Zanubrutinib is Well Tolerated and Effective in Ibrutinib/Acalabrutinib-Intolerant Patients with Waldenström Macroglobulinemia

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Presented at the 12th International Workshop on Waldenström's Macroglobulinemia (IWWM-12); October 17-19, 2024; Prague, Czech Republic

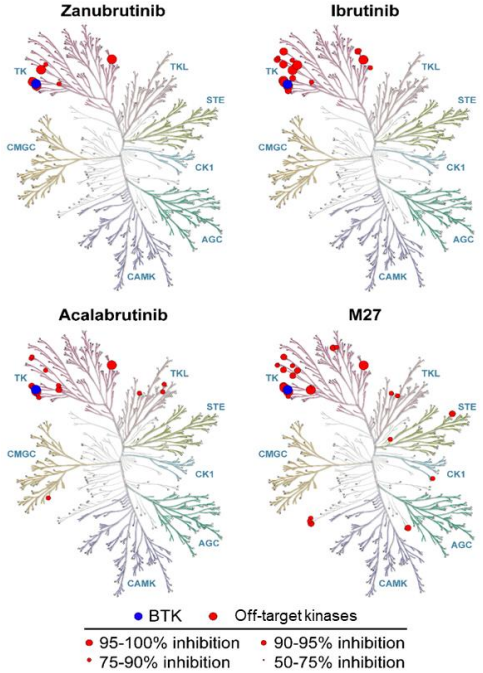
Disclosures for Mazyar Shadman

- Consultant: AbbVie, Genentech, AstraZeneca, Genmab, Janssen, BeiGene, BMS, MorphoSys/Incyte, Kite Pharma, Lilly, Fate Therapeutics, Nurix, Merck; Research funding: Mustang Bio, Genentech, AbbVie, BeiGene, AstraZeneca, Genmab, MorphoSys/Incyte, Vincerx; Stock: Koi Biotherapeutics; Employment: BMS (spouse)

Introduction

- Patients with WM often require continuous treatment with BTK inhibitors; however, difficult-to-manage AEs may lead to treatment discontinuation[1]
- Zanubrutinib is a potent and selective next-generation BTK inhibitor designed to maximize BTK occupancy and minimize off-target kinase binding and associated AEs[2,3]
- Phase 3 studies in patients with CLL/SLL and WM have demonstrated that zanubrutinib has a more favorable safety profile than ibrutinib, especially regarding cardiovascular toxicities[4,5]
- Early data from the BGB-3111-215 study (NCT04116437) have shown that zanubrutinib is well tolerated in patients with B-cell malignancies who are intolerant of ibrutinib or acalabrutinib[3]
- Here, we present updated data on patients with WM from the BGB-3111-215 study

