

# High Overall Response Rate With the BTK Inhibitor BGB-3111 in Patients With Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma: an Update on Safety and Activity

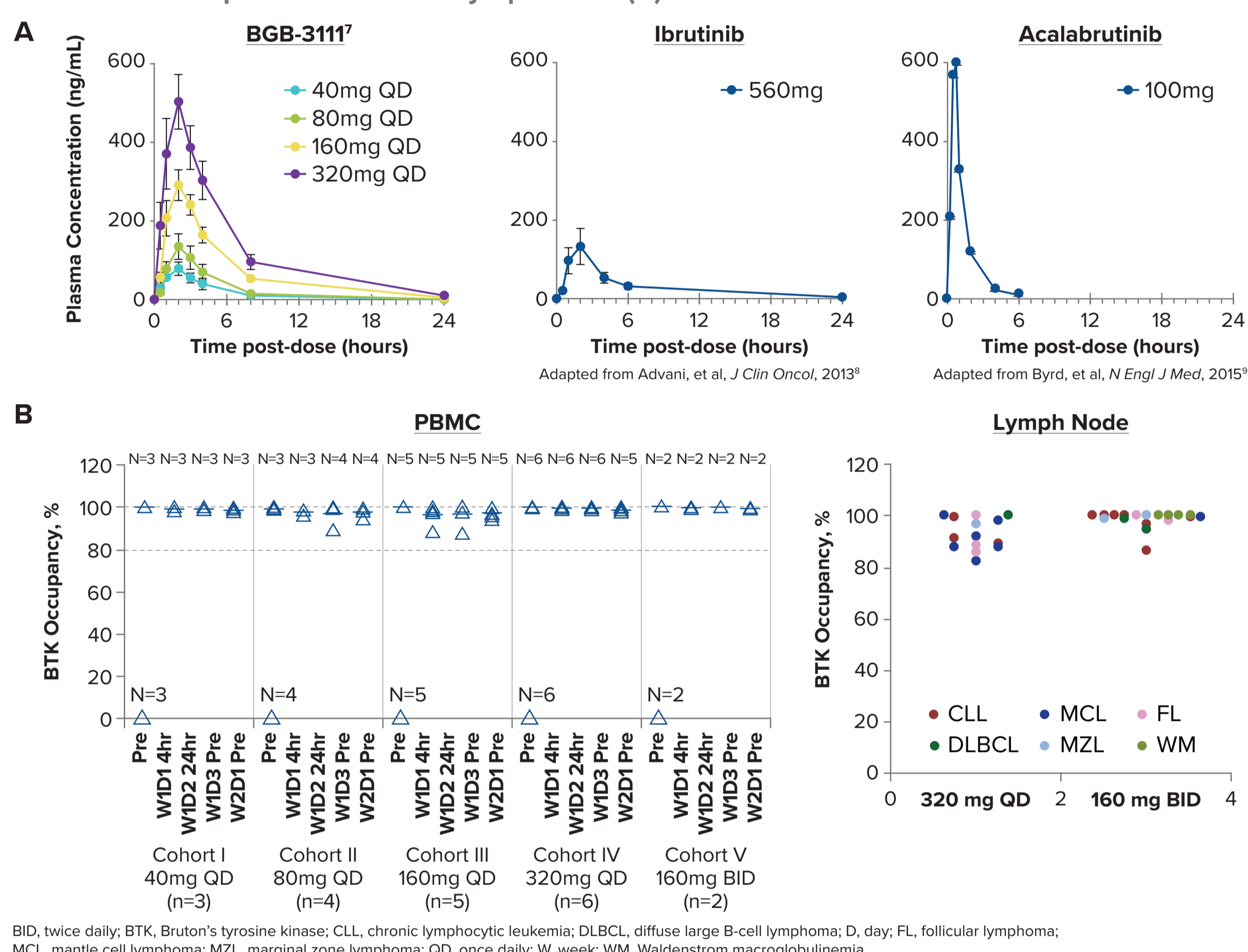
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## INTRODUCTION

