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

Pier Luigi Zinzani

Speaker disclosures

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Correspondence: Pier Luigi Zinzani, MD, PhD; pierluigi.zinzani@unibo.it

Author list and affiliations

Pier Luigi Zinzani,[1] Mazyar Shadman,[2] Moshe Y. Levy,[3] Ryan Porter,[4] John M. Burke,[5] Jennifer L. Cultrera,[6] Jamal Misleh,[7] Jeff P. Sharman,[8] Syed F. Zafar,[9] Kunthel By,[10] Aileen Cohen,[10] Rocco Crescenzo,[10] Adam Idoine,[10] Ian W. Flinn[11]

[1]Institute of Hematology “Seràgnoli,” University of Bologna, Bologna, Italy
[2]Fred Hutchinson Cancer Center, University of Washington, Seattle, WA, USA
[3]Texas Oncology-Baylor Charles A. Sammons Cancer Center, Dallas, TX, USA
[4]SSM Health Dean Medical Group, St. Louis, MO, USA
[5]Rocky Mountain Cancer Centers, Aurora, CO, USA
[6]Florida Cancer Specialists and Research Institute, The Villages, FL, USA
[7]Medical Oncology Hematology Consultants PA, Newark, DE, USA
[8]Willamette Valley Cancer Institute and Research Center, Eugene, OR, USA
[9]Florida Cancer Specialists and Research Institute, Cape Coral, FL, USA
[10]BeiGene USA, Inc, San Mateo, CA, USA
[11]Sarah Cannon Research Institute/Tennessee Oncology, Nashville, TN, USA

Background

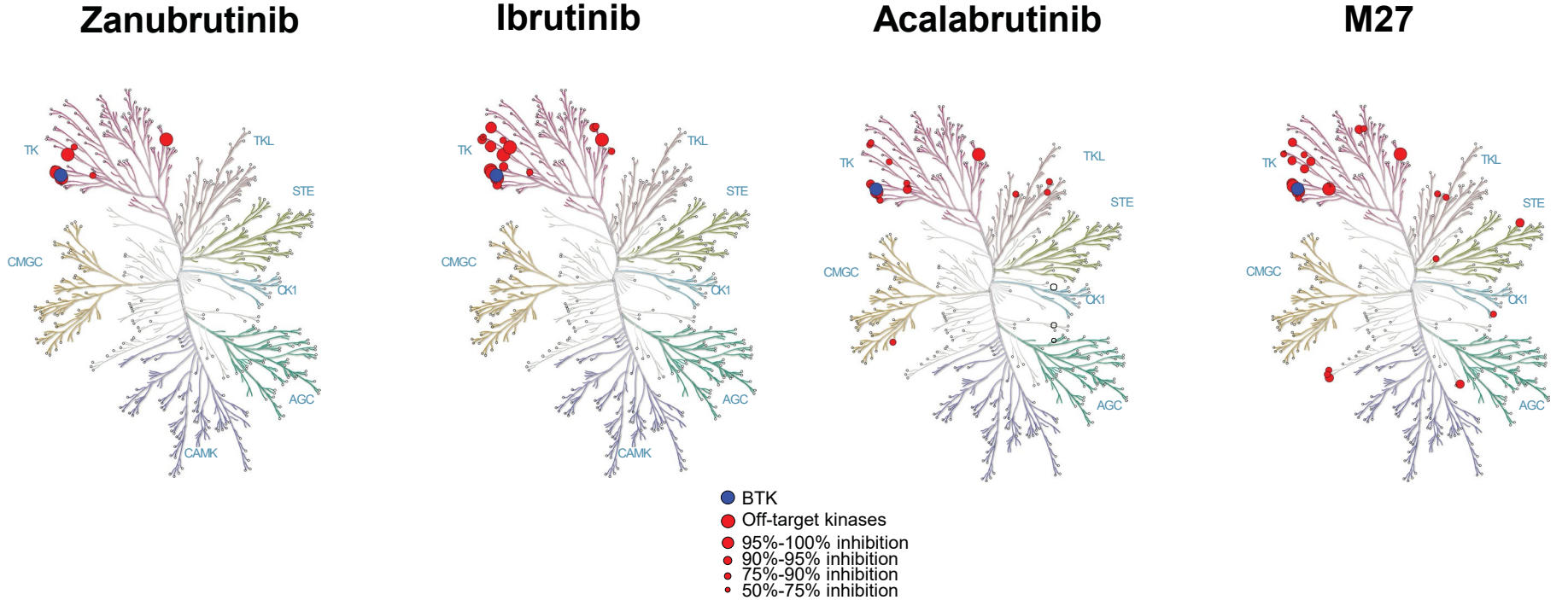
- Patients with B-cell malignancies treated with BTKis require continuous therapy[1]
- Ibrutinib and acalabrutinib are effective, but many patients discontinue therapy because of treatment-related intolerance, possibly caused by off-target kinase binding[2]
- Zanubrutinib is a next-generation BTKi designed to maximize tolerability by minimizing off-target kinase binding and associated AEs[3]
- Kinase profiling demonstrated that zanubrutinib has higher selectivity than ibrutinib, acalabrutinib, and acalabrutinib's major metabolite (M27)[4,5]
- This phase 2 study (BGB-3111-215; NCT04116437) demonstrated that zanubrutinib is well tolerated in patients who were 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 for all patients in the BGB-3111-215 study, at a median follow-up of 25.2 months

