

Zanubrutinib is Well Tolerated and Effective in Acalabrutinib-Intolerant Patients With B-Cell Malignancies: A Long-Term Follow-Up

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CONCLUSIONS

- With three additional years of follow-up, these data continue to demonstrate that patients with prior intolerance of acalabrutinib can safely and efficaciously switch to zanubrutinib
- Despite longer median treatment duration with zanubrutinib vs prior acalabrutinib (18.2 vs 5.7 months, respectively), 67% of prior acalabrutinib-intolerance events did not recur
- Switching treatment to zanubrutinib resulted in a disease control rate of 92% in efficacy-evaluable patients
- In summary, in acalabrutinib-intolerant patients, switching to zanubrutinib may be a well-tolerated and effective treatment option

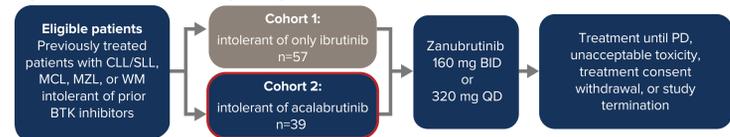
INTRODUCTION

- While Bruton tyrosine kinase (BTK) inhibitors are a mainstay of treatment for B-cell malignancies, their use can be limited by adverse events (AEs)
- In clinical trials, 15%-23% of patients treated with acalabrutinib discontinued treatment due to AEs¹⁻³
- Zanubrutinib is a highly potent and selective next-generation BTK inhibitor designed to maximize BTK occupancy, providing greater efficacy with fewer off-target bindings compared with other BTK inhibitors⁴
- Previous results from this phase 2 study (BGB-3111-215; NCT04116437) showed that zanubrutinib was well tolerated in patients with B-cell malignancies intolerant of ibrutinib and/or acalabrutinib⁴
- Here, we report long-term results, with 3 additional years of follow-up, of the tolerability and efficacy of zanubrutinib in patients intolerant of acalabrutinib (i.e, study cohort 2 only; see **Figure 1**)

METHODS

- Eligible patients had chronic lymphocytic leukemia/small lymphocytic lymphoma, Waldenström macroglobulinemia, mantle cell lymphoma, or marginal zone lymphoma and were intolerant of acalabrutinib and/or ibrutinib (**Figure 1**)
- Acalabrutinib intolerance was defined as an unacceptable toxicity where, in the opinion of the investigator, treatment should be discontinued despite optimal supportive care as a result of one of the following:
 - Grade ≥ 1 nonhematologic toxicities with ≥ 3 recurrent episodes or episodes lasting >7 days, or grade ≥ 3 toxicities of any duration
 - Grade 3 neutropenia with infection or fever of any duration
 - Grade 4 heme toxicity persisting 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 whose disease progressed with prior BTK inhibitor therapy were excluded

Figure 1. BGB-3111-215 Study Design



Primary objective: evaluate safety of zanubrutinib in acalabrutinib-intolerant patients, as assessed by recurrence and change in severity of acalabrutinib-intolerance AEs

Secondary objective: evaluate efficacy of zanubrutinib by investigator-assessed ORR, DCR, PFS, and patient-reported outcomes

Abbreviations: AE, adverse event; BID, twice daily; BTK, Bruton tyrosine kinase; CLL, chronic lymphocytic leukemia; DCR, disease control rate; MCL, mantle cell lymphoma; MZL, marginal zone lymphoma; ORR, overall response rate; PD, progressive disease; PFS, progression-free survival; QD, once daily; SLL, small lymphocytic lymphoma; WM, Waldenström macroglobulinemia.

