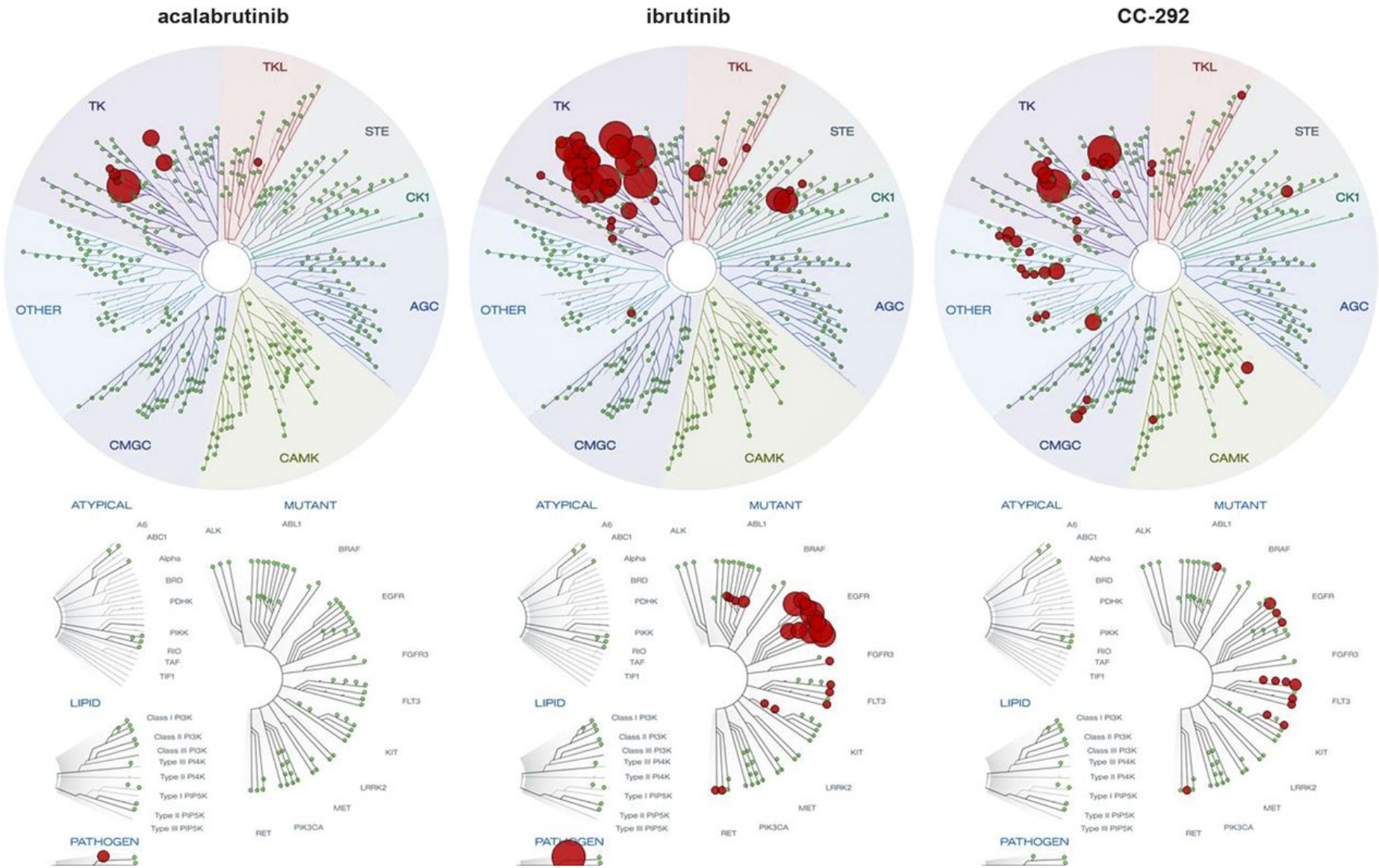
Second Generation BTK Inhibitors Acalabrutinib (ACP-196) and Zanubrutinib (BGB-3111)

Constantine (Con) S. Tam

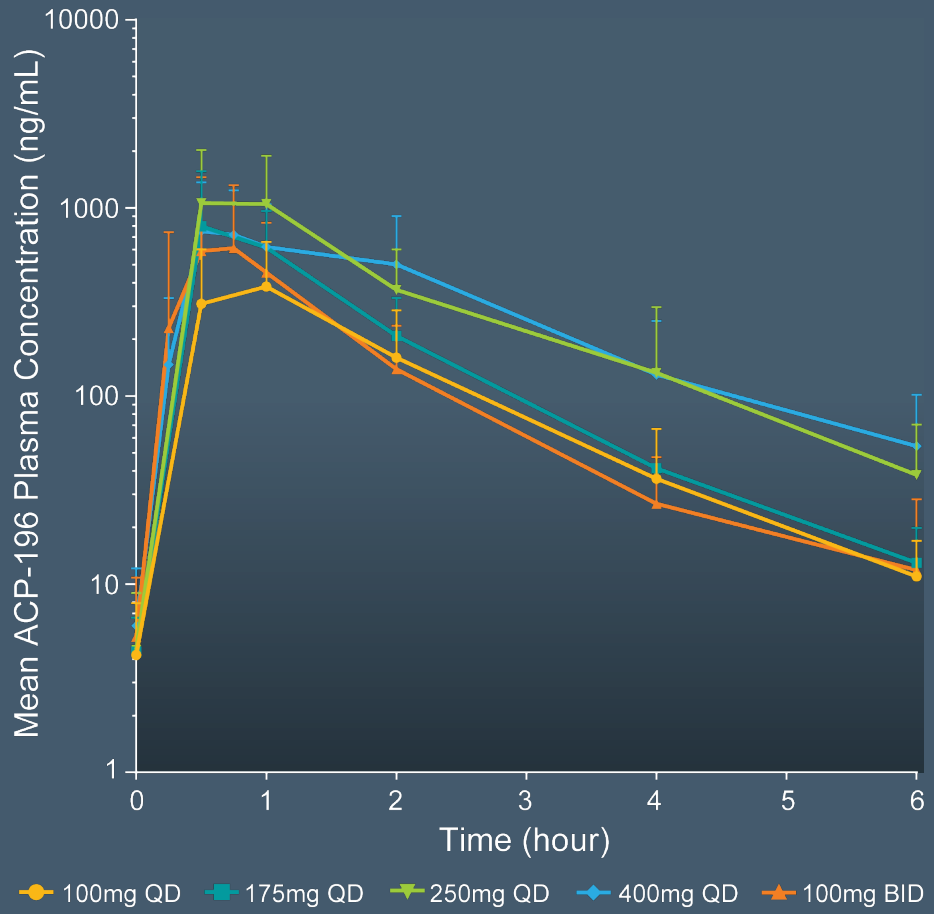
Director of Haematology, St Vincent's Hospital Melbourne; Lead for Chronic Lymphocytic Leukemia and Indolent Lymphoma, Peter MacCallum Cancer Centre; Associate Professor of Haematology, University of Melbourne

