Becky Campbell: Good afternoon, good evening, and welcome to our webinar. My name is Becky Campbell, and I'm the senior manager of medical content here at PCF. I so appreciate everyone joining tonight and taking time out of your evening or afternoon.

It's really because of your interest and your support that we put on these webinars. So I thank you once again for attending. I'd also like to thank our supporters of tonight's event, Lantheus, Novartis and Veracyte for helping make this possible.

We have additional support from Exelixis and Dendreon. And I just want to note, before we get started, that all the views expressed during the webinar represent those of the speakers.

Here's a brief overview of our agenda. We're going to start out with an introduction to the immune system, which can be kind of a complex and confusing topic. So we want to set the stage there.

We'll talk about current uses of immunotherapy. Then what's on the horizon. We have a patient who's going to join us to share his experience. And we also have time for some Q&A at the end with our experts.

In terms of housekeeping, this webinar is being recorded. So if you want to go back and review, we will be sending out a link, with the link to the recording via email in a few days. If you do have questions at any time, please type them using the Q&A icon at the bottom of your screen. We'll get to as many as we can. We also received a number of questions in advance that we'll try to address. But please note that this is not a substitute for medical advice from your personal doctor, so please consult them for specific medical advice.

We also received a number of questions about other topics that you can see there listed--excellent questions. We might not be addressing those tonight, but you can find more information on our website through the recorded webinar series or recordings of the patient summits that we have. We also have patient guides.

In case you're not familiar with the Prostate Cancer Foundation, I wanted to give a brief overview. So we were founded in 1993 to reduce death and suffering from prostate cancer. And we do this primarily through funding research. So far, more than 2200 projects around the world at different institutions. Many of the treatments that are used today were developed with early-stage funding from PCF, including immunotherapy, initially funded some of the early work funded by PCF back in the late ‘90s, Dr. Jim Allison.

We also are funding research on how to improve survivorship and quality of life for patients, since many have the opportunity to live longer lives after their diagnosis. We also want to empower patients with knowledge so that they can make the best decisions about their care with their physician. You can find patient guides as I mentioned, recordings of webinars on a number of topics, virtual summits, we have online support groups, and we're excited to announce that in Q1 of next year,

we'll be launching a new website so that much of this information is much easier to find on the new design.

I'd also like to encourage everyone to visit ProstateCancerPatientvoices.com. This is our partner website that features the voices of patients and caregivers in their own words.

You can help support our mission, if you feel so inclined as we reach the year-end, year-end giving. In 2023, we funded more than $27 million in research awards, and 2024 awards will be announced soon.

Just one such award, I'm going to just describe here, in immunotherapy--so you can see it's a pretty complex title. But the goal of this award is to develop a new type of therapy--immunotherapy, using what's called natural killer cells. And you'll learn about more of those, later in the program. And this was awarded to Dr. Nicholas Zorko of the University of Minnesota, and he is actually our host for tonight.

So I'm going to introduce our amazing panel. Dr. Zorko is an assistant professor of medicine at the University of Minnesota. As I mentioned, he has research expertise and interest in immunotherapy and he also, in addition to seeing GU oncology patients, he attends on the bone marrow transplant unit. And he's received a number of awards, including the PCF Young Investigator Award that I mentioned before. So we thank Dr. Zorko.

Dr. Neeraj Agarwal is a professor of medicine at the University of Utah Huntsman Cancer Institute. He directs the GU oncology program, serves as Senior Director of Clinical Research. He's an internationally recognized leader in this field and has developed a number of experimental agents in GU cancers. He's also authored or coauthored nearly 500 publications. So welcome Dr. Agarwal.

And Dr. Subudhi is associate professor in the Division of Cancer Medicine at MD Anderson. His research focuses also on immunotherapy, developing biomarkers to predict which patients might be suitable and do well on certain therapies. He's also received, in addition to--I'm sure, a number of other awards--two PCF awards in the past.

And then finally we have Mr. Stephen Eisenmann. We're so glad that he is willing to join us to share his experience as a patient who received immunotherapy. I'm not going to go into great detail with his bio because you're going to meet him a little bit later in the program.

So without further ado, I'd like to welcome Dr. Zorko, who is going to give us an introduction to immunotherapy in prostate cancer and thanks, everyone, again for attending this evening.

Dr. Nicholas Zorko: Thank you for the introduction, Becky. And I just want to say I'm really thankful for the funding for my Young Investigator Award from PCF. It's been really exciting, and we're looking forward to talking more about immunology…

So here's the introduction. Immunotherapies for prostate cancer, a primer.

So the goal of this talk is to cover about five years of graduate school-level immunology in about seven minutes so we can go in to Dr. Subudhi and Dr. Agarwal's talks with some basics there…

These are my disclosures…

So the immune system is really complex. There are a number of cells and it can be overwhelming. But we can basically divide the immune system into two different components. We have the innate immune response and the adaptive immune response. We can see that there are numerous types of cells here. But within the innate immune response we have, my favorite cell, natural killer cells. But we also have monocytes, macrophages, neutrophils and other cells. And these are the rapid response force that come to site of a tumor site of infection within minutes to hours. And they start collecting and surveilling and killing off what they can that doesn't belong. The adaptive immune response happens over days to months to years. And this is what we talk about--immune memory where it remembers something that had seen years or months ago and goes back after it much more quickly. So what's important is the interface between these two types of immune--and the innate and the immune--the innate and the adaptive immune response so we can see highlighted in those boxes there. And basically this interface, what I refer to as--for where my patients is, this is, "Look what I found! You should remember this!" So the innate response telling the adaptive response what to do.

The immune system is all about balance. So like anything in life it's about balance too much or too little. And it doesn't work very well. We have too much of an immune response. We have autoimmune disorders, such as lupus and Sjogren's syndrome, where the immune system starts to recognize and destroy normal organs in the body as foreign. So we don't want that. But also, if immune surveillance or if the immune system is weakened, cancer can develop because of lack of surveillance and lack of anti-tumor activity. So--and there are so many elements to this, it's hard to balance, but in general we talk about activation versus tolerance.

What we know, along with this activation versus tolerance, is that there is increased cancer incidence in patients who are immune suppressed. So patients who have undergone solid organ transplants or bone marrow transplants or are immune suppressed for it because of another autoimmune disorder.

And, in this slide shared from Dr. Subudhi, here, I think this highlights this really well, as we see, patients that are immunosuppressed have a higher rate of prostate cancer than expected. So if you take the normal expected rate for prostate cancer in that sample, of about five, but there is actually eleven patients in that sample set that develop prostate cancer. So almost twice the rate of prostate cancer in the context of immune suppression. And we see that this isn't just isolated to prostate cancer, but to many of our cancers--many other cancers that we face. And importantly, we know that natural killer cells, again, its the cell that I study, are really important for immune surveillance. That's one of their main goals--is cancer and infection surveillance. And this is in patients already that have prostate cancer, but we know that

higher infiltration of natural killer cells leads to improve patient outcomes as well. So important to think about, and as we move forward.

So every day your body is generating hundreds of thousands to millions of cancer cells. But what's important is your body has a process called "immune surveillance" that prevents the vast, vast majority of these cancers—more than 99.9% of those of those tumors--from actually growing into something clinically significant.

