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RATIONALE-306: Randomized, global, placebo-controlled, double-blind Phase 3 study of tislelizumab plus chemotherapy versus chemotherapy as first-line treatment for advanced or metastatic esophageal squamous cell carcinoma

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Disclosures of conflict of interest

Dr. Harry H. Yoon reports relevant financial relationship(s) with industry (all honoraria paid to institution) OncXerna (advisory board), Merck (advisory board, steering committee), Zymeworks (advisory board), MacroGenics (advisory board, steering committee), BMS (advisory board), BeiGene (advisory board, steering committee, education symposium, research), and AstraZeneca (advisory board) and funding from Merck, BMS, MacroGenics, BeiGene, Boston Biomedical, Elevar Therapeutics, and CARsgen

Introduction

ESCC is the predominant histologic subtype of esophageal cancer, accounting for ≥ 85% of cases worldwide[1]

Platinum-based chemotherapy has historically been recommended for first-line treatment of advanced or metastatic ESCC, but median survival remains poor, at < 1 year[2–5]

Recently, the addition of anti-PD-1 antibodies to first-line chemotherapy has been shown to improve survival in patients with advanced or metastatic ESCC.[2,6] However, to date global Phase 3 trials have only studied these agents in combination with cisplatin plus 5-FU[2,6]

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Tislelizumab, an anti-PD-1 monoclonal antibody, has high affinity and specificity for PD-1 and has demonstrated survival benefit as second-line monotherapy in patients with advanced or metastatic ESCC (RATIONALE-302)[7,8]

The **global double-blind Phase 3 RATIONALE-306 study** is evaluating **first-line tislelizumab plus chemotherapy** vs placebo plus chemotherapy for **advanced or metastatic ESCC – here we report interim analysis results**

1. Arnold M, et al. Gut 2020;69:1564–71; 2. Doki Y, et al. N Engl J Med 2022;386:449–62; 3. Lee S, et al. BMC Cancer 2015;15:693; 4. Moehler M et al. Ann Oncol 2020;31:228–35; 5. Enomoto N, et al. Glob Health Med 2021;3:378–85; 6. Sun JM, et al. Lancet 2021;398:759–71; 7. Zhang T, et al. Cancer Immunol Immunother 2018;67:1079–90; 8. Shen L, et al. J Clin Oncol 2022 Apr 20:JCO2101926

5-FU, 5-fluorouracil; ESCC, esophageal squamous cell carcinoma; PD-1, programmed cell death protein 1

RATIONALE-306: Study design

Key eligibility criteria

- Unresectable locally advanced or metastatic ESCC
- No prior systemic treatment for advanced disease
- ECOG PS 0 or 1
- Measurable or evaluable disease per RECIST v1.1

R 1:1 DB

N=649

Tislelizumab 200 mg IV Q3W + investigator-chosen chemotherapy

Treatment until disease progression, intolerable toxicity, or withdrawal for other reasons

Matching placebo IV Q3W + investigator-chosen chemotherapy

Investigator-chosen chemotherapy:

- **Option A**: **Platinum + fluoropyrimidine**
  Cisplatin or oxaliplatin* + fluoropyrimidine†
- **Option B**: **Platinum + paclitaxel**
  Cisplatin or oxaliplatin* + paclitaxel‡

Stratification factors

- Geographic region (Asia [excluding Japan] vs Japan vs Rest of World)
- Prior definitive therapy (yes vs no)
- Investigator-chosen chemotherapy (platinum/fluoropyrimidine vs platinum/paclitaxel)

Endpoints

- **Primary endpoint:** OS in all randomized patients (ITT population)
- **Secondary endpoints**: PFS, ORR and DoR by investigator, OS in the PD-L1 score ≥ 10% subgroup§, HRQoL, and safety

Statistical consideration:

- Approximately 488 death events were required to provide 90% power to detect a HR of 0.74 at a one-sided alpha of 0.025 at the final analysis
- An interim analysis was prespecified when approximately 423 death events were observed; the updated one-sided p value boundary at the interim analysis was 0.0144 based on 422 actual observed death events
- Secondary endpoints of PFS, ORR, OS in the PD-L1 score ≥10% subgroup and HRQoL would have been tested sequentially with a one-sided alpha of 0.025, if the null hypothesis for primary endpoint was rejected

