Second-line tislelizumab vs chemotherapy in advanced or metastatic esophageal squamous cell carcinoma: RATIONALE 302 Japanese subgroup

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Conflict of interest disclosure slide for representative speakers or investigators

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	No	If yes, please specify the name of company and/or organization, your status.
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fees of testimony, judgment, comment, etc.	X	
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profit of stock	X	
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contributions	X	
fees of testimony, judgment, comment, etc.	X	
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Introduction and methods

- Advanced or metastatic ESCC has a poor prognosis, with an estimated 5-year survival rate of ~5%[1]
- Tislelizumab is an anti-PD-1 monoclonal antibody designed to minimize FcγR binding on macrophages to limit antibody-dependent phagocytosis, a mechanism of T-cell clearance and a potential resistance to anti-PD-1 therapy[2,3]
- Primary results from the global Phase 3 RATIONALE 302 study (NCT03430843) demonstrated statistically significant improvement in overall survival (median OS: 8.6 vs 6.3 months, HR 0.70, p=0.0001) with tislelizumab compared with chemotherapy alone as second-line treatment in patients with advanced or metastatic ESCC[4]
- Here, we report the results of a subgroup analysis of Japanese patients from the RATIONALE 302 study
- **Scan QR code to view the primary results of the RATIONALE 302 study:**

ClinicalTrials.gov Identifier: NCT03430843

ESCC, esophageal squamous cell carcinoma; FcγR, Fcγ receptor; OS, overall survival; PD-1, programmed cell death protein 1

1. Howlader N, et al. SEER Cancer Statistics Review, 1975–2017. National Cancer Institute, MD, USA (2020); 2. Qin S, et al. Future Oncol 2019;15:1811–22; 3. Zhang T, et al. Cancer Immunol Immunother 2018;67:1079–90;
4. Shen L, et al. J Clin Oncol. 2021;29:4012 (Poster 4012) [presented at ASCO 2021]

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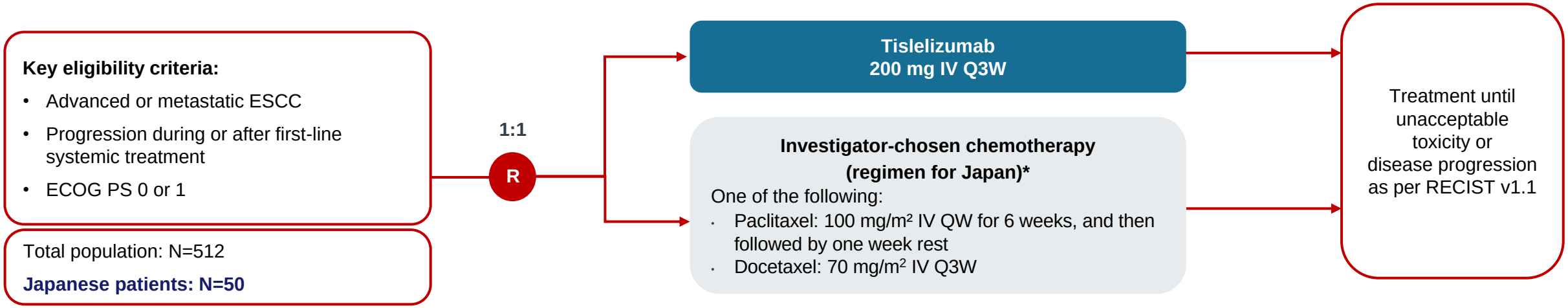
Study design and patient population



Stratification factors

- Region: Asia (excl. Japan) vs Japan vs Europe/North America
- ECOG PS: 0 vs 1
- Chemotherapy option: Paclitaxel vs docetaxel vs irinotecan

Endpoints

- **Primary endpoint:** OS in all randomized patients (ITT population)
- **Key secondary endpoint:** OS in the PD-L1 TAP score ≥ 10% population†
- **Other secondary endpoints:** PFS, ORR, DoR, and safety

- Of the 512 randomized patients, 50 (9.8%) Japanese patients were randomized to receive tislelizumab (n=25) or chemotherapy (n=25)
- As of final analysis data cut-off on December 1, 2020, median (range) follow-up‡ was 9.8 (2.7–22.0) months for tislelizumab and 6.1 (0.2–20.3) months for chemotherapy

