Randomized, Phase 3 Study of Second-Line Tislelizumab vs Chemotherapy in Advanced or Metastatic Esophageal Squamous Cell Carcinoma, RATIONALE 302: Asia Subgroup

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Disclosure of conflicts of interest

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Background and methods

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- Advanced or metastatic 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-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 OS with second-line tislelizumab compared with chemotherapy in patients with advanced or metastatic ESCC (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 FDA 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 the QR code to view the methodology and primary results of the RATIONALE 302 study

1. Howlader N, et al. SEER Cancer Statistics Review, 1975–2017. National Cancer Institute, MD, USA (2020); 2. Zhang H, et al. *Chin J Cancer.* 2012;31:281–6; 3. Kurumi H and Isomoto H. *Cancers.* 2020; 12:2898; 4. Pakzad R, et al. *Ann Transl Med.* 2016;4:29; 5. Zhang T, et al. *Cancer Immunol Immunother.* 2018;67:1079–90; 6. Qin S, et al. *Future Oncol.* 2019;15:1811–22; 7. Shen L, et al. *J Clin Oncol.* 2021;39:4012; 8. OncLive. FDA Accepts BLA for Tislelizumab in Esophageal Squamous Cell Carcinoma. Available at: https://www.onclive.com/view/fda-acc epts-bla-for-tislelizumab-in-esophageal-squamous-cell-carcinoma. Accessed December 2021.

ESCC, esophageal squamous cell carcinoma; FDA, Food and Drug Administration; HR, hazard ratio; OS, overall survival; PD-1, programmed cell death protein 1.

Patient demographics and baseline characteristics

Data cut off: December 1, 2020

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- 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)[1]
- 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)
- Median (range) follow-up in months was 8.2 (0.2–31.7) for tislelizumab and 5.8 (0.0–30.8) for chemotherapy

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%[a]	67 (33.3)	58 (28.6)
TAP score < 10%[a]	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)

1. Shen L, et al. *J Clin Oncol.* 2021;39:4012.

[a]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.

Tislelizumab improved OS compared with chemotherapy in the Asia subgroup

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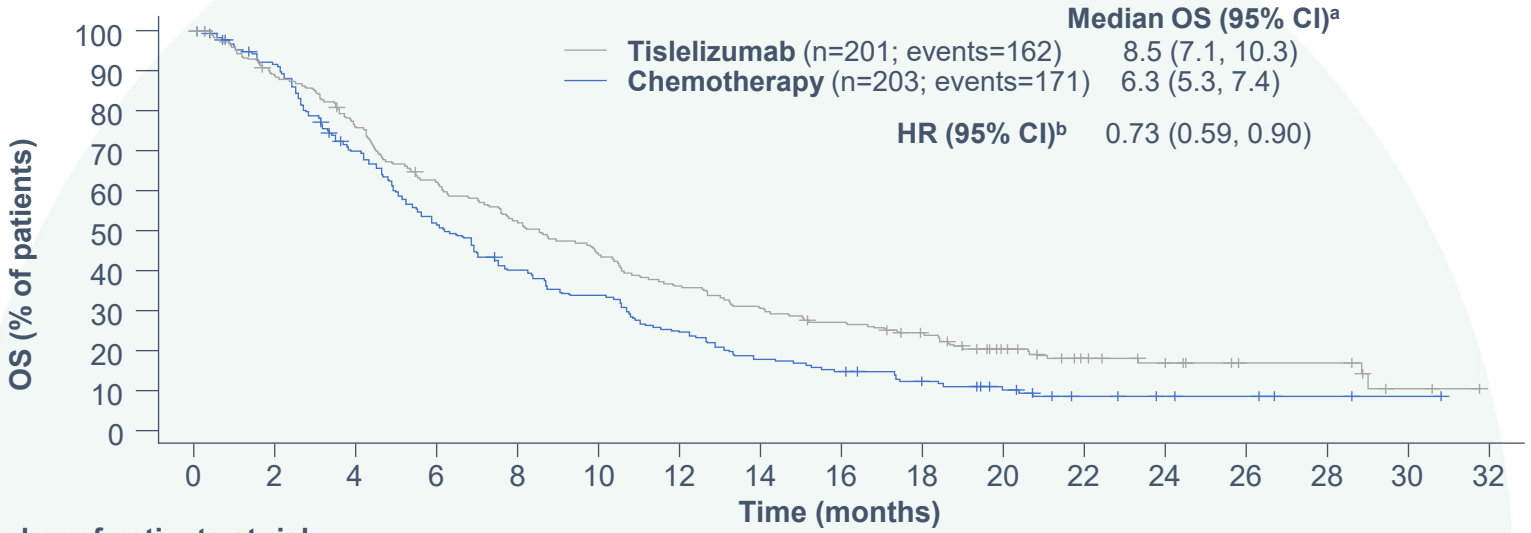
- Median OS was 8.5 months with tislelizumab and 6.3 months with chemotherapy
- A 27% reduction in the risk of death (HR 0.73; 95% CI 0.59, 0.90) with a 2.2-month improvement in median OS was observed in Asian patients within the intent-to-treat population
- Median PFS was 1.5 months with tislelizumab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



