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

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3PS 3PSOLUTION

CONFLICT OF INTEREST STATEMENT

I hereby declare that I do not conduct activities that would involve a conflict of interest with CME-accreditable training, but that in the past 2 years I have received the funding listed below from the following sources:

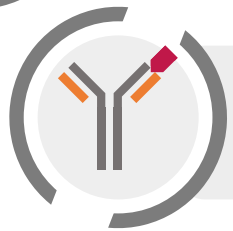
1. Medical writing assistance – BeiGene
2. Grants or contracts paid to my institution – Amgen, Bayer, Boehringer Ingelheim, Bristol-Myers Squibb, Celgene, Ipsen, Lilly, Merck Sharp & Dohme, Merck KGaA, Novartis, Roche, Servier
3. Consulting fees – Array, Astellas, Astrazeneca, Bayer, BeiGene, Biocartis, Boehringer Ingelheim, Bristol-Myers Squibb, Celgene, Daiichi, Halozyme, GSK, Incyte, Ipsen, Lilly, Merck Sharp & Dohme, Merck KGaA, Novartis, Pierre Fabre, Roche, Servier, Sirtex, Taiho

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 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, 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. Available at 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; OS, overall survival; PD-1, programmed cell death 1 receptor; PD-L1, programmed cell death-ligand 1.

RATIONALE-302 (NCT03430843): Study Design

Key eligibility criteria

- Advanced/metastatic ESCC
- Progression during or after first-line systemic treatment
- ECOG PS 0 or 1

N=512

R 1:1

Tislelizumab 200 mg IV Q3W

Investigator-chosen chemotherapy

One of the following:

- Paclitaxel 135-175 mg/m² IV Q3W or 80-100 mg/m² IV QW[a]
- Docetaxel 75 mg/m² IV Q3W[b]
- Irinotecan 125 mg/m² IV on Days 1 and 8, Q3W

Treatment until disease progression or intolerable toxicity or treatment withdrawal

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)

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; PFS, progression-free survival; QW, once weekly; Q3W, every three weeks; R, randomized; vCPS, visually-estimated combined positive score.

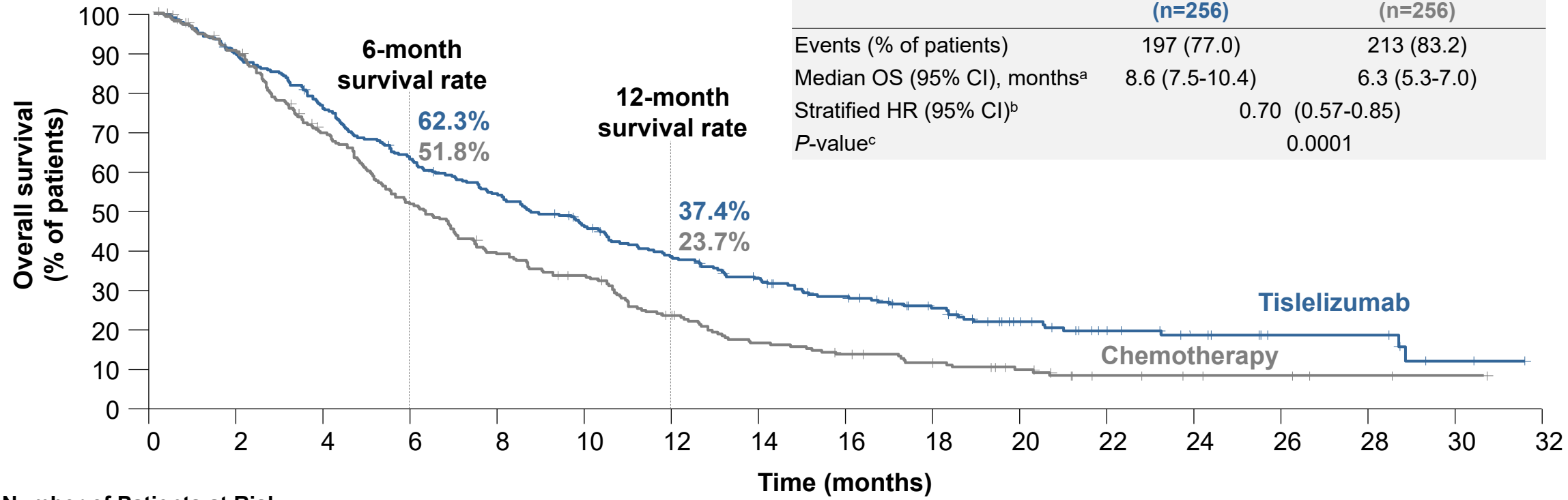
Patient Baseline Characteristics in All Randomized Patients

