Phase 2 Study of Zanubrutinib in BTK Inhibitor-Intolerant Patients With Relapsed/Refractory B-cell Malignancies

Abstract 1410

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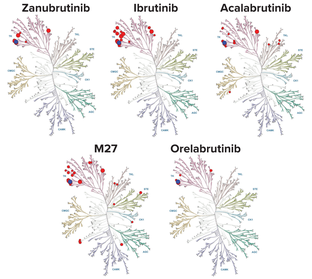
INTRODUCTION

- BTKi provide effective treatment to several B-cell malignancies; however, duration of treatment is limited by AEs leading to treatment discontinuation, which occur early[1-3]
- BTKi-associated AEs are believed to be due to off-target effects of BTKi
- Zanubrutinib, a BTKi approved for treatment of mantle cell lymphoma, marginal zone lymphoma, and WM, was designed to optimize selectivity and maximize BTK occupancy (**Figure 1**)
- In the ASPEN trial comparing zanubrutinib to ibrutinib in patients with WM, zanubrutinib showed lower rates of AEs leading to death (1% vs 4.1%), discontinuation (4% vs 9.2%), dose reduction (13.9% vs 23.5%), and dose holds (46.5% vs 56.1%); and a lower rate of atrial fibrillation/flutter (2% vs 15.3%)[4]
- In the interim analysis of the ALPINE trial comparing zanubrutinib to ibrutinib in patients with relapsed/refractory chronic lymphocytic leukemia/small lymphocytic lymphoma, zanubrutinib showed lower rates of AEs leading to death (3.9% vs 5.8%), discontinuation (7.8% vs 13%), dose reduction (11.3% vs 12.1%), and dose holds (39.7% vs 40.6%), and lower rates of atrial fibrillation/flutter (2.5% vs 10.1%)[5]
- **BGB-3111-215** is a phase 2, multicenter, US, single-arm, open-label study of the safety and efficacy of zanubrutinib in patients intolerant to ibrutinib and/or acalabrutinib with previously treated B-cell malignancies (**Figure 2**)

Figure 1. Kinase Selectivity of Zanubrutinib, Ibrutinib, Acalabrutinib, M27, and Orelabrutinib



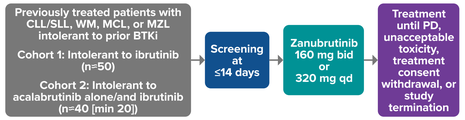
- Zanubrutinib demonstrated higher selectivity than ibrutinib, acalabrutinib, and acalabrutinib's major metabolite (M27), comparable selectivity to orelabrutinib, by kinase profiling
- Kinase selectivity was assessed at 100X IC_{50} (against BTK) for zanubrutinib, ibrutinib, acalabrutinib, M27, and orelabrutinib (Reaction Biology Corp.)
  - IC_{50} (against BTK, n=3):
    - Zanubrutinib: 0.71±0.09 nM
    - Ibrutinib: 0.32±0.09 nM
    - Acalabrutinib: 24±9.2 nM
    - M27: 63±28 nM
    - Orelabrutinib: 15±5.5 nM
- Of the 370 kinases tested, zanubrutinib, ibrutinib, acabrutinib, M27, and orelabrutinib demonstrated >50% inhibition of 7, 17, 15, 23 and 5 kinases, respectively

OBJECTIVES

- Primary objective: To evaluate the safety of zanubrutinib in patients intolerant to ibrutinib and/or acalabrutinib treatment compared with their ibrutinib and/or acalabrutinib intolerance as assessed by the recurrence and the change in severity of AEs
- Secondary objectives: To evaluate the efficacy of zanubrutinib with respect to investigator-assessed objective response rate, investigator-assessed disease control rate, investigator-assessed progression-free survival, and patient-reported outcomes

