Treatment of Patients with Relapsed or Refractory Mantle–Cell Lymphoma with Zanubrutinib, a Selective Inhibitor of Bruton's Tyrosine Kinase

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ABSTRACT

Purpose: Mantle-cell lymphoma (MCL) is an incurable mature B-cell neoplasm with high initial response rates followed almost invariably by relapse. Prognosis for patients following relapse is poor, and treatment choices are limited. We evaluated the efficacy and safety of zanubrutinib, an investigational selective Bruton's tyrosine kinase (BTK) inhibitor.

Patients and Methods: Patients with relapsed/refractory MCL were enrolled in this ongoing phase II, single-arm, open-label study, and treated with oral zanubrutinib 160 mg twice daily. The primary endpoint is overall response rate (ORR) assessed by an independent review committee (per Lugano 2014 classification); secondary endpoints include duration of response (DOR), time to response, progression-free survival (PFS), and safety.

Results: Eighty-six patients (median age, 60.5 years) were enrolled after a median of 2 prior lines of therapy, received ≥1 dose of the study drug, and were evaluable for safety and efficacy. After a median follow-up of 18.4 months, 72 (84%) patients achieved an objective response, with 59 (68.6%) achieving a complete response (CR). Median DOR and PFS were 19.5 and 22.1 months, respectively; 12-month event-free estimates for DOR and PFS are 78% and 76%, respectively. Most common grade ≥3 adverse events (AE) were neutropenia (19.8%) and lung infection/pneumonia (9.3%). Three patients experienced major bleeding events, and there were no reports of atrial fibrillation. Eight (9.3%) patients discontinued zanubrutinib for AEs.

Conclusions: These results demonstrate high and durable ORR and CR rates in patients with relapsed/refractory MCL. Zanubrutinib was generally well tolerated; grade ≥3 BTK inhibitor-associated toxicities (hemorrhage, rash, hypertension, diarrhea, atrial fibrillation) were uncommon.

Introduction

Mantle-cell lymphoma (MCL) is an aggressive, phenotypically distinct, mature B-cell neoplasm that comprises approximately 4% and 7% to 9% of all malignant lymphomas in the United States and Europe, respectively (2). In China, MCL comprises 3.1% of all malignant lymphomas and 4.6% of B-cell lymphomas (3). The mainstay of MCL management is immunochemotherapeutic combinations (4, 5). Initial response rates are high, with response durations varying from 18 to 30 months; however, almost all patients eventually relapse (2). Until recently, therapeutic options for patients with relapsed/refractory (R/R) MCL have been limited, and their associated outcomes have been generally poor (6–8).

Insights into the molecular pathogenesis of MCL have led to the development of mechanism-based treatment strategies. Bruton's tyrosine kinase (BTK), an intermediary in the B-cell receptor signaling pathway, has been validated as a therapeutic target on the basis of clinical data generated from BTK inhibitor–treated patients with a variety of B-cell malignancies. Ibrutinib, the first oral BTK inhibitor, is approved for the treatment of R/R MCL in the United States, European Union, and China on the basis of a phase II study that demonstrated overall and complete response (CR) rates of 68% and 21%, respectively (9). However, off-target inhibition of EGFR and other structurally similar kinases has been implicated in ibrutinib-associated toxicities, such as diarrhea, rash, bleeding (10, 11), and atrial fibrillation (12, 13).

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Translational Relevance

Mantle-cell lymphoma is an aggressive B-cell malignancy with overall poor prognosis. Patients with *TP53*-mutated tumors have particularly dismal outcomes, with median overall survival of less than 2 years following intensive first-line chemoimmunotherapy; novel therapeutic approaches are needed for such patients. BTK inhibition has been shown to be an effective therapeutic strategy in MCL, but *TP53* mutation is still associated with poor outcomes with the first-generation BTK inhibitor, ibrutinib. Pharmacodynamic studies of zanubrutinib have demonstrated complete and persistent BTK occupancy in lymph node tissues (1). In this study, zanubrutinib demonstrated high response rates and promising durations of response overall in this difficult-to-treat population; results of the study reported herein were the basis in part for accelerated approval by the U.S. FDA for the treatment of patients with MCL who have had ≥1 prior therapy. We hypothesize that the complete and sustained BTK inhibition achieved with zanubrutinib partially overcomes *TP53*-mutation–mediated resistance. Further study will be required to confirm this observation in a broader population.

Zanubrutinib (formerly BGB-3111) is a novel, irreversible inhibitor of BTK that was designed to minimize off-target kinase inhibition while achieving maximal exposure (14, 15). In kinase inhibition and cell-based assays, zanubrutinib was shown to be more selective than ibrutinib for inhibition of BTK, exhibiting less off-target activity against EGFR, TEC, IL2 tyrosine kinase, and other kinases (14, 15). In preclinical studies, zanubrutinib demonstrated good oral bioavailability, achieved higher exposures, and showed more complete BTK inhibition in target tissues than ibrutinib (15). In phase I studies conducted inside [BGB-3111–1002 (NCT03189524)] and outside [BGB-3111-AU-003 (NCT02343120)] of China, zanubrutinib demonstrated good tolerability without dose-limiting toxicities at daily doses up to 320 mg. The recommended phase II dose was determined to be 160 mg administered twice daily, based on promising clinical activity demonstrated across a broad spectrum of B-cell malignancies, including MCL (1). In the BGB-3111-AU-003 study, an overall response rate (ORR) of 86.5% was observed in 37 patients with R/R MCL [median age, 70 years; median (range) prior therapies, 1 (1–4)], including 11 CRs, in conjunction with a median duration of response of 15.4 months; in this study, metabolic imaging was not a requirement for confirmation of a CR (16). On the basis of early results from phase I studies, we initiated a phase II study of zanubrutinib in Chinese patients with R/R MCL (ClinicalTrials.gov identifier NCT03206970).

