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Off-the-shelf Immune Drug for Aggressive Multiple Myeloma: Teclistamab

U.S. Food and Drug Administration (FDA) has granted Breakthrough Therapy Designation (BTD) for teclistamab in the treatment of relapsed or refractory multiple myeloma. This follows a PRIME (PRIority MEdicines) designation from the European Medicines Agency (EMA) received earlier this year.

The Breakthrough and PRIME designations are supported by data from the Phase 1 MajesTEC-1 study, an open-label, multicenter clinical trial evaluating the safety and efficacy of teclistamab in adults with measurable multiple myeloma that is relapsed or refractory to established therapies or be intolerant of those established multiple myeloma therapies.

Multiple Myeloma that has relapsed and has become refractory to treatment, represents a patient population with unmet needs. Teclistamab is a bispecific IgG4 antibody that binds BCMA and CD3 to redirect T cells to multiple myeloma cells. According to the investigators, the current study is—to their knowledge—the first report of a T-cell–redirecting bispecific antibody for the treatment of patients with cancer.

The Myeloma panel of Gary Petersen, Jack Aiello, and Cynthia Chmielewski takes a deep dive on Teclistamab with Dr. Alfred L. Garfall hematologist oncologist from University of Pennsylvania.

Full Transcript:

Priya Menon: Hello and welcome to CureTalks. I'm Priya Menon, your host. Today on CureTalks we are discussing Teclistamab in the treatment of multiple myeloma. Teclistamab was recently granted breakthrough therapy designation by the FDA. Our featured guest today is hematologist, oncologist. Dr. Alfred L. Garfall, Director of Autologous Hematopoietic Stem Cell Transplantation and Assistant Professor of Medicine at the Hospital of the University of Pennsylvania. Joining Dr. Garfall on the panel are Patient Advocates, Gary Petersen, Jack Aiello, and Cynthia Chmielewski. Once again, everybody welcome to CureTalks. Dr. Garfall I want to just jump right in Teclistamab is an off-the-shelf T-cell redirecting bispecific antibody targeting both these B-Cell Maturation antigens and CD3 receptors. It's really confusing. Can you please explain in simple words what this new drug is all about and how it will act on myeloma and what the entire excitement is all about?

Dr. Alfred L. Garfall: Sure. So, thank you very much for having me. It's nice to be here and it's nice to see some familiar faces too from the patient panel. So, there are host of immunotherapies for cancer, immunotherapies for myeloma that their goal is to find a way to get the patient's immune system to recognize and kill the multiple myeloma cells. And so, the most simple form of these are conventional, monoclonal antibodies where the drug is an antibody against myeloma. Just like your immune system would make antibodies against the virus or bacteria, antibodies can be generated in the lab against multiple myeloma cells and those antibodies can bind to the multiple myeloma cells and hopefully then kind of recruit different aspects of the immune system to kill the multiple myeloma cells. So, the antibodies allow the

immune system to recognize the multiple myeloma cells. So, typical antibodies, the part of the immune system that they trigger will be called the innate immune system. It sells like macrophages and natural killer cells and neutrophils to recognize the myeloma cells. What is different about these bispecific antibodies is that they force T cells to recognize the multiple myeloma cells, which is a different arm of the immune system. And what we've learned over the years is that the ability of activated T cells to kill cancer cells seems to be a little bit more potent and what we can get with neutrophils and macrophages, and we've learned that in large part from the story with CAR-T cells. So, when CAR-T cell therapy was actually taking T cells out of the body genetically engineering them and reinfusing them into the body. And we've seen really remarkable responses across a few different types of blood cancers, including multiple myeloma with CAR-T cells. And so, the bispecific antibodies are trying to engineer that kind of T Cell Activation against the myeloma in the form of an antibody with the benefit being that it can be given as a drug rather than having to undertake this more complicated process of genetically engineering CAR-T cells. So, the way Teclistamab works and Teclistamab is similar to a number of drugs in this category that is being developed for multiple myeloma is that instead of just recognizing one molecule on the surface of the myeloma cell. Teclistamab recognizes two molecules, one on the surface of the myeloma cell and one on the surface of the T-cell. And so, the way the drugs are thought to work is it kind of grabs with one hand the multiple myeloma cell in with the other hand, a T-cell and brings them together and forces the T-cell to recognize and be activated against the myeloma cell and thereby kill all the myeloma cell.

Priya Menon: That's really great. So, Dr. Garfall can you talk a little bit also about the trial findings. Like, how did the patients respond to treatment? What do we know about the durability of the response? And what were some of the toxicities that were observed?

