Metastatic Prostate Cancer: Current Trends and Future Landscape

An estimated 1 in 10 men will develop prostate cancer in their lifetime. In 2016, an estimated 180,890 new cases were diagnosed, and 26,120 men died of the disease, making prostate cancer the second-leading cause of cancer death in US men after lung cancer.

In the United States, 92% of prostate cancers are found in local or regional stages, where the 5-year survival rate nears 100%; however, when the cancer has metastasized, this rate drops to 28% despite continuous advances in diagnosis, staging, and treatment of metastatic and advanced prostate cancer. In the past 6 years, 5 agents have joined docetaxel as FDA-approved treatments for metastatic castration-resistant prostate cancer (mCRPC) based on an increase in overall survival (OS): abiraterone, cabazitaxel, enzalutamide, radium-223, and sipuleucel-T. Nevertheless, prostate cancer remains a complex disease with many controversial aspects.

Advanced prostate cancer results from any combination of lymphatic, blood, or contiguous local spread. Manifestations may include weight loss, anemia, bone marrow suppression, spinal cord compression, pain, hematuria, ureteral and/or bladder outlet obstruction, urinary retention or incontinence, or renal failure.

As a result of its genetic linkage, prostate cancer is more common in males with a strong family history of the illness. Other risks include older age, cigarette smoking, and a diet high in animal fat. In addition, black males are at increased risk and tend to have more aggressive and progressive prostate cancer, leading to more advanced disease and higher-grade disease at diagnosis.

Optimal treatment of newly diagnosed prostate cancer requires assessment of risk. Guidelines from the National Comprehensive Cancer Network (NCCN) incorporate a risk-stratification scheme that assigns patients to risk groups using a minimum of stage, grade, and prostate-specific antigen (PSA) score (Table 1). In patients with organ-confined disease, these groupings are used to select appropriate treatment and predict the probability of biochemical failure after local therapy. Other modules evaluating similar variables in a continuous model such as the University of San Francisco Cancer of the Prostate Risk Assessment score or Kattan nomograms allow better discrimination of individual risk for progression, but they are more complex. Overall, current risk schemes are imperfect, and better stratification is one of the key challenges for prostate cancer research going forward.
Table 1. NCCN Risk Stratification for Prostate Cancer

<table>
<thead>
<tr>
<th>Risk Group</th>
<th>Factors</th>
</tr>
</thead>
</table>
| Clinically localized | Very low       | • T1c  
• Gleason score ≤6  
• PSA <10 ng/mL  
• <3 prostate biopsy cores positive; ≤50% cancer in each core  
• PSA density <0.15 ng/mL/g  |
|            | Low            | • T1-T2a  
• Gleason score ≤6  
• PSA <10 ng/mL  |
|            | Intermediatea | • T2b-T2c or  
• Gleason score 7 or  
• PSA 10-20 ng/mL  |
|            | Higha         | • T3a or  
• Gleason score 8-10 or  
• PSA >20 ng/mL  |
| Locally advanced | Very high     | • T3b-T4 or  
• Primary Gleason pattern 5 or  
• >4 cores with Gleason score 8-10  |
| Metastatic |                | • Any T, N1, or  
• Any T, any N, M1  |

NCCN, National Comprehensive Cancer Network; PSA, prostate-specific antigen

a Patients with multiple adverse factors may be shifted into the next highest risk group.

Genomic tools also have been developed with the purpose of stratifying patients to help guide care, and 4 such tools are available: Decipher, Oncotype DX, Prolaris, and ProMark. These biomarkers can be helpful for decision making in low-risk patients and postradical prostatectomy in selected risk groups; however, further prospective studies are needed to confirm the utility of these new technologies.

Screening and Staging

The declining death rate in prostate cancer in the last 2 decades: suggests that increased public awareness, earlier detection, and more effective treatment have affected mortality. Even with this progress, many issues remain to be resolved, including the role of PSA screening.

