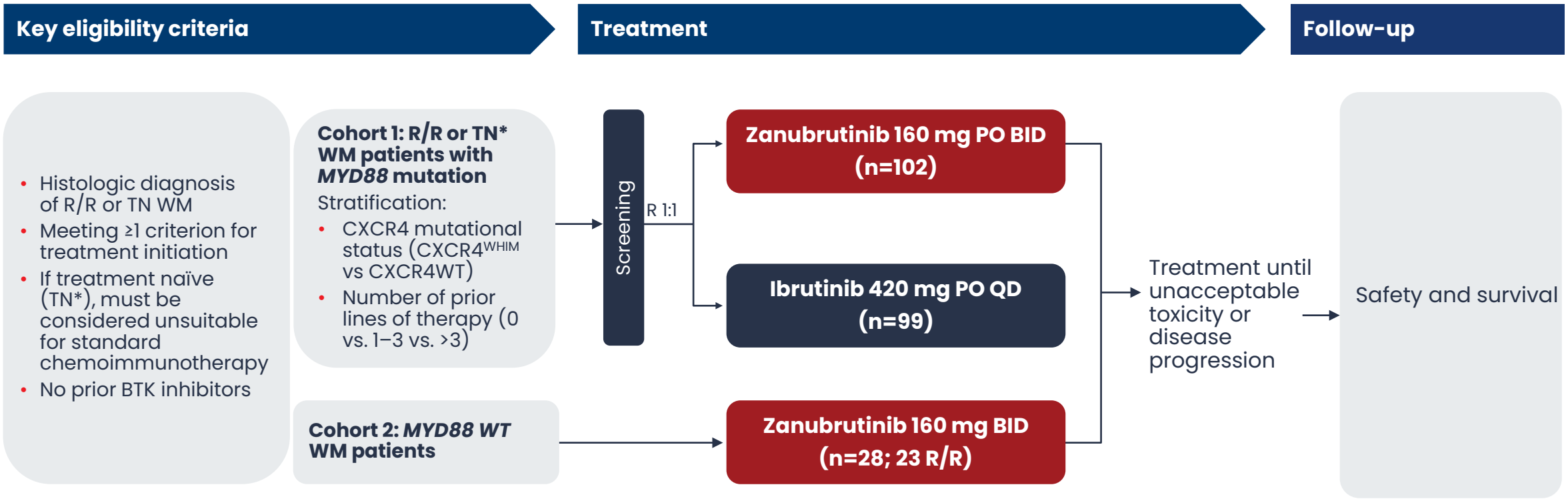
ASPEN

ASPEN Trial Design

Phase 3

Study Identifier:
BGB-3111-302, NCT03053440

Primary Endpoints: CR/VGPR rate
Secondary Endpoints: MRR (≥PR), PFS, DoR, symptom resolution, OS, safety



Data cutoff: October 31, 2021.
[a]Must be considered inappropriate candidates for treatment with a standard chemo-immunotherapy regimen.
BID=twice daily, BTK, Bruton tyrosine kinase, CR=complete response, CXCR4=C-X-C motif chemokine receptor 4, DoR=duration of response, MRR=major response rate, OS=overall survival, PFS=progression-free survival, PO=per oral, PR=partial response, QD=once daily, R=randomized, R/R=relapsed/refractory, TN=treatment naïve, VGPR=very good partial response, WHIM=warts, hypogammaglobulinemia, infections, and myelokathexis, WM=Waldenström macroglobulinemia, WT=wild type.
1. ClinicalTrials.gov. https://clinicaltrials.gov/ct2/show/NCT03053440. Accessed October 9, 2025; 2. Dimopolous MA et al. *JCO*. 2023 doi:10.1200/JCO.22.02830.

