# SAFETY AND EFFICACY OF ZANUBRUTINIB IN PATIENTS WITH RELAPSED/REFRACTORY MARGINAL ZONE LYMPHOMA (MAGNOLIA PHASE 2 STUDY)

Abstract 107

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## INTRODUCTION

- B-cell receptor-mediated signaling has been identified as a critical step in marginal zone lymphoma (MZL) pathogenesis[1]
- Bruton tyrosine kinase (BTK) plays a critical role in B-cell receptor signaling, which mediates B-cell proliferation, migration, and adhesion[2-4]
  - First-generation BTK inhibitor ibrutinib has shown activity in relapsed/refractory (R/R) MZL, demonstrating a 48% overall response rate (ORR)[5]
- Zanubrutinib (BGB-3111) is a next-generation BTK inhibitor designed to maximize BTK occupancy and minimize off-target inhibition of TEC- and EGFR-family kinases
  - Zanubrutinib has been shown to be an irreversible, highly potent, selective, and bioavailable BTK inhibitor with potentially advantageous pharmacokinetic/pharmacodynamic properties[6]
- The safety and efficacy of zanubrutinib in patients with R/R MZL were evaluated in the MAGNOLIA study
  - Study enrollment is complete; a total of 68 patients received at least 1 dose of zanubrutinib

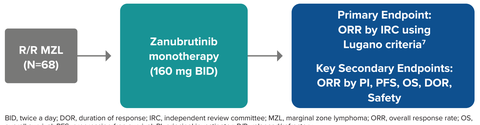
## OBJECTIVES

- The primary endpoint was ORR as determined by an independent review committee based on the Lugano 2014 classification[7]

## METHODS

- MAGNOLIA (BGB-3111-214) is a phase 2, single-arm, multicenter study of zanubrutinib in patients with R/R MZL who had received ≥1 CD20-based regimen (**Figure 1**)

### Figure 1. Study Schema



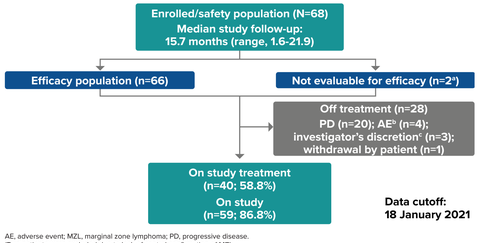

BID, twice a day; DOR, duration of response; IRC, independent review committee; MZL, marginal zone lymphoma; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; PI, principal investigator; R/R, relapsed/refractory.

## KEY ELIGIBILITY CRITERIA

- Age ≥18 years
- Histologically confirmed MZL including splenic, nodal, and extranodal subtypes
- Previously received ≥1 CD20-directed regimen, with documented failure to achieve at least partial response or documented progressive disease after the most recent systemic treatment
- Measurable disease by computerised tomography or magnetic resonance imaging
- Adequate organ function
- No prior BTK inhibitor exposure

## RESULTS

### Figure 2. Patient Disposition




AE, adverse event; MZL, marginal zone lymphoma; PD, progressive disease.
[a]Two patients were excluded due to lack of central confirmation of MZL.
[b]Four patients discontinued due to AE (pyrexia later attributed to disease progression, n=1; fatal myocardial infarction in a patient with pre-existing cardiovascular disease, n=1; COVID-19 pneumonia leading to death, n=2).
[c]Three patients discontinued per the investigator's discretion (requiring prohibited medications).

