Becky Campbell: Hi, my name is Becky Campbell, and I'm the senior manager of medical content here at PCF. I'm so excited to be joined today by Dr. Tanya Dorff and Dr. Saul Priceman to discuss their publication of the results of a clinical trial of a new immunotherapy called CAR-T cells for advanced prostate cancer. Dr. Dorff and Dr. Priceman, congratulations on the publication and thank you so much for joining me today.

Dr. Saul Priceman: Nice to be here.

Dr. Tanya Dorff: Thank you.

Becky Campbell: Can you please each introduce yourselves and then-briefly-and then we'll get into the details. Dr. Dorff?

Dr. Tanya Dorff: Hi, I'm Tanya Dorff. I'm a genitourinary medical oncologist. I lead the GU program here at City of Hope.

Becky Campbell: And I should add, Dr. Dorff is the principal investigator on a PCF 2022 TACTICAL award that will further research into this treatment strategy that we're going to discuss in just a moment. And Dr. Priceman?

Dr. Saul Priceman: I am an associate professor at City of Hope and run a research lab developing cellular therapies for solid tumors.

Becky Campbell: Wonderful. And Dr. Priceman received a 2015 PCF Young Investigator award that helped to develop this treatment as well. And we'll talk about that later. So, I'd like to start by setting the stage for the unmet need and the motivation for developing a new therapy for advanced prostate cancer. So, the patients in this trial had been through many previous treatments. Broadly speaking, Dr. Dorff, what is the situation that patients are facing? That was, you know, part of the impetus to develop a new treatment.

Dr. Dorff: So, despite significant improvements in our treatments for prostate cancer, unfortunately, many patients who develop castration resistant progressive disease will still die from their cancer. So, we've had, you know, the advancements of PARP inhibitors for molecularly selected patients. We have radioligand therapy, but immunotherapy has been difficult, and patients will sequence one treatment after another--it extends their life and improves their quality of life. But one thing that's been missing is a treatment that can yield a really deep and long-lasting remission, the kind which might, in the future, allow patients to not require ongoing lifelong testosterone suppression or castration, which is sort of the current state of affairs. Everything else we do for patients with advanced prostate cancer is layered on top of taking away testosterone. But if we could get a deep remission, that's one of the major hopes and one of the major things that's missing.

Becky Campbell: Thank you for that. And, Dr. Priceman, this is an immunotherapy--and I'm going to ask you to describe kind of how it works

in a minute--can you explain why has immunotherapy not worked as well in patients with prostate cancer?

Dr. Saul Priceman: I think to date, we've realized a few things, but there are certainly black boxes in trying to understand what patients may respond to immunotherapy. But in general, prostate cancer patients lack some of the qualities that would make them amenable to immunotherapy, including involvement of the immune system inside their cancer mass, which if you think about responsive tumors like melanoma or lymphoma, there are immune cells that are there ready to fight the cancer. They're being suppressed. And so much of the immunotherapies release those brakes and allow the immune system to work but in prostate cancer, those immune cells are largely void in the cancer. The other thing is prostate cancer on the spectrum of highly-mutated tumors is very low. And its mutational burden, which we think is also involved in responsiveness to immunotherapy.

Becky Campbell: Understood. Thank you. So, let's get into the details of the treatment. It's called PSCA CAR-T cells.

Now, people may know about PSMA--this is a similar-sounding name, but it's different. Please tell us a little bit about how this therapy works. And I know you have some slides that are going to help us understand that, from a visual perspective.

Dr. Saul Priceman: Yeah. So, this was almost ten years ago where we were looking at the types of targets on a prostate cancer cell one may go after with this type of CAR-T cell therapy or chimeric antigen receptor engineered T cell therapy--and I'll show a slide in a second. PSMA, which is prostate specific membrane antigen, which we've come to know and love because of the recent approvals with radioligand therapy targeting PSMA and imaging diagnostics for looking at disease in patients, also looking at PSMA expression. For many reasons, we actually focused on prostate stem cell antigen, or PSCA, because of its equivalently high expression in prostate cancer like PSMA. But also, as we think about developing immunotherapy strategies, a target that could be seen in other cancer types was also attractive to us; where PSMA is sort of restricted to prostate cancer in its expression, PSCA is expressed in a number of cancers, including bladder cancer and pancreatic cancer. So, we could develop a therapy that, if effective in prostate cancer, could be applicable to other patients with those types of cancers.

