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ASPEN: RESULTS OF A PHASE 3 RANDOMIZED TRIAL OF ZANUBRUTINIB VERSUS IBRUTINIB FOR PATIENTS WITH WALDENSTRÖM MACROGLOBULINEMIA (WM)

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Azienda Unità Sanitaria Locale della Romagna

DISCLOSURES

- Alessandra Tedeschi: Consulting/Advisory Role and Speakers Bureau for Abbvie, AstraZeneca, Janssen, BeiGene
- Meletios Dimopoulos: Honoraria from Amgen, Takeda, BeiGene, Janssen, BMS
- Stephen Opat: Honoraria from Roche, Janssen, Abbvie, Celgene, Takeda, Merck, Gilead, AstraZeneca. Consulting/Advisory Role for Roche, Janssen, Abbvie, Celgene, Takeda, Merck, Gilead, Mundipharma, AstraZeneca, CSL. Research funding from BeiGene, Roche, Janssen, Abbvie, Takeda, Merck, Gilead, Epizyme, AstraZeneca. Travel expenses from Roche
- Shirley D'Sa: Honoraria from BeiGene, Janssen. Travel expenses from Janssen, Sanofi. Consulting/Advisory Role for BeiGene, Janssen, Sanofi. Leadership or Fiduciary Role for WMUK, Lymphoma Action
- Wojciech Jurczak: Grants or contracts from BeiGene. Advisory Role for BeiGene
- Hui-Peng Lee: No conflicts of interest
- Gavin Cull: No conflicts of interest
- Roger G. Owen: Honoraria from BeiGene, Janssen, Celgene, AstraZeneca. Consulting/Advisory Role for BeiGene, Janssen
- Paula Marlton: Consulting fees from Janssen, Abbvie, Roche, Novartis, Astellas, AstraZeneca. Honoraria from Roche, Novartis. Advisory Role for BeiGene, Janssen, Abbvie, Roche, Novartis, Astellas, AstraZeneca. Travel expenses from Roche
- Björn E. Wahlin: Grants or contracts from Gilead. Honoraria from Roche. Advisory Role for Incyte
- Ramon Garcia Sanz: Honoraria from Janssen, Novartis, MSD, Astellas. Payment for expert testimony for IVS technologies. Travel expenses from Janssen, Novartis, MSD, Astellas. Receipt of equipment from Diagnostica Longwood
- Helen McCarthy: Honoraria from Janssen. Consulting/Advisory Role for AstraZeneca
- Stephen Mulligan: No conflicts of interest
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- Jaroslaw Czyz: No conflicts of interest
- Carlos Fernández de Larrea: Grants or contracts/Consulting Fees/Honoraria and Travel expenses from Janssen

DISCLOSURES (cont.)

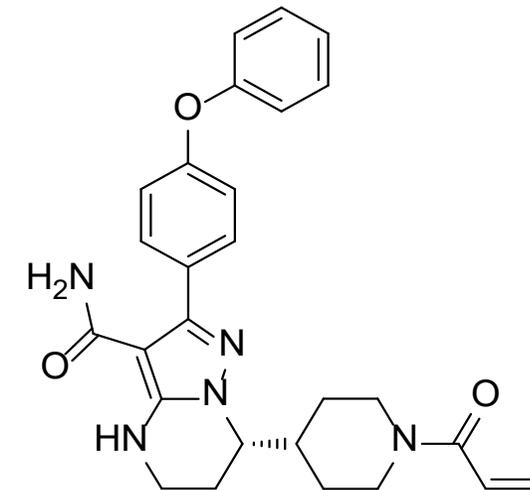
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- Wai Y. Chan: Employment, Stock or Other Ownership at BeiGene
- Jingjing Schneider: Employment, Stock or Other Ownership at BeiGene
- Aileen Cohen: Employment, Stock or Other Ownership at BeiGene
- Jane Huang: Employment, Stock or Other Ownership at BeiGene
- Constantine S. Tam: Honoraria from Janssen, Abbvie, BeiGene. Research funding from Janssen, Abbvie

BTK Inhibition in WM

- BTK plays a critical role in B-cell receptor signaling; this pathway is constitutively activated in WM (>90% with *MYD88* mutations), leading to malignant cell survival^{1,2}
- BTK inhibition is a new standard of care for WM³
- Zanubrutinib is a next-generation BTK inhibitor designed to maximize BTK occupancy and minimize off-target inhibition of TEC- and EGFR-family kinases

- ✓ **Potent, selective, irreversible**
- ✓ **Equipotent against BTK compared with ibrutinib; fewer off-target effects due to high selectivity for binding EGFR, ITK, JAK3, HER2, and TEC⁴**
- ✓ **Advantageous PK/pharmacodynamic properties:** complete and sustained BTK occupancy in PBMC and lymph nodes⁵
- ✓ **Favorable drug-drug interaction properties:** can be coadministered with strong/moderate CYP3A inhibitors at a reduced dose, proton pump inhibitors, acid-reducing agents, and antithrombotic agents^{6,7}

Zanubrutinib (BGB-3111)



Abbreviations: BTK, Bruton tyrosine kinase; CYP3A, cytochrome P450, family 3, subfamily A; EGFR, epidermal growth factor receptor; HER2, human epidermal growth factor receptor 2; ITK, IL-2-inducible T-cell kinase; JAK3, Janus-associated kinase 3; MCL, mantle cell lymphoma; PBMC, peripheral blood mononuclear cell; PK, pharmacokinetic; R/R, relapsed/refractory; WM, Waldenström macroglobulinemia.

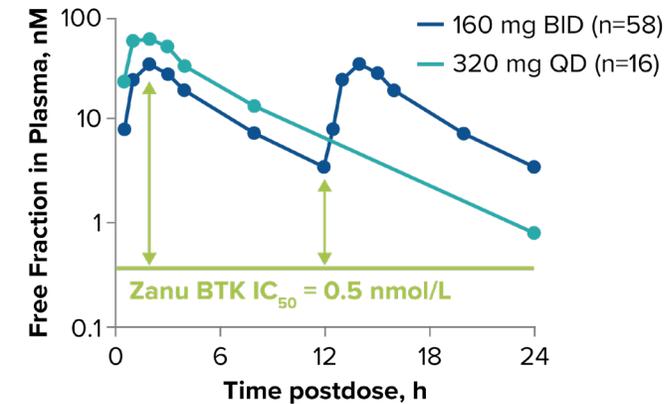
1. Rickert RC. *Nat Rev Immunol.* 2013;13:578-591. 2. Argyropoulos KV, et al. *Leukemia.* 2016;30:1116-1125. 3. Treon SP, et al. *J Clin Oncol.* 2020;38:1198-1208. 4. Guo Y, et al. *J Med Chem.* 2019;62:7923-7940. 5. Tam CS, et al. *Blood.* 2019;134:851-859. 6. Mu S, et al. *Cancer Chemother Pharmacol.* 2020;85:391-399. 7. Data on file.

