BGB 3111 in MCL

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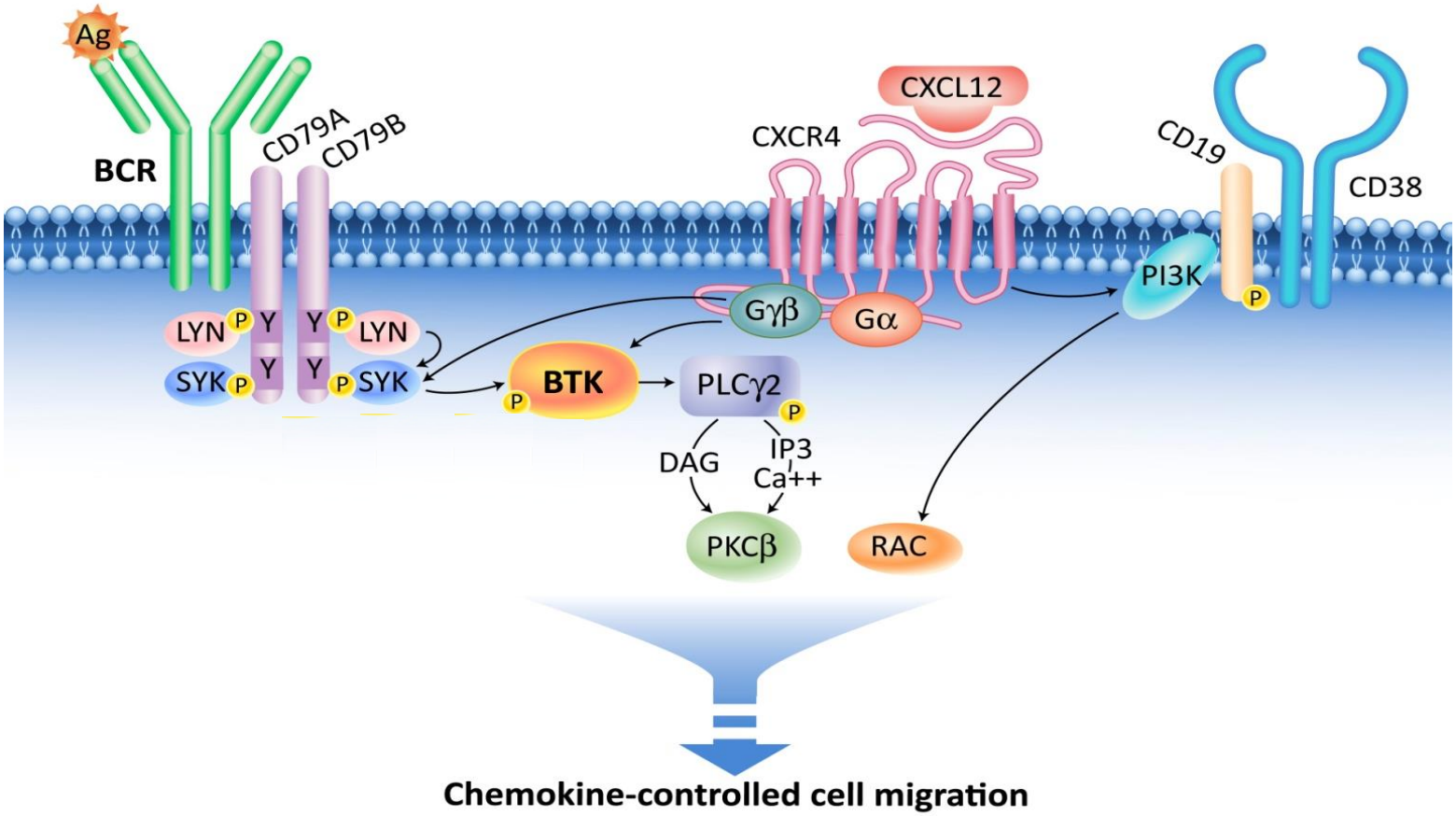
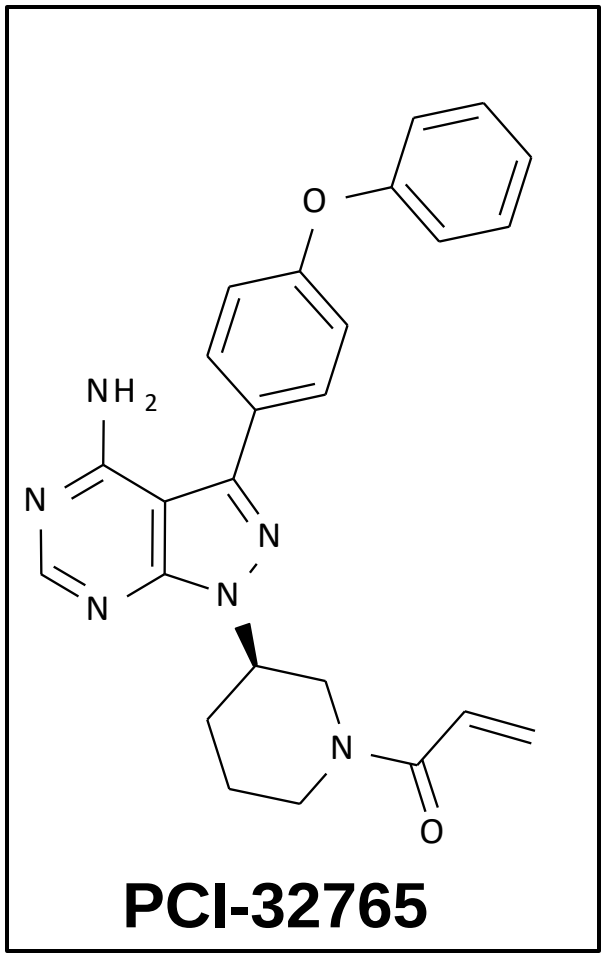
Bruton's Tyrosine Kinase (BTK): A Critical Kinase for Lymphoma Cell Survival and Proliferation



- Bruton's tyrosine kinase (BTK) is an essential element of the BCR signaling pathway (Niiro, NRI 2002)
- Inhibitors of BTK block BCR signaling and induce apoptosis
- BTK also acts downstream of certain chemokine receptors impacting integrin molecules that help in promoting egression from the lymph node environment

PCI-32765: First-in Class Inhibitor of Btk



PCI-32765

- Forms a specific and irreversible bond with cysteine-481 in Btk
- Highly potent Btk inhibition at IC_{50} = 0.5 nM
- Orally administered with once daily dosing resulting in 24-hr target inhibition
- Blocks mantle cell migration and adhesion
- Blocks pERK, pJNK, and NF-kB pathways in mantle cell lymphoma lines.

