ASPEN: Long-Term Follow-Up Results of a Phase 3 Randomized Trial of Zanubrutinib versus Ibrutinib in Patients With Waldenström Macroglobulinemia

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DISCLOSURES

- **Meletios Dimopoulos** served as a Consultant with Amgen, BeiGene, BMS, Janssen-Cilag, and Takeda, and received honoraria from Amgen, BeiGene, BMS, and Janssen-Cilag.

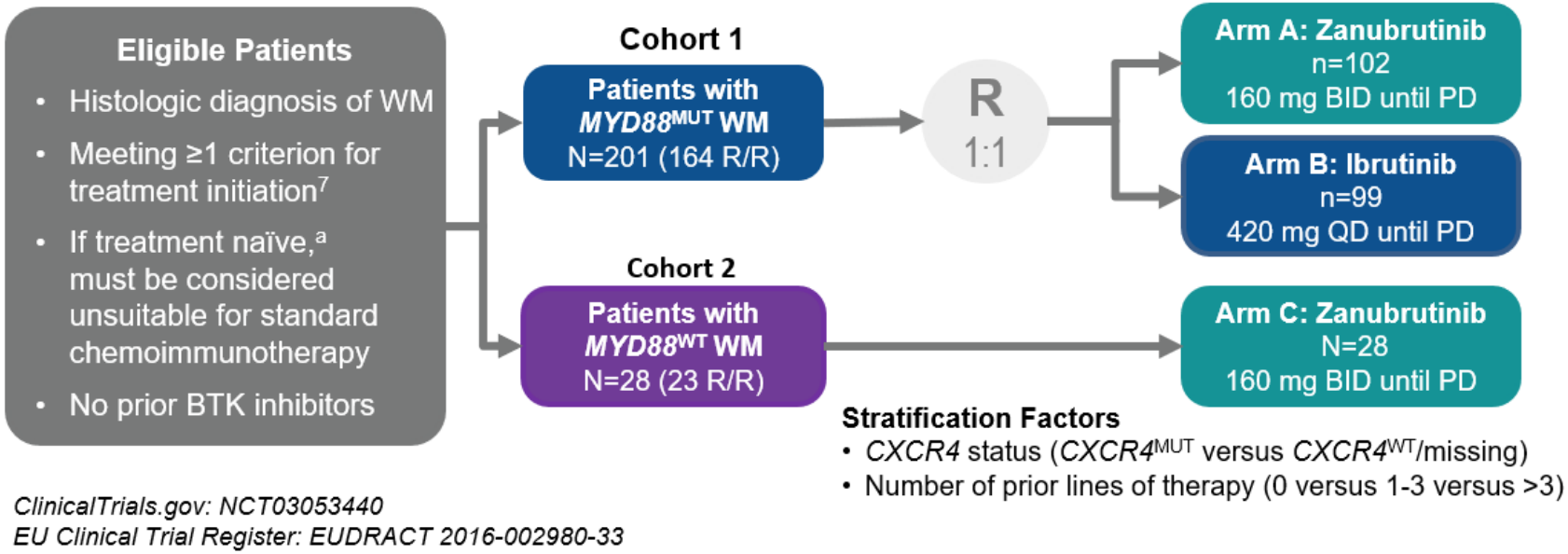
INTRODUCTION

- Zanubrutinib is a potent, selective, and irreversible next-generation Bruton tyrosine kinase (BTK) inhibitor designed to maximize BTK occupancy and minimize inhibition of off-target kinases[1]
- Zanubrutinib has demonstrated a complete and sustained BTK occupancy in peripheral blood mononuclear cells and lymph nodes[2]
- Zanubrutinib has shown equipotency against BTK compared with ibrutinib.[1]
- Zanubrutinib has high selectivity for BTK and minimal off-target inhibition of TEC- and EGFR-family kinases[1]
- Favorable drug interaction properties allow zanubrutinib to be co-administered with strong or moderate CYP3A inhibitors (eg, antifungals) at a reduced dose, as well as PPIs, acid-reducing agents, and antithrombotic agents[3,4]

CYP3A, cytochrome P450 3A; EGFR, epidermal growth factor receptor; PPI, proton pump inhibitor; TEC, tyrosine kinase expressed in hepatocellular carcinoma.

1. Guo et al. *J Med Chem* 2019;62:7923-7940. 2. Tam et al. *Blood* 2019;134:851-859. 3. Mu et al. *Cancer Chemother Pharmacol* 2020;85:391-399. 4. Ou et al. *Clin Transl Sci* 2021;14:764-77.

