FAQs on Multiple Myeloma Following Relapse

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Transcript

Mary DeRome (MMRF): Welcome everyone and thank you for joining us for another session of Frequently Asked Questions on Multiple Myeloma Following Relapse. I'm Mary DeRome, Senior Director of Medical Communications and Education at the Multiple Myeloma Research Foundation.

Today I am joined by Dr. Nitya Nathwani and nurse practitioner Jennifer Bautista with the City of Hope Medical Center in Duarte, California, and Ms. Janet Anderson who is a patient from Lake Forest, California.

Dr. Nathwani, many patients relapse after receiving a combination of treatments. How do you know which drug or drugs that the patient received is no longer working? Is it usually all the drugs that they no longer respond to?

Nitya Nathwani, MD: One of the key things is multiple myeloma is not one disease but a spectrum of diseases. We know that multiple relapses can occur but, fortunately, we have many therapies now that we can employ along the way in a patient's myeloma journey. There's this idea of clonal evolution, so the myeloma that one starts out with is not necessarily what they end up with. Meaning, patients acquire genetic abnormalities in their myeloma cells.

Sometimes it may be that one clone of myeloma is more sensitive to certain drugs than another so we're able to eradicate that clone but a different clone subsequently surfaces. In part because of these multiple clones, we often use multiple drugs as treatment, both in the newly diagnosed setting as well as the relapse setting. Since it's difficult to know specifically which drug is not working, we want to attack the myeloma cells in many ways and try to prevent them from becoming resistant to treatment. So, we tend to switch around the different classes and agents at the time of a relapse.

Mary DeRome (MMRF): Jennifer, many patients ask about which tests patients should follow to be aware of potential disease recurrence. For example, should patients be watching their light chain values, M-spike proteins, or something else?

Jennifer Bautista, MSN, APRN, FNP-C: So, the SPEP is the main test that we use to find out how much myeloma protein there is. Positive results show monoclonal protein (M-spike or M-protein). Around 20% of patients do not produce intact proteins and will only produce free light chains. These patients are said to have light chain myeloma. There is a specialized test called the serum

free light assay which quantifies it. These are the two tests commonly used to routinely monitor for disease recurrence.

Mary DeRome (MMRF): When talking to patients about lab values, are they familiar with what you're talking about? Do they understand what you are measuring or do they have a difficultly with that?

Jennifer Bautista, MSN, APRN, FNP-C: It depends on what part of the disease progression they're at. Early on they are not very familiar but that's the time when I can break it down and explain to them what type of light chain myeloma we're categorizing them under and what labs to look for at that point.

Mary DeRome (MMRF): I suppose that as they move towards multiple relapses they become more and more familiar with the disease. That makes sense.

Jennifer Bautista, MSN, APRN, FNP-C: Correct.

Mary DeRome (MMRF): Dr. Nathwani, at what point in a patient's treatment course is a change in treatment warranted? Is it when patients are not responding to a course of treatment, or is it after their labs are done, and you see increasing M-protein after response?

Nitya Nathwani, MD: We generally change treatment when it's not working, obviously. There can be a lack of response from the very beginning or an increase in the M-protein or light chains after an initial response. So, if the M-protein or the involved light chains increase by more than a certain amount, we need to change treatment. Now, this could be within the first month or two after starting a new treatment or M-protein could rise five years after being on a given treatment. So, one of the important things to keep in mind is there must be a clear increase that meets a certain minimum threshold in order to warrant changing treatment. For example, usually, if the M-protein increases by more than 25% and that increase is confirmed on a second reading we will change treatment. There are also specific criteria for light chains as well.

Another important thing to keep in mind is that we need to give the treatment enough time to start working and we usually want to wait a few weeks from the time we start a new treatment before we say it's not working. Some treatments can take longer to achieve their full potential.

Mary DeRome (MMRF): Janet, let's talk a little bit about your disease journey. How did you find out that you had a relapse? Was it through a lab test or did you feel any specific symptoms when you relapsed? Could you tell even before you went to the doctor that you were relapsing?

