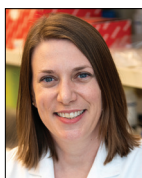


# CLL IN FOCUS

Current Developments in the Management of Chronic Lymphocytic Leukemia

## Pirtobrutinib in Relapsed or Refractory CLL and SLL



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**H&O** What are the mechanisms of action of pirtobrutinib and other Bruton tyrosine kinase (BTK) inhibitors?

**JW** All of the currently available BTK inhibitors work by inhibiting the signaling function of BTK. Ibrutinib (Imbruvica, Pharmacyclics/Janssen), acalabrutinib (Calquence, AstraZeneca), and zanubrutinib (Brukinsa, BeiGene) are all covalent inhibitors of BTK, meaning that they form a covalent bond at the cysteine amino acid at position 481. Pirtobrutinib is different in that it is a noncovalent BTK inhibitor, and binds to sites that are distinct from those where the covalent BTK inhibitors bind.

**H&O** How does pirtobrutinib compare with other BTK inhibitors that are currently used in chronic lymphocytic leukemia (CLL) and small lymphocytic leukemia (SLL)?

**JW** Right now, the data we have on pirtobrutinib pertain to patients who have previously been treated with a covalent BTK inhibitor—ibrutinib, acalabrutinib, or zanubrutinib. These patients discontinued the covalent BTK inhibitor owing to either disease progression or intolerance. Pirtobrutinib is subsequently administered in such cases. When patients relapse while on a covalent BTK inhibitor, switching within the covalent class is not feasible owing to shared mechanisms. However, because pirtobrutinib binds to a different site on BTK, its initial investigation has been as a salvage agent after the covalent BTK inhibitors. The drug is currently approved by the US

Food and Drug Administration (FDA) for use after both a covalent BTK inhibitor and venetoclax; however, ongoing phase 3 studies are investigating the use of pirtobrutinib in earlier lines of therapy (NCT05254743, NCT05023980, NCT04965493, NCT04666038).

Pirtobrutinib effectively filled a niche that no other medication was filling at the time.

**H&O** With the FDA's recent approval of pirtobrutinib for CLL and SLL, how does this impact the current treatment options available for patient care, and what changes can we expect?

**JW** Before the approval of pirtobrutinib, there were no FDA-approved agents that had significant clinical activity in patients who are double-refractory, meaning their CLL has progressed after treatment with a covalent BTK inhibitor and venetoclax. Pirtobrutinib effectively filled a niche that no other medication was filling at the time. Lisocabtagene maraleucel, also known as liso-cel (Breyanzi, Bristol Myers Squibb) received expanded approval

on March 14 for the same indication. Nevertheless, at the time that pirtobrutinib was approved, it addressed an unmet need in CLL. Patients who have progressed through multiple lines of therapy should always be evaluated for clinical trials. But for patients where a clinical trial might not be the best option or who are unable to participate in one, this approval provides another line of therapy that any oncologist can use to treat their patients.

### **H&O** What are the key findings from studies evaluating pirtobrutinib in relapsed or refractory (R/R) CLL and SLL?

**JW** All of the data currently available comes from the ongoing phase 1/2 BRUIN study, which involves approximately 300 patients with R/R CLL. They were treated with pirtobrutinib monotherapy in both the dose-escalation portion and the expansion phase. In this study, we have observed an overall response rate (ORR) approaching 75% and a median progression-free survival (PFS) of 19.6 months. It also looks like patients with fewer prior lines of therapy tend to exhibit better responses and longer remission durations. This trend is evident when comparing patients previously treated with venetoclax vs those who were not; those with prior venetoclax therapy demonstrated a shorter median PFS, likely attributed to multiple lines of therapy.

### **H&O** What adverse events (AEs) are associated with pirtobrutinib, and how are they managed?

**JW** Pirtobrutinib has proven to be an extremely well-tolerated agent. Its high selectivity for BTK translates to minimal toxicity, with most AEs being grade 1 or 2. Toxicities typically associated with covalent BTK inhibitors, such as hypertension, atrial fibrillation, and arthralgias, were observed at very low rates with pirtobrutinib.

Most patients can tolerate the full dose of pirtobrutinib for their entire treatment duration without the need for dose interruptions or decreases. The dose can be decreased or held if necessary. However, apart from significant events like arrhythmia, severe bleeding episodes, or fungal infection, there is usually no reason to change the dose of therapy.

### **H&O** What are the upcoming studies of pirtobrutinib in CLL/SLL?

**JW** There are several phase 3 trials currently ongoing

as well as numerous investigator-initiated studies either ongoing or in development. These studies are investigating pirtobrutinib either alone or in combination. There are also emerging data suggesting the potential efficacy of pirtobrutinib in Richter's transformation (RT). Although the remission duration may not be long, there appears to be significant activity of pirtobrutinib in patients with RT, making it a potential option for bridging to further treatment modalities.

### **H&O** In your opinion, what's next for pirtobrutinib?

**JW** I am particularly excited to see the data as they mature, especially in combination with drugs like venetoclax or CD20 monoclonal antibodies, to see if we can further improve the remission duration currently observed with pirtobrutinib. Also, I am interested in seeing more data regarding its use as monotherapy in patients who have not previously been exposed to venetoclax or those who do not have a lot of previous lines of treatment.

### **Disclosures**

*Dr Woyach has consulted for AbbVie, AstraZeneca, BeiGene, Genentech, Janssen, Loxo/Lilly, Merck, Newave, and Pharmacyclics; and has received research funding from AbbVie, Janssen, Pharmacyclics, and Schrödinger.*

### **Suggested Readings**

FDA grants accelerated approval to pirtobrutinib for relapsed or refractory mantle cell lymphoma [press release]. FDA. Updated January 27, 2023. Accessed March 28, 2024.

Follows G, Burke JM, Grosicki S, et al. BRUIN CLL-321: a phase 3 open-label, randomized study of pirtobrutinib versus investigator's choice of idelalisib plus rituximab or bendamustine plus rituximab in BTK inhibitor pretreated chronic lymphocytic leukemia/small lymphocytic lymphoma [ASCO abstract TPS7582]. *J Clin Oncol*. 2023;41(16)(suppl).

Mato AR, Shah NN, Jurczak W, et al. Pirtobrutinib in relapsed or refractory B-cell malignancies (BRUIN): a phase 1/2 study. *Lancet*. 2021;397(10277):892-901.

Mato AR, Woyach JA, Brown JR, et al. Pirtobrutinib after a covalent BTK inhibitor in chronic lymphocytic leukemia. *N Engl J Med*. 2023;389(1):33-44.

US FDA approves Bristol Myers Squibb's Breyanzi® as the first and only CAR T cell therapy for adults with relapsed or refractory chronic lymphocytic leukemia (CLL) or small lymphocytic lymphoma (SLL) [press release]. Bristol Myers Squibb. March 14, 2024. Accessed March 28, 2024.

Woyach JA, Brown JR, Ghia P, et al. Pirtobrutinib in post-cBTKi CLL/SLL: ~30 months follow-up and subgroup analysis with/without prior BCL2i from the phase 1/2 BRUIN study [ASH abstract 325]. *Blood*. 2023;142(1)(suppl).

Woyach JA, Coombs CC, Lewis KL, et al. BRUIN CLL-314: a phase 3, open-label, randomized study of pirtobrutinib versus ibrutinib in patients with chronic lymphocytic leukemia/small lymphocytic lymphoma [ASCO abstract TPS7584]. *J Clin Oncol*. 2023;41(16)(suppl).