Zanubrutinib (BGB-3111) in Combination With Rituximab in Patients With Relapsed/Refractory Non-Hodgkin Lymphoma

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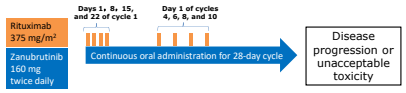
INTRODUCTION

- Bruton's 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).[1]
- Zanubrutinib, a potent and selective BTKi, showed minimized off-target activities against interleukin-2-inducible T cell kinase (ITK) and reduced interference of ITK-mediated, rituximab-induced, antibody-dependent cellular cytotoxicity.[2]
- This study is evaluating the efficacy, safety, and tolerability of zanubrutinib with rituximab in patients with relapsed/refractory (R/R) non-Hodgkin lymphoma (NHL).

METHODS

- Ongoing single-arm, multicenter, phase 2 study (NCT03520920) of zanubrutinib + rituximab in patients with R/R non-germinal center B-cell-like (non-GCB) DLBCL, FL, and marginal zone lymphoma (MZL).

Figure 1. Study design and treatment



Eligibility:

•R/R non-GCB DLBCL patients previously received standard anthracycline ± rituximab-based treatment; R/R FL or MZL patients received 1 or more prior therapy.
•With at least 1 measurable lesion
•Excluded known CNS lymphoma involved

Endpoints:

- Primary: Overall response rate (ORR) determined by investigator according to Lugano classification 2014
- Secondary: Duration of response (DOR), complete response (CR) rate, progression-free survival (PFS), overall survival (OS), safety, and tolerability

RESULTS

- With a median follow-up of 10.28 months (range, 0.8-19.8 months), 34.1% of patients continued treatment as of cutoff date (August 31, 2019).

Figure 2. Patient disposition and reason for discontinuation

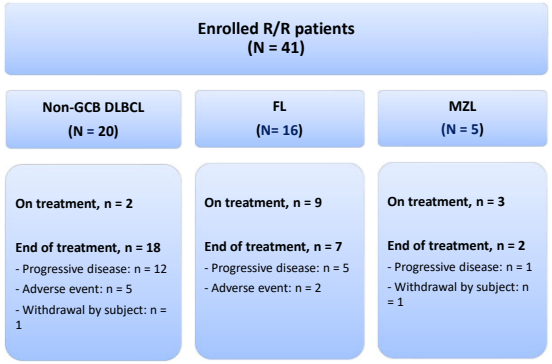


Table 1. Patient and Disease Characteristics

	Non-GCB DLBCL (N = 20)	FL (N = 16)	MZL (N = 5)
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 0-1, n (%)	18 (90.0)	15 (93.8)	5 (100.0)
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 to high risk, 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)
Median number of prior lines of therapy (range)	2 (1-5)	2 (1-7)	1 (1-4)

Abbreviation: ECOG PS, Eastern Cooperative Oncology Group performance status
[a]IPI score applied for non-GCB DLBCL and MZL cohort, and FLIPI score applied for FL cohort.

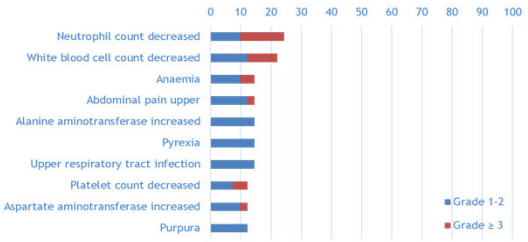
Table 2. Disease response

	Non-GCB DLBCL (N = 20)	FL (N = 16)	MZL (N = 5)
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 the 1st tumor assessment	3 (15.0)	2 (12.5)	0 (0.0)
ORR, n (%) (95% CI[a])	7 (35.0) (15.4-59.2)	9 (56.3) (29.9-80.2)	3 (60.0) (14.7-94.7)
DOR (months) Median (95% CI) [b]	8.79 (0.72-14.78)	NE	NE
PFS (months) [b] Median (95% CI) [b]	3.38 (2.69-5.49)	NE (5.49-NE)	NE (11.01-NE)
12-month event free rate (%) (95% CI) [c]	17.4 (4.3-37.7)	66.0 (36.5-84.3)	75.0 (12.8-96.1)

Abbreviations: BOR, best overall response; CR, complete response; DOR. duration of response; ORR, overall response rate; PD, progressive disease; PFS, progression free survival; PR, partial response; SD, stable disease; NE, not estimable.
[a]CI was calculated using the Clopper-Pearson method.
[b]Estimated by Kaplan-Meier method with 95% CIs estimated using the method of Brookmeyer and Crowley
[c]Estimated by Kaplan-Meier method with 95% CIs estimated using the Greenwood's formula.

- Adverse events occurred in 97.6% patients, and 46.3% patients had at least one grade 3 or above events.
- Serious events were reported in 19.5% patients.

Figure 3. Most common adverse events (in ≥10% patients)



- Infection and hemorrhage events occurred in 34.1% and 26.8% of patients, respectively.
- Grade ≥3 infection events were reported in 9.8% of patients, and no grade ≥3 hemorrhage events were reported.
- Fatal TEAEs (N=3) were reported in the non-GCB DLBCL cohort (dyspnea, death in setting of PD, and suicide), but none were reported in the FL or MZL cohorts.
- Fourteen (10.0% non-GCB DLBCL, 56.3% FL and 60.0% MZL) patients were still remained on treatment.

CONCLUSIONS

- This study demonstrated preliminary results for antitumor activity of zanubrutinib in combination with rituximab in patients with R/R non-GCB DLBCL, FL, and MZL.
- Safety profile of this study was consistent with previous results of zanubrutinib.
- The results encouraged further investigation of the combination of zanubrutinib and anti-CD20 antibodies in FL and MZL and prompted the development of mechanism-based treatment combinations and biomarker-driven individualized treatment in patients with non-GCB DLBCL.

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