LONG-TERM EXPOSURE TO TISLELIZUMAB, AN INVESTIGATIONAL ANTI-PD-1 ANTIBODY, IN A FIRST-IN-HUMAN PHASE 1 STUDY

Jayesh Desai[1], Benjamin Markman[2], Michael Friedlander[3], Hui Gan[4], Lisa Horvath[5], Amanda Townsend[6], Michael Millward[7], Michael Jameson[8], Chia-Jui Yen[9], Ming-Mo Hou[10], Jeannie Hou[11], John Wu[11], Liang Liang[12], Sanjeev Deva[13]

[1]Peter MacCallum Cancer Centre and Royal Melbourne Hospital, Parkville, Australia; [2]Monash Health and Monash University, Melbourne, Australia; [3]Prince of Wales Hospital, Randwick, Australia; [4]Austin Hospital, Heidelberg, Australia; [5]Chris O'Brien Lifehouse, Camperdown, Australia; [6]The Queen Elizabeth Hospital, Woodville South, Australia; [7]Linear Clinical Research, Nedlands, Australia; [8]Regional Cancer Centre, Waikato Hospital, and the University of Auckland Waikato Clinical Campus, Hamilton, New Zealand; [9]National Cheng Kung University Hospital, Tainan City, Taiwan; [10]ChangGung Memorial Hospital, Linkou, Taiwan; [11]BeiGene USA, Inc., San Mateo, CA; [12]BeiGene (Beijing) Co., Ltd., Beijing, China; [13]Auckland City Hospital, Auckland, New Zealand

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BACKGROUND

- The programmed cell death-1 (PD-1)/programmed cell death ligand-1 (PD-L1) axis plays a central role in suppressing antitumor immunity; dysregulation of the PD-1/PD-L1 axis can be used by cancer cells to evade the immune system[1,2]
- Antibodies against PD-1 can block the binding of PD-L1 to PD-1, which then allows activated T cells to induce tumor cells to undergo programmed cell death[2,3]
- Monoclonal antibodies (mAb) against PD-1 have demonstrated antitumor activity in a multitude of tumor types[4] and patients receiving PD-(L)1 therapy for less than 12 months have been associated with higher rates of relapse[5]
- A long-term safety analysis of patients treated with the PD-1 inhibitor nivolumab reported no cumulative toxicities with prolonged exposure and that most adverse events (AEs) occurred within the first 6 months of therapy[6]
- Tislelizumab (BGB-A317) is an investigational 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 resistance to anti-PD-1 therapy[1,7]
- Previous reports from this first-in-human study (FIH; NCT02407990)[8–10] indicated that tislelizumab was generally well tolerated and had antitumor activity in patients with advanced solid tumors
- Here we report the clinical effects of long-term exposure (LTE; >12 months) to tislelizumab in a subset of patients enrolled in the FIH study

METHODS

Overall Design and Study Objectives

- This FIH study was a dose-escalation/indication-expansion study of tislelizumab in patients with advanced tumors
  - In phase 1A, 10 mg/kg IV Q2W was the maximum administered dose; maximum tolerated dose was not reached
  - All patients in phase 1B received tislelizumab as a 5 mg/kg IV infusion Q3W
  - Radiographic assessment was performed approximately every 9 weeks
- PD-L1 expression was retrospectively assessed with the VENTANA PD-L1 (SP263) assay
  - Tumors were considered PD-L1-positive (PD-L1+) if there was ≥1% expression on tumor cells
- Response rates were defined as follows: objective response rate (ORR) = complete response (CR) + partial response (PR); disease control rate (DCR) = CR + PR + stable disease (SD); clinical benefit rate (CBR) = CR + PR + SD with a duration of ≥24 weeks
- Safety and tolerability were assessed by monitoring AEs (NCI-CTCAE v4.03 grade and severity) and by evaluating results from physical examinations, ophthalmologic examinations, electrocardiograms, and laboratory investigations

Patient Population

- Adult patients (aged ≥18 years) with histologically/cytologically confirmed advanced or metastatic solid tumors who have at least one measurable lesion, have not received prior anti-PD-1 or PD-L1 treatment, and an Eastern Cooperative Oncology Group (ECOG) performance status of ≤1 were enrolled; patients were excluded if they had a history of severe hypersensitivity reactions to other mAbs or if they had a prior malignancy active within the previous 2 years
- This analysis focuses on a subgroup of patients who received tislelizumab for >12 months

