Dr. Neal Shore: So we're going to focus, for the next 15 or 18 minutes or so, Dr. Sartor and myself, on the remarkable advances in metastatic hormone-sensitive prostate cancer that tends to subsume biology or the disease burden characteristics that says when we lower the testosterone level, the disease is some is to--for simplistic purposes, is in remission.

And when you see that black box, on top of where it says mHSPC, and this is where we've had a dramatic, number of what we call "doublet" and now "triplet" therapies - that doublet is meaning or couplet therapy is adding testosterone suppression, in addition to an oral agent that blocks the androgen receptor.

We have a lot of different acronyms for this. And sometimes it's confusing: novel hormonal agents, androgen receptor signaling inhibitors. I think there seems to be more and more consensus to call abiraterone and enzalutamide, apalutamide, darolutamide, androgen receptor pathway inhibitors or "ARPIs."

And I think one of the things we've gotten better at for patients and families and caregivers is to try to demystify some of the "word salad soup," I call it, or the acronym confusion.

But ultimately this is working on the androgen receptor, which is one of the key receptors, which stimulates prostate cancer cells in addition to lowering testosterone, which turns on the androgen receptor. And then we, of course, have triplets where we add an oral agent such as darolutamide or abiraterone to well-described benefit of docetaxel, which is a chemotherapy, in more resistant disease.

And, interestingly, that was approved in - the docetaxel and resistant disease was approved in 2004 for the first life-prolonging therapy. 20 years later, we now have about 12 or 14 life-prolonging therapies. So it's really been a great advance in this area. Next slide please.

And this is a busy slide and you'll be able to get this. And I really love this slide. I'm not going to go over it in complete detail, but really what it tells me, what it teaches me, and I think what it teaches everyone listening, is the remarkable benefits that we've had in a 20-year period. Over two decades, we went from docetaxel on the far left and now all the way to the far right. We have PARP inhibitors, which are unique novel mechanism of action. We're going to talk more about that today, as well as the importance--the absolute importance of genetic testing.

Radioligand therapies, which is called out when we see lutetium PSMA-617. There are more to come. We have radio-pharmaceutical benefits from radium-223 back in 2013 and then we also have all the different oral androgen receptor pathway inhibitors, which are described in this timeline. In addition to immunotherapies. In 2010 we had Sipuleucel-T, which was the first immunotherapy approved that had a benefit for survival prolongation in any solid tumor.
Quite a remarkable achievement.

And additionally we see pembrolizumab, which is listed as an indicator when you're doing the appropriate genetic testing and you happen to have the MSI-high, or the MMR alterations.

What this teaches us is that there's so many ways to help patients benefit. The real question is, in addition to shared decision-making, multidisciplinary teams: Are our patients in the United States and globally, for that matter, are they having an active and full-throated discussion on all the opportunities where they can benefit, and that would assume accessibility to the therapies?

Next slide please. And you know, it's grayed out and then it's highlighted here. Not for any particular really important reason. But this is a--just a nice summary of all these really important phase three global trials that have changed the landscape and guidelines, whether it's by … you know, NCCN, approval by FDA, approvals and regulatory inclusion and other guidelines associations around the world, other organizations within the United States, ASCO, AUA.

Really, really important. It speaks to the wonderment that I continue to have regarding clinical trials and how absolutely important they are. And, you know, it's PCF and other really great nonprofit organizations that fund these trials that lead to life-prolonging therapies.

As you can see, when on the far right of the slide, the benefit of no longer just having monotherapy ADT. So let me stop with that, Oliver, and try to get some--what are some of your thoughts? I covered a lot. And it's a bit overwhelming, but the folks will be able to get these slides, from an archival standpoint, after we're done.

Dr. Oliver Sartor: Gosh, thank you, Neal. And really beautiful introduction. You know, I'm going to focus kind of from the perspective of patients who have just been diagnosed with advanced prostate cancer. What are the most important things that you want to convey to that patient? This is a newly diagnosed metastatic prostate cancer, what do you want that patient to think about?

Dr. Neal Shore: Yeah. First of all, anybody getting a diagnosis of cancer. It's a devastating thing to have that stamped on your life portfolio, your life passport. And you know, oftentimes that requires, you know, opportunity for the patient and their family to digest that and try to better understand where they are and making their decisions.

I think that the thing that I always like to explain to my patients and their families and their caregivers is that we have a multitude of options for them, and we've made these great advances that we saw in that--those earlier slides on these timelines. With advanced disease, meaning disease that spreads outside the prostate, we can't really very comfortably say, “well, I'm going to cure you. I'm going to completely eradicate this disease.” But that is absolutely our goal. That's your goal. That's my goal. I know that's Drs. Heath and Morgans when they come on.

