***Title (Italian)*:** EFFICACIA E SICUREZZA A LUNGO TERMINE DI ZANUBRUTINIB IN PAZIENTI CON LINFOMA DELLA ZONA MARGINALE RECIDIVATO/REFRATTARIO: ANALISI FINALE DELLO STUDIO MAGNOLIA (BGB-3111-214)

***Title (English)*:** 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: The MAGNOLIA study (NCT03846427) primary analysis results led to approval of ZANU (BGB-3111), a potent next-generation Bruton tyrosine kinase inhibitor, for the treatment (tx) of R/R MZL. Here we report the final results of MAGNOLIA.

Methods: MAGNOLIA was a phase 2, multicenter, single-arm study in adults requiring systemic tx for R/R MZL with ≥1 prior CD20-directed regimen. All pts received ZANU 160 mg twice daily until disease progression or unacceptable toxicity. The primary endpoint was overall response rate (ORR) by independent review committee (IRC) per the Lugano criteria. Secondary endpoints included investigator-assessed ORR, duration of response (DOR), progression-free survival (PFS), overall survival (OS), and safety. Efficacy was assessed by positron emission tomography in pts with IRC-confirmed fluorodeoxyglucose-avid disease; non-avid disease was assessed with computed tomography (CT)–based criteria. Sensitivity analysis with only CT-based criteria was also done.

Results: As of May 4, 2022, 68 pts were enrolled and treated. Median age was 70 y. MZL subtypes included extranodal (38.2%), nodal (38.2%), splenic (17.6%), and unknown (5.9%). Most pts (89.7%) received prior chemoimmunotherapy; 32.4% had refractory disease at study entry. After a median follow-up of 28.0 mo and tx duration of 24.2 mo, 66 pts were evaluable for

efficacy (**Table**). ORR was 64.0% (extranodal), 76.0% (nodal), 66.7% (splenic), and 50.0% (unknown subtype); the complete response (CR) rate was 40.0%, 20.0%, 8.3%, and 25.0%, respectively. Median DOR, PFS, and OS were not reached. Sensitivity analysis (CT-based criteria by IRC) showed an ORR of 66.7% and a CR rate of 24.2%. At study completion, 31 pts deriving benefit rolled over to a long-term extension study (NCT04170283); 24 pts discontinued due to disease progression and 5 due to adverse events (AEs), 2 required prohibited medications, and 1 withdrew consent. The most common tx-emergent AEs were bruising (23.5%) and diarrhea (22.1%). Neutropenia (8.8%) and COVID-19 pneumonia (5.9%) were the most common grade ≥3 AEs; 5 pts died due to unrelated AEs. Hypertension occurred in 3 pts (4.4%) and atrial fibrillation and atrial flutter in 1 pt (1.5%) each; none led to tx withdrawal.

Conclusion: With a median study follow-up of >2 years, ZANU 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, n (%)	**R/R MZL (N=68)[a]**		
Male sex	36 (52.9)		
ECOG PS 0-1	63 (92.7)		
Bone marrow involvement	29 (42.6)		
Extranodal sites	53 (77.9)		
Stage III/IV	59 (86.8)		
FDG-avid disease (by IRC)	61 (89.7)		
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 mo, [95% CI], %	72.9 [54.4-84.9]	66.8 [46.4-81.0]	60.8 [44.8-73.6]
PFS rate at 24 mo, [95% CI], %	70.9 [57.2-81.0]	64.9 [51.2-75.6]	57.9 [44.8-68.9]
OS rate at 24 mo, [95% CI], %	85.9 [74.7-92.4]		
Safety, n (%)[c]	**(N=68)[a]**		
Any TEAE	68 (100)		
Grade ≥3 TEAE	33 (48.5)		
Drug-related grade ≥3 TEAE[d]	10 (14.7)		
Serious TEAE	30 (44.1)		
Drug-related serious TEAE[d]	7 (10.3)		
TEAE leading to dose interruption	25 (36.8)		
Drug-related TEAE leading to dose interruption[d]	8 (11.8)		
TEAE leading to dose reduction	0		

Data cutoff: May 4, 2022.

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

[a] The safety analysis set is defined as all pts who received at least 1 dose of study drug.

[b] The efficacy analysis set is defined as all pts in the safety analysis set with a 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 the study before the first response assessment.

[c] TEAE is defined as an adverse event with an onset date or a worsening in severity from baseline (pretreatment) on or after first dose of study drug and 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 is also considered a TEAE (if it is before the start of a new anticancer therapy).
[d] Based on INV assessment.