PRELIMINARY RESULTS OF A PHASE 2 STUDY OF ZANUBRUTINIB IN PATIENTS WITH PREVIOUSLY TREATED B CELL MALIGNANCIES INTOLERANT TO IBRUTINIB/ACALABRUTINIB

Abstract EP642

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INTRODUCTION

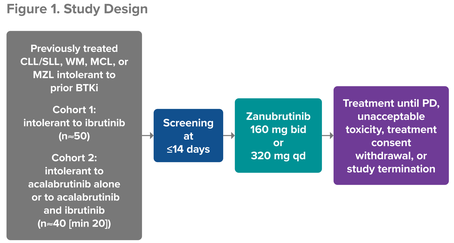
- Bruton tyrosine kinase inhibitor (BTKi) therapy is effective in several B-cell malignancies; however, its use is limited by adverse events (AEs) leading to discontinuation in some patients, which tend to occur early in treatment[1-3]
- Zanubrutinib, a BTKi approved for the treatment of mantle cell lymphoma (MCL) and in development for other malignancies, is optimized for BTK selectivity and occupancy
- In the ASPEN trial comparing zanubrutinib to ibrutinib in patients with Waldenström macroglobulinemia, 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]
- **BGB-3111-215** is a phase 2, multicenter, US, single-arm, open-label study of the safety and efficacy of zanubrutinib in ibrutinib- and/or acalabrutinib-intolerant patients with previously treated B-cell malignancies (**Figure 1**)

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, and investigator-assessed progression-free survival and with respect to patient-reported outcomes

METHODS

Figure 1. 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 any BTKi treatment

CLL, chronic lymphocytic leukemia; bid, twice daily; BTKi, Bruton tyrosine kinase inhibitor; MCL, mantle cell lymphoma; MZL, marginal zone lymphoma; PD, progressive disease; qd, once daily; SLL, small lymphocytic lymphoma; WM, Waldenström macroglobulinemia.

RESULTS

- Patient demographics and baseline characteristics are described in **Table 1**

Table 1. Patient Demographics and Baseline Characteristics

Characteristics	Cohort 1 (n=57)	Cohort 2 (n=7)	Total (N=64)
Indication			
CLL	38 (66.7)	4 (57.1)	42 (65.6)
WM	9 (15.8)	1 (14.3)	10 (15.6)
SLL	6 (10.5)	0 (0)	6 (9.4)
MCL	2 (3.5)	1 (14.3)	3 (4.7)
MZL	2 (3.5)	1 (14.3)	3 (4.7)
Age, median (range), y	71 (49-91)	71 (65-76)	71 (49-91)
Male, n (%)	30 (52.6)	5 (71.4)	35 (54.7)
ECOG PS 0, n (%)	33 (57.9)	4 (57.1)	37 (57.8)
No. of prior therapy regimens, median (range)	1 (1-12)	3 (2-5)	2 (1-12)
Prior BTKi, n (%)			
Ibrutinib monotherapy	50 (87.7)	5 (71.4)[a]	55 (85.9)
Ibrutinib combination therapy	8 (14.0)[b]	0 (0)	8 (12.5)
Acalabrutinib monotherapy	NA	7 (100)	7 (10.9)
Time on most recent prior BTKi, median (range), mo	9.7 (1.1-73.7)	2.1 (0.5-26.8)	9.2 (0.5-73.7)
On-study zanubrutinib dosing regimen			
160 mg bid	35 (61.4)	5 (71.4)	40 (62.5)
320 mg qd	22 (38.6)	2 (28.6)	24 (37.5)

Data cutoff: 01 Mar 21.
BTKi, Bruton tyrosine kinase inhibitor; bid, twice daily; CLL, chronic lymphocytic leukemia; ECOG PS, Eastern Cooperative Oncology Group performance status; MCL, mantle cell lymphoma; MZL, marginal zone lymphoma; NA, not applicable; qd, once daily; SLL, small lymphocytic leukemia; WM, Waldenström macroglobulinemia.
[a] Five patients had both prior ibrutinib and acalabrutinib therapies.
[b] One patient received ibrutinib combination therapy followed by ibrutinib monotherapy.