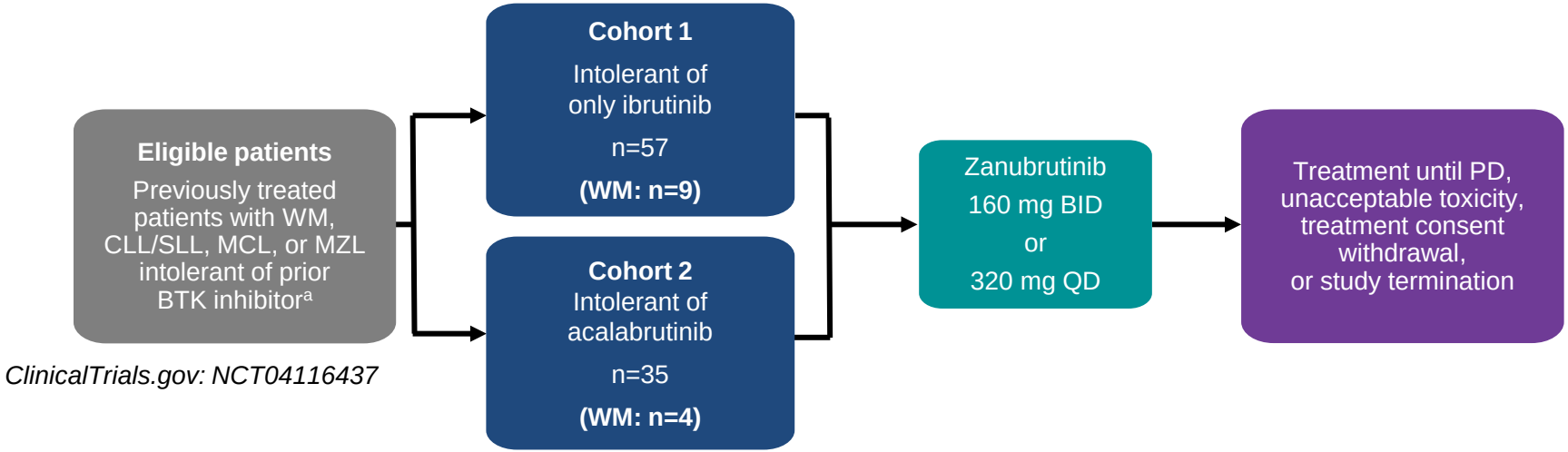
Kinase Selectivity of Zanubrutinib, Ibrutinib, Acalabrutinib, and Acalabrutinib Metabolite M27



AE, adverse event; BTK, Bruton tyrosine kinase; CLL, chronic lymphocytic leukemia; SLL, small lymphocytic lymphoma; WM, Waldenström macroglobulinemia.

1. Ntanasis-Stathopoulos I, et al. *Ther Adv Hematol.* 2021;12:2040620721989586. 2. Guo Y, et al. *J Med Chem.* 2019;62(17):7923-7940.
3. Shadman M, et al. *Lancet Haematol.* 2023;10(1):e35-345. 4. Brown JR, et al. *N Engl J Med.* 2023;388(4):319-332. 5. Dimopoulos MA, et al. *J Clin Oncol.* 2023;41(33):5099-5106.

BGB-3111-215 Study Design



ClinicalTrials.gov: NCT04116437

- **Objective:** to report preliminary tolerability and efficacy results in patients with WM treated with zanubrutinib after discontinuation of ibrutinib or acalabrutinib for intolerance

[a] Intolerance to ibrutinib and/or acalabrutinib is defined as an unacceptable toxicity where, in the opinion of the investigator, treatment should be discontinued in spite of optimal supportive care; please refer to next slide for detailed information.

BID, twice daily; BTK, Bruton tyrosine kinase; CLL, chronic lymphocytic leukemia; MCL, mantle cell lymphoma; MZL, marginal zone lymphoma; PD, progressive disease; QD, once daily; SLL, small lymphocytic lymphoma; WM, Waldenström macroglobulinemia.

BGB-3111-215 Inclusion and Exclusion Criteria

Key Inclusion Criteria

- Ibrutinib or acalabrutinib intolerance
  - Grade ≥2 nonhematologic toxicity for >7 days
  - Grade ≥3 nonhematologic toxicity for any duration
  - Grade 3 neutropenia with infection or fever
  - Grade 4 hematologic toxicity that persists until BTK inhibitor therapy is discontinued because of toxicity
- Additional acalabrutinib intolerance criteria
  - Grade ≥1 nonhematologic toxicity for >7 days or with ≥3 recurrent episodes
  - Inability to use acid-reducing agents or anticoagulants due to current BTK inhibitor use

Key Exclusion Criteria

- Disease progression during prior BTK inhibitor treatment

BTK, Bruton tyrosine kinase.

