RATIONALE 302: RATIONALE 302: Randomized, Phase 3 study of tislelizumab vs chemotherapy as second-line treatment for advanced unresectable/metastatic esophageal squamous cell carcinoma

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Tislelizumab: A Novel Monoclonal Anti-PD-1 Antibody

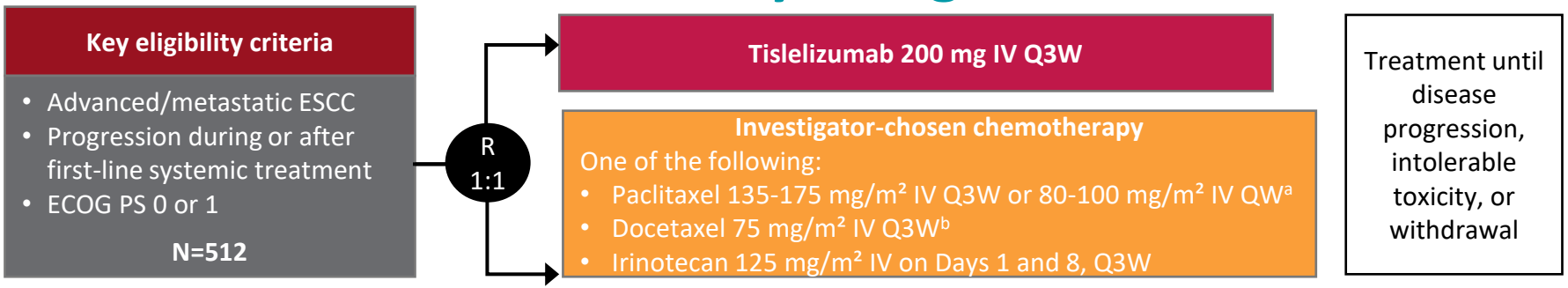
- Advanced or metastatic ESCC has an estimated 5-year survival rate of 5%[1]
- Single-agent chemotherapy is recommended when ESCC progresses after first-line therapy but is associated with limited survival and poor tolerability[2-6]
- Second-line use of anti-PD-1/L1 monoclonal antibodies has improved OS versus chemotherapy[3-5]
- Tislelizumab has high affinity and specificity for PD-1 and was designed to minimize binding to FcγR on macrophages to limit antibody-dependent phagocytosis[7]

We report data from the overall and EU/NA populations in the RATIONALE 302 study (NCT03430843) that evaluated the efficacy and safety of second-line tislelizumab in patients with advanced or metastatic ESCC[8]

1. Howlader N, et al. SEER Cancer Statistics Review, 1975–2017. National Cancer Institute, Bethesda, MD, USA (2020). https://seer.cancer.gov/csr/1975_2017/. 2. Ford HE, et al. *Lancet Oncol*. 2014;15:78-86. 3. Huang J, et al. *Lancet Oncol.* 2020;21:832-842. 4. Kato K, et al. *Lancet Oncol*. 2019;20:1506-1517. 5. Kojima T, et al. *J Clin Oncol*. 2020;38:4138-4148. 6. NCCN Clinical Practice Guidelines in Oncology. Esophageal and Esophagogastric Junction Cancers, Version 2.2021 – March 9, 2021. https://www.nccn.org/professionals/physician_gls/pdf/esophageal.pdf. 7. Zhang T, et al. *Cancer Immunol Immunother.* 2018;67:1079-1090. 8. Shen L, et al. Poster presented at ASCO 2021 Virtual Conference, June 4-8, 2021.

Abbreviations: ESCC, esophageal squamous cell carcinoma; EU, European Union; NA, North America; OS, overall survival; PD-1, programmed cell death protein-1; PD-L1, programmed death- ligand 1.

RATIONALE 302: Study Design



Stratification factors

- Region (Asia [excluding 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
- Key secondary endpoint: OS in patients with vCPS ≥10%[c]
- Other secondary endpoints: PFS, ORR, DoR, HRQoL, and safety

- The study required ~400 death events to achieve 82% power to detect an HR of 0.75 at 0.025 significance level (one-sided) for the primary endpoint of OS in all randomized patients (ITT analysis set)

ClinicalTrials.gov: NCT03430843

Assessment of tumor-response status was performed approximately every 6 weeks (± 7 days) for the first 6 months and every 9 weeks (± 7 days) thereafter.

