XXXI ZJAZD POLSKIEGO TOWARZYSTWA HEMATOLOGÓW TRANSFUZJOLOGÓW
KATOWICE 14-16 września 2023 r.

Updated Safety and Efficacy Results of Zanubrutinib in Patients With B-Cell Malignancies Who Are Intolerant of Ibrutinib and/or Acalabrutinib

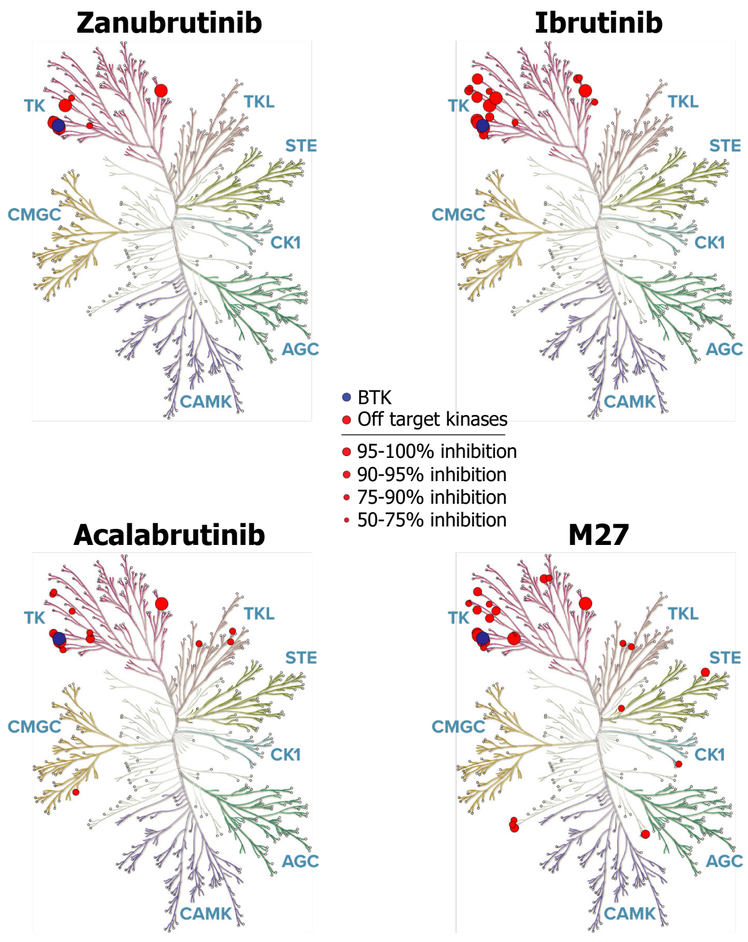
Sebastian Grosicki,[1] Mazyar Shadman,[2] Moshe Y. Levy,[3] John M. Burke,[4] Jennifer L. Cultrera,[5] Jamal Misleh,[6] Jeff P. Sharman,[7] Syed F. Zafar,[8] Kunthel By,[9] Aileen Cohen,[9] Rocco Crescenzo,[9] Adam Idoine,[9] Ian W. Flinn[10]

[1]Medical University of Silesia, Katowice, Poland; [2]Fred Hutchinson Cancer Research Center, University of Washington, Seattle, WA, USA; [3]Texas Oncology-Baylor Charles A. Sammons Cancer Center, Dallas, TX, USA; [4]Rocky Mountain Cancer Centers, Aurora, CO, USA; [5]Florida Cancer Specialists and Research Institute, Leesburg, FL, USA; [6]Medical Oncology Hematology Consultants PA, Newark, DE, USA; [7]Willamette Valley Cancer Institute and Research Center, Eugene, OR, USA; [8]Florida Cancer Specialists and Research Institute, Fort Myers, FL, USA; [9]BeiGene USA, Inc, San Mateo, CA, USA; [10]Sarah Cannon Research Institute/Tennessee Oncology, Nashville, TN, USA

INTRODUCTION

- Patients with B-cell malignancies treated with BTK inhibitors require continuous therapy[1]
- Ibrutinib and acalabrutinib are effective; however, many patients discontinue therapy because they experience treatment-related intolerance potentially caused by off-target kinase binding[2]
- Zanubrutinib is a next-generation BTK inhibitor designed to maximize tolerability by minimizing off-target kinase binding and associated AEs[3]
- Kinase profiling indicated that zanubrutinib had demonstrated higher selectivity than ibrutinib, acalabrutinib, and acalabrutinib's major metabolite (M27) (**Figure 1**)[4,5]

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.