Baseline Characteristics of Patients With WM

Baseline Characteristics

Characteristic	Total (N=13)
Age, median (range), years	73 (58-87)
Sex, n (%)	
Male	7 (53.8)
Female	6 (46.2)
No. of prior regimens, median (range)	2 (1-12)
Time on prior BTKi treatment, median (range), months	
Ibrutinib[a]	11.8 (0.9-73.7)
Acalabrutinib	3.4 (1.6-26.3)
On-study zanubrutinib dosing regimen, n (%)[b]	
160 mg BID	7 (53.8)
320 mg QD	6 (46.2)

Disease Staging and Genomic Status at Study Entry

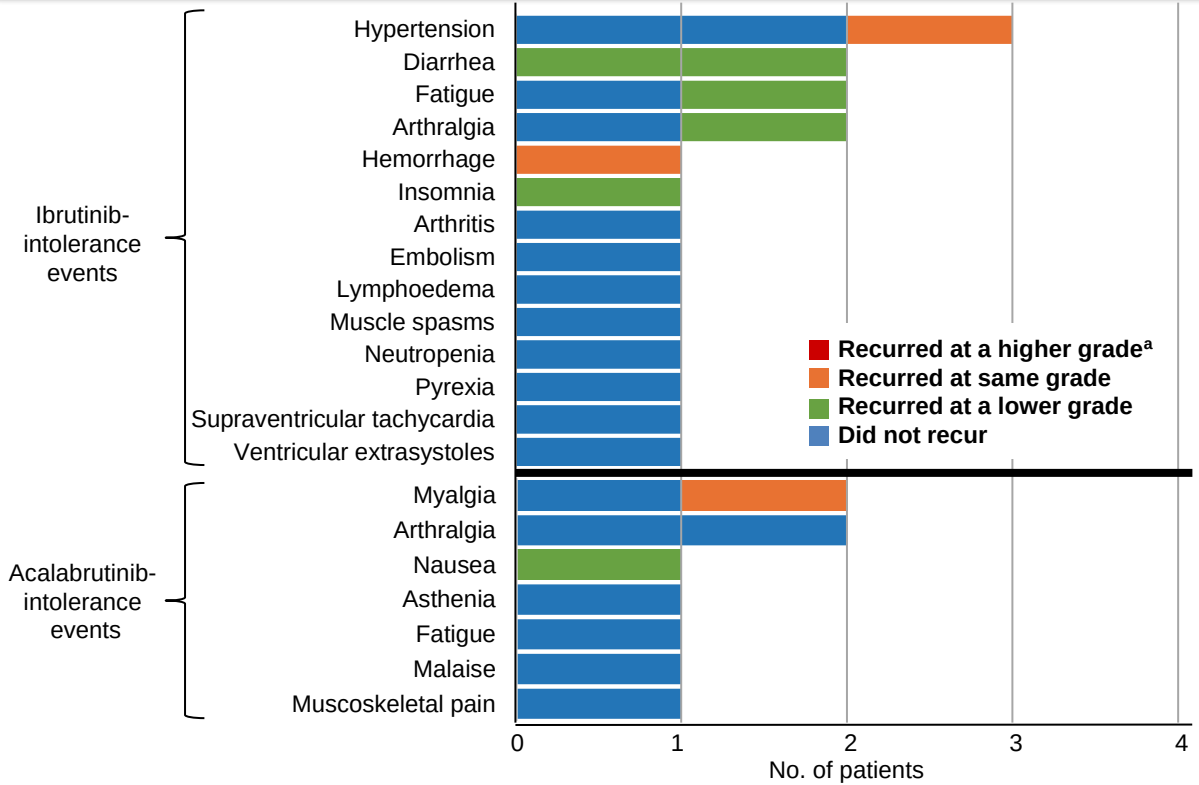
Characteristic	Total (N=13)
Disease staging, n (%)[c]	
Low risk	6 (46.2)
Intermediate risk	7 (53.8)
High risk	0

Median follow-up on May 1, 2024: 34.1 months. Median duration of zanubrutinib treatment: 34.1 months (range, 6.5-46.0 months); median duration of zanubrutinib treatment in cohorts 1 and 2: 38.9 months and 14.6 months.

