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# Tislelizumab Plus Chemotherapy as First-line Treatment for Advanced Esophageal Squamous Cell Carcinoma and Gastric/Gastroesophageal Junction Adenocarcinoma

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## ABSTRACT

**Purpose:** This phase II study (NCT03469557) assessed safety/tolerability and antitumor activity of first-line tislelizumab, a monoclonal antibody against programmed cell death-1, plus chemotherapy in patients with locally advanced/metastatic esophageal squamous cell carcinoma (ESCC) or gastric/gastroesophageal junction (G/GEJ) adenocarcinoma.

**Patients and Methods:** Patients with ESCC received tislelizumab [200 mg i.v. every 3 weeks (Q3W)] plus cisplatin (80 mg/m$^2$ i.v. Q3W for ≤6 cycles) and fluorouracil (800 mg/m$^2$/day i.v., Days 1–5 Q3W for ≤6 cycles); patients with G/GEJ adenocarcinoma received tislelizumab (200 mg i.v. Q3W) plus oxaliplatin (130 mg/m$^2$ i.v. Q3W for up to six cycles) and oral capecitabine (1,000 mg/m$^2$ twice daily, Days 1–14 Q3W). The safety/tolerability profile of combination therapy was the primary endpoint; secondary endpoints included objective response rate (ORR), duration of response (DoR), disease control rate (DCR), and progression-free survival per RECIST v1.1. Exploratory endpoints included overall survival and potential predictive biomarkers.

**Results:** As of March 31, 2019, 30 patients ($n = 15$ per cohort) were enrolled. Most common adverse events considered related to tislelizumab and/or chemotherapy were anemia ($n = 18$), decreased appetite ($n = 17$), nausea ($n = 16$), and asthenia ($n = 15$). One patient experienced fatal hepatic dysfunction, confounded by progressive disease and underlying hepatitis, attributed to treatment by the investigator. Confirmed ORRs and DCRs were 46.7% and 80%, respectively, for both ESCC and G/GEJ adenocarcinoma. In ESCC, median DoR was 12.8 months (95% confidence interval, 3.5–12.8); DoR was not yet mature for the G/GEJ cohort.

**Conclusions:** Tislelizumab plus chemotherapy demonstrated durable responses with manageable tolerability in patients with advanced ESCC or G/GEJ adenocarcinoma.

## Introduction

Globally, esophageal cancer (EC) and gastric cancer (GC) rank in the top seven most common cancers and in the top six in terms of mortality (1). Incidence rates for both cancer types are significantly higher in East Asia (1). Esophageal cancers are histologically classified as squamous cell carcinoma (ESCC) or adenocarcinoma, and ESCC accounts for 87% of all cases of EC (2). Combination chemotherapy is the recommended first-line treatment for advanced-stage ESCC and GC. The combination of cisplatin plus paclitaxel or 5-fluorouracil (5-FU) is the standard first-line regimen for patients with distant metastatic or recurrent ESCC (3); patients with diagnosed inoperable, locally advanced, or metastatic GC generally receive chemotherapy regimens containing a platinum and a fluoropyrimidine, with or without an additional chemotherapy agent (e.g., taxanes; refs. 4, 5). However, the prognosis for patients treated with standard-of-care treatment for either advanced-stage ESCC or GC remains poor (6, 7).

The interplay between immune checkpoint pathway proteins, programmed cell death-1 (PD-1) and programmed cell death-1 ligand (PD-L1), plays a significant role in antitumor immunity. Dysregulation of the PD-1/PD-L1 axis in tumor cells results in evasion of immune surveillance, detection, and destruction (8–12). Moreover, increasing evidence suggests that the antitumor activity of chemotherapy is mediated not only through cytotoxic effects, but also through immunologic effects, including reducing T-regulatory cell activity and enhancing cross-presentation of tumor antigens (13–15). As such, combining immune checkpoint inhibitors with chemotherapy may synergistically improve antitumor activity (13–15). Ongoing trials are currently investigating anti–PD-1 antibodies in combination with chemotherapy as first-line treatment of advanced ESCC (16) and advanced gastric/gastroesophageal junction (G/GEJ) adenocarcinoma (17, 18). In the first-line setting, pembrolizumab monotherapy was noninferior to chemotherapy for overall survival (OS) in patients with combined positive score (CPS) ≥1 and had clinically meaningful improvement for OS in CPS ≥10; pembrolizumab in combination with standard chemotherapy did not show superior OS in patients with CPS ≥1 or CPS ≥10 (18). There are currently no efficacy data reported for first-line treatment with anti–PD-L1 antibodies plus chemotherapy in patients with advanced ESCC.

Tislelizumab is a humanized monoclonal antibody (mAb) with high affinity and specificity for PD-1 that was engineered to minimize binding to FcγR on macrophages to greatly reduce antibody-dependent phagocytosis, a potential mechanism of T-cell clearance and resistance to anti–PD-1 therapy (19). Using structure-guided mutagenesis and Biacore studies, tislelizumab has been found to be structurally differentiated from both pembrolizumab and nivolumab

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**Note:** Supplementary data for this article are available at Clinical Cancer Research Online (http://clincancerres.aacrjournals.org/).