- Bruton's tyrosine kinase (BTK) plays a critical role in B-cell receptor signaling, which mediates B-cell proliferation, migration, and adhesion<sup>1,2</sup>
- BTK is a potent and irreversible BTK inhibitor with advantageous pharmacokinetics (Figure 1) designed to minimize off-target inhibition of other TEC- and epidermal growth factor (EGFR)-family kinases (Table 1)
- Ibrutinib, the first-generation BTK inhibitor, has shown activity in and is approved for treatment of both relapsed/refractory (R/R) and treatment-naïve (TN) CLL/SLL<sup>3,4</sup>
- BGB-3111 achieved complete and sustained BTK occupancy in peripheral blood mononuclear cells (PBMCs) and lymph nodes (Figure 1)
- There remains an opportunity to improve upon the efficacy and safety of ibrutinib with more potent and targeted BTK inhibition

Figure 1. Pharmacokinetics of BGB-3111, Ibrutinib and Acalabrutinib (A); BTK Occupancy for BGB-3111 in Peripheral Blood and Lymph Node (B)



BID, twice daily; BTK, Bruton's tyrosine kinase; CLL, chronic lymphocytic leukemia; DLBCL, diffuse large B-cell lymphoma; FL, follicular lymphoma; MCL, mantle cell lymphoma; MZL, marginal zone lymphoma; QD, once daily; W, week; WM, Waldenström macroglobulinemia.

Table 1. BGB-3111 Kinase Selectivity

Targets	Assays	Ibrutinib IC <sub>50</sub> (nM)	BGB-3111 IC <sub>50</sub> (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 Occupation Cellular Assay	189	3265	17
	p-PLC $\gamma$ 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

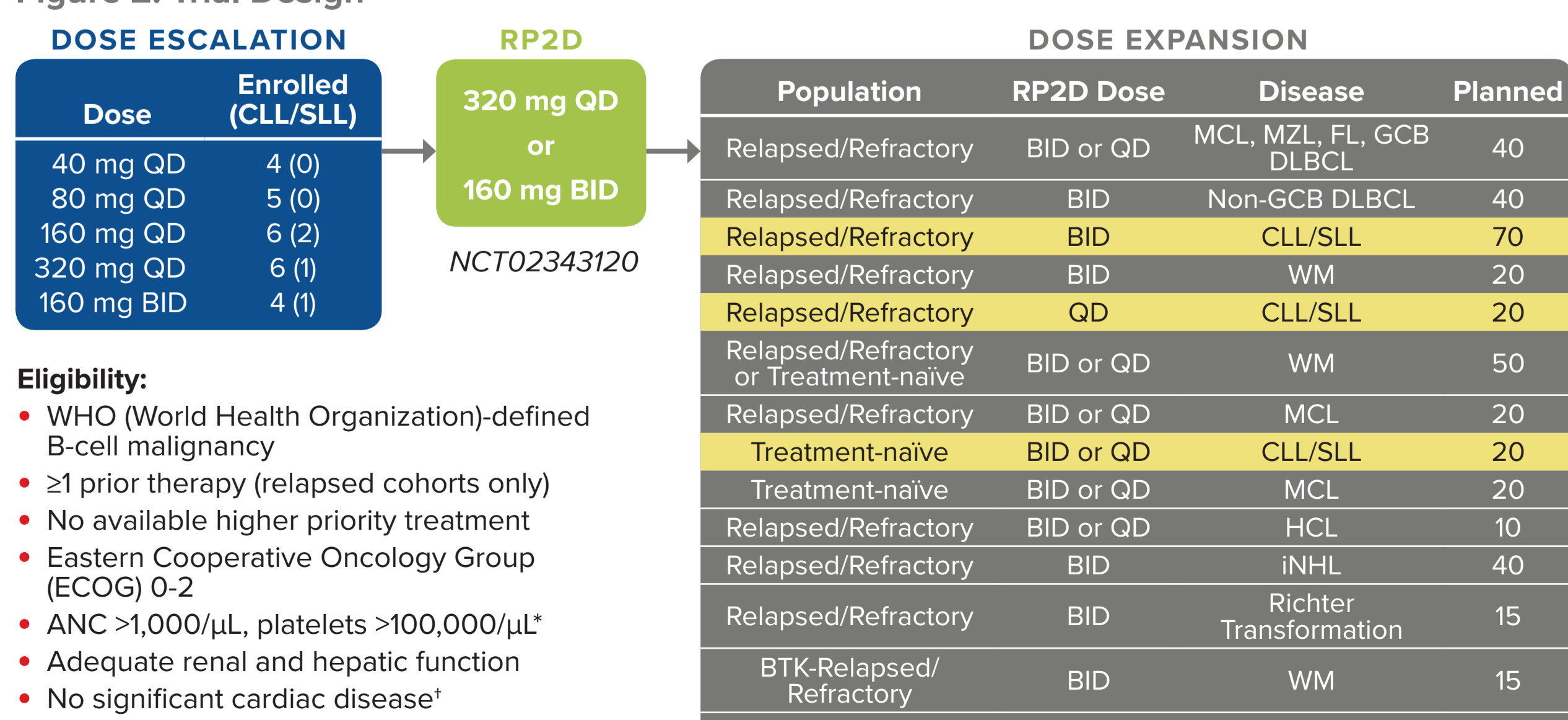
BTK, Bruton's tyrosine kinase; EGFR, epidermal growth factor receptor; IC<sub>50</sub>, drug concentration causing 50% inhibition of the desired activity; ITK, interleukin-2 inducible T-cell kinase; JAK3, Janus kinase 3.