ASPEN: Phase 3 Study of Zanubrutinib Versus Ibrutinib in WM[1,2]



ClinicalTrials.gov: NCT03053440
EU Clinical Trial Register: EUDRACT 2016-002980-33

Primary objectives
- Efficacy of zanubrutinib versus ibrutinib in patients with activating *MYD88*^{MUT} WM
- Primary endpoint was CR+VGPR rate

Secondary objectives
- Efficacy, clinical benefit, and anti-lymphoma effects of zanubrutinib versus ibrutinib
- Safety and tolerability of zanubrutinib versus ibrutinib

Exploratory objectives
- Efficacy and safety of zanubrutinib in patients with *MYD88*^{WT} WM
- Efficacy of zanubrutinib versus ibrutinib according to *CXCR4* gene mutation in patients with *MYD88*^{MUT} WM

- At median follow-up of nearly 4 years, 66% of patients remained on treatment with zanubrutinib versus 52% with ibrutinib

[a]Up to 20% of the overall population.
BID, twice a day; BTK, Bruton tyrosine kinase; CR, complete response; *CXCR4*, C-X-C chemokine receptor type 4 gene; MUT, mutant; *MYD88*, myeloid differentiation primary response 88 gene; PD, progressive disease; QD, once a day; R, randomization; R/R. relapsed/refractory; VGPR, very good partial response; WM, Waldenström macroglobulinemia; WT, wild type.
1. Tam et al. *Future Oncol* 2018;14(22):2229-2237. 2. Tam et al. *Blood* 2020;136(18):2038-2050.