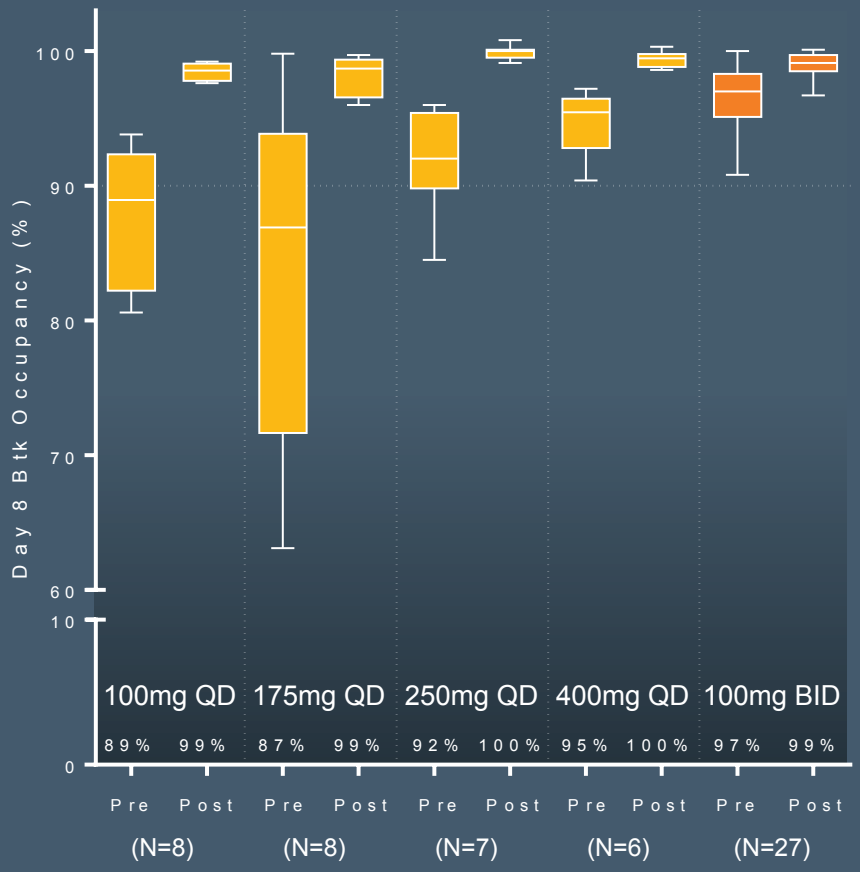
Kinome Profile of BTK Inhibitors



Acalabrutinib : PK / PD Profile

1 hour half-life; Rapid oral absorption; Full Btk occupancy

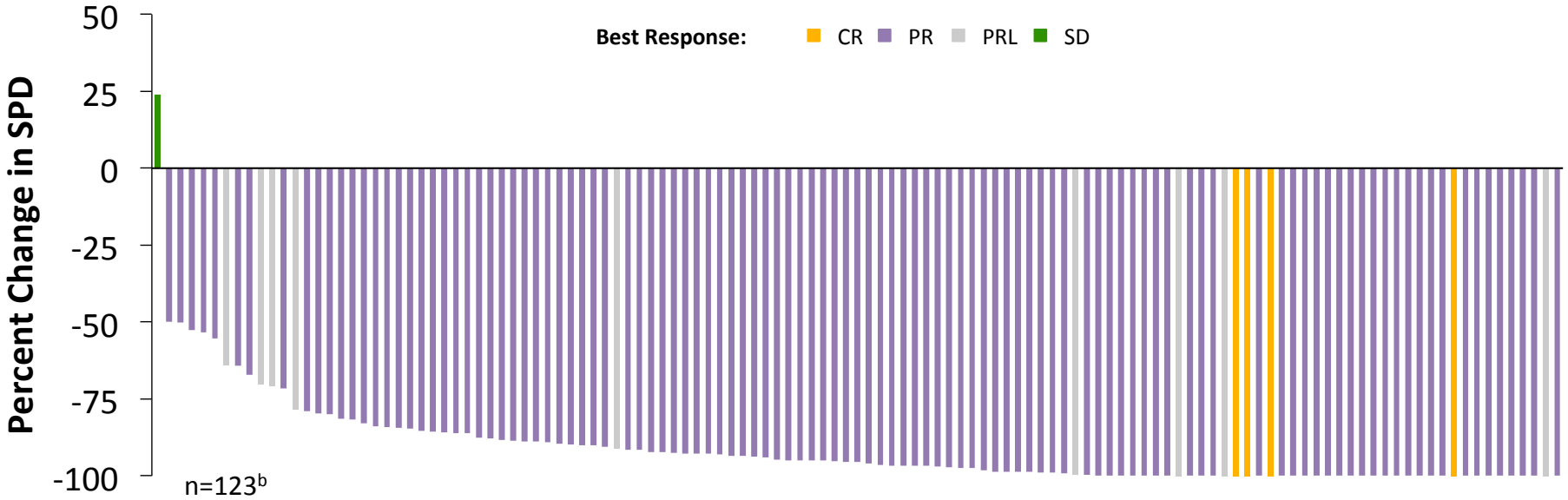




Pre, predose at 24 hrs; Post, 4 hrs postdose.

ACE-CL-001 Study: Single Agent Acalabrutinib in Relapsed / Refractory Chronic Lymphocytic Leukemia

