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

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## Conclusion

**Tislelizumab plus chemotherapy demonstrated a clinically meaningful improvement in OS compared with placebo plus chemotherapy as 1L treatment in patients with advanced or metastatic ESCC in the non-Asia subgroup.**

**Tislelizumab plus chemotherapy had a manageable safety profile as 1L treatment for advanced or metastatic ESCC, with no new safety signals identified in the non-Asia subgroup.**

**The treatment benefits and the safety profile of tislelizumab plus chemotherapy in the non-Asia subgroup were consistent with the published results in the overall study population.**

## Background

Esophageal squamous cell carcinoma (ESCC) is the predominant histologic subtype of esophageal cancer, accounting for 85% of cases worldwide.[1] Platinum-based chemotherapy has been used for first-line (1L) treatment of advanced or metastatic ESCC, but median survival remains poor at <1 year.[2-5]

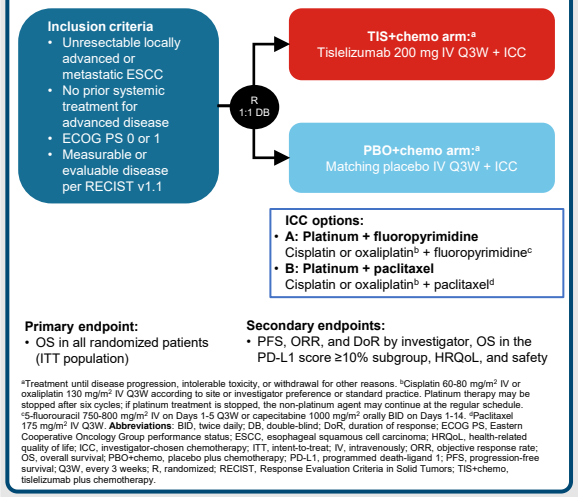
Tislelizumab is a monoclonal antibody with high affinity and binding specificity for programmed cell death protein 1.[6] In the interim analysis of the overall population of the phase 3 RATIONALE-306 study (NCT03783442), tislelizumab plus chemotherapy (TIS+chemo) demonstrated a statistically significant and clinically meaningful overall survival (OS) benefit as 1L treatment in patients with advanced or metastatic ESCC, compared with placebo plus chemotherapy (PBO+chemo).[7]

Here, we report interim analysis results for the non-Asia subgroup: Europe, North America, and Oceania.

## Methods

- Patients were randomized to receive either tislelizumab 200 mg intravenously (IV) every 3 weeks (Q3W) plus investigator-chosen chemotherapy (ICC), or placebo IV Q3W plus ICC (**Figure 1**)

### Figure 1. RATIONALE-306 Study Design




[a]Treatment until disease progression, intolerable toxicity, or withdrawal for other reasons. [b]Cisplatin 60-80 mg/m$^2$ IV or oxaliplatin 130 mg/m$^2$ IV Q3W according to site or investigator preference or standard practice. Platinum therapy may be stopped after six cycles; if platinum treatment is stopped, the non-platinum agent may continue at the regular schedule. [c]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. [d]Paclitaxel 175 mg/m$^2$ IV Q3W. **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; ICC, investigator-chosen chemotherapy; ITT, intent-to-treat; IV, intravenously; ORR, objective response rate; OS, overall survival; PBO+chemo, placebo plus chemotherapy; PD-L1, programmed death-ligand 1; PFS, progression-free survival; Q3W, every 3 weeks; R, randomized; RECIST, Response Evaluation Criteria in Solid Tumors; TIS+chemo, tislelizumab plus chemotherapy.

