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

5663

Mazyar Shadman,[1,2] Ian W. Flinn,[3] Moshe Y. Levy,[4] Steven W. Papish,[5] John M. Burke,[6] Jamal Misleh,[7] Jennifer L. Cultrera,[8] Habte A. Yimer,[9] Edwin C. Kingsley,[10] Charles M. Farber,[11] James D'Olimpio,[12] Nan Sun,[13] Adam Idoine,[14] Jeff P. Sharman[15]

[1]Fred Hutchinson Cancer Center, Seattle, WA, USA; [2]University of Washington, Seattle, WA, USA; [3]Tennessee Oncology/OneOncology, Nashville, TN, USA; [4]Texas Oncology-Baylor Charles A. Sammons Cancer Center, Dallas, TX, USA; [5]Summit Medical Group-MD Anderson Cancer Center, Morristown, NJ, USA; [6]Rocky Mountain Cancer Centers, US Oncology Research, Aurora, CO, USA; [7]Medical Oncology Hematology Consultants, Newark, DE, USA; [8]Florida Cancer Specialists & Research Institute, Leesburg, FL, USA; [9]Texas Oncology-Tyler, US Oncology Research, Tyler, TX, USA; [10]Comprehensive Cancer Centers of Nevada, Las Vegas, NV, USA; [11]Atlantic Hematology Oncology, Morristown Medical Center, Morristown, NJ, USA; [12]Clinical Research Alliance, Westbury, NY, USA; [13]BeOne Medicines, Ltd, Shanghai, China; [14]BeOne Medicines, Ltd, San Carlos, CA, USA; [15]Willamette Valley Cancer Institute and Research Center, US Oncology Research, Eugene, OR, USA

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

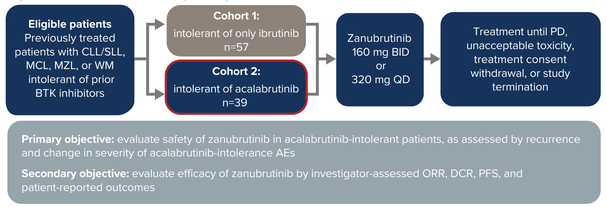
INTRODUCTION

- 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 AEs[1-3]
- 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 inhibitors[4]
- 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 acalabrutinib[4]
- 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

Data cutoff: May 1, 2025.

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)

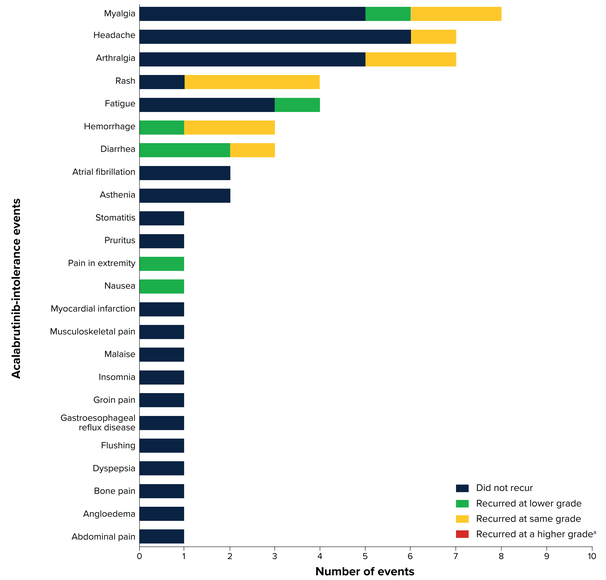
[a]Adverse events leading to discontinuation from treatment were diarrhea (n=2) and rash, maculo-papular rash, skin toxicity, neutropenia, fall, and myalgia (n=1 each). [b]Causes of deaths were progressive disease, unknown, and other (cardiac arrest >30 days after treatment discontinuation) (n=1 each).

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



[a]No 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 ≥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

[a]The most common grade ≥3 adverse events (≥2 patients) included hypertension (n=5), neutrophil count decreased (n=4), neutropenia (n=3), cellulitis (n=2) and COVID-19 pneumonia (n=2).

Abbreviation: TEAE, treatment-emergent adverse event.

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

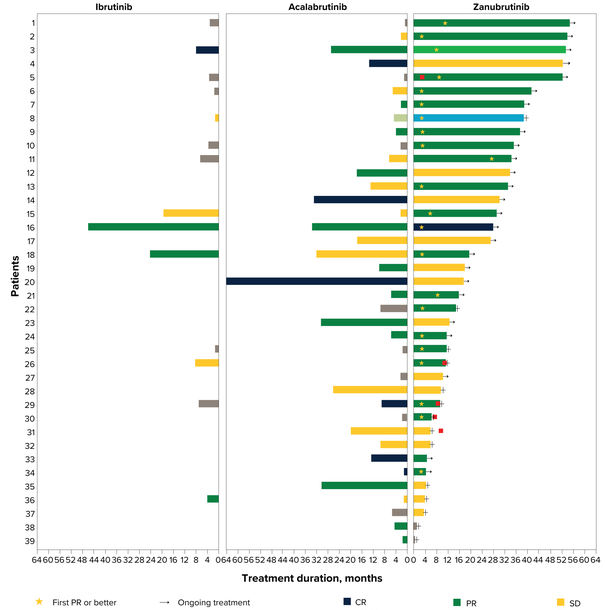
Patients, n (%)	Any grade (n=39)	Grade ≥3 (n=39)
Any TEAE	39 (100)	19 (48.7)
Diarrhea	14 (35.9)	1 (2.6)
Fatigue	13 (33.3)	1 (2.6)
COVID-19	12 (30.8)	1 (2.6)
Arthralgia	10 (25.6)	0
Contusion	10 (25.6)	0
Hypertension	10 (25.6)	5 (12.8)
Cough	8 (20.5)	0
Dizziness	8 (20.5)	0

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.

REFERENCES

1. Sharman JP, et al. *Blood*. 2023;142(suppl 1):636.
2. Ghia P, et al. *Hemasphere*. 2022;6(12):e801.
3. Seymour JF, et al. *Blood*. 2023;142(8):687-699.
4. Shadman M, et al. *Lancet Haematol*. 2023;10(1):e35-e45.

ACKNOWLEDGMENTS

The authors thank the patients and their families, investigators, co-investigators, and the study teams at each of the participating centers. This study was sponsored by BeOne Medicines, Ltd. Medical writing support was provided by Alex Coulthard, BSc, of Nucleus Global, an Inizio company, and supported by BeOne Medicines.

CORRESPONDENCE: Mazyar Shadman, mshadman@fredhutch.org

Presented at the 67th ASH Annual Meeting and Exposition; December 6-9, 2025; Orlando, FL