Honigberg LA et al: Proc Natl Acad Sci 2010
Chang, D et al. Proc ASH 2011

BGB-3111

- Small molecule, orally-administered, inhibitor of BTK
- Forms covalent bond to Cys 481 within ATP binding pocket of BTK protein
- Highly selective for BTK compared with ibrutinib
  - Significantly less EGFR/JAK3/TEC/ITK inhibition
- High oral bioavailability and exposure levels in vivo
- In preclinical murine studies, complete target inhibition in B cells residing outside peripheral blood (e.g. bone marrow, lymph nodes, spleen)

Li *et al.*, AACR, 2015

BGB-3111: Kinase Selectivity Relative to Ibrutinib

Selectivity in Assays — IC_{50} (nM)

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

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

The BTK Inhibitor, BGB-3111, is Safe, Tolerable, and Highly Active in Patients with Relapsed/ Refractory B-Cell Malignancies: Initial Report of a Phase 1 First-in-Human Trial

Constantine Tam[1,2], Andrew P Grigg[3], Stephen Opat[4,5], Gavin Cull[6], Judith Trotman[7], Matthew Ku[3], Michael Gilbertson[4], Mary Ann Anderson[2,8,9], John F Seymour[1,2], David S Ritchie[8], Bradley Auguston[6], Emma Verner[7], Carmen Dicorleto[4], Belinda Dimovski[1], Eric Hedrick[10], Jianxin Yang[10], Lai Wang[10], Lusong Luo[10], Ling Xue[10], and Andrew W Roberts[2,8,9]

[1]Peter MacCallum Cancer Centre, East Melbourne, Australia, [2]University of Melbourne, Melbourne, Australia, [3]Austin Health, Melbourne, Australia, [4]Monash Health, Melbourne, Australia, [5]Monash University, Melbourne, Australia, [6]Sir Charles Gairdner Hospital, Perth, Australia, [7]Concord Repatriation Hospital, Sydney, Australia, [8]Royal Melbourne Hospital, Melbourne, Australia, [9]Walter and Eliza Hall Institute of Medical Research, Melbourne, Australia, [10]BeiGene (Beijing) Co, Ltd, Beijing, China.

Objectives

- **Determine:**
  - **the maximum tolerated dose and/or the recommended Phase 2 dose of BGB-3111 in patients with relapsed or refractory B-cell malignancies**
  - **the pharmacokinetic profile of BGB-3111 when administered orally daily or twice-daily**
  - **the degree of sustained BTK inhibition in both circulating and nodal lymphocytes**
  - **the safety and tolerability profile of BGB-3111**
  - **early evidence of activity of BGB-3111 in various B-cell malignancies:**
    - **CLL, per 2012 modification of the 2008 IWCLL Response Guidelines[1]**
    - **NHL, per the 2014 Lugano Classification[2]**
    - **WM, per the 2012 International Workshop criteria[3]**

[1] Hallek, Blood 2012
[2] Cheson, J Clin Oncol 2014
[3] Owen, Br J Haem 2012

Key Eligibility/ Exclusion Criteria

- **Inclusion:**
  - **Relapsed or refractory WHO classification defined B-lymphoid malignancy following at least one line of therapy, with no therapy of higher priority available**
  - **ECOG performance status of 0-2**
  - **Neutrophils ≥ 1.0 x 10^9/L and platelets ≥ 50 x 10^9/L[1]**
  - **Adequate renal, hepatic, and cardiac function**

- **Exclusion[2]:**
  - **Histologically transformed disease**
  - **Prior BTK inhibitor therapy**
  - **Allogeneic stem cell transplantation within 6 months**
  - **Known HIV, or active hepatitis B or hepatitis C infection**
  - **QTc prolongation (>450ms)**

[1]Patients with neutrophils < 1.0 x 10^9/L due to marrow infiltration are allowed to receive growth factors; patients with platelets <50 x 10^9/L due to marrow infiltration are allowed to receive platelet transfusion.

[2]Patients with atrial fibrillation, and those on anti-coagulation with warfarin, were not excluded

Patient Characteristics

	Total (N=39)
Age, median (range)	68 (45-84)
ECOG Performance Status	
0	23
1	13
2	3
Prior medical history	
Atrial Fibrillation/ flutter	6 (15%)
Concomitant Medication	
Warfarin/ rivaroxaban	2 (5%)
Aspirin	8 (21%)

	Total (N=39)
Diagnosis	
CLL	14
MCL	10
WM	7
DLBCL	4
Indolent NHL (FL, MZL)	2
Burkitt-like lymphoma	1
Hairy cell leukemia	1
Number of prior therapies, median (range)	2 (0-7)*
Refractory to last therapy**	14 (36%)
Prognostic factor (CLL-only, n=14)	
p53mut/17p-	3 (21%)
11q-	6 (43%)
PD within 36 months of FCR	6 (43%)

