Castrate-resistant Prostate Cancer— Recent Advances in Therapy and Future Perspectives

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Abstract

For many years, few therapeutic options were available for the treatment of advanced prostate cancer. Recent advances in our understanding of the molecular biology of prostate cancer, particularly in the transition to castrate resistant disease, have led to the development of more potent and selective endocrine therapies. In addition, elucidation of the many factors in the bone microenvironment that promote the development and subsequent progression of skeletal metastases has led to the discovery of new bone-targeting agents that can delay the onset of skeletal related events and improve quality of life and survival. This review will highlight recently approved novel agents as well as others currently under investigation for the treatment of castrate-resistant prostate cancer (CRPC).

Keywords

Metastatic castrate-resistant prostate cancer (mCRPC), androgen receptor (AR), androgen receptor signaling inhibitor (ARSI), skeletal related event (SRE), bone metastasis-free survival (bMFS), granulocyte-macrophage colony-stimulating factor (GM-CSF), PSA doubling time (PSADT), radiographic progression-free survival (rPFS), overall survival (OS)

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Prostate cancer remains the most common non-cutaneous malignancy afflicting men in North America and the second leading cause of death. In men who relapse after surgery or radiation therapy with curative intent, initial androgen-deprivation therapy (ADT) achieved through medical or surgical castration results in biochemical, objective, and symptomatic improvement in a majority of men. However, this therapy alone is not curative and patients invariably progress to a lethal or castrate-resistant phase of the disease.

It is known that in the castrate-resistant state, androgen signaling persists despite low levels of testicular androgens. At the same time, molecular changes in the castrate-resistant (CRPC) cell occur that enable it to take up and convert small amounts of adrenal androgen precursors to testosterone and DHT.[1–3] This *de novo* synthesis is facilitated by an over-expression and up-regulation of intracellular enzymes required for androgen synthesis.[1–3] In addition, amplification and sensitization of the androgen receptor occurs leading to ligand-independent activation.[1–3]

