SAFETY AND EFFICACY OF LONG-TERM EXPOSURE (LTE) TO TISLELIZUMAB IN CHINESE PATIENTS WITH ADVANCED SOLID TUMORS

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BACKGROUND

- The programmed cell death protein-1/programmed death-ligand 1 (PD-1/PD-L1) axis plays a central role in suppressing antitumor immunity; dysregulation of the axis can be used by cancer cells to evade the immune system[1]
  - Monoclonal antibodies against PD-1 have demonstrated antitumor activity in a multitude of tumor types,[2] and patients receiving PD-(L)1 therapy for less than 12 months have been associated with higher rates of relapse[3]
- Tislelizumab, an anti-PD-1 antibody, was engineered to minimize binding to FcγR on macrophages to abrogate antibody-dependent phagocytosis, a potential mechanism of T-cell clearance and resistance to anti-PD-1 therapy[4,5]
- Tislelizumab is approved in China for previously treated relapsed/refractory classical Hodgkin lymphoma and locally advanced/metastatic urothelial carcinoma with PD-L1–high expression; supplemental new drug applications were accepted for review of tislelizumab plus chemotherapy as first-line treatment for advanced squamous and nonsquamous non-small cell lung cancer (NSCLC), as well as second-line treatment for hepatocellular carcinoma
- In a global first-in-human (FIH) study, the approved clinical dose of tislelizumab (200 mg every 3 weeks [Q3W]) demonstrated antitumor activity, and adverse events (AEs) were manageable[6]
  - Patients treated with tislelizumab for more than 12 months (median treatment exposure: 21.7 months) reported that AEs were generally of mild or moderate severity[7]
  - Single-agent tislelizumab elicited durable responses in patients with a variety of tumor types, regardless of PD-L1 status
- Data from the current phase 1/2 dose-verification/indication-expansion study conducted in China (BGB-A317-102; NCT04068519)[8] confirmed the recommended dose and clinical outcomes reported in the FIH study
  - Among evaluable patients (n=251), the objective response rate (ORR) was 18% and responses were observed in multiple tumor types regardless of PD-L1 expression
  - Median overall survival (OS) for all patients was 11.5 months (95% CI: 9.1, 15.0) and median progression-free survival was 2.6 months (95% CI: 2.2, 4.0)
- Here, we present the clinical effects and safety of long-term exposure (LTE; >12 months) to tislelizumab in Chinese patients from BGB-A317-102

METHODS

Overall Design and Study Objectives

- A full description of the design, patient population, and treatment administration for this study is presented in the primary publication[8]
- Briefly, adult patients (aged ≥18 years) with histologically or cytologically confirmed advanced/metastatic disease, who had progressed on, or were unable to tolerate, standard antitumor treatment received tislelizumab 200 mg intravenously (IV) Q3W until patients had no evidence of continued clinical benefit, unacceptable toxicity, or withdrawal of consent
  - Enrolled patients had no available standard treatment or refused standard therapy
- Disease assessment by radiographic imaging (enhanced CT or MRI) was performed approximately every 9 weeks during the first 12 months and approximately every 12 weeks thereafter according to Response Evaluation Criteria in Solid Tumors (RECIST) v1.1 criteria
- Adverse events were graded and recorded throughout the study according to National Cancer Institute Common Terminology Criteria for Adverse Events v.4.03
- PD-L1 expressed on tumor cells was centrally assessed using the VENTANA PD-L1 (SP263) assay
  - PD-L1 positivity was defined as ≥10% of tumor cells with PD-L1 membrane staining at any intensity
- This analysis focuses on a subgroup of patients who received tislelizumab for more than 12 months

RESULTS

Demographics and Baseline Disease Characteristics of Patients With LTE to Tislelizumab

- At the data cutoff of 31 May 2020, 300 patients were enrolled; 70 had received tislelizumab for >12 months and were considered patients with LTE to tislelizumab
  - A total of 36 patients (51.4%) remained on treatment; reasons for discontinuation included disease progression (n=22), AE (n=8), protocol deviation (n=1), withdrawal of consent (n=1), or other (n=2)
- In the 70 patients with LTE, the median age was 54 years, 49% had received ≥2 lines of prior systemic therapy, and the most common tumor types were NSCLC (n=16) and nasopharyngeal cancer (NPC; n=8) (Table 1)
  - Median duration of treatment was 25.3 months and 33 patients were treated beyond progression
  - Twenty-six percent of patients had more than ≥10% of their tumor cell (TC) membranes stain for PD-L1 at any intensity

Table 1: Demographics and Baseline Characteristics (ITT Analysis Set)

