Abstract 1548777

A Phase 2 Study of Zanubrutinib in Previously Treated B-Cell Malignancies Intolerant to Ibrutinib and/or Acalabrutinib: Preliminary Results for Patients With CLL/SLL

Mazyar Shadman,[1] John M. Burke,[2] Syed F. Zafar,[3] Jamal Misleh,[4] Subramanya S. Rao,[5] Charles M. Farber,[6] Aileen Cohen,[7] Rocco Crescenzo,[7] Adam Idoine,[7] Kunthel By,[7] Ian W. Flinn,[8] Jeff P. Sharman[1,9]

[1]Fred Hutchinson Cancer Center, Division of Medical Oncology, University of Washington, Seattle, WA; [2]Rocky Mountain Cancer Centers, US Oncology Research, Aurora, CO; [3]Florida Cancer Specialists & Research Institute, Fort Myers, FL; [4]Medical Oncology Hematology Consultants, Newark, DE; [5]Affiliated Oncologists, Alpha Med Physicians Group, Tinley Park, IL; [6]Atlantic Hematology Oncology, Morristown Medical Center, Morristown, NJ; [7]BeiGene USA, Inc, San Mateo, CA; [8]Sarah Cannon Research Institute/Tennessee Oncology, Nashville, TN; [9]Willamette Valley Cancer Institute and Research Center, US Oncology Research, Eugene, OR

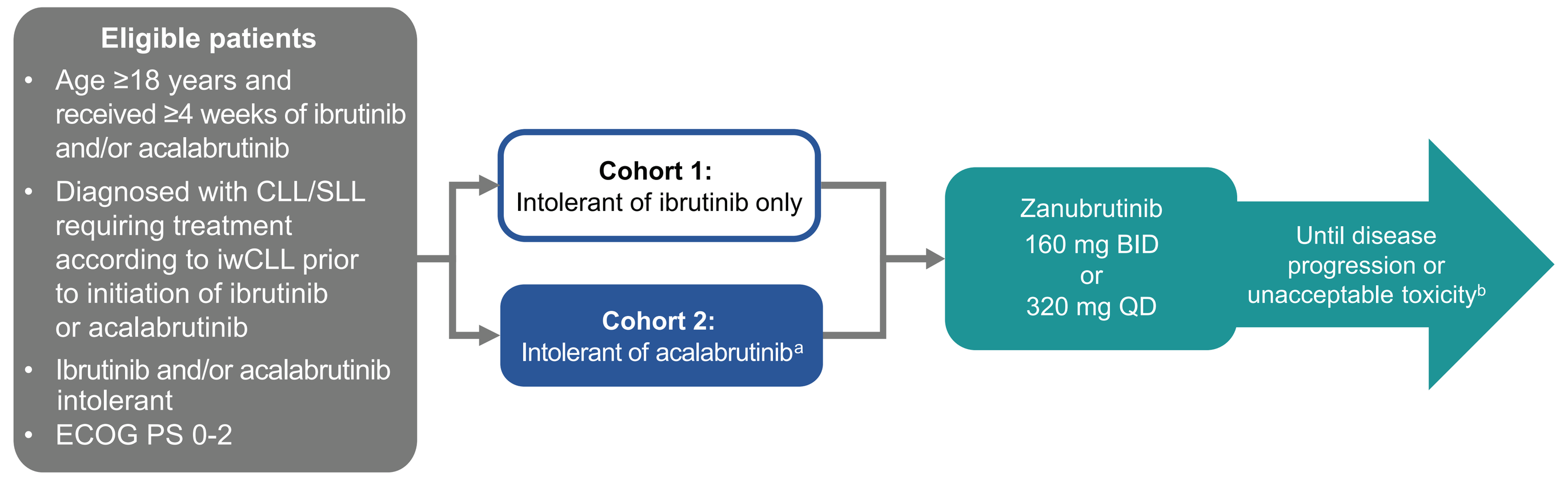
INTRODUCTION

- Chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL) is the most common form of leukemia in the Western world[1]
- BTK inhibitors have become important and effective therapeutic options for CLL/SLL; however, the use of BTK inhibitors can be limited by intolerability, likely due to off-target inhibition of other kinases[2]
- Zanubrutinib is a potent and selective next-generation BTK inhibitor that was recently approved in the US,[3] EU,[4] and China[5] for the treatment of CLL/SLL
- Zanubrutinib is designed to maximize BTK occupancy and minimize off-target kinase binding and associated AEs[6]
  - Zanubrutinib demonstrated higher selectivity against BTK vs ibrutinib and acalabrutinib[6,7]
- Results from this ongoing phase 2 study (BGB-3111-215; NCT04116437) have been previously published and show that zanubrutinib is effective and well tolerated in patients with B-cell malignancies who are intolerant of other BTK inhibitors (ibrutinib and/or acalabrutinib)[7]
- Here, preliminary longer-term results in patients with CLL/SLL are presented