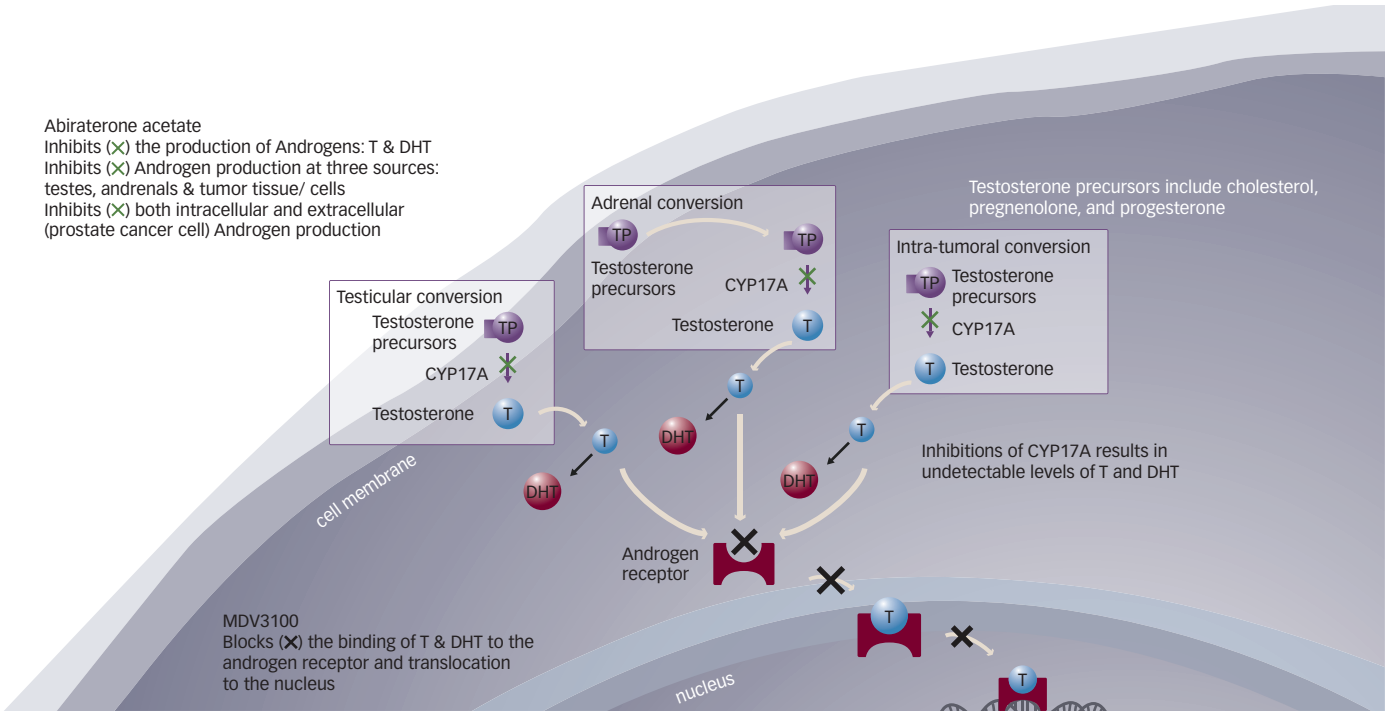
New Hormonal Therapies

Abiraterone Acetate (Zytiga)

Abiraterone blocks the production of testicular, adrenal, and intra-tumoral androgens by irreversibly inhibiting CYP17, an enzyme vital for the synthesis of dihydroepiandrosterone (DHEA) and androstenedione, the direct precursors of testosterone synthesis in humans. This results in a decrease in downstream androgen signaling (see *Figure 1*). The efficacy of abiraterone was confirmed in a large Phase III multicenter, randomized, double-blind, placebo-controlled trial in which 1195 me with metastatic CRPC (mCRPC) who had previously received docetaxel-based chemotherapy were randomized 2:1 to receive abiraterone 1,000 mg orally daily and prednisone 5 mg orally twice daily or prednisone 5 mg orally twice daily and placebo.[4] The primary endpoint of this study was OS (OS). Approximately 90 % of patients had bone metastases and of these, 44 % had clinically significant pain. Treatment was continued until disease progression, defined as a composite of objective progression, symptomatic progression, and a rising prostate specific antigen (PSA). The trial was terminated after an interim analysis conducted at a median follow-up of 13 months showed a significant improvement in OS in the abiraterone and prednisone treated group compared to placebo (14.8 months versus 10.9 months; p<0.0001, HR 0.646). Secondary endpoints of progression-free survival, PSA response and time to PSA progression were also significantly improved in the abiraterone treated group. In a recent subset analysis, abiraterone significantly reduced pain from skeletal metastases and increased the time to development of first skeletal related event (SRE), defined as pathologic fracture, spinal cord compression, or requirement for palliative radiation therapy or surgery, compared with placebo.[4] Inhibition of CYP17 by abiraterone can lead to increased mineralcorticoid production by the adrenal glands resulting in hypokalemia, hypertension, and fluid retention.[5] While the incidence of these side effects was more common in the abiraterone treated group, they were generally mild (grade one or two) and ameliorated by concurrent prednisone administration.

Abiraterone has also been approved for asymptomatic patients or mildly symptomatic patients with mCRPC who have not yet received prior

Figure 1: Mechanisms of Action—Abiraterone (Zytiga) and Enzalutamide (Xtandi)



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chemotherapy (COU-AA-302) This study was recently unblinded after a planned interim analysis showed improvements in the co-primary endpoints of the study, radiographic progression-free survival (rPFS) and OS for the abiraterone and prednisone treated patients compared to those receiving placebo and prednisone.[6] At a median follow-up of 22.2 months, rPFS and OS for the prednisone and placebo group was 8.3 months and 27.2 months, respectively, but had not yet been reached for the abiraterone treated group. Secondary endpoints of time to opiate use (for cancer related pain), time to chemotherapy initiation, time to Eastern Cooperative Oncology Group-Performance Status (ECOG-PS) deterioration, and time to PSA progression also favored the abiraterone arm. As previously demonstrated, the safety and tolerablility of abiraterone was quite acceptable. COU-AA 302 is the first randomized study to show a benefit in both rPFS and OS in chemotherapy-naïve mCRPC patients and supports the concept that initiation of chemotherapy can be significantly delayed by continuous inhibition of extragonadal androgen synthesis. Clinical trial with other promising and selective CYP17 inhibitors such as TAK-700 (orteronel)[7] are currently in progress.

