May 27, 2025 - Hormone Therapy: Why, When, and How

Phillip Koo, MD: Great. Thank you very much, Becky, and thank you all for joining, and I'd also like to thank Pfizer for supporting this event.

You know, when I heard about this topic, I was very excited, because as we all know, hormone therapy is the backbone of treating patients with prostate cancer, but there's a lot of confusion, and admittedly, it's a very complicated topic, and we really have two national, international leaders to help sort of simplify this for us from different perspectives: Dr. Dan George, who's a medical oncologist, and Dr. David Morris, who's a urologic oncologist. So, thank you both for joining us today.

David Morris, MD: Thank you.

Daniel George, MD: Thanks, Phil. Happy to be here.

Phillip Koo, MD: So, wonderful. So, before we get started, let's sort of level set and start with the why. And David, I'll start with you. Tell us a little bit about the basics of physiology and why hormones are so important in prostate cancer.

David Morris, MD: Sure, the way that I'll typically try to explain this, at least on a non-scientific level, is that testosterone often acts like food for cancer cells, and largely that's driven by testosterone receptors that drive DNA turnover, drive the cell to create, basically, more cells and lead to cell division, and so with that, any testosterone is essential for prostate cancer cells and normal prostate cells to live. And as part of our steps is utilizing things to take away that testosterone, take away that food so that we can basically try to put cells into a form of hibernation and not be dividing as quickly.

Phillip Koo, MD: Great. So then, you know, Dan, we know that these cells change over time, and just sort of give us an overview of what that change looks like. Maybe quickly why that happens, and what sort of feeds it later on?

Daniel George, MD: Yeah, Phil, you know, just as David said, you know, I think that the truth is we, you know, when we give hormonal therapy we do two things to the prostate cancer: One, we stop it from growing, we stop it from spreading, and that's really important. And then the other is, you know, that we kill some of the cells. We actually can see some prostate cancer tumors shrink, we can see, you know, on bone scans, some lesions kind of take up less bone activity in prostates and lymph nodes shrink.

But... but we're not killing all the cancer. Even when the PSA goes down to zero, we know that, in most cases, there's still cancer present. And so, what's going on there? You know,

as David said, you know, these cells have kind of put them into a resting or hibernation state. But... but it's a weakened state. And one of the most important things we've learned in the last, you know, 5 or 10 years is that combining therapies with this sort of testosterone suppression, or we call it androgen deprivation therapy, combining therapies at that time is really critical. When the cancer is weakened, that's when we want to hit it with additional therapies, and whether that's local therapies or systemic therapies.

And the reason is, is because it won't stay weakened forever. Sooner or later, those cancer cells develop other genetic alterations that lead to, you know, disease progression, what we call now castration resistance, and we don't like that term, but that's kind of the term we use. And if you think about it, the way hormonal therapy works, in part, you know, David mentioned, you know, it's targeting the DNA repair, and it's targeting the DNA proliferation, the growth of these cells.

And when we lower down testosterone, we damage the DNA repair mechanisms, and that's why some of the cells die. But the ones that don't die, they can develop genetic alterations almost because of the hormonal therapy. So, it's almost like a double-edged sword kind of leads to some of this resistance that develops up over time. But while it's weakened, that's... that's why, you know, I think you've seen a lot of progress in the field that we'll talk about today, and why hormonal therapy is so critical early in the disease course.

Phillip Koo, MD: Great, thank you. So, you know, we're going to shift gears and talk about when hormonal therapy is utilized, and we're going to talk about, sort of, four distinct disease spaces, and then within those, just to level set, we're going to talk about ADT, androgen deprivation therapy, and we're going to talk about ARPIs, androgen receptor pathway inhibitors, which is a more novel class of drugs. We're not going to talk about, sort of, the varieties of drugs within those classes, but just sort of talk about big groupings, how they might be used, and then later on, we're going to talk about the individual types of drugs within those categories. So, David, I'm going to start with you.

So, a patient presents with what we presume is localized disease. It's confined to the prostate gland. So, we think. How are hormones sort of prescribed or used in that setting for those patients?

David Morris, MD: I think Dan really pointed out nicely that hormones make other things work better. And so, some of the earliest research done by our radiation oncology colleagues is that hormone therapy and lowering testosterone can make cancer cells more susceptible to radiation.

And so, there are certain disease risk categories, and the first thing we do as clinicians for localized disease is trying to assign risk categories.

They include things like Gleason score, which many men know as two numbers combined. It's a complex system to kind of explain, then there's a grade group system, which is a newer system. Thankfully, much simpler. It's a 1 through 5 ranking of risk.

We take things like that, and what the clinical stage is, and what the PSA is, and we put them into a risk category, and those risk categories determine how aggressive we are with treatment. And so, typically, those risk factors, if there's enough of them, they get to kind of a medium, high-medium, or what we call unfavorable intermediate risk, or above. Those are usually people, if we're choosing radiation, we add in hormone therapy, and we vary the duration based off exactly how risky the cancer cells are. So, unfavorable intermediate, high risk, and very high risk, all include some hormones in their therapy.

But it's important to recognize, if you have low-risk disease. There really has not been much added benefit of adding hormone therapy in that situation, and then you're adding a lot of toxicity that may not have a benefit trade-off, and so we focus mainly ADT use in those with the highest risk.

Phillip Koo, MD: All right, and how about use with surgery? Is it ever used with surgery?

