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

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Aim: MAGNOLIA (NCT03846427) primary results led to approval of zanubrutinib, a next-generation Bruton tyrosine kinase inhibitor, for relapsed/refractory marginal zone lymphoma (MZL); final results are reported.

Method: MAGNOLIA was a phase 2, multicenter, single-arm study in relapsed/refractory 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 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–based Lugano criteria (IRC-confirmed fluorodeoxyglucose-avid disease) or computed tomography–based criteria (non-avid disease).

Results: 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; 32.4% had refractory disease at study entry. Sixty-six patients were evaluable for efficacy (median follow-up, 28.0 months) (**Table**). ORRs were 64.0% (extranodal), 76.0% (nodal), 66.7% (splenic), and 50.0% (unknown subtype); complete response rates were 40.0%, 20.0%, 8.3%, and 25.0%, respectively. Median DOR, PFS, and OS were not reached. At study completion, 31 patients deriving benefit rolled over to

a long-term extension study (NCT04170283); 24 discontinued due to disease progression and 5 due to adverse events (AEs), 2 required prohibited medications, and 1 withdrew consent. The most common treatment-emergent AEs were bruising (23.5%) and diarrhea (22.1%). The most common grade ≥3 AEs were neutropenia (8.8%) and COVID-19 pneumonia (5.9%); 5 patients died due to unrelated AEs. Hypertension occurred in 3 patients and atrial fibrillation and flutter in 1 each; none led to treatment withdrawal.

Conclusion: Zanubrutinib continues to be effective with high response rates and durable disease control. Zanubrutinib is generally well tolerated; no new safety signals were observed.

Table. Efficacy Results[a]

	IRC (n=66)		**Investigator (n=66)**
	PET and/or CT	CT only[b]	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]
Complete response, n (%)	17 (25.8)	16 (24.2)	19 (28.8)
Partial response, n (%)	28 (42.4)	28 (42.4)	31 (47.0)
Stable disease, n (%)	13 (19.7)	16 (24.2)	10 (15.2)
Progressive disease, n (%)	6 (9.1)	5 (7.6)	5 (7.6)
24-month DOR rate [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]		

CT, computed tomography; PET, positron emission tomography.
[a] n=2 excluded from analysis (centrally confirmed transformation to diffuse large B-cell lymphoma);
[b] Sensitivity analysis using only CT-based Lugano criteria regardless of PET status at baseline.