00:00:00:00 - 00:01:33:24
Unknown
Hello. Good evening, everybody. My name is William Oh. I'm the chief medical officer for the Prostate Cancer Foundation. And I welcome you to our next seminar on metastatic castration resistant disease. This is a series that some of you may have joined us previously, and if not, that is available as content on PCF.org around metastatic hormone sensitive prostate cancer.

00:01:33:24 - 00:01:58:01
Unknown
This is the second part. Next slide, please. Just as a reminder, PCF has been funding research for now for 30 years with a mission to reduce death and suffering from prostate cancer. We have funded the most promising research for treatments and cures with a global footprint around the world, and many of the therapies that are in use today actually developed were developed with seed funding from PCF.

00:01:58:02 - 00:02:24:24
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Next slide. There's a lot of content available on some of the websites that we host, including PCF.org. There are multiple guides, you can sign up for updates, view past webinars as I mentioned, and join an online support group. There's also a newer website that I encourage you to go to, *prostate cancer patient voices* to hear other men who've gone through this diagnosis and treatment and who are sharing their experiences.

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We have funded over 50 research projects in 2022, totaling more than 30 million so far. In 2023, we funded over 6 million to young investigator areas and another 6 million to challenge awards and more to be announced. All of these investigators are working towards the mission of alleviating death and suffering from prostate cancer. So please think about us in your end of year charitable giving, given our focus on really defeating this disease.

00:02:54:04 - 00:03:30:03
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So I'm delighted to welcome two colleagues and friends to this panel. Dr. Mary Ellen Taplin is a medical oncologist at Dana-Farber Cancer Institute and a professor of medicine at Harvard Medical School in Boston. Mary Ellen has focused on new therapies and prostate cancer and has had a real impact in this field over many years. I've worked with her when I was in Boston, and she continues to be a very productive researcher, understanding how prostate cancer is driven to grow and how we can use ways to block the cancer from growing, using androgen receptor blockers and using these in earlier and earlier disease states.

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Next slide. Our other speaker is Rana McKay. Dr. McKay is an associate professor of medicine at the University of California in San Diego and she treats patients with all kinds of urogenital cancers, including prostate cancer. And she's designed clinical trials that have been quite novel and looking at mechanisms of resistance and response to specific cancer therapies. She was a recipient of a PCF Young Investigator Award in 2015.

00:03:59:18 - 00:04:28:10
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So I'm going to ask them both to join me now. Hello, Rana. Hello, Mary Ellen. Nice to see you both. Thank you for joining me. So I wanted to start by really talking a little bit about definitions, and I'm going to share some slides that really define a little bit about what patients are unfortunately, going through when they deal with prostate cancer.

00:04:28:12 - 00:04:52:13
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And as their cancer becomes more resistant. So let me just share my slides here and maybe I can ask you, Mary Ellen, to start by kind of talking a little bit about this process and natural history and what we're going to talk about tonight. Could you just describe how you how you frame this for patients?

00:04:52:15 - 00:05:27:21
Unknown
Yes, thank you, William.
It's really a continuum. And patients meet us with the prostate cancer diagnosis at various points across this continuum from being diagnosed with what is or thought to be a localized prostate cancer. And then after local therapies, it's possible a cancer relapses with a rising PSA and then subsequent to that of prostate cancer become metastatic, or sometimes a patient is diagnosed at the time when the prostate cancer is already metastatic.

00:05:27:23 - 00:05:49:14
Unknown
And then the subsequent stage that you outline here are an effect of the hormone therapy. When patients are on it over time, they develop resistance to that therapy and I think we're going to discuss it. But there's various terms to call it, and a more common one is castration resistant prostate cancer.

00:05:49:14 - 00:06:23:20
Unknown
Well, let's talk about those titles right now.
Could you address what CRPC, what does it mean and why do we use that term?
So what CRPC means is, in essence, when patients' testosterone levels are very, very low, the prostate cancer is continuing to grow. And that could be manifested as a rise in PSA, even though the testosterone levels are very, very low. Or it could be manifested as new spots that show up on a scan, whether it be a bone scan or a CT scan or an MRI.

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And so it's disease progression despite very low levels of testosterone and so very low levels of testosterone have been termed **castration**, hence the term castration resistance. And we've we've moved away from the term hormone resistance, and that's many of these tumors, even though they're progressing on hormone therapy, may still be responsive to other iterations or other forms of hormone therapy.

00:06:51:12 - 00:07:17:17
Unknown
So that's been this evolution away from the term hormone resistance, because it's technically they can still be hormone sensitive, but they're castration resistant because they're growing despite a very low T. And so that's where this this term comes from. And it's not a nice term. I think many people don't like the term castration resistance, but it's defining the state of low T is essentially.

00:07:17:17 - 00:07:38:06
Yeah, it's a word that we as doctors use to communicate with each other. It's the words that the FDA uses to define the state in which a drug is indicated. But it really just means that a patient has a low testosterone and their PSA is rising or their cancer is growing on a scan.

00:07:38:08 - 00:08:01:18
Unknown
So, Mary Ellen, is there a specific number that defines castration resistance? Like if you're on ADT - the definition of ADT is androgen deprivation therapy. We talked about it at the last webinar, and it means that you're on a drug like leuprolide? or one of the many other drugs that may lower your testosterone and your PSA is rising usually or your cancer is growing in the bones.

00:08:01:18 - 00:08:34:13
Unknown
Is there a PSA cutoff for what castration resistance might be? Mary Ellen?

For me, no, it's it's really just this the state of a consecutively rising PSA. So one PSA might go up a little. I'm not sure I believe it, but have the patient come back, and a second one or the third one. If you have consecutively rising PSA is despite a low level of testosterone from therapy, then for me, that's the definition of castration resistance.

00:08:34:13 - 00:09:17:06
Unknown
And it doesn't really matter if the PSA is 0.2 or two or 20, you know, people will turn over into that definition at various levels of PSA.

