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The Future of mCSPC: Molecular Profiling and Biomarker-Directed Therapies

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Dr. McKay:
Welcome, everyone. This is CE on ReachMD, and I'm Dr. Rana McKay. Today, we're going to be discussing the future of metastatic castration-sensitive prostate cancer, really focusing in on molecular profiling and biomarker-directed therapies.

And with me here today is Dr. Neeraj Agarwal, an internationally renowned prostate cancer expert. Welcome, Dr. Agarwal.

Dr. Agarwal:
Thank you, Dr. McKay. Pleasure.

Dr. McKay:
So we're going to dive in with our first topic. Dr. Agarwal, what genetic alterations can inform treatment selection? When do you get testing done? How do you get testing? And why should you be tested?

Dr. Agarwal:
This is a very important question. Molecular profiling is becoming more important than ever in metastatic castration-sensitive or hormone-sensitive prostate cancer, now known as androgen pathway modulation-sensitive prostate cancer, or APMS. Historically, prostate cancer treatment was almost entirely built around the androgen receptor axis. We intensified ADT with agents like abiraterone, enzalutamide, apalutamide, darolutamide, or even docetaxel chemotherapy. But the treatment selection was not always biologically individualized, and that is changing now.

So the most established molecular testing in prostate cancer has been homologous recombination repair testing, especially BRCA1, BRCA2, but now it is going to expand to non-BRCA1, BRCA2 HRR gene alterations to identify patients who may benefit from concurrent PARP inhibitor-based approaches, in addition to the ADT plus ARPI.

But we are now recognizing that this mAPMS, or mCSPC, is a molecularly heterogeneous disease, and not all resistance biology is driven by androgen receptors. So, for example, PTEN loss, it's a very important example. PTEN is a tumor suppressor gene that codes for a protein that normally helps regulate the PI3/AKT pathway. So, when the PTEN protein is lost, the PI3/AKT survival pathway can become activated, and it can give tumor a growth and survival advantage that may even bypass androgen receptor blockade to some extent, and that's why PTEN loss is not just a prognostic marker, but it is also potentially a predictive marker for AKT pathway-targeted therapy.

So in practice, I think molecular profiling should include both germline and somatic testing. Germline testing is important for those inherited DNA repair alterations, family counseling, and treatment selection. And somatic tumor testing can identify HRR gene

alterations, PTEN loss, MSI-high disease, TMB-high disease, mismatch repair deficiency, and some other actionable findings.

So, depending on tissue availability, we can use archival tissue, fresh metastatic biopsy tissue, or even circulating tumor DNA if we can get enough sufficient amount of circulating tumor DNA.

So the key point is molecular testing is no longer something we should reserve for late-stage resistant refractory disease. In metastatic hormone-sensitive state, newly diagnosed prostate cancer setting, molecular profiling can actually increasingly inform first-line treatment selection and clinical trial enrollment.

Dr. McKay:
Thank you so much for that summary. I think we've seen an evolving slew of data over the last year that's been presented around therapeutic implications based off of various alterations, I think, so it's critically important.

And as you so rightfully stated, we're talking about molecular profiling here, both germline testing to look for inherited alterations, certainly for the HRR genes, and also profiling the tumor. And profiling the tumor can come from either tissue, which is preferred but not always feasible, or ctDNA. So thank you so much for highlighting that. So maybe we're going to delve a little bit deeper into PTEN and the significance of PTEN loss in metastatic hormone-sensitive prostate cancer. Why is PTEN an important therapeutic target? And what does the data show?

Dr. Agarwal:
PTEN loss is important because it represents a different biology of resistance to ADT and ARPIs. So if we only think about prostate cancer as an androgen receptor-driven disease, we may miss patients whose tumors are using a parallel survival pathway, such as PTEN loss, which activates the PI3/AKT pathway that can promote tumor growth, survival, and resistance to AR-directed therapies.

