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Zanubrutinib in Acalabrutinib-Intolerant Patients With B-Cell Malignancies

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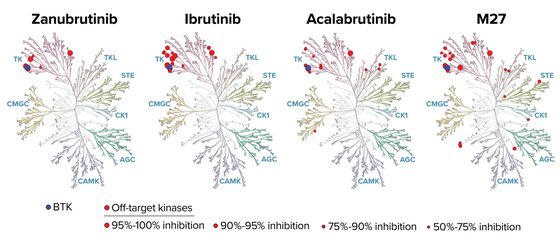
INTRODUCTION

- Bruton tyrosine kinase (BTK) inhibitors are a mainstay of treatment for B-cell malignancies; however, their use can be limited by adverse events (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 an ongoing phase 2 study (BGB-3111-215; NCT04116437) showed that zanubrutinib is well tolerated in patients who are intolerant of ibrutinib and/or acalabrutinib[5]
- Zanubrutinib demonstrated higher selectivity than ibrutinib, acalabrutinib, and acalabrutinib's major metabolite, M27, by kinase profiling (**Figure 1**)[5,6]
- Zanubrutinib, ibrutinib, acalabrutinib, and M27 (metabolite of acalabrutinib) demonstrated >50% inhibition of 7, 17, 15, and 23 kinases, respectively, of the 370 kinases tested
- Here, we report updated results on the tolerability and efficacy of zanubrutinib in patients intolerant of acalabrutinib (Cohort 2)

Figure 1. Kinase Selectivity of Zanubrutinib, Ibrutinib, Acalabrutinib, and Acalabrutinib Metabolite M27



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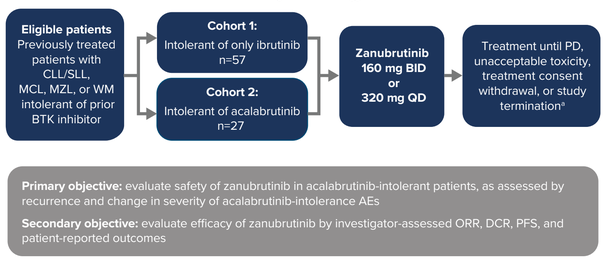
METHODS

- BGB-3111-215 is an ongoing phase 2 study (**Figure 2**) in patients with previously treated B-cell malignancies who were intolerant of acalabrutinib, as defined by 1 of the following:
  - Grade ≥1 nonhematologic toxicities with ≥3 recurrent episodes or lasting >7 days, or grade ≥3 of any duration
  - Grade ≥3 febrile neutropenia of any duration
  - Grade 4 heme toxicity that persisted to the point that the investigator chose to stop therapy due to toxicity, not progression
  - Inability to use acid-reducing agents or anticoagulants (eg, proton pump inhibitors, warfarin) due to concurrent acalabrutinib use
- Patients with Richter transformation or progressive disease (PD) while on prior BTK inhibitor treatment were excluded

Figure 2. BGB-3111-215 Study Design



ClinicalTrials.gov: NCT04116437; data cutoff: May 15, 2023
[a] Study is ongoing.
CLL, chronic lymphocytic leukemia; DCR, disease control rate; MCL, mantle cell lymphoma; MZL, marginal zone lymphoma; SLL, small lymphocytic lymphoma; WM, Waldenström macroglobulinemia.

RESULTS

Patients

- As of May 15, 2023, 27 acalabrutinib-intolerant patients had enrolled (**Table 1**); 13 of these patients were also intolerant of ibrutinib

Table 1. Patient Demographics and Baseline Characteristics

Characteristic	Acalabrutinib-Intolerant (n=27)
Indication, n (%)	
CLL	17 (63)
SLL	2 (7)
MCL	2 (7)
MZL	2 (7)
WM	4 (15)
Age, median (range), years	73 (51-87)
Sex, n (%)	
Male	17 (63)
Female	10 (37)
ECOG PS, n (%)	
0	18 (67)
1	7 (26)
2	2 (7)
No. of prior anticancer therapy regimens, median (range)	2 (1-6)
Prior BTK inhibitor, n (%)	
Ibrutinib monotherapy	12 (44)
Ibrutinib combination therapy	1 (4)
Acalabrutinib monotherapy	26 (96)
Acalabrutinib combination therapy	1 (4)
Cumulative acalabrutinib exposure, median (range), months	5.4 (0.5-33.7)
On-study zanubrutinib dosing regimen, n (%)	
160 mg BID	19 (70)
320 mg QD	8 (30)

CLL, chronic lymphocytic leukemia; ECOG PS, Eastern Cooperative Oncology Group performance status; MCL, mantle cell lymphoma; MZL, marginal zone lymphoma; SLL, small lymphocytic lymphoma; WM, Waldenström macroglobulinemia.

