MMRF Livestream – FAQs on BCMA-Targeted Bispecific Antibodies in Multiple Myeloma

April 14, 2023

Transcript

Mary Derome (MMRF): Welcome, everyone, and thank you for joining us for today's session, Frequently Asked Questions on BCMA-Targeted Bispecific Antibodies in Multiple Myeloma. I'm Mary Derome, Senior Director of Medical Communications and Education at the Multiple Myeloma Research Foundation (MMRF). Today, I'm joined by Dr. Saad Usmani and Ms. Anna Howard from the Memorial Sloan Kettering Cancer Center in New York City. They're here to answer your questions about the latest multiple myeloma therapy option. My first question is for you, Dr. Usmani. What is the difference between a bispecific antibody and other antibodies like Darzalex (daratumumab) or Sarclisa (isatuximab)?

Saad Usmani, MD, MBA, FACP: Let me start by explaining these different technologies. Antibodies like daratumumab and elotuzumab are what we call monoclonal naked antibodies. They target a specific protein on the surface of myeloma cells and they rely on the usual immune-mediated mechanisms to kill the myeloma cells, whereas the bispecific antibodies are a little different. One part of the bipecific antibody can recognize the surface protein on the cancer cell, and the other part recognizes the surface marker on immune cells like T cells. The bispecific antibodies bind the patient's immune cell, which could be a T cell or we're also looking at natural killer (NK) cell bispecifics now in clinical trials. The idea is you bind the patient's immune cell to the cancer cell and help kill it. It's a very unique modality and it is showing extremely good results in several cancers, including multiple myeloma.

Mary Derome (MMRF): Anna, the next question is for you. We use the phrase "off-the-shelf" a lot when referring to bispecific antibodies, especially when comparing them to a CAR T-cell therapy. Can you explain to us what off-the-shelf means?

Anna Howard, RN: Yes. Off-the-shelf means that the bispecific antibodies don't have to be tailor-made to each patient. Especially when you compare them to something like CAR T, where the T cells have to be collected and then manufactured for each patient specifically. How long that process takes varies, but it can even take a month—sometimes more, sometimes less. With the bispecific antibodies, what we have in stock is what we're giving to all the patients. That's what we mean when we say off-the-shelf.

Mary Derome (MMRF): Dr. Usmani, patients are usually surprised that bispecific antibody therapy is given as a single agent, because most of the time people are taking combinations of therapies. This is just a single-agent therapy, similar to CAR T, but different. Can you clarify what “single agent” means and what makes bispecific antibodies so different from other myeloma drugs that are given in combination?

Saad Usmani, MD, MBA, FACP: Yes, certainly. Single-agent treatment means you're just getting one drug. Before the bispecifics and CAR Ts were developed in multiple myeloma, all the other treatments that we had evaluated in clinical trials that led to approval in the relapsed/refractory space were single agents. These include drugs such as carfilzomib (Kyprolis), pomalidomide (Pomalyst), bortezomib (Velcade), lenalidomide (Revlimid), and daratumumab. The activity of these drugs was somewhere in the 20% to 30% range. That means that if we treat ten patients, two to three would have a good response to treatment.

With that in mind, once those drugs showed activity, we started to combine them together so that we could get higher levels of activity. It was amazing to see that with CAR T and bispecifics on their own, these therapies can give very high response rates. The bispecific antibodies can give a response rate of 60% to 70%. That is quite remarkable. Based on these remarkable results, the bispecific antibody, teclistamab (Tecvayli), was approved by the FDA and in Europe last year as a single agent for patients with more advanced relapsed or refractory myeloma.

Mary Derome (MMRF): Dr. Usmani, considering the important role that T cells play in the effectiveness of bispecific antibodies, do patients have to be screened for the numbers or activity of their T cells prior to receiving a bispecific antibody therapy?

