# Improved depth of response with increased follow-up in phase 1 trial of patients with Waldenström macroglobulinemia (WM) treated with oral Bruton tyrosine kinase (BTK) inhibitor zanubrutinib (BGB-3111)

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# Disclosures

- I receive honoraria and research funding from Beigene, Janssen and AbbVie.

# Introduction

- Bruton's tyrosine kinase (BTK) plays a critical role in B-cell receptor signaling, which mediates B-cell proliferation, migration, and adhesion[1–3]
  - BTK is constitutively activated in WM and is a key mediator in cell survival[4,5]
- First-generation BTK inhibitor Ibrutinib has shown activity in WM and become a standard of care[6,7]
  - Major response rate: 73% (including 16% very good partial response)[8]
  - 68% 3-year event-free survival[9]

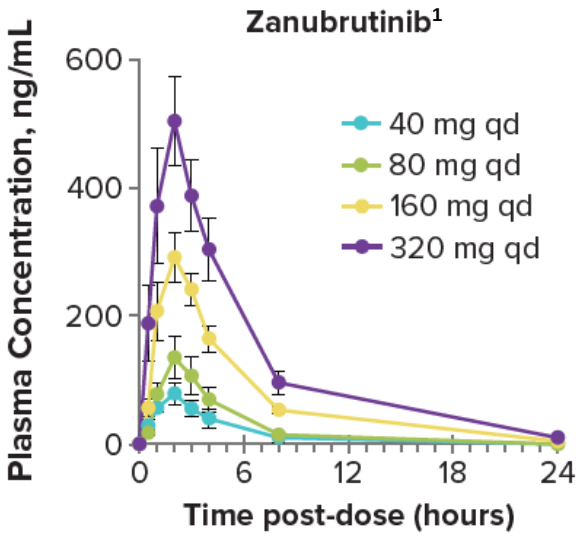
1. Rickert RC. *Nat Rev Immunol.* 2013;13:578-591. 2. Choe H, Ruan J. *Oncology* (Williston Park). 2016;30:847-858. 3. Aalipour A, Advani RH. *Br J Haematol*. 2013;163:436-443. 4. Treon SP, et al. *Blood*. 2014;123:2791-2796.; 5. Argyropoulos KV, et al. *Leukemia*. 2016;30:1116-1125.
6. IMBRUVICA® (ibrutinib). Full Prescribing Information. February 2018. 7. IMBRUVICA® (ibrutinib). Summary of Product Characteristics. February 2018.
8. Treon SP, et al. *N Engl J Med*. 2015;372:1430-1440. 9. Palomba ML, et al. IWWM. 2016 [abstract].

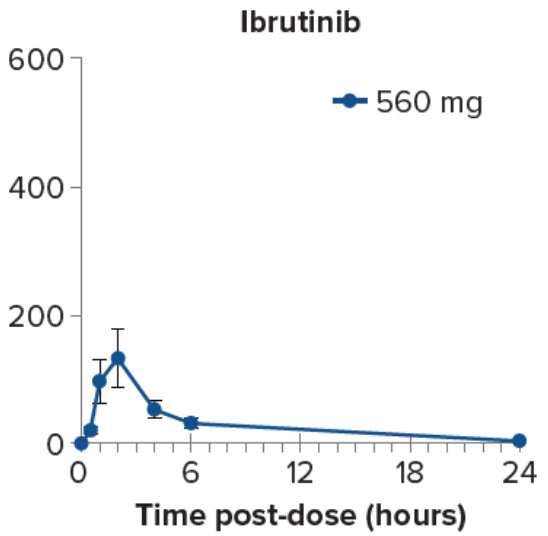
# Zanubrutinib - kinase selectivity relative to ibrutinib

| | Targets | Assays | Zanubrutinib[1] $IC_{50}$ (nM) | Ibrutinib[1] $IC_{50}$ (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 | 1.0 |
| | | 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 | 606 | 189 | 17 |
| | | p-$PLC_{\gamma 1}$ 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 |

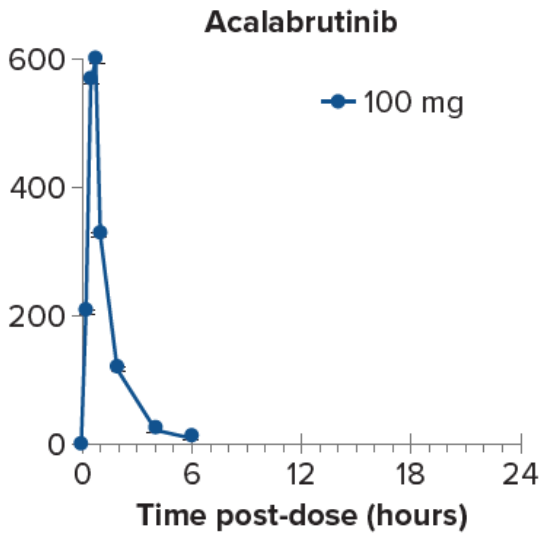
1. BeiGene, Data on file.

