ASPEN: Results of a Phase 3 Randomized Trial of Zanubrutinib Versus Ibrutinib For Patients With Waldenström Macroglobulinemia

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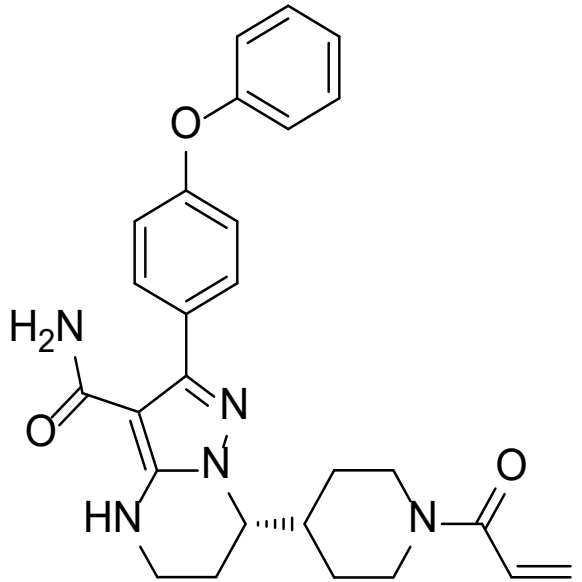
Abstract: S225

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 with ibrutinib;** higher selectivity vs EGFR, ITK, JAK3, HER2 and TEC[4]
  - **Advantageous PK/pharmacodynamic properties**: complete and sustained BTK occupancy in PBMC and lymph nodes[5]
  - **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]
  - **Approved for treatment of patients with R/R MCL in the United States Nov 2019**



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.

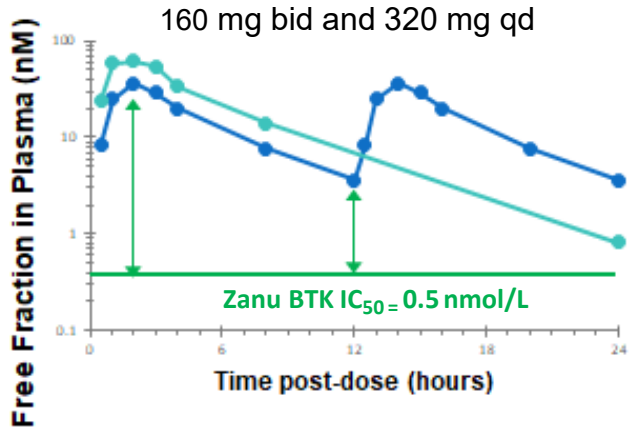
1. Rickert RC. *Nat Rev Immunol*. 2013;13:578-591. 2. Argyropoulos KV, et al. *Leukemia*. 2016;30:1116-1125. 3. Treon SP et al, *J Clin Oncol.* 2020;38:1198-1208. 4. Guo Y, et al. *J Med Chem.* 2019;62:7923-7940. 5. Tam CS, et al. *Blood*. 2019;134:851-859. 6. Mu S et al. *Cancer Chemother Pharmacol.*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

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

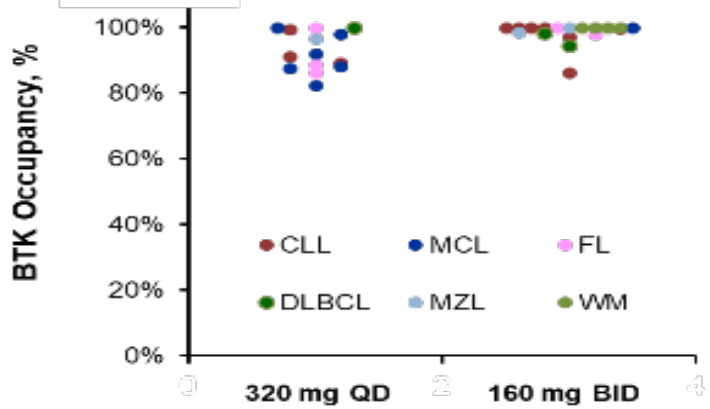
- Potent, selective, irreversible; minimize off-target inhibition

Targets	Assays	Zanubrutinib IC_{50} (nM)	Ibrutinib IC_{50} (nM)	Ratio (Zanubrutinib:Ibrutinib)
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 h



