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

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- Jingjing Schneider: Employment, Stock or Other Ownership at BeiGene
- Aileen Cohen: Employment, Stock or Other Ownership at BeiGene
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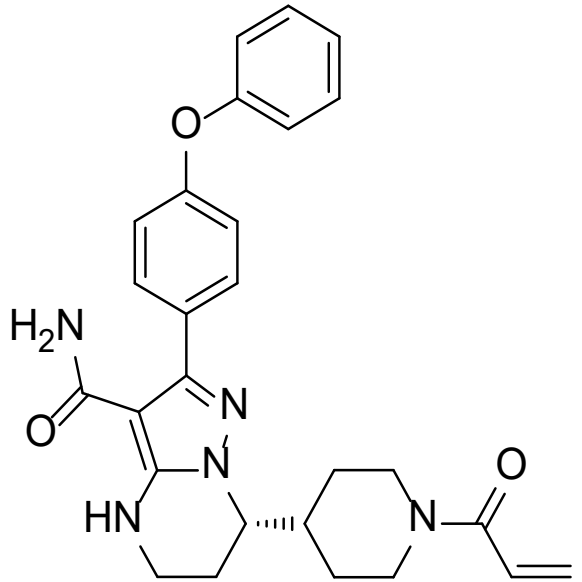
# BTK Inhibition in WM

- 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 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;** fewer off-target effects due to high selectivity for binding 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]

**Zanubrutinib (BGB-3111)**




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.

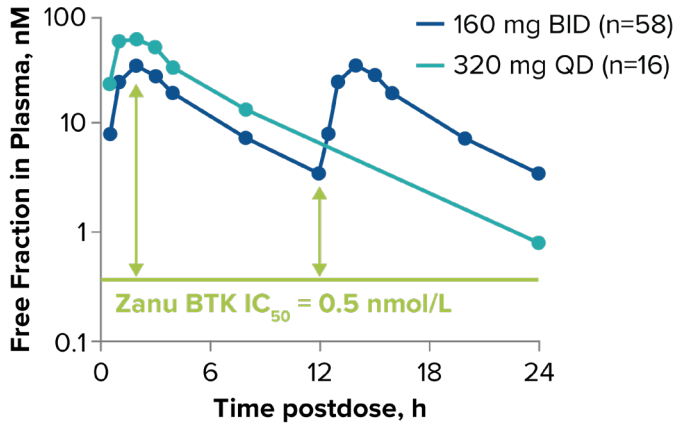
**Abbreviations:** BTK, Bruton tyrosine kinase; CYP3A, cytochrome P450, family 3, subfamily A; EGFR, epidermal growth factor receptor; HER2, human epidermal growth factor receptor 2; ITK, IL-2–inducible T-cell kinase; JAK3, Janus-associated kinase 3; MCL, mantle cell lymphoma; PBMC, peripheral blood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

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

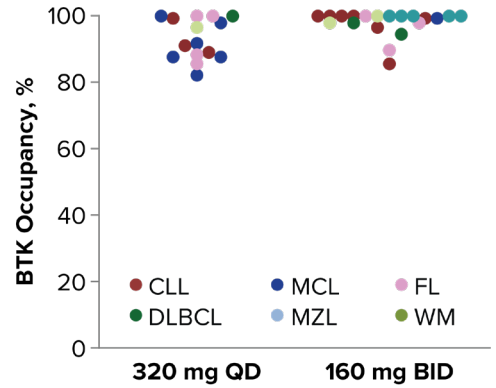
- Potent, selective, irreversible; minimize off-target inhibition

| | 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 $IC_{50}$ Over 24 Hours



