Speaker 1:

Hello everyone. Welcome to our webinar tonight. Thank you for joining. My name is William Oh. I'm the Chief Medical Officer for the Prostate Cancer Foundation, and we're going to be talking tonight about a hormonal therapy. So first we want to acknowledge Sumitomo Pharma America for their support of this event, but I'll remind you that all views expressed during this webinar represent those of the speakers. So just as a reminder, Prostate Cancer Foundation was founded 30 years ago with a mission to reduce death and suffering from prostate cancer. PCF funds the most promising research in over 28 countries around the world. We have teams of scientists across disciplines and institutions that collaborate and share data, and we're trying to identify and close gaps in prostate cancer treatment implementation for diagnosed patients. What that means is we want to make sure that every person who's a candidate for a treatment is able to receive those treatments.

There's resources available for you. Obviously we're going to cover an important topic today, but you may want to read about it afterwards. Please go to pcf.org, sign up for updates, download guides, and view past webinars as well as this webinar, which will be available in a short time. In addition, we have a new website called Prostate Cancer Patient Voices, where you can listen to other men who've gone through diagnosis and treatment and share their experiences with you. So it's a really wonderful website. I encourage you to go to Prostate Cancer Patient Voices. Our two guests today are distinguished panelists, Dr. Alicia Morgans. She's a genitourinary medical oncologist, Medical Director of the Survivorship Program at Dana-Farber Cancer Institute and Harvard Medical School. She has studied prostate cancer survivorship for many years through clinical trials, through patient reported outcomes and is doing everything to make prostate cancer patient experience and family experiences as favorable as possible.

She's also been awarded two challenge awards and a creativity award from the Prostate Cancer Foundation. Our other panelist joining us in the second half is a prostate cancer survivor, Dr. Michael Holick. But he's also, as you can see, a very distinguished endocrinologist professor of medicine at Boston University School of Medicine and the Emeritus Director of the Bone Health Clinic there. He has seen thousands of children and adults with metabolic bone disease. He's one of the most influential physician scientists in the world. Based on his research, has authored over 650 peer reviewed publications and over 220 review articles and book chapters. And he's going to talk about both his expertise in this space, but also his own personal experience. So let's dive right in and I'll welcome Dr. Morgans to join me. Hi Alicia.

Speaker 2:

Hi, nice to be here with you, William. Very excited to have everybody here today.

Speaker 1:

Well, thank you. This is an important topic. I think that's why there's so much interest. Obviously hormonal therapy is a topic that many men with prostate cancer hear about. Let's start at the start. What does hormonal therapy refer to? What does it mean?

Speaker 2:

So hormonal therapy is a couple different approaches to treatment, but the main backbone of hormonal therapy is the use of medicines called GnRH agonists or GnRH antagonists to essentially turn off testicular production of testosterone. So what that means is men's testosterone levels plummet from maybe 400 down to 40, and they can have side effects that are related to low testosterone, more so

than the medicine itself. And I think also importantly in men, testosterone is actually converted to estrogen. So it undergoes this thing called peripheral aromatization, which just means the hormones are converted into other hormones and those hormones are estrogens. So men end up with low testosterone, but because they're not having this side production of these other hormones, they end up with really low estrogen levels as well. Those are lower than postmenopausal women in most cases. So they have a very low hormone state, and this is what I think of as hormonal therapy, and I think this is what we're focusing on today.

I would say that just for participants to kind of think about and understand what we're talking about, there are other medicines usually delivered as pills that can block the action of testosterone at the level of the prostate cancer cell. That's not really what we're talking about so much today. And the other one is something that stops the adrenal production of testosterone, again, sort of beyond the scope of what we're talking about today, but hormonal therapy, the goal is lower testosterone, turn off the testes and try to starve prostate cancer cells of the food or fuel they need to grow, spread, divide, and cause trouble.

Speaker 1:

So I want to just reiterate something important that you said. The prostate and thus the prostate cancers that develop from it feed on testosterone, male hormone. So actually hormonal therapy is probably the wrong name. It's actually anti-hormonal therapy. These treatments, whether they're shots or pills, they lower testosterone and in doing so, they put the cancer into remission and can control the cancer. So sometimes people say, "Oh, you're not getting hormones, you're actually getting an anti-hormonal treatment." So what type of prostate cancer patients receive hormonal therapy? Just on a broad level, who's getting hormonal therapy for prostate cancer?

