

CLL IN FOCUS

Current Developments in the Management of Chronic Lymphocytic Leukemia

The Emerging Role of Pirtobrutinib in Chronic Lymphocytic Leukemia



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H&O How has the advent of Bruton tyrosine kinase (BTK) inhibitors impacted the treatment of patients with chronic lymphocytic leukemia (CLL)?

NL The advent of BTK inhibitors has truly transformed the way we treat patients with CLL. At the 2021 American Society of Hematology (ASH) annual meeting, follow-up data from studies such as ALLIANCE, FLAIR, SEQUOIA, and ASCEND demonstrated that BTK inhibitors continue to improve progression-free survival (PFS) compared with chemoimmunotherapy (CIT) in both the up-front and relapsed settings. In addition, the benefit to patients with high-risk disease, such as those with 17p deletion, *TP53* mutations, or unmutated immunoglobulin heavy-chain variable (*IGHV*) status, has solidified the use of these agents over CIT in this setting. Patients with high-risk disease should no longer receive CIT.

H&O What are the limitations of covalent BTK inhibitors?

NL Despite the great efficacy of BTK inhibitors, treatment failure, through either the development of resistance or intolerance, results in discontinuation rates as high as 40%. Mechanisms of resistance to covalent BTK inhibitors, such as BTK C481 or phospholipase C gamma mutations, appear to be the most common contributing factor to resistance to covalent BTK inhibitors in CLL and a reason why some of our patients ultimately progress on these therapies. With regards to resistance, there is some speculation that covalent BTK inhibition might be limited by incomplete target inhibition toward the

end of the dosing interval in patients with more proliferative tumors that have higher rates of BTK turnover, potentially driving drug resistance. As noted, intolerance is the other common reason that patients discontinue treatment with covalent BTK inhibitors. Some reasons for discontinuation include cardiac issues, joint arthralgias, gastrointestinal dysfunction, bleeding abnormalities, and fatigue.

H&O How does pirtobrutinib differ from the earlier BTK inhibitors?

NL Pirtobrutinib is a highly selective, reversible BTK inhibitor with low nanomolar potency that is equal against both wild-type and C481-mutated BTK. Pirtobrutinib achieves greater than 300-fold selectivity for BTK vs other kinases, reducing the potential for off-target toxicities. This drug was also designed to reach exposures exceeding 90% of the maximal BTK inhibition concentration at trough, and thus delivers tonic inhibition throughout the dosing period, regardless of BTK turnover.

H&O What was the design of the BRUIN trial?

NL The BRUIN trial is an open-label, phase 1/2 study of pirtobrutinib in relapsed B-cell malignancies. The trial enrolled 261 patients with CLL or small lymphocytic lymphoma (SLL). The patients had received at least 2 previous lines of therapy. During the phase 1 dose-escalation portion of the study, 3 to 6 patients were enrolled in each cohort, as per a traditional 3-plus-3 design. Pirtobrutinib was administered orally as monotherapy once daily

in 28-day cycles. In the phase 1 portion, 7 dose levels were administered that ranged from 25 mg to 300 mg per day. In addition, an expanded enrollment of up to a cumulative total of 150 additional patients was permitted across all dose cohorts previously declared safe in order to further investigate the tolerability, pharmacokinetics, and biological activity of pirtobrutinib. During the phase 2 portion, a cumulative 120 patients were enrolled into 1 of 6 cohorts based on the type of B-cell malignancy, previous therapies, and BTK mutational status.

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H&O What were the efficacy results in patients with CLL or SLL?

NL Efficacy was observed at all dose levels. Although safety data supported selection of a 300-mg dose, 200 mg was selected as the recommended phase 2 dose. The dose of 200 mg daily corresponded to unbound pirtobrutinib trough steady-state exposure, with BTK concentration corresponding to 96% target inhibition. There were no dose-limiting toxicities, and therefore no maximum tolerated dose was established.

As reported at the 2021 ASH annual meeting, the overall response rate was 68%. The best response consisted of a complete response in 1% of patients, a partial response in 54%, a partial response with lymphocytosis in 13%, and stable disease in 25%. The median PFS was not estimable in patients who had received a median of 3 prior lines of therapy and 18 months in patients who had received a median of 5 prior lines of therapy.

