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

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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 → **RP2D**[a] 320 mg qd or 160 mg bid → **DOSE EXPANSION**

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)

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

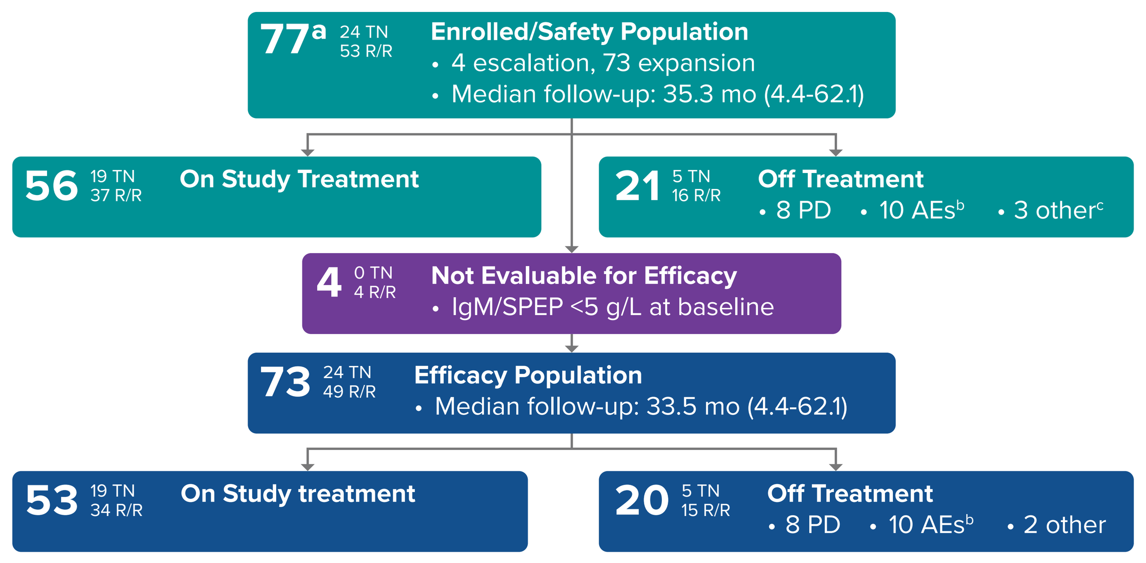
Key Eligibility
- WHO-defined B-cell malignancy
- >1 prior therapy (relapsed cohorts only)
- No available higher-priority treatment
- ECOG PS 0-2
- ANC >1000/μL, platelets >100,000/μL[b]
- Adequate renal and hepatic function; no significant cardiac disease[c]

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 naïve; 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 naïve; WM, Waldenström macroglobulinemia.
[a]WM patients with no prior BTK inhibitor exposure (1 patient was excluded as had prior ibrutinib). [b]Detailed in **Table 3**. [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)

