Trial in Progress: A Phase 2, Multicenter, Single-Arm Study of Zanubrutinib (BGB-3111) in Patients With Previously Treated B-Cell Malignancies Intolerant to Prior Treatment With Ibrutinib or Acalabrutinib

Abstract TPS8066

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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]
  - BTK inhibitor (BTKi) ibrutinib is approved for treatment of patients with chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL), Waldenström macroglobulinemia (WM), and mantle cell lymphoma (MCL) who have received ≥1 prior therapy, or marginal zone lymphoma (MZL) who require systemic therapy and have received ≥1 prior anti-CD20-based therapy[4]
    - Adverse events (AEs) were reported to be the most common reason for discontinuing ibrutinib (50% and 63% of discontinuations in relapsed/refractory [R/R] and newly diagnosed patients, respectively)[5]
      - The most common toxicities that led to treatment discontinuation in the front-line setting were arthralgia (42%), atrial fibrillation (25%), and rash (17%); and in the R/R population were atrial fibrillation (12%), infection (11%), pneumonitis (10%), bleeding (9%), and diarrhea (7%)[5]
  - The second-generation BTKi acalabrutinib is also approved by the FDA for treatment of patients with CLL/SLL or MCL who have received ≥1 prior therapy[6]
  - In a Phase 2 study of acalabrutinib in ibrutinib-intolerant patients with CLL, treatment discontinuation rate due to AE was 12%. The AEs that led to treatment discontinuation were pneumonia (3%), headache, endometrial cancer, arthralgia, and subdural hematoma (2% each)[7]
- Zanubrutinib is a next-generation BTKi designed to maximize BTK occupancy and minimize off-target inhibition of TEC-and EGFR-family kinases
  - Increased specificity may minimize toxicities reported with ibrutinib[8]
  - Has been shown in nonclinical studies to be a highly potent, selective, bioavailable, and irreversible BTKi with potentially advantageous pharmacokinetic/pharmacodynamic properties[9]
  - Complete and sustained BTK occupancy in both peripheral blood mononuclear cells and lymph nodes[9] (**Figure 1**)
- Zanubrutinib was approved by the FDA for use in patients with R/R MCL
- 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
  - Co-administration of proton pump inhibitors or other acid-reducing agents does not affect zanubrutinib exposure
  - Patients have been allowed to receive anticoagulant and antiplatelet medications on zanubrutinib trials
  - Zanubrutinib has not been found to affect QT interval
- Pooled clinical data (n=682) from 6 zanubrutinib monotherapy trials in non-Hodgkin lymphoma, WM, or CLL/SLL suggest that zanubrutinib has been generally well tolerated among patients with B-cell malignancies[10]
  - Some toxicities often associated with BTKi 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%)[10]
- Results from the Phase 3 head-to-head trial in patients with WM demonstrated fewer patients receiving zanubrutinib vs ibrutinib discontinued treatment due to AEs (4% vs 9.2%) and experienced atrial fibrillations of any grade (2% vs 15.3%), respectively[11]
- Results from the Phase 1/2 AU-003 trial in patients with B-cell malignancies have demonstrated zanubrutinib activity in WM, MCL, CLL, and MZL[8,12-14]
- This trial is an ongoing study to evaluate the feasibility and utility of zanubrutinib monotherapy as a therapeutic option for patients with B-cell malignancies who have become intolerant to ibrutinib or acalabrutinib

Zanubrutinib (BGB-3111)

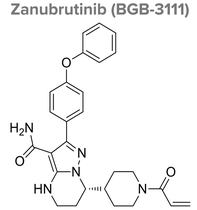
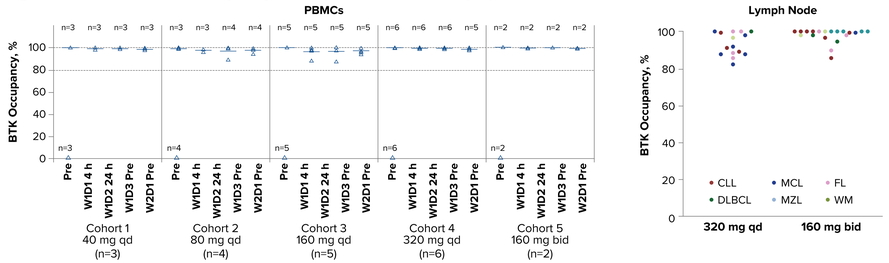


