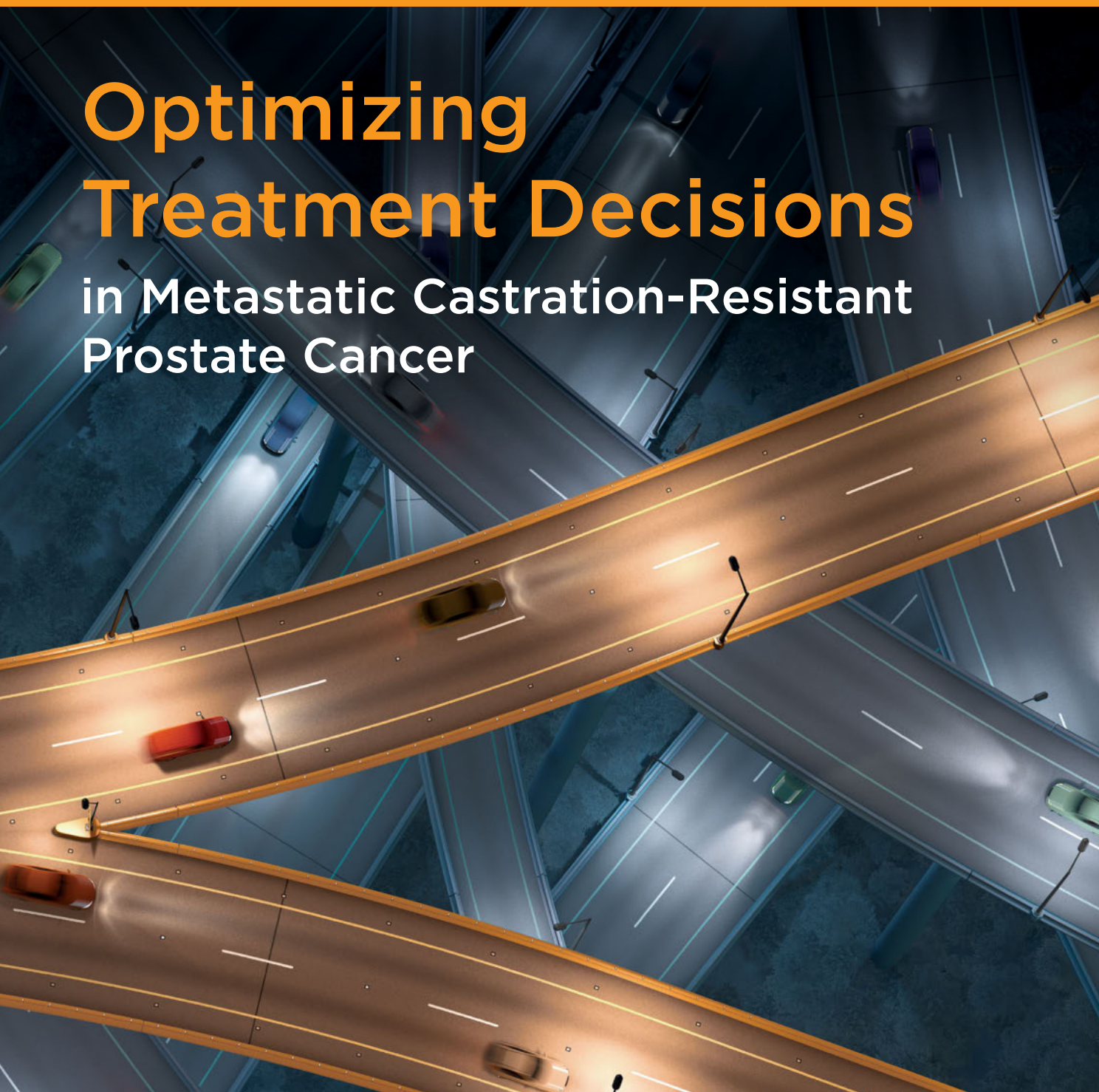
A PROMOTIONAL SUPPLEMENT TO
Urology Times®

Optimizing Treatment Decisions

in Metastatic Castration-Resistant Prostate Cancer



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INTRODUCTION

The landscape for the management of men with castration-resistant prostate cancer (CRPC) and high-risk metastatic hormone-sensitive prostate cancer (mHSPC) is being positively impacted by ongoing developments in diagnostic/predictive biomarkers and novel therapies. In particular, the number of FDA-approved androgen receptor (AR)-targeted therapies has increased and the indications for these agents are broadening so that they are being used earlier in the spectrum of prostate cancer (Table).

Drug	Mechanism	mHSPC	nmCRPC	mCRPC
Abiraterone* (Zytiga®)	Androgen biosynthesis inhibitor	X		X
Apalutamide (Erleada®)	AR inhibitor	X	X	
Darolutamide (Nubeqa®)	AR inhibitor	Anticipated	X	
Enzalutamide (Xtandi®)	AR inhibitor	Coming	X	X

*Administered with prednisone

Abbreviations: AR, androgen receptor; mCRPC, metastatic castration-resistant prostate cancer; mHSPC, metastatic hormone-sensitive prostate cancer; nmCRPC, nonmetastatic castration-resistant prostate cancer.

It is anticipated that abiraterone, apalutamide, and enzalutamide will be widely used in men with metastatic hormone-sensitive prostate cancer (mHSPC), irrespective of disease volume or risk, and that abiraterone, enzalutamide, apalutamide, and darolutamide will be utilized to some degree in men with nonmetastatic CRPC (nmCRPC). Based on this, it is anticipated that when patients progress, there will be a need for biomarkers that may help identify patients for further AR-directed therapies as compared to chemotherapy and alternative approaches.

In this evolving space, urologists and oncologists representing different practice settings and all with extensive experience managing men with CRPC joined in a tele-round table to share their perspectives and approaches for optimizing patient care. This supplement presents highlights from their discussion, in which they addressed common questions about patient evaluation and management, including the role and impact of the commercially available androgen receptor splice variant 7 (AR-V7) test (Oncotype DX AR-V7 Nucleus Detect® test, Genomic Health) to guide treatment decisions for men with metastatic CRPC (mCRPC).

FACULTY

MODERATOR

Andrew J. Armstrong, MD, ScM, FACP, is a professor of medicine, surgery, pharmacology and cancer biology, and the director of research at the Duke Cancer Institute Center for Prostate and Urologic Cancers, divisions of medical oncology and urology, at Duke University in Durham, NC.

PANELISTS

Mahdi Taha, DO, FACOI, FACP, is a medical oncologist at Cancer Treatment Centers of America (CTCA) in Atlanta, GA.

Lawrence I. Karsh, MD, FACS, is the director of research and attending urologist, codirector of the Advanced Therapeutics Clinic, and a certified principal investigator at the Urology Center of Colorado in Denver, CO.

Paul Dato, MD, is the urologist and medical director at Genesis Healthcare Partners in San Diego, CA.

