LONG-TERM EFFICACY AND SAFETY OF ZANUBRUTINIB (ZANU) IN PATIENTS (PTS) WITH RELAPSED/REFRACTORY (R/R) MARGINAL ZONE LYMPHOMA (MZL): FINAL ANALYSIS OF THE MAGNOLIA (BGB-3111-214) TRIAL

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Background: Zanubrutinib (BGB-3111) is a potent next-generation Bruton tyrosine kinase inhibitor approved in various countries for the treatment of R/R MZL based on the primary analysis results of the MAGNOLIA study (NCT03846427).

Aims: To present the final analysis of MAGNOLIA at a median follow-up of 28 months (mo).

Methods: MAGNOLIA is a phase 2, multicenter, single-arm study of adult pts requiring systemic treatment for R/R MZL with ≥1 prior line of therapy including ≥1 CD20-directed regimen. All pts received zanubrutinib 160 mg twice daily until disease progression or unacceptable toxicity. Primary endpoint was overall response rate (ORR) by 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 (PET)-based Lugano criteria for pts with IRC-confirmed fluorodeoxyglucose (FDG)-avid disease at baseline; non-avid pts 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 pts were enrolled and treated. Median age was 70 years (range 37-95).

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 pts. Most (89.7%) pts received prior chemoimmunotherapy. Sixty-one (89.7%) pts had IRC-assessed FDG-avid disease. After a median follow-up of 28.0 mo (range 1.6-32.9) and a median treatment duration of 24.2 mo (range 0.9-32.9), 66 pts were evaluable for efficacy (Table). IRC-assessed ORR (complete response [CR] + partial response [PR]) was 68.2% (CR 25.8%). ORR was 64.0%, 76.0%, 66.7%, and 50.0% in extranodal, nodal, splenic, and unknown subtypes, respectively. CR rate was 40.0% in extranodal, 20.0% in nodal, 8.3% in splenic, and 25.0% in unknown subtypes. Median DOR, PFS, and OS were not reached. At the 2-year landmark by independent review, >70.0% of pts were alive or progression-free. Sensitivity analysis using only CT-based criteria (n=66) by IRC assessment showed an ORR of 66.7% (CR 24.2%). Median DOR and median PFS were not reached. At study completion, 31 (45.6%) pts deriving benefit rolled over to a long-term extension (LTE) study (NCT04170283); 24 (35.3%) pts discontinued owing to disease progression (investigator assessed); 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 in >20% of pts were bruising (23.5%), and diarrhea (22.1%). Neutropenia (8.8%) and COVID-19 pneumonia (5.9%) were the most common grade ≥3 AEs. Five (7.4%) pts 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, pt in CR). Hypertension occurred in 3 (4.4%) pts, atrial fibrillation and atrial flutter in 1 (1.5%) pt each; none led to treatment withdrawal. One (1.5%) pt experienced grade 3 gastrointestinal hemorrhage while receiving rivaroxaban for pulmonary embolism; pt fully recovered and rolled over to the LTE study.

Summary/Conclusion: With more than 2 years of median study follow-up, zanubrutinib continues to be effective as demonstrated by high response rates and durable disease control, and is generally well tolerated with no new safety signals observed.

Table: Baseline Characteristics, Efficacy, and Safety Outcomes

Baseline Characteristics	**R/R MZL (N=68)[a]**		
Male sex, n (%)	36 (52.9)		
ECOG PS 0-1, n (%)	63 (92.7)		
Bone marrow involvement, n (%)	29 (42.6)		
Extranodal sites, n (%)	53 (77.9)		
Stage III/IV, n (%)	59 (86.8)		
Efficacy	**(N=66)[b]**		
	IRC		**INV**
	PET and/or CT	CT only	PET and/or CT
ORR, n (%) [95% CI]	45 (68.2) [55.6, 79.1]	44 (66.7) [54.0, 77.8]	50 (75.8) [63.6 85.5]
Best response, n (%)			
CR	17 (25.8)	16 (24.2)	19 (28.8)
PR	28 (42.4)	28 (42.4)	31 (47.0)
SD	13 (19.7)	16 (24.2)	10 (15.2)
PD	6 (9.1)	5 (7.6)	5 (7.6)
DOR rate at 24 months, % [95% CI]	72.9 [54.4, 84.9]	66.8 [46.4, 81.0]	60.8 [44.8, 73.6]
PFS rate at 24 months, % [95% CI]	70.9 [57.2, 81.0]	64.9 [51.2, 75.6]	57.9 (44.8, 68.9]

OS rate at 24 months, % [95% CI]	85.9 [74.7, 92.4]
Safety[c]	**(N=68)**[a]
Any TEAE, n (%)	68 (100)
Grade ≥3 TEAE, n (%)	33 (48.5)
Drug-related grade ≥3 TEAE, n (%)[d]	10 (14.7)
Serious TEAE, n (%)	30 (44.1)
Drug-related serious TEAE, n (%)[d]	7 (10.3)
TEAE leading to dose interruption, n (%)	25 (36.8)
Drug-related TEAE leading to dose interruption, n (%)[d]	8 (11.8)
TEAE leading to dose reduction, n (%)	0

Data cutoff: May 4, 2022.

CR, complete response; CT, computed tomography; DOR, duration of response; ECOG PS, Eastern Cooperative Oncology Group performance status; INV, investigator; IRC, independent review committee; MZL, marginal zone lymphoma; ORR, overall response rate; PD, progressive disease; PET, positron emission tomography; PR, partial response; R/R, relapsed/refractory; SD, stable disease; TEAE, treatment-emergent adverse event.

[a]Safety analysis set is defined as all patients who received at least 1 dose of study drug.

[b]Efficacy analysis set is defined as all patients in the safety analysis set with centrally confirmed diagnosis of MZL. Two pts were excluded from analysis owing to centrally confirmed transformation to diffuse large B-cell lymphoma. One pt discontinued study before first response assessment.

[c]TEAE is defined as an adverse event that had an onset date or a worsening in severity from baseline (pretreatment) on or after the first dose of study drug up to 30 days after study drug discontinuation or initiation of a new anticancer therapy. Worsening of an event to grade 5 beyond day 30 after last dose of study drug of a TEAE is also considered a TEAE (if it is before start of new anticancer therapy).

[d]Based on assessment by the investigators.