TISLELIZUMAB IN COMBINATION WITH CHEMOTHERAPY FOR CHINESE PATIENTS WITH GASTRIC CANCER/ GASTROESOPHAGEAL JUNCTION ADENOCARCINOMA OR ESOPHAGEAL SQUAMOUS CELL CARCINOMA

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BACKGROUND

- Gastric cancer is the fifth most common cancer worldwide, with a 5-year overall survival (OS) rate of approximately 18% when diagnosed at an advanced stage[1,2]
  - In China, gastric cancer ranks as the fourth cancer for incidence and second for mortality[3]
  - Standard chemotherapy consisting of fluoropyrimidine with a platinum agent, with or without a cytotoxic drug, is recommended first-line treatment for patients with advanced gastric cancer or gastroesophageal junction (GEJ) adenocarcinoma[4,5]
- Globally, esophageal cancer (EC) ranks as the seventh most common cancer worldwide and the sixth most common in terms of mortality, and is associated with a poor OS rate at 5 years (10%)[1,6]
  - In China, EC ranks as the eighth cancer for incidence and the sixth for mortality[3]
  - Esophageal cancers are histologically classified as squamous cell carcinoma (ESCC) or adenocarcinoma; in 2012, the global incidence of ESCC was 87% of all cases of esophageal cancer[7]
  - Chemotherapy with a combination of cisplatin plus fluorouracil is the standard first-line regimen for patients with distant metastatic or recurrent ESCC[8]
- Tislelizumab is an investigational humanized monoclonal antibody (mAb) with high affinity and specificity for PD-1 that was engineered to minimize binding to FcγR on macrophages in order to abrogate antibody-dependent phagocytosis, a potential mechanism of T-cell clearance and resistance to anti-PD-1 therapy[9]
- Tislelizumab, as a single agent, showed a favorable safety profile and promising evidence of antitumor activity in patients with advanced solid tumors, including gastric cancer and EC[10,11]
- Here we present the safety and preliminary antitumor activity of tislelizumab in combination with standard first-line chemotherapy treatment for patients with advanced gastric cancer or GEJ (G/GEJ) adenocarcinoma or ESCC

METHODS

Study Design and Objectives

- This two-cohort phase 2 study (NCT03469557) was conducted in China
- Patients with G/GEJ adenocarcinoma received tislelizumab (200 mg intravenous [IV] three times weekly [Q3W]), oxaliplatin (130 mg/m^2 IV Q3W), and oral capecitabine (1000 mg/m^2 twice daily, Days 1-15 Q3W); patients with ESCC received tislelizumab, cisplatin (80 mg/m^2 IV Q3W), and 5-FU (800 mg/m^2/d, Days 1-5 IV Q3W)
- Oxaliplatin, cisplatin, and 5-FU were administered for up to six cycles, and tislelizumab and capecitabine were administered until disease progression, intolerable toxicity, or treatment discontinuation
- The primary objective of this study was to evaluate the safety and tolerability of tislelizumab in combination with chemotherapy
- Secondary objectives included antitumor response and progression-free survival (PFS)

Key Eligibility Criteria

- Adult patients (18-75 years) with a pathologically confirmed diagnosis of HER2-negative G/GEJ adenocarcinoma or ESCC, with at least one measurable or evaluable lesion considered to be inoperable, locally advanced, or metastatic, were eligible for inclusion
- Patients must have had an Eastern Cooperative Oncology Group performance status of 0 or 1 and a life expectancy ≥12 weeks
- Patients were excluded if they received prior systemic therapy for advanced or metastatic disease (patients may have completed prior neoadjuvant/adjuvant therapy at least 6 months prior to enrollment), had a history of severe hypersensitivity reactions to other mAbs or platinum agents, or had previously received anti-PD-1, PD-L1, or PD-L2 for any indication

Study Assessments and Statistical Analyses

- Treatment-emergent adverse events (TEAEs) were assessed by monitoring the incidence and severity of adverse events (AEs) according to the National Cancer Institute-Common Terminology Criteria for Adverse Events v4.03 and by physical examinations, vital signs, clinical laboratory assessments, and electrocardiograms
- Secondary endpoints included confirmed objective response rate (ORR; ie, complete response [CR] plus partial response [PR]), duration of response (DoR), disease control rate (DCR; ie, CR plus PR plus stable disease [SD]), and PFS and were assessed by the investigator following RECIST v1.1 criteria
  - Tumor assessment occured at baseline, every 9 weeks for the first year, and every 12 weeks thereafter
  - Progression-free survival was estimated using Kaplan-Meier analysis

