

BGB-3111-215



BGB-3111-215 Trial Design



Phase 2 Exploratory

Study Identifier:
BGB-3111-215, NCT04116437

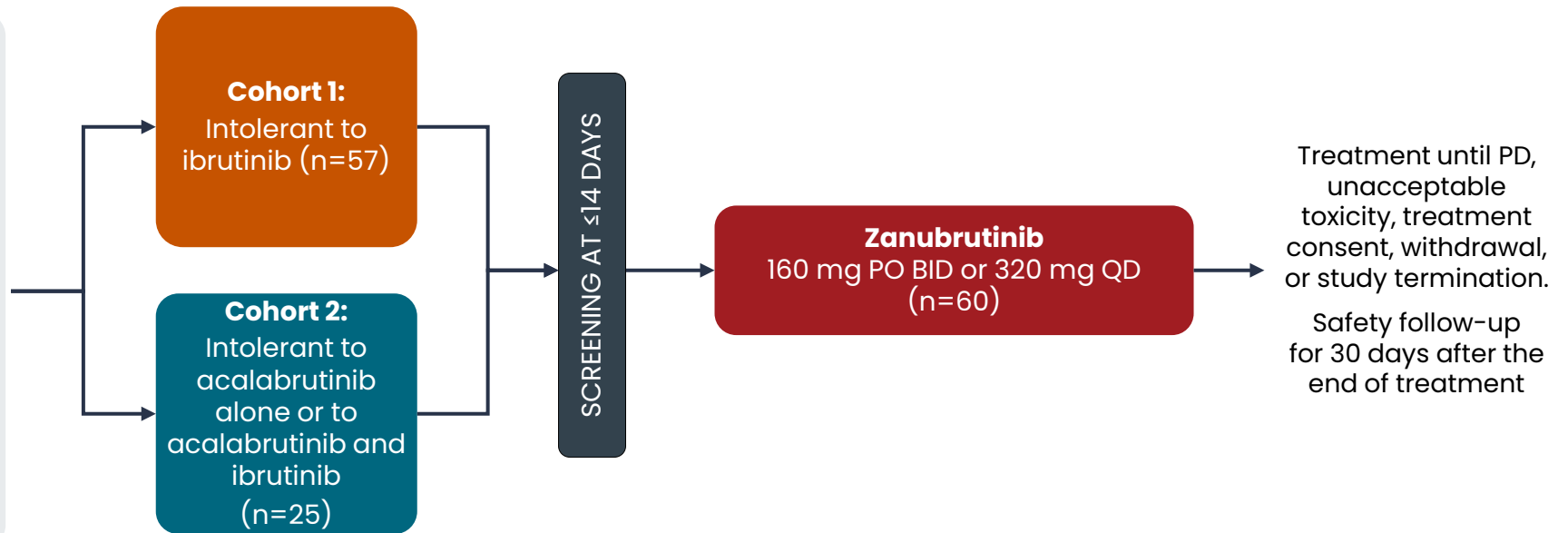
Primary Endpoint: Investigator-assessed recurrence and change in severity of ibrutinib or acalabrutinib intolerance events^a

Key Secondary Endpoints: ORR, DCR, DoR, PFS, and HRQoL

Key eligibility criteria

- Previously treated CLL/SLL, WM, MCL, or MZL patient intolerant of ibrutinib and/or acalabrutinib^b
- ≥18 years old
- Indication for treatment per iwCLL prior to ibrutinib
- Ibrutinib- and/or acalabrutinib intolerant in opinion of investigator^c
- Ibrutinib- and/or acalabrutinib-related toxicities resolved to grade ≤1 or baseline
- ECOG PS ≤2
- ANC ≥1000/mm³ and platelet count ≥50,000/mm³
- No documented PD during ibrutinib and/or acalabrutinib treatment^d
- No clinically significant cardiovascular disease

