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Current Treatment Strategies for Advanced Prostate Cancer

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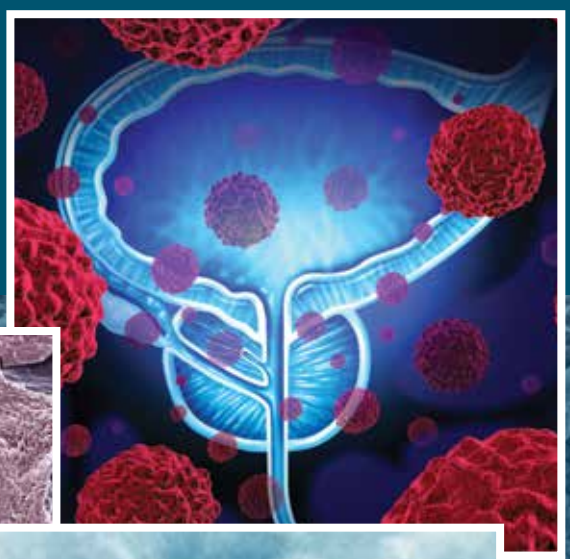

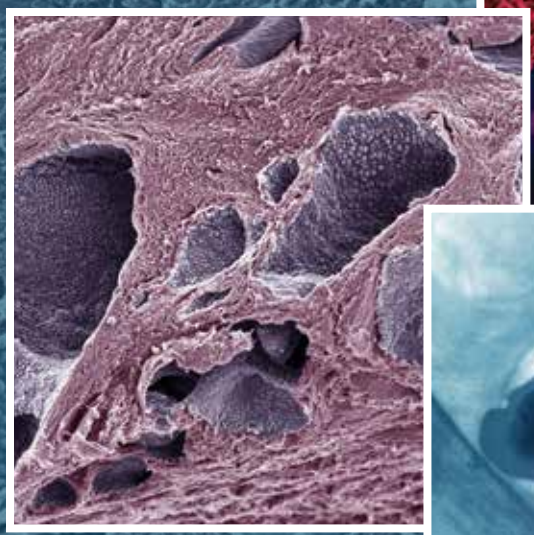

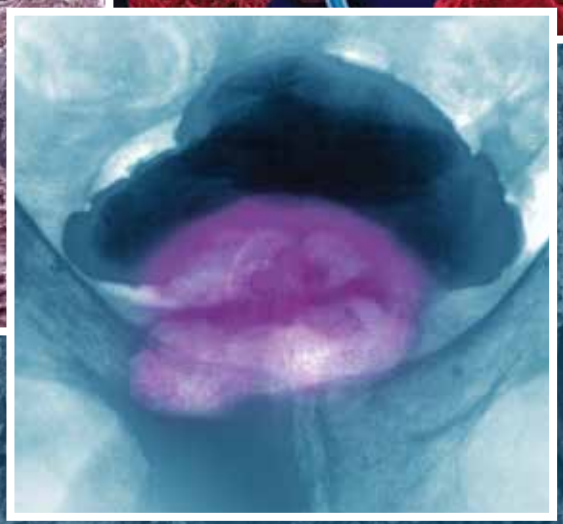

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AUDIENCE:

This activity was planned for health care providers who manage and treat patients with prostate cancer.

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LEARNING OBJECTIVES:

1. Identify best practices for integrating currently available treatment options for advanced prostate cancer, including immunologic therapies, new secondary hormonal agents, chemotherapy, and radiopharmaceuticals
2. Describe new management options for metastatic hormone-sensitive prostate cancer (mHSPC)
3. Outline considerations for current and emerging therapies in the management of patients with metastatic castration-resistant prostate cancer (mCSPC)
4. Understand how the molecular and biochemical underpinnings of mCRPC can impact treatment course and selection

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Current Treatment Strategies for Advanced Prostate Cancer

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Overview of the Current State of Prostate Cancer

An estimated 161,000 men will be diagnosed with prostate cancer in 2017.[1] Except for skin cancer, prostate cancer remains the most common cause of cancer in American men. As with many forms of cancer, the earlier the disease is caught, the better chance the patient has of long-term survival. Most men are diagnosed with prostate cancer at the localized stage (79%) and have a greater than 99% 5-year relative survival rate.[1,2] The majority of patients will seek treatment through surgery or radiation, and among those patients, approximately one-third will experience disease recurrence.[3] Although androgen deprivation therapy (ADT) achieves temporary tumor control or regression in 90% of these individuals, most patients will ultimately progress (**FIGURE 1**).