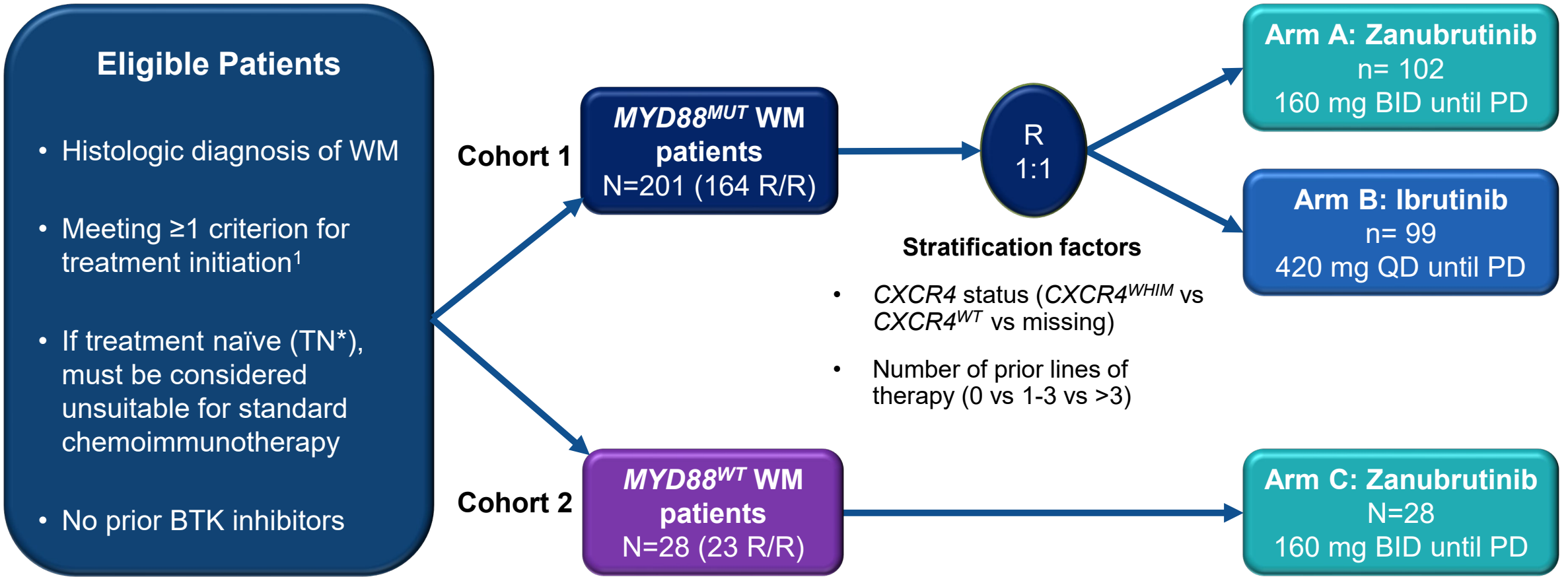
Complete, Sustained BTK Occupancy



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; IC_{50}, 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; qd: once daily; 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*, 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.

*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 end point was CR+VGPR rate in patients with activating mutations (*MYD88*^{MUT}) WM

Secondary Objectives

- To further compare the efficacy, clinical benefit, and antilymphoma effects of zanubrutinib vs ibrutinib
- To evaluate safety and tolerability of zanubrutinib vs ibrutinib as measured by the incidence, timing, and severity of TEAEs according to NCI-CTCAE (v4.03)

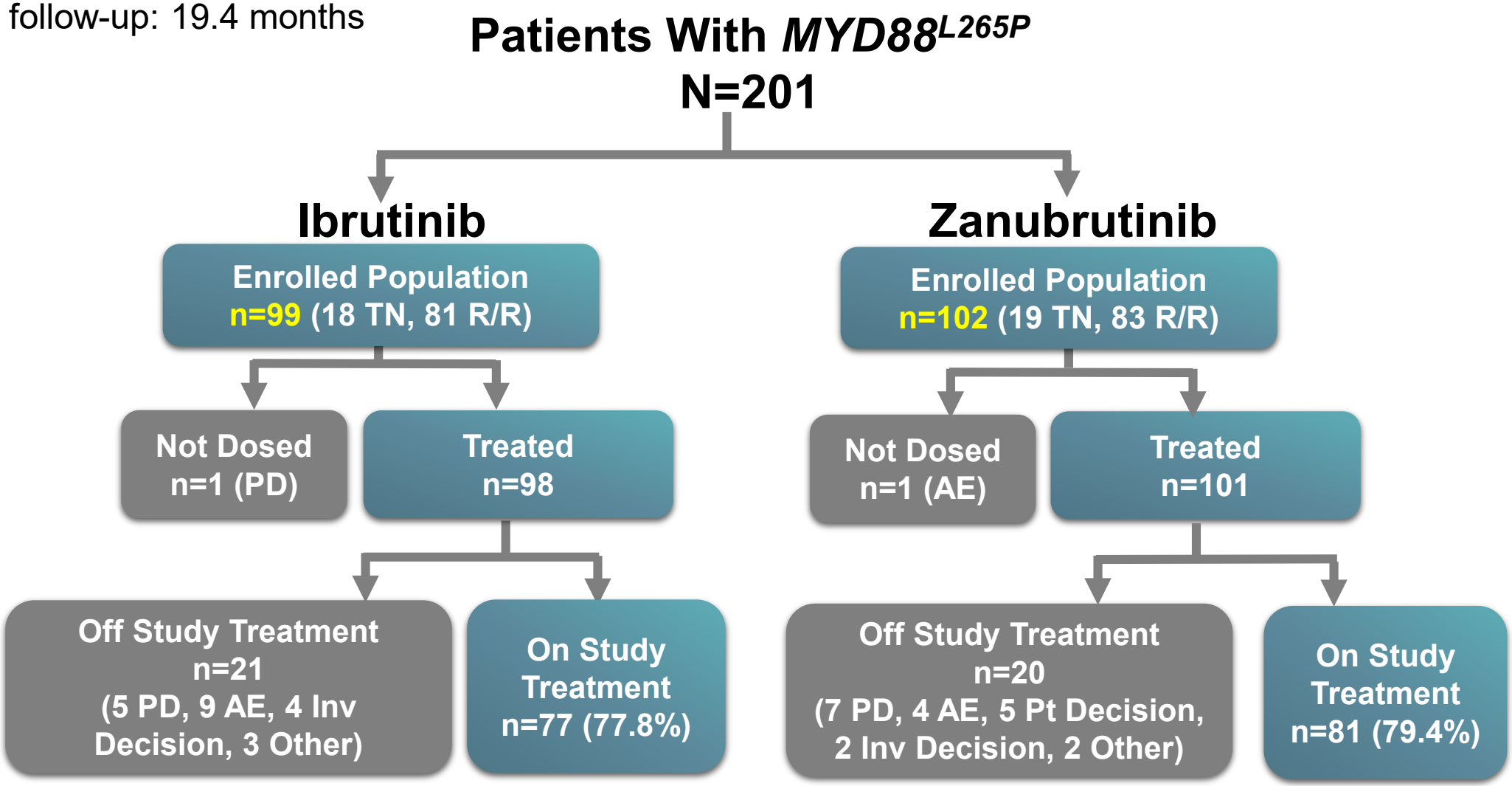
Exploratory Objectives

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

AE, adverse event; CR, complete response; EORTC QLQ-C30, European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire - Core Questionnaire; EQ-5D, EuroQoL-5D; *MYD88*^{MUT}, myeloid differentiation primary response gene 88 mutant; NCI-CTCAE (v4.03), National Cancer Institute Common Terminology Criteria for Adverse Events (version 4.03); PK, pharmacokinetics; QoL, quality of life; TEAE, treatment-emergent AE; VGPR, very good partial response; WM, Waldenström macroglobulinemia.