In 2012, the United States Preventive Services Task Force (USPSTF) assigned a grade D recommendation to PSA screening, thereby discouraging its use, although this remains controversial. Since then, the use of this test has declined among men 50 years of age and older, and a correlative decrease in the incidence of early-stage prostate cancer was observed in this group between 2012 and 2013.
New screening modalities continue to be explored with the goal of better identifying patients likely to have higher-risk prostate cancer. The Stockholm 3 model incorporates plasma protein biomarkers, genetic polymorphisms, and clinical variables, and was shown to be superior to PSA screening alone in its ability to detect prostate cancer with a Gleason score greater than 6 in men aged 50 to 69 years. Use of this and other proposed models could significantly reduce the number of biopsies performed.

Staging is one of the most important factors in treatment selection and prognosis in prostate cancer. Initial suspicion of prostate cancer is based on an abnormal digital rectal exam or elevated PSA level. Definitive diagnosis requires biopsy of the prostate, usually performed by a urologist using a needle under transrectal ultrasonography guidance. A pathologist assigns a Gleason primary and secondary grade to the biopsy specimen. Clinical staging is based on the TNM 2010 classification (Table 2).

### Table 2. TNM Staging System for Prostate Cancer

<table>
<thead>
<tr>
<th>Primary tumor (T)</th>
<th>TX</th>
<th>Primary tumor cannot be assessed</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>T0</td>
<td>No evidence of primary tumor</td>
</tr>
<tr>
<td></td>
<td>T1</td>
<td>Clinically unapparent tumor neither palpable nor visible by imaging</td>
</tr>
<tr>
<td></td>
<td></td>
<td>T1a Tumor found incidentally during TURP; histologic finding in ≤5% of tissue resected</td>
</tr>
<tr>
<td></td>
<td></td>
<td>T1b Tumor found incidentally during TURP; histologic finding in &gt;5% of tissue resected</td>
</tr>
<tr>
<td></td>
<td></td>
<td>T1c Tumor identified by needle biopsy</td>
</tr>
<tr>
<td></td>
<td>T2</td>
<td>Tumor palpable during DRE or observed on imaging; confined within prostate&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td></td>
<td>T2a Tumor involves ≤1/2 of 1 lobe</td>
</tr>
<tr>
<td></td>
<td></td>
<td>T2b Tumor involves &gt;1/2 of 1 lobe but not both lobes</td>
</tr>
<tr>
<td></td>
<td></td>
<td>T2c Tumor involves both lobes</td>
</tr>
<tr>
<td></td>
<td>T3</td>
<td>Tumor extends through the prostatic capsule&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td></td>
<td>T3a Tumor extends beyond prostate but not into seminal vesicle(s)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>T3b Tumor invades seminal vesicle(s)</td>
</tr>
<tr>
<td></td>
<td>T4</td>
<td>Tumor invades adjacent structures other than seminal vesicles: bladder, levator muscles, and/or pelvic wall</td>
</tr>
<tr>
<td>Regional lymph nodes (N)</td>
<td>NX</td>
<td>Regional lymph nodes not assessed</td>
</tr>
<tr>
<td></td>
<td>N0</td>
<td>No regional lymph node metastasis</td>
</tr>
<tr>
<td></td>
<td>N1</td>
<td>Metastasis in regional lymph node(s)</td>
</tr>
<tr>
<td>Distant metastasis (M)</td>
<td>M0</td>
<td>No distant metastasis</td>
</tr>
<tr>
<td></td>
<td>M1</td>
<td>Distant metastasis</td>
</tr>
<tr>
<td></td>
<td></td>
<td>M1a Nonregional lymph node involvement</td>
</tr>
<tr>
<td></td>
<td></td>
<td>M1b Bone involvement</td>
</tr>
<tr>
<td></td>
<td></td>
<td>M1c Other organ involvement ± bone involvement</td>
</tr>
</tbody>
</table>

DRE, digital rectal examination; TURP, transurethral resection of the prostate

<sup>a</sup> Tumor found in 1 or both lobes by needle biopsy, but not palpable or reliably visible by imaging, is classified as T1c.

<sup>b</sup> Invasion into prostatic apex or into (but not beyond) prostatic capsule is not classified as T3, but as T2.