H&O What adverse events were reported?

NL The analysis of adverse events was based on all patients enrolled in the trial. Pirtobrutinib is a very well-tolerated agent. Adverse events of grade 3 or higher were uncommon; the majority of all adverse events were grade 1 or 2. The most common adverse event of grade 3 or higher was

neutropenia, which occurred in 14% of patients. Neutropenia was not dose-dependent. The adverse events of any grade occurring in at least 15% of patients consisted of fatigue (in 23%), diarrhea (in 19%), and contusion (in 17%). Only 1% of patients permanently discontinued treatment owing to an adverse event.

When we think of some of the common adverse events associated with covalent BTK inhibitors, cardiac events such as atrial fibrillation and bleeding issues come to mind. Atrial fibrillation/flutter was noted in only 10 patients during the study (2%). Bruising of any grade was reported in 20% of patients. Bleeding occurred in 8% of patients, but only 1% of cases were grade 3 or higher. In general, to date, there is a low rate of important BTK-mediated toxicities seen with pirtobrutinib.

H&O Were there any particularly notable findings from the study?

NL The patients with CLL were a heavily pretreated group in general, with a median of 3 prior lines of therapy. The overall response rate was 68%. The overall response rate was similar regardless of whether disease progression or toxicity led the patient to discontinue previous treatment with a covalent BTK inhibitor. The response was also similar in patients with or without a BTK C481 mutation. What is particularly noteworthy is that efficacy was observed in CLL patients who had received prior treatment with both covalent BTK inhibitors and venetoclax. Typically, these patients are refractory to treatment.

H&O How might pirtobrutinib address unmet needs in CLL?

NL The current results from the BRUIN study demonstrate that patients who have relapsed after covalent BTK inhibitors, and even after venetoclax, can be salvaged by this noncovalent BTK inhibitor. Pirtobrutinib offers a very good option for patients who have already received both standard-of-care covalent BTK inhibitors and venetoclax. Longer follow-up regarding response duration in this setting is ongoing and needed. Questions remain regarding how to best sequence pirtobrutinib with these currently available therapies in order to maximize the response duration to these agents. Combination studies with pirtobrutinib are also being performed.

H&O Are there any upcoming studies of pirtobrutinib in CLL?

NL There are several upcoming studies of pirtobrutinib in CLL. The BRUIN CLL-321 study is an open-label, randomized phase 3 trial comparing pirtobrutinib vs the

investigator's choice of idelalisib plus rituximab or bendamustine plus rituximab in patients with CLL or SLL who have received previous treatment with a BTK inhibitor. BRUIN CLL-322 is a randomized phase 3 study comparing fixed-duration pirtobrutinib plus venetoclax and rituximab vs venetoclax and rituximab in patients with previously treated CLL or SLL. Investigators are also exploring whether pirtobrutinib can be used earlier in the treatment course. BRUIN CLL-313 is an open-label, randomized phase 3 study comparing pirtobrutinib vs bendamustine plus rituximab in untreated patients with CLL/SLL.

H&O Do you have any other observations regarding the use of pirtobrutinib in CLL?

NL I look forward to seeing longer follow-up and more data for pirtobrutinib. It remains to be seen whether noncovalent BTK inhibitors have a real advantage over the currently available covalent BTK inhibitors. Longer follow-up is needed to determine whether pirtobrutinib is associated with improved efficacy and/or toxicity. Given the current data, it is not known whether pirtobrutinib should be administered prior to other covalent BTK inhibitors or saved for the relapsed/refractory setting.

Pirtobrutinib can be used in patients who require additional treatment after receiving covalent BTK inhibitors or venetoclax, as well as in patients who develop a BTK C481-resistant mutation. It is exciting to have another drug that can be used as salvage therapy for patients in this setting.

Disclosure

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Genentech, Janssen, LOXO/Eli Lilly, and Pharmacyclics. She has received institutional research funding from AbbVie, AstraZeneca, BeiGene, Genentech, LOXO/Eli Lilly, MingSight, Octapharma, Oncternal, TG Therapeutics, and Verastem.

Suggested Readings

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