What happens is when your cells are normally dividing and doing the job that they do, there are occasionally mistakes that are made in the DNA, which is the directions for the cell. Those can turn into cancer cells, but it's 1 or 2. And immune surveillance, using T-cells, dendritic cells, natural killer cells and other immune components are able to quickly and easily clear those cells most of the time. So that's with the elimination you can see in the bottom left.

Occasionally we reach an equilibrium where the tumor and the immune cells are kind of at a detente where they're not growing. But it's not getting smaller either. But we know that tumors are also smart and they are really, really evasive. And so at some point, when we have a clinically significant tumor or prostate cancer, we know that immune escape has happened.

And there are multiple ways that the tumor can escape from the immune system. And I'm going to describe these other therapies in ways that I describe them to my patients. So some of the tumor-intrinsic mechanisms are to delete the recognized target. So what the original, innate immune system told the adaptive immune system to "take a look at this and remember," it just deletes that. And so it can't find it. You can also have a failure of T-cell priming or trafficking. So it prevents showing what was found in the first place and prevents that interaction between the innate and the adaptive immune system.

You can also surround yourself when you're a tumor and you want to protect yourself. You surround yourself with suppressive cells that prevent the immune system from clearing. So it's like having a bodyguard. And then finally, immune exhaustion is the other thing that can happen where the tumor cell shuts down the immune response and basically says, "nothing to see here." Or really, my favorite analogy is an invisibility cloak that prevents the immune system from seeing the tumor.

Immune therapies aren't new, but they're ever-evolving and this is another great slide shared with me from Dr. Subudhi, but we've had immune therapies for over 100 years and the first one was in 1891 from William Coley, and it was called Coley's Toxin.

It was basically broken-up bacteria that were injected into the tumor, and it generated an immune response, and it was actually quite effective, particularly for soft tissue sarcoma. So we see that out of 100 patients treated, only 38 did not have a response. So more than 60 of those patients did have a response. And these responses were durable for more than 20 years in some patients. So we can just see an example on the

figure on the right there of what that was. We certainly evolved since then.

But prostate cancer is immunologically cold. And we really haven't been able to take advantage of many of the immune therapies that have developed for other cancers, such as melanoma, kidney cancer and small cell lung cancer. So that's really complicated our efforts. Prostate cancer is what we call a cold tumor. It's immune-deficient. It's immunotherapy-resistant in general, with a few exceptions that you'll learn about tonight. But basically what happens is the immune systems don't infiltrate or the immune cells don't infiltrate into the prostate cancer as frequently. There are a lot more immune-suppressive signals, and in general, it's a much more harsh environment on these cells. So the immune cells have a hard time working and destroying the prostate cancer tumor.

Compare that to an immunologically hot tumor like melanoma or kidney cancer and see many, many more immune cells infiltrating into these tumors, much more inflammation, and then we also see breakdown of what was called the extracellular matrix. So these cells can infiltrate and do their job really well.

So the question is, "How do we overcome this cold tumor microenvironment?" We've progressed a long way since 1891, grinding up bacteria or freezing them and making bacterial particles and injecting it, but we have a long way to go too. So here's a few of the examples you'll hear about tonight. We know about vaccines, for example, Sipuleucel-T. And this is basically boosts the 'look what I found and I remember it' signal, specifically towards prostate cancer. You also have immune checkpoint inhibitors such as pembrolizumab, and this blocks that 'nothing to see here' signal. Or, as I tell my patients, it blocks the invisibility cloak and allows the immune system to actually see the tumor.

This area gets much more into my area of interest, but Bispecific Engagers bind the immune cell to the tumor and basically don't let it go until the tumor is killed. So we can see in the figure on the right there, that immune cell is coated with those blue and purple molecules, those stick the two together, and really don't release them until the tumor is killed. And then finally, a patient's favorite, Chimeric Antigen Receptors. This is basically an anti-tumor Pac-Man that we generate from your own cells. It goes around chewing up the cancer. But it's very specific and has been engineered that way.

Importantly, immune therapies require balance to be effective and tolerable. We can't just take all the brakes off the immune system. We have to make them tolerable. If we have too many side effects then nobody can tolerate that and then it doesn't really benefit anybody. So it's really a balance between a healthy immune system and overstimulation and understimulation, and achieving this balance is much harder than it seems.

So our conclusions from this first part, my basic primer of immunology,

prostate cancer is immunologically cold and hard to treat with immune therapies, although we have some successes. We're hoping to build on this. We already have some FDA-approved immune therapies for prostate cancer, and you'll hear about those. We have numerous options that are under investigation as well. And you'll hear about some of these earlier studies in these concepts. And finally, we have to balance efficacy with toxicity because that's the key to future therapies.

Thank you very much. That's the end of my presentation.

Becky Campbell: Great. Thank you so much, Dr. Zorko, for that excellent introduction. I know that, you know, you mentioned some therapies that are available for use today. And Dr. Subudhi is going to cover those. So I will go ahead and turn it over to you, Dr. Subudhi.

Dr. Sumit Subudhi: Thank you, Dr. Zorko. Thank you for an excellent introduction. And then I'd like to thank all the participants for attending this PCF webinar, and then I also like to thank PCF for my Young Investigator Award, as well as Challenge Award, for supporting our exciting research.

So today I'm going to talk about current uses of immunotherapy in prostate cancer. Here are my disclosures, none of which are relevant.

So when we think about the systemic treatment options for metastatic castration-resistant prostate cancer, there are several that are listed here. In the form of hormonal therapies, chemotherapies, radioligand therapies, PARP inhibitors and then in red I've highlighted two of the immunotherapies that Dr. Zorko has already spoken about.

So the first one we're going to talk about is Sipuleucel-T, otherwise known as Provenge. So if you're a patient and you're going to get Provenge, you first have to go through a procedure called leukapheresis, where you lay on a medical table for about three to four hours, and what happens is the leukapheresis machine will take some of your immune cells, not all of them, so you won't be immunodeficient. It'll take some of those immune cells and when it collects a sufficient amount, it's mailed to a company that will take those immune cells and put them in a tissue culture dish, then that tissue culture dish is actually put together with the drug Sipuleucel-T which is in the form of “PAP” or prostatic acid phosphatase, which is a protein that's expressed highly in metastatic prostate cancer and an immune molecule known as GMCSF, that activate your immune system. Once your immune system is activated, three days later, the vaccine is put back into the patient, and then that vaccine teaches the T-cells, which are the soldiers of the immune cell-- sorry, of the immune system to actually fight the cancer.

And so this is process is repeated two weeks later and then another two weeks later. So week zero, week two, week four, and one month. You're done.

So this is work done by Larry Fong when he was at UCSF, now at University of Washington. But he treated some patients with Sipuleucel-T versus untreated, and what you can see, is we're staining for T-cells in purple.

And you can see the untreated patients have very few T-cells within the prostate tumor, whereas the patients treated with Sipuleucel-T have significantly more number of T-cells. They're showing that Sipuleucel-T is able to recruit T-cells into the prostate tumor microenvironment.

So there was a randomized phase three study called the IMPACT study that evaluated Sipuleucel-T versus placebo in patients with metastatic castration-resistant prostate cancer. They enrolled 512 patients, all of which were asymptomatic or minimally symptomatic. I mean asymptomatic, meaning no cancer-related pain, or minimally symptomatic, meaning that patients required ibuprofen or acetaminophen for their pain, and they were randomized in a two-to-one ratio. So for every three patients, two would get Sipuleucel-T, one would get the placebo. And they were evaluated until progression.