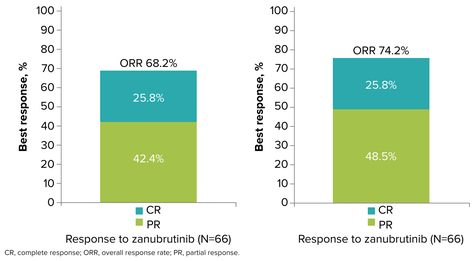
## RESULTS *(CONTINUED)*

### Table 1. Patient and Disease Characteristics

| Characteristic | Total (N=68) |
|---|---|
| **Age, median (range), y** | 70 (37-95) |
| **Age category, n (%)** | |
| ≥65 y | 41 (60.3) |
| ≥75 y | 19 (27.9) |
| **Male, n (%)** | 36 (52.9) |
| **ECOG PS, n (%)** | |
| 0-1 | 63 (92.6) |
| **Disease status, n (%)** | |
| Relapsed | 44 (64.7) |
| Refractory | 22 (32.4) |
| **MZL subtypes, n (%)** | |
| Extranodal | 26 (38.2) |
| Nodal | 26 (38.2) |
| Splenic | 12 (17.6) |
| Unknown[a] | 4 (5.9) |
| **Lymphoma involvement in bone marrow, n (%)** | 29 (42.6) |
| **Prior lines of systemic therapy, median (range)** | 2 (1-6) |

ECOG PS, Eastern Cooperative Oncology Group performance status; MZL, marginal zone lymphoma.
[a]Four patients presented with both nodal and extranodal lesions; investigators were unable to classify the MZL subtype.

### Figure 3. ORR by (A) Independent Review and (B) Investigator Assessment




CR, complete response; ORR, overall response rate; PR, partial response.

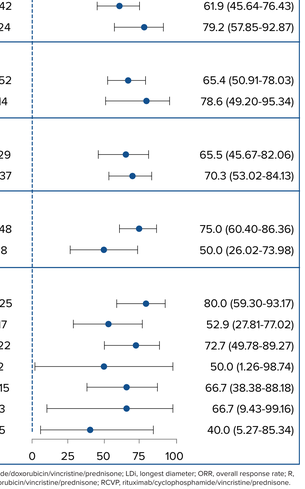
### Table 2. Best Overall Response by Independent Review and MZL Subtypes

| Best response | Extranodal (n=25) | Nodal (n=25) | Splenic (n=12) | Unknown (N=4) | Total (N=66[a]) |
|---|---|---|---|---|---|
| **ORR (CR or PR), n (%)** | 16 (64.0) | 19 (76.0) | 8 (66.7) | 2 (50.0) | 45 (68.2) |
| **95% CI[b]** | 42.52-82.03 | 54.87-90.64 | 34.89-90.08 | 6.76-93.24 | 55.56-79.11 |
| CR | 10 (40.0) | 5 (20.0) | 1 (8.3) | 1 (25.0) | 17 (25.8) |
| PR | 6 (24.0) | 14 (56.0) | 7 (58.3) | 1 (25.0) | 28 (42.4) |
| SD | 4 (16.0) | 5 (20.0) | 3 (25.0) | 1 (25.0) | 13 (19.7) |
| Non-PD | 1 (4.0)[c] | 0 | 0 | 0 | 1 (1.5) |
| PD | 3 (12.0) | 1 (4.0) | 1 (8.3) | 1 (25.0) | 6 (9.1) |
| Discontinued before first assessment | 1 (4.0)[d] | 0 | 0 | 0 | 1 (1.5) |

Data cutoff: January 18, 2021.
CR, complete response; CT, computed tomography; FDG, fludeoxyglucose; MZL, marginal zone lymphoma; ORR, overall response rate; PET, positron emission tomography; PD, progressive disease; PR, partial response; SD, stable disease.
[a]Two patients were excluded due to lack of central confirmation of MZL.
[b]Two-sided Clopper-Pearson 95% CI.
[c]One patient with FDG-avid disease missed the PET scan at cycle 3 and was assessed as having non-PD disease by independent review due to missing PET scan. CT scan results showed stable disease at cycle 3.
[d]One patient (extranodal MZL) withdrew consent before the first disease assessment.

