Zanubrutinib for the Treatment of Patients With Waldenström Macroglobulinemia: 4 Years of Follow-Up

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DISCLOSURES

- **Judith Trotman** received research funding from BeiGene, Celgene, Janssen, Philadelphia Coalition for a Cure, Roche, and Takeda.

INTRODUCTION

- Bruton tyrosine kinase (BTK) inhibitors have established therapeutic activity in patients with WM[1,2]
- Zanubrutinib is a potent and selective next-generation BTK inhibitor designed to maximize BTK occupancy and minimize off-target inhibition of TEC-, ITK-, and EGFR-family kinases[3]
- Zanubrutinib was investigated in a phase 1/2 study (BGB-3111-AU-003) designed to evaluate the safety, pharmacokinetics, antitumor activity, and optimal dosing in patients with B-cell malignancies[4]
- The study comprises disease-specific cohorts, including patients with treatment-naïve (TN) or relapsed/refractory (R/R) WM
- Here we report safety and efficacy data for the 78 patients with WM treated with single-agent zanubrutinib at a median follow-up of 43.4 months

EGFR, epidermal growth factor receptor; ITK, IL2-inducible T-cell kinase; WM, Waldenström macroglobulinemia.

1. Tam CS, et al. *Blood.* 2020;136(18):2038-2050. 2. Treon AP, et al. *N Engl J Med*. 2015;372(15):1430-40. 3. Guo Y, et al. *J Med Chem*. 2019;62(17):7923-7940. 4. Trotman J, et al. *Blood*. 2020 Oct 29;136(18):2027-2037.

BGB-3111-AU-003 Study Design

DOSE ESCALATION

Dose	All dosed (WM)
40 mg QD	3 (1)
80 mg QD	4 (2)
160 mg QD	5 (1)
320 mg QD	1 (0)
160 mg BID	4 (0)

→ **RP2D[a]**: 320 mg QD or 160 mg BID →

DOSE EXPANSION

Pop.	RP2D dose	Disease	All dosed (WM)
R/R	QD	All B-cell	18 (1)
R/R	BID	All B-cell	21 (1)
R/R	BID	Non-GCB DLBCL	38
R/R	BID	CLL/SLL	71
R/R	BID	WM	22 (22)
R/R	QD	CLL/SLL	20
Any	Any	WM	50 (50)
R/R	Any	MCL	20
TN	Any	CLL/SLL	21
TN	Any	MCL	20
R/R	Any	HCL	11
R/R	BID	iNHL	39
R/R	BID	Richter transformation	15
R/R	BID	All B-cell (prior BTKi)	3