Rana, does everyone have a rising PSA? Do some men not have a rising PSA in the setting of a low *[ADT]* and still have castration resistance?
So, it can, it's not all predicated on PSA. Like Mary Ellen was saying, that there the PSA could be undetectable, but they could have, you know, new disease on a scan or new spots on a scan, even though the PSA is very, very low or not rising at all.

00:09:17:08 - 00:09:48:08
Unknown
So I think…. and not every single man develops castration resistant disease, but when the disease is more advanced, there's an increased likelihood of developing it. But it's not absolute that every single person actually does, in fact develop castration resistance.
That's a really important point. This is a schematic that tries to average out every single person that has prostate cancer, and many people have very different experiences with the disease.

00:09:48:10 - 00:10:21:03
Unknown
In fact, the majority of men who have prostate cancer are cured with clinically localized disease and may have surgery or radiation and may never go down this pathway. So men don't necessarily have to develop castration resistance. But if you ….basically if the cancer is metastatic, we recognize that eventually it can become resistant.
So I showed this schema at the last webinar and I'm going to show it again, and we're going to drill down to some of these.

00:10:21:03 - 00:10:40:04
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On this slide, on the left side is hormone sensitive disease. That means the cancer is still responding to androgen deprivation therapy. That means you go on a drug like leuprolide and your PSA goes down and and almost everyone does that. And there are other drugs that you might use in this setting. And we talked a lot about it at the last webinar. Please go to that excellent webinar to learn about hormone sensitive disease.

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Unknown
But today we're going to talk about the right side, this concept of castration resistance and it is a long list. And we're going to talk a little bit about these drugs when we drill down on a patient case. But I just wanted to maybe get, Mary Ellen, you to talk a little bit about what this picture looked like when you and I first started many years ago and how it has evolved to this and what that means for the average patient.

00:11:09:03 - 00:11:47:22
Unknown
Yeah, it's really, truly amazing and a testament to a lot of hard work from prostate cancer researchers and you know generous funding from Prostate Cancer Foundation and others. So when I started in prostate cancer, it was 33 years ago. And besides surgical castration and drugs

like Lupron, we had very few effective therapies for prostate cancer. In fact, common drugs like steroids were used and antibiotics like Ketoconazole that had this effect that's similar to abiraterone.

00:11:47:22 - 00:12:15:10
Unknown
30 years ago, we had very little therapy. In fact, when I started practicing, PSA just came into the clinic. And so most of the men who were diagnosed with prostate cancer, unlike today, thankfully, back then they were diagnosed with metastatic disease to begin with. So it's so exciting and I'm so grateful and thankful to have been involved in this evolution of care.

00:12:15:10 - 00:12:40:23
Unknown
I look at this slide, like all these new treatments and all of us will acknowledge it's not what we need. We need to be light years ahead of this. And, you know, my patients always ask me, you know, what's happening next and how do you feel about it? And I think the technology is booming right now and the technology booms and then our therapies follow upon it as our tools get better.

00:12:40:23 - 00:13:08:05
Unknown
So before we have all of these conversations, I just want to say I'm very optimistic about the future for our prostate cancer patients.
Thank you for that. I mean, to be around in this space and see so much happen and this time it's been very, very exciting. But as you said, our work is still ahead of us because until we have a cure for advanced prostate cancer, we have to keep doing research and finding new treatments.

00:13:08:07 - 00:13:36:23
Unknown
So I'm going to start with you, Rana, on this patient. This is a patient very similar to ones we see every day in our practice. A 63 year old man presents to the clinic. He has bone pain, fatigue, a poor appetite. This was a few years ago. His PSA was 270. We don't know anything about whether he had PSAs before then, and he has a biopsy that shows Gleason 9 prostate cancer.

00:13:36:23 - 00:13:55:04
Unknown
Because of the year he had this diagnosis, he had two older scans. We can talk about the newer scans in a minute, but he had a bone scan that showed multiple bone lesions throughout the spine, ribs and pelvis and a CAT scan, a CT scan that showed enlarged lymph nodes as well as the disease in the bones. So so we're going to talk a little bit more about what happens next.

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But what's your general sense of a person like this? Do this men, in a PSA era where men are getting PSA screening, do they still show up in your clinic? Are there men who come in with this kind of presentation?
Absolutely. There are definitely men who come in with this kind of presentation. It's not uncommon that we see this.

00:14:12:09 - 00:15:00:10
Unknown
I think there's been a lot of, quite honestly, just confusion around PSA screening. You know, the US Preventive Services Task Force had come up initially with various recommendations against screening and then updated the recommendation. So, you know, I think there's a lot of confusion about whether men do or don't need to be screened for prostate cancer. And I think there's also, you know, could be some taboo elements around screening for prostate cancer or discussing these factors with your primary care doctor or requesting a PSA test, and so I think it's critically important to actually educate both the patient community, the physician community at the front gates of sort of primary care where patients may present.

00:15:00:10 - 00:15:34:04
Unknown
I think within the medical oncology and urologic community, we are very adept at having those conversations around PSA screening and PSA testing. But this is not an uncommon scenario, and we're actually seeing it increasingly more common, you know, with just confusion around PSA screening.
Yeah, unfortunately, the evidence suggests we're going in the wrong direction, which is really sad because we've learned so much about the fact that early detection really avoids a lot of the problems that this particular patient is is going through.

00:15:34:06 - 00:15:57:22
Unknown
And the Gleason 9, just as a reminder to everyone, means that this is a particularly aggressive disease, that the usual scale is anywhere from 6 to 10. So he's in the highest category of risk. And his PSA, a normal PSA, would be under in a man this age under 4. So 270 is obviously very high. So he undergoes standard treatment with leuprolide and abiraterone, which is a next generation hormone pill.

00:15:57:24 - 00:16:18:01
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And in 2020 this was a standard of care. And so he received the standard of care and he had a very nice response. His pain gets better and his PSA goes way down. We always like to see this. Patients love it and we're so delighted when this happens. But of course, this is only in the first year.