## METHODS

### TRIAL DESIGN

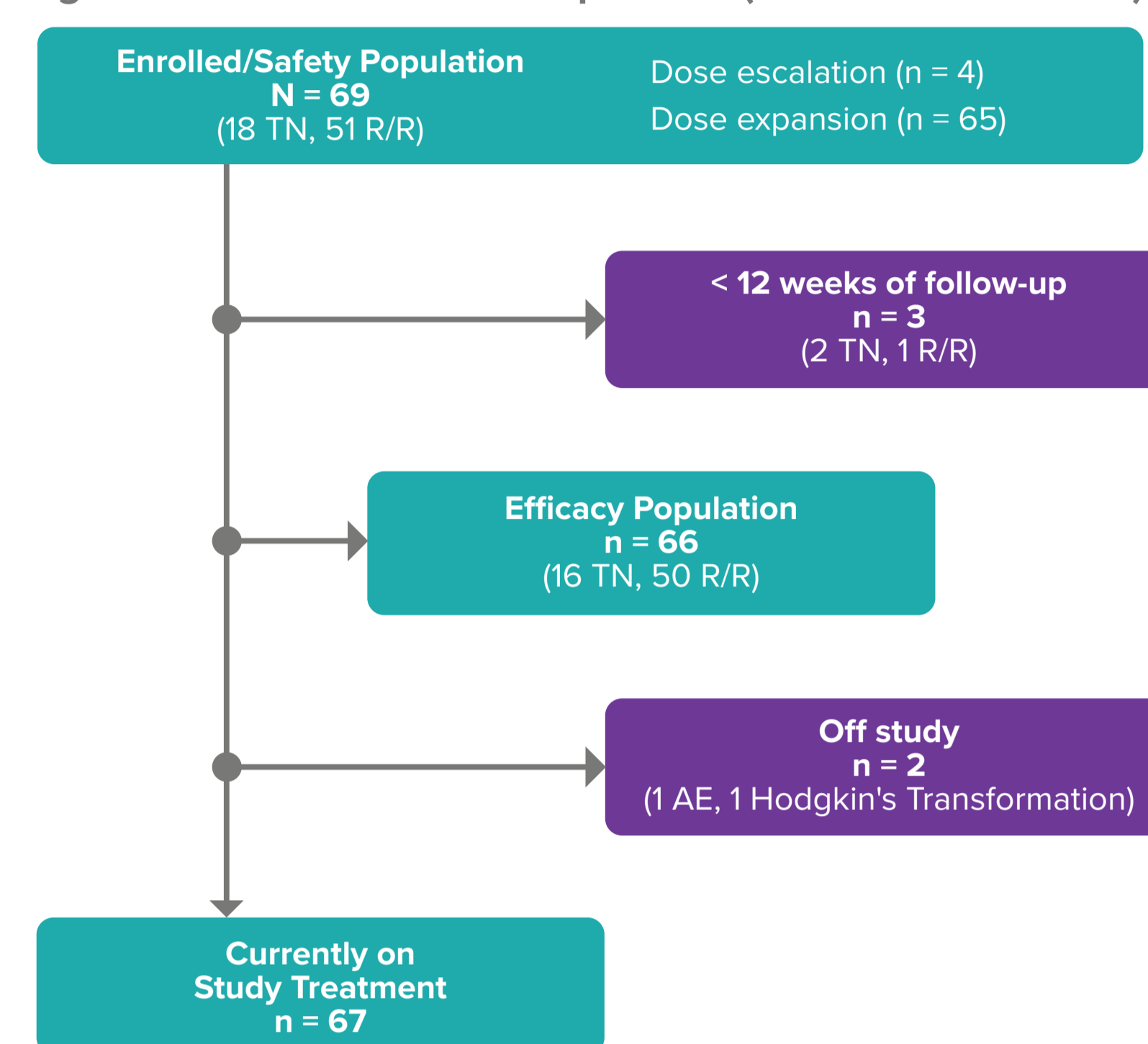
- This first-in-human study of BGB-3111 consisted of a dose-escalation phase and dose-expansion phase in patients with TN or R/R B-cell malignancies (Figure 2)
- **Primary endpoints**
  - Safety, including adverse events (AEs), serious AEs (SAEs) per the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) Version 4.03, physical examination, and laboratory measurements
  - Recommended phase 2 dose (RP2D)—Part 1 only
- **Selected secondary endpoints**
  - Pharmacokinetics
  - Efficacy, including overall response rate (ORR), progression-free survival (PFS), overall survival, and duration of response