RESULTS

Patient Disposition

- As of 31 March 2019, 30 patients (G/GEJ, n=15; ESCC, n=15) were enrolled in the study (Table 1)
- At the time of data cut-off, eight patients remained on treatment (G/GEJ, n=4 [26.7%]; ESCC, n=4 [26.7%])
  - Twenty-two (G/GEJ, n=11 [73.3%]; ESCC, n=11 [73.3%]) patients discontinued the study treatment due to TEAEs (n=6, 27.3%), withdrawal of consent (n=3, 13.6%), radiographic disease progression (n=7, 31.8%), clinical disease progression (n=5, 22.7%), and patient refused further treatment (n=1, 4.5%)
- Demographics and baseline characteristics were similar in both cohorts

Table 1: Demographics and Baseline Characteristics (Safety Analysis Set, N=30)

		G/GEJ (n=15)	ESCC (n=15)	All (N=30)
Age, years, median (range)		59.0 (42, 74)	61.0 (47, 68)	60.5 (42, 74)
Age group, n (%)	<65	10 (66.7)	10 (66.7)	20 (66.7)
	≥65	5 (33.3)	5 (33.3)	10 (33.3)
Sex, n (%)	Male	11 (73.3)	14 (93.3)	25 (83.3)
	Female	4 (26.7)	1 (6.7)	5 (16.7)
ECOG status, n (%)	0	1 (6.7)	4 (26.7)	5 (16.7)
	1	14 (93.3)	11 (73.3)	25 (83.3)
Metastatic site, n (%)	Lymph nodes	6 (40)	4 (26.7)	10 (33.3)
	Liver	7 (46.7)	3 (20.0)	10 (33.3)
	Lung	3 (20.0)	0	3 (10.0)
	Mediastinum	0	1 (6.7)	1 (3.3)
	Retroperitoneal mass	0	1 (6.7)	1 (3.3)
	Bone	0	1 (6.7)	1 (3.3)
	Other	12 (80.0)	12 (80.0)	24 (80.0)
Prior anticancer surgeries	Curative	3 (20.0)	3 (20.0)	6 (20.0)
	Palliative	0	0	0
	Surgery after recurrence of limited disease	1 (6.7)	1 (6.7)	2 (6.7)
Prior anticancer drug therapies	Adjuvant	2 (13.3)	2 (13.3)	4 (13.3)
	Neoadjuvant	0	1 (6.7)	1 (3.3)

Abbreviations: ECOG, Eastern Cooperative Oncology Group; ESCC, esophageal squamous cell carcinoma; G/GEJ, gastric/gastroesophageal junction.

Safety and Tolerability

- Treatment with tislelizumab, in combination with chemotherapy, was generally well tolerated in patients with G/GEJ adenocarcinoma and ESCC
- Treatment-emergent AEs occurred in all patients; grade 3-4 TEAEs occurred in 11 patients (G/GEJ, n=6; ESCC, n=5; Table 2)
- Adverse events related to chemotherapy occurred in all patients; AEs considered related to tislelizumab occurred in 90% of patients (G/GEJ, n=13; ESCC, n=14)
  - Decreased appetite and anemia (n=17 each) were the most commonly reported AEs considered related to chemotherapy; decreased appetite (n=15), anemia and nausea (n=13 each) were the most commonly reported AEs considered related to tislelizumab
  - The majority of treatment-related AEs were of mild or moderate severity
- Serious AEs (SAEs) were reported in 13 patients (G/GEJ, n=5; ESCC, n=8)
  - Serious TEAEs reported in ≥2 patients in either cohort were increased blood bilirubin (G/GEJ, n=2), dysphagia (ESCC, n=3), and fatigue (ESCC, n=2)
    - The cases of increased blood bilirubin and one case each of dysphagia and fatigue were considered possibly related to tislelizumab
  - Tislelizumab-related SAEs occurred in 11 patients (G/GEJ, n=5; ESCC, n=6)
  - Chemotherapy-related SAEs occurred in 10 patients (G/GEJ, n=5; ESCC, n=5)
- One patient in the ESCC cohort experienced a fatal AE of hepatic dysfunction mainly attributed to progressive disease, which may possibly have been related to study treatment or confounded by underlying HBV infection