00:16:18:03 - 00:16:43:06
Unknown

In year 2, the following happens. His PSA starts to rise. It's now up to 12.4 and he starts having new pain. His testosterone is very low. It's under 3 - with a normal range, which is usually 300 or higher. And he remains on on the two treatments he started with. He gets another bone scan, which shows some new spots in his femur and his spine and the lymph nodes are growing.

00:16:43:06 - 00:17:10:03
Unknown
So, Mary Ellen, what additional tests would you do in this patient? Is there anything you would do in or in order to really help you make a decision about what to do next for him?
Well, since I see metastasis on the what we call the conventional imaging, the bone scan and CAT scan, I don't necessarily feel like I need to do a PSMA PET scan.

00:17:10:05 - 00:17:41:19
Unknown
Sometimes when I'm choosing which tests to do, I might start with a PSMA PET scan. We're getting coverage for them very frequently now. Insurance coverage seems to be less of an issue than it was a few years ago. I definitely like the idea of getting molecular testing to see if there's a specific genetic mutation either that the patient has in their normal cells or in the tumor cells.

00:17:41:19 - 00:18:05:23
Unknown
So that's two types of testing. One is a blood test or a saliva test for what we call germline testing. And the other is specifically to try to look at the the tumor cells themselves to see if they've evolved a mutation over time that can be different from the patient's normal cells. And that testing is done either on a tumor sample like a biopsy of a metastasis.

00:18:05:23 - 00:18:30:23
Unknown
Those types of biopsies are done in radiology. It's a needle biopsy, a day procedure, or it also can be done on a blood test. So, yes, that I think we have good imaging and I would like to see some molecular testing and now seems like a good time since it's a time where the patient is considering a therapy change.

00:18:31:00 - 00:18:51:19
Unknown
So I want to just repeat what you said because you said a lot of really important things there. One is that nowadays you might do a PSMA PET instead of a bone or CT scan. This is an older scenario where we didn't have the PSMA PET so you wouldn't repeat it. But now in a patient who's progressing, you might do it as the primary treatment first and foremost.

00:18:51:21 - 00:19:14:06
Unknown
And there's two kinds of tests listed on this slide. There's a molecular test on is biopsy something we call somatic, which is the tumor itself might have molecular changes or mutations

that can help you to decide what to do. And you also would test his germline, which is a saliva or blood test. That means what did he inherit from his mother or father that might actually help you to decide what to do for him.

00:19:14:08 - 00:19:34:18
Unknown
So this is not about testing himself to help his family only, although it could, for example, if he had a BRCA mutation, it could help him and his family. But it's really, primarily, the reason to do it now in him is that it could help him. Right? Okay. So I'm going to stop sharing here. Rana, is there anything else you would do differently?

00:19:34:18 - 00:19:52:20
Unknown
Are there any other tests you would do? Would you do a biopsy on this patient, an additional biopsy, or would you use the prostate biopsy that he had initially to do the testing?

You know, very good question. And I actually think when we think about timing of the use of the genetic testing, I actually like to do it upfront.

00:19:52:20 - 00:20:20:10
Unknown
I like to do it when…. like this gentleman was diagnosed with high risk, high volume, de novo, meaning, you know, at diagnosis, metastatic prostate cancer. And so this is a high risk scenario where I would want to know that testing upfront. So I would have even considered doing the testing when he first got diagnosed, testing his original biopsy, testing the germline as well.

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Unknown
And then, you know, when the disease is changing after the selective pressure of the therapy that he's been on, we could consider repeating the somatic tumor testing. And that could… because acquired resistance happens, because patients' tumors can evolve, new mutations can develop, old mutations may go away. It's nice to think about repeating the test, and that could be done through a blood test.

00:20:49:13 - 00:21:15:18
Unknown
Like Dr. Taplin was saying, looking at circulating tumor DNA and testing that. The beauty about that is it's minimally invasive and actually you get back the results in about, you know, two weeks or so. You could consider repeating a biopsy, potentially biopsy one of the lymph nodes that's growing, if it was readily accessible. But the turnaround time for a tissue test is a little bit longer.

00:21:15:24 - 00:21:43:21
Unknown

And if this person is, you know, having kind of a rapidly rising PSA, new bone spots, new symptoms, you may be thinking about initiating therapy, utilizing that original testing, maybe getting a blood test just to expedite and then kind of going from there. But it's critically important because of actually the role that PARP inhibitors play, and other therapies that we have at our disposal even today to treat based off of molecular profiling results.

00:21:43:23 - 00:22:08:08
Unknown
Thank you. So the summary here is molecular testing of the original biopsy right at the time of his original diagnosis might be helpful because you get that information, you know, and you don't have to wait for it later. But some patients may not have had that testing as soon as this process is happening, they should ask their doctors to test the tissue, either from the original biopsy or to do something called a liquid biopsy.

00:22:08:10 - 00:22:33:17
Unknown
In addition to that germline test or hereditary cancer test, if they haven't already had that, even if they didn't have a family history, that's the other important thing. We have a great webinar where Kara Maxwell talked about this exact issue. It is complicated, but it's actually quite simple. You should get your your germline tested and you should get your tumor tested to give you as many options as possible because this is a long list.

00:22:33:19 - 00:23:00:22
Unknown
What I did was I took this graph and I took all the colors and I made sure they were color coded and I put them on a single slide. So I'm going to go back to you, Mary Ellen. And this is a man who already received abiraterone right upfront. And can I just ask you to just briefly talk about the different categories that we're looking at because it looks like a lot of choices, and it is a lot of choices.

00:23:00:24 - 00:23:35:02
Unknown
How does somebody know what those choices mean from a mechanistic point of view? And then what would you recommend for this patient typically?
The general categories in pink are therapies that work on what we call the androgen or the testosterone axis. And so they're what most patients refer to as hormone therapies. In yellow are what are traditionally thought of as chemotherapies.

