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Randomized, Global, Phase 3 Study of Tislelizumab Plus Chemotherapy vs Chemotherapy as First-Line Therapy for Advanced or Metastatic Esophageal Squamous Cell Carcinoma (RATIONALE-306): Asia Subgroup

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Declaration of interests

Dr Ken Kato reports:

- Serving in consulting roles for AstraZeneca, Bayer, BeiGene, Bristol Myers Squibb, MSD, and ONO
- Receipt of honoraria from Bristol Myers Squibb, MSD, and ONO

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Introduction

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

Platinum-based chemotherapy is the standard of care 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, most clinical trials to date have only allowed use of a single platinum doublet (either cisplatin plus 5-FU or cisplatin plus paclitaxel)[2,7-8]

Tislelizumab is an anti-PD-1 monoclonal antibody with high affinity for PD-1; in the overall population of RATIONALE-306, tislelizumab plus chemotherapy demonstrated statistically significant and clinically meaningful survival benefit as a first-line treatment in patients with advanced or metastatic ESCC[9-11]

The global double-blind phase 3 RATIONALE-306 study (NCT03783442) is evaluating first-line tislelizumab plus investigator-chosen chemotherapy vs placebo plus investigator-chosen chemotherapy for advanced or metastatic ESCC – here we report interim analysis results for the Asia subgroup.

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

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RATIONALE-306

Overall 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

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[a] + fluoropyrimidine[b]
- **Option B**: **Platinum + paclitaxel**
  Cisplatin or oxaliplatin[a] + paclitaxel[c]

Cisplatin was used in countries where oxaliplatin substitution is not permitted, including China, Taiwan, and Japan[a]

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[d],
  HRQoL, and safety

ClinicalTrials.gov: NCT03783442. [a]Cisplatin 60-80 mg/m^2 IV or oxaliplatin 130 mg/m^2 IV on Day 1 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. [b]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. [c]Paclitaxel 175 mg/m^2 IV on Day 1 Q3W. [d]PD-L1 expression was determined centrally by PD-L1 score (defined as the total percentage of the tumor area 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.

Abbreviations: BID, twice daily; DB, double-blind; DoR, duration of response; ECOG PS, Eastern Cooperative Oncology Group performance status; ESCC, esophageal squamous cell carcinoma; 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 3 weeks; R, randomized; RECIST, Response Evaluation Criteria in Solid Tumors.

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Population characteristics

Generally balanced between treatment arms in the Asia subgroup

	Asia subgroup (n=486)		Overall population (N=649)	
	Tislelizumab + chemotherapy (n=243)	Placebo + chemotherapy (n=243)	Tislelizumab + chemotherapy (n=326)	Placebo + chemotherapy (n=323)
Median age (range), yrs	63 (26, 84)	64 (40, 82)	64 (26, 84)	65 (40, 84)
Male, n (%)	212 (87.2)	222 (91.4)	282 (86.5)	281 (87.0)
Region, n (%)				
Asia[a]	243 (100.0)	243 (100.0)	243 (74.5)	243 (75.2)
Rest of World[b]	0 (0)	0 (0)	83 (25.5)	80 (24.8)
Race, n (%)				
Asian	243 (100.0)	243 (100.0)	243 (74.5)	243 (75.2)
White	0 (0)	0 (0)	79 (24.2)	76 (23.5)
Other[c]	0 (0)	0 (0)	4 (1.2)	4 (1.2)
ECOG PS, n (%)				
0	78 (32.1)	74 (30.5)	109 (33.4)	104 (32.2)
1	165 (67.9)	169 (69.5)	217 (66.6)	219 (67.8)
Smoking status, n (%)				
Never	52 (21.4)	64 (26.3)	68 (20.9)	81 (25.1)
Current/former	180 (74.1)	169 (69.5)	247 (75.8)	231 (71.5)
Missing	11 (4.5)	10 (4.1)	11 (3.4)	11 (3.4)

