

ASPEN: Results of a Phase 3 Randomized Trial of Zanubrutinib Versus Ibrutinib for Patients With Waldenström Macroglobulinemia (WM)

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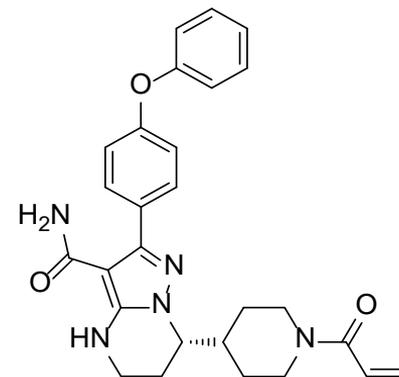
Disclosures of Alessandra Tedeschi

Company name	Research support	Employee	Consultant	Stockholder	Speakers bureau	Advisory board	Other
ABBVIE			X		X	X	
ASTRAZENECA			X		X	X	
BEIGENE			X		X	X	
JANSSEN			X		X	X	

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.

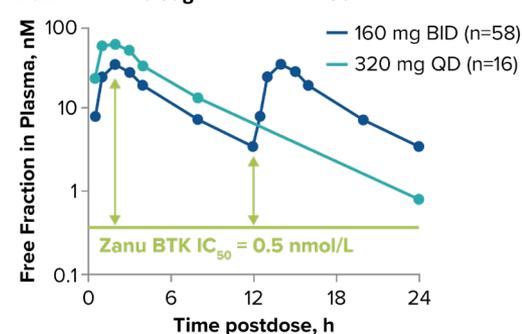
1. Rickert RC. *Nat Rev Immunol.* 2013;13:578-591. 2. Argyropoulos KV, et al. *Leukemia.* 2016;30:1116-1125. 3. Treon SP, et al. *J Clin Oncol.* 2020;38:1198-1208. 4. Guo Y, et al. *J Med Chem.* 2019;62:7923-7940. 5. Tam CS, et al. *Blood.* 2019;134:851-859. 6. Mu S, et al. *Cancer Chemother Pharmacol.*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

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

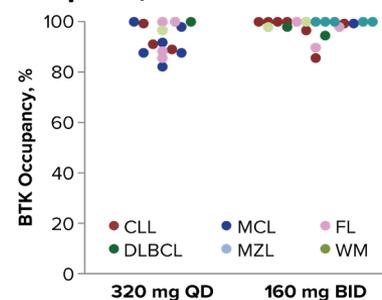
Potent, selective, irreversible; minimize off-target inhibition

		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-PLCγ1 Cellular Assay	3433	77	45
			IL-2 Production Cellular Assay	2536	260	9.8
			ITK Biochemical Assay	30	0.9	33
	JAK3	JAK3 Biochemical Assay	200	3.9	51	
	HER2	HER2 Biochemical Assay	661	9.4	70	
	TEC	TEC Biochemical Assay	1.9	0.8	2.4	

