First-line Tislelizumab Plus Chemotherapy Versus Placebo Plus Chemotherapy in Advanced/Metastatic Esophageal Squamous Cell Carcinoma (ESCC): RATIONALE-306 Japanese Subgroup Analysis With Longer Follow-up

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Conclusions

After 3 years, tislelizumab (TIS; BGB-A317) plus investigator-chosen chemotherapy (ICC) maintained clinically meaningful improvements in overall survival (OS) compared to placebo (PBO) plus ICC in all randomized patients, with more than 50% of patients alive at 2 years from randomization. OS benefit was similar in patients with a programmed death-ligand 1 (PD-L1) Tumor Area Positivity (TAP) score of ≥10%.

Improvements in secondary efficacy endpoints, including progression-free survival (PFS), durable antitumor response, and a tolerable safety profile, were maintained in Japanese patients as first-line (1L) therapy for advanced/metastatic ESCC in the RATIONALE-306 study, consistent with the overall population.

These findings from the longer follow-up of the RATIONALE-306 Japanese subgroup align with the previous report (median follow-up 18.8 months), reinforcing the sustained improvement in efficacy and the manageable safety profile of TIS plus ICC and further supporting its use as 1L treatment of ESCC.

Background

Esophageal cancers rank among the most prevalent cancer types globally, representing the 7th leading cause of cancer-related mortality.[1] ESCC is the primary histological subtype, comprising up to 90% of all esophageal cancer cases worldwide.[2,3] Treatment with monoclonal anti-programmed cell death protein-1 (PD-1) antibodies in combination with platinum-based chemotherapy has shown superior survival benefits in the 1L setting for ESCC compared to platinum-based chemotherapy alone.[3-8]

RATIONALE-306 (NCT03783442) was 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] After a minimum 3-year follow-up, TIS plus ICC demonstrated a statistically significant and clinically meaningful improvement (stratified hazard ratio [HR]=0.70; 95% confidence interval [CI]: 0.59, 0.83) in OS vs PBO plus ICC, with a manageable safety profile.[10] Here, we report updated efficacy and safety data for the Japanese subgroup of patients after a minimum of 3 years of follow-up.

Methods

- Systemic therapy-naïve adults (aged ≥18 years) with unresectable locally advanced, recurrent/metastatic ESCC, an 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]
- Eligible patients enrolled in Japan were randomized 1:1 to receive either TIS 200 mg or PBO intravenously 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 a PD-L1 TAP score of ≥10%, and safety
- A post hoc analysis of concordance of TAP score and combined positive score (CPS) at multiple thresholds was conducted
- PD-L1 expression was stained using the VENTANA PD-L1 (SP263) Assay (Roche) and determined by TAP score in RATIONALE-306. For exploratory purposes, pathologists in the central laboratory scored the same stained samples according to CPS

Results

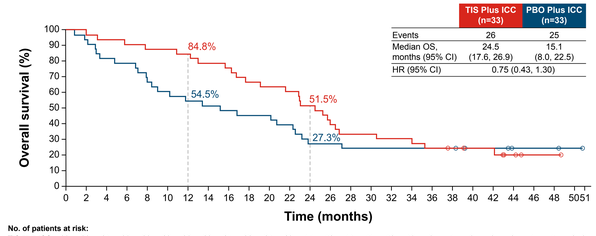
Patient Disposition and Baseline Characteristics

- Of the 649 randomized patients, 66 (10.2%) were Japanese (TIS plus ICC: n=33; PBO plus ICC: n=33)
- Baseline characteristics were generally balanced between treatment groups; median age was 67.0 years and 89.4% were male
- At study entry, ECOG performance status was 0 for 77.3% of patients (ITT population: 32.8%), and 97.0% had metastatic disease (ITT population: 86.4%)
- At data cutoff (November 24, 2023), after a minimum study follow-up of 37.9 months, 26 (78.8%) vs 28 (84.8%) Japanese patients on TIS plus ICC vs PBO plus ICC received at least 1 post-systemic therapy (ITT population: 51.5% vs 57.9%), of whom 15 (45.5%) vs 21 (63.6%) had post-treatment immunotherapy, respectively
- 64 patients (97.0%) in the Japanese subgroup discontinued from treatment (TIS plus ICC: 31 [93.9%]; PBO plus ICC: 33 [100.0%]) and 51 patients (77.3%) discontinued the study (TIS plus ICC: 26 [78.8%]; PBO plus ICC: 25 [75.8%])

