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

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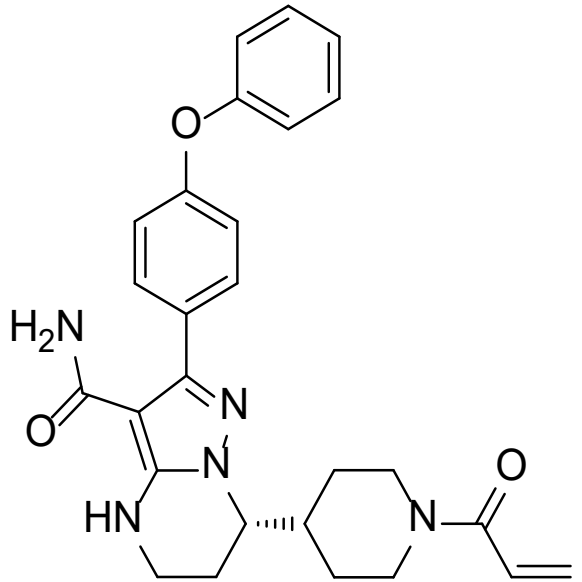
Abstract: 8007

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 an emerging standard of care for WM[3]
- 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 to ibrutinib;** higher selectivity vs EGFR, ITK, JAK3, HER2 and TEC[4]
  - **Advantageous PK, PD properties**: complete and sustained BTK occupancy in PBMC and lymph nodes [5]
  - **Favorable drug-drug interaction properties:** can be co-administered with strong/moderate CYP3A inhibitors at a reduced dose, proton pump inhibitors, acid-reducing agents, and anti-thrombotic agents.[6,7]
  - **Approved for patients with R/R MCL in the United States Nov 2019**



BTK, Bruton tyrosine kinase; EGFR, epidermal growth factor receptor; HER2, human epidermal growth factor receptor 2; ITK, IL2-inducible T-cell kinase; JAK3, Janus tyrosine kinase 3; PD, pharmacodynamic; PK, pharmacokinetic; WM, Waldenström Macroglobulinemia.

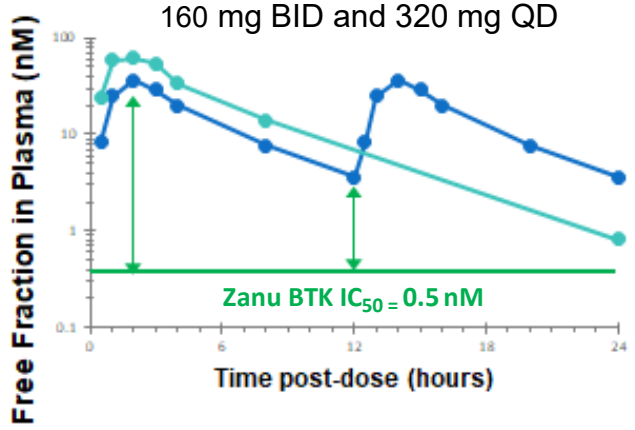
1. Rickert RC. *Nat Rev Immunol*. 2013;13:578-591. 2. Argyropoulos KV, et al. *Leukemia*. 2016;30:1116-1125. 3. Treon SP et al, *J Clin Oncol.* 2020;38:1198-1208 . 4. Guo Y, et al. *J Med Chem.* 2019;62:7923-7940. 5. Tam CS, et al. *Blood*. 2019;134:851-859. 6. Mu S et al. *Cancer Chemother Pharmacol.*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

Zanubrutinib: A Potent and Selective BTK Inhibitor[1,2]

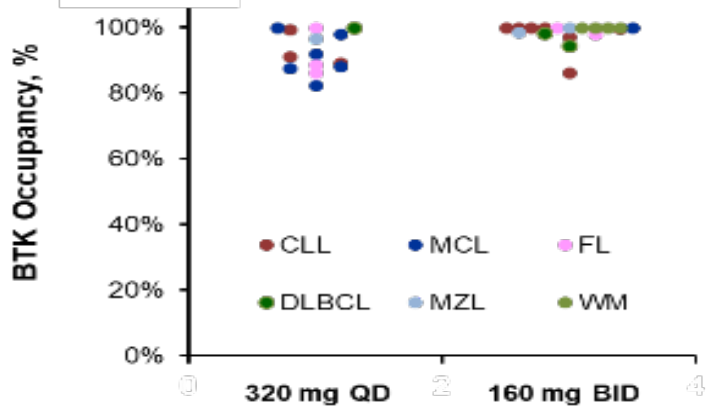
- Potent, selective, irreversible; minimize off-target inhibition

Targets	Assays	Zanubrutinib IC_{50} (nM)	Ibrutinib IC_{50} (nM)	Ratio (Zanubrutinib:Ibrutinib)
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	1.0
	BTK Biochemical Assay	0.22	0.2	1.1
EGFR	p-EGFR HTRF Cellular Assay	606	101	6
	A431 Proliferation	3210	323	9.9
ITK	ITK Occupancy Cellular Assay	606	189	17
	p-$PLC_{\gamma1}$ 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 IC_{50} over 24 hours