# Pharmacokinetics of zanubrutinib, ibrutinib, and acalabrutinib




Adapted from Advani RH, et al. *J Clin Oncol.* 2013[2]

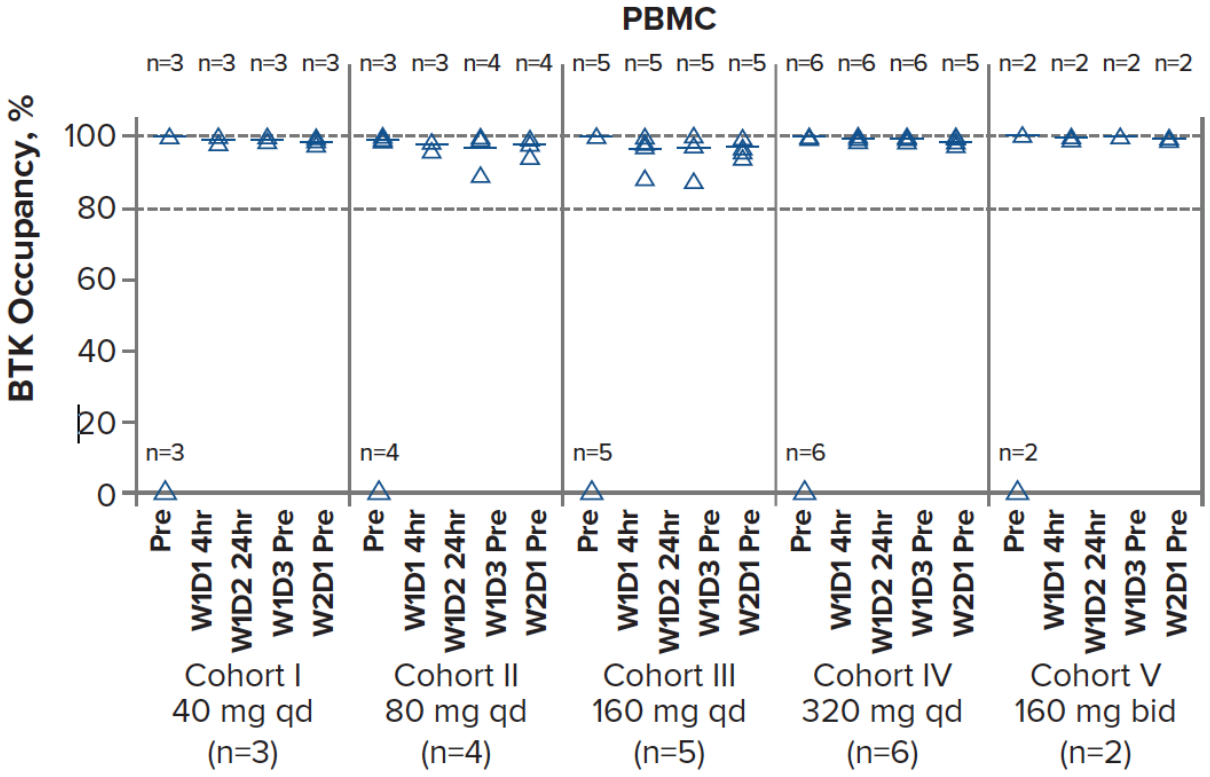


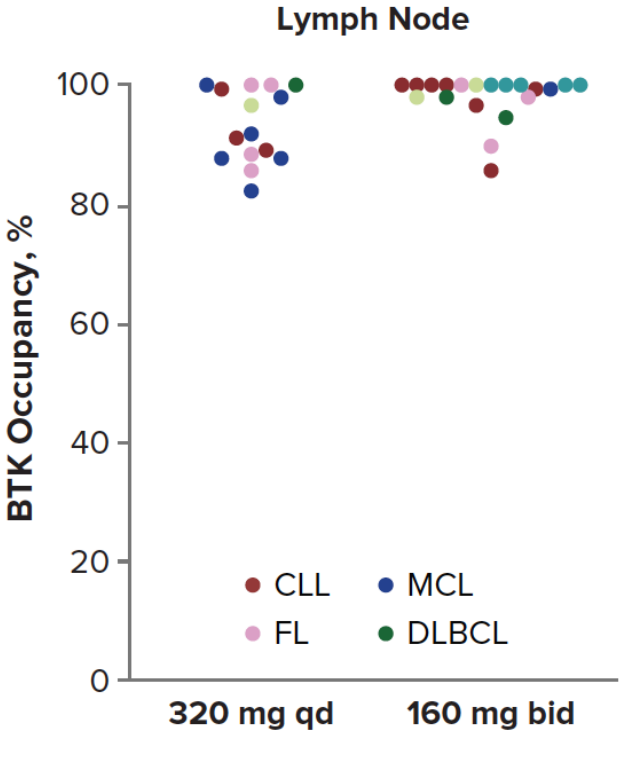

Adapted from Byrd JC, et al. *N Engl J Med.* 2015[3]

**Note: these data are from 3 separate analyses and differences in studies should be considered.**


1. Tam CS, et al. *Blood*. 2015;126:832 [oral presentation].
2. Advani RH, et al. *J Clin Oncol.* 2013;31:88-94.
3. Byrd JC, et al. *N Engl J Med*. 2016;374:323-332.

# Sustained BTK inhibition in peripheral blood and lymph nodes




Complete and sustained BTK occupancy is seen in paired PBMC (left figure) and lymph node biopsy samples (right figure) collected pre-dose on day 3. In blood samples, complete BTK occupancy was seen at the lowest dose (40 mg). Note, 100% median trough occupancy at a dose of 160 mg bid with 94% of patients having >90% occupancy in lymph nodes across malignancies.

