# Phase 2 Study of Zanubrutinib (BGB-3111) in Patients with Relapsed/Refractory Marginal Zone Lymphoma (R/R MZL)

MAGNOLIA
Phase 2 Relapsed/Refractory MZL

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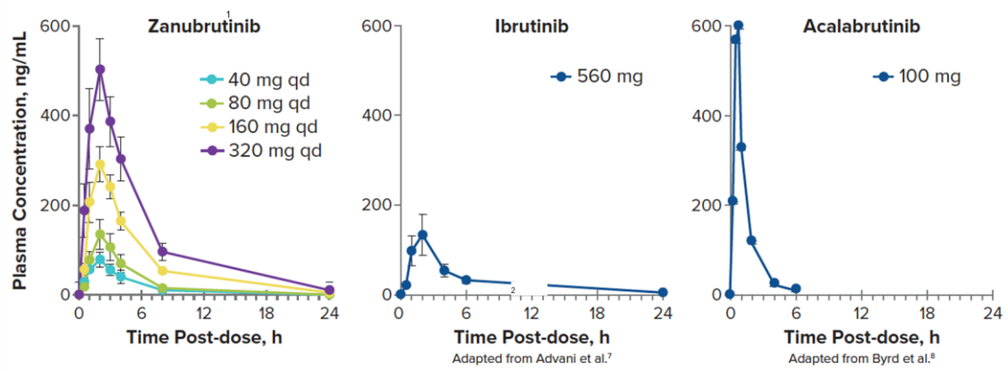
## BACKGROUND

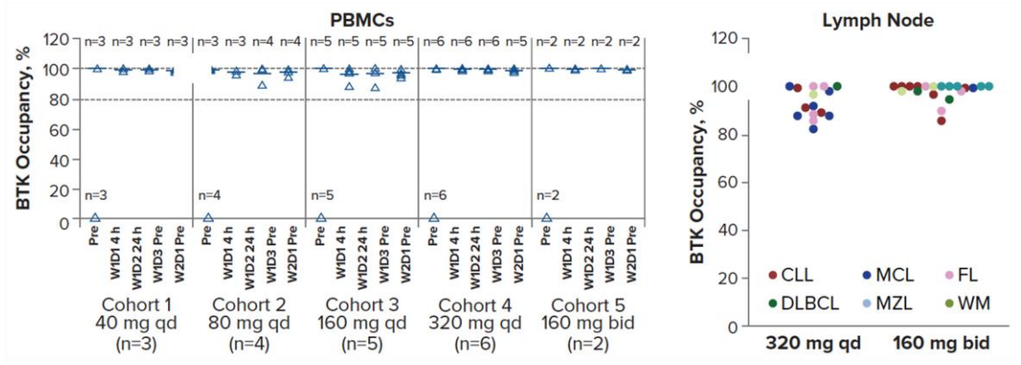
- Bruton tyrosine kinase (BTK) plays a critical role in B-cell receptor signaling, mediating B-cell proliferation, migration, adhesion and survival[1-3]
  - BTK inhibition has emerged as a strategy for targeting B-cell malignancies, including MZL[4]
- Zanubrutinib (BGB-3111) is an investigational, next-generation 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




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




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.

- Advanced MZL is generally incurable, and the patients' prognosis is poor when relapsed or failed to respond to treatment due to lack of approved therapies specially for MZL.
- Preliminary results from the MZL cohort enrolled in the open-label, multicenter, phase 1 study demonstrated responses in 7 of 9 patients for an overall response rate (ORR) of 78%[6]
- Cumulative safety data also showed that zanubrutinib monotherapy was associated with infrequent incidence of atrial fibrillation and major hemorrhage and infrequent drug discontinuation due to treatment-related adverse events
- This study is designed to evaluate the safety and efficacy of zanubrutinib in patients with R/R MZL

## 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

**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 ENDPOINTS

### 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

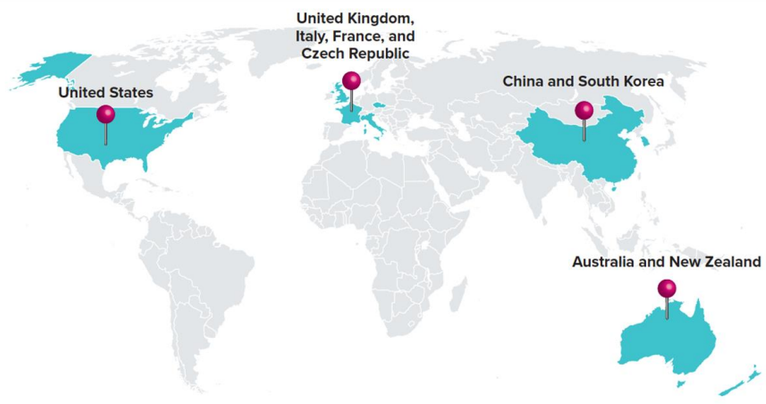
## MAGNOLIA KEY ELIGIBILITY CRITERIA

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

## REFERENCES

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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

**RM:** Served as a consultant/advisor and provided expert testimony for Gilead; received honoraria from Roche-Genentech; participated in a speaker's bureau for Roche; travel, accommodations, expenses paid for by Roche and Takeda

**CP:** Served as a consultant/advisor for Genentech, Amgen, and Bayer; received research funding from AbbVie, Roche/Genentech, Infinity, Acerta/AstraZeneca, TG Therapeutics, BeiGene, Kite, and Xencor

**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

**HG:** Employed by and owns stock in BeiGene

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

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