00:23:35:04 - 00:24:06:21
Unknown
And docetaxel has been a standard for for a couple of decades actually. In blue are a few newer treatments that are in a category called radiopharmaceuticals. And I like to refer to them with my patients as liquid radiation because they're given intravenously and they work by delivering

a radioactive particle to or near the tumor. And then in gray are some treatments that we have that have very unique mechanism of action.

00:24:06:21 - 00:24:39:23
Unknown
Sipuleucel T is an immune therapy based. The PARP inhibitors or targeted therapy that work best against tumors that carry certain mutations. And then pembrolizumab is another type of immune therapy that commonly works in other tumors like kidney cancer and lung cancer very commonly. But in prostate cancer maybe only works 4 to 5% of the time in tumors that have very specific alterations.

00:24:40:00 - 00:25:07:06
Unknown
So those are the general categories.
That's really helpful. And it is hard to categorize. I mean, again, you pointed it out very well earlier. We have we have a lot of choices, which is really good for our patients. We only want one choice, which is one that gets rid of the cancer in the long run. Right. But you and I both remember when we started that we had zero choices, or the first choice was in fact chemotherapy, which is still a very good treatment.

00:25:07:08 - 00:25:28:11
Unknown
So we're going to talk a little bit more about some of these other choices further in a minute. But let me go to you Rana. This is a man who received abiraterone with leuprolide in the beginning, and now he's progressing, has metastatic castration resistant prostate cancer. What would you typically offer him? Let's….we don't have any molecular testing available yet.

00:25:28:11 - 00:26:00:20
Unknown
And as you said, he's progressing quickly and symptomatic and you've sent everything off. You don't know that he has any germline or somatic mutations. What would you offer a patient like this?
Honestly, in this situation, this is where I tend to lean towards chemotherapy. The PSA is rising rapidly. There's progressive bony disease, there's painful bony metastases, it's multifocal metastases that may not necessarily be amenable to focal radiation strategies to target all sites of progressing disease.

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Unknown
He's got growth of lymph nodes as well. You know, so in those scenarios, I really lean towards docetaxel chemotherapy, and docetaxel chemotherapy is a life-prolonging agent. It has improved overall survival for patients with this disease. And though chemotherapy, you know, there's a lot of different thoughts around chemotherapy, but there's a lot of different strategies

that we can implement in the clinic to maintain quality of life even while patients are actively receiving chemotherapy.

00:26:30:16 - 00:27:01:16
Unknown
And so there's a lot that we can do to help patients along.
Yeah. Mary Ellen, would you agree with that assessment for this patient?
I think so. And I try to look at what I call the big picture, which is….Rana touched on it, but what are the individual characteristics of this particular patient that got them to this point?

00:27:01:16 - 00:27:35:09
Unknown
Meaning, you know, did they have a high Gleason score? Did they have just a few bone metastases or many bone metastases? Were they on hormone therapy for one year or four or five years before they got to castration resistant? Do they have symptoms or do they not have symptoms? So every patient is an individual. The individual story, if you will, and this patient, as Dr. McKay mentioned, has some more concerning features that I would probably also reach for chemotherapy.

00:27:35:09 - 00:28:10:10
Unknown
But let's change the features a little bit and say his Gleason score was 7 and he was on hormone therapy for four years and he only had two bone metastases initially and they were radiated. In that patient I might think of maybe some of the other options that might have a little bit more favorable quality of life profile, like maybe even sipuleucel T, because I would feel like that patient is stable and is not at risk for a cancer-related problem in the short term, or maybe even try a second hormone therapy. This patient had ZYTIGA; could consider enzalutamide.

00:28:10:10 - 00:28:40:06
Unknown
The overall response rate to that is only in the 20% range. But some patients do have a second response to another hormone therapy. So it really depends on that individual patient's details. And we all like to individualize and discuss the pros and cons of each approach. And then aim for what's going to be the best quality of life for that particular patient.

00:28:40:08 - 00:29:05:12
Unknown
I think you both brought up such important issues. The first is that for this particular patient, there were a lot of concerning features. A high grade cancer, a relatively rapid progression, a lot of symptoms. And it brings up the fact that chemotherapy, even though it's an older treatment and has a bad reputation, is one that the three of us have seen work many, many times, not only to prolong life but to make patients' lives better.

00:29:05:18 - 00:29:29:23

Unknown
I have a patient with Parkinson's disease. He's in a wheelchair. He really, really wanted to get Lu-177 [i.e., Lutetium PSMA radionuclide] therapy. He's a candidate for it. But we knew we had to give him chemo first, and he's done very well with chemo. But to your point, we have modified the dose. We gave him a much lower dose and he's tolerating it well and his PSA is going down and he's doing quite well.

00:29:30:00 - 00:30:01:16
Unknown
He's somebody who had already received many, many of these other therapies. So, yeah, this person did, in fact receive docetaxel chemotherapy and his PSA went down. You remember it was 12.4 and and in fact went down to 1.1 and he stopped after eight cycles for a treatment holiday. Rana, now, can you talk a little bit about how you give chemo, how chemo is typically done and why somebody would give a treatment holiday. It sounds like a nice vacation, but it's not really, right?

00:30:01:16 - 00:30:31:04
Unknown
It's something different.
Absolutely. And I think just to kind of piggyback on the prior discussion, I think in addition to sort of understanding the patient's characteristics and what risk factors when you're deciding on a therapy, I think it's really important to tease out, you know, what are the goals for each individual patient, because every patient that we see coming into the clinic, they may have the same exact clinical picture with the same exact PSA, same exact Gleason, but their goals may be different from somebody else's goals.

00:30:31:04 - 00:30:57:04
Unknown
And that is also going to affect the decision around what treatment to give. So I think there are other factors that come into play, and the patient you know, maybe not wanting to receive an I.V. therapy or they live really far away or we're worried about infection or worried about other things. So I think there's a lot that goes into decision to say, you know, this agent versus another agent.

