Zanubrutinib in Patients Intolerant to Ibrutinib/Acalabrutinib

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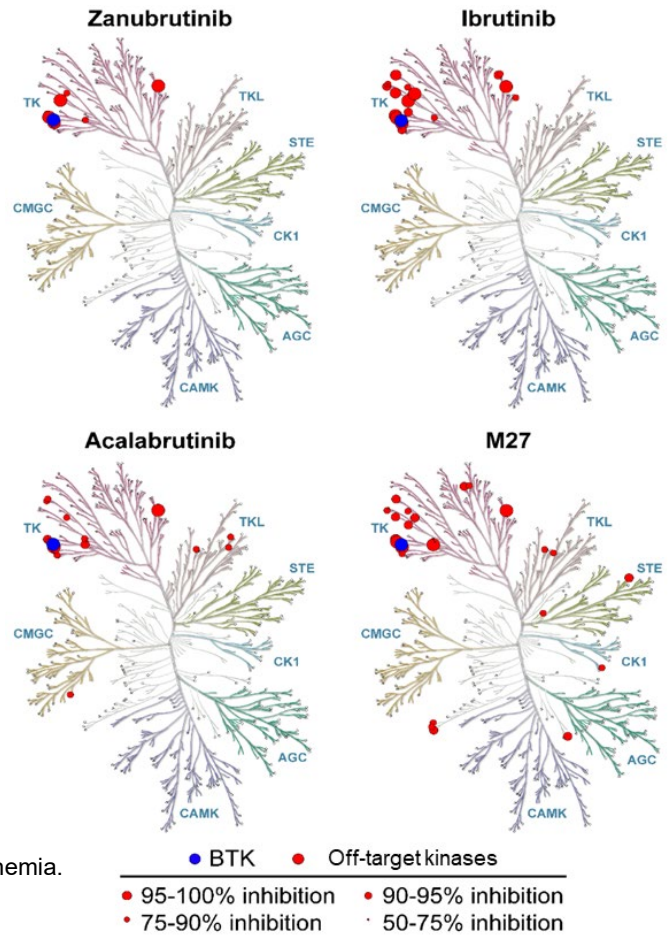
DISCLOSURES

- **Mazyar Shadman** served as a consultant and sat on advisory boards, steering committees or data safety monitoring committees for AbbVie, Adaptimmune, Adaptive Biotechnologies, AstraZeneca, Atara Biotherapeutics, BeiGene, Bristol Myers Squibb, Eli Lilly, Epizyme, Fate Therapeutics, Genentech, Innate Pharma, Kite Pharma, MEI Pharma, Merck, MorphoSys/Incyte, Mustang Bio, Pharmacyclics, Regeneron, Sound Biologics and TG Therapeutics; received research funding from AbbVie, AstraZeneca, Atara Biotherapeutics, BeiGene, Bristol Myers Squibb, Celgene, Genentech, Genmab, Gilead, MorphoSys/ Incyte, Mustang Bio, Pharmacyclics, Sunesis, and TG Therapeutics.

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 to ibrutinib or acalabrutinib[3]
- Here, we present data on patients with WM from the BGB-3111-215 study

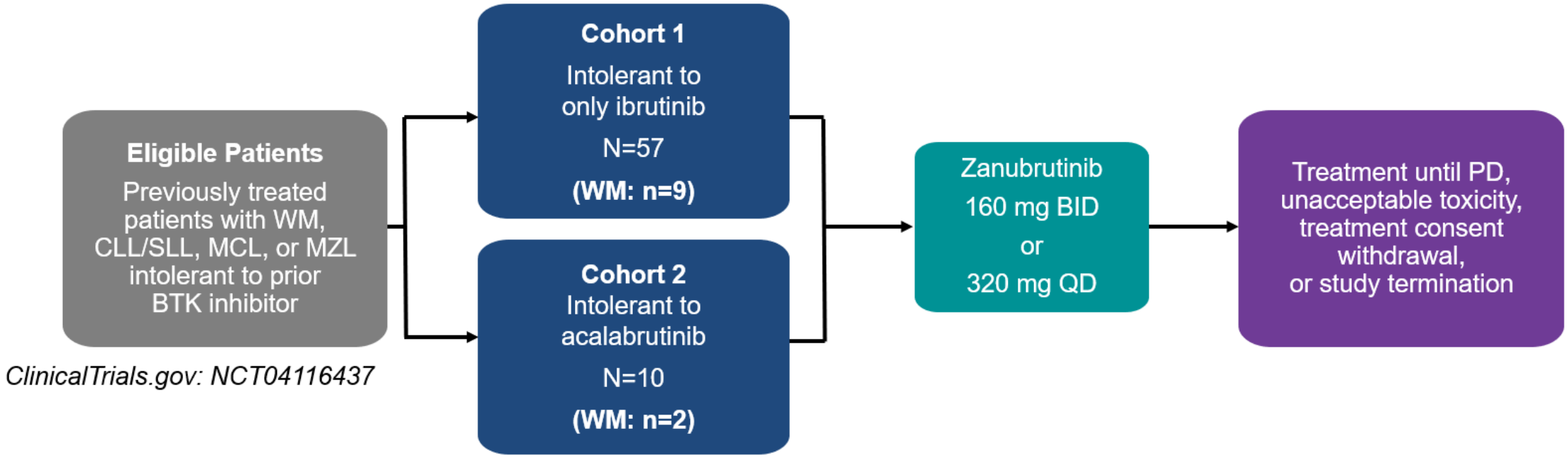
Kinase Selectivity of Zanubrutinib, Ibrutinib, Acalabrutinib, and Acalabrutinib Metabolite M27



