RATIONALE 302: Randomized, Phase 3 Study of Tislelizumab vs Chemotherapy as Second-Line Treatment for Advanced Unresectable/Metastatic Esophageal Squamous Cell Carcinoma (ESCC)

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Disclosures for Dr. Moehler

Consultant for BeiGene and Novartis.

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/PD-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]

ESCC, esophageal squamous cell carcinoma; FcγR, Fc gamma receptor; OS, overall survival; PD-1, programmed cell death 1 receptor; PD-L1, programmed cell death-ligand 1.

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.

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)
- If OS in all randomized patients (ITT analysis set) was statistically significant, OS in patients with vCPS>10% (PD-L1+ analysis set) was tested sequentially

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.

DoR, duration of response; ECOG PS, Eastern Cooperative Oncology Group performance status; ESCC, esophageal squamous cell carcinoma; HR, hazard ratio; IV, intravenous; 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.

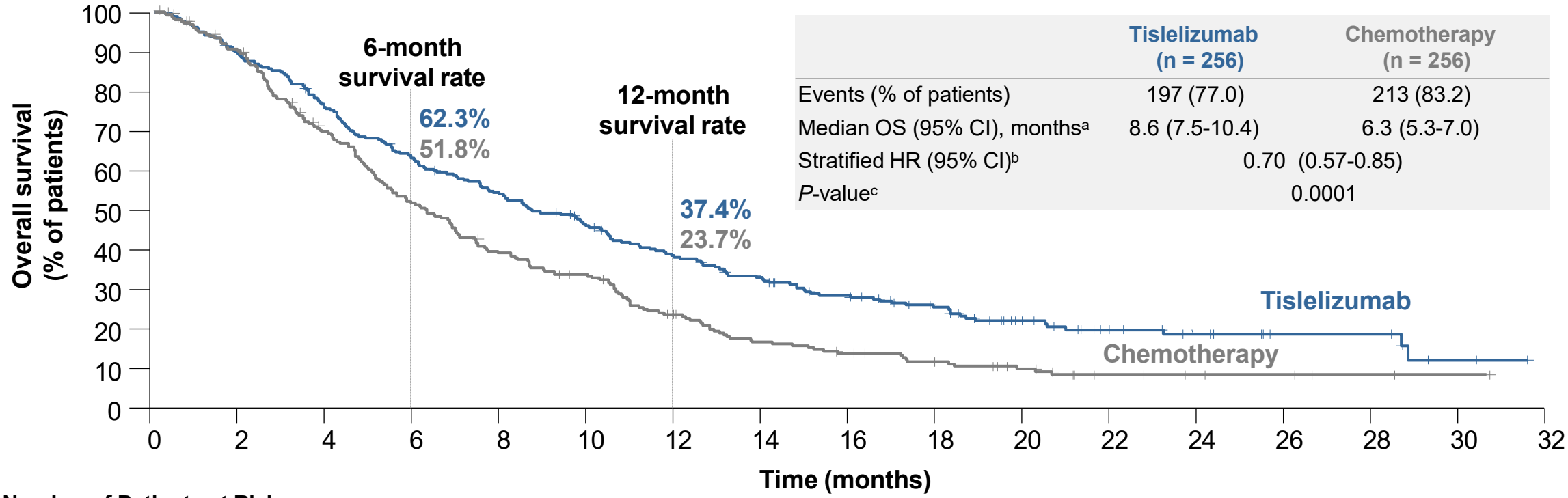
Patient Baseline Characteristics in All Randomized Patients

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)

- 512 patients were randomized (256 to tislelizumab and 256 to chemotherapy) from 132 sites in 11 countries/regions in Asia, Europe, and North America
- Treatment was received by 255 patients (99.6%) for tislelizumab and 240 patients (93.8%) for chemotherapy