ClinicalTrials.gov: NCT03783442. *Cisplatin 60–80 mg/m^2 IV or oxaliplatin 130 mg/m^2 IV Q3W (except in China, Taiwan, Japan, and countries where oxaliplatin substitution is not permitted) according to site or investigator preference or standard practice. Platinum therapy may be stopped after six cycles, per site or investigator preference or standard practice. If platinum treatment is stopped, the non-platinum agent may continue at the regular schedule. †5-fluorouracil 750–800 mg/m^2 IV on Days 1–5 Q3W or capecitabine 1000 mg/m^2 orally BID on Days 1–14. ‡Paclitaxel 175 mg/m^2 IV Q3W. §PD-L1 expression was determined centrally by PD-L1 score (defined as the total percentage of the tumor area [tumor and any desmoplastic stroma] covered by tumor cells with PD-L1 membrane staining at any intensity and tumor-associated immune cells with PD-L1 staining at any intensity, as visually estimated) using the VENTANA PD-L1 (SP263) assay. BID, twice daily; DB, double-blind; DoR, duration of response; ECOG PS, Eastern Cooperative Oncology Group performance status; 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; Q3W, every three weeks; R, randomized

Baseline characteristics were generally balanced between treatment arms

		Tislelizumab + chemotherapy (n=326)	Placebo + chemotherapy (n=323)
Baseline characteristics			
Median age (range), years		64.0 (26, 84)	65.0 (40, 84)
Male, n (%)		282 (86.5)	281 (87.0)
Region, n (%)	Asia (excl. Japan)	210 (64.4)	210 (65.0)
	Japan	33 (10.1)	33 (10.2)
	Rest of World*	83 (25.5)	80 (24.8)
Race, n (%)	Asian	243 (74.5)	243 (75.2)
	White	79 (24.2)	76 (23.5)
	Other†	4 (1.2)	4 (1.2)
ECOG PS, n (%)	0	109 (33.4)	104 (32.2)
	1	217 (66.6)	219 (67.8)
Smoking status, n (%)	Never	68 (20.9)	81 (25.1)
	Current/former	247 (75.7)	231 (71.5)
	Missing	11 (3.4)	11 (3.4)
Histologic type, n (%)	Squamous cell carcinoma	325 (99.7)	323 (100.0)
	Other‡	1 (0.3)	0 (0)