Dr. Alfred L. Garfall: Sure, so this trial has been kind of reported incrementally over the years, over a couple of years now as more and more patients have been treated and we have more and more follow-up and that we should be getting an update at the upcoming ASH meeting next month with more recent results. But what we've seen at each of the updates is that about two-thirds of patients seem to respond to this therapy. And remember this is the Phase I study, so it really was conducted in patients who are really running out of options for the treatment of multiple myeloma. So, patients who had mostly seen all the typical therapies, and have previously had all the typical therapies for multiple myeloma, were really running out of options, as a single drug, this drug-induced responses. So, we say at least a 50% reduction in the amount of multiple myeloma in the patients, in about two-thirds of patients. And so that's I think the sort of the main point in terms of effectiveness that we saw, that's really stunning. Suddenly a high response rate in this type of patient population who's really running out of other options for a single drug to have that kind of effect and so that's really impressive. From the point of view of response durability what's really nice too is that most of the patients who responded, continued the long-term responses and we still don't know what the average is going to be because most of those patients are still having ongoing responses. But it's quite long for patients who are responding, and we've had patients here at PENN who have been on the drug for over two years now, who are some of the initial responders. And that's also a really impressive finding in this group of patients who had exhausted so many of their standard treatment options to have a drug that can work for that long. And the third thing I would say is really encouraging is the safety of the drug. And so, we know from the experience with CAR-T cells, that therapies that activate T cells against cancer, have the potential to stimulate a lot of inflammation in the body. We call that cytokine release syndrome and that can be challenging toxicity to manage. And what we've seen with this drug is that we do see that actually most patients, develop some cytokine release syndrome, but it was all low-grade, meaning that while there's always the potential for cytokine release to cause really severe abnormalities that almost all the patients who develop cytokine release syndrome on this study, had low-grade cytokine release syndrome. Meaning that it really just manifested as fevers, maybe a little bit of need for some oxygen, a little bit of low blood pressure to that all could be managed without requirements for intensive care. In patients, there's an antidote to cytokine release syndrome called tolucizumab and that was effective in most patients who develop some of those more concerning findings like blood pressure and some difficulty breathing, and that was successful in treating the cytokine release and keeping it a low grade. And that's a side effect also, that is really concentrated in the first few doses of the drug. And in our patients, who have been on the drug for a long time. It's really impressive that they have very little if any cumulative toxicity and that's a real breath of fresh air for multiple myeloma therapy. So, we've been fortunate for a while in multiple myeloma to have relatively

safe drugs as far as cancer therapies go. But all of these drugs, as patients are on them for months and months really do lead to accumulative toxicity. Sometimes not with severe problems, but certainly problems that really wear on people over time. Fatigue, gastrointestinal issues, effects on the blood count that make it hard to continue the therapies indefinitely. We really haven't seen much of that with teclistamab. The most concerning toxicities are concentrated in those first couple doses and the patients who have been on it for a month after month have very little cumulative toxicity and it's a drug that's given as a subcutaneous injection. So, it's really remarkable this drug that could be given once every week or two as a subcutaneous injection can have this kind of long-term beneficial effect on the myeloma with very little cumulative toxicity.

Priya Menon: Thank you. Dr. Garfall. With that I think I would hand it over to the patient panel. They have a whole lot of questions for you. Gary, please start with your questions.

Gary Petersen: Thank you. And Doctor, thank you so much for coming today. I think CAR-T is really taken center stage, and lately and bispecific is something relatively new. What are the advantages and disadvantages of bispecific over CAR-T or Vice Versa?

