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

Poster 1592

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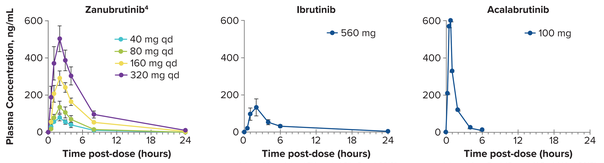
INTRODUCTION

- 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 pharmacokinetics[6] (**Tables 1, Figures 1-2**)

Table 1. Zanubrutinib - kinase selectivity

	Targets	Assays	Zanubrutinib IC_{50} (nM)[7]	Ibrutinib IC_{50} (nM)[7]	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

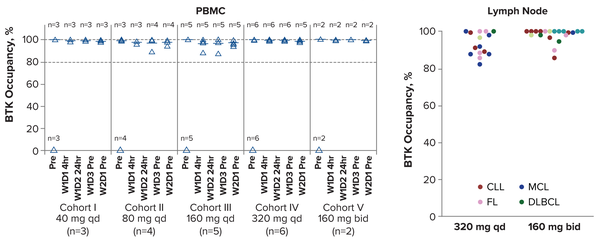
Figure 1. Pharmacokinetics of zanubrutinib, ibrutinib, and acalabrutinib



Adapted from Advani RH, et al. *J Clin Oncol*. 2013[8] | Adapted from Byrd JC, et al. *N Engl J Med*. 2015[5]

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 study[10]

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 ≥1000/μL, platelets ≥50000/μL (growth factor/transfusions allowed)
  - Adequate renal and hepatic function
  - No significant cardiac disease (anticoagulation allowed)

Figure 3. Trial design (NCT02343120)

DOSE ESCALATION

Dose	Enrolled (MCL)
40 mg QD	4 (1)
80 mg QD	5 (2)
160 mg QD	6 (2)
320 mg QD	6 (1)
160 mg BID	4 (0)

RP2D

Dose: 320 mg QD; 160 mg BID

Both doses RP2D but as of protocol v.6 all patients encouraged to switch to 160 mg BID

DOSE EXPANSION

Population	Dose	Disease	Enrolled† (MCL)
R/R	BID or QD	All B-cell	40 (12)
R/R	BID	Non-GCB DLBCL	40
R/R	BID	CLL/SLL	70
R/R	BID	WM	20
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
TN	BID or QD	MCL	20 (9)
R/R	BID or QD	HCL	10
R/R	BID	iNHL	40 (1)
R/R	BID	Richter's	15
R/R (prior BTK)	BID	All B-cell	15

Cohorts containing patients with MCL in blue

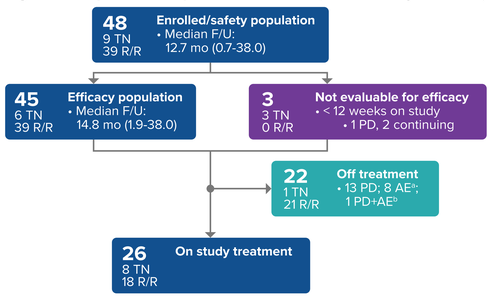
†Enrollment in expansion is ongoing: planned enrollment shown, with MCL enrollment as of data cutoff noted in parentheses.

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; QD, once daily; WM, Waldenström macroglobulinemia.

- 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

Figure 4. Disposition for patients with MCL (data cut July 24, 2018)



[a]Detailed in **Table 3**.
[b]Both 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.

Table 2. Patient and disease characteristics

Characteristic	Total (N=48)
Age, years, median (range)	71 (42-90)
ECOG performance status, n (%)	
0	21 (43.8)
1	23 (47.9)
2	4 (8.3)
Prior treatment status	
Treatment-naïve, n (%)	9 (18.8)
Relapsed/refractory (R/R), n (%)	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	
I	3 (6.3)
II	1 (2.1)
III	3 (6.3)
IV	41 (85.4)
LDH at baseline, median (range) in U/L	250 (117–782)
Bulky disease,[a] n (%)	3 (6.3)
Blastoid variant,[b] n (%)	3 (6.3)
MIPI,[c] n (%)	
Low	11 (22.9)
Intermediate	17 (35.4)
High	18 (37.5)

[a]Any lymph node longest diameter > 10 cm at baseline.
[b]n=9 blastoid status is unknown.
[c]n=2 MIPI is unknown.
ECOG, Eastern Cooperative Oncology Group; LDH, lactate dehydrogenase; MIPI, Mantle Cell Lymphoma International Prognostic Index.

