Long-Term Efficacy and Safety of Zanubrutinib in Relapsed/Refractory Marginal Zone Lymphoma (R/R MZL): Final Analysis of the MAGNOLIA (BGB-3111-214) Trial

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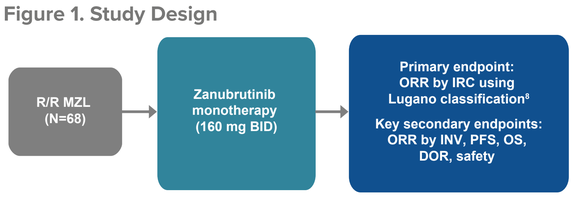
INTRODUCTION

- 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 3A (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 was 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
  - Computed tomography (CT)–based criteria for non–FDG-avid patients
  - Additional sensitivity analysis in 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 v4.03
  - The data cutoff date was May 4, 2022

Figure 1. Study Design

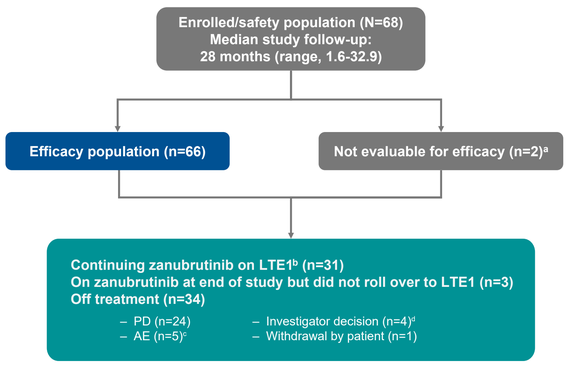


INV, principal investigator.

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: May 4, 2022.
LTE, long-term extension.
[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 (NCT04170283). [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 and 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).

Table 1. Baseline Demographics and Disease History

Characteristics	Total (N=68)
Age, median (range), years	70 (37-95)
≥65 years, n (%)	41 (60)
≥75 years, n (%)	19 (28)
Male, n (%)	36 (53)
ECOG PS 0 or 1, n (%)[a]	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)
Prior lines of systemic therapy, median (range)[b]	2 (1-6)
Immunochemotherapy, n (%)	61 (90)[b]
Rituximab monotherapy, n (%)	7 (10)

[a] Overall, 43% of patients had ECOG PS of 1 or 2. [b] Rituximab-based chemotherapy in most patients (n=60 [88%]).

- 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

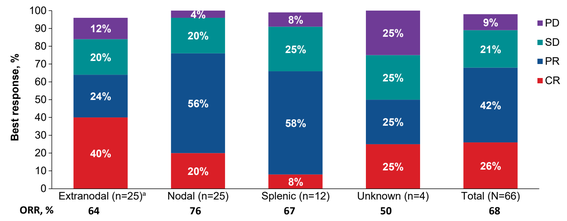
Table 2. Best Overall Response by IRC and INV Assessment

	(N=66)[a]		
	IRC		INV
Efficacy	PET and/or CT (primary endpoint)[b]	CT only (sensitivity analysis)[f]	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	<.0001[c]		
Best response, n (%)			
CR	17 (26)	16 (24)	19 (29)
PR	28 (42)	28 (42)	31 (47)
SD	14 (21)[d,e]	16 (24)	10 (15)
PD	6 (9)	5 (8)	5 (8)
Discontinued study prior to first assessment, n (%)	1 (1)	1 (1)	1 (1)
Time to response, median (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 an alternative of ORR >30%. [d] Five patients (7.6%) with SD are remaining on study treatment (after 12-18 cycles). [e] Included 1 patient with FDG-avid disease who missed the PET scan at cycle 3 and was assessed as non-PD; CT showed stable disease at cycle 3. [f] Additional sensitivity analysis using CT-based Lugano criteria in all 66 evaluable patients regardless of PET status at baseline.

- The ORR was high 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%)

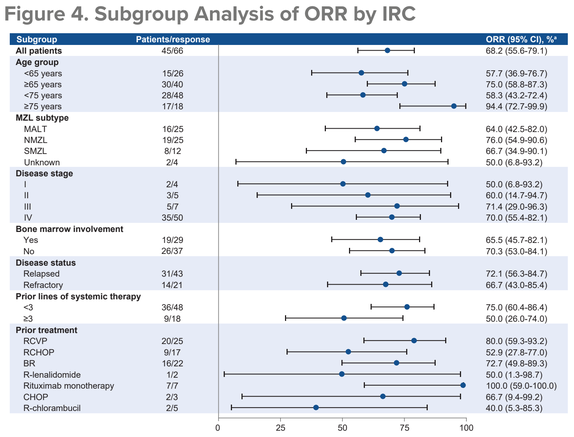
Figure 3. Best Overall Response by IRC and MZL Subtypes



[a] One patient (extranodal MZL) who withdrew consent prior to the first disease assessment is not shown in the figure.