DISCLOSURES: *Dr. Armstrong* receives research support (to Duke) from Dendreon, Sanofi Aventis, Pfizer, Astellas, Janssen, Bayer, Merck, BMS, Constellation, Genentech/Roche, Arvinas, Forma, Astra Zeneca, and Novartis. He is on the consulting/advisory board for Janssen, Astellas/Pfizer, Bayer, Astra Zeneca, Clovis, and Merck and is a speaker for Dendreon and Bayer. ***Dr. Taha*** speaks on behalf of Eisai, Genomic Health, and Merck. ***Dr. Karsh*** receives research funding from Astellas, Allergan, AstraZeneca, Augmenix, Bayer, BioXcel, CU Optics, CUSP Lancelot, Dendreon, Exact Sciences, Ferring, FKD, Genentech/Roche, GenomeDx, Janssen, Merck, Myovant, Nucleix, Pfizer, Pharmtech/Veru, Precision Biopsy, Precision Med, Siemens, Spectrum, and UroGen. He is on the consultant/advisory board for 3D Biopsy, AbbVie, Astellas, Astra-Zeneca, Augmenix, Bayer, Dendreon, Ferring, Genomic Health, Janssen, Pfizer, Precision Biopsy, Spectrum, and Vaxiion. He is on the speaker bureaus of Amgen, Astellas, Bayer, Janssen, and Pfizer and owns stock in Swan Valley Medical. ***Dr. Dato*** is on the speaker bureaus of Bayer, Janssen, Astellas, Pfizer, and Myriad. He has been a consultant to Bayer, Janssen, Astellas, Sanofi-Aventis, and Genomic Health.

Defining nonmetastatic CRPC versus metastatic CRPC

Andrew J. Armstrong, MD, ScM, FACP: Let's begin the discussion by talking about staging and the implications for choosing treatment for men with CRPC. Nonmetastatic castration-resistant prostate cancer (nmCRPC) or M0 CRPC disease would be defined by the presence of a rising prostate-specific antigen (PSA) despite medical or surgical castration with no evidence of distant metastasis on standard imaging. Considering what we are finding now using newer positron emission tomography (PET)-based imaging modalities to look for metastases, do you think that M0 CRPC patients really exist?

Lawrence I. Karsh, MD, FACS: The term nonmetastatic or M0 is probably a misnomer, because these patients with CRPC are likely to have micrometastatic disease. It is just that the sites are not detected with computed tomography (CT) or bone scan imaging. Nevertheless, I still categorize men as M0 CRPC if they have a castrate level of testosterone and rising PSA without evidence of metastatic disease by conventional bone scan, CT scan, or magnetic resonance imaging (MRI), as this was how the clinical trial eligibilities in this setting were defined.

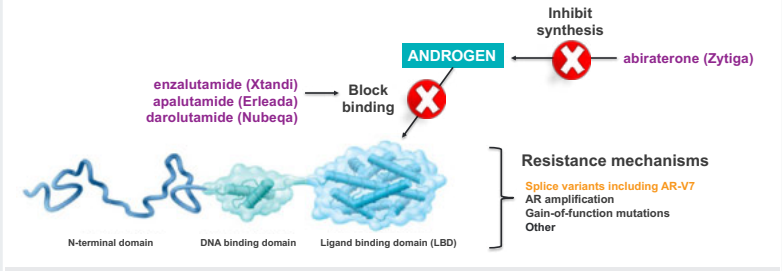
Dr. Armstrong: Would you categorize a patient with pelvic adenopathy as M0?

Dr. Karsh: It depends on the location of the enlarged lymph nodes. According to the American Joint Committee on Cancer (AJCC) Cancer Staging Manual, the patient is categorized as having locoregional disease (N1) if the positive nodes are the pelvic lymph nodes, which are those that lie below the bifurcation of the common iliac arteries.[1] If the enlarged nodes lie outside the confines of the true pelvis, it is considered to be distant metastasis and staged as M1.[1]

Paul Dato, MD: I also classify pelvic nodal disease as N1 and true retroperitoneal adenopathy as M1a per the AJCC classification.

AR-V7 TESTING WITH THE ONCOTYPE DX AR-V7 NUCLEUS DETECT® TEST

The presence of the AR-V7 protein, a splice variant of the androgen receptor is a primary mechanism of resistance to AR-targeted therapy that can emerge upon exposure to these therapies. AR-V7 encodes a truncated androgen receptor protein that retains the transactivating N-terminal and DNA-binding domain, but lacks the ligand-binding domain required for the interaction of AR-targeted therapies with the androgen receptor (Figure 1).



The AR-V7 variant emerges upon exposure to AR-targeted therapies

Figure 1. AR-targeted therapies converge on the ligand-binding domain of the androgen receptor to exert their anti-tumor activity. Presence of AR-V7, which lacks the ligand-binding domain, explains resistance to AR-targeted therapy.

The Oncotype DX AR-V7 Nucleus Detect test specifically looks at the presence/absence of the AR-V7 protein in the nucleus of circulating tumor cells to predict resistance to AR-targeted therapies. It is the first and only commercially available test that is validated in three studies.[1-3]

The test is available across the US and covered by Medicare. It requires only a simple blood draw and generates an easy-to-interpret, actionable binary result (AR-V7+ or AR-V7–) (Figure 2).

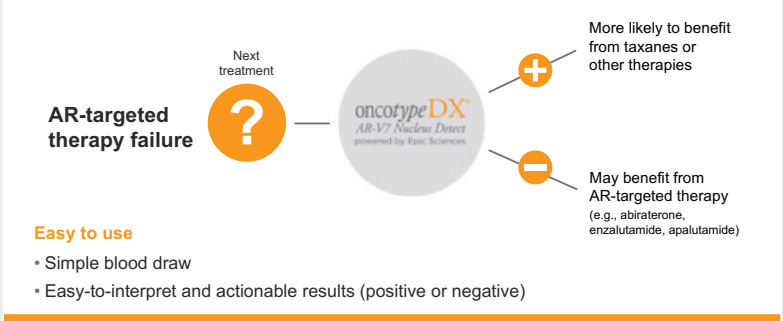


Figure 2. The Oncotype DX AR-V7 Nucleus Detect® test helps guide mCRPC treatment decisions

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3. Armstrong AJ, Halabi S, Luo J, et al. Prospective multicenter validation of androgen receptor splice variant 7 and hormone therapy resistance in high-risk castration-resistant prostate cancer: the PROPHECY Study. *J Clin Oncol.* 2019;37(13):1120-1129.

Dr. Armstrong: Considering that the labels of M1 and M0 are fairly arbitrary when the staging is based on standard imaging, do you feel it is important to do prostate-specific PET imaging such as with choline, fluciclovine F18 (Axumin®), or sodium fluoride tracers to make a treatment decision?

