Bruton's Tyrosine Kinase (BTK) Inhibitor BGB-3111 Demonstrates High Very Good Partial Response (VGPR) Rate in Patients with Waldenström Macroglobulinemia (WM)

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Background

- Bruton's Tyrosine Kinase (BTK), a critical signaling component of the B-cell receptor, is constitutively activated in WM, and a key mediator in cell survival[1-3]
- Ibrutinib, the first generation BTK inhibitor, has shown activity in WM
  - Major response rate: 73% (including 16% VGPR)[4]
  - 68% 3-year EFS[5]
  - Significant side effect profile: bruising/bleeding, diarrhea, cardiac arrhythmias
- BGB-3111 is a potent and specific BTK inhibitor, designed to minimize off target inhibition of TEC- and EGFR-family kinases
- Presented here are interim results from a cohort with WM treated within an ongoing phase 1 trial

[1] Yang G, et al. *Blood*. 2014;20:548-556. 2 Treon SP, et al. *Blood*. 2014;123:2791-2796; 3 Argyropoulos KV, et al. *Leukemia*. 2016;30:1116-1125.[4] Treon SP, et al. *N Engl J Med*. 2015;372:1430-1440. [5] Palomba ML, et al. IWWM. 2016 [abstract].

BGB-3111: Kinase Selectivity Relative to Ibrutinib

Equipotent against BTK compared to ibrutinib

Targets	Assays	Ibrutinib IC_{50} (nM)	BGB-3111 IC_{50} (nM)	Ratio (BGB-3111: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

BGB-3111: Kinase Selectivity Relative to Ibrutinib

Highly selective inhibition of BTK relative to similar tyrosine kinases

Targets	Assays	Ibrutinib IC_{50} (nM)	BGB-3111 IC_{50} (nM)	Ratio (BGB-3111: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	3,210	9.9
ITK	ITK Occupancy Cellular Assay	189	3,265	17
	p-$PLC_{\gamma 1}$ Cellular Assay	77	3,433	45
	IL-2 Production Cellular Assay	260	2,536	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

Trial Design

DOSE ESCALATION

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

320 mg QD

or

160 mg BID

DOSE EXPANSION

Population	RP2D Dose	Disease	Planned (WM enrolled)
Relapsed/Refractory	BID or QD	MCL, MZL, FL, GCB DLBCL , WM	40 (2)
Relapsed/Refractory	BID	Non-GCB DLBCL	40
Relapsed/Refractory	BID	CLL/SLL	70
Relapsed/Refractory	BID	WM	20 (20)
Relapsed/Refractory	QD	CLL/SLL	20
Relapsed/Refractory or Treatment-naïve	BID or QD	WM	50 (22)
Relapsed/Refractory	BID or QD	MCL	20
Treatment-naive	BID or QD	CLL/SLL	20
Treatment-naive	BID or QD	MCL	20
Relapsed/Refractory	BID or QD	HCL	10
Relapsed/Refractory	BID	iNHL	40
Relapsed/Refractory	BID	Richter Transform.	15
Relapsed/Refractory from prior btk-i	BID	WM	15