Patients and Methods

Patients

Eligible patients had MCL with cyclin D1 overexpression, translocation t(11;14)(q13;q32), or both as confirmed by central pathological review of archival or fresh tumor biopsy tissue, and measurable disease (≥1 lymph node >1.5 cm in longest diameter and measurable in two perpendicular dimensions on CT or MRI scan). Patients had received at least one prior line of therapy and had relapsed or were refractory (i.e., achieved neither partial nor complete response) to their last regimen. Other eligibility criteria included age 18 to 75 years; Eastern Cooperative Oncology Group performance status of 0, 1, or 2; and adequate organ function. At study entry, patients were required to have an absolute neutrophil count of at least 1×10^9/L and a platelet count of at least 75×10^9/L (50×10^9/L for patients with bone marrow involvement), both independent of growth factor support or transfusion for at least 7 days. Patients were excluded if they had a history of central nervous system lymphoma, prior exposure to a BTK inhibitor, allogeneic hematopoietic stem cell transplantation, clinically significant cardiovascular disease, a requirement for concomitant strong cytochrome P450 3A inhibitors or inducers, known infection with HIV, or active hepatitis B or C infection. Patients with a history of cardiac arrythmia that was adequately controlled at the time of enrollment were eligible.

Study design and treatment

Patients were enrolled at 13 clinical trial sites in China in this ongoing, phase II, open-label study. All patients received continuous single-agent zanubrutinib administered orally at a dose of 160 mg twice daily in 28-day cycles for up to 3 years or until disease progression, unacceptable toxicity, death, withdrawal of consent, or study termination.

This study was designed and monitored in accordance with sponsor procedures in compliance with the ethical principles of Good Clinical Practice, International Conference on Harmonization guidelines, the Declaration of Helsinki, and applicable local regulatory requirements. All patients provided written, informed consent. The protocol, any amendments, and informed consent forms were reviewed and approved by the institutional review boards/independent ethics committees.

Assessments

The primary endpoint was ORR, defined as either a partial response or CR according to the Revised International Working Group Criteria for Malignant Lymphomas (the Lugano Classification; ref. 17). Response evaluations were based on fluorodeoxyglucose positron emission tomography (FDG-PET)-CT scans, bone marrow biopsies, and gastrointestinal endoscopy, as assessed by an independent review committee (IRC; PAREXEL Informatics). Responses for patients with positive bone marrow or gastrointestinal biopsies at the time of complete metabolic response were downgraded to partial response. Response assessments, including imaging studies, were performed every 12 weeks for 96 weeks and every 24 weeks thereafter until disease progression or withdrawal from study. Secondary endpoints included duration of response (DOR), time to response, progression-free survival (PFS), and safety. Overall survival (OS) was an exploratory endpoint. Adverse events (AEs) were coded using the Medical Dictionary for Regulatory Activities, version 20.0. The severity of AEs was graded using the NCI Common Toxicity Criteria, version 4.03. We evaluated the incidence and severity of adverse events of interest (AEI), prespecified on the basis of the known and theoretical toxicity for the BTK inhibitor class. These include infections, bleeding (including major hemorrhage), hypertension, atrial fibrillation/flutter, second primary malignancies, tumor lysis syndrome, and peripheral blood cytopenias.

TP53 mutational analysis

TP53 mutational status was evaluated by hybrid capture-based next-generation sequencing, as previously published (18, 19), targeting a panel of 175 genes (KingMed Center for Clinical Laboratory Co., Ltd.). DNA was extracted from formalin-fixed paraffin-embedded tissue samples in which tumor content was greater than 40%. Target genes were enriched by capture probes that cover all exons and parts of introns for a panel of 175 genes. Subsequent sequencing was carried

out on the Illumina Nextseq500 platform. Somatic mutations and insertions/deletions were identified by Pisces and GATK. Common SNPs were excluded using ExAC and gnomAD databases. Synonymous mutations and intron mutations were also excluded from analyses.

Statistical analysis

Approximately 80 patients were planned for enrollment, primarily on the basis of the intended level of precision of the estimated ORR. We calculated that a sample of 80 patients would provide 99% power to rule out a response rate of 40%, the minimal threshold for clinically meaningful benefit if the true response rate is 70%, at a one-sided α level of 0.025 using a binomial exact test. All results are presented through February 15, 2019 (the data cut-off date).

Efficacy and safety analyses included patients who received at least one dose of zanubrutinib. Analysis of subgroups defined by demographic and baseline disease characteristics was performed for the proportion of patients achieving an objective response.

Time-to-event endpoints, including DOR and PFS, were analyzed using the Kaplan–Meier method with 95% confidence intervals (CI; refs. 20, 21). Event-free rates at 12 months were estimated using the Kaplan–Meier method with 95% CIs (21, 22). Patient was censored at the last adequate disease assessment (including imaging) before the initiation of subsequent anticancer therapy for PFS and DOR. Patients lacking either a baseline or at least one postbaseline response assessment were censored on the first day of study treatment.

