Genomic landscape of patients in a phase II study of zanubrutinib in ibrutinib- and/or acalabrutinib-intolerant patients with B-cell malignancies


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Genomic landscape of patients in a phase II study of zanubrutinib in ibrutinib- and/or acalabrutinib-intolerant patients with B-cell malignancies

Running head (50 characters): BTK inhibitor intolerance

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Clinical Trial: BGB-3111-215 (NCT04116437)

Data Sharing Statement

BeiGene voluntarily shares anonymous data on completed studies responsibly and provides qualified scientific and medical researchers access to anonymous data and supporting clinical trial documentation for clinical trials in dossiers for medicines and indications after submission and approval in the United States, China, and Europe. Clinical trials supporting subsequent local approvals, new indications, or combination products are eligible for sharing once corresponding regulatory approvals are achieved. BeiGene shares data only when permitted by applicable data privacy and security laws and regulations. In addition, data can only be shared when it is feasible to do so without compromising the privacy of study participants. Qualified researchers may submit data requests/research proposals for BeiGene review and consideration through BeiGene’s Clinical Trial Webpage at https://www.beigene.com/our-science-and-medicines/our-clinical-trials/.

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Author Contributions

MS, IWF, MYL, RP, JMB, SFZ, JLC, JM, ECK, HAY, BF, AC, PKT, MDG, SM, and JPS enrolled
patients and collected clinical data. LX, RC, KB, AC, D-YC, AI and VR contributed to intellectual content, conception, and design. LX and KB performed data processing, statistical analysis, generated figures, and wrote the manuscript. All authors contributed to data interpretation and revised the manuscript.

Conflict of interest

LX, RC, KB, AC, AI, and VR are employees of and hold stock/shares in BeiGene Co.

MS is a consultant for Abbvie, Genentech, AstraZeneca, Sound Biologics, Pharmacyclics, BeiGene, Bristol Myers Squibb, Morphosys/Incyte, TG Therapeutics, Innate Pharma, Kite Pharma, Adaptive Biotechnologies, Epizyme, Eli Lilly, Adaptimmune, Mustang Bio, Regeneron, Merck, Fate therapeutics, MEI pharma and Atara Biotherapeutic and receives research funding from Mustang Bio, Celgene, Bristol Myers Squibb, Pharmacyclics, Gilead, Genentech, AbbVie, TG Therapeutics, Beigene, AstraZeneca, Sunesis, Atara Biotherapeutics, Genmab, Morphosys/Incyte

IF has membership on board of directors or advisory committees at Vincerx.

ML receives consulting fees from Abbvie, Amgen, AstraZeneca, BeiGene, Bristol Myers Squibb, Genmab, GSK, Incyte, Janssen, Karyopharm, Kite, Lilly, Sanofi, Seagen, and Takeda, payment or honoraria from Abbvie, Amgen, AstraZeneca, BeiGene, Bristol Myers Squibb, Genmab, GSK, Incyte, Janssen, Karyopharm, Kite, Lilly, Sanofi, Seagen, and Takeda, travel support from Abbvie, Amgen, AstraZeneca, BeiGene, Bristol Myers Squibb, Genmab, GSK, Incyte, Janssen, Karyopharm, Kite, Lilly, Sanofi, Seagen, and Takeda, and has a leadership or fiduciary role from Sellas.

JMB receives consulting fees from Abbvie, Adaptive Biotechnologies, AstraZeneca, BeiGene, Bristol Myers Squibb, Constellation, Eli Lilly, Epizyme, Foresight, Genentech, Genmab, Kura,
Kymera, Morphosys, Novartis, Nurix, TG Therapeutics, Verastem, and X4 Pharmaceuticals and receives payments/honoraria from SeaGen and BeiGene.

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MDG receives honoraria from Karyopharm, TG Therapeutics, Janssen, and GSK.

RC has equity with Pfizer and GSK and individual stocks in SAGA Diagnostics.

D-YC has equity with BeiGene.

