Title: Safety and Efficacy of Zanubrutinib in Patients with Relapsed/Refractory Marginal Zone Lymphoma (MAGNOLIA Phase 2 Study)

Author list: Judith Trotman, MBChB, FRACP, FRCPA[1], Alessandra Tedeschi, MD[2], Kim Linton, MBChB, MRCP, PhD[3], Pamela McKay, MBChB (Hons), FRCP, FRCPath[4], Bei Hu, MD[5], Henry Chan, MBChB, FRACP, FRCPA[6], Jie Jin, MD[7], Magdalena Sobieraj-Teague, MBBS, FRACP, FRCPA, M.Sc[8], Pier Luigi Zinzani, MD, PhD[9], Morton Coleman, MD[10], Peter Browett, BMedSci, MBChB, FRACP, FRCPA[11], Xiaoyan Ke, MD, PhD[12], Mingyuan Sun, MD[13], Robert Marcus, MA, FRCP, FRCPath[14], Craig Portell, MD[15], Catherine Thieblemont, MD, PhD[16], Keshu Zhou, MD[17], Anna Marina Liberati, MD[18], Emmanuel Bachy, MD, PhD[19], Federica Cavallo, PhD[20], Régis Costello, MD, PhD[21], Sunil Iyengar, MD[22], Roberto Marasca, MD[23], Heidi Mociková, MD[24], Jin Seok Kim, MD, PhD[25], Dipti Talaulikar[26], Melannie Co, MD[27], Wenxiao Zhou, MD[27], Jane Huang, MD[27], Stephen Opat[28]

Author affiliations:

[1]Concord Repatriation General Hospital, University of Sydney, Concord, Australia; [2]ASST Grande Ospedale Metropolitano Niguarda, Milan, Italy; [3]The Christie, Manchester, UK; [4]Beatson West of Scotland Cancer Centre, Glasgow, UK; [5]Levine Cancer Institute/Atrium Health, Charlotte, USA; [6]North Shore Hospital, Auckland, New Zealand; [7]The First Affiliated Hospital, Zhejiang University, Hangzhou, China; [8]Flinders Medical Centre, Bedford Park, Australia; [9]Institute of Hematology "Seràgnoli" University of Bologna, Bologna, Italy; [10]Clinical Research Alliance, Lake Success, USA; [11]Auckland City Hospital, Grafton, New Zealand; [12]Peking University Third Hospital, Beijing, China; [13]Institute of Hematology & Blood Diseases Hospital, Chinese Academy of Medical Sciences, Peking Union Medical College, Tianjin, China; [14]Sarah Cannon Research Institute UK, London, UK; [15]University of Virginia Health System, Charlottesville, USA; [16]APHP, Hôpital Saint-Louis, Hemato-oncology, Paris University Diderot, Paris, France; [17]Henan Cancer Hospital, Zhengzhou, China; [18]Azienda Ospedaliera Santa Maria Di Terni, Terni, Italy; [19]Centre Hospitalier Lyon Sud, Pierre Bénite, Rhone, Italy; [20]Azienda Ospedaliera Città della Salute e della Scienza di Torino, Torino, Italy; [21]Hôpital de la Conception – APHM, Marseille, France; [22]Royal Marsden Hospital, London, UK; [23]AOU Policlinico di Modena, Modena, Italy; [24]Fakultní nemocnice Královské Vinohrady, Praha 10, Czech Republic; [25]Severance Hospital, Seoul, Republic of Korea; [26]The Canberra Hospital, Canberra, Australia; [27]BeiGene (Beijing) Co., Ltd., Beijing, China and BeiGene USA, Inc., San Mateo, CA, USA; [28]Monash Health, Monash University, Clayton, Australia

Introduction: Zanubrutinib is a potent, specific next-generation BTK inhibitor with high selectivity for BTK vs the TEC- and EGFR-family kinases, which may be related to off-target toxicities.

Methods: This is a single-arm, multicenter study of adults with R/R MZL who previously received ≥1 prior therapy including ≥1 CD20 antibody regimen. All received zanubrutinib 160 mg bid until disease progression/unacceptable toxicity. Primary endpoint was overall response rate (ORR) by independent review committee (IRC). Secondary endpoints include investigator-assessed (INV) ORR, duration of response (DOR), progression-free survival (PFS), and safety.

Results: By January 11, 2021, 68 patients (pts) were enrolled and treated. Median age was 70 years (range, 37-95). Subtypes included extranodal (38%), nodal (38%), splenic (18%), and indeterminate in 6% of pts. Median number of prior therapies was 2 (range, 1-6), and 32% had disease refractory to last therapy.

Median duration of drug exposure was 59.1 weeks (range, 3.7-84.1). At a median follow-up of 15.5 months (range, 1.6-21.7), INV ORR was 74% with a CR rate of 24%. Responses were observed in all subtypes. Median DOR and PFS were not reached. IRC review is ongoing.

Twenty-eight (41%) pts discontinued treatment. The most common treatment-emergent AEs reported in ≥10% of pts were diarrhea (22%), bruising (21%), and constipation (15%). Neutropenia was the most common grade ≥3 AE (10%). All-grade AEs of interest included neutropenia (13%), thrombocytopenia (13%), atrial fibrillation/flutter (3%), and hypertension (3%). No major/serious hemorrhage was reported. No AEs led to dose reductions.

Conclusions: Zanubrutinib demonstrated high response rates and durable disease control with a favorable safety profile in pts with R/R MZL. EA - previously submitted to EHA 2021.

Table

	R/R MZL (N=68)[a]
Baseline Characteristics	
Age ⩾65 and <75 years	22 (32)
⩾75 years	19 (28)

Male sex, n (%)	36 (53)
ECOG PS 0-1, n (%)	63 (93)
Bone marrow involvement, n (%)	29 (43)
Efficacy (investigator assessment)	**(N=66)[b]**
ORR, n (%) [95% CI]	49 (74) [62, 84]
Complete response	16 (24)
Partial response	33 (50)
Stable disease[c]	11 (17)
Progressive disease	5 (8)
Discontinued study before first assessment	1 (2)
Time to response (months), median (range)	2.8 (1.7, 8.5)
Safety[d]	**(N=68)[a]**
Any AE	65 (96)
Grade ⩾3 AE, n (%)	26 (38)
Serious AE, n (%)	25 (37)
AE leading to dose interruption, n (%)	19 (28)

AE, adverse event; ECOG PS, Eastern Cooperative Oncology Group performance status; MZL, marginal zone lymphoma; ORR, overall response rate; R/R, relapsed/refractory

[a]Safety analysis set: pts who received ≥1 dose of study drug.

[b]Efficacy-evaluable set: pts who received ≥1 dose of study drug and with centrally-confirmed MZL diagnosis (2 pts were excluded due to transformation to diffuse large B-cell lymphoma).

[c]Three pts with stable disease were continuing on treatment.

[d]Treatment-emergent AEs.