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Randomized, Phase 3 study of second-line tislelizumab vs chemotherapy in advanced or metastatic esophageal squamous cell carcinoma (RATIONALE 302) in the overall population and the Europe/North America subgroup

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Disclosure of Conflict of Interest

- **Honoraria:** Acrotech Biopharma; Aduro Biotech; Amgen; Astellas Pharma; AstraZeneca; Bristol-Myers Squibb; Daiichi Sankyo; DAVA Pharmaceuticals; Lilly; Merck; OncoTherics; Zymeworks

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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 vs 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]

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

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RATIONALE-302: 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*
- Docetaxel 75 mg/m² IV Q3W†
- Irinotecan 125 mg/m² IV on Days 1 and 8, Q3W

Treatment until disease progression or intolerable toxicity

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 (ITT population)
- Key secondary endpoint: OS in patients with vCPS ≥10%‡
- Other secondary endpoints: PFS, ORR, DOR, HRQoL, and safety

The study required ~400 death events to achieve 82% power to detect a HR of 0.75 at 0.025 significance level (1-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 every 9 weeks (± 7 days) thereafter

*For Japan: paclitaxel 100 mg/m² IV in cycles consisting of weekly dosing for 6 weeks, followed by one week of rest; †For Japan: docetaxel 70 mg/m² IV Q3W; ‡PD-L1 expression centrally assessed by immunohistochemistry with the Ventana SP263 assay

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; vCPS, visually-estimated combined positive score

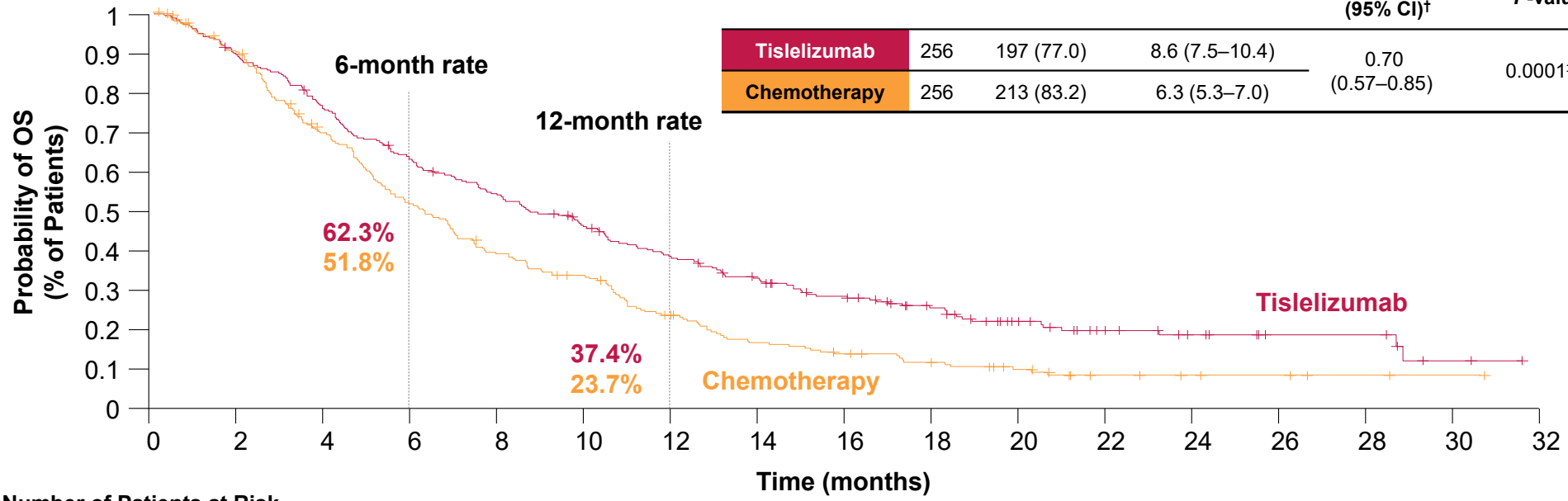
Demographics and Baseline Patient Characteristics