JPS receives consulting fees from TG Therapeutics, Genentech, AbbVie AstraZeneca, BeiGene, Bristol-Myers Squibb, and Merck, and research funds from Genentech, Celgene, Gilead Sciences, TG Therapeutics, Merck, and Takeda.
Bruton tyrosine kinase inhibitors (BTKi) have shown remarkable efficacy in the treatment of B-cell malignancies, yet many patients develop intolerance leading to treatment discontinuation. Ibrutinib, the first-in-class BTKi, can cause adverse effects including cardiotoxicities, bleeding, and cytopenias leading to discontinuation in up to 16% of patients, largely due to off-target activity.\(^1\) The second-generation more selective BTKi, acalabrutinib, also leads to adverse effects and treatment discontinuation in up to 23% of patients.\(^2\) Zanubrutinib is a next-generation covalent, irreversible BTKi that has been approved world-wide for the treatment of patients with B-cell malignancies including chronic lymphocytic leukemia (CLL), small lymphocytic lymphoma (SLL), previously treated mantle cell lymphoma (MCL), Waldenström macroglobulinemia (WM), and relapsed or refractory (R/R) marginal zone lymphoma (MZL). Preclinical and clinical studies have demonstrated that zanubrutinib has superior potency, selectivity, efficacy, and a more favorable toxicity profile compared to ibrutinib.\(^3\) \(^4\) \(^5\) \(^6\) Results from BGB-3111-215 (NCT04116437), an ongoing phase 2 study to evaluate the safety and efficacy of zanubrutinib monotherapy, demonstrate that zanubrutinib can be a safe treatment option for patients with B-cell malignancies who exhibited intolerance to prior treatment with ibrutinib (cohort 1) or to ibrutinib and/or acalabrutinib (cohort 2).\(^6\)

To date, it is unclear if the genomic profile of patients with B-cell malignancies who are intolerant to ibrutinib and/or acalabrutinib is associated with intolerance or response to subsequent therapy. In this post-hoc analysis, a highly sensitive targeted next-generation sequencing (NGS) panel (PredicineHEMET\(^\text{TM}\); Predicine, Hayward, CA, USA) with full exon coverage of 106 genes commonly mutated in hematological malignancies was used to explore the genetic profiles of patients enrolled in study BGB-3111-215.\(^7\) This study was conducted in accordance with the Declaration of Helsinki and the International
Conference on Harmonization Guidelines for Good Clinical Practice. Written informed consent was obtained from each patient and institutional review board approval was obtained at each study site.

Samples were sequenced to a median depth of >20,000 reads, with a validated sensitivity of 0.25% mutant allele frequency for all genomic regions and 0.1% for mutational hotspots. Variant allele frequency (VAF) <0.1% for hotspot mutations and <0.25% for non-hotspot mutations were excluded from analysis. Germline and CHIP mutations were also excluded from analysis. Baseline blood samples from 95.9% (71/74) of all patients enrolled in the study and from 77.8% (7/9) patients with disease progression (CLL: n=5; SLL: n=1; MCL: n=1) at data cutoff were available for analysis. Baseline demographics and disease characteristics were similar between cohorts and are summarized in Table S1. Of note, most patients enrolled in this study had CLL/SLL (n=54).

We identified mutations in 91.5% (65/71) of baseline samples and in all (7/7) progressive disease samples (median = 4 mutations per sample; range, 1-14). The types of mutations identified as well as mutation frequencies are shown in Figure 1. Across all BTKi-intolerant patients, the most common baseline mutations were in TP53 (32%), SF3B1 (23%), ATM (18%), NOTCH1 (17%), and CHEK2 (15%) (Figure 1B). Mutation spectra of these genes were visualized with lollipop plots (Figure S1) and are similar to what has been observed in other studies. As expected, mutation prevalence at baseline differed among disease indications and was mostly consistent with previous studies of R/R patients in various B-cell malignancies (Figure 1B). In patients with CLL/SLL, the most frequently mutated genes were TP53 (16/54, 30%), SF3B1 (15/54, 28%), ATM (13/54, 24%), and NOTCH1 (11/54, 20%)—all within cell signaling pathways (e.g., DNA damage response and NOTCH signaling) known to be associated with disease susceptibility and/or poor prognosis in these patients. Observed rates of baseline TP53 (5/8 vs 11/46, p=0.04), ATM (4/8 vs 9/46, p=0.08), and SF3B1 (5/8 vs 10/46,
mutations were higher in patients who later developed progressive disease (n=8) compared to patients who did not (n=46; Figure 2A). Patients with these mutations also had shorter progression-free survival (PFS) compared to patients without mutations in these genes as evidenced by the observed hazard ratios and 95% confidence intervals: (TP53) 3.2 (0.84, 11.8), (SF3B1) 5.9 (1.48, 23.77), or (ATM) 5.5 (1.47, 20.72) (Figure 2B-2D), which is consistent with previous reports.9,10 However, the mutation frequency of NOTCH1 was similar between patients with and without disease progression (Figure 2A) and NOTCH1 mutation status was not correlated with PFS (Figure 2E)- inconsistent with a previous study of patients with R/R CLL treated with ibrutinib where NOTCH1 mutations were strongly associated with a shorter PFS (P=0.00002) and overall survival (P=0.0001).11 This discrepant finding was not due to the increased sensitivity of the PredicineHeme panel as patients with NOTCH1 VAF<1% (45.5% [5/11]) exhibited a similar PFS to patients with NOTCH1 VAF>1%. Instead the finding suggests the possibility that, in contrast to ibrutinib, zanubrutinib may uniquely suppress the outgrowth of clones with NOTCH1 mutations. Although patients with WM, MCL, and MZL were enrolled at smaller numbers in our study and association analyses could not be performed, mutation profiles of these patients are reported for reference (Figure 1).

