Zanubrutinib in 13 Acalabrutinib-Intolerant Patients With B-Cell Malignancies

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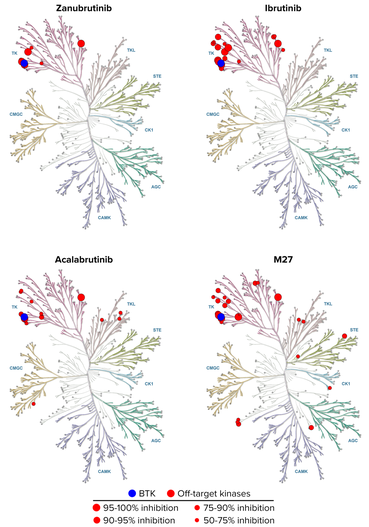
INTRODUCTION

- BTKi provide an effective treatment for patients with B-cell malignancies; however, the duration of treatment is limited by AEs leading to early treatment discontinuation[1,2]
- BTKi-associated AEs are attributed to off-target effects of the inhibitors[4]
- Zanubrutinib, a BTKi approved for treatment of MCL, MZL, and WM was designed to optimize selectivity and maximize BTK occupancy[3,4] (**Figure 1**)
- The ASPEN trial compared zanubrutinib to ibrutinib in patients with WM; zanubrutinib showed lower rates of AEs leading to death (3.0% vs 5.1%), discontinuation (8.9% vs 20.4%), and dose reduction (15.8% vs 26.5%) and a lower rate of atrial fibrillation/flutter (7.9% vs 23.5%)[7]
- In the interim analysis of the ALPINE trial comparing zanubrutinib to ibrutinib in patients with relapsed/refractory CLL/SLL, zanubrutinib showed numerically 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 a lower rate of atrial fibrillation/flutter (2.5% vs 10.1%)[8]
- BGB-3111-215 is a phase 2, single-arm, open-label, multicenter study in the United States of the safety and efficacy of zanubrutinib in patients with previously treated B-cell malignancies who are intolerant to ibrutinib and/or acalabrutinib (**Figure 2**)
- The data presented here focus on a subgroup of patients with acalabrutinib intolerance (cohort 2)

Figure 1: Kinase Selectivity of Zanubrutinib, Ibrutinib, Acalabrutinib, and M27



- Zanubrutinib demonstrated higher selectivity than ibrutinib, acalabrutinib, and acalabrutinib's major metabolite (M27) by kinase profiling
- Of the 370 kinases tested, zanubrutinib, ibrutinib, acalabrutinib, and M27 demonstrated >50% inhibition of 7, 17, 15, and 23 kinases, respectively
- Kinase selectivity was assessed at 100X IC_{50} (against BTK) for zanubrutinib, ibrutinib, acalabrutinib, and M27 (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

OBJECTIVES

Primary

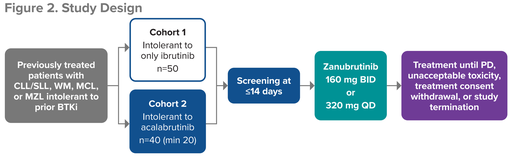
- To evaluate the safety of zanubrutinib in patients who are intolerant to acalabrutinib treatment compared with their acalabrutinib intolerance as assessed by the recurrence and change in the severity of AEs

Secondary

- To evaluate the efficacy of zanubrutinib by investigator-assessed ORR, DCR, PFS, and patient-reported outcomes

METHODS

Figure 2. Study Design



Key Inclusion Criteria for Acalabrutinib Intolerance

- Grade ≥1 nonhematologic toxicity for >7 days
- Grade ≥1 nonhematologic toxicity of any duration with ≥3 recurrent episodes
- 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
- Inability to use acid-reducing agents or anticoagulants due to current BTKi use
- Resolution of grade ≥2 BTKi toxicities to grade ≤1 or baseline and resolution of grade 1 BTKi toxicities to grade 0 or baseline before initiating zanubrutinib treatment

Key Exclusion Criteria

- Disease progression during prior BTKi treatment

RESULTS

Table 1. Patient Demographics and Baseline Characteristics

Characteristics	Cohort 2 (N=13)
Indication, n (%)	
CLL	7 (54)
SLL	2 (15)
WM	2 (15)
MCL	1 (8)
MZL	1 (8)
Age, median (range), years	73 (51-83)
Sex, n (%)	
Male	7 (54)
ECOG PS, n (%)	
0	6 (46)
1	5 (39)
2	2 (15)
No. of prior therapy regimens, median (range)	2 (1-6)
Prior BTKi, n (%)	
Ibrutinib monotherapy	8 (62)
Acalabrutinib monotherapy	13 (100)
Cumulative acalabrutinib exposure, median (range), months	4.6 (0.5-26.9)
On-study zanubrutinib dosing regimen	
160 mg BID	9 (69)
320 mg QD	4 (31)

Data cutoff: 6 January 2022

RESULTS (cont.)

