TISLELIZUMAB (BGB-A317) FOR RELAPSED/REFRACTORY EXTRANODAL NK/T-CELL LYMPHOMA: PRELIMINARY EFFICACY AND SAFETY RESULTS FROM A PHASE 2 STUDY

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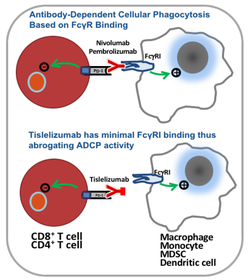
INTRODUCTION

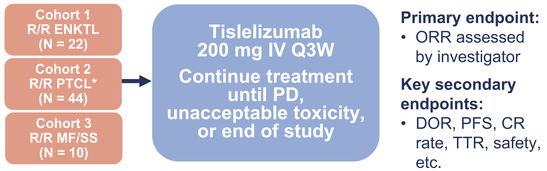
- Patients with relapsed/refractory (R/R) extra nodal natural killer (NK)/T-cell lymphoma (ENKTL) have a poor prognosis after failure of an L-asparaginase (LASP)–based regimen.
- ENKTL cells are invariably infected by Epstein-Barr virus, which upregulates programmed death ligand 1 (PD-L1) expression on lymphoma cells. The PD-L1/PD-1 axis is therefore a potential target for NK/T-cell lymphomas. Some PD-1 inhibitors, such as nivolumab and pembrolizumab, have shown clinical antitumor activity.
- Binding to FcγR on macrophages compromises antitumor activity of PD-1 antibodies through activation of antibody-dependent macrophage-mediated killing of T effector cells.[1,2]
- Tislelizumab is a humanized IgG4 investigational anti– PD-1 mAb specifically designed to minimize binding to FcγR on macrophages.
- Presented here are the results of a phase 2 trial of tislelizumab in patients with R/R ENKTL (Cohort 1).



mAb, monoclonal antibody; FcγR, Fc region of IgG receptors; IgG, immunoglobulin; PD-1, programmed cell death-1.

METHOD(S)

Figure 1. Global Phase 2, Multicenter, Open-Label, Single-Arm Trial



Primary endpoint:
- ORR assessed by investigator

Key secondary endpoints:
- DOR, PFS, CR rate, TTR, safety, etc.

Patients with R/R ENKTL:
- Previously received 1 or more appropriate systemic therapies (eg, non-anthracycline-based regimens such as L-asparaginase–based therapy). Radiation therapy alone would not be acceptable as previous therapy.

Response assessments:
- Responses for cohorts 1 and 2 were assessed by investigator using PET-based imaging according to the Lugano classification.[3]

*Cohort 2 enrolled PTCL-NOS, ALCL, and AITL. The result could be referred to Abstract EP1235. Data of cohort 3 is not mature due to the relatively short follow-up time.

CR, complete response; DOR, duration of response; ORR, overall response rate; PD, progressive disease; PFS, progression-free survival; R/R, relapsed/refractory; TTR, time to response.

RESULT(S)

Table 1. Patient Disposition and Reasons for Treatment Discontinuation

	Total (N = 22)
Number of patients enrolled	22
Number of patients treated[a] (%)	22 (100)
Patients discontinued from treatment[b], n (%)	16 (72.7)
Reason for discontinuation[b], n (%)	
Progressive disease	12 (54.5)
Adverse event	3 (13.6)
Withdrawal by subject	1 (4.5)
Other	0 (0)
Patients remained on treatment[b], n (%)	6 (27.3)

[a]Percentages are based on number of patients enrolled.
[b]Percentages are based on number of patients received treatment.

