Next Generation BTK Inhibitors: BGB-3111

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BGB-3111: Kinase Selectivity Relative to Ibrutinib

Equipotent against BTK compared to ibrutinib
Higher selectivity vs EGFR, ITK, JAK3, HER2 and TEC

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

BGB-3111 First-in-Human Study

Part 1

Dose Escalation → **RP2D**

Cohort	Dose	n	# CLL/SLL Patients
1	40 mg QD	4	0
2	80 mg QD	5	0
3	160 mg QD	6	2
4a	320 mg QD	6	1
4b	160 mg BID	4	1

Eligibility:
- WHO defined B cell malignancy
- >1 prior therapy (relapsed cohorts only)
- No available higher priority treatment
- ECOG 0-2
- ANC >1,000/ul, platelets >100,000/ul[1]
- Adequate renal and hepatic function
- No significant cardiac disease[2]

[1] Growth factor/ transfusion allowed
[2] Anti-coagulation allowed

Part 2a (paired LN biopsy)

QD, 20 R/R MCL, MZL, FL, GCB DLBCL

BID, 20 R/R MCL, MZL, FL, GCB DLBCL

Part 2b

BID, R/R non-GCB DLBCL, n=20

Part 2c

BID, R/R CLL/SLL, n=20

Part 2d

BID, R/R WM, n=20

Part 2e

QD, R/R CLL/SLL, n=20

Part 2f

QD, TN & R/R WM, n=20

Part 2g

QD, R/R MCL, n=20

Part 2h

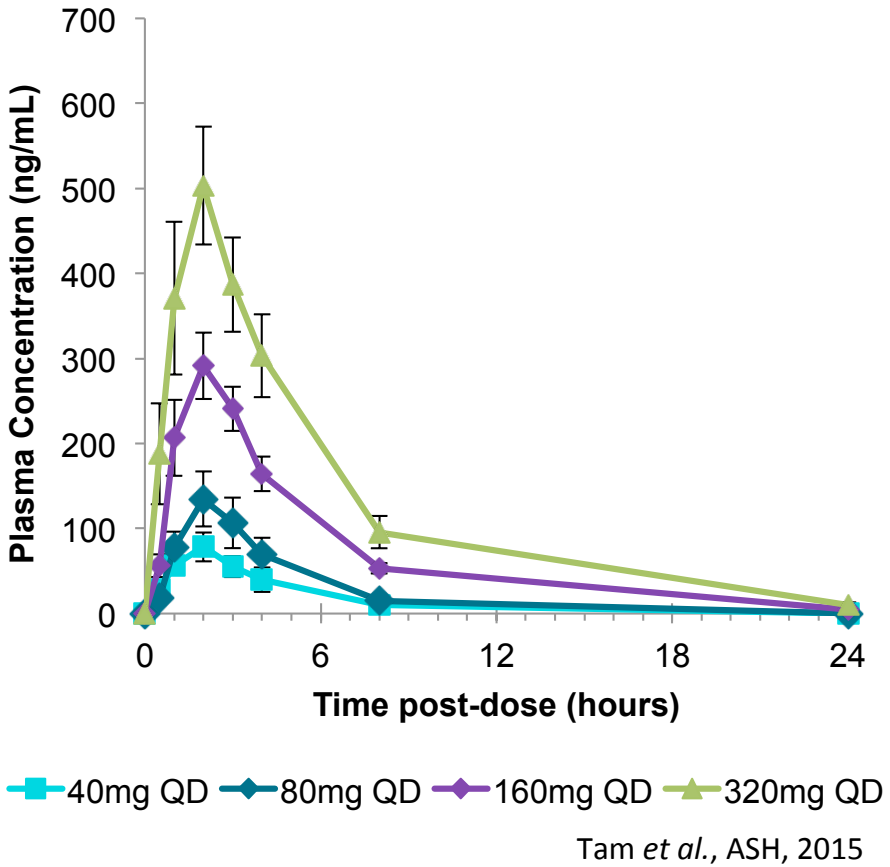
QD, TN CLL/SLL, n=20

Part 2i

QD, TN MCL, n=20

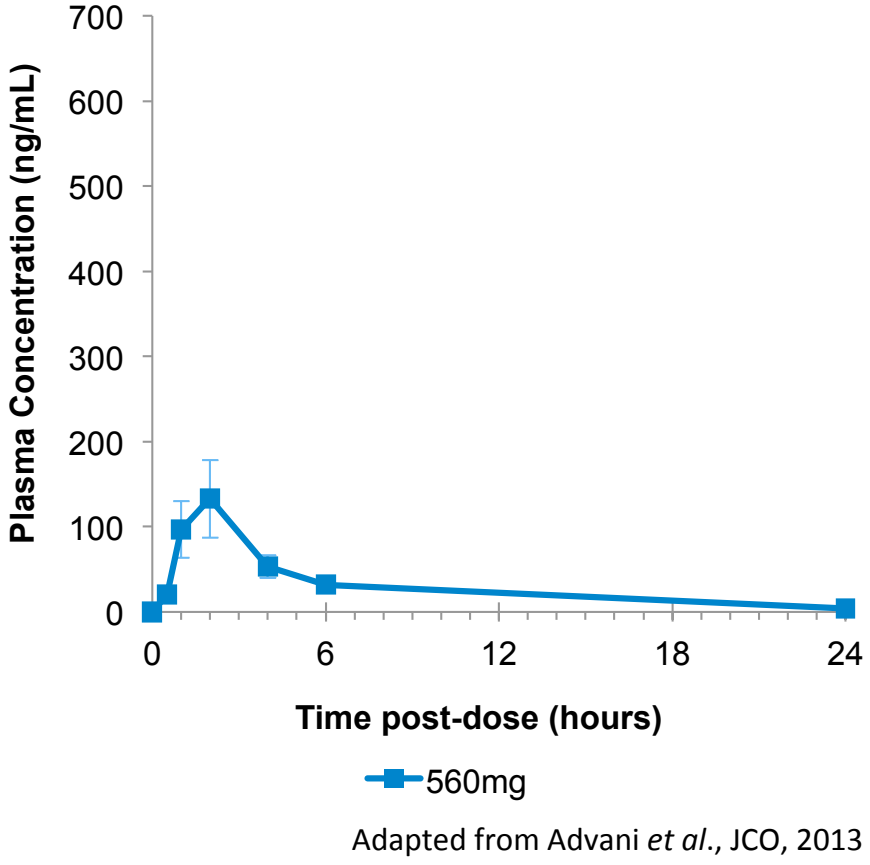
Plasma Exposure Comparison for BGB-3111 & Ibrutinib

BGB-3111



Tam *et al.*, ASH, 2015

Ibrutinib

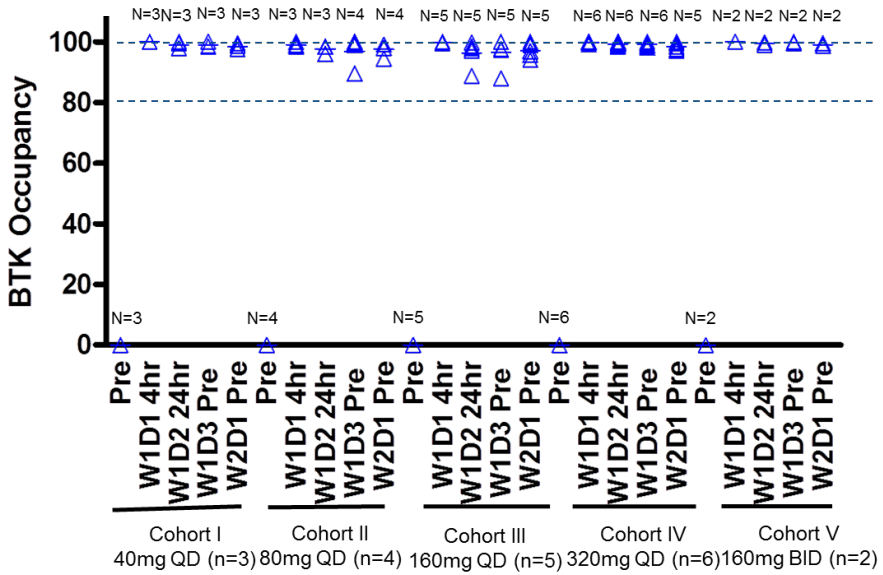


Adapted from Advani *et al.*, JCO, 2013

- C_{max} and AUC of BGB-3111 at 80 mg is similar to those of ibrutinib at 560 mg
- Free drug exposure of BGB-3111 at 40 mg is comparable to that of ibrutinib at 560 mg