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.

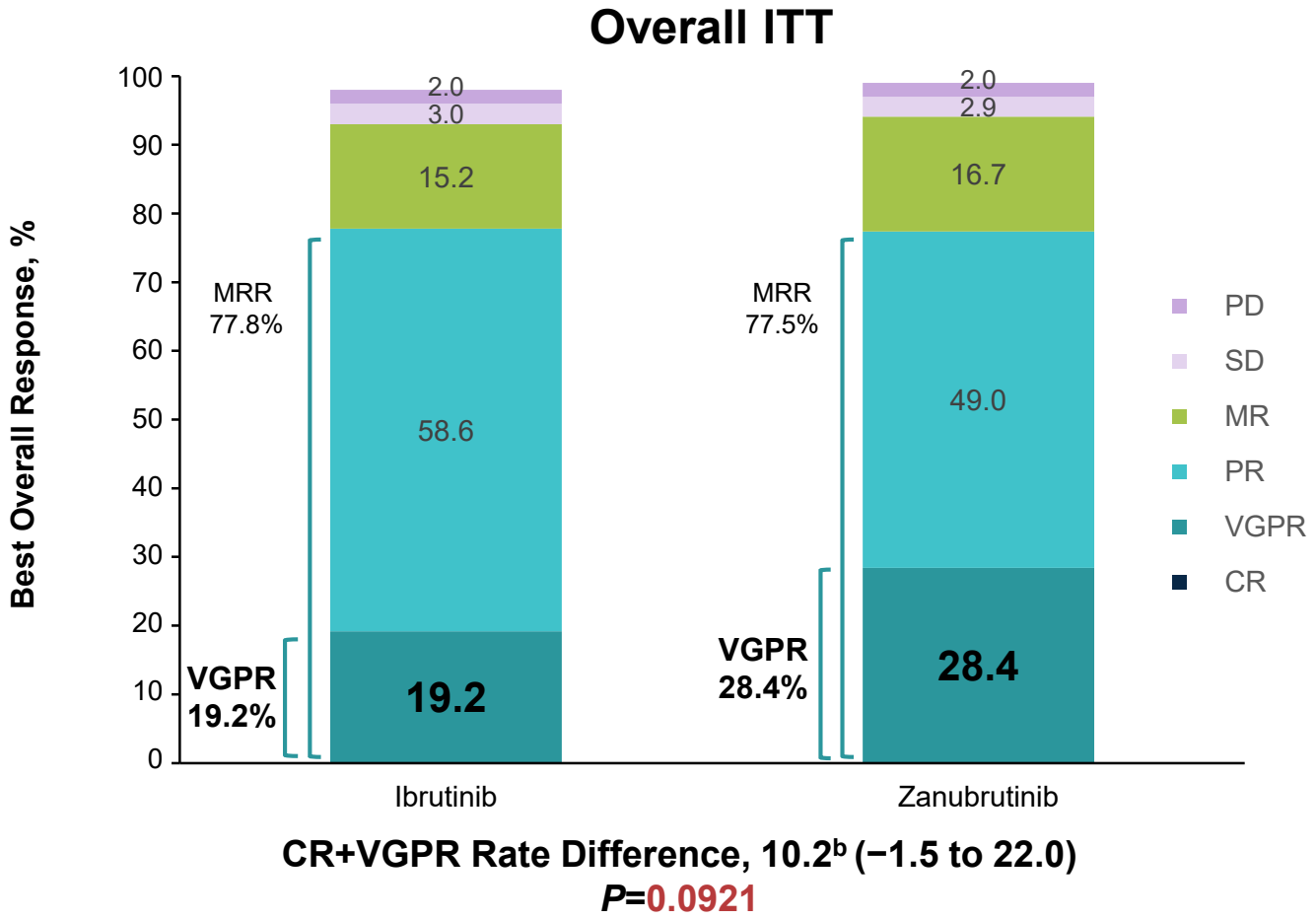
ASPEN: Demographics and Disease Characteristics

Characteristics, n (%)	Overall ITT	
	Ibrutinib (n=99)	Zanubrutinib (n=102)
Age 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 (%)		
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; WT, wild-type.
[a]Wild-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.

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

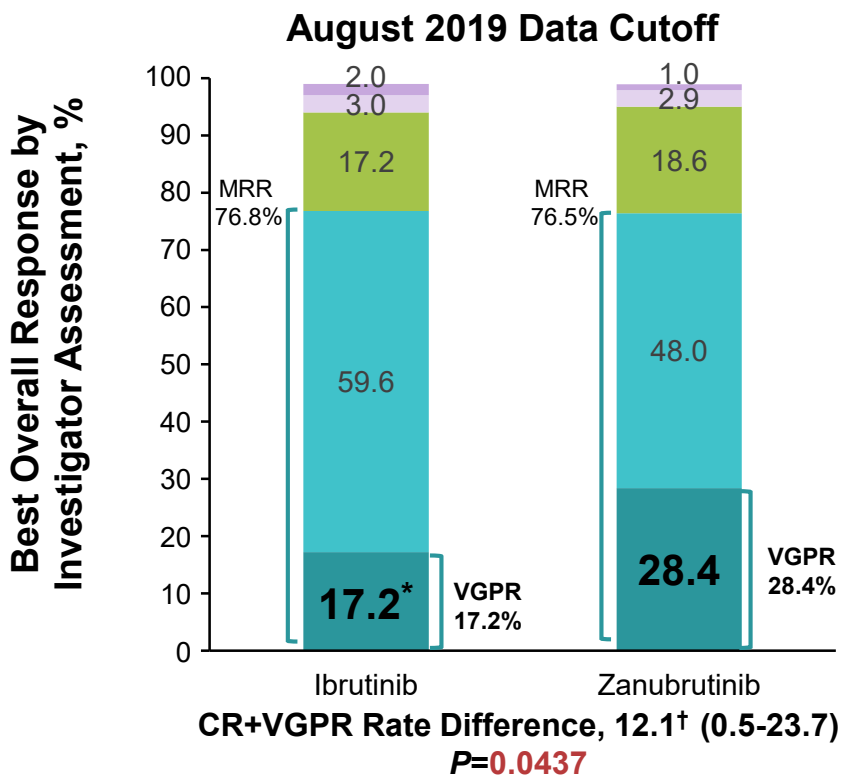
- Superiority in CR+VGPR rate compared with ibrutinib in R/R population (primary study hypothesis) was not significant[a]