<sup>c</sup> When >1 site of metastasis is present, most advanced category is used.

[View Larger]
In addition to the TNM system, others may be used to determine risk for recurrence after local therapy. For example, the D’Amico system uses PSA level, Gleason score, and T stage to estimate the risk that the cancer has spread. Regardless of the method used, staging is important to help determine treatment options and the outlook for survival or cure.

**Initial Treatment for Prostate Cancer**

For early-stage/localized disease, many therapeutic modalities are available, including surgery, radiation therapy (RT), brachytherapy, androgen-deprivation therapy (ADT), medical or surgical castration, androgen blockade, and chemotherapy. RT techniques have evolved over the past several decades to allow for the safe administration of higher doses. Cryosurgery, also known as cryotherapy or cryoablation, is an evolving minimally invasive therapy that damages tumor tissue through local freezing. Other emerging local approaches, such as high-intensity focused ultrasound and vascular-targeted photodynamic therapy, warrant further study. The selection of these modalities is highly varied among oncologists and urologists.

For patients with locally advanced or intermediate-/high-risk prostate cancer, ADT is recommended in combination with RT and has been shown to improve survival. Use of ADT as the primary therapy for patients with organ-confined prostate cancer generally is not recommended.

Despite established data for the benefits of ADT, a number of recent studies suggest that even after 6 and 12 months on ADT, patients were more likely to demonstrate impaired cognitive performance compared with matched controls not on ADT. Another study detected an association between the use of ADT in the treatment of prostate cancer and an increased risk for Alzheimer’s disease in a general population cohort. Therefore, although the use of ADT is integral to the treatment of prostate cancer, it is not without potential long-term adverse consequences.

**Chemotherapy for Hormone-Sensitive Prostate Cancer**

Docetaxel, which has been a standard of care (SOC) for the treatment of CRPC for many years, recently also demonstrated an OS benefit in hormone-sensitive prostate cancer.

In the CHAARTED trial, 790 patients with metastatic hormone-sensitive prostate cancer were randomized to receive ADT plus docetaxel or ADT alone. After a median follow-up of 28.9 months, the median OS was 13.6 months longer with ADT plus docetaxel than with ADT alone (57.6 vs 44.0 months; hazard ratio [HR], 0.61; 95% confidence interval [CI], 0.47-0.80; \( P<0.001 \)). The median time to biochemical, symptomatic, or radiographic progression was 20.2 months in the combination group vs 11.7 months in the ADT-alone group (HR, 0.61; 95% CI, 0.51-0.72; \( P<0.001 \)). In the combination group, the rates of grade 3/4 febrile neutropenia, grade 3/4 infection with neutropenia, and grade 3 sensory and motor neuropathies were 6.2%, 2.3%, and 0.5%, respectively. When patients were stratified between high- and low-volume metastases, the clinical benefit of ADT plus docetaxel was limited to those with a higher burden of metastasis. A quality of life (QoL) analysis of the CHAARTED trial further found that although ADT plus docetaxel was associated with decreased QoL at 3 months, it was better than ADT alone by 12 months.

The STAMPEDE trial recruited men (N=2,962) with high-risk, locally advanced, metastatic or recurrent prostate cancer who were starting first-line long-term hormone therapy. Patients were randomized 2:1:1:1 to SOC treatment only, SOC plus zoledronic acid, SOC plus docetaxel, and SOC plus zoledronic acid plus docetaxel. Data for the docetaxel groups were as follows: median OS of 81 months for SOC plus docetaxel (HR, 0.78; 95% CI, 0.66-0.93; \( P=0.006 \)) and 76 months for
SOC plus zoledronic acid plus docetaxel (HR, 0.82; 95% CI, 0.69-0.97; \( P=0.022 \)) and grade 3 or greater adverse events (AEs) in 288 patients (52%) receiving SOC plus docetaxel and 269 (52%) receiving SOC plus zoledronic acid plus docetaxel. The authors concluded that zoledronic acid showed no evidence of survival improvement and should not be part of SOC for this population, whereas docetaxel should become part of SOC for adequately fit men commencing long-term hormone therapy.20