*Patients in countries other than Japan received paclitaxel 135–175 mg/m² IV Q3W or 80–100 mg/m² IV QW, docetaxel 75 mg/m² IV Q3W, or irinotecan 125 mg/m² IV on Days 1 and 8, Q3W; †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; ‡Study follow-up time is defined as the time from randomization date to study discontinuation date (due to death, consent withdrawal or lost to follow-up) or to study cut-off date if a patient is ongoing in the study

DoR, duration of response; ECOG PS, Eastern Cooperative Oncology Group performance score; ESCC, esophageal squamous cell carcinoma; ITT, intent-to-treat; IV, intravenously; ORR, objective response rate; OS, overall survival; PD-L1, programmed cell death ligand 1; PFS, progression-free survival; Q3W, every three weeks; QW, once weekly; R, randomized; RECIST, Response Evaluation Criteria in Solid Tumours; TAP, tumor area positivity

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Demographics and baseline characteristics: Japanese subgroup

Characteristic	Tislelizumab (n=25)	Chemotherapy (n=25)	Total (N=50)
Age - median (range), years	67.0 (47–83)	63.0 (52–77)	65.0 (47–83)
Age ≥ 65 years, n (%)	17 (68.0)	9 (36.0)	26 (52.0)
Sex - Male, n (%)	20 (80.0)	19 (76.0)	39 (78.0)
ECOG PS, n (%)			
0	14 (56.0)	14 (56.0)	28 (56.0)
1	11 (44.0)	11 (44.0)	22 (44.0)
PD-L1 status, n (%)*			
TAP ≥ 10%	12 (48.0)	7 (28.0)	19 (38.0)
TAP < 10%	6 (24.0)	13 (52.0)	19 (38.0)
Missing†	7 (28.0)	5 (20.0)	12 (24.0)
Disease status at baseline, n (%)			
Locally advanced	0 (0.0)	4 (16.0)	4 (8.0)
Metastatic	25 (100.0)	21 (84.0)	46 (92.0)
Prior therapies, n (%)			
Surgery	11 (44.0)	8 (32.0)	19 (38.0)
Radiotherapy	20 (80.0)	15 (60.0)	35 (70.0)
Platinum-based chemotherapy	23 (92.0)	25 (100.0)	48 (96.0)

Data cut-off: December 1, 2020

*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; †Missing refers to the patients without sample collection or not evaluable at baseline

ECOG PS, Eastern Cooperative Oncology Group performance score; PD-L1, programmed cell death ligand 1; TAP, tumor area positivity

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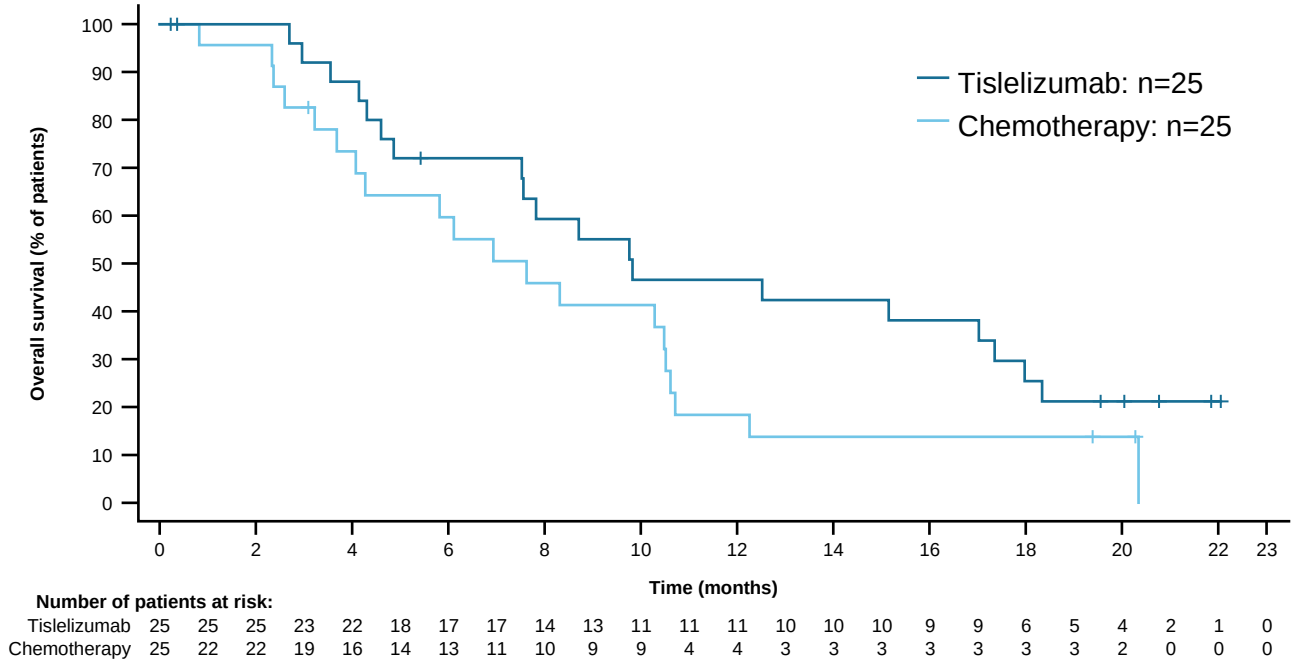
Overall survival: Japanese subgroup