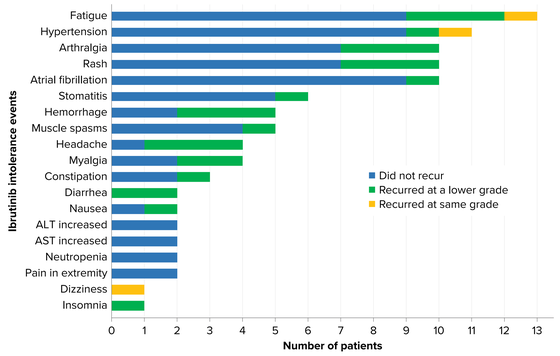
- At data cutoff, 7 patients had discontinued treatment, and 2 had discontinued the study (**Table 2**)
- Overall, 3 patients discontinued zanubrutinib due to AEs, none of which were due to a recurrence of prior intolerance event

Table 2. Patient Disposition

	Cohort 1 (n=57)	Cohort 2 (n=7)	Total (N=64)
Patients discontinued from treatment, n (%)	7 (12.3)	0 (0)	7 (10.9)
Adverse event	3 (5.3)[a]	0 (0)	3 (4.7)
Progressive disease	2 (3.5)	0 (0)	2 (3.1)
Physician decision	1 (1.7)[b]	0 (0)	1 (1.6)
Withdrawal by patient	1 (1.7)[c]	0 (0)	1 (1.6)
Patients remained on treatment, n (%)	50 (87.7)	7 (100)	57 (89.1)
Patients discontinued from study, n (%)	2 (3.5)	0 (0)	2 (3.1)
Death	1 (1.7)[d]	0 (0)	1 (1.6)
Withdrawal by patient	1 (1.7)[c]	0 (0)	1 (1.6)
Patients remaining on study, n (%)	55 (96.5)	7 (100)	62 (96.9)
Zanubrutinib exposure, median (range), mo	6.2 (0.6-16.6)	5 (3.2-8.7)	5.9 (0.6-16.6)
Follow-up, median (range), mo	NA	NA	6 (0.7-16.6)

Data cutoff: 01 Mar 21.
NA, not applicable.
[a] AEs leading to discontinuation were a penile bleed, COVID-19 pneumonia, and increased alanine aminotransferase and aspartate transaminase.
[b] Patient not responding to treatment.
[c] Patient withdrew from study after grade 3 syncope related to diabetes.
[d] Death due to COVID-19 pneumonia.

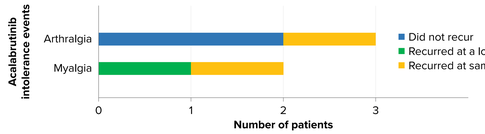
Figure 2. Recurrence of Ibrutinib Intolerance Events on Zanubrutinib[a]



Data cutoff: 01 Mar 21.
ALT, alanine aminotransferase; AST, aspartate transaminase.
[a] Intolerance events occurring in ≥2 patients or recurring in ≥1 patient shown here.

- 86/115 ibrutinib intolerance events (75%) did not recur (**Figure 2**)
  - Of the 29 recurrent ibrutinib intolerance events, 26 (90%) recurred at a lower severity, and 3 (10%) at the same severity

Figure 3. Recurrence of Acalabrutinib Intolerance Events on Zanubrutinib[a]



Data cutoff: 01 Mar 21.
[a] Intolerance events occurring in ≥2 patients shown here.

- 3/5 patients intolerant to both ibrutinib and acalabrutinib experienced recurrence of their acalabrutinib event (**Figure 3**)
- 2 patients had the same intolerance event on ibrutinib and acalabrutinib; neither event recurred on zanubrutinib
  - Patient 1 had grade 2 pain in extremity on ibrutinib and acalabrutinib emergent after 7 days and 3 days, respectively (on study for ~7 months)
  - Patient 2 had atrial fibrillation on ibrutinib (grade 3) and acalabrutinib (grade 2) emergent after 8 months and 20 months, respectively (on study for ~6 months)
- 9/12 acalabrutinib intolerance events (75%) did not recur
  - Of the 3 recurrent acalabrutinib intolerance events, 1 (33%) recurred at a lower severity, and 2 (67%) at the same severity

Recurrence Summary

- 75% of ibrutinib and acalabrutinib intolerance events did not recur on zanubrutinib
- No ibrutinib or acalabrutinib intolerance recurred at a higher grade on zanubrutinib
- All grade 4 intolerance events did not recur on zanubrutinib (neutropenia [n=2], alanine aminotransferase increase [n=1], aspartate transaminase increase [n=1])
- Most (68.3% [28/41]) grade 3 intolerance events did not recur on zanubrutinib
  - Of the grade 3 intolerance events that recurred, all recurred at a lower severity
- 20 ibrutinib intolerance events and 7 acalabrutinib intolerance events occurred in 1 patient each and did not recur on zanubrutinib
- 2 ibrutinib intolerance events, dizziness and insomnia, occurring in 1 patient each, recurred while on zanubrutinib at the same severity and lower severity, respectively

