Dr. William Oh:

Hello everyone. My name is William Oh. I'm the Chief Medical Officer for the Prostate Cancer Foundation, and I am happy to really welcome you to this webinar on clinical trials. I'm going to ask you to talk a little bit about eligibility. We've been getting questions about eligibility and is there too old an age to go on clinical trials or who goes on clinical trials and why? Can you talk a little bit about age and race and socioeconomic status and geography and how that impacts clinical trials?

Dr. Sam Washington:

Yeah, I mean it's an important group of questions cause all those factors impact whether or not you can realistically be part of a clinical trial. Eligibility is just the criteria. A list of characteristics or details about you and the disease that you're dealing with that say, yes, this person should be included in the trial. This is the person we want to study with this drug or intervention of some kind, drug or not. They say for this trial, these patients we do not want to include for this study because it may impact the results that we see, so on and so forth. Eligibility can be a lot of different factors together, age being one of them. Commonly we see patients who are in roughly the 60 to 75 year old age group being included in clinical trials. We have less information about people older than 75 for example. We know across the country, African American men and other groups compared to the general population.

Lower numbers are included in clinical trials for all of the reasons that we discussed. Geography, race, structural issues, if it's feasible for them to get to a center that has a clinical trial. All of these things play into it, even where you get your care, where in the country you are, if you're seen at an academic center that does the bulk of the clinical trials or a community center that sees the bulk of patients but may not be participating in that clinical trial. All of those different factors kind of layer on one another, but it's always good as discussed before to ask. So second opinion, can I be seen somewhere? Can I be considered for a clinical trial? Are there locations that are doing clinical trials near me or all good questions to ask.

Dr. William Oh:

Somebody just asked, how do you get a second opinion if somebody wants to see you at UCSF and they live in Sacramento, how do they get an appointment with you and get a second opinion?

Dr. Sam Washington:

Yeah, so I say the first step is asking, and I think that's the biggest hurdle for a lot of patients because they're worried about what the provider may think or is concerned about. I tell all my patients, get as many opinions as you need to feel comfortable about what's going to happen to you. A lot of times it ends up on the structural institutional issues. Do you need a referral from your primary care doctor or the provider that's treating you, the urologist that you're seeing now, do they need to reach out or get you connected with someone at an academic center, for example, to ask about clinical trials? What about barriers? Obviously we've heard about geographic barriers. We heard ILA say that maybe there are other issues around the inconvenience and maybe for some people if they're working they can't take time off of work.

Dr. William Oh:

Do we know about how we can address those kinds of issues and give people as much access as possible to a trial that might be the right one for them?

Dr. Sam Washington:

Yeah, it's a big question. We used to think of this solely in terms of money because we think of the cost, how much does the drug cost, how much does insurance cover? We realized that there are all these other costs that are not money. How much time am I taking away from work or taking care of family to participate in a trial? How far am I driving? If it's farther away, how am I going to pay for lodging? These are all barriers to that are not direct cost, but large burdens. Those are all things that are currently being explored to different degrees at different centers. I wish there was a one size fits all answer, but you'll notice that these costs and these barriers will change based on where you are you in the country, your specific things that you're dealing with, responsibilities, and how far you may be from the next center doing a clinical trial.

Dr. William Oh:

Do insurance companies pay for clinical trials? Does the company sponsoring the study pay for the trial? Does the hospital pay for the trial? Who pays for the clinical trial?

Dr. Sam Washington:

Yeah, it can be all of the above. Oftentimes the company wanting their drug to succeed will cover the costs of this medication for people who are on the trial. Clinical sites want this study to be done there. They want everything that comes with a clinical trial. Oftentimes they'll chip into some of the financial burdens or costs. Sometimes there's an insurance coverage or out-of-pocket costs. These are all important questions to ask before starting that trial. Even though we're always kind of focused on survival alone, we need to understand how it impacts our wallet, quality of life, daily activities.

Dr. William Oh:

When you talk to a patient about a clinical trial you may be doing and you're a urologist, so a lot of questions have come up about whether all clinical trials are in advanced disease. You may be doing a clinical trial in early disease or looking at genetics or a new type of ablative therapy for prostate cancer. What do you say to them when you're sitting across from them, what kind of conversation are you having about why they would want to go on your trial, on the clinical trial versus let's say a standard of care like prostatectomy or salvage radiation therapy?