00:30:57:06 - 00:31:23:16
Unknown
And I think coming to kind of a mutual kind of shared alliance around the treatment is really important. You know, I think regards to how we give chemotherapy, it's a varies a little bit depending on the state in which we're giving it. And I think generally in the hormone sensitive setting, we generally don't necessarily push too much beyond six cycles, kind of stopping up to six cycles of chemo.

00:31:23:18 - 00:31:48:14
Unknown

And let me clarify and step back and say what a cycle is. So usually chemotherapy, when it's given, it's not necessarily given every day like an oral pill. It's generally given as an IV infusion that is spaced out every couple of weeks apart. And the general way that it's given is IV once every three weeks and three weeks is considered a cycle.

00:31:48:16 - 00:32:18:16
Unknown
And generally we give anywhere from 4 to 6 to upwards to 10 cycles for patients that are doing well and can tolerate it. In some individuals, they may not be able to tolerate a full dose once every three weeks. In some individuals we may actually divide the dose and give a baby dose … two weeks on, one week off so that we split that dose so patients can tolerate it better.

00:32:18:18 - 00:32:41:06
Unknown
And so for those patients that are doing well that they've had a good response, their disease is stabilized, the intent is to not continue chemotherapy indefinitely. The intent is to give it for a finite period of time and then give people, patients a break from the chemotherapy, let their body recover, let their blood counts recover, let some of their symptoms get better.

00:32:41:08 - 00:33:00:12
Unknown
And then depending on how that patient is doing, they can do well for a long period of time before we need to think about an additional therapy. Or, we can sort of see what happens to them based off their PSA or their numbers. And in some situation, we may be able to re challenge with the same chemotherapy because they had a really good response.

00:33:00:14 - 00:33:23:17
Unknown
They got a long treatment free interval. And then, you know, maybe when the PSA rises again, we could rechallenge or consider something else. You know, maybe they may be in a different situation. But I think treatment holidays are really, really important. And I think it's a balance between keeping the disease in check, maintaining quality of life and, you know, mitigating side effects of treatment.

00:33:23:19 - 00:33:52:13
Unknown
Yeah, I think these are really important points. Customization, personalization of the treatment plan is really in the hands of both the patient, his family, and also the doctor and the team. The goal here is to do everything you can to fight the cancer, but also make sure the quality of life is as is a good one. And I will say, you know, there's there is a myth about chemotherapy, and Rana and Mary Ellen, and you both pointed out that you adjust the dose.

00:33:52:13 - 00:34:13:11
Unknown

It's usually given…by the book, it's given IV every three weeks. But many of us give lower doses. We may give it weekly or every two weeks instead of every three weeks. It's tolerated differently. And I gave that anecdote of my patient because, you know, I knew that he might not tolerate the standard dosing, and that is what you want to definitely consider for each patient.

00:34:13:11 - 00:34:33:14
Unknown
But I definitely don't think…don't ever assume that chemo couldn't help you because it's a very good treatment, even though it's one of the older treatments. So, Mary Ellen, back to you. And this patient, you know, he's received now two treatments over three years. Well, he's received three treatments, he's received androgen deprivation therapy. He got leuprolide or Lupron.

00:34:33:16 - 00:35:03:18
Unknown
There are some questions about whether there's other drugs that are androgen deprivation. The list is very long. Everyone….there's a very long list, including the newer ones like Firmagon and Orgovyx. Any drug that lowers your testosterone as first-line treatment, it's considered androgen deprivation therapy, and they all work basically similarly. So he's been on that. He's been on abiraterone (or Zytiga) and he stopped that because the cancer started to grow and then he went on 8 treatments of chemotherapy.

00:35:03:20 - 00:35:28:13
Unknown
What would you do next for this patient? I mean, what other information…let's say he did not have a genetic abnormality. All the tests came back negative. He did not have a BRCA mutation or other types of mutation that would make him a candidate for what we call a PARP inhibitor. He did not have the finding what we call MSI high tumors that would make him the few percent of patients who are candidates for pembrolizumab.

00:35:28:15 - 00:35:57:03
Unknown
What would you need next to make a decision for him, Mary Ellen?
Well, I think a PSMA PET scan would be helpful because we use that as a biomarker for it to consider one of the newer treatments, which is trade name Pluvicto. So a lot of patients know it as the PSMA Lutetium. So I would get a PET scan and see what we see.

00:35:57:05 - 00:36:24:17
Unknown
You know, upwards of 90% of patients will have their metastases show up with the PSMA PET scan. So that's the good news. It's a very common biomarker. And then if the PET scan is positive for metastasis, then I would consider Pluvicto therapy. So here's his PET scan. You know, I happen to have it here. What are we looking at here, Mary Ellen?

00:36:24:17 - 00:37:01:15

Unknown
So you're looking at the patient. You're facing the patient. His arms are up and you can see the little black spots along the arms. Those are prostate cancer metastasis. And then as you work your way further down, there's spots in the spine, in the pelvis, in the legs, the the femurs there. And then some of the darker spots are normal excretion of the tracer in the kidneys (that is not tumor) or in the bladder.

00:37:01:17 - 00:37:26:24
Unknown
And then further up in the salivary glands, that's not tumor. But there is quite a few. One of the questions in the chat was: what does innumerable mean? And this is an example of a scan with innumerable metastases, because it's very unlikely that the radiologist reading the scan is going to call out each one of these little spots and count them all out.

00:37:27:00 - 00:37:53:02
Unknown
So that's a lot of little tiny prostate cancer spots or metastasis in the bones of this patient.

So this is a you know, this is obviously coming from a published paper here, but this is a patient, an example of a super responder to Pluvicto or 177-PSMA. His PSA was at 80. And he received actually only a single dose, although you're allowed to get up to six doses.

