# 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

Abstract P1084

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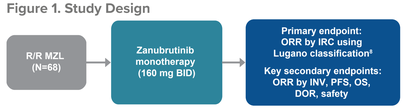
## INTRODUCTION

- 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

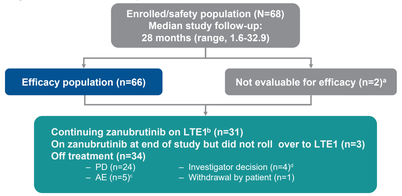



INV, principal investigator.

## 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 (NCT04770285). [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

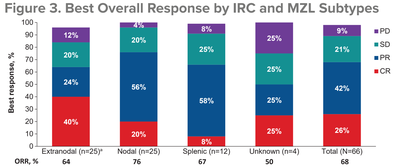
### Table 2. Best Overall Response by IRC and INV Assessment

| | (N=66)[a] | | |
|---|---|---|---|
| | IRC | | INV |
| Efficacy | PET and/or CT (primary endpoint)[b] | CT only (sensitivity analysis)[c] | 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. [c]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%)

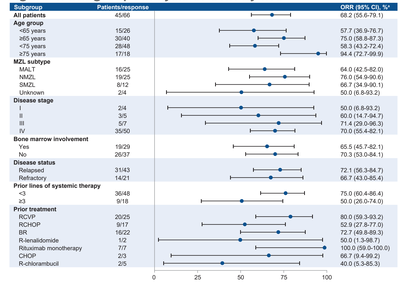
### Figure 3. Best Overall Response by IRC and MZL Subtypes




[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**)

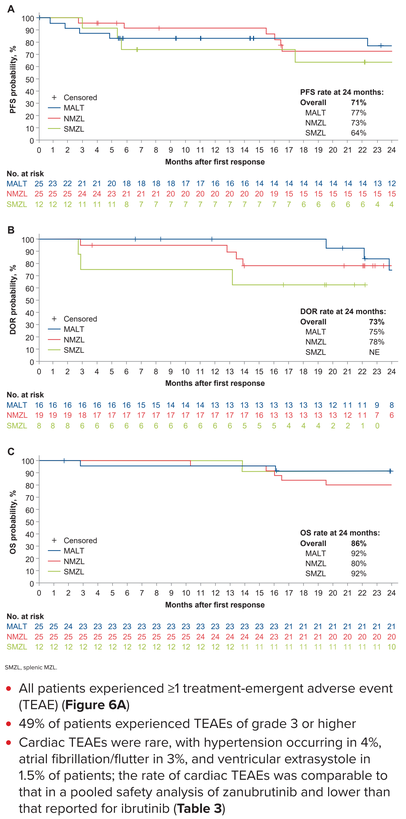
### Figure 4. Subgroup Analysis of ORR by IRC




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.

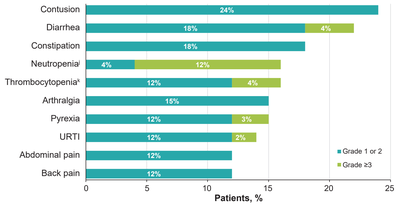
- All patients experienced ≥1 treatment-emergent adverse event (TEAE) (**Figure 6A**)
- 49% of patients experienced TEAEs of grade 3 or higher
- Cardiac TEAEs were rare, with hypertension occurring in 4%, atrial fibrillation/flutter in 3%, and ventricular extrasystole in 1.5% of patients; the rate of 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.

### 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.[7] [b]Including ventricular tachyarrhythmia (SMQ narrow) and ventricular arrhythmias and cardiac arrest (High Level Term MedDRA v24.0). [c]Including hypertension (SMQ narrow).

## 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

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## DISCLOSURES

**SO:** Employee of Monash Health; Consultant for AbbVie, AstraZeneca, Janssen, and Roche; research funding from AbbVie, AstraZeneca, BeiGene, Gilead, Janssen, Pharmacyclics, Roche, Sandoz, and Takeda; honoraria from AbbVie, AstraZeneca, Celgene, CSL Behring, Gilead, Janssen, Merck, Roche, and Takeda; member of board of directors or advisory committee for AbbVie, AstraZeneca, Celgene, CSL Behring, Gilead, Janssen, Merck, Roche, and Takeda. **AT:** Consultant for BeiGene, AstraZeneca, AbbVie, and Janssen; honoraria from BeiGene, AstraZeneca, AbbVie, and Janssen; speakers bureau for BeiGene, AstraZeneca, AbbVie, and Janssen; received travel funds from BeiGene, AstraZeneca, AbbVie, and Janssen. **BH:** Research funding from BeiGene, BMS/Celgene, and Roche; member of the board of directors or advisory committee for ADC Therapeutics, BeiGene, and Morphosys. **KML:** Consultant for Celgene, Gilead/Kite, BeiGene, Genmab, and Roche; speakers bureau for Genmab, member of the board of directors or advisory committee for Genmab. **PM:** Honoraria from Roche, BeiGene, Recordati Rare Disease, Gilead/Kite, BMS/Celgene, Takeda, AstraZeneca, AbbVie, Epizyme, and Incyte; speakers bureau for Janssen, Incyte, Roche, and Kite; travel funds from Takeda. **PLZ:** Consultant for Eusapharma, MSD, and Novartis; speakers bureau for Celltrion, Gilead, Janssen-Cilag, BMS, Servier, MSD, TG Therapeutics, Takeda, Roche, Eusapharma, Kyowa Kirin, Novartis, Incyte, and BeiGene; member of the advisory board of 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 from AbbVie; member of the board of directors or advisory committee of MSD and Janssen. **CTh:** Consultant for Roche, AbbVie, GenMab, Gilead/Kite, Takeda, Novartis, Incyte, Celgene, and BMS; research funding from Roche; travel funds from Novartis, Gilead, and BMS. **EB:** Honoraria from Gilead Sciences, Janssen, Roche, AbbVie, Novartis, and BMS; consultant for Roche, MAbQi, MedXCell, and BMS; travel funds from Roche and Gilead Sciences. **FC:** Consultant for Roche and AstraZeneca; speakers bureau for Servier; travel funds from Takeda, AstraZeneca, and Roche. **JT:** Research funding from BMS, Roche, Janssen, BeiGene, Cellectar, and PCYC. **ZL, JX, CTa, RD, MC:** Employees of and may own stock in BeiGene, Inc. **JJ, SL, MS, MS-T, AML, RC, SI, RM, HM, JSK, DT:** Nothing to disclose.

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