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ORAL ABSTRACTS

642.CHRONIC LYMPHOCYTIC LEUKEMIA: CLINICAL AND EPIDEMIOLOGICAL

Genomic Evolution and Resistance during Pirtobrutinib Therapy in Covalent BTK-Inhibitor (cBTKi) Pre-Treated Chronic Lymphocytic Leukemia Patients: Updated Analysis from the BRUIN Study

Jennifer R. Brown, MD PhD[1], Sai Prasad Desikan, MD[2], Bastien Nguyen, PhD[3], Helen Won, PhD[3], Shady I. Tantawy, MD[4], Samuel McNeely, PhD[5], Narasimha Marella, PhD[3], Kevin Ebata, PhD[3], Jennifer A. Woyach, MD[2], Krish Patel, MD[6], Constantine S. Tam, MD MBBS[7], Toby A. Eyre, MBChB, DipMedEd, MRCP, FRCPath, MD[8], Chan Y. Cheah, MBBS, FRACP, FRCPA, DMSc[9], Nirav N. Shah, MD[10], Paolo Ghia, MDPhD[11], Wojciech Jurczak, MDPhD[12], Minna Balbas, PhD[3], Binoj Nair, PhD[3], Paolo Abada, MD[3], Chunxiao Wang, PhD[5], Ying (Denise) Wang, PhD[3], Lindsey E. Roeker, MD[13], Varsha Gandhi, PhD[14], William G. Wierda, MD PhD[4]

[1] Chronic Lymphocytic Leukemia Center, Division of Medical Oncology, Dana-Farber Cancer Institute and Harvard Medical School, Boston, MA
[2] The Ohio State University Comprehensive Cancer Center, Columbus, OH
[3] Loxo@Lilly, Indianapolis, IN
[4] MD Anderson Cancer Center, Houston, TX
[5] Eli Lilly and Company, Indianapolis, IN
[6] Swedish Cancer Institute, Seattle, WA
[7] Alfred Health and Monash University, East Melbourne, Australia
[8] Oxford University Hospitals NHS Foundation Trust, Churchill Cancer Center, Oxford, United Kingdom
[9] Linear Clinical Research and Sir Charles Gairdner Hospital, Perth, Australia
[10] Medical College of Wisconsin, Milwaukee, WI
[11] Università Vita-Salute San Raffaele and IRCCS Ospedale San Raffaele, Milan, Italy
[12] Maria Skłodowska - Curie National Research Institute of Oncology, Kraków, Poland
[13] Memorial Sloan Kettering Cancer Center, New York, NY
[14] Department of Experimental Therapeutics, The University of Texas MD Anderson Cancer Center, Houston, TX

Background: The majority of patients (pts) discontinue covalent (c) Bruton tyrosine kinase (BTK) inhibitors (BTKi) for either progression or intolerance. BTK Cysteine 481 substitution is known to contribute to cBTKi acquired resistance to ibrutinib, acalabrutinib, and zanubrutinib.Pirtobrutinib, a highly selective, non-covalent (reversible) BTKi has favorable oral pharmacology that enables continuous BTK inhibition throughout the daily dosing interval regardless of intrinsic rate of BTK turnover. Pirtobrutinib has demonstrated broad efficacy in pts with chronic lymphocytic leukemia (CLL) following prior therapy, including those treated with a prior cBTKi, independent of BTK C481 mutational status (Mato *et al*, NEJM, 2023). Here we report the largest systematic evaluation of genomic evolution in pts with CLL treated with pirtobrutinib conducted to date, using a larger cohort of pts and longer follow-up than previously reported.
Methods: Relapsed cBTKi pre-treated CLL pts in the phase 1/2 BRUIN trial (NCT03740529) who subsequently developed disease progression (PD) on pirtobrutinib monotherapy were included. Targeted next-generation sequencing (NGS) was centrally performed on peripheral blood mononuclear cells collected at baseline and within four months of PD .
Results: As of May 5, 2023, 86cBTKi pre-treated CLL pts had paired NGS data available at baseline and pirtobrutinib progression. In this group, the median age was 69 years (range, 36-86), median number of prior lines of therapy was 4 (range, 1-10), 74 pts (86%) had discontinued prior cBTKi due to PD and 12 pts (14%) discontinued due to toxicity/other. Pts received one or more of the following prior cBTKi: ibrutinib (n=77, 90%), acalabrutinib (n=15, 17%), or zanubrutinib (n=2, 2%). Median time on pirtobrutinib treatment was 16 months (range, 1.2-39 months). Among these 86 pts who ultimately progressed on pirtobrutinib, the ORR (including partial response with lymphocytosis) was 83% (95%CI, 73-90). The most common baseline alterations were mutations in *BTK* (53%), *TP53* (48%), *SF3B1* (35%), *ATM* (23%), *NOTCH1* (20%), *XPO1* (16%), *PLCG2* (14%), and *BCL2* (9%). In 46 pts, 64 *BTK* mutations were detected at baseline and included C481S (n=45), C481F/R/Y (n=11), T474I/F/S (n=6), A428D (n=1), D149G (n=1). Among 42 pts with C481, BTK C481 VAF decrease or complete clearance was observed at PD in the majority of pts (86%, 36/42, complete clearance = 55%, 23/42). NGS of samples at PD showed 69% (59/86) of pts acquired