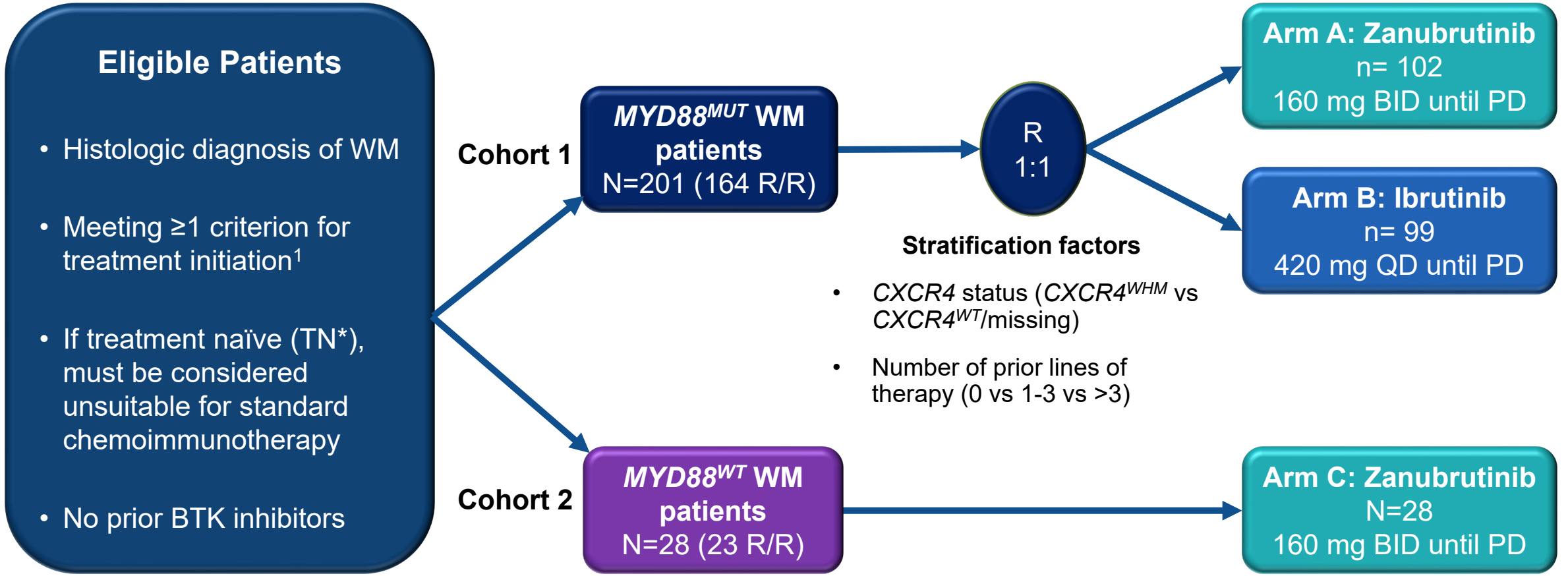
Complete, sustained BTK occupancy



BID, twice daily; QD: once daily; BTK, Bruton tyrosine kinase; CLL, chronic lymphocytic leukemia; DLBCL, diffuse large B-cell lymphoma; EGFR, epidermal growth factor receptor; FL, follicular lymphoma; HER2, human epidermal growth factor receptor 2; HRRF, Homogeneous Time Resolved Fluorescence; IC_{50}, half maximal inhibitory concentration; ITK, IL2-inducible T-cell kinase; JAK3, Janus tyrosine kinase 3; MCL, mantle cell lymphoma; MZL, marginal zone lymphoma; PLC, phospholipase C; WM, Waldenström Macroglobulinemia; Zanu, zanubrutinib.

1. Guo Y, et al. *J Med Chem.* 2019;62:7923-7940. 2. Tam CS, et al. *Blood*. 2019;134:851-859.

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



Abstract: e20056

EUDRACT 2016-002980-33; NCT03053440

BID, twice daily; BTK, Bruton tyrosine kinase; CXCR4, C-X-C Motif Chemokine Receptor 4; MYD88^{MUT}, myeloid differentiation primary response gene 88 mutant; PD, progressive disease; QD, daily; R, randomization; R/R, relapsed/refractory; TN, treatment naïve; WM, Waldenström Macroglobulinemia; WT, wild-type.
*Up to 20% of the overall population.

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

ASPEN Study Objectives

Primary Objective

- To compare the efficacy of zanubrutinib vs ibrutinib
  - Primary endpoint was CR + VGPR rate in patients with activating mutations (*MYD88*^{MUT}) WM

Secondary Objectives

- To further compare the efficacy, clinical benefit, and anti-lymphoma effects of zanubrutinib vs ibrutinib
- To evaluate safety and tolerability of zanubrutinib versus ibrutinib as measured by the incidence, timing, and severity of TEAEs according to NCI-CTCAE (version 4.03)