Enzalutamide (Xtandi)

Enzalutamide or Xtandi (formerly MDV 3100) is a novel oral androgen receptor signal inhibitor (ARSI). In preclinical studies, enzalutamide was shown to slow growth and induce apoptosis in cancer cells resistant to bicalutamide through its triple inhibition of testosterone and dihydrotestostrerone (DHT) binding to the androgen receptor (AR), translocation of AR to the prostate cancer cell nucleus, and binding of AR to DNA (see *Figure 1*). Enzalutamide is the first androgen receptor signal inhibitor (ARSI) to show a survival benefit in men with metastatic CRPC previously treated with docetaxel (AFFIRM trial). The results of AFFIRM were recently presented at a Joint Genitourinary Cancers Symposium.[8] In this multi-national, randomized, double-blind, placebo-controlled Phase III trial, 1199 men with mCRPC were randomized 2:1 to receive enzalutamide 160 mg/ day or matched placebo. Treatment with corticosteroids was allowed but not required. The primary endpoint was OS. Secondary endpoints included radiographic PFS, time to first skeletal-related event (SRE), time to PSA progression, and circulating tumor cell count conversion rate. Median OS was 18.4 months in the enzalutamide arm and 13.6 months in the placebo arm (P<0.0001; hazard ratio (HR) 0.631). Median radiographic (rPFS) was also superior in the enzalutamide treated group (8.3 versus 2.9 months) (P<0.0001). The survival benefit extended to all pre-specified subgroups. Enzalutamide was well tolerated and more grade three or higher adverse events were reported in the placebo arm (53.1 % versus 45.3 %). Based on the results of the AFFIRM trial, enzalutamide was recently approved by the US Food and Drug Administration (FDA) in the post-chemotherapy setting for men with metastatic CRPC.

A companion trial examining the potential efficacy of enzalutamide compared with matched placebo in chemotherapy naïve patients with mCRPC (PREVAIL trial) with primary endpoints of OS and PFS recently completed accrual. Results of the first interim analysis from this study are expected shortly. Clinical trials with other ARSIs, i.e. ARN-509, are currently in progress.

Immunotherapeutic Approaches

The rationale for the development of therapeutic prostate cancer vaccines is based on the identification of cell surface tumor associated antigens (notably prostatic alkaline phosphatase (PAP), PSA, and cytotoxic T lymphocyte antibody 4 (CTLA4) that can serve as specific targets for immunotherapy[9] Sipuleucal-T (Provenge) is an autologous dendritic cell vaccine in which the patient's own mononuclearcells are

harvested during a standard leukopheresis procedure.[10] The harvested cells are then co-cultured ex-vivo with a recombinant fusion protein containing both an immune-stimulatory component granulocyte-macrophage colony-stimulating factor (GM-CSF) and antigenic component (PAP). The activated antigen-loaded dendritic cells are then infused into the patient, where they stimulate a T-cell response to cells expressing PAP. The initial phase III trial comparing Sipuleucal-T with placebo was completed in 2006 and was the first to demonstrate prolonged survival by a vaccine treatment for prostate cancer.[10] The results of a confirmatory phase III trial (the IMPACT trial) in which asymptomatic or minimally symptomatic men with mCRPC were randomized to receive either Sipuleucal-T or placebo were presented in 2009.[11] Although no differences in PSA response or time to disease progression were observed between the two treatment arms, median survival was extended by 4.2 months in the vaccine arm compared with placebo (25.8 versus 21.7 months; p=0.03). Provenge was approved by the FDA for the treatment of mCRPC in April 2010.

PROSTVAC-VF (Prostvac) was the first viral vector vaccine to be tested in prostate cancer. In this type of vaccine, genes that encode tumor-associated antigens or co-stimulatory proteins are inserted into attenuated pox viral vectors. The efficacy of the vaccine is enhanced by the addition of co-stimulatory molecules to enhance T-cell stimulation and GM-CSF to increase tumor-specific immunity.[12] These viral vectors stimulate antigen-presenting cells and induce a specific T-cell response to tumor cells expressing PSA. A randomized Phase II trial of PROSTVAC-VF in men with mCRPC did not meet its primary endpoint of PFS, but OS was significantly longer at 3 years in the PROSTVAC-VF treated arm versus placebo (25.1 months versus 16.6 months; p=0.006).[13] A Phase III trial of PROSTVAC-VF in men with asymptomatic or minimally symptomatic mCRPC is currently in progress.