Janet Anderson: No, I mean, up to this point I have never had any actual physical symptoms. I check the City of Hope patient portal and I look at my

kappa light chains. I don't have M-spike I have kappa light chain myeloma. Thankfully, I've not had any symptoms.

Mary DeRome (MMRF): So, it was the lab test that tipped you off?

Janet Anderson: Yes. They test my light chains every month and so, I would watch them in the beginning. The first couple of lines of treatment the increases would just creep, but as I got further along the third-line and fourth-line therapies, I'd see a lot of bigger jumps.

Mary DeRome (MMRF): Dr. Nathwani, what causes a patient to relapse? Whether it's their first-line relapse or after their third-, fourth-, or fifth-line therapy? Does relapse have anything to do with chromosomal abnormalities or any other characteristics that a patient might have?

Nitya Nathwani, MD: Generally, the first remission is the longest, but after each subsequent relapse the duration of response seems to be shorter. But, with some of the newer therapies, which we're very excited about, we are now getting longer remissions even in patients getting therapies in the fifth line and beyond. So, why is the disease different at each stage? Some of it is this idea of clonal evolution that I talked about earlier. Meaning patients acquire genetic abnormalities in their myeloma cells that can potentially make the myeloma more aggressive as it starts to come back.

The chromosomal abnormalities are one of the important determinants of relapse. For example, patients with high-risk myeloma have very specific chromosomal abnormalities that occur inside their plasma cells. This is not something they're born with; it's acquired over time. For patients with high-risk myeloma the response to each line of treatment tends to be shorter than in patients with standard-risk myeloma who do not have these specific genetic abnormalities. The good news is that with the newer treatments we're seeing significant improvements in outcomes.

Mary DeRome (MMRF): We do have a lot of good news in the myeloma community nowadays with all the new therapies we've got. That is great. Jennifer, what do patients need to know about their cytogenetic test results? I know that these results can be confusing for patients, and they don't really understand what they mean. How do you help them process this information? Why is it useful in discussing treatment plans?

Jennifer Bautista, MSN, APRN, FNP-C: Great question. Cytogenetic test results are difficult to interpret. I would advise the patients to ensure that FISH testing has been performed at diagnosis and to discuss these results with the treating team.

Mary DeRome (MMRF): Do you do anything beyond that? Are you doing next-generation sequencing or anything like that?

Jennifer Bautista, MSN, APRN, FNP-C: We are.

Mary DeRome (MMRF): Good. There's a lot of information there. Janet, are you aware and do you know if you have any cytogenetic abnormalities in your myeloma?

Janet Anderson: Yes, I have a lot. I started out with 17p deletion, then picked up gain of 1q, and monosomy 13 as more relapses came. Although not a cytogenetic abnormality, I have extramedullary disease, so that's another high-risk factor.

Mary DeRome (MMRF): Dr. Nathwani, do any therapies exist for relapse and refractory patients who have specific chromosomal abnormalities or patients who are high-risk?

Nitya Nathwani, MD: Absolutely. There is an ongoing coordinated effort to provide targeted therapy for specific chromosomal abnormalities. This is being done through the Multiple Myeloma Research Consortium (MMRC), in a study called MyDRUG. So, first, we perform genomic sequencing of the cancer cells in the bone marrow. If there is a specific therapy that exists for a certain chromosomal abnormality, then that specific therapy is given in combination with standard myeloma therapies.

I'd like to highlight a subset of patients with myeloma who have a very specific abnormality called translocation 11;14 [t(11;14)]. This means a piece of chromosome number 11 breaks off and gets reattached to chromosome 14. It's not that uncommon. It probably occurs in somewhere between 15% and 20% of patients with myeloma. There are some data that suggest standard treatment may be a bit less effective in this subset of patients. The good news is that there is a medication called venetoclax which is a pill that's very effective in this specific subset of patients. It's not approved in multiple myeloma, but it has been approved in other blood cancers. We have another clinical trial at our institution that specifically targets this t(11;14) with another agent. So, targeted treatment is becoming more common, and it's establishing the role of precision medicine in myeloma.