Once disease progresses despite castrate levels of circulating androgens (T <50 ng/dL), it is considered castration-resistant prostate cancer (CRPC). Progression may be biochemical, clinical and/or radiographic, as evidenced by a continuous rise in serum levels of prostate-specific antigen (PSA), progression of pre-existing disease, and/or appearance of new metastases.[3] If the disease spreads to the regional lymph nodes, seminal vesicles, and distant sites such as the bones (metastatic castration-resistant prostate cancer [mCRPC]), the 5-year survival rate drops to approximately 30%.[2,4,5]

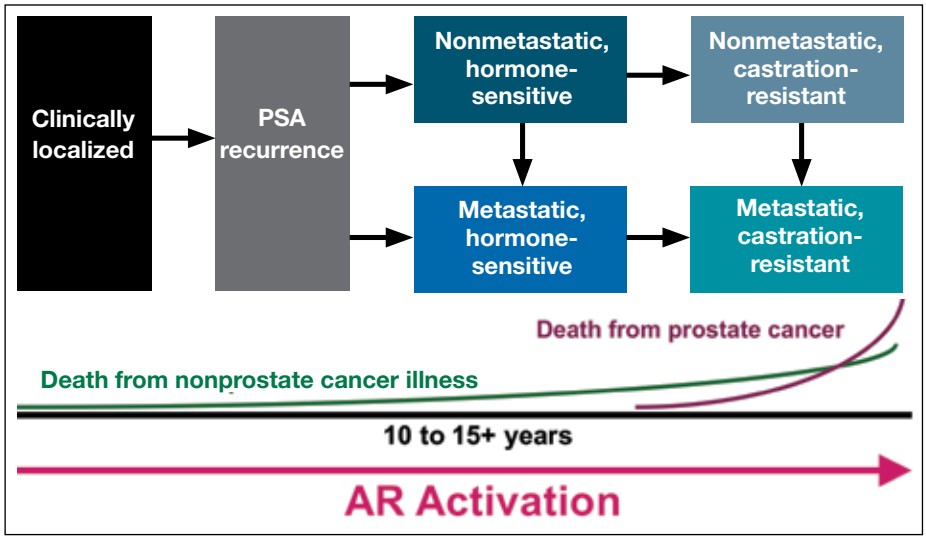
The exact underlying endocrine physiology and molecular underpinnings involved in the transition from castration-sensitive to castration-resistant disease is still not fully understood. However, we do now know that the androgen receptor (AR) remains active despite castrate levels of androgens, continuing to drive prostate cancer progression.[6-8] Reactivation of the AR can occur through AR gene mutations,[9,10] AR splice variant expression,[11] AR gene overexpression,[12,13] increased expression of transcriptional coactivators,[14,15] upregulation of the enzymes involved in androgen synthesis (ie, CYP17 α-hydroxylase and C17–20-lyase [CYP17]),[16] and tumor cell synthesis of testosterone from cholesterol.[8] These are not mutually exclusive; multiple pathways and mechanisms can be occurring concomitantly in a given tumor cell.

While the treatment of CRPC presents a significant clinical challenge, there is potential for improvements in its management, largely due to advances in our understanding of biologic mechanisms underlying progression to the lethal phenotype, and more basic understandings of malignant proliferation, angiogenesis, and metastatic potential. Through a greater understanding of the underlying pathways involved in CRPC and mCRPC, critical advancements have been made in drug development and treatment protocols.

Current Management of mCRPC

Over the past decade, the treatment landscape for prostate cancer has changed dramatically with the introduction of various agents that have demonstrated a survival benefit in mCRPC **(FIGURE 2**). Current US Food and

FIGURE 1. Clinical States of Prostate Cancer



Abbreviations: AR, androgen receptor; PSA, prostate-specific antigen.

Drug Administration (FDA)-approved agents for the treatment of mCRPC, include early docetaxel for newly diagnosed metastatic hormone-sensitive prostate cancer (HSPC),[5,16,17] novel endocrine therapies that deprive or block prostate cancers from the effects of androgens (abiraterone,[18-22] enzalutamide,[23,24] immunotherapeutic strategies that act to induce antitumor responses [sipuleucel-T[25]], new radiopharmaceuticals to target bony metastases [Radium-223[26]], and novel chemotherapeutic agents, [cabazitaxel][27,28]) (**TABLE**).

Each case of prostate cancer requires individual consideration and precision care. However, for patients with mCRPC that has progressed after ADT, there is no consensus regarding the optimal second-line (and beyond) therapy and numerous options are included in the list of recommended agents in National Comprehensive Care Network (NCCN) and American Urological Association (AUA) guidlines.[4,31] In absence of definitive clinical trial data, clinicians consider a variety of factors, including physical status/comorbidities, presence or absence of disease-related symptoms (ie, bone pain, fatigue, weight loss/anorexia), sites of metastatic disease (node only vs extensive bone/visceral), disease characteristics (ie, poor PSA expressing tumor, tumor volume, high-grade disease, short-interval response to primary ADT), and treatment history. Classes of FDA-approved agents for mCRPC treatment are briefly described below.

