Improved Depth of Response With Increased Follow-Up For Patients With Waldenström Macroglobulinemia (WM) Treated With Bruton's Tyrosine Kinase Inhibitor Zanubrutinib (BGB-3111)

Abstract PS1186

Judith Trotman,[1,2] Constantine S Tam,[3,4,5,6] Paula Marlton,[7,8] David Gottlieb,[9] David Simpson,[10] Gavin Cull,[11,12] David Ritchie,[3,4,6] Emma Verner,[1] Javier Munoz,[13] Sumita Ratnasingam,[14] Mary Ann Anderson,[3,4,6] Peter Wood,[7,8] Eric Hedrick,[15] Jane Huang,[15] Sunhee Ro,[15] James Hilger,[15] John F Seymour,[3,4,6] Andrew W Roberts,[3,4,6] Stephen Opat[14,16]

[1]Concord Repatriation General Hospital, Australia; [2]University of Sydney, Concord, Australia; [3]Peter MacCallum Cancer Centre, Melbourne, Victoria, Australia; [4]University of Melbourne, Parkville, Victoria, Australia; [5]St Vincent's Hospital, Fitzroy, Victoria, Australia; [6]Royal Melbourne Hospital, Parkville, Victoria, Australia; [7]Princess Alexandra Hospital, Brisbane, Australia; [8]University of Queensland School of Medicine, Brisbane, Australia; [9]University of Sydney, Westmead Hospital, Westmead, Australia; [10]North Shore Hospital, Auckland, New Zealand; [11]Sir Charles Gairdner Hospital, Perth, Australia; [12]University of Western Australia, Perth, Australia; [13]Banner MD Anderson Cancer Center, Gilbert, AZ, USA; [14]Monash Health, Clayton, Victoria, Australia; [15]BeiGene (Beijing) Co. Ltd., Beijing, China and Emeryville, CA, USA; [16]Monash University, Clayton, Victoria, Australia

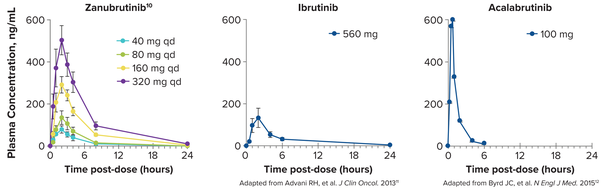
INTRODUCTION

- Bruton's tyrosine kinase (BTK) plays a critical role in B-cell receptor signaling, which mediates B-cell proliferation, migration, and adhesion[1–3]
  - BTK is constitutively activated in WM and is a key mediator in cell survival[4,5]
- First-generation BTK inhibitor Ibrutinib has shown activity in WM and become a standard of care[6,7]
  - Major response rate: 73% (including 16% very good partial response)[8]
  - 68% 3-year event-free survival[9]
- Based on preclinical data, zanubrutinib (BGB-3111) was shown to be a potent, highly selective, and irreversible BTK inhibitor with advantageous pharmacokinetics, designed to minimize off-target inhibition of TEC- and EGFR-family kinases (**Table 1**, **Figure 1**)[10]
  - Complete and sustained BTK occupancy in peripheral blood mononuclear cells AND lymph nodes (**Figure 2**)

Table 1. Zanubrutinib - kinase selectivity relative to ibrutinib

	Targets	Assays	Zanubrutinib IC_{50} (nM)	Ibrutinib IC_{50} (nM)	Ratio (Zanubrutinib:Ibrutinib)
ON TARGET	BTK	BTK-pY223 Cellular Assay	1.8	3.5	0.5
		Rec-1 Proliferation	0.36	0.34	1.1
		BTK Occupation Cellular Assay	2.2	2.3	1
		BTK Biochemical Assay	0.22	0.2	1.1
OFF TARGET	EGFR	p-EGFR HTRF Cellular Assay	606	101	6
		A431 Proliferation	3210	323	9.9
	ITK	ITK Occupancy Cellular Assay	606	189	17
		p-$PLC_{\gamma1}$ Cellular Assay	3433	77	45
		IL-2 Production Cellular Assay	2536	260	9.8
		ITK Biochemical Assay	30	0.9	33
	JAK3	JAK3 Biochemical Assay	200	3.9	51
	HER2	HER2 Biochemical Assay	661	9.4	70
	TEC	TEC Biochemical Assay	1.9	0.8	2.4