Dr. Alfred L. Garfall: Yeah, so there are some pros and cons to each approach, and I think we still have a lot of learning to do in comparing these two different approaches. There's been a very small number of patients who have gotten both. But for the most part, these have been therapies given on clinical trials where patients who had gotten one had not gotten the other and so we have a lot to learn about how we might choose one versus the other for patients once they're approved by the FDA and how we might sequence one after the other, for instance. But I would think of the big differences between them, one is the complexity of initiating the therapy, and so, with CAR-T cells you have the product manufacturing patient-specific way. So, T cells have to be collected from the patient, sent off to the company where the CAR-T cells are manufactured delivered back to the site where they are going to be administered, the patient has to receive some chemotherapy to allow the CAR-T cells to graft in the patient and then the patient receives the CAR-T cells. So that introduces a lot of logistical complexity and so patients have to number one, that whole process of collecting, self-shipping them, returning them. That's not something that every community oncology centre is going to be set up to do, that's something that is probably going to be for time be restricted to a few different sub-speciality centres around the country. So that's going to restrict, how many people have access to CAR-T cell therapy at least without a lot of extra effort and planning on the part of the patient. And also, there's a time delay built into that. So, you can't decide on Monday to give someone CAR-T cells and give them on a Wednesday or Friday. You have to kind of plan about six weeks in advance these and related to that the companies right now that have FDA, the one company that has an FDA approved CAR-T cell product and it's probably going to be the case for a little while with even subsequent companies their supply is not endless, there is also a lot of complexity on the part of the pharmaceutical companies to make these things. They have to have all their infrastructure setup and what we've seen so far with CAR-T Cell therapy is that that can limit the supply availability. The advantage of CAR-T cells, however, is that as kind of a one-time therapy and what we've seen in patients who have responded to CAR-T cells that they can keep their myeloma under control for months or even years. But just this one-time therapy and not require, continuous ongoing therapy, which is the case with most of our multiple myeloma therapies and also so far with bispecific antibodies. On the other hand, so the pros of bispecific antibodies are that they're monoclonal antibodies and they can just be given off the shelf as they say, and so just like, we have daratumumab is a monoclonal antibody for myeloma, Elotuzumab is a monoclonal antibody for myeloma, Teclistamab and others like it are antibodies. If Spectra continues to be able to make large quantities of them, and we store them in our pharmacy, and when we're ready to give them to somebody who just mix it up and give it to somebody. You don't have to go through this complicated process. Right now, it seems like because of the toxicity that can come with those first couple of doses, those first couple of doses might have to be given in a more monitored setting maybe as part of a short hospital stay but there are not nearly as much logistical challenges with getting them started, and I expect that a wider range of Cancer Centres and oncology offices you're going to be able to administer bispecific antibodies and apparently able to get CAR-T cells. The downside though is sales bispecific antibodies, is that these, for now, seem like a therapy that's going to have to be given continuously. We still don't know if we stop it, after someone has a complete response does, we compromise the long-term outcomes. And at least right now, there are different bispecific antibodies that are being developed, are being developed as continuous therapies at least for a year or two.

And we will learn with time that is more of a burden on the patient obviously to have to get a therapy continuously compared to CAR-T cells that could be this one-time therapy. I would say the second thing about bispecific antibodies as a potential downside is that while we're still figuring this out and it's probably premature to state any of these comparisons with certainty. Some of the results we are seeing with CAR-T cells maybe a little bit better than what we're seeing with the bispecific antibodies in terms of the response rates for instance.

Gary Petersen:… in some cases 100%, right?

Dr. Alfred L. Garfall: Yeah, some of the best CAR-T cells that are out there have response rates of 80, 90, 100%. Whereas, the bispecific antibodies, it seems to be more in the 60-80 pe%rcent range. Now, you have to be really careful about comparing between these studies which are relatively small and it's going to be a long time before we get any kind of comparative studies, but I think that the CAR-T cells in their best form, might be more potent and I also think that, in terms of the future, the amount of engineering that can be done with the CAR-T cell technology to make it better is there's probably more room to grow in terms of making those therapies more sophisticated over the years compared to bispecific antibodies. And so, I think, I can imagine, and I know there are a lot of cool Innovations being tested on CAR-T cells that are really only possible with that type of genetic engineering technology. And I don't know if we'll see if there's this much room to grow with the antibody technology, but the drug companies keep on coming up with clever ideas. So maybe there is.

Gary Petersen: So, could this be a bridge to CAR-T , because in 75% is pretty good. I mean, given, some of the ones that have just been approved like Selinexor etc.?

Dr. Alfred L. Garfall: I could imagine that bispecific antibodies could be used as a bridge to CAR-T cells. And so that's just a lingo I want to translate a little bit for the broader audience here. Because CAR-T cells can't be given immediately. Somebody who has rapidly progressing disease, often needs, even if we plan to give them CAR-T cells need something that we refer to as bridging therapy, which is some therapy to just kind of tie them over for those six weeks or so before they can get the CAR-T cell therapy. So, there are discussions about whether bispecific antibodies could be that bridge, in an essence you kind of get the best of both worlds. You can start a really potent therapy quickly when the patient needs it. But then transition over to a one-time therapy, the CAR-T cell therapy that would provide a durable response without the need for ongoing therapy. And I think that's really an attractive combination. The other advantage of that is that I would say that the toxicity profile with the bispecific antibodies is a little bit better than what we're seeing with the CAR-T cells. With the CAR-T cells, you use those T cells, and then they do their thing in the body. And that's a little bit of an unpredictable process and once the T cells are in, you have to deal with whatever happens in terms of side effects. The same side effects that I mentioned are cytokine release syndrome. And then there's another variety of CAR-T cell toxicity called neurologic toxicity, which has been really tough to handle in the rare cases where it's severe. So those are side effects of both bispecific antibodies and CAR-T cells. With bispecific antibodies, the way we give them, we give like a tiny dose and then a little bit higher dose a couple of days later, a little bit higher dose the day after that, and that allows some controlling and some adjustment of the dosing in response to toxicity. So, if we give that tiny dose and we get real toxicity, we can wait a few days before we give the next dose. On the other hand, if we give the tiny dose and nothing happens, we can give the next dose a day or two later you can't do that type of adjustment with CAR-T cells. You just give the CAR-T cells and you deal with whatever toxicity happens and what we've learned with that…