If the patients were on the Sipuleucel-T arm and at the time of progression, the physicians would then treat the patients with the next standard of care option, and then for the placebo arm at the time of progression, the physician could treat with another standard care option versus sending the patient to get Sipuleucel-T, so this is a crossover and 64% of patients in the placebo arm actually crossed over to get Sipuleucel-T. And then both groups were evaluated for survival.

And when you look at the median overall survival, so on the y axis is the probability of survival, and on the x axis is time in months, you can see the arm with Sipuleucel-T, which is the black arm, had improved survival compared to the placebo arm in green / gold. And it's a difference of 25.8 months versus 21.7 months. The hazard ratio of death was 0.775, meaning there was a reduction in risk of death of 22% if you received Sipuleucel-T.

And then there was a retrospective analysis to see who actually benefited most from Sipuleucel-T, and what they did was they looked at median overall survival, which is shown on the y axis versus different quartiles of PSA at baseline. So the first quartile is less than 22.1 nanograms per mL. The next one is greater than 22.1 to 50.1. The third one is greater than 50.1 to 134.1, and then the last one is greater than 134.1. And you can see in the bars to the very left, that's with the lowest quartile. So that means that's when the patients' PSA was less than or equal to 22.1. The patients in the gray bars who received Sipuleucel-T did much better than the placebo or control arm in black. So there was a survival benefit of 13 months versus if you go to the other extreme all the way to the right, where patients' PSA were much higher at greater than 134.1, the survival benefit was only 2.8 months of Sipuleucel-T versus placebo.

Then they did a real-world analysis looking at African American men versus Caucasian men who received Sipuleucel-T. And you can see the African American men did significantly better. This is a big surprise to us, because this is the only therapy where African American men had actually done better than Caucasian men.

In addition, in general, African American men have a worse prognosis of prostate cancer compared to Caucasian men, despite even normalizing for socioeconomic differences.

So key points to remember, the vaccine boosts your immune system to fight the prostate cancer. There's only three doses, so you finish in one month - week zero, week two, week four. And there are minimal side effects compared to other cancer drugs. The biggest side effect is infusion reactions and I've given this drug for the last 11 years and I've only had seven patients who left the hospital still feeling the infusion reactions, which are flu-like symptoms.

So conclusions is that Sipuleucel-T improves survival in asymptomatic or minimally symptomatic men with metastatic castration-resistant prostate cancer, and it likely benefits patients with lower baseline serum PSA levels, as well as African American men. And I don't want people to walk out of here saying that if you're not African American, that you won't benefit from this because that's not true.

So now I want to take you to the bottom, the immune checkpoint therapy and talk about where that's improved. So if we look at a melanoma patient, so in the bottom part of the pictogram, you see actually someone's actual melanoma on their skin, which is a deadly skin cancer. And, above it, you see what we see under a microscope by immunohistochemistry. And we're staining in brown for CD8 T-cells. These are the soldiers that actually kill the cancer cells or the soldiers that are immune, of the immune system, I should say. And you can see in the red bar, everything above the red bar is outside the tumor, and you can see a lot of T-cells hanging out outside of the tumor, but below the red bar is a tumor itself, and you can see very few CD8 T-cells there. However, when you give treatment with Anti-PD-(L)1 or PD-(L)1 with, like pembrolizumab, you see that you bring in a lot of the T-cells inside the tumor. And as a result, you can see a lot of the tumor in that pictogram below that disappear. So this patient is actually benefiting from this sort of approach.

Here we have a patient who also has melanoma. But if you look on the microscope there's very few CD8 T-cells outside the tumor or even inside the tumor.

And when you give the immunotherapy, you can see you don't bring any T-cells in and as a result the tumor content continues to grow and this patient did not benefit from this immunotherapy. So when we look at patients with prostate cancer - and here's a table looking at two different types of patients with prostate cancer - those who have a lot of PD-(L)1 inside the tumor and those who don't, So PD-(L)1 positive versus PD-(L)1 negative. And you can see the response rates are somewhere between 6% for PD-(L)1 positive and 3% for PD-(L)1 negative. So really low response rates. Just to put it in perspective, the response rates for this sort of approach in melanoma is somewhere around 30% for just monotherapy.

And the reason why it's low, because you can see in prostate cancer, which is just a few T-cells present, you don't see a lot of brown staining inside this prostate cancer and that's why the PD-1--the Anti-PD-(L)1 or pembrolizumab fails to work well in most of our patients.

However, there are a subset of patients, about 3 to 5% that have something called “mismatch repair defect” in their tumors. And this leads to more T-cells coming into the prostate tumor. You can see the brown staining in this slide and you can see it's so much more compared to the one on the left. As a result, I should point out that this mismatch repair defect is not unique to prostate cancer. Actually… It's actually if you look at this--the pie chart, you can see that prostate cancer is represented in purple but most of the patients are actually, or majority are in red and these are colorectal patients which have a lot of mismatch repair defects.

But what we're seeing in the bottom are patients who are treated with anti-PD-1 or pembrolizumab treatment and you can see a lot of the bars are below zero and so these bars are showing that the cancer is actually shrinking. And that's so… patients with mismatch repair defects, many of them are going to have responses or shrinkage with anti-PD-1 therapy whereas very few will have tumors that are progressing where the bars are going up. And I want to point out in these bars, there's a few of those that are purple in the very right that are showing complete responses to this approach.

So Wassim Abida, my colleague at Memorial Sloan-Kettering Cancer Center, has treated the most patients with prostate cancer and mismatch repair defects. And what he found is that 50% of patients will actually have a response with Anti-PD-1 treatment, however, only 50% of those will have a durable response. So if you take all prostate cancer patients with mismatch repair defects, approximately 25% will get a long-term durable response.

So in conclusion, responses to Anti-PD-1 or PD-(L)1 monotherapies are linked to how much T-cells you have within the tumor. And prostate cancer has few T-cells, which limits its response to this approach, however, there are exceptions here, too. One that I talked about already, mismatch repair defects, and the other one is high tumor mutational burden or TMB. Thank you.

Becky Campbell: Thank you so much, Dr. Subudhi, for that overview. I have a question. How would a patient know that they might be eligible for, let’s start with Sipuleucel-T. Just so we're really clear about if a patient's out there wondering, “should I ask my doctor about this?” How would you tell them to start that conversation?

Dr. Sumit Subudhi: That's a great question. I think no matter where you are in your disease state, you should always ask your doctors about what drugs are available. Even if you don't qualify for now, it's good to know that you have this in your back pocket in the future. But it's--the patients that are eligible are those that are metastatic castration-resistant prostate cancer. So that means that they have already failed Lupron or Eligard or some sort of androgen deprivation therapy, and their cancer’s progressing or the PSA is going up and I usually, personally, in my clinic use it as first-line treatment for patients who are asymptomatic or minimally symptomatic for that.

Becky Campbell: Okay, so that's the Sipuleucel-T, and then how would a patient know that they might be a reasonable candidate for pembrolizumab?

Dr. Sumit Subudhi: That's a great question. So that's a little bit different. That actually requires a genomic test to be done. And that genomic test will tell you two different things. One, if you have mismatch repair defect or if you have high TMB or both, and if you have mismatch repair defect or TMB or both, then you qualify for getting pembrolizumab or anti-PD-1 therapy.