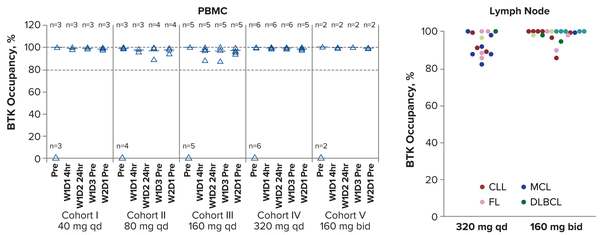
Figure 1. Pharmacokinetics of zanubrutinib, ibrutinib, and acalabrutinib



Adapted from Advani RH, et al. *J Clin Oncol.* 2013[11]

Adapted from Byrd JC, et al. *N Engl J Med.* 2015[12]

Figure 2. Sustained BTK inhibition in peripheral blood and lymph nodes



Complete and sustained BTK occupancy is seen in paired PMBC (left figure) and lymph node biopsy samples (right figure) collected pre-dose on day 3. In blood samples, complete BTK occupancy was seen at the lowest dose (40 mg). Note, 100% median trough occupancy at a dose of 160 mg twice bid with 94% of patients having > 90% occupancy in lymph nodes across malignancies.

- Presented here are updated results from a cohort of patients with WM treated within an ongoing phase 1 zanubrutinib trial (NCT02343120)

METHODS

- First-in-human, open-label, multicentre, phase 1 study of zanubrutinib in patients with B-cell malignancies (**Figure 3**)

Figure 3. Trial design

DOSE ESCALATION

Dose	Enrolled (WM)
40 mg qd	4 (1)
80 mg qd	5 (2)
160 mg qd	6 (1)
320 mg qd	6 (0)
160 mg bid	4 (0)

RP2D

320 mg qd or 160 mg bid*

DOSE EXPANSION

Population	RP2D Dose	Disease	Enrolled† (WM)
R/R	bid or qd	All B-cell	40 (2)
R/R	bid	Non-GCB DLBCL	40
R/R	bid	CLL/SLL	70
R/R	bid	WM	20 (20)
R/R	qd	CLL/SLL	20
R/R or TN	bid or qd	WM	50 (41)
R/R	bid or qd	MCL	20
TN	bid or qd	CLL/SLL	20
TN	bid or qd	MCL	20
R/R	bid or qd	HCL	10
R/R	bid	iNHL	40
R/R	bid	Richter's	15
R/R from prior BTK inhibitor	bid	All B-cell	15

*As of protocol v.6 all pts encouraged to switch to 160 mg bid due to favourable occupancy data.
†Enrollment in dose expansion is ongoing: planned enrollment shown for dose expansion cohorts, with WM enrollment as of data cutoff noted in parentheses.

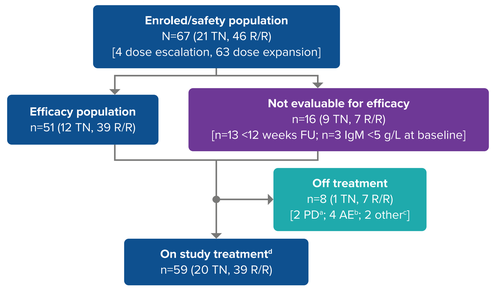
bid, twice daily; CLL/SLL, chronic lymphocytic leukaemia/small lymphocytic lymphoma; DLBCL, diffuse large B-cell lymphoma; FL, follicular lymphoma; GCB, germinal center B-cell–like; HCL, hairy cell leukaemia; iNHL, indolent non-Hodgkin lymphoma; MCL, mantle cell lymphoma; MZL, marginal zone lymphoma; RP2D, recommended phase 2 dose; qd, once daily; WM, Waldenström macroglobulinemia.