Dr. Sam Washington:

A lot of times it depends what the trial is and oftentimes we focus on drugs, but there are other trials talking about new imaging studies, new techniques in the operating room or even impact of diet and lifestyle outside. It's kind of framing everything. This is what we typically do, our standard of care for this type of cancer that you have, and this is what may be added or the benefits you may get from this clinical trial.

The goal is never to give you less than the standard of care. It's what benefit can you gain from being on this clinical trial compared to the standard of care?

Dr. William Oh:

Yeah. I think there's something called equipoise, that's the term.

Dr. Sam Washington:

Yep.

Dr. William Oh:

Can you just define what equipoise means?

Dr. Sam Washington:

Yeah. The goal here is really to understand that we are trying to benefit patients. Overall we're trying to not harm patients. There's obviously a long history of this happening and questions around trials being done, and we need to hold ourselves to a greater standard to make sure that patients are benefiting from this and if we have another treatment, they're not going to be harmed compared to what we give to everyone as the standard. So our new treatment, our new question, our new study is not giving you less than what you would get from the standard of care.

Dr. William Oh:

Right. I think that's such an important point that no research community, no, IRB, nobody would ever approve a study where the balance did not favor the patient. In other words, you'll always get what is the standard of care or something very close to it where that's the minimum and the maximum could be that a new drug is added to it or given in substitution of it for it be so that you can actually improve the total care for that patient and also for society. If we don't keep trying new treatments, we're going to be giving the same treatments today that we've been doing 10 years from now, and nobody wants that. Everybody wants the field to move forward. Are there other barriers that you can think of, Sam, that we have to overcome in terms of getting more patients on clinical trials?

Because my understanding is that only a very small percentage of patients with prostate cancer and other cancers actually go on clinical trials. How do we overcome some of those barriers and what other barriers are there?

Dr. Sam Washington:

Yeah, so generally speaking, if we take a hundred men who are being treated, maybe three out of that 100 will be on a clinical trial. Oftentimes we talk about barriers and we talk about patient characteristics, but we also have to understand what's going on at the institution. Is the place that you're at offering clinical trials, are the places doing clinical trials, do they know what barriers there are for patients? We have to understand, okay, what are the biggest issues for patients where I practice, for example. We know in other studies ones that gave reimbursements to patients, it was gas, parking, and tolls. One study showed that parking fees at a cancer center were a huge barrier for people getting care.

People were using their own cars so the costs associated with that. There's a lot of things that interact and play with this, including monitoring throughout the trial that become barriers because of how much coordination is needed for a clinical trial. It ends up being a larger discussion between you and your providers to understand what things may be the cutoff point or kind of the branch point for you being in a clinical trial or not, and then understanding what resources may be around you or in the cancer center or in your clinic that can help.

Dr. William Oh:

Thank you. I'm going to ask Dr. Garaway to rejoin us, and thank you for that Dr. Washington. Really excellent points about all the barriers that we need to still overcome. First of all, somebody asked what is an IRB. An IRB, I said that, it's an institutional review board. Every institution that does research has a panel of both doctors, but also patients and patient advocates who basically review the rationale for the trial and approve it. Specifically, it's a patient protection to make sure that we're doing research that's

ethical. There's an interesting question about what new medications or drugs have had encouraging data to treat prostate cancer that are now being tested in clinical trials. Either treatment or device or new type of research that's going on right now that you're most excited about. I'll start with you Isla, and then I'll go to Sam.

Dr. Isla Garraway:

What I always find most interesting as a urologist is bringing treatments that were previously reserved for more advanced disease earlier into care to try to really prolong, especially for patients who have more aggressive features in their prostate cancer at diagnosis, to try to really prolong disease-free survival and make it less likely that they're going to recur by to really trying to bring these more advanced treatments up earlier and seek earlier cures to more advanced or aggressive disease. In particular, I think we're really excited about the PSMA therapeutics. The PSMA was first described as more of an imaging modality. It basically targets a very specific marker on prostate cancer cells so that you can really see where those prostate cancer cells are in the body, if they've moved out of the prostate. We can now also use that imaging to see better in the prostate of where prostate cancer foci are or areas of cancer are in the prostate that we could potentially use for advantage for targeted therapy in the prostate as well.