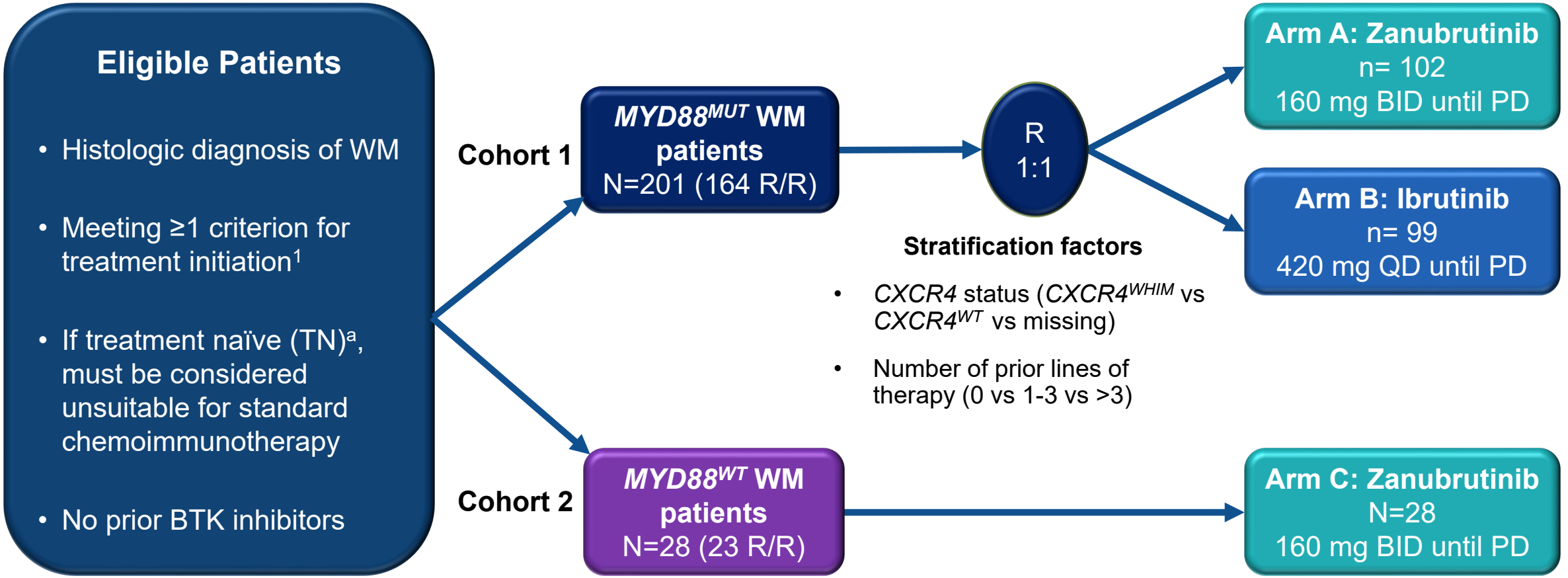

## Complete, Sustained BTK Occupancy




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; $IC_{50}$, 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; 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*

[a]Up 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 the efficacy, clinical benefit, and antilymphoma effects
- Evaluate safety and tolerability of zanubrutinib vs ibrutinib as measured by incidence, timing, and severity of TEAEs per NCI-CTCAE (v4.03)

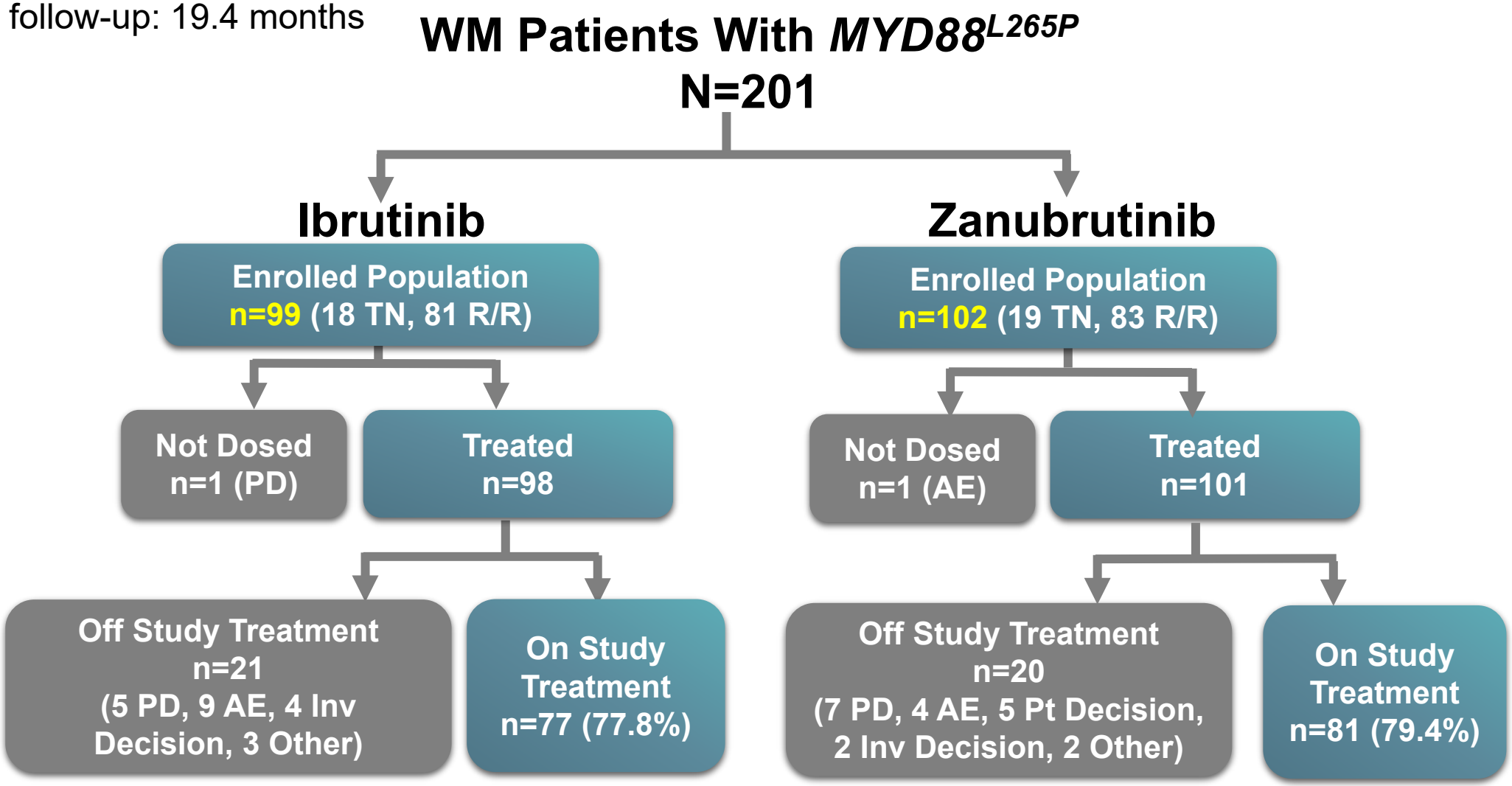
## Exploratory Objectives

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

**Abbreviations:** CR, complete response; EORTC QLQ-C30, European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire - Core Questionnaire; EQ-5D, EuroQoL-5D; 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




