

Zanubrutinib in Acalabrutinib-Intolerant Patients With B-Cell Malignancies

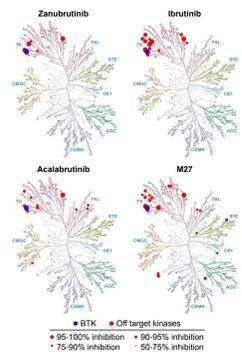
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INTRODUCTION

- 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 AEs⁴
- 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 acalabrutinib⁵
- 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

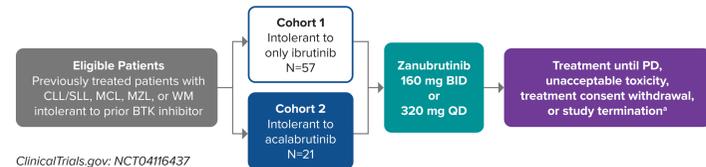
- To evaluate the safety of zanubrutinib in patients who were intolerant to acalabrutinib treatment as assessed by the recurrence and change in severity of their acalabrutinib intolerance AEs

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



ClinicalTrials.gov: NCT04116437

*Study is ongoing.

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

^aCombination therapy is defined as a regimen of 2 or more drugs that contains ibrutinib or acalabrutinib.

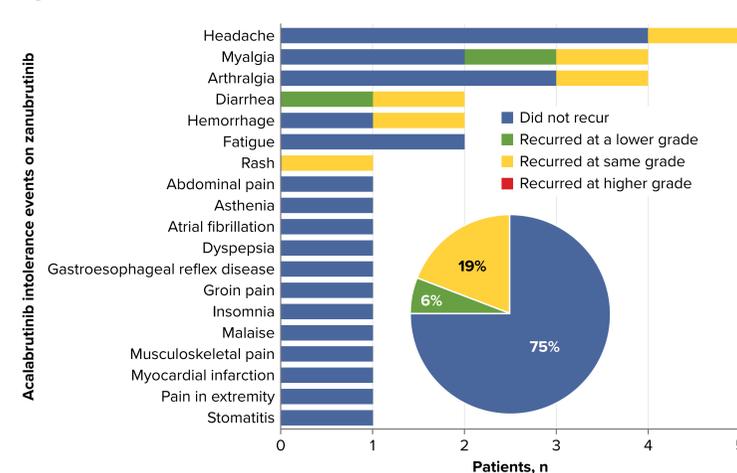
Table 2. Patient Disposition

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)

^aMyalgia (n=1), diarrhea (n=1). ^bDue 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)

^aAny grade events occurring in ≥2 patients or grade ≥3 events occurring in ≥1 patients. ^bSome 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 (%)	17 (94)
(95% CI)	(72.7, 99.9)
ORR (better than SD), n (%)	11 (61)
(95% CI)	(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)

^aIncludes 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

- Stephens DM, Byrd JC. Blood 2019;131(2):298-307
- Farber CM, et al. Leukemia 2022;36(1):120-128
- Miao AI, et al. Hematology 2018;2018(1):174-179
- Guo Y, et al. JAMA Oncol 2019;5(10):1562-1568
- Shadman M, et al. Cancer 2021;131(10):1911-1919
- 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; IC₅₀, 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 lymphocyte SD, once a day; SD, stable disease; SLL, small lymphocytic lymphoma; VGPR, very good partial response; WM, Waldenström macroglobulinemia.

DISCLOSURES

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