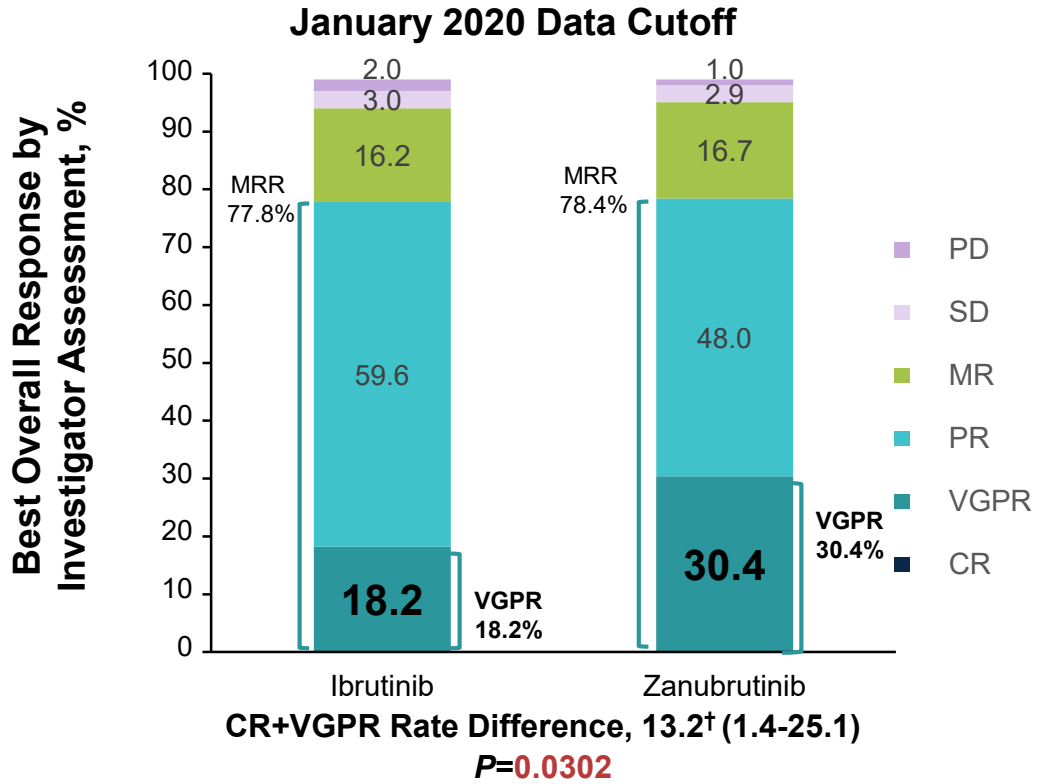


Overall concordance between IRC and investigators was 94%.
CR, complete response; IRC, independent review committee; ITT, intention-to-treat; MRR, major response rate; MR, minor response; PD, progressive disease; PR, partial response; R/R, relapsed/refractory; SD, stable disease; VGPR, very good PR.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

ASPEN: Secondary Efficacy End Points
Assessment of Response According to Investigator

