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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CONCLUSIONS

- 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
- 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

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]
- RATIONALE-306 (NCT03783442) is a randomized, double-blind, phase III study and the first global 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

METHODS

- 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 recruited[9]
- 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 ≥10%, and safety

RESULTS

Patient Disposition and Baseline Characteristics

- Baseline characteristics were generally balanced between both arms, as described previously[9]
- 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**)

Safety

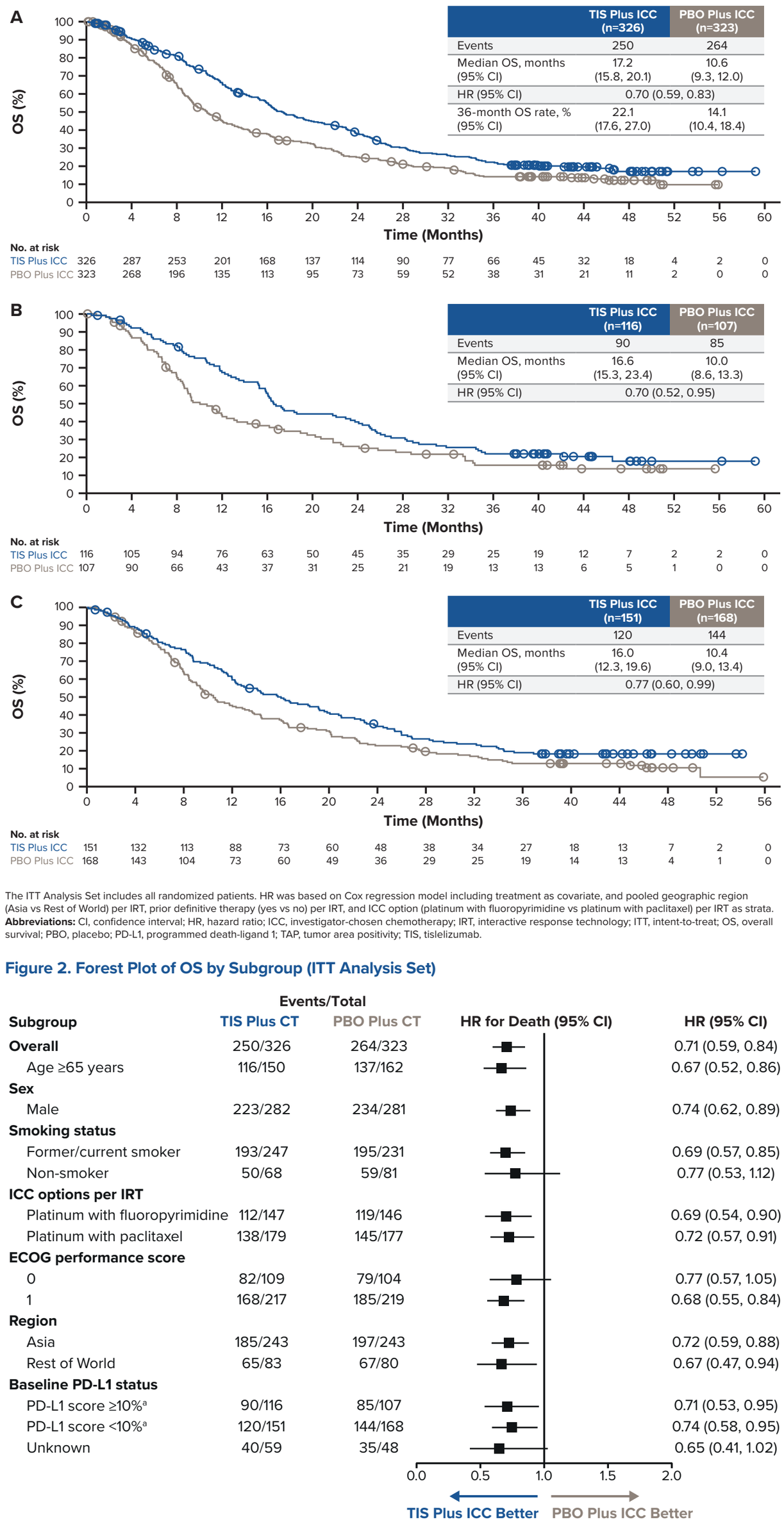
- Median exposure was longer for TIS plus ICC (6.4 months; range: 0.1-59.2) than for PBO plus ICC (4.9 months; range: 0.6-36.4), with 18 patients (5.6%) treated with TIS plus ICC for ≥36 months
- Incidences of any-grade and grade ≥3 treatment-related adverse events (TRAEs) were comparable between patients 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 1. Secondary Efficacy Endpoints (ITT Analysis Set)

	TIS Plus ICC (n=326)	PBO Plus ICC (n=323)
Median PFS (95% CI), months[a]	7.3 (6.9, 8.3)	5.6 (4.9, 6.0)
HR (95% CI)	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: CI, confidence 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 1. Kaplan-Meier Curves of OS for (A) All Patients, (B) Patients With PD-L1 TAP Score ≥10%, and (C) Patients With PD-L1 TAP Score <10% (ITT Analysis Set)



The ITT Analysis Set includes all randomized patients. HR was based on Cox regression model including treatment as covariate, and pooled geographic region (Asia vs Rest of World) per IRT, prior definitive therapy (yes vs no) per IRT, and ICC option (platinum with fluoropyrimidine vs platinum with paclitaxel) per IRT as strata.
Abbreviations: CI, confidence interval; 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.

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

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.

Table 2. Summary of TEAEs and TRAEs (Safety Analysis Set)

n (%)	TIS Plus ICC (n=326)	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)

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

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DISCLOSURES

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