Updated Safety and Efficacy Data in the Phase 1/2 Trial of Zanubrutinib in Patients With Mantle Cell Lymphoma

Abstract 191

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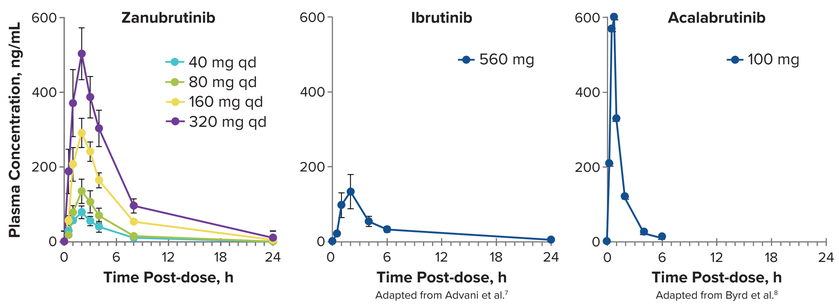
INTRODUCTION

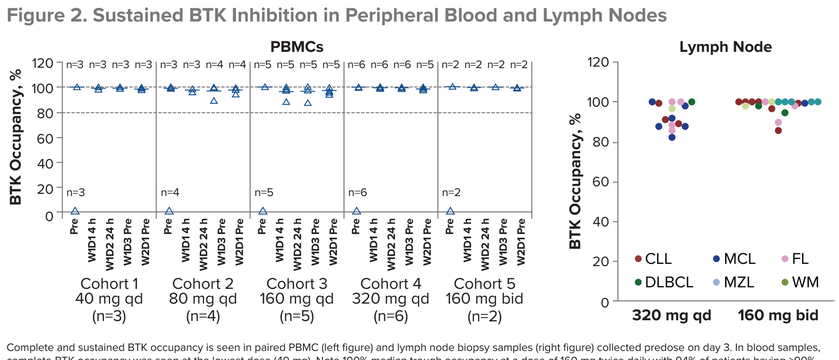
- Bruton tyrosine kinase (BTK) plays a critical role in B-cell receptor signaling, which mediates B-cell proliferation, migration, and adhesion[1-3]
  - BTK is constitutively activated in mantle cell lymphoma (MCL) and is a key mediator in cell survival
- First- and second-generation BTK inhibitors ibrutinib and acalabrutinib have shown activity in MCL[4,5]
- Zanubrutinib (BGB-3111) is an investigational, 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 pharmacokinetic/pharmacodynamic properties[6] (**Figure 1**)
  - Complete and sustained BTK occupancy in both peripheral blood mononuclear cells and lymph nodes[6] (**Figure 2**)

Figure 1. Pharmacokinetics of Zanubrutinib, Ibrutinib, and Acalabrutinib



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

Figure 2. Sustained 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 predose 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 daily with 94% of patients having >90% occupancy in lymph nodes across malignancies.

bid, twice daily; BTK, Bruton tyrosine kinase; CLL, chronic lymphocytic leukemia; D, day; DLBCL, diffuse large B-cell lymphoma; FL, follicular lymphoma; MCL, mantle cell lymphoma; MZL, marginal zone lymphoma; PBMC, peripheral blood mononuclear cell; Pre, predose; qd, once daily; W, week; WM, Waldenström macroglobulinemia.

