

## CLINICAL TRIALS AND OBSERVATIONS

# Mutational profile in previously treated patients with chronic lymphocytic leukemia progression on acalabrutinib or ibrutinib

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## KEY POINTS

- **BTK C481S was most common in both groups; in the acalabrutinib arm, low-VAF T474I (9/47; 8 co-occurring with C481S) but no L528W was seen.**
- **More patients receiving acalabrutinib acquired BTK mutations, though overall, patients with BTK mutation did not fare worse vs those without.**

**Chronic lymphocytic leukemia (CLL) progression during Bruton tyrosine kinase (BTK) inhibitor treatment is typically characterized by emergent B-cell receptor pathway mutations. Using peripheral blood samples from patients with relapsed/refractory CLL in ELEVATE-RR (NCT02477696; median 2 prior therapies), we report clonal evolution data for patients progressing on acalabrutinib or ibrutinib (median follow-up, 41 months). Paired (baseline and progression) samples were available for 47 (excluding 1 Richter) acalabrutinib-treated and 30 (excluding 6 Richter) ibrutinib-treated patients. At progression, emergent BTK mutations were observed in 31 acalabrutinib-treated (66%) and 11 ibrutinib-treated patients (37%; median variant allele fraction [VAF], 16.1% vs 15.6%, respectively). BTK C481S mutations were most common in both groups; T474I (n = 9; 8 co-occurring with C481) and the novel E41V mutation within the pleckstrin homology domain of BTK (n = 1) occurred with acalabrutinib, whereas neither mutation occurred with ibrutinib. L528W and A428D mutations presented in 1 ibrutinib-treated patient. Pre-existing TP53 mutations were present in 25 acalabrutinib-treated (53.2%) and 16 ibrutinib-treated patients (53.3%) at screening. Emergent TP53 mutations occurred with**

**acalabrutinib and ibrutinib (13% vs 7%; median VAF, 6.0% vs 37.3%, respectively). Six acalabrutinib-treated patients and 1 ibrutinib-treated patient had emergent TP53/BTK mutations. Emergent PLCG2 mutations occurred in 3 acalabrutinib-treated (6%) and 6 ibrutinib-treated patients (20%). One acalabrutinib-treated patient and 4 ibrutinib-treated patients had emergent BTK/PLCG2 mutations. Although common BTK C481 mutations were observed with both treatments, patterns of mutation and mutation frequency, mutation VAF, and uncommon BTK variants varied with acalabrutinib (T474I and E41V) and ibrutinib (L528W and A428D) in this patient population. The trial was registered at [www.clinicaltrials.gov](http://www.clinicaltrials.gov) as #NCT02477696.**

## Introduction

Covalent Bruton tyrosine kinase (BTK) inhibitors (BTKis) are highly effective in the treatment of chronic lymphocytic leukemia (CLL) and have resulted in a paradigm shift in the management of the disease.<sup>1</sup> However, disease progression in patients receiving covalent BTKis eventually occurs in most patients and is often characterized by B-cell receptor pathway

mutations at relapse, which commonly occur in the BTK and PLCG2 genes.<sup>2-8</sup> BTK mutations often occur at the C481 residue and disrupt binding to, and inactivation of, BTK by all covalent BTKis.<sup>9-11</sup> C481 mutations preclude irreversible binding of ibrutinib to BTK, resulting in a greatly reduced drug potency; these mutations were subsequently associated with resistance to acalabrutinib and zanubrutinib.<sup>10,12,13</sup> This has led to the development of noncovalent BTKis designed to avoid

the resistance mechanisms associated with these mutations.<sup>14</sup> Mutations in *PLCG2*, which acts downstream of BTK, also allow for B-cell receptor signaling irrespective of BTK inhibition,<sup>10</sup> which also may affect the efficacy of noncovalent BTKis.<sup>15</sup>

Ibrutinib is a first-generation covalent BTKi first approved in 2013 for relapsed/refractory (R/R) mantle cell lymphoma, and, subsequently, other B-cell malignancies (CLL, Waldenström macroglobulinemia, and marginal zone lymphoma).<sup>16,17</sup> Acalabrutinib is a selective next-generation covalent BTKi first approved for R/R mantle cell lymphoma in 2017 and for CLL in 2019.<sup>18,19</sup> In the head-to-head ELEVATE-RR trial (NCT02477696), which comprised a population of patients with R/R CLL and higher-risk genetic features (del(17p) and/or del(11q)), acalabrutinib demonstrated noninferior progression-free survival (PFS) with an improved safety and tolerability profile, including fewer cardiovascular adverse events, vs ibrutinib. However, to our knowledge, no data to date have directly compared the mutational profiles of patients who progress on acalabrutinib and ibrutinib. Herein, we report comparative clonal evolution of genes implicated in resistance, including but not limited to *BTK* and *PLCG2*, in patients with CLL progression on acalabrutinib or ibrutinib in the ELEVATE-RR clinical trial.