Gary Petersen: Fractional doses for CAR-T too just like you're doing for bispecific?

Dr. Alfred L. Garfall: So, we've done some of that here at PENN for CAR-T cell that we've been to that we've developed here, but none of the products that are going forward in commercial development are like that and it doesn't reduce a whole other layer of logistical complexity because of the company that has to make these different doses and send them back. But what we have learned though is that with more severe toxicity, with CAR-T cells, there seems to be a higher risk of severe toxicity in patients that have a lot of myelomas. And so, if you have a high burden of multiple myeloma years at a higher risk of some of these

more severe toxicities, so you can imagine that if we have a very effective therapy with more controllable toxicity, like bispecific antibodies you could use that to get the myeloma level down and then that would make the administration a little bit safer that's the idea of sequencing them and using one of the bridgings for the other but that's all the million ideas that have to be tested in a clinical trial. And I really am hoping that we'll see some clinical trials testing that in the next year or two.

Gary Petersen: One thing that was mentioned was about CAR-T was the problem with having availability and Dr. Fonseca had sent a tweet out one time where Dr. Fonseca said bispecific is the one that's going to win over CAR-T because there is no CAR-T because there's no availability. So that was kind of an issue you addressed as well. And I was just wondering if you had ever heard of the company, Presigen. And what they're doing. They're talking at these about being able to distribute their product to various locations in that with then be able to be done on-site anyways..

Dr. Alfred L. Garfall: No, I'm aware of the one that, but I'm a little bit more aware of is an effort by a company called Miltenyi using a device called Prodigy, but I understand there are a couple of these out there. I would say those are I agree that that's an appealing approach and I think should be investigated. I also have some help though from the experience that myeloma is not the first disease that's been treated with FDA-approved CAR-T cells. We now have a few years of experience with lymphoma and there are now several products approved as CAR-T Cell therapies for lymphoma. My friends and my colleagues who treat lymphoma say that there really isn't much of a supply limitation for those products. And so, I have optimism that following that model, that what we're seeing with the multiple myeloma and the BCMA product is just some growing teams..and with time the supply issue is not going to be as major an issue.

Gary Petersen: Well, that's longer we're here. So, thank you so much for mentioning that and the last thing I wanted to ask was, what's haunted CAR-T has been side effects and costs, and you mentioned a little bit about it that this new bispecific drug has some of those same things. Are there any showstoppers with the new bispecific drug?

Dr. Alfred L. Garfall: What do you mean by showstoppers in terms of…

Gary Petersen: Well, the neurological. Are there any? The things that you mentioned. For example, I know that some type of CAR-T originally almost didn't survive because of the cytokine release syndrome and that was very very problematic and that was resolved, and so, you mentioned some of the things that you referenced there and my assumption is that given that there doesn't seem to be any, but you would be the one that would know is there any things like with covid where you can have actually a heart issue with some of the vaccines. So, is there something out there that you've seen in the clinical trials that is lurking in the background that I could? I'm just curious.

Dr. Alfred L. Garfall: Yeah, so that's a good question. So, I would say that we should be a little bit cautious first of all, with all of our conclusions because right now most of the data we have on these therapies are from Phase 1 clinical trials. And so, we're talking about trials, where these drugs have been given to dozens of patients, not thousands of patients. And a lot of these, more concerning rare toxicities, might emerge only when you really give the drugs to thousands of patients, so, I suspect that based on Phase 2 studies where the drug has been given to a couple of hundred patients will have a better sense of, whether there might be rare toxicities that would be concerning. But what we've seen so far in the Phase 1 studies are the expected side effects of cytokine release syndrome and neurologic toxicity that we expect these side effects based on the prior experience, with CAR-T cells. Incidentally, there is actually a bispecific antibody already approved for leukemia. And there's a drug called Blinatumomab (Blincyto) that is chemically a little bit different from the bispecific antibody in myeloma but is the same basic principle and we see some of the same side effects with that drug. And so bottom line is, I think we've seen so far, are toxicities that we expect based on the way, we know the drugs to work, and they've been manageable, those still serious in some cases, but I think manageable but not showstoppers as you said in terms of really precluding, the widespread use of these drugs. There is with a couple of these the…. first BCMA bispecific antibody that came out in the first published Phase 1 clinical trial of a bispecific antibody was the drug from Amgen that was published a couple of years ago in the journal of clinical oncology. In addition to the usual side effects, they did see an unusual