		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)
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*	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†, 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: 01 Dec 2020. Overall population was stratified according to region, ECOG PS, and chemotherapy treatment
*Including categories of 'not reported', 'unknown', and 'other'; †PD-L1 expression centrally assessed by immunohistochemistry with the Ventana SP263 assay
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*	Tislelizumab vs Chemotherapy	
				Hazard Ratio (95% CI)†	*P*-value
Tislelizumab	256	197 (77.0)	8.6 (7.5–10.4)	0.70 (0.57–0.85)	0.0001‡
Chemotherapy	256	213 (83.2)	6.3 (5.3–7.0)		



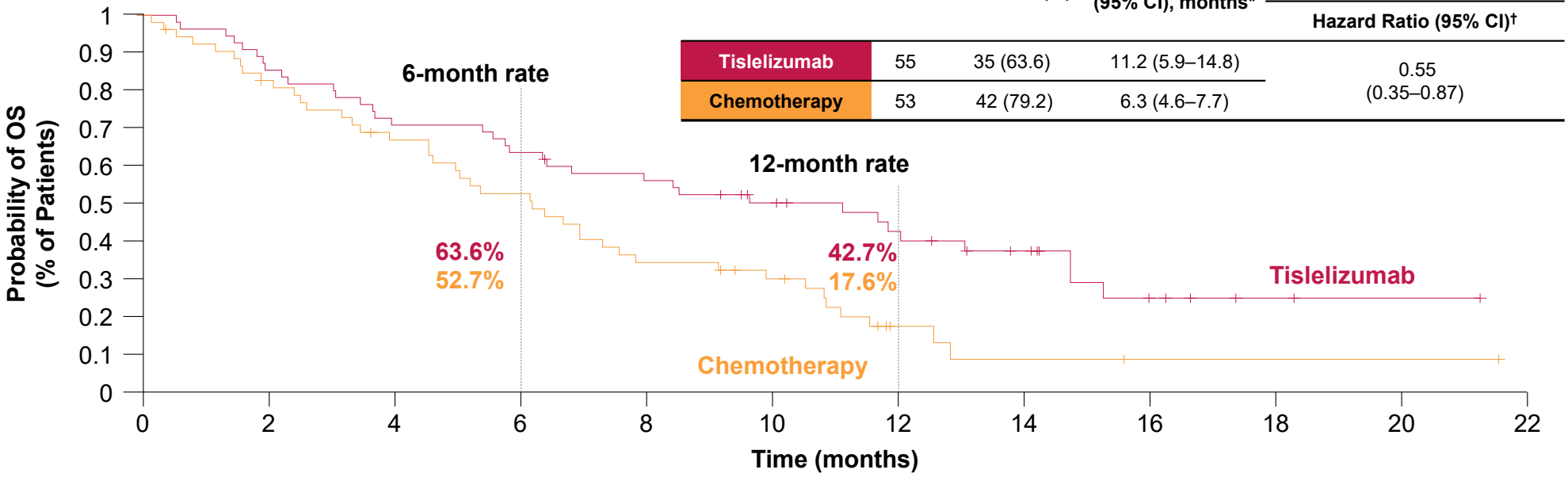
Number of Patients at Risk

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

Data cut-off date: 01 Dec 2020. Overall population was stratified according to region, ECOG performance score, and chemotherapy treatment
*Medians were estimated by Kaplan-Meier method with 95% CIs estimated using the method of Brookmeyer and Crowley. †Hazard ratio was based on a Cox regression model
‡One-sided *p*-value was estimated from a stratified log rank test
CI, confidence interval; ECOG, Eastern Cooperative Oncology Group; OS, overall survival

Overall Survival: EU/NA Subgroup

Treatment	N	Events, n (%)	Median OS (95% CI), months*	Tislelizumab vs Chemotherapy Hazard Ratio (95% CI)†
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: 01 Dec 2020
*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
†Hazard ratio was based on unstratified Cox regression model only including treatment as covariate
CI, confidence interval; EU, European Union; NA, North America; OS, overall survival