- Of 27 acalabrutinib-intolerant patients, 7 (26%) discontinued zanubrutinib treatment (**Table 2**) (AE, n=2; physician decision, n=2; withdrawal by patient, n=2; PD, n=1)

Table 2. Patient Disposition

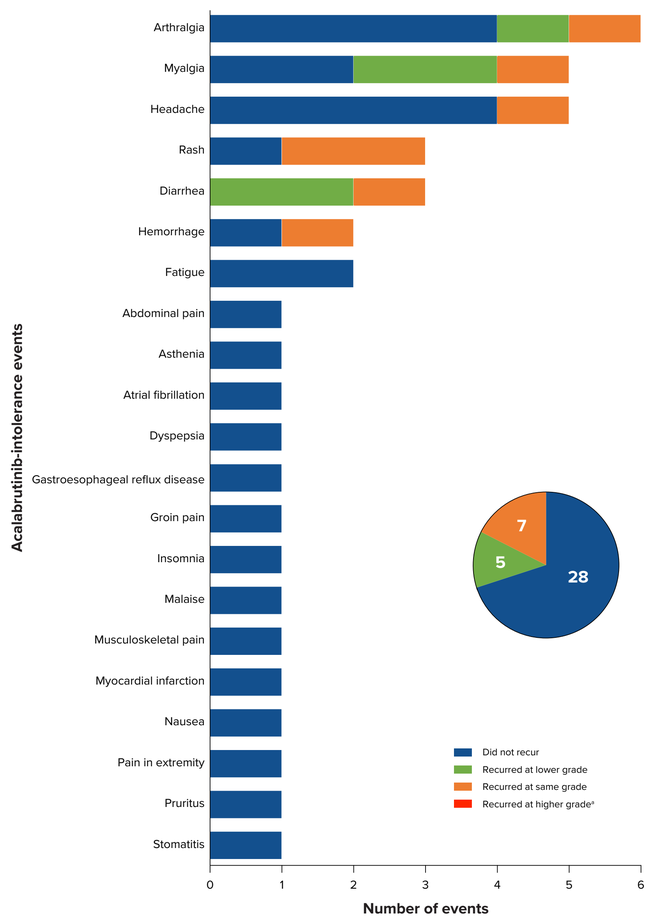
Patients, n (%)	Acalabrutinib-Intolerant (n=27)
Remaining on treatment	20 (74)
Remaining on study	23 (85)
Discontinued from treatment	7 (26)
AE	2 (7)[a]
Physician decision	2 (7)
Withdrawal by patient	2 (7)
PD	1 (4)
Death, n (%)	1 (4)
Zanubrutinib treatment duration, median (range), months	11.4 (0.5-32.2)
Survival follow-up, median (range), months	12.4 (1.6-32.2)

[a] Myalgia (n=1), diarrhea (n=1).

Safety

- Of 40 acalabrutinib-intolerance events that were reported by 27 patients, the most common (≥2 events) were arthralgia (n=6), headache (n=5), myalgia (n=5), diarrhea (n=3), rash (n=3), fatigue (n=2), and hemorrhage (n=2) (**Figure 3**)
- Most acalabrutinib-intolerance events (28 of 40; 70%) did not recur at any grade with zanubrutinib; of the 12 that did recur, none recurred at a higher severity
- Seventeen of 27 patients (63%) did not experience any recurrence of their prior acalabrutinib-intolerance events
- Two patients discontinued zanubrutinib due to recurrence of a prior acalabrutinib-intolerance event (grade 2 myalgia, n=1; and grade 3 diarrhea, n=1; both recurred at the same grade)
- Three of 27 patients (11%) experienced the same intolerance event (pain in extremity, diarrhea, and atrial fibrillation; n=1 each) with ibrutinib and acalabrutinib
  - Two (67%) did not have a recurrence of those events with zanubrutinib
  - One (33%) had a recurrence at a lower grade (diarrhea)

Figure 3. Recurrence of Acalabrutinib-Intolerance Events on Zanubrutinib



[a] No events recurred at a higher grade.

