Next Generation BTK Inhibitors: Zanubrutinib (BGB-3111)

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How can Ibrutinib be improved?

- Some Ibrutinib side-effects may be related to off-target toxicity
  - Platelet dysfunction / bleeding (~50% overall, <5% serious)
  - Atrial fibrillation 5 – 15 %
  - Self-limiting diarrhea / rash (EGFR) ~50%
  - Toxicities are likely due to “off-target” inhibition of EGFR/JAK3/TEC
- Relatively low oral bioavailability
- Interference with anti-CD20 mediated ADCC in vitro
- BTK 481 and PLCg mutations conferring resistance

Zanubrutinib (BGB-3111) Timeline at VCCC

Beigene visit / Phase 1 draft

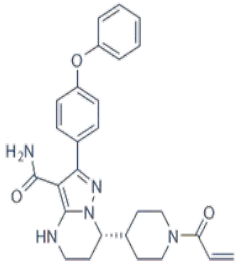
First patient enrolled

ASH Oral

NASDAQ Listing ($31)

Blood paper

July 2013 | **August 2014** | **Dec 2015** | **May 2016** | **Sep 2019**



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CLINICAL TRIALS AND OBSERVATIONS

Phase 1 study of the selective BTK inhibitor zanubrutinib in B-cell malignancies and safety and efficacy evaluation in CLL

Nasdaq

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
HER2	HER2 Biochemical Assay	9.4	661	70
TEC	TEC Biochemical Assay	0.8	1.9	2.4

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

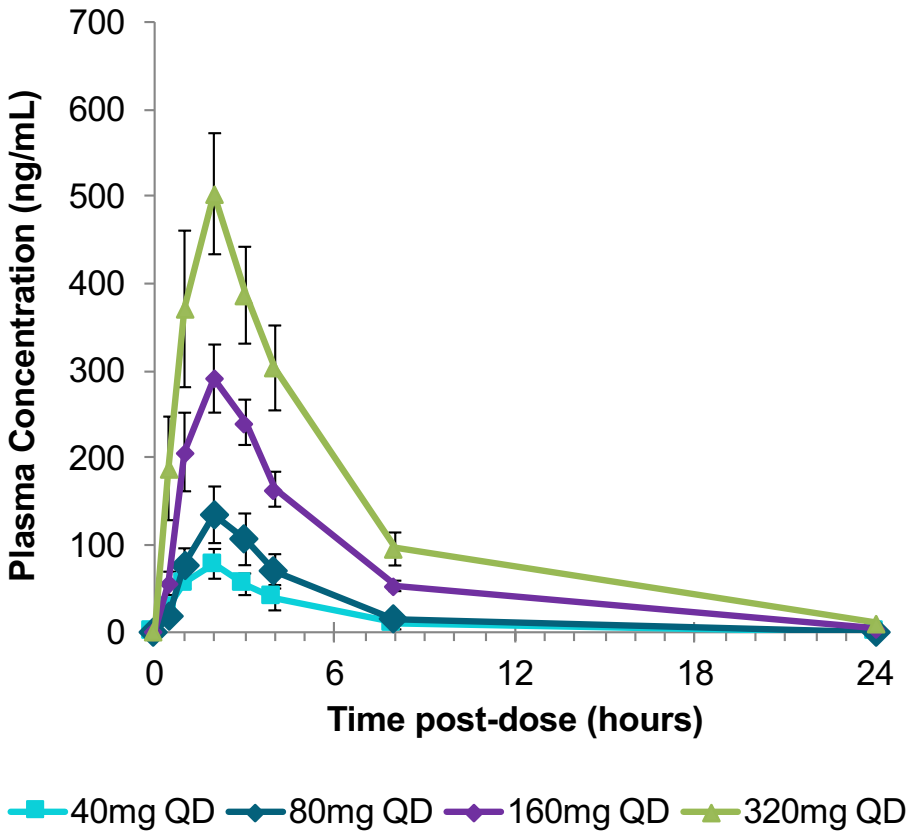
QD, TN CLL/SLL, n=20

Part 2i

QD, TN MCL, n=20

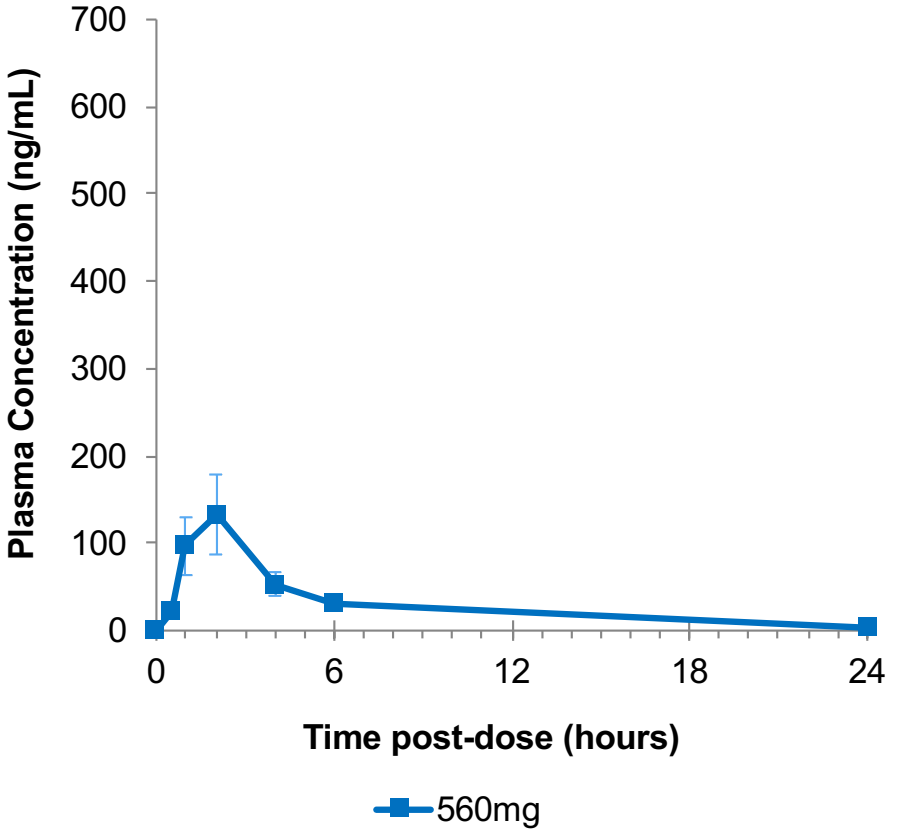
Plasma Exposure Comparison for BGB-3111 & Ibrutinib