Saad Usmani, MD, MBA, FACP: That's a very good question. Typically, we do not screen them. In fact, in all the early clinical trials, this is not something that we've really done. We know that when myeloma is diagnosed, many times the T cells are already dysfunctional. That dysfunction stays or it may increase over time as patients receive several lines of treatment. The fact that even in more advanced, relapsed/refractory myeloma patients who've had four or more prior lines of treatment, we are seeing 60% to 70% responses, tells us that we need some level of T cell activity. But the challenge for us, as scientists and clinicians, has been defining what that number or activity level is. That's actually something that we're studying right now to understand it better. I hope that makes sense.

Mary Derome (MMRF): it does. It makes total sense. Anna, what are the main similarities and differences in the patient experience between receiving an antibody therapy like Darzalex or Sarclisa and receiving a bispecific antibody therapy like Tecvayli—specifically talking about infusion or injection times, need

for hospitalization, need for premedications, or need for a caregiver, etc? What can you tell us?

Anna Howard, RN: The main difference with teclistamab or the bispecific antibodies compared to the other medications that you mentioned would be the need for hospitalization. There are some specific toxicities that we're concerned about with medications like teclistamab, which we'll talk more about later in the discussion. Because of the concern for those toxicities that are most likely to happen during the initial doses, we administer teclistamab through step-up dosing, meaning that you get a small dose, a medium dose, and then the final full dose of the medication. That process has to take place as a hospital inpatient so that you can be closely monitored for those toxicities. I usually tell my patients to plan to be admitted in the hospital for about a week while the step-up dosing is done. It can be a little bit shorter or sometimes longer if there are complications. That's probably the biggest difference with teclistamab versus something like daratumumab. Once the patient receives the full dose, then the rest of the injections are administered in the outpatient setting.

Similar to daratumumab, teclistamab is a once-weekly injection. It's given subcutaneously in the fatty part of the stomach. You also asked about pre-medications with that: we typically give premedications with teclistamab for the step-up dosing like Benadryl (diphenhydramine) or steroids like dexamethasone. Once an outpatient, we typically don't do premedications for patients. In terms of caregiver needs, there are no restrictions about patients being able to drive to and from their outpatient appointments when they're receiving the teclistamab. So, they don't have to have a caregiver come with them if they're not able to.

Mary Derome (MMRF): Okay. Tecvayli is the first bispecific that has been approved in myeloma and it specifically binds to B-cell maturation antigen, or BCMA, on the myeloma cell. Dr. Usmani, what can you tell us about BCMA and why it's a good target for antibodies? Why not just use a target like CD38, which is also on myeloma cells?

Saad Usmani, MD, MBA, FACP: BCMA is an acronym for B-cell maturation antigen, which is a protein or surface marker that is present or expressed on mature B cells, as well as on plasma cells. It's an important surface marker or protein for maturation as well as growth and differentiation of plasma cells. It's a good marker because it is kind of unique to just the mature B cells and plasma cells. So, we do not anticipate a lot of off-target effects with these treatments because the safety and side effect profile would be better with that particular target.

Mary Derome (MMRF): BCMA is found on all plasma cells including myeloma cells, which are the cancerous plasma cells, and also on noncancerous plasma

cells. If you're targeting BCMA with this bispecific antibody, would that prevent a patient from producing other normal antibodies while on this form of therapy?

Saad Usmani, MD, MBA, FACP: Technically, yes. That's one of the reasons why when we treat patients with teclistamab or other BCMA-directed bispecific treatments or even with CAR-T therapy, we have to watch for infections. Many times we see that patients start developing low total immunoglobulin (Ig) levels, or what we call hypogammaglobulinemia, and they might require IVIG replacement in that case. Because the immune system can be affected, we sometimes put patients on prophylactic antiviral or antimicrobial coverage as well. This is something that we see with both CAR-T and bispecifics. The difference is that with bispecifics we continue treatment and the disease stays under control. We're trying to figure out other ways in which we can dose or schedule these therapies to reduce that risk of infection.

