

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

Authors: Stephen Opat,¹ Alessandra Tedeschi,² Bei Hu,³ Kim M. Linton,⁴ Pamela McKay,⁵ Henry Chan,⁶ Jie Jin,⁷ Mingyuan Sun,⁸ Magdalena Sobieraj-Teague,⁹ Pier Luigi Zinzani,¹⁰ Peter Browett,¹¹ Xiaoyan Ke,¹² Craig A. Portell,¹³ Catherine Thieblemont,¹⁴ Kirit Ardeshta,¹⁵ Fontanet Bijou,¹⁶ Patricia Walker,¹⁷ Eliza A. Hawkes,¹⁸ Shir-Jing Ho,¹⁹ Keshu Zhou,²⁰ Zhiyu Liang,²¹ Jianfeng Xu,²¹ Chris Tankersley,²¹ Richard Delarue,²¹ Melannie Co,²¹ and Judith Trotman²²

Affiliations: ¹Monash Health and Monash University, Clayton, Victoria, Australia; ²ASST Grande Ospedale Metropolitano Niguarda, Milan, Italy; ³Levine Cancer Institute/Atrium Health, Charlotte, NC, USA; ⁴Manchester Cancer Research Centre, Division of Cancer Sciences, Manchester, UK; ⁵Beatson West of Scotland Cancer Centre, Glasgow, UK; ⁶North Shore Hospital, Auckland, New Zealand; ⁷The First Affiliated Hospital, Zhejiang University, Hangzhou, Zhejiang, China; ⁸Institute of Hematology & Blood Diseases Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Tianjin, China; ⁹Flinders Medical Centre, Bedford Park, South Australia, Australia; ¹⁰Institute of Hematology “Seràgnoli” University of Bologna, Bologna, Italy; ¹¹Auckland City Hospital, Grafton, New Zealand; ¹²Peking University Third Hospital, Beijing, China; ¹³University of Virginia, Comprehensive Cancer Center, Charlottesville, VA, USA; ¹⁴APHP, Hôpital Saint-Louis, Hemato-oncology, Paris University Diderot, Paris, France; ¹⁵University College London Hospitals, London, UK; ¹⁶Institut Bergonié, Bordeaux, France; ¹⁷Peninsula Private Hospital, Frankston, Victoria, Australia; ¹⁸Box Hill Hospital, Box Hill, Victoria, Australia; ¹⁹St. George Hospital, Kogarah, New South Wales, Australia; ²⁰Henan Cancer Hospital, Zhengzhou, Henan, China; ²¹BeiGene (Beijing) Co., Ltd., Beijing, China, BeiGene Switzerland GmbH and BeiGene USA, Inc., San Mateo, CA, USA; and ²²Concord Repatriation General Hospital, University of Sydney, Concord, New South Wales, Australia

Background/Introduction: Advanced-stage MZL is generally considered incurable, characterized by periods of remission and relapse. Zanubrutinib (BGB-3111) is a potent and highly specific next-generation Bruton tyrosine kinase (BTK) inhibitor recently approved by the US Food and Drug Administration and Health Canada for the treatment of patients (pts) with R/R MZL based on the primary analysis results of the MAGNOLIA study (BGB-3111-214; NCT03846427). Here, we present the final analysis of MAGNOLIA at a median follow-up of 28 months.

Methods: MAGNOLIA is a phase 2, multicenter, single-arm study of adult pts requiring systemic treatment for R/R MZL with ≥ 1 prior line of therapy including ≥ 1 CD20-directed regimen. All pts were treated with zanubrutinib 160 mg twice daily until disease progression or unacceptable toxicity. Use of long-term antiplatelets and anticoagulants was permitted. The primary endpoint was overall response rate (ORR) as determined by an independent review committee (IRC) in accordance with the Lugano classification. Secondary endpoints included ORR by investigator assessment, duration of response (DOR), progression-free survival (PFS), overall survival (OS), and safety. Efficacy was assessed by positron emission tomography (PET)-based Lugano criteria for pts with IRC-confirmed fluorodeoxyglucose (FDG)-avid disease at baseline; non-avid pts were assessed by computed tomography (CT)-based criteria. A sensitivity analysis using only CT-based criteria was also performed.