- Eligibility
  - WHO-defined B-cell malignancy
  - No available higher priority treatment
  - Eastern Cooperative Oncology Group performance status 0-2
  - ANC ≥1000/μL, platelets ≥50000/μL (growth factor/transfusions allowed)
  - Adequate renal and hepatic function
  - No significant cardiac disease (anticoagulation allowed)
- Primary endpoints
  - Safety including AEs and SAEs per the NCI CTCAE v4.03, based on physical examination and laboratory measurements
  - Recommended phase 2 dose
- Select secondary endpoints
  - Pharmacokinetics
  - Efficacy, including overall response rate, progression-free survival, overall survival, and duration of response

RESULTS

- 67 patients with WM have been enroled (**Table 2**); 59 of whom remain on study treatment (**Figure 4**) with median follow-up of 15.5 months (range, 0.1-37.6)

Figure 4. Disposition for patients with WM (as of November 3, 2017)



[a]Week 24 after SD, Week 49 after PR; [b]Worsening bronchiectasis, prostate adenocarcinoma, gastric adenocarcinoma, acute myeloid leukemia (all unrelated to zanubrutinib per investigator); [c]Radiation/transplant, noncompliance.
[d]One patient post PD still on treatment.
AE, adverse event; FU, follow-up; PD, progressive disease; R/R, relapsed/refractory; TN, treatment-naïve.

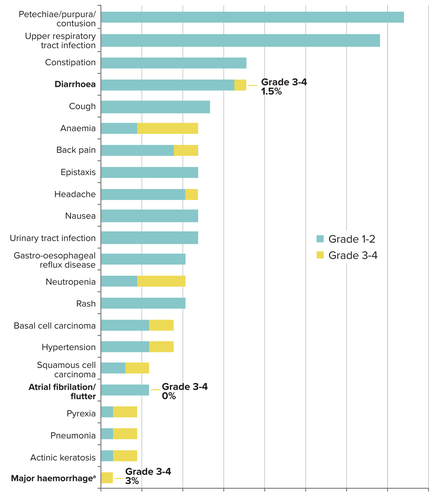
Table 2. Patient and disease characteristics

Characteristic	Total (N=67)
Age, years, median (range)	66 (44-87)
ECOG performance status, n (%)	
0	24 (36)
1	41 (61)
2	2 (3)
Prior treatment status	
Treatment-naïve, n (%)	21 (31)
Relapsed/refractory, n (%)	46 (69)
Number of prior therapies, median (range)	2 (1-8)
Prior anti-CD20 treatment, n (% of R/R)	43 (93)
Genotype, n (%)	
MYD88^{L265P}/*CXCR4*^{WT}	28 (42)
MYD88^{L265P}/*CXCR4*^{WHIM}	5 (7)
MYD88^{WT}	8 (12)
Unavailable	26 (39)

ECOG, Eastern Cooperative Oncology Group.

- The most common AEs in patients with WM were primarily grade 1-2 in severity (**Figure 5**)

Figure 5. Most common adverse events and BTK inhibitor events of interest, regardless of causality



Note: Common AEs include all grade ≥10% or grade 3-4 ≥2%. BTK inhibitor events of interest are in bold.
*Grade ≥3 haemorrhage, or CNS haemorrhage of any grade.

- AEs of interest:
  - Major haemorrhage (any grade ≥3 haemorrhage or any grade CNS haemorrhage) was reported in 2 patients (3%; both grade 3-4)
  - Atrial fibrillation/flutter was reported in 4 patients (6%; 0 grade 3-4)
  - Diarrhoea was reported in 12 patients (18%; grade 3-4 in 1 patient [1.5%])
- 26 patients (39%) had ≥1 grade ≥3 AE
- 22 patients (33%) had ≥1 serious AE (SAE)
  - SAEs possibly related to zanubrutinib were hemothorax, atrial fibrillation, colitis, febrile neutropenia, and headache (each n=1)
- 4 patients (6%) had AEs leading to discontinuation (all unrelated to zanubrutinib per investigator)
  - Worsening bronchiectasis (fatal), gastric adenocarcinoma, prostate adenocarcinoma, and acute myeloid leukemia (each n=1)