BGB-3111



Tam *et al.*, Blood, 2019

Ibrutinib

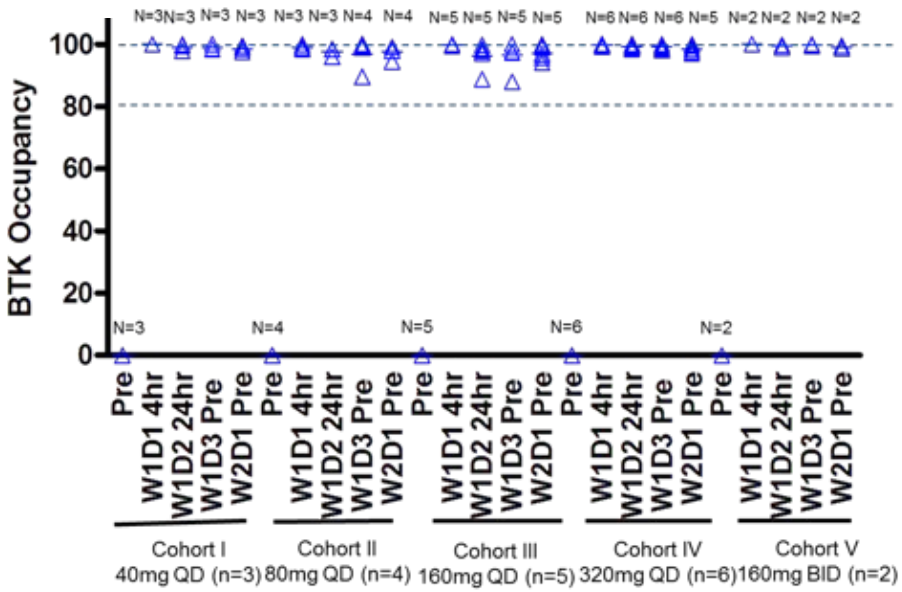


Adapted from Advani *et al.*, JCO, 2013

- 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

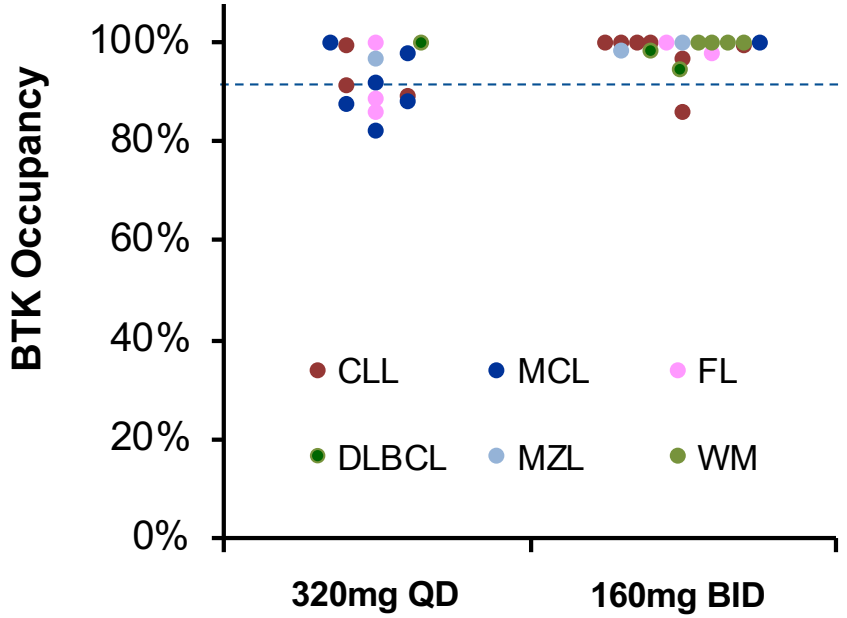
Complete and Sustained BTK Occupancy in PBMC and Lymph Node

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 >95% trough occupancy: 89% (160mg BID) vs 50% (320mg QD), p=0.034

Tam, Blood 2019; 134:851

Phase I Zanubrutinib: CLL/SLL Patients (n=94)

Parameter	Dose escalation* Part 1: n = 17; and cohort 2a, part 2: n = 39	CLL/SLL† Part 2: n = 94
Age, median (range), y	67 (41-85)	69 (24-87)
Sex		
Male	42 (75.0)	73 (77.7)
Female	14 (25.0)	21 (22.3)
Race		
White	45 (80.4)	86 (91.5)
Black or African American	0	1 (1.1)
Asian	9 (16.1)	4 (4.3)
Other	2 (3.6)	3 (3.2)
ECOG performance status		
0	27 (48.2)	47 (50.0)
1	24 (42.9)	42 (44.7)
2	5 (8.9)	5 (5.3)
Prior treatment status		
Treatment-naive	1 (1.8)	22 (23.4)
Relapsed or refractory	55 (98.2)	72 (76.6)
No. of prior therapies, median (range)‡	2 (0-7)	2 (1-9)§
Cytogenetics, n/N evaluable‖		
del(17p) or *TP53* mutation	—	18/94 (19.1)
del(11q)	—	17/73 (23.3)
Unmutated IgHV	—	14/21 (66.7)
Bulky disease, >10 cm	0	5 (5.3)

- Median follow-up : 13.7 months (0.4 - 30.5)
- 94.7% still on treatment
- 2 progressions (not Richter) at 15 and 16 months
- 2 ceased due to AEs

	Treatment Naïve (n=22)	Relapsed / Refract (n=56)*
Overall Response (%)	100	94.6
Complete Remission (%)	4.5	1.8
Partial Remission/ PR-L (%)	95.4	92.9
Stable disease (%)	0	3.6
Progressive disease (%)	0	0