- This phase 2 study (BGB-3111-215; NCT04116437) demonstrated that zanubrutinib is well tolerated in patients previously intolerant of ibrutinib and/or acalabrutinib at a median follow-up of 12.0 months[4]
- Here, we report updated safety and efficacy results from the BGB-3111-215 study at a median follow-up of 25.2 months

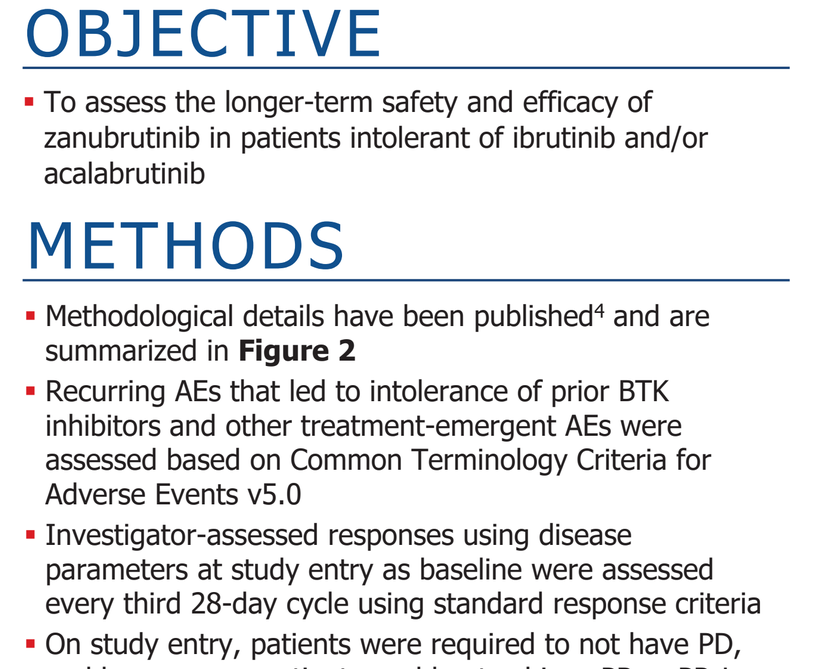
OBJECTIVE

- To assess the longer-term safety and efficacy of zanubrutinib in patients intolerant of ibrutinib and/or acalabrutinib

METHODS

- Methodological details have been published[4] and are summarized in **Figure 2**
- Recurring AEs that led to intolerance of prior BTK inhibitors and other treatment-emergent AEs were assessed based on Common Terminology Criteria for Adverse Events v5.0
- Investigator-assessed responses using disease parameters at study entry as baseline were assessed every third 28-day cycle using standard response criteria
- On study entry, patients were required to not have PD, and hence some patients could not achieve PR or PR-L on study
- Safety was assessed in all patients who received at least one dose of zanubrutinib; patients were considered evaluable for efficacy if they had at least one baseline and postbaseline disease assessment or discontinued the study due to AEs or death prior to their first disease assessment

Figure 2. Study Design



CLL/SLL, chronic lymphocytic leukemia/small lymphocytic lymphoma; ECOG PS, Eastern Cooperative Oncology Group performance status; MCL, mantle cell lymphoma; MZL, marginal zone lymphoma; WM, Waldenström macroglobulinemia.
[a] Study enrollment and follow-up are ongoing.

