Results of a Phase 2 Expanded Access Study of Zanubrutinib in Patients With Waldenström Macroglobulinemia

Abstract P1160

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INTRODUCTION

- WM is an indolent B-cell non-Hodgkin lymphoma characterized by IgM-secreting clonal lymphoplasmacytic cells in bone marrow and extramedullary sites[1]
- Zanubrutinib (BGB-3111) is a second-generation BTK inhibitor designed to maximize BTK occupancy and minimize activation of off-target kinases which may contribute to the AE profile of this class of drugs[2,3]
- BTK inhibitors, including zanubrutinib, have been shown to be effective treatments for patients with WM, as demonstrated by the results of the phase 3 ASPEN study[4]
- Zanubrutinib has also demonstrated fewer toxic effects compared with the first-generation BTK inhibitor ibrutinib in the phase 3 ASPEN study[4]
- In June 2021, zanubrutinib was added as a preferred therapy for WM per the NCCN Guidelines® in Oncology version 1.2022[5]
- On August 31, 2021, zanubrutinib was approved by the FDA for the treatment of adult patients with WM at a dose of 320 mg QD or 160 mg BID[6]

OBJECTIVES

Primary

- To provide real-world experience with zanubrutinib for treatment of patients with WM for whom no other clinical trials were available

Secondary

- To assess safety of zanubrutinib in patients with WM
- To assess efficacy of zanubrutinib in patients with WM

METHODS

- A phase 2 expanded access study (BGB-3111-216; NCT04052854) in patients with TN or R/R WM in academic and community medical centers across the United States
- Eligible patients with TN or R/R WM were enrolled and received zanubrutinib monotherapy in 28-day cycles at a dose of 320 mg QD or 160 mg BID based on the investigator's discretion
- Efficacy assessments were performed based on modified Owen criteria (6th International Workshop on WM[7]) at least every 6 months
- AEs reported on this study included: any-grade serious AEs, grade 3/4 AEs, and the following AEs at any severity level: anemia, atrial fibrillation or flutter, hemorrhage, hypertension, infections, major hemorrhage, myalgias or arthralgias, neutropenia, second primary malignancies, thrombocytopenia, and tumor lysis syndrome
- The study was terminated by the sponsor in July 2021, when all patients were given the option to continue commercial zanubrutinib therapy through a patient-assistance program

RESULTS

- Fifty patients were enrolled and treated (R/R n=33; TN n=17) across 10 academic and community medical centers in the United States (**Table 1**)
- Most patients had either intermediate (n=27; 54.0%) or high-risk (n=20; 40.0%) disease
- Forty-one patients were assigned to receive zanubrutinib 160 mg BID, and 9 patients were assigned to receive zanubrutinib 320 mg QD
- Median number of prior therapies for patients with R/R WM was 2
- Nine patients discontinued drug before the first response assessment (**Figure 1**)
  - Eight transitioned to commercial supply of zanubrutinib due to study closure
  - One discontinued based on investigator decision

Table 1. Baseline Characteristics

Characteristics	TN (N=17)	R/R (n=33)	Overall (N=50)
Age, median (range), years	72 (61-83)	72 (47-93)	72 (47-93)
≤65 years, n (%)	2 (11.8)	7 (21.2)	9 (18.0)
Male, n (%)	10 (58.8)	17 (51.5)	27 (54.0)
Race, n (%)			
Asian	1 (5.9)	1 (3.0)	2 (4.0)
Native Hawaiian or other pacific islander	0	1 (3.0)	1 (2.0)
White	12 (70.6)	29 (87.9)	41 (82.0)
Multiple	0	1 (3.0)	1 (2.0)
Other[a]	4 (23.6)	1 (3.0)	5 (10.0)
ECOG PS, n (%)			
0	3 (17.6)	4 (12.1)	7 (14.0)
1	12 (70.6)	27 (81.8)	39 (78.0)
2	2 (11.8)	2 (6.1)	4 (8.0)
Time from initial diagnosis to first dose, median (range), months	3.7 (0.7-141.7)	92.9 (8.0-302.0)	70.4 (0.7-302.0)
Prognostic group at study entry for WM, n (%)			
Low risk	2 (11.8)	0	2 (4.0)
Intermediate risk	10 (58.8)	17 (51.5)	27 (54.0)
High risk	5 (29.4)	15 (45.5)	20 (40.0)
Missing	0	1 (3.0)	1 (2.0)
Number of prior lines of therapy, n (%)			
0	17 (100.0)	0	17 (34.0)
1-3	0	29 (87.9)	29 (58.0)
>3	0	4 (12.1)	4 (8.0)

[a]Includes patients with race not reported, unknown, or other.

