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Chairperson Perspective: Core Concepts for Community-Based Practice: The Evolving Role of Bispecific Antibody Therapy in Relapsed or Refractory Follicular Lymphoma

Announcer:
Welcome to CME on ReachMD. This activity, titled “Chairperson Perspective: Core Concepts for Community-based Practice: The Evolving Role of Bispecific Antibody Therapy in Relapsed or Refractory Follicular Lymphoma” is provided by AXIS Medical Education.

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Dr. Phillips:
Hello. My name is Dr. Tycel Phillips. I'm coming from the City of Hope National Medical Center. And I want to thank you for joining this brief overview of core concepts for community-based practice, the evolving role of bispecific antibody therapy in relapsed or refractory follicular lymphoma.

Currently, if we look at the current treatment options for relapsed/refractory follicular lymphoma, there are only two currently approved regimens for second-line relapsed/refractory follicular lymphoma. These are lenalidomide/rituximab based on the AUGMENT study. We do have chemotherapy and transplant, which has sort of fallen out of favor. And then we have tazemetostat for relapsed/refractory follicular lymphoma patients who have no other satisfactory options.

There are additional options in third-line plus follicular lymphoma. Again, we have tazemetostat for patients with EZH2 mutations. We have obinutuzumab and zanubrutinib based on the ROSEWOOD study with its pending confirmatory phase 3 trial, MAHOGANY. And then we have the bispecific antibodies; mosunetuzumab based on the clinical trial GO29781, and epcoritamab from the EPCORE NHL-1 study. Additionally, there are three approved CAR T-cell products in this space, axicabtagene autoleucel from the ZUMA-5 study, tisagenlecleucel from the ELARA study, and lisocabtagene maraleucel from the TRANSCEND FL trial.

So specifically, we will discuss bispecific antibodies. So, we have mosunetuzumab, odronextamab, and epcoritamab as agents being evaluated in patients with follicular lymphoma.

Mosunetuzumab gained approval based on the GO29781 clinical trial. In this study, mosunetuzumab was given as an IV infusion every 3 weeks after initial step-up dosing. This study did not require any mandatory hospitalization. Mosunetuzumab is also being studied as a subcutaneous formulation.

So looking at the response rate from the initial pivotal study, we see the overall response rate is 78% and a complete response rate of 60%. Time to first response was 1.4 months, which corresponds with the first on-study disease assessment, and time the first CR was 3 months. If we look at high-risk subsets in this patient population, those are EZH2 mutations, TP53 mutations, BCL mutations, CREBBP, KMT2D. Again, we do see fairly equivalent rates of overall response and complete response rate in these high-risk subsets.

Looking at durability of response, the median duration of response was not reached in these 90 patients with a 24-month duration of response of 53%. For those who obtained a complete response, again, median is not reached. And a 24-month duration of complete response of 63%.

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Now turning our attention to safety. The most important safety aspect in dealing with patients with bispecific antibodies is typically cytokine release syndrome. 44% of the patients had any grade cytokine release syndrome, with the majority of patients having grade 1 or grade 2. This is very important as we talk about management of patients with cytokine release syndrome, as typically grade 1 cytokine release syndrome does not require any hospitalization or introduction of tocilizumab. All patients with CRS had resolution of the event at the conclusion of study protocol.

So, mosunetuzumab was approved for patients with relapsed/refractory follicular lymphoma based on the results of this open-label study. The boxed warning for this mentions cytokine release syndrome as one of the main concerns. But this does not require a mandatory hospitalization, as we did see with the bispecific antibodies approved in multiple myeloma, or any suggestion or requirement of hospitalization, as we see in the FDA approval for the bispecific antibodies in diffuse large B cell lymphoma.

So next we will look epcoritamab, which was approved in the EPCORE NHL-1 study. This was given as a subcutaneous injection. The initial study proceeded with step-up dosing at 0.16, 0.8, and then 48 mg. Due to rates of CRS, there was a Cycle 1 optimization introduced to reduce the rates of CRS and hopefully prevent these patients from requiring hospitalization. And so in this situation, patients were given prophylaxis with dexamethasone. But also there was an introduction of an intermediary dose of 3 mg with Cycle 1 Day 15, and thus pushing the full dose back to Cycle 1 Day 22 in this cohort of patients.

So taking all patients together, even the optimization cohort and those treated traditionally with the three step-up dosing mechanism, you see high overall response rate of 84%, complete response rate of 65%. Again, between the two cohorts, the optimization and the pivotal trial, you see equivalent CR rates and overall response rate; thus, the introduction of the intermediate dose did not add any sort of detriment to the overall response in this patient population.

So looking at some high-risk subsets, and you can see equivalency in this patient population of high overall response rate and complete response rates, with the highest being 97% overall response rate and complete response rate of 79% in those who were considered to be non-double refractory. But, even in the double refractory patients, we have a high overall response rate of 76% and a complete response rate of 56%. This all compares very favorably with mosunetuzumab.

So they did look at some rates of MRD negativity. Those who were MRD undetectable in this protocol tend to have very prolonged and durable responses.