METHODS

- Data from patients with CLL/SLL from the ongoing phase 2, multicenter, US-based, single-arm BGB-3111-215 trial of zanubrutinib monotherapy in patients who were intolerant of prior BTK inhibitors are presented (**Figure 1**)
- Patients were included if ≥1 of the following occurred during prior BTK inhibitor therapy:
  - Grade ≥2 nonhematologic toxicities for >7 days
  - Grade ≥3 nonhematologic toxicity of any duration
  - Grade 3 neutropenia with infection or fever of any duration
  - Investigator chose to stop therapy due to grade 4 heme toxicity
  - Grade ≥1 nonhematologic toxicities of any duration with ≥3 recurrent episodes (acalabrutinib only)
  - Grade ≥1 nonhematologic toxicities for >7 days (acalabrutinib only)
  - Inability to use acid-reducing agents or anticoagulants (eg, proton pump inhibitors, warfarin) due to concurrent acalabrutinib use (acalabrutinib only)
- Patients were excluded if they had PD while receiving prior ibrutinib and/or acalabrutinib treatment

Figure 1. BGB-3111-215 Study Design



Eligible patients
Age ≥18 years and received ≥4 weeks of ibrutinib and/or acalabrutinib
Diagnosed with CLL/SLL requiring treatment according to iwCLL prior to initiation of ibrutinib or acalabrutinib
Ibrutinib and/or acalabrutinib intolerant
ECOG PS 0-2
Cohort 1: Intolerant of ibrutinib only
Cohort 2: Intolerant of acalabrutinib[a]
Zanubrutinib 160 mg BID or 320 mg QD
Until disease progression or unacceptable toxicity[b]

ClinicalTrials.gov: NCT04116437

Primary endpoint: Safety of zanubrutinib compared with ibrutinib- and/or acalabrutinib-intolerance AE profile
Secondary endpoints: ORR by INV, DCR by INV, DOR, time to first response, time to best overall response, PFS by INV, HRQOL
Exploratory endpoints: Improvements in response in patients with previous response to ibrutinib and/or acalabrutinib

ECOG PS, Eastern Cooperative Oncology Group performance status; HRQOL, health-related quality of life; INV, investigator assessment; iwCLL, International Workshop on CLL.
[a] Includes patients intolerant of ibrutinib in addition to acalabrutinib; [b] Study is ongoing.

RESULTS

Patients

- As of January 3, 2023, 61 patients with CLL/SLL (44 with only ibrutinib intolerance and 17 with acalabrutinib intolerance [9 intolerant of acalabrutinib only and 8 intolerant of both ibrutinib and acalabrutinib]) were enrolled in the study and received ≥1 dose of zanubrutinib (**Table 1**)

Table 1. Patient Baseline Demographics and Disease Characteristics

	Ibrutinib intolerant (n=44)	Acalabrutinib intolerant[a] (n=17)	Total (N=61)
Indication, n (%)			
CLL	38 (86.4)	15 (88.2)	53 (86.9)
SLL	6 (13.6)	2 (11.8)	8 (13.1)
Male sex, n (%)	23 (52.3)	9 (52.9)	32 (52.5)
Age, median (range), years	71.5 (49-91)	71 (51-83)	71 (49-91)
ECOG PS, n (%)			
0	26 (59.1)	11 (64.7)	37 (60.7)
1	18 (40.9)	4 (23.5)	22 (36.1)
2	0	2 (11.8)	2 (3.3)
No. of prior anticancer regimens, median (range)	1 (1-7)	2 (1-6)	1 (1-7)
Duration of prior ibrutinib therapy, median (range), months	12.9 (1.2-64.8)	6.2 (3.1-46.4)	9.5 (1.2-64.8)
Duration of prior acalabrutinib therapy, median (range), months	NA	5.1 (1.2-33.7)	5.1 (1.2-33.7)
del(17p) mutation, n (%)[b]			
Present	4 (9.1)	2 (11.8)	6 (9.8)
Absent	32 (72.7)	8 (47.1)	40 (65.6)
Unmutated *IGHV*, n (%)[b]			
Present	10 (22.7)	1 (5.9)	11 (18.0)
Absent	8 (18.2)	3 (17.6)	11 (18.0)
***TP53* mutation, n (%)[b]**			
Present	11 (25.0)	3 (17.6)	14 (23.0)
Absent	27 (61.4)	6 (35.3)	33 (54.1)

[a] Includes patients intolerant of ibrutinib in addition to acalabrutinib. [b] Missing data not shown.