Zanubrutinib: A Potent and Selective BTK Inhibitor^{1,2}

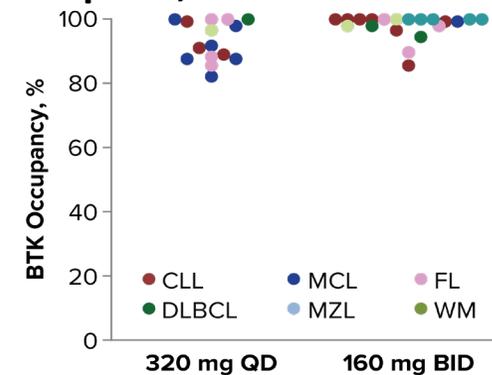
Potent, selective, irreversible; minimize off-target inhibition

	Targets	Assays	Zanubrutinib IC ₅₀ (nM)	Ibrutinib IC ₅₀ (nM)	Ratio (Zanubrutinib:Ibrutinib)
ON TARGET	BTK	BTK-pY223 Cellular Assay	1.8	3.5	0.5
		Rec-1 Proliferation	0.36	0.34	1.1
		BTK Occupation Cellular Assay	2.2	2.3	1
		BTK Biochemical Assay	0.22	0.2	1.1
OFF TARGET	EGFR	p-EGFR HTRF Cellular Assay	606	101	6
		A431 Proliferation	3210	323	9.9
	ITK	ITK Occupancy Cellular Assay	3265	189	17
		p-PLCy1 Cellular Assay	3433	77	45
		IL-2 Production Cellular Assay	2536	260	9.8
	JAK3	JAK3 Biochemical Assay	30	0.9	33
	HER2	HER2 Biochemical Assay	200	3.9	51
	TEC	TEC Biochemical Assay	661	9.4	70
		TEC Biochemical Assay	1.9	0.8	2.4

C_{max} and C_{trough} > BTK IC₅₀ Over 24 Hours



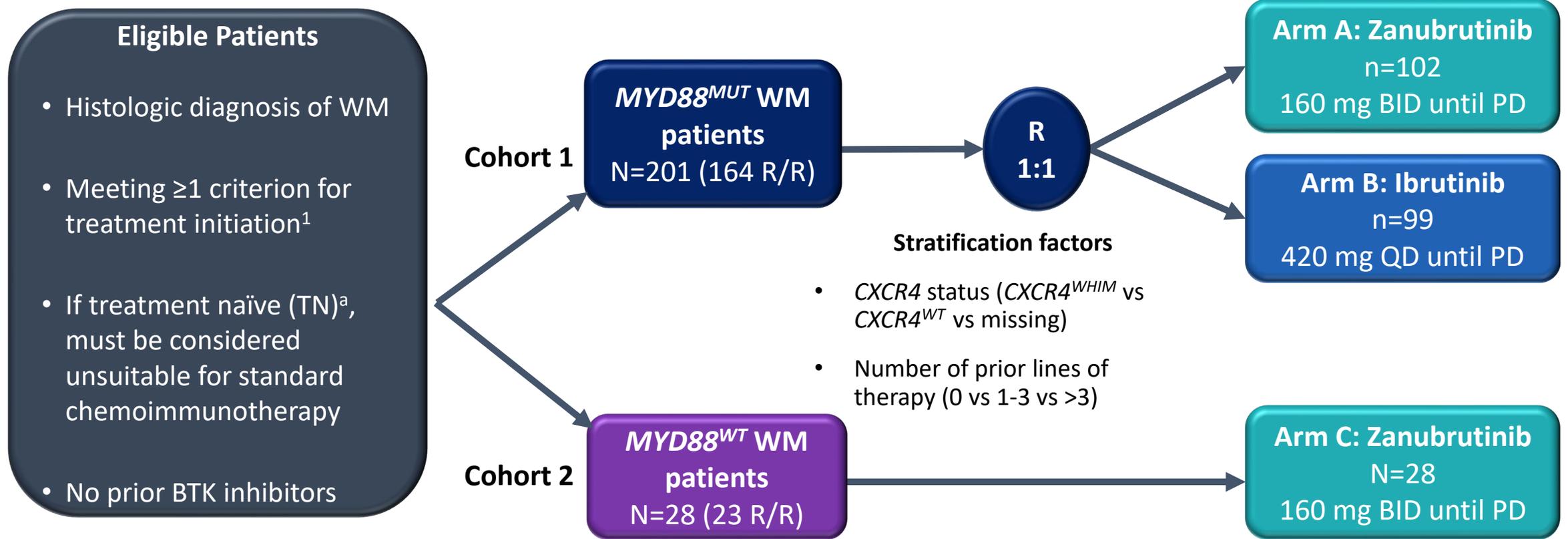
Complete, Sustained BTK Occupancy



1. Tam CS, et al. ICML Session 7, June 16, 2017 [abstr]. 2. Tam CS, et al. *Blood*. 2019;134:851-859.

Abbreviations: BID, twice daily; BTK, Bruton tyrosine kinase; CLL, chronic lymphocytic leukemia; C_{max}, maximum concentration; C_{trough}, trough concentration; DLBCL, diffuse large B-cell lymphoma; EGFR, epidermal growth factor receptor; FL, follicular lymphoma; HER2, human epidermal growth factor receptor 2; HTRF, homogeneous time resolved fluorescence; IC₅₀, half maximal inhibitory concentration; ITK, IL-2-inducible T-cell kinase; JAK3, Janus-associated kinase 3; MCL, mantle cell lymphoma; MZL, marginal zone lymphoma; PD, pharmacodynamic; PK, pharmacokinetic; PLC, phospholipase C; TEC, tyrosine-protein kinase Tec; QD, once daily; WM, Waldenström macroglobulinemia; Zanu, zanubrutinib.

ASPEN Study Design: Zanubrutinib vs Ibrutinib in *MYD88^{MUT}* WM



^aUp to 20% of the overall population.

1. Dimopoulos MA, et al. *Blood*. 2014;124:1404-1411.

ASPEN Cohort 1 Study Objectives

Primary Objective

- Compare the efficacy of zanubrutinib vs ibrutinib
 - Primary endpoint was CR+VGPR rate

Secondary Objectives

- Further examine efficacy, clinical benefit, and antilymphoma effects
- Evaluate safety and tolerability as measured by incidence, timing, and severity of TEAEs per NCI-CTCAE (v4.03)