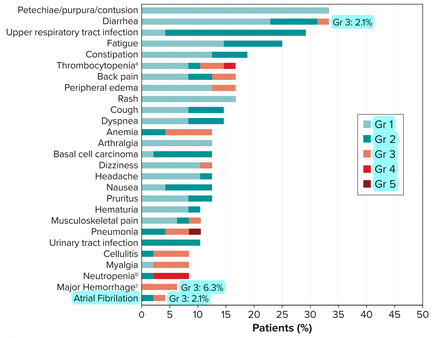
- Median follow-up for safety population: 12.7 months (range, 0.7-38.0)
- The most common adverse events (AEs) in patients with MCL were primarily grade 1/2 (**Table 3**, **Figure 5**)
- 4 deaths due to AEs were determined to be unrelated to zanubrutinib

Table 3. Adverse events overview

Event	n (%)
Patients with ≥1 AE Grade ≥3	27 (56.3)
Patients with ≥1 serious AE	16[a] (33.3)
AE leading to treatment discontinuation	9[b] (18.8)
Fatal AE	4[c] (8.3)
AE of interest	
Petechiae/purpura/contusion	16 (33.3)
Diarrhea	16 (33.3)
Hypertension	4 (8.3)
Major hemorrhage[d]	3 (6.3)
Atrial fibrillation/flutter	2 (4.2)

[a]SAEs determined to be possibly related to zanubrutinib (n=3): G3 leukocytosis, G3 peripheral edema + G3 worsening back pain, G3 cellulitis.
[b]G5 Cerebral infarction, G5 pneumonia, G5 worsening congestive cardiac failure, G3 acute kidney injury + G3 ANC Vasculitis, G5 Sepsis + G2 fever, G3 pneumonia, G3 joint effusion + G3 peripheral edema, G4 myelodysplastic syndrome, G3 renal hematoma. All but one event (peripheral edema) determined to be unrelated to study drug.
[c]Cerebral infarction, pneumonia, worsening congestive cardiac failure, sepsis. All determined to be unrelated to study drug.
[d]Defined as any grade ≥3 hemorrhage or any grade CNS hemorrhage: one patient had G3 gastrointestinal hemorrhage, one patient had G3 tumor hemorrhage, one patient had G3 renal hematoma.

Figure 5. common adverse events (>10%), G3-5 adverse (n≥3), and BTK-i events of interest, regardless of causality



[a]Combines platelet count decreased and thrombocytopenia.
[b]Combines neutrophil count decreased and neutropenia.
[c]Grade ≥3 hemorrhage, or CNS hemorrhage of any grade.

Table 4. Best overall response by investigator

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	**6 (100)**	**34 (87.2)**	**40 (88.9)**
CR	2 (33.3)	10 (25.6)	12 (26.7)
PR	4 (66.7)	24 (61.5)	28 (62.2)
SD	0	2 (5.1)	2 (4.4)
PD	0	3 (7.7)	3 (6.7)

CR, complete response; ORR, overall response rate; PD, progressive disease; PR, partial response; R/R, relapsed/refractory; 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).

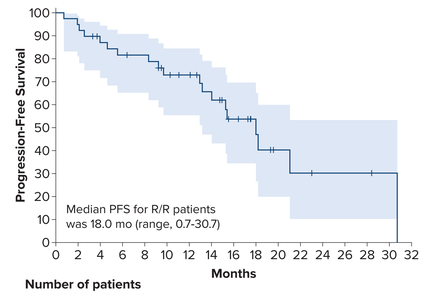
- 53.3% (24/45) of efficacy evaluable patients remained on treatment (**Figure 7**)

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 in efficacy evaluable population.

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

Figure 8. Progression-free survival in all treated R/R patients (n=39)



Shaded area shows the 95% CI.
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 ≥ 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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