Characteristic	Tislelizumab (n=256)	Chemotherapy (n=256)
Median age (range), years	62.0 (40-86)	63.0 (35-81)
Male, n (%)	217 (84.8)	215 (84.0)
Region, n (%)		
Asia	201 (78.5)	203 (79.3)
Europe/North America	55 (21.5)	53 (20.7)
ECOG PS, n (%)		
0	66 (25.8)	60 (23.4)
1	190 (74.2)	196 (76.6)
PD-L1 status, n (%)[a]		
vCPS ≥10%	89 (34.8)	68 (26.6)
vCPS <10%	116 (45.3)	140 (54.7)
Unknown	51 (19.9)	48 (18.8)
Disease status at baseline, n (%)		
Locally advanced	5 (2.0)	20 (7.8)
Metastatic	251 (98.0)	236 (92.2)
Prior therapies, n (%)		
Surgery	94 (36.7)	99 (38.7)
Radiotherapy	169 (66.0)	163 (63.7)
Platinum-based chemotherapy	249 (97.3)	252 (98.4)

[a]PD-L1 expression centrally assessed by immunohistochemistry with the Ventana SP263 assay.
Abbreviations: ECOG PS, Eastern Cooperative Oncology Group performance score; PD-L1, programmed death ligand 1; vCPS, visually-estimated combined positive score.

Overall Survival in All Randomized Patients (Primary Endpoint)

	Tislelizumab (n=256)	Chemotherapy (n=256)
Events (% of patients)	197 (77.0)	213 (83.2)
Median OS (95% CI), months[a]	8.6 (7.5-10.4)	6.3 (5.3-7.0)
Stratified HR (95% CI)[b]	0.70 (0.57-0.85)	
P-value[c]	0.0001	

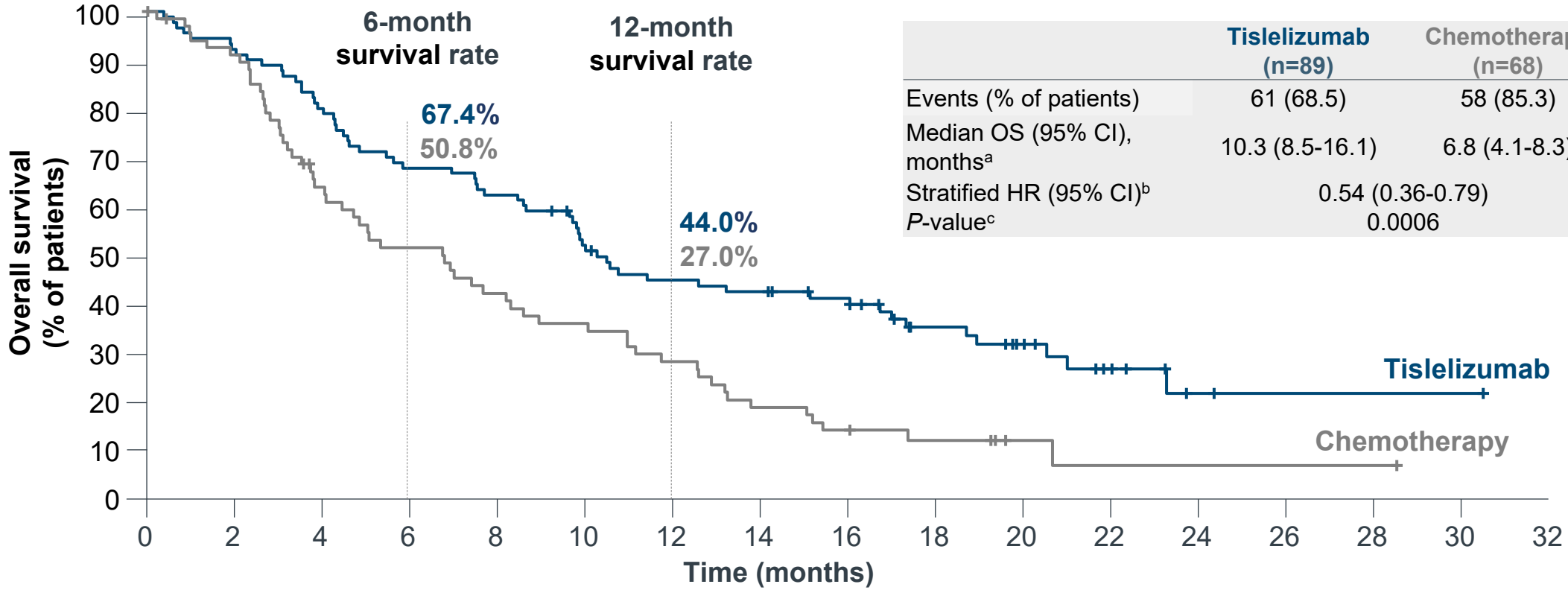


Number of Patients at Risk

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

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 [c]One-sided *P*-value was estimated from a stratified log rank test.
Abbreviations: CI, confidence interval; ECOG, Eastern Cooperative Oncology Group; HR, hazard ratio; OS, overall survival.