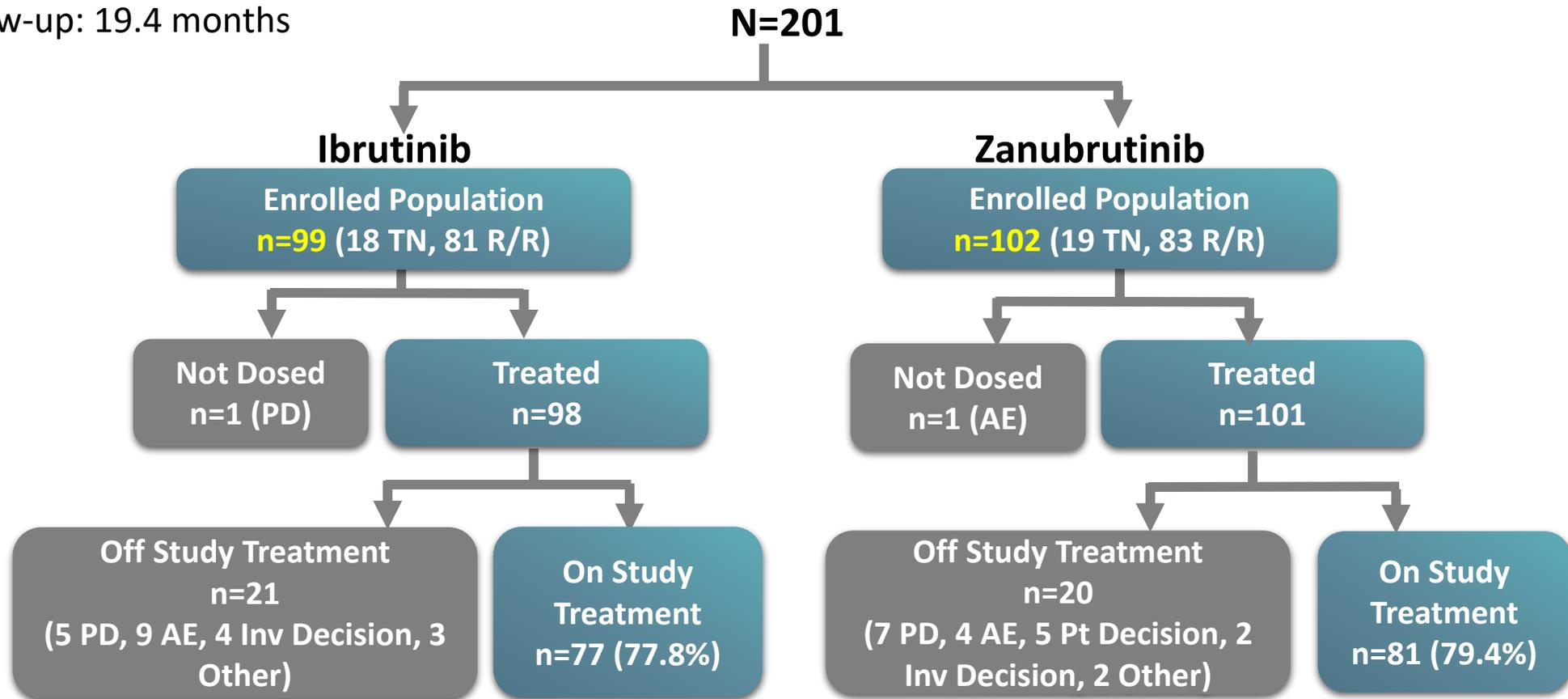
Exploratory Objectives

- Characterize the PK of zanubrutinib in patients with WM
- Compare QoL by EORTC QLQ-C30 and EQ-5D

ASPEN: Patient Disposition

WM Patients With *MYD88*^{L265P}

Median follow-up: 19.4 months



ASPEN: Demographics and Disease Characteristics

Characteristics, n (%)	Overall ITT	
	Ibrutinib (n=99)	Zanubrutinib (n=102)
Age median (range), y	70.0 (38-90)	70.0 (45-87)
>65 y	70 (70.7)	61 (59.8)
>75 y	22 (22.2)	34 (33.3)
Sex, n (%)		
Male	65 (65.7)	69 (67.6)
Female	34 (34.3)	33 (32.4)
Prior lines of therapy, n (%)		
0	18 (18.2)	19 (18.6)
1-3	74 (74.7)	76 (74.5)
>3	7 (7.1)	7 (6.9)
Genotype by central lab ^a , n (%)		
<i>MYD88</i> ^{L265P} / <i>CXCR4</i> ^{WT}	90 (90.9)	91 (89.2)
<i>MYD88</i> ^{L265P} / <i>CXCR4</i> ^{WHIM}	8 (8.1)	11 (10.8)
IPSS WM ¹		
Low	13 (13.1)	17 (16.7)
Intermediate	42 (42.4)	38 (37.3)
High	44 (44.4)	47 (46.1)
Hemoglobin ≤110 g/L	53 (53.5)	67 (65.7)

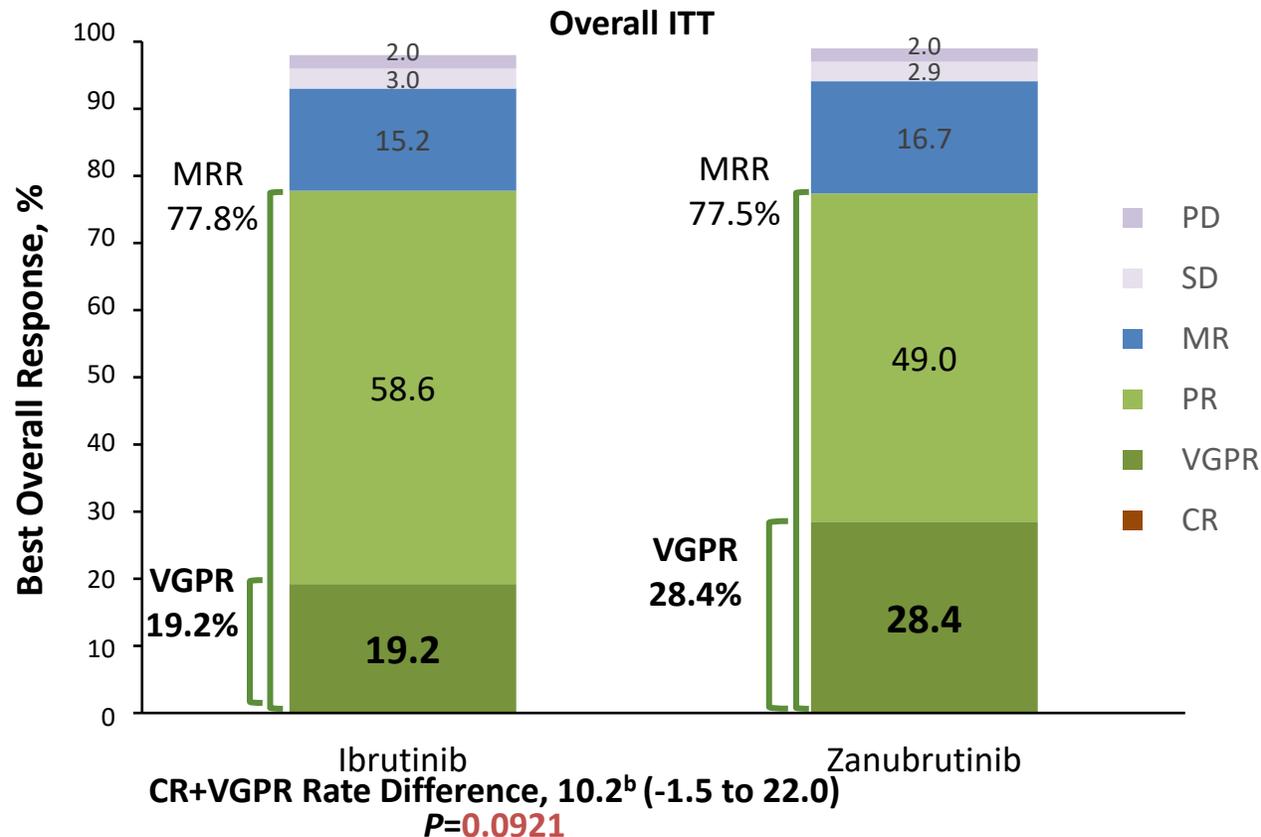
^aWild-type–blocking polymerase chain reaction for *MYD88* and Sanger sequencing for *CXCR4* using bone marrow aspirates. One patient had local next-generation sequencing testing results of *MYD88*^{L265P}/*CXCR4* Unknown.