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

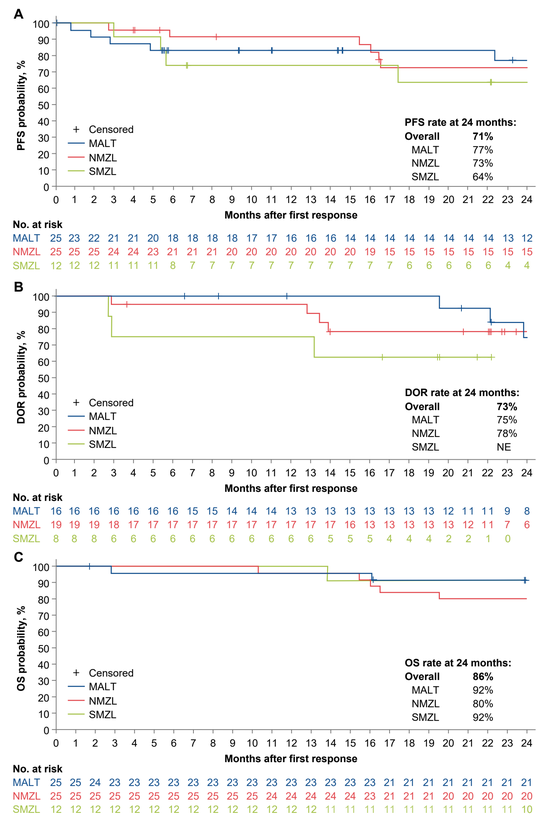
Figure 4. Subgroup Analysis of ORR by IRC



BR, bendamustine plus rituximab; CHOP, cyclophosphamide, hydroxydaunorubicin hydrochloride, vincristine sulfate, and prednisone; MALT, mucosa-associated lymphoid tissue; NMZL, nodal MZL; R, rituximab; RCHOP, rituximab, cyclophosphamide, hydroxydaunorubicin hydrochloride, vincristine sulfate, and prednisone; RCVP, rituximab, cyclophosphamide, vincristine sulfate, and prednisone; SMZL, splenic MZL.
[a] Two-sided Clopper-Pearson test; 95% CIs for ORR.

- 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



SMZL, splenic MZL.

- All patients experienced ≥1 treatment-emergent adverse event (TEAE) (**Figure 6A**)
- 49% 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 that in a pooled safety analysis of zanubrutinib and lower than that reported for ibrutinib (**Table 3**)
- The most common TEAEs (≥18%) included contusion, diarrhea, and constipation (**Figure 6B**)

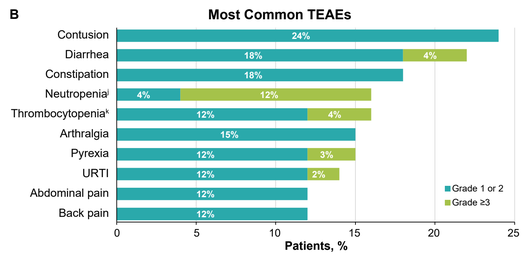
Figure 6. Safety Summary

A

TEAEs in all patients, n (%)	N=68
≥1 TEAE	68 (100)
Grade ≥3	33 (49)
Serious	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



URTI, upper respiratory tract infection.
[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); and 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); and septic encephalopathy (n=1). [d] Fatal infection: COVID-19 pneumonia (n=2). [e] Gastrointestinal hemorrhage (day 862) in a patient who also received anticoagulant for pulmonary embolism; the patient continued zanubrutinib with no recurrent bleeding episode. [f] Two 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; it was nonserious, 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). [j] Includes neutropenia and neutrophil count decreased. [k] Includes thrombocytopenia and platelet count decreased.