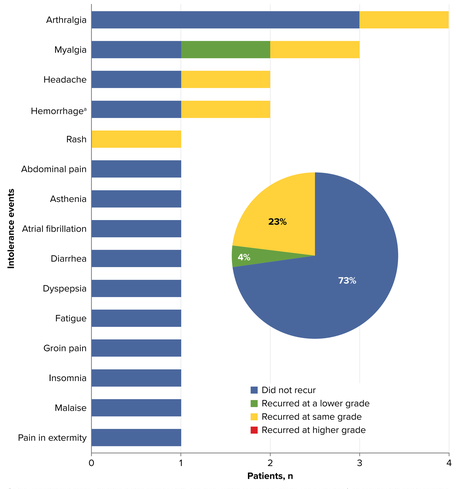
Table 2. Patient Disposition

Disposition	Cohort 2 (N=13)
Patients, n (%)	
Remaining on treatment	10 (77)
Remaining on study	10 (77)
Discontinued from treatment	3 (23)
AE	1 (8)[a]
PD	1 (8)
Withdrawal by patient	1 (8)
Death	1 (8)[b]
Zanubrutinib treatment duration, median (range), months	9.2 (0.5-16.0)
Follow-up, median (range), months	12.9 (0.8-16.0)

[a]Myalgia. [b]Due to PD >30 days after the last dose.

- The most common acalabrutinib intolerances were arthralgia (n=4), myalgia (n=3), headache (n=2), and hemorrhage (n=2)
- Most (16 of 22 [73%]) acalabrutinib intolerance events did not recur on zanubrutinib at any grade
  - One of 22 (5%) events recurred at lower severity, and 5 of 22 (23%) events recurred at the same severity
- Four of 5 (80%) grade 3 acalabrutinib intolerance events did not recur while on zanubrutinib
  - The grade 3 acalabrutinib intolerance event that recurred was of lower severity
- Most (8 of 13 [62%]) patients who were intolerant to acalabrutinib did not have any recurrence of that event on zanubrutinib
- No acalabrutinib intolerance events recurred at a higher severity (**Figure 3**)
- One of 13 (8%) patients discontinued zanubrutinib due to recurrence of a prior acalabrutinib intolerance event (myalgia; same grade)
- Three patients who experienced the same intolerance event (pain in extremity, diarrhea, and atrial fibrillation) on ibrutinib and acalabrutinib did not have a recurrence of those on zanubrutinib [data not shown]

Figure 3. Recurrence of Acalabrutinib Intolerance Events on Zanubrutinib



[a]Patient experienced grade 1 bruising during acalabrutinib treatment, which recurred at grade 1 on study day 2 on zanubrutinib and is ongoing.

Table 3. Adverse Events

AEs, n (%)	Any grade (N=13)	Grade ≥3 (N=13)
Any AE	12 (92)	3 (23)[a]
Fatigue	4 (31)	-
Myalgia	4 (31)	-
Arthralgia	3 (25)	-
Contusion	3 (25)	-
Back pain	2 (15)	-
Cough	2 (15)	-
Decreased appetite	2 (15)	-
Dyspnea	2 (15)	-
Neutrophil count decreased	2 (15)	2 (15)
Oropharyngeal pain	2 (15)	-
Pain in extremity	2 (15)	-
Palpitations	2 (15)	-
Pyrexia	2 (15)	-
Rash	2 (15)	-
COVID-19	-	1 (8)
Febrile neutropenia	-	1 (8)
Gastroenteritis salmonella	-	1 (8)
Hypertension	-	1 (8)
Serious AE	3 (23)	-
Leading to treatment discontinuation	1 (8)	-
Leading to dose interruption	7 (54)	-
Leading to dose reduction	2 (15)	-
Leading to death	-	-

[a]Some patients had more than 1 grade ≥3 event.