## Methods

### Study design

The study design and primary results of ELEVATE-RR have been published previously.<sup>20</sup> Briefly, in this phase 3, randomized, multicenter, open-label, noninferiority trial, eligible patients were adults with previously treated CLL, an Eastern Cooperative Oncology Group performance status  $\leq 2$ , and presence of del(17p) and/or del(11q). Cytogenetic testing of peripheral blood was performed by a central laboratory using fluorescence in situ hybridization and stimulated karyotyping. Complex karyotype was defined based on the patient having  $\geq 3$  chromosomal abnormalities and  $\geq 1$  structural abnormalities. The study was conducted in accordance with local laws, the protocol, the Declaration of Helsinki, and International Conference on Harmonization Guidelines for Good Clinical Practices. All patients provided written informed consent. Patients were randomly assigned to receive acalabrutinib 100 mg twice daily or ibrutinib 420 mg once daily until disease progression or unacceptable toxicity.

### Mutational analysis

Peripheral blood samples were collected at baseline and at relapse. DNA was extracted from enriched CD19<sup>+</sup> cells (Robo-Sep) and subjected to a 50-gene AmpliSeq next-generation sequencing assay (LifeTech)<sup>6</sup> covering the full *BTK* and *PLCG2* coding regions with a mean depth of 2000 to 4000 reads, producing a validated sensitivity cutoff of 0.5% variant allele fraction (VAF) for resistance-associated mutations. Forty-eight other genes associated with CLL were assessed at 1% to 2% VAF (based on call depth/quality), including full coding regions of *ASXL1*, *B2M*, *BCL2*, *BCOR*, *BCORL1*, *BIRC3*, *BRAF*, *CARD11*, *CXCR4*, *DDX41*, *DNMT3A*, *ELANE*, *EZH2*, *ETV6*, *FBXW7*, *GATA2*, *GNA13*, *KLF2*, *KRAS*, *MAP2K1*, *MEF2B*, *NOTCH1*, *NOTCH2*, *NRAS*, *PIM1*, *POT1*, *PTEN*, *PTPRD*, *SAMHD1*, *SETD2*, *SF3B1*, *SH2B3*, *STAT6*, *TERC*, *TERT*, *TET2*, *TP53*, and

*ZRSR2* and the recurrently mutated regions (from public variant databases) of *CD79B*, *CREBBP*, *KIT*, *MYD88*, *PIK3CA*, *PIK3CD*, *PIK3CG*, *RPS15*, *U2AF1*, and *XPO1*. Mutational data were examined in relation to PFS, which was defined as the time from random assignment to disease progression or death from any cause. Data cutoff was the same as the published primary analysis (15 September 2020).

### Statistical analysis

Survival analysis using Kaplan-Meier analysis was performed to determine the median time of PFS between acalabrutinib and ibrutinib for patients who developed mutations during the trial. Proportional-hazards Cox regression analysis was used to calculate the hazard ratio and corresponding *P* value to assess whether a significantly increased risk of developing a mutation in 1 treatment arm vs the other existed. Median VAFs were calculated as the median of the maximum VAF values derived by gene mutation and by patient. For genes with mutations present in both treatments in  $\geq 2$  patients, *P* values were calculated using Wilcoxon rank sum test to determine significant difference at 95% confidence.

The study protocol and informed consent were approved by the appropriate institutional review board/independent ethics committee at each of the study sites before initiation of the study and during the study.