And so, actually with a PCF Challenge Award that we were awarded in 2014, we embarked on developing a PSCA-directed CAR-T cell therapy. I could share a slide and just show a general schema of how CAR-T cells work. And--hopefully you can see that better - that aphoresis or a large blood draw from a patient, and in many cases, and in this case, we sort of enrich for specific immune cell type called a T cell, which is the main cell type that attacks a virally infected cell or a cancer cell, very selectively, we enrich those from the blood. We activate those cells so they can rapidly divide. And we engineer these cells with a chimeric antigen receptor, which is a surface receptor, on those T cells that will then recognize the cancer cell.

And I'll show an illustration of that on the next slide. That's actually engineered using a virus that doesn't cause a viral infection, but allows viruses to do what they do best, which is integrate into the genome of a cell and deliver genes of interest. In this case, that chimeric antigen receptor. Those immune cells are expanded to the billions, in many cases, they're frozen back. There's a bunch of quality control assays that are done, ultimately releasing that product to be infused back into the patient. And you can see that's the number 5 point where we infuse. And Tanya can go through the whole design process in a second. In terms of the biology behind it, there are a number of reasons why one would redirect a T cell to see a tumor cell.

And as I mentioned before, there are very few T cells in prostate cancer that are ready to attack a prostate cancer cell. So, taking those immune cells out of the body, engineering them, and rewiring them to see the cancer cell, putting them back in, essentially proactively engineers an immune response to the cancer. If you look at the top right here, that's basically what happens. We have an immune cell, a T cell that then recognizes a surface receptor protein on the surface of the tumor cell.

And on the bottom right is an illustration of how we engineer those T cells to be CAR positive, to recognize the tumor antigen on the tumor cell, directly. And because of the close proximity of the T cell and the tumor cell, the T cell then becomes activated, secretes, or puts out into the microenvironment a number of molecules that will ultimately kill that tumor cell.

Becky Campbell: Amazing. Thank you so much for that. It is, you know, truly astonishing science. I know it's been many, many years in development. Dr. Dorff, moving on to the clinical trial itself, and this has just been recently published, tell us about the study and what you found. Let's start with--how well did this therapy work in patients?

Dr. Tanya Dorff: Okay. So, this is a phase one first in human--and really first and foremost, it's a question of is this safe? Is it feasible? And, of course, we're looking for efficacy, but we're not necessarily expecting it right out the gate. These treatments have been really effective in hematologic malignancies, but solid tumors are very different. So, we actually started the trial with the very basic question of, “Do we need lymphodepletion chemotherapy?”, which is traditionally given with CAR-T cells in their sort of FDA-approved usage in heme malignancies.

But we didn't know whether we needed that chemotherapy to serve the same purpose because removing some of the immune cells made sense more in the heme malignancy. So, the first three patients we just gave 100 million of the PSCA engineered CAR-T cells. And we did, actually, surprisingly, see a little bit of a PSA response in one patient.

But it was clear that they--the CAR-T cells weren't able to expand and work as robustly. So, the next cohort of patients got lymphodepletion chemotherapy, followed by the 100 million CAR-T cells. And that's where we actually saw a stronger efficacy signal. We didn't have, you know, a cure. We didn't have responses in every patient, but there were patients whose cancer got better, and in one case, quite dramatically better with the PSA going all the way down, the soft tumor metastases that had been biopsy-proven disappearing, the bone metastases getting better, and his remission didn't last as long as we would have liked, but it lasted close to 8-9 months. So, it showed that the CAR-T cells together with the lymphodepletion can be effective, which is really exciting. But we probably need more of them. We need to help them find ways to continue to proliferate and persist, which they did not in this experience. And part of the trouble is the side effects, the toxicity.

So, PSCA is expressed in the bladder, and we had some bladder toxicity that limited our ability to give a higher dose and potentially see that really deep, long lasting remission or more remissions. So, then we just had to go back to the lab and say, "What modifications can we make so that we can get to that greater efficacy without having too much toxicity?"

Becky Campbell: So, there was a fairly small number of patients in this trial. Is that correct?

Dr. Tanya Dorff: Right. We ended up closing this study after treating 14 patients because we wanted to rethink how we were going to administer this treatment most successfully. But from this small, early experience, we can already say several things. We can say that these CAR-T cells can be effective against prostate cancer.

