Zanubrutinib in Patients With B-Cell Malignancies Intolerant to Acalabrutinib

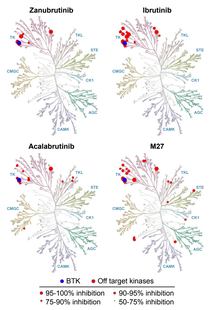
Syed Zafar,[1] Mazyar Shadman,[2] Ian W. Flinn,[3] Edwin C. Kingsley,[4] Benjamin Freeman,[5] Moshe Y. Levy,[6] Houston Holmes,[6] Charles M. Farber,[7] Arvind Chaudhry,[8] Rocco Crescenzo,[9] Adam Idoine,[9] Xiaoping Zhang,[9] Aileen Cohen,[9] Kunthel By,[9] and Jeff P. Sharman[10]

[1]Florida Cancer Specialists and Research Institute, Fort Myers, FL, USA; [2]Fred Hutchinson Cancer Research Center, University of Washington, Seattle, WA, USA; [3]Sarah Cannon Research Institute/Tennessee Oncology, Nashville, TN, USA; [4]Comprehensive Cancer Centers of Nevada, Las Vegas, NV, USA; [5]Summit Medical Group, Florham Park, NJ, USA; [6]Texas Oncology-Baylor Charles A. Sammons Cancer Center, Dallas, TX, USA; [7]Atlantic Hematology Oncology, Morristown Medical Center, Morristown, NJ, USA; [8]Summit Cancer Centers, Spokane, WA, USA; [9]BeiGene (Beijing) Co., Ltd., Beijing, China and BeiGene USA, Inc., San Mateo, CA, USA; and [10]Willamette Valley Cancer Institute and Research Center, Eugene, OR, USA

INTRODUCTION

- Bruton tyrosine kinase (BTK) inhibitors are a mainstay of treatment for B-cell malignancies; however, treatment-related adverse events (AEs) limit the use of BTK inhibitors, potentially due to off-target inhibition of other tyrosine kinases[1-3]
- Zanubrutinib is a potent and selective next-generation BTK inhibitor designed to maximize tolerability by minimizing off-target kinase binding[4]
- Previous results from this ongoing phase 2 study (BGB-3111-215; NCT04116437) showed that zanubrutinib is well tolerated in patients who are intolerant to ibrutinib (cohort 1) and/or acalabrutinib (cohort 2)[5]
- Here, we report updated results of the tolerability and efficacy of zanubrutinib in patients intolerant to acalabrutinib (cohort 2)

Figure 1. Kinase Selectivity of Zanubrutinib, Ibrutinib, Acalabrutinib, and Acalabrutinib's Major Metabolite (M27)



- Zanubrutinib demonstrated higher selectivity than ibrutinib, acalabrutinib, and M27 by kinase profiling (**Figure 1**)[5,6]
- Of the 370 kinases tested, zanubrutinib, ibrutinib, acalabrutinib, and M27 demonstrated >50% inhibition of 7, 17, 15, and 23 kinases, respectively
- Kinase selectivity was assessed at 100× IC_{50} (against BTK) for zanubrutinib, ibrutinib, acalabrutinib, and M27 (Reaction Biology Corp)
  - IC_{50} (against BTK; n=3):
    - Zanubrutinib: 0.71 ± 0.09 nM
    - Ibrutinib: 0.32 ± 0.09 nM
    - Acalabrutinib: 24 ± 9.2 nM
    - M27: 63 ± 28 nM

OBJECTIVES

Primary

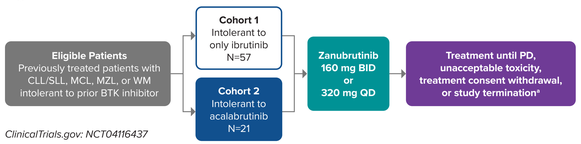
- To evaluate the safety of zanubrutinib in patients who were intolerant to acalabrutinib treatment as assessed by the recurrence and change in severity of their acalabrutinib intolerance AEs

Secondary

- To evaluate the efficacy of zanubrutinib by investigator-assessed overall response rate (ORR), disease control rate (DCR), progression-free survival (PFS), and patient-reported outcomes

METHODS

Figure 2. BGB-3111-215 Study Design



ClinicalTrials.gov: NCT04116437

[a]Study is ongoing.
BID, twice a day; CLL, chronic lymphocytic leukemia; MCL, mantle cell lymphoma; MZL, marginal zone lymphoma; PD, progressive disease; QD, once a day; SLL, small lymphocytic lymphoma; WM, Waldenström macroglobulinemia.