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

1. Ntanasis-Stathopoulos et al. *Ther Adv Hematol* 2021;12:2040620721989586. 2. Guo et al. *J Med Chem* 2019;62(17):7923-7940.
3. Shadman et al. *Lancet Haematol.* Forthcoming 2022. 4. Hillmen et al. EHA 2021. Abstract LB1900. 5. Tam et al. ASCO 2022. Abstract 7521.

BGB-3111-215 Study Design



ClinicalTrials.gov: NCT04116437

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

BID, twice a day; 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 and 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
  - Resolution of BTK inhibitor toxicities to grade ≤1 or baseline before initiating zanubrutinib treatment
- Additional acalabrutinib intolerance criteria
  - Grade ≥1 nonhematologic toxicity for >7 days
  - Grade ≥1 nonhematologic toxicity of any duration with ≥3 recurrent episodes
  - Inability to use acid-reducing agents or anticoagulants due to current BTK inhibitor use
- Resolution of grade 1 BTK inhibitor toxicities to grade 0 or baseline before initiating zanubrutinib treatment

Key Exclusion Criteria

- Disease progression during prior BTK inhibitor treatment

BTK, Bruton tyrosine kinase.

Baseline Characteristics of Patients With WM

Baseline Characteristics

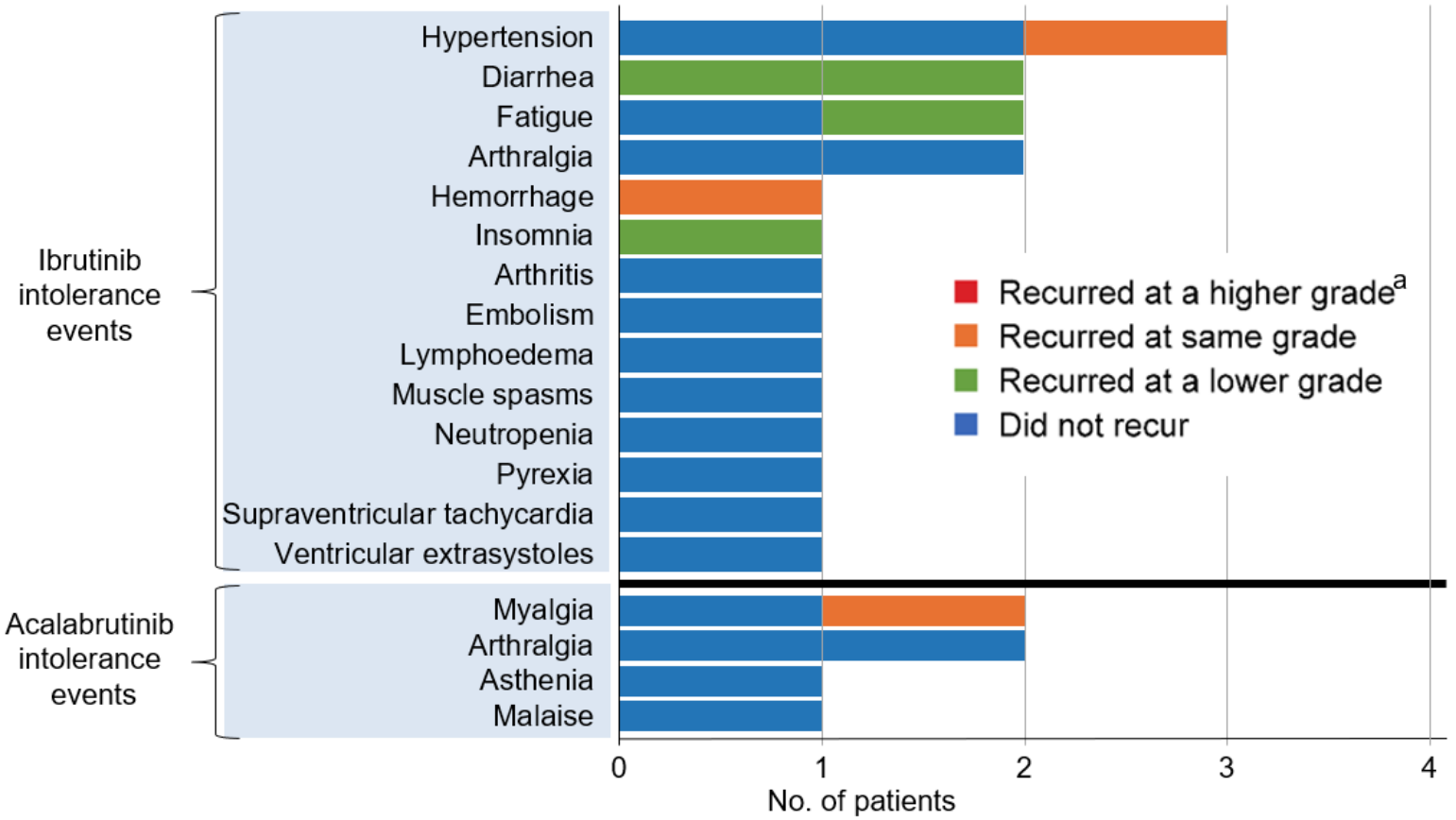
Characteristic	Total (N=11)
Median age, years (range)	71 (58-80)
Sex, n (%)	
Male	6 (54.5%)
Female	5 (45.5%)
No. of prior regimens, median (range)	2 (1-12)
Median time on prior BTKi treatment, months (range)	
Ibrutinib	11 (0.9-73.7)
Acalabrutinib	3 (1.6-4.6)
On-study zanubrutinib dosing regimen,[a] n (%)	
160 mg BID	6 (54.5)
320 mg QD	5 (45.5)