# Objective

- Presented here are updated results from patients with WM treated within an ongoing phase 1 zanubrutinib trial (NCT02343120)

# Trial design (NCT02343120)

## DOSE ESCALATON

| Dose | Enrolled (WM) |
|---|---|
| 40 mg QD | 4 (1) |
| 80 mg QD | 5 (2) |
| 160 mg QD | 6 (1) |
| 320 mg QD | 6 (0) |
| 160 mg BID | 4 (0) |

## RP2D

| Dose |
|---|
| 320 mg QD |
| 160 mg BID |

Both doses RP2D but as of protocol v.6 all pts encouraged to switch to 160 mg BID

## DOSE EXPANSION

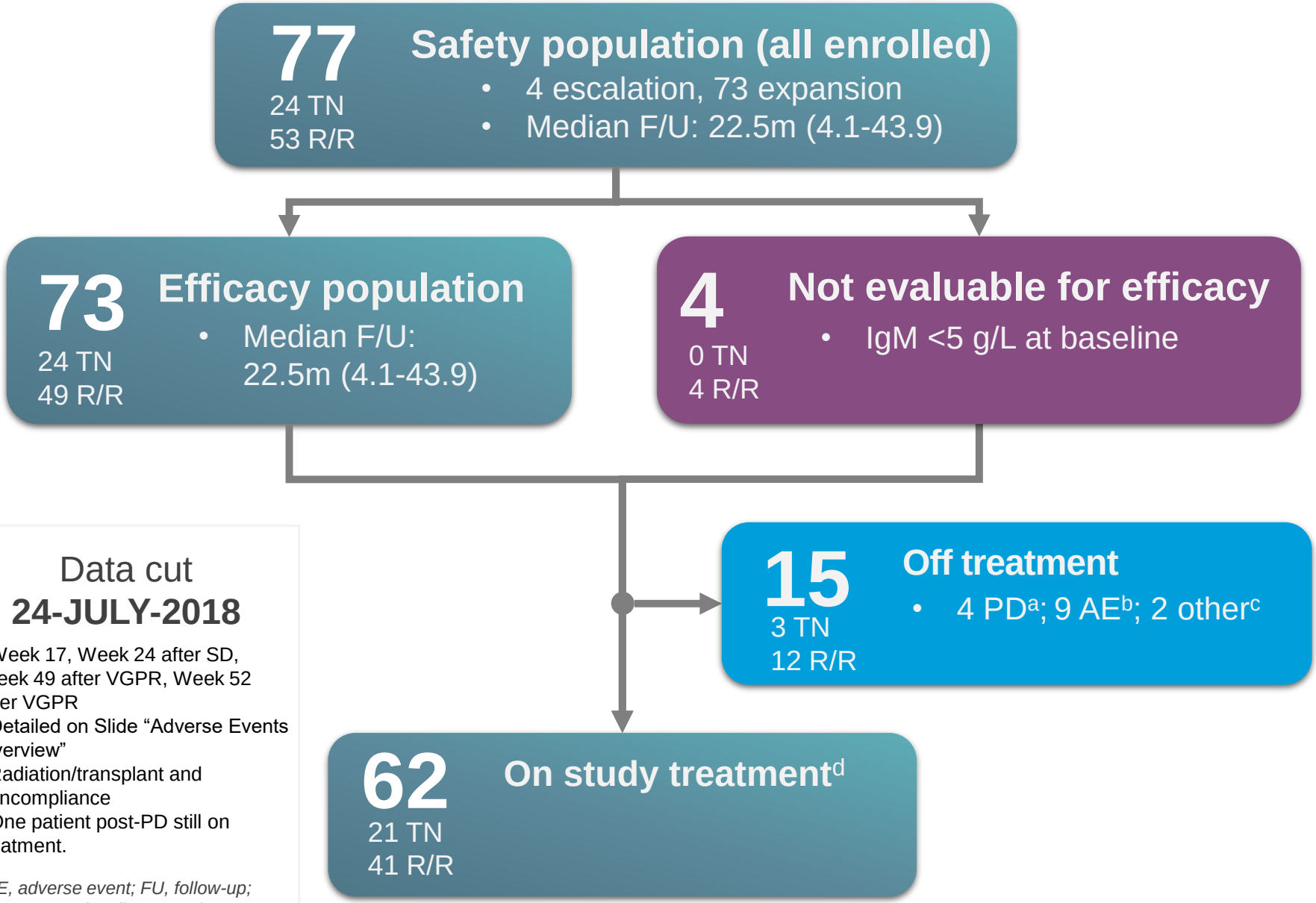
| Population | RP2D Dose | Disease | Enrolled† (WM) |
|---|---|---|---|
| R/R | BID or QD | All B-cell | 40 (2) |
| R/R | BID | Non-GCB DLBCL | 40 |
| R/R | BID | CLL/SLL | 70 |
| R/R | BID | WM | 20 (21) |
| R/R | QD | CLL/SLL | 20 |
| R/R or TN | BID or QD | WM | 50 (50) |
| R/R | BID or QD | MCL | 20 |
| TN | BID or QD | CLL/SLL | 20 |
| TN | BID or QD | MCL | 20 |
| R/R | BID or QD | HCL | 10 |
| R/R | BID | iNHL | 40 |
| R/R | BID | Richter's | 15 |
| R/R (prior BTK) | BID | All B-cell | 15 |