≥1 mutation. In 38 (44%) pts, 52 acquired *BTK* mutations were detected and most commonly included gatekeeper mutations (T474I/F/S/L/Y, n=25 in 22 pts), kinase-impaired (L528W, n=14 in 14 pts), C481S/R/Y (n=6 in 4 pts) and others proximal to the ATP-binding pocket (n=7 in 5 pts), including D539A/G/H (n=3 in 1 pt), V416L (n=2 in 2 pts), Y545N (n=1) and A428D ([n=1] **Figure**). A total of 83 non-BTK acquired mutations were observed at PD in 45 pts (52%), including 14 *TP53* mutations in 12 pts (14%), 6 *PLCG2* mutations in 6 pts (7%), 6 *PIK3CA* mutations in 6 pts (7%) and 3 *BCL2* mutations in 3 pts (3%).

Conclusions: Despite this cohort representing the first relapsing CLL patients from BRUIN and presenting with frequent baseline BTK mutations, response to pirtobrutinib was high, with an ORR of 83%, and substantial clearance of *BTK* C481 clones. At progression, the majority of pts (56%) either acquired non-BTK mutations or did not acquire any resistance mutations in this targeted panel, suggesting alternative resistance mechanisms. A smaller group of patients (44%) displayed emergence of non-C481 clones, particularly gatekeeper T474 and kinase-impaired L528W mutations. Whether similar patterns of resistance would manifest if pirtobrutinib was utilized in earlier lines of therapy or prior to cBTKi treatment remains uncertain.

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OffLabel Disclosure: Pirtobrutinib is approved in the USA to treat R/R mantle cell lymphoma after at least two lines of systemic therapy including prior BTKi treatment.

Figure. Number of patients with acquired mutations according to *BTK* status at baseline and prior type of cBTKi. The color gradient indicates the mean VAF at progression.

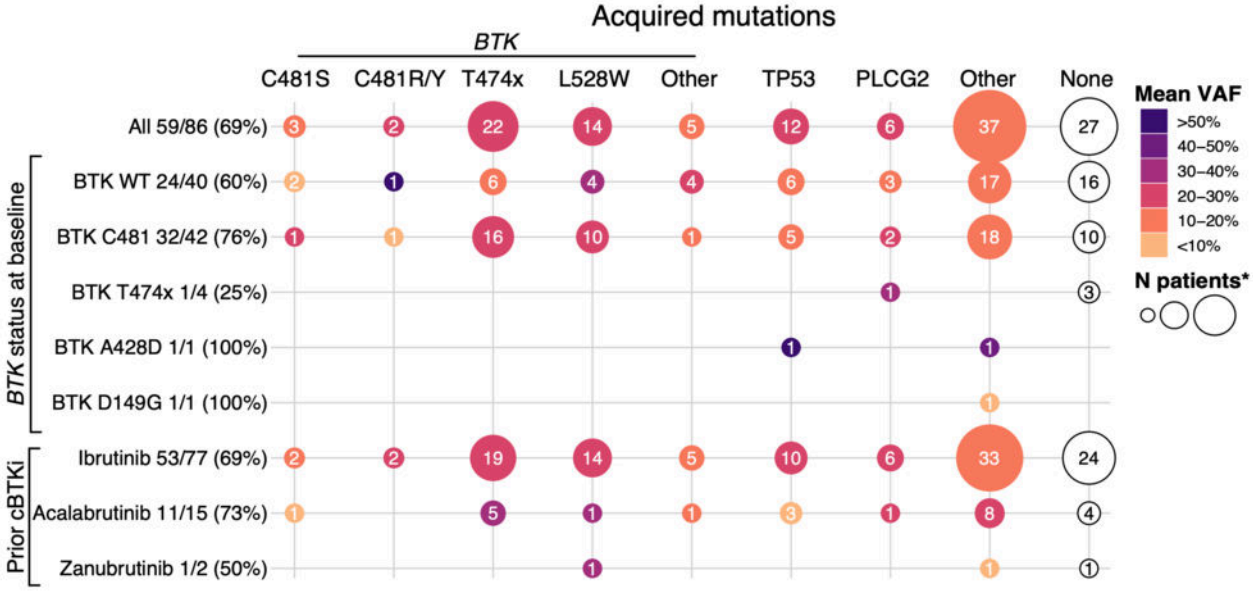

Figure 1

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