RESULTS

- As of January 3, 2023, 82 patients had enrolled; 57 patients (69.5%) were intolerant of only ibrutinib and 25 (30.5%) of acalabrutinib (acalabrutinib only, n=14; both acalabrutinib and ibrutinib, n=11) (**Table 1**)
- Most patients experienced >1 intolerance event on prior BTK inhibitors, with 124 ibrutinib-intolerance events occurring among 68 patients and 37 acalabrutinib-intolerance events occurring among 25 patients

Table 1. Baseline Characteristics and Patient Demographics

Characteristic	Ibrutinib intolerant (n=57)	Acalabrutinib ± ibrutinib intolerant (n=25)	Total (N=82)
Indication, n (%)			
CLL	38 (66.7)	15 (60.0)	53 (64.6)
SLL	6 (10.5)	2 (8.0)	8 (9.8)
MCL	2 (3.5)	2 (8.0)	4 (4.9)
MZL	2 (3.5)	2 (8.0)	4 (4.9)
WM	9 (15.8)	4 (16.0)	13 (15.9)
Age, median (range), years	71.0 (49-91)	74.0 (51-87)	71.5 (49-91)
Sex, n (%)			
Male	30 (52.6)	15 (60.0)	45 (54.9)
Female	27 (47.4)	10 (40.0)	37 (45.1)
ECOG PS, n (%)			
0	33 (57.9)	16 (64.0)	49 (59.8)
1	24 (42.1)	7 (28.0)	31 (37.8)
2	0 (0)	2 (8.0)	2 (2.4)
No. of prior anticancer therapy regimens, median (range)	1 (1-12)	2 (1-6)	2 (1-12)
Prior BTKi exposure, median (range), months			
Ibrutinib	10.6 (1.2-73.7)	6.2 (0.9-46.4)[a]	9.2 (0.9-73.7)
Acalabrutinib	—	5.1 (0.5-33.7)	5.1 (0.5-33.7)
Planned zanubrutinib dosing regimen, n (%)			
160 mg BID	35 (61.4)	18 (72.0)	53 (64.6)
320 mg QD	22 (38.6)	7 (28.0)	29 (35.4)

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.
[a] Data available for 13 of 14 patients who received ibrutinib in this group.