Investigator-Assessed Response



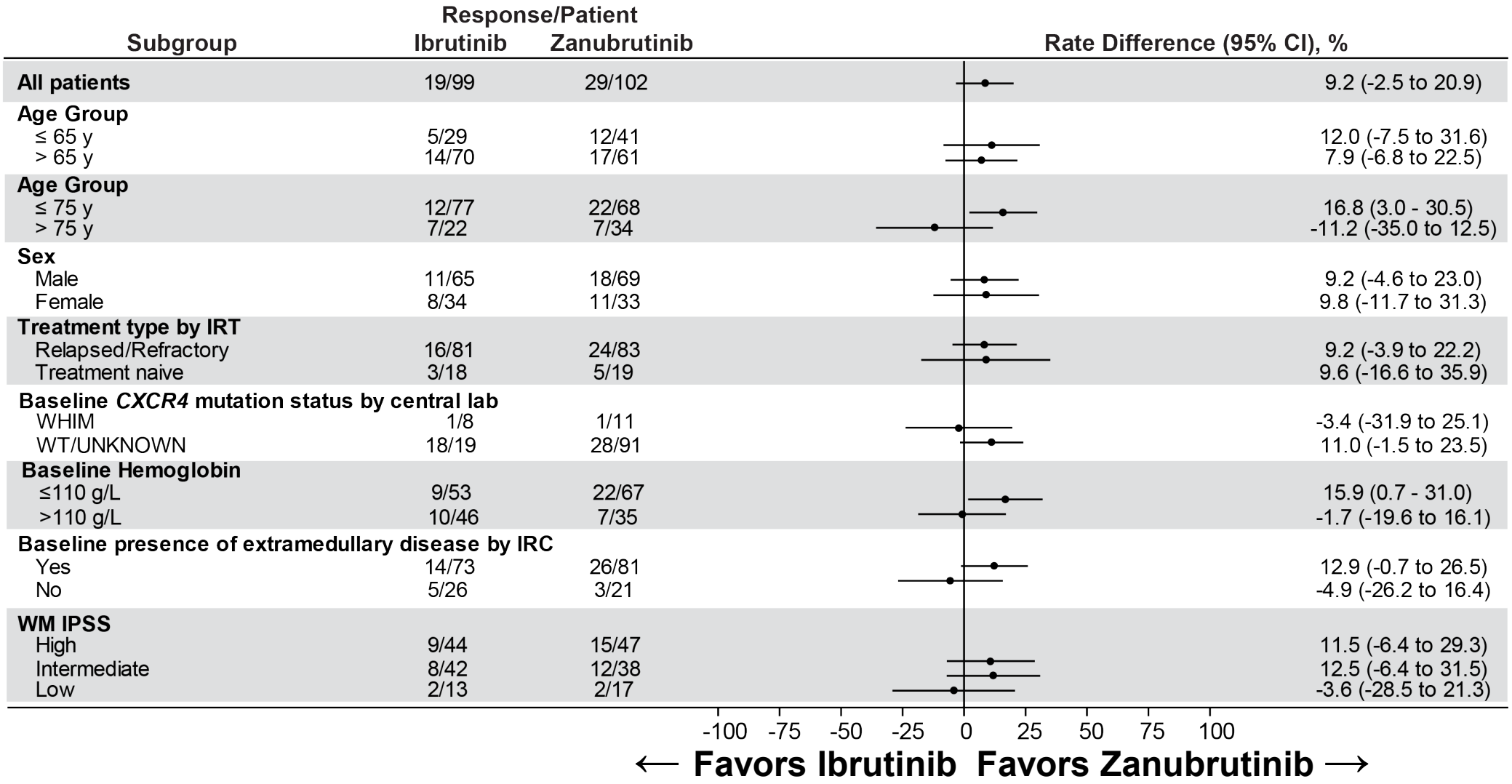


IgM Reduction

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

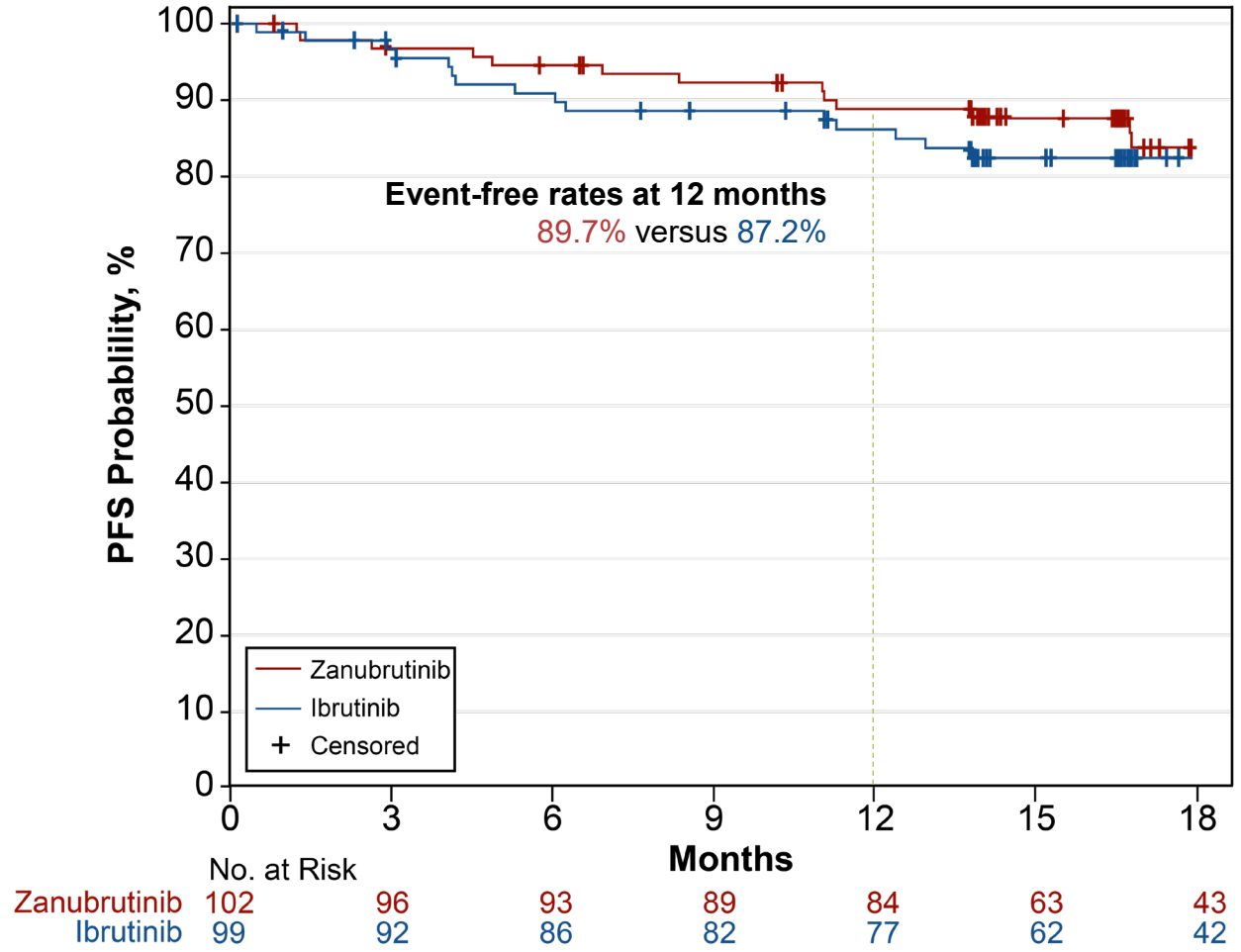
AUC, area under the curve; CR, complete response; IRC, independent review committee; MRR, major response rate; MR, minor response; PD, progressive disease; PR, partial response; SD, stable disease; VGPR, very good PR.
*Excluded 2 patients with VGPR by IRC: MR (extramedullary disease present) and PR (immunoglobulin M assessment by local serum protein electrophoresis M-protein test).
†Adjusted for stratification factors and age group. *P* value is for descriptive purpose only.