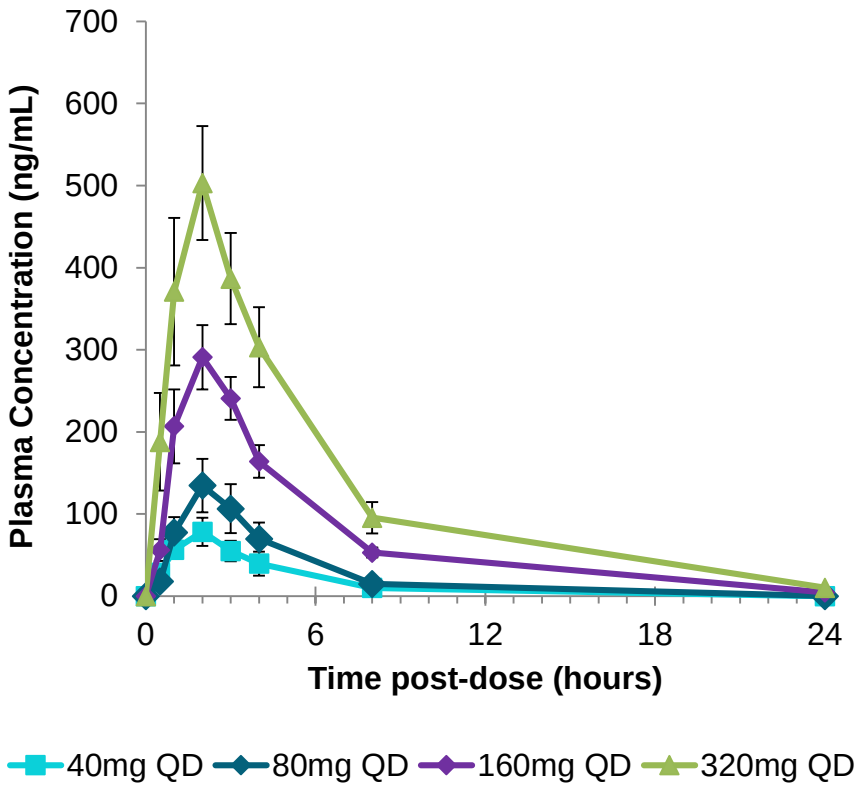
Eligibility:

- ≥1 prior therapy (relapsed cohorts only)
- No available higher priority treatment
- ECOG 0-2
- ANC >1,000/µl, PLT >50,000/µl

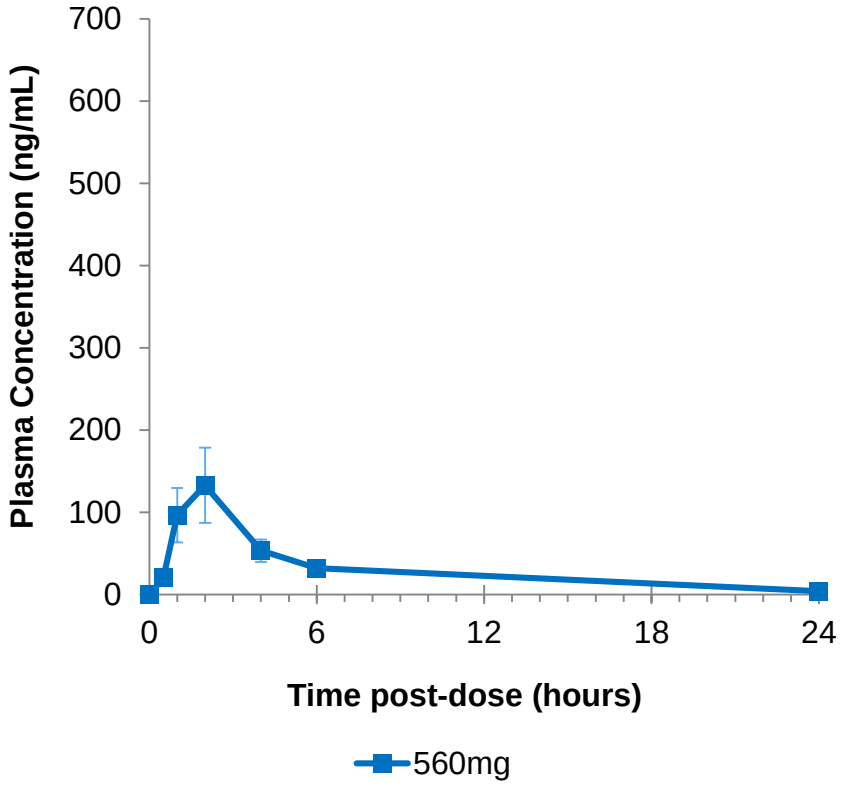
NCT02343120

Plasma Exposure Comparison for BGB-3111 and Ibrutinib

BGB-3111[1]



