Phase 2 Study of Zanubrutinib (BGB-3111) in Patients With Relapsed/Refractory Marginal Zone Lymphoma

Abstract TPS7568

MAGNOLIA
Phase 2 Relapsed/Refractory MZL

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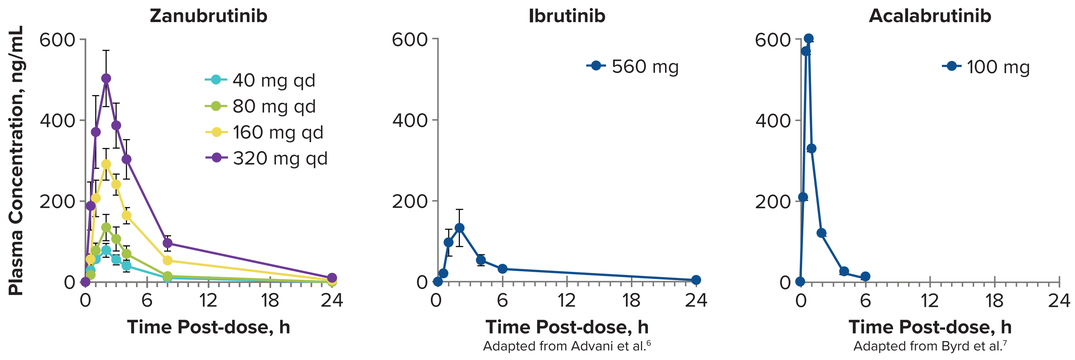
BACKGROUND

- Bruton tyrosine kinase (BTK) is a critical component of the B-cell receptor signaling pathway mediating B-cell proliferation, migration, and adhesion[1-3]
  - Inhibition of BTK is an established therapeutic strategy in B-cell malignancies, including marginal zone lymphoma (MZL)[4]
- 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[5] (**Figure 1**)
  - Complete and sustained BTK occupancy observed in both peripheral blood mononuclear cells and in lymph nodes[5] (**Figure 2**)

Figure 1: Pharmacokinetics of Zanubrutinib, Ibrutinib, and Acalabrutinib

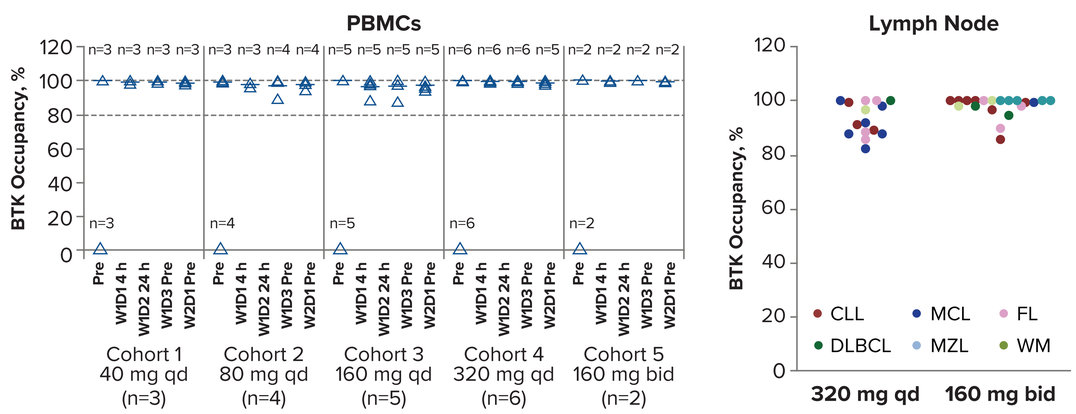


Adapted from Advani et al.[6]

Adapted from Byrd et al.[7]

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
- Results of early phase studies indicate that single-agent zanubrutinib was active in several non-Hodgkin lymphoma subtypes including chronic lymphocytic leukemia,[8] mantle cell lymphoma,[9,10] and Waldenstrom macroglobulinemia[11]
- In the phase 1 study, single-agent zanubrutinib was associated with a response in 7 of 9 evaluable patients with relapsed/refractory (R/R) MZL[12]
- Atrial fibrillation, major hemorrhage, and zanubrutinib discontinuation because of adverse events were infrequent
- To further evaluate the safety and efficacy of single-agent zanubrutinib in patients with R/R MZL, the MAGNOLIA study (BGB-3111-214; NCT03846427) was initiated

MAGNOLIA STUDY DESIGN

- Global, phase 2, open-label, multicenter study of single-agent zanubrutinib in patients with R/R MZL who have received ≥1 prior line of systemic therapy (**Figure 3**)

Figure 3. Study Design

R/R MZL (N=65)
- Measurable disease by CT scan
- ≥1 prior systemic therapy including a CD20-directed regimen (no prior BTK inhibitor)
- Adequate marrow and organ function

→ **Zanubrutinib monotherapy**
160 mg po bid until PD

bid, twice daily; BTK, Bruton tyrosine kinase; CT, computed tomography; po, by mouth; PD, disease progression.