Speaker 2:

At the end of the day, it's about half of prostate cancer patients who end up with some period of exposure to hormonal or as you said, anti-hormonal therapy. So it's going to be people who have metastatic prostate cancer or prostate cancer that has spread outside of the prostate, might be in more distant lymph nodes or in lymph nodes around the prostate. In many cases, potentially in bone or somewhere farther away. Those individuals may be on this type of hormonal type therapy for years and years and years sort of indefinitely. The other group that I think of most commonly is a group of patients who are getting radiation and might have intermediate risk prostate cancer, usually unfavorable intermediate risk or high risk or very high risk prostate cancer. Those words may not sound familiar to people on the call, but when the risk of the prostate cancer, even though it's still all in the prostate is a little bit higher and we're using radiation. Lowering testosterone really amplifies the effect of the radiation, weakens the cancer cells, makes them vulnerable and the radiation is much more able to powerfully incinerate or eradicate them.

So these are two big buckets of patients where I think of hormonal therapy. The one other place that's more nuanced is the group of people who have had a prostatectomy or have had radiation and this type of hormonal therapy, or maybe not, but they've had radiation to treat their prostate cancer. And these individuals, hopefully we thought that they were going to be cured from their treatment for the localized prostate cancer that was all in the prostate. But at some point, the PSA started to go up and even those scans couldn't find any sign of prostate cancer in any area on their body. They have a PSA that continues to rise, that suggests that there are cancer cells in their body. This is called biochemical recurrence or PSA only recurrence. And these individuals may also receive hormonal therapy that could be intermittent, it could be continuous, it could be a hodgepodge of ways that we deliver this, but this

group can also get hormonal therapy. So ultimately, long story short, about half of people with the diagnosis of prostate cancer.

Speaker 1:

We're going to dig into each of those groups in turn to give people a sense of how the hormones are used. But basically some patients who get it right up front at the time of their original radiation, they may get it to help the radiation. Some patients recur after surgery or radiation, they may get it to suppress the PSA. And most patients who present with metastatic disease will always get it for some period of time that could be indefinite. I think people have figured out that there's a Q&A and we see that... You can actually type in your questions. We know that there's a lot of questions. We're going to try to get to as many as possible, but if we can't, I really encourage you to go to those websites I mentioned earlier and a lot of the questions are listed there and you'll find answers there.

So let's start in the beginning. Let's say for a patient who presents with high risk prostate cancer, that might be a high Gleason score. The cancer's not visible anywhere else. It hasn't spread to the bone or the lymph nodes, but they otherwise, let's say, have a high Gleason score. Their doctor's worried and they recommend radiation to that patient. How long should those patients get hormonal therapy and how's that decision made about whether it's short or long term?

Speaker 2:

So great question, and I would emphasize for everybody on this webinar that these are going to be decisions and discussions that you have with your oncologist, your urologist and your radiation oncologist. And there are nuances about every individual that may push people in one direction or another. So I just want to put that out there. But in general, when we have high risk or very high risk prostate cancer that's still all in the prostate, so localized prostate cancer. We think about somewhere between usually 18 to 36 months of hormonal treatment with androgen deprivation therapy. I think new data suggests or newer data suggests that for people who are even on the higher end of that spectrum in terms of their risk, we want to use extra pills to further block testosterone production from the adrenal glands and we add that abiraterone or Zytiga medicine on there to try to again, further block.

But in general, we're thinking about somewhere between 18 and 36 months. I generally tend to hit around 24 months. And I think one of the reasons that I do that is that that's where a fair amount of data for this intensified strategy with extra medicines is. But it's also because we know when you're on that hormonal suppressive therapy for that long, it's going to actually be a bit of time after you stop that medicine that it will actually take for the testosterone to come back up. So even if you go to 18 months, it may be 24 months or even longer before your testosterone recovers. And so you want to be as careful as you can and also make decisions at every visit as patients are coming in, as you're coming into your doctor, to make sure it's still worth it to you. But that's the general [inaudible 00:10:56] when we're planning the treatment in the beginning.

