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Choosing the Right ARPI in Metastatic Castration-Sensitive Prostate Cancer

Dr. McDonough:
This is *Project Oncology* on ReachMD, and I'm Dr. Brian McDonough. Today, I am joined by Dr. Bilal Siddiqui to explore how patient characteristics can guide the selection of androgen receptor, or AR, pathway inhibitors in metastatic castration-sensitive prostate cancer. Dr. Siddiqui is an Assistant Professor in the Department of Genitourinary Medical Oncology at the University of Texas MD Anderson Cancer Center in Houston.

Dr. Siddiqui, it's great to have you here today.

Dr. Siddiqui:
Thank you so much for having me.

Dr. McDonough:
Let's start by setting the stage, Dr. Siddiqui. Why has it become so important to individualize therapy when selecting an AR pathway inhibitor for patients with newly diagnosed metastatic castration sensitive prostate cancer?

Dr. Siddiqui:
So in 2026, it's clear that the addition of an androgen receptor pathway inhibitor, or ARPI, to standard androgen deprivation therapy improves clinical outcomes with our patients. So it's a matter now of which ARPI to give to our patients. There are four that are FDA approved: enzalutamide, apalutamide, and darolutamide—the direct androgen receptor antagonists—as well as abiraterone, the androgen biosynthesis inhibitor. So our treatment decisions go beyond simply adding an AR pathway inhibitor to, which one is the best drug for the patient?

And there are a few different factors and a few different considerations that we take into account that can drive our variability and our outcomes. These are heterogeneity of the patients themselves. These include their age, their comorbidities, their functional status, as well as their concomitant medications that they're on, the differences among the drugs in terms of their safety profiles, their drug-drug interactions, as well as the impact that each of them has on quality of life. This means that we can't simply adopt a one-size-fits-all approach for our patients here.

Dr. McDonough:
With that context in mind, what are the most important patient specific factors you consider? And how do they influence your treatment selection?

Dr. Siddiqui:
So the most important things that I think about when I am counseling a patient—and when I'm teaching the fellows about how to select these drugs—are the side effect profile, drug-drug interactions, cost, comorbidities, as well as that patient's functional status.

And it's really important to note that chronological age does not equal biological age. Functional status and physiologic reserve is really important when we're addressing these patients. A single age cutoff, for example, is insufficient here. So ECOG performance status remains really important for us to anchor our patient's performance status, and the comorbidities and overall health conditions that they have also shape how we think the patient is going to tolerate these drugs.

So taking all of those factors into account—performance status, chronological but more so biological age, drug-drug interactions, and cost—really helps guide our decision.

Dr. McDonough:

Now, cardiovascular risk often comes up when choosing an agent. So how do you evaluate and weigh those risks when selecting an AR-targeted therapy?

Dr. Siddiqui:
So it's important to note that the treatment selection comes down to more of a risk mitigation rather than a complete absolute contraindication or strict exclusion from criteria.

And I generally think about the risks differently for the androgen biosynthesis inhibitor abiraterone as opposed to the AR antagonists. So abiraterone is most commonly associated with mineralocorticoid-related events such as hypertension and fluid retention. We worry about its use in patients with heart failure, and there is a low but non-zero risk of cardiac arrhythmias. And so I'm careful with it in patients with an arrhythmia history such as atrial fibrillation.

The other AR inhibitors also have their own cardiovascular considerations, chiefly hypertension, but they have different patterns of risks. So I take into account history of heart failure, hypertension, and coronary disease when I'm choosing among these agents.

Dr. McDonough:
For those just tuning in, you're listening to *Project Oncology* on ReachMD. I'm Dr. Brian McDonough, and I'm speaking with Dr. Bilal Siddiqui about personalized treatment selection in metastatic castration-sensitive prostate cancer.

So, Dr. Siddiqui let's now focus on how disease characteristics influence the decision-making process. What role do disease volume, visceral metastases, or aggressive features play when you're choosing an AR pathway inhibitor?

Dr. Siddiqui:
So we've known for years now that the outcomes are different based on some of these prognostic features such as disease volume. And a common set of criteria we use are what are known as the CHAARTED volume criteria. So high volume disease by CHAARTED criteria is four or more bone metastases, one of which being outside of the axial skeleton, or the presence of a visceral metastasis. These are patients, overall, with a poor prognosis, and these are patients in whom, in the original CHAARTED study, benefited from the addition of docetaxel chemotherapy.

And so as we think about these patients with more aggressive disease in whom we are considering for docetaxel chemotherapy, there are two clinical trials that have given us randomized, phase three evidence. And these are the ARASENS study, with darolutamide added to ADT plus docetaxel, and abiraterone in the PEACE-1 study, added to docetaxel. So if I have a patient with aggressive disease biology in whom I'm adding docetaxel, I will choose either abiraterone or darolutamide in that setting.

Now, that being said, not every patient with high volume disease by CHAARTED criteria necessarily requires docetaxel. And so if we are not adding docetaxel in that setting, then any of the four AR pathway inhibitors are generally appropriate here. And so again, we often have to interpret our efficacy data and our decision to choose therapies based on the individual patient in front of us, not simply the generalized data that we get from the clinical trials.

Dr. McDonough:
Now, given that there are long treatment durations in metastatic castration-sensitive prostate cancer, how do you balance efficacy with side effect profiles and quality of life considerations?

Dr. Siddiqui:
This is absolutely critical, as the lifespan for our patients with metastatic prostate cancer is lengthening over time—which is a great thing. But patients will be on these therapies for years. So these side effects play a really important role in our conversation.

So I discuss with my patients what the different side effect profiles look like and what that means for them. I'll give you one patient example, of someone who is a lawyer and needs to do really intensive cognitive work. And for that patient, enzalutamide and the risk of cognitive impairment that came with that was a dealbreaker. Now, the other drugs can also contribute. It can also contribute to this, so it has to be a really personalized decision. And the quality-of-life elements here are increasingly central because of this prolonged therapy duration.

The other thing that I often discuss with our patients—for those who are able to achieve an excellent response to therapy—is that intermittent strategies are also very important in terms of giving them time with testosterone and mitigating some of these side effects that come with them.

Dr. McDonough:
Before we wrap up our discussion, Dr. Siddiqui, let's really anchor this in everyday practice. What are the most important steps that our audience can follow to match the right AR pathway inhibitor to the right patient?

Dr. Siddiqui:
It's important to individualize. This is decision making that is layered; it's not necessarily algorithmic. But one approach to start with is assess the general eligibility for those drugs, then the comorbidities, the medications and the drug-drug interactions, and the patient preferences—what side effects they may be willing to accept and what they may not be.

So we often talk about the fatigue and the cognitive side effects that come with enzalutamide, but I have had patients who have told me that they're exceedingly worried about the skin toxicities that come with apalutamide, for example. And maybe they're unwilling to accept those. And so our goal is to align the drug characteristics with the patient context and their values and not try to develop one single one-size-fits-all ranking for these agents.

Dr. McDonough:
Those are very helpful takeaways for us to think on as we come to the end of today's program. And I want to thank my guest, Dr. Bilal Siddiqui, for joining me to share these real-world strategies for selecting AR-targeted therapy in metastatic castration-sensitive prostate cancer. Dr. Siddiqui, thank you so much for joining us.

Dr. Siddiqui:
Thanks very much.

Dr. McDonough:
For ReachMD, I'm Dr. Brian McDonough. 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.