Mary Derome (MMRF): I know that's a very serious matter with bispecifics. We talk about that a lot at some of the scientific meetings. It's becoming more and more of an issue. Anna, which patients are able to receive BCMA-targeted bispecific antibodies like Tecvayli? How easy or difficult is it for patients to get access to that therapy?

Anna Howard, RN: Tecvayli or teclistamab was just FDA approved at the end of 2022. The current FDA approval is for patients who have had four or more prior lines of therapy, meaning that they've progressed through four different lines of treatment. There are also some specifications about medications that they had to have received prior. In terms of access for patients, we talked about that a little bit at the beginning. The fact that it is available off-the-shelf does make it a little bit easier to access for patients. One kind of barrier does depend on where patients are because hospitals have to be enrolled in a Risk Evaluation and Mitigation Strategy (REMS) program for teclistamab. They have to have certain certifications and training to be able to administer it in the inpatient setting. Not all the hospitals near patients have been enrolled in that yet. That's definitely a barrier for access right now for patients. It is an option for patients to go to hospitals that are enrolled in the REMs program, receive the teclistamab there for their inpatient step-up dosing, and then return to their regular local outpatient setting to receive the rest of the weekly doses. We've done that for patients at Memorial Sloan Kettering Cancer Center as well. That helps to broaden access to more patients.

Mary Derome (MMRF): Right. Is there any age limit for patients receiving a bispecific antibody treatment?

Anna Howard, RN: There's no specific strict age limit or upper age limit for these therapies. With every treatment, we obviously assess each patient individually

and assess their functional status and see if the treatment would be appropriate for them.

Mary Derome (MMRF): Great. Thank you. Dr. Usmani, can you tell us why patients have to go through multiple relapses before they can get bispecific antibody therapy? Does the success rate of this type of therapy decrease if a patient is heavily pretreated and their immune system is already weakened more than it would be in an earlier course of the disease?

Saad Usmani, MD, MBA, FACP: The way that we develop new therapies, especially if it's a new treatment that's coming into clinical trials, is to see if it will work in patients who have had their disease progress or not respond to other treatments that are already available to us. That's kind of how clinical drug development works and we need to make sure that the treatment is safe and effective for our patients before we move to the frontline treatment. Right now, teclistamab is currently approved for four or more prior lines of treatment because the clinical trial that led to its approval included only those patients. In terms of activity, it's quite active. The response rate in the clinical trial, as I previously mentioned, was 63%. So, it is quite active, even though patients have had other treatments in the past. The next logical question is will the activity be better in earlier lines of treatment? I think we are looking for that answer right now in clinical trials. Hopefully, we'll have that in the next few years for our patients.

Mary Derome (MMRF): It's really interesting to see some of these therapies move to earlier lines. There are some interesting studies ongoing with Tecvayli in combination with other therapies, which really seem to increase its already impressive activity. We'll see how all that data comes out. Anna, how are patients followed in the clinic after they've received Tecvayli?

Anna Howard, RN: As I mentioned earlier, patients continue to get weekly subcutaneous injections of Tecvayli. With each of those injections, we monitor their lab tests, such as a basic metabolic panel and a complete blood count. Then we see patients monthly in the clinic once during a cycle.

Mary Derome (MMRF): Dr. Usmani, is a BCMA-targeted bispecific antibody like Tecvayli effective in a patient who's previously relapsed after receiving another BCMA-targeted therapy like CAR T: Abecma (idecabtagene vicleucil), or Carvykti (ciltacabtagene autoleucel)? This is such a big topic of conversation right now with some of these BCMA-targeted therapies. What can you tell us?

Saad Usmani, MD, MBA, FACP: There is very limited data that's out in the public domain. We have done studies where prior BCMA-exposed patients have been given teclistamab. What we find is that about half of the patients do respond. We have 50% responses reported in one of the cohorts in clinical trials.

