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

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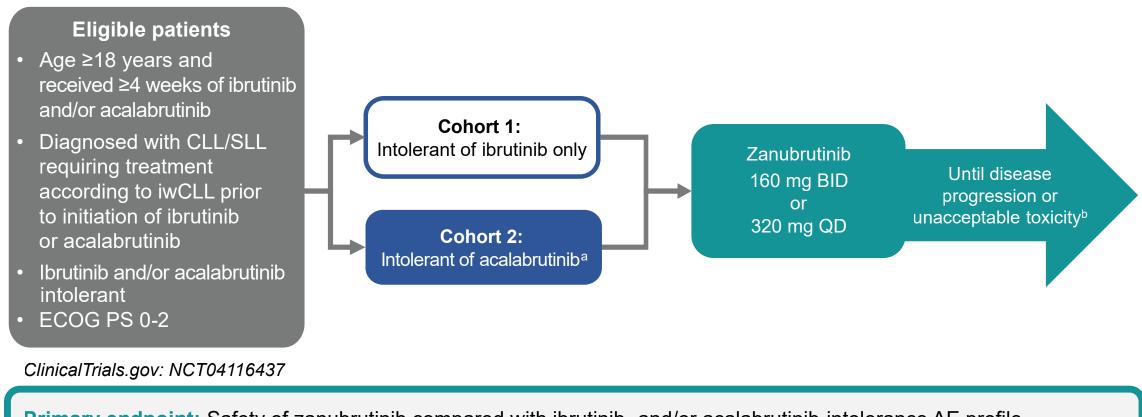
INTRODUCTION

- Chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL) is the most common form of leukemia in the Western world¹
- 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 kinases²
- Zanubrutinib is a potent and selective next-generation BTK inhibitor that was recently approved in the US,³ EU,⁴ and China⁵ for the treatment of CLL/SLL
- Zanubrutinib is designed to maximize BTK occupancy and minimize off-target kinase binding and associated AEs⁶
- 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



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

	J 1		
	lbrutinib intolerant (n=44)	Acalabrutinib intolerantª (n=17)	Total (N=61)
ndication, 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 <i>IGHV</i> , n (%) ^ь			
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

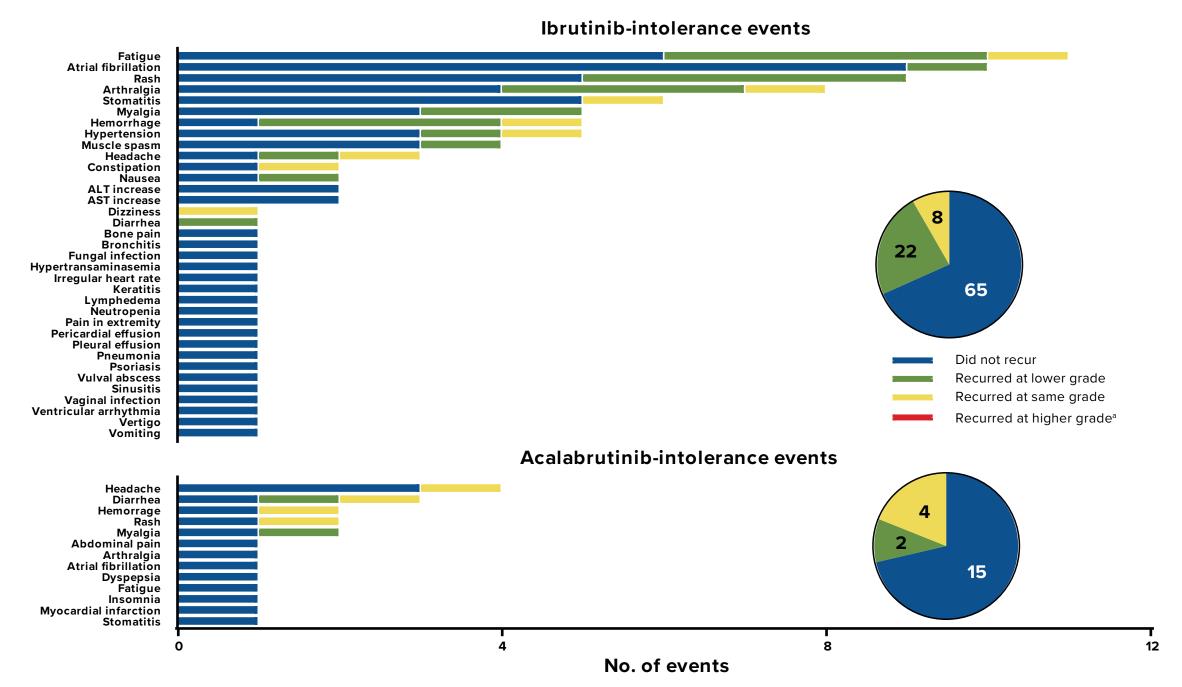
	lbrutinib intolerant (n=44)	Acalabrutinib intolerantª (n=17)	Total (N=61)
Remaining on treatment, n (%)	29 (65.9)	12 (70.6)	41 (67.2)
Remaining on study, n (%)	35 (79.5)	14 (82.4)	49 (80.3)
Discontinued from treatment, n (%)	15 (34.1)	5 (29.4)	20 (32.8)
AE	4 (9.1)	1 (5.9)	5 (8.2)
PD	5 (11.4)	1 (5.9)	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 acalabrutinibintolerance AE

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



^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 \geq 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 intolerantª (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 intolerantª (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

3			
	Ibrutinib intolerant	Acalabrutinib intolerant ^a	Total
ORR and DCR			
n	43	14	57
DCR, n (%) (95% Cl) ^ь	41 (95.3) (84.2-99.4)	13 (92.9) (66.1-99.8)	54 (94.7) (85.4-98.9)
ORR, n (%) (95% Cl) ^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.

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