Zanubrutinib (BGB-3111) in Combination with Obinutuzumab in Patients with Chronic Lymphocytic Leukemia and Follicular Lymphoma

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INTRODUCTION

- Bruton's Tyrosine Kinase (BTK) plays a critical role in B cell receptor (BCR) signaling, which mediates B cell proliferation, migration, and adhesion[1-3]
  - The BCR pathway is an established therapeutic target in chronic lymphocytic leukemia (CLL) and pathway members are frequently mutated in follicular lymphoma (FL)[4,5]
- Ibrutinib, the first generation BTK inhibitor, has activity in FL and CLL/small lymphocytic lymphoma (SLL) in combination with rituximab[6,7]
- Based on preclinical data, zanubrutinib (BGB-3111) was shown to be a potent and specific BTK inhibitor with advantageous pharmacokinetics,[8] designed to minimize off target inhibition of TEC- and EGFR-family kinases
  - Zanubrutinib achieved complete and sustained BTK occupancy in peripheral blood mononuclear cells and lymph nodes
  - Zanubrutinib showed minimal inhibitory effects against ITK and did not inhibit ITK-mediated rituximab-induced antibody-dependent cell-mediated cytotoxicity[9]
- Here we present updated interim Phase 1b results in patients with CLL/SLL and follicular lymphoma in an ongoing study of zanubrutinib in combination with obinutuzumab

METHODS

- Ongoing, open-label, multicenter, Phase 1b study of zanubrutinib + obinutuzumab in patients with B-cell malignancies, with indication-specific expansion cohorts (**Figure 1**)
- Primary endpoints of expansion cohorts: response rate and duration of response by standard International Working Group criteria for each disease
- Key secondary endpoint: safety of the combination

Figure 1. Trial Design

DOSE ESCALATION

Cohort	Zanubrutinib* (D1-28/28-D cycles)	Obinutuzumab	Patients Dosed
1a	320 mg QD	Cycle 1 D2: 100 mg Cycle 1 D3: 900 mg Cycle 1 D9 and D16: 1000 mg Cycles 2-6 D1: 1000 mg	4
1b	160 mg BID		5

DOSE EXPANSION

Population	Disease	Planned n
TN	CLL/SLL	20
R/R	CLL	20
R/R	non-GCB DLBCL	20
R/R	FL, MCL, MZL, and WM	20
R/R	FL	40

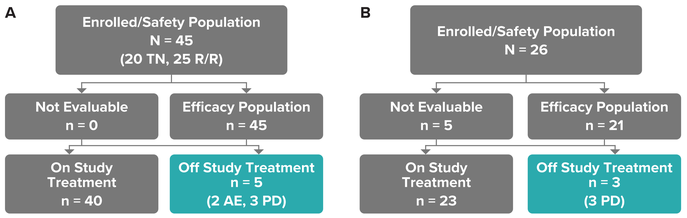
NCT02569476

Eligibility:
- WHO defined B cell lymphoid malignancy
- ≥1 prior therapy (relapsed cohorts only)
- No available higher priority treatment
- ECOG performance status 0-2
- ANC >1,000/µl, platelets >40,000/µl†
- Adequate renal and hepatic function
- No significant cardiac disease‡

*Zanubrutinib treatment continued until progression, death, or unacceptable toxicity.
†Growth factor/transfusion allowed.
‡Anti-coagulation allowed.
ANC, absolute neutrophil count; BID, twice daily; CLLSLL, chronic lymphocytic leukemia/small lymphocytic lymphoma; D, day; DLBCL, diffuse large B-cell lymphoma; FL, follicular lymphoma; GCB, germinal center B-cell-like; MCL, mantle cell lymphoma; MZL, marginal zone lymphoma; QD, once daily; R/R, relapsed/refractory; TN, treatment-naïve; WHO, World Health Organization; WM, Waldenström macroglobulinemia.

RESULTS

Figure 2. Disposition for Patients With (A) CLL/SLL or (B) FL (as of 15 September 2017)



AE, adverse event; PD, progressive disease; TN, treatment-naive; R/R, relapsed/refractory.