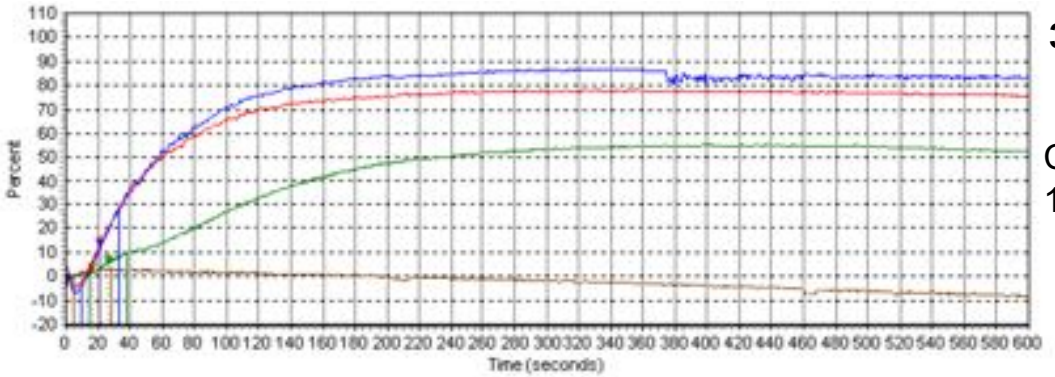
*1 non-evaluable

Tam, Blood 2019; 134:851

CLL / SLL Cohort: Adverse Events (>5%) and Recurrent Grade 3-4 Adverse Events

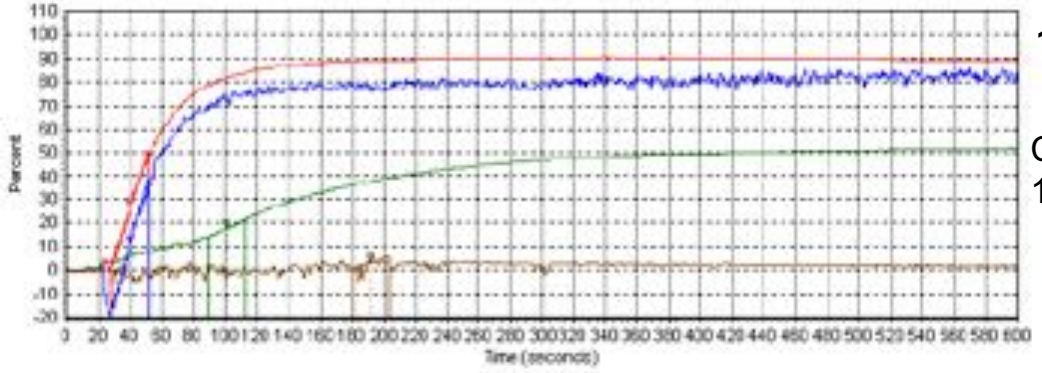
AE	CLL/SLL, n = 94	
	Any grade	Grade 3/4
Any event, n (%)	89 (94.7)	34 (36.2)
Contusion	33 (35.1)	0
Upper respiratory tract infection	31 (33.0)	0
Cough	24 (25.5)	0
Diarrhea	20 (21.3)	0
Fatigue	18 (19.1)	0
Back pain	14 (14.9)	1 (1.1)
Hematuria	14 (14.9)	0
Headache	13 (13.8)	0
Nausea	13 (13.8)	1 (1.1)
Rash	12 (12.8)	0
Arthralgia	11 (11.7)	0
Muscle spasms	11 (11.7)	0
Urinary tract infection	10 (10.6)	1 (1.1)
Petechiae	8 (8.5)	0
Constipation	7 (7.4)	0
Purpura	7 (7.4)	1 (1.1)
Neutropenia	7 (7.4)	6 (6.4)
Pneumonia	7 (7.4)	2 (2.1)
Sinusitis	7 (7.4)	0
Limb injury	6 (6.7)	0
Abdominal pain	5 (5.3)	0
Basal cell carcinoma	5 (5.3)	0
Dizziness	5 (5.3)	0
Dry mouth	5 (5.3)	0
Peripheral edema	5 (5.3)	0
Postprocedural contusion	5 (5.3)	0
Hypertension	5 (5.3)	2 (2.1)
Cellulitis	5 (5.3)	1 (1.1)
Nasopharyngitis	5 (5.3)	0
Squamous cell carcinoma of the skin	5 (5.3)	1 (1.1)
Anemia	3 (3.2)	2 (2.1)

- Atrial Fibrillation in 1 patient
- Major subcutaneous bleeding in 1 patient (on concomitant aspirin)