Results: As of May 4, 2022, 68 pts were enrolled and treated. The median age was 70 years (range 37-95), with 27.9% aged ≥ 75 years. MZL subtypes included extranodal (mucosa-associated lymphoid tissue) in 38.2%, nodal in 38.2%, splenic in 17.6%, and unknown in 5.9% of pts. The median number of prior therapies was 2 (range 1-6); 32.4% of pts had disease refractory to last therapy. Most (89.7%) pts

received prior chemoimmunotherapy and 7 (10.3%) received rituximab monotherapy as their only prior treatment. Sixty-one (89.7%) pts had IRC-assessed FDG-avid disease.

After a median follow-up of 28.0 months (range 1.6-32.9) and a median treatment duration of 24.2 months (range 0.9-32.9), 66 pts were evaluable for efficacy (**Table**). IRC-assessed ORR (complete response [CR] + partial response [PR]) was 68.2% (CR 25.8%). Responses were observed in all MZL subtypes, with an ORR of 64.0%, 76.0%, 66.7%, and 50.0% in extranodal, nodal, splenic, and unknown subtypes, respectively. CR rate was 40.0% for extranodal, 20.0% for nodal, 8.3% for splenic, and 25.0% for unknown subtypes. The median DOR, PFS, and OS were not reached. More than 70.0% of pts were alive or progression-free at the 2-year landmark by independent review (**Figure**).

Sensitivity analysis using only CT-based criteria (n=66) by IRC assessment showed an ORR of 66.7% and CR of 24.2%. Similarly, median DOR and median PFS were not reached.

At study completion, 31 (45.6%) pts deriving benefit rolled over to a long-term extension (LTE) study (NCT04170283); 24 (35.3%) pts discontinued owing to disease progression (investigator assessed); 5 (7.4%) due to adverse events (AEs), 2 (2.9%) required prohibited medications, and 1 (1.5%) withdrew consent.

The most common treatment-emergent AEs in >10% of pts were bruising (23.5%), diarrhea (22.1%), constipation (17.6%), arthralgia (14.7%), pyrexia (14.7%), upper respiratory tract infection (13.2%), abdominal pain and back pain (each 11.8%). Neutropenia (8.8%) and COVID-19 pneumonia (5.9%) were the most common grade ≥ 3 AEs. Five (7.4%) pts died due to unrelated AEs: COVID-19 pneumonia (n=2), acute myeloid leukemia (n=1, prior alkylating agent exposure), myocardial infarction (n=1, preexisting coronary artery disease), and septic encephalopathy (n=1, pt in CR). Hypertension occurred in 3 (4.4%) pts, atrial fibrillation and atrial flutter in 1 (1.5%) pt each; none led to treatment withdrawal. One (1.5%) pt experienced grade 3 gastrointestinal hemorrhage while receiving rivaroxaban for pulmonary embolism; pt fully recovered and rolled over to the LTE study.

Conclusion: In this final analysis with more than 2 years of median study follow-up, zanubrutinib continues to be effective as demonstrated by high response rates and durable disease control. Zanubrutinib was generally well tolerated, with no new safety signals observed.

Table: Baseline Characteristics, Efficacy, and Safety Outcomes

Baseline Characteristics	R/R MZL (N=68)^a		
Male sex, n (%)	36 (52.9)		
ECOG PS 0-1, n (%)	63 (92.7)		
Bone marrow involvement, n (%)	29 (42.6)		
Extranodal sites, n (%)	53 (77.9)		
Stage III/IV, n (%)	59 (86.8)		
Efficacy	(N=66)^b		
	IRC		INV
	PET and/or CT	CT only	PET and/or CT
ORR, n (%) [95% CI]	45 (68.2) [55.6, 79.1]	44 (66.7) [54.0, 77.8]	50 (75.8) [63.6 85.5]
Best response, n (%)			
CR	17 (25.8)	16 (24.2)	19 (28.8)
PR	28 (42.4)	28 (42.4)	31 (47.0)
SD	13 (19.7)	16 (24.2)	10 (15.2)
PD	6 (9.1)	5 (7.6)	5 (7.6)
DOR rate at 24 months, % [95% CI]	72.9 [54.4, 84.9]	66.8 [46.4, 81.0]	60.8 [44.8, 73.6]
PFS rate at 24 months, % [95% CI]	70.9 [57.2, 81.0]	64.9 [51.2, 75.6]	57.9 (44.8, 68.9)
OS rate at 24 months, % [95% CI]	85.9 [74.7, 92.4]		
Safety^c	(N=68)^a		
Any TEAE, n (%)	68 (100)		
Grade ≥3 TEAE, n (%)	33 (48.5)		
Drug-related grade ≥3 TEAE, n (%) ^d	10 (14.7)		
Serious TEAE, n (%)	30 (44.1)		
Drug-related serious TEAE, n (%) ^d	7 (10.3)		
TEAE leading to dose interruption, n (%)	25 (36.8)		
Drug-related TEAE leading to dose interruption, n (%) ^d	8 (11.8)		
TEAE leading to dose reduction, n (%)	0		