Mary DeRome (MMRF): That's great. I know that venetoclax is involved in the MyDRUG trial, right? We've been waiting for this drug to be approved in multiple myeloma for quite some time. I think we may see that happen, perhaps, in the next year. That would be great because we all know how effective it is for that subset of patients.

Jennifer, some patients might not have a lasting response. Usually, after they have stem cell transplant, consolidation, and maintenance therapy that can normally be their longest ever period of being disease free before they relapse again. Does that mean a future transplant would be unsuccessful and would not be an option at relapse? I don't know how common it is to have more than one stem cell transplant, but I know that there are patients who are particularly high-risk who undergo stem cell transplant more than once.

Jennifer Bautista, MSN, APRN, FNP-C: Yes, correct. Well, Mary, that's a hard question. It is an individual decision depending on the duration of the response to the first transplant and the available treatment options for an individual patient. Generally, we say that the duration of response to a second transplant is approximately half the duration of response to the first transplant.

Mary DeRome (MMRF): I know usually when patients undergo their first stem cell transplant they have enough stem cells collected to be able to do at least one more and sometimes two more depending on how successful the collection is.

Certainly, if you have all those cells stored, even in later sections of your disease when you're having trouble with your blood counts et cetera they will take those stem cells and reintroduce them back into the patients in the absence of having a stem cell transplant just to get blood counts to come back up. So, it's a really good resource for patients if they can collect a lot of those cells.

Janet, what can you tell us about your treatment journey? For example, what was your initial treatment and what have you been treated with since your diagnosis? I know that you've been through several things.

Janet Anderson: Yeah. So, I've had myeloma for about 8.5 years and I've had five different lines of treatment up to this point. So, my first treatment I didn't have an upfront stem cell transplant. We found out I was high risk with a 17p deletion, Dr. Nathwani enrolled me in a clinical trial for newly diagnosed high-risk patients. I used elotuzumab and dexamethasone. I got about a 4.5-year remission from that and then, when I relapsed then we went ahead and did the stem cell transplant followed up with Revlimid-Velcade maintenance after 60 days. That lasted for 2.5 years. When I relapsed, I went on to my third-line therapy, which was a clinical trial for one of the bispecific antibody drugs. I was in the arm with talquetamab, daratumumab, Pomalyst, and dexamethasone. So, that was a lot of drugs.

That remission only lasted about 9 months, and I noticed that my light chains were going up dramatically. So, obviously, I had the clone change like Dr. Nathwani was talking about. After that relapse I went on to my fourth-line treatment which was Cytoxan, carfilzomib, and dexamethasone. That remission only lasted about 4 months, then my numbers started going up. I've always responded to treatment thankfully but I could see the trend that my remissions

were getting shorter and shorter. Where do you go after your last one's only 4 months? I was feeling like the curtains were starting to close. That's when Dr. Nathwani called me, like an angel of mercy, and was able to get me into the CAR T-cell Abecma therapy. So, I had my T-cells collected around the end of July and received them back middle of September this year.

Mary DeRome (MMRF): That's great.

Janet Anderson: I am doing great. I am in remission. I guess I can say a complete remission? My numbers are low, my PET scan was good so, life is good right now.

Mary DeRome (MMRF): Good for you. Being able to get one of these CAR T-cell therapies is like winning the lottery. So, they're extremely effective drugs but it's hard to get on the list and it takes a long time to make them once the cells are collected.

Janet Anderson: Right.

Mary DeRome (MMRF): So, it's a very effective therapy but it's not without its issues.

Janet Anderson: With Abecma there were no hangups in the manufacturing of it. It was pretty much on schedule. I know that's not necessarily the situation with other agents.

Mary DeRome (MMRF): That's true. Dr. Nathwani, we now have 3 different agents available that target the B cell maturation antigen (BCMA), and Abecma is one of those. So, there are two CAR T-cell therapies, Abecma and Carvykti that are associated with the BCMA and then there's another bispecific antibody Tecvayli, which was just recently approved. What's the difference between those agents and how do you choose which one to get? Sequencing is also a very big issue.