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



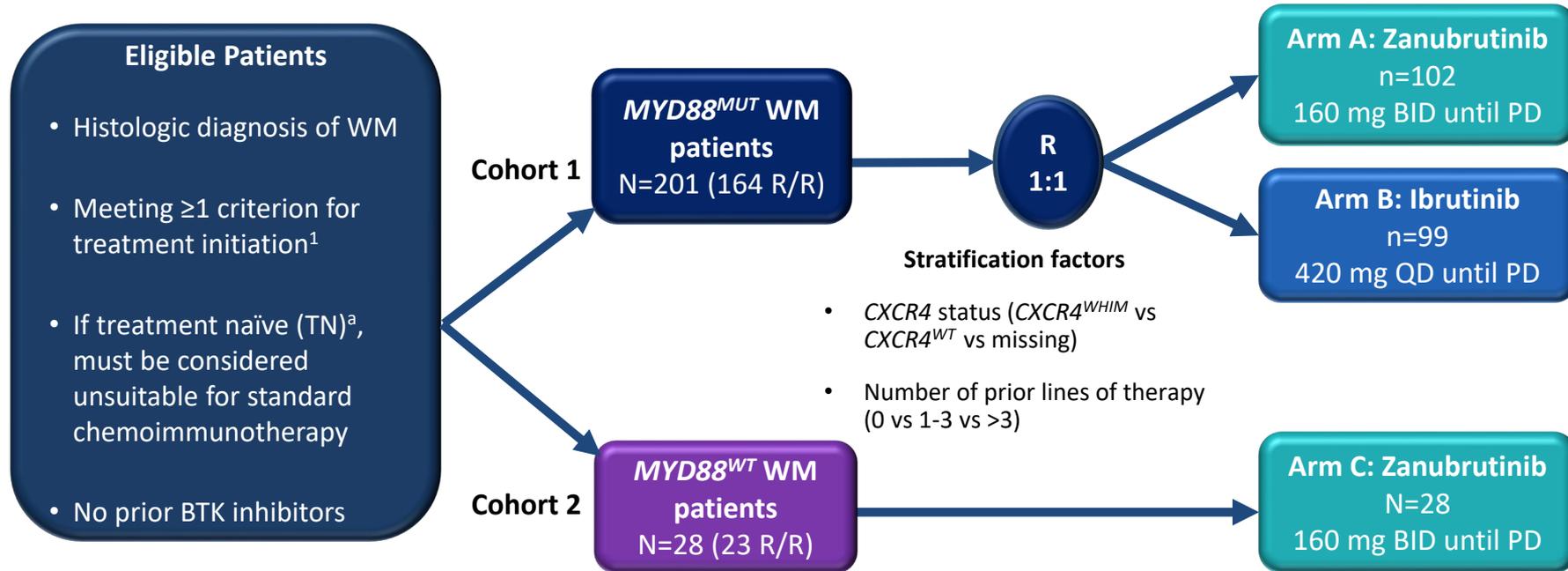
Complete, Sustained BTK Occupancy



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



EUDRACT 2016-002980-33; NCT03053440

^aUp to 20% of the overall population.

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

Abbreviations: BID, twice daily; BTK, Bruton tyrosine kinase; *CXCR4*, C-X-C motif chemokine receptor 4; *MYD88*, myeloid differentiation primary response gene 88; MUT, mutant; PD, progressive disease; QD, daily; R, randomization; R/R, relapsed/refractory; TN, treatment naïve; WM, Waldenström macroglobulinemia; WT, wild-type.

ASPEN Cohort 1 Study Objectives

Primary Objective

- Compare the efficacy of zanubrutinib vs ibrutinib
 - Primary end point 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)