[a]For Japan: paclitaxel 100 mg/m² IV in cycles consisting of weekly dosing for 6 weeks, followed by 1 week of rest. [b]For Japan: docetaxel 70 mg/m² IV Q3W. [c]PD-L1 expression centrally assessed by immunohistochemistry with the Ventana SP263 assay.

Abbreviations: DoR, duration of response; ECOG PS, Eastern Cooperative Oncology Group performance score; ESCC, esophageal squamous cell carcinoma; HR, hazard ratio; HRQoL, health-related quality of life; ITT, intent-to-treat; IV, intravenously; ORR, objective response rate; OS, overall survival; PD-L1, programmed death-ligand 1; PFS, progression-free survival; QW, once weekly; Q3W, every three weeks; vCPS, visually-estimated combined positive score.

Demographics and Baseline Patient Characteristics

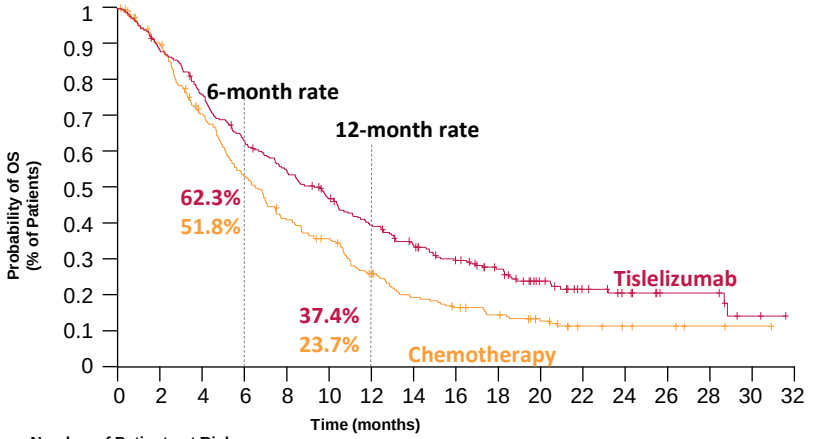
		Overall Population		EU/NA Subgroup	
		Tislelizumab (n=256)	Chemotherapy (n=256)	Tislelizumab (n=55)	Chemotherapy (n=53)
Median Age (range), years		62 (40–86)	63 (35–81)	65 (41–86)	65 (35–80)
Male, n (%)		217 (84.8)	215 (84.0)	37 (67.3)	36 (67.9)
Region	Asia	201 (78.5)	203 (79.3)	0.0	0.0
	Europe/North America	55 (21.5)	53 (20.7)	55 (100)	53 (100.0)
	Spain	14 (5.5)	10 (3.9)	14 (25.5)	10 (18.9)
Race, n (%)	Asian	201 (78.5)	207 (80.9)	0.0	4 (7.5)
	White/Caucasian	53 (20.7)	44 (17.2)	53 (96.4)	44 (83.0)
	Black/African American	0.0	2 (0.8)	0.0	2 (3.8)
	Other[a]	2 (0.8)	3 (1.2)	2 (3.6)	3 (5.7)
ECOG PS, n (%)	0	66 (25.8)	60 (23.4)	23 (41.8)	18 (34.0)
	1	190 (74.2)	196 (76.6)	32 (58.2)	35 (66.0)
PD-L1 Status[b], n (%)	vCPS ≥10%	89 (34.8)	68 (26.6)	22 (40.0)	10 (18.9)
	vCPS <10%	116 (45.3)	140 (54.7)	27 (49.1)	37 (69.8)
	Unknown	51 (19.9)	48 (18.8)	6 (10.9)	6 (11.3)
Disease Status at Baseline, n (%)	Locally advanced	5 (2.0)	20 (7.8)	2 (3.6)	6 (11.3)
	Metastatic	251 (98.0)	236 (92.2)	53 (96.4)	47 (88.7)
Prior Therapies, n (%)	Surgery	94 (36.7)	99 (38.7)	9 (16.4)	10 (18.9)
	Radiotherapy	169 (66.0)	163 (63.7)	34 (61.8)	34 (64.2)
	Platinum-based chemotherapy	249 (97.3)	252 (98.4)	54 (98.2)	53 (100.0)

Data cut-off date: December 1, 2020. Overall population was stratified according to region, ECOG PS, and chemotherapy treatment.
[a]Including categories of "not reported," "unknown," and "other." [b]PD-L1 expression centrally assessed by immunohistochemistry with the Ventana SP263 assay.
Abbreviations: ECOG PS, Eastern Cooperative Oncology Group performance score; EU, European Union; NA, North America; PD-L1, programmed death-ligand 1; vCPS, visually-estimated combined positive score.

