Poster DP002

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; however, it is known that B-cell receptor (BCR) signaling is critical to MZL pathogenesis[1,2]
- Inhibition of Bruton tyrosine kinase (BTK), a key BCR signaling protein, has demonstrated antitumor activity in various B-cell malignancies[2,3]
- Zanubrutinib (BGB-3111) is a potent and highly specific next-generation BTK inhibitor that has been designed to maximize BTK occupancy and minimize off-target inhibition[3-5]
  - Recently, zanubrutinib was approved for the treatment of R/R MZL based on the primary analysis of the MAGNOLIA study (BGB-3111-214; NCT03846427)[6]
- Here we present the final analysis of MAGNOLIA at a median follow-up of 28 months

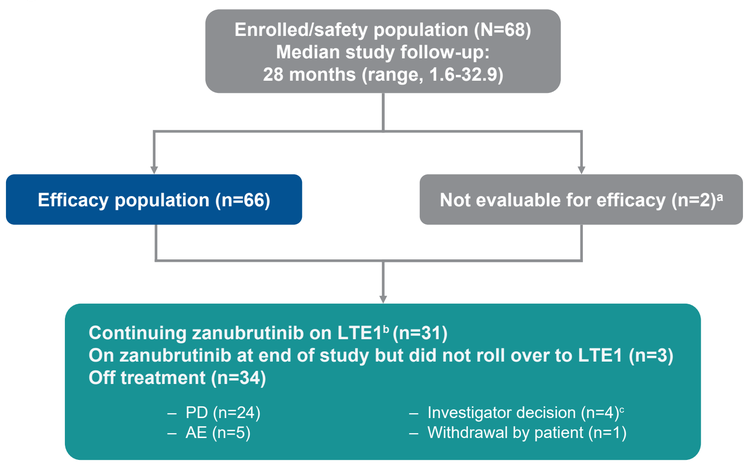
METHODS

- MAGNOLIA was a phase 2, multicenter, open-label, single-arm study[3]
- 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; prior treatment with a BTK inhibitor was not permitted
- All patients received zanubrutinib monotherapy 160 mg twice daily (BID)
- The primary endpoint was overall response rate (ORR) by independent review committee (IRC) per Lugano classification for non-Hodgkin lymphoma (NHL)[7]
  - Positron emission tomography (PET)–based criteria were used for patients with IRC–confirmed fluorodeoxyglucose (FDG)-avid disease
  - Computed tomography (CT)–based criteria were used for non–FDG-avid disease
  - Additional sensitivity analysis was done in all evaluable patients per CT-based criteria
- Key secondary endpoints were ORR by investigator (INV), progression-free survival (PFS), overall survival (OS), duration of response (DOR), and safety
- Adverse events (AEs) were assessed and graded per CTCAE v4.03

RESULTS

- A total of 68 participants were enrolled in the study (**Figure 1**)
- Baseline characteristics are shown in **Table 1**

Figure 1. 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] Three due to patient requirement for prohibited medications; 1 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, ORR by IRC was 68%; ORR by principal investigator (INV) was 76% (**Table 2**)

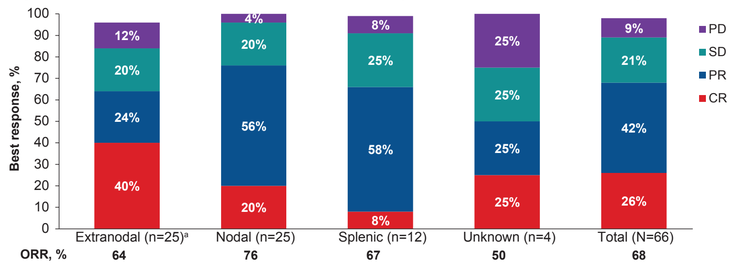
Table 2. Best Overall Response by IRC and INV Assessment

Efficacy	(N=66)[a]		
	IRC		INV
	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 analysis due 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 remain 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 SD 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 2**)

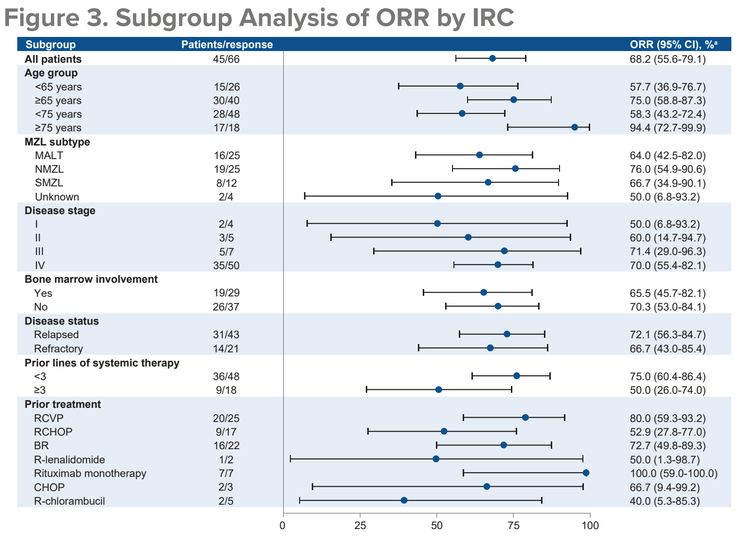
Figure 2. Best Overall Response by IRC and MZL Subtypes



[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 3**)