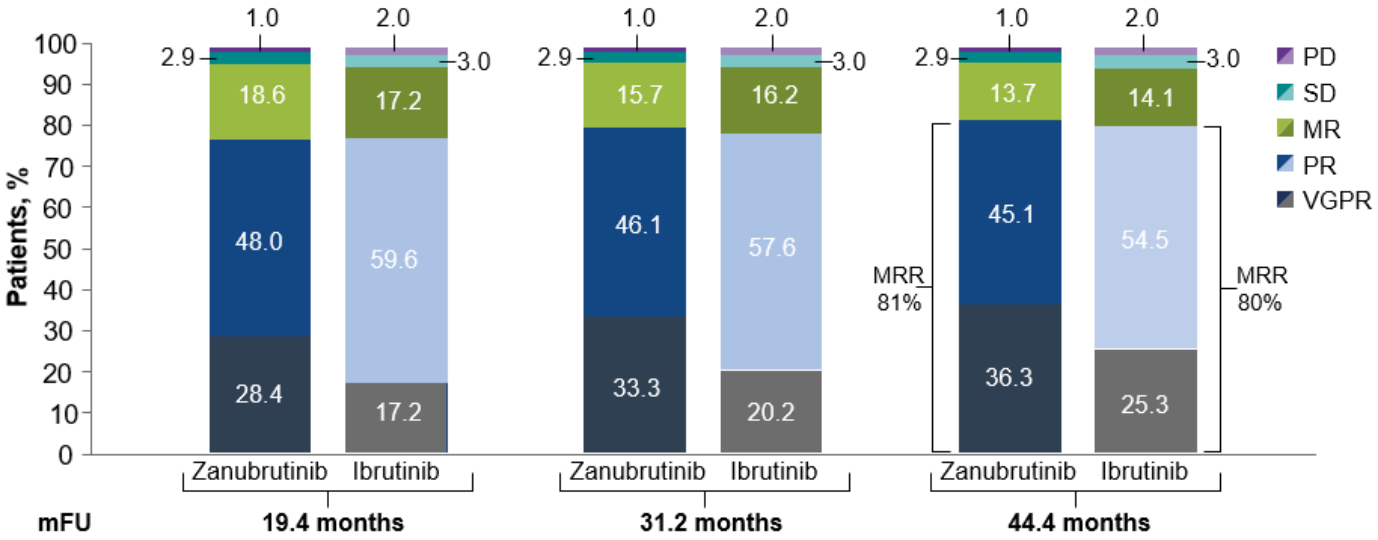
Baseline Characteristics

Characteristics	Cohort 1		Cohort 2
	Ibrutinib (n=99)	Zanubrutinib (n=102)	Zanubrutinib (N=28)
Age, median (range), years	70 (38-90)	70 (45-87)	72 (39-87)
>65, n (%)	**70 (70.7)**	61 (59.8)	19 (67.9)
>75, n (%)	22 (22.2)	**34 (33.3)**	12 (42.9)
Sex, n (%)			
Male	65 (65.7)	69 (67.6)	14 (50.0)
Prior lines of therapy, n (%)			
0	18 (18.2)	19 (18.6)	5 (17.9)
1-3	74 (74.7)	76 (74.5)	20 (71.4)
>3	7 (7.1)	7 (6.9)	3 (10.7)
Genotype by NGS, n (%)			
CXCR4^{WT}	72 (72.7)	65 (63.7)	27 (96.4)
CXCR4^{MUT} / *CXCR4*^{NS}	20 (20.2) / 13 (13.1)	**33 (32.4)** / 14 (13.7)	1 (3.6) / 0
Unknown	7 (7.1)	4 (3.9)	0
IPSS WM high score, n (%)	44 (44.4)	47 (46.1)	12 (42.9)
Hemoglobin ≤110 g/L, n (%)	53 (53.5)	**67 (65.7)**	15 (53.6)
Baseline IgM (central lab), median (range), g/L	34.2 (2.4-108.0)	31.8 (5.8-86.9)	28.5 (5.6-73.4)
Bone marrow involvement, median (range), %	60 (0-90)	60 (0-90)	22.5 (0-50)
Extramedullary disease by investigator, n (%)	66 (66.7)	63 (61.8)	16 (57.1)

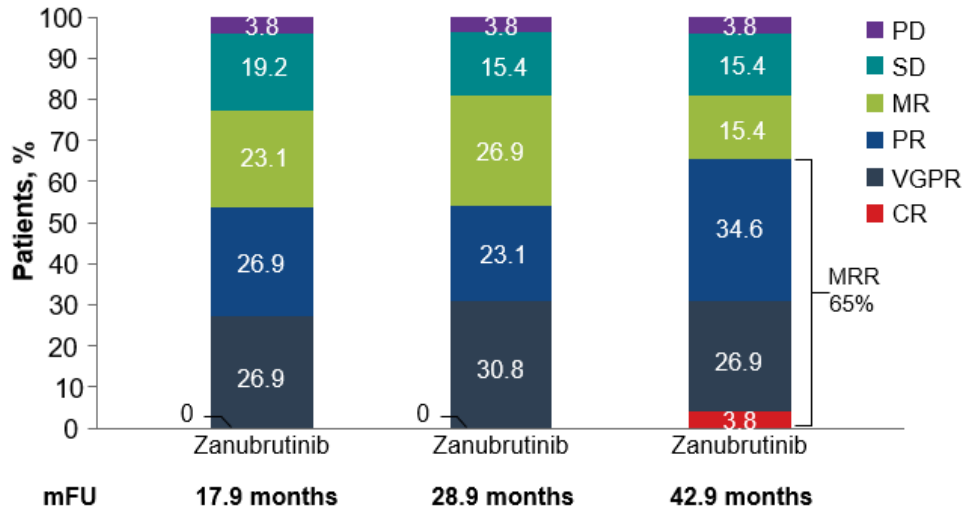
Bold blue text indicates >10% difference between arms in cohort 1.
CXCR4, C-X-C chemokine receptor type 4 gene; IPSS, International Prognostic Scoring System; MUT, mutant; NGS, next-generation sequencing; NS, nonsense mutation; WM, Waldenström macroglobulinemia; WT, wild type.

