49° CONGRESSO NAZIONALE SIE
Società Italiana di Ematologia

Zanubrutinib in Acalabrutinib-Intolerant Patients with B-Cell Malignancies

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ROMA 26-28 Settembre 2022
Marriott Park Hotel

Disclosures for Pier Luigi Zinzani

Honoraria from Roche, Gilead, Novartis, Servier, Incyte, Takeda, EUSA Pharma, Kyowa Kirin, BeiGene, Sanofi, Merck, BMS, Janssen; consulting role with Roche, Gilead, Novartis, Servier, Incyte, Takeda, EUSA Pharma, Kyowa Kirin, BeiGene, Sanofi, Merck, BMS, Janssen; speakers' bureau for Roche, Gilead, Novartis, Incyte, Takeda, Kyowa Kirin, Sanofi, Merck, Janssen.

Introduction

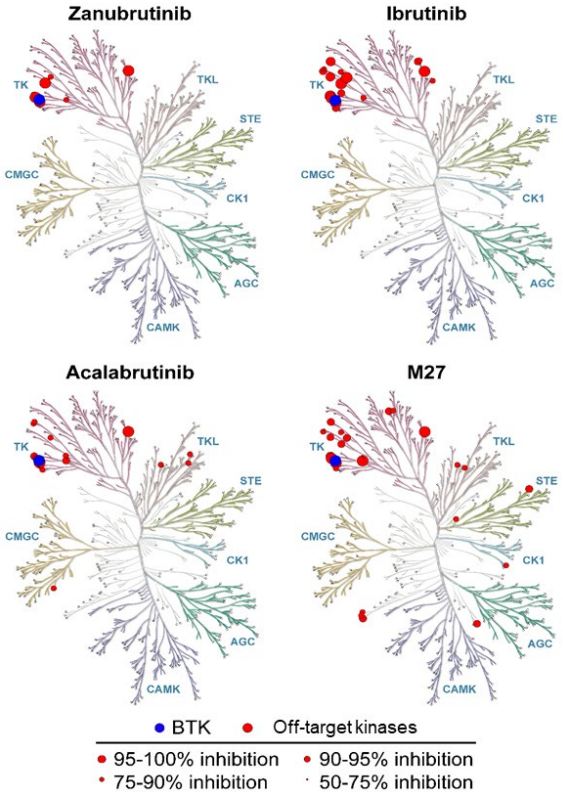
- BTK inhibitors provide an effective treatment for patients with B-cell malignancies; however, the duration of treatment is limited by AEs leading to early treatment discontinuation[1-3]
- BTK inhibitor-associated AEs are attributed to off-target effects of the inhibitors[4]
- Zanubrutinib, a BTK inhibitor approved for the treatment of MCL, MZL, and WM was designed to optimize selectivity and maximize BTK occupancy[5,6]
- The ASPEN trial compared treatment using zanubrutinib with 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 treatment using zanubrutinib with ibrutinib in patients with relapsed/refractory CLL/SLL, 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 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 focused on the safety and efficacy of zanubrutinib in patients with previously treated B-cell malignancies who are intolerant to ibrutinib and/or acalabrutinib
- The data presented here focus on a subgroup of patients with acalabrutinib intolerance (cohort 2)

AE, adverse event; BTK, Bruton tyrosine kinase; CLL, chronic lymphocytic leukemia; MCL, mantle cell lymphoma; MZL, marginal zone lymphoma; SLL, small lymphocytic lymphoma; WM, Waldenström macroglobulinemia.

1. Mato AR, et al. *Haematologica* 2018;103(5):874-879; 2. Yazdy MS, et al. *Blood* 2019;134(suppl 1):4311; 3. Tam CS, et al. EHA 2019. Abstract PS1159; 4. O'Brien SM, et al. *Front Oncol* 2021;11:720704;
5. Brukinsa® (zanubrutinib) [package insert]. BeiGene; 2021; 6. Guo Y, et al. *J Med Chem* 2019;62(17):7923-7940; 7. Tam CS, et al. ASCO 2022. Abstract 7521; 8. Hillmen P, et al. EHA 2021. Abstract LB1900.

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



BTK, Bruton tyrosine kinase; IC, inhibitory concentration.