Overall Survival in Patients With vCPS ≥10% (Key Secondary Endpoint)



	Tislelizumab (n=89)	Chemotherapy (n=68)
Events (% of patients)	61 (68.5)	58 (85.3)
Median OS (95% CI), months[a]	10.3 (8.5-16.1)	6.8 (4.1-8.3)
Stratified HR (95% CI)[b]	0.54 (0.36-0.79)	
P-value[c]	0.0006	

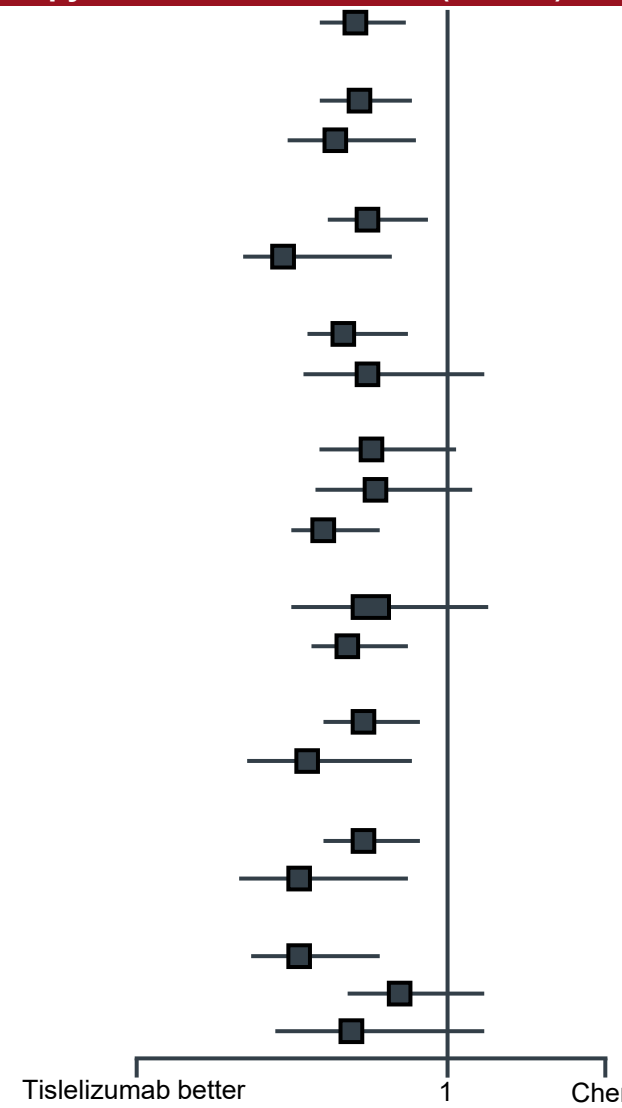
Number of patients at risk

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	89	85	82	79	71	63	60	59	55	52	43	37	36	35	34	32	30	25	19	17	14	11	8	6	2	1	1	1	1	1	1	0	0
Chemotherapy	68	63	60	51	40	35	32	29	26	22	22	19	17	14	11	11	8	6	5	5	2	1	1	1	1	1	1	1	1	0	0	0	0

[a]Medians were estimated by Kaplan-Meier method with 95% CIs estimated using the method of Brookmeyer and Crowley. [b]HR was based on a Cox regression model.
[c]One-sided *P*-value was estimated from a stratified log rank test.
Abbreviations: CI, confidence interval; HR, hazard ratio; OS, overall survival; vCPS, visually-estimated combined positive score.