320mg

Collagen 10ug/ml



160mg

Collagen 10ug/ml

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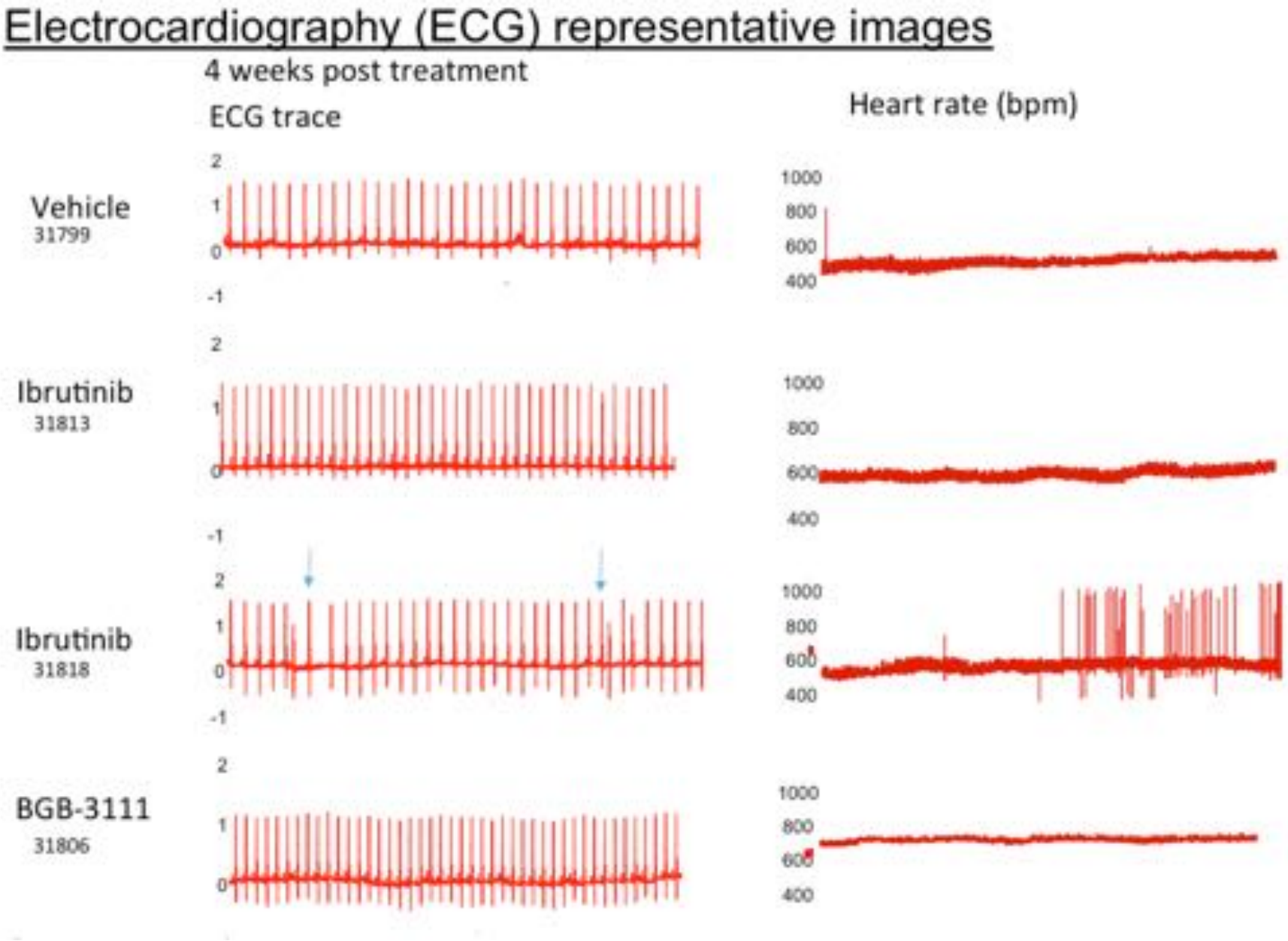
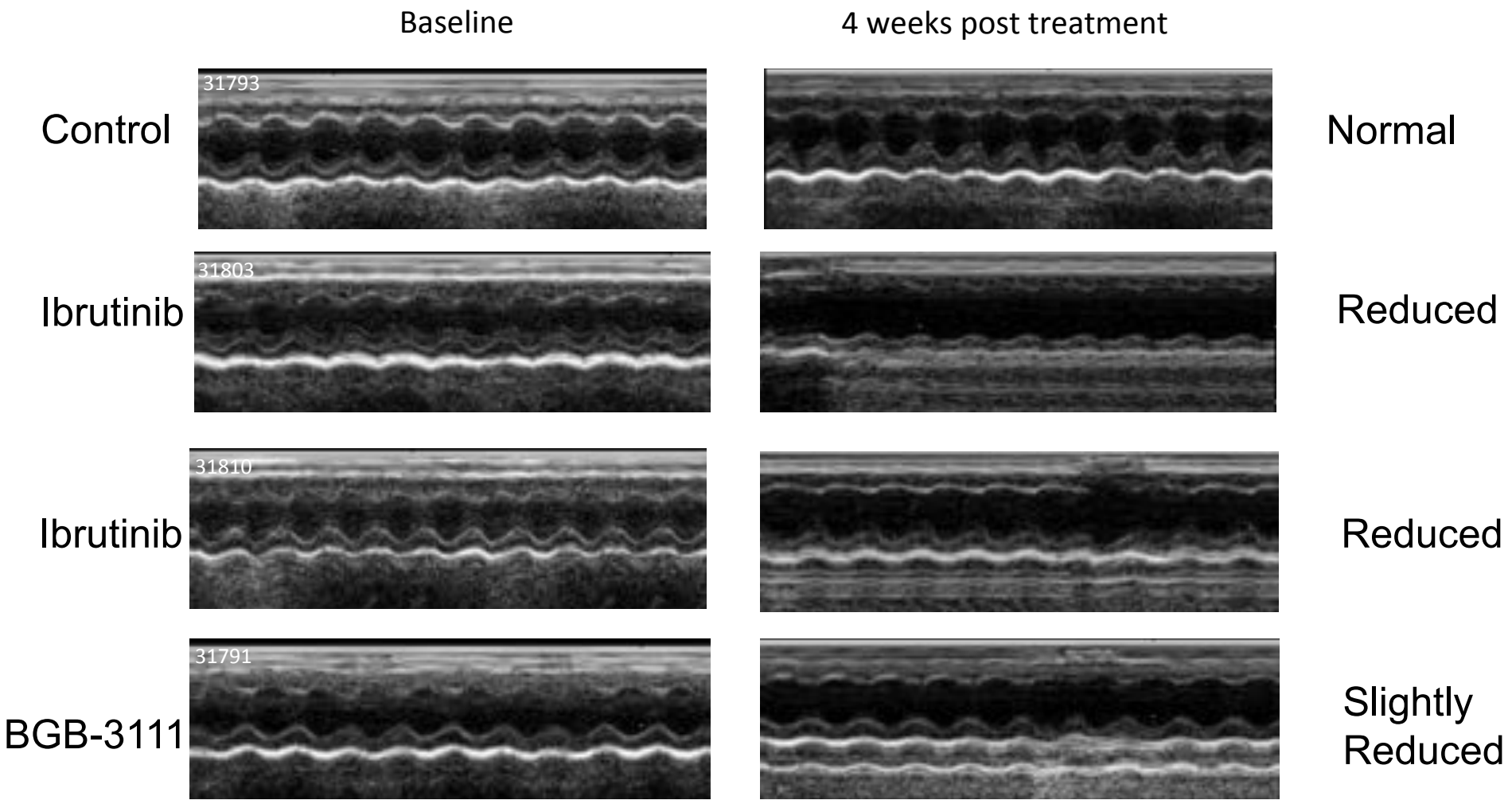
BTKi Cardiotoxicity Experiments in Mice