Overall Survival

Overall Population

Treatment	N	Events, n (%)	Median OS (95% CI), months[a]	Tislelizumab vs Chemotherapy	
				Hazard Ratio (95% CI)[b]	*P*-value
Tislelizumab	256	197 (77.0)	8.6 (7.5–10.4)	0.70 (0.57–0.85)	0.0001[c]
Chemotherapy	256	213 (83.2)	6.3 (5.3–7.0)		

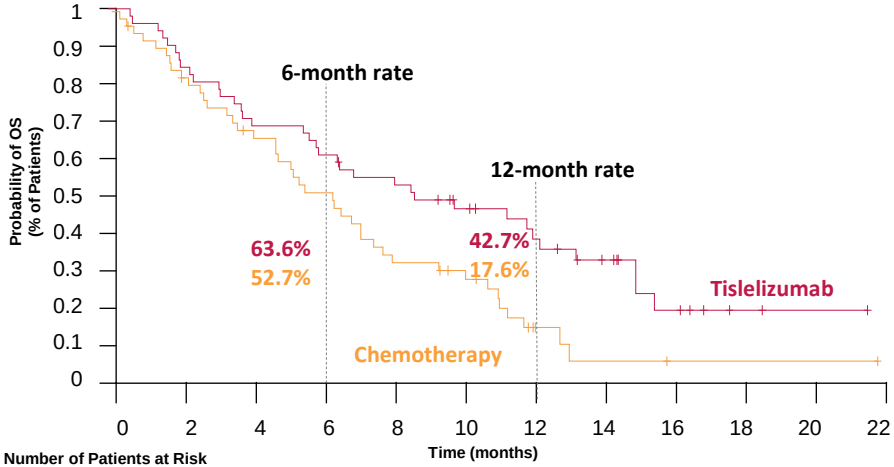


Number of Patients at Risk

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	256	245	226	214	191	172	157	144	134	122	110	96	88	81	73	63	59	52	44	35	30	25	20	18	13	11	8	8	8	3	2	1	0
Chemotherapy	256	235	219	191	167	143	124	105	93	83	77	59	51	42	36	34	29	26	21	19	15	11	7	6	5	4	4	2	2	1	1	0	0

EU/NA Subgroup

Treatment	N	Events, n (%)	Median OS (95% CI), months[a]	Tislelizumab vs Chemotherapy
				Hazard Ratio (95% CI)[b]
Tislelizumab	55	35 (63.6)	11.2 (5.9–14.8)	0.55 (0.35–0.87)
Chemotherapy	53	42 (79.2)	6.3 (4.6–7.7)	



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
Tislelizumab	55	53	49	45	40	39	35	31	31	28	23	20	17	15	12	7	6	3	2	1	1	1	0
Chemotherapy	53	48	42	38	34	30	26	22	17	17	13	9	4	2	2	2	1	1	1	1	1	1	0

