Zanubrutinib for the Treatment of Patients With Waldenström Macroglobulinemia: Three Years of Follow-up

Abstract 8051

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INTRODUCTION

- Bruton tyrosine kinase (BTK) is an integral component of the B-cell receptor (BCR) pathway which mediates B-cell proliferation, migration, and adhesion, and is constitutively activated in Waldenström macroglobulinemia (WM)[1-3]
  - Inhibitors of BTK have established therapeutic activity in patients with WM[4]
- Zanubrutinib, a potent, selective, and irreversible BTK inhibitor (BTKi), was designed to maximize BTK occupancy and minimize off-target inhibition of Tyrosine protein kinase-Tec (TEC), interleukin-2-inducible T-cell kinase (ITK), and epidermal growth factor receptor (EGFR)-family kinases[5,6]
- Zanubrutinib was investigated in a first-in-human phase 1/2 study (AU-003) designed to evaluate the safety, pharmacokinetics, and antitumor activity of zanubrutinib in patients with B-cell malignancies
  - Study includes disease-specific cohorts, including patients with treatment-naive (TN) and relapsed/refractory (R/R) WM
  - Enrollment is complete, and a total of 384 patients have been dosed in this study, including 77 patients with WM
- At a median follow-up of **35.3 months**, we report safety and efficacy data for the 77 patients with WM treated with single-agent zanubrutinib

STUDY OBJECTIVES

- The objectives of this analysis were to evaluate safety, pharmacokinetics, and preliminary efficacy of zanubrutinib monotherapy in patients with TN or R/R WM

METHODS

- AU-003 is a first-in-human, open-label, multicenter, phase 1/2 study of zanubrutinib in patients with B-cell malignancies (**Figure 1**)

Figure 1. AU-003 Study Schema
Indication-Specific Expansion Cohorts

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	21 (21)
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

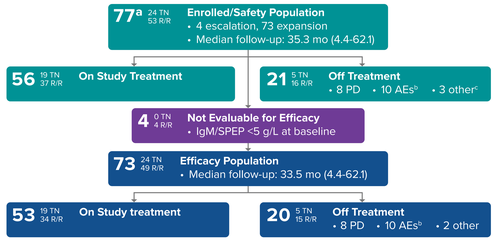
- WHO-defined B-cell malignancy
- >1 prior therapy (relapsed cohorts only)
- No available higher-priority treatment
- ECOG PS 0-2
- ANC >1000/μL, platelets >100,000/μL[b]
- Adequate renal and hepatic function; no significant cardiac disease[c]

Cohorts containing WM patients shown in blue

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 naive; WHO, World Health Organization; WM, Waldenström macroglobulinemia.
[a]Both doses RP2D, but as of protocol v.6, all patients were encouraged to switch to 160 mg bid. [b]Growth factor/transfusion allowed. [c]Anticoagulation allowed.

RESULTS

Figure 2. Disposition of Patients With WM



Data cutoff: January 29, 2020.
AE, adverse event; IgM, immunoglobulin M; PD, progressive disease; R/R, relapsed/refractory; SPEP, serum protein electrophoresis; TN, treatment naive; WM, Waldenström macroglobulinemia.
[a]WM patients with no prior BTK inhibitor exposure (1 patient was excluded as had prior ibrutinib). [b]Detailed in **Table 4**. [c]Radiation/transplant (n=1), noncompliance (n=1), and investigator decision (n=1).

Table 1. Patient and Disease Characteristics

Characteristic	TN (n=24)	R/R (n=53)	Total (N=77)
Age			
Median (range), y	65 (40-87)	68 (45-87)	67 (40-87)
>75 years, n (%)	3 (12.5)	13 (24.5)	16 (20.8)
Male, n (%)	16 (67)	45 (85)	61 (79)
ECOG PS, n (%)			
0/1	24 (100)	50 (94)	74 (96)
2	0 (0)	3 (6)	3 (4)
Extramedullary disease, n (%)[a]			
Lymphadenopathy	13 (54)	26 (49)	39 (51)
Splenomegaly	9 (38)	17 (32)	26 (34)
No. of prior systemic therapies, median (range)	NA	2 (1-8)	2 (1-8)
Genotype, n (%)[b]			
MYD88^{L265P}/*CXCR4*^{WT}	14 (58.3)	26 (49.1)	40 (51.9)
MYD88^{L265P}/*CXCR4*^{WHIM}	4 (16.7)	7 (13.2)	11 (14.3)
MYD88^{L265P}/*CXCR4*^{UNK}	2 (8.3)	5 (9.4)	7 (9.1)
MYD88^{WT}/*CXCR4*^{WT}	3 (12.5)	8 (15.1)	11 (14.3)
Missing	1 (0.04)	7 (13.2)	8 (10.4)
Study follow-up, median (range), mo	28.3 (8-44.4)	50 (4.4-62.1)	35.3 (4.4-62.1)