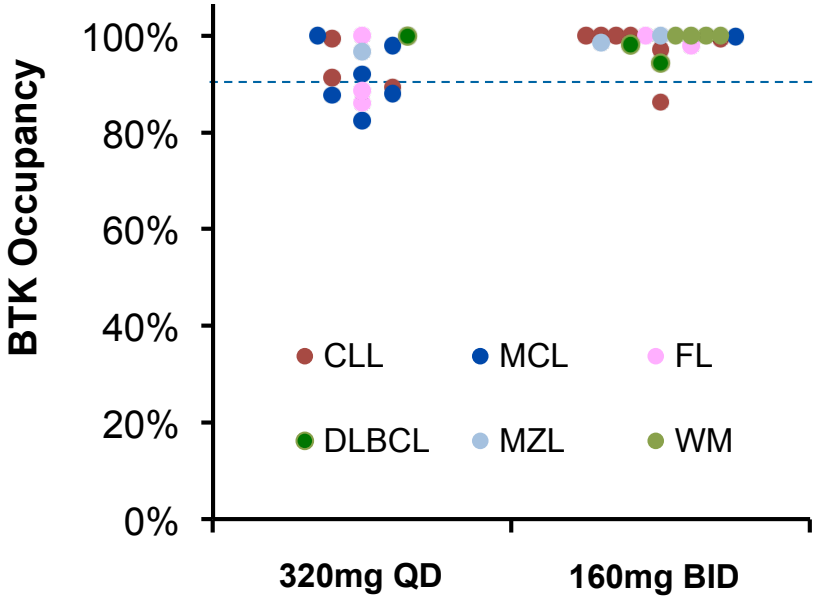
Complete and Sustained BTK Occupancy in PBMC and Lymph Node

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
- Proportion >90% trough occupancy: 94% (160mg BID) vs 58% (320mg QD), p=0.027

Phase I CLL/ SLL: Patient Characteristics

Characteristic	Total (N = 69)
Age, years, median (range)	68 (24-87)
ECOG Performance Status, n (%) 0 1 2	 34 (49) 33 (48) 2 (3)
Follow-up, months, median (range)	10.3 (0.4-26.8)
Prior treatment status Treatment-naïve, n (%) Relapsed/refractory, n (%) Number of prior therapies, median (range)	 18 (26) 51 (74) 2 (1-7)
Bulky disease,* n (%)	4 (6)
Molecular risk factors, n (%) del17p/p53mut (n = 51) 11q- (n = 44) IgHV unmutated (n = 16)	 20 (39) 14 (32) 11 (69)

ECOG, Eastern Cooperative Oncology Group; LN, lesion.

* Any lymph node >10 cm in maximum diameter.

CLL / SLL: Most Frequent Adverse Events (> 10%) Independent of Causality (N = 69)

Adverse Event	All Grade		Grade 3-4	
	n (pts)	% (N = 69)	n (pts)	% (N = 69)
Petechiae/purpura/contusion	32	46%	1	1%
Fatigue	20	29%	0	0%
Upper respiratory tract infection	19	28%	0	0%
Cough	16	23%	0	0%
Diarrhea	15	22%	0	0%
Headache	13	19%	0	0%
Hematuria	10	15%	0	0%
Nausea	9	13%	0	0%
Rash	9	13%	0	0%
Arthralgia	8	12%	0	0%
Muscle spasms	8	12%	0	0%
Urinary tract infection	8	12%	0	0%

pts, patients.

CLL / SLL : Adverse Events of Interest

	SAE	n (pts)	% (N = 69)	Grade	Led to Treatment Discontinuation
Purpura (subcutaneous hemorrhage)	Y	1	1%	G3	No
Diarrhea	Y	1	1%	G2	No
Atrial fibrillation	N	1	1%	G2	No

- A total of 18 SAEs were experienced by 13 patients
  - Additional SAE's not listed in **Table 4** (1 each) were also reported: CLL, delirium, febrile neutropenia, Invasive ductal breast carcinoma, lower respiratory tract infection, pleural effusion, renal colic, sepsis, splenectomy, splenomegaly, painful swelling in right neck, cardiac failure, coronary artery stenosis, ventricular extrasystole, pneumonia, and hemorrhoidal infection