David Morris, MD: So, as a surgeon myself, I'd love to say, yes, it has a niche role within surgery, but that has not been the case. Historically, early trials looked at using hormones before surgery to see if it impacted the outcomes after surgery, and really, there was not much of a difference.

It tended to shrink the cancer a little bit, but it didn't really make a difference in the long run in terms of how the cancer did. And so, that's really fallen out of favor. It's not really part of any of the current guidelines to use hormone therapy if you're planning surgical treatment.

Phillip Koo, MD: All right, great. So, you had these patients who are, you know, let's say unfavorable intermediate, or worse, they're getting radiation, they get hormones with their radiation.

Unfortunately, we know that, you know, many of these patients will recur. The PSAs will go down, but, you know, they might start rising later, which, you know, we call recurrent disease or biochemically recurrent disease.

So, Dr. George, in that setting, now that patients are sort of recurring, what's the role of hormones in that patient group?

Daniel George, MD: Yeah, Phil, it's really important to recognize that there's a distinction between patients who recur who have already recovered their testosterone. So, like you said, they stopped their hormonal therapy, and then, you know, their testosterone recovers into the normal range, and then their PSA goes up. And that recurrence is different than a

patient who gets hormonal therapy, and their testosterone goes down, and it stays down. And it's still down, and then their PSA starts going up, because that patient that has got recurrence with a really low testosterone, they're probably castration-resistant prostate cancer. Whereas the patient that maybe had, you know, testosterone recovery and then a PSA relapse, they're likely to be still sensitive to hormonal therapy, so we can treat them again with hormonal therapy alone. And what I mean by that is androgen deprivation therapy.

Now, what's really important is, you know, we, as I mentioned earlier. You know, combinations seem to be really successful in this setting. So, where the androgen deprivation therapy is not curing anybody, it's sensitizing the tumors to other therapies, and some of those other therapies are other hormonal therapies, the androgen receptor pathway inhibitors that you mentioned that that block, you know, either more testosterone or the testosterone receptor, and kind of give you a double hit, if you will, on the pathway, and that creates sort of a greater treatment effect, a deeper hormonal therapy inhibition, if you will, more complete inhibition, and so in many of the settings where maybe we use just androgen deprivation alone with radiation therapy, when they recur, we'll use a combination strategy like that.

Phillip Koo, MD: So, in patients who recur, who are still sensitive to hormones, what's your approach? Do you use ADT? When do you use ADT plus one of those ARPIs?

Daniel George, MD: Yeah, probably the biggest distinguishing factor here is going to be the PSA doubling time. I mean, a lot of people are doing PSMA PET scans, and we're going to get to that. I know that's your favorite.

But the truth is, is that what's really prognostic, what really predicts for survival in this setting is the PSA doubling time. That's how long it takes from the PSA to go to 1 to 2, or 2 to 4. It's different than the velocity. PSA velocity is, you know, how fast it's going up each year, is it going up one point? Is it going up 10 points? That's not as prognostic as the doubling time. And we can go into that in a little more detail later, if you like, but it's important to recognize that patients with a, you know, the median, sort of, average doubling time is about 9 months. If their PSA doubling time's shorter than 9 months, that's the population of patients we want to use this combination approach with.

For the patients whose PSA doubling time is really long, you know, is a year or more. These are the patients we feel comfortable, frankly, just still watching. You know, because this isn't necessarily rapidly progressive disease. This is smoldering disease. This is where that PET scan might help us identify a single lesion or two that we can radiate and avoid the hormonal therapies, at least delay the hormonal therapy a little bit longer.

So, so that's kind of how we'll tease out that population, by the PSA doubling time, by the PET scan findings. And then determine, do they need immediate hormonal therapy and combination therapy, or can we kind of focus on more of a tumor-directed approach.

Phillip Koo, MD: You know, that's great. So, it's nice. It seems like the approach is trying to understand how aggressive that patient's tumor is, and sort of tailoring the treatment to the aggressiveness. So, let's sort of move forward a little bit further.

And David, there are going to be patients who have metastatic disease, where the disease gets outside of the prostate, and they still are sensitive to hormones, so they haven't reached that castration-resistant disease state yet. Sort of, what's your approach to using hormones in that patient population?

David Morris, MD: That's probably the fastest growing patient population, honestly, in many of our clinics. Combination, obviously, in the news recently with a former president being diagnosed with a likely metastatic prostate cancer that probably fits in that description of someone who is going to be hormone responsive, who's not been on hormones yet, but is already metastatic. And most of those people are new diagnoses that are really high risk, and we get imaging and find that they're spread. And there's some men who've had treatment 10, 15 years ago who haven't silently come back, and lo and behold, it spread under the watchful eye, hopefully, of physicians, or sometimes they just... we stopped doing surveillance, and then we capture that somebody gets back in the clinic and has spread noted on x-ray.

So, almost universally, the guidelines all state at that point to start with combination hormone therapy. So, some sort of androgen deprivation with something else added in. And I think this is one of Dan and I's biggest passions, is just getting that message out in the community, that hormone medicine by itself, if you have metastatic disease, is not enough in the vast, vast majority of patients. And so, if you've been diagnosed with metastatic prostate cancer, and you've been told, here's your hormone medicine, that's all you need, then you may need to get another opinion to check and make sure that there's not something else that should be added in that situation, because almost all the guidelines now support adding in the ARPIs, which you mentioned, which are usually pills in combination with another hormone medicine. And there are even some combinations moving not just from two medications, but to three medications, including things like chemotherapy, which has been a mainstay in prostate cancer for over 20 years. It's now coming back to the front, and we're using it again up front, because it has benefit when you add another line of therapy. Like Dan mentioned, you've weakened the cells, and that is the time to hit it the hardest, and you get the best bang for your buck up front by using more

medications when patients feel stronger and they can get the therapy, and then they can hopefully get a more durable benefit out of that combination medication.