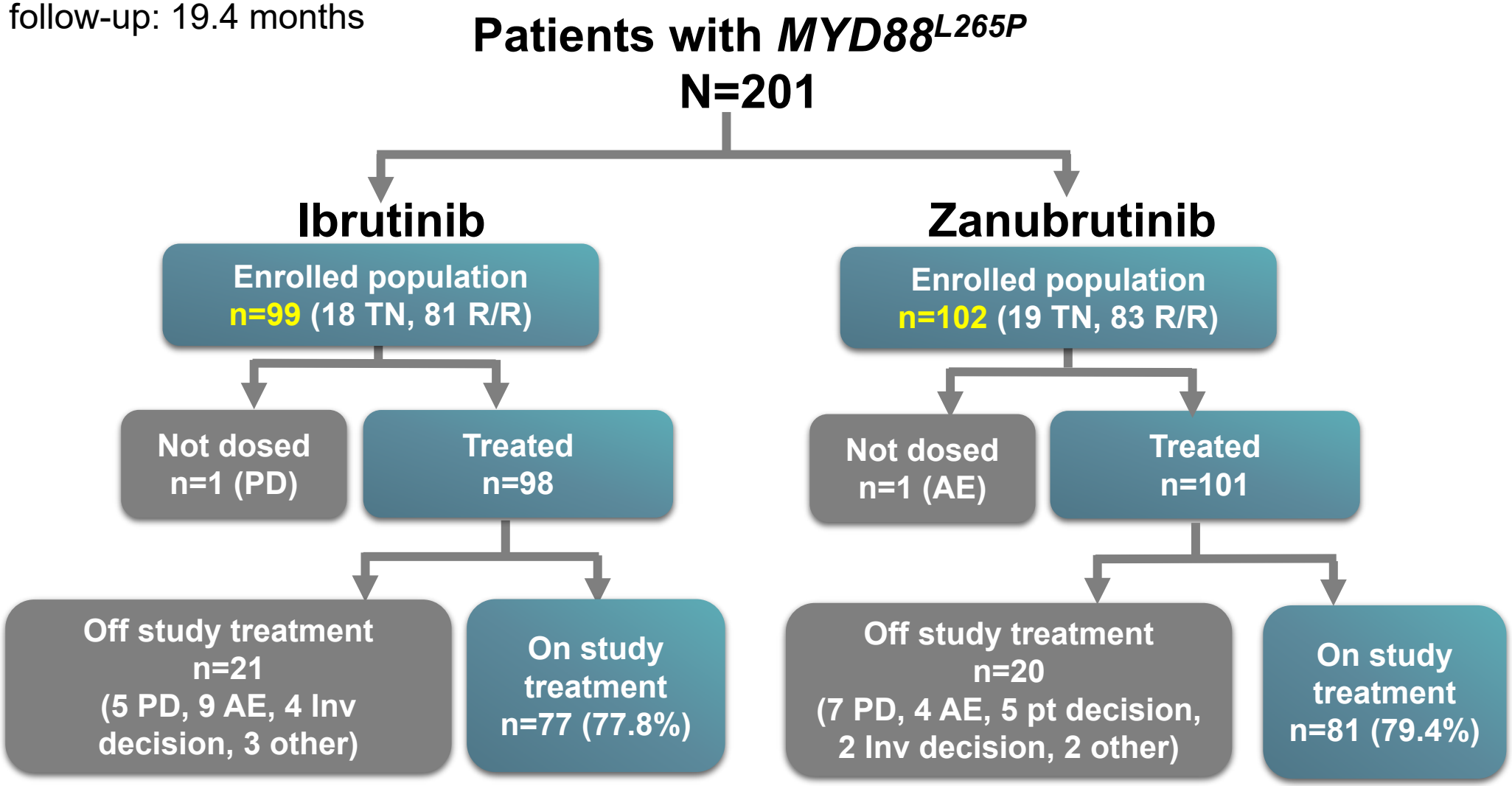
Exploratory Objectives

- To characterize the PK of zanubrutinib in patients with WM
- To compare QoL by EORTC QLQ-C30 and EQ-5D

AE, adverse event; EORTC QLQ-C30, EORTC Quality of Life Questionnaire - Core Questionnaire; EQ-5D, EuroQoL-5D; MYD88^{MUT}, myeloid differentiation primary response gene 88 mutant; NCI-CTCAE, National Cancer Institute Common Terminology Criteria for Adverse Events; PK, pharmacokinetics; QoL, quality of life; TEAE, treatment-emergent AE.

ASPEN: Patient Disposition

- Median follow-up: 19.4 months



AE, adverse event; Inv, Investigator; MYD88, myeloid differentiation primary response gene 88; PD, progressive disease; pt, patient; R/R, relapsed/refractory; TN, treatment-naïve.

ASPEN: Demographics and Disease Characteristics

Characteristics, n (%)	Overall ITT	
	Ibrutinib (n = 99)	Zanubrutinib (n =102)
Age, years median (range)	70.0 (38, 90)	70.0 (45, 87)
> 65 years	**70 (70.7)**	61 (59.8)
> 75 years	22 (22.2)	**34 (33.3)**
Gender, 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*, n (%)		
MYD88^{L265P}/*CXCR4*^{WT}	90 (90.9)	91 (89.2)
MYD88^{L265P}/*CXCR4*^{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)**

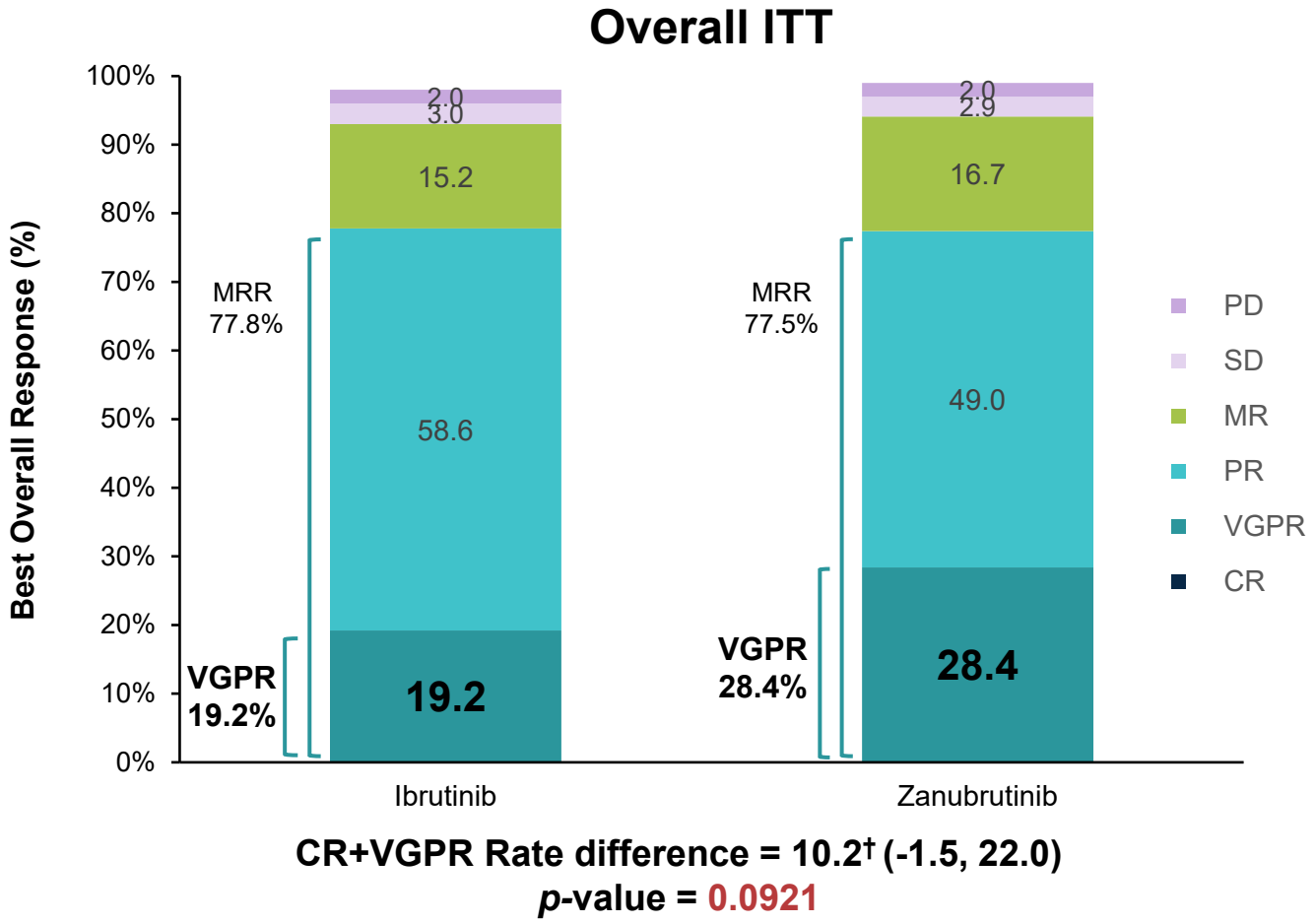
CXCR4, C-X-C Motif Chemokine Receptor 4; ITT, intention-to-treat; IPSS WM, International Prognostic Scoring System for Waldenström macroglobulinemia; MYD88, myeloid differentiation primary response gene 88; NGS, next-generation sequencing.