Figure 1: Sustained BTK Occupancy in Peripheral Blood and Lymph Nodes

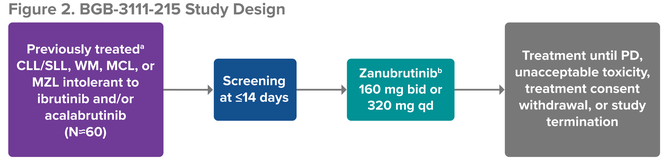


Complete and sustained BTK occupancy is seen in paired PMBC and lymph node biopsy samples collected predose on Day 3. In blood samples, complete BTK occupancy was seen at the lowest dose (40 mg). Note, 100% median trough occupancy at a dose of 160 mg twice daily with 94% of patients having >90% occupancy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

BGB-3111-215 STUDY DESIGN

- Phase 2, US, multicenter, single-arm, open-label study (BGB-3111-215; NCT04116437; **Figure 2**)
  - Approximately 60 patients with B-cell malignancies will be enrolled from ~30 primarily community medical centers
  - The primary objective of this study is to evaluate the safety of zanubrutinib in patients with previously treated CLL/SLL, WM, MCL, or MZL intolerant to prior ibrutinib and/or acalabrutinib treatment, compared with their ibrutinib and/or acalabrutinib intolerance AE profile as assessed by the recurrence and the change in severity of AEs

Figure 2. BGB-3111-215 Study Design



bid, twice daily; qd, once a day; CLL/SLL, chronic lymphocytic leukemia/small lymphocytic lymphoma; MCL, mantle cell lymphoma; MZL, marginal zone lymphoma; PD, progressive disease; WM, Waldenström macroglobulinemia.
[a]There is a ≥7-day washout period for any anticancer therapy (other than immunotherapy) and a ≥4-week washout period for immunotherapy, taken alone or as part of a chemoimmunotherapy regimen. [b]Safety follow-up 30 days after end of treatment.

BGB-3111-215 KEY ELIGIBILITY CRITERIA

Key Inclusion Criteria	Key Exclusion Criteria
• Meet disease criteria for treatment in respective disease prior to initiation of ibrutinib or acalabrutinib – CLL or SLL by iwCLL criteria requiring treatment – Histologically confirmed MCL diagnosis based on WHO 2016 classification – Histologically confirmed diagnosis of MZL requiring treatment – Clinical and definitive histologic diagnosis of WM meeting ≥1 IWWM criterion • Ibrutinib and/or acalabrutinib intolerance[a] • Resolution of ibrutinib- and/or acalabrutinib-related toxicities to Grade ≤1 or baseline prior to initiating treatment with zanubrutinib • ECOG PS ≤2 • ANC ≥1000/mm^3 and platelet count ≥50,000/mm^3	• Documented disease progression during any BTKi treatment[b] • Current or past Richter transformation • History of ischemic stroke 180 days before first zanubrutinib dose • History of CNS hemorrhage • Known infection with HIV • Active HBV or HCV • History of opportunistic infection while on ibrutinib and/or acalabrutinib • Clinically significant cardiovascular disease • Requires ongoing need for corticosteroid treatment >10 mg daily of prednisone or equivalent corticosteroid.

ANC, absolute neutrophil count; BTKi, Bruton tyrosine kinase inhibitor; CLL, chronic lymphocytic leukemia; CNS, central nervous system; ECOG PS, Eastern Cooperative Oncology Group performance status; HBV, hepatitis B virus; HCV, hepatitis C virus; iwCLL, International Workshop on CLL; IWWM, International Workshop on Waldenström Macroglobulinemia; MCL, mantle cell lymphoma; MZL, marginal zone lymphoma; PD, progressive disease; SLL, small lymphocytic lymphoma; WM, Waldenström macroglobulinemia .
[a]Intolerance is defined as an unacceptable toxicity where, in the opinion of the investigator, treatment should be discontinued in spite of optimal supportive care as a result of one of the following: Grade ≥2 non-hematological toxicities for >7 days; Grade ≥3 non-hematological toxicity of any duration; Grade 3 neutropenia with infection or fever; or Grade 4 heme toxicity which persists to the point that the investigator chose to stop therapy due to toxicity not progression. [b]A disease flare meeting PD criteria while the patient is off BTKi treatment is not considered to be a true PD.