Disease Staging and Genomic Status at Study Entry

Characteristic	Cohort 1 (n=9)	Cohort 2 (n=2)	Total (N=11)
Disease staging,[b] n (%)			
Low-risk group	2 (3.5)	0	2 (3.0)
Intermediate-risk group	3 (5.3)	1 (10.0)	4 (6.0)
High-risk group	0	0	0
Unknown	4 (7.0)	1 (10.0)	5 (7.5)

Median follow-up on March 17, 2022: 14.9 months. Median duration of treatment: 14.9 months (range, 6.5-20.5).
[a]Received ≥1 zanubrutinib dose. [b]WM International Staging System.
BID, twice daily; BTKi, Bruton tyrosine kinase inhibitor; *CXCR4*, C-X-C chemokine receptor type 4 gene; *MYD88*, myeloid differentiation primary response 88 gene; QD, once daily; WM, Waldenström macroglobulinemia.

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



- 68% (13/19) of AEs that resulted from ibrutinib treatment did not recur with zanubrutinib
- 83% (5/6) of AEs that resulted from acalabrutinib treatment did not recur with zanubrutinib
- Events that did recur mostly recurred at a lower grade (diarrhea, fatigue, insomnia)
- 45% (5/11) of patients did not experience recurrence of any prior BTK inhibitor–related intolerance AE on zanubrutinib

Median follow-up on March 17, 2022: 14.9 months. Median duration of treatment: 14.9 months (range, 6.5-20.5).
[a]No intolerance AEs recurred at a higher grade.
AE, adverse event; BTK, Bruton tyrosine kinase; WM, Waldenström macroglobulinemia.

Any-Grade AEs Occurring in ≥2 Patients and All-Grade ≥3 AEs

AE, n (%)	Any grade (N=11)	Grade ≥3 (N=11)
Any AE	11 (100)	2 (18.2)
Contusion	4 (36.4)	0
Fatigue	4 (36.4)	0
Alopecia	2 (18.2)	0
Back pain	2 (18.2)	0
Diarrhea	2 (18.2)	0
Dizziness	2 (18.2)	0
Fall	2 (18.2)	0
Muscle spasms	2 (18.2)	0
Myalgia	2 (18.2)	0
Neutrophil count decreased	2 (18.2)	1 (9.1)[a]
Petechiae	2 (18.2)	0
Pyrexia	2 (18.2)	0
Rash	2 (18.2)	0
Thrombocytopenia	2 (18.2)	0
Urinary tract infection	2 (18.2)	0
ALT increased	0	1 (9.1)[b]
AST increased	0	1 (9.1)[b]
Neutropenia	0	1 (9.1)[a]
Platelet count decreased	0	1 (9.1)[a]

