CLL IN FOCUS

Current Developments in the Management of Chronic Lymphocytic Leukemia

The Sequencing of Covalent and Noncovalent BTK Inhibitors in CLL

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H&O What are the most important differences between covalent and noncovalent Bruton tyrosine kinase (BTK) inhibitors?

JW The covalent BTK inhibitors that have US Food and Drug Administration (FDA) approval for use in chronic lymphocytic leukemia (CLL) are ibrutinib (Imbruvica, Pharmacyclics/Janssen), acalabrutinib (Calquence, AstraZeneca), and zanubrutinib (Brukinsa, BeiGene). Covalent BTK inhibitors all have the same binding site, which is a cysteine at amino acid 481 (C481) of the BTK protein, and they form an irreversible covalent bond with that cysteine site. The noncovalent BTK inhibitors, which include the approved agent pirtobrutinib (Jaypirca, Lilly), bind noncovalently at multiple points of contact with the BTK enzyme, and they engage and disengage in a reversible manner. The contact points vary depending on the noncovalent BTK inhibitor. The half-life is longer for noncovalent BTK inhibitors than for covalent BTK inhibitors because consistent drug exposure is needed to accommodate the binding and unbinding. In contrast, covalent BTK inhibitors usually have a very short half-life because binding to BTK needs to occur only once until the protein is resynthesized.

H&O What are the potential advantages and disadvantages of using noncovalent BTK inhibitors first in CLL?

JW The main advantage of pirtobrutinib, which has the potential for the soonest use in the frontline setting, is that it is a very well-tolerated drug. Because of its noncovalent reversible binding and greater selective activity against BTK, it may offer a more favorable safety profile than the covalent BTK inhibitors do. This increase in selectivity has not been shown to decrease efficacy, so we expect to see long remissions with the frontline use of pirtobrutinib. Because target inhibition is more complete with pirtobrutinib than with covalent BTK inhibitors, it may also provide greater efficacy.

The disadvantage of using pirtobrutinib as a frontline treatment is that we do not know how effective a covalent inhibitor will be afterward. We already have a good understanding of the mutations that eventually occur in people who take covalent BTK inhibitors, causing resistance. Studies have shown that switching to noncovalent BTK inhibitors can successfully overcome this resistance. In the studies of pirtobrutinib in relapsed/refractory CLL, *BTK* mutations can occur at sites distinct from C481, and these mutations in some cases confer cross-resistance to covalent BTK inhibitors. Does this mean that using a noncovalent inhibitor first would prevent a covalent inhibitor from working after resistance develops? Although the patterns of resistance may be a little different when pirtobrutinib is used in the frontline setting rather than after a covalent BTK inhibitor, we do not have the answer to this question. As a result, we have concerns about using pirtobrutinib as first-line therapy.

H&O What are the most important studies to look at using noncovalent BTK inhibitors first in these patients?

JW The most relevant trials to look at the first-line

use of pirtobrutinib in CLL are BRUIN CLL-313[1] and BRUIN CLL-314,[2] both of which were presented at the 2025 American Society of Hematology Annual Meeting and simultaneously published in the *Journal of Clinical Oncology*. The BRUIN CLL-313 population was entirely treatment-naive, whereas the BRUIN CLL-314 study population was a combination of treatment-naive and pretreated patients, with none of them having previously received a BTK inhibitor.

> Right now, I see pirtobrutinib as an attractive drug for people who are older or frail—specifically, those patients who are expected to require no more than 1 or 2 lines of therapy in their lifetime.

BRUIN CLL-313 is a phase 3 study in which 282 patients with previously untreated CLL or small lymphocytic leukemia (SLL) and no 17p deletion were randomly assigned in a 1:1 ratio to pirtobrutinib (n=141) or bendamustine plus rituximab (BR; n=141). The first results of this study showed that after a median follow-up of 28 months, the median 24-month progression-free survival (PFS) rate was 93.4% (95% CI, 87.6%-96.5%) in the pirtobrutinib group and 70.7% (95% CI, 61.5%-78.1%) in the BR group. Pirtobrutinib reduced the risk of disease progression or death by 80% in comparison with BR (hazard ratio [HR], 0.20; 95% CI, 0.11-0.37; *P*<.001). PFS was longer with pirtobrutinib than with BR in all prespecified subgroups, including those with *IGHV*-mutated disease and those with *IGHV*-unmutated disease.