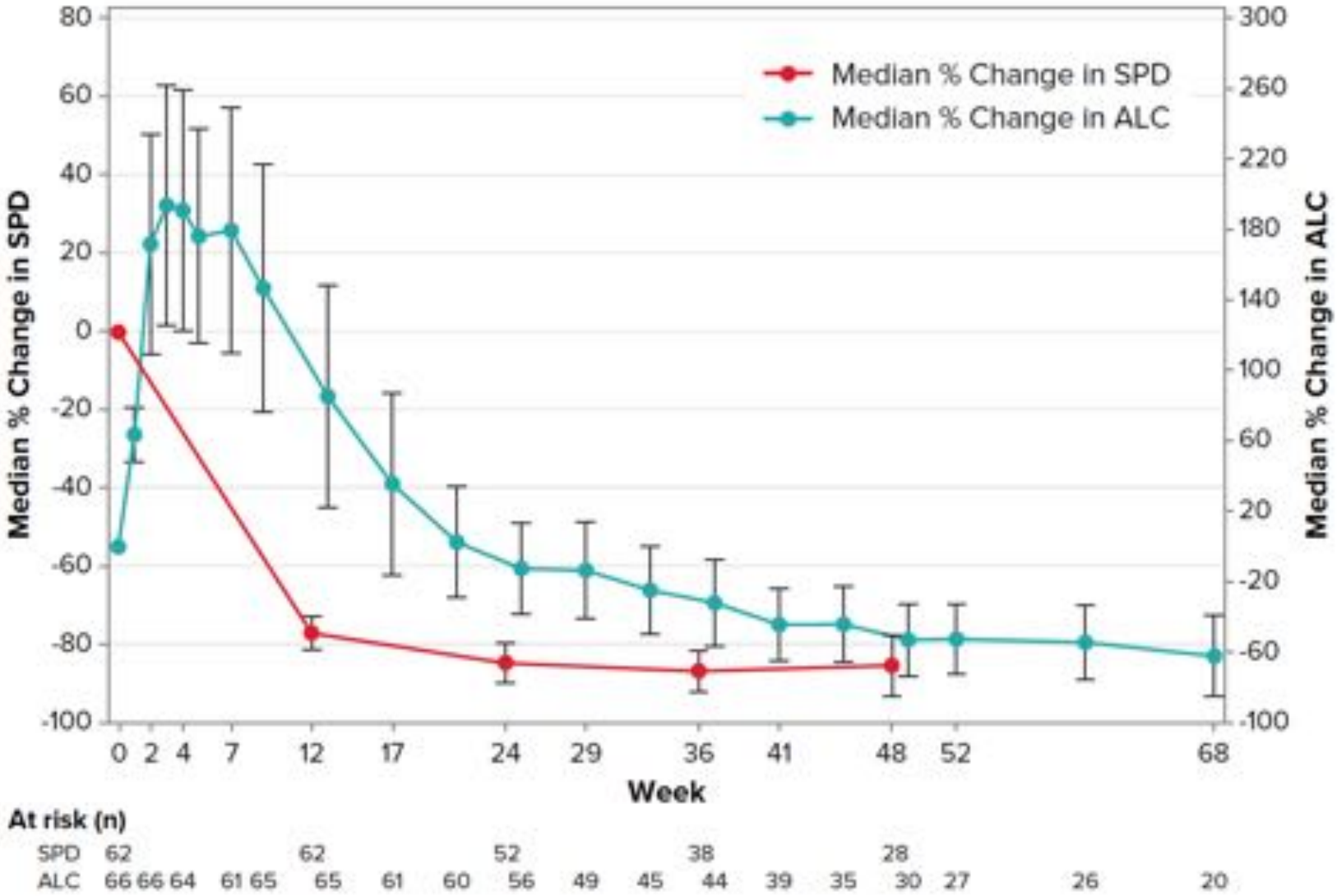
McMullen, Unpublished data

BTKi Cardiotoxicity Experiments in Mice: Early Evidence of Ventricular Dysfunction on Echo



McMullen, Unpublished data

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.