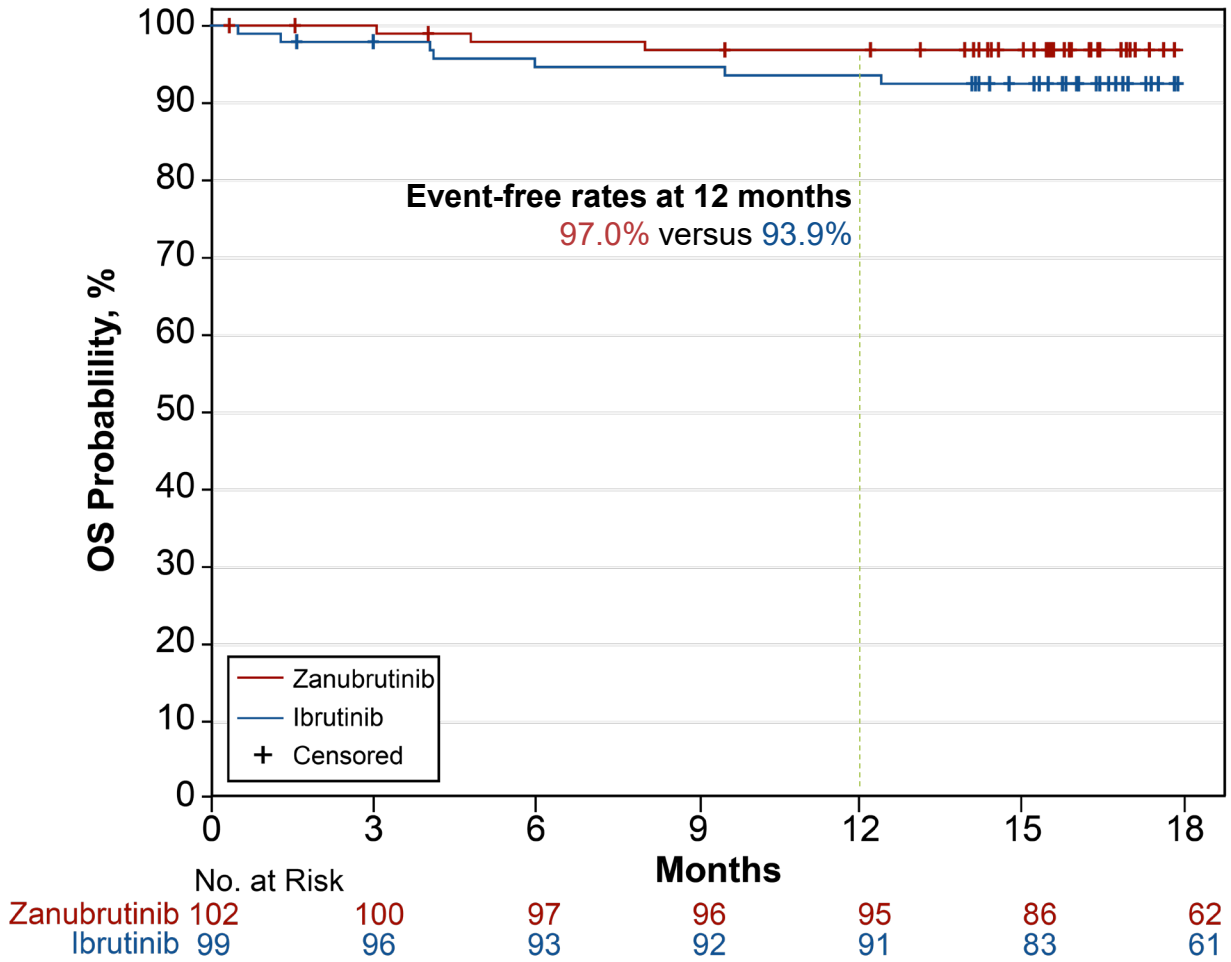
ASPEN: Forest Plot of CR+VGPR Response Rate Difference by IRC, in Overall ITT Population



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.
IRC, independent review committee; PFS, progression-free survival; OS, overall 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)

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 red).
AE, adverse event; PT, preferred term.
†Descriptive 2-sided $P<0.05$

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*	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).
AE, adverse event; BTKi, Bruton tyrosine kinase inhibitor; PT, preferred term.
*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.

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

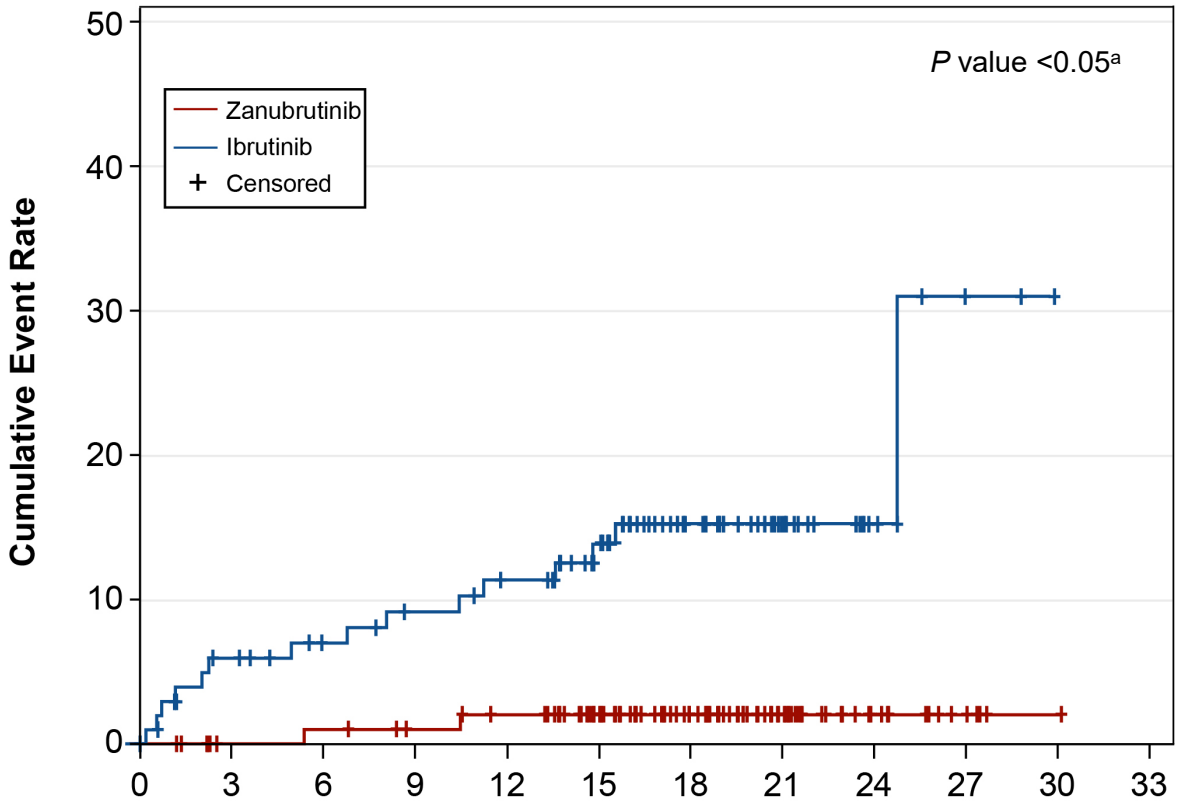
- **An additional 5 patients in the ibrutinib arm discontinued treatment because of AEs vs 0 in the zanubrutinib arm (14.3% vs 4%)**

