A Phase 3, Randomized, Open-Label Study Comparing Zanubrutinib Plus Rituximab Versus Bendamustine Plus Rituximab in Patients With Previously Untreated Mantle Cell Lymphoma Who Are Ineligible for Stem Cell Transplantation

Abstract TPS8071

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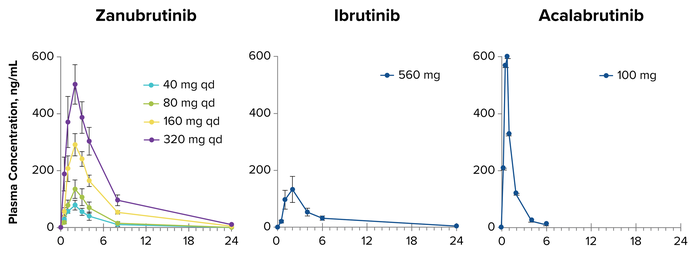
BACKGROUND

- Bruton tyrosine kinase (BTK) mediates B-cell proliferation, migration, and adhesion and is constitutively active in mantle cell lymphoma (MCL)[1-3]
- Several BTK inhibitors have been approved for relapsed/refractory (R/R) MCL, including zanubrutinib, a next-generation BTK inhibitor[4-6]
- Zanubrutinib is designed to maximize BTK occupancy and minimize off-target inhibition of TEC- and epidermal growth factor receptor (EGFR)-family kinases[7]
  - Increased specificity may minimize toxicities (eg, diarrhea, thrombocytopenia, bleeding, atrial fibrillation) reported with ibrutinib, potentially due to off-target inhibition[8]
  - Has been shown in nonclinical studies to be a highly potent, selective, bioavailable, and irreversible BTK inhibitor with potentially advantageous pharmacokinetic/pharmacodynamic (PK/PD) properties[7] (**Figure 1**)
  - Demonstrated complete and sustained BTK occupancy in both peripheral blood mononuclear cells and lymph nodes[7] (**Figure 2**)

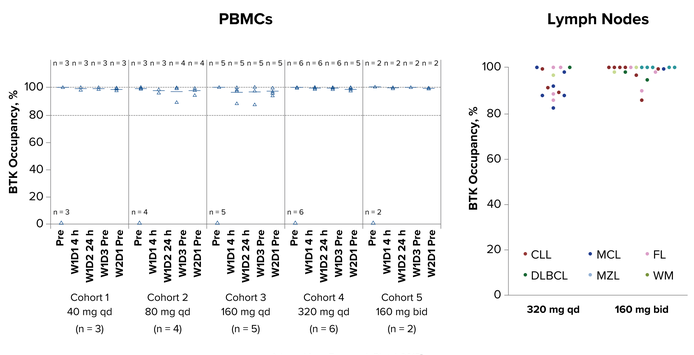
Figure 1: Pharmacokinetics of Zanubrutinib, Ibrutinib, and Acalabrutinib



Adapted from Tam, et al. *Blood.* 2015[7] | Adapted from Advani, et al. *J Clin Oncol.* 2013[9] | Adapted from Byrd, et al. *N Engl J Med.* 2016[10]

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



Adapted from Tam, et al. *Blood.* 2015[7]

Complete and sustained BTK occupancy is observed in paired PBMC and lymph node biopsy samples collected pre dose on day 3. In blood samples, complete BTK occupancy was seen at the lowest dose (40 mg). Note that there is 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; h, hour; MCL, mantle cell lymphoma; MZL, marginal zone lymphoma; PBMC, peripheral blood mononuclear cell; Pre, pre dose; qd, once daily; W, week; WM, Waldenström macroglobulinemia.