- The median study follow-up was 28.2 months (range, 1.0-36.2 months) in cohort 1 and 10.1 months (range, 0.6-27.1 months) in cohort 2 (**Table 2**)
- At data cutoff, 29 patients (65.9%) in cohort 1 and 12 patients (70.6%) in cohort 2 remained on treatment

Table 2. Patient Disposition

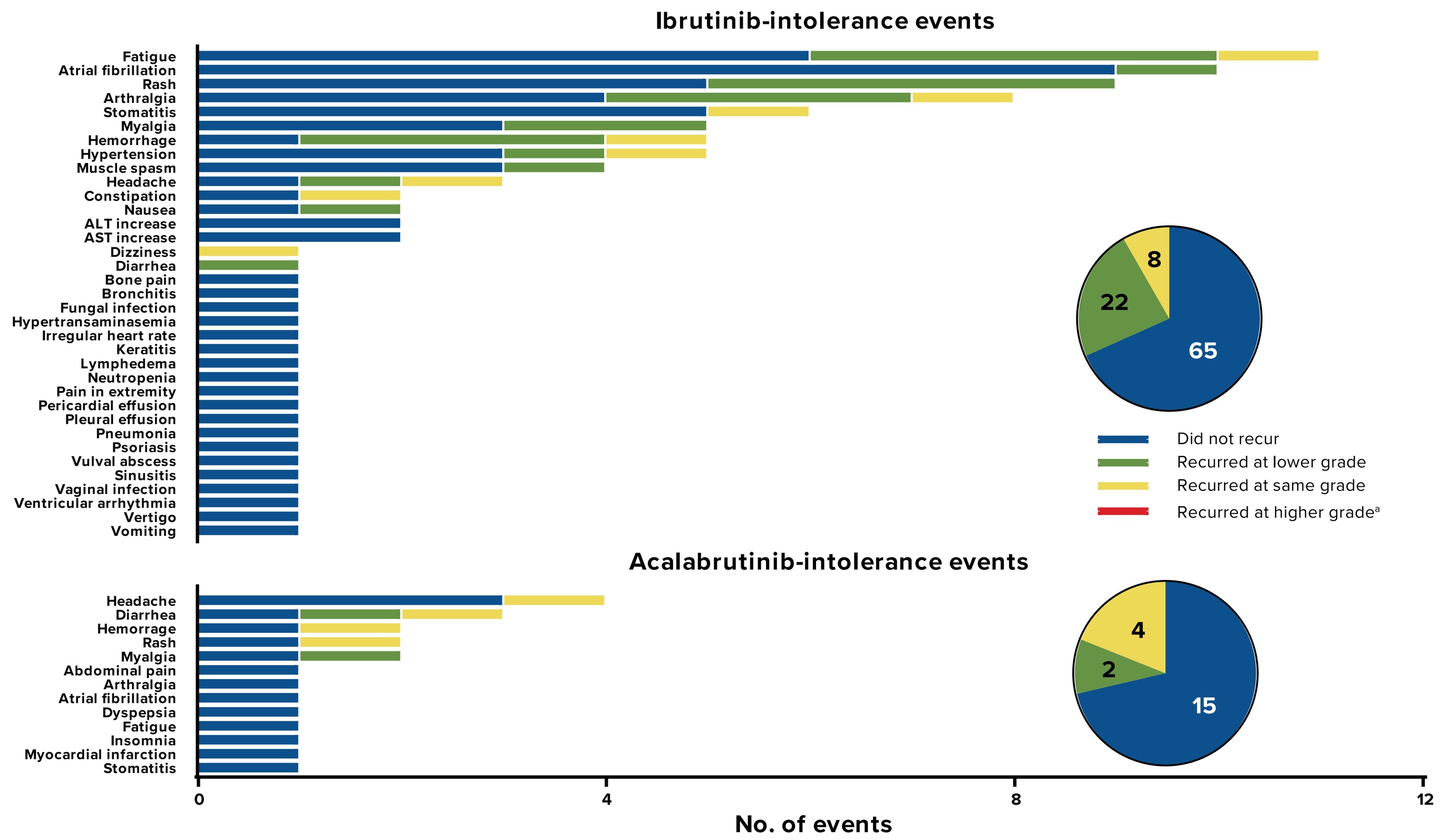
	Ibrutinib intolerant (n=44)	Acalabrutinib intolerant[a] (n=17)	Total (N=61)
Remaining on treatment, n (%)	29 (65.9)	12 (70.6)	41 (67.2)
Remaining on study, n (%)	35 (79.5)	14 (82.4)	49 (80.3)
Discontinued from treatment, n (%)	15 (34.1)	5 (29.4)	20 (32.8)
AE	4 (9.1)	1 (5.9)	5 (8.2)
PD	5 (11.4)	1 (5.9)	6 (9.8)
Withdrawal by patient	2 (4.5)	2 (11.8)	4 (6.6)
Physician decision	2 (4.5)	1 (5.9)	3 (4.9)
Other	2 (4.5)	0	2 (3.3)
Death, n (%)	5 (11.4)	1 (5.9)	6 (9.8)
Zanubrutinib treatment duration, median (range), months	27.1 (0.6-36.2)	8.1 (0.5-27.1)	23.7 (0.5-36.2)
Study follow-up, median (range), months	28.2 (1.0-36.2)	10.1 (0.6-27.1)	25.6 (0.6-36.2)