1. Morel P, et al. *Blood*. 2009;113:4163-4170.

Abbreviations: *CXCR4*, C-X-C motif chemokine receptor 4; ITT, intention-to-treat; IPSS WM, International Prognostic Scoring System for Waldenström macroglobulinemia; *MYD88*, myeloid differentiation primary response gene 88; WT, wild-type.

ASPEN: Efficacy – Response by IRC (Data Cutoff: 31 August 2019)

- Superiority in CR+VGPR rate compared with ibrutinib in R/R population (primary study hypothesis) was not significant^a



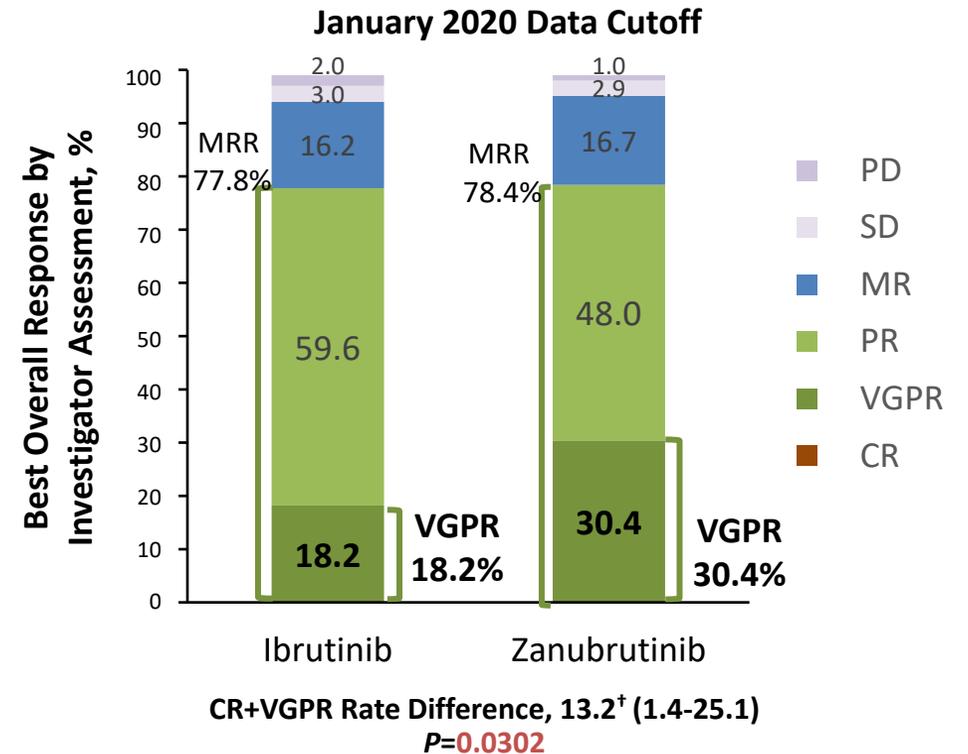
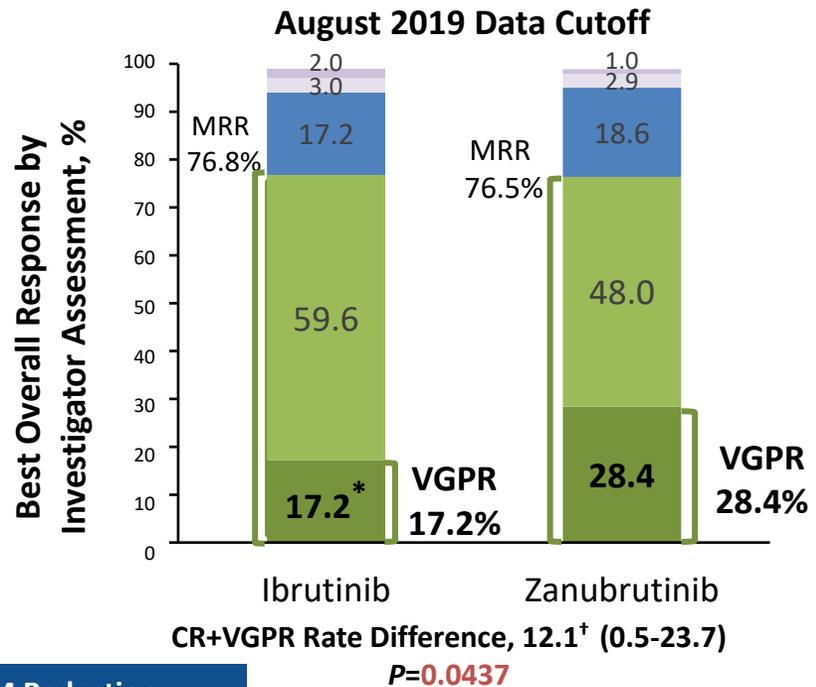
Overall concordance between IRC and investigators was 94%.

^aAll other P values are for descriptive purposes only; ^bAdjusted for stratification factors and age group.

Abbreviations: CR, complete response; IRC, independent review committee; ITT, intention-to-treat; MR, minor response; MRR, major response rate; PD, progressive disease; PR, partial response; R/R, relapsed/refractory; SD, stable disease; VGPR, very good PR.

ASPEN: Secondary Efficacy Endpoints Assessment of Response According to Investigator