Nitya Nathwani, MD: I think the good news for patients to remember is that all 3 products are incredibly effective and we are seeing durable responses in most patients who have received multiple prior lines of treatment. On average these patients in the clinical trials have received six prior lines of treatment. As Jennifer said, there are a lot of factors to consider while deciding on treatment.

So, CAR T-cells use a patient’s own T-cells, which is a part of their immune system. These T-cells are manipulated in the lab to kill myeloma cells. They are then infused in a patient in a very controlled manner. They are incredibly effective. Another very appealing aspect is it's given once, followed by a hopefully long treatment-free interval depending on how long they work for. But the challenge is that CAR T-cells, as you talked about, are harder to get. One

must be on a waitlist to get this and it takes a while to manufacture the cells in the lab. So, if a patient has very aggressive myeloma it may not be practical to wait for this treatment. In terms of deciding between the two FDA-approved CAR T-cell products, I would say they're both very active and if a patient is eligible, we give either product. We often decide depending on which one is available sooner.

Another message we're trying to get out to the referring doctors and patients and their caregivers is that if there is a patient with relapsed myeloma, it makes sense for them to be referred to a CAR T-cell center early. While they may not be ready for CAR T-cells, at least they get in the system and we're aware of them so that when they need it, hopefully they're already on the list and we're able to move quicker to therapy.

The bispecifics have two targets: one half of the antibody recognizes the target on the myeloma cell, and the other half of the antibody recognizes the receptor on the T-cells. So, this antibody grabs a T-cell with one arm and grabs the myeloma cell with the other arm, then pulls them together and activates the T-cell in the process so that it can kill the myeloma cell.

So, teclistamab (Tecvayli) is an off-the-shelf treatment, so no need to wait for this long process of genetic engineering that's required with CAR T-cells. It offers a very active option to many more patients. The disadvantage of this medication is that it's given weekly. With continued treatment the risk of infections appears to be higher as it depletes B-cells, which help with immunity to infection.

To summarize, all 3 treatments targeting BCMA, both CAR T-cells and the approved bispecific are very effective. What to use is an individualized decision. We consider many factors including how aggressive a patient's myeloma is and whether it makes sense to wait for the CAR T-cells.

Mary DeRome (MMRF): I know that waiting period can sometimes be quite prolonged. As you mentioned, if a patient is very ill it can mean that they just can't wait. Let's talk a little bit more about BCMA-targeted agents and some of the nuances.

Jennifer, can a patient who had a stem cell transplant get CAR T-cell therapy?

Jennifer Bautista, MSN, APRN, FNP-C: Yes, they can.

Mary DeRome (MMRF): Sometimes patients get confused because when they have a transplant, they're collecting cells and when they need CAR T-cell therapy, they're collecting cells. So, can you talk a little bit about the differences between these two?

Nitya Nathwani, MD: So, you know, it's a similar process. Both are outpatient procedures. CAR T-cell collection is generally much quicker, and you don't need

shots to mobilize them. With stem cells you require shots called G-CSF to push the stem cells out into the periphery and then it's like a blood donation where you sit in this chair and have your blood spin through a machine and you separate out the stem cells, which you collect, freeze, and store for a future stem cell transplant.

Mary DeRome (MMRF): It's totally different types of cells that you're collecting, right? For transplant you're collecting stem cells but for CAR T-cell therapy you're collecting T-cells, right? They're totally not the same thing so, you can't use one type of cell for the other thing.

Nitya Nathwani, MD: Exactly.

Mary DeRome (MMRF): Dr. Nathwani, do patients have to be tested for BCMA expression to receive a drug that targets BCMA? Is there a connection there?

Nitya Nathwani, MD: That's a good question. So, you know, we have not been routinely testing for BCMA before giving a BCMA-targeted drug for the first time. There may be some value in testing for BCMA expression if we are considering giving a second BCMA-targeted drug if the patient had received BCMA-targeted treatment recently.