Results

Patients and treatments

Between March 2, 2017 and September 27, 2017, a total of 86 patients were enrolled into the study, received at least one dose of the study drug, and were evaluable for safety and efficacy. The median number of treatment cycles was 19.3 (range, 0.2–25.6), and median relative treatment intensity was 100% (range, 46%–107%). At study entry, 78 (90.7%) patients had Ann Arbor stage III or IV disease, 61 (70.9%) had extranodal disease, 37 (43%) had at least one lesion >5 cm in longest diameter, 72 (83.7%) had intermediate- or high-risk Biologic Mantle Cell Lymphoma International Prognostic Index (MIPI-b) scores, and 45 (52.3%) were refractory to their most recent therapy (**Table 1**). A total of 73 (84.9%) patients received prior CHOP or CHOP-like therapy, of which 46 (60%) included rituximab. Twenty-three (26.7%) patients received a regimen that included continuous-infusion anthracycline including R-EPOCH or R-hyper-CVAD (A), and 33 (38.4%) received a high-dose cytarabine-containing regimen including DHAP, ESHAP, or hyper-CVAD (B).

After a median follow-up of 18.4 months (range, 0.3–23.5), 34 (39.5%) patients had discontinued zanubrutinib, and 52 (60.5%) were continuing treatment. Reasons for treatment discontinuation included progressive disease ($n = 24$), AEs ($n = 8$), investigator discretion ($n = 1$), and withdrawal of consent after achieving a CR ($n = 1$). AEs leading to treatment discontinuation included three pulmonary events (lung infection, pneumonia, and interstitial lung disease), as well as single occurrences of thrombocytopenia, cerebral hemorrhage, traffic accident, infection, and unspecified.

Table 1. Demographic and baseline disease characteristics.

Characteristic	$N = 86$
Sex, *n* (%)	
Male	67 (77.9)
Female	19 (22.1)
Race, *n* (%)	
Chinese	86 (100)
Age, years	
Median (range)	60.5 (34–75)
≥65 years, *n* (%)	22 (25.6)
ECOG performance status, *n* (%)	
0/1	82 (95.3)
2	4 (4.7)
Patients with prior systemic therapies, *n* (%)	86 (100.0)
Median (range) number of prior therapies	2.0 (1–4)
≥3 prior therapies, *n* (%)	29 (33.7)
Prior regimens[a], *n* (%)	
Patients with ≥ 1 rituximab-containing regimen	64 (74.4)
R-CHOP, R-CHOP–like	46 (53.5)
CHOP, CHOP-like	31 (36.0)
High-dose cytarabine-containing regimen[b]	33 (38.4)
(R) hyper-CVAD (A)/EPOCH	23 (26.7)
Lenalidomide	12 (14.0)
Bortezomib	7 (8.1)
Stem cell transplant	3 (3.5)
Blastoid histology	12 (14)
Bulky disease	
>5 cm tumor mass, *n* (%)	37 (43)
Extranodal disease, *n* (%)	61 (70.9)
Bone marrow involvement	39 (45.3)
Gastrointestinal involvement	15 (17.4)
MIPI-b, *n* (%)[c]	
Low risk	12 (14.0)
Intermediate risk	39 (45.3)
High risk	33 (38.4)
Missing	2 (2.3)
Refractory disease[d]	45 (52.3)
TP53-mutated ($N = 54$)[e]	15 (27.8)

Note: Percentages may not add up to 100% because of rounding.
Abbreviations: CHOP, cyclophosphamide, doxorubicin, vincristine, and prednisone; ECOG, Eastern Cooperative Oncology Group; EPOCH, etoposide, prednisone, vincristine, cyclophosphamide, and doxorubicin; hyper-CVAD, cyclophosphamide, vincristine, doxorubicin, and dexamethasone.
[a]Categories are not mutually exclusive as patients may be included under multiple regimens.
[b]High-dose cytarabine-containing regimens included dexamethasone, cytarabine, and cisplatin (DHAP); etoposide, methylprednisolone, cytarabine, and cisplatin (ESHAP); methotrexate and cytarabine (hyper-CVAD B); cyclophosphamide, etoposide, cytarabine, methylprednisolone, vincristine, and nedaplatin (CDEADP).
[c]MIPI-b score was derived with the use of four baseline clinical prognostic factors (age, ECOG performance status, lactate dehydrogenase level, and white blood cell count) plus percent Ki-67 expression in tumor cells, and its range depends on the range of these characteristics (44, 45). The index classifies patients as having low-, intermediate-, or high-risk disease, as defined by scores of <5.7, ≥5.7 to <6.5, and ≥6.5, respectively.
[d]Refractory disease was defined as the lack of at least a partial response to the last therapy before study entry, as assessed by the investigator.
[e]Fifty-four patients had baseline sequencing. For the remaining patients, 21 did not provide consent, 9 lacked adequate tumor tissue, and for 2, the assay failed at the library preparation step.