Investigator-Assessed Response



IgM Reduction

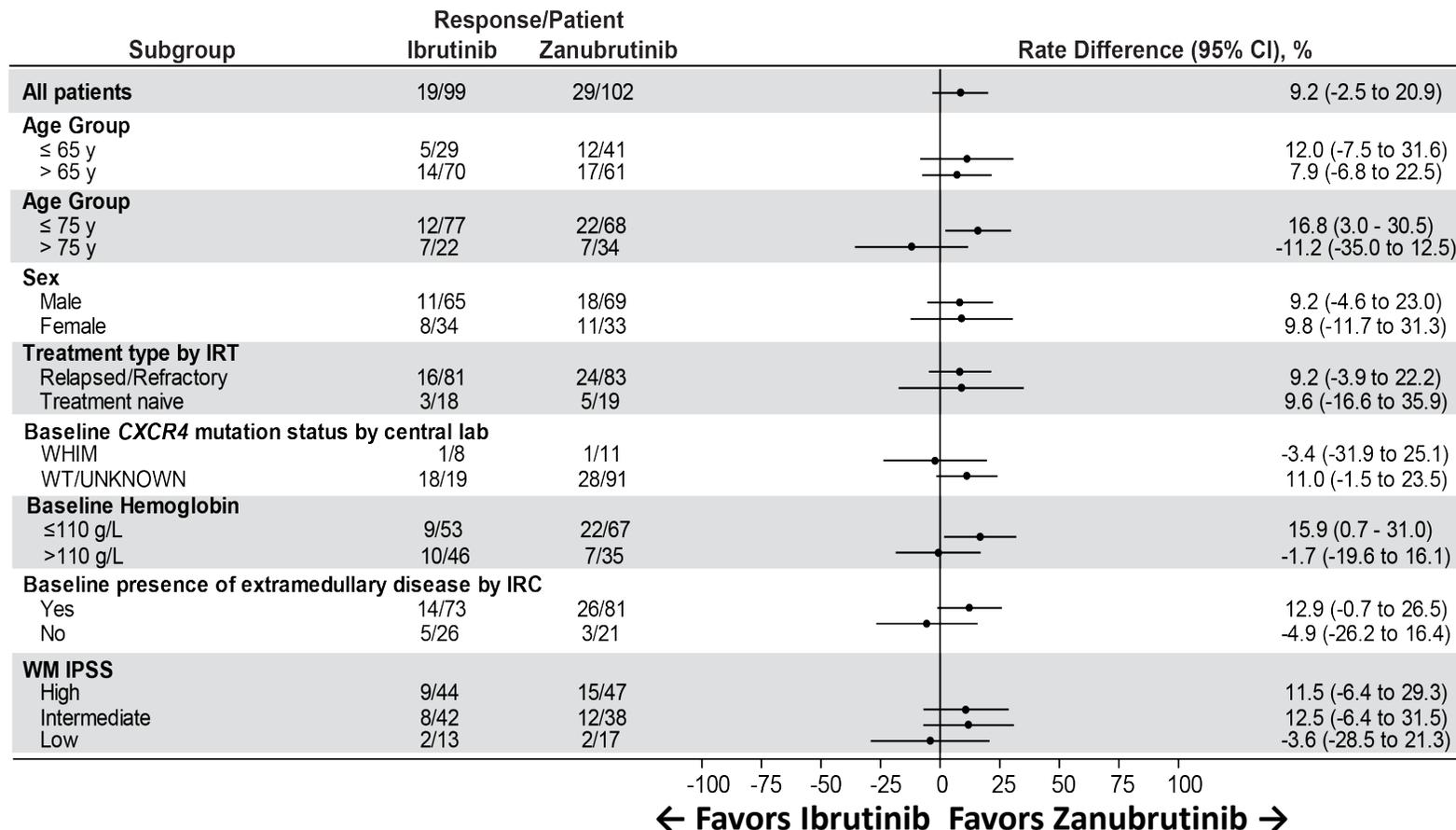
- AUC for IgM reduction over time was significantly greater for zanubrutinib vs ibrutinib ($P=0.037$)

*Excluded two patients with VGPR by IRC: MR (extramedullary disease present) and PR (immunoglobulin M assessment by local serum protein electrophoresis M-protein test).

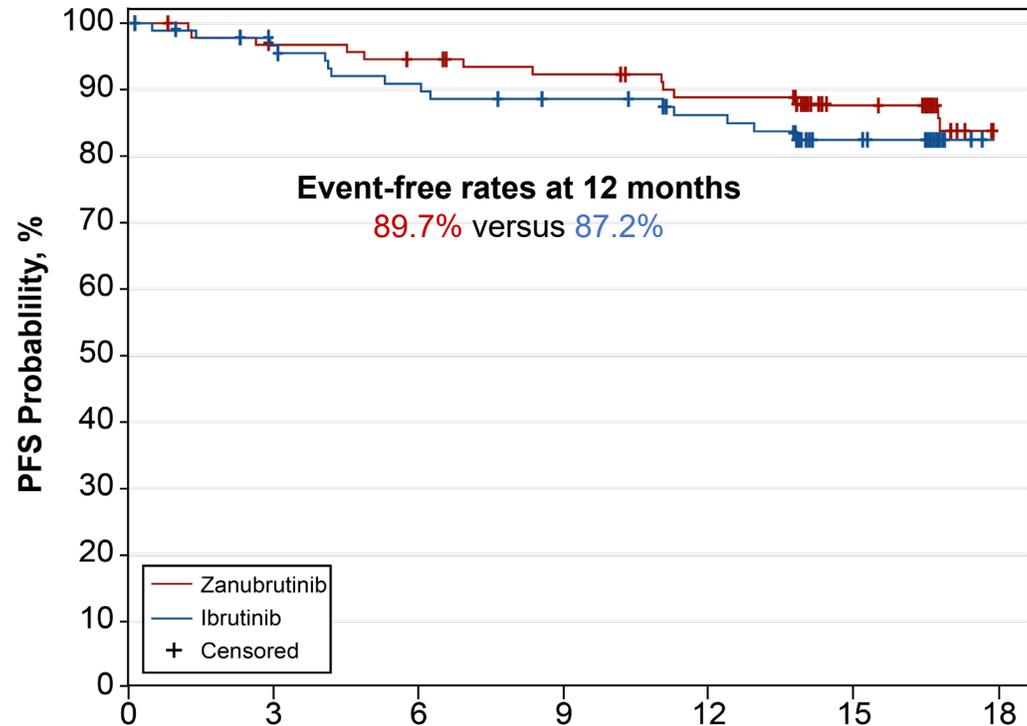
[†]Adjusted for stratification factors and age group. P value is for descriptive purpose only.

Abbreviations: AUC, area under the curve; CR, complete response; IRC, independent review committee; MR, minor response; MRR, major response rate; PD, progressive disease; PR, partial response; SD, stable disease; VGPR, very good PR.

