REGULAR ARTICLE

blood advances

Zanubrutinib monotherapy in relapsed/refractory indolent non-Hodgkin lymphoma

Tycel Phillips,[1] Henry Chan,[2] Constantine S. Tam,[3,4] Alessandra Tedeschi,[5] Patrick Johnston,[6] Sung Yong Oh,[7] Stephen Opat,[8,9] Hyeon-Seok Eom,[10] Heather Allewelt,[11] Jennifer C. Stern,[12] Ziwen Tan,[11] William Novotny,[11] Jane Huang,[13] and Judith Trotman[14,15]

[1]Hematology Clinic, Rogel Cancer Center, University of Michigan Health System, Ann Arbor, MI; [2]Department of Haematology, Waitematā District Health Board, Auckland, New Zealand; [3]Haematology and Disease Group, Peter MacCallum Cancer Centre, Melbourne, VIC, Australia; [4]Haematology and Disease Group, University of Melbourne, Parkville, VIC, Australia; [5]Hematology, ASST Grande Ospedale Metropolitano Niguarda, Milan, Italy; [6]Hematology, Mayo Clinic, Rochester, MN; [7]Hemato-Oncology, Dong-A University Medical Center, Busan, South Korea; [8]Clinical Haematology, Monash Health, Clayton, VIC, Australia; [9]Department of Haematology, Monash University, Clayton, VIC, Australia; [10]Department of Cancer Biomedical Science, National Cancer Center of Korea, Goyang, South Korea; [11]BeiGene, San Mateo, CA; [12]BeiGene, Cambridge, MA; [13]BeiGene, Shanghai, China; [14]Haematology Department, Concord Repatriation General Hospital, Concord, NSW, Australia; and [15]Concord Clinical School, University of Sydney, Concord, NSW, Australia

Key Points

- Zanubrutinib is a second-generation Bruton's tyrosine kinase inhibitor with a favorable safety and tolerability profile.
- Zanubrutinib demonstrated anti-tumor activity in patients with relapsed/refractory marginal zone and follicular lymphomas.

Outcomes for marginal zone lymphoma (MZL) and follicular lymphoma (FL) remain suboptimal, owing to the limited number of approved agents and the incurable nature of the diseases. BGB-3111-AU-003 was a phase 1/2, open-label, multicenter, single-agent study of the selective Bruton's tyrosine kinase inhibitor zanubrutinib in 385 patients with B-cell malignancies. Here, we present safety and efficacy outcomes for the 53 enrolled patients with relapsed/refractory MZL (n = 20) and relapsed/refractory FL (n = 33), all of whom were enrolled during the part 2 dose expansion, and therefore received zanubrutinib at the recommended phase 2 dose. Treatment with zanubrutinib was generally well tolerated, with most adverse events being ≤ grade 2. Atrial fibrillation/flutter was not reported. Two patients required dose reduction, and 4 patients discontinued treatment because of adverse events. Response was assessed by an independent review committee for MZL and the investigators for FL, per Lugano 2014 classification for non-Hodgkin lymphoma. In patients with MZL, the overall response rate (ORR) was 80%, and the complete response (CR) rate was 20%. With median follow-up of 33.8 months, median progression-free survival (PFS) was not reached. In patients with FL, the ORR was 36.4%, and the CR rate was 18.2%. After a median follow-up of 33.9 months, median PFS was 10.4 months. In conclusion, the results of this study suggest a favorable benefit–risk profile and support zanubrutinib as a potentially meaningful addition to available therapies for patients with relapsed/refractory MZL and FL. This trial was registered at www.clinicaltrials.gov as #NCT02343120.

Introduction

Marginal zone lymphoma (MZL) and follicular lymphoma (FL) are generally considered incurable with standard chemoimmunotherapy (CIT), and toxicities accumulated from previous therapies can further limit treatment options. Improved biologic understanding of the malignant B-cell cell growth and survival

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The full-text version of this article contains a data supplement.

pathways continues to alter the therapeutic landscape for indolent non-Hodgkin lymphoma (NHL).[1] In 2019, the US Food and Drug Administration (FDA) approved lenalidomide in combination with a rituximab product for the treatment of previously treated patients with MZL and FL.[2] Accelerated approvals for the treatment of patients with relapsed or refractory (R/R) MZL and/or R/R FL have also been granted to phosphoinositide 3-kinase inhibitors (PI3K) (copanlisib[3] and umbralisib[4]), an enhancer of the zeste homolog 2 (EZH2) inhibitor (tazemetostat[5]), and a chimeric antigen receptor (CAR) T-cell product (axicabtagene ciloleucel[6]). Although these targeted therapies may offer improvements in efficacy over CIT approaches, each is associated with unique toxicities or hinderance to accessibility that could limit utilization.[3,4,6,7] Therefore, the need remains for newer therapies with improved efficacy and tolerability to improve outcomes for patients with MZL and FL.