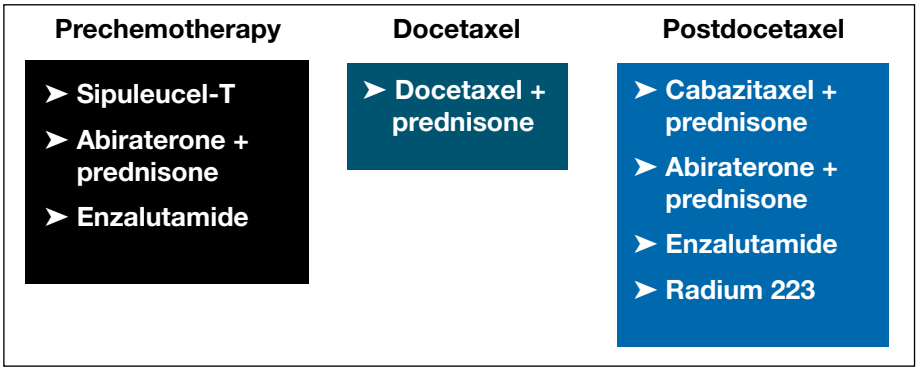
AR Targeting Agents

Abiraterone acetate is a second-generation AR-signaling pathway inhibitor that has been approved in both the pre- and postchemotherapy settings. Abiraterone acetate inhibits the CYP17 enzyme required for androgen biosynthesis in testicular, adrenal, and prostatic tumor tissue, whereas ADTs decrease androgen production in testes, but do not affect androgen production by the adrenals or in prostatic tumor tissue.[32] The ability of abiraterone acetate to target these alternative sites of androgen production make it an attractive treatment option for patients progressing on ADT. However, abiraterone acetate can also trigger mineralocorticoid excess, which result in hypokalemia, hypertension, and fluid retention and can promiscuously activate the AR and thereby drive prostate cancer growth.[32] As such, abiraterone acetate is administered in conjunction with prednisone, which dampens adrenocorticotropic hormone (ACTH) upregulation and decreases mineralocorticoid production.[33]

The approval of abiraterone acetate plus prednisone (AAP) for treatment of post-docetaxel mCRPC and chemotherapy-naïve mCRPC was based on the results of 2 large phase 3 trials: COU-AA-301 and COU-AA-302, respectively. In COU-AA-301, patients with mCRPC previously treated with docetaxel-containing regimens who were treated with AAP had a modest improvement in median overall survival (OS) of approximately 4 months.[18,19] AAP also improved the time to PSA progression (8.5 vs 6.6 months; hazard ratio [HR] 0.63; 95% confidence interval [CI], 0.52–0.78; $P<.0001$), and radiographic progression-free survival

(rPFS; 5.6 vs 3.6 months; HR 0.66; 95% CI, 0·58–0.76; *P*<.0001). The COU-AA-302 trial focused on patients with mCRPC who had not received cytotoxic chemotherapy and had metastases to the bone, soft tissue, or lymph nodes.[20,21] Similar improvements in OS were observed in these patients, along with a more substantial improvement in rPFS (16.5 vs 8.2 months; HR, 0.52; 95% CI, 0.45–0.61; *P*<.0001). In chemotherapy-naïve mCRPC patients, AAP also prolonged the time to the initiation of chemotherapy, need for opiates for cancer pain, PSA progression, and declines in performance status.[20-22]

FIGURE 2. Current FDA-Approved Agents for the Management of mCRPC



Abbreviations: FDA, US Food and Drug Administration; mCRPC, metastatic castration-resistant prostate cancer.

Enzalutamide is a potent competitive AR antagonist that inhibits ligand binding to the AR, as well as AR translocation to the nucleus and binding its cognate response elements.[34] In contrast to abiraterone, enzalutamide does not require administration of prednisone. Enzalutamide is approved by the FDA for both postdocetaxel and chemotherapy-naïve mCRPC based on the results of 2 phase 3 placebo-controlled studies: AFFIRM[23] and PREVAIL.[24] The AFFIRM trial demonstrated that enzalutamide therapy in postdocetaxel mCRPC had a 4.8-month median OS benefit compared with placebo (HR, 0.63; *P*<.001).[23] In the PREVAIL study of patients with asymptomatic or minimally symptomatic progressive metastatic disease who failed ADT but had not yet been treated with chemotherapy, patients treated with enzalutamide, compared with those receiving placebo, experienced a statistically significant 29% reduction in risk of death (HR, 0.70; 95% CI, 0.60–0.84; *P*=.0001) and an 81% reduction in risk of radiographic progression (HR, 0.186; 95% CI, 0.15–0.23; *P*<.0001).[24]

