Melanie Cole, MS (Host): Welcome to the podcast series from the specialists at Penn Medicine. I'm Melanie Cole. And we're here to highlight Afami-cel in the treatment of synovial cancers. Joining me is Dr. Daniel Lefler. He's a Clinical Assistant Professor of Medicine and the Associate Clinical Director of Sarcoma Medical Oncology at the University of Pennsylvania.

Dr. Lefler, it's such a pleasure to have you join us today. Can you first give us a brief outline of the genetic landscape of synovial cancers themselves? What makes them amenable to immunotherapy?

Dr. Daniel Lefler: Thank you for having me, Melanie. Synovial sarcoma is an interesting disease. It's a rare disease. So, kind of just to set the stage, sarcomas are only about 1% of all adult tumors. And synovial sarcomas are about 5-10% of all soft tissue sarcomas. So, we're talking about a rare version of a rare subset of tumors. They may be rare, but they're also serious. And synovial sarcomas can happen anywhere in the body. They occur mostly in people in their 20s and 30s, and they're aggressive. They grow fast, and they can spread fast. So, it's a life-threatening diagnosis, life-changing diagnosis. And our therapies are definitely less effective than we would want for our patients. And treatment usually involves high doses of chemotherapy, which can be hard for people to tolerate. And we do our best to support them, of course, so it's always good to talk about new options for treatments like this.

Synovial sarcomas, to answer your question, are not usually thought to be susceptible to the standard immunotherapies. These are monoclonal antibodies that usually act on immune checkpoints, allowing the natural immune system to attack cancer more effectively. But in this case, there is a new therapy that uses a different mechanism of action to allow our immune system to attack the synovial sarcoma. And so even though it's not susceptible to most immunotherapies that we usually think about, it can be made susceptible to immunotherapies in a different novel way.

Host: This is such an interesting topic, Dr. Lefler. So, what is Afami-cel's mechanism of action? How is it like or unlike that of CAR T therapy? Tell us a little bit about this.

Dr. Daniel Lefler: So, Afami-cel, the other name is Tecelra. It's a T-cell therapy, so that's like CAR T-cells. But this one uses a different way of allowing the T-cells to attack cancer. So, this uses an engineered T-cell receptor, or a TCR, and this is the first of its kind that has

made it to humans, and made it to getting treated patients commercially. And it won't be the last one of those for the record, even in synovial sarcoma, I don't think.

So in essence, this takes the normal T-cells from a patient and switches out the T-cell receptor or TCR that allows those cells to recognize a specific protein expressed in the cancer cells. And that protein is called MAGE-A4. So usually, our T-cells would not recognize this expressed on cells, and it wouldn't necessarily kill the cancer cells, but this engineering allows the T-cells to notice the cancer cells and kill them effectively. CAR T-cell therapy famously saw development here at Penn, but the way they are manufactured, instead of giving a new T-cell receptor, CAR T-cells are given a different novel receptor called a chimeric antigen receptor, CAR.

And although this is a bit of a nuanced difference, both have their pros and cons. Traditionally, CAR T-cells can be given to anyone whose tumor cells express a certain marker, which makes them widely applicable to a wide swath of patients with certain diseases, but it also means that they can have off-cancer effects and kill normal cells with that marker. Obviously, that technology is still being developed and refined and improved. TCR T-cells have the benefit of using the normal T-cell receptor that our immune system uses. And therefore, it's more targeted in a natural way of our immune system killing cells, with the downside being that it's only going to then be available to a certain population of patients whose T-cells look a certain way and have a certain marker on them.

Host: Dr. Lefler, the published indications for Afami-cel suggest that it's administered only after radiation, chemo, and surgery have failed in people with unresectable or metastatic synovial sarcoma. Why can Afami-cel not be used earlier in the course of treatment, and why might a synovial cancer be refractory to a standard care of therapy?

Dr. Daniel Lefler: The short answer is that we don't know exactly if it could be given earlier or in a different setting to these patients because of the way the trial was designed. And basically, cancers have all sorts of ways to evade the treatments that we give them, because they're smart. They figure out ways to either like pump the chemotherapy out of the cells so that it doesn't kill the tumor, or they gain mutations that make them resistant to treatment. And as for using the Afami-cel only after chemo, all I can say is that this is based on the trial design. So in the clinical trial that established this as an effective way to treat patients, it was only given to people who have had chemo prior and it seemed to work well in that setting.

So, that's why the FDA approved it that way. Maybe it works better earlier, but we just don't know.

But one thing that's worth mentioning is that Afami-cel seems to work best in patients who had fewer and smaller tumors. So, what we say is ~~like~~ less tumor burden. And this is consistent with the data from CAR T-cell trials and clinical experience. And so, it does seem beneficial to reduce the burden of tumors or shrink them as much as possible with our standard treatments prior to giving a Afami-cel, because it looks especially effective in that setting.