Number of patients at risk:

Time:	0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31	32
Tislelizumab	201	192	177	169	151	133	122	113	103	94	87	76	71	66	61	56	53	49	42	34	29	24	20	18	13	11	8	8	8	3	2	1	0
Chemotherapy	203	187	177	153	133	113	98	83	76	66	64	50	47	40	34	32	28	25	20	18	14	10	7	6	5	4	4	2	2	1	1	0	0

Data cut-off date: December 1, 2020

[a]Medians were estimated by Kaplan-Meier method with 95% CIs estimated using the method of Brookmeyer.

[b]HR was based on unstratified Cox regression model.

HR, hazard ratio; OS, overall survival.

Antitumor activity per RECIST v1.1

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- Tislelizumab was associated with a higher ORR compared with chemotherapy, 20.4% vs 9.4%, respectively

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

Parameter	Tislelizumab (n=201)	Chemotherapy (n=203)
ORR, % (95% CI)[a]	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[b]	16 (8.0)	52 (25.6)
Median DoR, months (95% CI)[c]	7.4 (4.1, 12.3)	4.0 (2.6, 8.4)

Data cut-off: December 1, 2020.
[a]ORR is unconfirmed and defined as the proportion of number of patients with a PR or CR per RECIST v1.1; two-sided 95% CI was calculated using Clopper-Pearson method.
[b]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.
[c]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 (CR or PR).
CI, confidence interval; CR, complete response; DoR, duration of response; ORR, overall response rate; PR, partial response; RECIST, response evaluation criteria in solid tumors.