00:37:53:04 - 00:38:17:14
Unknown
And in this patient just with a single dose after one and three months, this is what his scan looked like. Rana, have you seen responses like this with Pluvicto, with Lu-177?
We have. Yeah. We have seen we have seen dramatic responses. You know, with the therapy. I think the PSA 50 response rate is - meaning of 50% decline in PSA from baseline - is right around 50%.

00:38:17:16 - 00:38:44:06
Unknown
The PSA 80 to 90 response rate is right around 30%. So there are a subset of patients that can really have a dramatic response with significantly declining PSA. You know, something to consider as well. You know, as we think about deciding on a therapy for any given patient, it's really critical, I think, along the way to always be thinking about clinical trials.

00:38:44:07 - 00:39:09:18
Unknown
And at every single time that a treatment decision is being made, even if somebody is newly diagnosed, it's important to think about clinical trials. I think sometimes there may be a myth that, “I'm just going to go through my standard of care options and save clinical trials for later or save things for later.” I think in every juncture it's important to ask your doctor, “Are there any clinical trials that you think are going to be relevant for me right now?”

00:39:09:20 - 00:39:27:24
Unknown
Which ones do you think makes sense for me?" So I think that that is something a question to always kind of to think about, you know, and some clinical trials may be the right options for patients, some may not be. But it's always good to think about that. But we yeah, we've seen dramatic responses to the radiopharmaceutical therapy. I mean, it's like Dr. Taplin was saying, you know, targeted liquid radiation.

Mary Ellen, do you have to have a positive PSMA PET scan to be eligible for Lu-177 therapy?

Yes. In our institution.

You said 90% of patients will have a positive PET scan with CRPC, right?
Correct. On the large VISION trial, 87% of the patients who screened were positive for a PET scan.

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Unknown
So, yes. You know, and if patients don't have a positive PSMA PET scan, the other radiopharmaceutical Radium-223 is a good option for patients who have bone metastases, but a negative PSMA PET scan.

Yeah. So radium has been around a little bit longer, maybe 15 years. And radium works if you have cancer in your bones. But if you don't have a positive PSMA PET scan. But there was a question about if a person's a candidate, if they don't have any PSMA expression, and if you don't, then it won't work because this is a targeted treatment. If if it doesn't light up, then the drug won't hit it. The other thing the important thing is we have seen these amazing responses, but there are patients who have, you know, may not respond as well.

00:40:55:08 - 00:41:17:09
Unknown
And it's also not curative. So Rana, can you talk a little bit about what the goals We've mentioned it a few times. Obviously, even in my original timeline, the goal here is to control the cancer. But can we cure metastatic castration resistant prostate cancer? Do we know if we can cure it?

Yeah. Now, very good question. I think this comes up a lot. You know, unfortunately, this disease state is not one that tends to be amenable to cure. I think that, you know, the treatments are… they can be effective at prolonging life, improving symptoms, delaying the disease, keeping the disease burden low. But at the end of the day, when we think about a curative therapy, we think about a therapy that's actually literally able to target every single cancer cell and kill every single cancer cell.

00:41:45:05 - 00:42:25:05
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And a lot of times when people get into the hormone resistant or castration resistant setting, their disease can be very mixed. There can be a lot of mechanisms of resistance that can be very difficult to overcome. I remember when I was at the Farber, training with Dr. Taplin, so it's awesome to be on this webinar with her. I remember we used to always have the gumball analogy. And Phil Kantoff who was there would always kind of comment about, you know, think of prostate cancer and all the different cells like, like a gumball machine and there's all different kinds of cells. It's not all one cell. There's, you know, blue cells that have x mutation and red cells that have x mutation and pink cells and white cells and yellow cells. And you may give a certain therapy that targets, you know, the red, yellow and green cells. But the pink cells and the black cells are still around and, you know, they're not high in number, but then they may grow and increase.

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And so I think one of the things that we struggle with is actually being able to maximally target all of the different cells. And I think that's when we think about Lutetium PSMA therapy, it's a very specific therapy. It's targeting PSMA, which is a certain protein on specific cancer cells. And if cancer cells don't have that protein, those cells are not going to be targeted and they're going to grow despite the therapy.

00:43:14:04 - 00:43:37:05
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And so that's why it's important to test, check a PSMA PET, and make sure that the disease is actually avid, to see that and make sure that, yeah, that's going to actually work. And I think there was actually studies that were done looking at people who actually did not meet the VISION [trial] criteria and still got PSMA radioligand therapy, and they did not do well with the therapy.

00:43:37:07 - 00:44:01:23
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And so I think this is why these criteria are set in place to not subject patients to toxicity, to treatment that may not actually improve their outcomes.

Yeah. I mean, as we learn more about the biology of what makes prostate cancer tick and what it how it grows and and the fact that some cancers cells are different from others and your gumball analogy, not all the cancer cells are exactly the same. That's why it's such a tricky enemy, right? That's why we may kill 99% of the cancer cells, but 1% may persist and start to grow later. And that is that our goal is to keep knocking them down. Somebody asked, Can we just throw all of these drugs out at a person and get rid of them all? And the answer is we can't.

For one, actually, very practical reason, people can't tolerate all of these treatments at once. They each have different side effects, but people are looking at how to prevent resistance, how to how to slow down resistance and so on.

One question that I'm not sure we explained well enough, Mary Ellen, and may be worth going into is: we talked about doing this molecular and genetic testing and we said this could help your doctor make a decision. And the patient case that I described, it didn't help him.

We didn't talk about it. It was partly because it was a prior webinar, but also because not everyone is going to have it. But can you just go over again, what are we looking for in the germline and tissue testing that we're doing? And in 2023, what are the drugs? What are the types of drugs that would matter the most based on those results?

Well, the most common mutation. Let's just start with somatic, which is our term for the tumor genes, which may be different from the germline because tumor genes are common where we could say is unstable and they can change over time as the tumor grows.