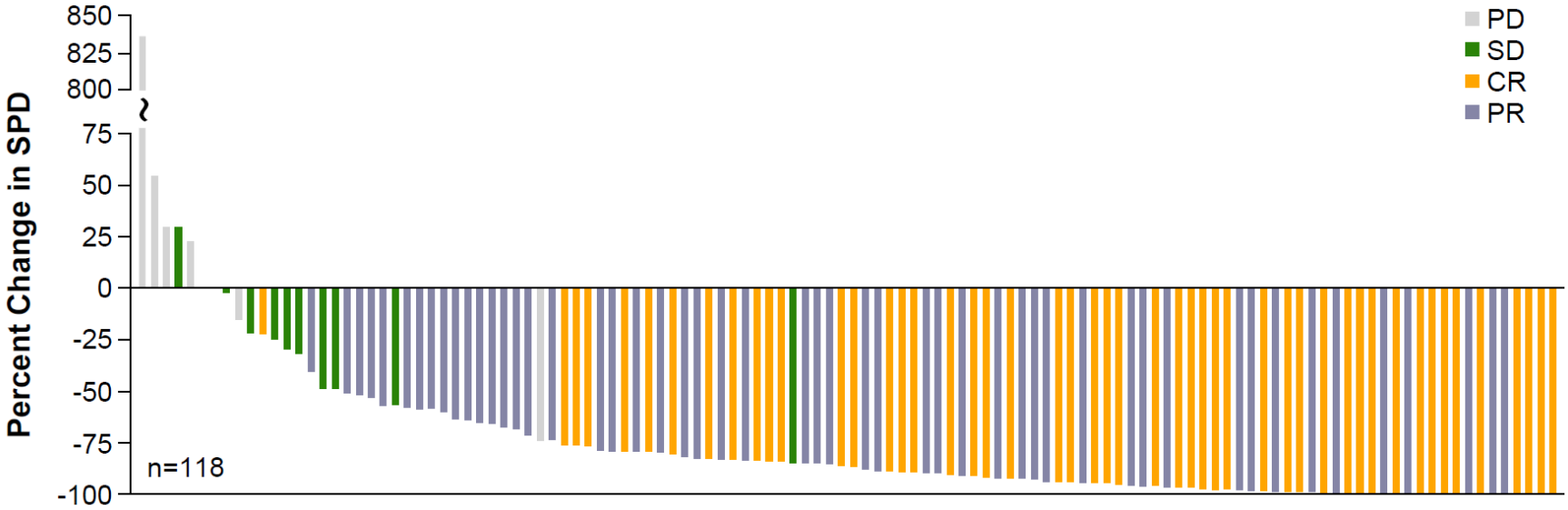
- Nearly all patients (99%) experienced a reduction in lymphadenopathy[a]



[a]Lymphadenopathy is defined as presence of any node with a diameter >1.5 cm.
[b]Patients without the following were excluded from analysis: lymphadenopathy at baseline, post-baseline lymph node measurements, and post-baseline overall response assessment.
CR = complete response; PR = partial response; PRL = partial response with lymphocytosis; SD = stable disease; SPD = sum of product diameters.

ACE-LY-004 Study: Single Agent Acalabrutinib in Relapsed / Refractory Mantle Cell Lymphoma

- Most patients (94%) experienced a reduction in lymphadenopathy[a]

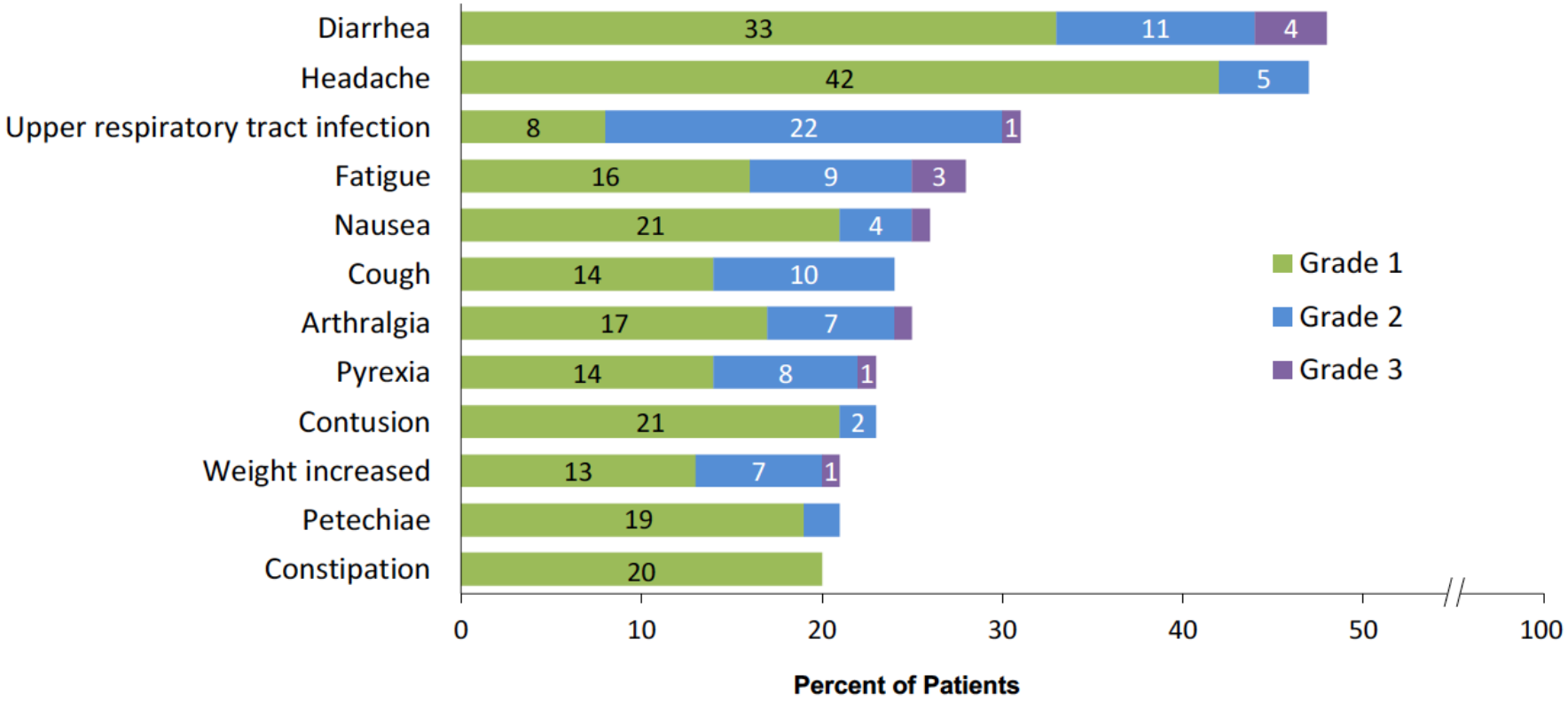


[a] Maximum change from baseline in SPD for all treated patients with baseline and ≥1 postbaseline lesion measurement. Six subjects were excluded due to early PD by evidence other than CT (n=4), started subsequent anticancer therapy (n=1) or death (n=1).

CR = complete response; CT = computed tomography; PD = progressive disease; PR = partial response; SD = stable disease; SPD = sum of product diameters.