Ibrutinib

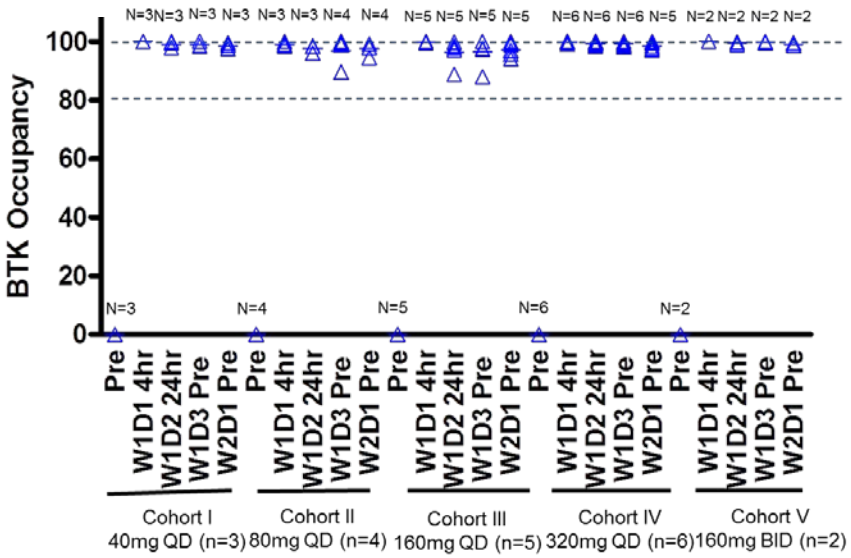


Adapted from Advani *et al*[2]

[1] Tam CS, et al. *Blood*. 2015;126:832.
[2] Advani RH, et al. *J Clin Oncol*. 2013;31:88-94.

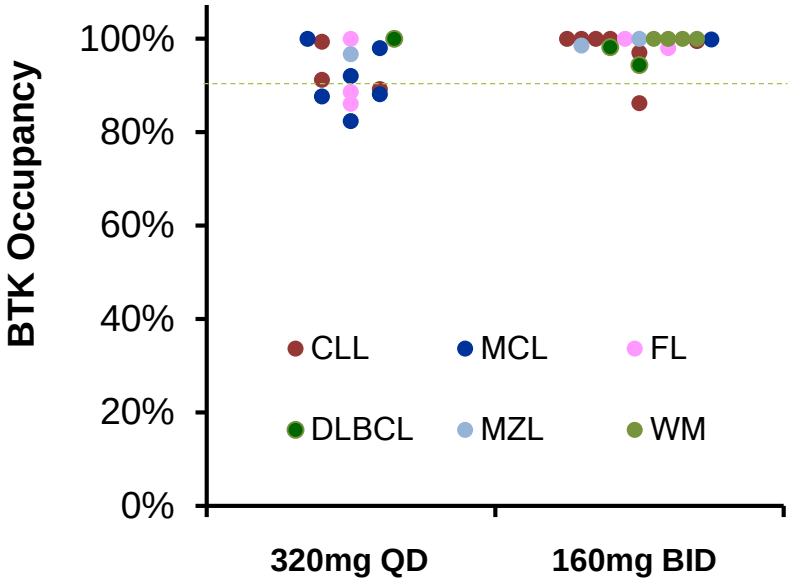
Complete and Sustained BTK Occupancy in PBMC and Lymph Node

PBMC



- Complete BTK occupancy in PBMCs at the starting dose (40 mg)