Ipilimumab (Yervoy) is an immunostimulatory antibody that binds to CTLA-4, an antibody expressed on cytotoxic T lymphocytes which play a pivotal role in regulating natural immune responses.[14] The ability of ipilimumab to block CTLA-4 enhances the immune system's T cell response to cancer cells.[15] Ipilimumab was approved for the treatment of metastatic melanoma in 2010. A potential benefit for ipilimumab in combination with standard ADT in downstaging patients with both early and more advanced stage prostate cancer was suggested in two early Phase II clinical trials.[16,17] Potential synergy was also suggested for ipilimumab in combination with radiation in a randomized open label phase I/II study.[18] The main grade 3/4 toxicities included colitis, diarrhea, and hepatitis. These side effects were not exacerbated by use of concurrent radiation therapy. Phase III clinical trials of ipilimumab in chemotherapy-naïve patients with CRPC and in combination with bone targeted radiation therapy in CRPC patients who previously received docetaxel are in progress.

Tubulin-targeting Agents

Microtubule inhibitors have historically been the most widely studied and active chemotherapeutic agents in the treatment of advanced prostate cancer. These agents can promote assembly of tubulin and stabilize microtubules resulting in cell cycle arrest and inhibiton of tumor cell proliferation. In addition to targeting the mitotic spindles, taxanes can inhibit AR signaling and downstream activation of AR targets genes such as PSA following translocation of AR from the cytoplasm to the nucleus.[19]

Cabazitaxel (Jevtana) is a second generation taxane which demonstrated antitumor activity against both taxane-sensitive and taxane-resistant animal tumor models.[20] Cabazitaxel also inhibited growth of docetaxel-resistant cell lines suggesting that it might be a poor substrate for the MDR P-glycoprotein efflux pump. In early clinical studies, cabazetaxel showed activity in patients with taxane-resistant breast cancer.[21] Based on these pre-clinical observations and a favorable toxicity profile in Phase I and II clinical trials, the potential efficacy of cabazitaxel in men with docetaxel-resistant mCRPC was further explored in the TROPIC trial.[22] In this trial, 755 men who had progressed during or after treatment with a docetaxel-based regimen were randomized 1:1 to receive cabazitaxel 25 mg/m^2 intravenously every three weeks and prednisone 10mg orally daily for 10 cycles or mitoxantrone 12 mg/m^2 intravenously every three weeks and prednisone 10 mg orally daily for 10 cycles. The primary endpoint of this study was OS. Secondary endpoints included PFS, response rate, and safety. Approximately 85 % of patients had received only one prior docetaxel-containing regimen and only 2 % had received three or more regimens. Patients were required to have received at least three cycles of docetaxel prior to study entry. Cabazitaxel demonstrated a significantly longer OS compared with mitoxantrone (15.4 months versus 12.7 months P<0.0001; HR 0.70). Investigator-assessed tumor response rate, a secondary endpoint, also significantly favored cabazitaxel over mitoxantrone (14.4 % versus 4.4 %; p=0.05). The most common grade 3-4 hematologic adverse event in the cabazitaxel group was neutropenia (82 %). However, primary prophylaxis with G-CSF was not permitted in this trial. The most common non-hematologic adverse events associated with cabazitaxel were diarrhea (6 %), fatigue (5 %) and asthenia (5 %). Interestingly, grade 3–4 peripheral neuropathy and peripheral edema, side effects more often associated with docetaxel therapy, were observed in <1 % of cabazitaxel treated patients. Additional areas of clinical interest pertain to the optimal dose of cabazitaxel (i.e 25 mg/m^2 or 20 mg/m^2) and it's activity as a first-line treatment in patients with metastatic CRPC compared with docetaxel. This is currently being addressed in the FIRSTANA trial. The primary endpoint of this study is OS.

Bone-targeting Agents

Denosumab (Xgeva)

Bone metastases are present in more than 80 % of patients with advanced prostate cancer. It is known that tumor cells can secrete a variety of osteoclast-stimulating factors, including receptor activation of NF-kB ligand (RANKL). These factors can both promote tumor growth and exacerbate destructive bone resorption.[23,24]

Denosumab (Xgeva), a monoclonal antibody that binds to RANKL, was compared to Zoledronic acid (Zometa) in men with CRPC and established skeletal metastases.[25] In this Phase III study, patients treated with denosumab had a 3.6 month improvement in time to initial skeletal related event compared with zelodronic acid. There were no differences in rates of hypocalcemia, osteonecrosis of the mandible, or renal toxicity between the two treatment arms.

The potential for denosumab to delay development of bone metastases was recently explored in a randomized Phase III trial.[26] Patients with high-risk non-metastatic CRPC (defined as PSA of > 8 or a PSADT < 10 months at study entry) were randomized 1:1 to receive denosumab or placebo. The primary endpoint was bone metastasis-free survival (bMFS).

