SAFETY AND EFFICACY OF ZANUBRUTINIB IN PATIENTS WITH RELAPSED/ REFRACTORY MARGINAL ZONE LYMPHOMA (MAGNOLIA PHASE 2 STUDY)

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Introduction: Zanubrutinib is a potent, specific next-generation BTK inhibitor with higher selectivity for BTK compared with TEC- and EGFR-family kinases, which may be related to off-target toxicities. The initial efficacy and safety results of zanubrutinib in patients with relapsed/refractory marginal zone lymphoma (R/R MZL) enrolled in the MAGNOLIA study (BGB-3111-214; NCT03846427) are presented.

Methods: In this single-arm, multicenter study, adults with R/R MZL who had received one or more prior therapy including at least one CD20 antibody regimen were treated with zanubrutinib 160 mg twice daily until disease progression or unacceptable toxicity. The primary endpoint was overall response rate (ORR) by independent review committee (IRC). Secondary endpoints included investigator-assessed ORR (ORR_{INV}), duration of response (DOR), progression-free survival (PFS), and safety.

Results: As of January 11, 2021, 68 patients were enrolled and treated. Median age was 70 years (range, 37-95) and 28% of patients were aged ≥75 years. Patients had the following MZL subtypes: extranodal (38%), nodal (38%), splenic (18%), and indeterminate (6%). Median number of prior therapies was 2 (range, 1-6), and 32% of patients had disease refractory to last therapy.

Median duration of drug exposure was 59.1 weeks (range, 3.7-84.1). At a median follow-up of 15.5 months (range, 1.6-21.7), ORR_{INV} was 74% with a complete response rate of 24% (**Table**). Responses were observed in all subtypes, with an ORR of 68%, 84%, 75%, and 50% in extranodal, nodal, splenic, and indeterminate subtypes, respectively. Median DOR and PFS were not reached. IRC review is ongoing.

Twenty-eight (41%) patients discontinued treatment (20 due to disease progression; 4 due to adverse events [AEs]). The most common treatment-emergent AEs reported in ≥10% of patients were diarrhea (22%), bruising (21%), and constipation (15%). Neutropenia was the most common grade ≥3 AE (10%). All-grade AEs of interest included neutropenia (13%), thrombocytopenia (13%), atrial fibrillation/flutter (3%), and hypertension (3%). AEs leading to treatment discontinuation included fatal Covid-19 pneumonia (n=2), fatal myocardial infarction in a patient with pre-existing coronary artery disease, and pyrexia attributed to disease transformation. No major/serious hemorrhage was reported. No AEs led to dose reductions.

Conclusions: Zanubrutinib demonstrated high response rates and durable disease control with a favorable safety profile in patients with R/R MZL.

Table. Efficacy and Safety Outcomes in R/R MZL

	R/R MZL (N=68)[a]
Efficacy (investigator assessment)	**(N=66)[b]**
ORR, n (%) [95% CI]	49 (74) [62, 84]
Complete response	16 (24)
Partial response	33 (50)
Stable disease[c]	11 (17)
Progressive disease	5 (8)
Discontinued study before first assessment	1 (2)
Time to response (months), median (range)	2.8 (1.7, 8.5)
Safety[d]	**(N=68)[a]**
Any AE	65 (96)
Grade ≥3 AE, n (%)	26 (38)
Serious AE, n (%)	25 (37)
AE leading to dose interruption, n (%)	19 (28)

[a]Safety analysis set: patients who received ≥1 dose of study drug.
[b]Efficacy-evaluable set: patients who received ≥1 dose of study drug and with centrally confirmed MZL diagnosis (2 patients were excluded due to transformation to diffuse large B-cell lymphoma).
[c]Three patients with stable disease were continuing on study treatment.
[d]Treatment-emergent AEs.
AE, adverse event; MZL, marginal zone lymphoma; ORR, overall response rate; R/R, relapsed/refractory.