ALPINE: Phase 3 Trial of Zanubrutinib (BGB-3111) Versus Ibrutinib in Patients With Relapsed/Refractory (R/R) Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma (CLL/SLL)

Abstract 4307

ALPINE
Phase 3 Relapsed/Refractory CLL/SLL

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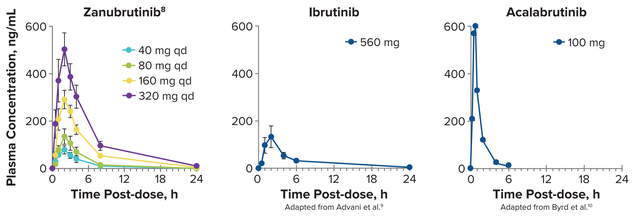
BACKGROUND

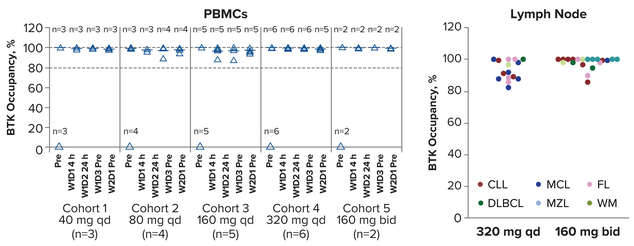
- Bruton tyrosine kinase (BTK) plays a critical role in B-cell receptor signaling, which mediates B-cell proliferation, migration, and adhesion[1-3]
  - Targeting the B-cell receptor pathway is an established therapeutic strategy in chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL)[4]
  - 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
  - Increased specificity may minimize toxicities (eg, diarrhea, thrombocytopenia, bleeding, atrial fibrillation, rash, and fatigue) reported with ibrutinib potentially due to off-target inhibition[7]
  - Has been shown in nonclinical studies to be a highly potent, selective, bioavailable, and irreversible BTK inhibitor with potentially advantageous pharmacokinetic/pharmacodynamic properties[8] (**Figure 1**)
  - Complete and sustained BTK occupancy in both peripheral blood mononuclear cells and lymph nodes[8] (**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 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 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 cell; Pre, predose; qd, once daily; W, week; WM, Waldenström macroglobulinemia.

- Based on drug–drug interaction studies and population PK analyses (internal data):
  - Zanubrutinib may be coadministered with strong or moderate CYP3A inhibitors at a reduced dose
  - Coadministration of proton pump inhibitors or other acid-reducing agents does not affect zanubrutinib exposure[11]
  - Patients have been allowed to receive anticoagulant and antiplatelet medications on zanubrutinib trials[11]
  - Zanubrutinib has not been found to affect QT interval
- Pooled clinical data (n=682) from 6 zanubrutinib monotherapy trials of non-Hodgkin lymphoma, Waldenström macroglobulinemia, or CLL/SLL suggest that zanubrutinib has been generally well tolerated among patients with B-cell malignancies[11]
  - Some toxicities often associated with BTK inhibitors were infrequent with zanubrutinib, including atrial fibrillation/flutter (1.9%; grade ≥3, 0.6%), major hemorrhage (2.5%; grade ≥3, 2.1%), fatigue (10.9%; grade ≥3, 0.7%), rash (18.0%; grade ≥3, 0.1%), thrombocytopenia (18.3%; grade ≥3, 6.6%), and diarrhea (19.4%; grade ≥3, 0.9%)[11]
- Early clinical data in patients with treatment-naïve (TN; n=22) or relapsed/refractory (R/R; n=56) CLL/SLL showed that zanubrutinib was highly active, with an objective response rate (ORR) of 96% (**Table 1**)[12]
  - Zanubrutinib was generally well tolerated; most adverse events (AEs) were grade 1/2, and 2 patients discontinued from AEs
  - Most common AEs were contusion (35%; no grade 3/4), upper respiratory tract infection (33%; no grade 3/4), cough (26%; no grade 3/4), and diarrhea (21%; no grade 3/4)

Table 1. Efficacy of Zanubrutinib in CLL/SLL Patients From Phase 1b Study BGB-3111-AU-003 (NCT02343120)[12]