Overall Survival by Subgroup in All Randomized Patients

Subgroup	Event/total: Tislelizumab	Event/total: Chemotherapy	HR for death (95% CI)	HR (95% CI)
Overall	197/256	213/256		0.69 (0.57-0.84)
Age				
Age <65	128/157	133/161		0.73 (0.57-0.93)
Age ≥65	69/99	80/95		0.64 (0.47-0.89)
Sex				
Male	171/217	178/215		0.74 (0.60-0.92)
Female	26/39	35/41		0.47 (0.27-0.80)
Smoking status				
Former/current smoker	139/188	161/192		0.67 (0.54-0.84)
Nonsmoker	58/68	52/63		0.75 (0.51-1.10)
Chemotherapy option				
Paclitaxel	197/256	68/85		0.76 (0.58-1.01)
Docetaxel	197/256	44/53		0.77 (0.56-1.07)
Irinotecan	197/256	101/118		0.61 (0.48-0.78)
ECOG PS				
0	45/64	45/63		0.73 (0.48-1.11)
1	152/192	168/193		0.69 (0.55-0.86)
Region				
Asia	162/201	171/203		0.73 (0.59-0.90)
Europe/North America	35/55	42/53		0.55 (0.35-0.87)
Race				
Asian and other	164/203	179/212		0.72 (0.59-0.90)
White	33/53	34/44		0.53 (0.32-0.87)
Baseline PD-L1 status				
PD-L1 vCPS ≥10%	61/89	58/68		0.53 (0.37-0.77)
PD-L1 vCPS <10%	97/116	121/140		0.85 (0.65-1.11)
Missing	39/51	34/48		0.69 (0.43-1.10)

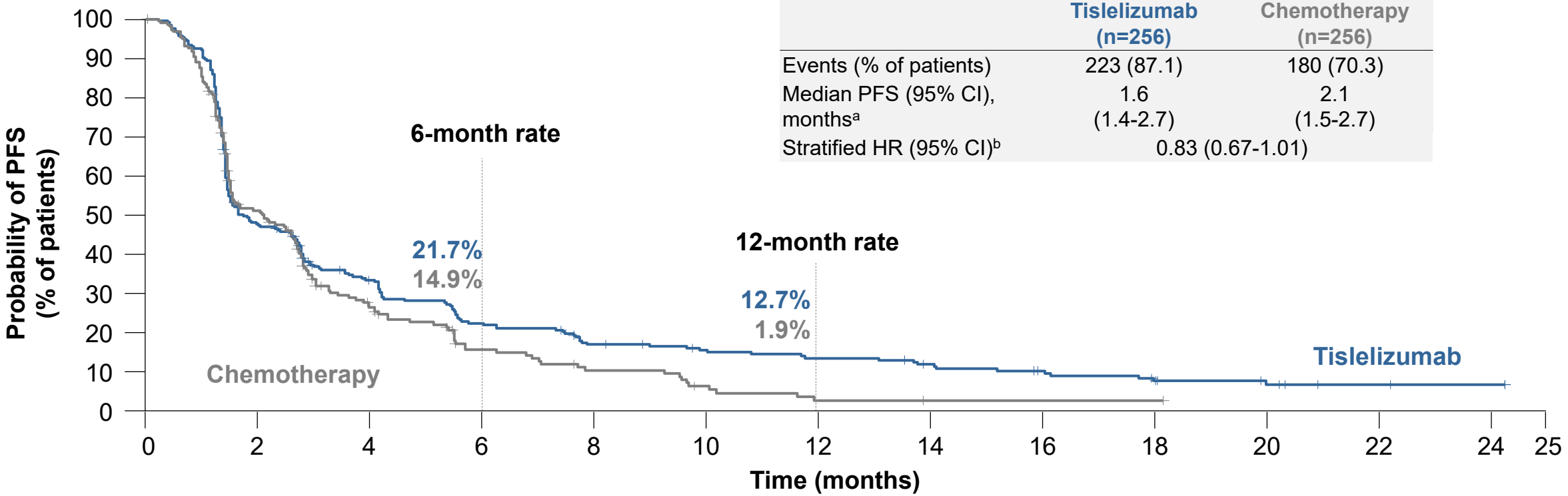


HR was based on an unstratified Cox regression model including treatment as covariate.

Abbreviations: CI, confidence interval; ECOG PS, Eastern Cooperative Oncology Group performance score; HR, hazard ratio; PD-L1, programmed death ligand 1; vCPS, visually-estimated combined positive score.

Progression-Free Survival in All Randomized Patients

	Tislelizumab (n=256)	Chemotherapy (n=256)
Events (% of patients)	223 (87.1)	180 (70.3)
Median PFS (95% CI), months[a]	1.6 (1.4-2.7)	2.1 (1.5-2.7)
Stratified HR (95% CI)[b]	0.83 (0.67-1.01)	



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

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]HR was based on a Cox regression model.
Abbreviations: CI, confidence interval; HR, hazard ratio; PFS, progression-free survival.