Treatment



^aTEAEs of interest: arthralgia, atrial fibrillation, diarrhea, fatigue, hemorrhage, hypertension, muscle spasms, myalgia, rash. ^bThere is a ≥7-day washout period for any anticancer therapy and a ≥4-week washout period for immunotherapy, taken alone or as part of a chemoimmunotherapy regimen. ^cIntolerance is defined as an unacceptable toxicity where, in the opinion of the investigator, treatment should be discontinued in spite of optimal supportive care as a result of: grade ≥2 non-hematologic toxicities for >7 days; grade ≥3 non-hematologic toxicity of any duration; grade 3 neutropenia with infection or fever; or grade 4 hematologic toxicity that persists until ibrutinib therapy is discontinued due to toxicity NOT until progression. ^dA disease flare meeting PD criteria while the patient is off ibrutinib and/or acalabrutinib treatment is not considered to be true PD.

ANC=absolute neutrophil count, BID=twice daily, BTKi=Bruton tyrosine kinase inhibitor, CLL=chronic lymphocytic leukemia, DCR=disease control rate, DoR=duration of response, ECOG PS=Eastern Cooperative Oncology Group performance status, HRQoL=health-related quality of life, iwCLL=International Workshop on CLL, MCL=mantle cell lymphoma, MZL=marginal zone lymphoma, ORR=overall response rate, PD=progressive disease, PFS=progression-free survival, PO=per oral, QD=once daily, SLL=small lymphocytic lymphoma, TEAE=treatment-emergent adverse event, WM=Waldenström macroglobulinemia.

1. Shadman M et al. *Lancet Haematol*. 2022. 10(1):E35-E45. 2. Shadman M et al. Poster presented at EHA 2023; Abstract number: P683 This study is registered at ClinicalTrials.gov ([NCT04116437](https://clinicaltrials.gov/ct2/show/study/NCT04116437)).

Baseline Characteristics and Patient Demographics: CLL/SLL Population

Characteristic	Ibrutinib Intolerant (n=44)	Acalabrutinib ± Ibrutinib Intolerant (n=27)	Total (N=71)
Age, median (range), years	72 (49-91)	68 (51-84)	71 (49-91)
Male, n (%)	23 (52.3)	13 (48.1)	36 (50.7)
Disease type, n (%)			
CLL	38 (86.4)	25 (92.6)	63 (88.7)
SLL	6 (13.6)	2 (7.4)	8 (11.3)
ECOG PS, n (%)			
0	26 (59.1)	18 (66.7)	44 (62.0)
1	18 (40.9)	7 (25.9)	25 (35.2)
2	0	2 (7.4)	2 (2.8)
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)	6.6 (3.1-46.4)	9.8 (1.2-64.8)
Duration of prior acalabrutinib therapy, median (range), months	NA	5.7 (0.2-58.6)	5.7 (0.2-68.6)

Characteristic	Ibrutinib Intolerant (n=44)	Acalabrutinib ± Ibrutinib Intolerant (n=27)	Total (N=71)
Cytopenia status, n (%)			
Hemoglobin \leq 110 g/L	6 (13.6)	5 (18.5)	11 (15.5)
Platelet count \leq 100 \times 10 ⁹ /L	5 (11.4)	1 (3.7)	6 (8.5)
ANC \leq 1.5 \times 10 ⁹ /L	3 (6.8)	0	3 (4.2)
Bulky disease \geq5 cm, n (%)	8 (18.2)	3 (11.1)	12 (16.9)
Binet stage C at diagnosis, n (%)	4 (9.1)	0	4 (5.6)
Del(11q), n (%)	8 (18.2)	2 (7.4)	10 (14.1)
Del(17p), n (%)	4 (9.1)	2 (7.4)	6 (8.5)
Del(13q) monosomy, n (%)	12 (27.3)	5 (18.5)	17 (23.9)
Unmutated IGHV, n (%)	10 (22.7)	3 (11.1)	13 (18.3)
TP53 mutation, n (%)	11 (25.0)	5 (18.5)	16 (22.5)