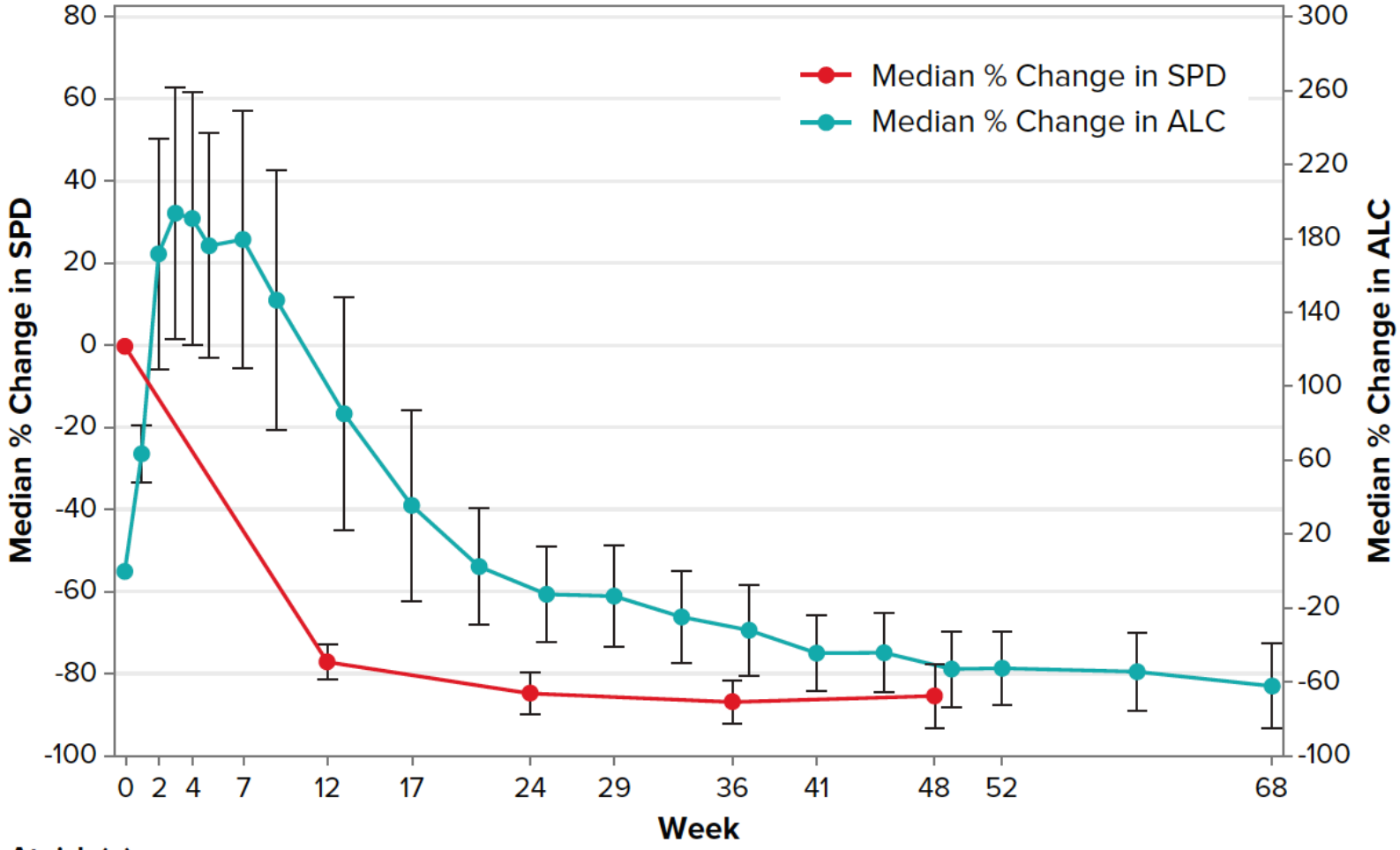
CLL/ SLL: Response

Response	Treatment Naïve (n = 16)	Relapsed/Refractory (n = 50)	Total (n = 66)
Median follow-up, mo (range)	7.6 (3.7-11.6)	14.0 (2.2-26.8)	10.5 (2.2-26.8)
Best Response			
ORR	**16 (100%)**	**46 (92%)**	**62 (94%)**
CR	1 (6%)	1 (2%)	2 (3%)
PR	13 (81%)	41 (82%)	54 (82%)
PR-L	2 (13%)	4 (8%)	6 (9%)
SD	0	3 (6%)	3 (5%)
D/C prior to assessment	0	1 (2%)	1 (2%)

CR, complete response; D/C, discontinuation; ORR, overall response rate; PR, partial response; PR-L, partial response with lymphocytosis; SD, stable disease.