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## Translational Relevance

Advanced stages of esophageal and gastric cancer are associated with 5-year survival rates of ≤10%. Historically, first-line treatment consists of doublet chemotherapy, but novel immuno-oncology therapies are being developed. Immune checkpoint proteins, programmed cell death-1 (PD-1) and its ligand, programmed death ligand-1 (PD-L1), play a central role in suppressing antitumor immunity, and dysregulation of the PD-1/PD-L1 axis may be used by cancer cells for immune evasion. PD-1 is an inhibitory receptor involved in negative regulation of T-cell activation that is mainly expressed on activated T cells and is found to be upregulated in tumor-infiltrating lymphocytes. Here, we demonstrate that tislelizumab, a monoclonal antibody against PD-1, plus standard-of-care platinum-doublet chemotherapy as first-line treatment, was generally well tolerated and demonstrated durable antitumor activity in Chinese patients with advanced esophageal squamous cell carcinoma or gastric/gastroesophageal junction adenocarcinoma.

by its unique binding epitopes and binding kinetics (20). In two early-phase studies (NCT02407990, CTR20160872), tislelizumab (200 mg) administered intravenously every 3 weeks (Q3W) was generally well tolerated and demonstrated promising antitumor activity in both Asian and non-Asian patients with advanced solid tumors, including EC and GC (21, 22). The primary objective of this study was to investigate the safety of tislelizumab in combination with 5-FU plus cisplatin in patients with advanced ESCC, or with oxaliplatin plus capecitabine in patients with advanced G/GEJ adenocarcinoma. A secondary objective was to assess the preliminary antitumor activity of tislelizumab in combination with chemotherapy as first-line treatment for advanced ESCC and G/GEJ adenocarcinoma.

## Patients and Methods

### Study design and treatment

This was a phase II (NCT03469557), multicohort study of tislelizumab in combination with chemotherapy, conducted at six sites in China. Patients were concurrently enrolled in an ESCC or G/GEJ adenocarcinoma cohort (Supplementary Fig. S1). During the initial phase, six patients were enrolled in each cohort and safety data were reviewed by a Safety Monitoring Committee after the completion of the first 21-day treatment cycle. As no significant or severe safety event(s) occurred, enrollment was expanded to 15 patients per cohort. Treatment-emergent adverse events (TEAE) were considered related to study treatment if the investigator assessed the TEAE to be definitely related, probably related, possibly related, or possibly unrelated to study treatment, or with missing assessment of the causal relationship.

The study was comprised of a 28-day screening period; a treatment period that lasted until the occurrence of disease progression, intolerable toxicity, or withdrawal for other reasons; a 30-day safety follow-up period; and a survival follow-up period. During each 21-day cycle, patients in the ESCC cohort received tislelizumab 200 mg i.v. and cisplatin 80 mg/m$^2$ i.v. on Day 1, and 5-FU 800 mg/m$^2$/day i.v. with a continuous pumping system on Days 1–5. Treatment continued for up to six cycles for cisplatin and 5-FU and until disease progression, intolerable toxicity, or treatment discontinuation due to any other reason for tislelizumab. During each 21-day cycle, patients in the G/GEJ adenocarcinoma cohort received tislelizumab 200 mg i.v. and oxaliplatin 130 mg/m$^2$ i.v. on Day 1, and oral capecitabine 1,000 mg/m$^2$ twice daily from the evening of Day 1 through the morning of Day 15. Treatment continued for up to six cycles for oxaliplatin and until disease progression, intolerable toxicity, or treatment discontinuation due to any other reason for tislelizumab and capecitabine. To account for potential pseudoprogression, patients could continue treatment beyond initial disease progression per RECIST v1.1 to confirm disease progression status.

### Eligibility

Adult Chinese patients (ages 18–75 years) with a pathologically confirmed diagnosis of ESCC or G/GEJ adenocarcinoma, with at least one measurable or evaluable lesion considered to be inoperable, locally advanced, or metastatic, were eligible for enrollment. For patients with G/GEJ adenocarcinoma, HER testing was required at local laboratories prior to enrollment. Patients with HER2-positive status, defined as having a HER2-neu expression score of 2+ by immunohistochemistry (IHC) and confirmed by fluorescence *in situ* hybridization or expression score of 3+ by IHC were ineligible (23). Patients must not have received prior systemic therapy for advanced or metastatic disease. However, prior neoadjuvant or adjuvant therapy including chemoradiotherapy was allowed, provided it was completed ≥6 months prior to enrollment. Patients must have had an Eastern Cooperative Oncology Group (ECOG) performance status score of 0 or 1 and a life expectancy ≥12 weeks. Patients were not eligible for this study if they had a history of severe hypersensitivity reaction to other mAbs, 5-FU, or cisplatin agents; if they had received prior therapies targeting PD-1, PD-L1, or PD-L2; if they had active autoimmune disease or history of autoimmune disease that might relapse; or if they required systemic treatment with immunosuppressive medications within 14 days of study drug administration.

The study protocol and all amendments were approved by each institution's institutional review board or ethics committee. The study was done in accordance with the protocol and its amendments and Good Clinical Practice Guidelines. All patients provided written informed consent before enrollment.

