TISLELIZUMAB IN COMBINATION WITH CHEMOTHERAPY IN CHINESE PATIENTS WITH ADVANCED GASTRIC OR GASTROESOPHAGEAL JUNCTION CANCER: RESULTS FROM ONE COHORT OF AN ONGOING PHASE 2 STUDY

Yuxian Bai[1], Enxiao Li[2], Buhai Wang[3], Xianglin Yuan[4], Nong Xu[5], Yunxin Chen[6], Xiang Li[6], Huanli Wang[6], Jianming Xu[7]

[1]Harbin Medical University Cancer Hospital, Harbin, China; [2]The First Affiliated Hospital of Xi'an Jiao Tong University, Xi'an, China; [3]Northern Jiangsu People's Hospital, Yangzhou, China; [4]Tongji Hospital, Wuhan, China; [5]The First Affiliated Hospital of Zhejiang University, Hangzhou, China; [6]BeiGene (Beijing) Co., Ltd., Beijing, China; [7]307 Hospital of the Chinese People's Liberation Army, Beijing, China

BOARD E1: Abstract 11

Gastrointestinal Cancers Symposium of the American Society of Clinical Oncology

January 17–19, 2019, San Francisco, CA

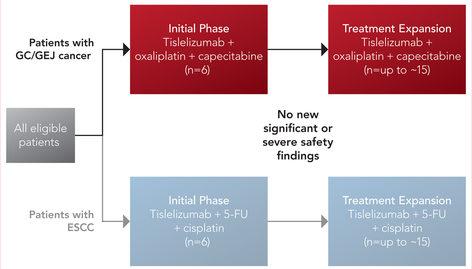
BACKGROUND

- Gastric cancer (GC) is a commonly diagnosed cancer that poses a major clinical challenge due to limited treatment options[1]
- For patients with unresectable, metastatic HER2-negative GC or gastroesophageal junction (GEJ) cancer, the main treatment option is chemotherapy[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, including GC/GEJ cancer
- Programmed death-ligand 1 (PD-L1) expression increases after gastrointestinal cancer cell lines are treated with 5-fluorouracil, suggesting that the PD-1/PD-L1 axis may play a role in resistance to chemotherapy[3]
- Tislelizumab (BGB-A317) is an investigational humanized IgG4 mAb with high affinity and binding specificity against PD-1[4]
- Tislelizumab was specifically engineered to minimize $Fc\gamma R$ binding on macrophages in order to abrogate antibody-dependent phagocytosis[4,5]
- Previous reports from early phase studies suggest tislelizumab was generally well tolerated and had antitumor activity in patients with advanced solid tumors[6,7]

METHODS

- The study design of this two-cohort phase 2 study (NCT03469557) is detailed in Figure 1
- Adult patients with histologically or cytologically confirmed HER2-negative GC/GEJ cancer or esophageal squamous cell carcinoma (ESCC) were eligible for inclusion in the study
  - 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, fluoropyrimidine, or platinum agents
  - Patients were excluded if they had previously received PD-1, PD-L1, or PD-L2 antibody for any indication
  - Patients who had a prior malignancy that was active within the previous 2 years, except for GC, and who had locally recurring cancers that have 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 GC/GEJ cancer were treated with tislelizumab (200 mg IV Q3W) + oxaliplatin (130 mg/m² IV Q3W for up to six cycles) + capecitabine (1000 mg/m² BID, Days 1–14 Q3W)
  - Oxaliplatin was administered for ≤6 cycles; tislelizumab and capecitabine were 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, tolerability, and antitumor activity of tislelizumab in combination with chemotherapy in the cohort of patients with GC/GEJ cancer
  - The safety and tolerability profile for the cohort of patients with ESCC is presented at BOARD E4: Abstract 14

Figure 1: Study Design



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

RESULTS

Patient Disposition

- As of 13 June 2018, 15 patients with GC/GEJ cancer had enrolled in this study
- Most patients were male (73%), had an Eastern Cooperative Oncology Group (ECOG) status of 1 (93%), and had stage IV disease (93%) (Table 1)

Table 1: Demographics and Baseline Disease Characteristics of Patients With GC/GEJ Cancer

