Global, Randomized, Phase III Study of Tislelizumab Plus Chemotherapy Versus Placebo Plus Chemotherapy as First-line Treatment for Advanced/Metastatic Esophageal Squamous Cell Carcinoma (RATIONALE-306 Update): Minimum 3-year Survival Follow-up

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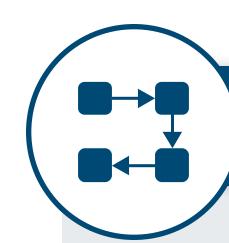


After a minimum of 3 years of follow-up, first-line (1L) treatment with tislelizumab (TIS; BGB-A317) plus investigator-chosen chemotherapy (ICC) continued to demonstrate clinically meaningful improvements in overall survival (OS), as well as improved progression-free survival (PFS) and durable antitumor response in patients with advanced/metastatic esophageal squamous cell carcinoma (ESCC) compared with placebo (PBO) plus ICC.

Conclusions

Background

Esophageal cancer is among the most common cancer types worldwide and is the seventh most prevalent cause of death due to cancer.¹ ESCC is the predominant histologic subtype of esophageal cancer, accounting for up to 90% of all cases worldwide.^{2,3} Monoclonal anti-programmed cell death protein 1 (PD-1) antibodies in combination with platinum-based chemotherapy have demonstrated superior survival benefits as 1L treatment for ESCC vs platinum-based chemotherapy alone.³⁻⁸



Nethods

- Systemic therapy-naïve adults (aged ≥18 years) with unresectable locally advanced recurrent/metastatic ESCC, Eastern Cooperative Oncology Group (ECOG) performance status of 0-1, and measurable or evaluable disease per Response Evaluation Criteria in Solid Tumors (version 1.1) were recruited⁹
- Patients were randomized 1:1 to receive either TIS 200 mg or PBO intravenously once every 3 weeks plus ICC (platinum plus fluoropyrimidine or platinum plus paclitaxel) until disease progression or intolerable toxicity
- The primary endpoint was OS in the intent-to-treat (ITT) population
- Secondary endpoints included investigator-assessed PFS, objective response rate (ORR), duration of response (DoR), OS in the subgroup with programmed death-ligand 1 (PD-L1) tumor area positivity (TAP) score $\geq 10\%$, and safety



Results

Patient Disposition and Baseline Characteristics

- Baseline characteristics were generally balanced between both arms, as described previously⁹
- At data cutoff (November 24, 2023), minimum study follow-up time was 36.0 months in 649 patients randomized (TIS plus ICC: n=326; PBO plus ICC: n=323)
- 630 patients (97.1%) discontinued from treatment (TIS plus ICC: 310 [95.1%]; PBO plus ICC: 320 [99.1%]). Reasons for discontinuation were progressive disease (63.3%), withdrawal by patient (13.6%), adverse event (9.2%), physician decision (2.0%), treatment interruption (1.4%), non-compliance with study drug (0.2%), or other reasons (7.4%)
- 567 patients (87.4%) discontinued the study (TIS plus ICC: 276 [84.7%]; PBO plus ICC: 291 [90.1%])
- 168 patients (51.5%) in the TIS plus ICC arm vs 187 (57.9%) in the PBO plus ICC arm received post-treatment systemic therapy, of whom 50 (15.3%) vs 80 (24.8%), respectively, had post-treatment immunotherapy

