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

Poster #132

Stephen Opat[1], Alessandra Tedeschi[2], Bei Hu[3], Kim M. Linton[4], Pamela McKay[5], Sophie Leitch[6], Jie Jin[7], Mingyuan Sun[8], Magdalena Sobieraj-Teague[9], Pier Luigi Zinzani[10], Peter Browett[11], Xiaoyan Ke[12], Craig A. Portell[13], Catherine Thieblemont[14], Kirit Ardeshna[15], Fontanet Bijou[16], Patricia Walker[17], Eliza A. Hawkes[18], Shir-Jing Ho[19], Keshu Zhou[20], Zhiyu Liang[21], Jianfeng Xu[21], Chris Tankersley[21], Richard Delarue[21], Melannie Co[21], and Judith Trotman[22]

[1]Monash Health and Monash University, Clayton, VIC, Australia; [2]ASST Grande Ospedale Metropolitano Niguarda, Milan, Italy; [3]Levine Cancer Institute/Atrium Health, Charlotte, NC, USA; [4]Manchester Cancer Research Centre, Division of Cancer Sciences, Manchester, UK; [5]Beatson West of Scotland Cancer Centre, Glasgow, UK; [6]North Shore Hospital, Auckland, New Zealand; [7]The First Affiliated Hospital, Zhejiang University, Hangzhou, Zhejiang, China; [8]Institute of Hematology & Blood Diseases Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Tianjin, China; [9]Flinders Medical Centre, Bedford Park, SA, Australia; [10]Institute of Hematology "Seràgnoli" University of Bologna, Bologna, Italy; [11]Auckland City Hospital, Grafton, New Zealand; [12]Peking University Third Hospital, Beijing, China; [13]University of Virginia, Comprehensive Cancer Center, Charlottesville, VA, USA; [14]APHP, Hôpital Saint-Louis, Hemato-oncology, Paris University Diderot, Paris, France; [15]University College London Hospitals, London, UK; [16]Institut Bergonié, Bordeaux, France; [17]Peninsula Private Hospital, Frankston, VIC, Australia; [18]Box Hill Hospital, Box Hill, VIC, Australia; [19]St. George Hospital, Kogarah, NSW, Australia; [20]Henan Cancer Hospital, Zhengzhou, Henan, China; [21]BeiGene (Beijing) Co., Ltd., Beijing, China, BeiGene Switzerland GmbH and BeiGene USA, Inc., San Mateo, CA, USA; and [22]Concord Repatriation General Hospital, University of Sydney, Concord, NSW, Australia

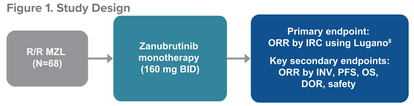
INTRODUCTION

- Advanced-stage MZL is generally incurable[1]
- B-cell receptor (BCR) signaling is a critical pathway in MZL pathogenesis[2]
- Bruton tyrosine kinase (BTK) plays a key role in BCR signaling[2]
  - BTK inhibition has antitumor activity in various B-cell malignancies[2,3]
- Zanubrutinib (BGB-3111) is a potent and highly specific next-generation BTK inhibitor
  - Designed to maximize BTK occupancy and minimize off-target inhibition of tyrosine kinase expressed in hepatocellular carcinoma (TEC)- and epidermal growth factor receptor (EGFR)-family kinases[3-5]
  - Can be coadministered with strong/moderate cytochrome P450 (CYP3A) inhibitors at a reduced dose, proton pump inhibitors, acid-reducing agents, and antithrombotic agents[6,7]
  - Recently approved for the treatment of patients with R/R MZL based on the primary analysis results of the MAGNOLIA study (BGB-3111-214; NCT03846427)[7]
- Here we present the final analysis of MAGNOLIA at a median follow-up of 28 months

METHODS

- MAGNOLIA is a phase 2, multicenter, open-label, single-arm study (**Figure 1**)
- Eligible patients were ≥18 years old, had R/R MZL, had received ≥1 CD20-directed regimen, and had an Eastern Cooperative Oncology Group Performance Status (ECOG PS) of 0, 1, or 2
  - Patients with prior treatment with a BTK inhibitor were excluded
- All patients received zanubrutinib monotherapy 160 mg twice daily (BID)
- Response to treatment was measured based on the Lugano classification for non-Hodgkin lymphoma (NHL)[8]
  - Positron emission tomography (PET)-based criteria for patients with independent review committee (IRC)-confirmed fluorodeoxyglucose (FDG)-avid disease
  - Computerized tomography (CT)-based criteria for non-FDG-avid patients
  - Additional sensitivity analysis for all evaluable patients using CT-based criteria
- Adverse events (AEs) were assessed and graded per the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) v4.03
  - The data cutoff date was May 4, 2022

Figure 1. Study Design

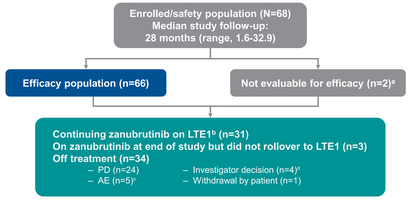


BID, twice daily; DOR, duration of response; INV, principal investigator; IRC, independent review committee; MZL, marginal zone lymphoma; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; R/R, relapsed/refractory.