Antitumor Activity per RECIST v1.1 (Investigator-Assessed) in All Randomized Patients

	Tislelizumab (n=256)	Chemotherapy (n=256)
Unconfirmed ORR		
n	52	25
% (95% CI)[a]	20.3 (15.6-25.8)	9.8 (6.4-14.1)
Odds ratio (95% CI)[b]	2.4 (1.4-4.0)	
Best overall response, n (%)		
Complete response	5 (2.0)	1 (0.4)
Partial response	47 (18.4)	24 (9.4)
Stable disease	68 (26.6)	82 (32.0)
Progressive disease	116 (45.3)	86 (33.6)
Not evaluable/assessable[c]	20 (7.8)	63 (24.6)
Median DoR (95% CI), months[d]	7.1 (4.1-11.3)	4.0 (2.1-8.2)
Patients with ongoing response, n/N (%)	10/52 (19.2)	0/25 (0)

[a]Two-sided 95% CI was calculated using 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; ORR, overall response rate.

Safety: Summary of AEs

	Tislelizumab (n=255) n (%) / n (%)	Chemotherapy (n=240) n (%) / n (%)
Patients with at least one TEAE/TRAE	244 (95.7) / 187 (73.3)	236 (98.3) / 225 (93.8)
≥ Grade 3 TEAE/TRAE	118 (46.3) / 48 (18.8)	163 (67.9) / 134 (55.8)
Serious TEAE/TRAE	105 (41.2) / 36 (14.1)	105 (43.8) / 47 (19.6)
TEAE/TRAE leading to treatment discontinuation	49 (19.2) / 17 (6.7)	64 (26.7) / 33 (13.8)
TEAE/TRAE leading to death[a]	14 (5.5) / 5 (2.0)	14 (5.8) / 7 (2.9)

Tislelizumab showed a favorable safety profile compared with chemotherapy, with no new safety signals identified

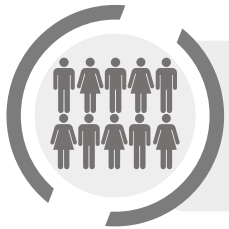
All AEs are treatment-emergent and graded based on National Cancer Institute–Common Terminology Criteria for Adverse Events (version 4.03).
[a]Death events due to disease progression were excluded.
Abbreviations: AE, adverse event; TEAE, treatment-emergent adverse event; TRAE, treatment-related adverse event.

Treatment-Related AEs Reported in ≥10% of Patients*

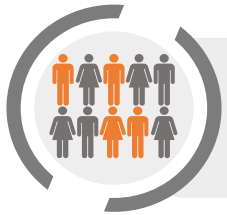
Preferred term	Tislelizumab (n=255) n (%)	Chemotherapy (n=240) n (%)
Aspartate aminotransferase increased	29 (11.4)	9 (3.8)
Anemia	28 (11.0)	83 (34.6)
Hypothyroidism	26 (10.2)	0 (0.0)
Fatigue	19 (7.5)	33 (13.8)
Decreased appetite	16 (6.3)	75 (31.3)
Diarrhea	14 (5.5)	66 (27.5)
Asthenia	12 (4.7)	28 (11.7)
Malaise	10 (3.9)	35 (14.6)
Weight decreased	8 (3.1)	25 (10.4)
Nausea	7 (2.7)	66 (27.5)
Leukopenia	7 (2.7)	30 (12.5)
White blood cell count decreased	5 (2.0)	98 (40.8)
Vomiting	4 (1.6)	43 (17.9)
Constipation	4 (1.6)	25 (10.4)
Neutrophil count decreased	3 (1.2)	94 (39.2)
Neutropenia	2 (0.8)	31 (12.9)
Alopecia	0 (0.0)	42 (17.5)

TRAEs included AEs that were considered by the investigator to be related to study drug or AEs with a missing causality.
*In either treatment group.
Abbreviations: AE, adverse event; TRAE, treatment-related adverse event.

Conclusions



Tislelizumab demonstrated a statistically significant and clinically meaningful improvement in OS vs chemotherapy in advanced or metastatic ESCC patients whose tumor progressed during or after first-line treatment



Survival benefit was observed across pre-defined subgroups, including PD-L1 expression status, race, and region

Tislelizumab resulted in higher and more durable antitumor response than chemotherapy

Tislelizumab showed a favorable safety profile compared with chemotherapy, with no new safety signals identified

Tislelizumab represents a potential new second-line treatment option for patients with advanced or metastatic ESCC

Abbreviations: ESCC, esophageal squamous cell carcinoma; OS, overall survival; PD-L1, programmed death ligand 1.

Acknowledgement

- We would like to thank the site support staff, study sponsors, and collaborators as well as participating patients and their families

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