Best Overall Response by Investigator Over Time

Responses Over Time in Patients With *MYD88*^{MUT}



Responses Over Time Observed in *MYD88*^{WT}

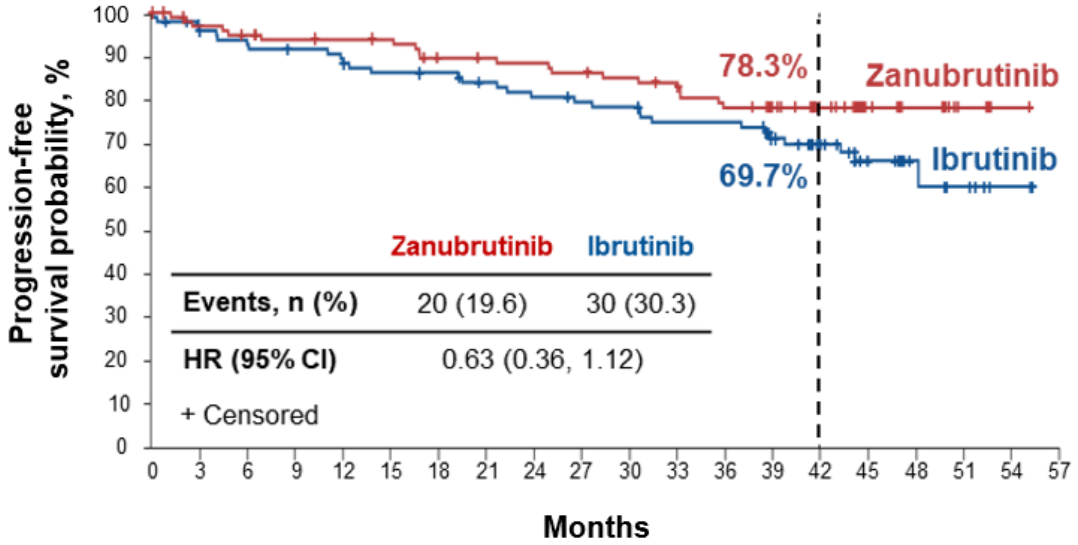


- At 44.4-month median follow-up, CR+VGPR rates by investigator were 36.3% (zanubrutinib) versus 25.3% (ibrutinib)

Data cutoff: October 31, 2021.
CR, complete response; *CXCR4*, C-X-C chemokine receptor type 4 gene; mFU, median follow-up; MR, major response; MRR, major response rate; MUT, mutant; *MYD88*, myeloid differentiation primary response 88 gene; PD, progressive disease; PR, partial response; SD, stable disease; VGPR, very good partial response; WT, wild type.

PFS and OS in ITT population (Cohort 1)

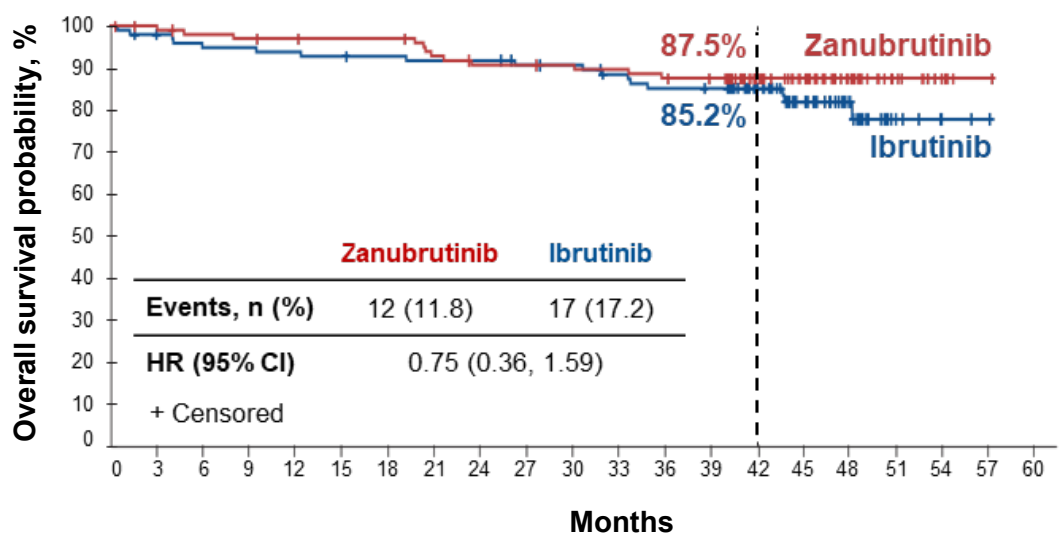
Progression-Free Survival[a]



No. of Patients at Risk:

Zanubrutinib	102	96	93	90	89	88	82	81	80	78	76	74	68	60	43	25	15	8	1	0
Ibrutinib	99	92	88	85	83	79	78	74	71	69	68	64	64	52	41	27	11	6	2	0

Overall Survival[a]



No. of Patients at Risk:

Zanubrutinib	102	100	97	96	95	94	94	89	86	86	85	84	82	80	65	49	27	13	5	1	0
Ibrutinib	99	96	93	92	91	90	89	88	88	85	84	80	77	76	62	43	21	7	3	1	0

- In patients with *MYD88*^{MUT} WM, median PFS and median OS were not yet reached, with hazard ratio estimates favoring zanubrutinib

Data cutoff: October 31, 2021.
[a]By investigator assessment.
HR, hazard ratio; MUT, mutation; *MYD88*, myeloid differentiation primary response 88 gene; PFS, progression-free survival; OS, overall survival; WM, Waldenström macroglobulinemia; WT, wild type.