Chemotherapy for Castration-Resistant Prostate Cancer

Castration-resistant prostate cancer (CRPC) refers to disease that has progressed after androgen deprivation. CRPC is defined as rising serum PSA in the face of castrate levels of testosterone (<50 ng/dL or 1.7 nmol/L) and progressive disease on imaging and consensus criteria. It may or may not be metastatic.33 In general, 4 mechanisms for the development of CRPC have been described: 1) increased sensitivity of the androgen receptor to its agonists; 2) androgen receptor (AR) mutations that render the receptor responsive to alternate, non-androgen ligands; 3) ligand-independent AR activation; and 4) AR-independent mechanisms (Figure 1).34

Figure 1. Mechanisms of resistance in CRPC.34

(1) AR overexpression + continued tumor steroidogenesis;
(2) promiscuous binding and activation of mutant AR by alternative ligands, such as E2, P, C, and F;
(3) ligand-independent mechanisms of AR activation via crosstalk with Akt, HER2, and Ack1 kinases that phosphorylate the AR and via long non-coding RNAs (eg, PCGEM1) that bind to the AR to stimulate transcription of AR target genes; and
AR-independent pathways, in which cancer cell survival and growth are directed by Stat3 signaling or by upregulation of anti-apoptotic Bcl-2.

AR, androgen receptor; ARE, androgen response element; Bcl, B-cell lymphoma; CBP, cyclic AMP response element-binding protein; CRPC, castration-resistant prostate cancer; DHT, dihydrotestosterone; E2, estrogen; F, flutamide; G, glucocorticoid; GR, glucocorticoid receptor; HER, human epidermal growth factor receptor; P, progesterone; Pcgem, prostate-specific transcript; PSA, prostate-specific androgen; Stat, signal transducer and activator of transcription; TBP, TATA binding protein; TFII, transforming growth-interacting factor; TMPRSS, transmembrane protease serine

Docetaxel

It has been approximately 12 years since the publication of 2 seminal articles detailing the survival advantage of docetaxel over mitoxantrone in mCRPC. The phase 3 PRINCE trial (N=187) explored continuous vs intermittent dosing of docetaxel (12 weeks of treatment followed by a pause until disease progression [defined as either serum PSA >4 ng/mL with a 50% increase over baseline, or radiologic or symptomatic progression], then reinitiation). In this study, 1-year survival was 72.6% with continuous dosing vs 75.8% with intermittent dosing, and median OS was 18.3 vs 19.3 months, respectively (P=0.535). Intermittent treatment met noninferiority criteria for 1-year survival but not OS, according to a post hoc analysis. The differences between the study arms in progression-free survival (PFS) and time to treatment failure were not significant. Safety profiles were comparable. This suggests that it is safe to allow some patients to temporarily discontinue docetaxel chemotherapy.

Cabazitaxel

Cabazitaxel is a tubulin-binding taxane that was FDA-approved in 2010 for mCRPC that has progressed on docetaxel. Approval was based on the TROPIC trial, which randomized patients to either cabazitaxel or mitoxantrone. The study met its primary end point, with a 2.4-month improvement in median OS (15.1 vs 12.7 months; HR, 0.70; 95% CI, 0.59-0.83; P<0.0001). Median PFS was 2.8 months with cabazitaxel and 1.4 months with mitoxantrone (HR, 0.74; 95% CI, 0.64-0.86; P<0.0001). The most common grade 3 or higher AEs were neutropenia (82% vs 58%) and diarrhea (6% vs <1%). Eight percent of patients in the cabazitaxel group and 1% in the mitoxantrone group had febrile neutropenia.

Two studies evaluated the dosing of cabazitaxel at 25 mg/m² (recommended in the prescribing information) vs 20 mg/m² in mCRPC. In the PROSELICA trial (N=1,200, post-docetaxel) median survival did not differ significantly between treatment arms, and HR boundaries were within the noninferiority margin assumptions, thus meeting the study’s noninferiority end point. PSA and RECIST response rates were higher with the higher dose, as were overall grade 3/4 AEs (54.5% vs 39.7%), and rates of grade 4 laboratory neutropenia (48.6% vs 21.3%) and neutropenic sepsis/infection (6.1% vs 2.2%).