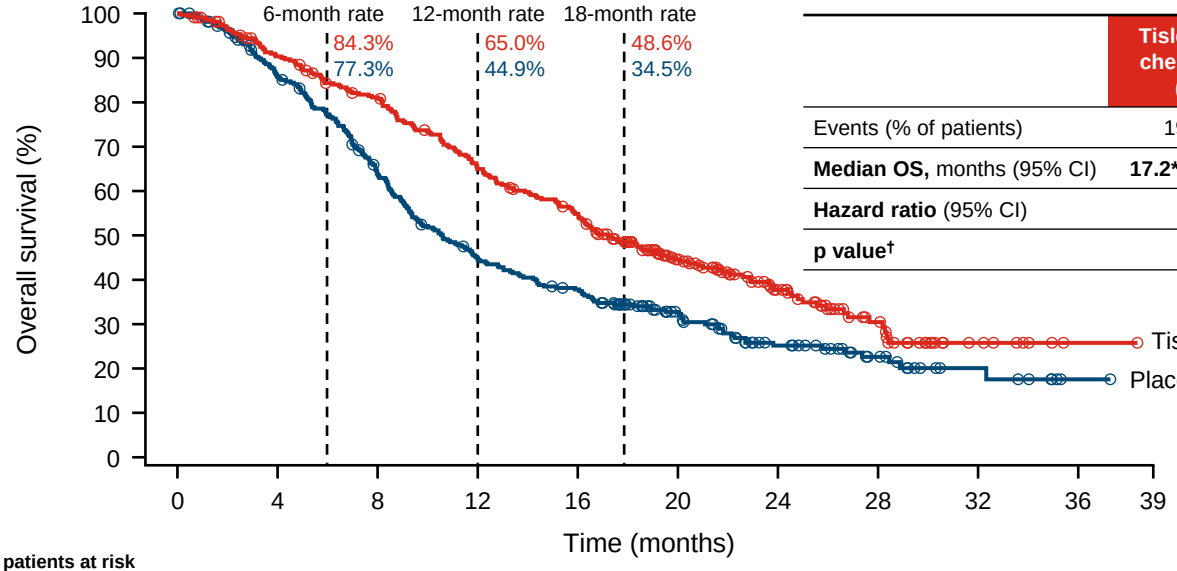
		Tislelizumab + chemotherapy (n=326)	Placebo + chemotherapy (n=323)
Baseline characteristics			
Disease status at baseline, n (%)	Metastatic	279 (85.6)	282 (87.3)
	Locally advanced	47 (14.4)	41 (12.7)
Prior definitive therapy, n (%)	Definitive surgery§	107 (32.8)	107 (33.1)
	Definitive RT§	40 (12.3)	40 (12.4)
Centrally-assessed PD-L1 status¶, n (%)	PD-L1 score ≥ 10%	123 (37.7)	113 (35.0)
	PD-L1 score < 10%	165 (50.6)	176 (54.5)
	Unknown‖	38 (11.7)	34 (10.5)
Treatment			
Median duration of tislelizumab / placebo treatment, month (range)		6.4 (0.1–38.3)	4.9 (0.6–34.9)
Investigator-chosen chemotherapy options, n (%)	Platinum + fluoropyrimidine	147 (45.1)	146 (45.2)
	Platinum + paclitaxel	179 (54.9)	177 (54.8)
Post-treatment systemic therapies, n (%)	Systemic therapy	157 (48.2)	177 (54.8)
	Immunotherapy	46 (14.1)	72 (22.3)

Data cutoff: February 28, 2022

*Australia, Belgium, Czech Republic, France, Germany, Italy, Poland, Romania, Russia, Spain, United Kingdom and United States. †Including categories of 'American Indian', 'Alaska Native', 'not reported' and 'unknown'. ‡Patient had neuroendocrine tumor histology. §Definitive surgery included surgery with or without (neo)adjuvant treatment; definitive RT included RT with or without chemotherapy; four patients in the tislelizumab arm and six in the placebo arm had received both definitive surgery and definitive RT. ¶PD-L1 expression was determined centrally by PD-L1 score (defined as the total percentage of the tumor area [tumor and any desmoplastic stroma] covered by tumor cells with PD-L1 membrane staining at any intensity and tumor-associated immune cells with PD-L1 staining at any intensity, as visually estimated) using the VENTANA PD-L1 (SP263) assay. ‖Patients without sample collection or not evaluable at baseline.
ECOG PS, Eastern Cooperative Oncology Group performance status; excl., excluding; PD-L1, programmed death-ligand 1; RT, radiotherapy

The primary endpoint was met, with a statistically significant and clinically meaningful improvement in OS

OS in all randomized patients (primary endpoint)



	Tislelizumab + chemotherapy (n=326)	Placebo + chemotherapy (n=323)
Events (% of patients)	196 (60.1)	226 (70.0)
Median OS, months (95% CI)	**17.2*** (15.8, 20.1)	**10.6** (9.3, 12.1)
Hazard ratio (95% CI)	**0.66** (0.54, 0.80)	
p value†	**p < 0.0001**	

Number of patients at risk

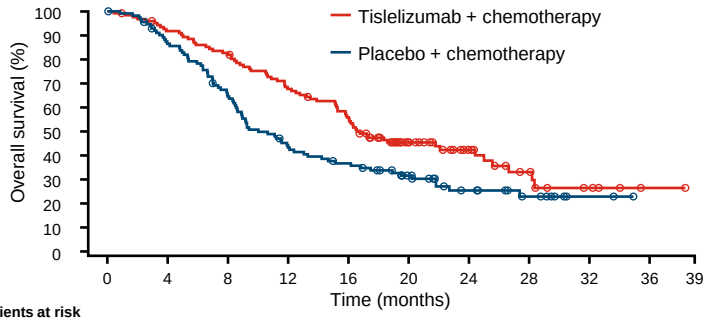
Time	0	2	4	6	8	10	12	14	16	18	20	22	24	26	28	30	32	34	36	38
Tislelizumab + chemotherapy	326	311	287	264	253	227	201	183	167	136	101	79	58	41	28	14	8	4	1	1
Placebo + chemotherapy	323	304	268	239	195	158	135	122	112	91	71	54	40	32	22	11	8	6	1	0

