Comparative Efficacy and Safety of Tislelizumab vs Other Anti–PD-1 Treatments in First-Line Esophageal Squamous Cell Carcinoma: A Network Meta-Analysis

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CONCLUSIONS

- Findings from this indirect treatment comparison suggest that tislelizumab + CT had significantly better PFS versus nivolumab + CT, had numerically favorable but not statistically significant results for PFS versus pembrolizumab + CT or OS versus either comparator
  - This finding was consistent in subgroups stratifying by PD-L1 status
- The safety outcomes demonstrated numerically but not statistically significant benefits for tislelizumab + CT versus pembrolizumab + CT or nivolumab + CT
- Based on these results, tislelizumab + CT represents an effective treatment option for 1L ESCC. The PFS benefit of tislelizumab + CT over nivolumab + CT provides a potential rationale for adopting the use of tislelizumab
- Indirect treatment comparisons such as NMAs rely on assumptions (eg, sufficient similarity across trials). The results should be interpreted with caution

INTRODUCTION

- Patients with advanced esophageal squamous cell carcinoma (ESCC) have poor prognosis; median estimated overall survival (OS) is less than 1 year and 5-year survival rates historically range between 10% and 30%[1-5]
- Recently, combining programmed cell death protein 1 (PD-1) inhibitors with chemotherapy (CT) has demonstrated promising results in randomized trials. This is underscored by the Food and Drug Administration (FDA) approval of nivolumab and pembrolizumab in combination with chemotherapy for advanced ESCC[6,7]
- Tislelizumab is a next-generation PD-1 inhibitor that both the FDA and the European Medicines Agency (EMA) have recently approved in combination with CT for first-line (1L) treatment of ESCC in patients whose tumors express PD-L1 (PD-L1 ≥1 by FDA, and with a Tumor Area Positivity [TAP] score ≥5% by EMA) based on the results of the RATIONALE-306 trial (NCT03783442)[8-12]
- To date, there are no head-to-head studies comparing tislelizumab with other relevant 1L immunotherapy ESCC treatments (eg, pembrolizumab and nivolumab)
- This network meta-analysis (NMA) was conducted to evaluate the relative efficacy and safety of tislelizumab + CT compared with other 1L immunotherapy regimens for the treatment of patients with unresectable, locally advanced, or metastatic ESCC

METHODS

Systematic Literature Review

- A systematic literature review (SLR) was conducted (June 2023) to identify published randomized controlled trials (RCTs) that reported efficacy and safety outcomes for treatments used for 1L unresectable, locally advanced, or metastatic ESCC[13]

Feasibility Assessment

- An NMA feasibility assessment was conducted to assess heterogeneity across all relevant trials identified in the clinical SLR
  - Network geometry, trial design characteristics, patient eligibility criteria, baseline patient characteristics, and outcome definitions were evaluated
  - Key outcomes feasible for comparison included:
    - Progression-free survival (PFS)
    - OS
    - Grade ≥3 treatment-related adverse events (TRAEs)

Network Meta-Analyses

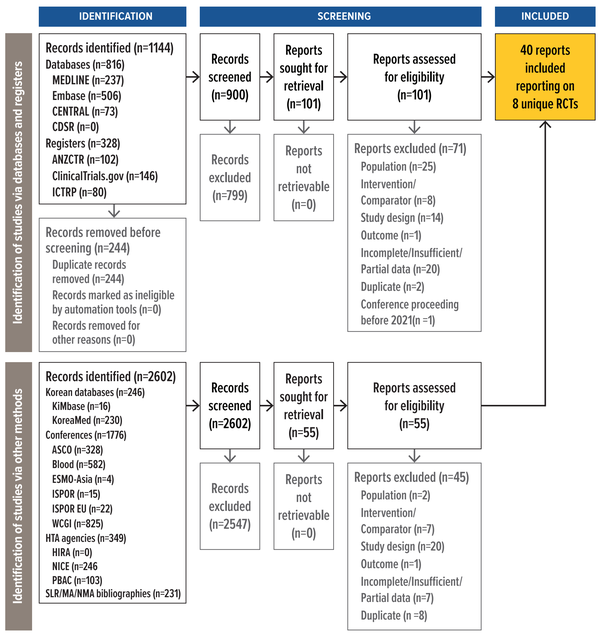
- NMAs were conducted using a Bayesian framework and performed using R version 3.6.1, Just Another Gibbs Sampler, and WinBUGS[14]
  - Markov chain Monte Carlo methods were used to estimate hazard ratios (HRs)/odds ratios (ORs) and 95% credible intervals (CrIs)
- Subgroup analyses were conducted to assess OS and PFS by PD-L1 status (≥1, ≥5), as measured by TAP score for tislelizumab + CT and combined positive score for nivolumab + CT and pembrolizumab + CT, as well as CT backbone and geographic region
  - No subgroup analyses were performed for safety outcomes due to a lack of available data