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Baseline Demographics and Disease Characteristics

Characteristics	Cohort 1		Cohort 2
	Ibrutinib (n=99)	Zanubrutinib (n=102)	Zanubrutinib (n=28)
Age, years median (range)	70 (38-90)	70 (45-87)	72 (39-87)
≥65 years, n (%)	**70 (70.7)**	61 (59.8)	19 (67.9)
≥75 years, 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)	19 (67.9)
CXCR4^{MUT}	20 (20.2)	**33 (32.4)**	1 (3.6)
Unknown[a]	7 (7.1)	4 (3.9)	8 (28.6)
IPSS WM, n (%)			
Low	13 (13.1)	17 (16.7)	5 (17.9)
Intermediate	42 (42.4)	38 (37.3)	11 (39.3)
High	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 (g/L, central lab), median (range)	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 (0-90)
Extramedullary disease by investigator, n (%)	66 (66.7)	63 (61.8)	16 (57.1)

Data cutoff: October 31, 2021.
Bold text indicates >10% difference between arms in cohort 1. [a]Confirmatory genotyping by NGS was performed for ad hoc analyses. Nineteen patients (11 in Cohort 1, two in Cohort 2) had unknown *CXCR4* mutation status because of withdrawal of consent (one), quality control failure (nine), or sample not collected (nine); two patients in Cohort 2 had unknown *MYD88* mutation status because of insufficient sample.
CXCR4=C-X-C motif chemokine receptor 4, IPSS=international prognostic scoring system, MUT=mutant, NGS=next generation sequencing, WM=Waldenström macroglobulinemia, WT=wild type.
Dimopolous MA et al. *JCO.* 2023 doi:10.1200/JCO.22.02830.

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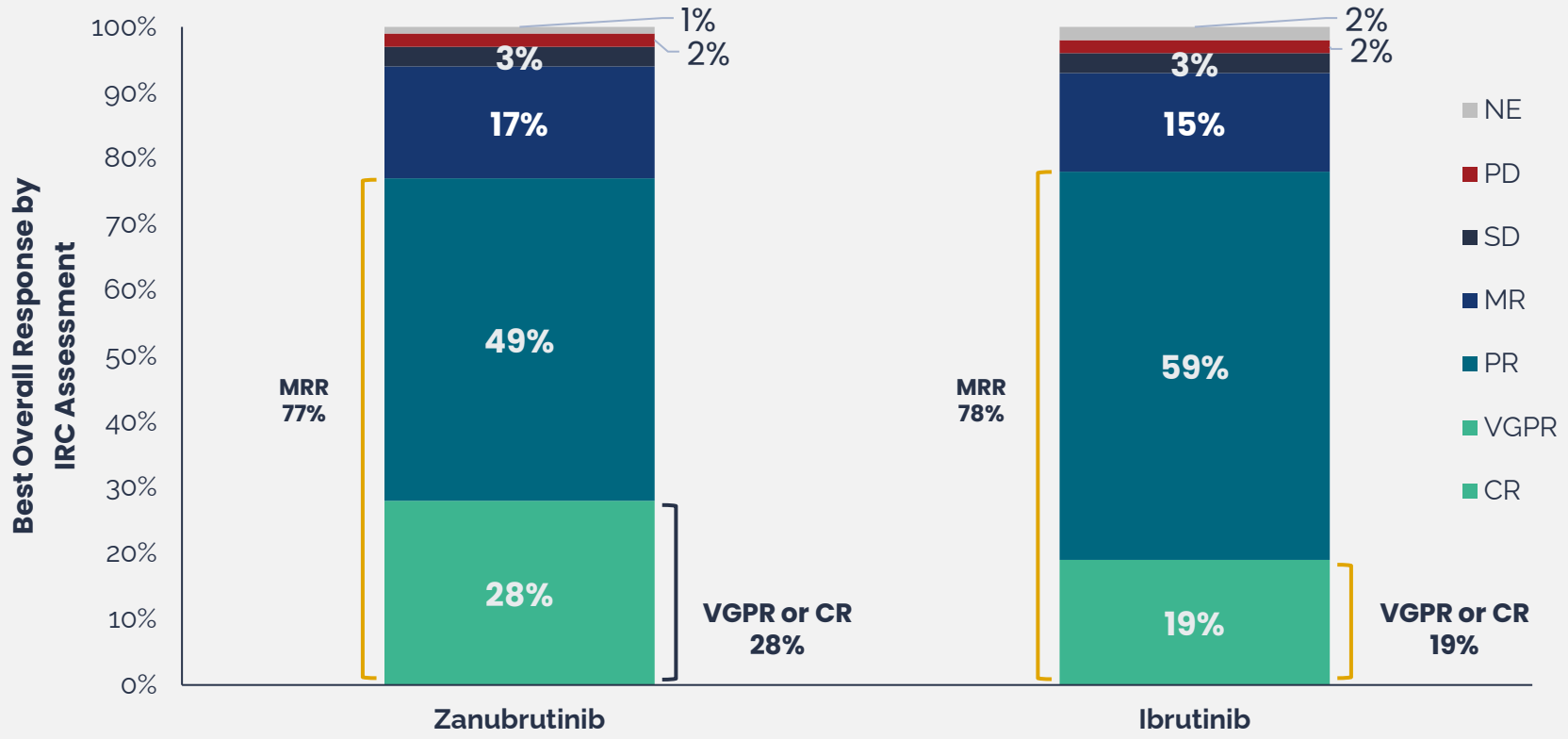
Primary Endpoint: Best Overall Response by Investigator