		Patients With LTE (N=70)
Median age, years (range)		54 (33, 75)
Sex, n (%)	Male	52 (74.3)
	Female	18 (25.7)
ECOG status, n (%)	0	25 (35.7)
	1	45 (64.3)
Tumor type, n (%)	Non-small cell lung cancer	16 (22.9)
	Nasopharyngeal cancer	8 (11.4)
	MSI-H/dMMR	7 (10.0)
	Melanoma	7 (10.0)
	Renal cell carcinoma	7 (10.0)
	Hepatocellular cancer	6 (8.6)
	Urothelial cancer	6 (8.6)
	Gastric cancer	4 (5.7)
	Esophageal squamous cell carcinoma	3 (4.3)
	Other	6 (8.6)
Prior lines of systemic therapies, n (%)[a]	0	5 (7.1)
	1	31 (44.3)
	2	18 (25.7)
	≥3	16 (22.9)
Median time from locally advanced/metastasis to first dose, months (range)[b]		13.6 (0.3, 120.8)
PD-L1 expression, n (%)[c]	PD-L1 ≥10%	18 (25.7)
	PD-L1 <10%	45 (64.3)
	Unknown/missing	7 (10.0)

[a]Prior systemic treatment included neoadjuvant, adjuvant, and palliative therapies.
[b]Time reported represents whichever came first.
[c]PD-L1 expression represents the percent of tumor cells with PD-L1 membrane staining at any intensity.
Abbreviations: dMMR, defective mismatch repair; ECOG, Eastern Cooperative Oncology Group; ITT, intention-to-treat; LTE, long-term exposure; MSI-H, microsatellite instability-high; PD-L1, programmed death-ligand 1.

Antitumor Activity

- For all patients with LTE, the ORR was 55.7%, with a median study follow-up of 29.7 months
- Similar ORR was observed in patients with both PD-L1 TC expression ≥10% and <10% (Table 2)

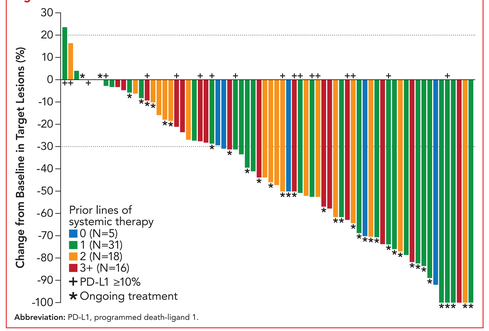
Table 2: Confirmed Best Overall Response by PD-L1 Status (Safety Analysis Set)

		PD-L1 ≥10% (n=18)	PD-L1 <10% (n=45)	PD-L1 Missing (n=7)	Total (N=70)
Best Overall Response, n (%)	Complete response	0 (0.0)	1 (2.2)	0 (0.0)	1 (1.4)
	Partial response	10 (55.6)	23 (51.1)	5 (71.4)	38 (54.3)
	Stable disease	6 (33.3)	19 (42.2)	1 (14.3)	26 (37.1)
	Progressive disease	2 (11.1)	2 (4.4)	1 (14.3)	5 (7.1)
ORR (CR+PR), % (95% CI)		55.6 (30.76, 78.47)	53.3 (37.87, 68.34)	71.4 (29.04, 96.33)	55.7 (43.34, 67.59)
DCR (CR+PR+SD), % (95% CI)		88.9 (65.29, 98.62)	95.6 (84.85, 99.46)	85.7 (42.13, 99.64)	92.9 (84.11, 97.64)
CBR (CR+PR+SD >16 weeks), % (95% CI)		88.9 (65.29, 98.62)	95.6 (84.85, 99.46)	85.7 (42.13, 99.64)	92.9 (84.11, 97.64)

Abbreviations: CBR, clinical benefit rate; CI, confidence interval; CR, complete response; DCR, disease control rate; ORR, objective response rate; PD-L1, programmed death-ligand 1; PR, partial response; SD, stable disease.

- Tumor reductions were reported regardless of PD-L1 expression status or number of prior lines of systemic therapy and 6 patients experienced a 100% reduction in target lesions (Figure 1)

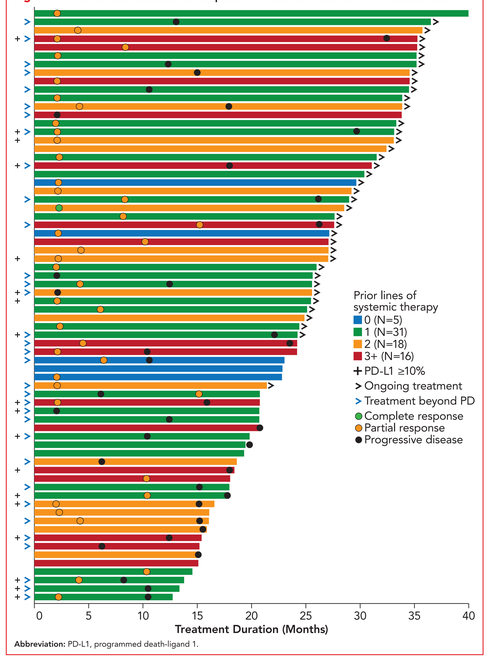
Figure 1: Maximum Tumor Reduction in Patients Treated With Tislelizumab



Abbreviation: PD-L1, programmed death-ligand 1.