At the data cutoff for this analysis, nine patients (12.7%; 9/71) who were intolerant to ibrutinib and/or acalabrutinib and who were subsequently treated with zanubrutinib developed progressive disease. We assessed BTKi resistance mutations in BTK or PLCG2 in these patients (Table 1). At baseline, BTK C481S mutations were detected in 4.2% (3/71) of patients (Figure 1B). Of these, two patients progressed on zanubrutinib; patients no. 3 and no. 9 progressed at 4.6 months and 17.7 months of zanubrutinib treatment, respectively (Table 1). A third patient (not shown) with a baseline BTK C481S mutation died from COVID-19 shortly after enrollment before disease assessments could be made. Patient no. 3, with CLL, had a high frequency (VAF=60.9%) of BTK C481S mutations at baseline. This patient had long exposure to
ibrutinib treatment (~65 months) prior to enrolling in the study and had disease progression after 4.6 months of zanubrutinib treatment (Table 1). Patient no. 9, with CLL, who also had long prior exposure to ibrutinib (51.9 months), initially presented with low frequency of *BTK* C481S mutations (VAF=0.9%) that increased in frequency at the time of disease progression (VAF=20.4%) (Table 1). This patient also had new *PLCG2* mutations (L845F and D993H; VAF<1% for both mutations) at disease progression (Table 1). It is worth noting that this patient stayed on zanubrutinib treatment for 17.7 months before disease progression with stable disease as best overall response. This suggests that *BTK* C481S mutations at low VAF did not prevent zanubrutinib efficacy in this patient. At the time of disease progression, patients no. 1 (CLL) and no. 2 (SLL) had developed new *BTK* and *PLCG2* mutations. Patient no. 1 acquired high frequencies of *BTK* C481S mutations (VAF=19.2%) as well as low frequency mutations in *PLCG2* (L845F, N750D, and R665W; VAF<1% for all three *PLCG2* mutations) that had not been observed at baseline (Table 1). This patient was on zanubrutinib treatment for 9.2 months before disease progression. Patient no. 2 acquired *BTK* mutations (C481S: VAF=3.8%; C481Y: VAF=14.0%) and *PLCG2* mutations (S707F, L845V, M1141K, and E1139del; VAF <6% for all *PLCG2* mutations) at disease progression (Table 1). This patient was on zanubrutinib treatment for 17.9 months prior to disease progression. All *BTK* mutations detected in this study were located at the BTKi binding site (C481S or C481Y).

The remaining five patients with disease progression had no *BTK* or *PLCG2* mutations detected at baseline or at disease progression. Patient no. 5, with MCL, had a *CCND1-IGH* fusion mutation at both baseline and disease progression; *CCND1-IGH* fusions are reported to be associated with ibrutinib resistance in MCL patients. Four other patients with CLL harbored mutations in genes associated with poor prognosis, including *TP53*, *ATM*, and *SF3B1* (Table S2).
Here we show that the gene mutational profile of patients with B-cell malignancies who were intolerant to ibrutinib and/or acalabrutinib is comparable to patients with R/R disease. For example, patients with mutations in \textit{TP53}, \textit{SF3B1}, or \textit{ATM} genes had less favorable prognosis in this study and is similar to what has been previously observed in BTKi-treated patients.\textsuperscript{9,10}

Further, PFS was comparable between zanubrutinib-treated patients with or without \textit{NOTCH1} mutations. Lastly, 4/7 intolerant patients who progressed on zanubrutinib acquired new \textit{BTK} mutations and/or had an increase in the frequency of \textit{BTK} mutations. Although there are limitations to this study (e.g., small sample size, short follow-up times, and a lack of direct comparison to non-intolerant patients), this is the first study to describe the genomic landscape of patients with B-cell malignancies who were intolerant to ibrutinib and/or acalabrutinib and were switched to treatment with zanubrutinib.
REFERENCES


Table 1. Relapse on zanubrutinib was associated with known BTK inhibitor resistance mutations.