### Endpoints and assessments

The safety and tolerability of tislelizumab in combination with chemotherapy was the primary endpoint of the study. Safety was assessed by monitoring the incidence and severity of adverse events (AE) graded according to the NCI Common Terminology Criteria for Adverse Events version 4.03 guidelines, and changes in physical examinations, vital signs, clinical laboratory assessments, and 12-lead electrocardiogram measurements. Secondary endpoints included objective response rate (ORR), defined as the proportion of patients who had a complete response (CR) or a partial response (PR); duration of response (DoR), defined as the time from the determination of an objective response to the first determination of progression or death, whichever came first; disease control rate (DCR), defined as the proportion of patients who achieved CR, PR, and stable disease (SD); and progression-free survival (PFS), defined as the time from the first dose of the study drug to the first determination of disease progression or death, whichever came first. Tumor responses were assessed by the investigator based on the RECIST v1.1 criteria; radiographic imaging by CT or MRI were conducted within 28 days prior to enrollment, every 9 weeks during the first year of treatment, and every 12 weeks thereafter until disease progression. An exploratory endpoint evaluated the association between PD-L1 expression and microsatellite instability (MSI) status as potential predictive biomarkers of antitumor activity. Expression of PD-L1 on tumor cells was retrospectively evaluated by a central laboratory using the VENTANA™ PD-L1

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(SP263) assay (24). To determine MSI, DNA was extracted from tissue samples and analyzed using the OncoScreen™ Plus panel (Burning Rock, Guangzhou, China); MSI status was determined by the percentage of unstable loci in the tumor sample (25).

### Study population and statistical analyses

The planned sample size for this study was approximately 30 patients (15 per cohort), which was deemed adequate to provide an initial safety evaluation. Descriptive statistics were used to summarize safety data. The Kaplan–Meier method was used to estimate the median time and 95% confidence interval (CI) for PFS and OS. The safety analysis set (SAF) included all patients who received any dose of tislelizumab or chemotherapy and was used as the primary analysis set for the safety and efficacy analyses.

### Data sharing statement

Upon request, and subject to certain criteria, conditions, and exceptions, BeiGene will provide access to individual de-identified participant data from BeiGene-sponsored global interventional clinical studies conducted for medicines (i) for indications that have been approved or (ii) in programs that have been terminated. BeiGene will also consider requests for the protocol, data dictionary, and statistical analysis plan. Data requests may be submitted to medicalinformation@beigene.com.

## Results

### Patient disposition, demographics, and baseline disease characteristics

A total of 35 patients were recruited and five patients did not meet the eligibility criteria and were excluded. Between July 18, 2017 and March 22, 2018, a total of 30 patients (ESCC, $n = 15$ and G/GEJ adenocarcinoma, $n = 15$) were enrolled in the study. As of March 31, 2019, 14 patients remained in the study; eight patients remained on treatment [ESCC, $n = 4$ (26.7%) and G/GEJ adenocarcinoma, $n = 4$ (26.7%)]. Twenty-two patients [ESCC, $n = 11$ (73.3%) and G/GEJ adenocarcinoma, $n = 11$ (73.3%)] discontinued the study treatment. Reasons for discontinuation included radiographic disease progression ($n = 7$, 31.8%), TEAEs ($n = 6$, 27.3%), clinical disease progression ($n = 5$, 22.7%), withdrawal of consent ($n = 3$, 13.6%), and noncompliance ($n = 1$, 4.5%; Supplementary Fig. S2).

Demographics and baseline characteristics were similar between cohorts (**Table 1**). Overall, the median age was 60.5 years (range: 42.0–74.0) and most patients were male ($n = 25$, 83.3%). Across both cohorts, 80% of patients ($n = 24/30$) had tumor–node–metastasis (TNM) stage IV [ESCC, $n = 10$ (66.7%) and G/GEJ adenocarcinoma, $n = 14$ (93.3%)]. The majority of metastatic sites were in visceral tissues (e.g., lymph nodes, liver). Eight patients had prior anticancer surgeries [26.7%; ESCC and G/GEJ adenocarcinoma, $n = 4$ each (26.7%)] and five patients had prior anticancer therapies [16.7%; ESCC, $n = 3$ (20.0%) and G/GEJ adenocarcinoma, $n = 2$ (13.3%)].

### Treatment exposure

The median tislelizumab treatment duration for patients in the ESCC cohort was 34.4 weeks (range: 3–67), for treatment with cisplatin was 19.0 weeks (range: 2–20), and for treatment with 5-FU was 19.0 weeks (range: 3–20). The median relative dose intensity was 95.9% (range: 59.2–100) for tislelizumab, 93.3% (range: 59.5–100) for cisplatin, and 90.0% (range: 15.4–97.7) for 5-FU.

In the G/GEJ adenocarcinoma cohort, the median treatment duration with tislelizumab was 26.1 weeks (range: 3–75), for treatment with oxaliplatin it was 18.4 weeks (range: 3–24), and for treatment with capecitabine it was 25.4 weeks (range: 1–72). Median relative dose intensity was 95.5% (range: 61.5–102.4) for tislelizumab, 94.3% (range: 74.3–102.5) for oxaliplatin, and 90.2% (range: 37.0–108.7) for capecitabine. Dose modification of tislelizumab occurred in six patients (40.0%) in the ESCC cohort and in eight patients (53.3%) with G/GEJ adenocarcinoma; all were dose delays.