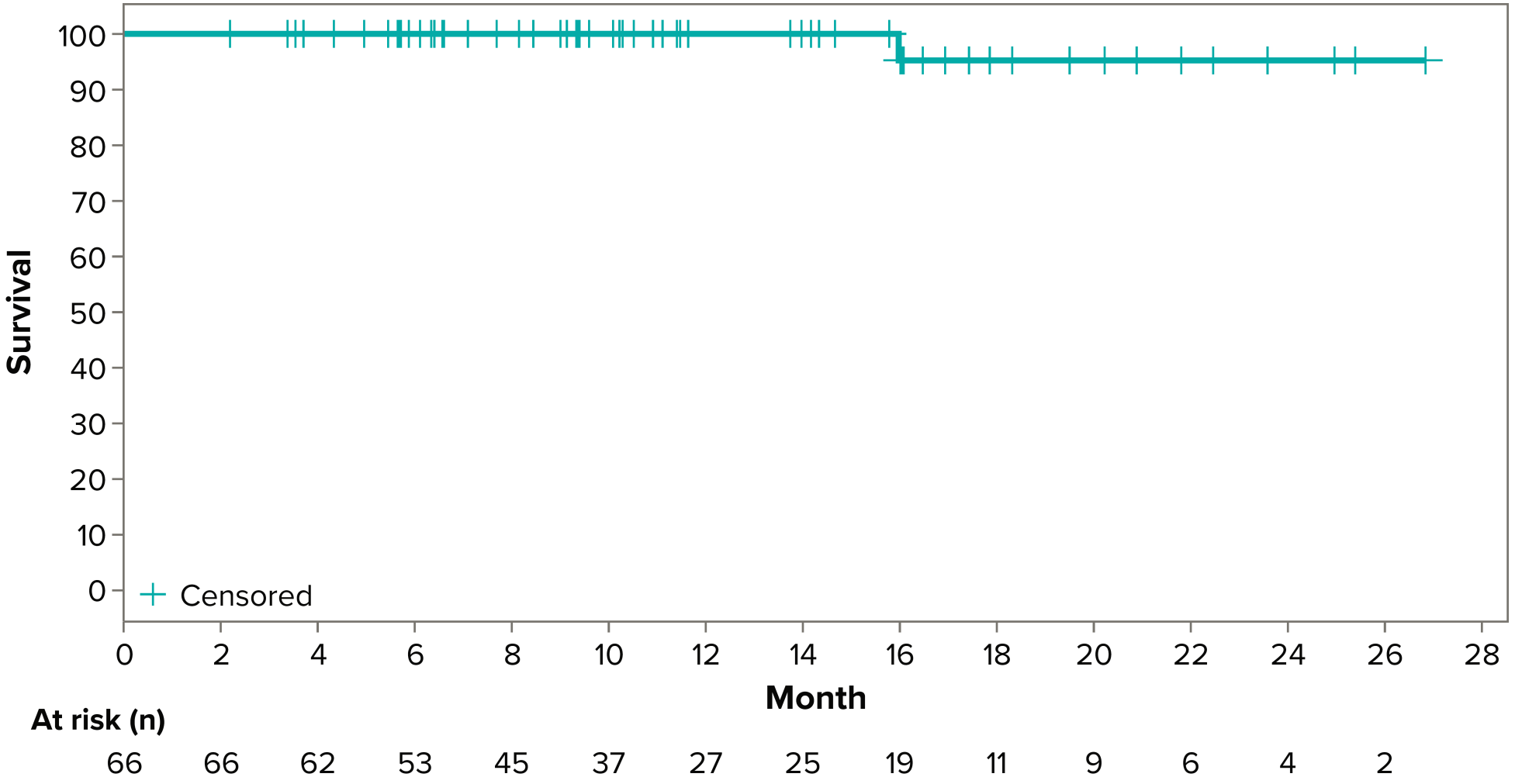
- The ORR in patients with del17p and/or 11q- (n = 22) was 96%

CLL/ SLL: Kinetics of ALC and SPD Response



Note: Error bars represent 95% confidence intervals; 4 patients with SPD data at week 37 were combined with 34 patients with SPD data at week 36; 2 patients with SPD data at week 49 were combined with 26 patients with SPD data at week 48.
ALC, absolute lymphocyte count; SPD, sum of the products of lymph node diameters by CT scan.

CLL / SLL: Progression-Free Survival



Efficacy Summary in WM (n = 42)