Efficacy

A total of 72 (84%) patients achieved an objective response (95% CI, 74.2–90.8; $P < 0.0001$); 59 (68.6%) patients achieved a CR (**Table 2**). Subgroup analysis revealed that ORRs were generally high across all subgroups analyzed, including poor prognostic subgroups (three or more lines of prior therapy; high-risk MIPI-b scores; refractory disease; **Fig. 1**). CR rates in patients with and without a history of prior rituximab-containing therapies were similar: 42 of 64 (65.6%)

Table 2. Independent review committee–assessed efficacy outcomes.

Efficacy variable	$N = 86$
Objective response, *n* (%)	
Complete	59 (68.6)
Partial	13 (15.1)
No response[a]	14 (16.3)
Overall	72 (84)
95% CI for overall response	(74, 91)
Time to response (months)	
Median (range)	2.7 (2.5–16.6)
Response duration (months)	
Median[b] (range)	19.5 (0.9–19.5)
95% CI	(16.6, NE)
Event-free rates[c] at 12 months (%)	78.3
95% CI	(67, 86)
PFS (months)	
Median[b] (range)	22.1 (0.0+, 22.3+)
95% CI	(17.4, NE)
Event-free rates[c] at 12 months (%)	75.5
95% CI	(65, 83)

Abbreviations: FDG-PET, [^{18}F]-fluorodeoxyglucose positron emission tomography; NE, not estimable.

[a]No response was defined as a best response of stable disease ($n = 1$) or progressive disease ($n = 6$). Six patients with no on-treatment response assessments and one with no evidence of disease at baseline are also included in the no response category.

[b]Medians were estimated by Kaplan–Meier methodology with 95% CIs estimated using the Brookmeyer and Crowley method. + denotes censored observations.

[c]Denotes the proportion of patients who neither progressed nor died. Event-free rates were estimated by Kaplan–Meier methodology with 95% CIs estimated using Greenwood's formula.

and 17 of 22 (77.3%), respectively; PFS was also similar in those who had or had not received prior rituximab (Supplementary Fig. S1). However, CR rates for patients with three or four prior regimens were inferior to those with one to two prior therapies [14/29 (48.3%) and 45/57 (78.9%), respectively]. Median time to response and time to CR were similar at 2.7 and 2.9 months; 32 and 43 patients achieved CRs by weeks 12 and 24, respectively. In the 39 patients with baseline bone marrow involvement, resolution was documented in 15 (38.5%), and for the 15 patients with baseline gastrointestinal involvement, resolution was documented in 6 (40.0%) patients at follow-up endoscopy/biopsy. A waterfall plot depicting maximal reductions in target lesion tumor burden is presented in Supplementary Fig. S2.

After a median follow-up of 16.4 months from initial response, the estimated median DOR was 19.5 months. Notably, only two responders were at risk for progression when the last event occurred, rendering the median DOR estimate unstable. At 12 months, an estimated 78% of responders were alive and progression free (**Table 2**; **Fig. 2A**). After a median follow-up of 19.2 months, the estimated median PFS was 22.1 months with an estimated 76% of patients alive and without disease progression at 12 months (**Table 2**; **Fig. 2B**). Similarly, only 4 patients were at risk for progression when the last event occurred, rendering the median PFS estimate unstable. A total of 14 patients died as of the data cut-off date; the OS rate at 12 months was 84.1%.

Of 54 patients tested for the presence of *TP53* mutation at baseline, 15 (27.8%) had *TP53*-mutated tumors. Patients with *TP53*-mutated tumors had an ORR comparable to those with wild-type disease [80.0% (95% CI, 51.9–95.7) vs. 87.2% (95% CI, 72.6–95.7)]. As might be predicted for patients with *TP53* mutations, median DOR (14.5 months vs. 19.5 months) and PFS (14.7 months vs. 22.1 months) were shorter in these patients compared with patients without *TP53*-mutated tumors (Supplementary Fig. S3). Median DOR among patients with ≤30% and >30% Ki-67 tumor staining were not estimable (NE) and 14.5 months, respectively; the corresponding median PFS estimates were NE and 12.9 months, respectively. For patients with and without blastoid variant tumors, median DOR was NE and 19.5 months, and median PFS was 16.8 and 22.1 months, respectively (Supplementary Table S1). Notably, the estimated median DOR or PFS is unstable for several of these subsets with only a small number of patients at risk at the later timepoints.

Safety

Almost all patients (96.5%) experienced at least one AE, with the majority being grade 1 or 2 in severity; grade ≥3 AEs were reported in 41.9% of patients (**Table 3**). The most common (all grade) hematologic AEs were neutropenia (48.8%), leukopenia (34.9%), and thrombocytopenia (32.6%), and the most common nonhematologic AEs were upper respiratory infection (34.9%) and rash (33.7%). The most common grade ≥3 AEs were neutropenia (19.8%) and lung infection/pneumonia (9.3%).

Adverse events of interest

Most patients (83.7%) reported at least one AEI with 35% reporting at least one grade ≥3 AEI (Supplementary Table S2). Infections were the most common category of AEIs, with 62% of patients having reported at least one infection (14% grade ≥3). Predictably, these were primarily mucosal infections of the sinopulmonary and urinary tracts (upper respiratory tract infection, lung infection/pneumonia, urinary tract infection). The most common grade ≥3 infections were lung infection/pneumonia ($n = 8$). One patient experienced acute reactivation of hepatitis B infection on study day 253, which resolved after interruption of zanubrutinib and initiation of antiviral therapy. The patient subsequently resumed zanubrutinib 16 days later at a reduced dose without further complications.