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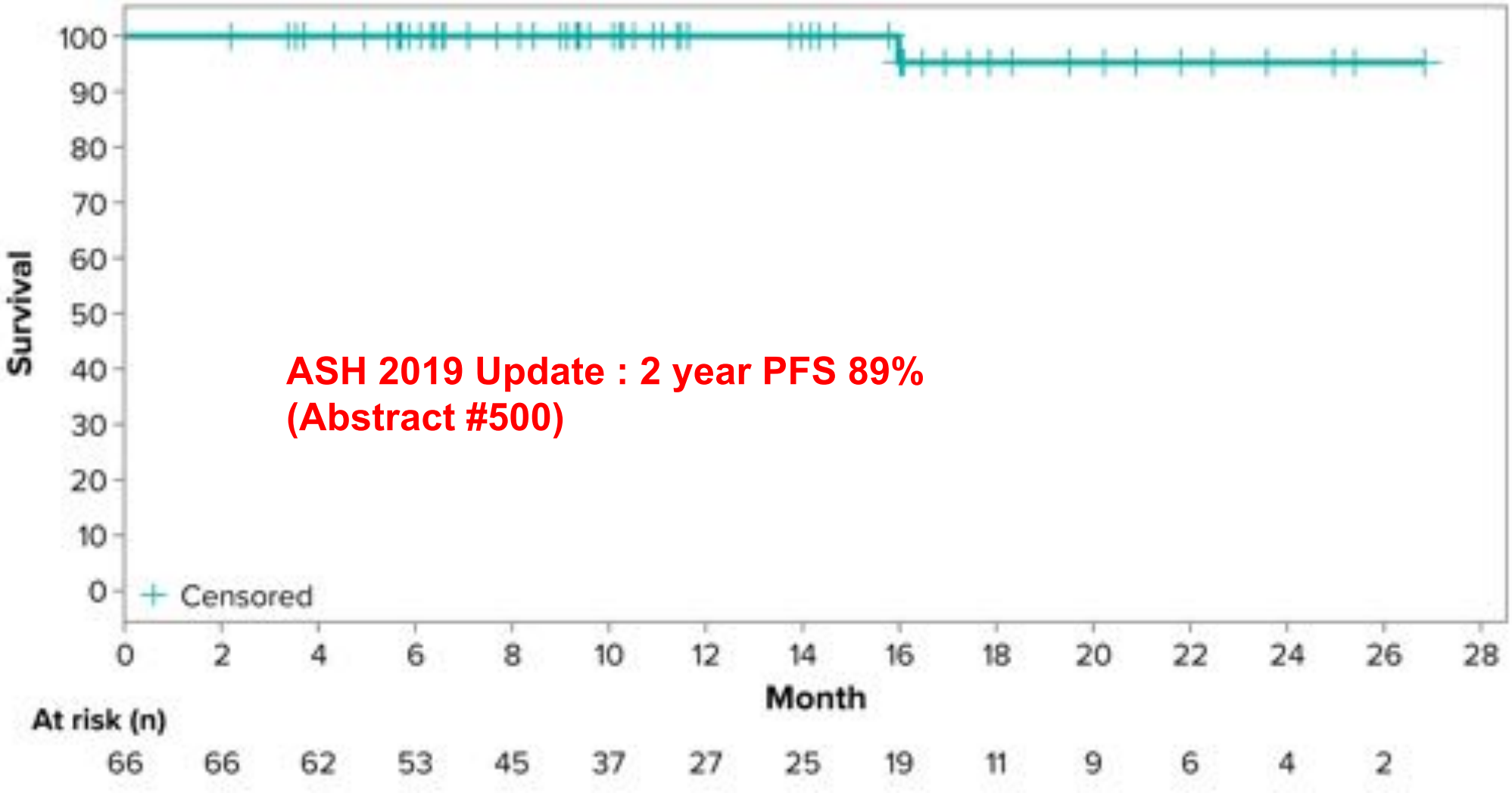
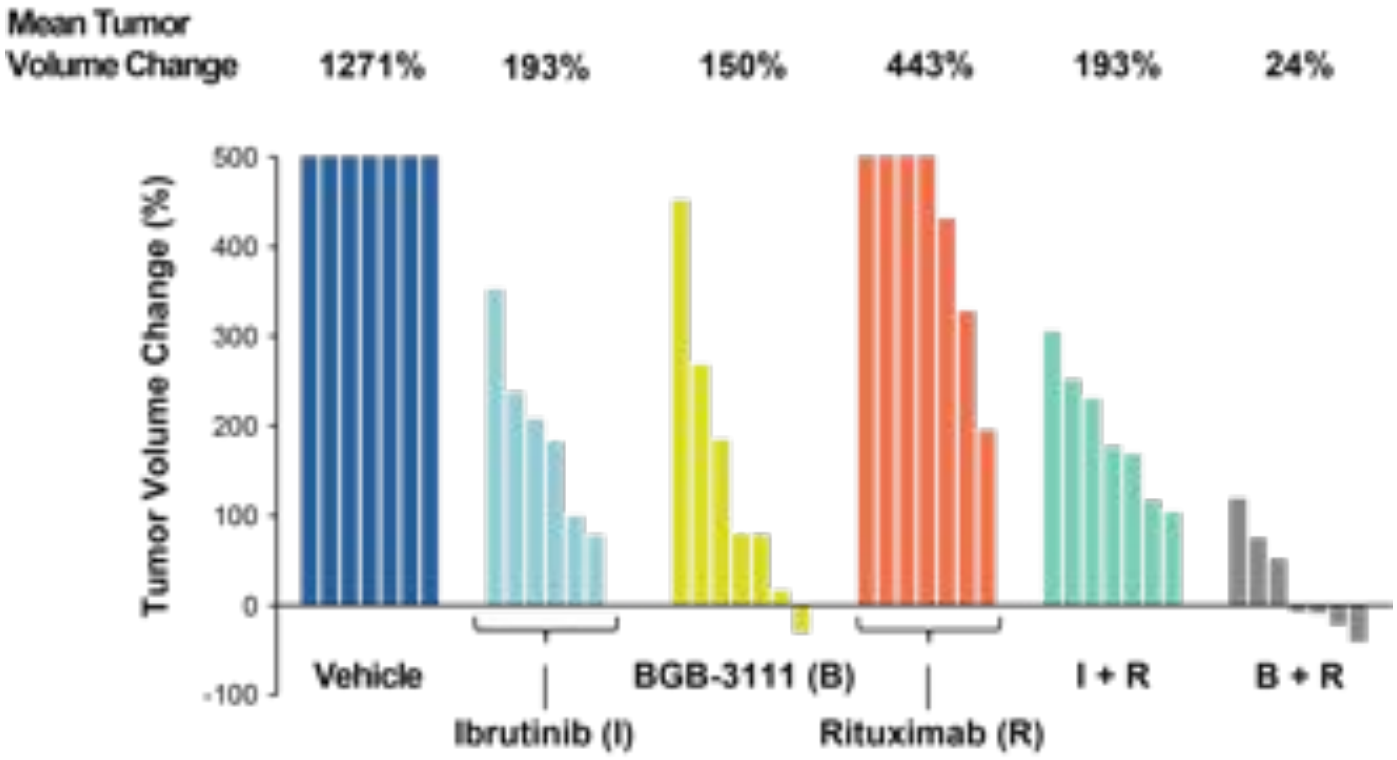
CLL / SLL: Progression-Free Survival



ASH 2019 Update : 2 year PFS 89%
(Abstract #500)

Tam, Blood 2019; 134:851

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].