Becky Campbell: And so should patients, in general, think about having this special type of testing? Like how does the testing--how does the test work? Is it a blood test or--?

Dr. Sumit Subudhi: That's right, great question. So it's been done both, what we call a liquid biopsy or a blood test. But it turns out that if that doesn't work, it's always best to get the tumor tissue itself, because that can give you--it can enrich for patients, having that--the way it's sometimes harder to find with the liquid biopsies or blood specimens. And then who should be getting that? I think any patients with high-risk prostate cancer. So anyone with a Gleason 8 to 10, anyone with metastatic disease, and in fact, my own father, when he got localized prostate cancer and it was Gleason 8, I made him get that test right away to see if he would qualify in the future.

Becky Campbell: Okay, that's really good to know. Those are important types of tests that patients may not have maybe talked to their doctor yet or heard about. So this isn't mCRPC patients. This is even high-risk localized prostate cancer might want to consider these types of tests.

Dr. Sumit Subudhi: Yeah. And I just wanted to clarify. It's not that you would use it in the localized setting. It's just that patients with high-risk localized disease have greater than 50% chance of the cancer returning. So we just wanted to anticipate in case my dad's cancer came back. And unfortunately, it did come back. And now it's in his bones but he unfortunately does not qualify for pembrolizumab because he did not have either mismatch repair defect or high TMB. Understood.

Becky Campbell: Understood. Well, I'm sorry to hear about your father. But I'm glad that he, you know, got some tests to at least understand what his options were. And then I know we received some questions in advance. Where can patients get these types of treatments? They sound pretty specialized. Would any institution would have these, or where should they go?

Dr. Sumit Subudhi: Yeah. So the Anti-PD-1 or pembrolizumab treatment pretty much, I think, any treatment center will have those available. The Sipuleucel-T is a little bit more tricky because it requires that leukapheresis to be done, and that's--that requires usually specialized centers, but there are a lot of community centers out there that are actually actively doing it and you just have to ask your doctors--and if you want it--I've had my patients--because many of my patients are out of state or international--they want to get it locally, so I just have them ask their doctor if they can get it locally, and if the doctor itself

can't do it, they'll find a partner at a different center nearby that could actually do it.

Becky Campbell: Okay. Well, thank you so much. That's great sort of practical information. I want to turn it over to Dr. Agarwal, who's going to talk about the really exciting future of immunotherapy in prostate cancer, talk about some clinical trials, which is a very important piece of this. And it's how we get to know these new therapies. So, Dr. Agarwal, I'm going to call up your slides and let you take it away one moment.

Dr. Neeraj Agarwal: Becky, I'm so honored to be here, so happy to see you all. While we are--you're pulling up the slides, I must want to--I want to make a comment on this genetic testing or genomic testing of the tumors. And unfortunately, less than 40% of patients had that testing done even in a metastatic setting until very recently, I would say 2023. So it is very important as Dr. Subudhi mentioned, that we should talk to our doctors and make sure and--or clinicians--that we have the testing done in a timely fashion. So I'll be talking about immunotherapy advancements in advanced prostate cancer.

This is my introduction. You have already introduced myself, but this is where I work. It is Huntsman Cancer Institute at the University of Utah.

This is my conflict of interest. I have no conflict of interest with any pharma since May 2021.

So let me start by talking about this immune checkpoint inhibitor. Both Dr. Zorko and Dr. Subudhi talked about pembrolizumab not being effective in most patients, except when they have these markers like MSI high or other mutations like TMB high status. But then we decided to combine this immune checkpoint inhibitor, Atezolizumab, which is similar to Pembrolizumab with Cabozantinib. Just to give you an introduction on Cabozantinib. So Cabozantinib is an oral tyrosine kinase inhibitor. And what does it mean is that it blocks several drivers of cancer progression within the cancer cells. And this drug is already approved for patients with metastatic kidney cancer, liver cancer, and thyroid cancer. So this is not entirely an experimental drug. And this is being used in the clinic for almost, I would say, ten years now. Now what we did, we combined the Cabozantinib drug with one of those immune checkpoint inhibitors and in this case it was Atezolizumab.

And just to date, go back five years, we decided to do a phase one trial with this combination and saw encouraging responses. Now, when we decided to design the phase three trial. So in this phase three trial, we decided to exclude patients who only had one metastasis. And that was based on the perception that bone metastasis may have artificial--artifactual effect because of Cabozantinib. So after discussion with the regulatory bodies, the decision was to only include those patients who had measurable soft tissue disease, and those patients were perceived to be those with lymph nodes. And as you know, lymph nodes are very common sites of metastases in patients with metastatic prostate cancer. So this trial was different from other prostate cancer trials in the sense that patients could not have bone-only disease. They had to have measurable

soft tissue metastases. And when we started enrolling patients, to our surprise, we ended up enrolling almost a quarter of patients who had liver metastases because we were emphasizing measurable disease.

So in addition to lymph nodes, we also had a large proportion of patients with liver metastases. And just for the viewers, I want to emphasize that liver metastases are the most lethal form, the most aggressive form of metastases in patients with prostate cancer. And in this trial, the progression-free survival was the primary endpoint. And overall survival was another primary. And so there were two primary endpoints for the trial. So when you look at the results in this patient population who had such high aggressive or high-risk features, this was a clinically--meaning like, what you call, statistically significant improvement in progression-free survival. There was about 35% reduction in risk of progression or death in these patients. And if you look at liver metastasis patients where disease progressed so fast that you hardly have a CT scan done, where you don't see disease progression in this patient population, and you can see on the right side, right upper side of the picture, the patients who had liver metastases, they are down almost three times prolongation of that progression-free survival. So that was one of the intriguing findings we had in this clinical trial.

We waited for these patients who have disease progression and ultimately we looked at overall survival endpoint which was not superior with cabo-atezo or this--the combination of these two agents. But then, if you look at patients with liver metastases, again, the most aggressive form of metastatic prostate cancer, there was an increase in survival from seven months to 12 months. Now these may not seem like very high numbers, but if you look at patients with liver metastases in the clinic, we essentially tell them that they have--they don't have much time left. So in this context, we saw really encouraging data in the context of patients with liver metastases and then if you just look at bone metastases and-obviously I'm pulling up those subsets which are of interest to us, to our patients-we look at bone metastasis subset. And again we saw some benefit with cabo-atezo, but benefit was…a significant benefit, but benefit was more significant in patients with liver metastases.

Now moving on to other therapies. So I would like to mention the CAR-T cell therapy now. So what is CAR-T cell therapy? It is a kind of personalized therapy. And Dr. Zorko and Dr. Subudhi have already talked about T-cells being one of the most potent defense cells. So CAR-T cell is a personalized therapy where we use your own immune cell to fight cancer. And how does it work? It seems like a complicated picture. So what we do, essentially, is we collect your T-cells. So you collect the blood first, then T-cells are taken out. And again these are the most important type of defense cells or one of the most important type of defense cells. Then in the laboratory these T-cells are programed to recognize the cancer cells. And that is done by adding special protein on the surface of these T-cells. So they are called S-chimeric antigen receptor T-cells.

