Zanubrutinib (BGB-3111) in CLL

Constantine Tam

St Vincent's Hospital
Peter MacCallum Cancer Center
University of Melbourne

Rationale for Next Generation BTKi

- Improved selectivity may reduce side-effects
  - Diarrhea, Rash (EGFR)
  - Bleeding
  - Atrial fibrillation
- May combine better with anti-CD20 antibodies due to lack of ITK effect
- However, all currently available drugs bind to C481 on BTK, and are susceptible to BTK and PLCy mutations

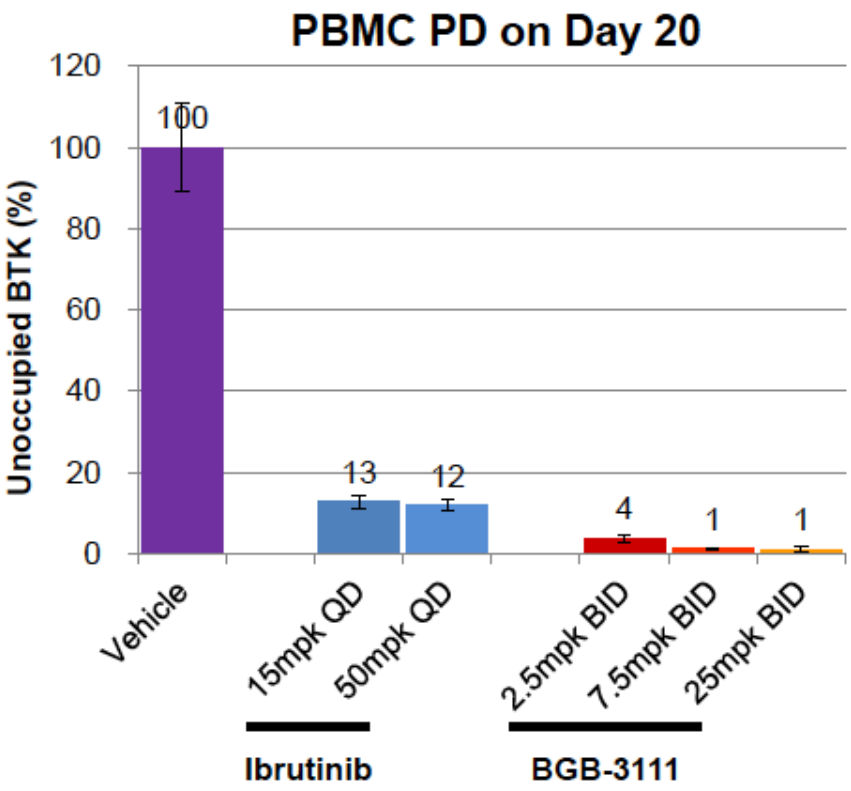
BGB-3111 Kinase Selectivity

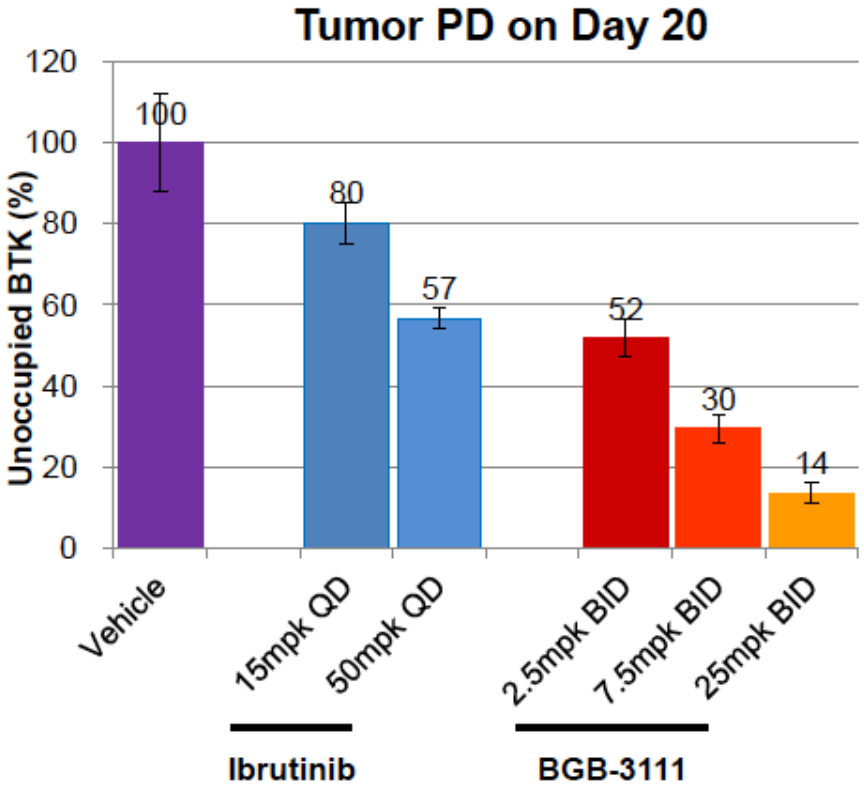
Targets	Assays	Ibrutinib IC_{50} (nM)	BGB-3111 IC_{50} (nM)	Ratio (BGB-3111:Ibrutinib)
BTK	BTK-pY223 Cellular Assay	3.5	1.8	0.5
	Rec-1 Proliferation	0.34	0.36	1.1
	BTK Occupation Cellular Assay	2.3	2.2	1.0
	BTK Biochemical Assay	0.2	0.22	1.1
EGFR	p-EGFR HTRF Cellular Assay	101	606	6.0
	A431 Proliferation	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; IC_{50}, drug concentration causing 50% inhibition of the desired activity; ITK, interleukin-2 inducible T-cell kinase; JAK3, Janus kinase 3.

BGB-3111 *vs.* Ibrutinib
PD Study in Rec-1 Xenograft Model

- BTK inhibition in tumor tissue much weaker than that in PBMC
- BGB-3111 demonstrated better tumor PD activity, consistent with tumor efficacy





Ideas that Drove Design of Phase I (July 2013)

- Ibrutinib may not have realized the full potential for total body BTK inhibition
  - Let's push the dose right up there
  - Let's dose the drug twice daily
  - Let's biopsy the lymph nodes to prove sustained tissue BTK inhibition

- Selectivity for BTK may allow high drug levels with reduced / equivalent side-effects
  - Boys with BTK deficiency don't have rash, diarrhea, bleeding or AF

BGB-3111 First-in-Human Study

Enrolled August 2014- April 2015

Part 1

Dose Escalation

RP2D

Cohort	Dose	n	Follow-Up Days Median (range)
1	40 mg QD	4	377 (11-398)
2	80 mg QD	5	327 (84-329)
3	160 mg QD	6	272 (148-285)
4a	320 mg QD	6	226 (215-242)
4b	160 mg BID	4	229 (20-236)