There are several important clinical lessons regarding AAP and enzalutamide use. It is unclear whether a patient who has had AAP or enzalutamide as their first line of treatment for mCRPC should receive the other agent in the second line. Initial data suggests that PSA responses are low if the patient receives the other agent in the second line, but it is difficult to make an accurate assessment based on the currently available case series. Also, it is important to recognize that for patients who are on either AAP or enzalutamide, rising PSA is not sufficient evidence to discontinue therapy—patients should remain on treatment in the absence of other signs of progression (clinical or radiographic).[35] Furthermore, in patients with rising PSA but stable radiographic disease except for a single painful metastatic bone lesion, the lesion can be targeted with palliative radiation and patients can continue AAP or enzalutamide.

Immunotherapy

At this time, sipuleucel-T is the only immunotherapy approved by the FDA for treating asymptomatic or minimally symptomatic mCRPC patients. Sipuleucel-T is a personalized cellular immunotherapy developed from the patient's own immune cells aimed at targeting the prostate cancer antigen, prostatic acid phosphatase.[36] FDA approval is based on results of the randomized placebo-controlled phase 3 IMPACT trial that enrolled patients with asymptomatic or minimally symptomatic chemotherapy-naive mCRPC.[25] Similar to other approved agents, the medianimprovement in OS was approximately 4 months with sipuleucel-T, but there were no significant effects on PSA response rate, radiologic

TABLE. Summary of Approved Therapies with Survival Benefit for mCRPC[21-30]

Agent	Indication	Route Schedule	Cortico-steroids	Symptoms	Contra-indications	PSA Response	Median OS Benefit, Mos
Sipuleucel-T	Pre/post-doc	IV every 2 wk x 3	No	Asymptomatic, minimally sx	Narcotics for pain, liver mets	No	4.1
Abiraterone	Pre/post-doc	Oral, empty stomach	Yes*	Not specified	Severe liver dysfx, low K, heart failure	Yes	Post-doc: 4.6 Pre-doc: 4.4
Enzalutamide	Pre/post-doc	Oral	No	Not specified	Seizures	Yes	Post-doc: 4.8 Pre-doc: 4.0
Docetaxel	mCRPC	IV every 3 wk	Yes*	Not specified	Moderate liver dysfx, cytopenias	Yes	2.4
Cabazitaxel	Post-doc	IV every 3 wk	Yes*	Not specified	Moderate liver dysfx, cytopenias	Yes	2.4
Radium-223	Post-doc or not fit for docetaxel	IV, every 4 wks for 6 doses	Not Required	Symptomatic bone metastases	Visceral mets	NR	3.6

Abbreviations: Doc, docetaxel; dysfx, dysfunction; K, potassium; mCRPC, metastatic castration-resistant prostate cancer; NR, not reported; OS, overall survival; PSA, prostate-specific antigen.
*In clinical trials and on FDA label.

responses, or time to progression. Adverse events are primarily related to infusion reactions, nausea, fever, headache, and fatigue. A retrospective subgroup analysis of the IMPACT study found that patients who had lower PSA levels (≤22.1 ng/mL) garnered the most benefit from sipuleucel-T in OS.[37] Therefore, the ideal patient to receive sipuleucel-T is one who is asymptomatic, with a baseline PSA ≤22.1 ng/mL.

Studies of immune checkpoint inhibitors are currently investigational, but have yielded lackluster results for treatment of mCRPC thus far. However, the addition of pembrolizumab to patients progressing on enzalutamide has demonstrated promising initial results in an ongoing clinical trial, with 19% of treated patients obtaining a confirmed and sustained PSA response and 21% patients with stable disease >6 months.[38] A currently ongoing phase 1b/2 combination trial in mCRPC (KEYNOTE 365) is assessingthe efficacy of treating patients with pembrolizumab combination therapies following prior doce-taxel, abiraterone, or enzalutamide.[39] While several other interesting combination studies are underway involving 1 or more immunotherapies in combination with other agents,[39] until trial results are available, the role of these agents for the treatment of mCRPC remains unclear.