AE, adverse event; BTK, Bruton tyrosine kinase inhibitor.

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.

Kinase selectivity of zanubrutinib, ibrutinib, acalabrutinib, and acalabrutinib metabolite M27



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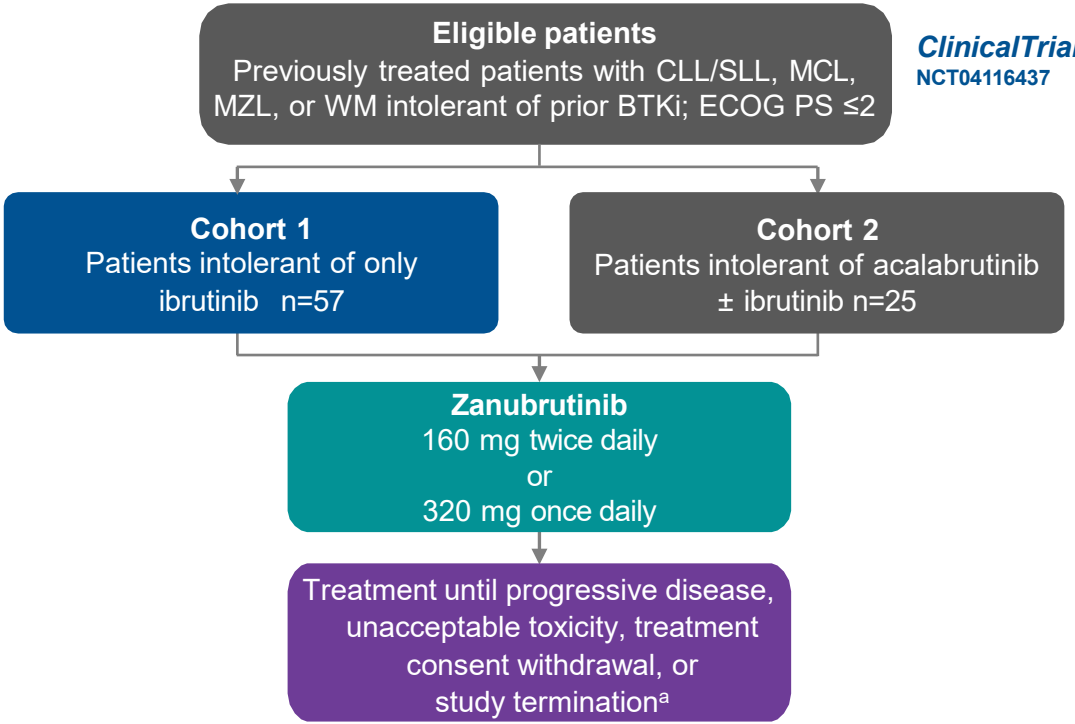
BTK, Bruton tyrosine kinase.

Study design



ClinicalTrials.gov:
NCT04116437

BTKi, Bruton tyrosine kinase inhibitor; 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] Study enrollment and follow-up are ongoing.