Objectives

Primary

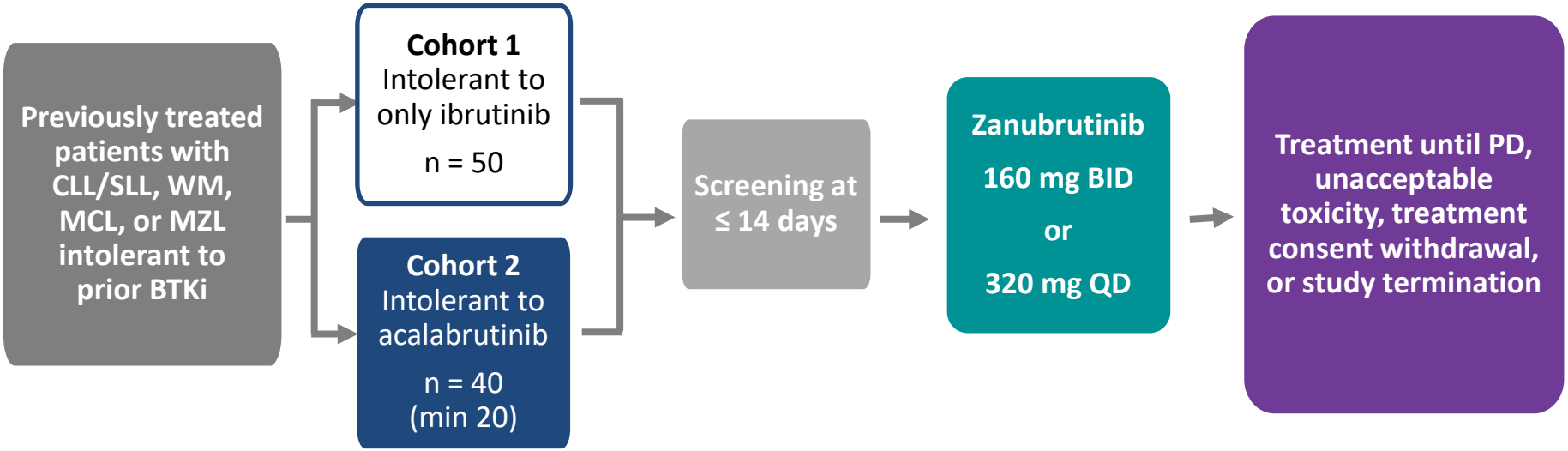
- To evaluate the safety of zanubrutinib in patients who are intolerant to acalabrutinib treatment compared with their acalabrutinib intolerance as assessed by the recurrence and change in the severity of AEs

Secondary

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

AE, adverse event; DCR, disease control rate; PFS, progression-free survival; ORR, overall response rate.

Study Design



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

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

BTKi, Bruton tyrosine kinase inhibitor.

Patient Demographics and Baseline Characteristics[a]

Characteristic	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)
Male, n (%)	7 (54)
ECOG PS, n (%)	
0	6 (46)
1	5 (39)
2	2 (15)
Prior therapy regimens, median (range), n	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, n (%)	
160 mg BID	9 (69)
320 mg QD	4 (31)

[a]Data cutoff: 6 January 2022.

BID, twice daily; 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; QD, once daily; SLL, small lymphocytic lymphoma; WM, Waldenström macroglobulinemia.