Cytotoxic Therapy

Docetaxel is the first therapy to demonstrate a modest, although statistically significant survival advantage in mCRPC and was subsequently approved by the FDA for this indication.[29,30] Another taxane, cabazitaxel, has been assessed for treatment of post-docetaxel and chemotherapy-naïve patients. In mCRPC patients who progressed during and after treatment with a docetaxel-based regimen, treatment with cabazitaxel plus prednisone conferred a modest improvement in the median overall survival compared to mitoxantrone plus prednisone (15.1 months vs 12.7 months, respectively; HR, 0.72; 95% CI, .61-.84; *P*<.0001).[27] Based upon these results, the FDA approved cabazitaxel for treatment of mCRPC in the post-docetaxel setting. However, results from the FIRSTANA trial found that cabazitaxel plus prednisone was not superior to docetaxel plus prednisone in the first-line setting.[28]

DNA Damage Agents

Radium-223 is a calcium mimetic that homes to bone and emits a high energy alpha particle with a very short linear range.[26] The alpha particles cause double-strand DNA breaks in nearby tumor cells, but due to the limited penetration of alpha emitters (~2-10 cell diameters), there is highly localized killing of tumor cells with minimal collateral damage to normal tissue in surrounding area. As a result, radium-223 has a relatively modest toxicity to the bone marrow, and is generally well tolerated (increased rates of anemia, neutropenia, thrombocytopenia, bone pain, diarrhea, nausea, vomiting, and constipation have been reported).[26] Radium-223 was approved by the FDA for treating mCRPC with bone metastases based on results from the phase 3 ALSYMPACA trial.[26] This trial enrolled patients previously treated with docetaxel (or unfit for docetaxel) with confirmed symptomatic CRPC, ≥2 bone metastases, and no known visceral metastases. There was an OS benefit of 4.6 months in patients with no prior docetaxel use (HR,0.745;95%CI,0.562–0.987;*P*=.03932) and 3.1 months in patients with prior docetaxel use (HR, 0.710; 95% CI, 0.565–0.891; *P*=.00307). Ongoing trials will inform the optimal use of Radium-223 in combination with currently approved AR-targeting agents (NCT02034552: Radium-223 ± Abiraterone OR Enzalutamide; NCT02043678: Abiraterone ± Radium-223; NCT02463799: Sipuleucel-T ± Radium-223).

Does the Earlier Use of Chemotherapy or Next Generation AR-Targeting Agents Improve Survival in Hormone-Sensitive Prostate Cancer (HSPC)?

Three randomized controlled trials assessed whether docetaxel added to ADT at the onset of treatment improves OS: the GETUG study,[40] the CHAARTED study,[16] and the STAMPEDE multiarm study.[41] For men with chemo-naïve HSPC, there is a striking survival advantage for adding docetaxel to ADT (62.1 months, 57.6 months, 60 months) vs ADT alone (48.6 months, 47.2 months, 45 months [GETUG, CHAARTED, and STAMPEDE trials, respectively]). Based on the CHAARTED study, the improvement in OS seems to be restricted to patients with high metastatic burden (≥4 bonemetastases, including at least one metastasis in the appendicular skeleton, or visceral metastases) This 10-to 15-month survival advantage with docetaxel added to ADT is particularly striking given that docetaxel treatment of castrate-resistant men improves survival by only approximately 2.5 months.[29,30]

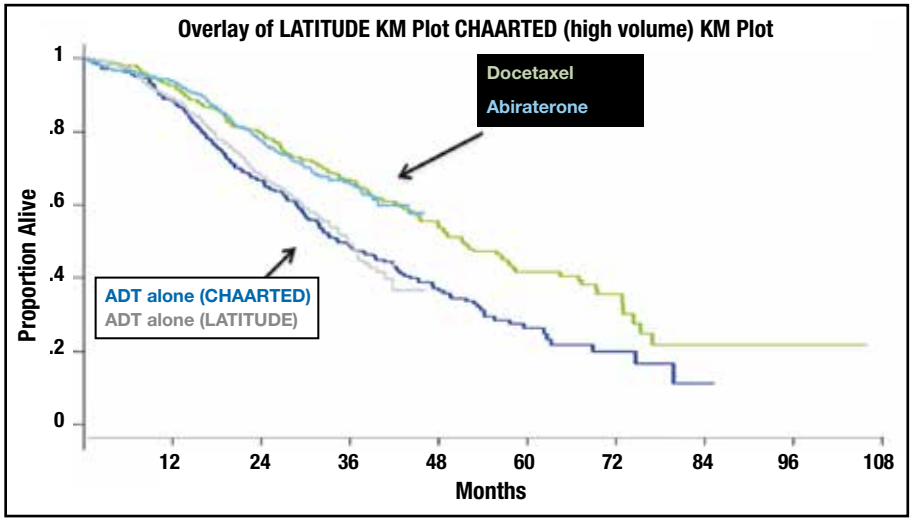
Similarly, the LATITUDE[42] and STAMPEDE[41] studies assessed whether AAP added to ADT at the onset of treatment improves overall survival in men with hormone-treatment-naïve advanced prostate cancer. Both studies found a 37% to 38% reduction in the risk of death when AAP was added to ADT.