	Asia subgroup (n=486)		Overall population (N=649)	
	Tislelizumab + chemotherapy (n=243)	Placebo + chemotherapy (n=243)	Tislelizumab + chemotherapy (n=326)	Placebo + chemotherapy (n=323)
Disease status at baseline, n (%)				
Metastatic	212 (87.2)	222 (91.4)	279 (85.6)	282 (87.3)
Locally advanced	31 (12.8)	21 (8.6)	47 (14.4)	41 (12.7)
Investigator-chosen chemotherapy options, n (%)				
Platinum + fluoropyrimidine	85 (35.0)	86 (35.4)	147 (45.1)	146 (45.2)
Platinum + paclitaxel	158 (65.0)	157 (64.6)	179 (54.9)	177 (54.8)
Post-treatment systemic therapies, n (%)				
Systemic therapy	120 (49.4)	141 (58.0)	157 (48.2)	177 (54.8)
Immunotherapy	42 (17.3)	63 (25.9)	46 (14.1)	71 (22.0)
Median follow-up (range), months	16.5 (0.1, 38.4)	10.6 (0.1, 37.3)	15.6 (0.1, 38.4)	12.6 (0.1, 37.3)

Data cutoff: February 28, 2022. [a]Including Japan. [b]Australia, Belgium, Czech Republic, France, Germany, Italy, Poland, Romania, Russia, Spain, UK, and US. [c]Including categories of 'American Indian,' 'Alaska Native,' 'not reported,' and 'unknown.'
Abbreviations: ECOG PS, Eastern Cooperative Oncology Group performance status; PD-L1, programmed death-ligand 1; yrs, years.

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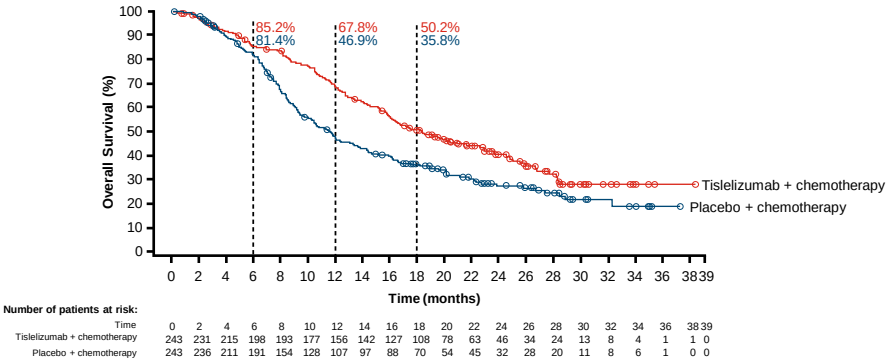
OS: Asia subgroup and overall population

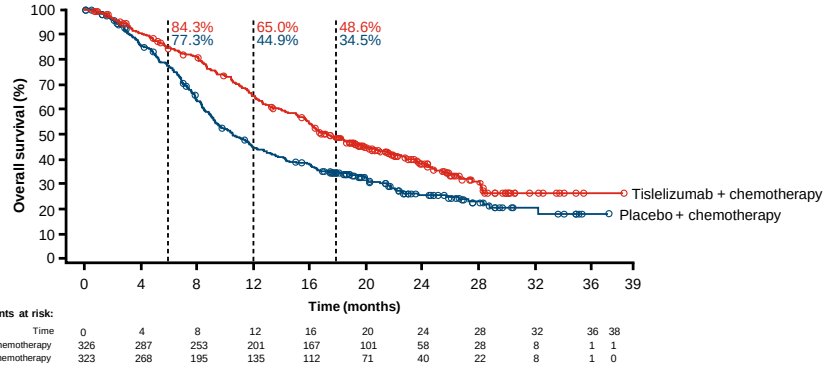
Consistent with the overall population, a clinically meaningful OS improvement in the Asia subgroup

OS – Asia subgroup



	Tislelizumab + chemotherapy (n=243)	Placebo + chemotherapy (n=243)
Events (% of patients)	143 (58.8)	169 (69.5)
Median OS, months (95% CI)	**18.3** (15.8, 22.6)	**11.5** (9.4, 13.6)
Unstratified hazard ratio[a] (95% CI)	**0.67** (0.54, 0.84)	

OS – Overall population (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)
Stratified hazard ratio (95% CI)	**0.66** (0.54, 0.80)	
***P* value**[b]	***P*<0.0001**	

Data cutoff: February 28, 2022. [a]HR was based on an unstratified Cox regression model including only treatment as covariate. [b]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). Abbreviations: CI, confidence interval; HR, hazard ratio; OS, overall survival.

