UPDATED SAFETY AND EFFICACY DATA FROM A COHORT OF PATIENTS WITH WALDENSTRÖM MACROGLOBULINEMIA IN A PHASE 1/2 TRIAL TREATED WITH THE BRUTON TYROSINE KINASE INHIBITOR ZANUBRUTINIB (BGB-3111)

Abstract PF481

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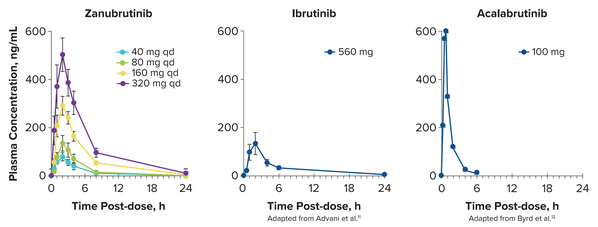
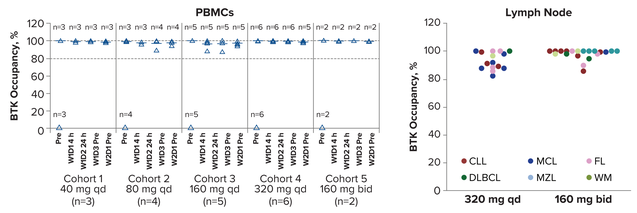
- Bruton tyrosine kinase (BTK) plays a critical role in B-cell receptor signaling, which mediates B-cell proliferation, migration, and adhesion[1–3]
  - BTK is constitutively activated in Waldenström macroglobulinemia (WM) and is a key mediator in cell survival[4,5]
- First-generation BTK inhibitor ibrutinib has shown activity in WM and become a standard of care[6,7]
  - Major response rate: 73% (including 16% very good partial response [VGPR])[8]
  - 3-year event-free survival: 68%[9]
- 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[10] (**Figure 1**)
  - Complete and sustained BTK occupancy in both peripheral blood mononuclear cells and lymph nodes[10] (**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; Pre, predose; 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 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
  - Patients have been allowed to receive anticoagulant and antiplatelet agents on zanubrutinib trials

OBJECTIVES

- Presented here are the updated safety and efficacy data in patients with WM treated with an oral investigational BTK inhibitor, zanubrutinib, from an ongoing phase 1/2 global, open-label, multicenter trial (NCT02343120)
- We report the results for patients with WM from the cohorts who had no prior BTK inhibitor therapy and were assessed by an independent review committee (IRC)

METHODS

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

Eligibility

- World Health Organization-defined B-cell malignancy with no available higher priority treatment
- Eastern Cooperative Oncology Group performance status 0-2
- 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 per the NCI CTCAE v4.03, based on physical examination and laboratory measurements
- Recommended phase 2 dose

Select secondary end points

- Pharmacokinetics
- Efficacy, including overall response rate, progression-free survival, overall survival, and duration of response by IRC

Figure 3. Trial Design (NCT02343120)

DOSE ESCALATION

Dose	Enrolled (WM)
40 mg qd	3 (1)
80 mg qd	4 (2)
160 mg qd	5 (1)
320 mg qd	4 (0)
160 mg bid	1 (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] (WM)
R/R	bid or qd	All B-cell	39 (2)
R/R	bid	Non-GCB DLBCL	32
R/R	bid	CLL/SLL	67
R/R	bid	WM	20 (20)
R/R	qd	CLL/SLL	20
R/R or TN	bid or qd	WM	50 (50)
R/R	bid or qd	MCL	20
TN	bid or qd	CLL/SLL	21
TN	bid or qd	MCL	11
R/R	bid or qd	HCL	11
R/R	bid	iNHL	40 (1)
R/R	bid	Richter	11

Cohorts containing WM pts in blue

bid, twice daily; RP2D, recommended phase 2 dose; R/R, relapsed/ refractory; qd, once daily; TN, treatment-naive; WM, Waldenström macroglobulinemia.
[a]Enrollment in expansion is ongoing: actual enrollment shown, with WM enrollment of the evaluable population as of data cutoff 16th September 2018. Patients with prior BTK inhibitors not included.