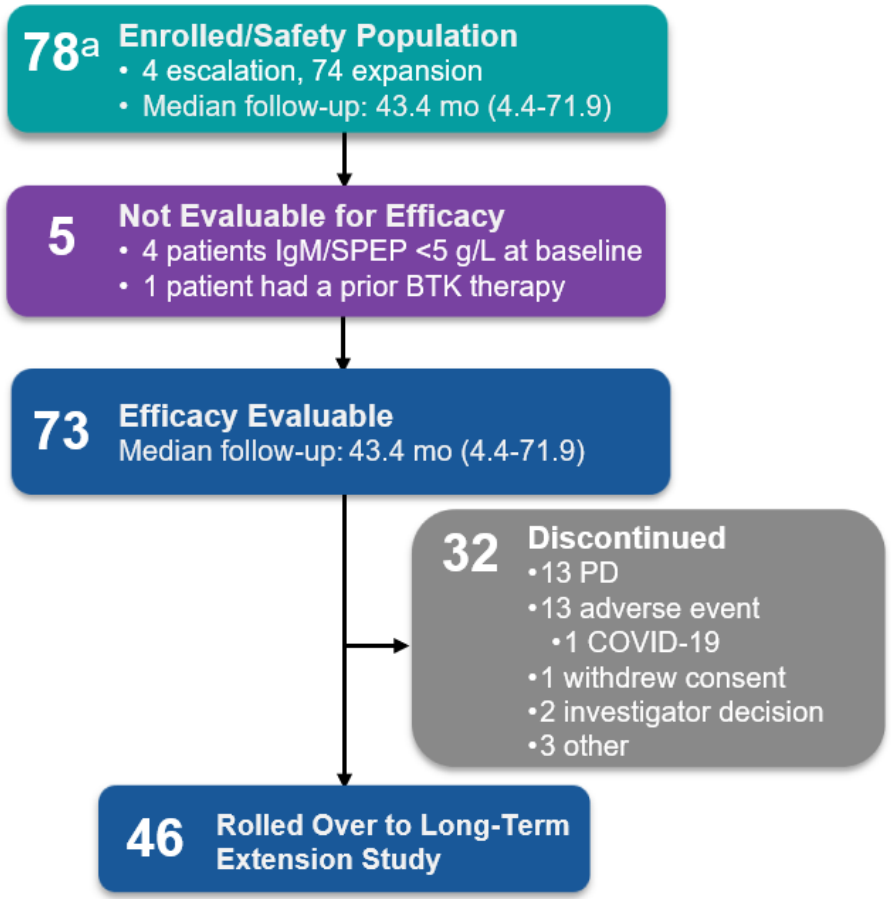
Key Eligibility

- WHO-defined B-cell malignancy
- >1 prior therapy (relapsed cohorts only)
- No available higher-priority treatment
- ECOG PS 0-2
- ANC >1000/μL, platelets >100,000/μL[b]
- Adequate renal and hepatic function; no significant cardiac disease[c]

Cohorts containing WM patients shown in blue

[a]Both doses RP2D, but as of protocol v6, all patients were encouraged to switch to 160 mg BID. [b]Growth factor/transfusion allowed. [c]Anticoagulation allowed.
ANC, absolute neutrophil count; BID, twice daily; BTKi, Bruton tyrosine kinase inhibitor; CLL, chronic lymphocytic leukemia; ECOG PS, Eastern Cooperative Oncology Group performance status; GCB-DLBCL, germinal center B-cell–like diffuse large B-cell lymphoma; HCL, hairy cell leukemia; iNHL, indolent non-Hodgkin lymphoma; MCL, mantle cell lymphoma; QD, once daily; R/R, relapsed/refractory; RP2D, recommended phase 2 dose; SLL, small lymphocytic lymphoma; TN, treatment naïve; WHO, World Health Organization; WM, Waldenström macroglobulinemia.

Patient Disposition and Baseline Characteristics



Characteristic	TN (n=24)	R/R (n=54)	All WM (N=78)
Age, Median (range), y	65 (40-87)	69 (45-87)	67 (40-87)
≥75, n (%)	4 (17)	16 (30)	20 (26)
Male, n (%)	16 (67)	46 (85)	62 (79)
ECOG PS, n (%)			
0/1	24 (100)	51 (94)	75 (96)
2	0	3 (6)	3 (4)
EMD, n (%)[a]			
Lymphadenopathy	13 (54)	27 (50)	40 (51)
Splenomegaly	9 (38)	17 (31)	26 (33)
No. of prior systemic therapies, median (range)	N/A	2 (1-8)	1 (0-8)
Genotype, n (%)[b]			
MYD88^{L265P}	20 (83)	39 (72)	59 (76)
CXCR4^{WT}	14 (58)	27 (50)	41 (53)
CXCR4^{WHIM}	4 (17)	7 (13)	11 (14)
CXCR4^{UNK}	2 (8)	5 (9)	7 (9)
MYD88^{WT}	3 (13)	8 (15)	11 (14)
Missing	1 (4)	7 (13)	8 (10)

Data cutoff: March 31, 2021.

[a]Identified by either computed tomography or physical examination. [b]Genotype data were obtained from baseline bone marrow aspirate samples, or, if not available, from postbaseline samples and determined by LDT/NGS.

BTK, Bruton tyrosine kinase; ECOG PS, Eastern Cooperative Oncology Group performance status; EMD, extramedullary disease; N/A, not applicable; PD, progressive disease; R/R, relapsed/refractory; SPEP, serum protein electrophoresis; TN, treatment naïve; UNK, unknown; WHIM, warts, hypogammaglobulinemia, infections, and myelokathexis; WT, wild type.