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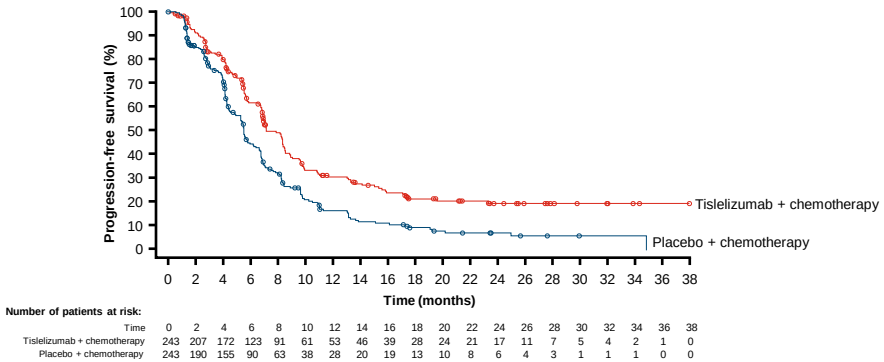
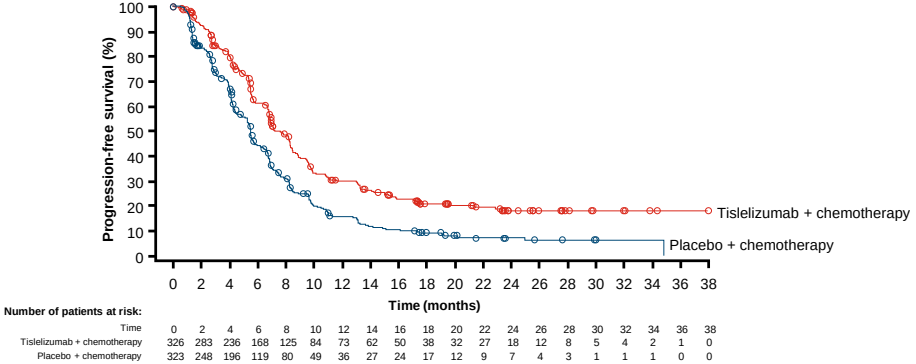
PFS: Asia subgroup and overall population

Consistent prolongation of PFS seen with tislelizumab plus chemotherapy

PFS – Asia subgroup[a]



PFS – Overall population (secondary endpoint)[a]



	Tislelizumab + chemotherapy (n=243)	Placebo + chemotherapy (n=243)
Events (% of patients)	157 (64.6)	190 (78.2)
Median PFS, months (95% CI)	**7.2** (6.9, 8.5)	**5.6** (4.9, 6.4)
Unstratified HR[b] (95% CI)	**0.62** (0.50, 0.76)	

	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)
Stratified HR[c] (95% CI); ***P* value**[d]	**0.62** (0.52, 0.75); ***P*<0.0001**	

Data cutoff: February 28, 2022. [a]PFS assessed by investigator. [b]HR was based on an unstratified Cox regression model including only treatment as covariate. [c]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). [d]1-sided *P* value was estimated from stratified log rank test. The *P* value for PFS was lower than pre-defined 1-sided alpha of 0.025 for secondary endpoints testing.
Abbreviations: CI, confidence interval; HR, hazard ratio; PFS, progression-free survival.

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Tumor response: Asia subgroup and overall population

Tumor responses were consistently greater and more durable with tislelizumab plus chemotherapy

Tumor response – Asia subgroup[a]

	Tislelizumab + chemotherapy (n=243)	Placebo + chemotherapy (n=243)
ORR[b], n	156	104
% (95% CI)[c]	**64.2** (57.8, 70.2)	**42.8** (36.5, 49.3)
Odds ratio for ORR[b], (95% CI)	**2.40** (1.66, 3.45)	
ORR difference[b], % (95% CI)	**21.4** (12.7, 30.1)	
BOR, n (%)		
Complete response	8 (3.3)	4 (1.6)
Partial response	148 (60.9)	100 (41.2)
Stable disease[e]	56 (23.0)	96 (39.5)
Progressive disease	12 (4.9)	32 (13.2)
Not determined[f]	19 (7.8)	11 (4.5)
DoR[g]		
Median (95% CI), months	**7.1** (5.6, 8.4)	**5.6** (4.4, 7.1)
Patients with ongoing response, n (%)[h]	29 (18.6)	9 (8.7)