Table 1: Demographics and Baseline Disease Characteristics

		Patients With LTE (N=65)
Median age, years (range)		64 (24–81)
Sex, n (%)	Male	39 (60)
	Female	26 (40)
ECOG status, n (%)	0	32 (49)
	1	33 (51)
Tumor type (occurring in ≥2 patients), n (%)	NSCLC	9 (14)
	HCC	8 (12)
	Ovarian cancer	5 (8)
	Bladder cancer	5 (8)
	Colorectal cancer*	4 (6)
	Gastric cancer	4 (6)
	Head and neck squamous cell carcinoma	4 (6)
	Renal cell carcinoma	4 (6)
	Merkel cell carcinoma	4 (6)
	Esophageal carcinoma	3 (5)
	Endometrial cancer	3 (5)
	Cutaneous squamous cell carcinoma	2 (3)
	Sarcoma	2 (3)
Prior systemic anticancer therapy regimens, n (%)	Neoadjuvant	3 (5)
	Adjuvant	20 (31)
	Metastatic	20 (31)
	Locally advanced	5 (8)
	Palliative	26 (40)
Median duration of prior treatment, months (range)		21.7 (12.0–36.9)
Prior anticancer radiotherapy		33 (51)
Prior surgery related to current cancer		49 (75)

*Two patients were microsatellite instability-high (MSI-H) and mismatch repair deficient (dMMR), one patients was MSI-H only, and one patient was dMMR only.
Abbreviations: ECOG, Eastern Cooperative Oncology Group; HCC, hepatocellular cancer; LTE, long-term exposure; NSCLC, non-small cell lung cancer.

RESULTS

Patient Demographics and Baseline Disease Characteristics

- As of 27 October 2018, 65 of the 451 enrolled patients received tislelizumab for >12 months and were included in the LTE group
- Twenty-five patients with LTE were enrolled as part of phase 1A:
  - Two patients received 2 mg/kg Q2W and nine received 2 mg/kg Q3W
  - Five received 5 mg/kg Q2W and six received 5 mg/kg Q3W
  - Three received 200 mg Q3W
- The remaining 40 patients were part of phase 1B and received 5 mg/kg Q3W
- In the 65 patients in the LTE cohort, the median age was 64 years, 51% had received prior anticancer radiotherapy, and 75% had prior anticancer surgery (Table 1)

Antitumor Activity

- In the LTE cohort, the ORR was 68% with a median follow-up of 27.2 months
- Four LTE patients achieved CR (Table 2)
  - These included cutaneous squamous cell carcinoma, and endometrial, bladder, and esophageal cancers (n=1 each)
  - All four patients were PD-L1+
- Partial responses and SD were observed in both PD-L1+ and PD-L1-negative tumors (Table 2 and Figure 2)
- A 61-year-old female with PD-L1+ cervical cancer, previously treated with cisplatin and radiation, had pseudo-progression during Cycle 4 (Figure 3)
- In patients with objective responses, the median duration of CR/PR was 21.1 months in those with LTE (n=44) and 6.3 months in those who responded but did not remain on treatment for >12 months (n=16)

Figure 1: Maximum Tumor Reduction in Patients Treated With Tislelizumab

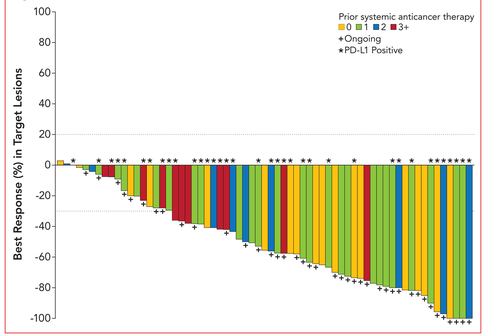

Figure 2: Time to and Duration of Response in Patients Treated With Tislelizumab

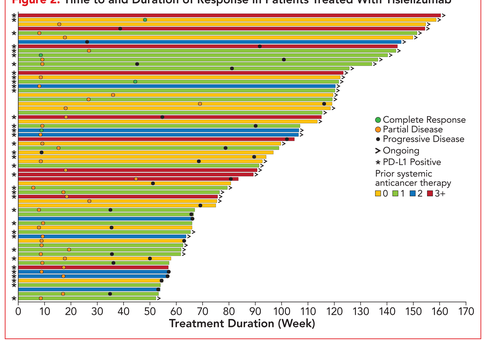

Figure 3: Radiographic Images of a Patient With PD-L1+ Cervical Cancer Who Had Pseudo-Progression With Long-Term Exposure to Tislelizumab