Cohorts containing WM pts in blue

†Enrollment in expansion is ongoing: planned enrollment shown, with WM enrollment as of data cutoff noted in parentheses.
BID, twice daily; CLL/SLL, chronic lymphocytic leukemia/small lymphocytic lymphoma; DLBCL, diffuse large B-cell lymphoma; FL, follicular lymphoma; GCB, germinal center B-cell–like; HCL, hairy cell leukemia; iNHL, indolent non-Hodgkin lymphoma; MCL, mantle cell lymphoma; MZL, marginal zone lymphoma; RP2D, recommended phase 2 dose; QD, once daily; WM, Waldenström macroglobulinemia

# Methods

- First-in-human, open-label, multicenter, phase 1 study of zanubrutinib in patients with B-cell malignancies
- Eligibility
  - WHO-defined B-cell malignancy with no available higher priority treatment
  - Eastern Cooperative Oncology Group 0-2
  - ANC ≥1000/μL, platelets ≥50000/μL (growth factor/transfusions allowed)
  - Adequate renal and hepatic function
  - No significant cardiac disease (anticoagulation allowed)
- Primary endpoints
  - Safety including AEs and SAEs per the NCI CTCAE v4.03, based on physical examination and laboratory measurements
  - Recommended phase 2 dose
- Select secondary endpoints
  - Pharmacokinetics
  - Efficacy, including overall response rate, progression-free survival, overall survival, and duration of response




Data cut
**24-JULY-2018**

[a] Week 17, Week 24 after SD, Week 49 after VGPR, Week 52 after VGPR
[b] Detailed on Slide "Adverse Events Overview"
[c] Radiation/transplant and noncompliance
[d] One patient post-PD still on treatment.

*AE, adverse event; FU, follow-up; PD, progressive disease; R/R, relapsed/refractory; TN, treatment-naïve.*

# Patient and disease characteristics

***Data cut** 24-JULY-2018*

| Characteristic | Total (N=77) |
|---|---|
| Age, years, median (range) | 67 (40-87) |
| ECOG performance status, n (%) | |
| 0 | 27 (35.1) |
| 1 | 47 (61) |
| 2 | 3 (3.9) |
| Prior treatment status | |
| Treatment-naïve, n (%) | 24 (31.2) |
| Relapsed/refractory (R/R), n (%) | 53 (68.8) |
| Number of prior therapies for R/R patients, median (range) | 2 (1-8) |
| Genotype, n (%) | |
| $MYD88^{L265P}/CXCR4^{WT}$ | 49 (63.6) |
| $MYD88^{L265P}/CXCR4^{WHIM}$ | 6 (7.8) |
| $MYD88^{WT}$ | 12 (15.6) |
| Unavailable | 10 (13) |

ECOG, Eastern Cooperative Oncology Group.

