Pirtobrutinib Shows Promise for Chronic Lymphocytic Leukemia

BY CATLIN NALLEY

A recent Phase I/II study demonstrated the efficacy of pirtobrutinib—a highly selective, noncovalent, BTK inhibitor—as a treatment for heavily pretreated chronic lymphocytic leukemia (CLL) or small lymphocytic lymphoma (SLL) patients who had previously received a covalent BTK inhibitor (N Engl J Med 2023; doi: 10.1056/NEJMoa2300696).

“This is a study of a reversible (noncovalent) BTK inhibitor, pirtobrutinib, in patients with CLL/SLL previously treated with an irreversible (covalent) BTK inhibitor,” noted study author Jennifer Woyach, MD, a hematologist/oncologist at the OSUCCC – James and Professor in the Division of Hematology at The Ohio State University. “Many times, mutations in BTK (C481 site) lead to acquired resistance to covalent BTK inhibitors like ibrutinib/acalabrutinib/zanubrutinib.”

She explained that pirtobrutinib is a reversible, extremely selective, inhibitor of BTK that binds distinct from the covalent BTK inhibitors, so it was hypothesized to be active in patients who are resistant to the covalent BTK inhibitors. “This Phase I/II trial proves this hypothesis and shows that pirtobrutinib is active in patients previously treated with other chronic lymphocytic leukemia therapies, including covalent BTK inhibitors,” Woyach told Oncology Times.

Study Details
The Phase I/II BRUIN trial included patients with relapsed or refractory B-cell cancers who received pirtobrutinib (NCT03740529). This research was conducted in 49 sites across 10 countries, including Australia, France, Italy, Japan, Poland, South Korea, Sweden, Switzerland, the U.K., and the U.S.

Study participants underwent pirtobrutinib monotherapy in either the Phase I or II portions of the study. In Phase I, the drug was administered at dose ranges from 25 mg to 300 mg once daily in 28-day cycles. Patients included in Phase II were given the recommended dose of 200 mg once daily. The researchers continued treatment until disease progression, unacceptable toxicity, or patient withdrawal. If the investigators determined there was ongoing clinical benefit, patients with disease progression were allowed to continue their treatment.

The primary endpoint of this study was overall response rate—partial response or better—per the 2018 International Workshop on Chronic Lymphocytic Leukemia response criteria. Secondary endpoints included overall response, including partial response with lymphocytosis, progression-free survival, overall survival, safety, and exploratory analysis of biomarkers.

Partial findings from the study were previously reported in The Lancet (2021; doi: 10.1016/S0140-6736(21)00224-5). This initial data showed that “pirtobrutinib was safe and active in multiple B-cell malignancies, including patients previously treated with covalent BTK inhibitors,” according to the study authors, who noted this treatment could potentially address a growing unmet need for alternative therapies for these patients.

The most recent results, published in the New England Journal of Medicine, are highlighted below. This data included efficacy results among patients with CLL or SLL who previously received a BTK inhibitor, as well as safety data for the entire CLL/SLL patient population.

Efficacy & Safety Findings
A total of 773 patients with B-cell malignancies were enrolled in the trial between March 21, 2019, and July 29, 2022. This included 317 individuals with CLL or SLL. Of those, 247 previously received at least one BTK inhibitor—ibrutinib (n=216), acalabrutinib (n=44), zanubrutinib (n=7), nemtabrutinib (n=7), vecabrutinib (n=3), spebrutinib (n=3), and tirabrutinib (n=1).

Among CLL/SLL patients with prior BTK inhibitor treatment, the median number of previous lines of therapy was three (range: 1-11), and 40.5 percent also had a BCL2 inhibitor such as venetoclax. Other prior therapies included anti-CD20 antibody (87.9%), chemotherapy (78.9%), PI3K inhibitors (18.2%), chimeric antigen receptor (CAR) T-cell therapy (5.7%), and allogeneic stem cell transplantation (2.4%). In most patients, discontinuation of previous BTK inhibitor therapy occurred due to disease progression (76.9%). BTK inhibitor treatment was stopped in the rest of patients because of toxicity or other reasons (23.1%).

The median age of these 247 patients was 69, and 68 percent were male. Most had an ECOG performance status of 0 (53.8%) followed by 1 (39.3%) and 2 (6.9%). The majority of patients (85%) who were pretreated with a BTK inhibitor were administered at least one dose of pirtobrutinib at the recommended Phase II dose (200 mg once daily), according to Woyach and colleagues.