Speaker 1:

So you used the term androgen deprivation therapy or ADT. There's unfortunately a lot of jargon in medicine and ADT is the same thing as what we're talking about, hormonal therapy, which means you're lowering the testosterone. And so one thing you're saying here, Alicia, is that the higher the risk, the longer your doctor will probably put you on hormones and may even double up with other medicines. We're going to have another seminar in the future about some of those next generation hormonal pills that some people may be on like abiraterone or enzalutamide and others. For today, we're going to

focus on ADT or primary hormonal therapy. And as you said, a lot of doctors will have different opinions based on the risk of the patient and also a lot of other factors, their age, their comorbidities and so on.

So I should point out a lot of people in the Q&A are asking about side effects. We're going to focus on side effects in the second half of this webinar when Dr. Holick joins us. So let's shift to the idea of a biochemical recurrence or a rising PSA state. A man gets surgery, let's say, and he'd never been on hormones. And after surgery, let's say he had a Gleason eight prostate cancer, the surgeon removed it, usually says, "I got it all." But then the PSA does not go to zero, and then it starts to rise after. What does that mean to that patient and when should that person go on hormonal therapy?

Speaker 2:

So really importantly, this is not hormonal treatment, but just to really importantly emphasize. If you've had your prostate out, your PSA should go to undetectable or zero or the lowest, lowest, lowest level that the lab can measure. If that level starts to rise, you need to think about what we call salvage therapy. And the reason is that, what William was just referring to, this means there's still some cancer in the body, even if the surgeon feels like she or he got everything out, we can't see everything as doctors and it only takes one cell to take root somewhere else. If the PSA is going up or never gets to undetectable, that means there's still some prostate cancer in there. In most cases, just to put this on the side, we use radiation of the prostate area and even the pelvis around it to try to zap and kill any rogue prostate cancer cell that may have gotten out of that prostate.

If that has already been done and sometimes in combination with that radiation, we use ADT or hormonal therapy to try to again treat those cancer cells or weaken those cancer cells. So the radiation is more effective. If we've already done radiation and still the level is rising, we really try to time our use of these medicines to lower testosterone to be those people with the most aggressive forms of prostate cancer that we actually think will either cause metastatic prostate cancer or prostate cancer that we can see on a scan or maybe kill someone from prostate cancer. And we try to target our treatments to those highest risk individuals rather than giving everybody these medicines the lower testosterone. Because in this setting, biochemical recurrence or PSA only recurrence, in many cases, patients will actually feel more side effects from the treatment of the hormonal therapy than they will feel from the cancer itself because really there's not enough cancer to even cause a symptom.

In any event, if this happens, the cancer is still there. We need to do something. It may involve radiation, it may involve hormonal therapy, but we need to work together as usually a multidisciplinary team to come up with the right treatment plan.

Speaker 1:

You brought up some very important points that I think are worth repeating. First, if you had surgery and your PSA starts to rise, you're a candidate often for radiation because that could actually cure you. So you want to be cured, you want to eradicate the cancer. But if all attempts have been made to eradicate the cancer and your PSA still rising, the question is when and should you receive hormonal therapy? And as you point out, we really actually don't know the exact answer to this because we've never done the right studies to figure out when. And there's something called PSA anxiety, which many people in the audience understand and you and I both understand as practitioners. And sometimes I'd say patients have anxiety, but also doctors have anxiety. We sometimes treat... So what are the things that will make you treat a patient? What's maybe one or two most important factors that you see in terms of, let's say, the PSA rise that make you determined to go ahead and start hormonal therapy sooner rather than later?

Speaker 2:

I think the most important thing is to calculate something called a PSA doubling time. And this is, as the name suggests, the amount of time that it takes for the PS A to double. Importantly, it's not just one number to the next doubling. It's really kind of an assessment of PSA over time and you can plug it into calculators and it gives you sort of a longitudinal or overtime assessment and calculates that PSA doubling time. If that's under 10 months, that's when I think that's going to be a person who's going to have a higher risk prostate cancer that we do need to think about treating. One other important caveat when the number is 0.01 or 0.02, it takes almost no time and even potentially lab error to cause the PSA to double.