One thing we don't know is how long that activity will last. My general sense is if someone had a BCMA-directed CAR-T therapy more than six months ago and the disease is making a comeback it’s not because myeloma cells lose the BCMA. For the vast majority of patients, that's not the mechanism of how the disease becomes resistant to a BCMA treatment. So, you can still give a BCMA bispecific to those patients. We are actually looking at this very actively in our commercial drug use. One of my fellows, Dr. Firestone, will be presenting this information at the upcoming American Society of Clinical Oncology (ASCO) meeting as well.

Mary Derome (MMRF): Excellent. I look forward to seeing that presentation. We're going to talk now about side effects of treatment, which we've sort of touched on already. It seems that myeloma therapies that activate a patient's T cells, like bispecific antibodies and CAR T, are associated with a unique set of side effects that we haven't observed with some of the other therapies that patients are given. Anna, when you prepare a patient to receive Tekvayli, what do you explain to them regarding side effects they should be aware of and may experience?

Anna Howard, RN: One of the biggest things that we educate patients on prior to them receiving Tekvayli is the risk of cytokine release syndrome or CRS, which is basically an inflammatory reaction that can occur as the T cells are activated by the medication. Some side effects that manifest are fevers, headaches, low blood pressure, or difficulty breathing. This is one of the main reasons that we have patients admitted in the hospital during step-up dosing because the highest risk of CRS is during initial and step-up dosing. It's good that patients are in the hospital for this because they can be very closely monitored for these effects and managed with the resources that the hospital has. That's the biggest thing we want to make sure patients are aware of going into their admission. Then we continue to monitor for those symptoms when they're outpatient, as well as some symptoms that we see with some of the other treatments, like gastrointestinal distress. Bone pain is a common side effect that we see in these patients as well.

Mary Derome (MMRF): Interesting. Dr. Usmani, neurotoxicity is another side effect that's associated with bispecific antibody treatment. Is that type of neurotoxicity similar or different than the type that patients experience with Velcade (bortezomib)? Are the bispecific antibody-related neurotoxicities permanent or do they fade over time after treatment is completed?

Saad Usmani, MD, MBA, FACP: Neurotoxicity is a very broad term and with CAR-T therapies, we have this condition called immune effector cell-associated neurotoxicity syndrome (ICANS) where patients can have more pronounced symptoms of altered mental status and even seizures if it's high grade. With bispecifics we don't see those kind of side effects. In fact, the most common

neurotoxicity is just headaches, which are treated with Tylenol, etc. We can sometimes see confusion in some patients; which happens very rarely. It's kind of transient. Very rarely peripheral neuropathy has been reported, which is, again, transient. It's very different from the kind of neurologic side effects that you would observe with bortezomib, where you get tingling and numbness because the drug is affecting the nerves directly. It really has to do with BCMA being expressed in certain organs at a very low level. The bispecific antibody and the T cells can act on those organs. Neurotoxicity for the most part is not a big concern for bispecific antibody administration compared to CAR T.

Mary Derome (MMRF): If a patient experiences any of these toxicities that we've been discussing, how are they managed in the clinic?

Anna Howard, RN: It depends on the severity of some of these toxicities, especially when or if anything occurs during step-up dosing. We'll typically wait to give the next dose until the symptoms have resolved. More mild symptoms we manage with Tylenol, as Dr. Usmani mentioned. We give IV fluids as well, which is just supportive care to help manage them. For a while when they're inpatient, if they were to have a more significant CRS, there's a medication called tocilizumab that we give that helps calm the immune system down. Then for peripheral neuropathy, there are some patients who need gabapentin or other similar medications to help with that. Then, as Dr. Usmani mentioned earlier, we're looking at spacing out the doses a little bit more for patients who especially experience some of these side effects and toxicity.

Mary Derome (MMRF): Great. Dr. Usmani, we're going to go back a little bit to infection risk. We already talked about that a little bit. This is high for patients on bispecifics. Is the infection risk that patients on bispecifics experience similar to when they have a stem cell transplant? Is the patient's immunity impaired for as long as they're taking the bispecific antibody? Is the impairment reversible once they're off treatment?