Initiated- April 2015

Part 2a*

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

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

Part 2b

BID, 20 R/R non-GCB DLBCL

Part 2c

BID, 20 R/R CLL/SLL**

Part 2d

BID, 20 R/R WM**

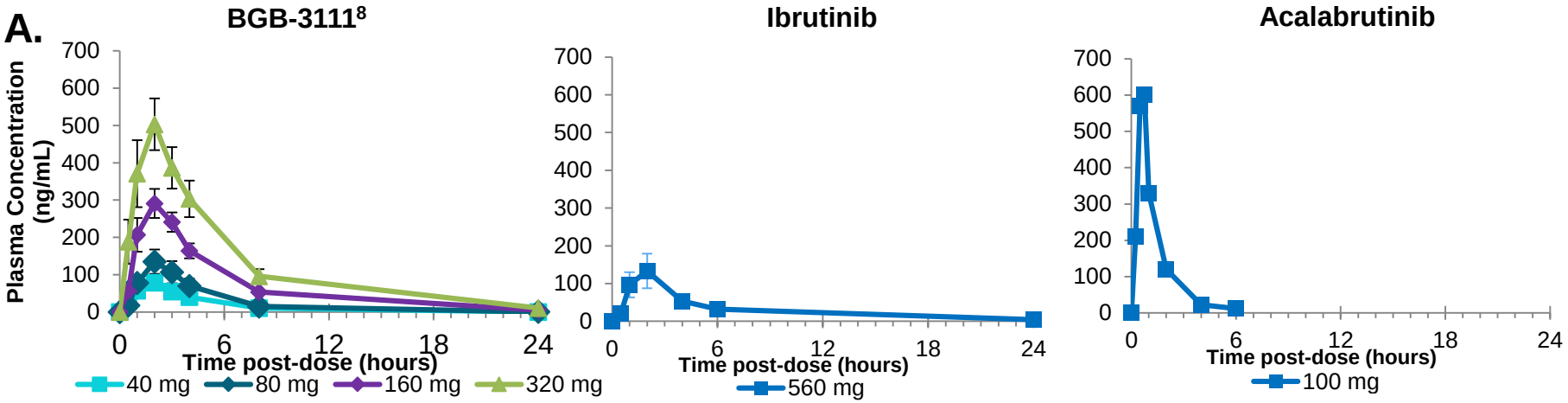
* Paired lymph node biopsy required

** Separate CLL and WM cohorts initiated 6/2015

39 patients (enrolled before August 1, 2015) are included in this analysis (Dose-Escalation Part, n=25; Expansion Part, n=14)
Data cut-off: Oct 19th, 2015

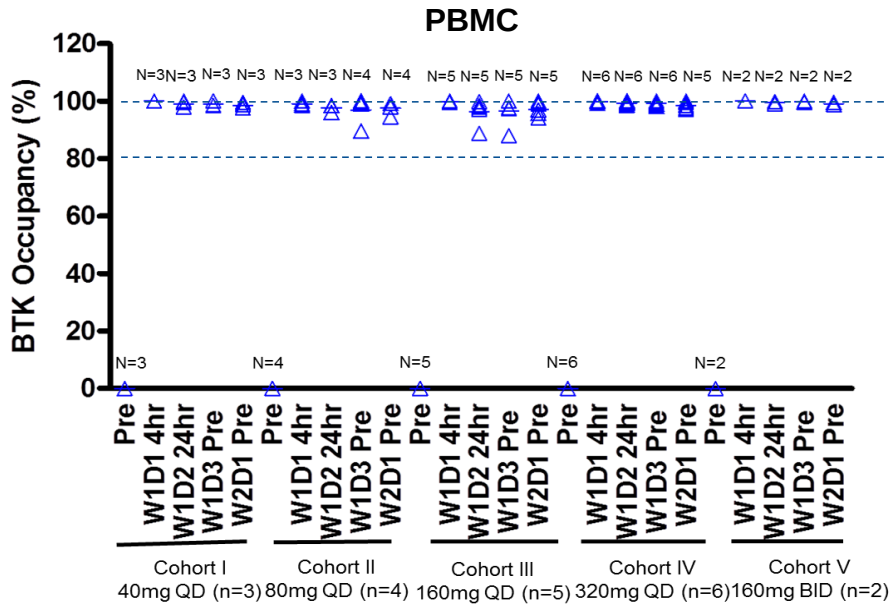
Pharmacokinetics of BGB-3111, Ibrutinib and Acalabrutinib, and BTK Occupancy in Blood and Lymph Nodes