Host: That's so interesting. So in the SPEARHEAD-1 clinical study, that was the basis of the FDA approval that we're just talking about, 39% of treated patients had a duration of response longer than a year. Put this into perspective for us in regards to synovial cancers. Do we know why the majority of patients didn't have a more durable response and what might be changed in the targeted administration of the treatment to improve the overall response?

Dr. Daniel Lefler: Well, the durability of response is actually one of the really great things about this. In terms of the number of patients who had responses, less than half seems like it would be bad in terms of patients responding for a treatment. And we certainly want to keep advancing our science and our treatments to make sure that all patients benefit eventually.

But in this case, in synovial sarcoma patients who have already received treatment, so already received one line of chemotherapy, our treatments, our second line, third line, and beyond treatments, usually respond less than 15% of the time. Many quote 5-10% of the time.

And by work, I mean shrink tumors. So, around 40% or nearing 40% of patients responding is amazing. It's remarkable compared to that benchmark. But perhaps even more impressively, as you are alluding, it's the duration of response in the patients who did respond at all.

And so, the response to this one-time treatment can last for on average a year, but many patients longer than that. And so, that means that's time that patients don't need more chemo. They're not getting chemo and chemo and chemo every three weeks, every four weeks, or a pill that's making them feel sick. And so, that is a big quality of life consideration in terms of time off of treatment for these patients. And overall, patients had a 30% chance of not

needing any further treatment after two years, which is kind of amazing and rather unheard of in this world.

As for why some patients didn't respond, it's not clear. And obviously, the scientists, the clinical investigators who ran the trial will be looking into markers of how we can predict who will respond and who won't. It can be for a lot of reasons, both particular to patients and for individual tumors. There was some recent data presented at an international sarcoma conference that a similar TCR T-cell product with a different target called NY-ESO-1 had promising results in synovial sarcoma as well. So, maybe we'll learn how to choose patients for the MAGE-A4 Afami-cel versus the NY-ESO-1 targeting other T-cell receptor therapy. And obviously, we'll see that as our field moves forward.

Host: Dr. Lefler. Afami-cel is expensive. According to the Medical Letter on Drug Therapy, a single dose could cost $727,000. What's the basis for this cost? How has the insurance industry responded to this?

Dr. Daniel Lefler:

In terms of the cost, the financial calculations work happens in the background by people who aren't necessarily doctors. It's expensive to develop any drug, and I can imagine it's much, much more expensive to develop a special product that uses each individual patient's own cells. It requires collection from a patient, and transport, and inserting an engineered T-cell receptor into those cells, and then growing them to make them viable to kill cancer. CAR T-cell therapies, probably the nearest comparison, are quoted into the $400,000, $500,000 range of treatment. And so, that's not too far off. And I'm not sure if something is different about this process that makes it a little bit more expensive. Insurance companies have been paying for CAR T-cells. But obviously, the cost is eye-catching. It's a continuing debate among the medical community about the resource intensity of these treatments and how to make that payoff worth it for everybody.

But maybe more broadly, just to couch that, the cost of medical care generally is incredibly high and it affects all of us, especially our patients. And there's a need to make therapies more affordable. I was recently at an international sarcoma conference talking with a colleague, and I learned that a treatment that we prescribe is over $600,000 a year, and that's an oral pill. Six hundred thousand dollars a year is the estimated cost. And so if that treatment is working for a year or maybe a year and a half or two years, you know, you're approaching the cost of something like this as well. And people don't think of pills as costing

as much as that, but they can. So while Afami-cel is unique, it's also part of a bigger problem that's really important.

Host: So, give us your key takeaways from this talk that we've had today on Afami-cel for synovial cancers, what you would like other providers to take away in the key messaging.

Dr. Daniel Lefler: I think that the exciting thing here is that we have an effective therapy that can have a really durable response, a population of patients who we have not had that before. And that can be really meaningful, especially the time off of treatment, where patients aren't necessarily getting chemo. I think that freedom is something that is not stressed enough, because it means a lot to a patient to be able to not be getting infused every three weeks or every four weeks with chemotherapy. And so, that can be life-changing for people who have a life-changing illness.

I think it's really exciting for the medical community because this represents a novel way of treating patients that's like CAR T-cell therapy, but a little bit different. And that's really exciting as well because it could potentially benefit our patients greatly.

I know that there are going to be limited number of sites that are participating in this. And so, we're hoping that we can offer a good solution to patients from wherever they come. And we're working with the cellular therapy group here, who has a lot of experience working with CAR T-cell therapies to make sure that this is a streamlined, good experience for patients as much as we can.

Host: Dr. Lefler, thank you so much for joining us today and sharing your incredible expertise for other providers. To refer your patient to Dr. Lefler at Penn Medicine, please call our 24/7 provider-only line at 877-937-PENN, or you can submit your referral via our secure online referral form by visiting our website at pennmedicine.org/referyourpatient. That concludes this episode from the specialists at Penn Medicine. I'm Melanie Cole. Thanks so much for joining us today.