The FIRSTANA trial randomized 1,168 chemotherapy-naive patients to cabazitaxel 20 mg/m², cabazitaxel 25 mg/m², or docetaxel 75 mg/m². Neither dose of cabazitaxel was superior to docetaxel in OS (24.5, 25.2, and 24.3 months, respectively). Tumor responses were superior with higher-dose cabazitaxel (41.6%) than docetaxel (30.9%; P=0.0370). Grade 3/4 AEs were 41.2% with cabazitaxel 20 mg/m², 60.1% with cabazitaxel 25 mg/m², and 46.0% with docetaxel. Febrile neutropenia, diarrhea, and hematuria occurred more frequently with cabazitaxel 25 mg/m²; and peripheral neuropathy, peripheral edema, alopecia, and nail disorders were more common with docetaxel. Although FIRSTANA did not show improved OS with cabazitaxel, it did demonstrate
different AE profiles between these 2 taxanes. However, the findings likely are not practice changing.

**Hormone Therapy**

**Abiraterone**

Abiraterone is a potent inhibitor of CYP17, an enzyme involved in the production of testosterone. It was approved by the FDA in 2011 for mCRPC after treatment with docetaxel based on the COU-AA-301 trial, in which treatment with abiraterone plus prednisone led to a 3.9-month improvement in OS (the primary end point) vs placebo plus prednisone. The most common AE was fatigue, which occurred at similar rates in both groups. More mineralocorticoid symptoms (fluid retention) and more hypokalemia were observed in the abiraterone group, although the majority of these occurrences were grade 1 in severity.

In 2012, the indication for abiraterone was expanded to include chemotherapy-naive patients. This was based on the COU-AA-302 trial, which demonstrated an 8.2-month improvement in radiographic PFS with abiraterone vs placebo. Although the initial evaluation for OS did not pass the prespecified value for the interim analysis, the final OS analysis demonstrated median OS of 34.7 and 30.3 months for abiraterone and placebo, respectively.

**Enzalutamide**

Enzalutamide is an AR antagonist that inhibits DNA binding of the AR and downstream transcription. It received FDA approval in 2012 for mCRPC after treatment with a docetaxel-containing regimen. This was based on the AFFIRM trial, met its primary end point, extending OS by 4.8 months over placebo. Improvement in the secondary end points of radiographic PFS (8.3 vs 2.9 months) and time to first skeletal-related event (16.7 vs 13.3 months) were noted as well.

In 2014, approval for enzalutamide was extended to chemotherapy-naive patients based on the PREVAIL trial. The 2 primary end points were radiographic PFS (65% with enzalutamide vs 14% with placebo at 12 months (P<0.001) and OS. In 2015, an updated analysis of PREVAIL was presented, with median OS of close to 3 years for enzalutamide.

Common AEs in both trials were fatigue, hypertension, hot flashes, and pain. In the AFFIRM trial, 5 seizures occurred in the enzalutamide arm and none in the placebo arm, leading to a warning against the use of enzalutamide in patients with a history of seizures. In the PREVAIL study, only 1 seizure was noted in each arm.

In early 2016, the FDA accepted a supplemental new drug application for enzalutamide to include findings from the phase 2 TERRAIN and STRIVE studies. TERRAIN enrolled patients with metastatic prostate cancer whose disease progressed despite treatment with a luteinizing hormone-releasing hormone (LHRH) analogue therapy or after bilateral orchiectomy, and the results supported the use of enzalutamide rather than bicalutamide in patients with asymptomatic or mildly symptomatic metastatic CRPC. STRIVE randomized 257 patients with metastatic and 139 with nonmetastatic CRPC and found that enzalutamide significantly reduced the risk for disease progression or death compared with bicalutamide. AEs reported more frequently with enzalutamide included fatigue, back pain, hot flashes, falls, hypertension, dizziness, and decreased appetite; AEs reported more frequently with bicalutamide included constipation, diarrhea, anemia, and urinary tract infection.
Immunotherapy