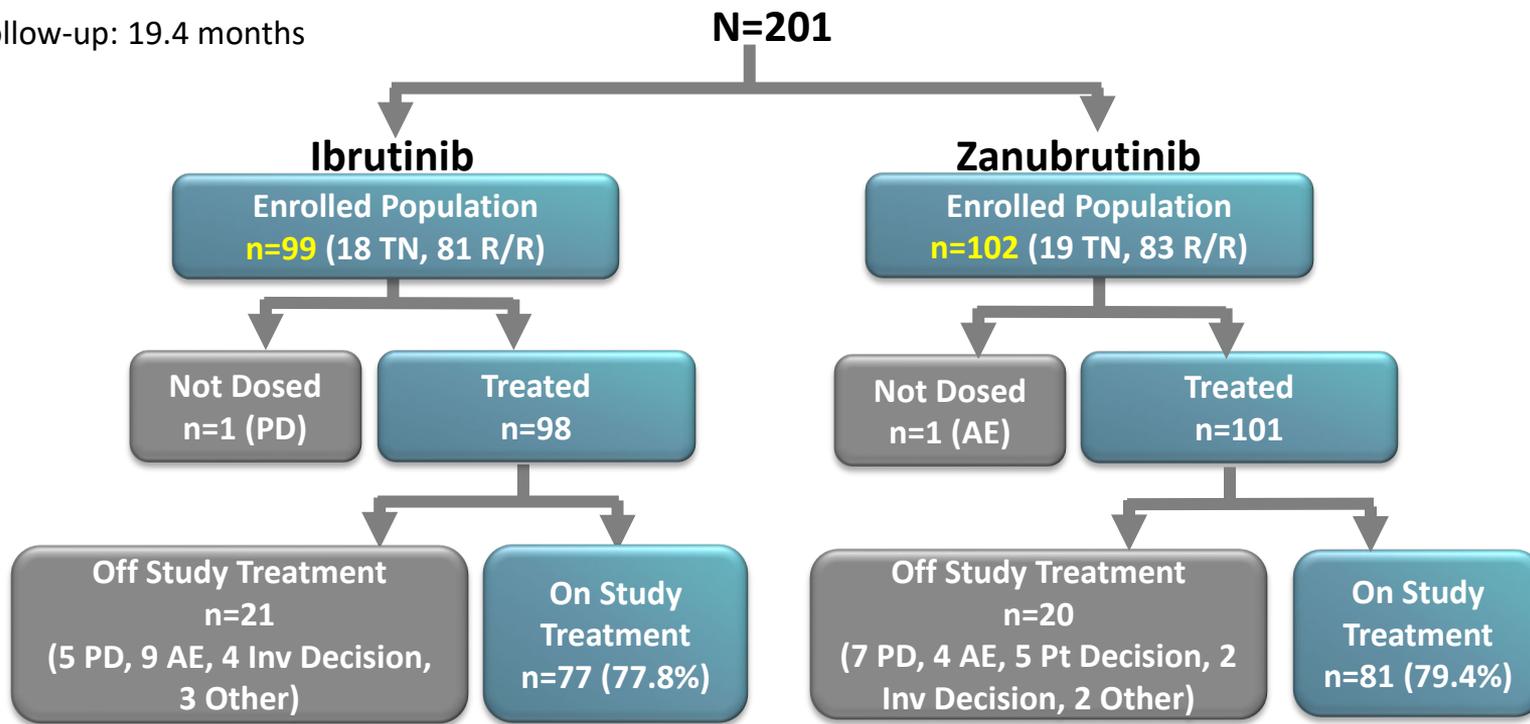
Exploratory Objectives

- 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



Abbreviations: AE, adverse event; Inv, investigator; *MYD88*, myeloid differentiation primary response gene 88; PD, progressive disease; Pt, patient; R/R, relapsed/refractory; TN, treatment-naïve; WM, Waldenström macroglobulinemia.

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)