Data cutoff: February 28, 2022. *In the associated late-breaking abstract, the reported median OS was 17.3 months for the tislelizumab + chemotherapy arm. The reason for the discrepancy is due to the update made in the program logic to properly populate the censor date. †The O'Brien Fleming efficacy 1-sided p value boundary based on 422 death events observed at interim analysis for superiority is 0.0144.
HR was based on Cox regression model including treatment as covariate and using the predefined strata (pooled geographic region [Asia vs Rest of World], prior definitive therapy and investigator-chosen chemotherapy option)
CI, confidence interval; HR, hazard ratio; OS, overall survival

OS benefit with tislelizumab plus chemotherapy was observed regardless of baseline PD-L1 expression status

OS by centrally-assessed baseline PD-L1 expression status

Patients with PD-L1 score ≥ 10% (secondary endpoint)

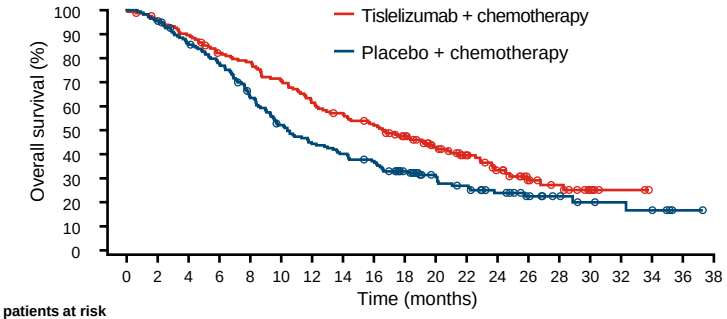


Number of patients at risk

Time	0	2	4	6	8	10	12	14	16	18	20	22	24	26	28	30	32	34	36	38
Tislelizumab + chemotherapy	123	119	111	104	100	90	81	74	66	51	36	28	21	15	11	6	5	3	1	1
Placebo + chemotherapy	113	110	95	86	70	55	46	42	38	33	25	17	14	12	8	4	2	1	0	0

	Tislelizumab + chemotherapy (n=123)	Placebo + chemotherapy (n=113)
Events (% of patients)	73 (59.3)	79 (69.9)
Median OS, months (95% CI)	**16.6** (15.3, 24.4)	**10.0** (8.6, 13.0)
Hazard ratio* (95% CI); **p value**†	**0.62** (0.44, 0.86); **p=0.0020‡**	

Patients with PD-L1 score < 10%



Number of patients at risk

Time	0	2	4	6	8	10	12	14	16	18	20	22	24	26	28	30	32	34	36	38
Tislelizumab + chemotherapy	165	157	146	131	125	113	98	90	82	68	53	41	28	17	13	6	2	0	0	0
Placebo + chemotherapy	176	168	149	134	109	87	75	67	61	47	35	29	21	15	10	7	6	5	1	0

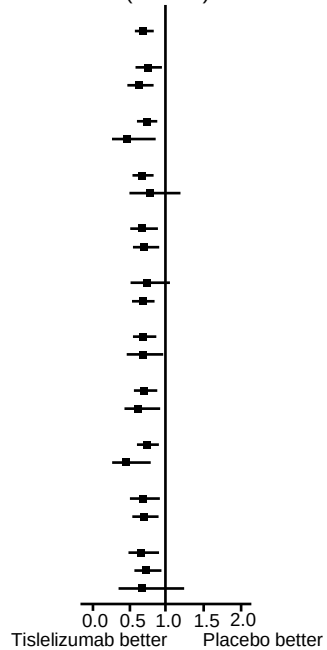
	Tislelizumab + chemotherapy (n=165)	Placebo + chemotherapy (n=176)
Events (% of patients)	105 (63.6)	127 (72.2)
Median OS, months (95% CI)	**16.7** (13.0, 20.1)	**10.4** (9.1, 13.0)
Hazard ratio* (95% CI)	**0.72** (0.55, 0.94)	