*"Wildtype-blocking PCR" for *MYD88* and Sanger sequencing for *CXCR4* using bone marrow aspirates. One patient had local NGS testing results of *MYD88 L265P/ CXCR4* Unknown.

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

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

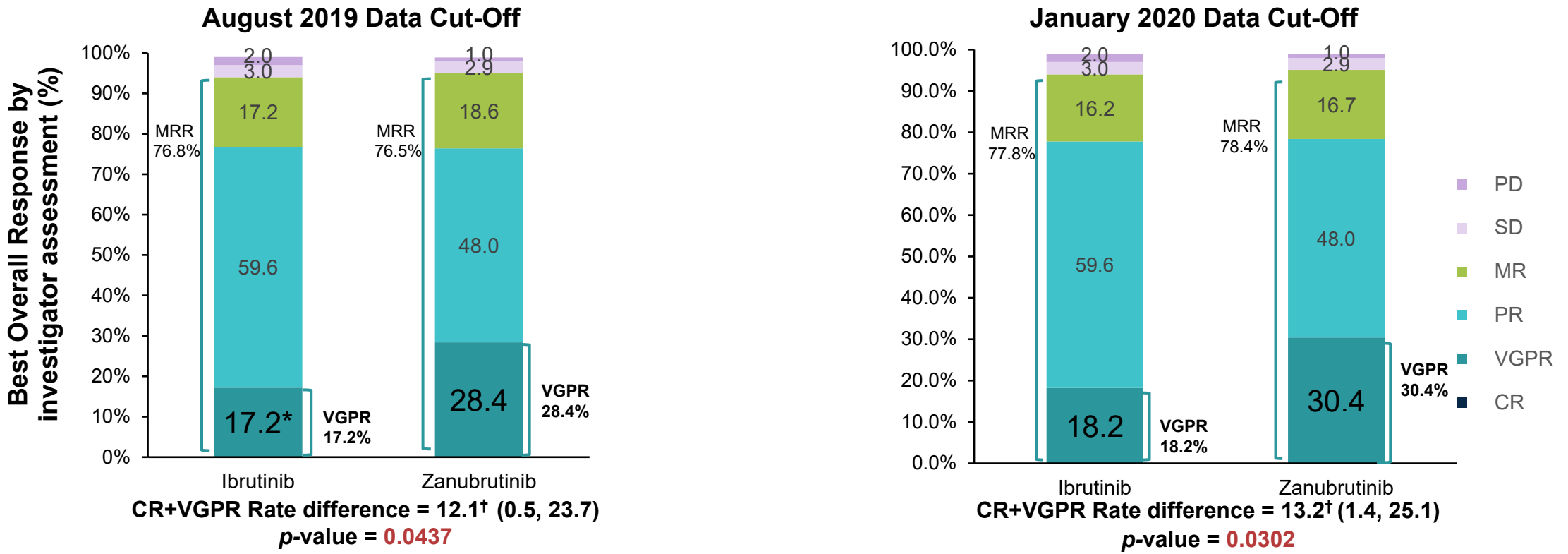
- Superiority in CR+VGPR rate compared to ibrutinib in relapsed/refractory population (primary study hypothesis) was not significant*



CR, complete response; IRC, independent review committee; ITT, intention-to-treat; MRR, major response rate; MR, minor response; ; ORR, overall response rate; PD, progressive disease; PR, partial response; R/R, relapsed/refractory; SD, stable disease; VGPR, very good PR.
Overall concordance between Independent review and investigators = 94%
* All other *P* values are for descriptive purposes only. †Adjusted for stratification factors and age group.

ASPEN: Secondary Efficacy Endpoints
Assessment of Response According to Investigator and IgM Analysis

Investigator-Assessed Response



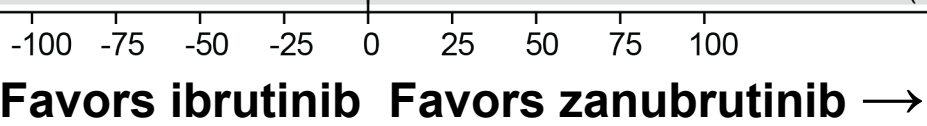
IgM Reduction

- Area-under-the-curve (AUC) for IgM reduction over time was significantly greater for zanubrutinib vs ibrutinib (p=0.037)

CR, complete response; EMD, extramedullary disease; IgM, Immunoglobulin M; IRC, independent review committee; MRR, major response rate; MR, minor response; ; ORR, overall response rate; PD, progressive disease; PR, partial response; SD, stable disease; SPEP, serum protein electrophoresis; VGPR, very good PR.
*Excluded two patients with VGPR by IRC: MR (EMD present) and PR (IgM assessment by local SPEP M-protein)
†Adjusted for stratification factors and age group. *P* value is for descriptive purpose only.