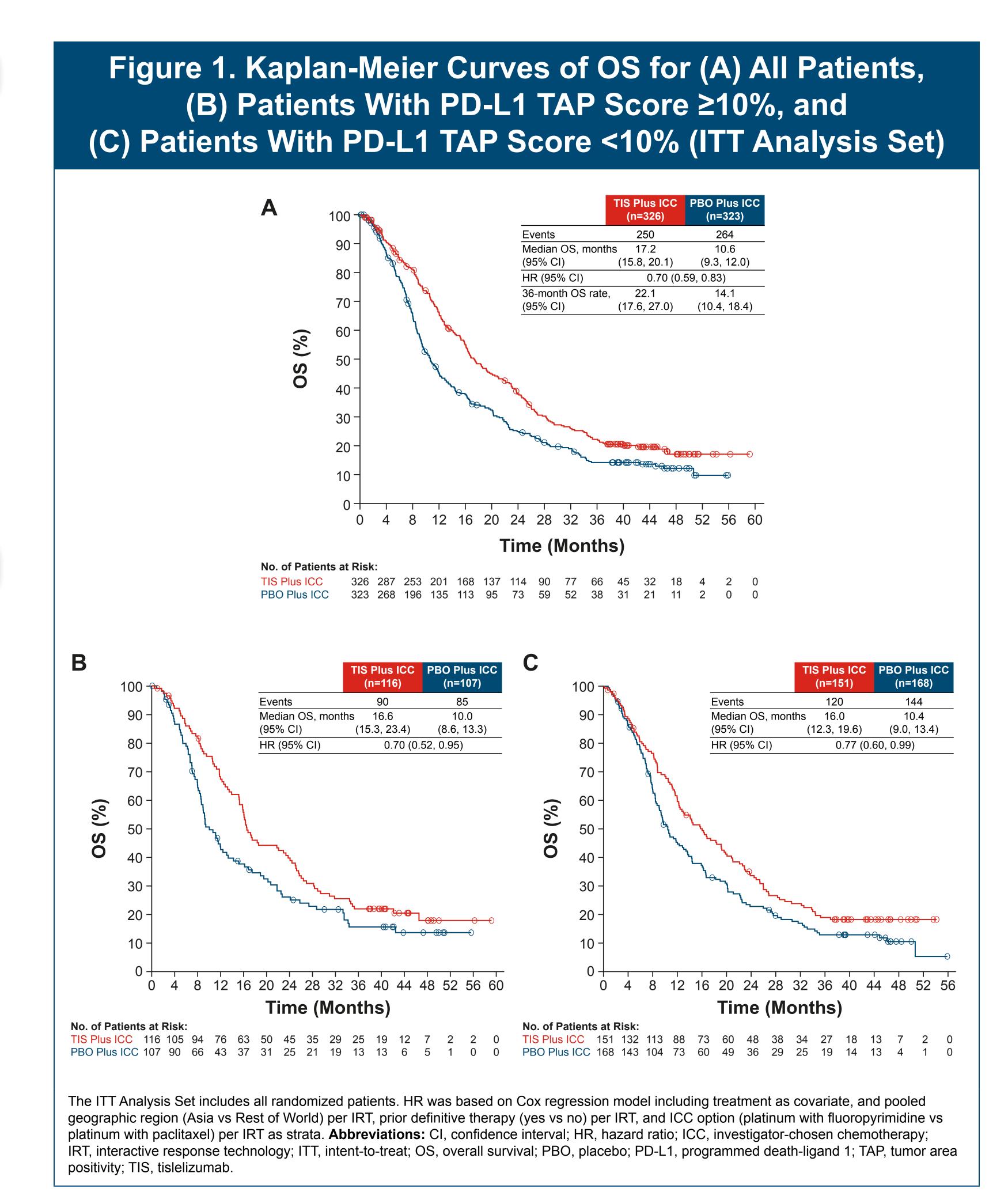
Efficacy

- Clinically meaningful improvements in OS (Figure 1A and 1B), PFS, DoR, and ORR with TIS plus ICC vs PBO plus ICC were maintained relative to the IA (Table 1)⁹
- The HR for OS with TIS plus ICC vs PBO plus ICC was 0.70 (95% CI: 0.59, 0.83)
- The 36-month OS rate was 22.1% with TIS plus ICC vs 14.1% with PBO plus ICC (Figure 1A)
- OS benefit was observed across all prespecified subgroups (**Figure 2**)

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RATIONALE-306 (NCT03783442) is a randomized, double-blind, phase III study to investigate anti-PD-1 therapy in combination with different ICC options as 1L treatment of advanced/metastatic ESCC.⁹ At IA, TIS plus ICC demonstrated a statistically significant and clinically meaningful improvement (stratified hazard ratio [HR]=0.66; 95% confidence interval [CI]: 0.54, 0.80) in OS vs PBO plus ICC, with a manageable safety profile.⁹ Here, we report updated efficacy and safety data with a minimum of 3 years of follow-up after study unblinding at IA.



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These findings from the 3-year follow-up of the RATIONALE-306 study align with the 2-year follow-up and interim analysis (IA), reinforcing the sustained efficacy and manageable safety profile of TIS plus ICC and providing further support for the therapeutic advantages of TIS plus ICC over PBO plus ICC as 1L treatment of ESCC.

Table 1. Secondary Efficacy Endpoints (ITT Analysis Set)					
	TIS Plus ICC (n=326)	PBO Plus ICC (n=323)			
Median PFS (95% CI), months ^a HR (95% CI)	7.3 (6.9, 8.3) 5.6 (4.9, 6.0) 0.60 (0.50, 0.72)				
36-month PFS rate (95% CI), % ^a	15.0 (10.8, 19.9)	2.9 (1.1, 6.2)			
ORR (95% CI), % ^a	63.5 (58.0, 68.7)	42.4 (37.0, 48.0)			
Median DoR (95% CI), months ^a	7.1 (6.1, 8.1)	5.7 (4.4, 7.1)			
36-month DoR rate (95% CI), % ^{a,b}	17.7 (12.3, 24.0)	5.0 (1.5, 11.8)			

The ITT Analysis Set includes all randomized patients, a Per investigator, b TIS plus ICC; n=207; PBO plus ICC; n=137, Abbreviations; CL confider interval; DoR, duration of response; HR, hazard ratio; ICC, investigator-chosen chemotherapy; ITT, intent-to-treat; ORR, objective response rate; PBO, placebo; PFS, progression-free survival; TIS, tislelizumab.