Zanubrutinib was associated with a CR/VGPR response rate of **28% compared with ibrutinib of 19%** (*P*=0.09).
No patient achieved a CR.

- The primary hypothesis of superiority in CR/VGPR rate (by IRC) was not met

Median follow-up: 19.4 months



Data cutoff: August 31, 2019.
Percentages are based on N, the number of randomized patients. *NE includes patients with unknown response, disease flare, and study discontinuation prior to first disease assessment.
CR=complete response, IRC=independent review committee, MR=minimal response, MRR=major response rate, NE=not evaluable, PD=progressive disease, PR=partial response, SD=stable disease, VGPR=very good partial response.
Tam CS et al. *Blood.* 2020;136(18):2038-2050.

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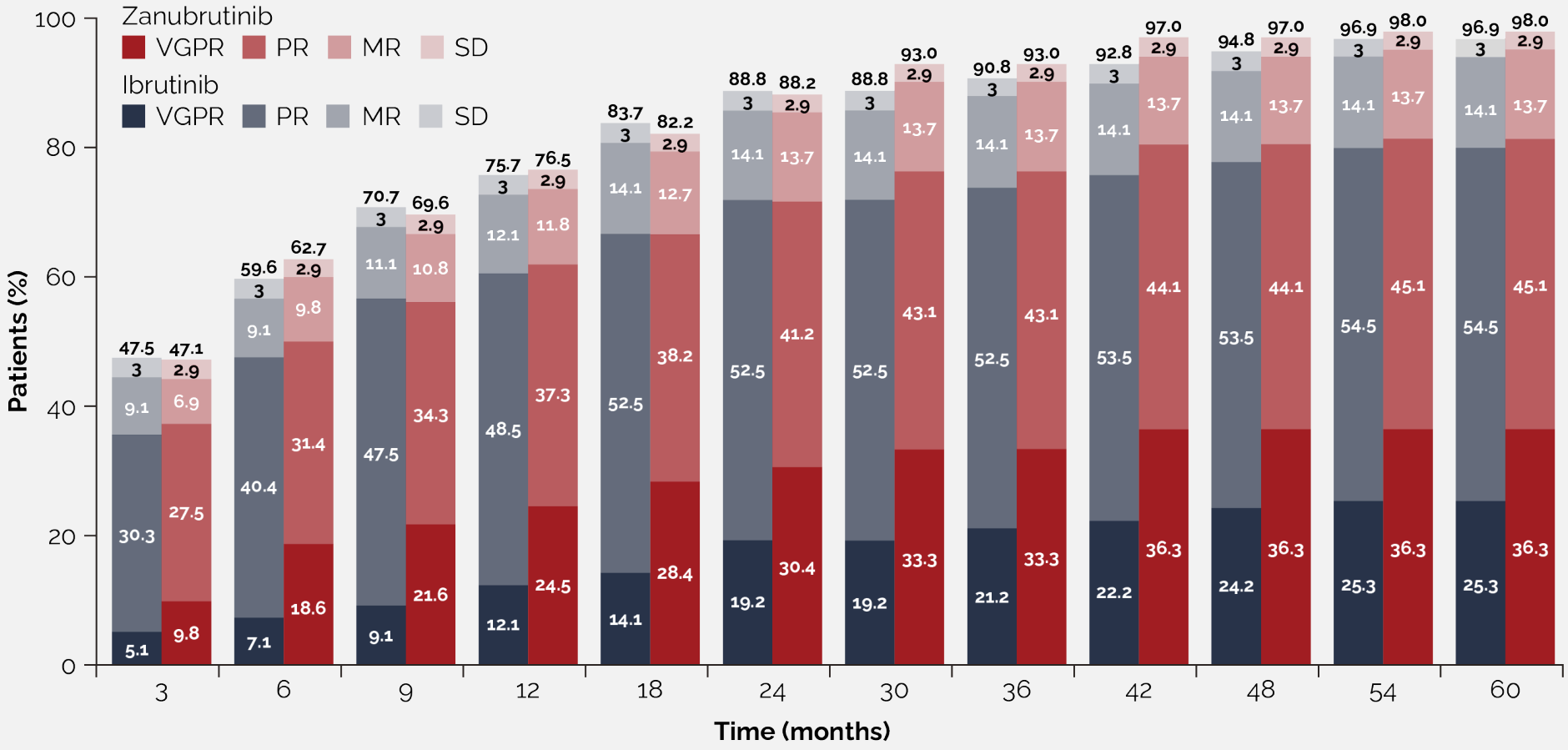
Best Overall Response by Investigator Over Time



Median follow-up: 44.4 months

- VGPR rates increased over time and were numerically higher with zanubrutinib than ibrutinib at all time points

Image adapted from Dimopoulos MA et al. *J Clin Oncol*. 2023. DOI: 10.1200/JCO.22.02830.
Data cutoff: October 31, 2021.
MR=minor response, PR=partial response, SD=stable disease, VGPR=very good partial response.
Dimopolous MA et al. *JCO*. 2023. doi:10.1200/JCO.22.02830.

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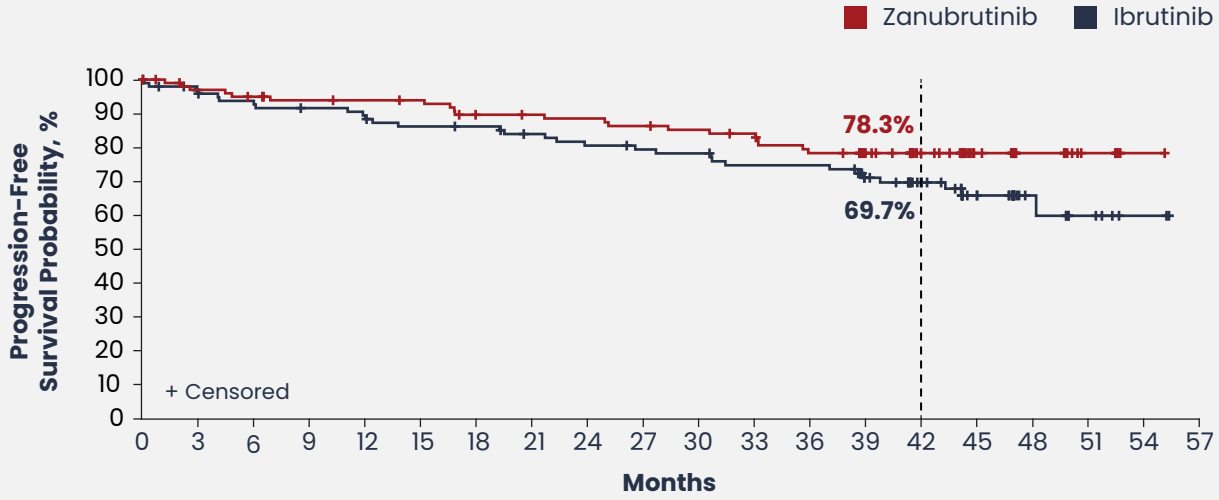
Progression-Free and Overall Survival in ITT Population