<table>
<thead>
<tr>
<th>Patient</th>
<th>Indication</th>
<th>Cohort</th>
<th>Duration of prior ibrutinib (mo)</th>
<th>Duration of prior acalabrutinib (mo)</th>
<th>Time on zanubrutinib (mo)</th>
<th>BTK mutations at baseline (VAF)</th>
<th>BTK mutations at/after PD (VAF)</th>
<th>PLCG2 mutations at baseline</th>
<th>PLCG2 mutations at/after PD (VAF)</th>
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<tbody>
<tr>
<td>1</td>
<td>CLL</td>
<td>2</td>
<td>6.7</td>
<td>10.1</td>
<td>9.2</td>
<td>ND†</td>
<td>C481S, 1442G&gt;C (19.2%) C481S, 14421T&gt;A (1.1%)</td>
<td>ND</td>
<td>L845F, 2535A&gt;C (1.0%) N750D, 2248A&gt;G (0.8%) R665W, 1993C&gt;T (0.3%)</td>
</tr>
<tr>
<td>2</td>
<td>SLL</td>
<td>1</td>
<td>17.3</td>
<td>NA</td>
<td>17.9</td>
<td>ND</td>
<td>C481S, 1442G&gt;C (0.3%) C481S, 14421T&gt;A (3.8%) C481Y, 1442G&gt;C (14.0%)</td>
<td>ND</td>
<td>S707F, 2120C&gt;T (5.8%)</td>
</tr>
<tr>
<td>3</td>
<td>CLL</td>
<td>1</td>
<td>64.8</td>
<td>NA</td>
<td>4.6</td>
<td>C481S, 1442G&gt;C (60.9%) C481S, 1442G&gt;C (69.1%)</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
</tr>
<tr>
<td>4</td>
<td>CLL</td>
<td>2</td>
<td>3.1</td>
<td>1.2</td>
<td>13.4</td>
<td>ND†</td>
<td>ND</td>
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<tr>
<td>5</td>
<td>MCL</td>
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<tr>
<td>6</td>
<td>CLL</td>
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<td>12.8</td>
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<tr>
<td>7</td>
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<td>7.8</td>
<td>NA</td>
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<tr>
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<tr>
<td>9</td>
<td>CLL</td>
<td>1</td>
<td>51.9</td>
<td>NA</td>
<td>17.7</td>
<td>C481S, 1442G&gt;C (0.9%) C481S, 1442G&gt;C (20.4%)</td>
<td>ND</td>
<td>L845F, 2535A&gt;C (0.4%) D993H, 2977G&gt;C (0.6%)</td>
<td></td>
</tr>
</tbody>
</table>

*Initial sample collected on study day 87. †Initial sample collected on study day 141. BTK, Bruton tyrosine kinase gene; CLL, chronic lymphocytic leukemia; MCL, mantle cell lymphoma; mo, months; NA, not applicable; ND, not detected; PD, progressive disease; PLCG2, phospholipase C gamma 2 gene; SLL, small lymphocytic lymphoma; VAF, variant allele frequency.
FIGURE LEGENDS

Figure 1. Variant classification and heatmap representation of mutations detected at baseline in at least three patients with B-cell malignancies. Samples were sequenced to a median depth of >20,000 reads, with a validated sensitivity of 0.25% mutant allele frequency for all genomic regions, and 0.1% for mutational hotspots. Variant allele frequency (VAF) <0.1% for hotspot mutations and <0.25% for non-hotspot mutations were excluded from analysis. Germline and CHIP mutations were also excluded from analysis. Number of variants is shown in the X-axis (A). DNA mutation profile of patients and the distribution of mutations among different study cohorts by mutation type and treatment status. Each column represents one patient, and each row represents one gene (represented by the gene symbol on left). Mutation rates of each gene are shown on the right. Mutation type is color-coded as shown in the figure legend (B).

Amp, amplification; CLL, chronic lymphocytic leukemia; Del, deletion; Ins, insertion; MCL, mantle cell lymphoma; MZL, marginal zone lymphoma; SLL, small lymphocytic lymphoma; UTR, untranslated region; WM, Waldenström macroglobulinemia.