So we do need the PSA to get to a number that's high enough that it seems like it's actually a real number and that a doubling is a real increase rather than just lab error. Which certainly I wouldn't want anybody to get treatment with hormonal therapy because the lab is a little less calibrated in terms of their equipment than we wish for perfect lab treatments. So that's one thing. The other thing that I think about in terms of treatment, and that's probably the main one, PSA doubling time. When the PSA gets to a certain point, in my practice at least, it's usually somewhere between 0.2 and 0.5. I perform a PSMA PET scan. So this is a PET scan or an imaging study that is more sensitive or has a higher ability to find prostate cancer cells in the body than our standard scans like CT scans or CAT scans and bone scans.

It can find things that those types of scans can miss and I perform that scan. If I can see something lighting up on that scan, I'm probably going to treat that patient. And it's, actually in that case, probably going to be a combination of hormone treatment and radiation to try again. Maybe we can cure some of these people who have so little prostate cancer that we can just see a spot or two on those scans. But again, to your point before, we have so much work to do and many questions unanswered, and that this question is one of them.

Speaker 1:

So you brought up the issue of these new PET scans and what is the definition of metastatic disease because that is the third category of men who receive hormonal therapy and that traditionally might have been from an old scan, like a bone scan or a CAT scan. Are we treating all patients who present with metastatic disease with hormonal therapy and how do you define metastatic disease nowadays?

Speaker 2:

Great question. Thank you for that, William, because I know you know that that's a really hard one. So when we use things like bone scans and CAT scans exclusively, and I have to tell everyone in the audience. We're actually still using these scans and we use them and we rely on them very heavily. So especially when people have cancer that we can see on a CAT scan or on a bone scan, we're usually monitoring those people over time with CAT scans and bone scans and not things like PET scans. So that's normal, that's expected and that's per the guidelines. So that's what's happening to you. That's what we would all do. So how do I define metastatic disease? If I can see it on a CAT scan or a bone scan, that's metastatic disease. Usually PSAs were 20 or above when they were really being shown on those types of scans.

And I think that's so different, that what we're talking about 0.2, 0.51 as your PSA value and we're seeing areas of what we can measure in terms of saying, "Okay, there's a cluster of prostate cancer cells in a group that's big enough for me to see on this PET scan, which is more sensitive, easier to detect. I do not treat patients with PET scan only metastatic disease in most cases with indefinite and ongoing forever hormonal therapy. I would in most cases, unless there was an issue with other medical problems

or the patient's not really doing well, I would treat a person with a bone scan or a CT scan with cancer that I can measure. I would treat them with indefinite or ongoing for the rest of their life potentially, hormonal treatment.

So the distinction from my view is, it's still metastatic on a PET scan, it's still in a cluster that I can see these cells, but I try to design my treatments to allow patients to maybe get treatments that include a radiation and a hormonal treatment and maybe we can stop and maybe we've gotten rid of all of it. Whereas in a traditional CT scan or bone scan, there are very few instances where I think I can get rid of all the cancer and stop the hormonal therapy at some point. And I feel like that's a very roundabout way of answering your question, William. I hope that was okay.

Speaker 1:

Of course. I mean, it's an evolving field. As you said, we're getting better technologies that can see smaller and smaller amounts of disease. But a lot of our research studies and clinical trials were done in an era when we had more traditional scans. So we want to make sure that patients get the benefit of the clinical trials, but we need more data with the newer studies. So you brought up the stopping versus continuous hormonal therapy or ADT. Can you just comment on intermittent hormonal therapy or intermittent ADT? Who do you do that in? Who is it appropriate for? How do you do it?

