Updated Safety and Activity of the Investigational Bruton's Tyrosine Kinase Inhibitor Zanubrutinib (BGB-3111) in Patients with Mantle Cell Lymphoma

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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 mantle cell lymphoma (MCL) and is a key mediator in cell survival
- First- and second-generation BTK inhibitors ibrutinib and acalabrutinib have shown activity in MCL^{4,5}
- Zanubrutinib (BGB-3111) is a next-generation BTK inhibitor designed to maximize BTK occupancy and minimize off-target inhibition of TEC- and EGFR-family kinases
- Has been shown to be a highly potent, selective, bioavailable, and irreversible BTK inhibitor with potentially advantageous pharmacokinetics⁶ (**Tables 1, Figures 1-2**)

Table 1. Zanubrutinib - kinase selectivity

	Targets	Assays	Zanubrutinib IC ₅₀ (nM) ⁷	lbrutinib IC₅₀ (nM) ⁷	Ratio (Zanubrutinib:Ibrutinib)
_		BTK-pY223 Cellular Assay	1.8	3.5	0.5
RGET	DTV	Rec-1 Proliferation	0.36	0.34	1.1
N TA	BIK	BTK Occupation Cellular Assay	2.2	2.3	1
		BTK Biochemical Assay	0.22	0.2	1.1
	EGED	p-EGFR HTRF Cellular Assay	606	101	6
	LOIK	A431 Proliferation	3210	323	9.9
		ITK Occupancy Cellular Assay	606	189	17
GET	ITV	p-PLC _{y1} Cellular Assay	3433	77	45
TAR		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



Note: these data are from 3 separate analyses and differences in studies should be considered.

Figure 2. BTK inhibition in peripheral blood and lymph nodes



Complete and sustained BTK occupancy is seen in paired PBMC (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 bid with 94% of patients having >90% occupancy in lymph nodes across malignancies.

• Single-agent zanubrutinib (BGB-3111) was recently shown to be generally well tolerated with encouraging activity in multiple NHL subtypes, including MCL in a Phase 1b study¹⁰

OBJECTIVE

• Presented here are updated results from patients with MCL treated within an ongoing phase 1 zanubrutinib trial (NCT02343120)

METHODS

- First-in-human, open-label, multicenter, phase 1 study of zanubrutinib in patients with B-cell malignancies (**Figure 3**)
- Eligibility
- WHO-defined B-cell malignancy with no available higher priority treatment
- Eastern Cooperative Oncology Group 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)

Figure 3. Trial design (NCT02343120)

-	DOSE ESCA	ALATION		RP2D	_	D	OSE EX	PANSION	
	Dose	Enrolled (MCL)		Dose 320 mg QD		Population	Dose	Disease	Enrolled ⁺ (MCL)
	40 mg QD	4 (1)		160 mg BID		R/R	BID or QD	All B-cell	40 (12)
	80 mg QD 160 mg QD	5 (2) 6 (2)		Both doses RP2D but as		R/R	BID	Non-GCB DLBCL	40
	320 mg QD	6 (1)		v.6 all patients encouraged to switch to		R/R	BID	CLL/SLL	70
	160 mg BID	4 (0)				R/R	BID	WM	20
				IOU IIIG BID		R/R	QD	CLL/SLL	20
						R/R or TN	BID or QD	WM	50
						R/R	BID or QD	MCL	20 (20)
						TN	BID or QD	CLL/SLL	20
С	Cohorts containing	patients with N	/ICL	in blue		TN	BID or QD	MCL	20 (9)
†E e c	Enrollment in expan nrollment shown, v utoff noted in pare	nsion is ongoir with MCL enro entheses.	ng: Ilme	planned ent as of data		R/R	BID or QD	HCL	10
B Ie	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; RP2D, recommended phase 2 dose;			R/R	BID	iNHL	40 (1)		
				R/R	BID	Richter's	15		
				R/R (prior BTK)	BID	All B-cell	15		

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
- Response to treatment was assessed per the Lugano classification (Cheson J Clin Oncol 2014); PET scans were optional

RESULTS

^aDetailed in Table 3.