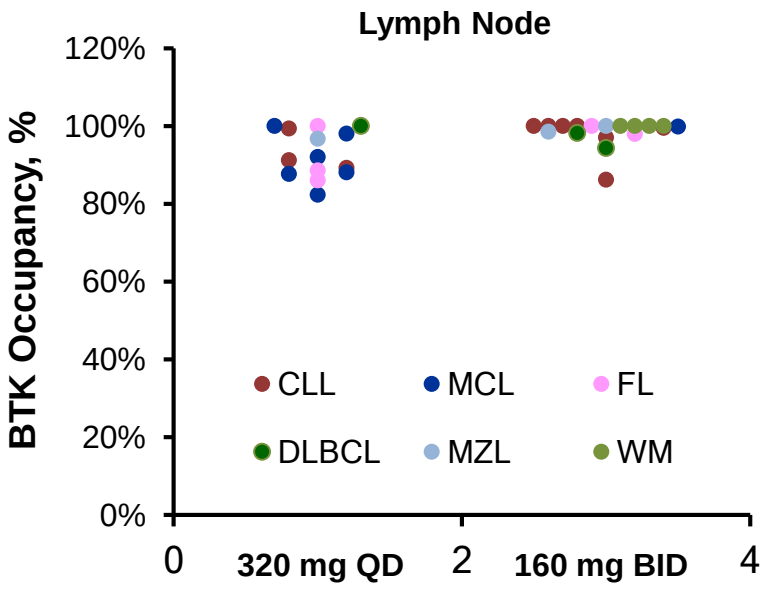
A.



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

B.





CLL Data from Phase I Monotherapy (Seymour, ICML 2017)

DOSE ESCALATION

Dose	Enrolled (CLL/SLL)
40 mg QD	4 (0)
80 mg QD	5 (0)
160 mg QD	6 (2)
320 mg QD	6 (1)
160 mg BID	4 (1)