[a] Time on prior ibrutinib treatment in cohort 1: 12.9 months (range, 1.3-73.7 months). [b] Received ≥1 zanubrutinib dose. [c] WM International Staging System.

BID, twice daily; BTKi, Bruton tyrosine kinase inhibitor; QD, once daily; WM, Waldenström macroglobulinemia.

Recurrence and Severity Change of Intolerance AEs on Zanubrutinib in Patients With WM



- 63% (12/19) of AEs that resulted from ibrutinib treatment did not recur with zanubrutinib
- 78% (7/9) of AEs that resulted from acalabrutinib treatment did not recur with zanubrutinib
- Events that did recur mostly recurred at a lower grade
- 38% (5/13) of patients did not experience recurrence of any prior BTK inhibitor-related intolerance AE on zanubrutinib

Median follow-up on May 1, 2024: 34.1 months. Median duration of treatment: 34.1 months (range, 6.5-46.0 months).
[a] No intolerance AEs recurred at a higher grade.
AE, adverse event; BTK, Bruton tyrosine kinase; WM, Waldenström macroglobulinemia.

Treatment-Emergent AEs During Zanubrutinib Treatment in Patients With WM

Overall TEAE Summary

Patients, n (%)	Any grade (N=13)
Grade ≥3	6 (46.2)
Serious AE	5 (38.5)
Leading to treatment discontinuation	3 (23.1)[a]
Cardiac AEs	0
Leading to dose interruption	9 (69.2)
Leading to dose reduction	4 (30.8)
Leading to death	0

Any Grade TEAEs Occurring in ≥3 Patients

Patients, n (%)	Any grade (N=13)
Any AE	13 (100)
Fatigue	6 (46.2)
Diarrhea	5 (38.5)
Back pain	4 (30.8)
Contusion	4 (30.8)
Pyrexia	4 (30.8)
Upper respiratory tract infection	4 (30.8)
Dizziness	3 (23.1)
Nausea	3 (23.1)
Rash	3 (23.1)
Urinary tract infection	3 (23.1)

All Grade ≥3 TEAEs

Patients, n (%)	Grade ≥3 (N=13)
Any Grade 3+ TEAE	6 (46.2)
ALT increased	1 (7.7)
Arthritis bacterial	1 (7.7)
AST increased	1 (7.7)
Cellulitis	1 (7.7)
Febrile neutropenia	1 (7.7)
Myocardial infarction	1 (7.7)
Neutropenia	1 (7.7)
Neutrophil count decreased	1 (7.7)
Platelet count decreased	1 (7.7)
Sepsis	1 (7.7)
Septic shock	1 (7.7)
Small intestine obstruction	1 (7.7)

Median follow-up on May 1, 2024: 34.1 months. Median duration of treatment: 34.1 months (range, 6.5-46.0 months).

[a] Treatment discontinuation due to myalgia, diarrhea and ALT increased.

AE, adverse event; ALT, alanine aminotransferase; AST, aspartate aminotransferase; TEAE, treatment-emergent adverse event; WM, Waldenström macroglobulinemia.

Cardiovascular Disorders in Patients With B-Cell Malignancies

Category	Pooled analysis B-cell malignancies[d]	
	Zanubrutinib[e] (N=1,550)	Ibrutinib (N=422)
Treatment duration, median, months	34.4	25.7
Any cardiovascular AE, n (%)	324 (20.9)	147 (34.8)
Atrial fibrillation/flutter	75 (4.8)	66 (15.6)
	EAIR: 0.2 vs 0.64 per 100 person-month (*P*<.0001)[f]	
Ventricular arrhythmia (all grade)[a]	4 (0.3)	2 (0.5)
Symptomatic idiopathic arrhythmia (all grade)[b]	11 (0.7)	7 (1.7)
	EAIR: 0.02 vs 0.06 per 100 person-years (*P*=.1449)[f]	
Hypertension[c]	259 (16.7)	99 (23.5)
Any cardiovascular medical history, n (%)		
Atrial fibrillation/flutter	101 (6.5)	26 (6.2)
Ventricular arrhythmia[a]	14 (0.9)	1 (0.2)
Hypertension[c]	668 (43.1)	207 (49.1)

