Becky Campbell: We’re going to shift to a disease state where the cancer continues to progress despite low testosterone.

So, Dr. Sartor, I'd like to bring you back on to kick off this session with Dr. Morgans, and Dr. Morgans, I know you have some very informative slides to share with us about this disease state. So, thank you so much, Dr. Morgans and Dr. Sartor.

Dr. Alicia Morgans: Alright, and thank you, Becky, for that kind introduction, and Oliver for working with me on this section. So, this is a jam-packed session. So we'll try to go through succinctly, but happy to take questions as we end. So what is metastatic castration resistant prostate cancer?

I think that many people on this webinar know that the majority of prostate cancer is actually defined as localized prostate cancer. So you may see a bar chart here, sort of on the left-hand side of this slide, that shows the percentage of patients who are diagnosed at different stages: localized, regional, which generally means pelvic lymph nodes around the prostate might be involved with the cancer, and distant, which means that the cancer has spread outside of the prostate, outside of the pelvis, and into something farther away.

Maybe we would term that metastatic, and you could see that the bar on the left-hand side there is much higher than the other two bars because most patients have localized prostate cancer, whether it's low, intermediate, or high risk at the time of diagnosis.

But what's also illustrated on this slide is that there's about a 20 to 40% chance of patients, particularly with high-risk disease, to have that cancer come back.

And there are some high-risk features in the table on the right hand-side of the slide that make the likelihood of the cancer coming back and potentially becoming metastatic, make that higher chance of happening. Things that can be in that category that make it a higher risk include things like a PSA being over 20, a Gleason score being over eight, a large tumor that's extending outside of the prostate, or the overall constellation of factors that we would call “high-risk disease,” which are actually the three factors above.

So, many patients diagnosed with localized disease can develop metastatic disease that has spread outside of the prostate. I think we also know, and this is another schematic, trying to help us understand the different stages of prostate cancer, that as we move from the left-hand side of this slide to the right-hand side of this slide, the stage of the prostate cancer in terms of its treatment history, are moving forward, marching down the treatment pathway.

On the left-hand slide, this is really illustrating the number of patients with that localized disease diagnosis. And then BCR in the green bubble represents the patients who have biochemical recurrent disease or a rising PSA after their treatment. If we follow the pathway up to the top where many patients end up finding themselves, if they have recurrent prostate

cancer, that blue circle represents metastatic hormone-sensitive prostate cancer.

This means that the cancer has spread outside of the prostate, but, if we start something like androgen deprivation therapy or ADT and lower testosterone levels, that cancer is going to actually start to starve and shut down and really be injured, impaired, stalled by that low hormone level. However, those cancer cells, which are really shut down by having low levels of testosterone at first, can ultimately progress over time and start to be able to grow, spread, divide, cause trouble, even though there's no testosterone, there's no fuel around to drive them, but they find other forms of fuel or they start making their own testosterone. So that's what we call "castration-resistant." That's if we move to the right again and find ourselves in that orange-yellow ball or bubble, "M" stands for metastatic. "CRPC" stands for castration-resistant prostate cancer. Castration is the way that we describe low levels of testosterone, whether we've caused it by a medication or whether we've caused it by surgery, and if we are castration-resistant, that means that cancer can grow despite, or in spite of low levels of testosterone, despite, or in spite of having castrate levels of testosterone.

And really, we're going to focus for this discussion on patients who have cancer that spread outside of the prostate. And the cancer can grow, even though we've already tried to stop it by causing low levels of testosterone. And there are multiple lines of therapy there.

This is a very--another very busy slide, and I want to focus all of our attention on the right side of this slide where we see orange boxes also labeled "mCRPC." Just like that last slide with those bubbles. If you look below those mCRPC boxes, metastatic castration-resistant prostate cancer boxes, you can see there's a list of many different treatments things like chemotherapies, docetaxel and cabazitaxel, immunotherapy like Sipuleucel-T or Provenge and abiraterone and enzalutamide, which are testosterone receptor-targeting agents or agents that decrease testosterone production. And these are all options. And in the box below, the orange outlined box, we see newer things too, like Lutetium-PSMA, also Olaparib, Rucaparib, over to the right. These are PARP inhibitors. So the number of treatments has expanded and expanded and includes all of these options in the mCRPC space.

Here I have a final schematic to help us get things under in sort of in context. mCRPC first line, mCRPC second line representing multiple lines of treatment in that advanced castration-resistant setting. And I've listed many, many different options. And the take home message here is there's lots of stuff that we can do in these advanced settings. And they involve lots of different approaches to treatment. And that's important because the mechanism of action, the way that we attack the cancer, needs to be different along the journey, so that the cancer cells that might be resistant to one approach are hopefully not going to be resistant to the next approach or the next approach or the next approach.

