Long-term efficacy and safety of zanubrutinib (ZANU) in relapsed/refractory marginal zone lymphoma (R/R MZL): final analysis of the MAGNOLIA (BGB-3111-214) trial

Authors: Judith Trotman,[1] Alessandra Tedeschi,[2] Bei Hu,[3] Kim M. Linton,[4] Pamela McKay,[5] Sophie Leitch,[6] Jie Jin,[7] Mingyuan Sun,[8] Magdalena Sobieraj-Teague,[9] Pier Luigi Zinzani,[10] Peter Browett,[11] Catherine Thieblemont,[12] Anna Marina Liberati,[13] Emmanuel Bachy,[14] Federica Cavallo,[15] Régis Costello,[16] Sunil Iyengar,[17] Roberto Marasca,[18] Heidi Mociková,[19] Jin Seok Kim,[20] Dipti Talaulikar,[21] Zhiyu Liang,[22] Jianfeng Xu,[22] Chris Tankersley, [22] Richard Delarue,[22] Melannie Co,[22] and Stephen Opat[23]

Affiliations: [1]Concord Repatriation General Hospital, University of Sydney, Concord, NSW, Australia; [2]ASST Grande Ospedale Metropolitano Niguarda, Department of Hematology, Milan, Italy; [3]Levine Cancer Institute/Atrium Health, Charlotte, NC, USA; [4]Manchester Cancer Research Centre, Division of Cancer Sciences, Manchester, UK; [5]Beatson West of Scotland Cancer Centre, Glasgow, UK; [6]North Shore Hospital, Auckland, New Zealand; [7]The First Affiliated Hospital, Zhejiang University, Hangzhou, Zhejiang, China; [8]Institute of Hematology & Blood Diseases Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Tianjin, China; [9]Flinders Medical Centre, Bedford Park, SA, Australia; [10]Institute of Hematology "Seràgnoli" University of Bologna, Bologna, Italy; [11]Auckland City Hospital, Grafton, New Zealand; [12]APHP, Hôpital Saint-Louis, Hemato-oncology, Paris University Diderot, Paris, France; [13]Università degli Studi di Perugia, Azienda Ospedaliera Santa Maria di Terni, Terni, Italy; [14]Hematology Department, Lyon-Sud Hospital, University of Lyon, Lyon, France; [15]Division of Hematology, Department of Molecular Biotechnologies and Health Sciences, University of Torino/AOU Città della Salute e della Scienza di Torino, Torino, Italy; [16]Hematology and Cellular Therapy Department, Conception University Hospital, Marseille, France; [17]Royal Marsden Hospital and Institute of Cancer Research, Sutton, UK; [18]University of Modena e Reggio Emilia, Modena, Italy; [19]Department of Clinical Hematology, University Hospital Královské Vinohrady and Third Faculty of Medicine, Charles University, Prague, Czech Republic; [20]Division of Hematology, Department of Internal Medicine, Yonsei University College of Medicine, Seoul, Republic of Korea; [21]Australian National University, Canberra, ACT, Australia; [22]BeiGene (Beijing) Co., Ltd., Beijing, China, BeiGene Switzerland GmbH, Basel, Switzerland, and BeiGene USA, Inc., San Mateo, CA, USA; and [23]Monash Health and Monash University, Department of Haematology, Clayton, Victoria, Australia

Introduction: ZANU (BGB-3111), a potent next-generation Bruton tyrosine kinase inhibitor, is approved in various countries for R/R MZL based on the MAGNOLIA study (NCT03846427) primary analysis. At a median follow-up of 28 months (mo), we present the MAGNOLIA study final analysis.

Methods: Eligible adult patients (pts) received ZANU 160 mg twice daily until disease progression/unacceptable toxicity. Primary endpoint was overall response rate (ORR) by independent review committee (IRC) in accordance with Lugano 2014 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 (70 [range: 37-95] median years); 66 pts were efficacy-evaluable (median follow-up 28.0 mo [range: 1.6-32.9]; median treatment duration 24.2 mo[range: 0.9-32.0]). Pts had the following MZL subtypes: 38.2% extranodal (mucosa-associated lymphoid tissue), 38.2% nodal, 17.6% splenic, 5.9% unknown. Sixty-one (89.7%) pts had IRC-assessed

FDG-avid disease. IRC-assessed ORR (complete response [CR] + partial response [PR]) was 68.2% (CR 25.8%; Table). ORR (CR rate) was 64.0% (40.0%) in extranodal, 76.0% (20.0%) in nodal, 66.7% (8.3%) in splenic, and 50.0% (25.0%) in unknown subtypes. Median DOR, PFS, and OS were not reached. At the 2-year landmark by IRC, >70.0% of pts were alive/progression-free. Sensitivity analysis using only CT-based criteria (n=66) by IRC showed an ORR of 66.7% (CR 24.2%). Median DOR and median PFS were not reached. At study completion, 31 (45.6%) pts deriving benefit rolled over to a long-term extension study (NCT04170283); 24 (35.3%) discontinued due to disease progression (investigator assessed); 5 (7.4%) to adverse events (AEs), 2 (2.9%) required prohibited medications, and 1 (1.5%) withdrew consent. Most common treatment-emergent AEs in >20% of pts were bruising (23.5%) and diarrhea (22.1%). 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 (2 COVID-19 pneumonia, 1 acute myeloid leukemia [prior alkylating agent exposure], 1 myocardial infarction [preexisting coronary artery disease], 1 septic encephalopathy [pt in CR]). Hypertension occurred in 3 (4.4%) pts, atrial fibrillation and atrial flutter in 1 (1.5%) pt; none led to treatment withdrawal.

Conclusions: With >2 years of median study follow-up, ZANU continues to demonstrate high response rates, durable disease control, and is 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.

[a]Safety analysis set is defined as all patients who received at least 1 dose of study drug.

[b]Efficacy 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.

[c]TEAE 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 is also considered a TEAE (if it is before start of new anticancer therapy).

[d]Based on assessment by the investigators.

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; pt, patient; R/R, relapsed/refractory; SD, stable disease; TEAE, treatment-emergent adverse event.