type of peripheral neuropathies, not neurological involving the brain but peripheral neuropathy that resembled a disease called Guillain Barre syndrome, which is a type of neuropathy that can develop sort of immunologic type for neuropathy. So far to my knowledge, that is only really been seen with that drug and maybe I saw it on a press release one of the other bispecifics. We haven't seen it in Teclistamab at least to my knowledge on any of the studies. So, I don't know if that would be something that I would be treated more patients and use the drug more widely that comes out as a rare side effect. And maybe we've just been lucky with the Teclistamab so far that we haven't seen it and it's working someplace to be seen in the future. But other than that, I don't see any showstoppers as you say with Teclistamab and BCMA drug in bispecific antibodies.

Gary Petersen: Okay, and then the last one there was about cost. Do you see this like I know one company has a CAR-T that they are talking about providing and they've just dropped out of Europe because of it? They wanted a million nine for it. So that's kind of a showstopper on cost. Do you see this being far more reasonable?

Dr. Alfred L. Garfall: Cost is so complicated, I think. So, the BCMA CAR-T cell-like ___ one that is FDA-approved I think is priced comparably to the other CAR-T cells that have been FDA approved for lymphoma. And that's gone forward in the United States obviously and it is paid for by insurance companies. With the bispecific antibodies who knows what they're going to cost. I'm sure they will be expensive because everything seems to be expensive these days and this is an extremely kind of complicated area, how we do this and how we price these drugs. I hope for our patients that these drugs are affordable for our health system and that at the very least, the costs are passed on to our patients, who are already shouldering an enormous burden of being a myeloma patient, just the medical side of it and the health side of it, let alone the financial side of it. And I think it's really important for us as clinicians and researchers and for patients to kind of speak up and in sound and advocate for affordability. I also of course, I understand the other imperative that it cost a ton of money to develop these drugs and we're really grateful that they're being developed. And so, we have to find a way to walk that balance.

Gary Petersen: Well, thank you so much for that and thank you for all of the great information. It's been it's been remarkable. So, I'll go on now and Cindy, are you available?

Cynthia Chmielewski: Okay. Thanks so much for what you've been talking about Dr. Garfall. One, quick question, how is Teclistamab administered? Is it IV, subcutaneous, how often?

Dr. Alfred L. Garfall: So, both IV and subcutaneous dose have been tested which seems to be really promising, and going forward to subcutaneous dosing, which is very convenient for the patients and well-tolerated. Right now, it's being given weekly and then patients, who are responding well after some number of months can transition over to every other week dosing. I know there are plans to test even less frequent dosing and some of that has started. And so, I don't know, ultimately, the end of the day, how we will give this drug most commonly in terms of the schedule that will be worked out, but I think subcutaneous dosing is very likely and as actually has been very convenient and easy for patients.

Cynthia Chmielewski: Good. Thank you. The marker that Teclistamab goes after on the myeloma cells BCMA, can you talk a little bit about BCMA. And now there's all these drugs are going after that same BCMA marker taking one with the excluding from taking another, do patients lose this BCMA marker? Does everyone have it? Can you just talk about what this BCMA is? Why it's a target and what's that sequencing like?

Dr. Alfred L. Garfall: Yes, lots of good questions there. So, all of these Immunotherapies have to have a way to Recognize the myeloma cell and distinguish the myeloma cell from other normal cells in the body. So, we don't want to immunotherapy that's going to go and kill every white blood cell in the immune system. It really needs to have a way to train the therapy on the myeloma cells specifically. And so BCMA stands for and so we've had immunotherapies targeted against molecules on myeloma cells for a while. So that medication daratumumab, target cd38, there's a medication called Elotuzumab, target called CS-1. But you're right there that I've mentioned before I think is pretty unprecedented, the number of therapies that