Table 2. Patient and Disease Characteristics

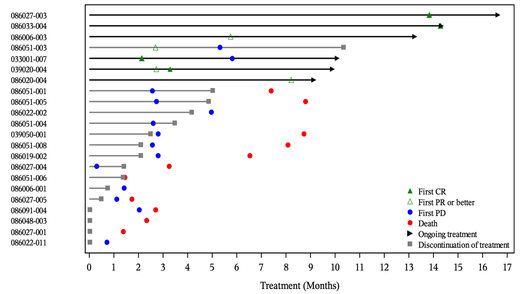
	Total (N = 22)
Median age, years (range)	47.5 (24-76)
Age group ＞60 years, n (%)	9 (45)
Gender, male/female, n (%)	14 (63.6)/ 8 (36.4)
Race, n (%)	
Asian	19 (86.4)
White	2 (9.1)
Not reported	1 (4.5)
ECOG , n (%)	
0-1	20 (90.9)
2	2 (9.1)
Median time from initial diagnosis to study entry, months (range)	16.8 (5.5-95.0)
Stage IV at study entry, n (%)	12 (54.5)
EBER positive, n (%)	22 (100)
Prior lines of regimens, median (range)	2 (1-5)
Type of prior therapy, n (%)	
L-asparagine (LASP)	8 (36.4)
Radiotherapy	16 (72.7)
Allo-SCT	1 (4.5)

Table 3. Efficacy: Best Overall Response by Investigator

Best Overall Response[a], n (%)	N = 22
ORR (CR+PR), n (%) [95% CI][b]	7 (31.8) [13.9, 54.9]
Complete response	4 (18.2)
Partial response	3 (13.6)
Stable disease	1 (4.5)
Progressive disease	11 (50.0)
Discontinued prior to first assessment[c]	3 (13.6)

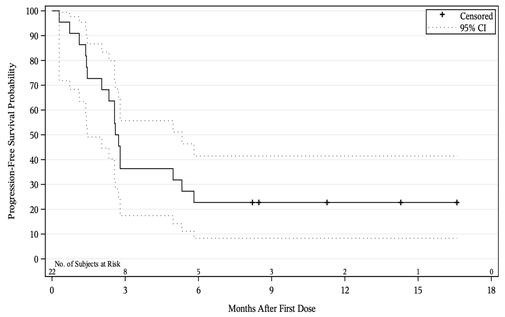
[a] Response criteria: Lugano 2014.
[b] 1-sided Clopper-Pearson 95% CI.
[c] Two subjects discontinued study before first tumor assessment timepoint due to 'death of unknown reason' One subject discontinued study due to tumor compression (grade 5).

Figure 2. Duration of Treatment and Time to Response



- The median DOR has not been reached.
- Median TTR was 5.75 months (range, 2.14-14.29)

Figure 3. Kaplan-Meier Plot of Progression-Free Survival: Investigator



- Median PFS was 2.7 months (95% CI, 1.45, 5.32).
- Median PFS follow-up duration was 11.3 months.

Table 4. Summary of Treatment-Emergent Adverse Events (TEAEs)

Event, n (%)	N = 22
Grade ≥3 TEAEs	11 (50)
Serious TEAEs	8[a] (36.4)
TEAEs leading to treatment discontinuation	1[b] (4.5)
TEAEs leading to death	1 (4.5)
Immune-related (ir) TEAEs (by aggregate category)	7 (31.8)
≥1 irTEAE[c]	3 (13.6)
Skin adverse reactions	1 (4.5)
Investigations (blood thyroid-stimulating hormone decreased)	1 (4.5)
Eye disorders (retinopathy)	1 (4.5)
Musculoskeletal and connective tissue disorders (arthralgia)	1 (4.5)
Gastrointestinal disorders (abdominal pain)	
Infections and infestations (upper respiratory tract infection)	

[a] SAEs in 4 patients determined to be possibly related to tislelizumab.
[b] Grade 5, respiratory failure (n = 1); not related to tislelizumab as assessed by investigator

[c] Only one Grade 3 irTEAE 'upper respiratory tract infection', others are Grade 1-2

CONCLUSION(S)

- Tislelizumab is an investigational anti–PD-1 mAb specifically designed to minimize binding to FcγR on macrophages.
- Tislelizumab had modest antitumor activity in patients with R/R ENKTL and tolerable toxicity. Although several patients achieved CR, the PFS is short.
- Future studies in such aggressive diseases should include consideration for combination regimens and biomarker strategy.

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