RP2D

320 mg QD
or
160 mg BID

NCT02343120

DOSE EXPANSION

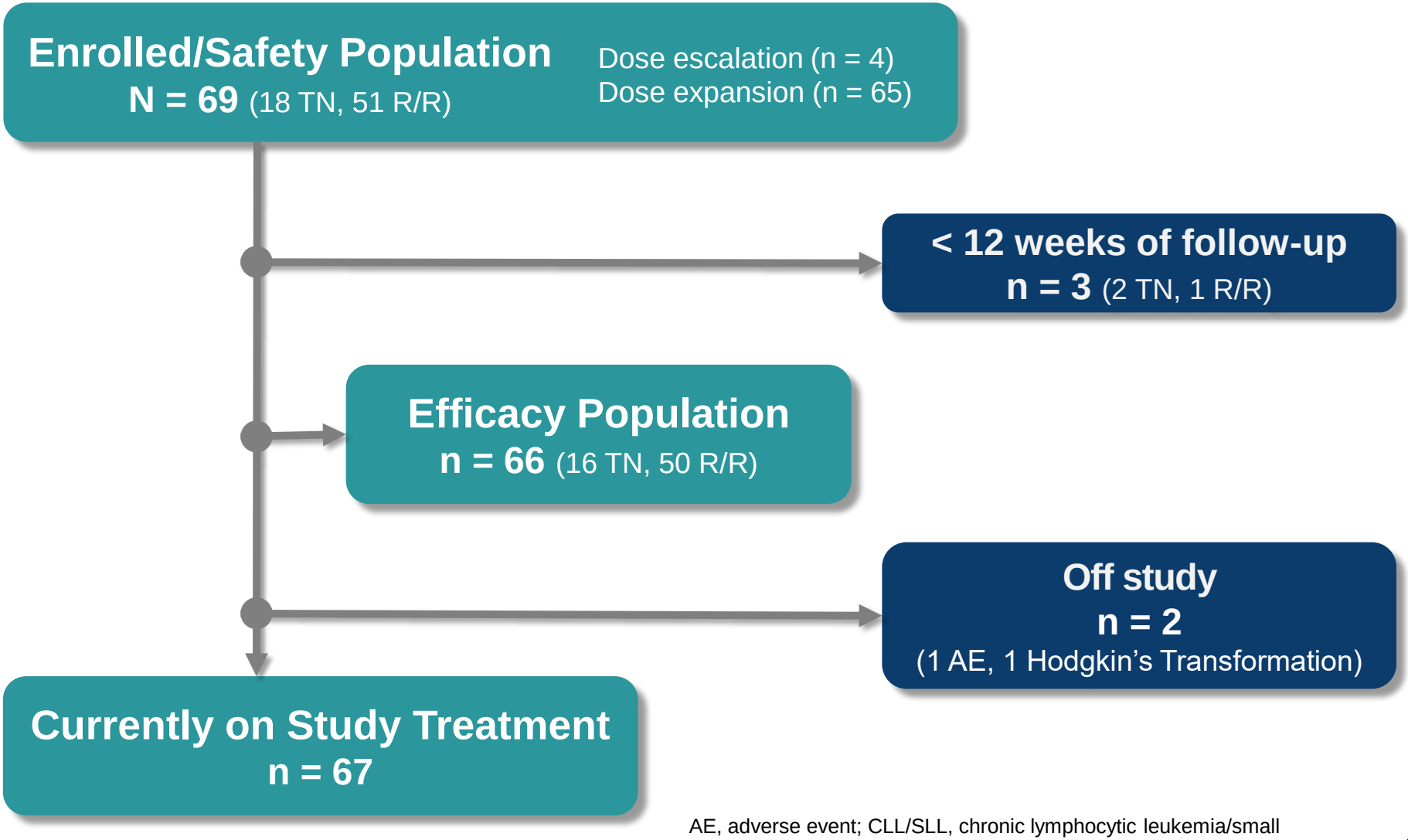
Population	RP2D Dose	Disease	Planned
Relapsed/Refractory	BID or QD	MCL, MZL, FL, GCB DLBCL	40
Relapsed/Refractory	BID	Non-GCB DLBCL	40
Relapsed/Refractory	BID	CLL/SLL	70
Relapsed/Refractory	BID	WM	20
Relapsed/Refractory	QD	CLL/SLL	20
Relapsed/Refractory or Treatment-naïve	BID or QD	WM	50
Relapsed/Refractory	BID or QD	MCL	20
Treatment-naïve	BID or QD	CLL/SLL	20
Treatment-naïve	BID or QD	MCL	20
Relapsed/Refractory	BID or QD	HCL	10
Relapsed/Refractory	BID	iNHL	40
Relapsed/Refractory	BID	Richter Transformation	15
BTK-Relapsed/ Refractory	BID	WM	15

Eligibility:

- WHO (World Health Organization)-defined B-cell malignancy
- ≥1 prior therapy (relapsed cohorts only)
- No available higher priority treatment
- Eastern Cooperative Oncology Group (ECOG) 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; QD, once daily; RP2D, recommended phase 2 dose; WM, Waldenström macroglobulinemia.

CLL/SLL Patient Disposition as of 31 March 2017



AE, adverse event; CLL/SLL, chronic lymphocytic leukemia/small lymphocytic lymphoma; R/R, relapsed/refractory; TN, treatment naïve.

CLL 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.

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.