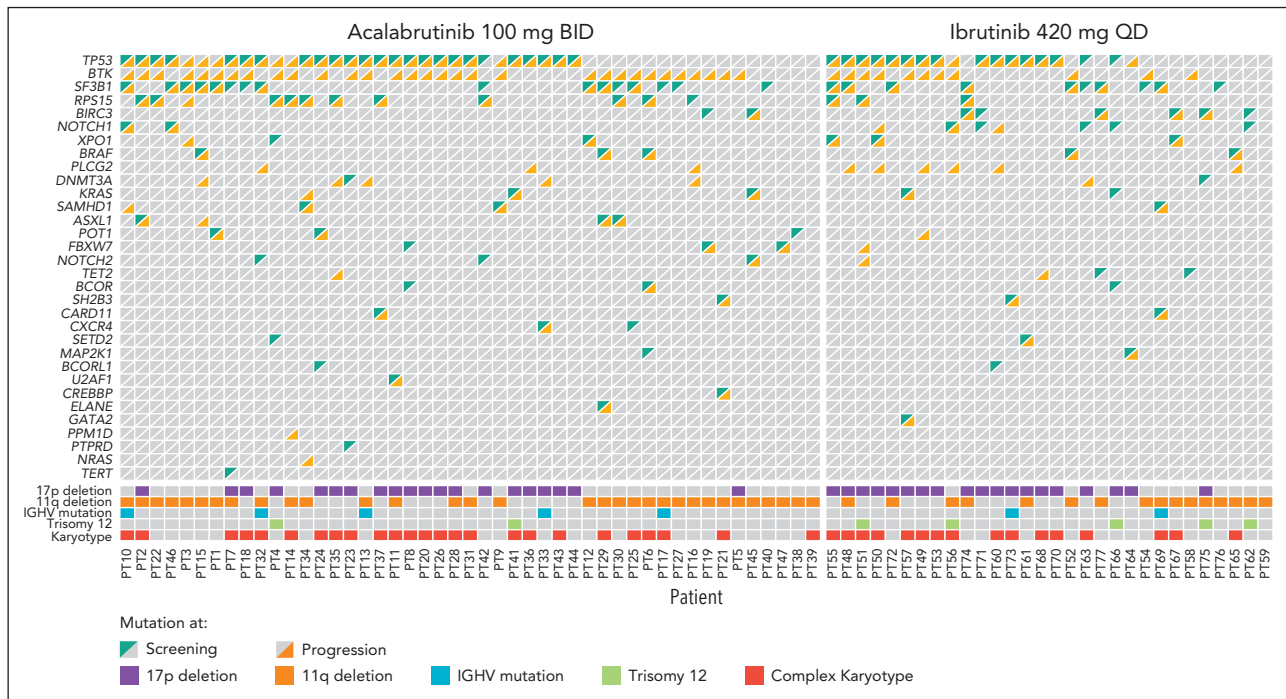
## Results

### Patients

In total, 268 and 265 patients were randomly assigned to receive acalabrutinib and ibrutinib, respectively. Demographics and baseline characteristics were reported previously.<sup>20</sup> At baseline, 45.1% and 45.3% of acalabrutinib- and ibrutinib-treated patients, respectively, had del(17p), 62.3% and 66.0% had del(11q), 37.3% and 42.3% had *TP53* mutations, 82.1% and 89.4% had unmutated immunoglobulin heavy chain variable region genes (IGHV), and 46.3% and 47.2% had a complex karyotype.<sup>20,21</sup>

### Mutation analysis

Paired (baseline and progression) samples were available and included in the analysis for 47 of 82 (57.3%) and 30 of 68 patients (44.1%) who experienced disease progression while receiving acalabrutinib and ibrutinib, respectively (supplemental Figure 1, available on the *Blood* website). One additional acalabrutinib-treated patient and 6 additional ibrutinib-treated patients who had Richter transformation as their mode of progression were excluded from analysis; mutational analysis for these patients can be found in supplemental Figures 2 and 3. Full data (excluding patients with Richter transformation) including mutations at screening and emergent mutations for both treatment arms are presented in Figure 1. The most common mutations at screening were *TP53* mutations in both groups (supplemental Figure 4). Baseline cytogenetics for patients included in this analysis are summarized in Table 1. A summary of the change in mutations by the end of treatment is presented in supplemental Figure 5. Among patients with paired samples, the median time to progression was numerically longer for acalabrutinib vs ibrutinib (32.9 months vs 21.9 months, respectively), but the PFS hazard ratio was not



**Figure 1. Mutations by treatment arm.** BID, twice daily; QD, once daily.

significantly different between treatment groups (supplemental Figure 6).