“In a finding that was consistent with a heavily pretreated population with advanced disease, high-risk molecular features were common,
including the presence of a del(17p) or TP53 mutation or both (90 of 193 patients [46.6%]), complex karyotype (24 of 57 [42%]), and unmutated IGHV (168 of 198 [84.8%]), the researchers noted.

Efficacy data showed that patients who were previously treated with a BTK inhibitor had an overall response rate of 73.3 percent, including four complete responses, one modal partial response, and 176 partial responses (71.3%). When partial response with lymphocytosis was considered, Woyach and colleagues reported an overall response rate of 82.2 percent.

“The percentage of patients with a response, including partial response with lymphocytosis, was consistent across most subgroups defined according to patient demographic characteristics, molecular features, or the extent of additional previous therapy, and the percentage was 56 percent in the small number of patients (n=18) with PLCG2 mutation,” the research team stated.

When looking at the subgroup of patients who previously underwent both a BTK and BCL2 inhibitor, Woyach and colleagues observed an overall response rate of 70 percent. This increased to 79 percent when the researchers included partial response with lymphocytosis.

Among the overall efficacy cohort, the investigators found that—at a median follow-up of 19.4 months—the median progression-free survival was 19.6 months. Patients who were pretreated with both a BTK and BCL2 inhibitor had a median progression-free survival of 16.8 months compared with 22.1 months for those who previously received a BTK inhibitor but not a BCL2 inhibitor.

“Among patients who had received all five classes of available CLL or SLL therapy, including BTK, BCL2, and PI3K inhibitors, as well as chemoimmunotherapy (chemotherapy and an anti-CD20 antibody), the median progression-free survival was 13.8 months,” Woyach and her team noted. “Similar estimates of progression-free survival were observed regardless of BTK C481 mutation status or patient age (<75 vs. ≥75 years), with estimates ranging from 17.5 to 20.0 months.”

As of the data cutoff, 277 (87.4%) of the 317 patients with CLL or SLL who received pirtobrutinib were administered at least one dose at the recommended Phase II dose of 200 mg once daily. The median duration of treatment was 16.5 months for these patients. Among this patient cohort, the most common adverse events were as follows: infections (71%), bleeding (42.6%), and neutropenia (32.5%). Additionally, the most frequently observed adverse events of Grade 3 or higher were infections (28.1%) and neutropenia (26.8%). The most frequently reported treatment-related adverse event of Grade 3 or higher was neutropenia (14.8%), according to Woyach.

“Only 2.8 percent of patients with CLL or SLL discontinued the drug because of a treatment-related adverse event. Moreover, the low incidences of atrial fibrillation, major hemorrhage, and hypertension are encouraging as compared with other agents in the BTK inhibitor class, although additional long-term follow-up is needed to further assess the incidence of these important adverse events,” Woyach and colleagues reported. “The more favorable toxic effect profile that was observed in this analysis is consistent with the high degree of BTK selectivity of pirtobrutinib and a relative absence of off-target inhibition.”

Takeaways & Next Steps
The research team acknowledged this analysis does have limitations that must be considered, including a lack of both an active control group and prospective data for other modern therapies following the use of BTK inhibitors. “[These restraints] limit direct comparisons with other available therapies in this clinical context,” they noted.

“Moreover, some of the subgroups that were defined according to previous therapy or molecular findings have a limited sample size, which led to wide confidence intervals around key efficacy measures,” the investigators said. “Finally, because many patients with CLL or SLL will be treated with BTK inhibitors for a considerable duration, the long-term safety of pirtobrutinib remains to be defined.”

However, despite these limitations, this Phase I/II trial demonstrated the efficacy of pirtobrutinib among patients with heavily pretreated CLL or SLL whose disease progressed during prior treatment with a covalent BTK inhibitor.

“These findings indicate that reestablishing BTK inhibition with pirtobrutinib is a potential therapeutic option regardless of whether previous covalent BTK inhibitor therapy is discontinued owing to disease progression, toxic effects, or other reasons,” Woyach and colleagues suggested.

“This study shows that pirtobrutinib induces a response in over 80 percent of patients with relapsed/refractory chronic lymphocytic leukemia,” emphasized Woyach while discussing the research with Oncology Times. “Responses occur in patients with high-risk disease and even those patients who are ‘dual refractory’; meaning that their disease has progressed after both a BTK inhibitor and a BCL2 inhibitor. This is a group of patients with very limited therapeutic options, so it is very exciting to see the activity of this drug in these patients.”

Pirtobrutinib is currently being evaluated for CLL and other hematologic malignancies in several studies, including multiple international, randomized, Phase III clinical trials where it is being compared to standard-of-care treatments (NCT05023980, NCT05254743, NCT04666038, and NCT04965493).

Catlin Nalley is a contributing writer.