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

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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^{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 survival⁹
- 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 IC₅₀ (nM)	Ibrutinib IC₅₀ (nM)	Ratio (Zanubrutinib:Ibrutinib)				
F		BTK-pY223 Cellular Assay	1.8	3.5	0.5				
RGE	DTV	Rec-1 Proliferation	0.36	0.34	1.1				
N TA	DIK	BTK Occupation Cellular Assay	2.2	2.3	1				
0		BTK Biochemical Assay	0.22	0.2	1.1				
		p-FGFR HTRF Cellular Assav	606	101	6				
	EGFR	A431 Proliferation	3210	323	9.9				
		ITK Occupancy Cellular Assay	606	189	17				
GET	171/	p-PLC _{v1} Cellular Assay	3433	77	45				
TAR	IIK	IL-2 Production Cellular Assay	2536	260	9.8				
OFF		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



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 ESC	ALATION	RP2D	DOSE EXPANSION							
Dose	Enrolled (WM)	320 mg qd or →	Population	RP2D Dose	Disease	Enrolled⁺ (WM)				
40 mg qd	4 (1)	160 mg bid*	R/R	bid or qd	All B-cell	40 (2)				
80 mg qd	5 (2)		R/R	hid	Non-GCB	40				
160 mg qd	6 (1)				DLBCL					
320 mg qd	6 (0)		R/R	bid	CLL/SLL	70				
160 ma bid	4 (0)		R/R	bid	WM	20 (20)				
			R/R	qd	CLL/SLL	20				

*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.

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 R/R bid iNHL 40 R/R bid Richter's R/R from orior BTK bid All B-cell 15

- Eligibility
- WHO-defined B-cell malignancy
- No available higher priority treatment
- Eastern Cooperative Oncology Group performance status 0-2
- ANC $\geq 1000/\mu$ L, platelets $\geq 50000/\mu$ L (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



^aWeek 24 after SD, Week 49 after PR; ^bWorsening bronchiectasis, prostate adenocarcinoma, gastric adenocarcinoma, acute myeloid leukemia (all unrelated to zanubrutinib per investigator); ^cRadiation/transplant, noncompliance. 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.

severity (**Figure 5**)

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

1	-
	Petechiae/purpura/
	Upper respiratory
	tract infection
	Constipation
	_
	Diarrhoea _
	Cough
	-
	Anaemia -
	Back pain
	- Epistovis
	Epistaxis -
	Headache
	- Nausea
	-
	Jrinary tract infection
	Gastro-oesophageal
	reflux disease _
	Neutropenia -
	Rash
	-
	Basal cell carcinoma
	Hypertension
	- Squamous cell
	carcinoma
	Atrial fibrilation/ flutter
	- Pyrevia
	Pneumonia
	- Actinic keratosis
Gra	-
<u> </u>	Major haemorrhage ^a

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

- AEs of interest:
- 26 patients (39%) had ≥1 grade ≥3 AE
- 22 patients (33%) had ≥1 serious AE (SAE)
- zanubrutinib per investigator)

• The most common AEs in patients with WM were primarily grade 1-2 in



- Major haemorrhage (any grade \geq 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%])

 SAEs possibly related to zanubrutinib were hemothorax, atrial fibrillation, colitis, febrile neutropenia, and headache (each n=1)

• 3 patients (5%) had AEs leading to discontinuation (all unrelated to

- Worsening bronchiectasis (fatal), gastric adenocarcinoma, and prostate adenocarcinoma (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

		By MYD88 Status											
Best response, n (%)	OVERALL (n=51)	<i>MYD88^{L265P}/ CXCR4^{wт} (n=25)</i>	MYD88 ^{L265P} / CXCR4 ^{WHIM} (n=5)	<i>МҮD88^{wт}</i> (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)								
MP minor response: PP partial response: SD stable disease: VCPP your good partial response													

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

• 39 of the 51 evaluable patients had \geq 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



• 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)



Estimated 12 month PFS of 91% (Figure 8)

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

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		patie																	
	51	51	47	42	42	39	36	28	23	18	16	15	10	4	4	4	4	3	0
^a Evaluat	ole pa	tients	s defir	ned in	Figur	e 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

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