### Safety and tolerability of tislelizumab in combination with chemotherapy

All patients ($n = 30$, 100%) had at least one TEAE (**Table 2**). In the ESCC cohort, TEAEs reported in ≥20% of patients included anemia ($n = 12$, 80.0%); decreased appetite ($n = 11$, 73.3%); nausea ($n = 9$, 60.0%); leukopenia ($n = 8$, 53.3%); decreased weight ($n = 7$, 46.7%); asthenia, vomiting, decreased neutrophil count, and decreased white blood cell count ($n = 6$ each, 40.0%); and hypoalbuminemia, cough, and hyponatremia ($n = 5$ each, 33.3%; **Table 3**). In the G/GEJ adenocarcinoma cohort, TEAEs reported in ≥20% of patients included asthenia and increased aspartate aminotransferase (AST; $n = 9$ each, 60.0%); decreased platelet count ($n = 8$, 53.3%); nausea, vomiting, increased alanine aminotransferase (ALT), and increased blood bilirubin ($n = 7$ each, 46.7%); anemia, decreased appetite, and decreased neutrophil count ($n = 6$ each, 40.0%); and leukopenia, hypoalbuminemia, pyrexia, and diarrhea ($n = 5$ each, 33.3%; **Table 3**).

TEAEs related to treatment reported in ≥20% of all patients are presented in Supplementary Table S1. TEAEs considered to be related to chemotherapy occurred in all patients and TEAEs considered related to tislelizumab occurred in 27 of 30 (90%) total patients [ESCC, $n = 14$ (93.3%) and G/GEJ adenocarcinoma, $n = 13$ (86.7%)]. The most commonly reported TEAEs considered related to study treatment were anemia [chemotherapy and tislelizumab, $n = 18$ (60.0%); chemotherapy, $n = 17$ (56.7%); and tislelizumab, $n = 13$ (43.3%)], decreased appetite [chemotherapy and tislelizumab, $n = 17$ (56.7%); chemotherapy, $n = 17$ (56.7%); and tislelizumab, $n = 15$, (50%)], and nausea [chemotherapy and tislelizumab, $n = 16$ (53.3%); chemotherapy, $n = 16$ (53.3%); and tislelizumab, $n = 11$ (36.7%)]. The most commonly reported TEAEs of grade ≥3 considered to be treatment related were vomiting [chemotherapy, $n = 5$ (16.7%) and tislelizumab, $n = 4$ (13.3%)] and hyponatremia [chemotherapy, $n = 3$ (10.0%) and tislelizumab, $n = 4$ (13.3%)].

Serious AEs (SAE) were reported in 13 of 30 (43.3%) patients [ESCC, $n = 8$ (53.3%) and G/GEJ adenocarcinoma, $n = 5$ (33.3%); **Table 2**]. SAEs reported in ≥2 patients in either cohort were increased blood bilirubin [G/GEJ adenocarcinoma, $n = 2$ (13.3%)], dysphagia [ESCC, $n = 3$ (20.0%)], and fatigue [ESCC, $n = 2$ (13.3%)]. The case 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 [36.7%; ESCC, $n = 6$ (40.0%); G/GEJ adenocarcinoma, $n = 5$ (33.3%)]. Chemotherapy-related SAEs occurred in 10 patients [33.3%; ESCC, $n = 5$ (33.3%); G/GEJ adenocarcinoma, $n = 5$ (33.3%)]. One patient in the ESCC cohort experienced a fatal AE (hepatic dysfunction), which was considered mainly due to progressive disease, but was also possibly related to study treatment and underlying hepatitis B (HBV) infection. This patient tested positive for HBV infection at baseline and had rapidly progressing liver metastasis. The fatal event was considered by the investigator to be possibly related to tislelizumab, cisplatin, and 5-FU due to an increase in the number of DNA copies of HBV after tislelizumab dosing, as well as the known adverse effects of cisplatin and 5-FU on liver function. A total of 23 patients [76.7%; ESCC, $n = 12$ (80.0%);

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**Table 1.** Demographics and baseline characteristics (SAF, $N = 30$).

| | ESCC ($n = 15$) | G/GEJ adenocarcinoma ($n = 15$) | All ($N = 30$) |
|---|---|---|---|
| Age, years, median (range) | 61.0 (47–68) | 59.0 (42–74) | 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 | 14 (93.3) | 11 (73.3) | 25 (83.3) |
| Female | 1 (6.7) | 4 (26.7) | 5 (16.7) |
| ECOG status, *n* (%) | | | |
| 0 | 4 (26.7) | 1 (6.7) | 5 (16.7) |
| 1 | 11 (73.3) | 14 (93.3) | 25 (83.3) |
| TNM stage, *n* (%) | | | |
| Stage III (IIIA, IIIB, IIIC) | 3 (20.0) | 1 (6.7) | 4 (13.3) |
| Stage IV | 10 (66.7) | 14 (93.3) | 24 (80.0) |
| NA | 1 (6.7) | 0 | 1 (3.3) |
| Histologic grade of primary tumor, *n* (%) | | | |
| GX | 1 (6.7) | 3 (20.0) | 4 (13.3) |
| G1 | 0 | 1 (6.7) | 1 (3.3) |
| G2 | 6 (40.0) | 2 (13.3) | 8 (26.7) |
| G3 | 5 (33.3) | 9 (60.0) | 14 (46.7) |
| Other[a] | 2 (13.3) | 0 | 2 (6.7) |
| Missing | 1 (6.7) | 0 | 1 (3.3) |
| Metastatic site, *n* (%) | | | |
| Lymph nodes | 4 (26.7) | 6 (40) | 10 (33.3) |
| Liver | 3 (20.0) | 7 (46.7) | 10 (33.3) |
| Lung | 0 | 3 (20.0) | 3 (10.0) |
| Mediastinum | 1 (6.7) | 0 | 1 (3.3) |
| Retroperitoneal mass | 1 (6.7) | 0 | 1 (3.3) |
| Bone | 1 (6.7) | 0 | 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) |
| Other | 0 | 0 | 0 |
| Prior anticancer drug therapies | | | |
| Adjuvant | 2 (13.3) | 2 (13.3) | 4 (13.3) |
| Neoadjuvant | 1 (6.7) | 0 | 1 (3.3) |
| Other | 0 | 0 | 0 |