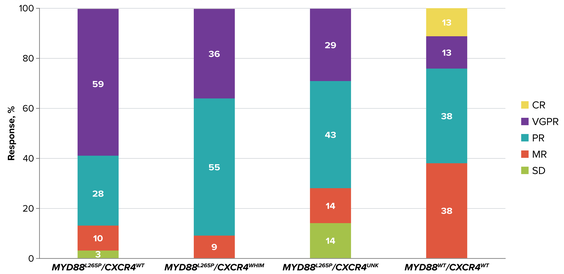
ECOG PS, Eastern Cooperative Oncology Group performance status; R/R, relapsed/refractory; TN, treatment naive; UNK, unknown; WT, wild-type.
[a]Identified by either computed tomography (CT) exam or physical exam [b]Genotype data were obtained from baseline bone marrow aspirate samples, or, if not available, post-baseline samples and determined by LDT/NGS.

Table 2. Best Overall Response by IWWM-6 by Investigator Assessment

Best Response, n (%)	TN Patients (n=24)	R/R Patients (n=49)	All Efficacy Evaluable (n=73)
ORR, n (%)[a]	24 (100)	46 (94)	70 (96)
MRR[b]	21 (88)	39 (80)	60 (82)
CR	0 (0)	1 (2)	1(1)
VGPR	9 (38)	24 (49)	33 (45)
PR	12 (50)	14 (29)	26 (36)
MR	3 (13)	7 (14)	10 (14)
SD	0 (0)	3 (6)	3 (4)
Time to response (≥PR), median (range), mo	1.87 (1.0-15.7)	1.84 (0.9-24.6)	1.87 (0.9-24.6)
Study follow-up, median (range), mo	28.3 (8-44.4)	40.8 (4.4-62.1)	33.5 (4.4-62.1)
36-mo PFS, % (95% CI)	91.5 (70.0-97.8)	75.3 (60.6-85.2)	80.3 (69.0-87.8)
36-mo OS, % (95% CI)	91.7 (53.9-98.8)	80 (64.9-89.2)	83.4 (71-90.9)
Genotype, n (%)			
MYD88^{L265P}/*CXCR4*^{WT}	14 (58.3)	25 (51.0)	39 (53.4)
MYD88^{L265P}/*CXCR4*^{WHIM}	4 (16.7)	7 (14.3)	11 (15.1)
MYD88^{L265P}/*CXCR4*^{UNK}	2 (8.3)	5 (10.2)	7 (9.6)
MYD88^{WT}/*CXCR4*^{WT}	3 (12.5)	5 (10.2)	8 (11.0)
Missing	1 (0.04)	7 (14.3)	8 (11.0)

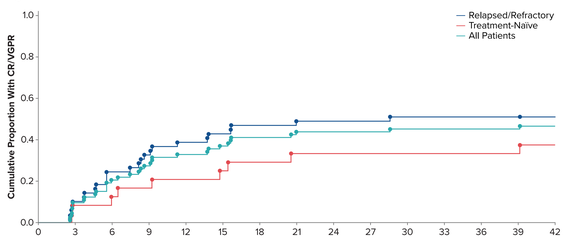
CI, confidence interval; CR, complete response; IWWM-6, 6th International Workshop on Waldenström Macroglobulinemia (requires reduction in EMD if present at baseline); LDT/NGS, laboratory developed test/next-generation sequencing; MR, minor response; MRR, major response rate; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; PR, partial response; R/R, relapsed/refractory; SD, stable disease; TN, treatment naive; UNK, unknown; VGPR, very good partial response; WT, wild-type.
[a]ORR: MR, PR, VGPR, CR. [b]MRR: PR, VGPR, CR.

