Title: Efficacy and Safety of Zanubrutinib in Patients with Relapsed/Refractory Marginal Zone Lymphoma: Initial Results of the MAGNOLIA (BGB-3111-214) Trial

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Background: Marginal zone lymphoma (MZL) is rare and heterogeneous and it has been difficult to define optimal therapeutic strategies. Like other indolent non-Hodgkin lymphomas, advanced stage disease is considered incurable, with most patients experiencing a continuing pattern of relapse and remission. MZL is typically dependent on B-cell receptor (BCR) signaling suggesting a role for BCR pathway targeting via inhibition of Bruton's tyrosine kinase (BTK). The utility of this approach was confirmed by the pivotal phase 2 study demonstrating a 48% objective response rate (ORR) to ibrutinib in patients with relapsed/refractory (R/R) MZL (Noy et al. *Blood*. 2017;129:2224-2232).

Zanubrutinib (BGB-3111) is a potent, highly specific, and irreversible next-generation BTK inhibitor. It was specifically designed to maximize BTK occupancy and minimize off-target inhibition of TEC- and EGFR-family kinases, which are thought to be related to atrial fibrillation, thrombocytopenia, and bleeding events. In an early-phase study (BGB-3111-AU-003) of 20 patients with R/R MZL treated with zanubrutinib, at a median follow-up of 27.1 months, the ORR was 80%, with a complete response (CR) rate of 15%, and partial response (PR) rate of 65% (Tedeschi et al. EHA 2020, abstract 2804). Presented

here are initial efficacy and safety data in patients with R/R MZL enrolled in the MAGNOLIA trial (BGB-3111-214).

Methods: MAGNOLIA is a phase 2, multicenter, single-arm study of adult patients requiring systemic treatment for R/R MZL who had previously received one or more lines of therapy including at least one CD20-directed regimen. All patients were treated with zanubrutinib 160 mg twice daily until disease progression or unacceptable toxicity. Use of long-term antiplatelet and anticoagulation agents was permitted. The primary end point was ORR as determined by an independent review committee in accordance with the Lugano classification. Secondary end points include ORR by investigator assessment, duration of response (DOR), progression-free survival (PFS), and safety.

Results: In total, 68 patients were enrolled and treated. The median age was 70 years (range, 37-95), with 28% aged ≥75 years. MZL subtypes included extranodal (mucosa-associated lymphoid tissue) in 38%, nodal in 38%, splenic in 18%, and unknown in 6% of patients. The median number of prior therapies was 2 (range, 1-6), and 35% of patients had disease refractory to last therapy.

At a median follow-up of 6.8 months (range, 1.6-12.8), 67 patients were evaluable for efficacy. Investigator-assessed ORR (CR + PR) was 60% (CR 15%, PR 45%, stable disease 27%). Responses were observed in all MZL subtypes, with an ORR of 58%, 64%, 58%, and 50% in extranodal, nodal, splenic, and unknown subtypes, respectively. CR rate was 23% for extranodal MZL, 12% for nodal, and 50% for unknown subtype. CR was not observed in patients with splenic MZL. The median DOR and median PFS were not reached.

Twenty-one (30.9%) patients discontinued study treatment. Treatment discontinuation was mainly due to disease progression (16 patients; 23.5%); 1 withdrew consent, 2 required prohibited medications, and 2 due to adverse events (AEs) – 1 from pyrexia (later attributed to disease transformation) and 1 from myocardial infarction. The most common treatment-emergent AEs reported in ≥10% of patients were diarrhea (19.1%), bruising (17.6%), constipation (13.2%), pyrexia (10.3%), upper respiratory tract infection (10.3%), and nausea (10.3%). Most AEs were low grade. Neutropenia was the most common grade ≥3 AE (7.3%). Treatment-related serious AEs included atrial flutter, pyrexia, pneumonia, and thrombocytopenia (1 patient each). One patient with pre-existing coronary artery disease died from myocardial infarction, which was assessed as unrelated to zanubrutinib. All-grade AEs of interest included neutropenia (10.3%), thrombocytopenia (10.3%), and atrial flutter (1.5%). To date, no major hemorrhage, serious opportunistic infection, or tumor lysis syndrome have been reported.

Conclusion: Preliminary results of this phase 2 study suggest that zanubrutinib is active in R/R MZL, with a favorable safety profile. (NCT03846427)

Table: Baseline Characteristics, Efficacy, and Safety Outcomes

	R/R MZL (N = 68)[a]
Baseline Characteristics	
Male sex, n (%)	36 (52.9)
ECOG PS 0-1, n (%)	63 (92.6)
Bone marrow involvement, n (%)	29 (42.6)
Efficacy (investigator assessment)	**(N = 67)[b]**
ORR, n (%) [95% CI]	40 (60.0) [47.00, 71.51]

Best response, n (%)	
CR	10 (15.0)
PR	30 (45.0)
SD[c]	18 (27.0)
PD	7 (10.0)
Not evaluable[c]	1 (1.5)
Discontinued study before first assessment	1 (1.5)
Safety[d]	**(N = 68)**[a]
Any AE	61 (89.7)
Grade ≥3 AE, n (%)	20 (29.4)
Serious AE, n (%)	18 (26.5)

AE, adverse event; CR, complete response; ECOG PS, Eastern Cooperative Oncology Group performance status; MZL, marginal zone lymphoma; ORR, overall response rate; PD, progressive disease, PR, partial response; R/R, relapsed/refractory; SD, stable disease.

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

[b] Efficacy-evaluable set is defined as patients who had either undergone at least one response assessment or permanently discontinued study before any response assessment.

[c] Continuing on study treatment (8 patients with stable disease; 1 non-evaluable)

[d] Treatment-emergent AEs including AEs that had an onset date or worsening of severity from baseline (pretreatment) on or after the first dose of study drug and up to 30 days after study drug discontinuation or initiation of a new anticancer therapy.