No *BTK* mutations were observed at screening. Acquired *BTK* mutations were observed in 31 acalabrutinib-treated patients (66.0%) and 11 ibrutinib-treated patients (36.7%) at time of progression (Table 2). The median VAF for *BTK* mutations was not significantly different in the acalabrutinib group (16.1%) vs the ibrutinib group (15.6%; supplemental Table 1). When analyzed by *BTK* mutation status in both treatment arms combined, time to progression was significantly ( $P = .03$ ) longer in patients with vs without a *BTK* mutation (Figure 2). Among those with acquired *BTK* mutations, 29 of 31 acalabrutinib-treated (93.5%) and 10 of 11 ibrutinib-treated patients (90.9%) had C481S mutations; 2 (6.5%) and 2 (18.2%) had C481F mutations; 2 (6.5%) and 1 (9.1%) had C481Y mutations; and 1 (3.2%) and 1 (9.1%) had C481R mutations (Figure 3A). The VAF

for C481S mutations ranged from 0.7% to 95.6% with acalabrutinib and from 2.0% to 67.3% with ibrutinib (Figure 3B). Of 31 acalabrutinib-treated patients, 9 (29.0%) had T474I mutations (gatekeeper mutation), only 1 of which did not co-occur with *BTK* C481 mutations; VAF ranged from 0.5% to 4.5%. A novel E41V mutation within the pleckstrin homology domain of *BTK* was seen in 1 acalabrutinib-treated patient, with a VAF of 16.1% (Figure 3A-B). Initial preclinical investigation in TMD8 cells suggests this E41V mutation may not independently confer resistance to acalabrutinib (see methodology and results in supplemental Figure 7). In the ibrutinib group, L528W (kinase-dead mutation) and A428D mutations were observed in 1 patient (and did not co-occur with C481S mutation), with VAFs of 4.6% and 8.7%, respectively, and 1 patient had C481W mutation (VAF, 4.2%; Figure 3A-B). No statistical difference was seen in the proportions of acalabrutinib- or ibrutinib-treated patients who acquired *BTK* mutations among patients with

**Table 1. Baseline genetics**

Baseline genetics, n (%)	Acalabrutinib, 100 mg BID (n = 47)	Ibrutinib, 420 mg QD (n = 30)	P value
11q deletion	32 (68.1)	16 (53.3)	.232
17p deletion	20 (42.6)	19 (63.3)	.103
Unmutated IGHV	42 (89.4)	28 (93.3)	.699
Complex karyotype	25 (53.2)	16 (53.3)	1
<i>TP53</i> mutation	24 (51.1)	16 (53.3)	1
Trisomy 12 positive	2 (4.3)	5 (16.7)	.103

BID, twice daily; QD, once daily.

**Table 2. Emergent mutations summary**

Gene, n (%)	Acalabrutinib, 100 mg BID (n = 47)	Ibrutinib, 420 mg QD (n = 30)	P value
<i>BTK</i>	31 (66.0)	11 (36.7)	.0185
<b>By baseline cytogenetics*</b>			
11q deletion	24 (77.4)	5 (45.5)	.0664
17p deletion	12 (38.7)	7 (63.6)	.18
Unmutated IGHV	28 (90.3)	11 (100.0)	.554
Complex karyotype	18 (58.1)	8 (72.7)	.485
Trisomy 12 positive	1 (3.2)	2 (18.2)	.163
<i>TP53</i>	6 (12.8)	2 (6.7)	.472
<i>DNMT3A</i>	5 (10.6)	1 (3.3)	.395
<i>PLCG2</i>	3 (6.4)	6 (20.0)	.142
<i>ASXL1</i>	1 (2.1)	0	—
<i>KRAS</i>	1 (2.1)	0	—
<i>NRAS</i>	1 (2.1)	0	—
<i>PPM1D</i>	1 (2.1)	0	—
<i>RPS15</i>	1 (2.1)	0	—
<i>SAMHD1</i>	1 (2.1)	0	—
<i>TET2</i>	1 (2.1)	1 (3.3)	1
<i>XPO1</i>	1 (2.1)	0	—
<i>FBXW7</i>	0	1 (3.3)	—
<i>NOTCH2</i>	0	1 (3.3)	—
<i>NOTCH1</i>	0	2 (6.7)	—
<i>POT1</i>	0	1 (3.3)	—
Any emergent non- <i>BTK</i> mutation†	14 (29.8)	10 (33.3)	.804
Any emergent mutation‡	36 (76.6)	16 (53.3)	.0464

Abbreviations are explained in Table 1.

\*Percentages based on patients with *BTK* mutation.

†Patients who had any newly emergent mutation during treatment in non-*BTK* genes (ie, a new mutation that was not present at baseline, excluding patients with *BTK* mutations).