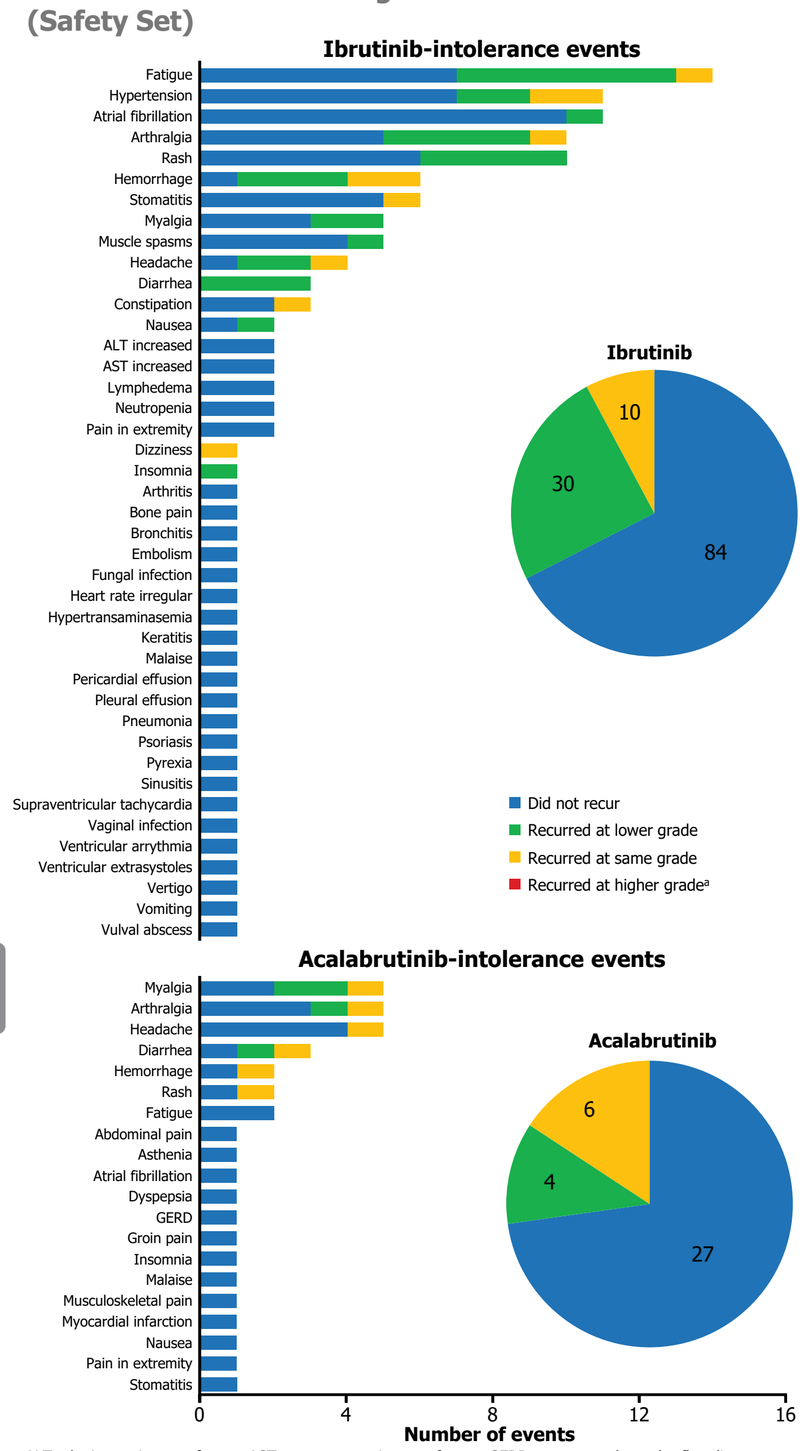
- Of 82 patients, 24 (29.3%) discontinued treatment (**Table 2**) (reasons: AE, n=7 [myalgia, stomatitis, penile hemorrhage, COVID-19 pneumonia, alanine and aspartate aminotransferases increased, autoimmune hemolytic anemia, diarrhea]; PD, n=7; other, n=10)

Table 2. Patient Disposition

	Ibrutinib intolerant (n=57)	Acalabrutinib ± ibrutinib intolerant (n=25)	Total (N=82)
Patients, n (%)			
Remaining on treatment	39 (68.4)	19 (76.0)	58 (70.7)
Remaining on study	46 (80.7)	21 (84.0)	67 (81.7)
Discontinued from treatment	18 (31.6)	6 (24.0)	24 (29.3)
AE	5 (8.8)	2 (8.0)	7 (8.5)
PD	6 (10.5)	1 (4.0)	7 (8.5)
Withdrawal by patient	3 (5.3)	2 (8.0)	5 (6.1)
Deaths, n (%)	5 (8.8)	1 (4.0)	6 (7.3)
Zanubrutinib treatment duration, median (range), months	26.2 (0.6-36.2)	8.1 (0.5-27.9)	23.7 (0.5-36.2)

- While receiving zanubrutinib, 84 of 124 (67.7%) ibrutinib- and 27 of 37 (73.0%) acalabrutinib-intolerance events did not recur
- Of those AEs that did recur during zanubrutinib treatment, none recurred at a higher grade, and 30 of 40 (75.0%) ibrutinib- and 4 of 10 (40.0%) acalabrutinib-intolerance events were lower grade (**Figure 3**)

Figure 3. Recurrence of Ibrutinib- and Acalabrutinib-Intolerance Events During Zanubrutinib Treatment (Safety Set)



ALT, alanine aminotransferase; AST, aspartate aminotransferase; GERD, gastroesophageal reflux disease.
[a] No intolerance events recurred at a higher grade.