Data cutoff: February 28, 2022. PD-L1 expression was determined centrally by PD-L1 score (defined as the total percentage of the tumor area [tumor and any desmoplastic stroma] covered by tumor cells with PD-L1 membrane staining at any intensity and tumor-associated immune cells with PD-L1 staining at any intensity, as visually estimated) using the VENTANA PD-L1 (SP263) assay.
*HR was based on Cox regression model including treatment as covariate and using the predefined strata (pooled geographic region [Asia vs Rest of World], prior definitive therapy and investigator-chosen chemotherapy option).
†One-sided p value was estimated from the stratified log rank test. ‡In the associated late-breaking abstract, the reported median OS was 16.8 vs 10.0 months (HR 0.61 [95% CI 0.44, 0.85], p=0.0017) for patients with PD-L1 score ≥ 10% in the tislelizumab + chemotherapy arm versus the placebo + chemotherapy arm. The reason for the discrepancy is due to the update made in the program logic to properly populate the censor date.
CI, confidence interval; HR, hazard ratio; OS, overall survival; PD-L1, programmed death-ligand 1

OS benefit with tislelizumab plus chemotherapy was consistently observed across prespecified subgroups

OS by subgroup

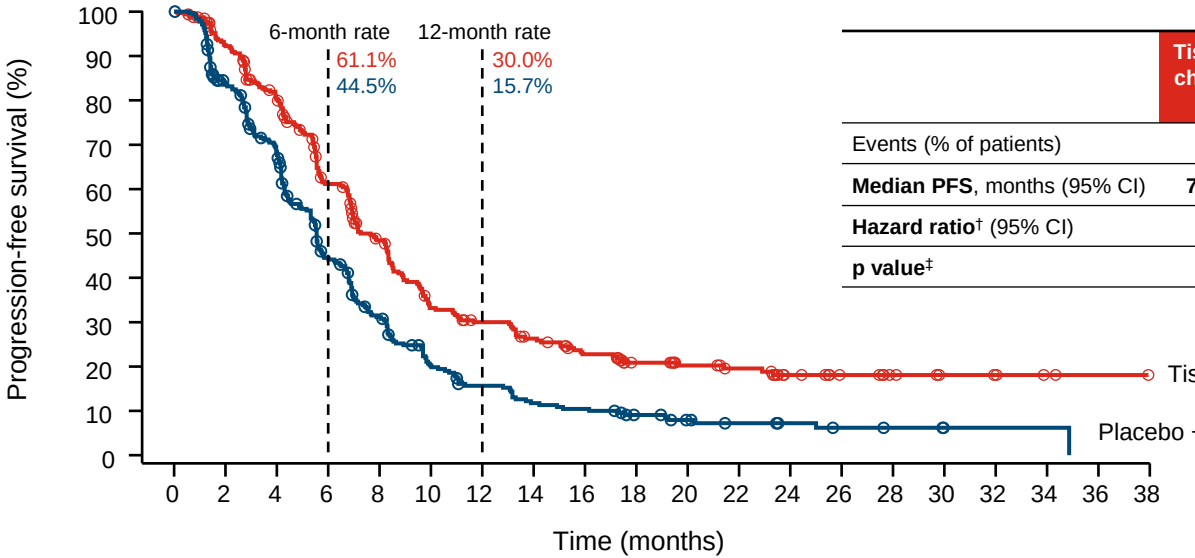
Subgroup	Event / total: Tislelizumab + chemotherapy	Event / total: Placebo + chemotherapy	HR (95% CI)
Overall	196 / 326	226 / 323	0.68 (0.56, 0.82)
Age			
Age < 65	113 / 176	112 / 161	0.73 (0.56, 0.95)
Age ≥ 65	83 / 150	114 / 162	0.62 (0.47, 0.82)
Sex			
Male	179 / 282	202 / 281	0.72 (0.59, 0.88)
Female	17 / 44	24 / 42	0.46 (0.24, 0.85)
Smoking status			
Former/current smoker	153 / 247	172 / 231	0.65 (0.52, 0.81)
Non-smoker	37 / 68	45 / 81	0.77 (0.50, 1.19)
Investigator-chosen chemotherapy options*			
Platinum with fluoropyrimidine	85 / 147	99 / 146	0.66 (0.49, 0.88)
Platinum with paclitaxel	111 / 179	127 / 177	0.69 (0.54, 0.89)
ECOG performance score			
0	58 / 109	62 / 104	0.72 (0.51, 1.04)
1	138 / 217	164 / 219	0.66 (0.53, 0.83)
Region			
Asia	143 / 243	169 / 243	0.67 (0.54, 0.84)
Rest of World†	53 / 83	57 / 80	0.66 (0.45, 0.96)
Race			
Asian and Other‡	146 / 247	171 / 247	0.69 (0.56, 0.87)
White	50 / 79	55 / 76	0.61 (0.41, 0.89)
Disease status at study entry			
Metastatic	175 / 279	198 / 282	0.72 (0.59, 0.88)
Locally advanced	21 / 47	28 / 41	0.44 (0.25, 0.78)
Prior definitive therapy*			
Yes	81 / 143	96 / 141	0.67 (0.49, 0.90)
No	115 / 183	130 / 182	0.68 (0.53, 0.87)
Centrally-assessed baseline PD-L1 status§			
PD-L1 score ≥ 10%	73 / 123	79 / 113	0.65 (0.47, 0.89)
PD-L1 score < 10%	105 / 165	127 / 176	0.71 (0.55, 0.92)
Unknown	18 / 38	20 / 34	0.65 (0.34, 1.23)



