TISLELIZUMAB IN COMBINATION WITH CHEMOTHERAPY FOR THE TREATMENT OF CHINESE PATIENTS WITH ESOPHAGEAL SQUAMOUS CELL CARCINOMA (ESCC): SAFETY AND TOLERABILTY RESULTS FROM ONE COHORT OF AN ONGOING PHASE 2 STUDY

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BOARD E4: Abstract 14

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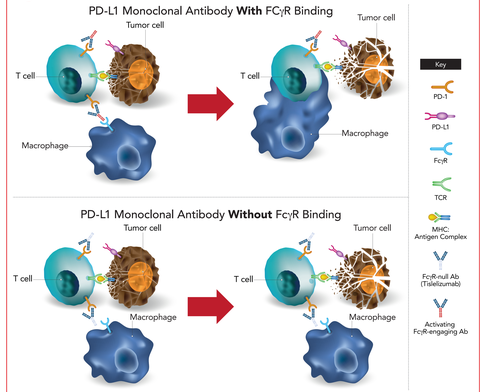
BACKGROUND

- Esophageal cancer is the seventh most common cancer worldwide and the sixth most common cause of cancer-related deaths[1]
- Globally, esophageal squamous cell cancer (ESCC) remains the predominant histological subtype and accounts for most deaths from esophageal cancer; it has a higher prevalence in Asian countries[2]
- Monoclonal antibodies (mAbs) against immune checkpoint inhibitory receptors, such as programmed cell death-1 (PD-1), have demonstrated promising antitumor activity across multiple malignancies,[3] including ESCC[4]
- Tislelizumab (BGB-A317) is an investigational humanized IgG4 mAb with high affinity and binding specificity against PD-1[5]
- Tislelizumab was specifically engineered to minimize FcγR binding on macrophages in order to abrogate antibody-dependent phagocytosis (Figure 1),[5] a potential mechanism of T-cell clearance and potential resistance to anti-PD-1 therapy[6]
- Previous reports from early phase studies suggest tislelizumab was generally well tolerated and had antitumor activity in patients with advanced solid tumors[7–9]

Figure 1: Tislelizumab Mechanism of Action

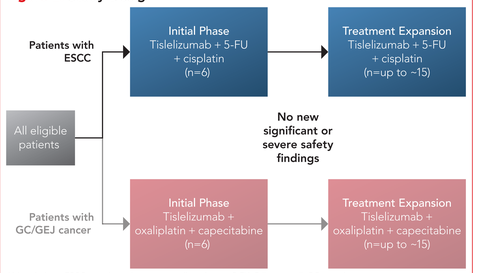


Abbreviations: Ab, antibody; MHC, major histocompatibility complex; PD-1, programmed cell death-1; PD-L1, programmed cell death-1 ligand; TCR, T-cell receptor.

METHODS

- The study design of this two-cohort phase 2 study (NCT03469557) is detailed in Figure 2
- Adult patients with histologically or cytologically confirmed HER2-negative gastric cancer (GC) or gastroesophageal junction (GEJ) cancer or ESCC were eligible for inclusion in the study

Figure 2: Study Design



Abbreviations: ESCC, esophageal squamous cell carcinoma; 5-FU, 5-fluorouracil; GC, gastric cancer; GEJ, gastroesophageal junction.

- Patients must have ≥1 measurable or evaluable lesion considered inoperable, locally advanced, or metastatic at the time of enrollment; must not be amenable to radiation therapy alone; and must not have received prior systemic therapy for advanced or metastatic disease (prior neoadjuvant or adjuvant therapy including chemoradiation was allowed, provided it was completed ≥6 months prior to enrollment)
- Patients were excluded if they had a history of severe hypersensitivity reactions to other mAbs or platinum agents such as fluorouracil or cisplatin
- Patients were excluded if they had previously received PD-1, PD-L1, or PD-L2 antibody therapy for any indication
- Patients who had a prior malignancy that was active within the previous 2 years, except for ESCC, and who had locally recurring cancers that had undergone curative intent treatment, such as basal or squamous cell skin cancer, superficial bladder cancer, or carcinoma in situ of the cervix or breast, were excluded

- Patients with ESCC were treated with tislelizumab (200 mg IV Q3W), cisplatin (80 mg/m² IV Q3W), and fluorouracil (800 mg/m²/d, Days 1–5 IV Q3W)
  - Cisplatin and 5-FU were administered for ≤6 cycles; tislelizumab will be administered until disease progression, intolerable toxicity, or treatment discontinuation
- Safety and tolerability were assessed through monitoring of adverse events (AEs), defined and graded according to CTCAE v4.03; tumor responses were assessed by investigators based on RECIST v1.1 criteria every 9 weeks during the first year, and every 12 weeks thereafter
- Here, we present the safety and tolerability profile of tislelizumab in combination with chemotherapy in the cohort of patients with ESCC
  - Assessment of the antitumor activity of tislelizumab in the ESCC cohort is ongoing
  - Safety, tolerability, and antitumor activity data for the cohort of patients with GC is presented at BOARD E1: Abstract 11

RESULTS

Patient Disposition

- As of 13 June 2018, 15 patients with ESCC had enrolled in this study
- Most patients were male (93%), had an Eastern Cooperative Oncology Group (ECOG) status of 1 (73%), and stage IV disease (53%) (Table 1)
- The median treatment duration was 108 days (range: 21–201)
  - Mean relative dose intensity was 0.92 for tislelizumab, 0.91 for cisplatin, and 0.78 for 5-FU

