Comparative Efficacy and Safety of Tislelizumab vs Other Anti–PD-1 Treatments in First-Line Gastric or Gastroesophageal Junction Cancer: A Network Meta-Analysis

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CONCLUSIONS

- In the absence of head-to-head RCTs, an NMA was conducted. The results showed that tislelizumab + CT was comparable across efficacy outcomes to nivolumab + CT and pembrolizumab + CT
  - Results were largely consistent across subgroup analyses, including those by PD-L1 status
- Additionally, tislelizumab + CT had a significantly more favorable safety profile compared with nivolumab + CT and a comparable safety profile to pembrolizumab + CT
- Overall, the results of the NMA indicate that the comparable efficacy and favorable safety gives tislelizumab a therapeutic advantage for metastatic HER2-negative patients with GC/GEJC
- Indirect treatment comparisons such as NMAs rely on assumptions (eg, sufficient similarity across trials). The results should be interpreted with additional caution compared to those from a head-to-head trial

INTRODUCTION

- First-line (1L) treatments for advanced or metastatic gastric cancer/gastroesophageal junction cancer (GC/GEJC) have historically included fluoropyrimidine- or platinum-based chemotherapies (CT), although these regimens are associated with a poor median overall survival (OS) of less than 1 year[1]
- In recent years, programmed cell death protein 1 (PD-1) inhibitors have demonstrated added benefit in combination with CT in randomized trials and received broad regulatory approval for 1L treatment of GC/GEJC[2-6]
- Tislelizumab is a next-generation PD-1 inhibitor that both the Food and Drug Administration (FDA) and European Medicines Agency (EMA) have recently approved in combination with CT for 1L treatment of GC/GEJC in patients whose tumors express programmed death-ligand 1 (PD-L1; ≥1 by FDA, and with a Tumor Area Positivity [TAP] score ≥5% by EMA) based on the results of the RATIONALE-305 trial (NCT03777657)[2]
- To date, there are no head-to-head studies comparing tislelizumab with other relevant 1L immunotherapy GC/GEJC 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 GC/GEJC

METHODS

Systematic Literature Review

- A systematic literature review (SLR) was conducted (February 2024) to identify published randomized controlled trials (RCTs) that reported efficacy and safety outcomes for treatments used for 1L unresectable, locally advanced, or metastatic HER2-negative GC/GEJC

Feasibility Assessment

- An NMA feasibility assessment was conducted to evaluate clinical 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 (JAGS), and WinBUGS[7]
  - Markov chain Monte Carlo methods were used to estimate hazard ratios (HRs)/odds ratios (ORs) and 95% credible intervals (CrIs)
- Subgroup analyses were conducted by PD-L1 status, as measured by TAP score for tislelizumab + CT and combined positive score for nivolumab + CT and pembrolizumab + CT, as well as CT backbone, primary tumor location, and geographic region for OS, and by PD-L1 status and geographic region for PFS
  - Safety outcomes were not adequately reported to allow for subgroup analysis

RESULTS

Systematic Literature Review

- A total of 5410 unique records were screened from database searches, with an additional 3336 records identified from additional sources
- Following screening, 83 records reporting on 41 unique RCTs met the eligibility criteria and were included in the feasibility assessment[8]

Feasibility Assessment

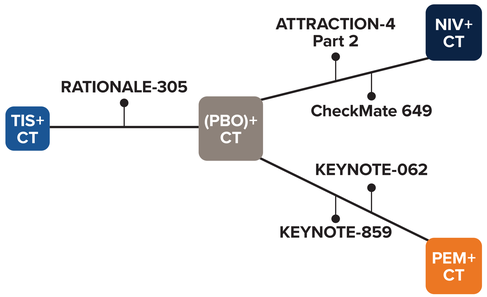
- After restricting the analysis to immunotherapy agents approved for the 1L treatment of HER2-negative GC/GEJC by both the FDA and EMA, four trials were deemed feasible for comparison with RATIONALE-305[2] (tislelizumab + CT), including ATTRACTION-4 Part 2[3] and CheckMate 649[4] (nivolumab + CT), and KEYNOTE-062[6] and KEYNOTE-859[5] (pembrolizumab + CT). The study population characteristics across trials are shown in **Table 1**
  - These five trials were able to form a network with placebo + CT as a common comparator (**Figure 1**)

Table 1. Baseline Characteristics Across Included Trials Compared With RATIONALE-305

	RATIONALE-305 (TIS+CT)[2]	ATTRACTION-4 (NIV+CT)[3]	CheckMate 649 (NIV+CT)[4]	KEYNOTE-062 (PEM+CT)[6]	KEYNOTE-859 (PEM+CT)[5]
Median age	61	64.5[a]	61.5[a]	62	61.5[a]
Male (%)	69.4	72.2	69.2	72.6	67.8
Geographic region, (%)					
Asia	75	100	24.7	24.5	33.2
ECOG PS, (%)					
0	32.4	53.7	42.9	47.8[b]	36.9
Disease at entry, (%)					
Locally advanced	1.1	NR	3.9	NR	3.7
Metastatic	98.7	NR	95.7	94.8	96.3
Recurrent	0.1	NR	0.5	NR	NR
Organs with metastases by type, (%)					
Peritoneum	43.5	46.4	23.8	NR	NR
Liver	37.9	36.5	38.6	NR	39.6
PD-L1, (%)					
≥1%	86.2	15.7	81	100	78.2
≥5%	54.7	NR	59.6	NR	NR
≥10%	27.1	NR	47.9	36.8	34.9
Method used	TAP	NR	CPS	CPS	CPS
Smoking status, (%)					
Never	51.3	NR	48.9	NR	NR
Former or current	48.7	NR	48.1	NR	NR
Unknown	0	NR	3	NR	NR
Prior therapy					
Surgery	32.9	28.9	21.3	NR	21.2
Radiotherapy	1.5	NR	9.6	NR	NR
Adjuvant or neoadjuvant	20.8	17.5	13.7	NR	NR