Sipuleucel-T is an immunomodulating agent best described as an autologous cellular immunotherapy generated after apheresis of the patient’s own immune cells.\textsuperscript{4} It was approved by the FDA in 2010 for mCRPC, based in part on the results of the pivotal IMPACT study. In this study, sipuleucel-T was associated with a 4.1-month OS advantage over placebo.\textsuperscript{5} Grade 1/2 AEs occurred in 65.2\% of patients receiving sipuleucel-T, most within 1 day of infusion, and most commonly chills, fever, headache, flu-like illness, myalgia, hypertension, hyperhidrosis, and groin pain (likely related to infusion catheter placement). Only 0.9\% of patients were unable to receive all 3 doses as a result of infusion-related AEs.\textsuperscript{6} Ongoing trials of sipuleucel-T include an examination of its use with or without the pTVG-HP DNA booster vaccine (NCT01706458).

Radiotherapy

Radium-223 is a bone-targeted, α-emitting radiopharmaceutical FDA-approved for mCRPC in 2013\textsuperscript{8} based on the ALSYMPCA trial, in which 921 patients received SOC plus radium-223 or placebo.\textsuperscript{9} The trial met its primary end point of OS (3.6-month advantage for radium-223) and secondary end point of time to first symptomatic SRE (15.6 months for radium-223, 9.8 months for placebo) and was stopped by the data monitoring committee as a consequence of the prespecified statistical analysis plan. Fewer total AEs occurred in the radium-223 arm, including those leading to discontinuation; however, more thrombocytopenia and neutropenia were noted in the radium-223 arm. Radium-223 is an NCCN category 1 option to treat symptomatic bone metastases without visceral metastases.\textsuperscript{10}

After the ALSYMPCA study and before regulatory approval of radium-223, an early-access, single-arm phase 3 study was performed to investigate the safety and efficacy of radium-223 in 839 patients with mCRPC.\textsuperscript{11} Results showed that radium-223 can be combined safely with abiraterone or enzalutamide, with longer OS in those receiving abiraterone, enzalutamide, or both vs none of these agents (median, no response [NR] vs 13 months) and in those receiving vs not receiving denosumab (median, NR vs 13 months). Treatment-related AEs (TRAEs) of any grade occurred in 281 patients (40\%); the most common grade 3 or greater TRAEs were anemia (5\%), thrombocytopenia (2\%), neutropenia (1\%), and leukopenia (1\%). Serious AEs occurred in 35\% of patients.\textsuperscript{12,13}

Novel Strategies With Currently Available Therapies

In addition to the trials just reviewed, several others are exploring different switching, sequencing, and combination approaches for advanced prostate cancer using currently approved agents. TAXYNERGY is a randomized phase 2 trial evaluating an early switch from first-line docetaxel to cabazitaxel or vice versa in mCRPC.\textsuperscript{14} Sixty-three patients were randomized 2:1 to docetaxel or cabazitaxel, and circulating tumor cells (CTCs) were used as biomarkers for AR nuclear localization (ARNL). Eight of 15 patients (53\%) who did not have at least a 30\% decline in PSA by cycle 4 of taxane chemotherapy achieved a 50\% or greater PSA response after switching, including 29\% in the docetaxel group and 14\% in the cabazitaxel group who switched. Overall, 35 patients (56\%) had a confirmed PSA response of at least 50\%. Mean ARNL in CTCs decreased by 6.5\% in these individuals and increased by 6.1\% in those with PSA decline of less than 50\% ($P=0.029$). The authors concluded that the trial met its co-primary clinical and biomarker end points, with an early switch in taxane resulting in a higher PSA response rate compared with historical controls. They noted that ARNL may indicate taxane sensitivity/resistance.\textsuperscript{15}
The combination of carboplatin plus cabazitaxel was explored in a randomized phase 1/2 study, with early results finding the combination safe and effective on measures of PFS and response rate in mCRPC. Updated results confirmed the improvement in median PFS and demonstrated improved response rates with a trend toward improved median OS (17.4 months for cabazitaxel alone vs 19.2 months for carboplatin plus cabazitaxel; \( P=0.489 \)). The authors noted that patients meeting criteria for aggressive variant prostate carcinoma benefited most from the combination regimen.