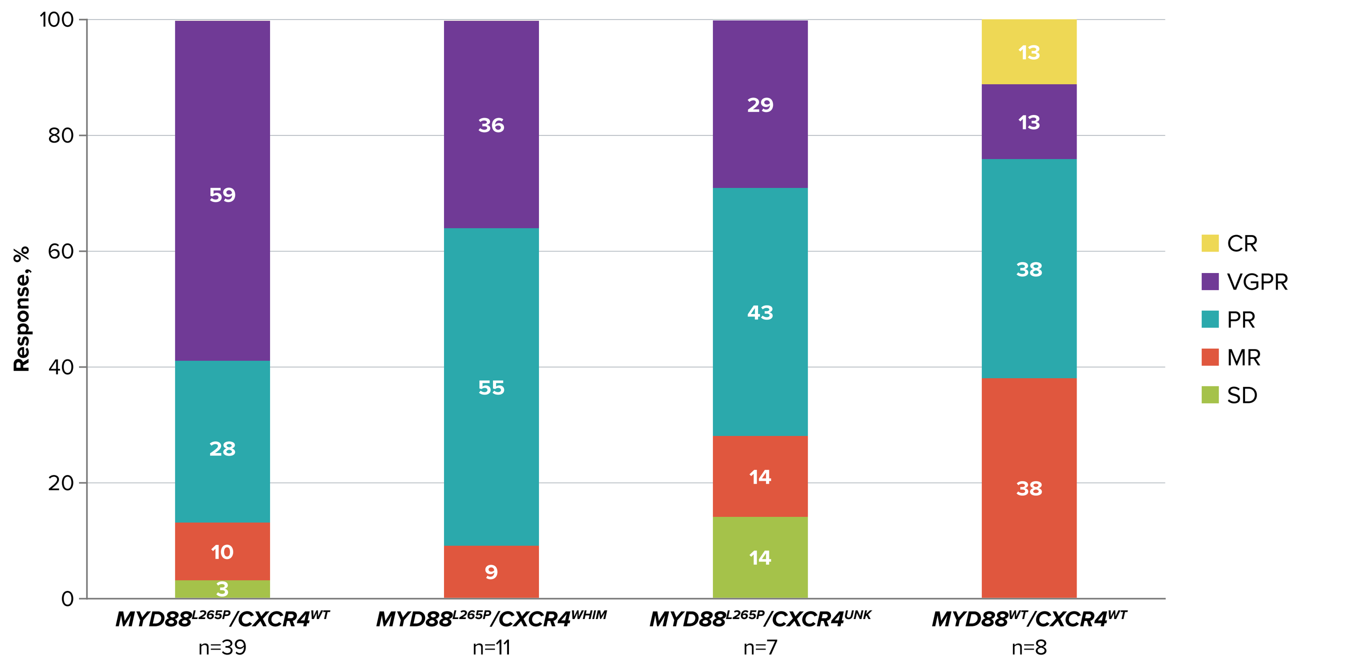
ECOG PS, Eastern Cooperative Oncology Group performance status; R/R, relapsed/refractory; TN, treatment naïve; UNK, unknown; WT, wild-type.
[a]Identified by either computed tomography (CT) exam or physical exam [b]Genotype data were obtained from baseline bone marrow aspirate samples, or, if not available,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

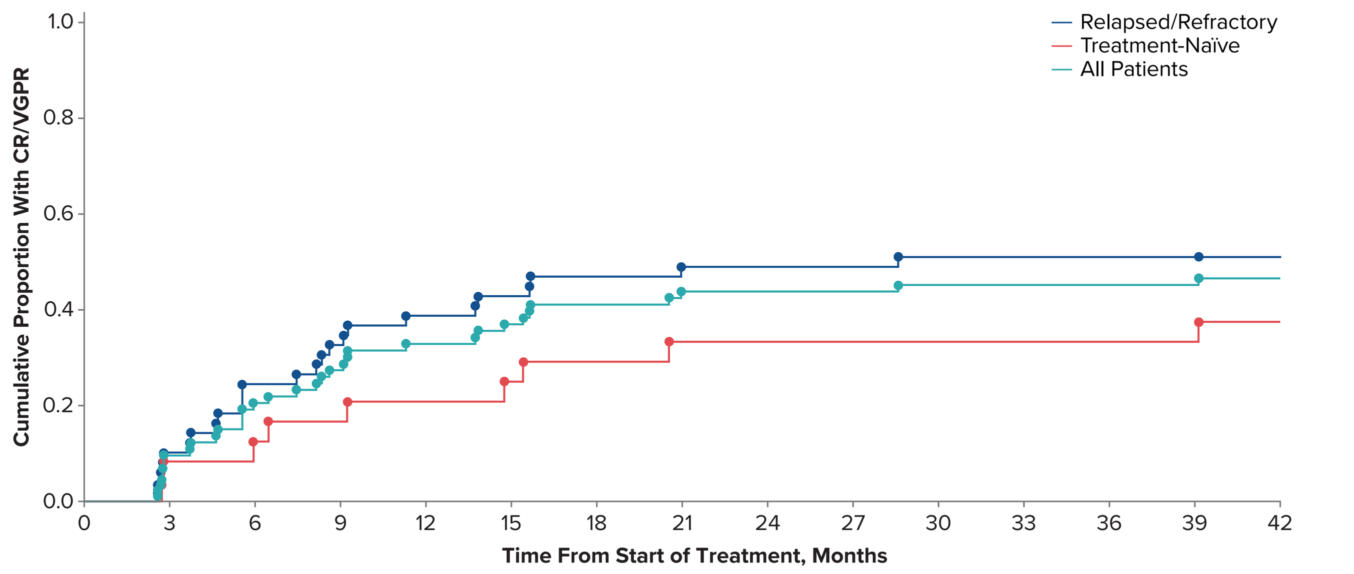
CI, confidence interval; CR, complete response; IWWM-6, 6th International Workshop on Waldenström Macroglobulinemia (requires reduction in EMD if present at baseline); LDT/NGS, laboratory developed test/next-generation sequencing; MR, minor response; MRR, major response rate; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; PR, partial response; R/R, relapsed/refractory; SD, stable disease; TN, treatment naïve; 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