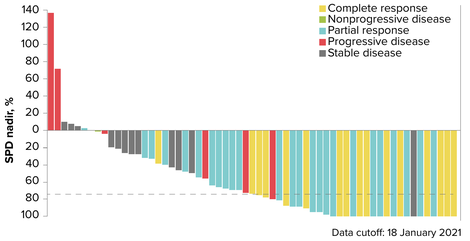
### Figure 4. Subgroup Analysis of ORR by Independent Review

| | Patients/n | ORR (95% CI)[a] |
|---|---|---|
| All patients | 45/66 | 68.2 (55.56-79.11) |
| Age group | | |
| <65 y | 15/26 | 57.7 (36.92-76.65) |
| ≥65 y | 30/40 | 75.0 (58.80-87.31) |
| <75 y | 28/48 | 58.3 (43.21-72.39) |
| ≥75 y | 17/18 | 94.4 (72.71-99.86) |
| Disease status | | |
| Relapsed | 31/43 | 72.1 (56.33-84.67) |
| Refractory | 14/21 | 66.7 (43.03-85.41) |
| Bulky disease | | |
| LDi ≤5 cm | 26/42 | 61.9 (45.64-76.43) |
| LDi >5 cm | 19/24 | 79.2 (57.85-92.87) |
| Baseline extranodal disease | | |
| Yes | 34/52 | 65.4 (50.91-78.03) |
| No | 11/14 | 78.6 (49.20-95.34) |
| Bone marrow involvement | | |
| Yes | 19/29 | 65.5 (45.67-82.06) |
| No | 26/37 | 70.3 (53.02-84.13) |
| Prior line of systemic therapy | | |
| <3 | 36/48 | 75.0 (60.40-86.36) |
| ≥3 | 9/18 | 50.0 (26.02-73.98) |
| Prior treatment | | |
| RCVP | 20/25 | 80.0 (59.30-93.17) |
| RCHOP | 9/17 | 52.9 (27.81-77.02) |
| BR | 16/22 | 72.7 (49.78-89.27) |
| R-lenalidomide | 1/2 | 50.0 (1.26-98.74) |
| Rituximab monotherapy | 10/15 | 66.7 (38.38-88.18) |
| CHOP | 2/3 | 66.7 (9.43-99.16) |
| R-chlorambucil | 2/5 | 40.0 (5.27-85.34) |



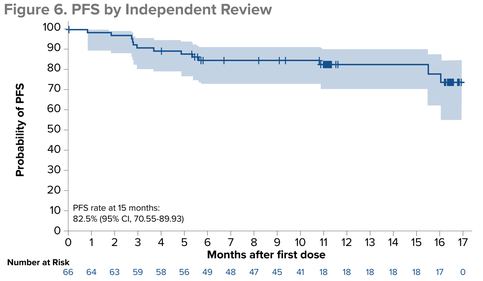

BR, bendamustine/rituximab; CHOP, cyclophosphamide/doxorubicin/vincristine/prednisone; LDi, longest diameter; ORR, overall response rate; R, rituximab; RCHOP, rituximab/cyclophosphamide/doxorubicin/vincristine/prednisone; RCVP, rituximab/cyclophosphamide/vincristine/prednisone.
[a]Two-sided Clopper-Pearson 95% CIs for ORR.

### Figure 5. Change in Target Lesion SPD From Baseline by Independent Review



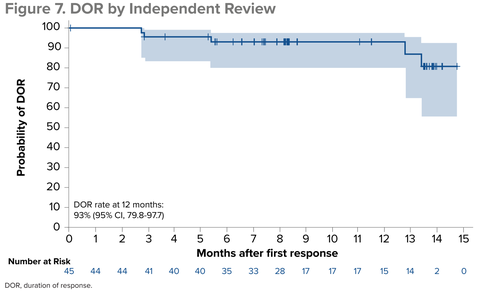

Only patients with nonmissing best overall response and SPD percent changes were included (n=61).
Dashed lines = median reduction in SPD (-74%).
SPD, sum of products of perpendicular diameters.

### Figure 6. PFS by Independent Review




PFS, progression-free survival.

### Figure 7. DOR by Independent Review



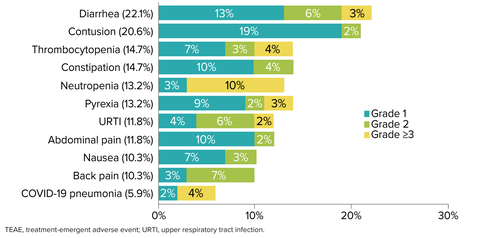

DOR, duration of response.