Other novel combinations of currently approved agents that are being investigated include enzalutamide with or without abiraterone in patients with mCRPC (NCT01949337), abiraterone plus prednisone plus radium-223 (NCT02043678), and abiraterone plus enzalutamide plus radium-223 (NCT02034552). In addition, the phase 3 CABA-DOC trial will investigate patient preference between cabazitaxel and docetaxel in first-line chemotherapy for mCRPC (NCT02044354).

**Emerging Therapeutic Approaches**

Several novel agents also are being investigated for the treatment of prostate cancer (Table 3). One area of much interest is immunotherapy, with activity in 5 broad categories: therapeutic vaccines, oncolytic virus therapies, checkpoint inhibitors, adoptive cell therapies, and adjuvant immunotherapies.

<table>
<thead>
<tr>
<th>Class/MOA</th>
<th>Agent</th>
<th>Phase</th>
<th>Patient Population (N)</th>
<th>Clinicaltrials.gov Identifier (Trial Name)</th>
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<tbody>
<tr>
<td>PSA vaccine</td>
<td>Rilimogene galvavirepvac</td>
<td>3</td>
<td>Asymptomatic/minimally symptomatic mCRPC (1,298)</td>
<td>NCT01322490 (PROSPECT)</td>
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<td>Checkpoint inhibitors</td>
<td>Pembrolizumab</td>
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<td>mCRPC previously treated with enzalutamide (28)</td>
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<td>Atezolizumab</td>
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<td>Advanced solid tumors, including prostate cancer (725)</td>
<td>NCT02458638</td>
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<tr>
<td></td>
<td>Nivolumab + bilmunab</td>
<td>2</td>
<td>Metastatic hormone-resistant prostate cancer expressing AR-V7 (15)</td>
<td>NCT02601014 (STARVE-PC)</td>
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<tr>
<td>PARP inhibitor</td>
<td>Olaparib</td>
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<td>Advanced CRPC (89)</td>
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<td>Non-metastatic CRPC (1,200)</td>
<td>NCT01682772 (SPARTAN)</td>
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<td>AR-V7+ mCRPC (148)</td>
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<td>ODM-201</td>
<td>3</td>
<td>Metastatic castration-sensitive prostate cancer (1,300)</td>
<td>NCT02799602 (ARASENS)</td>
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AR, androgen receptor; CRPC, castration-resistant prostate cancer; mCRCP, metastatic castration-resistant prostate cancer; MOA, mechanism of action; PARP, poly (adenosine diphosphate-ribose) polymerase; PSA, prostate-specific antigen.

Cancer vaccines are designed to elicit an immune response against tumor-specific or tumor-associated antigens. Rilimogene galvavirepvac is a therapeutic cancer vaccine that uses vaccinia and fowlpox viruses as vectors to deliver the PSA antigen, along with 3 costimulatory molecules, directly to cancer cells. It is under investigation in patients with prostate cancer, including the phase
3 PROSPECT trial (NCT01322490). Oncolytic virus therapy uses a modified virus that can cause tumor cells to self-destruct and in the process, generate a greater immune response against the cancer. Checkpoint inhibitors work by targeting molecules involved in the regulation of the immune response; by blocking inhibitory molecules or activating stimulatory molecules, these treatments are designed to induce or enhance preexisting anticancer immune responses. Checkpoint inhibitors currently under investigation in mCRPC include nivolumab and ipilimumab (NCT02601014), pembrolizumab (NCT02312557), and atezolizumab (NCT02458638); however, at this point, these agents have demonstrated limited activity. Adoptive cell therapy—which involves the removal, enhancement, and reintroduction of a patient’s T cells—and adjuvant immunotherapies are in phase 2 trials in patients with prostate cancer.