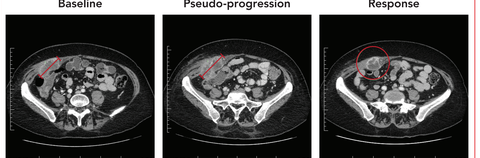

Table 2: Confirmed Best Overall Response by PD-L1 Status (Safety Analysis Set)

		PD-L1 Positive (n=36)	PD-L1 Negative (n=23)	Missing (n=6)	Total (N=65)
Best overall response per RECIST v1.1 (confirmed), n (%)	CR	4	0	0	4 (6)
	PR	22	14	4	40 (62)
	SD	9	9	2	20 (31)
	PD	1	0	0	1 (2)
ORR, % (95% CI)		72 (54.8, 85.8)	61 (38.5, 80.3)	67 (22.3, 95.7)	68 (55.0, 78.8)

Abbreviations: CI, confidence interval; CR, complete response; ORR, objective response rate; PD, progressive disease; PD-L1, programmed cell death ligand-1; PR, partial response; SD stable disease.

Safety and Tolerability

- Long-term exposure to tislelizumab was generally well tolerated
- As of 27 October 2018, 52 of the 65 patients with LTE (80%) experienced ≥1 treatment-related AE (TRAE), most of which were mild to moderate in severity (Table 3)
- Rash was the only TRAE reported in ≥15% of patients; no rash event was grade ≥3
  - The only grade ≥3 TRAEs reported with tislelizumab LTE were arthritis, diarrhea, fatigue, granuloma, hyperglycemia, increased alanine aminotransferase, rash papular, and lichenoid keratosis (n=1 each)
- Serious TRAEs occurred in 3 patients (pyrexia, n=2 and arthritis, n=1); all serious TRAEs resolved
- In patients in the LTE cohort, three patients experienced AEs that eventually led to discontinuation
  - After approximately 23 months, one patient developed grade 3 arthritis
  - After approximately 14 months, one patient developed grade 2 non-serious pneumonitis
  - After approximately one year, one patient experienced grade 2 dyspnea
- No fatal AEs occurred

Table 3: Treatment-Related Adverse Events in ≥5% of LTE Patients

	LTE Patients (N=65)	
	Any Grade	Grade ≥3
Any TRAE*	52 (80)	7 (11)
Rash	15 (23)	0
Hypothyroidism	10 (15)	0
Diarrhea	9 (14)	1 (2)
Rash, maculopapular	9 (14)	0
Fatigue	9 (14)	1 (2)
Pruritus	7 (11)	0
Infusion-related reaction	6 (9)	0
Nausea	5 (8)	0
Generalized pruritus	5 (8)	0
Dry eye	5 (8)	0
Hyperthyroidism	4 (6)	0
Dry mouth	4 (6)	0
Peripheral edema	4 (6)	0
Arthralgia	4 (6)	0
Alopecia	4 (6)	0
Dry skin	4 (6)	0

*Patients may have had more than one TRAE.
Abbreviations: LTE, long-term exposure; TRAE, treatment-related adverse event.

CONCLUSIONS

- Treatment with tislelizumab remained generally well tolerated when given for >12 months
  - Adverse events reported across these cohorts were generally of mild or moderate severity and were consistent with prior reports for tislelizumab monotherapy
- Single-agent tislelizumab elicited durable responses in patients with a variety of tumor types, regardless of PD-L1 status
- Tislelizumab, as monotherapy and in combination, is being further evaluated in multiple tumor types in phase 2 and phase 3 clinical studies
  - Phase 2: Esophageal, gastric, or gastroesophageal junction (GEJ) carcinoma (NCT03469557); HCC (NCT03419897); NSCLC/small cell lung cancer (NCT03432598); bladder cancer (CTR20170071)
  - Phase 3: Esophageal squamous cell carcinoma (NCT03430843); HCC (NCT03412773); NSCLC (NCT03358875, NCT03594747, NCT03663205); esophageal squamous cell carcinoma (NCT03783442); gastric or GEJ carcinoma (NCT03777657)

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