So funny like a complicated name, but for your own understanding, a special protein is put on the surface of T-cells. It's like a GPS, which

allows T-cells to find cancer cells. And then those T-cells are--after they get the GPS, they get the--we give the T-cells back into the patients by infusing back into the bloodstream. And when you do that, the T-cells with the new GPS, which is the special protein on the surface, they start seeking the cancer cells. So the technology seems very exciting but so far it is in the relatively early stages of development. As we can see in these two trials, these are early trials. Very few patients have been treated. And we saw some encouraging responses. But I would say at this point in time they are not close to be prescribed on a clinical basis. So you cannot expect your clinicians, your doctors, your providers to prescribe you CAR-T cell therapies.

So next one I would like to discuss is T-cell Engagers. So what is T-cell Engager? So again, I would like to simplify. T-cell engagers are again a type of T-cells. They are T-cells like….let's make it even more simple. You take a protein and, as we heard from Dr. Zorko's talk, Dr. Subudhi's talk, the prostate cancer is immunologically inert. It doesn't invoke your immune system to go after that. Sometimes-- somehow they are able to hide from the immune cells. So how can we make the immune cells recognize your prostate cancer? And that is done by these special proteins called T-cell engagers. And these are proteins which have two arms. On one side, they catch hold of the T-cells and the other side they catch hold of the prostate cancer cells and basically, to put it simply, it drags the T-cells close to the prostate cancer. And when it does that, when T-cells get too close to the prostate cancer, they recognize the T-cells--they recognize the prostate cancer cells, and they start making holes in them. And then it leads to destruction of the cancer cells. So again, just for the sake of repetition and to simplify this complicated mechanism of action, this is a special protein which bridges the distance between the cancer cell and the defense cells or the T-cells and bring drag T-cells down or close to the cancer cells.

And again this is a crowded slide but I want to bring your attention to those two. T-cell engagers would seem quite promising at this time. At this point in time. I'd like to bring your attention to this one, Xaluritamig, and this is a T-cell engager which targets a special protein, or a special antigen, or I would say, something which is quite present on the prostate cancer cell surface. As we can see here, majority of patients in this study, almost 90% patients had STEAP-1 antigen present on the cancer cells. And it turns out STEAP-1 helps prostate cancer multiply, invade and differentiate to more aggressive type of phenotype. So in this study many patients--actually a majority of patients expressed STEAP-1, thus making it a good target for our drugs.

So what happens in this trial where Xaluritamig, which is a protein which binds with STEAP-1 on one side and T-cells on the other side, this patient population, and again very early phase—trial, phase one trial. And these patients had a lot of treatments given in the past. We saw encouraging responses. And you can see here, this is a drop--it's a drop in the PSA level. And we can see this is called waterfall plot. And we can see most--like almost half of the patients had very impressive PSA responses when you treated them with Xaluritamig. And this drug has already gone into phase three trials, which are being conducted in multiple centers across the world.

So you can go on NCI.com website [editor's note: https://www.cancer.gov/research/participate/clinical-trials-search] or clinicaltrials.gov website or many other websites, including the resources provided by the PCF to know where this trial or where this drug may be available.

We cannot finish any discussion about a drug with the side effects, especially with the new drugs. So a common side effect, which is seen with even CAR-T cell or T-cell Engagers is cytokine release syndrome. So what is cytokine release syndrome? So when we treat these cells, with these T-cell engagers, what really happens is it leads to flu-like symptoms. And flu-like symptoms can comprise of fever, chills, rigors, sometimes low blood pressure. And because this is given in a controlled environment, patients are admitted--next dose is delayed or next dose is not given until you have fully recovered. Fortunately, as we can see in this trial, most of the patients are very mild cytokine release syndrome and most of them had grade one syndrome. It means it really did not require a lot of interventions to fix those symptoms.

I'd like to bring your attention to another T-cell engager known as Tarlatamab. And fortunately, this T-cell engager has already been approved for patients who have lung cancer and had this neuroendocrine differentiation, which is the most aggressive, one of the most aggressive forms of prostate cancer. So when you treat prostate cancer with multiple agents, ultimately they develop this phenotype or this new characteristics--they develop--they acquire this new characteristic which is known as neuroendocrine prostate cancer and this neuroendocrine prostate cancer express this DLL3 antigen which can be recognized by this T-cell engager known as Tarlatamab.

This was an early phase trial where we saw encouraging responses. About 22% patients had responses with Tarlatamab. In those--especially in those patients who had high expression of DLL3 antigen.

Again the side effects were quite well tolerated. And fortunately, cytokine release syndrome was mild in most of those patients. So just to summarize, T-cell engagers are really promising at this time. And we look forward to those phase three trials which hopefully will show their results in the next 2 or 3 years. So I'd like to conclude my talk by saying that we are seeing a revolution in the development of immunotherapy--novel immunotherapies in patients with metastatic prostate cancer. And my take on this is none of these immunotherapies will be curative by themselves. Maybe in a small number of patients, but in most patients they will lead to great disease control and improve survival outcomes, but ultimately we will need to combine these immunotherapies with other agents like you have heard on other PCF webinars, like radioligand therapies, androgen receptor blockers, new androgen receptor targeting agents, and ultimately we will see in the near future, I remain very optimistic, that we will have a patient coming into the clinic, and we will design a personalized cocktail for that patient, whether they need to receive this immunotherapy, whether they need to receive radioligand therapy or other signaling inhibitors, or a combination of all of that.

With that, I'd like to thank you for your kind attention.

Becky Campbell: Thank you so much, Dr. Agarwal, for the detailed description of some of these exciting therapies. And I know you've worked on, you know, some of these yourself. Just one quick question. Before we bring in our patient, Mr. Eisenmann, you mentioned clinical trials, which are so important to finding these new potential treatments. If a patient out there is wondering whether they should join a clinical trial, how would you recommend that they broach that with their physician?

Dr. Neeraj Agarwal: Yeah, that's a great question. We still believe that clinical trials provide one of the best treatment options to our patients, not only because the drugs are newer, we always administer standard of care therapies. When you are on clinical trials, there's definitely an option where you will get, you know, either you have already progressed on the standard of care therapies or you are going to receive them. So nobody is really deprived of many therapies which are already available there. So many patients think clinical trials is only for those patients who have been failed by other therapies. And often these T-cell engager, CAR-T cell therapies are more effective in those patients who have lower disease volume, who are--whose immune system is robust, who have better health status. So I would say talk to your doctor always about the possibility of clinical trials and always look around. Go to ClinicalTrials.gov website, go to cancer.net website or at American Cancer Society and, of course, Prostate Cancer Foundation websites and look for clinical trials. It doesn't take much time nowadays with internet being available almost universally to explore clinical trial options, but everybody should do that with any advanced cancer. And even early-stages cancer, which are more aggressive.

Becky Campbell: Wonderful. Thank you for that big picture view of clinical trials. And that's something that people can take away with them tonight. So our last segment before we switch to Q&A, I'd like to invite Dr. Zorko and Mr. Eisenmann to come on the line. And I know you're going to have a conversation about Stephen’s real-world experience. And so I'm so pleased to have you here. Stephen, thank you so much for joining us.

Mr. Stephen Eisenmann: Happy to be here.

Dr. Nicholas Zorko: Stephen, you have a really intriguing story. Would you be able to tell us a little bit about yourself and your family before we get into your prostate cancer journey?