^bBoth progression and AE listed as primary reason for discontinuation. AE, adverse event; FU, follow-up; PD, progressive disease; R/R, relapsed/refractory; TN, treatment-naïve.

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Table 2. Patient and disease characteristics	
Characteristic	otal (N=48)
Age, years, median (range)	71 (42-90)
ECOG performance status, n (%)	
0 1	21 (43.8) 23 (479)
2	4 (8.3)
Prior treatment status	
Treatment-naïve, n (%) Relapsed/refractory (R/R), n (%)	9 (18.8) 39 (81 3)
No. of prior R/R therapies, median (range)	1 (1-4)
Patients with prior Rituximab-containing regimens, n (%)	36 (75)
Stage at Study Entry	3 (6 3)
	1 (2.1)
	3 (6.3)
I DH at baseline median (range) in U/I	250 (117_78
Bulky disease. ^a n (%)	3 (6.3)
Blastoid variant, ^b n (%)	3 (6.3)
MIPI, ^c n (%)	
Low	11 (22.9)
Intermediate Hiah	17 (35.4) 18 (37.5)
Any lymph node longest diameter > 10 cm at baseline.	
n=9 blastoid status is unknown. n=2 MIPI is unknown.	
COG, Eastern Cooperative Oncology Group; LDH, lactate dehydrogenase; MIPI, Mant International Prognostic Index.	le Cell Lymph
Median follow-up for safety population: 12.7 months (range	e, 0.7-38.0
The most common adverse events (AEs) in patients with M primarily grade 1/2 (Table 3 , Figure 5)	ICL were
4 deaths due to AEs were determined to be unrelated to z	anubrutir
Table 2 Adverse averts averyiow	
able 5. Adverse events overview	
	n (%)
Event Patients with \geq 1 AE Grade \geq 3	n (%) 27 (56.3)
Event Patients with ≥1 AE Grade ≥3 Patients with ≥1 serious AE	n (%) 27 (56.3) 16ª (33.3)
Event Patients with ≥1 AE Grade ≥3 Patients with ≥1 serious AE AE leading to treatment discontinuation	n (%) 27 (56.3) 16ª (33.3) 9 ^b (18.8) 4 ^c (8 3)
Event Patients with ≥1 AE Grade ≥3 Patients with ≥1 serious AE AE leading to treatment discontinuation Fatal AE AE of interest	n (%) 27 (56.3) 16ª (33.3) 9 ^b (18.8) 4 ^c (8.3)
EventPatients with ≥1 AE Grade ≥3Patients with ≥1 serious AEAE leading to treatment discontinuationFatal AEAE of interest Petechiae/purpura/contusion	n (%) 27 (56.3) 16ª (33.3) 9 ^b (18.8) 4 ^c (8.3)
Event Patients with ≥1 AE Grade ≥3 Patients with ≥1 serious AE AE leading to treatment discontinuation Fatal AE AE of interest Petechiae/purpura/contusion Diarrhea Hypertension	n (%) 27 (56.3) 16^{a} (33.3) 9^{b} (18.8) 4^{c} (8.3) 16 (33.3) 4 (8.3)
Event Patients with ≥1 AE Grade ≥3 Patients with ≥1 serious AE AE leading to treatment discontinuation Fatal AE AE of interest Petechiae/purpura/contusion Diarrhea Hypertension Major hemorrhage ^d	n (%) 27 (56.3) 16ª (33.3) 9 ^b (18.8) 4 ^c (8.3) 16 (33.3) 16 (33.3) 4 (8.3) 3 (6.3)
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Event Patients with ≥1 AE Grade ≥3 Patients with ≥1 serious AE AE leading to treatment discontinuation Fatal AE AE of interest Petechiae/purpura/contusion Diarrhea Hypertension Major hemorrhage ^d Atrial fibrillation/flutter SAEs determined to be possibly related to zanubrutinib (n=3): G3 leukocytosis, G3 performed pack pain, G3 cellulitis.	n (%) 27 (56.3) 16ª (33.3) 9 ^b (18.8) 4 ^c (8.3) 16 (33.3) 4 (8.3) 3 (6.3) 2 (4.2) ipheral edema
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Neutropenia^b