In addition to immunotherapies, several other agents are under investigation in patients with mCRPC. Olaparib, a poly (adenosine diphosphate-ribose) polymerase (PARP) inhibitor approved for previously treated germline BRCA-mutated advanced ovarian cancer,58 was tested in a phase 2 trial of 50 men with mCRPC. Next-generation sequencing identified homozygous deletions, deleterious mutations, or both in DNA-repair genes in 16 of 49 patients who could be evaluated (33%). Of these 16 patients, 14 (88%) had a response to olaparib, including all 7 patients with BRCA2 loss and 4 of 5 with ATM aberrations. These findings highlight the potential for olaparib in patients with defects in DNA-repair genes. Other PARP inhibitors under investigation for the treatment of mCRPC include velaparib (NCT01576172) and niraparib (NCT02500901).

Other agents under investigation for mCRPC include the AR inhibitors ARN-509 and ODM-201,60 as well as the bromodomain inhibitors ZEN003694 (NCT02711956 and NCT02705469), MK-8628 (NCT02698176), GS-5829 (NCT02392611), and GSK525762 (NCT01587703).

Conclusion

Prostate cancer is a complex disease, with many controversial aspects of management. This includes the fortunate problem of having many therapies available but a paucity of data comparing these agents with one another establishing an optimal sequence. Today’s clinician must take into account several variables, including adjusted life expectancy, disease characteristics, predicted outcomes, cost, and patient preferences, to tailor therapy. Progress certainly has been made in the treatment of prostate cancer—for metastatic disease, 5 agents that improve OS have been approved in the past 6 years—however, no comparative trials have been published, no combination is known to be superior to a single agent, and no sequence is known to be superior to any other. Clinicians should encourage patient participation in clinical trials, as more data are necessary to clarify strategies for the use of single agents, sequences, and combinations that will improve outcomes.

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Credits:

Co-Chairs

- **Michael A. Carducci, MD**
  AEGON Professor in Prostate Cancer Research
  Associate Center Director for Clinical Research
  Sidney Kimmel Comprehensive Cancer Center
  Johns Hopkins Medical Institutions
  Baltimore, Maryland

- **David M. Nanus, MD**
  Mark W. Pasmantier Professor of Hematology and Oncology in Medicine
  Professor of Medicine and Urology
  Chief, Division of Hematology and Medical Oncology
  Joan and Sanford I. Weill Department of Medicine
  Weill Cornell Medicine
  New York, New York

Goal

The goal of this activity is to educate health care professionals about improving patient outcomes in metastatic prostate cancer.

Learning Objectives

At the completion of this activity, participants should be better able to:

1. Communicate with patients and colleagues about the pathophysiology, risk factors, symptoms, and genetics of prostate cancer.
2. Create individualized treatment plans for patients with prostate cancer based on current screening and staging guidelines and evidence for monotherapy, combination therapy, and sequencing of therapies.

Intended Audience
The intended audience for this activity comprises health care providers who care for patients with metastatic prostate cancer, including medical oncologists, hematologists/oncologists, oncology nurses, urologists, and specialty pharmacists.

**Estimated Time for Completion**

1 hour

**Course Format**

Monograph

**Accreditation Statement**

This activity has been planned and implemented in accordance with the accreditation requirements and policies of the Accreditation Council for Continuing Medical Education (ACCME) through the joint providership of Global Education Group (Global) and Applied Clinical Education. Global is accredited by the ACCME to provide continuing medical education for physicians.

**Credit Designation**

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**Method of Participation**

To receive CME credit, participants should complete the pre-test, post-test, and activity evaluation. CME certificates will be made available immediately upon successful completion.

**Fees**

Free

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- Michael A. Carducci, MD: Astellas, AstraZeneca, Medivation, Merck (consultant/independent contractor)
- David M. Nanus, MD: Genentech (data safety monitoring board)

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• Jennifer Kulpa: Nothing to disclose
• Dru Dace, PhD: Nothing to disclose
• Andrea Funk: Nothing to disclose
• Amanda Glazer, PhD: Nothing to disclose

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System Requirements
• Operating System: Windows or Macintosh
• Media Viewing Requirements: Flash Player or Adobe Reader
• Supported Browsers: Microsoft Internet Explorer, Firefox, Google Chrome, Safari, and Opera
• A good Internet connection

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