And that's what we keep striving for. And so going from 2004 with the approval of a taxane chemotherapy, now into 2024, two decades later,

there's a multitude of therapies, not just when the disease is metastatic and sensitive, but later on we'll have additional lines of therapy that we need to be judicious about how we sequence these for the patient. It's really incumbent upon the physician, regardless of their specialty, to make sure they can explain to the patient and their support team what their options are.

Dr. Oliver Sartor: You know, one of the things that's a little bit interesting, Neal, we have newer imaging. And I didn't hear much about the newer imaging, things like PSMA-PET. And I wonder if you might sort of bring the idea of oligometastatic disease to our listeners.

I didn't quite hear that during the first part, but I think it's increasingly one of the discussion items during the PSMA-PET era.

Dr. Neal Shore: Yeah, it's a great question. You know, we talk about, you know, the PSMA-PET era, which is here now. We were a little bit delayed in the United States. Many of our colleagues in other parts of the world, Germany, Australia, Northern Europe, even parts of Latin America had access to the PSMA--prostate specific membrane antigen--PET scan prior to us getting really, accessibility. And all things typically American, now that we've gotten approval a couple of years ago—PSMA PET, there's numerous different modalities with different sponsors fortunately, which now make it rather, very accessible throughout the United States, which I think is great. And the distinction is, is that we talk about conventional imaging, and I think that the listeners should understand conventional imaging is the full body CT scan with and without contrast.
As well as a Technetium bone scan.

The PSMA PET scans really give you a much greater accuracy, higher sensitivity to where disease is on smaller volumes. And there's still a big learning curve that's going on. But baked into your question is, “well, what if we have low-volume disease?”

Is there an opportunity to use localized radiation therapy, perhaps early on, in conjunction with or without testosterone suppression, with or without, oral ARPIs. And this is an area that is really ripe for ongoing trials. Many of them are ongoing. And a lot of that decision is very, very important to do in a multidisciplinary way.

Dr. Oliver Sartor: Right. Thank you. Neal. Imagine for a moment if someone is diagnosed and I call it “polymetastatic disease,” beyond that which we would refer to as “oligometastatic.”

I wonder if you could help patients understand what degree of remission or time on initial therapy they might be able to anticipate. And yes, we're all hopeful, but now we have multiple ARPI trials that sort of indicate “X” amount. What might that “X” be for somebody diagnosed with metastatic disease from the get-go? How long can they expect to be controlled with ARPI, ADT type regimens?

Dr. Neal Shore: Yeah, it's such a vital question. I love it because that is a very commonly asked question. “Oh, how long am I going to be on this disease, doctor? --I'm sorry, “on this therapy?” And the answer is I tend

to break it down into, I call it a “three-legged stool” to--for simplicity purposes.

First and foremost, are you tolerating the therapy well? Are you having any toxicities or side effects? The PCWG, the prostate cancer working group, you know, years ago came up with this really, kind of wonderful acronym called “no longer clinically benefiting.” And I think that's very, very important. Are you tolerating this therapy? Well, that's first and foremost. So subjectively, how are you doing? Are you feeling well on the therapy? Quality of life matters. The second two are the two other parameters of that three-legged stool are, of course, there's labs and everybody tends to overly focus, but appropriately to some degree on the PSA.

What's the PSA doing? And I finally like to tell everyone, you know, PSA oftentimes, rather than prostate specific antigen, stands for patient-physician stimulated anxiety. But we look at PSA. We look at all the other lab work the CBC, the CMP, the complete metabolic profile, genetic testing, which we're going to talk about later. So lab parameters, subjective parameters, and third is imaging. As you said earlier, we're entering this new era moving away from conventional imaging and more into reliance upon PSMA PET.

As a general rule, new lesions are a real problem. Stabilization of disease, regression is even better, but as long as they're not new lesions, we're very happy.

The answer to, you know, the black and white. Well, how long will I be on the therapy? It can be as short as only a few months to even a couple - a few years. And that goes to this notion around heterogeneity, which I think keeps us all so fascinated by the art of medicine and how heterogeneity - just because I have metastatic prostate cancer and my neighbor does, and maybe my uncle and, or my brother, that biology can be very, very, different. And so everybody can respond fairly differently. And so it's not always so easy to say, “well, you're only going to be on this X number of months or years.” We always hope for the best for the duration of response to be as long as possible.