Now PSMA also can be made into a drug essentially. A very specific drug to target prostate cancer. It's really going to be interesting to see that was initially approved and it is approved right now for patients with really advanced disease so treatment resistant disease, essentially. Now there are trials to look at it earlier in the disease process before the disease gets really resistant. That will be interesting as well. I'm really excited about those types of therapies and just all of the precision oncology therapy. Precision oncology is a term that we use when we're doing genetic testing of the cancer cells and also sometimes of the patient's just normal cells to see if they have particular alterations that can be specifically targeted by certain therapies or drugs. It really is a personalized approach to treatment because based on exactly what the mutations are or alterations are in your tumor. Of course expanding our pool of precision oncology treatments it's going to be really great to hopefully target and make the cancer treatments more personalized.

Dr. William Oh:

Yeah, I think PSMA targeted therapies are here. U177 PSMA is available unfortunately for some may not know there's a slight shortage or a manufacturing delay, but a new factory is just opened in New Jersey, most of the PSLU177 was made in Italy and the new factory was just opened in New Jersey. So we expect the backlog to really be caught up very soon. There's a lot of other PSMA targeted treatments including immunotherapy, CAR T-cells, which are an type of using these activated T-cells that target PSMA, also new radiopharmaceuticals using actinium and some other molecules that are attached to PSMA, kind of a smart bomb technology. These drugs do work if your cancer makes PSMA. Right now that's in patients who are post chemotherapy. As you mentioned Isla, it's moving earlier and earlier and there will be more clinical trials testing before chemotherapy and even at the time of diagnosis, we're going to see more and more studies like that. Sam, what are you most excited about in clinical trials?

Dr. Sam Washington:

I was going to say imaging and genomics, biggest areas. I would say just for full representation, there are trials looking at diet and exercise because patients often ask me, "Okay, what should I be doing differently? Was it something I ate or something I did over the last five years?" There's work that's been funded by PC F, looking at diet and exercise combination of the two ongoing randomized trials and those

domains and digital platforms. Can we get people enrolled or are there trials using technology to access people that we could not before? Can you avoid the long travel distance and still be part of some of these trials? Dr. Garraway mentioned one opportunity that should be coming soon, that'll be exciting. And then there are other online or digital platforms that allow many more people to be involved in trials and studies than there were before. Those are two exciting domains for me as well.

Dr. William Oh:

Sam, do you recommend genetic testing on every patient with advanced prostate cancer?

Dr. Sam Washington:

I would say I go strongly by guidelines. So I think when I diagnose someone with advanced disease, particularly those who had no idea of it and were diagnosing it for the first time, I would recommend genetic testing, genetic counseling, so we understand what's going on, not just for the tumor, but at the DNA level, so deeper level and what may be risk factors for other family. It's a discussion not just for the patient but for their kids and family members as well. Highly recommended.

Dr. William Oh:

Isla, do you test the tumor itself for molecular changes that might make a patient a candidate for a clinical trial?

Dr. Isla Garraway:

Yeah, and again, it depends on the clinical scenario for sure. So not everybody at this point it seems needs to be tested for a molecular precision oncology therapy. It's really more reserved for those advanced patients with advanced disease with metastatic disease essentially. Anyone with metastatic disease, we try our best to test that tumor to see whether or not they might be a candidate for one of these new precision oncology treatments, if not right now in their treatment later down the line if that treatment fails.

Dr. William Oh:

The most important gene to test for is BRCA-2 in prostate cancer. You can either test it in the blood, as Dr. Washington mentioned, which is what you inherit from your mother or father, the DNA you inherit from your mother or father, or you can test it on the tumor itself if you have metastatic advanced disease. It turns out that about one in five men with advanced prostate cancer, metastatic prostate cancer will have either an abnormality in their blood that they inherited or in the tumor which they didn't inherit, but may make them eligible for specific drugs. But it turns out that molecular testing can actually help with other clinical trials. There's a lot of targeted treatments that are in clinical trials, and the only way to know if you might be eligible for those precision oncology treatments is to do the testing.

For advanced patients, for metastatic patients, I do think it's important to make sure your doctor does test you. Let me ask you about the role of artificial intelligence. This is one of the questions. We are hearing about ChatGPT and all of these new approaches. Is that playing a role in clinical trials? Are there trials now, Sam, looking at AI and how it might read your scans or your pathology slides and helping to tell people whether they should go on a clinical trial or not? Are you using this in your practice?