# Adverse events overview

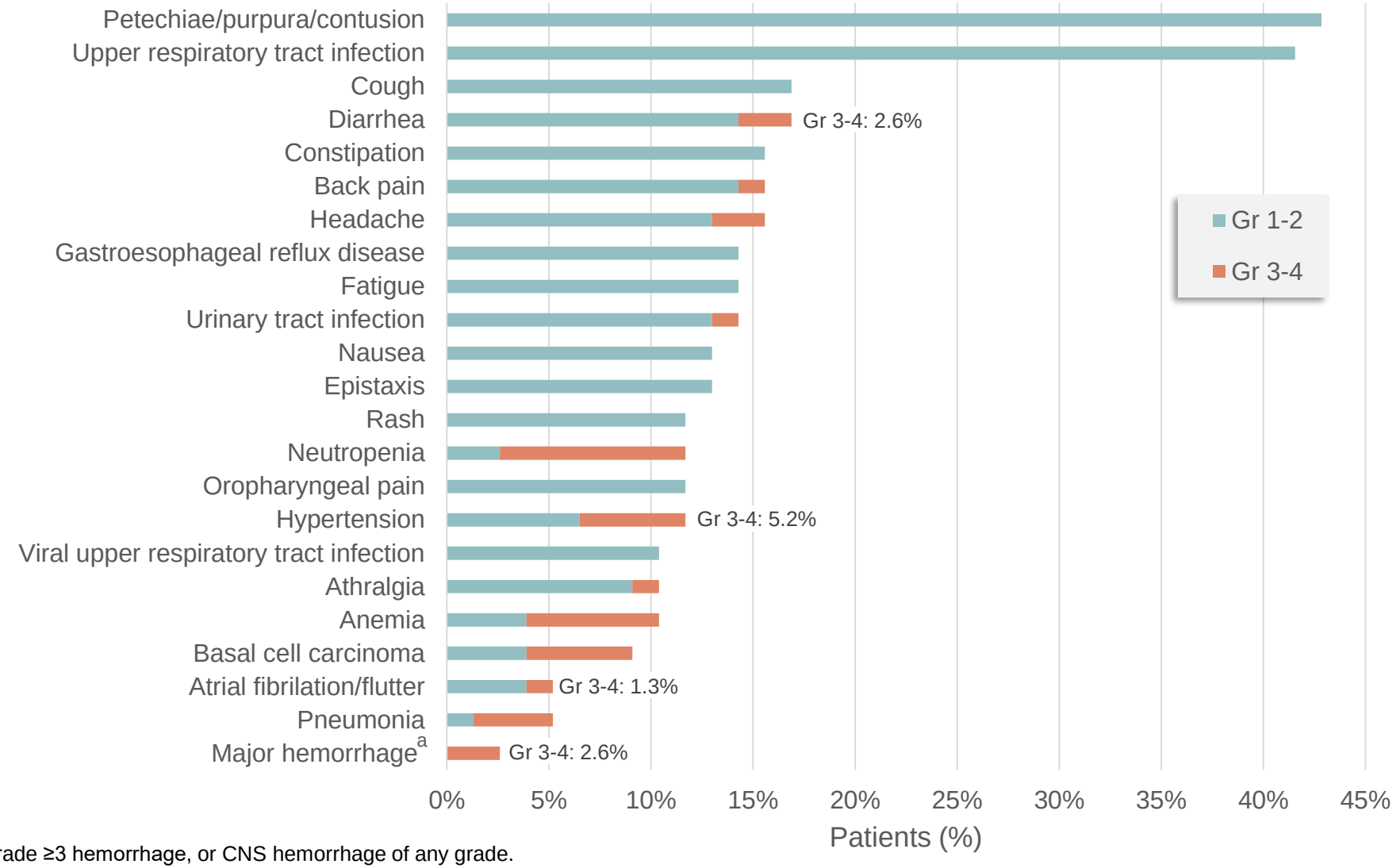
***Data cut** 24-JULY-2018*

| Event | n (%) |
|---|---|
| Patients with ≥1 AE Grade ≥3 | 39 (50.6) |
| Patients with ≥1 serious AE* | 32 (41.6) |
| AE leading to treatment discontinuation | 9[†] (11.7) |
| Fatal AE | 5[‡] (6.5) |
| AE of special interest | |
| Petechiae/purpura/contusion | 33 (42.9) |
| Diarrhea | 13 (16.9) |
| Hypertension | 9 (11.7) |
| Major hemorrhage[§] | 2 (2.6) |
| Atrial fibrillation/flutter | 4 (5.2) |

*SAEs possibly related to zanubrutinib (n=5): hemothorax, atrial fibrillation, colitis, febrile neutropenia, and pneumonia (each n=1).
[†]Abdominal sepsis (fatal), septic shoulder, worsening bronchiectasis, scedosporium infection, gastric adenocarcinoma (fatal), prostate adenocarcinoma, metastatic neuroendocrine carcinoma, acute myeloid leukemia, breast cancer (each n=1, all unrelated).
[‡]Septic shoulder, worsening bronchiectasis, abdominal sepsis + appendicitis + renal failure, gastric adenocarcinoma, scedosporium infection: all unrelated.
[§]Defined as any grade ≥3 hemorrhage or any grade CNS hemorrhage, gastrointestinal hemorrhage, hematuria, renal hematoma: one pt had G3 hemothorax and Melena, one pt had G3 hemorrhagic cystitis.

# Common adverse events (>10%), G3-4 adverse (n≥3), and BTK-i events of interest, regardless of causality

***Data cut** 24-JULY-2018*




[a]Grade ≥3 hemorrhage, or CNS hemorrhage of any grade.

# Best overall response

| Best response, n (%) | All Efficacy Evaluable (n=73) | TN Patients (n=24) | R/R Patients (n=49) |
|---|---|---|---|
| ORR | 67 (91.8) | 23 (95.8) | 44 (89.8) |
| MRR | 60 (82.2) | 21 (87.5) | 39 (79.6) |
| VGPR | 30 (41.1) | 6 (25.0) | 24 (49.0) |
| PR | 30 (41.1) | 15 (62.5) | 15 (30.6) |
| MR | 7 (9.6) | 2 (8.3) | 5 (10.2) |
| SD | 5 (6.8) | 1 (4.2) | 4 (8.2) |
| PD | 1 (1.4) | 0 (0) | 1 (2.0) |
| **Time to response (≥PR), median (range)** | | | |
| Days | 85 (55-749) | 87 (55-693) | 85 (56-749) |

**Median follow-up: 22.5 mo (4.1-43.9) – 10.6 mo for TN, 23.1 mo for R/R**

MR, minor response; PD, progressive disease; PR, partial response; SD, stable disease; VGPR, very good partial response.

# Best overall response by *MYD88* mutation status

***Data cut** 24-JULY-2018*

| Best response, n (%) | All Efficacy Evaluable (n=73) | *MYD88*$^{L265P}$ | | *MYD88*$^{WT}$ |
|---|---|---|---|---|
| | | *CXCR4*$^{WT}$ (n=48) | *CXCR4*$^{WHIM}$ (n=6) | (n=9) |
| ORR | 67 (91.8) | 45 (93.8) | 6 (100) | 8 (88.9) |
| MRR | 60 (82.2) | 42 (87.5) | 6 (100) | 6 (66.7) |
| VGPR | 30 (41.1) | 23 (47.9) | 2 (33.3) | 2 (22.2) |
| PR | 30 (41.1) | 19 (39.6) | 4 (66.7) | 4 (44.4) |
| MR | 7 (9.6) | 3 (6.3) | 0 | 2 (22.2) |
| SD | 5 (6.8) | 3 (6.3) | 0 | 1 (11.1) |
| PD | 1 (1.4) | 0 | 0 | 0 |