Dr. Karsh: I only use PET imaging when I am looking at a patient with castration-sensitive biochemical recurrence and if I am going to consider metastasis-directed therapy for oligometastatic disease. Back when AR-targeted therapies were only approved for treating mCRPC, we wanted to find metastases so that we could use those drugs. Now we have three drugs approved to treat M0 patients that have been shown to be very effective in delaying metastasis. Therefore, I do not feel the need to do PET imaging to look for metastases. I only do bone and CT scans and occasionally MRI when patients cannot tolerate or are allergic to iodinated contrast.

Dr. Dato: I use PET imaging in this situation as well, in large measure to find oligometastatic disease for which I would offer radiotherapy to selected metastatic sites.

Dr. Armstrong: What would you do if you see a patient who has biochemical recurrence and no evidence of metastasis on standard imaging but is found to have bone or lymph node metastasis using a prostate-specific PET imaging technique?

Mahdi Taha, DO, FACOI, FACP: We have been using the fluciclovine F18 PET scan and have found that it has a substantial false-positive rate, meaning that when a confirmative biopsy is done, it comes back negative. So, I would attempt to do a biopsy to confirm the metastasis identified by the PET scan and look at other tests that can be indicative of disease progression. For example, I would consider the magnitude of the patient's PSA increase, the PSA velocity, inflammatory markers, and if the patient is symptomatic.

Dr Dato: The fact that there are false negatives on PET scanning is at least as important as the potential for false positives, because the presence of false negatives supports the idea that M0 is a misnomer. These patients may still have M1 disease that is simply not yet visualized on PET imaging.

Nonmetastatic CRPC and follow-up

Dr. Armstrong: Certainly, the US Food and Drug Administration (FDA) clearance of many of the PET imaging tracers encourages confirmation of the suspected recurrence site with histopathologic tissue evaluation, and we follow that recommendation in our practice when possible. The problem is that it can be very challenging to biopsy some sites, particularly if it is the spine or the ribs or a small, 3-mm pelvic lymph node.

Dr. Taha, how would the biopsy findings guide your approach to management and what would you do if you could not do the biopsy? Would you continue to follow the patient and watch the suspicious areas before deciding on therapy? Or are there situations where you feel empiric therapy for metastatic disease is appropriate?

Dr. Taha: If the biopsy is positive, I treat the patient accordingly with mCRPC-specific therapies, such as enzalutamide or abiraterone, or sipuleucel-T (Provenge). If the biopsy is negative or it could not be done and the patient meets the criteria for M0 classification, I start treatment with one of the newer AR-targeted therapies—apalutamide, enzalutamide, or darolutamide—if the patient has a fast PSA doubling time (PSADT) and wishes to pursue active therapy in addition to androgen deprivation therapy (ADT).

The decision is made based on a thorough and detailed discussion of risks (side effects, costs) and benefits with the patient, in which I share the data we now have from the PROSPER, SPARTAN, and ARAMIS clinical trials showing that AR inhibitors prolong metastasis-free survival (MFS) for men with nmCRPC.[2-4] We need to acknowledge to patients that we do not yet have data showing these drugs improve overall survival (OS), but usually men who are young and active are interested in preventing or delaying development of metastatic disease and want to start on AR-targeted therapy.

Dr. Karsh: I believe that MFS is a meaningful and now approvable endpoint that may correlate with overall survival in nmCRPC patients. In the ICECaP study, MFS was a strong surrogate for overall survival in patients with localized disease, but that discussion is beyond the scope of this one.[5] The bottom line is that we may see the same relationship between MFS and OS in patients who have nmCRPC. However, the OS endpoint in the SPARTAN, PROSPER, and ARAMIS trials is not yet mature and longer follow-up is required before we can know for sure about the surrogacy of MFS for OS.

I agree that it is essential to have a discussion with the patient when deciding on treatment options for patients with nmCRPC. We need to consider that these men are generally asymptomatic from their cancer and can experience toxicity from active treatment with the AR-targeted agents.

When deciding about treatment, I also look at PSADT because it has been shown that patients with shorter PSADT have a worse prognosis and shorter time to bone metastasis. In addition, I consider treatment depending on factors such as patient preference, age, and comorbidities. If I decide not to treat, I monitor PSA every 3 months because the PSADT can change rapidly in many patients and we do not want to miss an appropriate treatment window.

Dr. Dato: I also use PSADT when considering whether to start treatment with one of the newer medications in this setting. I agree that clinicians need to have a thorough discussion with the patient because the medications can be very well tolerated by some patients, but they can also cause significant adverse effects.

Dr. Armstrong: Dr. Taha, you mentioned that you discuss with patients the benefit of treatment with AR inhibitors for delaying metastasis and the fact that we

do not have survival data yet that are robust enough for guiding decisions. What issues do you consider when trying to decide whether to use darolutamide, apalutamide, or enzalutamide?

Dr. Taha: Those three drugs are similar with regard to mechanism of action, and the median MFS and relative differences in MFS compared with placebo that were found for each in their respective clinical trials were also pretty similar.[2-4] Side effects do differ among these agents, but no direct head-to-head comparisons have been made and quality of life is high for most of these patients over time.

Therefore, my decision is mostly based on accessibility for patients, and that depends on their insurance coverage. I do not want to create a financial burden for a patient by prescribing something that has a huge copay when another option may be more affordable. It is also great that we have three very good drugs to choose from, because then we can have an alternative if a patient develops treatment-limiting toxicity on one of these medications.

Dr. Karsh: I agree that apalutamide, darolutamide, and enzalutamide are all efficacious drugs and are good choices. Apalutamide and enzalutamide are structurally very similar, although apalutamide is more commonly associated with skin rashes. Both cross the blood-brain barrier and can have CNS effects, including fatigue and falls with the risk for fractures, although seizures are rare. Structurally, darolutamide is a different molecule and it may not cross the blood-brain barrier. Therefore, I may consider darolutamide for an older and frailer patient. I also agree with Dr. Taha that insurance coverage and copays will influence the decision-making process.

Dr. Dato: I consider side effects and access when selecting among the three agents. I typically see a greater magnitude of fatigue with enzalutamide than with apalutamide, and I see pruritus and occasional rash with apalutamide, but it is substantially less than what was reported in the SPARTAN trial. I do not have experience with darolutamide, but it looks intriguing because of its side-effect profile.

Management of nmCRPC patients on AR inhibitor therapy

Dr. Armstrong: How do you follow a patient with nmCRPC after he is started on one of the AR inhibitors?

Dr. Karsh: I usually check PSA every 3 months and follow the RADAR [Radiographic Assessments for Detection of Advanced Recurrence] I guidelines for imaging.[6] For biochemical-recurrent patients, the guidelines recommend getting a first conventional scan when the PSA is between 5 and 10 ng/mL, and if that is negative, a second scan when the PSA is 20 ng/mL, and then at every doubling of the PSA thereafter based on checking it every 3 months. Although the RADAR guidelines suggest waiting for doublings, we need to use our clinical judgment. I will consider imaging if the patient develops symptoms or a change in performance status to suggest progression of disease. If none of these criteria are met, I will image these patients at least yearly.