Data cutoff: February 28, 2022. Hazard ratio was based on unstratified Cox regression model including treatment as covariate.
*Per case report form. †Australia, Belgium, Czech Republic, France, Germany, Italy, Poland, Romania, Russia, Spain, United Kingdom and United States. ‡Other includes American Indian or Alaska Native, not reported, and unknown.
§PD-L1 expression was determined centrally by PD-L1 score (defined as the total percentage of the tumor area [tumor and any desmoplastic stroma] covered by tumor cells with PD-L1 membrane staining at any intensity and tumor-associated immune cells with PD-L1 staining at any intensity, as visually estimated) using the VENTANA PD-L1 (SP263) assay.
CI, confidence interval; ECOG PS, Eastern Cooperative Oncology Group performance status; HR, hazard ratio; OS, overall survival; PD-L1, programmed death-ligand 1

PFS was significantly improved with tislelizumab plus chemotherapy

PFS in all randomized patients (secondary endpoint)*



	Tislelizumab + chemotherapy (n=326)	Placebo + chemotherapy (n=323)
Events (% of patients)	220 (67.5)	254 (78.6)
Median PFS, months (95% CI)	**7.3** (6.9, 8.3)	**5.6** (4.9, 6.0)
Hazard ratio† (95% CI)	**0.62** (0.52, 0.75)	
p value‡	**p < 0.0001**	

Number of patients at risk

Time	0	2	4	6	8	10	12	14	16	18	20	22	24	26	28	30	32	34	36	38
Tislelizumab + chemotherapy	326	283	236	168	125	84	73	62	50	38	32	27	18	12	8	5	4	2	1	0
Placebo + chemotherapy	323	248	196	119	80	49	36	27	24	17	12	9	7	4	3	1	1	1	0	0