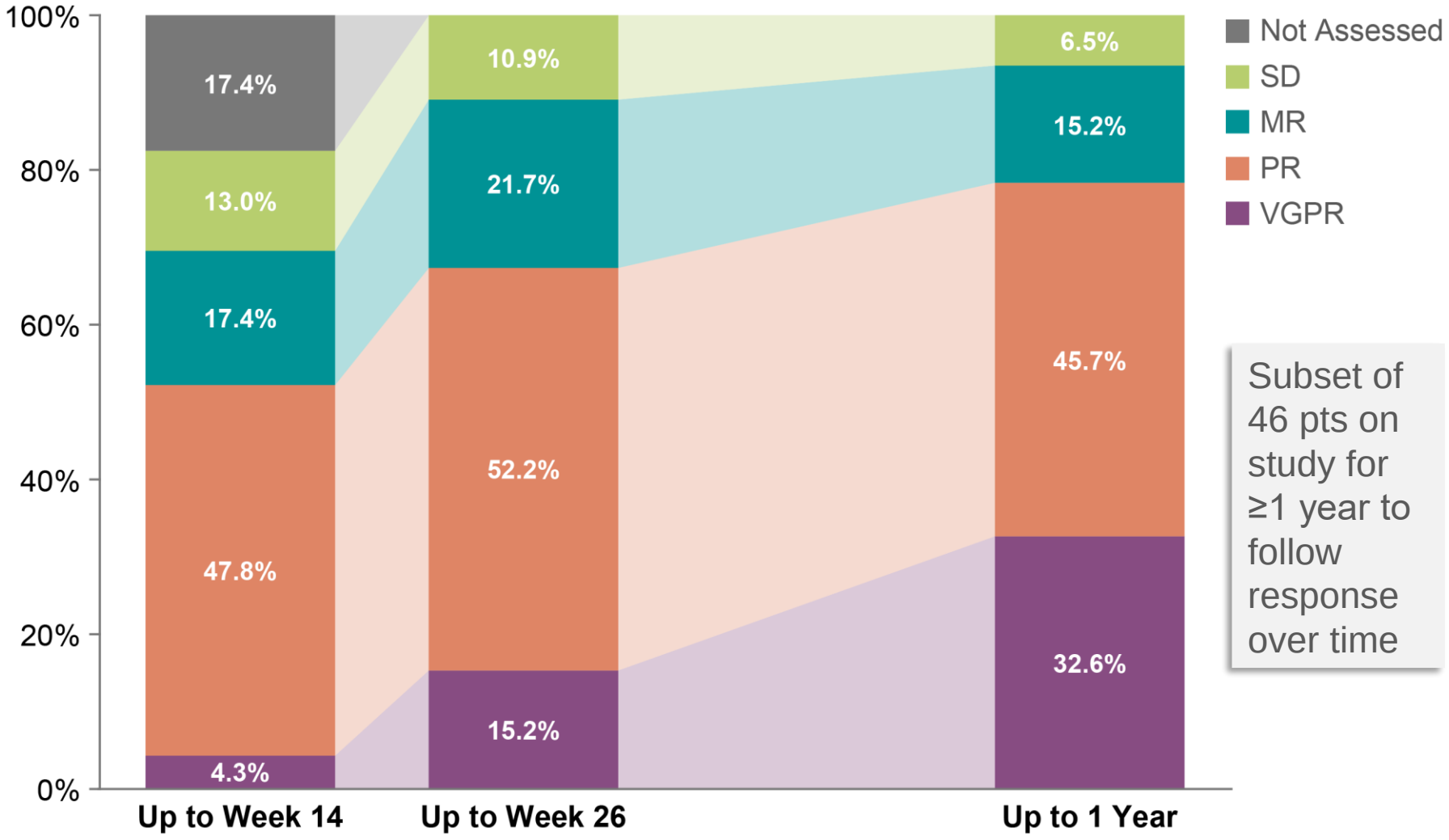


**Median follow-up: 22.5 mo (4.1-43.9)**

MR, minor response; PD, progressive disease; PR, partial response; SD, stable disease; VGPR, very good partial response.