One or more bleeding events were reported in 25.6% of patients. These were primarily grade 1 or 2 mucocutaneous bleeds (petechia/purpura/contusion, ecchymosis, epistaxis, hematuria). Among the 22 patients who reported a bleeding event, 1 had concurrent grade 4 thrombocytopenia, and 1 patient each had concurrent antithrombotic and antiplatelet drug use. Three patients had major bleeding events. A 70-year-old male with a history of three prior systemic regimens, blastic histology at diagnosis, as well as extensive nodal and extranodal disease and a high-risk MIPI-b score at study entry, presented with a left occipital lobe hemorrhage 6 days after initiation of zanubrutinib, which led to treatment discontinuation and subsequent death. Although this patient exhibited no signs or symptoms of central nervous system involvement at study entry, it is noteworthy that blastic histology and a high-risk MIPI-b score are risk factors for central nervous system MCL (23). A 61-year-old male, with two prior lines of therapy and biopsy-proven extranodal involvement in the terminal ileum and right kidney at study entry, presented with hematemesis on study day 429; upper endoscopy revealed the presence of a new tumor in the gastric fundus thought to be consistent with disease progression and no evidence of ulcer or other active source of bleeding. Finally, a 53-year-old male with three prior lines of therapy experienced two separate gastrointestinal bleeding events (serious, grade 2) approximately 1 month apart (the first on study day 495), both of which resolved spontaneously after approximately 5 days without

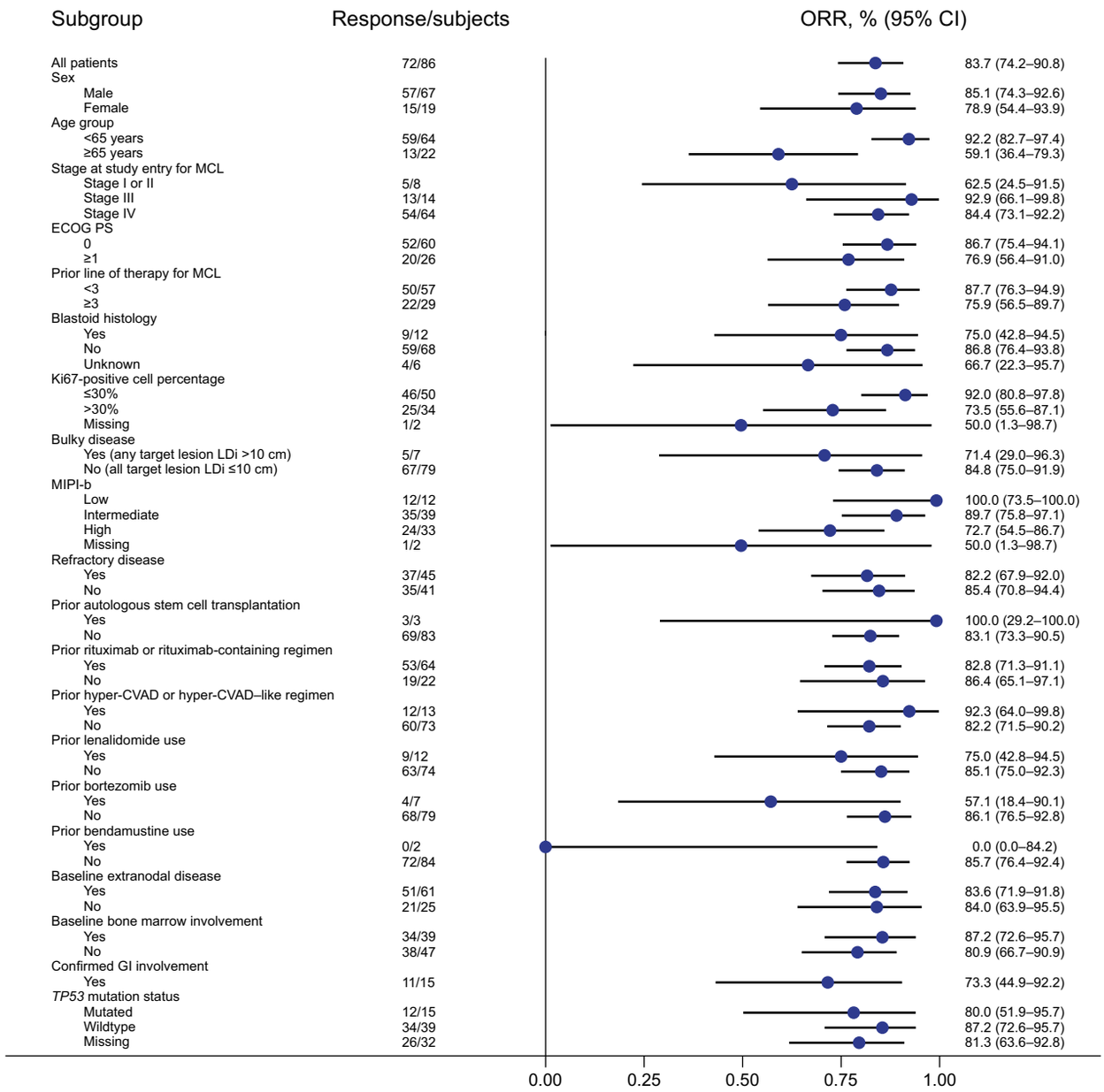

Figure 1.
Overall response rate according to subgroup.

study treatment modification; no endoscopy or other diagnostic evaluations were performed.