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

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

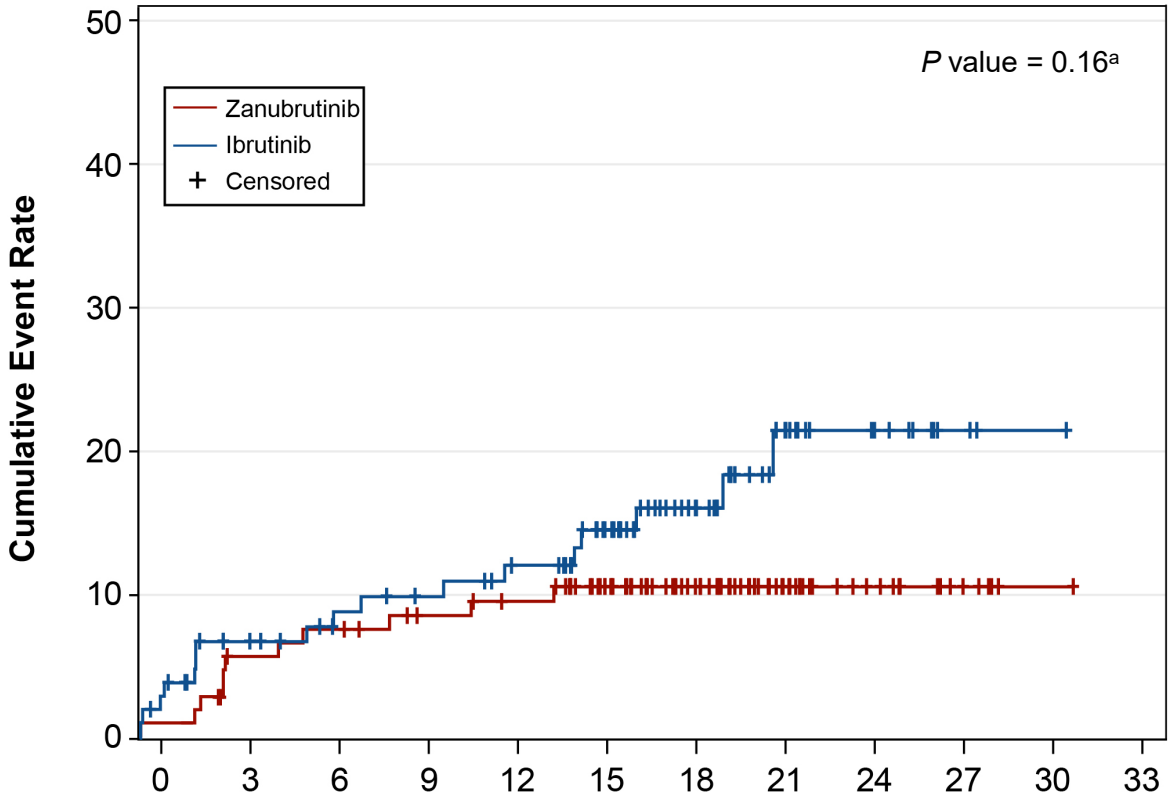
Kaplan-Meier Curve: Time to **Atrial Fibrillation/Flutter**



