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

Abstract TPS7572

ALPINE
Phase 3 Relapsed/Refractory CLL/SLL

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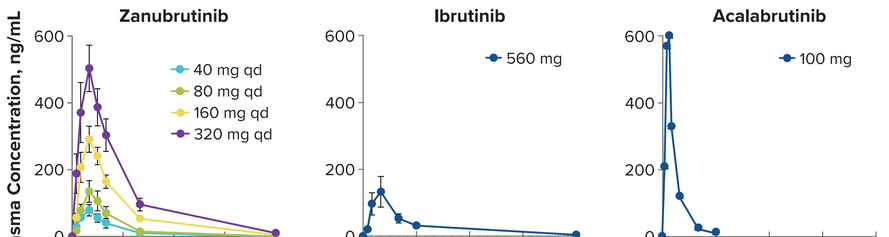
BACKGROUND

- 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
  - 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**)

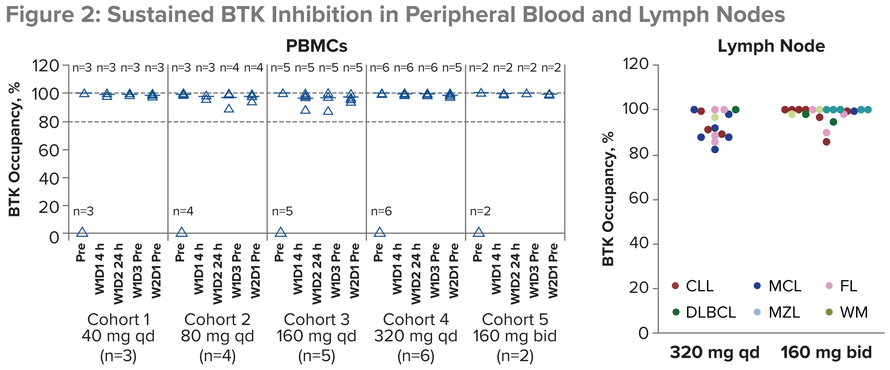
Figure 1: Pharmacokinetics of Zanubrutinib, Ibrutinib, and Acalabrutinib



Adapted from Advani et al.[8] Adapted from Byrd et al.[9]

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

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, Waldenstrom macroglobulinemia.

- Based on drug interaction studies:
  - Co-administration with strong CYP3A inhibitors is permitted (includes important agents in management of leukemia/lymphoma patients, such as azole anti-fungals)
  - Co-administration of proton pump inhibitors or other acid-reducing agents does not affect zanubrutinib exposure
  - Patients have been allowed to receive warfarin and aspirin on zanubrutinib trials
- Preliminary data from a multicenter phase 1b trial in patients with treatment-naïve or relapsed/refractory (R/R) CLL/SLL (N=69) showed an objective response rate (ORR) of 94% with single-agent zanubrutinib (**Table 1**)[10]
  - Zanubrutinib was generally well tolerated; 19% of patients had serious adverse events of any cause and 1% discontinued due to adverse events (pleural effusion, transformation)
  - Most common adverse events were petechiae/purpura/contusion (46%; 1% grade 3/4), fatigue (29%, no grade 3/4), upper respiratory track infection (28%, no grade 3/4), cough (23%, no grade 3/4), and diarrhea (22%, no grade 3/4)
- Given the encouraging clinical activity and tolerability of zanubrutinib in the phase 1b trial, a head-to-head trial comparing zanubrutinib and ibrutinib in a broad population of patients with R/R CLL/SLL was warranted

Table 1. Preliminary Efficacy of Zanubrutinib in CLL/SLL Patients From Phase 1b Study BGB-3111-AU-003 (NCT02343120)[10]

Response	Treatment Naïve (n = 16)	Relapsed/Refractory (n = 50)	Total (N = 66)
Follow-up, median (range), mo	7.6 (3.7-11.6)	14.0 (2.2-26.8)	10.5 (2.2-26.8)
Best response			
ORR[a]	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)
PD	0	0	0
D/C before assessment	0	1 (2)	1 (2)[b]

CLL/SLL, chronic lymphocytic leukemia/small lymphocytic lymphoma; CR, complete response; D/C, discontinued; ORR, objective response rate; PD, progressive disease; PR, partial response: PR-L, partial response with lymphocytosis; SD, stable disease.
[a]ORR in patients with del17p and/or 11q- (n = 22) was 96%.
[b]D/C because of adverse event of pleural effusion.