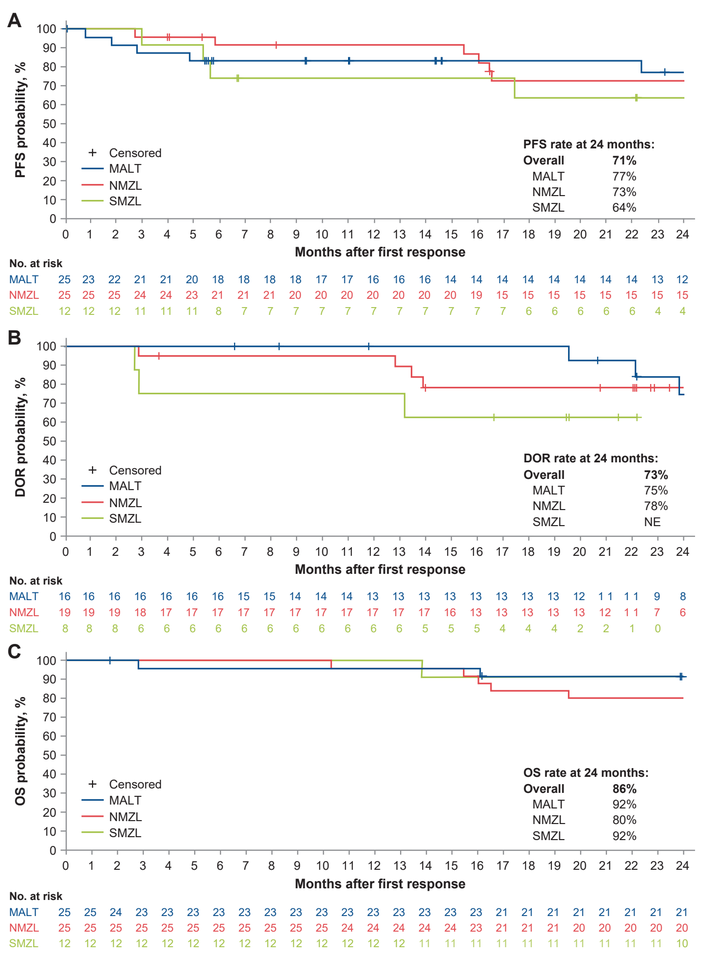
Figure 3. Subgroup Analysis of ORR by IRC



[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 4A**), duration of response (DOR) rate by IRC was 73% (**Figure 4B**), and overall survival (OS) rate was 86% (**Figure 4C**)

Figure 4. PFS by IRC (A), DOR by IRC (B), and OS (C) by MZL Subtypes



SMZL, splenic MZL.

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 rates 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

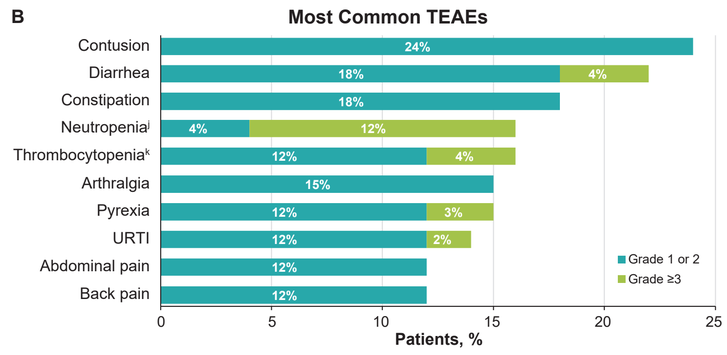
- All patients experienced ≥1 treatment-emergent adverse event (TEAE) (**Figure 5A**)
- 49% of patients experienced TEAEs of grade 3 or higher
- Cardiac TEAEs were rare, with hypertension occurring in 4%, atrial fibrillation/flutter in 3%, and ventricular extrasystole in 1.5% of patients; the rate of cardiac TEAEs was comparable to that in a pooled safety analysis of zanubrutinib and lower than that reported with ibrutinib (**Table 3**)
- The most common TEAEs (≥18%) included contusion, diarrhea, and constipation (**Figure 5B**)

Figure 5. 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



CVD, cardiovascular disease; GI, gastrointestinal; MI, myocardial infarction; PE, pulmonary embolism; URTI, upper respiratory tract infection.
[a] COVID-19 pneumonia (n=2); MI with preexisting CVD (n=1); AML in patient with prior alkylating agent exposure (n=1); and septic encephalopathy following radical cystectomy and ileal conduit in 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] COVID-19 pneumonia (n=2); pyrexia later attributed to disease progression (n=1); MI (n=1); septic encephalopathy (n=1). [d] Fatal infection: COVID-19 pneumonia (n=2). [e] GI hemorrhage (day 862) in patient who also received anticoagulant for PE; the patient continued zanubrutinib with no recurrent bleeding episode. [f] New-onset hypertension (n=2); none led to treatment reduction or discontinuation. [g] Atrial fibrillation in 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] In 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 AML (with prior chemotherapy with alkylating agent). [j] Includes neutropenia and neutrophil count decreased. [k] Includes thrombocytopenia and platelet count decreased.

Table 3. Cardiac TEAEs of Clinical Interest

Cardiovascular disorders	MAGNOLIA	Pooled analysis B-cell malignancies[a]	
	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)
Hypertensionc	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 incidence rate; MedDRA, Medical Dictionary for Regulatory Activities; SMQ, standardized MedDRA query.
[a] Pooled analyses of 10 clinical studies of zanubrutinib.[8] [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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