So now, the standard across the board for hormone-sensitive metastatic disease is combination with ADT, with something else added in.

Phillip Koo, MD: You know, I think this is a great, you know, teaching point for all of us, especially the patients.

If you have metastatic hormone-sensitive disease, you need to be on more than just one ADT. You need sort of combinations, and I think this is something we all need to, and patients need to advocate for, and that's a great take-home message.

So now, Dan, we're going to fast-forward a little bit more to that most aggressive state where patients are metastatic castration-resistant. And what's the approach to using ADT plus ARPIs in that group of patients?

Daniel George, MD: Yeah, Phil, and just, if I could make one point on the last population there that we talked about, the metastatic hormone-sensitive.

There's now a population as well, and I alluded to it, these recurrent prostate cancer patients that don't have metastatic disease but have vast doubling times.

That's a population where we have one of our more recent studies, the EMBARC study, that demonstrated a doubling of the time to more overt metastases by adding this second hormone agent. In this case, it was Enzalutamide or Xtandi to the ADT versus ADT, and I just wanted to follow up on David's point. It's just one more iteration of where these combinations have dramatically changed the natural history of the disease, why we really think about that. So, I forgot to make that point when I was talking about the relapse patient, but that's exactly the other setting besides the metastatic hormone setting, where we're using these combinations up front.

Now, to your question around castration-resistant prostate cancer, that population of patients I mentioned earlier who had low suppressed testosterone from their ADT, but now their disease is progressing. And they may or may not have had exposure to a second hormonal agent and androgen receptor pathway inhibitor, but either way, we define that population as castration-resistant.

They're not necessarily the same. If somebody's been on just ADT and is castration-resistant, that patient population should really respond well to adding an androgen receptor pathway inhibitor, even though the androgen deprivation therapy is no longer completely holding the cancer there is a real benefit, a survival benefit, to adding the

androgen receptor pathway inhibitor. It's not as dramatic as the earlier settings, but it's still really valuable and important to recognize.

For the patients who have been on an androgen receptor pathway inhibitor and ADT and now have disease progression, that population of patients, we're in a little bit of flux. So, we have a brand-new approval for a radioligand therapy called Pluvicto, it's Lutetium-177, and it targets the PSMA-positive tumor cells, and it's been shown to be really beneficial in delaying disease progression in that setting.

We still have Docetaxel chemotherapy, tried and true, 20 years, as David said, for that, but it comes with its own, you know, pound of flesh, and so we balance that quality of life with early chemotherapy, versus now, this Pluvicto therapy. And there are still patients that get treated with targeted therapies, patients that harbor, in that setting, a genetic alteration, and the only way we know that is if we check.

So, if it wasn't done earlier, this castration-resistant prostate cancer setting, early castration resistance, that's when we want to check for any genetic alterations.

And, you know, probably about 20% of patients will harbor some kind of genetic alteration that will predispose them to another class of drug, a drug that also targets the DNA repair called a PARP inhibitor. And those patients can really benefit from a PARP inhibitor early in this castration-resistant prostate cancer disease state. And if they haven't had an androgen receptor pathway inhibitor, we have an indication for combination of the androgen receptor pathway inhibitor and a PARP inhibitor.

So, this is sort of where we're kind of getting back to what we're saying about combinations, where you know, when we can create susceptibility with hormonal therapy, whether that's upfront with ADT, or combinations with androgen receptor pathway inhibitors, adding another agent, like a PARP inhibitor, when there's a genetic susceptibility, is really important, and we don't want to wait until the end of castration resistance, when we've utilized all our other therapies to do that. We want to do it early on.

So, getting genetically tested, then, is really important. Even if it was done originally, if the tumor was really old it's worth checking the blood again for that, you know, for circulating DNA, that might, you know, predict for a genetic alteration.

Phillip Koo, MD: Great, so, you know, I think that's wonderful. It sounds like clearly hormone therapies are still very, very important in that castration-resistant setting. But then, sort of, there are a lot of options that could be used in combination. So, let's sort of go back to the beginning again, and I want to talk about just duration of hormone therapy.

And we'll talk about those four buckets. So, I'll start with you, David. In that localized setting, how long, and I know it's going to be different for every patient, but in general, how long should patients be on hormone therapy when they have localized disease?

David Morris, MD: So, typically, for an unfavorable risk, that would be a 4 plus 3 Gleason score, grade group of 3. Unfavorable intermediate's usually going to be a short duration with radiation, so that's somewhere around 6 months. And some people fudge that a little bit shorter, a little bit longer.

I want to be very clear that there's no clear standard that everyone should have this duration, because there have been trials run on 6 months, 9 months, 12 months, 14 months, and all the different comparisons between them, and we make generalized comparisons that, shorter is probably sufficient for most people with medium-risk disease. In fact, there are some next-generation tests being run to try to decide if the genomics of those cancer cells mean that you really need to give the hormones with the radiation, or there's even a subset where maybe you could shorten the amount of hormones that you give with the radiation to spare some of the side effects. But when you get into the high risk and the very high risk, we're talking Gleasons, 8s, 9s, and 10s, or the grade groups 4 and grade group 5, that's when you're really looking at more like 18 to 36 months, so it's more a long-term ADT use with radiation. So, you're basically starting hormones, getting your radiation, and then you're staying on hormones for a period of time.