Ibrutinib was approved under the accelerated pathway as the first-in-class Bruton's tyrosine kinase (BTK) inhibitor for patients with MZL who require systemic therapy and have previously received an anti-CD20 monoclonal antibody-based regimen.[8] This approval was based on an overall response rate (ORR) of 48% in a phase 2, open-label trial of single-agent ibrutinib in patients with previously treated R/R MZL.[9] Ibrutinib monotherapy did not show significant benefit over rituximab-based treatment in R/R FL.[8] However, there remained rationale for further evaluation of other BTK inhibitors in FL.

Zanubrutinib is a potent and irreversible BTK inhibitor that has demonstrated deep and durable responses in Waldenström macroglobulinemia (WM),[10] chronic lymphocytic leukemia (CLL)/small lymphocytic lymphoma,[11] and mantle cell lymphoma (MCL).[12,13] Zanubrutinib was designed with improved BTK selectivity, which may confer tolerability advantages over ibrutinib, particularly for treatment-limiting toxicities caused by the inhibition of off-target tyrosine kinases.[14] In the randomized, phase 3 ASPEN (BGB-3111-302) study, clinically meaningful safety and tolerability advantages were observed with zanubrutinib vs ibrutinib, specifically a reduction in the risk of atrial fibrillation/flutter (2% vs 15.3%) and lower rates of major bleeding events (5.9% vs 9.2%), diarrhea (20.8% vs 31.6%), and hypertension (10.9% vs 17.3%). Treatment with zanubrutinib was also associated with fewer dose reductions (13.9% vs 23.5%) and treatment discontinuations (4.0% vs 9.2%) caused by adverse events (AEs).[15] Zanubrutinib has been FDA approved under the accelerated approval pathway for the treatment of patients with MZL who have received 1 prior anti-CD20–based therapy and for patients with MCL who have received ≥1 prior therapy.[16]

The multicenter, single-arm phase 1/2 study BGB-3111-AU-003 of zanubrutinib in B-cell malignancies enrolled a total of 385 patients to histology-specific disease cohorts. Methods and results of the Part 1 dose escalation have been described previously.[17] Outcomes of zanubrutinib treatment for patients with CLL,[17,18] MCL,[13] and WM[19] have been published previously. Here, we present outcomes of treatment with zanubrutinib in 20 patients with R/R MZL and 33 patients with R/R FL who were enrolled in BGB-3111-AU-003.

Methods

Study design and treatment

BGB-3111-AU-003 (NCT02343120) was a phase 1/2, open-label, single-agent study of zanubrutinib conducted at 24 sites in 6 countries. The study had 2 parts: (1) part 1 (dose escalation) determined the recommended phase 2 dose (RP2D), and (2) part 2 (dose expansion) comprehensively evaluated zanubrutinib at the RP2D in a variety of histologic subtypes of B-cell malignancies, including R/R MZL and R/R FL (per protocol amendments). The methods and results of the part 1 dose escalation have been described previously.[17] No dose-limiting toxicity was observed in part 1; therefore, no maximally tolerated dose was identified. Pharmacokinetics, BTK inhibition in peripheral blood mononuclear cells, safety and tolerability, and preliminary efficacy were used to determine the RP2D and regimen. The 320-mg once-daily and 160-mg twice-daily dosing schedules were selected as RP2D for further study in part 2.

The protocol was amended several times to add the disease-specific expansion cohorts. Enrollment of approximately 380 patients was planned for the expansion cohorts in part 2. In general, the sample size for individual disease types was based on the safety profile and estimates of the response rates for zanubrutinib in specific B-cell malignancies that did not include MZL or FL. The RP2D was later modified to 160 mg twice daily for all subsequent patients enrolled in part 2 of the study. Patients enrolled to applicable cohorts receiving a dose of 320 mg once daily had the option to switch to 160 mg twice daily. Treatment with zanubrutinib was continued in 28-day cycles until unacceptable toxicity or disease progression.

Ethics

The BGB-3111-AU-003 study was conducted according to the principles of the Declaration of Helsinki and the International Conference on Harmonization guidelines, and the protocol was approved by the institutional review boards/independent ethics committees at each site. All enrolled patients provided written informed consent, and the study conduct was approved by local human investigations committees or institutional review boards in accordance with assurances filed with and approved by the US Department of Health and Human Services.

