Managing Metastatic Hormone-Resistant Prostate Cancer

Phillip Koo, MD [00:00:00] So, now we're gonna welcome Dr. Szmulewitz from University of Chicago to join us. And we're going to transition to metastatic castration-resistant prostate cancer. So, Russell, thanks for joining us. Help us define what is mCRPC.

Russell Szmulewitz, MD [00:00:17] Sure, I mean, it's pretty simple, meaning that it's disease that has spread from the prostate like we talked about earlier when we defined metastatic disease. The only difference is that now that disease is progressing by imaging and / or PSA in the context of a testosterone that is low. By definition less than 50, but often less than 20 is what we're looking at. So, it's progressive disease, despite being on treatment that has lowered a testosterone.

Phillip Koo, MD [00:00:56] So, this concept of non-metastatic CRPC, so if we go back, obviously there are a lot of trials with drugs that were used in this setting. How should patients approach this concept of non-metastatic, does it really exist? What advice do you have for us?

Russell Szmulewitz, MD [00:01:12] It's a fair question and it can get a little confusing because all of those studies that define this status of non-metastatic castration-resistant were done before PSMA PET scans, which are much more sensitive. And in my practice, it's not really an entity that I see often or that I spend much time talking about because most of the time when you actually do a PSMA PET scan, you're seeing a metastatic disease.

There are rare instances where you might see PSMA expression only in the prostate in somebody who was on hormonal therapy and has never received radiation or surgery to their prostate. In those instances, I consider referring back to my radiation oncology colleagues to take care of that. It's not an entity that I really think is going to be in the lexicon of our management plans for very long.

Phillip Koo, MD [00:02:13] So, Oliver, this question comes up often is if castration-resistant is sort of disease progressing despite low testosterone, why do we still have patients on ADT?

Oliver Sartor, MD [00:02:26] Yeah, great question. And you know, there's a lot of controversy around that because in some of the early years, the idea was, well, we'll just stop the therapy and then see what happens. The truth is, there were some randomized trials that showed that if you stop the therapy with the androgen deprivation therapy, the people ended up progressing more rapidly and actually dying more rapidly. And on the basis of those studies, which were performed many years ago, we typically do maintain suppression.

One of the things that's a little bit hard to get our heads around, is the fact that castrate-resistant disease is often more sensitive to small amounts of testosterone. But it seems a bit of a paradox. It's resistant, but the truth is that even small changes in testosterone can be important. We've seen cases where the testosterone might go from 20 to 30 to 40, still technically in the castrate range. And the PSA responds, the typical patient, that would not necessarily occur. So, castrate-resistant disease is a little bit of a mixed bag. The majority of patients actually are quite sensitive to small changes in the testosterone. And our practice typically is to maintain the hormonal suppression, believing that that provides the best outcome for the patient.

Phillip Koo, MD [00:03:41] That's great. Thank you. So, Russell, give us, there's so many new drugs that are now approved for metastatic CRPC. And, you know, that's for a variety of reasons. Walk us through sort of big level buckets of these types of drugs and sort of your thoughts on where we are today versus 10 years ago.

Russell Szmulewitz, MD [00:04:02] Sure, I'll do my best. I mean, as you know, there are a lot of medicines. But what you will see, if we look at the mHRPC, is that many of those same drugs that you see on this graph are drugs that we also see in the mHSPC setting. So, drugs like abiraterone, drugs like docetaxel, drugs like enzalutamide, so I think that, although there are a lot of drugs, they follow into several buckets. One is that same ARPI bucket. One is microtubule-inhibiting chemotherapy, so classic chemotherapy, docetaxel, cabazitaxel. And then we have radiotherapeutics that are given intravenously. Lutetium-177 PSMA is one, radium-223 is another.

And lastly, we have a class of agents for specific mutations. We talked about PARP inhibitors, and then there are immunotherapies like pembrolizumab, which you see at the bottom, for a very, very rare subset of mutation-driven cancer. So, it's a lot of words on that slide, but they come into, three or four larger buckets.

Phillip Koo, MD [00:05:20] So that's wonderful, but it's also confusing because now we have to figure out what drugs you use in what order. How do we demystify that for patients that like, yeah, how do we maximize the efficacy?

Russell Szmulewitz, MD [00:05:35] So, it's a great question and I'll start, and I'm sure Oliver has a different take or an additional take, but I'll say that there is the first consideration is our clinical consideration. So, one, what else have you gotten already? So, what drugs has the cancer been exposed to or what classes of drugs has the cancer been exposed to? What does the imaging look like? Is it bone only disease? Is there a lung disease? Is there liver disease? And is it two or three spots that are progressing or is it many? What are the genomics? We spent a fair amount of time with Dana talking about somatic testing, meaning in that moment of HRPC, are there mutations that have developed that could impact your decision making.