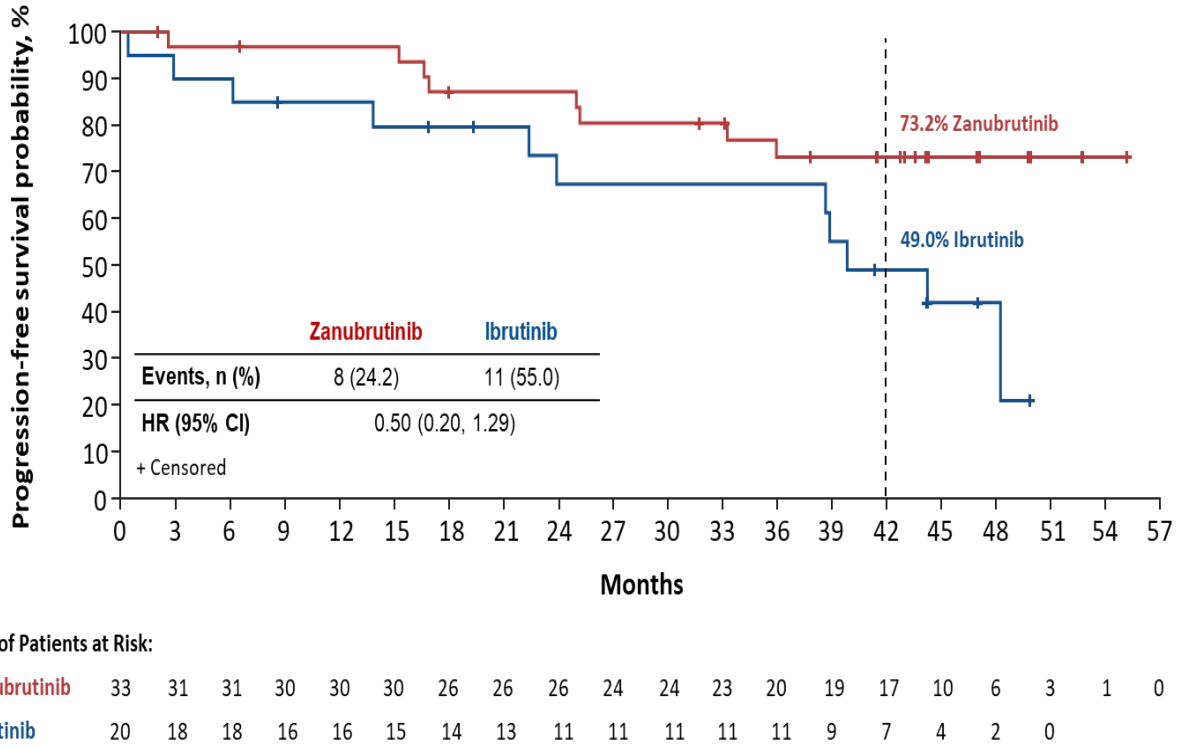
Response and PFS in Patients With *MYD88*^{MUT} by *CXCR4*^{MUT} Status

Response Assessment by *CXCR4* Status[a]

Response	*CXCR4*^{MUT} Ibrutinib (n=20)	*CXCR4*^{MUT} Zanubrutinib (n=33)	*CXCR4*^{WT} Ibrutinib (n=72)	*CXCR4*^{WT} Zanubrutinib (n=65)
VGPR or better, n (%)	2 (10.0)	**7 (21.2)**	22 (30.6)	**29 (44.6)**
Major response, n (%)	13 (65.0)	**26 (78.8)**	61 (84.7)	54 (83.1)
Overall response, n (%)	19 (95.0)	30 (90.9)	68 (94.4)	63 (96.9)
Median time to major response, median (months)	6.6	3.4	2.8	2.8
Median time to VGPR, median (months)	31.3	11.1	11.3	6.5

Bold blue text indicates >10% difference between arms.

PFS in Patients With *MYD88*^{MUT}*CXCR4*^{MUT}



Data cutoff: October 31, 2021.

[a]*CXCR4* mutation determined by NGS. Ninety-two ibrutinib patients and 98 zanubrutinib patients had NGS results available.

CXCR4, C-X-C chemokine receptor type 4 gene; HR, hazard ratio; MR, major response; MUT, mutant; PFS, progression-free survival; VGPR, very good partial response.

