Acquired mutations in patients with relapsed/refractory chronic lymphocytic leukemia (CLL) that progressed in the ALPINE study

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ABSTRACT

Objectives: Patients who receive covalent Bruton tyrosine kinase inhibitors (cBTKis) for CLL can develop drug resistance, leading to disease progression. cBTKi binding site mutations (C481) are most common. Less frequent are non-C481 mutations (eg, at T474 and L528). For insights into cBTKi resistance in a randomized CLL patient population, we performed next-generation sequencing (NGS) on samples from patients who progressed on zanubrutinib or ibrutinib in the phase 3 ALPINE study (NCT03734016).

Methods: Progressive disease (PD) per Hallek et al (*Blood*. 2008) was determined by independent review (n=139) and/or investigator (n=132); 57 patients (median follow-up: zanubrutinib, 25.4 months; ibrutinib, 28.1 months; median prior lines of therapy, 1) had PD samples collected (zanubrutinib, n=26; ibrutinib, n=31). Paired peripheral blood samples collected at baseline and at or after PD and prior to subsequent therapy from patients without Richter transformation at PD were included (zanubrutinib, n=24; ibrutinib, n=28) (**Table 1**). A high-sensitivity NGS panel of 106 genes, including *BTK, PLCG2,* and 27 putative CLL driver genes, was used. *BTK* and *PLCG2* mutations were reported at a variant allele frequency (VAF) of ≥0.25%; for all other genes, pathogenic mutations at a VAF ≥1%. Chromosome abnormalities such as del(17p), IGHV mutation, and complex karyotype (CKT) status ≥3 were assessed at baseline.

Results: At baseline, no *BTK* mutations were detected; 2 patients had *PLCG2* mutations (zanubrutinib, R589C; ibrutinib, E914STOP). Nine patients acquired *BTK*/*PLCG2* mutations: 8 in *BTK* (zanubrutinib, n=5 [20.8%]; ibrutinib, n=3 [10.7%]), 2 in *PLCG2* (both in ibrutinib, 7.1%); 1 patient had both *BTK* and *PLCG2* mutations. Of 18 single-nucleotide variants (SNV) in *BTK*, 77.8% (zanubrutinib, n=11; ibrutinib, n=3) were at C481. Non-C481 *BTK* mutations were detected in 3/24 patients at PD on zanubrutinib (**Table 2**). Median treatment duration at PD was shorter in patients without (zanubrutinib: n=19, 16.8 months; ibrutinib: n=25, 15.9 months) vs with (zanubrutinib: n=5, 29.7 months; ibrutinib: n=3, 30.8 months) acquired *BTK* mutations. At baseline, SNV or indels in 18/27 driver genes were observed in 48/52 pts. Most frequent: *NOTCH1* (n=21), *TP53* (n=19), *BRAF* (n=10), *SF3B1* (n=8), and *ATM* (n=8). Twenty-three patients had copy number aberrations (CNA) in 9/27 driver genes. Most frequent: *CCND2* (n=10, amplification [amp]), *ATM* (n=8, deletion [del]), *TP53* (n=6, del), and *KMT2D* (n=6, amp). At PD, 6 patients acquired SNV (zanubrutinib: *TP53* and *XPO1* in n=1; ibrutinib: *TP53*, *SETD2*, *SF3B1* [each n=1], *ASXL1* in n=2). Ten patients had acquired CNA in driver genes (most frequent: *KRAS* amp: zanubrutinib,

n=3; *NRAS* amp: ibrutinib, n=2; *CDKN1B* amp: zanubrutinib, n=2, ibrutinib, n=1; *BIRC3* del: ibrutinib, n=2). Acquired driver gene mutations were not associated with del(17p), IGHV mutation, or CKT status.

Conclusions: Of the 52 pts, most (82.6%) did not acquire *BTK* or *PLCG2* mutations. Among the zanubrutinib pts, 12.5% developed non-C481 *BTK* mutations. These data suggest *BTK* and/or *PLCG2* mutations are not the sole factors driving PD in this population. Given the low incidence of non-C481 mutations in patients with PD in ALPINE, patients with CLL treated with cBTKis likely remain sensitive to other BTK-targeting therapies.

Table 1. Paired Sample Availability and Richter Transformation Status at PD

Patients, n	Zanubrutinib (n=26)	Ibrutinib (n=31)	Total (N=57)
Paired baseline and PD samples available; no RT at PD	24	28	52
PD sample but no baseline sample; no RT at PD	0	1[a]	1
Paired baseline and PD samples available; RT at PD	2[a]	0	2
PD sample but no baseline sample; RT at PD	0	2[a]	2

Of 53 patients without Richter Transformation (RT) at PD, none had subsequent RT reported as of data cutoff: August 8, 2022.
[a] No acquired *BTK/PLCG2* mutations were detected.

Table 2. Acquired *BTK* and *PLCG2* Mutations

Patient ID	Treatment arm	Acquired *BTK* mutation at PD: coding DNA description (VAF, %)	Acquired *BTK* mutation at PD: protein description	Acquired *PLCG2* mutation at PD: coding DNA description (VAF, %)	Acquired *PLCG2* mutation at PD: protein description
1	Ibrutinib	c.1442G>C (1.29)	p.C481S	Not detected	Not detected
2	Ibrutinib	c.1442G>C (7.95)	p.C481S	Not detected	Not detected
				Not detected	Not detected
3	Ibrutinib	c.1442G>C (0.88)	p.C481S	c.2535A>C (0.6)	p.L845F
		c.127G>C (0.51)	p.D43H		
4	Ibrutinib	Not detected	Not detected	c.3422T>A (5.69)	p.M1141K
5	Zanubrutinib	c.1442G>C (8.80)	p.C481S	Not detected	Not detected
6	Zanubrutinib	c.1283C>A (31.10)	p.A428D	Not detected	Not detected
		c.1442G>C (4.72)	p.C481S		
		c.1441T>A (2.48)	p.C481S		
7	Zanubrutinib	c.1442G>C (16.22)	p.C481S	Not detected	Not detected
		c.1583T>G (8.22)	p.L528W		
		c.1441T>A (4.28)	p.C481S		
		c.1442G>A (1.83)	p.C481Y		
		c.1442G>T (1.70)	p.C481F		
		c.1441T>C (1.01)	p.C481R		
8	Zanubrutinib	c.1583T>G (1.76)	p.L528W	Not detected	Not detected
9	Zanubrutinib	c.1442G>C (74.39)	p.C481S	Not detected	Not detected
		c.1441T>C (2.30)	p.C481R		
		c.1441T>A (0.45)	p.C481S		