Association between use of antibiotics and clinical outcomes with tislelizumab monotherapy

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Introduction

- Immune checkpoint inhibitors (ICIs) have changed the therapeutic landscape of many cancer types and improved clinical outcomes. However, the efficacy of ICIs varies greatly among patients[1]
- Retrospective analyses suggest that the use of antibiotics close to the administration of ICIs can have a negative impact on response rates and survival outcomes. This may be linked to changes to the gut microbiota.[2] Several preclinical and clinical studies have highlighted the role of the gut microbiota in modulating the efficacy of ICIs by promoting a strongly immune-reactive microenvironment[3–4]
- However, there has been significant heterogeneity between analyses so far and it is unclear whether the negative impact on efficacy is due to antibiotics or other factors such as patient ethnicity, geographic diversity, different definitions of antibiotic use, limited sample size, etc.[2]
- Tislelizumab is an anti-programmed cell death protein-1 (PD-1) antibody engineered to minimize binding to Fcγ receptors (FcγR) on macrophages, thereby abrogating antibody-dependent phagocytosis, a potential mechanism of resistance to anti-PD-1 therapies[5]
- Tislelizumab monotherapy was generally well tolerated and demonstrated antitumor activity in five single-arm Phase 1/2 studies in multiple tumor types, including esophageal squamous cell carcinoma (ESCC), hepatocellular carcinoma (HCC), non-small cell lung cancer (NSCLC), and urothelial carcinoma (UC)[6–10]
- The impact of antibiotic use on the clinical outcomes of tislelizumab monotherapy was assessed in this pooled analysis

Methods

Pooled data

- Data were pooled from five tislelizumab monotherapy single-arm clinical trials:
  - NCT02407990: Phase 1A/1B study of tislelizumab in patients with advanced solid tumors
  - CTR20160872: Phase 1/2 study of tislelizumab in Chinese patients with advanced solid tumors
  - NCT03419897: Phase 2 study of tislelizumab in patients with advanced HCC
  - CTR20170071: Phase 2 study of tislelizumab in Asian patients with locally advanced/metastatic UC
  - NCT03209973: Phase 2 study of tislelizumab in patients with relapsed or refractory classical Hodgkin lymphoma
- The study designs of the five trials have been described previously.[6–10] Data were included from patients in Asia, Europe, Oceania, and North America[6,9,11–13]
- Patients were dichotomized by timing of systemic antibiotic use. Patients with systemic antibiotic use within ±30 days of Day 1 tislelizumab monotherapy were considered "Antibiotic+", and patients not treated with antibiotics within ±30 days of Day 1 of tislelizumab monotherapy were considered "Antibiotic-"
- Analyses were performed in pooled data and per tumor type in the following indications with a relatively high proportion of antibiotic use and relatively large sample size: ESCC, HCC, NSCLC, and UC

Primary analysis with propensity score weighting

- Survival probability was estimated by the Kaplan–Meier method and compared by the log-rank test. A Cox model of overall survival (OS) was used to compute hazard ratios (HR) and 95% confidence intervals (CI)
- Propensity score (PS) weighting was employed to correct for bias from unbalanced baseline characteristics

$$PS = P(\text{patients in "Antibiotic+" group} \mid \text{observed confounding factors})$$

- To adjust for difference between the two groups, stabilized standardized mortality/morbidity ratio weighting (SMRW) was implemented where the stabilized SMR weights served as case weights to generate 'pseudo' populations

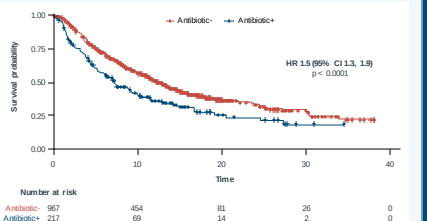
$$SMRW = \frac{PS*(1-\text{proportion of patients in "Antibiotic+" group})}{(1-PS)*\text{Proportion of patients in "Antibiotic+" group}}$$

- Confounding factors for pooled data and per tumor type are listed in **Table 1**

Conclusions and discussion

- In the primary analysis, propensity score weighting was employed to correct for the existing bias from unbalanced baseline characteristics
- A negative association was identified between antibiotic use (±30 days of Day 1 tislelizumab monotherapy) and OS benefit in the pooled data, ESCC, HCC, and UC; a worse trend was observed in NSCLC
- Landmark analysis was also conducted to mitigate guarantee-time bias, which was overlooked in previous studies. Landmark analysis identified time intervals in which antibiotic use had a significant negative impact on OS for ESCC, HCC, and UC, and these time intervals varied
- Antibiotic use (±30 days of Day 1 tislelizumab monotherapy) was not significantly associated with reduced OS in NSCLC. This is not consistent with previous studies[14,15] and may be attributed to differences in sample size, patient characteristics, anticancer therapy, and type of antibiotics
- Although confounders were included in score weighting to eliminate bias, there may still be some influential variables not taken into account
- Due to the *ad hoc* nature of this study, limited sample size and indications, care should be taken when extrapolating the conclusions to other data or studies
- The results are largely consistent with the collective results of previous retrospective analyses, suggesting negative associations of antibiotic use and survival benefit in patients treated with ICIs across a range of tumor types[4–16]
- Future studies are needed to assess the impact of prophylactic antibiotic use, the type of antibiotics, etc. on ICI outcomes across tumor types

Figure 1. OS by antibiotic use for pooled data weighted using SMRW



CI, confidence interval; HR, hazard ratio; OS, overall survival; SMRW, standardized mortality/morbidity ratio weighting