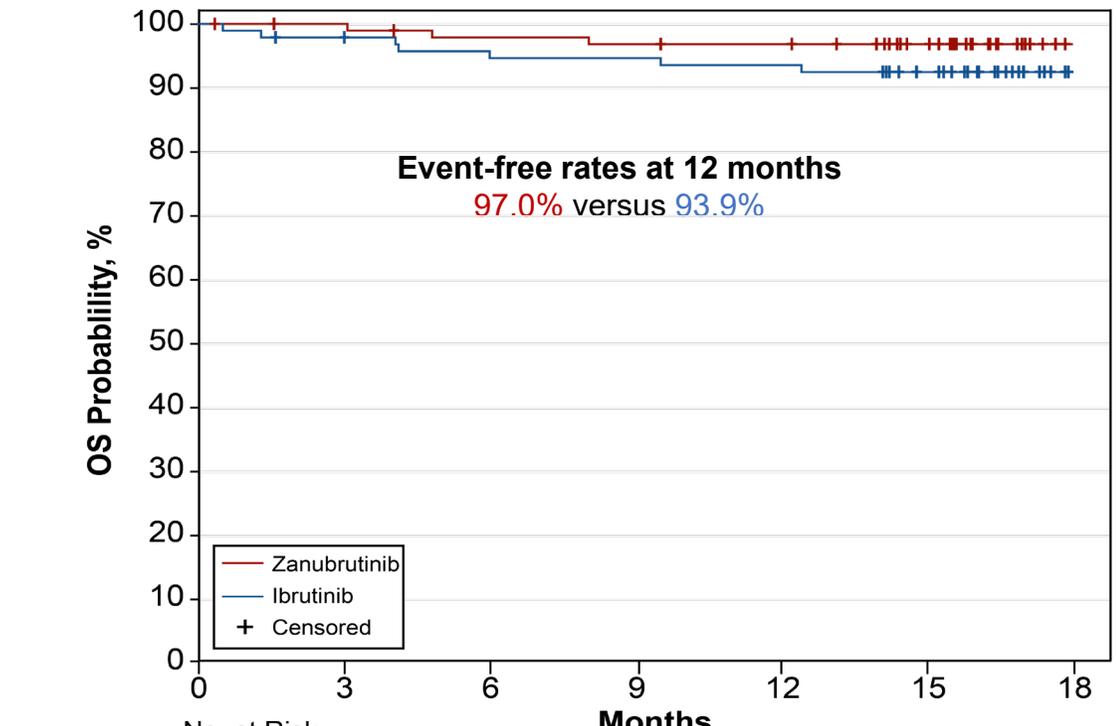
ASPEN: Forest Plot of CR+VGPR Response Rate Difference by IRC (ITT)



ASPEN: PFS and OS Survival in ITT Population



	0	3	6	9	12	15	18
Zanubrutinib	102	96	93	89	84	63	43
Ibrutinib	99	92	86	82	77	62	42



	0	3	6	9	12	15	18
Zanubrutinib	102	100	97	96	95	86	62
Ibrutinib	99	96	93	92	91	83	61

Disease progression determined by IRC.

Abbreviations: IRC, independent review committee; ITT, intention-to-treat; OS, overall survival; PFS, progression-free survival; VGPR, very good partial response.

ASPEN: Safety and Tolerability

Category, n (%)	Overall	
	Ibrutinib (n=98)	Zanubrutinib (n=101)
Patients with ≥ 1 AE	97 (99.0)	98 (97.0)
Grade ≥ 3	62 (63.3)	59 (58.4)
Serious	40 (40.8)	40 (39.6)
AE leading to death	4 (4.1) ^a	1 (1.0) ^b
AE leading to treatment discontinuation	9 (9.2) ^c	4 (4.0) ^d
AE leading to dose reduction	23 (23.5)	14 (13.9)
AE leading to dose held	55 (56.1)	47 (46.5)
Patients with ≥ 1 treatment-related AE	84 (85.7)	80 (79.2)
Patients with ≥ 1 AE of interest	81 (82.7)	86 (85.1)

^aCardiac failure acute; sepsis (n=2); unexplained death.

^bCardiac arrest after plasmapheresis.

^cG5 sepsis (n=2); G5 unexplained death; G3 acute myocardial infarction; G3 hepatitis; G3 pneumonia; G2 drug-induced liver injury; G2 pneumonitis; G1 pneumonitis.

^dG5 cardiac arrest after plasmapheresis; G4 neutropenia; G4 subdural hemorrhage; G2 plasma cell myeloma.

Abbreviations: AE, adverse event (treatment-emergent); G, grade.

ASPEN: Most Common AEs

Event Preferred Term*, n (%)	All Grades (≥20%)		Grade ≥3 (≥5%)	
	Ibrutinib (n=98)	Zanubrutinib (n=101)	Ibrutinib (n=98)	Zanubrutinib (n=101)
Diarrhea	31 (32)	21 (21)	1 (1)	3 (3)
Upper respiratory tract infection	28 (29)	24 (24)	1 (1)	0
Contusion	23 (24)	13 (13)	0	0
Muscle spasms [†]	23 (24)	10 (10)	1 (1)	0
Peripheral edema [†]	19 (19)	9 (9)	0	0
Hypertension	16 (16)	11 (11)	11 (11)	6 (6)
Atrial fibrillation [†]	14 (14)	2 (2)	3 (3)	0
Neutropenia [†]	12 (12)	25 (25)	8 (8)	16 (16)
Pneumonia [†]	12 (12)	2 (2)	7 (7)	1 (1)
Anemia	10 (10)	12 (12)	5 (5)	5 (5)
Thrombocytopenia	10 (10)	10 (9)	3 (3)	6 (5)

*Including most common AEs and AEs with ≥10% or ≥5% differentials, respectively (higher frequency in bold red).

[†]Descriptive 2-sided P<0.05

Abbreviation: AE, adverse event.

ASPEN: AE Categories of Interest (BTKi Class AEs)

AE Categories, n (%) (Pooled Terms)	All Grades		Grade ≥3	
	Ibrutinib (n=98)	Zanubrutinib (n=101)	Ibrutinib (n=98)	Zanubrutinib (n=101)
Atrial fibrillation/flutter [†]	15 (15.3)	2 (2.0)	4 (4.1)	0 (0.0)
Diarrhea (PT)	31 (31.6)	21 (20.8)	1 (1.0)	3 (3.0)
Hemorrhage	58 (59.2)	49 (48.5)	8 (8.2)	6 (5.9)
Major hemorrhage*	9 (9.2)	6 (5.9)	8 (8.2)	6 (5.9)
Hypertension	17 (17.3)	11 (10.9)	12 (12.2)	6 (5.9)
Neutropenia ^{†,‡}	13 (13.3)	30 (29.7)	8 (8.2)	20 (19.8)
Infection	66 (67.3)	67 (66.3)	19 (19.4)	18 (17.8)
Second malignancy	11 (11.2)	12 (11.9)	1 (1.0)	2 (2.0)

Higher AE rate in bold red with ≥10% difference in any grade or ≥5% difference in grade 3 or above. No tumor lysis syndrome was reported. Opportunistic infection ibrutinib (n=2), zanubrutinib (n=1).

*Defined as any grade ≥3 hemorrhage or any grade central nervous system hemorrhage.

[†]Descriptive 2-sided P<0.05.

[‡]Including PT terms of neutropenia, neutrophil count decreased, febrile neutropenia, agranulocytosis, neutropenic infection, and neutropenic sepsis.

Abbreviations: AE, adverse event; BTKi, Bruton tyrosine kinase inhibitor; PT, preferred term.