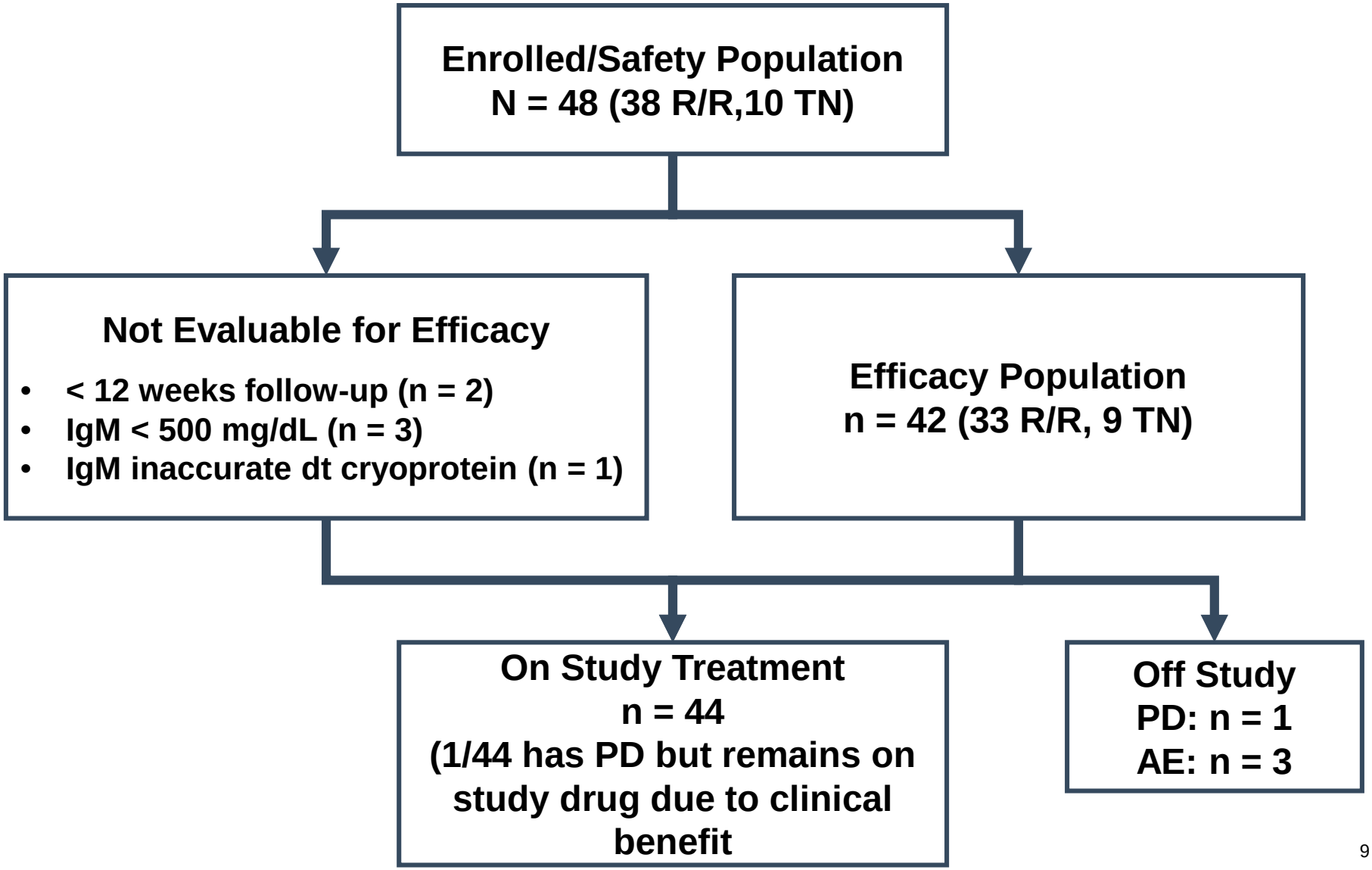
Lymph Node



- Paired lymph node biopsies were collected during screening and pre-dose on day 3
- Median trough occupancy: 100% (160mg BID) vs 94% (320mg QD), p=0.002

WM Patient Disposition

As of March 31, 2017



Patient Characteristics

Characteristic	Total (N = 48)
Age, years, median (range)	66 (44-87)
ECOG Performance Status, n (%) 0 1	 14 (29) 34 (71)
Follow-up, months, median (range)	10.6 (1.4-30.5)
Prior Treatment Status, n (%) Treatment-naïve Relapsed/refractory Number of prior therapies, median (range) Prior rituximab (% R/R pts)	 10 (21) 38 (79) 1 (1-8) 28 (74%)
Genotype $MYD88^{L265P}$/ $CXCR4^{WT}$ $MYD88^{L265P}$/ $CXCR4^{WHIM}$ $MYD88^{WT}$ Unavailable	 21 (43.8) 5 (10.4) 5 (10.4) 17 (35.4)

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.

