Zanubrutinib + Obinutuzumab + Sonrotoclax in Patients With Treatment-Naive CLL/SLL: Initial Results From an Ongoing Phase 1/1b Study, BGB-11417-101

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Jacob D. Soumerai,[1] Stephen S. Opat,[2] Chan Y. Cheah,[3-5] Mazyar Shadman,[6,7] Emma Verner,[8,9] Monica Tani,[10] Marc S. Hoffmann,[11] Lori A. Leslie,[12] Shuo Ma,[13] Yiqian Fang,[14] Gabriel Man,[15] Binghao Wu,[14] Charity Henrich,[15] Sheel Patel,[15] Remus Vezan,[15] Constantine S. Tam[16]

[1]Massachusetts General Hospital Cancer Center and Harvard Medical School, Boston, MA, USA; [2]Lymphoma Research Group, School of Clinical Sciences at Monash Health, Monash University, Clayton, VIC, Australia; [3]Sir Charles Gairdner Hospital, Nedlands, WA, Australia; [4]Medical School, University of Western Australia, Crawley, WA, Australia; [5]Linear Clinical Research, Nedlands, WA, Australia; [6]Fred Hutchinson Cancer Center, Seattle, WA, USA; [7]University of Washington, Seattle, WA, USA; [8]Concord Repatriation General Hospital, Concord, NSW, Australia; [9]University of Sydney, Sydney, NSW, Australia; [10]Santa Maria delle Croci Hospital, Ravenna, Italy; [11]University of Kansas Cancer Center, Kansas City, KS, USA; [12]John Theurer Cancer Center-Hackensack University Medical Center, Hackensack, NJ, USA; [13]Robert H. Lurie Comprehensive Cancer Center, Northwestern University Feinberg School of Medicine, Chicago, IL, USA; [14]BeOne Medicines, Ltd, Shanghai, China; [15]BeOne Medicines, Ltd, San Carlos, CA, USA; [16]Alfred Hospital and Monash University, Melbourne, VIC, Australia

CONCLUSIONS

- Combination therapy with zanubrutinib + obinutuzumab + sonrotoclax 320 mg was well tolerated by patients with TN CLL/SLL
  - No deaths or discontinuations of any study drug due to TEAEs were observed, and no laboratory or clinical TLS occurred during sonrotoclax ramp-up
- Substantial efficacy was observed, with a 100% ORR
- 100% of patients with an available cycle 15 blood MRD assessment by NGS achieved uMRD5, discontinued treatment per protocol, and remain in remission (median time off treatment, 5.5 months [range, 3.4-8.5 months])
- With a median study follow-up of approximately 18.0 months, no PFS events have occurred, indicating the potential for zanubrutinib + obinutuzumab + sonrotoclax to provide deep and durable remission in TN patients with CLL/SLL
- This combination is being further evaluated in a phase 2 investigator-initiated trial (NCT06849713)

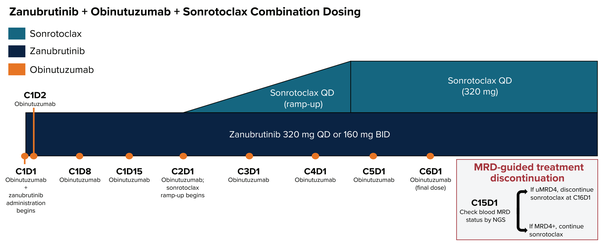
INTRODUCTION

- Combination therapy with zanubrutinib, obinutuzumab, and venetoclax has demonstrated efficacy in patients with treatment-naive (TN) chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL), including those with high-risk disease features[1]
- Zanubrutinib is highly effective in patients with TN and relapsed/refractory (R/R) CLL/SLL, regardless of risk factors[2,3]
  - Zanubrutinib has shown superior progression-free survival (PFS) and favorable safety/tolerability compared with ibrutinib, including fewer cardiac adverse events, in patients with R/R CLL/SLL[4]
- Sonrotoclax (BGB-11417), a next-generation B-cell lymphoma 2 (BCL2) inhibitor, is a more selective and pharmacologically potent inhibitor of BCL2 than venetoclax, with a shorter half-life and no accumulation[5,6]
- BGB-11417-101 is an ongoing, first-in-human, phase 1/1b dose-escalation/expansion study in patients with various B-cell malignancies
- Presented here are initial safety and efficacy data for zanubrutinib + obinutuzumab + sonrotoclax 320 mg combination therapy in patients with TN CLL/SLL in BGB-11417-101

