ZANUBRUTINIB IN OLDER PATIENTS (PTS) WITH RELAPSED/REFRACTORY (R/R) MARGINAL ZONE LYMPHOMA (MZL): SUBGROUP ANALYSIS OF THE MAGNOLIA STUDY

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Background: MZL is the second most common lymphoma in older pts. Choosing an optimal treatment can be challenging because of patient- or disease-related risk factors and treatment-related toxicities (*Curr Opin Oncol.* 2019;31(5):386-393). Zanubrutinib is a potent, irreversible next-generation Bruton tyrosine kinase (BTK) inhibitor designed to maximize BTK occupancy and minimize off-target kinase inhibition, which may improve efficacy outcomes and minimize toxicities, such as cardiac arrythmias and bleeding events. Zanubrutinib received accelerated approval from the United States FDA for the treatment of pts with R/R MZL (*Haematologica*. 2022;107(1):35-43).

Aims: We aim to present a subgroup analysis of efficacy and safety of zanubrutinib in pts aged ≥65 years with R/R MZL enrolled in MAGNOLIA (BGB-3111-214; NCT03846427).

Methods: MAGNOLIA is a phase 2, multicenter, single-arm study of adults with R/R MZL who had received ≥1 line of therapy including ≥1 CD20-directed regimen. All 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 endpoint was overall response rate (ORR; complete response [CR] and partial response [PR]) determined by an independent review committee (IRC) in accordance with the Lugano classification. Secondary endpoints include ORR by investigator assessment (INV), duration of response (DOR), progression-free survival (PFS), and safety. All pts gave informed consent.

Results: As of 18 January 2021, a total of 68 pts were enrolled (Table). Forty (61%) pts were ≥65 years old with a median age of 73 (range, 65-85); 18 pts were ≥75 years old. Median number of prior therapies was 2 (range, 1-6) and 10 (25%) pts were refractory to last therapy. Most pts received prior rituximab + cyclophosphamide + vincristine + prednisone (48%) or bendamustine + rituximab (30%), while 5 (13%) pts received rituximab monotherapy. MZL subtypes included extranodal (n=17, 43%), nodal (n=14, 35%), and splenic (n=8, 20%). Median duration of treatment was 14.4 months (mo; range, 0.9-19.6). At a median follow-up of 15.8 mo (range, 2.8-21.8), ORR by IRC was 75% (CR 25%, PR 50%; Table). Responses were observed in all subtypes, with an ORR of 71%, 86%, and 75% in extranodal, nodal, and splenic subtypes, respectively (CR 41%, 21%, and 0%, respectively). Median DOR and PFS were not reached; 15-month PFS was 87% and 12-month DOR was 93%. Most (63%) pts are continuing zanubrutinib. Treatment discontinuation due to disease progression was 28% by INV. Most common treatment-emergent adverse events (AEs) observed in ≥20% of pts include contusion (28%), diarrhea (25%), and constipation (20%). Grade ≥3 neutropenia occurred in 5% of pts. The most common infection was upper respiratory tract infection (10%). Two (5%) pts discontinued zanubrutinib due to unrelated fatal AEs (COVID-19 pneumonia and myocardial infarction in a patient with pre-existing coronary artery disease). Atrial fibrillation/flutter and hypertension occurred in 2 (5%) pts each and did not lead to treatment discontinuation. No pts required dose reductions, or experienced major or serious hemorrhage.

Conclusions: The safety profile of zanubrutinib observed in older pts was consistent with previously published results (*Clin Cancer Res*. 2021;27(23):6323-6332). Zanubrutinib was well tolerated and effective, as demonstrated by a high response rate and durable disease control in older pts with R/R MZL.

Table: Baseline Characteristics, Efficacy, and Safety Outcomes

	Patients ≥65 Years (n = 40)	**Patients ≥75 Years (n = 18)**
Baseline Characteristics		
Male sex, n (%)	23 (58)	11 (61)
ECOG PS 0-1, n (%)	35 (88)	15 (83)
Bone marrow involvement, n (%)	18 (45)	9 (50)
Lines of prior therapies, median (range)	2 (1-6)	1 (1-4)
Efficacy (IRC assessment)		
ORR, n (%) [95% CI]	30 (75) [58.8, 87.3]	17 (94) [72.7, 99.9]
CR	10 (25)	4 (22)
PR	20 (50)	13 (72)
SD	7 (18)	1 (6)
PD	3 (8)	0 (0)
Time to response (months), median (range)	2.81 (1.7, 11.1)	2.83 (1.7, 5.6)
Safety		
Any TEAE, n (%)	37 (93)	16 (89)
Grade ≥3 TEAE, n (%)	18 (45)	9 (50)

Serious TEAE, n (%)	16 (40)	8 (44)

CI, confidence interval; CR, complete response; ECOG PS, Eastern Cooperative Oncology Group performance status; IRC, independent review committee; ORR, overall response rate; PD, progressive disease; PR, partial response; SD, stable disease; TEAE, treatment-emergent adverse event