Zanubrutinib (BGB-3111) in NHL

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BTKi in Waldenstrom Macroglobulinemia

- First-generation BTK inhibitor Ibrutinib has shown activity in WM and become a standard of care
  - Major response rate: 73% (including 16% very good partial response)
  - 68% 3-year event-free survival

- INNOVATE Study confirmed superiority of ibrutinib + rituximab vs placebo + rituximab

Trotman, ICML 2017

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

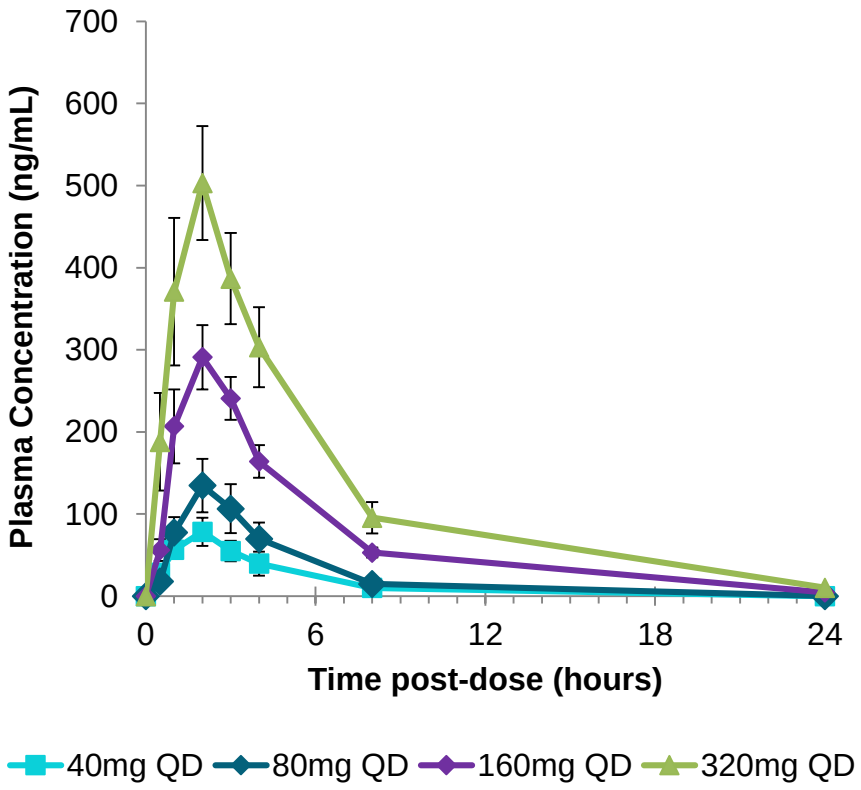
Eligibility:

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

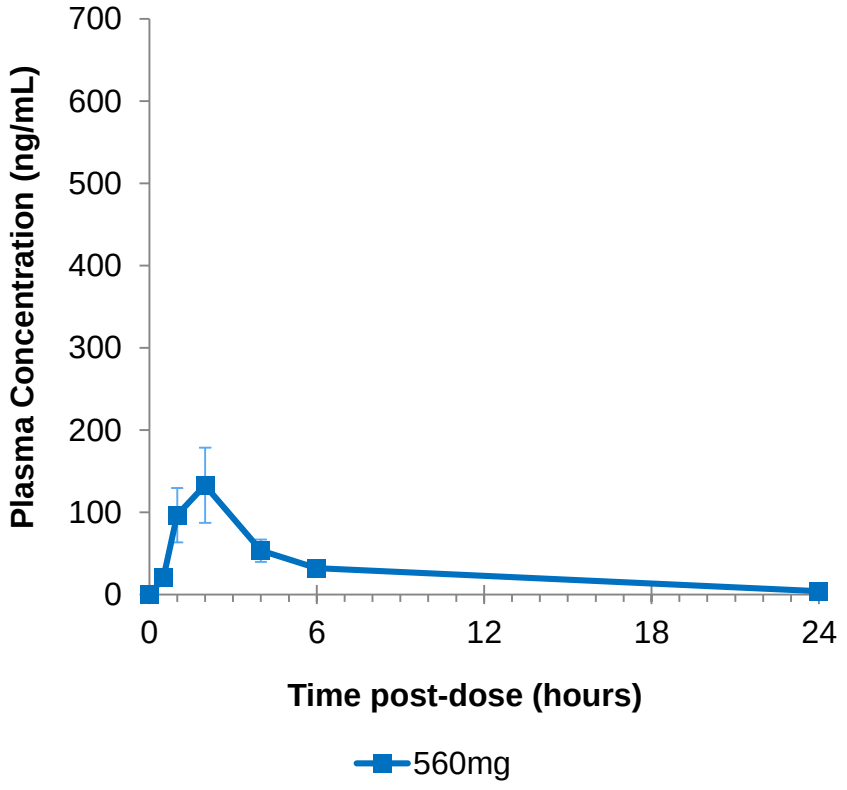
NCT02343120

Plasma Exposure Comparison for BGB-3111 and Ibrutinib

BGB-3111[1]



