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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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]

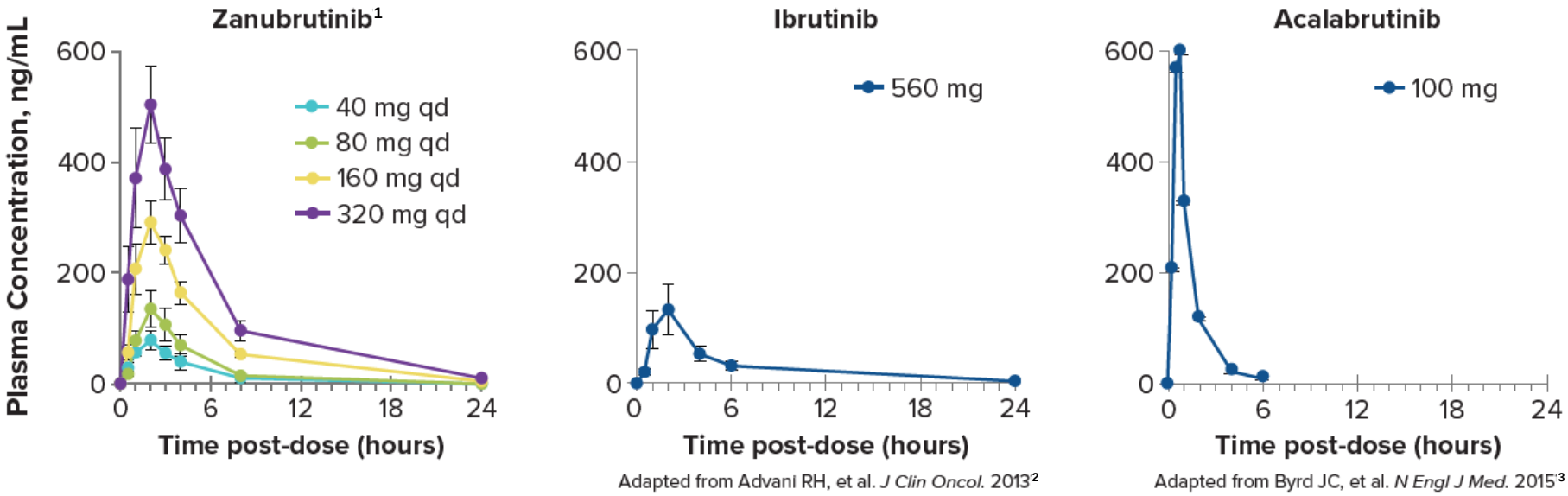
1. Rickert RC. *Nat Rev Immunol*. 2013;13:578-591. 2. Choe H, Ruan J. *Oncology* (Williston Park). 2016;30:847-858. 3. Aalipour A, Advani RH. *Br J Haematol*. 2013;163:436-443. 4. Treon SP, et al. *Blood*. 2014;123:2791-2796. 5. Argyropoulos KV, et al. *Leukemia*. 2016;30:1116-1125. 6. IMBRUVICA® (ibrutinib). 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