Modified IWWM Response Criteria

Category	Criteria
Complete Response (CR)	• Normal serum IgM values • Disappearance of monoclonal protein by immunofixation • No histological evidence of bone marrow involvement • Complete resolution of lymphadenopathy/splenomegaly (if present at baseline)
Very Good Partial Response (VGPR)	• ≥90% reduction of serum IgM from baseline **or normal IgM values** • **Reduction** in lymphadenopathy/splenomegaly (if present at baseline)
Partial Response (PR)	• ≥50% reduction of serum IgM from baseline • Reduction in lymphadenopathy/splenomegaly (if present at baseline)
Minor Response (MR)	• At least 25% but <50% reduction of serum IgM from baseline
Stable Disease (SD)	• Not meeting criteria for CR, VGPR, PR, MR, or progressive disease
Progressive Disease (PD)	At least one of the following: • Confirmed ≥25% increase in serum IgM and **total increase of ≥500 mg/dL from nadir (on treatment)** • New lymph nodes >1.5 cm, or ≥50% increase from nadir in SPD of >1 node, or ≥50% increase in longest diameter of previously identified node >1 cm in short axis • New splenomegaly or ≥50% increase from nadir in enlargement • New extranodal disease • New or recurrent involvement in bone marrow • New symptomatic disease

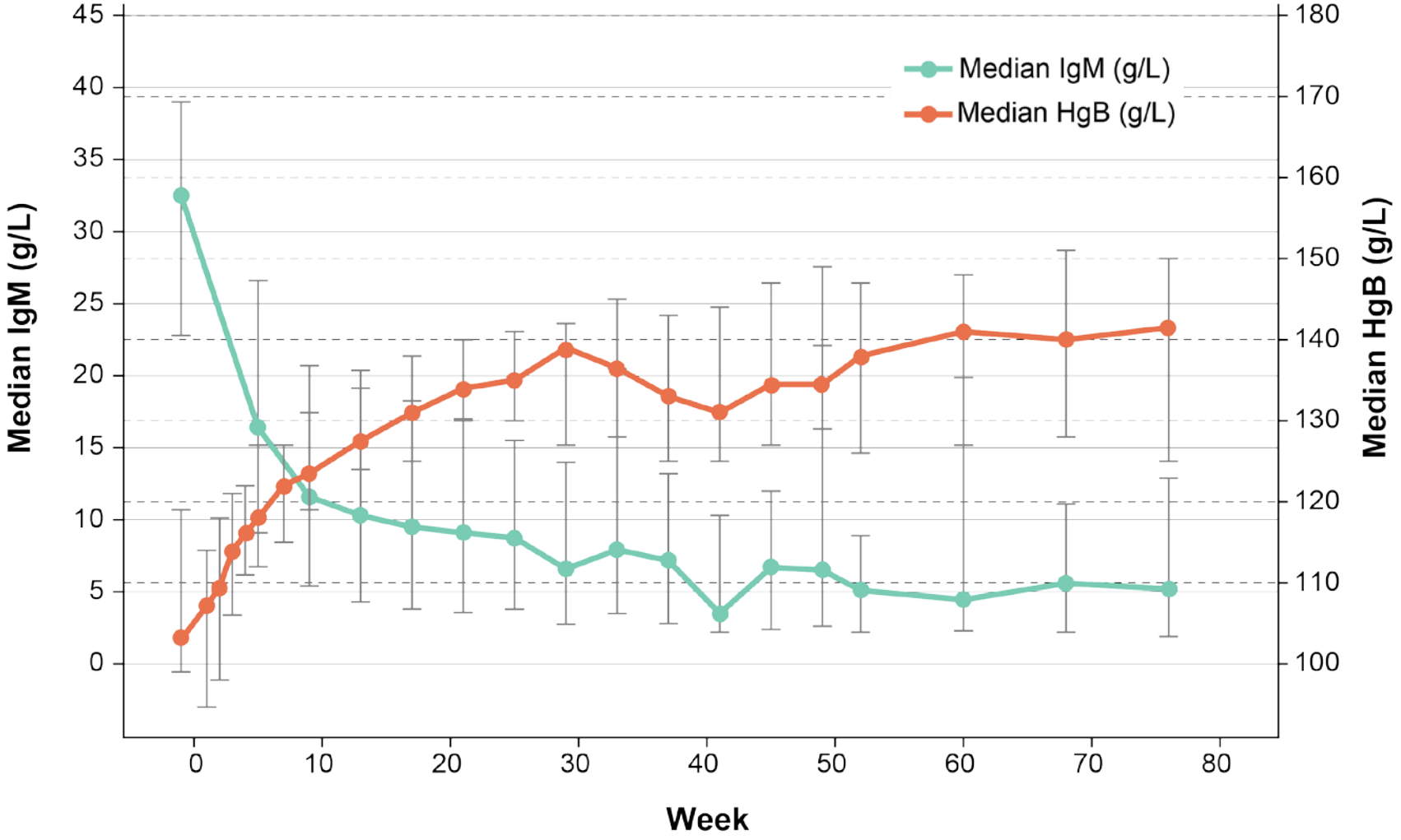
Owen RG, et al. *Br J Haematol.* 2013;160:171-176.