Patients

Eligible patients whose outcomes are reported here had histologically confirmed World Health Organization–defined MZL, including splenic (SMZL), nodal (NMZL), and extranodal (mucosa-associated lymphoid tissue [MALT]) subtypes or FL, and required systemic therapy. Patients with grade 1, 2, 3A, and 3B FL were eligible. Patients were ≥18 years old, had received ≥1 prior line of systemic therapy, and had an Eastern Cooperative Oncology Group (ECOG) performance status score of ≤2, with adequate organ function as demonstrated by the following parameters: neutrophil count ≥ 1×10^9/L, platelet count ≥ 50×10^9/L, creatinine clearance ≥ 30 mL/min, aspartate aminotransferase and alanine aminotransferase levels ≤ 2.5 times the upper limit of normal, and total bilirubin ≤ 1.5 times the upper limit of normal. Key exclusion criteria included prior exposure to a BTK inhibitor, central nervous system (CNS) involvement by lymphoma, clinically relevant cardiovascular disease, and active infection. Patients requiring concurrent strong CYP3A inhibitors/inducers were excluded, but antiplatelet agents and anticoagulants, including warfarin, were permitted.

Assessments

Primary end points included the evaluation of treatment-emergent AEs (TEAEs; AEs occurring on or after the first dose and within 30

Table 1. Demographics and baseline disease characteristics

Characteristic	R/R MZL (N = 20)	R/R FL (N = 33)
Age, y		
Median (range)	69.5 (52-85)	63 (38-79)
Age category, n (%)		
≥65 y	16 (80.0)	13 (39.4)
≥75 y	4 (20.0)	1 (3.0)
Sex, n (%)		
Male	10 (50.0)	20 (60.6)
Female	10 (50.0)	13 (39.4)
Baseline ECOG performance status score, n (%)		
0	7 (35.0)	18 (54.5)
1	11 (55.0)	13 (39.4)
2	2 (10.0)	2 (6.1)
Bulky disease*, n (%)	5 (25.0)	8 (24.2)
Bone marrow involvement, n (%)	14 (70.0)†	13 (39.4)
Extranodal disease, n (%)	20 (100.0)‡	18 (54.5)
Refractory disease§	4 (20.0)	11 (33.3)
Baseline cytopenia‖	6 (30.0)	8 (24.2)
MZL subtypes		
Extranodal	9 (45.0)	–
Nodal	5 (25.0)	–
Splenic	6 (30.0)	–
FLIPI scores		
High	–	14 (42.4)
Intermediate	–	6 (18.2)
Low	–	11 (33.3)
Not derived	–	2 (6.1)¶
Number of previous therapies		
Median (range)	2 (1-5)	3 (1-8)
Previous therapy, n (%)		
Rituximab-based chemoimmunotherapy	19 (95.0)	32 (97.0)
Rituximab monotherapy	4 (20.0)	19 (57.6)
RCVP	13 (65.0)	9 (27.3)
BR	4 (20.0)	7 (21.2)
RCHOP	5 (25.0)	19 (57.6)
Rituximab/lenalidomide	0	0
Radiation therapy	1 (5.0)	9 (27.3)
Splenectomy	1 (5.0)	0
Autologous hematopoietic stem cell transplant	0	6 (18.2)

BR, bendamustine/rituximab; ECOG, Eastern Cooperative Oncology Group; FDG, ^{18}F fluorodeoxyglucose; RCHOP, rituximab/cyclophosphamide/doxorubicin/vincristine/prednisone; RCVP, rituximab/cyclophosphamide/vincristine sulfate/prednisone.

*Bulky disease is defined as longest transverse diameter (LDi) >5 cm for MZL and ≥6 cm for FL.

†Derived from baseline tumor biopsy/aspiration per investigator assessment.

‡Extranodal disease is defined as patients with extranodal baseline target or nontarget lesions or bone marrow involvement by biopsy as per investigator assessment.

§Refractory disease is defined as best overall response of stable disease or progressive disease from last prior anticancer treatment regimen.

‖Cytopenia is defined as baseline neutrophils ≤ 1.5 × 10^9/L or baseline platelet ≤ 100 × 10^9/L or baseline hemoglobin ≤ 110 g/L.

¶FLIPI score not derived because of no nodal site involved at baseline.

days after the last dose of zanubrutinib or prior to the initiation of new anticancer therapy, whichever was sooner) and clinically significant laboratory and vital sign abnormalities. TEAE severity was graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (version 4.03).

Efficacy end points included ORR (CR and partial response [PR]), progression-free survival (PFS), duration of response (DOR), and overall survival (OS). Disease response was assessed in accordance with the Lugano classification.[20] Response assessments were performed by investigators, and an evaluation by an independent review committee (IRC) was added to confirm response data in patients with MZL. Imaging studies (contrast-enhanced computed tomography or magnetic resonance imaging) were conducted at screening, every 12 weeks during the first year, and then every 24 weeks thereafter until disease progression. Positron emission tomography (PET) was performed at the investigator's discretion and used to confirm response for patients who had PET-avid disease at screening. Repeat bone marrow evaluation and/or endoscopy was required to confirm complete response (CR) in patients with bone marrow and/or gastrointestinal involvement at baseline.