Ibrutinib

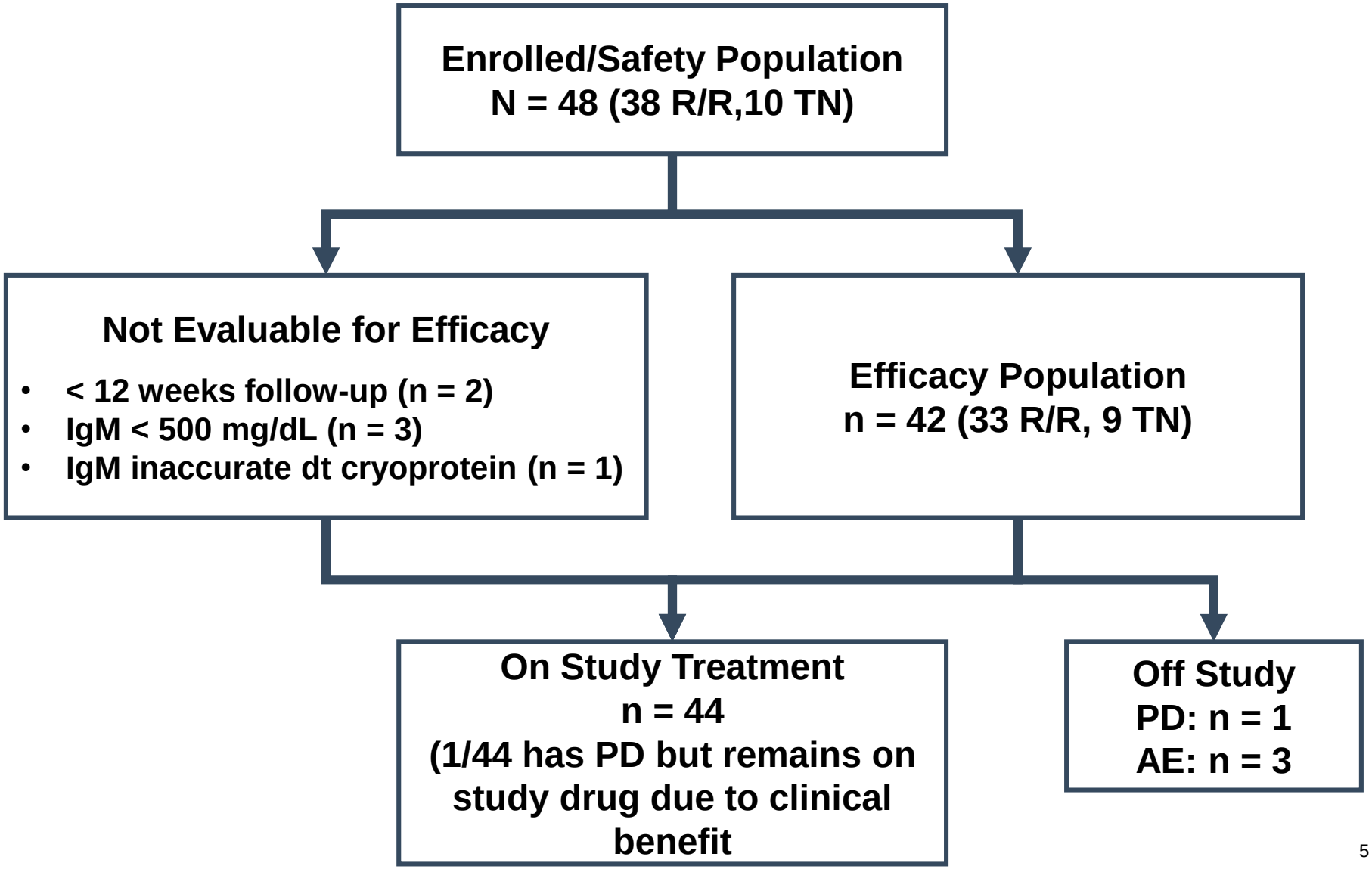


Adapted from Advani *et al*[2]

