# Zanubrutinib Is Well Tolerated and Effective in Acalabrutinib-Intolerant Patients With B-Cell Malignancies

P232

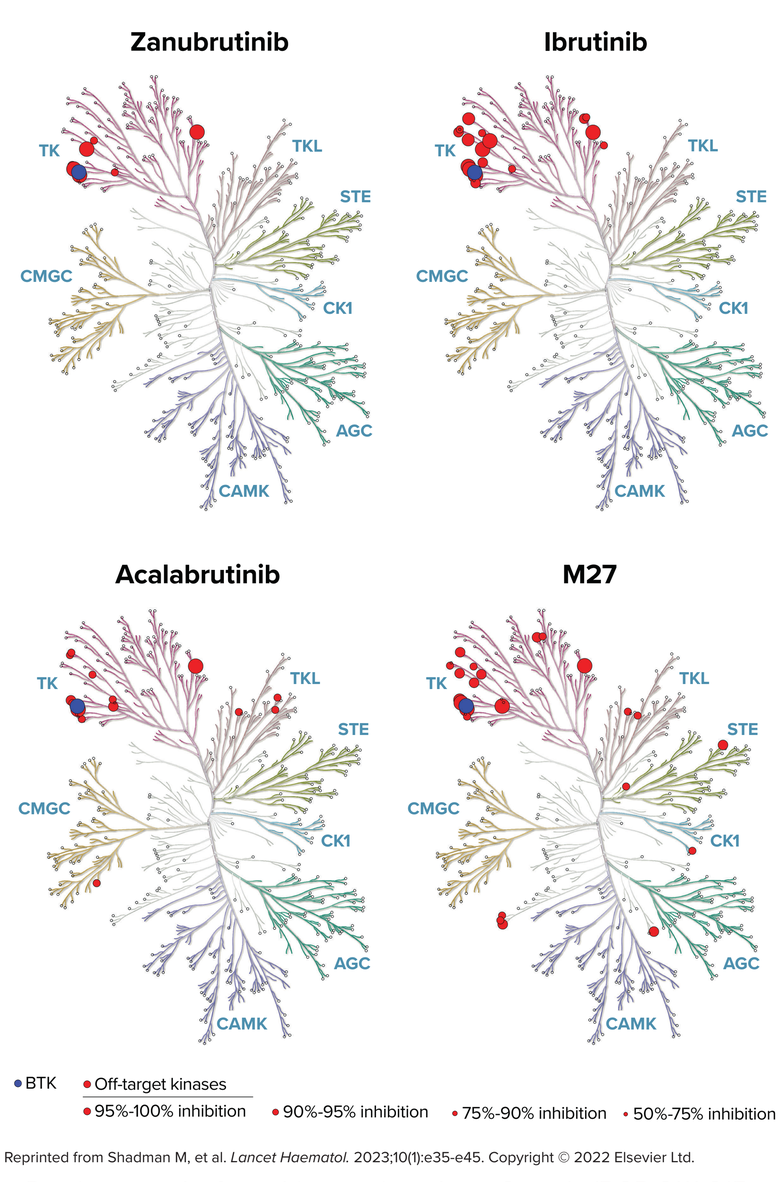
Emmanuelle Ferrant,[1] Mazyar Shadman,[2,3] Ian W. Flinn,[4] Moshe Y. Levy,[5] Benjamin B. Freeman,[6] Ben Zhang,[7] John M. Burke,[8] Jennifer L. Cultrera,[9] Habte A. Yimer,[10] Edwin C. Kingsley,[11] Charles M. Farber,[12] James D'Olimpio,[13] Hui Yao,[14] Adam Idoine,[15] Qi An,[15] Jeff P. Sharman[16]

[1]CHU de Lyon-Sud, Lyon-Sud, France; [2]Fred Hutchinson Cancer Center, Seattle, WA, USA; [3]University of Washington, Seattle, WA, USA; [4]Tennessee Oncology/OneOncology, Nashville, TN, USA; [5]Texas Oncology-Baylor Charles A. Sammons Cancer Center, Dallas, TX, USA; [6]Summit Medical Group, Florham Park, NJ, USA; [7]Minnesota Oncology Clinic, Burnsville, MN, USA; [8]Rocky Mountain Cancer Centers, US Oncology Research, Aurora, CO, USA; [9]Florida Cancer Specialists & Research Institute, Leesburg, FL, USA; [10]Texas Oncology-Tyler, US Oncology Research, Tyler, TX, USA; [11]Comprehensive Cancer Centers of Nevada, Las Vegas, NV, USA; [12]Atlantic Hematology Oncology, Morristown Medical Center, Morristown, NJ, USA; [13]Clinical Research Alliance, Westbury, NY, USA; [14]BeiGene (Shanghai) Co, Ltd, Shanghai, China; [15]BeiGene USA, Inc, San Mateo, CA, USA; [16]Willamette Valley Cancer Institute and Research Center, US Oncology Research, Eugene, OR, USA

