Phase 3 Zanubrutinib (BGB-3111) vs Bendamustine Plus Rituximab in Patients With Treatment-Naïve Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma

Abstract PS7581

SEQUOIA
Phase 3 Treatment-Naïve CLL/SLL

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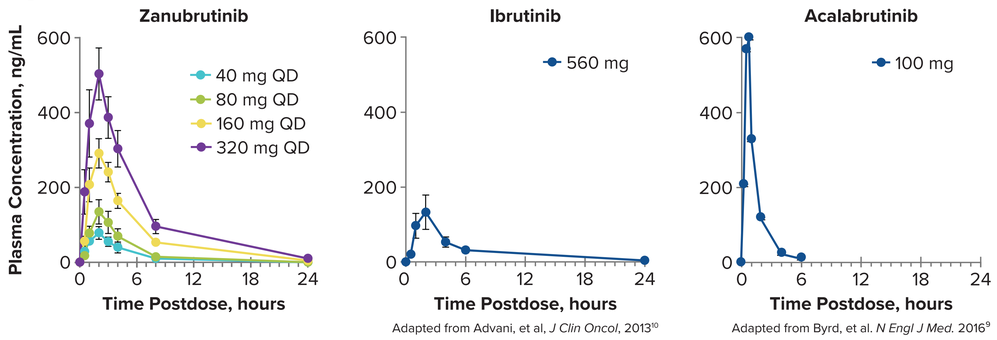
INTRODUCTION

- Bruton 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/small lymphocytic lymphoma (CLL/SLL)[4] and the first-generation BTK inhibitor ibrutinib has become a standard of care[5,6]
- Based on preclinical data, zanubrutinib (BGB-3111) was shown to be a potent, highly selective, and irreversible BTK inhibitor with advantageous pharmacokinetics, designed to minimize off-target inhibition of TEC- and EGFR-family kinases (**Figure 1**)[7]
  - Complete and sustained BTK occupancy in peripheral blood mononuclear cells AND lymph nodes was observed (**Figure 2**)

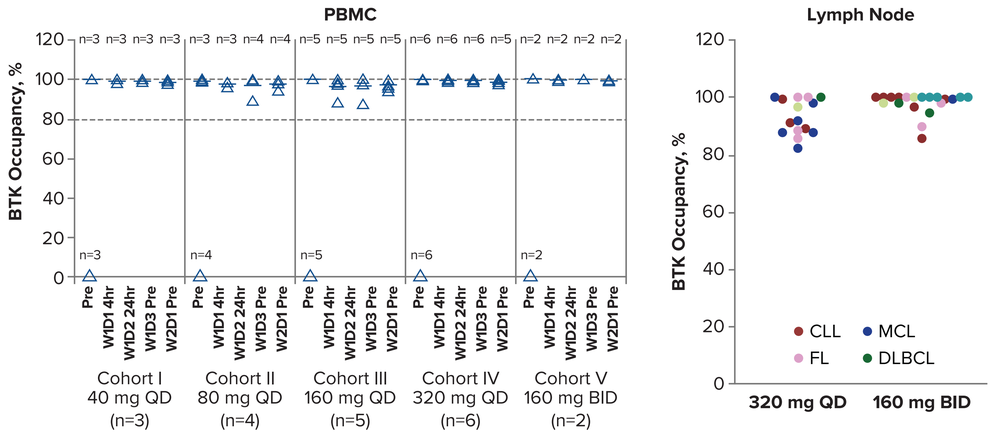
Figure 1. Pharmacokinetics of Zanubrutinib, Ibrutinib, and Acalabrutinib



Adapted from Advani, et al, *J Clin Oncol*, 2013[10]

Adapted from Byrd, et al. *N Engl J Med.* 2016[9]

Figure 2. Sustained BTK Inhibition in Peripheral Blood and Lymph Nodes



Complete and sustained BTK occupancy is seen in paired PMBC and lymph node biopsy samples collected predose on day 3. In blood samples, complete BTK occupancy was seen at the lowest dose (40 mg). Note, 100% median trough occupancy at a dose of 160 mg twice daily with 94% of subjects having > 90% occupancy in lymph nodes across malignancies.

BID, twice daily; BTK, Bruton tyrosine kinase; CLL, chronic lymphocytic leukemia; DLBCL, diffuse large B-cell lymphoma; FL, follicular lymphoma; MCL, mantle cell lymphoma; PBMC, peripheral blood mononuclear cells; QD, once daily.