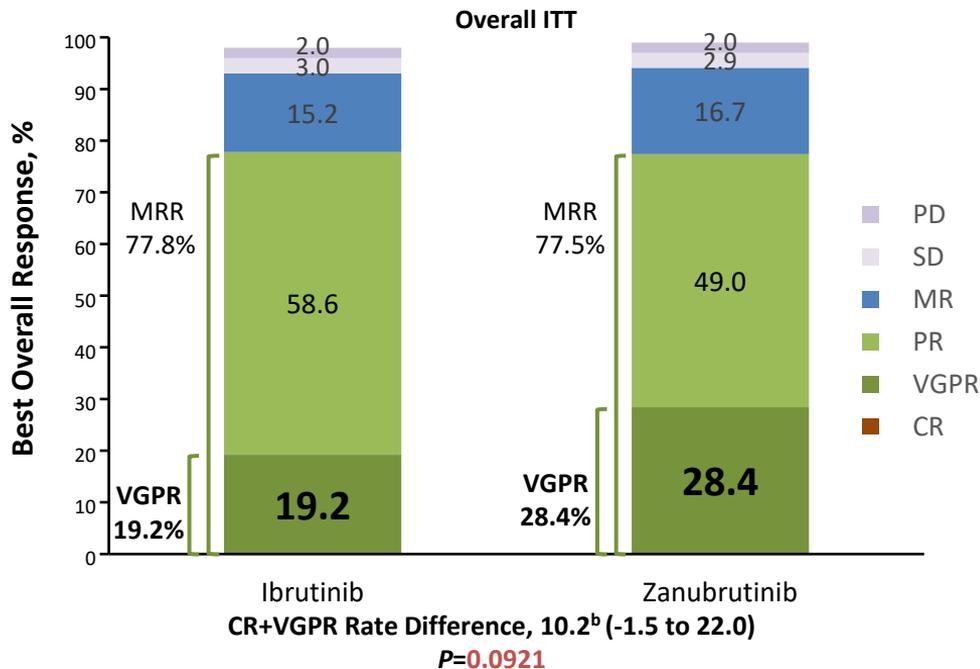
^aWild-type–blocking polymerase chain reaction for *MYD88* and Sanger sequencing for *CXCR4* using bone marrow aspirates. One patient had local next-generation sequencing testing results of *MYD88*^{L265P}/*CXCR4* Unknown.

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.

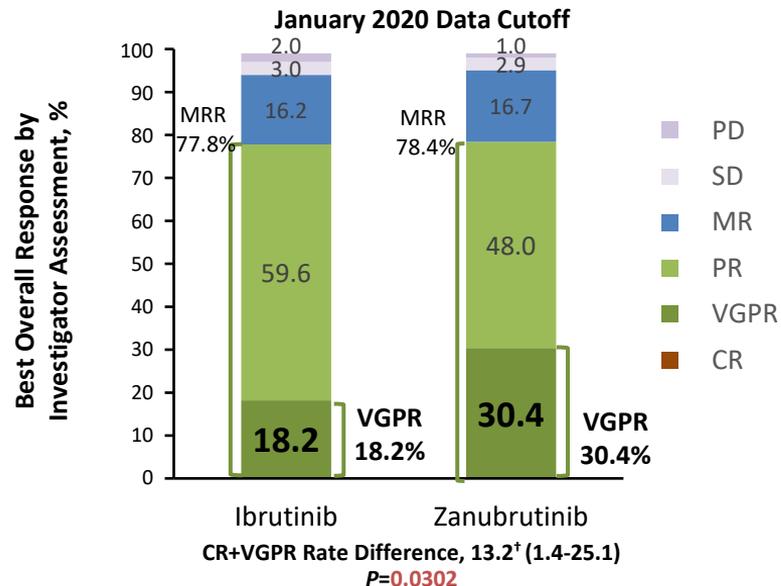
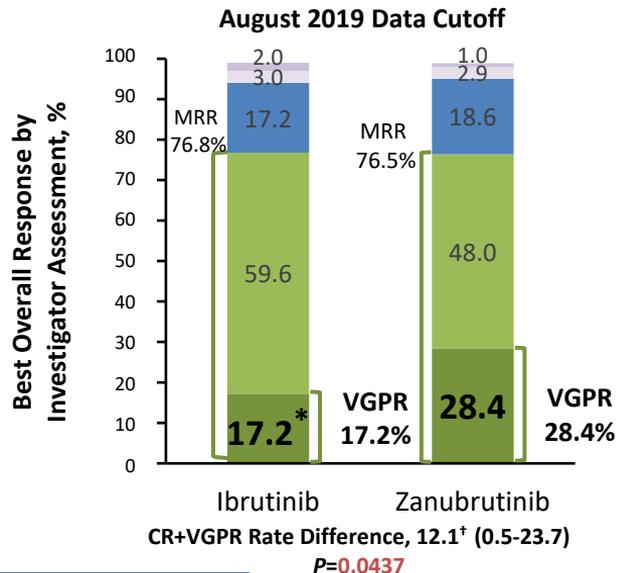
Abbreviations: CR, complete response; IRC, independent review committee; ITT, intention-to-treat; MR, minor response; MRR, major response rate; PD, progressive disease; PR, partial response; R/R, relapsed/refractory; SD, stable disease; VGPR, very good PR.