AE, n (%)	Any grade (N=11)	Grade ≥3 (N=11)
Serious AE	1 (9.1)[c]	0
Leading to treatment discontinuation	2 (18.2)	1 (9.1)[b]
Cardiac AEs	0	0
Leading to dose interruption	3 (27.3)	1 (9.1)[b]
Leading to dose reduction	2 (18.2)	0
Leading to death	0	0

Median follow-up on March 17, 2022: 14.9 months. Median duration of treatment: 14.9 months (range, 6.5-20.5).
[a]Grade 3 neutrophil count decreased, neutropenia, and platelet count decreased all occurred in the same patient. [b]Grade 3 ALT increased and AST increased occurred in the same patient, leading to dose interruption and treatment discontinuation. [c]Due to COVID-19 pneumonia.
AE, adverse event; ALT, alanine aminotransferase; AST, aspartate aminotransferase.

Cardiovascular Disorders in Patients With B-Cell Malignancies

Category	Pooled analysis B-cell malignancies[d]	
	Zanubrutinib (N=1550)	Ibrutinib (N=422)
Median treatment duration, months	26.64	19.96
Any cardiovascular AE, n (%)		
Atrial fibrillation/flutter*	60 (3.9)	60 (14.2)
	EAIR: 0.13 vs 0.82 person-month ($p < 0.0001$)	
Ventricular arrhythmia (grade ≥2)[a]	11 (0.7)	6 (1.4)
Symptomatic Idiopathic (grade ≥2)[b]	5 (0.3)*	6 (1.4)*
	EAIR: 0.14 vs 0.87 per 100 person-years ($p = 0.0028$)	
Hypertension[c,*]	225 (14.5)	85 (20.1)
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]	669 (43.2)	206 (48.8)

Data cutoff: March 31, 2021.
[a]Including ventricular tachyarrhythmia (SMQ narrow), ventricular arrhythmias and cardiac arrest (high-level term MedDRA v24.0). [b]Symptomatic idiopathic ventricular arrhythmia was defined as a ventricular arrhythmia occurring in structurally normal hearts in the absence of myocardial scarring as well as active infections and grade ≥2 per CTCAE. [c]Including hypertension (SMQ narrow). [d]Pooled analysis of 10 clinical studies of zanubrutinib.[1] *p<0.05 for EAIR difference between treatments.
AE, adverse event; CTCAE, Common Terminology Criteria for Adverse Events; MedDRA, Medical Dictionary for Regulatory Activities; SMQ, standardized MedDRA query.
1. Tam et al. LL&M 2022. Abstract 1324736.

Efficacy by Investigator Assessment

Response	WM (n=11)
DCR [SD or better], n (%)	11 (100)
ORR [better than SD], n (%)	10 (90.9)
BOR rate, n (%)	
VGPR	5 (45.5)
PR	3 (27.3)
MR or better	2 (18.2)
SD	1 (9.1)
Median time to BOR, months (range)	5.6 (2.7-8.8)
Median time to first overall response, median, months (range)	4.6 (2.7-8.5)

Median follow-up on March 17, 2022: 14.9 months. Median duration of treatment: 14.9 months (range, 6.5-20.5).
BOR, best overall response; DCR, disease control rate; MR, minor response; ORR, overall response rate; PR, partial response; SD, stable disease; VGPR, very good partial response; WM, Waldenström macroglobulinemia.

CONCLUSIONS

- Consistent with a more selective BTK inhibition, zanubrutinib demonstrated few AEs associated with off-target kinase activity in patients with WM intolerant to ibrutinib and/or acalabrutinib
- Most AEs that led to ibrutinib and/or acalabrutinib treatment discontinuation did not recur with zanubrutinib
- All efficacy evaluable patients with WM maintained (n=1; 9.1%) or improved (n=10; 90.9%) their disease status from baseline on study entry
- Our safety data demonstrate that zanubrutinib was well tolerated in patients with WM previously intolerant to ibrutinib and/or acalabrutinib
  - Few patients discontinued zanubrutinib due to AEs
  - Cardiovascular AEs were less common in patients receiving zanubrutinib compared with ibrutinib
- Designed to minimize side effects associated with off-target binding, zanubrutinib is a viable treatment option for patients with WM intolerant to other BTK inhibitors

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

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