**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 (%) | | |
| *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)** |

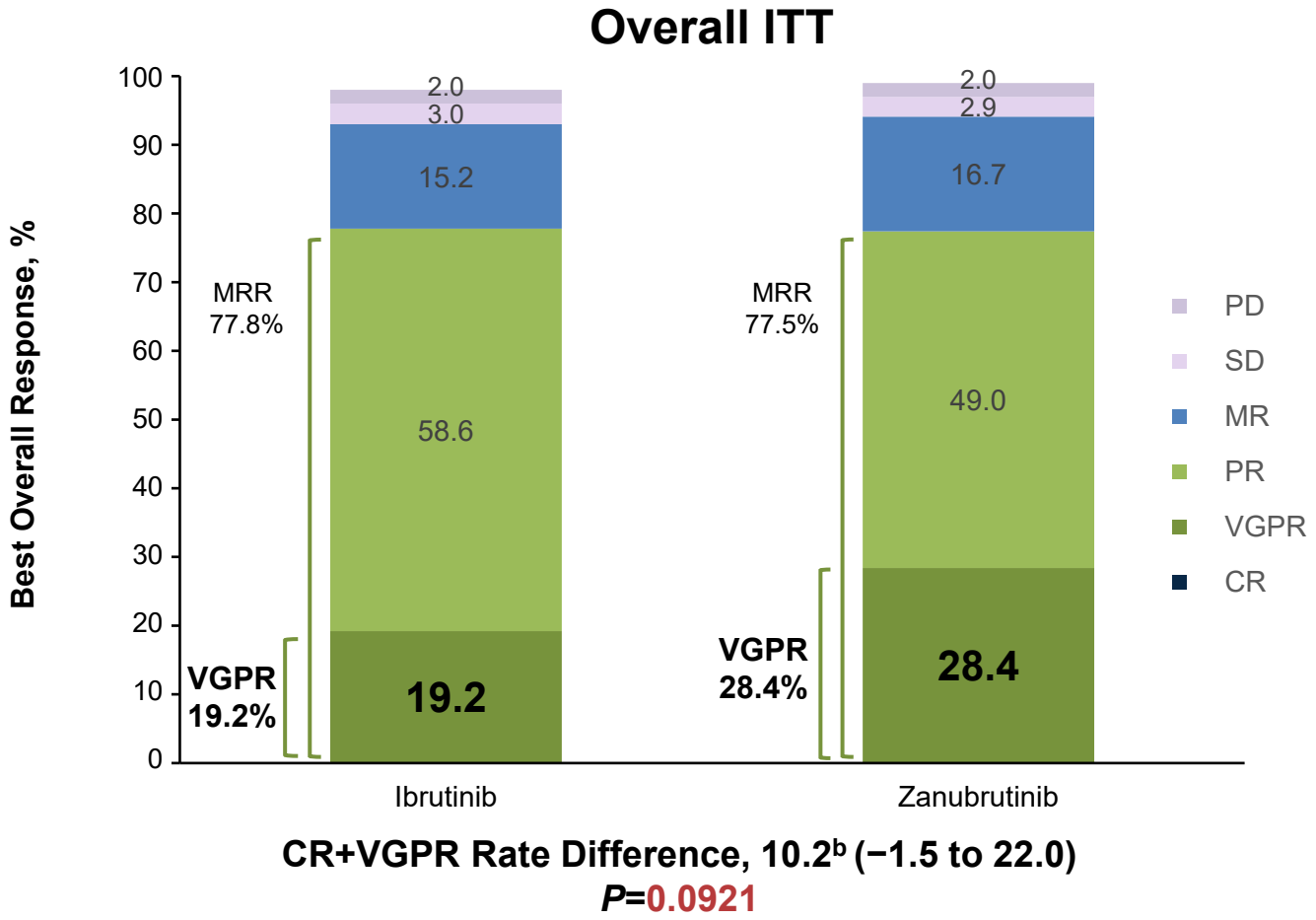
[a]Wild-type–blocking polymerase chain reaction for *MYD88* and Sanger sequencing for *CXCR4* using bone marrow aspirates. One patient had local next-generation sequencing testing results of *MYD88*$^{L265P}$/*CXCR4* Unknown.