In a comparison of the median OS between LATTITUDE (AAP + ADT),[42] STAMPEDE (AAP + ADT)[41] and high-volume CHAARTED (docetaxel + ADT),[16] the HR were almost identical (0.62, 0.63, and 0.63, respectively). The 3-year OS rate was also nearly identical in the AAP + ADT treatment arm in the LATTITUDE study and the docetaxel + ADT treatment arm in the CHAARTED study (66% and 65%, respectively). **FIGURE 3** shows an overlay of the LATITUDE Kaplan-Meier (KM) plot on the CHAARTED (high volume) KM plot as a visual comparison of OS for docetaxel vs AAP.[43] Based on the results of these studies, the benefit of adding AAP vs docetaxel to ADT is approximately the same. When deciding between these options for treating castration-sensitive prostate cancer, toxicity may become the dominant deciding factor; toxicity is substantially less with the nonchemotherapy option. The benefit of adding these agents to M0 HSPC (eg, locally advanced disease) has not yet been unequivocally established.

Investigational Biomarkers and Companion Therapies

Advances in genetic sequencing have focused on identifying biomarkers that can predict drug sensitivity or prognosis.[44-46] Current approaches to molecular biomarkers include targeted analysis of circulating tumor DNA in plasma (*AR, BRCA1/2, ATM*); targeted analysis of circulating tumor cells (AR-v7); imaging

FIGURE 3. Comparing OS of Docetaxel vs Abiraterone Across Studies in Newly Diagnosed High-risk Metastatic Prostate Cancer[43]



Abbreviations: ADT, androgen-deprivation therapy; KM, Kaplan-Meier; OS, overall survival.
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(functional evaluation-18F sodium fluoride [NaF], dihydrotestosterone [DHT], prostate-specific membrane antigen [PSMA]); and metastatic biopsy (whole exome/transcriptome, targeted analysis of actionable genomic lesions, DNA methylation), among others.[47] The relatively high frequency of detectable mutations in advanced prostate cancer affords the opportunity to assess the utility of biomarkers with the hope that investigational molecular biomarkers will improve clinical decision making for prostate cancer.[47,48]

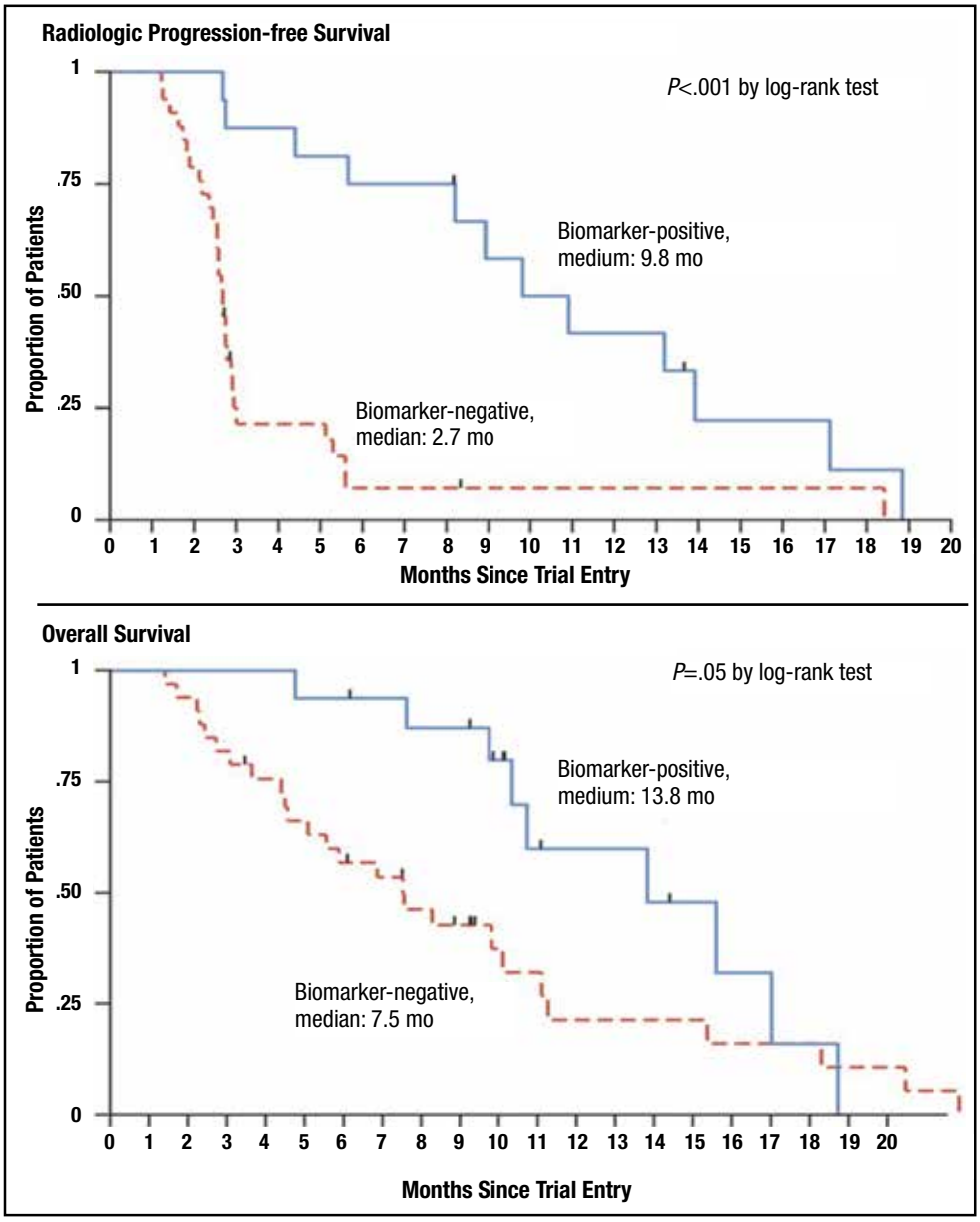
Circulating tumor cell (CTC) DNA and circulating DNA analyses in patients with CRPC has the potential to track changes in response and resistance during treatment.[47] Given the molecular diversity of tumors within a single patient, analyses of this type of DNA may be preferable because it represents all tumors as they shed DNA into the bloodstream as opposed to a biopsy, which only will represent one site of disease. Recently, detection of AR splice variant-7 mutation, AR-V7, in the CTCs of men with mCRPC was found to be associated with resistance to abiraterone and enzalutamide therapy.[46] AR-V7 is an abnormally spliced mRNA isoform of the AR that remains active and can drive CRPC growth despite the inability to bind its ligand.[49]