Efficacy

- Clinically meaningful improvements in OS (**Figure 1**) were observed in all patients
  - Median OS with TIS plus ICC was 24.5 months (95% CI: 17.6, 26.9) vs 15.1 months (95% CI: 8.0, 22.5) with PBO plus ICC; HR=0.75 (95% CI: 0.43, 1.30)
  - The 12-month and 24-month OS rates with TIS plus ICC vs PBO plus ICC were 84.8% (95% CI: 67.4, 93.4) vs 54.5% (95% CI: 36.3, 69.6) and 51.5% (95% CI: 33.5, 66.9) vs 27.3% (95% CI: 13.6, 42.9), respectively
  - In patients with a PD-L1 TAP score ≥10%, median OS with TIS plus ICC was 25.5 months (95% CI: 10.9, not estimable [NE]) vs 16.8 months (95% CI: 0.9, NE) with PBO plus ICC; HR=0.79 (95% CI: 0.26, 2.36)
- Improvements in median PFS as assessed by the investigator were observed in patients receiving TIS plus ICC as compared to PBO plus ICC (**Table 1**)
  - Median PFS (investigator assessed) with TIS plus ICC was 6.8 months (95% CI: 4.4, 8.4) vs 4.5 months (95% CI: 4.1, 6.7) with PBO plus ICC; HR=0.77 (95% CI: 0.45, 1.32)
  - The 12-month and 24-month PFS rates with TIS plus ICC vs PBO plus ICC were 18.5% (95% CI: 6.9, 34.6) vs 13.3% (95% CI: 4.2, 27.6) and 7.4% (95% CI: 1.3, 20.9) vs 8.8% (95% CI: 1.8, 23.0), respectively
- Efficacy benefits were also observed with TIS plus ICC vs PBO plus ICC in the secondary endpoints investigator-assessed DoR and ORR, consistent with the overall ITT population (**Table 1**)

Figure 1. Kaplan–Meier Curves of OS (Japanese Subgroup)



HR for TIS plus ICC vs PBO plus ICC was based on an unstratified Cox regression model only including treatment as a covariate.
Abbreviations: CI, confidence interval; HR, hazard ratio; ICC, investigator-chosen chemotherapy; OS, overall survival; PBO, placebo; TIS, tislelizumab.

Table 1. Secondary Efficacy Endpoints (Efficacy Analysis Set)

	Japan TIS Plus ICC (n=33)	Japan PBO Plus ICC (n=33)	Overall TIS Plus ICC (n=326)	Overall PBO Plus ICC (n=323)
PD-L1 ≥10%, n (%)	12 (36.4)	7 (21.2)	116 (35.6)	107 (33.1)
Median OS by PD-L1 ≥10%, mo (95% CI)	25.5 (10.9, NE)	16.8 (0.9, NE)	16.6 (15.3, 23.4)	10.0 (8.6, 13.3)
HR (95% CI)	0.79 (0.26, 2.36)		0.70 (0.52, 0.95)[b]	
Median PFS, mo (95% CI)[a]	6.8 (4.4, 8.5)	4.5 (4.1, 6.7)	7.3 (6.9, 8.3)	5.6 (4.9, 6.0)
HR (95% CI)	0.77 (0.45, 1.32)		0.60 (0.50, 0.72)[b]	
Median DoR, mo (95% CI)[a]	5.3 (4.2, 8.5)	4.4 (2.4, 8.4)	7.1 (6.1, 8.1)	5.7 (4.4, 7.1)
ORR, n (%)[a]	21 (63.6)	15 (45.5)	207 (63.5)	137 (42.4)

[a] Investigator assessed. [b] Stratified.
Abbreviations: CI, confidence interval; DoR, duration of response; HR, hazard ratio; ICC, investigator-chosen chemotherapy; mo, months; NE, not estimable; ORR, objective response rate; OS, overall survival; PBO, placebo; PD-L1 programmed death-ligand 1; PFS, progression-free survival; TIS, tislelizumab.