Figure 2. The presence of TP53, SF3B1, or ATM mutations is associated with inferior outcomes of CLL/SLL patients. (A) Distributions of baseline mutations between patients who developed progressive disease (PD) and those who did not were compared using proportions. (B-E) The association between genetic mutations and progression-free survival (PFS, defined as time from the date of first zanubrutinib dose to date of first PD or death) was quantified by the log rank test and the hazard ratio and summarized by the Kaplan-Meier method. As of the June 6, 2022, data cutoff, patients were censored for PFS if 1) they had no documented disease progression or death, 2) they initiated subsequent anti-cancer therapy prior to PD, or 3) they progressed or died after more than one consecutive missed disease assessment. All analyses were performed using either R or SAS (version 9.4). Patients with mutations in TP53, SF3B1, and ATM, but not NOTCH1, showed shorter PFS. CLL, chronic lymphocytic leukemia; MUT, mutant; PD, progressive disease; PFS, progression-free survival; SLL, small lymphocytic lymphoma; WT, wild type.
**A** Mutation Distribution by Progression Status

- **TP53**: Non-progressive Disease (P=0.04), Progressive Disease (P=0.08)
- **ATM**: Non-progressive Disease (P=0.08), Progressive Disease (P=0.03)
- **SF3B1**: Non-progressive Disease (P=1.0), Progressive Disease (P=1.0)

**B** TP53

- **At Risk (Events)**
  - MUT: 16 (0)
  - WT: 38 (0)
- **Months Since First Dose**
  - 0: MUT 16 (0), WT 38 (0)
  - 6: MUT 13 (1), WT 28 (2)
  - 12: MUT 9 (4), WT 26 (2)
  - 18: MUT 4 (5), WT 13 (4)
  - 24: MUT 1 (5), WT 8 (4)
  - 30: MUT 0 (5), WT 0 (4)

- **Hazard Ratio**: 3.16 (0.84, 11.8)
- **2-sided P**: 0.07

**C** ATM

- **At Risk (Events)**
  - MUT: 13 (0)
  - WT: 41 (0)
- **Months Since First Dose**
  - 0: MUT 13 (0), WT 41 (0)
  - 6: MUT 7 (3), WT 34 (0)
  - 12: MUT 6 (4), WT 29 (2)
  - 18: MUT 1 (5), WT 16 (4)
  - 24: MUT 0 (5), WT 9 (4)
  - 30: MUT 0 (5), WT 0 (4)

- **Hazard Ratio**: 5.53 (1.47, 20.72)
- **2-sided P**: <0.01

**D** SF3B1

- **At Risk (Events)**
  - MUT: 15 (0)
  - WT: 39 (0)
- **Months Since First Dose**
  - 0: MUT 15 (0), WT 39 (0)
  - 6: MUT 11 (2), WT 30 (1)
  - 12: MUT 8 (5), WT 27 (1)
  - 18: MUT 3 (6), WT 14 (3)
  - 24: MUT 1 (6), WT 8 (3)
  - 30: MUT 0 (6), WT 0 (3)

- **Hazard Ratio**: 3.16 (0.84, 11.8)
- **2-sided P**: <0.01

**E** NOTCH1

- **At Risk (Events)**
  - MUT: 11 (0)
  - WT: 43 (0)
- **Months Since First Dose**
  - 0: MUT 11 (0), WT 43 (0)
  - 6: MUT 10 (0), WT 31 (3)
  - 12: MUT 8 (1), WT 27 (5)
  - 18: MUT 3 (2), WT 14 (7)
  - 24: MUT 1 (2), WT 8 (7)
  - 30: MUT 0 (2), WT 0 (7)

- **Hazard Ratio**: 0.94 (0.2, 4.54)
- **2-sided P**: 1.0
### Supplemental Table 1. Patient demographics and baseline information.