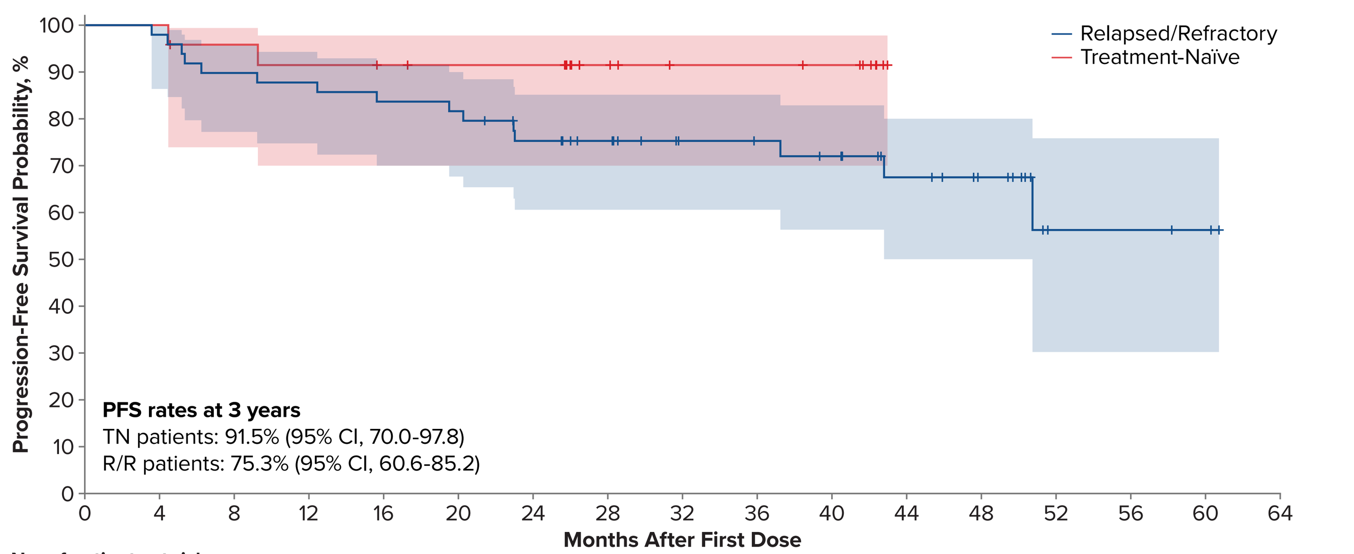


No. of patients in response

	3	6	9	12	15	18	21	24	27	30	33	36	39	42
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 naïve; VGPR, very good partial response; WM, Waldenström macroglobulinemia.