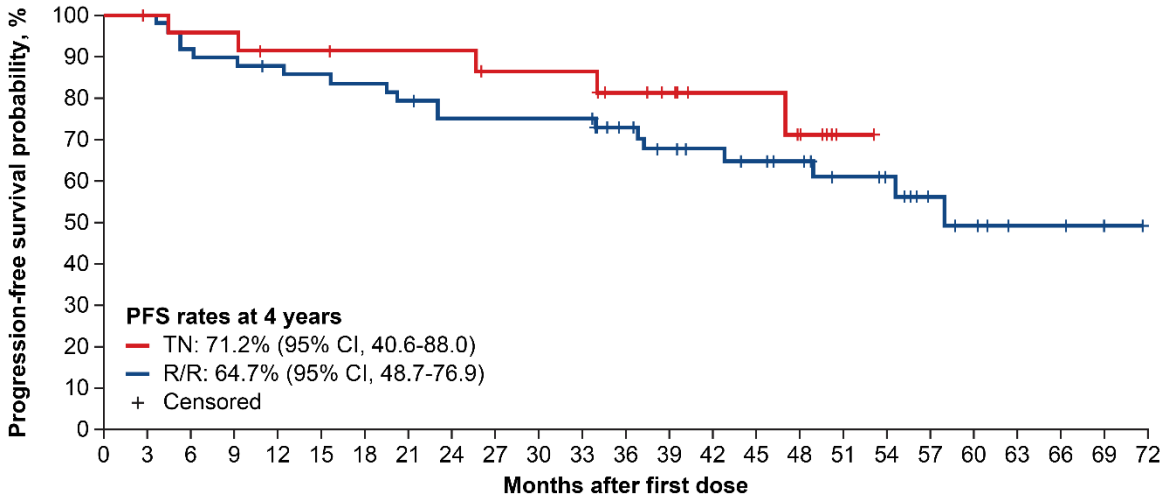
Best Overall Response per IWWM-6 by Investigator Assessment

Best response	TN (n=24)	R/R (n=49)	All efficacy evaluable (N=73)
Overall response rate, n (%)[a]	24 (100)	46 (94)	70 (96)
Complete response	1 (4)	1 (2)	2 (3)
Very good partial response	8 (33)	24 (49)	32 (44)
Partial response	12 (50)	14 (29)	26 (36)
Minor response	3 (13)	7 (14)	10 (14)
Major response rate, n (%)[b]	21 (88)	39 (80)	60 (82)
Stable disease, n (%)	0	3 (6)	3 (4)
Time to response (≥PR), median (range), mo	2.8 (1.9-15.7)	2.8 (0.3-12.0)	2.8 (0.3-15.7)
Study follow-up, median (range), mo	39.6 (8.0-55.2)	48.8 (4.4-71.9)	42.8 (4.4-71.9)

Data cutoff: March 31, 2021.
[a]ORR: complete response, very good partial response, partial response, minor response. [b]MRR: complete response, very good partial response, partial response.
MRR, major response rate; ORR, overall response rate; PR, partial response; R/R, relapsed/refractory; TN, treatment naïve.