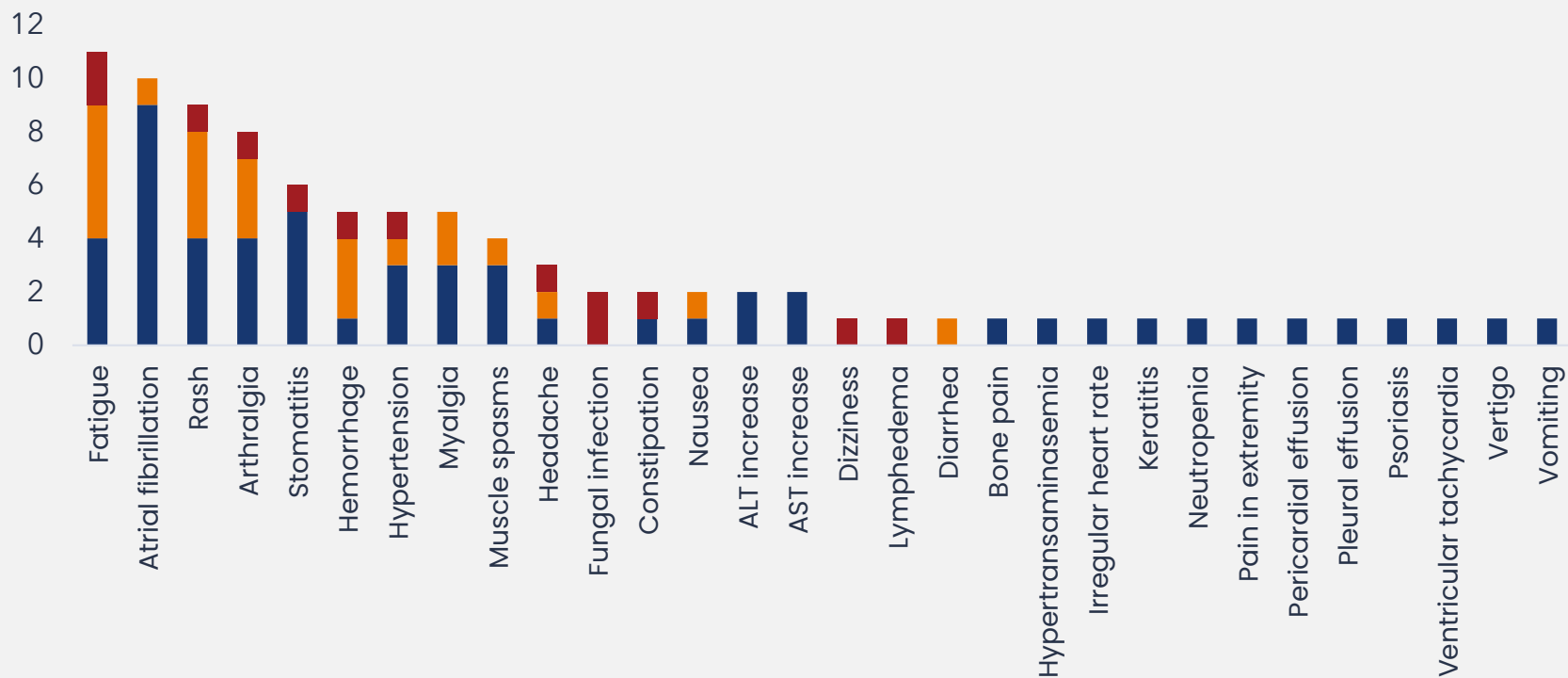
Data cutoff: May 1, 2024.

ANC=absolute neutrophil count, CLL=chronic lymphocytic leukemia, ECOG PS=Eastern Cooperative Oncology Group performance status, SLL=small lymphocytic lymphoma.

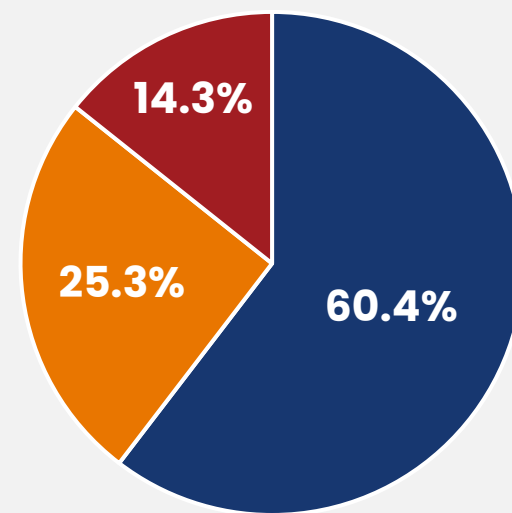
Shadman M, et al. Blood Adv. 2025 Aug 26;9(16):4100-4110.