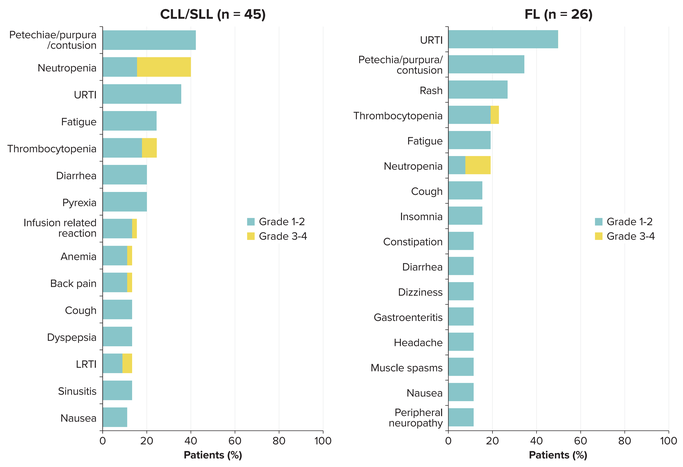
Table 1. Patient and Disease Characteristics

Characteristic	CLL/SLL (n = 45)	FL (n = 26)
Age, years, median (range)	68 (38-82)	60 (41-86)
ECOG performance status, (%) 0 1 2	 20 (44.4) 24 (53.3) 1 (2.2)	 19 (73.1) 6 (23.1) 1 (3.8)
Median follow-up, mo (range)	11.8 (6.0-19.5)	8.6 (0.3-19.7)
Prior treatment status Treatment-naïve, n (%) Relapsed/refractory, n (%) Number of prior therapies, median (range)	 20 (44.4) 25 (55.6) 1 (1-4)	 0 26 (100) 2 (1-7)
Bulky Disease*, n (%)	0	2 (7.7)
Molecular risk factors (n = 37), n (%) del17p/p53mut del11q Unmutated *IGHV* Complex karyotype	 6 (16.2) 6 (16.2) 19 (51.4) 7 (18.9)	 N/A N/A N/A N/A

*Any lymph node >10 cm in maximum diameter.

- The most common adverse events (AEs) in patients with CLL/SLL and FL were primarily grade 1/2 (**Figure 3**)
- Discontinuation due to AEs was uncommon in both populations (**Table 2**)

Figure 3. Most Common Adverse Events (Regardless of Causality)



LRTI, lower respiratory tract infection; URTI, upper respiratory tract infection.

Table 2. Safety Summary

Event, n (%)	CLL/SLL (n = 45)	FL (n = 26)
Patients with ≥ 1 Grade ≥ 3 AE	26 (57.8)	7 (26.9)
Patients with ≥ 1 SAE	15 (33.3)	5 (19.2)
Patients with events leading to treatment discontinuation	1 (2.2)*	0
Patients with fatal AEs	1 (2.2)*	0

* Patient with a history of squamous cell carcinoma discontinued due to squamous cell carcinoma.
AE, adverse event; SAE, serious adverse event.

Table 3. Adverse Events of Special Interest

	CLL/SLL (n = 45)		FL (n = 26)	
Event, n (%)	All Grade	Grade ≥ 3	All Grade	Grade ≥ 3
Diarrhea	9 (20.0)	0	3 (11.5)	0
Serious hemorrhage*	0	0	0	0
Atrial fibrillation	0	0	0	0
Hypertension	3 (6.7)	1 (2.2)	1 (3.8)	1 (3.8)
Infusion-related reactions	11 (24.4)	1 (2.2)	2 (7.7)	0

* ≥ Grade 3 hemorrhage, or central nervous system hemorrhage of any grade.