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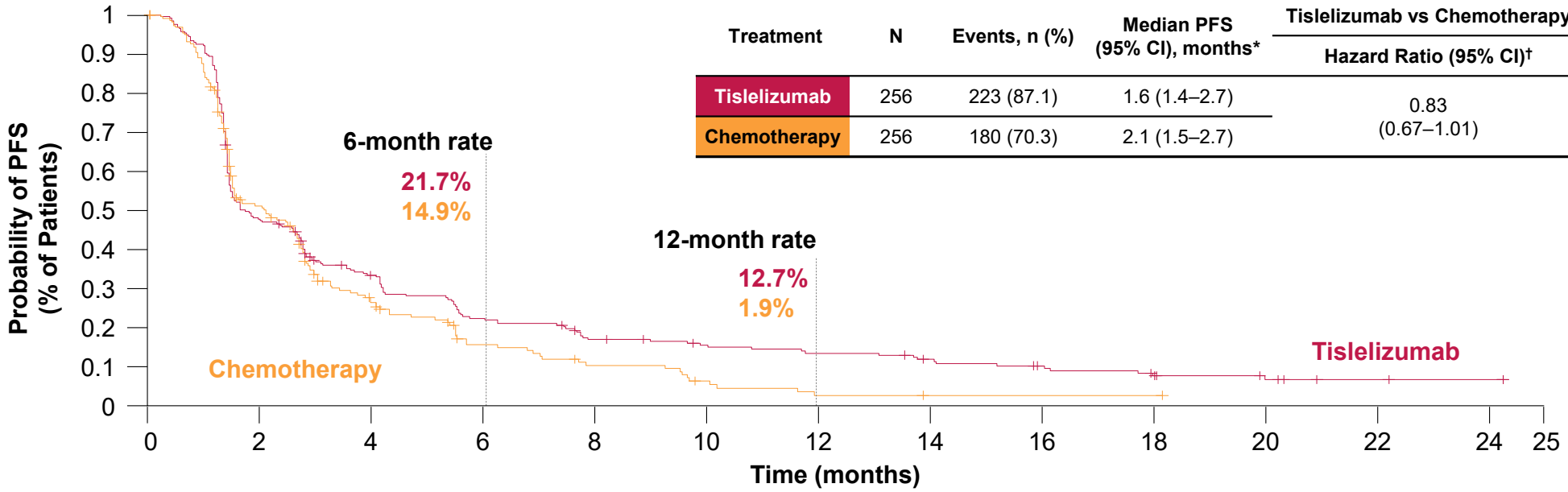
PFS: Overall and EU/NA Populations

Treatment	N	Events, n (%)	Median PFS (95% CI), months*	Tislelizumab vs Chemotherapy Hazard Ratio (95% CI)†
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: 01 Dec 2020. Overall population was stratified according to region, ECOG performance score, and chemotherapy treatment
*Medians were estimated by Kaplan-Meier method with 95% CIs estimated using the method of Brookmeyer and Crowley. †Hazard ratio was based on a Cox regression model
CI, confidence interval; ECOG, Eastern Cooperative Oncology Group; EU, European Union; HR, hazard ratio; NA, North America; PFS, progression-free survival

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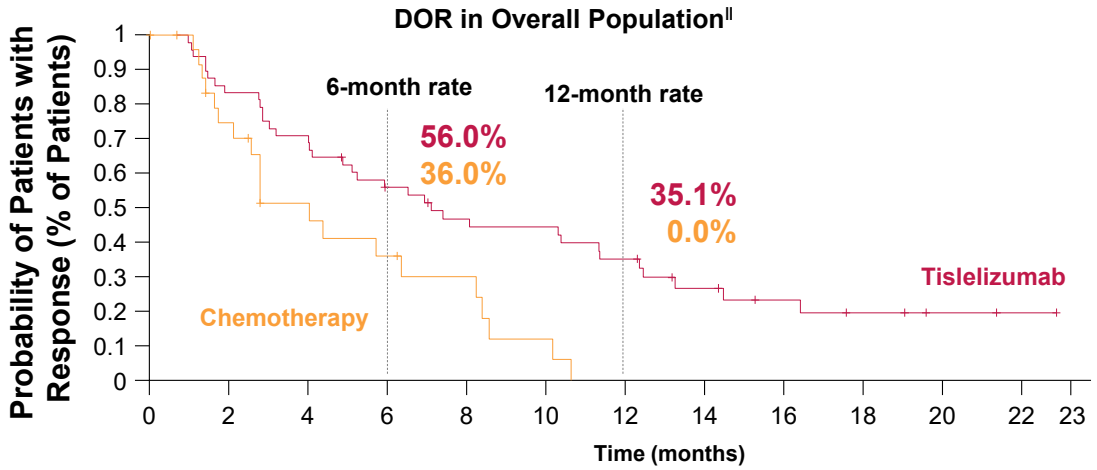
ORR and DOR: Overall Population