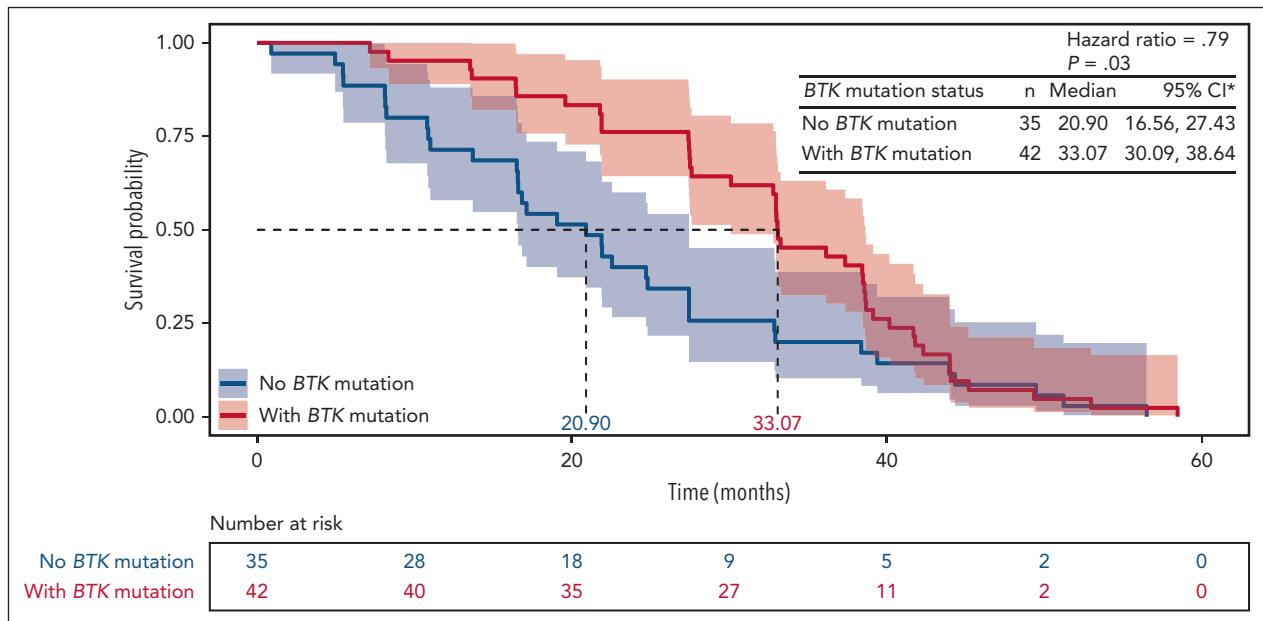
‡Patients who had any newly emergent mutation during treatment in any gene including *BTK* (ie, a new mutation that was not present at baseline).

del(17p), del(11q), complex karyotype, unmutated IGHV, or trisomy 12 positivity (Table 2).

No *PLCG2* mutations were observed at screening. Emergent *PLCG2* mutations occurred in 3 acalabrutinib-treated (6.4%) and 6 ibrutinib-treated patients (20.0%;  $P = .142$ ; Table 2), with median VAFs of 1.9% and 9.5%, respectively (supplemental Table 1); only 1 acalabrutinib-treated patient had co-occurrence of *BTK* and *PLCG2* mutations vs 4 ibrutinib-treated patients (Figure 3A). One patient in the acalabrutinib group and 3 in the ibrutinib group had  $\geq 4$  co-occurring *PLCG2* mutation variants. The most common acquired *PLCG2* variants in acalabrutinib- and ibrutinib-treated patients, respectively, were M1141K (1 vs 3 patients), S707F (0 vs 3 patients), D993H

(0 vs 3 patients), and R665W (2 vs 2 patients; Figure 3A). All other variants occurred in 1 patient each.

Preexisting *TP53* mutations were present in 25 (53.2%) and 16 patients (53.3%) at screening, among whom 1 acalabrutinib-treated patient and 2 ibrutinib-treated patients lost *TP53* mutation by the end of treatment (all 3 had del(17p) at baseline; supplemental Figure 5). After *BTK*, *TP53* mutations were the next most frequent emergent mutation in the acalabrutinib arm ( $n = 6$  [12.8%]); 2 patients (6.7%) in the ibrutinib arm had emergent *TP53* mutations (Table 2); the median VAF was 6.0% in the acalabrutinib arm and 37.3% in the ibrutinib arm (supplemental Table 1). The VAF for *TP53* mutations at screening and the end of treatment for each patient is shown in



**Figure 2. PFS by BTK mutation status.** \*Kaplan-Meier survival estimate. CI, confidence interval.

supplemental Figure 8. Six acalabrutinib-treated patients and 1 ibrutinib-treated patient had *TP53* and *BTK* comutations (the 1 ibrutinib-treated patient had co-occurring *TP53*, *BTK*, and *PLCG2* mutations; supplemental Figure 9).