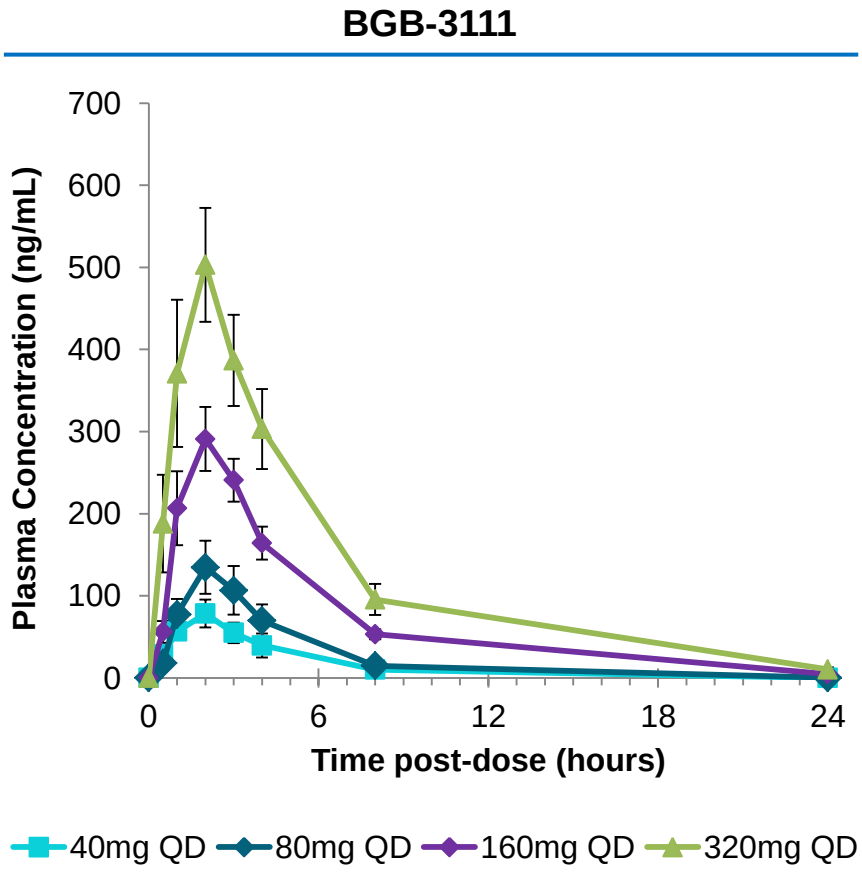
*** Includes 1 patient with prior RT**
**** Progression within 6 months of last therapy**

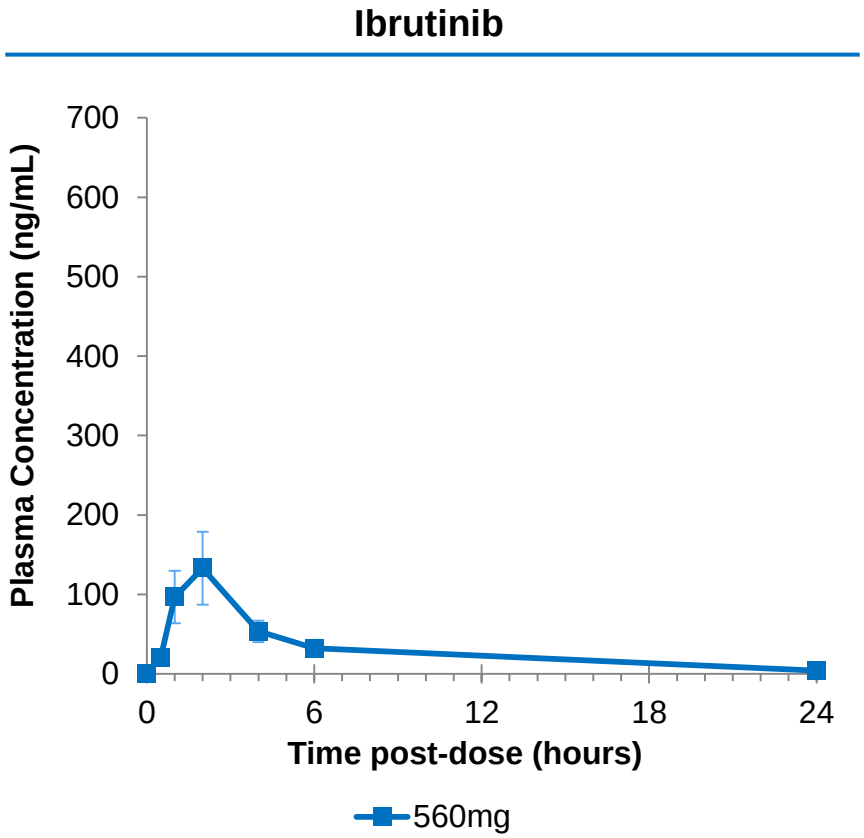
Disposition

	Dose Escalation Phase (n=25)	Expansion Phase (n=14)
Follow-up, days Median (range)	**242 (11-398)**	**121 (28-182)**
Patients discontinued	**5**	**3**
Reason for discontinuation		
Disease Progression	**4**	**2**
Adverse Event	**1***	**1***
Patient or Physician Decision	**0**	**0**
Deaths on study	**1****	**2****

*Complications related to refractory underlying malignancy
**Disease progression or complications of disease progression