In the recent study conducted by Antonarakis and associates, a multivariate analysis revealed a significant correlation between treatment outcomes and detection of CTC and AR-V7 mRNA.[46] The outcomes were best for CTC negative patients (presumably lowest tumor burden), intermediate for CTC positive/AR-V7 negative patients (high tumor burden, but variant is not present), and worst for CTC positive/AR-V7 positive patients (high tumor burden with the variant) in both the first-line and second-line novel hormonal cohorts. The outcome is believed to be worst in patients with detectable CTC and AR-V7 due to the high tumor burden, which, for the most part, is not likely to respond to either AAP or enzalutamide because of AR-V7. In addition, the biology of the tumors that express the AR-V7 may be intrinsically more aggressive. The use of AR-V7 as a molecular biomarker has the potential to be both predictive and prognostic. Prospective AR-V7 biomarker-driven trials are underway, as well as the development of a standardized, certified AR-V7 assay.

Assessing DNA-repair mutations is another potential source of biomarkers. The incidence of germline mutations in genes mediating DNA-repair processes among men with mCRPC is significantly higher than the incidence among men with localized prostate cancer, most commonly occurring as aberrations of *BRCA2, BRCA1*, and *ATM*.[47,48,50] Testing men with mCRPC for DNA-repair gene mutations could assist in predicting the results of therapeutic options. For example, poly-(ADP-ribose) polymerase (PARP) inhibition results in frequent and sometimes durable antitumor activity in men with mCRPC and mutations in DNA damage repair genes. PARP is a large family of proteins that interacts with

proteins involved in multiple cellular process including DNA repair, transcription, apoptosis, chromatin structure, and histone modification.[50] There are at least 5 different PARP inhibitors in phase 3 clinical trials: olaparib, rucaparib, niraparib, velaparib, and talazoparib for treatment of ovarian, breast, gastric, pancreatic, prostate, lung adenocarcinoma, and glioblastoma cancers. Recently, outcomes from the phase 2 study of olaparib in mCRPC (TOPARP-A) resulted in the FDA granting olaparib breakthrough therapy designation for the treatment of BRCA1/2 or ATM gene mutated mCRPC.[44] In this open-label, single-group, two-stage, phase 2, multisite study, 88% of the mCRPC patients with a mutation in a homologous recombination repair gene had a response to olaparib, whereas only 6% of patients without a DNA repair alteration had a response (**FIGURE 4**). These results provide a striking example of how precisiononcologycanimprove patient outcomes. Additional trials with olaparib are ongoing (NCT02861573: KEYNOTE-365, NCT03012321: AAP +/- olaparib vs olaparib mono-therapy in mCRPC patients with *ATM*, *BRCA1*, or *BRCA2* mutations, among others). Other studies include the phase 3, randomized TRITON3 study of patients with mCRPC and evidence of a homologous recombination gene deficiency (deleterious mutation in the *BRCA1/2* or *ATM* gene) treated with rucaparib versus treatment with a physician's choice of AAP, enzalutamide, or docetaxel (NCT02975934), as well as the phase 2 study

FIGURE 4. Precision Oncology at Work: Increased Efficacy of Olaparib in Patients with a DNA Repair Alteration[44]



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of niraparib in men with metastatic CRPC and DNA repair anomalies (NCT02854436).