Mary DeRome (MMRF): There's a lot of work going on now to really look at the sequencing of different agents because there are so many agents that target BCMA and the question is, if you have one BCMA-targeting agent, can you then get a second one directly after that?

There was an interesting presentation at ASH, which suggested that if you were a patient who had received a BCMA-targeting agent, for example, Tecvayli or maybe Blenrep which is an antibody-drug conjugate that targets BCMA, if you then had Abecma, it wouldn't be quite as effective as if you hadn't had a BCMA agent. This was at least within a 6-month period or something like that. So, clearly this is something that a lot of people are working on trying to understand a little bit better.

Jennifer, do patients have to be admitted to the hospital to receive these types of treatments?

Jennifer Bautista, MSN, APRN, FNP-C: We're doing CAR T-cell therapy at outpatient. As far as the bispecifics, we are admitting them for step-up dosing with the goal of continuing as an outpatient.

Mary DeRome (MMRF): Dr. Nathwani, if a patient has CAR T-cell therapy and relapses after the therapy, can they have the other CAR T-cell therapy?

Nitya Nathwani, MD: The short answer is yes. They can get the other one. But we have very effective approaches using different targets. For example, there's a CAR T-cell product using a different target called GPRC5D from a small study but the results were very promising with around 70% percent of patients responding. To clarify, both CAR T-cell products that have been approved by the Food and Drug Administration target BCMA. The GPRC5D as a target doesn't have any approved therapy yet.

Mary DeRome (MMRF): That is the target of talquetamab, right?

Nitya Nathwani, MD: Exactly, and there are other targets as well including FcRH5.

Mary DeRome (MMRF): Right. Hopefully, we'll see one of these new bispecifics that have a different target approved. I think that would really help a lot of folks with this sequencing issue because you could target something different and then relapse and then target a second different thing. It would be helpful.

Jennifer, some patients may have multiple relapses and as a result, they are heavily pretreated. Does this limit the use of specific treatments? For example, maybe a patient's kidney function was diminished over time or they have another issue that was caused by prior treatments. Is this a problem in these heavily pretreated patients?

Jennifer Bautista, MSN, APRN, FNP-C: When a patient develops relapsed myeloma, we consider several factors while selecting therapy. We will often use the mnemonic TRAP. T for timing of the relapse, R is response to prior therapy, A for aggressiveness of the relapse, and P for performance status.

We also factor in the patient’s comorbidities, convenience, and lifestyle. Can they stay near the CAR T-cell center for up to 2 months? Do they have a caregiver? We can't do CAR T-cell therapy without a caregiver. So, there are several factors involved.

Mary DeRome (MMRF): Janet, how do you handle your day-to-day since being diagnosed, and the various treatments that you've had over the course of your journey? Have you had to deal with some severe side effects?

Janet Anderson: I've been lucky in the side effects arena. Of course, stem cell transplants have the usual side effects that we all know. Probably, dexamethasone has had the worst ongoing side effects, especially if you're at 40 milligrams. I learned early on that I had to watch my carbohydrate intake because apparently it affects how your body metabolizes carbohydrates. I've learned that you don't fight insomnia, just take advantage of all that energy, and when you crash you just sleep.

With talquetamab, I had some significant peeling of skin on my hands and eventually on my feet. It was burning and it looked bad. But, Dr. Nathwani did prescribe an ointment for that, and I ordered a big box of disposable cotton gloves, and so I was able to continue. What has been important is to be able to continue having a normal life. With all the crazy side effects going on, we always seem to want to gravitate towards feeling like we can have a normal life.

The CAR T-cell side effects were just what I'd read about and what Dr. Nathwani told me would happen. I did get the CRS (cytokine release syndrome) within hours of getting the infusions, so that was fast. So, high fevers, body aches, and then, I had about 24 hours of total amnesia, and I didn't remember anything.

