Randomized, Phase 3 study of second-line tislelizumab versus chemotherapy in advanced or metastatic esophageal squamous cell carcinoma, RATIONALE 302: Asia subgroup

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Background and methods

- Advanced or metastatic esophageal squamous cell carcinoma (ESCC) has a poor prognosis, with an estimated 5-year survival rate of ~5%[1]
- ESCC continues to be one of the major types of esophageal cancer in Asia, with more than 75% of global ESCC cases occurring in Asia[2–4]
- Tislelizumab is an anti-programmed cell death protein 1 (PD-1) monoclonal antibody with high affinity and specificity for PD-1, engineered to minimize binding to FcγR on macrophages to limit antibody-dependent phagocytosis, a mechanism of T-cell clearance and a potential mechanism of resistance to anti-PD-1 therapy[5,6]
- Primary results from the global Phase 3 RATIONALE 302 study (NCT03430843) demonstrated statistically significant improvement in overall survival (OS) with second-line tislelizumab compared with chemotherapy in patients with advanced or metastatic ESCC (hazard ratio [HR]: 0.7, p=0.0001, median OS of 8.6 months [95% CI: 7.5, 10.4] for tislelizumab and 6.3 months [5.3, 7.0] for chemotherapy)[7]
- Based on the primary data, the US Food and Drug Administration has accepted for review a biologics license application for tislelizumab as a potential therapeutic option in patients with unresectable recurrent locally advanced or metastatic ESCC following previous systemic therapy[8]
- Here we report the results of the Asia subgroup analysis for RATIONALE 302
- **Scan QR code to view the primary results of the RATIONALE 302 study:**

Results

Patients

- In total, 512 patients across 11 countries/regions in Asia, Europe, and North America were randomized 1:1 to receive either tislelizumab (n=256) or chemotherapy (n=256)[7]
- Of the 512 randomized patients, 404 (79%) were enrolled from China (including Taiwan), Japan, and Korea and constituted the Asia subgroup (tislelizumab, n=201, chemotherapy, n=203) (**Table 1**)
- As of final analysis data cut-off (December 1, 2020):
  - Median (range) follow-up in months was 8.2 (0.2–31.7) for tislelizumab and 5.8 (0.0–30.8) for chemotherapy

Table 1. Demographics and baseline characteristics in patients from the Asia subgroup

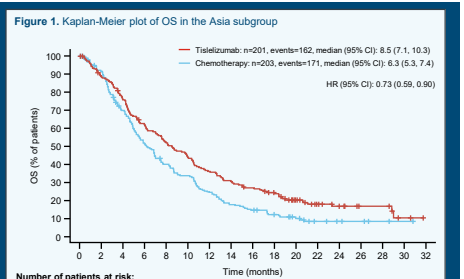
Characteristic	Tislelizumab (n=201)	Chemotherapy (n=203)
Median age (range), years	61.0 (40–83)	62.0 (41–81)
Male, n (%)	180 (89.6)	179 (88.2)
Race, n (%)		
Chinese	161 (80.1)	162 (79.8)
Japanese	25 (12.4)	25 (12.3)
Korean	15 (7.5)	16 (7.9)
ECOG PS, n (%)		
0	43 (21.4)	42 (20.7)
1	158 (78.6)	161 (79.3)
PD-L1 status, n (%)		
TAP score ≥ 10%*	67 (33.3)	58 (28.6)
TAP score < 10%*	89 (44.3)	103 (50.7)
Unknown	45 (22.4)	42 (20.7)
Disease status at study entry, n (%)		
Locally advanced	3 (1.5)	14 (6.9)
Metastatic	198 (98.5)	189 (93.1)
Prior therapies, n (%)		
Surgery	85 (42.3)	89 (43.8)
Radiotherapy	135 (67.2)	129 (63.5)
Platinum-based chemotherapy	193 (96.0)	199 (98.0)

*PD-L1 expression was centrally assessed using the analytically validated VENTANA PD-L1 (SP263) assay with TAP score, which is defined as the total percentage of the tumor area covered by tumor cells with any membrane staining above background and tumor-associated immune cells with any staining above background
ECOG PS, Eastern Cooperative Oncology Group performance score; PD-L1, programmed death-ligand 1; TAP, tumor area positivity

Conclusions

- In the Asia subgroup, tislelizumab **improved OS and tumor response** compared with chemotherapy as second-line treatment in patients with advanced or metastatic ESCC and showed **a well-tolerated safety profile**
- These findings were consistent with published results in the overall population of RATIONALE 302[7]

Figure 1. Kaplan-Meier plot of OS in the Asia subgroup



Data cut-off: December 1, 2020
Medians were estimated by Kaplan-Meier method with 95% CIs estimated using the method of Brookmeyer; †HR was based on unstratified Cox regression model
HR, hazard ratio, OS, overall survival