Statistical analysis

All patients with R/R MZL or R/R FL receiving any dose of zanubrutinib were included in the analysis. Safety end points for all patients who received ≥1 dose of zanubrutinib were summarized using standard descriptive statistics.

Subgroup analyses were performed using prespecified variables for patients achieving an overall response, and the percentages of responders for each category were summarized with 95% confidence intervals (CIs).[21] Median PFS, DOR, and OS were estimated using the Kaplan-Meier method with corresponding 95% CIs.[22] As efficacy end points were not primary end points in this study, these analyses were not hypothesis driven. The reverse Kaplan-Meier method was used to estimate follow-up times for PFS, DOR, and OS.

Results

Patients and baseline characteristics

A total of 385 patients were enrolled in the BGB-3111-AU-003 study, with 17 in part 1 and 368 in part 2 of the study. Between August 4, 2015, and February 26, 2018, 20 patients with MZL and 33 patients with FL were enrolled and dosed. No patients diagnosed with MZL or FL were enrolled in part 1. All patients included in this report were treated with zanubrutinib at the RP2D in part 2. Baseline characteristics and disease history are summarized in Table 1.

MZL. The most common MZL subtype was extranodal (n = 9, 45%); 6 patients (30%) had SMZL, and 5 patients (25%) had NMZL. Four patients (20%) were refractory to their last anticancer regimen. The median number of prior regimens was 2 (range, 1-5).

Fourteen patients (70%) had lymphomatous involvement of the bone marrow, and all patients had extranodal disease. At a median follow-up of 35.2 months (range, 8.3-59.2), 8 (40%) patients

Table 2. Any-grade treatment-emergent AEs in ≥20% of patients, grade ≥3 treatment-emergent AEs in >5% of patients (in either subgroup), and all AEs of special interest

Any-grade TEAE in ≥ 20%, n (%)	MZL	FL
Patients with ≥1 AE	20 (100)	32 (97)
Diarrhea	7 (35)	4 (12.1)
Contusion	7 (35)	8 (24.2)
Rash	7 (35)	3 (9.1)
Upper respiratory tract infection	6 (30)	9 (27.3)
Neutropenia	6 (30)	6 (18.2)
Pyrexia	5 (25)	4 (12.1)
Nasopharyngitis	5 (25)	0
Sinusitis	4 (20)	1 (3)
Nausea	4 (20)	8 (24.2)
Fatigue	4 (20)	7 (21.2)
Musculoskeletal pain	4 (20)	0
Cough	3 (15)	8 (24.2)
Urinary tract infection	2 (10)	8 (24.2)
Grade ≥ 3 TEAE in > 5%		
Patients with ≥ 1 Grade ≥ 3 AE	11 (55)	22 (66.7)
Neutropenia	4 (20)	6 (18.2)
Thrombocytopenia	2 (10)	1 (3)
Pneumonia	1 (5)	3 (9.1)
Pyrexia	2 (10.0)	0
Hypertension	1 (5)	2 (6.1)
Anemia	3 (15)	5 (15.2)
Urinary tract infection	0	6 (18.2)
Sepsis	0	2 (6.1)
Abdominal pain	0	2 (6.1)
Any grade/Grade ≥ 3 AESI, n (%)		
Patients with ≥ 1 AESI	19 (95)/10 (50)	28 (84.8)/17 (51.5)
Bleeding	12 (60)/1 (5)	18 (54.5)/1 (3)
Major hemorrhage*	2 (10)/1 (5)	1 (3)/1 (3)
Atrial fibrillation/flutter	0/0	0/0
Hypertension	1 (5)/1 (5)	2 (6.1)/2 (6.1)
Second primary malignancies	3 (15)†/2 (10)	3 (9.1)/1 (3)
Skin cancers	1 (5)/0	1 (3)/0
Infections	15 (75)/4 (20)‡	21 (63.6)/10 (30.3)
Opportunistic infections	1 (5)/0	1 (3)/0
Tumor lysis syndrome	0/0	0/0
Anemia§	3 (15)/3 (15)	5 (15.2)/5 (15.2)
Neutropenia‖	6 (30)/4 (20)	6 (18.2)/6 (18.2)
Thrombocytopenia	3 (15)/2 (10)	3 (9.1)/1 (3)

AE indicates adverse event (preferred term); AESI, AE of special interest; FL, follicular lymphoma; MedDRA, Medical Dictionary for Regulatory Activities; MZL, marginal zone lymphoma.

*Defined as any serious or grade ≥3 bleed at any site, or central nervous system bleed of any grade.

†Includes invasive ductal breast carcinoma, lentigo maligna, prostate cancer.

‡Includes *Escherichia* urinary tract infection/*Escherichia* sepsis, influenza/pneumonia, pyelonephritis, skin infection, carbuncle, *Clostridium difficile* colitis, gastroenteritis.