ASPEN: Secondary Efficacy Endpoints

Assessment of Response According to Investigator

Investigator-Assessed Response



IgM Reduction

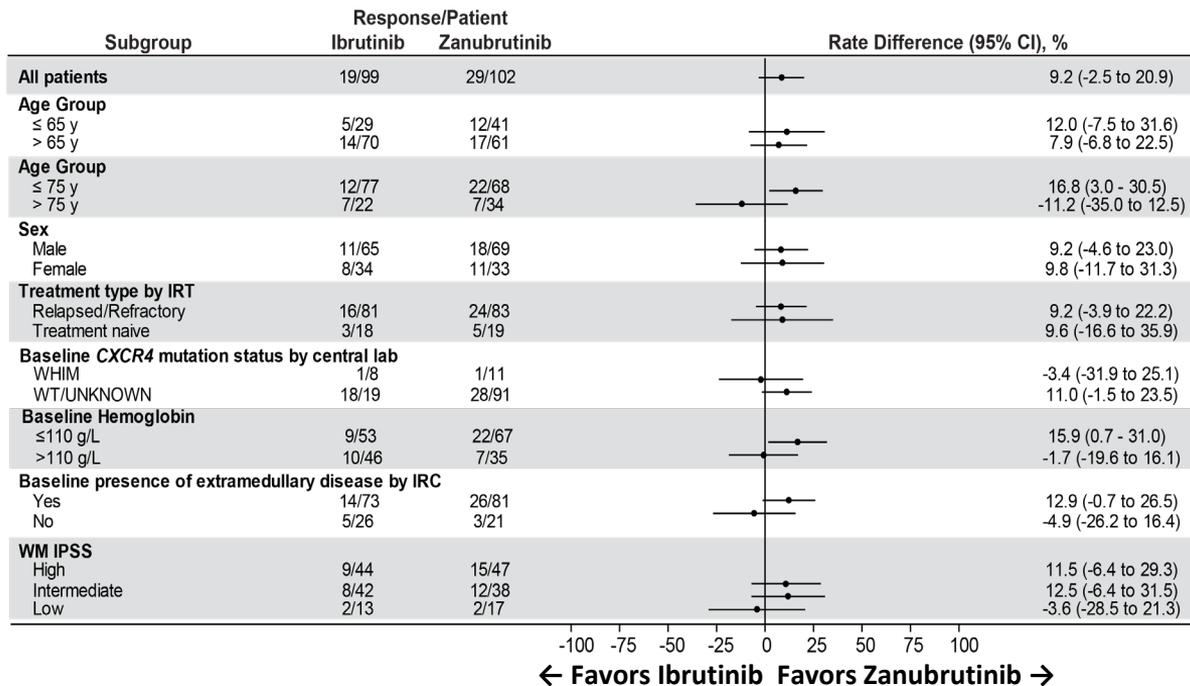
- AUC for IgM reduction over time was significantly greater for zanubrutinib vs ibrutinib ($P=0.037$)

*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.