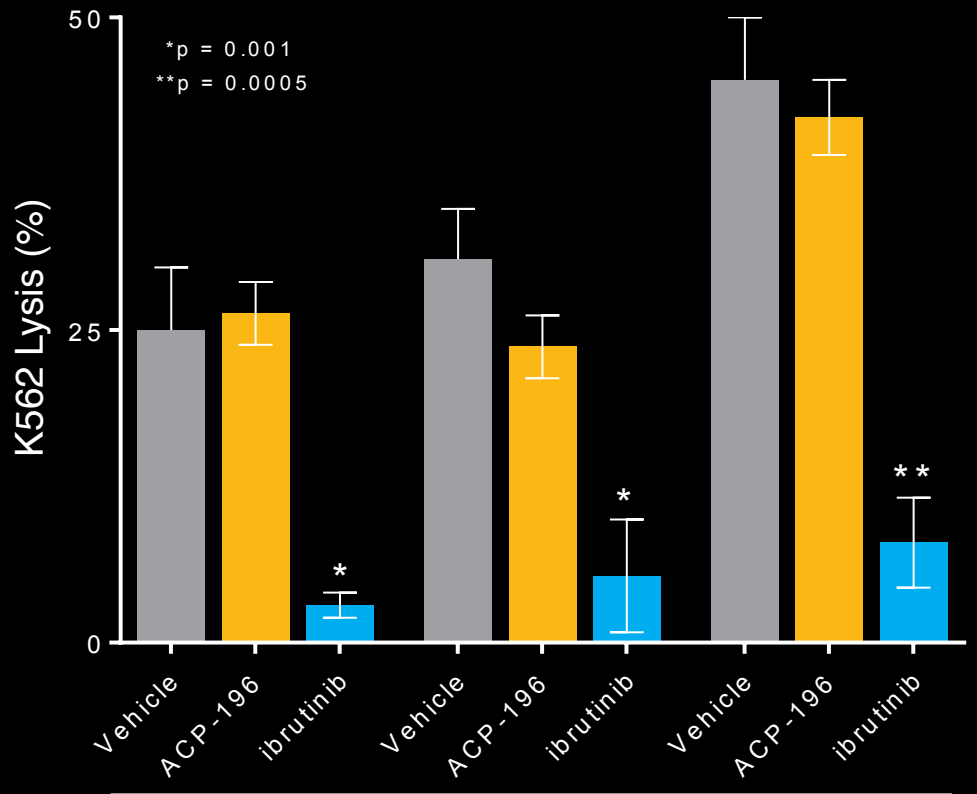
1. Cheson BD, et al. *J Clin Oncol.* 2014;32:3059-68.

Most Common Adverse Events (≥20% of All Patients)

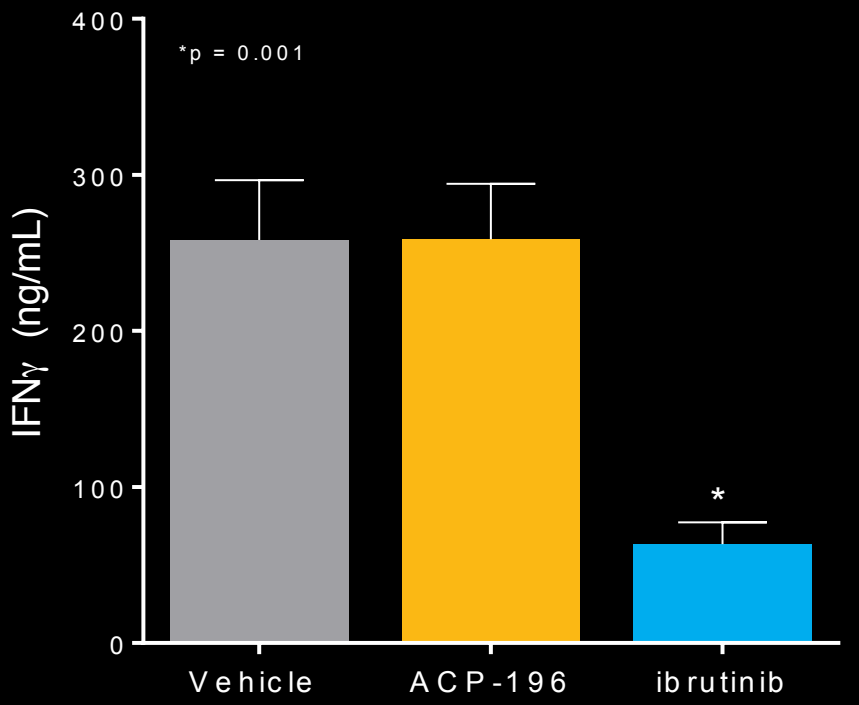


Acalabrutinib: A Better Potential Partner for Monoclonal Antibodies Due to Reduced ITK Binding

Non ADCC-mediated NK cell lysis; CD8+ T cell IFNγ production



ACP-196 does not inhibit NK cell cytolytic activity†



ACP-196 does not inhibit IFNγ CD8+ T cells‡

Lannutti AACR 2015. Abstract 408.
†Cells were preincubated with ACP-196 and ibrutinib (500nM each), then washed before being assayed.

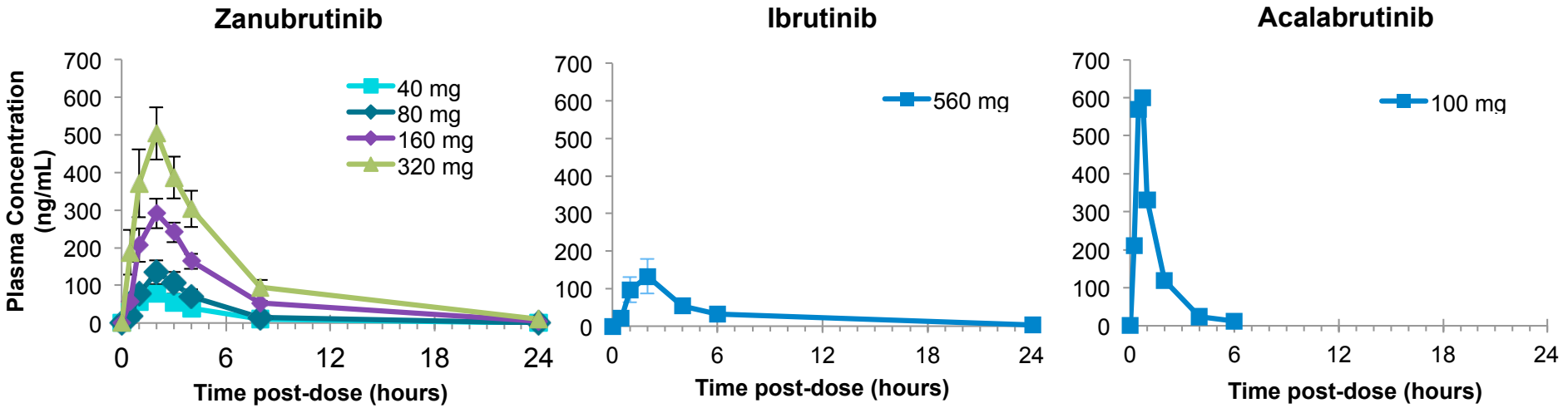
‡Cells were preincubated with ACP-196 and ibrutinib (500nM each), then washed before being assayed.
CD8+ T cells were stimulated with anti-TCR Ab to produce IFNγ.