Figure 2. Trial Design



\*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.

Figure 3. 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.

Table 2. Patient Characteristics

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

\*Any lymph node >10 cm in maximum diameter. ECOG, Eastern Cooperative Oncology Group.

## DOSE ESCALATION AND RP2D: RESULTS

- A total of 25 patients with B-cell malignancies were enrolled in the dose-escalation phase
  - No dose-limiting toxicities were experienced
- No maximum-tolerated dose (MTD) was reached during dose escalation
- The RP2D was established as either 320 mg QD or 160 mg BID, and both doses were used during dose expansion

Table 3. 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.

Table 4. 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
  - SAEs 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

Table 5. Events Leading to Permanent Treatment Discontinuation

Event	n (pts)	% (N = 69)
Adverse event (Pleural effusion)	1*	1%
Hodgkin's transformation	1	1%

\* Taken off study prior to first response assessment. pts, patients.

- No patients have progressed with a C481S mutation

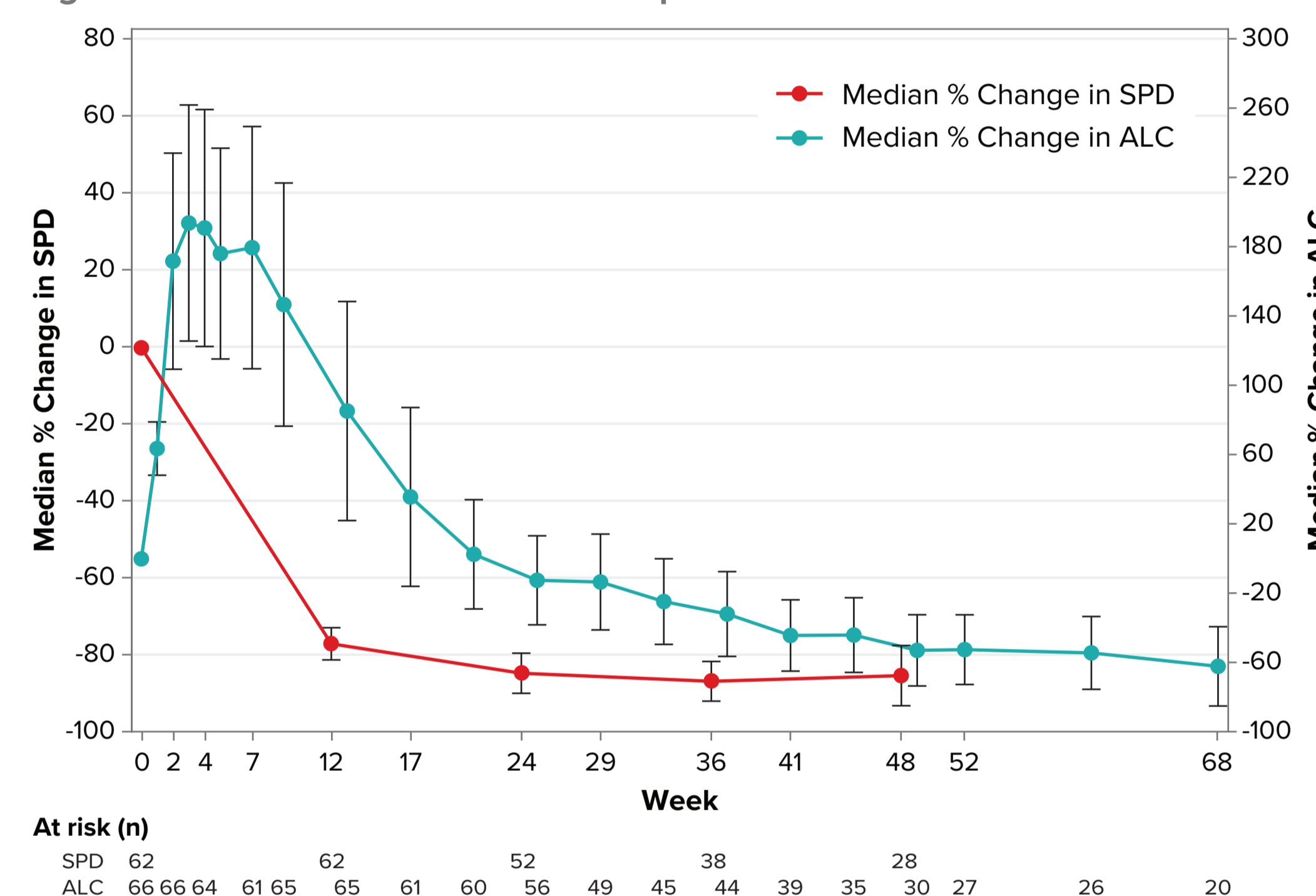
Table 6. Response

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.