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

WM Patient Disposition

As of March 31, 2017



Patient Characteristics

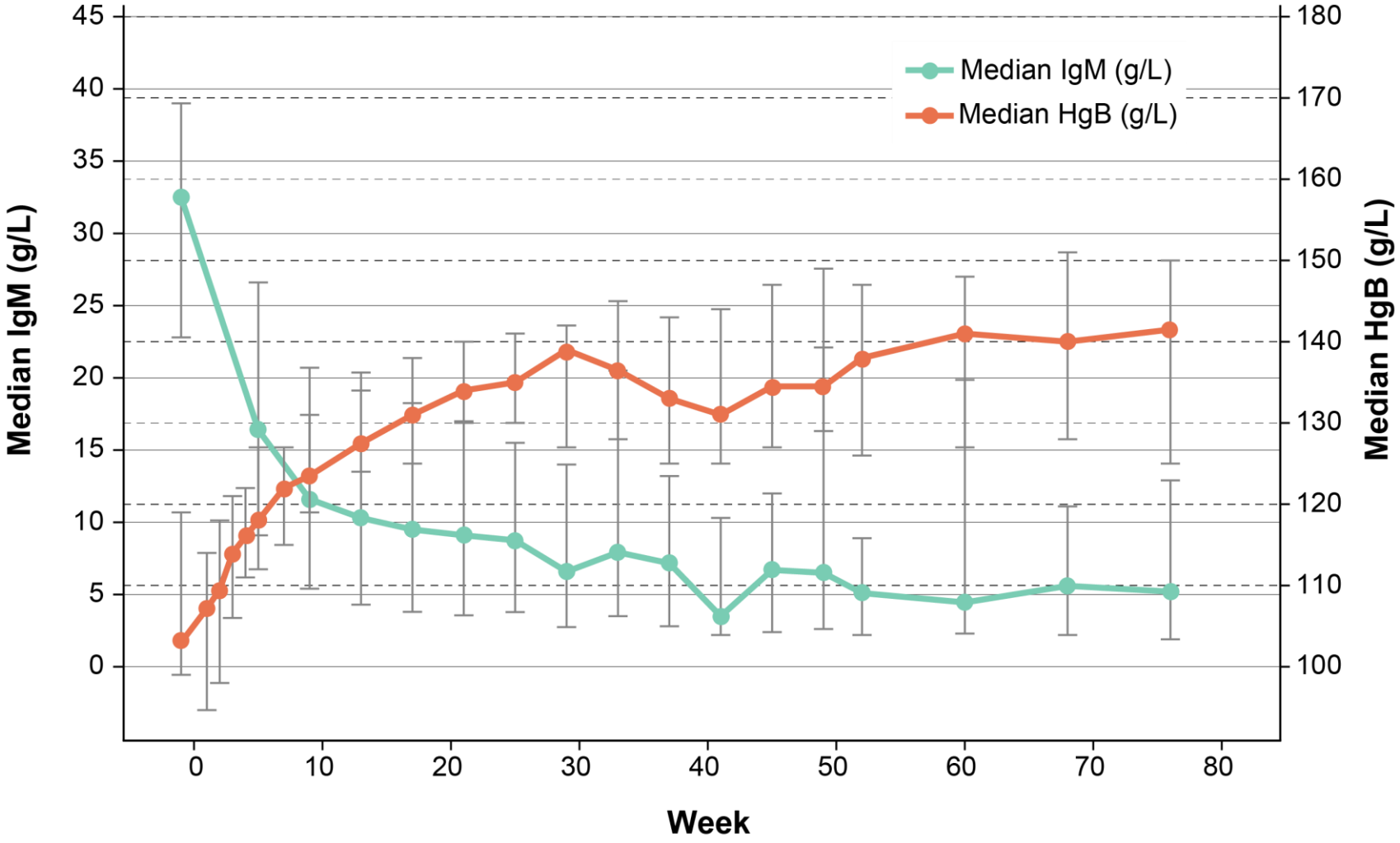
Characteristic	Total (N = 48)
Age, years, median (range)	66 (44-87)
ECOG Performance Status, n (%) 0 1	 14 (29) 34 (71)
Follow-up, months, median (range)	10.6 (1.4-30.5)
Prior Treatment Status, n (%) Treatment-naïve Relapsed/refractory Number of prior therapies, median (range) Prior rituximab (% R/R 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)

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

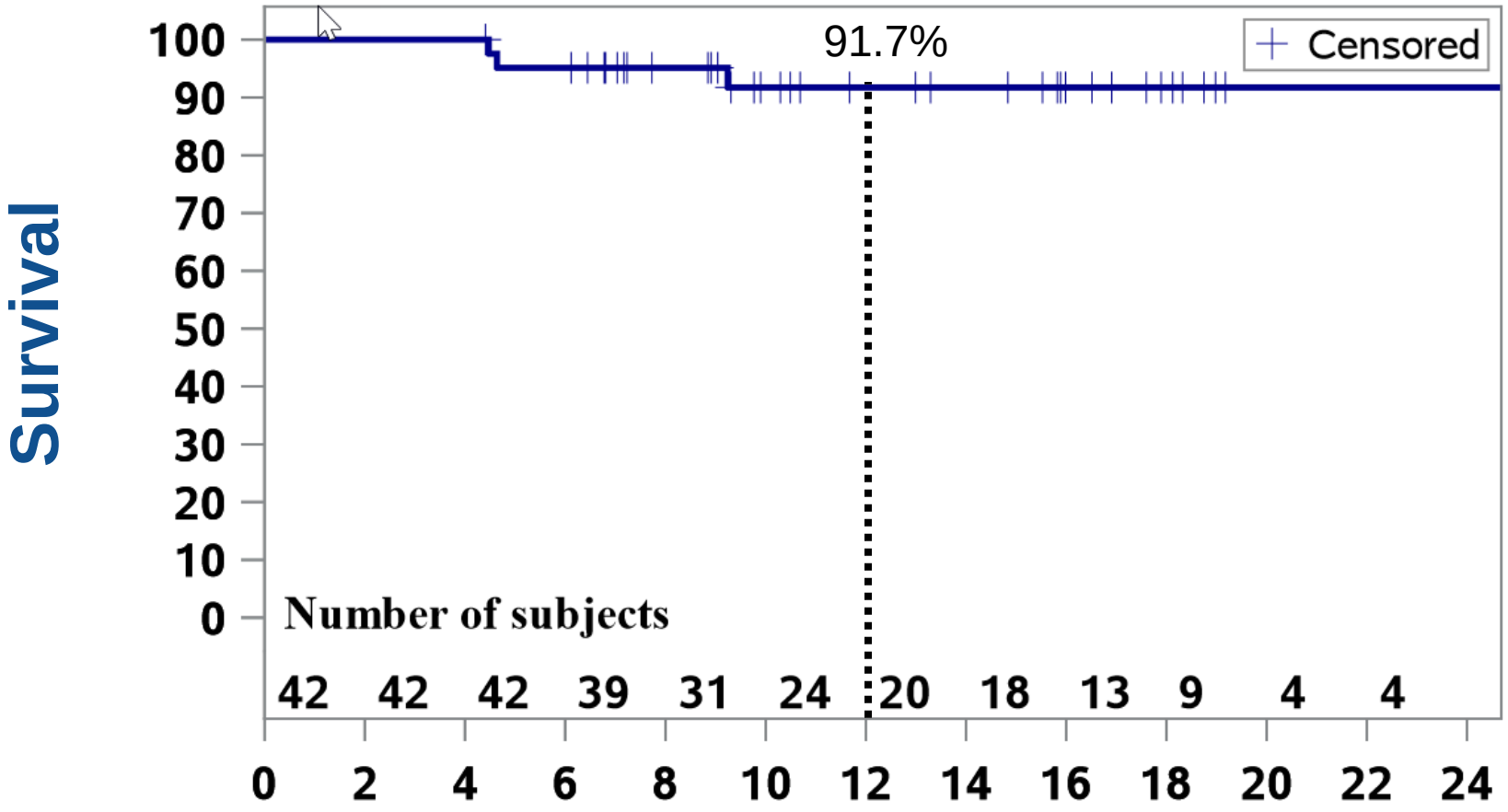
Decreased IgM and Improved Hemoglobin Levels over time



