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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Introduction: Advanced-stage MZL is characterized by recurring periods of remission and relapse. Zanubrutinib (BGB-3111) is a potent, selective next-generation Bruton tyrosine kinase (BTK) inhibitor approved for the treatment of R/R MZL. Here, we present the final analysis of the phase 2 MAGNOLIA (NCT03846427) study.

Methods: Eligible patients included adults requiring systemic treatment for R/R MZL with ≥1 prior CD20-directed regimen. All patients received zanubrutinib 160 mg twice daily until disease progression or unacceptable toxicity. Long-term use of antiplatelets and anticoagulants was permitted. Primary endpoint was overall response rate (ORR) by independent review committee (IRC) based on Lugano criteria. 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 (PET)-based Lugano criteria for patients with IRC-confirmed fluorodeoxyglucose (FDG)-avid disease at baseline; non-avid patients 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 (66 efficacy-evaluable) patients were enrolled and treated. Median age was 70 years (range 37-95), with 27.9% aged ≥75 years. Median number of prior systemic therapies was 2 (range 1-6), 32.4% of patients had disease refractory to last therapy; 61 (89.7%) and 7 (10.3%) patients receiving chemoimmunotherapy or rituximab monotherapy, respectively. Sixty-one (89.7%) patients had IRC-assessed FDG-avid disease. MZL subtypes included extranodal (38.2%), nodal (38.2%), splenic (17.6%), and unknown (5.9%).

Median follow-up was 28 months (range 1.6-32.9) and median treatment duration was 24.2 months (range 0.9-32.9). IRC-assessed ORR was 68.2%; complete response (CR) was 25.8%. Responses were observed in all MZL subtypes (ORR of 64.0% extranodal, 76.0% nodal, 66.7% splenic, 50.0% unknown; CR of 40.0% extranodal, 20.0% nodal, 8.3% splenic, 25.0% unknown). Median DOR, PFS, and OS were not reached. At the 2-year landmark by IRC, >70.0% of patients were alive or progression-free. Sensitivity analysis using only CT-based criteria (n=66) by IRC assessment showed an ORR of 66.7% and CR of 24.2%. Similarly, median DOR and median PFS were not reached. At study completion, 31 (45.6%) patients deriving benefit rolled over to a long-term extension study (NCT04170283), 24 (35.3%) discontinued owing to investigator-assessed disease progression, 5 (7.4%) due to adverse events (AEs), 2 (2.9%) required prohibited medications, and 1 (1.5%) withdrew consent. Most common treatment-emergent AEs were bruising (23.5%), diarrhea (22.1%), constipation (17.6%), arthralgia (14.7%), pyrexia (14.7%), upper respiratory tract infection (13.2%), abdominal pain and back pain (11.8% each). Most common grade ≥3 AEs were neutropenia (8.8%) and COVID-19 pneumonia (5.9%). Five (7.4%) patients died due to unrelated AEs. Three (4.4%) patients reported hypertension, 1 (1.5%) atrial fibrillation, and 1 (1.5%) atrial flutter; none led to treatment withdrawal.

Conclusion: With more than 2 years of follow-up, zanubrutinib has shown clinically meaningful benefits demonstrated by high response rates, durable disease control, and a tolerable AE profile.