## 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 next-generation BTK inhibitor designed to maximize BTK occupancy and potency as well as increased selectivity to increase efficacy and to minimize off-target kinase binding and associated AEs[4]
  - Zanubrutinib demonstrated higher selectivity than ibrutinib, acalabrutinib, and acalabrutinib's major metabolite, M27, by kinase profiling (**Figure 1**)[5,6]

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



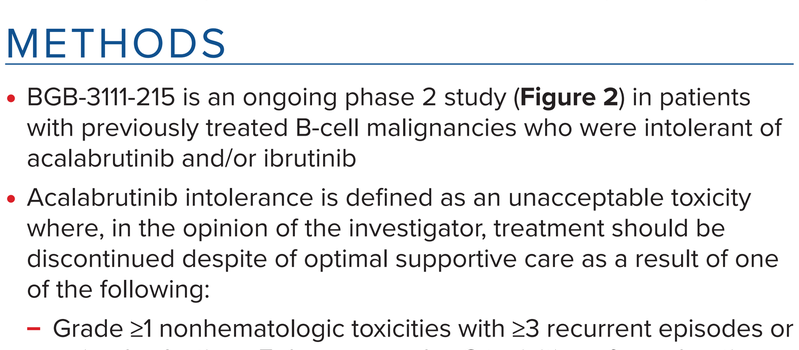

Reprinted from Shadman M, et al. *Lancet Haematol.* 2023;10(1):e35-e45. Copyright © 2022 Elsevier Ltd.

- Previous results from this ongoing phase 2 study (BGB-3111-215; NCT04116437) showed that zanubrutinib was well tolerated in patients who were intolerant of ibrutinib and/or acalabrutinib[5]
- We report updated results on the tolerability and efficacy of zanubrutinib in patients intolerant of acalabrutinib (cohort 2)

## 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 and/or ibrutinib
- Acalabrutinib intolerance is defined as an unacceptable toxicity where, in the opinion of the investigator, treatment should be discontinued despite of 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
- Data is reported for both the safety analysis set (SAS) and the efficacy evaluable set (EES)
  - The EES is defined as patients in the SAS who had a baseline disease assessment and ≥1 post-baseline disease assessment; patients who discontinued the study due to AEs or death prior to their first scheduled disease assessment are included in the EES
- Patients with Richter transformation or progressive disease (PD) while receiving prior BTK inhibitor treatment were excluded

**Figure 2. BGB-3111-215 Study Design**




Data cutoff: May 1, 2024.
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, 2024, 35 patients intolerant of prior acalabrutinib had enrolled (**Table 1**); 14 of these patients were also intolerant of prior ibrutinib

**Table 1. Patient Demographics and Baseline Characteristics**

| Characteristic | Acalabrutinib-intolerant (n=35) |
|---|---|
| **Indication, n (%)** | |
| CLL | 25 (71.4) |
| WM | 4 (11.4) |
| SLL | 2 (5.7) |
| MCL | 2 (5.7) |
| MZL | 2 (5.7) |
| **Age, median (range), years** | 71 (51-87) |
| **Sex, n (%)** | |
| Male | 19 (54.3) |
| Female | 16 (45.7) |
| **ECOG PS, n (%)** | |
| 0 | 23 (65.7) |
| 1 | 10 (28.6) |
| 2 | 2 (5.7) |
| **No. of prior anticancer therapy regimens, median (range)** | 2 (1-6) |
| **Prior BTK inhibitor, n (%)** | |
| Acalabrutinib monotherapy | 32 (91.4) |
| Acalabrutinib combination therapy | 3 (8.6) |
| Ibrutinib monotherapy | 13 (37.1) |
| Ibrutinib combination therapy | 1 (2.9) |
| **Cumulative acalabrutinib exposure, median (range), months** | 5.7 (0.2-68.6) |

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 35 acalabrutinib-intolerant patients, 23 (65.7%) received zanubrutinib 160 mg twice daily, and 12 (34.3%) received 320 mg once daily
- 11 patients (31.4%) discontinued zanubrutinib treatment (**Table 2**)