Dr. Taha: Like Dr. Karsh, I see patients every 3 months, and I look at PSADT, PSA velocity, and the performance status or ECOG [Eastern Cooperative Oncology Group] score. I order imaging if the results from one of those measures suggest there may be disease progression.

Dr. Dato: I also follow patients every 3 months once they have reached steady state, although I follow patients more closely initially if they are on apalutamide because of its potential to cause skin rash. As I already mentioned, however, the frequency of skin rash with apalutamide in my experience is lower than it was in the SPARTAN study.

Dr. Armstrong: In the PREVAIL study that investigated enzalutamide in men with chemotherapy-naïve mCRPC, approximately 25% of men on enzalutamide had radiographic progression in the absence of PSA progression.[7] Do you think we will see a change in the pattern of progression in men who are on AR-targeted therapy?

Dr. Karsh: To your point, that may be a reason to consider more frequent imaging in spite of the PSA, but are you suggesting that by starting treatment earlier we may be creating a resistant beast? That is an interesting thought, but so far it seems that earlier treatment is still better. An interesting exploratory endpoint in the SPARTAN trial looked at second-progression–free survival (PFS2), which was defined as the time from randomization to investigator-assessed disease progression during the first subsequent treatment for metastatic castration-resistant disease or death from any cause.[3] Importantly, the clock was started at the beginning of the study and not when men progressed on apalutamide or placebo. The study found PFS2 was significantly longer in the apalutamide group than in the placebo group.

Dr. Armstrong: Would you continue AR inhibitor therapy through PSA progression until the patient develops clinical or radiographic progression?

Dr. Taha: Yes, I would continue AR inhibitor therapy for these patients. Once there is clinical or radiographic progression, I would change systemic treatment to a different mechanism of action and introduce taxane systemic chemotherapy.

Dr. Karsh: One of the points that I adopted from the Prostate Cancer Clinical Trials Working Group 3 is to continue with therapy until I find the patient is no longer clinically benefiting (NLCB).[8] Because I expect that the patient will not do as well on the next therapy, I try to get as much "mileage" as I can out of the first treatment before switching.

Dr. Armstrong: Continuing a treatment until the patient is no longer benefiting clinically seems reasonable. The endpoint of NLCB is hard to define, but experienced clinicians know it when we see it. It may be that the patient is deteriorating symptomatically based on pain, weight loss, or anemia, or has crossed the threshold to obvious radiographic progression, and then we offer new therapy.

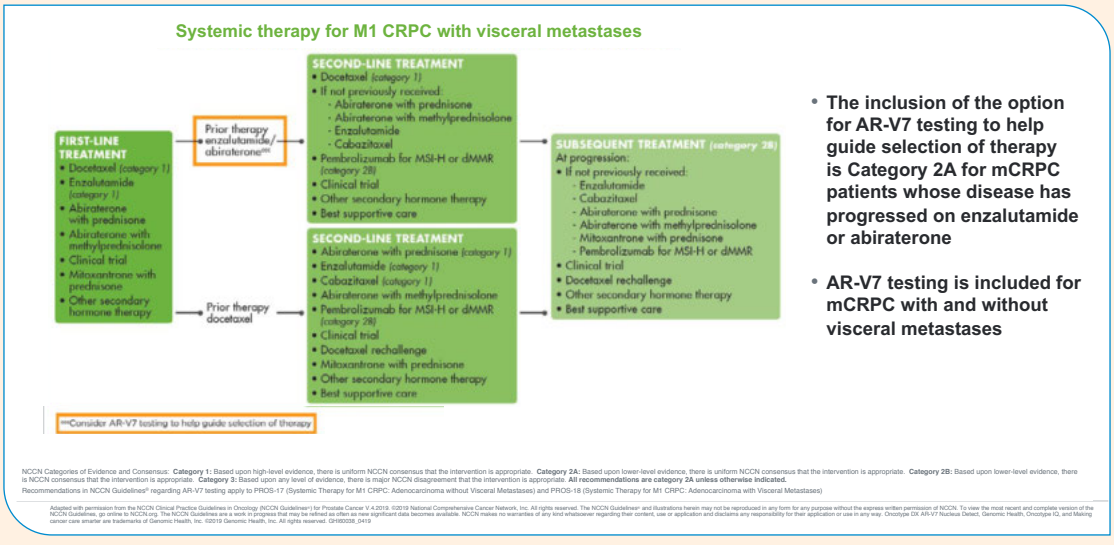


Figure 1. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Prostate Cancer Version 4.2019 recommend that physicians consider AR-V7 testing to help guide selection of therapy for men with M1 CRPC with and without visceral metastases who have disease progression after first-line treatment with enzalutamide or abiraterone.[9]

Transition to mCRPC and role of AR-V7 testing (Oncotype DX AR-V7 Nucleus Detect® test)

Dr. Armstrong: Do you think that now when patients progress to M1 CRPC, most have already been on one of the potent AR inhibitors?

Dr. Karsh: I believe that is the case. Now that we have effective oral AR therapies for mHSPC, M0 CRPC, and chemotherapy-naïve mCRPC, we are able to delay the use of chemotherapy. Then when patients progress while on AR-targeted therapy, we can consider biomarkers to inform therapeutic decisions.

Dr. Armstrong: Which specific biomarker test or tests are you ordering when a patient has progressed while on an AR inhibitor? [See sidebar: Germline and Somatic Testing]

Dr. Karsh: We now have a biomarker assay to detect AR-V7 that is a commercially available blood test (Oncotype DX AR-V7 Nucleus Detect test) and the NCCN Clinical Practice Guidelines In Oncology (NCCN Guidelines®) recommend that physicians consider AR-V7 testing to help guide therapy selection for mCRPC patients who progressed while on first-line treatment with enzalutamide or abiraterone (Figure 1).[9] I use that test to look for resistance to AR-targeted therapy and determine if the patient might respond to a second oral oncolytic. We also have genomic tests, both germline and somatic, including next-generation sequencing, that could help to identify patients eligible for clinical trials as well as guide selection of some available therapies such as poly (ADP ribose) polymerase (PARP) inhibitors.

I also look at microsatellite instability (MSI) because it is an actionable marker. Although it is uncommon in prostate cancer, it may give patients who are positive another option. Pembrolizumab (Keytruda) is approved for treatment of patients with MSI-high cancer and starting this immunotherapy may allow us to further delay chemotherapy. These tests and others in development are getting us closer to our goal for personalized medicine.

Regarding the AR-V7 Nucleus Detect® test, the results are reported within a week, which means that I can make a decision about the next treatment pretty quickly. One of the criticisms that has been raised about the test is its cost. But I would argue against that objection because by doing the test and finding out that a patient is likely to be resistant to AR inhibitor therapy, we can avoid putting him through a 2- or 3-month "experiment" with a drug that may be ineffective, has potential toxicity, and probably will cost more than the AR-V7 Nucleus Detect test.

