	52 (28.7)	32 (17.0)
Discontinuation of tislelizumab/placebo	20 (11.0)	11 (5.9)
Discontinuation of any chemotherapy	46 (25.4)	30 (16.0)

Data cutoff: February 28, 2022.
Abbreviations: ICC, investigator-chosen chemotherapy; TEAE, treatment-emergent adverse event; TRAE, treatment-related adverse event.

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Disclosures

Disclosure information is available online with the abstract details.

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