Denosumab reduced the overall risk for developing skeletal metastases by 15 %. In the subset of patients whose PSADT was < 6 months, bMFS was 6.5 months shorter for the placebo group than those receiving denosumab (18.7 months versus 25.2 months). Although these results are favorable, denosumab is not currently approved for treatment of non-metastatic CRPC patients at higher risk for developing bone metastasis.

Rad-223 Chloride (Alpharadin)

Rad-223 Chloride is a novel radiopharmaceutical that emits alpha particles. Radium is known to mimic calcium and binds to osteoclasts and other bone matrix targets resulting in inhibition of new bone growth associated with metastasis in CRPC patients.[27] The alpha particles emitted by radioisotope Rad-223 (which subsequently decays) can deliver lethal DNA damaging doses of radiation selectively to areas of osseous metastases. Because alpha particles have a shorter degree of penetrance than gamma or beta particles, they have the ability to spare collateral damage to surrounding healthy tissues. Radium-223 Chloride can be administered by IV injection in an outpatient setting.

The potential of Rad-223 chloride to improve OS in men with CRPC was explored in the recently completed ASLYMCA trial.[28] In this trial, men who were not considered fit for docetaxel or had previously received docetaxel were randomized 2:1 to receive intravenous Rad-223 chloride or placebo. The primary endpoint was OS. Treatment with cytotoxic or radioisotope therapy was not allowed while patients were on study drug. At the time of the initial interim analysis, the majority of study patients had either six to 20 bone lesions (44–48 %) or greater than 20 bone lesions (40 %). Approximately one-half of patients (54 %) were receiving opioid analgesics. The median OS in the Rad-223 chloride group was improved by 2.8 months in (14 versus 11.2 months; p=0.0185; HR 0.695). Significant improvements in clinically meaningful secondary endpoints were also observed in the Rad-223 chloride arm. The occurrence of first SRE was delayed by five months with a risk reduction of 40 %. The incidence of pathologic bone fracture, determined by pathologic report and the need for intervention with palliative radiation or surgery was also reduced, as was the incidence of spinal cord compression. Concomitant use of bisphosphonates appeared to enhance the efficacy of Rad-223 chloride. Rad-223 chloride was well tolerated with a lower incidence of adverse events compared with placebo. Hematologic toxicity was rare with grade 3/4 neutropenia and thrombocytopenia observed in only 2 % and 4 % of patients, respectively. Diarrhea was more common in the Rad-223 chloride treated group. Only 10 % of patients discontinued treatment due to adverse events.

An updated analysis of the ASLYMCA trial was recently conducted prior to crossover to Rad 223-Chloride for placebo patients.[29] The median OS benefit for Rad 223 increased from 2.8 months to 3.6 months (median 14.9 mo versus 11.3 mo; HR 0.695) and time to to first SRE increased to 5.8 months (15.6 mo versus 9.8 mo; HR 0.658) with confirmation of a highly favorable safety profile. A submission to the US Food and Drug Administration for approval is planned.

XL184 (Cabozantinib)

XL184 is an oral inhibitor of several receptor tyrosine kinases, including MET and VEGFR-2, whose role in promoting tumor growth, invasiveness, and angiogenesis is well established.[30,31] In particular,

Table 1: Novel Agents Recently Approved or Under Investigation for Treatment of Metastatic Castrate-resistant Prostate Cancer

Hormonal Therapies	Bone-targeting Agents
*Abiraterone (Zytiga)	*Denosumab (Xgeva)
*Enzalutamide (Xtandi)	Rad 223 Chloride (Alpharadin)
TAK 700	(XL-184) Cabozantinib
ARN-509	
Immunotherapies	**Clusterin Inhibition**
*Sipuleucal-T (Provenge)	OGX-011 (Custirsen)
PROSTVAC	**Chemotherapy**
Ipilimumab (Yervoy)	*Cabazitaxel (Jevtana)

**US Food and Drug Administration (FDA)-approved.*

MET is over-expressed in early stage and advanced prostate cancer with high levels of expression in bone metastasis.[30] Altered expression of c-Met and hepatocyte growth factor in prostate tumors and the bone microenvironment is believed to contribute to the growth and progression of bone metastasis.[31]