Overall Safety Summary

Category, n (%)	Cohort 1		Cohort 2
	Ibrutinib (n=98)	Zanubrutinib (n=101)	Zanubrutinib (n=28)
Patients with ≥1 AE	98 (100.0)	100 (99.0)	26 (92.9)
Grade ≥3	71 (72.4)	75 (74.3)	20 (71.4)
Serious	49 (50.0)	57 (56.4)	14 (50.0)
AE leading to death	5 (5.1)[a]	3 (3.0)[b]	3 (10.7)[c]
AE leading to treatment discontinuation	20 (20.4)	9 (8.9)	6 (21.4)
Cardiac AEs[d]	4 (4.1)	1 (1.0)	1 (3.6)
AE leading to dose reduction	26 (26.5)	16 (15.8)	2 (7.1)
AE leading to dose held	62 (63.3)	63 (62.4)	18 (64.3)
COVID-19–related AE	4 (4.1)	4 (4.0)	2 (7.1)

- Most common AEs that led to discontinuation were cardiac disorder (n=4 [4%], includes 2 due to atrial fibrillation) and infection (4%) with ibrutinib, versus second malignancy (4%) with zanubrutinib

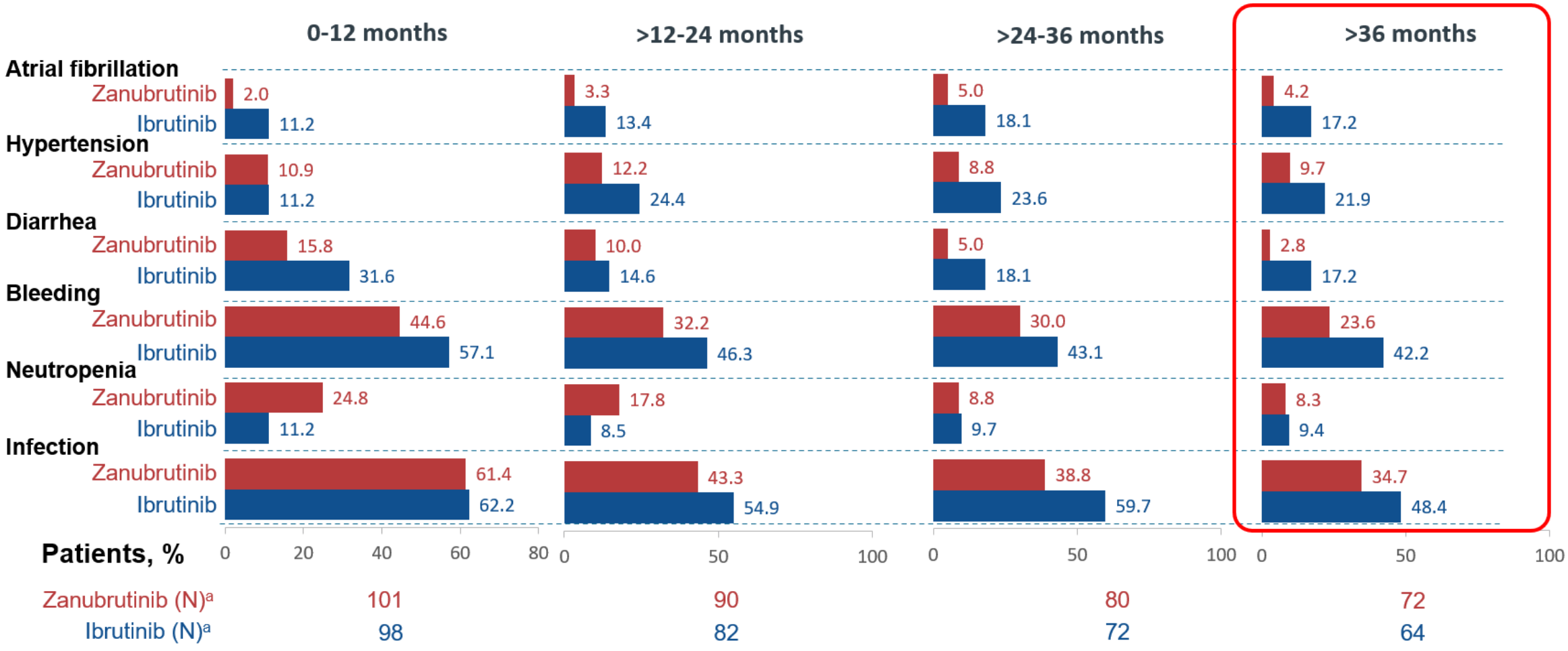
Data cutoff: October 31, 2021.
[a]Cardiac failure acute, death (unexplained), pneumonia, sepsis (n=2). [b]Cardiomegaly (cardiac arrest after plasmapheresis), metastatic malignant melanoma, subdural hematoma (after a fall). [c]Cardiac arrest, COVID-19 infection, lymphoma transformation. [d]Cardiac disorder system organ class. AE, adverse event