# Best response over time in patients with ≥1 year of follow-up (n=46)

*Data cut 24-JULY-2018*

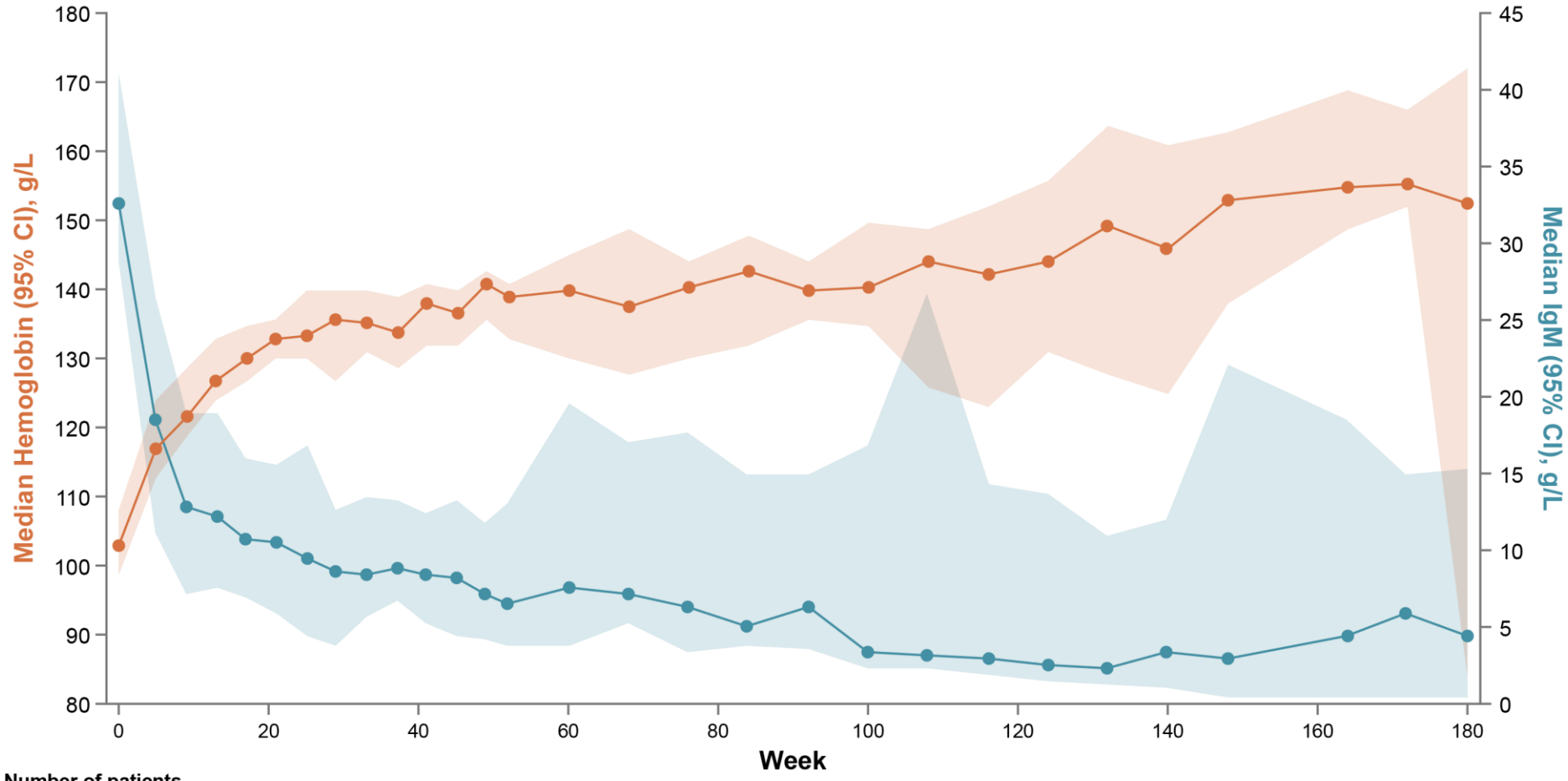



Subset of 46 pts on study for ≥1 year to follow response over time

MR, minor response; PR, partial response; SD, stable disease; VGPR, very good partial response.

