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

Session SCO 8
Lymphoproliferative syndromes

Stephen Opat,[1] Catherine Thieblemont,[2] Fontanet Bijou,[3] Emmanuel Bachy,[4] Régis Costello,[5] Alessandra Tedeschi,[6] Bei Hu,[7] Kim M. Linton,[8] Pamela McKay,[9] Sophie Leitch,[10] Jie Jin,[11] Mingyuan Sun,[12] Magdalena Sobieraj-Teague,[13] Pier Luigi Zinzani,[14] Peter Browett,[15] Xiaoyan Ke,[16] Craig A. Portell,[17] Kirit Ardeshna,[18] Patricia Walker,[19] Eliza A. Hawkes,[20] Shir-Jing Ho,[21] Keshu Zhou,[22] Zhiyu Liang,[23] Jianfeng Xu,[23] Chris Tankersley,[23] Richard Delarue,[23] Melannie Co,[23] and Judith Trotman[24]

[1]Monash Health and Monash University, Clayton, Victoria, Australia; [2]APHP, Hôpital Saint-Louis, Hemato-oncology, Paris University Diderot, Paris, France; [3]Institut Bergonié, Bordeaux, France; [4]Centre Hospitalier Lyon Sud, Pierre Bénite, France; [5]Centre Hospitalier Lyon Sud, Pierre Bénite, France; [6]ASST Grande Ospedale Metropolitano Niguarda, Milan, Italy; [7]Levine Cancer Institute/Atrium Health, Charlotte, NC, USA; [8]Manchester Cancer Research Centre, Division of Cancer Sciences, Manchester, UK; [9]Beatson West of Scotland Cancer Centre, Glasgow, UK; [10]North Shore Hospital, Auckland, New Zealand; [11]The First Affiliated Hospital, Zhejiang University, Hangzhou, Zhejiang, China; [12]Institute of Hematology & Blood Diseases Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Tianjin, China; [13]Flinders Medical Centre, Bedford Park, South Australia, Australia; [14]Institute of Hematology "Seràgnoli" University of Bologna, Bologna, Italy; [15]Auckland City Hospital, Grafton, New Zealand; [16]Peking University Third Hospital, Beijing, China; [17]University of Virginia, Comprehensive Cancer Center, Charlottesville, VA, USA; [18]University College London Hospitals, London, UK; [19]Peninsula Private Hospital, Frankston, Victoria, Australia; [20]Box Hill Hospital, Box Hill, Victoria, Australia; [21]St. George Hospital, Kogarah, New South Wales, Australia; [22]Henan Cancer Hospital, Zhengzhou, Henan, China; [23]BeiGene (Beijing) Co., Ltd., Beijing, China, BeiGene Switzerland GmbH and BeiGene USA, Inc., San Mateo, CA, USA; and [24]Concord Repatriation General Hospital, University of Sydney, Concord, New South Wales, Australia

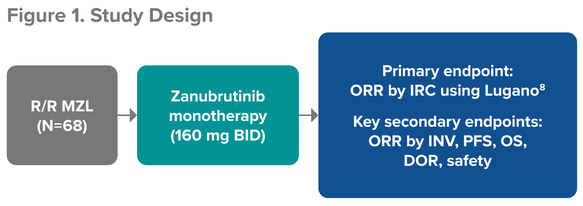
INTRODUCTION

- Advanced-stage MZL is generally incurable[1]
- B-cell receptor (BCR) signaling is a critical pathway in MZL pathogenesis[2]
- Bruton tyrosine kinase (BTK) plays a key role in BCR signaling[2]
  - BTK inhibition has antitumor activity in various B-cell malignancies[2,3]
- Zanubrutinib (BGB-3111) is a potent and highly specific next-generation BTK inhibitor
  - Designed to maximize BTK occupancy and minimize off-target inhibition of tyrosine kinase expressed in hepatocellular carcinoma (TEC)- and epidermal growth factor receptor (EGFR)-family kinases[3-5]
  - Can be coadministered with strong/moderate cytochrome P450 (CYP3A) inhibitors at a reduced dose, proton pump inhibitors, acid-reducing agents, and antithrombotic agents[6,7]
  - Recently approved for the treatment of patients with R/R MZL based on the primary analysis results of the MAGNOLIA study (BGB-3111-214; NCT03846427)[7]
- Here we present the final analysis of MAGNOLIA at a median follow-up of 28 months