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

**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)

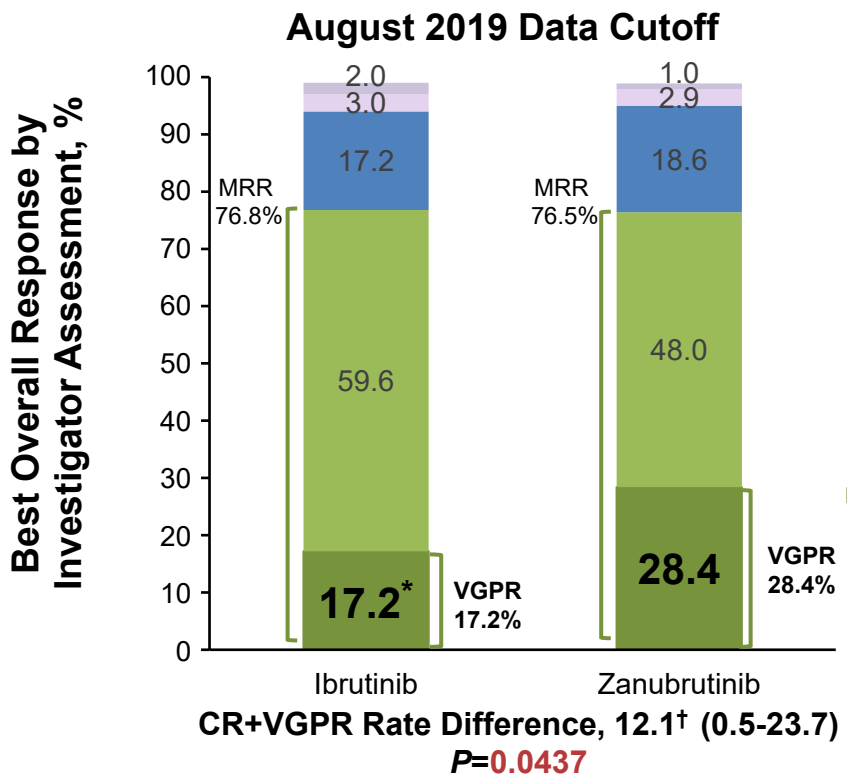
- Superiority in CR+VGPR rate compared with ibrutinib in R/R population (primary study hypothesis) was not significant[a]

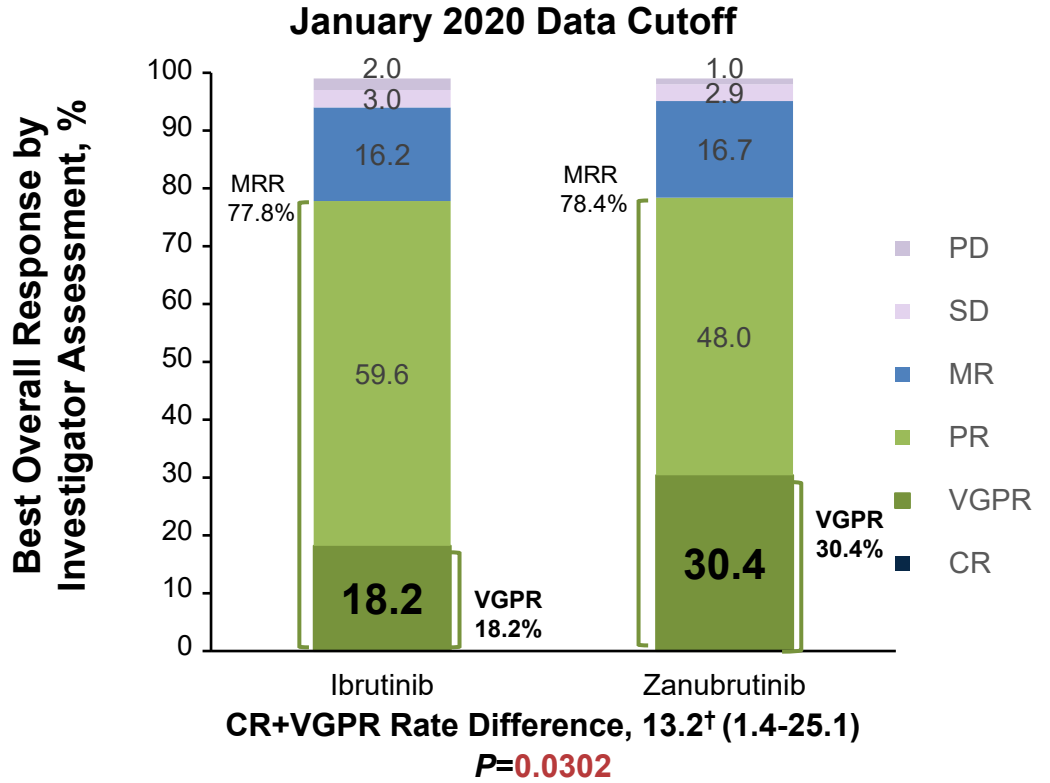



Overall concordance between IRC and investigators was 94%.
[a]All other *P* values are for descriptive purposes only.
[b]Adjusted for stratification factors and age group.
**Abbreviations:** CR, complete response; IRC, independent review committee; ITT, intention-to-treat; MR, minor response; MRR, major 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



