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Optimizing mCRPC Care: Treatment Selection and Sequencing Strategies

Dr. Turck:
Welcome to *Project Oncology* on ReachMD. I'm Dr. Charles Turck, and joining me to discuss treatment selection and sequencing for patients with metastatic castration-resistant prostate cancer are Drs. Hannah McManus and Andrew Armstrong. Dr. McManus is a medical oncologist and an Assistant Professor of Medicine at Duke University and also works at the Duke Cancer Institute Center for Prostate and Urologic Cancers. Dr. McManus, thanks for being here today.

Dr. McManus:
Yeah, thanks so much for having me. Excited to talk with you.

Dr. Turck:
And not only is Dr. Armstrong a Professor of Medicine, Surgery, Pharmacology, and Cancer Biology at Duke University, but he's also the Director of Research at the Duke Cancer Institute Center for Prostate and Urologic Cancers. Dr. Armstrong, it's great to have you with us as well.

Dr. Armstrong:
Thank you, Dr. Turck. Pleasure to be here with Hannah too.

Dr. Turck:
Well, starting with you, Dr. McManus, what do you consider when selecting an initial therapy? And how do patient-specific factors like comorbidities and prior treatments influence that?

Dr. McManus:
Yeah, it's an important question talking about our patients here specifically with metastatic castration-resistant prostate cancer where we typically have multiple therapeutic options to really balance individual patient factors to help select with them what the optimal therapy for them is. And so you mentioned, I think, some really important factors amongst many, but those are really those patient-specific factors, which can be cancer related; so what prior therapies have they had to help us decide what might be active therapies after those therapies; but then also patient-specific things like comorbidities performance status; and even then I think it's important always to put in their patient goals, preferences, and those nonmedical patient-specific factors as well to think about what that optimal therapy might be for that individual. I think trying to strike a balance there of efficacy—giving them the best cancer outcome—but also balancing that with quality of life and what that patient strikes as their major priorities.

Dr. Turck:
And how about you, Dr. Armstrong? How do you assess therapeutic options for patients taking into account aspects like treatment history and disease progression?

Dr. Armstrong:
I completely agree with Hannah. I mean, it's always about shared decision-making; getting as much information you can about the patient and their cancer, genetic testing, both germline and somatic, and really help inform that first decision. A PSMA PET scan—if they already had an AR pathway inhibitor—may inform that initial frontline mCRPC therapy. But just listening to the patient's experience with those prior therapies, if they have had docetaxel and had a rough experience with that, they may not be eager to go right to another taxane but may be looking for an alternative mechanism of attack against that cancer. And like Hannah said, balancing quality of life and that shared decision-making is really how we should approach this.

Dr. Turck:
And coming back to you, Dr. McManus, would you elaborate on the impact of cross-resistance in metastatic disease and how therapies with novel mechanisms of action can help us navigate that challenge?

Dr. McManus:
I think this is really evolving as our treatment landscape for earlier settings of disease changes as well. So we talk about cross-resistance in the context of choosing therapies because while we have multiple mechanisms of action for our therapies, some overlap. So Andy mentioned our androgen-receptor pathway inhibitors. We have multiple agents within that space. And while there can be some activity using one after another, we know from multiple studies at this point that kind of sequential use can limit the efficacy of a subsequent AR pathway inhibitor. And so I think about those factors when meeting that patient and hearing what their prior therapies have been to help say, "Do I think each individual therapy may have more or less efficacy for that patient?"

Dr. Turck:
For those just tuning in, you're listening to *Project Oncology* on ReachMD. I'm Dr. Charles Turck, and I'm speaking with Drs. Hannah McManus and Andrew Armstrong about the factors they consider when selecting treatments for patients with metastatic castration-resistant prostate cancer.

Now, Dr. Armstrong, how do you approach treatment sequencing, particularly when transitioning from androgen-receptor targeted therapies to other options like conventional chemotherapy or radioligand therapy?

Dr. Armstrong:
Absolutely. So in the review article that accompanies this podcast, we lay out all the level 1 evidence for life-prolonging therapies, and then we have some very nice tables and figures that give you a synopsis and a flow chart for how to think about patients that incorporate tumor genetics, prior therapies, patient host factors, comorbidities, and side effects that patients experience as well as costs and health economics. Other factors that are really emerging are the PSMA PET avidity of that tumor. We're getting into much more precision medicine where we're incorporating things like DNA repair deficiencies to select PARP inhibitors. We're using PSMA PET positivity to select PSMA radioligand therapies; mismatch repair deficiencies for that rare subgroup of patients really can respond beautifully to PD-1 blockade.

