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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Rationale: Zanubrutinib is a next-generation Bruton tyrosine kinase inhibitor approved for the treatment of R/R MZL based on the primary results of MAGNOLIA (NCT03846427). Final analyses are reported here.

Method: MAGNOLIA was a phase 2, single-arm study in patients with R/R MZL treated with ≥1 prior CD20-directed regimen. Patients received zanubrutinib 160 mg twice daily until disease progression or unacceptable toxicity. The primary endpoint was overall response rate (ORR) by independent review committee (IRC) per Lugano classification. 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 (PET)–based Lugano criteria (IRC-confirmed fluorodeoxyglucose [FDG]-avid disease) or computed tomography (CT)–based criteria (non–FDG-avid disease).

Result: By May 4, 2022, 68 patients were treated (median age, 70 years). MZL subtypes included extranodal (38.2%), nodal (38.2%), splenic (17.6%), and unknown (5.9%). Most patients (89.7%) received prior chemoimmunotherapy. Sixty-six patients were evaluable for efficacy (median follow-up, 28 months). IRC-assessed ORR was 68.2% (**Table**). ORRs were 64.0% (extranodal), 76.0% (nodal), 66.7% (splenic), and 50.0% (unknown). Median DOR, PFS, and OS were not reached. At the 2-year landmark, >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%. Median DOR and median PFS were not reached. At study completion, 31 patients deriving benefit enrolled in a long-term extension (LTE) study (NCT04170283). Patients discontinued owing to disease progression (n=24), adverse events (AEs) (n=5), prohibited medications (n=2), and consent withdrawal (n=1). The most common treatment-emergent AEs in >20% of patients 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 patients died due to unrelated AEs. Hypertension occurred in 3 patients and atrial fibrillation and atrial flutter in 1 patient each; none led to treatment withdrawal. One patient experienced grade 3 gastrointestinal hemorrhage while receiving rivaroxaban for pulmonary embolism, fully recovered, and rolled over to the LTE study.

Conclusion: Zanubrutinib continued to be effective in suitable patients with MZL, with high response rates and durable disease control; zanubrutinib was generally well tolerated with no new safety signals observed, consistent with the primary results of MAGNOLIA.

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

CR, complete response; ECOG PS, Eastern Cooperative Oncology Group performance status; INV, investigator; PD, progressive disease; PR, partial response; SD, stable disease; TEAE, treatment-emergent adverse event.

[a] The safety analysis set is defined as all patients who received ≥1 dose of study drug.

[b] The efficacy analysis set is defined as all patients in the safety analysis set with centrally confirmed diagnosis of MZL. Two patients were excluded from analysis owing to centrally confirmed transformation to diffuse large B-cell lymphoma. One patient discontinued the study before the 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 date of 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 is also considered a TEAE (if it is before the start of new anticancer therapy).

[d] Based on assessment by the investigators.