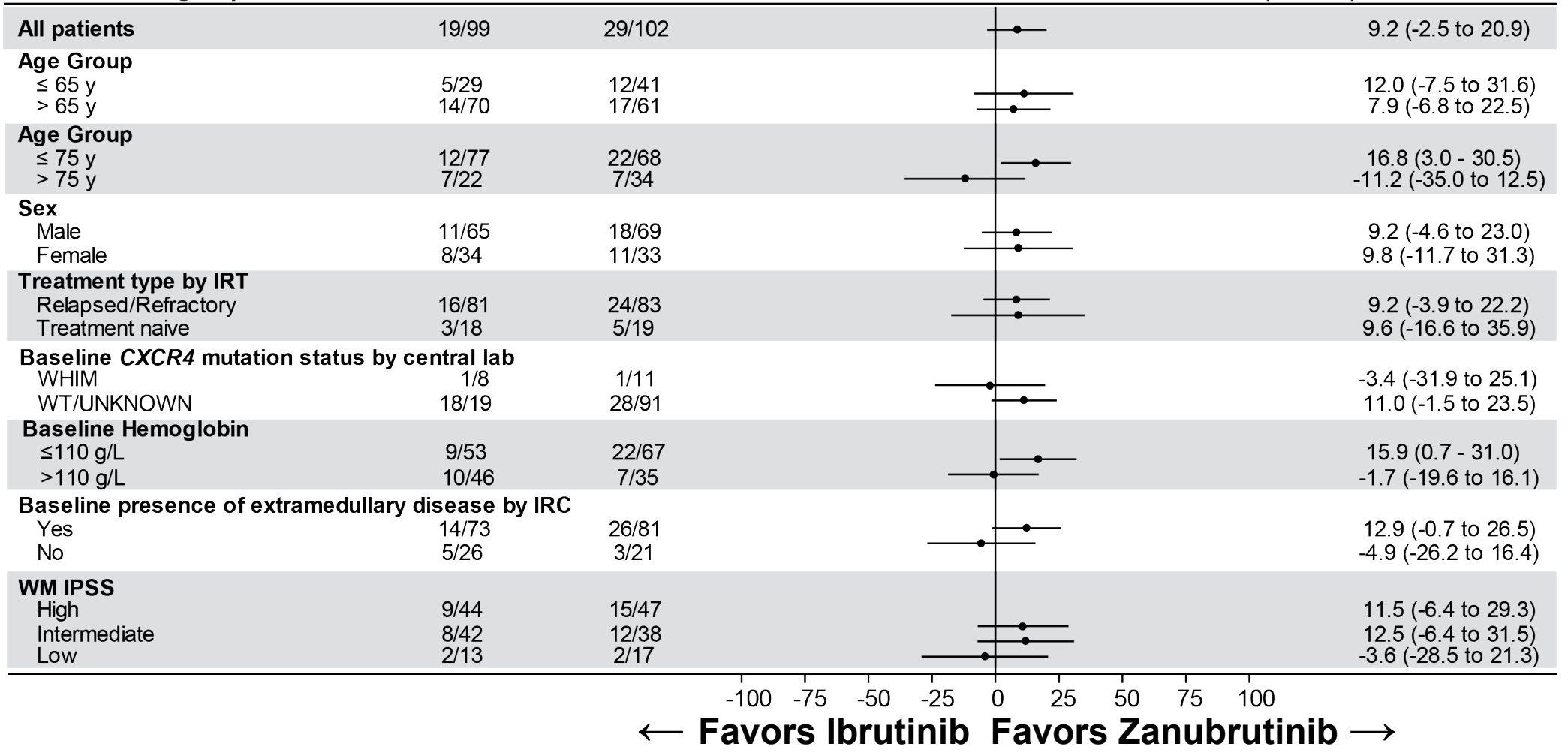

### IgM Reduction

- 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.

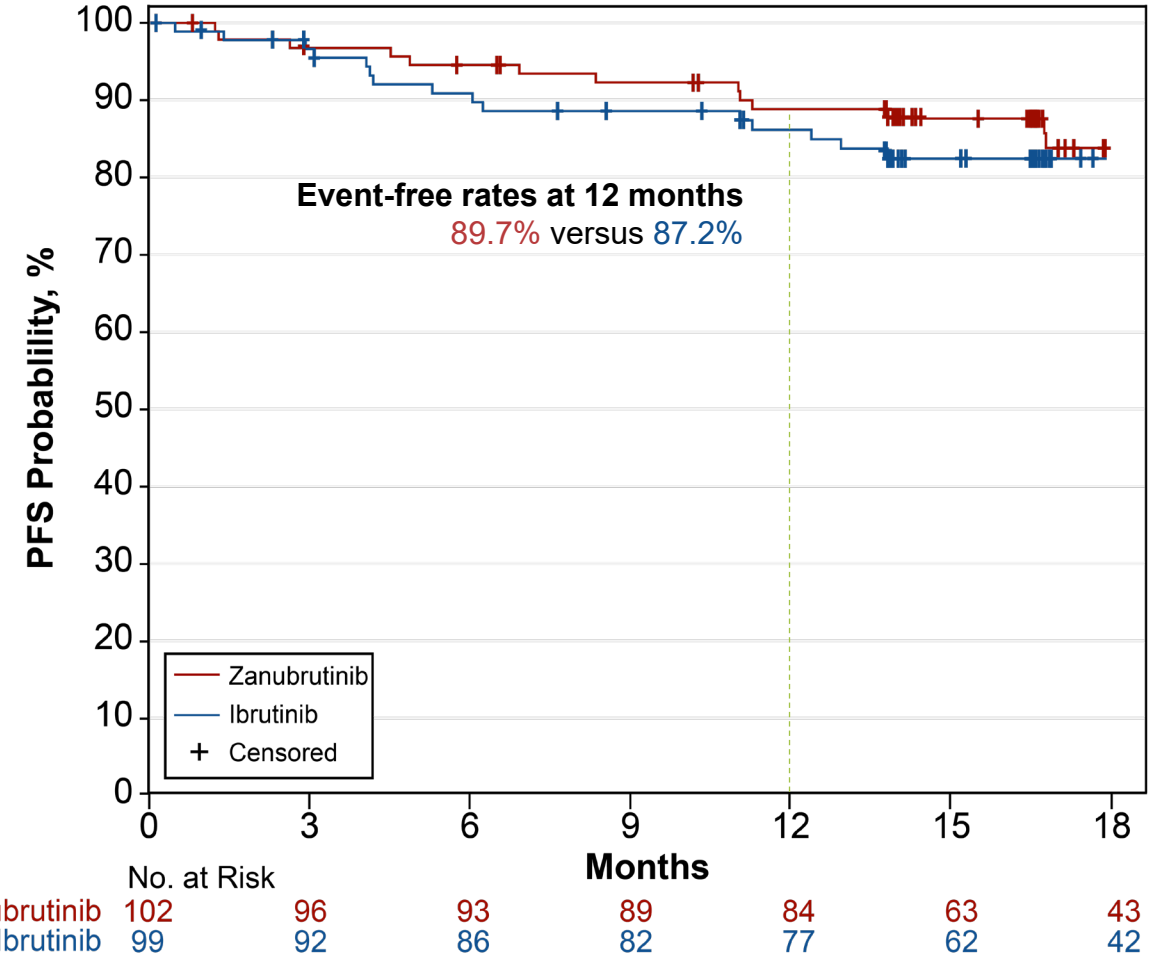
# ASPEN: Forest Plot of CR+VGPR Response Rate Difference by IRC in Overall ITT Population