RESULTS

Systematic Literature Review

- A total of 900 unique records were screened from database searches, with an additional 2602 records identified from additional sources (**Figure 1**)
- Following screening, 40 records reporting on eight unique RCTs met the eligibility criteria and were included in the feasibility assessment[13]

Figure 1. PRISMA Flow Diagram of Clinical Evidence

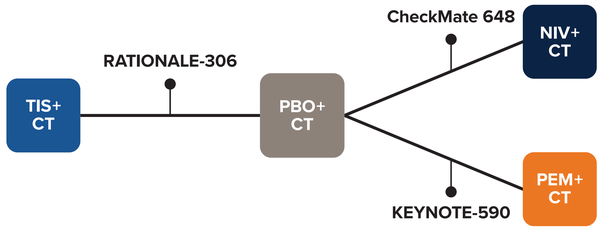


Abbreviations: ASCO, American Society of Clinical Oncology; ANZCTR, Australian New Zealand Clinical Trials Registry; CDSR, Cochrane Database of Systematic Reviews; ESMO, European Society for Medical Oncology; HIRA, Health Insurance Review & Assessment Service; HTA, health technology assessment; ICTRP, International Clinical Trials Registry Platform; ISPOR, International Society for Pharmacoeconomics and Outcomes Research; NICE, National Institute for Health and Care Excellence; PBAC, Pharmaceutical Benefits Advisory Committee; PRISMA, Preferred Reporting Items for Systematic reviews and Meta-Analyses; RCT, randomized controlled trial; SLR, systematic literature review; WCGI, World Congress on Gastrointestinal Cancer.

Feasibility Assessment

- After restricting the analysis to broadly used immuno-oncology + CT regimens for 1L ESCC (ie, nivolumab + CT and pembrolizumab + CT), two trials were deemed feasible for comparison with RATIONALE-306[8] (tislelizumab + CT; data cut-off: February 28, 2022): KEYNOTE-590[15] (pembrolizumab + CT; data cut-off: July 2, 2020) and CheckMate 648[16] (nivolumab + CT; data cut-off: January 18, 2021)
  - These three trials were able to form a network with placebo + CT as a common comparator (**Figure 2**)

Figure 2. Network Diagram for All Outcomes Evaluated



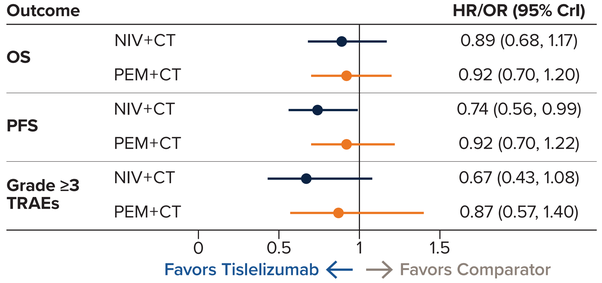
Abbreviations: CT, chemotherapy; NIV, nivolumab; PBO, placebo; PEM, pembrolizumab; TIS, tislelizumab.