Median PFS and OS were not reached after a median follow-up of 44.4 months

Progression-Free Survival (INV Assessed)

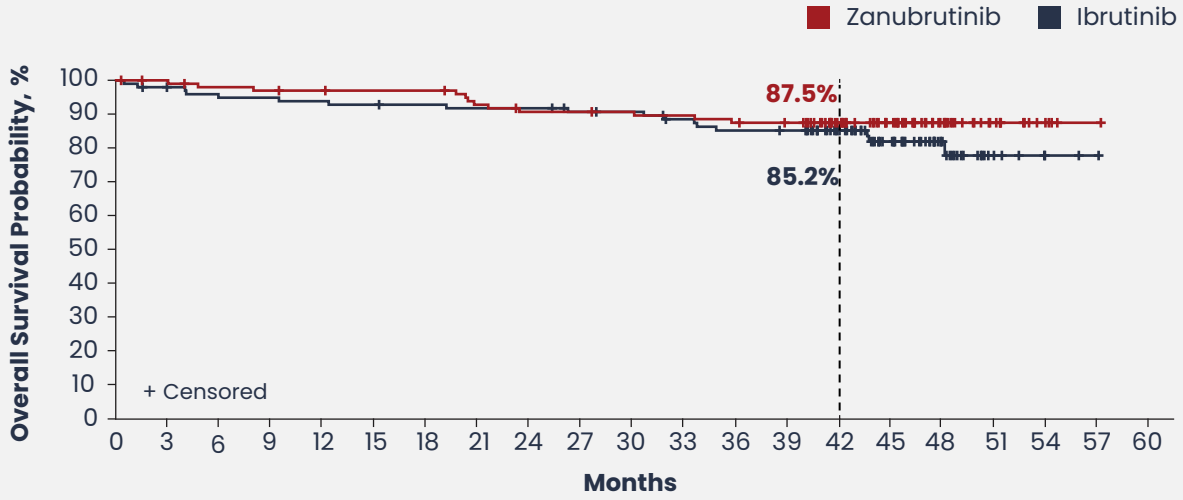


No. of Patients at Risk:

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

	Zanubrutinib	Ibrutinib
Events, n (%)	20 (19.6)	30 (30.3)
HR (95% CI)	**0.63** (0.36, 1.12)	

Overall Survival (INV Assessed)



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

	Zanubrutinib	Ibrutinib
Events, n (%)	12 (11.8)	17 (17.2)
HR (95% CI)	**0.75** (0.36, 1.59)	

Data cutoff: October 31, 2021.
CI=confidence interval, HR=hazard ratio, INV=investigator, ITT=intention-to-treat, OS=overall survival, PFS=progression-free survival.
Dimopoulos MA, et al. *J Clin Oncol*. 2023;00:1-8.