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



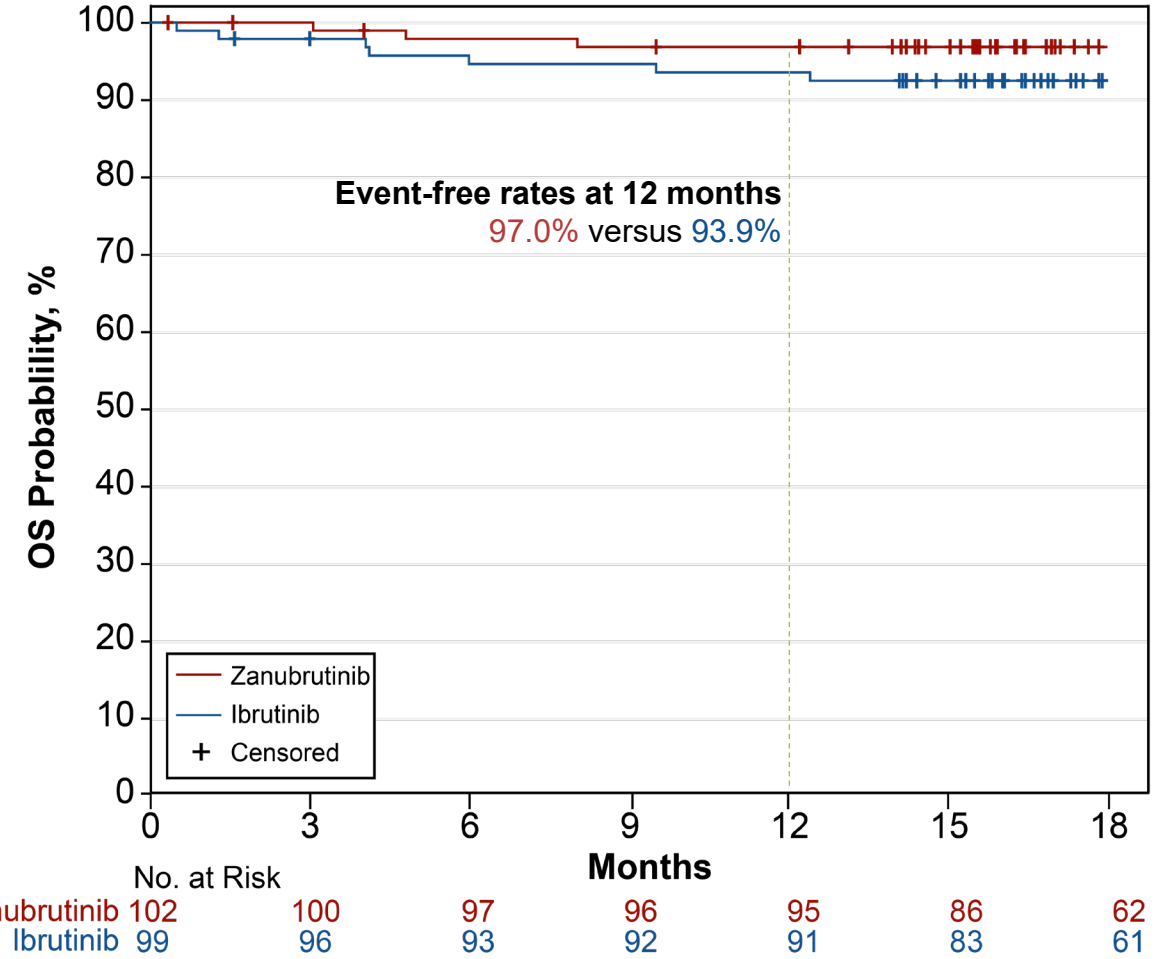

**Abbreviations:** CR, complete response; *CXCR4*, C-X-C motif chemokine receptor 4; IRC, independent review committee; IRT, interactive response technology; ITT, intention-to-treat; VGPR, very good partial response; WM IPSS, Waldenström macroglobulinemia International Prognostic Scoring System.

