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ReachMD
www.reachmd.com
info@reachmd.com
(866) 423-7849

Making the Right Moves in Metastatic CSPC: Intensification, Imaging, and Impact

Announcer:
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Dr. Agarwal:
Hi. My name is Dr. Neeraj Agarwal. I'm a professor of medicine in medical oncology specializing in prostate cancer at the Huntsman Cancer Institute, University of Utah, Salt Lake City. We have the pleasure and honor of having Dr. Rana McKay talking about the metastatic castration-sensitive prostate cancer, the recent developments, and insights.

Dr. McKay:
Rana McKay. I'm a GU medical oncologist at the University of California in San Diego, and it's a pleasure for me to be here with you today.

Dr. Agarwal:
So which patients, Rana, benefit most from intensified combination strategies? And let's explore that today.

Dr. McKay:
Thank you so much for that question. I think we've proven time and time again that the addition of ARPI to the backbone of ADT improves overall survival, and that is the rationale to move forward with this strategy for the majority of patients who present with metastatic hormone-sensitive disease.

I think the big question is more so around which ARPI, and whether patients should get triplet therapy versus doublet therapy, as opposed to whether you should give ADT alone.

There are a lot of things to consider, and I like to break it up into 3 buckets. What are the clinical factors? What are the disease-related factors? And what are other psychosocial issues to consider?

When we think about the disease-related factors, we're largely talking about volume of disease—high-volume, low- volume. We're talking about presence of visceral mets—liver mets, lung mets. We're talking about synchronous versus asynchronous disease—symptomatic disease and symptomatology. Maybe it may be genetic features, tumor suppressor gene loss alterations, HRR gene alterations. Those are all really critically important disease-related factors to consider.

When we talk about patient-derived factors, I think it's important to think of patients' comorbidities, their polypharmacy, their fitness level, frailty, what's their ability to do their ADLs independently, caregiver support are all things to consider around intensifying therapy.

Also, psychosocial events matter as well. What are the cost of drugs? Need to give oral therapy versus intravenous therapy, distance from the center at which they're receiving their care, transportation issues, insurance issues—these are all things to consider.

It's not a black-and-white decision. I think it's a matter of an informed discussion with your patient, reviewing their clinical disease and psychosocial factors.

Dr. Agarwal:
That's so well said. So many things together we have to decide, take into account before we make the treatment decision.

Let's review the data supporting the ADT intensification in metastatic CSPC now. Could you summarize the key evidence for doublet versus triplet regimens we use nowadays?

Dr. McKay:
Absolutely. And maybe, I think, this requires a little bit of historical context. Prior to 2015, we were largely treating mCSPC, and I really should call it APMS now, androgen pathway modulation sensitive, based off of the new Prostate Cancer Working Group 4, but hormone-sensitive or castration-sensitive disease, we were largely treating with ADT. And then CHAARTED and STAMPEDE demonstrated that actually escalation with chemotherapy improves outcomes and improves overall survival in a dramatic way in which you can't make up for it if you give docetaxel in the CRPC setting.

Around that same time, there was a series of trials that were conducted testing each of the individual ARPIs. The first was abiraterone, which was looked at in the context of STAMPEDE and also LATITUDE, which enrolled predominantly a high-risk population. Both of those trials were positive, demonstrating a statistically significant improvement in overall survival with the addition of abiraterone to the backbone of ADT.

And sequentially, additional trials also answered this question with various respective ARPIs. For example, TITAN looked at apalutamide and ADT. ARCHES looked at enzalutamide and ADT. And there was actually 2 studies that looked at enzalutamide and ADT, ARCHES and ENZAMET. A distinguishing feature between ENZAMET was that it did allow for investigator choice of utilization of docetaxel. So there are some patients within the ENZAMET cohort who received concurrent docetaxel.

Given that the backbone of therapy had changed from ADT/doce [docetaxel] in 2015, a series of other studies actually looked at the role of triplet therapy, of adding an ARPI to the backbone of ADT/docetaxel. So ARASENS looked at adding darolutamide to ADT/docetaxel, and PEACE-1, which was actively enrolling and accruing patients when the CHAARTED data became standard of care, was modified to allow utilization of docetaxel in the standard of care arm. So it ultimately ended up looking at triplet therapy.

The newest kid on the block is darolutamide. Darolutamide was evaluated in the ARANOTE trial and also ARASENS study, which we will soon be seeing data about, demonstrating improvement in outcomes.

So we have a plethora of riches, of multiple studies demonstrating that utilization of ADT and an ARPI improved overall survival in the hormone-sensitive setting and that there is a role for triplet therapy, though there's never been any head-to-head comparison of triplet versus doublet in the classic sense.

There have been studies that we are eagerly awaiting to be presented looking at de-escalation strategies for those patients who reach a PSA nadir after a prolonged period of ADT in the hormone-sensitive setting, seeing if we can actually discontinue ADT without compromising long-term outcomes.

So there's a study called A-DREAM that looked at de-escalation strategies based off of PSA response, and we'll be awaiting those data.