Data cutoff: May 4, 2022.

CR, complete response; CT, computed tomography; DOR, duration of response; ECOG PS, Eastern Cooperative Oncology Group performance status; INV, investigator; IRC, independent review committee; MZL, marginal zone lymphoma; ORR, overall response rate; PD, progressive disease; PET, positron emission tomography; PR, partial response; R/R, relapsed/refractory; SD, stable disease; TEAE, treatment-emergent adverse event.

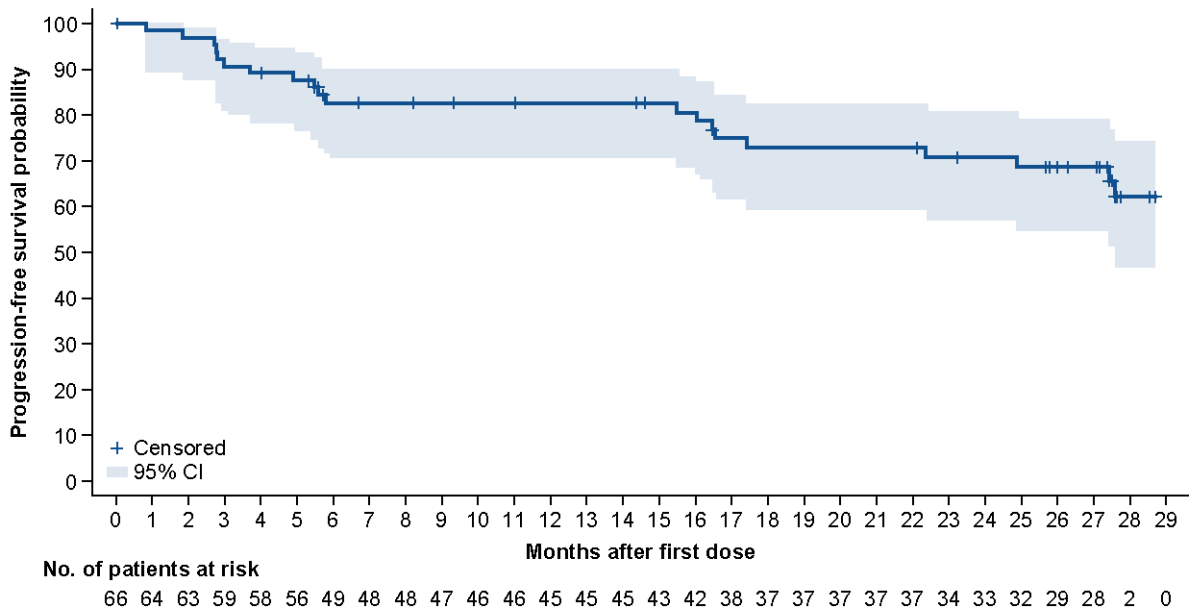
^aSafety analysis set is defined as all patients who received at least 1 dose of study drug.

^bEfficacy analysis set is defined as all patients in the safety analysis set with centrally confirmed diagnosis of MZL. Two pts were excluded from analysis owing to centrally confirmed transformation to diffuse large B-cell lymphoma. One pt discontinued study before first response assessment.

^cTEAE is defined as an adverse event that had an onset date or a worsening in severity from baseline (pretreatment) on or after the first dose of study drug up to 30 days after study drug discontinuation or initiation of a new anticancer therapy. Worsening of an event to grade 5 beyond day 30 after last dose of study drug of a TEAE is also considered a TEAE (if it is before start of new anticancer therapy).

^dBased on assessment by the investigators.

Figure: Progression-Free Survival



Data cutoff: May 4, 2022.