As I mentioned with the introduction of the C1 optimization, you can see a marked reduction in the rates of cytokine release syndrome, specifically a reduction in rates of Cycle 2 and above cytokine release syndrome, or CRS. Again, reduction in the use of tocilizumab. None of these events led to discontinuation epcoritamab. All patients had resolution Overall, the C1 optimization cohort and the safety profile compares very favorably to mosunetuzumab, again, suggesting that with this optimization, patients can be treated in an outpatient setting without the need for hospitalization or heavy utilization of tocilizumab.

And so, based on this, epcoritamab was approved in June of 2024 thus providing a second sort of CD20/CD3 bispecific in this patient protocol. And again, we do have some concern and warnings for CRS, of an immune effector cell-associated neurological syndrome. This is minor compared to what we see with chimeric antigen receptor therapy. This did not require hospitalization for epcoritamab with the additional step-up dosing in this optimization cohort. So, epcoritamab and mosunetuzumab both can be given in an outpatient setting without the need for 24-hour hospitalization monitoring.

So, if we look at some more information with epcoritamab in follicular lymphoma, we have the EPCORE NHL-2 study, which looked at epcoritamab plus the immunomodulatory drug lenalidomide. This drug is a currently approved agent in patients with relapsed/refractory follicular lymphoma, based on the AUGMENT study. In this study, they did add epcoritamab to the R^2 backbone in this situation. In this phase 2 trial, there is a very high overall response rate of 96%, a complete response rate at 87%. This was given breakthrough designation for patients with relapsed/refractory follicular lymphoma, who have received at least one prior line of therapy. This is being studied in a phase 3 randomized study, EPCORE FL-1, which will randomize R^2 versus R^2 plus epcoritamab.

So the third bispecific antibody being explored in follicular lymphoma is odronextamab from the ELM-2 study. There is a little bit more complicated step-up dosing with odronextamab compared to epcoritamab and mosunetuzumab. So we have split dosing of 0.2/0.7 mg on Cycle 1 Day 1 and Day 2. We do then have on Cycle 8 Day 9, 2 and 2, for a total of 4 mg. Split dosing on cycle Day 15 and 16, 10 and 10. And then thereafter you get to work your way toward the full dose. But from Cycles 2 to 4, patients get weekly doses of 80 mg, and thereafter they get, every 2 weeks at 160 mg. This increase in optimization was sort of introduced initially during the early parts to reduce the rates of CRS with odronextamab.

So looking at the response rate, we still see high overall response rate, complete response rate with odronextamab, 81.8% and 75.2%. With investigator evaluation, there was a slight decrease in the complete response rate, but overall, relatively stable. And again, with the change in step-up dosing, you do see that there is no detriment in patients' overall and complete response rate. And you actually see a higher complete response rate with the additional step-up dosing, with the improvement in safety.

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You do see a decrease in the rates of grade 2 and grade 3 cytokine release syndrome, with the improvement with the extra dose and expansion of the step-up dose in this patient population in fairly equivalent patients, Overall, the cytokine release syndrome rate was fairly similar, but again, more patients had grade 1 CRS, and , a marked reduction in grade 2 and grade 3. Very important as you try to transition this drug into an outpatient setting. Looking at ICANS, there was no ICANS reported with the additional prolonged step-up dosing regimen. There were some reports of infusion-related reaction, but this was fairly equivalent and then what we would expect with this treatment cohort.

So looking at response, the 12-month duration of response of 68.8%, 18-month duration of response at 55%, 12-month duration of complete response of 72.2%, and 18-month duration of complete response at 59.1%. And this study is ongoing with more maturation of the data expected in the relatively near future.

So just summarizing what we have with follicular lymphoma, there is equivalency for the most part, with the overall response rate, complete response rate, and the progression-free survival of all three of these drugs. Again, the top two agents are currently FDA approved. The third one is being evaluated for FDA approval, thus cementing the sort of efficacy of these bispecific antibodies in patients with relapsed/refractory follicular lymphoma, even as single agents.

So, when to consider bispecifics over other treatments? So, we're looking at patient selection for now, these drugs are limited to third-line and beyond. And so the benefits we have here, they have an improved overall response rate, duration of response, and progression-free survival versus non-CAR-T options, which include tazemetostat, and obinutuzumab-zanubrutinib. And specifically with mosunetuzumab, that is a finite treatment option, meaning that treatment will stop, as compared to these other options, which are given to progression or intolerance. Again, safety with these agents, again, after completion of step-up dosing, the tolerability of bispecific antibodies compares very favorably with other agents, except for possibly tazemetostat, which has a very safe and sort of patient-friendly patient profile. If we look at administrative convenience, we have subcutaneous options with epcoritamab and potentially in the future, mosunetuzumab, as well as the IV options with mosunetuzumab currently and if odronextamab gets an approval.