DRUG ADMINISTRATION
- Zanubrutinib: administered as two 80-mg capsules taken orally twice per day (160 mg twice per day) with or without food
- To be continued until disease progression, unacceptable toxicity, treatment consent withdrawal, or study termination

STUDY SIZE
- Approximately 65 patients will be enrolled

MAGNOLIA STUDY END POINTS

PRIMARY
- Overall response rate (ORR; complete response [CR] + partial response [PR]) according to Lugano classification as determined by independent central review (ICR)

SECONDARY
- ORR according to Lugano classification as determined by investigator assessment
- ORR according to Lugano classification as determined by ICR using positron emission tomography for patients with fluorodeoxyglucose (FDG)-avid disease
- Progression-free survival
- Overall survival
- Duration of response
- Time to response
- Time to treatment failure
- Time to next line of therapy
- Patient-reported outcomes
- Safety
- Pharmacokinetics

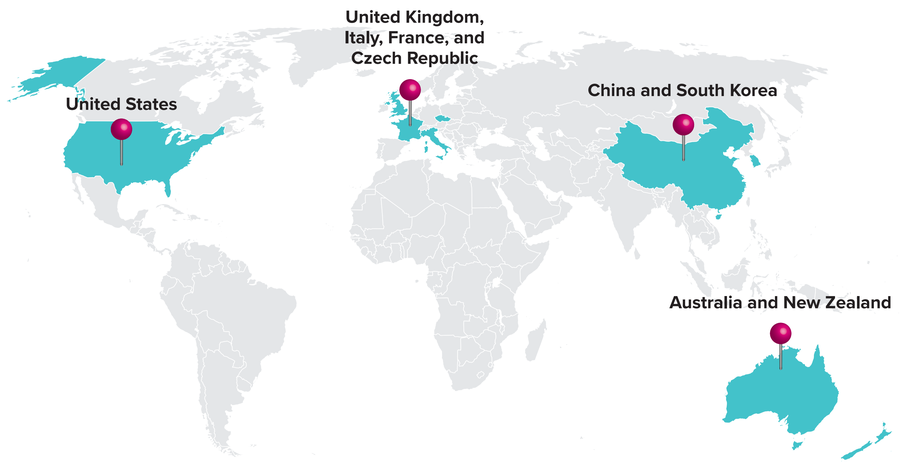
MAGNOLIA KEY ELIGIBILITY CRITERIA

Key Inclusion Criteria	Key Exclusion Criteria
• Histologically confirmed diagnosis of splenic, nodal, or extranodal MZL requiring systemic therapy in the investigator's opinion • Gastric MZL must be *H pylori-negative or H pylori-positive* that has remained stable, progressed, or relapsed after antibiotic therapy • Previously failed ≥1 systemic therapy including ≥1 CD20-directed regimen • Measurable disease by CT or MRI • Age ≥18 years • ECOG performance status 0–2 • Adequate bone marrow,[a] hepatic, and renal function	• Known transformation to aggressive lymphoma • Prior treatment with a BTK inhibitor • Clinically significant cardiovascular disease • History of severe bleeding disorders • History of stroke or intracranial hemorrhage within 180 days of first dose of study drug • Central nervous system involvement

BTK, Bruton tyrosine kinase; CT, computed tomography; ECOG, Eastern Cooperative Oncology Group; MRI, magnetic resonance imaging; MZL, marginal zone lymphoma.
[a]Absolute neutrophil count ≥1000/μL and platelets ≥75,000/μL (750/μL and ≥50,000/μL, respectively, in patients with bone marrow involvement).

MAGNOLIA STUDY STATUS

- This study opened to accrual in October 2018 and will be recruiting patients from approximately 50 participating sites in 9 countries



ENROLLMENT

- Enrollment opened in October 2018
- Contact information:
  - William Reed, MD, or Melannie Co, MD
  - clinicaltrials@beigene.com

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DISCLOSURES

SO: Served as a consultant/advisor for and received honoraria from Roche, Janssen, AbbVie, Celgene, Takeda, Merck, Gilead, and Mundipharma; received research funding from BeiGene, Roche, Janssen, AbbVie, Takeda, Merck, Gilead, Epizyme

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WR: Employed by/owns stock in and has had travel, accommodations, expenses paid for by BeiGene

MC: Is an employee of BeiGene; owns stock in and has had travel, accommodations, expenses paid for by Pharmacyclics and BeiGene

JH: Employed by and owns stock in BeiGene

JT: Received research funding from PCYC, Roche, Janssen, Celgene, and BeiGene

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