Dr. Taha: I also order the AR-V7 Nucleus Detect test when a patient on AR-targeted therapy shows the first signs of progression. The test provides significant value because it not only detects possible resistance to an AR inhibitor but it also helps us with prognostication (Figure 2).[10,11] A positive AR-V7 test indicates the patient has a more aggressive type of disease and that starting systemic chemotherapy is the most reasonable approach.

If the AR-V7 test is negative, I feel more confident about proceeding with a second-generation AR-targeted therapy in this second-line setting. This testing can be especially important when I am faced with a patient who is not a good candidate for chemotherapy because he has poor performance status or is someone who is fearful about starting chemotherapy.

A negative result with the AR-V7 Nucleus Detect test does not guarantee response or benefit using this second-line AR-tar-

geted therapy, and I anticipate that there will not be a tremendous response due to other cross-resistance mechanisms. However, there is evidence that patients with an AR-V7 negative test have essentially the same outcome and survival whether treated with AR-targeted therapy or systemic chemotherapy. Thus, a negative test supports the use of AR-targeted therapy.

In addition to the Oncotype DX AR-V7 Nucleus Detect® test, I order next-generation sequencing to look for mutations that may be common in prostate cancer patients and in particular for BRCA mutations with the idea of incorporating a PARP inhibitor with the patient's treatment. Many times, however, I am challenged with not having a recent tissue specimen, which causes me to use the liquid biopsy test.

Dr. Armstrong: The commercially available AR-V7 Nucleus Detect® test is a nuclear-specific protein assay that detects the protein in the nucleus of circulating tumor cells (CTCs). There is also an mRNA AR-V7 assay that is done at Johns Hopkins University that tests for AR-V7 specific mRNA. Do you feel there are any significant differences between the two tests?

Dr. Karsh: Before the nuclear-specific AR-V7 Nucleus Detect test was available from Genomic Health, we would try to have the mRNA test done at Hopkins, but it was not covered by insurance and that created a significant barrier because the patient was required to pay for the test upfront. I am not sure if the coverage situation has changed, but with access to the commercially available AR-V7 Nucleus Detect test, I am no longer trying to use the Hopkins assay.

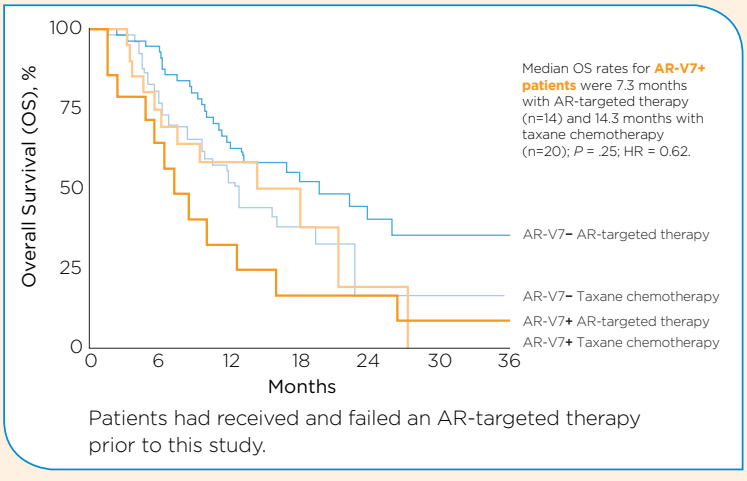
In addition, some companies are claiming they can provide RNA reports for AR-V7 and some can provide AR gene mutation reports. There is only evidence in the published literature to show that nuclear AR-V7 protein in CTCs is a marker for definite resistance to AR-targeted therapies in mCRPC patients that have received and failed an AR-targeted therapy.[10-12] Furthermore, the PROPHECY trial showed that the positive predictive value for predicting lack of response was greater for the AR-V7 nuclear-specific assay than the Johns Hopkins mRNA assay.[12] Although the mRNA assay had greater sensitivity, its specificity was a little lower. For these reasons, the nuclear-specific assay is more appealing to me.

Dr. Armstrong: How do you communicate the results of the AR-V7 test to patients?

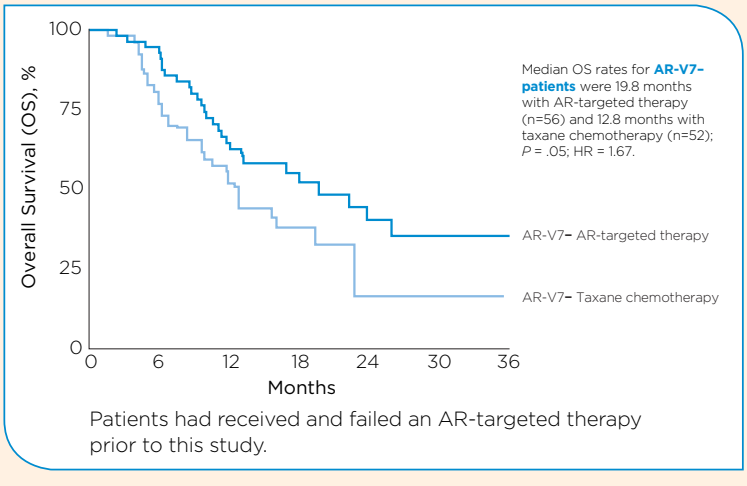
Dr. Karsh: I tell my patients that there are a number of mechanisms by which prostate cancer develops resistance and that the development of resistance explains why we cannot cure prostate cancer. To date, AR-V7 is the most common cause of resistance and we have a blood test for it that can help us make a decision for their next therapy.

I explain that the result is binary, positive or negative, and that no test or treatment is perfect. But if the AR-V7 test is negative, it means they can go on to treatment with another oral oncolytic. If the test is positive, I recommend starting taxane chemotherapy. With that information, patients understand that the test results help us to

Figure 2. In the Scher et al (2018) validation study for the Oncotype DX AR-V7 Nucleus Detect® test, AR-V7+ patients were found likely to live longer on taxane chemotherapy than on AR-targeted therapy (top) whereas AR-V7– patients were found likely to live longer on AR-targeted therapy than on taxane chemotherapy (bottom).[11]



Patients had received and failed an AR-targeted therapy prior to this study.



Patients had received and failed an AR-targeted therapy prior to this study.

decide if we can delay chemotherapy or if it should be started sooner. Patients often prefer to delay chemotherapy if possible.

Dr. Armstrong: Have you had patients who responded well to abiraterone or enzalutamide after progressing on previous AR inhibitor therapy?

Dr. Taha: I have had patients on an AR inhibitor who had stable disease for a significant time, perhaps a year, who went on to start a different AR inhibitor and were able to remain on the second agent for another year or so before needing systemic chemotherapy. Some patients are very concerned about being placed on chemotherapy, and I take their fears into consideration when deciding when to start it. But I explain to patients that it is important to start systemic chemotherapy while their performance status is still reasonably good, because then they will be able to tolerate the treatment better. It is also important to educate patients that single-agent taxane therapy, when given appropriately, is fairly well tolerated. Educating patients about chemotherapy helps to mitigate their fears about starting it when it seems indicated.