Table 1: Demographics and Baseline Disease Characteristics of Patients With ESCC

		ESCC Population (N=15)
Median age, years		61
Sex, n (%)	Male	14 (93)
	Female	1 (7)
ECOG status, n (%)	0	4 (27)
	1	11 (73)
Tumor stage, n (%)	0–II	0
	III	6 (40)
	IV	8 (53)
	Not applicable[a]	1 (7)
Prior systemic anticancer therapy regimens, n (%)	Neoadjuvant chemotherapy	1 (7)
	Adjuvant chemotherapy	2 (13)
	Targeted therapy	0
	Concurrent radiochemotherapy	0
	Radiation therapy	1 (7)
Prior surgery related to current cancer, n (%)		4 (27)

[a]One patient was staged as TxN1Mo.
Abbreviations: ECOG, Eastern Cooperative Oncology Group; ESCC, esophageal squamous cell carcinoma.

Safety and Tolerability

- Treatment with tislelizumab, in combination with chemotherapy, was generally well tolerated in patients with ESCC
- A summary of the safety and tolerability profile of tislelizumab in combination with chemotherapy is provided in Table 2
  - Grade ≥3 chemotherapy-related AEs were reported in seven patients; one patient reported grade ≥3 tislelizumab-related AEs
- A total of four patients discontinued study treatment due to AEs
  - Three patients discontinued due to chemotherapy or tislelizumab-related AEs (grade 2 pneumonitis, grade 3 increase in aspartate aminotransferase, grade 3 lung infection)
  - One patient discontinued due to an AE unrelated to study treatment (grade 3 tracheal fistula)

Table 2: Summary of Adverse Events Reported With Tislelizumab Combined With Chemotherapy in Patients With ESCC

	ESCC Population (N=15)
Patient reporting at least ≥1 treatment-related AE	15 (100)
Grade ≥3 treatment-related AE	7 (47)
Serious AE	5 (33)
Treatment-related serious AE	4 (27)
AE leading to treatment discontinuation	4 (27)
AE leading to death[a]	1 (7)
Treatment-related AE leading to death[a]	1 (7)

[a]One patient experienced grade 5 abnormal hepatic function considered mainly related to progressive disease, and possibly related to chemotherapy, tislelizumab, or underlying type B hepatitis.
Abbreviations: AE, adverse event; ESCC, esophageal squamous cell cancer.

Table 3: Adverse Events Considered Related to Treatment Occurring in >2 Patients With ESCC

	ESCC Population (N=15)					
	Chemotherapy-related		Tislelizumab-related		Any treatment-related[a]	
	All grades	Grades ≥3	All grades	Grades ≥3	All grades	Grades ≥3
Decreased appetite	9 (60)	1 (7)	2 (13)	0	9 (60)	1 (7)
Nausea	8 (53)	0	0	0	8 (53)	0
Anemia	6 (40)	1 (7)	0	0	6 (40)	1 (7)
Decreased white blood cell count	6 (40)	1 (7)	0	0	6 (40)	1 (7)
Decreased neutrophil count	5 (33)	1 (7)	0	0	5 (33)	1 (7)
Vomiting	5 (33)	3 (20)	0	0	5 (33)	3 (20)
Asthenia	4 (27)	1 (7)	2 (13)	0	4 (27)	1 (7)
Hypoalbuminemia	4 (27)	0	0	0	4 (27)	0
Thrombocytopenia	4 (27)	1 (7)	0	0	4 (27)	1 (7)

Data presented as n (%). [a]Adverse events could be considered related to more than one treatment.
Abbreviation: ESCC, esophageal squamous cell cancer.

- Adverse events related to chemotherapy occurred in 14 of the 15 patients with ESCC; AEs considered related to tislelizumab occurred in eight patients
- Adverse events reported in this cohort (Table 3) were consistent with the known tolerability profile of PD-1 inhibitors in combination with chemotherapy
  - Most of the reported AEs were considered related to chemotherapy and were mild-to-moderate in severity
- A total of five patients experienced ≥1 serious AE
  - Tracheal fistula was not considered related to treatment
  - Abnormal hepatic function was considered related to both chemotherapy and tislelizumab
  - Pneumonitis was considered at least possibly related to tislelizumab
  - All other serious AEs were considered related to chemotherapy
- One patient experienced grade 5 abnormal hepatic function, which was considered mainly related to progressive disease
  - The event was considered also possibly related to study treatment or underlying type B hepatitis

CONCLUSIONS

- First-line tislelizumab plus chemotherapy was generally a well-tolerated therapy in patients with ESCC
- Reported AEs were consistent with the known tolerability profile of PD-1 inhibitors in combination with chemotherapy
  - Most AEs were mild or moderate in severity
  - All four AEs leading to study discontinuation were manageable; two were considered related to tislelizumab
- The preliminary safety and tolerability profile from this study support continued development of tislelizumab in patients with ESCC
  - A global, randomized, phase 3 study of tislelizumab compared with chemotherapy as second-line treatment of advanced unresectable/metastatic ESCC is currently enrolling
  - A global, randomized, phase 3 study of tislelizumab in combination with chemotherapy as first-line treatment in patients with unresectable, locally advanced recurrent or metastatic ESCC is currently enrolling

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