have been targeted against BCMA and got into clinical trials against BCMA for just one disease. It's really remarkable, just how many have been stood up in clinical trials over the last few years. So BCMA stands for B cell Maturation Antigen. This is a molecule that is on the surface of multiple myeloma cells and on normal plasma cells. So, the normal counterpart of multiple myeloma cells is normal plasma cells. These are the antibody-secreting cells of the immune system. They also seem to express BCMA and there seems to be a very little expression, elsewhere in the body, maybe a couple of minor subsets of other immune system cells, but that's what's made it a very safe and effective immunotherapy target. It seems like you could eliminate every BCMA molecule in the body and every cell that expresses it and not have any real significant toxicity against other organs in the body or other parts of the immune system or other white blood cells. And that's why there have been so many therapies developed against BCMA. BCMA is pretty widely expressed on multiple myeloma. So almost all patients with multiple myeloma express BCMA. Some express higher or a little lower level of BCMA and that's something we're learning about over time, kind of how BCMA expression goes up and down on multiple myeloma cells and responses to certain therapies. We always worry about it with potent immunotherapy, like CAR-T cells or bispecific antibodies that if we go really aggressively after this target, that the myeloma cells can get away from the therapy by getting rid of that target. So, if a multiple myeloma cell didn't express BCMA, there'd be no way for the immunotherapy to recognize the myeloma cell and when we look at leukemias and lymphomas that have been treated with CAR-T cells targeting cd19 we know that that's a problem and those diseases where patients can get cd19 directed CAR-T cells and the disease can escape the therapy by getting rid of cd19. So, the question is, does that also happen with BCMA in multiple myeloma? And what we know is that there have been just a couple cases reported of BCMA negative myeloma emerging in somebody who had been previously responding to a BCMA directed immunotherapy. So that is definitely something that can happen with multiple myeloma but right now we think it is a relatively rare occurrence. So, most patients that we've been able to profile who are progressing on a BCMA directed therapy, the myeloma still has BCMA on it. And therefore, it's possible that they may be able to respond to a second therapy that targets BCMA especially if the therapy works a little bit differently. So, for example, the first drug that targets BCMA, that's been approved for multiple myelomas a drug called belantamab. This is an antibody against BCMA and attached to this antibody is the potent chemotherapy molecule. So, you can really think of this drug as a chemotherapy delivery device that delivers the chemotherapy specifically to the multiple myeloma cell, that's a different mechanism of action than bispecific antibodies and CAR-T cells. And we have seen patients and it's been now reported in some publications who responded to the belantamab and then eventually progressed on belantamab and then responded to anti-BCMA CAR-T cells. So, we know that can happen and there are a lot of clinical trials now on these drugs that are specifically, testing them in patients who have received prior BCMA directed therapy. So, I think we will learn in short order some of the more details about how likely somebody is to respond to a second BCMA, a therapy after progressing on a first BCMA, a therapy. So, I think that addresses at least one of your questions. I'm sorry if I got too far in the field and forgot to answer the rest.

Cynthia Chmielewski: That's fine. Jack tells me I ask too many questions anyway. So, something you brought up earlier when you were explaining that BCMA is also found on normal plasma cells, as in myeloma cells. So, I think I heard that because of that, sometimes your normal plasma cells are killed off and you might need IVIG infusions. Can you tell us a little bit about that and what that looks like?

Dr. Alfred L. Garfall: Yes, and so I would say that all our therapies for multiple myeloma affect the immune system. And that's largely a big part of that, is that our myeloma therapy is also killing normal plasma cells, and therefore like, is in plasma cells are the antibody factories in the immune system, and so patients, who were killing off normal plasma cells are going to have low antibody levels. And that will impair the ability to fight infection. I probably should have mentioned that more prominently when I was talking about the side effects of these drugs, we focus on serious and neurologic toxicity. There's also a real potentially suppressive effect on the immune system that patients will have very low antibody levels on some of these therapies that will affect their ability to fight infection, will affect their ability to respond to vaccines. And so, we've seen patients that are receiving these potent anti-BCMA therapies, for example, they don't make very good responses to the covid-19 vaccines. And those vaccines are probably less effective in those patients. So, one way we can get around some of that is to give patients antibodies. It's just like we can give a red cell transfusion when someone's anemic, or platelet transfusion when the play the levels are low, somebody

who's not making their own antibodies you can give an antibody infusion. So, you can think of what we call IVIG, which stands for Intravenous Immunoglobulin. This is really giving donor antibodies to patients as a therapy. And so, it's not quite like red cells and platelets in that we don't get these from the blood bank. But basically, there are companies that have a large pool, a panel of donors that sign up to be antibody donors. And then and so we take serum from those patients, not we, but the companies take serum from these patients, purify it and treat in a way that can be kind of pulled together and given safely as a drug and then we give them to patients who have low antibody levels while they are on multiple myeloma therapy. And is typically given every one to three months when it's needed to try and keep the healthy antibody levels in an acceptable range that we think will help patients fight off infections.