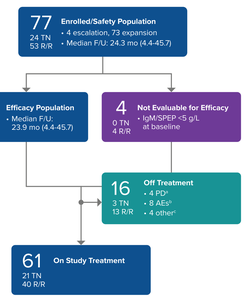
CONCLUSIONS

- Zanubrutinib, a highly selective oral BTK inhibitor showed high plasma concentrations and complete sustained BTK occupancy in blood and lymph nodes
- Updated results from an ongoing phase 1/2 trial in patients with B-cell malignancies suggest that zanubrutinib was generally well tolerated and highly effective in the cohort of patients with WM who had no prior BTK inhibitor therapy
  - Based on modified IWWM-6 as assessed by IRC, ORR was 92% including 43% CR/VGPR rate
  - Estimated PFS rate at 12 months and 24 months was 90% and 81%, respectively
  - With a median follow-up of 24 months, discontinuation due to AEs was reported in 10% of patients
- A phase 3 trial comparing zanubrutinib with ibrutinib in patients with WM is ongoing

RESULTS

- Out of the 359 patients enrolled in the study, were 77 patients with WM (**Table 1**), 61 of whom remain on study treatment (**Figure 4**)

Figure 4. Disposition for Patients with WM



Data cut:16 September, 2018
AE, adverse event; F/U, follow-up; IgM, immunoglobulin M; PD, progressive disease; R/R, relapsed/refractory; SD, stable disease; TN, treatment-naive; VGPR, very good partial response.
[a]Best response before progression: PD (n=1), SD (n=1) VGPR (n=2).
[b]Detailed in **Table 2**.
[c]Radiation/transplant (n=1), Non compliance (n=2) and investigator decision (n=1)

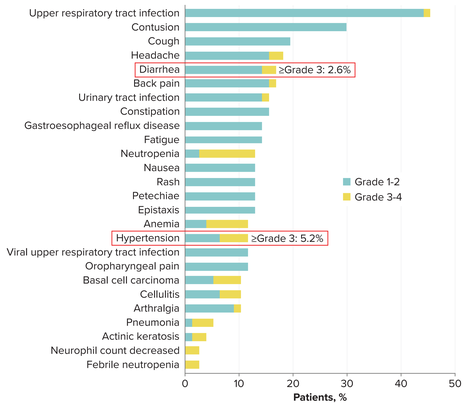
Table 1. Patient and Disease Characteristics

Characteristic	Total (N=77)
Age, median (range), y	67 (40-87)
ECOG PS, n (%)	
1	74 (96.1)
2	3 (3.9)
Prior treatment status	
TN, n (%)	24 (31.2)
R/R, n (%)	53 (68.8)
No. of prior therapies for R/R patients, median (range)	2 (1-8)
Genotype, n (%)	
MYD88^{L265P}/*CXCR4*^{WT}	52 (67.5)
MYD88^{L265P}/*CXCR4*^{WHIM}	6 (7.8)
MYD88^{WT}	11 (14.3)
Unavailable	8 (10.4)

ECOG PS, Eastern Cooperative Oncology Group performance status; R/R, relapsed/refractory; TN, treatment naive.

- The most common AEs in patients with WM were predominantly grade 1-2 in severity (**Figure 5**)
- AEs of special interest are shown in **Table 2**

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



Note: Common AEs include all grade ≥10% or grade 3-4 ≥2%.

Table 2. Adverse Events Overview

Patients With an Event	n (%)
Patients with ≥1 AE grade ≥3	40 (51.9)
Patients with ≥1 serious AE	36[a] (46.8)
AE leading to treatment discontinuation	8[b] (10.4)
Fatal AE	5[c] (6.5)
AE of special interest	
Petechiae	10 (13.0)
Purpura	1 (1.3)
Contusion	23 (29.9)
Diarrhea	13 (16.9)
Hypertension	9 (11.7)
Major hemorrhage	2[d] (2.6)
Atrial fibrillation/flutter	4 (5.2)

AE, adverse event.
[a]Includes serious AEs possibly related to zanubrutinib (n=6): hemothorax+pleural effusion+anemia (n=1), atrial fibrillation (n=1), colitis (n=1), febrile neutropenia (n=1), pneumonia (n=1), and cellulitis (n=1); septic arthritis relatedness was unknown.
[b]Abdominal sepsis (fatal), septic arthritis (fatal), worsening bronchiectasis (fatal), gastric adenocarcinoma (fatal), prostate adenocarcinoma, metastatic neuroendocrine carcinoma, acute myeloid leukemia, and breast cancer (each n=1).
[c]Septic arthritis (patient also reported disease progression), worsening bronchiectasis, abdominal sepsis, gastric adenocarcinoma, and scedosporium infection (each n=1).
[d]Defined as any grade ≥3 hemorrhage or any-grade central nervous system hemorrhage, gastrointestinal hemorrhage (n=1), grade 3 hemorrhagic cystitis (n=1).