Saad Usmani, MD, MBA, FACP: One very important thing to understand is that almost all patients who have had four or five lines of treatment are going to be immune compromised and inherently be at risk for infection. That's number one. Then with the bispecifics, once we discontinue the treatment, that baseline risk doesn't go away. But, the general risk of infection attributed to the bispecific, that does get better. For example, with bispecifics, we are sometimes seeing reactivation of uncommon viral infections like cytomegalovirus (CMV) or Epstein-Barr virus (EBV), that kind of risk goes down. But, if someone is at higher risk of getting chest or respiratory infections, because of having myeloma and being immunocompromised that risk doesn't go away.

Mary Derome (MMRF): Anna, patients have heard that some bispecifics can affect a patient's sense of taste or smell. Can you clarify if this is general to all bispecifics or only to some of the drugs in that class?

Anna Howard, RN: The changes to taste and smell are something that we are still learning about. It's more of a rare and unusual side effect that we don't see that commonly with these bispecifics. We're still trying to get information to figure out exactly what is causing those changes to help better manage them as well.

Mary Derome (MMRF): Okay. That makes sense. Dr. Usmani, can patients expect any more bispecific antibodies to become approved and available? If so, when do you think that's going to happen?

Saad Usmani, MD, MBA, FACP: We have over a dozen different bispecifics in clinical trials.

Mary Derome (MMRF): There are a lot of them.

Saad Usmani, MD, MBA, FACP: They are at various phases of development. It's not just the BCMA-directed bispecifics. We also have GPRC5D-targeted bispecifics. GPRC5D is another surface marker on myeloma cells. There is another protein that is a cell surface marker on malignant plasma cells called FcRH5. So there are bispecific antibodies targeting, not just BCMA, but also these other markers. I would say that maybe in a year from now we might have one or two more bispecifics that get approved. Then it will be only a matter of time that others start getting approved. This provides measured hope for all of our patients for sure. I'm using the phrase "measured hope" because getting the drugs approved, the FDA, the benchmarks continue to change. Based on what we're seeing right now, we expect these drugs to come out in the market a year from now, but that may change depending on how FDA looks at this data.

Mary Derome (MMRF): Great. In general, this is a really exciting new class of therapies that patients are very interested in.

Saad Usmani, MD, MBA, FACP: Maybe we can take a look to see if there are any questions coming in.

Mary Derome (MMRF): Actually, we do have a little time. We only have two. Here's the first one. Are there any patients for whom bispecific antibodies aren’t an option? What conditions, if any, would rule out this therapy?

Saad Usmani, MD, MBA, FACP: I don't think there are any specific contraindications. The only thing that I would worry about is performance tests and frailty. I'm concerned that patients may not be able to withstand the CRS or infection risk if they’re frail, that would be the only situation. But, we've treated

patients with bispecifics who are in their 80s who've tolerated treatment very well and responded well.

Mary Derome (MMRF): That's great. Okay, so here's another question. Do patients need a certain left ventricular ejection fraction (LVEF) level to tolerate the CRS of bispecifics? And does the target matter?

Saad Usmani, MD, MBA, FACP: There is no cutoff for that for bispecifics, but maybe for CAR-T therapies. This is where we can distinguish using one versus the other. We do feel that the target matters right now. BCMA is the target that's been studied the most. BCMA doesn't get mutated or lost very commonly when myeloma progresses. So, you can potentially use different BCMA treatments for patients in sequence. We're just learning that's probably not the case for GPRC5D. The GPRC5D marker can get lost and it doesn't recover. So, sequencing treatments will become a very interesting topic over the next two or three years as more become available to us.

Mary Derome (MMRF): Again, thank you, Dr. Usmani, for being with us. Thank you, Anna, for being with us.