Global, Randomized, Phase 3 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+ICC over PBO+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 (CT) have demonstrated superior survival benefits as 1L treatment for ESCC versus platinum-based CT alone[3-8]
- RATIONALE-306 (NCT03783442) is a randomized, double-blind, phase 3 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+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 versus PBO+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

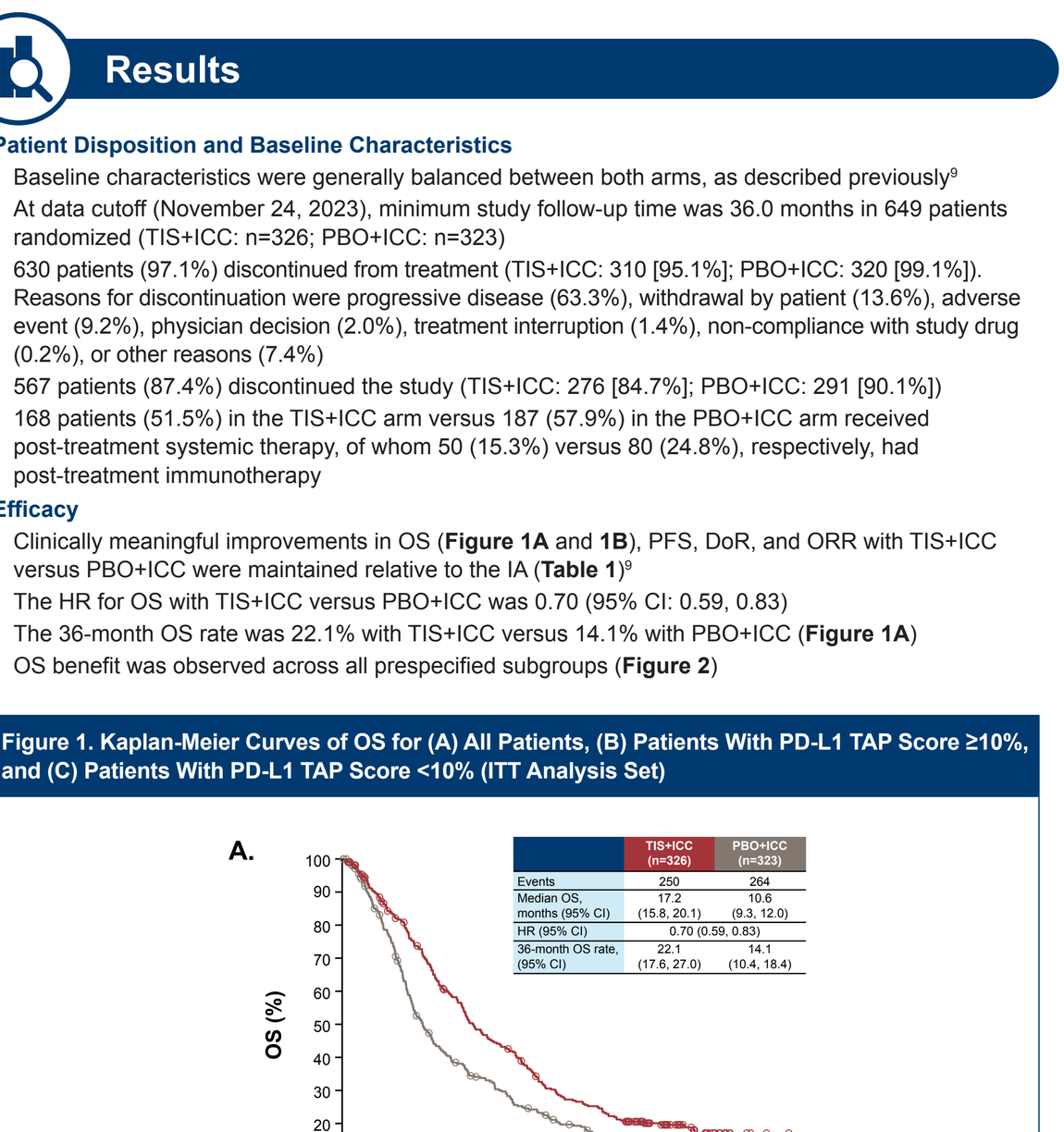
Patient Disposition and Baseline Characteristics

- 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+ICC: n=326; PBO+ICC: n=323)
- 630 patients (97.1%) discontinued from treatment (TIS+ICC: 310 [95.1%]; PBO+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+ICC: 276 [84.7%]; PBO+ICC: 291 [90.1%])
- 168 patients (51.5%) in the TIS+ICC arm versus 187 (57.9%) in the PBO+ICC arm received post-treatment systemic therapy, of whom 50 (15.3%) versus 80 (24.8%), respectively, had post-treatment immunotherapy

Efficacy

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

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.
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.

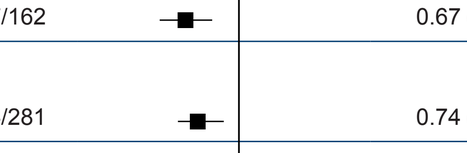
Table 1. Secondary Efficacy Endpoints (ITT Analysis Set)

	TIS+ICC (n=326)	PBO+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.
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 2. Forest Plot of OS by Subgroup (ITT Analysis Set)

Subgroup	TIS+ICC	PBO+ICC	HR for Death (95% CI)
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 the 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)



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.
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.

Safety

- Median exposure was longer for TIS+ICC (6.4 months; range: 0.1-59.2) than for PBO+ICC (4.9 months; range: 0.6–36.4), with 18 patients (5.6%) treated with TIS+ICC for ≥36 months
- Incidences of any-grade and grade ≥3 treatment-related adverse events (TRAEs) were comparable between patients receiving TIS+ICC and PBO+ICC (**Table 2**)
- Serious TRAEs and treatment-emergent adverse events (TEAEs) leading to treatment discontinuation occurred more frequently with TIS+ICC versus PBO+ICC
- TEAEs leading to dose modification were comparable with TIS+ICC versus PBO+ICC
- The most common grade ≥3 TRAEs (TIS+ICC vs PBO+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+ICC (n=324)	PBO+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.
ICC, investigator-chosen chemotherapy; PBO, placebo; TEAE, treatment- emergent adverse event; TIS, tislelizumab; TRAE, treatment-related adverse event.

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Presenter Disclosures
Rossana Berardi reports serving as a consultant/advisory board member for AstraZeneca, BMS, Boehringer Ingelheim, EISAI, Eli Lilly, GSK, Incyte, Italfarmaco, MSD, Novartis, Otsuka, Pierre Fabre, Roche, and Seagen, outside the submitted work.

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