Dr. Sam Washington:

Yeah, so I would say it hasn't reached my clinical practice, but definitely involved in our sphere of research in this space, really understanding can machine learning or AI, can a program look at an imaging study and detect disease maybe at a better rate than people like me looking at an imaging study. It's a tool for us to use to improve care.

The applications as everyone is seeing, are starting to go in many different exciting directions. Both in terms of looking at your pathology, so the tissue that's obtained from a biopsy or surgery, and then also your imaging. Any scans, MRIs, PET scans that you've undergone at any point people are looking at how can we use programs to evaluate these with a much more detailed finer lens than maybe we had with our eyes.

Dr. William Oh:

Isla, if you go on a clinical trial and you don't like the way it's making you feel or you really decide it's not for you, do you have to stay in the trial?

Dr. Isla Garraway:

No, definitely there's no obligation to stay on the trial. You can quit for any reason. It's really important to have really great communication with your doctors and the team and the coordinators on the trial so that you can raise any concerns that you have and that you can have those addressed and if necessary, go off the trial if you just don't feel comfortable being on the trial anymore. You absolutely can stop a trial at any time. The care team will just make sure it's safe. Of course, sometimes it's not safe to just cold turkey stop a drug, but they'll just make sure that the conditions are safe for you to pull out of the trial.

Dr. William Oh:

We're going to go back to the question of placebos because people really hate the idea of a placebo. One question that came up is, do you find out which arm you're on? Are you always told what drug you're getting in a clinical trial or do they sometimes not tell you which drug you were on? If they don't tell you, why would they not tell you?

Dr. Sam Washington:

Yeah, so that's really the difference between open or blinded studies. Open studies, everyone knows what you're getting. Blinded studies, depending on how it's framed and created and structured, patients and/or researchers may not know what drug you're getting. That's really to make sure that everyone is working within the structure and framework of the study and you're not introducing bias. People evaluating the drug's response are treating every person the same because they don't know which patient is on the drug or not. There's little room for them to interpret things one way or another because they don't have the knowledge of what drug or intervention you're getting.

Dr. William Oh:

I know there's a lot of debate in the medical community about whether we need to do all trials as double blinded where the doctor and the patient doesn't know. Isla brought up that many studies now, if you get a placebo, you are unblinded and you're allowed to cross over so that everyone gets access to the drug. More and more studies are like that. Also you're seeing a lot more studies where it's weighted two to one, where you have two out of two chances to everyone who's assigned to a placebo arm, for example. Mostly to make it more appealing to patients and also still to be able to answer the question.

Because in the end, to answer a question about whether a drug really helps a person to live longer or treats the cancer more effectively, you need that control arm, the comparison arm. I think that there's a lot of sensitivity to the idea that it's not just about science, it's really about helping the patients who are actually on the trial.

As Dr. Garraway pointed out, sometimes the drug turns out not to work, and that is one of the risks of a clinical trial that the drug may not wind up working. And the only way we really find out is to do these phase three or large clinical trials. One question about genetic testing, Isla, do you always have to have a surgical procedure to get the material for let's say, testing your tumor?

Dr. Isla Garraway:

Yeah, that's a good question. I think it's important to remember, there's two different, William has brought this up and so is Sam. There are really two different types of genetic testing that we're talking about when we're talking about prostate cancer. The first type can be just the sample, can be just a routine blood draw. It can be a swab of your cheek. It's really simple. Just some saliva even. That's used to just collect a general sample of DNA that's that's in all of your normal cells and do genetic testing on that, looking for those alterations that can be passed down from your family member. The most common example probably is the BRCA gene, which is associated with both breast cancer and prostate cancer, and that can be passed down among families. That's one type of testing, and that's just very simple. Anybody can pretty much give a sample for that test.

The other type of testing though, that is again, in the situation where we have prostate cancer, we really only reserve for patients who have distant metastasis or metastatic disease, I guess in general. And that's when you're testing the tumor itself. And that does require an actual piece of the cancer, a sample of the tumor specimen. That can come either from the prostate. So in some cases we can use even the diagnostic biopsy, the original biopsy where you got that diagnosis. Even though it's years old sometimes we can still get DNA from that sample that we can use for the genomic or gen genetic testing. Other times though, we do need to get a new sample if that one doesn't work.

However, we don't always have to get a sample from an actual metastatic site. We can sometimes get a blood sample just like we do routinely get for the normal genetic testing. This time we're looking for circulating tumor cells. So there's tumor cells that actually circulate in the bloodstream that we can sometimes access through a RO routine blood sample and then get information, personalized information on that tumor. So sometimes you have to have the actual tissue, tumor tissue, but nowadays you can sometimes also get the same information from a regular blood test.