Key Inclusion Criteria for Acalabrutinib Intolerance Leading to Discontinuation

- Grade ≥1 nonhematologic toxicity for >7 days
- Grade ≥1 nonhematologic toxicity of any duration with >3 recurrent episodes
- Grade ≥3 nonhematologic toxicity for any duration
- Grade 3 neutropenia with infection or fever
- Grade 4 hematologic toxicity that persists until BTK inhibitor therapy is discontinued due to toxicity
- Inability to use acid-reducing agents or anticoagulants due to current BTK inhibitor use
- Resolution of grade ≥2 BTK inhibitor toxicities to grade ≤1 or baseline and resolution of grade 1 BTK inhibitor toxicities to grade 0 or baseline before initiating zanubrutinib treatment

Key Exclusion Criteria

- Disease progression during prior BTK inhibitor treatment

RESULTS

Table 1. Patient Demographics and Baseline Characteristics

Characteristic	Cohort 2 (N=21)
Indication, n (%)	
CLL	13 (62)
SLL	2 (10)
MCL	1 (5)
MZL	2 (10)
WM	3 (14)
Age, median (range), years	73 (51-87)
Sex, n (%)	
Male	13 (62)
Female	8 (38)
ECOG PS, n (%)	
0	13 (62)
1	6 (29)
2	2 (10)
No. of prior anticancer therapy regimens, median (range)	2 (1-6)
Prior BTK inhibitor, n (%)	
Ibrutinib monotherapy	10 (48)
Ibrutinib combination therapy[a]	1 (5)
Acalabrutinib monotherapy	20 (95)
Acalabrutinib combination therapy[a]	1 (5)
Cumulative acalabrutinib exposure, median (range), months	4.6 (0.2-26.9)
On-study zanubrutinib dosing regimen, n (%)	
160 mg BID	14 (67)
320 mg QD	7 (33)

Data cutoff: 1 September 2022
[a]Combination therapy is defined as a regimen of 2 or more drugs that contains ibrutinib or acalabrutinib.
ECOG PS, Eastern Cooperative Oncology Group performance status.

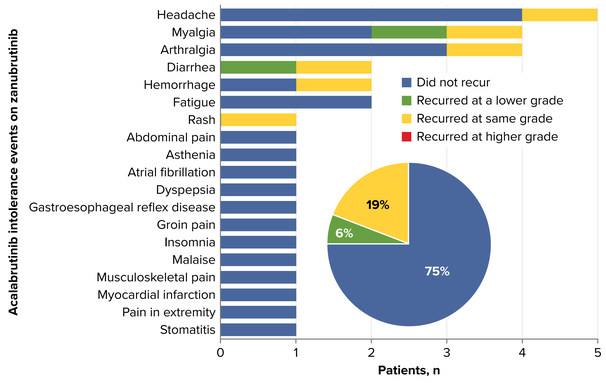
Table 2. Patient Disposition

Disposition	Cohort 2 (N=21)
Patients, n (%)	
Remaining on treatment	16 (76)
Remaining on study	17 (81)
Discontinued from treatment	5 (24)
AE	2 (10)[a]
PD	1 (5)
Withdrawal by patient	2 (10)
Death	1 (5)[b]
Zanubrutinib treatment duration, median (range), months	7.6 (0.1-23.8)
Study follow-up, median (range), months	8.6 (0.1-23.8)

[a]Myalgia (n=1), diarrhea (n=1). [b]Due to PD >30 days after the last dose.

- Twenty-one patients reported 32 acalabrutinib intolerance events
- The most common acalabrutinib intolerances were headache (n=5), arthralgia (n=4), myalgia (n=4), diarrhea (n=2), fatigue (n=2), and hemorrhage (n=2)
- Most (24 of 32 [75%]) acalabrutinib intolerance events did not recur on zanubrutinib at any grade, and no acalabrutinib intolerance events recurred at a higher severity (**Figure 3**)
- Fourteen (67%) of 21 patients did not experience any recurrence of their prior acalabrutinib intolerance events
- Two (10%) of 21 patients discontinued zanubrutinib due to recurrence of their prior acalabrutinib intolerance events (myalgia and diarrhea)
- Three (14%) of 21 patients experienced the same intolerance event (pain in extremity, diarrhea, and atrial fibrillation) on ibrutinib and acalabrutinib
  - Two did not have a recurrence of those on zanubrutinib
  - One had a recurrence at lower grade (diarrhea)