Thirteen (15.1%) patients developed treatment-emergent hypertension, three of which were grade 3 events; four patients had a history of hypertension. None required zanubrutinib treatment modification.

No patient experienced atrial fibrillation or flutter, second primary malignancy, or tumor lysis syndrome.

A total of 14 (16.3%) patients died during the study, 7 within 30 days of the last study treatment (6 from complications of AEs and 1 from disease progression). AEs leading to death included one case each of traffic accident, left occipital lobe hemorrhage (as previously described), and pneumonia, and three deaths due to unknown causes. Of seven deaths that occurred more than 30 days after the last dose of study drug, five were due to progressive disease, one was from complications of fungal pneumonia, and one was due to unknown cause after receiving three additional lines of therapy.

Discussion

Historically, treatment options for R/R MCL were limited because of poor tolerability and modest response rates that were relatively short-lived. The proteasome inhibitor bortezomib has demonstrated an ORR of 35% (8% CRs) and a median DOR of only 9.2 months (7). Peripheral neuropathy, the principal toxicity associated with

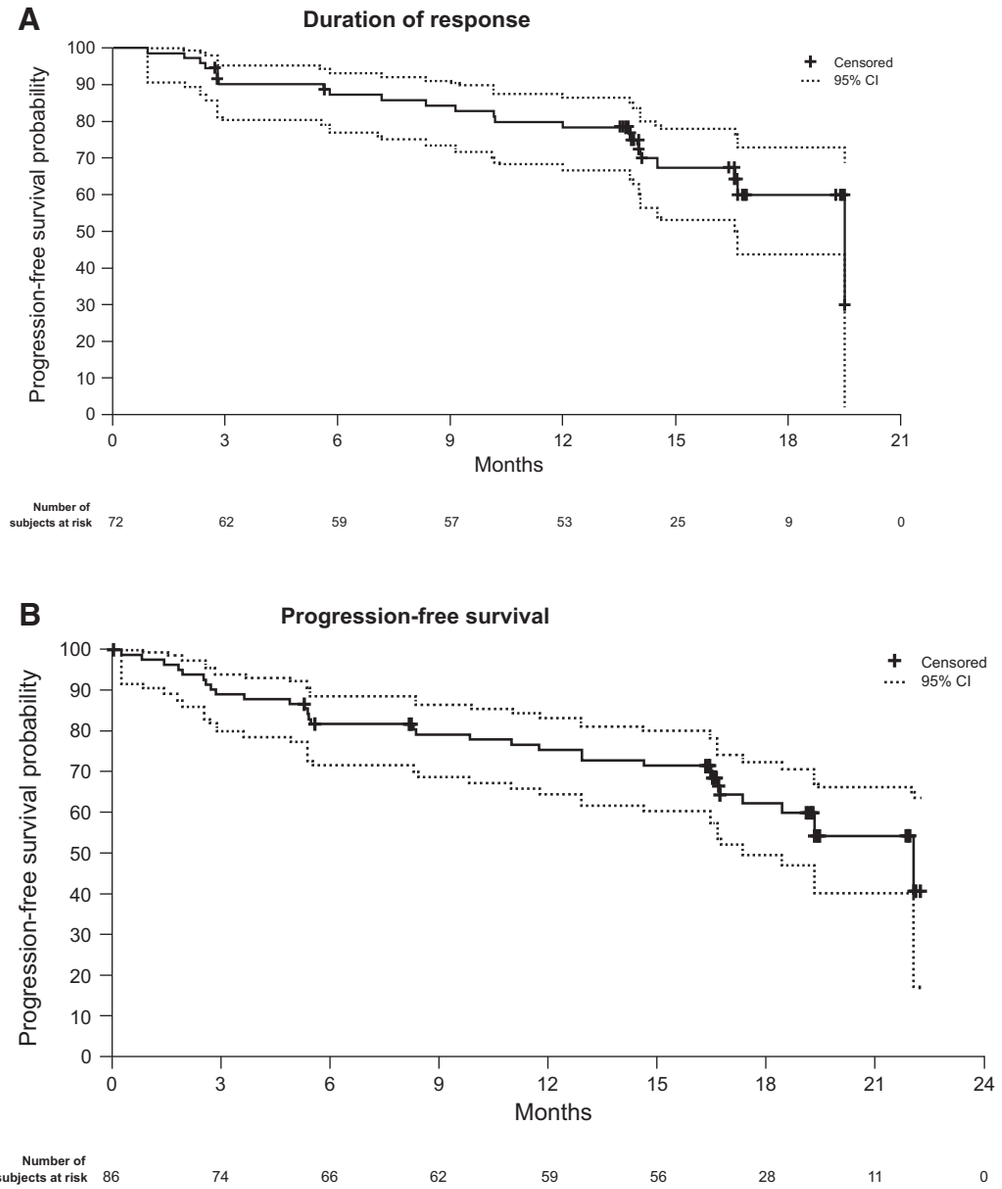

Figure 2.
A, Duration of response. **B,** Progression-free survival.

bortezomib treatment, was reported in approximately 40% of patients (10% grade ≥3; ref. 7). Treatment with lenalidomide led to an ORR of 28% (7.5% CR/CR unconfirmed); DOR was somewhat longer at 16.6 months, but the small number of responders limits the overall benefit of this agent (6). In two randomized phase III studies, treatment with the mTOR inhibitor temsirolimus (approved in the EU for R/R MCL) led to an ORR of only 22% to 40% and a median PFS of 4.8 to 6.2 months (8, 24).