Most patients, unfortunately, don't have actionable genetics. It's probably about 75 percent of patients. So in those patients, we're talking about different mechanisms of attack against the cancer to extend life as long as we can and offering patients as many of these therapies along their journey as possible, whether that's Sipuleucel-T, an autologous cellular immunotherapy; radium; a bone-targeted radiopharmaceutical; first- and second-line taxane chemotherapies, docetaxel, cabazitaxel; and then, of course, PSMA lutetium, which is probably one of the more exciting therapies in the past two years. And we're just seeing the PSMAfore trial get published where we're seeing benefits irrespective of whether you've had docetaxel or not, and that's certainly weighing on the FDA's decision-making right now as far as whether to offer that as an approved option before docetaxel.

So in our center at Duke University, most of our patients are receiving an AR pathway inhibitor in the hormone-sensitive setting or in the nonmetastatic setting prior to mCRPC, so by the time that I see and probably Hannah sees an mCRPC patient, really they're post ARPI, and so deciding which of those patients is appropriate for a second ARPI, perhaps those with slow progression, low-volume disease, lower-risk disease, or those who need a more aggressive non-cross-resistant approach, such as those with pain, rapid progression, visceral metastases particularly in the liver, and then opening up the options for PSMA lutetium as that becomes approved in the next couple months.

Dr. Turck:
And, Dr. McManus, I wanted to get your take on the roles of biomarkers and genetic profiling and treatment sequencing and how we can optimize related testing.

Dr. McManus:
Yeah, absolutely. Building on some really good points Andy made there, biomarker and genetic profiling I think are increasingly important and already extremely important parts of how we make these upfront decisions. From a biomarker standpoint, I think about the sort of PSMA PET avidity outside of our genetic testing. You can use factors like sites of disease. But then in the genetic testing setting, there's several findings that are really actionable, so that small but very important group of patients with homologous recombination repair deficiency; and then smaller, but I think also important are patients that may have microsatellite instability or high tumor mutational burdens. For each of these, the former opening up our PARP inhibitors or now even PARP inhibitor androgen receptor pathway inhibitor combinations, or for that latter group of patients, this is a setting where our immune checkpoint inhibitors can have some efficacy. And so it's really important to have this testing to be able to offer those options, right? You don't know that a patient has

one of these genetic changes if you haven't done the testing, and so I tend to do this testing early, so in the metastatic hormone-sensitive setting if I'm seeing patients before then so that you have sort of that data available for treatment options; but then, potentially repeating testing at disease progression I think is another kind of lesser used but important feature just to being adapting as the disease is adapting.

Dr. Turck:
And finally, Dr. Armstrong, taking out your crystal ball for a moment, which ongoing studies do you think hold the most potential to redefine future treatment options for metastatic castration-resistant prostate cancer?

Dr. Armstrong:
Well, that's a big question, and I like to think of prostate cancer in different buckets here. When a patient has developed progression despite an AR pathway inhibitor, we know from biopsy studies that there are several different types of genetically defined types of prostate cancer. There's the ones that remain very dependent on the androgen receptor where that tumor undergoes activation, amplification, and alternative splice variants that mediate cross-resistance. We're working on that subset of patients with newer AR degraders, cofactor inhibitors, and new radioligands, such as PSMA or HK2, everything that we can do to target that hormone-dependent tumor. Even though it's resistant to our commonly used conventional hormone therapies, it doesn't mean that we can't get more mileage and survival benefits from tackling that hormone signaling.

The second type is really tumors that have lost that hormone dependence, and we have neuroendocrine or small-cell transformations, really a different type of prostate cancer that makes different markers, loses PSA, has bulky disease, and a very poor prognosis—probably our biggest unmet need in all of prostate cancer—and trials are looking at newer radioligands, combinations of chemotherapy and immunotherapy like our ongoing CHAMP study, and new targets like DLL3 and GPC3; some of the newer targets that are able to be used in antibody drug conjugates, radioimmunotherapies, BiTEs, and CAR T-cells are really tackling a very different kind of cancer.

And then the final bucket is those tumors that have lost all those markers, so not neuroendocrine and not hormone dependent. We call those double-negative prostate cancers. That's also a very big challenge because we're looking for markers, and I think finding those cell surface antigens helps with drug development, again tackling those antigens specifically. And so getting a sense for the precision medicine biology will help inform those tumor treatments. So that's a very broad answer, but lots of potential for success.

Dr. Turck:
Well, with those forward-looking thoughts in mind, I want to thank my guests, Drs. Hannah McManus and Andrew Armstrong, for joining me to discuss therapeutic sequencing and selection in metastatic castration-resistant prostate cancer. Dr. McManus, Dr. Armstrong, it was great having you both on the program.

Dr. McManus:
Thank you so much. It was a joy to talk with you. And putting a plug, check out our review article with sort of more details on this great conversation we had today.

Dr. Armstrong:
Thank you, Dr. Turck. It was a pleasure being with you both.

Dr. Turck:
For ReachMD, I'm Dr. Charles Turck. To access this and other episodes in our series, visit *Project Oncology* on ReachMD.com, where you can Be Part of the Knowledge. Thanks for listening.