Speaker 2:

So I would say that kind of in any setting, if the patient's really not tolerating the treatment, but the cancer itself is not causing many symptoms, intermittent therapy may be appropriate. So I would put that out there. And when I say not tolerating, I mean having a severe side effect and that's defined by any individual patient and that patient's physician and family and caregiver team. So that's kind of a nuanced thing in itself. In general though, when we think about intermittent therapy for prostate cancer, this is mostly utilized in the biochemical recurrent or PSA only relapse setting. In that setting, we do not have perfect data regarding when to start hormonal treatments, when to stop hormonal treatment and when it meaningfully changes the trajectory of the cancer's growth so that we can help people live longer. The only information we have is that for higher risk people with biochemical recurrence, so those PSA doubling times that are super short. We might be able to meaningfully improve their trajectory in terms of prolonging the time to them getting metastatic prostate cancer or cancer we can see on scans.

If we start therapy a little earlier and sometimes intensify that therapy and that's new data, this is rapidly evolving. But in most cases, we believe that we can start and stop our hormonal therapy without losing much, but with allowing patients to have that recovery of testosterone, improvement of quality of life in those off periods. We do have some data that in metastatic prostate cancer, when we can see the cancer on scans, that we are potentially sacrificing some durability of cancer control. What that means in English is we're potentially saying that people might live a little less long if we do intermittent therapy, but sometimes they actually feel better. So there are some people who would say, "Because of the side effects, I'm feeling it's worth it to me. To live a little less long and do intermittent therapy even in metastatic prostate cancer." But that is much less common.

Speaker 1:

So just a couple of important points about hormonal therapy. One is that it works for years on average, and I think this is an important point I always tell patients. This is not a treatment that works on average for months or weeks. This is something that works for years. And in some patients, many of us have patients like this, at decades. And we want to understand why some patients do respond for long

periods of time and why others don't. Are there biomarkers that are being developed or tests that can help us understand who might be more responsive or less? Can you tell us about what the future of the kind of predicting response durations might be?

Speaker 2:

Well, as a scientist, I feel very excited about some of these assessments. So I'll just mention that there are some things that we can find on genetic testing that we think may show that people might have a longer response to hormonal therapy. One of these genetic mutations is in a gene called SPOP. So that's something to think about. It's important also to know that just because you have a mutation in a certain gene doesn't mean that you're going to have a better or lesser response. It's just on average in populations of people. So informative for what it is, but not perfect as a metric. There is also really exciting technology being developed using artificial intelligence, believe it or not, on slides that are obtained from or gathered from prostate biopsies or prostatectomies. And this artificial intelligence program gathers information from those slides that is probably stuff that's even inscrutable to the human eye. And calculates it all together and can say, "Okay, this person, because of all these things I've measured, is going to actually benefit from this hormonal treatment and that person's not."

It's really fascinating. I think that these assays are actually, these tests are coming into our clinical practice little by little, coming into our guidelines that help us as doctors understand how to help care for people. But I think that this may be a huge step forward in a way of the future, especially because this kind of test doesn't require a blood draw. It doesn't require a new biopsy, at least at this point in time. It doesn't require that you have anybody take a piece of any part of you. It's really based on the slides that were made at the initial period of diagnosis or surgery. And so in that way too is a non-invasive way that can really help give people information without poking or prodding them.

Speaker 1:

I think in the future we will not be using Gleason scores. We'll be using computerized predictors of how patients will do and even maybe what treatment will be best for them. There's some questions, I'm going to get to a few of the questions here. Are there some patients who never recover their testosterone after they're on hormonal therapy? And what percentage of patients might not recover their testosterone?

Speaker 2:

Well, I think that one of the unfortunate truths of hormonal therapy is that there are definitely people who will never... We turn off the testes from producing testosterone and their bodies will never turn them back on. This is more common in people who are older and in the prostate cancer world, that might be people in late seventies, eighties and plus. And the older you are, usually on average, the harder it is to turn back on the testes. And that's actually probably related to natural aging, which leads to a natural and normal decline in testosterone as we get older. But the other group of people is the group of people who have a long, long period of low testosterone treatment. So the people who have only six months of treatment with this hormonal therapy might recover their testosterone within three to six months. But the people who have two years of hormonal deprivation therapy might take four years, five years to recover their testosterone.