Mr. Stephen Eisenmann: Sure, Dr. Zorko. I'm an eight+ year stage four prostate cancer survivor. I'm married to Elizabeth, who's been my life partner since we were married about 21 years ago. We have four children and ten grandchildren. I'm a graduate of Temple University with a Bachelor of Science degree in business administration and professionally, I have 45+ years of insurance industry experience in start-up, acquisition and management of casualty, US and international insurance entities. Currently, I am Managing Director of the Princeton Partnership and serve as Executive Vice President and Chief Claims Officer of EmPRO Insurance Company, a medical malpractice insurer in New York.

Dr. Nicholas Zorko: Thank you for the for the background about yourself. What could you tell us about your journey with prostate cancer before immunotherapy was introduced to your treatment plan?

Mr. Stephen Eisenmann: So in 2016, at the age of 60, I was diagnosed with stage four metastatic prostate cancer. I had cancer in my lymph nodes and in my bones. And I thought this was, you know, a death sentence based on the information that I reviewed. But there's no way I was going down without a fight. So I used every resource at my disposal. I found the Prostate Cancer Foundation and learned that the PCF is an organization leading the fight to improve outcomes for prostate cancer patients with a great website, and it contained really credible information, which I utilized to really educate myself as much as possible about prostate cancer. I was accepted as a patient by PCF-funded researcher and medical oncologist Dr. Dana Rathkopf at Memorial Sloan Kettering in New York City. Dr. Rathkopf put me on the standard of care treatment at the time, continuous hormone therapy with six cycles of chemotherapy. At the same time, I learned from the Prostate Cancer Foundation that there were three things that I was able to control in my battle against prostate cancer. I could control my diet, my attitude, and my exercise routine, and with the help of my wife, Elizabeth, we embarked on doing all three of those things, which we continue to do today.

Elizabeth and I have always been partners during our marriage, and she researched the most effective diet for keeping prostate cancer at bay. We focused on eating green leafy vegetables, only getting sugar from natural fruits and vegetables. I gave up some of the foods that I love, like pasta, ice cream, cakes. My weight went from 210 to 185. We also exercised and tried to maintain a very positive attitude. After completing the initial treatment, the chemotherapy, in December of 2016, the PSA went down to non-detectable and Dr. Rathkopf told me that I had a very good response to the treatment and that I should go live my life.

Dr. Nicholas Zorko: So it sounds like you had a great response to first-line therapy, like many of our patients do. How did immunotherapy become an option, and what was that conversation that you had?

Mr. Stephen Eisenmann: So yeah, that's--it was a good response. And I had hoped it was going to last longer than the 18 months that it lasted. But about a year and a half after completion of my chemo, even though my PSA was not detectable, Dr. Rathkopf decided to perform repeat imaging, and it showed that I had enlarged lymph nodes. The prostate cancer was back, even though I wasn't making any PSA, which I thought wasn't a big deal because we had talked about this. And since I knew the initial treatment was only effective for about an average of two years at that time, we talked about going to the next drug.

Unfortunately, it wasn't that simple. In 2018, for me, most treatments, and clinical trials were for prostate cancer patients making PSA. I learned that approximately 5% of prostate cancer patients don't make any PSA. And when the prostate cancer is active, I was one of them, I learned the next drug wasn't going to work, and it didn't, and there were no trials for men in my situation. But Dr. Rathkopf clarified, and in

keeping with a positive attitude, I tried to stay positive. While there were few treatment protocols for my prostate cancer, there might be a precision drug, and she biopsied my cancer to figure out if there were any genome markers that had responded to a precision drug. And then the world kind of aligned for me.

Dr. Arul Chinnaiyan from the University of Michigan, with funding from the Prostate Cancer Foundation, was conducting a trial on immunotherapy for prostate cancer patients. However, they had published a report that basically concluded immunotherapy was not an effective treatment for prostate cancer patients. However, two days before my test results came back on June 14th, 2018, a supplemental paper was put out by Dr. Chinnaiyan describing that about 7% of prostate cancer patients in the trial had a mutation in a gene named CDK12, and some of those patients had responded to pembrolizumab and immuno-drug therapy. Two days later, on June 16th, 2018, I got the best of the worst news. I had the CDK12 gene mutation marker in my cancer, and Dr. Rathkopf wanted to give the pembrolizumab immunotherapy a try. But she also was very thorough and wanted me to get a second opinion, so there was no stone left unturned. She referred me to John Hopkins to see another PCF-funded investigator and oncologist, Dr. Emmanuel Antonarakis, and he agreed that the Pembro was the best treatment option for me at that time.

After only three cycles of pembrolizumab, I'll never forget it, Dr. Rathkopf brought her whole staff in to tell me that the scans came back, that the results of the imaging showed a complete response to the treatment.

Dr. Nicholas Zorko: That must have been really exciting to be one of the first patients to get that treatment. But what questions did you have, and your family have about this treatment?

Mr. Stephen Eisenmann: So, initially, Elizabeth and I wanted to know the chance that the treatment would work and the effectiveness of the treatment if it did work. So we learned from Dr. Antonarakis that he believed that the chance of treatment working was less than 10%. But under intense questioning from Elizabeth, we were told that there was a chance that all of my cancer contained the CDK12 gene and that pembrolizumab would likely kill all cells that contain CDK12. Elizabeth, being the positive person that she is, connecting the dots and said, “well, he'll be cured.”

And Dr. Antonarakis has told us that the preferred term is “complete remission.” We also asked about the treatment protocol. And again, I was one of the early ones. So I learned that I was basically an N of one, or my very own clinical trial of one person. Since all of the patients in the Michigan study that had CDK12 and their prostate cancer made PSA. So the exact treatment protocol for me was not set in stone. We learned that the pembro treatment would consist of 30-minute IV every three weeks. And because of my unique circumstances, after it was found that the treatment was working, the length of the treatment would be determined by my response. We wanted to know the potential side effects and there are many and there's papers that are published that show them,

but the three that impacted me were I no longer have any hair, but it's a small price to pay, and I got no problem with that. I had a problem with my thyroid, which I now take medication to control. And then there's the potential that pembro might attack healthy organs such as the lungs. And ultimately, in September of 2022, about four years after I started the pembro treatment, my scan showed nodules in my lungs that were increasing, and the fear was that this was cancer. But the good news was the biopsy was negative for cancer. However, it showed organizing pneumonia, which was ultimately believed to be from the pembro treatment. So the treatment was discontinued.

Dr. Nicholas Zorko: That's a lot of information to take in as a patient. What other concerns did you have at the time as you were making these decisions?

Mr. Stephen Eisenmann: So as we were making the decisions, our concern was whether the pembro treatment would be effective for me. And that was particularly concerning since there were no other known effective treatments for the way my prostate cancer had become active. When the pembro was discontinued, I was then concerned that my prostate cancer may become active again.

Dr. Nicholas Zorko: Can you tell us a little bit about about your experience receiving the Pembrolizumab?

Mr. Stephen Eisenmann: Yeah, the treatment was nothing like the chemo treatment. I used to tell people that from the standpoint of chemo, it was like getting hit with a sledgehammer in the middle of your head. So pembro wasn't like that. It was a few hours out of my life every three weeks. It was an IV, and it was a small price to pay when long considered the alternatives at that time. So if immunotherapy is a treatment options for others, I would recommend it.

Dr. Nicholas Zorko: And importantly, how are you doing now?