- Based on drug interaction studies:
  - Co-administration with strong or moderate CYP3A inhibitors (including agents such as azole anti-fungals, important in the management of patients [pts] with leukemia/lymphoma) is permitted at a reduced dose
  - Co-administration of proton pump inhibitors or other gastric acid-reducing agents does not affect zanubrutinib exposure
  - Pts have been allowed to receive anticoagulant and antiplatelet agents on zanubrutinib trials

OBJECTIVE

- Presented here are updated safety and efficacy results from pts with MCL treated within an ongoing phase 1/2 global, open-label, multicenter trial of oral investigational BTK inhibitor zanubrutinib (NCT02343120)

METHODS

- First-in-human, open-label, multicenter, phase 1/2 study of zanubrutinib in pts with B-cell malignancies (**Figure 3**)

Eligibility

- WHO-defined B-cell malignancy with no available higher priority treatment
- Eastern Cooperative Oncology Group performance status of 0 to 2
- Absolute neutrophil count ≥1000/μL, platelets ≥50 000/μL (growth factor/transfusions allowed)
- Adequate renal and hepatic function
- No significant cardiac disease (anticoagulation allowed)

Primary end points

- Safety including adverse events (AEs) and serious AEs (SAEs) per the National Cancer Institute's Common Terminology Criteria for Adverse Events version 4.03 based on physical examination and laboratory measurements
- Recommended phase 2 dose

Select secondary end points

- Pharmacokinetics
- Efficacy, including overall response rate (ORR), progression-free survival, overall survival, and duration of response

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 pts encouraged to switch to 160 mg bid

DOSE EXPANSION

Population	RP2D Dose	Disease	Enrolled[a] (MCL)
R/R	bid or qd	All B-cell	40 (11)
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 (16)
R/R	bid or qd	HCL	10
R/R	bid	iNHL	40
R/R	bid	Richter	15
R/R (prior BTK)	bid	All B-cell	15

Data cut: 13 December, 2018

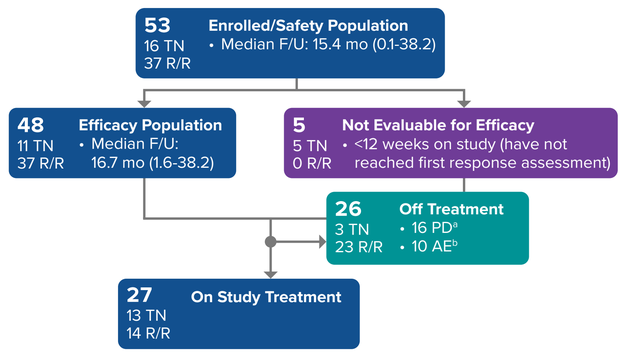
Cohorts containing MCL pts in blue

[a]Enrollment in expansion is ongoing: planned enrollment shown, with MCL enrollment as of data cutoff noted in parentheses.
bid, twice daily; RP2D, recommended phase 2 dose;
R/R, relapsed/refractory; qd, once daily; TN, treatment-naïve.

RESULTS

- 53 pts with MCL have been enrolled (**Table 1**), 27 of whom remain on study treatment (**Figure 4**)

Figure 4. Disposition for Patients With MCL



Data cutoff: 13 December, 2018.
[a]One pt listed as having both progression and AE as primary reason for discontinuation.
[b]Detailed in **Table 2**.
AE, adverse event; F/U, follow-up; PD, progressive disease; R/R, relapsed/refractory; TN, treatment-naïve.

Table 1. Patient and Disease Characteristics

Characteristic	Treatment-Naïve (n=16)	Relapsed/Refractory (n=37)	Total (N=53)
Age, median (range), y	78 (69-90)	70 (42-86)	74 (42-90)
ECOG PS, n (%)			
0	3 (18.8)	19 (51.4)	22 (41.5)
1	8 (50.0)	15 (40.5)	23 (43.4)
2	5 (31.3)	3 (8.1)	8 (15.1)
Prior treatment status			
No. of prior therapies, median (range)	-	1 (1-4)	1 (0-4)
Pts with prior rituximab or rituximab-containing regimens, n (%)	-	34 (91.9)	34 (64.2)
Stage at study entry			
I	0 (0.0)	3 (8.1)	3 (5.7)
II	0 (0.0)	1 (2.7)	1 (1.9)
III	4 (25.0)	1 (2.7)	5 (9.4)
IV	11 (68.8)	32 (86.5)	43 (81.1)
Missing	1 (6.3)	0 (0.0)	1 (1.9)
LDH at baseline, median (range), U/L	224 (95-519)	244 (117-782)	236 (95-782)
Bulky disease,[a] n (%)	1 (6.3)	3 (8.1)	4 (7.5)
Blastoid variant,[b] n (%)	3 (18.8)	2 (5.4)	5 (9.4)
MIPI,[c] n (%)			
Low	2 (12.5)	10 (27.0)	12 (22.6)
Intermediate	4 (25.0)	14 (37.8)	18 (34.0)
High	10 (62.5)	13 (35.1)	23 (43.4)