- For the 73 patients evaluable for response, the overall response rate (ORR) was 92% by Modified IWWM-6 (**Table 3**) and as assessed by IRC
  - CR/VGPR rate was 42.5% by Modified IWWM-6 as assessed by IRC
- Activity is seen in both treatment-naive (TN) and relapsed/refractory (R/R) patients, and both *MYD88*^{L265P} and *MYD88*^{WT} populations (**Table 4**)

Table 3. Best Overall Response by Modified IWWM-6 by IRC Assessment

Best Response, n (%)	All Efficacy Evaluable (n=73)	TN Patients (n=24)	R/R Patients (n=49)
ORR[a]	67 (92)	23 (96)	44 (90)
CR	1 (1)	0 (0)	1 (2)
VGPR	30 (41)	7 (29)	23 (47)
PR	29 (40)	14 (58)	15 (31)
MR	7 (10)	2 (8)	5 (10)
SD	5 (7)	1 (4)	4 (8)
PD	1 (1)	0 (0)	1 (1)
Time to response (≥PR), median (range), mo	1.87 (0.9-24.6)	1.87 (1.0-15.7)	1.84 (0.9-24.6)
Study follow-up, median (range), mo	23.9 (4.4-45.7)	12.3 (5.9-28.0)	24.8 (4.4-45.7)

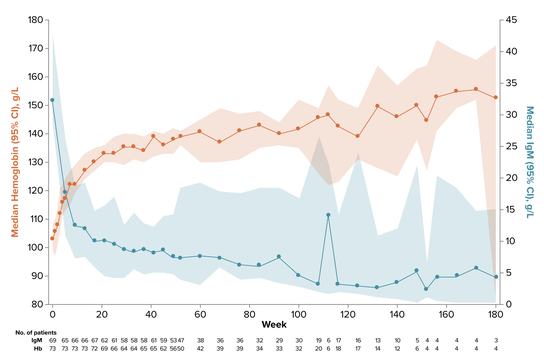
Modified IWWM-6 (Owen et al, 2013) to include IgM decreases only, and not extramedullary disease.
CR, complete response; IRC, independent review committee; IWWM-6, 6th International Workshop on Waldenstrom Macroglobulinemia; MR, minor response; ORR, overall response rate; PD, progressive disease; PR, partial response; R/R, relapsed/refractory; SD, stable disease; TN, treatment-naive; VGPR, very good PR.
[a]ORR: MR, PR, VGPR, CR

Table 4. Best Overall Response by *MYD88* Mutation Status

Best Response, n (%)	All Efficacy Evaluable (n=73)	*MYD88*^{L265P} (n=57)	*MYD88*^{WT} (n=8)	Unavailable (n=8)
ORR	67 (91.8)	52 (91.2)	7 (87.5)	8 (100.0)
CR	1 (1.4)	0 (0.0)	1 (12.5)	0 (0.0)
VGPR	30 (41.1)	26 (45.6)	1 (12.5)	3 (37.5)
PR	29 (39.7)	23 (40.4)	3 (37.5)	3 (37.5)
MR	7 (9.6)	3 (5.3)	2 (25.0)	2 (25.0)
SD	5 (6.8)	4 (7.0)	1 (12.5)	0 (0.0)
PD	1 (1.4)	1 (1.8)	0 (0.0)	0 (0.0)

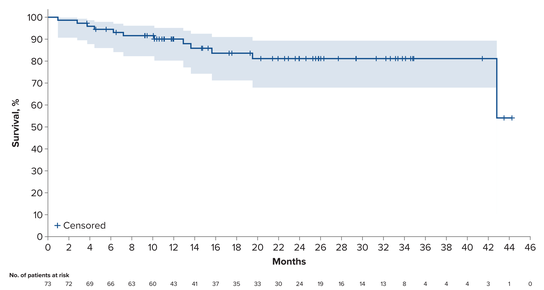
CR, complete response; IRC, independent review committee; MR, minor response; ORR, overall response rate; PD, progressive disease; PR, partial response; SD, stable disease; VGPR, very good PR.

Figure 6. Changes in Hemoglobin and IgM Levels Over Time



Shaded areas show the error bars associated with each assessment. Four patients in the efficacy-evaluable set didn't have IgM test results at baseline. Response assessments for these patients were based on SPEP M-protein.
IgM, immunoglobulin M; Hb, hemoglobin.

Figure 7. Progression-free Survival in Evaluable Patients (n=73)



Shaded area shows the 95% CI.

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DISCLOSURES

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