[a]Weighted median was calculated using treatment arm medians.
[b]Reported ECOG PS of 1 in 52.2% of participants, while ECOG PS for the remaining 47.8% of patients was not reported. Per eligibility criteria, only patients with ECOG PS of 0 or 1 were included in the trial.
Abbreviations: CPS, combined positive score; CT, chemotherapy; ECOG, Eastern Cooperative Oncology Group; NIV, nivolumab; NR, not reported; PD-L1, programmed death-ligand 1; PEM, pembrolizumab; TAP, Tumor Area Positivity; TIS, tislelizumab.

Figure 1. Network Diagram for All Outcomes Evaluated



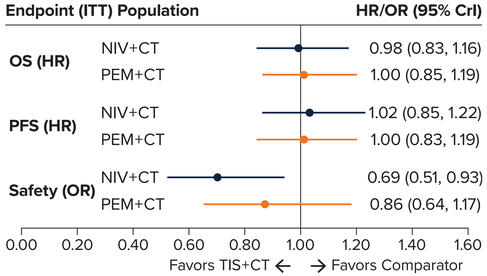
Abbreviations: CT, chemotherapy; NIV, nivolumab; PBO, placebo; PEM, pembrolizumab; TIS, tislelizumab.

Network Meta-Analyses

Relative Efficacy and Safety – Base Case Analyses

- Tislelizumab + CT demonstrated comparable efficacy compared with nivolumab + CT and pembrolizumab + CT for both PFS and OS (**Figure 2**)
- Grade ≥3 TRAEs statistically favored tislelizumab + CT compared with nivolumab + CT (OR 0.69, 95% CrI 0.51-0.93) and numerically favored tislelizumab + CT compared to pembrolizumab + CT (OR 0.86, 95% CrI 0.64-1.17) (**Figure 2**)

Figure 2. Base Case Analyses for Efficacy and Safety Outcomes – Fixed-Effect Models

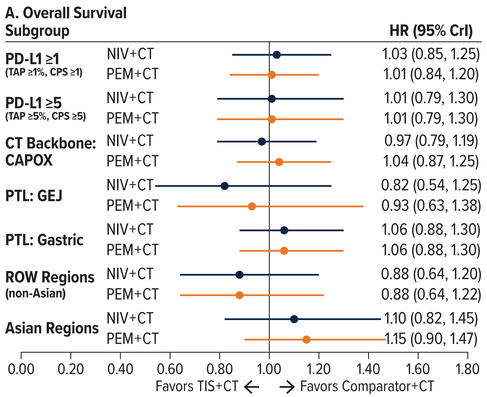


Note: For OS and PFS comparisons, an HR >1 indicates TIS + CT has greater hazard than the comparator therapy. For safety comparison, an OR <1 implies TIS + CT has lower odds of grade ≥3 TRAE than the comparator therapy.
Abbreviations: CrI, credible interval; CT, chemotherapy; HR, hazard ratio; ITT, intention-to-treat; 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; ROW]), primary tumor location, and CT backbone subgroups were consistent with the base case analyses with no significant differences observed between tislelizumab + CT and either immunotherapy comparator (**Figure 3**)
- For PFS, subgroup analyses by PD-L1 status, and geographic region (Asia, ROW) were consistent with the base case analyses, with no significant differences observed between tislelizumab + CT and either immunotherapy comparator (**Figure 3**)

Figure 3. Subgroup Analyses for OS (A) and PFS (B) – Fixed-Effect Models



An HR >1 indicates TIS + CT has greater hazard than the comparator therapy. RATIONALE-305 data are reflective of the TAP score method; CheckMate 649, KEYNOTE-062, and KEYNOTE-859 data are reflective of the CPS method; ATTRACTION-4 Part 2 methods are not specified. Data for PD-L1 status subgroups were sourced from a recent FDA publication.[9]
[a]Comparison vs NIV + CT was not conducted due to lack of data.
Abbreviations: CAPOX, capecitabine and oxaliplatin; CPS, combined positive score; CrI, credible interval; CT, chemotherapy; GEJ, gastroesophageal junction; HR, hazard ratio; NIV, nivolumab; OS, overall survival; PEM, pembrolizumab; PD-L1, programmed death-ligand 1; PFS, progression-free survival; PTL, primary tumor location; ROW, rest of world; TAP, Tumor Area Positivity; TIS, tislelizumab.

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DISCLOSURES

MAM: Received consulting fees from AstraZeneca, Bristol Myers Squibb, Lilly, Merck Sharp & Dohme, and Servier Laboratories; payment or honoraria from Amgen, Bristol Myers Squibb, Lilly, Merck Sharp & Dohme, Roche, and Servier Laboratories; and travel support from Lilly.

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