ZANUBRUTINIB (BGB-3111) IN COMBINATION WITH RITUXIMAB IN PATIENTS WITH RELAPSED/REFRACTORY NON-HODGKIN LYMPHOMA

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Background: Bruton tyrosine kinase inhibitors (BTKi) have therapeutic activity in mantle cell lymphoma, chronic lymphocytic leukemia, and Waldenström macroglobulinemia and antitumor activity in follicular lymphoma (FL) and diffuse large B-cell lymphoma (DLBCL). Rituximab is an anti-CD20 monoclonal antibody widely approved for CD20+ non-Hodgkin lymphomas (NHL). Zanubrutinib, a potent and selective BTKi, has good combined activity with rituximab in preclinical studies, with reduced interference of anti-CD20–induced antibody-dependent cellular cytotoxicity.

Aims: This study is evaluating the efficacy, safety, and tolerability of zanubrutinib with rituximab in patients with relapsed/refractory (R/R) NHL.

Methods: In this ongoing, single-arm, multicenter phase 2 study (NCT03520920), patients received continuous zanubrutinib 160 mg twice a day orally with 375 mg/m$_2$ IV rituximab on days 1, 8, 15, and 22 of cycle 1 and on day 1 of cycles 4, 6, 8, and 10 until disease progression or unacceptable toxicity. Patients with R/R non-germinal center B-cell–like (non-GCB) DLBCL had prior standard anthracycline ± rituximab-based treatment; patients with FL or marginal zone lymphoma (MZL) had ≥1 prior therapy. All patients had ≥1 measurable lesion at baseline imaging assessment. The primary endpoint is investigator-assessed overall response rate (ORR) using the Lugano classification (Cheson, 2014). Secondary endpoints include duration of response (DOR), complete response (CR) rate, progression-free survival (PFS), overall survival (OS), safety, and tolerability.

Results: Four sites in China enrolled and treated 41 patients, including 20 non-GCB DLBCL, 16 FL, and 5 MZL. The median study follow-up was 10.28 months (range, 0.8-19.8 months) at the data cutoff date (Aug. 31, 2019). In total, 27 patients (65.9%) discontinued treatment (18 for progressive disease [PD]; 7 for adverse events; 2 for patient withdrawal). The ORR was 35%, 56.3%, and 60% in the non-GCB DLBCL, FL, and MZL cohorts, respectively. One (5%) non-GCB DLBCL patient, 3 (18.8%) FL patients, and 1 (20%) MZL patient achieved CR. In the non-GCB cohort, the median DOR was 8.79 months (95% CI: 0.72, 14.78), and the median PFS was 3.38 months. The median DOR and median PFS were not reached in the FL and MZL cohorts. The estimated 12-month PFS event-free rates were 17.4%, 66%, and 75% for the non-GCB DLBCL, FL, and MZL cohorts, respectively.
The most frequently reported treatment-emergent adverse events (TEAEs) were neutrophil count decrease (24.4%), white blood cell count decrease (22%), and upper abdominal pain, alanine aminotransferase increase, anemia, pyrexia, and upper respiratory tract infection (6 [14.6%] patients each). Grade ≥3 TEAEs in ≥2 patients were neutrophil count decrease (14.6%), white blood cell count decrease (9.8%), and anemia, dyspnea, hypokalemia, lung infection, and platelet count decrease (2 [4.9%] patients each). Infection and hemorrhage occurred in 34.1% and 26.8% of patients, respectively. Grade ≥3 infection was reported in 9.8% of patients, and no grade ≥3 bleeding events were reported. Three fatal TEAEs were reported in the non-GCB DLBCL cohort (dyspnea, death in setting of PD, and suicide) but none in the FL or MZL cohorts. TEAEs led to treatment discontinuation in 5 DLBCL and 2 FL patients.
Image/Pictures:

	Non-GCB DLBCL (n = 20)	FL (n = 16)	MZL (n = 5)
Demographics and other baseline characteristics			
Male, n (%)	13 (65.0)	8 (50.0)	2 (40.0)
Age ≥65 years, n (%)	6 (30.0)	1 (6.3)	2 (40.0)
ECOG PS of 1-2, n (%)	7 (35.0)	5 (31.3)	2 (40.0)
Median time since initial diagnosis to first dose (months, range)	10.15 (2.1-54.0)	17.91 (2.4-139.6)	50.96 (6.0-106.2)
Intermediate- or high-risk disease, n (%)[a]	15 (75.0)	13 (81.3)	3 (60.0)
Stage III/IV at study entry, n (%)	14 (70.0)	11 (68.8)	3 (60.0)
Received ≥2 prior lines of therapy, n(%)	12 (60.0)	9 (56.3)	2 (40.0)
BOR rate, n (%)			
CR	1 (5.0)	3 (18.8)	1 (20.0)
PR	6 (30.0)	6 (37.5)	2 (40.0)
SD	4 (20.0)	5 (31.3)	2 (40.0)
PD	6 (30.0)	0 (0.0)	0 (0.0)
Discontinued prior to first assessment, n (%)	3 (15.0)	2 (12.5)	0 (0.0)
ORR, n (%) (95% CI)[b]	7 (35.0) (15.4, 59.2)	9 (56.3) (29.9, 80.2)	3 (60.0) (14.7, 94.7)
Safety, n (%)			
Any TEAE	20 (100.0)	15 (93.8)	5 (100.0)
Serious TEAE	7 (35.0)	1 (6.3)	0 (0.0)
TEAE leading to treatment discontinuation	5 (25.0)	2 (12.5)	0 (0.0)
TEAE leading to death	3 (15.0)	0 (0.0)	0 (0.0)

Abbreviations: BOR, best overall response; CI, confidence interval; CR, complete response; ECOG PS, Eastern Cooperative Oncology Group performance status; FL, follicular lymphoma; FLIPI, Follicular Lymphoma International Prognostic Index; GCB DLBCL, germinal center B-cell–like diffuse large B-cell lymphoma; IPI, International Prognostic Index; MZL, marginal zone lymphoma; ORR, overall response rate; PD, progressive disease; PR, partial response; SD, stable disease; TEAE, treatment emergent adverse event.

[a]IPI score applied for non-GCB DLBCL and MZL cohort, and FLIPI score applied for FL cohort.

[b]CI was calculated using the Clopper-Pearson method.

Summary/Conclusion: This study provided preliminary results for activity of zanubrutinib in combination with rituximab in patients with R/R non-GCB DLBCL, FL, and MZL. Further investigation of zanubrutinib combined with anti-CD20 antibodies in B-cell lymphoma is ongoing.