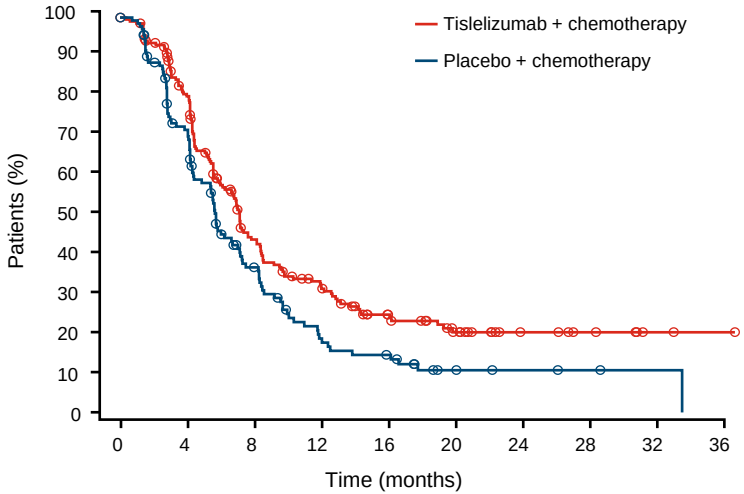
Data cutoff: February 28, 2022. *PFS assessed by investigator. †HR was based on Cox regression model including treatment as covariate and using the predefined strata (pooled geographic region [Asia vs Rest of World], prior definitive therapy and investigator-chosen chemotherapy option). ‡One-sided p value was estimated from stratified log rank test.
CI, confidence interval; HR, hazard ratio; PFS, progression-free survival

Tumor response was greater and more durable with tislelizumab plus chemotherapy

Tumor response in all randomized patients (secondary endpoint)*

	Tislelizumab + chemotherapy (n=326)	Placebo + chemotherapy (n=323)
ORR†, n	207	137
% (95% CI)‡	63.5 (58.0, 68.7)	42.4 (37.0, 48.0)
Odds ratio for ORR†, (95% CI)	2.38 (1.73, 3.27); p < 0.0001	
ORR difference†, % (95% CI)	21.2 (13.7, 28.6)	
BOR, n (%)		
Complete response	15 (4.6)	8 (2.5)
Partial response	192 (58.9)	129 (39.9)
Stable disease	83 (25.5)	122 (37.8)
Progressive disease	13 (4.0)	42 (13.0)
Not determined§	23 (7.1)	22 (6.8)
DoR¶		
Median (95% CI), months	7.1 (6.1, 8.1)	5.7 (4.4, 7.1)
Patients with ongoing response, n (%)	40 (19.3)	13 (9.5)

DoR (secondary endpoint)*¶



Number of patients at risk

Time	0	2	4	6	8	10	12	14	16	18	20	22	24	26	28	30	32	34	36
Tislelizumab + chemotherapy	207	186	152	103	75	58	50	39	31	27	19	14	9	9	6	5	2	1	1
Placebo + chemotherapy	137	113	86	52	38	24	18	14	13	7	5	4	3	3	2	1	1	0	0

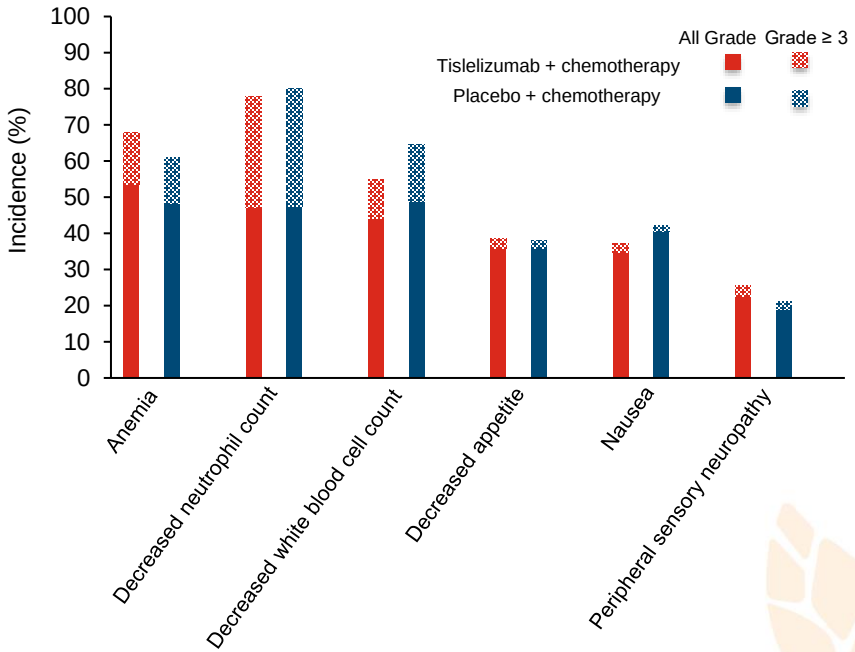
Data cutoff: February 28, 2022. *Tumor responses were assessed by investigators. †ORR, ORR differences and odds ratios between arms were calculated using the Cochran-Mantel-Haenszel method using pre-defined strata (pooled geographic region [Asia vs Rest of World], prior definitive therapy and investigator-chosen chemotherapy option). ‡Two-sided 95% CI was calculated using Clopper-Pearson method. §Including those with no post-baseline response assessment or evaluable assessment. ¶Duration of response analysis included patients with unconfirmed objective response.
BOR, best overall response; CI, confidence interval; DoR, duration of response; ORR, objective response rate