STATISTICAL METHODS

- All analyses will be done in the safety analysis set, which includes all patients who receive at least 1 dose of zanubrutinib
- No formal hypothesis testing is planned for this study; all analyses are descriptive in nature
- Outputs for patients with prior BTKi exposure will be presented separately depending on sample size
- The primary endpoint will be summarized overall and for each component
  - Reoccurrence and severity changes will be evaluated by comparing occurrence and worst severity of event while on zanubrutinib with those with prior BTKi exposure for the same patient
- Overall response rate (ORR) will be analyzed as binary outcome and progression-free survival will be analyzed using survival analysis methods

BGB-3111-215 STUDY ENDPOINTS

Primary

- Recurrence and change in severity of treatment-emergent diarrhea (Grade ≥2), myalgia (Grade ≥2), muscle spasms (Grade ≥2), arthralgia (Grade ≥2), hypertension (Grade ≥2), fatigue (Grade ≥2), rash (Grade ≥2), atrial fibrillation (Grade ≥2), and hemorrhage (Grade ≥2, excluding central nervous system (CNS; hemorrhage of any grade) compared with ibrutinib and/or acalabrutinib intolerance events within each patient

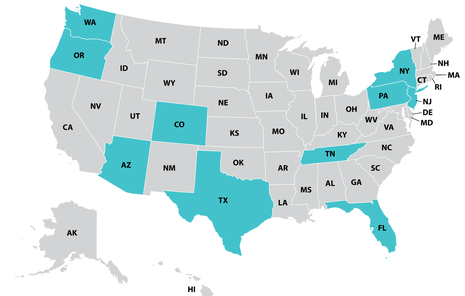
Secondary

- ORR (defined by each disease state) by investigator[a]
- Progression-free survival (PFS) by investigator
- Patient-reported outcomes measured by EQ-5D-5L and EORTC QLQ-C30 questionnaires

[a]CLL patients will be evaluated using the 2008 iwCLL guidelines (Hallek M, et al. *Blood*. 2008;111:5446-5456.); SLL, MCL, and MZL will be evaluated using the Lugano classification for NHL (Cheson, et al. *Blood*. 2014;32-3068.); WM patients will be evaluated using the serum IgM level per the modified IWWM-6 response criteria.

BGB-3111-215 STUDY STATUS

- This study opened to accrual in October 2019 and is recruiting patients from 22 sites in the United States



ENROLLMENT

- Enrollment initiated in October 2019 and is ongoing
- Contact information:
  - clinicaltrials@beigene.com
  - Medical Monitor: dihyih.chen@beigene.com

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DISCLOSURES

IF: equity ownership at Johnson & Johnson; consultancy at AbbVie, Seattle Genetics, TG Therapeutics, Verastem, Roche, Gilead Sciences, Kite Pharma, Janssen, BeiGene, Takeda, AstraZeneca, Juno Therapeutics, Unum Therapeutics, MorphoSys, Nurix Therapeutics, Shanghai Yingli Pharmaceutical; research funding from AbbVie, Acerta Pharma, Agios, ArQule, AstraZeneca, BeiGene, Calithera Biosciences, Celgene, A Bristol-Myers Squibb Company, Constellation Pharmaceuticals, Curis, F. Hoffmann-La Roche Ltd, Forma Therapeutics, Forty Seven, Genentech, Gilead Sciences, Incyte, Infinity Pharmaceuticals, Janssen, Juno Therapeutics, Karyopharm Therapeutics, Kite Pharma, Merck, MorphoSys, Novartis, Pfizer, Pharmacyclics, Portola Pharmaceuticals, Roche, Seattle Genetics, Takeda, Teva, TG Therapeutics, Trillium Therapeutics, Unum Therapeutics, and Verastem. **MS:** consultancy at AbbVie, ADC Therapeutics, AstraZeneca, Atara Biotherapeutics, BeiGene, Genentech, Pharmacyclics, Sound Biologics,and Verastem; research funding from Mustang Bio, Celgene, A Bristol-Myers Squibb Company, Pharmacyclics, Gilead, Genentech, AbbVie, TG therapeutics, BeiGene, AstraZeneca, Sunesis, Acerta Pharma, BeiGene, and Merck. **BF:** nothing to disclose. **D-YC:** employed by BeiGene and Acerta Pharma and equity ownership with BeiGene. **XZ:** employed by and equity ownership with BeiGene. **AC:** employed by BeiGene; equity ownership at BeiGene; travel expenses from BeiGene. **SR:** employed by BeiGene; equity ownership at BeiGene and Amgen; travel expenses from BeiGene. **JH:** employed by BeiGene; leadership role with BeiGene; equity ownership with BeiGene. **JPS:** consultancy at AbbVie, Acerta, AstraZeneca, Celgene, A Bristol-Myers Squibb Company, TG Therapeutics, Pharmacyclics, and; research funding from AbbVie, Acerta, AstraZeneca, TG Therapeutics, Pharmacyclics, and Celgene, A Bristol-Myers Squibb Company.

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ACKNOWLEDGMENTS

We would like to thank the site support staff, study sponsors, and collaborators as well as participating patients and their families.

This study is sponsored by BeiGene. Editorial support was provided by Bio Connections, LLC and funded by BeiGene.