METHODS

- BGB-11417-101 (NCT04277637) is an ongoing, phase 1/1b, open-label, multicenter, dose-escalation and -expansion study of sonrotoclax as monotherapy or combination therapy in patients with various B-cell malignancies
- On cycle 1 day 1, patients begin treatment with oral zanubrutinib (160 mg twice daily or 320 mg once daily) and intravenous obinutuzumab (cycle 1 to cycle 6); on cycle 2 day 1, oral sonrotoclax is introduced with a ramp-up schedule to reach the recommended phase 2 dose of 320 mg (**Figure 1**)
- Patients who achieve undetectable minimal residual disease (uMRD4; <1 CLL cell per 10,000 leukocytes) in peripheral blood by next-generation sequencing (NGS) after 15 treatment cycles may discontinue treatment; others may continue to receive treatment until disease progression or unacceptable toxicity
- Study endpoints include safety and tolerability, overall response rate (ORR; defined as a partial response with lymphocytosis or better), and rate of blood uMRD4 as measured by ERIC-approved NGS and/or flow cytometry assay, depending on the time point

Figure 1. BGB-11417-101 Study Design



Abbreviations: BID, twice daily; C, cycle; CLL/SLL, chronic lymphocytic leukemia/small lymphocytic lymphoma; D, day; MRD, minimal residual disease; NGS, next-generation sequencing; QD, once daily; R/R, relapsed/refractory; TN, treatment-naive; uMRD, undetectable minimal residual disease.

RESULTS

- As of August 29, 2025, a total of 15 patients with TN CLL/SLL have been enrolled and have received at least one cycle of zanubrutinib + obinutuzumab + sonrotoclax
- Ten patients (67%) discontinued treatment after reaching uMRD4 per NGS; 5 patients (33%) remain on treatment and have not yet reached cycle 15 as of the data cutoff date
- Across dose cohorts, the median age was 62 years, and 53% were male (**Table 1**)
  - Ten patients (67%) had unmutated IGHV and 1 patient (7%) had a high tumor burden

Table 1. Baseline Patient Characteristics

Characteristic	Zanu + O + Sonrotoclax 320 mg (N=15)
Study follow-up time, median (range), months	18.0 (8.4-22.2)
Age, median (range), years	62 (32-76)
Male, n (%)	8 (53)
Risk status, n (%)	
del(17p) and/or *TP53* mutation	0
del(13q)	5 (33)
del(11q)	3 (20)
Unmutated IGHV, n (%)	10 (67)
High tumor risk at baseline, n (%)[a]	1 (7)

[a]LNs ≥10 cm or LNs >5 cm and ALC >25×10⁹/L.
Abbreviations: ALC, absolute lymphocyte count; IGHV, immunoglobulin heavy chain variable region; LN, lymph node; O, obinutuzumab; zanu, zanubrutinib.

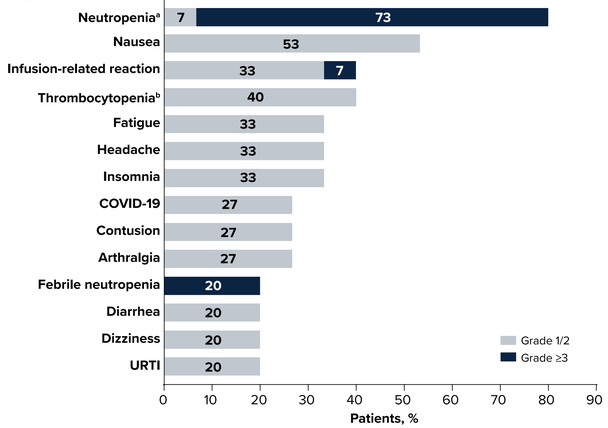
- An overall summary of treatment emergent adverse events (TEAEs) is shown in **Table 2**
  - No TEAEs led to death or discontinuation of any study drug
- The most common any-grade TEAEs were neutropenia (80%), nausea (53%), infusion-related reaction (40%), and thrombocytopenia (40%) (**Figure 2**)
  - The most common grade ≥3 TEAE was neutropenia (73%), which was transient and did not lead to higher rates of grade ≥3 infections
  - The most common serious TEAE was febrile neutropenia (20%)
- Infections occurred in 73% of patients; 13% of patients had grade 3 infections
- No cases of laboratory or clinical tumor lysis syndrome (TLS) occurred during sonrotoclax ramp-up
  - One patient experienced laboratory TLS after obinutuzumab infusion and prior to starting sonrotoclax

Table 2. Safety Summary

Patients, n (%)	Zanu + O + Sonrotoclax 320 mg (N=15)
Any TEAE	15 (100)
Grade ≥3	13 (87)
Serious TEAEs	5 (33)
Led to death	0
Led to zanu discontinuation	0
Led to O discontinuation	0
Led to sonrotoclax discontinuation	0
Relative sonrotoclax dose intensity, median, %	99

Abbreviations: O, obinutuzumab; TEAE, treatment-emergent adverse event; zanu, zanubrutinib.