Dr. William Oh:

Yeah, I think it's unusual that a doctor will order a biopsy or do a procedure just for a piece of tissue because of these liquid biopsies, the circulated DNA and tumor cells.

Dr. Isla Garraway:

Agreed.

Dr. William Oh:

Or you can get it from an old biopsy that might have been several years ago. Sam, there's a question about surveillance and clinical trials with surveillance. Obviously we know that in advanced disease there's very active research going on with new drugs for metastatic or castration resistant prostate

cancer. Are there questions being asked in the surveillance stage? Is that an active area of research? Can patients find trials in that low grade setting?

Dr. Sam Washington:

Yeah, there's still very much discussion going on around active surveillance across the country. Another thing, active surveillance, which may change based on where you live and who you see. There are a lot of studies looking at active surveillance and how we can better risk stratify you. Understand not just looking at your tumor on a microscope, but can we look at the DNA of the tumor? Can we look at other factors to see your risk of needing treatment at some point in the future?

Also, these are areas where we can obtain tissue from biopsies so we can understand the genetic genomic components of prostate cancer. That tissue that's already being obtained can be used for research as well. Lastly, there's a lot of research and active surveillance, again, looking at how diet, exercise, lifestyle can impact disease changes over time. So this is another area of research that is starting to blossom and grow.

Dr. William Oh:

Thank you for that. There's a question about immunotherapy. Some of you may know there actually were four negative trials in prostate cancer with the most common immunotherapy drug called Keytruda or pembrolizumab in prostate cancer, whereas it seems to work in lung cancer and melanoma and bladder cancer. What's the problem here? Why are we just doing it wrong? Is there some problem with immunotherapy and prostate cancer and how are we going to overcome that Isla?

Dr. Isla Garraway:

Yeah, I know it's always really disappointing when such a promising therapy that's working well in other cancers is not working well in prostate cancer. There are many different reasons why immunotherapy might not work well in the prostate and particular surrounding. If you're looking, it depends on the immune landscape or the microenvironment that we call of the tumor and how many immune cells that are ready to be activated and attack that cancer. And if there aren't immune cells to begin with in the location, then the drug isn't going to work well. I think a lot of studies are trying to focus on how to get the prostate cancer more immune hot, get more of those immune cells in the areas where they need to be so that they can be activated by the immunotherapy agents. I mean, there's other things besides those types of inhibitors, however, on the immunotherapy front that we can look at in prostate cancer, as William already mentioned, there are CAR-T therapies now that are going to be investigated.

Those are maybe more like tumor vaccines, the type of an approach where you're really trying to train up your immune cells to focus on very specific targets in the prostate cancer cell as opposed to just trying to activate what's already there, your compliment of T-cells or immune cells that are already there. There are other approaches. The other thing we probably need to do also is really characterize our tumors better. We still don't really do a great job yet in prostate cancer of really understanding the different subtypes of tumors, some of which may be more responsive to immunotherapy and others may not, may be less responsive and we need to focus on other types of the therapies for those cancers.

Dr. William Oh:

Thank you, Isla. The last question to you, Sam. What are you most excited about for the future of prostate cancer research and clinical trials?

Dr. Sam Washington:

I think overall it's expanding in areas we didn't really think about before. Understanding what's going on from the patient side, institution side, and then how do we integrate the genomics, the imaging to expand the reach. How can this get to more people than that 3 out of 100 that there was before? I think for me, as a research idea and interest overall, this is the most exciting space. How can we change access in the landscape so more people can get involved with safe and beneficial trials?

Dr. William Oh:

That's great. From my perspective, we have to get better treatments for people who have the highest risk disease, who may die of their cancer or otherwise suffer. We have to figure out who we can leave alone and not over treat because there are many men who probably can be watched or surveyed without treatment.

I think as you said, genetics and new insights into the way prostate cancer is really different from person to person is something that we're going to learn more about and already are learning a lot about. I think that's our time. I really want to thank Dr. Washington and Dr. Garraway for their participation tonight. We learned a lot, and I know there are many, many questions. We hope we answered as many as possible. We really appreciate your interest and we hope you go to some of the resources that Prostate Cancer Foundation can provide. Thank you very much. Goodnight.