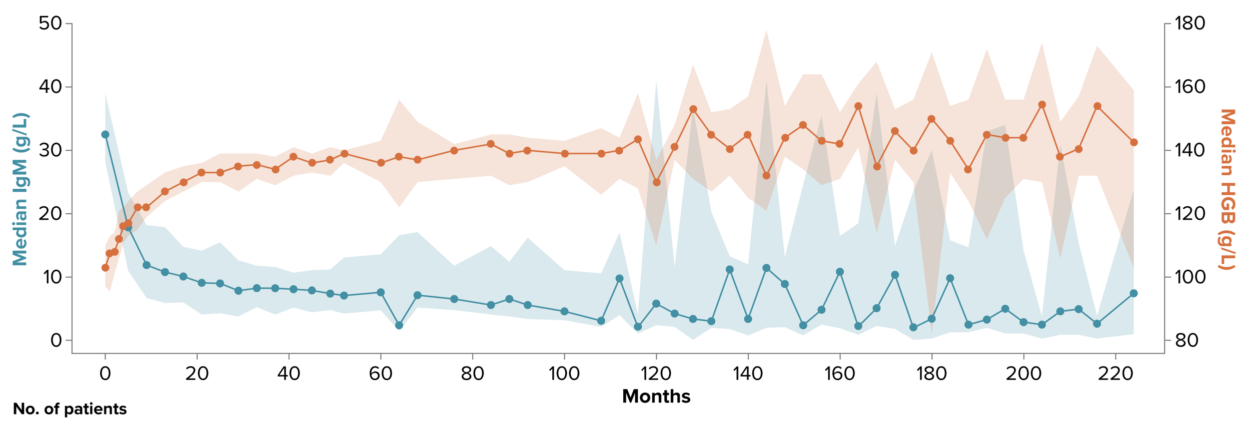
Figure 5. PFS in TN and R/R WM Patients



No. of patients at risk
R/R 49 49 48 45 44 43 43 42 41 41 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 naïve; 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

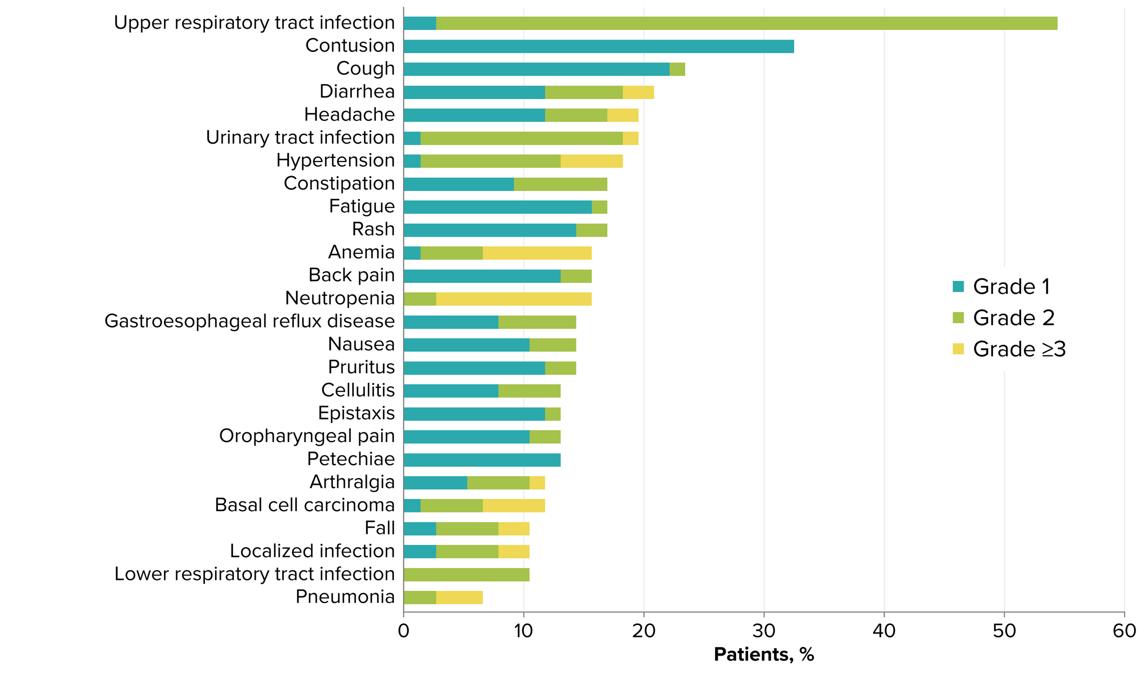
Note: Shaded areas show the error bars associated with each assessment. Four patients in the efficacy-evaluable set did not have IgM test results at baseline. Response assessments for these patients were based on SPEP M-protein.
HGB, hemoglobin; IgM, immunoglobulin M; SPEP, serum protein electrophoresis.

