ADVANCES IN LLM

Current Developments in the Management of Leukemia, Lymphoma, and Myeloma

Section Editor: Susan O'Brien, MD

Mosunetuzumab, the First Bispecific Approved for Follicular Lymphoma

Lihua Elizabeth Budde, MD, PhD
Associate Professor
Division of Lymphoma, Department of Hematology & Hematopoietic Cell Transplantation
Executive Medical Director, Immune Effector Cell Program
City of Hope
Duarte, California

H&O What is mosunetuzumab (Lunsumio, Genentech) and how does it work?

LEB Mosunetuzumab is a bispecific antibody-based T-cell engager with 2 binding sites. Unlike conventional monoclonal antibodies, mosunetuzumab has the ability to utilize a single binding site to target a specific molecule on the tumor cell. In the case of follicular lymphoma (FL), mosunetuzumab targets CD20, a protein found on most lymphoma cells. The other binding site recognizes the CD3 protein, which is present on immune T cells in the body. Essentially, mosunetuzumab redirects the immune T cells and forces them to recognize the lymphoma cells. Then, the immune T cells become activated and initiate the process of killing the lymphoma cells through a CD20-dependent pathway. Mosunetuzumab functions as both a targeted therapy and immunotherapy, as it does not involve chemotherapy but rather activates the body's immune response.

H&O How is mosunetuzumab different from other approved treatments for FL?

LEB Mosunetuzumab has a distinct design aimed at redirecting endogenous immune T cells to target and treat lymphoma cells. The method of action is different from traditional monoclonal antibodies, like rituximab and obinutuzumab (Gazyva, Genentech), which are gentler but less potent. These antibodies are typically used as adjuncts to other treatments and are not nearly as effective as mosunetuzumab. Unlike mosunetuzumab, they do not engage powerful T cells. On the other hand, radiation therapy is a localized treatment and is typically not curative. It is commonly used as palliative care, a bridge to the next treatment, or as consolidation therapy. Then, there is chimeric antigen receptor (CAR) T-cell therapy, an immune therapy that also uses T cells but requires the extraction of immune cells from a patient's body, which then are genetically modified to express a lymphoma-specific CAR. These modified cells expand outside of the body before being reintroduced into the patient. CAR T-cell therapy is very potent and powerful, providing a one-time treatment; but it requires a waiting period for the patient while the personalized CAR T cells are manufactured and is only available at selective treatment centers. In contrast, mosunetuzumab is readily available and does not require personalized manufacturing for each patient. It is an off-the-shelf therapy, consisting of the same mosunetuzumab formula with anti-CD20 and CD3 properties for all patients. Its favorable safety profile in the outpatient setting positions the treatment to be given in the community setting.

H&O Can you describe the clinical trial that led to the approval of mosunetuzumab for patients with FL?

LEB The phase 1/2 GO29781 trial that led to the approval of mosunetuzumab was the first trial conducted

to study this treatment. The study provided valuable insights into the safety and administration of mosunetuzumab. We adopted step-up dosing to determine the appropriate dosage for patients. Because every patient's immune system is unique, some individuals require a gentle push, whereas others benefit from a higher and stronger one. The goal of step dosing is to mitigate side efforts and maximize the therapeutic benefit for a broader range of patients.

This trial also informed the recommended phase 2 dosing schedule for mosunetuzumab. It included a pivotal FL extension cohort within the phase 2 portion, specifically targeting patients who had undergone at least 2 prior lines of systemic treatment for FL without achieving remission. The objective was to determine how mosunetuzumab worked in these heavily pretreated patients and evaluate the balance between its benefits and side effects. Results showed that 60% of patients achieved a complete remission (CR) and 80% achieved a CR or partial response, indicating a positive response rate. The duration of response (DOR) was encouraging, with some patients remaining in remission for more than 2 years.

Based on these data, mosunetuzumab was approved for use in patients with FL in December 2022. The safety profile is more favorable than that of CAR T-cell therapy or other T-cell–based therapies, and the agent does not require specific risk evaluation and mitigation strategies. This approval has paved the way for more patients in the community to benefit from therapy for FL.

H&O How does the approval impact the treatment landscape for FL?

LEB The approval of mosunetuzumab has had a significant impact on the treatment landscape for FL. Currently, it is indicated for patients with 2 prior lines of therapy. In the past, patients who needed third-line or later treatment typically received chemotherapy or an approved drug like the phosphoinositide 3-kinase inhibitor copanlisib (Aliqopa, Bayer), which has lower initial response rates and a lower DOR than mosunetuzumab. Although 2 CAR T-cell products are approved in similar settings, mosunetuzumab provides an alternative option for patients. Some patients may not be suitable candidates for CAR T-cell treatment owing to potential neurologic toxicities or the requirement to receive treatment at a CAR T cell–certified center. Mosunetuzumab does not have these limitations, and it demonstrates a very high response rate. Although trial-to-trial comparisons are challenging, the 80% response rate observed in mosunetuzumab places it in a similar benefit range as CAR T-cell therapies for patients in the community.