Dr. Armstrong: Can anyone share a specific case that shows how testing with the Oncotype DX AR-V7 Nucleus Detect® test guided your treatment decision for a patient (Figure 3)?

Dr. Karsh: In early 2015, a 64-year-old patient of mine was enrolled in a clinical trial comparing ADT plus enzalutamide versus ADT plus placebo versus enzalut-

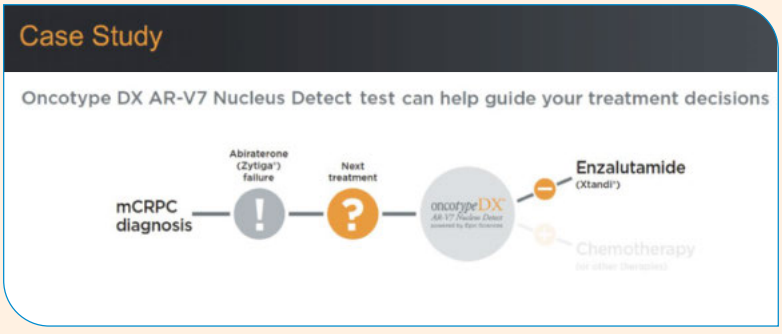


Figure 3. Testing with the Oncotype DX AR-V7 Nucleus Detect® test can help guide treatment decisions when a patient with mCRPC fails AR-targeted therapy. In this case, the decision was made to start treatment with enzalutamide in a patient found to be AR-V7– after progressing while on abiraterone.

GERMLINE AND SOMATIC TESTING

Dr. Armstrong: Dr. Karsh, could you please explain the differences between germline and somatic genetic testing?

Dr. Karsh: Germline testing provides information about inherited cancer risk. It identifies mutations in hereditary cancer risk genes that are present in all cells. The results inform us not only about the patient but can also have implications for family members. For example, clinical trials are investigating PARP inhibitors for advanced prostate cancer associated with certain germline mutations (BRCA1/2), or because of the increased risk for colon cancer, the decision may be made to avoid radiation therapy for localized prostate cancer in a man with Lynch syndrome genes. If a man with prostate cancer carries the BRCA1/2 germline DNA mismatch-repair alterations or mutations, any daughters of his would have a 50/50 chance of inheriting the gene variant that also predisposes to hereditary breast and ovarian cancer. Any offspring who are found to be carriers could begin early or more aggressive cancer-specific screening.

Somatic genetic testing identifies genetic mismatch-repair alterations that are present in the tumor and many have been acquired after patients receive multiple lines of therapy. The results can be relevant for selecting available treatments, such as PARP inhibitors, or facilitate a patient's candidacy for clinical trials. Ultimately, there will be specific treatments for different gene alterations, but a lot more work is needed.

Although many gene mutations can be identified with germline or somatic testing, many are variants of unknown significance and are not yet actionable.

Dr. Armstrong: When do you consider ordering the various tests?

Dr. Karsh: The key is to obtain a really good family history. Up until now, that has been lacking not only in my practice but also in most urology practices. Its importance has become clear over the past few years. That being said, the time to discuss germline testing is when a patient has developed metastatic disease, but I would probably wait to do somatic testing with cell-free DNA or tissue until the patient is on a trajectory of progression and I need to start a second-line therapy. My goal with that testing is to guide a decision for targeted treatment that might be expected to be most helpful for the patient. Also, we know that genomic alterations within a tumor can change over time as the patient advances along the spectrum of prostate cancer. So, I would want to know the current molecular profile of the tumor.

amide monotherapy in hormone-naïve men with PSA progression after local therapy. A year later, the patient developed metastatic disease with a painful lytic lesion in the distal humerus that required surgery for stabilization. Biopsy of the bone was positive for metastatic prostate cancer, and the patient received palliative radiation to the bone lesion and was withdrawn from the trial. His PSA was 11 ng/mL, he continued on ADT, and was started on abiraterone/prednisone as well as denosumab (Xgeva®). Enzalutamide was not offered because I did not know whether or not he had received it during the clinical trial.

The patient's PSA nadired to nondetectable. Sipuleucel-T was added 3 months later, and PSA remained relatively stable (<6 ng/mL) for about 2 years. In November 2018, the patient's PSA increased to 9 ng/mL and he was found to have a biopsy-proven left adrenal metastasis that was treated with radiation. Docetaxel chemotherapy was started, but it was stopped after three cycles due to intolerable side effects. Imaging in March 2019 showed resolution of the adrenal lesion. We discussed options, including evaluation with the commercially available Oncotype DX AR-V7 Nucleus Detect® test. The patient agreed to the test, the result was negative, and he was started on enzalutamide. His PSA decreased to 4 ng/mL and has remained stable, although the patient developed a bone recurrence for which he received radiation and was started on radium-223. Although the use of radium-223 in the setting of a visceral metastasis may be questionable, the adrenal metastasis was no longer present, and I felt that this was an appropriate window to add radium to enzalutamide.

Additional treatment considerations for mCRPC

Dr. Armstrong: Talking again about a theoretical patient who progresses to mCRPC after being on AR inhibitor therapy in the hormone-sensitive or M0 setting, if the AR-V7 assay is negative and other biomarker testing does not reveal any actionable alterations, is there anything else you would consider to help you decide what to do next?

Dr. Taha: I would look at the patient's whole clinical picture, including the performance status and PSA parameters. For example, if the patient is elderly, does not have a high tumor burden, is not symptomatic, and does not have declining performance status, I would proceed with AR-targeted therapy because it will give him better quality of life. However, if I have a patient whose PSA velocity has taken off or he has diffused metastatic disease, a high tumor burden, and symptoms, I would typically move on to intravenous chemotherapy after progression on first-line AR-targeted therapy. I would give six cycles of chemotherapy before reimaging the patient to check for a response and

Dr. Armstrong: Would you recommend MSI testing for all patients with metastatic disease or those with a strong family history of Lynch syndrome and high-risk disease?

Dr. Karsh: I would, because as mentioned, it gives information that is clinically actionable and it is simple and easy to perform.

Dr. Taha: I agree fully, although I was initially skeptical about the MSI test considering the biology of adenocarcinoma of the prostate. What changed my mind was the experience I had with a patient who had progressed on AR-targeted therapies, taxane chemotherapy, and platinum-based chemotherapy. After running out of therapeutic options, I ordered next-generation sequencing with genomic tests. The results revealed that the patient had a high tumor mutation burden (TMB) of 45 and an MSI high. I placed the patient on immunotherapy with pembrolizumab and was not expecting a significant result with his PSA value. Not only did his PSA drop but the patient also had a radiographic response, and he is now in his 9th month of immunotherapy with pembrolizumab. Genomic testing utilizing MSI and TMB can be really helpful for supporting personalized medicine and help us choose therapy that may provide significant benefit for an individual.

Dr. Dato: I agree as well. I have no experience with liquid biopsy, but I have done tissue biopsy for somatic testing of MSI and DNA mismatch-repair alterations. I do germline testing as early as possible so that information is available when patients are referred to a medical oncologist.