CONCLUSIONS

- The median exposure to zanubrutinib was longer than the median exposure to the prior BTK inhibitor before discontinuation
- In this longer-term analysis, 67.7% of ibrutinib-intolerance events and 73.0% of acalabrutinib-intolerance events did not recur
- Zanubrutinib provided disease control in ≥95% of efficacy-evaluable patients who were responding to, but intolerant of, prior treatment with ibrutinib and/or acalabrutinib
- These longer-term safety and efficacy outcomes suggest that patients who are intolerant of other BTK inhibitors can attain clinical benefit by switching to zanubrutinib
- Study enrollment and follow-up are ongoing

Safety

- The safety profile observed during this longer follow-up was consistent with what has been previously reported for zanubrutinib
- A total of 37 patients (45.1%) experienced grade ≥3 AEs, and 19 (23.2%) had serious AEs; 6 deaths (7.3%) occurred (1 due to AE) (**Table 3**)
- The most common AEs are shown in **Table 4**

Table 3. Overall Safety Summary

	Ibrutinib intolerant (n=57)	Acalabrutinib ± ibrutinib intolerant (n=25)	Total (N=82)
Patients with ≥1 AE, n (%)	55 (96.5)	23 (92.0)	78 (95.1)
Grade 3 or higher	29 (50.9)	8 (32.0)	37 (45.1)
Serious	15 (26.3)	4 (16.0)	19 (23.2)
Leading to treatment discontinuation	5 (8.8)	2 (8.0)	7 (8.5)
Leading to dose interruption	27 (47.4)	11 (44.0)	38 (46.3)
Leading to dose reductions	14 (24.6)	4 (16.0)	18 (22.0)
Leading to death	1 (1.8)	0 (0)	1 (1.2)

Table 4. Most Common Adverse Events (Incidence ≥10% in All Patients)

AEs, n (%)	Ibrutinib intolerant (n=57)	Acalabrutinib ± ibrutinib intolerant (n=25)	Total (N=82)
Fatigue	18 (31.6)	6 (24.0)	24 (29.3)
Contusion	14 (24.6)	4 (16.0)	18 (22.0)
Arthralgia	12 (21.1)	5 (20.0)	17 (20.7)
COVID-19	14 (24.6)	3 (12.0)	17 (20.7)
Diarrhea	10 (17.5)	7 (28.0)	17 (20.7)
Myalgia	10 (17.5)	5 (20.0)	15 (18.3)
Cough	6 (10.5)	6 (24.0)	12 (14.6)
Dizziness	9 (15.8)	3 (12.0)	12 (14.6)
Rash	9 (15.8)	3 (12.0)	12 (14.6)
Hypertension	5 (8.8)	5 (20.0)	10 (12.2)
Nausea	9 (15.8)	1 (4.0)	10 (12.2)
Upper respiratory tract infection	8 (14.0)	2 (8.0)	10 (12.2)
Constipation	9 (15.8)	0 (0)	9 (11.0)
Headache	6 (10.5)	3 (12.0)	9 (11.0)
Insomnia	8 (14.0)	1 (4.0)	9 (11.0)
Urinary tract infection	7 (12.3)	2 (8.0)	9 (11.0)

Efficacy

- Among the 76 efficacy-evaluable patients receiving zanubrutinib, ≥95% of patients across cohorts had controlled disease and ≥65% achieved a PR, thereby maintaining or improving response (**Table 5**)

Table 5. Efficacy Outcomes (Efficacy-Evaluable Patients)

	Ibrutinib intolerant (n=56)	Acalabrutinib ± ibrutinib intolerant (n=20)	Total (N=76)
DCR (SD or better), n (%) [95% CI])	54 (96.4) [87.7-99.6]	19 (95.0) [75.1-99.9]	73 (96.1) [88.9-99.2]
ORR (better than SD), n (%) [95% CI]	41 (73.2) [59.7-84.2]	13 (65.0) [40.8-84.6]	54 (71.1) [59.5-80.9]
CR[a]	1 (1.8)	0 (0)	1 (1.3)
PR[b]	40 (71.4)	13 (65.0)	53 (69.7)
SD	13 (23.2)	6 (30.0)	19 (25.0)
PD	1 (1.8)	1 (5.0)	2 (2.6)
Time to BOR, median (range), months[c]	5.7 (2.6-28.1)	3.0 (2.7-11.1)	5.6 (2.6-28.1)
Time to first overall response, median (range), months[c]	3.0 (2.6-28.1)	2.9 (2.7-11.1)	3.0 (2.6-28.1)