Table 2: Treatment-Emergent Adverse Events Occurring in ≥20% of All Patients

	G/GEJ (n=15)		ESCC (n=15)		All (N=30)	
	Any Grade	Grade 3-4	Any Grade	Grade 3-4	Any Grade	Grade 3-4
Patients with ≥1 TEAE	**15 (100)**	**10 (66.7)**	**15 (100)**	**13 (86.7)**	**30 (100)**	**23 (76.7)**
Anemia	6 (40.0)	0	12 (80.0)	2 (13.3)	18 (60.0)	2 (6.7)
Decreased appetite	6 (40.0)	1 (6.7)	11 (73.3)	1 (6.7)	17 (56.7)	2 (6.7)
Nausea	7 (46.7)	0	9 (60.0)	0	16 (53.3)	0
Asthenia	9 (60.0)	0	6 (40.0)	1 (6.7)	15 (50.0)	1 (3.3)
Leukopenia	5 (33.3)	0	8 (53.3)	2 (13.3)	13 (43.3)	2 (6.7)
Vomiting	7 (46.7)	1 (6.7)	6 (40.0)	4 (26.7)	13 (43.3)	5 (16.7)
Decreased neutrophil count	6 (40.0)	1 (6.7)	6 (40.0)	0	12 (40.0)	1 (3.3)
Decreased platelet count	8 (53.3)	0	4 (26.7)	1 (6.7)	12 (40.0)	1 (3.3)
Increased AST	9 (60.0)	1 (6.7)	1 (6.7)	1 (6.7)	10 (33.3)	2 (6.7)
Decreased weight	3 (20.0)	0	7 (46.7)	2 (13.3)	10 (33.3)	2 (6.7)
Hypoalbuminemia	5 (33.3)	0	5 (33.3)	0	10 (33.3)	0
Pyrexia	5 (33.3)	0	4 (26.7)	0	9 (30.0)	0
Increased ALT	7 (46.7)	1 (6.7)	2 (13.3)	0	9 (30.0)	1 (3.3)
Increased blood bilirubin	7 (46.7)	1 (6.7)	2 (13.3)	0	9 (30.0)	1 (3.3)
Decreased WBC count	3 (20.0)	1 (6.7)	6 (40.0)	0	9 (30.0)	1 (3.3)
Neutropenia	4 (26.7)	1 (6.7)	4 (26.7)	1 (6.7)	8 (26.7)	2 (6.7)
Hyponatremia	2 (13.3)	1 (6.7)	5 (33.3)	3 (20.0)	7 (23.3)	4 (13.3)
Cough	3 (20.0)	0	5 (33.3)	1 (6.7)	8 (26.7)	1 (3.3)
Thrombocytopenia	4 (26.7)	1 (6.7)	3 (20.0)	1 (6.7)	7 (23.3)	2 (6.7)
Diarrhea	5 (33.3)	1 (6.7)	2 (13.3)	0	7 (23.3)	1 (3.3)
Hypokalemia	2 (13.3)	1 (6.7)	4 (26.7)	1 (6.7)	6 (20.0)	2 (6.7)
Increased weight	4 (26.7)	0	2 (13.3)	1 (6.7)	6 (20.0)	1 (3.3)
Dizziness	2 (13.3)	0	4 (26.7)	0	6 (20.0)	0
Hypoesthesia	3 (20.0)	0	3 (20.0)	0	6 (20.0)	0

All data are presented as *n* (%).
Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; ESCC, esophageal squamous cell carcinoma; G/GEJ, gastric/gastroesophageal junction; TEAE, treatment-emergent adverse event; WBC, white blood cell.

Preliminary Antitumor Activity of Combination Therapy

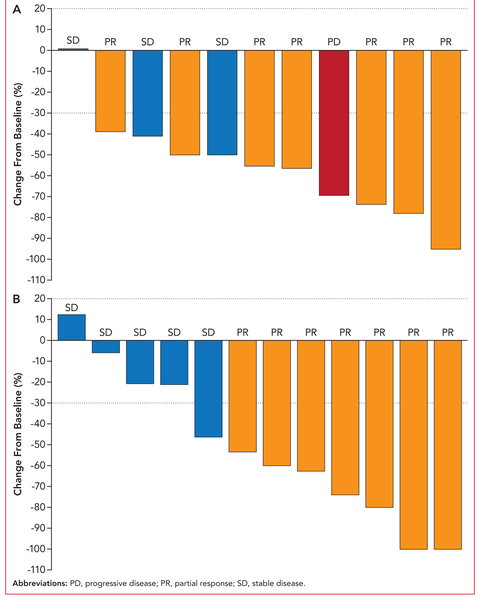
- Tislelizumab was associated with durable clinical response in both the G/GEJ and ESCC cohorts (Table 3; Figures 1-2)
- Confirmed ORR (46.7%; 95% CI: 21.27, 73.4) and DCR (80%; 95% CI: 51.91, 95.67) were the same in both cohorts
- The median time to response among patients who had achieved ORR was 9.3 weeks (range: 8.6, 9.7) in the G/GEJ cohort and 10.0 weeks (range: 9.1, 10.1) in the ESCC cohort
- Median PFS was 6.1 months (95% CI: 3.79, NE) and 10.4 months (95% CI: 5.55, 15.11) in the G/GEJ and ESCC cohorts, respectively
  - Despite the long median follow-up in both the G/GEJ (15.4 months; 95% CI: 14.7, 17.2) and ESCC cohorts (13.0 months; 95% CI: 10.3, 15.5), median OS had not been reached
  - In the G/GEJ cohort, the OS rate was 85% (95% CI: 51%, 96%) at 6 months and 62% (95% CI: 31%, 82%) at 12 months
  - In the ESCC cohort, the OS rate was 71% (95% CI: 41%, 88%) at 6 months and 50% (95% CI: 23%, 72%) at 12 months
- Median DoR was not mature in the G/GEJ cohort; median DoR was estimated as 12.8 months (95% CI: 3.5, 12.8) in the ESCC cohort