§Includes the MEDRA preferred terms "anaemia" and "haemoglobin decreased".

‖Includes the MedDRA preferred terms "neutropenia," "neutrophil count decreased," and "febrile neutropenia".

¶Includes the MedDRA preferred terms "thrombocytopenia" and "platelet count decreased."

discontinued study treatment (progressive disease [PD], n = 5; withdrew consent, n = 2; TEAE, n = 1).

FL. No patients with grade 3B FL were enrolled. Fourteen patients (42.4%) had high Follicular Lymphoma International Prognostic Index (FLIPI)[23] scores: 6 (18.2%) had intermediate, and 11 (33.3%) had low; FLIPI score was not derived for 2 patients. The median time from initial diagnosis to first dose of zanubrutinib was 6.0 years (range, 0.4-17.2 years). Eleven (33.3%) patients were refractory to their last anticancer regimen. The median number of prior regimens was 3 (range, 1-8). Thirteen (39.4%) patients had lymphomatous involvement of the bone marrow, and 18 (54.5%) had extranodal disease. At a median study follow-up of 32.8 months (range, 1.8-58.7), 27 (81.8%) patients discontinued study treatment (PD, n = 19; TEAE, n = 3; withdrew consent, n = 2; investigator decision, n = 2; other, n = 1).

Safety

MZL. All 20 patients with MZL experienced ≥1 TEAE of any grade, and 55.0% of patients reported ≥1 grade ≥3 TEAE (Table 2). The most common TEAEs (>20%) included diarrhea, contusion, and rash in 35.0%, upper respiratory tract infection and neutropenia in 30.0%, nasopharyngitis and pyrexia in 25.0%, and sinusitis, nausea, fatigue, and musculoskeletal pain in 20.0% each. The most common grade ≥ 3 AEs were neutropenia (20.0%), anemia (15.0%), thrombocytopenia (10.0%), and pyrexia (10.0%; Table 2). Infections were reported in 15 patients (75.0%); none of the grade ≥ 3 infections reported in 4 patients were classified as opportunistic, and no infections had a fatal outcome or led to treatment discontinuation. Bleeding events were reported in 12 (60.0%) patients. Major hemorrhage, defined as serious or grade ≥ 3 bleeding at any site or CNS bleeding of any grade, was reported in 2 patients, including a grade 1 postoperative contusion immediately following mastectomy, which worsened to a serious grade 2 contusion 6 months later in a patient on long-term cardiac prophylaxis with aspirin, and a grade 3 episode of hemoptysis in a patient with concurrent upper respiratory tract infection, without concomitant antithrombotic or antiplatelet therapy. Hemoptysis was considered unrelated to the study drug and resolved in 1 day with no action taken. Grade 3 hypertension was reported in 1 patient. Atrial fibrillation/flutter was not observed. No AE leading to death was observed. Ten patients (50.0%) had dose interruptions caused by an AE. Two patients required dose reductions, 1 because of an AE and 1 because of investigator decision.

FL. All but 1 patient (97.0%) with FL reported ≥ 1 AE of any grade, and 66.7% of patients reported ≥ 1 grade ≥ 3 AE (Table 2). The most common AEs (≥20%) included upper respiratory tract infection (27.3%), contusion (24.2%), nausea (24.2%), urinary tract infection (24.2%), cough (24.2%), and fatigue (21.2%). Grade ≥ 3 AEs reported in >1 patient were urinary tract infection (18.1%), pneumonia (9.1%), neutropenia (18.2%), anemia (15.2%), abdominal pain (6.1%), hypertension (6.1%), and sepsis (6.1%; Table 2). Infections were reported in 21 patients (63.6%); none of the grade ≥ 3 infections were classified as opportunistic. An AE of bilateral pneumonia led to sepsis and had a fatal outcome in 1 patient. No other patients had infection AEs that led to treatment discontinuation. Bleeding events were reported in 18 (54.5%) patients. Major hemorrhage, defined as serious or grade ≥ 3 bleeding at any site or

Table 3. Analysis of response with zanubrutinib treatment, as assessed by Independent Review Committee for MZL and by investigators for FL, based on the Lugano classification