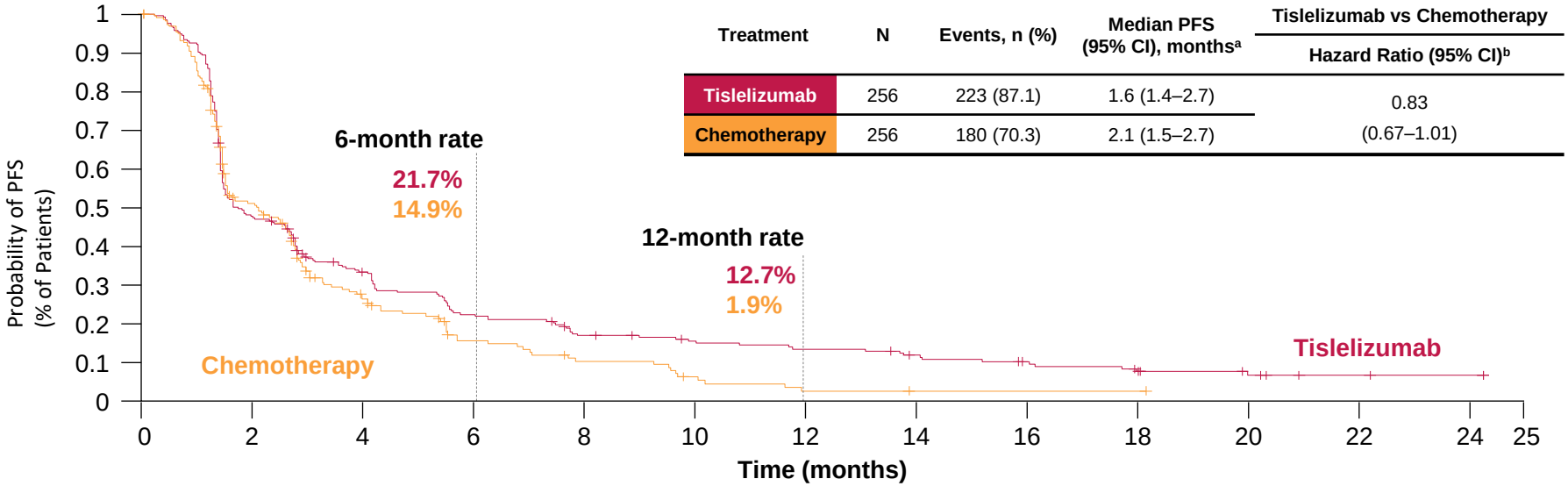
Data cut-off date: December 1, 2020. Overall population was stratified according to region, ECOG performance score, and chemotherapy treatment.

[a]Medians were estimated by Kaplan-Meier method with 95% CIs estimated using the method of Brookmeyer and Crowley; OS rates (cumulative probability of OS) were estimated by Kaplan-Meier method with 95% CIs estimated using Greenwood's formula. [b]Hazard ratio was based on unstratified Cox regression model only including treatment as a covariate. [c]One-sided *P*-value was estimated from a stratified log rank test.

Abbreviations: CI, confidence interval; ECOG, Eastern Cooperative Oncology Group; EU, European Union; NA, North America; OS, overall survival.

Progression Free Survival

Treatment	N	Events, n (%)	Median PFS (95% CI), months[a]	Tislelizumab vs Chemotherapy Hazard Ratio (95% CI)[b]
Tislelizumab	256	223 (87.1)	1.6 (1.4–2.7)	0.83 (0.67–1.01)
Chemotherapy	256	180 (70.3)	2.1 (1.5–2.7)	



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
Tislelizumab	256	233	119	85	74	62	49	46	35	32	28	27	25	25	20	18	15	13	9	8	6	3	3	2	2	0
Chemotherapy	256	184	98	57	42	33	20	16	12	12	6	4	2	2	1	1	1	1	1	0	0	0	0	0	0	0

In the EU/NA subgroup, there was no meaningful difference in PFS between the two arms (HR=0.97; 95% CI: 0.64–1.47)

Data cut-off date: December 1, 2020. Overall population was stratified according to region, ECOG performance score, and chemotherapy treatment.
[a]Medians were estimated by Kaplan-Meier method with 95% CIs estimated using the method of Brookmeyer and Crowley. [b]Hazard ratio was based on a Cox regression model.
Abbreviations: CI, confidence interval; ECOG, Eastern Cooperative Oncology Group; EU, European Union; HR, hazard ratio; NA, North America; PFS, progression-free survival.