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}

BGB-3111 in Waldenstrom Macroglobulinemia

- Phase 3 Study of Zanubrutinib + Ibrutinib in WM now fully accrued.

Zanubrutinib in Other NHL

- Phase I data summarized and presented at ASH 2017:
  - **Aggressive lymphoma** including R/R DLBCL and MCL
  - **Indolent lymphoma** including FL and MZL

Trial Design: First-in-Human, Open-label, Multicenter, Phase 1b Study of Zanubrutinib in Patients With B-cell Malignancies

DOSE ESCALATION

Dose		Enrolled (indolent, aggressive)
40 mg	QD	4 (0, 1)
80 mg	QD	5 (0, 1)
160 mg	QD	6 (0, 2)
320 mg	QD	6 (0, 1)
160 mg	BID	4 (0, 2)

RP2D

320 mg QD or 160 mg BID

DOSE EXPANSION

Population	RP2D Dose	Disease	Planned
R/R	BID, QD	MCL, MZL, FL, GCB DLBCL	40
R/R	BID	Non-GCB DLBCL	40
R/R	BID	CLL/SLL	70
R/R	BID	WM	20
R/R	QD	CLL/SLL	20
R/R, TN	BID, QD	WM	50
R/R	BID, QD	MCL	20
TN	BID, QD	CLL/SLL	20
TN	BID, QD	MCL	20
R/R	BID, QD	HCL	10
R/R	BID	iNHL	40
R/R	BID	Richter Transform.	15
R/R or intolerant	BID	BTK-R/R WM	15

Eligibility:

- World Health Organization-defined B-cell malignancy
- No available higher priority treatment
- Eastern Cooperative Oncology Group 0-2
- ANC >1,000/µL, platelets >100,000/µL*
- Adequate renal and hepatic function
- No significant cardiac disease†

*Growth factor/transfusion allowed. †Anti-coagulation allowed.
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; Pop, population; RP2D, recommended phase 2 dose; QD, once daily; WM, Waldenström macroglobulinemia.

Patient Characteristics

Characteristic	Indolent (FL, MZL) n = 34	Aggressive (DLBCL, MCL) n = 65	Total N = 99
Age, years, median (range)	65 (41-79)	70 (20-86)	68 (20-86)
ECOG Performance Status, (%) 0 1 2	 16 (47) 15 (44) 3 (9)	 28 (43) 29 (45) 8 (12)	 44 (44) 44 (44) 11 (11)
Prior treatment status Treatment-naïve, n (%) Relapsed/refractory, n (%) Number of prior therapies, median (range)	 0 34 (100) 2 (1-8)	 2 (3) 63 (97) 2 (1-10)	 2 (2) 97 (98) 2 (1-10)
Bulky disease,* n (%)	0	3 (5)	3 (3)
Stage at Study Entry (per disease type) I II III IV	 2 (6) 3 (9) 7 (21) 22 (65)	 2 (3) 7 (11) 12 (18) 43 (66)	 4 (4) 10 (10) 19 (19) 65 (66)
LDH at baseline, median (range) in µkat/L	4.1 (2.2-23.1)	4.4 (2-77.6)	4.2 (2-77.6)
DLBCL: GCB vs. non-GCB†	-	4 vs. 23	-

* Any lymph node >10 cm in maximum diameter. †Defined by Hans algorithm.

DLBCL, diffuse large B-cell lymphoma; ECOG, Eastern Cooperative Oncology Group; GCB, germinal center B-cell like; LDH, lactate dehydrogenase; LN, lesion.[13]

Follicular and Marginal Zone Lymphomas: Best Responses

Response (based on CT for majority of pts)	**FL n = 17**	**MZL n = 9**	**Indolent Total N = 26**
Median efficacy follow-up, mo (range)	7.8 (1.9-22.3)	7 (2.8-22)	7.5 (1.9-22.3)
Best Response, n (%)			
ORR	**7 (41)**	**7 (78)**	**14 (54)**
CR	3 (18)	0	3 (12)
PR	4 (24)	7 (78)	11 (42)
SD	7 (41)	2 (22)	9 (35)
PD	1 (6)	0	1 (4)
NE*	2 (12)	0	2 (8)

CR, complete response; NE, not evaluable; ORR, overall response rate; PD, progressive disease; PR, partial response; PR-L, partial response with lymphocytosis; SD, stable disease.
* Both due to withdrawal of consent.

