ALPINE: Phase 3 Trial of Zanubrutinib (BGB-3311) Versus Ibrutinib in Patients With Relapsed/Refractory (R/R) Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma (CLL/SLL)

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BACKGROUND
• B-cell receptor signaling plays a critical role in B-cell proliferation, migration, and adhesion.
• Targeting the B-cell receptor pathway is an established therapeutic strategy in chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL).
• The Bruton tyrosine kinase (BTK) inhibitor ibrutinib has become a standard of care in CLL/SLL.1
• Zanubrutinib (BGB-3311) is an investigational, non-pan-BTK inhibitor designed to have potent BTK occupancy and minimize off-target inhibition of TSC and EGFR family kinases.
• Increased specificity may enable longer-term engagement, improved pharmacokinetics, altered distribution, and better reported with ibrutinib potential for off-target inhibition.

STUDY DESIGN
• Global phase 3, randomized, open-label study of zanubrutinib vs ibrutinib in adults with R/R CLL/SLL (BGB-3311-305; NCT03739241; Figure 1)
• 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 ORR at 180 days (present vs absent)
• Treatment toxic effects may continue until progression
• Primary objective is to compare efficacy of zanubrutinib vs ibrutinib (ORR) in R/R patients

ALPINE KEY ELIGIBILITY CRITERIA
Key Inclusion Criteria
• DLBCL or FL by battling criteria requiring treatment
• NHL or other systemic therapy for CLL/SLL
• Measurable lymphoproliferative by CT or MRI
• Age ≥18 years
• ECOG PS 0-2
• Adequate BM function

Key Exclusion Criteria
• Known prolymphocytic involvement
• Current or past B-cell transformation
• History of severe bleeding
• Prior treatment with a BTK inhibitor
• Known infection with HIV
• Active HBV or HCV
• Clinically significant cardiovascular disease

ALPINE STUDY END POINTS
PRIMARY
• ORR in patients with del(17p) and/or TP53 mutation with or without comorbidities
SECONDARY
• Progression-free survival (PFS) by IRC and investigator assessment (IWCLL)
• Duration of response by IRC and NCI
• Time to first treatment
• Rate of new treatment
• CONCLUSIONS
• Confronting clinical outcomes and the prognostic and predictive biomarkers
• Pharmacokinetic parameters

STUDY DESIGN
• Open-label, 2-arm, 1:1 randomized in 2 parts
• Eligible patients (≥18 years; ≥12 weeks post-line of therapy discontinuation)
• Eligible patients (≥18 years): 30% sex, 30% race, 30% tumor type, 10% random
• 100% randomization will be performed to arm A or arm B
• 90% of participants will be randomized to arm A or arm B
• Patients with or without comorbidities

STATISTICAL METHODS
• Primary objective of the study is to demonstrate non-inferiority of zanubrutinib to ibrutinib in R/R
• Superiority will be tested if non-inferiority is demonstrated

ENROLLMENT
• Investment started in November 2016 and is recruiting patients from sites in 15 countries

REFERENCES