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Approved Bispecific Antibodies for RRMM: Review of the Pivotal Trials

Announcer:
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Dr. Lonial:
This is CME on ReachMD, and I'm Dr. Sagar Lonial. Here with me today is Dr. Caitlin Costello.

The addition of bispecific antibodies and CAR T-cell therapies to the current treatment guidelines has dramatically changed the way we treat patients with relapsed and refractory disease following 4 or more prior lines of therapy.

Dr. Costello, what can you tell us about the approved bispecific antibodies in myeloma?

Dr. Costello:
Thank you, Dr. Lonial. There are currently 3 bispecific T-cell engagers that are approved for the treatment of multiply relapsed and refractory multiple myeloma. There are 2 that are specific to targeting BCMA. There is 1 that is targeting GPRC5D. So let's touch base on each of these 3 a bit.

I think it's important to say that the mechanism of action is similar across all 3 of them. The intent is that we are trafficking specifically our T cells to target 1 of those 2 specific antigens that lives on the myeloma cell surface. By doing so, there's different analogies that people talk about. It's an opportunity with the drug to kind of, if you will, handcuff the myeloma cell to the immune system cell. I've thought of it as a double-sided magnet; I've heard double-sided tape. But I think the intent, however, is to say, “Hey, immune system, here's the bad guy myeloma cell. This is where you're supposed to fight.” So the mechanism of action, regardless of the antigen of interest, is the same.

Now with different drugs, there’s slightly different kind of dosing intervals in terms of timing, but all 3 of them have the same intent of an initial step-up dosing process. We know that these drugs can be associated with toxicities, such as cytokine release syndrome [CRS] and neurotoxicity. And with both of those side effects, it's important to do kind of very small doses and step-up dosing intervals. As I explain to my patients, maybe small amounts of drug results in small amounts of toxicity, if you will. It's a way that the drug can be safely administered. And at least from the get-go, many of us were administering these drugs in the hospital for the purpose exactly of that, safe administration. As we are becoming more comfortable with the drug, we're learning how we can potentially mitigate, prophylax against, be prepared for some of those side effects, and do it maybe in a more user-friendly environment outside of the hospital.

For any facility, physician, the infrastructure is required in order to safely do this both in and out of the hospital. There are REMS [Risk Evaluation and Mitigation Strategy] programs that are designed that require education across the board so that it can be administered. Patients are taught; physicians are aware; everyone knows the side effects to look for and has a good understanding of how to manage them.

The safety profile, as mentioned, include the CRS, cytokine release syndrome, and ICANS [immune effector cell-associated

neurotoxicity syndrome]; however, it's important to recognize that cytopenias and target-specific toxicity is also known, whether that is infections or whether those are in keratinized tissues such as the skin, taste, nails. There are a variety of different side effect profiles we've seen with different targets.

There are lots of trials that are ongoing to supplement the initial trials that led to the accelerated approval of these bispecific T-cell engagers. These ongoing confirmatory trials will allow for kind of novel combinations, exciting ways to administer these drugs, and whether it's continuing in late-line therapy or potentially moving them up to earlier-line therapy, I think there's much to be excited about.

Dr. Lonial:
Thank you very much, Dr. Costello. A great summary of, clearly, an active area of research. And I think the points that you hit are so important. The step-up dosing – and I think it's important for clinicians to recognize that step-up dosing doesn't mean you're giving ineffective doses. In fact, I've had patients after 1 step-up dose actually go into complete remission, as measured by light chain. So these are highly effective doses. And it's really a way to ease into the treatment, as you described. I've always been fascinated by the idea that proximity of a T cell to a myeloma cell is what either enhances its efficacy, or it can be used to limit efficacy if a T cell is not close and then a T-cell engager or a bispecific, as you nicely described, helps us get there more frequently and much more effectively.

And finally, understanding how to manage some of the adverse events. While these are not directly cytotoxic, they can cause local bone marrow injury associated with CRS, and that likely leads to some of the cytopenias that we see as well.

So I think all of these things together mean that with some experience, as well as education, even the earliest of providers can get used to this kind of work and these kinds of agents and really ultimately make a big difference on outcomes for patients with myeloma.

Well, this has been a great bite-sized discussion. Thank you again for listening.

Announcer:
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