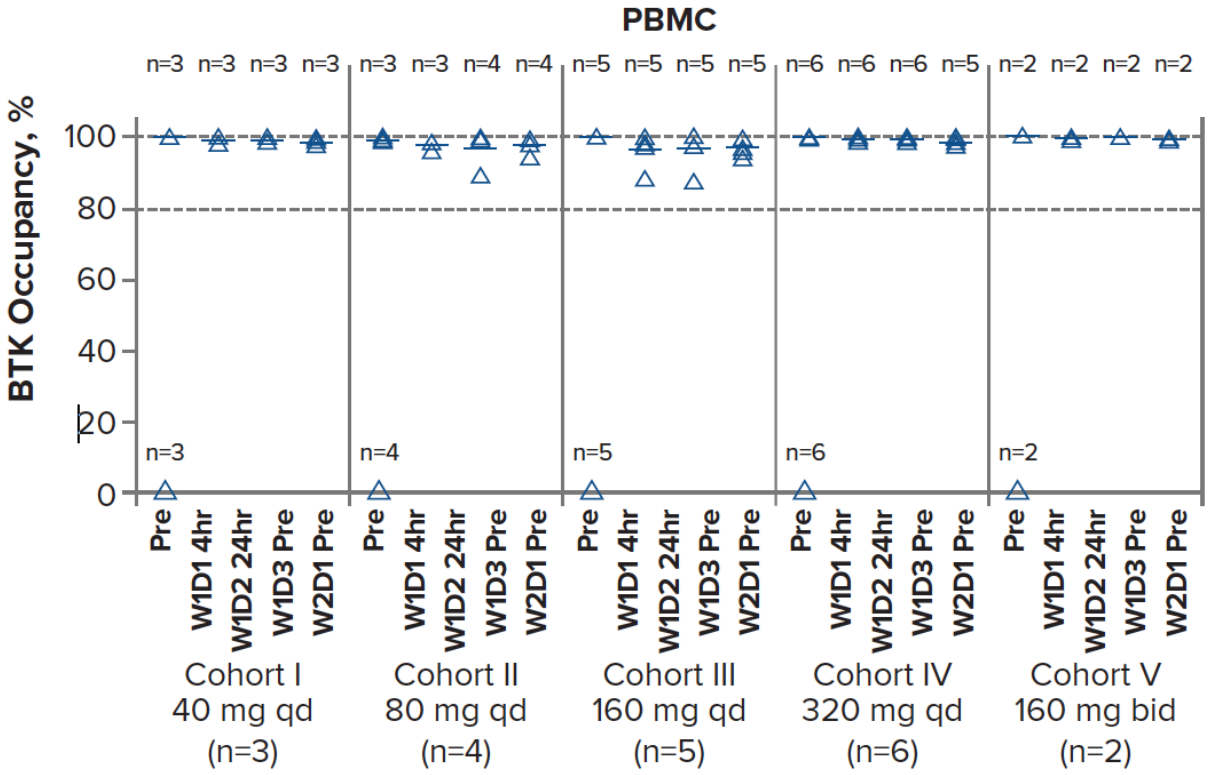
Adapted from Advani RH, et al. *J Clin Oncol.* 2013[2]

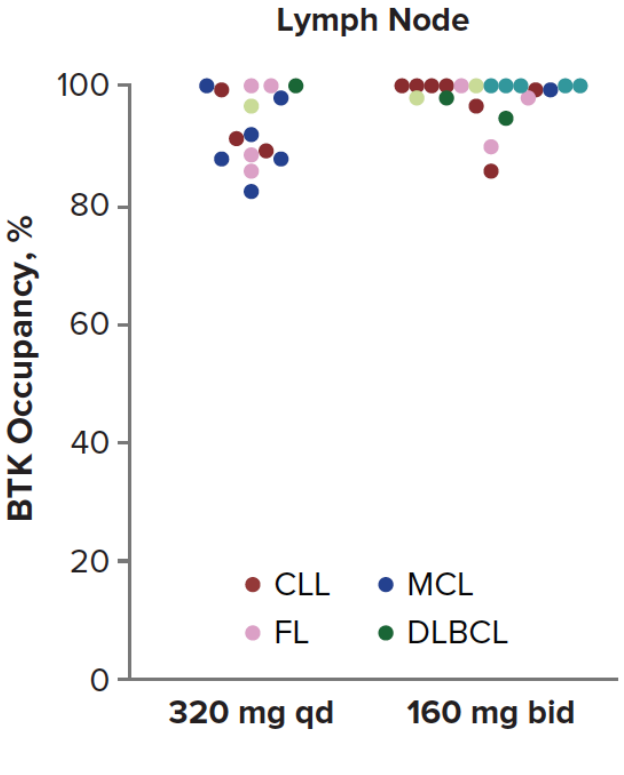
Adapted from Byrd JC, et al. *N Engl J Med.* 2015[3]