Although the overall survival (OS) data were immature, a trend toward improved OS was observed with pirtobrutinib even though more than half of the patients whose disease had progressed while they were on BR crossed over to receive pirtobrutinib. After a median follow-up of 32 to 33 months, the OS rate was 97.8% (95% CI, 93.3%-99.3%) in the pirtobrutinib group and 93.0% (95% CI, 87.0%-96.3%) in the BR group (HR, 0.26; 95% CI, 0.07-0.93; *P*=.0261).

Pirtobrutinib was well tolerated; the rate of discontinuation due to treatment-related adverse events was 4.3% vs 15.4% with BR. The rates of atrial fibrillation or flutter were low in both the pirtobrutinib group and the BR group, at 1.4% and 1.5%, respectively. These data, which are based on a large group of patients, support the frontline use of pirtobrutinib for patients with untreated CLL/SLL. I look forward to seeing more results from this study over time.

In BRUIN CLL-314, we randomly assigned 662 patients with CLL/SLL who were naive to BTK inhibitors to either pirtobrutinib (n=331) or ibrutinib (n=331) in a 1:1 ratio. This was the first randomized study to compare a noncovalent BTK inhibitor with a covalent BTK inhibitor in patients with CLL/SLL.

The overall response rate with pirtobrutinib was noninferior to that with ibrutinib in both the intention-to-treat group (87.0% vs 78.5%) and the relapsed/refractory group (84.0% vs 74.8%). In addition, a trend toward improved 18-month PFS rates was noted with pirtobrutinib vs ibrutinib in the intention-to-treat group (86.9% vs 82.3%), the relapsed/refractory group (81% vs 79.2%), and the treatment-naive group (95% vs 87.6%).

Pirtobrutinib was well tolerated; the rates of discontinuation were 9.4% vs 10.8% with ibrutinib. The rate of atrial fibrillation or flutter was numerically lower with pirtobrutinib than with ibrutinib, at 2.4% vs 13.5%, and the difference was even bigger in patients aged 75 years and older, at 4.5% vs 21.4%.

A major strength of the BRUIN CLL-314 trial is that it compares pirtobrutinib with another BTK inhibitor rather than with chemoimmunotherapy, which is no longer in common use as a treatment for CLL.

H&O Do certain situations exist in which it currently might make sense to use noncovalent BTK inhibitors first in CLL?

JW We will have a better answer to this question when we have longer follow-up from the CLL-313 and CLL-314 studies and understand more about resistance to pirtobrutinib in the frontline setting. Right now, I see pirtobrutinib as an attractive drug for people who are older or frail—specifically, those patients who are expected to require no more than 1 or 2 lines of therapy in their lifetime. We know we will be able to use venetoclax (Venclexta, AbbVie/Genentech) after pirtobrutinib in these patients, but we do not yet know whether covalent BTK inhibitors will be effective. I like the idea of using pirtobrutinib as a frontline option because of its safety. As for whether this decision might be affected by factors such as treatment-naive or relapsed/refractory status, 17p deletion status, *TP53* mutation status, or *IGHV* mutation status, we simply do not know at this point. We need to

continue to follow the data to understand which patients will be the best candidates for this approach.

H&O How do you approach the decision regarding what to use first with your patients?

JW At this time, I discuss the use of frontline pirtobrutinib only with patients who are older or less fit. I provide a detailed description of the risks and benefits of pirtobrutinib vs those of a covalent BTK inhibitor and make my recommendation. For all other patients, I would say it is too early to prioritize pirtobrutinib over a covalent BTK inhibitor. We want to start with a covalent BTK inhibitor and proceed to pirtobrutinib only if the patient cannot tolerate the first agent or it stops working. Of course, this discussion will be very different if the FDA approves pirtobrutinib for use as first-line therapy.

Disclosures

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

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