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Cohort 1 (Intolerant to ibrutinib) (n=56)</th>
<th>Cohort 2 (Intolerant to ibrutinib and/or acalabrutinib) (n=15)</th>
<th>Total (N=71)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Indication, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CLL</td>
<td>37 (66.1)</td>
<td>9 (60.0)</td>
<td>46 (64.8)</td>
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<tr>
<td>WM</td>
<td>9 (16.1)</td>
<td>2 (13.3)</td>
<td>11 (15.5)</td>
</tr>
<tr>
<td>SLL</td>
<td>6 (10.7)</td>
<td>2 (13.3)</td>
<td>8 (11.3)</td>
</tr>
<tr>
<td>MCL</td>
<td>2 (3.6)</td>
<td>1 (6.7)</td>
<td>3 (4.2)</td>
</tr>
<tr>
<td>MZL</td>
<td>2 (3.6)</td>
<td>1 (6.7)</td>
<td>3 (4.2)</td>
</tr>
<tr>
<td>Age, median (range), year</td>
<td>71 (49-91)</td>
<td>73 (51-87)</td>
<td>71 (49-91)</td>
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<td>Male, n (%)</td>
<td>30 (53.6)</td>
<td>9 (60.0)</td>
<td>39 (54.9)</td>
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<td>ECOG PS 0, n (%)</td>
<td>33 (58.9)</td>
<td>8 (53.3)</td>
<td>41 (57.7)</td>
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<tr>
<td>No. of prior therapy regimens, median (range)</td>
<td>1 (1-12)</td>
<td>2 (1-6)</td>
<td>1.0 (1-12)</td>
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<tr>
<td>Prior BTKi, n (%)</td>
<td>56 (100)</td>
<td>15 (100)</td>
<td>71 (100)</td>
</tr>
<tr>
<td>ibrutinib monotherapy</td>
<td>48 (85.7)&lt;sup&gt;b&lt;/sup&gt;</td>
<td>7 (46.7)&lt;sup&gt;a&lt;/sup&gt;</td>
<td>54 (76.1)</td>
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<td>ibrutinib combination therapy</td>
<td>9 (16.1)&lt;sup&gt;b&lt;/sup&gt;</td>
<td>0</td>
<td>9 (12.7)</td>
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<td>Acalabrutinib monotherapy</td>
<td>0</td>
<td>8 (53.3)</td>
<td>7 (9.9)</td>
</tr>
<tr>
<td>Time on prior BTKi&lt;sup&gt;c&lt;/sup&gt;, median (range), months</td>
<td>10.61 (1.1-73.7)</td>
<td>3.33 (0.5-26.9)</td>
<td>NA</td>
</tr>
<tr>
<td>Zanubrutinib exposure, median (range), months</td>
<td>17.0 (0.6-28.5)</td>
<td>14.5 (0.5-19.6)</td>
<td>17.0 (0.5-28.5)</td>
</tr>
<tr>
<td>Follow-up, median (range), months</td>
<td>21.2 (1.0-31.7)</td>
<td>10.4 (1.1-20.9)</td>
<td>19.4 (1.0-31.7)</td>
</tr>
</tbody>
</table>

<sup>a</sup> Seven patients in cohort 2 had both prior ibrutinib and acalabrutinib therapies.  
<sup>b</sup> One patient received ibrutinib combination therapy followed by ibrutinib monotherapy.  
<sup>c</sup> Cumulative ibrutinib exposure for cohort 1 and acalabrutinib for cohort 2. Data cutoff: 6 June 2022.

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; NA, not applicable; PD, progressive disease; SLL, small lymphocytic lymphoma; WM, Waldenström macroglobulinemia.
Figure S1. Somatic mutation spectra throughout the whole protein sequences of the four most frequently mutated genes. Lollipop plots depicting common mutations in *TP53* (A), *ATM* (B), *SF3B1* (C), *NOTCH1* (D), and *CHK2* (E). Protein domains and mutation type are color-coded and described in figure legends. Del, deletion; Ins, insertion.
Table S2. Patients with progressive disease who did not have mutations in \textit{BTK} or \textit{PLCG2} had mutations in other known BTK inhibitor resistance genes at baseline.

<table>
<thead>
<tr>
<th>Patient</th>
<th>Indication</th>
<th>Baseline gene mutations associated with progressive disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>4</td>
<td>CLL</td>
<td>\textit{ATM, FBXW7}</td>
</tr>
<tr>
<td>5</td>
<td>MCL</td>
<td>\textit{CCND1-IGH} fusion</td>
</tr>
<tr>
<td>6</td>
<td>CLL</td>
<td>\textit{MCL1, TP53}</td>
</tr>
<tr>
<td>7</td>
<td>CLL</td>
<td>\textit{TP53, SF3B1, FBXW7}</td>
</tr>
<tr>
<td>8</td>
<td>CLL</td>
<td>\textit{TP53, NOTCH1, BRAF, SF3B1, MAPK14}</td>
</tr>
</tbody>
</table>