ASPEN: AE Categories of Interest (BTKi Class AEs) With Additional 5-Month Follow-Up (Data Cutoff: 31 January 2020)

- An additional 5 patients in the ibrutinib arm discontinued treatment because of AEs vs 0 in the zanubrutinib arm (**14.3% vs 4%**)

AE Categories, n (%) (Pooled Terms)	All Grades		Grade ≥3	
	Ibrutinib (n=98)	Zanubrutinib (n=101)	Ibrutinib (n=98)	Zanubrutinib (n=101)
Atrial fibrillation/flutter [†]	18 (18.4)	3 (3.0)	7 (7.1)	0 (0.0)
Diarrhea (PT)	32 (32.7)	22 (21.8)	2 (2.0)	3 (3.0)
Hemorrhage	59 (60.2)	51 (50.5)	9 (9.2)	6 (5.9)
Major hemorrhage*	10 (10.2)	6 (5.9)	9 (9.2)	6 (5.9)
Hypertension	20 (20.4)	13 (12.9)	15 (15.3)	8 (7.9)
Neutropenia ^{†,‡}	15 (15.3)	32 (31.7)	8 (8.2)	23 (22.8)
Infection	70 (71.4)	70 (69.3)	23 (23.5)	19 (18.8)
Second malignancy	12 (12.2)	13 (12.9)	1 (1.0)	3 (3.0)

Higher AE rate in bold red with ≥10% difference in any grade or ≥5% difference in grade 3 or above.

*Defined as any grade ≥3 hemorrhage or any-grade central nervous system hemorrhage.

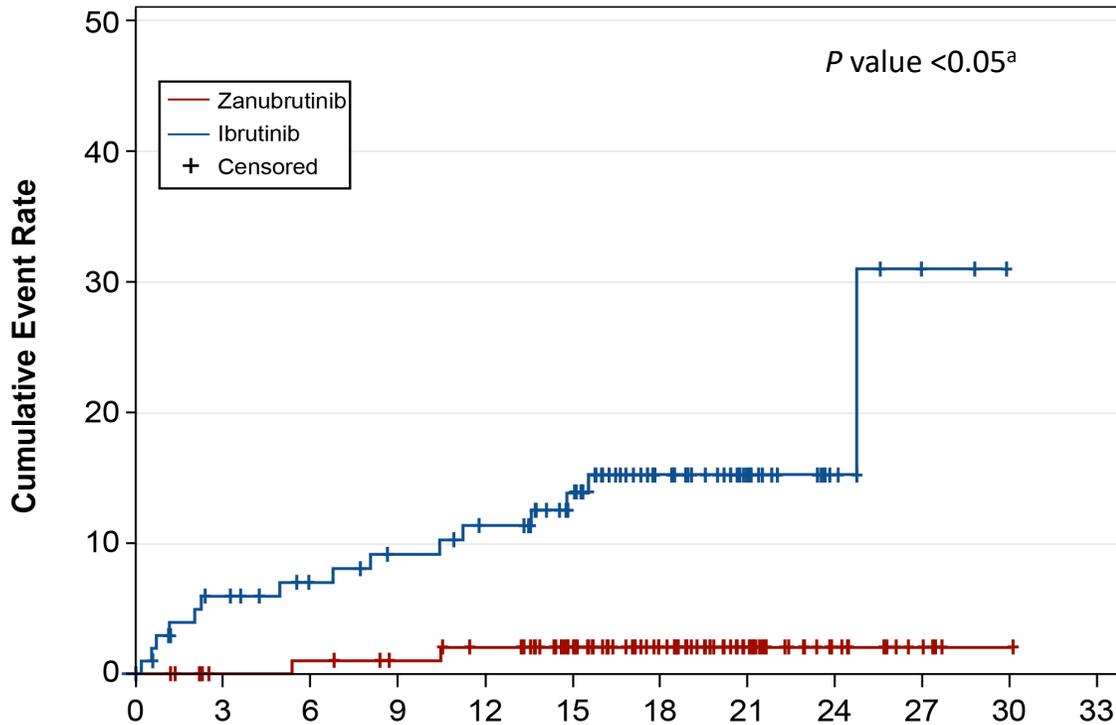
[†]Descriptive 2-sided $P < 0.05$.

[‡]Including PT terms of neutropenia, neutrophil count decreased, febrile neutropenia, agranulocytosis, neutropenic infection, and neutropenic sepsis.

Abbreviations: AE, adverse event; BTKi, Bruton tyrosine kinase inhibitor; PT, preferred term.

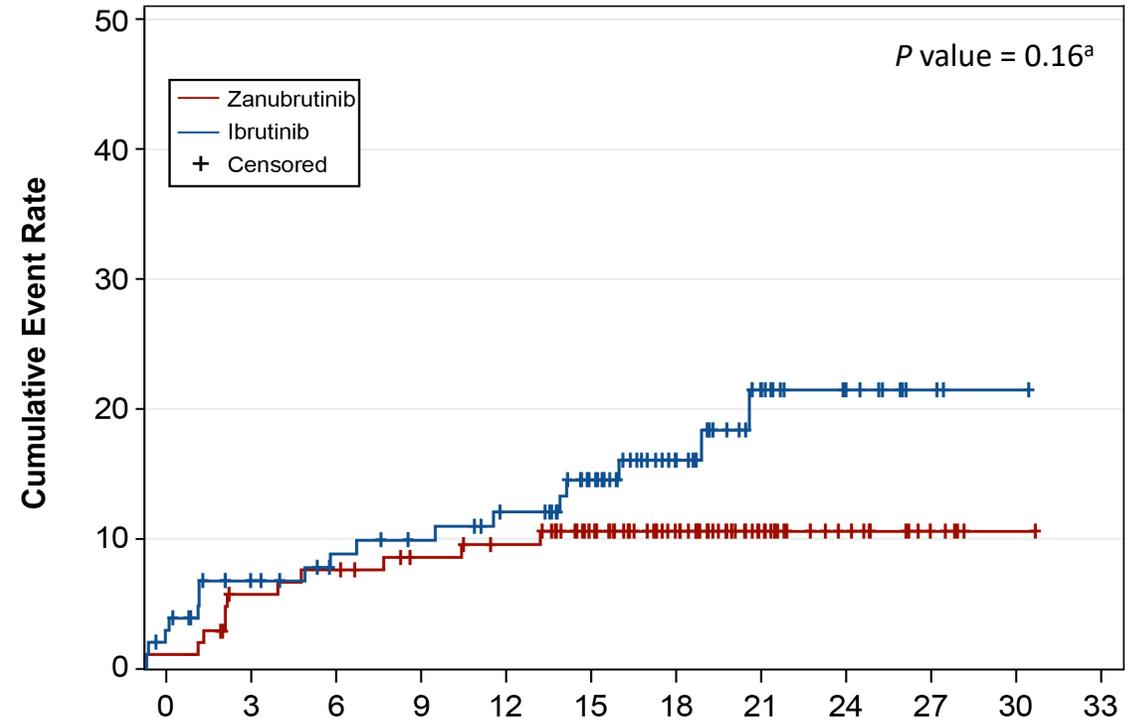
ASPEN: Time to AE – Risk Analysis Over Duration of Treatment

Kaplan-Meier Curve: Time to **Atrial Fibrillation/Flutter**



	No. at Risk											
	0	3	6	9	12	15	18	21	24	27	30	33
Zanutrutinib	101	95	94	92	89	81	57	34	15	7	1	0
Ibrutinib	98	87	83	78	74	66	46	28	13	3	1	0