Zanubrutinib (BGB-3111): High BTK Selectivity

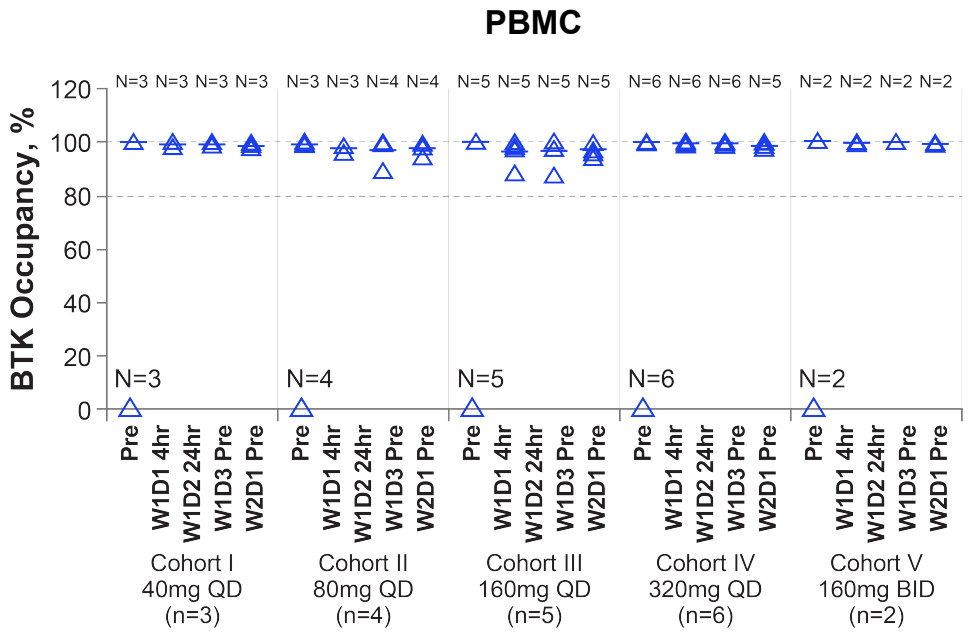
Targets	Assays	Ibrutinib IC_{50} (nM)	Zanubrutinib IC_{50} (nM)	Ratio (Zanubrutinib:Ibrutinib)
BTK	BTK-pY223 Cellular Assay	3.5	1.8	0.5
	Rec-1 Proliferation	0.34	0.36	1.1
	BTK Occupation Cellular Assay	2.3	2.2	1.0
	BTK Biochemical Assay	0.20	0.22	1.1
EGFR	p-EGFR HTRF Cellular Assay	101	606	6.0
	A431 Proliferation	323	3210	9.9
ITK	ITK Occupancy Cellular Assay	189	3265	17
	p-$PLC_{\gamma 1}$ Cellular Assay	77	3433	45
	IL-2 Production Cellular Assay	260	2536	9.8
	ITK Biochemical Assay	0.9	30	33
JAK3	JAK3 Biochemical Assay	3.9	200	51
HER2	HER2 Biochemical Assay	9.4	661	70
TEC	TEC Biochemical Assay	0.8	1.9	2.4

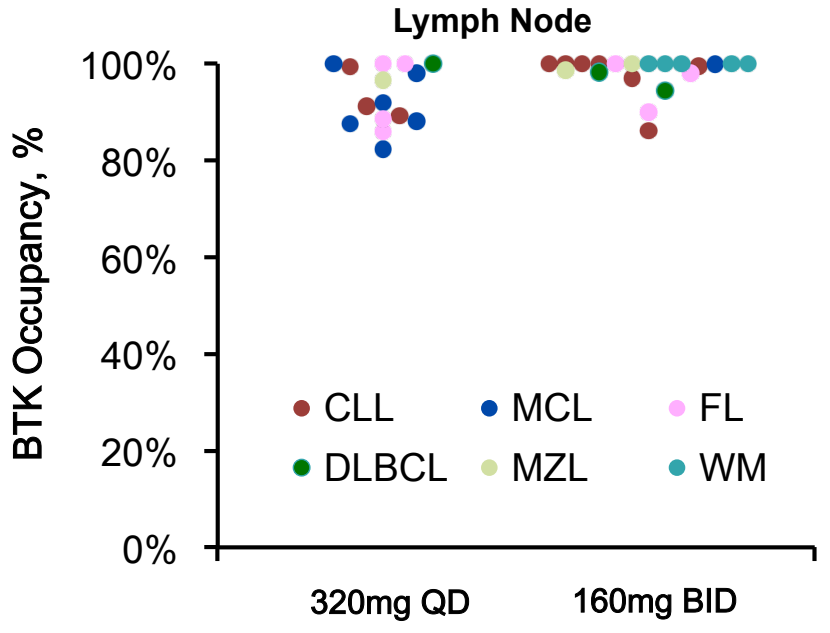
BTK, Bruton's tyrosine kinase; EGFR, epidermal growth factor receptor; IC50, drug concentration causing 50% inhibition of the desired activity; ITK, interleukin-2 inducible T-cell kinase; JAK3, Janus kinase 3.

Zanubrutinib: Favorable Pharmacokinetics, Biopsy Proven Continuous Nodal BTK inhibition