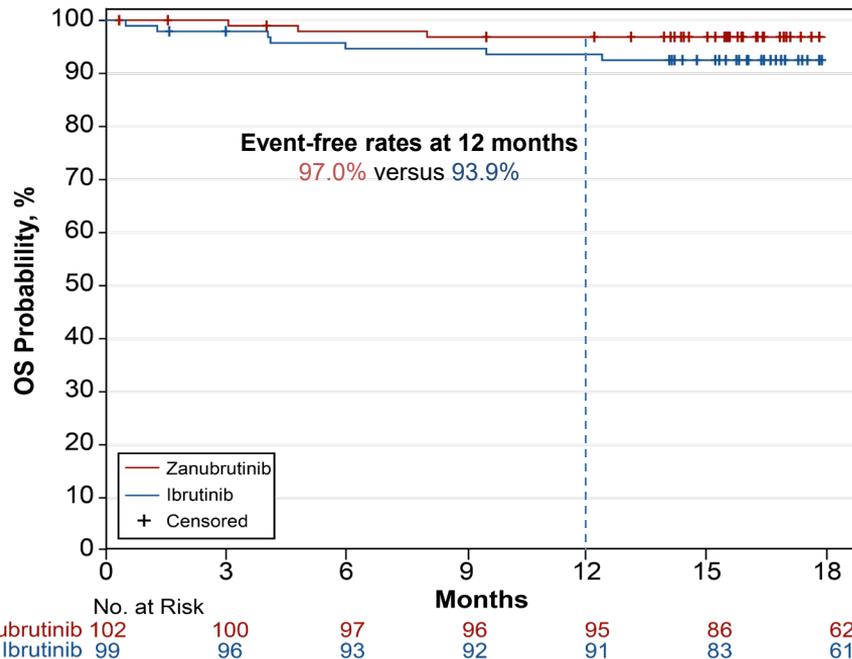
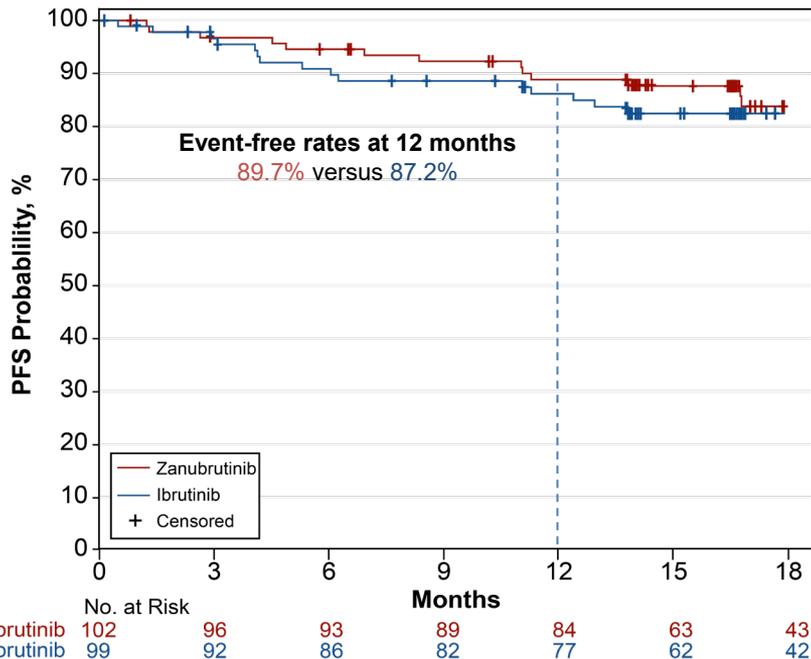
ASPEN: Forest Plot of CR+VGPR Response Rate Difference by IRC (ITT)



Abbreviations: CR, complete response; *CXCR4*, C-X-C motif chemokine receptor 4; IRC, independent review committee; IRT, interactive response technology; ITT, intention-to-treat; VGPR, very good partial response; WM IPSS, Waldenström macroglobulinemia International Prognostic Scoring System.



ASPEN: PFS and OS Survival in ITT Population



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.