Figure 2. Forest Plot of OS by Subgroup (ITT Analysis Set)

	Event	:/Total		HR for I	Death (95% CI)		HR (95% CI)
Subgroup	TIS Plus ICC	PBO Plus ICC					
Overall	250/326	264/323			-		0.71 (0.59, 0.84)
Age ≥65 years	116/150	137/162			_		0.67 (0.52, 0.86)
Sex							
Male	223/282	234/281			—		0.74 (0.62, 0.89)
Smoking status							
Former/current smoker	193/247	195/231			-		0.69 (0.57, 0.85)
Non-smoker	50/68	59/81			┏─┼─		0.77 (0.53, 1.12)
ICC options per IRT							
Platinum with fluoropyrimidine	112/147	119/146			—		0.69 (0.54, 0.90)
Platinum with paclitaxel	138/179	145/177			—		0.72 (0.57, 0.91)
ECOG performance score							
0	82/109	79/104			┏─┼		0.77 (0.57, 1.05)
1	168/217	185/219			-		0.68 (0.55, 0.84)
Region							
Asia	185/243	197/243			-		0.72 (0.59, 0.88)
Rest of World	65/83	67/80					0.67 (0.47, 0.94)
Baseline PD-L1 status							
PD-L1 score ≥10% ^a	90/116	85/107					0.71 (0.53, 0.95)
PD-L1 score <10% ^a	120/151	144/168					0.74 (0.58, 0.95)
Unknown	40/59	35/48					0.65 (0.41, 1.02)
				0 5			
			0.0	0.5	1.0 1.5	2.0	
			Favors T	IS Plus IC	C Favors PBO	Plus ICC	

The ITT Analysis Set includes all randomized patients. HR was based on unstratified Cox regression model including treatment as covariate ^a PD-L1 score based on TAP score. Abbreviations: CI, confidence interval; ECOG, Eastern Cooperative Oncology Group; HR, hazard ratio; ICC, investigator-chosen chemotherapy; IRT, interactive response technology; ITT, intent-to-treat; OS, overall survival; PBO, placebo; PD-L1, programmed death-ligand 1; TAP, tumor area positivity; TIS, tislelizumab

Disclosures

Harry H. Yoon reports speaker fees from BeiGene; writing engagements with BeiGene; expert testimony fees from MJH Life Sciences; advisory roles for Amgen, Astellas, AstraZeneca, BeiGene, Bristol Myers Squibb, Elevation Oncology, Macrogenics, Merck, Novartis, OncXerna, and Zymeworks; research grants from BeiGene, Bristol Myers Squibb, CARsgen Therapeutics, and Merck; and support for travel from BeiGene.



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Safety

- Median exposure was longer for TIS plus ICC (6.4 months; range: 0.1-59.2) than for PBO plus ICC (4.9 months; range: 0.6-36.4), with 18 patients (5.6%) treated with TIS plus ICC for ≥36 months
- Incidences of any-grade and grade ≥3 treatment-related adverse events (TRAEs) were comparable between patients receiving TIS plus ICC and PBO plus ICC (Table 2)
- Serious TRAEs and treatment-emergent adverse events (TEAEs) leading to treatment discontinuation occurred more frequently with TIS plus ICC vs PBO plus ICC
- TEAEs leading to dose modification were comparable with TIS plus ICC vs PBO plus ICC
- The most common grade ≥3 TRAEs (TIS plus ICC vs PBO plus ICC) were decreased neutrophil count (30.9% vs 32.7%), anemia (14.8% vs 12.8%), and decreased white blood cell count (10.8% vs 15.6%)

Table 2. Summary of TEAEs and TRAEs (Safety Analysis Set)						
	TIS Plus ICC (n=324)	PBO Plus ICC (n=321)				
Patients with ≥1 TRAE, n (%)	313 (96.6)	309 (96.3)				
Grade ≥3	217 (67.0)	207 (64.5)				
Serious	97 (29.9)	63 (19.6)				
Leading to death	6 (1.9)	4 (1.2)				
Patients with ≥1 TEAE leading to any treatment discontinuation, n (%)	104 (32.1)	71 (22.1)				
Patients with ≥1 TEAE leading to any dose modification, n (%)	247 (76.2)	229 (71.3)				

Fhe Safety Analysis Set includes all enrolled patients who received ≥1 dose of study drug. Adverse event grades were evaluated based on Nationa 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. Abbreviations: ICC, investigator-chosen chemotherapy; PBO, placebo; TEAE, treatmentemergent adverse event; TIS, tislelizumab; TRAE, treatment-related adverse event.

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