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, comparable to those in the zanubrutinib pooled safety analyses, and lower than reported with ibrutinib
  - No new safety signals were observed
- These data support the use of zanubrutinib as treatment for patients with R/R MZL

Table 3. Cardiac TEAEs of Clinical Interest

	MAGNOLIA	Pooled analysis B-cell malignancies[a]	
Cardiovascular disorders	Zanubrutinib (n=68)	Zanubrutinib (n=1550)	Ibrutinib (n=422)
Treatment duration, median, 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[b]	0	14 (0.9)	1 (0.2)
Hypertension[c]	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)[b]	1 (1.5)	11 (0.7)	6 (1.4)
Hypertension[c]	3 (4)	225 (14.5)	85 (20.1)

EAIR, exposure-adjusted incident rate; MedDRA, Medical Dictionary for Regulatory Activities; SMQ, standardized MedDRA query.
[a] Pooled analyses of 10 clinical studies of zanubrutinib.[9] [b] Including ventricular tachyarrhythmia (SMQ narrow) and ventricular arrhythmias and cardiac arrest (High Level Term MedDRA v24.0). [c] Including hypertension (SMQ narrow).

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DISCLOSURES

JT: Research funding: BMS, Roche, Janssen, BeiGene, Cellectar, and PCYC. **AT:** Consultancy: BeiGene, AstraZeneca, AbbVie, and Janssen; Honoraria: BeiGene, AstraZeneca, AbbVie, and Janssen; Speakers bureau: BeiGene, AstraZeneca, AbbVie, and Janssen; Travel, accommodations, expenses: BeiGene, AstraZeneca, AbbVie, and Janssen. **BH:** Research funding: BeiGene, BMS/Celgene, and Roche; Member of the board of directors or advisory committee: ADC Therapeutics, BeiGene, and Morphosys. **KML:** Consultancy: Celgene, Gilead/Kite, BeiGene, Genmab, and Roche; Speakers bureau: Genmab; Member of the board of directors or advisory committee: Genmab. **PM:** Honoraria: Roche, BeiGene, Recordati Rare Disease, Gilead/Kite, BMS/Celgene, Takeda, AstraZeneca, AbbVie, Epizyme, and Incyte; Speakers bureau: Janssen, Incyte, Roche, and Kite; Travel, accommodations, expenses: Takeda. **PLZ:** Consultancy: Eusapharma, MSD, and Novartis; Speakers bureau: Celltrion, Gilead, Janssen-Cilag, BMS, Servier, MSD, TG Therapeutics, Takeda, Roche, Eusapharma, Kyowa Kirin, Novartis, Incyte, and BeiGene; Member of the advisory board: Secura Bio, Celltrion, Gilead, Janssen-Cilag, BMS, Servier, Sandoz, MSD, TG Therapeutics, Takeda, Roche, Eusapharma, Kyowa Kirin, Novartis, ADC Therapeutics, Incyte, and BeiGene. **PB:** Honoraria: AbbVie; Member of the board of directors or advisory committee: MSD and Janssen. **CTh:** Consultancy: Roche, AbbVie, GenMab, Gilead/Kite, Takeda, Novartis, Incyte, Celgene, and BMS; Research funding: Roche; Travel, accommodations, expenses: Novartis, Gilead, and BMS. **EB:** Honoraria: Gilead Sciences, Janssen, Roche, AbbVie, Novartis, and BMS; Consultancy: Roche, MAbQi, MedXCell, and BMS; Travel, accommodations, expenses: Roche and Gilead Sciences. **FC:** Consultancy: Roche and AstraZeneca; Speakers bureau: Servier; Travel, accommodations, expenses: Takeda, AstraZeneca, and Roche. **SO:** Employment: Monash Health; Consultancy: AbbVie, AstraZeneca, Janssen, and Roche; Research funding: AbbVie, AstraZeneca, BeiGene, Gilead, Janssen, Pharmacyclics, Roche, Sandoz, and Takeda; Honoraria: AbbVie, AstraZeneca, Celgene, CSL Behring, Gilead, Janssen, Merck, Roche, and Takeda; Member of board of directors or advisory committee: AbbVie, AstraZeneca, Celgene, CSL Behring, Gilead, Janssen, Merck, Roche, and Takeda. **ZL, JX, CTa, RD, MC:** Employment and may own stock: BeiGene, Inc. **JJ, SL, MS, MS-T, AML, RC, SI, RM, HM, JSK, DT:** Nothing to disclose.

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ACKNOWLEDGMENTS

The authors thank the patients and their families, investigators, co-investigators, and the study teams at each of the participating centers. This study was sponsored by BeiGene, Ltd. Medical writing support was provided by Nicole Lopez, PhD, of Articulate Science, LLC, and supported by BeiGene.

Presented at the 17th International Conference on Malignant Lymphoma (ICML); June 13-17, 2023; Lugano, Switzerland

Data originally presented at the 64th ASH Annual Meeting and Exposition; December 10-13, 2022; New Orleans, LA. Abstract 234.