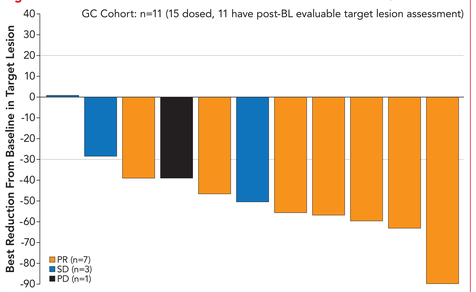
		GC/GEJ Cancer Population (N=15)
Median age, years		59
Sex, n (%)	Male	11 (73)
	Female	4 (27)
ECOG status, n (%)	0	1 (7)
	1	14 (93)
Tumor stage, n (%)	0–II	0
	III	1 (7)
	IV	14 (93)
Median treatment duration, days (min, max)		171 days (21–251)
Prior systemic anticancer therapy regimens, n (%)	Neoadjuvant chemotherapy	0
	Adjuvant chemotherapy	2 (13)
	Targeted therapy	0
	Concurrent radiochemotherapy	0
Prior surgery related to current cancer, n (%)		4 (27)

Abbreviations: ECOG, Eastern Cooperative Oncology Group; GC, gastric cancer; GEJ, gastroesophageal junction.

Preliminary Antitumor Activity

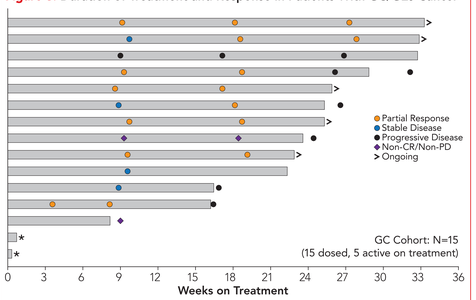
- The median follow-up was 26 weeks (range: 1–38 weeks)
- Eleven of the 15 enrolled patients were evaluable for response (defined as having a measurable baseline tumor assessment and at least one evaluable post-baseline tumor response assessment prior to discontinuation)
  - Unevaluable patients had nontarget lesions at baseline (n=2) or withdrew consent before postbaseline assessment (n=2)
- Among all patients, the confirmed objective response rate was 47% (n=7/15) and the disease control rate was 80% (n=12/15) (Table 2)
  - Seven patients achieved a confirmed partial response (PR), three achieved stable disease (SD), and two with non-target disease only at baseline had non-complete response (CR)/non-progressive disease (PD)
- The antitumor activity of tislelizumab in combination with chemotherapy is presented in Figures 2–3

Figure 2: Maximum Tumor Reduction in Evaluable Patients With GC/GEJ Cancer



Abbreviations: BL, baseline; GC, gastric cancer; GEJ, gastroesophageal junction; PD, progressive disease; PR, partial response; SD, stable disease.

Figure 3: Duration of Treatment and Response in Patients With GC/GEJ Cancer



*Two patients withdrew consent before postbaseline assessment.

Abbreviations: CR, complete response; GC, gastric cancer; GEJ, gastroesophageal junction; PD, progressive disease.

Table 2: Clinical Responses in All Patients With GC/GEJ Cancer

Response Category		GC/GEJ Cancer Population (N=15)
BOR per RESIST 1.1, n (%)	CR	0
	PR	7 (47)
	SD	3 (20)
	Non-CR/Non-PD[a]	2 (13)
	PD	1 (7)
	NE	0
	Missing[b]	2 (13)
ORR, n (%)		7 (47)

[a]Two patients had nontarget lesions at baseline.
[b]Two patients did not have a postbaseline assessment.

Abbreviations: BOR, best overall response; CR, complete response; GC, gastric cancer; GEJ, gastroesophageal junction; NE, not evaluable; ORR, objective response rate; PD, progressive disease; PR, partial response; SD, stable disease.

Table 3: Adverse Events Considered Related to Treatment Occurring in >2 Patients With GC/GEJ Cancer

	GC/GEJ Cancer Population (N=15)					
	Chemotherapy-related		Tislelizumab-related		Any treatment-related[a]	
	All grades	Grades ≥3	All grades	Grades ≥3	All grades	Grades ≥3
Any TRAE	14 (93)	8 (53)	10 (67)	5 (33)	14 (93)	9 (60)
Asthenia	8 (53)	0	4 (27)	0	8 (53)	0
Increased AST	7 (47)	0	3 (20)	1 (7)	7 (47)	1 (7)
Nausea	7 (47)	0	1 (6)	0	7 (47)	0
Increased ALT	6 (40)	0	3 (20)	1 (7)	6 (40)	1 (7)
Vomiting	6 (40)	1 (7)	1 (7)	0	6 (40)	1 (7)
Increased blood bilirubin	5 (33)	1 (7)	0	0	5 (33)	1 (7)
Thrombocytopenia	5 (33)	1 (7)	0	0	5 (33)	1 (7)
Decreased platelet count	5 (33)	0	2 (13)	0	5 (33)	0
Decreased appetite	5 (33)	1 (7)	1 (7)	1 (7)	5 (33)	1 (7)
Anemia	4 (27)	0	0	0	4 (27)	0
Diarrhea	4 (27)	1 (7)	2 (13)	0	4 (27)	1 (7)
Leukopenia	3 (20)	0	0	0	3 (20)	0
Neutropenia	3 (20)	0	0	0	3 (20)	0
Decreased neutrophil count	3 (20)	1 (7)	2 (13)	1 (7)	3 (20)	1 (7)
Decreased white blood cell count	3 (20)	0	2 (13)	0	3 (20)	0
Hypoesthesia	3 (20)	0	0	0	3 (20)	0

Data presented as n (%).
[a]Adverse events could be considered related to more than one treatment.