	Tislelizumab (n=25)	Chemotherapy (n=25)
Events (% of patients)	19 (76.0)	20 (80.0)
Median OS (95% CI), months*	9.8 (7.5, 17.3)	7.6 (4.1, 10.5)
HR (95% CI)†	0.59 (0.31, 1.12)	

Tislelizumab improved OS compared with chemotherapy in the Japanese subgroup (ITT population)

Data cut-off: December 1, 2020

*Medians were estimated by Kaplan-Meier method with 95% CIs estimated using the method of Brookmeyer and Crowley; †Hazard ratio was based on unstratified Cox regression model only including treatment arm as a factor

CI, confidence interval; HR, hazard ratio; ITT, intent-to-treat; OS, overall survival

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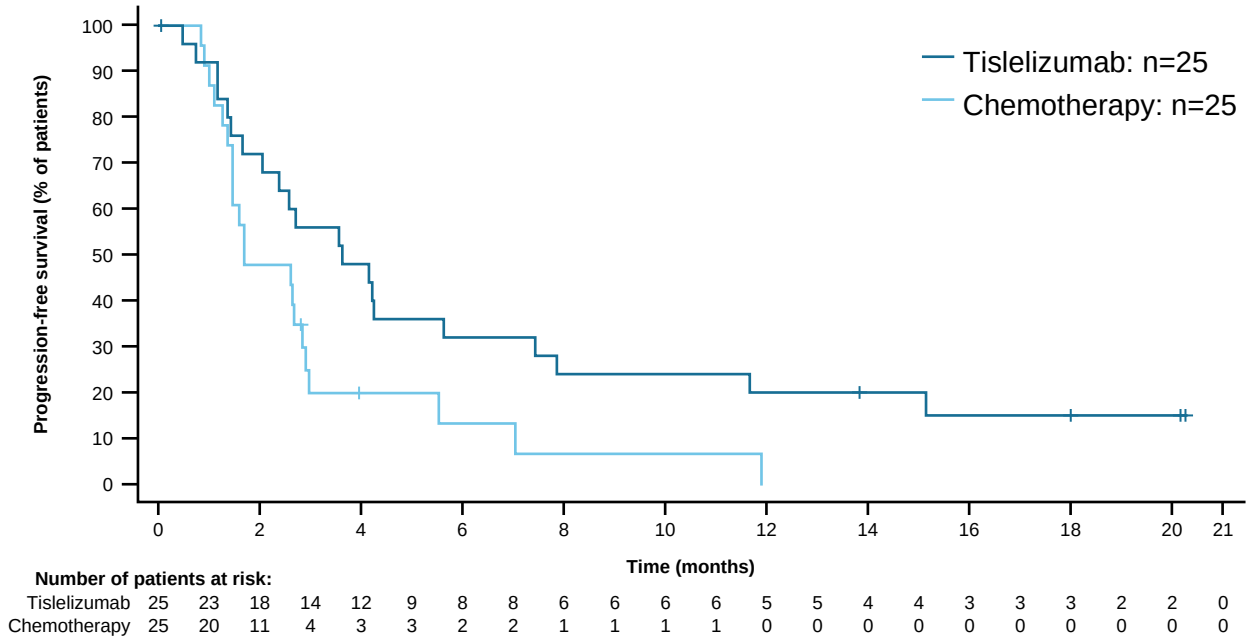
Progression-free survival: Japanese subgroup