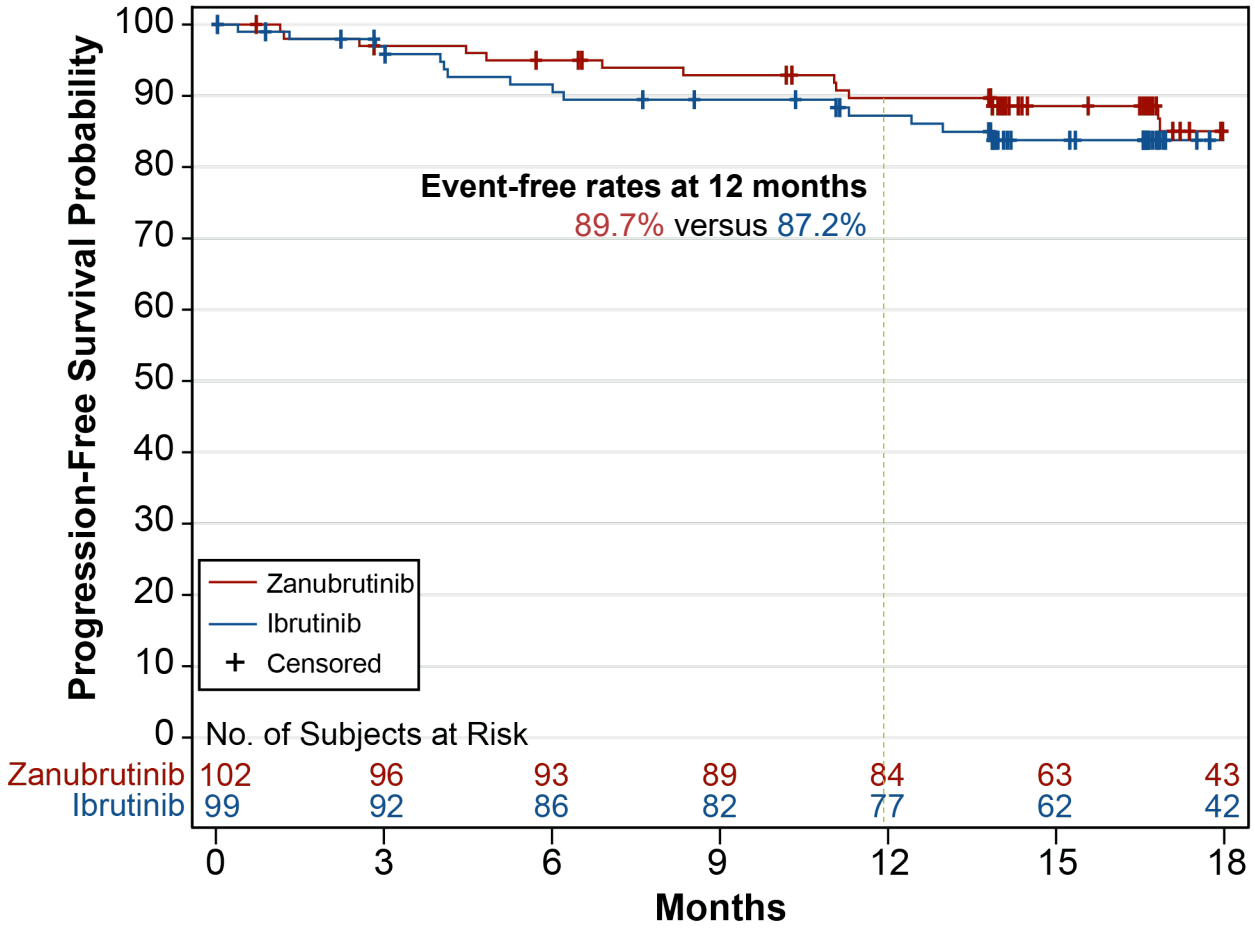
ASPEN: Forest Plot of CR+VGPR Response Rate Risk Difference by IRC, in overall ITT population