We can say that we know what the side effect is that we're looking for, which in addition to the kind of typical lymphodepletion chemo side effects, is this unique side effect of the cystitis. But when we did open a cohort with modified lymphodepletion chemo, we found much less severe bladder toxicity. So, that's part of our strategy in the path forward.

But we also know we need to get more of those CAR-T cells in, and we might need combination therapy. So, we've opened a phase 1B trial where we're able to ask those kinds of questions, which will be a little bit more focused on efficacy.

Becky Campbell: Wonderful. So that kind of gets me to my next question is, what guidance would you have for patients who have advanced prostate cancer, who are maybe looking at this type of clinical trial option?

How can they start talking to their doctor about different treatment options with mCRPC and even accessing a clinical trial?

Dr. Tanya Dorff: It's challenging to know when is the right time, to pause from our list of sequential life-extending therapies and sequence in a clinical trial, especially something that's novel and phase 1 early study, like the CAR-T cell therapy.

Probably this therapy is going to work better in earlier phases of the disease, before the disease becomes more heterogeneous. But on the other hand, we don't want to deny patients from the known life-prolonging therapies. So, it's a very personal decision. I will say that patients on this trial and some of the other CAR-T cell therapy trials for prostate cancer *did* go on to get other treatments after, if this didn't work.

So that means we're not saying you're not going to get the known treatments, we're just going to *add* something, give you an extra option by sequencing in something novel, something unknown, but something that we're hopeful about, in between some of our existing treatments. So, I think that's the conversation that patients and their physicians need to have.

We know the number of treatments we have. We know what they get us. They don't get us long-lasting, complete responses, by and large. And so, if we want to have that potential, if we want to add extra, then we need to be looking at clinical trials.

And for some patients, CAR-T cell therapy is an option. It is pretty demanding. You have to stay near our cancer center for many weeks or even months because of the monitoring that comes with CAR-T cell therapy. So there are other kinds of clinical trials that are not as intensive or demanding that might be a better fit for people who live very far away, for instance, or for other reasons aren't good candidates. But I think it's always a question to ask. You know, "I need a new treatment. My cancer's progressing." These are the standard options. Is there a clinical trial that is a good option that provides some promise of efficacy, which we can now say with this treatment and then, you know, we fill in the details and go from there.

Becky Campbell: Wonderful. Thank you so much, Dr. Dorff, because I know we have--this is a question that we frequently get at PCF and no doubt you do too, in your practices.

"How can I--how can I help, you know, get help in choosing the next step in my treatment, whether it's this clinical trial, or another, or standard, standard care?"
Dr. Priceman, you had mentioned, back in 2014 you received some funding from PCF to embark on this effort. Can you tell us a little bit about how PCF was involved in moving this research forward?

Dr. Saul Priceman: I think PCF had a thought ten years ago that was based on, as Tanya mentioned, the incredible early evidence that CAR-T cells would be effective for hematologic malignancies like leukemia and lymphoma. And they said, "Well, if it works for those diseases, why are we not pushing forward for this type of therapy in prostate cancer?"

And so, they reached out to us at City of Hope and said, you know, effectively, "Do that." And we were thinking about and developing it for other cancer types, and so, you know, in 2014, we embarked on it. And since then they've been absolutely fully supportive of that, not only, as

you mentioned, Young Investigator Award for myself to help springboard the lab, but in 2017 also, in part--and with a match funding—that funded the phase 1 clinical trial that we're talking about today. And then just last year, have now, as part of five institutions, funded their largest award mechanism, the TACTICAL Award, where we're now, formally and through PCF, collaborating with a number of institutions around the States in a concerted effort to sort of build on our clinical experience with CAR-T cells for prostate cancer.

And the end of that, we'll hopefully better understand why these therapies are working when they do, what sort of the resistance pathways are preventing it from working. As Tanya mentioned, it doesn't work for all patients, and we know it's not as durable as we would like it to be. And with this now open phase 1B trial, which is also partially supported by Prostate Cancer Foundation, but also some near future goals at opening trials at these institutions will help answer those questions.

Becky Campbell: Wonderful. Well, thank you both so much for your time today and for sharing the results of this exciting research. We know there's much ahead. And we'll continue to build on the work that's come before. So, thank you so much for taking the time and once again, congratulations.

Dr. Tanya Dorff: Thank you.

Dr. Saul Priceman: Thanks.