METHODS

Figure 2. Study Design



Key Inclusion Criteria

- Ibrutinib and acalabrutinib intolerance
  - Grade ≥2 nonhematologic toxicity for >7 days
  - Grade ≥3 nonhematologic toxicity for any duration
  - Grade 3 neutropenia with infection or fever
  - Grade 4 hematologic toxicity that persists until BTKi therapy is discontinued due to toxicity
  - Resolution of BTKi toxicities to grade ≤1 or baseline before initiating zanubrutinib treatment
- Additional acalabrutinib intolerance criteria
  - Grade ≥1 nonhematologic toxicity for >7 days
  - Grade ≥1 nonhematologic toxicity of any duration with ≥3 recurrent episodes
  - Inability to use acid-reducing agents or anticoagulants due to current BTKi use
- Resolution of grade 1 BTKi toxicities to grade 0 or baseline before initiating zanubrutinib treatment

Key Exclusion Criteria

- Disease progression during prior BTKi treatment

Table 1. Patient Demographics and Baseline Characteristics

Characteristics	Cohort 1 (prior ibrutinib) (n=57)	Cohort 2 (prior acalabrutinib +/- ibrutinib) (n=10)	Total (N=67)
Indication, n (%)			
CLL	38 (66.7)	5 (50.0)	43 (64.2)
WM	9 (15.8)	2 (20.0)	11 (16.4)
SLL	6 (10.5)	1 (10.0)	7 (10.4)
MCL	2 (3.5)	1 (10.0)	3 (4.5)
MZL	2 (3.5)	1 (10.0)	3 (4.5)
Age, median (range), year	71.0 (49-91)	73.5 (65-83)	71.0 (49-91)
Male, n (%)	30 (52.6)	6 (60.0)	36 (53.7)
ECOG PS 0, n (%)	33 (57.9)	4 (40.0)	37 (55.2)
No. of prior therapy regimens, median (range)	1.0 (1-12)	2.5 (1-5)	1.0 (1-12)
Prior BTKi, n (%)	57 (100)	10 (100)	67 (100)
Ibrutinib monotherapy	49 (86.0)	6 (60.0)[a]	55 (82.1)
Ibrutinib combination therapy	9 (15.8)[b]	0	9 (13.4)
Acalabrutinib monotherapy	0	10 (100)	10 (14.9)
Time on prior BTKi,[c] median (range), months	10.61 (1.1-73.7)	3.33 (0.5-26.9)	—
On-study zanubrutinib dosing regimen			
160 mg bid	35 (61.4)	7 (70.0)	42 (62.7)
320 mg qd	22 (38.6)	3 (30.0)	25 (37.3)

Data Cutoff: 8 September 2021

[a]Six patients had both prior ibrutinib and acalabrutinib therapies. [b]One patient received ibrutinib combination therapy followed by ibrutinib monotherapy. [c]Cumulative ibrutinib exposure for cohort 1 and acalabrutinib for cohort 2.