BGB-3111 Plasma Exposure By Dose Comparison with Ibrutinib



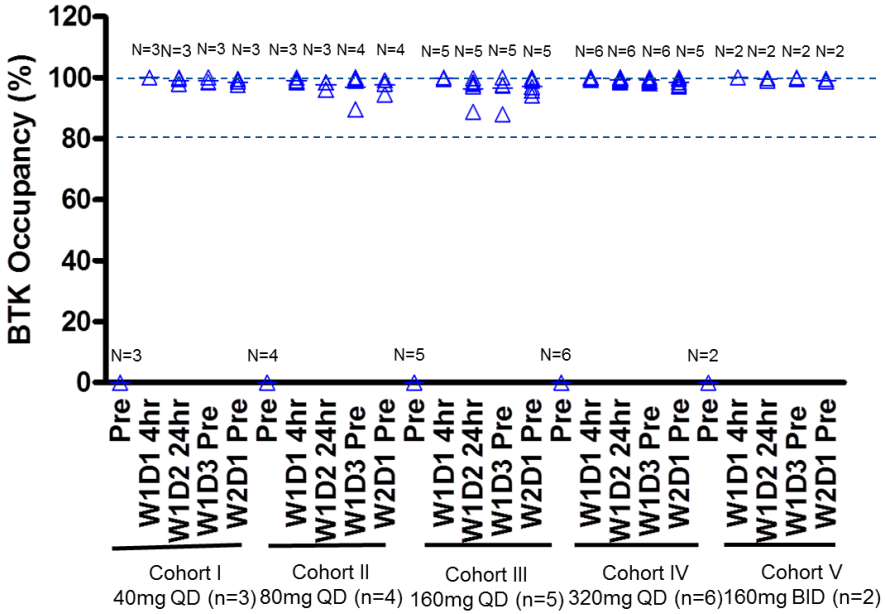


Derived from Advani *et al*., JCO, 2013

- 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

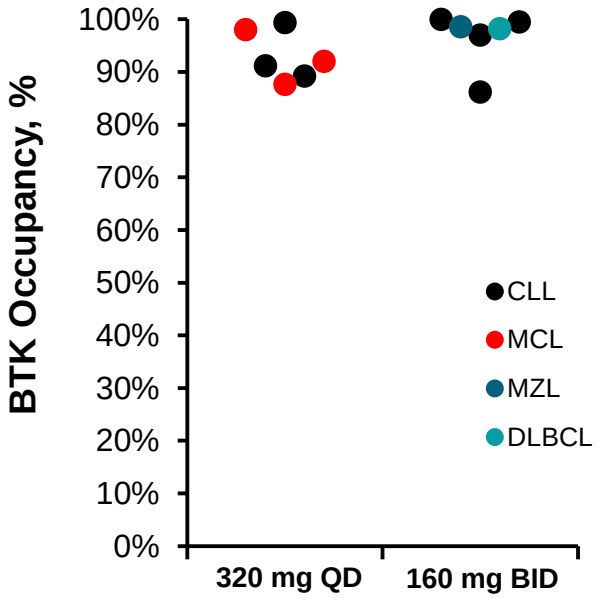
Sustained BTK Occupancy in both Blood and Lymph Node

PBMCs



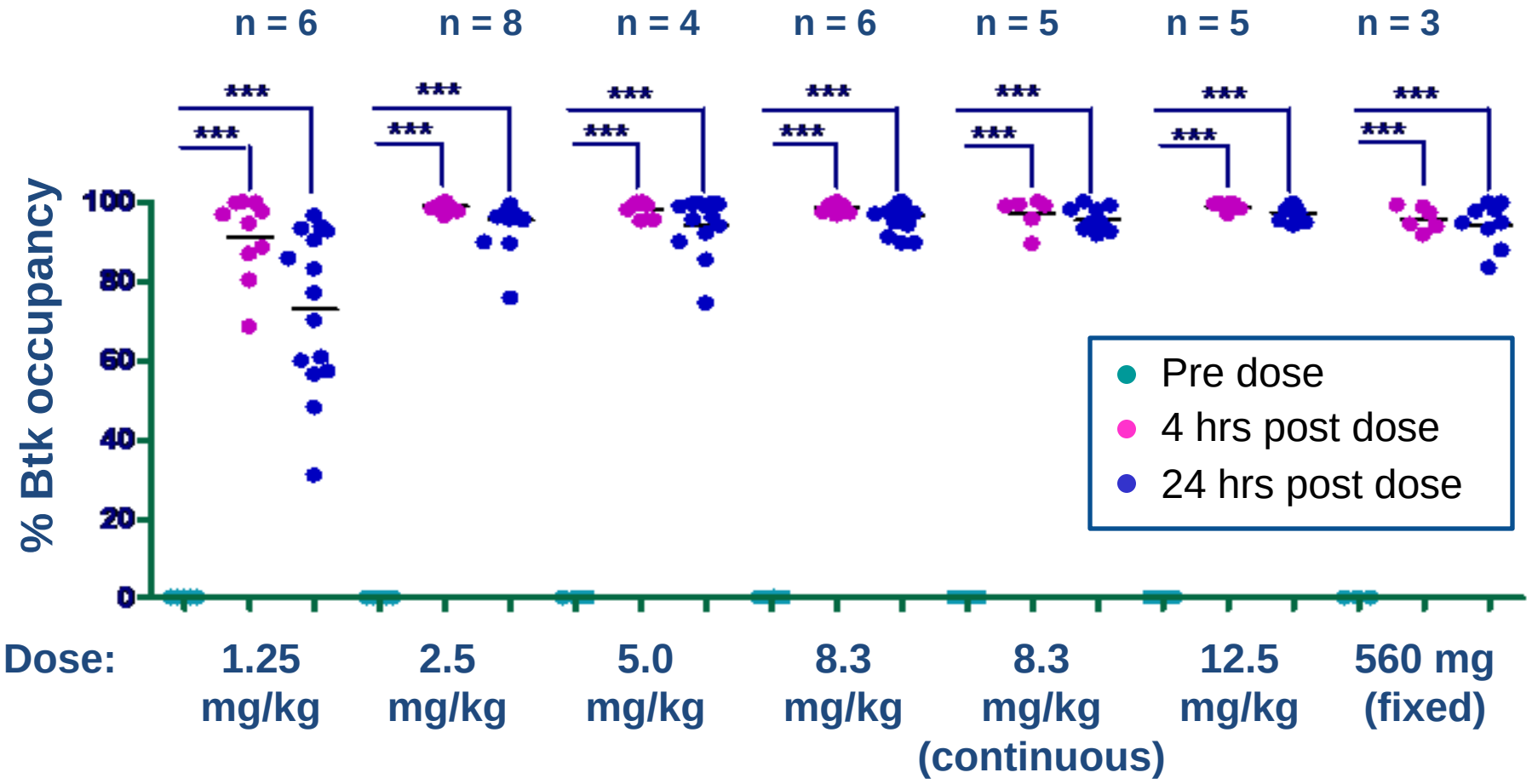
- Near complete BTK occupancy in PBMCs at the starting dose (40 mg)
- PD of BGB-3111 at 40 mg is comparable to that of ibrutinib at 560 mg