Efficacy Summary (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

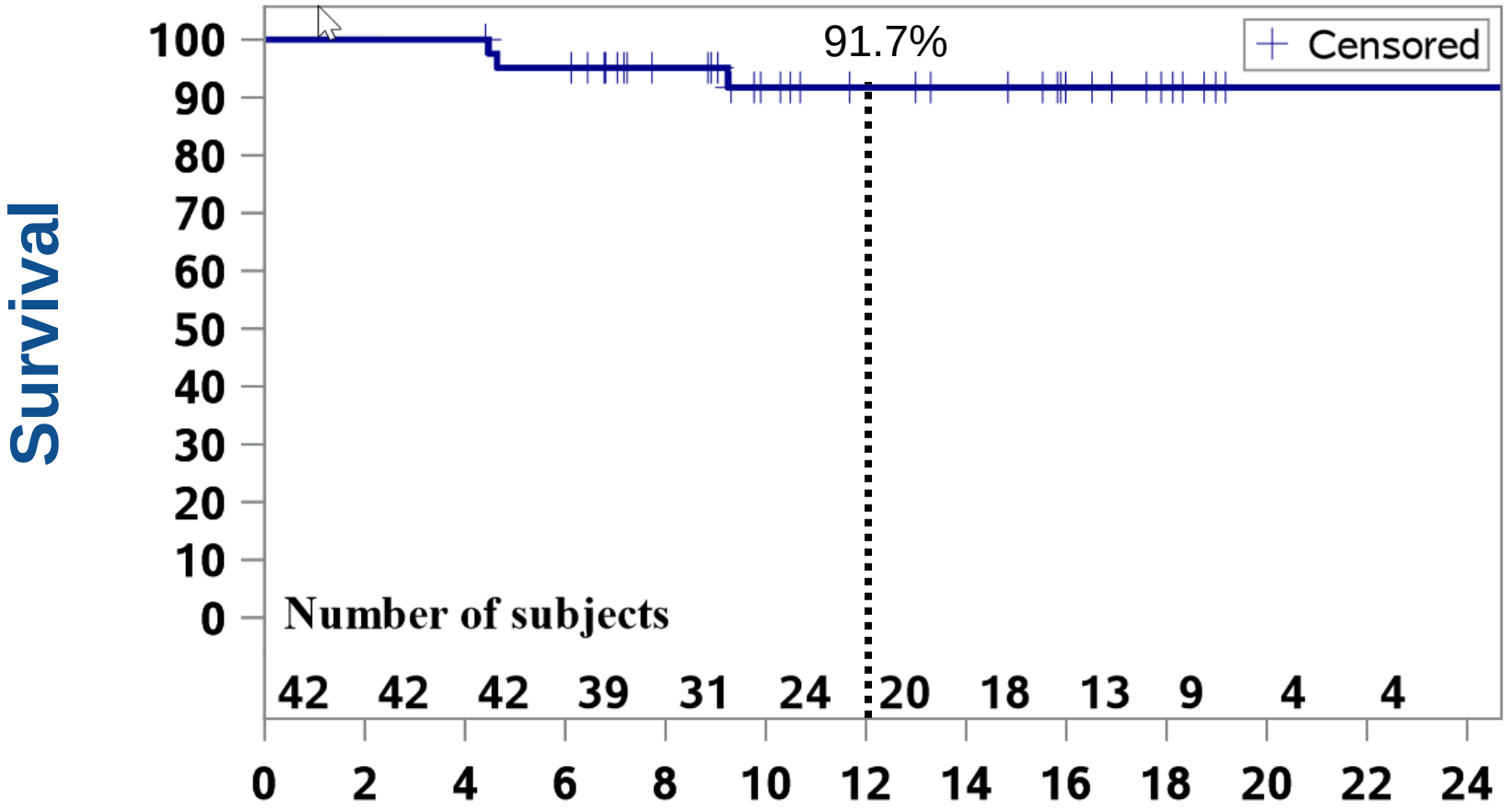
Decreased IgM and Improved Hemoglobin Levels over time