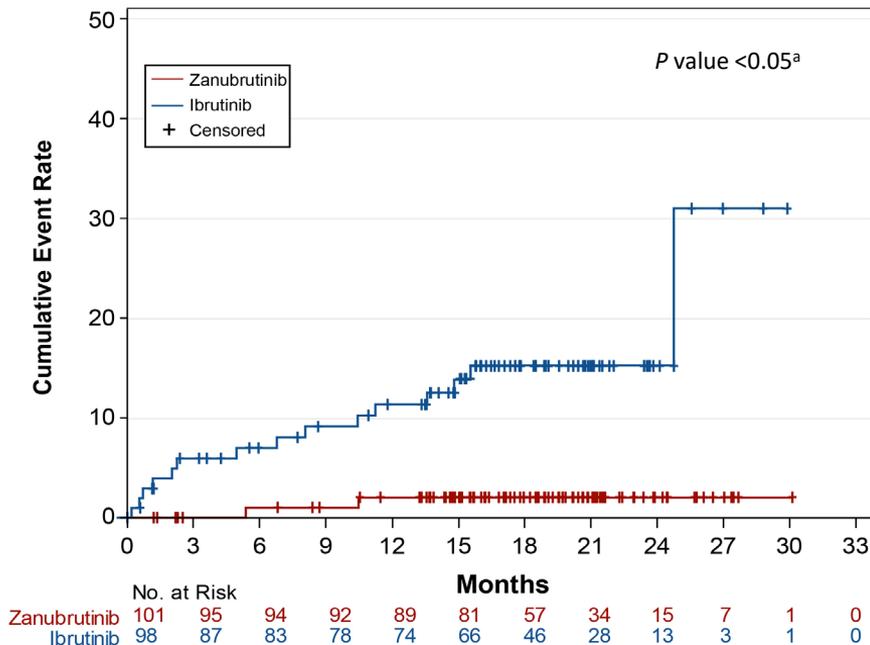
[†]Descriptive 2-sided $P < 0.05$.

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

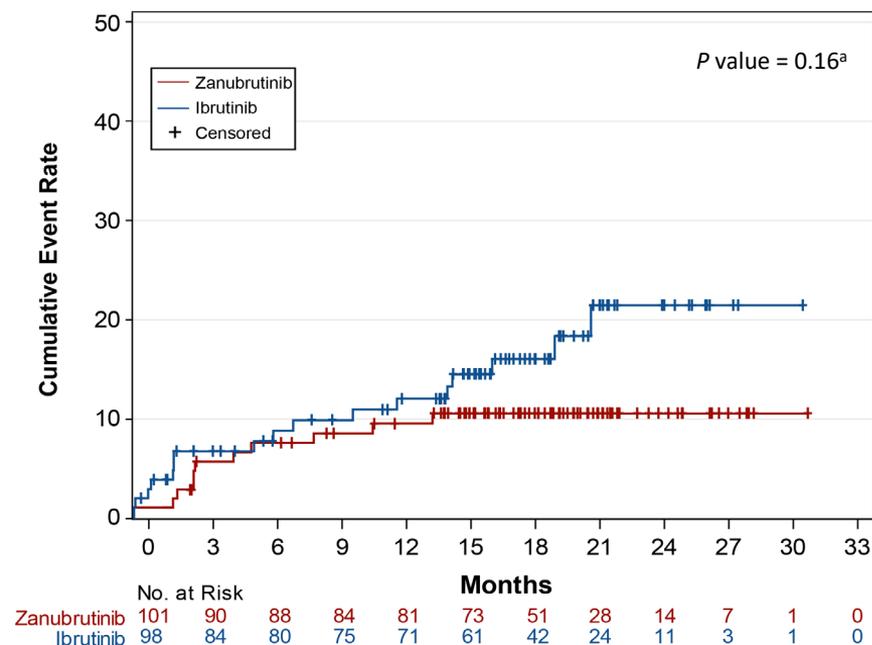
Abbreviations: AE, adverse event; BTKi, Bruton tyrosine kinase inhibitor; PT, preferred term.