Once they give you the tocilizumab, it reverses things, and you start getting back to normal. I haven't had too much peripheral neuropathy. From the very beginning Dr. Nathwani had recommended B complex vitamins and alpha-lipoic acid and I attribute that to why my neuropathy is very minimal. I still get my quarterly Zometa. I found that if they increase the infusion just a little bit it makes a big difference in the body aches.

I'll get IVIG periodically if my IgG falls below 400 mg/mL. For the last two, shortly after the infusion I got horrible nausea. I'm not a nausea person. But they gave me Zofran, and that pretty much takes care of it. So, I don't know if it's the longer you've been on those drugs the worse the side effects get. But I feel very blessed to have been able, all this time, to live a normal life. I have a great support system with my family and my employer. I'm at City of Hope under Dr. Nathwani's care so, it's probably doesn't get any better than that. I've tried to do everything in my power to help myself. I focus on healthy eating, getting exercise, and I listen to visualization and affirmation tapes to keep the positive thinking.

Mary DeRome (MMRF): Oh yeah, so important.

Janet Anderson: It truly is. I am a firm believer in that mind-body connection. Dr. Nathwani told me in the very beginning this was a marathon and not a sprint. You must be in it for the long haul mentally because you do go through so many ups and downs. You're up when the treatment's working and you can get down when it's not working. So, you must strengthen yourself mentally as preparation for all this.

Mary DeRome (MMRF): Sure.

Janet Anderson: I've connected with a lot of other people in different myeloma platforms. People who have also 17p deletion, are on CAR T-cell therapy, or on bispecifics. It's been helpful to be able to connect with them where they are along the way. The administrators of these groups are very good about saying, “We only share scientific data not just our belief about why we think this is happening.” For me it's important to make plans. It gives me hope for the future,

and things to look forward to, so I do not feel like I'm getting to the very end. That's why it's great to be in a center like City of Hope where you have all these clinical trials available. I probably wouldn't be here if it wasn't for that.

Mary DeRome (MMRF): Certainly, it's very important that when one is diagnosed with myeloma to find a myeloma specialist to take charge of your care because this is a very complicated disease. To have the best outcomes, which it sounds like Janet is having, you must be working with someone who knows all the best new treatments because there's new treatments around the corner all the time. That's what makes being a myeloma patient these days so much better than being a myeloma patient 15 or 20 years ago when there were literally, no drugs, right?

Janet Anderson: But it's amazing how many people aren't being seen by a specialist. They're just being seen by a general hematologist. Maybe they live in an area where they don't really have access to a specialist.

Mary DeRome (MMRF): Possibly.

Janet Anderson: We always tell them, "Go, find a specialist if you can find somebody somewhere."

Mary DeRome (MMRF): Certainly, if it is a person who has a myeloma subtype like you, which does sound like it's a little bit high-risk, then it is especially important for them to find a specialist for their care. Because, maybe if you have low-risk or standard-risk myeloma, then it's more or less okay to be seen by the hematologist down the street. But if you have high-risk disease, then it certainly behooves you to, at least when you're first diagnosed, get several opinions from different doctors, and one of them should be a myeloma specialist. That way, you'll know that you're going in the right direction. Even if you're seen by a community hematologist, have that person consult occasionally with a myeloma specialist to make sure that what you're doing is keeping you on the right track.

Janet, you sound like a very resilient person to have made it this far, right?

Janet Anderson: I don't know, I just put my blinders on and do the Pollyanna dance.

Mary DeRome (MMRF): Whatever it takes to get through, right?

Janet Anderson: Because Dr. Nathwani is a specialist, and he's been a doctor in myeloma for a long time, none of this is new to him. My cytogenetic abnormalities, extramedullary disease, all of that he's seen before. So, that gives me a lot of faith in him.

Mary DeRome (MMRF): Right. So, you have confidence that you're seeing a person who can really help you with your best outcome. That is great.

Janet Anderson: Yes.

Mary DeRome (MMRF): Dr. Nathwani, many patients realize that CAR T-cell therapy may also eventually fail to work. What options are available to patients who have relapsed from CAR T-cell therapy? I know we already talked a little bit about repeating CAR T-cell therapy which may work but may not, right?