Progression-Free Survival in Patients With TN or R/R WM

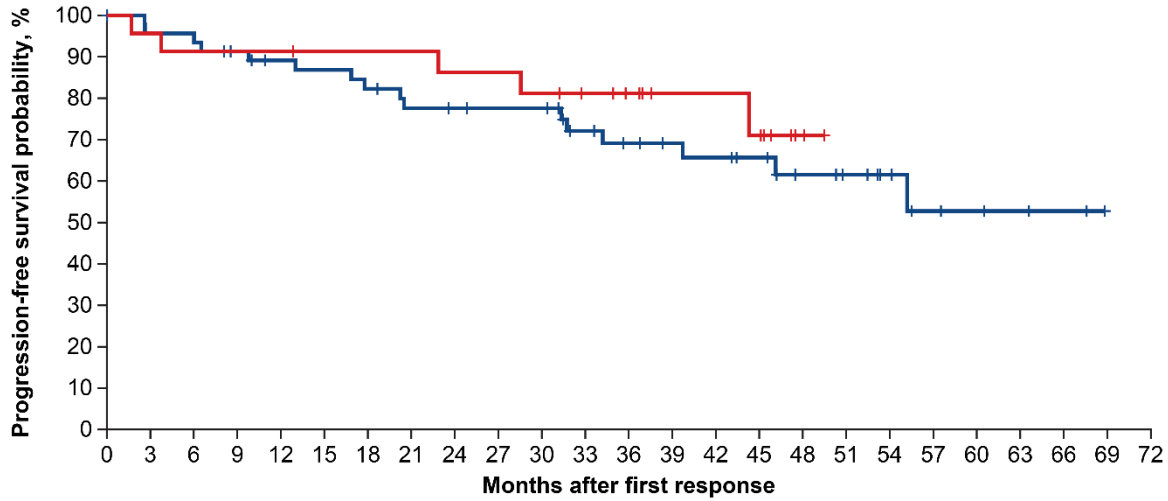
Progression-free survival



No. of patients at risk:

TN	24	23	22	22	20	20	19	19	19	17	17	17	13	11	8	8	6	1	0				
RR	49	49	45	44	42	41	40	38	35	35	35	35	29	25	23	21	19	15	13	8	6	3	3	1	0