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

OS 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	

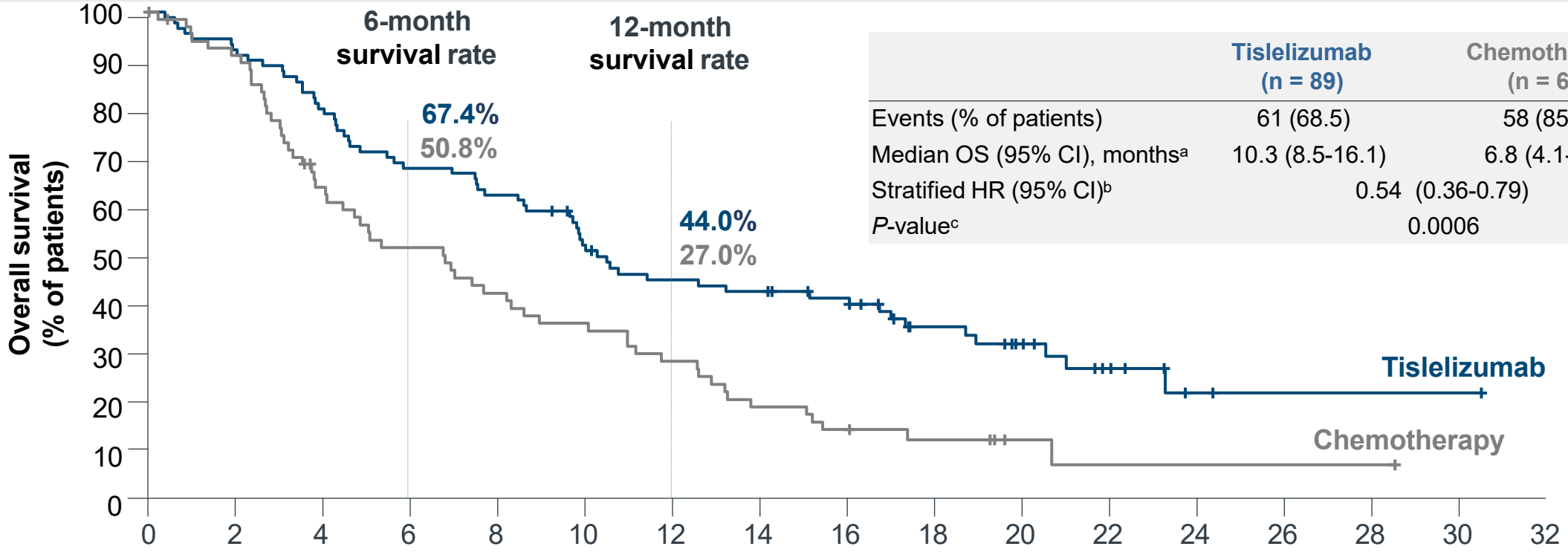
Number of Patients at Risk

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

- Tislelizumab significantly improved OS vs chemotherapy in all randomized patients, and in patients with vCPS ≥ 10%
- A 30% reduction in the risk of death with a 2.3-month improvement in median OS in all randomized patients was observed

Data cut-off date: December 1, 2020. Overall population was stratified according to region, ECOG performance status, 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.
ECOG, Eastern Cooperative Oncology Group; OS, overall survival; vCPS, visually-estimated combined positive score.

OS 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

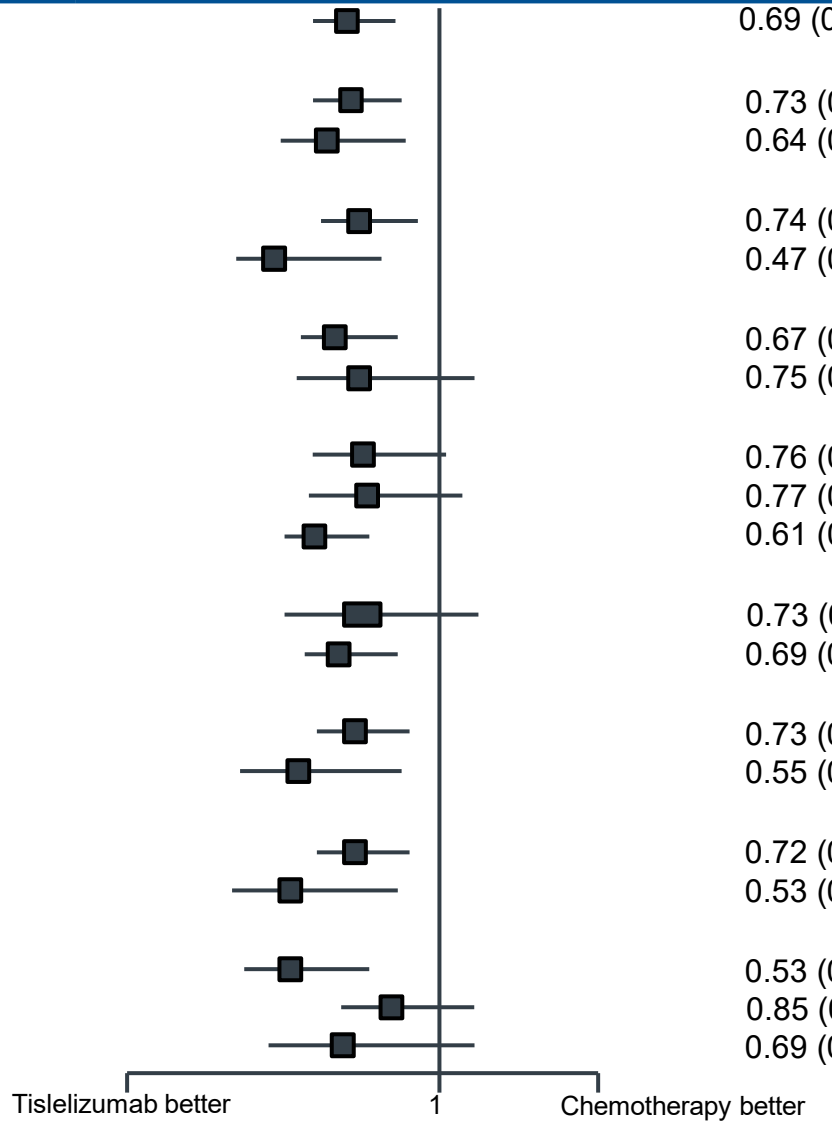
Time	0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31	32
Tislelizumab	89	85	82	79	71	63	60	59	55	52	43	37	36	35	34	32	30	25	19	17	14	11	8	6	2	1	1	1	1	1	1	0	0
Chemotherapy	68	63	60	51	40	35	32	29	26	22	22	19	17	14	11	11	8	6	5	5	2	1	1	1	1	1	1	1	1	0	0	0	0