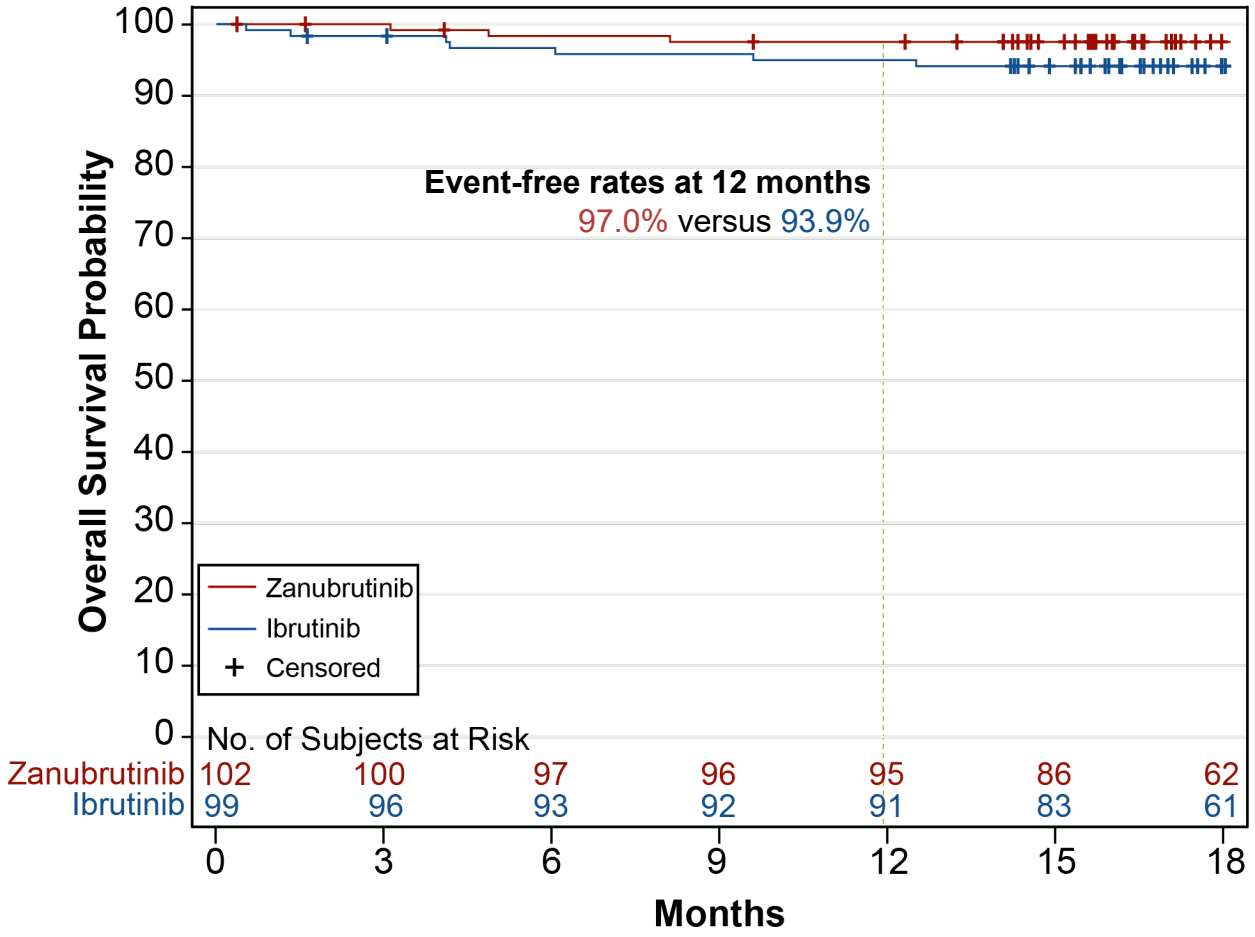
Subgroup	Response/Subject Ibrutinib	Response/Subject Zanubrutinib	Risk Difference (95% CI), % [a]
All patients	19 / 99	29 / 102	9.2 (-2.5, 20.9)
Age Group			
<= 65 years	5 / 29	12 / 41	12.0 (-7.5, 31.6)
> 65 years	14 / 70	17 / 61	7.9 (-6.8, 22.5)
Age Group			
<= 75 years	12 / 77	22 / 68	16.8 (3.0, 30.5)
> 75 years	7 / 22	7 / 34	-11.2 (-35.0, 12.5)
Gender			
Male	11 / 65	18 / 69	9.2 (-4.6, 23.0)
Female	8 / 34	11 / 33	9.8 (-11.7, 31.3)
Treatment type by IRT			
Relapsed/Refractory	16 / 81	24 / 83	9.2 (-3.9, 22.2)
Treatment Naive	3 / 18	5 / 19	9.6 (-16.6, 35.9)
Baseline CXCR4 mutation status by central lab			
WHIM	1 / 8	1 / 11	-3.4 (-31.9, 25.1)
WT/UNKNOWN	18 / 91	28 / 91	11.0 (-1.5, 23.5)
Baseline Hemoglobin			
<=110 g/L	9 / 53	22 / 67	15.9 (0.7, 31.0)
>110 g/L	10 / 46	7 / 35	-1.7 (-19.6, 16.1)
Baseline presence of extramedullary disease by IRC			
Yes	14 / 73	26 / 81	12.9 (-0.7, 26.5)
No	5 / 26	3 / 21	-4.9 (-26.2, 16.4)
WM IPSS			
High	9 / 44	15 / 47	11.5 (-6.4, 29.3)
Intermediate	8 / 42	12 / 38	12.5 (-6.4, 31.5)
Low	2 / 13	2 / 17	-3.6 (-28.5, 21.3)



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 PR; WM IPSS, Waldenström macroglobulinemia International Prognostic Scoring System.

ASPEN: Progression-Free and Overall Survival in ITT population





IRC, independent review committee; VGPR, very good partial response.
Disease progression determined by IRC.

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)

AE, adverse event (treatment-emergent); G, grade.
[a] cardiac failure acute; sepsis (n=2); unexplained death.
[b] cardiac arrest after plasmapheresis
[c] G5 sepsis (n=2); G5 unexplained death; G3 acute myocardial infarction; G3 hepatitis ; G3 pneumonia; G2 drug-induced liver injury; G2 pneumonitis; G1 pneumonitis.
[d] G5 cardiac arrest after plasmapheresis; G4 neutropenia; G4 subdural hemorrhage ; G2 plasma cell myeloma.

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 blue).
AE, adverse event; PT, preferred term.
†Descriptive two-sided *P*-value < 0.05

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[a]	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[b]†	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 blue 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).
AE, adverse event; BTKi, Bruton tyrosine kinase inhibitor; PT, preferred term.
[a]Defined as any grade ≥ 3 hemorrhage or any grade central nervous system hemorrhage.
[b]Including PT terms of neutropenia, neutrophil count decreased, febrile neutropenia, agranulocytosis, neutropenic infection and neutropenic sepsis.
† Descriptive two-sided *P*-value < 0.05.

ASPEN: AE Categories of Interest (BTKi Class AEs) with additional 5 months follow-up (Data cutoff: 31 January 2020)

- **An additional 5 patients had discontinued ibrutinib treatment due to AEs versus 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[a]	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[b]†	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 blue with ≥ 10% difference in any grade or ≥ 5% difference in grade 3 or above.