Lymph Nodes

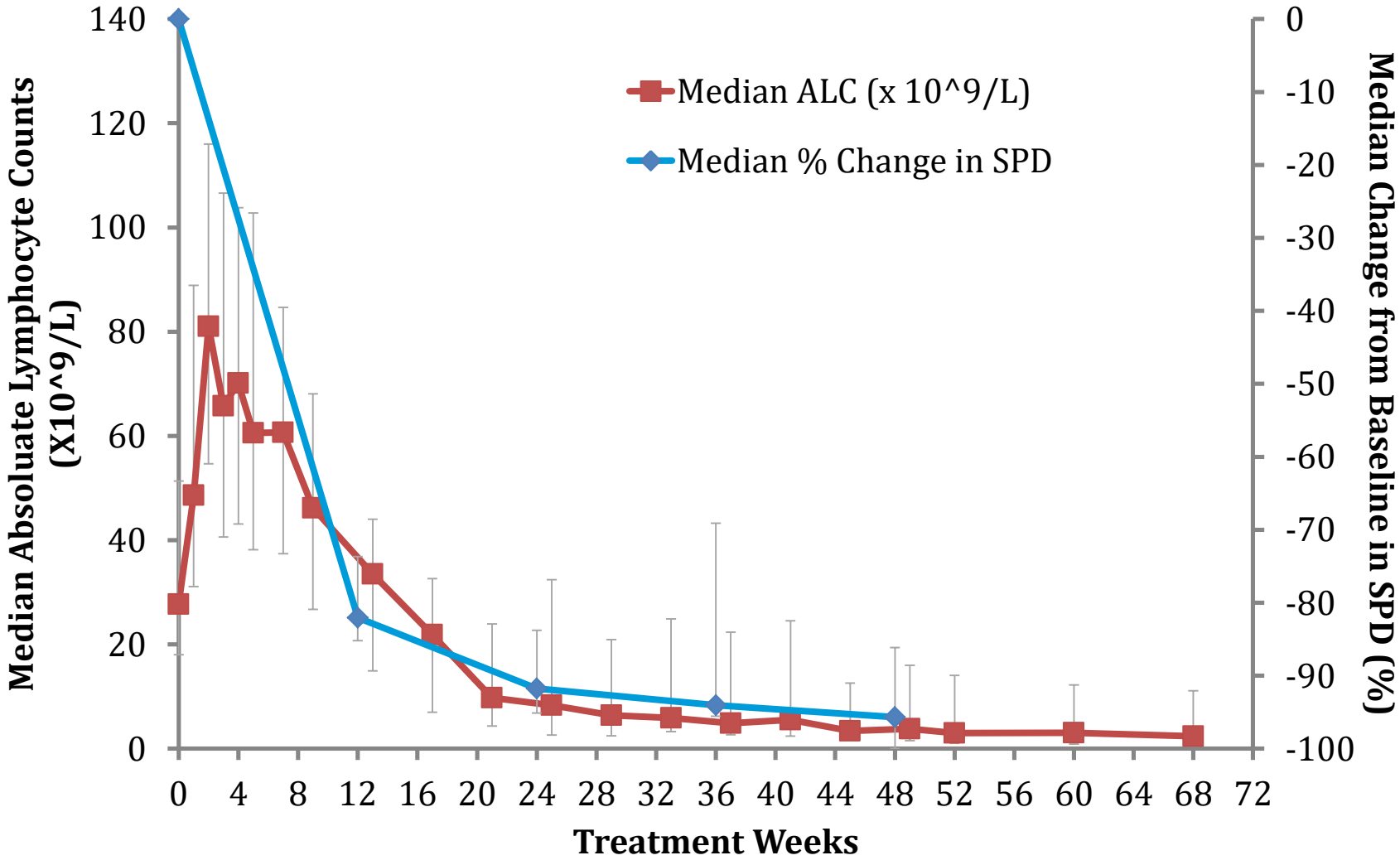


- Paired lymph node biopsies were collected during screening or pre-dose on day 3
- 24 hours post-dose for QD pts and 12 hours post-dose for BID pts

Complete occupancy of Btk at all doses ≥ 2.5 mg/kg/day (Ibrutinib)