No. at Risk

Zanubrutinib	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**

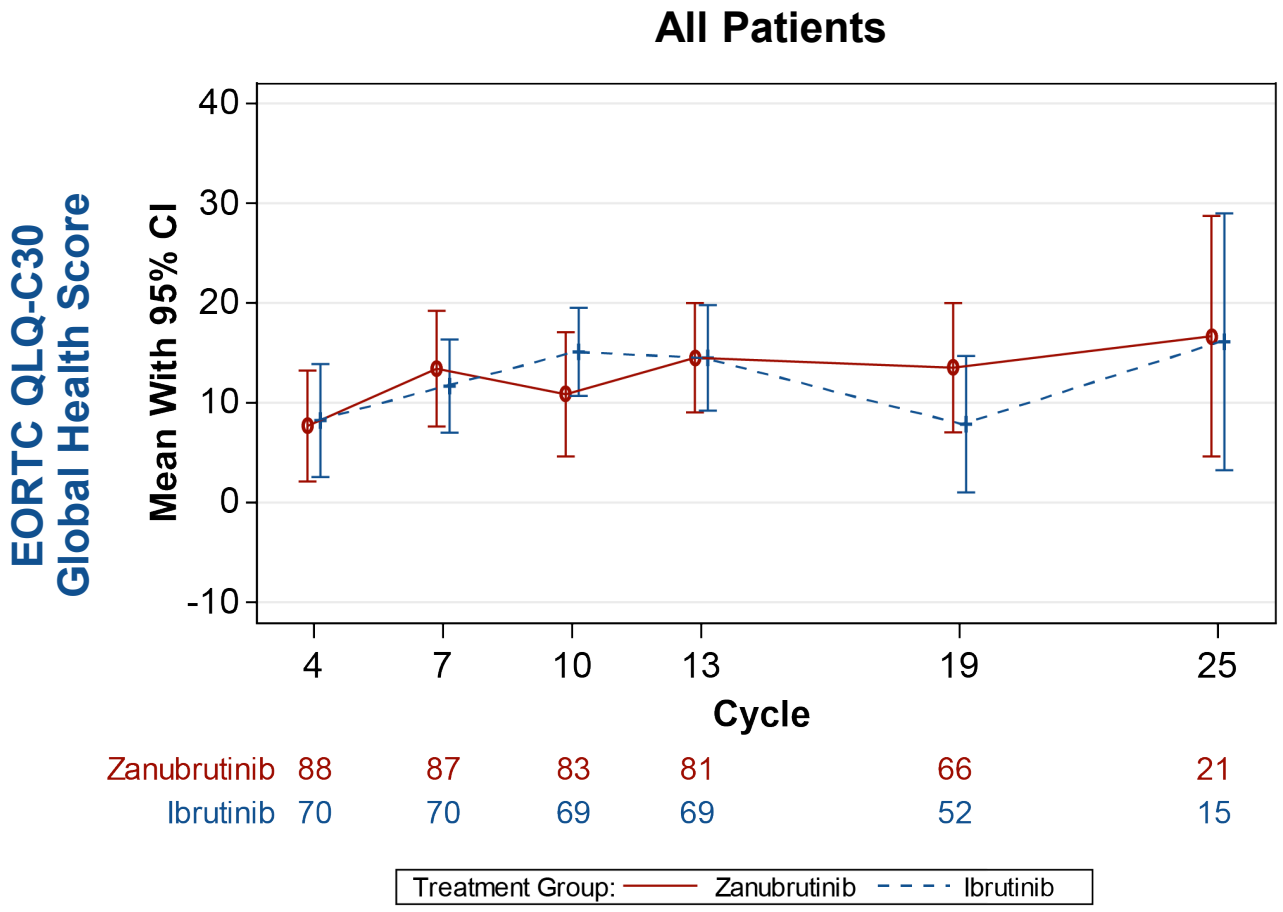


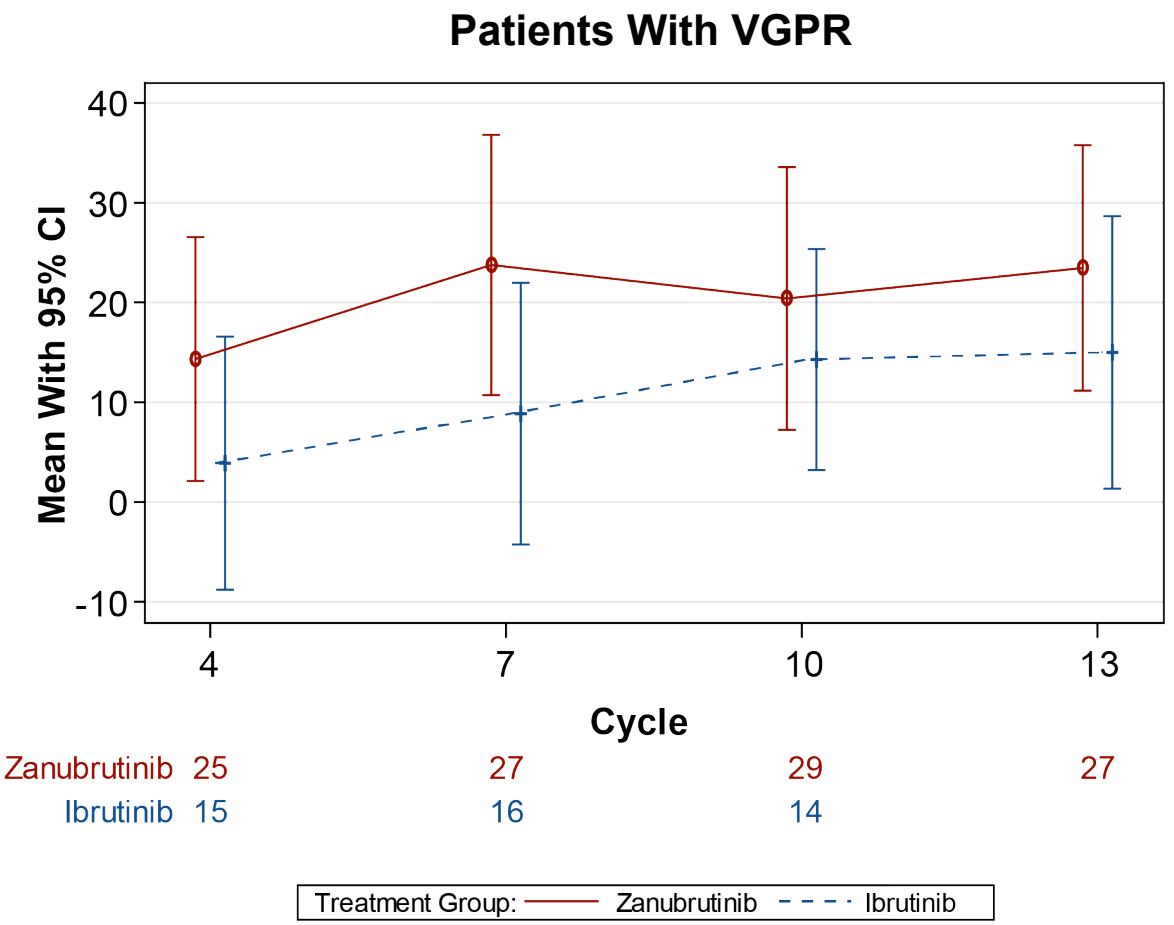
No. at Risk

Zanubrutinib	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

AE, adverse event.
[a]Descriptive purpose only.

ASPEN: Quality of Life – Change From Baseline Over Time





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)**
  - 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[a])
  - Deeper and sustained IgM reduction over time (*P*=0.04[a])
  - 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[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

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.
[a]Descriptive purpose only.

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