Primary Endpoint: Recurrence of Intolerance Events – Ibrutinib-Intolerant Cohort

- 28 of 52 patients (54%) did not experience any recurrence of the prior ibrutinib intolerance events
- While receiving zanubrutinib, 55 of 91 (60%) ibrutinib-intolerance events did not recur
 - Of those AEs that did recur during zanubrutinib treatment, none recurred at a higher grade, and 23 of 36 (64.0%) ibrutinib-intolerance events were lower grade



Total Intolerance Events (N=91)



- Did not recur
- Recurred at lower grade
- Recurred at same grade
- Recurred at higher grade^a

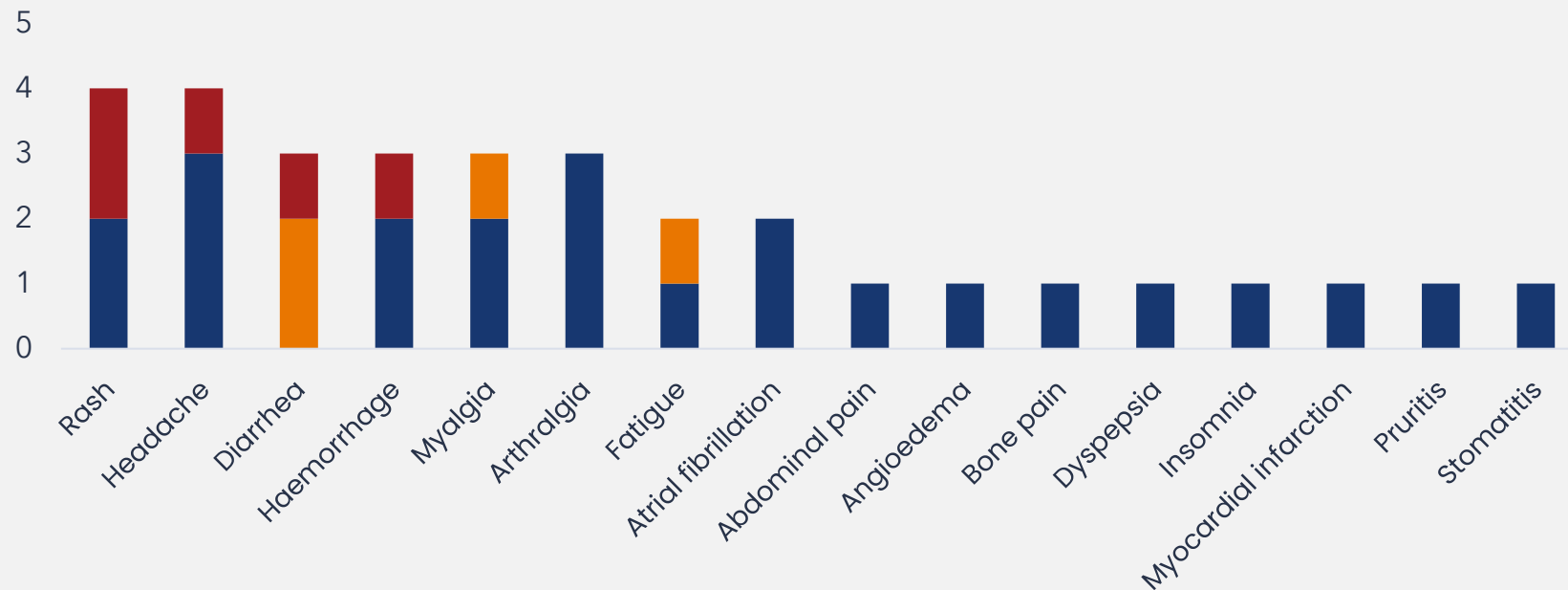
Data cutoff: May 1, 2024.