[a] Includes patients intolerant of ibrutinib in addition to acalabrutinib.

Safety

- With zanubrutinib, 65 of 95 ibrutinib-intolerance AEs (68.4%) and 15 of 21 acalabrutinib-intolerance AEs (71.4%) did not recur (**Figure 2**)
- 32 of 52 patients (61.5%) with ibrutinib intolerance and 12 of 17 patients (70.6%) with acalabrutinib intolerance did not experience recurrence of any of their intolerance events
  - No intolerance AEs recurred at a higher severity
  - Of those that did recur, 22 of 30 ibrutinib-intolerance AEs (73.3%) and 2 of 6 acalabrutinib-intolerance AEs (33.3%) recurred at a lower grade
  - One patient discontinued treatment due to an ibrutinib-intolerance AE and 1 due to an acalabrutinib-intolerance AE

Figure 2. Recurrence and Severity Change of Intolerance AEs From Prior Ibrutinib or Acalabrutinib Exposure During Zanubrutinib Treatment in Patients With CLL/SLL



Ibrutinib-intolerance events
Fatigue
Atrial fibrillation
Rash
Arthralgia
Stomatitis
Myalgia
Hemorrhage
Hypertension
Muscle spasm
Headache
Constipation
Nausea
ALT increase
AST increase
Dizziness
Diarrhea
Bone pain
Bronchitis
Fungal infection
Hypertransaminasemia
Irregular heart rate
Keratitis
Lymphedema
Neutropenia
Pain in extremity
Pericardial effusion
Pleural effusion
Pneumonia
Psoriasis
Vulval abscess
Sinusitis
Vaginal infection
Ventricular arrhythmia
Vertigo
Vomiting
8
22
65
Did not recur
Recurred at lower grade
Recurred at same grade
Recurred at higher grade[a]
Acalabrutinib-intolerance events
Headache
Diarrhea
Hemorrage
Rash
Myalgia
Abdominal pain
Arthralgia
Atrial fibrillation
Dyspepsia
Fatigue
Insomnia
Myocardial infarction
Stomatitis
4
2
15
0
4
8
12
No. of events

[a] No intolerance AEs recurred at a higher grade.

- Fifty-seven patients (93.4%) reported ≥1 treatment-emergent AE (TEAE) while taking zanubrutinib (**Table 3**)
- Grade ≥3 TEAEs were reported in 50.8% of patients, with the most common being neutropenia (11.5%), COVID-19 (6.6%), and pneumonia (6.6%)
- One patient experienced a TEAE leading to death (COVID-19 pneumonia)
- The most common TEAEs are shown in **Table 4**

Table 3. TEAE Summary

n (%)	Ibrutinib intolerant (n=44)	Acalabrutinib intolerant[a] (n=17)	Total (N=61)
Any TEAE	42 (95.5)	15 (88.2)	57 (93.4)
Grade ≥3 TEAEs	24 (54.5)	7 (41.2)	31 (50.8)
Serious TEAEs	12 (27.3)	4 (23.5)	16 (26.2)
TEAEs leading to death	1 (2.3)	0	1 (1.6)
TEAEs leading to treatment discontinuation	4 (9.1)	1 (5.9)	5 (8.2)
TEAEs leading to dose interruption	22 (50.0)	8 (47.1)	30 (49.2)
TEAEs leading to dose reduction	12 (27.3)	3 (17.6)	15 (24.6)

[a] Includes patients intolerant of ibrutinib in addition to acalabrutinib.