While definitive biomarkers for mCRPC have not been elucidated, by understanding the molecular pathways involved in CRPC, as well as how agents target these pathways, clinicians will gain a better understanding of how to treat specific patient populations—ie, precision oncology—and improve patient outcomes. Of note, the FDA recently granted accelerated approval of pembrolizumab for the treatment of adult and pediatric patients with unresectable or metastatic solid tumors that have been identified as having a biomarker referred to as microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR). This represents the first cancer treatment approved based upon a particular biomarker. In the future, targeting prostate cancer patients carrying these biomarkers for treatment with pembrolizumab may be an effective application of precision oncology, given that up to 12% of advanced prostate cancers are hypermutated due to mismatch repair gene mutations and MSI.[51]

Special Considerations for the VA Patient

Among the approximately 40,000 cancer cases reported in the Veterans Affairs Central Cancer Registry (VACCR) each year, prostate cancer is the most commonly diagnosed; approximately 1 in 3 cancer diagnoses are prostate cancer.[52] Of note, prostate cancer accounts for 42.7% of cancers in African-American veterans compared to 28.9% of cancers in white veterans.[52,53] This is important to keep in mind since prostate cancer often presents earlier and is more aggressive in African American men—African American men are more than twice as likely to die of prostate cancer than white American men.[53] Another risk factor for prostate cancer in the VA population is Agent Orange exposure. While not definitive, there is an increased incidence of prostate cancer among patients with a history of exposure to Agent Orange or to 2,3,7,8-tetrachlorodibenzo-p-dioxin.[54-56] In addition, these patients develop the disease at a younger age, have a 2-fold increase in the proportion of Gleason scores ≥8, and are more likely to have metastatic disease at presentation.[54-56] It remains unclear as to whether there is a difference in the molecular drivers of Agent Orange-related prostate cancer vs other prostate cancers.

Recognizing the importance of the interface between molecular medicine and cutting-edge, patient-centered cancer care, the Department of Veteran Affairs (VA) created a new clinical program called the Precision Oncology Program (POP).[57,58] The goal of this program is to integrate knowledge about molecular medicine in cancer with a database of observations from previously treated veterans that "assures access to modern genomic oncology practice in the VA, removes disparities of access across the VA network of clinical centers, disseminates the products of learning that are generalizable to non-VA settings, and systematically presents opportunities for patients to participate in clinical trials of targeted therapeutics."[57] In addition, genetic counselors can be sought through VA Choice Program or through remote consult to a genetics counselor at a VA site that has such services.

As part of the increasing focus on more personalized medicine, the VA and the Prostate Cancer Foundation have created a precision oncology initiative to expand prostate cancer research within the VA system to speed the development of treatments and cures for prostate cancer among veterans.[59] The goal of this initiative, known as POPCAP (Precision Oncology Program Cancer of the Prostate) is to not only increase the number of VA facilities involved in precision medicine/prostate cancer clinical trials, but also facilitate the sequencing of patients' tumors and enroll these patients in clinical trials based upon the specific tumor profile.

Conclusions

Rapid development and FDA approval of multiple agents over the last 5 to 10 years has outpaced our ability to understand the optimal integration, combinations, and sequencing of agents for the management of patients with mCRPC. While the introduction of these agents significantly improved the prognosis of many men with advanced prostate cancer, other men continue to progress despite

treatment. There is limited data available regarding sequencing beyond second-line therapy for heavily pretreated patients with advanced prostate cancer. In addition, there is ongoing discussion of potential cross-resistance within drug classes and between different drug classes, which may impact optimal therapy sequencing. Given possible cross-resistance between drugs and the progression of resistant tumors, the efficacy of subsequent agents may be reduced, making these patients even more challenging to treat. As such, ongoing clinical trials are aimed at determining if these newer agents can be combined to improve efficacy without significantly impacting safety. Other studies are focused on determining the optimal sequencing of these agents. Moreover, as additional novel agents and combinations are evaluated, the treatment landscape will continue to expand. As we learn more about the underlying biology of this disease, precision oncology focused on targeting patient-specific molecular alterations will play a greater role as the fundamental treatment strategies evolve.

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