Patient Disposition

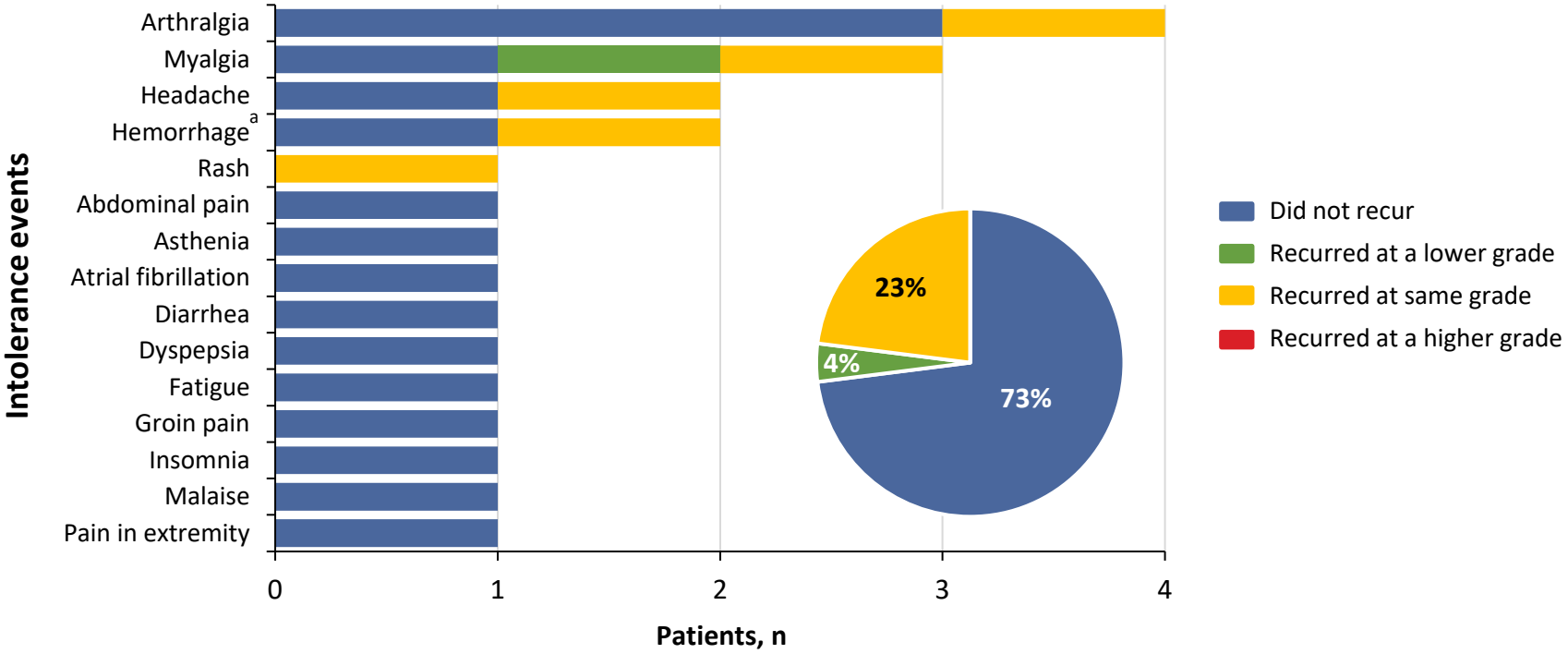
Disposition	Cohort 2 (n = 13)
Patients, n (%)	
Remaining on treatment	10 (77)
Remaining on study	10 (77)
Discontinued from treatment	3 (23)
AE	1 (8)[a]
PD	1 (8)
Withdrawal by patient	1 (8)
Death, n (%)	1 (8)[b]
Zanubrutinib treatment duration, median (range), months	9.2 (0.5-16.0)
Follow-up, median (range),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

[a]Myalgia. [b]Due to PD > 30 days after the last dose.
AE, adverse event; PD, progressive disease.

Results

- 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 patients (8 of 13; 62%) who were intolerant to acalabrutinib did not have any recurrence of that event on zanubrutinib
- No acalabrutinib intolerance events recurred at a higher severity
- One of 13 patients (8%) 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

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.

Adverse Events

- The most common Grade ≥ 3 AE was neutrophil count decreased, 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

	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.
AE, adverse event; COVID-19, coronavirus disease of 2019.

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.
BOR, best overall response; DCR, disease control rate; ORR, overall response rate; PD, progressive disease; PR, partial response; PR-L, PR with lymphocytosis; SD, stable disease; VGPR, very good PR.

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

				***BTK* mutational status**		***PLCG2* mutational status**	
Patient	**Indication**	**Best response to zanubrutinib**	**Days on zanubrutinib**	**At start of study**	**At/after progression**	**At start of the 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[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

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

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[1]; [d]Initial sample was collected on day 141.
BTK, Bruton tyrosine kinase; BTKi, BTK inhibitor; *CCDN1-IGH*, cyclin D1-immunoglobulin heavy chain; CLL, chronic lymphocytic leukemia; MCL, mantle cell lymphoma; PD, progressive disease; PLCG2, phosphatidylinositol-specific phospholipase C gamma 2; PR, partial response; SD, stable disease; SLL, small lymphocytic lymphoma.
1. Mohanty A, et al. *Oncotarget* 2016;7(45):73558-73572.

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 patient (8%) 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

Acknowledgments

We would like to thank the investigators, site support staff, and especially the patients and their caregivers for participating in this study.

This study was sponsored by BeiGene.

Editorial support was provided by Medical Expressions and funded by BeiGene.

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