METHODS

- MAGNOLIA is a phase 2, multicenter, open-label, single-arm study (**Figure 1**)
- Eligible patients were ≥18 years old, with R/R MZL, received ≥1 CD20-directed regimen, and had an Eastern Cooperative Oncology Group Performance Status (ECOG PS) of 0, 1, or 2
  - Patients with prior treatment with a BTK inhibitor were excluded
- All patients received zanubrutinib monotherapy 160 mg twice daily (BID)
- Response to treatment was measured based on the Lugano classification for non-Hodgkin lymphoma (NHL)[8]
  - Positron emission tomography (PET)-based criteria for patients with independent review committee (IRC)-confirmed fluorodeoxyglucose (FDG)-avid disease
  - Computerized tomography (CT)-based criteria for non-FDG-avid disease patients
  - Additional sensitivity analysis for all evaluable patients using CT-based criteria
- Adverse events (AEs) were assessed and graded per the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) v4.03
  - The data cutoff date was 04 May 2022

Figure 1. Study Design

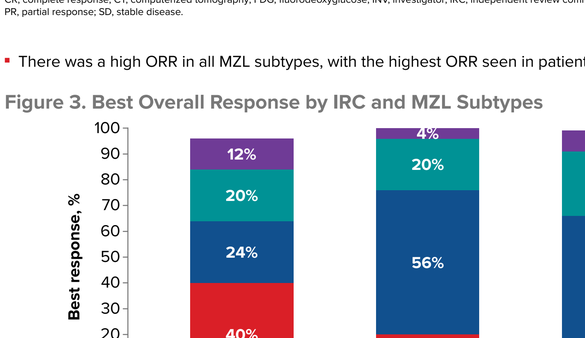


BID, twice daily; DOR, duration of response; INV, principal investigator; IRC, independent review committee; MZL, marginal zone lymphoma; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; R/R, relapsed/refractory.

RESULTS

- A total of 68 participants were enrolled in the study (**Figure 2**)
- Median follow-up was 28 months
- At the cutoff date, 34 patients were still receiving zanubrutinib
- The most common reason for treatment discontinuation was progressive disease (PD)

Figure 2. Patient Disposition



Data cutoff date: 04 May 2022.
[a]Two patients were excluded owing to lack of central confirmation of MZL. [b]BGB-3111-LTE1 is a BeiGene-sponsored, global, open-label extension study (NCT04170283). [c]Five patients discontinued treatment owing to AEs (2 patients with fatal COVID-19 pneumonia; 1 patient with pyrexia later attributed to disease progression; 1 patient with fatal myocardial infarction in a patient with preexisting cardiovascular disease; 1 patient who died from septic encephalopathy after bladder surgery [in CR at the time of death]). [d]Four patients discontinued per investigator decision (3 patients required prohibited medications; 1 patient due to lack of clinical benefit).
AE, adverse event; CR, complete remission; LTE, long-term extension; MZL, marginal zone lymphoma; PD, progressive disease.

Table 1. Baseline Demographics and Disease History

Characteristics	Total (N=68)
Median age (range), years	70 (37-95)
≥65, n (%)	41 (60)
≥75, n (%)	19 (28)
Male, n (%)	36 (53)
ECOG PS 0/1, n (%)	63 (93)
MZL subtypes, n (%)	
Extranodal	26 (38)
Nodal	26 (38)
Splenic	12 (18)
Unknown	4 (6)
Disease status, n (%)	
Relapsed	44 (65)
Refractory	22 (32)
Stage III/IV, n (%)	59 (87)
FDG-avid (by IRC), n (%)	61 (90)
Extranodal site involvement, n (%)	53 (78)
Bone marrow infiltration, n (%)	29 (43)
Median prior lines of systemic therapy (range)[a]	2 (1-6)
Immunochemotherapy, n (%)	61 (90)[b]
Rituximab monotherapy, n (%)	7 (10)

[a]Rituximab-based chemotherapy in most patients (n=60; 88%).
ECOG PS, Eastern Cooperative Oncology Group Performance Status; FDG, fluorodeoxyglucose; IRC, independent review committee; MZL, marginal zone lymphoma.

