Zanubrutinib for Patients With Relapsed or Refractory Chronic Lymphocytic Leukemia or Small Lymphocytic Lymphoma (CLL/SLL)

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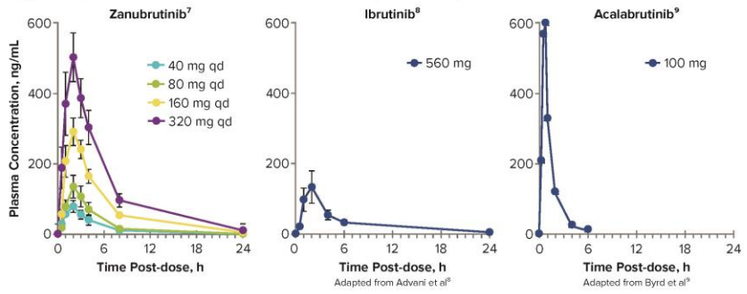
INTRODUCTION

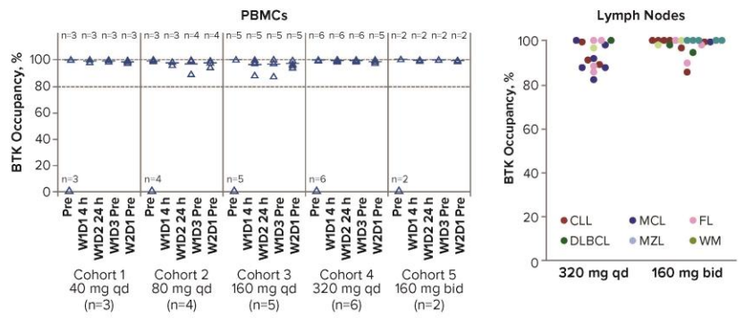
- Bruton tyrosine kinase (BTK) plays a critical role in B-cell receptor signaling, which mediates B-cell proliferation, migration, and adhesion[1-3]
  - Targeting the B-cell receptor pathway is an established therapeutic strategy in CLL/SLL[4]
  - The first-generation BTK inhibitor ibrutinib has become a standard of care in CLL/SLL[5,6]
- Zanubrutinib (BGB-3111) is an investigational, next-generation BTK inhibitor designed to maximize BTK occupancy and minimize off-target inhibition of TEC- and EGFR-family kinases
  - Has been shown to be a highly potent, selective, bioavailable, and irreversible BTK inhibitor with potentially advantageous pharmacokinetic/pharmacodynamic properties[7] (**Figure 1**)
  - Complete and sustained BTK occupancy in both peripheral blood mononuclear cells and lymph nodes[7] (**Figure 2**)

Figure 1. Pharmacokinetics of Zanubrutinib, Ibrutinib, and Acalabrutinib



Note: these data are from 3 separate analyses, and differences in studies should be considered.
qd, once daily.

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



Complete and sustained BTK occupancy is seen in paired PBMC (left figure) and lymph node biopsy samples (right figure) 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 bid with 94% of patients having >90% occupancy in lymph nodes across malignancies.
bid, twice daily; BTK, Bruton tyrosine kinase; CLL, chronic lymphocytic leukemia; D, day; DLBCL, diffuse large B-cell lymphoma; FL, follicular lymphoma; MCL, mantle cell lymphoma; MZL, marginal zone lymphoma; PBMC, peripheral blood mononuclear cells; Pre, predose; qd, once daily; W, week; WM, Waldenstrom macroglobulinemia.

- Based on drug interaction studies:
  - Co-administration with strong or moderate CYP3A inhibitors (including agents such as azole anti-fungals, important in the management of patients with leukemia/lymphoma) is permitted at a reduced dose
  - Co-administration of proton pump inhibitors or other gastric acid-reducing agents does not affect zanubrutinib exposure
  - Patients have been allowed to receive anticoagulant and antiplatelet agents on zanubrutinib trials

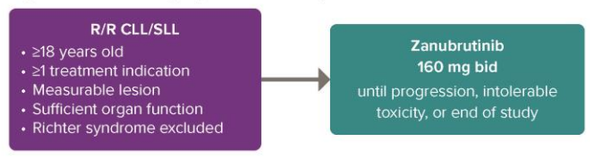
OBJECTIVE

- Presented here are safety and efficacy results from Chinese patients with relapsed/refractory (R/R) CLL/SLL treated within an ongoing phase 2 trial of zanubrutinib (NCT03206918)

METHODS

- Single-arm, open-label, multi-center phase 2 study in patients with histologically-confirmed CLL/SLL who are R/R after ≥1 prior regimen (**Figure 3**)

Figure 3. Trial Design (BGB-3111-205)



bid, twice daily; CLL, chronic lymphocytic leukemia; R/R, relapsed/refractory; SLL, small lymphocytic lymphoma.