- For the 51 patients evaluable for response, the overall response rate (ORR) was 92% and the major response rate (MRR) was 80% (**Table 3**)
  - 43% of patients achieved VGPR
  - Presence of *MYD88*^{L265P} may be associated with response rate and depth; activity also present in patients with *MYD88*^{WT}

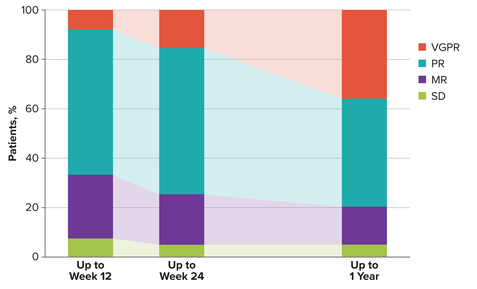
Table 3. Best response in evaluable patients (n=51); overall and by *MYD88* mutations status

Best response, n (%)	OVERALL (n=51)	By *MYD88* Status			
		MYD88^{L265P}/*CXCR4*^{WT} (n=25)	*MYD88*^{L265P}/*CXCR4*^{WHIM} (n=5)	*MYD88*^{WT} (n=6)	Unknown Status (n=15)
ORR	47 (92)	23 (92)	5 (100)	5 (83)	14 (93)
MRR	41 (80)	21 (84)	4 (80)	3 (50)	13 (87)
VGPR	**22 (43)**	**14 (56)**	**2 (40)**	**1 (17)**	**5 (33)**
PR	19 (37)	7 (28)	2 (40)	2 (33)	8 (53)
MR	6 (12)	2 (8)	1 (20)	2 (33)	1 (7)
SD	4 (8)	2 (8)	0	1 (17)	1 (7)

MR, minor response; PR, partial response; SD, stable disease; VGPR, very good partial response.

- 39 of the 51 evaluable patients had ≥1 year of follow-up as of the data cutoff date; of the 12 remaining, 9 had <1 year of follow-up and 3 discontinued prior to 1 year (reasons for discontinuation in **Figure 4**)
  - For those 39 patients, depth of response increased over time; rate of VGPR increased from 8% at 12 weeks to 36% at 1 year (**Figure 6**)

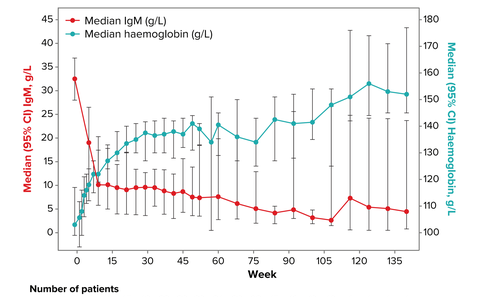
Figure 6. Best response over time in patients with ≥1 year of follow-up (n=39)



MR, minor response; PR, partial response; SD, stable disease; VGPR, very good partial response.

- IgM markedly decreased and hemoglobin markedly increased over time with zanubrutinib treatment (**Figure 7**)

Figure 7. Changes in IgM and haemoglobin over time in evaluable patients (n=51)



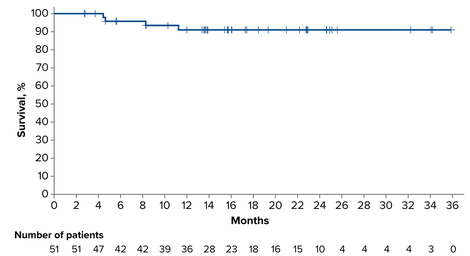
Number of patients

IgM	51	50	49	45	43	39	39	33	34	28	22	17	16	13	10	4	4	4	4
Haemoglobin,	51	44	51	46	42	42	40	37	38	29	23	18	17	14	10	4	4	4	4

Note: patient numbers shown only at timepoints with data for both IgM and haemoglobin.

- Estimated 12 month PFS of 91% (**Figure 8**)

Figure 8. Progression-free survival in evaluable patients[a] (n=51)



Number of patients

	51	51	47	42	42	39	36	28	23	18	16	15	10	4	4	4	4	3	0

[a]Evaluable patients defined in Figure 3.