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

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

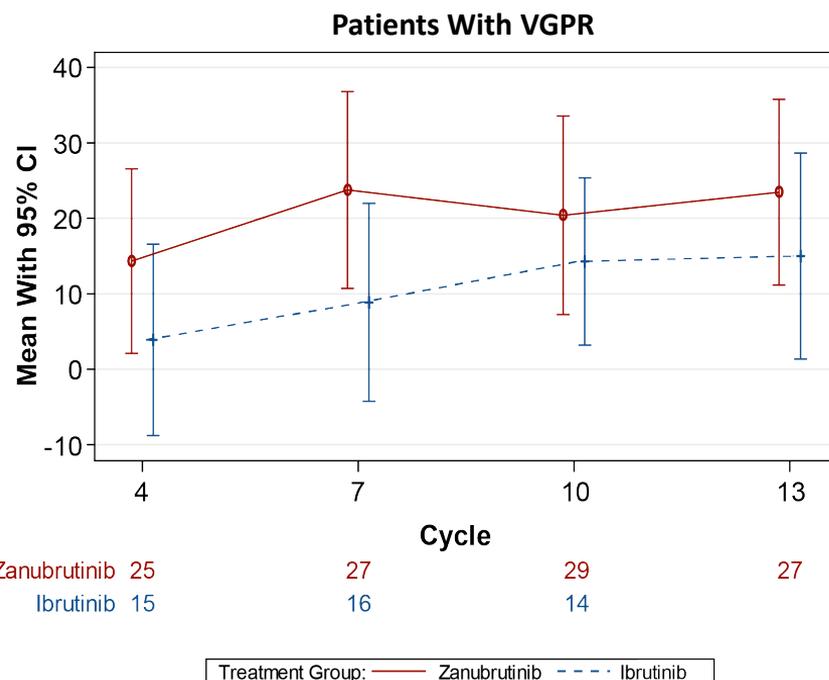
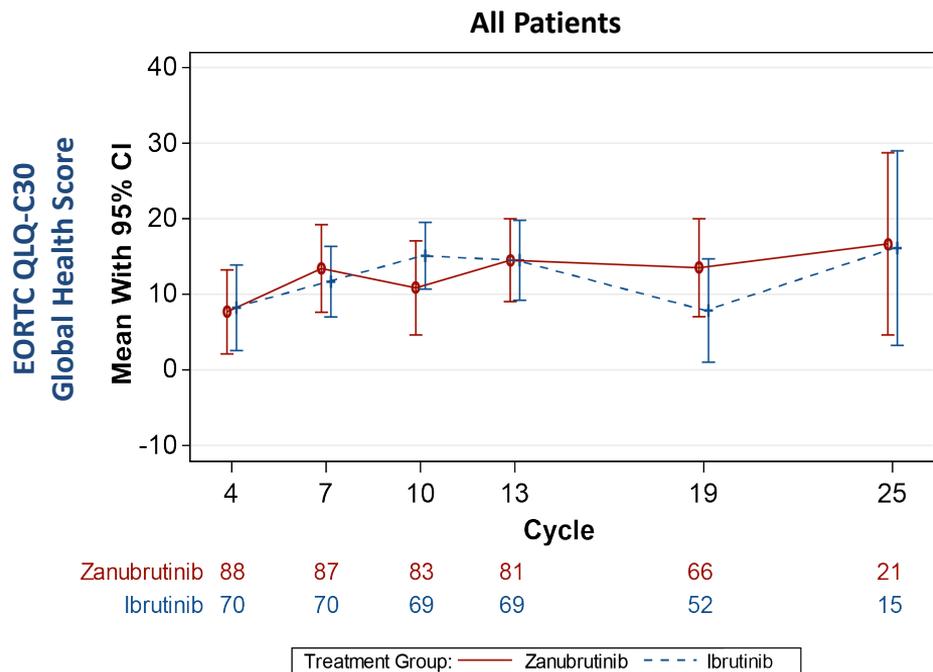


Kaplan-Meier Curve: Time to **Hypertension**



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

ASPEN: Quality of Life – Change From Baseline Over Time



Abbreviations: EORTC QLQ-C30, European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire - Core Questionnaire; VGPR, very good partial response.

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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