RESULTS

- A total of 68 participants were enrolled in the study (**Figure 2**)
- Median follow-up was 28 months
- At the cutoff date, 34 patients were still receiving zanubrutinib
- The most common reason for treatment discontinuation was progressive disease (PD)

Figure 2. Patient Disposition



Data cutoff date: 04 May 2022.
[a]Two patients were excluded owing to lack of central confirmation of MZL. [b]BGB-3111-LTE1 is a BeiGene-sponsored, global, open-label extension study (NCT04702763). [c]Five patients discontinued treatment owing to AEs (2 patients with fatal COVID-19 pneumonia; 1 patient with pyrexia later attributed to disease progression; 1 patient with fatal myocardial infarction in a patient with preexisting cardiovascular disease; 1 patient who died from septic encephalopathy after bladder surgery [in CR at the time of death]). [d]Four patients discontinued per investigator decision (3 patients required prohibited medications; 1 patient due to lack of clinical benefit).
AE, adverse event; CR, complete remission; LTE, long-term extension; MZL, marginal zone lymphoma; PD, progressive disease.

Table 1. Baseline Demographics and Disease History

Characteristics	Total (N=68)
Median age (range), years	70 (37-95)
≥65, n (%)	41 (60)
≥75, n (%)	19 (28)
Male, n (%)	36 (53)
ECOG PS 0/1[a], n (%)	63 (93)
MZL subtypes, n (%)	
Extranodal	26 (38)
Nodal	26 (38)
Splenic	12 (18)
Unknown	4 (6)
Disease status, n (%)	
Relapsed	44 (65)
Refractory	22 (32)
Stage III/IV, n (%)	59 (87)
FDG-avid (by IRC), n (%)	61 (90)
Extranodal site involvement, n (%)	53 (78)
Bone marrow infiltration, n (%)	29 (43)
Median prior lines of systemic therapy (range)[b]	2 (1-6)
Immunochemotherapy, n (%)	61 (90)[c]
Rituximab monotherapy, n (%)	7 (10)

[a]Overall, 43% of patients had ECOG PS 1/2. [b]Rituximab-based chemotherapy in most patients (n=60; 88%).
ECOG PS, Eastern Cooperative Oncology Group Performance Status; FDG, fluorodeoxyglucose; IRC, independent review committee; MZL, marginal zone lymphoma.

- After a median follow-up of 28 months, overall response rate (ORR) by IRC was 68%; ORR by principal investigator (INV) was 76% (**Table 2**)
- 26% of patients had a complete response (CR) by IRC, and 29% had a CR by INV; the median time to response was approximately 3 months

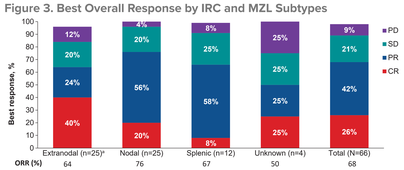
Table 2. Best Overall Response by IRC and INV Assessment

Efficacy	IRC (N=66)[a] PET and/or CT (primary endpoint)[b]	IRC CT only (sensitivity analysis)[c]	INV PET and/or CT
ORR, n (%)	45 (68)	44 (67)	50 (76)
[95% CI]	[55.6, 79.1]	[54.0, 77.8]	[63.6, 85.5]
p-value	<0.0001[d]		
Best response, n (%)			
CR	17 (26)	16 (24)	19 (29)
PR	28 (42)	28 (42)	31 (47)
SD	14 (21)[f,g]	16 (24)	10 (15)
PD	6 (9)	5 (8)	5 (8)
Discontinued study prior to 1st assessment, n (%)	1 (1)	1 (1)	1 (1)
Median time to response (range), months	2.8 (1.7-11.1)	3.0 (1.8-22.2)	2.8 (1.7-16.6)

[a]Two patients were excluded from the efficacy population owing to lack of central confirmation of MZL. [b]Patients with IRC-confirmed FDG-avid disease were assessed by PET-based criteria; non–FDG-avid patients were assessed by CT-based Lugano criteria. [c]P-value for the primary endpoint was computed with the binomial exact test against the null hypothesis of ORR = 30% with alternative of ORR > 30%. [d]Five (7.6%) patients with stable disease are remaining on study treatment (after 12-18 cycles). [e]Includes one patient with FDG-avid disease who missed the PET scan at cycle 3 and was assessed as non-PD. [f]CT showed stable disease at Cycle 3. [g]Additional sensitivity analysis using CT-based Lugano criteria for all 66 evaluable patients regardless of PET status at baseline.
CR, complete response; CT, computerized tomography; FDG, fluorodeoxyglucose; INV, investigator; IRC, independent review committee; MZL, marginal zone lymphoma; ORR, overall response rate; PD, progressive disease; PET, positron emission tomography; PR, partial response; SD, stable disease.