Methods

- Recurrence of AEs that led to intolerance of prior BTKis and other TEAEs were assessed based on CTCAE v5.0
- Investigator-assessed responses using disease parameters at study entry as baseline were assessed every third 28-day cycle using standard response criteria

Safety set (n=82)	Efficacy-evaluable set (n=76)
All patients who received ≥1 dose of zanubrutinib	Patients with ≥1 disease assessment or those who discontinued the study due to AEs or died prior to their first disease assessment

AE, adverse event; BTK, Bruton tyrosine kinase inhibitor; CTCAE, Common Terminology Criteria for Adverse Events; PD, progressive disease; TEAE, treatment-emergent adverse event.

Characteristics of patients intolerant of ibrutinib and of acalabrutinib ± ibrutinib were similar

- The data cutoff was January 3, 2023; of 82 enrolled patients, 57 (69.5%) were intolerant of ibrutinib, and 25 (30.5%) were intolerant of acalabrutinib (acalabrutinib only, n=14; both acalabrutinib and ibrutinib, n=11)
- Most patients experienced >1 intolerance event on prior BTKis, with 124 ibrutinib intolerance events occurring in 68 patients and 37 acalabrutinib intolerance events occurring in 25 patients

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	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)	9.2 (0.9-73.7)
Acalabrutinib	NA	5.1 (0.5-33.7)	5.1 (0.5-33.7)
Zanubrutinib dosing regimen, n (%)			
160 mg twice daily	35 (61.4)	18 (72.0)	53 (64.6)
320 mg once daily	22 (38.6)	7 (28.0)	29 (35.4)

BTKi, Bruton tyrosine kinase inhibitor; CLL, chronic lymphocytic leukemia; ECOG PS, Eastern Cooperative Oncology Group performance status; MCL, mantle cell lymphoma; MZL, marginal zone lymphoma; NA, not available; SLL, small lymphocytic lymphoma; WM, Waldenström macroglobulinemia.

Patients received zanubrutinib for a median of 24 months

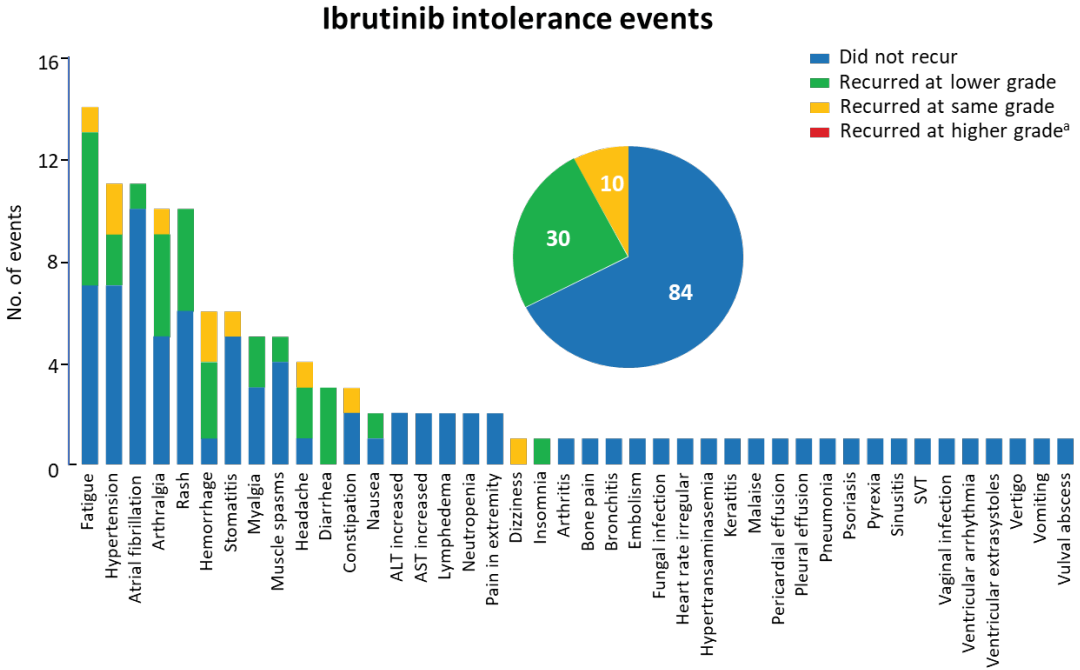
- In the safety set (N=82), 24 patients (29.3%) discontinued treatment: 7 due to AEs, 7 due to PD, and 10 for other reasons

	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)[a]
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)

AE, adverse event; PD, progressive disease.
[a] The AEs include myalgia, stomatitis, penile hemorrhage, COVID-19 pneumonia, alanine and aspartate aminotransferases increased, autoimmune hemolytic anemia, and diarrhea.