Figure 3. Best Overall Response by *MYD88* and *CXCR4* Mutation Status in All WM Patients



Data cutoff: January 29, 2020.
CR, complete response; MR, minor response; PR, partial response; SD, stable disease; UNK, unknown; VGPR, very good partial response; WM, Waldenström macroglobulinemia; WT, wild-type.

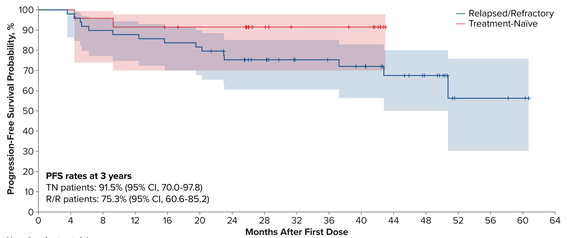
Figure 4. CR/VGPR Rate Increases Over Time



No. of patients in response															
R/R	5	12	16	19	21	23	24	24	24	25	25	25	25	25
TN	2	3	4	5	6	7	8	8	8	8	8	8	8	9
All Patients	7	15	20	24	27	30	32	32	32	33	33	33	33	34

CR, complete response; R/R, relapsed refractory; TN, treatment naive; VGPR, very good partial response; WM, Waldenström macroglobulinemia.

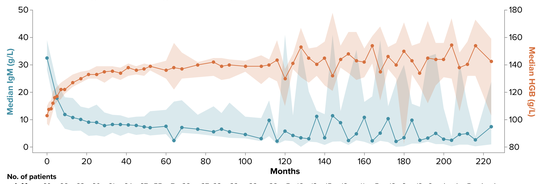
Figure 5. PFS in TN and R/R WM Patients



No. of patients at risk																															
R/R	49	49	48	45	44	43	43	42	41	41	41	40	38	35	32	30	26	24	24	23	22	21	18	15	13	11	9	3	3	3	3	2	0
TN	24	24	24	22	22	21	21	21	20	19	19	19	19	14	11	9	8	8	8	8	7	5	0										

Shaded area shows the 95% CI.
CI, confidence interval; PFS, progression-free survival; R/R, relapsed refractory; TN, treatment naive; WM, Waldenström macroglobulinemia.

Figure 6. Changes in Hemoglobin and IgM Levels Over Time



No. of patients																															
IgM	69	66	63	60	61	64	67	55	7	38	37	23	32	22	28	5	16	13	15	18	11	5	18	6	12	6	4	4	5	4	4
Hb	73	73	69	65	67	67	67	59	7	39	37	35	53	25	29	5	17	14	15	10	14	18	7	13	5	7	4	4	5	4	4

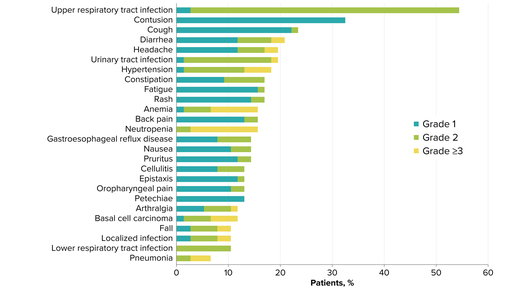
Note: Shaded areas show the error bars associated with each assessment. Four patients in the efficacy-evaluable set did not have IgM test results at baseline. Response assessments for these patients were based on SPEP M-protein.
HGB, hemoglobin; IgM, immunoglobulin M; SPEP, serum protein electrophoresis.