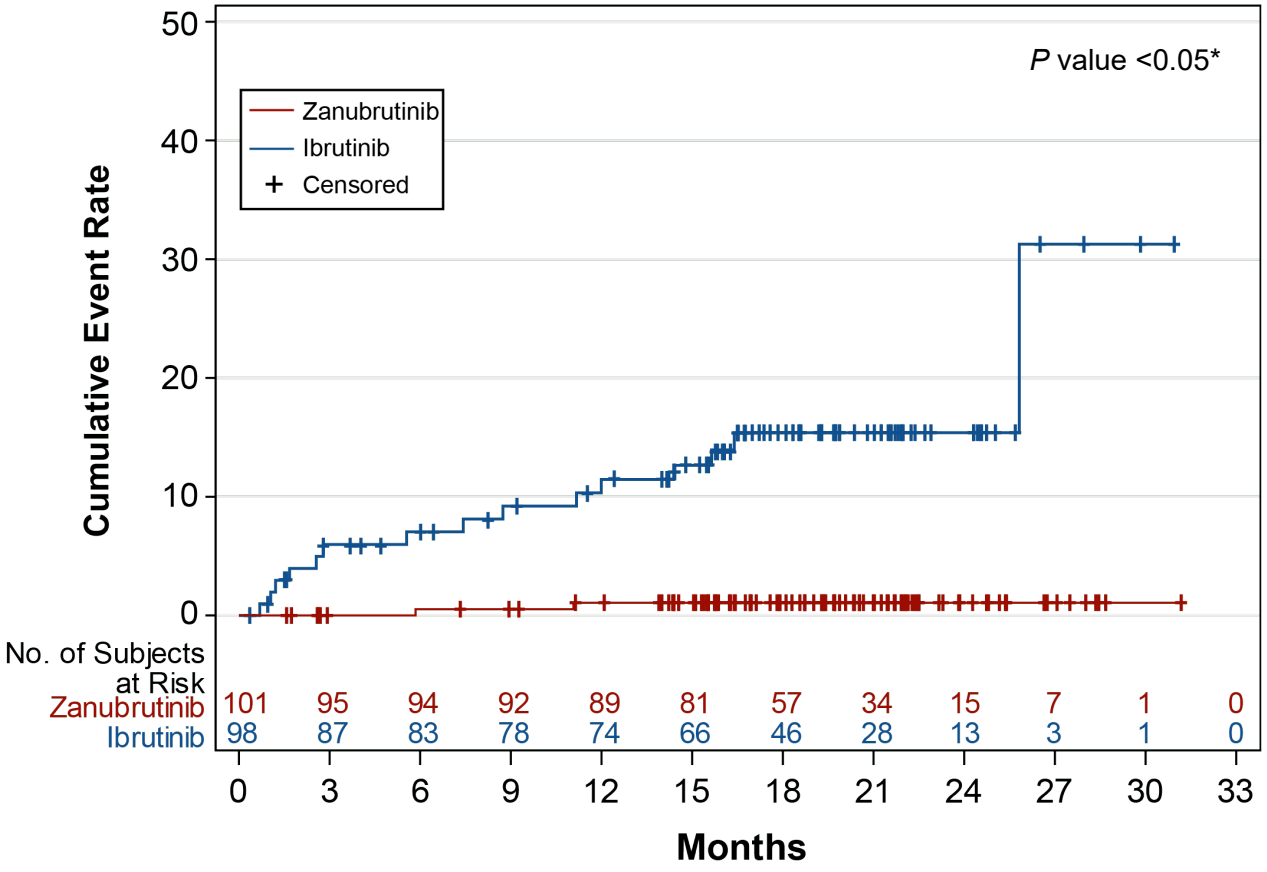
[a]Defined as any grade ≥ 3 hemorrhage or any grade central nervous system hemorrhage.

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

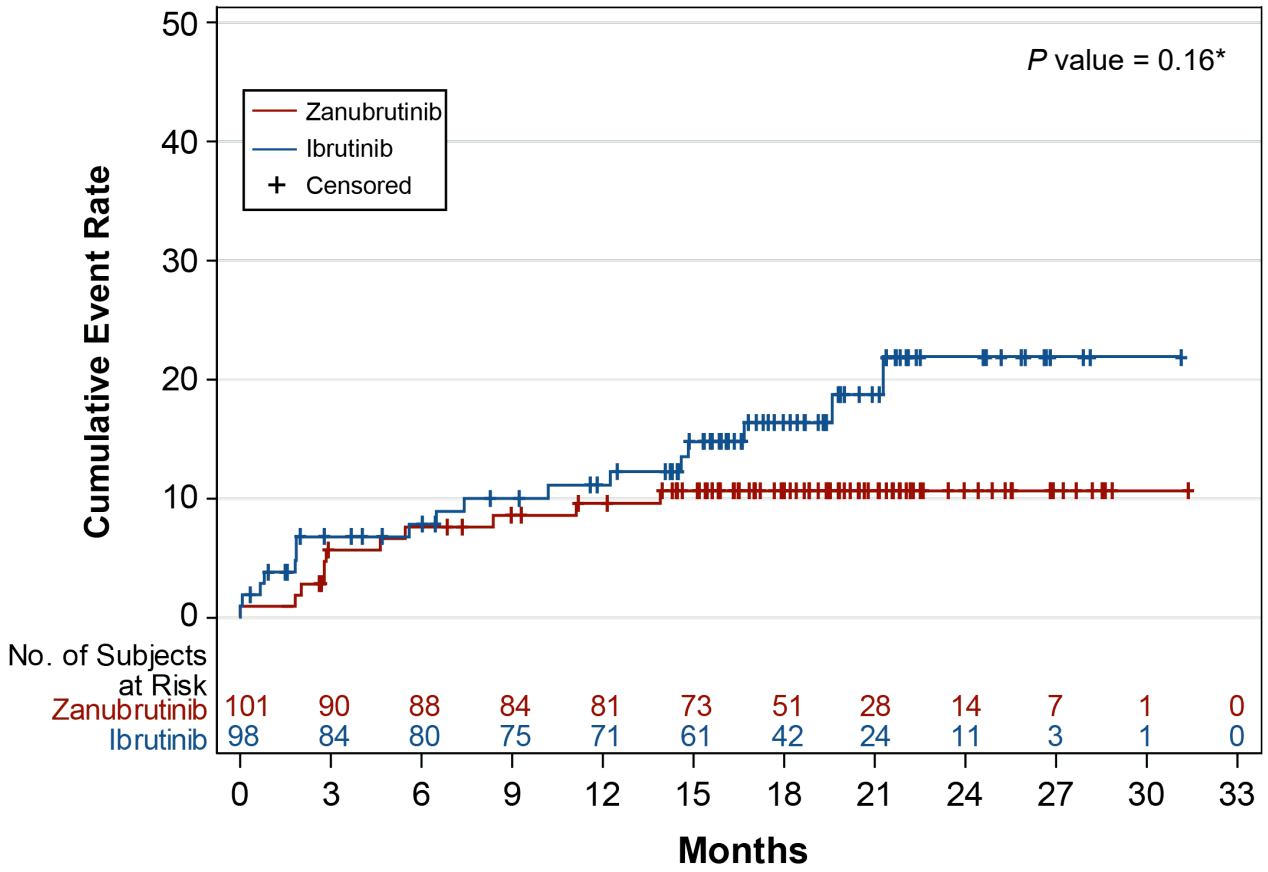
† Descriptive two-sided *P*-value < 0.05.