- After a median follow-up of 28 months, overall response rate (ORR) by IRC was 68%; ORR by principal investigator (INV) was 76% (**Table 2**)
- 26% of patients had a complete response (CR) by IRC, and 29% had a CR by INV; the median time to response was approximately 3 months

Table 2. Best Overall Response by IRC and INV Assessment

	(N=66)[a]		
	IRC		INV
Efficacy	**PET and/or CT (primary endpoint)[b]**	**CT only (sensitivity analysis)[f]**	**PET and/or CT**
ORR, n (%)	45 (68)	44 (67)	50 (76)
[95% CI]	[55.6, 79.1]	[54.0, 77.8]	[63.6, 85.5]
p-value	<0.0001[c]		
Best response, n (%)			
CR	17 (26)	16 (24)	19 (29)
PR	28 (42)	28 (42)	31 (47)
SD	14 (21)[d,e]	16 (24)	10 (15)
PD	6 (9)	5 (8)	5 (8)
Discontinued study prior to 1st assessment, n (%)	1 (1)	1 (1)	1 (1)
Median time to response (range), months	2.8 (1.7-11.1)	3.0 (1.8-22.2)	2.8 (1.7-16.6)

[a]Two patients were excluded from the efficacy population owing to lack of central confirmation of MZL. [b]Patients with IRC-confirmed FDG-avid disease were assessed by PET-based criteria; non–FDG-avid patients were assessed by CT-based Lugano criteria. [c]*P*-value for the primary endpoint was computed with the binomial exact test against the null hypothesis of ORR = 30% with alternative of ORR > 30%. [d]Five (7.6%) patients with stable disease are remaining on study treatment (after 12-18 cycles). [e]Includes one patient with FDG-avid disease who missed the PET scan at cycle 3 and was assessed as non-PD; CT showed stable disease at Cycle 3. [f]Additional sensitivity analysis using CT-based Lugano criteria for all 66-evaluable patients regardless of PET status at baseline.
CR, complete response; CT, computerized tomography; FDG, fluorodeoxyglucose; INV, investigator; IRC, independent review committee; MZL, marginal zone lymphoma; ORR, overall response rate; PD, progressive disease; PET, positron emission tomography; PR, partial response; SD, stable disease.

- There was a high ORR in all MZL subtypes, with the highest ORR seen in patients with nodal MZL (76%), and the highest CR in patients with extranodal MZL (40%)

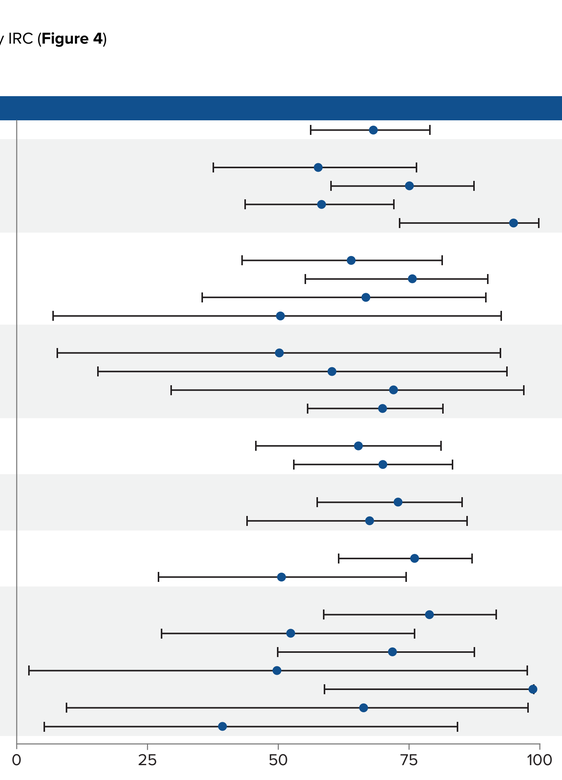
Figure 3. Best Overall Response by IRC and MZL Subtypes

[a]One patient (extranodal MZL) who withdrew consent prior to the first disease assessment was not shown in the graph.
CR, complete response; IRC, independent review committee; MZL, marginal zone lymphoma; ORR, overall response rate; PD, progressive disease; PR, partial response; SD, stable disease.