Duration of response

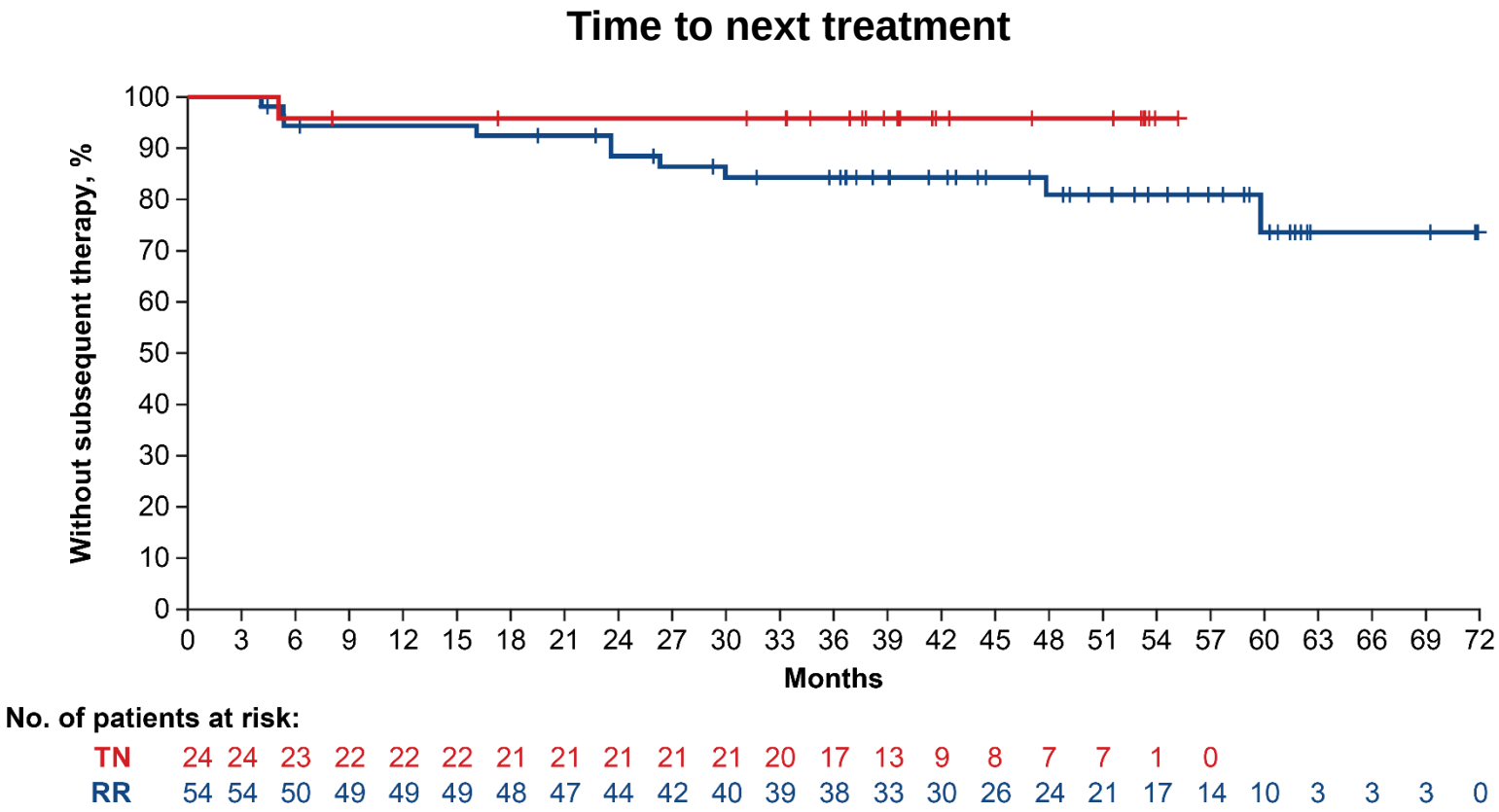


No. of patients at risk:

TN	24	22	21	19	19	18	18	18	17	17	16	13	11	8	8	7	2	0					
RR	46	44	44	42	39	38	36	33	32	31	31	25	22	20	19	17	13	11	8	5	4	3	2	0

PFS, progression-free survival; RR, relapsed refractory; TN, treatment naïve; WM, Waldenström macroglobulinemia.

Time to Next Treatment in Patients With TN or R/R WM



RR, relapsed refractory; TN, treatment naïve; WM, Waldenström macroglobulinemia.

Safety Summary

Event, n (%)	All patients with WM (N=78)
Any TEAE	78 (100)
Most common (in ≥20% of patients)	
Upper respiratory tract infection	43 (55)
Contusion	26 (33)
Cough	20 (26)
Diarrhea	18 (23)
Anemia	16 (21)
Headache	16 (21)
Grade ≥3	50 (64)
Serious	42 (54)
Leading to treatment discontinuation	13 (17)[a]
Cardiac	0
Leading to death	8 (10)[b]

Data cutoff: March 31, 2021.
Note: Richter transformation reported as AE and PD (unrelated).
[a]Abdominal sepsis (grade 5), septic arthritis (grade 5), acute myeloid leukemia (grade 5), *Escherichia coli* sepsis (grade 5), COVID-19 (grade 5), worsening bronchiectasis (grade 5), gastric adenocarcinoma (grade 5), *Scedosporium* infection (grade 5), pneumonia, prostate adenocarcinoma, metastatic neuroendocrine carcinoma, hematuria, purpura, breast cancer, cervical vertebral fracture (each n=1). [b]COVID-19, acute myeloid leukemia, *Escherichia coli* sepsis, abdominal sepsis, septic arthritis, worsening bronchiectasis, gastric adenocarcinoma, *Scedosporium* infection (subset of AEs leading to treatment discontinuation).
AE, adverse event; PD, progressive disease; TEAE, treatment-emergent adverse event; TN, treatment naïve; WM, Waldenström macroglobulinemia.

Adverse Events of Interest

AEs of interest, n (%)[a]	AU-003 WM (N=78)	
	Any grade	Grade ≥3
Infections	72 (92.3)	23 (29.5)
Minor bleeding[b]	52 (66.7)	8 (10.3)
Second primary malignancies[c]	23 (29.5)	10 (12.8)
Neutropenia[d]	15 (19.2)	13 (16.7)
Anemia	16 (20.5)	9 (11.5)
Thrombocytopenia[e]	8 (10.3)	2 (2.6)
Major hemorrhage[f]	8 (10.3)	8 (10.3)

Data cutoff: March 31, 2021.
[a]Pooled terms where appropriate. [b]Pooled term of minor bleeding; does not include bruising, petechiae or major hemorrhage. [c]Pooled term of second primary malignancies. [d]Pooled term includes neutropenia, neutrophil count decreased, or febrile neutropenia. [e]Thrombocytopenia or platelet count decreased. [f]Defined as any grade ≥3 hemorrhage.
AE, adverse event; WM, Waldenström macroglobulinemia.