Tumor response – Overall population (secondary endpoint)[a]

	Tislelizumab + chemotherapy (n=326)	Placebo + chemotherapy (n=323)
ORR[b], n	207	137
% (95% CI)[c]	**63.5** (58.0, 68.7)	**42.4** (37.0, 48.0)
Odds ratio for ORR[b], (95% CI); *P* value[d]	**2.38** (1.73, 3.27); ***P*<0.0001**	
ORR difference[b], % (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[e]	83 (25.5)	122 (37.8)
Progressive disease	13 (4.0)	42 (13.0)
Not determined[f]	23 (7.1)	22 (6.8)
DoR[g]		
Median (95% CI), months	**7.1** (6.1, 8.1)	**5.7** (4.4, 7.1)
Patients with ongoing response, n (%)[h]	40 (19.3)	13 (9.5)

Data cutoff: February 28, 2022. [a]Tumor responses were assessed by investigators. [b]ORR, ORR differences, and odds ratios between arms were calculated using the Cochran-Mantel-Haenszel method, and for the overall population was stratified by pooled geographic region (Asia vs Rest of World), prior definitive therapy, and investigator-chosen chemotherapy option. [c]2-sided 95% CI was calculated using Clopper-Pearson method. [d]The *P* value for ORR was lower than pre-defined 1-sided alpha of 0.025 for secondary endpoints testing. [e]Stable disease includes SD and non-CR/non-PD. [f]Including those with no post-baseline response assessment or no evaluable assessment. [g]Duration of response analysis included patients with unconfirmed objective response. [h]Among responders. Includes patients ongoing without PD and with no post-baseline assessments.
Abbreviations: BOR, best overall response; CI, confidence interval; CR, complete response; DoR, duration of response; ORR, objective response rate; PD, progressive disease; SD, stable disease.

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Safety and tolerability profile: Asia subgroup and overall population

Tislelizumab plus chemotherapy had a manageable safety profile, consistent between the Asia subgroup and the overall study population

Summary of safety and tolerability – Asia subgroup

n (%)	Tislelizumab + chemotherapy (n=241)	Placebo + chemotherapy (n=243)
Patients with ≥1 treatment-related TEAE[a]	235 (97.5)	240 (98.8)
≥ Grade 3	169 (70.1)	166 (68.3)
Serious	72 (29.9)	48 (19.8)
Leading to death[b]	5 (2.1)	3 (1.2)
Patients with ≥1 TEAE leading to any treatment discontinuation	68 (28.2)	44 (18.1)
Discontinuation of tislelizumab/placebo	27 (11.2)	15 (6.2)
Discontinuation of any chemotherapy	61 (25.3)	42 (17.3)

Summary of safety and tolerability – Overall population

n (%)	Tislelizumab + chemotherapy (n=324)	Placebo + chemotherapy (n=321)
Patients with ≥1 treatment-related TEAE[a]	313 (96.6)	309 (96.3)
≥ Grade 3	216 (66.7)	207 (64.5)
Serious	93 (28.7)	62 (19.3)
Leading to death[b]	6 (1.9)	4 (1.2)
Patients with ≥1 TEAE leading to any treatment discontinuation	103 (31.8)	72 (22.4)
Discontinuation of tislelizumab/placebo	42 (13.0)	21 (6.5)
Discontinuation of any chemotherapy	95 (29.3)	70 (21.8)

Data cutoff: February 28, 2022. For each row category, a patient with two or more adverse events in that category was counted only once. AE 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. [a]Treatment-related TEAEs included TEAEs that were considered by the investigator to be related to study drug or TEAEs with a missing causality. [b]Deaths due to disease progression are not included as TEAEs leading to death.
Abbreviations: AE, adverse event; TEAE, treatment-emergent adverse event.