Incidences of most common treatment-related TEAEs were similar between treatment arms

Summary of safety and tolerability

n (%)	Tislelizumab + chemotherapy (n=324)	Placebo + chemotherapy (n=321)
Patients with ≥ 1 treatment-related TEAE*	313 (96.6)	309 (96.3)
≥ Grade 3	216 (66.7)	207 (64.5)
Serious AE	93 (28.7)	62 (19.3)
Leading to death†	6 (1.9)	4 (1.2)
Patients with ≥ 1 TEAE leading to discontinuation	103 (31.8)	72 (22.4)
Patients with ≥ 1 immune-mediated AE	70 (21.6)	19 (5.9)
≥ Grade 3	28 (8.6)	5 (1.6)

Most common treatment-related TEAEs (incidence ≥ 20%)



Data cutoff: February 28, 2022. For each row category, a patient with two or more adverse events in that category was counted only once. AEs grades were evaluated based on National Cancer Institute–Common Terminology Criteria for Adverse Events (version 4.03). AE terms were coded using Medical Dictionary for Drug Regulatory Affairs version 24.0.
*Treatment-related TEAEs included TEAEs that were considered by the investigator to be related to study drug or TEAEs with a missing causality. †Deaths due to disease progression are not included as treatment-related TEAEs leading to death. AE, adverse event; TEAE, treatment-emergent adverse event

Conclusions

Tislelizumab plus chemotherapy as first-line treatment demonstrated a statistically significant and clinically meaningful improvement in OS compared with chemotherapy alone, in patients with advanced or metastatic ESCC

- Median OS: 17.2 vs 10.6 months; HR 0.66 (95% CI 0.54, 0.80); p < 0.0001; in all randomized patients*
- Median OS: 16.6 vs 10.0 months; HR 0.62 (95% CI 0.44, 0.86); p=0.0020; in patients with PD-L1 score ≥10%*
- Consistent OS benefit across all prespecified subgroups, including geographic regions, races, investigator-chosen chemotherapy options and PD-L1 expression status†

The OS benefit with tislelizumab plus chemotherapy was accompanied by significant improvements in PFS and ORR, with a more durable tumor response compared with placebo plus chemotherapy

Tislelizumab plus chemotherapy had a manageable safety profile in patients with advanced or metastatic ESCC, with no new safety signal identified

Results of the RATIONALE-306 study support tislelizumab plus chemotherapy as a standard first-line therapy option for patients with advanced or metastatic ESCC

*In the associated late-breaking abstract, the reported median OS was 17.3 months for all randomized patients in the tislelizumab + chemotherapy arm and the reported median OS was 16.8 vs 10.0 months (HR 0.61 [95% CI 0.44, 0.85], p=0.0017) for patients with PD-L1 score ≥ 10% in the tislelizumab + chemotherapy arm versus the placebo + chemotherapy arm. The reason for the discrepancy is due to the update made in the program logic to properly populate the censor date. †Geographic region: Asia or Rest of World; Race: Asian and other or White; investigator-chosen chemotherapy options: platinum with fluoropyrimidine or platinum with paclitaxel; PD-L1 expression status: score ≥ or < 10%.

CI, confidence interval; ESCC, esophageal squamous cell carcinoma; HR, hazard ratio; ORR, objective response rate; OS, overall survival; PD-L1, programmed death-ligand 1; PFS, progression-free survival

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