ECOG PS, Eastern Cooperative Oncology Group performance status; LDH, lactate dehydrogenase; MIPI, Mantle Cell Lymphoma International Prognostic Index.
[a]Any lymph node longest diameter >10 cm at baseline.
[b]n=4 blastoid status is unknown.
[c]MIPI score was calculated with cutoffs as low (<5.7), intermediate (5.7 to <6.2), and high (≥6.2)

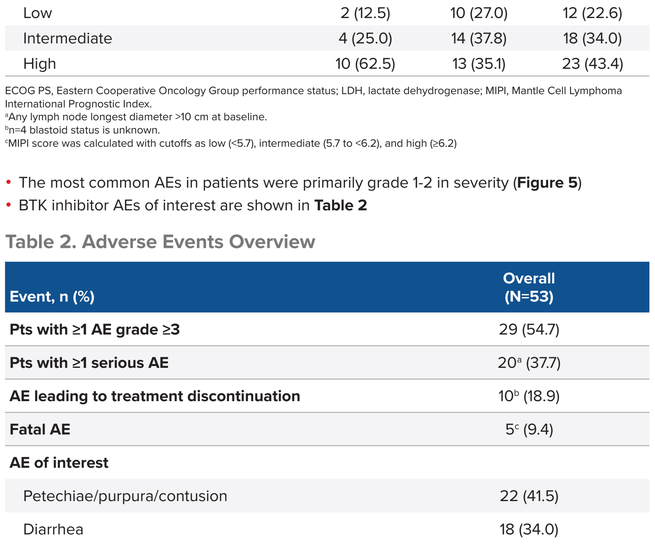
- The most common AEs in patients were primarily grade 1-2 in severity (**Figure 5**)
- BTK inhibitor AEs of interest are shown in **Table 2**

Table 2. Adverse Events Overview

Event, n (%)	Overall (N=53)
Pts with ≥1 AE grade ≥3	29 (54.7)
Pts with ≥1 serious AE	20[a] (37.7)
AE leading to treatment discontinuation	10[b] (18.9)
Fatal AE	5[c] (9.4)
AE of interest	
Petechiae/purpura/contusion	22 (41.5)
Diarrhea	18 (34.0)
Hypertension	4 (7.5)
Major hemorrhage	4[d] (7.5)
Atrial fibrillation/flutter	4 (7.5)

AE, adverse event; SAE, serious AE.
[a]SAEs determined to be possibly related to zanubrutinib (n=4): grade 3 leukocytosis, grade 3 peripheral edema + grade 3 worsening back pain, grade 3 cellulitis, grade 3 subdural hematoma.
[b]Grade 5 Cerebral infarction, grade 5 pneumonia, grade 5 worsening congestive cardiac failure, grade 3 acute kidney injury + grade 3 ANCA vasculitis, grade 3 pneumonia, grade 3 peripheral edema (related), grade 4 myelodysplastic syndrome, grade 3 renal hematoma, grade 2 small cell lung cancer, grade 3 subdural hematoma (related) (each n=1). One additional patient was reported as progressive disease but also had grade 5 sepsis + grade 2 fever.
[c]Cerebral infarction (n=1), pneumonia (n=1), worsening congestive cardiac failure (n=1), sepsis (n=2). All determined to be unrelated to study drug.
[d]Defined as any grade ≥3 hemorrhage or any-grade CNS hemorrhage: 1 patient had grade 3 gastrointestinal hemorrhage, 1 patient had grade 3 tumor hemorrhage, 1 patient had grade 3 renal hematoma and 1 patient with grade 3 subdural hematoma (related).