And as Dan mentioned, combinations are moving earlier and earlier, and as we get to the very high-risk population, now there's even a subset where we use combination hormone medications, so not just one, but two hormone medications for around 2 years, when they're getting radiation therapy. So, I think the general trend over the last 5 years has been, if you're on hormone medication, in the future, I would think it's very likely that if you're going to be on one, you're probably going to be on two, in most disease settings where we need to be aggressive. The one caveat to that is the lower, the medium-risk patients there's really some discussion about, do we need to be using it at all, and can we use a short amount as possible just to make the radiation more effective, and then get off the medications to spare where we're going to spend the last half hour talking about, which is all the trade-offs from being on hormone medication. So, it's not all great news from being on hormone medication, as all 900 guys on this call can attest to, it's not perfect to be on hormone medication.

Phillip Koo, MD: Yeah, absolutely, and I think the goal would be less if possible, but obviously we want to make sure we're maximizing our outcomes. So, we're going to fast-forward a little. Dan, and we're going to focus on that patient who is recurrent, biochemically recurrent, but still hormone sensitive.

You talked about this concept of maybe even delaying androgen deprivation therapy, and then you also mentioned those who are more aggressive maybe starting a drug like enzalutamide. So just talk to us about duration in that space.

Daniel George, MD: Yeah, yeah, Phil, you know, I think, you know, when we're dealing with recurrent prostate cancer it's a struggle because there's a wide spectrum of prognosis here, and I mentioned PSA doubling time as being really helpful in really kind of figuring out who needs that sort of immediate treatment, and who can we delay. But the truth of the matter is, is that with hormonal therapies today, we're by and large not curing this patient population.

So, one of the reasons we delay is we think of it as kind of intermittent hormonal therapy, and why not start with the break, rather than start with the therapy in the patients that are slow going. For the patients that have fast-going disease we start the therapy because we don't want it to become metastatic, or if it is metastatic, more metastatic. So, we'll start the hormonal therapy, and we'll treat, typically, in that setting, for 9 months. That was the EMBARC study. We built into it a stopping rule for the patients that achieved an undetectable PSA, and for those on the combination therapy, it was, like, 90%.

And there was even an arm, interesting arm, of Enzalutamide alone, no ADT. So, you can... you can block this pathway without suppressing testosterone, by just blocking the testosterone receptor. And they demonstrated it in that study, 85% of the patients on enzalutamide alone at 9 months had an undetectable PSA, and with ADT alone, it's like 80%.

So, the hormones work pretty well, even in this kind of fast-moving patient population, fast-moving PSA, setting. Stopping the therapy has a sort of unpredictable course, and that's because some patients recover their testosterones really quickly, particularly the patients on enzalutamide alone, but even those on ADT. And then some patients will take year or two years to recover their testosterone. So the timing of restarting can vary. And of course, again, if they start relapsing while their testosterone's low that's castration resistance. But if it eventually recovers, and then they relapse, we kind of follow that PSA doubling time again. And typically, kind of a threshold, somewhere between a PSA of 2 to 5 is usually when we'll consider restarting. And now with PET scans we're able to image that disease even before the PSA reaches that 2 to 5 range. And sometimes we can target a lesion or two or three and change that trajectory a little bit. So we use it as an intermittent course but again, I don't want to mislead people. We're talking about long-term hormonal therapy. Most of the patients, the vast majority are going to end up going back on hormonal therapy at some point, and it's going to be kind of an off-and-on. Eventually, those times off hormonal therapy become shorter and shorter. It's just not worth the break and the stress

of PSAs rising and falling will tend to keep people on it, you know, continuously at that point in time.

Phillip Koo, MD: Agreed. So, we'll talk about intermittent therapy and sort of testosterone recovery in a little bit, but I love how you sort of set it up for those who, David, who develop metastatic hormone-sensitive disease. What's their duration of hormone therapies there? Is it pretty much just all the time now?

David Morris, MD: Well, I would say the guidelines would say it's likely continuous until progression, and that's usually measured in the clinical trials as the PSA's rising, and now you've become castrate-resistant, or actually your imaging is progressing and showing worsening of disease.

Now, that's the guidelines. There's a lot of clinical trials that Dan and I have probably participated in that are looking into building in breaks. We have some people who respond very well and have deep responses in their PSA, and we'd love to get people off medicine if they really aren't getting much extra benefit from it, and so, there are studies looking at keeping people on medication for a period of time induction, whether that's 9 months like EMBARC, or longer, like 2 years, and if you get down to a PSA that's undetectable, and you didn't have cancer, unfortunately, all over your body, and it was a fairly limited spread, then those are people it's a risk-benefit discussion with the patient and the provider to sometimes say, we're going to try a holiday for a while. And see if you recover and feel better, and maybe you don't have side effects from the medication.

And the hope is that if we have to restart it, we get a response again, maybe not as long as the first response, but are able to buy you a total amount of time that might be a little bit longer but using less therapy during that period of time.