### Table 3. Safety Summary

| | N=68 n (%) |
|---|---|
| **Patients with at least 1 TEAE** | 65 (95.6) |
| **Grade 3 or higher TEAE** | 27 (39.7) |
| **Serious TEAE** | 26 (38.2) |
| **TEAE leading to dose interruption** | 20 (29.4) |
| **TEAE leading to study drug discontinuation** | 4 (5.9)[a] |
| **TEAE leading to death** | 3 (4.4)[a] |
| **TEAE leading to dose reduction** | 0 |

TEAE, treatment-emergent adverse event.
[a]One patient discontinued due to pyrexia (later attributed to disease progression); 1 patient died from myocardial infarction; 2 patients died from COVID-19 pneumonia.

### Figure 8. TEAEs Occurring in ≥10% of Patients Regardless of Causality




TEAE, treatment-emergent adverse event; URTI, upper respiratory tract infection.

### Table 4. TEAEs of Interest

| TEAE of interest | All grade (N=68) | Grade ≥3 (N=68) |
|---|---|---|
| Infection | 31 (45.6) | 11 (16.2) |
| Hemorrhage | 25 (36.8) | 0 |
| Diarrhea | 15 (22.1) | 2 (2.9) |
| Thrombocytopenia[a] | 10 (14.7) | 3 (4.4) |
| Neutropenia[b] | 9 (13.2) | 7 (10.3) |
| Second primary malignancy[c] | 5 (7.4) | 3 (4.4) |
| Atrial fibrillation/flutter[d] | 2 (2.9) | 1 (1.5) |
| Hypertension | 2 (2.9) | 1 (1.5) |
| Major hemorrhage | 0 | 0 |

TEAE, treatment-emergent adverse event.
[a]Includes thrombocytopenia and platelet count decreased.
[b]Includes neutropenia and neutrophil count decreased.
[c]Includes basal cell and squamous cell carcinoma (in 2 patients with history of skin cancer); papillary thyroid carcinoma (in 1 patient with pre-existing thyroid nodule); recurrent bladder cancer (in 1 patient with history of bladder cancer), and acute myeloid leukemia (in 1 patient with prior chemotherapy with alkylating agents).
[d]Atrial fibrillation occurred in a patient with pre-existing atrial fibrillation (21 days after end of treatment due to disease progression).

## CONCLUSIONS

- The MAGNOLIA study met its primary endpoint
- Zanubrutinib was highly active with a favourable safety profile in patients with R/R MZL
- After a median study follow-up of 15.7 months:
  - High ORR of 68.2% and CR rate of 25.8% by independent review
    - ORR higher than prespecified null ORR of 30% ($P<0.0001$)
    - Responses were observed in all MZL subtypes
  - Median PFS and median DOR not reached
    - 93% of responders were progression/death-free at 12 months after initial response
    - PFS rate was 82.5% at 15 months
  - Treatment discontinuation due to AEs occurred in 4 patients; none were considered related to zanubrutinib
  - Grade 5 AEs occurred in 3 patients (including 2 patients who died from COVID-19 pneumonia)
  - Atrial fibrillation/flutter occurred in 2 patients
  - No major haemorrhage was reported