Tislelizumab improved DoR compared with chemotherapy in the Asia subgroup

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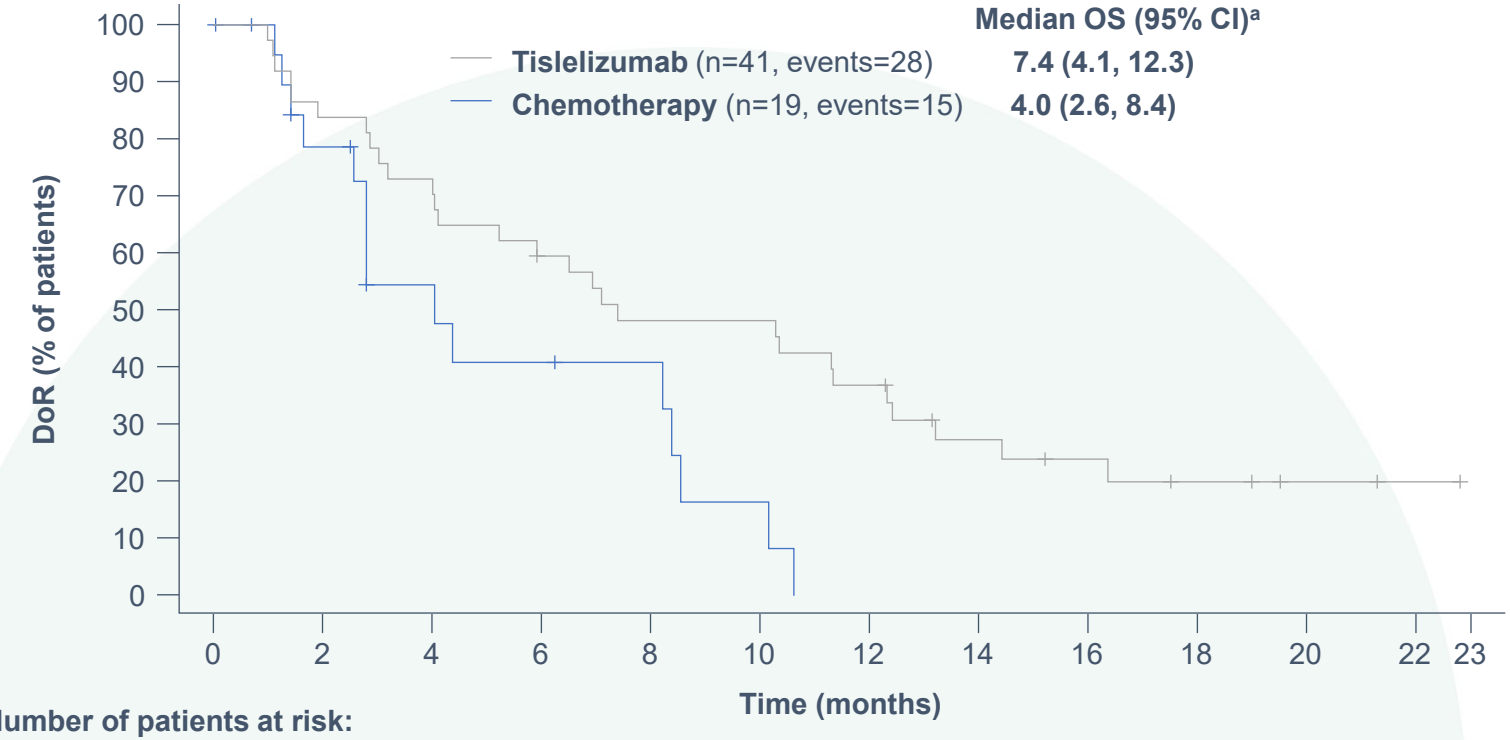
- Tislelizumab resulted in more durable response compared with chemotherapy, 7.4 vs 4.0 months



Number of patients at risk:

Time:	0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23
Tislelizumab	41	36	31	29	27	24	21	19	17	17	17	15	13	10	8	7	6	5	4	3	2	2	1	0
Chemotherapy	19	19	14	8	8	6	6	5	5	2	2	0	0	0	0	0	0	0	0	0	0	0	0	0

Data cut-off: December 1, 2020

[a]Medians were estimated by Kaplan-Meier method with 95% CIs estimated using the method of Brookmeyer.

CI, confidence interval; DoR, duration of response.

Safety findings in the Asia subgroup were consistent with the safety results in the overall patient population[1]

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- 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%)

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

Patients, n (%)	Tislelizumab (n=201)	Chemotherapy (n=191)
Patients with at least one TEAE[a]	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[b]	11 (5.5)	9 (4.7)
Treatment-related TEAE leading to death[b]	3 (1.5)	5 (2.6)

1. Shen L, et al. *J Clin Oncol.* 2021;39:4012.
[a]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.
[b]Death events due to disease progression were excluded.
TEAE, treatment-emergent adverse event.

Conclusions

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- 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[1]

1. Shen L, et al. *J Clin Oncol.* 2021;39:4012.

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