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

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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

STUDY 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

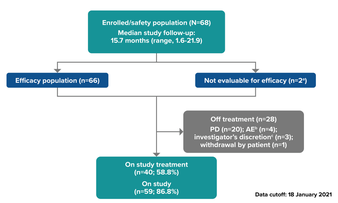
Abbreviations: BID, twice a day; DoR, duration of response; IRC, independent review committee; MZL, marginal zone lymphoma; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; PI, principal investigator; R/R, relapsed/refractory.

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 computerized tomography or magnetic resonance imaging
- Adequate organ function
- No prior BTK inhibitor exposure

RESULTS

Figure 2. Patient Disposition



[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).
Abbreviations: AE, adverse event; MZL, marginal zone lymphoma; PD, progressive disease.

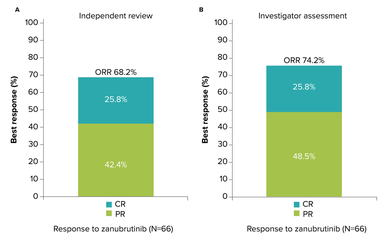
RESULTS *(continued)*

Table 1. Demographics and Disease Characteristics

Characteristics, n (%)	Total (N=68)
Age median (range), years	70 (37-95)
Age category, n (%)	
≥65 years	41 (60.3)
≥75 years	19 (27.9)
Male, n (%)	36 (2.9)
ECOG performance status, 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)

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

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



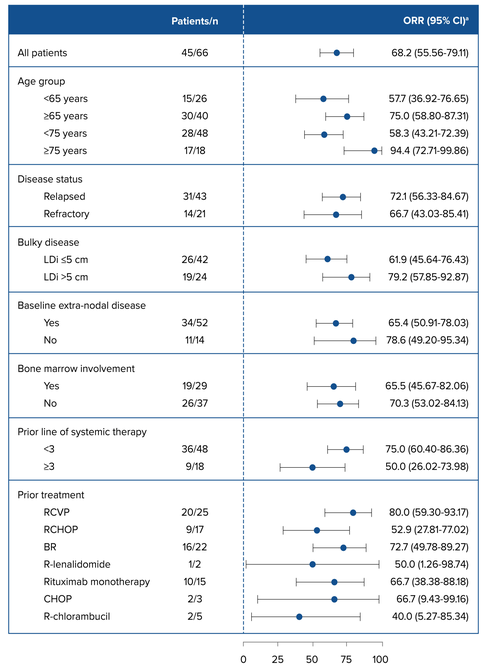
Abbreviations: CR, complete response; ORR, overall resonse rate; PR, partial response.

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 (%) 95% CI[b]	16 (64.0) (42.52-82.03)	19 (76.0) (54.87-90.64)	8 (66.7) (34.89-90.08)	2 (50.0) (6.76-93.24)	45 (68.2) (55.56-79.11)
Complete response	10 (40.0)	5 (20.0)	1 (8.3)	1 (25.0)	17 (25.8)
Partial response	6 (24.0)	14 (56.0)	7 (58.3)	1 (25.0)	28 (42.4)
Stable disease	4 (16.0)	5 (20.0)	3 (25.0)	1 (25.0)	13 (19.7)
Nonprogressive disease	1 (4.0)[c]	0	0	0	1 (1.5)
Progressive disease	3 (12.0)	1 (4.0)	1 (8.3)	1 (25.0)	6 (9.1)
Discontinued prior to first assessment	1 (4.0)[d]	0	0	0	1 (1.5)

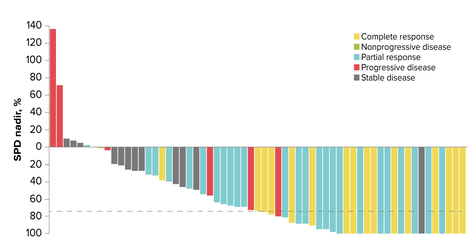
Data cutoff: 18 January 2021.
[a]Two patients were excluded due to lack of central confirmation of MZL.
[b]Two-sided Clopper-Pearson 95% CI.
[c]One patient with FDG-avid disease missed the PET scan at Cycle 3 and was assessed as having nonprogressive disease by independent review due to missing PET scan.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

Figure 4. Responses Were Generally Consistent Across Subgroups



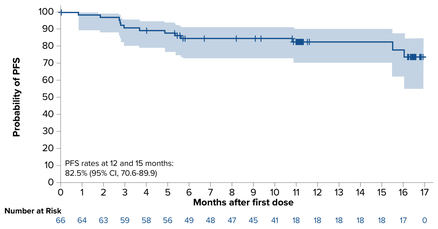
[a]Two-sided Clopper-Pearson 95% CIs for ORR.
Abbreviations: BR, bendamustine/rituximab; CI, confidence interval; CHOP, cyclophosphamide/doxorubicin/vincristine/prednisone; LDi, longest diameter; ORR, overall response rate; R, rituximab; RCHOP, rituximab/cyclophosphamide/doxorubicin/vincristine/prednisone;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

Figure 5. Majority of Patients Had Reduction in Tumor Burden



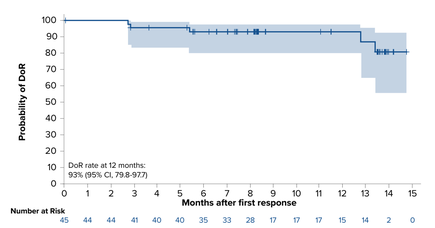
Only patients with nonmissing best overall response and SPD percent changes were included (n=61).
Dashed lines = median reduction in SPD (-74%).
Abbreviation: SPD, sum of the products of the longest perpendicular diameters.

Figure 6. PFS by Independent Review



Abbreviations: CI, confidence interval; PFS, progression-free survival.

Figure 7. DoR by Independent Review



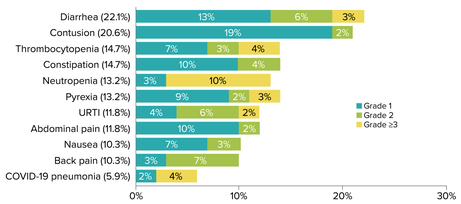
Abbreviations: CI, confidence interval; DoR, duration of response.

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

[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.
Abbreviation: TEAE, treatment-emergent adverse event.

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



Abbreviations: 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

[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).
Abbreviation: TEAE, treatment-emergent adverse event.

CONCLUSIONS

- The MAGNOLIA study met its primary endpoint
- Zanubrutinib was highly active with a favorable 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-free/alive at 12 months after initial response
    - PFS rate was 82.5% at 15 months
  - Treatment discontinuation due to AEs occurred in four patients; none were considered related to zanubrutinib
  - Grade five AEs occurred in three patients (including two patients who died from COVID-19 pneumonia)
  - Atrial fibrillation/flutter occurred in two patients
  - No major hemorrhage was reported

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