Figure 3. Recurrence of Acalabrutinib Intolerance Events on Zanubrutinib



Safety

- The most common grade ≥3 AE was neutrophil count decreased, which occurred in 2 (10%) patients (**Table 3**)
- No atrial fibrillation, anemia, or thrombocytopenia/platelet count decreased occurred in any patient

Table 3. Most Frequent Adverse Events[a]

AEs, n (%)	Any grade (N=21)	Grade ≥3 (N=21)
Any AE	20 (95)	4 (19)[b]
Fatigue	6 (29)	0
Diarrhea	5 (24)	1 (5)
Hypertension	5 (24)	1 (5)
Arthralgia	4 (19)	0
Cough	4 (19)	0
Myalgia	4 (19)	0
COVID-19	3 (14)	1 (5)
Contusion	3 (14)	0
Decreased appetite	3 (14)	0
Dyspnea	3 (14)	0
Night sweats	3 (14)	0
Pain in extremity	3 (14)	0
Pyrexia	3 (14)	0
Rash	3 (14)	0
Back pain	2 (10)	0
Dizziness	2 (10)	0
Peripheral edema	2 (10)	0
Oropharyngeal pain	2 (10)	0
Palpitations	2 (10)	0
Maculopapular rash	2 (10)	0
SARS-CoV-2 test positive	2 (10)	0
Urinary tract infection	2 (10)	0
Neutrophil count decreased	2 (10)	2 (10)
Febrile neutropenia	1 (5)	1 (5)
Gastroenteritis salmonella	1 (5)	1 (5)

[a]Any grade events occurring in ≥2 patients or grade ≥3 events occurring in ≥1 patients. [b]Some patients had >1 grade ≥3 event.

Table 4. Summary of Serious Adverse Events and Adverse Events Leading to Dose Modification

AEs, n (%)	Any grade (N=21)
Serious AE	2 (10)
Leading to treatment discontinuation	2 (10)
Leading to dose interruption	11 (52)
Leading to dose reduction	3 (14)
Leading to death	0

Efficacy

- Among the 18 efficacy-evaluable patients on zanubrutinib, 17 (94%) achieved stable disease (SD) or better, and 11 (61%) achieved a partial response (PR) or better (**Table 5**)
- Eight (67%) of 12 efficacy-evaluable patients with CLL/SLL on zanubrutinib achieved a PR-L or better

Table 5. BOR by Investigator Assessment

Response	Cohort 2 (N=18)
DCR (SD or better), n (%) (95% CI)	17 (94) (72.7, 99.9)
ORR (better than SD), n (%) (95% CI)	11 (61) (35.7, 82.7)
BOR rate, n (%)	
PR/PR-L/VGPR	11 (61)
SD	6 (33)
PD	1 (6)
Time to BOR, median (range), months	3 (2.7-11.1)
Time to first overall response, median (range), months	3 (2.7-11.1)

BOR, best overall response; DCR, disease control rate; ORR, overall response rate; PD, progressive disease; PR, partial response; PR-L, PR with lymphocytosis; SD, stable disease; VGPR, very good PR.

CONCLUSIONS

- With a median zanubrutinib exposure of 7.6 months, longer than the reported cumulative acalabrutinib exposure before discontinuation (4.6 months), most (67%) patients did not experience any recurrence of their prior acalabrutinib intolerance events
- Zanubrutinib provided clinically meaningful benefit to 17 (94%) of 18 efficacy-evaluable patients who were previously intolerant to acalabrutinib
- These outcomes suggest that switching to zanubrutinib may yield clinical benefit in patients intolerant to acalabrutinib

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DISCLOSURES

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IWF: advisory role with Vincerx
MYL: consulting and speaker bureau for AbbVie, Amgen, BMS, Janssen, Karyopharm, MorphoSys, Seagen, Takeda, AstraZeneca, BeiGene, Gilead, Kite, TG Therapeutics, Epizyme, GSK, Novartis
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CMF: honoraria from BMS; consulting and speaker bureau for ADP Therapeutics, Genentech, Kite/Gilead, MorphoSys/Incyte, Seagen
RC: employment with BeiGene; equity with BeiGene, Pfizer, and GSK; stocks with SAGA Diagnostics
AI, XZ, ACo: employment and stocks with BeiGene
KB: employment with BeiGene
JPS: research funding from Genentech, Celgene, Gilead Sciences, TG Therapeutics, Merck, Takeda; consulting for TG Therapeutics, Genentech, AbbVie, AstraZeneca, BeiGene, BMS, Merck
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CORRESPONDENCE

Syed Zafar, MD
Florida Cancer Specialists & Research Institute
Fort Myers, FL, USA
SZafar@flcancer.com

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