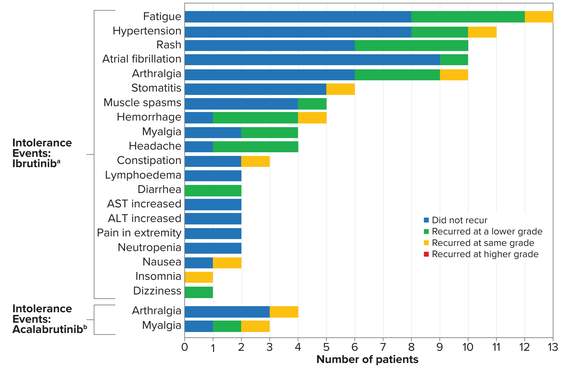
Table 2. Patient Disposition

	Cohort 1 (prior ibrutinib) (n=57)	Cohort 2 (prior acalabrutinib +/- ibrutinib) (n=10)	Total (N=67)
Patients remaining on treatment, n (%)	48 (84.2)	8 (80.0)	56 (83.6)
Patients remaining on study, n (%)	54 (94.7)	10 (100)	64 (95.5)
Patients discontinued from treatment, n (%)	9 (15.8)	2 (20.0)	11 (16.4)
Adverse event	4 (7.0)[a]	1 (10.0)[b]	5 (7.5)
Progressive disease	3 (5.3)	1 (10.0)	4 (6.0)
Physician decision	1 (1.8)[c]	0	1 (1.5)
Withdrawal by patient	1 (1.8)[d]	0	1 (1.5)
Death	1 (1.8)[e]	0	1 (1.5)
Zanubrutinib exposure, median (range), months	11.6 (0.6-20.3)	9.8 (0.5-12.0)	11.1 (0.5-20.3)
Follow-up, median (range), months	12.3 (1.0-22.8)	10.4 (0.5-15.0)	12.0 (0.5-22.8)

[a]Penile bleed, COVID-19 pneumonia (fatal), increased alanine aminotransferase/aspartate transaminase, and autoimmune hemolytic anemia. [b]Myalgia. [c]Patient not responding to treatment. [d]Patient withdrew from study after grade 3 syncope related to diabetes. [e]COVID-19 pneumonia.

RESULTS

Figure 3. Recurrence of Ibrutinib and Acalabrutinib Intolerance Events on Zanubrutinib



[a]18 ibrutinib intolerance events (arthritis, bone pain, bronchitis, embolism, heart rate irregular, malaise, pericardial effusion, pleural effusion, pneumonia, psoriasis, pyrexia, sinusitis, subcutaneous abscess, supraventricular tachycardia, transaminases increased, ventricular extrasystoles, vertigo, and vomiting) occured in 1 patient and did not recur on zanubrutinib. [b]11 acalabrutinib intolerance events (abdominal pain, asthenia, atrial fibrillation, dyspepsia, fatigue, groin pain, headache, insomnia, malaise, pain in extremity, and rash) occurred in 1 patient and did not recur on zanubrutinib (not shown in **Figure 3**).

- **Most ibrutinib and acalabrutinib intolerances did not recur on zanubrutinib**
- **No ibrutinib or acalabrutinib intolerance events recurred at a higher severity (Figure 3)**
- 81/115 (70.4%) ibrutinib intolerance events and 15/18 (83.3%) acalabrutinib intolerance events did not recur
  - Of the 34 recurrent ibrutinib intolerance events, 26 (76.5%) recurred at lower severity, and 8 (23.5%) recurred at the same severity
  - Of the 3 recurrent acalabrutinib intolerance events, 1 (33.3%) recurred at lower severity, and 2 (66.6%) recurred at the same severity
- 34/57 (59.6%) of patients who took ibrutinib and 7/10 (70.0%) of patients who took acalabrutinib did not have recurrence of any intolerance event
- 25/38 (65.8%) grade 3 ibrutinib intolerance events and 3/4 (75.0%) grade 3 acalabrutinib intolerance events did not recur while on zanubrutinib
  - Of the grade 3 ibrutinib intolerance events that recurred, 12 recurred at a lower severity and 1 at the same severity
  - Of the grade 3 acalabrutinib intolerance events that recurred, all recurred at a lower severity
- **All grade 4 intolerance events (neutropenia [n=2], ALT increase [n=1], AST increase [n=1]) did not recur on zanubrutinib**
- 1 patient (1.5%) discontinued zanubrutinib due to recurrence of a prior intolerant event (myalgia; acalabrutinib)

Table 3. Safety Summary

Category, n (%)	Cohort 1 (prior ibrutinib) (n=57)	Cohort 2 (prior acalabrutinib +/- ibrutinib) (n=10)	Total (N=67)
Patients with at least 1 AE	54 (94.7)	10 (100)	64 (95.5)
Grade ≥3	17 (29.8)	3 (30.0)	20 (29.9)
Serious AE	6 (10.5)	2 (20.0)	8 (11.9)
AE leading to treatment discontinuation	4 (7.0)	1 (10.0)	5 (7.5)
AE leading to dose interruption	16 (28.1)	4 (40.0)	20 (29.9)
AE leading to dose reduction	5 (8.8)	1 (10.0)	6 (9.0)
AE leading to death	1 (1.8)[a]	0	1 (1.5)

[a]COVID-19 pneumonia.