**Table 2. Patient Disposition**

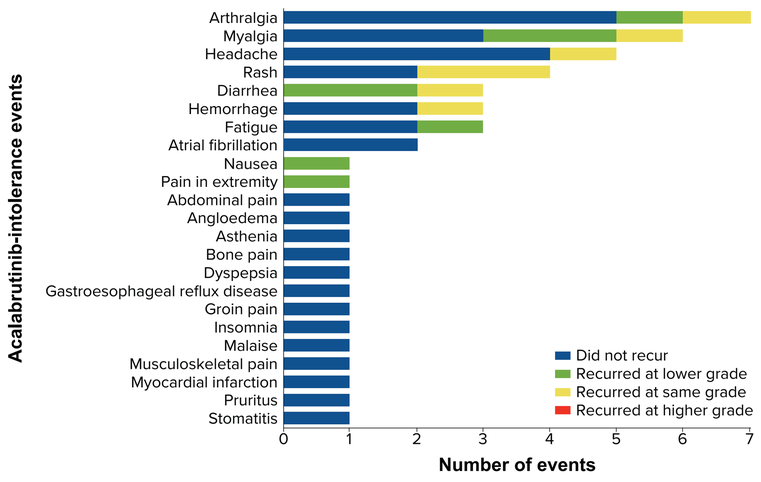
| Patients, n (%) | Acalabrutinib-intolerant (n=35) |
|---|---|
| **Remaining on study** | 31 (88.6)[a] |
| **Remaining on treatment** | 24 (68.6) |
| **Discontinued from treatment** | 11 (31.4) |
| AE | 5 (14.3)[b] |
| Physician decision | 3 (8.6) |
| PD | 2 (5.7) |
| Withdrawal by patient | 1 (2.9) |
| **Death, n (%)** | 1 (2.9)[c] |
| **Zanubrutinib treatment duration, median (range), months** | 14.8 (0.1-43.8) |
| **Survival follow-up, median (range), months** | 18.9 (0.1-43.8) |

[a] Study discontinuations were due to patient withdrawal (n=2), lost to follow-up (n=1), and death (n=1). [b] Diarrhea (n=2), skin toxicity, myalgia, and rash (n=1 for each). [c] PD.
AE, adverse event; PD, progressive disease.

### Safety

- 23 of 35 patients (66%) did not experience any recurrence of the prior acalabrutinib-intolerance events
- Most acalabrutinib-intolerance events (33 of 48 [69%]) did not recur at any grade with zanubrutinib (**Figure 3**)
- Of the 15 that did recur, none recurred at a higher severity (8 at a lower grade; 7 at the same grade)
- 3 patients discontinued zanubrutinib due to recurrence of a prior acalabrutinib-intolerance event (myalgia, rash, and diarrhea; all recurred at the same grade)
- Of the 4 patients (11%) who experienced the same intolerance event with prior ibrutinib and acalabrutinib:
  - 2 patients (1 experiencing atrial fibrillation and the other hemorrhage) did not have a recurrence of those events with zanubrutinib
  - 2 patients (1 experiencing grade 3 diarrhea with ibrutinib and grade 2 with acalabrutinib; the other experiencing grade 2 pain in extremity with both ibrutinib and acalabrutinib) had a recurrence with zanubrutinib at a lower grade (both grade 1)

**Figure 3. Recurrence of Acalabrutinib-Intolerance Events on Zanubrutinib**




## CONCLUSIONS

- Zanubrutinib was well-tolerated in patients with prior acalabrutinib intolerance
- Among the minority of recurrent events, none recurred at a higher grade, and few (3/15) led to discontinuation of zanubrutinib
- Zanubrutinib provided a clinically meaningful efficacy benefit in patients who were previously intolerant of acalabrutinib, as measured by a disease control rate of 94%, maintaining response after treatment, and deepening of response on treatment with zanubrutinib
- The results from this study demonstrated that switching to zanubrutinib may be an excellent treatment option for patients who are intolerant of other covalent BTK inhibitors, ibrutinib[5] and acalabrutinib

- No AEs led to death (**Table 3**)
- The most common TEAEs (any grade occurring in ≥15% of patients) are shown in **Table 4**
  - The most common grade ≥3 AE was neutrophil count decreased, which occurred in 3 patients (8.6%)
  - Anemia and thrombocytopenia did not occur at any grade

**Table 3. Overall Summary of TEAEs for Patients on Zanubrutinib**

| Patients, n (%) | Any Grade (n=35) |
|---|---|
| **Serious TEAE** | 9 (25.7) |
| **Grade ≥3 TEAE** | 17 (48.6)[a] |
| **Leading to treatment discontinuation** | 5 (14.3) |
| **Leading to dose interruption** | 23 (65.7) |
| **Leading to dose reduction** | 8 (22.9) |
| **Grade 5 TEAE** | 0 |

[a] The most common grade ≥3 AEs (≥2 patients) included cellulitis, COVID-19 pneumonia, hypertension, neutrophil count decreased, and neutropenia.
SAE, serious adverse event; TEAE, treatment-emergent adverse event.