- All key patient subgroups had a response as evaluated by IRC (**Figure 4**)

Figure 4. Subgroup Analysis of ORR by IRC

Subgroup	Patients/response	ORR, % (95% CI)[a]
All patients	45/66	68.2 (55.6, 79.1)
Age group		
<65	15/26	57.7 (36.9, 76.7)
≥65	30/40	75.0 (58.8, 87.3)
<75	28/48	58.3 (43.2, 72.4)
≥75	17/18	94.4 (72.7, 99.9)
MZL subtype		
MALT	16/25	64.0 (42.5, 82.0)
NMZL	19/25	76.0 (54.9, 90.6)
SMZL	8/12	66.7 (34.9, 90.1)
Unknown	2/4	50.0 (6.8, 93.2)
Disease stage		
I	2/4	50.0 (6.8, 93.2)
II	3/5	60.0 (14.7, 94.7)
III	5/7	71.4 (29.0, 96.3)
IV	35/50	70.0 (55.4, 82.1)
Bone marrow involvement		
Yes	19/29	65.5 (45.7, 82.1)
No	26/37	70.3 (53.0, 84.1)
Disease status		
Relapsed	31/43	72.1 (56.3, 84.7)
Refractory	14/21	66.7 (43.0, 85.4)
Prior lines of systemic therapy		
<3	36/48	75.0 (60.4, 86.4)
≥3	9/18	50.0 (26.0, 74.0)
Prior treatment		
RCVP	20/25	80.0 (59.3, 93.2)
RCHOP	9/17	52.9 (27.8, 77.0)
BR	16/22	72.7 (49.8, 89.3)
R-lenalidomide	1/2	50.0 (1.3, 98.7)
Rituximab monotherapy	7/7	100.0 (59.0, 100.0)
CHOP	2/3	66.7 (9.4, 99.2)
R-chlorambucil	2/5	40.0 (5.3, 85.3)

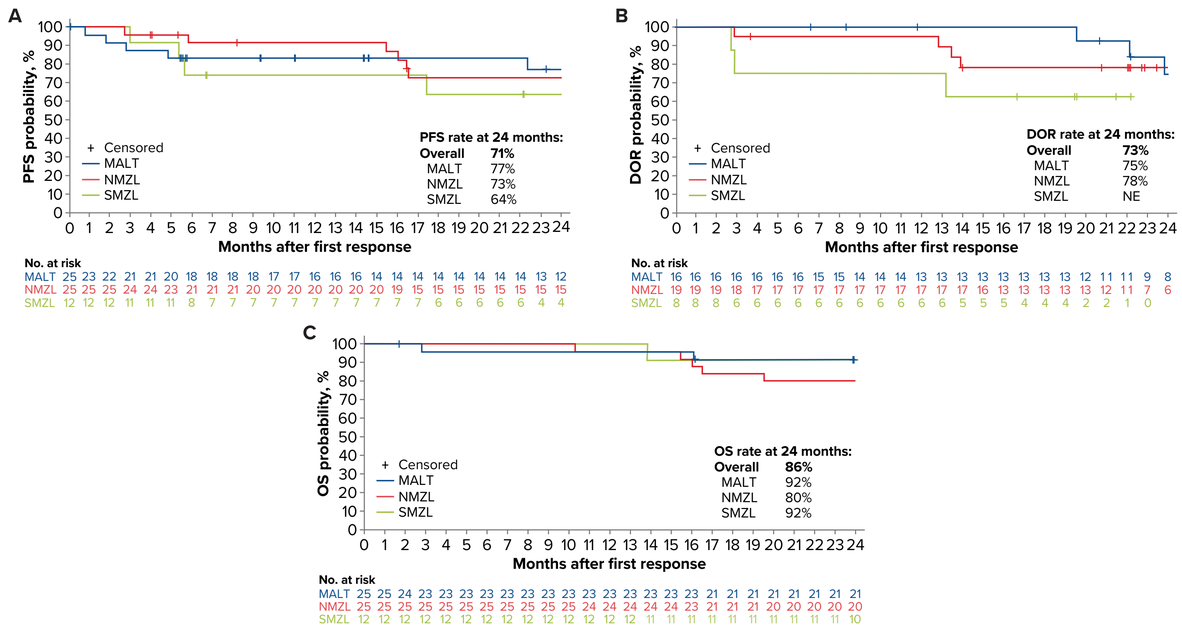


[a]Two-sided Clopper-Pearson. 95% CIs for ORR.
BR, bendamustine plus rituximab; CHOP, cyclophosphamide, hydroxydaunorubicin hydrochloride, vincristine sulfate, and prednisone; CI, confidence interval; IRC, independent review committee; MALT, mucosa associated lymphoid tissue; MZL, marginal zone lymphoma; NMZL, nodal MZL; ORR, overall response rate; RCHOP, rituximab, cyclophosphamide, hydroxydaunorubicin hydrochloride, vincristine sulfate, and prednisone; R, rituximab; RCVP, rituximab, cyclophosphamide, vincristine sulfate, and prednisone; SMZL, splenic MZL.