BOR, best overall response; CLL, chronic lymphocytic leukemia; DCR, disease control rate; WM, Waldenström macroglobulinemia.
[a] Includes CR in all patients and CR with incomplete bone marrow recovery in CLL. [b] Includes PR in all patients, PR with lymphocytosis or better in patients with CLL, and minor response or better in patients with WM. [c] In patients with a BOR that is better than SD.

REFERENCES

1. Burger JA. *Cancer J.* 2019;25(6):386-393.
2. Stephens DM, Byrd JC. *Blood.* 2019;133(12):1298-1307.
3. Guo Y, et al. *J Med Chem.* 2019;62(17):7923-7940.
4. Shadman M, et al. *Lancet Haematol.* 2023;10(1):e35-e45.
5. Shadman M, et al. *Blood.* 2021;138(suppl 1):1410-1413.

DISCLOSURES

MS: Research funding from Mustang Bio, Celgene, BMS, Pharmacyclics, Gilead, Genentech, AbbVie, TG Therapeutics, BeiGene, AstraZeneca, Sunesis, Atara Biotherapeutics, Genmab, MorphoSys/Incyte; Consulting for AbbVie, Genentech, AstraZeneca, Sound Biologics, Pharmacyclics, BeiGene, BMS, MorphoSys/Incyte, TG Therapeutics, Innate Pharma, Kite, Adaptive Biotechnologies, Epizyme, Eli Lilly, Adaptimmune, Mustang Bio, Regeneron, Merck, Fate Therapeutics, MEI Pharma, Atara Biotherapeutics. **MYL:** Consulting and speakers bureaus for AbbVie, Amgen, BMS, Janssen, Karyopharm, MorphoSys, Seagen, Takeda, AstraZeneca, BeiGene, Gilead, Kite, TG Therapeutics, Epizyme, GSK, Novartis. **JMB:** Consulting for BeiGene, Kymera, Bristol Myers Squibb, X4 Pharma, Seagen, TG Therapeutics, Lilly, Verastem, MorphoSys, Adaptive Biotechnologies, AstraZeneca, Roche/Genentech, Epizyme, Kura, AbbVie; Honoraria from BeiGene and Seagen. **JPS:** Employment by US Oncology Network; Consulting for TG Therapeutics, Genentech, AbbVie, Acerta Pharma/AstraZeneca, BeiGene, Bristol Myers Squibb, Merck; Research funding from Pharmacyclics, Genentech, Celgene, Acerta Pharma, Gilead Sciences, Seagen, TG Therapeutics, Merck, Takeda. **SFZ:** Honoraria from Merck. **KB, AC, RC, AI:** Employment by BeiGene and may hold stock. **IWF:** Advisory role with Vincerx. **SG, JLC, JM:** No disclosures.

ACKNOWLEDGMENTS

We thank the study patients, their supporters, and investigators and clinical research staff at study centers. This study was sponsored by BeiGene, Ltd. Medical writing and editorial assistance were provided, under the direction of the authors, by Reema Anwar, PharmD, and Apurva Davé, PhD, of Medical Expressions and supported by BeiGene.

CORRESPONDENCE: Mazyar Shadman, MD, MPH; mshadman@fredhutch.org

31st Congress of the Polish Society of Hematology and Transfusion Medicine, 14-16 September 2023, Katowice, Poland
Data originally presented at EHA 2023 Hybrid Congress; June 8-15, 2023; Frankfurt, Germany; Abstract P633