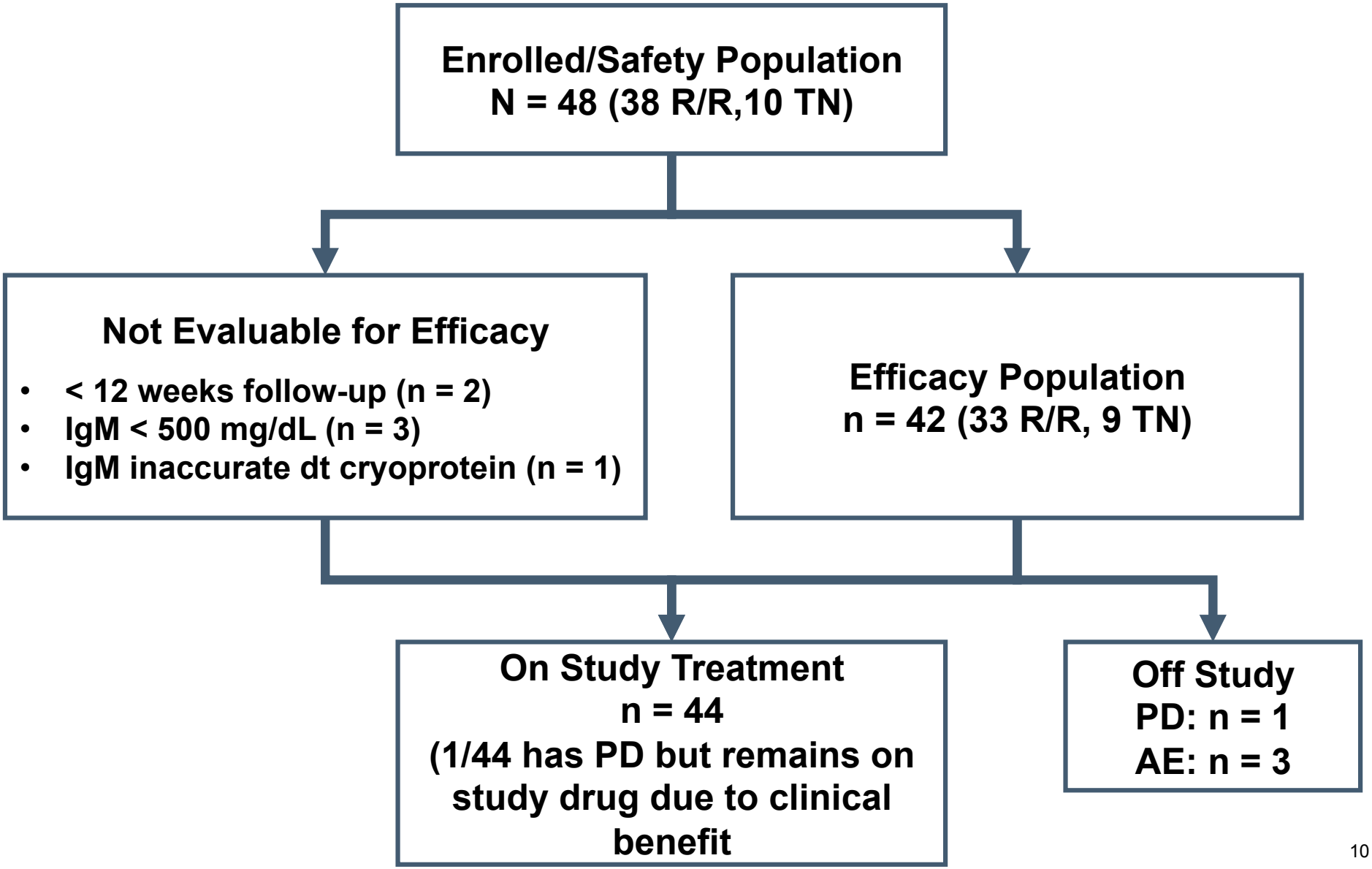
Adapted from Advani, et al, *J Clin Oncol*, 2013[9]





Phase I Zanubrutinib: Waldenstrom Population

As of March 31, 2017

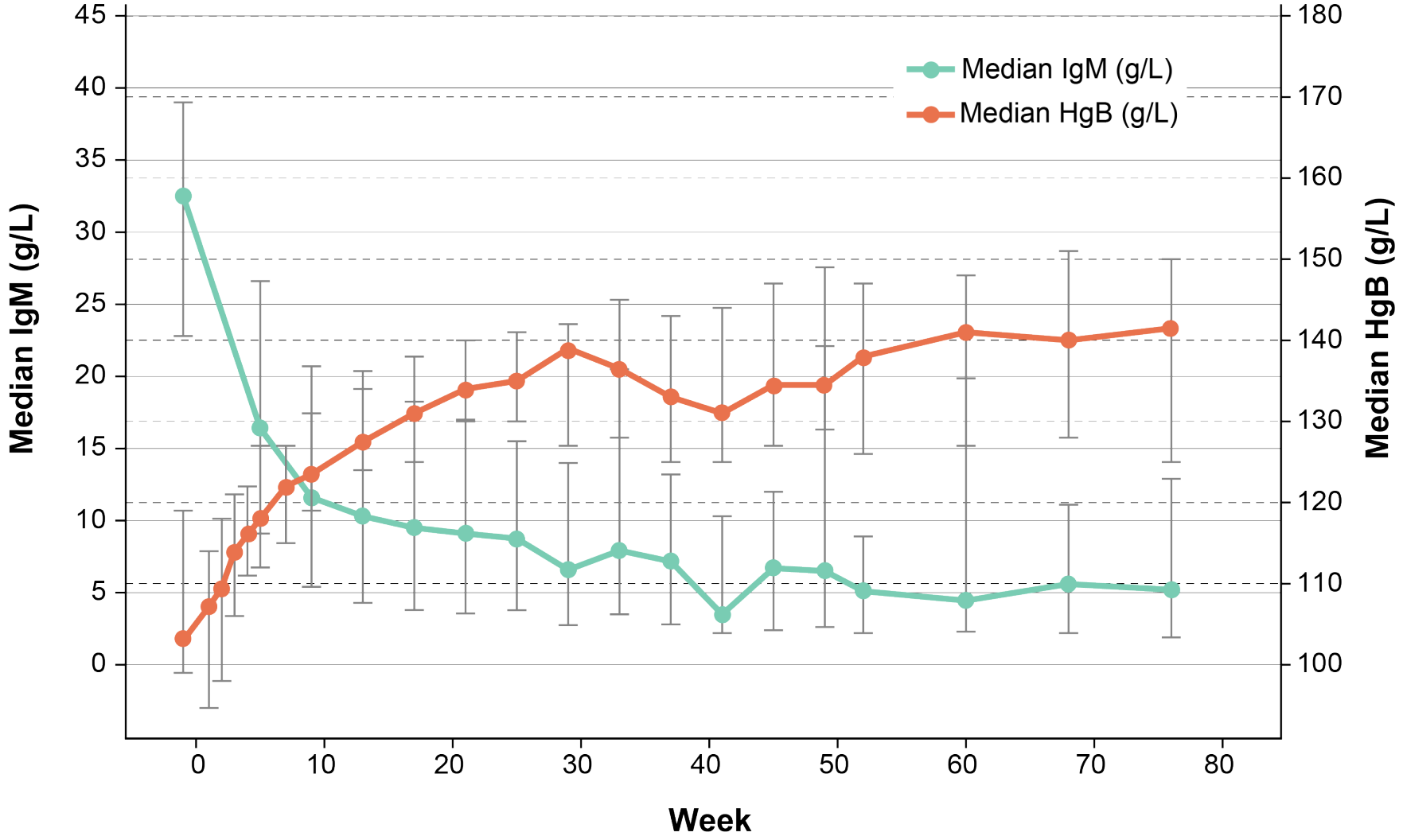


Phase I Zanubrutinib: Response in WM (n = 42)

