Tislelizumab (BGB-A317) for Relapsed/Refractory Classical Hodgkin Lymphoma: Preliminary Efficacy and Safety Results from a Phase 2 Study

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Background: Tislelizumab is a humanized IgG4 monoclonal antibody with high affinity/specificity for programmed cell death protein 1 (PD-1). Tislelizumab was specifically engineered to minimize binding to FcγR on macrophages, thereby abrogating antibody-dependent phagocytosis, a potential mechanism of T-cell clearance and resistance to anti-PD-1 therapy (Dahan 2015). Results of tumor growth inhibition studies suggest that tislelizumab had superior antitumor activity compared with nivolumab in xenograft mice transplanted with human cancer cells and peripheral blood mononuclear cells. Favorable results with other PD-1 inhibitors in patients with relapsed or refractory (R/R) classical HL (cHL) provide a strong rationale to investigate tislelizumab in this disease.

Methods: BGB-A317-203 (clinicaltrials.gov NCT03209973) is a single-arm, open-label, multicenter, phase 2 study of tislelizumab in Chinese patients with R/R cHL; all patients received tislelizumab 200 mg intravenously every 3 weeks until progression or unacceptable toxicity. Patients were eligible if they (a) failed to achieve a response or progressed after autologous stem cell transplant (ASCT) or (b) received ≥2 prior systemic chemotherapy regimens for cHL and were ineligible for ASCT. Diagnosis of cHL was confirmed in all patients by central pathologic review. The primary endpoint was overall response rate (ORR) determined using the Lugano criteria (Cheson, 2014) as assessed by an independent review committee (IRC). Key secondary

endpoints included progression-free survival (PFS), duration of response, rate of complete response (CR), time to response, safety, and tolerability. Treatment emergent adverse events (TEAEs) were summarized according to NCI-CTCAE v4.03.

Results: In total, 70 patients were enrolled from 11 Chinese centers; patient characteristics are shown in the Table. With a data cutoff date of 25 May 2018, the median follow-up was 7.9 months (range, 3.4 to 12.7). The IRC-assessed ORR was 85.7%, based on PET-CT scans. A total of 43 patients (61.4%) achieved CR, 38 of whom were in CR at the first on-study response assessment. At data cutoff, 53 patients remained on treatment and 17 had discontinued (11 for progressive disease [PD]; 4 for TEAEs; 1 withdrew consent; 1 due to pregnancy). The estimated 6-month PFS rate was 80%. The most frequently reported (≥15%) TEAEs due to any cause were pyrexia (52.9%), hypothyroidism (30.0%), increased weight (28.6%), upper respiratory tract infection (27.1%) and cough (17.1%). Grade ≥3 TEAEs reported in ≥2 patients were upper respiratory tract infection (2.9%) and pneumonitis (2.9%). Immune-related TEAEs were reported in 23 patients (32.9%); Grade ≥3 in 5 patients (7.1%): pneumonitis (n=2), organizing pneumonia, nephritis (focal segmental glomerulosclerosis) and increased creatine phosphokinase (each n=1). There were no Grade 5 TEAEs. TEAEs that led to treatment discontinuation in 4 patients (5.7%) included pneumonitis (n=2), organizing pneumonia (n=1), and focal segmental glomerulosclerosis (n=1). One patient died on study due to PD.

Conclusions: In this study, tislelizumab therapy was shown to be highly active resulting in a high CR rate in patients with R/R cHL who had failed or were ineligible for ASCT. Tislelizumab was generally well-tolerated in Chinese patients with R/R cHL. The safety profile was generally consistent with that of other PD-1 inhibitors for the treatment of cHL.

Table. Patient Demographics and Baseline Characteristics

	N = 70
Median age, y	32.5
<65 y, n (%)	66 (94.3)
≥65 and <75 y, n (%)	4 (5.7)
Sex, n (%)	
Female	30 (42.9)
Male	40 (57.1)
Median time from initial cHL diagnosis to study entry, mo	25.3
Stage IV disease, n (%)	42 (60.0)
Bulky disease[a], n (%)	8 (11.4)
Bone marrow involvement, n (%)	22 (31.4)
B-symptom(s), n (%)	26 (37.1)
Patients with any prior radiation therapy, n (%)	21 (30.0)
Ineligible for prior ASCT[b], n (%)	57 (81.4)
Failure to achieve an objective response to salvage chemotherapy	53 (75.7)
Inadequate stem cell collection or unable to collect stem cells	2 (2.9)
Co-morbidities	2 (2.9)
Type of prior systemic therapy, n (%)	
Chemotherapy	70 (100.0)
ASCT	13 (18.6)
Immunotherapy[c]	15 (21.4)
Median lines of prior therapy (range)	3 (2-11)

[a]Bulky disease defined as mediastinal mass ratio of 0.33 or size of any single node/nodal mass ≥ 10 cm in diameter.
[b]All received ≥2 prior regimens.
[c]Immunotherapy included brentuximab-vedotin, rituximab, cytokine-induced killer cell transfusion, thalidomide, or lenalidomide.