CONCLUSIONS

- Zanubrutinib, a highly selective oral BTK inhibitor achieved high plasma concentrations and complete sustained BTK occupancy in blood and lymph nodes
- Updated results from an ongoing phase 1 trial in patients with B-cell malignancies suggest that zanubrutinib was generally well-tolerated and highly active in patients with WM
  - Overall response rate of 92% including 43% with VGPR
  - Increased depth of response over time
  - Estimated 12 month PFS of 91%
  - Discontinuation due to AEs was uncommon and not related to zanubrutinib treatment
- A phase 3 trial comparing zanubrutinib with ibrutinib in patients with WM is ongoing

REFERENCES

1. Rickert RC. *Nat Rev Immunol.* 2013;13:578-591.
2. Choe H, Ruan J. *Oncology* (Williston Park). 2016;30:847-858.
3. Aalipour A, Advani RH. *Br J Haematol.* 2013;163:436-443.
4. Treon SP, et al. *Blood.* 2014;123:2791-2796.;
5. Argyropoulos KV, et al. *Leukemia.* 2016;30:1116-1125.
6. IMBRUVICA® (ibrutinib). Full Prescribing Information. February 2018.
7. IMBRUVICA® (ibrutinib). Summary of Product Characteristics. February 2018.
8. Treon SP, et al. *N Engl J Med.* 2015;372:1430-1440.
9. Palomba ML, et al. WWM. 2016 [abstract].
10. Tam CS, et al. *Blood.* 2015;126:832 [oral presentation].
11. Advani RH, et al. *J Clin Oncol.* 2013;31:88-94.
12. Byrd JC, et al. *N Engl J Med.* 2016;374:323-333.

ACKNOWLEDGEMENTS

We would like to thank the investigators, site support staff, and especially the patients for participating in this study
This study was sponsored by BeiGene. Editorial support was provided by Bio Connections LLC and funded by BeiGene

DISCLOSURES

J Trotman: research funding from Pharmacyclics, Roche, Janssen, and Celgene
C Tam: honoraria from Janssen, AbbVie, Roche, and BeiGene; travel expenses from Janssen and BeiGene; research funding from Janssen and AbbVie
P Marlton: honoraria from and consulting/advisory role with Roche, Celgene, AbbVie, and Novartis; travel expenses from BMS
D Gottlieb: consulting/advisory role with AbbVie, Indee, Pfizer, and Link
D Simpson: honoraria from and consulting/advisory role for Roche, Janssen, Celgene, and MSD; travel expenses from Celgene and Gilead; research funding from Amgen, Pharmacyclics, Acerta, BeiGene, Roche, and AbbVie
G Cull: travel expenses from AbbVie; research funding from BeiGene and AbbVie
D Ritchie: travel expenses from Takeda; consulting/advisory role for Amgen, BMS, and Novartis
E Verner, S Ratnasingam, A Roberts: no relevant financial relationship to disclose
J Munoz: speaker's bureau for Kite Pharma and Bayer
MA Anderson: expert testimony for, travel expenses, and research funding from AbbVie
P Wood: honoraria from Bayer, BMS, and Boehringer
E Hedrick: employment, leadership role, equity awards, and consulting/advisory role with BeiGene
J Huang, J Hilger: employment and equity awards with BeiGene
S Ro: employment and equity awards with and research funding from BeiGene and Amgen
J Seymour: speaker's bureau for AbbVie, Celgene, Janssen, and Roche; honoraria from and consulting/advisory role for AbbVie, Celgene, Janssen, Roche, Sunesis, and Takeda; travel expenses from AbbVie, Celgene, and Roche; research funding from AbbVie, Celgene, Janssen, and Roche
S Opat: honoraria from Roche, Janssen, Celgene, Takeda, AbbVie, Gilead, Merck, and Mundipharma; travel expenses from Roche and BMS; consulting/advisory role Roche, Janssen, Celgene, Takeda, AbbVie, Gilead, Merck, Mundipharma, and Novartis; research funding from Roche, Janssen, Celgene, Takeda, AbbVie, Gilead, Merck, and BeiGene

Copies of this poster obtained through Quick Response (QR) Code are for personal use only and may not be reproduced without permission from EHA® and the author of this poster.