Dr. Armstrong: Dr. Karsh, do you discuss the germline testing yourself with patients and then refer them for genetic counseling if something is identified in the test, or do you refer all patients to a genetic counselor first?

Dr. Karsh: I am involved in some clinical trials where the testing is being done upfront. In that situation, we are ordering the testing and then I refer the patient to a genetic counselor if the test identifies abnormalities. In clinical practice, we have been referring patients to genetic counselors to discuss the testing because the counselors have more expertise for helping patients and their families fully understand the implications of doing the testing. As we become more comfortable with the counseling, we will probably try to do more of the testing ourselves.

There are a limited number of genetic counselors, and they will be overwhelmed by the growing demand, making access more difficult for patients. Therefore, urologists need to become educated in this area so that we can one day provide the counseling ourselves.

then decide on further treatment based on the imaging findings. Any decision, however, is made after having a discussion with the patient and considering his lifestyle and preferences with the goal of providing care that is best for that individual.

Dr. Karsh: I refer to the index patients in the guidelines from the American Urological Association (AUA) as well as the NCCN Guidelines® when deciding on management for a patient who has progressed to the M1 stage after treatment with AR inhibitor therapy.[9,13] I also utilize pathway and guideline recommendations that we developed in UroGPO. Although I incorporate guidelines, ultimately, I rely on my "gestalt" and nearly 10 years of experience with the next-generation approved therapies for CRPC when making decisions.

Generally, progression to the M1 stage might be detected early in a patient who is being followed while on treatment for M0 disease. In that situation, I might consider sipuleucel-T before moving on to other therapies.

Dr. Armstrong: Let me ask about radium-223, considering the negative results from the study investigating it as frontline treatment for asymptomatic mCRPC.[14] Do you think it is still a valuable alternative to chemotherapy in that setting?

Dr. Karsh: In the ALSYMPCA trial that enrolled men with symptomatic CRPC with skeletal metastases, the primary endpoint was OS and benefit was achieved if the patients received all six cycles of radium-223 regardless of whether it was given before or after chemotherapy and it was given with best standard-of-care treatment at that time.[15] On that basis, radium-223 may be worth using if you have a 6-month window during which the patient can receive it. If the patient is progressing rapidly and is very symptomatic, I may just go right to chemotherapy.

I would not use radium-223 with abiraterone based on the results of ERA 223, but considering the PEACE III trial, I would use enzalutamide with radium-223.[14,16]

Dr. Armstrong: PEACE III showed radium-223 and enzalutamide could be used together safely with no increased fracture risk as long as patients were given concurrent denosumab (Xgeva) or zoledronic acid (Reclast®).[16]

Dr. Karsh: Perhaps one of the reasons why there was an increased risk of fracture in patients in the radium-223/abiraterone arm in the ERA 223 trial is that a low percentage of patients were on an antiresorptive agent despite guidelines recommending their use.

Dr. Armstrong: There is an assumption that patients doing well with AR-targeted therapy do not need to be treated with an antiresorptive agent, but that overlooks the fact that those drugs can impair bone health and healing and promote osteoporosis. So, it is important to have these patients on antiresorptive therapy.

Dr. Karsh: That brings up the important point about addressing bone health for men with prostate cancer. We start treatment for fracture prevention when patients are started on ADT for biochemical recurrence. Men starting on ADT are given vitamin D and supplemental calcium, and we also check their bone mineral density with a dual-energy x-ray absorptiometry scan to decide about initiating treatment with an antiresorptive agent. If they have osteoporosis, they will receive either low-dose denosumab (Prolia®), zoledronic acid (Reclast), or alendronate (Fosamax®), although my preference is denosumab because it is the only therapy shown to prevent fractures in men. High-dose antiresorptive therapy is started in all patients who develop castration-resistant metastatic disease, either denosumab (Xgeva) or zoledronic acid (Zometa®).

Role of metastatic biopsy

Dr. Armstrong: Most patients who have progressed to mCRPC have not had tissue collected since their diagnostic biopsy or prostatectomy. When would you consider doing a metastatic biopsy?

Dr. Taha: There are a few scenarios where I perform a biopsy for metastasis. One situation is when a patient has radiographic metastatic disease to the liver, and there I am looking for possible transformation to small-cell carcinoma. I have seen that transformation in several cases and then switched the patient's systemic therapy to a regimen for small-cell carcinoma. Although the prognosis with small-cell carcinoma is poor, these patients usually get a good radiographic response and a significant PSA response after changing treatment.

I also do a metastatic biopsy if metastasis develops 4 or more years after the patient had prostatectomy or the diagnostic biopsy. The purpose of the biopsy is to acquire tissue for genomic testing. Although liquid biopsy is available, it is helpful to have new tissue for the genomic studies and the biopsy also provides confirmation of metastasis.

Dr. Armstrong: I agree with your approaches. I would add that some clinical trials require tissue acquisition from a metastatic lesion or genomic results to help identify specific molecular subsets of patients such as for PARP inhibitor trials. Germline testing is recommended for all men now with metastatic prostate cancer and in men with high-risk localized disease to help guide therapy and counseling.

Dr. Dato: Another situation where I will get a biopsy is in a patient who has lytic bone lesions. Lytic bone lesions are uncommon in patients with prostate cancer, and when I saw that in a patient of mine who had nodal metastases, I did a biopsy that showed myeloma. The biopsy was definitely beneficial for making that diagnosis.

Dr. Armstrong: Do you think that the results from liquid tumor biopsies are as reliable as those from the sequencing techniques that use tissue?

Dr. Taha: There have not yet been any studies formally comparing the FDA-cleared or commercially marketed cell-free plasma tests for prostate cancer

against those which use tissue, nor have the liquid biopsy tests been used with a specific treatment regimen in prospective clinical trials. There are emerging data showing good concordance between liquid and solid tumor tests. In particular, some recent publications show good concordance for MSI in cell-free DNA as long as there is enough cell-free DNA in the sample.[17,18] One of the challenges with plasma assays is there may not be enough tumor content in the sample, and then the test is inconclusive.

That limitation also holds true for tissue acquisition from a metastatic biopsy. You have to biopsy the tumor and have enough tumor content to get an informative test result. Most of the issues around discordance between tests are due to low tumor content in the samples rather than true tumor heterogeneity, although heterogeneity does occur because there can be genetic differences between tumors at different sites of metastasis. There can also be clonal evolution at metastatic sites, and so it is reasonable to do repeated biopsies over time as we try to open the door for patients to have access to therapies that could ultimately help them.

Even though there are not comparative data, based on my clinical experience, I prefer tissue testing because it seems more reliable than liquid biopsy. There are times, however, when liquid testing is our only option.

Dr. Armstrong: Dr. Taha brought up development of small-cell prostate cancer, which is certainly one of the greatest concerns with this disease. Although it can be platinum-responsive, it is very hard to treat. Is there any reason to believe that the earlier use of AR-targeted therapies may promote the existence of AR-negative or AR-indifferent tumors over time?