So let's go through some of them and just highlight some key concepts. So genetic mutations can be quite common in this advanced prostate cancer setting with mCRPC. Over 20% of people will have DNA mutations,

essentially. So mutations in the code book that designs and dictate how each cell is made, there's mutations in that code book. And those DNA repair changes can actually be targeted with certain medicines. We know that the number of these mutations actually increases with each step down that advanced prostate cancer pathway we go. And so it's really important for us to do genetic testing to understand if a person has something that we can target with treatment. These are the guidelines that help us as physicians understand how to best make sure that we do all the things we need to do in taking care of a patient with prostate cancer and actually for other cancers as well, there are separate guidelines.

And what this is specifically outlining is that if a patient has prostate cancer and has metastatic prostate cancer, that spread outside of the prostate or has high risk features in that prostate cancer, or if that person is of Ashkenazi Jewish heritage, we should be checking their genetics to understand the type of genetics that inform us as to whether they might have inherited something from their family that could be driving their prostate cancer.

There is another type of genetics, and that's called somatic genetics. That's in the middle of this table here. Somatic mutations. These are mutations that happen only in the prostate cancer itself, not in the person. It didn't come from their family. It happened by chance in that cancer cell. And somatic mutations, in that column, and germline mutations, which are mutations that come from our family are present in prostate cancer cells and can be targeted. Either type can be targeted. And if we look back at mutations, BRCA2 mutations, in particular, are the most common somatic mutations and the most common germline mutations.

For a combined rate of happening in patients with metastatic castration resistant prostate cancer of around 10%, and these are the ones that are most responsive to our treatments: PARP inhibitors.

So DNA is the instruction manual for cells, I mentioned that before. It's always being copied. And when it's being copied so that cells can replicate or duplicate themselves, errors happen, does not go perfectly.

And PARP proteins, just a type of protein in our system, is basically the spellcheck that's trying to come in and fix those errors. If those proteins don't do their job and the DNA is not repaired, the cell will self-destruct. So what we try to do, is stop those PARP proteins with inhibitors so they can't repair the spellcheck errors, and the cells self-destruct.

So we have two drugs that are now approved to stop that protein from fixing things through Rucaparib and Olaparib.
And those are both drugs that target those mutations that are causing these--that would normally repair the errors in DNA. So these are PARP inhibitors approved for patients who have these mutations with metastatic CRPC.

And here we can see curves that are in our large studies that try to show us which arm is better, which treatment is better, with one treatment being illustrated here in a blue line. And another treatment being

illustrated in a red line. And what we can see is the curves do not touch each other. They're separated, suggesting that there's a difference between the two options, and in both of these options, the Olaparib, the blue line, is better than the red line, which is the other treatment option in these studies. These are a little bit easier to interpret, perhaps. The lines going down from the black line--that's the horizontal line--show that there's shrinkage of tumor when treated with Rucaparib, on the left, and a decrease in PSA because the lines are going down below that black line on the right, again, when patients are treated with Rucaparib. So we have to think about side effects here, low blood counts GI effects, nausea, those kinds of things. And we can support patients to get them, but we have to watch these side effects.

And the other thing I'll say about these PARP inhibitors is that we can combine them with things like Enzalutamide or abiraterone hormone treatments, and we can maybe even be more effective with that combination. So now there are three combinations of PARP inhibitors. And those hormonal treatments approved for treatment of metastatic-castration resistant prostate cancer with these mutations.

Pembrolizumab is also something that we have to be aware of in immunotherapy for mCRPC for patients with certain mutations in MSH or MLH genes, as well as PMS2 and several others.

And what we can see here is that, although these are very rare mutations, only 2 to 3% of people having them, on the right, we can see CT scans or CAT scans that show that the little things that we've outlined, areas of disease actually shrink down really, really beautifully. And PSA can decrease with treatment with pembrolizumab, but really only for people who have these certain mutations. So we have to look for the mutations to treat them.

And then just to sort of round this out, Lutetium PSMA-617, also called Pluvicto, is an agent that is a radioactive agent that targets a protein on the cell surface called PSMA. On the left-hand side of the picture, we can see a blue, little thing. It looks almost like a turret on a castle, that is a PSMA protein, and it is being targeted by a PSMA-targeting small molecule with a radioactive lutetium particle on there. You could see sort of see all the radioactivity in blue shooting out from that particle. And what we can see is that these PET scans, which are showing areas of prostate cancer in red, they are lighting up areas of prostate cancer that has a little PSMA protein on its surface.