- Many patients were receiving ongoing treatment at the time of data cutoff (Figure 2)
- Median duration of response was 30.4 months, with a median follow-up of 26.6 months

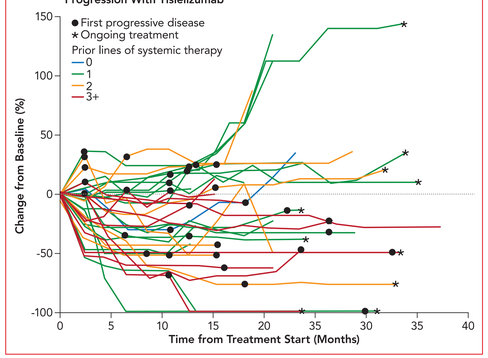
Figure 2: Time to and Duration of Response in Patients Treated With Tislelizumab



Abbreviation: PD-L1, programmed death-ligand 1.

- Continued tumor reduction was observed in patients who were treated beyond progression (Figure 3)
- 4 patients (NPC, n=1; melanoma, n=1, NSCLC, n=2) had an increase of >50% in the sum of target lesion diameters
  - Of the two patients with NSCLC, one is receiving ongoing tislelizumab treatment and the other is alive, but discontinued treatment due to progressive disease
  - The patients with NPC and melanoma died six months after discontinuation of treatment
- With a median follow-up of 32.1 months, median OS was not reached for patients with LTE

Figure 3: Change in Sum of Target Lesion Diameters in Patients Treated Beyond Progression With Tislelizumab



Safety and Tolerability

- Long-term exposure to tislelizumab was generally well tolerated
- Commonly reported treatment-related AEs (TRAEs) included increased alanine aminotransferase (ALT; n=24, 34.3%) and increased aspartate aminotransferase (AST; n=22, 31.4%) (Table 3)
  - Treatment-related AEs across the entire study were mostly of grade ≤2 severity
  - The only grade ≥3 TRAEs occurring in more than 5% of patients were increased ALT (n=4, 5.7%) and increased AST (n=4, 5.7%)
- Three patients (4.3%) had TRAEs leading to treatment discontinuation (interstitial lung disease, pneumonia, and malaise; n=1 each)

Table 3: Treatment-Related Adverse Events in ≥10% of LTE Patients

Preferred Term, n (%)[a]	LTE Patients (N=70) Any Grade	Grade ≥3
Any treatment-related adverse event	65 (92.9)	18 (25.7)
Alanine aminotransferase increased	24 (34.3)	4 (5.7)
Aspartate aminotransferase increased	22 (31.4)	4 (5.7)
Blood bilirubin increased	20 (28.6)	0 (0.0)
Hypothyroidism	15 (21.4)	0 (0.0)
Proteinuria	15 (21.4)	1 (1.4)
Bilirubin conjugated increased	14 (20.0)	0 (0.0)
Blood bilirubin unconjugated increased	14 (20.0)	0 (0.0)
White blood cell count decreased	14 (20.0)	0 (0.0)
Pruritus	11 (15.7)	0 (0.0)
Anemia	9 (12.9)	2 (2.9)
Neutrophil count decreased	8 (11.4)	0 (0.0)
Diarrhea	8 (11.4)	0 (0.0)
Gamma-glutamyltransferase increased	7 (10.0)	2 (2.9)
Malaise	7 (10.0)	0 (0.0)

[a]Patients may have had more than one treatment-related adverse event.
Abbreviation: LTE, long-term exposure.

CONCLUSIONS

- Tislelizumab remained generally well tolerated
  - Adverse events reported across these cohorts were generally of mild or moderate severity and were consistent with prior reports for tislelizumab monotherapy
- Patients treated beyond progression demonstrated long treatment duration and tumor reductions were observed in patients treated beyond progression
- Based on these data, tislelizumab is being investigated in multiple ongoing pivotal clinical trials

- Immune-mediated AEs were reported in 26 patients (37%); and the incidence of grade ≥3 immune-mediated AEs was low (Table 4)
- No patients with LTE reported a TRAE or immune-mediated TRAE leading to death

Table 4: Immune-mediated Adverse Events in LTE Patients

Category, n (%)[a]	LTE Patients (N=70) Any Grade	Grade ≥3
Any immune-mediated adverse event	26 (37.1)	6 (8.6)
Hypothyroidism	14 (20.0)	0 (0.0)
Pneumonitis	6 (8.6)	3 (4.3)
Skin adverse reaction	4 (5.7)	1 (1.4)
Hyperthyroidism	3 (4.3)	0 (0.0)
Hepatitis	2 (2.9)	2 (2.9)
Adrenal insufficiency	1 (1.4)	0 (0.0)
Thyroiditis	1 (1.4)	0 (0.0)

[a]Patients may have had more than one immune-mediated adverse event.
Abbreviation: LTE, long-term exposure.

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CONFLICTS OF INTEREST

JG reports grants from Betta Pharmaceuticals Co., Ltd., during the conduct of the study; serves as a member on the advisory board of MSD, Roche, Pfizer, Bayer, Novartis, Simcere, Shanghai Junshi Biosciences, and Oriengene. **QZ** declares an honorarium from AstraZeneca and Roche. **YG**, **SY**, **YL**, and **JZ** are employees of BeiGene who hold stock options. **All remaining authors** had nothing to disclose.

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