Objectives

- Primary: overall response rate (ORR) assessed by independent review committee (IRC)
- Secondary: progression-free survival (PFS), duration of response, time to response, safety
- Exploratory: biomarkers

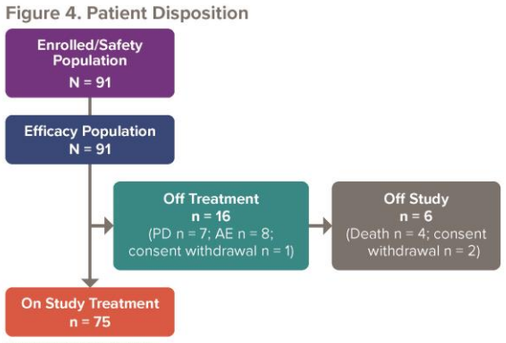
Response assessment

- International Workshop on CLL (iwCLL) 2008 criteria for CLL with 2012 modification for partial response with lymphocytosis (PR-L)[10,11]
- Computed tomography-based assessment according to Lugano Classification for SLL[12]

RESULTS

- Enrollment was open from March to December in 2017
- A total of 91 patients (82 CLL, 9 SLL) were enrolled from 11 study centers (**Figure 4**, **Table 1**)
- At a data cutoff date of December 14, 2018, median study follow-up time was 15.1 months (range, 0.8-21.2)

Figure 4. Patient Disposition



Data cutoff: December 14, 2018.
AE, adverse event; PD, progressive disease.

Table 1. Patient and Disease Characteristics

Characteristic	N = 91
Age, median (range), y	61.0 (35-87)
Male sex, n (%)	52 (57.1)
Late stage,[a] n (%)	63 (69.2)
Prior therapy, n (%)	
Alkylator (including bendamustine)	68 (74.7)
Purine analog	52 (57.1)
Anti-CD20 antibody	54 (59.3)
Refractory to last therapy, n (%)	72 (79.1)
ECOG PS 0/1, n (%)	88 (96.7)
Bulky disease, n (%)	
LDi ≥5 cm	40 (44.4)
Beta-2 microglobulin >3.5 mg/L, n (%)	68 (74.7)
Splenomegaly, n (%)	56 (61.5)
Hepatomegaly, n (%)	11 (12.1)
Absolute lymphocyte count, n (%)	
<25 × 10^9/L	57 (62.6)
25-100 × 10^9/L	26 (28.6)
>100 × 10^9/L	8 (8.8)
***TP53* mutation and/or 17p deletion, n (%)**	22 (24.2)
***IGHV* unmutated, n (%)**	51 (56.0)
Cytogenetic abnormalities, n (%)	
17p deletion	17 (18.7)
11q deletion	20 (22.0)
13q deletion	41 (45.1)
Trisomy 12	21 (23.1)

CLL, chronic lymphocytic leukemia; ECOG PS, Eastern Cooperative Oncology Group performance status; LDi, longest diameter; SLL, small lymphocytic lymphoma.
[a]Percentages are based on number of CLL patients with Binet C and SLL patients with stage III and IV.