- A 46% reduction in the risk of death with a 3.5-month improvement in median OS in patients with PD-L1 vCPS ≥ 10% was observed

[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.
OS, overall survival; PD-L1, programmed death cell-ligand 1; vCPS, visually-estimated combined positive score.

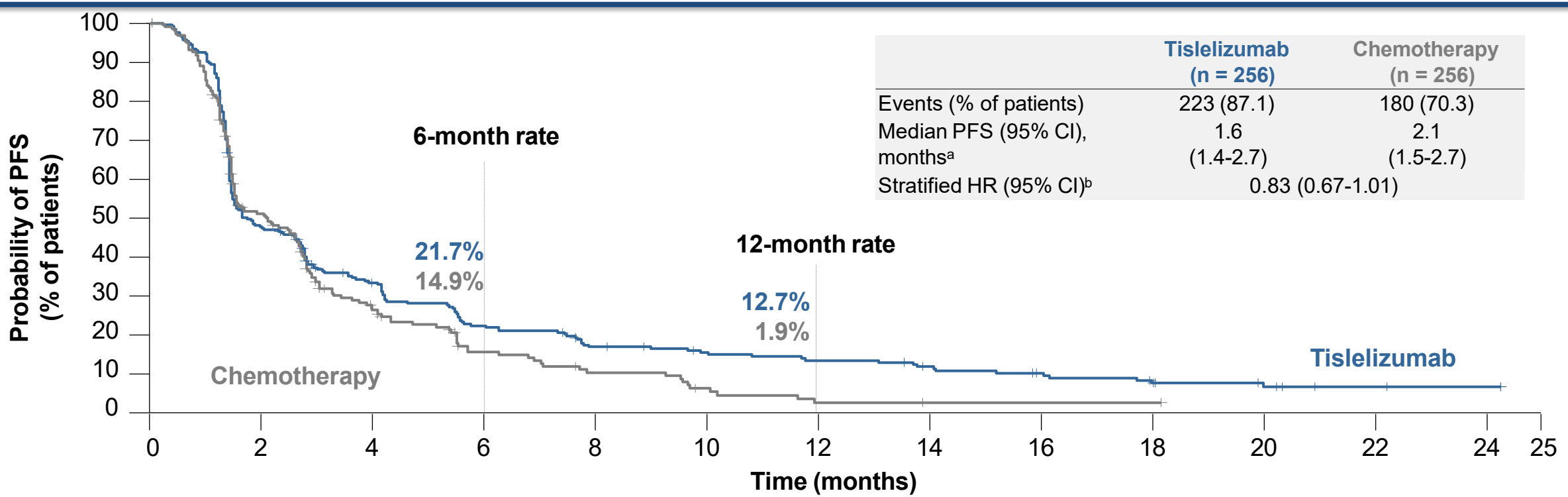
OS by Subgroup in All Randomized Patients

Subgroup	Event/total: Tislelizumab	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
ECOG PS, Eastern Cooperative Oncology Group performance score; OS, overall survival; PD-L1, programmed death cell-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

- The PFS Kaplan-Meier curves began to separate approximately 3 months after randomization in favor of tislelizumab

Data cut-off date: December 1, 2020. Overall population was stratified according to region, ECOG PS, 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.
ECOG PS, Eastern Cooperative Oncology Group performance status; 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)

- Tislelizumab was associated with a greater ORR (20.3% vs 9.8%; odds ratio 2.4, CI 1.4-4.0) and a more durable tumor response (median DoR: 7.1 months vs 4.0 months) than chemotherapy

[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).
DoR, duration of response; ORR, overall response rate; RECIST, response evaluation criteria in solid tumors.

Safety: Summary of AEs

Event, n(%)	Tislelizumab (n = 255)	Chemotherapy (n = 240)
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 were 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.
AE, adverse event; TEAE, treatment-emergent adverse event; TRAE, treatment-related adverse event.

Treatment-Related AEs Reported in ≥ 10% of Patients[a]

Preferred term, n (%)	Tislelizumab (n = 255)	Chemotherapy (n = 240)
AST 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.
[a]In either treatment group.
AE, adverse event; AST, aspartate aminotransferase.

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

Acknowledgments

We would like to thank the investigators, site support staff, and especially the patients and their caregivers for participating in this study.

This study was sponsored by BeiGene

Editorial support was provided by Medical Expressions and funded by BeiGene

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