Response	R/R MZL (N=20)	R/R FL (N=33)
Median (range) study follow-up time, months	35.2 (8.3–59.2)	32.8 (1.8–58.7)
Best overall response, n (%)		
ORR, n (%) (95% CI)	16 (80) (56.3–94.3)	12 (36.4) (20.4–54.9)
Complete response, n (%)	4 (20)	6 (18.2)
Partial response, n (%)	12 (60)	6 (18.2)
Stable disease, n (%)	2 (10)	13 (39.4)
Progressive disease, n (%)	1 (5)	5 (15.2)
Not evaluable, n (%)*	1 (5)	0
Discontinued study prior to first assessment	0	3 (9.1)
Median (range) TTR (≥PR), months	2.8 (2.6–23.1)	2.7 (1.6–5.6)
Best response by subtype, n (%)		
Extranodal (MALT), ORR, n (%)	8/9 (88.9)	
Nodal, ORR, n (%)	5/5 (100)	
Splenic, ORR, n (%)	3/6 (50)	
Median and event-free rate		
Median DOR, months (95% CI)	NE (8.4–NE)	NE (8.3–NE)
6-month DOR, % (95% CI)	87.5 (58.6–96.7)	100 (NE–NE)
12-month DOR, % (95% CI)	71.6 (40.3–88.4)	74.1 (39.1–90.9)
24-month DOR, % (95% CI)	71.6 (40.3–88.4)	64.8 (31–85.2)
36-month DOR, % (95% CI)	71.6 (40.3–88.4)	64.8 (31–85.2)
Median PFS, months (95% CI)	NE (20.3–NE)	10.4 (7.7–22.9)
6-month PFS, % (95% CI)	90 (65.6–97.4)	70 (50.2–83.1)
12-month PFS, % (95% CI)	84 (57.9–94.6)	38.2 (20.9–55.3)
24-month PFS, % (95% CI)	72 (45–87.4)	30.1 (14.4–47.5)
36-month PFS, % (95% CI)	72 (45–87.4)	25.8 (11.2–43.2)
Median OS, months (95% CI)	NE (NE–NE)	NE (37.3–NE)
6-month OS, % (95% CI)	100.0 (NE–NE)	90.3 (72.7–96.8)
12-month OS, % (95% CI)	100.0 (NE–NE)	86.8 (68.5–94.8)
24-month OS, % (95% CI)	83.9 (59.7–94.5)	76.1 (56.1–87.9)
36-month OS, % (95% CI)	83.9 (59.7–94.5)	76.1 (56.1–87.9)

Percentages are based on the number of patients who received ≥1 dose of zanubrutinib. Efficacy analysis set: 2-sided Clopper-Pearson 95% CI. Medians were estimated by Kaplan–Meier method with 95% CIs estimated using the Brookmeyer and Crowley method. Event-free rates were estimated by Kaplan–Meier method with 95% CIs estimated using the Greenwood formula.

*For 1 patient, the IRC reported no measurable disease, and only splenomegaly was present. Per IRC charter, if there was no measurable disease, an assessment of "not evaluable" was reported.

CI indicates confidence interval; DOR, duration of response; FL, follicular lymphoma; MALT, mucosa-associated lymphoid tissue, MZL, marginal zone lymphoma; NE, not estimable; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; PR, partial response; R/R, relapsed/refractory; TTR, time to response; +, censored.

CNS bleeding of any grade, was reported in only 1 patient with hematuria. Atrial fibrillation/flutter was not observed. For 1 patient, abdominal pain caused by disease progression was reported as an AE with a fatal outcome. Twelve patients (36.4%) had dose interruptions because of AEs, and 3 patients (9.1%) permanently discontinued zanubrutinib because of AEs. There were no dose reductions in patients with FL.

Efficacy

Patients received either 160 mg twice daily (n = 17 with MZL, n = 27 with FL) or 320 mg once daily (n = 3 with MZL, n = 6 with FL) of zanubrutinib. Two patients with MZL and 1 with FL later switched from 320 mg once daily to 160 mg twice daily. Median relative dose intensity, the ratio of actual to planned dose intensity, was 97.9% (range 77.4% to 100%) for patients with MZL and 98.5% (range, 81.9%-100%) for patients with FL. Response data are summarized in Table 3. Forest plots of subgroup analyses are presented in supplemental Figures 1 and 2. ORRs and waterfall plots for reductions in lymph node sum of products of perpendicular diameters by best overall response are shown in supplemental Figures 3 and 4.

MZL. The ORR, as assessed by the IRC, was 80.0% (95% CI, 56.3-94.3), and the CR rate was 20.0% (95% CI, 5.7-43.7). The ORR by subtypes were 88.9% for extranodal (n = 8/9), 100% for NMZL (n = 5), and 50.0% for SMZL (n = 3 of 6). The median time to response was 2.8 months (range, 2.6-23.1). The median DOR and PFS were not yet reached (Figure 1A-B). With a median follow-up of 33.8 months, the estimated PFS rate was 84% at 12 months and 72% at both 24 and 36 months. The median OS was not yet reached. OS rates were 100% at 12 months and 83.9% at both 24 and 36 months.