	Total
Median follow-up (range)	12.3 months (4.4-30.5)
Best Response (n = 42) CR VGPR PR MR SD	 0 18 (43%) 14 (33%) 6 (14%) 4 (10%) **90% ORR†** **76% MRR***
IgM reduction (median, %)	32.7 g/L to 6.1 g/L (81.3%)
Hemoglobin change (median)	104.5 g/L to 142 g/L
Lymphadenopathy reduction by CT (n, range)	45.5% (median) (16, 18.2%-81.4%)

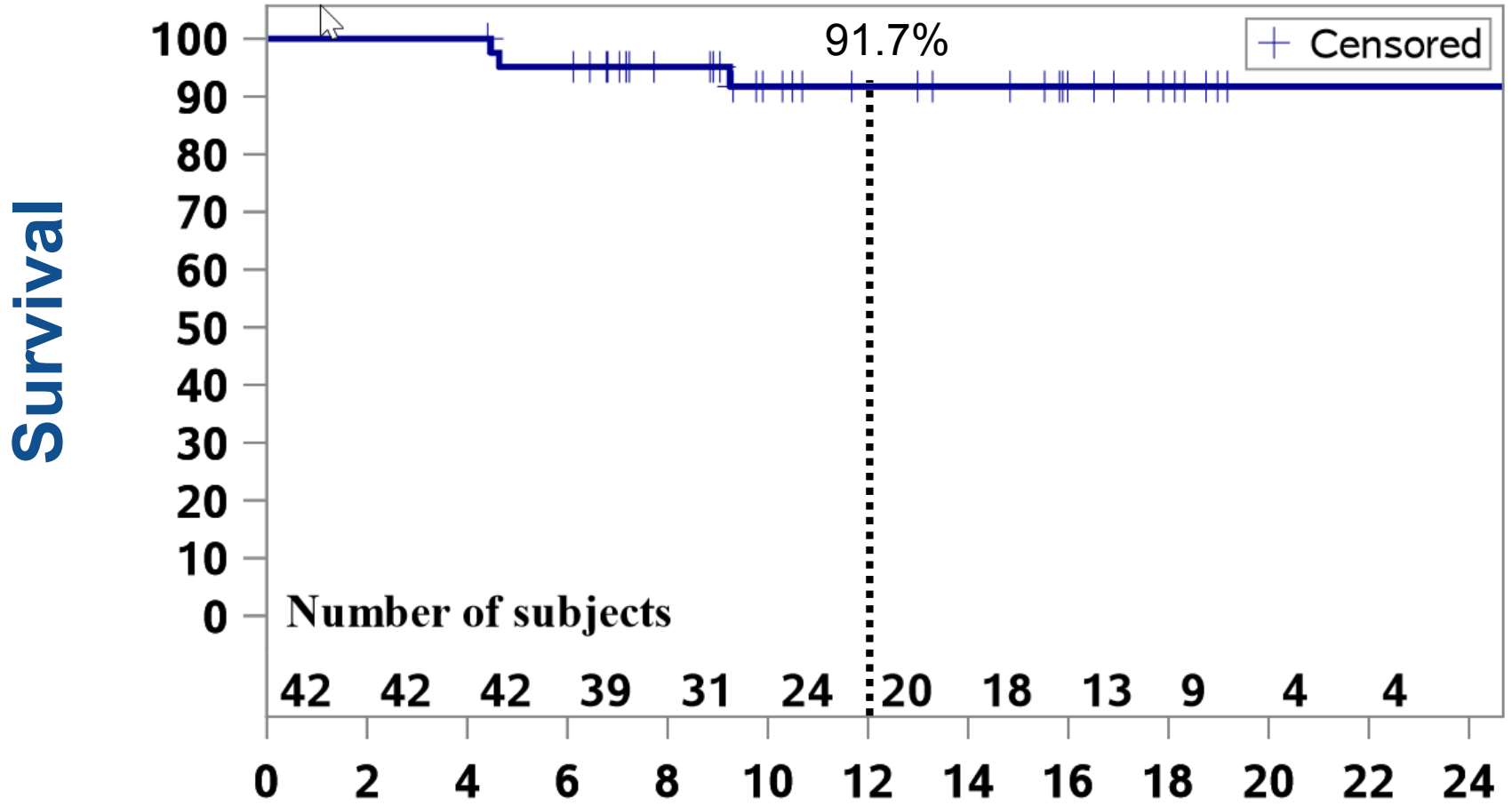
† Overall response rate
* Major response rate

Decreased IgM and Improved Hemoglobin Levels over time



At risk (n)																		
IgM	39	38	36	38	39	35	36	34	27	26	23	21	22	20	16	14	11
HgB	42	42	42	42	42	42	42	39	38	37	32	31	27	24	22	21	19	15	12

Phase I Zanubrutinib: PFS in WM



1 PD patient is *MYD88*^{WT}
1 PD patient is *MYD88*^{mut}/ *CXCR4*^{mut}

Adverse Events in >10%. Independent of Causality
(Safety Population: N = 48)

Adverse Event	All Grade		Grade 3-4	
	n (pts)	%	n (pts)	%
Petechiae/purpura/contusion	17	35%	0	0%
Upper respiratory tract infection	15	31%	0	0%
Constipation	12	25%	0	0%
Diarrhea	9	19%	1	2%
Epistaxis	9	19%	0	0%
Nausea	8	17%	0	0%
Cough	7	15%	0	0%
Anemia	7	15%	4	8%
Headache	7	15%	1	2%
Neutropenia	6	13%	4	8%
Rash	6	13%	0	0%

Selected Adverse Events

Event	All Cause	
	n (pts)	%
Patients with at least one AE Grade ≥3	20	42%
Patients with at least one SAE	18	38%†
Events leading to treatment discontinuation	3‡	6%