- No AEs led to death, and 2 events (7%) led to treatment discontinuation (**Table 3**)
- The most common grade ≥3 AE was neutrophil count decreased, which occurred in 3 patients (11%) (**Table 4**)
- Anemia and thrombocytopenia/platelet count decreased did not occur

Table 3. Adverse Event Summary

Patients, n (%)	Any Grade (n=27)
Serious AE	7 (26)
Leading to treatment discontinuation	2 (7)
Leading to dose interruption	16 (59)
Leading to dose reduction	6 (22)
Leading to death	0

CONCLUSIONS

- The median zanubrutinib exposure was 6 months longer than the reported cumulative acalabrutinib exposure before discontinuation (11.4 months vs 5.4 months, respectively)
- Most patients (63%) did not experience any recurrence of their prior acalabrutinib-intolerance event
- Of the 40 acalabrutinib-intolerance events, 28 did not recur; of the 12 that did recur, none recurred at a higher grade
- Zanubrutinib provided clinically meaningful benefit in efficacy-evaluable patients who were previously intolerant of acalabrutinib, as measured by a disease control rate of 96%
- The results from this study demonstrate that zanubrutinib may be a viable treatment option for patients who are intolerant of acalabrutinib

Table 4. Select Adverse Events[a]

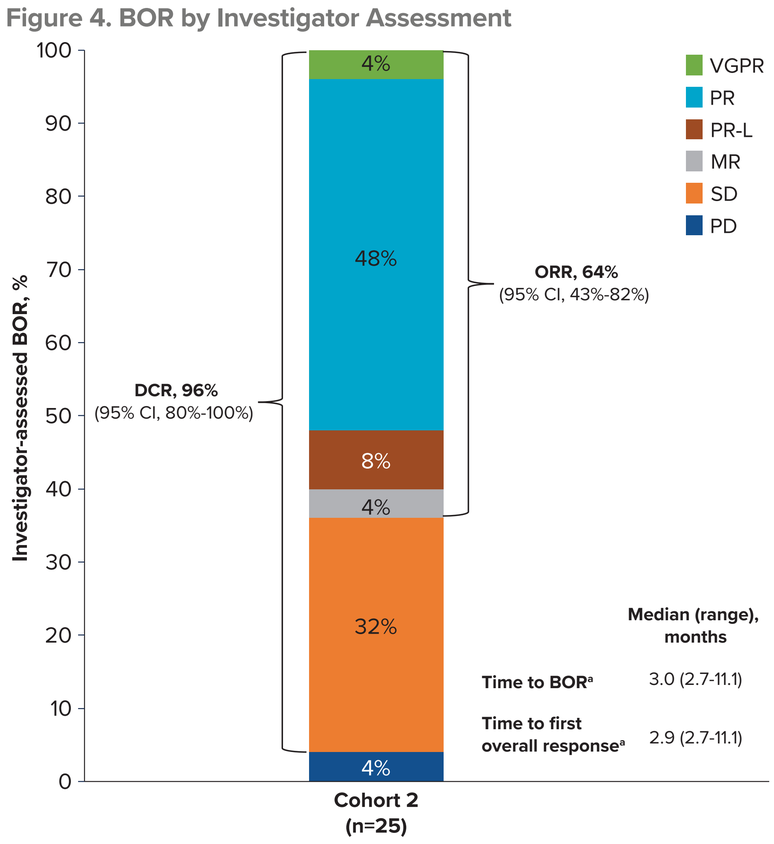
Patients, n (%)	Any Grade (n=27)	Grade ≥3 (n=27)
Any AE	26 (96)	12 (44)[b]
Neutrophil count decreased	3 (11)	3 (11)
Neutropenia	2 (7)	2 (7)
Diarrhea	12 (44)	1 (4)
Hypertension	6 (22)	1 (4)
COVID-19	5 (19)	1 (4)
Maculopapular rash	3 (11)	1 (4)
Abdominal pain	2 (7)	1 (4)
Bacteremia	1 (4)	1 (4)
Cellulitis	1 (4)	1 (4)
COVID-19 pneumonia	1 (4)	1 (4)
Fall	1 (4)	1 (4)
Febrile neutropenia	1 (4)	1 (4)
Gastroenteritis salmonella	1 (4)	1 (4)
Hip fracture	1 (4)	1 (4)
Pneumonia	1 (4)	1 (4)
Small intestinal obstruction	1 (4)	1 (4)

[a] AEs shown in this table occurred in at least 1 patient at grade ≥3 severity; any-grade data for these select AEs are also shown.
[b] Some patients had more than 1 grade ≥3 event.

Efficacy

- Among the 25 efficacy-evaluable patients on zanubrutinib, 24 (96%) achieved SD or better (SD, 32%) and 16 (64%) achieved minor response (MR) or better (**Figure 4**)
- Twelve of 17 efficacy-evaluable patients (71%) with CLL/SLL on zanubrutinib achieved a partial response with lymphocytosis (PR-L) or better

Figure 4. BOR by Investigator Assessment



[a] In patients with a BOR better than SD.
BOR, best overall response; DCR, disease control rate; MR, minor response; PR-L, partial response with lymphocytosis.

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