Mr. Stephen Eisenmann: So I'm doing very well. My most recent scans in June 2024 showed no evidence of metastatic disease in my body. And so I'd like to point out that in 2018 had Prostate Cancer Foundation not funded Dr. Chinnaiyan’s trial on immunotherapy, had Dr. Rathkopf not been plugged into the prostate cancer research at that time, had the supplemental paper not been published when the grad students on Dr. Chinnaiyan’s trial had crunched some numbers that showed some patients with the CDK genome might benefit from Pembro, I wouldn't be here today.

While Dr. Chinnaiyan’s trial from a statistical perspective, as you've talked about, you know, being for multiple patients and things of that nature, was not approved for prostate cancer patients with the CDK12 marker, Elizabeth and I continue to counter that as a success, because statistics boil down to people, and in our case, one life saved.

Dr. Nicholas Zorko: What advice would you give to other patients who are in your shoes?

Mr. Stephen Eisenmann: So, when I was diagnosed, I determined this is my health and when patients are diagnosed, it's your health, so patients diagnosed with prostate cancer should take charge of their health and become educated, seek precision prostate cancer treatment centers and talented doctors such as yourself and the others on this webinar who are also prostate cancer researchers. Control what you can control, maintain a positive attitude, exercise and eat a healthy diet, and also be careful of the information about prostate cancer on the internet. I went on the internet when I was diagnosed and there was some very scary stuff out there. Go to PCF.org, which has credible and comprehensive information for prostate cancer patients.

And in concluding, I want to thank all the medical professionals, including those on this webinar, you, Dr. Zorko and the others, Dr. Subudhi and Dr. Agarwal, for the work that you are doing, because it wasn't that long ago that stage four prostate cancer patient had a two-year life expectancy when diagnosed with stage four prostate cancer. And so there are so many things that are happening now for people like me and they would only happen for them as a result of the research that you guys are really doing, and I'm really appreciative of that. I'm also very thankful to the Prostate Cancer Foundation for all that they've done and all that they're doing for patients like me to reduce and hopefully eliminate suffering and death from prostate cancer. Thank you.

Dr. Nicholas Zorko: Thank you for sharing your story with us, Stephen. It's really inspiring and it's really important for everyone to hear the outcomes of a new therapy. And from a patient who had a great experience from it. I think we're up for questions next, right, Becky? Dr. Agarwal or Dr. Subudhi, can you comment on moving these forward to all non-metastatic or earlier stages in metastatic disease?

Dr. Sumit Subudhi: Yeah, I can start and Dr. Agarwal can add on. But we strongly believe that the prostate cancer is less immunosuppressive or more responsive to immunotherapies early on in disease. However, most of our early trials or new drugs are tested in the metastatic castration-resistant setting, partly because there's not much known about these new drugs. And there's a--we always have to do a risk-benefit analysis. And we feel like that because the metastatic castration-resistant setting is one where patients' life expectancy is usually measured in years or months or years. It's--that's where we should start when we're trying to understand the safety of the drugs.

But as we get more safety data, then there is a tendency to move things into the metastatic castration-sensitive setting, the biochemical recurrent setting, and even the localized high-risk setting. So we are seeing those trends happen, but they usually start in the latter stages where the cancer is most immunosuppressive.

Dr. Agarwal: I'd just like to add, Dr, Subudhi has explained it so well, an example is ARPIs or androgen receptor pathway inhibitors. They were originally tested after chemotherapy had already failed our patients and now many of them--enzalutamide, darolutamide, apalutamide--they are being tested right in localized settings where patients had just had surgery

and for localized prostate cancer and I think more of these drugs are going to be tested earlier.

And especially in the context of immunotherapy, we expect them to be more effective and better tolerated, actually, in patients who have healthier immune status. They're not already being exhausted by multiple therapies given to them, especially, you know, immunosuppressive drugs, which can be a part of chemotherapies. So I think answer is yes. And it is already happening.

Dr. Nicholas Zorko: Great. Thank you very much. And I think that to lead into that, or going along with this, too, there's a question about gene editing as part of prostate cancer treatments. I think one way to think about that is our CAR T-cells, which are gene-edited. While we're not editing the prostate cancer itself, we're editing the immune system to make it more effective. So there is, if you view it that way, gene-editing is a part of the experimental prostate cancer treatments that are ongoing.

Let's see one of the next questions here. There was another question about lowering cost. And I think, for these treatments, and I think that really leads into the clinical trials as well. Just--we have to get these approved first in that space.

There was another, I believe, several questions about "Does Medicare cover these--treat these immunotherapies?"

Dr. Sumit Subudhi: Yeah. So they do for Sipuleucel-T, which is FDA-approved as well as for Anti-PD-1 treatments such as Pembrolizumab. Also, as long as you have mismatch repair defect or high TMB setting, then they would be approved. But if you do not have that, then your choices are clinical trials. So such as what our patient advocate, Stephen, has just nicely described, or trying to get off-label use, which is similar to what Dr. Agarwal has mentioned with the DLL3 by CD3 bispecific, I've forgotten exactly the generic name, but you can add to that. But it's been FDA-approved and small-cell lung cancer, but we can actually use it in patients who have new endocrine prostate cancer.

Dr. Neeraj Agarwal: And yeah, and I always struggled with this name. Like Dr. Subudhi said, Tarlatamab, which is approved for non-lung cancer patients with that neuroendocrine differentiation, which is also present in patients with prostate cancer after they have been treated with multiple lines of therapies.

Just to add one more point, another attraction I have for clinical trials is that our patients get those drugs literally for free when they are getting the drug through clinical trials. So that is something we should not miss telling our patients.

Dr. Sumit Subudhi: That's right. And then some of the trials actually cover travel costs.

Dr. Neeraj Agarwal: Yeah.

Dr. Nicholas Zorko: I think those are those are really great points, as patients will often have a lot of questions about clinical trials and some hesitancy about clinical trials as well. So thanks for bringing up those important points for patients who are really trying to make sure we have equal access to as many of our patients as possible.

I think you both briefly alluded to this in your talks, but one of the questions is “these treatments appear to extend life, but do they clear or eliminate the cancer?” And I think this is referring to the metastatic state. But I'm curious if you could weigh in on that again.

Dr. Sumit Subudhi: Yeah. When they work, they can actually clear the cancer and lead to durable responses as Stephen just described with his own experience. However, that's not always the case. Sometimes it leads to a partial response that can last weeks to months but sometimes the cancer will come back, just like we have with the hormonal therapies and chemotherapies, where you can see the treatments lasting for quite some time. But then, with scans or sometimes your PSA, you can tell that cancers are progressing. And then finally, there's a subset of patients where it just doesn't work at all, and they just progress immediately.

Dr. Neeraj Agarwal: And every trial, every single trial, every drug has a subset of patients who are exceptional responders, 5%, 10%, 20%. It really varies from one drug to another drug. So the key is to allow our patients or maximize the number of treatment options my patients can avail, because there is a chance there is a 10% statistical probability that a given patient will have exceptional response to one drug. If I can give them five drugs, different types of drugs sequencing-wise, there is a 50% chance the patient will respond.

Obviously, you know, it doesn't happen always, but Stephen is a good, great example sitting right in front of us.

Dr. Nicholas Zorko: But there are quite a few questions about individual cases, and I know it's part of the housekeeping. We didn't--we mentioned that we wouldn't necessarily address individual cases, but I think an overarching question is about individual therapy and qualifying for clinical trials.