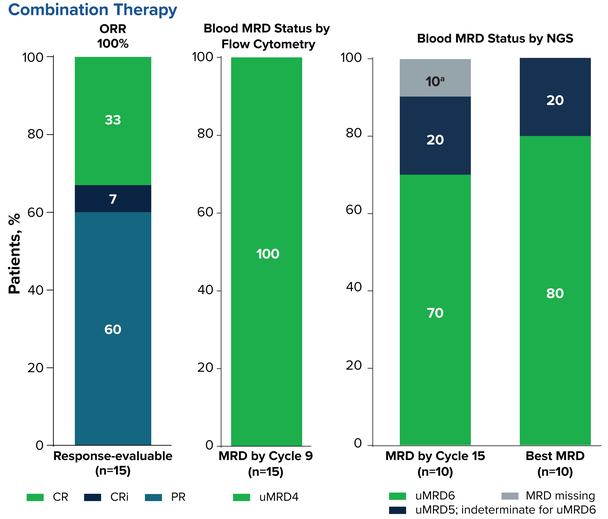
Figure 2. TEAEs in ≥20% of Patients



[a]Neutropenia combines preferred terms "neutrophil count decreased" and "neutropenia." [b]Thrombocytopenia combines preferred terms "platelet count decreased" and "thrombocytopenia".
Abbreviations: TEAE, treatment-emergent adverse event; URTI, upper respiratory tract infection.

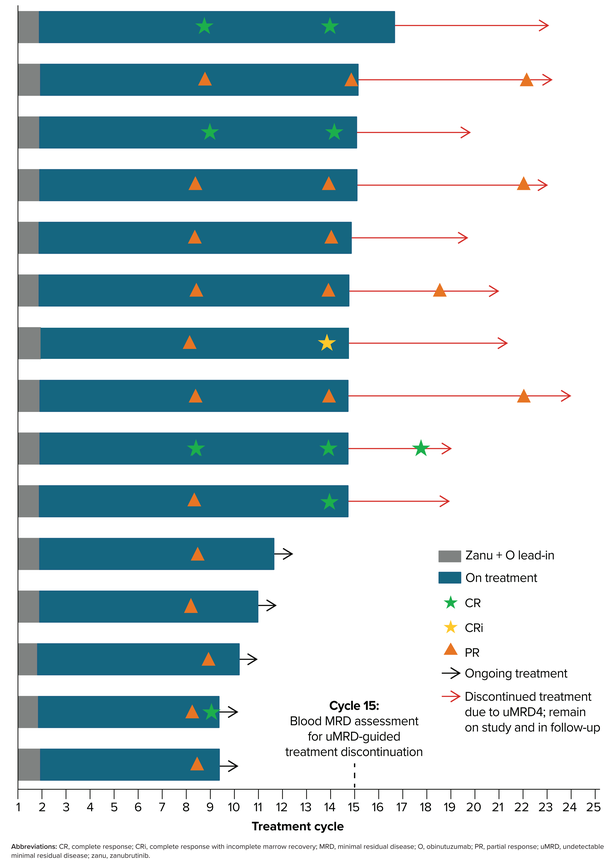
- With a median study follow-up of 18.0 months, the ORR in 15 efficacy-evaluable patients was 100%, which included a complete response/complete response with incomplete marrow recovery (CR/CRi) rate of 40% (**Figures 3** and **4**)
- As of the data cutoff date, 100% of MRD-evaluable patients achieved uMRD5 per NGS, discontinued treatment as mandated by the protocol, and remain in remission
- The median time off treatment was 5.5 months (range, 3.4-8.5 months)

Figure 3. Response Rates and Blood MRD Status With Sonrotoclax 320 mg Combination Therapy



[a]One patient had a missing MRD evaluation at cycle 15 but it was collected late at cycle 16.
Abbreviations: CR, complete response; CRi, complete response with incomplete marrow recovery; MRD, minimal residual disease; NGS, next-generation sequencing; ORR, overall response rate; PR, partial response; uMRD, undetectable minimal residual disease.

Figure 4. Treatment Duration and Investigator-Assessed Responses



Abbreviations: CR, complete response; CRi, complete response with incomplete marrow recovery; MRD, minimal residual disease; O, obinutuzumab; PR, partial response; uMRD, undetectable minimal residual disease; zanu, zanubrutinib.

- With a median study follow-up of 18.0 months (range, 8.4-22.2 months), median PFS was not reached
  - No PFS events were observed, and all patients who achieved uMRD remain in remission

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CORRESPONDENCE: Jacob D. Soumerai, jsoumerai@mgh.harvard.edu

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