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## DISCLOSURES

**JT** received research funding from BeiGene, Celgene, Janssen, Pharmacyclics LLC, Roche, and Takeda.
**AT** served as a consultant for AbbVie, AstraZeneca, BeiGene, and Janssen and as speakers' bureau for AbbVie, AstraZeneca, BeiGene, and Janssen.
**KL** served as a consultant for BeiGene, Celgene, Gilead, Karyopharm, Roche, and Takeda; received research funding for BeiGene, Genmab, Pharmacyclics, and Roche; received honoraria from Roche; and received travel expenses from Bristol Myers Squibb, Celgene, Janssen, and Roche.
**PM** served as a consultant for BeiGene, Celgene, Janssen, and Kite and received honoraria from Recordati and Roche.
**BH** served as a consultant for Cellectar Biosciences and Kite and received research funding from BeiGene, Celgene, and Roche/Genentech.
**HC** served as a consultant for AbbVie, EUSA Pharma, and Janssen and received honoraria from Janssen and travel expenses from Celgene and, Janssen.
**PLZ** served as a consultant for ADC Therapeutics, Bristol Myers Squibb, Celltrion, EUSA Pharma, Gilead, Janssen-Cilag, Kyowa Kirin, Merck Sharp and Dohme Corp, MSD, Roche, Sanofi, Servier, Sandoz, TG Therapeutics, Takeda, and Verastem and as speakers' bureau for Bristol Myers Squibb, Celltrion, EUSA Pharma, Gilead, Janssen-Cilag, Kyowa Kirin, Merck Sharp and Dohme Corp, Roche, Servier, Takeda, TG Therapeutics, and Verastem.
**MC** received research funding from AbbVie, AstraZeneca, Bristol Meyers Squibb, Celgene, and Pharmacyclics.
**PK** served as a consultant for Janssen-Cilag and Merck Sharp and Dohme Corp and received research funding from Roche and Shire.
**RM** served as a consultant for MEI Pharma.
**CP** served as a consultant for BeiGene, Genentech, Janssen, Kite/Gilead, Morphosys, and Pharmacyclics and received research funding from AbbVie, Acerta, AstraZeneca, Genentech, Infinity, Kite, SeaGen, TG Therapeutics, VelosBio, and Xencor.
**CT** served as a consultant for and received honoraria from Celgene/Bristol Myers Squibb, Gilead, Janssen, Novartis, and Roche and received travel expenses from Bristol Myers Squibb, Celgene, Gilead, Novartis, and Roche.
**AML** served as a consultant for Amgen, Servier, and Celgene; received research funding from Novartis, Janssen, AbbVie, Roche, Amgen, Celgene, Bristol Meyers Squibb, Takeda, Incyte, Pfizer, BeiGene, Oncopeptides, AB, Verastem, Karyopharm, Archiego, CTI Biopharma Corp, Debiopharm International, Morphosys, Fribrogen, and Onconova Therapeutics Inc; and received travel expenses from Roche, Takeda, AbbVie, Novartis, Sanophy-Genzyme, Verastem, and Bristol Myers Squibb.
**FC** served as a consultant for Roche and received honoraria from Janssen, Celgene, and Gilead and travel expenses from Amgen.
**SI** served as a consultant for Beigene, Gilead, and Takeda; served on speakers' bureau for AbbVie, Gilead, Janssen, Takeda, Takeda, and received travel expenses from Janssen and Takeda.
**RM** received honoraria from AbbVie.
**DT** Served as a consultant for EUSA Pharma, George Clinical, and Roche; served on speakers' bureau for Roche; and received research funding and travel expenses from Roche.
**MC** and **WZ** have current employment with and stock ownership in BeiGene.
**JH** has current employment, leadership, stock ownership, patents/royalties/other intellectual property, and travel expenses from BeiGene.
**SO** served as a consultant for AbbVie, AstraZeneca, Celgene, CSL, Gilead, Janssen, Merck, Munishpharma, Roche, and Takeda; received honoraria from AbbVie, AstraZeneca, Celgene, Gilead, Janssen, Merck, Roche, and Takeda; received research funding from AbbVie, AstraZeneca, BeiGene, Epizyme, Gilead, Janssen, Merck, Roche, and Takeda; and received travel expenses from Roche.
**JJ, MS-T, XK, MS, KZ, EB, RC, HM,** and **JSK** have nothing to disclose.

## ACKNOWLEDGMENTS

We thank the investigators, site support staff, and especially the patients and their caregivers for participating in the MAGNOLIA (BGB-3111-214) study.
This study was sponsored by BeiGene. Editorial support was provided by Bio Connections, LLC and funded by BeiGene.
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