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

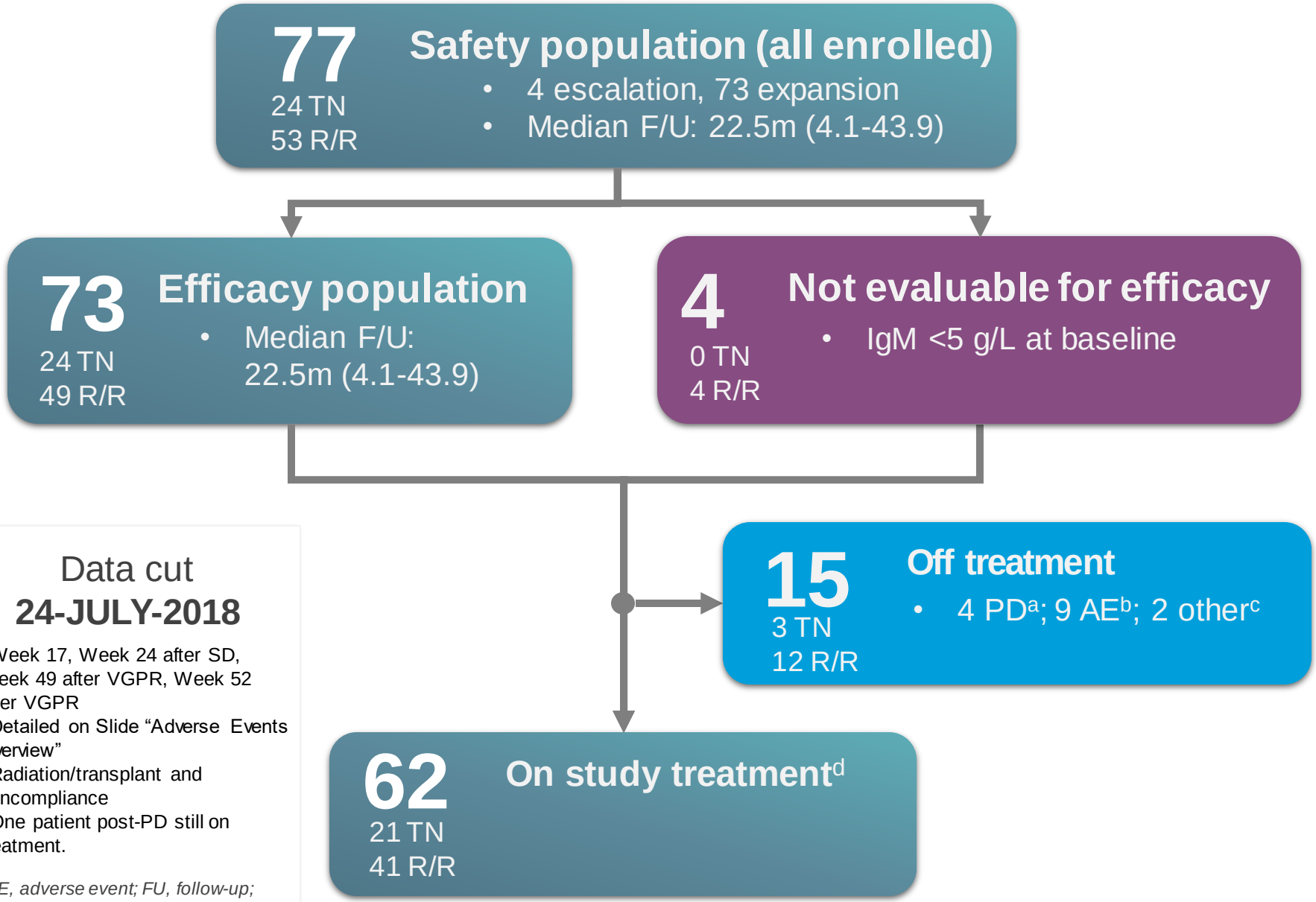
Cohorts containing WM pts in blue

†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