Table 4. Adverse Events

Most Common AEs in ≥7.5% of Patients, n (%)	All Grades (N=67)	Grade ≥3 (N=67)
Contusion/bruising	15 (22.4)	0
Fatigue	14 (20.9)	0
Myalgia	10 (14.9)	0
Arthralgia	9 (13.4)	0
Diarrhea	9 (13.4)	1 (1.5)
Hypertension	8 (11.9)	1 (1.5)
Dizziness	7 (10.4)	0
Nausea	7 (10.4)	0
Pain in extremity	6 (9.0)	0
Cough	5 (7.5)	0
Epistaxis	5 (7.5)	0
Insomnia	5 (7.5)	0
Muscle spasms	5 (7.5)	0
Neutropenia	5 (7.5)	5 (7.5)
Neutrophil count decreased	5 (7.5)	3 (4.5)
Petechiae	5 (7.5)	0
Rash	5 (7.5)	0
Urinary tract infection	5 (7.5)	0

- The most common grade ≥3 AEs
  - Neutropenia/neutrophil count decrease: 8 (12.0%)
  - Syncope: 2 (3.0%)
- Bleeding events occurred in 25 patients (37.3%; grade 1: 19 [28.4%], grade 2: 6 [9.0%])
- Atrial fibrillation occurred in 3 patients (4.5%; all grade 2)
  - 2 patients had prior history of atrial fibrillation. First patient developed grade 3 atrial fibrillation after starting ibrutinib and rituximab, and was treated with digoxin. Second patient had history of grade 2 atrial fibrillation prior to starting ibrutinib and was treated with diltiazem. In both patients, atrial fibrillation resolved after treatment. Zanubrutinib was never held, or dose reduced. Both patients remain on study
  - 1 patient had a prior history of hypertension (grade 1). The patient was treated with metoprolol and zanubrutinib dose was held. Atrial fibrillation remains ongoing. Patient remains on study
- Infections occurred in 26 patients (38.8%; grade 1: 3 [4.5%], grade 2: 18 [26.9%], grade 3: 6 [6.0%]; grade 5: 1 [COVID-19; 1.5%])
- Anemia occurred in 3 patients (3.1%; grade 1: 1 [1.5%], grade 2: 2 [3.0%])
- Thrombocytopenia/platelet count decrease occurred in 3 patients (4.5%; all grade 1)

Table 5. Efficacy by Investigator Assessment in Patients With >90-Day Study Duration

Response[a]	Cohort 1 (prior ibrutinib) (n=57)	Cohort 2 (prior acalabrutinib +/- ibrutinib) (n=7)	Total (N=64)
Disease control rate [SD or better], n (%)	54 (94.7)	6 (85.7)	60 (93.8)
Overall response rate [better than SD], n (%)	36 (63.2)	5 (71.4)	41 (64.1)
BOR rate, n (%)			
PR or better[b]	36 (63.2)	5 (71.4)	41 (64.1)
SD	18 (31.6)	1 (14.3)	19 (29.7)
PD	1 (1.8)	1 (14.3)	2 (3.1)
Not done	2 (3.5)[c]	0	2 (3.1)
Time to BOR, median (range), months	5.5 (2.6-11.3)	7.9 (2.9-11.1)	5.6 (2.6-11.3)
Time to first overall response, median (range), months	2.92 (2.6-11.1)	3.02 (2.7-11.1)	2.96 (2.6-11.1)

[a]**Disease parameters performed at study entry, in most cases after recent BTKi therapy, were used as baseline for response assessment.** [b]PR or better includes nodular partial response and very good partial response. [c]1 patient withdrew from study before first assessment timepoint due to syncope; 1 patient died from COVID-19 pneumonia before first response assessment.