- By IRC, the ORR was 84.6%, including 62.6% with complete or partial response (CR, PR; **Table 2**)
- High concordance rate for ORR between IRC and investigator assessments (91.2%)
  - By investigator, the ORR was 91.2% (95% CI, 83.4-96.1), including 72.5% (95% CI, 62.2, 81.4) with CR or PR

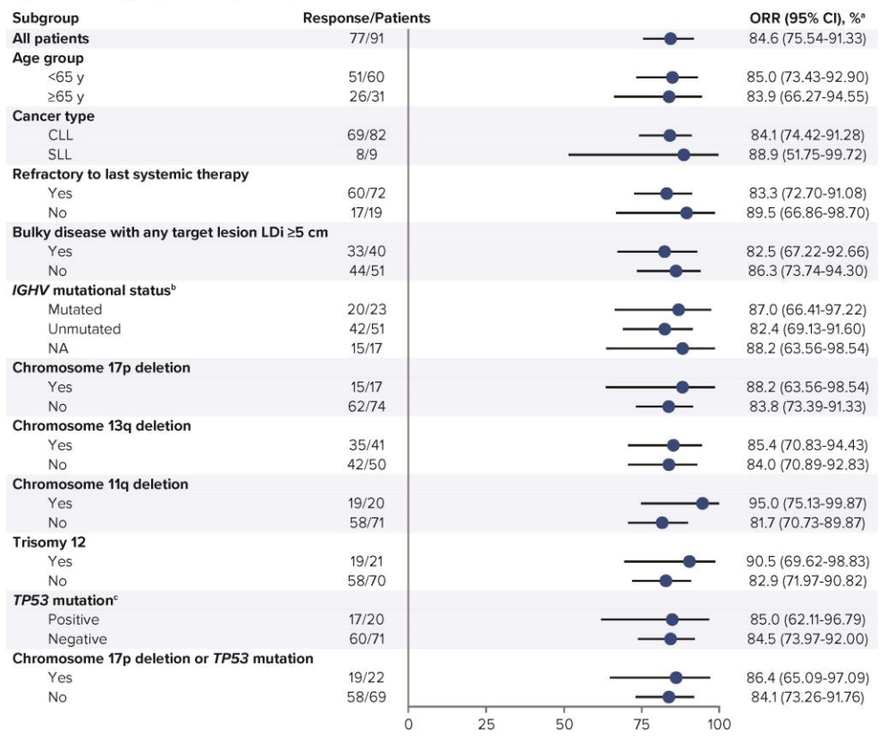
Table 2. Best Overall Response by IRC

Response by IRC	N = 91
ORR, n (%)	77 (84.6)
Best overall response, n (%)	
CR	3 (3.3)
PR	54 (59.3)
PR-L	20 (22.0)
SD	4 (4.4)
PD	4 (4.4)
Not evaluable[a]	3 (3.3)
Discontinued before first post-baseline assessment	3 (3.3)

CR, complete response; IRC, independent review committee; ORR, overall response rate; PD, progressive disease; PR, partial response; PR-L, PR with lymphocytosis; SD, stable disease.
[a]Missing anatomy imaging for 2 patients, and without evidence of response maintenance for at least 2 months for 1 patient, separately.

- ORRs per IRC were generally consistent across all subgroups examined (**Figure 5**)
  - ORRs were 86.4% and 82.4% for the 17p deletion/*TP53* mutation and the unmutated *IGHV* subgroups, respectively

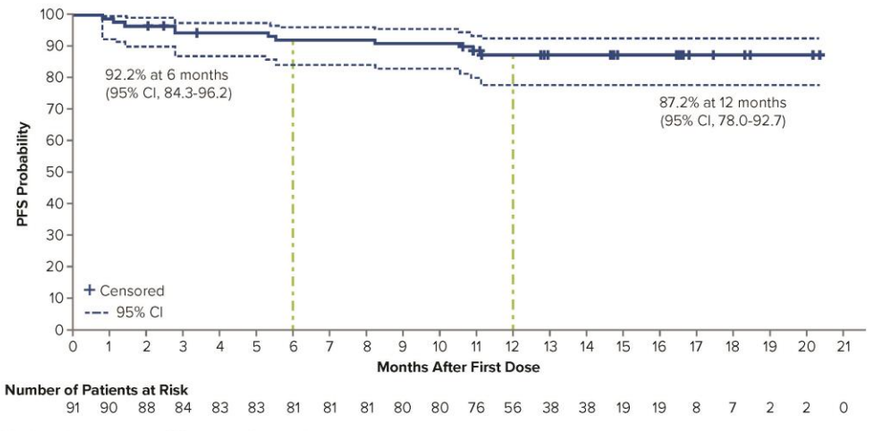
Figure 5. Subgroup Efficacy Analysis



CLL, chronic lymphocytic leukemia; IRC, independent review committee; LDi, longest diameter; ORR, overall response rate; SLL, small lymphocytic leukemia.
[a]2-sided Clopper-Pearson 95% CIs.
[b]*IGHV* mutational status was not assessable for the following cases: *IGHV* gene rearrangement undetected (3 patients); multiclonal *IGHV* gene rearrangement detected (13 patients); test failed (1 patient).
[c]Sample from 1 patient was detected as negative with Sanger sequencing method instead of next generation sequencing.

