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The Role of GPRC5D in the Multiple Myeloma Treatment Paradigm

Announcer:
You're listening to *Project Oncology* on ReachMD. Here's your host, Dr. Charles Turck.

Dr. Turck:
Welcome to *Project Oncology* on ReachMD. I'm Dr. Charles Turck, and joining me to discuss G protein-coupled receptor, class C, group 5, member D, or GPRC5D for short, and its role in the multiple myeloma treatment paradigm is Dr. Joshua Richter. He's an Associate Professor of Medicine at the Tisch Cancer Institute in the Division of Hematology and Oncology and the Director of Multiple Myeloma at the Blavatnik Family Chelsea Medical Center at Mount Sinai in New York. Dr. Richter, thanks for being here today.

Dr. Richter:
Thank you so much for having me.

Dr. Turck:
So, Dr. Richter, would you tell us about the current treatment landscape for relapsed or refractory multiple myeloma?

Dr. Richter:
Absolutely. So multiple myeloma has been an exciting area of innovation and new drug development. And I think we all have some general concepts of how we approach newly diagnosed patients. In the United States, the general patient gets something like RVD as a combination, though sometimes we expand that to things like dara-RVD. But what happens when we get into the relapsed and refractory realm? Well, in the relapsed refractory world of myeloma, we really divide it into two groups, early relapse disease and late relapse disease. Early relapse refers to one to three prior lines of therapy, and later relapses, four plus lines of therapy.

In the early relapse, we really focus on some of our core combination classes of agents. And basically, what that means is we look to things like anti-CD38 antibodies, like daratumumab and isatuximab. We look at our proteasome inhibitors, like bortezomib, carfilzomib, and ixazomib. And then we look to our immunomodulatory drugs, the IMiDs, like lenalidomide and pomalidomide. And we often use different combinations of these drugs in the early relapse setting. Sometimes, we even include some of the older classes of agents, like alkylators, drugs like cyclophosphamide. But once you get beyond two or three lines of these therapies, the patient enters a realm that we call triple-class refractory myeloma.

So triple-class refractory is refractory to a proteosome inhibitor, an immunomodulatory drug, and an anti-CD38 monoclonal antibody. Now patients nowadays can become refractory to these class of agents very quickly. And essentially, we're really looking towards the new generation of therapies to take up the slack and the later relapse. And a lot of these therapies are focusing on T-cell redirection, either in the form of a CAR T-cell therapy or a bispecific antibody.

Dr. Turck:
And what else can you tell us about disease progression in relapsed or refractory multiple myeloma?

Dr. Richter:
Absolutely. So disease progression becomes a multifactorial and a broad spectrum of activities that lead to this. One of the things that we think about in disease progression is that, in myeloma, you're often on therapy as long as you tolerate it and until you progress, which means once you progress on a given therapy, you're already refractory to that drug. And even though there may be other drugs within that class, refractoriness to one drug within a class confers some degree of refractoriness to other drugs, which is why we oftentimes consider switching classes of agents when we relapse.

What leads to this relapse is a combination of events, including things like acquired genomic abnormalities and things called antigen loss. So if we use a drug that targets an antigen on the myeloma cell, if that antigen goes away, sometimes that's part of the progression of myeloma. There are a number of immunologic factors. So as our own immune system continues to attack the myeloma with T-cells and NK cells, as those levels decrease, our own body's immunity may not be as good at working with the therapy to control the myeloma. So that's part of the reason why the disease progresses. So really, this is always leading us to look for newer and newer modalities of myeloma cell kill.

Dr. Turck:
For those just tuning in. You're listening to *Project Oncology* on ReachMD. I'm Dr. Charles Turck, and I'm speaking with Dr. Joshua Richter about relapsed or refractory multiple myeloma.

So would you tell us a little bit about GPRC5D and how it might address gaps in the current treatment landscape?

Dr. Richter:
Absolutely. So for those of you who are not already familiar with this mouthful of a name GPRC, also known as G protein-coupled receptor, class C, group 5, member D. GPRC5D is an antigen that's expressed on myeloma cells, almost exclusively on myeloma cells. It's actually expressed on a few other areas, like some hair follicles of the squamous epithelium on the hands and the skin on the palm of your hands and the bottom of your feet and the salivary glands in the lining of the GI tract. But it's very heavily expressed on myeloma cells. And it's become a key potential target for many of our newer therapies, both in terms of bispecific antibodies and CAR T-cells. Now the fact that it's mostly expressed on myeloma cells makes it a really great target for these type of immune therapies.

The other thing that really makes this target exciting is that some of our other targets are heavily expressed on other immune cells, like B cells. And when you give those targeted agents, you not only kill your own myeloma cells but you can kill a fair amount of your own immune system, which makes things not as good in terms of controlling the disease, but also higher risk of infection. Because GPRC5D is not really expressed as much on things like mature B cells, we don't have the same degree of infectious complications as some of our other targets like BCMA.

So we're really excited that GPRC5D is coming along, and we're able to target this, as again, both in CAR T's and bispecifics and really excited that the bispecific, talquetamab, has been filed for FDA approval, and we're hoping to see that later in 2023.

Dr. Turck:
Now lastly, Dr. Richter, are there any final thoughts you'd like to share with our audience about what we've discussed today?

Dr. Richter:
Absolutely. One of the things that has become one of the most unanswered questions of myeloma is sequencing. What's the optimal sequence? And again, I always like to think of myeloma like a chess game, you've got to think three or four moves ahead. If I give this therapy, how does it affect future therapies? For example, if you give a SLAMF7 inhibitor, SLAMF7 inhibitors need NK cells. So if you give a CD38 antibody, which kills all NK cells, or most of them before you give a SLAMF7, it doesn't work as well. So figuring out the optimal sequence is very key.

So one of the things that GPRC5D is bringing up is that right now GPRC5D bispecific antibodies have mostly been studied in patients who have previously received BCMA-based therapies. So we talk about the original three drugs, IMiDs, proteasome inhibitors, and CD38 antibodies. After that comes the BCMA agents, and we have bispecifics and CAR T's approved that target BCMA. Now we're going to have GPRC5D. And right now, we're giving it after because it's going to be approved after.

But what we're really having a great opportunity for is the concept of taking real-world data and finding out in a landscape where we have FDA-approved GPRC5D therapies and BCMA therapies that are approved in a similar line of therapy. And it's going to be dealer's choice when it comes to prescriptions from our academic and community caregivers. What happens when you give anti-GPRC5D before BCMA? So this is going to give a great opportunity in the coming years to better understand what the optimal sequence is and which drugs to give which patients and what order.

Dr. Turck:
Those are great takeaways as we end our program, and I want to thank my guest, Dr. Joshua Richter, for joining me to discuss GPRC5D and its potential role in the multiple myeloma treatment landscape. Dr. Richter, it was great having you on the program.

Dr. Richter:
Thank you so much, really appreciate it.

Announcer:
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