- There was a high ORR in all MZL subtypes, with the highest ORR seen in patients with nodal MZL (76%), and the highest CR in patients with extranodal MZL (40%)

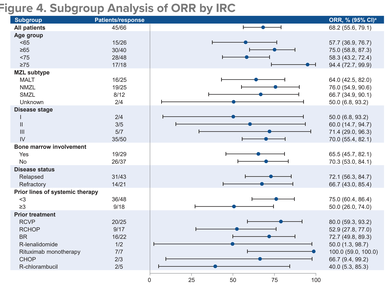
Figure 3. Best Overall Response by IRC and MZL Subtypes



[a]One patient (extranodal MZL) who withdrew consent prior to the first disease assessment was not shown in the graph.
CR, complete response; IRC, independent review committee; MZL, marginal zone lymphoma; ORR, overall response rate; PD, progressive disease; PR, partial response; SD, stable disease.

- All key patient subgroups had a response as evaluated by IRC (**Figure 4**)

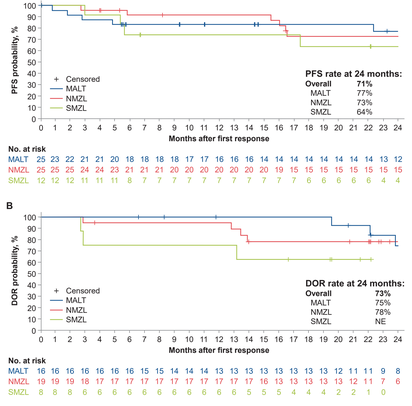
Figure 4. Subgroup Analysis of ORR by IRC



[a]Two-sided Clopper-Pearson. 95% CIs for ORR.
BR, bendamustine plus rituximab; CHOP, cyclophosphamide, hydroxydaunorubicin hydrochloride, vincristine sulfate, and prednisone; CI, confidence interval; IRC, independent review committee; MALT, mucosa-associated lymphoid tissue; MZL, marginal zone lymphoma; NMZL, nodal MZL; ORR, overall response rate; R(CHOP, rituximab, cyclophosphamide, hydroxydaunorubicin hydrochloride, vincristine sulfate, and prednisone; R, rituximab; R(CVP, rituximab, cyclophosphamide, vincristine sulfate, and prednisone; SMZL, splenic MZL.

- At a follow-up of 24 months, progression-free survival (PFS) rate by IRC was 71% (**Figure 5A**), duration of response (DOR) rate by IRC was 73% (**Figure 5B**), and overall survival (OS) rate was 86% (**Figure 5C**)

Figure 5. PFS by IRC (A), DOR by IRC (B), and OS (C) by MZL Subtypes



DOR, duration of response; IRC, independent review committee; MALT, mucosa associated lymphoid tissue; MZL, marginal zone lymphoma; NMZL, nodal MZL; OS, overall survival; PFS, progression-free survival; SMZL, splenic MZL.

- All patients experienced at least 1 treatment-emergent adverse event (TEAE; **Figure 6A**)
- 48% of patients experienced TEAEs of Grade 3 or higher
- Cardiac TEAEs were rare, with hypertension occurring in 4%, atrial fibrillation/flutter in 3%, and ventricular extrasystole in 1.5% of patients; the rate of cardiac TEAEs was comparable to a pooled safety analysis of zanubrutinib, and lower than reported for ibrutinib (**Table 3**)
- The most common TEAEs (≥18%) included contusion, diarrhea, and constipation (**Figure 6B**)

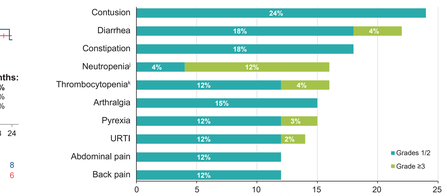
Figure 6. Safety Summary

A

TEAEs in all patients, n (%)	N=68
Patients with ≥1 TEAE	68 (100)
Grade ≥3 TEAE	33 (48)
Serious TEAE	30 (44)
Leading to death	5 (7)[a]
Leading to dose interruption	25 (37)[b]
Leading to study drug discontinuation	5 (7)[c]
Leading to dose reduction	0