And so that is becoming newer, but I will say the guideline answer is stay on hormones until you progress. So, it's a case-by-case basis. It's not wrong to stay on it. It's also not wrong to say, hey, I want to advocate for myself, I'm having bad side effects, I want to trade a little bit of risk of the cancer getting worse, for seeing if maybe I feel better by getting rid of some of these medications. So that's a shared decision making.

Phillip Koo, MD: I love that, and I agree, it really needs to be a discussion, because the side effects sometimes are going to be very, very difficult. So, Dan, we're going to fast-forward to that final disease state of castration-resistant prostate cancer. Is it continuous there as well? Sort of, what do patients need to think about?

Daniel George, MD: Yeah, Phil, you know, totally what David said, you know, if you look at our clinical trial data, everything is predicated on staying on hormonal therapy continuously, for life at that point, and keeping testosterone suppressed. But if you think

about why that is, the reason is for consistency in the clinical trials, so that everybody in both the control arm and the experimental arm will have low testosterone, so they can really isolate the clinical benefit of the investigational therapy they're adding to that. It's not because we believe that keeping that testosterone suppressed at that point in time is necessarily helping.

Now, there have been studies that have looked at stopping the hormonal therapy, and there have been some rapid progressors in those cases in some time. So it's important to recognize that those are older studies when we essentially didn't have any additional therapeutic agents besides hormonal therapy and the castrate-resistant setting. So, you know, when we were using other agents that are effective. You know, we're not necessarily getting the same kind of synergy, the same kind of sensitivity and, you know, additional benefit with combinations in that setting.

So, I've been a little more liberal in allowing patients who want to come off hormonal therapy to come off. Recognize that many of my patients have been on for years are just not going to recover their testosterone, so it's a little bit of a moot point, but we can measure it and see, and we can always re-suppress, but for some patients, you know, we've been able to do that. They've been able to recover some testosterone and actually feel okay.

There's even some studies out of Johns Hopkins, primarily, Sam Denmeade and others, suggesting that an intermittent approach of testosterone, what they termed a bipolar testosterone, two weeks up, and then two weeks down, in the setting of suppressed you know, testicular testosterone can actually cause some DNA damage and have a therapeutic benefit.

So, you know, I think the jury is out. You know, we just haven't really asked the question in the current contemporary landscape of how critical testosterone suppression is at that setting, we do it out of habit, and out of just the fact that that's been mandated in our clinical trials. I just want to be clear, it's not for a strong biologic reason at that point.

Phillip Koo, MD: That's great. So, it's interesting. So, we have clinical trials, and, you know, obviously that helps inform us and guide our decision-making, but there's sort of some other things to consider, and if patient's [Testosterone] doesn't recover, you know, we can ask ourselves, what is the ADT doing? And I think that could be a really good discussion that patients have with their physician. So, wonderful. This has been a great discussion. We're going to transition a little into demystifying the different types of ADT and the different types of ARPIs.

Which, it's a smorgasbord of words that sometimes are difficult to pronounce.

So, David, we're going to start with you and talk about ADTs, and what are the various you know, types of drugs, and sort of what distinguishes one from another.

David Morris, MD: Sure, I'd say androgen deprivation is basically anything designed to lower your testosterone less than 50. That is the FDA definition.

You know, 50 years ago, that was orchiectomy. So that was surgery to remove the testicles, which is still an option in some men who are very cost-conscious and are going to be on hormone medication, theoretically, the rest of their lives.

But in most modern practice, it's revolved around injections. And a newer, developed oral medication. So, the injections are all basically designed to kind of attack the pituitary hypothalamic axis, which is a scientific way of saying the brain signal to the testicles to make testosterone, and one of them immediately goes in there and turns the volume down. Those are the antagonists, and there's an injectable on the market that's an antagonist.

Then there are a whole bunch of different agonists, which go in there and actually turn the volume up so loud that the radio breaks, and then it can't send a signal to the testicles anymore. And so, it stops making testosterone.

And so, the agonists have been around for much longer, and there's a whole host of different ones, and there's, I joke that there's one-month flavors and three-month flavors and four-month flavors, and 6-month flavors, and in fact, there used to be 12-month implantable flavors, so there's all these different ways to get hormone medication in the body.

The field changed, now a couple years ago, with the release of Relugolix, which is an oral agent. It's an antagonist, so it goes in there and immediately turns the volume down, and it basically the antagonists have a very quick onset, and so that can be very helpful if you have a lot of cancer. And if they're spread all over, and we're worried about this phenomenon called flare, where if we actually turn up the dial just a little bit with the volume, and you have testosterone goes up for just a short period of time, you can actually make the cancer cells grow for the first few weeks, and it could cause new pain or new problems. And so, in those situations, antagonists seem to be preferred, because they immediately turn the volume down.

You can block that flare phenomenon by adding other medications into the injectable, so it's not wrong to use an injectable, as long as you block the flare if you're worried about it. But in reality, there's a bunch of ways to skin this cat, and at the end of a month, no matter which medication you're on, your testosterone is very likely, like, 98% chance that your testosterone is going to be down under 50.

So, it really comes down in a lot of markets to what the doctor carries and has on the shelf. Sometimes it comes down to what your insurance is going to cover and what's on formulary or not.

And I will be very clear, if my dad had prostate cancer and needed a hormone medication, I don't need to nitpick which brand of injectable he's getting. As long as he's getting an injectable, and then considering does he need to add something else into it.