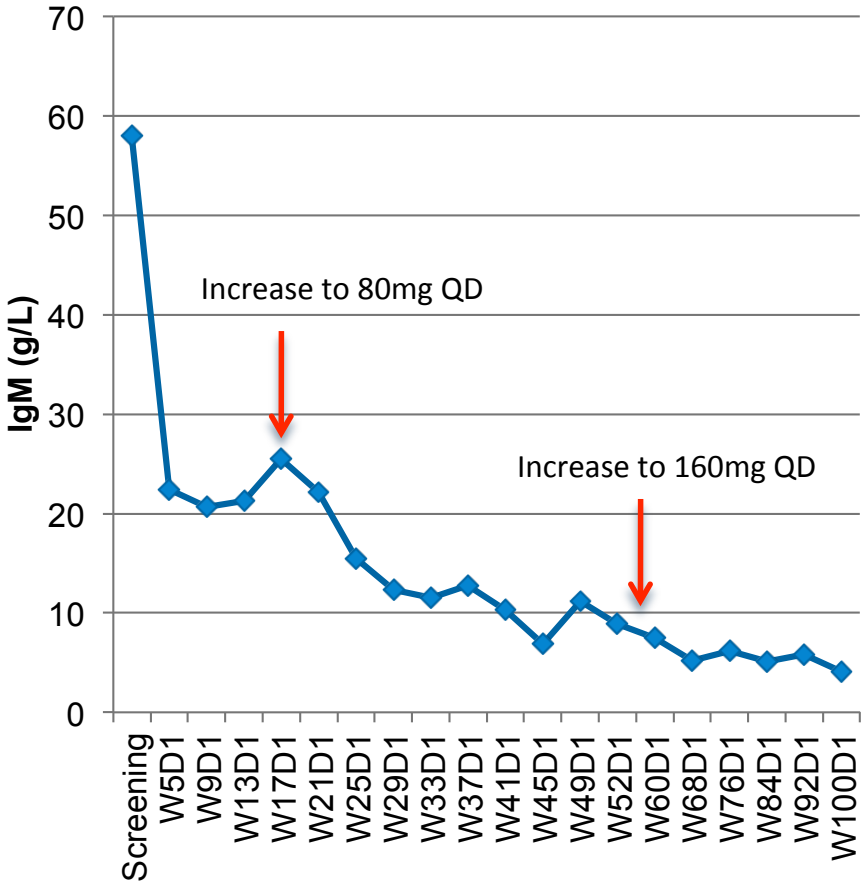
† SAE pos. related to BGB-3111: haemothorax, atrial fib, colitis, febrile neutropenia, headache (all n=1)
‡ Bronchiectasis, adenocarcinoma of pylorus, prostate adenocarcinoma (all n=1)

AE of Special Interest	All Grade		Grade 3-4	
	n (pts)	%	n (pts)	%
Diarrhea	9	19%	1	2%
Serious hemorrhage§	1	2%	1	2%
Atrial fibrillation	3	6%	0	0

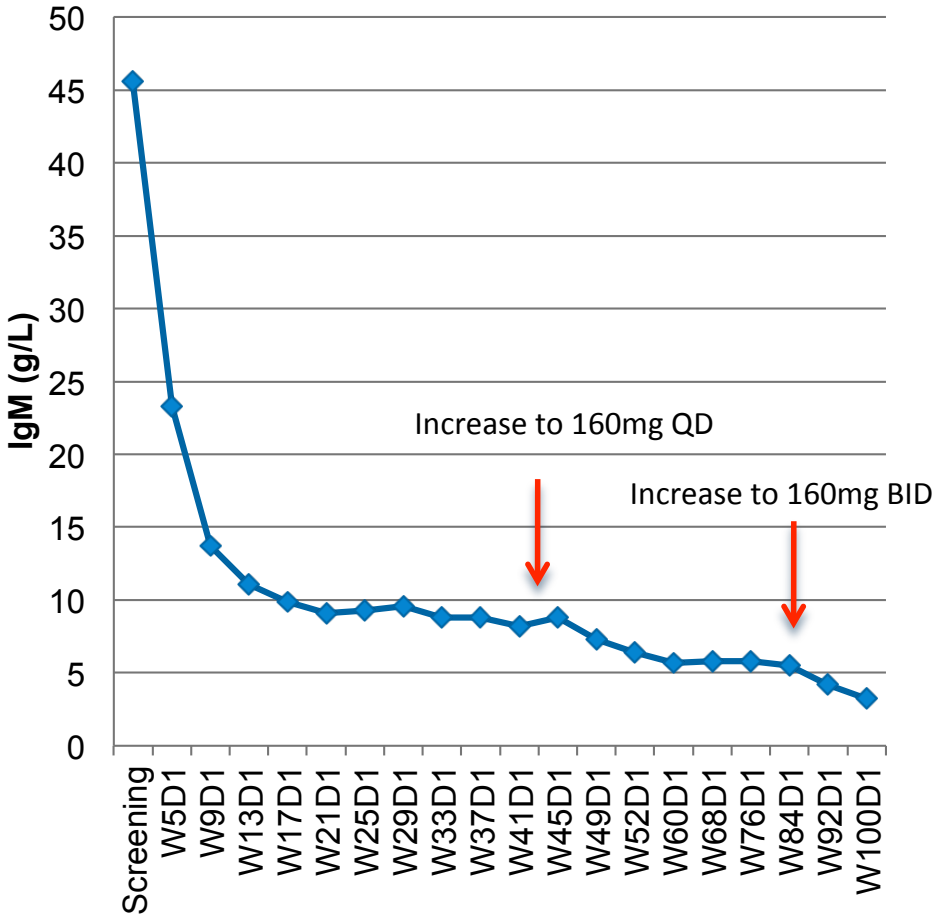
§Defⁿ serious hemorrhage: grade ≥3, or CNS hemorrhage of any grade.

WM: Intrapatient Dose Escalation

S401: Initial dose 40mg QD



S101: Initial dose 80mg QD



Response Rate By *MYD88* Mutation Status Preliminary Results

Genotype N=31*	Best Response			
	VGPR	PR	MR	SD
MYD88^{L265P}/*CXCR4*^{WT} (n = 22)	11 (50%)	7 (32%)	2 (9%)	2 (9%)
MYD88^{L265P}/*CXCR4*^{WHIM} (n = 4)	1 (25%)	2 (50%)	1 (25%)	0
MYD88^{WT} (n = 5)	1 (20%)	1 (20%)	2 (40%)	1 (20%)

* Patients evaluable for response with mutation data

BGB-3111-302: Waldenströms Phase 3 Trial Design

Cohort 1: R/R or TN* WM with *MYD88* mutation

*TN must be unsuitable for standard chemoimmunotherapy

MYD88^{MUT} WM patients
(N=150)

→ R 1:1

Arm A
Zanubrutinib
160 mg BID until PD
(n = 75)

Arm B
Ibrutinib
420mg QD until PD
(n = 75)

Stratification factors:
- *CXCR4* mutational status (*CXCR4^{WHIM}* vs *CXCR4^{WT}*)
- No. of prior lines of therapy (0 vs 1-3 vs > 3)

Cohort 2: WM with wild type MYD88; present in ~10% of enrolled patients

MYD88^{WT} WM patients
(N = 15-20)

→

Arm C
Zanubrutinib
160 mg BID until PD

This study is registered at ClinicalTrials.gov (NCT03053440) 1

Conclusions

- Second generation BTKi have improved selectivity with the potential for reduced off-target effects
  - Acalabrutinib : Relatively lower doses, aiming to improve tolerability
  - Zanubrutinib : Relatively higher doses, aiming to improve efficacy
- All current BTKi rely on covalent binding to C481, and are liable to resistance from C481 mutations.
- Late phase studies are underway.