Figure 1. Patient Disposition

Efficacy

- A total of 41 patients had ≥1 response evaluations while on study (efficacy evaluable, n=41; **Table 2**)
- Overall, 85.4% (35/41) of patients responded to treatment, with 73.2% (30/41) achieving a major response and 39.0% (16/41) achieving a very good partial response
- Responses were similar between patients with TN or R/R and in patients who received doses of 160 mg BID or 320 mg QD
- PFS and OS were immature due to short follow-up, and the median was not met

Table 2. BOR by Investigator Assessment

BOR by investigator assessment,[a] n (%)	Patients		Dose		Overall (N=41)
	TN (n=11)	R/R (n=30)	160 mg BID (n=33)	320 mg QD (n=8)	
Very good partial response	**3 (27.3)**	**13 (43.3)**	**13 (39.4)**	**3 (37.5)**	**16 (39.0)**
Partial response	**4 (36.4)**	**10 (33.3)**	**12 (36.4)**	**2 (25.0)**	**14 (34.1)**
Minor response	**1 (9.1)**	**4 (13.3)**	**4 (12.1)**	**1 (12.5)**	**5 (12.2)**
Stable disease	2 (18.2)	0	1 (3.0)	1 (12.5)	2 (4.9)
Progressive disease	1 (9.1)	3 (10.0)	3 (9.1)	1 (12.5)	4 (9.8)
Very good partial response or complete response	**3 (27.3)**	**13 (43.3)**	**13 (39.4)**	**3 (37.5)**	**16 (39.0)**
Major response rate[b]	**7 (63.6)**	**23 (76.7)**	**25 (75.8)**	**5 (62.5)**	**30 (73.2)**
Overall response rate[c]	**8 (72.7)**	**27 (90.0)**	**29 (87.9)**	**6 (75.0)**	**35 (85.4)**

[a]Efficacy evaluable population. [b]Major response rate includes patients achieving very good partial response and partial response. [c]Overall response rate includes patients that achieved very good partial response, partial response or minor response.

Safety

- Median duration of treatment exposure was 9.20 months (**Table 3**)
- Thirty-eight (76.0%) patients experienced ≥1 TEAE (**Table 4**)
- Thirty-six (72.0%) patients experienced ≥1 TEAE of interest (**Table 5**)
- No new safety signals were observed; and no major differences were seen in the safety profile between patients with TN or R/R and in those assigned to 160 mg BID or 320 mg QD

Table 3. Treatment Exposure

Treatment exposure	TN (n=17)	R/R (n=33)	Overall (N=50)
Duration of exposure, median (range), months[a]	8.3 (1.8-19.5)	9.8 (1.4-20.0)	9.2 (1.4-20.0)
<3 months, n (%)	4 (23.5)	3 (9.1)	7 (14.0)
3 to <6 months, n (%)	3 (17.6)	2 (6.1)	5 (10.0)
6 to <9 months, n (%)	2 (11.8)	9 (27.3)	11 (22.0)
9 to <12 months, n (%)	1 (5.9)	6 (18.2)	7 (14.0)
>12 months, n (%)	7 (41.2)	13 (39.4)	20 (40.0)
Number of treatment cycles received, median (range)[b]	9.0 (2.0-21.2)	10.7 (1.5-21.7)	10.0 (1.5-21.7)
Patients with dose reduction, n (%)[c]	1 (5.9)	4 (12.1)	5 (10.0)

[a]Duration of exposure is calculated as (last dose date first dose date + 1)/30.4375. [b]One cycle is defined as 28 days of treatment. The 'x cycle(s)' indicates patients completed at least x cycle(s) but less than x+1 cycles. [c]All dose reductions due to adverse events.

Table 4. TEAEs (≥5% in the Overall Population)

TEAE[a,b]	TN (n=17)		R/R (n=33)		Overall (N=50)	
	Any grade	Grade ≥3	Any grade	Grade ≥3	Any grade	Grade ≥3
Patients with ≥1 TEAE, n (%)	13 (76.5)	2 (11.8)	25 (75.8)	11 (33.3)	38 (76.0)	13 (26.0)
Arthralgia	3 (17.6)	0	7 (21.2)	1 (3.0)	10 (20.0)	1 (2.0)
Contusion	2 (11.8)	0	3 (9.1)	0	5 (10.0)	0
Epistaxis	1 (5.9)	0	4 (12.1)	0	5 (10.0)	0
Hypertension	0	0	5 (15.2)	4 (12.1)	5 (10.0)	4 (8.0)
Increased tendency to bruise	2 (11.8)	0	3 (9.1)	0	5 (10.0)	0
Pneumonia	1 (5.9)	1 (5.9)	4 (12.1)	1 (3.0)	5 (10.0)	2 (4.0)
Skin infection	1 (5.9)	0	3 (9.1)	0	4 (8.0)	0
Upper respiratory tract infection	1 (5.9)	0	2 (6.1)	0	3 (6.0)	0
Urinary tract infection	1 (5.9)	0	2 (6.1)	0	3 (6.0)	0
Leading to treatment discontinuation, n (%)[c]	1 (5.9)		2 (6.1)		3 (6.0)	
Leading to treatment dose reduction, n (%)[d]	1 (5.9)		3 (9.1)		4 (8.0)	
Leading to treatment dose interruption, n (%)[e]	1 (5.9)		5 (15.2)		6 (12.0)	
Leading to death	0		0		0	

[a]Adverse event grades are evaluated based on NCI-CTCAE (version 5.0). [b]Patients with multiple events for a given system organ class or preferred term are counted only once for each category. [c]TEAE leading to treatment discontinuation: pericardial effusion, pleural effusion, skin hemorrhage, soft tissue sarcoma (each n=1). [d]TEAE leading to treatment dose reduction: arthralgia, contusion, fatigue, pruritus, skin hemorrhage (each n=1). [e]TEAE leading to treatment dose interruption: arthralgia (n=2), contusion, fatigue, glomerular filtration rate decreased, hematuria, hypertension, pruritus, skin hemorrhage, infection, urinary tract (n=1 each).