So, I don't think there's any data suggesting any of them are efficacious-wise any better than the other. They all do a very good job of lowering testosterone. Almost all the studies just looked at, does it get it down at the end of a year. And they were all equivalent in terms of how well they did that. Now, there are little nuance differences, which we may touch on in terms of some people like shots, they don't have to take an extra pill. Some people like pills, they don't want to take a shot.

There's been a lot of arguments about, are some classes of medicine safer than other classes of medicine? And honestly, I think most of those scientific literature is that's still an unanswered question. So, I want to make it clear that it is not wrong to be on any of the medicines.

It's not like there is a preferred ADT on the market, and most clinicians, and I'd love to hear Dan kind of throwing his weight on that, and then talk about the ARPIs, because I just... there's not a lot of head-to-head information between the different agents.

Phillip Koo, MD: Dan, your thoughts? So... so it sounds like injectable versus oral, you know, maybe nuances, but in the end doesn't matter as much. Antagonist versus agonist, you know, some nuances, but in the end, gets the job done. Dan, any sort of thoughts here?

Daniel George, MD: Yeah, I mean, I'd love to agree with David. I'll just point out one circumstance, you know, David talked earlier about the short-term, you know, say 6 months, or 12 months or 18 months of hormonal therapy around radiation therapy, and one of the advantages of the inhibitors, you know, immediate signal off versus the- I love that sound, you know, kind of drowning it out so that there's no signal anymore.

You know, with the agonists. One of the real advantages of the agents that block the signal from the hypothalamus, the GnRH, is that it's more easily reversible. When you take that inhibitor away, the signal's still there. So, it can start working relatively quickly, and we see testosterone levels come back up within a couple of months.

In the case of the agonist, it's much less reversible, particularly when you've been on it for more than a year. For many of these patients, you know, it can take almost as long as you're on the hormonal therapy, that long to recover. So, if you're taking, sort of, one year of

hormonal therapy with your injection, and then you stop it, it's really 2 years. It's really another year before that testosterone level gets back up again. And if it's 2 years, it can be a year and a half, three years, you know, 2 years additional before the testosterone really recovers, and some people don't recover, so... So, you know, that's probably the one setting where I prefer the antagonist over the agonist for that reason.

But most of the patients with recurrent disease where we're going to be going kind of on and off, you know, kind of indefinitely, it's less critical. It is nice to have that. I prefer the control. I mean, to me, if we can control when the testosterone's suppressed and when it isn't, I like that better than just leaving it up to the body to recover. And, you know, I've had patients who haven't recovered where I've had to give testosterone back to. And we do that. You know, we'll have prostate cancer patients we give testosterone to, because it's important to recover that, and the body hasn't done it. So, but we can largely avoid those scenarios with the antagonist.

Now, in terms of the AR inhibitors, the androgen receptor pathway inhibitors, I'm just going to briefly, you know, break them down, because again, to David's point, yeah, we haven't had head-to-head prospective clinical trial data to compare these. And, you know, the first one was Abiraterone, and Abiraterone is... it's an interesting drug. It's actually a hormone in and of itself. And it is a, you know, an androgen synthesis inhibitor, so it blocks the production of testosterone. You might think, well, that's what ADT's doing. Not really. You know, ADT is suppressing testosterone from the testes, but there are other sources of testosterone, including the prostate itself, the adrenal glands, even the tumors can make some testosterone. I mean, they're from the prostate, they're a... A hormonal gland tumor, so... So, recognizing that testosterone is not simply from the testes, you know, abiraterone was proven to be quite effective. Now, it has a metabolite that also blocks the androgen receptor, so It's a little bit of a mixed mechanism. But it was a first drug, and if it was the only drug we have, we'd be super happy.

Right? But we happen to have even cleaner drugs that specifically target the androgen receptor without causing a partial activation of it, really pure inhibitors. And these include Enzalutamide, Apalutamide, and now Darolutamide.

And these have shown data that have been, you know, remarkably impressive in the castration-resistant setting, particularly in the non-metastatic castrate-resistant setting and the metastatic hormone-sensitive setting.

Enzalutamide, being a little bit older drug, actually, showed benefits even in the metastatic castrate-resistant setting, even in patients after chemotherapy, so really through the whole

spectrum, prostate cancer [Enzalutamide] has demonstrated this clinical benefit, this survival benefit associated with it.

But the other drugs look... show very similar data. It's interesting that Darolutamide is a little bit different structure than the other two, so it might have some slightly different you know, kinetics associated with it, but by and large, these drugs have overlapping toxicity profiles. Most of our patients, 80% of our patients are able to tolerate these drugs. I'm kind of like David on this one. As long as you're taking one of these drugs, I'm happy. These are all good drugs. Some people might tolerate one better than another, so maybe about 10% of our patients will switch from one drug to another because of side effects. That may or may not work out, but at least we have options, and these are all reasonable options.

The Abiraterone probably has the most diffuse side effects, because it affects other hormones besides testosterone. So, we have to be careful about the adrenal gland and its function. We can see some cardiac issues associated with it, certainly see some hypertension and other things. You have to take some Prednisone. So, to me, it's a little bit less attractive drug for those reasons, but if it's all that you can afford, it's still way better than just ADT alone.

So, so that's kind of my, just... top-of-the-line, you know, information on this. I will say one last thing: real-world evidence. You know, we tend not to play up this, right? We hold up our clinical trials, our Phase III trials, like it's gospel, right? But when it comes to real-world evidence, we kind of think of it as just kind of a little bit of background music, but the truth is, is that our studies with real-world evidence are actually the closest thing we have to the patients we're treating in clinic. And these studies tend to look at thousands, sometimes 10,000 patients, and we have a number of different data sets.