I don't have a statistic to tell you what percentage of people. I think that it would be really nice if we developed algorithms that meshed age and duration of hormonal therapy because these are the two factors that most influence. And of course, I'm sure there are other things and our models could help us understand what those are. But recent data suggested if you're on for six months, I think the average

period of time to recover testosterone production is about 12 months. And if you're on for two years, I think the average period of recovery was five years. Now, that means that some people recover much more quickly, some people do not recover or some people take longer to recover and some people never recover. So these are averages, but these are real numbers. And I think new information is bringing this to the forefront that we as clinicians, we as patients need to be aware that these things matter. And we do have some control, but not all control on when testosterone might come back.

Speaker 1:

So many important points. So many good questions, and I'm sorry we're not going to be able to get to all of them. I'm just going to ask one clarifying question before we bring Dr. Holick on board. And that is, you mentioned it quickly in the beginning, Alicia, which are the different types of hormonal therapy. So a question was about orchiectomy or surgical removal of the testicles versus LHRH agonists like leuprolide, which has been around for 40 plus years. Versus these new drugs like elagolix or relugolix, which is the first oral hormonal therapy that suppresses testosterone. So can you just briefly talk about those three types of treatments and why they're different and why a doctor might use one over the other?

Speaker 2:

Sure. So to start off with surgery, this is the removal of, in some cases, the entire testicle. But I think in newer surgeries is really removal of a portion of the testicle that makes the testosterone. And just to add a little story here, I had a patient a few years ago who underwent this removal of that part of the testicle that makes testosterone. There was a bit of a language barrier. He was actually from Eastern Europe, and of course I'm not a surgeon, so I just said, "They're going to remove your testicle." So he woke up from his surgery and they were still there. And so they had only removed a portion and he felt like they were still there because there was still quite a bit of testicular tissue left, and his testosterone was completely suppressed. So just to put it out there, having the surgery does not mean that you necessarily lose your testicles.

You may just lose a portion of them. So don't be surprised if you have the surgery and you wake up and there's still something there in the scrotum. In any event, this type of an approach to lowering testosterone is not a reversible approach. So this is for people who know that they're going to be on indefinite hormonal suppression, do not have any plans to turn things back on. And in most cases is a group of people who have metastatic prostate cancer that is not going to be cured and needs to have treatment with lifelong low hormone treatment. This is something that I advised for people to consider when they are not excited about having pills on a daily basis or shots on a regular basis.

For people who don't want to have that kind of tie to the medical field. And actually, my grandfather had prostate cancer, and that's the approach he took, and it was because he was just not a fan of doctors. So in any event, this gives you control. You do not have to worry if a pandemic hits and you can't get into your clinic because your testosterone is not coming back. So that's an approach, but it is permanent. If you use a GnRH agonist, then I would say most people, probably 90% of people, use a medical treatment to lower their testosterone. The primary way that people are doing that right now, or the most common way based on history and the way that our practice patterns have been, has been to use GnRH agonists. We have different durations of treatment that could be a shot that lasts one month, a shot that lasts three months, a shot that lasts four months, a shot that lasts six months.

And there's even a way to do a 12-month suppression. And these medicines act to turn off the testicles and stop them from making testosterone. These are interesting because they cause an initial surge of testosterone or increase in testosterone when you have your first initial shot. They're all given by shots.

And so we have to just be aware of that and use a medicine to usually block that testosterone at the very beginning. The third option is the GnRH antagonist. These are the medicines you referred to as degarelix and relugolix. One of them is a shot that lasts for one month. So every month you get a shot. One of them is a pill that you take every day. These medicines don't have a surge, so they don't have the increase in testosterone before the decrease. And so that can be really important for certain patients who have prostate cancer that might be causing imminent trouble right now, like pushing on the spinal cord and causing them to be paralyzed or causing a blockage of their kidneys and causing their kidneys to not function properly.

And that can be really, really important for them. And so this is just another strategy. One interesting thing about the pills is that when you stop the pill, one, you do have a little control as the person who's taking the pill each day, that you could stop it and that's your decision. But two, the testosterone seems to recover maybe a little bit faster than when you're on some of the injection version. So this is something that some people do consider, but these are the three main categories. There are more nuances, but we-

Speaker 1:

Yes.

Speaker 2:

Time.

Speaker 1:

No, that's great overview.