Table 3. Safety Summary

Category, n (%)	Cohort 1 (n=57)	Cohort 2 (n=7)	Total (N=64)
Patients with at least 1 AE	45 (78.9)	7 (100)	52 (81.3)
Grade ≥3	11 (19.3)	3 (42.9)	14 (21.9)
Serious AE	3 (5.3)[a]	2 (28.6)[b]	5 (7.8)
AE leading to treatment discontinuation	3 (5.3)[c]	0 (0)	3 (4.7)
AE leading to dose interruption	11 (19.3)	4 (57.1)	15 (23.4)
AE leading to dose reduction	2 (3.5)	1 (14.3)	3 (4.7)
AE leading to death	1 (1.8)[d]	0 (0)	1 (1.6)

Data cutoff: 01 Mar 21.
AE, adverse event.
[a] Pain in jaw (grade 2), COVID-19 pneumonia (grade 5), anemia (grade 2).
[b] Febrile neutropenia (grade 3) and gastroenteritis salmonella (grade 3), COVID-19 (grade 3).
[c] Penile bleed (grade 2), COVID-19 pneumonia (grade 5), increased alanine aminotransferase and aspartate transaminase (grade 3).
[d] COVID-19 pneumonia.

Table 4. Adverse Events

Most Common AEs in ≥5% of Patients, n (%)	All Grade (N=64)	Grade ≥3 (N=64)
Contusion	11 (17.2)	0 (0)
Fatigue	11 (17.2)	0 (0)
Myalgia	10 (15.6)	0 (0)
Neutrophil count decreased/neutropenia	9 (14.1)	7 (10.9)
Dizziness	7 (10.9)	0 (0)
Cough	6 (9.4)	0 (0)
Diarrhea	6 (9.4)	1 (1.6)
Epistaxis	5 (7.8)	0 (0)
Pain in extremity	5 (7.8)	0 (0)
Hypertension	4 (6.3)	1 (1.6)
Muscle spasms	4 (6.3)	0 (0)
Nausea	4 (6.3)	0 (0)
Pruritus	4 (6.3)	0 (0)
Rash	4 (6.3)	0 (0)

Data cutoff: 01 Mar 21.
AE, adverse event.

- 81.3% of all patients experienced at least 1 AE (**Table 3**)
- The most common grade ≥3 AE was neutropenia/neutrophil count decrease (n=7 [10.9%]; **Table 4**)
- Bleeding events occurred in 18 patients (28.1%)
  - Grade 1: 14 (21.9%)
  - Grade 2: 4 (6.3%)
- Atrial fibrillation/flutter occurred in 1 patient (grade 2, 1.6%); this was a recurrence of an ibrutinib intolerance (grade 3). Patient was treated with digoxin and remains on zanubrutinib treatment
- Infections occurred in 15 patients (23.4%)
  - Grade 1: 1 (1.6%)
  - Grade 2: 11 (17.2%)
  - Grade 3: 2 (3.1%; COVID-19 and gastroenteritis salmonella)
  - Grade 5: 1 (1.6%; COVID-19–related pneumonia)
- The disease control rate was 89.6% (**Table 5**)

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

Response[a]	Cohort 1 (n=41)	Cohort 2 (n=7)	Total (n=48)
DCR [SD or better], n (%)	37 (90.2)	6 (85.7)	43 (89.6)
ORR [better than SD], n (%)	21 (51.2)	3 (42.9)	24 (50.0)
BOR, n (%)			
CR	1 (2.4)	0 (0)	1 (2.1)
VGPR	2 (4.9)	0 (0)	2 (4.2)
PR	14 (34.1)	2 (28.6)	16 (33.3)
PR-L	4 (9.8)	1 (14.3)	5 (10.4)
Stable disease	16 (39.0)	3 (42.9)	19 (39.6)
Progressive disease	1 (2.4)	1 (14.3)	2 (4.2)
Not evaluable[b]	1 (2.4)	0 (0)	1 (2.1)
Not done[c]	2 (4.9)	0 (0)	2 (4.2)
Time to BOR, median (range), wk	23.6 (11-49)	12.4 (12-26)	12.4 (11-49)

BOR, best overall response; DCR, disease control rate; CR, complete response; ORR, overall response rate; PR, partial response; PR-L, PR with lymphocytosis; SD, stable disease; VGPR, very good partial response.
[a] Disease parameters performed at study entry were used as baseline for response assessment.
[b] IgM values were not measured for Waldenström macroglobulinemia patient.
[c] One patient withdrew from study before first assessment timepoint because of syncope; 1 patient died from COVID-19 pneumonia before first response assessment.