# Hemoglobin and IgM over time in evaluable patients (n=73)

*Data cut 24-JULY-2018*



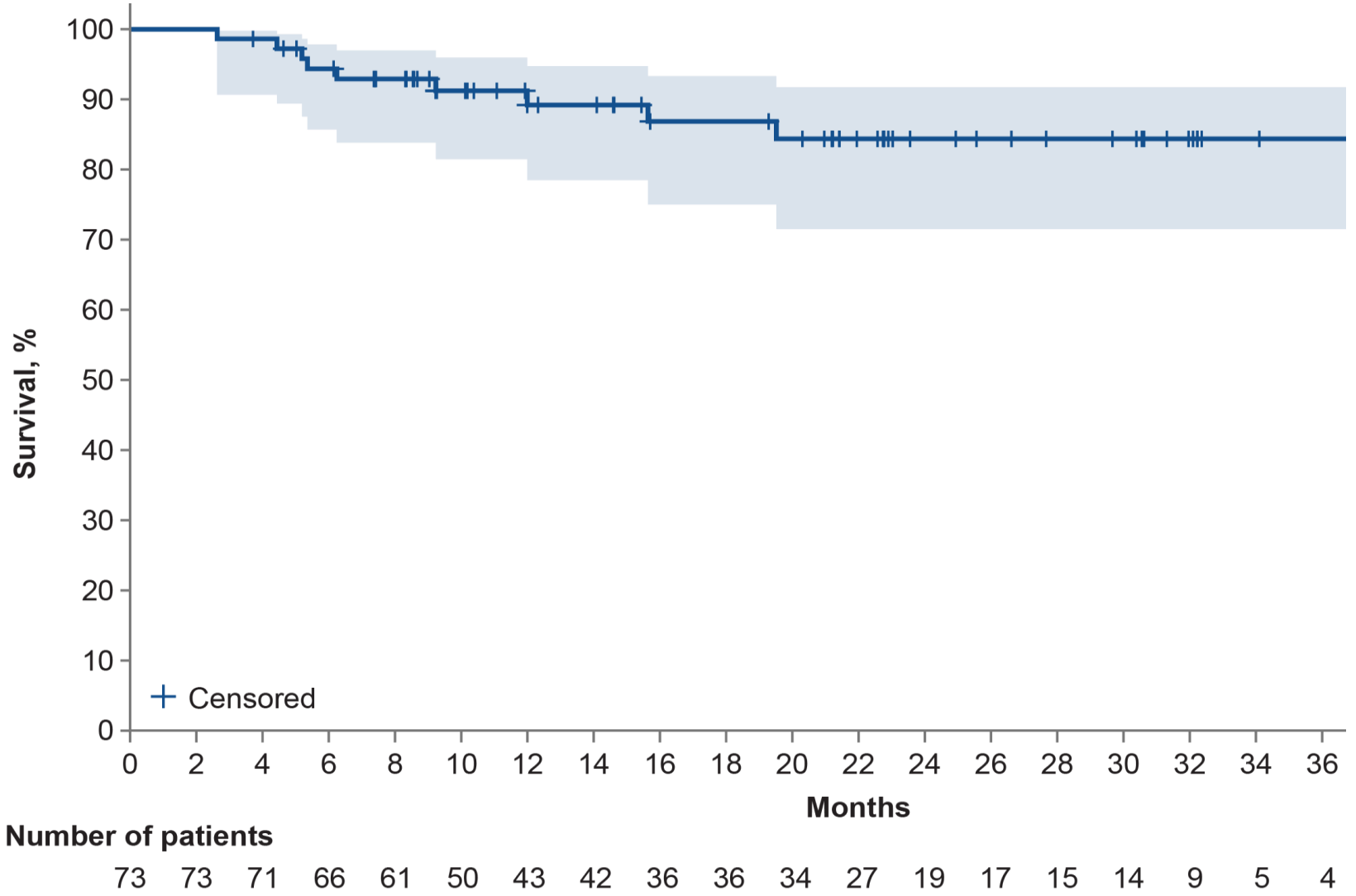

**Number of patients**

| | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **IgM** | 73 | 69 | 70 | 70 | 71 | 65 | 62 | 59 | 61 | 58 | 55 | 52 | 48 | 44 | 39 | 38 | 37 | 33 | 30 | 27 | 19 | 18 | 15 | 12 | 10 | 5 | 4 | 4 | 3 |
| **Hgb** | 73 | 73 | 73 | 73 | 72 | 68 | 64 | 63 | 64 | 63 | 57 | 52 | 48 | 45 | 41 | 38 | 38 | 35 | 34 | 28 | 20 | 18 | 15 | 14 | 10 | 5 | 4 | 4 | 4 |

Shaded areas show the error bars associated with each assessment.
Median IgM decreased from 32.7 g/L (range, 5.3-91.9) at baseline to 8.2 g/L (range, 0.3-57.8).
Of 32 patients with hemoglobin <10 g/dL at baseline, the median increased from 8.85 g/dL (range, 6.3-9.8) to 13.4 g/dL (range, 7.7-17.0).

# Progression-free survival in evaluable patients through 36 months (n=73)

***Data cut** 24-JULY-2018*




Shaded area shows the 95% CI.

# Conclusions

- Zanubrutinib, an investigational, highly selective oral BTK inhibitor showed high plasma concentrations and complete sustained BTK occupancy in blood and lymph nodes

- Updated results from an ongoing phase 1 trial in patients with B-cell malignancies suggest that zanubrutinib was generally well-tolerated and highly active in patients with WM
  - Overall response rate of 92% including 41% with VGPR
  - Increased depth of response over time
  - Estimated 12 month PFS of 89%
  - Discontinuation due to AEs occurred in 11.7% of patients and was determined not to be related to zanubrutinib treatment

- A phase 3 trial comparing zanubrutinib with ibrutinib in patients with WM is ongoing

# Acknowledgments


- We would like to thank the investigators, site support staff, and especially the patients for participating in this study
- This study was sponsored by BeiGene. Editorial support was provided by Bio Connections and funded by BeiGene

# Back-Up

# Best overall response by *MYD88* mutation status

***Data cut** 24-JULY-2018*

| Best response, n (%) | All Efficacy Evaluable (n=73) | *MYD88*$^{L265P}$ | | *MYD88*$^{WT}$ | Unknown Status |
|---|---|---|---|---|---|
| | | *CXCR4*$^{WT}$ (n=48) | *CXCR4*$^{WHIM}$ (n=6) | (n=9) | (n=10) |
| ORR | 67 (91.8) | 45 (93.8) | 6 (100) | 8 (88.9) | 8 (80) |
| MRR | 60 (82.2) | 42 (87.5) | 6 (100) | 6 (66.7) | 6 (60) |
| VGPR | 30 (41.1) | 23 (47.9) | 2 (33.3) | 2 (22.2) | 3 (30) |
| PR | 30 (41.1) | 19 (39.6) | 4 (66.7) | 4 (44.4) | 3 (30) |
| MR | 7 (9.6) | 3 (6.3) | 0 | 2 (22.2) | 2 (20) |
| SD | 5 (6.8) | 3 (6.3) | 0 | 1 (11.1) | 1 (10) |
| PD | 1 (1.4) | 0 | 0 | 0 | 1 (10) |



**Median follow-up: 22.5 mo (4.1-43.9)**

MR, minor response; PD, progressive disease; PR, partial response; SD, stable disease; VGPR, very good partial response.