Comparative Efficacy and Safety of Tislelizumab Versus Anti–PD-1 Treatments in Second-Line Esophageal Squamous Cell Carcinoma (ESCC): Simulated Treatment Comparisons (STC)

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Conclusions

This analysis supports comparable overall survival (OS), progression-free survival (PFS), and toxicities for tislelizumab versus other key anti–programmed cell death protein-1 (anti–PD-1) immunotherapies (nivolumab and pembrolizumab) for second-line (2L) therapy in patients with ESCC

These findings were consistent across primary, sensitivity, and subgroup analyses. Specifically, results were similar to the base case when using the latest RATIONALE data cutoff (DCO), and there were no statistically significant differences in the programmed death ligand-1 (PD-L1)– and Eastern Cooperative Oncology Group (ECOG)–specific subgroups

However, the analysis is limited by the uncertainty surrounding the estimates and the assumptions inherent to the methodology employed to obtain the indirect comparisons

Background

- Esophageal carcinoma (EC) is the seventh leading cause of cancer-related mortality worldwide, exhibiting a mortality rate of 5.48 per 100,000 individuals.[1] Esophageal squamous cell carcinoma constitutes about 90% of EC incidences[2]
- The aggressive progression of EC is mirrored in low survival rates, with 5-year OS estimated at 10% in Europe, 20% in the US and Eastern Asia, 30% in China, 31%-33% in South Korea, and 36% in Japan[3-6]
- For locally advanced or metastatic ESCC, treatment options include immunotherapy, chemo-radiotherapy, chemotherapy, chemo-immunotherapy, or radiation therapy
- In a recent phase 3 study (RATIONALE-302, N=512, NCT03430843),[7] tislelizumab demonstrated a statistically significant and clinically meaningful survival benefit over chemotherapy (median OS of 8.6 vs 6.3 months; hazard ratio [HR], 0.70; 95% confidence interval [CI], 0.57-0.85; *P*=0.0001), regardless of PD-L1 expression level, with an acceptable safety profile for 2L ESCC
- Subsequently, the Food and Drug Administration (FDA) and European Medicines Agency (EMA) approved tislelizumab for use in 2L ESCC; the National Comprehensive Cancer Network (NCCN) also recommended tislelizumab in the treatment of unresectable, recurrent, or metastatic ESCC.[8-10] While nivolumab and pembrolizumab monotherapies are 2L options, pembrolizumab is only approved for patients with PD-L1 combined positive score (CPS) ≥10[8] in the US. Notably, pembrolizumab monotherapy is pending approval for 2L ESCC in the European Union (EU)
- The objective of this analysis was to identify the evidence on existing 2L treatments for ESCC and derive relative efficacy and safety estimates versus tislelizumab through indirect treatment comparisons (ITCs)

Methods

Systematic Literature Review

- A systematic literature review (SLR) was conducted to identify and summarize all available published data on the clinical efficacy and safety of existing 2L treatment regimens for patients with unresectable, advanced, or metastatic ESCC. One original and two subsequent SLR updates contributed to the evidence base
- The SLR yielded 25 records pertaining to 13 distinct trials that were deemed relevant for analysis (**Figure 1**)

Evidence Synthesis Feasibility Assessment

- For the purposes of evidence synthesis, the focus was narrowed to pivotal studies evaluating key immunotherapies considered in the EU and the UK. These included the following: RATIONALE-302 tislelizumab,[7] ATTRACTION 3 (nivolumab),[11,12] RAMONA (nivolumab with ipilimumab),[13] and KEYNOTE-181 (pembrolizumab)[14]
- A rigorous process was employed to identify effect-modifying and prognostic variables, which included a thorough examination of individual patient data (IPD) from RATIONALE-302, alignment with previous ITCs within the same medical domain, and consultation with clinical experts

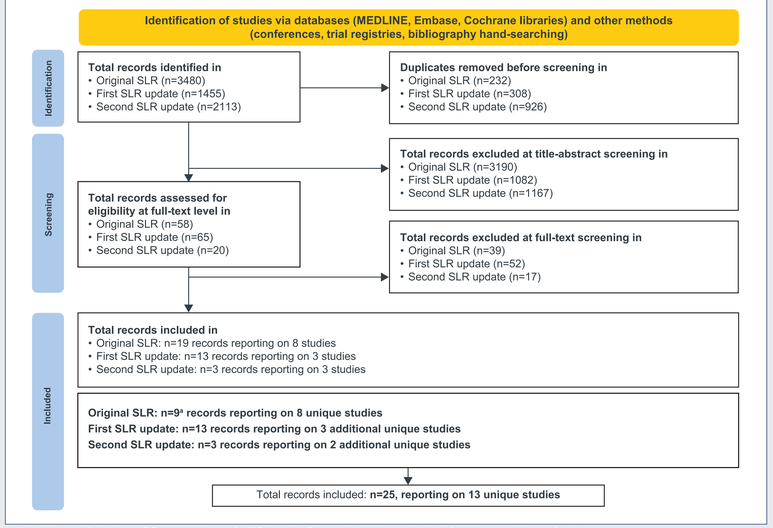
Outcomes and Interventions

- Primary outcomes of interest were OS, PFS, and the incidence of grade ≥3 treatment-related adverse events (TRAEs). The comparator interventions under scrutiny were nivolumab and pembrolizumab