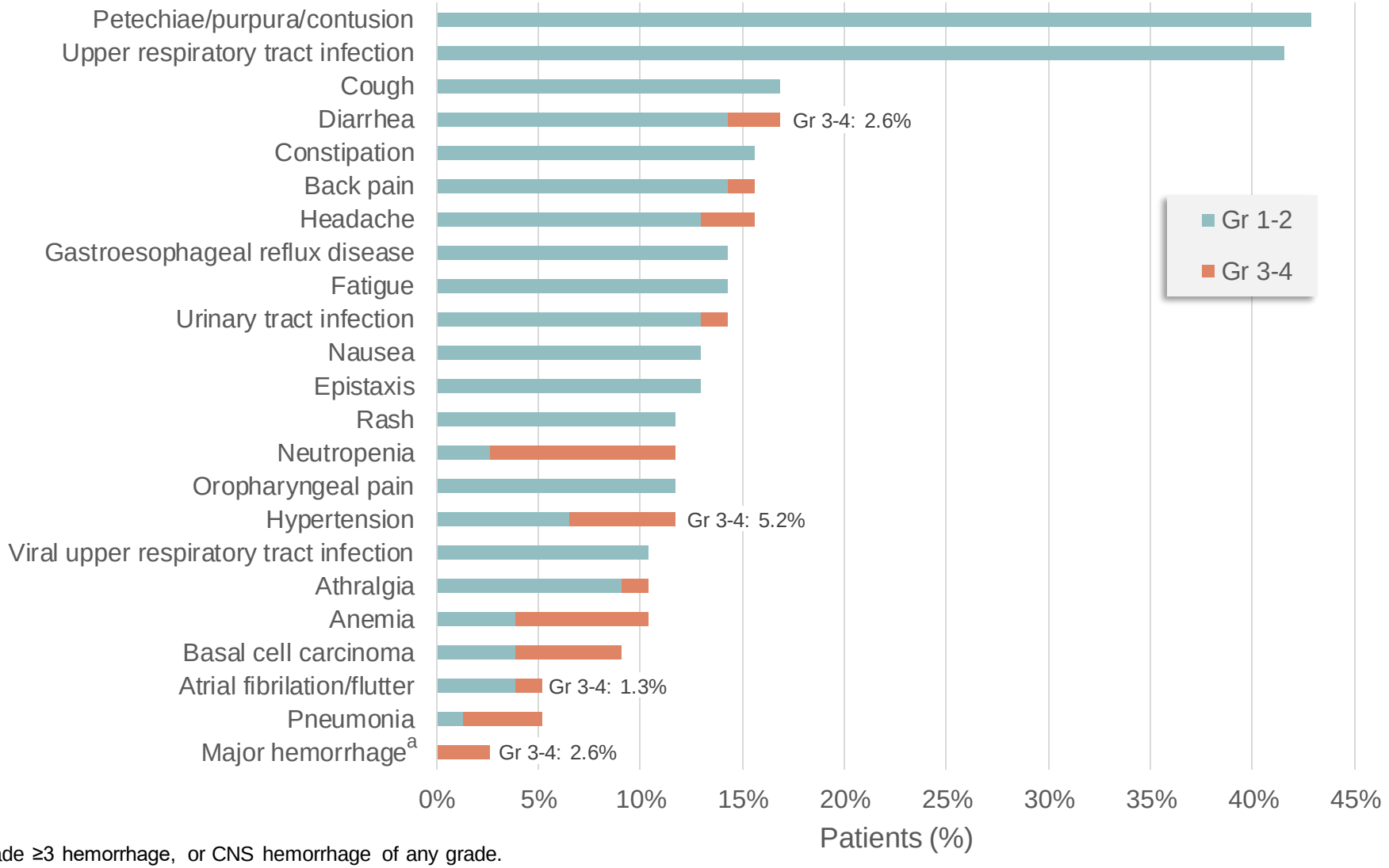
***Data cut** 24-JULY-2018*

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)

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)