RESULTS (cont.)

- At a follow-up of 24 months, progression-free survival (PFS) rate by IRC was 71% (**Figure 5A**), duration of response (DOR) rate by IRC was 73% (**Figure 5B**), and overall survival (OS) rate was 86% (**Figure 5C**)

Figure 5. PFS by IRC (A), DOR by IRC (B), and OS (C) by MZL Subtypes



DOR, duration of response; IRC, independent review committee; MALT, mucosa associated lymphoid tissue; MZL, marginal zone lymphoma; NMZL, nodal MZL; OS, overall survival; PFS, progression-free survival; SMZL, splenic MZL.

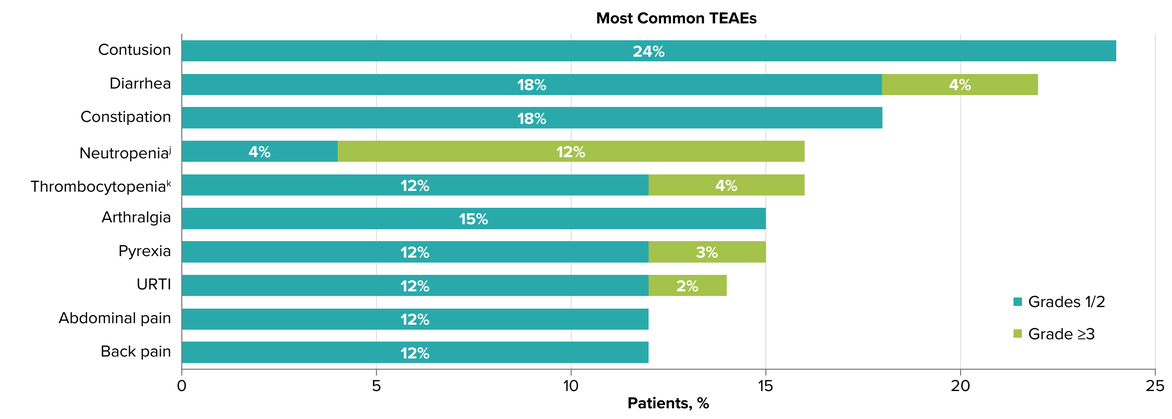
- All patients experienced at least 1 treatment-emergent adverse event (TEAE; **Figure 6A**)
- 48% of patients experienced TEAEs of Grade 3 or higher
- Cardiac TEAEs were rare, with hypertension occurring in 4%, atrial fibrillation/flutter in 3%, and ventricular extrasystole in 1.5% of patients; the rate of cardiac TEAEs was comparable to a pooled safety analysis of zanubrutinib, and lower than reported for ibrutinib (**Table 3**)
- The most common TEAEs (≥18%) included contusion, diarrhea, and constipation (**Figure 6B**)

Figure 6. Safety Summary

A

TEAEs in all patients, n (%)	N=68	
Patients with ≥1 TEAE	68 (100)	
Grade ≥3 TEAE	33 (48)	
Serious TEAE	30 (44)	
Leading to death	5 (7)[a]	
Leading to dose interruption	25 (37)[b]	
Leading to study drug discontinuation	5 (7)[c]	
Leading to dose reduction	0	
TEAEs of clinical interest, n (%)	**All grade**	**Grade ≥3**
Infections	38 (56)	15 (22)[d]
Hemorrhage	28 (41)	1 (1.5)[e]
Cardiac		
Hypertension	3 (4)[f]	2 (3)
Atrial fibrillation/flutter	2 (3)[g]	1 (1.5)
Ventricular extrasystole	1 (1.5)[h]	0
Second primary malignancy	5 (7)[i]	3 (4)