DLBCL and Mantle Cell Lymphoma: Best Responses

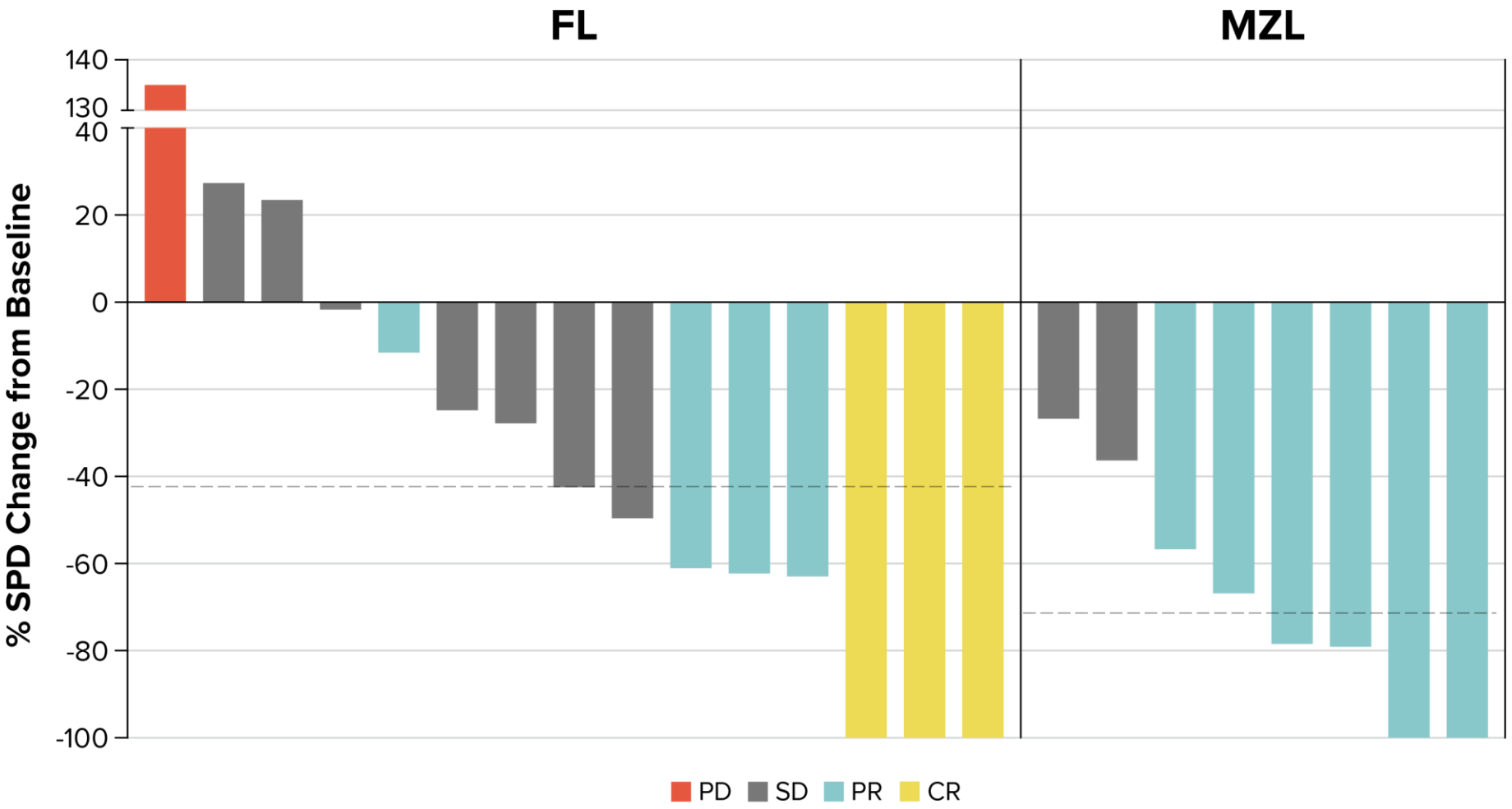
Response (based on CT for majority of pts)	DLBCL* n = 26	MCL*** n = 32	Aggressive Total N = 58
Median efficacy follow-up, mo (range)	4.2 (0.1-24)	9.5 (0.8-31.9)	5.6 (0.1-31.9)
Best Response, n (%)			
ORR	**8 (31)**	**28 (88)**	**36 (62)**
CR	4 (15)	8 (25)	12 (21)
PR	4 (15)	20 (63)	24 (41)
SD	4 (15)	1 (3)	5 (9)
PD	13 (50)	1 (3)	14 (24)
NE**	1 (4)	2 (6)	3 (5)

CR, complete response; NE, not evaluable; ORR, overall response rate; PD, progressive disease; PR, partial response; PR-L, partial response with lymphocytosis; SD, stable disease.
*ORR was 25% (1 of 4) and 32% (7 of 22) for GCB and non-CGB, respectively.
** n = 1 DLBCL withdrew consent, n = 2 MCL off study for adverse event before response assessment