**Table 4. Most Common TEAEs (Any Grade Occurring in ≥15%) in Patients on Zanubrutinib**

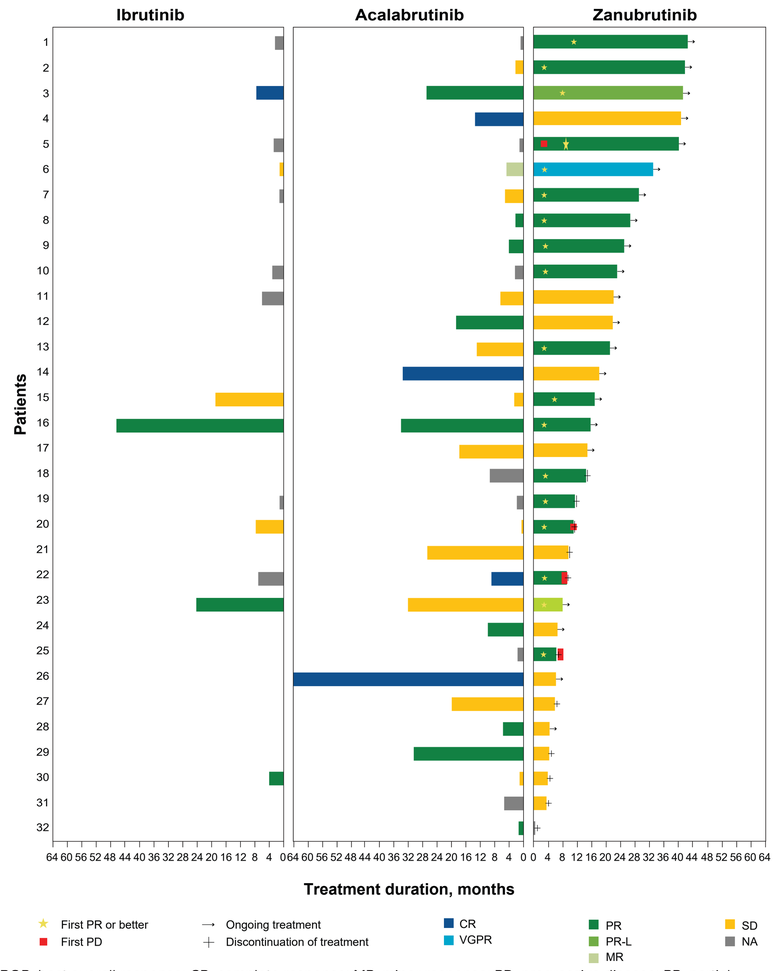
| Patients, n (%) | Any Grade (n=35) | Grade ≥3 (n=35) |
|---|---|---|
| **Any TEAE** | 33 (94.3) | 17 (48.6) |
| Arthralgia | 8 (22.9) | – |
| Contusion | 6 (17.1) | – |
| Cough | 8 (22.9) | – |
| COVID-19 | 9 (25.7) | 1 (2.9) |
| Diarrhea | 12 (34.3) | 1 (2.9) |
| Fatigue | 10 (28.6) | 1 (2.9) |
| Hypertension | 8 (22.9) | 2 (5.7) |

TEAE, treatment-emergent adverse event.

### Efficacy

- In the 32 efficacy-evaluable patients, the disease control rate was 93.8% (95% CI, 79.2%-99.2%). Thirteen patients (40.6%) had a best response of stable disease and 17 patients (53.1%) had a better response; 1 patient (3.1%) had PD (**Figure 4**)

**Figure 4. Treatment Duration With BOR by Investigator Assessment**




BOR, best overall response; CR, complete response; MR, minor response; PD, progressive disease; PR, partial response; PR-L, partial response with lymphocytosis; SD, stable disease; VGPR, very good partial response.

## 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. *Haematologica*. 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*. 2023;10(1):e35-e45.
6. Shadman M, et al. *Blood*. 2021;138(suppl 1). Abstract 1410.

## 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 BeiGene, Ltd. Medical writing support was provided by Nancy Tang, PharmD, of Nucleus Global, an Inizio company, and supported by BeiGene.

*The author's Conflict of Interest (COI) disclosures may be obtained through the Quick Response (QR) code*

*CORRESPONDENCE: Emmanuelle Ferrant, emmanuelle.ferrant2@chu-lyon.fr*

*Presented at the 45th SFH Annual Meeting; April 2-4, 2025; Paris, France*
*Data originally presented at the 66th ASH Annual Meeting and Exposition; December 7-10, 2024; San Diego, CA. Abstract 4632*