And one interesting finding is the study in castrate-resistant prostate cancer of Abiraterone and Enzalutamide. Enzalutamide consistently shows a survival benefit. You know, it may only be 10 or 20% longer survival, but it's a consistent finding across you know, multiple, multiple different data sets. So, to me, it's another way of kind of understanding how these drugs might differ using real-world evidence, and I think it's something that we should be paying more attention to.

Phillip Koo, MD: Great, thank you, Dan. So, you know, it seems... clearly we have a lot of options in both types of drugs. I think here, it's really important for patients to speak up, talk about what they're feeling, their side effects, because you could switch to something else and see if that works better for you, because, again, it's really hard for physicians to know how patients will react to specific drugs.

So, when we talk about ADT, I think we all know, and you guys know better than I do, just the side effects are really, at many times, sort of crippling, and, you know, David, I'll start with you. What are some of the side effects that patients are seeing with the ADT types of drugs, and sort of some advice that you have for the patients who are on the line?

David Morris, MD: Sure, so my basic talk tack on ADT is it's going to make you go through menopause, so, you know, if you have a spouse or caregiver who's there with you, they can kind of explain to you what's going to happen in some ways.

So, the common things that almost everybody sees are hot flashes and fatigue. Almost across the board mild effects. If you don't have those, congratulations, but almost everybody has some impact on that. It can often impact their sleep, because they're waking up and having hot flashes, and sometimes leaning on a spouse who's gone through menopause can explain how to deal with some of these things, honestly.

Um, fatigue is one that just impacts you every day. Guys lose their get-up-and-go. That's what testosterone is for a lot of men, and so you take it away, and you've taken away that drive. And so, we do see things like weight gain, depression, inactivity, and those are probably the biggest things that they can impact by trying to stay active. Almost every trial that's looked at how to mitigate the side effects of ADT medications are activity, exercise, diet, those sorts of things have the best data supporting them. So, stimulants, supplements, acupuncture, everybody's looking at everything under the sun, and honestly, it comes back to, if you can stay active, and if you've not been active before, if you can start a walking regimen, that is better than doing nothing. But the people that go home and get fatigued and lay on their couch have a really hard time getting up again and get going.

Um, and so, exercise, staying active, hydration is important, that kind of helps along with the same activities, and staying full and continuing to get calories in, but not junk calories. Those are all the basic things I talk to my guys about. And usually I try to pull in the caregivers, the daughters, the spouses, because they can help encourage that sort of behavior to keep going, because it's going to impact those basic functions, and then it's going to take away the testosterone that leads to sex drive and libido. And that's an emotional drag on the guys, and so it's not wrong to admit you have mood issues. If you have depression that develops because of ADT, because of cancer diagnosis, there's a lot of resources out there for help. And guys tend to internalize and often don't express that, and don't seek help.

So, we need to destigmatize that so people feel comfortable about bringing it up in the clinical office. That's what they're there for, and I'm not a psychiatrist, I don't write a lot of those medications, but I can point them to the right people who can.

And we just need to make sure the guys know that it's normal to feel this way going through hormone medications. They're not the first person to feel like that.

Phillip Koo, MD: That's great. So, you know, diet and exercise, and speak up about some of those side effects. David, can you just quickly touch on cardiovascular health. You know, we're learning more about this

David Morris, MD: So, there's been a lot of attention now on cardiovascular health, especially with the combinations, because the ARPIs all have, like, warnings on them about cardiovascular health. And I'll just say, none of these medicines make your heart any better. All of the guys going on these medicines are generally in their 60s and 70s and 80s, they all have cardiovascular risk factors, they have hypertension or lipid problems.

So, what I do is just try to make sure that they have a regular doctor that looks at their heart health. Their cardiologists cannot be me, it can't be Dan, it can't be you, Dr. Koo. It has to be A real person who pays attention to their heart health. Because I can't fix those things, but every time I've asked the cardiologist, they will say, if they need it for their cancer, use it, but we just have to do our best to control those other risk factors, like hypertension, and not ignore them. So, as long as we can maximize their heart health going into it then generally, they're as protected as we can make them. There is some argument that the antagonist may be slightly healthier for the heart than the agonist, and I will say there are other studies that show the complete opposite of that. So, I'm not a big believer that any class of ADT medication is heart-safe They're all bad for your heart, just slightly. And so, we just got to do our best to make sure your hearts are healthy before you go on the medication.

Phillip Koo, MD: That's a great take-home message. Be heart healthy. Dan, you know, you talked a little about testosterone recovery, sort of using different intermittent strategies, whatnot.

Can you talk to us about that? Because if we can find ways to recover their testosterone or do testosterone replacement, obviously, a lot of the side effects get mitigated or resolved. What's your approach to that?

Daniel George, MD: Yeah, Phil, I mean, first, David did a great summary, and all of that applies in the intermittent setting. So, we're recovering testosterone will not restore your energy. Recovering testosterone will not build your muscle, you will not lose weight recovering testosterone, unless you exercise, unless you diet, unless you do all the things that David pointed out.

This is not a wonder drug, right? But it's just permissive. It allows you. It allows your body to recover, but you've still got to put the work in.