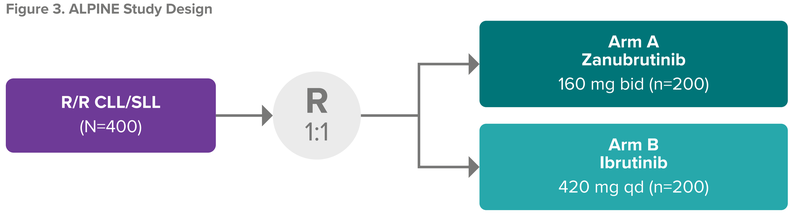
Response	Treatment Naïve (n = 22)	Relapsed/ Refractory (n = 56)	Total (N = 78)
Follow-up, median (range), mo	13.7 (0.4-30.5)		
Best response, n (%)			
ORR[a]	22 (100)	53 (95)	75 (96)
CR	1 (4.5)	1 (2)	2 (3)
PR	18 (82)	45 (80)	63 (81)
PR-L	3 (14)	7 (13)	10 (13)
SD	0	2 (4)	2 (3)
PD	0	0	0
Missing/not evaluable	0	1 (2)	1 (1)

[a]ORR in patients with del(17p) and/or *TP53* (n=16) was 100%.
CLL/SLL, chronic lymphocytic leukemia/small lymphocytic lymphoma; CR, complete response; ORR, objective response rate; PD, progressive disease; PR, partial response; PR-L, partial response with lymphocytosis; SD, stable disease.

ALPINE STUDY DESIGN

- Global, phase 3, randomized, open-label study of zanubrutinib vs ibrutinib in adults with R/R CLL/SLL (BGB-3111-305; NCT03734016; **Figure 3**)
  - Approximately 400 patients to receive either zanubrutinib (arm A) or ibrutinib (arm B)
    - Stratified by age (<65 vs ≥65 years), refractory status (yes vs no), geographic region (China vs other), and del(17p)/*TP53* mutation status (present vs absent)
    - Treatment in both arms may continue until progression
  - Primary objective of study is to compare efficacy of zanubrutinib vs ibrutinib in ORR (PR or higher)

Figure 3. ALPINE Study Design



bid, twice daily; CLL/SLL, chronic lymphocytic leukemia/small lymphocytic lymphoma; ORR, objective response rate; PR, partial response; qd, once daily; R, randomized; R/R, relapsed/refractory.
Note: Safety follow-up 30 days after end of treatment.

ALPINE KEY ELIGIBILITY CRITERIA

Key Inclusion Criteria	Key Exclusion Criteria
• CLL or SLL by iwCLL criteria requiring treatment • R/R to ≥1 prior systemic therapy for CLL/SLL[a] • Measurable lymphadenopathy by CT or MRI • Age ≥18 years • ECOG PS 0-2 • Adequate BM function[b] • Adequate organ function	• Known prolymphocytic leukemia • Current or past Richter transformation • History of severe bleeding • Prior treatment with a BTK inhibitor • Known infection with HIV • Active HBV or HCV • Clinically significant cardiovascular disease

BM, bone marrow; BTK, Bruton tyrosine kinase; CLL, chronic lymphocytic leukemia; CT, computed tomography; ECOG PS, Eastern Cooperative Oncology Group performance status; HBV, hepatitis B virus; HCV, hepatitis C virus; HIV, human immunodeficiency virus; iwCLL, International Workshop on CLL; MRI, magnetic resonance imaging; R/R, relapsed/refractory; SLL, small lymphocytic lymphoma.
[a]A line of therapy is defined as completing ≥2 cycles of treatment of standard regimen according to current guidelines or of an investigational regimen on a clinical trial.
[b]Absolute neutrophil count ≥1000/μL and platelets ≥75,000/μL (≥750/μL and ≥50,000/μL, respectively, in patients with BM involvement).

STATISTICAL METHODS

- Primary objective of the study is to demonstrate non-inferiority of zanubrutinib to ibrutinib in ORR
  - Superiority will be tested if non-inferiority is demonstrated

ALPINE STUDY END POINTS

PRIMARY

- ORR by independent review committee (IRC) per 2008 International Workshop on CLL (iwCLL) criteria[13] with modification for treatment-related lymphocytosis[14] for CLL and Lugano Classification for non-Hodgkin lymphoma[15] for SLL

SECONDARY

- Progression-free survival (PFS) by IRC and investigator assessment (INV)
- Duration of response by IRC and INV
- Time to treatment failure
- Rate of partial response with lymphocytosis or higher by IRC
- Overall survival
- European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30 (EORTC QLQ-C30) and EuroQol 5-dimension 5-level version (EQ-5D-5L) scores
- Safety

EXPLORATORY

- Correlation between clinical outcomes and the prognostic and predictive biomarkers
- Pharmacokinetic parameters

ALPINE STUDY STATUS

- This study opened to accrual in November 2018 and is recruiting patients from sites in 15 countries

ENROLLMENT

- Enrollment started in November 2018
- Contact information:
  - clinicaltrials@beigene.com

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DISCLOSURES

PH: consultant/advisor for Acerta, Janssen, and AbbVie; research funding from AbbVie, Pharmacyclics, Janssen, Gilead, and Roche; and honoraria from AbbVie and Janssen

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