^aCombines platelet count decreased and thrombocytopenia ^bCombines neutrophil count decreased and neutropenia. ^cGrade \geq 3 hemorrhage, or CNS hemorrhage of any grade.

nd disease characteristics

Total (N=48)
71 (42-90)
21 (43.8) 23 (47.9) 4 (8.3)
9 (18.8) 39 (81.3) 1 (1-4) 36 (75)
3 (6.3) 1 (2.1) 3 (6.3) 41 (85.4)
250 (117–782)
3 (6.3)
3 (6.3)
11 (22.9) 17 (35.4) 18 (37.5)

cology Group; LDH, lactate dehydrogenase; MIPI, Mantle Cell Lymphoma

were determined to be unrelated to zanubrutinib

events overview

	n (%)
e ≥3	27 (56.3)
E	16ª (33.3)
discontinuation	9 ^b (18.8)
	4 ^c (8.3)
tusion	16 (33.3) 16 (33.3) 4 (8.3) 3 (6.3) 2 (4.2)

related to zanubrutinib (n=3): G3 leukocytosis, G3 peripheral edema + G3 monia, G5 worsening congestive cardiac failure, G3 acute kidney psis + G2 fever, G3 pneumonia, G3 joint effusion + G3 peripheral edema,

3 renal hematoma. All but one event (peripheral edema) determined to be

rhage or any grade CNS hemorrhage: one patient had G3 gastrointestinal } tumor hemorrhage, one patient had G3 renal hematoma.

adverse events (>10%), G3-5 adverse events of interest, regardless of causality



Best response, n (%)	TN (n=6)	R/R (n=39)	All Efficacy Evaluable (n=45)
Median follow-up for efficacy evaluable patients, months (range)	9.2 (3.7, 23.3)	15.3 (1.9, 38.0)	14.8 (1.9, 38.0)
ORR CR PR	6 (100) 2 (33.3) 4 (66.7)	34 (87.2) 10 (25.6) 24 (61.5)	40 (88.9) 12 (26.7) 28 (62.2)
SD	0	2 (5.1)	2 (4.4)
PD	0	3 (7.7)	3 (6.7)

SD, stable disease; TN, treatment-naïve.

• Duration of response in months, median (95% CI) [range]

- TN: NR (NE, NE) [0.3, 20.2]
- R/R: 16.2 (11.5, 28.2) [1.1, 28.2]
- Overall: 16.2 (12.6, 28.2) [0.3, 28.2]
- The majority of patients were assessed via CT-scan; PET scan was optional per trial protocol
- Best overall response by investigator was assessed utilizing PET scan in 3 patients

Figure 6. Maximum improvement in SPD in efficacy evaluable patients



2 patients without measurable baseline target lesions and 2 patients without post-baseline CT scans were not included. Dashed lines indicates the median reduction in SPD (-88% for R/R, -91% for TN).

• 53.3% (24/45) of efficacy evaluable patients remained on treatment (Figure 7)

Figure 7. Duration of treatment in efficacy evaluable patients



One patient progressed but had not ended treatment as of data cut-off and one patient progressed but was not included i efficacy evaluable population.

• 16 patients (15 R/R, 1 TN) evaluable for safety had progressed at the data cut off date



39 37 32 30 29 24 22 18 12 8 4 3 2 2 2 1 0 Shaded area shows the 95% Cl.

Median time to progression for all PD patients (n=16): 10.6 mo (0.7-30.7)

CONCLUSIONS

- Zanubrutinib, an investigational, oral BTK inhibitor showed 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 MCL
- Most common AEs of any grade included petechiae/ purpura/contusion and diarrhea, each occurring in one third of patients
- Grade \geq 3 AEs occurred in 56% of patients and 19% of patients discontinued due to AEs, most considered to by the investigator as unrelated to study treatment
- Overall response rate of 89% including 27% with CR
- Median PFS for R/R patients was 18 months
- 53% (24/45) of efficacy evaluable patients remained on treatment
- Based on these results, further evaluation of zanubrutinib in late-stage trials is being conducted
- Oral presentation earlier at this meeting: Song et al. Safety and activity of the investigational Bruton tyrosine kinase inhibitor zanubrutinib (BGB-3111) in patients with mantle cell lymphoma from a Phase 2 trial. Abstract 148.

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