Table 6. *BTK* and *PLCG2* Mutational Status at Start of Study and at/after Progression

Patient	Indication	Best Response to Zanubrutinib	Days on Zanubrutinib	*BTK* Mutational Status		*PLCG2* Mutational Status	
				At Start of Study	At/after Progression	At Start of Study	At/after Progression
1	CLL	PR	280	Not detected[a]	Detected	Not detected[a]	Detected
2	SLL	PR	545	Not detected	Detected	Not detected	Detected
3	CLL	PD	140	Detected	Detected	Not detected	Not detected
4	CLL	PD	288	Not detected	Not detected	Not detected	Not detected
5[b]	MCL	SD	264	Not detected[c]	Not detected	Not detected[c]	Not detected

[a]Initial sample collected on study day 87. [b]Patient with MCL with CCND1-IGH fusion at both baseline and relapse, which was reported to contribute to BTKi resistance in MCL.[6] [c]Initial sample collected on study day 141.

- 3 of 5 patients who progressed had *BTK*/*PLCG2* mutations associated with BTKi resistance at/after progression

CONCLUSIONS

- **Intolerable AEs experienced on ibrutinib and/or acalabrutinib were unlikely to recur while on zanubrutinib**
  - With a median follow-up of 12.0 months, 70.4% of ibrutinib intolerance events and 83.3% of acalabrutinib intolerance events did not recur while on zanubrutinib
  - Of the intolerance events that recurred, 76.4% of ibrutinib intolerance and 33.3% of acalabrutinib intolerance events recurred at a lower severity; 23.5% of ibrutinib intolerance and 66.6% of acalabrutinib intolerance events occurred at the same severity
  - No events recurred at a higher severity
  - Only 1 patient (1.5%) discontinued zanubrutinib due to recurrence of a prior intolerance event (acalabrutinib)
- **Zanubrutinib was tolerable with 83.6% of patients remaining on zanubrutinib, and 7.5% of patients discontinued zanubrutinib due to AEs at the time of data cutoff**
- **Zanubrutinib was effective in at least maintaining response in 93.8% or improving response from baseline in 64.1% of patients**
- Exploratory biomarkers analysis findings indicate that relapse on zanubrutinib was associated with BTKi-resistance mutations
- Zanubrutinib demonstrated favorable BTKi selectivity profiles over ibrutinib and acalabrutinib to support clinical findings
- These data suggest that zanubrutinib may provide a therapeutic option in patients intolerant to other BTKi across hematologic malignancies

DISCLOSURES

MS served as a consultant for AbbVie, Genentech, AstraZeneca, Sound Biologics, Pharmacyclics, BeiGene, Bristol Myers Squibb, MorphoSys, TG Therapeutics, Innate Pharma, Kite Pharma, Adaptive Biotechnologies, Epizyme, Eli Lilly, Atara Biotherapeutics, and Adaptimmune Therapeutics, received research funding from Mustang Bio, Celgene, Bristol Myers Squibb, Pharmacyclics, Gilead, Genentech, AbbVie, TG Therapeutics, BeiGene, AstraZeneca, Sunesis, Atara Biotherapeutics, and GenMab.