Table 3. 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]

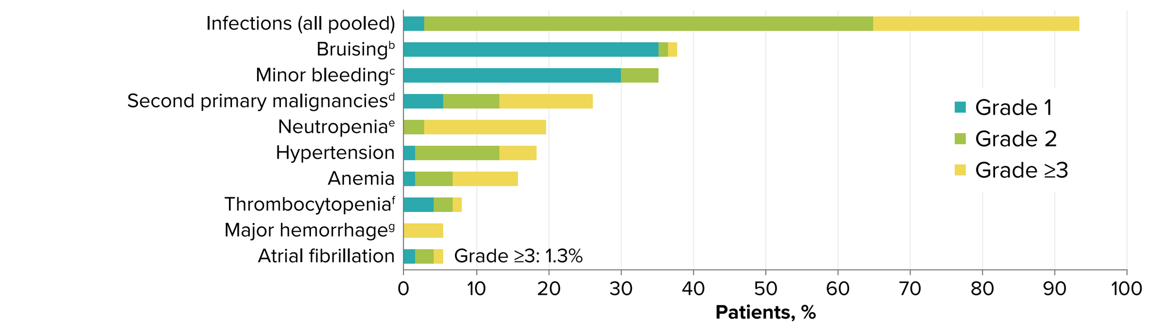
Data cutoff: January 29, 2020.
Note: Richter transformation reported as AE and PD (unrelated).
AE, adverse event; R/R, relapsed/refractory; TN, treatment naïve.
[a]Abdominal sepsis (Gr 5), septic arthritis (Gr 5), worsening bronchiectasis (Gr 5), gastric adenocarcinoma (Gr 5), *Scedosporium* infection (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



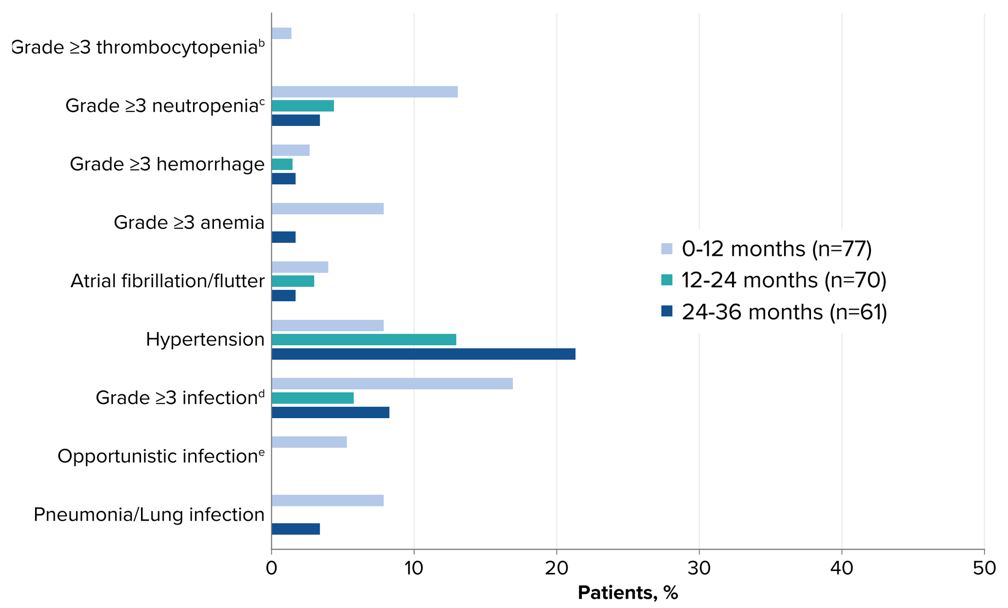
Data cutoff: January 29, 2020.
AE by preferred term.
Note: Figure includes all grades (≥10% of patients; and Grade 3/4 (≥2%). Grade 5 AEs were septic arthritis (missing relationship to zanubrutinib), *scedosporium* infection (unrelated), worsening of bronchiectasis (unrelated), abdominal sepsis (unrelated),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

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DISCLOSURES

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