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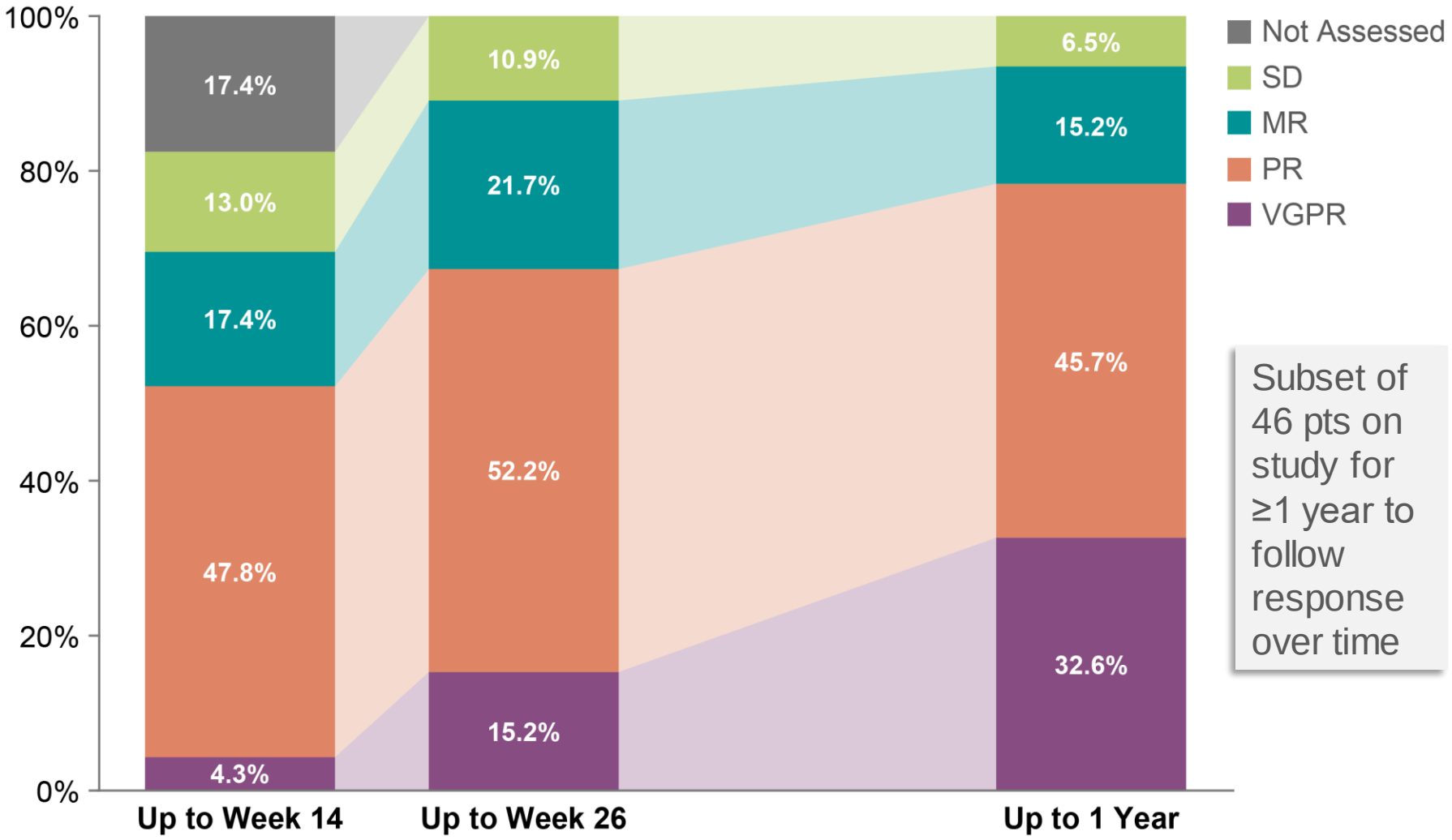
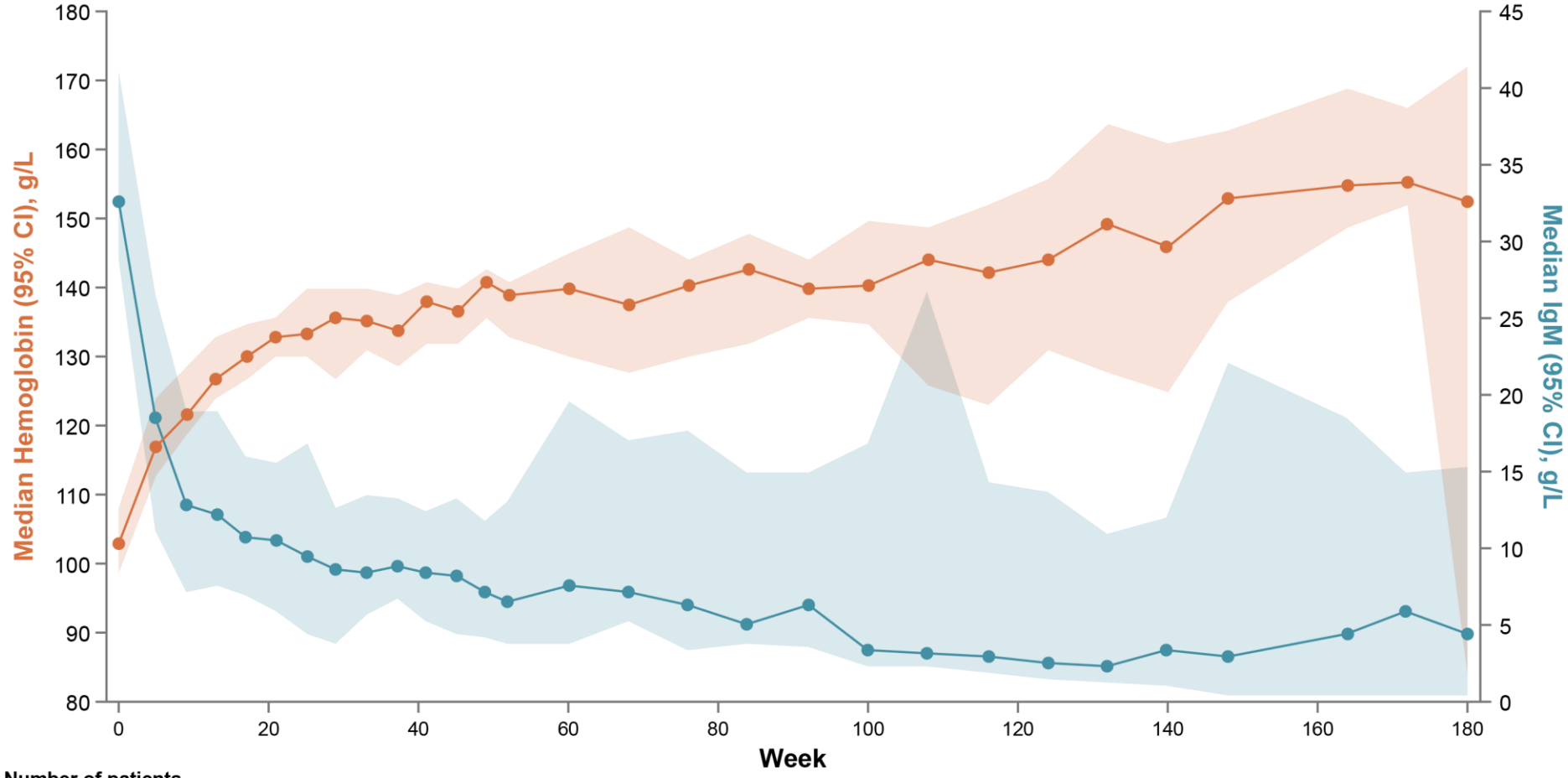