Efficacy

- Tislelizumab improved OS compared with chemotherapy in the Asia subgroup
  - Median OS was 8.5 months with tislelizumab and 6.3 months with chemotherapy
  - A 27% reduction in the risk of death (HR 0.73; 95% CI 0.59, 0.90) with a 2.2-month improvement in median OS was observed in Asian patients within the intent-to-treat population (**Figure 1**)
- Median PFS was 1.5 months with tislelizumab compared to 1.7 months with chemotherapy (HR 0.81; 95% CI 0.64, 1.02)

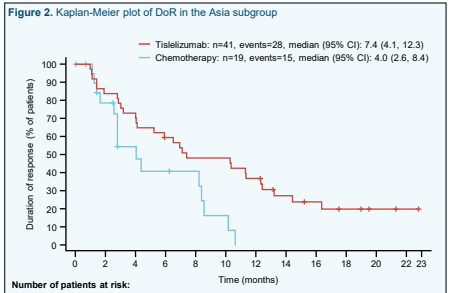
Table 2. Summary of antitumor activity per RECIST v1.1 (investigator-assessed)

	Tislelizumab (n=201)	Chemotherapy (n=203)
ORR, % (95% CI)*	20.4 (15.1, 26.6)	9.4 (5.7,14.2)
Odds ratio for ORR, (95% CI)	2.5 (1.4, 4.5)	
Best overall response, n (%)		
Complete response	3 (1.5)	1 (0.5)
Partial response	38 (18.9)	18 (8.9)
Stable disease	51 (25.4)	62 (30.5)
Progressive disease	93 (46.3)	70 (34.5)
Not determined†	16 (8.0)	52 (25.6)
Median DoR, months (95% CI)‡	7.4 (4.1, 12.3)	4.0 (2.6, 8.4)

*Data cut-off: December 1, 2020. *ORR is unconfirmed and defined as proportion of number of patients with a PR or CR per RECIST v1.1; Two-sided 95% CI was calculated using Clopper-Pearson method. †Not evaluable based on RECIST V1.1 or not assessable based on patients with no post-baseline tumor assessment by data cut-off, including those who discontinued study for any reason or died without having any post-baseline tumor assess. ‡Medians were estimated by Kaplan-Meier method with 95% CIs estimated using the method of Brookmeyer and Crowley. DoR analysis included patients with objective response (complete or partial response). CI, confidence interval; DoR, duration of response; ORR, overall response rate; RECIST, response evaluation criteria in solid tumors*

- Tislelizumab was associated with higher objective response rate compared with chemotherapy, 20.4% vs 9.4%, respectively (**Table 2**)
- Tislelizumab resulted in more durable response compared with chemotherapy, 7.4 vs 4.0 months (**Table 2, Figure 2**)

Figure 2. Kaplan-Meier plot of DoR in the Asia subgroup



Data cut-off: December 1, 2020
Medians were estimated by Kaplan-Meier method with 95% CIs estimated using the method of Brookmeyer; †HR was based on unstratified Cox regression model
CI, confidence interval; DoR, duration of response ; HR, hazard ratio

Safety

- Tislelizumab's safety profile in the Asia subgroup patients is shown in **Table 3**
  - These findings were consistent with the safety results in the overall population[7]
- A smaller proportion of patients in the Asia subgroup experienced ≥ Grade 3 TEAEs with tislelizumab (42.8%) compared with chemotherapy (67.0%)
- A smaller proportion of patients in the Asia subgroup discontinued tislelizumab compared with chemotherapy due to a TEAE (19.9% vs 25.7%)

Table 3. Overall summary of TEAEs and treatment-related TEAEs in the Asia subgroup

Patients, n (%)	Tislelizumab (n=201)	Chemotherapy (n=203)
Patients with at least one TEAE*	192 (95.5)	189 (99.0)
Treatment-related TEAE	149 (74.1)	182 (95.3)
≥ Grade 3 TEAEs	86 (42.8)	128 (67.0)
Treatment-related TEAEs of ≥ Grade 3	39 (19.4)	109 (57.1)
Serious TEAEs	83 (41.3)	82 (42.9)
Treatment-related serious TEAEs	31 (15.4)	40 (20.9)
TEAE leading to treatment discontinuation	40 (19.9)	49 (25.7)
Treatment-related TEAE leading to treatment discontinuation	15 (7.5)	31 (16.2)
TEAE leading to death†	11 (5.5)	9 (4.7)
Treatment-related TEAE leading to death†	3 (1.5)	5 (2.6)

Data cut-off: December 1, 2020
Per protocol, all adverse events were recorded during the study and for up to 30 days after the last dose of study drug or until the initiation of another anticancer therapy. †Death events due to disease progression were excluded.TEAE, treatment-emergent adverse event

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