# ASPEN: PFS and OS Survival in ITT Population




No. at Risk

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| Zanubrutinib | 102 | 96 | 93 | 89 | 84 | 63 | 43 |
| Ibrutinib | 99 | 92 | 86 | 82 | 77 | 62 | 42 |




No. at Risk

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| 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) |

[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.
**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.
**Abbreviations:** 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)

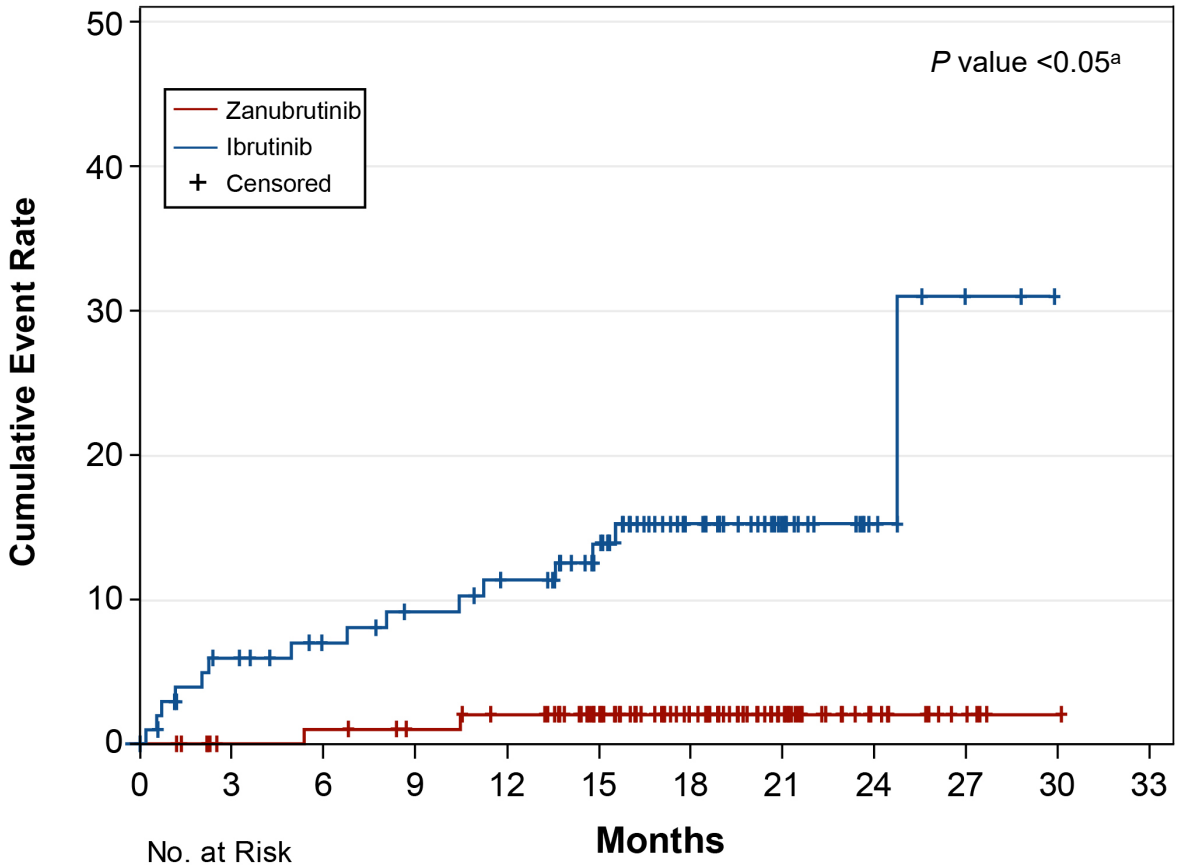
- **An additional 5 patients in the ibrutinib arm discontinued treatment because of AEs vs 0 in the zanubrutinib arm (14.3% vs 4%)**