Kinetics of ALC and Lymphadenopathy Response

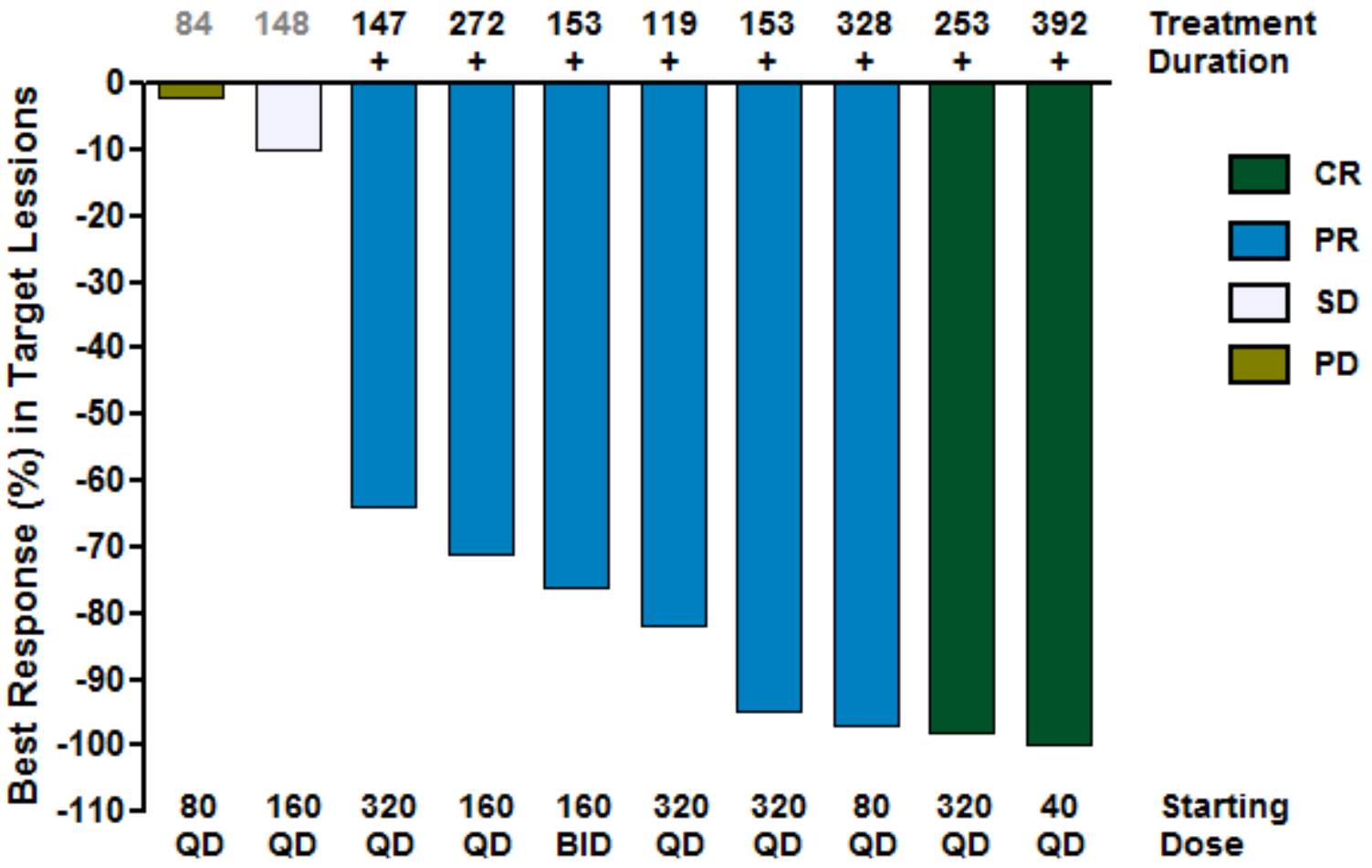


Efficacy Summary: Response Rate

	Follow-up Days Median (Range)	Best Response				ORR (CR + PR)
		CR	PR	SD	PD	
CLL	220 (83-329)	0/14 (0%)	13/14[1] (93%)	1/14 (7%)	0 (0%)	13/14 (93%)
MCL	148 (84-392)	2/10 (20%)	6/10 (60%)	1/10 (10%)	1/10 (10%)	8/10 (80%)
WM	271 (11-398)	0/7 (0%)	6/7[2] (86%)	0/7 (0%)	1/7 (14%)	6/7 (86%)
DLBCL	29 (20-236)	1/4 (25%)	0/4 (0%)	0/4 (0%)	3/4 (75%)	1/4 (25%)
Indolent NHL	233 (215-250)	0/2 (0%)	0/2 (0%)	2/2 (100%)	0/2 (0%)	0/2 (0%)
HCL	362	0/1 (0%)	1/1 (100%)	0/1 (0%)	0/1 (0%)	1/1 (100%)
BLL	84	0/1 (0%)	0/1 (0%)	0/1 (0%	1/1 (100%)	0/1 (0%)

[1] Includes 5 patients with lymphocytosis at latest assessment
[2] Includes 1 patient with very good PR (VGPR)

BGB-3111 Best Treatment Response (MCL Patients)



Adverse Events
Independent of Causality, Incidence ≥15%

	Grade 1-2		Grade 3-4		All Grade	
	n (pts)	% (n=39)	n (pts)	% (n=39)	n (pts)	% (n=39)
Petechiae, Contusion, Bruising	13	33%	0	0	13	33%
Upper Respiratory Tract Infection	11	28%	0	0	11	28%
Constipation	9	23%	0	0	9	23%
Diarrhoea	8	21%	0	0	8	21%
Cough	8	21%	0	0	8	21%
Rash	6	15%	0	0	6	15%
Neutropenia	1	3%	6	15%	7	18%