	Tislelizumab (n=25)	Chemotherapy (n=25)
Events (% of patients)	21 (84.0)	21 (84.0)
Median PFS (95% CI), months*	3.6 (2.0, 7.4)	1.7 (1.4, 2.8)
HR (95% CI)†	0.50 (0.27, 0.95)	

Tislelizumab improved PFS compared with chemotherapy in the Japanese subgroup (ITT population)

Data cut-off: December 1, 2020

*Medians were estimated by Kaplan-Meier method with 95% CIs estimated using the method of Brookmeyer and Crowley; †Hazard ratio was based on unstratified Cox regression model only including treatment arm as a factor

CI, confidence interval; HR, hazard ratio; ITT, intent-to-treat; PFS, progression-free survival

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Disease response and duration of response: Japanese subgroup

	Tislelizumab (n=25)	Chemotherapy (n=25)
ORR, % (95% CI)	32.0 (14.9, 53.5)	20.0 (6.8, 40.7)
Odds ratio for ORR, (95% CI)	2.15 (0.55, 8.45)	
Best overall response, n (%)		
Complete response	1 (4.0)	1 (4.0)
Partial response	7 (28.0)	4 (16.0)
Stable disease	10 (40.0)	6 (24.0)
Progressive disease	7 (28.0)	11 (44.0)
Not determined*	0 (0)	3 (12.0)
Median DoR (95% CI), months	8.8 (2.9, NE)	2.6 (1.1, 10.6)

Tislelizumab was associated with higher ORR and a more durable antitumor response compared with chemotherapy in the Japanese subgroup (ITT population)

Data cut-off: December 1, 2020

Disease response and duration of response per RECIST 1.1

*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

CI, confidence interval; DoR, duration of response; ITT, intent-to-treat; NE, not evaluable; ORR, objective response rate; RECIST, Response Evaluation Criteria in Solid Tumours

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Safety: Japanese subgroup

	Tislelizumab (n=25)	Chemotherapy (n=23)
Patients with at least one TEAE	24 (96.0)	22 (95.7)
Treatment-related TEAE	17 (68.0)	22 (95.7)
≥ Grade 3 TEAEs	11 (44.0)	16 (69.6)
Treatment-related TEAEs of ≥ Grade 3	6 (24.0)	11 (47.8)
Serious TEAEs	9 (36.0)	10 (43.5)
Treatment-related serious TEAEs	4 (16.0)	2 (8.7)
TEAE leading to treatment discontinuation	2 (8.0)	4 (17.4)
Treatment-related TEAE leading to treatment discontinuation	2 (8.0)	2 (8.7)
TEAE leading to death	1 (4.0)	1 (4.3)
Treatment-related TEAE leading to death	0 (0)	0 (0)

Tislelizumab showed a favorable safety profile compared with chemotherapy, with no new safety signals identified in the Japanese subgroup*

Data cut-off: December 1, 2020

All AEs were graded based on National Cancer Institute–Common Terminology Criteria for Adverse Events (version 4.03); TRAEs include TEAEs that were considered by the investigator to be related to study drug or TEAEs with a missing causality

*The safety population included all patients who received ≥ 1 dose of study treatment

AE, adverse event; TEAE, treatment-emergent adverse event; TRAE, treatment-related adverse event

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Conclusions

- In Japanese patients in the RATIONALE 302 study
  - **Tislelizumab improved OS compared with chemotherapy** as second-line treatment in patients with advanced or metastatic ESCC
  - Tislelizumab also showed a favorable improvement in PFS, and a higher and more durable antitumor response compared with chemotherapy
  - **The safety profile of tislelizumab was favorable compared to that of chemotherapy, with no new safety signals identified**
- The above findings were consistent with published results in the overall patient population of study RATIONALE 302[1]

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ESCC, esophageal squamous cell carcinoma; OS, overall survival; PFS, progression-free survival

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

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