Cardiovascular Disorders

Cardiovascular disorders, n (%)	AU-003 WM	Pooled analysis B-cell malignancies[d]	
	Zanubrutinib (n=78)	Zanubrutinib (N=1550)	Ibrutinib (N=422)
Median treatment duration, months	40.13	26.64	19.96
Any cardiovascular AE			
Atrial fibrillation/flutter	7 (9.0)	60 (3.9)	60 (14.2)
		EAIR: 0.13 vs 0.82 person-month ($p < 0.0001$)	
Ventricular arrhythmia (grade ≥2)[a]	0	11 (0.7)	6 (1.4)
Symptomatic Idiopathic (grade ≥2)[b]	0	5 (0.3)	6 (1.4)
		EAIR: 0.14 vs 0.87 per 100 person-years ($p = 0.0028$)	
Hypertension[c]	15 (19.2)	225 (14.5)	85 (20.1)
Any cardiovascular medical history			
Atrial fibrillation/flutter	4 (5.1)	101 (6.5)	26 (6.2)
Ventricular arrhythmia[a]	0	14 (0.9)	1 (0.2)
Hypertension[c]	24 (30.8)	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]
AE, adverse event; CTCAE, Common Terminology Criteria for Adverse Events; MedDRA, Medical Dictionary for Regulatory Activities; SMQ, standardized MedDRA query; WM, Waldenström macroglobulinemia.
1. Tam et al. LL&M 2022. Abstract 1324736.

Comparable Response Rate Between the QD and BID Doses in Patients With WM and Other B-Cell Malignancies in Study AU-003

Response, n (%)	160 mg BID	320 mg QD
R/R MCL	**n=14**	**n=18**
CR	4 (29)	4 (22)
ORR[a]	12 (86)	15 (83)
R/R and TN CLL	**n=81**	**n=40**
CR	11 (14)	9 (23)
ORR	76 (94)	40 (100)
R/R and TN WM	**n=47**	**n=22**
VGPR + CR rate	23 (49)	7 (32)
ORR	46 (98)	20 (91)

- Both regimens have been approved for WM and MZL by the US FDA, Health Canada, AUS, EMA and ROW
- Comparable safety, PK (AUC) and PD (BTK occupancy)
- No apparent exposure safety and efficacy relationships, which allows for extrapolation despite the small number of patients treated QD
- A total of 216 patients treated with 320 mg QD in zanubrutinib clinical studies as of May 2022

AUC, area under the curve; AUS, Australia; BID, twice daily; BTK, Bruton tyrosine kinase; CLL, chronic lymphocytic leukemia; CR, complete response; EMA, European Medicine Agency; MCL, mantle cell lymphoma; MZL, marginal zone lymphoma; ORR, overall response rate; PD, progressive disease; PK, pharmacokinetics; QD, once daily; R/R, relapsed/refractory; ROW, real-world evidence; TN, treatment naïve; US FDA, US Food and Drug Administration; VGPR, very good partial response; WM, Waldenström macroglobulinemia.

Tam C, et al. *Expert Rev Clin Pharmacol* 2021;14(11):1329-1344. Ou YC, et al, *Leuk Lymphoma* 2021;62(11):2612-2624.

CONCLUSIONS

- Long-term treatment with zanubrutinib was generally well tolerated and resulted in deep and durable responses
- Deep responses were observed in both TN patients and patients with R/R WM and in all molecular subtypes including *MYD88*^{WT}
- At median follow-up of 43.4 months, 17% of patients discontinued owing to AEs
- Based on the safety and efficacy data in the BGB-3111-AU-003 study, the optimal daily zanubrutinib dose was determined to be 320 mg QD or 160 mg BID

AE, adverse event; BID, twice daily; *MYD88,* myeloid differentiation primary response 88 gene; QD, once daily; R/R, relapsed/refractory; TN, treatment naïve; WM, Waldenström macroglobulinemia; WT, wild type.

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