Abbreviations: ECOG, Eastern Cooperative Oncology Group; ESCC, esophageal squamous cell carcinoma; G/GEJ, gastric/gastroesophageal junction; G1, well differentiated; G2, moderately differentiated; G3, poorly differentiated; GX, differentiation could not be assessed; NA, not available; SAF, safety analysis set.
[a]Patients were specified as not done.

**Table 2.** Overview of AEs.

| | ESCC ($n = 15$) *n* (%) | G/GEJ ($n = 15$) *n* (%) | All ($N = 30$) *n* (%) |
|---|---|---|---|
| Patients with at least one TEAE | 15 (100) | 15 (100) | 30 (100) |
| Tislelizumab-related TEAE | 14 (93.3) | 13 (86.7) | 27 (90.0) |
| Chemotherapy-related TEAE | 15 (100) | 15 (100) | 30 (100) |
| Infusion-related reaction TEAE | 1 (6.7) | 0 | 1 (3.3) |
| Grade 3 or higher TEAE | 13 (86.7) | 10 (66.7) | 23 (76.7) |
| Serious TEAE | 8 (53.3) | 5 (33.3) | 13 (43.3) |
| TEAE leading to death | 1 (6.7) | 0 | 1 (3.3) |

Abbreviations: AE, adverse event; ESCC, esophageal squamous cell carcinoma; G/GEJ, gastric/gastroesophageal junction; TEAE, treatment-emergent adverse event.

G/GEJ adenocarcinoma, $n = 11$ (73.3%)] reported ≥1 immune-related AE (irAE); grade ≥3 irAEs occurred in 11 patients (36.7%; Supplementary Table S2).

### Antitumor activity of combination therapy

Tislelizumab was associated with durable clinical responses in both ESCC and G/GEJ adenocarcinoma regardless of PD-L1 status (**Table 4**; **Figs. 1** and **2**). The impact of MSI status was inconclusive, as no evaluable tumor samples were MSI-high (**Fig. 1**). Confirmed ORR (46.7%; 95% CI, 21.27–73.4) and DCR (80%; $n = 12/15$; 95% CI, 51.91–95.67) were the same in both the ESCC and G/GEJ adenocarcinoma cohorts. A total of seven patients in each cohort achieved a confirmed PR. Five patients in the ESCC cohort had SD. In the G/GEJ adenocarcinoma cohort, three patients had SD and two patients with only non-target lesions at baseline achieved a non-CR/non-PD. One patient with ESCC achieved a CR after study discontinuation due to

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**Table 3.** TEAEs occurring in ≥20% of all patients.

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

Note: 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.

**Table 4.** Disease response per RECIST (SAF, $N = 30$).

| | ESCC ($n = 15$) | G/GEJ adenocarcinoma ($n = 15$) |
|---|---|---|
| Best overall response per RECIST 1.1, *n* (%) | | |
| CR | 0 | 0 |
| PR | 7 (46.7) | 7 (46.7) |
| SD | 5 (33.3) | 3 (20.0) |
| Progressive disease | 0 | 1 (6.7) |
| Non-CR/non-PD[a] | 0 | 2 (13.3) |
| Not applicable[b] | 3 (20.0) | 2 (13.3) |
| ORR, % (95% CI)[c] | **46.7 (21.27–73.41)** | **46.7 (21.27–73.41)** |
| DCR, % (95% CI)[d] | **80.0 (51.91–95.67)** | **80.0 (51.91–95.67)** |
| Time to response, weeks, median (range)[e] | **10.0 (9.1–10.1)** | **9.3 (8.6–9.7)** |

Abbreviations: CI, confidence interval; CR, complete response; DCR, disease control rate; ESCC, esophageal squamous cell carcinoma; G/GEJ, gastric/gastroesophageal junction; ORR, objective response rate; PD, progressive disease; PR, partial response; RECIST, Response Evaluation Criteria in Solid Tumors; SAF, safety analysis set; SD, stable disease.

[a]Patients with only non-target lesions at baseline.

[b]Patients without post-baseline tumor assessment.

[c]ORR = CR + PR.

[d]DCR = CR + PR + SD + non-CR/nonprogressive disease.