*****In mantle cell patients treated with minimum of 320 mg/d ORR is 93% and CR is 28%**

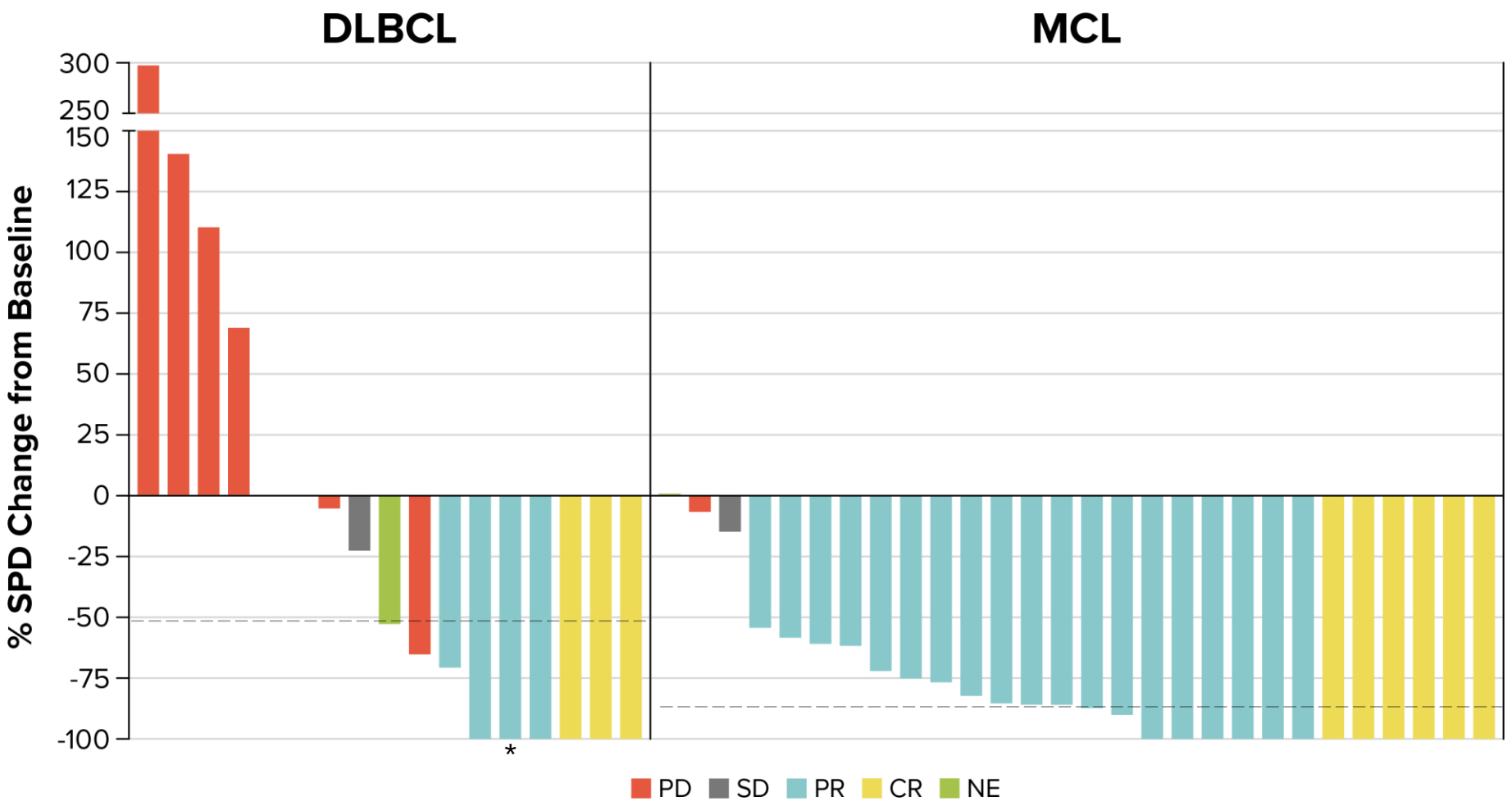
PET scanning not mandated for trial

Indolent Lymphoma (FL, MZL): SPD Response



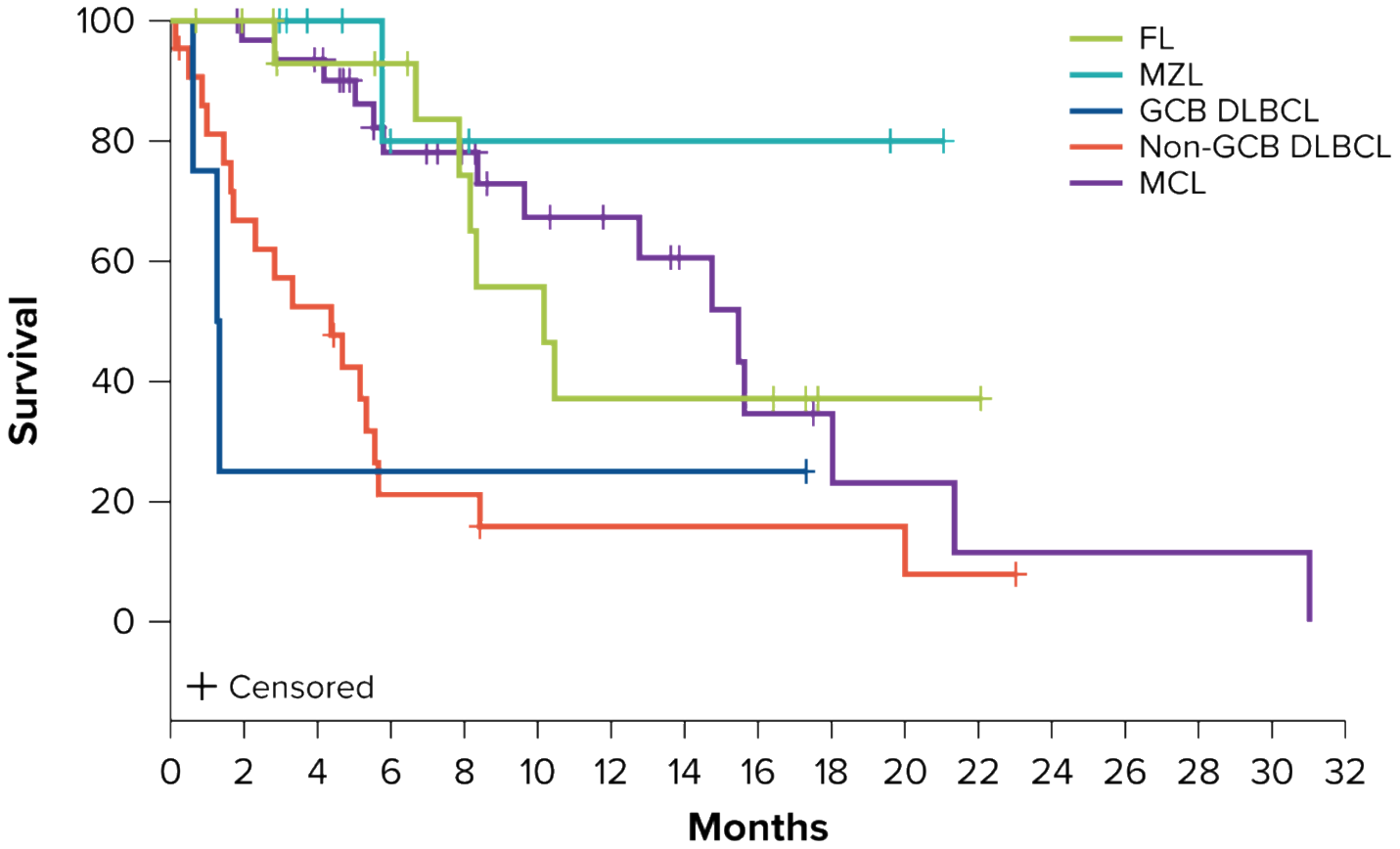
Note: 1 subject had no measurable lesions at baseline, 2 subjects did not have a post baseline scan.
Dashed lines = median reduction in SPD (-42% for FL, -73% for MZL).
SPD, sum of the products of lymph node diameters by CT scan.

Aggressive Lymphoma (DLBCL, MCL): SPD Response



*Patient had GBC-DLBCL.
Note: 4 subjects had no measurable lesions at baseline, 9 subjects did not have a post baseline scan.
Dashed lines = median reduction in SPD (-53% for DLBCL, -87% for MCL).
SPD, sum of the products of lymph node diameters by CT scan.

