ADVANCES IN LLM

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Recent Approval of Pirtobrutinib for Mantle Cell Lymphoma

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H&O What is pirtobrutinib and how does it work?

JC Pirtobrutinib (Jaypirca, Lilly) is a recently approved therapy for patients with relapsed or refractory mantle cell lymphoma (MCL). It belongs to a class of drugs called Bruton tyrosine kinase (BTK) inhibitors. These oral therapies target a pathway that is active in patients with B-cell malignancies, such as MCL. By inhibiting BTK, pirtobrutinib effectively blocks the activation and growth of malignant B cells, which are characteristic of MCL. This mechanism of action helps to prevent the proliferation of cancer cells and ultimately leads to regression or control of the disease. Patients typically take this medication once a day indefinitely for the treatment of lymphoma.

H&O What are the benefits of BTK inhibition for patients with MCL?

JC BTK inhibition has significantly changed our approach to managing patients with MCL. In the past, patients who had relapsed disease had very few treatment options, often receiving treatments that had limited benefit and significant toxicities. However, since the initial approval of BTK inhibitors nearly 10 years ago, the outcome for patients with relapsed disease has changed dramatically. Patients now have access to oral therapies that are well tolerated and, in many cases, will be effective for several years, resulting in prolonged quality of life. We have consistently seen a very high rate of response to therapy and that these responses persist for quite some time, often 2 or more years. Pirtobrutinib represents the latest addition to this class of drugs and demonstrates efficacy even in patients in whom prior BTK inhibitors have stopped working.

> The FDA's approval of pirtobrutinib represents a significant step forward in our treatment approach. It is incredibly exciting that we now have this option for patients with MCL.

H&O How does pirtobrutinib compare with other BTK inhibitors that are currently being evaluated for use in MCL?

JC Pirtobrutinib is a noncovalent BTK inhibitor, which distinguishes it from the other 2 currently approved therapies, zanubrutinib (Brukinsa, BeiGene) and acalabrutinib (Calquence, AstraZeneca). What we have observed is that whereas other drugs may lose effectiveness quickly, pirtobrutinib seems to continue working over time, even

in patients who have previously received a BTK inhibitor. By binding in a different fashion, the thought is that pirtobrutinib can inhibit a BTK molecule, disengage from that molecule, and identify additional BTK to inhibit. In this fashion, it continues to target the cancer and is not used up between doses. Therefore, we believe that this treatment provides an option for patients whose disease has previously progressed on a BTK inhibitor. The other benefit of this therapy, as opposed to some of the others, is that it is less likely to cause the toxicities that are commonly associated with BTK inhibitors, such as neutropenia, atrial fibrillation, bleeding, and diarrhea. As a result, patients who have discontinued a previous BTK inhibitor have been able to go on pirtobrutinib and tolerate it quite well.

H&O How does the US Food and Drug Administration's (FDA's) recent approval of pirtobrutinib for MCL impact the current treatment options in patient care?

JC The FDA's approval of pirtobrutinib represents a significant step forward in our treatment approach. It is incredibly exciting that we now have this option for patients with MCL. In the past, patients who experienced disease progression after receiving a covalent BTK inhibitor generally faced poor outcomes. Although some of these patients can now go on to receive immunotherapies, such as chimeric antigen receptor (CAR) T-cell therapy, there are other patients who may not be eligible for or interested in such an approach. With the introduction of pirtobrutinib, we now have an additional option that is both well tolerated and highly active, even in patients who have previously received other BTK inhibitors.

H&O Could you describe the BRUIN trial?

JC The BRUIN trial was a large study initially designed as a phase 1 trial to identify the most appropriate dose of pirtobrutinib. It was later expanded to explore the use of pirtobrutinib in various B-cell malignancies, including MCL, chronic lymphocytic leukemia (CLL), and other lymphoma subtypes. This study identified an appropriate dose of pirtobrutinib and then expanded to evaluate this preferred dose in several lymphoma subtypes, including MCL. We found that even though most patients had previously received a BTK inhibitor, less than half of patients experienced a disease response and were able to stay on the drug for a long time. The findings from this study were instrumental in obtaining the approval of pirtobrutinib for the treatment of patients with MCL, and it holds promise for potential approval in other lymphoma subtypes and CLL in the near future.

H&O Are there any other clinical studies that have been conducted that are evaluating pirtobrutinib, and what were the results?

JC The BRUIN trial is the primary study so far that has looked at pirtobrutinib. However, there are several other trials currently underway. Some of these trials are comparing pirtobrutinib with other BTK inhibitors, whereas others are exploring the combination of pirtobrutinib with other therapies for various lymphoma subtypes. In the coming months and years, we anticipate the release of additional studies that will provide new data to help us understand where this therapy is most useful.

H&O What are the common side effects associated with pirtobrutinib, and how are they managed?

JC Pirtobrutinib is generally well tolerated, but there are some side effects that require monitoring. In general, BTK inhibitors carry a risk of bleeding and the development of atrial fibrillation. Although these risks appear to be less common in patients receiving pirtobrutinib, patients still need to be monitored for them. Hematologic toxicities, including neutropenia and thrombocytopenia, have also been observed with this therapy and require close monitoring. Additionally, this class of drugs is associated with an increased risk of infection. Although most patients will not experience an infectious complication, it is important for patients to be aware of this risk and promptly seek evaluation if they present with infectious symptoms. Other toxicities, including gastrointestinal (GI) symptoms and occasional rash, have also been reported, but pirtobrutinib is a well-tolerated therapy for most patients. GI toxicities can generally be managed with appropriate therapies, such as antidiarrheals. Most side effects can be safely managed in the clinic with drugs to counteract the side effects, a brief period of holding the drug, or dose reduction. It is rare that patients would need to be hospitalized. I recommend aggressive management of cardiac toxicities in collaboration with a cardiologist. For more severe toxicities, like bleeding and infection, it is often necessary to hold the drug and then have a thorough discussion with the patient regarding the risks vs benefits of resumption.

H&O Where do you think we are going next with pirtobrutinib?

JC Currently, pirtobrutinib is primarily used in patients with relapsed MCL who have progressed after or are intolerant to a BTK inhibitor. There is a lot of interest, however, in exploring the potential of using this therapy

earlier in the treatment course. Studies are underway to compare the performance of pirtobrutinib with that of other BTK inhibitors. There is also a lot of interest in combining this therapy with other active agents to see if the rate of complete response and the remission duration can improve.

Given these developments, it is expected that the coming years will bring substantial advancements as we gain more experience with this therapy. The evolving landscape holds promise for further refinement in the application of pirtobrutinib, and ongoing research will provide valuable insights into its optimal use.

H&O Is there anything else you would like to add?

JC I would like to emphasize that pirtobrutinib has gained approval based on the positive results of its clinical trial. This highlights the importance of conducting clinical trials for novel therapies in patients with lymphoma. Many patients with relapsed disease do not benefit significantly from currently available therapies. I strongly advise individuals to consider participation in clinical trials, as they play a pivotal role in making therapies like pirtobrutinib available to patients in need.

Disclosures

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Suggested Readings

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