FL. The ORR, as assessed by investigator, was 36.4% (95% CI, 20.4-54.9), and the CR rate was 18.2% (95% CI, 7-35.5). The median time to response was 2.7 months (range, 1.6-5.6 months). Median DOR was not yet reached (Figure 1C). For those patients who achieved at least a PR, the median DOR event-free rate was 64.8% (95 CI, 31-85.2) at both 24 and 36 months. Median PFS was 10.4 months (95% CI, 7.7-22.9; Figure 1D). With a median follow-up of 33.9 months, the estimated PFS rate was 38.2% at 12 months, 30.1% at 24 months, and 25.8% at 36 months. Median OS was not yet reached. OS rates were 86.8% at 12 months and 76.1% at both 24 and 36 months.

Discussion

Optimal management for R/R MZL and FL is ill defined. Despite serial rounds of systemic CIT, these diseases remain generally incurable, and therapy-associated toxicities further limit improvement in outcomes. Although newer, targeted therapies provide an alternative to CIT, these therapies may also carry treatment-limiting toxicities or have limits to accessibility. Treatment options with improved tolerability, ease of administration, and better disease control are desirable in this setting.

In this study, zanubrutinib was well tolerated, as demonstrated by a low incidence of treatment discontinuation (n = 4) and dose reductions (n = 2) caused by AEs, despite very high median relative dose intensities (97.9% in patients with MZL and 98.5% in patients with FL). Most AEs were low grade. AEs associated with zanubrutinib were typically manageable and reversible with temporary dose interruptions and supportive care. AEs of special interest were infrequent, and there were no occurrences of atrial fibrillation in patients with MZL or FL. Grade ≥ 3 neutropenia was observed in 20.0% of patients with MZL and 18.2% of patients with FL, although this was not associated with increased frequency of febrile neutropenia, sepsis, or opportunistic infections. The safety data observed in patients