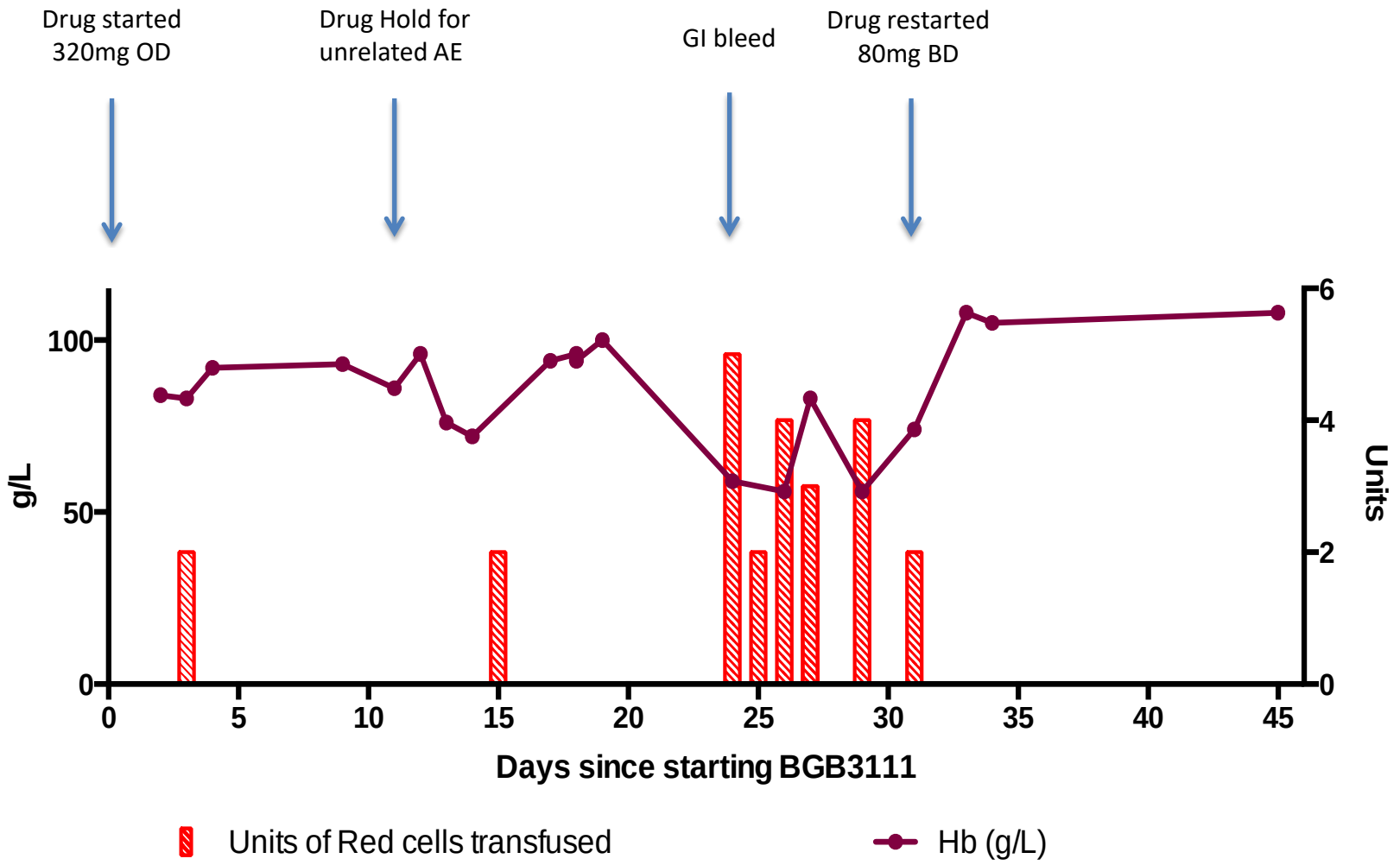
Safety Overview: Clinically Significant Events

	Total		Drug Related**	
	n	% (n=39)	n	% (n=39)
Subjects reporting ≥1 SAE(s)	9	23%	0	0
AEs leading drug discontinuation	2***	5%	0	0
Subjects reporting Grade ≥3 AE(s)	19	49%	4	10%
Atrial Fibrillation	0	0	0	0
Major Hemorrhage*	1	3%	0	0

*Defined as bleeding event ≥Grade 3 or intracranial bleeding event (any grade)
** Assessed as possibly related to study drug by the investigator
***Complications related to refractory underlying malignancy

- **Four drug-related grade 3/4 neutropenia events were transient and did not lead to drug discontinuation**
- **One major bleeding case: GI hemorrhage in MCL patient during drug hold (GI tract involvement); resolved with re-initiation of BGB-3111 treatment**

Bleeding from GI Involvement by MCL : Resolution Following BGB-3111 Re-Initiation



The BTK Inhibitor, BGB-3111, is Tolerable and Highly Active in Patients with Waldenström Macroglobulinemia: Interim Data From an Ongoing Phase 1 First-in-Human Trial

Constantine S Tam[1,2], Judith Trotman[3,4], Stephen Opat[5,6], Paula Marlton[7], Gavin Cull[8], David Simpson[9], David Gottlieb[4,10], Matthew Ku[11], David Ritchie[1,2,12], Emma Verner[3], Sumita Ratnasingam[5], Mary Ann Anderson[2,12], Peter Wood[7], Mark Kirschbaum[13], Lai Wang[13], Ling Xue[13], Eric Hedrick[13], John F Seymour[1,2], Andrew W Roberts[2,12]

[1]Peter MacCallum Cancer Center, East Melbourne, Victoria, Australia, [2]University of Melbourne, Parkville, Victoria, Australia, [3]Concord Repatriation General Hospital, Concord, Australia, [4]University of Sydney, Australia, [5]Monash Health, Clayton, Victoria, Australia, [6]Monash University, Clayton, Victoria, Australia, [7]Princess Alexandra Hospital and University of Queensland, Brisbane, Australia, [8]Sir Charles Gairdner Hospital, Perth, Western Australia, Australia, [9]North Shore Hospital, Auckland, New Zealand , [10]Westmead Hospital, Westmead, Australia, [11]Austin Health, Heidelberg, Victoria, Australia, [12]Melbourne Health, Parkville, Victoria, Australia, [13]BeiGene, Beijing, China

Most Frequent Adverse Events (>10%) Independent of Causality (n=33)

	All Grade		Grade 3-4	
	n (pts)	% (n=33)	n (pts)	% (n=33)
Upper respiratory tract infection	13	39%	0	0%
Petechiae/ purpura/ contusion	11	33%	0	0%
Nausea	8	24%	0	0%
Diarrhea	8	24%	1	3%
Constipation	7	21%	0	0%
Headache	6	18%	1	3%
Anemia	5	15%	4	12%
Rash	5	15%	0	0%
Neutropenia	4	12%	2	6%
Back pain	4	12%	0	0%
Urinary tract infection	4	12%	0	0%

Adverse Events of Significance and Special Interest

	All Cause	
	n (pts)	% (n=33)
Patients with at least one AE ≧Grade 3	16	48%[1]
Patients with at least one SAE	12	36%[2]
Events leading to treatment discontinuation	1[3]	3%