Additional emergent mutations observed with both acalabrutinib and ibrutinib were *DNMT3A* and *TET2* (Table 2); among the few patients who had mutations in these genes at screening, these mutations were lost by the end of treatment (supplemental Figures 4 and 5). Data regarding additional mutations and associated VAF at screening and the end of treatment are shown for the *SF3B1* gene in supplemental Figure 10 and for the *RPS15*, *BIRC3*, and *NOTCH1* genes in supplemental Figure 11.

## Discussion

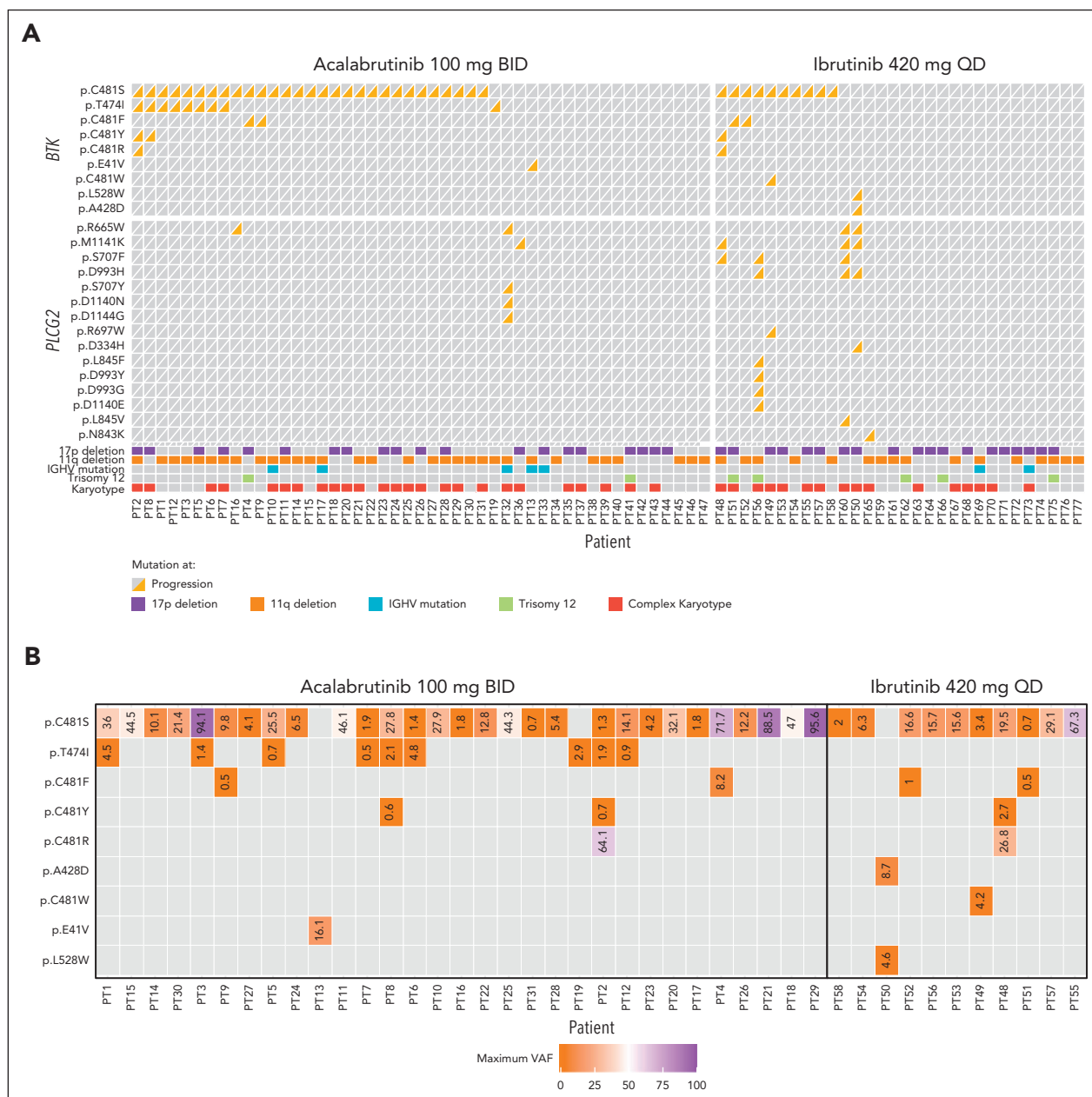
This analysis of the ELEVATE-RR study provided an opportunity to further characterize the profile of mutations observed in patients who progress on acalabrutinib and ibrutinib within a well-defined cohort of patients. Overall, the most common emergent mutation with both treatments, *BTK* C481S, was similar; however, the distribution of other mutations, including their respective VAFs, varied between treatment arms. Not all patients who progressed had a mutation in *BTK* C481, but in those who did, the VAF was highly variable; therefore, other mechanisms of resistance may exist. Baseline cytogenetics did not appear to result in differences between treatment arms in the proportion of patients with *BTK* mutations. No particular pattern regarding the proportion of patients with non-*BTK* mutations was observed in either treatment arm. Emergent *BTK* mutation was associated with longer time to progression than the absence of *BTK* mutation.