	Tislelizumab (n=256)	Chemotherapy (n=256)
ORR, n	52	**25**
% (95% CI)*	20.3 (15.6–25.8)	9.8 (6.4–14.1)
Odds Ratio for ORR, (95% CI)†	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)
DOR§		
Median (95% CI), months	7.1 (4.1–11.3)	4.0 (2.1–8.2)
Pts with Ongoing Response, n (%)	10 (19.2)	0 (0.0)



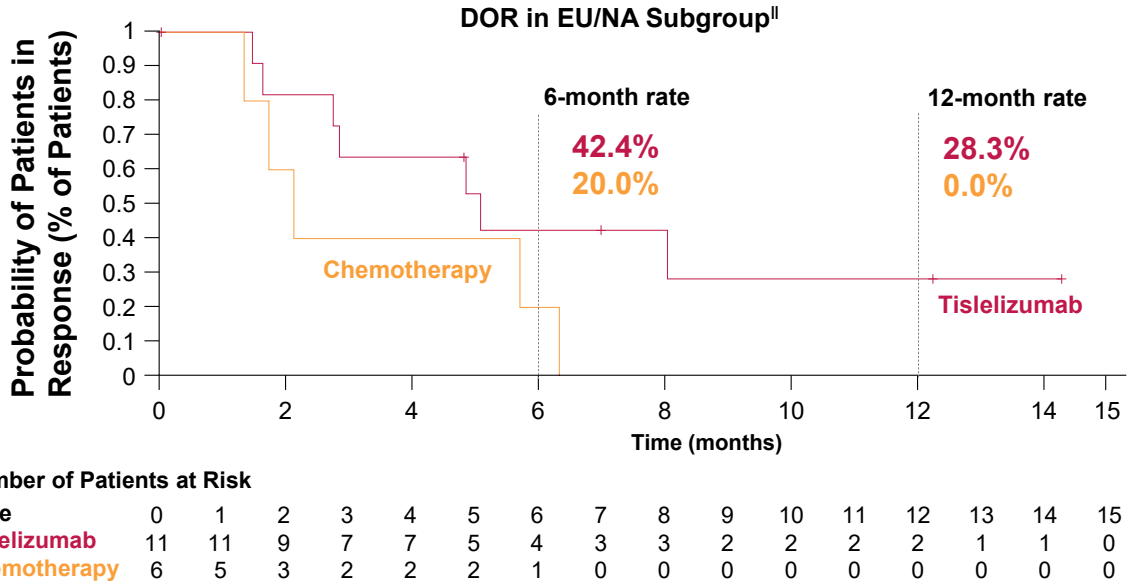
Number of Patients at Risk

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
Tislelizumab	52	47	40	36	34	29	25	22	20	19	19	17	15	11	9	7	6	5	4	3	2	2	1	0
Chemotherapy	25	24	17	10	10	8	7	5	5	2	2	0	0	0	0	0	0	0	0	0	0	0	0	0

Data cut-off date: 01 Dec 2020. Overall population was stratified according to region, ECOG performance score, and chemotherapy treatment. Data are investigator assessed per RECIST v1.1.
*Two-sided 95% CI was calculated using Clopper-Pearson method. †Calculated using the Cochran-Mantel-Haenszel Chi-square test. ‡Including those with no post-baseline assessment or an unevaluable post-baseline assessment. §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). ¶Hazard ratio was based on unstratified Cox regression model including treatment as covariate. ‖DOR rates (cumulative probability of DOR) were estimated by Kaplan-Meier method with 95% CIs estimated using Greenwood's formula
CI, confidence interval; DOR, duration of response; ECOG, Eastern Cooperative Oncology Group; ORR, overall response rate; pts, patients; RECIST, response evaluation criteria in solid tumors