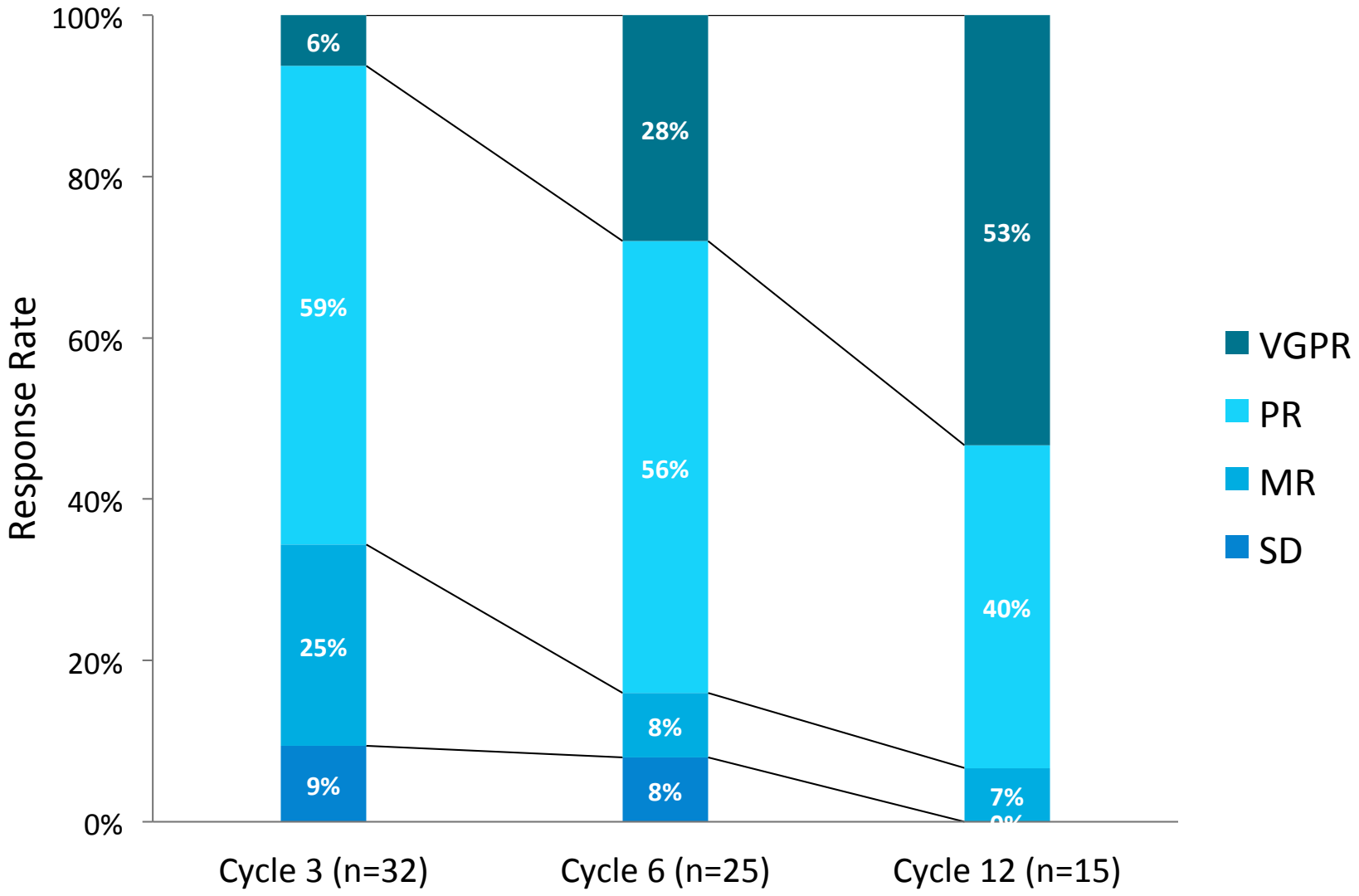
	Total
Median follow-up (range)	12.3 months (4.4-30.5)
Best Response (n = 42)	
CR	0
VGPR	18 (43%)
PR	14 (33%)
MR	6 (14%)
SD	4 (10%)
IgM reduction (median, %)	32.7 g/L to 6.1 g/L (81.3%)
Hemoglobin change (median)	104.5 g/L to 142 g/L
Lymphadenopathy reduction by CT (n, range)	45.5% (median) (16, 18.2%-81.4%)

90% ORR†

76% MRR*

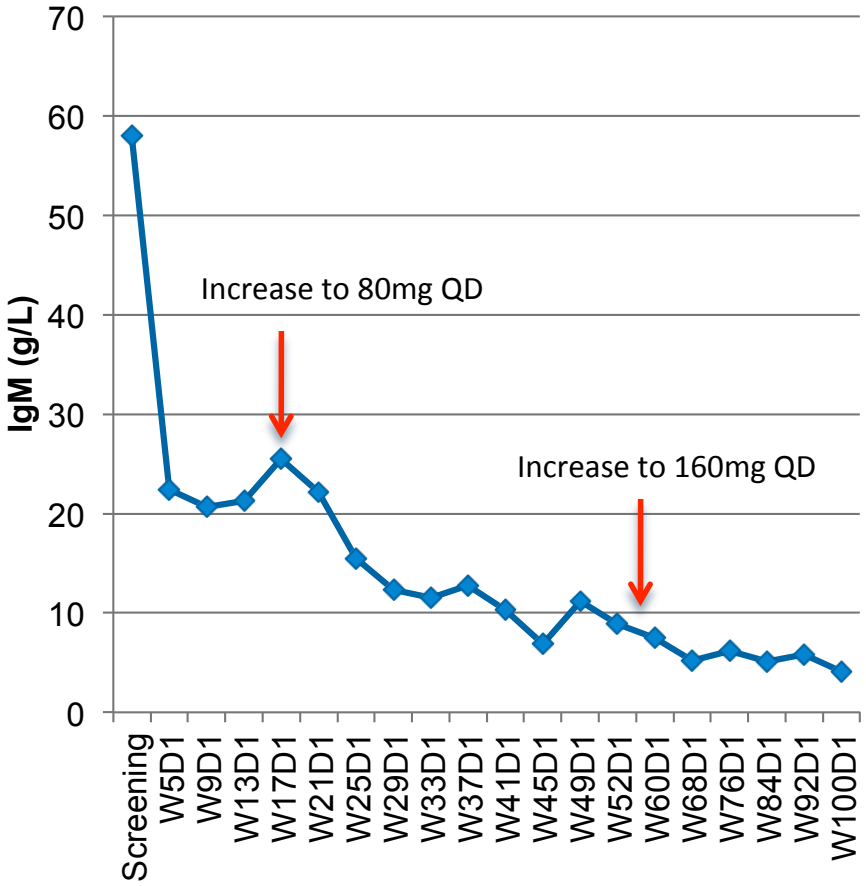
† Overall response rate
* Major response rate