Table 5. TEAEs of Interest per Dosing Group

TEAE[a]	Zanubrutinib 160 mg BID (n=41)	Zanubrutinib 320 mg QD (n=9)	Overall (N=50)
Patients with ≥1 TEAE of interest, n (%)	31 (75.6)	5 (55.6)	36 (72.0)
Grade ≥3	7 (17.1)	1 (11.1)	8 (16.0)
Hypertension	4 (9.8)	0	4 (8.0)
Infection	3 (7.3)	1 (11.1)	4 (8.0)
Atrial fibrillation or flutter	1 (2.4)	0	1 (2.0)
Neutropenia	1 (2.4)	0	1 (2.0)
Second primary malignancy	1 (2.4)	0	1 (2.0)

[a]Safety population.

CONCLUSIONS

- Despite differences in demographic characteristics and baseline disease status compared to the phase 3 ASPEN study (older age distribution, worse ECOG PS, longer disease course duration, and poorer prognosis), observed response rates and toxicity profile were comparable
- In patients with ≥1 post-baseline response evaluations, this study demonstrated a higher very good partial response rate, similar major response rate, and lower overall response rate compared to those of the phase 3 ASPEN study
- The higher rate of PD and thus lower ORR compared to that of ASPEN, may be attributed to the less frequent response assessments on this study (every 6 months), in which response assessments were performed monthly for the first year; therefore, any responses that may have been achieved between response assessments (ie, during months 1-5, or months 7-11) would not be captured
  - When considering the 4 patients with a BOR of PD, 3 of these patients had IgM levels reported during the first 6 months (ie, prior to the first response assessment), which indicated a response
- The results of this real-world expanded access study were consistent with the established zanubrutinib profile in WM and other B-cell malignancies when administered as monotherapy at a daily dose of 320 mg orally (either as 160 mg BID or 320 mg QD) in patients with intermediate or high-risk R/R or TN WM

REFERENCES

1. Argyropoulos et al. *Hematol Oncol Clin North Am* 2018;32(5):853-864
2. Guo et al. *J Med Chem* 2019;62(17):7923-7940
3. Tam et al. *Blood* 2019;134(1):851-859
4. Tam et al. *Blood* 2020;136(18):2038-2050
5. NCCN Guidelines for Waldenström Macroglobulinemia/Lymphoplasmacytic Lymphoma. V1.2022
6. US Food and Drug Administration. Accessed May 11, 2022. tinyurl.com/yc2a6b43
7. Owen et al. *Br J Haematol* 2013;160(2):171-176

ABBREVIATIONS

AE, adverse event; BID, twice daily; BOR, best overall response; BTK, Bruton tyrosine kinase; ECOG PS, Eastern Cooperative Oncology Group performance status; PD, progressive disease; FDA, US Food and Drug Administration; IgM, immunoglobulin M; NCCN, National Comprehensive Cancer Network; NCI-CTCAE, National Cancer Institute Common Terminology Criteria for Adverse Events; ORR, overall response rate; PD, progressive disease; QD, once daily; R/R, relapsed/refractory; TEAE, treatment-emergent adverse event; TN, treatment naïve; WM, Waldenström macroglobulinemia.

DISCLOSURES

JJC: consulting with Janssen, Roche/Genentech, BeiGene, AbbVie/Pharmacyclics, Polyneuron; research funding from Pharmacyclics, AbbVie, Janssen, BeiGene, TG Therapeutics, AstraZeneca
MN: consulting with BeiGene, BMS, Celgene, DSI, Takeda; speakers bureau with BeiGene, BMS, Takeda
HAY: stock with Karyopharm; speakers bureau with AstraZeneca, Janssen, BeiGene, GSK, Sanofi, Karyopharm, Amgen, Pharmacyclics
JMM: consulting with TG Therapeutics; speakers bureau with Janssen, AstraZeneca
MC: stock with Immunomedics; research funding from AbbVie, BMS, Celgene, Genentech, Gilead, BeiGene, InnoCare, Merck, Pfizer, Roche
CMF: stock with Alexion; honoraria from BMS; consulting with ADC Therapeutics, BeiGene, Gilead, Morphosys/Incyte, TG Therapeutics; speakers bureau with ADC Therapeutics, Genentech, Gilead, Morphosys/Incyte Seagen, TG Therapeutics
JS: honoraria and consulting with Seagen, TG Therapeutics
EHM, XZ, AC: employment and stock with BeiGene
JH: employment and patents with BeiGene; leadership with BeiGene, Protara; research funding from BeiGene; stock with BeiGene, Roche
ECK, CAD, MG: nothing to disclose

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