ORR and DoR: Overall Population and EU/NA Subgroup

	Overall Population		EU/NA Subgroup	
	Tislelizumab (n=256)	Chemotherapy (n=256)	Tislelizumab (n=55)	Chemotherapy (n=53)
ORR, n	52	25	11	6
% (95% CI)[a]	20.3 (15.6–25.8)	9.8 (6.4–14.1)	20 (10.4–33.0)	11.3 (4.3–23.0)
Odds Ratio for ORR, (95% CI)[b]	2.4 (1.4–4.0)		2 (0.7–5.8)	
Best Overall Response, n (%)				
Complete Response	5 (2.0)	1 (0.4)	2 (3.6)	0 (0.0)
Partial Response	47 (18.4)	24 (9.4)	9 (16.4)	6 (11.3)
Stable Disease	68 (26.6)	82 (32.0)	17 (30.9)	20 (37.7)
Progressive Disease	116 (45.3)	86 (33.6)	23 (41.8)	16 (30.2)
Missing/Not Evaluable[c]	20 (7.8)	63 (24.6)	4 (7.3)	11 (20.8)
DoR[d]				
Median (95% CI), months	7.1 (4.1–11.3)	4.0 (2.1–8.2)	5.1 (1.6–NE)	2.1 (1.3–6.3)
Pts With Ongoing Response, n (%)	10 (19.2)	0 (0.0)	4 (36.4)	0 (0.0)

Data cut-off date: December 1, 2020. Overall population was stratified according to region, ECOG performance score, and chemotherapy treatment. Data are investigator-assessed per RECIST v1.1.
[a]Two-sided 95% CI was calculated using the Clopper-Pearson method. [b]Calculated using the Cochran-Mantel-Haenszel Chi-square test. [c]Including those with no post-baseline assessment or an unevaluable post-baseline assessment. [d]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).
Abbreviations: CI, confidence interval; DoR, duration of response; ECOG, Eastern Cooperative Oncology Group; EU, European Union; NA, North America; ORR, overall response rate; Pts, patients; RECIST, response evaluation criteria in solid tumors.

Summary of Adverse Events

	Overall Population		EU/NA Subgroup	
	Tislelizumab (n=255)	Chemotherapy (n=240)	Tislelizumab (n=54)	Chemotherapy (n=49)
Patients with ≥1 TEAE	**244 (95.7)**	**236 (98.3)**	**52 (96.3)**	**47 (95.9)**
Grade 3–5	118 (46.3)	163 (67.9)	30 (55.6)	35 (71.4)
Serious AEs	105 (41.2)	105 (43.8)	21 (38.9)	23 (46.9)
Leading to death[a]	14 (5.5)	14 (5.8)	3 (5.6)	5 (10.2)
Leading to treatment discontinuation	49 (19.2)	64 (26.7)	8 (14.8)	15 (30.6)
Most Common (Incidence ≥20%) TRAEs				
Anemia	28 (11.0)	83 (34.6)	2 (3.7)	13 (26.5)
Decreased appetite	16 (6.3)	75 (31.3)	5 (9.3)	12 (24.5)
Diarrhea	14 (5.5)	66 (27.5)	7 (13.0)	16 (32.7)
Nausea	7 (2.7)	66 (27.5)	3 (5.6)	12 (24.5)
White blood cell count decreased	5 (2.0)	98 (40.8)	0	2 (4.1)
Neutrophil count decreased	3 (1.2)	94 (39.2)	0	5 (10.2)

Data cut-off date: December 1, 2020. Overall population was stratified according to region, ECOG performance score, and chemotherapy treatment.

[a]Death events due to disease progression were excluded. All AEs are treatment-emergent and 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.

Abbreviations: AE, adverse event; ECOG, Eastern Cooperative Oncology Group; EU, European Union; NA, North America; TEAE, treatment-emergent adverse event; TRAE, treatment-related adverse event.

Conclusions

In the overall population, tislelizumab demonstrated **statistically significant and clinically meaningful improvement in OS** versus chemotherapy in patients with advanced or metastatic ESCC whose tumor progressed during or after first-line treatment

The OS benefit of tislelizumab over chemotherapy in the overall population was **consistently observed in patients from the EU/NA subgroup**

Tislelizumab showed a **higher and more durable antitumor response** in the overall population as well as in the EU/NA subgroup compared with chemotherapy

Tislelizumab demonstrated a **tolerable safety profile** compared with chemotherapy in the overall population

- Safety profile of tislelizumab in the EU/NA subgroup was **consistent with the overall population**

Data from this study suggests that tislelizumab represents a potential new second-line treatment option for patients with advanced or metastatic ESCC

Abbreviations: ESCC, esophageal squamous cell carcinoma; EU, European Union; NA, North America; OS, overall survival.