Figure 5. Common Adverse Events of Interest, Regardless of Causality



Note: Common AEs include all grade ≥10% or grades 3-5 n≥3.
AE, adverse event.

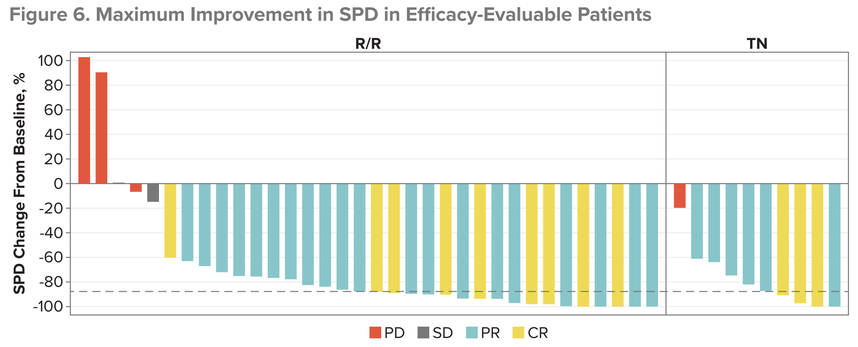
Table 3. Best Overall Response by Investigator

Best Response	TN (n=11)	R/R (n=37)	All Efficacy Evaluable (n=48)
Follow-up for efficacy-evaluable pts, median (range), mo	8.3 (1.6-27.9)	19.4 (1.9-38.2)	16.7 (1.6-38.2)
ORR, n (%) [95% CI]	**9 (81.8)** [48.2-97.7]	**32 (86.5)** [71.2-95.5]	**41 (85.4)** [72.2-93.9]
CR, n (%) [95% CI]	3 (27.3) [6.0-61.0]	11 (29.7) [15.9-47.0]	14 (29.2) [17.0-44.1]
PR, n (%)	6 (54.5)	21 (56.8)	27 (56.3)
SD, n (%)	0	2 (5.4)	2 (4.2)
PD, n (%)	1 (9.1)	3 (8.1)	4 (8.3)
Efficacy-evaluable and ongoing without postbaseline tumor assessment, n (%)	1 (9.1)	0 (0.0)	1 (2.1)
DOR, median [95% CI], mo	NE [9.2-NE]	15.4 [11.5-28.2]	16.2 [11.5-28.2]

CR, complete response; DOR, duration of response; NE, not evaluable; ORR, overall response rate; PD, progressive disease; PR, partial response; pts, patients; R/R, relapsed/refractory; SD, stable disease; TN, treatment-naïve.