CONCLUSIONS

- Intolerable AEs experienced on ibrutinib or acalabrutinib were unlikely to recur with zanubrutinib
  - 75% (86/115) of ibrutinib intolerance events and 75% (9/12) of acalabrutinib intolerance events did not recur with zanubrutinib
  - Of the intolerance events that recurred, 90% (26/29) of ibrutinib intolerance events and 33% (1/3) of acalabrutinib intolerance events recurred at a lower severity; 10% (3/29) of ibrutinib and 67% (2/3) of acalabrutinib events occurred at the same severity, and no events recurred at a higher severity
  - No recurrence of a prior intolerance event led to zanubrutinib discontinuation
- Zanubrutinib was tolerable, with 89% of patients (57/64) remaining on zanubrutinib, and 4.7% of patients (3/64) discontinued zanubrutinib due to AEs at the time of data cutoff
- Zanubrutinib was effective; patient's disease was controlled or responded to therapy
- These data suggest that zanubrutinib may provide a therapeutic option in patients intolerant to other BTK inhibitors across hematologic malignancies

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DISCLOSURES

MS served as a consultant for AbbVie, Genentech, AstraZeneca, SoundBiologics, Pharmacyclics, Verastem, ADC Therapeutics, BeiGene, Celltech; Bristol Myers Squibb, Morphosys, TG Therapeutics, Innate Pharma, Kite Pharma, Adaptive Biotechnologies, Epizyme, and Atara Biotherapeutics and received research funding from Mustang Bio, Celgene, Bristol Myers Squibb, Pharmacyclics, Gilead, Genentech, AbbVie, TG Therapeutics, BeiGene, AstraZeneca, and Sunesis.

JPS served as a consultant for Pharmacyclics, Celgene, TG Therapeutics, Genentech, AbbVie, Acerta Pharma/AstraZeneca, BeiGene, Pfizer, and Bristol Myers Squibb and received research funding from Pharmacyclics, Genentech, Celgene, Acerta Pharma, Gilead Sciences, Seattle Genetics, TG Therapeutics, Merck, and Takeda.

MY1, has current employment at Baylor University Medical Center and served as a consultant and received research funding from BeiGene.

SFZ has current employment with Florida Cancer Specialists and Research Institute and received research funding from Sarah Cannon Research Institute, honoraria from Karyopharm, AstraZeneca and Bristol Myers Squibb, travel expenses from AstraZeneca and Bristol Myers Squibb.

JMB served as a consultant for Genentech/Roche, AbbVie, Seattle Genetics, Bayer, Adaptive Biotechnologies, Verastem, Morphosys, Kura Oncology, Epizyme, BeiGene, Kymera, and Novartis and served on the speakers' bureaus for Seattle Genetics and BeiGene.

ACh served as a consultant and received honoraria from Bayer and holds stocks in Novartis.

HAY has current employment at Texas Oncology; served as a consultant for AstraZeneca, Amgen, Karyopharm; is on the speakers' bureaus for Janssen, AstraZeneca, BeiGene, Karyopharm, Amgen, and Takeda; received research funding from Janssen and BeiGene and travel expenses from Janssen, AstraZeneca, BeiGene, Karyopharm, and Amgen; and holds stock in Epizyme, and Karyopharm.

JLC has current employment with Florida Cancer Specialists, received research funding from BeiGene, Takeda, Genentech, Merck, Acerta Pharma, Lilly, AstraZeneca, Bristol Myers Squibb, EMD Serono, Seattle Genetics, and was on the speakers' bureaus for Celgene, Amgen, and Aurobindo.

THG has current employment with Genesis Care LTD.

DYC, XZ, AI, ACo have current employment and stock ownership at BeiGene.

KB has current employment at BeiGene.

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

JH has current employment, leadership, patents/stock ownership, and travel expenses from BeiGene.

IF served as a consultant for AbbVie, AstraZeneca, BeiGene, Genentech, Gilead Sciences, Great Point Partners, Ikisuda Therapeutics, Janssen, Juno Therapeutics, Kite Pharma, MorphoSys, Nurix Therapeutics, Pharmacyclics, Roche, Seattle Genetics, Takeda, TG Therapeutics, Unum Therapeutics, Verastem, and Yingli Pharmaceuticals and received research funding from AbbVie, Acerta Pharma, Agios, ArQule, AstraZeneca, BeiGene, Calithera 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, Seattle Genetics, Takeda, Teva, TG Therapeutics, Trillium Therapeutics, Triphase Research & Development Corp, Unum Therapeutics, and Verastem.

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