Zanubrutinib in Acalabrutinib-Intolerant Patients With B-Cell Malignancies

BSH23-PO36

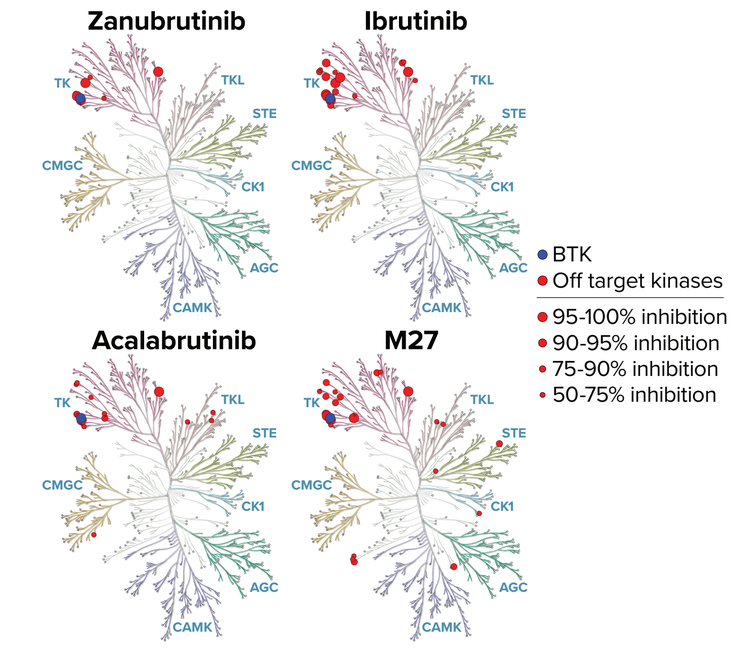
Rocco Crescenzo,[1] Mazyar Shadman,[2] Ian W. Flinn,[3] Edwin C. Kingsley,[4] Benjamin Freeman,[5] Moshe Y. Levy,[6] Houston Holmes,[6] Charles M. Farber,[7] Arvind Chaudhry,[8] Adam Idoine,[1] Xiaoping Zhang,[1] Aileen Cohen,[1] Kunthel By,[1] and Jeff P. Sharman[9]

[1]BeiGene (Beijing) Co., Ltd., Beijing, China & BeiGene USA, Inc., San Mateo, CA, 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; and [9]Willamette Valley Cancer Institute & Research Center, Eugene, OR, USA

INTRODUCTION

- BTK inhibitors are a mainstay of treatment for B-cell malignancies; however, their use can be limited by AEs, many of which are potentially caused by off-target inhibition of other tyrosine kinases[1-3]
- Zanubrutinib is a potent and selective next-generation BTK inhibitor designed to maximize BTK occupancy and minimize off-target kinase binding and associated AEs[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 and/or acalabrutinib[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 Metabolite M27



- Zanubrutinib demonstrated higher selectivity than ibrutinib, acalabrutinib, and acalabrutinib's major metabolite (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× IC50 (against BTK) for zanubrutinib, ibrutinib, acalabrutinib, and M27 (Reaction Biology Corp)
  - IC50 (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

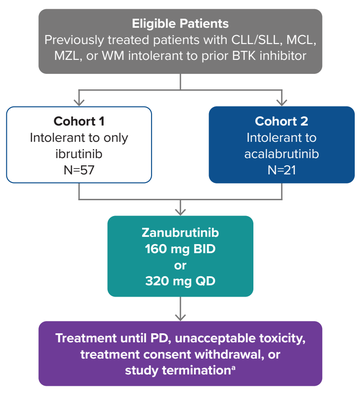
- To evaluate the safety of zanubrutinib in patients who were intolerant to acalabrutinib treatment as assessed by the recurrence and change in severity of their acalabrutinib intolerance AEs

Secondary

- To evaluate the efficacy of zanubrutinib by investigator-assessed ORR, DCR, PFS, and patient-reported outcomes

METHODS

Figure 2. BGB-3111-215 Study Design



[a]Study is ongoing.
ClinicalTrials.gov: NCT04116437

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 BTKi therapy is discontinued due to toxicity
- Inability to use acid-reducing agents or anticoagulants due to current BTKi use
- Resolution of grade ≥2 BTKi toxicities to grade ≤1 or baseline and resolution of grade 1 BTKi toxicities to grade 0 or baseline before initiating zanubrutinib treatment

Key Exclusion Criteria

- Disease progression during prior BTKi 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 BTKi, n (%)	
Ibrutinib monotherapy	10 (48)
Ibrutinib combination therapy[a]	1 (4.8)
Acalabrutinib monotherapy	20 (95)
Acalabrutinib combination therapy[a]	1 (4.8)
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.