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Unknown
So a common one that people have heard of is the BRCA gene. And there are two types, BRCA1 and BRCA2. BRCA2 is the most commonly mutated gene in prostate cancer, maybe 10% of the time. So it's still a low percentage. And when a patient has a BRCA2 mutation, especially if…. every gene has two copies in the cell and if both copies of the gene are mutated, then those tumors can respond very well to a class of drug called PARP inhibitors.

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Unknown
There's three different PARP inhibitors, olaparib and talazoparib and niraparib. Different companies make them. They do they work very similarly, small differences. So if I had a patient who had a BRCA2 mutation or even a BRCA1 mutation, I would be enthusiastic about using a PARP inhibitor. There are other gene mutations in this class of gene. They're called DNA repair genes. And there were some excellent questions in the chat about these.

There's a whole list of them, but some of them are ATM and CHEK2 and PALB2 and others. I might try a PARP inhibitor in them but with less enthusiasm because the response rates tend not not to be as good.

00:47:12:18 - 00:47:38:16
Unknown
So those are the the DNA repair mutations. It's a just a short conversation on them given our limited time. There's another type of alteration that Dr. Oh had mentioned, which is just a higher mutation rate in the tumor. There's a metric for that. It's…we call it MSH high, and that's only seen in less than 5% prostate cancer. But when we see it, those are the tumors in which immune therapies could work.

The drugs you see advertised on the TV all the time, like pembrolizumab and others.

So unfortunately, we see that rarely. But when I if I did have a tumor, a patient with that, then I would would try one of those drugs. And then, as Dr. McKay mentioned, we're always thinking about clinical trials and there's a lot of different drug classes that are in development that can target some of the rare mutations that we see in prostate cancer, but that aren't necessarily FDA approved drugs in prostate cancer.

00:48:20:10 - 00:48:52:13
Unknown
So if I have a specific mutation, then that might lead me to looking for a specific type of trial to match up with that.

Rana, I'm going to go back to Mary Ellen about maybe some of these patients who actually have less aggressive CRPC than this patient. There are patients of ours who whose cancers grow really slowly in that heterogeneous population, but there's also those who are even more aggressive than this patient, who have so-called neuroendocrine prostate cancer. Sometimes you will see the term anaplastic or small cell. Can you talk a little bit about what a neuroendocrine prostate cancer is and how it shows up and what we can do about it now?

Very good question. So first thing I'll say is neuroendocrine prostate cancer is not common. I think there's a fear around it, but it is not a common phenomena.
It's probably seen around 10 to 20% of the time in later stages of the disease. Sometimes there can be neuroendocrine elements just from the get-go when people first present, just their tumor is just set up that way. Sometimes it could evolve over time. A tumor just being set up that way is even more rare than it developing over time, but it can happen.

And what neuroendocrine prostate cancer is, is actually within a lot of the glandular tissue and the prostate cancer evolves from the gland. There can be little baby nerves that are present within that tissue and actually these can develop cancerous elements. And that's where this neuroendocrine kind of term is coined. And it's defined based off of a biopsy, actually.

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Unknown
So getting a biopsy and looking at the tissue underneath the microscope, under the pathologist’s eye, they can define it by morphology, meaning just by looking. And sometimes they can stain the tissue and there's different staining patterns that would suggest that there are neuroendocrine features that are there. And I think this is why sometimes it's important to repeat a biopsy along the way when somebody may have, you know, their disease progressing.

00:50:44:04 - 00:51:15:14
Unknown
You know, I tend to do that, particularly when there's new organ metastases, particularly liver metastases, or if the PSA is kind of stable but then scans are kind of progressing. And there's

this disconnect between the PSA and the imaging. But, you know, generally that's what I like to get it. And if somebody does have neuroendocrine prostate cancer, usually I'm leaning towards treating with chemotherapy.

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Unknown
A lot of the hormone therapies may not work as well because these tumors are not as responsive to hormonal therapies, or the radioligand therapy may not work particularly that some targeted radioligand therapy may not work as well. There are clinical trials that are being designed specifically for tumors that have neuroendocrine elements testing different kinds of immunotherapies, targeted therapies, therapies that target methylation patterns, different kind of patterns, genetic patterns within the tumor.

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Unknown
But I think it's it's something to be mindful of, but it's certainly not a very, very common thing.

Yeah. I mean, I think sometimes we may be inducing it like on patients. We're seeing more, for example, liver metastases because we're driving the cancer out of the bones and these cancers, as we said, sometimes can be tricky. And I do think clinical trials are really the way to go.

Chemotherapy may work temporarily in neuroendocrine cancer, but if the cancer does seem to spread, I recommend that you get a second opinion in a center that might be doing research in this space because it's a pretty specialized problem.

Mary Ellen, what about the opposite? You must have some patients who have had castration resistant prostate cancer for many, many years like I have. You know, what happens to those men? They may not be like this person that I described in the case, what are you doing for those patients? Who is, you know, on abiraterone, their PSA is going up slowly, they have one new spot. You mentioned it a little bit about the different ways that we can accommodate people, different courses, their own personal beliefs. Can you just describe what you do for patients like that?

00:53:01:01 - 00:53:32:02
Unknown
Yeah, we have a lot of patients who do quite well for many, many years on on therapy. First point I want to make is never change therapy or panic if your PSA is rising slowly and your scans are stable. I never, ever change therapy just because the PSA is rising, especially if it's rising relatively slowly.

00:53:32:04 - 00:54:09:19
Unknown
It's always important to assess both the PSA and the imaging. And I always tell my patients that the imaging trumps the PSA. Like if your scans are stable, you're good. Like, we're not going to

fret too much about the PSA right now. If I do find a small -- now that we're doing more PSA PET scans for routine imaging, as one of the patients in the chat mentioned this as well -- you do find a few new spots and I might radiate them and leave the patient on the same therapy that they were on, if it was a drug like Zytiga or enzalutamide.