RESULTS

Patients

- As of May 1, 2025, 39 patients intolerant of prior acalabrutinib had received zanubrutinib (**Table 1**)
- Patients received a median of 2 prior therapies (range, 1-6), and 14 patients (36%) were also intolerant of prior ibrutinib

Table 1. Patient Demographics and Baseline Characteristics

Characteristic	Acalabrutinib intolerant (n=39)
Indication, n (%)	
CLL	28 (71.8)
WM	4 (10.3)
MCL	3 (7.7)
SLL	2 (5.1)
MZL	2 (5.1)
Age, median (range), years	71.0 (51-87)
Sex, n (%)	
Male	19 (48.7)
Female	20 (51.3)
ECOG PS, n (%)	
0	27 (69.2)
1	10 (25.6)
2	2 (5.1)
No. of prior anticancer therapy regimens, median (range)	2 (1-6)
Prior BTK inhibitor, n (%)	
Acalabrutinib monotherapy	35 (89.7)
Acalabrutinib combination therapy	4 (10.3)
Ibrutinib monotherapy	13 (33.3)
Ibrutinib combination therapy	1 (2.6)
Cumulative acalabrutinib exposure, median (range), months	5.7 (0.2-68.6)

Abbreviations: BTK, Bruton tyrosine kinase; 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 the 39 enrolled patients, 26 (67%) received zanubrutinib 160 mg twice daily and 13 (33%) received zanubrutinib 320 mg once daily
- At the data cutoff, 25 patients (64%) were still on zanubrutinib (**Table 2**)

Table 2. Patient Disposition

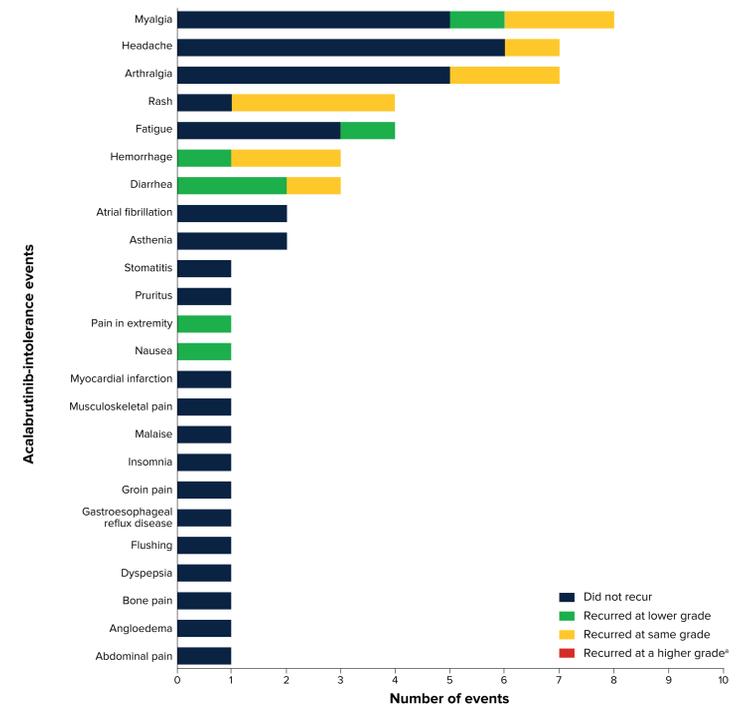
Patients, n (%)	Acalabrutinib intolerant (n=39)
Remaining on study	32 (82.1)
Remaining on treatment	25 (64.1)
Discontinued from treatment	14 (35.9)
AE	7 (17.9) ^a
Physician decision	4 (10.3)
PD	2 (5.1)
Withdrawal by patient	1 (2.6)
Death	3 (7.7) ^b
Zanubrutinib treatment duration, median (range), months	18.2 (0.5-55.8)
Study follow-up, median (range), months	28.5 (1.9-55.8)

Abbreviations: AE, adverse event; PD, progressive disease.

Safety

- Overall, 55 acalabrutinib-intolerance events were reported among the 39 patients
- Of the 55 acalabrutinib-intolerance events, 37 (67%) did not recur with zanubrutinib and of the 18 acalabrutinib-intolerance events that did recur with zanubrutinib, none recurred at a higher severity (11 recurred at the same grade and 7 at a lower grade) (**Figure 2**)
- Of the 39 patients, 24 (62%) did not have any acalabrutinib intolerance events recur as adverse events on zanubrutinib
- Three patients discontinued zanubrutinib due to an event with the same preferred term as that which led to acalabrutinib discontinuation (myalgia, rash, and diarrhea; all recurred at the same grade as with prior acalabrutinib)
- Five patients experienced intolerance events with the same preferred term while on prior acalabrutinib and while on ibrutinib treatment
 - Of these, four had either no recurrence or only grade 1 recurrence while on zanubrutinib
 - One patient had grade 3 diarrhea with all three BTK inhibitors

Figure 2. Recurrence of Acalabrutinib-Intolerance Events With Zanubrutinib



^aNo events recurred at a higher grade.