If we treat these areas, we can make that protein go away in follow up scans, if the treatment is highly effective for that individual person. And so we use this targeted treatment in many places across the pathway. And this schematic is a very simple schematic that's similar to the schematics I showed at the beginning going from localized prostate cancer all in the prostate on the left all the way to the most advanced mCRPC prostate cancer all the way on the right. And below that arrow, we can see the names of lots of different studies that have led to the integration and potentially someday will lead to the approval of Lutetium PSMA-617 or Pluvicto in various places to treat patients with mCRPC. Right now we can

use this drug after chemotherapy and after abiraterone or enzalutamide or one of those hormonal type pills. We'll see if we can move it sooner. And these are the curves that show that separation, with the blue curve being better in both settings. Showing the lutetium PSMA-617 treatment over the alternate treatment in the yellow.

So in conclusion, the treatment of these patients really is evolving rapidly. We can use things like PARP inhibitors on their own or in combination with hormone treatments to try to control the cancer for people with certain mutations. And the earlier we use those, I think it could be better. We can use PET scans to show who might be eligible for treatment with things like lutetium PSMA-617 or Pluvicto right now after chemotherapy and hormone pills, but perhaps before chemotherapy in the future.

And it's always important to think about clinical trials for these patients, as well. So I'm going to stop sharing and bring in Oliver to have any discussion if we have any time left.

Dr. Oliver Sartor: Thanks, Alicia. we just have a couple of quick questions, I'll shoot. Number one: neuroendocrine prostate cancer is something a lot of people talk about. I didn't hear it mentioned in your slides. Tell us briefly about neuroendocrine and how you might handle that particular disease.

Dr. Alicia Morgans: Sure. So neuroendocrine is actually relatively rare in terms of prostate cancer but can happen. These patients are usually treated with combination chemotherapy first.

So in addition to hormonal suppressive treatments like androgen deprivation therapy or ADT, usually we use a platinum-type chemo and often use that in combination with etoposide as our first try. And then there are newer agents targeting things like proteins on small cell cancer surface, like DLL, that might be useful in the future.

There was a drug recently approved for small cell cancer in the lungs, tarlatamab, that actually may be used and has been obtained, I know for several patients off label, when they have this high-grade neuroendocrine tumor that's actually called small cell, the highest grade of neuroendocrine tumors.

So there are these treatments, I think, that are increasingly being investigated that may ultimately become available. But I would encourage anyone with small cell or high-grade neuroendocrine tumor to try to make sure that they're seen by a Center of Excellence and consider clinical trial enrollment, because this is an area where there are fewer easy options, easy being all relative, there's no easy options for any of these patients or people to use. But they can be intensive therapies that can be hard to take. But new clinical trials are trying to think about new ways to support patients, investigate treatments that may be less intensive and less challenging for people to use.

Dr. Oliver Sartor: And one more question for you. This is a tough one. The patients get treated, they go through multiple options, and then they've

exhausted their conventional FDA approved options. How do you approach a patient like that? What do you tell the patient who might have exhausted all the conventional options?

Dr. Alicia Morgans: Well, you know, this is also something that happens to people, because we do have a lot of treatment options. But these options, none of them work forever. And so I think we are fortunate in that we often will have a clinical trial available for someone to try if they don't have standard options available, or I will reach out to friends who might have clinical trials available at other institutions for patients who can travel. And just for patients to be aware, the National Cancer Institute, if there's a trial for you that might work down there, they actually will pay for your travel. They'll pay for your lodging to go to the NCI and go for a clinical trial treatment there. But in other places, obviously patients would need to pay for their travel and lodging. So that can be hard, too. I think, you know, if patients really do want to stay local and there's nothing else, sometimes there comes a point where we focus, because we don't have cancer-directed treatments anymore, on living every day to be the best it can be, and I think that people need to do this across the course of their treatment and hopefully can do this even as they're on different treatments. But at some point, it can be the case that there aren't any more cancer-directed things that we can do. And so we transition to making sure that people have pain control, that they have their family around, that they have the resources they need to not have symptoms that really, that they can't control. And we try to support them, even still, to make sure that those symptoms are well managed and that they can still have good days.

Dr. Oliver Sartor: Yeah. And, you know, those are often very difficult conversations. And, so I agree with you, Alicia. We do our best. We offer clinical trials when there's an opportunity to be able to benefit people with nonstandard therapies. But we have to be cognizant of our limitations. You know, unfortunately, we're dealing with non-curative diseases here. So the castrate-resistant prostate cancer is not curable, and we end up facing tough decisions.