Tam, ICML 2019

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

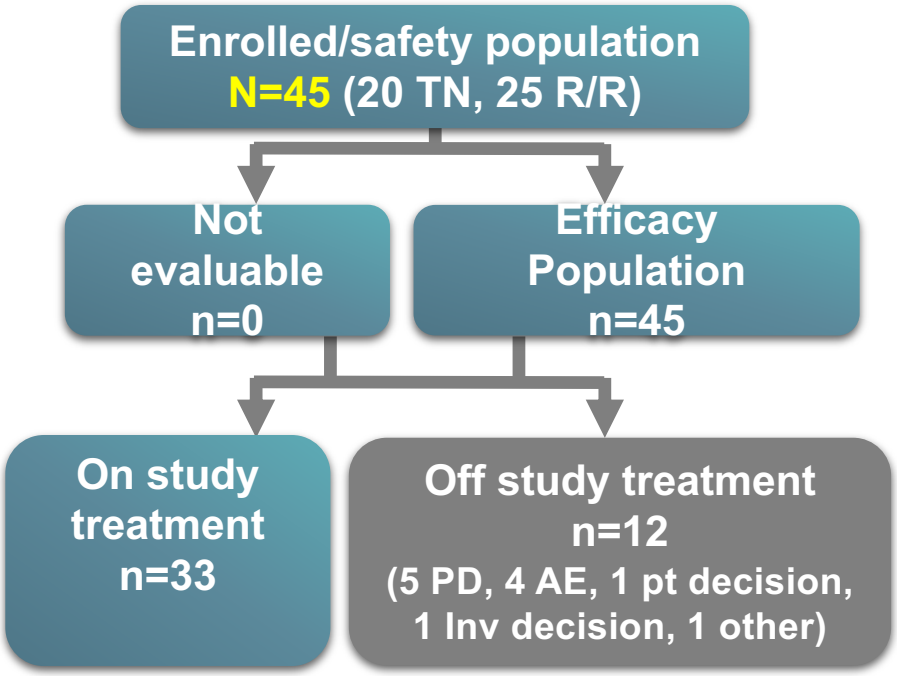
Tam, ICML 2019

NCT02569476

ZANU/GA101 Phase 1b: Patient disposition (as of 28 February, 2019)

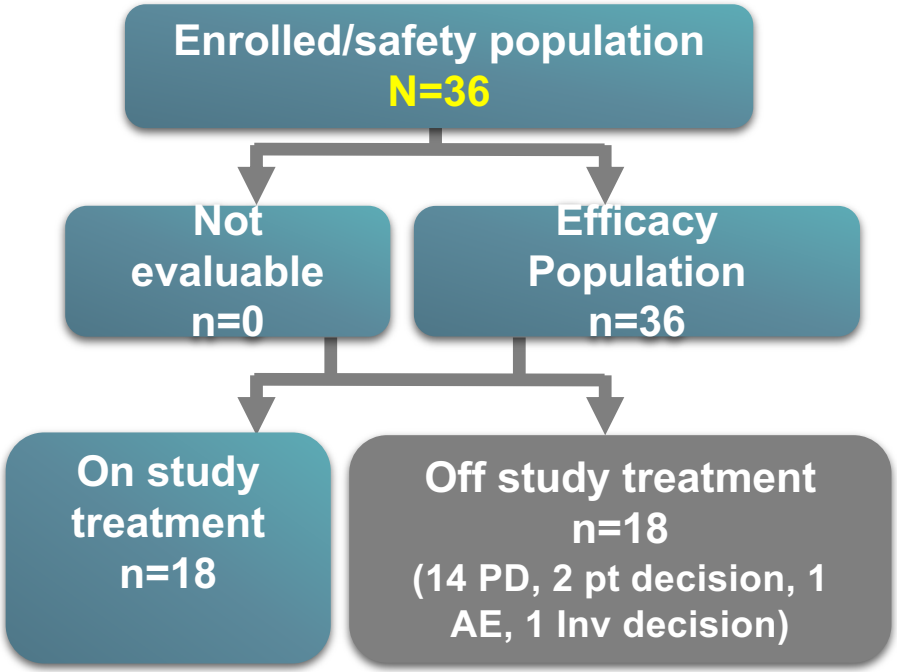
CLL/SLL

- Median follow up 28.9 mo (range, 7.9-36.9)



R/R FL

- Median follow up 20.1 mo (range, 2.3-37.2)



AE, adverse event; Inv, Investigator; PD, progressive disease; pt, patient; R/R, relapsed/refractory; TN, treatment-naïve.

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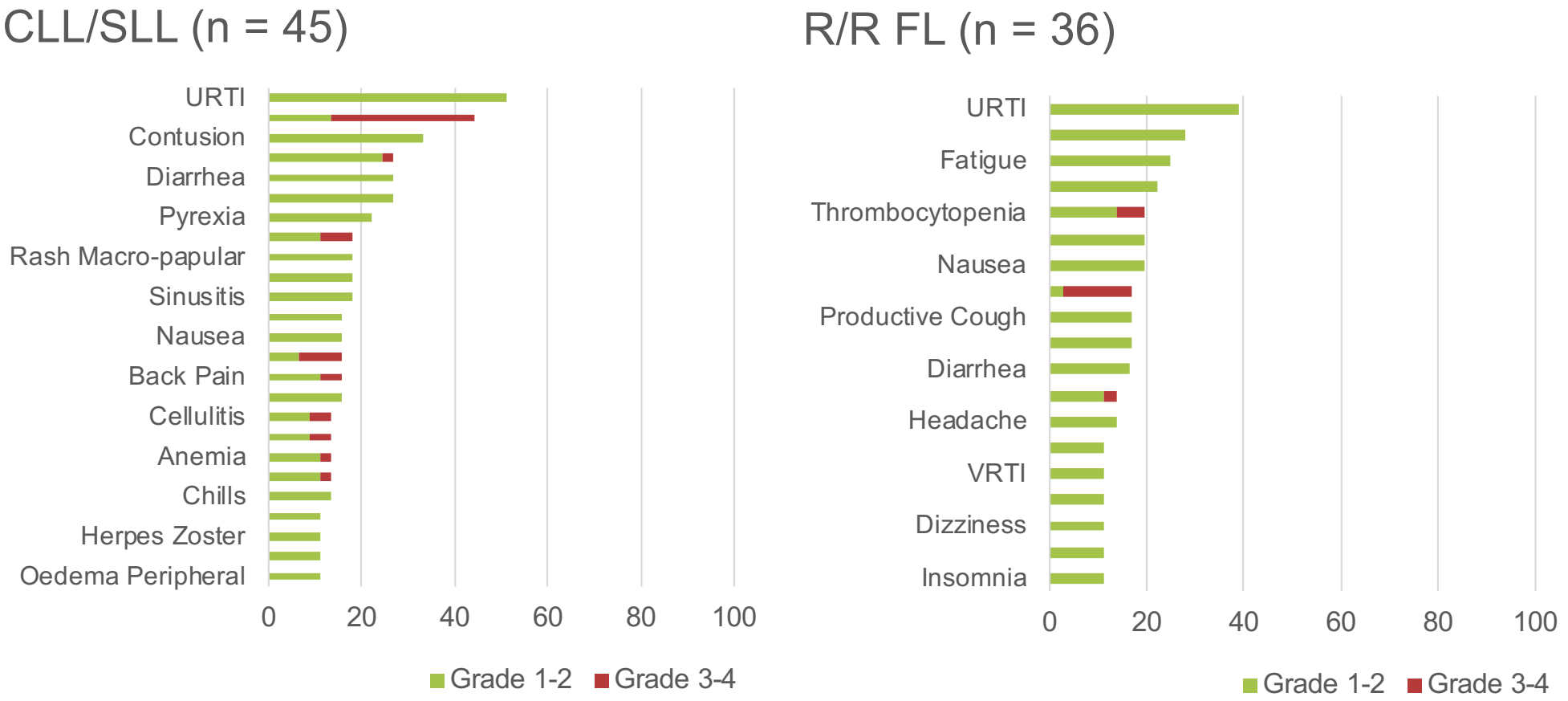
Most common (>10%) adverse events in patients with CLL/SLL and R/R FL were primarily low grade



LRTI, lower respiratory tract infection; PSN, peripheral sensory neuropathy; URTI, upper respiratory tract infection; VRTI, viral respiratory tract infection.