Subset of 46 pts on study for ≥1 year to follow response over time

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



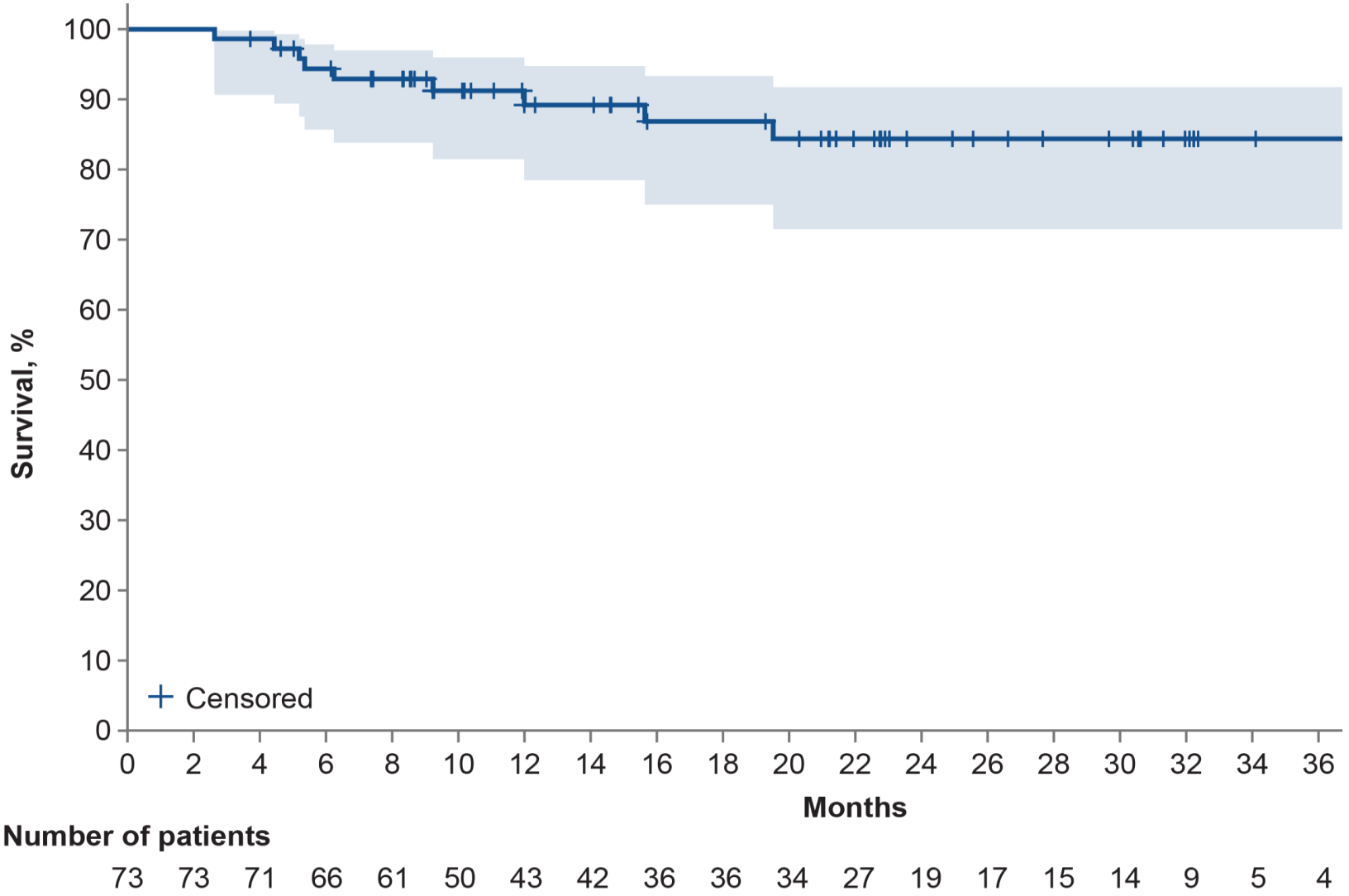
Number of patients

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.