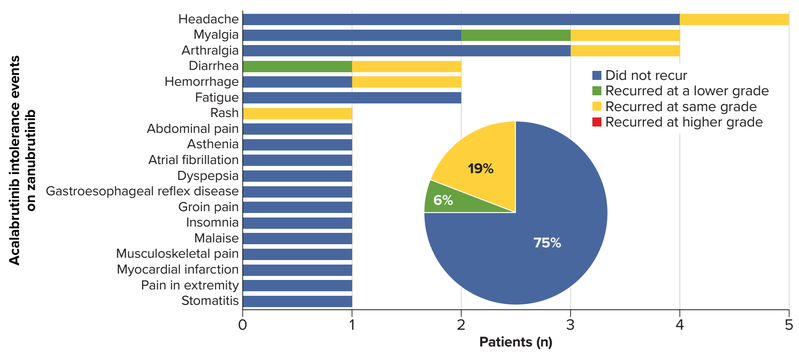
Table 2. Patient Disposition

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.

- The 21 cohort 2 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 SD or better, and 11 (61%) achieved a 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/VGPR[a]	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)

[a]Includes PR or better in all patients, PR-L or better in CLL.

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 patients who are intolerant to acalabrutinib can attain clinical benefit by switching to zanubrutinib

REFERENCES

1. Stephens DM, Byrd JC. *Blood* 2019;133(12):1298-1307
2. Furman RR, et al. *Leukemia* 2021;35(11):3201-3211
3. Mato AR, et al. *Haematol* 2018;103(5):874-879
4. Guo Y, et al. *J Med Chem* 2019;62(17):7923-7940
5. Shadman M, et al. *Lancet Haematol* Forthcoming 2022
6. Shadman M, et al. *Blood* 2021;138(suppl 1):1410

ABBREVIATIONS

AE, adverse event; BID, twice a day; BOR, best overall response; BTK, Bruton tyrosine kinase; BTKi, Bruton tyrosine kinase inhibitor; CLL, chronic lymphocytic leukemia; CR, complete response; DCR, disease control rate; ECOG PS, Eastern Cooperative Oncology Group performance status; IC_{50}, half maximal inhibitory concentration; MCL, mantle cell lymphoma; MZL, marginal zone lymphoma; ORR, overall response rate; PD, progressive disease; PFS, progression-free survival; PR, partial response; PR-L, partial response with lymphocytosis; QD, once a day; SD, stable disease; SLL, small lymphocytic lymphoma; VGPR, very good partial response; WM, Waldenström macroglobulinemia.

DISCLOSURES

RC: employment with BeiGene; equity with BeiGene, Pfizer, and GSK; stocks with SAGA Diagnostics
MS: research funding from Mustang Bio, Celgene, BMS, Pharmacyclics, Gilead, Genentech, AbbVie, TG Therapeutics, BeiGene, AstraZeneca, Sunesis, Atara Biotherapeutics, Genmab, MorphoSys/Incyte; consulting for AbbVie, Genentech, AstraZeneca, Sound Biologics, Pharmacyclics, BeiGene, BMS, MorphoSys/Incyte, TG Therapeutics, Innate Pharma, Kite, Adaptive Biotechnologies, Epizyme, Eli Lilly, Adaptimmune, Mustang Bio, Regeneron, Merck, Fate Therapeutics, MEI Pharma, Atara Biotherapeutic
IWF: advisory role with Vicerx
MYL: consulting and speaker bureau for AbbVie, Amgen, BMS, Janssen, Karyopharm, MorphoSys, Seagen, Takeda, AstraZeneca, BeiGene, Gilead, Kite, TG Therapeutics, Epizyme, GSK, Novartis
HH: research funding from Adicent Bio, Artiva, Autolus, BMS, Caribou Biosciences, Genentech, Incyte, Kite, Novartis, C4 Therapeutics; consulting for AstraZeneca, BMS, Crisper Biosciences, Epizyma, Janssen, Karyopharm, Kite, Novartis, Rigle, TG Therapeutics, C4 Therapeutics; honoraria from BMS, Kite; consultant or speaker bureau for Karyopharm, Kite, Rigle, Seagen; serves on the board of directors for Exuma Biotech
CMF: honoraria from BMS; consulting and speaker bureau for ADP Therapeutics, Genentech, Kite/Gilead, MorphoSys/Incyte, Seagen
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
ECK, ACh, BF: nothing to disclose

CORRESPONDENCE

Rocco Crescenzo
BeiGene USA, Inc.
San Mateo, CA, USA
rocco.crescenzo@beigene.com

ACKNOWLEDGMENTS

We would like to thank the investigators, site support staff, and especially the patients for participating in this study. This study was sponsored by BeiGene. Editorial support was provided by ArticulateScience, LLC and funded by BeiGene.