- Based on drug-drug interaction studies and PK/PD analyses
  - Zanubrutinib may be coadministered with strong or moderate CYP3A inhibitors at a reduced dose[4]
  - Coadministration of proton pump inhibitors or other acid-reducing agents does not affect zanubrutinib exposure[4]
  - Zanubrutinib has not been found to affect QT interval[4]
  - Antiplatelet medications and anticoagulants including warfarin have been allowed on zanubrutinib trials[11]
- Pooled analysis (n = 682) from 6 zanubrutinib monotherapy studies including patients with non-Hodgkin lymphoma (NHL) has shown that zanubrutinib has been generally well tolerated[11]
  - Some toxicities often associated with BTK inhibitors were infrequent, including atrial fibrillation/flutter (1.9%; grade ≥ 3, 0.6%), major hemorrhage (2.5%; grade ≥ 3, 2.1%), thrombocytopenia (18.3%; grade ≥ 3, 6.6%), and diarrhea (19.4%; grade ≥ 3, 0.9%)
- In two single-arm studies (BGB-3111-206 [NCT03206970] and BGB-3111-AU-003 [NCT02343120]), zanubrutinib monotherapy was generally well tolerated and highly active, in patients with R/R MCL (**Table 1**)[4,12,13]
  - The most common adverse events (AEs) were upper respiratory tract infection (39%), neutropenia and neutrophil count decreased (38%), rash (36%), thrombocytopenia and platelet count decreased (27%), and diarrhea (23%)[4]
    - Majority of AEs were grade 1/2; neutropenia and neutrophil count decreased was the most common ≥ grade 3 AE (15%)[4]
    - No atrial fibrillation/flutter was reported in BGB-3111-206; 2 cases (4.7%) were reported in BGB-3111-AU-003[14,15]
  - 7% of patients (n = 8) discontinued treatment due to AEs
    - The most frequent AE that led to discontinuation was pneumonia (3.4%)[4]
- Current frontline treatments for MCL, including rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP) and R-bendamustine (BR), result in high response rates but fail to cure most patients[16,17]
- Furthermore, the elderly and those with comorbidities are precluded from standard chemoimmunotherapeutic regimens and stem cell transplantation (SCT)[18]
  - These patients have limited options and treatment is largely palliative
  - No standard approach to treatment has been defined
- Given the encouraging clinical activity and tolerability of zanubrutinib in R/R MCL, investigation of zanubrutinib for patients with previously untreated MCL who are ineligible for SCT is warranted

Table 1. Efficacy of Zanubrutinib in 2 Prior Single-Arm Studies in R/R MCL

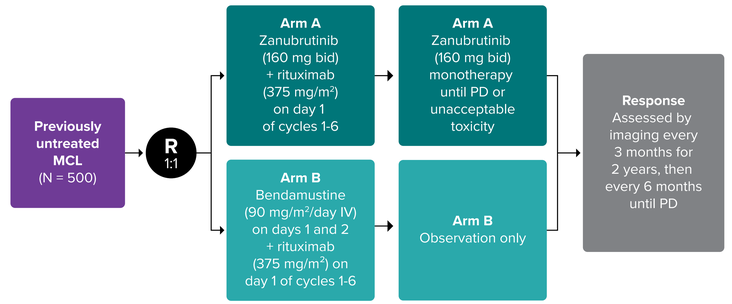
Response	BGB-3111-206[12] (N = 86)[a]	BGB-3111-AU-003[13] (N = 37)[b]
ORR (95% CI)	**84% (74, 91)**	**86% (71, 96)**
CR	69%	30%
PR	15%	57%
Median duration of response, mo (95% CI)	19.5 (16.6, NE)	15.4 (11.5, 28.2)

[a]IRC assessed. [b]Investigator assessed.
CI, confidence interval; CR, complete response; IRC, independent review committee; MCL, mantle cell lymphoma; NE, not estimable; ORR, overall response rate; PR, partial response; R/R, relapsed/refractory.

STUDY DESIGN

- Global, multicenter, phase 3, randomized, open-label, active-control study of zanubrutinib + rituximab followed by zanubrutinib monotherapy versus bendamustine + rituximab followed by observation only in 500 adult patients with previously untreated MCL who are ineligible for stem cell transplantation (BGB-3111-306; NCT04002297; **Figure 3**)
  - The primary objective of the study is to compare efficacy of the treatment arms, as measured by progression-free survival (PFS) and determined by IRC

Figure 3. Study Design



Stratification factors
- **Age:** < 70 vs ≥ 70 years
- **Region:** Asia Pacific vs North America/Europe
- **MCL International Prognostic Index Score:** low vs intermediate/high

Note: One cycle is 28 days.
bid, twice daily; MCL, mantle cell lymphoma; PD, progressive disease; R, randomized.