## Results

### Patient Disposition and Baseline Characteristics

- Of 649 randomized patients, 163 (25.1%) were in the non-Asia subgroup (TIS+chemo, n=83; PBO+chemo, n=80)
- Baseline characteristics were generally balanced between treatment arms, with the exception of sex (**Table 1**)
- As of February 28, 2022, median study follow-up time was 16.0 months in the TIS+chemo arm vs 8.4 months in the PBO+chemo arm (range: 0.8-30.1)

**Table 1. Baseline Characteristics**

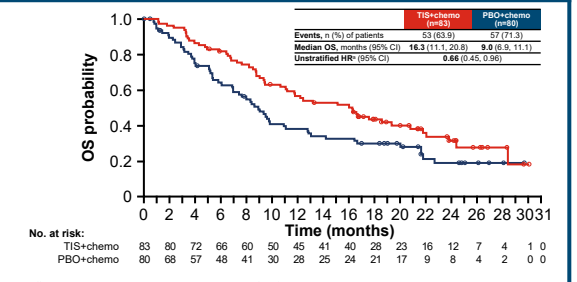
| | TIS+chemo (n=83) | PBO+chemo (n=80) |
|---|---|---|
| **Median age, years (range)** | 64 (38-78) | 66 (40-84) |
| **Sex, male** | 70 (84.3) | 59 (73.8) |
| **Race, white/other[a]** | 79 (95.2)/4 (4.8) | 76 (95.0)/4 (5.0) |
| **ECOG PS 0/1** | 31 (37.3)/52 (62.7) | 30 (37.5)/50 (62.5) |
| **Disease status at baseline** | | |
| Metastatic/locally advanced | 67 (80.7)/16 (19.3) | 60 (75.0)/20 (25.0) |
| **PD-L1 score** | | |
| ≥10%/<10%/unknown | 30 (36.1)/34 (41.0)/19 (22.9) | 17 (21.3)/45 (56.3)/18 (22.5) |
| **ICC options, n** | | |
| **A (platinum + 5-FU)** | n=44 | n=39 |
| Cisplatin/oxaliplatin + 5-FU | 23/21 | 24/15 |
| **(platinum + cap)** | n=18 | n=19 |
| Cisplatin/oxaliplatin + cap | 4/14 | 2/17 |
| **B (platinum + pac)** | n=21 | n=20 |
| Cisplatin/oxaliplatin + pac | 10/11 | 9/11 |
| **Post-treatment systemic therapy/immunotherapy** | 37 (44.6)/4 (4.8) | 36 (45.0)/8 (10.0) |

Data are n (%) unless otherwise specified. [a]Includes "not reported," "American Indian or Alaska Native," and "Unknown."
**Abbreviations:** 5-FU, 5-fluorouracil; cap, capecitabine; ECOG PS, Eastern Cooperative Oncology Group performance status; ICC, investigator-chosen chemotherapy; pac, paclitaxel; PBO+chemo, placebo plus chemotherapy; PD-L1, programmed death-ligand 1; TIS+chemo, tislelizumab plus chemotherapy.

### Efficacy

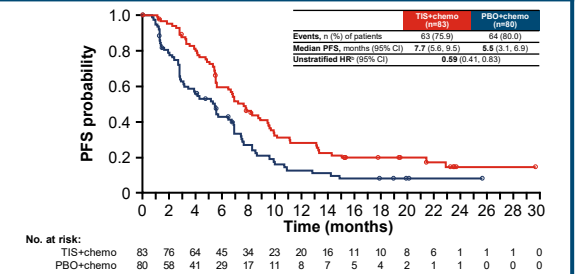
- OS (**Figure 2**) and progression-free survival (**Figure 3**) were improved in the TIS+chemo arm vs the PBO+chemo arm

**Figure 2. OS (Non-Asia Subgroup)**




Data cutoff: February 28, 2022. [a]HR was based on an unstratified Cox regression model including only treatment as a covariate.
**Abbreviations:** CI, confidence interval; HR, hazard ratio; OS, overall survival; PBO+chemo, placebo plus chemotherapy; TIS+chemo, tislelizumab plus chemotherapy.

**Figure 3. PFS[a] (non-Asia subgroup)**




Data cutoff: February 28, 2022. [a]PFS assessed by investigator. [b]HR was based on an unstratified Cox regression model including only treatment as a covariate. **Abbreviations:** CI, confidence interval; HR, hazard ratio; PBO+chemo, placebo plus chemotherapy; PFS, progression-free survival; TIS+chemo, tislelizumab plus chemotherapy.