Network Meta-Analyses

Relative Efficacy and Safety – Base Case Analysis

- Tislelizumab + CT demonstrated similar efficacy compared with nivolumab + CT and pembrolizumab + CT for OS, with both comparisons numerically favoring tislelizumab + CT (**Figure 3**)
- PFS statistically favored tislelizumab + CT compared to nivolumab + CT (HR 0.74, 95% CrI 0.56-0.99) and numerically favored tislelizumab + CT compared to pembrolizumab + CT (HR 0.92, 95% CrI 0.70-1.22) (**Figure 3**)
- Tislelizumab + CT had a numerical, but not statistically significant OR for reduced grade ≥3 TRAEs compared with nivolumab + CT and pembrolizumab + CT (**Figure 3**)

Figure 3. Forest Plots of Base Case Analyses for Efficacy and Safety Outcomes – Fixed Effect Models



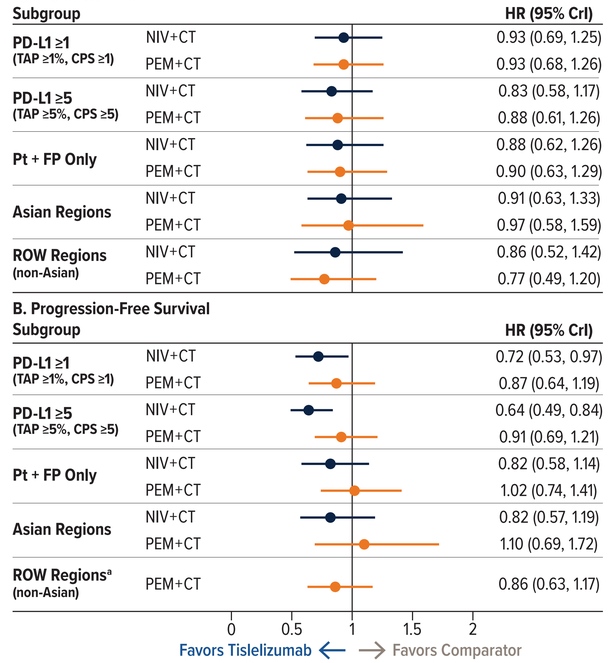
Note: For OS and PFS comparisons, an HR<1 indicates TIS + CT has lower hazard than the comparator therapy. For the grade ≥3 TRAEs comparison, an OR <1 implies TIS + CT has lower odds of grade ≥3 TRAEs than the comparator therapy.

Abbreviations: CrI, credible interval; CT, chemotherapy; HR, hazard ratio; ITT, intention-to-treat; NIV, nivolumab; OR, odds ratio; OS, overall survival; PEM, pembrolizumab; PFS, progression-free survival; TIS, tislelizumab; TRAE, treatment-related adverse event.

Relative Efficacy – Subgroup Analyses

- For OS, subgroup analyses by PD-L1 status, geographic region (Asia, rest of world [non-Asia]), and CT backbone subgroups were consistent with the base case analysis, with no significant differences observed between tislelizumab + CT and either immunotherapy comparator (**Figure 4**)
- For PFS, subgroup analyses for both PD-L1 ≥1% and PD-L1 ≥5% were consistent with the base case, demonstrating a statistically significant benefit for tislelizumab + CT versus nivolumab + CT and a numerically favorable result versus pembrolizumab + CT. No statistically significant differences between comparators were detected in subgroups based on CT backbone or geographic region (**Figure 4**)

Figure 4. Forest Plots of Subgroup Analyses for OS (A) and PFS (B) – Fixed Effect Models



An HR<1 indicates TIS + CT has lower hazard than the comparator therapy. RATIONALE-306 data are reflective of the TAP score method. CheckMate-648 and KEYNOTE-590 data are reflective of the CPS method. Data for PD-L1 status subgroups were sourced from a recent FDA publication for comparators.[17,18]

[a]Comparison vs NIV + CT was not conducted due to lack of data.

Abbreviations: CPS, combined positive score; CrI, credible interval; CT, chemotherapy; FP, fluoropyrimidine; HR, hazard ratio; NIV, nivolumab; OS, overall survival; PEM, pembrolizumab; PD-L1, programmed death-ligand 1; PFS, progression-free survival; Pt, platinum; ROW, rest of world; TAP, Tumor Area Positivity; TIS, tislelizumab.

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