In a recent Phase II discontinuation trial, 171 men with CRPC and symptomatic bone metastasis were treated with cabozanitib.[32] Those patients with stable measurable disease at 12 weeks were randomly assigned to cabozantinib or placebo. Seventy-two percent of patients had a regression in soft tissue lesions and 68 % of patients had improvements on bone scan including complete resolution in 12 %. The objective response rate at 12 weeks was 5 % with stable disease in 75 % of patients. Thirty-one patients with stable disease at week 12 were randomly assigned. Those patients who remained on study drug had significantly longer PFS than those receiving placebo (23.9 versus 5.9 weeks; P<0.001). On retrospective review, bone pain improved in 67 % of evaluable patients and 56 % were able to decrease narcotic analgesic use. The most common grade 3 side effects were fatigue (16 %), hypertension (12 %,) and hand-foot syndrome (8 %). Two phase III clinical trials are currently in progress. COMET-1 will evaluate the potential of cabozantinib to improve OS in men with metastatic CRPC and the COMET-2 will further evaluate cabozantinib's ability to reduce pain associated with bone metastasis in the CRPC setting.

Clinical Trials In Progress

Clusterin is a stress-activated cytoprotective chaperone that is highly expressed in poorly differentiated prostate tumors and CRPC. Forced over-expression of clusterin after treatment with various cancer therapies has been demonstrated in tumor models and upregulation of clusterin has been shown to confer resistance to chemotherapy, hormone therapy and radiation.[33,34] OGX-011 (custirsen) is a phosphorothioate antisense that inhibits clusterin production with the potential to enhance sensitivity to chemotherapy and delay the onset of resistance. A phase II randomized trial in men with mCRPC showed improved OS for patients randomized to docetaxel, prednisone, and OGX-011 compared to docetaxel and prednisone.[35] Two phase III studies of OGX-011 in combination with docetaxel (1st linesetting) and cabazitaxel (2nd line setting) in patients with mCRPC are currently in progress.

Future Perspectives

Over the past couple of years, the introduction of several new agents with novel mechanisms of action and favorable safety profiles has led to an improvement in OS and quality of life for men with metastatic CRPC. (see *Table 1*) The impetus for new drug development has followed important advances in our understanding of the molecular biology of prostate cancer, in particular the continued dependency of castrate resistant cells on the AR and AR signaling pathways and the ability of the bone microenvironment to promote skeletal metastasis through its influence on osteoblastic/osteolytic activities.

With significant advances in the treatment of CRCP taking place in a relatively short period of time, future initiatives will need to focus on how to best integrate these new therapies into the current treatment paradigm. From a clinical practice and clinical research perspective, a number of important questions remain. For example, should CYP17 inhibitors (Zytiga) or perhaps ARSI's (enzalutamide) be given to patients prior to or after chemotherapy? Is there an optimal sequence to the use of these agents or a role for combination therapy since they have different but complementary mechanisms of action and non-overlapping toxicities? (see *Figure 1*). Should bone-targeting agents with diverse mechanisms of action be given sequentially or concurrently to patients with established skeletal metastasis with the hope of further delaying time to first skeletal-related event? Is there a role for combining chemotherapy and immunotherapy in the treatment of metastatic CRPC[36] or using immunotherapeutic agents as adjuvant therapy in high risk patients or in those with non-metastatic CRPC at a time when the immune system is more robust and the tumor burden low?

Recent improvements in genomic technology using multiplex assays and microarrays to analyze the myriad germline, somatic mutations, gene copy number variations, and other alterations affecting gene expression present in individual tumor samples will afford a unique opportunity to develop strategies for truly personalized cancer treatment. Transcriptional and genomic profiling studies have identified recurrent gene fusions, chromosomal gains and losses, and deregulated pathways in prostate cancer including ETS genes, PTEN loss, and AR amplification that can drive the progression to metastatic CRPC.[37] Using exome-based profiling, a diverse group of recurrent and potentially driving mutations and copy number alterations in both known and novel genes and pathways has recently been identified in a cohort of heavily-pre-treated patients with lethal CRPC.[38] The creation of large integrative genomic databases will undoubtedly enable researchers to more fully explore and better understand the relationships between cancer genes and disease progression, mechanisms of resistance, and response to therapy with the goal of matching the most effective drug or drug combinations with the molecular characteristics of the individual patient. Given the rapid evolution of translational science, the introduction and approval of several new agents with unique and diverse mechanisms of action with others in late-stage development, and the eagerly awaited results of recently completed and ongoing clinical trials, the therapeutic climate in CRPC is more exciting than ever. ■

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