Cynthia Chmielewski: Okay. Do you think those IVIG infusions now contain some covid antibodies too?

Dr. Alfred L. Garfall: That's a good question. We don't know yet. I don't know exactly how long the supply chain is for those and what parts of the world they come from, not every part of the world has been so profoundly affected by covid-19 as the US has. And so, I don't know that there will be. I know that the source for some of these antibody infusions is actually international donors and so it depends on how prevalent covid-19 was in those areas.

Cynthia Chmielewski: Okay. In the beginning, you were talking about that this immunotherapy is a little bit different than engaging your innate immune system, it's engaging T cells and one of the things I heard was that with CAR-T Cell Therapy that the health of those T-cells really mattered, sometimes T cells are exhausted. Is that what we're seeing with bispecifics? Does the health of the T-cells matter? There are all different kinds of T cells, is it selective to different kinds of T cells? I'm just fascinated. I thought T cells were T cells but now I've learned there are many kinds… and they could be exhausted.

Dr. Alfred L. Garfall: Yeah, there are many, many different types of T cells, and I lose track of them myself. And we have people whose entire careers here are focused on studying and researching the different types of T cells and the different behavior they can adopt. And right now, all our therapies, whether it's CAR-T cells or bispecific antibodies are not very selective of the T cells. And so when we make CAR-T cells for someone, we take all the T cells and put them through that manufacturing process and what comes out comes out and likewise in bispecific antibodies, bispecific antibodies engage any T cell that they see in the body, but it could be that certain subtypes of T cells are better at affecting, better at killing myeloma cells than others that they would be better to use as the raw material for CAR-T cell manufacturing. And so, there's a lot of work going on in that area and I think is still a really open question. But you could imagine a situation in the future where instead of just taking all the T cells from someone's body and making CAR-T cells they do some selection of certain T cells and use those T cells that make the CAR-T cells. And likewise for bispecific antibodies right now, the bispecific antibodies recognize CD3 on the T cells, but it's also possible that you could incorporate additional specificities into the bispecific antibody, that lead them to engage certain types of T cells, for instance, or to change the phenotype of the T cells in the body, by engaging a second molecule on the T, cell surface, things like that. So, I think that will probably figure most prominently in real life. A lot of the stuff that we're talking about is really futuristic. But in real life what we're learning is that different multiple myeloma patients and different stages of multiple myeloma therapy come with different T-cell Health that if you imagine that before, you get multiple, myeloma, you hopefully have a healthy immune system, and all your T cells are really healthy. But as you get multiple myeloma and then as you are exposed to the multiple myeloma therapies that beat up the immune system a little bit, your T cells probably become progressively weaker over time. And so, in the distant future, we might be able to engineer T cells to make them healthy or maybe select the healthiest T- cell. While this is being tested almost immediately just to try to do somebodies therapies at earlier lines of multiple myeloma therapy. So, instead of waiting until someone has myeloma for five years and has seen six different lines of therapy to try these immunotherapies, maybe we try them early on when the myeloma is maybe under better control before patients have been exposed to a lot of therapies that degrade the health of the T-cells. Maybe just by doing it earlier we will get healthier T-cells to engage with these therapies and there are a lot of trials that are doing that right now and we're just starting to see some of the results from them. And probably too early to conclude from what I've seen at least whether that's ultimately going to be a successful strategy, but it's definitely being tried by a lot of academic centers and a lot of companies.

Cynthia Chmielewski: Sounds good. Do they have done T cell infusion so I could get a T Cell infusion before I get treated?

Dr. Alfred L. Garfall: Yeah, so that's another really good question. So, getting T cells from someone else, proposes immunologic problem, right. So, T cells are the main way your T cells in your body have been trained in your thymus and by their genetics not to recognize you as far and only recognize foreign invaders like foreign bacteria or cells that have been infected by viruses. If I give you someone else's T-cells those T cells have the ability to maybe recognize you as foreign. Now that said people are working on figuring that out. And so now with CRISPR Gene editing technology, you can take somebody else's T cells and remove the T Cell receptor from those T-cells that would recognize you as foreign and introduce into those T cells are CAR-T cells. So those T-cells might not be able to recognize you as foreign, we call that allogeneic CAR-T cell therapy or donor CAR-T cell therapy. And that also solves a little bit of the T-cell health problem. Your T cells might be beaten up from myeloma and we could manufacture these T cells from like a 20-year-old young, healthy immune system, maybe those T cells that make really good CAR-T cells. And so, we saw at ASH last year, some of the first reports of BCMA directed CAR-T cells made from third parties, from healthy donors that have been edited by Gene editing technology to remove the T Cell receptor to reduce the risk of that immunologic problem and they seem to work. Now, we don't know from The Phase 1 study, how the results stack up with conventional called autologous T-cells made from your own body or bispecific antibodies, but the technology is in the clinic, and it does seem to work. And the question will be over time whether that complexity of all that Gene editing, offers enough of a benefit to displace autologous CAR-T cells or bispecific antibodies from clinical practice.