Adverse Events of Interest (Cohort 1)

AEs,[a] n (%)	Any grade		Grade ≥3	
	Ibrutinib (n=98)	Zanubrutinib (n=101)	Ibrutinib (n=98)	Zanubrutinib (n=101)
Infection	78 (79.6)	80 (79.2)	**27 (27.6)**	22 (21.8)
Bleeding	61 (62.2)	56 (55.4)	10 (10.2)	9 (8.9)
Diarrhea	**34 (34.7)**	23 (22.8)	2 (2.0)	3 (3.0)
Hypertension*	**25 (25.5)**	15 (14.9)	**20 (20.4)***	10 (9.9)
Atrial fibrillation/ flutter*	**23 (23.5)***	8 (7.9)	**8 (8.2)***	2 (2.0)
Anemia	22 (22.4)	18 (17.8)	6 (6.1)	**12 (11.9)**
Neutropenia*[b]	20 (20.4)	**35 (34.7)***	10 (10.2)	**24 (23.8)***
Thrombocytopenia	17 (17.3)	17 (16.8)	6 (6.1)	11 (10.9)
Second primary malignancy/ nonskin cancers	17 (17.3)/ 6 (6.1)	17 (16.8)/ 6 (5.9)	3 (3.1)/ 3 (3.1)	6 (5.9)/ 4 (4.0)

Bold blue text indicates rate of AEs with ≥10% (all grades) or ≥5% (grade ≥3) difference between arms.
Data cutoff: October 31, 2021.
*Descriptive purposes only, 1-sided $P < 0.025$ in rate difference in all grades and/or grade ≥3. [a]Grouped terms. [b]Including preferred terms of neutropenia, neutrophil count decreased, febrile neutropenia, and neutropenic sepsis.
AE, adverse event.

Prevalence Analysis for Adverse Events of Interest (Cohort 1)



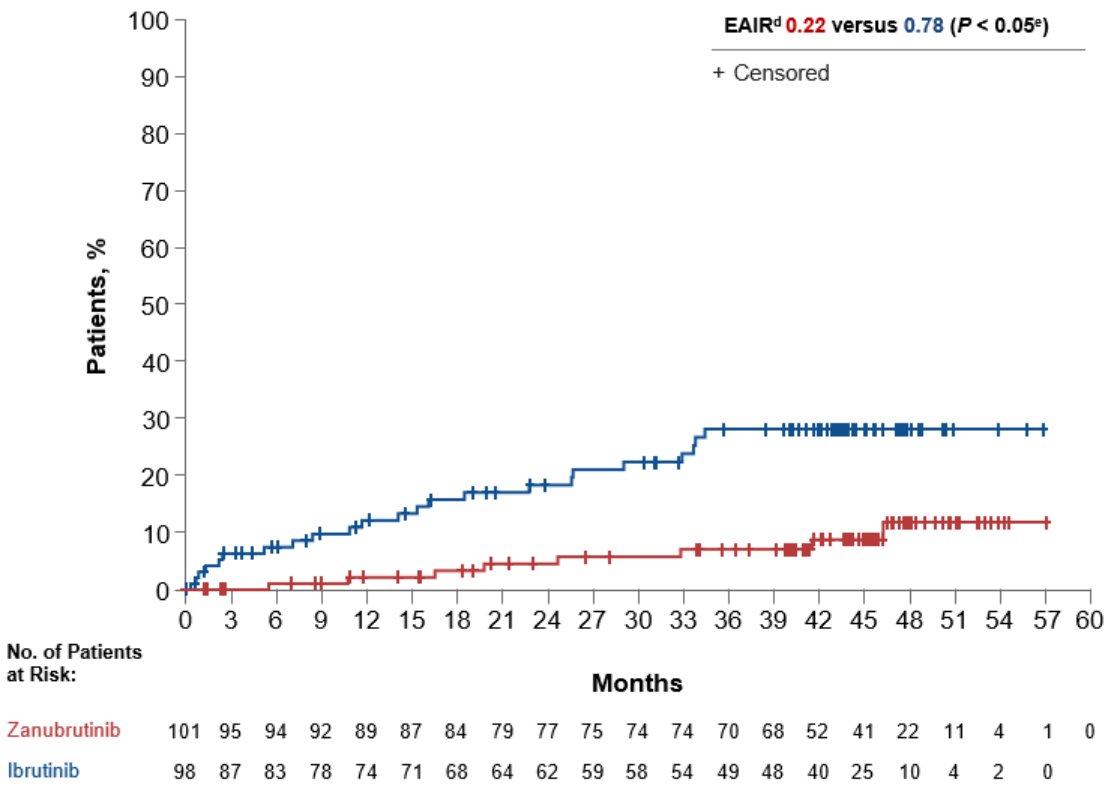
Data cutoff: October 31, 2021. Percentage is based on N. [a]N is the number of patients who are on treatment in each time interval or who discontinued treatment but on the time from first dose date to the earliest date (last dose date +30 days, initiation of new anticancer therapy, end of study, death or cutoff date) is within the time interval.