Table 4. Safety Summary

Event, n (%)	TN (n=24)	R/R (n=53)	Overall (N=77)
Any AE	24 (100)	53 (100)	77 (100)
Grade ≥3 AEs	11 (45.8)	37 (69.8)	48 (62.3)
Serious AEs	5 (20.8)	34 (64.2)	39 (50.6)
AEs leading to treatment discontinuation	3 (12.5)	7 (13.2)	10 (13.0)[a]
AEs leading to death	0 (0)	5 (9.4)	5 (6.5)[b]

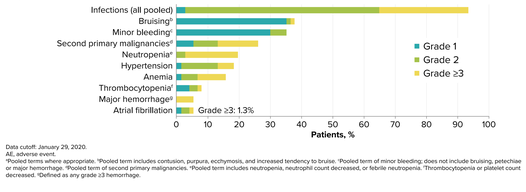
Data cutoff: January 29, 2020.
Note: Richter transformation reported as AE and PD (unrelated).
AE, adverse event; R/R, relapsed/refractory; TN, treatment naive.
[a]Abdominal sepsis (Gr 5), septic arthritis (Gr 5), worsening bronchiectasis (Gr 5), gastric adenocarcinoma (Gr 5), scedosporium infection (Gr 5), prostate adenocarcinoma, metastatic neuroendocrine carcinoma, acute myeloid leukemia, purpura, and breast cancer (each n=1). [b]Abdominal sepsis, septic arthritis, worsening bronchiectasis, gastric adenocarcinoma, scedosporium infection (subset of AEs leading to treatment discontinuation).

Figure 7. Common AEs Regardless of Causality



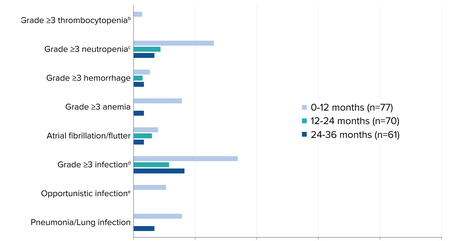
Data cutoff: January 29, 2020.
AE by preferred term.
Note: Figure includes all grades (≥10% of patients; and Grade 3/4 (≥2%). Grade 5 AEs were septic arthritis (missing relationship to zanubrutinib), scedosporium infection (unrelated), worsening of bronchiectasis (unrelated), abdominal sepsis (unrelated), and gastric adenocarcinoma (unrelated).
AE, adverse event.

Figure 8. AEs of Interest[a]



Data cutoff: January 29, 2020.
AE, adverse event.
[a]Pooled terms where appropriate. [b]Pooled term includes contusion, purpura, ecchymosis, and increased tendency to bruise. [c]Pooled term of minor bleeding; does not include bruising, petechiae or major hemorrhage. [d]Pooled term of second primary malignancies. [e]Pooled term includes neutropenia, neutrophil count decreased, or febrile neutropenia. [f]Thrombocytopenia or platelet count decreased. [g]Defined as any grade ≥3 hemorrhage.

Figure 9. Incidence of AEs of Interest Over Time[a]



Data cutoff: January 29, 2020.
AE, adverse event.
[a]Pooled terms where appropriate. [b]Thrombocytopenia or platelet count decreased. [c]Neutropenia, neutrophil count decreased, or febrile neutropenia. [d]All infection terms pooled. Only grade ≥3 infections reported here. [e]Opportunistic infections and pneumonia/lung infections are a subgroup of all pooled infections.

SUMMARY

- Long-term treatment with zanubrutinib was generally well tolerated and resulted in deep and durable responses
- Deep responses were observed in patients with both TN and R/R WM and in all molecular subtypes including *MYD88*^{WT}
- With a median 35 months of follow-up:
  - ORR of 96%, and CR/VGPR rate of 46% is excellent with the rate of CR/VGPR increasing over time
  - Discontinuation due to AEs occurred in 13% of patients
  - Grade 5 AEs occurred in 5 patients, none considered related to treatment
  - The rate of grade ≥3 atrial fibrillation was 1.3%

REFERENCES

1. Rickert RC. *Nat Rev Immunol*. 2013;13:578-591.
2. Choe H, Burn J. *Oncology (Williston Park)*. 2016;30:847-858.
3. Aalipour A, Advani RH. *Br J Haematol*. 2013;163:436-443.
4. Treon SP, et al. *Blood*. 2014;123:2791-2796.
5. Tam S, et al. ASH 2019. Abstract #499.
6. Tam CS, et al. *Blood*. 2019;134:851-859.

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DISCLOSURES

CST: Research funding from AbbVie, BeiGene, Janssen, Pharmacyclics, TG Therapeutics; consulting/advisory role with Abbvie, BeiGene, Janssen, LOXO, and Roche
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WN, ZT, EH, and SKA: Employment and equity ownership with BeiGene
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