- Preliminary clinical data from a phase 1 study indicate that zanubrutinib is generally well-tolerated and induces deep, sustained responses in patients with treatment-naïve or relapsed/refractory CLL/SLL, including those with high-risk factors (**Table 1**), with a 94% overall response rate (ORR) (**Table 2**)[10]
- The chemoimmunotherapy bendamustine plus rituximab (BR) is a standard first-line treatment for CLL/SLL in patients aged ≥ 65 years without comorbidities as well as younger patients with significant comorbidities

Table 1. Characteristics of Patients With CLL/SLL Treated With Zanubrutinib 160 mg PO BID in a Phase 1 Study

Characteristic	Total (N=69)
Median (range) age, years	68 (24–87)
ECOG performance status, n (%)	
0	34 (49)
1	33 (48)
2	2 (3)
Prior treatment status	
Treatment-naïve, n (%)	18 (26)
Relapsed/refractory, n (%)	51 (74)
Number of prior therapies, median (range)	2 (1–7)
Bulky disease,* n (%)	4 (6)
Molecular risk factors, n/N evaluable (%)	
del(17p)/p53mut	20/51 (39)
11q–	14/44 (32)
IgHV unmutated	11/16 (69)

BID, twice daily; ECOG, Eastern Cooperative Oncology Group; PO, by mouth.
*Any lymph node >10 cm in maximum diameter.

Table 2. Preliminary Efficacy From a Phase 1 Study of Zanubrutinib 160 mg PO BID in Patients With CLL/SLL

	Treatment-Naïve (n=16)	Relapsed/Refractory (n=50)	Total (N=66)
Median (range), follow-up, mo	7.6 (3.7–11.6)	14.0 (2.2–26.8)	10.5 (2.2–26.8)
Best response, n (%)			
ORR	16 (100)	46 (92)	62 (94)
CR	1 (6)	1 (2)	2 (3)
PR	13 (81)	41 (82)	54 (82)
PR-L	2 (13)	4 (8)	6 (9)
SD	0	3 (6)	3 (5)
D/C prior to assessment	0	1 (2)	1 (2)

BID, twice daily; CLL/SLL, chronic lymphocytic leukemia/small lymphocytic lymphoma; CR, complete response; D/C, discontinuation; ORR, overall response rate; PO, by mouth; PR, partial response; PR-L, partial response with lymphocytosis; SD, stable disease.

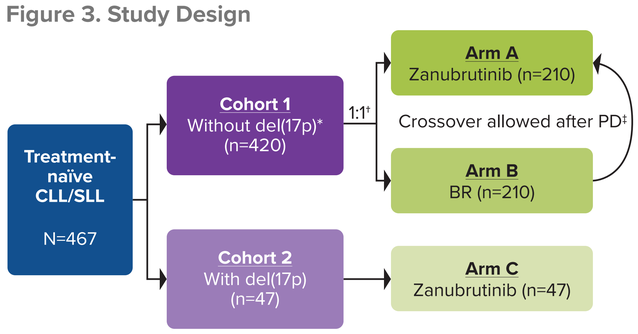
STUDY DESIGN

- International, open-label, phase 3, randomized study of zanubrutinib vs BR in patients with treatment-naïve CLL/SLL considered unsuitable for treatment with fludarabine, cyclophosphamide, plus rituximab (FCR) (**Figure 3**)
  - 420 patients without del(17p) (cohort 1) randomized to receive either zanubrutinib (arm A) or BR (arm B)
  - Approximately 47 patients with del(17p) (cohort 2) assigned to receive zanubrutinib monotherapy (arm C)

DRUG ADMINISTRATION

- Zanubrutinib: administered as two 80-mg capsules taken orally twice per day (160 mg twice per day) with or without food
- Bendamustine: administered intravenously at a dose of 90 mg/m^2/day on the first 2 days of each 28-day cycle for 6 cycles
- Rituximab: administered intravenously at a dose of 375 mg/m^2 on day 0 of cycle 1, and at a dose of 500 mg/m^2 on day 1 of cycles 2 through 6

Figure 3. Study Design



CLL, chronic lymphocytic leukemia; SLL, small lymphocytic lymphoma; BR, bendamustine plus rituximab; IGHV, immunoglobulin variable region heavy chain.
*By central laboratory fluorescence in situ hybridization.
†Stratified by age (< 65 vs ≥ 65 years), Binet stage (C vs A/B), IGHV mutational status (mutated vs unmutated), and geographic region (North America vs Europe vs Asia Pacific).
‡Crossover to arm A is allowed after disease progression is confirmed by independent central review.