ZANU/GA101 Phase 1b: Disease response

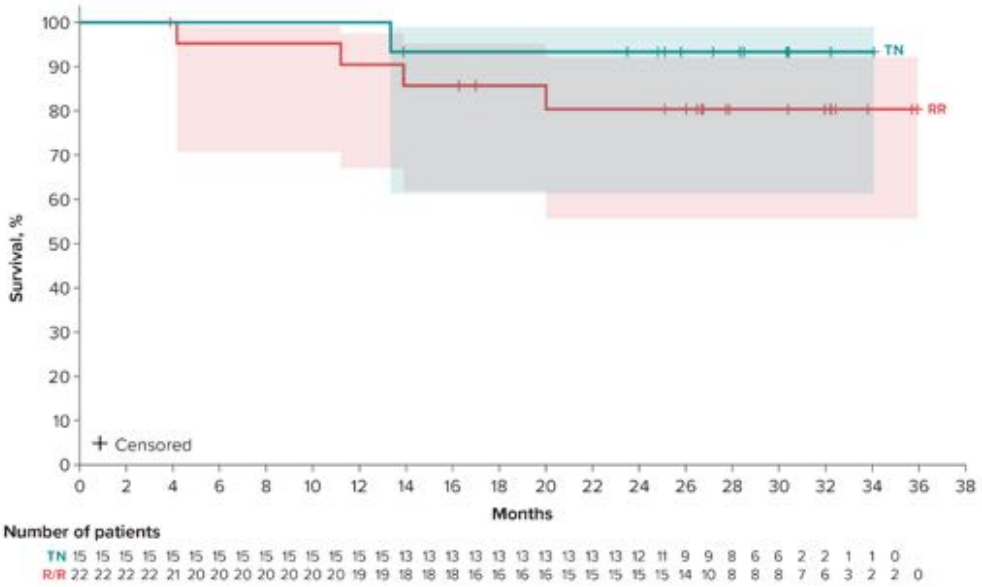
	TN CLL/SLL (n = 20)	R/R CLL/SLL (n = 25)	R/R FL (n = 36)
Follow-up median (range), mo	28.8 (13.9 - 34.8)	28.9 (7.9 – 36.9)	20.1 (2.3-37.2)
Best Response, n (%)			
ORR	**20 (100.0)**	**23 (92.0)**	**26 (72.2)**
CR*	6 (30.0)	7 (28.0)	14 (38.9)
PR	14 (70.0)	16 (64.0)	12 (33.3)
SD	0	2 (8.0)	6 (16.7)
PD	0	0	4 (11.1)
ORR for Del(17p) or p53	6 (100)	8 (80)	n/a

*3 of 6 tested were MRD negative at <10-4.

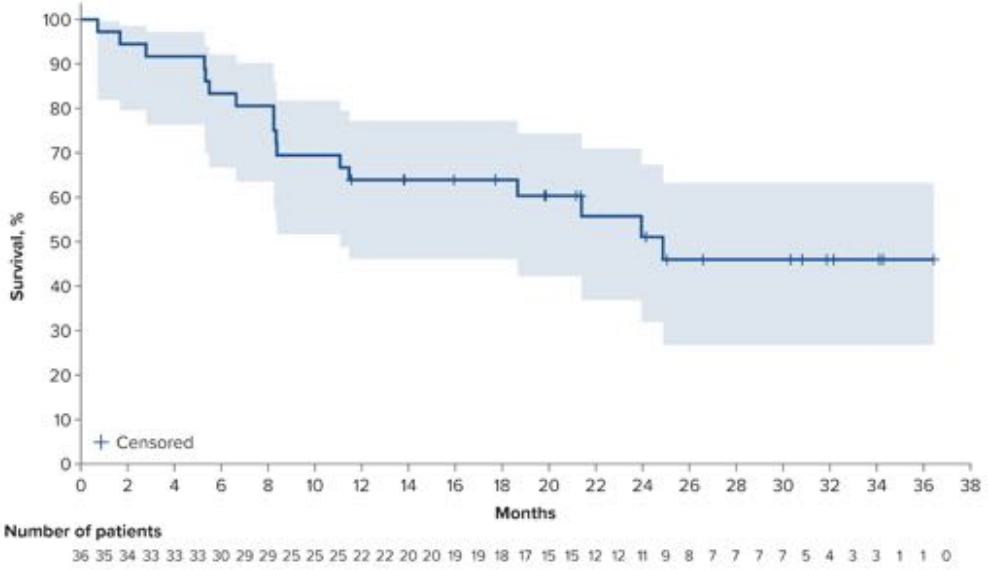
CLL/SLL, chronic lymphocytic leukemia/small lymphocytic lymphoma; CR, complete response; FL, follicular lymphoma; ORR, overall response rate; PD, progressive disease; PR, partial response; R/R, relapsed/refractory; SD, stable disease; TN, treatment-naïve.

ZANU / GA101 Phase 1b: Progression-free survival

CLL/SLL (median f/up 28.8 months)



R/R FL (median f/up 20.1 months)



Registration Studies

- WM : Phase 3 BGB-3111 vs Ibrutinib (1L/RR)
  - Completed recruitment
- CLL : Phase 3 BGB-3111 vs Benda-Ritux (1L)
  - Completed recruitment
  - "Arm D" Zanu + Venetoclax open for 17p- CLL
- CLL : Phase 3 Ibrutinib vs BGB-3111 (RR)
  - Completed recruitment