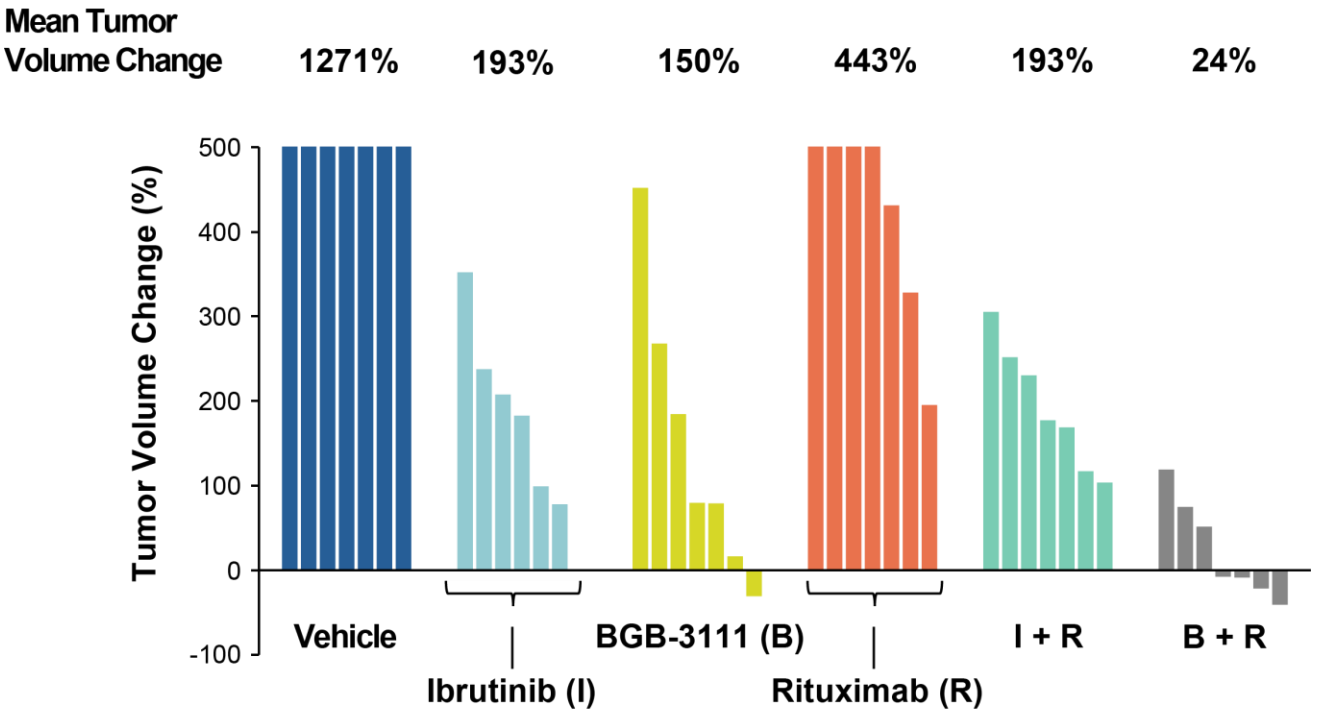
Progression-Free Survival



At risk (n)

FL	17	15	12	11	8	6	4	4	4	1	1	1	0				
MZL	9	9	6	3	3	2	2	2	2	2	1	0					
GCB DLBCL	4	1	1	1	1	1	1	1	1	0							
Non-GCB DLBCL	22	14	11	4	4	2	2	2	2	2	2	1	0				
MCL	32	30	28	19	16	12	10	7	4	3	2	1	1	1	1	1	0

BGB-3111 Does Not Impair Rituximab-Induced ADCC



- Published preclinical data suggest that off-target effects of ibrutinib may be detrimental to CD20 mAb-induced ADCC and the activity of the combination
- In a human MCL xenograft model, the combination of BGB-3111 and CD20 antibody demonstrated improved anti-tumor activity as compared to monotherapies and combination of ibrutinib and CD20 antibody

[1] Li N, et al. *Cancer Res.* 2015;75:2597 [abstract].

Study Design: BGB-3111 in Combination with Obinutuzumab

DOSE ESCALATION

Cohort	BGB-3111* (D1-28/28-day cycles)	Obinutuzumab	Patients Dosed
1a	320 mg QD	Cycle 1 D2: 100 mg Cycle 1 D3: 900 mg Cycle 1 D9 and D16: 1000 mg Cycles 2-6 D1: 1000 mg	4
1b	160 mg BID		5

* BGB-3111 treatment continued until progression, death, or unacceptable toxicity.
† Cohort -1a and -1b will be opened if 2 or more DLTs are observed in Cohorts 1a and 1b.

Eligibility:

- WHO defined B cell lymphoid malignancy
- ≥1 prior therapy (relapsed cohorts only)
- No available higher priority treatment
- ECOG 0-2
- ANC >1,000/µl, platelets >40,000/µl‡
- Adequate renal and hepatic function
- No significant cardiac disease§

‡ Growth factor/transfusion allowed.
§Anti-coagulation allowed.

DOSE EXPANSION

Pop	Disease	Planned
TN	CLL/SLL	20
R/R	CLL/SLL	20
R/R	non-GCB DLBCL	20
R/R	FL, MCL, MZL, and WM	20
R/R	FL	40

NCT02569476

Reduced IRR with BGB-3111 + Obinutuzumab

Adverse Events of Special Interest

Event, n (%)	CLL/SLL (n = 45)		FL (n = 26)	
	All Grade	Grade ≥ 3	All Grade	Grade ≥ 3
Diarrhea	9 (20.0)	0	3 (11.5)	0
Serious hemorrhage*	0	0	0	0
Atrial fibrillation	0	0	0	0
Hypertension	3 (6.7)	1 (2.2)	1 (3.8)	1 (3.8)
Infusion-related reactions	11 (24.4)	1 (2.2)	2 (7.7)	0

* ≥ Grade 3 hemorrhage, or central nervous system hemorrhage of any grade.

Zanubrutinib + Obinutuzumab : Responses

	TN CLL/SLL (n = 20)	R/R CLL/SLL (n = 25)	FL (n = 21)
Median follow-up, mo (range)	11.4 (6.0-17.3)	12.7 (7.9-19.5)	12.1 (0.8-19.7)
Best Response, n (%)			
ORR	**19 (95.0)**	**23 (92.0)**	**16 (76.2)**
CR	7 (35.0)	5 (20.0)	8 (38.1)
PR	12 (60.0)	18 (72.0)	8 (38.1)
SD	1 (5.0)	1 (4.0)	2 (10.0)
PD	0	1 (4.0)	3 (15.0)

CLL/SLL, chronic lymphocytic leukemia/small lymphocytic lymphoma; CR, complete response; FL, follicular lymphoma; ORR, overall response rate; PD, progressive disease; PR, partial response; PR-L, partial response with lymphocytosis; R/R, relapsed/refractory; SD, stable disease; TN, treatment-naïve.

- ORR in patients with high-risk CLL/SLL
  - del17p/p53mut (n = 6): 83.3%
  - del11q (n = 6): 100%
  - Unmutated *IGHV* (n = 19): 94.7%

Conclusions: Other NHL

- Activity in MCL is as expected for a potent BTK inhibitor
  - no clear efficacy advantages over ibrutinib and acalabrutinib
- High activity in MZL (ORR 78%)
  - Phase 2 study currently underway
- Obinutuzumab combination promising in follicular lymphoma
  - Phase 2 Zanu + GA101 vs GA101 underway