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

Authors: Emmanuelle Ferrant,[1] Jennifer R. Brown,[2] Jessica Li,[3] Barbara F. Eichhorst,[4] Nicole Lamanna,[5] Susan M. O'Brien,[6] Constantine S. Tam,[7] Luqui Qiu,[8] Ruiqi Huang,[9] Yang Shi,[10] Adam Idoine,[3] Tommi Salmi,[11] Aileen Cohen,[3] Mazyar Shadman[12]

Affiliations: [1]Département Hématologie, CHU de Lyon-Sud, France; [2]Dana-Farber Cancer Institute, Boston, MA, USA; [3]BeiGene USA, Inc, San Mateo, CA, USA; [4]Department of Internal Medicine, University of Cologne, Center for Integrated Oncology Aachen Bonn Köln Düsseldorf, Cologne, Germany; [5]Columbia University, New York, NY, USA; [6]University of California, Irvine, Irvine, CA, USA; [7]Alfred Hospital and Monash University, Melbourne, VIC, Australia; [8]Institute of Hematology and Blood Diseases Hospital, Chinese Academy of Medical Sciences, Tianjin, China; [9]BeiGene (Shanghai) Co, Ltd, Shanghai, China; [10]BeiGene (Beijing) Co, Ltd, Beijing, China; [11]BeiGene International GmbH, Basel, Switzerland; [12]Fred Hutchinson Cancer Center, University of Washington School of Medicine, Seattle, WA, USA

ABSTRACT

Introduction: Patients receiving covalent Bruton tyrosine kinase inhibitors (cBTKis) for CLL can develop drug resistance, leading to progressive disease (PD). cBTKi binding site mutations (C481) are most common. For insight 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).

Patients and méthodes: PD (per Hallek et al. *Blood*. 2008) was determined by independent review (n=139) and/or investigator (n=132); 57 patients (zanubrutinib, n=26; ibrutinib, n=31) had PD samples collected (median follow-up: zanubrutinib, 25.4 months; ibrutinib, 28.1 months). Paired blood samples collected at baseline and at or after PD and before subsequent therapy from patients without Richter transformation at PD were included (zanubrutinib, n=24; ibrutinib, n=28). A 106-gene NGS panel including 27 putative CLL driver genes was used (*BTK* and *PLCG2* mutations, variant allele frequency [VAF] ≥0.25%; all other genes: pathogenic mutations, VAF ≥1%). Baseline chromosome abnormalities were assessed.

Results: No baseline *BTK* mutations were detected. Nine patients acquired *BTK/PLCG2* mutations: 8 in *BTK* (zanubrutinib, n=5; ibrutinib, n=3); 2 in *PLCG2* (both ibrutinib; 1 in both *BTK* and *PLCG2*). Of 18 *BTK* single-nucleotide variants (SNVs), 77.8% (zanubrutinib, n=11; ibrutinib, n=3) were at C481; 3/24 zanubrutinib patients had non-C481 *BTK* mutations. 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. Baseline mutations in 18/27 driver genes were observed in 48/52 patients; 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 (CNAs) in 9/27 driver genes; most frequent: *CCND2* (n=10), *ATM* (n=8), *TP53* (n=6), and *KMT2D* (n=6). At PD, 6 patients acquired SNVs (zanubrutinib: *TP53* and *XPO1* in n=1; ibrutinib: *TP53*, *SETD2*, *SF3B1* [each n=1], *ASXL1* in n=2). Ten patients acquired CNAs in driver genes (most frequent: *KRAS* [zanubrutinib, n=3]; *NRAS* [ibrutinib, n=2]; *CDKN1B* [zanubrutinib, n=2; ibrutinib, n=1]; *BIRC3* [ibrutinib, n=2]). Acquired driver gene mutations were not associated with del(17p), IGHV mutation, or complex karyotype status.

Conclusion: Of 52 patients, most (82.6%) did not acquire *BTK/PLCG2* 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.