TEAEs of clinical interest, n (%)	All grade	Grade ≥3
Infections	38 (56)	15 (22)[d]
Hemorrhage	28 (41)	1 (1.5)[e]
Cardiac		
Hypertension	3 (4)[f]	2 (3)
Atrial fibrillation/flutter	2 (3)[g]	1 (1.5)
Ventricular extrasystole	1 (1.5)[h]	0
Second primary malignancy	5 (7)[i]	3 (4)

B



[a]Five patients died owing to AEs: COVID-19 pneumonia (n=2); myocardial infarction in a patient with preexisting cardiovascular disease (n=1); acute myeloid leukemia in a patient with prior exposure to an alkylating agent (n=1); septic encephalopathy following radical cystectomy and ileal conduit in a patient with recurrent bladder cancer (in CR at the time of death; [n=1]). [b]Most common AEs leading to dose interruption: COVID-19 pneumonia (n=4), neutropenia (n=3), diarrhea (n=2), lower respiratory tract infection (n=2), pneumonia (n=2), pyrexia (n=2), syncope (n=2), and tonsillitis (n=2). [c]Five patients discontinued owing to AEs: COVID-19 pneumonia (n=2); pyrexia later attributed to disease progression (n=1); myocardial infarction (n=1); septic encephalopathy (n=1). [d]Fatal infection: COVID-19 pneumonia (n=2). [e]Gastrointestinal hemorrhage (day 882) in a patient who also received anticoagulant for pulmonary embolism; patient continued zanubrutinib with no recurrent bleeding episode. [f]Two Z patients had new-onset hypertension; none led to treatment reduction or discontinuation. [g]Atrial fibrillation in a patient with preexisting atrial fibrillation (21 days after end of treatment owing to disease progression). Patient with atrial flutter recovered spontaneously and continued zanubrutinib. [h]Ventricular extrasystole in an 83-year-old patient with no known cardiac history, was non-serious, transient, resolved on the same day, and did not lead to treatment modification or discontinuation. [i]Includes basal cell and squamous cell carcinoma and basal cell carcinoma (with history of skin cancer), papillary thyroid carcinoma (with preexisting thyroid nodule), recurrent bladder cancer and prostate cancer (with history of bladder cancer), and acute myeloid leukemia (with prior chemotherapy with alkylating agent). Includes neutropenia and neutrophil count decreased. [a]Includes thrombocytopenia and platelet count decreased.
TEAE, treatment-emergent adverse event; URTI, upper respiratory tract infection.

Table 3. Cardiac TEAEs of Clinical Interest

Cardiovascular disorders	BGB-3111-214 Zanubrutinib (N=68)	Pooled analysis B-cell malignancies[c] Zanubrutinib (N=1550)	Pooled analysis B-cell malignancies[c] Ibrutinib (N=422)
Median treatment duration, months	24	26.64	19.96
Any cardiovascular medical history, n (%)			
Atrial fibrillation/flutter	8 (11.7)	101 (6.5)	26 (6.2)
Ventricular arrhythmia[a]	0	14 (0.9)	1 (0.2)
Hypertension[b]	21 (30.9)	669 (43.2)	206 (48.8)
Any cardiovascular AE, n (%)			
Atrial fibrillation/flutter	2 (3)	60 (3.9)	60 (14.2)
		EAIR: 0.13 vs 0.82 person-month ($P < .0001$)	
Ventricular arrhythmia (grade ≥2)[a]	1 (1.5)	11 (0.7)	6 (1.4)
Hypertension[b]	3 (4)	225 (14.5)	85 (20.1)

[a]Including ventricular tachyarrhythmia (SMQ narrow), ventricular arrhythmias and cardiac arrest (High Level Term MedDRA v24.0). [b]Including hypertension (SMQ narrow). [c]Pooled analyses of 10 clinical studies of zanubrutinib.[7]
AE, adverse event; CTCAE, Common Terminology Criteria for Adverse Events; EAIR, exposure-adjusted incident rate; MedDRA, Medical Dictionary for Regulatory Activities; SMQ, standardized MedDRA query; TEAE, treatment-emergent adverse event.

CONCLUSIONS

- At a median study follow-up of 28 months, zanubrutinib showed high response rates and durable disease control in R/R MZL
  - There were responses in all MZL subtypes and in difficult-to-treat subgroups
- Zanubrutinib was generally well tolerated
  - Hypertension and atrial fibrillation/flutter were uncommon and were comparable to the zanubrutinib pooled safety analyses, and lower than reported for ibrutinib
  - No new safety signals were observed
- These data support the use of zanubrutinib as treatment for patients with R/R MZL

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CORRESPONDENCE

stephen.opat@monashhealth.org

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