So this is the rationale for combining AKT pathway inhibition with standard androgen receptor pathway treatment. So, here, the goal is to block both the AR axis and the PI3/AKT pathway at the same time.

So, CAPItello-281 is a very important trial in this setting. This was a phase 3 trial which evaluated capivasertib, an AKT inhibitor, in combination with abiraterone and ADT in patients with PTEN-deficient de novo metastatic APMS or hormone-sensitive metastatic prostate cancer. The trial showed an improvement in radiographic progression-free survival, with a median rPFS improving from 25 months to 33 months, a 7.5-month benefit.

I would like to highlight that, in tumor testing, the PTEN loss was determined by immunohistochemistry, and patients had to have 90% or more PTEN loss, like loss of PTEN protein. Now, IHC testing is very easily available. Pretty much every institution's pathology lab can do IHC testing, as they have done for breast cancer or many other cancers. So easy-to-do test, and 90% or more loss was associated with a significant improvement in radiographic progression-free survival in this positive phase 3 trial.

Intriguingly, if you increase the degree of PTEN loss to 99% to 100%, the median rPFS with ADT plus abiraterone goes down further to 22 months, and median rPFS with the experimental arm was about 33 months. So as the PTEN loss increases in degree, the response to ADT and abiraterone goes down, and that is very important to remember.

There was another finding, actually. Many patients in this trial had radiographic progression, about 1/3 of these patients, without meeting the traditional criteria for PSA progression, and that brings up another important topic, which is not only about the treatment, but also how to monitor these patients. We cannot really rely on PSA alone to monitor these patients.

And I'll like to complete this discussion with the mention of IPATential150 trial, which was done in metastatic castration-resistant prostate cancer. In that study, ipatasertib, another AKT inhibitor, in combination with abiraterone, improved radiographic progression-free survival in patients with PTEN-loss tumor, but not overall survival, and rPFS was not improved in intention-to-treat population. So, technically, the trial did not meet the primary endpoint, and the drug was not approved.

But very encouragingly now, CAPItello trial being positive, we are looking forward to capivasertib certainly being available for our patients with PTEN-loss prostate cancer.

So the lesson here is patient selection matters. These agents are not necessarily for all-comers. The benefit is more compelling when we identify the biomarker-defined group, especially PTEN-deficient disease by immunohistochemistry.

Dr. McKay:
Thank you so much for providing that overview regarding the therapeutic implications. I think it's critically important to really understand and track the biology and be treating patients with the best therapeutic that basically targets the underlying pathogenesis for their unique tumor. So I think we're all excited to hear about what will become of capivasertib.

MID-TAG:
For those just tuning in, you're listening to CE on ReachMD. I'm Dr. Rana McKay, and here with me today is Dr. Neeraj Agarwal, and we're discussing molecular profiling and biomarker-directed therapies in the metastatic castration-sensitive prostate cancer setting. Welcome.

Maybe we can dive in a little bit about the application and reviewing how to actually integrate into practice. From our learnings in breast cancer and the use of these various agents and other contexts, there can be a very unique side effect profile that needs to be proactively monitored, and even an ounce of prevention is really a wonderful thing to kind of ensure year-around diarrhea management—for example, Imodium—and really tracking patients, and the GI side effects, and other side effects, hyperglycemia, that can happen with these various agents. So I think it's going to be really important to think about how they integrate into clinical practice.

So maybe you can discuss some of these future directions with these targeted therapies in this context.

Dr. Agarwal:
Of course. So the way I see this evolving is that molecular profiling will become part of the initial treatment decision in metastatic APMS, or castration-sensitive prostate cancer. We already think about disease volume, disease timing, symptoms, comorbidities, and patient preferences, but now biomarkers like PTEN loss and HRR alterations are already becoming increasingly a component of the first-line decision-making process.