^aNo intolerance events recurred at a higher grade.

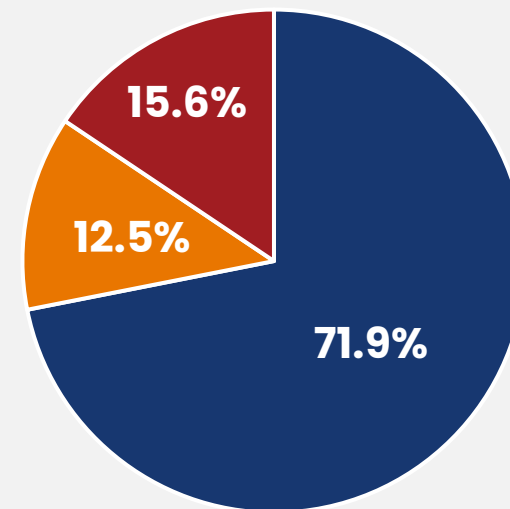
AE=adverse event, ALT=alanine aminotransferase, AST=aspartate aminotransferase, Shadman M, et al. Blood Adv. 2025 Aug 26;9(16):4100-4110.

Primary Endpoint: Recurrence of Intolerance Events – Acalabrutinib-Intolerant Cohort

- 19 of 27 patients (70%) did not experience any recurrence of the prior acalabrutinib intolerance events
- Most acalabrutinib-intolerance events (23 of 32 [72%]) did not recur at any Grade with Zanubrutinib
 - Of those AEs that did recur during zanubrutinib treatment, none recurred at a higher grade, and 4 of 9 (44.0%) acalabrutinib-intolerance events were lower grade



Total Intolerance Events (n=32)



- Did not recur
- Recurred at lower grade
- Recurred at same grade
- Recurred at higher grade^a

Safety Summary: CLL/SLL Population



TEAEs, n (%)	Ibrutinib Intolerant (n=44)	Acalabrutinib ± Ibrutinib Intolerant (n=27)	Total (N=71)
Any AE	43 (97.7)	25 (92.6)	68 (95.8)
Grade ≥3	28 (63.6)	15 (55.6)	43 (60.6)
Serious AEs	15 (34.1)	8 (29.6)	23 (32.4)
Leading to death	2 (4.5) ^a	0	2 (2.8) ^a
Leading to treatment d/c	5 (11.4)	3 (11.1)	8 (11.3)
Leading to dose interruption	28 (63.6)	17 (63.0)	45 (63.4)
Leading to dose reduction	14 (31.8)	6 (22.2)	20 (28.2)

TEAEs occurring in ≥15% of total patients, n (%)	Ibrutinib Intolerant (n=44)	Acalabrutinib ± Ibrutinib Intolerant (n=27)	Total (N=71)
Fatigue	15 (34.1)	8 (29.6)	23 (32.4)
COVID-19	15 (34.1)	5 (18.5)	20 (28.2)
Contusion	12 (27.3)	5 (18.5)	17 (23.9)
Diarrhea	10 (22.7)	7 (25.9)	17 (23.9)
Arthralgia	10 (22.7)	5 (18.5)	15 (21.1)
Cough	9 (20.5)	6 (22.2)	15 (21.1)
Hypertension	7 (15.9)	7 (25.9)	14 (19.7)
Constipation	11 (25.0)	1 (3.7)	12 (16.9)
URTI	9 (20.5)	3 (11.1)	12 (16.9)
Nausea	9 (20.5)	2 (7.4)	11 (15.5)
Sinusitis	9 (20.5)	2 (7.4)	11 (15.5)

Data cutoff: May 1, 2024.

^aCOVID-19 and cardiac arrest.

AE=adverse event, COVID=coronavirus disease, URTI=upper respiratory tract infection.

Shadman M, et al. Blood Adv. 2025 Aug 26;9(16):4100-4110.