And so first you have those clinical sort of stratifications, and then ultimately it comes down to shared decision making where you have to talk with the patient, what are your priorities? What are the side effects of these therapies? How do I maximize benefit and think about if I get this, what will it mean for my later therapies? And so, it's very, very individualized. There's no right answer.

My personal take is once I have all the data and I talk to my patients about what their priorities are, then my goal is to give them as many life-prolonging therapies with different mechanisms of action that I'm able to maximize, hopefully, their survival and their quality of life.

Phillip Koo, MD [00:07:24] Oliver, your thoughts?

Oliver Sartor, MD [00:07:25] Yeah, first of all, I agree. Very nice synopsis, Russ. The thing is I kind of view the patients in a couple of different buckets. First of all, as Russ said, very importantly, put prior therapies to be administered. So, if they've had prior chemotherapy or prior ARPI like abiraterone, enzalutamide, that's a little bit different patient with a castrate-resistant disease than those that have not. The ARPIs are super

important. If the patient has simply progressed on ADT alone or ADT plus docetaxel, which has been a classic combination, then the use of an ARPI is, to me, super important.

Stratification and understanding of the genomic alterations, things like the BRCA mutations, can be really important as well because some of the patients can do quite well on these PARP inhibitors, which are targeted for selected genetic alterations.

Immunotherapy is a topic that many people want to discuss, but as it turns out the immunotherapy with pembrolizumab, which is FDA-approved for anybody with a mismatch repair mutation. Getting a little bit complicated - MLH1, MSH2, MSH6, PMS2 [genes] - these mismatch repair mutations are pretty rare, 3-4%. But guess what? We find them, and under those circumstances, I do like to use the pembrolizumab, which is a PD-1, [programmed cell death-1] inhibitor, and it really is efficacious within the selected population of these mismatch repair or, hate to get more terminology, but MSI-high or high-tumor mutational burden. But Russ knows that.

Bottom line is, what do we do when we start out? We start worrying about what the patient's had before. Have they had chemo? Have they had an ARPI? Do they have a mutation?

The new kid on the block, relatively recent FDA approval, is the PSMA-617- lutetium-177. That lutetium-based therapy is specifically for PSMA PET-positive patients, and it turns out that in the study, about 90% of the patients had PSMA PET-positive disease when they progress after an ADT and ARPI. So today we have a new FDA-approved therapy, as of March of this year, of the use of the PSMA Lutetium. And that can be considered for those with a good PSMA PET scan compatible with the response for patients receiving Lutetium. So, a little bit more complicated.

I think that's probably enough said, but the bottom line is it's great to get an expert in the area who knows all the choices. And quite frankly, sometimes a clinical trial could be a great choice as well.

Phillip Koo, MD [00:10:03] You bring up an interesting option with Pluvicto, the lutetium-based therapy, and it's interesting because when it was first approved, it was approved very late-stage disease after chemotherapy. Then recently, there was a label, there were studies that showed it does well before chemotherapy. And then at the European meeting that's going to occur in Germany, I think in a week or so, we're going to see data that talks about the use in hormone-sensitive disease. So, these novel drugs are being used earlier and earlier. So then when do you get these drugs? You know, it's really tricky. So, Russell, take us through that.

Russell Szmulewitz, MD [00:10:43] Yeah, so nobody knows, is the short answer. And I think that again, we're trying to maximize benefit while also considering quality of life issues, patient factors that might influence our decision. So, things that I think about for, so there's a lot of drugs that are moving earlier. So, we talked about the PARP inhibitors early, maybe. Lutetium PSMA, maybe that will be a consideration for first line. But at the HRPC decision point, assuming a person's already gotten an ARPI, because I agree wholeheartedly that if they hadn't been exposed to that, that's your first endeavor. But assuming they've already gotten that in a castration-sensitive or hormone-sensitive setting and your decision matrix is consideration of chemotherapy, consideration of lutetium PSMA.

Then I think there are a couple of things that factor into that decision for me. One is how much PSMA disease and how high is that PSMA? We saw an analysis of the first phase 3 study, the VISION study, that showed that patients with the highest average PSMA expression seem to have the greatest benefit. We don't know if that's gonna be the same before chemotherapy, but I think that's one of the things that I consider. The other is, the lutetium PSMA is a radioisotope, so there are logistics. There are radiation safety logistics, and those have to be understood.