So for the PTEN-deficient tumors, AKT inhibition combined with AR pathway inhibition is a very rational strategy when available. The challenge will be, as you mentioned, Rana, to integrate these regimens safely and selecting the right patients. We will need to pay attention to toxicities, including rash, diarrhea, hyperglycemia, fatigue, and other class-specific adverse events. And these are on-target toxicities, which are really manageable with symptomatic conservative management, timely dose reductions, dose holds, and so on.

So this will require patient education, early recognition, dose modifications when appropriate, and multidisciplinary support. So I cannot really treat somebody with capivasertib who has mild diabetes, and who doesn't have a primary care physician. I think I like to have a close involvement of a PCP, and preferably an endocrinologist in patients with uncontrolled diabetes.

But delaying prostate cancer progression remains one of the key aspects of treatment because I tell patients, yes, these drugs have side effects, but a progressing prostate cancer can have a lot of side effects.

So looking ahead, we are also seeing next-generation PARP inhibitor strategies moving early in the disease course. We just saw the data from abiraterone plus niraparib combination from the AMPLITUDE trial, enzalutamide plus talazoparib in TALAPRO-3 trial, and the next PARP inhibitor we are eagerly awaiting to arrive in the clinic is saruparib. This is a selective PARP inhibitor, or PARP1 inhibitor, which is expected to have less hematologic toxicities.

The trials, such as PETRANHA trial and EvoPAR-Prostate01 trial, are already ongoing. PETRANHA is the early-phase trial, which have showed efficacy of this agent, saruparib, in combination with our ARPIs, or AR pathway inhibitors. EvoPAR-Prostate01 trial is testing saruparib in combination with various ARPIs, such as darolutamide and abiraterone, in metastatic hormone-sensitive prostate cancer.

But the broader direction is clear. We are moving from treating mCSPC or mAPMS as 1 disease toward treating it as a molecularly defined set of subgroups. So, the future will likely involve combining clinical risk, imaging, and molecular profiling to select treatment more precisely. The goal is to give the right patient the right intensification early on when we have the greatest opportunity to change the entire course of disease.

Dr. McKay:
That's a really wonderful overview, and it's really exciting how far we've come in the mHSPC setting. I think by the end of the year we could be in a situation where you've got a HRR-mutated patient that would be appropriate to receive a PARP inhibitor based off of the AMPLITUDE trial or the TALAPRO-3 data that you just recently presented that were just published in the *New England Journal*. You could envision a situation where somebody with PTEN deficiency, and I think it's still going to be determined what the threshold for a therapeutic is going to be, would be getting capivasertib.

You could envision a scenario where patients with other TSG alterations, P53, RB, maybe those individuals are getting triplet therapy with docetaxel, and conceivably everybody else that has a PSMA PET-positive scan without these other alterations would be getting lutetium.

This way we are raising the bar for each one of these subgroups that is associated with worse outcomes, each one of these molecular drivers with worse outcomes, to more biologically driven personalized strategy in the mHSPC setting.

So I'm super excited to see what the future is going to unfold over the next year, especially as these drug approvals come into play.

So it's really been a fascinating conversation. And before we wrap up, Dr. Agarwal, I just want to share your final take-home message, if you will, around our discussion today.

Dr. Agarwal:
So my take-home message is that molecular profiling, including PTEN testing and HRR gene alteration testing, is becoming essential in metastatic hormone-sensitive prostate cancer. We are moving beyond a single AR axis model toward a more biomarker-directed treatment where profiling results can directly change the treatment plan.

Dr. McKay:
Thank you so much for that. I completely agree. I think putting this all into a conceptualized framework, I think thinking beyond the AR axis and recognizing the molecular heterogeneity in this disease space, and really, I love what you said, it's the right agent for the right patient at the right time.

So we've come to the end, and we're deeply appreciative of all of you who've joined us, and I'd like to express my sincerest gratitude to Dr. Agarwal for joining me and for sharing all his valuable insights. It's really been wonderful speaking with you all today.

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