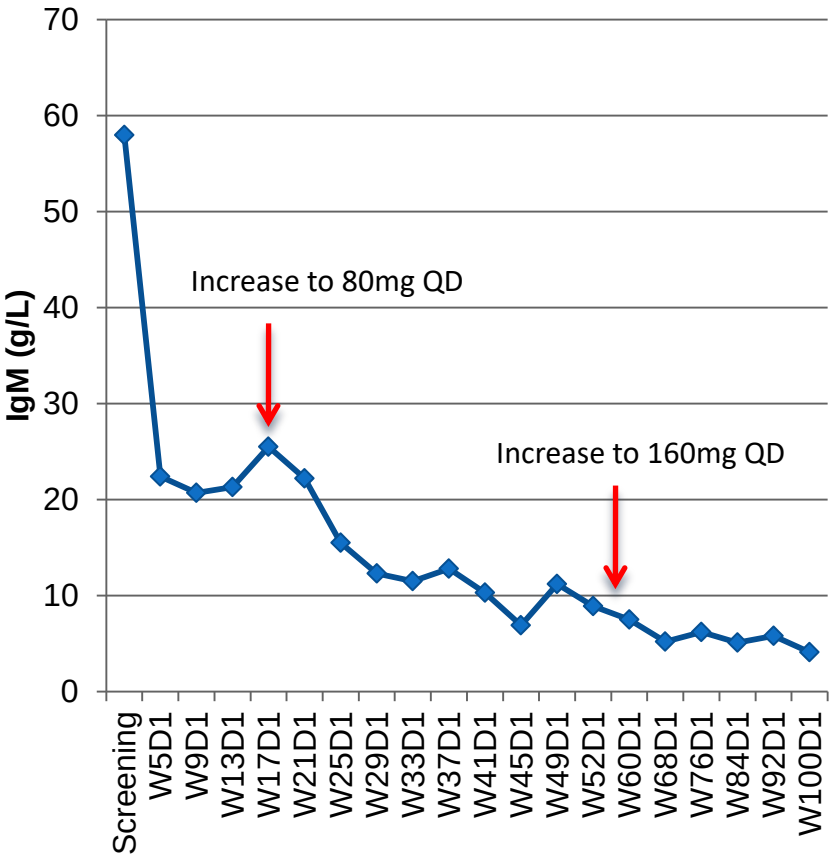
1. Grade ≥3 events considered possibly related to BGB-3111: neutropenia (n=2), diarrhea, hypertension, pneumonia, increased LFTs, cryptococcal meningitis, pulmonary hypertension, vomiting(all n=1)
2. SAE considered possibly related to BGB-3111: atrial fibrillation, cryptococcal meningitis, pneumonia, vomiting (all n=1)
3. Bronchiectasis

AE of Special Interest	All Grade		Grade 3-4	
	n (pts)	% (n=33)	n (pts)	% (n=33)
Diarrhea	8	24%	1	3%
Serious hemorrhage*	0	0%	0	0%
Atrial fibrillation	3**	9%	0	0%

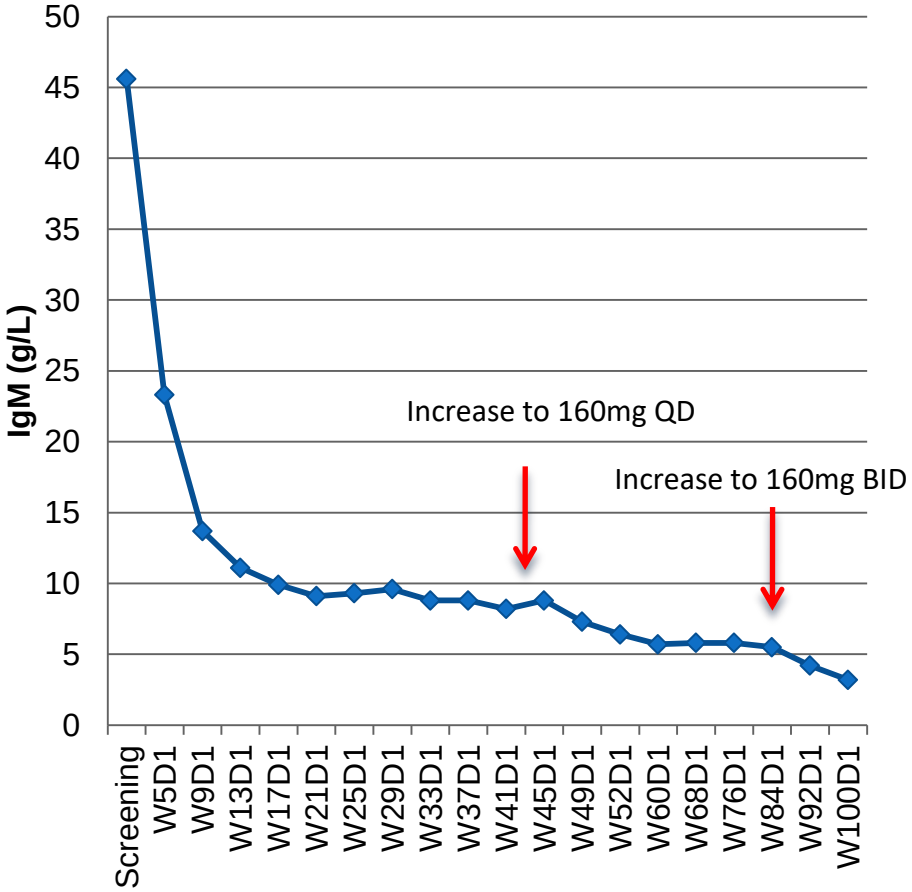
*Grade ≥3 hemorrhage, or CNS hemorrhage of any grade
** 2 patients had pre-existing atrial fibrillation

Intrapatient Dose Escalation

S401: Initial dose 40mg QD



S101: Initial dose 80mg QD



Conclusions

- **BTK inhibitor BGB-3111:**
  - **Is associated in high serum exposure levels**
  - **Results in complete and sustained BTK inhibition in both circulating and nodal lymphocytes**
  - **Is associated with a highly favorable safety and tolerability profile**
    - **Overall adverse event profile consistent with relative selectivity for BTK**
    - **Treatment related serious bleeding and new-onset atrial fibrillation rare**
  - **Induces frequent and rapid responses in patients with relapsed or refractory chronic lymphocytic leukemia, mantle cell lymphoma, and Waldenström macroglobulinemia**
  - **On-going trials ….**