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

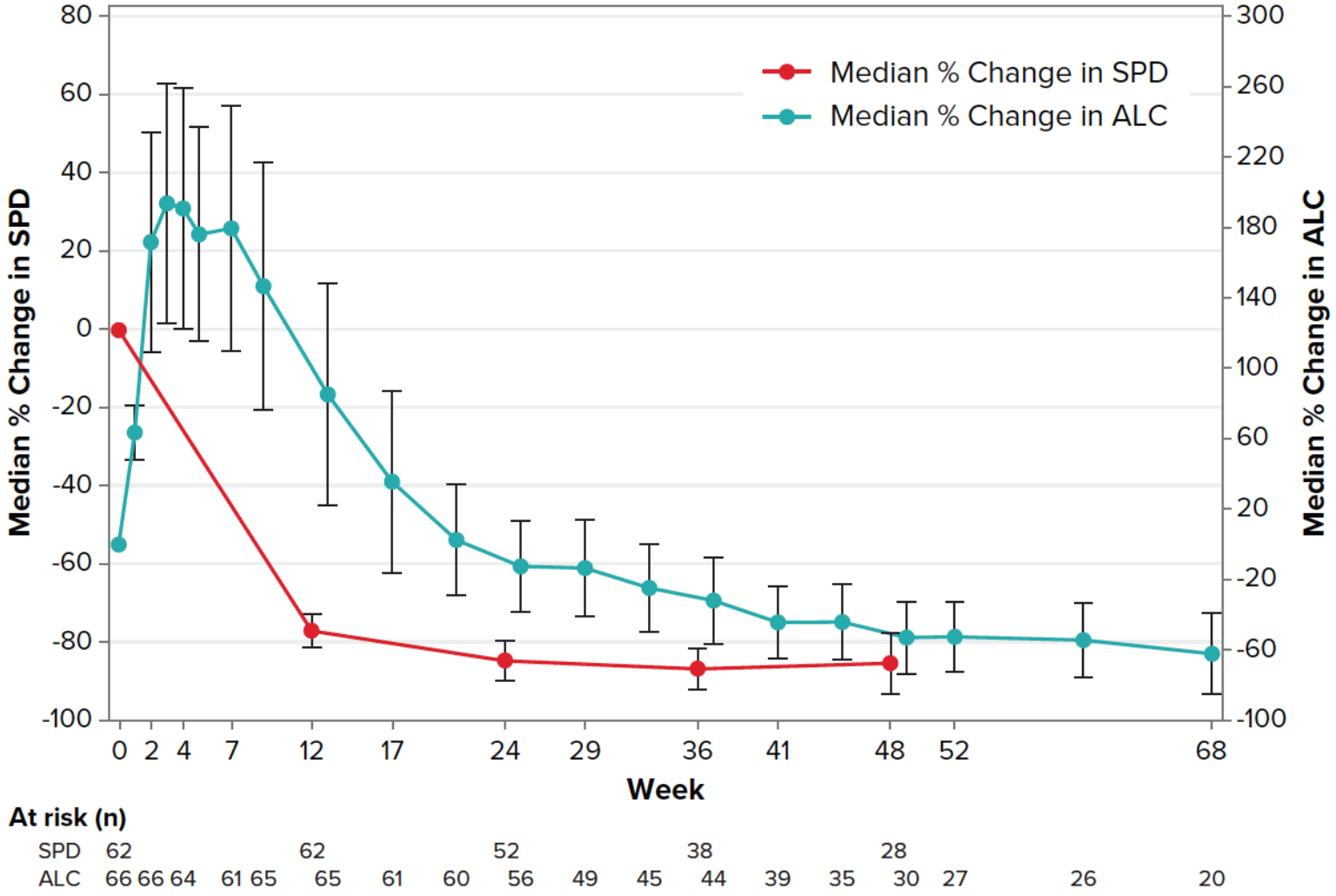
Response

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.