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

Kaplan-Meier Curve: Time to **Atrial fibrillation/flutter**

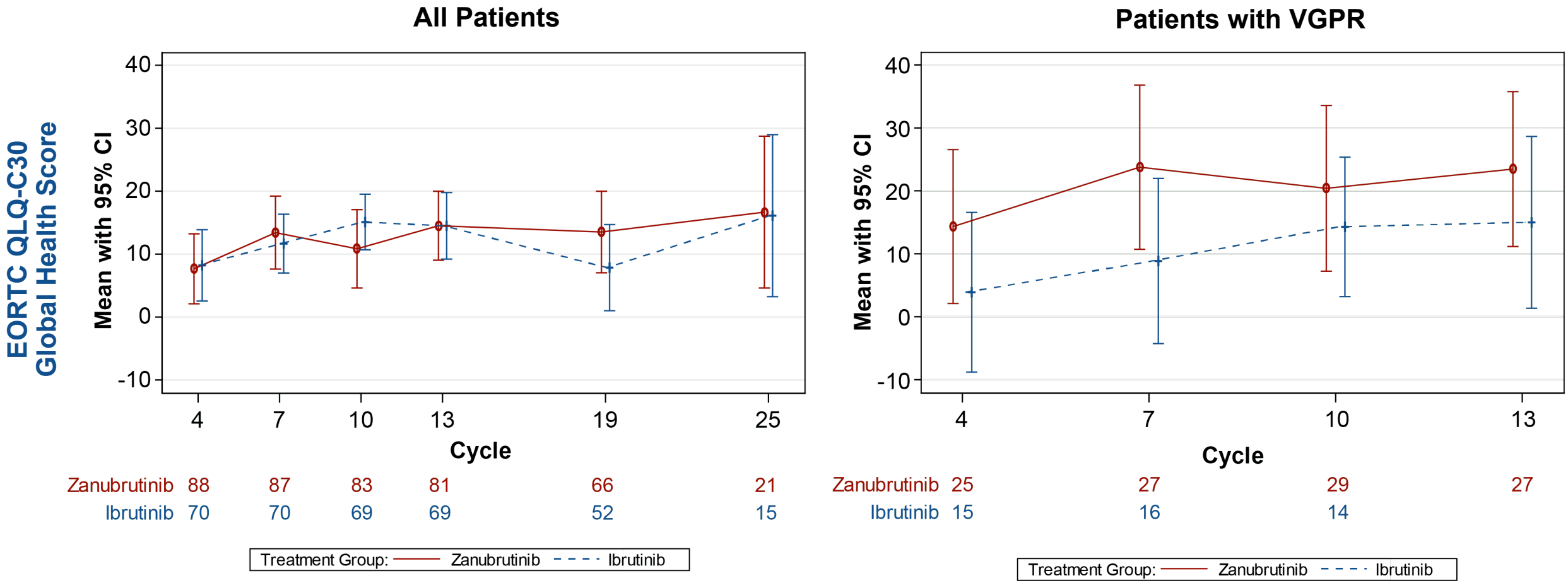


Kaplan-Meier Curve: Time to **Hypertension**



AE, adverse event.
*Descriptive purpose only.

ASPEN: Quality of Life – Change from baseline over time



EORTC QLQ-C30, EORTC 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 to ibrutinib of 19.2% (p= 0.0921)**
  - The primary hypothesis of superiority in CR+VGPR rate (by IRC) was not met
  - Greater CR+VGPR response rate by investigator assessment (ITT: 28.4% vs 17.2%, *P*=0.04*)
  - Deeper and sustained IgM reduction over time (*P*=0.04*)
  - Major response rates were comparable, with directionally favorable PFS, OS and QoL

- **Zanubrutinib demonstrated clinically meaningful advantages in safety and tolerability**
  - A reduction in the risk of atrial fibrillation/flutter (2.0% vs 15.3%, p= 0.0008*)
  - Lower rates of major bleeding (5.9% vs 9.2%), diarrhea (20.8% vs 32.7%), 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

AEs, (treatment-emergent) adverse events; CR, complete response; IgM, Immunoglobulin M; IRC, independent review committee; ITT, intention-to-treat; OS, overall survival; PFS, progression-free survival; QoL, quality of life; VGPR, very good partial response.
*Descriptive purpose only.

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