Cardiovascular Disorders

Cardiovascular AEs

Cardiovascular Disorders, n (%)	ASPEN cohort 1 WM		Pooled analysis B-cell malignancies	
	Ibrutinib (n=98)	Zanubrutinib (n=101)	Ibrutinib (N=422)	Zanubrutinib (N=1550)
Median treatment duration, months	42.23	43.37	19.96	26.64
Any Cardiovascular AE				
Atrial fibrillation/flutter*	23 (23.5)	8 (7.9)	60 (14.2)	60 (3.9)
Ventricular arrhythmia (VA)[a] Grade ≥2	1 (1.0)	0	6 (1.4)	11 (0.7)
Symptomatic idiopathic VA[b]	1 (1.0)	0	6 (1.4)*	5 (0.3)*
Hypertension[c,*]	25 (25.5)	15 (14.9)	85 (20.1)	225 (14.5)
Any Cardiovascular Medical History				
Atrial fibrillation/flutter	8 (8.2)	10 (9.9)	26 (6.2)	101 (6.5)
Ventricular arrhythmia[a]	0	1 (1.0)	1 (0.2)	14 (0.9)
Hypertension[c]	45 (45.9)	39 (38.6)	206 (48.8)	669 (43.2)

Atrial Fibrillation/Flutter



[a]Ventricular arrhythmia including ventricular tachyarrhythmia (SMQ narrow), ventricular arrhythmias and cardiac arrest (High Level Term MedDRA version 24.0). [b]Symptomatic idiopathic ventricular arrhythmia is defined as a ventricular arrhythmia occurring in structurally normal hearts in the absence of myocardial scarring and active infections and were grade ≥2 per CTCAE. [c]Including hypertension (SMQ narrow). [d]EAIR, as incidence per 100 person-month. [e]Descriptive 2-sided *P* value. **P* <0.05 for EAIR difference between treatments.
AE, adverse event; EAIR, exposure-adjusted incidence rates; SMQ, Standardized MedDRA (Medical Dictionary for Regulatory Activities) queries; VA, ventricular arrhythmia.

CONCLUSIONS

- With long-term follow-up, zanubrutinib continued to demonstrate clinically meaningful efficacy in patients with WM
  - Although not statistically significant at primary analysis, a consistent trend of deeper, earlier, and more durable responses (CR+VGPR) compared with ibrutinib was observed over time
  - PFS and OS continued to favor zanubrutinib treatment compared with ibrutinib
- Zanubrutinib provided faster and deeper responses in patients with *MYD88*^{MUT} *CXCR4*^{MUT} compared to ibrutinib, and responses to zanubrutinib in patients with *MYD88*^{WT} (cohort 2) continued to deepen over time
- Safety advantages of zanubrutinib remained consistent with less off-target activity compared with ibrutinib
  - Fewer patients discontinued zanubrutinib owing to AEs
  - Cardiovascular adverse events were less common in patients receiving zanubrutinib

AE, adverse event; CR, complete response; *CXCR4*, C-X-C chemokine receptor type 4 gene; *MYD88*, myeloid differentiation primary response 88 gene; VGPR, very good partial response; MUT, mutant; OS, overall survival; PFS, progression-free survival; WM, Waldenström macroglobulinemia; WT, wild type.

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