Nitya Nathwani, MD: Right. Excellent question. Fortunately, we have effective options even for patients who have relapsed following CAR T-cell therapy. As we talked about earlier, both FDA-approved CAR T-cell products target BCMA. So, it would make sense to try a clinical trial perhaps with a different target. I'll talk about two other main targets. So, one of them is called GPRC5D and there are clinical trials with the CAR T-cell product. There's also this bispecific antibody that we talked about briefly called talquetamab, which we are very excited about. It's not approved yet, but there is tremendous excitement about it.

Updated results were presented at ASH 2022. It demonstrated an overall response rate above 70%. Even in patients who had received prior T-cell directed therapy, the response rate was over 60%. These were very important findings, so much so that they were highlighted again on the last day at ‘the best of ASH session’, where the most impactful research findings are highlighted. An important thing to mention with this GPRC5D target is that as Janet mentioned it's expressed on keratinized tissue. That means your nails and hair follicles are affected and that's why it's unique in some of its side effects.

The other target to talk about is called FcRH5, which is also incredibly exciting. We've had patients who have been on a bispecific targeting FcRH5. In one of the trials this drug is given for 1 year, so it is incredible that we have a fixed duration of treatment. We don't continue the drug indefinitely. We've had patients who've been off this drug for 2 or 3 years now and are still in remission.

If a patient has relapsed following CAR T-cell therapy, we can continue with the same BCMA target. In fact, there was a recent presentation at ASH 2022 where a subset of patients in a small study who had received prior BCMA-targeted treatment including CAR T-cells therapy still responded to another BCMA target with a bispecific antibody. The response rate was above 50% with the same target, just this time a bispecific.

Mary DeRome (MMRF): I attended some of those presentations. If you have something that targets BCMA that you take before a CAR T-cell, which would normally have a 70% or 75% response rate, that response will then drop to 50%, right? But you still are getting a response even though it's the same target. I think that sort of sequencing information is going to become more important as time

goes on. The more targets we can pick up for these bispecific antibodies and CAR T-cells, I think the better off all patients will be. It'll be much easier to switch targets, and the efficacy should remain, hopefully. But we'll see what comes out in clinical trials.

Another thing that we heard about at ASH 2022 was the new iberdomide drug. There was a presentation on mezigdomide. Can you tell us a little bit about that?

Nitya Nathwani, MD: Absolutely. There are a lot of exciting developments. There's this whole new class of medication called CELMoDs, which bind to the same target as lenalidomide and pomalidomide that many of you are very familiar with. The big benefit is that this class of medications binds with higher affinity and degrades the target proteins much more effectively. So, one of these medications is called iberdomide.

The very appealing thing about this medication is that other than lowering the blood counts it doesn't have any of the other common side effects that most myeloma patients experience such as fatigue, diarrhea, and neuropathy.

Mezigdomide is in the same CELMoD class of medications. It's even more potent than iberdomide. A very encouraging feature of this medication is that we have seen responses in patients with extramedullary disease, meaning, myeloma outside the bone marrow. We have a clinical trial using this medication at our institution.

About venetoclax, which we talked about earlier, we're very excited that we now can specifically target t(11;14).

Allogeneic CAR T-cells, meaning CAR T-cells from a donor that undergo gene editing are also in clinical trials. These have the potential to be given to more patients, and they would not have to necessarily wait a long time for the cells to be manufactured. We also have clinical trials using allogeneic CAR T-cells at our center. Besides all these, there are newer CAR T-cells, which are being studied that have been engineered to remain in the body for longer. There are also drugs called gamma secretase inhibitors that increase BCMA expression, and we also have a clinical trial using that at our institution.

Mary DeRome (MMRF): Wow. There are a lot of new things coming up, that's for sure. Is mezigdomide an oral medication like Revlimid or is it infused?

Nitya Nathwani, MD: Mezigdomide is an oral medication.

Mary DeRome (MMRF): On behalf of the MMRF I'd like to thank Dr. Nathwani, Ms. Bautista, and Ms. Anderson for joining us today.