- At a median follow-up time for PFS of 12.9 months (range, 0.8-20.4), median PFS has not been reached (**Figure 6**)

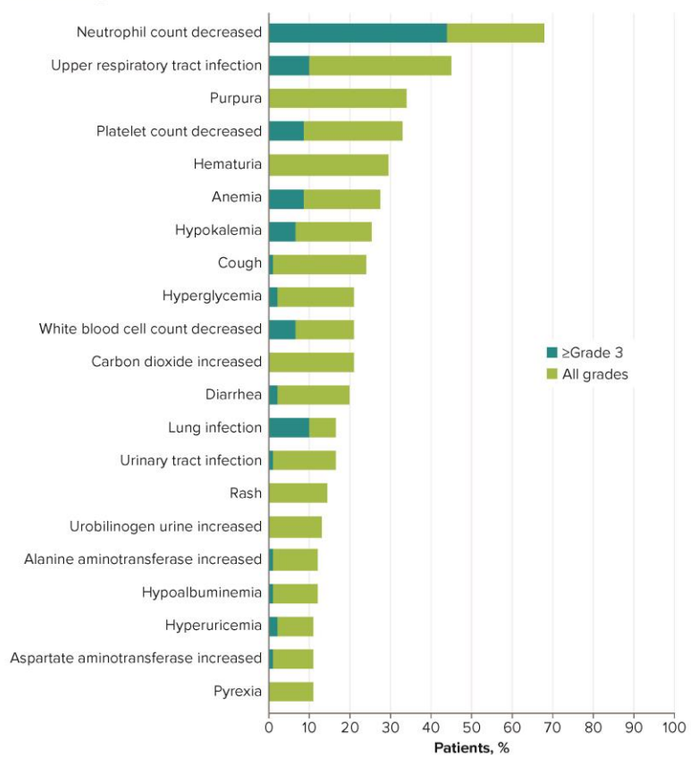
Figure 6. PFS by IRC



IRC, independent review committee; PFS, progression-free survival.

- The most common treatment-emergent adverse events (AEs) were primarily grade 1-2 in severity (**Figure 7**)

Figure 7. Common Treatment-Emergent Adverse Events (≥10%), Regardless of Causality



- Serious AEs were reported in 33% of patients
- There were 8 patient-reported AEs leading to treatment discontinuation
- There were 3 patient-reported AEs leading to death, all within 30 days of last dose
  - Lung infection/cardiac failure/respiratory (unlikely related)
  - Cardiopulmonary failure (unlikely related)
  - Multiple organ dysfunction syndrome (not related) in the setting of disease progression

CONCLUSIONS

- Zanubrutinib demonstrated a high ORR of 84.6% as assessed by IRC in R/R patients with CLL/SLL, including poor prognostic subgroups
  - 86.4% in patients with *TP53* mutation or 17p deletion
  - 82.4% in patients with unmutated *IGHV*
- The safety and tolerability profile shown in Chinese patients with R/R CLL/SLL was consistent with previous reports in other CLL/SLL patients
- Data from study BGB-3111-205 has been submitted to the Chinese National Medical Products Administration seeking approval for zanubrutinib in R/R CLL/SLL
- Confirmatory studies including a head-to-head study with ibrutinib in R/R patients (BGB-3111-305) and comparison with bendamustine + rituximab in treatment-naïve patients (BGB-3111-304) are ongoing

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DISCLOSURES

WX, SY, KZ, LP, ZL, JZ, SG, DZ, JH, RF, HH, JL: nothing to disclose
MJ, HG, JH, WN, SF: employment and stock options with BeiGene

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