B



[a]Five patients died owing to AEs: COVID-19 pneumonia (n=2); myocardial infarction in a patient with preexisting cardiovascular disease (n=1); acute myeloid leukemia in a patient with prior exposure to an alkylating agent (n=1); septic encephalopathy following radical cystectomy and ileal conduit in a patient with recurrent bladder cancer (in CR at the time of death; [n=1]). [b]Most common AEs leading to dose interruption: COVID-19 pneumonia (n=4), neutropenia (n=3), diarrhea (n=2), lower respiratory tract infection (n=2), pneumonia (n=2), pyrexia (n=2), syncope (n=2), and tonsillitis (n=2). [c]Five patients discontinued owing to AEs: COVID-19 pneumonia (n=2); pyrexia later attributed to disease progression (n=1); myocardial infarction (n=1); septic encephalopathy (n=1). [d]Fatal infection: COVID-19 pneumonia (n=2). [e]Gastrointestinal hemorrhage (day 862) in a patient who also received anticoagulant for pulmonary embolism; patient continued zanubrutinib with no recurrent bleeding episode. [f]Two 2 patients had new-onset hypertension; none led to treatment reduction or discontinuation. [g]Atrial fibrillation in a patient with preexisting atrial fibrillation (21 days after end of treatment owing to disease progression). Patient with atrial flutter recovered spontaneously and continued zanubrutinib. [h]Ventricular extrasystole in an 83-year-old patient with no known cardiac history, was non-serious, transient, resolved on the same day, and did not lead to treatment modification or discontinuation. [i]Includes basal cell and squamous cell carcinoma and basal cell carcinoma (with history of skin cancer); papillary thyroid carcinoma (with preexisting thyroid nodule); recurrent bladder cancer and prostate cancer (with history of bladder cancer); and acute myeloid leukemia (with prior chemotherapy with alkylating agent). [j]Includes neutropenia and neutrophil count decreased. [k]Includes thrombocytopenia and platelet count decreased. TEAE, treatment-emergent adverse event; URTI, upper respiratory tract infection.

Table 3. Cardiac TEAEs of Clinical Interest

	BGB-3111-214	Pooled analysis B-cell malignancies[c]	
Cardiovascular disorders	**Zanubrutinib (N=68)**	**Zanubrutinib (N=1550)**	**Ibrutinib (N=422)**
Median treatment duration, months	24	26.64	19.96
Any cardiovascular medical history, n (%)			
Atrial fibrillation/flutter	8 (11.7)	101 (6.5)	26 (6.2)
Ventricular arrhythmia[a]	0	14 (0.9)	1 (0.2)
Hypertension[b]	21 (30.9)	669 (43.2)	206 (48.8)
Any cardiovascular AE, n (%)			
Atrial fibrillation/flutter	2 (3)	60 (3.9)	60 (14.2)
		EAIR: 0.13 vs 0.82 person-month (*P* < .0001)	
Ventricular arrhythmia (grade ≥2)[a]	1 (1.5)	11 (0.7)	6 (1.4)
Hypertension[b]	3 (4)	225 (14.5)	85 (20.1)

[a]Including ventricular tachyarrhythmia (SMQ narrow), ventricular arrhythmias and cardiac arrest (High Level Term MedDRA v24.0). [b]Including hypertension (SMQ narrow). [c]Pooled analyses of 10 clinical studies of zanubrutinib.[9]
AE, adverse event; CTCAE, Common Terminology Criteria for Adverse Events; EAIR, exposure-adjusted incident rate; MedDRA, Medical Dictionary for Regulatory Activities; SMQ, standardized MedDRA query; TEAE, treatment-emergent adverse event.

CONCLUSIONS

- At a median study follow-up of 28 months, zanubrutinib showed high response rates and durable disease control in R/R MZL
  - There were responses in all MZL subtypes and in difficult-to-treat subgroups
- Zanubrutinib was generally well tolerated
  - Hypertension and atrial fibrillation/flutter were uncommon and were comparable to the zanubrutinib pooled safety analyses, and lower than reported for ibrutinib
  - No new safety signals were observed
- These data support the use of zanubrutinib as treatment for patients with R/R MZL

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CORRESPONDENCE

Catherine Thieblemont, MD, PhD
2APHP, Hôpital Saint-Louis, Hemato-oncology,
Paris University Diderot, Paris, France
catherine.thieblemont@aphp.fr

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