STUDY ENDPOINTS

PRIMARY
- PFS determined by IRC using the 2014 Lugano Classification for NHL

SECONDARY
- PFS determined by investigator assessment (IA)
- ORR (proportion of patients achieving CR or PR) determined by IRC and IA
- Duration of response determined by IRC and IA
- Overall survival (OS)
- Rate of CR or complete metabolic response
- Time to response determined by IRC and IA
- Patient-reported outcomes as measured by EQ-5D-5L and EORTC QLQ C30 questionnaires
- Safety parameters

EXPLORATORY
- PK parameters
- Correlation between clinical outcomes and the prognostic and predictive biomarkers
- Mechanisms of resistance to zanubrutinib

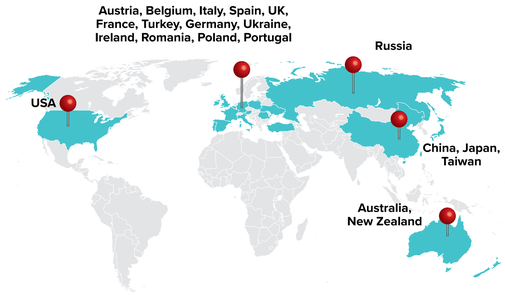
ELIGIBILITY CRITERIA

Key Inclusion Criteria	Key Exclusion Criteria
• Must be ineligible for SCT – Adults aged ≥ 70 years, or ≥ 65 and < 70 years with comorbidities precluding ASCT including at least 1 of the following • Cardiac ejection fraction ≤ 40% • DLCO ≤ 60% predicted • Creatinine clearance < 70 but ≥ 30 mL/min • Histologically confirmed MCL • No prior systemic treatments for MCL • Presence of measurable disease • ECOG PS 0-2 • Adequate organ function	• Known CNS involvement by lymphoma • Prior hematopoietic SCT • Prior treatment with a BTK inhibitor • Patients for whom the goal of therapy is tumor debulking prior to SCT • Prior malignancy within the past 3 years except for curatively treated basal or squamous cell skin cancer, superficial bladder cancer, carcinoma in situ of the cervix or breast, or localized Gleason score 6 prostate cancer • Clinically significant cardiovascular disease • History of severe bleeding • Known infection with HIV or active HBV/HCV

ASCT, autologous stem cell transplant; BTK, Bruton tyrosine kinase; CNS, central nervous system; DLCO, diffusing capacity for carbon monoxide; ECOG PS, Eastern Cooperative Oncology Group performance status; HBV, hepatitis B virus; HCV, hepatitis C virus; HIV, human immunodeficiency virus; MCL, mantle cell lymphoma; SCT, stem cell transplant.

STUDY STATUS

- This study opened to accrual in July 2019 and will be recruiting patients from sites in Australia, Austria, Belgium, China, France, Germany, Italy, Ireland, Japan, New Zealand, Poland, Portugal, Romania, Russia, Spain, Taiwan, Turkey, Ukraine, United Kingdom, and the United States



ENROLLMENT

- Enrollment started in August 2019
- Contact information
  - Rebecca Elstrom, MD or Melannie Co, MD
  - clinicaltrials@beigene.com

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DISCLOSURES

MD: Has received honoraria from Bayer, Celgene, Gilead, Janssen, and Roche; served as consultant/advisor for Acerta, Bayer, Celgene, Gilead, Janssen, Novartis, Roche, and Sandoz; and received research funding from Celgene, Janssen, and Roche. **CST:** Has served as consultant/advisor for BeiGene, Janssen, Roche, AbbVie, and Loxo and received research funding from Janssen, AbbVie, BeiGene, Pharmacyclics, and TG Therapeutics. **MW:** Owns stock in MORE Health; has received honoraria from Pharmacyclics, Janssen, AstraZeneca, OMI, Targeted Oncology, and OncLive; served as consultant/advisor for Pharmacyclics, Celgene, Janssen, AstraZeneca, MORE Health, and Pulse; received research funding from Pharmacyclics, Janssen, AstraZeneca, Kite Pharma, Juno, and Celgene; and received travel/accommodation/expenses from Janssen, Pharmacyclics, Celgene, OMI, Kite Pharma, and AstraZeneca. **SDS:** Has served as consultant/advisor for AstraZeneca and BeiGene and received research funding from Acerta, AstraZeneca, Ayala (family member), Bristol Myers Squibb (family member), Genentech/Roche, Ignyta (family), Incyte, Merck Sharp & Dohme, Pharmacyclics, and Portola. **ML:** Has received honoraria, research funding, travel/accommodations/expenses and has served as a consultant/advisor for AbbVie, Acerta, Amgen, Archigen, Celgene, ADC Therapeutics, Gilead, Novartis, Johnson & Johnson, Roche, Roche Diagnostics, Sandoz, Takeda, and BeiGene. **HH:** Has nothing to disclose. **RE:** Employee of and owns stock in BeiGene. **MC:** Employee of, owns stock in and receives travel expenses from BeiGene. **EH:** Employee of and owns stock in BeiGene. **JH:** Employee of, owns stock in and has a leadership role with BeiGene. **SLG:** Has nothing to disclose.

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.