And I'll say this is really hard, you know, because it's easy to judge, you know, when we're not taking hormonal therapy. But there's a consistent pattern that I see in my patients on hormonal therapy. They lose motivation. It doesn't matter how motivated you are going in it's just hard to maintain that because of this hormonal therapy effect. So having a routine is so important.

I tell my patients,: you need to have a routine to your lifestyle. And the exercise has to be part of that routine, the diet has to be part of it, sleep has to be part of that routine, and the consistency around that. So those... and when you recover testosterone, that routine has to maintain, and if anything, now you need to amplify a little bit, because now you have the ability to do more. And as you have the ability to do more, you need to do more to build that muscle and get that strength back.

Bone is another really important... it's a silent killer. We have huge issues with bone complications 10 years into prostate cancer. The prevention needs to start early on. Exercise is a huge help for bone strength, calcium, vitamin D, but being active, really, really important for all of those things, and recovering testosterone can help as well.

So, to me, when we do this intermittent approach, it's not to give people a holiday. I'd say, look, this is like boot camp 2.0. Now you got to kind of go back at it, and hopefully the motivation improves, and that's when patients really start feeling the benefit. Not everybody feels benefit from testosterone recovery, but a lot do. These are some of the things that can help increase those odds.

Phillip Koo, MD: Great, I like that. So, you know, those breaks aren't holidays, they're sort of boot camps, and an opportunity to sort of refocus and keep that consistency. So, is there a role for T replacement? You know, you see things all the time, and it kind of varies, but just really quickly, we're running out of time, but I'll start with you, David, and I'll go back to you, Dan.

David Morris, MD: Yes, in a limited subset where we think we have potentially cured a man, there is no reason for him to be testosterone suppressed for the remainder of his life.

There... I would let someone try to recover, and if the goal was for them to recover and they don't recover, we will often start with testosterone replacement to try to get them back to normal. We don't try to get to super normal because that might create other issues, but we do try to get them to normal and see if that helps them with their generalized recovery.

Phillip Koo, MD: Great, thanks. Dan?

Daniel George, MD: Yeah, I really like to check testosterones before we start hormonal therapy for this precise reason, because if somebody's really low to begin with. Say they're

in the 1 to 200s, and then we give them hormonal therapy, they're very unlikely to recover. And waiting 5 years for something that's not going to happen makes no sense.

So, these are the patients, you know, maybe they were on testosterone before they got prostate cancer, we held it. These are the patients I'm going to come back to sooner rather than later, because guess what? What's the worst-case scenario? We give them testosterone; the PSA goes up. I didn't cause the cancer to come back, it was there, right? We just smoked it out. And now, at least we can justify that low testosterone in the patient, because we know that there's still prostate cancer present. So that's kind of how I think about testosterone replacement. I'm a little bit more aggressive, particularly in the patients that are low to begin with.

Phillip Koo, MD: Great. So, we have 4 minutes left. I'm going to sort of turn to each of you to give sort of your closing comments, advice you might have for patients, you know, perhaps with regards to how they might have these conversations, and we've heard a lot, and hopefully patients feel empowered to have really meaningful discussions with their providers. So, David, I'll start with you.

David Morris, MD: Sure, my question is always just, how long do I need to be on this, and do I need to be on it with something else?

And, if you've got those two things in mind, the next hurdle is always cost and affordability, and there's a lot of programs available to get these medications to men without breaking their piggy bank, so there's a lot of government and assistance funds and industry support.

So, make sure your provider can help loop you into those, or get you to a specialty pharmacy that can help loop you into those assistance networks, because almost everyone should be able to afford ADT plus something else if needed. And the goal would be, maybe down the road, we're able to get men off of this if we've used it appropriately.

Phillip Koo, MD: You know, that's great, and we wanted to talk about this, and there have been a lot of questions about the financial toxicity related to these drugs, and it's really good to know that there are resources out there, so... please talk about that with, you know, your physicians, and they can point you in the right direction. We also have some links on our website that might be able to help. Dr. George?

Daniel George, MD: Yeah, I would lean into your physician to say, what resources do you have for me to help me manage my, you know, low testosterone. So, you know, David pointed out some of the, you know, kind of, psychological, you know, issues and things like that. So, if there's a social worker or a medical therapist in the group.

If there's an exercise physiologist, or it's somebody that... if there's a program that they're affiliated with, even a... you know, YMCA or whatnot If they're a dietitian they could speak to, because it's one thing to say diet, it's another thing to say how.

So, this is where, again, we're not the experts, but we have them. So, but if you don't ask, sometimes we don't tell, so it's important to ask. So don't feel bad about asking about resources like that.

And then I think support groups. I mean, I think patient-to-patient support groups are fantastic and probably underutilized. I'm sure PCF has a bunch of them. But that's another resource to kind of lean into. You are not alone in this journey. You and your caregiver, there's a lot of support out there, and I think these things can really help you feel like, okay, I'm not the only person going through this, and help you cope, and help you help other people coping. It's a great way to build resiliency in this disease

Daniel George, MD: Those are wonderful closing words. You know, we could probably top an hour about each of these little areas, but we covered a lot in this hour.

You know, if the listeners have any comments, suggestions for future, you know, areas that we could dive into, please let us know, and we could help address and build a program around that as well.

Really, really grateful to you, Drs. George and Morris. I couldn't think of a better panel, and thank you just so much for taking the time to educate all of us on the importance and sort of the side effects and what to be aware of when it comes to hormone therapy.

Daniel George, MD: My pleasure, thanks so much.

David Morris, MD: Thank you.