Statistical Methods

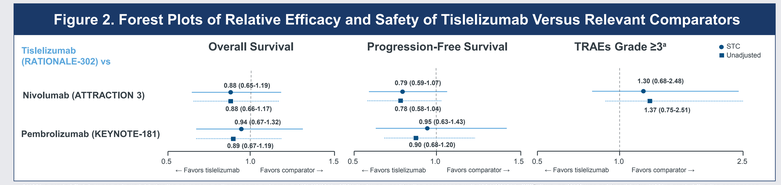
- Aligned with recent updates to methods guidance, STCs were preferred over matching-adjusted indirect comparisons (MAICs) for population adjustment in this anchored setting.[15] The STC approach, based on NICE DSU TSD18,[16] was extended to adjust for both binary and multilevel categorical characteristics and to enable the estimation of population-average treatment effects[17,18]
- Using IPD from RATIONALE-302, a Cox model was fit to OS and PFS model, and a binomial generalized linear model was fit to grade ≥3 TRAEs, incorporating effect modifiers as interactions with the treatment arm[16]
- Simulated treatment comparisons for OS and PFS were adjusted for ECOG Performance Status (PS), disease status, PD-L1 expression, and the presence of liver and lung metastases. Simulated treatment comparisons for grade ≥3 TRAEs were adjusted for age, ECOG PS, PD-L1 expression, liver metastasis, and prior treatments
- Analyses were conducted with both available RATIONALE-302 DCOs from December 1, 2020, and December 28, 2022; the former was used for the base case and the latter for sensitivity analysis. Subgroup analyses considered PD-L1 category and baseline ECOG PS
- The base case STC analyses are presented in **Figure 2**, providing HRs for OS and PFS, and odds ratios for grade ≥3 TRAEs, along with their respective 95% CIs

Figure 1. Identification of PICOS-Eligible Studies Based on Original SLR and Subsequent Updates (From Database Inception to October 2023)



[a]Nineteen publications from the original SLR were rescreened in the first SLR update, and 10 publications were excluded based on "conference abstract superseded by full text."
Note: Time frame for database searches: Original SLR: May 2021; first SLR update: May 2021-November 2022; second update: November 2022-October 2023.
PICOS, Population, Intervention, Comparison, Outcomes and Study; SLR, systematic literature review.

Figure 2. Forest Plots of Relative Efficacy and Safety of Tislelizumab Versus Relevant Comparators

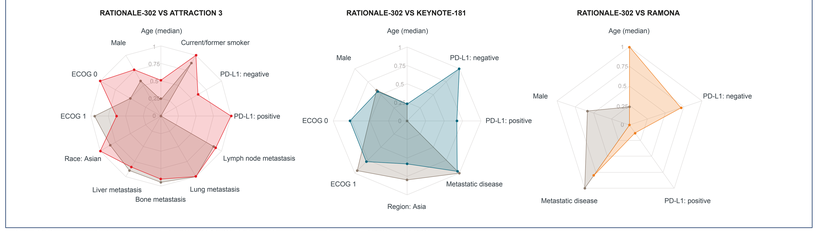


[a]TRAEs grade ≥3 data were not available for the squamous cell carcinoma subgroup of KEYNOTE-181[14] that was used for the comparison with RATIONALE-302[7]; thus, an STC was not feasible for TRAEs grade ≥3 in the comparison with pembrolizumab.
STC, simulated treatment comparison; TRAE, treatment-related adverse event.

Results

- All included studies compared an anti–PD-1 antibody with chemotherapy, and clinical consensus anticipated minimal heterogeneity, validating its use as a common anchor. The overlap of populations between RATIONALE-302 and comparator studies, based on effect-modifying variables, is depicted in **Figure 3**

Figure 3. Visual Representation of Population Overlap Between RATIONALE-302 (Gray Area) and Comparator Studies (Colored Area). The covariate range is normalized across studies.



Note: PD-L1–negative patients are those with TPS <1% or CPS <10. PD-L1–positive patients are those with TPS ≥1% or CPS ≥10.
CPS, combined positive score; ECOG PS, Eastern Cooperative Oncology Group Performance Status; PD-L1, programmed death-ligand 1; TPS, tumor positivity score.

- The trial design and inclusion criteria of RAMONA significantly diverged from those of RATIONALE-302, precluding its inclusion in the ITC. Conversely, ATTRACTION 3 and KEYNOTE-181 were sufficiently comparable to RATIONALE-302 in most effect-modifying aspects, despite some differences in baseline characteristics
- Following population adjustment, the analyses revealed no significant differences in OS, PFS, or grade ≥3 TRAEs when comparing tislelizumab with other anti–PD-1 agents (nivolumab and pembrolizumab for survival outcomes; only nivolumab for safety outcomes)
- However, tislelizumab was found numerically favorable over both comparators in OS and PFS [vs nivolumab, OS HR (95% CI), 0.88 (0.65-1.19) and PFS HR (95% CI), 0.79 (0.59-1.07); vs pembrolizumab, OS HR (95% CI), 0.94 (0.67-1.32) and PFS HR (95% CI), 0.95 (0.63-1.43)]
- Both sensitivity and subgroup analyses were consistent with the base case, revealing no significant disparities
- Notably, these estimates are not directly comparable due to differing target populations. Specifically, the results of each STC cannot be compared to the results of other STCs (eg, nivolumab STC results are independent of pembrolizumab STC results), as RATIONALE-302 data are always adjusted to the average baseline characteristics of the comparator trial's population, and therefore, each estimate is only relevant to the enrolled population of that particular study

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