Most Ibrutinib intolerance events did not recur when treated with zanubrutinib

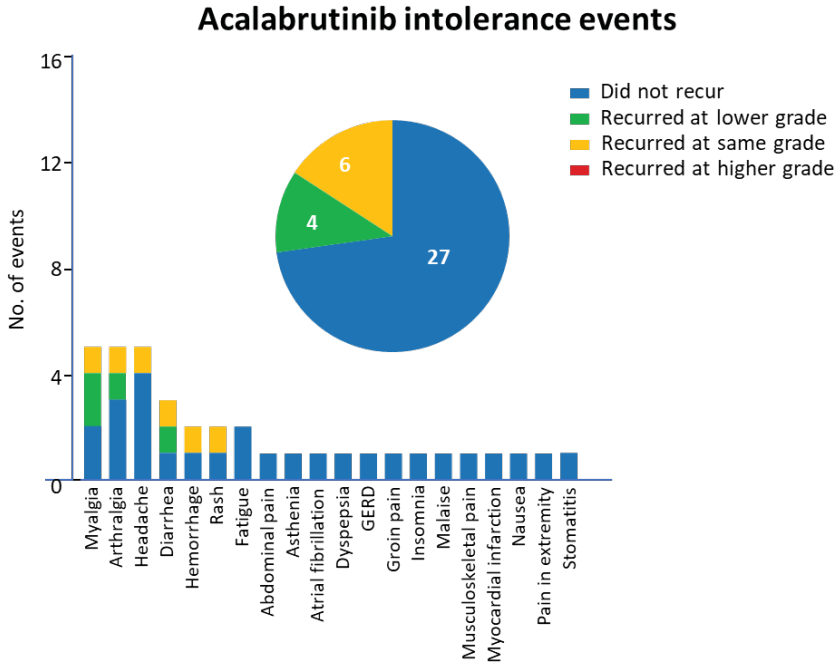
- While receiving zanubrutinib, 84 of 124 (67.7%) ibrutinib intolerance events did not recur
- Of those AEs that recurred during zanubrutinib treatment, none recurred at a higher grade, and 30 of 40 (75.0%) ibrutinib intolerance were lower grade



ALT, alanine aminotransferase; AST, aspartate aminotransferase; SVT, supraventricular tachycardia.

Most acalabrutinib intolerance events did not recur when treated with zanubrutinib (cont.)

- While receiving zanubrutinib, 27 of 37 (73.0%) acalabrutinib intolerance events did not recur
- Of those AEs that recurred during zanubrutinib treatment, none recurred at a higher grade, and 4 of 10 (40.0%) acalabrutinib intolerance events were lower grade



GERD, gastroesophageal reflux disease.

The safety profile was consistent with the known risks of 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 of COVID-19)

	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	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	1 (1.2)

AE, adverse event.

The most commonly observed AEs for Zanubrutinib were consistent with those reported in published literature

AEs ≥10% in all patients, 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	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)

AE, adverse event.

Zanubrutinib demonstrated efficacy in both cohorts

- Among the 76 efficacy-evaluable patients receiving zanubrutinib, ≥95% had controlled disease, and ≥65% achieved a PR; therefore, responses were either maintained or improved
- Some patients had low disease burden on study entry, hence they could not achieve PR or PR-L during the study

	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	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; CR, complete response; DCR, disease control rate; ORR, objective response rate; PD, progressive disease; PR, partial response; PR-L, partial response with lymphocytosis; SD, stable disease; WM, Waldenström macroglobulinemia.
[a]Includes CR in all patients and CR with incomplete bone marrow recovery in patients with 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.

Conclusions

- The median exposure to zanubrutinib was longer than the median exposure to the prior BTKi 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

BTK, Bruton tyrosine kinase inhibitor.

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