Agents that target BTK have shown promise in treating B-cell malignancies, including MCL (9, 25–27). The first-in-class BTK inhibitor, ibrutinib, has become a standard of care for R/R MCL, but its use has been limited by adverse drug reactions, such as bleeding (in 50% of patients), atrial fibrillation (11%), and diarrhea (54%), some of which are believed to be attributable to off-target effects and lead to discontinuation of therapy in approximately 10% of patients with MCL (28, 29). As a selective BTK inhibitor, zanubrutinib was designed to reduce treatment-limiting, off-target toxicities.

In this study, baseline demographic and disease characteristics were generally comparable to those reported in the phase II studies of ibrutinib and acalabrutinib, although there were some notable differences. The age distribution in this study was somewhat younger (median age, 61 years; 26% ≥65 years) compared with that reported for the aforementioned studies (median age, 68 years; 65% ≥ 65 years in the acalabrutinib study; refs. 9, 30). Although there were no meaningful differences in response rates for patients younger than 65 years of age versus those ≥65 years in either the ibrutinib or acalabrutinib

Table 3. Adverse events[a].

Event	All grades, *n* (%)	Grade ≥3, *n* (%)
Patients with at least one adverse event	83 (96.5)	34 (41.9)
Hematologic events		
Neutropenia[b]	42 (48.8)	17 (19.8)
Leukopenia[c]	30 (34.9)	6 (7.0)
Thrombocytopenia[d]	28 (32.6)	4 (4.7)
Anemia	13 (15.1)	5 (5.8)
Nonhematologic events		
Upper respiratory tract infection	30 (34.9)	0
Rash	29 (33.7)	0
Hypokalemia	14 (16.3)	1 (1.2)
Diarrhea	13 (15.1)	0
Hypertension[e]	13 (15.1)	3 (3.5)
Alanine aminotransferase increased	12 (14.0)	1 (1.2)
Lung infection[f]	11 (12.8)	8 (9.3)

[a]Data are for adverse events reported from first dose date to 30 days following study drug discontinuation or initiation of new anticancer therapy in the 86 patients included in the study. Any-grade events occurred in at least 10% of patients and grade ≥3 events occurred in at least 3% of patients on or before the data cut-off date of February 15, 2019. "Bolded" terms correspond to individual categories of AEI (Supplementary Table S2).
[b]Includes preferred terms neutropenia, febrile neutropenia ($n = 1$, grade 3), and neutrophil count decreased.
[c]Includes preferred terms leukopenia and white blood cell count decreased.
[d]Includes preferred terms thrombocytopenia and platelet count decreased.
[e]Includes preferred terms hypertension and blood pressure increased.
[f]Includes preferred terms lung infection and pneumonia.

studies (9, 30), older patients demonstrated inferior overall and CR rates in this study (**Fig. 1**; Supplementary Table S1). The reason(s) for the poorer response rates among patients ≥65 years are not entirely clear. However, more patients in the latter age group required at least one treatment interruption (27.3% vs. 21.9%); 9 (14.1%) of 64 patients <65 years and 4 (18.2%) of 22 patients ≥65 years required two or more interruptions. Of note, in 37 patients with R/R MCL treated with zanubrutinib in the phase I study AU-003, ORR was numerically higher in patients over the age of 65 (92.6%) than in those under 65 years (50%; ref. 16). Although all patients in this study received prior combination chemotherapy regimens that are generally consistent with consensus guidelines (31, 32), only 74% of patients had received a prior rituximab-containing regimen in this study compared with 89% in the ibrutinib study (9) and 95% in the acalabrutinib study (30). Recognizing the limitation of small sample sizes, it is noteworthy that in this study, ORRs and PFS were similar in patients with or without prior rituximab exposure (**Fig. 1**; Supplementary Fig. S1). A minority of patients in this study had prior exposure to lenalidomide (14%), bortezomib (8%), or bendamustine (2%). By comparison, in the ibrutinib study, 24% and 43% had prior exposures to lenalidomide and bortezomib, respectively (bendamustine exposure was not reported), whereas in the acalabrutinib study, 7%, 19%, and 22% of patients had prior exposure to these respective therapies (9, 30). In addition, more patients had undergone prior high-dose chemotherapy followed by ASCT in the acalabrutinib study (18%) and ibrutinib study (11%) compared with this study (4%; refs. 9, 30). The above-described differences in age and prior treatment history limit the comparability of efficacy outcomes across studies (9, 30).

In this study, patients with R/R MCL treated with zanubrutinib achieved a high level of overall and complete responses. The treatment benefit as measured by ORR was generally consistent across subgroups, including in 9 of 12 patients with blastoid variant and 12 of 15 patients with *TP53*-mutated tumors. The results reported herein compare favorably with a pooled analysis of 370 ibrutinib-treated patients from three studies in which ORRs and CR rates were 69.7% and 27%, respectively, although it is noteworthy that the studies represented in this analysis required PET scanning only when a CR was suspected by conventional imaging methods (33). Our results also compare favorably to those from the phase II study of acalabrutinib, in which the IRC-assessed overall response and CR rates using the same (Lugano classification; ref. 17) response criteria were 80% and 40%, respectively (30). The deep responses observed in this study may be attributable to the selectivity and favorable pharmacokinetic profile of zanubrutinib, the relevance of which is highlighted by complete and sustained BTK occupancy observed in both peripheral blood mononuclear cells and lymph node biopsy tissue in patients receiving zanubrutinib (1). In addition, the 12-month DOR and PFS reported in this study (78% and 76%) compare favorably with those reported for ibrutinib (approximately 67% and 50%) and acalabrutinib (72% and 67%; refs. 9, 30).