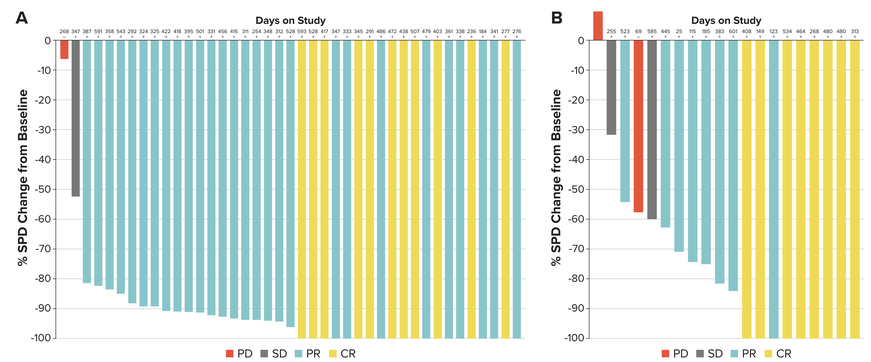
Table 4. Disease Response

	TN CLL/SLL (n = 20)	R/R CLL/SLL (n = 25)	FL (n = 21)
Median follow-up, mo (range)	11.4 (6.0-17.3)	12.7 (7.9-19.5)	12.1 (0.8-19.7)
Best Response, n (%)			
ORR	**19 (95.0)**	**23 (92.0)**	**16 (76.2)**
CR	7 (35.0)	5 (20.0)	8 (38.1)
PR	12 (60.0)	18 (72.0)	8 (38.1)
SD	1 (5.0)	1 (4.0)	2 (9.5)
PD	0	1 (4.0)	3 (14.3)

CLL/SLL, chronic lymphocytic leukemia/small lymphocytic lymphoma; CR, complete response; FL, follicular lymphoma; ORR, overall response rate; PD, progressive disease; PR, partial response; PR-L, partial response with lymphocytosis; R/R, relapsed/refractory; SD, stable disease; TN, treatment-naïve.

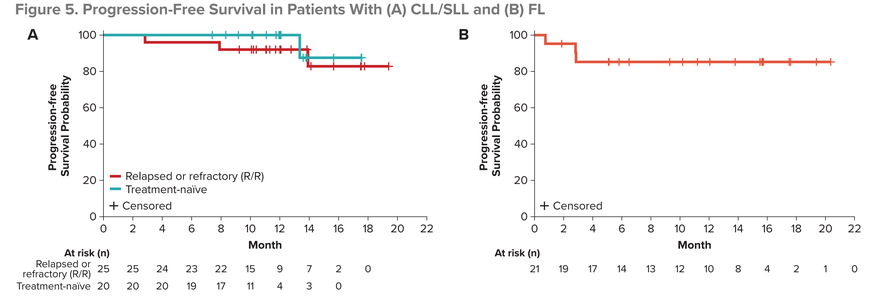
- ORR in patients with high-risk CLL/SLL
  - del17p/p53mut (n = 6): 83.3%
  - del11q (n = 6): 100%
  - Unmutated *IGHV* (n = 19): 94.7%
- The majority of patients with CLL/SLL and FL had >90% and >80% reduction in SPD (sum of the product of the longest perpendicular dimensions) from baseline, respectively (**Figure 4**)
- The majority of patients remain on treatment
- For patients with CLL/SLL and FL:
  - Median time to first response was 11.9 weeks (range, 7.3-24.3) and 12.0 weeks (range, 3.1-24.1), respectively
  - Median time to CR was 30.5 weeks (range, 11.3-60.4) and 12.1 weeks (range, 11.6-75.9), respectively
- Median progression-free survival has not been reached in either population (**Figure 5**)

Figure 4. Maximum Improvement in SPD* in Patients With (A) CLL/SLL and (B) FL



*Patients with no target lesions at baseline are not shown.

Figure 5. Progression-Free Survival in Patients With (A) CLL/SLL and (B) FL



CONCLUSIONS

- Updated interim results from the Phase 1b trial suggest that BTK inhibitor zanubrutinib (BGB-3111) and the anti-CD20 antibody obinutuzumab were generally well-tolerated when given in combination in patients with CLL/SLL and FL
- Compared to the expected rates with BTK-inhibitors or anti-CD20 antibodies alone:
  - CR rate in CLL/SLL is favorable
  - Frequency and depth of response (ORR and CR rate) in FL are favorable
- A pivotal trial for the combination of zanubrutinib and obinutuzumab in relapsed/refractory FL is ongoing

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DISCLOSURES

C Tam, H Quach, A Nicol, H Rose, M Leahy, R Eek, N Wickham, S Patil, and **I Flinn**: no relevant financial relationships to disclose
X Badoux: Roche
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