Safety

- The most common grade ≥3 AE was neutrophil count decrease, which occurred in 2 (15%) patients
- Bleeding events occurred in 4 (31%) patients (contusion: n=3, epistaxis: n=1, hematoma: n=1)
- Infections occurred in 6 (46%) patients (n=1 each of cellulitis, COVID-19, COVID-19 pneumonia, diverticulitis, fungal skin infection, gastroenteritis salmonella, and urinary tract infection)
- No atrial fibrillation, anemia, or thrombocytopenia/platelet count decrease occurred in any patient

Table 4. Efficacy by Investigator Assessment in Patients with >90-Day Study Duration

Response[a]	Cohort 2 (N=10)
DCR [SD or better], n (%)	8 (80)
ORR [better than SD], n (%)	7 (70)
BOR rate, n (%)	
PR/VGPR	6 (60)
PR-L	1 (10)
SD	1 (10)
PD	1 (10)
Not done	1 (10)
Time to BOR, median (range), months	5.9 (2.8-11.1)
Time to first overall response, median (range), months	3.0 (2.7-11.1)

[a]Disease parameters at study entry were used as a baseline for response assessment, in most cases after recent acalabrutinib therapy.

Table 5. *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 the study	At/after progression
1	**CLL**	**PR**	**280**	**Not detected**[d]	**Detected**	**Not detected**[d]	**Detected**
2	SLL	PR	545	Not detected	Detected	Not detected	Detected
3	CLL	PD	140	Detected	Detected	Not detected	Not detected
4[b]	**CLL**	**PD**	**388**	**Not detected**	**Not detected**	**Not detected**	**Not detected**
5[c]	MCL	SD	264	Not detected[d]	Not detected	Not detected[d]	Not detected

Bold indicates patients in cohort 2.
[a]Initial sample was collected on study day 87. [b]Patient progressed due to the detection of new lesions, continued zanubrutinib treatment beyond progression and subsequently achieved a PR. [c]Patient with MCL with *CCND1-IGH* fusion at both baseline and relapse, which was reported to contribute to BTKi resistance in MCL.[9] [d]Initial sample was collected on day 141.

- Three of 5 patients who progressed had *BTK*/*PLCG2* mutations associated with BTKi resistance at/after progression (includes both cohorts)

CONCLUSIONS

- Acalabrutinib intolerance events were unlikely to recur while on zanubrutinib
- With a median follow-up of 12.9 months, 73% of acalabrutinib intolerance events did not recur while on zanubrutinib
  - Of the acalabrutinib intolerance events that recurred, most (83%) recurred at the same severity; no events recurred at a higher severity
- Only 1 (8%) patient discontinued zanubrutinib due to recurrence of a prior acalabrutinib intolerance event
- Zanubrutinib was tolerable, with 77% of patients remaining on zanubrutinib; 1 (8%) patient in cohort 2 discontinued zanubrutinib due to AEs at the time of data cutoff
- Zanubrutinib effectively maintained response in 80% and improved response from baseline in 70% of patients
- Exploratory biomarker analysis findings indicate that relapse on zanubrutinib was associated with BTKi-resistant mutations
- These data suggest that zanubrutinib may provide a therapeutic option in patients intolerant to acalabrutinib across B-cell malignancies

REFERENCES

1. Mato et al. *Haematologica* 2018;103(5):874-879
2. Yazdy et al. *Blood* 2019;134(suppl 1):4311
3. Tam et al. EHA 2019. Abstract PS1159
4. O'Brien et al. *Front Oncol* 2021;11:720704
5. BRUKINSA® (zanubrutinib) [package insert]. BeiGene; 2021
6. Guo et al. *J Med Chem* 2019;62(17):7923-7940
7. Tam et al. ASCO 2022. Abstract 7521
8. Hillmen et al. EHA 2021. Abstract LB1900
9. Mohanty et al. *Oncotarget* 2016;7(45):73558-73572

ABBREVIATIONS

AE, adverse event; BID, twice a day; BOR, best overall response; BTK, Bruton tyrosine kinase; BTKi, BTK inhibitor; CCDN1-IGH, cyclin D1- immunoglobulin heavy chain; CLL, chronic lymphocytic leukemia; DCR, disease control rate; ECOG PS, Eastern Cooperative Oncology Group performance status; IC, inhibitory concentration; MCL, mantle cell lymphoma; min, minimum; MZL, marginal zone lymphoma; ORR, overall response rate; PD, progressive disease; PFS, progression-free survival; PLCG2, Phosphatidylinositol-specific phospholipase C gamma 2; PR, partial response; PR-L, PR with lymphocytosis; QD, once daily; SD, stable disease; SLL, small lymphocytic lymphoma; VGPR, very good PR; WM, Waldenström macroglobulinemia.

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RC, AI, XZ, ACo: employment and stock with BeiGene
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