And that also, in my practice, sometimes affects patients. They might be the sole caretaker for their spouse or things of that nature. So, I think we have to have a multifaceted discussion. But again, the goal is to give patients the opportunity to have as many of these options because unfortunately, we are very, you know, we're not going to be able to cure them. And even with the best therapies we have, there's progress that still needs to be made.

Phillip Koo, MD [00:12:50] You know, I think one thing that becomes very clear and hopefully the patients and family members and loved ones on the line get this is, it's really complicated. There are so many nuances. And one of the take home messages I'm seeing is you have to communicate, you have talk, you have advocate, you have to be honest about challenges that you're seeing, priorities in your life, certain goals. And I think that communication pathway is so, so critical here.

So, we're going to shift gears a little. Oliver, you were on the mHSPC conversation where Dana had said that you don't get as many actionable mutations and perhaps there aren't as many opportunities for some of those drugs in that hormone-sensitive space. What does that look like in the CRPC space.

Oliver Sartor, MD [00:13:41] Yeah, so when we talked about the PARP inhibitors and I briefly mentioned the immunotherapy with what we call PD-1 inhibitor pembrolizumab, the probability goes up a little bit because the patients have a little more advanced disease and sometimes you can actually acquire mutations that were not present initially. So, the combination of germline testing and somatic testing may be a little more applicable to those patients with advanced metastatic castrate-resistant disease.

If I wanted to come up with a number, and I think there's a little bit of debate around the number. Some people say it's as high as 25-27%. Honestly, I think it's a bit lower because some of the mutations that are supposedly actionable are not really that active for treating with PARP inhibitors. But the bottom line is, you know, we're probably talking about 15% of patients. And even though it's not a large percentage, it's a very important percentage. Because when you find those mutations and the patients do well with precision therapy. It's very, very important.

Phillip Koo, MD [00:14:40] So, oh, go ahead Russell.

Russell Szmulewitz, MD [00:14:42] Yeah, I just want to add onto that. I mean, I think there's also some question about how to do the testing. And you asked Dana the question and put her on the spot earlier and she sort of hedged and said, well, it's important to just get it. And that's a great start. And I think in the CRPC setting where you have perhaps a higher percentage of actionable mutations, this question comes up a lot. Do I use cell-free DNA? Of which there are several assays, do I find something to biopsy and look at that tumor? And so, there's no right way to do it. In my practice, in this HRPC, in the resistance

setting, I'll usually use the cell-free DNA first because that gives you a global picture regardless of where the tumors are if they're spilling into the blood.

And if that shows an actual mutation, then you're good to try one of these medicines. If it's negative, and there are, especially if it's negative, but there might be tumors that are behaving differently, like a new liver metastasis or something that's growing while others are not growing, then I'll actually biopsy fresh to get a higher yield of tissue, to get better chance of getting tumor material to test.

Phillip Koo, MD [00:16:00] That's interesting. So, germline you only need to get once. Somatic testing, are you going to get either the somatic tissue sample or the blood test every time a patient develops a new metastasis?

Russell Szmulewitz, MD [00:16:15] Nobody is quite certain, but what I do is, when there's a major change in the disease course, so a transition from hormone-sensitive to resistant is one of those. If the patient develops a new metastatic location, a visceral disease like liver and lung when they hadn't had it before, or if there's heterogeneous progression where there's some that's been controlled, but there's a bunch more that isn't, and I'm thinking that there might be an evolution, a change in the mutational landscape, then that will be another indication.

Oliver Sartor, MD [00:16:54] I wanted to bring up one thing that may be a little bit off-kilter, but we talked extensively about what we call the oligometastatic disease in the hormone-sensitive setting. At times, that's true within the castrate-resistance setting as well or it can be oligoprogressive. In other words, the patient may have three or four stable lesions but progression on one or two. And I'm welcoming of the opportunity to be able to treat those areas that are oligoprogressive or oligometastatic, even for castrate-resistant disease. And we do have prospective randomized trials that would indicate that the outcome is better when metastasis-directed therapy.

Now, Jason mentioned earlier about how many lesions would constitute oligometastatic disease. The study that I'm thinking of was actually one to five. So, the patients had one to five mutations with metastasis directly therapy. That’s SBRT treated to the metastases, the radiation actually did better. So that's something else to consider in this broad kind of purview of metastatic CRPC.

Phillip Koo, MD [00:17:59] Yeah, I think that's a great point that radiation can be used in this space as well. So, you know, when appropriate, you should go have a referral and consult with RadOnc as well. So, Russell last question for this section. Clinical trials. So, clinical trials in the past, you know, we oftentimes think of it as a last option. Now in CRPC we have so many options, so many studies that help guide us on how we can manage patients. What role does clinical trials have and what advice do you have for patients?