| 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

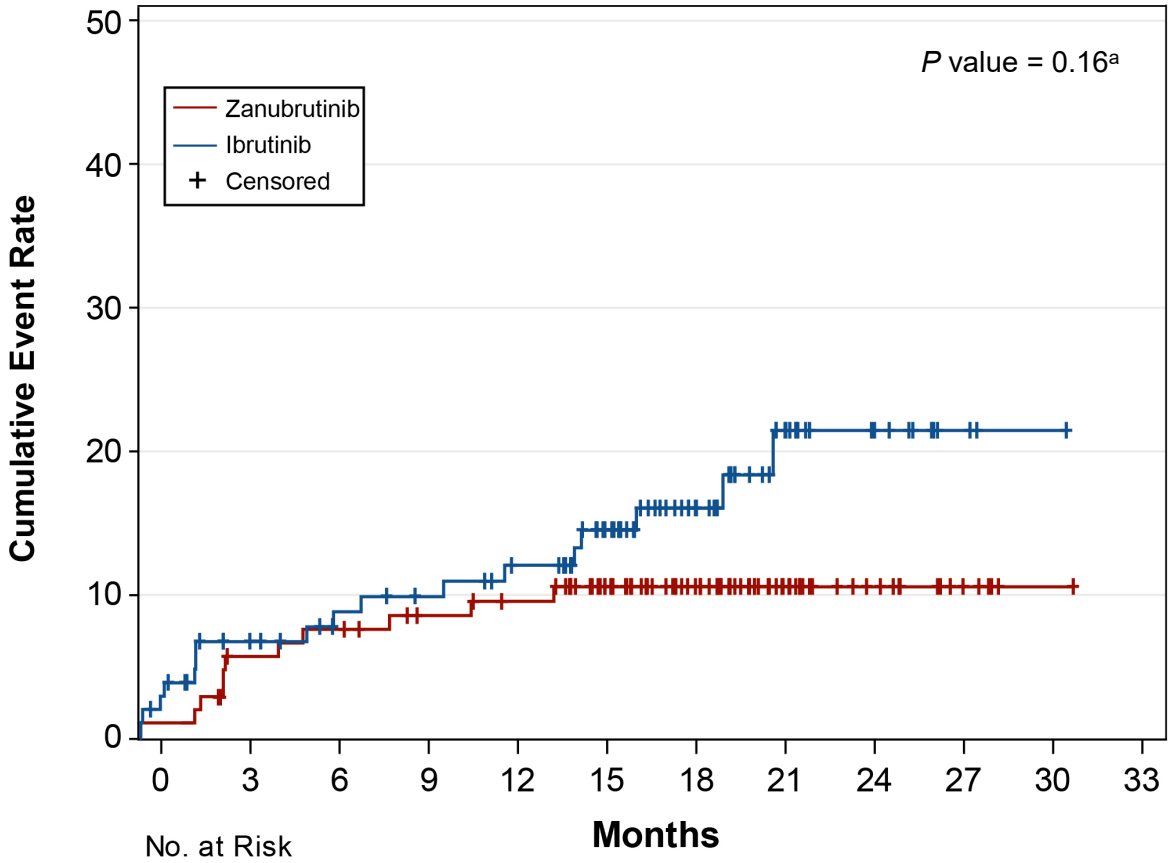
Kaplan-Meier Curve: Time to **Atrial Fibrillation/Flutter**




No. at Risk

| | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 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**

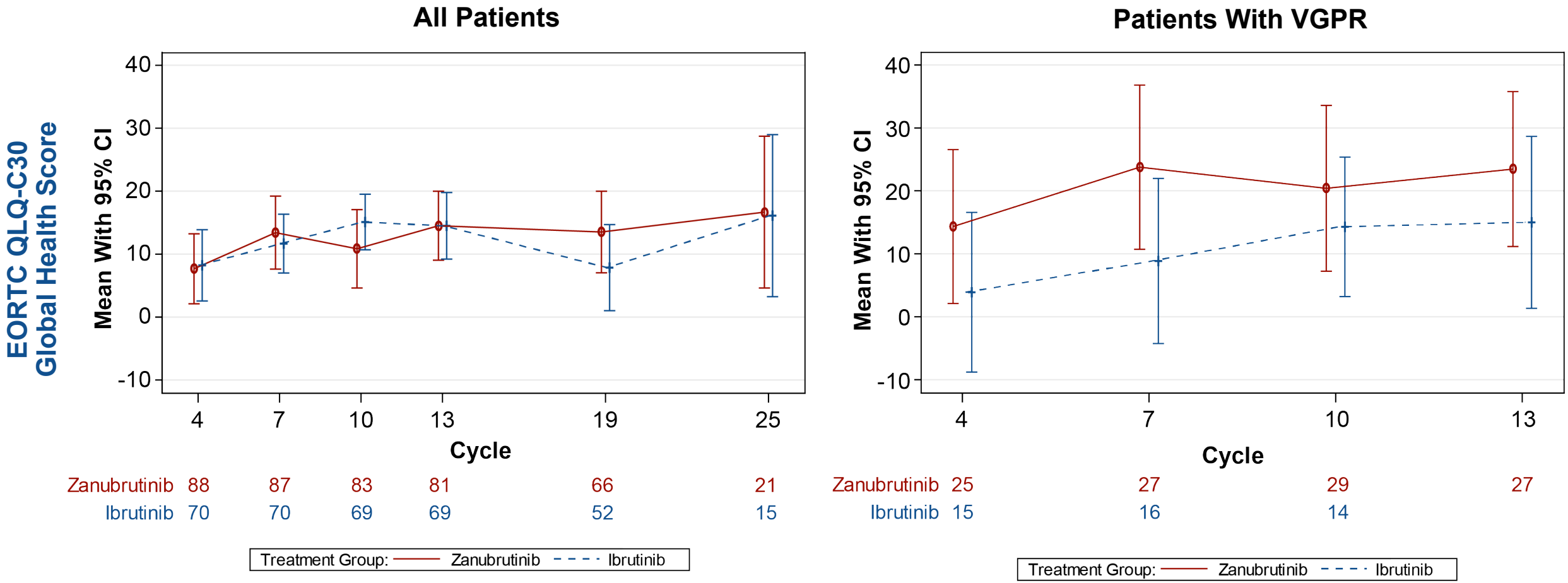



No. at Risk

| | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 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 |

**Abbreviation:** AE, adverse event.
[a]Descriptive purpose only.

# 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

[a]Descriptive 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.

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