PD-L1 TAP Score vs CPS Concordance

- PD-L1 TAP score and CPS showed substantial concordance at multiple cutoffs (**Table 2**)

Table 2. PD-L1 TAP Score vs CPS Concordance in RATIONALE-306 (Japanese Subgroup and Overall Population)

	TAP/CPS 1%/1	TAP/CPS 5%/5	TAP/CPS 10%/10
Japanese Subgroup			
PPA (n/N)	0.94 (49/52)	0.79 (27/34)	0.70 (16/23)
NPA (n/N)	1.00 (4/4)	0.73 (16/22)	0.91 (30/33)
OPA (n/N)	0.95 (53/56)	0.77 (43/56)	0.82 (46/56)
Cohen's Kappa (95% CI)	0.70 (0.38, 1.00)	0.52 (0.29, 0.75)	0.62 (0.41, 0.83)
Overall Population[11]			
PPA (n/N)	0.98 (470/480)	0.90 (309/343)	0.86 (196/228)
NPA (n/N)	0.89 (51/57)	0.76 (147/194)	0.92 (283/309)
OPA (n/N)	0.97 (521/537)	0.85 (456/537)	0.89 (479/537)
Cohen's Kappa (95% CI)	0.85 (0.77, 0.92)	0.67 (0.60, 0.73)	0.78 (0.72, 0.83)

Strength of agreement (Kappa)

Slight (0.01-0.20)	Fair (0.21-0.40)	Moderate (0.41-0.60)	Substantial (0.61-0.80)	Almost perfect (0.81-1.0)

Abbreviations: CI, confidence interval; CPS, combined positive score; NPA, negative percent agreement; OPA, overall percent agreement; PPA, positive percent agreement; TAP, Tumor Area Positivity.

Safety

- Safety profile in the Japanese subgroup was manageable and comparable to the overall population (**Table 3**)
- Incidence of any-grade treatment-related adverse events (TRAEs) was comparable between patients receiving TIS plus ICC and PBO plus ICC (**Table 3**)
- TRAEs of grade ≥3 and serious TRAEs occurred more frequently with TIS plus ICC vs PBO plus ICC
- No TRAEs leading to death were reported in Japanese patients
- The most common grade ≥3 treatment-emergent adverse events with TIS plus ICC vs PBO plus ICC were decreased neutrophil count (24.2% vs 36.4%), anemia (21.2% vs 6.1%), and hyponatremia (15.2% vs 3.0%)

Table 3. Summary of TRAEs (Safety Analysis Set)

	Japan TIS Plus ICC (n=33)	Japan PBO Plus ICC (n=33)	Overall TIS plus ICC (n=324)	Overall PBO plus ICC (n=321)
Patients with ≥1 TRAE, n (%)	15 (45.5)	12 (36.4)	226 (69.8)	195 (60.7)
Grade ≥3	9 (27.3)	2 (6.1)	104 (32.1)	65 (20.2)
Serious	8 (24.2)	1 (3.0)	64 (19.8)	27 (8.4)
Leading to death	0	0	5 (1.5)	2 (0.6)
Patients with ≥1 TRAE leading to any treatment discontinuation, n (%)	7 (21.2)	6 (18.2)	43 (13.3)	21 (6.5)
Patients with ≥1 TRAE leading to any dose modification, n (%)	29 (87.9)	31 (93.9)	174 (53.7)	128 (39.9)

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 the study drug or TEAEs with a missing causality.
Abbreviations: ICC, investigator-chosen chemotherapy; PBO, placebo; TEAE, treatment-emergent adverse event; TIS, tislelizumab; TRAE, treatment-related adverse event.

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