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

Progression-Free Survival



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

Conclusions

- BGB-3111, a highly selective oral BTK inhibitor achieves high plasma concentrations and complete BTK occupancy in blood and lymph nodes

- BGB-3111 is very well tolerated
  - To date: No treatment discontinuation due to BGB-3111 related toxicity
  - One AE-related death (due to pre-existing bronchiectasis, while in VGPR)
- Highly active in WM
  - Overall response rate 90%, with 43% VGPR

A Phase 3 trial comparing BGB-3111 to ibrutinib in WM is ongoing
Information on the Phase 3 trial of BGB-3111 vs ibrutinib (Abstract OT06) will be presented Thursday (today) at 18:05

Acknowledgments

- We would like to thank the investigators, site support staff and especially the patients for participating in this study

Backup

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

Efficacy Summary

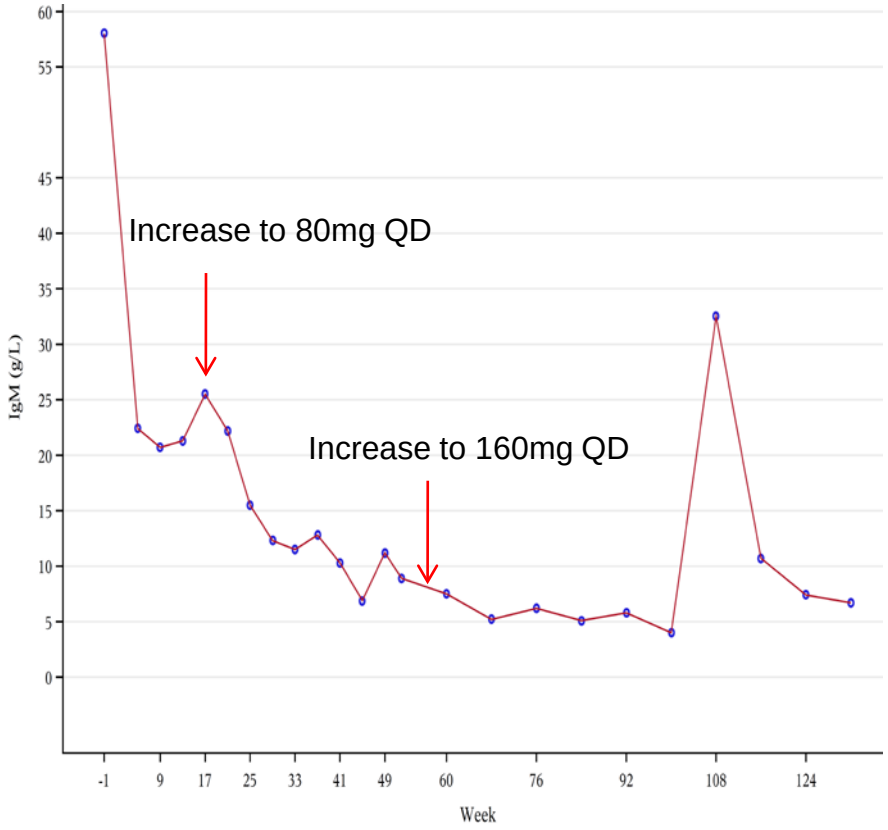
	TN N=9	Relasped/refractory N=33	Total N=42
Median follow-up (range)	9.3 months (6.1-11.7)	15.5 months (4.4-30.5)	12.3 months (4.4-30.5)
Best Response			
CR	0	0	0
VGPR	2 (22%)	16 (49%)	18 (43%)
PR	5 (56%)	9 (27%)	14 (33%)
MR	2 (22%	4 (12%)	6 (14%)
SD	0	4 (12%)	4 (10%)

90% ORR† **76% MRR***

* Major response rate.
† Overall response rate.

Intrapatient Dose Escalation

S401: Initial dose 40mg QD



S101: Initial dose 80mg QD