Russell Szmulewitz, MD [00:18:28] It's a great question and PCF being a champion of many of these trials, especially early phase trials. They're crucial. Obviously, from a disease landscape, from a global perspective, this is how we make that next discovery that leads to the next major advance. That being said, for this conversation, it's also a very personal decision, and I would say that, to use the baseball analogy because it's that season, you want as many at-bats as you can. And you don't know which therapy might be the one that really makes a difference for one of these newer investigational clinical trials.

And so, I think that it's always an appropriate question to ask your provider, hey, are there any clinical trials that you think I should look into or that I might be eligible for? And, you know, we have standards of care and they're good. We need to do better. But again, as many at-bats as you can have, the greater the chances of you hitting a double off the wall or something out the park.

Oliver Sartor, MD [00:19:42] Yeah, you know, one of the things just briefly, Phil, you know, all the therapies that we have today, whether it be Pluvicto, abiraterone, docetaxel were first available in clinical trials. Now, we can't always say that a clinical trial is going to be containing a winner. But we look carefully at our clinical trial portfolio. And quite frankly, at times, a clinical trial can be a very good choice for a patient. You have to do your homework, you have to have a good discussion with the patient, the physician, and any other friends and colleagues who might be expert in the field. But at the time, clinical trials could be a great option for patients.

We have a Mr. Mike Morris, not Dr. Mike Morris, but Mr. Morris is gonna be coming on a little bit later talking about his experience with a clinical trial, which is extraordinarily positive. And I'll simply say, without clinical trials, we would not make progress.

Phillip Koo, MD [00:20:35] Agreed. And again, it was said earlier, but we're so grateful to all the patients for being a part of many of these trials that led to these new drugs. So, we're going to shift to the Q&A section. And Russell, I'll start with you. What triggers a cancer to flip from hormone-sensitive to castration-resistant? It's probably not a flip but explain a little bit about the physiology.

Russell Szmulewitz, MD [00:21:04] I must have muted myself. It's a great question. And I think it's one that those of us that try to understand the biology and the science of the disease still beat our heads against. And I don't think it's an all of a sudden thing. So, we have this notion of clonal evolution or over time, the cancer is going to adapt to the therapies we give. So, and that can happen by a couple of ways.

One, you could kill off all the stuff that is sensitive and what's left is inherently resistant, and it grows out to the point that you can detect it, or the cancer is partially sensitive and develops new mutations or new adaptation that renders it the ability to grow despite a low testosterone. And Oliver mentioned earlier that one of the early resistance mechanisms is to become sensitive to very small amounts of hormones. Which is why these ARPIs are very effective if one hasn't received those before. So that's an adaptive mechanism. It makes more of the receptors so that it can survive with low amounts of hormone receptor.

And there are many, both adaptations that are mutation and are transcriptional. It's very heterogeneous. And even within a patient, there can be multiple heterogeneous mechanisms that are driving that resistance. But I don't think it's like an all of a sudden switch.

Phillip Koo, MD [00:22:33] So Oliver, this question's for you. This question comes up often. Patients are on drugs, let's say an ARPI with ADT for a year, two years. How do you approach this idea of a drug holiday? And then the second part would be, how do you know when you need to switch?

Oliver Sartor, MD [00:22:51] Yeah, two great questions. And particularly in the hormone-sensitive setting where we have a terrific, terrific response, we engage in this question about the drug holiday. And I'll simply say that I do it in my practice among those who are

robust responders. In fact, as I just saw a patient yesterday and recommended a drug holiday for him, his PSA was totally undetectable, been undetectable for almost two years. And he was having some side effects from therapy. And we all know that some of the effects of the androgen deprivation and the ARPIs are actually a bit cumulative. Things like muscle loss, weight gain, kind of the general fatigue, osteoporosis, osteopenia that can affect the bones. So, patients and drug holiday is a little bit of a complex discussion, but I do engage in that discussion for patients that have a great response in the hormone-sensitive setting.

Now, drug holiday in the castrate-resistant setting is a little more problematic because rarely do we have these super deep responses, although occasionally we do. So, one of the things that's gotten a lot of discussion is for the lutetium-based therapies, the Pluvictos, like, do you need to have all six [infusions/doses] in a row? Or might you get a couple with a great response, then wait a little while and treat at the time of relapse? These are research questions we're still working through. Bottom line is intermittent therapies, drug holidays, can be part of the discussion, particularly in those patients who are responding well.