H&O Are there any other clinical studies evaluating mosunetuzumab, and what were the results of those?

LEB Multiple clinical trials continue to evaluate mosunetuzumab, either as a single agent or in combination. As a single agent, it has proven to be highly effective in the third-line or later setting.

Mosunetuzumab is currently being tested in the first-line setting for patients with newly diagnosed FL based on certain risk factors. This trial includes elderly patients who cannot tolerate chemotherapy. There is also a cohort for patients with diffuse large B-cell lymphoma and another for patients with mantle cell lymphoma. It is also being tested earlier in the treatment pathway, both as a stand-alone treatment and in combination with lenalidomide, an immune modulator. This combination is being studied in the frontline setting and in the first line–plus setting, allowing patients who have already undergone 1 prior line of therapy to participate. These trials are currently ongoing. Furthermore, a phase 3 clinical trial is underway that is comparing the efficacy of mosunetuzumab plus lenalidomide with the current standard of care of rituximab plus lenalidomide. This global study is still in progress, but we hope it will be completed soon. The aim is to assess mosunetuzumab's activity and determine if it provides a novel treatment option at an earlier stage of the disease.

Another promising combination therapy involves mosunetuzumab and the antibody-drug conjugate polatuzumab vedotin (Polivy, Genentech) for patients with aggressive B-cell lymphoma. This regimen has shown significant efficacy, with nearly half of the patients achieving a CR, irrespective of whether they had prior CAR T-cell treatment or other prior lines of therapy. Notably, the mosunetuzumab/polatuzumab combination has shown remarkable effectiveness in the outpatient setting, making it a powerful treatment option. Based on these positive results, there is a global phase 3 study currently comparing mosunetuzumab/polatuzumab with standard chemotherapy. I am hopeful that this regimen will not only be available in clinical trials but also for patients in the community.

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

LEB The approval of mosunetuzumab for treating FL highlights the efficacy of bispecific antibodies in lymphoma treatment. Although other bispecific antibodies are also being tested for various lymphomas, mosunetuzumab stands out owing to its favorable study profile.

Mosunetuzumab is given in the outpatient setting. Some patients may experience a low-grade fever during the intravenous infusion, which can be attributed to the activation of immune cells. Typically, these fevers occur during the initial treatment cycle and can be easily managed. All patients who experienced a fever in clinical trials recovered without complications. Severe toxicities are rare with mosunetuzumab. Although the agent can cause temporary low blood counts, this usually does not persist. If needed, growth-factor support can be given to facilitate white blood cell recovery.

One caution regarding mosunetuzumab is that treatment may lead to a depletion of normal B cells because CD20 is present on both lymphoma cells and normal B cells. These normal B cells are responsible for producing good antibodies, known as immunoglobulin. It is important to monitor immunoglobulin levels throughout mosunetuzumab treatment. If immunoglobulin levels are low, an intravenous immunoglobulin infusion can be given to boost the patient's immunity. This monitoring and intervention may significantly reduce the risk of infections.

H&O Where are we going next with mosunetuzumab?

LEB In terms of the next steps with mosunetuzumab, our focus is on gaining a deeper understanding of resistance mechanisms. If every patient responded positively to mosunetuzumab, we would need not worry, but there are still 20% to 40% of patients who do not experience a long-term response, even if they initially show a response. Therefore, significant efforts are being devoted to learning about the resistance mechanisms and exploring strategic combinations of mosunetuzumab with other drugs that have different mechanisms of action and side effects. The goal is to attack the lymphoma cells from multiple angles, making it more challenging for them to adapt and evolve. Additionally, we are exploring the sequencing of mosunetuzumab with other novel treatments, like CAR T-cell therapy.

H&O What implications does mosunetuzumab have for future research in the field of oncology?

LEB As I mentioned earlier, mosunetuzumab serves as a highly successful proof of concept for this kind of therapy in lymphoma. The impact is evident in our goal to design more immune-based treatments that can eventually replace chemotherapy. Mosunetuzumab demonstrates the capacity of activated immune cells to eliminate lymphoma cells, erasing the need for chemotherapy and achieving deep and curable remissions. Currently, mosunetuzumab represents the first generation of bispecific antibodies. However, there is ongoing development of a second generation of bispecific antibodies that can deliver a second signal to further enhance T-cell stimulation and performance. These advancements are very exciting within the field. Additionally, similar technology is being developed in leukemia, multiple myeloma, and solid tumors. Immunotherapy continues to play an increasingly significant role in the oncology treatment landscape.

Disclosures

Dr Budde has received research funding from AstraZeneca, Merck, Amgen, and MustangBio; and has served on the advisory board/consulted for AbbVie, Genentech, Roche, Gilead Sciences, Bristol Myers Squibb, Nurix, and ADC Therapeutics.

Suggested Readings

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