- No treatment-emergent adverse events (TEAEs) led to death (**Table 3**)
- The most common TEAEs (any grade occurring in $\geq 20\%$ of patients) are shown in **Table 4**

Table 3. Overall Summary of TEAEs in Patients on Zanubrutinib

Patients, n (%)	Acalabrutinib intolerant (n=39)
Serious TEAE	10 (25.6)
Grade ≥ 3 TEAE	19 (48.7) ^a
Leading to treatment discontinuation	6 (15.4)
Leading to dose interruption	30 (76.9)
Leading to dose reduction	13 (33.3)
Grade 5 TEAE	0

Abbreviations: TEAE, treatment-emergent adverse event.

Table 4. Most Common TEAEs (Any Grade Occurring in $\geq 20\%$) in Patients on Zanubrutinib

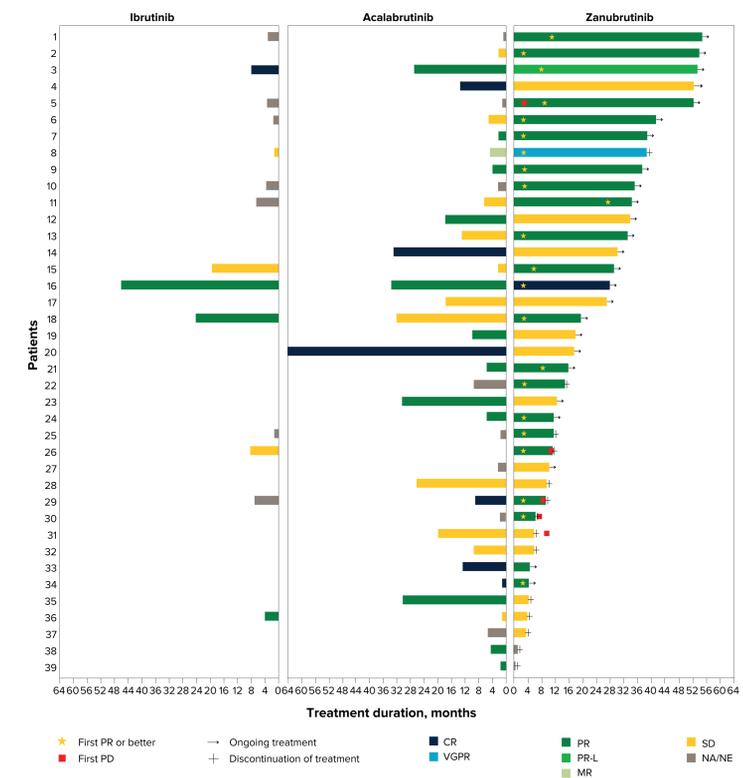
Patients, n (%)	Any grade (n=39)	Grade ≥ 3 (n=39)
Any TEAE	39 (100)	19 (48.7)
Diarrhea	14 (35.9)	1 (2.6)
Fatigue	13 (33.3)	1 (2.6)
COVID-19	12 (30.8)	1 (2.6)
Arthralgia	10 (25.6)	0
Cotusion	10 (25.6)	0
Hypertension	10 (25.6)	5 (12.8)
Cough	8 (20.5)	0
Dizziness	8 (20.5)	0

Abbreviation: TEAE, treatment-emergent adverse event.

Efficacy

- In 39 efficacy-evaluable patients, the disease control rate was 92%, with 22 patients (56%) having a response better than stable disease (**Figure 3**)
- The progression-free survival rate at 24 months was 84% (median was not reached)

Figure 3. Treatment Duration and Best Overall Response per Investigator Assessment



Abbreviations: CR, complete response; MR, minor response; NA, not applicable; NE, not evaluable; PD, progressive disease; PR, partial response; PR-L, partial response with lymphocytosis; SD, stable disease; VGPR, very good partial response.

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