Table 4. TEAEs Occurring in ≥15% of Total Patient Population

TEAE, n (%)	Ibrutinib intolerant (n=44)	Acalabrutinib intolerant[a] (n=17)	Total (N=61)
Fatigue	14 (31.8)	4 (23.5)	18 (29.5)
COVID-19	13 (29.5)	1 (5.9)	14 (23.0)
Contusion	10 (22.7)	3 (17.6)	13 (21.3)
Diarrhea	8 (18.2)	4 (23.5)	12 (19.7)
Arthralgia	8 (18.2)	2 (11.8)	10 (16.4)
Cough	5 (11.4)	5 (29.4)	10 (16.4)
Myalgia	7 (15.9)	3 (17.6)	10 (16.4)

[a] Includes patients intolerant of ibrutinib in addition to acalabrutinib.

CONCLUSIONS

- AEs that previously caused patients with CLL/SLL to discontinue ibrutinib or acalabrutinib treatment were unlikely to recur with zanubrutinib; recurrences were mostly at a lower severity
- Disease was controlled in 95% of patients, suggesting that patients with CLL/SLL who were intolerant of ibrutinib or acalabrutinib are likely to receive clinical benefit from switching to zanubrutinib
- These data suggest that zanubrutinib is a viable treatment option for patients with CLL/SLL who are intolerant of ibrutinib or acalabrutinib

Efficacy

- In 57 evaluable patients, the DCR was 94.7% and the ORR was 71.9% (**Table 5**)
- The 12-month PFS rate was 88.3% (95% CI, 75.7%-94.6%)

Table 5. Investigator-Assessed Responses

	Ibrutinib intolerant	Acalabrutinib intolerant[a]	Total
ORR and DCR			
n	43	14	57
DCR, n (%) (95% CI)[b]	41 (95.3) (84.2-99.4)	13 (92.9) (66.1-99.8)	54 (94.7) (85.4-98.9)
ORR, n (%) (95% CI)[c]	31 (72.1) (56.3-84.7)	10 (71.4) (41.9-91.6)	41 (71.9) (58.5-83.0)
Best overall response, n (%)			
CR	1 (2.3)	0	1 (1.8)
PR	25 (58.1)	8 (57.1)	33 (57.9)
PR with lymphocytosis	5 (11.6)	2 (14.3)	7 (12.3)
SD	10 (23.3)	3 (21.4)	13 (22.8)
PD	1 (2.3)	1 (7.1)	2 (3.5)
Not done[d]	1 (2.3)	0	1 (1.8)
Time to best overall response			
n	31	10	41
Median (range), months	5.7 (2.6-28.1)	2.9 (2.7-8.4)	5.6 (2.6-28.1)
PFS[e]			
n	44	17	61
12-month event-free rate (95% CI), %	90.3 (76.3-96.3)	74.3 (24.5-93.9)	88.3 (75.7-94.6)
DOR[e]			
n	31	10	41
12-month event-free rate (95% CI), %	89.2 (70.1-96.4)	80.0 (20.4-96.9)	88.0 (70.8-95.3)

[a] Includes patients intolerant of ibrutinib in addition to acalabrutinib; [b] Defined as SD or better; [c] Defined as PR with lymphocytosis or better; [d] Patient died prior to first disease assessment; [e] Median PFS and DOR were not reached.

REFERENCES

1. Zelenetz AD, et al. *J Natl Compr Canc Netw*. 2015;13(3):326-362.
2. Hallek M, Al-Sawaf O. *Am J Hematol.* 2021;96(12):1679-1705.
3. Brukinsa (zanubrutinib). Package insert. BeiGene USA; 2021.
4. Brukinsa (zanubrutinib). Summary of product characteristics. BeiGene Ireland Ltd; 2021.
5. BeiGene. BeiGene receives new approvals for BRUKINSA® (zanubrutinib) in China; 2023. Accessed May 22, 2023. https://ir.beigene.com/news/beigene-receives-new-approvals-for-brukinsa-zanubrutinib-in-china/7e5cd979-7835-4263-8dde-f426c721fb3e/.
6. Guo Y, et al. *J Med Chem*. 2019;62(17):7923-7940.
7. Shadman M, et al. *Lancet Haematol*. 2023;10(1):e35-e45.