Dr. Agarwal:
That's great. It looks like doublets of ADT plus ARPI have not been beaten by the triplet of ADT plus ARPI plus docetaxel yet. And Dr. McKay, you are leading a trial, ASPIRE trial through Alliance, to answer this question. Until we have the answer from the ASPIRE trial, it looks like both doublets of ADT plus ARPI and the triplet of ADT plus ARPI plus docetaxel remain standard of care, until we have more data coming from other triplet therapies, such as ADT plus ARPI plus PARP inhibitor, ADT plus ARPI plus AKT inhibitor—capivasertib,

assuming it will get approval—and of course, ADT plus ARPI plus lutetium PSMA. We are anticipating approval of this triplet in the near future. They will definitely pose new challenges on patient selection, but it's a good problem to have, I think.

So let's finally discuss how to apply these data to our practice and within a team-based model, if you will. So, Dr. McKay, could you start by describing how do you choose these doublets versus triplet? The volume of disease, de novo metastasis, patient characteristics, preexisting diabetes, for example, any of that—how do you choose doublet versus triplet with docetaxel chemotherapy?

Dr. McKay:
Again, we don't really have any level 1 evidence, and a lot of it is based off of understanding the patient's disease characteristics and clinical characteristics. I'm generally leaning towards triplet therapy for patients who have visceral metastases, for patients who have asymptomatic, high volume, high burden of disease, maybe individuals that are presenting with a skeletal-related event as their first presentation of advanced prostate cancer.

I look at the genomics to the extent that they're available. Tumor suppressor gene loss alterations—RB, PTEN, TP53—we know those all bode poorly from a prognosis standpoint. So I think these are all the factors that I take into account.

I also take into account where the patient's at—what are their comorbidities? What is their fitness for chemotherapy? What is their level of frailty? What is their level of home support? Are they living alone and independent? Will putting them on chemotherapy put them at risk of losing some of their independence? And what would that look like for any given patient? So I think these are all the things that we talk about in deciding what's the right strategy for any one given individual.

But there's no black or white here. There's just a lot of gray, in actuality. Not to say you can't make a wrong decision; I think it's important to make an informed decision. I think for every patient that's coming through our doors, we should constantly ask ourselves: okay—ADT/ARPI. I think it’s very hard to make a case for ADT alone. But ADT/ARPI, select the ARPI—which is the right ARPI for this individual patient? And then, who needs chemo? And go through that thought process every time so we don't miss an opportunity to positively impact the patient's long-term outcome.

Dr. Agarwal:
I agree fully. So let's talk about management of potential toxicities, which come up. You just mentioned toxicities, and that's a very nice segue to the next question: how to manage these adverse events, especially affecting the bones, cardiovascular health, fatigue? We see this all the time in our patients who lose their testosterone, and then we are treating them with these additional drugs. How does quality of life matter in this decision-making? And how about sexual function? How about, as I said, all these side effects which come together with prolongation of survival? How do you manage all of this?

Dr. McKay:
Very good question. I spent the bulk of my clinic visits, as probably many prostate cancer doctors do, talking about these very items, especially in the hormone-sensitive setting, where patients can be in a state of response for some time and be at risk of side effects from treatment.

So I think it's critically important to address the metabolic health—addressing exercise, weight gain, adiposity, metabolic derangements, blood sugar, lipid panel control—all of those things are critically important. And understanding who is taking ownership from the care team around those elements.

It's important to consider bone health and risk of osteoporosis, getting a baseline DEXA in the select patients that are at risk, discussing vitamin D and calcium supplementations and also appropriate exercises.

It's also really important to address the vasomotor issues, as those can be very prevalent and can dramatically impact quality of life, sleep, and function.

It's also critically important to address the sexual and psychosocial effects of hormone therapy. This could be the body dysmorphia that may take place, change in body shape, habitus, erectile dysfunction, libido, mood alterations. And there's a lot of resources that are available for patients through men's health programs, psychology, psychiatry, and sexual health programs that can help mitigate those side effects.

So, I think in totality, it's really important to be addressing these things so patients can be living their best life while they're on active cancer therapy.

Dr. Agarwal:
That's just such a great description of how to manage side effects. I fully agree with you.

I just like to add, regarding the bone health, the goal here is to prevent ADT-related bone loss, osteopenia and osteoporosis, and we shouldn't be using bone-modifying agents in metastatic castrate-resistant prostate cancer dosing, which are more often frequent dosing, higher dosing to prevent skeletal-related events in metastatic CRPC setting. Would you agree?

Dr. McKay:
I would completely agree. I think we see a lot of that in variable practice. But the role for bone-modifying agents in the hormone-sensitive setting, as you stated so accurately, is mitigation of ADT-associated bone loss, not reduction of skeletal-related events. We have not demonstrated that higher, more frequent dosing to reduce the onset of a skeletal-related event actually is beneficial in this setting.

Dr. Agarwal:
And that's all the time we have today. So I want to thank our audience for listening, and thank you, Dr. McKay, for being a fountain of knowledge on this vital topic.

Dr. McKay:
You're so welcome. It's really been my pleasure. I think ADT alone is really no longer an acceptable first-line therapy for patients with metastatic disease. We've been seeing an increased utilization of ADT/ARPI, though we're still nowhere near where we need to be. ADT plus apalutamide or enzalutamide or abiraterone or darolutamide, for that context, should be considered for patients with metastatic hormone-sensitive prostate cancer.

And I think it's really important to contextualize the patient's volume, spread of disease, other genomic factors, clinical factors, disease factors in making a decision around the addition of docetaxel.

It's really been a pleasure kind of highlighting these things. It's just incredibly practical, something that we encounter every single day in our practice and warrant some thoughtful consideration.

Dr. Agarwal:
Thank you very much.

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