The rate of emergent *BTK* mutations reported with acalabrutinib at relapse in our study (66%) was consistent with the rate of *BTK* mutations at relapse reported previously with acalabrutinib

in a single-center study of patients with treatment-naïve or R/R CLL (69%).<sup>12</sup> However, the proportion of emergent *BTK* mutations seen in the ibrutinib arm (37%) at relapse in our study was much lower than that previously reported in the literature (49%-67%), including real-world evidence.<sup>11,22</sup> A greater number of samples were available for analysis in the acalabrutinib arm vs ibrutinib arm ( $n = 47$  vs  $n = 30$ ) and a greater number of patients in the ibrutinib arm ( $n = 6$ ) were also excluded vs the acalabrutinib arm ( $n = 1$ ) from the analysis due to Richter transformation, resulting in a greater proportion of paired samples being included for acalabrutinib (57% of progressed patients) than ibrutinib (44% of progressed patients), which could have affected the results from our analysis. With covalent BTKis, C481 mutations are typically the most common resistance mutations encountered,<sup>11</sup> and most of the *BTK* mutations (>50%) in both treatment groups of this study were C481 mutations.

Mutations occurring at codon T474 are considered a gate-keeper change because they often interfere with BTKi (both covalent and noncovalent) binding to BTK, allowing for normal B-cell signaling.<sup>23</sup> In patients with ibrutinib resistance, the T474I mutation has been previously observed co-occurring with the C481S mutation.<sup>7</sup> Co-occurring mutations in *BTK* have been observed as a potential additional escape mechanism for BTKis based on preclinical data.<sup>24</sup> Both of these mutations are considered kinase proficient, still allowing BTK kinase activity in the presence or absence of BTKis.<sup>25</sup> T474I mutations were observed in 9 acalabrutinib-treated patients in our study, albeit at low VAF. In all but 1 of these patients, *BTK* C481S was also present.

The L528W mutation results in a kinase-dead BTK, hindering BTK catalytic activity; however, B-cell signaling is thought to continue via a BTK scaffolding mechanism that recruits other kinases for B-cell signaling.<sup>25,26</sup> A recent study of the covalent BTKi zanubrutinib also identified *BTK* C481 mutations in 5 of 8 patients



**Figure 3. Emergent BTK and PLCG2 variants.** (A) BTK and PLCG2 variants; (B) BTK mutation variant allele frequency.

with zanubrutinib resistance, 1 of whom also harbored an L528W mutation.<sup>13</sup> Another study showed that the L528W mutation was more prevalent in patients with CLL who had disease progression while receiving zanubrutinib than those receiving ibrutinib.<sup>27</sup> Similarly, mutational analysis of the phase 3 ALPINE study showed L528W mutation in 2 of 5 patients with BTK mutations treated with zanubrutinib and in none of the 3 patients with BTK mutations treated with ibrutinib.<sup>28</sup> In this study, L528W mutation was observed in 1 ibrutinib-treated patient and no acalabrutinib-treated patients. We also observed a novel E41V mutation at relapse in 1 acalabrutinib-treated patient but no ibrutinib-treated patients. A previous in vitro study in murine NIH 3T3 cells demonstrated the E41K mutation to be a BTK-activating mutation.<sup>29</sup> Mutations at this location in the pleckstrin homology domain of BTK have resulted in higher binding affinity for inositol 1,2,3,4,5,6-hexakisphosphate, which may be involved in

hematopoietic cell differentiation by activating the BTK/Tec/ITK family.<sup>30</sup> To our knowledge, our study is the first time a BTK mutation at this residue has been observed in a treated population. The clinical relevance of the VAF of the specific mutations discussed above (C481, T474I, L528W, and E41K), however, is not well understood and is an area for further research.