DISCLOSURES

MS: served as a consultant and on advisory boards, steering committees, or data safety monitoring committees for AbbVie, Genentech, AstraZeneca, Sound Biologics, Pharmacyclics, BeiGene, Bristol Myers Squibb, MorphoSys/Incyte, TG Therapeutics, Innate Pharma, Kite Pharma, Adaptive Biotechnologies, Epizyme, Lilly, Adaptimmune, Mustang Bio, Regeneron, Merck, Fate Therapeutics, MEI Pharma, and Atara Biotherapeutics; and received research funding from Mustang Bio, Celgene, Bristol Myers Squibb, Pharmacyclics, Gilead, Genentech, AbbVie, TG Therapeutics, BeiGene, AstraZeneca, Sunesis, Atara Biotherapeutics, Genmab, and MorphoSys/Incyte. **JMB:** served as a consultant for BeiGene, Kymera, Bristol Myers Squibb, X4 Pharma, Seagen, TG Therapeutics, Lilly, Verastem, MorphoSys, Adaptive Biotechnologies, AstraZeneca, Roche/Genentech, Epizyme, Kura, and AbbVie; and received honoraria from BeiGene and Seagen. **SFZ:** received honoraria from Merck. **AC** and **AI** are employed by BeiGene and hold stock with BeiGene. **RC:** employed by BeiGene and holds stock with BeiGene, Pfizer, and GSK. **KB:** employed by BeiGene. **IWF:** served as a consultant for AbbVie, AstraZeneca, BeiGene, Century Therapeutics, Genentech, Genmab, Gilead Sciences, Great Point Partners, Hutchison MediPharma, Iksuda Therapeutics, InnoCare Pharma, Janssen, Juno Therapeutics, Kite Pharma, MorphoSys, Novartis, Nurix Therapeutics, Pharmacyclics, Roche, Seagen, Servier Pharmaceuticals, Takeda, TG Therapeutics, Unum Therapeutics, Verastem, Vincerx Pharma, and Yingli Pharmaceuticals; and received funding support from AbbVie, Acerta Pharma, Agios, ArQule, AstraZeneca, BeiGene, Biopath, Bristol Myers Squibb, CALIBR, CALGB, Celgene, City of Hope National Medical Center, Constellation Pharmaceuticals, Curis, CTI BioPharma, Fate Therapeutics, Forma Therapeutics, Forty Seven, Genentech, Gilead Sciences, InnoCare Pharma, IGM Biosciences, Incyte, Infinity Pharmaceuticals, Janssen, Kite Pharma, Loxo, Merck, Millennium Pharmaceuticals, MorphoSys, Myeloid Therapeutics, Novartis, Nurix, Pfizer, Pharmacyclics, Portola Pharmaceuticals, Rhizen Pharmaceuticals, Roche, Seagen, Tessa Therapeutics, TCR2 Therapeutics, TG Therapeutics, Trillium Therapeutics, Triphase Research and Development, Unum Therapeutics, and Verastem. **JPS:** employed by US Oncology Network; serves as a consultant for TG Therapeutics, Genentech, AbbVie, Acerta Pharma/AstraZeneca, BeiGene, Bristol Myers Squibb, and Merck; and has received research funding from Pharmacyclics, Genentech, Celgene, Acerta Pharma, Gilead Sciences, Seagen, TG Therapeutics, Merck, and Takeda. **JM**, **SSR**, and **CMF** have nothing to disclose.

CORRESPONDENCE

Mazyar Shadman, MD, MPH
Fred Hutchinson Cancer Research Center, University of Washington
Seattle, WA
mshadman@fredhutch.org

ACKNOWLEDGMENTS

The authors thank the patients and their families, investigators, co-investigators, and the study teams at each of the participating centers. This study was sponsored by BeiGene, Ltd. Medical writing and editorial assistance were provided by Hayley White, PhD, and Apurva Dave, PhD, of Medical Expressions and supported by BeiGene.

Presented at the 20th International Workshop on Chronic Lymphocytic Leukemia (iwCLL) Biennial Meeting; October 6-9, 2023; Boston, MA, USA.
Data originally presented at the 17th International Conference on Malignant Lymphoma (ICML); June 13-17, 2023; Lugano, Switzerland; Poster 345