[e]Time to response was analyzed among patients who had achieved an objective response.

dermatitis, prior to receiving any additional anticancer treatments. The median time to response among patients who had achieved ORR was 10.0 weeks (range: 9.1–10.1) in the ESCC cohort and 9.3 weeks (range: 8.6–9.7) in the G/GEJ adenocarcinoma cohort. Median DoR was estimated as 12.8 months (95% CI, 3.5–12.8) in the ESCC cohort; despite the long follow-up, median DoR was immature in the G/GEJ adenocarcinoma cohort. Median PFS was 10.4 months (95% CI, 5.55–15.11) and 6.1 months (95% CI, 3.78, not evaluable) in the ESCC and G/GEJ adenocarcinoma cohorts, respectively (Supplementary Fig. S3).

Despite the long median survival follow-up in both the ESCC (13.0 months; 95% CI, 10.3–15.5) and G/GEJ adenocarcinoma (15.4 months; 95% CI, 14.7–17.2) cohorts, median OS had not been reached as of March 31, 2019. 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. In the G/GEJ adenocarcinoma cohort, the OS rate was 85% (95% CI, 51%–96%) at 6 months and 62% (95% CI, 31%–82%) at 12 months. Swimmer plots of OS show long OS regardless of PD-L1 expression levels; the impact of MSI status was inconclusive, as no evaluable tumor samples were MSI-high (Supplementary Fig. S4).

## Discussion

This phase II, multicohort study in China investigated the safety and antitumor activity of tislelizumab in combination with standard first-line chemotherapy for patients with inoperable, locally advanced, or metastatic ESCC ($n = 15$) or G/GEJ adenocarcinoma ($n = 15$). As of the data cut-off date (March 31, 2019), this study showed that tislelizumab plus chemotherapy has a manageable safety profile with

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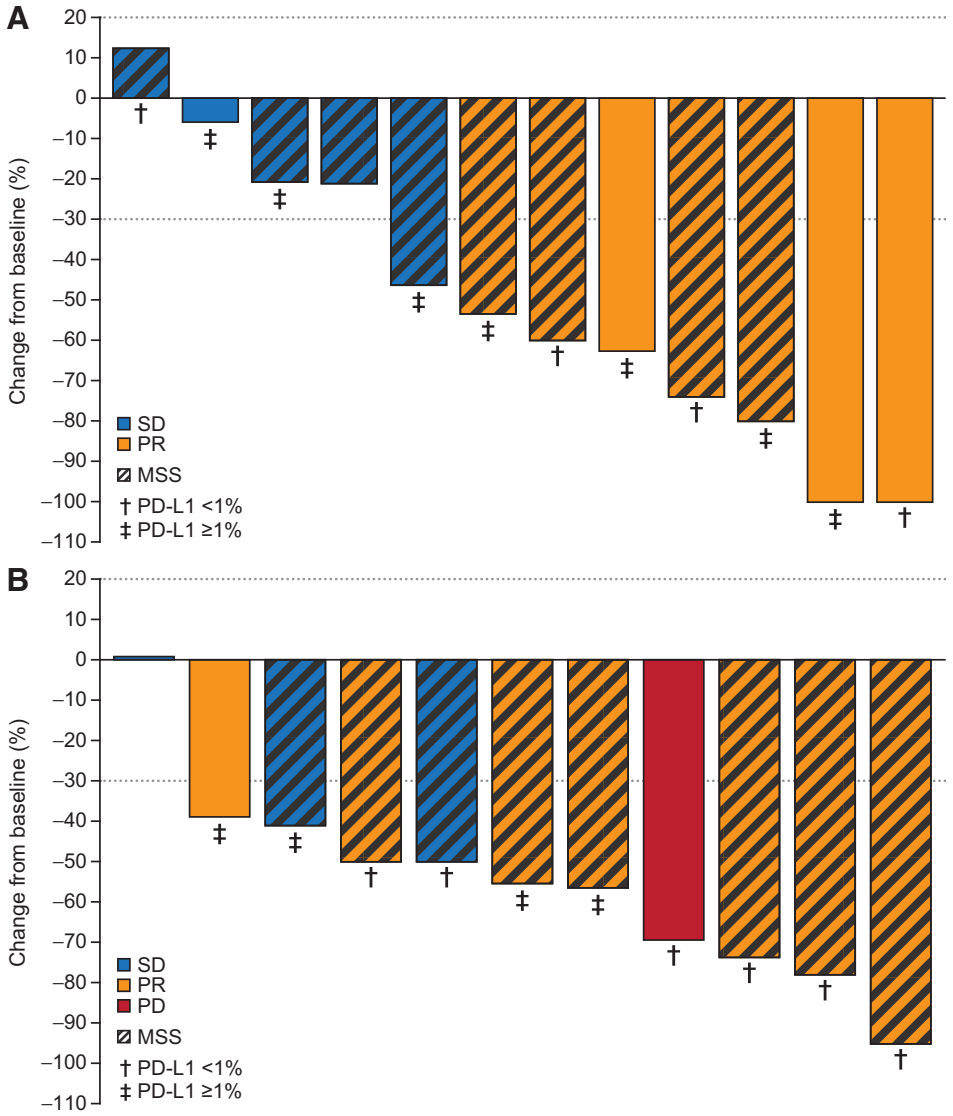


**Figure 1.**
Maximum tumor reduction in patients with ESCC (**A**) and G/GEJ adenocarcinoma (**B**). Two patients ($n = 1$ each cohort) with an evaluable target lesion did not have PD-L1 expression results. Seven patients ($n = 4$, ESCC; and $n = 3$, G/GEJ adenocarcinoma) with an evaluable target lesion had missing/inconclusive MSS results. ESCC, esophageal squamous cell carcinoma; G/GEJ, gastric/gastroesophageal junction; MSS, microsatellite stability; PD, progressive disease; PD-1, programmed cell death-1; PD-L1, programmed cell death-1 ligand; PR, partial response; SD, stable disease.

preliminary antitumor activity in the first-line treatment of advanced ESCC and G/GEJ adenocarcinoma.