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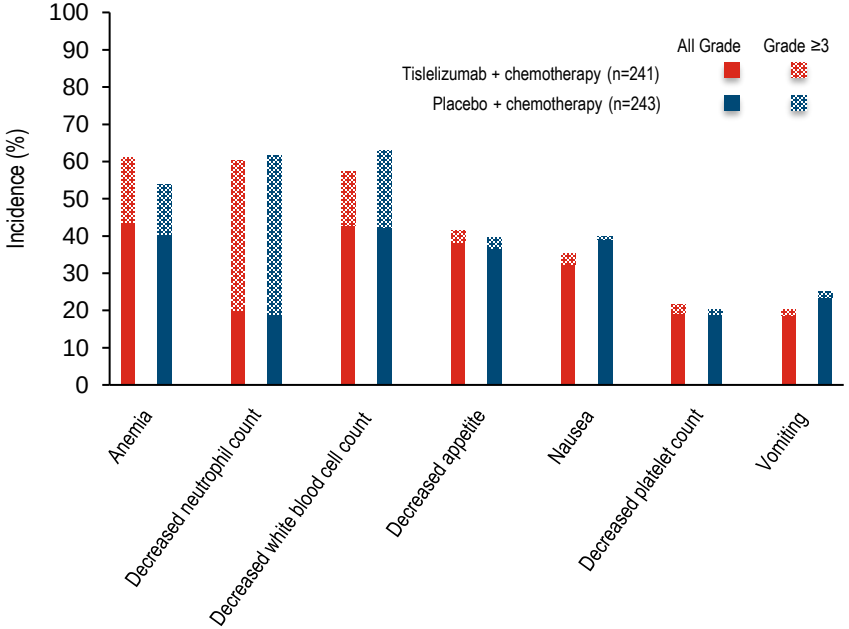
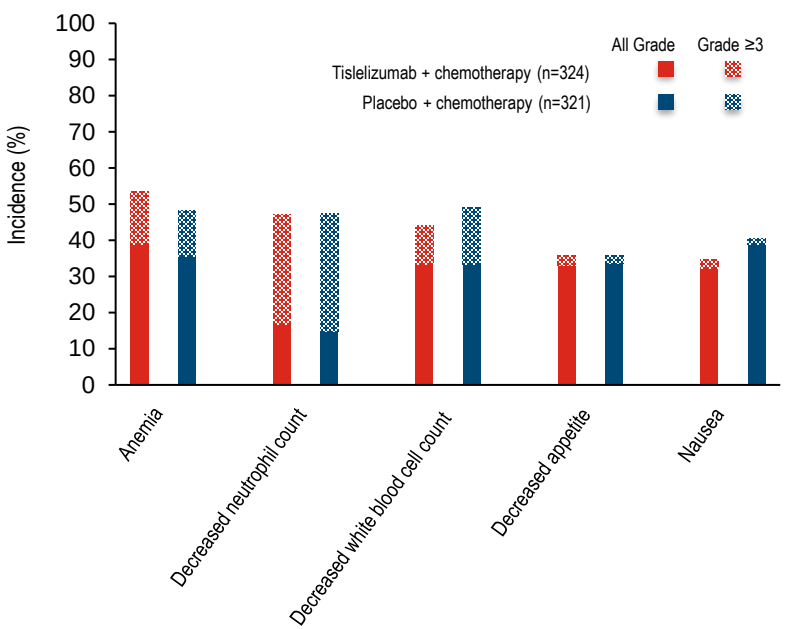
Treatment-related TEAEs: Asia subgroup and overall population

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

Most common treatment-related TEAEs (incidence ≥20%[a]) – Asia subgroup



Most common treatment-related TEAEs (incidence ≥20%[a]) – Overall population



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Abbreviations: AE, adverse event; TEAE, treatment-emergent adverse event.

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Conclusions

Within the Asia subgroup of RATIONALE-306, tislelizumab plus chemotherapy as first-line treatment demonstrated a clinically meaningful improvement in OS compared with placebo plus chemotherapy in patients with advanced or metastatic ESCC:

- Median OS: 18.3 vs 11.5 months; HR 0.67 (95% CI 0.54, 0.84)

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

Tislelizumab plus chemotherapy had a manageable safety profile as a first-line treatment in Asian patients with advanced or metastatic ESCC, with no new safety signals identified.

The treatment benefits and the safety profile of tislelizumab plus chemotherapy in the Asia subgroup were consistent with those in the overall study population.

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 Asia and globally.

Abbreviations: CI, confidence interval; ESCC, esophageal squamous cell carcinoma; HR, hazard ratio; ORR, objective response rate; OS, overall survival; PFS, progression-free survival.

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