[a] Including ventricular tachyarrhythmia (SMQ narrow), and ventricular arrhythmias and cardiac arrest (high-level term MedDRA v24.0). [b] Symptomatic idiopathic ventricular arrhythmias were defined as grade >2 ventricular arrhythmia events per CTCAE. [c] Including hypertension (SMQ narrow). [d] B-cell malignancies include Waldenström macroglobulinemia, chronic lymphocytic leukemia, small lymphocytic lymphoma and marginal zone lymphoma. [e] Pooled analysis of 10 clinical studies of zanubrutinib. [f] EAIR analyses based on pooled ASPEN/ALPINE analysis; EAIR rates were consistent with those in the pooled analysis. AE, adverse event; CTCAE, Common Terminology Criteria for Adverse Events; EAIR, exposure-adjusted incidence rate; MedDRA, Medical Dictionary for Regulatory Activities; SMQ, standardized MedDRA query.

Moleshi JJ. et al. *Blood Adv*. 2024;8:2478-2490.

Efficacy by Investigator Assessment

Response	WM (n=13)
Disease control rate (SD or better), n (%)	13 (100)
ORR (better than SD), n (%)	11 (84.6)
BOR, n (%)	
VGPR	5 (38.5)
PR	5 (38.5)
MR or better	1 (7.7)
SD	2 (15.4)
Time to BOR, median (range), months	5.9 (2.7-27.9)
Time to first overall response, median (range), months	5.6 (2.7-8.5)

- No progressive disease or deaths occurred with a 34.1-month median duration of treatment

Median follow-up on May 1, 2024: 34.1 months. Median duration of treatment: 34.1 months (range, 6.5-46.0 months).
BOR, best overall response; MR, minor response; ORR, overall response rate; PR, partial response; SD, stable disease; VGPR, very good partial response; WM, Waldenström macroglobulinemia.

Conclusions

- Consistent with its more selective BTK inhibition, zanubrutinib demonstrated few AEs associated with off-target kinase activity in patients with WM intolerant of ibrutinib and/or acalabrutinib
- Most AEs that led to ibrutinib and/or acalabrutinib treatment discontinuation did not recur with zanubrutinib
- Despite longer exposure to zanubrutinib compared with prior exposure to ibrutinib (38.9 vs 12.9 months) in cohort 1 or acalabrutinib (14.6 vs 3.4 months) in cohort 2, zanubrutinib was better tolerated, with low recurrence of adverse events that occurred on prior BTK inhibitors
- Our safety data demonstrated that zanubrutinib was well tolerated in patients with WM previously intolerant of ibrutinib and/or acalabrutinib
  - Few patients discontinued or reduced the dose of zanubrutinib due to AEs
- All patients with WM had maintained (n=2, 15.4%) or improved (n=11, 84.6%) disease status from baseline on study entry
- Zanubrutinib may be a viable treatment option for patients with WM intolerant of ibrutinib or acalabrutinib

AE, adverse event; BTK, Bruton tyrosine kinase; WM, Waldenström macroglobulinemia.

Acknowledgments

- We thank the investigators, site support staff, and especially the patients for participating in this study
- We also thank Ian W. Flinn, Moshe Y. Levy, Benjamin B. Freeman, Ben Zhang, John M. Burke, Jennifer L. Cultrera, Habte A. Yimer, Edwin C. Kingsley, Charles M. Farber, James D'Olimpio, Hui Yao, Adam Idoine, Qi An, and Jeff P. Sharman for their contributions to this research and presentation
- This study was sponsored by BeiGene, Ltd. Editorial support was provided by Nucleus Global, an Inizio company, and funded by BeiGene