I think one of the points we could maybe emphasize is that each clinical trial is different in its inclusion criteria. And just because you're excluded from one clinical trial may not exclude you from another one. One of those recurring themes has been patients who have been treated with immune therapy for other cancers and whether they might be eligible to use immune therapy for prostate cancer, as well.

Dr. Sumit Subudhi: So I'll start. So we had that come up. So you can't have another active cancer unless the active cancer is considered somewhat benign, and a good example I saw on the chat, someone was asking about CLL [editor’s note: Chronic Lymphocytic Leukemia) and so that's one example of cancer that's not considered aggressive. Another one is like, basal cell skin cancer or some squamous cells skin cancers are examples, and then there's also the noninvasive bladder cancer that comes to my

mind where they're not considered aggressive cancers. And many clinical trials will allow patients on those. But if you have a more aggressive cancer, many clinical trials will have a 3 to 5 year period where you have to be disease-free from that cancer in order to qualify for a prostate cancer clinical trial. And if you've had--received other therapies, whether it's chemotherapy or immunotherapy as used in this example, then you usually are allowed to go on and get to trial for prostate cancer.

Dr. Nicholas Zorko: Thanks for that explanation. I think it's a really important point to understand clinical trials. Even myself, only a few years ago, I didn't have a necessarily great grasp on clinical trials until I became involved with them.

I think another one of the questions that seems to be recurring is diet and diet changes. And are there anything, any supplements or any diet--in diets in particular, that can boost the immune system?

Dr. Neeraj Agarwal: I think it's always good to talk to your doctors about the diet. If--or clinicians about their diet. Even they may not know, they may not be the doctor or they may not be the board-certified dietitian, they have access to board-certified or qualified dietitian, almost every cancer center has access to dietitians. So it's very important for anyone with advanced prostate cancer to make sure they talk to a dietitian.

And as Stephen is a great example, sitting right in front of us who has changed his life and he has lost, Stephen, if I'm—if I heard you correctly, 25 pounds, and you feel healthier than ever. So this is a story of many of my patients.

Mr. Stephen Eisenmann: Yes, and you're right. I lost a significant amount of weight when I was diagnosed. And the exercise--I exercise 5 to 7 days a week now, still, and I feel better. You know, I feel as good as I can possibly feel.

Dr. Neeraj Agarwal: Yeah. And I say dietitian, because many doctors, clinicians are very busy. They may not spend that much of time on you to talk about diet for the next 35 minutes. That's why it is very important to seek certified dietitians when you have cancer, when you have prostate cancer, or for that matter, any cancer. And being treated with cancer therapies. It does change lives of my patients. And of course, exercise comes with it.

Dr. Sumit Subudhi: And I have to say, the majority of my exceptional responsers to immunotherapies have been people who have been the most fit and have an active lifestyle. So that means that they're eating healthy and they're also working out.

Dr. Nicholas Zorko: Thank you all for your insight on that. And I think PCF has some great resources as well about diet and exercise too, that are very patient-centric.

I think we've talked a lot about genetic testing, but one of the questions that has been coming up too is "when should you get genetic testing done?"

And I think you maybe made a distinguish or--distinction earlier too, between somatic testing and germline testing.

Dr. Neeraj Agarwal: I can take that. So if you look at five guidelines, there are five different languages for genetic testing in localized prostate cancer, I think, is that there is a unanimous--unanimity out there regarding genetic testing in metastatic prostate cancer. Everyone with advanced prostate cancer should get both germline and genomic testing. And just for the sake of discussion, germline is where it's--germline is to make sure this is not something that you got from your mom and dad, and not sharing with your siblings and have not passed it on to your children.

The somatic testing is done on tumor tissue itself, and that is usually done, you know, on biopsy tissue or a metastatic site, but metastatic patients, patients with metastatic disease should have both. In a localized setting, as Dr. Subudhi mentioned, anyone with high-risk disease should have germline testing and potentially somatic testing because there is a very high risk that they will develop metastatic prostate cancer.

Dr. Sumit Subudhi: Yeah, I couldn't agree more.

Dr. Nicholas Zorko: We always recommend genetic testing when appropriate, too. We are big proponents of that at Minnesota also.

So one of the other questions that came up was "what about side effects from immune therapy?" And I know they're broad, you know, it depends, it's very treatment-dependent. But in general, what are some of the major side effects you could anticipate?

Dr. Sumit Subudhi: So there's a class effect. So I'll just try to go over some of the things we talked about. So with vaccines, it's more an infusion reaction that's similar to a flu-like symptom. With the specifics that Dr. Agarwal has nicely outlined in his part of the talk, there's something called cytokine release syndrome, which is different from the infusion reaction, but also has flu-like symptoms as well. And then with the immunotherapies or immune checkpoint therapies I should say, like anti-PD-1 anti-CTLA4 like pembrolizumab, ipilimumab. These one can--this is when you can boost your immune system so much that it can attack other parts of your body. So I think Stephen actually brought up a few examples of this. So besides the most common one, which is a rash, he actually had one that affected his thyroid organ. So it actually destroyed his thyroid organ. But the good part is that that can be replaced with a single pill and that's what I imagine Stephen's been taking and so it's not something that's life-threatening at all as long as you take that pill.

And then the third reaction he had, he had something called pneumonitis where it attacked his lung and that tends to happen somewhere between 3

and 10% of patients, depending on the trial. But those are just some examples. And then you can talk about CAR-T cells, Dr. Zorko.

Dr. Nicholas Zorko: Yeah. CAR-Ts are very similar - cytokine release syndrome is the most common side effect that we see with CAR-Ts, but there's also immune effector cell-associated neurotoxicity syndrome where basically you're not yourself, where the inflammation can cause changes in your cognition, and so we have to monitor very closely when giving the bispecific antibody engagers, but also the CAR-Ts. So there's usually a series of questions you ask, or you're asked multiple times a day. They seem really basic. They seem really easy until you develop some of the neurotoxicity.

And that's relatively rare. But it's still possible. And it's important to make sure that we're addressing and catching it early and treating it to tamp it down and to make sure that it doesn't get worse.

Becky Campbell: Well, Dr. Zorko I want to thank you. I'm going to just jump in here. I know that we are running late on time, and I think some folks are you know, getting hungry for dinner and I want to just thank everyone for attending this webinar tonight. You stuck with us until the end. We had a lot of information, an amazing story from Stephen Eisenmann. I really want to thank our panelists who are really just true experts in the field, and just tremendous resources that we have here tonight. You're really hearing from the experts. So, I want to thank you all for your participation. Any last words? From the panel.

Dr. Nicholas Zorko: I want to say thank you to all the attendees. Thank you to PCF. Thank you to Dr. Agarwal, to Stephen, and to Dr. Subudhi as well. And thank you, Becky, for inviting all of us.

Dr. Neeraj Agarwal: I agree. Thank you for having me. It has been an honor.

Dr. Sumit Subudhi: Yes. Same here. And I also want to say that I know there are a lot of questions that were left unanswered. And if they were more generalized questions about immunotherapies, I'm happy to answer them. The more personal ones, I feel a little bit uncomfortable without really having the patient in front of me with all their medical information. So, with that, I'm happy to help.

Mr. Stephen Eisenmann: And again, I want to thank all the panelists. You guys are great. You're going to help people like me. And I really appreciate it. And I appreciate the Prostate Cancer Foundation. And Becky, thank you for having me.

Becky Campbell: Thank you for joining. I wish everyone well and good night.