Long-term efficacy and safety of zanubrutinib in patients with relapsed/refractory (R/R) marginal zone lymphoma (MZL): final analysis of the MAGNOLIA (BGB-3111-214) trial

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ABSTRACT

Objective: Advanced-stage MZL is generally considered incurable and is characterized by periods of remission and relapse. Zanubrutinib (BGB-3111) is a potent and highly specific next-generation Bruton tyrosine kinase (BTK) inhibitor recently approved by the US Food and Drug Administration and Health Canada for the treatment of patients with R/R MZL based on the primary analysis results of the MAGNOLIA study (BGB-3111-214; NCT03846427). Here, we present the final analysis of MAGNOLIA at a median follow-up of 28 months.

Methods: MAGNOLIA is a phase 2, multicenter, single-arm study in adult patients requiring systemic treatment for R/R MZL who received ≥1 prior line of therapy, including ≥1 CD20-directed regimen. All patients were treated with zanubrutinib 160 mg twice daily until disease progression or unacceptable toxicity. Use of long-term antiplatelets and anticoagulants was permitted. The primary endpoint was overall response rate (ORR) as determined by an independent review committee (IRC) in accordance with the Lugano classification. Secondary endpoints included ORR by investigator assessment, duration of response (DOR), progression-free survival (PFS), overall survival (OS), and safety. Efficacy was assessed by positron emission tomography–based Lugano criteria in patients with IRC-confirmed

fluorodeoxyglucose (FDG)-avid disease at baseline; patients with non-avid disease were assessed by computed tomography (CT)–based criteria. A sensitivity analysis using only CT-based criteria was also performed.

Results: As of May 4, 2022, 68 patients were enrolled and treated. The median age was 70 years (range, 37-95 years), with 27.9% aged ≥75 years. MZL subtypes included extranodal (mucosa-associated lymphoid tissue) in 38.2%, nodal in 38.2%, splenic in 17.6%, and unknown in 5.9% of patients. The median number of prior therapies was 2 (range, 1-6); 32.4% of patients had disease that was refractory to last therapy. Most (89.7%) patients received prior chemoimmunotherapy, and 7 (10.3%) received rituximab monotherapy as their only prior treatment. Sixty-one patients (89.7%) had IRC-assessed FDG-avid disease. After a median follow-up of 28.0 months (range, 1.6-32.9 months) and a median treatment duration of 24.2 months (range, 0.9-32.9 months), 66 patients were evaluable for efficacy. Two patients were excluded from analysis owing to centrally confirmed transformation to diffuse large B-cell lymphoma. IRC-assessed ORR (complete response [CR] + partial response [PR]) was 68.2% (CR, 25.8%; PR, 42.4%). Responses were observed in all MZL subtypes, with an ORR of 64.0%, 76.0%, 66.7%, and 50.0% in extranodal, nodal, splenic, and unknown subtypes, respectively. The CR rate was 40.0% in extranodal, 20.0% in nodal, 8.3% in splenic, and 25.0% in unknown subtypes. The median DOR, PFS, and OS were not reached. More than 70.0% of patients were alive and progression free at the 24-month landmark by independent review (DOR rate by IRC, 72.9%; 95% CI, 54.4%-84.9%; PFS rate by IRC, 70.9%; 95% CI, 57.2%-81.0%; OS rate, 85.9%; 95% CI, 74.7%-92.4%). Sensitivity analysis using only CT-based criteria (n=66) by IRC assessment showed an ORR of 66.7% and a CR rate of 24.2%. Similarly, median DOR and median PFS were not reached (24-month DOR rate, 66.8%; 95% CI, 46.4%-81.0%; 24-month PFS rate, 64.9%; 95% CI, 51.2%-75.6%). At study completion, 31 patients (45.6%) deriving benefit rolled over to a long-term extension (LTE) study (NCT04170283); 24 patients (35.3%) discontinued owing to disease progression (investigator assessed) and 5 (7.4%) due to adverse events (AEs), 2 (2.9%) required prohibited medications, and 1 (1.5%) withdrew consent. All patients experienced ≥1 treatment-emergent AE. The most common treatment-emergent AEs in >10% of patients were bruising (23.5%), diarrhea (22.1%), constipation (17.6%), arthralgia (14.7%), pyrexia (14.7%), upper respiratory tract infection (13.2%), and abdominal pain and back pain (each 11.8%). Grade ≥3 treatment-emergent AEs were experienced by 33 patients (48.5%). Neutropenia (8.8%) and COVID-19 pneumonia (5.9%) were the most common grade ≥3 AEs. Thirty patients (44.1%) experienced serious treatment-emergent AEs; 25 patients (36.8%) had treatment-emergent AEs leading to dose interruption, and no patients experienced treatment-emergent AEs that led to dose reduction. Five patients (7.4%) died due to unrelated AEs: COVID-19 pneumonia (n=2), acute myeloid leukemia (n=1, prior alkylating agent exposure), myocardial infarction (n=1, preexisting coronary artery disease), and septic encephalopathy (n=1, patient in CR). Hypertension occurred in 3 patients (4.4%) and atrial fibrillation and atrial flutter in 1 patient (1.5%) each; none led to treatment withdrawal. One patient (1.5%) experienced grade 3 gastrointestinal hemorrhage while receiving rivaroxaban for pulmonary embolism; the patient fully recovered and rolled over to the LTE study.

Conclusion: In this final analysis with a median study follow-up of >2 years, zanubrutinib continues to be effective, as demonstrated by high response rates and durable disease control. Zanubrutinib was generally well tolerated, with no new safety signals observed.