Second question, when do you switch? Little more complex, you know, with the way we look at progression in prostate cancer has changed over time. We always have PSA as a parameter, we have imaging as a parameter, we have circulating tumor DNA as a parameter, and we of course have symptoms in classic markers, things like alkaline phosphatase as markers as well. So, I kind of divide the world into some of the biochemical parameters, the radiographic parameters, which are imaging, and the clinical parameters.

If it's just a PSA progression and it's slow, I may just watch a little bit, but a rapid PSA progression is never really a good thing, and that can trigger a switch. Imaging can trigger switch as well, but if it's oligometastatic or oligoprogression, then perhaps I just use a little SBRT and keep everything else the same. For the patient with polymetastatic progression, particularly on imaging accompanied by a rise in PSA, that's a different story. I want to get switching. I want to treat the patient something more effective.

Russ made a really good point about the heterogeneity and the fact that not all the patients are really the same. Sometimes you may just have a break off of a little subclone. Sometimes you have progression that occurs over time. Sometimes it's not even apparent what you have and there can be complex scenarios with progression in the liver and response elsewhere. So, the site of progression, the type of progression, the number of lesions at the time of progression, the markers you're utilizing as well as the circulating tumor DNA and the symptoms can all lead together to what I hope is good decision making, but it's a little bit complex and it's hard to kind of cookie cutter it into something oversimplified.

Phillip Koo, MD [00:26:10] Sure, so this question comes up often, you know, Pluvicto, a very exciting drug that's added another wonderful tool in our armamentarium. Russ, do patients, do they stay on their other drugs, like an ADT and a darolutamide ARPI while they're getting Pluvicto, or you just sort of switch? What's your approach to things like that?

Russell Szmulewitz, MD [00:26:29] It's a great question. I mean, you're asking me when Oliver is the senior author on these studies, but I'll do my best, and he can direct me. So, the VISION study, the one at the end, a post-chemotherapy, that study was standard of

care change, which oftentimes was a switch from abiraterone to enzalutamide or to another hormonal medicine alone or with lutetium. And the pre-chemotherapy PSMAfore study was a switch in hormonal medicines versus the lutetium PSMA alone. And biologically, we think that there might be a reason to keep on hormonal suppression. So, first off, maintain the androgen deprivation, Oliver talked about that. So that's going to be maintained.

The question about the androgen receptors pathway inhibitor is an unanswered one. There's an ongoing study right now that everybody will get lutetium PSMA and half will get an addition of an ARPI added to it because it's really not known. In my practice, if an individual has slow progression, and is tolerating their ARPI well, and their PSMA expression is high, I usually leave it on, at least for the first cycle, where I think it might drive PSMA expression, but I'm interested to know what Oliver would do.

Oliver Sartor, MD [00:28:00] Oh, Russ, I think that was perfect, actually. You know, we don't know a lot of the things we'd like to know. And in the VISION study, we did, in fact, use the ARPI switch for those patients who may not have had prior ARPIs. And there appeared to be kind of a trend toward doing better when you combine the ARPI with the lutetium. But the truth is that there was a selection bias when doing that. And we ran rigorous statistics that didn't really hold up.

There is a prospective trial now, as you alluded to, running everybody getting Pluvicto as a monotherapy and some of the patients getting randomized to receive the ARPI in a second-line setting. Great trial, hope to answer the question. Right now, a little bit of an unknown. I do use an ARPI in combination with Pluvicto, not infrequently, but not dogmatically. So, it's a great question, but we don't always have great answers.

Phillip Koo, MD [00:28:58] So Oliver, really quick, there's a question about actinium. When do we expect to see actinium available routinely in the US?

Oliver Sartor, MD [00:29:06] Yeah, I mean, great question. And I think everybody would like to know that there's some important actinium trials that are in progress right now, both with small molecules as well as antibodies. And for the small molecules, we have PSMA-617, which is the same ligand that is used in the lutetium Pluvicto. But just simply, instead of putting the lutetium, they're using the actinium into the bond or into the chelate. So that study is going to be up and going. There's another compound called PSMA-INT, and this is in the AstraZeneca camp, and they're going to be looking at the actinium bound to the INT molecule, which also targets PSMA. Now, one of the things that you might ask about, but I don't hear a lot of questions, but it's important. The alphas versus the betas. So, the beta particles are things like lutetium-177, we might put terbium-161 in that group. The alphas are the actinium, which is the best known, but they're also a new wave of studies coming with things like lead-212, which is another alpha emitter, or maybe even astatine-211. So, as we look, the trial's gonna have to be performed, both are gonna be available. Now simply say, that with so much activity I am expecting some success, but it probably will not be in 2026. I think the earliest possible would be 2027, it might even be 2028.