Regarding other gene mutations observed in our study, PLCG2 mutations have been shown previously to confer resistance to ibrutinib by promoting B-cell receptor signaling despite continued inhibition of BTK by ibrutinib.<sup>10</sup> PLCG2 mutations were the second most frequent emergent mutations observed with ibrutinib after BTK mutations in our study, although the difference between treatment arms was not significant ( $P = .142$ ). Certain PLCG2 variants have been shown previously to be associated with ibrutinib resistance<sup>31</sup> and appeared with

both acalabrutinib and ibrutinib in our analysis; *PLCG2* mutations R665W and M1141K were reported in both arms, whereas other mutations were seen only in the ibrutinib arm (S707F, D993H, D993Y, L845F, and L845V) or only in the acalabrutinib arm (S707Y and D1140N). *TP53* mutations were the second most common emergent mutations in acalabrutinib-treated patients after *BTK* mutations. Although *TP53* mutation typically predisposes patients to relapse, *TP53* mutation is not a known cause of disease progression with BTKi therapy, whereas mutated *BTK* is often associated with relapse.<sup>32</sup> There were 3 patients whose preexisting *TP53* mutations were no longer detectable at progression (1 treated with acalabrutinib and 2 treated with ibrutinib), and all 3 patients had 17p deletion. Loss of preexisting *TP53* mutations has been observed previously in ibrutinib-treated patients.<sup>22</sup>

Despite shared resistance mutations such as C481S, differing patterns of mutation frequency, mutation VAFs, and uncommon *BTK* variants were observed with acalabrutinib vs ibrutinib in this R/R CLL population. For example, T474I occurred with acalabrutinib but not with ibrutinib. This analysis established a mutational profile in this population using a unique comparative data set; however, because of the limited sample size, the clinical significance of the mutations data reported herein is not known. In addition, for ~33% of patients with disease progression, no emergent mutations in *BTK* were detected, and these patients had shorter PFS, suggesting additional research is needed to better understand mechanisms of resistance that may occur outside the B-cell receptor pathway. It is also not clear whether the higher-risk genomic features of patients in ELEVATE-RR contributed to genetic instability or affected the generalizability of the results. With limited data, the mechanism of resistance to BTKi is becoming increasingly complex. The ability to clinically sequence covalent to noncovalent BTKis may be dependent on the combination of co-occurring mutations that impart resistance to covalent and noncovalent BTKis and the VAF of each mutational clone in the tumor. It will become increasingly important to further understand the patterns of mutations commonly observed with the various BTKis to best optimize and appropriately sequence these important drugs for their maximal clinical benefit.

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## Authorship

Contribution: J.C.B. designed the study; J.A.W., W.J., T.R., Á.I., A.P.K., P.G., J.C.B., and J.F.S. were study investigators; J.A.W., W.J., T.R., Á.I., A.P.K., P.G., J.C.B., J.F.S., and R.L. provided patients or study materials; D.J., W.J., T.R., Á.I., J.C.B., S.L., S.B., T.-H.L., G.d.B., and R.L. participated in collection and assembly of data; D.J., J.C.B., S.L., S.B., N.M., G.D.J., and S.R. participated in data analysis; J.A.W., D.J., Á.I., A.P.K., P.G., J.C.B., J.F.S., S.B., T.-H.L., N.M., G.D.J., and V.M. participated in data interpretation; J.A.W., D.J., W.J., Á.I., P.G., J.C.B., T.-H.L., N.M., and G.D.J. participated in manuscript preparation; and all authors participated in the critical review and revision of the manuscript and provided approval for the manuscript submission.

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## Footnotes

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Data underlying the findings described in this manuscript may be obtained in accordance with AstraZeneca's data sharing policy described at <https://astrazenecagrouptrials.pharmacm.com/ST/Submission/Disclosure>. Data for studies directly listed on Vivli can be requested through Vivli at [www.vivli.org](http://www.vivli.org). Data for studies not listed on Vivli can be requested through Vivli at <https://vivli.org/members/enquiries-about-studies-not-listed-on-the-vivli-platform/>. AstraZeneca Vivli member page is also available outlining further details at <https://vivli.org/ourmember/astrazeneca/>.

The online version of this article contains a data supplement.

There is a [Blood Commentary](#) on this article in this issue.

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