IWWM Response Over Time on Treatment

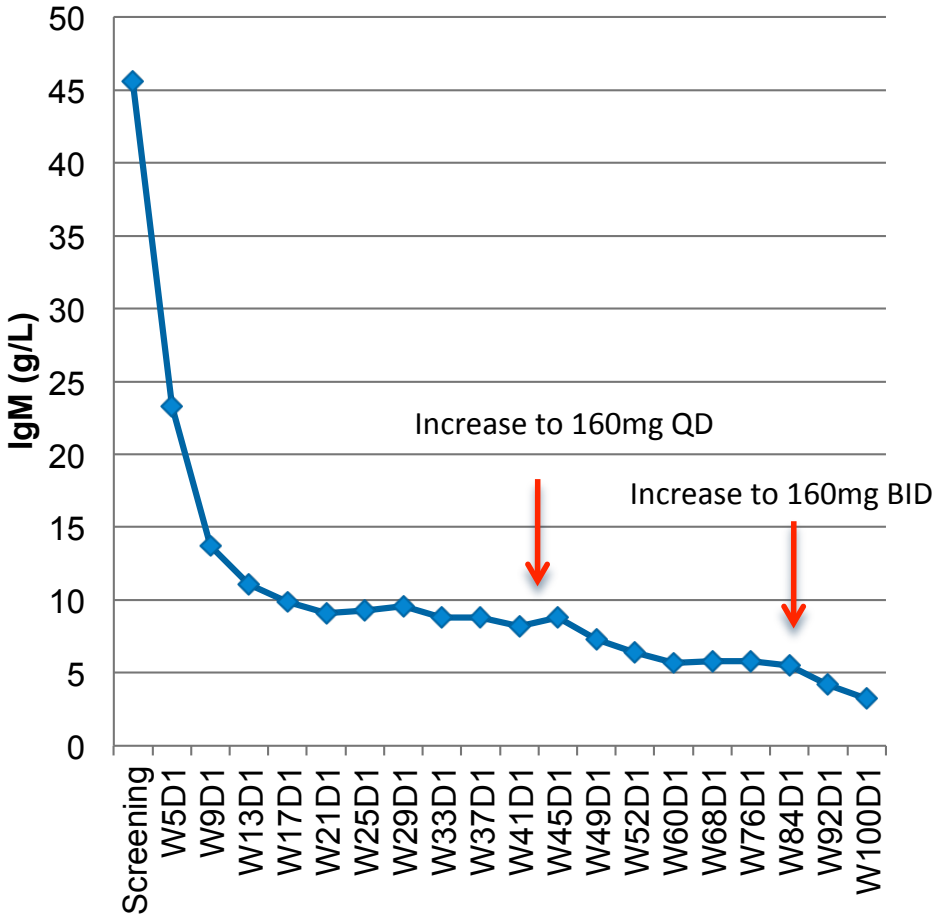


WM: Intrapatient Dose Escalation

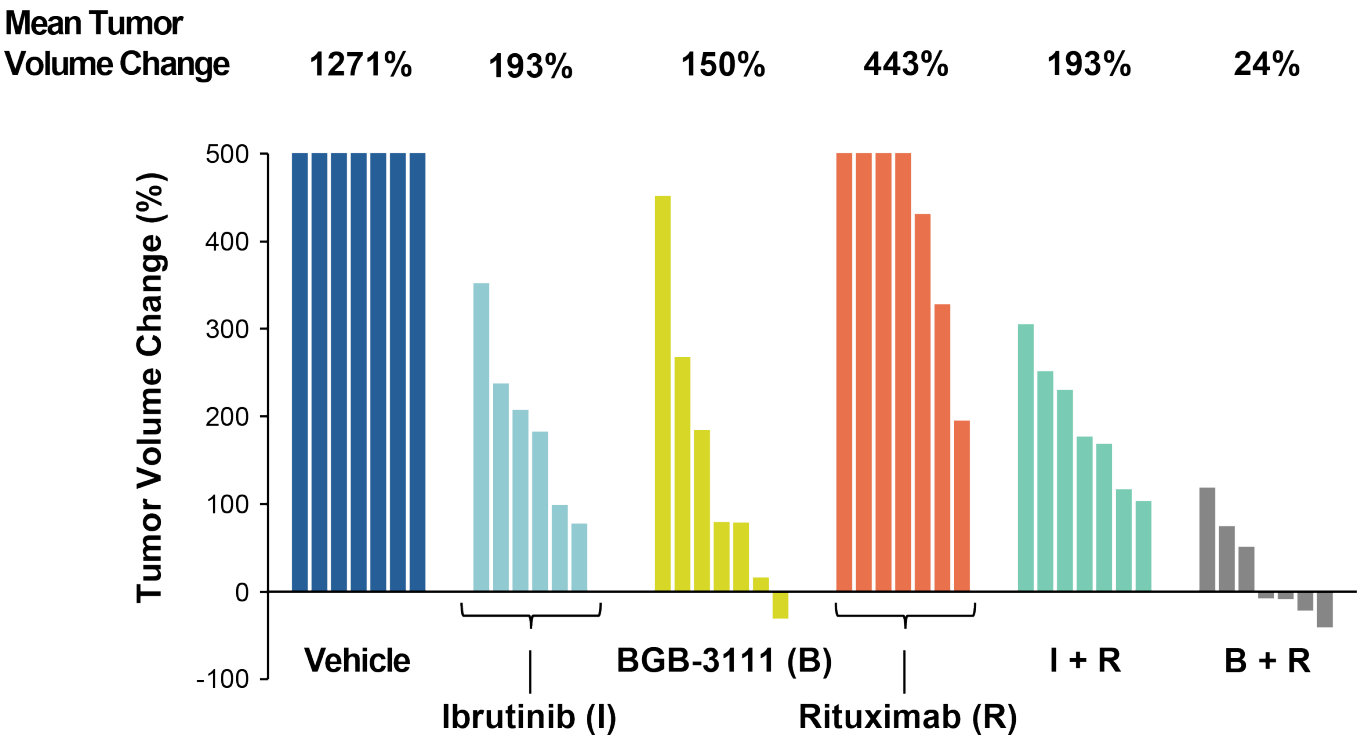
S401: Initial dose 40mg QD



S101: Initial dose 80mg QD



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

BGB-3111 + GA101: Selected Adverse Events

Event, n (%)	CLL/ SLL (n = 45)	FL (n = 17)
Patients with at least one AE Grade ≥3	19 (42.2)	4 (23.5)
Patients with at least one SAE	11 (24.4)	4 (23.5)
Events leading to treatment discontinuation	1 (2.2)*	0

* Patient with a history of squamous cell carcinoma discontinued due to squamous cell carcinoma

AE of Special Interest, n (%)	CLL/SLL (n = 45)		FL (n = 17)	
	All Grade	Grade 3-4	All Grade	Grade 3-4
Diarrhea	7 (15.6)	0	3 (17.6)	0
Serious hemorrhage*	0	0	0	0
Atrial fibrillation	0	0	0	0
Infusion-related reactions	11 (24.4)	1 (2.2)	1 (5.9)	0

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

BGB-3111 + GA101: Disease Response

Follow-up and Response	TN CLL/SLL (n = 18)	R/R CLL/SLL (n = 25)	FL (n = 15)
Median follow-up, mo (range)	7.0 (2.8-11.8)	8.0 (3.8-14.0)	6.2 (1.2-10.7)
Best Response			
ORR	**16 (88.9)**	**23 (92.0)**	**11 (73.3)**
CR	4 (22.2)	4 (16.0)	5 (33.3)
PR	12 (66.7)	19 (76.0)	6 (40.0)
PR-L	0	0	N/A
SD	2 (11.1)	1 (4.0)	2 (13.3)
PD	0	1 (4.0)	2 (13.3)

Registration Studies

- WM : Phase 3 BGB-3111 vs Ibrutinib (1L/RR)
- CLL : Phase 3 BGB-3111 vs Benda-Ritux (1L)
- FL : Phase 2R BGB-3111 + Obinutuzumab vs Obinutuzumab (RR)