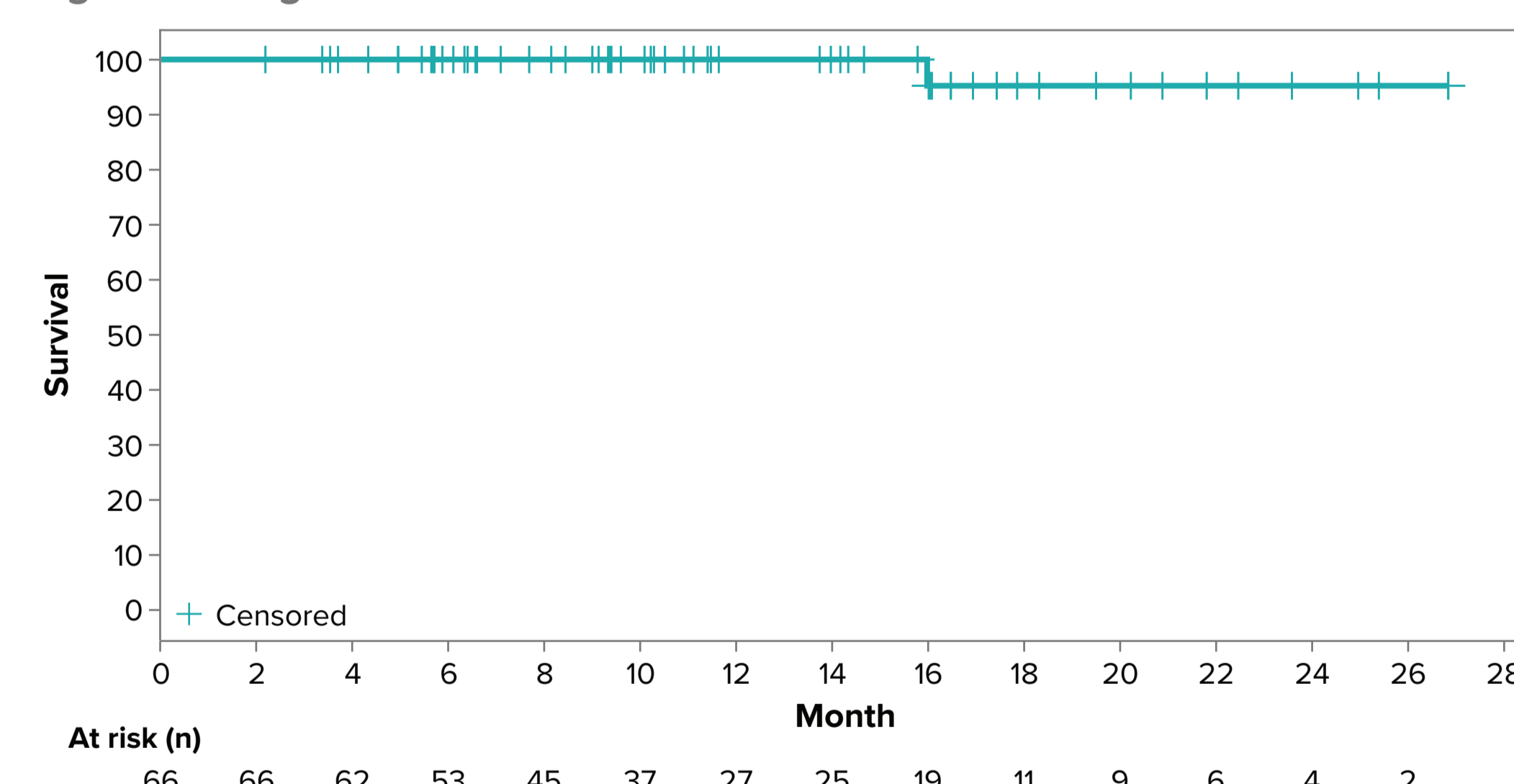
- The ORR in patients with del17p and/or 11q- (n = 22) was 96%

Figure 4. 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.

Figure 5. Progression-Free Survival



## CONCLUSIONS

- BGB-3111 is highly active in CLL/SLL
  - Very high rate (94%) of durable response, independent of poor-risk features
  - Rapid response kinetics in ALC and SPD
  - With a median follow-up of 10.3 months, only one patient has experienced disease progression
- BGB-3111 is safe and well tolerated in CLL/SLL
  - Only one patient with AE-related treatment discontinuation
  - Very low incidence of serious diarrhea (1%), and serious bleeding (1%). One non-serious event of atrial fibrillation (1%) was reported
- BGB-3111 dose at 160 mg BID was chosen over 320 mg daily as the recommended phase 2 dose due to better 24-hour BTK occupancy
- These updated results support Phase 3 trials of BGB-3111 in a broad population of CLL/SLL patients

Data on BGB-3111 in CLL in combination with obinutuzumab (Abstract #103) will be presented in Session 7 of Friday, June 16th

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