Dr. Karsh: It is certainly a concern, and the possibility that the tumors are changing is something that we worry about in all patients. They do morph into having small-cell or neuroendocrine components, and we are seeing that more often now with the availability of treatments that are keeping patients alive longer. As men are living longer with prostate cancer, it is likely that they may develop resistant and more aggressive disease.

FINAL THOUGHTS

Dr. Armstrong: The availability of AR-targeted therapies to treat men in both the hormone-sensitive and nonmetastatic CRPC settings is improving survival for patients with prostate cancer, but with the earlier use of these agents, patients who develop metastatic disease may have already been exposed to AR therapy. Having results from biomarker tests, including AR-V7 and broad molecular panels, is helping to inform treatment decisions. These decisions are not made in isolation but rather are reached in conjunction with the patient and made in the context of a variety of factors, including patient preferences, comorbidities, symptoms, and pattern of cancer spread.

Our group is in agreement about following the NCCN Guidelines® and AUA Guidelines when deciding on taxane chemotherapy versus AR-targeted therapy or radium-223 for patients with mCRPC in the first- or second-line setting. We believe that sipuleucel-T has a place for improving survival in patients with asymptomatic or minimally symptomatic mCRPC. Following progression on an AR inhibitor/ADT in the mHSPC setting or the M0/M1 CRPC setting, we generally agree that AR-V7 can be helpful in informing this decision on further AR inhibition versus taxane chemotherapy utility.

More treatment options for mCRPC are coming, including PARP inhibitors and new immunotherapies that are showing promise in select groups of patients. Molecular testing, both germline and somatic testing, could help identify men who are suitable for and may benefit from those treatments.

Dr. Karsh: I totally agree with Dr. Armstrong. We are in an exciting time for patients with advanced prostate cancer because we have a number of new options for treatment and more therapies as well as combination treatments are in the pipeline. Important tests like AR-V7 biomarker and genetic sequencing are helping us to personalize therapy for our patients, and we need to learn how to optimize their use. In addition to all of these developments, guidelines and our clinical experience will help us sequence therapies so that we can improve survival and maintain a good quality of life for our patients.

Dr. Taha: I am very enthusiastic about the AR-V7 test for evaluating men with mCRPC, both because of its value as a prognostic indicator and helping us make challenging and important clinical decisions for our patients (Figure 4). I am excited about future developments in the treatment of prostate cancer.

Dr. Dato: We are all in agreement that there have been significant advances in treatment for patients with prostate cancer. This progress is allowing us to give our patients great hope, which is one of the best things we can give them.

AR-V7 Nucleus Detect® test - Positive

- Poorer prognosis than AR-V7 negative[10-12]
- Extremely unlikely to respond to abiraterone or enzalutamide[10-12]
- More likely to live longer when treated with taxanes compared to AR-targeted therapy[11]

AR-V7 Nucleus Detect® test - Negative

- More favorable prognosis than AR-V7 positive[10-12]
- May benefit from another AR-targeted therapy[10-12]
- May live longer with AR-targeted therapy[11]

Figure 4. Summary of prognostic information provided by the Oncotype DX AR-V7 Nucleus Detect® test.

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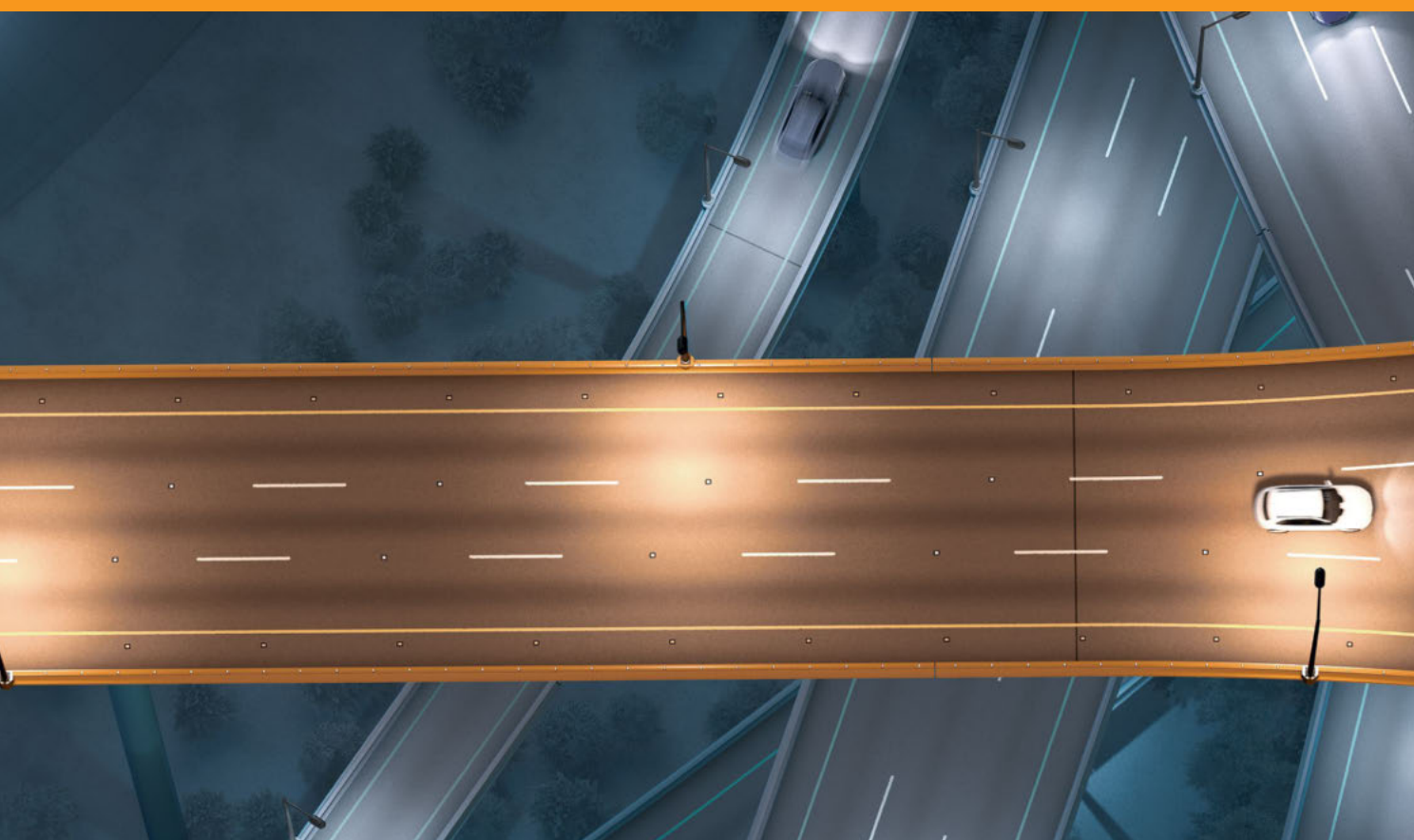

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