Landmark analysis

- Landmark analysis was conducted supplementary to the primary analysis to explore the association of antibiotic use and OS across time to mitigate guarantee-time bias

Table 1. Confounding factors used for propensity score weighting

Indication	Confounding factors
Pooled data	Age, sex, ECOG PS
ESCC	Race, age, sex, ECOG PS, smoking status
HCC	Race, age, sex, alpha-fetoprotein at baseline, hepatitis infection status, number of prior lines of systemic therapy, ECOG PS
NSCLC	Race, age, sex, disease stage, PD-L1 expression, liver metastases at baseline, ECOG PS, smoking status
UC	Race, age, sex, PD-L1 expression, ECOG PS, smoking status, metastasis in lymph nodes only, liver metastasis, visceral metastasis, number of prior lines of systemic therapy

ECOG PS, Eastern Cooperative Oncology Group Performance Status; ESCC, esophageal squamous cell carcinoma; HCC, hepatocellular carcinoma; NSCLC, non-small cell lung cancer; PD-L1, programmed death-ligand 1; UC, urothelial carcinoma.

Results

Baseline characteristics

- A total of 1183 patients were included in the analysis, of whom 217 (18.3%) were Antibiotic+ and 966 (81.7%) were Antibiotic-
- For specific tumor types, 26.9% of patients with ESCC, 11.4% of patients with HCC, 25.7% of patients with NSCLC, and 25% of patients with UC were Antibiotic+
- The most common reasons for antibiotic use were adverse events (31.6%) and prophylaxis (7.4%)

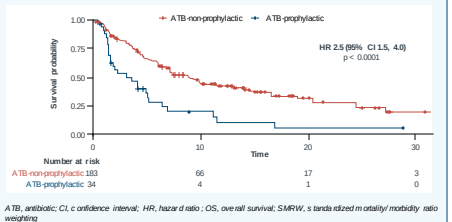
Association of antibiotic use and OS (primary analysis; pooled data)

- OS was significantly decreased in the Antibiotic+ group compared with the Antibiotic- group (HR: 1.5; 95% CI: 1.3, 1.9; p < 0.0001) (**Figure 1**)
- In the Antibiotic+ group, OS was significantly decreased with prophylactic antibiotic treatment compared with non-prophylactic antibiotic treatment (HR 2.5; 95% CI: 1.5, 4.0; p < 0.0001) (**Figure 2**)

Association of antibiotic use and OS per tumor type (primary analysis)

- A significant association between antibiotic use and decreased OS with tislelizumab treatment was shown in patients with ESCC (HR: 3.0; 95% CI: 1.3, 7.2; p = 0.0032), HCC (HR: 1.8; 95% CI: 1.1, 2.9; p = 0.0063), and UC (HR 2.3; 95% CI: 1.3, 3.9, p = 0.00091) (**Figure 3A–C**)
- A trend toward OS was observed for patients with NSCLC in the Antibiotic+ group compared with the Antibiotic- group, but this was not significant (HR: 1.6; 95% CI: 0.74, 3.6; p = 0.26) (**Figure 3D**)

Figure 2. OS by prophylactic use of antibiotics for pooled data weighted using SMRW

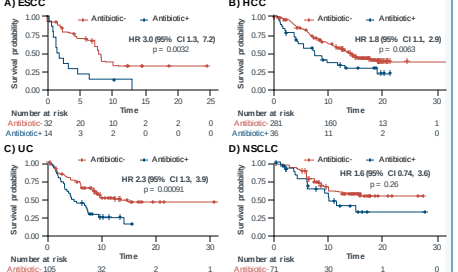


ATB, antibiotic; CI, confidence interval; HR, hazard ratio; OS, overall survival; SMRW, standardized mortality/morbidity ratio weighting

Landmark analysis per tumor type

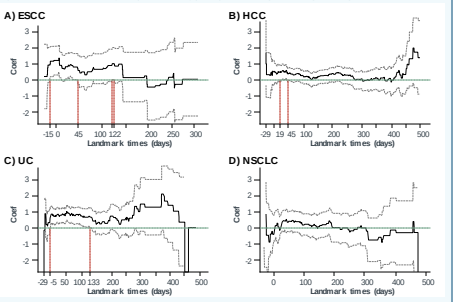
- Landmark analysis identified time intervals, in relation to Day 1 of tislelizumab treatment, when antibiotic use had a significant negative impact on OS for ESCC, HCC, and UC (**Figure 4A–C**)
  - ESCC: Day -15 to Day 45
  - HCC: Day 19 to Day 45
  - UC: Day -5 to Day 133
- No significant association between antibiotic use and OS was identified in patients with NSCLC across landmark time points (**Figure 4D**)

Figure 3. OS by antibiotic use per tumor type: A) ESCC; B) HCC; C) UC; D) NSCLC



CI, confidence interval; ESCC, esophageal squamous cell carcinoma; HCC, hepatocellular carcinoma; HR, hazard ratio; NSCLC, non-small cell lung cancer; OS, overall survival; SMRW, standardized mortality/morbidity ratio weighting; UC, urothelial carcinoma

Figure 4. Landmark analysis per tumor type: A) ESCC; B) HCC; C) UC; D) NSCLC



Red lines: time intervals, in relation to Day 1 of tislelizumab treatment, when antibiotic use had a significant negative impact on OS; Black line: coefficients of univariate Cox models across landmark times; Gray lines: 95% CIs of the coefficients. CI, confidence interval; Coef, coefficient; ESCC, esophageal squamous cell carcinoma; HCC, hepatocellular carcinoma; NSCLC, non-small cell lung cancer; UC, urothelial carcinoma

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