Abbreviations: AE, adverse event; ALT, alanine aminotransferase; AST, aspartate aminotransferase; GC, gastric cancer; GEJ, gastroesophageal junction; TRAE, treatment-related adverse event.

Safety and Tolerability

- Treatment with tislelizumab, in combination with chemotherapy, was generally well tolerated in patients with GC/GEJ cancer
- Adverse events related to chemotherapy occurred in 14 of the 15 patients with GC/GEJ cancer; AEs considered related to tislelizumab occurred in 10 patients (Table 3)
- Most of the reported AEs were mild to moderate in severity
  - Eight patients reported grade ≥3 chemotherapy-related AEs and five patients reported grade ≥3 tislelizumab-related treatment-related AEs
- Immune-related AEs (hypothyroidism, pneumonitis, rash, elevated ALT and AST) of any grade occurred in three patients; one patient had grade ≥3 immune-related AEs (increased ALT and AST)
- No fatal AEs occurred
- Three patients discontinued treatment due to ascites (n=1), increased ALT/AST (n=1), or increased total bilirubin (n=1)

CONCLUSIONS

- First-line tislelizumab plus chemotherapy was generally well tolerated and antitumor activity was observed in patients with HER2-negative advanced GC/GEJ cancer
- 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
- Among all patients, seven patients achieved a confirmed PR; no patients achieved complete response
  - Three patients achieved a confirmed best overall response of SD
  - Two patients with non-target disease only at baseline had non-CR/non-PD
- The safety, tolerability, and antitumor activity data observed in this study support continued development of tislelizumab in patients with GC/GEJ cancer
  - A global, randomized, phase 3 study comparing tislelizumab in combination with platinum and fluoropyrimidine chemotherapy versus placebo plus platinum and fluoropyrimidine chemotherapy as first-line treatment in patients with locally advanced unresectable or metastatic GC/GEJ cancer is currently enrolling

REFERENCES

1. Van Cutsem E, Sagaert X, Topal B, Haustermans K, Prenen H. Gastric cancer. *Lancet.* 2016;388(10060):2654-2664.
2. Jou E, Rajdev L. Current and emerging therapies in unresectable and recurrent gastric cancer. *World J Gastroenterol.* 2016;22(20):4812–4823.
3. Van Der Kraak L, Goel G, Ramanan K, et al. 5-Fluorouracil upregulates cell surface B7-H1 (PD-L1) expression in gastrointestinal cancers. *J Immunother Cancer.* 2016;4:65.
4. Zhang T, Song X, Xu L, et al. The binding of an anti-PD-1 antibody to FcgammaRIota has a profound impact on its biological functions. *Cancer Immunol Immunother.* 2018;67(7):1079–1090.
5. Dahan R, Sega E, Engelhardt J, Selby M, Korman AJ, Ravetch JV. FcgammaRs modulate the anti-tumor activity of antibodies targeting the PD-1/PD-L1 axis. *Cancer Cell.* 2015;28(4):543.
6. Desai J, Markman B, Sandhu SK, et al. A phase I dose-escalation study of BGB-A317, an anti-programmed death-1 (PD-1) mAb in patients with advanced solid tumors. *J Immunother Cancer.* 2016;4(suppl 1):P154.
7. Desai J, Millward M, Chao Y, et al. Preliminary results from subsets of patients (pts) with advanced gastric cancer (GC) and esophageal carcinoma (EC) in a dose-escalation/expansion study of BGB-A317, an anti-PD-1 monoclonal antibody (mAb). *Ann Oncol.* 2017;28(suppl 5):v122–v141.

ACKNOWLEDGMENTS

The authors wish to acknowledge the investigative center study staff and study patients, as well as recognize those from BeiGene who have substantially contributed to the development of this presentation. BeiGene, Ltd. provided financial support for this presentation, including writing and editorial assistance by Stephan Lindsey, PhD, at SuccinctChoice Medical Communications (Chicago, IL).

Please address any questions or comments regarding this poster to Clinicaltrials@beigene.com