BGB-3111-304 STUDY OBJECTIVES

- All efficacy and safety objectives in cohort 1 [patients without del(17p)] will compare zanubrutinib versus BR

PRIMARY

- To compare efficacy between treatment groups in cohort 1, as measured by progression-free survival (PFS) determined by independent central review

SECONDARY

- To evaluate efficacy in cohort 1, as measured by the following:
  - ORR determined by independent central review and by investigator assessment
  - Overall survival (OS)
  - Duration of response (DOR) determined by independent central review and by investigator assessment
- To compare safety between the treatment groups in cohort 1

STUDY ENDPOINTS

PRIMARY ENDPOINT

- PFS of zanubrutinib vs BR in cohort 1, as measured by independent central review, according to the International Workshop on Chronic Lymphocytic Leukemia (iwCLL) guidelines with modification for treatment-related lymphocytosis

SECONDARY ENDPOINTS

- Efficacy in cohort 1 [patients without del(17p)]: ORR, OS, duration of response, investigator-assessed PFS, patient-reported outcomes (PROs)
- Safety in cohort 1
- Efficacy in cohort 2 [patients with del(17p)]: ORR, OS, PFS by independent central review, DOR
- Pharmacokinetics of zanubrutinib in patients who received this treatment (arms A and C)

EXPLORATORY ENDPOINTS

- Investigator-assessed PFS2 (time to second objective disease progression)
- Prognostic and predictive biomarkers
- PROs in cohort 2

ELIGIBILITY CRITERIA

Key Inclusion Criteria	Key Exclusion Criteria
• Confirmed CD20-positive CLL/SLL requiring treatment per iwCLL criteria	• Prior systemic treatment for CLL/SLL
• Binet stage C disease or stage A/B disease requiring treatment as defined by previously described criteria[12]	• History of prolymphocytic leukemia or Richter's transformation
• Age ≥ 65 years or < 65 years and unsuitable for treatment with FCR	• Central nervous system involvement
• ECOG performance status 0–2	• History of severe bleeding disorder
• Adequate bone marrow function*	• Clinically significant cardiovascular disease
• Adequate renal and hepatic function	• Active infection with hepatitis B or C or HIV

CLL/SLL, chronic lymphocytic leukemia/small lymphocytic lymphoma; ECOG, Eastern Cooperative Oncology Group; FCR, fludarabine, cyclophosphamide, plus rituximab; iwCLL; International Workshop on Chronic Lymphocytic Leukemia; HIV, human immunodeficiency virus.
*Absolute neutrophil count ≥ 1000/mm^3 and platelets ≥ 75,000/mm^3 (≥ 750/mm^3 and ≥ 50,000/mm^3, respectively, in patients with bone marrow involvement).

STUDY STATUS

- This study opened to accrual in October of 2017 and will be recruiting patients from 165 participating sites throughout the European Union, Asia-Pacific, and North America.

ENROLLMENT

- Enrollment started in November of 2017
- Contact information:
  - Aileen Cohen, MD, PhD, or Carol Marimpietri, RN
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DISCLOSURES

JRB: Has served as a consultant/advisor for AbbVie, Astellas Pharma, AstraZeneca, Celgene, Gilead Sciences, Infinity Pharmaceuticals, Janssen, Pharmacyclics, Redx Pharma, Roche/Genentech, and Sun Pharma; received honoraria from AbbVie and Janssen Oncology; and received research funding from Gilead Sciences
BK: Has served as a consultant/advisor for Celgene, Gilead, Seattle Genetics, and Genentech; received research funding from ADC Therapeutics
PG: Has served as a consultant/advisor for AbbVie Adaptive Biotechnologies, Gilead Sciences, Janssen, Pharmacyclics, and Roche; received research funding from Gilead Sciences, GlaxoSmithKline, and Roche; served on a speakers' bureau for Gilead Sciences
TR: Has served as a consultant/advisor for and received honoraria and research funding from Janssen; received research funding from Pharmacyclics
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SF, CM, AC, and **JH:** Are employees of and own stock in BeiGene

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