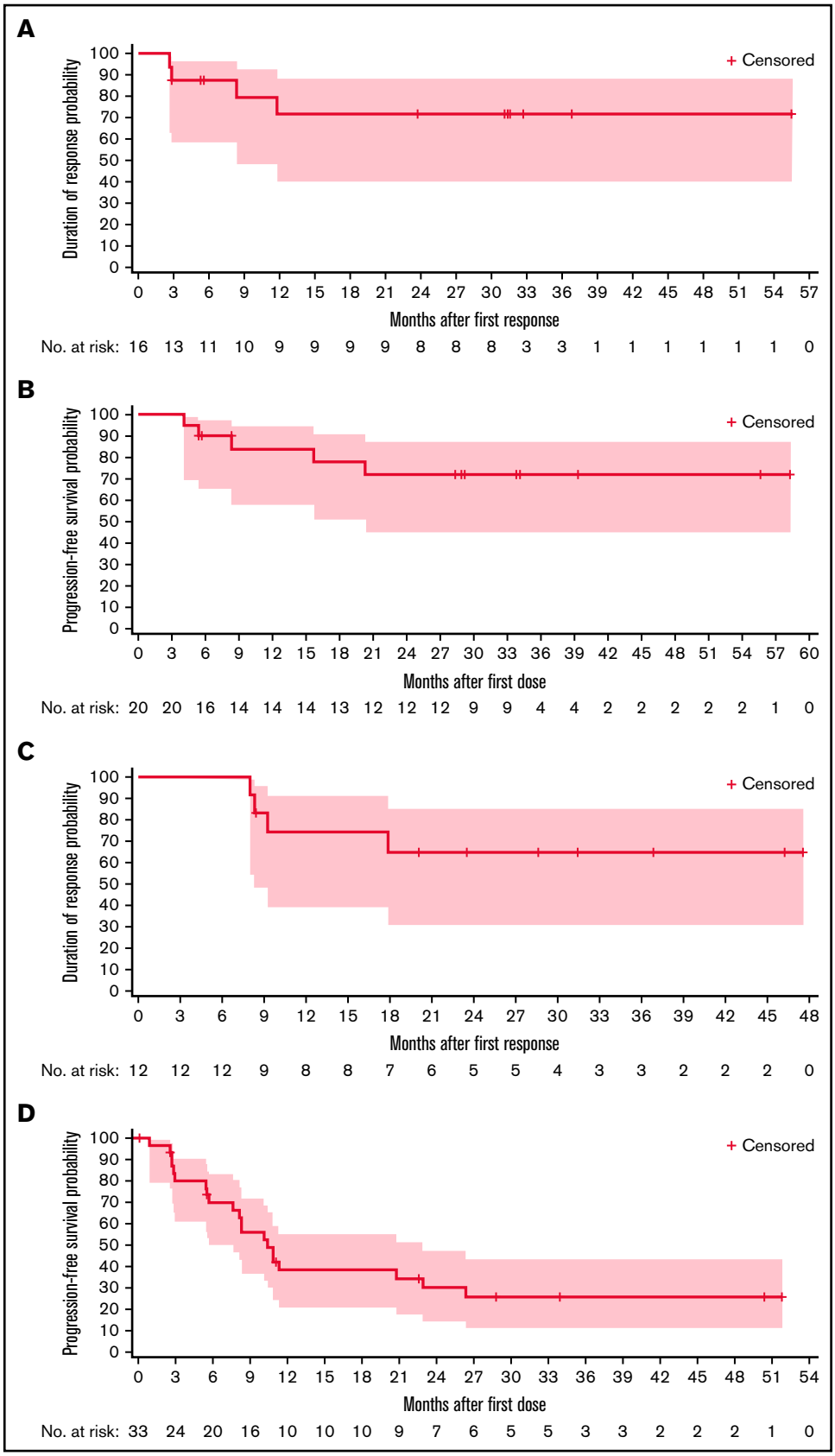

Figure 1. Kaplan-Meier plots. (A) DOR with zanubrutinib treatment per IRC assessment for patients with MZL. (B) PFS with zanubrutinib per IRC assessment for patients with MZL. (C) DOR with zanubrutinib per investigator assessment for patients with FL. (D) PFS with zanubrutinib per investigator assessment for patients with FL.

with R/R MZL and R/R FL were consistent with the known, favorable safety profile of zanubrutinib.[10-13,15,24]

Zanubrutinib was shown to be active in patients with R/R MZL with respective ORR and CR rates of 80.0% and 20.0%, as assessed by the IRC. Although small patient numbers limit analyses of subgroups, responses were observed in patients with various MZL subtypes and difficult-to-treat subgroups, including patients with stage IV or bulky disease, bone marrow involvement, or those previously treated with ≥2 prior regimens. Responses were durable, with median PFS and DOR not reached at a median study follow-up of 35.2 months. Some activity was also seen in those with R/R FL, with ORR and CR rates of 36.4% and 18.2%, respectively. For patients with R/R FL, median PFS was 10.4 months (95% CI, 7.7-22.9), and median DOR was not reached at a median study follow-up of 32.8 months.

Together with the data from the phase 2, single-arm MAGNOLIA study of 68 patients with R/R MZL (ORR, 68.2%; CR rate, 25.8%),[24] the BGB-3111-AU-003 study provided supportive data for the accelerated FDA approval of zanubrutinib for patients with R/R MZL. BGB-3111-214 and BGB-3111-AU-003 enrolled patients with similar baseline characteristics. Use of PET was not required in this study, whereas PET was used in the MAGNOLIA study for patients with IRC-confirmed PET-avid disease. The key difference between the studies, and the most significant contribution of this report to the literature, is the longer duration of treatment and follow-up. The median duration of exposure was 13.8 months (range, 0.9-19.6) in the MAGNOLIA study, and 32.1 months (range, 4.5-58.6) in BGB-3111-AU-003. The median follow-up was 15.7 months (range, 1.6-21.9 months) in the MAGNOLIA study and 35.2 months (range, 8.3-59.2 months) in BGB-3111-AU-003. The CR rate was similar (25.8% and 20.0%, respectively). In the MAGNOLIA study, 5 patients with best response of stable disease remained on treatment.[24] Late responses were observed in some patients on this study, at up to 23.1 months from onset of zanubrutinib treatment. Responses as late as 16.4 months from treatment onset also have been reported with ibrutinib.[8] Collectively, these data support the position that the ORR observed in the MAGNOLIA trial may increase with longer follow-up.

Although direct cross-trial comparisons are not possible, the OR and CR rates observed with zanubrutinib therapy for MZL in this small, single-arm trial appear similar to those reported for other available targeted therapies.[1-4,7,9] Likewise, ORR and CR rates observed for FL in this small trial are in line with those reported for the PI3K inhibitors.[3,4] Although responses to zanubrutinib monotherapy in R/R FL are limited, the promising tolerability profile supports its candidacy for combination therapy. We eagerly await the results of the ongoing ROSEWOOD study (BGB3111-212), which is examining the efficacy and safety of the combination of zanubrutinib with obinutuzumab vs obinutuzumab monotherapy.

In conclusion, the selective BTK inhibitor zanubrutinib was well tolerated and was active in R/R MZL and FL. Although the small size of this study limits broad conclusions, the safety and efficacy results reported suggest a favorable benefit-risk profile and highlights the potential for zanubrutinib as a clinically meaningful addition to available therapies.

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Authorship

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ORCID profiles: H.C., 0000-0002-0156-4655; C.S.T., 0000-0002-9759-5017; S.O., 0000-0002-0308-6458; H-S.E., 0000-0002-0484-2067; J.T., 0000-0001-8009-4593.

Correspondence: Tycel Phillips, Hematology Clinic, Rogel Cancer Center, University of Michigan Health System, 1500 E. Medical Center Dr, Ann Arbor, MI 48109; e-mail: tycelp@umich.edu.

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