### Efficacy, Ctd.

- For TIS+chemo versus PBO+chemo, respectively, the objective response rate was 61.4% (95% confidence interval [CI]: 50.1, 71.9) vs 41.3% (95% CI: 30.4, 52.8) (complete response, 8.4% vs 5.0%; partial response, 53.0% vs 36.3%; stable disease, 32.5% vs 32.5%; progressive disease, 1.2% vs 12.5%; not assessable [no postbaseline tumor assessment by data cutoff], 4.8% vs 13.8%)
- Median duration of response was longer with TIS+chemo than PBO+chemo (7.1 months [95% CI: 5.6, 9.6] vs 5.7 months [95% CI: 3.8, 8.3], respectively)

### Safety

- A summary of the safety findings is shown in **Table 2**
- For TIS+chemo and PBO+chemo, respectively, treatment-related adverse events (TRAEs) occurring in ≥15% of patients in either arm were peripheral sensory neuropathy (38.6% vs 30.8%), stomatitis (34.9% vs 30.8%), diarrhea (33.7% vs 34.6%), nausea (32.5% vs 42.3%), anemia (31.3% vs 30.8%), fatigue (22.9% vs 19.2%), neutropenia (21.7% vs 24.4%), asthenia (20.5% vs 28.2%), decreased appetite (19.3% vs 24.4%), and vomiting (9.6% vs 16.7%)
- The most common ≥grade 3 TRAEs (occurring in ≥10% of patients in either arm) in the TIS+chemo vs PBO+chemo arms, respectively, were stomatitis (10.8% vs 9.0%), neutropenia (9.6% vs 16.7%), and anemia (6.0% vs 10.3%)

**Table 2. Safety Summary (Safety Analysis Set)**

| n (%) | TIS+chemo (n=83) | PBO+chemo (n=78) |
|---|---|---|
| **Patients with ≥1 TRAE[a]** | 78 (94.0) | 69 (88.5) |
| ≥Grade 3 | 47 (56.6) | 41 (52.6) |
| Serious | 21 (25.3) | 14 (17.9) |
| Leading to death[b] | 1 (1.2) | 1 (1.3) |
| **Patients with ≥1 TEAE leading to any treatment discontinuation** | 35 (42.2) | 28 (35.9) |
| Discontinuation of tislelizumab/placebo | 15 (18.1) | 6 (7.7) |
| Discontinuation of any chemotherapy | 34 (41.0) | 28 (35.9) |

Data cutoff: February 28, 2022. [a]TRAEs 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:** PBO+chemo, placebo plus chemotherapy; TEAE, treatment-emergent adverse event; TIS+chemo, tislelizumab plus chemotherapy; TRAE, treatment-related adverse event.

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## Disclosures

**ER, EG,** and **LW:** no conflicts of interest; **RH**: BeiGene, Boston Scientific, Ipsen, Novartis, and Roche; **EVC**: Array, Astellas, AstraZeneca, Bayer, BeiGene, Biocartis, Boehringer Ingelheim, Bristol-Myers Squibb, Celgene, Daiichi, Halozyme, GSK, Incyte, Ipsen, Lilly, Merck Sharp & Dohme, Merck KGaA, Novartis, Pierre Fabre, Roche, Servier, Sirtex, and Taiho; **PJ-F**: Amgen, HRA Pharma, BMS, MSD, Lilly, Mylan, Novartis, LeoPharma, Sanofi, and Rovi; **RP-C**: BeiGene, Celgene, Eisai, and Roche; **JX, LW, YP,** and **LL**: BeiGene, Ltd; **KK**: Bayer, BeiGene, BMS, Lily, MSD, Oncolys Biopharma, and ONO; **HHY**: ALX Oncology, Amgen, Astellas, AstraZeneca, BeiGene, BMS, CARsgen Therapeutics, Macrogenics, Merck, Novartis, OncXerna, and Zymeworks.

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