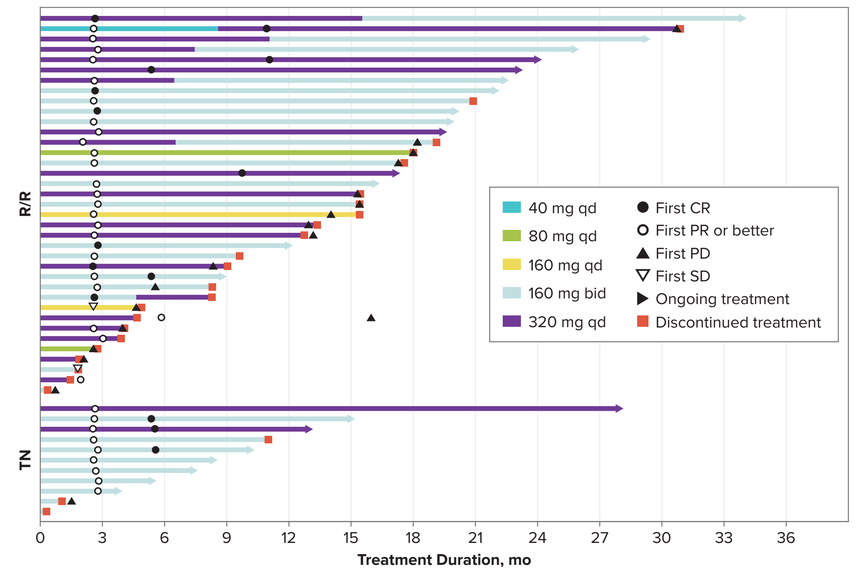
- For the 48 pts evaluable for response, ORR was 85% including 29% with complete response (**Table 3**)
- Duration of response in months, median (95% CI) [range]
  - Relapsed/refractory (R/R): 15.4 (11.5-28.2) [0.03-28.2]; overall: 16.2 (11.50-28.2) [0.03-28.2]
- The majority of pts were assessed via CT-scan; PET scan was optional, per trial protocol
  - Best overall response was upgraded in 3 pts based on PET assessment
- 45.8% of efficacy evaluable pts (22/48) remained on treatment (**Figure 7**)

Figure 6. Maximum Improvement in SPD in Efficacy-Evaluable Patients



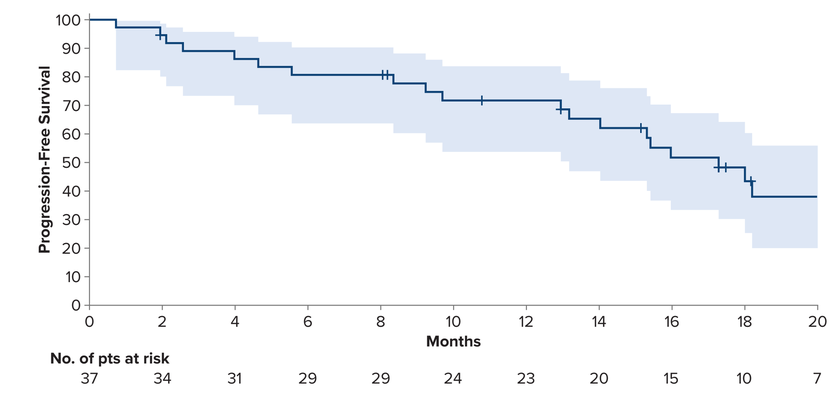
Dashed line indicates the median reduction in SPD (−87.5%).
CR, complete response; PD, progressive disease; PR, partial response; R/R, relapsed/refractory; SD, stable disease; SPD, sum of product of diameters; TN, treatment-naïve.

Figure 7. Duration of Treatment in Efficacy-Evaluable Patients



bid, twice daily; CR, complete response; PD, progressive disease; PR, partial response; qd, once daily; R/R, relapsed/refractory; SD, stable disease; TN, treatment-naïve.

Figure 8. Progression-Free Survival in All Treated R/R Patients (n=37)



Shaded area shows the 95% CI.
pt, patient; R/R, relapsed/refractory.

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 pts with MCL
  - Most common AEs include contusion, diarrhea and upper respiratory infections
  - Hypertension, atrial fibrillation, and major hemorrhage were reported in <10%
  - Grade ≥3 AEs occurred in 55% of patients
    - 19% of patients discontinued due to AEs, 2 (3.8%) were considered related to zanubrutinib
    - All 5 (9%) fatal AEs were considered unrelated to zanubrutinib
  - ORR was 85%, including 29% CR
  - Median PFS for R/R pts was 17.3 months
  - 50.9% of all treated pts (27/53) remain on treatment
- Based on these results, further evaluation of zanubrutinib in late-stage trials is being conducted

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DISCLOSURES

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