ORR and DOR: EU/NA Subgroup

	Tislelizumab (n=55)	Chemotherapy (n=53)
ORR, n	11	6
% (95% CI)*	20 (10.4–33.0)	11.3 (4.3–23.0)
Odds Ratio for ORR, (95% CI)†	2 (0.7–5.8)	
ORR Difference, % (95% CI)	8.7 (-4.9–22.3)	
Best Overall Response, n (%)		
Complete Response	2 (3.6)	0 (0.0)
Partial Response	9 (16.4)	6 (11.3)
Stable Disease	17 (30.9)	20 (37.7)
Progressive Disease	23 (41.8)	16 (30.2)
Not Evaluable‡	4 (7.3)	11 (20.8)
DOR§		
Median (95% CI), months	5.1 (1.6–NE)	2.1 (1.3–6.3)
Pts with Ongoing Response, n (%)	4 (36.4)	0 (0.0)



Data cut-off date: 01 Dec 2020. Data are investigator assessed per RECIST v1.1 criteria

*Two-sided 95% CI was calculated using Clopper-Pearson method. †Calculated using the Cochran-Mantel-Haenszel Chi-square test. ‡Including those with no post-baseline assessment or an unevaluable post-baseline assessment. §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). ¶Hazard ratio was based on unstratified Cox regression model including treatment as covariate. ‖Duration of response rates (cumulative probability of DOR) were estimated by Kaplan-Meier method with 95% CIs estimated using Greenwood's formula

CI, confidence interval; DOR, duration of response; EU, European Union; NA, North America; NE, not evaluable; 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*	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: 01 Dec 2020. Overall population was stratified according to region, ECOG performance score, and chemotherapy treatment
*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
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** vs 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 compared with chemotherapy

- Antitumor response in the EU/NA subgroup was **consistent with the overall population**

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**

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

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

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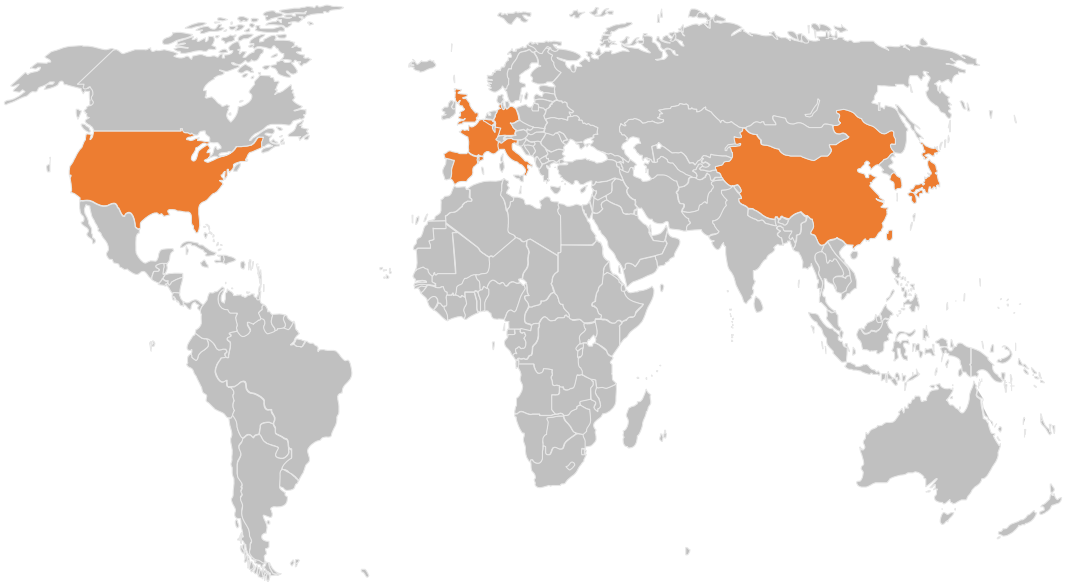

132 sites in 11 countries/regions
in Asia, Europe, and North America

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