As previously reported, patients with *TP53*-mutated MCL have a particularly dismal prognosis and derive minimal benefit from chemoimmunotherapy (34, 35). In the ibrutinib experience, ORR was 55% among patients with *TP53*-mutated tumors (no CRs) compared with 70.2% (including 31 CRs) in wild-type patients; both PFS and OS were substantially inferior in patients with *TP53*-mutated tumors (33). The median PFS in this study compares favorably with that reported for ibrutinib in patients with *TP53*-mutated MCL [14.7 months vs. 4 months (33), respectively]. Acknowledging that differences in patient characteristics and small patient numbers in this study limit direct comparison, the longer PFS observed with zanubrutinib in this particularly challenging subset of patients with MCL is encouraging and suggests that zanubrutinib could provide a treatment option for these patients. In this study, zanubrutinib was generally well tolerated. The most commonly reported AEs (cytopenias, infections, rash, and diarrhea) were generally consistent with previous reports of zanubrutinib treatment in patients with various B-cell malignancies, and mostly grade 1 or 2 (36). An important component of the safety evaluation for this study was the assessment of AEIs, identified on the basis of clinical experience with other BTK inhibitors. In this regard, zanubrutinib compares favorably with ibrutinib in terms of the lower frequency of grade ≥3 events, such as diarrhea (0%), neutropenia (19.8%), thrombocytopenia (4.7%), anemia (5.8%), infection (14%) and hemorrhage (1.2%; refs. 9, 28). No cases of atrial fibrillation/flutter were reported in this study. The reduced incidence of grade ≥3 severity for these and other AEs suggests that the higher selectivity of zanubrutinib for BTK may confer benefits in terms of allowing greater treatment intensity, longer treatment durations, and overall improved outcomes. Retrospective analyses of ibrutinib treatment intensities in both CLL/SLL (37, 38) and Waldenström macroglobulinemia (39) indicate that treatment interruptions (including those lasting ≥8 days) are associated with shorter PFS. Avoidance of dose reductions and treatment interruptions and by inference maintenance of sustained BTK inhibition appear to be critical for optimal disease control in patients with B-cell neoplasms.

Similar to other BTK inhibitors, zanubrutinib is primarily metabolized by CYP3A. No ethnic differences in the pharmacokinetics of zanubrutinib have been observed between Asian and non-Asian patients (40). Clinical drug–drug interactions (DDI) with CYP3A inhibitors have the potential to contribute to dose reduction and treatment interruptions of BTK inhibitors. These agents significantly increase exposure levels of ibrutinib in clinical DDI studies (41, 42),

thus for patients on ibrutinib treatment, coadministration with strong CYP3A inhibitors other than posaconazole and voriconazole is not recommended (28, 43). The impact of CYP inhibitors on the metabolism of zanubrutinib (2.6-fold increase in C_{max} upon itraconazole coadministration; ref. 40) is significantly lower compared with that of ibrutinib (6.7- and 29-fold increase in C_{max} upon voriconazole and ketoconazole coadministration; refs. 41, 42).

There are several limitations of this study. Principal among these is the single-arm design, which limits direct comparisons of safety and efficacy with other BTK inhibitors. As noted, the age distribution for patients in this study skewed younger than those in the ibrutinib and acalabrutinib phase II studies. In addition to the qualitative differences in prior treatment history previously cited, patients in the ibrutinib study were more heavily pretreated, with a median of three prior regimens versus two for this study, and 55% versus 33.7% of patients, respectively, had received three or more prior regimens (9). In the aforementioned pooled analysis of ibrutinib-treated patients, ORR, CR rates, PFS, and DOR were all inferior among patients with ≥2 prior lines of therapy compared with those who received ibrutinib in the second line (33). Other prognostic variables, such as the presence of bulky disease, refractoriness to last prior regimen, extranodal disease involvement, and proportion with intermediate/high prognostic index scores, were similar. Conversely, comparison to patients enrolled on the acalabrutinib pivotal trial reveals that this study included a higher proportion of patients with refractory disease (52% vs. 24%) as well as intermediate- or high-risk MIPI score (30), arguing against more favorable patient characteristics as an explanation for the higher CR rate observed with zanubrutinib.

In conclusion, this phase II study of patients with R/R MCL has shown that twice-daily administration of zanubrutinib resulted in high overall response and CR rates that are durable. As a selective BTK inhibitor, zanubrutinib offers a new therapy that has improved safety and tolerability over existing treatment options, and therefore, a favorable benefit versus risk profile in patients with R/R MCL.

Disclosure of Potential Conflicts of Interest

J. Huang, W. Novotny, H. Guo, L. Zhou, R. Elstrom, and R. Wei are employees/paid consultants for BeiGene. No potential conflicts of interest were disclosed by the other authors.

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