Table 3: Disease Response per RECIST (Safety Analysis Set, N=30)

		G/GEJ (n=15)	ESCC (n=15)
Best overall response per RECIST v1.1, n (%)	Complete response	0	0
	Partial response	7 (46.7)	7 (46.7)
	Stable disease	3 (20.0)	5 (33.3)
	Progressive disease	1 (6.7)	0
	Non-CR/non-PD[a]	2 (13.3)	0
	Not applicable[b]	2 (13.3)	3 (20.0)
Objective response rate, % (95% CI)[c]		46.7 (21.27, 73.41)	46.7 (21.27, 73.41)
Disease control rate, % (95% CI)[d]		80.0 (51.91, 95.67)	80.0 (51.91, 95.67)
Time to response, weeks, median (range)[e]		9.3 (8.6, 9.7)	10.0 (9.1, 10.1)

[a]Patients with only non-target lesions at baseline.
[b]Patients without post-baseline tumor assessment.
[c]Objective response rate = complete response + partial response.
[d]Disease control rate = complete response + partial response + stable disease + non-complete response/non-progressive disease.
[e]Time to response will be analyzed among patients who have achieved an objective response.
Abbreviations: CI, confidence interval; CR, complete response; ESCC, esophageal squamous cell carcinoma; G/GEJ, gastric/gastroesophageal junction; PD, progressive disease; RECIST, Response Evaluation Criteria in Solid Tumors; SD, standard deviation.

Figure 1: Maximum Tumor Reduction in Patients With Gastric Cancer or Gastroesophageal Junction Adenocarcinoma (A) and Esophageal Squamous Cell Carcinoma (B)

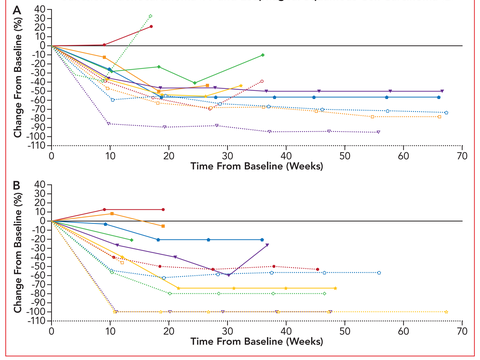


Abbreviations: PD, progressive disease; PR, partial response; SD, stable disease.

CONCLUSIONS

- Treatment with tislelizumab in combination with standard first-line chemotherapy was generally well tolerated in patients with HER2-negative G/GEJ adenocarcinoma or ESCC
  - Reported AEs were consistent with the known tolerability profile of PD-1 inhibitors in combination with chemotherapy
  - Most treatment-emergent AEs were mild or moderate in severity
- Tislelizumab plus chemotherapy provided durable responses and meaningful survival results in patients with a high unmet need
  - Confirmed ORR and DCR were the same in both the G/GEJ and ESCC cohorts
  - Despite the long median follow-up, OS had not been reached in either cohort
- The results from this study support continued clinical development of tislelizumab plus chemotherapy for the treatment of G/GEJ adenocarcinoma and ESCC
  - Two randomized, double-blind phase 3 studies of tislelizumab plus chemotherapy versus placebo plus chemotherapy as first-line treatment in patients with advanced G/GEJ adenocarcinoma (NCT03777657) or ESCC (NCT03783442) are currently enrolling

Figure 2: Tumor Response in Patients With Gastric Cancer or Gastroesophageal Junction Adenocarcinoma (A) and Esophageal Squamous Cell Carcinoma (B)



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CONFLICT OF INTERESTS

XL, **YL**, **XW**, and **SY** are employees of BeiGene. **YB**, **NX**, **XY**, **BW**, **EL**, and **JX** declare no conflicts of interest.

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