IF served as a consultant for AbbVie, AstraZeneca, BeiGene, Century Therapeutics, Genentech, Gilead Sciences, Great Point Partners, Hutchison MediPharma, Ikaufa Therapeutics, Janssen, Juno Therapeutics, Kite Pharma, MorphoSys, Novartis, Nurix Therapeutics, Pharmacyclics, Roche, Seagen, Servier Pharmaceuticals, Takeda, TG Therapeutics, Umoja Therapeutics, Verastem, Vincerx Pharma, and Yingli Pharmaceuticals, and received research funding from AbbVie, Acerta Pharma, Agios, ArQule, AstraZeneca, BeiGene, Caribou Biosciences, Celgene, Constellation Pharmaceuticals, Curis, Forma Therapeutics, Forty Seven, Genentech, Gilead Sciences, IGM Biosciences, Incyte, Infinity Pharmaceuticals, Janssen, Juno Therapeutics, Karyopharm Therapeutics, Kite Pharma, Loxo, Merck, MorphoSys, Novartis, Pfizer, Pharmacyclics, Portola Pharmaceuticals, Rhizen Pharmaceuticals, Roche, SeaGen, Takeda, Tesaro, Trillium Therapeutics, Trphan Biotech & Development Corp, Unum Therapeutics, and Verastem.

MYL served as a consultant for AbbVie, Amgen, AstraZeneca, Bristol Myers Squibb, BeiGene, Gilead Sciences, Janssen, Jazz, Karyopharm, MorphoSys, Seagen, Takeda, TG Therapeutics, Dova, Epizyme, GSK, and Novartis, received honoraria from AbbVie, Amgen, AstraZeneca, Bristol Myers Squibb, BeiGene, Gilead Sciences, Janssen, Jazz, Karyopharm, MorphoSys, Seagen, and Takeda, served as a promotional speaker for AbbVie, Amgen, Bristol Myers Squibb, Janssen, Karyopharm, MorphoSys, Seagen, Takeda, Dova, Epizyme, GSK, and Novartis.

JMB served as a consultant for AstraZeneca, MorphoSys, Verastem, Adaptive Biotechnologies, Genentech/Roche, Kura Oncology, Epizyme, AbbVie, BeiGene, Kymera, Bristol Myers Squibb, X4 Pharmaceuticals, and SeaGen and served on the speakers' bureaus for BeiGene and SeaGen.

JLC has received research funding from BeiGene.

EK has current employment at Comprehensive Cancer Centers of Nevada.

HAY has current employment at Texas Oncology, is on the speakers' bureaus for Janssen, AstraZeneca, BeiGene, Karyopharm, **GSK**, Sanofi, Amgen and Pharmacyclics, and holds stock in Karyopharm.

ACh has current employment at Medical Oncology Associates and holds stocks in Novartis.

PKT has current employment at Texas Oncology.

MDG has received honoraria from GSK, Karyopharm, and TG Therapeutics.

SM received honoraria from MorphoSys and hold stock in GenMab.

DYC, KB, YL have current employment and equity ownership with BeiGene.

AC has current employment, equity ownership, and received travel expenses from BeiGene.

LX has current employment at BeiGene and previous employment with AstraZeneca.

JPS served as a consultant for AbbVie, AstraZeneca, BeiGene, BMS, Lilly, Pharmacyclics, TG Therapeutics, and Centessa; honoraria from AbbVie, AstraZeneca, BeiGene, Lilly, Pharmacyclics, TG Therapeutics, ADC Therapeutics, and Genentech; holds stock and serves on the advisory board of Centessa.

RP, SFZ, JM, BF, SSR, THG have nothing to disclose.

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ABBREVIATIONS

AE, adverse event; ALT, alanine aminotransferase; AST, aspartate aminotransferase; bid, twice daily; BOR, best overall response; BTK, Bruton tyrosine kinase; BTKi, Bruton tyrosine kinase inhibitor; CLL, chronic lymphocytic leukemia; ECOG PS, Eastern Cooperative Oncology Group performance status; MCL, mantle cell lymphoma; MZL, marginal zone lymphoma; PD, progressive disease; PLCG2, phospholipase C gamma 2 gene; PR, partial response; qd, once daily; SD, stable disease; SLL, small lymphocytic lymphoma; WM, Waldenström macroglobulinemia.

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