The AE profile noted for tislelizumab in combination with chemotherapy was generally manageable and the chemotherapy-related AEs reported were consistent with AEs known to be associated with chemotherapy (3, 26). No new tislelizumab safety signals were observed with combination therapy and most of the AEs were reported to be mild-to-moderate in severity. All AEs had resolved or were resolving after discontinuation of study treatment and concomitant medications, with the exception of one case of lung infection related to chemotherapy resulting in death due to progressive disease. A fatal AE (hepatic dysfunction) considered possibly related to treatment by the investigator occurred in one patient in the ESCC cohort. The event was confounded by progressive disease and by underlying HBV infection.

The safety/tolerability signals from our large phase I studies (NCT02407990, $n = 451$ and CTR20160872, $n = 300$) are consistent with previous important trials of PD-1 inhibitors. Therefore, it is currently unclear whether the minimized FcγR binding and/or binding kinetics of tislelizumab result in an improved safety/tolerability profile compared with other PD-1 inhibitors. Future investigations to determine whether the effects of minimized FcγR binding and/or binding kinetics on the safety/tolerability profile may have contributed these differences may be warranted.

For advanced-stage ESCC, combination chemotherapy is typically given as first-line treatment. Treatment regimens commonly include a platinum agent (cisplatin or oxaliplatin) in combination with paclitaxel or 5-FU (27). The ORRs and median survival durations appear generally comparable across the various regimens. First-line chemotherapy has an ORR of 37%–58%, but the median DoR is only 4–7 months (3, 21, 28, 29). The median PFS and OS in first-line chemotherapy are approximately 4.8–7.9 months and 10.4–13.5 months, respectively (3, 21, 28, 29). In this study, the ORR was 46.7% with a median DoR of 12.8 months. While no CRs were observed during the study period, it should be noted that one patient in follow-up after study discontinuation due to dermatitis achieved a CR prior to receiving any additional anticancer treatments. Although direct comparisons are problematic due to potential differences in patient populations, standard chemotherapy with platinum and fluoropyrimidines in Japanese patients with advanced ESCC resulted in an ORR of 33% and a median DoR of 5.75 months (30). In the

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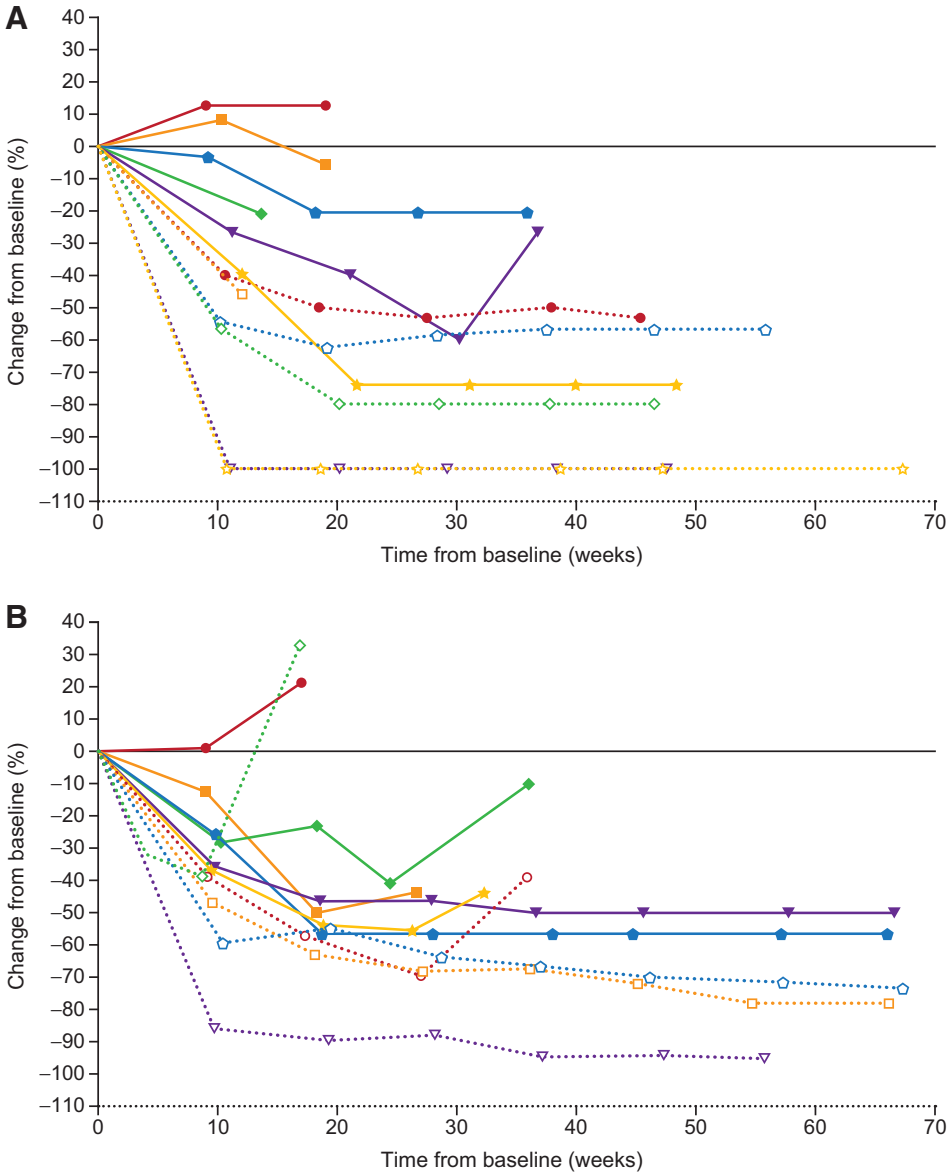