So there are some limitations. The risk of CRS and ICANS was low, but they still require some sort of structure to be in place to help manage those who might have this event. Again, it's not a zero-sum situation, even with these optimizations that we've implemented. So there needs to be some sort of plan in place when things do go bad. Typically, we'll have a champion to guide a team of support staff, whether that's a physician or nurse, to help sort of coordinate with the other team. A standard operating procedure would be beneficial for most academic centers or clinical facilities to help manage these patients. Tocilizumab needs to be sort of accessible in case patients do have grade 2 and beyond CRS, as you do a sort of mitigation of this will be very important to prevent any sort of severe adverse events. Outside of that, there's risk of viral infections with bispecific antibodies. So, monitoring IgG levels is important, and sometimes supplementation on IVIG is needed. And then as far as comfort, there is limited experience of some providers with bispecifics so there will be a learning curve not too dissimilar from what we saw with the introduction of monoclonal antibodies, and some of these other agents, such as venetoclax, into the community setting.

So when comparing CAR T-cell therapy and a bispecific in this space, again, the agents are very similar. The benefits to bispecifics, excellent efficacy, shorter follow-up, they are off the shelf, logistically less complex than what we need with CAR T-cell therapy. With mosunetuzumab, you do have a one and done therapy. Epcoritamab, as of right now, as a treat to progression, but there are some studies evaluating limited therapy. You don't require lymphodepleting chemotherapy, lower risk of CRS and neurotoxicity, usually outpatient, and likely to be less cumbersome and burdensome to a hospital system due to less cost over time, especially for the finite treatment options.

So plan to have a plan in place. Again, patient selection, patient education. Educating the patient is very important, as some of these events may happen outside of the time of an office being open, so patients should know what to do. Drug administration, in an outpatient setting, are you equipped to manage this in case of any adverse reactions happen. Self or inpatient monitoring, none of these bispecific antibodies in follicular lymphoma require in-hospital stay so education of the patient, having the patient make sure they have a thermometer, in some cases, a blood pressure cuff is important for monitoring and having a plan in place of what to happen when they have a fever, or if they have other events that may occur related to cytokine release syndrome. And continue therapy as directed if no issues occur. And a management plan in place, an SOP for CRS management and neurotoxicity management in these patients.

So premedication, prophylactic corticosteroids, are recommended with both agents to help prevent sort of cytokine release syndrome. Epcoritamab does have a little bit longer duration of corticosteroid, usually Days 1 through 4, where mosunetuzumab is typically given at the time of the infusion. Step-up dosing has been implemented with all these agents based on our experience with blinatumomab. Hospitalization can be considered for some patients, but again, it's not required with any of these bispecific antibodies in follicular lymphoma. A slower infusion, so you can slow down the infusion rate with mosunetuzumab. That will eventually go away with the subcutaneous injection. But subcutaneous injections themselves typically have a longer sort of uptake. So you don't get as quick of a peak with a T-cell expansion in these patient populations with these bispecific antibodies, as we just mentioned on the last point.

So looking at cytokine release syndrome, for the most part, these typically occur within the first 24 hours around the treatment initiation.

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The events are typically confined to step-up dosing, so once you get out of step-up dosing, the risk of this is generally very minimal, if at all. Subcutaneous formulations may reduce the risk of CRS, given a slow uptake, but it may also cause a delay at the occurrence of CRS, so you have to be aware that this may not occur within the first 24 hours, and something you should keep in mind through the first 48 to 96 hours. With supportive care, prompt administration of IL-6 receptor blocking antibodies such as tocilizumab; steroids, sometimes a pill in the pocket to send patients home with; antipyretics or anti-fever medications, acetaminophen; IV fluid administration; support of blood pressures; oxygen supplementation when needed. And then with severe cytokine release syndrome, then you would typically want to withhold the drug or permanently discontinue in this situation.

Although neurotoxicity is a very low incidence in this patient population, it can occur. So some of the same mechanisms that actually prevent CRS are there, except that in neurological toxicity, the main agent to utilize to prevent this will be corticosteroids. So steroids are far more important for management of immune effector cell associated neurological syndrome than tocilizumab. And depending on the severity of ICANS or neurotoxicity, you would withhold or permanently discontinuity drug.

So lastly, we'll cover some bispecific antibodies in clinical trials. There are several phase 3 studies ongoing, looking at bispecific antibodies versus what we consider to be standard of care. Epcoritamab and R^2 versus R^2 in a relapsed/refractory setting, and versus chemoimmunotherapy in previously untreated follicular lymphoma patients. Odronextamab has several clinical trials. And mosunetuzumab plus zanubrutinib for relapsed/refractory follicular lymphoma.

So with that, we'll shift to key takeaways, which is that bispecific antibodies are an important addition to the armamentarium for patients with relapsed/refractory follicular lymphoma. I would highly anticipate these agents will move up beyond where they're currently situated in the third-line plus follicular lymphoma. And we eventually see these agents being utilized in untreated patients with follicular lymphoma. These antibodies do allow the option of retreatment depending on the duration of treatment that the patients will get with the initial therapy. So very exciting future as we move forward in bispecifics in follicular lymphoma. As we are shifting into the community space, comfort with these agents are very important. Having a plan in place is very important. All these will improve the experience of both the physician and the patient with use of these bispecific antibodies.

And with that, I'd like to thank you for participating in this activity.

Announcer:

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