Kaplan-Meier Curve: Time to **Hypertension**

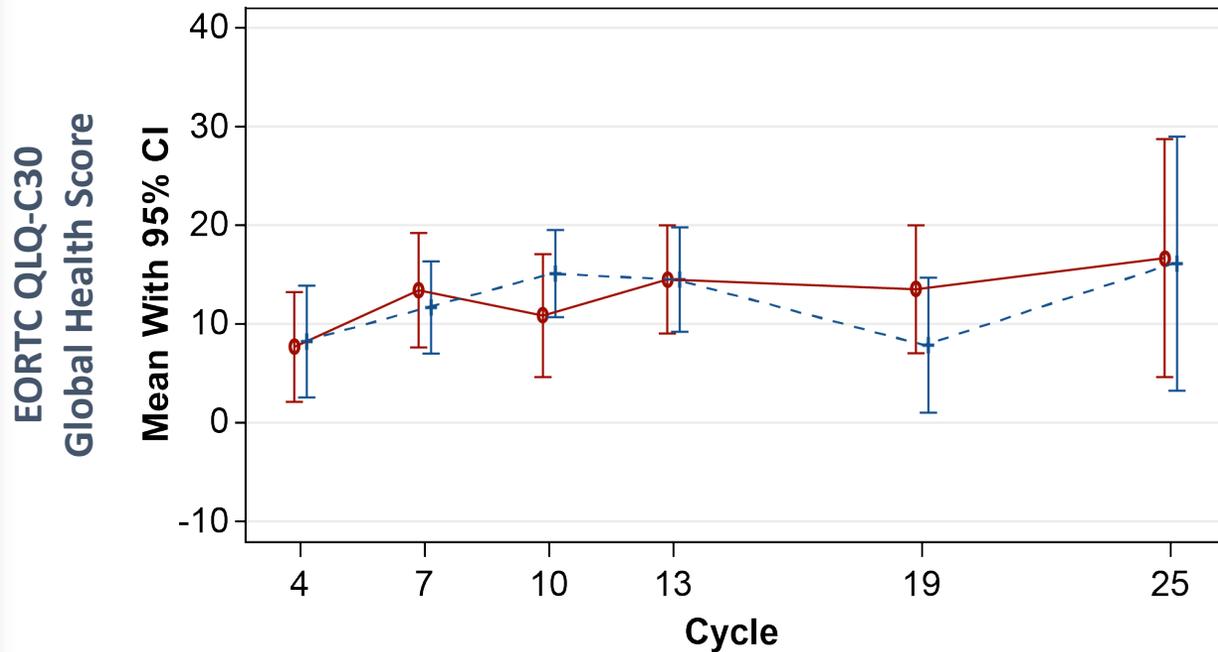


	No. at Risk											
	0	3	6	9	12	15	18	21	24	27	30	33
Zanutrutinib	101	90	88	84	81	73	51	28	14	7	1	0
Ibrutinib	98	84	80	75	71	61	42	24	11	3	1	0

^aDescriptive purpose only. **Abbreviation:** AE, adverse event.

ASPEN: Quality of Life – Change From Baseline Over Time

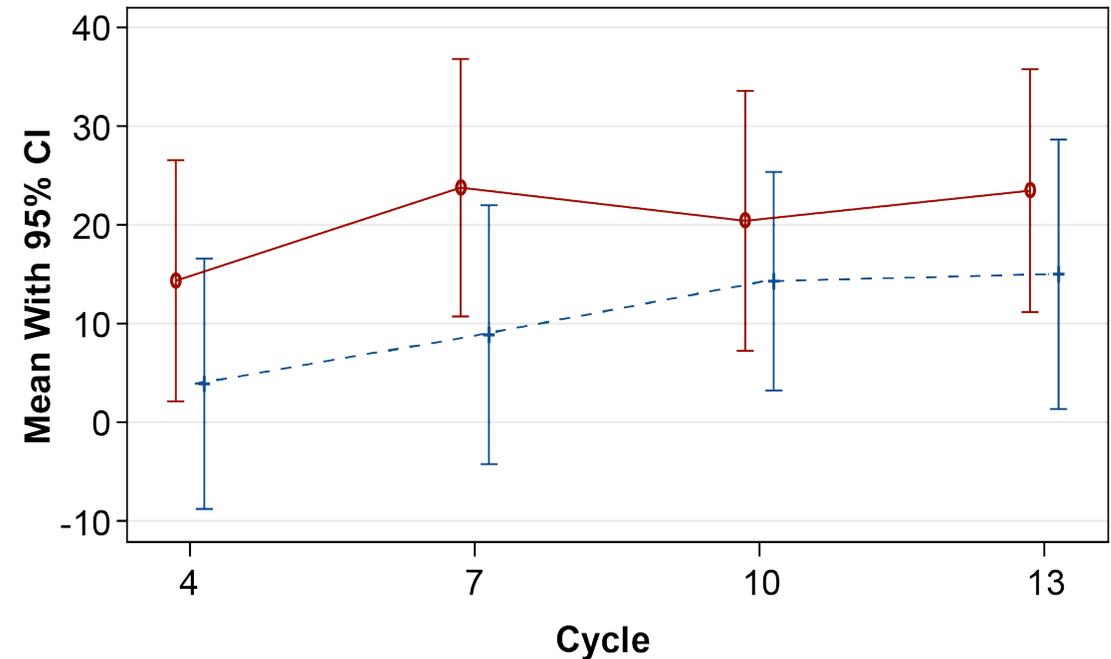
All Patients



Zanubrutinib	88	87	83	81	66	21
Ibrutinib	70	70	69	69	52	15

Treatment Group: — Zanubrutinib - - - Ibrutinib

Patients With VGPR



Zanubrutinib	25	27	29	27
Ibrutinib	15	16	14	

Treatment Group: — Zanubrutinib - - - Ibrutinib

ASPEN Conclusions

- **Zanubrutinib was associated with a CR+VGPR response rate of 28.4% compared with ibrutinib of 19.2% ($P=0.0921$) in *MYD88*^{MUT} WM patients**
 - The primary hypothesis of superiority in CR+VGPR rate (by IRC) was not met
 - No CRs were observed
 - Greater VGPR rate by investigator assessment (ITT, 28.4% vs 17.2%; $P=0.04^a$)
 - Deeper and sustained IgM reduction over time ($P=0.04^a$)
- **Zanubrutinib demonstrated clinically meaningful advantages in safety and tolerability**
 - Lower risk of atrial fibrillation/flutter compared with ibrutinib (2.0% vs 15.3%; $P=0.0008^a$)
 - Lower rates of major bleeding (5.9% vs 9.2%), diarrhea (20.8% vs 31.6%), and hypertension (10.9% vs 17.3%)
 - There was no difference in the rate of infection despite higher rates of neutropenia with zanubrutinib
 - Fewer AEs leading to death, treatment discontinuation, or interruption with zanubrutinib

^aDescriptive purpose only.

Abbreviations: AEs, adverse events; CR, complete response; IgM, immunoglobulin M; IRC, independent review committee; ITT, intention-to-treat; *MYD88*, myeloid differentiation primary response gene 88; *MUT*, mutant; OS, overall survival; PFS, progression-free survival; QoL, quality of life; VGPR, very good partial response; WM, Waldenström macroglobulinemia.

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