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Unknown
But also what's really important is to treat the whole patient. So we focus a lot on the cancer and what's going on in the PSA. But I would say I spend more of my time talking about general health. Let's keep your muscles strong, let's keep your bones strong. Are you doing your walking routine? How's your diet? Let's think about your hemoglobin A1c.

I think general health and keeping a person's general health strong helps them with their prostate cancer treatment, and especially for a patient who is stable over long periods of time on hormone therapy, like those types of things are really hard, like having a good diet, and getting out when you're tired. And I like to really strategize on a lot of those issues with my patients.

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Unknown
That's really an important point. Lifestyle, diet, exercise. It makes a huge difference for our patients. And you know, what I often hear from spouses is, “They won't listen to me, but they'll listen to you, doctor.” So I think it's very important both for physicians and for the families to do everything they can do to support lifestyle. You know, Rana, can you talk a little bit about some of the promising new treatments in CRPC?
We have a couple of questions about Actinium PSMA. What is Actinium? And, you know, is it a promising approach for prostate cancer?

Yeah, I know. Very good questions. I mean, I think it's really been exciting looking at the spectrum of the different types of drugs that we even have FDA approved today, from hormonal agents to chemo agents to immunotherapies, PARP inhibitors, radioligands.
And there's a lot of other novel agents that are being developed, additional radioligand therapy. So I think if we're going to break down radioligand therapy -- and it sounds like there was a prior kind of a webinar on this -- but there is the ligand that you're actually, what are you targeting? And then if we think about like the payload, what is the actual treatment that is causing the cells to die?

00:56:16:14 - 00:56:50:05
Unknown
And so with radium-223, it's a “naked” alpha particle. It's not actually targeting a specific protein, it's an alpha particle that goes and lands in areas where there's calcium turnover in the bone and emits a small dose of radiation. The alpha particles tend to have a higher energy dose and they have a more finite activity range, if you will, on the order of 2 to 10 cells.

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Unknown
So those are alpha particles. Lutetium-PSMA is a beta emitting radioligand therapy that's linked to a small molecule that targets PSMA. And so actinium is -- instead of a beta emitter that emits a little lower dose of radiation compared to an alpha emitter and has a wider range of activity. So when we think about toxicity, that can play into effect.

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Unknown
Actinium is a is an alpha emitter linked to PSMA and there's different ways to link. You can link with a small molecule. You can link with a monoclonal antibody.
There's different kinds of ways you can target the target on the cell surface of the cancer cell. And I think this concept of a drug with a target, it's not just pertinent to radioligand therapy, it's actually pertinent also to what we call ADCs or antibody drug conjugates, where you have a targeted chemotherapy, which is the active agent linked to something that's going to be targeted on a cell surface.

00:58:05:02 - 00:58:33:20
Unknown
And the same is true for immunotherapy. There's now bispecific, you know, antibodies that will target a specific protein and try to harness the immune system to kind of get to that area. So I think this concept of more strategic, more targeted therapy, this is sort of the next iteration of drugs that I think we're optimistic about entering into the treatment landscape.

00:58:33:22 - 00:59:07:24
Unknown
Yeah. So what you're saying, I think, is that smarter delivery of the drugs, even chemotherapy, that's what an ADC is or immunotherapy, or in this case radioactive particles - is the future, instead of drugs that go everywhere, you know, make people lose their hair or have side effects that are unintended. These “smart bomb” technologies, I think are going to become more and more the way that we're going to deliver, you know, cancer killing cells. Actinium will be coming, I think, Actinium-PSMA therapies.

It's an alpha particle, as you said. And I do think there's so many people studying this right now, so many companies developing better next-generation radioligand therapies that we're going to all see them in the clinic. But Mary Ellen, we just had at the European meeting that just presented the PSMAfore study which said that you don't have to get chemo in order to get Pluvicto (Lu-177).

So do you expect that patients will not have to receive chemo in order to get Pluvicto, Lu-177-PSMA?

Yes, I think that's coming in short order as soon as the company presents their data to the FDA and the FDA agrees that it's effective and safe, then we'll get the approval, which then we'll get the insurance approval that we can give it before chemo.

The whole pre-chemo / post-chemo paradigm in prostate cancer is very artificial to my mind and was, you know, I think somewhat unnecessary. But it's started 12, 15 years ago when Zytiga was developed and then just got pulled along with other agents. And I would like to see that go away, personally. But yes, I think we'll have Pluvicto soon for patients - will not have to have had chemotherapy.

01:00:35:24 - 01:01:02:13
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So I know people are asking about the slides. We will make the slides available. This webinar will be also available online for you to review again. I know there were many, many really excellent questions. Obviously, we couldn't get to them all. It was a wonderful conversation. I'm going to ask you each to just end on one note about what you see in the future for prostate cancer and and for treatment of advanced prostate cancer.

And I'll start with you, Mary Ellen, and then go to- end with you, Rana.

I think as a field, we'll get better at characterizing tumors and tumor changes over time, genetic changes over time, tumor drivers over time, and how they change, probably by liquid biopsies. I think the liquid biopsy has gotten better. But, you know, there's a way to go to make them more practically usable.
And then we'll use that sort of iterative personal information over time to choose therapies that make sense for individual patients.

Thank you. Rana, last word.

Yeah. Yeah, I know. I agree. I think the goal is trying to better personalize the therapy and better target sort of the heterogeneity or the different variety of the different cancer cells that may be present in any one given patient.

And I think what's really exciting is thinking about, you know, I know we're focused here on castration resistant disease, but actually thinking about how can we cure our patients with more intensified multi-modality treatment and, you know, when people first get diagnosed with advanced disease or low-volume metastatic disease, and actually Dr. Taplin has pioneered a lot of that work.
And so my hope is that we will continue to improve outcomes and ensure that our patients are living longer and living better in the future.

Well, thank you. With that optimistic note from both of you, I want to really thank you for your time and your wisdom and thank all of you for joining us tonight. And have a very good night, everyone.