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Most Common Adverse Events (Cohort 1)

Adverse events[a], n (%)	All grades (≥20%)		Grade ≥3 (≥5%)	
	Ibrutinib (n=98)	Zanubrutinib (n=101)	Ibrutinib (n=98)	Zanubrutinib (n=101)
Diarrhea	34 (34.7)	23 (22.8)	2 (2.0)	3 (3.0)
Upper respiratory tract infection	32 (32.7)	33 (32.7)	1 (1.0)	0
Muscle spasms[b]	28 (28.6)[b]	12 (11.9)	1 (1.0)	0
Contusion	27 (27.6)	19 (18.8)	0	0
Arthralgia	24 (24.5)	24 (23.8)	0	3 (3.0)
Hypertension	24 (24.5)	15 (14.9)	19 (19.4)	10 (9.9)
Peripheral edema	21 (21.4)	18 (17.8)	0	0
Epistaxis	21 (21.4)	17 (16.8)	0	1 (1.0)
Atrial fibrillation	21 (21.4)[b]	7 (6.9)	6 (6.1)[b]	2 (2.0)
Cough	20 (20.4)	19 (18.8)	0	0
Fatigue	19 (19.4)	26 (25.7)	1 (1.0)	1 (1.0)
Pneumonia[b]	18 (18.4)[b]	5 (5.0)	10 (10.2)[b]	1 (1.0)
Syncope	8 (8.2)	5 (5.0)	6 (6.1)	5 (5.0)

Data cutoff: October 31, 2021.
[a]Preferred terms by Medical Dictionary for Regulatory Activities v24.0; excluding cytopenia. [b]Descriptive purposes only, 1-sided P<0.025 in rate difference in all grades and/or grade ≥3..
Dimopoulos MA, et al. *J Clin Oncol*. 2023;00:1-8.

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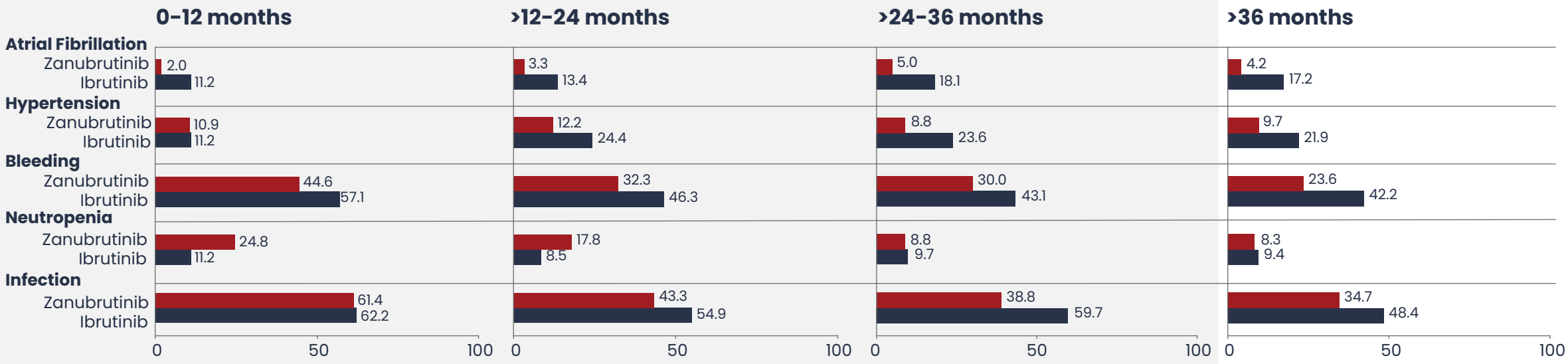
AEs of Special Interest

Except for neutropenia, prevalence of AEs of interest were lower with zanubrutinib than ibrutinib at all time points.

Prevalence Analysis for Adverse Events of Interest



Patients, %				
Zanubrutinib (N)[a]	101	90	80	72
Ibrutinib (N)[a]	98	82	72	64

Data cutoff: October 31, 2021.
[a]N is the number of patients who are on treatment in each time interval or who discontinued treatment. 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. The prevalence of each interval is the No. of patients with a new or ongoing event during the interval, shown as % of N.
AE=adverse event.
Dimopoulos MA, et al. *J Clin Oncol*. 2023;00:1-8.