ALPINE KEY ELIGIBILITY CRITERIA

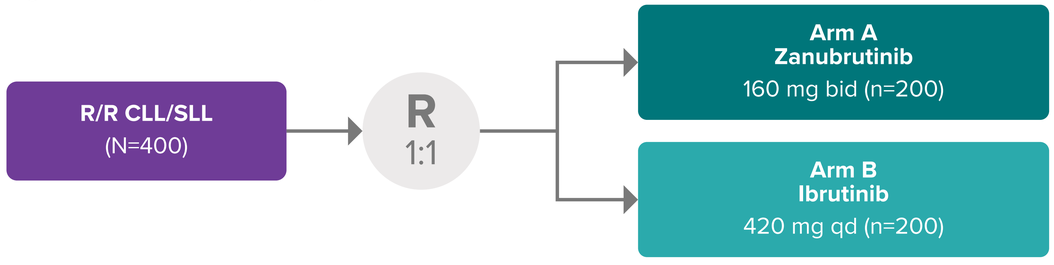
Key Inclusion Criteria	Key Exclusion Criteria
• CLL or SLL by iwCLL criteria requiring treatment • R/R to ≥1 prior systemic therapy for CLL/SLL[a] • Measurable lymphadenopathy by CT or MRI • Age ≥18 years • ECOG PS 0-2 • Adequate BM function[b] • Adequate organ function	• Known prolymphocytic leukemia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

BM, bone marrow; BTK, Bruton tyrosine kinase; CT, computed tomography; ECOG PS, Eastern Cooperative Oncology Group performance status; HBV, hepatitis B virus; HCV, hepatitis C virus; iwCLL, International Workshop on Chronic Lymphocytic Leukemia; 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).

ALPINE STUDY DESIGN

- Global, phase 3, randomized, open-label study of zanubrutinib versus ibrutinib in adults with R/R CLL/SLL (BGB-3111-305; NCT03734016; **Figure 3**)

Figure 3. ALPINE Study Design



bid, twice daily; CLL/SLL, chronic lymphocytic leukemia/small lymphocytic lymphoma; EOT, end of treatment; PD, progressive disease; qd, once daily; R, randomize; R/R, relapsed/refractory.
[a]Safety follow-up 30 days after EOT.

- 400 Patients to receive either zanubrutinib (arm A) or ibrutinib (arm B)
- Primary objective of study is to compare efficacy of zanubrutinib versus ibrutinib in ORR (PR or higher)

ALPINE STUDY END POINTS

PRIMARY

- ORR by independent review committee (IRC) per 2008 International Workshop on CLL (iwCLL) criteria[11] with modification for treatment-related lymphocytosis[12] for CLL and Lugano Classification for non-Hodgkin lymphoma[13] 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

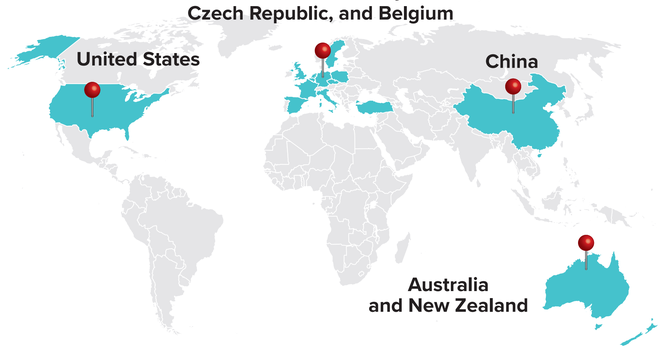
EXPLORATORY

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

ALPINE STUDY STATUS

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

United Kingdom, Turkey, Spain, Sweden, Poland, Italy, The Netherlands, Germany, France, Czech Republic, and Belgium



ENROLLMENT

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

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DISCLOSURES

PH: Served as a consultant/advisor for Janssen, AbbVie and Acerta; received research funding from Janssen, AbbVie, Gilead, Roche, and Pharmacyclics; and participated in a speakers' bureau for Janssen and AbbVie

JRB: Served as a consultant/advisor for Abbvie, Acerta, Astra Zeneca, BeiGene, Gilead, Invectys, June/Celgene, Kite, Loxo, Pfizer, Morphosys, Novartis, Pharmacyclics, Roche/Genentech, Sunesis, TG Therapeutics, and Verastem; received honoraria from Janssen and Teva; received research funding from Gilead, Loxo, Sun, and Verastem

JCB: Served as a consultant/advisor for Acerta, Pharmacyclics, Genentech, and Jazz Pharmaceuticals; received research funding from Genentech, Acerta, Pharmacyclics, and Janssen

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SMO: Employed by University of California – Irvine; served as a consultant/advisor for Amgen, Celgene, GSK, Janssen Oncology, Aptose Biosciences, Vaniam Group, AbbVie Genentech, Sunesis Pharma, Astellas Pharma, Gilead, Pharmacyclics, TG Therapeutics, Pfizer, and Sunesis Pharmaceuticals; received honoraria from Celgene, Janssen, Pharmacyclics, Gilead Sciences, Pfizer, Amgen, Astellas Pharma, GSK, Aptose Biosciences, Vaniam Group, AbbVie, Sunesis Phama, Alexion Pharma, Loxo, Eisai, and TG Therapeutics; received research funding from Acerta Pharma, Regeneron, Gilead Sciences, Pfizer, TG Therapeutics, Pharmacyclics, Kite Pharma, and Sunesis Pharmaceuticals; travel, accommodations, expenses paid for by Celgene, Janssen, Gilead Sciences, Regeneron, and Janssen Oncology

LQ: Has nothing to disclose

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