**Figure 2.**
Tumor response in patients with ESCC (**A**) and G/GEJ adenocarcinoma (**B**). ESCC, esophageal squamous cell carcinoma; G/GEJ, gastric/gastroesophageal junction.

current study, PFS was estimated as 10.4 months, and despite a median survival follow-up of approximately 13 months, median OS was not yet reached. The results of tislelizumab in combination with chemotherapy support continued development of tislelizumab in patients with advanced ESCC.

First-line chemotherapy for advanced GC contains a platinum agent and a fluoropyrimidine. The ORR typically observed can range from approximately 25% to 75% with median DoR up to 4.8 months; median OS of approximately 9–13 months is typical (31–35). Within the G/GEJ adenocarcinoma cohort of this study, the ORR was 46.7% and the responses were durable, with median DoR not yet reached (range: 2.99–13.11+ months). A total of four responders remained on treatment at the time of data cutoff, and the median OS was also not reached despite a median follow-up time of 15.4 months. Our data are consistent with a previous report from patients with PD-L1 CPS ≥1 G/GEJ adenocarcinoma treated with pembrolizumab plus chemotherapy, where ORR was 48.6% and PFS was estimated as 6.9 months (range: 5.7–7.3; ref. 18). Furthermore, OS was 12.5 and 11.1 months for patients receiving combination therapy and chemotherapy alone, respectively (18). In addition, a phase II study (KEYNOTE-059) of pembrolizumab combined with chemotherapy resulted in an ORR of 60% and median PFS was estimated as 6.6 months (95% CI, 5.9–10.6) after a median follow-up of 13.8 months (36). Taken together, the results of tislelizumab in combination with chemotherapy support continued development of tislelizumab in patients with advanced G/GEJ adenocarcinoma.

As this was a single-arm study, the antitumor activity of each individual treatment component could not be determined; however, two early-phase studies (NCT02407990, CTR2016087) demonstrated that patients with ESCC and GC had antitumor responses when treated with tislelizumab monotherapy (21, 22). While conclusions on safety/tolerability and survival data in this phase II study are limited by the small sample size, no new safety signals were observed. Another possible limitation is that this trial consisted of only Chinese patients, and potential geographical differences in clinical presentation should be considered when extrapolating the

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results of this study to a Western population (37). Efficacy and safety/tolerability of tislelizumab in combination with chemotherapy will be further elucidated in a larger, global population in phase III studies.

Tislelizumab plus chemotherapy demonstrated durable responses with manageable tolerability in patients with advanced ESCC or G/GEJ adenocarcinoma. Two randomized, double-blind phase III studies of tislelizumab plus chemotherapy versus placebo plus chemotherapy as first-line treatment in patients with advanced ESCC (NCT03783442) and G/GEJ adenocarcinoma (NCT03777657) are underway.

## Disclosure of Potential Conflicts of Interest

J. Wang, X. Li, and X. Wang report employment with BeiGene. No potential conflicts of interest were disclosed by the other authors.

## Authors' Contributions

**J. Xu:** Conceptualization, resources, data curation, supervision, validation, investigation, visualization, methodology, writing-original draft, project administration, writing-review and editing. **Y. Bai:** Conceptualization, resources, data curation, validation, investigation, writing-original draft, writing-review and editing. **N. Xu:** Resources, data curation, validation, investigation, writing-original draft, writing-review and editing. **E. Li:** Resources, data curation, validation, investigation, writing-review and editing. **B. Wang:** Resources, data curation, validation, investigation, writing-review and editing. **J. Wang:** Conceptualization, data curation, supervision, funding acquisition, validation, methodology, project administration, writing-review and editing. **X. Li:** Data curation, funding acquisition, validation, visualization, writing-original draft, project administration, writing-review and editing. **X. Wang:** Data curation, software, formal analysis, validation, visualization, methodology, writing-review and editing. **X. Yuan:** Resources, data curation, validation, investigation, writing-review and editing.

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# Tislelizumab Plus Chemotherapy as First-line Treatment for Advanced Esophageal Squamous Cell Carcinoma and Gastric/Gastroesophageal Junction Adenocarcinoma

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