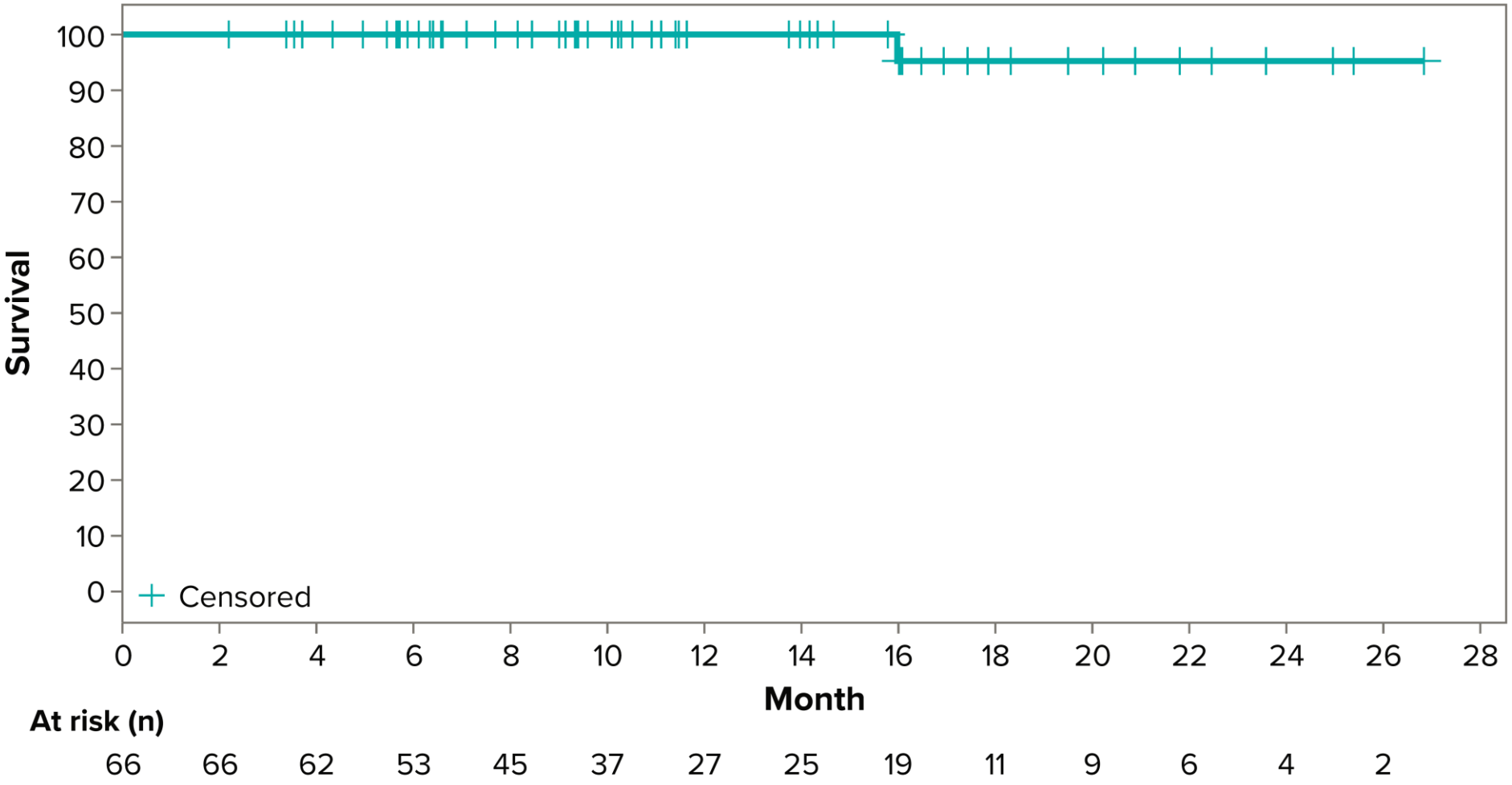
- The ORR in patients with del17p and/or 11q- (n = 22) was 96%

Kinetics of ALC and SPD Response in CLL



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.

BGB-3111 Monotherapy: PFS in CLL



Conclusions

- Zanubrutinib at 160mg BID shows acceptable toxicity profile and promising clinical activity:
  - Drug exposure approximately 8x higher than ibrutinib
  - Biopsy-proven continuous BTK inhibition in lymph nodes

- Phase 3 studies underway in CLL
  - Frontline: Zanubrutinib vs Bendamustine-rituximab
  - Relapsed / Refractory: Zanubrutinib vs Ibrutinib