Cynthia Chmielewski: Thank you. I'll stop here now.

Jack Aiello: I think I'm up next then. Cindy, great questions, and Dr. Garfall, I really appreciate your very clear answers. Teclistamab appears to be further along in trials than other bispecifics, but there are at least half a dozen others in trial and including another one from Jansen and maybe we'll hear more at the upcoming ASH meeting. Do you envision a trial where it is possibly able to learn the most effective bispecifics for different myeloma type patients?

Dr. Alfred L. Garfall: Yeah, that's a good question. So, I guess the question is, are these different from one another materially, right? So, there are multiple anti-BCMA bispecific antibodies, that in the phase 1 studies they really do have similar response rates and toxicity profiles. And so, I think it's going be a long time for us to figure out whether one is better than the other. Right now, I think it's a mad race from the different companies to get the trials done fast enough to be the first one that's FDA-approved. I think this is all really good for patients, this competition, we will see over time. Now, we also have a couple of instances about bispecific antibodies that are not using BCMA as their target on the myeloma cells. And those are really interesting and I think there's definitely going to be room for some of those target molecules other than BCMA and so Jansen is running a program, testing it bispecific antibody, that recognizes molecule called GPRC5D on the multiple myeloma cells that have a sort of similar response rate to Teclistamab and are being tested in patients for whom Teclistamab stopped working maybe for a loss of BCMA and that could be enough for someone whose disease has lost BCMA. There's also another target called FcRH5, and my colleague Adam Cohen has presented at ASH some data with that. And that also seems to have a similar, high response rate. It was interesting that molecule may be more expressed in certain subtypes of multiple myeloma. So, there's a subtype of multiple myeloma where one of the genetic abnormalities is an increased amount of chromosome 1 Q. An extra copy of chromosome 1 and FcRH5 maybe a little bit higher expressed in those myelomas. So, we may see over time that this may be a therapy that works really well for that subtype with multiple myeloma. But just having multiple targets available for patients who have progressed on BCMA directed therapies because there are so many BCMA directed therapies is really exciting also.

47:00

Jack Aiello: Thank you. You mentioned step dosing earlier when you talked about starting off by giving a tiny dose, and then a larger dose, and then a larger dose, is that done in the other bispecifics as well? And would you expect that to be part of the final recommended dose scheduling for Teclistamab?

Dr. Alfred L. Garfall: Yeah, it's my knowledge, of all the bispecific antibodies are given that way, and we learned that from Blinatumomab, I mentioned, that was the first bispecific antibody that was developed for ALL- Acute. Lymphoblastic leukemia, that's given in a staged fashion. And I think based on that experience, most of the bispecific antibody trials, in myeloma I think all of them have adopted some version of that step-up dosing. It differs from drug to drug, but I do anticipate that's really the safest way to give these medicines and it is how they'll be eventually used.

Jack Aiello: Thank you. And then finally the bispecifics appear to be developed either as IV or subcutaneous formulations. Is it even possible to create an oral therapy of bispecifics or is that not possible, given that it's an antibody?

Dr. Alfred L. Garfall: Yeah. I'm not aware of any antibody therapy that is delivered orally for any of these. Yeah, I think that's just because these are proteins, and our digestive process as a way of kind of chewing up proteins. Some of them are absorbed but most of them would be expected to be degraded in the digestive process in a way that they wouldn't survive the circulation, I think.

Jack Aiello: Thank you very much. I will end there and turn it back over Priya.

Priya Menon: Thank you. Thank you, Jack. Multiple myeloma that has relapsed and has become refractory to treatment represents a patient population with unmet needs. And I believe, according to the investigators our current study is to the best of their knowledge. The first report of a T cell redirecting bispecific antibodies of the treatment of patients with cancer. And with this FDA approval, we may see the drug move to every line of therapy as a single agent or in combination. So, with that, we're wrapping up today's discussion. Dr. Garfall, thank you so very much for taking the time to join us on CureTalks today. It was a pleasure talking to you. Gary, Jack, and Cindy thanks for joining and as always, for the great questions. We thank the University of Pennsylvania. The talk will be available on curetalks.com. Thank you and have a great day, everyone.